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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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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 B₁₂ 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 B₁₂ and D deficiencies, respectively. In Sri Lankan, Indonesian and Brazilian populations, those carrying a high B₁₂-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 B₁₂ 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 B₁₂/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.
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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.

Several studies have shown that healthy lifestyle may modify the association between genetic risk and metabolic disease-related traits. 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, which could be attributed to genetic heterogeneity and differences in the dietary patterns across multiple ethnic groups.

Majority of the gene–lifestyle interactions have focused on metabolic disease-related outcomes and only a few have focused on vitamins B12 and D, two critical vitamins which have been shown to be associated with age-related cardiometabolic diseases.

Genetic studies have implicated several gene loci associated with vitamin B12 and D concentrations and only a few have focused on vitamins B12 and D, respectively. These vitamins have been shown to be associated with age-related cardiometabolic diseases.

Several Mendelian randomisation studies have explored the relationship between genetically instrumented vitamin B12 and D concentrations and metabolic disease-related outcomes; however, the findings have been inconsistent. 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 B12/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, it is crucial to explore gene–diet interactions in multiple ethnicities, which will enable us to personalise diet according to each ethnic group. 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.

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, Brazil, Turkey, Thailand, Sri Lanka, Indonesia, 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 B12/D status, the GeNuIne Collaboration was established to address this missing gap in nutritional science.

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 and vitamin B12/D 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.

There are several approaches for generating a GRS such as weighted and unweighted methods. 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. 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 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 B12/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 B12 status and metabolic diseases in ethnically diverse populations

Several epidemiological studies have shown associations between metabolic diseases and micronutrient deficiencies including vitamin B12; however, the findings have been inconsistent due to high level of confounding. Given that genetic associations are less prone to confounding, studies conducted as part of the GeNuIne Collaboration used a nutrigenetics approach to examine this relationship.

South Asians have been shown to exhibit increased visceral fat and waist circumference, hyperinsulinaemia and insulin resistance; this has been termed the ‘South
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\(\pm\)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.
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 B₁₂ 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 (75).

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 (77). Similarly, there are also studies which have shown associations between metabolic disease-related genes and 25(OH)D concentrations (78,79). 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–disease associations (75,76).

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

| Population   | Study design          | Vitamin B₁₂-related SNPs                                             | Metabolic disease-related SNPs                                      |
|--------------|-----------------------|---------------------------------------------------------------------|-------------------------------------------------------------------|
| Sri Lankan   | Cross-sectional       | Methylene tetrahydrofolate reductase [MTHFR] – rs1801133             | Fat mass and obesity-associated [FTO] – rs9393609 and rs8050136    |
|              | study(36)             | Carbamoyl-phosphate synthase 1 [CPS1] – rs1047891                   | MCT4 – rs17782313 and rs2229616                                  |
|              |                       | Cubulin [CUBN] – rs180122                                            | Transcription factor 7-like 2 [TCF7L2] – rs12255372 and rs7903146 |
|              |                       | CD320 molecule [CD320] – rs2336573                                   | Potassium voltage-gated channel subfamily J member 11 [KCNJ1] – rs5219 |
|              |                       | TCN2 – rs1131603                                                     | Calpain 10 [CAPN10] – rs3792267, rs2975760 and rs5030952         |
|              |                       | Citrate lyase β-like [CLYBL] – rs41281112                            |                                                                  |
|              |                       | FUT2 – rs602662                                                     |                                                                  |
|              |                       | Transcobalam 1 [TCN1] – rs34324219                                  |                                                                  |
|              |                       | Fucosyltransferase 6 [FUT6] – rs778805                              |                                                                  |
|              |                       | Methylmalonyl-CoA mutase [MUT] – rs1141321                           |                                                                  |
| Brazilian    | Cross-sectional       | Fucosyltransferase [FUT2] – rs602662                                 |                                                                  |
|              | study(36)             | Transcobalam 2 [TCN2] – rs1801198                                    |                                                                  |
|              |                       | 5-Methyltetrahydrofolate-homocysteine methyltransferase or methionine synthase [MTR] – rs1805087 |                                                                  |
|              |                       | 5-Methyltetrahydrofolate-homocysteine methyltransferase or methionine synthase [MTR] – 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)             |                                                                     |                                                                  |
| Indonesian   | Cross-sectional       | MTHFR – rs1801133                                                   |                                                                  |
|              | study(36)             | CPS1 – rs1047891                                                    |                                                                  |
|              |                       | CUBN – rs180122                                                    |                                                                  |
|              |                       | CD320 – rs2336573                                                   |                                                                  |
|              |                       | TCN2 – rs1131603                                                   |                                                                  |
|              |                       | FUT2 – rs602662                                                   |                                                                  |
|              |                       | TCN1 – rs34324219                                                  |                                                                  |
|              |                       | FUT6 – rs778805                                                    |                                                                  |
|              |                       | MUT – rs1141321                                                   |                                                                  |

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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
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 B12/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. 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. 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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Fig. 3. Results from the vitamin D-related nutrigenetic studies in South Asians and Southeast Asians. (a) A nutrigenetic study in Asian Indians: 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 = 0.003). (b) A nutrigenetic study in Southeast Asians (Indonesia): interaction between the vitamin D-GRS and dietary carbohydrate intake (g) on body fat percentage (%) (P_interaction = 0.049). 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 = 0.016). GRS: genetic risk score.
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 nutrigenomics 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\(^{(38)}\). 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\(^{(13,94,95)}\). 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\(^{(96,98,99,105,78,87)}\) 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.

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Conflict of Interest

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Authorship

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References

1. Zobel DP, Andrewsen CH, Grarup N et al. (2009) Variants near MC4R are associated with obesity and influence obesity-related quantitative traits in a population of middle-aged people: studies of 14,940 Danes. Diabetes 58, 757–764.
2. Di Cesare M, Soric M, Bovet P et al. (2019) The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC Med 17, 212.
3. Niessen LW, Mohan D, Akuoku JK et al. (2018) Tackling socioeconomic inequalities and non-communicable diseases in low-income and middle-income countries under the sustainable development agenda. Lancet 391, 2036–2046.
4. Miranda JJ, Barrientos-Gutierrez T, Corvalan C et al. (2019) Understanding the rise of cardiometabolic diseases in low- and middle-income countries. Nat Med 25, 1667–1679.
5. Vimalesswaran KS & Loos RJ (2010) Progress in the genetics of common obesity and type 2 diabetes. Expert Rev Mol Med 12, e7.
6. Vimalesswaran KS (2020) A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: findings from the GeNuIne Collaboration. Proc Nutr Soc 79, 194–204.
7. Vimalesswaran KS (2017) Gene–nutrient interactions on metabolic diseases: findings from the GeNuIne Collaboration. Nutr Bull 42, 80–86.
8. Vimalesswaran KS, Cavadino A & Hypponen E (2012) Evidence for a genetic interaction in allergy-related responsiveness to vitamin D deficiency. Allergy 67, 1033–1040.
9. Radha V, Vimalesswaran KS, Deepa R et al. (2003) The genetics of diabetes mellitus. Indian J Med Res 117, 225–238.
10. Vimalesswaran KS, Li S, Zhao JH et al. (2009) Physical activity attenuates the body mass index–increasing influence of genetic variation in the FTO gene. Am J Clin Nutr 90, 425–428.
11. Vimalesswaran KS, Franks PW, Barroso I et al. (2008) Habitual energy expenditure modifies the association between NOS3 gene polymorphisms and blood pressure. Am J Hypertens 21, 297–302.
12. Vimalesswaran KS, Bodhini D, LakshmiPriya N et al. (2016) Interaction between FTO gene variants and lifestyle factors on metabolic traits in an Asian Indian population. Nutr Metab (Lond) 13, 39.
13. Vimalesswaran KS, Cavadino A & Hypponen E (2013) APOA5 genotype influences the association between 25-hydroxyvitamin D and high density lipoprotein cholesterol. Atherosclerosis 228, 188–192.
14. Bodhini D, Gaal S, Shatwan I et al. (2017) Interaction between TCF7L2 polymorphism and dietary fat intake on high density lipoprotein cholesterol. PLoS ONE 12, e0188382.
15. Heianza Y & Qi L (2017) Gene–diet interaction and precision nutrition in obesity. Int J Mol Sci 18, 787.
16. Vimalesswaran KS, Bodhini D, Jiang J et al. (2021) Circulating adiponectin mediates the association between omentin gene polymorphism and cardiometabolic health in Asian Indians. PLoS ONE 16, e0238555.
17. Dietrich S, Jacobs S, Zheng J et al. (2019) Gene–lifestyle interaction on risk of type 2 diabetes: a systematic review. Obes Rev 20, 1557–1571.
18. Radha V, Vimalesswaran KS, Babu HN et al. (2006) Role of genetic polymorphism peroxisome proliferator-activated receptor-gamma2 Pro12Ala on ethnic susceptibility to diabetes in South-Asian and Caucasian subjects: evidence for heterogeneity. Diabetes Care 29, 1046–1051.
19. Vimalesswaran KS (2020) Comment: ‘Evaluation of the association of Omentin 1 rs2274907 A>T and rs2274908 G>A gene polymorphisms with coronary artery disease in Indian population: a case control study’. J Pers Med 10, 190.
20. Du H, Vimalesswaran KS, Angquist L et al. (2011) Genetic polymorphisms in the hypothalamic pathway in relation to subsequent weight change – the DiOGenes study. PLoS ONE 6, e17436.
21. Fisher E, Meidtner K, Angquist L et al. (2012) Influence of dietary protein intake and glycemic index on the association between TCF7L2 HapA and weight gain. Am J Clin Nutr 95, 1468–1476.

22. Isgin-Atici K, Alsulami S, Turan-Demirci B et al. (2021) FTO gene–lifestyle interactions on serum adiponectin concentrations and central obesity in a Turkish population. Int J Food Sci Nutr 72, 375–385.

23. Matusheski NV, Caffrey A, Christensen L et al. (2021) Diets, nutrients, genes and the microbiome: recent advances in personalised nutrition. Br J Nutr 126, 1–9.

24. Chakraverty R & Chakraborty P (2018) Recent insights into the role of vitamin B12 and vitamin D upon cardiovascular mortality: a systematic review. Acta Sci Pharm Sci 2, 61–65.

25. Surendran S, Adakalakoteswari A, Saravanan P et al. (2018) An update on vitamin B12-related gene polymorphisms and B12 status. Genes Nutr 13, 2.

26. Berry DJ, Vimaleswaran KS, Whittaker JC et al. (2012) Evaluation of genetic markers as instruments for Mendelian randomization studies on vitamin D. PLoS ONE 7, e37465.

27. Alathari BE, Sabta AA, Kalpana CA et al. (2020) Vitamin D pathway-related gene polymorphisms and their association with metabolic diseases: a literature review. J Diabetes Metab Disord 19, 1701–1729.

28. Vimaleswaran KS, Cavadino A, Berry DJ et al. (2013) Genetic association analysis of vitamin D pathway with obesity traits. Int J Obes (Lond) 37, 1399–1406.

29. Moen GH, Quigstad E, Birkeland KI et al. (2018) Are serum concentrations of vitamin B-12 causally related to cardiometabolic risk factors and disease? A Mendelian randomization study. Am J Clin Nutr 108, 398–404.

30. Vimaleswaran KS, Berry DJ, Lu C et al. (2013) Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 10, e1001383.

31. Jiang X, Ge T & Chen CY (2021) The causal role of circulating vitamin D concentrations in human complex traits and diseases: a large-scale Mendelian randomization study. Sci Rep 11, 184.

32. Dmirakopoulos VI, Tsilidis KK, Haycock PC et al. (2017) Circulating vitamin D concentration and risk of seven cancer: Mendelian randomization study. Br Med J 359, j4761.

33. Palaniappan LP, Carnethon MR & Fortmann SP (2002) Heterogeneity in the relationship between ethnicity, BMI, and fasting insulin. Diabetes Care 25, 1351–1357.

34. Vimaleswaran KS (2020) A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: findings from the GeNuIne Collaboration. Proc Nutr Soc 79, 194–204.

35. Vimaleswaran KS & Reddy GB (2021) Comment on ‘Guiding global best practice in personalized nutrition based on genetics: the development of a nutrigenomics care map’. J Acad Nutr Diet 121, 1215–1216.

36. Surendran S, Morais CC, Abdalla DSP et al. (2019) The influence of one-carbon metabolism gene polymorphisms and gene–environment interactions on homocysteine, vitamin B12, folate and lipids in a Brazilian adolescent population. Diabetol 10, 110–122.

37. Sae-Tan S & Vimaleswaran KS (2017) From nutrigenetics to personalised nutrition. KMITNB Int J App Sci Technol 10, 161–162.

38. Surendran S, Alsulami S, Lankeshwara R et al. (2020) A genetic approach to examine the relationship between vitamin B12 status and metabolic traits in a South Asian population. Int J Diabetes Dev Ctries 40, 21–31.

39. Surendran S, Aji AS, Ariyasra U et al. (2019) A nutrigenetic approach for investigating the relationship between vitamin B12 status and metabolic traits in Indonesian women. J Diabetes Metab Disord 18, 1–11.

40. Surendran S & Vimaleswaran KS (2021) A nutrigenetic approach to examine the relationship between vitamin B12 status and cardio-metabolic traits in multiple ethnic groups – findings from the GeNuIne Collaboration. Nutr Bull 46, 185–194.

41. Bradfield JP, Taal HIR, Timpson NJ et al. (2012) A genome-wide association meta-analysis identifies new childhood obesity loci. Nat Genet 44, 526–531.

42. Willer CI, Speliotes EK, Loos RJ et al. (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41, 25–34.

43. Ng MC, Hester JM, Wing MR et al. (2012) Genome-wide association of BMI in African Americans. Obesity (Silver Spring) 20, 622–627.

44. Schlauch KA, Read RW, Lombardi VC et al. (2020) A comprehensive genome-wide and phenome-wide examination of BMI and obesity in a northern Nevada cohort. G3 (Bethesda) 10, 645–664.

45. Vimaleswaran KS, Tachmazidou I, Zhao JH et al. (2012) Candidate genes for obesity-susceptibility show enriched association within a large genome-wide association study for BMI. Hum Mol Genet 21, 4537–4542.

46. Nongmaithem SS, Joglekar CV, Krishnaveni GV et al. (2017) GWAS identifies population-specific new regulatory variants in FUT6 associated with plasma B12 concentrations in Indians. Hum Mol Genet 26, 2589.

47. Jiang X, O’Reilly PF, Aschard H et al. (2018) Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat Commun 9, 260.

48. Udler MS, McCarthy MI, Florez JC et al. (2019) Genetic risk scores for diabetes diagnosis and precision medicine. Endocr Rev 40, 1500–1520.

49. Lewis CM & Vassos E (2020) Polygenic risk scores: from research tools to clinical instruments. Genome Med 12, 44.

50. Torkamani A & Topol E (2019) Polygenic risk scores expand to obesity and cardio-metabolic disease. Nat Rev Genet 20, 518–520.

51. Igo RP Jr, Kinzy TG & Cooke Bailey JN (2019) Genetic risk scores. Curr Protoc Hum Genet, e95.

52. Huls A, Kramer U, Carlsten C et al. (2017) Comparison of weighting approaches for genetic risk scores in gene–environment interaction studies. BMC Genet 18, 115.

53. Xie T, Wang B, Nolte IM et al. (2020) Genetic risk scores for complex disease traits in youth. Circ Genom Precis Med 13, e002775.

54. Knight BA, Shields BM, Brook A et al. (2015) Lower circulating B12 is associated with higher obesity and insulin resistance during pregnancy in a non-diabetic white British population. PLoS ONE 10, e0135268.

55. Mahabir S, Ettinger S, Johnson L et al. (2008) Measures of adiposity and body fat distribution in relation to serum folate levels in postmenopausal women in a feeding study. Eur J Clin Nutr 62, 644–650.

56. Lee YJ, Wang MY, Lin MC et al. (2016) Associations between vitamin B-12 status and oxidative stress and inflammation in diabetic vegetarians and omnivores. Nutrients 8, 118.

57. Mohan V & Deepa R (2006) Adipocytokines and the expanding ‘Asian Indian phenotype’. J Assoc Physicians India 54, 685–686.
58. Patel SA, Shivashankar R, Ali MK, et al. (2016) Is the 'South Asian phenotype' unique to South Asians?: comparing cardiometabolic risk factors in the CARRS and NHANES studies. Glob Heart 11, 89–96, e83.

59. Surendran S, Jayashri R, Drysdale L et al. (2019) Evidence for the association between FTO gene variants and vitamin B12 concentrations in an Asian Indian population. Genes Nutr 14, 26.

60. Jayawardena R (2014) Energy and nutrient intakes among Sri Lankan adults. Int Arch Med 7, 34–34.

61. Medagama A, Fernando D & Widanapathirana H (2015) Energy and nutrient intakes of Sri Lankan patients with type 2 diabetes mellitus: a cross-sectional survey. BMC Res Notes 8, 753.

62. Schroders J, Wall S, Hakimi M et al. (2017) How is Indonesia coping with its epidemic of chronic non-communicable diseases? A systematic review with meta-analysis. PLoS ONE 12, e0179186.

63. IDF (2017) International Diabetes Federation. IDF Diabetes Atlas. Brussels, Belgium: International Diabetes Federation.

64. Conde WL & Monteiro CA (2014) Nutrition transition and double burden of undernutrition and excess of weight in Brazil. Am J Clin Nutr 100, 1617S–1622S.

65. Monteiro CA, Conde WL & Popkin BM (2004) The burden of disease from undernutrition and overnutrition in countries undergoing rapid nutrition transition: a view from Brazil. Am J Public Health 94, 433–434.

66. Monteiro CA, Mondini L, de Souza AL et al. (1995) The nutrition transition in Brazil. Eur J Clin Nutr 49, 105–113.

67. Ribeiro AL, Duncan BB, Brant LC et al. (2016) Cardiovascular health in Brazil: trends and perspectives. Circulation 133, 422–433.

68. Souza RA, Yokoo EM, Sichieri R et al. (2015) Energy and macronutrient intakes in Brazil: results of the first nationwide individual dietary survey. Public Health Nutr 18, 3086–3095.

69. Morenga LT, Williams S, Brown R et al. (2010) Effect of a relatively high-protein, high-fiber diet on body composition and metabolic risk factors in overweight women. Eur J Clin Nutr 64, 1323–1331.

70. Anderson JW, Baird P, Davis RH Jr et al. (2009) Health benefits of dietary fiber. Nutr Rev 67, 188–202.

71. Kaczmarczak M, Miller MJ & Freund GG (2012) The health benefits of dietary fiber: beyond the usual suspects of type 2 diabetes mellitus, cardiovascular disease and colon cancer. Metabolism 61, 1058–1066.

72. Hossein-nezhad A & Holick MF (2013) Vitamin D for health: a global perspective. Mayo Clin Proc 88, 720–755.

73. Wacker M & Holick MF (2013) Sunlight and vitamin D: a global perspective for health. Dermatovenerodinology 5, 51–108.

74. Vimalaswaran KS, Forouhi NG & Khunti K (2021) Vitamin D and COVID-19. Br Med J 372, n544.

75. Valer-Martinez A, Martinez JA, Sayon-Orea C et al. (2019) Vitamin D and cardio-metabolic risk factors in overweight adults: an overview of the evidence. Curr Pharm Des 25, 2407–2420.

76. Vimalaswaran KS, Cavadino A, Berry DJ et al. (2014) Association of vitamin D status with arterial blood pressure and hypertension risk: a Mendelian randomisation study. Lancet Diabetes Endocrinol 2, 719–729.

77. Vimalaswaran KS, Power C & Hyponen E (2014) Interaction between vitamin D receptor gene polymorphisms and 25-hydroxyvitamin D concentrations on metabolic and cardiovascular disease outcomes. Diabetes Metab 40, 386–389.

78. Alathari BE, Bodhini D, Jayashri R et al. (2020) A nutrigenetic approach to investigate the relationship between metabolic traits and vitamin D status in an Asian Indian population. Nutrients 12, 1357.

79. Selvarajan S, Gunaseelan V, Anandabaskar N et al. (2017) Systematic review on vitamin D level in apparently healthy Indian population and analysis of its associated factors. Indian J Endocrinol Metab 21, 765–775.

80. Harinarayan CV, Ramalakshmi T, Prasad UV et al. (2007) High prevalence of low dietary calcium, high phosphate consumption, and vitamin D deficiency in healthy south Indians. Am J Clin Nutr 85, 1062–1067.

81. Jayashri R, Venkatesan U, Shanthirani CS et al. (2020) Prevalence of vitamin D deficiency in urban south Indians with different grades of glucose tolerance. Br J Nutr 124, 1–8.

82. Aji AS, Erwinda E, Rasyid R et al. (2020) A genetic approach to study the relationship between maternal vitamin D status and newborn anthropology measurements: the vitamin D pregnant mother (VDPM) cohort study. J Diabetes Metab Disord 19, 91–103.

83. Aji AS, Erwinda E, Yusrawati Y et al. (2019) Vitamin D deficiency status and its related risk factors during early pregnancy: a cross-sectional study of pregnant Minangkabau women, Indonesia. BMC Pregnancy Childbirth 19, 183.

84. Ilmiawati C, Oviana A, Friadi A et al. (2020) Sunlight exposed body surface area is associated with serum 25-hydroxyvitamin D (25(OH)D) level in pregnant Minangkabau women, Indonesia. BMC Nutr 6, 18.

85. Lipoeto NI, Agus Z, Oenzil F et al. (2004) Dietary intake and the risk of coronary heart disease among the coconut-consuming Minangkabau in West Sumatra, Indonesia. Asia Pac J Clin Nutr 13, 377–384.

86. Lipoeto NI, Mmedsci, Agus Z et al. (2001) Contemporary Minangkabau food culture in West Sumatra, Indonesia. Asia Pac J Clin Nutr 10, 10–16.

87. Alathari BE, Aji AS, Arijayarsa U et al. (2021) Interaction between vitamin D-related genetic risk score and carbohydrate intake on body Fat composition: a study in Southeast Asian Minangkabau women. Nutrients 13, 326.

88. Pittas AG, Lau J, Hu FB et al. (2007) The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 92, 2017–2029.

89. Adab P, Pullan M & Whincup PH (2018) Is BMI the best measure of obesity? Br Med J 360, k1274.

90. Liang W, Zhao Y & Lee AH (2014) An investigation of the significance of residual confounding effect. Biomed Res Int 2014, 658056.

91. Vimalaswaran KS, Le Roy CI & Claus SP (2015) Foodomics for personalized nutrition: how far are we? Curr Opin Food Sci 4, 129–135.

92. Ibanez C, Valdes A, Garcia-Canas V et al. (2012) Global foodomics strategy to investigate the health benefits of dietary constituents. J Chromatogr A 1248, 139–153.

93. Fenech M, El-Sohemy A, Cahill L et al. (2019) Vitamin D and vitamin B12 concentrations in an Asian Indian population and analysis of its associated factors. Indian J Endocrinol Metab 21, 765–775.

94. Marcum JA (2020) Nutrigenetics/nutrigenomics: viewpoints on the current status and future perspectives. J Nutrigenet Nutrigenomics 4, 69–89.

95. de Toro-Martin J, Arsenault BJ, Despres JP et al. (2017) Precision nutrition: a review of personalized nutritional
approaches for the prevention and management of metabolic syndrome. *Nutrients* **9**, 913.

96. Bordoni L & Gabbianelli R (2019) Primers on nutrigenetics and nutri(epi)genomics: origins and development of precision nutrition. *Biochimie* **160**, 156–171.

97. Ozdemir V & Kolker E (2016) Precision nutrition 4-0: a big data and ethics foresight analysis – convergence of agrigenomics, nutrigenomics, nutriproteomics, and nutrimebolomics. *OMICS* **20**, 69–75.

98. Palmnas M, Brunius C, Shi L et al. (2020) Perspective: metabotyping – a potential personalized nutrition strategy for precision prevention of cardiometabolic disease. *Adv Nutr* **11**, 524–532.

99. Zeisel SH (2020) Precision (personalized) nutrition: understanding metabolic heterogeneity. *Annu Rev Food Sci Technol* **11**, 71–92.

100. Reddy VS, Palika R, Ismail A et al. (2018) Nutrigenomics: opportunities & challenges for public health nutrition. *Indian J Med Res* **148**, 632–641.

101. Zeisel SH (2010) A grand challenge for nutrigenomics. *Front Genet* **1**, 2.

102. Kohlmeier M, De Caterina R, Ferguson LR et al. (2016) Guide and position of the international society of nutrigenetics/nutrigenomics on personalized nutrition: part 2 – ethics, challenges and endeavors of precision nutrition. *J Nutrigenet Nutrigenomics* **9**, 28–46.

103. Lovegrove JA & Gitau R (2008) Personalized nutrition for the prevention of cardiovascular disease: a future perspective. *J Hum Nutr Diet* **21**, 306–316.

104. Sales VM, Ferguson-Smith AC & Patti ME (2017) Epigenetic mechanisms of transmission of metabolic disease across generations. *Cell Metab* **25**, 559–571.