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Barriers in Translating Existing Nutrigenetics Insights to Precision Nutrition for Cardiometabolic Health in Ethnically Diverse Populations

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Keywords
Nutrigenetics · Nutrigenomics · Ethnically diverse · Genetic diversity · Precision nutrition

Abstract
Background: Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease mortality (more than three-quarters) occurring in low- and middle-income countries. There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors. Despite the remarkable progress, several factors need to be considered before the translation of nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations. Some of these factors include variations in genetic predispositions, cultural and lifestyle factors as well as socio-economic factors. ***Summary:*** This review aimed to explore the factors that need to be considered in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities. Several factors might influence variations among individuals with regard to dietary exposures and metabolic responses, and these include genetic diversity, cultural and lifestyle factors as well as socio-economic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics, and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition although more research is needed to confirm the practicality and effectiveness of this approach. Conducting gene-diet interaction studies in diverse populations is essential and studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate their application in clinical practice. ***Key Messages:*** Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Conducting gene-diet interaction studies in diverse populations is essential giving the genetic diversity and variations in dietary patterns. Integrating data from disciplines such as metabolomics, epigenetics, and the gut microbiome could help in early identification of individuals at risk of cardiometabolic diseases as well as the implementation of precise dietary interventions for preventing and managing cardiometabolic diseases.

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Introduction

Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease (CVD) mortality (more than three-quarters) occurring in low- and middle-income countries (LMICs) [1]. According to the Centres for Disease Control and Prevention [2], individuals in LMICs are often affected by cardiometabolic diseases during the peak of their productivity, which coupled with huge healthcare expenses and limited employment opportunities worsens the financial burden of cardiometabolic diseases in these countries. Thus, cardiometabolic diseases present severe health and economic consequences for individuals, families, and communities [1], necessitating further research into the prevention and management of these conditions. Risk factors such as dyslipidaemia, hypertension, and obesity have been shown to be influenced by genetic factors [3–7]. However, unlike monogenic disorders like sickle cell anaemia which are usually caused by mutations in a single gene [8], most cardiometabolic diseases, such as CVDs, are influenced by numerous genes and are also impacted by environmental factors [9–13].

There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors [9, 11, 14–17]. Thus, a genetic variant might not always pose a higher risk of a disease as its effects might be modulated by the environmental factors that interact with it [18]. Defined as the scientific field that investigates the impact of genetic variability on individual responses to diet [19], nutrigenetics focuses on understanding gene-diet interactions that predispose to specific diseases, offering the potential to design personalised dietary guidelines for preventing and managing cardiometabolic diseases [20, 21].

Gene-diet interaction studies have been extended to cover previously under-represented populations [22–27], although there is still limited research in some areas [28, 29] and most studies have not been replicated [28, 30]. Despite the remarkable progress in nutrigenetics research, several factors need to be considered before the translation of existing nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations [31, 32]. Ethnic diversity covers a broad range of factors including variations in genetic predispositions, cultural and lifestyle factors which can hinder the worldwide application of nutrigenetics findings [33]. Therefore, this review aimed to explore the potential barriers and challenges in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities.

Genetic Diversity

One of the main challenges (shown in Fig. 1) in translating existing nutrigenetics insights to personalised and precision nutrition in various ethnic groups is the genetic diversity that exists among populations. Numerous studies have shown that individuals of different ethnic backgrounds have distinct genetic variations that impact how their bodies metabolise certain nutrients [10, 19, 34–36]. Therefore, research covering populations that represent different ethnicities is required to gain a better understanding of the genetic variations and specific nutritional requirements within these groups. Research by the gene-nutrient interaction (GeNuIne) collaboration identified that the genetic influence on obesity in different Asian populations was influenced by different dietary factors [19, 34, 37–42]. Using a genetic risk score (GRS), it was observed that South Asians with a higher GRS had a greater susceptibility to obesity when consuming a high-carbohydrate diet, whereas South East and Western Asian populations with a higher GRS displayed an increased risk of central obesity in response to a high-protein diet [19]. Similarly, research by the Diabetes Heart Study [43–45] indicates that African Americans have elevated levels of circulating arachidonic acid (AA) in comparison with individuals of European ancestry. Notable differences were also observed in allele frequencies of various SNPs within the fatty acid desaturase (*FADS*) gene cluster which have been shown to play a significant role in determining circulating levels of fatty acids. In particular, the "GG" genotype of the SNP rs174537, which is linked to elevated AA levels, was present in 81% of African Americans compared to 46% of European Americans [45]. Thus, while research conducted on individuals of European descent suggests that only a small fraction of dietary linoleic acid is converted to AA in humans, this minimal conversion rate may not be consistent across all populations [43–45]. Given that AA and its metabolites play crucial roles in immune responses and inflammation, thereby influencing the onset and advancement of various diseases including diabetes and CVDs [46, 47], tailored dietary recommendations regarding the intake of PUFA might be beneficial for this population.

One of the most widely studied genes in relation to cardiometabolic diseases is the apolipoprotein E (*ApoE*) gene [48–53], and variations in the frequency of the E4

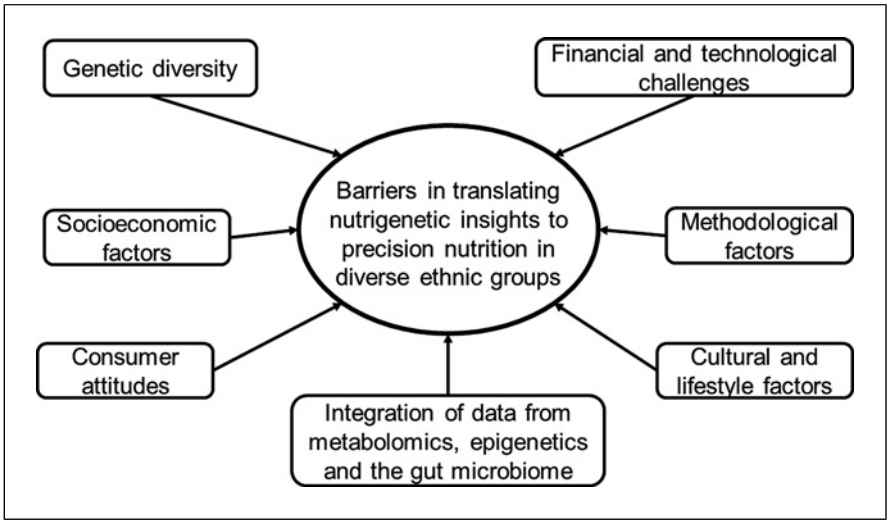

Fig. 1. Barriers affecting the translation of existing nutrigenetics insights to precision nutrition in ethnically diverse populations.

isoform of the gene, which is associated with increased risk of CVDs, have been reported [54, 55]. African and Asian populations tend to have higher frequencies of the E4 isoform (29–40% in Central Africa) compared to Caucasians [54, 55] which could contribute to differences in susceptibility to certain diseases among these populations. Furthermore, within Europe there are regional variations in the frequency of the E4 isoform, ranging from 5 to 10% in Spain, Portugal, Italy, and Greece; up to 16% in France, Belgium, and Germany; and further rising to up to 23% in the Scandinavian peninsula, with the Saami population of Finland showing frequencies as high as 31% [54, 55]. However, the link between the E4 isoform and increased low-density lipoprotein cholesterol levels is more pronounced in populations with diets high in saturated fat and cholesterol compared to other groups [56, 57], suggesting that interventions targeting a reduction in saturated fatty acid (SFA) intake could be effective for CVD prevention and management in populations with a high frequency of the E4 isoform.

The use of a GRS has been shown to be effective in assessing the genetic contribution to complex traits such as dyslipidaemia since it allows the combined effects of multiple genetic variants to be analysed [58–60]. A weighted GRS, which takes into account the effect sizes of the risk alleles, is used by some studies [61–63]. However, most of the published data on effective sizes come from GWA studies which have been conducted in populations of European ancestry and it has been reported that effective sizes may vary across populations [37, 63], suggesting that using a weighted GRS might not be ideal for populations which are under-represented in GWA studies. In a study by the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe), consisting of 10,366 African American, 26,647 European American, 1,410 Hispanic, and 717 Chinese American individuals from nine cohorts [64], there were marked differences in effect sizes across the ethnic groups for some of the SNPs, and this has also been reported in a review of nutrigenetic studies [35]. The effect size of the cholesteryl ester transfer protein (*CETP*) SNP rs4783961, the "A" allele of which is associated with higher concentration of high-density lipoprotein cholesterol, was uniformly larger in African American cohorts (0.17 to 0.24) compared to European Americans (0.09 to 0.15) [64]. In contrast, another high-density lipoprotein cholesterol-associated SNP, rs17231506, also in *CETP*, had larger effect sizes in European Americans and Hispanics (0.21 to 0.28) compared to African Americans (0.06 to 0.26). A potential reason for this finding as explained by the authors [64] is that African Americans and European Americans possess the same underlying causal variant within a gene, yet because of ethnicity-specific variations in the frequencies of major and minor alleles, a SNP might have varying degrees of correlation with the underlying variant, resulting in varying effect sizes and degrees of association.

Methodological Factors

Aside genetic diversity, another barrier that affects the translation of nutrigenetics is the lack of replication in most gene-diet interaction studies [30, 36, 65]. Conducting replication studies, especially in diverse populations, is vital in enhancing the reliability of findings

and facilitating their application in clinical practice [18]. In a systemic review of gene-diet interaction studies in relation to CVDs [30], it was observed that many of the studies that identified significant interactions had not been replicated, with only a small number of studies examining the same dietary and genetic factors. Similarly, a lack of replication was reported in a systemic review of gene-lifestyle interaction studies conducted by our team [36] in which it was identified that most of the studies were conducted only once. Furthermore, a systematic review of nutrigenetic studies focusing on omega-3 fatty acid and plasma lipid, lipoprotein, and apolipoproteins [65] highlighted a lack of replication of previously identified interactions. To strengthen the evidence and enhance comparability across studies, it is important for studies to be replicated in independent samples [30, 36].

In addition to the lack of replication, sample size has been cited as a methodological issue that affects the quality of the evidence generated by gene-diet interaction studies [30, 35, 36, 65]. A large sample size improves the power to detect interactions with minimal effect sizes, and this is especially important for multifactorial traits where the main effects of genetic variants are often subtle [30, 66, 67]. Moreover, there is a scarcity of genotype-based dietary intervention studies [19]. It has been highlighted that dietary intervention studies can help raise the evidence level of gene-diet interactions identified in observational studies once they have been replicated [18]. In a 12-week randomised controlled trial involving 145 participants with overweight or obesity, participants were first identified as being responsive to fat or carbohydrate based on a GRS, before being randomised to a high-fat or high-carbohydrate diet [68]. Although no differences in weight loss were observed between participants who were randomised to the appropriate diet based on their genotype and those who were not [68], studies utilising this approach could help determine the effectiveness of dietary interventions based on genotypes and facilitate the translation of nutrigenetics into precision nutrition.

Cultural and Lifestyle Factors

Cultural and lifestyle factors also need to be considered in translating nutrigenetics and implementing precision nutrition. Ethnic groups often have long-standing dietary traditions, specific food preferences, and cooking practices that have been passed down through generations, making them a fundamental part of their cultural identity [69, 70]. Therefore, incorporating precision nutrition based on nutrigenetics into these cultural practices without compromising their valued traditions might be challenging. A systematic review of 20 qualitative studies revealed that the food preferences of individuals of Asian, African, and other minority ethnic communities were impacted by social and cultural elements besides nutritional and health considerations [70]. It was observed that individuals from African, Asian, and other minority ethnic backgrounds place significant value on traditional foods, viewing them as symbols of their ethnic identity and belonging [70]. Similarly, in African Americans, despite a disproportionate prevalence of cardiometabolic diseases in comparison with white Americans [71, 72], adherence to dietary guidelines has been found to be influenced by a preference for a dietary intake that reflects a cultural tradition known as "soul food" [72]. This diet often consists of fatty meats, added fat, sugar, and salt and involves methods of cooking such as deep frying and others that raise the amount of calories and sodium in the diet [72]. Accordingly, African Caribbean individuals living in Britain were found to prioritise spending on traditional foods such as yams over potatoes, thereby preserving their cultural food preferences [73]. Moreover, specific practices such as adhering to a vegetarian diet, avoiding pork and beef, and following certain cooking procedures are considered valuable to people of Asian and African backgrounds [70, 74]. Moreover, the concept of "local food" has attracted a lot of attention in recent years, with many consumers preferring products that have travelled short distances or been directly marketed by producers [75–77]. However, the extent to which individuals adhere to their traditional dietary practices is influenced by several factors, with younger individuals more likely to adopt new dietary habits [69, 78].

With regard to diet and cardiometabolic diseases, examining the overall dietary pattern is believed to offer several advantages since foods and the nutrients they contain often have synergistic effects, which can make it difficult to identify the influence of a single food or nutrient [79]. Moreover, it has been shown that it is not specific nutrients but rather the overall dietary pattern that exerts the most significant impact on cardiometabolic diseases [79–81]. Dietary pattern is defined as the regular consumption of various foods, drinks, and nutrients in specific quantities and combinations, including the frequency at which they are consumed [82]. Recognising a dietary pattern could lead to a stronger correlation with a specific health indicator and provide a broader and more inclusive understanding of how nutrients and other bioactive compounds in our food are

consumed, as well as how patterns of consumption affect health outcomes [82, 83]. In a study involving South Asian Surinamese, African Surinamese, and Dutch participants in the Netherlands [84], three dietary patterns, categorised as "noodle/rice and white meat," "red meat, snacks, and sweets," and "vegetables, fruits, and nuts," were identified. In contrast to Dutch participants, those of Surinamese origin had a stronger adherence to the "noodle/rice and white meat" pattern, which reflected the dietary preferences typical of the traditional Surinamese diet. Dutch participants on the other hand showed a higher level of adherence to the "red meat, snacks, and sweets" and "vegetables, fruits, and nuts" patterns [85]. Variations in dietary consumption and factors shaping dietary behaviours across different ethnic groups were also observed in a systematic review of 49 studies [86]. Consumption of fruits and vegetables was found to be low in populations of African ancestry and higher in Hispanic and Latino populations, while fish consumption was low in white and Hispanic populations. In contrast, white and Asian populations were found to have the highest dairy intake (2.17 and 1.3 servings per day, respectively) compared to populations of African ancestry (0.58 servings per day) [86]. These findings indicate a low tendency towards fruit and vegetable consumption as well as reduced intake of dairy in African ancestry populations in comparison with the other ethnic groups, highlighting a need for ethnic-specific initiatives. It should be noted that within the same ethnic group, there are variations in dietary pattern depending on whether they are living in developed countries or in their native countries [85], indicating that public health priorities with regard to diet and disease prevention might differ based on geographic location.

Traditional diets for certain ethnic groups have often been associated with health benefits [87]. The traditional South Asian diet in particular is composed mainly of fresh fruits and vegetables along with beans, legumes, nuts, and spices [87]. However, a rise in type 2 diabetes (T2D) and CVDs has been seen in South Asians [19, 37] and this has partly been linked to unhealthy modifications to the traditional diet, shifting from nutrient-rich fresh produce to refined products and the use of large amounts of saturated cooking oils [87]. Similarly, the traditional African diet is enriched with fresh vegetables such as okra, spinach, and other green leafy vegetables [88, 89]. Nonetheless, a shift away from traditional meals towards processed foods and soft drinks has been reported across African countries [90]. Hence, understanding cultural and lifestyle factors that shape food preferences and dietary habits is vital in translating existing nutrigenetic insights to various ethnic groups.

Socio-Economic Factors

Socio-economic and geographical disparities are also important factors to consider in the translation of nutrigenetics to precision nutrition. Ethnic populations may experience disparities in access to healthcare, technologies, and resources required for implementing precision nutrition effectively. The allocation of money to healthcare has been reported to vary across countries depending on their level of economic development, with high-income countries allocating on average, USD 3,000 per person towards healthcare, while low-income countries only spend around USD 30 per person [91]. Similarly, a report by the World Health Organization [92] indicated that healthcare costs in low-income countries were mainly covered by individuals paying directly (44%) and aid from external sources (29%), while government funding played a predominant role in high-income countries (70%). Moreover, socio-economic and political factors also influence the distribution of food, adjustments in food composition, or the implementation of optional taxes on unhealthy food products as well as the adoption of dietary guidelines promoting the consumption of healthy options such as fruits and vegetables [93, 94].

Aside cost and infrastructure, the knowledge and attitudes of healthcare providers, including dietitians, towards nutrigenetics, are crucial for its integration into clinical practice, which may also be influenced by socio-economic-related educational opportunities [95]. Healthcare professionals need to understand genetic influences on public health, evaluate the clinical relevance and utility of genetic tests as well as analyse the individual's background in order to recommend genetic assessments, screening or lifestyle adjustments [96]. It has been highlighted that nutritional genetics has emerged as a relatively new field over the past two decades, with much of its scientific knowledge not integrated into healthcare education [97]. Consequently, healthcare professionals lack the essential foundation to provide effective nutrigenetic counselling [97]. Available evidence on knowledge and attitudes of healthcare professionals towards nutrigenetics mainly comes from studies conducted in high-income countries, and the findings indicate a general lack of awareness among healthcare professionals [98–101]. In a survey of 390 dietitians in the UK [98], it was observed that, despite being involved in the management of polygenic conditions such as diabetes, obesity, and CVDs which are influenced by both genetic and dietary factors, majority of the participants were not engaged in activities related to genetics or nutrigenetics

and expressed low confidence in undertaking such activities. Similarly, a survey involving 1,844 dietitians from Australia (390), the USA (461), and the UK (993) [99] revealed that the participants had limited knowledge, engagement, and confidence in nutrigenetics. Giving the lack of resources in LMICs, knowledge and awareness of nutrigenetics are likely to be even lower. In this regard, initiatives such as the GeNuIne collaboration are required [34]. Through funding from the British Nutrition Foundation (BNF), the GeNuIne collaboration was started at the University of Reading in 2013, and it has been instrumental not only in conducting nutrigenetics studies in diverse ethnic groups, but also in facilitating training and resource development to improve the ability of professionals and policymakers in low-income countries to effectively apply nutrigenetics findings within their domains [19, 34, 36, 41, 95, 102].

Financial and Technological Challenges

Funding from public bodies is vital for developing innovative approaches within nutrition programmes, promoting collaboration among scientists, facilitating the distribution of nutrigenetics information through modern virtual communication technologies as well as establishing a well-trained public health nutrition workforce [103]. Several studies have highlighted the necessity for enhancing capacity in public health nutrition across individual, organisational, and systemic levels [103–106]. However, global initiatives such as the Scaling Up Nutrition (SUN) movement which is focused on addressing the complex causes of malnutrition through the implementation of evidence-based, nutrition-specific interventions in developing countries face challenges due to financial constraints in most countries [107].

In a report by Sight and Life [108], it was noted that personalised nutrition appears not only feasible and rational but also cost-effective in terms of developing effective nutrition interventions to alleviate the burden of diseases and improve health outcomes in LMICs. However, several implementation challenges were highlighted including how to extend the application of personalised nutrition approaches to benefit a larger population giving the financial constraints, deciding which methods offer the greatest potential for successful adoption, what resources are necessary to expand the implementation of personalised nutrition, and whether there is sufficient support and interest in introducing personalised nutrition approaches to LMICs [108]. Moreover, it has been recognised that the integration of nutrigenetics into healthcare systems requires a multisystem approach that includes the gut microbiome and environmental factors [21], which poses a huge challenge in LMICs. According to Sight for Life [108], personalised nutrition approaches that are more specific are less readily available in LMICs and these include genetic and microbiome analysis and counselling, alongside tools for assessing metabolic markers such as glucose monitors and energy intake sensors.

Consumer Attitudes towards Nutrigenetics and Personalised Nutrition

There is a growing interest in nutrigenetics and personalised nutrition, although at present, accessibility is limited to a narrow group of highly motivated individuals with high socio-economic status [109]. Commercial companies offering nutrigenetic testing exist mostly in Europe and North America [110], with the aim of enabling consumers to identify their genetic susceptibility to diseases and offering personalised dietary recommendations to promote health [110, 111]. The growing interest in direct-to-consumer (DTC) genetic testing has been associated with social elements such as enhanced internet access to information and a cultural shift towards individuals taking greater responsibility for their health and lifestyle choices, while relying less on conventional expert guidance [112]. However, there are concerns about the accuracy and usefulness of the health-related data provided by DTC genetic testing companies as well as potential adverse outcomes if consumers or their healthcare providers misinterpret such information [113–116]. In a study of 1,648 participants [117], it was observed that before undertaking personalised DTC genetic testing, consumers were mostly interested in information about ancestry (73.7%), traits (72.2%), and disease risks (71.9%). In terms of susceptibility to disease, heart disease (68%), breast cancer (67%), and Alzheimer's disease (66%) attracted a high level of interest [117]. It should be noted that the participants were mostly women, Caucasian, and from a high socio-economic background [117]. Similarly, a survey of 1,048 customers of DTC genetic testing [112] indicated that the customers' individual circumstances and subjective understanding of disease susceptibility were linked to specific health-related behaviours they undertake upon receiving their test results. More specifically, various aspects of the participants' lives such as having a chronic condition, a family history of diseases tested by the DTC service, self-reported health issues, and regular visits to a doctor were significantly correlated with several health-related

behaviours individuals displayed following receipt of their results [112]. Along these lines, a survey of 2,037 customers of DTC services showed that the response to genetic testing was influenced by both the perceived severity and sense of control over the condition of interest. Higher perceived severity and lower perceived control were linked to increased, though not clinically significant, levels of anxiety and distress [118].

With regard to attitudes of the general public towards personalised nutrition, a survey of 9,381 participants across nine European countries (the UK, Germany, Ireland, Spain, Greece, Poland, Portugal, the Netherlands, and Norway) [119] indicated that the trust and preference consumers have for personalised nutrition services are key indicators of their likelihood to embrace such services. Variations in trust in the national health service as a regulatory body and source of information, as well as trust in dietitians and nutritionists as service providers, were observed across the countries, although in all the countries, family doctors emerged as the most relied-upon sources of information [119]. Similarly, a study conducted in the UK and Ireland by Food4Me [120] identified that there was a preference for government-led services delivered in person, which was believed to enhance trust, transparency, and overall value. In both countries, paying for nutritional advice was associated with heightened commitment and motivation to adhere to guidelines [120]. Furthermore, a study involving 438 Dutch participants [121] showed that consumers' acceptance of personalised nutrition was positively influenced by consensus among expert stakeholders, benefits for consumers or scientists, ease of implementation, and freedom of choice. In line with these findings, a study consisting of 1,425 Canadian participants [122] revealed that most of the participants (93.3%) regarded dietitians as the most suitable professionals to provide personalised dietary advice based on nutrigenetic testing. In this study [122], health and disease prevention were cited as the primary benefits for nutrigenetic testing and there were concerns regarding accessibility to genetic testing through telemarketing companies and spam as well as companies using personal genetic data to promote sales [122]. Although there are limited data on the attitudes of consumers in LMICs towards nutrigenetics, previous studies by our group indicated a reluctance to give blood samples for genetic testing. Hence, individuals from various sociodemographic backgrounds may have varying levels of trust in service providers, regulators, and online information delivery. Consequently, preferences regarding the manner and source of personalised nutrition services might vary across countries and cultural settings [119].

Integration of Data from Multiple Fields

Precision nutrition is centred around integrating data from multiple disciplines such as metabolomics, epigenetics, and the gut microbiome as this is argued to be important in enhancing the scientific understanding of inter-individual variability in response to dietary interventions, although the practicality and effectiveness of this process are still being explored [123, 124]. So far, progress has been made in the mechanistic understanding of dietary interventions through the integration of omics technologies such as metabolomics and the gut microbiome [125]. Metabolomics focuses on analysing small molecules (metabolites) found in biological samples to understand changes in metabolism under various conditions [123]. Metabolites are the direct products of dietary consumption and metabolism, enabling a more accurate assessment of biological and physiological pathways as well as the related biomarkers for diet or disease [125]. Metabolic profiles have been linked to variations in nutritional needs and responses to diet, which offers the potential to stratify populations with similar metabolic and phenotypic profiles, enabling the development of tailored dietary recommendations [126]. Moreover, an accurate assessment of dietary intake is essential in understanding the link between diet and diseases, and methods currently used to assess dietary intake such as food frequency questionnaires, weighed food diaries, and 24-h recalls are prone to errors including underestimation of energy intake [123]. By applying metabolomics, specific biomarkers associated with foods eaten can be obtained, and this involves participants consuming specific foods and the collection of biofluid samples over time [123]. These biomarkers could provide useful information to supplement self-reported dietary intake [126].

Using metabolomics, a possible explanation of the mechanisms underlying the health benefits of low glycaemic index diets was reported in a 6-month parallel randomised trial involving 122 adult participants with overweight and obesity [127]. An analysis of plasma metabolites revealed that a low glycaemic index diet resulted in higher levels of serine, lower levels of valine and leucine, and alterations in a group of two sphingomyelins, two lysophosphatidylcholines, and six phosphatidylcholines. These changes in plasma amino acids and lipid species were found to be correlated with changes in body weight, glucose levels, insulin, and certain inflammatory markers [127]. Similarly, a metabolomic study identified underlying risks for T2D, insulin resistance, and related comorbidities through analysis of

blood metabolites in participants who had normoglycaemia and no clinical symptoms [128]. In this study [128], metabolomic analysis was performed at baseline and after the implementation of a personalised lifestyle intervention for 100 days. By combining metabolites associated with specific disease risks and calculating risk scores, the baseline analysis showed that some of the participants had moderate to high risks for insulin resistance, T2D, and CVDs. However, when the analysis was repeated following the personalised lifestyle intervention, specific metabolites that were previously outside the normal range had returned to the normal range, thereby reducing potential health risks during the second time point [128].

The gut microbiome supports the host by interacting directly or indirectly with host cells through the production of bioactive molecules, and this interaction allows the gut microbiome to regulate various biological processes related to immunity and energy balance [129]. This ability to interact with the host depends on the types of bacteria present and their distribution within the gut microbial community [130]. The application of the gut microbiome in precision nutrition involves using the gut microbiome as a biomarker to predict how specific dietary components affect host health, and the use of this information to design precision dietary interventions aimed at promoting health [129]. It has been highlighted that the way individuals respond to certain dietary interventions may be influenced by the composition and function of the gut microbiota which differs among individuals with distinct metabolic profiles [130]. In a study involving 14 men with obesity [131], controlled diets supplemented with resistant starch or non-starch polysaccharide and a weight-loss diet were found to result in distinct changes in the microbiota composition. The resistant starch diet was linked to an increase in several Ruminococcaceae phylotypes, while the non-starch polysaccharide primarily resulted in an increase in Lachnospiraceae phylotypes, and the weight-loss diet significantly decreased *Bifidobacteria*. It was concluded that since the dietary response of an individual's microbiota varied significantly and was inversely related to its diversity, individuals could be classified as responders or non-responders based on the characteristics of their intestinal microbiota [131]. In another study involving a cohort of 800 participants with no previous diagnosis of T2D [132], variations in postprandial glycaemic responses to similar standardised meals were observed. A machine learning algorithm was then developed by integrating blood parameters, dietary habits, anthropometric data, physical activity, and gut microbiota information from the same cohort and was found to be effective in predicting personalised postprandial glycaemic responses to real-life meals. Subsequently, a blinded randomised controlled dietary intervention based on the algorithm resulted in significantly reduced postprandial responses and consistent changes in gut microbiota composition [132].

Epigenetics covers the molecular processes that can alter the activity of genes without changing the DNA sequence, and these processes include DNA methylation, histone modifications, and alterations in noncoding RNAs [133]. Epigenetic changes might explain individual differences in metabolic health and responses to diet, and have the potential to identify novel biomarkers for precision nutrition and targets for precise interventions [134]. Similarly, transcriptomics technologies have been applied in nutrition research to understand the molecular and signalling pathways associated with nutrients [135]. In an interventional study, a transcriptomic approach was used to assess the impact of a high-carbohydrate or high-protein diet on gene expression profiles in blood leukocytes [136]. The findings showed that the high-carbohydrate breakfast resulted in changes in the expression of genes related to glycogen metabolism, while the high-protein breakfast led to changes in the expression of genes associated with protein biosynthesis [136]. Another interventional study [137], utilising a transcriptomic approach to assess the postprandial effect of consuming different fatty acids on the gene expression profiles of peripheral blood mononuclear cells, reported that intake of PUFA was associated with a decrease in the expression of genes in liver X receptor signalling, while consumption of SFA led to an increase in the expression of these genes. Consumption of PUFA also resulted in an increase in the expression of genes linked to cellular stress responses, while MUFA had a moderate effect on several genes [137]. The findings suggest that data from multiple individuals undergoing postprandial gene expression profiling in peripheral blood mononuclear cells could enable the stratification of gene expression profiles as "healthy" or "unhealthy," as well as the identification of particular meals that could be categorised as healthy or unhealthy for such individuals [123].

With regard to obesity, a significant interaction was observed between SFA intake and the *APOA2* SNP rs5082 on the risk of obesity in a study of 3,462 participants from three populations in the USA (the Framingham Offspring Study [1,454 whites], the Genetics of Lipid Lowering Drugs and Diet Network Study [1,078 whites], and the Boston-Puerto Rican Centers on Population Health and Health Disparities Study [930 Hispanics of Caribbean

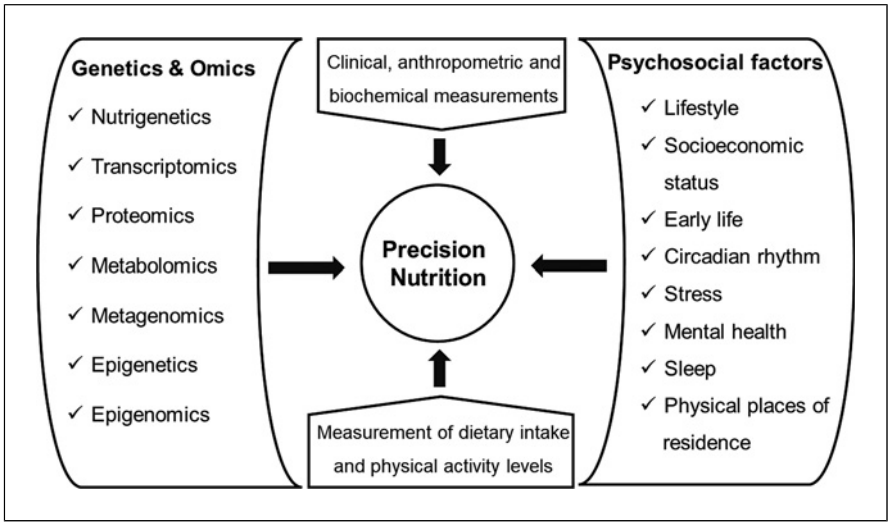

Fig. 2. List of factors that should be considered for the implementation of precision nutrition.

origin]) [22]. This finding was also replicated in Chinese, Asian Indians, and whites from the Valencia Region of Spain [138]. Individuals with the "CC" genotype had an increased risk of obesity compared to those with the "TT" or "TC" genotypes only when their SFA intake was high (≥22 g/day) [22, 138]. To explore the mechanisms underlying this interaction, the authors performed a multi-omics study involving methylome, transcription, and metabolomic analyses from three different populations (the Boston Puerto Rican Health Study, the Genetics of Lipid Lowering Drugs and Diet Network Study, and the Framingham Heart Study) [139]. The epigenetic state of the *APOA2* regulatory region was found to be linked to SFA intake and the rs5082 genotype, causing differences in *APOA2* expression between the "CC" and "TT" genotypes on a high-SFA diet and influencing branched-chain amino acid and tryptophan metabolism [139]. Therefore, integrating data from nutrigenetics, metabolomics, the gut microbiome, epigenetics, phenotypic traits, and lifestyle factors might help in designing personalised and precise nutrition interventions. Machine learning and artificial intelligence enable the integration of data from various fields by identifying patterns in large datasets and grouping similar data to create predictive models and algorithms [140]. A machine learning model utilising age, systolic blood pressure, routine blood and urine tests as well as dietary intake values has been reported to be effective in identifying young, asymptomatic individuals at higher risk of CVDs [141]. Similarly, integrating data on lifestyle factors, gut microbiome, clinical variables, subcutaneous adipose tissue gene expression, and metabolomics derived from serum, urine, and faeces were found to be effective in identifying biomarkers linked to insulin sensitivity [142]. Thus, integrating data from multiple disciplines could help in designing personalised and precise dietary interventions for the prevention and management of cardiometabolic diseases, although the effectiveness and practicality of this approach are still being explored (Fig. 2).

Conclusion

Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Several factors might influence variations among individuals with regard to dietary exposures and metabolic responses, and these include genetic diversity, cultural and lifestyle factors as well as socio-economic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics, and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition, although more research is needed to confirm the practicality and effectiveness of this approach. Therefore, conducting gene-diet interaction studies in diverse populations is essential to improve their clinical application worldwide. To bridge the gap between existing nutrigenetic insights and their application in clinical practice, it is vital for initial findings to be replicated in independent samples, followed by dietary intervention studies. Studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention

studies will be required to further strengthen the evidence and facilitate their application in clinical practice. The issues discussed in this review are particularly important, given the current diverse climate, which poses significant risks to food security and diet quality, making vulnerable populations across the world susceptible to various forms of malnutrition [143].

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

K.S.V. conceived the study; R.W. and K.S.V. wrote the manuscript and approved the final version of the manuscript.

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