Diets, nutrients, genes and the microbiome: recent advances in personalised nutrition

Nathan V. Matusheski1*, Aoife Caffrey2, Lars Christensen3, Simon Mezgec4, Shelini Surendran5, Mads F. Hjorth3, Helene McNulty2, Kristina Pentićeva2, Henrik M. Roager3, Barbara Koroušić Seljak6, Karani Santhanakrishnan Vimalaswaran5, Marcus Remmers7 and Szabolcs Péter8

1Nutrition Science and Advocacy, DSM Nutritional Products LLC, Parsippany, NJ, USA
2Nutrition Innovation Centre for Food and Health (NICHE), School of Biomedical Sciences, Ulster University, Coleraine BT52 1SA, Northern Republic of Ireland
3Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Rolighedsvej 26, 1958 Frederiksberg, Frederiksberg, Denmark
4Jožef Stefan International Postgraduate School, Jamova cesta 39, 1000 Ljubljana, Slovenia
5Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences, University of Reading, Whiteknights, Reading RG6 6DX, UK
6Computer Systems Department, Jožef Stefan Institute, Jamova cesta 39, 1000 Ljubljana, Ljubljana, Slovenia
7Koninklijke DSM N.V., Geleen, The Netherlands
8Nutrition Innovation Center, DSM Nutritional Products Ltd, Kaiseraugst, Switzerland

(Submitted 13 July 2020 – Final revision received 13 January 2021 – Accepted 23 January 2021 – First published online 29 January 2021)

Abstract

As individuals seek increasingly individualised nutrition and lifestyle guidance, numerous apps and nutrition programmes have emerged. However, complex individual variations in dietary behaviours, genotypes, gene expression and composition of the microbiome are increasingly recognised. Advances in digital tools and artificial intelligence can help individuals more easily track nutrient intake and identify nutritional gaps. However, the influence of these nutrients on health outcomes can vary widely among individuals depending upon life stage, genetics and microbial composition. For example, folate may elicit favourable epigenetic effects on brain development during a critical developmental time window of pregnancy. Genes affecting vitamin B12 metabolism may lead to cardiometabolic traits that play an essential role in the context of obesity. Finally, an individual’s gut microbial composition can determine their response to dietary fibre interventions during weight loss. These recent advances in understanding can lead to a more complete and integrated approach to promoting optimal health through personalised nutrition, in clinical practice settings and for individuals in their daily lives. The purpose of this review is to summarise presentations made during the DSM Science and Technology Award Symposium at the 13th European Nutrition Conference, which focused on personalised nutrition and novel technologies for health in the modern world.

Key words: Personalised nutrition; Epigenetics; Folate; Vitamin B12; Obesity; Microbiome; Deep learning

Although most dietary recommendations today are based on population averages, it is now possible to identify population sub-groups, and even individuals, who may benefit from modified nutrition guidance. As technology continues to advance, it is becoming easier for individuals to determine when they may be at increased risk for disease or a nutritional deficiency. They can access commercially available tools that provide precise guidance relevant to their genetics, phenotype and preferences(1). However, personalised nutrition approaches, such as consumer nutrigenetics testing, have come under scrutiny(2). Such systems require robust scientific substantiation, as recently described in a set of guiding principles(3) and outlined by the Academy of Nutrition and Dietetics for application to dietetic practice(4). Over the past several decades, it has become increasingly clear that a complex set of interactions exist among the genetic and environmental variables affecting individual responses to diet and lifestyle behaviours. Since the early 1990s, candidate gene studies have identified several genetic variations which have
led to the understanding of the pathophysiological mechanisms and pathways that underlie complex diseases(3). In the last 15 years, significant advances have been made through genome-wide association studies, with the discovery of several novel loci for complex traits(3). However, these studies have shown that only a small amount of individual variability can be explained by genetics alone(3). More recently, a holistic view has emerged regarding the interaction of genetics and other individual factors(40). Such interactions can be behavioural, like the relationships between individuals and their food preferences and dietary intake, or physiological, such as genotype or microbiome. These interactions, and the underlying individual variations that drive them, play a significant role in personal health and well-being over time. However, they also challenge our existing approaches to research and complicate the application of research findings for the development of personalised nutrition guidance.

In this paper, we review four recent advances in the field of personalised nutrition that can lead to an improved understanding of individual health: (1) the influence of epigenetic changes and gene expression on cognitive function in early life, (2) the association genotype with nutrient status and corresponding metabolic responses in the context of obesity, (3) the relationship of gut microbial composition (enterotype) with the efficacy of fibre-rich dietary interventions for body weight management and (4) advanced technologies such as deep learning to improve the accuracy of dietary intake measurements. By examining these sources of inter-individual variability, and considering their possible interactions, we can better understand the nuances of individualised guidance and better define future research approaches to advance both personal and public health.

**Folate during pregnancy, epigenetic changes and child health outcomes**

Maternal nutrition during pregnancy is essential for optimal offspring development, reducing lifelong disease burden and optimising health throughout life(35). In particular, folate is required for one-carbon metabolism, a network of metabolic pathways involved in nucleotide synthesis, DNA repair and numerous methylation reactions(39). In early pregnancy, there is conclusive evidence that periconceptional folate acid supplementation prevents neural tube defects(11,12). Maternal folate supplementation may also affect neurocognitive development in early life(39). This section focuses on the evidence linking folate nutrition in pregnancy, DNA methylation changes and health outcomes in the child.

**Folate, DNA methylation and brain development during pregnancy**

Inadequate folate intake can interfere with early brain development and function, the consequences of which can vary depending on the timing of the deficiency relative to the development of the neurological structures(14). The third trimester of pregnancy until 2 years after birth is a critical period of rapid growth and development of some regions of the brain such as cortical and subcortical grey matter(35). Therefore, the continuation of folic acid supplementation beyond the first trimester (after the recommended period for the prevention of neural tube defects) may optimise folate status for prenatal brain development(14,16). As such, maternal folate insufficiency appears to influence the developing brain(17), which may result in lasting changes in child brain function(19).

The effect of folate nutrition during pregnancy on health outcomes in the child is thought to involve the essential role of folate in one-carbon metabolism, which may impact neurodevelopment(10,16). Folate-related epigenetic changes, and specifically DNA methylation, have been proposed as a plausible mechanism underpinning associations between maternal folate nutrition and various offspring health outcomes(39). Epigenetic processes, including histone modifications, RNA interference and DNA methylation, involve changes to the genome that can alter gene expression without changing the underlying DNA sequence(20). Early life development, ranging from preconception to childhood, is considered to be a critical window of the lifecycle, characterised by rapid DNA methylation changes, susceptibility to environmental factors and programming of epigenetic marks that may have lasting health effects in infants born to mothers with inadequate nutritional status(21).

Observational studies have reported that folate acid supplementation by women during pregnancy was associated with changes in DNA methylation patterns of candidate genes in cord blood(22), with decreased methylation of LINE-1 and PEG3 and increased methylation of IGF2 in cord blood(23) and offspring(24). However, associations between maternal folate exposure and the offspring methylome have been inconsistent(25).

The Folic Acid Supplementation in the Second and Third Trimester (FASST) trial is thus far the only randomised trial of folate acid supplementation in pregnancy examining DNA methylation and maternal folate and homocysteine responses and related effects in the newborn(26). In an analysis of biobanked samples from this trial, changes were found in DNA methylation of LINE-1 and candidate genes related to brain development such as IGF2 and BDNF, in the newborns of mothers who received folic acid(27). Using an epigenome-wide (EWAS) approach, changes in newborn DNA methylation at the imprint regulator ZFP57 were also shown(28).

**Cognitive performance in offspring related to folate nutrition in pregnancy**

Several observational studies have shown positive associations between self-reported folate acid supplement use in early pregnancy and childhood neurodevelopmental outcomes such as language delay, cognitive function score and verbal and motor function(29–31). Likewise, clinical studies have reported reduced cognitive ability in the offspring of mothers with suboptimal folate status(32,33). Over 40 years ago, Gross et al.(34) showed that children born to mothers with diagnosed folate-related megaloblastic anaemia in the third trimester of pregnancy had abnormal neurodevelopment and lower intellectual abilities(34). Several decades later, a longitudinal study of 256 mother–child pairs linked maternal folate deficiency in later pregnancy with reduced brain volume in the children aged 6–8 years, as measured using MRI(35). However, the evidence is inconsistent, as
other observational studies have found no significant associations of folate status in pregnancy with cognitive performance or infant neurodevelopment.

The few very randomised trials conducted to date in this area have investigated the effect of multiple micronutrient supplements, not folate supplementation alone. The FASSTT Offspring trial studied the effect of folic acid supplementation during the 2nd and 3rd trimesters on the subsequent cognitive performance of the child using validated assessment tools. The children of folic acid-treated mothers scored significantly higher than the placebo group in several cognitive domains at 3 and 7 years. When compared with nationally representative samples of British children at 7 years, test scores were significantly higher in children from folic acid-treated mothers for Verbal IQ, Performance IQ, General Language and Full-Scale IQ, suggesting a role for folate-mediated epigenetic changes in genes related to brain development.

Whilst folate-mediated epigenetic changes in genes related to brain development and function offer a biological basis to link maternal folate with offspring cognitive effects, this area of research is still in its infancy. Further carefully designed randomised trials with validated cognitive tests and ideally incorporating objective brain imaging techniques are warranted. Such studies could shed further light on the links between folate nutrition during pregnancy and offspring health outcomes and the underpinning epigenetic mechanisms. Personalised approaches, such as accurate dietary assessment of folate intake, or minimally invasive testing for folate status, are needed to identify individuals at risk of folate insufficiency or deficiency. More research is required in the case of 10% of the worldwide population who are homozygous for the methylenetetrahydrofolate reductase C677T polymorphism as they have impaired folate metabolism and may thus have higher dietary requirements for folate.

Genes affecting vitamin B12 metabolism and potential role in cardiometabolic disease

Cardiometabolic diseases such as obesity, type 2 diabetes and CVD are worldwide health problems and are now increasingly prevalent. The role of vitamins in cardiometabolic disease risk has more recently been the subject of research in this area. While most of the research has concentrated on vitamin D, interest in vitamin B12 as a modulator of metabolic disease risk has been increasing.

Vitamin B12 deficiency and cardiometabolic diseases

The relationship between low plasma or serum vitamin B12 concentrations and cardiometabolic phenotypes could be the result of several mechanisms. Vitamin B12 is a coenzyme which converts methylmalonyl-CoA to succinyl-CoA, a critical step in the metabolism of odd-chain fatty acids. If this reaction cannot occur, methylmalonyl-CoA levels elevate, inhibiting the rate-limiting enzyme of fatty acid oxidation (carnitine palmitoyltransferase), leading to lipogenesis and insulin resistance. On the other hand, reduced vitamin B12 concentrations in obese individuals could result from a nutrient-poor diet and increased nutrient requirements related to increased body size. Additionally, deficiency of vitamin B12 can impair the remethylation of homocysteine in the methionine cycle resulting in raised homocysteine levels, which is associated with an increased risk of CVD.

Although vitamin B12 deficiency is associated with a wide range of chronic diseases and conditions, the relationship between low vitamin B12 status and cardiometabolic-related traits has remained inconsistent in numerous studies. Polymorphisms in the key genes coding for proteins involved in the absorption, cellular uptake and intracellular metabolism of vitamin B12 may emerge as a feasible explanation for the vitamin B12 variability observed within these studies. Genetic studies have identified several genetic variants related to vitamin B12 status, during the last few years. At present, only three studies in European populations have investigated the effect of genetically instrumented vitamin B12 concentrations on cardiometabolic traits such as BMI, blood pressure and cardiometabolic risk, indicating the need to study more diverse ethnic groups.

Vitamin B12 concentrations, which vary widely among individuals, are responsive to changes in diet and are dependent on the quality and consumption of animal protein. Therefore, controlling diet is recommended in preventing vitamin B12 deficiency. As mentioned previously, deficiencies of vitamin B12 and folate during pregnancy can affect DNA methylation, suggesting that interactions between genes and nutrients may also play a role in the development of cardiometabolic disease. Given that the genetic make-up varies from individual to individual, and there is variation in genetic heritage and food consumed worldwide, it is vital to examine the interactive effects between dietary factors and genetics on vitamin B12 concentrations and metabolic traits.

Gene–nutrient interactions with vitamin B12

Whilst only a few nutrigenetics studies have been carried out in lower-middle-income countries, a large-scale collaborative project called the ‘gene–nutrient interactions (GeNuIne) Collaboration’ was established. One of the objectives of the overall project was to investigate the effect of gene–nutrient interactions on vitamin B12 concentrations and cardiometabolic traits using population-based studies from various ethnic groups. The first vitamin B12 pilot study of the GeNuIne Collaboration was the Genetics of Obesity and Diabetes study. This study explored the relationship of vitamin B12 status and metabolic traits in 109 healthy Sinhalese adults in Colombo, Sri Lanka. Genetic risk scores (GRS) were derived using ten vitamin B12-associated SNP (B12-GRS). While there was a significant association between the B12-GRS and B12 concentrations, there was no significant interaction of genetically instrumented B12 concentrations on any of the metabolic traits. However, there was a significant interaction between the B12-GRS and protein energy (%) on waist circumference, suggesting that a genetically lowered vitamin B12 concentration may have an impact on central obesity in the presence of lower dietary protein intakes.

The Minangkabau Indonesia Study is another nutrigenetic study in South East Asians conducted in Indonesia as part of

https://doi.org/10.1017/S0007114521000374 Published online by Cambridge University Press
the GeNuIne Collaboration. The B12-GRS was constructed based on nine vitamin B12 SNP, and a metabolic disease-related GRS (metabolic-GRS) was developed based on nine metabolic disease-related SNP. The study examined the relationship of these risk scores with vitamin B12 levels and different metabolic traits in 117 healthy Minangkabau Indonesian women. This study demonstrated the impact of genetically instrumented B12 concentrations on HbA1C levels, a marker of glycaemic control, through the influence of dietary fibre intake.

Given the increased prevalence of type 2 diabetes among Asian Indians, the Chennai Urban Rural Epidemiology Study from South India examined the association between two commonly studied fat mass and obesity-associated gene (FTO) SNP on metabolic traits and vitamin B12 concentrations in 548 Asian Indians (GeNuIne Collaboration). The study identified significant associations between the two FTO SNP not only with a higher risk of obesity but also with a lower vitamin B12 concentration. These results suggest that increases in BMI could potentially contribute to the adverse health effects associated with vitamin B12 deficiency. A more recent study has shown that long-term supplementation with vitamin B12 influences the regulation of several type 2 diabetes-associated genes by methylation of miRNA-coding gene, miR21, and could thus epigenetically regulate the risk of obesity, insulin resistance and type 2 diabetes.

While these findings are fascinating and highlight novel possibilities of gene–nutrient interactions, they need to be replicated in an independent cohort utilising a larger number of samples. Further understanding of the role of these gene–diet interactions at the molecular level is necessary before diets can be personalised according to varying ethnicity or genotype.

Importance of microbial enterotypes in personalised obesity management

As the prevalence of obesity has reached epidemic proportions globally, the search for effective management continues. Through multiple dietary intervention studies to reduce energy content, it has become evident that there is considerable weight loss variation among participants, indicating that no ‘one diet fits all’. Accordingly, dietary weight loss success is likely dependent on several individual characteristics, including host genetics and gut microbiota. While gut microbiota-modulating interventions can alleviate obesity in mice, similar causal findings appear absent in human clinical trials. However, this has also revealed the enormous variability of the human gut microbiome within and across populations.

To reduce complexity, researchers have proposed stratification of individuals according to distinct gut microbiota composition types termed ‘enterotypes’. Primarily two enterotypes have consistently been found across populations; one type dominated by Prevotella species, the other by Bacteroides species. The establishment of these types seems to occur during early childhood and to be highly influenced by long-term dietary habits, with the Prevotella enterotype associated with a carbohydrate- and fibre-rich diet. Conversely, the Bacteroides enterotype is associated with a ‘Western diet’ low in fibre, and high in fats and refined sugars. Factors such as age, sex, cultural background and geography have been found to have little influence on the establishment of enterotypes.

Enterotype predicts success in weight loss when consuming high-fibre diets

Following the discovery of enterotypes, epidemiological studies have found conflicting associations between enterotypes and metabolic health. Enterotypes as the enterotypes seem to differ in their ability to degrade dietary fibre, it is adjacent to speculate that metabolic responses of the enterotypes depend on dietary composition. Recent dietary intervention studies with healthy European subjects point to a more beneficial role of a high-fibre diet for individuals with a Prevotella enterotype than individuals with the Bacteroides enterotype.

In 2015, Kovatcheva and co-workers convincingly linked enterotypes to glucose metabolism after consuming a high-fibre, barley-rich diet for 3 days. Specifically, they found that individuals with the Prevotella enterotype improved their enzymatic capacity for fibre degradation and glucose metabolism as a result of the diet, an effect not seen among Bacteroides enterotype subjects.

Since then, Hjorth and co-workers reanalysed a 26-week ad libitum study with a fibre-rich New Nordic Diet (NND) and an average Danish diet, lower in fibre (43 g/d v. 28 g/10 MJ), and predicted dietary success based on pre-treatment faecal Prevotella-Bacteroides (P:B) ratio. While the high P:B group lost weight on NND compared with the control diet, the low P:B group did not. Interestingly, during the 1-year follow-up period, subjects with the high P:B ratio who changed from the control diet to the recommended NND managed to maintain their weight loss, whereas subjects with the low P:B ratio who changed from the control diet to the NND regained weight.

To validate these findings, two other dietary intervention studies aimed at weight loss were stratified by enterotype. Similarly, these studies observed that subjects who consumed a high-fibre diet for 6 months lost more weight if they had a high P:B ratio. Conversely, the colonic enzymatic degradation capacity of especially the prevalent Prevotella enterotype, likely due to a beneficial match between species enzymatic degradation capacity of especially the prevalent Prevotella species, P. copri. In comparison, the colonic functional and ecological properties seem less uniform among subjects with a Bacteroides enterotype.

Enterotypes at lower taxonomical levels and host digestive capacity

Until recently, the majority of dietary intervention studies have been limited to genus level taxonomy by 16S rRNA gene sequencing. Although with continuous advances in the field of sequencing, species-level taxonomy is now widespread, revealing a large inter-individual variation in Bacteroides and Prevotella species. Moreover, at the strain level, recent
pioneering microbiome studies demonstrated that \textit{P. copri} is not a monotypic species, but encompasses four distinct clades with substantial functional diversity differences including the ability to degrade whole-grain fibres\cite{82}. Consequently, if weight loss is affected by the colonic bacterial enzymatic capacity, future enterotype studies need deep-level sequencing to explain potential weight loss variability further.

Another intriguing factor in obesity management is the ability of the host to degrade the major polysaccharide component of diets, starch\cite{83}. If dietary starches escape host digestion in the small intestine, it will primarily feed \textit{Prevotella} and \textit{Bacteroides} species located distally in the gut. Amylase secreted from the salivary glands and pancreas determines the amount of starch escaping host digestion, and genetically the salivary amylase gene (AMY-1) exhibits some of the greatest copy numbers (CN) of any human gene\cite{84}. Stratification of participants of the 26-week NND study (discussed above) according to AMY-1 CN (i.e. low and high AMY-1 CN groups, respectively) further explained weight loss variability\cite{85}. Here, the majority of weight loss difference between enterotypes was observed in the low AMY-1 CN group with a strong linear relationship between P:B ratio and weight loss, which was not found for the high AMY-1 CN group. This indicates that not only dietary fibre but also the total pool of fermentable substrate reaching the colon play a role in the weight loss difference between the enterotypes.

Moving this field forward, there is furthermore a need to understand the underlying mechanisms linking microbial fibre fermentation to host metabolic alterations. To elucidate this, microbial metabolites produced in the colon that enter circulation and interact with host cells need to be investigated (e.g. SCFA)\cite{86}. In conclusion, microbial enterotypes are currently highly interesting biomarkers for explaining variability in weight loss upon intake of dietary fibre and whole-grain-rich diets\cite{87}. Soon, it might be possible to complement personalised dietary weight-loss strategies with microbial enterotype tests, thus ensuring dietary preferences of both the individual and the colonic microbes. Such a personalised approach may, in fact, support dietary adherence and long-term weight maintenance.

**Advanced technologies for food image recognition in nutrient intake assessment**

Dietary assessment is a crucial step in the real-world deployment of any personalised nutrition programme. The ability of an individual to track their food intake plays a role in self-monitoring as a critical aspect of behaviour change\cite{88}. It can also provide a professional diettian with information on how a client is adhering to their individualised meal plan. However, assessing dietary intake with traditional methods carries considerable costs and burden to the individual. Such methods are also prone to errors as they often rely on self-reporting\cite{89}.

Advanced solutions are needed to objectively quantify food and beverage intake\cite{90}. Food image recognition is a promising strategy because most individuals own a smartphone with a camera, so the barrier to entry is low, and it can reach a large population. However, automatically recognising food items from images is a challenging computer vision problem due to a variety of issues: (1) foods are typically deformable objects, (2) foods can lose their visual information during preparation, (3) different foods can appear visually similar, (4) the same food can appear differently depending on the lighting or angle and (5) limited amount of visual information for beverages\cite{91}. Only after foods are visually recognised, can they be reliably linked to a food composition database\cite{92}.

The introduction of the Pittsburgh Fast-Food Image Dataset in 2009 facilitated early research in this area based on manual recognition methods, but these approaches mostly achieved only 10–40\% classification accuracy\cite{93,94}. In 2014, deep learning was first used to recognise food images. Deep learning, or deep neural networks, allows computational models composed of multiple processing layers to learn relevant image features through training on a set of input images\cite{95,96}. Deep convolutional neural networks are inspired by the visual system of animals, where individual neurons assess the visual input by reacting to overlapping regions in the visual field\cite{97}. Because they can classify each pixel of the image, they can recognise any number of items, along with their location and size, allowing for food volume and food weight estimation. This approach has achieved substantially better results than other methods, resulting in an increased focus on deep learning in recent research\cite{98,99}.

A novel deep learning architecture for food image recognition, called 	extit{NutriNet}, has been developed by Mezgec and Koroušič Seljak\cite{91}. It is a modification of the well-known AlexNet architecture\cite{100}, with increased image size and an additional convolutional layer at the beginning of the neural network\cite{93}. 	extit{NutriNet} was first trained on 225 953 freely available images that were downloaded from the Internet and organised into appropriate food classes (520 unique food items). When tested against three popular deep learning architectures of the time (AlexNet\cite{100}, GoogLeNet\cite{101} and ResNet\cite{102}), 	extit{NutriNet} was found to be superior to AlexNet and GoogLeNet and faster to train than all three of the other architectures. The deep learning approach was then used to recognise any number of items in a single food image using a training set obtained from the ‘fake food buffet’\cite{103}, which is visually similar to real food. Fully convolutional networks, introduced by Long et al.\cite{104}, were applied to perform semantic segmentation, partitioning the image into logical parts and classifying each part on a pixel level. Due to the complexity of food images, an fully convolutional network variant that can segment images at the finest grain (fully convolutional network-8s)\cite{104} was used to train a model on the fake food buffet image data set. Output predictions of the trained model were compared with the ground-truth labels using the pixel accuracy measure\cite{104}, and the final accuracy of the trained fully convolutional network-8s model was 92–18\%.

In recent years, deep learning has been validated numerous times as a suitable solution for recognising food images\cite{98}. Availability of food image data sets has been improving\cite{105,106} although there is a need for validation against data sets from different regions across the world. Future work will focus on real-world food images, which exhibit more variance compared with the test images used in the research environment. In the future, such technology could be used to improve dietary assessment in clinical trials. For example, it can play a role in human studies in the...
areas mentioned above, where accurate quantification of folate, vitamin B₁₂ and energetic intake is critical. Consumer wellness apps can also apply this solution in the future, improving the dietary assessment of individuals and facilitating self-monitoring towards positive behaviour change.

**Looking towards the future: considerations to facilitate individualised nutrition guidance**

From the four examples discussed here, it is clear that scientific evidence about individualised responses to nutrient intakes continues to emerge. By recognising these sources of individual variation, we have the potential to improve the conduct and interpretation of clinical trials. For example, in studies of folate status and epigenetics, dietary intake assessment may be enhanced by the use of an advanced technique such as the one described here. In obesity research, understanding genes related to salivary amylase and vitamin B₁₂ metabolism, and gut microbiota composition, may enable better prediction of responders and non-responders and dietary adherence to an intervention could be assessed by photo recognition.

Such approaches can also play a role in the development of personalised nutrition programmes in the public health arena. For maternal health, such an app could help to identify women at risk of folate deficiency, providing them with guidance on how to identify foods with adequate folate, or supplementation options that meet their individual preferences. A weight management app could integrate automated dietary intake assessment with information on genotype and microbiome composition to provide a user with more pertinent and individualised guidance.

As new information comes to light, such as that described in the four examples in this paper, confidence in individualised nutrition guidance is likely to increase. In the meantime, companies and organisations developing personalised nutrition programmes must take science-based, ethical and rigorous approaches in developing their guidance. In this way, personalised nutrition approaches can maintain their credibility, provide maximum benefit to the individual and advance public health.

**Acknowledgements**

S. M. and B. K. S. would like to thank Tamara Bucher from the University of Newcastle, Australia, for providing the fake-food image data set. A. C., H. M. and K. P. would like to acknowledge the researchers on the ‘EpiFASSTT’ and ‘EpiBrain’ projects. S. S. and K. S. V. acknowledge support from the British Council, Newton Fund, British Nutrition Foundation and the authors of the GeNutri Collaboration.

S. M. and B. K. S. were supported by the European Union’s Horizon 2020 research and innovation programmes (grant numbers 863059 – ENS-Cloud, 769661 – SAAM); and the Slovenian Research Agency (grant number P2-0098). The European Union and Slovenian Research Agency had no role in the design, analysis or writing of this article. A. C., H. M. and K. P. were supported in part by the HSC Research and Development Division of the Public Health Agency, Northern Ireland (Enabling Research Award STL/STL/5043/14); the Biology and Biological Sciences Research Council and the Economic and Social Research Council (Grant Ref: ES/N000323/1 ‘EpiFASSTT’ and the European JPI ERA-HDHL “Nutrition & the Epigenome” scheme jointly funded by the Biology and Biological Sciences Research Council and the Medical Research Council (Grant Ref: BB/S020350/1 ‘EpiBrain’). The Northern Ireland Department for Economy (DfE) funded the PhD studenthip for Aoife Caffrey. The funders had no role in the design, analysis or writing of this article. S. S. and K. S. V. were supported in part by GeNutri Collaboration: British Nutrition Foundation; Sri Lankan (GENUINE) study: Farnborough College of Technology, UK; Indonesian (MINANG) study: British Council Newton Fund Researcher Links Travel Grant: 2016-RLTG7-10215; and Indian (Chennai Urban Rural Epidemiology Study) study: Research Society for the Study of Diabetes in India (RSSDI) (Project No: RSSDI/HQ/Grants/2014/250).

N. V. M., A. C., L. C., S. M. and S. S. drafted the manuscript; M. H., H. M., K. P., H. R., B. K. S., K. S. V., M. R. and S. P. contributed important intellectual content and critically revised and edited the manuscript. All authors read and approved the final manuscript.

N. V. M., M. R. and S. P. are employees of DSM Nutritional Products, a provider of personalised nutrition products and services. M. F. H. and L. C. are co-inventors on a pending provisional patent application for the use of biomarkers to predict responses to weight loss diets.

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