Paving the way to better population health through personalised nutrition

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Abstract

As each individual person differs from the next in multiple ways, it is a beguiling idea that our individual nutritional needs also differ. In support of this idea, findings from nutritional intervention studies provide ample evidence of considerable interindividual variation in response to the same dietary exposure. We have a limited understanding of the mechanisms responsible for this variation but, following sequencing of the human genome, the role of genes in explaining interindividual differences has been centre stage. In addition, evidence of diet–gene interactions that influence phenotype, including health, emphasises the importance of both nature and nurture. Eating patterns are major determinants of health, so public health advice to reduce the risk of common complex diseases focuses on diet. However, most dietary interventions are relatively ineffective and personalised approaches that tailor the intervention to the individual may be more acceptable and more effective. That idea was tested in the Food4Me study in which adults from seven European countries were randomised to one of four treatment groups in an internet-delivered dietary intervention. Compared with the Control (standardised healthy eating advice), those people randomised to a personalised nutrition intervention had bigger, sustained changes, in eating behaviour after 6 months. However, including more complex phenotypic and/or genotypic information in developing the personalised nutrition advice had no added benefit. Research in personalised nutrition is broadening its scope to consider effects mediated by the gut microbiome as well as multiple aspects of genotype and phenotype. Such research has the potential to explain interindividual differences in the response to specific dietary factors and may provide a scientific basis for more refined approaches to personalised nutrition. However, if this research is to make a significant contribution to improving public health, it will need to address the psychological, social, economic and cultural factors that influence eating patterns to ensure that advice is converted into action and that improved dietary habits are sustained in perpetuity.

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1. **Public health context for personalised nutrition**

Non-communicable diseases (NCD) including cardiovascular disease (CVD), type 2 diabetes, musculoskeletal diseases, dementia and depression are major causes of morbidity and reduced lifespan not only in economically developed countries but also globally. In each case, lifestyle choices including diet, physical activity, sedentary behaviours and smoking are major risk factors (GBD, 2015 Risk Factor Collaboration, 2016) that drive changes in disease incidence. The world-wide increase in prevalence of obesity since 1980 (Ng et al., 2014) is a very obvious manifestation of recent pervasive changes in lifestyle and, in particular, of the consequences of higher consumption of energy-rich foods unmatched by increased physical activity. Unsurprisingly, these trends have focused the attention of health authorities on improving lifestyle choices as a means to address this global, and rising, burden of morbidity. For example, the World Health Organization has targeted diet and physical activity in its global action plan for the prevention and control of NCD (WHO, 2013). However, sustained efforts over the past two decades to improve eating behaviours in economically developed countries have produced very modest changes and it is clear that providing information (education) on healthy choices is insufficient to ensure behaviour change (Kelly and Barker, 2016). At the same time, the public is becoming more aware that dietary choices can have profound effects on individual health in the medium to longer term as well as having short-term effects on body weight and well-being. This is driving demand for products that can help individuals make better food-based choices and, in turn, multiple providers have emerged who offer personalised nutrition (PN)-related products. In some cases, these PN offerings have a specific focus on health and well-being, but others are geared to enable consumers to exercise personal preferences, e.g. to avoid certain foods/food ingredients.

From a research perspective, it is well established that there is substantial interindividual variability in responses to the same dietary exposure. For example, in a recent well designed weight loss trial, some individuals lost up to 40 kg body weight over 12 months, whereas other individuals gained up to 10 kg in the same trial (Gardner et al., 2018). There are also wide interindividual differences in biological responses to taking a dietary supplement. For example, the concentration of triacylglycerols (TAG) in blood (a marker of CVD risk) fell markedly in some people after taking fish oils, whereas in others TAG concentration remained unchanged or even increased (Madden et al., 2011). This provides a biological rationale for the concept that, with better understanding of the basis for this interindividual variation, it may be possible to design dietary advice/food products that are tailored for the individual. However, until relatively recently, there was little attempt to investigate the biological nature of interindividual variation in response to diets, foods and nutrients, but that has changed rapidly since the sequencing of the human genome and the development of post-genomic technologies.

2. **Is genetic information special?**

Success in sequencing of the human genome has stimulated rapid technological development that has reduced the cost of undertaking large-scale investigations of the relationships between genotype, nutrition and multiple health-related outcomes. This provided a major stimulus for the concept of personalised nutrition, especially the idea that dietary advice could be tailored to match individual genotype and that this approach might lead to improved health. To explore whether genetics is ‘special’ in influencing diet-related behaviours, I discuss below outcomes from three different types of study design.

In the earliest study, Bloss et al. (2011) reported the outcomes from a study in which > 1,900 employees of health and technology companies purchased a genome-wide risk assessment test at a discounted rate. Compared with baseline, the receipt of individualised genetics-based disease risk estimates had no effect on measures of anxiety or on key health behaviours (dietary fat intake or physical activity) approximately 6 months later (Bloss et al., 2011). In addition, although study participants perceived that risk of some diseases, e.g. type 2 diabetes could be modulated by lifestyle, this perception did not lead to changed behaviour (Boeldt et al., 2015). In contrast, being informed that they carried a risk variant of the ACE gene that can increase sensitivity to the adverse effects of high salt intake, resulted in a reduced sodium intake 12 months later by young adults recruited to a randomised controlled trial carried out in Canada. However, there were no effects on the intakes of caffeine, vitamin C or sugars when participants were informed that they carried risk variants in the CYP1A2, GSTM1 and GSTT1, and TAS1R2 genes, respectively (Nielsen and El-Sohemy, 2014). More recently, Turnwald et al. (2019) tested the hypothesis that providing individualised genetic risk information (regardless of whether it was actually true) would alter actual risk by making people more likely to exhibit the expected changes in gene-related physiology, behaviour and subjective experience.
For both a physical activity-related gene (CREB1) and for an obesity/satiety-related gene (FTO), Turnwald and colleagues observed that learning one’s genetic risk changed physiology independent of actual genetic risk. Whether such changes persisted in the medium to longer term remains to be discovered (Turnwald et al., 2019).

3. State-of-the-art for personalised nutrition: evidence from human intervention studies

In theory, using personalised approaches to improve dietary behaviour may be more effective in improving eating patterns and longer term health outcomes than conventional ‘one-size-fits-all’ approaches, for at least two reasons. Firstly, because such approaches are more relevant, i.e. there is a biological rationale for tailoring dietary intake at the individual level and, secondly, because such approaches feel more relevant to each individual and, therefore, improve motivation and compliance with the dietary advice. To date, relatively few human intervention studies have tested the PN concept and each has used quite different approaches.

The Pioneer 100 Wellness Project monitored a large number of cardiovascular, diabetes, inflammation and nutrition biomarkers over 9 months in 107 adults. Using this information, the researchers identified ‘actionable possibilities’ for each participant designed to enhance his/her health and made recommendations about lifestyle changes when the individual’s biomarkers fell outside the clinical reference range (Price et al., 2017). Wide excursions in blood glucose concentration after a meal (glycaemia) may be undesirable and, so, Zeevi et al. (2015) used this as their outcome of interest. They observed substantial interindividual differences in glycaemia in response to standard meals and using data on individual characteristics, including blood-based measurements, anthropometry and the gut microbiome, they developed an algorithm called the Personalised Nutrition Predictor. In a subsequent small intervention study (n = 26), Zeevi et al. (2015) showed that the ‘predictor’ could select ‘good’ and ‘bad’ diets for individuals that resulted good control of blood glucose or wide excursions in glycaemia, respectively, after consumption of the test diets. Very recently, Mendes-Soares and colleague (2019) tested this model in a study of 327 individuals without diabetes from a study lasting 6 days. They observed that using features of each individual, including clinical characteristics, physiological variables, and the microbiome, in addition to nutrient content, was more predictive of postprandial glycaemia that approaches that use information on the energy and/or carbohydrate content of foods alone (Mendes-Soares et al., 2019). This is unsurprising as it is well established that glycaemic responses are determined not only by the foods consumed but also by attributes of the consumer of those foods (Vega-López et al., 2007).

The EU FP7-funded Food4Me study is the largest randomised controlled trial (RCT) to date that has tested the PN concept. This study was designed to determine: (1) whether a PN approach was more effective in improving eating behaviour that the conventional ‘one-size-fits-all’ approach; (2) what types of information used for developing the PN advice were more effective; and (3) whether an internet-based approach could be used to deliver a scalable PN intervention (Celis-Morales et al., 2015). More than 1,600 adults from seven European countries were recruited to the Food4Me study and randomised to a Control ‘one-size-fits-all’ intervention (Level 0) based on current European healthy eating advice or to one of three PN interventions. The latter used a hierarchical design to examine the effects of PN advice based upon an analysis of current diet (Level 1), based on current diet plus phenotype (Level 2) or based on current diet, phenotype and genotype (Level 3). The primary outcome was healthfulness of the overall diet after 6 months intervention (Celis-Morales et al., 2015). Those participants randomised to PN reported bigger improvements in diet (measured using the Healthy Eating Index; Guenther et al., 2013) than those randomised to the Control (Level 0) but there were no differences between the effects of Levels 1–3 of PN (Celis-Morales et al., 2017). In conclusion, the Food4Me study showed that personalising a dietary intervention resulted in greater improvements in diet in the medium term (6 months) but there was no evidence of added advantage in using more sophisticated (and expensive) phenotypic and genotypic information in generating that personalisation. In addition, the internet-based approach proved to be feasible and acceptable and so provides evidence that PN can be delivered at scale with potential to improve public health.

4. Future challenges for research in personalised nutrition

Although the principle that PN approaches may be an effective way of enabling individuals to choose healthier diets has been established, as yet, there is limited evidence about which individual
characteristics are most useful in engaging members of the public and motivating and enabling them to adopt healthier eating patterns. Indeed, research on PN is still in its early stages and there are many gaps in both fundamental underpinning science and in translational research some of which are outlined below.

4.1. Understanding interindividual variation using single-subject or n-of-1 studies

Conventional study designs, such as RCTs, provide strong evidence of the effect of a treatment averaged across the participants in the study. However, as noted above, such treatment effects represent the mean of sometimes widely differing individual effects. As a consequence, such designs do not allow us to predict the benefit (or detriment) of a particular treatment, e.g. change in dietary intake, for any specific individual (Madden et al., 2011; Gardner et al., 2018). To address this issue, current research is exploring the utility of single-subject (also known as n-of-1) studies that are designed specifically to provide evidence of how an individual responds to a particular intervention (Schork and Goetz, 2017). Several different designs for n-of-1 studies have been proposed for nutritional investigations (Schork and Goetz, 2017) and de Roos and Brennan (2017) have suggested that the combination of individual genotyping with phenotyping of individual responses to a series of controlled dietary interventions could be used as the evidence base for personalised nutrition. In addition, the CONSORT extension for N-of-1 trials (CENT) group have published guidelines on how to report n-of-1 trials including a checklist and a recommended diagram for depicting an individual n-of-1 trial (Vohra et al., 2015).

As yet, there have been no formal n-of-1 trials reported from nutritional investigations. However, the approaches adopted by Zeevi et al. (2015) and by Mendes-Soares et al. (2019), to obtain individual-level evidence of predictors of glycaemic responses to standard meals, is an important step in that direction. It seems likely that such n-of-1 studies will lend themselves to investigation of interindividual variation in short-term (minutes to days) physiological or psychological responses to dietary changes and challenges. In addition, there may be opportunities to use ‘continuous’ monitoring of environmental, physiological, behavioural and psychological variables by body worn devices (so-called ‘wearables’) linked to smart phones or other internet-enabled devices to collect detailed, objective data in real time in response to dietary factors. This will generate large volumes of complex data, which are discussed below in the section on ‘big data’. However, given the difficulties in longer term compliance with a given intervention and in addressing confounding factors, it seems unlikely that n-of-1 studies will be suitable for investigation of health outcomes.

4.2. Using ‘big data’ in personalised nutrition

‘Big data’ describes the massive increase in volume, types and complexity of data that are being generated, usually in digital forms, in everyday life. Such data are being captured and mined by governments, business, research organisations and others for multiple uses including surveillance, decision-making and commercial purposes. Doug Laney (distinguished analyst at Gartner) has summarised the characteristics of big data as the 3 ‘Vs’, i.e. Volume (vast amounts of data available to process), Velocity (large volumes of data being generated continuously and arriving for analysis) and Variety (data becoming available in multiple forms, sometimes in unstructured forms that are a challenge for conventional analytical approaches). From a scientific perspective, there is an important fourth ‘V’. This is Veracity, i.e. the reliability of the data being generated. Here the problems may include uncertainties due to data inconsistencies and incompleteness, ambiguities, deception and assumptions/ approximations inherent in the models being used for its analysis (http://saphanatutorial.com/what-is-big-data/).

The use of ‘omics approaches and the large-scale collection of personal physiological and other data via wearables and other devices is now revolutionising the collection of individual-level ‘big data’ that can be used to underpin personalised nutrition. Already, we have several examples of ‘big data’ being generated and intended for use in delivering personalised feedback and advice to individuals. These include the Pioneer 100 Wellness Project (Price et al., 2017) discussed earlier. In the future, it seems highly likely that this approach will expand to combine: (1) laboratory-based measurements using ‘omics approaches on biological samples (buccal cells, blood, hair, urine, stool, exhaled air, etc.) collected by individuals at home using simple, safe and inexpensive technologies; (2) frequently sampled environmental, physiological, behavioural and psychological data collected automatically by
internet-enabled wearables or other devices in each individual’s possession or vicinity; (3) (food) purchasing data and, more controversially; and (4) health record data. The research challenges in this area are both conceptual (what is the overall model which allows us to integrate this diverse assembly of dynamic data?) and practical (how should such data be structured and interrogated so that robust ‘actionable’ information is extracted?). There are also potential ethical and governance issues that require careful assessment and research.

4.3. Genetic basis of behaviour change

There has been widespread interest in the use of genetic information to achieve behaviour change. Much of this has focused on the idea that knowledge of genetic risk of a (future) disease may motivate individuals to change appropriate behaviours, including eating patterns (McBride et al., 2010). However, accumulating evidence shows that such interventions based on provision of information on single-gene variants with low-risk probabilities, has little impact on behaviour (McBride et al., 2010). Indeed, a systematic review and meta-analysis found that communicating DNA-based risk estimates had no effect on diet or on other major lifestyle factors including smoking cessation and physical activity (Hollands et al., 2016).

Of course, this does not mean that genetics is irrelevant to personalised nutrition. It is possible that future research will find more effective ways of communicating and/or using genetic information and as individuals and populations become more familiar with DNA-based information, its utility may increase. In addition, as behaviours themselves are the result of complex interactions between genetics and the environment, research on such interactions are likely to offer new opportunities for intervention. There is limited research in this area in humans, but analysis of the genetic architecture of behaviours is being conducted in model organisms, e.g. *Drosophila melanogaster* (Anholt and Mackay, 2015), which may have read across to humans.

4.4. Features of personalised nutrition interventions that motivate improved dietary choices

To date, there has been very little systematic research on what characteristics of the individual are most useful when designing and delivering PN. As noted above, genotype has been a major focus of such research, but this is unlikely to be a particularly useful lever in effecting behaviour change. Focusing research effort on understanding individual aspirations and the barriers and facilitators to altered food choices is more likely to yield new insights that can be translated into PN interventions. If such insights are to be used in scalable, internet-based interventions, then it will be critical to: (1) find ways to capture the relevant individual characteristics systematically; and (2) develop and validate algorithms to use that information in an evidence-based manner to deliver actionable advice and support. In addition, future research on PN will need to address the psychological, social, economic and cultural factors that influence eating patterns to ensure that advice is converted into action and that improved dietary habits are sustained in perpetuity.

4.5. Impact of personalised nutrition interventions on health inequalities

Within any given country, both dietary behaviour and health are patterned socioeconomically so that poorer diets and higher burdens of disease and disability occur among those who are more socioeconomically disadvantaged (Chetty et al., 2016). It has been argued that personalised nutrition approaches may exacerbate such health inequalities if PN interventions are more accessible to, or more readily adopted by, those with greater socioeconomic advantage. Analysis of the characteristics of the 5,662 people from seven European countries who expressed an interest in participating in the internet-based Food4Me study showed that these individuals were broadly representative of the European adult population in terms of demographic, anthropometrical and health-related characteristics (Livingstone et al., 2016). Most of these individuals reported adequate nutrient intakes, but could benefit from improved dietary choices and greater physical activity (Livingstone et al., 2016). These finding suggested that future use of internet-based PN approaches may be attractive to a wide target audience. The ability to access PN advice via the internet may be particularly important for more vulnerable sections of the community who may find it difficult to comply with conventional face-to-face interventions. In addition, such internet-based approaches may be more scalable, more cost effective and capable of being tailored to meet the specific needs, in respect of language or other
cultural preferences, of different sections of the community. However, further formal research on the impact of PN approaches on health inequalities is required.

5. Conclusions

The science underpinning personalised nutrition is growing and the limited evidence available from well-designed intervention studies suggests that PN approaches engage members of the public and can improve dietary choices. Given the appetite for products and services that help individuals to choose foods and diets that meet their aspirations, e.g. for improved health and well-being, the potential market for personalised nutrition is huge and, already, many companies offer PN services. However, PN is in the market-place before there is good evidence of what works (in terms of helping people make healthier dietary choices) and, equally important, of what does not work. This aspect of commerce has developed without regulatory oversight, defined standards and consumer protection (Ordovas et al., 2018). For example, it is difficult to assess the rigour of, and evidence base for, most commercial PN offerings because they use proprietary algorithms that are not subject to independent verification. If PN approaches are to be useful in improving public health and in ameliorating diet-related health disparities, there is a need for more research on the effectiveness of PN-based interventions. In addition, we need better evidence of how to personalise dietary advice so that it enables, and motivates, individuals to make appropriate changes to their eating patterns and to sustain those changes indefinitely. More broadly, PN will need to address the psychological, social, economic and cultural factors that influence eating patterns to ensure that advice is converted into action and that improved dietary habits are sustained in perpetuity.

References


Abbreviations

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<tr>
<td>CENT</td>
<td>CONSORT extension for N-of-1 trials</td>
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<td>CVD</td>
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<td>NCD</td>
<td>non-communicable diseases</td>
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<td>PN</td>
<td>personalised nutrition</td>
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