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Diet, blood pressure and heart disease - precision nutrition approaches to understand response to diet and predict disease risk

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Before the start of the epidemiological investigations of the Framingham study in 1949, hypertension was considered a benign condition. As blood pressure was likely to increase with age, high blood pressure was considered normal in the elderly. It was therefore deemed appropriate to '*ignore labile and systolic elevations of blood pressure*' (1). Seventy years later, we have learned that hypertension risk does not diminish with age, and stratified risks have been characterized for different population and age groups (1). Hypertension is currently considered a major global public health problem, with increased systolic and diastolic blood pressure representing one of our most important risk factors for atherosclerotic cardiovascular disease (1). We have also learned that the risk and management of hypertension can be significantly improved by lifestyle and diet. Dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH), Nordic and Mediterranean diets, generally rich in fruit, vegetables, whole grains, legumes, seeds, nuts, fish and low-fat dairy foods, and low in red meat, sugar-sweetened foods/beverages and alcohol, have been shown to significantly lower average levels of systolic and diastolic blood pressure in populations in randomized controlled trials (2). But many of these randomized controlled trials have also demonstrated that less than half of the population may effectively respond to a dietary intervention (3). To elucidate who responds to which dietary interventions, and understand why, it is imperative to advance the application of precision nutrition approaches.

In the past decades, a range of novel technological tools, including metabolomics, transcriptomics, proteomics, and metagenomics, have been developed to investigate the interactions between nutrition and the host metabolome, genome and proteome. These studies have already played an important role in enhancing our understanding of the actions of diets, foods and nutrients on the cellular level (4). Increasingly, nutrigenomic approaches are also being applied to identify existing and novel efficacy biomarkers that can be used to improve the prediction of (early) disease development, or to monitor how populations and individuals respond to diets. An elegant example of this has been published in the current issue of the American Journal of Clinical Nutrition (5), where a combination of baseline and postprandial clinical and metabolomics markers were analyzed in healthy subjects with and without subclinical atherosclerosis in an Asian population. Models were trained using a range of methodologies, to produce a novel model based on postprandial systolic or diastolic blood pressure and age to detect subclinical atherosclerosis in a low coronary heart disease risk group (5). This study highlights the importance of finding more sensitive biomarkers that can detect early-stage disease development. This is a stage when nutrition could make a significant impact, but where mechanistic pathways are often poorly understood. It also highlights the importance of including postprandial measurements, including postprandial blood pressure, since monitoring metabolic changes after a glucose, lipid or mixed meal challenge, rather than relying on baseline or fasting measurements alone, may deliver better predictors of health or disease status, especially in low-risk populations (6).

From a nutritional perspective, an important next step would be the identification of existing or novel efficacy biomarkers that can help to predict which individuals or population groups may respond more or less favorably to a specific diet. Thus far, the variability in blood pressure (or indeed other cardiovascular risk factors or biomarkers of disease) between and within subjects has often obscured the precise relationship between diets and clinical disease outcomes in randomized controlled trials. However, across studies, an important finding has been that the inter-individual variability in such risk factors is often higher than their intra-individual variability, and this concept could be exploited when trying to understand individual responsiveness to interventions in precision nutrition (4). Indeed, for some trial designs in the field of precision nutrition, such as N-of-1 studies, the capture of variation in, for example, blood pressure or dietary intake outcomes, by taking multiple measurements over time, will allow the development of unique regression models that consider the influence of individualized predictors on a health or disease outcomes (7). Data from longitudinal studies that include postprandial measurements (to catch the phenotypic flexibility of individuals as an early marker of disease status), and those that exploit metabolomics platforms (to expand the number of clinical and biochemical outcomes), in hundreds rather than tens of subjects (to have sufficient statistical power for model development, particularly when considering many candidate biomarkers), will be instrumental in enabling the examination of individual responsiveness when further developing the field of precision nutrition (4). Provided we are able to take enough measurements on the individual level, and develop accurate and sophisticated prediction models on the basis of well-powered, large scale studies, we may be able to predict, with reasonable accuracy, whether a given individual will respond favorably to a specific diet.

The NIH has established a timely vision for the research field of precision nutrition to develop more precise, targeted and individualized dietary interventions and guidelines (8). An aspiration could be that in the future, precision nutrition approaches may enable the identification of dietary interventions which, for certain individuals or population groups, may be equally if not more effective than a mainstream pharmacological intervention to modulate disease risk. This is not an inconceivable scenario. For blood pressure, for example, a series of studies have already proven that intervention with riboflavin, a cheap and readily available B vitamin, lowers blood pressure in cardiovascular disease patients that are homogenous for the MTHFR 677C→T polymorphism. These patients have significantly higher baseline blood pressure levels, and intervention with riboflavin will thus decrease their genetic risk of hypertension. Interestingly, in this group, riboflavin supplementation works, on average, as effectively as administering ACE inhibitors (9). Such findings may shift the way we consume diets and nutrients, and the way we provide (preventative) healthcare in relation to blood pressure and other conditions.

References

(1) Kannel WB. Fifty years of Framingham Study contributions to understanding hypertension. *Journal of Human Hypertension* 2000;14(2):83–90.

(2) Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Dietary patterns and blood pressure in adults: a systematic review and meta-analysis of randomized controlled trials. *Advances in Nutrition* 2016;7(1):76–89.

(3) Tierney AC, McMonagle J, Shaw DI, Gulseth HL, Helal O, Saris WH, Paniagua JA, Golabek-Leszczynska I, Defoort C, Williams CM, et al. Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome—LIPGENE: A European randomized dietary intervention study. *International Journal of Obesity* 2011;35(6):800–809.

(4) Brennan L, de Roos B. Nutrigenomics: lessons learned and future perspectives. *American Journal of Clinical Nutrition* 2021;113(3):503–516.

(5) Valsesia A, Egli L, Bosco N, Magkos F, Ching Kong S, Sun L, Jen Goh H, Weiting H, Arigoni F, Khee-Shing Leow, et al. Clinical and omics-based models of subclinical atherosclerosis in healthy Chinese adults: A cross-sectional study. *American Journal of Clinical Nutrition* 2021;[*tbc*].

(6) Krug S, Kastenmüller G, Stückler F, Rist MJ, Skurk T, Sailer M, Raffler J, Römisch-Margl W, Adamski J, Prehn C, et al. The dynamic range of the human metabolome revealed by challenges. *FASEB Journal* 2012;26(6):2607– 2619.

(7) Potter T, Vieira R and de Roos B. Perspective: Application of N-of-1 Methods in Personalized Nutrition Research. *Advances in Nutrition* 2021:12(3):579-589.

(8) 2020–2030 strategic plan for NIH nutrition research: A report of the NIH Nutrition Research Task Force. NIH; 2020 [Internet]. Available form: https://www.niddk.nih.gov/about-niddk/strategic-plans-reports.

(9) Wilson CP, Ward M, McNulty H, Strain JJ, Trouton TG, Horigan G, Purvis J, Scott JM. Riboflavin offers a targeted strategy for managing hypertension in patients with the MTHFR 677TT genotype: a 4-y follow-up. American Journal of Clinical Nutrition 2012;95(3):766-72.