Getting a Grip on Complexity: Systems Nutrition

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The need to characterize the complexity of nutritional interactions

Malnutrition, either by lack or excess of nutritional components, poses challenges to global health. To improve nutrition-related health, there is a clear need to characterize the complexity of interactions between nutrients and the network of pathways, mechanisms, processes and organs that drive human health. Furthermore, it is evident that physical health is not a stand-alone aspect of nutrition-related health, but that mental and social health intimately interact with physical health. To move the global nutrition agenda forward, we advocate Systems Nutrition research using composite biomarkers of health and system intervention models covering the relevant physiological, mental and social domains.

Introduction

Over the past century, our understanding of the role of nutrition, including that of micronutrients, in relation to health has made tremendous progress. This was primarily achieved by a combination of epidemiological studies assessing micronutrient intakes and experiments *in vitro* and *in vivo* focusing on single targets or pathways affected by single micronutrients. As a result, significant progress has been made in meeting the need of numerous populations for vitamin A, zinc, iodine, and omega-3 fatty acids,[1] resulting in sufficiency in intake and status for these micronutrients and associated improvements in health status in large parts of the world.

Despite this progress, however, there is still a great need for further improvements in global health. More adequate nutrition could be a major contributor here. In order to achieve this, we must gain insights into the functional relationships between micronutrients and the complexity of biological processes that need to function optimally and in coherence so as to support the maintenance of health in the context of a specific environment (**Figure 1**). In the first instance, this needs to be done for physiological processes, but it also touches upon mental and socio-economic aspects. Nutrition research should thus evolve into a systems view towards measurements of the micronutrient status and health of people, as well as a systems modeling approach to interventions, taking the cultural and social context into consideration.

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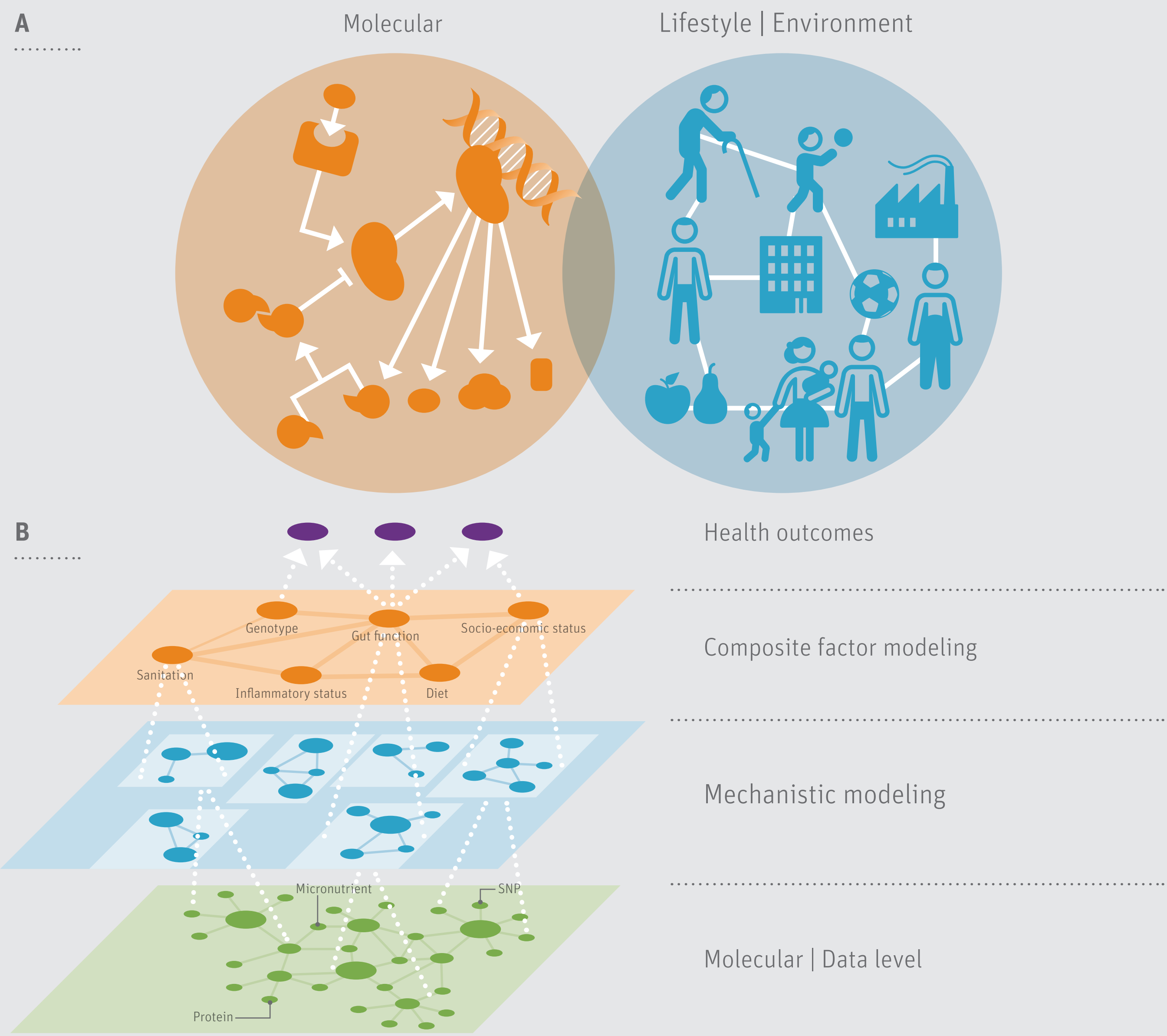
Micronutrient-supported metabolic health

Providing scientific evidence of the beneficial or detrimental relationships between dietary components and health has proven difficult. This is partly due to the subtleties of the effects of diet on health, but a more fundamental cause lies in the design of studies and the biomarkers used to determine health effects. Currently, substantiation is based on demonstrating that diet, or dietary ingredients, prevent(s) specific diseases by reducing disease risk biomarkers or surrogate endpoints derived from dietary intervention studies and epidemiological studies – in other words, it is based on the link of dietary components to the absence of disease.

There is a growing awareness that health is not merely the absence of disease but also involves adaptation to continuously changing environmental conditions. New definitions of health

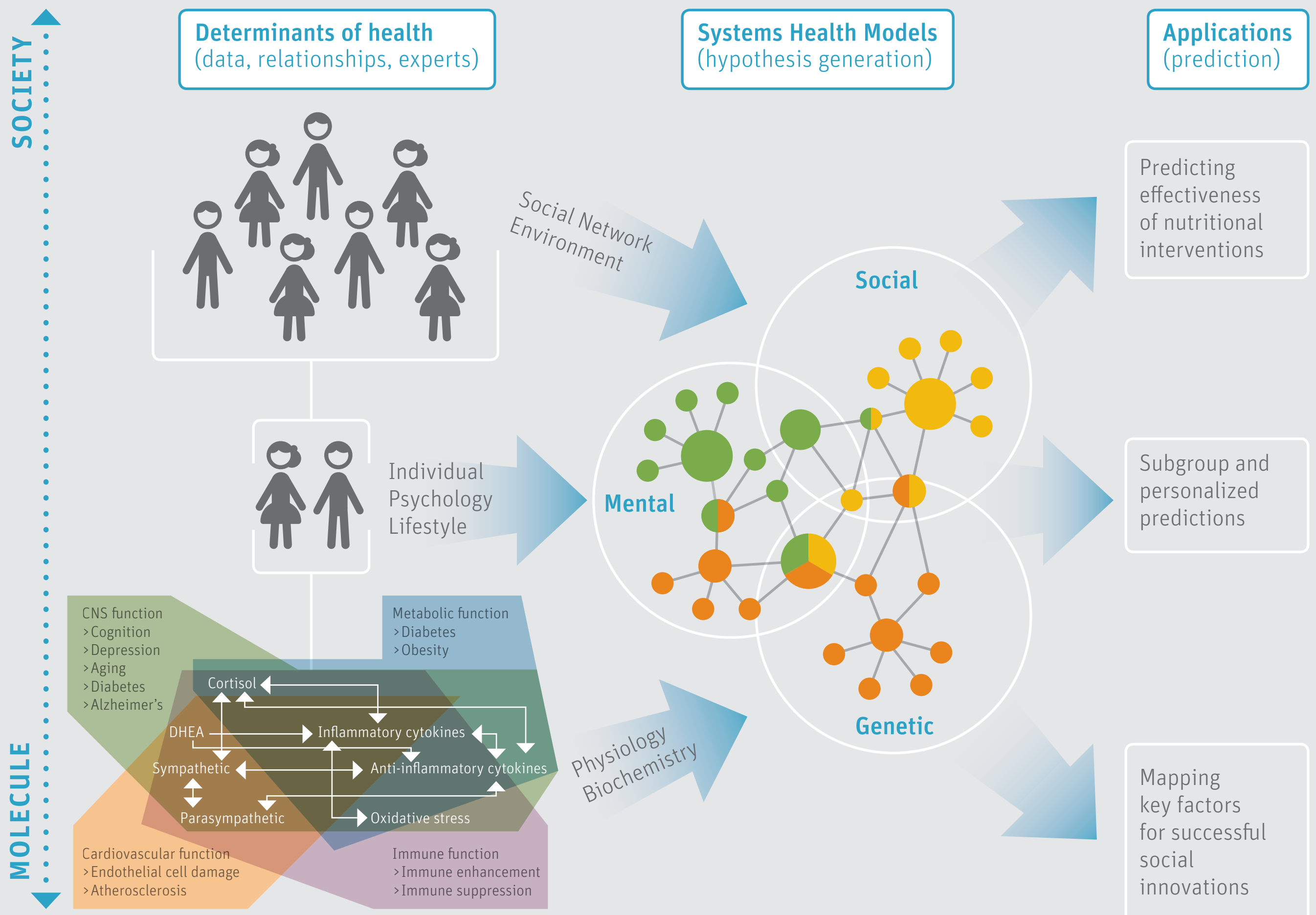
FIGURE 1: Health defined by gene-environment interaction. As the impact of nutrition on health and disease is defined by genetics and molecular pathways in close interaction with environmental factors, in-depth understanding and subsequent intervention developments necessitate an integrated view of both domains (**A**). This integrated view can subsequently be captured in multi-level models driving the identification of biomarkers (**B**).



emphasize the ability to adapt and self-manage in the face of physical, social and emotional challenges.[2] In the physiological domain, a healthy organism is capable of maintaining physiological homeostasis through changing circumstances, which is termed “allostasis”.[3] In the context of metabolic health, we term this ability to adapt “phenotypic flexibility”.[4]

Chronic stress may induce adaptation processes that go beyond the limits of normal phenotypic flexibility, leading to progressive inflexibility, which in turn contributes to the onset of disease. An excess or lack of food components in the diet introduces challenges to phenotypic flexibility. Micronutrients and bioactives play key roles in mechanisms underlying phenotypic flexibility, while excess of energy, high glucose and fructose intakes or certain trans-fatty acids cause a decline in phenotypic flexibility. Micronutrients are involved in many specific biochemical pathways with dedicated functions in the organism, which have mostly been studied in isolation. They act as co-factors in metabolic homeostasis (e.g., B vitamins) and in enzymes of importance for defense mechanisms (e.g., Se, Zn, Cu, Fe). Furthermore, they have antioxidant function (vitamins C and E), exert

FIGURE 2: Systems health models to get a grip on the complexity of nutrition. Comprehensive diagnoses of the problem at multiple levels of organization are integrated into systems health models. The models allow the simulation and optimization of systems nutrition intervention strategies.



an anti-inflammatory action (essential polyunsaturated fatty acids EPA, DHA), or are involved in hormonal regulation (iodine). These pathways and functions are interconnected in complex metabolic networks, driving overarching processes of metabolism, oxidation and inflammation that need to function optimally for maintaining optimal health. Together, this well-orchestrated machinery allows the organism to adapt to the continuously changing environment, of which food itself takes a major share, or to maintain phenotypic flexibility.

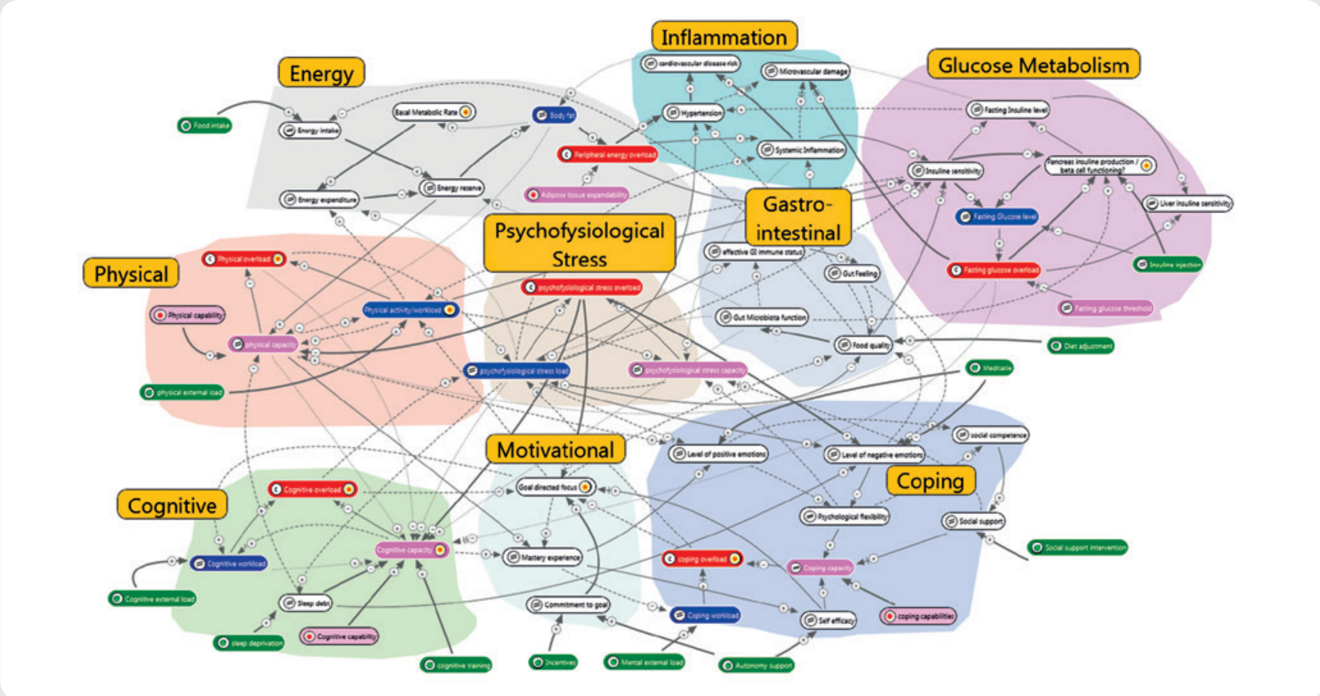
Biomarkers of health

As indicated above, many of the current insights into micronutrient-related health are based on epidemiological studies reporting a combination of estimated micronutrient intake, biomarkers of micronutrient status – which often do not reflect actual body pools of micronutrients – and biomarkers associated with disease or disease risk. The literature reviewed typically reports on group averages, often not taking into consideration aspects such as genetic background, gender, age, nutritional status including micronutrient status, food intake, physiological status, psychological stress and physical activity.

Human health is based on a complex network of interactions between pathways, mechanisms, processes and organs. Many of these processes have to function in a continuously changing environment (diet, infections, stress, temperature, exercise etc.), and thus strive to maintain internal homeostasis by adapting to these changes.[4] Due to a wide variety of reasons (genetic, epigenetic, exposure, diet, stress, exercise etc.) individuals differ in their "wiring" of phenotypic flexibility and therefore will react differently to acute and chronic stressors and develop a personal trajectory of metabolic-inflammatory health and disease.[4]

Acknowledging the importance of maintaining phenotypic flexibility as a key feature to optimal health calls for new research on the relationship between nutrition and health, in

FIGURE 3: Example of a systems model for intervention simulation. The model depicted, based on the MARVEL methodology,[8] describes key variables and their qualitative and semi-quantitative interactions in multiple domains relevant to metabolic health. This example was built based on actual data as well as expert knowledge input.



particular using "biomarkers of health", related to the dynamics of the regulatory processes concerning the processes described above. These "biomarkers of health" would ideally comprise key molecules in all pathways, making up the overarching processes of relevance to phenotypic flexibility. As such, multi-biomarker panels will emerge that act as composite descriptors of physiological processes.

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For example, in the case of vascular health, such a composite marker could be composed of flow-mediated dilation, a functional marker of endothelial function and blood pressure, resilience markers for endothelial damage after a metabolic challenge test such as sVCAM, sICAM, and E-selectin response, and total cholesterol.[5] Furthermore, these markers can be complemented with specific single nucleotide polymorphisms (SNPs) related to increased risk of cardio-metabolic disease development. By combining this into an integrated readout, a flexibility marker for vascular health can be obtained that has a broader value, both for substantiating the effects of food and nutrition on health and for healthcare.

Systems intervention models

In addition to improving the understanding of interactions of micronutrients with molecular pathways, the investigation of the interaction of environmental factors affecting phenotypic flexibility processes is a key step envisioned in bringing the understanding of global nutritional health to the next level. Environmental factors such as excess calories, poor sanitation, and mental stress have been known to affect physiological processes important for maintenance of phenotypic flexibility and, as such, health. This can be achieved by in-depth assessment of metadata for each nutritional study and the subsequent use of these data in combination with all available molecular and clinical data in complex data analysis approaches using state-of-the-art bioinformatics and multi-level modeling.[6]

The insights derived from these approaches will not only help to bring about scientific understanding of micronutrient-health relationships, but should also lead to better interventions aimed at improving global health. We have recently proposed a program called Essential Nutrients for Optimal Underpinning of Growth and Health (ENOUGH) for the application of systems nutrition in global nutrition.[7]

In this respect, the key to moving the global nutrition agenda forward is to adopt the paradigm that physical health is not a stand-alone aspect of nutrition-related health, but that mental and social health intimately interact with physical health (**Figure 2**). Malnutrition is a complex issue, arising from the interplay between many individual, social, and political factors. This intrinsically implies that deriving effective intervention programs not only requires biological knowledge of the interaction of nutrients with pathways underlying health and disease, but also needs a sound understanding of the nutrition-health relationship in the context of the environmental drivers of the other aspects of health.

In addition to many non-linear interactions, there are multiple feedback loops between, and different time scales for, each of these drivers. This makes it hard to derive optimal interventions by simply looking at the data-driven models. Recent developments in qualitative/semi-quantitative modeling may open ways to generate intervention simulation models describing the nutrition-health interactions, including all relevant drivers and potential success determinants. Building such a model starts with the mapping of all relevant relationships, including strengths and speeds.

This mapping is based on the exploration of perspectives of all relevant stakeholders to identify all important factors. As stakeholders are building towards a shared understanding, this process, called group model building, will facilitate future discussions on implementation of interventions. Subsequently, this map is turned into a model with the presence of reinforcing loops and balancing loops. Reinforcing loops indicate processes that can get out of control quickly, while balancing loops indicate processes which are stable under certain conditions (**Figure 3**). This reveals which factors cause large changes and might be important to measure, control and possibly intervene in.

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This model will allow the stakeholders to simulate the effect of multiple combinations of interventions on a set of defined goals. The simulated intervention effects depend on all the relationships, with their specific strengths and speeds, which are present in the model. Although the output of these simulations is understandably hypothetical, it may be a starting-point for selecting the high-potential interventions in a given setting, as well as identification of key aspects to address so as to allow for an optimal and sustainable intervention result.[8]

Concluding remarks

Without doubt, the reductionist approach towards understanding the mechanisms and health effects of individual micronutrients has greatly impacted global nutrition-related health. The current state of data generation and data analytical technologies enables the generation of insights into the complexity of interactions between nutrients and physiology. This will lead to identification of biomarkers of health that will allow harmonization of Systems Nutrition studies that will feed into generically applicable systems interventions models. We strongly believe that getting a grip on complexity is the next essential step towards a healthier world.

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