GeNuIne (gene-nutrient interactions) collaboration: towards implementing multi-ethnic population-based nutrigenetic studies of vitamin B12 and D deficiencies and metabolic diseases

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GeNuIne (gene–nutrient interactions) Collaboration: towards implementing multi-ethnic population-based nutrigenetic studies of vitamin B_{12} and D deficiencies and metabolic diseases

Karani S. Vimaleswaran[1,2]
[1]*Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences, University of Reading, Reading, UK*
[2]*The Institute for Food, Nutrition, and Health (IFNH), University of Reading, Reading, UK*

Gene–nutrient interactions (GeNuIne) collaboration, a large-scale collaborative project, has been initiated to investigate the impact of gene–nutrient interactions on cardiometabolic diseases using population-based studies from ethnically diverse populations. In this project, the relationship between deficiencies of vitamins B_{12} and D, and metabolic diseases was explored using a nutrigenetic approach. A genetic risk score (GRS) analysis was used to examine the combined effect of several genetic variations that have been shown to be associated with metabolic diseases and vitamin B_{12} and D deficiencies, respectively. In Sri Lankan, Indonesian and Brazilian populations, those carrying a high B_{12}-GRS had an increased risk of metabolic diseases under the influence of dietary protein, fibre and carbohydrate intakes, respectively; however, in Asian Indians, genetically instrumented metabolic disease risk showed a significant association with low vitamin B_{12} status. With regards to nutrigenetic studies on vitamin D status, although high metabolic-GRS showed an interaction with dietary carbohydrate intake on vitamin D status, the study in Indonesian women demonstrated a vitamin D GRS–carbohydrate interaction on body fat percentage. In summary, these nutrigenetic studies from multiple ethnic groups have provided evidence for the influence of the dietary factors on the relationship between vitamin B_{12}/D deficiency and metabolic outcomes. Furthermore, these studies highlight the existence of genetic heterogeneity in gene–diet interactions across ethnically diverse populations, which further implicates the significance of personalised dietary approaches for the prevention of these micronutrient deficiencies and metabolic diseases.

Keywords: Gene–nutrient interactions collaboration: Genetic risk score: Micronutrient intake: Gene–diet interaction: Cardiometabolic diseases

Metabolic diseases such as obesity and diabetes are vastly growing epidemics prevalent in both developed and developing countries, affecting all ages, genders, ethnicities and socioeconomic groups[1,2]. Metabolic diseases have been shown to reduce the quality of life for the individual by leading to severe and potentially life-threatening consequences, such as CVD, cancers, hypertension and musculoskeletal disorders[3,4]. Even

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; GeNuIne, gene–nutrient interactions; GRS, genetic risk score.
Corresponding author: Karani S. Vimaleswaran, email v.karani@reading.ac.uk

though the main influences of metabolic diseases are lifestyle factors such as diet and exercise, a substantial amount of evidence is emerging in the field of genetic epidemiology, suggesting that an individual's genetic profile may also play a key role in the development of these diseases[5–9].

Several studies have shown that healthy lifestyle may modify the association between genetic risk and metabolic disease-related traits[10–16]. Although some studies have shown that increased physical activity levels and healthy diet can attenuate the effect of genetic variants on metabolic traits, other studies have shown conflicting results[17], which could be attributed to genetic heterogeneity and differences in the dietary patterns across multiple ethnic groups[7,18,19]. Majority of the gene–lifestyle interactions have focused on metabolic disease-related outcomes[20–23] and only a few have focused on vitamins B_{12} and D, two critical vitamins which have been shown to be associated with age-related cardiometabolic diseases[24].

Genetic studies have implicated several gene loci associated with vitamin B_{12} and D concentrations[25–28]. Several Mendelian randomisation studies have explored the relationship between genetically instrumented vitamin B_{12} and D concentrations and metabolic disease-related outcomes; however, the findings have been inconsistent[29–32]. The aim of this paper is to provide an overview of ethnic-specific findings from gene–nutrient interactions (GeNuIne) collaboration that used a nutrigenetic approach to investigate the relationship between metabolic disease-related traits and vitamin B_{12}/D status, where the effects of macronutrient intake such as carbohydrate, fat and protein intake on these relationships were explored.

Role of British Nutrition Foundation Drummond Pump Priming Award in gene–nutrient interactions collaboration

Given that the genetic profile varies across various ethnic groups[33,34], it is crucial to explore gene–diet interactions in multiple ethnicities, which will enable us to personalise diet according to each ethnic group[23,35]. To address this issue, the GeNuIne Collaboration was initiated in 2013 to implement nutrigenetic studies on metabolic disease-related traits using population-based studies from multiple ethnic groups in lower-middle income countries[6,7]. The British Nutrition Foundation Drummond Pump Priming award was the seed funding for the initiation of the GeNuIne Collaboration, where the funds were used to establish a collaborative network with academic institutions in India[12], Brazil[36], Turkey[22], Thailand[37], Sri Lanka[38], Indonesia[39], Morocco and Pakistan. In addition, the Newton Fund British Council Researcher Links travel grants were obtained to carry out pilot studies in lower-middle income countries. Given that there were no nutrigenetic studies that had explored the relationship between metabolic diseases and vitamin B_{12}/D status, the GeNuIne Collaboration was established to address this missing gap in nutritional science[7,40].

Use of genetic risk scores as instruments for micronutrient deficiencies and metabolic diseases

Genome-wide association studies have discovered thousands of genetic variants associated with metabolic diseases[41–45] and vitamin B_{12}[25,46]/D[27,47] status, respectively; however, the individual SNPs explain only a small proportion of variation for obesity and diabetes, with limited ability for predicting disease risk. Given that these complex traits are influenced by several genetic variants, with each having a small effect on these traits, combining the effect of several variants as a polygenic score can provide a better understanding of disease risk than single variant approaches[48–50]. The idea of grouping individual SNPs into genetic risk scores (GRSs) has been used to predict and quantify a discrete increment in the overall risk of diseases, as well as capturing the overall variance in a trait[51]. There are several approaches for generating a GRS such as weighted and unweighted methods[52]. Fundamentally, a GRS is constructed by summarising genotype data across multiple genetic variants. The most commonly used method is summing the number of alleles that confer risk across all loci (zero, one or two). Employing the GRS approach for predicting disease risk has advantages over analysing the effect of individuals SNPs as it decreases the drawback of multiple testing, maximises statistical power and widens the scope of generalisability of genetic associations[48,51]. Previous studies have emphasised the potential of GRS for predicting the risk of complex diseases. Given that there were no previously reported effect sizes in lower-middle income countries, the nutrigenetic studies from the GeNuIne Collaboration used an unweighted GRS method[53] which was calculated for each participant by adding the number of risk alleles for metabolic diseases and micronutrient deficiencies, respectively. A value of zero, one and two was assigned to each SNP, which indicates the number of metabolic disease-related risk alleles and vitamin B_{12}/D lowering risk alleles, respectively. These values were then calculated by adding the number of risk alleles across each SNP. The risk allele score was then divided by the median into two groups: participants carrying a lower number of risk alleles and those with a higher number of risk alleles.

Findings from gene–nutrient interactions collaboration

Impact of genetic and dietary factors on vitamin B_{12} status and metabolic diseases in ethnically diverse populations

Several epidemiological studies have shown associations between metabolic diseases and micronutrient deficiencies including vitamin B_{12}[54–56]; however, the findings have been inconsistent due to high level of confounding. Given that genetic associations are less prone to confounding[26,30], studies conducted as part of the GeNuIne Collaboration used a nutrigenetics approach to examine this relationship (Fig. 1).

South Asians have been shown to exhibit increased visceral fat and waist circumference, hyperinsulinaemia and insulin resistance; this has been termed the 'South

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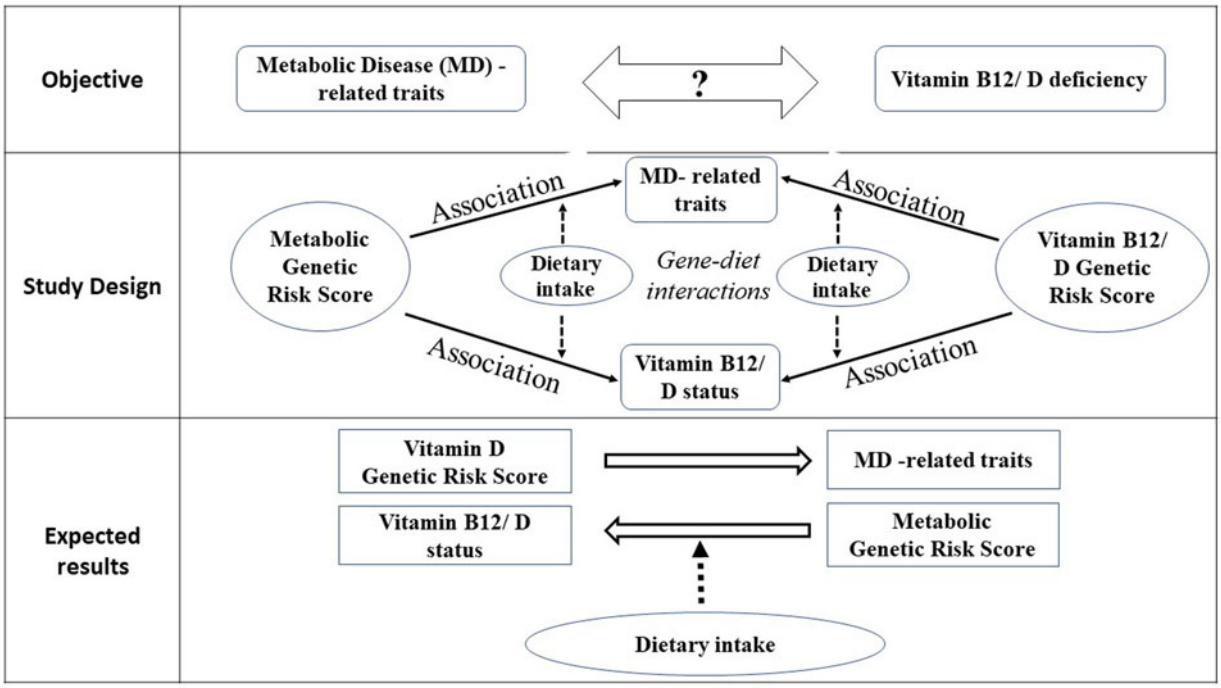

Fig. 1. Objective, study design and the expected results of the nutrigenetic studies from the GeNuIne Collaboration. Genetic associations are represented by one-sided arrows with unbroken lines and interactions between GRS and dietary intakes on metabolic traits and vitamin D/B_{12} status are shown as one-sided arrows with broken lines. The association of the metabolic-GRS with vitamin B_{12}/D status and metabolic traits, respectively, and the association of vitamin B_{12}/D-GRS with vitamin B_{12}/D status and metabolic traits, respectively, were tested. In addition, the effect of dietary factors on these genetic associations was examined.

Asian phenotype'[57,58]. Although there is a strong genetic component to developing the 'South Asian Phenotype', consuming an unhealthy diet and leading a sedentary lifestyle can further contribute to this phenotype[12]. A cross-sectional nutrigenetic study in nine hundred Asian Indians demonstrated that metabolic-GRS, that was developed using metabolic disease-related genetic variants (Table 1), was associated with vitamin B_{12} levels, where carriers of more than one risk allele for the GRS had significantly lower vitamin B_{12} concentrations, compared to those carrying zero risk alleles[59] (Fig. 2). This finding suggests that genetically instrumented metabolic disease could be a risk factor for vitamin B_{12} deficiency with implications on the possible targeting of relevant obesity prevention strategies. However, a cross-sectional nutrigenetic study in one-hundred and nine Sinhalese adults aged 25–50 years showed that vitamin B_{12}-GRS, that was developed using vitamin B_{12}-related genetic variants (Table 1), was associated with central obesity under the influence of protein consumption[38]. Given that the daily intake of protein is low in Sri Lankan adults[60,61], these findings may have significant public health implications in terms of revising dietary guidelines for this population, which could prevent central obesity and its related complications.

Countries in Southeast Asia, especially Indonesia, have undergone rapid epidemiological and nutritional transitions over the past few decades[62]. Indonesia has the seventh largest number of diabetic patients (about 10 million)[63] and non-communicable diseases are estimated to account for 73 % of all deaths of which, CVD contributed to 35 % followed by cancers (12 %) and diabetes (6 %). In a cross-sectional study of one-hundred and seventeen Indonesian women[39], those with high B_{12}-GRS (comprising nine B_{12}-related SNPs) and consuming a low fibre diet (4·90(SD 1·00) g daily) had significantly higher haemoglobin A1C levels compared to those with low B_{12}-GRS (Fig. 2). This study suggests that genetically instrumented low B_{12} levels might be a risk factor for the development of metabolic diseases such as type 2 diabetes.

Brazil is a developing country that is undergoing rapid economic, demographic and behavioural transition[64–66] which has resulted in an increased prevalence of CVD, one of the leading causes of mortality[67]. Studies have also reported unhealthy dietary patterns which are characterised by higher intakes of processed foods, refined grains and sugar sweetened beverages[68]. The first nutrigenetics study on vitamin B_{12} status in Brazil[36] was a cross-sectional study in one-hundred and thirteen adolescents (10–19 years old), recruited from a public school in the city of Goiânia, Goiás, Brazil. The study demonstrated that those who had high carbohydrate intake and high B_{12}-pathway-related genetic risk had significantly higher oxidised-LDL concentrations compared to those with low genetic risk suggesting the impact of genetically instrumented B_{12} status on cardiovascular risk factors.

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Table 1. Details of the SNPs that were examined in each ethnic group

Population	Study design	Vitamin B_{12}-related SNPs	Metabolic disease-related SNPs
Sri Lankan	Cross-sectional study[38]	Methylenetetrahydrofolate reductase [*MTHFR*] – rs1801133 Carbamoyl-phosphate synthase 1 [*CPS1*] – rs1047891 Cubulin [*CUBN*] – rs1801222 CD320 molecule [*CD320*] – rs2336573 *TCN2* – rs1131603 Citrate lyase β-like [*CLYBL*] – rs41281112 *FUT2* – rs602662 Transcobalamin 1 [*TCN1*] – rs34324219 Fucosyltransferase 6 [*FUT6*] – rs778805 Methylmalonyl-CoA mutase [*MUT*] – rs1141321	Fat mass and obesity-associated [*FTO*] – rs9939609 and rs8050136 Melanocortin 4 Receptor [*MC4R*] – rs17782313 and rs2229616 Transcription factor 7-like 2 [*TCF7L2*] – rs12255372 and rs7903146 Potassium voltage-gated channel subfamily J member 11 [*KCNJ11*] – rs5219 Calpain 10 [*CAPN10*] – rs3792267, rs2975760 and rs5030952
Brazilian	Cross-sectional study[36]	Fucosyltransferase [*FUT2*] – rs602662 Transcobalamin 2 [*TCN2*] – rs1801198 5-Methyltetrahydrofolate-homocysteine methyltransferase or methionine synthase [*MTR*] – rs1805087 5-Methyltetrahydrofolate-homocysteine methyltransferase reductase or methionine synthase reductase [*MTRR*] – rs1801394 Betaine-homocysteine *S*-methyltransferase [*BHMT*] –rs3797546 and rs492842 *MTHFR* – rs1801131 *MTHFR* – rs1801133 Catechol-*o*-methyl transferase [*COMT*] –rs4680 and rs4633	
Indian	Case–control study[59]	–	*FTO* – rs9939609 and rs2388405
Indonesian	Cross-sectional study[39]	*MTHFR* – rs1801133 *CPS1* – rs1047891 *CUBN* – rs1801222 *CD320* – rs2336573 *TCN2* – rs1131603 *FUT2* – rs602662 *TCN1* – rs34324219 *FUT6* – rs778805 *MUT* – rs1141321	*FTO* – rs9939609 and rs8050136 *MC4R* – rs17782313 and rs2229616 *TCF7L2* – rs12255372 and rs7903146 *KCNJ11* – rs5219 *CAPN10* – rs3792267 and rs5030952

Given that high fibre and protein diets are recommended for preventing metabolic disease outcomes[69–71], the gene–diet interaction findings observed in these nutrigenetic studies will have significant public health implications, where people carrying risk alleles for vitamin B_{12} deficiency could be advised to alter their diet according to their ethnic background.

Impact of genetic and dietary factors on vitamin D status and metabolic diseases in ethnically diverse populations

Vitamin D is a fat-soluble vitamin and a secosteroid prohormone that plays a crucial role in calcium absorption, immune function and protecting bone, muscle and heart health[72–74]. Deficiency of vitamin D has been found to contribute to the development of various cardiometabolic conditions such as obesity, diabetes and hypertension[75,76]. However, the association between vitamin D deficiency and these cardiometabolic conditions has not been firmly established. The application of a nutrigenetic approach to establish the link between vitamin D status and metabolic diseases is favoured over observational studies since genetic associations are less affected by confounding[26].

A recent review from the GeNuIne Collaboration team has identified seventy-three peer reviewed articles demonstrating ninety-two significant ethnic-specific associations between genes related to the synthesis and metabolism of 25-hydroxyvitamin D (25(OH)D) and metabolic disease-related outcomes such as obesity and diabetes traits[27]. Similarly, there are also studies which have shown associations between metabolic disease-related genes and 25(OH)D concentrations[28,77]. Using these disease-specific genetic variations, the studies from GeNuIne Collaboration used a nutrigenetic approach to examine the link between vitamin D status and metabolic diseases. In addition, the studies investigated the combined effects of multiple genetic variants using GRSs instead of the common single gene variant method in order to increase the statistical power to detect gene–diet interactions[48,51]. In this nutrigenetic approach, the studies tested whether dietary factors influenced the associations between vitamin D status and metabolic diseases.

The first nutrigenetic study of vitamin D and metabolic diseases was implemented in Asian Indians[78]. In this study, five hundred and forty-five Asian Indians were randomly selected from the Chennai Urban Rural Epidemiology Study, where two hundred and nineteen were normal glucose tolerant individuals, one hundred

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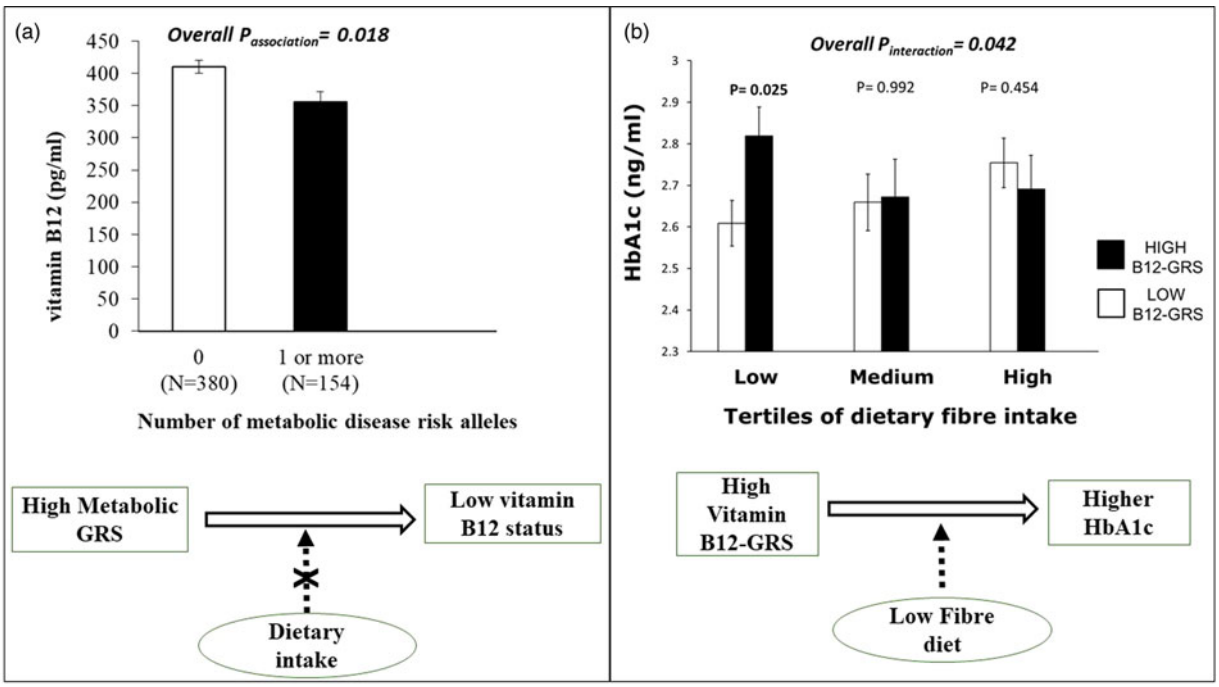

Fig. 2. Results from the vitamin B_{12}-related nutrigenetic studies in South Asians and Southeast Asians. (a) A nutrigenetic study in Asian Indians[59]: metabolic disease risk increasing alleles ranged from 0 to 3. The white bars indicate individuals with 0 risk alleles and the black bars indicate individuals carrying ≥1 alleles. Individuals who carried 1 or more risk alleles had significantly lower B_{12} concentrations compared to individuals carrying 0 risk alleles ($P = 0{\cdot}018$). (b) A nutrigenetic study in Southeast Asians (Indonesia)[39]: individuals who carried nine or more risk alleles for vitamin B_{12} deficiency (high B_{12}-GRS) had significantly higher HbAC1 concentrations (ng/ml) in the lowest tertile of fibre intake (g) (mean(SD): 4·90(SD 1·00) g) compared to those with eight or less risk alleles for vitamin B_{12} deficiency (low B_{12}-GRS). GRS: genetic risk score; HbAC1, haemoglobin AC1.

and fifty-one were with pre-diabetes and one hundred and seventy-five had type 2 diabetes. The study showed a significant interaction between metabolic GRS and carbohydrate intake on 25(OH)D, where individuals consuming a low carbohydrate diet (≤62 % of total energy intake) and those having lesser number of metabolic risk alleles had significantly higher levels of 25 (OH)D. However, among individuals who had a higher carbohydrate intake (>67 %), despite having lower number of metabolic risk alleles, did not show a significantly higher 25(OH)D concentrations. These findings demonstrate that individuals carrying a low genetic risk of metabolic diseases are likely to have higher 25(OH)D levels if they consume a low carbohydrate diet (Fig. 3). Given that previous studies have reported that Asian Indians have lower 25(OH)D concentrations[79–81], these findings suggest that, even if the metabolic genetic risk is lower, following the dietary carbohydrate recommendations (50–60 %) is required to improve the vitamin D status in this Asian Indian population.

To date, only a few studies have examined the influence of SNPs on 25(OH)D levels in populations within Southeast Asia[82]. The study from GeNuIne Collaboration focused on Minangkabau women from Padang, the capital of West Sumatra. The Minangkabau ethnic group is of particular interest given that the Minangkabau people have the largest matrilineal family structure in the world[83–86]. A nutrigenetic study to investigate the relationship between vitamin D status and metabolic traits in a cohort of one hundred and ten Minangkabau women from urban and rural areas of Padang was conducted[87]. The study identified a significant interaction between the vitamin D-GRS and carbohydrate intake (g) on body fat percentage, where individuals who consumed a high carbohydrate diet (mean(SD): 319 g daily(SD 46)) and carried >2 vitamin D-lowering risk alleles had significantly higher body fat percentage than those with ≤2 risk alleles (Fig. 3). These findings are biologically plausible as vitamin D has been shown to mediate the impact of reduced consumption of carbohydrate through its direct action on pancreatic β-cell function[88]. Given that percent body fat is a better predictor of cardiovascular risk factors[89], and that the main source of energy for the Minangkabau is carbohydrates, where rice, banana, cassava, maize, sweet potato, sago, noodles, glutinous rice and mung bean are part of their daily meals[86], these findings, if replicated, may have a significant public health implication in preventing CVD in Minangkabau women by developing dietary intervention strategies to reduce the intake of carbohydrates.

There are ethnic differences in body fat composition given the complex interaction between the genes, lifestyle and culture. Understanding of ethnic differences may

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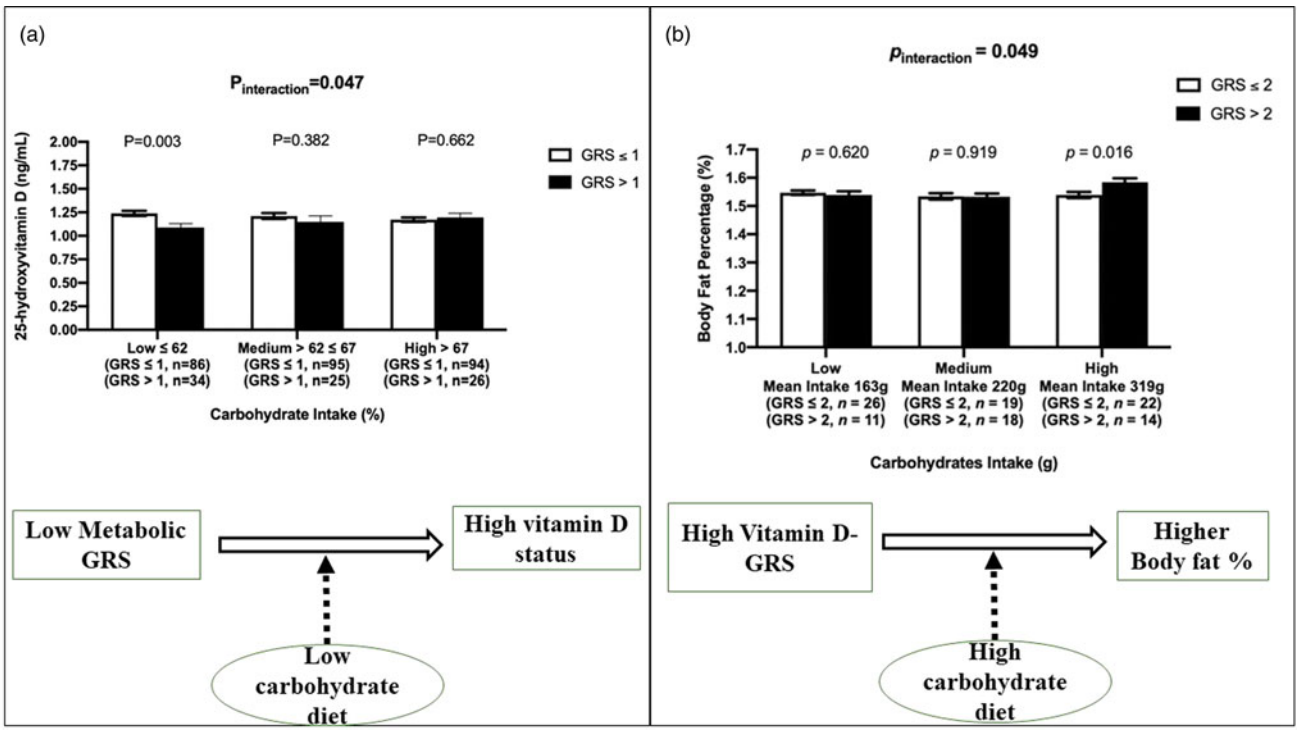

Fig. 3. Results from the vitamin D-related nutrigenetic studies in South Asians and Southeast Asians. (a) A nutrigenetic study in Asian Indians[78]: interaction between metabolic GRS and carbohydrate intake (%) on log 25(OH)D. White bars indicate individuals with GRS ≤1 risk allele; black bars indicate individuals with GRS >1 risk allele. Among individuals with low carbohydrates intake, those with <1 risk allele had significantly higher 25(OH)D concentrations compared to those with >1 risk allele ($P = 0{\cdot}003$). (b) A nutrigenetic study in Southeast Asians (Indonesia)[87]: interaction between the vitamin D-GRS and dietary carbohydrate intake (g) on body fat percentage (%) ($P_{interaction} = 0{\cdot}049$). Those who were on the highest tertile of carbohydrate intake and carried >2 risk alleles had significantly higher body fat percentage compared to individuals carrying ≤2 risk alleles ($P = 0{\cdot}016$). GRS: genetic risk score.

lead to the implementation of effective approaches to recognise and prevent metabolic diseases across different ethnic groups. It is important that the findings from these studies are replicated before consideration is given to personalised dietary advice for individuals carrying a higher genetic risk of vitamin D deficiency.

Strengths and limitations

Firstly, the studies from the GeNuIne Collaboration are the first nutrigenetic studies to evaluate the relationship of vitamin B_{12}/D status with metabolic disease risk in ethnically diverse populations. Secondly, the construction of the GRSs instead of a single-SNP approach had increased the statistical power to identify gene–diet interactions[51]. Thirdly, the use of a comprehensive, validated food frequency questionnaires collected by trained nutritionists increased the accuracy of dietary data collection. The study does have several limitations that should be acknowledged. The studies had a cross-sectional study design, and hence, causality cannot be inferred. Given that the studies were a pilot, the sample size was small; however, the studies were sufficiently powered to identify significant gene–diet interactions. Even though the study used a validated food frequency questionnaire, bias due to self-reported dietary intake information cannot be excluded. Age was adjusted in all the regression analyses; however, it is possible that the unmatched age in cases and controls, especially the study in Asian Indians, might have introduced a bias in the study. Furthermore, other confounders such as sex, BMI, disease status, socioeconomic status and locality, wherever appropriate, were adjusted in all our analyses; but residual confounding due to unknown factors cannot be excluded[90]. In addition, these studies investigated only a limited number of the increasingly identified metabolic-associated SNPs, thus there is a need to utilise a comprehensive panel of genetic variants to construct the GRS. Finally, the studies were conducted in specific ethnic groups and hence, the findings cannot be generalised to the countries.

From nutrigenetics to genotype-based dietary recommendations

Although remarkable improvements have been achieved in epidemiological studies in the field of nutrigenetics, future research should focus on understanding the metabolic pathways underlying gene–diet interactions. Therefore, science that identifies the connection between compounds in food and diet, and genetic susceptibility is needed. Food scientists and nutritionists have described a

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new discipline called 'Foodomics', which is defined as the application of new methodologies, or 'omics', to improve individual health[91,92]. This field has helped to identify the interactions of bioactive compounds from the diet at the molecular and cellular levels to provide evidence on their health benefits, and to understand variations and differential response to nutrition interventions.

Another approach is nutrigenomics, which investigates the effect of diet and its bioactive components on gene expression[93]. This field of research will help in understanding how diet interacts with the metabolic pathways, which may have a role in diet-related diseases. Although nutrigenetics investigates gene–diet interaction or in other words, explores how the genes (at the levels of SNPs) cause the disease in response to a particular diet[34]. The knowledge from these two fields will help in designing optimal diets that allow health maintenance and disease prevention in an individual[91].

Besides personalised nutrition, precision nutrition is another approach, which is aimed to develop more comprehensive nutritional recommendations based on the interaction between internal and external parameters of an individual's environment throughout life[15,94,95]. Precision nutrition takes into account the genetic factors, dietary habits, food behaviour, physical activity, the microbiota and the metabolome[96–99]. For implementing precision nutrition, the underlying science should be translated so that clinicians and other health care providers understand the scientific basis of heterogeneity in metabolic diseases and can deliver precision nutrition interventions to people with such chronic diseases. In addition, policy makers will need to understand the underlying science, so that they can enforce the use of precision nutrition in the implementation of policy recommendations and public health interventions. Although nutrigenetic and nutrigenomic studies hold immense promise for preventing metabolic diseases and micronutrient deficiencies, there are several challenges that need to be overcome[100,101].

In summary, clear guidance from nutrigenetics studies is required for the implementation of personalised nutrition[102] and foodomics[92], which can only be achieved by using large and well powered studies, examining various ethnic groups, considering the variety in dietary patterns globally and conducting additional testing for other modifiable factors such as physical activity.

Conclusions

The studies from GeNuIne Collaboration have provided evidence for the influence of the dietary factors on the relationship between vitamin B_{12}/D deficiency and metabolic outcomes[36,39,40,59,78,87] and highlighted the existence of genetic heterogeneity in gene–diet interactions across ethnically diverse populations. These differences in gene–diet interactions implicate the significance of personalised approaches for the prevention of vitamin B_{12} and D deficiencies and metabolic diseases. In terms of implementing ethnic-specific personalised dietary strategies, for Sri Lankans, Indonesians and Brazilians who are carrying a high B_{12}-GRS, it would be possible to prevent the development of metabolic diseases by modifying their dietary daily intakes of protein, fibre and carbohydrate, respectively. For Asian Indians with low metabolic-GRS, a low carbohydrate diet can improve the vitamin D status, and for Southeast Asian women, reducing the intake of carbohydrate-rich foods can overcome the genetic risk of obesity.

It is important that these gene–diet interactions are replicated, before public health recommendations can be enforced. Furthermore, prospective genotyping should be considered in future studies to avoid an imbalance in the frequency of genotype between groups, which might confound the findings, and to increase statistical and discriminatory power[103]. Also, it is important to further investigate whether people with increased weight require more vitamin B_{12}/D containing foods, for the possibility of implementing micronutrient deficiency screening programmes in the population. If low vitamin B_{12}/D concentrations stimulate metabolic diseases through a dietary influence, it is important that mechanistic studies are carried out to determine how vitamin B_{12}/D interacts with adipose tissue metabolism or how epigenetic mechanisms contribute to the epidemic of metabolic diseases[104]. These functional studies are highly warranted before applying personalised dietary strategies to prevent or treat these micronutrient deficiencies and metabolic diseases.

GeNuIne Collaborators

Hugh Sinclair Unit of Human Nutrition and Institute for Cardiovascular and Metabolic Research (ICMR), Department of Food and Nutritional Sciences, University of Reading UK: Prof. Julie Lovegrove; Dr Mohan's Diabetes Specialties Centre, Chennai, India: Prof. Mohan Viswanathan, Dr Anjana Mohan, and Dr Guha Pradeepa; Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, India: Dr Radha Venkatesan; Department of Foods, Nutrition and Dietetics Research, Madras Diabetes Research Foundation, Chennai, India: Mrs Sudha Vasudevan; School of Biosciences and Medicine, Faculty of Health and Medical Sciences, University of Surrey, UK: Dr Shelini Surendran; Faculty of Nutrition, Federal University of Goiás, Goiânia: Dr Maria Aderuza Horst; Faculty of Medicine, Andalas University, Padang, Indonesia: Prof. Nur Indrawathy Liputo, Dr Finny Fitri Yani; Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia: Prof Nurpudji A. Taslim; Department of Pediatrics, Medical Faculty of Sam Ratulangi University, Republic of Indonesia: Dr Nelly Mayulu; Department of Nutrition, Faculty of Health Science, Universitas Alma Ata, Yogyakarta, Indonesia: Dr Arif Sabta Aji; Grupo de Análisis para el Desarrollo, Lima, Peru: Dr Alan Sánchez; Instituto de Investigación Nutricional, Lima, Peru: Prof. Mary E Penny; Department of International Development, University of Oxford, UK: Dr Marta Favara; Centre for Biomedical and Nutrition

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Research (CBNR), Universiti Tunku Abdul Rahman (Kampar Campus), Malaysia: Dr Anto Cordelia Tanislaus Antony Dhanapal, Dr Eddy Seong Guan Cheah, and Dr Annaletchumy Loganathan; Faculty of Health and Social Care, University of Chester, Chester, UK: Prof. Basma Ellahi; Biochemistry and Biotechnology Department, College of Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana: Dr Reggie Annan; Department of Nutrition and Dietetics, Hacettepe University, Ankara, Turkey: Dr Zehra Buyuktuncer-Demirel; Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK: Dr Sanjay Kinra; Université Hassan II de Casablanca, Laboratoire de Biologie et Santé, Faculté des Sciences Ben M'Sik, Unité de Recherche en Nutrition Humaine, Casablanca, Morocco: Prof. Abdelfettah Derouiche, Dr Ali Jafri; Department of Food Science and Technology, Faculty of Agro-Industry, Kasetsart University, Bangkok, Thailand: Dr Parichat Hongsprabhas, Dr Sudathip Sae-tan; National Institute of Food Science and Technology, Faculty of Food, Nutrition and Home Sciences, University of Agriculture, Faisalabad, Pakistan: Dr Mian Kamran Sharif.

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Conflict of Interest

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Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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