
The Scientific Challenge of Expanding the Frontiers of Nutrition

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Abstract

Nutritional research is entering a paradigm shift which necessitates the modeling of complex interactions between diet, genetics, lifestyle, and environmental factors. This requires the development of analytical and processing capabilities for multiple data and information sources to be able to improve targeted and personalized nutritional approaches for the maintenance of health. Ideally, such knowledge will be employed to underpin the development of concepts that combine consumer and medical nutrition with diagnostic targeting for early intervention designed to maintain proper metabolic homeostasis and delay the onset of chronic diseases. Nutritional status is fundamental to any description of health, and when combined with other data on lifestyle, environment, and genetics, it can be used to drive stratified or even personalized nutritional strategies for health maintenance and preventive medicine. In this work, we will discuss the importance of developing new nutrient assessment methods and diagnostic capabilities for nutritional status to generate scientific hypotheses and actionable concepts from which to develop targeted and eventually personalized nutritional solutions for health protection. We describe efforts to develop algorithms for dietary nutrient intake and a holistic nutritional profiling platform as the basis of understanding the complex nutrition and health interactome.

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Introduction

The human body is a complex and dynamic network of physiological regulatory and adaptive processes that is constantly under modulation from multiple intrinsic (genetic, metagenetic, and metabolic) and extrinsic (lifestyle and environment) factors. Scientific evidence continues to grow on the pivotal role of

nutrition in maintaining health as well as in delaying the onset of chronic disorders. Indeed, the extension of human life expectancy and the pandemia of chronic and multifactorial disorders such as obesity, type-2 diabetes, and various neurological disorders are naturally positioning nutrition at the forefront of sustainable approaches for healthy aging and preventive medicine. This is logically understood as nutritional intake is the process that exposes the human body to a multitude of organic and inorganic substances contained in food and beverages on a chronic basis. Food and beverages provide the water, macronutrients, and micronutrients necessary to sustain the growth, metabolism, and repair of biological systems. Several so-called essential nutrients, such as vitamins, minerals, fatty acids, and amino acids, required for normal human body function are dependent on exogenous sources from dietary origins, for example, due to the inherent inability to either biosynthesize those nutrients at all or at a scale that does meet the body's metabolic requirements. Moreover, some nutrients can also be conditionally essential when their relative biosynthetic capacity is lower than the metabolic demand due to specific life stages or disease conditions.

Several eating habits, such as diet rich in saturated fats and trans fats, are known to be associated with an increased risk of cardiometabolic disorders. Moreover, there is growing scientific evidence regarding the links between nutrients and complex multifactorial diseases [1]. It is thus probable that people's expectations from dietary and nutrient recommendation guidelines will continue to grow together with the increasing scientific knowledge between nutrition and health. Reference recommendations have been established to provide dietary values evaluated as sufficient to meet nutrient requirements in a population group [2]. However, due to the lack of a standardized approach for determining nutrient recommendations at the global scale, the terminology, sometimes referring to dietary reference values, recommended dietary allowances, recommended nutrient intakes, nutrient intake values, or dietary reference intakes, and the reference values for particular nutrients vary substantially between countries [3]. Reference nutrient values are usually defined at the population scale and are largely based on scientific associations between dietary intake and health or clinical outcomes. For instance, in Europe and North America, dietary reference intake is calculated from the average requirement of a single nutrient incremented by twice its standard deviation in order to cover 97.5% of the general population. This calculation assumes a statistically normal distribution for the nutrient of interest. Thus, whilst these reference systems have enabled guidance for consumer and regulatory authorities for optimal nutrient intake, one should acknowledge that they are based on reductionist scientific methodology, i.e. one nutrient being considered at a time.

From Reductionist to 21st-Century System Nutrition

Nutrition is a multifactorial process as nutrients are neither absorbed nor metabolized one at a time but as a complex mixture of thousands of chemical entities delivered from foods and beverages. Nutrient-nutrient or other interactions can occur during the digestion, which subsequently modulate nutrient absorption and bioavailability [4]. The iron and ascorbic acid (vitamin C) interaction is a typical example showing that the latter enhances the intestinal absorption of non-heme iron from the diet [5]. On the other hand, genetic polymorphisms are increasingly recognized as important determinants of the biology of nutrients in humans. The known mutation in the gene encoding for 5,10-methylenetetrahydrofolate reductase, considered a genetic factor for developing vascular disease, illustrates this gene-nutrient axis with a reduced enzymatic activity that associates with impaired levels of homocysteine [6]. Another example has recently been reported for the genetic variation in the vitamin D binding protein and circulating levels of vitamin D metabolites following vitamin D supplementation. Results showed that genetic variation in the vitamin D binding protein was associated with a different nutrition status, which was measured using circulating levels of 25(OH)D vitamers, following supplementation with vitamin D₃ but not with vitamin D₂ [7]. Levels of several liposoluble vitamins such as α -tocopherol, γ -tocopherol, α -carotene, β -carotene, lycopene, β -cryptoxanthin, lutein, and zeaxanthin could also be related to variants of genes involved in lipid metabolism [8]. Genome-wide association studies revealed that variants in transferrin and hemochromatosis genes significantly associated with serum transferrin levels [9]. When considering genetic variability in mammalian superorganisms, one should also consider the contribution of the extended genome carried by symbiotic partners such as the gut microbiota. Indeed, the gut microbiota interacts with the host via a broad spectrum of metabolic reactions, including processes involved in nutrient digestion and energy recovery from foods. The gut microbiota is also reported to be involved in the production of vitamins, such as vitamin K (menaquinone) and group B vitamins (biotin, pyridoxine, cobalamin, riboflavin, folates, thiamine, and nicotinic and pantothenic acids) [10]. Consequently, understanding interindividual peculiarities in nutrient status should also consider the possible variability in the gut microbiota composition and function.

Thus, isolating the biological effect of a single nutrient does not reflect what happens in a highly complex network of nutrient metabolic interactions that can occur in a mammalian superorganism such as the human being. This complexity may explain in part the current lack of molecular knowledge about nutrient and micronutrient acquisition, as well as their metabolism, compartmentalization across different cell types, transport, and mechanism of action on specific

cellular phenotypes. Therefore, one of the most important scientific challenges of the 21st century is to understand the way dietary nutrients are taken up, stored, mobilized, and utilized by the body both at the system and at the cellular levels. Such a scientific challenge can be addressed through a paradigm shift which combines the conventional reductionist approach with an integrated systems approach where the nutrient-body interactome can be properly captured with its inherent complexity. Similar to postgenomic sciences such as metabolomics and proteomics, systems nutrition is expected to provide new insights into understanding the interindividual nutritional peculiarities with the aid of high-resolution phenotypic profiling that would be based on comprehensive measurements of the nutrient status together with other clinical parameters. Nutritional phenotypes could be leveraged to better define nutrient requirements for groups of people sharing nutrient metabolic phenotypes, in shared environments with similar genetic backgrounds. The outcomes of this research are thus expected to pave the way towards personalized nutrition to maintain health and prevent disease [1].

The Path Towards the Next Generation of Targeted and Personalized Nutrition

A principal scientific challenge to enable systems nutrition is to make the multiple components of what is known as the nutritional status more standardized. High-resolution nutritional profiling can then be used as the hallmark of modern nutrition: to identify unmet nutrient needs, and guide dietary and/or lifestyle adaptations to meet specific nutrient demands, and finally as a monitoring platform to measure the success of personalized programs. Nutritional status combines multiple measurements ranging from the evaluation of nutrient intake, anthropometric and clinical assessments to the quantitative analysis of nutrient levels, or some of their related status and functional biomarkers, in biological samples such as blood and urine.

The choice of diet results from a decision process that integrates educational, cultural, and socioeconomic factors, taste and palatability perception, and known biological determinants such as food intolerance or allergy. Moving towards personalized nutrition will require a greater empowerment of people's dietary choices and their culinary and cultural habits so that specific nutrient requirements are fulfilled. Moving towards personalized nutrition for health and wellness requires a paradigm shift from today's nutrition towards empowerment of people on nutrition for health and wellness (fig. 1). This implies the development of novel holistic solutions for people that will assist them in decisions

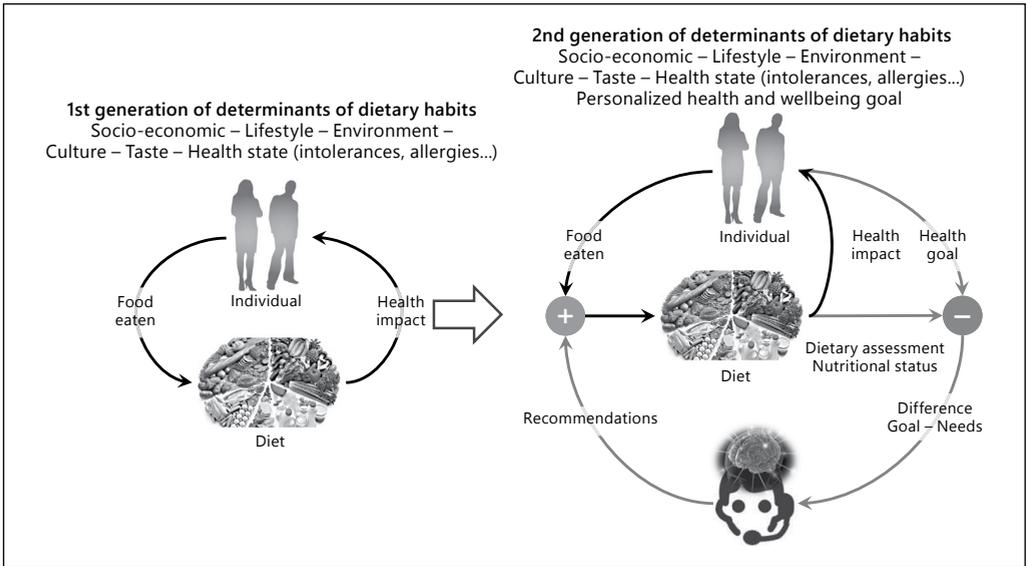


Fig. 1. Paradigm shift towards next-generation personalized nutrition.

for dietary adjustments to match their specific nutrient needs. To attain their ultimate goal for maintenance of optimal nutritional health, such solutions must be holistic, convenient, sustainable, and proven to be biologically effective for improvement of the nutritional status. The holistic aspect will require the discovery and integration of convenient and accurate nutrient intake and nutritional status assessments together with nutritional service and counseling offers as well as novel ways to produce, combine, and process whole foods and/or enhance their nutrient density with personalized nutrient fortification. A feedback loop to the person on his/her nutrient intake and nutritional status should be provided to demonstrate nutritional benefits of personalization through an intelligent recommendation engine (fig. 1). Empowerment of people would therefore require the integration of the three following components:

- (1) *Capability to intelligently assess the habits and nutrient density of the people's diet*
- (2) *Capability to effectively measure the nutritional status of people to identify unmet nutrient needs*
- (3) *Innovative mechanisms to deliver the needed or differential nutritional recommendations*

A convenient and holistic tool to assess people's dietary habits and nutrient intake is currently being developed as the Nutrition Health Concept (NHC). The NHC provides values relative to conventional dietary questionnaires through a method of scoring consumables, e.g. food/meals/diets, using a data-driven ap-

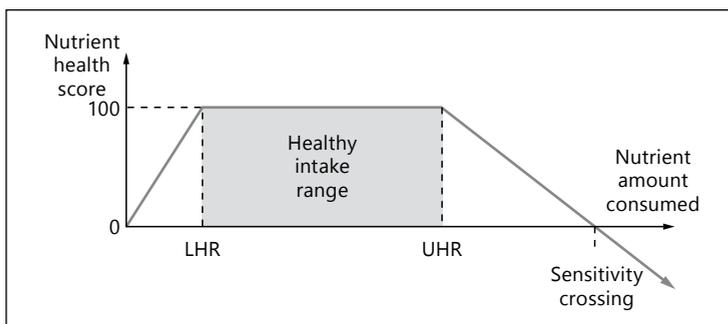


Fig. 2. An NHC score is designed by defining the nutrients to be included in the score, the lower (LHR) and the upper healthy range (UHR) and sensitivity crossing for each nutrient (as above) and the weights to perform a weighted average across all nutrient scores. A perfect NHC score = 100 is achieved when all individual nutrient health scores are within the consumed healthy range. Any nutrient or energy outside their healthy range will decrease the score depending on how far away from the healthy range the value is.

proach. The NHC defines nutritional health as consuming nutrients (broadly defined as the measurable components in food) within lower and upper healthy ranges. Those ranges are defined for each nutrient, including macro- and micro-nutrients, over a set period of time (i.e. 1 day or 1 week). Unlike other dietary assessment tools that classify nutrients into ‘good/bad’, ‘qualifying/disqualifying’, or ‘need to have more of/need to limit’ categories, the NHC does not depend on such a preclassification of foods. Basically, if all nutrients and even energy intake are given healthy ranges, then all nutrients and energy can be treated equally. A healthy range rather than a category determines the definition of nutrient health for the individual. As displayed in figure 2, each nutrient in an NHC score has a healthy range of consumption with both a lower healthy range and upper healthy range. Therefore, the NHC enables people to generate their nutrient and health score based upon their personal dietary choices. A perfect NHC score is indicated as 100 and is achieved when all individual nutrient health scores are within the consumed healthy range. One can then combine a set of foods so that the amount of all nutrients consumed fall within the targeted healthy range. As shown in figure 2, consumption outside the healthy range (low or high) will result in lower scores.

The design of the NHC provides thus a personalized scoring system that can be used to guide dietary recommendations to either maintain or enhance the health score to its optimal value. There is no singularly defined NHC score, but rather an infinite number of potential NHC scores that can be created based on the individual’s goals. As an example, a NHC score may be designed for a diabetic person who is trying to lose weight. In this case, the weight and sensitivity to the nutrient, sugar, might both be set high, and the caloric intake range lower,

which will drive nutritional recommendations accordingly. In another case, an individual may require more iron and protein consumption over a specified time and an NHC score can be designed to reflect the individual's needs and goals. When combined with the measurement of the individual's nutritional status, the NHC becomes an even more powerful dietary recommendation tool, because it takes the individual biological uniqueness of measured blood-based nutrient levels together with the diet consumed into account. With the feedback loop of nutritional status readouts, the NHC algorithm can then be further fine-tuned so that dietary choices can be optimized according to the individual nutritional response to specific dietary choices and nutrient intakes.

The field of biological analysis of the nutritional status is marked by the high number of different methodological protocols, which are often dedicated and optimized to either single or limited numbers of nutrients. Yet, technological advances in the field of analytics in both separation sciences, i.e. chromatography/detectors and mass spectrometry, open up unprecedented possibilities to resolve many nutrients in a single run while covering a fairly broad dynamic range of concentrations. Attempts to develop universal and standardized methodologies to quantitatively profile a spectrum of nutrients remain sporadic. Profiling of 16 trace elements in human serum was recently reported using inductively coupled plasma mass spectrometry [11]. Midttun et al. [12] recently published a method to quantify 10 molecular species related to vitamins B₆ and B₂ in human plasma using liquid chromatography coupled to tandem mass spectrometry. Priego Capote et al. [13] developed a method based on a similar technology to measure a series of 10 molecular species related to liposoluble vitamins and their metabolites in human serum. Nevertheless, the nutrition field has not benefited from a so-called 'one-stop shop' comprehensive profiling of nutrients encompassing minerals and trace elements, liposoluble and hydrosoluble vitamins, amino acids, fatty acids, and their related metabolites. This can be achieved using the centralization of multinutrient profiling methods. Such a nutrient profiling platform is foreseen to be a key enabler to modern systems nutrition by enhancing research possibilities to capture interindividual differences in nutrient status as a function of the genetic background, dietary habits, and health status (fig. 3). Applied in clinical studies, the analytical outcomes of such a platform will more holistically supply the nutrient determinants that may explain the degree of individual response to dietary or nutritional intervention, for example, thus opening up the way to identify more systematically specific nutritional requirements associated with health, disease, and environmental conditions.

In the future, it is expected that technological solutions for the biological analysis of nutritional status will evolve towards miniaturization enabling translation either into point-of-care diagnostics or, more long term, into wearable sensor

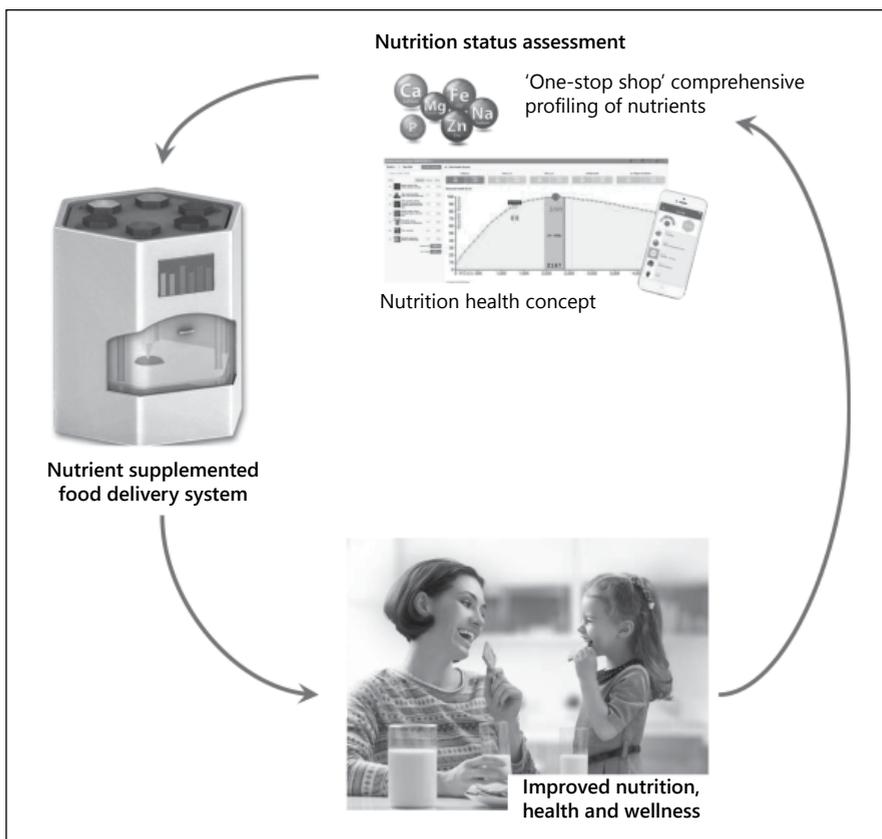


Fig. 3. The next generation of a comprehensive nutrient profiling platform for a personalized nutritional status.

technologies that will enable real-time feedback to people with information about their nutritional status. Technological evolution is also expected in the field of new food and nutrient delivery systems that will offer convenience and nutritional personalization of food and beverages to promote greater personalization of nutritional health with the longer-term ambition of slowing disease onset. The empowerment of nutritional health through application of simplified profiling systems has great promise for human health maintenance.

Disclosure Statement

S. Rezzi, E. Baetge and N. Bouche are employees of Nestlé Institute of Health Sciences and members of the Nestlé group; S. Solari is a former employee of Nestlé Institute of Health Sciences and member of the Nestlé group.

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