Feature Article

Systems biology of personalized nutrition

Ben van Ommen, Tim van den Broek, Iris de Hoogh, Marjan van Erk, Eugene van Someren, Tanja Rouhani-Rankouhi, Joshua C. Anthony, Koen Hogenelst, Wilrike Pasman, André Boorsma, and Suzan Wopereis

Personalized nutrition is fast becoming a reality due to a number of technological, scientific, and societal developments that complement and extend current public health nutrition recommendations. Personalized nutrition tailors dietary recommendations to specific biological requirements on the basis of a person's health status and goals. The biology underpinning these recommendations is complex, and thus any recommendations must account for multiple biological processes and subprocesses occurring in various tissues and must be formed with an appreciation for how these processes interact with dietary nutrients and environmental factors. Therefore, a systems biology–based approach that considers the most relevant interacting biological mechanisms is necessary to formulate the best recommendations to help people meet their wellness goals. Here, the concept of "systems flexibility" is introduced to personalized nutrition biology. Systems flexibility allows the real-time evaluation of metabolism and other processes that maintain homeostasis following an environmental challenge, thereby enabling the formulation of personalized recommendations. Examples in the area of macro- and micronutrients are reviewed. Genetic variations and performance goals are integrated into this systems approach to provide a strategy for a balanced evaluation and an introduction to personalized nutrition. Finally, modeling approaches that combine personalized diagnosis and nutritional intervention into practice are reviewed.

INTRODUCTION

Nutrition and health are intimately related, and the science underpinning this relationship is the basis for global public health dietary recommendations. Recognizing that food and nutrition play a role in numerous medical conditions (hypercholesteremia, hyperglycemia, hypertension, etc), various medical associations have established dietary guidelines for patient subgroups. Health-related societies and nutrition expert groups have also published dietary guidelines for specific healthy populations, such as children, the elderly, pregnant women, and athletes. Customized nutrition strategies have been added to patient treatment plans for many inborn errors of metabolism that

Affiliation: *B. van Ommen*, *T. van den Broek*, *I. de Hoogh*, *M. van Erk*, *E. van Someren*, *T. Rouhani-Rankouhi*, *K. Hogenelst*, *W. Pasman*, *A. Boorsma*, and *S. Wopereis* are with TNO (The Netherlands Organization for Applied Scientific Research), Zeist, the Netherlands. *J.C. Anthony* is with the Campbell Soup Company, Camden, New Jersey, USA.

Correspondence: *B. van Ommen*, TNO, Utrechtseweg 48, Postbox 360, 3700 AJ Zeist, the Netherlands. Email: ben.vanommen@tno.nl.

Key words: flexibility, nutrigenetics, nutrigenomics, personalized nutrition, systems biology.

doi: 10.1093/nutrit/nux029

Table 1 **Examples of personal goals in relation to personal nutrition**

Goal	Definition
Weight management	Maintaining (or attaining) an ideal body weight and/or body shaping that ties into heart, muscle, brain, and metabolic health
Metabolic health	Keeping metabolism healthy today and tomorrow
Cholesterol	Reducing and optimizing the balance between high-density lipoprotein and low-density lipoprotein cholesterol in individuals in whom this is disturbed
Blood pressure	Reducing blood pressure in individuals who have elevated blood pressure
Heart health	Keeping the heart healthy today and tomorrow
Muscle	Having muscle mass and muscle functional abilities. This is the physiological basis or underpinning of the consumer goal of "strength"
Endurance	Sustaining energy to meet the challenges of the day (eg, energy to do that report at work, energy to play soccer with your children after work)
Strength	Feeling strong within yourself, avoiding muscle fatigue
Memory	Maintaining and attaining an optimal short-term and/or working memory
Attention	Maintaining and attaining optimal focused and sustained attention (ie, being "in the moment" and being able to utilize information from that "moment")

have a specific nutrition component. Only recently, scientific evidence has shown that advances in analytical technologies, data science, molecular physiology, and nutritional knowledge may allow the subgrouping of populations to be refined to a more personal level. This has resulted in the definition and scientific substantiation of a range of personalized health and performance goals. Often, these goals extend beyond prevention and/or mitigation of chronic disease and include multiple aspects of well-being, such as mood, attention, endurance, and weight maintenance, as well as well-being equivalents of medical conditions (maintenance of glucose control, normal blood pressure, healthy levels of serum lipids and low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterols, etc). Indeed, with respect to nutrition, the boundaries between medical treatments, illness prevention strategies, and strategies to achieve optimal health have become artificial and are a legal hindrance to best nutritional practice. For example, the mechanisms of glycemic control and the nutritional approaches to optimize metabolic health and cure type 2 diabetes are almost identical, yet nutritional interventions are underused in medical practice. Already in 2002, the Diabetes Prevention Program established by the US National Institute of Diabetes and Digestive and Kidney Diseases provided evidence that a multiyear lifestyle modification program was more effective than metformin treatment in reducing the incidence of diabetes in high-risk persons.[1,2]

This article describes biological mechanisms from a systems perspective and outlines how the biology of personalized nutrition can be translated into recommendations for achieving specific health and performance goals for individuals (Table 1). The concept of "systems flexibility" is introduced as an overarching biological mechanism, and a number of relevant examples are examined in the context of metabolic health. Finally, this review demonstrates that macronutrient, micronutrient, and non-nutrient recommendations can be optimized at the individual level, depending on a person's biological characteristics and specific goals.

PERSONALIZED NUTRITION IN THE ERA OF LARGE-SCALE BIOLOGY

Public health recommendations for nutrition and diet are based on averages of population data. However, individuals who adhere to these recommendations will differ in their response because of the inherent variations in and complexity of individual genetic makeups that interact with a host of environmental stimuli. Overall, the so-called omics revolution provides a solid framework for a systems-based approach to personalized nutrition research. There are, however, limitations to the application of the current framework of evidence based on randomized controlled trials, which are designed to minimize variation across study population groups, to these new opportunities. In contrast, an approach to personalized research requires that individual variation be embraced, thus necessitating a different experimental approach. Indeed, enough inter-individual variation is available and can be quantified to fine-tune the genome–exome–phenome relationships. Until recently, this biological variation, now exposed by extensive and accurate phenotyping, was ignored (dismissed as confounders) or avoided (minimized through stratification). Tools to translate these genotypic and phenotypic variations into personalized recommendations using alternative research approaches, such as $n = 1$ research paradigms, are now available.[3]

Over the past 2 decades, various technological revolutions have provided the building blocks for a systems physiology approach. The time is approaching when personal genomes, thousands of plasma proteins and metabolites can be scrutinized affordably, and detailed

whole-body magnetic resonance imaging scans will become widely available. Methods to store, share, evaluate, integrate and interpret this staggering amount of personal health data are lagging behind, but several developments are promising and are worth mentioning here. Changes in plasma biomarkers can reveal broad networks of related cellular processes, as described previously for micronutrients.[4] Metabolomics technologies have been developed to elucidate the relationships between different cellular processes and micronutrient status.[5] Further, network biology applications based on correlation matrices of multiple omics databases allow the relationship between micronutrients and human biology to be examined at a systems level.[6] Similar approaches, combined with data from large cohorts, connect genetic variations with biomarker responses in plasma[7] and urine.[8] The integration of multiple human nutrigenomics studies with multiple omics knowledge bases enables the creation of combined theoretical–observation networks that provide a systems view of specific types of nutritional interventions to promote health and well-being.[9] For this type of approach, a standardized open-access depository of nutrigenomics studies is essential and available.[10]

ROLE OF SYSTEMS FLEXIBILITY IN ACHIEVING OPTIMAL HEALTH

The complexity of personalized nutrition requires a systems solution, not only from a (homeo)static viewpoint but also in the dynamic response to an environmental challenge. Because the relationship between nutrition and health is a continuously changing interaction between environment and physiology, it is important to understand how biological systems work together to maintain homeostasis. A key component is the ability of the physiological system to continuously adapt to the variety and amount of foods consumed as well as to the timing of food consumption. Humans eat food as meals and thus continuously switch from net anabolic to net catabolic conditions. This repeated switching both requires and trains systems flexibility,[11] although this advantage may become lost by the modern habit of regular snacking. An important aspect of the relationship between human nutrition and health is the management of energy supply and substrate metabolism. Energy is provided primarily by carbohydrates, lipids, and proteins. A tightly regulated control network ensures that energy is properly distributed, utilized, and stored and that plasma concentrations of essential metabolites, such as glucose, are kept in homeostasis. Peaks in plasma concentrations are corrected by master regulators (such as insulin and glucagon), which are assisted by a range of fine-tuning mechanisms that govern biological processes and organ functions.

Maintenance of homeostasis under continually changing conditions is referred to as phenotypic flexibility or systems flexibility. Under continued energy overload, the maintenance of homeostasis comes at a cost of adaptation: excess energy is stored as lipid in adipose tissue. Once storage exceeds normal physiological boundaries, insulin resistance and complications start to develop, which potentially leads to pathologies that include adipose deposits in and around major organs, rising plasma glucose concentrations causing oxidative damage to microvasculature, and persistent low-grade inflammation triggered by macrophage infiltration in adipose tissue. In a human intervention study, a 4-week overfeeding regimen kept the 3 core processes (glucose metabolism, lipid metabolism, and inflammation) stable, whereas most metabolic, inflammatory, and endocrine processes regulating these core processes were changed. These regulatory processes contribute to systems flexibility and illustrate the major molecular physiological efforts to maintain homeostasis.[12]

An advantage of considering regulatory processes in a systems-based approach is that it provides a means to identify changes in regulation before the onset of disease, and thus enables the application of proactive strategies to optimize health.

Different macronutrients act differently on overlapping regulatory processes involved in phenotypic flexibility (Figure 1). For example, carbohydrates directly trigger an insulin response through rising glucose levels in circulation. Triglycerides and fatty acids, on the other hand, do not induce an insulin response, but their metabolism is governed largely by insulin-dependent regulatory processes. Dietary protein consumed with carbohydrates can potentiate the insulin response, and individual amino acids can act as insulin secretagogues.[13] Insulin-dependent pathways also regulate protein turnover, which consists of protein biosynthesis (accomplished in part via the mechanistic target of rapamycin [mTOR] pathway)[14] and amino acid degradation, both of which provide energy. These processes are described in detail in numerous reviews and textbooks. For the purpose of this review, it is important to stress that multiple, overlapping, tightly regulated processes control energy metabolism. This regulation prevents the formation of excess concentrations of metabolic constituents by maintaining a complex machinery of metabolic flexibility that is distributed over many organs and processes. Redundant mechanisms ensure that this tight regulation is maintained. As noted above, the lack of phenotypic flexibility can lead to pathologies or to suboptimal health. However, pathology does not necessarily develop during the process or

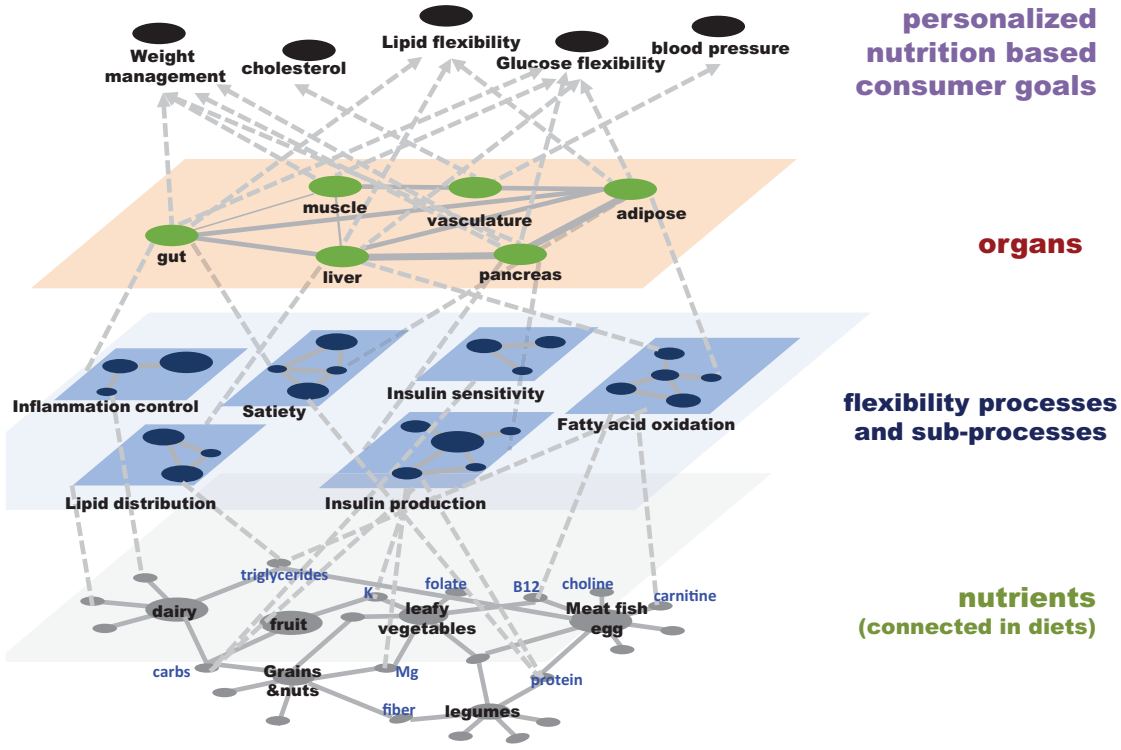

Figure 1 **A systems biology view on personalized nutrition. Four interacting layers are used to demonstrate the connection between personal nutrition–based consumer goals (top layer) and nutrients (bottom layer).** The 2 middle layers (the organ and process layers) connect nutrients to goals and represent the detailing of the biological processes involved. These 2 layers are extended in Figure 2. *Abbreviations:* K, potassium; Mg, magnesium.

within the organ where loss of flexibility occurs. For example, the failure of peripheral adipose tissue to adequately absorb glucose or convert it into fatty acids may lead to the accumulation of hepatic lipids.[15,16] Subsequently, other organs (muscle, liver) may also become insulin resistant. Several factors can cause insulin resistance, including nutrition (overnutrition or, in some cases, micronutritional inadequacies) and disease. Genetics may also contribute to the development of disease.[17–20] Insulin resistance can also cause increased accumulation of hepatic triglycerides, ultimately resulting in hepatic steatosis and fatty liver disease.[21] Accumulation of hepatic triglycerides can be caused by adipose tissue malfunctioning; it can also be caused by a shortage of choline resulting from genetic disorders, including those affecting phosphatidylethanolamine *N*-methyltransferase (PEMT) —an enzyme involved in the hepatic biosynthesis of phosphatidylcholine.[22] Alternatively, low dietary intake of carnitine, which is essential for shuttling fatty acids into the mitochondria, may contribute to fatty liver as a result of poor fatty acid oxidation.[23]

Both adipose tissue insulin resistance and hepatic insulin resistance affect systemic triglyceride handling and metabolic flexibility (the capacity to switch from glucose to fatty acids as fuel) in muscle. Metabolic flexibility is impaired in obese individuals with type 2 diabetes[24] and likely contributes to the selective accumulation of saturated fatty acids.[25] Figure 2 summarizes the major processes within and between liver, muscle, pancreas, and adipose tissue involved in the maintenance of plasma glucose homeostasis. It shows several examples of mechanisms related to the loss of metabolic flexibility, which can result in liver steatosis and other metabolic impairments. Thus, many processes are connected to form a metabolic system in which all parts must function optimally and in which malfunctioning (loss of flexibility) of one of the processes may become manifest in other processes or organs. Furthermore, different mechanisms may be impaired in different individuals with the same disease. Changes in strategies for handling energy open avenues for personalized "systems interventions," either by modifying the quantity, timing, and source of energy consumed, or by optimizing the processes involved, through the manipulation of nutrients or other lifestyle components. In other words, although impaired phenotypic flexibility may contribute to morbidities, the opposite is also true: regaining or optimizing phenotypic flexibility is the basis of prevention and cure of metabolic diseases. Interestingly, the concept of systems flexibility may be valid for both the health/disease trajectory and the aging

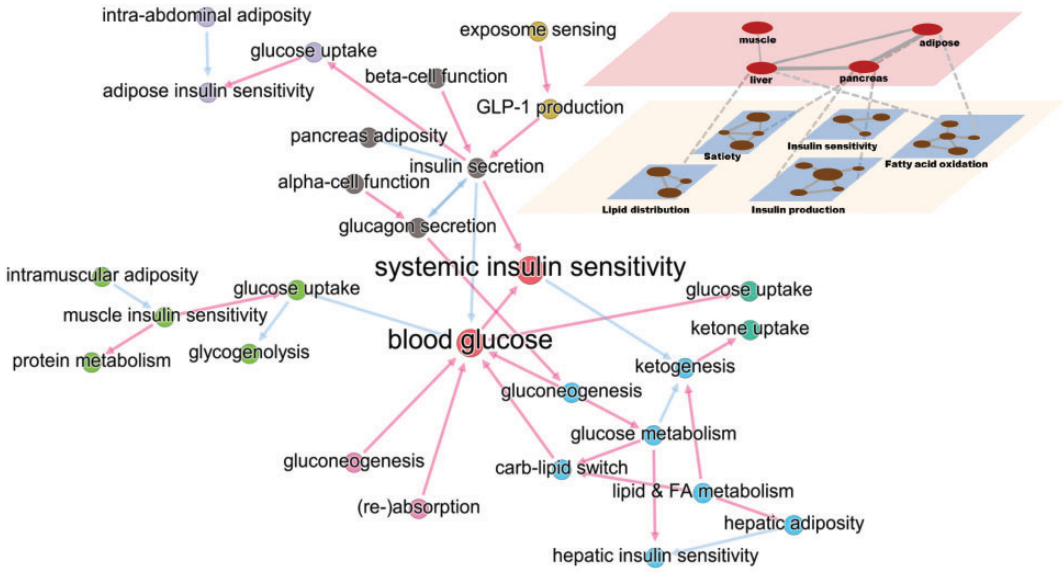

Figure 2 **Major processes in and between liver (blue), muscle (light green), pancreas (brown), brain (dark green), kidney (pink), gut (mustard), and adipose tissue (purple) involved in maintenance of plasma glucose homeostasis, each of them demonstrating aspects of glucose flexibility.** This biological network presents the middle part of the 4-layer scheme of Figure 1 (see insert top right). *Abbreviations:* FA, fatty acid; GLP-1, glucagon-like peptide-1.

trajectory. Many processes involved in aging and increased frailty (energy/glucose/insulin homeostasis, protein homeostasis, redox homeostasis, mitochondrial homeostasis, stress resistance, inflammation control) are part of the systems flexibility concept.[26,27]

In summary, systems flexibility is centrally positioned in health, disease, and, possibly, aging, and inter-individual variations may have multiple causes and consequences. Systems flexibility is a combination of all of the interacting systems, each of which may have a genome component, and a response to environmental factors. Often, single parameters of flexibility, such as glucose flexibility, are composites of many underlying processes, each possibly having individual characteristics. It is, therefore, important to observe, quantify, and intervene on a systems level and not only on the basis of single parameters.

QUANTIFICATION OF SYSTEMS FLEXIBILITY: BIOMARKERS OF STRESS RESPONSE

Traditionally, plasma biomarkers are measured under homeostatic (overnight fasting) conditions. If system flexibility is indeed important to health, the quantification of flexibility and its use as a biomarker is relevant. Flexibility can be quantified by using tolerance, challenge, or stress tests. Further, there should be a clear distinction between how markers behave in response to a challenge under conditions of health versus conditions of disease. A number of relevant biomarkers exist and are used in tolerance tests. For example, the oral glucose tolerance test is used clinically to quantify the plasma glucose response upon absorption of 75 g of glucose and provides quantitative information on various aspects of insulin sensitivity and glucose handling. This concept was extended by adding more analytical parameters (levels of insulin, inflammatory markers, fatty acids, triglycerides, etc) and other stressors (various lipid/carbohydrate/protein formulations). The science, technology, and applicability of these stress response biomarkers in nutrition research has been extensively reviewed by Stroeve et al.[28]

The application of both an oral glucose tolerance test and a standardized mixed-meal challenge test to compare processes between healthy and metabolically impaired individuals (ie, those with type 2 diabetes) revealed a large number of biological processes that were different between the 2 groups (S.W., unpublished data, 2017). The same 2 challenge tests accurately quantified health differences within a cohort of 100 healthy individuals ranging in age and fat percentage, substantiating the claim that these biomarkers can indeed be used to quantify health. This study used stress response biomarker panels comprising 120 measured markers that could quantify all relevant systems flexibility processes. A growing number of nutritional intervention studies, including challenge tests, are being performed. A database that focuses on nutritional intervention studies of systems flexibility has been established, the Nutritional Phenotype Database (http://www.dbnp.org/). Eventually, the use of a challenge test that quantifies systems flexibility could become standard procedure in health diagnostics.[29]

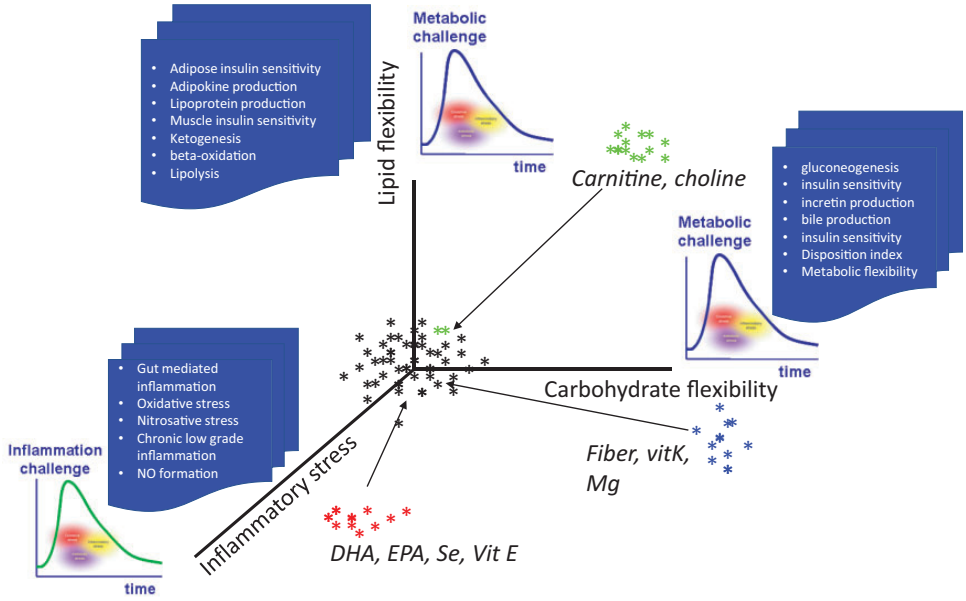

Figure 3 **The "health space" concept to visualize aspects of systems flexibility, the involvement of specific biological processes, and the effect of personalized nutritional interventions on these processes.** The 3-dimensional space is created by 3 distinct axes, on purpose defined to represent biologically relevant processes (this is in contrast with normal multivariate statistical approaches such as principle component analysis, where the axes are purely defined on statistical grounds). Each of the axes is constructed from the systems flexibility response biomarker profiles connected to the processes mentioned with each axis (see Stroeve et al[28] for a detailed explanation of the relationship between biomarkers and biological processes). The multivariate statistical approach is explained in Bouwman et al.[30] The effect of hypothetical nutritional intervention studies is demonstrated by the arrows. *Abbreviations:* DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; Mg, magnesium; Se, selenium; Vit E, vitamin E; Vit K, vitamin K.

A key question, then, is how to define and measure the state of optimal systems flexibility. This could be achieved in part by using single-parameter methods like the oral glucose tolerance test, which can be used to determine a curve derived from optimal homeostatic (fasting) plasma glucose concentration, optimal plasma glucose peak concentration and time, optimal time to return to homeostasis, etc. This method can be used if sufficient data from a range of health, disease, and age conditions are available to establish the comparison between the measured outcome and the desired health outcome. However, this method, underestimates the complexity of a systems-based approach because it disregards so many other processes involved in systems flexibility. To address this complexity, an emerging concept to visualize optimal systems flexibility is the "health space."[30] Essentially, a 3-dimensional space is created by using predefined axes that represent biological processes relevant to different aspects of systems flexibility, each constructed from multiple biomarkers using multivariate statistical methods. The axes can be tailored to the scope of the intervention. Figure 3[28,30] provides an example, tailored to the topic of this review, with the 3 axes constructed as carbohydrate flexibility, lipid flexibility, and inflammatory stress. To support the advancement of new health space models, detailed information about organ and process flexibility can be obtained through a number of biomarker panels. Until recently, these large biomarker panels have been too costly to be used outside of research projects. However, the cost of both genotypic and phenotypic biomarker panels is decreasing rapidly, and it is now possible to assess large research cohorts, patient populations, and even consumer groups on a routine basis, allowing new disruptive developments in healthcare, as described elsewhere.[29,31] Nevertheless, many questions remain: (1) Is "optimal systems flexibility" equal for all? (2) Are individual data points needed? If so, what determines individual differences, and how can this be quantified? and (3) Is "optimal systems flexibility" itself flexible (ie, how should the bandwidth of optimal systems flexibility be defined)? For example, does the definition of "optimal" vary, depending on an individual's life stage, health goals, or priorities?

SYSTEMS FLEXIBILITY AND NUTRITION: OPTIMIZING EACH PROCESS INVOLVED IN SYSTEMS FLEXIBILITY

Because multiple biological processes distributed over various organs, each of which might function suboptimally, are involved in systems flexibility, interventions that optimize these individual processes need to be designed. Different interventions targeting the same outcome are possible. Upon detailed analysis, results

from dietary interventions are often specific to responders or nonresponders. For example, caloric restriction[32] and physical activity[33] that lead to weight loss improve health by reversing insulin resistance and thus restoring multiple aspects of systems flexibility. However, the caloric restriction that successfully resulted in weight loss for all individuals after 6 months resulted in improved β-cell functioning in only part of the sample (responders).[34] Also, in the CordioPrev cohort, in which 642 participants maintained their body weight over 3 years of reporting on a dietary intervention (low-fat diet vs Mediterranean diet), individuals with a specific muscle-based insulin resistance were more likely to benefit from the Mediterranean diet, whereas individuals with specific liver-based insulin resistance were more likely to benefit from the low-fat diet.[35] Interestingly, the effects were determined by using the insulin and glucose time course following an oral glucose tolerance test as described in the previous paragraph. In another example, individuals with type 2 diabetes required significantly less insulin when a 43% carbohydrate diet was isocalorically (1800 kcal to maintain weight) substituted with a 70% carbohydrate diet with carbohydrates exclusively from whole-grain products, vegetables, fruits, and dairy.[36] The exact drivers of the changes in insulin sensitivity that occurred when individuals consumed the nutrient-dense, 70% carbohydrate diet are unknown but may include changes in fiber levels and other chemical components in the whole grains and vegetables. Regardless, organ insulin sensitivity strongly increased when individuals with diabetes consumed a nutrient-dense, low-glycemic-index diet, which demonstrates the power of dietary changes independent of weight loss. These studies, in which individuals responded differently to the diets based on their physiology, demonstrate the potential of personalized nutrition programs to optimize health.

PERSONALIZATION OF MACRONUTRIENTS IN THE AREA OF METABOLIC HEALTH BIOLOGY

People can utilize energy from all 3 macronutrient sources (carbohydrate, protein, lipid), and can cope with extreme changes in ratios between the three. Yet, abundance and reduction of macronutrients have their pros and cons depending on an individual's health state and/or goals.; however, dietary recommendations are often generalized, which may lead to individuals receiving health advice or changing their diet in ways that are counterproductive to personal and overall public health goals. For example, in the 1960s, concern about the supposed effect of saturated fat and cholesterol on cardiovascular health led to dietary recommendations to reduce intake of fat and saturated fat. An interesting mixture of science, medicine, and economics drove these recommendations.[37] Despite the decrease in dietary fat consumption that occurred as a result of these recommendations, the incidence of obesity and type 2 diabetes increased.[38] Although multiple factors led to the increased incidence of obesity and diabetes, some individuals adopted an extreme counter-current "sugar is toxic" message in response. Recent meta-analyses of the effect of macronutrients on important biomarkers like cholesterol, lipoproteins, and serum lipid[39] and on glucose control[40] have provided a more balanced view than the "fat is bad" and "sugar is toxic" extremes, and the scientific opinion on fat is gradually changing.39-41 Another example is that of high-protein diets, like Atkins and Paleo, which are popular because of the satiating and muscle-promoting effects of protein, but these diets may have adverse effects (eg, on calcium homeostasis and renal function).[42,43] Instead of generalized public health recommendations, recommendations based on personal health status and goals may be more effective for optimizing nutrition and improving health outcomes.

The first consideration when personalizing macronutrient ratios is the optimization of systems flexibility. From a systems perspective, many organs are important for the insulin control of glucose homeostasis: liver, muscle, pancreas, intestines, brain, adipose tissue, and vasculature (Figure 1). This section focuses on 3 key organs in systems flexibility: liver, muscle, and pancreas. As described previously, the contribution of each of these organs can be easily quantified with an oral glucose tolerance test, which provides insight into impaired glucose tolerance (emphasizing the contribution of muscle in glucose uptake), impaired fasting glucose (emphasizing the contribution of liver, which produces glucose through gluconeogenesis), and disposition index (focusing on acute insulin secretion by the pancreas corrected for the level of systemic insulin sensitivity).[44] For each of these phenotypes, specific macronutrient recommendations are available. The CordioPrev study demonstrated that 2 diets that differed in macronutrient composition had differential effects on liver and muscle insulin resistance.[35] Individuals with an impaired glucose tolerance phenotype (with insulin resistance focused in muscle) require relatively low amounts of rapidly absorbed carbohydrates from the diet[45] and thus should consume a diet low in carbohydrates, and with a low glycemic index. In contrast, individuals with impaired fasting glucose (with insulin resistance focused in liver) have no need for a low-carbohydrate diet in terms of energy percentage. For these individuals, the "quality" of the carbohydrates matters, and they should get their carbohydrates mainly from high fiber[46] or whole-grain products.[47] If, as a result of compromised

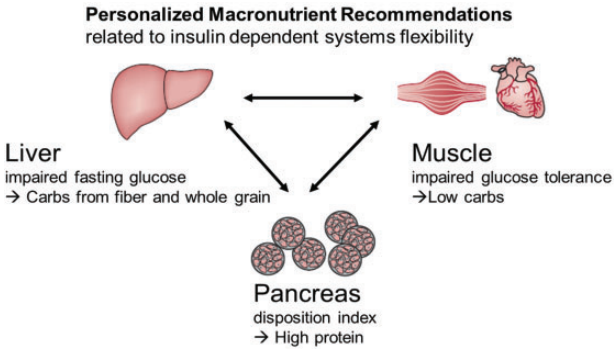

Figure 4 **Personalized macronutrient recommendations related to impaired insulin-dependent systems flexibility.** The same phenotype (glucose imbalance) may be caused by 3 different processes/organs, which can easily be determined in response to a challenge test, and the 3 subphenotypes require different macronutrient strategies. Other factors can be involved but are not visualized in order to demonstrate the concept.

insulin sensitivity caused by either impaired glucose tolerance or impaired fasting glucose, β-cell function is also decreased, individuals may also benefit from a high-protein diet because the ingestion of protein hydrolysate increases insulin secretion.[48–50]

Similarly, individual amino acids have been shown to regulate insulin secretion.[51] Leucine, as a supplemented amino acid, has been shown to modulate glucose homeostasis through various means. In animals, leucine improves glucose control and partially prevents diet-induced insulin resistance by targeting the pancreas. In humans, acute supplementation with protein has been shown to be insulinotropic.[48,49,52] It has been suggested that the insulinotropic effect of leucine is mediated by stimulation of protein synthesis in pancreatic β cells by the mTOR signaling pathway.[53] This pathway mediates insulin resistance by phosphorylation of IRS-1 by S6K1. Overstimulation of this pathway through hyperinsulinemia may contribute to insulin resistance in insulin-sensitive tissues. Insulin resistance in liver and muscle following hyperinsulinemia may be prevented by blocking this pathway. Furthermore, leucine may influence glucose homeostasis by increasing insulin sensitivity and decreasing gluconeogenesis in insulin-sensitive tissues, such as skeletal muscle or liver.[54] In summary, it is advisable for individuals with decreased β-cell function to consume a diet low in carbohydrates and high in protein. To avoid problems with renal function, personalized advice for high protein intake should not exceed the higher end of the acceptable macronutrient distribution range. Individuals who have both impaired glucose tolerance and decreased β-cell function should consume a diet low in carbohydrates and high in protein, whereas individuals who have impaired fasting glucose and decreased β-cell function should consume a diet with a normal energy percentage from carbohydrates, mainly from fiber and whole-grain products, and a high energy percentage from protein (Figure 4).

Personalized macronutrient recommendations can also be used for other phenotypes, such as hypertension or prehypertension phenotypes. A high-protein diet can improve blood pressure levels[55] and reduce the risk of hypertension.[56] In terms of total fat intake, evidence is conflicting. The Dietary Approaches to Stop Hypertension (DASH) diet, which is designed to lower hypertension, restricts total fat to approximately 27 E%. However, evidence suggests that not only the total amount of fat but also the type and source of fat are important.[57] Hypertensive individuals may benefit not only from a diet relatively low in total fat but also from a diet high in polyunsaturated fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid.[58] Of course, total fat restriction is not the only feature of the DASH diet in relation to blood pressure and glucose control; the DASH diet is also high in fiber and potassium and rich in many other nutrients from fruits, vegetables, and low-fat dairy products.[59]

For those whose phenotypes involve abnormal lipoprotein or postprandial triglyceride levels, focusing on the composition rather than the quantity of macronutrients can be beneficial. High-fiber diets, especially those high in pectin and β-glucans, and high intakes of monounsaturated fatty acids are associated with reduced LDL cholesterol levels.[60–62] Thus, the amount and the type of macronutrients need to be considered when optimizing the health status of people with different phenotype. The consumption of eicosapentaenoic acid and docosahexaenoic acid may be beneficial not only for lowering blood pressure but also for reducing triglyceride levels.[58]

PERSONALIZATION OF MICRO- AND PHYTONUTRIENTS IN METABOLIC HEALTH BIOLOGY

Micronutrients play an essential role in many processes involved in systems flexibility. Metabolism and related oxidative stress and inflammation are major overarching processes in the area of metabolic health.[4] A loss of flexibility in these processes contributes to the development of many chronic lifestyle-related disorders. Oxidative stress usually occurs when metabolic flexibility is impaired and peak concentrations of oxidative metabolites become too high. For example, oxidative microvascular damage related to insulin resistance is caused by formation of advanced glycation end products, activation of the protein kinase C pathways, and reduction of nicotinamide adenine dinucleotide phosphate by the polyol pathway.[63] Personalized micronutrient interventions mechanistically target the impaired

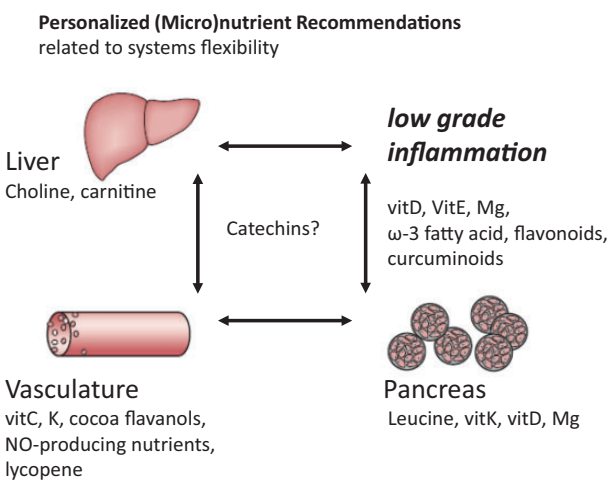

Figure 5 **Examples of nutrients involved in optimizing specific organ-related processes involved in maintaining systems flexibility.** Nutrients involved in maintaining inflammatory control are grouped under adipose tissue. Depending on the quantification of specific processes, personalized nutrition can focus on optimizing these with specific nutrients. *Abbreviations:* K, potassium; Mg, magnesium; NO, nitric oxide; Vit D, vitamin D; Vit E, vitamin E; Vit K, vitamin K.

processes, either by optimizing specific aspects of glucose metabolism with the micronutrients involved (eg, vitamin D, magnesium) or increasing the oxidative stress capacity with the micronutrients involved (eg, vitamin E).[63] Broadening the oxidative stress example to the metabolic disease spectrum, several additional aspects pertaining to the metabolic syndrome become apparent. Metabolic syndrome is defined as the presence of at least 3 of the following parameters: obesity, hypertriglyceridemia, low HDL cholesterol levels, hypertension, and increased fasting glucose levels. From a systems flexibility perspective, these risk factors are mechanistically connected (Figure 5[29,64]), and, to be effective, nutritional interventions should target one or more of these factors and their underlying processes.

Metabolism

Glucose homeostasis plays an important role in the metabolic shock absorption system and many micronutrients play a role in maintaining glucose homeostasis. Vitamin K intake has been shown to improve glucose metabolism in healthy individuals by affecting insulin secretion of pancreatic β cells (Figure 5); it has thus been suggested that recommendations for vitamin K intake are too low.[65–68] It is posited that vitamin K acts on β-cell function via the carboxylation of osteocalcin.[69] Furthermore, plasma vitamin D is inversely associated with 10-year risk of increase in postprandial 2-hour glucose and homeostatic model assessment–insulin resistance (HOMA-IR; a measure of insulin resistance). As with vitamin K, supplementation with vitamin D has been shown to improve insulin secretion and to improve systemic insulin sensitivity, albeit inconsistently. It has been suggested that vitamin D acts through peripheral mechanisms (eg, increasing glucose uptake through GLUT4) or on pancreatic β cells, thereby increasing insulin secretion.[70–72] Zinc is part of the insulin complex and has been shown to have a mechanistic connection to the activity of insulin on its target tissues.[73] Plasma zinc levels in individuals with type 2 diabetes are altered when compared with levels in healthy individuals.[74–78] Zinc thus appears to be a prime candidate for use as a supplement in individuals with type 2 diabetes. However, although some studies have reported a positive effect of zinc supplementation on glucose homeostasis, a systematic review of randomized controlled trials failed to demonstrate a benefit of zinc supplementation on insulin resistance, as measured by HOMA-IR.[79] Oxidative stress is an important factor in the etiology of diabetic complications, and zinc supplementation has beneficial effects on oxidative stress in the presence of type 2 diabetes.[80,81] The mechanism behind these effects of zinc has not yet been adequately elucidated, and further studies may help explain some of the inconsistencies observed. Finally, magnesium intake improves insulin resistance, as measured by HOMA-IR, in both individuals with diabetes and those without.[82–84] The beneficial effect of magnesium intake is strongest in individuals who have impaired glucose tolerance in concert with magnesium deficiency.[82,85] Although the exact mechanism of action remains to be elucidated, it appears that magnesium is important for the maintenance of peripheral glucose uptake, which is mediated by GLUT4.

Many non-nutritive dietary components have been shown to positively contribute to different aspects of glucose homeostasis. Several classes of polyphenolic compounds have been reported to improve dysregulated glucose homeostasis and other aspects of systems flexibility. Catechins (including epigallocatechin gallate) from tea have been shown to improve insulin sensitivity, as measured by HOMA-IR,[86] and may alter postprandial glucose response. These compounds are thought to act on glucose homeostasis through multiple mechanisms, such as inhibition of intestinal digestive enzymes (α-amylase, α-glucosidase, sucrase) and carbohydrate absorption, decrease in gluconeogenesis, and enhancement of insulin sensitivity in adipocytes.[87–90] Isoflavones improved glucose homeostasis, as measured by HOMA-IR. Soy isoflavone intake correlated with improved impaired fasting glucose in postmenopausal women, although nonobese individuals (body mass index [BMI] $<30\,kg/m^2$) were less affected,[91–93] which illustrates that the efficacy of soy isoflavones and other compounds in the optimization of glucose homeostasis

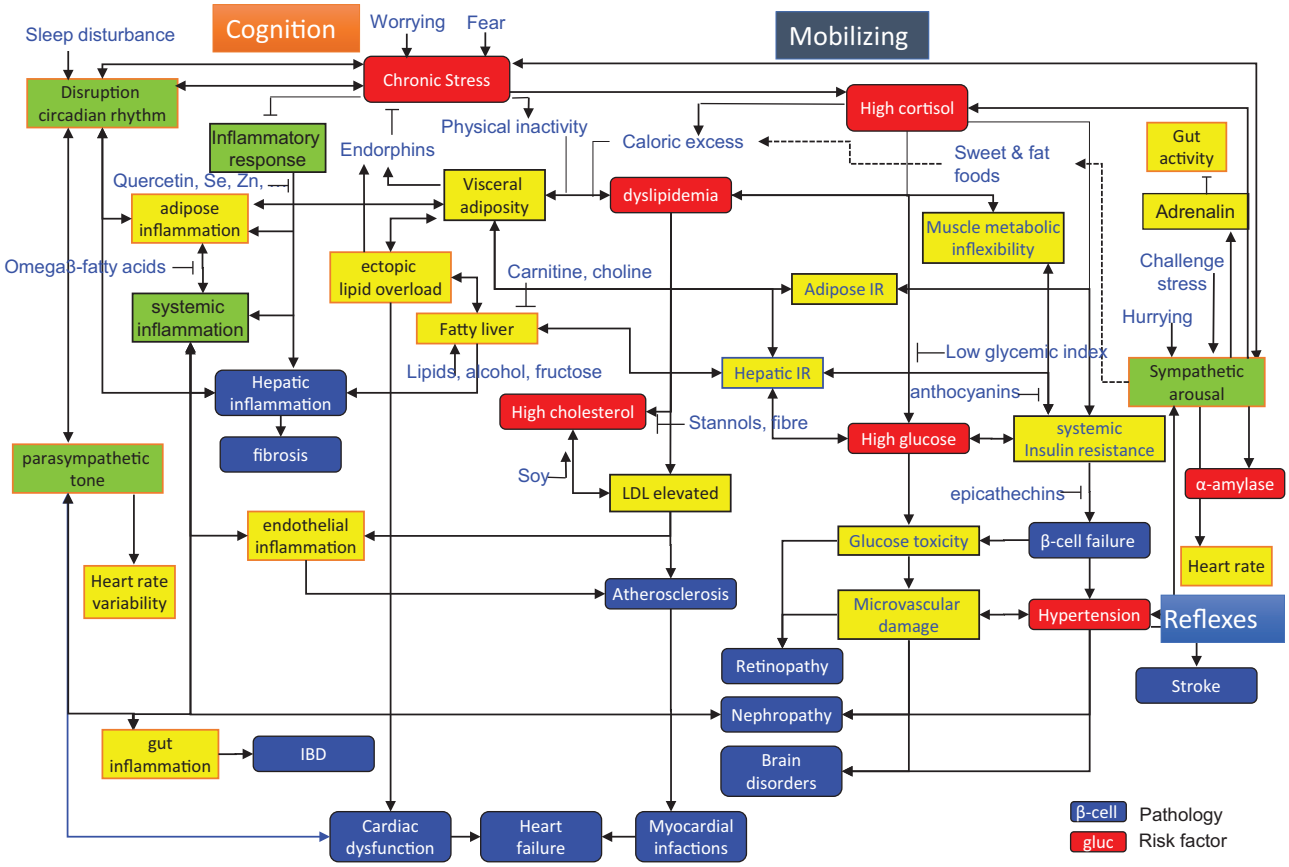

Figure 6 **A systems flexibility view in the context of personalized nutrition.** The inner part of the figure represents the metabolic inflammatory part (yellow boxes) connected to risk factors of the metabolic syndrome (red boxes), which is termed phenotypic flexibility (Van Ommen et al[29,64]). Imbalance or loss of flexibility leads to one or more pathologies (blue boxes). This system is connected to the outer circle of neurohormonal processes, which impact the system flexibility (green boxes). A number of nutrients are shown where they interfere with this flexibility scheme. *Abbreviations:* gluc, glucose; IBD, inflammatory bowel disease; IR, insulin resistance; LDL, low-density lipoprotein; Se, selenium; Zn, zinc.

depends on the physiological context. To translate the above information into personalized dietary recommendations, it may be useful to determine the specific insulin-dependent systems flexibility subtype of an individual (as depicted in Figure 3) together with the individual's vitamin D, magnesium, and vitamin K levels. Individuals with decreased β-cell function may be advised to take (a higher dose of) vitamin K, vitamin D, and magnesium. Individuals with the muscle insulin resistance phenotype may benefit from extra vitamin D, magnesium, and epigallocatechin gallate, whereas nonobese, postmenopausal female individuals with liver insulin resistance may benefit from soy isoflavones.

Inflammation

Chronic low-grade inflammation is involved in many pathologies,[94] its modulation can be quantified by various types of markers,[95] and many dietary components can alter it.[96] C-reactive protein (CRP), a biomarker of inflammation, decreases with intake of both vitamins E and D.[97,98] Vitamin D has been shown to inhibit nuclear factor kappa B (NF-κB) pathway–dependent transcriptional activation through activation of IκB-α, which may explain changes in CRP production.[99] Vitamin E decreases inflammation in several ways, including through activating protein kinase C α and subsequently inhibiting NF-κB and through inhibiting the release of interleukin 1β (IL-1β) from monocytes.[100,101] Meta-analyses have suggested an inverse relationship between magnesium intake and chronic inflammation. Magnesium deficiency might contribute to elevated CRP concentrations by activating macrophages via the N-methyl-D-aspartate receptor and subsequently releasing interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α).[102,103] Furthermore, a large cross-sectional study in the United States showed that flavonoid intake is inversely related to CRP levels in adults.[104]

The ability of long-chain n-3 fatty acids derived from the essential fatty acid alpha-linolenic acid to

modulate inflammation has been extensively studied. Administration of n-3 fatty acids has been correlated with reductions in a number of inflammatory markers, including CRP, IL-6, and TNF-α. Meta-analysis shows that the ingestion of these compounds is most effective in individuals with BMI $<30\ kg/m^2$. The n-3 polyunsaturated fatty acids are a minor component of the diet and are thought to optimize inflammatory control through the balancing and antagonistic effects of their metabolites (among others oxylipins, resolvins, and protectins) on the prostaglandin and related pathways.[105,106]

Flavonoids and flavonoid-rich foods have been found to reduce inflammation and associated biomarkers, including circulating concentrations of IL-1β, IL-6, TNF-α, and CRP.[107,108] Isoflavones from soy show benefits similar to cocoa flavonols on flow-mediated dilation in the vascular system in postmenopausal women. Isoflavones have been shown to reduce inflammation, as measured through plasma CRP, with a greater response to the anti-inflammatory actions of isoflavones seen in postmenopausal women with high sensitive CRP levels $>2.2\ mg/L$.[91] Curcuminoids are thought to mainly affect IL-6 and IL-1β, and, possibly, CRP, even though the compounds have very low bioavailability.[109]

Vascular health

Different mechanisms may contribute to hypertension, including endothelial dysfunction, malfunctioning of the renin-angiotensin-aldosterone system, or disturbance of the folate/homocysteine pathways.[110] It has been suggested that vitamin C improves endothelial function and therefore health status.[57] Vitamin C supplementation was shown to improve endothelial function in patients with diabetes, atherosclerosis, and heart failure, but no effect was observed in healthy volunteers.[111] Diets with both salt restriction and increased potassium are beneficial in preventing or controlling hypertension.[57,112,113] The European Food Safety Authority has authorized a health claim for the benefits of cocoa flavanols and walnuts in the maintenance or even improvement of normal endothelium-dependent vasodilation, as measured by flow-mediated dilation.[114–116] Positive action on vascular flexibility through the enhancement of nitric oxide production by endothelial nitric oxide synthase is thought to be the most probable mechanism by which cocoa flavanols and walnuts act.[114] In a randomized control trial, lycopene supplementation improved endothelial function in patients with cardiovascular disease, but not in healthy volunteers,[117] indicating that, similar to vitamin C, the beneficial effects of lycopene supplementation on endothelial function may relate to health status. Resveratrol also has beneficial effects on the vasculature and acts through several mechanisms, including increasing flow-mediated vasodilation, improving endothelial dysfunction, and preventing uncoupling of endothelial nitric oxide synthase.[57,118]

Personalization

Dietary advice based on nutrient intake or status markers provides a basic level of personalization; however, this advice is based on (epidemiological) association rather than the physiological function of the nutrient. Recommendations for nutrients based on their status should be augmented with information grounded more firmly in the physiology of metabolic health. The role of key organs in an individual's glucose homeostasis can be determined by parameters derived from an oral glucose tolerance test, and hsCRP assays can provide information on inflammatory status. Ideally, status-based micronutrient personalization should be fine-tuned based on target site active compound concentration because this represents the outcome of the sum of process variation. Vitamin D provides a good example because genetic variation modulates absorption, metabolism, efficacy, and excretion.[119] Because phytonutrients are not considered essential nutrients and deficiency and dietary reference intakes are mostly undefined, recommendations for their intake are based on their effects and not on status markers. Thus, phytonutrients can be selected to address issues (eg, glucose metabolism or inflammation) based on an individual's physiology. The European Food Safety Authority (EFSA) has sanctioned health claims for some phytonutrients, and South Korea has identified 55 non-nutrients with health benefits through a similar process. Dietary recommendations, including phenotype-based personalized recommendations, will benefit from further consensus as to the health benefits of various phytonutrients.[120] All of the non-nutrients regulated by EFSA and South Korea and mentioned herein, are attainable from the diet but, depending on personal taste and preferences, are not necessarily consumed in the quantities recommended. Opportunities thus exist for new product development, fortification, and supplementation.

The examples above illustrate that recommendations for the intake of micro- and phytonutrients can vary considerably according to the individual and can be based on many personal factors (eg, genetics, health status and biomarkers, environmental factors). Because multiple nutrients may act on a similar phenotype (ie, each has a unique and complementary role in complex physiological processes; the immune system is a good example[121]), it is important to understand the mechanisms involved and ideally incorporate these into a systems

approach. This approach was extensively discussed in another review.[4] Knowledge of the mechanisms underpinning specific aspects of systems flexibility can be used to connect evidence (both mechanistic and observational) from nutritional intervention studies of specific nutrients to personalized dietary advice aimed at optimizing system flexibility. This is illustrated in Figures 1, 2, and 5. Figure 6 illustrates how different compounds affect different aspects of physiology.

The health space in Figure 3 presents a simple method to visualize the various macro- and micronutrient interventions in relation to a personalized systems flexibility profile. A tailored intervention dependent on the individual's position in this health space can be designed to optimize all relevant flexibility processes and return optimal systems flexibility. An example of this approach was elaborated on in a systems biology–based nutritional intervention study using mostly homeostatic biomarker values.[30]

NUTRIGENETICS: CONTRIBUTION OF GENETIC VARIATION TO PERSONALIZED NUTRITION

Personalized nutrition is often directly associated with genetic variation or "nutrigenetics." Indeed, the human genome is packed with genetic variants, many of which have been identified in genome-wide association studies, that are involved in energy metabolism, satiety and appetite, growth, nutrient absorption, and many other nutrition-related processes, some of which are not yet understood. Translation from genetic variation to phenotypic expression is not straightforward, which highlights the importance of using a systems approach to create robust personalized recommendations.

For a number of rare diseases, rigid dietary control can help control the disease. The metabolic disease phenylketonuria is caused by a loss-of-function mutation in the phenylalanine hydroxylase gene (*PAH*). This mutation results in accumulation of phenylalanine, which can cause mental retardation, organ damage, and neurobehavioral abnormalities. If the disease is detected early, tight control of dietary phenylalanine intake and provision of sufficient tyrosine allow for normal growth and development.[122,123] Although the gene–nutrient interaction of phenylketonuria is relatively straightforward, phenylalanine tolerance may vary from patient to patient depending on residual *PAH* activity, among other things.[124]

Lactose intolerance also has a genetic component. The majority of the world population undergoes a genetically programmed decrease in lactase biosynthesis with age.[125] Interestingly, in large parts of Europe, the population has regained the ability to express lactase in adulthood. Variants in the *MCM6* gene (single nucleotide polymorphisms [SNPs] rs4988235 and rs182549) that influence the lactase gene are responsible for lactase persistence in Europe.[126,127] Yet, for both variants, there is no absolute correlation with dairy consumption or with occurrence of intolerance related to extended or abundant lactose consumption because many factors are involved in lactose intolerance, including other genetic factors (gene–gene interactions), changes in protein expression, and dietary factors (amount of lactose in dairy products, method of preparation, etc).

A more complex example of gene–nutrient interaction is the physiological (disease-related) outcome of mutations in the gene *MTHFR* and its interaction with various nutrients. *MTHFR* is translated into the enzyme methylenetetrahydrofolate reductase, which plays a key role in 1-carbon metabolism and is required for DNA and RNA biosynthesis, amino-acid metabolism, and methylation reactions. A common variant of the *MTHFR* gene is the SNP rs1801133 (677TT), which in homozygotes leads to (1) a 30% reduction in enzyme activity, (2) a possible lowering of folate bioavailability, and (3) elevated homocysteine levels, a risk factor for cardiovascular disease. Low folate bioavailability is associated with, and mechanistically related to, neural tube defects. Yet, despite the many studies performed on folate, health effects, and related genetics, no genetics-based dietary advice on folate intake during pregnancy exists.[128] Interestingly, recent work shows a clear association between the *MTHFR* 677TT variant and high blood pressure. Supplementation with riboflavin (vitamin B2), which serves as a cofactor in the form of flavin adenine dinucleotide for *MTHFR* activity, was shown to lower blood pressure, specifically in hypertensive individuals with the *MTHFR* 677TT variant.[129] Although the exact mechanism by which *MTHFR* 677TT interacts with riboflavin and affects blood pressure is not known, there are associations with the deregulation of nitric oxide, which is known to affect blood pressure by regulating vasodilatation. Also, higher concentrations of flavin adenine dinucleotide and folate cofactors stabilize MTHFR.[130]

An ultimate example of genetic adaptation to nutritional intake is found in Inuit, a group of indigenous people inhabiting the Arctic regions of Greenland. Inuit have lived for a long time in extreme conditions and on an extreme diet that is low in carbohydrates, high in protein and fats, and low in vegetables and fruits. Importantly, the diets are particularly high in polyunsaturated fatty acids. Despite high fat intake, (traditional) Inuit show low levels of cardiovascular disease. A recent study[131] found several variants in the fatty acids desaturase (*FADS*) genes that were present in almost all Inuit selected for the study; in contrast, these variants were seen in only 2% of Europeans. The variants lower the production of n-6 and n-3 fatty

acids, probably counteracting the already high intake of these fatty acids from the diet. Interestingly, these mutations lower LDL cholesterol levels and have a profound effect on height and weight. Other variants found in the Inuit population were associated with *TBX15* and have roles in the differentiation of brown and white adipocytes. This differentiation may be associated with adaption to cold in Inuit populations. A variant in *FN3KRP* is associated with protection from increased oxidative stress that could be caused by high intake of polyunsaturated fatty acids. Health effects of the Inuit diet are closely related to the population's specific genetic makeup and thus might not directly be translated to other populations.[127]

The above examples show the complexity of formulating dietary advice if the genetic variation occurs within one specific biochemical pathway. In many cases, the complexity is even higher because the pathway is one of many that work in concert to regulate an overarching process. A good example is satiety, which involves multiple signaling pathways that monitor both acute and chronic needs for energy. Within this complexity, some master regulators can overrule the subtleties of the network, and rare mutations may lead to morbid obesity.[132] The common variants of the gene *FTO*, which, among all the identified common genetic variants in obesity, contribute the most to the risk of obesity, provide an example of such an interaction.

Speliotes et al[133] found a cluster of several SNPs that impact adiposity by affecting expression of either *FTO* or its neighboring genes. In addition, Loos and Yeo[134] calculated that each individual risk allele of this cluster was associated with a 0.39 kg/m^2 increase in BMI and a 1.20-fold increase in risk of obesity. *FTO* is thought to have a role in appetite regulation, and SNPs associated with *FTO* are thought to cause decreased appetite control, which leads to weight gain in individuals with these mutations. Most studies assume a higher total energy intake for carriers of the *FTO* risk alleles. A meta-analysis of weight-loss studies that included 7700 individuals demonstrated that the TA and AA genotypes of the FTO variant rs9939609 together contributed to an average 0.20-kg additional weight loss as compared to the TT genotype.[135] For personalized nutrition, however, it is irrelevant that 7700 individuals experienced an average additional weight loss of 0.20 kg; what matters is what specific dietary (or coaching) advice should be given to an individual and whether that one individual loses 3.1 kg or gains 0.7 kg.

Interestingly, Claussnitzer et al[136] showed that the rs1421085 T-to-C variant of *FTO* influences expression of the nearby genes *IRX3* and *IRX5*, which repress mitochondrial thermogenesis in adipocyte precursor cells, resulting in a shift from energy-dissipating beige adipocytes to energy-storing white adipocytes. For this particular variant, weight gain might not necessarily be a result of higher energy intake but instead be related to reduced levels of energy-dissipating beige adipocytes, which is in line with the findings that this *FTO* variant is part of a gene–exercise interaction on obesity risk.[137] When formulating diet interventions, it is thus important to know the exact mechanism of action related to a genetic variant associated with a health condition because different genetic variants may require different interventions. At this stage, the *FTO* case is so complex that responders and nonresponders have not yet been identified. Additionally, despite the *FTO* variant contributing the most to obesity risk of all known variants, its contribution to obesity risk is still very small.

The complexity of such multifactorial phenotypes can partly be addressed by constructing a genetic susceptibility score or genetic risk score (GRS) which provides an overview of the cumulative theoretical contribution of genetics to a condition, such as obesity, for a given set of genetic variants.[138] This score is still based on average numbers obtained from large study cohorts and, thus, does not provide an ideal solution for personalized nutrition because it does not pinpoint the mechanism and, thereby, the specific intervention needed. Fine-tuning a risk score into contributing aspects or traits (for the case of obesity: BMI, fat mass, waist-to-hip-ratio, extreme phenotypes, waist circumference[138]) does not help if actionable mechanisms are not addressed. Genetic risk scores for insulin resistance and type 2 diabetes may become more useful as the underlying processes are more clearly identified and separated. This has been done for drug targets of specific type 2 diabetes processes, where process-based risk scores were defined based on genes associated with drug classes.[139] A very similar approach could be used to construct process-based GRSs for mechanisms underpinning phenotypic flexibility. Because no processes are completely independent, genetic variants might be part of more than one GRS, and the process-based GRS would serve to match the phenotypic quantification of the same process rather than being a mathematical fraction of the total GRS. Finally, existing dedicated catalogs of gene–diet and gene–environment interactions, of which the CardioGxE catalog is a good example,[140] will be of increasing importance for the construction of such process-based GRSs.

THE MASTERS OF SYSTEMS FLEXIBILITY: NEUROBIOLOGY OF PERSONALIZED NUTRITION

The brain acts as the master regulator of metabolism by utilizing multiple nutrient-sensing mechanisms and neuronal feedback control systems for metabolic

regulation. This has been reviewed by others.[141] Three important areas of this master regulation (satiety, chronobiology, intermittent fasting and motivation) are specifically related to nutrition, including personalization of nutrition. The importance of these areas of master regulation is apparent when looking at genetic variations in these systems. For example, mutations in the neural melanocortin receptors are responsible for the most common forms of monogenic obesity.[142]

Satiety

Caloric intake depends on food quantity and quality (type of macronutrient), and satiation is one of the major regulators of quantity. Satiety is tightly controlled by a network of neuronal, hormonal, and metabolic sensors, acting both short term (postprandial; triggered by volume, density, content) and long term (connected to set-point regulation). Signal hormones such as grehlin and leptin induce feelings of hunger and satiety, respectively, from the periphery to the hypothalamus.[143] Well-known satiety hormones such as cholecystokinine, glucagon-like peptide-1, and peptide YY increase after food intake, acting as signals for individuals to reduce food intake.[144] The satiety cascade[145] illustrates the different systems involved in appetite control, including sensory, cognitive, postingestive, and postabsorptive processes, which act acutely on satiation (the process that brings food intake to an end) and, after food consumption, on satiety, affecting the time between food intake.

Different macronutrients have different satiating properties, and thus changing the ratios of macronutrients can modulate feelings of satiety. The satiating effect of macronutrients has been studied in multiple populations, including lean and obese persons, men and women, and restrained and unrestrained eaters, with varied responses. Diets high in protein (up to 30 E%) may reduce appetite and support body-weight management compared with diets low in protein[146,147]; this may be due in part to a greater satiating effect of protein relative to other macronutrients. A high-protein diet has been shown to result in less ad libitum caloric intake, resulting in significant weight loss.[148] The increased energy expenditure reported with high-protein diets supports the negative energy balance theory for enabling weight loss and/weight maintenance.[147] Obese individuals show a clearer satiety response to fiber intake, especially when on a very low-energy diet.[149] Body-weight characteristics such as BMI and waist circumference, as well as *FTO* SNP allele status, can help determine the possible effects of macronutrients, especially protein and dietary fibers, on an individual's satiety. People with a high BMI and a large waist may, for example, be advised to eat more protein and more dietary fibers (more satiating food components), especially when they also have the *FTO* risk allele.

Chronobiology

The circadian clock system organizes multiple physiological functions, including digestion, absorption of food, and metabolism. It also influences energy expenditure, activity, and sleep.[150,151] The central internal clock system resides in the anterior hypothalamic suprachiasmatic nucleus. In normal physiological conditions, the suprachiasmatic nucleus synchronizes rhythms with peripheral tissues through a series of neural and hormonal pathways.[152,153] In addition, peripheral rhythms are entrained by various other factors, among which feeding/fasting is the most important.[154] Knowledge of the circadian rhythms in the digestive system and metabolic activity can be used to devise strategies for the optimal timing of food intake to preserve or improve health.[150] For example, sensitivity to elevated glucose concentration is highest in the early morning and declines over the course of the day.[155] Therefore, people with reduced insulin sensitivity may be best advised to eat evening meals low in carbohydrates or carbohydrates with a low glycemic index. Further, there is considerable interindividual variation in circadian patterns. These may derive from external factors relating to behavior and personal preferences, as well as from genetic influences such as the *CLOCK* gene.[154,156] A person's circadian preference or so called chronotype can be determined using the morningness–eveningness questionnaire developed by Horne and Östberg.[157]

Eveningness, as compared with morningness, has been linked with unhealthy eating, increased BMI, reduced HDL cholesterol,[158] and metabolic syndrome.[159] Those with evening chronotypes, as compared with those with morning chronotypes, tend to eat later in the day (ie, after 8 PM), which has been suggested to increase the risk of obesity.[150] This may be especially true for late sleepers[160] and those who get insufficient sleep (ie, $\leq$5 h).[161] Thus, those with morning chronotypes may be advised to consume the standard macronutrient compositions throughout the day, and those with evening chronotypes may be advised to eat more frequently during the day. Further, those with evening chronotypes may be advised to consume evening meals that are higher in protein and rich in fiber to promote satiation and thereby lower the individual's risk of overeating in the evening/night.

Intermittent fasting

Evidence is accumulating that intermittent fasting (ie, fasting periods of 16 h), during which a complete

catabolic metabolism, including fatty acid oxidation, glycogen depletion, and ketone production, is activated, benefits insulin sensitivity and optimizes brain bioenergetics and inflammatory control. Finally, implications for longevity have been reported, at least in model organisms.[11] Although intermittent fasting is not a usual dietary habit, it may be promising for individuals with insulin resistance and is a proven method for regaining insulin sensitivity in individuals with type 2 diabetes and obese persons.[162,163]

Motivation

The motivation to eat has physiological and nonphysiological origins and shows interindividual variation. First, motivation to eat is based on the feeling of satiety. Second, brain reward circuits may influence the salience of food and, thereby, the drive to eat.[151] Sleep restriction leads to increased activation of brain areas that are sensitive to food stimuli[164] and increased neural responses to unhealthy foods in nonobese individuals.[165] Thus, individuals who are sleep deprived may be more prone to eating nutritionally poor food (eg, simple sugars and high-fat foods). Counseling individuals to choose tasty and healthy alternatives at the right time may improve health. Third, because eating is rewarding and comforting, people may (over)eat to alleviate their negative mood or emotional distress.[166] Alternatively, eating may lift mood directly by affecting mood-regulating neurocircuits via a serotonergic mechanism.[167] Because there are considerable differences in mood and subjective well-being between individuals, both temporarily and over the long term,[168] it is important to consider mood and well-being when devising a personalized nutritional plan. With appropriate timing, overeating due to negative mood may be attenuated by providing satiating foods high in protein and fiber. Finally, there may be other external motivators to eat (eg, the desire to stay awake for nightshift workers).

INTEGRATING KNOWLEDGE INTO PRACTICE: PERSONALIZED SYSTEMS APPROACHES

The value of adding personalized nutrition and dietary advice to generic public health recommendations is supported by a large body of knowledge on biological mechanisms, observational studies, and nutritional and dietary interventions. The complexity of personalized nutrition is enormous, however, and it is practically impossible to perform randomized controlled trials for each genome–phenome–exome combination. Established evaluation procedures have been tried but have mostly resulted in inconclusive results, as described herein with regard to nutrigenetics. The use of alternative research approaches, such as $n = 1$ paradigms, must also be considered for the creation of effective recommendations. At this time, variations of the evidence pyramid[169] are commonly used by regulatory agencies and advisory boards, including the European Food Safety Authority. As an example, the recommendation for increased folate intake for pregnant women is now broadly accepted; however, the *MTHFR* 677TT genetic variation, which reduces the catalytic activity of a key enzyme in folate bioavailability,[170] has been the subject of more than 100 studies, but knowledge from these studies has not been used by public health agencies to modulate folate intake recommendations.[128] A global consortium of nutrigenetics experts currently oversees the consensus evaluation of nutrient–gene interactions, providing an initial guidance framework[171] (Grimaldi, in press), and this methodology is brought into practice by evaluations published in a growing and regularly updated library of nutrient gene cards in the online journal *Genes and Nutrition*.

For nutritional experts to keep track of the enormous complexity of nutrient—health relationships and quickly retrieve all relevant information, the use of appropriate knowledge management systems is imperative. Systems should use a multilevel organization of knowledge—that is, they should capture information on biological concepts at the intervention level (food, nutrient, compound, supplement, lifestyle, SNP), the intermediate molecular/biological level (marker, pathway, process, organ), and the phenotypic level (health, disease) (Figures 1 and 5). For each concept, information on known values/thresholds (eg, a dietary reference intake for vitamin D) and intervals (eg, lower and upper boundaries defining normal cholesterol levels) should be stored. In addition, information concerning the relationships between biological concepts should be captured by the system. A relationship between 2 concepts can be represented by a "triple" (a combination of subject, predicate, and object) or nanopublication. An example of a nanopublication is "angiotensin II" – "increases" – "lipogenesis." Each triple needs to be accompanied by information concerning the source of information (eg, a reference), the level of scientific evidence, and the conditions in which this relationship applies (eg, sex, age, ethnicity).

Based on this information, experts can design decision trees that define which recommendations to follow in a given personal situation. For example, IF "marker X" is "low" and "SNP Y" has "allele Z" AND "sex" is "male," THEN the advice for "nutrient A" should be "low." Complexity can be added by combining and integrating multiple decision trees into personalized dietary advice. A major benefit of the use of expert-derived decision trees is the transparency of the advice given.

Each piece of advice can be traced back to a particular decision point, and each decision point is based on established concepts and values.

Modeling methods help to provide personalized dietary advice based on personal health status and personal health and performance goals. For example, in the area of weight control, these modeling methods can range from simple logic ("I want to lose weight, so I will consume less calories") to multiparameter mathematical models.[172] If mechanisms are not known or only partly known, models may be descriptive, data fitting, and reliant on trainer-tester dataset validation. In these cases, it is essential that the modeling approach be open access and peer reviewed instead of "black-boxed."[173] Complex models are usually probabilistic (ie, all rules or assumptions contain uncertainty) and, if they are to be used practical advice, need to be carefully documented and ultimately validated. Personalized dietary advice based on scientifically validated rules according to set criteria become decision trees (ie, a relatively straightforward series of science-based choices or decisions that in essence narrow down the general population into specific subsets). As new trees are validated, progressively more personalized recommendations can be realized. Early models of these decision trees were successfully designed and applied in the Food4Me research project on personalized nutrition.[174]

Applying science-based personalized dietary advice not only at the time of initial phenotyping or goal setting but also in response to iterative diagnostics, with the advice optimized after each measurement to achieve the desired goal, is the next step in personalized nutrition. The energy intake in the simple example above ("I want to lose weight, so I will consume fewer calories") is easily optimized if connected to regular bodyweight checks. Even in complex decision trees, iterative fine tuning of personalized dietary advice based on a timeline of (a series of) biomarkers improves the quality of the advice. Mathematical applications such as Bayesian modeling can further improve this modeling process, especially if a large dataset of personal diet health records becomes available. This would be the real strength of a data democracy–driven health system.

PHYSICAL ACTIVITY AS PERSONALIZED NUTRITION GOAL

For normal daily activities the average recommendations for daily food intake and the mean macronutrient composition of approximately 50–55 E% carbohydrates, 30–35 E% fat, and 10–15 E% protein are adequate.[174] For people seriously participating in sport activities, endurance training, or strength training for multiple hours a day, increased energy needs are required.[175] For instance, cyclists in the Tour de France need to consume an average of 6000 kcal daily.[176] The extreme endurance performance that these cyclists deliver over a period of 3 weeks requires a well-adapted intestinal system that enables substrate uptake during activity. Personalizing nutrition for physical performance may involve specific nutrients for specific types of performance, as well as specific timing of nutrient intake.

For endurance sports, simple carbohydrates are the main substrate used during activity, with a mean uptake of approximately 1 g of carbohydrates per minute.[175,177] Optimization of intake of carbohydrates before, during, and after activity has been shown to enhance performance and endurance over time.[175,177] Duration of the exercise activity (<1 h, 1–2 h, 2–3 h, >3 h), the amount of carbohydrate needed (small amounts, 30 g/h, 60 g/h, 90 g/h), the recommended type of carbohydrate (single and/or multiple transportable carbohydrates), and consumption connected to this training have been studied for endurance sports.[177] For the well-trained runner, for example, carbohydrate intake should be 10–12 g/kg/d for 2–3 days before a marathon.[178] Training should include consumption of carbohydrates at the increased levels so endurance athletes can adjust to the digestion of these quantities of carbohydrates and learn to manage any intestinal discomfort. After exercise, sufficient and fast carbohydrate intake (ie, 1.2–1.5 g/kg within 4 hours) is recommended to replenish the glycogen stores in liver and muscle.[179] Endurance athletes mostly consume a high-carbohydrate diet (60–70 E%). Interestingly, there is debate about whether a high-carbohydrate diet is essential for well-trained people because they also show increased fat oxidation. This has recently resulted in an opposite theory—that a high-fat diet should be the diet of choice for elite athletes.[180] Essentially, this debate stresses the importance of metabolic flexibility (ie, the capacity of muscles to use both glucose and fatty acids as substrate) and suggests that at optimal flexibility the choice of energy source is less relevant. Figure 7 summarizes this reasoning and selections in a decision tree scheme.

In addition to an increased need for (simple) carbohydrates, endurance athletes have an increased need for protein because of its role in muscle damage and repair processes. For well-trained athletes, a level of 1.2–1.7 g of protein per kilogram of body weight is advised[175] instead of the 0.8–1.2 g of protein per kilogram of body weight recommended for people with average activity levels.

Caffeine intake (3 mg/kg) before exercise (<1 h) may improve endurance performance.[181] Several studies indicate that consuming approximately 500 mg of nitrate from beetroot juice or an equivalent food source may benefit endurance performance.[182] In particular, it is believed that low to moderately trained individuals benefit from extra nitrate in their diet. In professional athletes, the effects of extra nitrate are inconsistent.[182]

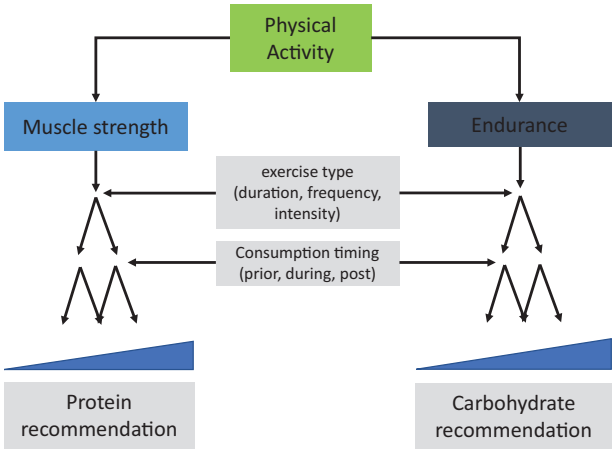

Figure 7 **Simplified decision tree of personalized nutrition in relation to physical activity.** The various components that provide evidence-based fine-tuning of dietary advice are visualized.

The American College of Sports Medicine has special position papers on the maintenance of fluid balance to enable optimal endurance performance and well-being. Performance deteriorates when individuals lose body water equivalent to 2%–3% of body weight, resulting in decreased temperature regulation and an increased risk of heat stroke. Fluid loss during exercise due to sweating should be compensated for by drinking isotonic before, during, and after exercise to prevent dehydration and hyponatremia. The amount of electrolytes, sugars, and water volume needed depend on environmental conditions, training status, and exercise performance (type, time, and intensity) and is mostly advised per kilogram of body weight.[183]

CONCLUSION

Personalized nutrition is here to stay, and more information on metabolic processes in the areas of nutrition and health is becoming available for use in personalized nutrition. Also, major opportunities exist to optimize nutrition recommendations for individuals with disease. Mechanistically, health and disease are tightly connected in the concept of systems flexibility, and nutrition plays a role in both optimizing and impairing flexibility processes. From a nutritional perspective, systems flexibility starts with the control of metabolic flexibility but extends to neurohormonal control of many processes involved in maintaining homeostasis. Essentially, a large part of the biochemical regulatory system is geared toward continuous adaptation to external challenges, and nutrition is a major component of this process. To understand the unique, integrated, and functional relationship of nutrition and health, one must have knowledge of the connected mechanisms that govern systems flexibility because many components of this flexibility machinery are subject to nutritional modulation and relate directly to health outcomes. This article presents many examples of these nutrient–flexibility–health relationships and the ways in which they can be personalized. Further expansion and maturation of personalized nutrition biology requires a systems flexibility approach, spanning increased mechanistic knowledge, modeling technologies, knowledge infrastructures, and alternatives to randomized controlled trials. This is a prerequisite for the professional and credible expansion of personalized nutrition in a healthy society and its food supply.

Acknowledgments

Funding/support. This review was written as part of the collaboration between TNO (The Netherlands Organization for Applied Scientific Research), Campbell Soup Company, and Habit LLC to establish the biology of a personalized nutritional advice system. It was funded by Habit LLC.

Declaration of interest. The authors have no relevant interests to declare.

REFERENCES

1. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
2. Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care. 2002;25:2165–2171.
3. van der Greef J, Hankemeier T, McBurney RN. Metabolomics-based systems biology and personalized medicine: moving towards n = 1 clinical trials? Pharmacogenomics. 2006;7:1087–1094.
4. van Ommen B, Fairweather-Tait S, Freidig A, et al. A network biology model of micronutrient related health. Br J Nutr. 2008;99(suppl 3):S72–S80.
5. Bayle M-L, Wopereis S, Bouwman J, et al. Semi-targeted metabolomic approaches to validate potential markers of health for micronutrients: analytical perspectives. Metabolomics. 2012;8:1114–1129.
6. Scott-Boyer MP, Lacroix S, Scotti M, et al. A network analysis of cofactor-protein interactions for analyzing associations between human nutrition and diseases. Sci Rep. 2016;6:19633. doi:10.1038/srep19633.
7. Shin S-Y, Fauman EB, Petersen A-K, et al. An atlas of genetic influences on human blood metabolites. Nat Genet. 2014;46:543–540.
8. Suhre K, Wallaschofski H, Raffler J, et al. A genome-wide association study of metabolic traits in human urine. Nat Genet. 2011;43:565–569.
9. Kelder T, Summer G, Caspers M, et al. White adipose tissue reference network: a knowledge resource for exploring health-relevant relations. Genes Nutr. 2015;10:439. doi:10.1007/s12263-014-0439-x.
10. Van Ommen B, Bouwman J, Dragsted LO, et al. Challenges of molecular nutrition research 6: the nutritional phenotype database to store, share and evaluate nutritional systems biology studies. Genes Nutr. 2010;5:189–203.
11. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A. 2014;111:16647–16653.
12. Kardinaal AFM, van Erk MJ, Dutman A E, et al. Quantifying phenotypic flexibility as the response to a high-fat challenge test in different states of metabolic health. FASEB J. 2015:29;4600–4613.
13. Regazzi R, Rodriguez-Trejo A, Jacovetti C. Insulin secretion in health and disease: nutrients dictate the pace. Proc Nutr Soc. 2016;75:19–29.
14. Anthony JC, Yoshizawa F, Anthony TG, et al. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway 1. J Nutr. 2000;130:2413–2419.

15. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective. Biochim Biophys Acta. 2010;1801:338–349.
16. Frayn K. Adipose tissue as a buffer for daily lipid flux. Diabetologia. 2002;45:1201–1210.
17. Vangipurapu J, Stančáková A, Pihlajamäki J, et al. Association of indices of liver and adipocyte insulin resistance with 19 confirmed susceptibility loci for type 2 diabetes in 6,733 non-diabetic Finnish men. Diabetologia. 2011;54:563–571.
18. Wang J, Ban MR, Zou GY, et al. Polygenic determinants of severe hypertriglyceridemia. Hum Mol Genet. 2008;17:2894–2899.
19. De Castro-Oros I, Cenarro A, Tejedor MT, et al. Common genetic variants contribute to primary hypertriglyceridemia without differences between familial combined hyperlipidemia and isolated hypertriglyceridemia. Circ Cardiovasc Genet. 2014;7:814–821.
20. Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. Am J Hum Genet. 2001;69:1161–1177.
21. Ress C, Kaser S. Mechanisms of intrahepatic triglyceride accumulation. World J Gastroenterol. 2016;22:1664. doi:10.3748/wjg.v22.i4.1664.
22. Macaluso FS, Maida M, Petta S. Genetic background in nonalcoholic fatty liver disease: a comprehensive review. World J Gastroenterol. 2015;21:11088–11111.
23. Malaguarnera M, Gargante MP, Russo C, et al. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis–a randomized and controlled clinical trial. Am J Gastroenterol. 2010;105:1338–1345.
24. Corpeleijn E, Saris WHM, Blaak EE. Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. Obes Rev. 2009;10:178–193.
25. Goossens GH, Moors CCM, Jocken JWE, et al. Altered skeletal muscle fatty acid handling in subjects with impaired glucose tolerance as compared to impaired fasting glucose. Nutrients. 2016;8:164. doi:10.3390/nu8030164.
26. López-Otín C, Galluzzi L, Freije JMP, et al. Metabolic control of longevity. Cell. 2016;166:802–821.
27. Furman D, Chang J, Lartigue L, et al. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. Nat Med. 2017;23:174–184.
28. Stroeve JHM, van Wietmarschen H, Kremer BHA, et al. Phenotypic flexibility as a measure of health: the optimal nutritional stress response test. Genes Nutr. 2015;10:459. doi:10.1007/s12263-015-0459-1.
29. Van Ommen B, Wopereis S. Next-generation biomarkers of health. Nestle Nutr Inst Workshop Ser. 2016;84:25–34.
30. Bouwman J, Vogels JT, Wopereis S, et al. Visualization and identification of health space, based on personalized molecular phenotype and treatment response to relevant underlying biological processes. BMC Med Genomics. 2012;5:1. doi:10.1186/1755-8794-5-1.
31. Sagner M, McNeil A, Puska P, et al. The P4 health spectrum—a predictive, preventive, personalized and participatory continuum for promoting healthspan. Prog Cardiovasc Dis. 2016;59:506–521.
32. Lim EL, Hollingsworth KG, Aribisala BS, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54:2506–2514.
33. Asano RY, Sales MM, Browne R, et al. Acute effects of physical exercise in type 2 diabetes: a review. World J Diabetes. 2014;5:659–665.
34. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very-low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiologic changes in responders and nonresponders. Diabetes Care. 2016:39;808–815.
35. Blanco-Rojo R, Alcala-Diaz JF, Wopereis S, et al. The insulin resistance phenotype (muscle or liver) interacts with the type of diet to determine changes in disposition index after 2 years of intervention: the CORDIOPREV-DIAB randomised clinical trial. Diabetologia. 2016;59:67–76.
36. Anderson JW, Ward K. High-carbohydrate hig-fiber diets for insulin-treated men with diabetes mellitus. Am J Clin Nutr. 1979;32:2312–2321.
37. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research. JAMA Intern Med. 2016;176:1680–1685.
38. Burke JP, Williams K, Gaskill SP, et al. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. Arch Intern Med. 1999;159:1450–1456.
39. Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva, Switzerland: WHO; 2016.
40. Imamura F, Micha R, Wu JHY, et al. Effects of saturated fat, polyunsaturated fat, monounsaturated fat, and carbohydrate on glucose-insulin homeostasis: a systematic review and meta-analysis of randomised controlled feeding trials. PLOS Med. 2016;13:e1002087. doi:10.1371/journal.pmed.1002087.
41. Ludwig DS. Lowering the bar on the low-fat diet. JAMA. 2016;2115:5–6.
42. Cuenca-Sanchez M, Navas-Carrillo D, Orenes-Pinero E. Controversies surrounding high-protein diet intake: satiating effect and kidney and bone health. Adv Nutr An Int Rev J. 2015;6:260–266.
43. Delimaris I. Adverse effects associated with protein intake above the recommended dietary allowance for adults. ISRN Nutr. 2013;2013:126929. doi:10.5402/2013/126929.
44. Bacha F, Lee S, Gungor N, Arslanian SA. From pre-diabetes to type 2 diabetes in obese youth: pathophysiological characteristics along the spectrum of glucose dysregulation. Diabetes Care. 2010;33:2225–2231.
45. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to beta-glucans from oats and barley and maintenance of normal blood LDL-cholesterol concentrations (ID 1236, 1299), increase in satiety leading to a reduction in energy intake (ID 851), reduction of post-prandial glycaemic responses (ID 821, 824), and "digestive function" (ID 850) pursuant to article 13(1) of regulation (EC) no 1924/2006. EFSA J. 2011;9:2207. doi:10.2903/j.efsa.2011.2207.
46. Silva FM, Kramer CK, de Almeida JC, et al. Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Nutr Rev. 2013;71:790–801.
47. Nettleton JA, McKeown NM, Kanoni S, et al. Interactions of dietary whole-grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies. Diabetes Care. 2010;33:2684–2691.
48. Manders RJF, Wagenmakers AJM, Koopman R, et al. Co-ingestion of a protein hydrolysate and amino acid mixture with carbohydrate improves plasma glucose disposal in patients with type 2 diabetes. Am J Clin Nutr. 2005;82:76–83.
49. Manders RJF, Hansen D, Zorenc AHG, et al. Protein co-ingestion strongly increases postprandial insulin secretion in type 2 diabetes patients. J Med Food. 2014;17:758–763.
50. Heer M, Egert S. Nutrients other than carbohydrates: their effects on glucose homeostasis in humans. Diabetes Metab Res Rev. 2015;31:14–35.
51. Newsholme P, Bender K, Kiely A, et al. Amino acid metabolism, insulin secretion and diabetes. Biochem Soc Trans. 2007;35(pt 5):1180–1186.
52. van Loon LJ, Kruijshoop M, Menheere PP, et al. Amino acid ingestion strongly enhances insulin secretion in patients with long-term type 2 diabetes. Diabetes Care. 2003;26:625–630.
53. Xu G, Kwon G, Cruz WS, et al. Metabolic regulation by leucine of translation initiation through the mTOR-signaling pathway by pancreatic β-cells. Diabetes. 2001;50:353–360.
54. Pedroso JAB, Zampieri TT, Donato J. Reviewing the effects of L-leucine supplementation in the regulation of food intake, energy balance, and glucose homeostasis. Nutrients. 2015;7:3914–3937.
55. Rebholz CM, Friedman EE, Powers LJ, et al. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am J Epidemiol. 2012;176(suppl 7):S27–S43.
56. Buendia JR, Bradlee ML, Singer MR, et al. Diets higher in protein predict lower high blood pressure risk in Framingham Offspring Study adults. Am J Hypertens. 2015;28:372–379.
57. Houston M. The role of nutrition and nutraceutical supplements in the treatment of hypertension. World J Cardiol. 2014;6:38. doi:10.4330/wjc.v6.i2.38.
58. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA) and maintenance of normal cardiac function (ID 504, 506, 516, 527, 538, 703, 1128, 1317, 1324, 1325), maintenance of normal blood glucose concentrations (ID 566), maintenance of normal blood pressure (ID 506, 516, 703, 1317, 1324), maintenance of normal blood HDL-cholesterol concentrations (ID 506), maintenance of normal (fasting) blood concentrations of triglycerides (ID 506, 527, 538, 1317, 1324, 1325), maintenance of normal blood LDL-cholesterol concentrations (ID 527, 538, 1317, 1325, 4689), protection of the skin from photo-oxidative (UV-induced) damage (ID 530), improved absorption of EPA and DHA (ID 522, 523), contribution to the normal function of the immune system by decreasing the levels of eicosanoids, arachidonic acid-derived mediators and pro-inflammatory cytokines (ID 520, 2914), and "immunomodulating agent" (4690) pursuant to article 13(1) of regulation (EC) no 1924/2006. EFSA J. 2010;8:1796. doi:10.2903/j.efsa.2010.1796.
59. Hinderliter AL, Babyak MA, Sherwood A, Blumenthal J. The DASH diet and insulin sensitivity. Curr Hypertens Rep. 2011;13:67–73.
60. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to pectins and reduction of post-prandial glycaemic responses (ID 786), maintenance of normal blood cholesterol concentrations (ID 818) and increase in satiety leading to a reduction in energy intake (ID 4692) pursuant to article 13(1) of regulation (EC) no 1924/2006. EFSA J. 2010;8:1747. doi:10.2903/j.efsa.2010.1747.
61. European Food Safety Authority. Scientific opinion on the substantiation of a health claim related to oat beta-glucan and lowering blood cholesterol and reduced risk of (coronary) heart disease pursuant to article 14 of regulation (EC) no 1924/2006. EFSA J. 2010;8:1885. doi:10.2903/j.efsa.2010.1885.
62. Whitehead A, Beck EJ, Tosh S, et al. Cholesterol-lowering effects of oat β-glucan: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;100:1413–1421.
63. Bartlett HE, Eperjesi F. Nutritional supplementation for type 2 diabetes: a systematic review. Ophthalmic Physiol Opt. 2008;28:503–523.
64. van Ommen B, van der Greef J, Ordovas JM, et al. Phenotypic flexibility as key factor in the human nutrition and health relationship. Genes Nutr. 2014;9:423. doi:10.1007/s12263-014-0423-5.
65. Sakamoto N, Nishiike T, Iguchi H, et al. Relationship between acute insulin response and vitamin K intake in healthy young male volunteers. Diabetes Nutr Metab. 1999;12:37–41.

66. Yoshida M, Jacques PF, Meigs JB, et al. Effect of vitamin K supplementation on insulin resistance in older men and women. Diabetes Care. 2008;31:2092–2096.
67. Choi HJ, Yu J, Choi H, et al. Vitamin K2 supplementation improves insulin sensitivity via osteocalcin metabolism: a placebo-controlled trial. Diabetes Care. 2011;34:e147. doi:10.2337/dc11-0551.
68. Sakamoto N, Nishiike T, Iguchi H, et al. Possible effects of one week vitamin K (menaquinone-4) tablets intake on glucose tolerance in healthy young male volunteers with different descarboxy prothrombin levels. Clin Nutr. 2000;19:259–263.
69. Manna P, Kalita J. Beneficial role of vitamin K supplementation on insulin sensitivity, glucose metabolism, and the reduced risk of type 2 diabetes: a review. Nutrition. 2016;32:732–739.
70. Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. Diabetes Obes Metab. 2012;14:789–794.
71. von Hurst PR, Stonehouse W, Coad J, et al. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient—a randomised, placebo-controlled trial. Br J Nutr. 2010;103:549–555.
72. Mitri J, Dawson-Hughes B, Hu FB, et al. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. Am J Clin Nutr. 2011;94:486–494.
73. Jansen J, Karges W, Rink L. Zinc and diabetes—clinical links and molecular mechanisms. J Nutr Biochem. 2009;20:399–417.
74. Aguilar MV, Saavedra P, Arrieta FJ, et al. Plasma mineral content in type-2 diabetic patients and their association with the metabolic syndrome. Ann Nutr Metab. 2007;51:402–406.
75. Quilliot D, Dousset B, Guerci B, et al. Evidence that diabetes mellitus favors impaired metabolism of zinc, copper, and selenium in chronic pancreatitis. Pancreas. 2001;22:299–306.
76. Pai LH, Prasad AS. Cellular zinc in patients with diabetes mellitus. Nutr Res. 1988;8:889–897.
77. Kinlaw WB, Levine AS, Morley JE, et al. Abnormal zinc metabolism in type II diabetes mellitus. Am J Med. 1983;75:273–277.
78. Al-Maroof RA, Al-Sharbatti SS. Serum zinc levels in diabetic patients and effect of zinc supplementation on glycemic control of type 2 diabetics. Saudi Med J. 2006;27:344–350.
79. El Dib R, Gameiro OL, Ogata MS, et al. Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance. Cochrane Database Syst Rev. 2015;5:CD005525. doi:10.1002/14651858.CD005525.pub3.
80. Roussel A-M, Kerkeni A, Zouari N, et al. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. J Am Coll Nutr. 2003;22:316–321.
81. Anderson RA, Roussel AM, Zouari N, et al. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. J Am Coll Nutr. 2001;20:212–218.
82. Mooren FC, Kruger K, Volker K, et al. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects—a double-blind, placebo-controlled, randomized trial. Diabetes Obes Metab. 2011;13:281–284.
83. Rumawas ME, McKeown NM, Rogers G, et al. Magnesium intake is related to improved insulin homeostasis in the framingham offspring cohort. J Am Coll Nutr. 2006;25:486–492.
84. Veronese N, Watutantrige SF, Luchini C, et al. Effect of magnesium supplementation on glucose metabolism in people with or at risk of diabetes: a systematic review and meta-analysis of double-blind randomized controlled trials. Eur J Clin Nutr. 2016:70;1354–1359.
85. Song Y, He K, Levitan EB, et al. Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet Med. 2006;23:1050–1056.
86. Zheng X-X, Xu Y-L, Li S-H, et al. Effects of green tea catechins with or without caffeine on glycemic control in adults: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2013;97:750–762.
87. Roghani M, Baluchnejadmojarad T. Hypoglycemic and hypolipidemic effect and antioxidant activity of chronic epigallocatechin-gallate in streptozotocin-diabetic rats. Pathophysiology. 2010;17:55–59.
88. Sakurai N, Mochizuki K, Kameji H, et al. (-)-Epigallocatechin gallate enhances the expression of genes related to insulin sensitivity and adipocyte differentiation in 3T3-L1 adipocytes at an early stage of differentiation. Nutrition. 2009;25:1047–1056.
89. Collins QF, Liu H-Y, Pi J, et al. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase. J Biol Chem. 2007;282:30143–30149.
90. Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. J Agric Food Chem. 2000;48:849–852.
91. Li S-H, Liu X-X, Bai Y-Y, et al. Effect of oral isoflavone supplementation on vascular endothelial function in postmenopausal women: a meta-analysis of randomized placebo-controlled trials. Am J Clin Nutr. 2010;91:480–486.
92. Dong J-Y, Wang P, He K, et al. Effect of soy isoflavones on circulating C-reactive protein in postmenopausal women: meta-analysis of randomized controlled trials. Menopause. 2011;18:1256–1262.
93. Fang K, Dong H, Wang D, et al. Soy isoflavones and glucose metabolism in menopausal women: a systematic review and meta-analysis of randomized controlled trials. Mol Nutr Food Res. 2016;60:1602–1614.
94. Calder PC, Albers R, Antoine J-M, et al. Inflammatory disease processes and interactions with nutrition. Br J Nutr. 2009;101(suppl):S1–S45.
95. Albers R, Bourdet-Sicard R, Braun D, et al. Monitoring immune modulation by nutrition in the general population: identifying and substantiating effects on human health. Br J Nutr. 2013;110(suppl):S1–S30.
96. Minihane AM, Vinoy S, Russell WR, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr. 2015;114:999–1012.
97. Chen N, Wan Z, Han S-F, et al. Effect of vitamin D supplementation on the level of circulating high-sensitivity C-reactive protein: a meta-analysis of randomized controlled trials. Nutrients. 2014;6:2206–2216.
98. Saboori S, Shab-Bidar S, Speakman JR, et al. Effect of vitamin E supplementation on serum C-reactive protein level: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2015;69:867–873.
99. Cohen-Lahav M, Shany S, Tobvin D, et al. Vitamin D decreases NF B activity by increasing I B levels. Nephrol Dial Transplant. 2005;21:889–897.
100. Devaraj S, Jialal I. The effects of alpha-tocopherol on critical cells in atherogenesis. Curr Opin Lipidol. 1998;9:11–15.
101. Nakamura T, Goto M, Matsumoto A, et al. Inhibition of NF-kappa B transcriptional activity by alpha-tocopheryl succinate. Biofactors. 1998;7:21–30.
102. Dibaba DT, Xun P, He K. Dietary magnesium intake is inversely associated with serum C-reactive protein levels: meta-analysis and systematic review. Eur J Clin Nutr. 2014;68:510–516.
103. Chacko SA, Song Y, Nathan L, et al. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. Diabetes Care. 2010;33:304–310.
104. Chun OK, Chung S-J, Claycombe KJ, et al. Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in U.S. adults. J Nutr. 2008;138:753–760.
105. Li K, Huang T, Zheng J, et al. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α: a meta-analysis. PLoS One. 2014;9:e88103. doi:10.1371/journal.pone.0088103.
106. Gabbs M, Leng S, Devassy JG, et al. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr. 2015;6:513–540.
107. Peluso I, Raguzzini A, Serafini M. Effect of flavonoids on circulating levels of TNF-α and IL-6 in humans: a systematic review and meta-analysis. Mol Nutr Food Res. 2013;57:784–801.
108. Rangel-Huerta OD, Pastor-Villaescusa B, Aguilera CM, et al. A systematic review of the efficacy of bioactive compounds in cardiovascular disease: phenolic compounds.
109. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res. 2014;28:633–642.
110. Pilic L, Pedlar CR, Mavrommatis Y, et al. Salt-sensitive hypertension: mechanisms and effects of dietary and other lifestyle factors. Nutr Rev. 2016;360:1903–1913.
111. Ashor AW, Siervo M, Lara J, et al. Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials. Br J Nutr. 2015;113:1182–1194.
112. Aaron KJ, Sanders PW, Aaron, Kristal J. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc. 2013;88:987–995.
113. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013;346:F1378–F1378.
114. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to walnuts and maintenance of normal blood LDL-cholesterol concentrations (ID 1156, 1158) and improvement of endothelium-dependent vasodilation (ID 1155, 1157) pursuant to article 13(1) of regulation (EC) no 1924/2006. EFSA J. 2011;9:2074. doi:10.2903/j.efsa.2011.2074.
115. European Food Safety Authority. Scientific opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to article 13(5) of regulation (EC) no 1924/2006. EFSA J. 2012;10:2809. doi:10.2903/j.efsa.2012.2809.
116. European Food Safety Authority. Scientific opinion on the modification of the authorisation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to article 13 (5) of regulation (EC) no 1924 / 2006 1 following a request in accordance with article 19 of regulation (EC) no 1924/2006. EFSA J. 2014;12;3654. doi:10.2903/j.efsa.2014.3654.
117. Gajendragadkar PR, Hubsch A, Mäki-Petäjä KM, et al. Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. PLoS One. 2014;9:e99070. doi:10.1371/journal.pone.0099070.

118. Kelly-Spratt KS, Pitteri SJ, Gurley KE, et al. Plasma proteome profiles associated with inflammation, angiogenesis, and cancer. PLoS One. 2011;6:e19721. doi:10.1371/journal.pone.0019721.
119. Mokry LE, Ross S, Ahmad OS, et al. Vitamin D and risk of multiple sclerosis: a Mendelian randomization study. PLOS Med. 2015;12:e1001866. doi:10.1371/journal.pmed.1001866.
120. Lupton JR, Atkinson S a, Chang N, et al. Exploring the benefits and challenges of establishing a DRI-like process for bioactives. Eur J Nutr. 2014;53(suppl 1):1–9.
121. Larbi A, Franceschi C, Mazzatti D, et al. Aging of the immune system as a prognostic factor for human longevity. Physiology (Bethesda). 2008;23:64–74.
122. Scriver CR. The PAH gene, phenylketonuria, and a paradigm shift. Hum Mutat. 2007;28:831–845.
123. Singh RH, Cunningham AC, Mofidi S, et al. Updated, web-based nutrition management guideline for PKU: an evidence and consensus based approach. Mol Genet Metab. 2016;118:72–83.
124. de Baulny HO, Abadie V, Feillet F, et al. Management of phenylketonuria and hyperphenylalaninemia. J Nutr. 2007;137(suppl 1):1561S–1563S; discussion 1573S–1575S.
125. Deng Y, Misselwitz B, Dai N, et al. Lactose intolerance in adults: biological mechanism and dietary management. Nutrients. 2015;7:8020–8035.
126. Enattah NS, Sahi T, Savilahti E, et al. Identification of a variant associated with adult-type hypolactasia. Nat Genet. 2002;30:233–237.
127. Mathieson I, Lazaridis I, Rohland N, et al. Genome-wide patterns of selection in 230 ancient Eurasians. Nature. 2015;528:499–503.
128. Levin BL, Varga E. *MTHFR*: addressing genetic counseling dilemmas using evidence-based literature. J Genet Couns. 2016;25:901–911.
129. Wilson CP, McNulty H, Ward M, et al. Blood pressure in treated hypertensive individuals with the *MTHFR* 677TT genotype is responsive to intervention with riboflavin: findings of a targeted randomized trial. Hypertension. 2013;61:1302–1308.
130. Lienhart WD, Gudipati V, MacHeroux P. The human flavoproteome. Arch Biochem Biophys. 2013;535:150–162.
131. Fumagalli M, Moltke I, Grarup N, et al. Greenlandic Inuit show genetic signatures of diet and climate adaptation. Science. 2015;349:1343–1347.
132. Xia Q, Grant SFA. The genetics of human obesity. Ann N Y Acad Sci. 2013;1281:178–190.
133. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42:937–948.
134. Loos RJF, Yeo GSH. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10:51–61.
135. Xiang L, Wu H, Pan A, et al. FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis. Am J Clin Nutr. 2016;103:1162–1170.
136. Claussnitzer M, Dankel SN, Kim K-H, et al. FTO obesity variant circuitry and adipocyte browning in humans. N Engl J Med. 2015;373:895–907.
137. Young AI, Wauthier F, Donnelly P. Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. Nat Commun. 2016;7:12724. doi:10.1038/ncomms12724.
138. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. Mol Cell Endocrinol. 2014;382:740–757.
139. Segrè AV, Wei N, Altshuler D, et al. Pathways targeted by antidiabetes drugs are enriched for multiple genes associated with type 2 diabetes risk. Diabetes. 2015;64:1470–1483.
140. Parnell LD, Blokker B, Dashti HS, et al. CardioGxE, a catalog of gene-environment interactions for cardiometabolic traits. BioData Min. 2014;7:21. doi:10.1186/1756-0381-7-21.
141. Roh E, Song DK, Kim M-S. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. Exp Mol Med. 2016;48:e216. doi:10.1038/emm.2016.4.
142. Tao YX. Molecular mechanisms of the neural melanocortin receptor dysfunction in severe early onset obesity. Mol Cell Endocrinol. 2005;239:1–14.
143. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007;8:21–34.
144. De Graaf C, Blom WAM, Smeets PAM, et al. Biomarkers of satiation and satiety. Am J Clin Nutr. 2004;79:946–961.
145. Blundell JE, Hill AJ, Rogers PJ. Hunger and the satiety cascade—their importance for food acceptance in the late 20th century. In: Thomson DMH, ed. Food Acceptability. London, UK: Elsevier; 1988:230–250.
146. Leidy HJ, Clifton PM, Astrup A, et al. The role of protein in weight loss and maintenance. Am J Clin Nutr. 2015;101:1320–1329.
147. Westerterp-Plantenga MS, Lemmens SG, Westerterp KR. Dietary protein—its role in satiety, energetics, weight loss and health. Br J Nutr. 2012;108(suppl 2):S105–S112.
148. Weigle DS, Breen PA, Matthys CC, et al. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. Am J Clin Nutr. 2005;82:41–48.
149. Pasman WJ, Saris WH, Wauters MA, et al. Effect of one week of fibre supplementation on hunger and satiety ratings and energy intake. Appetite. 1997;29:77–87.
150. Tahara Y, Shibata S. Chronobiology and nutrition. Neuroscience. 2013;253:78–88.
151. Chaput J-P, McCarthy S. Sleep patterns, diet quality and energy balance. Physiol Behav. 2014;134:86–91.
152. Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science. 2010;330:1349–1354.
153. Johnston JD. Physiological responses to food intake throughout the day. Nutr Res Rev. 2014;27:107–118.
154. Oosterman JE, Kalsbeek A, la Fleur SE, et al. Impact of nutrients on circadian rhythmicity. Am J Physiol—Regul Integr Comp Physiol. 2015;308:R337–R350.
155. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. Endocr Rev. 1997;18:716–738.
156. Ruiz-Lozano T, Vidal J, de Hollanda A, et al. Evening-chronotype associates with obesity in severe obese subjects: interaction with *CLOCK* 3111T/C. Int J Obes (London). 2016;40;1550–1557.
157. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4:97–110.
158. Lucassen EA, Zhao X, Rother KI, et al. Evening chronotype is associated with changes in eating behavior, more sleep apnea, and increased stress hormones in short sleeping obese individuals. PLoS One. 2013;8:e56519. doi:10.1371/journal.pone.0056519.
159. Yu JH, Yun CH, Ahn JH, et al. Evening chronotype is associated with metabolic disorders and body composition in middle-aged adults. J Clin Endocrinol Metab. 2015;100:1494–1502.
160. Baron KG, Reid KJ, Kern AS, et al. Role of sleep timing in caloric intake and BMI. Obesity (Silver Spring). 2011;19:1374–1381.
161. Markwald RR, Melanson EL, Smith MR, et al. Impact of insufficient sleep on total daily energy expenditure, food intake and weight gain. Proc Natl Acad Sci U S A. 2013;110:5695–5700.
162. Barnosky AR, Hoddy KK, Unterman TG, et al. Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. Transl Res. 2014;164:302–311.
163. Antoni R, Johnston KL, Collins AL, Robertson MD. Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants. Br J Nutr. 2016;115:951–959.
164. Benedict C, Brooks SJ, O'Daly OG, et al. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. J Clin Endocrinol Metab. 2012;97:443–447.
165. St-Onge M-P, Wolfe S, Sy M, et al. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. Int J Obes (London). 2014;38:411–416.
166. Adam TC, Epel ES. Stress, eating and the reward system. Physiol Behav. 2007;91:449–458.
167. Kroes MCW, van Wingen GA, Wittwer J, et al. Food can lift mood by affecting mood-regulating neurocircuits via a serotonergic mechanism. Neuroimage. 2014;84:825–832.
168. National Research Council. Subjective Well-Being Measuring Happiness, Suffering, and Other Dimensions of Experience. Washington, DC: The National Academies Press; 2013.
169. Pandis N. The evidence pyramid and introduction to randomized controlled trials. Am J Orthod Dentofac Orthop. 2011;140:446–447.
170. Molloy AM. Genetic aspects of folate metabolism. Subcell Biochem. 2012;56:105–130.
171. Grimaldi K, Van Ommen B, Ordovas JA, et al Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. Genes and Nutrition. In press.
172. Hall KDD, Bemis T, Brychta R, et al. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. Cell Metab. 2015;22:427–436.
173. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163:1079–1094.
174. Forster H, Walsh MC, O'Donovan CB, et al. A dietary feedback system for the delivery of consistent personalized dietary advice in the web-based multicenter Food4Me Study. J Med Internet Res. 2016;18:e150. doi:10.2196/jmir.5620.
175. American Dietetic Association, Dietitians of Canada, American College of Sports Medicine, et al. American College of Sports Medicine position stand. Nutrition and athletic performance. Med Sci Sport Exerc. 2009;41:709–731.
176. Saris WH, van Erp-Baart MA, Brouns F, et al. Study on food intake and energy expenditure during extreme sustained exercise: the Tour de France. Int J Sports Med. 1989;10(suppl 1):S26–S31.
177. Jeukendrup A. A step towards personalized sports nutrition: carbohydrate intake during exercise. Sport Med. 2014;44(suppl 1):25–33.
178. Burke LM. Nutrition strategies for the marathon: fuel for training and racing. Sports Med. 2007;37:344–347.

179. Stellingwerff T, Maughan RJ, Burke LM. Nutrition for power sports: middle-distance running, track cycling, rowing, canoeing/kayaking, and swimming. J Sports Sci. 2011;29(supp1):S79–S89.
180. Volek JS, Noakes T, Phinney SD. Rethinking fat as a fuel for endurance exercise. Eur J Sport Sci. 2015;15:13–20.
181. European Food Safety Authority. Scientific opinion on the substantiation of health claims related to caffeine and increase in physical performance during short-term high-intensity exercise (ID 737, 1486, 1489), increase in endurance performance (ID 737, 1486), increase in endurance capacity (ID 1488) and reduction in the rated perceived exertion/effort during exercise (ID 1488, 1490) pursuant to article 13(1) of regulation (EC) no 1924/2006. EFSA J. 2011;9:2053. doi:10.2903/j.efsa.2011.2053.
182. Bescós R, Sureda A, Tur JA, et al. The effect of nitric-oxide-related supplements on human performance. Sport Med. 2012;42:99–117.
183. American College of Sports Medicine, Sawka MN, Burke LM, et al. American College of Sports Medicine position stand. Exercise and fluid replacement. Med Sci Sports Exerc. 2007;39:377–390.