METABOLISM

Do diet and microbes really 'PREDICT' cardiometabolic risks?

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It is commonly accepted that dietary habits and cardiometabolic disorders are connected to the composition of the gut microbiota. However, can we really generalize and predict health by screening faecal microorganisms? A study has taken the plunge and identified a vast range of correlations supporting this possibility.

Refers to Asnicar, F. et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* https://doi.org/10.1038/s41591-020-01183-8 (2021).

Dietary habits are associated with the development of obesity and/or type 2 diabetes mellitus (T2DM), which are common risk factors for cardiovascular disease (CVD). Moreover, when diet is involved, the gut microbiota is complicit. Considerable interest has therefore focused on the role of human gut microbiota in health, CVD and metabolic disorders. Accumulating evidence from in vivo experiments in rodents has revealed that intestinal microbiota has an important role in health and metabolic disorders[1]; however, when it comes to humans, the role of the microbiota in (metabolic) diseases is unclear. Contrary to studies using rodents, defining interrelationships between diet, the microbiome and disease in large-scale human studies has proved difficult and faces problems of reproducibility. Notably, human studies are burdened with many confounding factors that are continuous sources of variability, which make it difficult to disentangle cause and effect[2].

In an impressive effort to overcome these issues, Asninar, Berry and colleagues[3] took nutritional investigation to the next level with their Personalized Responses to Dietary Composition Trial (PREDICT 1). This study aimed to quantify and predict individual variations in metabolic repsonses to standardized meals by deciphering diet–microbiome interactions in metabolic health. The researchers used in-depth nutritional assessments with standardized dietary challenges over 14 days, intensive in-clinic biometric and blood measures, habitual dietary data collection, continuous glucose monitoring and stool shotgun metagenomics sequencing for taxonomic and functional profiling of the microbiota. More than 1,000 participants have been recruited, with a UK discovery cohort ($n = 1{,}002$) and a validation population from the USA ($n = 100$). The study also included 480 identical and non-identical twins.

Among the numerous results, the study confirms that genetics have only a minor role in determining an individual nutritional response and that this response is very personalized[3]. In 56 of the 295 tested correlations, a statistically significant association was found between the structure of the microbiome and diet, personal characteristics and metabolic parameters (FIG. 1). As previously observed in other human studies[4,5], microbiota species richness was inversely associated with BMI, visceral adipose tissue mass and predicted hepatic steatosis. By contrast, species richness was positively correlated with cardiometabolic risk factors such as HDL cholesterol. In addition, PREDICT 1 also uncovered associations between microbiome richness and some emerging cardiometabolic biomarkers, including lipoprotein particle size and glycoprotein acetyl (an inflammatory biomarker)[3].

A strength of this study is that, rather than focusing on single nutrients, different diets were divided into four categories, based on whether they are plant-based or animal-based and on whether they are considered 'healthy'[3]. A healthy diet was defined as one that contained a mix of foods associated with a decreased risk of chronic disease. The authors found tight correlations between microbial composition and the different categories of diet. They also identified a panel of 15 gut microorganisms associated with decreased risks and 15 with increased risks for certain diseases, such as obesity and T2DM. Surprisingly, the strongest microbiome–habitual diet associations were driven by poorly characterized microorganisms, which strongly suggests that our knowledge of the bacteria — and their metabolic functions[6] — that can contribute to health is still far from complete.

> "the segregation of gut microorganisms into favourable and unfavourable clusters remains challenging"

Another interesting finding is that both *Prevotella copri* diversity and the presence of *Blastocystis* spp. (unicellular eukaryotic parasites) are markers of improved postprandial glucose responses[3]. Although *P. copri* was present in only 29.8% of the study population and *Blastocystis* spp. in 25.7%, both were strongly linked with favourable glucose homeostasis and decreased estimated visceral adipose tissue mass. However, the role of *P. copri* remains controversial as it has been linked with both beneficial or deleterious effects depending on the dietary situation[1]. This difference illustrates why the segregation of gut microorganisms into favourable and unfavourable clusters remains challenging, even when exploiting highly powerful bioinformatic tools. Indeed, according to the heterogeneity of the food source (healthy or unhealthy, animal or plant), diet quality (processed versus unprocessed) and dietary patterns, the authors clearly highlighted in their study[3] the importance of looking beyond nutrients and single foods in diet–microbiome research.

Of course, the key question of whether these 'novel' taxa are also causally linked with the metabolic phenotype observed still remains. Indeed, strong correlations,

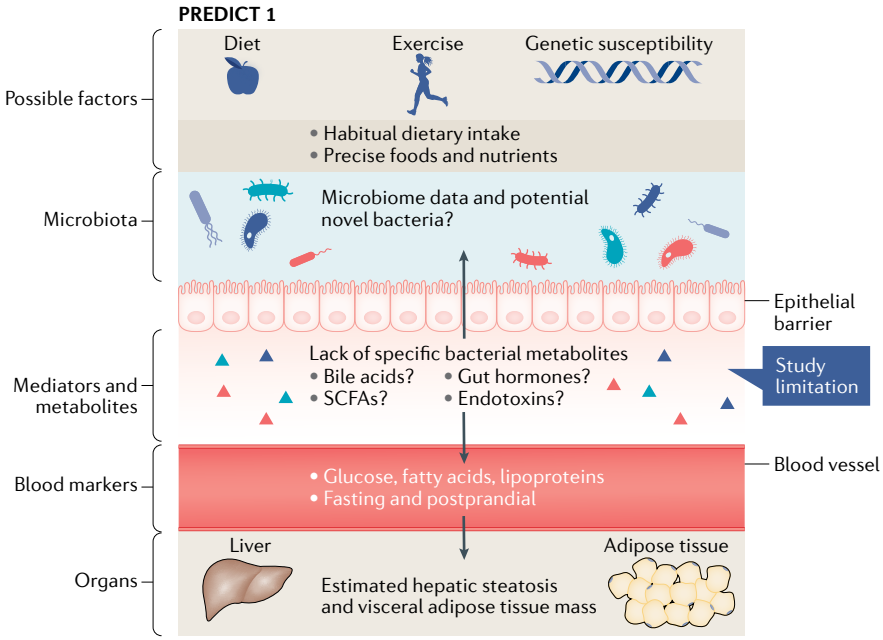

Fig. 1 | **Complex relationships between gut microorganisms, diet and host metabolism.** The PREDICT 1 study is fulfilling numerous key steps required to estimate and appreciate the role of complex and intertwined dialogues between the microbiota and its metabolites, diet and human metabolism. SCFAs, short-chain fatty acids.

even when repeatedly observed in different studies, are no guarantee for causality, as has been demonstrated by studies of *Subdoligranulum* spp.[7] and *Akkermansia muciniphila*[8]. *A. muciniphila* has been clearly causally associated with beneficial effects in proof-of-concept studies, whereas *Subdoligranulum* spp. are strongly correlated but apparently not causally associated[7,8].

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In the present study[3], microbiome-based machine learning models for selected clinical and emerging cardiometabolic biomarkers were developed to explore the connections between gut microorganisms and cardiometabolic factors. The researchers found modest concordance between microbiome models and different traditional clinical fasting cardiometabolic biomarkers. In fact, the gut microbiome was a poor predictor for postprandial glucose levels, which are mainly dependent on meal content. By contrast, postprandial triglycerides and insulin concentrations were highly predicted by the microbiota analysis. Strikingly, the authors argued that this finding was mainly due to the fact that individuals consume multiple mixed-nutrient meals throughout the day and spend most of their waking hours in the postprandial state. Although this hypothesis is probably correct, from a mechanistic point of view, we cannot exclude that postprandial differences might also be due to the different effects of the gut microbiome on important bioactive lipids, the bile acids. These are directly affected by both the diet and the microbiota composition and influence lipid absorption as well as energy metabolism[9] (FIG. 1). In other words, one might argue that the signatures observed in the present study are corresponding to the lowest common denominator rather than the real effectors. Therefore, are we not seeing the wood for the trees by using these bioinformatic approaches?

Of note, there are probably many other metabolites (for example, short-chain fatty acids, 3-indolepropionic acid or imidazole propionate) that are produced or at least affected by microbial activity and could be linked to the different metabolic responses observed in this study but that were not investigated (FIG. 1).

The PREDICT 1 study[3] represents the first diet–microbiome study to identify both individual components of the microbiome and an overall gut microbial signature associated with multiple measures of dietary intake and cardiometabolic health. The different signatures were reproduced across both UK and US populations but also multiple previously published studies.

In conclusion, this study is very complex, well performed, highly informative and represents a major step forward in personalized nutritional guidance. However, this study also highlights the current limitations due to the lack of 'evidence-based microbiome' studies. An obvious need exists to investigate diet–microbiome interactions at a higher resolution. We are excited to see what the PREDICT 2 (recently completed and adding another 1,000 participants in the USA) and PREDICT 3 (launched in 2020) will bring (such as weighed food record data).

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Competing interests
P.D.C. is the inventor on patent applications dealing with the use of *A. muciniphila* and its components in the treatment of metabolic disorders. P.D.C. is co-founder of A-Mansia biotech SA.