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Nutrition and the science of disease prevention: a systems approach to support metabolic health

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Progress in nutritional science, genetics, computer science, and behavioral economics can be leveraged to address the challenge of noncommunicable disease. This report highlights the connection between nutrition and the complex science of preventing disease and discusses the promotion of optimal metabolic health, building on input from several complementary disciplines. The discussion focuses on (1) the basic science of optimal metabolic health, including data from gene–diet interactions, microbiome, and epidemiological research in nutrition, with the goal of defining better targets and interventions, and (2) how nutrition, from pharma to lifestyle, can build on systems science to address complex issues.

Keywords: gene–diet interactions; body weight; gut microbiome; systems science; diabetes; obesity

Introduction

The field of nutrition science is complex in that a large number of factors interact to produce an outcome of interest. For example, the potency of a nutrient is determined by the genetic makeup, age, and health status of the host;[1] by the bioavailability of the nutrient, which is affected by conditions associated with growing, harvesting, storing, and preparing food for consumption;[2] and by the timing, frequency, and duration of dose and contextual factors (e.g., foods, medications, and diseases that aid or hinder absorption[3]). Although traditional linear, reductionist methods have contributed greatly to our understanding of nutritional factors and their contribution to various diseases, the ability of these methods to examine complex reciprocal relationships between, for example, dietary intake, activity levels, and manifestation of disease, is limited. Systems-based approaches enable study of the complex ways that nutrition interacts with genetic and environmental factors to influence the risk of chronic diseases, such as obesity and type 2 diabetes, and combine data from several complementary disciplines to explain the development of these diseases.[4–6] To discuss the application of systems-based approaches to the study of nutrition and metabolic health, leading researchers in genetics, physiology, microbiology, epidemiology, and behavioral sciences convened at the conference "Nutrition and the science of disease prevention: a systems approach to support metabolic health," held on April 16, 2015 and presented by the Sackler Institute for Nutrition Science at the New York Academy of Sciences. This report provides an overview of the topics presented at the conference, with a focus on (1) the basic science of optimal metabolic health, including data from gene–diet interactions, microbiome, and epidemiological research in nutrition, with the goal of defining better targets and interventions, and (2) how nutrition, from pharma to lifestyle, can build on systems science to address complex issues.

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The basic science of optimal metabolic health

Molecular physiology of the control of body weight

Rudolph Leibel (Columbia University) opened the first session with a presentation on the basic molecular physiology of, and newer strategies for understanding, body weight regulation. From an evolutionary perspective, body fat is critical to reproductive integrity and survival under circumstances of restricted and intermittent access to food. Long-term studies consistently show that successful weight reduction is often eventually followed by weight regain, such that weight-reduced individuals return to their starting weight.[7–9] Although there are indeed some individuals who are successful in maintaining weight reduction over time, it is achieved at the cost of extremely careful management of feeding behavior and energy expenditure.[8]

Weight regain shortly following weight reduction can be explained by the compensatory actions of metabolic, behavioral, neuroendocrine, and autonomic systems designed to maintain body energy (fat) stores, with homeostatic responses to perturbations in body fat being stronger in response to weight loss than gain.[10] These systems cause body weight to be maintained around a body weight "set point," a misnomer in that regulatory forces are asymmetrical in favor of the defense of body fat and a concept that Leibel prefers to instead refer to as a threshold. A major player in this system is leptin,[11] a hormone secreted from fat cells in proportion to mass (i.e., the size and number of fat cells), such that obese individuals (with larger and more fat cells) will produce more leptin than lean individuals. Leptin crosses the blood–brain barrier, interacting primarily with two brain regions, the arcuate nucleus of the hypothalamus and the brainstem, where the major physiological function of leptin is to signal states of negative energy balance and decreased energy stores.

In both obese and lean individuals, a decline in leptin levels below a critical individualized threshold triggers a powerful anabolic response, in which leptin drives an increase in energy intake (delayed satiation and perception of fewer calories ingested) and a decrease in energy expenditure (adaptive thermogenesis), in an effort to return to the original body weight.[12] Lean and obese individuals, however, differ in where this threshold lies, which is determined by genes (such as *MC4R* and *FTO*), development (pre- and postnatal effects on brain development), and environmental factors. Compared to lean individuals, those who are obese have higher threshold leptin concentrations at which energy expenditure decreases. Weight reduction, however, does not alter this threshold, ultimately meaning that leptin-regulated systems in weight-reduced individuals will sense a deficiency of body fat, conveyed physiologically in two ways: increased hunger and decreased energy expenditure, favoring weight regain.[10]

Leibel presented data from a series of weight-perturbation experiments, in which human subjects were studied at their initial weight and after a body weight reduction of 10%. Leptin was administered at doses that raised leptin levels back to initial pre–weight loss levels (with the aim of essentially signaling to the brain that fat had never been lost). Leibel and colleagues[13,14] found that, in weight-reduced individuals, leptin administration resulted in a smaller decline in energy expenditure, improved satiation, and reversed the increase in muscle contractile efficiency that normally occurs with weight reduction. In addition, neuroimaging studies revealed that leptin administration in weight-reduced subjects restored activity in diverse leptin-sensitive regions of the brain, including hypothalamic regions, that are typically altered following weight loss.[15]

Leibel next discussed the implications of these findings for the therapy of obesity. It has been shown that the primary challenge for most individuals is not in losing weight but in maintaining weight reduction over time,[7–9] and from a physiological or pharmacological perspective, restoring normal physiology can be accomplished more readily than can inducing weight loss. Leibel therefore suggested that the focus of obesity therapy should be restoring normal physiology in weight-reduced individuals rather than inducing weight loss. As discussed, one approach to restore normal physiology is to artificially signal to the brain that body weight has not been lost, by, for example, raising leptin concentrations after weight reduction.

Critical to the role of hypothalamic neurons in energy homeostasis is the ability to sense and respond to metabolic signals, including from leptin. Leibel concluded his presentation with discussion of a recent study from his laboratory, in which hypothalamic neurons were generated from embryonic and induced pluripotent stem cells obtained from the skin cells of patients with

monogenic types of obesity, such as Bardet–Biedl syndrome (BBS).[16] Leibel and colleagues found that leptin signaling was disrupted in BBS neurons, whereas control cells showed normal leptin signaling. Leibel expressed optimism about the potential of these hypothalamic-like neurons for enabling further study of the neurophysiology of body weight regulation and evaluating therapeutic interventions to restore normal physiology in the weight-reduced state.

Systems genetic approaches to gene–diet interactions

Continuing the session on the basic science of metabolic health, Brian J. Bennett (University of North Carolina at Chapel Hill) discussed systems genetic approaches to gene–diet interactions and, more specifically, the use of mice to identify gene–diet interactions as they relate to heart disease. Human genetics has been revolutionized by studies that investigate genetic susceptibility on a genome-wide basis (genome-wide association studies (GWASs)), which have resulted in the identification of dozens of novel genes for traits such as diabetes and cardiovascular disease (CVD).[17–21] However, elucidating the mechanisms underlying these novel loci has been difficult, potentially because of the challenges presented by nonlinear relationships[22] and epistatic gene–gene and gene–diet interactions.[23]

Mouse models are well suited for studies of gene–diet interactions because the environmental and housing conditions can be carefully controlled, ultimately reducing random environmental effects on a trait and increasing the portion of variance that can be explained by genetics. In mouse strains, complex traits typically have higher heritability and genetic loci often have stronger effects on the trait compared to in humans, partially owing to genetic history.[24–27] Furthermore, the use of genetic reference panels, in which multiple replicates per genotype are studied, is ideal for identifying gene–diet interactions because the additional replicates reduce false positives and improve precision. Another advantage of using mouse models for studying gene–diet interactions is that hypotheses can be validated *in vivo* in mice.

An advanced mouse resource, named the diversity outbred (DO) mouse population, was recently created from a common set of classical inbred and wild mice–derived strains, including A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLtJ, NZO/HILtJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ.[28–30] DO mice are systematically outbred to increase the number of recombination events per animal, estimated to be in excess of 400 recombinations per mouse in the most recent generation.[31] DO mice represent a valuable resource for improved resolution of quantitative trait loci (QTL) mapping, resulting in smaller genetic intervals encompassing fewer genes.

Bennett discussed a QTL mapping study in DO mice, in which his laboratory identified several QTL associated with atherosclerosis and related traits. These traits were quantitated while the mice were fed a synthetic, chemically defined control diet (AIN-76) and again after 16 weeks of being fed a low-fat, high-protein diet or a high-fat diet containing cholic acid designed to induce atherosclerosis. They refined the previously identified triglyceride QTL 1 (*Trigq1*) from approximately 12 Mb to a 1.4-Mb QTL interval containing only 34 candidate genes.[32] The use of DO mice to refine this previously identified QTL interval to a region containing a testable number of candidate genes for follow-up study provides a basis on which to better understand the biological mechanisms underlying associations between QTL and atherosclerosis.

In a subsequent series of animal and human studies,[33–37] Bennett's laboratory characterized several genetic polymorphisms, dietary factors, and microbial diversity affecting levels of trimethylamine *N*-oxide (TMAO), a gut microbiome–dependent metabolite associated with CVD in humans. TMAO is produced by microbial degradation of dietary phosphatidylcholine (PC) in the digestive tract; it is now known that this pathway includes both free choline and L-carnitine.[33,35] Initial studies with multiple inbred strains of mice suggested that TMAO explains approximately 11% (r^2) of the total variation of atherosclerosis.[36] Recent GWASs in humans failed to find robust and reproducible loci,[37] indicting that diet and microbial-dependent processes mitigate the genetic regulation of TMAO levels.

Bennett has also examined dietary perturbations affecting microbial diversity, circulating TMAO levels, and plasma lipids, in microbiome studies using a small panel of inbred mouse strains.[38] These studies used a high-fat cholic acid–containing diet, commonly referred to as the Paigen diet,

and extended previous results indicating that this diet modulates flavin-containing monooxygenase 3 (*Fmo3)* gene expression.[36] They found, by principal coordinates analysis, a by-strain separation in microbial diversity at baseline and a between-diet separation in community diversity. Interestingly, a strain–diet interaction was evident, with certain strains exhibiting greater separation between the atherogenic and control diets, and several differentially abundant taxa were consistently related to cardiometabolic parameters. Ultimately, these findings identified diet- and gene-regulated taxa related to metabolic risk factors.

In an attempt to integrate the study of the microbiome in future genetic experiments, Bennet's laboratory will directly investigate genetic regulation of these taxa, test the mechanism of effect, and aim to develop targeted microbiome-focused treatments for metabolic disease.

Investigation of gut microbiota niches and their relevance to metabolic health

Anne L. McCartney (University of Reading) gave a presentation on the role of gut microbiota in human systems biology and host health. In an initial overview, she explained that the bulk of the human gut microbiota is found in the lower intestinal tract, consisting of the ileocecal region (distal small intestine) and colon (proximal, transverse, and distal regions). The majority of studies on the human gut microbiota focus on the fecal microbiota representing microbial populations of the distal colon, because of the relative ease of noninvasive sampling.

However, the activity of microbial populations from other gut regions, such as from the ileocecal region, is likely to also play an important role in host metabolic health. Therefore, McCartney and colleagues, in collaboration with Lesley Hoyles (University of Westminster), examined the human cecal microbiota, using a polyphasic approach. In this study, weighted UniFrac analysis of 454 pyrosequencing data was not only able to split cecal samples of inflammatory bowel disease (IBD) and non-IBD patients, but was also able to separate the non-IBD group (i.e., separate individuals with healthy histology from those with complications). They found that the relative proportions of the main phyla obtained by fluorescence *in situ* hybridization and pyrosequencing showed comparable representation of *Firmicutes* abundance (∼49%) and lower *Bacteroidetes* (∼32% vs. ∼45 %, respectively) and higher *Actinobacteria* (∼4% vs. ∼0.1%, respectively) abundance. Cultivation work from the cecal-effluent samples led to the creation of a collection of approximately 600 cecal isolates comprising a mixture of typical gut (fecal, small intestine) and oral bacteria. Bacteriophages were also detected in some of the cecal-effluent samples ($\sim 1 \times 10^5$ virus-like particles/mL),[39] and a *Klebsiella pneumoniae* subsp. *pnuemoniae*–bacteriophage combination was isolated from the cecal effluent of a healthy female subject.[40] Phage KLPN1 was shown to infect only *K. pneumoniae* subsp. *pnuemoniae* clinical isolates of the same capsular type (K2) as the host strain, although the depolymerase activity displayed against the host strain was not exhibited against the clinical isolates. McCartney suggested that this phenomenon may be related to host-associated adaptations relevant to gut microbial ecology and human health.

Microbial metabolism is known to influence host (including metabolic) health, and the gut–liver axis is an emerging area of interest in the microbial–mammalian metabolic axis.[41] McCartney discussed *in vitro* functional studies that used in-house collections of human fecal and cecal bacteria to examine microbial use of the dietary methylamine TMAO. In pure culture, TMAO was rapidly reduced to trimethylamine (TMA) by gut bacteria, with *Enterobacteriaceae* producing the highest amount of TMA from TMAO. Cecal *Esherichia coli* strains produced significantly higher amounts of TMA and acetate from TMAO-containing medium than their fecal counterparts, demonstrating differing metabolic activity of strains of the same bacterial species isolated from different gut niches. TMA produced by gut bacteria is taken up by the liver and converted to TMAO by the enzyme FMO3, and circulating TMAO has been associated with CVD risk. On the basis of these data, McCartney concluded that microbial activity in the upper intestinal tract may be of greater relevance to the gut microbiota–driven TMA/FMO3/TMAO pathway[42] than microbial activity in colonic microbiota.

Keynote lecture: systems epidemiology approach to understanding nutrition, obesity, and diabetes

In the keynote lecture, Frank B. Hu (Harvard T.H. Chan School of Public Health) discussed a systems

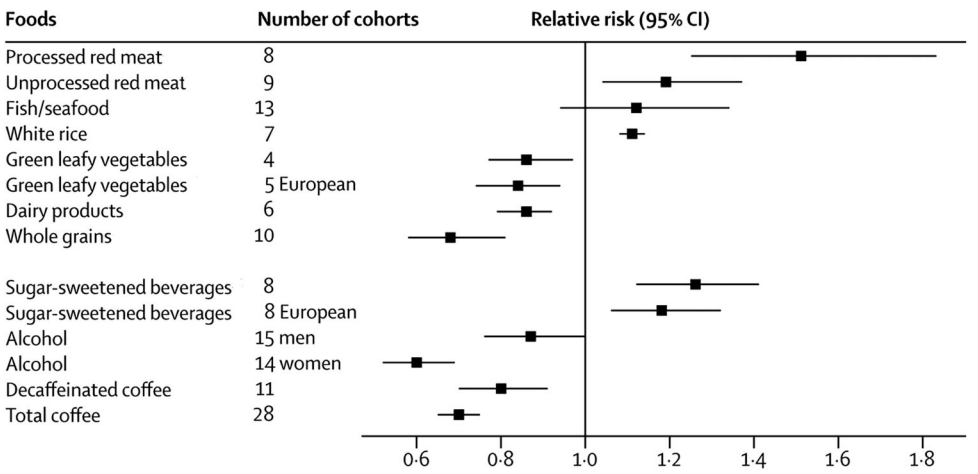

Figure 1. **Summary of meta-analyses of prospective cohort studies on food and beverage intake and type 2 diabetes. Relative risks are a comparison of extreme categories, except for processed meat (per 50 g/day increase), unprocessed red meat and fish or seafood (per 100 g/day), white rice (per each serving/day), whole grains (per 3 servings/day), sugar-sweetened beverages in European cohorts (per 336 g/day), and alcohol (22 g/day for men or 24 g/day for women, with abstainers). Adapted, with permission, from Ley *et al.*[45]**

epidemiology approach to understand metabolic diseases, particularly type 2 diabetes, which has become a major public health problem globally, largely because of an escalating obesity epidemic. The International Diabetes Federation estimated that the number of adults living with diabetes would increase from 382 million in 2014 to 592 million by 2035.[43] The major driver of this pandemic is diet and lifestyle changes that have led to increased consumption of calories, highly processed foods, and added sugars (from sweetened beverages in particular), as well as a dramatic reduction in physical activity levels, which, in many developing countries, has occurred in the context of rapid economic growth and urbanization.[44]

Traditional epidemiologic studies using large cohorts of populations have successfully identified numerous dietary risk factors for diabetes, independent of body weight. For example, the types or quality of dietary fats and carbohydrates consumed have been found to be more influential on diabetes risk than the quantity of these macronutrients. In addition, higher consumption of whole grains, fruits, vegetables, legumes, and nuts, and lower consumption of refined grains, red/processed meats, and sugar-sweetened beverages (SSBs), are associated with a decreased risk of type 2 diabetes, independent of body mass index (BMI) (Fig. 1).[45]

Despite major progress in understanding the relationship between a multitude of dietary factors and risk of diabetes, the biological mechanisms underlying this relationship are largely unknown. Recent advances in omics technologies have enabled the emergence of a systems epidemiology approach to improving our understanding of these biological mechanisms.[46] Systems epidemiology integrates a wide range of high-throughput technologies that enable investigation of genetic predisposition (genome), epigenetic changes (epigenome), the expression of genes (transcriptome), proteins (proteome), metabolites (metabolome), and gut microbiota (microbiome), in well-characterized large, prospective cohort studies for which biological samples are available (Fig. 2).[4] This approach has the potential to help elucidate the pathophysiology of type 2 diabetes and to enable early detection and interventions by identifying high-risk individuals.

Over the past several years, considerable progress has been made in the use of genomics and metabolomics for investigating the role of diet and nutrition in the etiology of obesity and diabetes. GWASs have identified nearly 100 loci that are significantly associated with BMI in the general population. Recently, Hu and colleagues[47] incorporated modern genomics into population-based cohort studies and identified a significant interaction between consumption of SSBs and genetic variants related to BMI in women and men from two prospective cohorts—the Nurses' Health Study (NHS) and the Health Professionals Follow-up

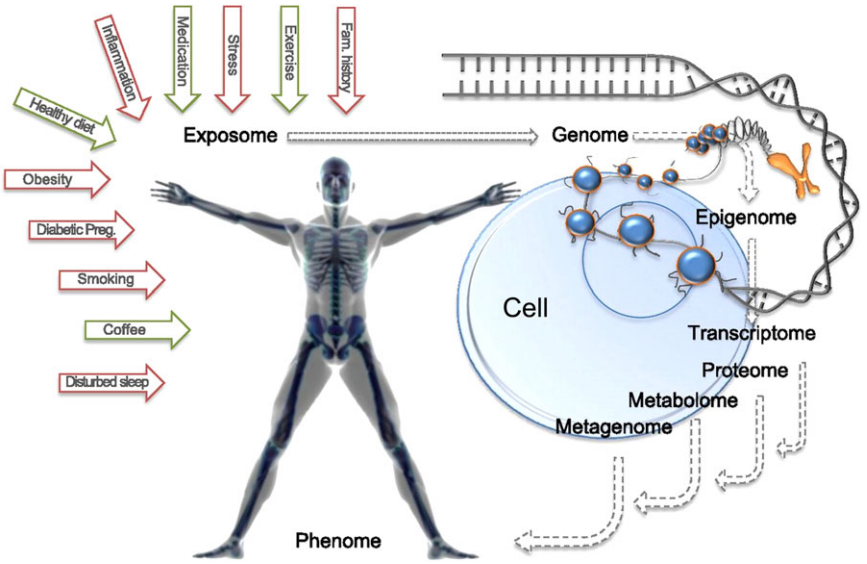

Figure 2. The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.[4]

Study (HPFS)—and then replicated the analysis in a large, independent, prospective cohort from the Women's Genome Health Study (WGHS). They calculated a genetic predisposition score on the basis of 32 BMI-associated loci identified from a GWAS and found that the genetic association with BMI was more pronounced among participants with higher intake of SSBs than among those with lower intake. In a combined analysis of the three large cohorts (NHS, HPFS, and WGHS), the increases in BMI per increment of 10 risk alleles were 1 unit for an intake of less than one serving per month, 1.12 for one to four servings per month, 1.38 for two to six servings per week, and 1.78 for ≥1 serving/day (Fig. 3), suggesting that the genetic association with adiposity is amplified by greater intake of SSBs. The implication of these findings is that a healthy beverage habit can mitigate deleterious effects of genetic factors that can potentially increase risk of weight gain and obesity.

Metabolomics involves the comprehensive analysis of all measurable metabolite concentrations in plasma, urine, or other specimens, which are the final products of preceding omics processes and, to a large degree, reflect end products of gene–environment interactions. Thus far, more than 30,000 unique metabolites have been identified, and several epidemiological studies recently found that higher plasma concentrations of metabolites such as branched-chain amino acids (BCAAs) are associated with increased risk of type 2 diabetes, independent of BMI and other diabetes risk factors.[48] Other novel metabolite classes have also been linked to diabetes, including short- and medium-chain acylcarnitines and the specific lipid classes of sphingomyelins, lysoPCs, and lysophosphatidylethanolamines. However, whether these metabolites could be used in clinical settings remains unclear because the cutoff points of BCAAs or other metabolites for elevated risk of diabetes have not been defined. In addition, whether these biomarkers add to the prediction of diabetes beyond traditional risk factors is yet to be determined.[49]

Metabolomics has also been used to identify metabolic and molecular signatures of specific foods, nutrients, and dietary patterns in both intervention and epidemiological studies.[48] For example, targeted or untargeted metabolomics platforms have been used to profile metabolites in human intervention studies of coffee, tea, cocoa, nuts, fiber, polyphenols, and vitamins.[48] Some of these metabolites can be used as biomarkers for food or nutrient intakes, which are difficult to measure using traditional dietary assessment methods, such as dietary questionnaires or diaries.

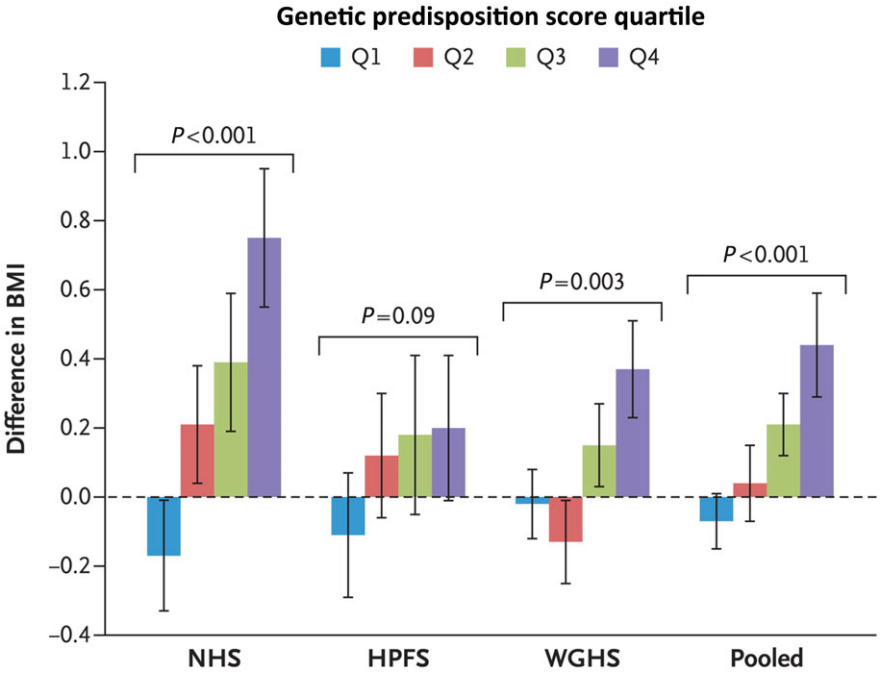

Figure 3. Difference in body mass index (BMI) associated with one serving of a sugar-sweetened beverage (SSB) per day, according to the quartile of the genetic predisposition score. The data show effect sizes (β coefficients ($\pm$ SE)) of SSB intake (one serving/day) on BMI (the weight in kilograms divided by the square of the height in meters), stratified according to the quartile of the genetic predisposition score. In the Nurses' Health Study (NHS) cohort, the median scores across the quartiles were 24.5 (range: 13.1–26.3), 27.8 (range: 26.4–29.0), 30.3 (range: 29.1–31.7), and 33.6 (range: 31.8–43.4); in the Health Professionals Follow-up Study (HPFS) cohort, the median scores were 24.9 (range: 16.0–26.5), 27.9 (range: 26.6–29.1), 30.4 (range: 29.2–31.7), and 33.6 (range: 31.8–41.9); and in the Women's Genome Health Study (WGHS) cohort, the median scores were 24.7 (range: 15.3–26.5), 27.8 (range: 26.6–29.1), 30.3 (range: 29.2–31.6), and 33.4 (range: 31.7–43.4). In the NHS and HPFS cohorts, the analyses were based on data collected from the first 4 years of the studies in women (1980–1984) and men (1986–1990), respectively, with adjustment for age, source of genotyping data, physical activity levels, time spent watching television, current smoking status, alcohol intake, and Alternative Healthy Eating Index score. In the Women's Genome Health Study (WGHS) cohort, the analyses were based on data collected from the first 3 years, with adjustment for age, geographic region, eigenvectors, physical activity levels, current smoking status, and alcohol intake. *P* values shown are for interactions, and I bars indicate SE. Reproduced, with permission, from Qi *et al.*[47]

In summary, system-level tools, such as nutritional genomics and metabolomics, applied to the study of obesity and type 2 diabetes have provided new insights into the etiology of these diseases and individual differences in response to diet. They have also revealed novel metabolic pathways that are potentially modulated by dietary and lifestyle changes. Hu concluded that, in future studies, harnessing the resources of existing large prospective studies, and randomized clinical trials within which biological samples have been archived and individual exposure data have been collected, will enable systems-level data to be integrated with data on diet and lifestyle. Continued technological advances in high-throughput methods, as well as increased affordability of these methods in analyzing large samples, will enable more widespread use of these technologies in nutrition and metabolic disease research, which may eventually help to achieve the goal of personalized nutrition for prevention and treatment of chronic diseases.[48]

How nutrition, from pharma to lifestyle, can build on systems science to address complex issues

Nutrition and the science of disease prevention: systems science for complex problems

In her presentation, Patricia Mabry (National Institutes of Health) described cutting-edge systems

science methods that enable the study of complex problems and that, more specifically, can help advance nutrition and obesity research by offering complementary approaches to traditional methods. In an in-depth overview of systems science, Mabry explained that the systems science family of methodologies allows study of the complexities of a problem in a tractable form by simplifying the problem and, at the same time, retaining its salient characteristics; and by addressing both the big picture of a complex problem and its individual components. Systems science methods are designed to capture dynamic behavior of a system (with change over time) and to study bidirectional (feedback loops) and nonlinear relationships, as well as time-delayed effects, such as delays in the effects of nutrition-related policies on consumption of affected foods. Furthermore, systems science methods can help detect unintended consequences (as in the case of taxation of SSBs leading to consumer avoidance of SSBs but new consumption of artificially sweetened beverages that are untaxed) and emergent properties, in which individual behavior leads to an aggregate outcome. These methods are also particularly valuable for conducting virtual experimentation (e.g., in *in silico* laboratories), which is conducted on the basis of available data in a simplified form within a simulation model and avoids having to wait to assess the full effects of nutrition-related policies decades after they have been implemented.

Modeling and simulation characterize most of the systems science methodologies. Mabry discussed the value and utility of modeling,[50] including their use in making mental models explicit; explaining (versus predicting); informing data collection (e.g., what data are needed to make the model more robust and reliable); illuminating core dynamics; demonstrating trade-offs; and bracketing outcomes with plausible ranges (Mabry pointed out that, although models are not always best for point prediction, they are useful for providing plausible ranges within which outcomes may fall).

As an example of system dynamics modeling to inform community-level food policy decisions, Mabry discussed the Prevention Impacts Simulation Model (PRISM), which is a comprehensive evidence-based system dynamics simulator, led by the Centers for Disease Control with support from the National Heart, Lung, and Blood Institute and the National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research. PRISM was originally designed to understand how policies can be combined to reduce CVD and other chronic disease–related mortality and costs, and integrates best evidence available into a testable framework for prospective planning and evaluation. The model can combine at least 34 possible interventions (e.g., junk food tax, fruit and vegetable intervention, reduction of sodium and trans fats, physical activity intervention) to examine the strength of the interventions and how they might affect the outcome of interest (e.g., CVD) over time. For example, some studies using PRISM have examined the effect of known risk factors, such as physical activity, on obesity rates at various time points to assess whether physical activity is continuing to have an effect over time, and have predicted the effects of interventions affecting obesity, such as the junk food tax.[51–55]

Finally, in addition to system dynamics modeling, Mabry discussed agent-based modeling in obesity research. In particular, she highlighted a model recently developed by Hammond *et al.*[56] with the future goal of examining interactions between genetic (dopamine), environmental (food geography, economic factors), social (body image, eating norms), physiological (energy regulation), and neurobiological (reward learning, executive control, homeostasis) factors and how these factors collectively influence eating behavior, body weight, and obesity.[57,58] Mabry ended her presentation by providing information on various resources in systems science applications in public health and nutrition research,[5,59] along with a summary of systems science–related activities at the NIH and federal funding opportunities for research using systems science–based approaches.[60,61]

The calculus of calories: mathematical modeling of human energy metabolism and body weight dynamics

In his presentation, Kevin D. Hall (National Institutes of Health) discussed the latest research on quantifying the dynamic relationship between changes in dietary calories and body weight. Until very recently, such calculations have typically been made using the 3500-calorie/pound rule, in which it was thought that eliminating 500 kcal/day from one's habitual diet will lead to a loss of approximately 1 lb of body weight per week (since

500 kcal × 7 days/week = 3500 kcal/week = 1 lb/week). However, this rule has recently been found to drastically overestimate actual body weight changes, especially over prolonged periods of time, because it neglects changes in metabolic rate that take place when diet is changed and body weight is reduced.[62]

Using data from several controlled-feeding studies in humans, new mathematical models of human metabolism and body weight change have been developed that correct the deficiencies of the previously standard calculations and that accurately capture the metabolic changes that take place when individuals change their diet, physical activity levels, and body weight.[63] For example, the NIH Body Weight Planner provides personalized diet and physical activity plans to help reach goal weight and maintain it afterward.[64] The model has been validated using data from studies that were not used to build the model, including from a recent study investigating the effect of 2 years of calorie restriction on body weight in 140 people, where the model was used to provide accurate measurements of energy intake changes by tracking body weight.[65]

Hall concluded by pointing out various applications of these dynamic models of human metabolism and body weight change, including predicting the effects of policy changes on population obesity prevalence[66,67] and quantifying the progressive increase of food waste in the United States[68] and the influence of national food supply trends on global obesity.[69] New models of metabolic changes during childhood growth[70] are also beginning to provide important insights on childhood obesity[71] and the potential effects of policy changes.[72]

Using behavioral science to inform the design of food policies

The behavioral sciences, including psychology and disciplines informed by psychology (e.g., behavioral economics), aim to understand the rationale for why individuals behave in the ways that they do and what interventions will cause them to behave differently. One of the insights emerging from these fields is that human behavior is sensitive to a number of forces that from a rational perspective ought not to matter, such as how choice options are arranged and how information is presented. In the final presentation, Christina A. Roberto (Harvard T.H. Chan School of Public Health) discussed how the behavioral sciences can inform the design of environments that influence choices of what to eat.

Provisions in the 2010 Affordable Care Act mandate that chain restaurants with 20 or more U.S. locations display calorie information on their menus so that it is visible at the point of purchase. The rationale behind this policy is that consumers eat at restaurants often but are uninformed about the calorie content in restaurant food.[73] The hope is that if consumers were better informed, they would make lower-calorie choices (at least some of the time). When menu labeling was proposed in New York City in 2006, there were very few published studies on the effects of restaurant menu labeling on consumer behavior. Initially, members of the restaurant industry argued that nutrition information was already available in restaurants and therefore including it on menus was unnecessary. However, Roberto and colleagues found that, even when nutrition information was available in restaurants, only six out of 4311 (0.1%) consumers sought out nutrition information,[74] suggesting that a different approach to disseminating this information was needed.

To investigate how menu labeling would influence how much adult consumers ordered and ate both at and after dinner, Roberto *et al.*[75] conducted a randomized controlled laboratory study and found that adults viewing calorie labels on menus during the meal ordered and ate less at the meal. They also tested a menu with a label specifying a recommendation of 2000 calories/day for adults—because putting calorie information in the context of a full day's calorie requirements may be more helpful than the numbers alone—and found that this contextual label was critical. Although all participants that were presented with calorie labels ate less during the meal, only those who were reminded of the daily calorie recommendation ate less overall (including the food consumed later that evening). These findings were communicated to key U.S. legislators and subsequently informed the U.S. Food and Drug Administration's current requirement that menus include a statement about recommended daily caloric intake. This example highlights the importance of testing the details of policy design in order to develop ways to maximize policy effectiveness and avoid unintended consequences.

Roberto also presented unpublished data on a new food policy proposal that aims to place warning labels on SSBs and discussed how the behavioral sciences can inform the design of such labels.[76] Included in this pilot study was a large subject pool of adults. Preliminary data showed that warning labels decreased purchase intent for SSBs and increased perception of disease risk associated with consumption of such beverages. Roberto concluded by highlighting the importance of strategic science for evidence-based food policies and of incorporating the behavioral sciences in nutrition research.

Summary and conclusion

The role of nutrition in the development and prevention of metabolic diseases is complex. Systems-level approaches can integrate different types of data from complementary disciplines to explain biological mechanisms underlying metabolic disease and to make predictions about the effects of nutrition-related policy interventions on disease outcomes. The application of systems-level approaches to the study of nutrition has helped to elucidate the complex interactions between nutrition and neurobiological, endocrinological, genetic, gut microbial, behavioral, and environmental factors, and how these interactions influence metabolic health and the development of chronic diseases such as obesity and type 2 diabetes. Systems approaches in, for example, epidemiology have the potential to unlock the "black box" in chronic disease epidemiology by offering deeper understanding of molecular and behavioral pathways underlying the relationships between dietary factors and metabolic diseases observed in epidemiological and clinical studies. Studies applying such systems approaches may help to improve early disease detection, clinical diagnosis, and prognosis; contribute to personalized nutritional interventions for improving metabolic health; and inform policy-level interventions.

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Conflicts of interest

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