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Personalised nutrition – phenotypic and genetic variation in response to dietary intervention

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Personalised nutrition allows individual differences in dietary, lifestyle, anthropometry, phenotype and/or genomic profile to be used to direct specific dietary advice. For personalised nutrition advice to be effective both sides need to be considered; firstly, that factors influencing variation in response to dietary intervention are identified and appropriate advice can be derived and secondly; that these are then used effectively in the provision of nutrition advice, resulting in a positive dietary and/or lifestyle behaviour change. There is considerable evidence demonstrating genetic and phenotypic influence on the biological response to the consumption of nutrients and bioactives. However, findings are often mixed, with studies often investigating at the level of a single nutrient/bioactive and/or a single genetic/phenotypic variation, meaning the derivation of specific advice at a dietary level in an individual/group of individuals can be complex. Similarly, the impact of using this information to derive personalised advice is also mixed, with some studies demonstrating no effectiveness and others showing a significant impact. The present paper will outline examples of phenotypic and genetic variation influencing response to nutritional interventions, and will consider how they could be used in the provision of personalised nutrition.

Nutrition: Personalised: Phenotype: Genotype

Inter-individual variation exists, and is visible in the variance of our physical features[1]. However, inter-individual variance also exists in response to food consumption, physiological and environmental stressors and other aspects of life, which in turn effects individuals' risk of related diseases[2,3]. Identifying and understanding this variance, specifically related to nutrition research is important for two reasons; firstly to understand how this variance effects our interpretation of the results of nutrition intervention studies and secondly, to harness these variations and tailor nutrition related advice and therefore deliver personalised nutrition (Fig. 1).

Controlled nutrition intervention studies can provide definitive evidence of inter-individual variation, however to date the importance and potential of this information are often overlooked. Whilst many researchers observe considerable variation in response to nutrition interventions, many do not report on this, other than noting outliers or large standard deviations and/or other variance statistics. In addition the intervention studies from where the data are derived are often tightly controlled to minimise variation in response. Researchers often apply strict inclusion and exclusion criteria in recruiting participants with the direct aim to minimise factors known to influence variation in response to the outcome being considered, often including factors such as sex, body weight and biochemical markers specific to the question being considered[4,5]. However, some studies have captured and reported on variance in response to the study intervention, either as the main outcome of

Abbreviations: MTHFR, methylene tetrahydrofolate reductase; OGTT, oral glucose tolerance test; OLTT, oral lipid tolerance test.
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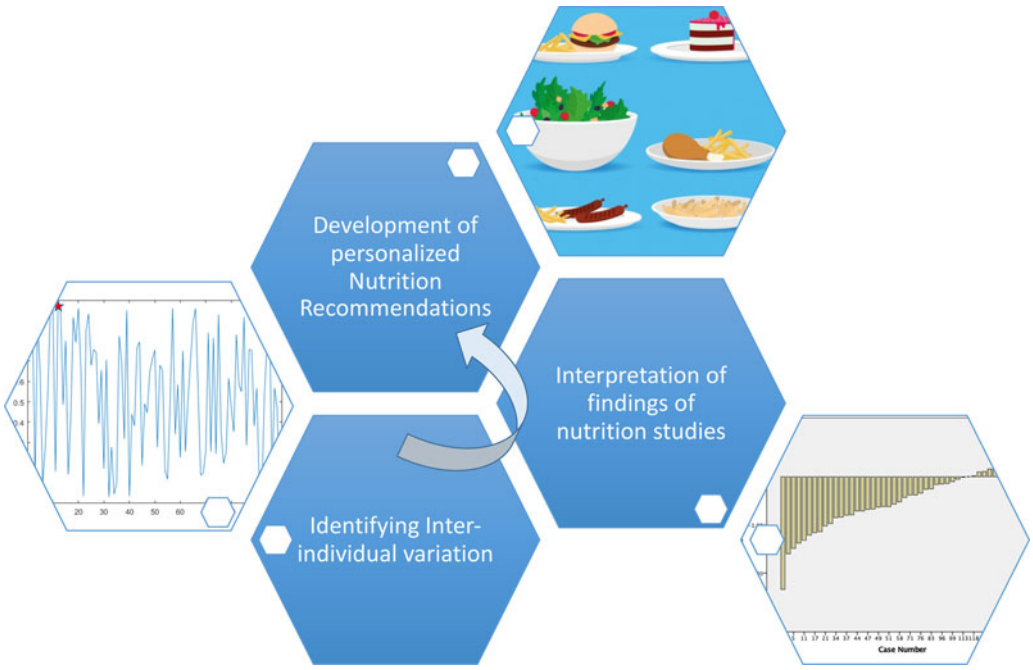

Fig. 1. (Colour online) Inter-individual variation and personalised nutrition.

their study or an observation following completion. The present paper will focus on examples of variation in response to nutrition intervention studies, focusing on phenotypic (Table 1) and genotypic (Table 2) factors influencing variability and will consider how they could be used in the provision of personalised nutrition.

Phenotypic variation influencing response to nutrition intervention studies

To date, several studies have focused on inter-individual variability to standardised (or semi-standardised) meals such as oral lipid tolerance tests (OLTT) and/or glucose tolerance tests (OGTT), with some examples given in Table 1. Examining glycaemic response first, studies such as Vega-Lopez *et al.*[6], demonstrated that the inter-individual variation in response to a glycaemic load is greater than the intra-individual variation, but didn't elucidate further on the factors influencing this variation. Following on from their initial examination of variance in repeated OLTT and OGTT in a healthy population. Morris *et al.*[8] examined factors influencing variation in response to the OGTT across the study cohort, using a statistical clustering of baseline characteristics. Using this method, researchers identified a distinct phenotype or 'metabotype' group, which had a significantly different response to OGTT, compared to all other clusters. This group of individuals had the highest BMI, highest circulating TAG, C-reactive protein, c-peptide and insulin levels, as well as the highest insulin resistance (HOMA-IR) score, compared to other clusters[8]. van Dijk *et al.*[9] noted that exercise levels, preceding the OGTT measurements also had a clear effect on the post-prandial glycaemic response, with subjects glycated haemoglobin levels related to the magnitude of response to exercise. Examining reported variance in response to OLTT, results from Morris *et al.*[12] and Ryan *et al.*[7], both from the same group and focusing on the MECHE (metabolic challenge) study, noted baseline characteristics similar to those influencing response to OGTT including age, TAG, circulating fatty acids, as well as SNP[7,12] (Table 1).

Two things stand out from these studies: firstly that there is a need for standardisation of parameters in the measurement of these standardised test meals, in order that results from differing studies are not influenced by procedural differences and can thus be both combined and interpreted correctly. In addition, baseline subject characteristics clearly influence the response, such as age, BMI, circulating TAG, C-reactive protein or insulin levels, for example. This information should be used in two ways: (1) to direct selection of study populations to ensure variance within intervention groups is minimised, and/or controlled for in statistical analysis and (2) to direct personalised or targeted nutrition messages to an identified group, which differ due to differing response to the standardised test meal.

Variation in response to non-standardised meals has also been reported in the literature (Table 1). Childs *et al.*[11], noted a significant difference in sex in response to a 6-month intervention replacing standard margarines and spreads with products enriched with α-linoleic acid, with a greater increase in the EPA content of plasma phospholipids in females compared to males after 6 months. Sex differences such as this are not unique and have been previously reported in other studies[26,27]. McMorrow *et al.*[15], noted a significant variation in response to consumption of an anti-inflammatory nutritional supplement. The authors of the present paper noted that the supplement modulated adiponectin levels, but not insulin resistance. However, they did note that

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Table 1. Examples of studies reporting phenotypic variation influencing response to nutrition intervention studies

Author (year)	Population	Study design/intervention	Variation identified	Potential impact/use in personalised nutrition advice
Vega-Lopez *et al*. (2007)[6]	23 healthy adults (20–70 years)	Assessment of glycaemic response following 50 g available carbohydrates from commercial white bread and glucose.	Results suggest that in response to a challenge of white bread relative to glucose, within-individual variability is a greater contributor to overall variability than among individual variability. Further understanding of all the sources of variability would be helpful in better defining the utility of glycaemic index values.	No information on factors influencing response, to be used in personalised nutrition advice.
Ryan *et al*. (2013)[7]	51 healthy adults aged 18–60 years	Within-person variation in repeated (*n* 2) OLTT.	Variation score (S(v)) low in most (82 %) of the adults S(v) significantly ($P < 0{\cdot}05$) associated with age, fasting TAG, TAG AUC and fasting nonessential fatty acids, as well as SNP in ApoA1, IL1α, IL1β, TLR4, TCF7L2, CCK1Rec and STAT3.	Stratify personalised nutrition messages with respect to lipid metabolism based on influencing factors – age, baseline lipid levels, and some SNP.
Morris *et al*. (2013)[8]	214 healthy adults aged 18–60 years	Within-person variation in repeated (*n* 2) OGTT	4 metabotypes with differing responses to OGTT: e.g. Cluster 1 highest BMI, TAG, hsCRP, c-peptide, insulin and HOMA-IR score and lowest VO_{2max}, and a differential response to insulin and c-peptide compared to other clusters.	Stratify personalised nutrition response based on identified metabotypes.
Van Dijk *et al*. (2013)[9]	60 type 2 diabetes patients	Randomised crossover experiment. Glycaemic function measured by continuous glucose monitoring over the 24-h period after a single bout of moderate-intensity endurance-type exercise or no exercise at all[10].	Moderate-intensity exercise (single bout or more) substantially improves glycaemic control throughout the subsequent day in type 2 diabetes patients. Subjects' HbA1c level was related to the magnitude of response to exercise.	Exercise needs to be considered when assessing glycaemic response in type 2 diabetics patients.
Childs *et al*. (2014)[11]	Healthy male (M; *n* 87) and female (F; *n* 63) participants aged 25–72 year	Replacement of normal margarine/butter with specially formulated margarines for 6 months. Data from the control and the 'high-ALA' which provided contained 41 g ALA/100 g compared with 1 g ALA/100 g in the control margarine are considered.	There was a significant difference between sexes in the response to increased dietary ALA, with women having a significantly greater increase in the EPA content of plasma phospholipids (mean + 2·0 % of total fatty acids) after six months of an ALA-rich diet compared to men (mean + 0·7 %, $P = 0{\cdot}039$). Age and BMI were identified as predictors of response to dietary ALA among women.	Sex specific advice needs to be considered in provision of personalised nutrition. Within women age and BMI also should be considered.
Morris *et al*. (2015)[12]	214 healthy adults aged 18–60 years	To identify lipidomic changes in response to an oral lipid tolerance test and identify the effect of aerobic fitness	Mixed model repeated measures analysis identified lipids which were significantly changing over the time course of the lipid challenge e.g. LPE a C18:2, LPE a C18:1, PE aa C36:2, PE aa C36:3 and N-C16:1-Cer. Fitness level had a significant impact on the response to the OLTT: in particular significant differences between fitness groups were observed for phosphatidylcholines, sphingomyelins and ceramides.	Fitness levels impact response to lipid consumption – personalised nutrition advice could be stratified by fitness level.

Kirwan *et al*. (2016)[13]	1607 healthy adults subjects	4 arm, 6-month parallel intervention study – level 0 (standard non-personalised dietary and physical activity guidelines), level 1 (personalised advice based on current diet and physical activity), level 2 (personalised advice based on current diet, physical activity and phenotype) and level 3 (personalised advice based on current diet, physical activity, phenotype and genotype).	Subjects were classified as responders or non-responders to dietary advice on the basis of the change in cholesterol level from baseline to month 6, with lower and upper quartiles defined as responder and non-responder groups, respectively. In a step-wise logistic regression model, age, baseline total cholesterol, glucose, five fatty acids and alcohol intakes factors that successfully discriminated responders from non-responders, with sensitivity of 82 % and specificity of 83 %.	Metabolic profiles can be used in identifying responders to specific nutritional advice, and advice tailored to this.
Feliciano *et al*. (2017)[14]	10 healthy men	Dose response study Examining inter-individual variability of absorption, metabolism and excretion of cranberry (poly)phenols.	Inter-individual variability of the plasma metabolite concentration was broad and dependent on the metabolite. The large inter-individual variation in metabolite profile may be due to variations in the gut microbiome.	Potentially stratify recommendations based on gut microbiome composition
McMorrow *et al*. (2018)[15]	78 adolescents (13–18 years)	8 week randomised controlled crossover trial of anti-inflammatory nutritional supplement or placebo.	The supplement was associated with bidirectional modulation of adipogenic gene methylation in weight-stable overweight adolescents. HOMA-IR decreased in a sub-cohort of adolescents with an adverse metabolic phenotype.	Give personalised advice, based on phenotype of responders and non-responders.
Aller *et al*. (2019)[16]	154 men (mean age 58 years) and women (mean age 52 years) with abdominal obesity and subclinical inflammation	Double-blind, controlled, crossover study, participants randomised to three supplemented phases of 10 weeks each: (1) 2·7 g/d of DHA[17], 2·7 g/d of EPA and (3) 3 g/d of maize oil, separated by 9-week washouts.	Supplementation with 2·7 g/d DHA or EPA had no meaningful effect on TAG concentrations in a large proportion of individuals with normal mean TAG concentrations at baseline. Although DHA lowered TAG in a greater proportion of individuals compared with EPA, the magnitude of TAG lowering among them was similar.	Give personalised advice, based on phenotype of responders and non-responders.

Abbreviations: OLTT, oral lipid tolerance test; OGTT, oral glucose tolerance test; AUC, area under the curve; IL1α, interleukin 1 alpha; IL1β, interleukin 1 beta; TLR4, toll like receptor 4; TCF7L2, transcription factor 7 like 2; CCK1Rec, cholecystokinin A receptor; STAT3, signal transducer and activator of transcription 3; hsCRP, high sensitivity c-reactive protein; HOMA-IR, insulin resistance index; HBA1C, glycated haemoglobin; ALA, α linoleic acid; IU, international unit; LPE, lysophosphoethanolamine; PE, phosphoethanolamine; PC, phosphatidylcholines; SM, sphingomyelins.

Table 2. Examples of studies reporting genotypic variation influencing response to nutrition intervention studies

Author (year)	Population	Study design/intervention	Variation identified	Potential impact/use in personalised nutrition advice
Shatwan *et al*. (2017)[18]	120 adults, with risk of CVD (mean age, 47 years).	Randomised, single-blind, parallel study with diet high in SFA, MUFA or *n*-6 PUFA for 16 weeks.	For the ApoE SNP (rs1064725), only TT homozygotes showed a significant reduction in total cholesterol after the MUFA diet compared to the SFA or *n*-6 PUFA diets.	Greater sensitivity of the ApoE SNP rs1064725 to dietary fat composition, advice could be tailored according to genotype.
Wang *et al*. (2016)[19]	733 overweight/obese subjects ($25 \leq$ BMI ≤ 40 kg/m^2) aged 30–70 years.	Randomised, controlled 2-year weight-loss trial, stratified using a GRS based on 14 fasting glucose-associated SNP.	GRS was associated with 6-month changes in fasting glucose, fasting insulin, HOMA-IR, and insulin sensitivity. Significant interactions were observed between the GRS and dietary fat on 6-month changes in fasting glucose, HOMA-IR and HOMA-S.	Participants with a higher GRS may benefit more by eating a low-fat diet to improve glucose metabolism.
Rundblad *et al*. (2019)[20]	35 healthy normotriglyceridemic subjects	Randomised controlled trial received 1·6 g EPA + DHA/day for 7 weeks. Secondary analysis, whereby TAG responders identified as subjects having a TAG reduction beyond the 20 % day-to-day variation and non-responders as having a TAG change between −20 % and +20 % after *n*-3 supplementation.	TAG responders and non-responders to omega-3 supplementation identified as having different lipoprotein subclasses and PBMC gene expressions. Compared to non-responders, the expression of 454 transcripts was differentially altered in responders ($P \leq 0{\cdot}05$). Pathway analyses revealed that responders had altered signalling pathways related to development and immune function.	Specific gene expression metabotypes respond differently to *n*-3 supplementation, and could be identified to tailor nutritional advice.
Caslake *et al*. (2008)[21]	312 adults aged 20–70 year recruited according to age, sex, and ApoE genotype,	Double-blind placebo-controlled crossover study; control oil, 0·7 g EPADHA/d, and 1·8 g EPADHA/d each for an 8-week intervention period, separated by 12-week washout periods	Significant sex treatment and sex genotype treatment interactions were observed, with the greatest TAG-lowering responses (reductions of 15 % and 23 % after 0·7g and 1·8g EPADHA/d, respectively) were evident in ApoE4men.	Stratify personalised nutrition EPA/DHA recommendations based on sex and ApoE genotype.
Wilson *et al*. (2012)[22]	83 patients with risk of CVD, representing all 3 MTHFR 677CT genotypes who participated in a placebo-controlled riboflavin intervention for 16 week in 2004.	Nested within this follow-up, those with the TT genotype (*n* 31) proceeded to intervention with riboflavin (1·6 mg/d for 16 week) or placebo, conducted in a crossover style whereby the 2004 treatment groups were placed in opposite intervention groups.	Riboflavin supplementation produced an overall decrease in systolic and diastolic BP.	Supplementation of riboflavin in MTHFR 677TT genotype group causes significant reduction in systolic and diastolic BP.
Chouinard-Watkins *et al*. (2015)[23]	90 healthy participants (35–70 years), recruited for ApoE genotype. In this analysis 41 ApoE4 carriers and 41 non-carriers were prospectively recruited.	Participants consumed HSF diet for 8-week followed by 8 week of consumption of an HSF diet with the addition of DHA and EPA (HSF + DHA diet; 3·45 g DHA/d and 0·5 g EPA/d).	ApoE4 carriers were lower plasma responders to the DHA supplement than were non-carriers but only in the high-BMI group.	ApoE4 carriers with higher BMI may need higher intakes of DHA for cardiovascular or other health benefits than do non-carriers.
Aller *et al*. (2019)[16]	270 obese patients, genotyped for variant (rs1501299 G-T) of an *ADIPOQ* gene	Randomised trial with two hypoenergetic diets (high-protein and low-carbohydrate diet *v.* standard diet) over 9 months of intervention.	In non-T-allele carriers (GG genotype) after both diets, the decrease in metabolic health markers was higher than T-allele carriers. Only no T-allele carriers showed an increase in adiponectin levels after both diets.	GG genotype of an *ADIPOQ* gene variant (rs1501299) is related to better improvement in adiponectin levels, insulin resistance, and lipid profile hypoenergetic diet.

Gardner *et al.* (2018)[24]	609 adults aged 18 to 50 years without diabetes with a BMI between 28 and 40.	Randomised clinical trial (DIETFITS), participants randomised to low-fat or low-carbohydrate diet for 12 months. The study examined study outcome (diet and insulin) interactions with 3 SNP multilocus genotype patterns.	There was no significant diet-genotype pattern interaction or diet-insulin secretion interaction with 12-month weight loss.	In the context of 2 common weight loss diet approaches, neither of the 2 hypothesised predisposing factors was helpful in identifying which diet was better for whom.
Celis-Morales *et al.* (2017)[25]	683 participants (18–73 years)	Food4me study – randomised trial, four arms: level 0, control group; level 1, dietary group; level 2, phenotype group; and level 3, genetic group. In this analysis, level 3 participants were stratified into risk carriers (AA/AT) and non-risk (TT) of the *FTO* gene (rs9939609).	Changes in adiposity markers were greater in participants who were informed that they carried the *FTO* risk allele (level 3 AT/AA carriers) than in the non-personalised group (level 0) but not in the other personalised groups (levels 1 and 2).	There are greater body weight and WC reductions in risk carriers than in non-risk carriers of the *FTO* gene.

Abbreviations: GRS, genetic risk score; HOMA-IR, insulin resistance index; HOMA-S, insulin secretion index; PBMC, peripheral blood mononuclear cell; MTHFR, methylene tetrahydrofolate reductase; BP, blood pressure; HSF, high-saturated fat; *ADIPOQ*, adiponectin gene; *FTO*, alpha-ketoglutarate-dependent dioxygenase; WC, waist circumference.

insulin resistance improved in a sub-cohort of adolescents and concluded that the baseline phenotype of responders was insulin resistant and dyslipidemic with higher insulin, HOMA-IR, HOMA-β, total cholesterol, LDL cholesterol and lower QUICKI (quantitative insulin sensitivity check index), than non-responders. It is interesting to note that the authors of the present paper reported that sex, age, BMI and body composition, were not different between responders and non-responders, which one might assume may be due to the homogeneous selection of their population, whereby only overweight and obese teens between 13–18 years were recruited. Feliciano *et al.*[28] also explicitly reported variable response in a study examining varying doses of cranberry polyphenols. The authors examined inter-individual variation by calculating the CV for C_{max} and area under the curve for each individual plasma metabolite, and demonstrated that CV for C_{max} was 51 %, and the CV of the area under the curve for the total (sum of all 60) metabolites was 53 %. This varied between metabolites with a CV of 43 % for dihydroferulic acid 4-O-sulfate and 216 % for vanillic acid. The authors note that inter-individual variability of the plasma metabolite concentration was broad and dependent on the metabolite, as had been noted previously[29]. There are a number of factors that are suggested to influence the metabolism and absorption of such metabolites, including sex, genetic polymorphisms of transporters or metabolising enzymes, environmental influences and likely the composition of the gut microbiome[30,31].

Again, such studies highlight that variation in response to any nutrition intervention will vary, and should be considered in both the interpretation, presentation and reporting of any study results. Recent work carried out by the COST Action POSITIVe, specifically investigated inter-individual variation in response to consumption of plant-based bioactive[3]. Whilst several meta-analyses to determine factors influencing variation were conducted, lack of consideration or reporting of such variance in publications meant analysis and conclusions were limited[32–34]. If factors influencing response are to be more fully investigated, then researchers will need to provide information and clearly address variance in response in their analyses[3].

Genotypic variation influencing response to nutrition intervention studies

Alongside specific phenotypic characteristics influencing response to intervention studies, much work has been conducted which examines and reports the differing response of specific genotypes to various nutrition interventions. Too many to mention all within the present paper, some examples are given in Table 2, and will be discussed below to give a flavour of how genetic variation can influence response. Several studies have examined the effect of various genetic variants on weight loss with participants on various diets (Table 1). Gardner *et al.*[24] in the DIETFITS study, examined the interaction of a multi-locus genotype pattern and the impact of a low-fat or low-carbohydrate diet on weight loss and found there was no significant interaction or diet-insulin secretion

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interaction with 12-month weight loss. In contrast, Aller *et al.*[16] examined the impact of the adiponectin (*ADIPOQ*) gene (rs1501299 G-T), on weight loss in a two-arm randomised trial with two hypoenergetic diets (high-protein and low-carbohydrate diet *v.* standard diet) over 9 months. In this study, the GG genotype group, regardless of the diet, the decrease in total cholesterol levels, LDL cholesterol, TAG levels, insulin levels and HOMA-IR levels were higher than T-allele carriers[16]. Likewise, Celis-Morales *et al.*[25], in a sub-analysis of the Food4me study, where participants were randomised to one of four arms: level 0, control group; level 1, dietary group; level 2, phenotype group; and level 3, genetic group, level 3 participants were stratified into risk carriers (AA/AT) and non-risk carriers (TT) of the alpha-ketoglutarate-dependent dioxygenase (*FTO*) gene (rs9939609). This analysis demonstrated that changes in adiposity markers were greater in participants who were informed that they carried the *FTO* risk allele (level 3 AT/AA carriers) than in the non-personalised group (level 0) but not in the other personalised groups (levels 1 and 2)[25]. However, this was not seen with respect to dietary changes in other genetic variants including ApoE[35] and methylene tetrahydrofolate reductase (MTHFR)[36].

Much work has also focused on the impact of genetic variation and response to lipid consumption, examining the impact of genetic variation in the ApoE gene on the metabolic response to consumption of differing fat types (Table 1). For example, Shatwan *et al.*[18] examined the impact of diets high in SFA, MUFA or *n*-6 PUFA over 16 weeks. Stratifying for ApoE SNP (rs1064725), they reported that only TT homozygotes showed a significant reduction in total cholesterol after the MUFA diet compared to the SFA or *n*-6 PUFA diets[18]. However, one must remember that whilst a study may be examining impact of genotype, that this may not be the only factor influencing response, for example, Caslake *et al.*[37], in a double-blind placebo-controlled crossover study, where the consumption of different amounts of EPA/DHA was examined, found significant genotype interactions in response to the intervention, whereby the greatest TAG-lowering responses (reductions of 15 % and 23 % after 0·7g and 1·8g EPA DHA/d, respectively) were evident in ApoE4 men. Similarly, Chouinard-Watkins *et al.*[23], in a study examining changes in circulating lipid profile following 8 weeks consumption of a high-saturated fat diet with the addition of DHA and EPA, found that ApoE4 carriers were plasma responders to the DHA supplement than were non-carriers but only in the high-BMI group. Again suggesting a genotype–phenotype interaction in response to the intervention.

Variations in folate metabolism have also been well researched with respect to response to consumption of B-vitamins and other nutrients, with much of the work focusing on variations in the enzyme MTHFR[38–40]. One of the most interesting papers in this area by Wilson *et al.*[22], examined the response of thirty-one MTHFR TT genotype patients with the risk of CVD. This study, was a 4-year follow on from a study where eighty-three participants representing all three MTHFR 677CT genotypes, were initially recruited to participate in a placebo-controlled riboflavin intervention for 16 weeks. In the initial study, the team found the TT group to be responsive with respect to reduction in blood pressure. To confirm these findings, the follow-up study, which only examined those with the TT genotype proceeded to confirm the effect of consumption of riboflavin (1·6 mg/d for 16 weeks) or placebo on blood pressure, conducted in a crossover style whereby the 2004 treatment groups were placed in opposite intervention groups. This study confirmed riboflavin supplementation produced an overall decrease in systolic and diastolic blood pressure in this genotype group[22].

Inter-individual variation and personalised nutrition

With many examples of an inter-individual response to consumption of foods/nutrients published to date, the challenge is now to potentially use this information in an informed and appropriate manner to tailor nutritional recommendations for individuals or groups of individuals, the cornerstone of personalised nutrition.

Firstly, how does inter-individual variation fit into the concept of personalised nutrition. There are many published definitions of personalised nutrition, which vary in their manner and/or depth of personalisation. More recently, definitions recognise that this must be broader, with definitions basing personalised nutritional advice on multiple characteristics, such as that used in Food4me (Grimaldi *et al.* 2018) which encompasses levels of information layering dietary, phenotypic and genotypic information from an individual[41]. Ordovas *et al.*[42], simply described personalised nutrition as 'an approach that uses information on individual characteristics to develop targeted nutritional advice', not defining the depth or nature of information required. Finally, more recently Stewart-Knox *et al.*[43], have built on these to contextualise the information by including factors influencing food choice determinants, and considering the framework in which the information would be offered. Examining and understanding variation in response to nutrition interventions is important to further the field of personalised nutrition. Using the examples discussed within the present paper, one might suggest that stratifying based on age, sex, baseline biomarkers and exercise levels with respect to glucose metabolism would be recommended (Table 1). Similarly, fitness level, baseline metabolic markers and identified SNP could also be considered when giving advice on lipid consumption and metabolism. However, there needs to be some caution. Whilst variation was observed in many of these studies, before recommendations could or should be used, confirmation in other studies and cohorts, and a full understanding of the mechanism of the variation needs to be elucidated. Furthermore, the impact of the recommendation based on the variation needs to be determined. Both of these issues were addressed in the recent Food4me project. Firstly, Grimaldi *et al.*[41] in their paper proposing guidelines to evaluate scientific validity and evidence for genotype-based dietary advice

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focus on a framework that considers study design, type of gene–nutrient interaction, biological plausibility and the scientific validity of the published evidence. Joining the reported presence of variability with some levels of biological explanation for this, ensures a scientific rigour in the development of tailored recommendations, ensuring that they have sound scientific rationale. Secondly, the findings of the Food4me proof of principle study are also of interest when discussing the use of known variation within personalised recommendations. Examining the impact of personalisation on change in dietary intake, researchers within Food4me undertook a large multicentre study, across Europe, which examined the impact of levels of personalised advice, on change in dietary intake. Following recruitment, interested and eligible participants were randomised to control (general healthy eating guidelines), level 1 (nutritional advice based on diet alone), level 2 (nutritional advice based on diet and phenotype) or level 3 (nutritional advice based on diet, phenotype and genotype). Full details of the study are published elsewhere[44]. A change in dietary intake and other parameters were examined at baseline (0), 3 and 6 months. Following completion comparisons were made between control and personalisation (levels 1, 2 and 3 together) and then across the levels of personalisation. The researchers found that there was a greater positive change in dietary intake in the personalised groups compared to the control group, but that there was no difference between the levels of personalisation, suggesting that participants are responsive to personalisation but the manner in which the advice was personalised didn't have an effect[45]. Further examination of response to knowledge of specific genetics variants had similar results[35,36]. For example, O'Donovan *et al.*[36], examined the impact of an individual's knowledge of their MTHFR 677 genotype, and found that the TT group (risk group), who were given specific advice on to increase consumption of folate (foods) or folic acid (supplement), there was no difference in the change of folate in the diet in this group compared to the non-risk group. Thus suggesting that even knowledge of their risk and a recommendation to increase the consumption of the specific nutrient, did not result in a greater behavioural change[36]. Whilst this pattern has also been found in previous studies, other studies have demonstrated a change with knowledge of risk; however, overall results are mixed[46].

This brings about a variation that also needs to be considered. Variation in response to personalised recommendations, not at a physiological level, but at a behavioural level. Consumer studies within the Food4me project explored associations between food choice motives, attitudes towards and intention to adopt personalised nutrition and found that food choice motives such 'weight control', 'mood', 'health' and 'ethical concern' had a positive association and 'price' had a negative association with attitude towards, and intention to adopt, personalised nutrition[47]. This suggests that underlying health perceptions, food beliefs and other psychological factors will influence variability in response to personalised advice, (which was given to address variability in an individuals' requirement), thus increasing an additional level of inter-individual variability when considering the response in large population cohorts.

Conclusion

Inter-individual variation in response to diet exists, but remains largely unexplored. Understanding what phenotypic and genotypic factors influence response will aid in the interpretation of nutrition intervention results and exploitation of such variation in the provision of personalised nutrition. However, to truly understand such variation, we need to both design specific studies to test the influence of factors (both phenotypic and genotypic) on variation and also report such variation in response in future publications.

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Authorship

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