

TITLE

Nutrigenetics & Nutrigenomics and Its clinical application

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Nutrigenetics & Nutrigenomics ant its clinical
application.

Thesis submitted by:

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For the award of Master of Philosophy

Faculty of Sport, Allied Health, and Performance Science,

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LIST OF ABBREVIATIONS

Angiotensin-converting enzyme	5-hydroxytryptamine receptor
Adiponectin	Interleukin 6
Beta-adrenergic receptor 2	Insulin
Beta-adrenergic receptor 3	Low density lipoprotein receptor
Endothelial nitric oxide synthase	Insulin
High-density lipoprotein (apo-) A-II	Leptin receptor
High-density lipoprotein A-V	Leptin-sensitive lipase
Body Mass Index	Minor allele frequency
C/EBP β -enhancer-binding protein β	Melanocortin-4 receptor
Monocyte chemoattractant protein 1	Multi-Ethnic Study of Atherosclerosis
Multi-Ethnic Study of Coronary Artery Risk Development in Young Adults	Nutritionists and dietitians
Type 2 diabetes mellitus	Nutrition and genetics
Dopamine D2 receptor	Orphan nuclear receptor, group C, member 1

direct-to-consumer	hormone and pro-protein type 1
poly B-cell factor 1	lipin
mass and obesity-associated protein	proopiomelanocortin convertase
arginine nucleotide-binding protein 3	persistent organic pollutant
genetic risk scores	gamma – gamma
genome-wide association studies	glucocorticoid receptor
hypoxia-inducible factor 3a	adipocyte factor-1
1 professional	Prader-Willi syndrome
histin	quantitative trait locus
socioeconomic position	coupling protein 2
single-minded gene 1	coupling protein 3
single nucleotide polymorphism	vitamin D receptor
transcription factor 7-like 2	World Health Organization
– tumour necrosis factor-alpha	– tumour necrosis factor-alpha
coupling protein 1	coupling protein 1
	World Health Organization

ABSTRACT

The Swiss population contrasts the recently developed weighted GRS and BMI with lifestyle factors. Also demonstrated that a simple weighted genetic score can show trends of the association between individuals or groups at risk for the disease even without detailed clinical follow-up, therefore a genetic risk score can be used as a predictable clinical tool. However, the weighted GRS may not be a true reflection of BMI genetic risk in Brazilian populations because of the lack of data for this population. Additionally, different lifestyle information was important in allowing the use of a robust statistical method to understand the influence of the genetic risk score on BMI in different countries, especially in such heterogenic populations. The current study demonstrates the likely utility of modelling BMI for new trajectories in future genetic studies and the need for sample sizes from different backgrounds to check for their ethnicity's genetic makeup. This approach would also allow for harmonization between studies that collected data from immigrants with different ethnical backgrounds in different countries, overall results show the importance of lifestyle and environment was more significant than the genetic scores alone. As a result of the new developments in the nutrition and genetics sector, the rushing of its commercial applications before the final scientific conclusions, and the importance of nutritionists/dietitians to give nutritional genomics recommendations, professionals specialist in nutritional therapies and clinical applications for the prevention of diseases need to understand the science in order integrate it into practice. the mean knowledge was low and for the highest qualification, reading literature and perceived benefits were all associated with higher total knowledge scores. Also, 43% of the professionals were unlikely or very unlikely to accurately interpret nutrigenomic patients' reports results however they are willing to undergo training. Spearman's correlation resulted in no association between the total knowledge score and the perceived risks score. Similarly, no correlation between the highest qualification and perceived benefits scores nor perceived risks score was noted. Hence, this thesis aims to investigate the knowledge of nutritional genomics and identify factors associated with it among nutritionists/dietitians in the UK and Brazil. It also provided an overall picture of the involvement, perceived benefits, and risks, and identified training needs in nutrition and genetics and its differences in both countries.

Conclusions: This Thesis data results in environmental, social and cross-cultural differences in health status differences and BMI levels. in addition, the study showed a major contribution to lifestyle in obesity than genetic risk score, moreover, alerts that obesity and chronic diseases are prevalent among immigrants in Switzerland and it is a public health concern. Health education and promotions towards immigrant

population in a country where more than 35% of the population are foreigners should be a priority due to the higher costs of health care in this country. Moreover, Knowledge of nutrition and genetics among nutritionists & dietitians in the UK and Brazil is currently low, and better knowledge is associated with higher qualification and relevant perceived benefits. The cost and validity of genetic tests and genetic discrimination concerned nutritionists/dietitians the most. Also, they seem interested in deep training and suggested nutritional genomics to become mandatory undergraduate module in nutrition/dietetic university degrees.

Keywords: Clustering; Genetic Risk Score; Obesity; Body Mass Index; Chronic Diseases.

1. INTRODUCTION AND RESEARCH OBJECTIVES

Obesity is a significant concern and has reached epidemic proportions worldwide. The World Health Organization (WHO) points to obesity as one of the most critical public health problems globally. It has been estimated that by 2025, 2.3 billion adults will be overweight and over 700 million obese. Overweight and obese children worldwide could reach 75 million if no measures are undertaken (Bahia et al., 2012). In Brazil, surveys indicate that over 50% of the population is overweight. Data from the Ministry of Health of Brazil indicates that 18.9% of the population over 18 years is obese in the Brazilian capitals.

Obesity shortens life expectancy by acting as a risk factor for several adverse health outcomes such as dyslipidaemias, coronary heart disease, myocardial infarction, non-metabolic diseases such as sleep disorders, depression, and musculoskeletal conditions. Obesity is also associated with comorbidities, such as reflux, and cancers, such as oesophageal adenocarcinoma (Rohde et al., 2019). Obesity tends to aggregate into families, which may be due to both genetic components and a shared “obesogenic” environment (Tyrrell et al., 2017).

Various hypotheses have been postulated to understand the contribution of genetics to obesity. Studies point out that genetic and environmental factors influence each other in developing metabolic complications. Most interindividual variation in adiposity is due to genetic factors (Passarino et al., 2016). Thus, it implies that individuals at high genetic risk for fat accumulation are more prone to the effects of an unhealthy environment. Research evidence suggests that a gene-environment interaction is essential not only in determining individual susceptibility to obesity but may also influence the outcome of the strategies used for weight loss in these individuals (Sun et al., 2017). In this context, the objective of the

research is to elucidate the role of genes and genetic variability in the development of obesity (Rosado, 2010).

In managing obesity, the gene-nutrient interactions can be investigated using two strategies: nutrigenomics and nutrigenetics. Nutrigenomics uses transcriptomics and other molecular tools to explore and understand the responses obtained through nutritional interventions. It seeks to delineate how caloric restriction and the composition of a particular diet can alter gene expression (Covas et al., 2015). On the other hand, nutrigenetics attempts to assess how genetic polymorphism among populations responds to nutritional interventions (Bouchard & Ordovas, 2012). In simple terms, nutrigenomics is the study of the effects of dietary components on gene expression (Karki et al., 2015; Valour et al., 2013), while nutrigenetics explores how the genetic profile of an individual influences nutrient absorption, metabolism, elimination, and other related biological processes (Fenech et al., 2011). Therefore, the study of nutrigenetics can aid in identifying suitable biomarkers for both treatments and diagnostics of chronic diseases (Konstantinidou et al., 2014).

To date, several genomics studies have led to a deeper understanding of the gene-disease relationship. This, in turn, allowed for the discovery of new drugs for obesity. However, genetics and genomics can explain only a tiny part of the total variance of factors associated with obesity. The pursuit of anti-obesity drugs has been highly challenging as obesity is a multifaceted disease, and drugs need to target multiple mechanisms and processes to achieve optimal disease management. This complexity has given rise to many hypotheses that drive research to investigate biological triggers (Hruby & Hu, 2015).

A standard and simple variable used in most studies to quantify obesity is the Body Mass Index (BMI), defined as a weight in kilograms divided by a height in square meters (Elks et al., 2012). Obesity arises when energy input is chronically higher than energy expenditure, resulting from overeating, a sedentary lifestyle, a disease state, or any other mechanism leading to an energy imbalance (Pereira-Lancha et al., 2012). Factors influencing energy imbalance can originate from genetic, environmental, psychological, psychosocial, and cultural factors. With the advancement in the field of genetics and the advent of human genome sequencing technology, hundreds of genes linked to various diseases have been identified and characterized. This makes it possible to comprehensively elucidate disease mechanisms and pave the way for a new generation of research tools to dissect and understand complex diseases.

Advancements in science and technology have increasingly highlighted the significance of genetics and nutritional genomics in understanding and managing obesity. Implementing genomics into healthcare

requires the collaborative efforts of various specialists, including nutritionists and dietitians. However, the level of nutritionists' and dietitians' knowledge and competence in nutrigenetics and nutrigenomics may vary across countries and require the development of specific curriculum plans.

The broad implementation of personalised genetic-based recommendations which can help diminish obesity frequency is being held back by several problems. Among them are the underrepresentation of certain ethnic groups in genetic research and databases and somehow low levels of knowledge of healthcare specialists. To address these problems, several objectives of this research have been postulated:

- To conduct a comprehensive literature analysis of candidate genes associated with obesity, of influence of environmental factors and lifestyle on risks of developing obesity.
- To analyse possible associations between certain obesity-related SNPs, lifestyle, and BMI in different ethnic groups (Brazilians and Swiss);
- To estimate and compare using surveys a current level of knowledge of nutritionists and dietitians regarding in nutrigenomics and nutrigenetics in Brazil and the UK.

2. LITERATURE REVIEW ON GENETIC CAUSES OF OBESITY

In this literature review, a systematic search for the most relevant scientific articles in indexed journals in PUBMED, MEDLINE, SCIELO, and GOOGLE ACADEMIC databases was conducted. Original articles, complete and preferably published in the last ten years, and books dedicated to the topic were included. The following keywords were used: *obesity; nutrigenomics; nutrigenetics; genes associated with obesity; gene-gene interactions; environmental genetics and obesity; population genetics and obesity*. Valuable information related to the subject matter with focused questions and variable research methods was engaged to synthesize all the available data to develop a narrative and explorative review.

2.1 Categories of Genetic Causes of Obesity

In 1907, Von Noorden proposed the idea of the innate biological (“endogenous”) cause of obesity (Thaker, 2017). Subsequently, research on rare syndromic diseases revealed that a defect in a single gene could

alter the total energy balance, leading to extreme obesity (Herrera & Lindgren, 2010). Some studies indicated that genes could influence and affect eating behaviour resulting in satiety dysfunction (Wardle et al., 2008). The genetic causes of obesity can be categorized into three distinct causes:

- Monogenic obesity, which involves either chromosomal deletions or single-gene defects
- Polygenic obesity comprising hundreds of polymorphisms, each with minor effects
- Syndromic obesity, associated with additional phenotypes such as mental retardation, dysmorphic features, and organ-specific developmental abnormalities.

Monogenic and syndromic forms of obesity are rarer conditions and account for only 5% to 10% of all cases. It attributes to mutations in a few genes that have a determinant relationship with the disease, such as the leptin (*LEP*) gene, the leptin receptor (*LEPR*) gene, the proopiomelanocortin convertase (*POMC*) gene, the prohormone and pro-protein type 1 (*PC1*), and melanocortin-4 receptor (*MC4R*) (Herrera & Lindgren, 2010; Hinney et al., 2010a). Several obesity-associated syndromes are caused by mild genetic defects or chromosomal abnormalities (Mason et al., 2014). Genetic syndromes such as Prader-Willi syndrome (PWS) and Barder-Biedl syndrome are commonly associated with obesity. In addition, evidence shows that variations in the Single-minded gene 1 (*SIMI*) are associated with hyperphagia and obesity. A deletion or rupture of *SIMI* results in the PWS phenotype or an early form of obesity associated with hyperphagia (Nunes et al., 2006). The major causes of obesity incidence are likely to arise because of complex polygenic associations (involving many genes that have a low effect-size impact) and an obesogenic environment (Hinney & Hebebrand, 2008; Nunes et al., 2006). Several studies support the hypothesis that the prevalence of polygenic obesity results from interactions between unfavourable lifestyles and specific genetic variations, such as single nucleotide polymorphisms (SNPs), which have discrete but converging effects (Domingue et al., 2014; Fenech et al., 2011). Polygenetic studies exploring the role of genes in obesity focus on genes involved in metabolism or located in chromosomal regions associated with obesity. However, the genetic influence on obesity is multifaceted and related to complex interactions of multiple genes and environmental factors (Fall & Ingelsson, 2014; Hinney et al., 2010a).

Determining which or how many genetic variations are required to result in the obesity phenotype is complicated because these variants are also found in people of a healthy weight or even underweight. Hence statistical analyses are employed to determine the alleles that occur most frequently in obese individuals compared to non-obese individuals. Earlier studies have concluded that the variations have only a modest contribution to the development of obesity. All chromosomes in the human genome (except

Y) are known to contain at least one locus associated with body weight regulation (Hinney et al., 2010b). With growing knowledge and understanding, numerous genes and genetic markers involved in obesity are continuously identified (Hinney et al., 2010b; Hinney & Hebebrand, 2008; Seal, 2011).

Rankinen et al. (2006) categorized five different phenotypes according to previously studied genes related to polygenetic obesity:

– **Thrifty phenotype (sparing or economic) involved in energy expenditure:** *ADRB2* (beta-adrenergic receptor 2); *ADRB3* (beta-adrenergic receptor 3); *UCP1* (uncoupling protein 1); *UCP2* (uncoupling protein 2); *UCP3* (uncoupling protein 3), and *FTO* – a well-known gene called “Fat mass and obesity-associated protein”, also known as alpha-ketoglutarate-dependent dioxygenase.

– **Low lipid oxygen phenotype:** *ACE* (angiotensin-converting enzyme); *ADIPOQ* (adiponectin); *GNB3* (guanine nucleotide-binding protein 3); *IL-6* (interleukin 6); *INS* (insulin); *LDLR* (Low-density lipoprotein receptor); *LIPE* (hormone-sensitive lipase); *RETN* (resistin); *TNF-alpha* (tumour necrosis factor-alpha).

– **Adipogenesis phenotype:** *PPAR-gamma* (gamma peroxisome proliferator-activated receptor); *VDR* (vitamin D receptor).

– **Sedentary phenotype:** *DRD2* (dopamine D2 receptor); *MC4R* (melanocortin receptor 4).

– **Hyperphagic phenotype** (regulation of hunger, appetite, and satiety): *DRD2* (dopamine D2 receptor); *HTR2C* (5-hydroxytryptamine receptor); *LEP* (leptin); *LEPR* (leptin receptor); *MC4R* (melanocortin 4 receptor); *NR3C1* (subfamily 3 nuclear receptor, group C, member 1).

Many of these genes also fall into the category of monogenic gene mutations and are mostly associated with severe obesity and hyperphagia. Also, the impact on the severity will depend on the type of mutation and the gene loci where the mutation occurs. One of the main challenges is understanding the regulation of genetic influences on polygenic obesity and why some individuals are more susceptible (Locke et al., 2015a; Schadt et al., 2003).

2.2 Research Approaches to Study Genes Involved in Complex Diseases

For nutrigenomics studies, the role of genes/gene discovery is studied using two main approaches (Rao et al., 2014):

- **The hypothesis-driven approach** (a candidate gene or a biological pathway)
- **The hypothesis-free approach** (genome-wide linkage and genome-wide association).

In 2006, data regarding obesity and genetics revealed 253 quantitative trait loci (QTLs) associated with obesity-related phenotypes derived from 61 genome-wide scan studies (Rankinen et al., 2006). In 2015, about 370 genes were identified to influence obesity (Butler et al., 2015). Most of these genes carry minimal risk in nature, and their impact on obesity is still unclear. As of 2021, there are nearly 60 genome-wide association studies (GWAS) related to obesity, which identified more than 1,100 loci associated with a range of obesity traits (Loos & Yeo, 2022).

Genes that exhibit high dominance or co-dominance have from 40 to 70% influence on body weight (Janani & Ranjitha Kumari, 2015). Their loci correlate with BMI, body fat distribution, response to calorie intake, metabolic rate, and fat and sugar absorption metabolism. Many of these genes are replicated in populations with diverse ancestries (Underwood et al., 2012; Yu et al., 2012).

2.2.1 Hypothesis-Driven Approach

Obesity is influenced by the interplay of many genes involved in the hypothalamic circuits regulating energy homeostasis. These genes encode proteins involved in regulating satiety and food intake and are also related to the regulation of prolonged survival when energy intake is low. They are commonly known as thrifty genes, i.e., genes that stimulate the storage of fats and promote the storage of fats in periods of food abundance (Janani & Ranjitha Kumari, 2015).

SNP analysis is an example of the hypothesis-driven approach, which needs prior knowledge of the genetic polymorphisms in a candidate gene or a biologic pathway and of their effects on a particular phenotype of interest (Rao et al., 2014). This approach is an efficient strategy only when identifying genetic variants with a small or modest impact on obesity. This approach helped identify a variety of thrifty genes implicated in obesity-related pathways. Among them are *FTO*, adipokines (Yu et al., 2012), *TNF-alpha* (Yu et al., 2012), *IL-6* (Underwood et al., 2012), *PPAR-gamma* (Queiroz et al., 2015), and *VDR* (Wang et al., 2016). In addition, many other genes were confirmed to be involved in various obesity-related metabolic pathways (Locke et al., 2015a, 2015b).

2.2.2 Hypothesis-Free Approach

The GWAS analysis is based on sequencing of a vast number of human genomes using the latest advanced high-throughput technology (i.e., high-density, genome-wide arrays to assay) (DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014). The goal is to identify nucleotide base changes that could affect protein-coding sequence, leading to protein translational changes that may or may not lead to a disease (Sandholt et al., 2015).

The GWAS has significantly improved the identification of obesity-susceptibility genes. To date, large-scale meta-analyses of GWAS are used to calculate genetic risk scores to identify obesity risk (Vimaleswaran et al., 2012). In 1996 the Obesity Gene Map compiled and listed genetic data from all the published results, including *in vivo* and *ex vivo* studies and QTL for conditions related to obesity (Rankinen et al., 2006). According to GeneMap, 127 candidate genes were reported to be involved in obesity, less than 20% of which were validated, leading to inconclusive findings (R. J. Loos, 2018).

2.3 Genes Associated with Obesity, Measures of Obesity, and Their Physiological Pathways

Food intake is regulated by a complex physiological system, which integrates various peripheral signals and central coordination regulated by polygenic factors (Hill et al., 2012). The discovery of leptin receptors in neurons has shown that the hypothalamus is the main target of this hormone in maintaining energy homeostasis (Münzberg & Morrison, 2015). The hypothalamus is the coordinator of the central nervous system; it receives information about the energy balance through neuronal and hormonal signals from the ventromedial, paraventricular, and arcuate nuclei (Goodarzi, 2018a). The arcuate nucleus is critical because it has two neuron systems: one that produces the agouti (agouti-related protein) and neuropeptide Y (NPY), and another which makes the POMC (which is cleaved by creating the stimulating hormone melanocyte, potent MC4 agonist) and CART (amphetamine-related transcript) (Yaswen et al., 1999). The former is orexigenic; it promotes food intake and decreases energy expenditure, while the latter causes an anorectic effect (Ignatieva et al., 2016; Nunes et al., 2006). Mutations involving a signalling pathway to obesity, including leptin gene mutations, have been previously described (Farooqi et al., 1998). Below, the genes and SNPs that are associated with obesity are identified. The minor allele frequencies (MAF) are also included; however, since allele frequencies vary depending on ethnicity, the MAFs based on the 1000Genomes project, which surveyed the allele frequencies on a global population scale, were used.

2.3.1 LEP Gene and Its Receptor LEPR

Human leptin, a peptide of 167 amino acids, is the product of *LEP* gene located on chromosome 7. Leptin synthesis occurs in adipocytes in response to food intake. Leptin in plasma concentrations is proportional to the size and the amount of energy stored in adipose tissue. Leptin is also a key regulator, signalling the brain about the energy supply (Münzberg & Morrison, 2015). The most critical functions of leptin are controlling food intake, maintaining body homeostasis, and regulating carbohydrate and lipid metabolism. For leptin to perform its tasks efficiently, it must bind to its receptor, LEPR (Pereira-Lancha et al., 2012). Studies reveal that *LEP* and *LEPR* gene polymorphisms are related to the risk of developing obesity (Oliveira et al., 2013; Yang et al., 2016). Monogenic abnormalities in *LEP*, which cause partial or total deficiency of leptin production, and resistance to leptin caused by a defect in *LEPR*, are associated with hypogonadotropic hypogonadism (Strobel et al., 1998), childhood-onset severe hyperphagia, and obesity (Farooqi et al., 1998; Montague et al., 1997).

Some studies demonstrated the association of LEPTIN rs7799039 (MAF: 0.4016) with obesity and BMI, specifically, the G allele (Ben Ali et al., 2009; Sahin et al., 2013; Dasgupta et al., 2015). This rs7799039 SNP is a G to A transition at nucleotide position 2548, upstream in the gene promoter region. Data show that the A allele is associated with an increased ability of adipocytes to produce and secrete leptin compared with the G allele (Hoffstedt et al., 2002). Since leptin is a fat homeostasis hormone released by adipocytes to keep a normal weight, the increased leptin production by the A allele carriers can explain its protection against obesity and the G allele carrier's susceptibility to impaired fat metabolism and obesity.

LEP gene is a vital study element in nutrigenetics, as evidence reveals that exercise can positively affect the regulation of leptin levels. Exercising was found to reduce leptin levels in those with homozygous wild-type (GG) genotype but to increase it in homozygous AA or heterozygous individuals (Huuskonen et al., 2010). In addition, reports have also demonstrated that the amount of dietary fibre ingested and diets with different amounts of saturated fat consumed can help regulate the *LEP* gene expression (Erez et al., 2011). However, the relationship between the concentration of plasma leptin and the development/maintenance of obesity is not yet clear. Both high and low leptin concentrations are related to hunger-appetite-satiety axis dysregulation, confirming the complexity of obesity and its dependence on the interaction between many factors which are not yet fully understood.

2.3.2 POMC Gene

Proopiomelanocortin is a protein that acts as a prohormone. Researchers believe that the most frequent cause of monogenic obesity is related to the loss of POMC gene function. The prohormone is post-translationally processed into more than ten active peptide hormones by convertases (Yaswen et al., 1999). These hormones play a role in pain, energy homeostasis, body weight, stimulation of melanocytes, regulation of hunger, and sexuality. Genetic variations, including mutations in *POMC* gene, have been linked to certain types of premature obesity, adrenal insufficiency, and red hair colour (Montague et al., 1997; Yaswen et al., 1999). Phenotypes with ACTH deficiency may exhibit adrenal insufficiency, cutaneous hypopigmentation, reddish hair mineral density, accelerated growth, and hyperinsulinemia without evidence of hypogonadism (Willer et al., 2009). Mutations in this gene are rare, and many of these polymorphisms have yet to be defined comprehensively.

2.3.3 MC4R Gene

The melanocortin 4 receptor gene is located at 18q22 and encodes for MC4R, the cellular hormone receptor expressed in the brain. It is an essential regulator of energy homeostasis, potentially influencing both food intake and energy expenditure (Farooqi et al., 2003). It was reported to be involved in the process of hunger development in the mammal brain and plays a vital role in regulating the organism's food intake and energy requirements (Widiker et al., 2010). Rare mutations in the coding region in the *MC4R* were associated with obesity (Farooqi et al., 2003). In the early onset of obesity and hyperphagia, patients with the mutation of the receptor of the *MC4* also exhibited increased lean mass (Vaisse et al., 1998). Gene variants located near the *MC4R* gene are associated with BMI, waist circumference, body mass, an increased level of basal insulin in the blood, and obesity that appears in childhood. One of the alleles of the *MC4R*, the C variant of rs17782313 (MAF: 0.2400), denotes a higher risk of obesity. Other studies have also shown the A variant to be associated with obesity (Xi, Takeuchi, et al., 2012). In children, hyperphagia and the degree of obesity correlate with the extent of the *MC4R* signalling damage, which disappears in adults.

Obesity, being polygenic in nature, is also known to harbour other polymorphisms in the *MC4R* gene (Loos et al., 2008). The common ones are rs2229616 (Val103Ile, MAF: 0.0162) and rs52820871 (Ile25Ileu, MAF: 0.0026) (Evans et al., 2014). Less frequently found are alleles related to a reduced risk of developing obesity. Ethnicity also influences the associations between the *MCR4R* gene and obesity. This can be witnessed in the European and Asian ethnic groups, while in the Africans, no obvious associations were found (Xi et al., 2012).

Despite considerable evidence associating *MC4R* and obesity, the causal or functional relationship leading to the development of the disease is not clear. Some authors suggest that polymorphisms in this gene influence food intake and food choices but are not related to energy expenditure (Farooqi et al., 2003). However, other studies found no association with nutritional factors (Holzapfel et al., 2010; Razquin et al., 2011).

2.3.4 FTO Gene

The alpha-ketoglutarate-dependent dioxygenase gene, *FTO*, belongs to the AlkB family proteins. It is located in chromosomal region 16q12.2, has nine exons and eight introns, a total of 2,348 SNP, and was the first to be related to basic forms of human obesity. Of these SNPs, 92 are associated with BMI. *FTO* has been the focus of many obesity-related studies (Bjørnland et al., 2017; Corella et al., 2012; da Silva et al., 2013; Fawcett & Barroso, 2010; Fredriksson et al., 2008; Frayling et al., 2007; Gerken et al., 2007; Holzapfel et al., 2010; Kalantari et al., 2016; Karra et al., 2013; Kilpeläinen et al., 2011; Labayen et al., 2016; NCD Risk Factor Collaboration (NCD-RisC), 2016; Qi et al., 2014; Razquin et al., 2011; Salinas et al., 2016; Stratigopoulos et al., 2008; Wardle et al., 2008). The gene locus is strongly associated with the accumulation of fat mass and obesity, and thus, researchers refer to it as the fat mass and obesity-associated (*FTO*) gene (Fredriksson et al., 2008). This gene is primarily expressed in the hypothalamus, the brain region responsible for hunger and satiation (Fredriksson et al., 2008).

The best-known polymorphism in this gene is rs9939609 (MAF: 0.3401); it is associated with the percentage of body fat and fat accumulation (the skin-fold thickness and waist circumference). People with the AA genotype have an average of 3 kg more body mass than people with the TT genotype (Corella et al., 2012). This gene variant's mode of action is believed to be associated with an increase in appetite, the feeling of hunger, and satiation. Individuals with the A variant are alleged to exhibit negative behaviour towards the quantities of food consumed and tend to choose more fatty and calorific foods (Labayen et al., 2016). This mutation occurs through a series of deletions in the nucleotides of the *FTO* gene, which has been located on chromosome 8 in mice, and homologous to chromosome 16 in humans (Gerken et al., 2007). The allele A is related to body fat accumulation, especially when in homozygous (AA) form (Frayling et al., 2007; Gerken et al., 2007). In a study involving 38,759 European volunteers, 16% of the individuals were found to be homozygous, and this allelic group was 1.2 times more likely to be overweight (BMI > 25 kg/m²) or 1.3 times more likely to be obese (BMI > 30 kg/m²) (Frayling et al., 2007). On average, individuals classified as obese had higher waist circumference and greater skinfold

thickness, demonstrating a higher amount of body fat. In another study, individuals carrying the genotype associated with a higher risk of obesity (AA) had reduced postprandial ghrelin suppression compared to the carriers of the TT genotype (Karra et al., 2013).

In children, the presence of allele A relative to the rs9939609 polymorphism has been associated with decreased satiety (Wardle et al., 2008) and hyperphagia even after a meal (da Silva et al., 2013; Wardle et al., 2008). The association of the allele A and the risk of SNP rs9939609 with the risk of obesity can be attenuated by about 27% in physically active adults, highlighting the importance of physical exercise, especially in genetically predisposed individuals (Kilpeläinen et al., 2011).

Considerable amounts of *FTO* mRNA have been found in the brain, specifically in the arcuate nucleus and hypothalamus (Stratigopoulos et al., 2008). Its expression is modulated by the fasting/feeding cycle, which indicates its functional involvement in the central control of energy homeostasis, with the FTO protein acting as the primary regulator of body fat accumulation. *FTO* is also expressed in many tissues/organs such as the adipose tissue, pancreas, liver, cardiac, striated skeletal muscles, kidneys, gonads, and others (Frayling et al., 2007; Kalantari et al., 2016).

Some of the *FTO* genetic variations are associated with low obesity risk, as revealed by Livingstone et al. (2015). Potential associations between *FTO* gene variants and intakes of total energy, fat, carbohydrate, and protein were evaluated in 177,330 adults. A significant association between variants of the *FTO* and effects of total energy, protein, and fat, but not carbohydrate intakes, on BMI was found. Therefore, these SNPs can become potential candidates for personalized interventions aimed at reducing the risk of obesity (Livingstone et al., 2015).

2.3.5 ADRB2 Gene

The *ADRB2* is activated by the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine); they are receptors expressed in white adipose tissue and are involved in the mobilization of triglycerides for energy generation (Stein, 1975). In obese individuals, the sympathetic nervous system's adaptive mechanisms are affected, which, in turn, modifies lipolysis (Lafontan & Berlan, 1993). *ADRB2* polymorphisms may contribute to obesity due to the role of adrenergic receptors in lipolysis. Changes in *ADRB2* function caused by functional SNPs seem to limit the mobilization of lipids and favour fat accumulation (Lima et al., 2007).

Among the various polymorphisms described in *ADRB2*, two functional ones are associated with the risk of developing obesity, hypertension, and type 2 diabetes mellitus (DM2). These polymorphisms occur at codons 16 (Arg16 Gly; rs1042713, MAF: 0.4756) and 27 (Gln27Glu; rs1042714, MAF: 0.2043), and the outcome is an alteration of the amino acid sequence at the extracellular N-terminal end of *ADRB2*, which may alter the function of the *ADRB2* receptor (Zhang et al., 2014). Studies indicate that appropriate nutritional interventions can control the development of obesity in those individuals with SNP Gln27Glu while excessive intake of total carbohydrates (>49% of the caloric value of total consumed daily), particularly in women with d allele Glu, may be associated with increased obesity risk (Martínez et al., 2003). In another study, women undergoing hypocaloric diets showed an interaction between the SNP Gln27Glu and changes in body weight, BMI, and lean mass. Women carriers of the Glu allele showed a more significant loss of lean mass than non-polymorphic carriers (Ruiz et al., 2011).

2.3.6 PPAR-gamma Gene

The *PPAR-gamma* gene encodes for the PPAR gamma receptor. It is a thrifty gene involved in development of fat cells, storing fat, the homeostasis of lipids and glucose, and insulin sensitivity (Janani & Ranjitha Kumari, 2015). For dietary planning, the variants of this gene are significant since they show how the body will react to the amount of fats consumed, and how this will affect BMI and insulin sensitivity. The C variant of the Pro12Ala genetic polymorphism (rs1801282) in the *PPARG* gene represents an active form of the receptor. In contrast, the allelic G variant represents a less active form of the receptor and is less frequently present. The low intake of saturated fatty acids and exercise have been shown to positively impact the effects of the G variant (Ruiz-Narváez et al., 2007).

2.3.7 APOA5 Gene

The *Apolipoprotein A-V (APOA5)* gene plays a vital role in regulating triglycerides in the blood; it is associated with obesity and the uptake of fat in humans (Hubacek et al., 2014). This gene codes for the A5 (APOA5) apolipoprotein, a regulator of triglyceride-rich lipoproteins (Xia et al., 2015). Variants of this gene are observed to have two significant negative impacts in individuals consuming imbalanced diets; the first is the accumulation of excessive amounts of subcutaneous fat leading to weight gain, and the second is the accumulation of triglycerides in the blood, which consequently damages the cardiovascular system (Garaulet et al., 2016; Hubacek et al., 2014).

Studies suggest that *APOA5* -1131T > C SNP polymorphism (rs662799) is associated with BMI depending on the type of diet consumed (Garaulet et al., 2016). The evidence revealed that even on a high-fat diet, having at least one C allele can promote less weight gain than people with homozygous T allele, which resulted in increased BMI due to increased fat intake (Corella et al., 2007), highlighting C allele's preventive capacity against weight gain. However, the C allele is also associated with higher triglyceride levels and risk for early-onset myocardial infarction (De Caterina et al., 2011). Hence, people with the C variant have a higher tendency to accumulate triglycerides in the blood and heart attack; therefore, they should focus more on consuming monounsaturated fatty acids and implement a more active lifestyle.

2.3.8 TCF7L2 Gene

The *Transcription factor 7-like 2* (*TCF7L2*, T-cell specific, HMG-box gene) is associated with insulin secretion and the metabolism of fats and is linked indirectly with DM2 (Lukacs et al., 2012). Polymorphism of this gene is associated with increased susceptibility to obesity (Mattei et al., 2012). Research indicates that for individuals with the CT heterozygous or TT homozygous allelic variants for the *TCF7L2* rs12255372 (MAF: 0.2139), who wish to lose weight, a low-fat diet is more appropriate (Mattei et al., 2012) as they lose weight faster which reduces their risk of DM2 (Strawbridge et al., 2011). In contrast, a more adequate approach for CC homozygotes variants would be to consume more complex carbohydrates (Cropano et al., 2017).

2.3.9. PLIN Gene

This gene encodes for the perilipin (PLIN) protein, one of the main proteins surrounding the lipid droplets in fat cells. It regulates the fat cells' metabolism by serving as a physical barrier, restricting the access of lipase and other enzymes to the lipid droplets. Therefore, it plays a vital role in fat storage (Garaulet et al., 2016) and is associated with obesity. Polymorphism in the *PLIN* gene is associated with variability in weight loss. A study carried out by Garaulet et al. (2016) found a connection between the A allele of *PLIN* 14995A>T variant (rs1052700, MAF: 0.2796) and the timing when the carrier eats lunch. Individuals carrying the major allele AA tend to lower weight-loss effectiveness if they consume late lunch. In another study, the A variant is associated with obesity in individuals who do not consume complex carbohydrates sufficiently (Richardson et al., 2011).

2.3.10 ADIPOQ Gene

The *ADIPOQ* gene, also referred to as *GBP-28*, *apM1*, *AdipoQ*, and *Acrp30*, codes for adiponectin hormone. It is produced in fatty tissue and regulates energy homeostasis (Pereira-Fernandes et al., 2014). The product of this gene also affects insulin sensitivity, displays anti-inflammatory properties, and is believed to inhibit the development of atherosclerosis (Fonseca et al., 2017).

The adiponectin level in the circulatory system is determined by genetic and environmental factors. Some gene variants also influence the gene's expression (Jee et al., 2010). Previous studies suggest that, to a certain extent, it is possible to regulate the adiponectin level in the blood with diet. The rs1501299 (MAF: 0.3003) was significantly associated with adiponectin concentration (Albuquerque et al., 2017). When dietary fibre intake was low, GG homozygotes exhibited significantly higher adiponectin concentrations than T allele carriers.

Specific interactions between genes and the environment can lower the adiponectin level in the blood. Low levels of adiponectin in the blood are associated with diabetes and obesity. Individuals with a low dietary fibre diet and carriers of the A variant are believed to have less adiponectin in the blood compared to CC homozygotes (Yu et al., 2012). Reports have also indicated that variants of the *ADIPOQ* gene show different effects on the risk of cardiovascular disease and DM2 in European subjects (Gable et al., 2007).

2.3.11 APOA2 Gene

The *apolipoprotein (apo-) A-II (APOA2)* gene encodes for the apolipoprotein, the second most abundant high-density lipoprotein. The protein is found in plasma in various forms, either as a monomer, homodimer, or heterodimer with apolipoprotein D. Any mutations in this gene can result in apolipoprotein A-II deficiency or hypercholesterolemia. Apolipoproteins combine with lipids to form several classes of lipoprotein particles with different densities, ranging from chylomicrons and very low-density lipoproteins to very high-density lipoproteins (Smith et al., 2013). APOA2 is considered the major component of high-density lipoprotein particles and the primary regulator of triglyceride and postprandial metabolism. Nutrigenetic effects of the interaction between the rs5082 APOA2 -265T/C (MAF: 0.2370) genotype and saturated fatty acids for obesity traits have been extensively studied compared to any other locus. A cross-sectional study was performed on two independent populations, and the interaction between the *APOA2* gene (-265T > C rs5082 SNP) and dairy food (high-fat diet) revealed that individuals who consumed a high-fat diet had greater BMI, found significant both in the Boston Puerto Rican Health Study and replicated in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study (Smith et al., 2013).

Therefore, multiple SNPs in multiple genes are associated with obesity predisposition through interactions with dietary factors. This review summarizes relevant interactions between polymorphisms of obesity-related genes and diets with obesity risk. Because the magnitude of associations between individual SNPs and adiposity traits is modest, studies using genetic risk scores (GRS) have examined the additive effect of multiple loci and diet interactions. These findings point strongly towards the involvement of environmental factors in obesity predisposition. In fact, according to Albuquerque (2017), gene-environmental factors may have the greatest influence on obesity (Albuquerque et al., 2017). The next part of the review focuses on different aspects of gene-environment interactions in obesity predisposition.

2.4 Gene-Environment Interactions in Obesity Predisposition

2.4.1 Population-Specific Findings

Different world populations exhibit unique patterns of SNPs due to their distinct evolutionary histories, environmental interactions, and migrations. As a result, the predisposition to obesity can vary among populations. Understanding these genetic differences can provide insights into the diverse prevalence rates and challenges associated with obesity across global communities.

Fesinmeyer et al. (2013) conducted a Population Architecture using Genomics and Epidemiology study to analyse the association between obesity and SNPs. Hispanics, European Americans, American Indians, East Asians, Pacific Islanders, and African Americans were included in the study. Linear regression, logistic regression, and meta-analysis were performed to compile the results. Nine out of 13 studied SNPs were associated with obesity in European Americans, wherein five were *FTO* SNPs. Six out of 13 SNPs were associated with obesity in Hispanics, three of which were *FTO* SNPs (Fesinmeyer et al., 2013).

To associate the gene variants in the *FTO* gene with obesity, a genome-wide association scan was performed by Scuteri et al (2007). European Americans, Hispanic Americans, and African Americans were included in the study. Results revealed that several SNPs were related to increased quantitative traits, such as hip circumference, BMI, and weight. This experiment was replicated, and two SNPs in the *FTO* gene were genotyped, i.e., rs9930506 and rs6602024. These SNPs were found to be strongly linked with all three obesity-related traits, where the Hispanic Americans and European Americans' rare A allele homozygotes were heavier (1.0-3.0 BMI units) than the common G allele homozygotes (Scuteri et al., 2007).

Much later, in 2016, the rs12253976 SNP of the *KLF6* gene and rs6866721 SNP of the *SEMA6A* gene were evaluated to identify a genetic link to obesity through a genome-wide association study. Different populations such as Hispanics, European Americans, African Americans, and Asians from the Multi-ethnic Study of Atherosclerosis (MESA) were included in the study. rs12253976 SNP of the *KLF6* gene in Hispanics and rs6866721 SNP of the *SEMA6A* gene in European Americans were significantly correlated with BMI. In addition, two BMI-association signals were found in the intronic regions of the *TCF7L2* gene in Hispanics, and another novel BMI-association signal was found in African Americans (Salinas et al., 2016).

Similar trends in the effect of gene variants on obesity were also observed in other population-based studies. One of them was methodically carried out by Tan et al. (2014) through a meta-analysis of various genome-wide association studies in different ancestries. In the study, the six most significant genes associated with obesity, such as *FTO*, *ADRB2*, *PPARG*, *CTNBL1*, *LEPR*, and *UCP2*, were replicated in different populations consisting of Hispanics, Caucasians, African Americans, and Chinese. Results reveal that *FTO*, *LEPR*, *CTNBL1*, and *PPARG* genes significantly contributed to obesity in four ethnicities. rs7185735 SNP of the *FTO* gene was the most strongly associated variant and showed an ethnic-specific association with obesity traits in the Caucasian group (Tan et al., 2014).

In previous studies within the European, Asian, and Mexican populations, *proprotein convertase subtilisin/kexin type 1 PCSK1* variants, the rs6232 and rs6235, have been linked with obesity. To ensure a similar association in the multi-ethnic American population, Choquet et al. conducted two multi-ethnic studies, namely the MESA and Coronary Artery Risk Development in Young Adults (CARDIA, Choquet et al., 2013). European Americans and African Americans were included in the CARDIA study, while in the MESA study, , African American, European-American, and Asians were included. No association was found between the variants among any ethnic group in the MESA study. However, in the CARDIA study, the rs6232 variant was strongly associated with BMI and obesity among the European-Americans, especially in the younger age group (Choquet et al., 2013).

Using the Bayesian hierarchical generalized linear model approach, Tiwari et al. analysed 30 candidate genes related to obesity. Nine single nucleotide polymorphisms in eight genes (*GHRL*, *AGRP*, *CPE*, *GLP1R*, *HTR2A*, *NPY5R*, *SOCS3*, and *STAT3*) were associated with obesity in European Americans. The analysis also revealed two other significant findings; the first is that the rs1745837 SNP in the *HTR2A*

gene had a more significant association with BMI in males, and the second is that there was an interaction between SNPs in the *SOCS3* gene and obesity in Hispanic Americans (Li et al., 2014; Talbert et al., 2009).

From these population studies, it can be established that polymorphism in specific genes can play a significant role in offsetting or heightening the risk of obesity. However, due to the multifaceted gene regulation in obesity and their interaction with the environment, as well as dietary and lifestyle influences, a definite conclusion is challenging to come by. It was observed different results across different ethnicities; hence more ethnic-specific or comparative studies are needed. Therefore, there is a need to incorporate more holistic and multifactorial parameters in population studies.

2.4.2 Gene × Environment Interaction Through Epigenetics

The epigenetic regulation of gene expression across the genome additionally complicates the task of estimating the risks of obesity. Epigenetic modifications allow for adaptability in gene expression based on environmental cues and experiences. They can occur in utero and early life, affecting long-term metabolic programming and responding to environmental factors throughout the individual's lifetime. Moreover, some epigenetic changes can be passed on to the next generation and potentially affect the metabolic health of their descendants.

Neel (1962) proposed one of the first hypotheses relating obesity to the environment. The hypothesis is known as the 'thrifty genotype hypothesis (Hales & Barker, 2001; Neel, 1962). The embryo-fetal period is a crucial phase in determining the onset of diseases. Maternal-fetal stress, poor nutrition, and toxic substance exposure can interfere with the programming of tissues and organs, resulting in many degenerative and chronic diseases (Hales & Barker, 2001; Neel, 1962).

Epigenetics focuses on the changes in gene expression without altering the nucleotide sequence. Epigenetic modifications can be heritable, and the most common ones contributing to gene-environmental interactions include DNA methylation, histone modification, and RNA-mediated processes (Van Soom et al., 2014). These epigenetic changes are induced by internal or external environmental factors play a vital role in cell division and contribute to stabilizing the phenotype (Petronis, 2010). Epigenetic studies indicate that lifestyle changes such as consuming a healthy diet can play a significant role along with genetics to improve human longevity (Lillycrop et al., 2014). In contrast, an unhealthy lifestyle or negative environmental stimuli can modify gene expression and cause diseases (Petronis, 2010). For instance, studies focusing on nutrigenomics and epigenetics suggest that a high-fat diet can decrease the

methylation of *MC4R* and *leptin* genes, contributing to a higher risk towards obesity (He et al., 2019; Widiker et al., 2010). Comparable results were obtained by Lima et al. (2017), where the consumption of polyunsaturated and monounsaturated fat reduced methylation levels of the *ADRB3* gene and provoked no reduction in weight in obese women. Other studies on the *SIMI* gene also confirmed that the methylation process is associated with obesity and a higher BMI percentile (Franks & Ling, 2010; He et al., 2019). A GWAS performed in European individuals also found similar trends where hypermethylation at the *hypoxia-inducible factor 3a (HIF3A)* locus in adipose tissue and blood cells was associated with increased BMI (Dick et al., 2014).

Various histone modifications can also alter gene expression and play a significant role in obesity development. During adipocyte differentiation, histone modifications can modulate the expression of regulatory genes such as *adipocyte protein (AP2)*, *CCAAT-enhancer-binding protein β (C/EBP β)*, *PPAR γ* , *preadipocyte factor-1 (Pref-1)* and *C/EBP α* (Zhang et al., 2012). Histone modifications such as decreased acetylation in lysine 9 of histone 3 (H3K9) of the *POMC* gene and increased acetylation of the histone in the proximity of the *Npy* gene resulted in altered gene expression in rats fed with a high-fat diet to induce obesity. An increase of histone H3 lysine 9 and 18 acetylation at *monocyte chemotactic protein 1 (Ccl2)* and *TNF α* genes was observed in obese mice (Mikula et al., 2014).

In 2006, Grun and Blumberg formulated the obesogenic hypothesis, proposing that some environmental chemicals can promote obesity (Grün, 2010), and some of them do that through epigenetic mechanisms. Xenobiotics could act in varied ways, such as inducing hyperplasia in adipocytes, perturbing lipid homeostasis, and stimulating adipogenic pathways where hyperplasia activation occurs during physiological development. Heavy metals, polychlorinated biphenyls, solvents, phthalates, pesticides, organic phosphate, diethylstilboestrol, and organotin are some of the “obesogens” that can promote adipogenesis by various mechanisms (Grün, 2010; Grün & Blumberg, 2007). Accumulation of persistent organic pollutants (POPs) in adipose tissue can interact with the gene expression of obesity marker genes, namely, *LEP* and *ADIPOQ*. The adiponectin and leptin levels found after exposure to POPs suggest that xenobiotics may potentially contribute to metabolic pathologies such as obesity (Pereira-Fernandes et al., 2014; Warner et al., 2014).

Weight gain during pregnancy, maternal obesity, and maternal cigarette smoking have also been associated with a higher risk of offspring adiposity (Lee et al., 2015; Oken et al., 2008). In addition, prenatal exposure to maternal smoking prompted interaction with *opioid receptor mu 1 OPRM1* genetic

variants, resulting in variable dietary preference for fat in offspring (Lee et al., 2015; Reynolds et al., 2010). Furthermore, studies reveal that females are more likely to develop obesity than males due to mutations in the *MC4R* gene (Dempfle et al., 2004).

The studies above indicate that the gene-environmental interaction is complex in nature, involving multiple factors, and requires more integrated and holistic investigations to comprehensively elucidate their influence on the predisposition and development of obesity. The involvement of epigenetic controlling mechanisms in gene expression may define observable differences in obesity predisposition among humans with the same genetic background.

2.4.3 Gene-Lifestyle Interaction Studies

Therefore, several risk factors, such as behavioural, demographic, physiological, genetic, and environmental factors, can contribute to the onset of diseases. Behavioural /lifestyle risk factors include alcohol intake, smoking tobacco, physical inactivity, and unhealthy eating. Environmental factors such as pollution, radiation damage, and climate change are some examples of risk factors contributing to the onset of diseases (Avinun & Hariri, 2019; Bjørnland et al., 2017; Dubois et al., 2012; Edwards et al., 2012; Fesinmeyer et al., 2013; Nakamura et al., 2016; Tessier et al., 2019).

One lifestyle risk factor that has evolved significantly over time is unhealthy eating habits. According to recent studies, caloric intake has increased dramatically during the last decades (Hurt et al., 2010). Increased consumption of total fat (especially saturated fats at more than 40% daily intake and trans-fat) and cholesterol (more than 300 mg (about the weight of ten grains of rice)), as well as simple sugars, are some indications of unhealthy eating (Hurt et al., 2010). Reduced physical activity is another contributing factor in promoting obesity (Hill et al., 2012). In addition, several other less prominent environmental and social-cultural factors can also contribute to a rising number of obesity cases. Some early environmental factors include low neonatal weight for gestational age, artificial lactation, gestational obesity, and the mother's health during gestation (for instance, if it occurs during menopause) (Reynolds et al., 2010; Van Soom et al., 2014). In addition, childhood and adolescent obesity could also potentially lead to obesity later in life.

Lifestyle factors can influence disease onset by altering gene expression, leading to a physiological response in the individual (Walley et al., 2009). Therefore, understanding the mechanisms of gene-

environment interactions of complex diseases is one of the more effective approaches to developing therapeutic targets.

Over the past few decades, lifestyle changes have played a significant role in causing obesity. Numerous studies on various populations and lifestyles have provided evidence for gene-lifestyle-environmental interactions (Kalantari et al., 2016). An example of this interaction was discovered in a study where 69% of Indians in Arizona were obese while living in an obesogenic environment. In contrast, only 13% of Indians in the Mexican Sierra Madre Mountains had obesity (Fesinmeyer et al., 2013), revealing that different lifestyles triggered different responses towards the prevalence of obesity despite similar genetic predispositions (Barker et al., 1989; Schellong et al., 2012).

The following describes the most common lifestyle factors influencing obesity in population-based genetic studies.

2.4.3.1 Physical activity

Reduced physical activity or physical inactivity is often related to obesity. For instance, a four-year cross-sectional study conducted by Gortmaker et al. (1996) observed a higher risk of obesity in children who watched TV for more than 5 hours a day than those who did for less than 2 hours. A study assessed the interaction between physical activity and genetic predisposition to obesity in individuals from the European Perspective Investigation of Cancer-Norfolk. Results obtained from 12 obesity-associated SNPs indicated a 40% reduction in the incidence of obesity and level of BMI in individuals involved in greater physical activity (Li et al., 2010). Similar trends were witnessed in the HUNT study. SNPs of the *FTO* and *MC4R* genes were genotyped in the HUNT study, and their interaction with lifestyle factors was analysed. A higher risk of obesity was found in young and physically inactive individuals and in men who had a regular intake of sugar-sweetened beverages (Bjørnland et al., 2017).

In a more recent investigation, Reddon et al. (2016) conducted a multi-ethnic longitudinal study to quantitatively measure the interaction between genetic predisposition and physical activity to obesity. Six ethnic groups involved in the study were Latin American, European, East Asian, African, South Asian, and Native North American. The study analysed the impact of 14 predisposing genes on obesity and physical activity. Results indicated that the BMI score was inversely proportional to physical activity. Among all, *FTO* rs1421085 and decreased physical activity were most strongly associated with adiposity (36-75%) in a multi-ethnic longitudinal cohort.

2.4.3.2 Dietary habits

To investigate the interaction between gene \times dietary pattern and obesity, 68,317 participants of European ancestry were analysed. No significant interactions were found between 32 studied SNPs and broad diet patterns. Only two SNPs had an impact on BMI. The authors speculate that the negative findings may have been due to the fact that the summary diet score in the study represents several dietary characteristics or components. Hence, individual SNP effects on each of the dietary components might have been masked by the generated summary score approach that attempted to capture all dietary components in one diet score. Meanwhile, a strong association between obesity traits and an unhealthy diet was observed (Nettleton et al., 2015; Qi et al., 2014). Contrasting results were obtained in another study, the HALE project. This study was conducted on European elderly individuals aged 70 to 90 years, focusing on the effects of lifestyle and Mediterranean diet on obesity. This study indicated that adherence to a Mediterranean diet and a healthful lifestyle were positively correlated in lowering the risk of obesity (Knoops et al., 2004).

Gene-environmental interactions can have varied effects on different populations. Corella et al. (2009) studied the interaction between diet, *APOA2* polymorphism, and BMI in three independent populations: non-Hispanic whites (the Framingham Offspring Study), individuals with European ancestry (the genetics of Lipid-Lowering Drugs and Diet Network Study), and Hispanics with Caribbean origin (Boston Puerto Rican Centres on Population Health and Health Disparities Study). A follow-up cross-sectional study and a case-control analysis were performed to assess the interaction between saturated fat consumption and *APOA2* – 265T>C polymorphism and obesity. Results revealed that individuals with the CC genotype that consumed high saturated fat were highly susceptible to obesity. However, the same association was not observed in low saturated fat consumption. The study also revealed that individuals with European ancestry were slightly more susceptible to obesity than others due to their high saturated fat intake (Corella et al., 2009).

2.4.3.3 Smoking

Increasing evidence suggests that smoking can moderate gene expression. A meta-analysis study conducted in the European population reported the interaction between BMI, smoking, and variation at the *CHRNA5-CHRNA3-CHRNA4* locus (rs1051730). In contrast, no association was observed in non-smokers. In former and current smokers, the risk allele was associated with a decrease in BMI of 0.16 and 0.33 kg/m², respectively (Freathy et al., 2011). A similar trend was repeated in another study involving

14,131 Pakistani adults. Results show that a minor allele (T) in *FLJ33534* interacted with smoking and resulted in a lower BMI, while a positive association was obtained in non-smokers (Ahmad et al., 2016).

2.4.3.4 Alcohol intake

Like smoking, alcohol intake can also moderate gene expression. In 2016, researchers revealed that increased alcohol intake was associated with a twenty-nine SNP GRS on BMI (Nakamura et al., 2016). Meanwhile, in another study with variable results across different ethnic groups; a significant interaction of the *PPARGCIA* rs4619879 gene was detected with high alcohol consumption in African Americans, but not Caucasians (Edwards et al., 2012; Nakamura et al., 2016).

Tessier et al. (2019) investigated the interactions of genes with nutrient consumption and alcohol intake involving four ethnic groups; Caucasians (European, Hispanic, and Middle Eastern), East Asians (Japanese, Chinese, Vietnamese, Korean, Thai, Filipino, and Cambodian), South Asians (Indian, Sri Lankan, Bangladeshi and Pakistani) and others (Afro-Caribbean's, First Nations Canadians and individuals who belong to more than two of four ethnocultural groups). Obesity-related phenotypes were analysed based on waist circumference and BMI with the help of penalized logistic regression and multifactor dimensionality reduction. Daily intake of macronutrients and alcohol and 54 SNPs in *IKBKB*, *NFKB1*, and *SOCS3* were included for assessment. There was no significant gene-environment interaction in any of the ethnic groups, but gene-gene interaction was present in the Caucasian population. MDR analysis showed gene-gene interaction between *IKBKB* rs3747811, *SOCS3* rs6501199, and rs4969172, affecting BMI. The interaction between *NFKB1* rs1609798 and *SOCS3* rs6501199 affected waist circumference (Tessier et al., 2019).

2.4.3.5 Psychological health status

Psychosocial stress is a significant contributor to ill health. A genome-wide analysis managed to identify the interaction between five SNPs in the Early B-cell Factor 1 (*EBF1*) gene, and psychosocial stress with hip circumference. The study revealed significant findings in 2,460 Whites in an MESA study. However, this interaction was insignificant in Blacks, Chinese Americans, and Hispanics. A higher correlation between the risk allele in *EBF1* on the hip circumference was observed in participants with chronic stress. The authors replicated the interaction study with three out of five SNPs (rs17056278 C>G, rs17056298 C>G, and rs17056318 T>C) in *EBF1* in the Framingham Offspring Cohort study (Singh et al., 2015). The same research group performed subsequent analysis on psychosocial stress interaction with waist

circumference in the Family Heart Study Whites and Duke Caregiver study. Results showed that chronic psychosocial stress could modulate the *EBF1* gene expression leading to increased BMI (Singh et al., 2015).

Specific psychological conditions such as depression were also reported to increase the risk of obesity (Avinun & Hariri, 2019). A study about their interactions indicated that eight out of the ten SNPs of the *FTO* gene in the depressive group were strongly associated with BMI. Additionally, depression-associated chronic sleep disturbances also played a role in triggering obesity (Lane et al., 2017).

2.4.3.6 Educational and Income Level

Epidemiological studies have revealed interactions between educational status or socioeconomic status with obesity. A negative association between academic status and BMI was observed in non-carriers of *MC4R* mutation (Corella et al., 2012). However, the same was not observed in the mutation carriers of the *MC4R* gene, therefore, indicating that high education status does not provide any protective effect on obesity risk (Stutzmann et al., 2008).

In another study, a gene \times education interaction was found in A allele carriers of the *FTO* gene. In these carriers, obesity risk was higher in individuals with no university education, thus, indicating a significant interaction between education, *FTO* SNP, and obesity (Corella et al., 2012). Similar trends were seen in another study involving European children. Individuals with favourable socioeconomic status were inversely correlated with obesity. However, these results were observed only with low-risk genotype TT in *FTO* rs993909 participants (Foraita et al., 2015). A meta-analysis study on socioeconomic position (SEP) as an intervention against obesity discovered an inverse association between SEP and childhood obesity. However, this association was only applicable in high-income countries and economically developed areas such as Europe, North America, and Oceania. The findings also further suggest that in children between the ages of 0-12, low SEP is correlated with a 10% higher risk of being overweight and a 41% higher risk of obesity (Wu et al., 2015).

2.5 Personalized Nutrition and Role of Nutritionists and Dietitians

Personalized nutrition, also referred to as precision nutrition, is a comprehensive diet strategy that involves the integrated application of an individual's genes, traits, nutrition, or other relevant information that can be used to optimise health and nutrition (Cherkas et al., 2010; Holzapfel et al., 2010; Stewart-Knox et al., 2009). Instead of deciding what is the best food or nutrient for all people, personalized nutrition focuses

on the individual. By identifying and applying personal characteristics or factors that influence a person's response to diet, this information may be used to create an individualized approach to improve health or conditions by optimizing diet and nutrition. In essence, the concept was built upon the notion that everyone is different or that different people respond differently to external stimuli like food, nutrients, and even drugs.

With the advent of precision nutrition, more targeted and effective diet interventions can be used to solve persisting conditions previously found challenging to control. For example, a person who regularly experiences allergies with a previously unknown trigger may have this condition to be caused by an ingredient in the food. Hence, a diet devoid of the allergen (e.g., egg, seafood, milk, etc.) is optimized to prevent future allergic reactions. Another person may have a reduced capacity to use folate effectively, which may lead to neural tube defects as a birth defect during pregnancy, and this may be due to a genetic mutation in the *MTHFR* gene. Hence, folate supplementation through an optimized diet plan or supplements to counter this may help mitigate the risks. This form of personalized nutrition where nutrients are optimized based on a person's genes is called nutrigenomics. In a nutshell, nutrigenomics is based on genetic testing of the person's genes for any genetic variation that is associated with a response to a diet or a nutrient. After the results are out, the person's diet can be optimized based on that information by increasing, decreasing, supplementing, or avoiding specific nutrients.

In order to successfully implement and harness the potential benefits of nutrigenomics, qualified professionals are needed, and nutritionists and dietitians are crucial players in this approach. Nutritionists and dietitians are experts in the food or nutritional aspects of nutrigenomics. However, nutrigenomics is still a relatively new area without an established global gold standard that can be followed to implement for patients/clients. Hence, the degrees undertaken by current nutritionists and dietitians may not have discussed or deeply tackled the implementation and practice of nutrigenomics during college, resulting in a low understanding of the subject matter that may be an issue during current clinical practice.

The factors affecting dietitians' and nutritionists' knowledge and involvement in the nutrigenomics area are important to advance its implementation and ensure that it has been correctly accomplished. A literature review to find published materials about professional knowledge and interest in nutrigenomics was conducted. The search was done in databases such as Pubmed, ResearchGate, and SciELO using the keywords "questionnaire", "survey", "dietitian's knowledge in nutrigenetics", "nutrigenomics", "the involvement of dietitian in genomics".

There is a paucity of such surveys, and the majority of the research was conducted in Canada, the USA, and the UK. Wright (2014) performed a systematic review from January 2000 to December 2012 to identify original research in all scientific databases. Any studies of either nutritionist and dietetics students or dietitians/nutritionists investigating current levels of knowledge or confidence in nutritional genomics or strategies to improve learning and confidence in this area were eligible. Eighteen articles (15 separate studies) met the inclusion criteria, with three articles assessed as negative, eight as neutral, and seven as positive. The overall ranking of evidence was low. Results suggested that professionals have low involvement, knowledge, lack of confidence in nutritional genomics, and the evidence for educational strategies is limited and methodologically weak (Wright, 2014).

McCarthy et al. (2008), Gilbride and Camp (2004), and Whelan et al. (2008) suggested that dietitians' perception of the importance of an understanding of genetics to the dietetics profession was positively associated with knowledge and involvement, confirming previous reports in small studies. The professionals who see the value of genetics may be more likely to seek out information and opportunities to be involved. Among dietitians, the factors that impact their knowledge, involvement, and confidence in genetics and nutritional genomics are variable, including having insufficient knowledge. However, while these surveys have been reported, they were conducted only in isolated, single-country surveys (Whelan et al., 2008).

Using electronic lists, Collins and colleagues (2013) undertook an international cross-sectional survey involving 1,844 dietitians from Australia, the USA, and the UK. The questionnaire focused on knowledge, actual involvement, and confidence in genetics and nutritional genomics. The results show that most of the participants scored higher in the genetics section and had lower knowledge scores regarding nutritional genomics. They also concluded that the knowledge, involvement, and confidence level in using nutrition and genetics testing are still low; however, this was a decade ago, and the current status is unclear (Collins et al., 2013).

Comparing the results found in this study and more recent surveys, data shows that dietitians still have similar perspectives. Cormier et al. (2014) published a survey to find out about the situation related to nutrigenomics in the practice of registered dietitians from the province of Quebec (Canada). Participants indicated that they were interested in the field; however, the majority still lacked the knowledge to integrate it into their clinical practice. In this cross-sectional study, 373 registered dietitians completed an online survey that included 34 questions, most of which were closed-ended. Overall, 76.9% of dietitians were familiar with the field of nutrigenomics. The study also concluded that 49.2% of dietitians with less

than five years of working experience had the correct answers in the nutrigenetics knowledge section of the survey, whereas this was the case for only 11.7% of the experienced professionals with over 25 years of experience. However, they found that 75.9% of dietitians working in clinical nutrition in the public sector perceived they did not have sufficient knowledge to integrate nutrigenomics in their practice compared to 62.9% of nutritionists in private practice. When asked about the main limitations of genetic testing related to nutrition, dietitians were sceptical about the accuracy and the methods of the tests, also finding a limitation about not considering other factors such as high costs and that there is a lack of scientific evidence.

Moreover, ethical and legal concerns scored high among the professionals surveyed. Additionally, since there is no established clinical practice guideline, another pressing concern is how to handle the risks of misleading information or misinterpretation of results by the professionals and the customers. The survey also concluded that the costs of the tests were also a barrier for the professionals. Finally, there is a high interest in nutrigenomics from the professionals' points of view, especially those with less working experience. However, they do not feel adequately skilled to integrate findings from nutrigenomics into their practice (Cormier et al., 2014).

2.6 Conclusion to the Literature Review

This review provided an overall insight into the complexity governing obesity. It provided evidence on the degree and nature of the interactions with numerous interconnected variables such as genes, diet, and environment in driving obesity. This review introduces the critical role of nutrigenetics and nutrigenomics to tackle some of these complexities, ranging from the diversity of an individual's genetic makeup, type of diet consumed, lifestyle, psychosocial stress, and socioeconomic position.

The first crucial step in working on a solution to the global obesity problem is recognizing and understanding the complex nature of obesity and how it is regulated, genetically and epigenetically. Much more work needs to be done to obtain a holistic understanding before effective interventions and treatments are implemented.

Another perspective is that the complete map of all genes and genetic variants influencing a person's response to diet and nutrients has not yet been fully uncovered. There is also a lack of genetic research on some ethnicities and ancestries or minor populations that may respond differently from the general

population. In fact, ethnic-specific differences have an important contribution to the nutrigenomics clinical management of patients/clients. For example, ethnicities with dark skin tones are more prone to Vitamin D deficiency than those with lighter skin, which suggests that people with darker skin tones often should modify their diet or supplement with vitamin D.

Scientific and technological advancements have resulted in a greater focus on the role of genetics and nutritional genomics play in the pathogenesis of disease and management. The delivery of genomics targets on health care will require the involvement of many professionals, including dietitians and nutritionists. The interest in personalized diet and testing is growing, while nutritional genetics testing, known as nutrigenomics, is the promise to deliver personalized information to the individual (Nielsen & El-Sohemy, 2012). However, there is a need to develop projects to up-skill nutrition and/or dietetics students and professionals in nutritional genomics through multidisciplinary partnerships with content area experts. Therefore, this research is aimed at improving knowledge on genetic determinants of obesity in different ethnic groups (Brazilians and Swiss) and in surveying the current confidence and competence in nutrigenomics and nutrigenetics of nutritionists and dietitians in different countries (Brazil and the UK). The results of this research may contribute to improving the nutrigenomics approach to obesity and provide important insights into the present situation with nutrigenomics implementation in the UK and Brazil.

3. ASSOCIATIONS AND DIFFERENCES IN GENETICS, LIFESTYLE, AND BMI BETWEEN BRAZILIAN AND SWISS POPULATIONS

Keywords: Genetic Risk Score – Obesity – Lifestyle – Chronic Diseases – Polymorphism

ABSTRACT

A cross-sectional study involving unrelated participants in Brazil and Switzerland was conducted. The study population included a total of 112 males and 310 females (N = 422). Anthropometric measurements, physical activity, and lifestyle information were obtained using self-reported questionnaires. Genotyping was performed for 22 SNPs, and genetic scores were calculated using allelic additive unweighted and multiplicative weighted models.

The findings suggested no differences in BMI between the study populations. In addition, regression analysis indicated that neither weighted nor non-weighted GRS are significant predictors of BMI. Based on existing literature, the lack of significance could be attributed to inadequate sample size, population genetic architecture, or the choice of SNPs used to construct GRS. It was also found that stress levels were positively correlated with BMI and physical activity was inversely associated with BMI. Together, these findings may imply that lifestyle plays a significant role in obesity, possibly due to the influence of DNA polymorphisms in the study population.

3.1 Introduction

Obesity is one of the leading causes of many diseases and preventable death. Management and prevention of obesity can help avert many prevalent diseases and common health problems, including high blood pressure, diabetes, and heart diseases. Also, the progression of obesity is a significant risk factor for various chronic diseases, including cardiovascular disease and cancer (Renehan et al., 2008). These diseases can pose a heavy financial and negative socioeconomic burden in households (Sun et al., 2017). The incidence of obesity is increasing globally, as 40% of adults worldwide are overweight, and 10-15% are obese (NCD Risk Factor Collaboration (NCD-RisC), 2016). Obesity has become a major health issue rather than a cosmetic concern. It is an epidemic in many developing and developed countries associated

with 2.8 million deaths annually (World Health Organization, 2021).

Increasing evidence suggests that obesity arises from the interaction between the genetic makeup of an individual and environmental factors such as little physical activity, over-eating, and low socioeconomic status (Albuquerque et al., 2015, 2017; Dubois et al., 2012; Fawcett & Barroso, 2010). The genetic predisposition, in combination with environmental factors, poses a risk for the onset of obesity. Early studies involving the genetics of obesity traced mutations to single genes (i.e., monogenic obesity), which are inherited as a single aberrant locus (Herrera & Lindgren, 2010; Mason et al., 2014). Monogenic obesity is linked to the leptin-melanocortin pathway, a key regulator of energy intake (Farooqi et al., 2003; Hinney & Hebebrand, 2008). Mutations in the genes or dysfunctional genes of this pathway, such as *LEP* and *LEPR*, *POMC*, and *PC1*, contribute to monogenic obesity. However, only 5-10% of genetic causes of obesity are monogenic, with the remaining being polygenic (Blundell et al., 2014; Hinney et al., 2010b).

Interestingly, the genetic variants/alleles predisposing to obesity have also been found in the lean and normal weight population. However, the genetic risk variant occurs more often in obese than non-obese individuals (Fall & Ingelsson, 2014). In addition, each risk allele makes only a small contribution to the development of obesity. For instance, the 103Ile allele of the Val103Ile single nucleotide polymorphism of the melanocortin-4 receptor gene *MC4R* was one of the first confirmed polygenetic variants with an influence on the body mass index. Two gene variants with small but replicable effects on body weight have unambiguously been identified so far for *MC4R* (Fall & Ingelsson, 2014). Other than that, variants in the *FTO* gene, such as rs9939609, rs1421085, rs3751812 and rs8050136 and SNPs in the *INSIG2* gene, rs7566605 were found to be associated with body mass index (Boiko et al., 2021; Talbert et al., 2009). These findings, however, have yet to be replicated and validated for their significant role in weight regulation (Jee et al., 2010; Nakamura et al., 2016; Rask-Andersen et al., 2017; Reddon et al., 2016a; Reddon et al., 2016b).

Establishing an association between the genes and disease phenotypes is vital before translating the findings into practice. Genome-wide association studies can be used to detect associations between specific phenotypes with SNPs. Regarding metabolic disorders, GWAS have provided a better understanding of the relationship between polygenic diseases and BMI (Goodarzi, 2018b). In contrast with the earlier concept of a single recessive or dominant gene in modulating *MCR4* or causing leptin deficiency, GWAS can identify numerous genes and a plethora of common genetic variants associated with obesity-related traits. These findings partly explain the complexity of body weight regulation. More than 100 loci are associated with BMI, but most of these studies were conducted in populations of

European ancestry (Young et al., 2018). Conclusions drawn from genetics studies are incomplete without including all major and minor ethnic groups of any region. Similarly, the under-representation of minority ethnic groups or populations of genetically mixed ancestry backgrounds in GWAS, such as Latin American individuals, leaves a gap in the comprehension of how genetics influence obesity in this specific group (Stryjecki et al., 2018). It is important to note that in a Latin American country, such as Brazil, 52.5% are overweight, and 17.9% of the population is obese (Gomes et al., 2019).

Only a handful of studies related to genetics and obesity have been conducted in Switzerland. The incidence of obesity is lower in Switzerland compared to other countries, but recent reports have indicated increasingly higher incidences of overweight and obesity (Elks et al., 2012; Hinney et al., 2010). In 2017, around 40% of the population in Switzerland was overweight, and 13% was obese.

There is a clear difference in obesity prevalence between the Brazilian and the Swiss populations. One may hypothesize that these disparities result from differences in genetics and lifestyle factors between these two populations. In this study, the aim was to explore the determinants of obesity in two different ethnic groups that share the same country of residence and potentially similar environments (i.e., Brazilian and Swiss populations living in Switzerland) and compare the differences in BMI between these two populations. Another aim was to explore the differences in BMI between these two populations and the population of Brazilians living in Brazil, sharing a similar ethnic background to Brazilians living in Switzerland but potentially a different environment. The differences in BMI, genetic predisposition to obesity, and lifestyle between the three population groups were used to determine if lifestyle or genetics play a more critical role in BMI in these populations.

3.2 Materials and Methods

3.2.1 Study Design and Participants

This cross-sectional study involved unrelated participants in Brazil and Switzerland. The study population included a total of 112 males and 310 females (N = 422), aged 18–86 years, subdivided into three groups:

- (1) Brazilian nationals living in Brazil;
- (2) Brazilian nationals living in Switzerland;
- (3) Swiss nationals living in Switzerland.

The participants were selected among visitors of nutritional or medical clinics who previously received information about nutrigenomics tests. These individuals consented to genetic testing and obtained nutritional advice and health information. In Brazil, there were no Swiss immigrants visiting the clinics, and, therefore, a “Swiss nationals living in Brazil” comparison group was not formed.

The participating clinics were selected based on the criteria of selling nutrigenomics and genetic tests to their customers. Two clinics in Brazil included Swiss Clinica, Av. Rodrigues Alves, 590 – RN – Nata, Brazil and (2) Swiss Clinica, Av. Paes Leme, 215 – Sao Paulo, Brazil. Two private clinics in Switzerland offer nutrigenomic testing: (1) Therme Zurzach Clinic – Dr. Martin Erb-Strasse 11, 5330 Bad Zurzach, Schweiz and (2) NGR Nutritional Genomics: Schweigwiesstrasse, 12 – 8735 – Feusisberg, Schweiz. The study took place from 2015 to 2019.

The exclusion criteria include participants who were not Brazilian or Swiss, pregnant women, individuals who had congenital, mental, or endocrine disorders (e.g., myxoedema and Cushing's syndrome), patients with cancer or having other comorbidities that were not controlled/stabilized such as uncontrolled hypertension, diabetes, cardiovascular, renal, or other issues, and individuals under 18 years of age. Participants were well-informed about the procedures involved, and the instructions were clear. After ensuring that participants understood the information, only those who provided written informed consent were enrolled in this study. All procedures were in line with the ethical standards of the Responsibility Committee for Human Experimentation, as detailed by the Helsinki Declaration of 1975, revised in 2000. The University Ethics Committee approved the study protocols.

3.2.2 Anthropometric Measurements

A trained health professional (HP) recorded body weights using a regularly calibrated medical weighing digital scale (Omron HBF-514). Participants were weighed barefoot and without excess clothing. Height was recorded using a portable height scale (weight data-field 21002), and measurements were recorded to the nearest 0.5 centimetres. Height and weight scales were standard across participating countries. Body mass index was calculated as weight (kg)/height (m²). The International Obesity Task Force criteria (WHO), age, gender, and specific BMI cut-off points were used for overweight and obesity classifications (Ray et al., 2017).

3.2.3 Physical Activity and Lifestyle Information

A self-reported questionnaire was delivered face-to-face, either in Portuguese or German, in each country

by a trained HP without the researcher. This allowed for eliminating any irrelevant or biased questions. The information collected included demographic and health-related variables, including chronic diseases, medically prescribed drugs, and over-the-counter supplementation. The questionnaire also included smoking status and physical activity engagement. The complete questionnaire is available in the supplementary section of this document.

3.2.4 DNA Extraction and Genotyping Procedure

DNA was extracted and isolated from oral epithelial cells, which were collected using a Swab DNA Evidence collection tube STRATEC (Birkenfeld, Germany). The extracted DNA was then stored at -20°C according to the manufacturer's instructions. Genotyping was performed using KASP PCR assay for genotyping in the LGC laboratory (Teddington, England). The samples were genotyped in batches of 22, 48, and 96. A candidate gene approach was employed to confirm GWAS findings in this unique population, filtering from 102 SNPs genotyped from the available nutrigenomics test. Nutrigenomics tests included genes related to nutritional matters, vitamins, and some chronic diseases related to nutritional pathway disruptions.

3.2.5 Candidate Genes

A total of 22 single nucleotide polymorphisms that play a potential role in BMI were analysed. Suitable SNPs were selected based on publications that include genes related to obesity. In addition, outcomes of genome-wide association scans and candidate gene studies revealed that the chosen loci are the most promising SNPs associated with obesity risk. These SNPs also confer a greater than 5% risk allele frequency in the general population. Deviation from Hardy-Weinberg equilibrium was tested on each allele using a chi-square test.

The SNPs included were: rs12970134 – *MC4R*, rs1800206 – *PPARA* (Peroxisome Proliferator Activated Receptor Alpha), rs10146997 – *NRXN3* (Neurexin 3), rs894160 – *PLIN1* (Perilipin 1), rs1801282 – *PPARG* (Peroxisome Proliferator Activated Receptor Gamma), rs699 – *AGT* (Angiotensinogen), rs328 – *LPL* (Lipoprotein Lipase), rs5443 – *GNB3* (G Protein Subunit Beta 3)/*CDCA3* (Cell Division Cycle Associated 3), rs9939609 – *FTO* (Alpha-Ketoglutarate Dependent Dioxygenase), rs7903146 – *TCF7L2* (Transcription Factor 7 Like 2), rs1042714 – *ADRB2* (Adrenoceptor Beta 2), rs1800795 – *IL6* (Interleukin 6), rs1501299 – *ADIPOQ* (Adiponectin, C1Q And Collagen Domain Containing)/*ADIPOQ-AS1* (*ADIPOQ* Antisense RNA 1), rs662799 – *APOA5* (Apolipoprotein A5), rs6548238 – *TMEM18* (Transmembrane Protein 18), rs5082 – *APOA2* (Apolipoprotein A2), rs4680 – *COMT* (Catechol-O-

Methyltransferase), rs1137101 – *LEPR* (Leptin Receptor), rs693 – *APOB* (Apolipoprotein B), rs17782313 – *MC4R* (Melanocortin 4 Receptor), rs4520 – *APOC3* (Apolipoprotein C3), and rs4988235 – *MCM6* (Minichromosomal Maintenance Complex Component 6) (Kupca et al., 2013; Locke et al., 2015b; Rao et al., 2014; Voisin et al., 2015; Welter et al., 2014).

3.2.6. Genetic Risk Score (GRS)

3.2.6.1 Genetic score for BMI using an allelic additive unweighted model

The GRS was constructed by measuring the cumulative impact of risk alleles on BMI for each sample (Igo et al., 2019). The GRS was calculated using the 22 SNPs, and then the number of risk alleles was summed up using an additive model. The variants in the genotype were coded as 0, 1, and 2 for the presence of no, one, or two risk alleles (i.e., homozygous non-risk, heterozygous, and homozygous risk genotype), respectively. Used genetic risk scores were not sex-specific as sex-specific information is not available for all tested SNPs.

3.2.6.2 Genetic score for BMI using effect size

Additionally, a weighted method based on the β -coefficient values to construct the multivariable weighted GRS was used (Park et al., 2010). The values were obtained from six SNPs tested from previously published GWAS with the assumption that each SNP is independently associated with obesity risk and included 6 out of 22 SNPs since only these have β -coefficients sourced from GWAS conducted in Caucasian populations. The 6 SNPs with β -coefficients available are located in the following genes: *M6MC* (Locke et al., 2015), *MC4R* (Xi et al., 2012), *FTO* (Gerken et al., 2007), *MC4R2* (Xi et al., 2012), *TCF7L2* (Cropano et al., 2017), and *TEM18* (Erez et al., 2011). The values of 0, 1, and 2 were assigned to the number of coded alleles present for each sample. The number of corresponding coded alleles (0, 1, or 2) was multiplied by the corresponding β -coefficient value, and all products were summed up. Finally, the score was divided by the number of effective SNP genotypes to achieve a mean value with the ratios standardized. For normalization of the variables, the final values were multiplied by 10 to be comparable to the non-weighted score.

Example of score calculation:

$$0.016 \times M6MC_rs4988235 [0,1,2] + 0.06 \times MC4R_rs17782313 + [0,1,2], 0.36 \times FTO_rs9939609[0,1,2] + 0.22 \times MC4R2_rs12970134 [0,1,2] + 0.023 \times TCF7L2_rs7903146 [0,1,2] + 0.28 \times TEM18_rs6548238 [0,1,2].$$

3.2.7 Statistical Analysis Overview

The data was analysed utilizing SPSS version 24.0 (Chicago, IL, USA). Continuous variables were expressed as means and standard deviations, whereas categorical variables were reported as absolute and relative frequencies. The distribution of study variables (normality) was screened using the Kolmogorov-Smirnov test.

This study utilized descriptive statistics to highlight the prevalence of overweight/obese individuals and classifications according to participant nationality and residence, age, sex, and lifestyle information. The lifestyle information includes smoking status, physical activity levels, use of prescribed medication and nutritional supplementation, and stress levels. Sex-stratification of data was not possible due to a relatively low sample size and an absence of sex-specific information for some SNPs used in the study, while sex-specificity must be confirmed at the level of primary GWAS analysis (Liu et al., 2012).

The allele frequencies observed for each SNP were compared between the Brazilians and the Swiss participants by the chi-squared test of associations. Differences in supplements and medication use, sex, presence of chronic disease, BMI classification, and smoking status between Brazilians living in Brazil, Brazilian immigrants in Switzerland, and Swiss nationals living in Switzerland were analysed using a chi-square test with Bonferroni correction for multiple comparisons.

The differences in stress and physical activity levels and BMI between the three groups of participants were analysed using the Kruskal-Wallis test or one-way ANOVA. The genotyping information was used to calculate the weighted and unweighted genetic scores. Together with the lifestyle factors, these scores were subsequently used to create a statistical model. Correlations between BMI, GRS, and lifestyle factors were explored using Spearman's or Pearson's correlation and relationships between these variables were analysed using multiple regression analysis. A two-tailed t-test with significance set at $p < 0.05$ was used for the evaluation of the statistical significance.

3.3 Results

3.3.1 Population Characteristics

A total of 422 individuals completed the questionnaire, and the overall population characteristics are displayed in Table 1. The participants constituted 73.5% female and the remaining 26.5% male, with

43.6% Brazilians and 56.4% Swiss participants. The population data indicated that most participants lived in Switzerland, i.e., 80.6%, whereas 19.4% lived in Brazil. Thus, the Brazilian immigrant percentage stood at 29.2%. From the self-reported data, 19.2% of participants were experiencing some sort of chronic disease. In addition, 18% of the participants self-reported high-stress levels, 40% – medium stress, 32.7% – low stress, and 9% did not experience any stress. 10.4% of the participants were on prescribed medications, while 53.6% consumed over-the-counter supplements. 16.1% of the participants did not engage in any physical activity, whereas 73.5% were involved in some physical activity, ranging from 1 to 7 sessions per day. A minority of the participants carried out two or more physical activity sessions per day. Of the total population size of 422, 10.2% were smokers, while 58.1% were overweight or obese.

Table 1. Descriptive characteristics of participants (N = 422)

		Frequency (N)	Percentage (%)
Sex	Women	310	73.5
	Men	112	26.5
Nationality	Brazilian	184	43.6
	Swiss	238	56.4
Residence	Brazil	82	19.4
	Switzerland	340	80.6
Chronic disease	Yes	81	19.2
	No	341	80.8
Stress level	No	38	9.0
	Low	138	32.7
	Medium	169	40.0
	High	76	18.0
	Missing	1	0.2
Medication	None	377	89.3
	Yes	44	10.4
	N/A	1	0.2
Supplement intake	None	196	46.4
	Yes	226	53.6
Physical activity	None	68	16.1
	1-3 sessions	148	35.1
	4-5 sessions	83	19.7
	6-7 sessions	79	18.7
	Two times per day	1	0.2
	More per day	25	5.9
	N/A	18	4.3
Smoking	No	378	89.6
	Yes	43	10.2
BMI classification	Overweight /obese	245	58.1
	Normal weight	174	41.2

	Frequency (N)	Percentage (%)
Underweight/ missing	3	0.7
	Mean ± SD (range)	
Age (years)	42 ± 12 (18-86)	
Weight (kg)	75.6 ± 17.6 (45-160)	
Height (cm)	167.8 ± 8.5 (150-198)	
BMI (kg/m ²)	26.7 ± 5.5 (18-59)	
Unweighted GRS	13.2 ± 3.1 (4-22)	
Weighted GRS	6.1 ± 3.8 (0.00-16.20)	

3.3.2 The Relationship Between Genetics, Lifestyle, and BMI

To reveal the association of studied variable with BMI, the regression analysis was conducted. Its results revealed that stress level ($\beta = 0.90$, $p < 0.00$), physical activity ($\beta = -0.55$, $p < 0.00$), chronic disease ($\beta = 2.29$, $p < 0.01$) and supplement intake ($\beta = -0.12$, $p < 0.02$) were associated with BMI. The overall model fit was $R^2 = 0.87$ (Table 2).

Table 2. Regression analysis of the relationship between genetics, lifestyle, and BMI

Variable	B	Std. error	β -coefficient	p-value
Unweighted-GRS	0.81	0.10	0.46	0.42
Weighted-GRS	0.05	0.09	-0.04	0.18
Stress level	0.90	0.30	0.14	0.00
PA	-0.55	0.17	-0.16	0.00
Res/Nat	0.98	0.41	0.07	0.53
CD	2.29	0.83	0.16	0.01
Medication	-0.90	1.02	-0.05	0.38
Supp. Intake	-1.28	0.54	-0.12	0.02

GRS: genetic risk score; PA: physical activity; Res/Nat: residency/nationality; CD: chronic diseases, Supplement intake.

3.3.3 Differences in Genetics, Lifestyle, and BMI According to Nationality and Place of Residence

At the next analysis stage, data on nationality and place of residence were taken into account. The results indicate (Table 3) that Brazilians living in Switzerland were more predisposed to chronic diseases than the other two groups, while the least reported chronic diseases were observed in Swiss participants ($p =$

0.003). Medication intake was higher in Brazilians living in Brazil compared to the immigrant Brazilians residing in Switzerland ($p = 0.004$). Although not significant, the trend seems to indicate that the Swiss living in Switzerland were taking two folds more supplements than the Brazilians were (both native and migrant) ($p = 0.103$). Swiss participants also consumed fewer prescribed drugs than the other two groups ($p = 0.004$) and were more physically active (Brazilians in Brazil versus Swiss: $p = 0.012$ and between Brazilians in Switzerland versus Swiss: $p = 0.039$). 19.5% and 20.6% of Brazilians living in either Brazil or Switzerland, respectively, exhibited high self-reported stress levels, while 47.3% of Swiss living in Switzerland exhibited medium stress levels.

Although there were no significant differences in BMI among the studied groups ($p = 0.860$), the weighted genetic risk score displayed a significant difference between the three groups, with Brazilians living in Brazil carrying a higher score than the other two groups ($p = 0.003$).

Table 3. Differences in genetics, lifestyle, and BMI according to nationality and place of residence (N = 422)

		Brazilian Brazil (N = 82)		Swiss Switzerland 238)		Brazilians Switzerland = 102)		p-value
		(N)	(%)	(N)	(%)	(N)	(%)	
Sex	Women	50	68	168	70.6	86	84.3	0.004 ¹
	Men	20	31	70	29.4	16	15.7	
Chronic dise	Yes	20	24	26	89.1	35	34.3	<0.001 ^{1**}
	No	62	75	212	10.9	67	65.7	
Stress level	No	1	13	13	5.5	14	13.7	0.016 ^{2***}
	Low	24	29	72	30.3	42	41.2	
	Medium	31	37	113	47.3	25	24.5	
	High	10	19	29	16.4	21	20.6	
	Missing	0	0.0	1	0.4	0	0.0	
Medication	None	71	86	222	93.3	84	82.4	<0.004 ¹
	Yes	11	13	16*	6.7*	17	16.7	
	Other	0	0.0	0	0.0	1	1.0	
Supplement intake	None	30	36	113	47.3	53	52.0	0.103 ¹
	Yes	52	63	125	52.7	49	48.0	
Physical acti	None	21	26	22	9.2	24	23.5	<0.039 ^{2**}
	1-3 sessions	20	31	85	35.3	37	36.3	
	4-5 sessions	14	17	58	24.4	11	10.8	
	6-7 sessions	17	13	54	22.7	14	13.7	

		Brazilian Brazil (N = 82)		Swiss Switzerland (N) (238)		Brazilians Switzerland (N = 102)		p-value
		(N)	(%)	(N)	(%)	(N)	(%)	
	2 times per	0	0.0	1	0.4	0	0.0	
	More per day	4	4.9	10	4.2	11	10.8	
	Other	5	6.1	8	3.4	5	4.9	
Smoking	No	71	91	208	87.4	95	93.1	0.504 ¹
	Yes	7	8.5	29	12.2	7	6.9	
	Missing	0	0.0	1	0.4	0	0.0	
BMI classification	Overweight obesity	40	56	137	57.6	62	60.8	0.860 ¹
	Normal weight	30	43	99	41.6	39	38.2	
	Low weight missing	0	0.0	2	0.8	1	1.0	
Comparisons according to nationality and place of residence for continuous variables								
BMI (kg/m ²)	Mean ±	26.1 ± 4.1		26.7 ± 5.5		27.2 ± 6.0		0.363
	(range)	(42)		(55)		(59)		
Unweighted		13.0 ± 2		13.4 ± 3.1		12.7 ± 3.1		0.117
Weighted-G		7.2 ± 4.1		6.1 ± 3.6		5.3 ± 3.1		0.003***
		(16.2)		(10.1)		(13.5)		

¹chi-square with Bonferroni correction and post-hoc comparison;

² Kruskal-Wallis test;

* significant (p < 0.05) difference

** all groups were significantly different, with p < 0.001 after chi-square analysis and post-hoc test with Bonferroni correction

*** statistical difference between Brazilians in Brazil and Brazilians in Switzerland (Stress level p = 0.016) and Weight-GRS (p = 0.003).

**** statistical difference between Brazilians in Brazil and Swiss physical activity (p = 0.039)

GRS: genetic risk score

3.4 Discussion

In this study, associations between BMI-associated SNP data, self-reported lifestyle information, and BMI was investigated in 422 individuals subdivided into three groups: Brazilians living in Brazil, Brazilians

residing in Switzerland, and Swiss living in Switzerland. The study also explored the differences in genetics, lifestyle, and BMI between the three distinct populations to formulate a hypothesis on factors contributing to differences in BMI in the three populations. Currently, there are numerous investigations and strong literature support regarding the association of lifestyle and diet with the development of obesity (Albuquerque et al., 2017; Dubois et al., 2012; Nakamura et al., 2016; Reddon et al., 2016b). However, a huge gap remains regarding the identification of suitable gene markers and gene-diet/environment interactions contributing to the “obesity epidemic” facing the world today. Importantly, there is a lack of genetic association research with obesity in Brazilian and Swiss populations. The first step in the attempt to fill this gap would be to identify suitable genetic markers that influence the progression of obesity. This could lead to further research into developing more targeted and cost-effective approaches to handle obesity in these countries (Jee et al., 2010).

3.4.1 Genetic Score and BMI in Different Populations

The current findings suggest that the weighted genetic risk scores based on BMI-specific SNP data differed significantly between Brazilians living in Brazil and those living in Switzerland. However, no differences in BMI between the study populations were detected. In addition, the regression analysis revealed that neither weighted nor non-weighted GRS were associated with BMI for the studied set of SNPs. The lack of significance could be attributed to the fact that the sample size may not have been large enough to be representative of the populations in Brazil and Switzerland. This makes it difficult to generalize the findings of current study to represent the general Swiss and Brazilian populations. Thus, here, the genetic risk score is not indicative of BMI.

Numerous studies have identified variants in several genes associated with weight gain and body fat distribution (Locke et al., 2015b). However, this trend was not observed in the current study; the conflicting results here may be due to several factors, including the differences in sample size, study design, and the genetic architecture of the population (Fernández-Rhodes et al., 2017). Another critical argument explaining the current study results is that effect sizes were used from studies conducted in the Caucasian population to calculate the genetic score for BMI due to the lack of available data in Latin American populations. This may not be suitable and feasible for this study. Hence, more emphasis must be placed on conducting large-scale research exploring genetic associations in underrepresented populations. Similar findings were obtained by Coenen et al. (2011) in a clinical trial that found no statistically significant association between BMI and GRS in Latino women. This suggests that β -coefficients from GWAS may not be suitable for determining the genetic score for BMI in this

underrepresented population (Mao et al., 2017).

Another potential explanation for the lack of association between GRS and BMI in the overall population may be the choice of SNPs used to construct the GRS; this was again based on Caucasian population data and may not represent the Latin American population. The Brazilian population has a heterogeneous genetic background (Alves-Silva et al., 2000; Mychaleckyj et al., 2017; Novoa & Burnham, 2011), resulting from five centuries of inter-ethnic crosses between Europeans, Africans, and native Brazilians. In addition, most of the immigrants from Switzerland originate from the Northern Brazilian region (Alves-Silva et al., 2000; Mörner, 1967). Young et al., 2018, presented the underrepresented ethnic groups in the GWAS catalogue. He stated that most of the studies deposited in the GWAS catalogue were on the European population; only 19% were of non-European and non-Asian origin (as in 2016), while the African descents remained at <3%, Hispanic/Latinos stood at <0.5% and other ancestries were at <0.3% (Young et al., 2018). This lack of information in the GWAS catalogue for the non-European population could be due to the lack of local resources to conduct scientific research in developing countries and low interest from private institutions. From this point of view, this research underlines the necessity to calculate GRC for underrepresented ethnic groups financing and supporting local large-scale studies.

Previous research highlighted that the population heterogeneity and diverse conditions stemming from a complex interaction between genetics and environmental factors may lead to utilizing BMI-associated loci and markers identified by GWAS that have variable linkage instability and thus cause inconsistent results (Ioannidis et al., 2007). With the advancement of genetics research, the polygenetic risk scores will tend to utilize more novel loci and markers that are more significant and relevant in specific populations. In turn, this may open new fronts to develop data-specific treatment modalities to benefit future populations (Elks et al., 2012; Torkamani & Topol, 2019).

3.4.2 The Associations Between Lifestyle and BMI

The results indicated that there were associations between lifestyle factors and BMI. More specifically, it was found that self-reported stress levels were positively correlated with BMI. From previous reports, it was clear that stress levels can interfere with the individual's behaviour, inducing overeating and consuming food of high calories, resulting in an increased BMI (Koski & Naukkarinen, 2017). Scientific evidence also reveals that obesity-related factors such as "weight stigma" can significantly enhance stress and, in turn, cause weight problems (Junne et al., 2017). To date, there has been no specific published information exploring the associations between genetic polymorphism, stress levels, and BMI in Brazil.

Thus, the inferences made in this study are valuable and provide insight into the influence of stress on BMI in the studied heterogeneous populations.

It was also found that a significant inverse association between physical activity levels and BMI. This relationship is consistent across different studies and populations (Hill et al., 2012; Li et al., 2010; Rask-Andersen et al., 2017). The population under investigation was inactive, as 16.1% of the participants had a sedentary lifestyle. More than 35% of the participants engaged in physical activity from one to 3 sessions per week. However, there are subjective and objective methods to measure physical activity, and so far, there is no “gold standard” method (Arvidsson et al., 2019). Although self-reported physical activity is an indirect measurement method, it offers the most practical and cost-effective method in population-based studies, but it comes with its limitations, such as exaggeration, biases, and lack of complete data from the participants (Dishman et al., 2001). However, self-reported lifestyle played a significant role in obesity in the current study.

3.4.3 Strengths and Limitations

This is the first cross-sectional study to examine gene-environment-obesity interaction among Brazilians, Brazilian immigrants, and the Swiss population using GRS, BMI, and lifestyle factors. The results of this study strongly suggest that there is a need to conduct deeper functional analysis to identify appropriate genetic markers for the Latin America populations such as the Brazilians.

In most circumstances, the risk allele frequencies of obesity loci identified through published GWAS studies are used; however, the effect sizes identified in Caucasians may not be appropriate for the Brazilian population. The same loci are typically observed as associated with obesity in different populations (allele frequency >10%), but risk allele frequencies can vary across populations (Lu & Loos, 2013), resulting in different genetic risk scores (Alves-Silva et al., 2000). Furthermore, low frequency (~1–5%) and rare (<1%) variants influencing polygenic obesity are not frequent enough to be captured by GWAS studies, nor are they sufficiently penetrant to be identified through traditional linkage studies (Albuquerque et al., 2017). Thus, the study reemphasized the need to conduct comprehensive genetic studies on specific underrepresented GWAS populations. In addition, a small sample size of Brazilians living in Swiss limits the extrapolation of these research findings to a larger population.

The results can be over- or underestimated when using BMI in the assessment of the genetic risk score. BMI may not be an ideal indicator of body fat as it does not precisely distinguish body adipose tissue from musculoskeletal mass and underreports visceral body fat (the most detrimental type of fat) (Low et

al., 2009). Assessments of these parameters were not made during this research. Furthermore, the general BMI cut-offs used in this study may not be applied to different ethnic groups, as different ethnicities may have lower BMI thresholds due to the increased risk of diseases associated with excessive fat mass (Hebebrand et al., 2017; Low et al., 2009). Also, food intake may explain a part of the BMI variance and this parameter was not measured in our study. Lastly, these results were based on self-reported data from participants, which could have been more precise if explored in conjunction with other clinical measurements or data (Austin et al., 1998).

3.4.4 Perspectives for Future Research

The results accentuate that multi-locus genotyping should be carried out for specific populations and that GRS should be calculated taking into account ethnicity. There is a need to construct a more robust genetic database from the in-depth and detailed genetic study of individuals from different ethnic backgrounds. This, in turn, can provide a deep insight into understanding polygenic obesity in diverse populations. Furthermore, future research is needed to establish trustworthy associations between the various parameters discussed above with obesity, BMI, and specific modalities that can solve the obesity epidemic. This research also highlighted the need to increase the sample sizes of genetic population studies for BMI and genetic scores data taken from extensive association studies.

3.5 Conclusion

The results support significant differences in genetic scores for obesity in the studied group; however, the association between GSR and BMI was not significant. Significant influence of specific lifestyle parameters on BMI points to the possible influence of genetic and lifestyle factors on the aetiology of obesity. These findings indicate that obesity prevention programs emphasizing physical activity and a healthier lifestyle for genetically at-risk subgroups may significantly contribute to the global fight against obesity.

The number of non-European GWAS is limited, hindering replication efforts. Using genetics and obesity predisposition with genetics scores from Caucasian studies may be inappropriate and not applicable to population studies involving non-Europeans. Thus, there is a need to expand genetic studies in multi-ethnic populations and work with large sample sizes to maximize discoveries. Moreover, detailed lifestyle measurements are crucial in revealing significant associations. Therefore, exploring the heterogeneity of

obese and overweight individuals will help identify population subgroups and help clinicians and policymakers examine strategies for more personalized interventions.

4. KNOWLEDGE, ATTITUDES, BARRIERS, FACILITATORS, AND EDUCATION PREFERENCES IN GENOTYPE-BASED DIETARY ADVICE: AN EVALUATION AMONG NUTRITIONISTS AND DIETITIANS IN THE UK AND BRAZIL

Keywords: nutritional genomics – involvement – perceived benefits – perceived risks – health professionals

ABSTRACT

Rationale/Aims: Nutrigenomics is an advanced precision nutrition approach using individual DNA variation to design effective diet regimens. Due to its huge potential to improve health and manage diseases, business commercialization and public interest are growing. Nutritionists/dietitians are central players in the implementation of nutrigenomics. However, since nutrigenomics is a relatively new field, standards and guidelines are not yet established in clinical practice. To understand the current status of nutrigenomics implementation, this survey aimed to analyse and compare the current situation of the nutrigenomics information and recognize factors defining it among nutritionists/dietitians in the UK and Brazil. This study also provided an overall picture of the involvement and the perceived benefits and identified training needs in nutrition and genetics.

Methods: Nutritionists/dietitians from the UK and Brazil were recruited to complete a 46-question online survey on knowledge, involvement, perceived benefits and risks, and education regarding nutritional genomics.

Results: Related to both countries: In the UK, with 93 and Brazil, with 160 surveys completed, the mean \pm SD knowledge was low at 7.72 ± 3.39 . The highest qualification ($F = 3.124, p < 0.05$), reading literature ($F = 3.841, p < 0.05$) and perceived benefits ($F = 4.001, p < 0.05$) were all associated with the higher total knowledge score. In addition, 43% of the professionals were unlikely or very unlikely to accurately interpret nutrigenomic patients' reports results; however, they were willing to undergo training. Spearman's correlation resulted in no association between total knowledge score and perceived risks score $r_s = -0.077, p = 0.212$. Similarly, no correlation was noted between the highest qualification and perceived benefits scores nor perceived risks score, $r_s = 0.048, p = 0.438$ and $r_s = -0.002, p = 0.977$, respectively. The cost and validity of genetic tests and genetic discrimination concerned nutritionists/dietitians the most. Lastly, it was observed that Brazilian patients are more likely to demand information from health

professionals about personalized tools.

Conclusion: Knowledge of nutrition and genetics among nutritionists/dietitians in the UK and Brazil is currently low, and better knowledge is associated with a higher qualification, relevant literature reading, and professional's perceived benefits. However, the results demonstrated that the interest of the professionals related to the use of nutrigenomics as a clinical practice tool is raising the demand for specific knowledge.

4.1 Introduction

Nutrition and Genetics (NGx) is a developing science that has enhanced the knowledge of individual nutrient responses due to genetic variations. NGx is known in the scientific and clinical field for two complementary approaches: the interaction of genetic variations with nutrients consumed (nutrigenetics) (Whelan et al., 2008), and the effect of nutrients on gene expression (nutrigenomics) (Whelan et al., 2008). Progresses in understanding these gene-diet interactions may ultimately grant nutritional therapy to utilise this science to optimise one's health by delivering personalised dietary advice, leading to more effective results in clinical practice (Wright, 2014).

With the progression of genomic technologies, precise medicine and tailored individual information has become easily available across Direct-to-Consumer (DTC) genetic testing (Nielsen & El-Soheby, 2012). Consumer interest in DTC tests seems to be increasing, resulting in a rise in companies offering such services without clear regulations and standards. Consequently, health professionals will increasingly be faced with patients/clients who need NGx services and, therefore, will need to be able to deliver such advice. Some studies claimed an interest in genotype-based advice among the public, with 50-66% of subjects willing to undergo a genetic test (Cherkas et al., 2010; Stewart-Knox et al., 2009). Others stated that consumers also assumed nutritionists and dietitians (NDs) to be the preferred HP to deliver such a service (Morin, 2009). Although there are not many studies available and most of them are conducted in English-speaking countries, these studies have shown that NDs are not well-informed and experienced in NGx (McCarthy et al., 2008; Whelan et al., 2008; Wright, 2014), thus generating a breakout between NGx's consumers and their needs.

It is a well-established fact that NDs need a better understanding of genetics. Hence, NDs' lack of genetic background, training, or knowledge can result in misleading information given to patients/clients. For

instance, the Human Genome Education Model conducted in the USA in 2000 surveyed 372 dietitians and found little to no confidence in providing genetic services due to the lack of genetic education and knowledge (McCarthy et al., 2008; Morin, 2009, Whelan et al., 2008). Furthermore, a European study interviewed 390 dietitians in the UK and suggested low knowledge, involvement, and confidence in NGx (Whelan et al., 2008).

While there is a limited number of studies in different countries exploring HP involvement in NGx, numerous advancements in NGx science and an acceleration of its commercial applications have been observed (Nielsen & El-Sohehy, 2012). Therefore, it is necessary to obtain updated information about the actual knowledge and involvement of NDs in NGx, while also including underrepresented countries such as Brazil, a country showing fast growth in the commercial provision of NGx services (Fischer et al., 2020). Further, there is a lack of Brazilian and UK genetic association research surrounding obesity, and for this study, the available data were obtained from a commercial entity. Since the UK is a first-world country with private and public nutrigenomics organizations, it was compared with Brazil, which is still developing in this field. Additionally, Brazilians are an underrepresented population in nutrigenomics research allowing this study to provide more understanding of their ethnic-specific genetic associations. and the genetic differences between European and South American ancestries were interesting to compare. Brazilian and UK populations were additionally chosen due to the differences in obesity prevalence, which may suggest potential genetic contributions. Therefore, the present study aims to investigate the knowledge in NGx and identify factors associated with it among NDs in the UK and Brazil, provide an actualized picture of the involvement, perceived benefits, and risks, and identify training needs in NGx in both countries.

4.2 Materials and Methods

4.2.1 Ethics Statement

Ethical approval of the study was granted by the School Ethics Sub-Committee of St. Mary's University, London, United Kingdom before conducting the study.

4.2.2 Recruitment and Participants

Participants were recruited from June to July 2020 via social media, online platforms, and Brazilian and UK Universities. To be eligible, participants had to be nutritionists or dietitians from all domains of

practice in the UK or Brazil. Both the “Brazilian Nutrition and Nutritionist Association (SBAN) federal” and the “Brazilian Association of Nutrition (ASBRAN) district” were emailed and contacted by phone; however, the support of these associations in Brazil was low. In addition, the “British Dietetic Association (BDA)/Association for Nutrition (AfN)” accredited courses were contacted. Anyone not practising in the UK or Brazil was excluded. Completion of the survey was voluntary and anonymous. Respectively, 160 and 104 completed surveys were obtained from Brazil and the UK, with a total of 264 participants.

4.2.3 Questionnaire

The survey was developed using a formerly validated questionnaire (McCarthy et al., 2008; Whelan et al., 2008), modified, internally piloted, and created using Jisc Online Surveys. Some questions were refined/removed to ensure the survey addresses current findings in NGx. The survey comprised a total of 46 questions covering five sections:

- 1) demographics and selection of participants;
- 2) knowledge section covering four emerging topics in NGx: obesity, diabetes, cancer, and hypertension;
- 3) practical involvement, interest, and awareness in the field of nutrigenomics;
- 4) professionals, confidence perceived benefits and risks of nutrigenomics;
- 5) education and training.

Four additional questions were added by the authors to reflect the most recent advances in the field, resulting in a total of 50 questions. Once refined, the survey was piloted by seven NDs in different sectors for internal review, and minor alterations were made upon feedback. The questionnaire can be found in the Appendices, Table A1.

4.2.4 Statistical Analyses

A total knowledge score ranging from questions 11 to 26 was calculated for the genetics and NGx sections as the sum of correct answers. Scores were also calculated in each section, dividing the questions about basic genetics and nutritional genomics. Similarly, scores were attributed to the metabolic disorders and the NGx concerns questions (0 – “I don't know”, 5 – “very likely/extremely concerned” per question). Continuous data are presented as mean \pm SD and categorical data as percentages unless stated otherwise. Kolmogorov-Smirnov test was used to test for normality.

Total Scores: NGx_knowledge = Nutrigenics + cardiovascular_disease + genetic_defect2 + MTHFR2 + salt_sensitivity2 + red_meat_eating + TCF7L2_gene2 + SNP_FTO_gene2 & Genetics Questions: gene + allele + phenotype + mutation + chromosome + genotype + polymorphism + PCR.

Parametric tests (one-way ANOVA) were used to test for differences in genetics and NGx scores and total knowledge scores between NDs. The total knowledge score was calculated by summing correct answers to questions 11 to 26, covering genetics and nutrigenomics (NGx). Multiple linear regression was developed to examine the associations with scores for knowledge, which initially included Hierarchical regression analysis to identify relevant factors (perceived benefits score, highest qualification, reading scientific articles). Further, Spearman's correlation was run to assess the relationship between total knowledge score and perceived benefits score, between total knowledge score and perceived risks score, and between highest qualifications and perceived benefits and risks. Preliminary analysis showed the relationships to be monotonic, as assessed by visual inspection of a scatterplot. In addition, a cluster analysis was performed to verify the most relevant factors related to knowledge scores. All tests were two-tailed, and statistical significance was set at 0.05. IBM SPSS statistics (version 26) was used for all statistical analyses.

4.3 Results

A total of 264 surveys were completed, of which 160 were completed in Brazil and 104 in the United Kingdom.

4.3.1 Results of the Survey Section 2 on Knowledge of Nutrigenomics and Genetics in the United Kingdom and Brazil

In Figures 1-8, the results from survey Section 2 containing questions on genetics and nutrigenomics are presented.

Figures 1 and 2 represent knowledge of the most basic terms of genetics: gene, allele, phenotype, and mutation. Considering that the UK sample size was approximately 1.6 times smaller than the Brazilian sample size, the basic genetic knowledge reflected as percent of the total in a country was better in the UK.

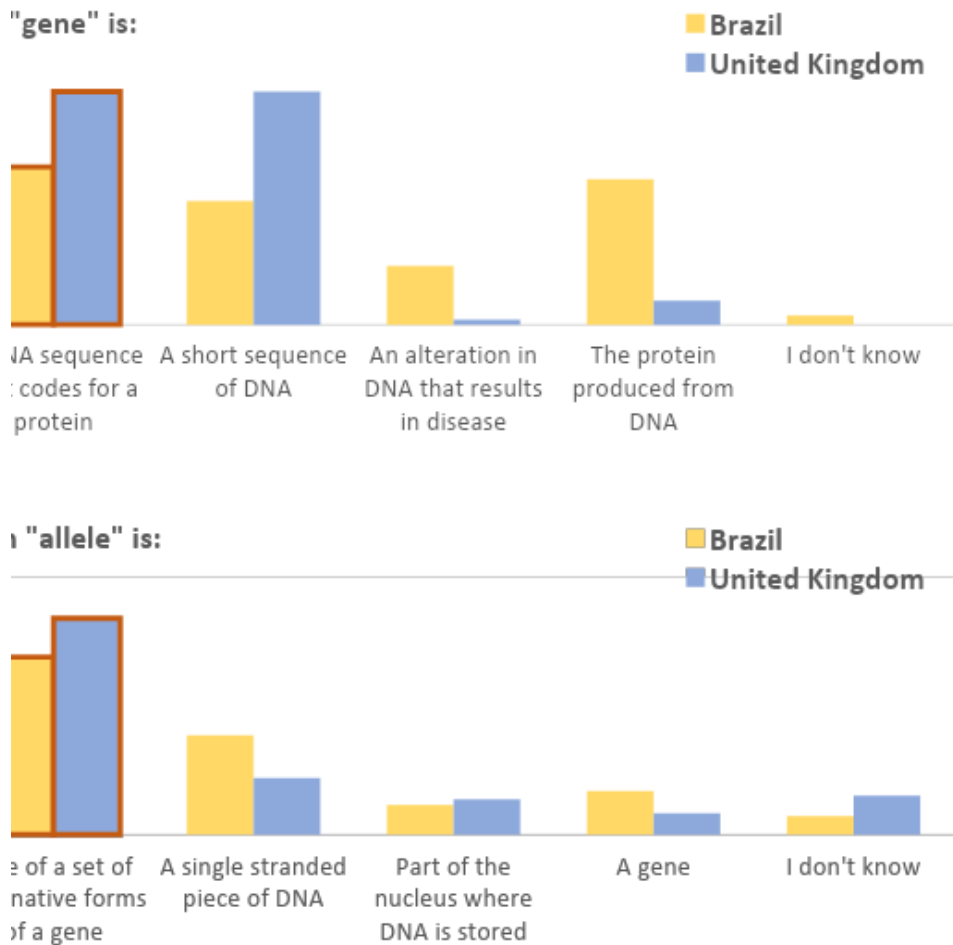


Figure 1. Bar chart visualization of the distribution of answers to survey questions 11 (top) and 12 (down) for Brazil and United Kingdom. Axis Y – a percent of participants in a country who chose the option (100% – all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

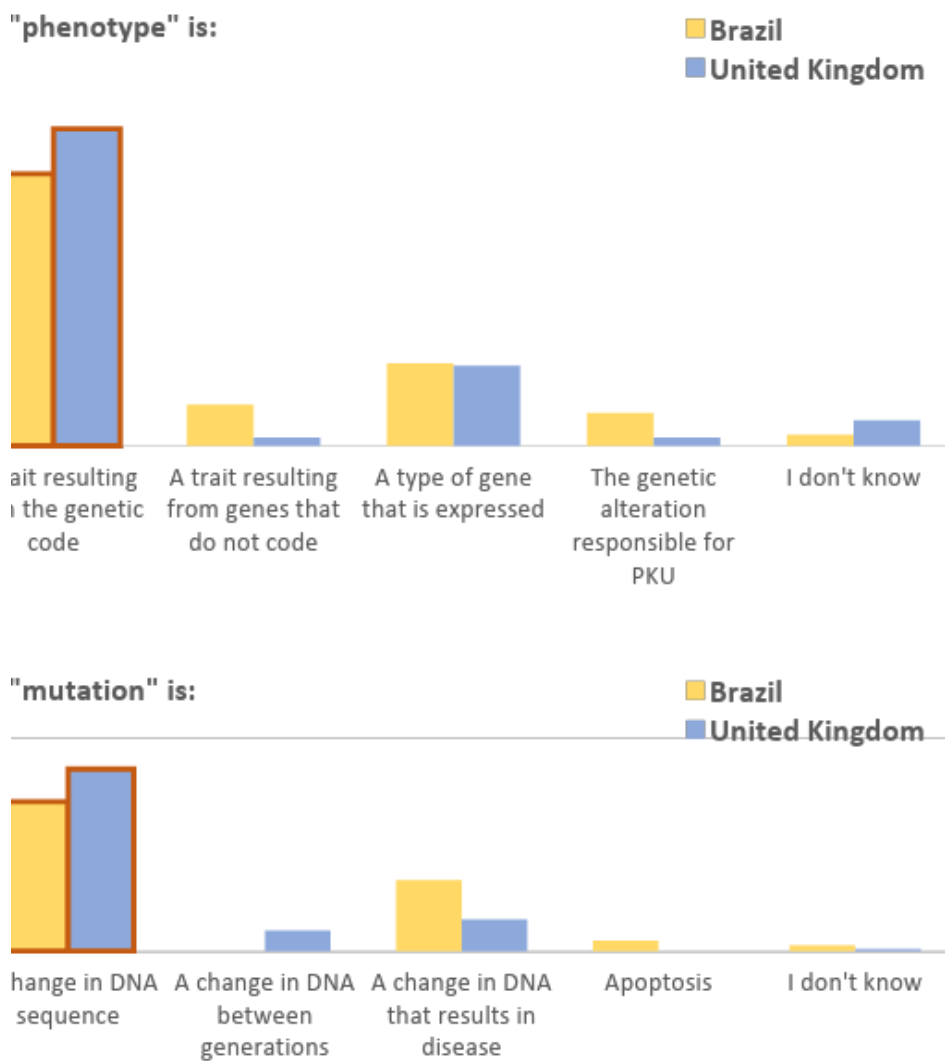


Figure 2. Bar chart visualization of the distribution of answers to survey questions 13 (top) and 14 (down) for Brazil and United Kingdom. Axis Y – a percent of participants in a country who chose the option (100% – all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

Figure 3 introduces first nutrigenomics-related questions in a survey, where must lower confidence in the correct answers can be spotted for both groups.

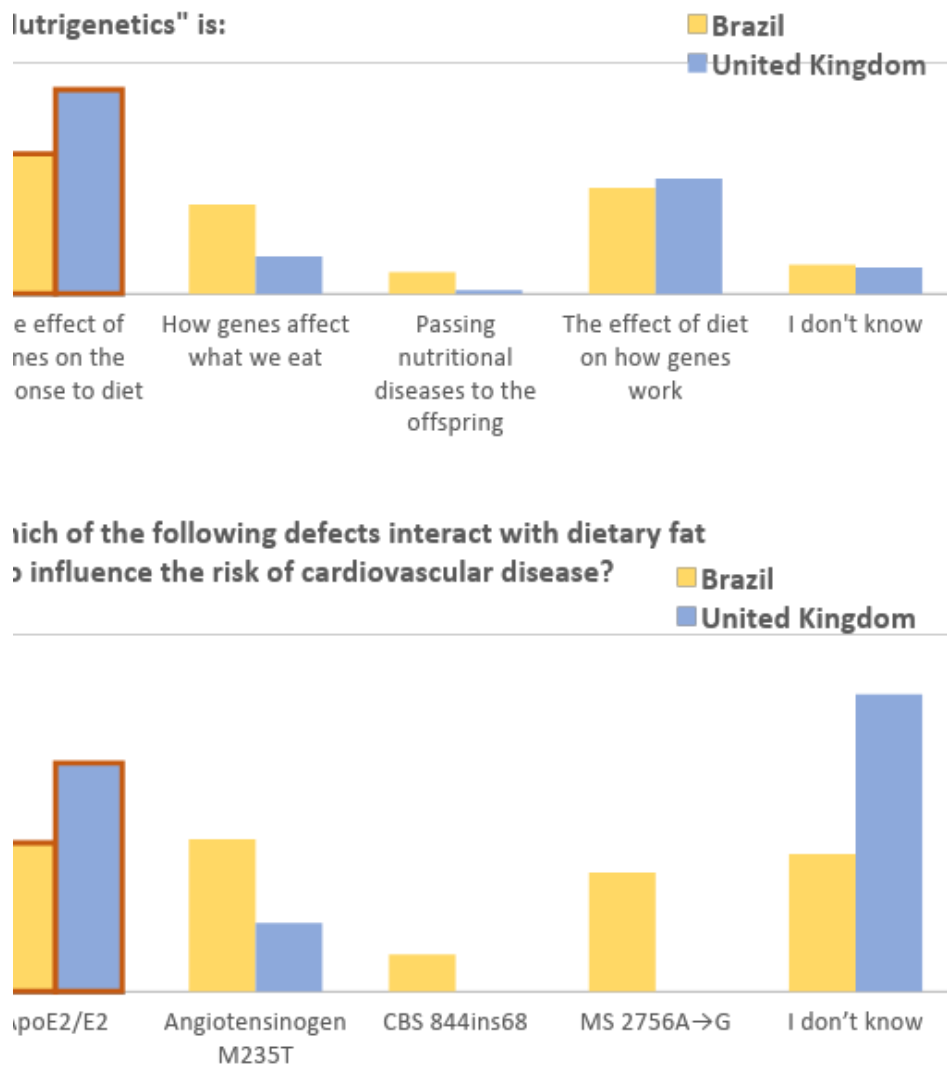


Figure 3. Bar chart visualization of the distribution of answers to survey questions 15 (top) and 16 (down) for Brazil and the United Kingdom. Axis Y – a percent of participants in a country who chose the option (100% – all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

Figures 4 and 5 demonstrate an understanding of deeper genetic concepts and methods, with a relatively higher proportion of correct answers from the UK group.

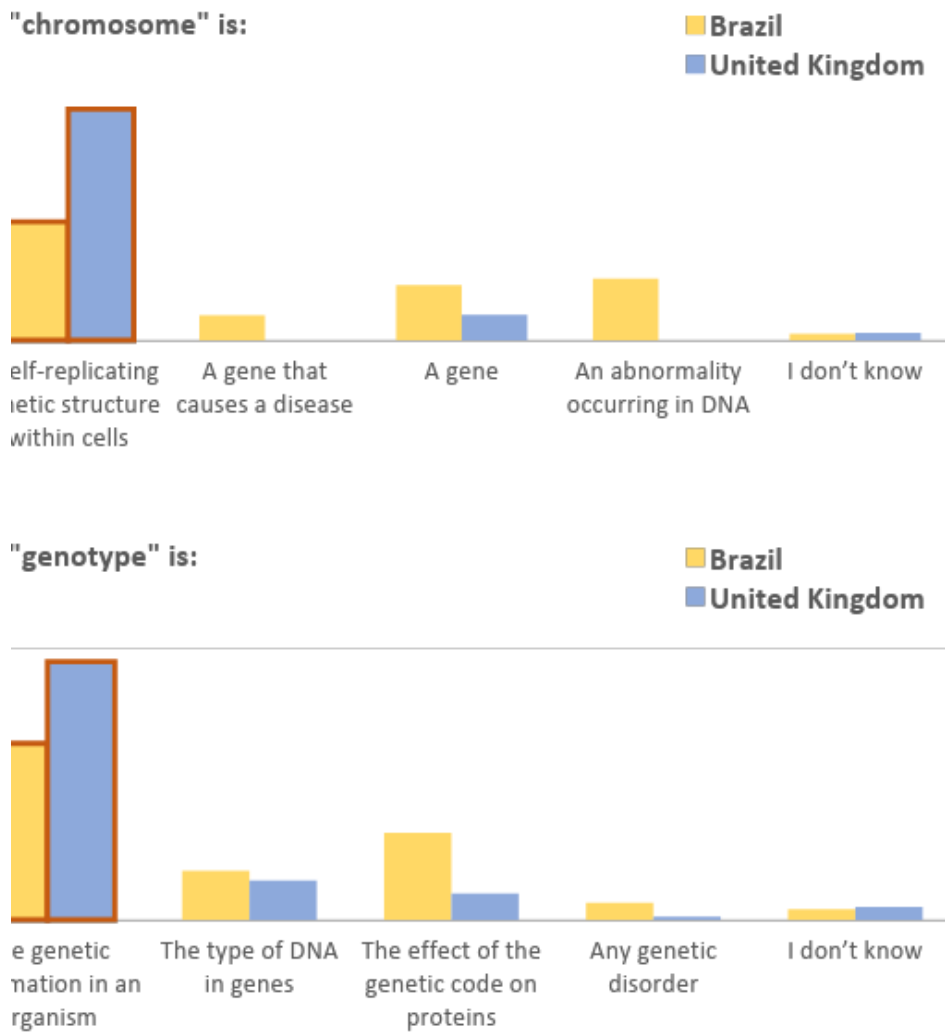


Figure 4. Bar chart visualization of the distribution of answers to survey questions 17 (top) and 18 (down) for Brazil and United Kingdom. Axis Y – a percent of participants in a country who chose the option (100% – all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

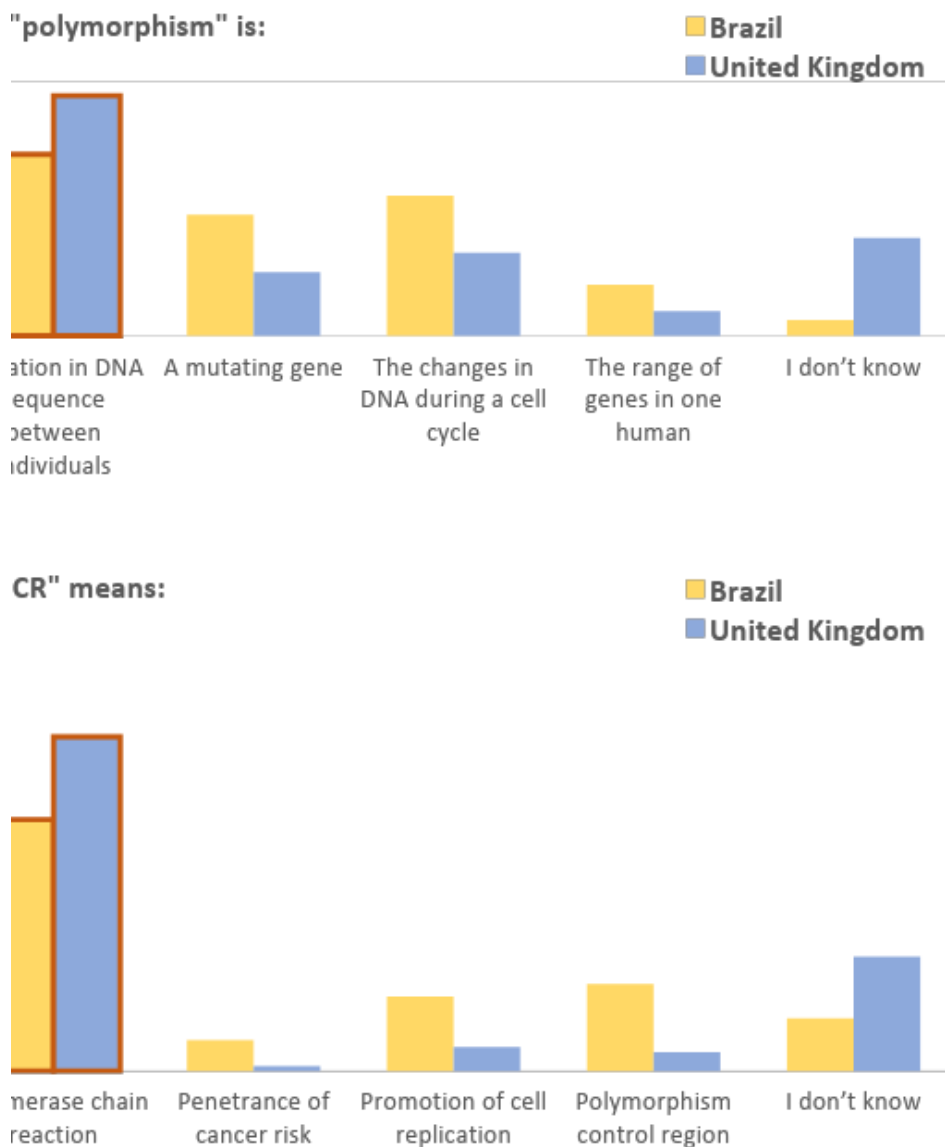
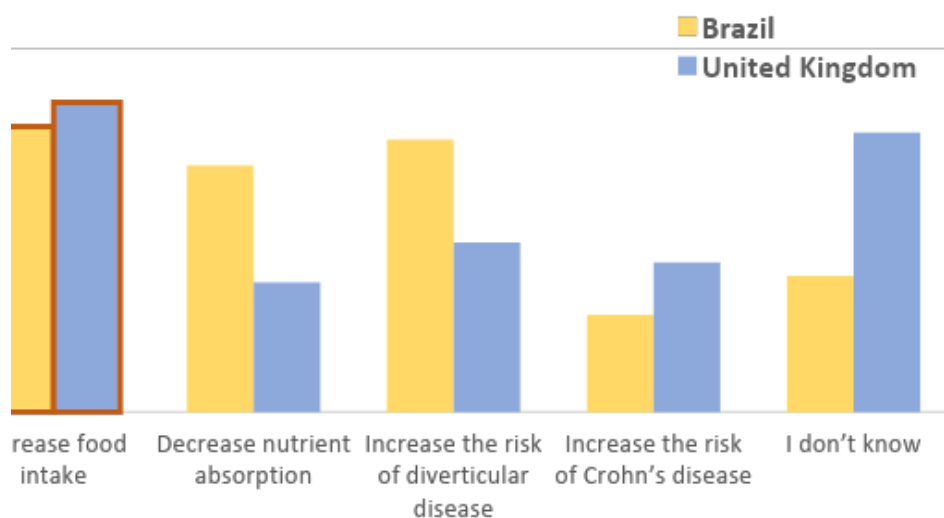


Figure 5. Bar chart visualization of the distribution of answers to survey questions 19 (top) and 20 (down) for Brazil and United Kingdom. Axis Y – percent of participants in a country who chose the option (100% - all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

Finally, Figures 6-8 reflect knowledge in specific nutrigenomics questions, where relatively higher proportion of correct answers is observed for the Brazilian group. However, most of the participants do not know the correct answer and choose the option “I don’t know” often in all questions of this section.

Which of the following is FALSE? "Genetic defects can..."



Which condition is NOT associated with the methylenetetrahydrofolate reductase (MTHFR) 677C→T defect

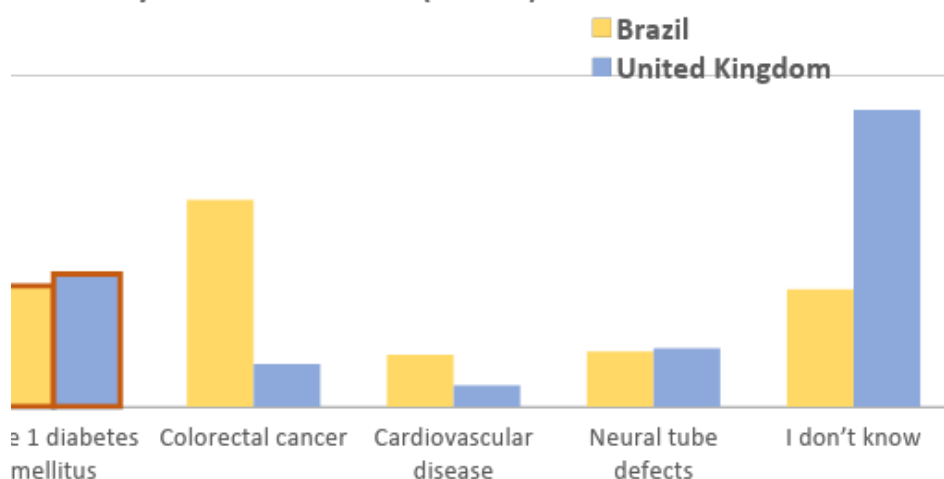


Figure 6. Bar chart visualization of the distribution of answers to survey questions 21 (top) and 22 (down) for Brazil and the United Kingdom. Axis Y – per cent of participants in a country who chose the option (100% - all participants from either Brazil or the UK). The first option in the axis X is the correct one (red frame)

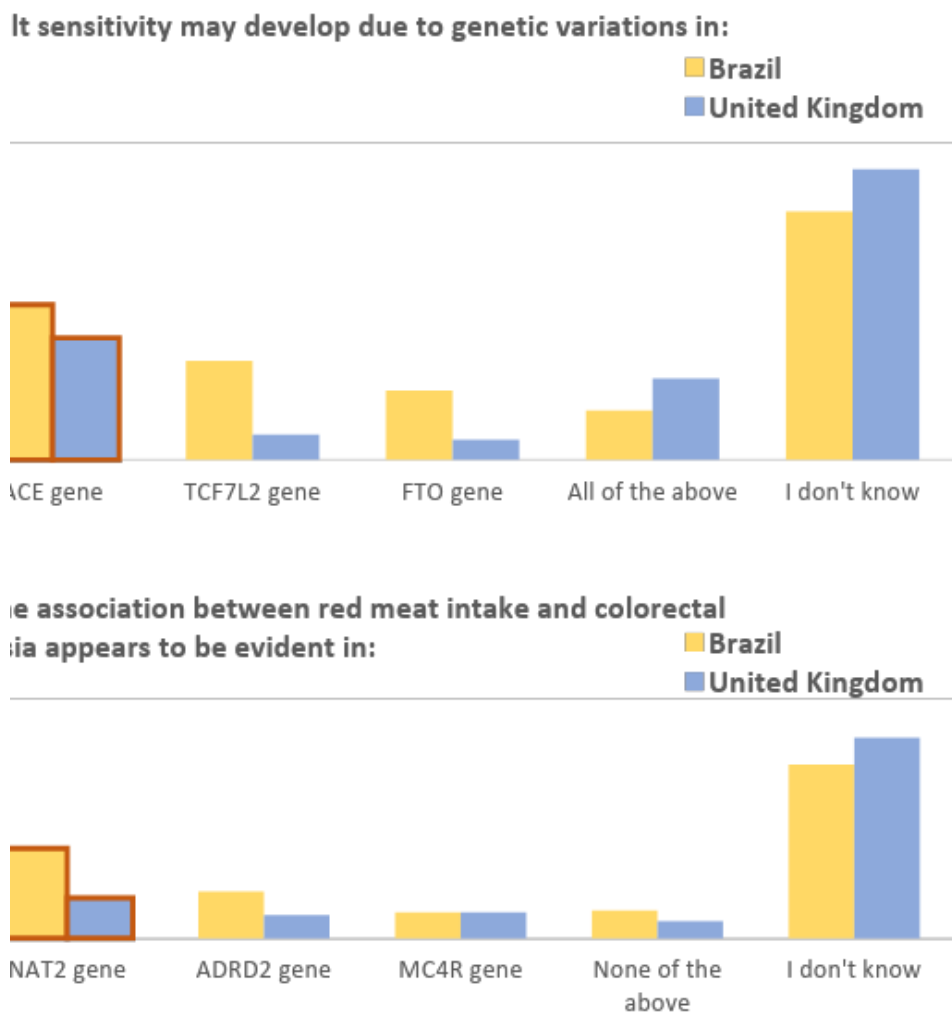


Figure 7. Bar chart visualization of the distribution of answers to survey questions 23 (top) and 24 (down) for Brazil and the United Kingdom. Axis Y – percent of participants in a country who chose the option (100% - all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

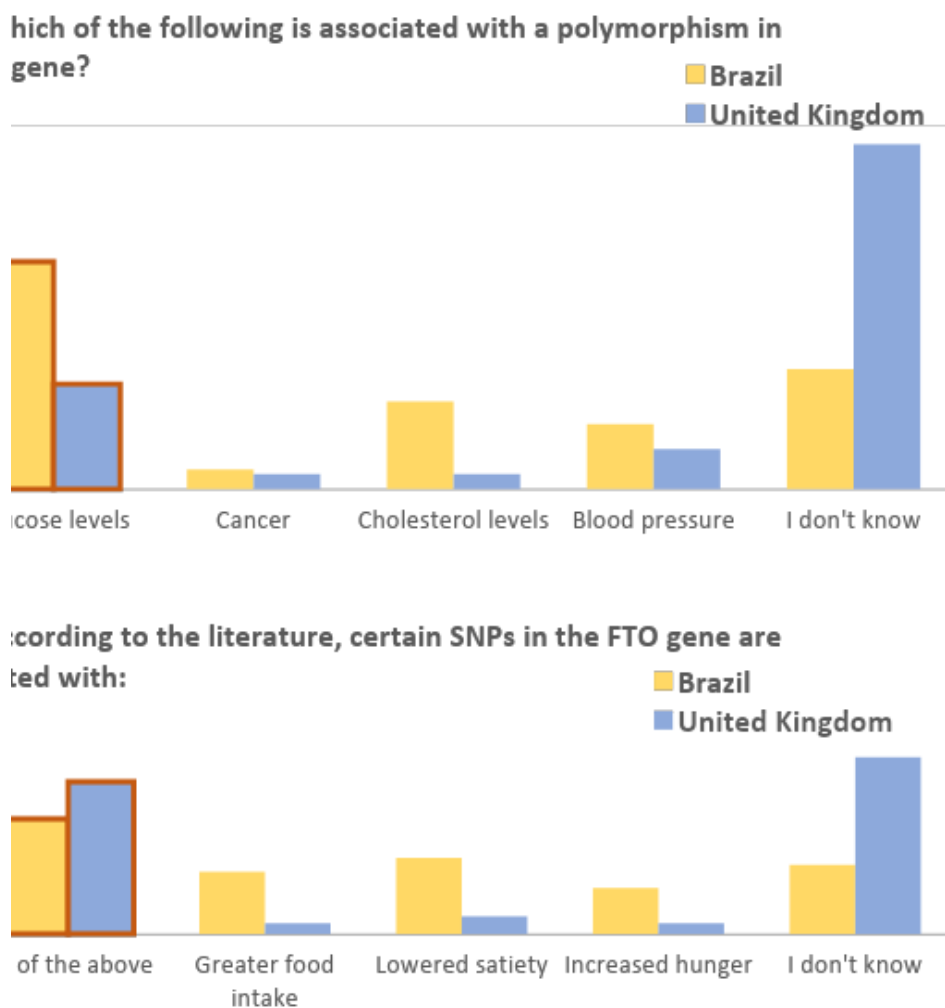


Figure 8. Bar chart visualization of the distribution of answers to survey questions 25 (top) and 26 (down) for Brazil and United Kingdom. Axis Y – a percent of participants in a country who chose the option (100% – all participants from either Brazil or the UK). First option in the axis X is the correct one (red frame)

The ANOVA was utilized to explore total knowledge scores in nutrigenomics (NGx) among diverse populations, specifically comparing the Brazilian and United Kingdom (UK) groups. The key findings are summarized in Table 4. The examination of "Between Groups," measuring the variability in total knowledge scores between the two groups, revealed a sum of squares of 101.742 with 7 degrees of freedom. The mean square was calculated as 14.535, resulting in an F-statistic of 0.644. However, the corresponding p-value (Sig.) was determined to be 0.719, signifying a lack of statistical significance. This indicates that there is no substantial difference in total knowledge scores between the Brazilian and UK groups.

Conversely, the "Within Groups" analysis, assessing variability within each group, demonstrated a sum of squares of 5778.621 with 256 degrees of freedom, resulting in a mean square of 22.573. Considering the overall analysis, encompassing total variability in knowledge scores across both groups, the total sum of squares was 5880.364 with a total of 263 degrees of freedom.

In summary, the ANOVA outcomes suggest that the observed variations in total knowledge scores between the Brazilian and UK groups lack statistical significance. The non-significant p-value (0.719) implies that the discrepancies in scores are more likely attributed to random factors rather than a genuine group effect.

According to the figures, the UK groups seemed to have better knowledge in general genetics (Figures 1-5) and the Brazilian group had higher scores in nutrigenetics (Figures 6-8).

The mean \pm standard deviation (SD) of the total knowledge score was calculated as 3.77 ± 1.36 , offering an overview of participants' collective performance in addressing questions related to the study. In the domain of genetics, participants demonstrated a lower level of understanding, evident from the mean \pm SD knowledge score of 1.53 ± 0.97 .

Upon examining individual survey questions, notable disparities in correct response rates were observed. For instance, a mere 9.5% of participants correctly identified the association between red meat intake and colorectal neoplasia. Similarly, only 10.6% recognized the relationship between polymorphism in the TCF7L2 gene and glucose levels. In contrast, a more substantial 68.6% accurately defined the term "mutation," signifying a comparatively higher level of comprehension in this particular area. These percentages underscore the diverse spectrum of knowledge and understanding among participants, highlighting specific areas where additional education or clarification may be beneficial.

Table 4. ANOVA of total knowledge of NGx across all populations – Total correct answers percentage between Brazilian group and United Kingdom group

Total Knowledge (total scores from NGx questions nutrigenomics)					
	Sum of squares	df	Mean square	F	Sig.
Between Groups	101.742	7	14.535	.644	.719
Within Groups	5778.621	256	22.573		
Total	5880.364	263			

4.3.2 Population variables in the combined sample

Variables in the structure of the surveyed population of NDs in Brazil and the UK are represented in Table 5. Across participants, 25.4% had Bachelors, and 32.6 % – Masters degrees. The highest representation of professionals was from private hospitals (25.4%), followed by sports nutrition (16.3%). The largest proportion had work experience from 1 to 5 years (40.2%), followed by 6–10 years of experience (24.2%).

Table 5. Variables in the combined sample of NDs in Brazil and the United Kingdom presented as the number of participants and percentages from the total surveyed population (N = 264; emphasized reflects the most frequent variable value)

Variables	
<i>Education</i>	
AS/A-Level	1 (0.4%)
Bachelor's degree	67 (25.4%)
Doctorate/PhD	25 (9.5%)
GCSE or equivalent certificate	3 (1.1%)
<u>Master's Degree</u>	<u>86 (32.6%)</u>
No formal qualification	1 (0.4%)
Other	2 (0.8%)
Postgraduate Diploma	79 (29.9%)
<i>Area of Practice</i>	
Academic/Research	28 (10.6%)
Food industry	22 (8.3%)
In the NHS - UK (Hospitals, Community)	21 (8%)
Media	11 (4.2%)
Other	24 (9.1%)
Pharmaceutical industry	10 (3.8%)
<u>Private Hospital</u>	<u>67 (25.4%)</u>
Public health	22 (8.3%)
Public health - UK	11 (4.2%)
Sports Nutrition	43 (16.3%)
Unemployed	5 (1.9%)
<i>Work Experience</i>	
Less than a year	35 (13.3%)
<u>1–5 years</u>	<u>106 (40.2%)</u>
6–10 years	64 (24.2%)
11–15 years	27 (10.2%)
16–20 years	13 (4.9%)
21–25 years	8 (3%)
26–30 years	7 (2.7%)
>31 years	4 (1.5%)

Variables	
<i>Number of scientific articles consulted</i>	
Four times a month	14 (5.3%)
<u>Less than once a month</u>	<u>179 (67.8%)</u>
More than four times a month	10 (3.8%)
Once a month	54 (20.5%)
Two to three times a month	7 (2.7%)

4.3.3 Practical Involvement, Interest and Awareness in the Field of Nutrigenomics

Third section of the questionnaire included questions related to involvement, interest and awareness of the participants in the field of nutrigenetics and nutrigenomics. The results are summed up in Table 6 and 7, showing that participants in both countries generally agree that nutrigenomics and nutrigenetics should be offered as a specialist field of practice for nutritionists/dietitians, at the same time doubting their own abilities to accurately interpret results of nutrigenomic and nutrigenetic testing to their patients.

Table 6. Survey results of the questionnaire section 3 questions regarding involvement, interest, and awareness, showing the number (N) and percentages (%) of people (relative to each local population) for each answer (Question 27)

27. Where did you first hear about nutrigenomics and nutrigenetics?			
		N	%
Brazil	Colleagues	11	6.90%
	Congress or professional meeting	21	13.10%
	Continuing Professional Development (CPD)	9	5.60%
	Internet	22	13.80%
	Social media	20	12.50%
	Newspaper articles	5	3.10%
	Other	3	1.90%

	<u>Other health professionals</u>	<u>24</u>	<u>15.00%</u>
	Patient	9	5.60%
	Radio	2	1.30%
	Scientific publications	11	6.90%
	Television	10	6.30%
	University courses	13	8.10%
United Kingdom	Colleagues	6	5.80%
	Congress or professional meeting	8	7.70%
	Continuing Professional Development (CPD)	10	9.60%
	Internet	8	7.70%
	Other health professionals	2	1.90%
	Scientific publications	10	9.60%
	Social media	6	5.80%
	<u>University courses</u>	<u>54</u>	<u>51.90%</u>

Table 7: Survey results of the questionnaire section 3 questions regarding involvement, interest, and awareness, showing the number (N) and percentages (%) of people (relative to each local population) for each answer (Question 28-34)

Country	Brazil	UK
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28. Do you know that there are many direct-to-consumer companies (DTC) that offer personalised nutrition advice based on genetics?		
No, I did not know there are such companies	43.80%	16.30%
Yes, I know there are such companies	56.30%	83.70%
29. What type of health professional should a patient accept to get consultation about nutrigenomics and nutrigenetics services be referred to? (more than one option can be selected)		
Option was not selected	7.50%	20.20%
Option was selected	92.50%	79.80%
Genetic counsellors		
Option was not selected	83.10%	47.10%
Option was selected	16.90%	52.90%
Doctors		
Option was not selected	45.60%	67.30%
Option was selected	54.40%	32.70%
Nurses		
Option was not selected	89.40%	89.40%
Option was selected	10.60%	10.60%
Other		
Option was not selected	100.00%	99.00%
Option was selected	-	1.00%

30. As a nutritionist/dietitian, do you believe that one of your roles might be to interpret information from nutrigenomics and nutrigenetic tests?

Believe	36.30%	40.40%
Do not believe	5.00%	9.60%
I don't know	1.90%	2.90%
Neutral	19.40%	23.10%
Strongly believe	36.30%	23.10%
Strongly do not believe	1.30%	1.00%

31. Do you believe that nutrigenomics and nutrigenetics should be offered as a specialist field of practice for nutritionists/dietitians?

I don't know	22.50%	7.70%
No	3.80%	4.80%
Yes	73.80%	86.50%

32. How likely are you to accurately interpret the results of nutrigenomic and nutrigenetic testing to your patients?

I don't know	9.40%	4.80%
Likely	28.80%	22.10%
Unlikely	35.60%	26.90%
Very likely	11.30%	5.80%
Very unlikely	15.00%	40.40%

33. Has a patient ever consulted you for information on nutrigenomics and nutrigenetics?

I don't remember	12.50%	2.90%
No	40.00%	82.70%
Yes	47.50%	14.40%

34. Please indicate the number of patients who have consulted you for information on nutrigenomics and nutrigenetics in the past year:		
0	48.80%	82.70%
1-5	35.00%	13.50%
Between 6 and 10	13.10%	1.90%
More than 10	3.10%	1.90%

ANOVA testing of the involvement, interest, and awareness scores in nutrigenomics in Brazil and UK showed several significant differences between these groups (Table 8). The differences included the first source of knowledge about nutrigenetics and nutrigenomics, the knowledge on DTC, and ways to integrate nutrigenomics in own practice. Also, the differences between groups were revealed concerning the number of participants who believe that nutrigenomics and nutrigenetics should be offered as a specialist field of practice for nutritionists/dietitians, likeliness to accurately interpret results of nutrigenomic and nutrigenetic testing to patients, encountering nutrigenomics and nutrigenetics questions during the consulting, and the number of patients who asked for information on nutrigenomics and nutrigenetics in the past year.

The use of ANOVA in this context is warranted as it enables the exploration of mean differences across multiple groups. In this instance, it effectively discerns variations in involvement, interest, and awareness scores between the Brazilian and UK groups regarding various facets of nutrigenomics. The statistically significant differences underscore the diverse perspectives and practices within these two populations, offering valuable insights for further examination and consideration in the realm of nutrigenomic education and integration into professional practices.

The results, outlined in the table, provide valuable insights into the significance of these variations. There are noteworthy variations in the sources from which participants initially learned about nutrigenomics and nutrigenetics, indicating diverse channels of information between the Brazilian and UK groups ($p < .001$). Substantial differences are observed in the awareness levels of participants from Brazil and the UK regarding direct-to-consumer companies that offer personalized nutrition advice based on genetics ($p < .001$). Significant differences emerge in the beliefs about possessing the knowledge to integrate nutrigenomics and nutrigenetics into their professional practices, showcasing varying confidence levels

($p < .001$).

No clear evidence indicates differences in beliefs regarding the role of interpreting information from nutrigenomic and nutrigenetic tests between the Brazilian and UK groups ($p = 0.103$). Differing opinions are evident regarding the belief that nutrigenomics and nutrigenetics should be offered as specialized fields of practice for nutritionists/dietitians ($p = 0.004$). Significant differences are noted in beliefs about the likelihood of accurately interpreting test results to patients, reflecting varying levels of confidence ($p < .001$). Variances in the frequency of patients consulting for information on nutrigenomics and nutrigenetics suggest differing experiences between the two groups ($p = 0.002$).

Significant differences in the number of patients seeking information in the past year underscore varying levels of interest or demand between the Brazilian and UK groups ($p < .001$). No clear evidence indicates differences in beliefs about understanding the limitations of nutrigenomics and nutrigenetics tests between the Brazilian and UK groups ($p = 0.821$).

In summary, the results highlight substantial distinctions in knowledge, beliefs, and experiences related to nutrigenomics and nutrigenetics between Brazilian and UK nutritionists/dietitians. These insights are crucial for tailoring educational approaches and professional guidelines to address the specific needs and perspectives of each group.

Table 8. ANOVA of the involvement, interest, and awareness in the field of nutrigenomics in Brazil and the United Kingdom populations in between groups and combined

	Sum of Squares	df	Mean Square	p-value Significance
27. Where did you first hear about nutrigenomic nutrigenetics?				
Between Groups	750.009	1		<.001
Within Groups	5245.805	262	20.022	
Total	5995.814	263		
28. Do you know that there are many direct-to-consumer companies (DTC) that offer personalised nutrition advice based on genetics?				
Between Groups	4.733	1		<.001
Within Groups	53.596	262	0.205	
Total	58.33	263		

	Sum of Squares	df	Mean Square	p-value Significance
43. Do you believe you have the knowledge to integrate nutrigenomics and nutrigenetics in your practice?	Between Groups	36.831	1	<.001
	Within Groups	755.76	262	2.885
	Total	792.591	263	
30. As a nutritionist/dietitian, do you believe that your roles might be to interpret information on nutrigenomics and nutrigenetic tests?	Between Groups	8.349	1	0.103
	Within Groups	819.273	262	3.127
	Total	827.621	263	
31. Do you believe that nutrigenomics and nutrigenetics should be offered as a specialist field of practice for nutritionists/dietitians?	Between Groups	10.775	1	0.004
	Within Groups	339.221	262	1.295
	Total	349.996	263	
32. How likely are you to accurately interpret results of nutrigenomic and nutrigenetic testing to your patients?	Between Groups	23.498	1	<.001
	Within Groups	405.135	262	1.546
	Total	428.633	263	
33. Has a patient ever consulted you for information on nutrigenomics and nutrigenetics?	Between Groups	3.469	1	0.002
	Within Groups	93.015	262	0.355
	Total	96.485	263	
34. Please indicate the number of patients who consulted you for information on nutrigenomics and nutrigenetics in the past year:	Between Groups	13.623	1	<.001
	Within Groups	293.282	262	1.119
	Total	306.905	263	
35. Do you believe that you know the limitations of nutrigenomics and nutrigenetics tests?	Between Groups	0.146	1	0.821
	Within Groups	740.76	262	2.827

	Sum of Squares	df	Mean Sq	p-value Significance
Total	740.905	263		

4.3.4 Survey Results of the Practical Involvement, Interest, and Awareness in Total Study Population

fourth section of the questionnaire was related to professionals' confidence, perceived benefits and risks of nutrigenomics. Sixty-seven respondents (25.4% of the total sample) reported first hearing about NGx in university courses. When asked about DTC companies with NGx services, 67% of respondents confirmed they were aware of such tests. While the majority (78.8%) agreed that NGx should be a specialist field of practice and 87.5% voted for nutrition/dietetics to be the suited profession to provide NGx advice, around 37.9% strongly believed, and 31.1% believed, that their roles might require interpreting information from NGx tests. However, 57.2% of NDs deemed that they may be very unlikely to interpret the results of NGx tests accurately. Meanwhile, 62.1% of respondents said that they did not remember having patients ask them for a consultation on NGx information.

4.3.4.1 Perceived benefits and risks

In the exploration of perceived benefits associated with Nutrigenomics (NGx), a comprehensive factor score was calculated based on pertinent criteria. This score was subsequently subjected to a comparative analysis across various educational levels, years of professional experience, and distinct practice area categories. The findings indicated noteworthy variations in perceived benefits related to educational backgrounds and years of experience, while no significant differences were observed across diverse practice areas.

A more in-depth investigation sought potential correlations between individuals' knowledge levels and their perceptions of benefits and risks. Surprisingly, the study revealed no substantial correlation between the total knowledge score and the comprehensive perceived benefits factor score. This suggests that possessing a higher level of knowledge does not necessarily correspond to an elevated perception of benefits associated with NGx.

Spearman's correlation analysis further unveiled an absence of association between the total knowledge score and the perceived risks score ($r_s = -0.077$, $p = 0.212$). This indicates that participants' knowledge levels were not indicative of their perceptions of the associated risks of NGx. Moreover, when examining the highest qualification attained, the study identified no significant correlation between the highest

qualification and perceived benefits scores ($r_s = 0.048$, $p = 0.438$) or perceived risks scores ($r_s = -0.002$, $p = 0.977$). These outcomes suggest that participants' highest qualification levels did not exert a significant influence on their perceptions of the benefits or risks linked to NGx.

In summation, the research uncovered that perceived benefits of NGx were notably influenced by participants' educational levels and years of experience, with no discernible impact based on the area of practice. Intriguingly, participants' knowledge levels and highest qualifications did not exhibit substantial correlations with their perceived benefits or risks associated with NGx. This underscores the possibility that factors beyond knowledge and qualifications contribute to shaping individuals' perceptions of the benefits and risks associated with Nutrigenomics.

4.3.4.2 Education and training

Whilst the majority of NDs claimed they “do not believe” (30.3%) and “strongly do not believe” (12.9%) that they have the knowledge to integrate NGx into practice, they were “interested” (43.2%) and “extremely interested” (28%) to undergo NGx training. Physically attending a course only of any duration was indicated by 14%, but attending a course of any duration along with online courses self-learning and CPD activities was indicated by 49%. On the other hand, 24% reported a preference for self-learning mixed with other learning activities. NDs considered that NGx should be a mandatory module as a part of a formal training program (34.1%) for future nutrition/dietetic students. Additionally, consulting scientific articles on NGx was not common among participants, and 67.8% consulted scientific articles less than once a month.

4.4 Discussion

One of the purposes of this study was to compare the statistics of surveys undertaken between two different countries: Brazil and the United Kingdom. This study is a comparative study as it evaluates the difference in overall knowledge between the two countries. It allows obtaining updated information about the current knowledge and involvement of NDs in NGx.

The study allowed identifying factors associated with knowledge, as well as the involvement, perceived benefits and risks, education, and training needs of the NDs in the UK and Brazil. Although the information and details about the DTC-NGx are thoroughly available, the actual application of NGx in the practice of NDs is still restricted. But still, there is a hope that the knowledge of this field will be added

to the regular practice of the NDs in the coming future. Therefore, the results of this study may provide vital insights for NDs that may contribute to the advancement and management of obesity in Brazilian and UK populations from the applications of NGx clinical management in the future.

4.4.1 Knowledge and Associated Demographic Factors

For the purpose of this research, the approximation of the knowledge of the participants was limited to the questions asked in this study. The scores do not reflect the total knowledge the respondents have in nutrigenomics and genetics. According to this study, only 33.7% of participants believe or strongly believe they have a good knowledge of NGx. Additionally, the mean score obtained was 2.81 and 3.58 (out of 5) for Brazilians and the UK participants, respectively. The overall knowledge score shows the lack of substantial knowledge in the participants. According to a study conducted in the Quebec province of Canada, 76.9% of participants believed to have good knowledge of nutrigenomics (Cormier et al., 2014). Another study conducted in the USA among 20 different healthcare professionals found that only half of the dietitians were aware of the term “nutrigenomics” (Mitchell, 2016). A study conducted in Poland to measure the state of nutrigenomic education among dietitians shows that most participants were aware of nutrigenomics and had a positive attitude toward it but still possess a low level of knowledge related to NGx (Mlodzik-Czyzewska & Chmurzynska, 2018). As expected, since nutrigenomics is an emerging field, the participants have more knowledge of genetics than nutrigenomics. For example, only 9.5% of participants correctly identified the association between red meat intake and colorectal neoplasia. Also, only 10.6% correctly identified polymorphism in the *TCF7L2* gene with glucose levels. In contrast, 68.6% correctly defined the term “mutation”, and 69% correctly defined the term “phenotype”. Regarding their first encounter with NGx, there were some participants (25%) who reported first hearing about NGx in university courses. This demonstrates that NGx is being newly recognised as a topic in university courses. However, the present study failed to find any strong relationship between demographic factors (such as age and level of education) and knowledge of NDs about nutrigenomics. Hence, if participants have already encountered NGx during college, it can be expected that later age and a higher level of education would be related to increased knowledge of NGx. Since results have shown low NGx knowledge scores, it may suggest that even if NGx concepts were introduced at a later age or during college, there is still a lack of NGx understanding by current NDs.

4.4.2 Involvement, Interest, and Awareness

67% of participants confirmed that they were aware of the direct-to-consumer services with nutrigenomics

tests, and this had no significant relation with their years of experience. A study in Canada showed that 49.2% of RDs with less than 5 years of experience knew about the testing as compared to 11.6% of RDs with more than 25 years of experience (Cormier et al., 2014). Regarding the comparison between both countries, results showed that 28.1% of Brazilian participants first heard about NGx in presentations, conferences, and professional meetings rather than in university courses. This means 71.9% of Brazilian participants first heard about NGx in their university courses. In contrast, 50% of the UK participants first heard about NGx in university courses. This may demonstrate that Brazilian universities are including NGx as a specialized course more often than UK universities.

An interesting point is that both countries (78.8%) agreed that NGx should be a specialized field of study for nutritionists and dietitians, and NDs must be a preferable profession to provide NGx services (87.5%), with a slightly higher mean score for the UK participants. Nutritionists and dietitians are specialized in biomedical and nutritional sciences combined; they are well suited to provide NGx information and health-related services to the public. However, when asked if they perceived they were competent to interpret the NGx test, 37.9% believed that their role might require them to be competent at interpreting the information. Yet, 62.1% did not think that they were competent. The confidence level is higher in the participants in the UK rather than in Brazilians. At present, awareness about NGx among the general population is very rare; almost half of the ND participants (43.2%) witnessed patients asking about NGx information. A study in Greece shows that 80.5% of consultants are willing to recommend their patients undergo nutrigenomic analysis to relate their nutrition and diet with genetics, but only 17% did so (Pavlidis et al., 2012). Similarly, since the majority of NDs in both countries (86.5% for the UK and 73.8% for Brazil) believe that nutrigenomics and nutrigenetics should be offered as a specialist field of practice for nutritionists/dietitians, it was also expected that they are also interested to recommend NGx services to their patients.

4.4.3 Perceived Benefits and Risks

In exploring the knowledge and perceptions of Nutrigenomics (NGx) among nutritionists/dietitians (NDs) in Brazil and the UK, the study uncovered noteworthy insights. Initially, when assessing awareness of limitations associated with NGx tests, both countries exhibited a common lack of confidence and understanding, falling within the "I don't know" to "neutral" categories. This consistency persisted across diverse experience levels, practice areas, and education levels.

Transitioning to perceived benefits, a distinct contrast emerged between Brazil and the UK, with Brazil

expressing a more positive outlook (mean score of 3.29) compared to the UK (mean score of 2.41). Despite Brazil's larger population, this discrepancy suggests a potential for successful NGx implementation, with potential implications for public health. Surprisingly, perceived benefits did not significantly differ across various practice areas, indicating a consistent perception among NDs.

Correlation analyses revealed intriguing findings. Despite heightened NGx knowledge, no expansion in the perception of benefits or risks was observed. This lack of correlation persisted across experience levels, education, and practice areas, implying that advanced knowledge alone might not be the sole determinant of shaping NDs' perceptions. These findings underscore the imperative need for targeted education and training to enhance understanding and foster a more positive perception of NGx among NDs. This is vital for expediting the adoption and progression of NGx in both the UK and Brazil, potentially unlocking the therapeutic benefits of precision nutrition in addressing genetic diseases and metabolic conditions.

4.4.4 Education and Training

Dietetic practitioners are experts in nutrition science, and interest in nutrigenomics is growing among members of this professional group. In contrast, this study shows that most of the participants (43.2%) do not believe that they can integrate nutrigenomics into their regular practice because they do not have enough knowledge to do so, which opens an opportunity for qualified institutions to offer NGx training to propel its advancement in their countries. The United Kingdom participants are more confident about their knowledge of NGx than Brazilians. Still, both are interested (85%) in undergoing training and education related to nutrigenomics. A study conducted in Israel shows that 94% of participants are not good at their knowledge of nutrition, and only 9.5% had received training in nutrigenomics (Kaufman-Shriqui et al., 2020). Another study conducted in Poland demonstrated a positive attitude (59%) and interest (63%) of their participants in gaining training in NGx despite their low level of knowledge on the topic (Mlodzik-Czyzewska & Chmurzynska, 2018). To check the preference of participants in the mode of learning, they were asked to select among some specific options. In total, 49% preferred it to be a professional course provided by the university or a professional, and very few were interested in adding it to the syllabus of bachelors or doctorate studies. Although the NGx course is not well known to the NDs at present, 78% of participants (with almost an equal ratio of both countries) agreed to add this course as a specialized field of practice for the NDs in the coming era.

Considering the lack of nutrigenomic awareness among the NDs, they are not used to reading about it.

The study provides information that 67.8% of the participants read less than one article in a month related to nutrigenomics. From a perspective, if the majority of NDs are not actively engaging in NGx educational advances like those found in journal publications, it may reflect that either they are confident and fully knowledgeable about the subject area or that there is no avenue or a platform that constantly makes them proactively learning or referring to NGx information. For example, if their clinic or institution has consistent patients/clients consulting for NGx, then highly confident and knowledgeable NDs do not need to read many NGx papers anymore. But if their clinic or institutions do not really receive patients/clients interested in personalized nutrition, then it may also be a reason for NDs to refrain or stop checking NGx publications since they may not have the need to use it. It is also possible that there is a lack of NGx advances that are currently being published; hence, it opens an opportunity for academic and clinical institutions to conduct more research studies and trials to expand the knowledge and application of NGx to patients.

Additionally, suppose there is also a standard clinical guideline for NGx implementation, then constant reading of new NGx publications may also not be needed since they prefer to follow the clinical guidelines. However, such guidelines are not established. Hence, the expectation is that NDs must actively read NGx publications. Since the results of present study show that NDs only read less than 1 article per month and there are no current gold-standard approved clinical NGx guidelines, it may imply that there are not many patients/clients consistently consulting for NGx and the existing protocols or their own guidelines are enough to perform regular NGx advice for clients/patients. However, since almost half of the NDs still believe that NDs do not have the practical knowledge to integrate NGx into their practice, then professional training and certifications are recommended.

Currently, there are nutrigenomics research groups and institutions that are expanding the understanding of the subject matter and training for the next generation of NGx specialists. At the forefront of developing NGx professionals, some universities already offer graduate degrees in nutrigenomics, including Manchester University (the UK), Universitat de les Illes Balears (Spain), and The University of British Columbia (Canada). Alternatively, NGx graduate or online courses are also available for learning the foundation or clinical practice for nutrition professionals.

4.4.5 Limitations

Possible response bias, resulting in under/overestimation of measures, is one of the study's limitations. Furthermore, due to the low response rate (24% in the UK and 41% in Brazil), the results were not

generalizable to the broader nutrition/dietetics profession. A larger number of participants for the survey may further strengthen the results. Furthermore, knowledge was limited to 16 multiple-choice questions, making it impossible to assess the entirety of knowledge in a wide field such as nutrigenomics, making the increase of questions on the questionnaires a future perspective that may provide more detailed information to contribute to current understanding. In addition, as Brazil is a large country, it would be important to survey different regions.

Future research is required to determine the breadth of genetics and NGx knowledge among NDs, as well as to identify associated factors and reach a consensus on involvement. Moreover, there may be other variables correlated with information not evaluated here.

4.4.6 Conclusion

Overall, a need to build up basic and deep NGx knowledge for NDs persists in both countries, particularly for those interested in integrating it into practice. Brazilian and UK NDs recognize some benefits of NGx in disease management/prevention and the importance of the role of dietitians/nutritionists in this field. However, they remain concerned about the validity, costs of the tests, and genetic discrimination. Factors such as higher qualifications, relevant literature reading, and perceived benefits of NGx could strengthen this knowledge and potentially improve its applications.

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APPENDICES

Table A1. Survey questionnaire with 50 questions divided into 5 sections

1 First section is related to demographics questions and selection of the participants

URN	Unique Response Number
Q1	Do you work in the field of nutrition and/or dietetics?
1	Yes
2	No
Q2	Please select the country you practise in
1	United Kingdom
2	Other
Q3	Please indicate that you have read and understood the Participant Information for this research project and that you consent to take part in this questionnaire continuing
1	Yes, I do consent to take part in this research
2	No, I do not consent to take part in this research
Q4	Do you think you have a good knowledge in the area of nutrigenomics and nutritional genomics?
1	Yes
2	No
Q5	What is your gender?
1	Male
2	Female
3	I don't want to answer
4	Other
Q5_a	If you selected Other, please specify:
Q6	Please specify your age
Q7	Please select your highest level of education
1	No formal qualification
2	GCSE or equivalent
3	AS/A-Level
4	Bachelor's degree
5	Postgraduate Diploma
6	Master's Degree
7	Doctorate/PhD
8	Other
Q7_a	If you selected Other, please specify:
Q8	Please select you area of practice:
1	In the NHS - UK (Hospitals, Community)
2	Public health - UK
3	Food industry
4	Pharmaceutical industry
5	Media
6	Sports Nutrition
7	Academic/Research
8	Other

9 unemployed

Q8_a If you selected Other, please specify:

Q9 How much work experience do you have in the field of nutrition and dietetics?

- 1 Less than a year
- 2 1 - 5 years
- 3 6 - 10 years
- 4 11 - 15 years
- 5 16 - 20 years
- 6 21 - 25 years
- 7 26 - 30 years
- 8 >31 years

Q10 Please indicate the organisation you are a member of:

- 1 Association for Nutrition
- 2 British Dietetic Association
- 3 The Nutrition Society
- 4 None
- 5 Other

2 Second section is related to genetics and disease association knowledge

Q10_a If you selected Other, please specify:

Q11 A 'gene' is:

- 1 An alteration in DNA that results in disease
- 2 The protein produced from DNA
- 3 A short sequence of DNA
- 4 A DNA sequence that codes for a protein
- 5 I don't know

Q12 An 'allele' is:

- 1 A single stranded piece of DNA
- 2 One of a set of alternative forms of a gene
- 3 A gene
- 4 Part of the nucleus where DNA is stored
- 5 I don't know

Q13 A 'Phenotype' is:

- 1 The genetic alteration responsible for PKU
- 2 A trait resulting from the genetic code
- 3 A type of gene that is expressed
- 4 A trait resulting from genes that do not code
- 5 I don't know

Q14 A 'mutation' is:

- 1 Apoptosis
- 2 A change in DNA sequence
- 3 A change in DNA between generations
- 4 A change in DNA that results in disease
- 5 I don't know

Q15 'Nutrigenetics' is:

- 1 The effect of diet on how genes work
- 2 How genes affect what we eat
- 3 The effect of genes on the response to diet
- 4 Passing nutritional diseases to the offspring
- 5 I don't know

Q16 Which of the following defects interact with dietary fat intake to influence the cardiovascular disease?

- 1 CBS 844ins68
- 2 Angiotensinogen M235T
- 3 ApoE2/E2
- 4 MS 2756A→G
- 5 I don't know

Q17 A 'chromosome' is:

- 1 A self-replicating genetic structure within cells
- 2 An abnormality occurring in DNA
- 3 A gene
- 4 A gene that causes a disease
- 5 I don't know

Q18 'Genotype' is:

- 1 The genetic information in an organism
- 2 The effect of the genetic code on proteins
- 3 The type of DNA in genes
- 4 Any genetic disorder
- 5 I don't know

Q19 A 'polymorphism' is:

- 1 The range of genes in one human
- 2 The changes in DNA during a cell cycle
- 3 A mutating gene
- 4 Variation in DNA sequence between individuals
- 5 I don't know

Q20 'PCR' means:

- 1 Promotion of cell replication

- 2 Polymorphism control region
- 3 Polymerase chain reaction
- 4 Penetrance of cancer risk
- 5 I don't know

Q21 Which of the following is FALSE? 'Genetic defects can...'

- 1 Increase food intake
- 2 Increase the risk of diverticular disease
- 3 Decrease nutrient absorption
- 4 Increase the risk of Crohn's disease
- 5 I don't know

Q22 What condition is NOT associated with the methylenetetrahydrofolate re (MTHFR) 677C→T defect

- 1 Cardiovascular disease
- 2 Colorectal cancer
- 3 Type 1 diabetes mellitus
- 4 Neural tube defects
- 5 I don't know

Q23 Salt sensitivity may develop due to genetic variations in:

- 1 *ACE* gene
- 2 *FTO* gene
- 3 *TCF7L2* gene
- 4 All of the above
- 5 I don't know

Q24 The association between red meat intake and colorectal neoplasia appears to be evide

- 1 *MC4R* gene
- 2 *NAT2* gene
- 3 *ADRD2* gene
- 4 None of the above
- 5 I don't know

Q25 Which of the following is associated with a polymorphism in *TCF7L2* gene?

- 1 Glucose levels
- 2 Blood pressure
- 3 Cholesterol levels
- 4 Cancer
- 5 I don't know

Q26 According to the literature, certain SNPs in the *FTO* gene are associated with:

- 1 Greater food intake

- 2 Lowered satiety
- 3 Increased hunger
- 4 All of the above
- 5 I don't know

3 Third section is related to practical involvement, interest, and awareness in the field of nutrigenomics, calculated from the sum of correct questions on educational and clinical experience and the mean score for the Likert scale response for each activity, further this can also be presented as percentage for graphic comparison.

Q27 Where did you first hear about nutrigenomics and nutrigenetics?

- 1 Newspaper articles
- 2 Colleagues
- 3 Congress or professional meeting
- 4 University courses
- 5 Internet
- 6 Social media
- 7 Continuing Professional Development (CPD)
- 8 Patient
- 9 Scientific publications
- 10 Television
- 11 Radio
- 12 Other health professionals
- 13 Other

Q27_a If you selected Other, please specify:

Q28 Do you know that there are many direct to consumer companies (DTC) that offer personalised nutrition advice based on genetics?

- 1 No, I did not know there are such companies
- 2 Yes, I know there are such companies

- 1 No, I did not know there are such companies
- 2 Yes, I know there are such companies

Q29 What type of health professional should a patient desiring nutrigenomics and nutri services be referred to? (more than one option can be selected)

- 1 Genetic counsellors
- 2 Nurses
- 3 Doctors
- 4 Nutritionists/Dietitians
- 5 Other

Q29_a If you selected Other, please specify:

Q30 As a nutritionist/dietitian, do you believe that one of your roles might be to i information from nutrigenomics and nutrigenetic tests?

- 1 Strongly believe
- 2 Believe
- 3 Neutral
- 4 Do not believe
- 5 Strongly do not believe
- 6 I don't know

Q31 Do you believe that nutrigenomics and nutrigenetics should be offered as a specialist practice for nutritionists/dietitians?

- 1 Yes
- 2 No
- 3 I don't know
- 4 Other

Q31_a If you selected Other, please specify:

Q32 How likely are you to accurately interpret results of nutrigenomic and nutrigenetic to your patients?

- 1 Very likely
- 2 Likely
- 3 Unlikely
- 4 Very unlikely
- 5 I don't know

Q33 Has a patient ever consulted you for information on nutrigenomics and nutrigenetics

- 1 Yes
- 2 No
- 3 I don't remember

Q34 Please indicate the number of patients who have consulted you for informa nutrigenomics and nutrigenetics in the past year:

- 1 0
- 2 1 to 5
- 3 Between 6 and 10
- 4 More than 10

4 Forth section is related to professionals' confidence, perceived benefits and risks of nutrigenomics.

Q35 Do you believe that you know the limitations of nutrigenomics and nutrigenetics tests?

- 1 Strongly believe
- 2 Believe
- 3 Neutral
- 4 Do not believe

- 5 Strongly do not believe
- 6 I don't know

Q36 Please specify how much you believe the application of nutrigenomics and nutrigenetics improve the practice of nutritionists/dietitians

- 1 Strongly believe
- 2 Believe
- 3 Neutral
- 4 Do not believe
- 5 Strongly do not believe
- 6 I don't know

Q37 How well can you explain the benefits and drawbacks of nutrigenomics and nutrigenetics to your patients?

- 1 Very well
- 2 Well
- 3 Neutral
- 4 Not well
- 5 Not at all
- 6 I don't know

Q38 Please indicate to what extent the following statements about nutrigenomics and nutrigenetics concern you

Q38_1 Anxiety caused to a patient

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q38_2 The test's results

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q38_3 Data confidentiality

- 1 Extremely concerned
- 2 Very concerned

- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q38_4 Financial costs associated with these tests

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q38_5 Genetic discrimination (e.g. insurance)

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q38_6 Validity of the tests

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned
- 5 Not at all concerned
- 6 I don't know

Q39 Referring to the question above, do you have any other concern(s) with regards to nutrigenetics?

- 1 Yes
- 2 No

Q40 Please specify what your other concern(s) is/are (not more than 2 areas):

Q40_a Please indicate to what extent your own statement(s) mentioned above about nutrigenetics concern you:

Q40_a_1 Your statement(s)

- 1 Extremely concerned
- 2 Very concerned
- 3 Moderately concerned
- 4 A little concerned

- 5 Not at all concerned
- 6 I don't know

Q41 In your opinion, how likely are the results of a nutrigenomics and nutrigenetics test to i recommendations for the following diseases?

Q41_1 Phenylketonuria

- 1 Very likely
- 2 Likely
- 3 Neutral
- 4 Unlikely
- 5 Very Unlikely
- 6 I don't know

Q41_2 Galactosemia

- 1 Very likely
- 2 Likely
- 3 Neutral
- 4 Unlikely
- 5 Very Unlikely
- 6 I don't know

Q41_3 Tyrosinemia

- 1 Very likely
- 2 Likely
- 3 Neutral
- 4 Unlikely
- 5 Very Unlikely
- 6 I don't know

Q41_4 Maple syrup urine disease

- 1 Very likely
- 2 Likely
- 3 Neutral
- 4 Unlikely
- 5 Very Unlikely
- 6 I don't know

Q41_5 Glycogen storage disease type 1

- 1 Very likely
- 2 Likely
- 3 Neutral
- 4 Unlikely
- 5 Very Unlikely
- 6 I don't know

Q41_6	Homocystinuria
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_7	Enzymatic defects
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_8	Hereditary cycle
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_9	Urea cycle
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_10	Celiac disease and Chron's disease
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_11	Obesity
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely

6	I don't know
Q41_12	Type 2 diabetes
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_13	Cystic fibrosis
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_14	Parkinson
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_15	Alzheimer
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_16	Cancer
1	Very likely
2	Likely
3	Neutral
4	Unlikely
5	Very Unlikely
6	I don't know
Q41_17	Hypertriglyceridemia
1	Very likely
2	Likely
3	Neutral
4	Unlikely

5 Very Unlikely
6 I don't know
Q41_18 Hypercholesterolemia

1 Very likely
2 Likely
3 Neutral
4 Unlikely
5 Very Unlikely
6 I don't know

Q41_19 Cardiovascular illnesses

1 Very likely
2 Likely
3 Neutral
4 Unlikely
5 Very Unlikely
6 I don't know

Q41_20 Osteoporosis

1 Very likely
2 Likely
3 Neutral
4 Unlikely
5 Very Unlikely
6 I don't know

Q42 Do you believe that nutrigenomics and nutrigenetics testing can facilitate positive be change and adherence to healthy lifestyle recommendations (eating habits, physical activit

1 Strongly believe
2 Believe
3 Neutral
4 Do not believe
5 Strongly do not believe
6 I don't know

Q43 Do you believe you have the knowledge to integrate nutrigenomics and nutrigenetics practice?

1 Strongly believe
2 Believe
3 Neutral
4 Do not believe

- 5 Strongly do not believe
- 6 I don't know

5 Fifth section is about Education and Training

Q44 Would you be interested to undergo training in nutrigenomics and nutrigenetics?

- 1 Extremely interested
- 2 Interested
- 3 Neutral
- 4 Not interested
- 5 Extremely Not interested

Q45 If you, working in the nutritionists/dietetics industry, were to receive nutrigenon nutrigenetics training, what level would you prefer to undertake?

- 1 No formal qualification (certificate of attendance only)
- 2 Certified courses (by a university or a professional body)
- 3 Bachelor's degree
- 4 Postgraduate Diploma
- 5 Master's Degree
- 6 Doctorate/PhD
- 7 Other

Q45_a If you selected Other, please specify:

Q46 How do you think students studying towards a nutrition or dietetics qualification be trained in nutrigenomics and nutrigenetics?

- 1 Optional/elective module (as part of an undergraduate program)
- 2 Optional/elective module (as part of a postgraduate program)
- 3 Mandatory module (as part of an undergraduate program)
- 4 Mandatory module (as part of a postgraduate program)
- 5 Stand-alone undergraduate program
- 6 Stand-alone postgraduate program
- 7 Other

Q46_a If you selected Other, please specify:

Q47 If you were to receive training, what method(s) would you prefer? (more than one can be selected)

- 1 Self-learning with (books, scientific papers, blogs)
- 2 Online courses
- 3 Physically attending a course (of any duration)
- 4 Continuing professional development (scientific meetings, conferences, etc)
- 5 Other

Q47_a If you selected Other, please specify:

Q48 Over the last five years, how many continuing education or professional development sessions in nutrition (provincial, national or international) have you attended?

- 1 0
- 2 1 to 2
- 3 3 to 4
- 4 5
- 5 More than 5
- 6 I don't know

Q49 Over the last five years, how many continuing education or professional development sessions in nutrigenomics and nutrigenetics (provincial, national or international) have you attended?

- 1 0
- 2 1 to 2
- 3 3 to 4
- 4 5
- 5 More than 5
- 6 I don't know

Q50 During the past year, how many times have you consulted scientific articles on nutrigenomics or nutrigenetics?

- 1 Less than once a month
- 2 Once a month
- 3 Two to three times a month
- 4 Four times a month
- 5 More than four times a month

Table A2: Survey result of questionnaire section 2 regarding NGx knowledge, showing the distribution of the number of people for each answer between Brazil and United Kingdom. Correct answers are marked with *

		Brazil	United Kingdom	TOTAL
11. A 'gene' is:	*A DNA sequence that for a protein	51	49	100
	A short sequence of DNA	40	49	89
	An alteration in DNA results in disease	19	1	20
	I don't know	3	0	3
	The protein produced DNA	47	5	52
Total		160	104	264
		Brazil	United Kingdom	TOTAL
12. An 'allele' is:	A gene	19	6	25
	A single stranded piece of	43	16	59
	I don't know	8	11	19
	*One of a set of alternative forms of a gene	77	61	138
	Part of the nucleus where is stored	13	10	23
Total		160	104	264
		Brazil	United Kingdom	TOTAL
13. A 'Phenotype' is:	A trait resulting from gene do not code	15	2	17
	*A trait resulting from genetic code	99	75	174
	A type of gene that is expressed	30	19	49
	I don't know	4	6	10
	The genetic alteration responsible for PKU	12	2	14
Total		160	104	264
		Brazil	United Kingdom	TOTAL
14. A 'mutation' is:	A change in DNA between generations	0	9	9
	*A change in DNA sequence	101	80	181
	A change in DNA that results in disease	48	14	62
	Apoptosis	7	0	7
	I don't know	4	1	5
Total		160	104	264
		Brazil	United Kingdom	TOTAL
15. 'Nutrigenetics' is:	How genes affect what we eat	37	10	47
	I don't know	12	7	19
	Passing nutritional diseases	9	1	10

	the offspring			
	The effect of diet on how work	44	31	75
	*The effect of genes on response to diet	58	55	113
Total		160	104	264
		Brazil	United Kingdom	TOTAL
16. Which of the following defects interact with dietary intake to influence the risk of cardiovascular disease?	Angiotensinogen M235T	41	12	53
	*ApoE2/E2	40	40	80
	CBS 844ins68	10	0	10
	I don't know	37	52	89
	MS 2756A→G	32	0	32
Total		160	104	264
		Brazil	United Kingdom	TOTAL
17. A 'chromosome' is:	A gene	33	10	43
	A gene that causes a disease	15	0	15
	*A self-replicating genetic structure within cells	71	90	161
	An abnormality occurring in DNA	37		38
	I don't know	4	3	7
Total		160	104	264
		Brazil	United Kingdom	TOTAL
18. 'Genotype' is:	Any genetic disorder	8	1	9
	I don't know	5	4	9
	The effect of the genetic information on proteins	41	8	49
	*The genetic information in an organism	83	79	162
	The type of DNA in genes	23	12	35
Total		160	104	264
		Brazil	United Kingdom	TOTAL
19. A 'polymorphism' is:	A mutating gene	38	13	51
	I don't know	5	20	25
	The changes in DNA during the cell cycle	44	17	61
	The range of genes in the human genome	16	5	21
	*Variation in DNA sequence between individuals	57	49	106
Total		160	104	264
		Brazil	United Kingdom	TOTAL
20. 'PCR' means:	I don't know	17	24	41
	Penetrance of cancer risk	10	1	11
	*Polymerase chain reaction	81	70	151
	Polymorphism control region	28	4	32
	Promotion of cell replication	24	5	29
Total		160	104	264
		Brazil	United Kingdom	TOTAL
21. Which of the following is FALSE? 'Genetic drift'	Decrease nutrient absorption	38	13	51
	I don't know	21	28	49

can...'	*Increase food intake	44	31	75
	Increase the risk of Cr disease	15	15	30
	Increase the risk of divert disease	42	17	59
Total		160	104	264
		Brazil	United Kin	TOTAL
22. What condition is associated with methylenetetrahydrofolate reductase (MTHFR) 677 defect	Cardiovascular disease	15	4	19
	Colorectal cancer	60	8	68
	I don't know	34	56	90
	Neural tube defects	16	11	27
	*Type 1 diabetes mellitus	35	25	60
Total		160	104	264
		Brazil	United Kin	TOTAL
23. Salt sensitivity may be due to genetic variations in	*ACE gene	47	24	71
	All of the above	15	16	31
	<i>FTO</i> gene	21	4	25
	I don't know	47	55	102
	<i>TCF7L2</i> gene	30	5	35
Total		160	104	264
		Brazil	United Kin	TOTAL
24. The association between meat intake and colorectal neoplasia appears to be explained by:	<i>ADRD2</i> gene	25	8	33
	I don't know	58	67	125
	<i>MC4R</i> gene	14	9	23
	* <i>NAT2</i> gene	48	14	62
	None of the above	15	6	21
Total		160	104	264
		Brazil	United Kin	TOTAL
25. Which of the following is associated with polymorphism in <i>TCF7L2</i> gene?	Blood pressure	20	8	28
	Cancer	6	3	9
	Cholesterol levels	27	3	30
	*Glucose levels	70	21	91
	I don't know	37	69	106
Total		160	104	264
		Brazil	United Kin	TOTAL
26. According to the literature, certain SNPs in the <i>FTO</i> gene are associated with:	*All of the above	50	43	93
	Greater food intake	27	3	30
	I don't know	30	50	80
	Increased hunger	20	3	23
	Lowered satiety	33	5	38
Total		160	104	264

Address and Activity

Mr. / Mrs _____

Name: _____

Firstname: _____

Street: _____

Postcode: _____

City: _____

Phone / Mobile: _____

Date of Birth: _____

Hight: ____cm Weight: ____kg

E-mail:
_____Language: D, E, F, PT, other: _____**Define your level of physical activity:**

Physical tasks, gardening, construction work, various housework or sport activities

- undemanding work in a sitting position and rare sporting activities
- 1 to 3x Active weekly
- 3 to 5x Active weekly
- 6 to 7x Active weekly
- 2x per Day**, Sport and or Physical work

What is your most common physical activity?
(Multiple choice possible)

- Fitness Dancing Martial arts
- Football Tennis Nordic Walking
- Running Swimming Mountaineering
- Aerobics Badminton Mountainbike
- Walking Basketball Cycling

Other: _____

Confidential Data

Take nutritional supplements?

 Yes NoIf Yes, what?
_____**Do you eat meat?** Yes No**Do you eat fish?** Yes No**Do you eat bread?** Yes No

How much per piece per day?

 1-2 3-4 5-6
 more than 6**Do you smoke:** Yes No**Stress Level** no Stress little Stress medium Stress high Stress**Are you a pregnant women?** Yes No

I am breastfeeding mother

 Yes No**Partner**

Reseller stamp

Inv. No.: _____

Inv.-Day: _____

Customer No.: _____

Info**BARCODE****Privacy and decision to Storage of the examined good****Action**

For genetic testing, only a small amount of saliva is needed. You will receive the necessary material including the user manual.

Legal basis:

Law on genetic testing in humans (GUMG)

Data protection

NGR follows the Swiss federal law on data protection (DSG) of 19 June 1992 (as of January 1, 2014). You hereby confirm that you have been advised in accordance with the law on genetic testing in humans GUMG), as well as enough time for questions and to have had reservations.

Decision to keep the investigation good

You determine how we should proceed with the data after the analysis: Please answer on the back,

Moreover, we also confirm with the signature that the explanations on the back have been understood!

Permission to Perform an Analysis

Genetic analyses performed by NUTRI-GENETICA RESEARCH AG (hereinafter NGR) encompass research of genetic variants that are associated with the metabolism of an individual. On the basis of these findings, NGR designs a personalized report, adapted to the nature of the ordered service. Testees shall receive their results in 4 to 8 weeks after we have received their saliva sample.

I am a person to be tested, a parent or an authorized representative of a person to be tested and

I DECLARE THAT:

I have received clear and detailed information on the nature of NGR's services and I am aware of the benefits and limitations arising from them. I agree to the General Terms of Business (which are an integral part of the Permission to perform a genetic analysis) of NGR and I concurrently agree to these important provisions:

- In order to allow NGR to perform an analysis and create a report, I permit the use of my (or my child's or constituent's) genetic material and I give my informed consent to the envisaged genetic testing.
- All of the entered personal and other data are correct and the genetic material provided is mine (or my child's or constituent's) and not from a third person.
- NGR must protect personal data in accordance with the Personal Data Protection Act and in accordance with NGR's General Terms of Business.
- The provisions in NGR's General Terms of Business are understandable and I agree to them completely; I have also been offered the possibility to consult a professional or NGR staff on all queries.
- I agree to NGR's procedures and other provisions that arise from the nature of the services and the general terms of service.
- NGR's report, including the accompanying recommendations and conclusions, does not substitute medical diagnoses, treatments, recommendations by doctors and other official medical institutions regarding medicine, nutrition, lifestyle and manner of treatment.
- NGR does not determine diseases, however, recommends a visit to a doctor in cases where disease is suspected.
- NGR does not determine various responses and allergies to the recommendations it provides, thus it recommends a visit and consultation with a doctor regarding all recommendations (nutrition, vitamins, supplements, lifestyle, etc.).
- NGR does not make diagnoses and does not determine the manner of disease treatment. It analyzes the obtained genetic material on the basis of current scientific research and publications that do not necessarily represent a precise reflection of a medical condition, as other factors and genetic information that are not analyzed by NGR can also influence it.
- Distributors (doctors, drugstores, medical institutions, etc.) and other partners of NGR, through which the services of NGR can be bought or ordered, do not assume responsibility for the services performed by NGR, and NGR does not assume any responsibility for any improper or inappropriate actions of distributors, partners or third

persons that pretend to be distributors or partners of NGR.

- Inadequately collected genetic material can cause insufficient laboratory information on analyzed genetic variants. If the missing data influence the analyzed area, NGR will perform one additional laboratory analysis on the basis of the data and Permission to perform a genetic analysis from their first analysis.

I confirm that I permit the analysis to be performed and I agree to the General Terms of Business. You can read the complete Terms at. www.nutri-genetica.ch

Voluntary research : NUTRI-GENETICA RESEARCH AG

research in the field of genetics that contributes to the development of this field and to the development and improvement of existing and new services. For this purpose, please select whether you agree to the use of anonymous genetic material (swab, saliva, etc.) and characteristics (sex, age, weight, height, etc. WITHOUT ANY PERSONAL DATA: name, surname, address, etc.) for research and development purposes and research that can contribute to the improvement of the quality of genetic services in other ways, enabling NGR to authorize other research institutions to access the genetic material for research purposes. Your permission is not a condition for receiving the services of NGR.

Tick as appropriate:

() I am a testee and I permit the use of my anonymous genetic material (swab, saliva, etc.)

() I am a parent and I permit the use of my child's anonymous genetic material (swab, saliva, etc.)

() I am an authorized representative and I permit the use of my constituent's anonymous genetic material (swab, saliva, etc.)

() I am a testee and I do not permit the use of my anonymous genetic material (swab, saliva, etc.)

() I am a parent and I do not permit the use of my child's anonymous genetic material (swab, saliva, etc.)

() I am an authorized representative and I permit the use of my constituent's anonymous genetic material (swab, saliva, etc.)

SIGNATURE OF THE TESTEE

PLACE AND DATE