frontiers | Research Topics

Genome-based nutrition strategies for preventing diet-related chronic diseases: Where genes, diet, and food culture meet

Edited by
Arturo Panduro, Omar Ramos-Lopez
and Claudia Ojeda-Granados

Published in
Frontiers in Nutrition

ISSN 1664-8714
ISBN 978-2-8325-5109-7
DOI 10.3389/978-2-8325-5109-7

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Genome-based nutrition strategies for preventing diet-related chronic diseases: Where genes, diet, and food culture meet

Topic editors

Arturo Panduro – University of Guadalajara, Mexico

Omar Ramos-Lopez – Universidad Autónoma de Baja California, Tijuana, Mexico

Claudia Ojeda-Granados – University of Catania, Italy

Citation

Panduro, A., Ramos-Lopez, O., Ojeda-Granados, C., eds. (2024). *Genome-based nutrition strategies for preventing diet-related chronic diseases: Where genes, diet, and food culture meet*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-5109-7

Table of contents

frontiers | Frontiers in Nutrition

TYPE Editorial
PUBLISHED 24 June 2024
DOI 10.3389/fnut.2024.1441685

OPEN ACCESS

EDITED AND REVIEWED BY
Annalisa Terranegra,
Sidra Medicine, Qatar

*CORRESPONDENCE
Arturo Panduro
✉ apanduro@prodigy.net.mx;
✉ apanduro53@gmail.com

RECEIVED 31 May 2024
ACCEPTED 06 June 2024
PUBLISHED 24 June 2024

CITATION
Panduro A, Ojeda-Granados C, Ramos-Lopez O and Roman S (2024) Editorial: Genome-based nutrition strategies for preventing diet-related chronic diseases: where genes, diet, and food culture meet. *Front. Nutr.* 11:1441685. doi: 10.3389/fnut.2024.1441685

Editorial: Genome-based nutrition strategies for preventing diet-related chronic diseases: where genes, diet, and food culture meet

Arturo Panduro[1,2]*, Claudia Ojeda-Granados[3], Omar Ramos-Lopez[4] and Sonia Roman[1,2]

[1]Department of Genomic Medicine in Hepatology, Civil Hospital of Guadalajara, Guadalajara, Jalisco, Mexico, [2]Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico, [3]Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia," University of Catania, Catania, Italy, [4]Medicine and Psychology School, Autonomous University of Baja California, Tijuana, Baja California, Mexico

KEYWORDS

personalized nutrition, personalized medicine, chronic diseases, gene polymorphisms, gene-environmental mismatch, ancestry, lifestyle factors, omic sciences

Editorial on the Research Topic
Genome-based nutrition strategies for preventing diet-related chronic diseases: where genes, diet, and food culture meet

Introduction

Weight gain is often the initial trigger for metabolic abnormalities and chronic diseases such as obesity, type 2 diabetes, cardiovascular disease, metabolic-associated steatotic liver disease, and many malignancies worldwide. These emerging diseases have spread across the global population, causing significant morbidity and mortality (1, 2). In the past, it was common to attribute the etiology of these disorders to "genetics" or label them as "multifactorial" when a definitive explanation was lacking. However, since the first human genome blueprint was released nearly 25 years ago, it has been a pivotal moment, signaling the transition from the pre-genomic to the genomic and post-genomic era[1] (3). This transition has led us to the development of the multi-omic sciences, an interdisciplinary field that provides a comprehensive and holistic understanding of gene structure, gene expression mechanisms, and how environmental interactions affect them (4–6). It is now clear that attributing most prevalent chronic diseases solely to genetics or the environment is no longer accurate (7). The interaction of these factors plays a significant role in maintaining our health or leading to disease, and they can be identified more precisely (8).

Almost 20 years ago, we recognized physical activity, emotions, and diet as the key lifestyle factors influencing our genes (9, 10). However, we also acknowledged the genetic heterogeneity that any region or population would exhibit due to local adaptation.

1 The Human Genome Project. Available online at: https://www.genome.gov/human-genome-project (accessed May 28, 2024).

Thus, regional studies are critical, focusing on the prevalence of such adaptive genes and assessing the influence of lifestyle changes at the population level (11, 12). Despite global modifications in lifestyle conditions, the human genome remains tailored to past environments. This leads to a key concept in the era of personalized medicine and nutrition- the gene-environmental mismatch (13). This mismatch underlines the importance of tailoring preventive strategies depending on the target population's genetic composition and environmental context rather than relying on general health guidelines to regain health.

A new era of genome-based nutrition strategies

This Research Topic on "*Genome-based nutrition strategies for preventing diet-related chronic diseases*" aimed to provide readers with a compilation of studies on the role of the genetic background of individuals and populations in diseases such as obesity and associated comorbidities as well as on prevention and intervention strategies that rely on evidence of the gene-environment mismatch or imbalance that contributes to the development of these diseases, to promote the consumption of genetically and culturally respectful and sustainable diets.

Roman et al.'s perspective on the end of the one-diet-fits-all paradigm underlines the necessity for personalized nutrition strategies based on the target population's genetic profile, regional foods, and food culture. Mexico, a country with admixed ancestry, heterogenic diet-related risk alleles, and a negative nutrition transition, is affected by the one-diet-fits-all regimen. It also discusses how the Genomex diet, a nutrigenetic strategy, can prevent and correct metabolic abnormalities among the population.

However, how can we start using a Personalized Nutrition approach to prevent chronic diseases? Panduro et al. suggest that understanding the impact of genes and the environment at the level of each geographical region is the first step toward developing prevention measures tailored to each population and individual. In their review, the authors define key factors that should be considered to prevent and treat the main chronic diseases, particularly liver diseases, through a Personalized Medicine and Nutrition (PerMed-Nut) model. In addition, they stress the need for training medical students and professionals in genomics education to guarantee the successful implementation of such strategies.

Genetic backgrounds and environmental contexts can affect major chronic metabolic disease predispositions and frequency patterns and must be considered in personalized and regionalized nutritional approaches. In their mini-review, Zambrano et al. discuss the connection between nutrition and genetic variants that cause hypertension and how these interactions affect groups differently in regions of Latin America. In contrast, Ojeda-Granados et al. discuss the epidemiology of cardiovascular diseases, particularly in Italy, where they are the leading cause of death, and the genetic, lifestyle/behavioral, and metabolic factors that increase risk.

Following this path, Nacis et al. confirm that to achieve the goals of a Precision Nutrition approach, gene-based nutrition, and lifestyle recommendations need to be integrated into clinical practice to address metabolic variability between individuals. Therefore, the authors present their MyGeneMyDiet® study protocol, which aims to evaluate the efficacy of providing nutrition and lifestyle recommendations based on individual genotypes of single nucleotide polymorphisms influencing body weight, calorie, and fat intake in weight management among adults.

Mera-Charria et al. examined the connection of numerous obesity-related gene polymorphisms with body mass index and weight loss therapy response in a multiethnic cohort to understand obesity and prevent its comorbidities. The authors' work shed light on hereditary factors affecting weight and weight loss treatment responsiveness. Rivera-Iñiguez et al. examined the link between gene polymorphisms regulating energy balance and food reward and appetitive traits in young Mexican subjects, particularly with disordered eating patterns and obesity. They found that genetic variables may increase hedonic food consumption and decrease satiety regulation, causing weight gain. The authors present more evidence for individualized nutrigenetic techniques to combat disordered eating.

To add evidence on how particular dietary patterns contribute to obesity and metabolic complications, Zhang et al. employed 16S rRNA sequencing and untargeted metabolomic analysis in a rat model to examine how a high-fat diet affects gut microbiota and metabolism to demonstrate how certain diets cause obesity and metabolic issues. Long-term high-fat diet consumption in rats caused dyslipidemia, intestinal bacteria changes, and plasma metabolism changes.

Traditional diets rich in fruit, vegetables, grains, and essential fatty acids improve chronic inflammatory profiles, which are prominent in diet-related chronic illnesses. Therefore, in the last study of our Research Topic, Díez-Sainz et al. explored the impact of vegetable-rich diets on inflammation and the identification of bioactive molecules and their mechanisms of action. They focused on the modulation of human pro-inflammatory genes by edible plant-derived microRNAs. Their findings revealed that particular microRNAs can promote an anti-inflammatory gene expression profile in human macrophages *in vitro* and that diet may increase bioavailability but eventually limit it at the intestine level.

Final considerations

The contributions in this Research Topic are evidence of the myriad of combined multi-omic sciences approaches and qualitative methodologies needed to provide personalized medicine or nutrition strategies based on the specific genetic and cultural aspects of health. Future studies worldwide will continue to provide regionalized data that can guide the implementation of such strategies. It will also require genomic education and training of past and future generations of scholars in the healthcare field to interpret genomic data and apply preventive measures to avoid chronic diseases among the target populations.

Author contributions

AP: Writing – review & editing, Writing – original draft, Conceptualization. CO-G: Writing – review & editing, Writing – original draft. OR-L: Writing – review & editing. SR: Writing – review & editing, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank the authors of the papers published in this Research Topic for their valuable contributions and the reviewers who shared time and expertise for their rigorous review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. World Health Organization. *World Health Statistics*. (2023). Available online at: https://www.who.int/data/gho/publications/world-health-statistics (accessed May 28, 2024).

2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Lond Engl.* (2020) 396:1204–22. 10.1016/S0140-6736(20)30925-9]10.1016/S0140-6736(20)30925-9

3. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. *Science.* (2001) 291:1304–51. doi: 10.1126/science.1058040

4. Krassowski M, Das V, Sahu SK, Misra BB. State of the field in multi-omics research: from computational needs to data mining and sharing. *Front Genet.* (2020) 11:610798. doi: 10.3389/fgene.2020.610798

5. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. *Genome Biol.* (2017) 18:83. doi: 10.1186/s13059-017-1215-1

6. Ramos-Lopez O, Martinez JA, Milagro FI. Holistic integration of omics tools for precision nutrition in health and disease. *Nutrients.* (2022) 14:4074. doi: 10.3390/nu14194074

7. Rappaport SM. Genetic factors are not the major causes of chronic diseases. *PLoS ONE.* (2016) 11:e0154387. doi: 10.1371/journal.pone.0154387

8. Ding E, Wang Y, Liu J, Tang S, Shi X. A review on the application of the exposome paradigm to unveil the environmental determinants of age-related diseases. *Hum Genomics.* (2022) 16:54. doi: 10.1186/s40246-022-00428-6

9. Panduro A, Vazquez-Castellanos JL. Genes y medio ambiente. *Investig En Salud.* (2001) lll:41–8. Available online at: https://www.redalyc.org/articulo.oa?id=14239907

10. Panduro Cerda A. *Biologia Molecular en la Clinica. 1st Edn.* Mexico City: McGraw-Hill Interamericana (2000).

11. Panduro A, Roman S. Personalized medicine in Latin America. *Pers Med.* (2020) 17:339–43. doi: 10.2217/pme-2020-0049

12. Roman S, Ojeda-Granados C, Ramos-Lopez O, Panduro A. Genome-based nutrition: an intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis. *World J Gastroenterol.* (2015) 21:3449–61. doi: 10.3748/wjg.v21.i12.3449

13. Lea AJ, Clark AG, Dahl AW, Devinsky O, Garcia AR, Golden CD, et al. Applying an evolutionary mismatch framework to understand disease susceptibility. *PLoS Biol.* (2023) 21:e3002311. doi: 10.1371/journal.pbio.3002311

frontiers | Frontiers in Nutrition

TYPE Methods
PUBLISHED 22 August 2023
DOI 10.3389/fnut.2023.1238234

OPEN ACCESS

EDITED BY
Moul Dey,
South Dakota State University, United States

REVIEWED BY
Sailendra Nichenametla,
Orentreich Foundation for the Advancement of Science, United States
Lacey McCormack,
Avera Research Institute Center for Pediatric and Community Research, United States

*CORRESPONDENCE
Jacus S. Nacis
✉ jacusnacis@gmail.com;
✉ jacus1.nacis@wur.nl

RECEIVED 11 June 2023
ACCEPTED 09 August 2023
PUBLISHED 22 August 2023

CITATION
Nacis JS, Labrador JPH, Ronquillo DGD, Rodriguez MP, Dablo AMFD, Frane RD, Madrid ML, Santos NLC, Carrillo JJV, Fernandez MG and Gonzales GBL (2023) A study protocol for a pilot randomized controlled trial to evaluate the effectiveness of a gene-based nutrition and lifestyle recommendation for weight management among adults: the MyGeneMyDiet® study. *Front. Nutr.* 10:1238234.
doi: 10.3389/fnut.2023.1238234

A study protocol for a pilot randomized controlled trial to evaluate the effectiveness of a gene-based nutrition and lifestyle recommendation for weight management among adults: the MyGeneMyDiet® study

Jacus S. Nacis[1,2]*, Jason Paolo H. Labrador[1], Diana Glades D. Ronquillo[1], Marietta P. Rodriguez[1], Aurora Maria Francesca D. Dablo[1], Ruby D. Frane[1], Marilou L. Madrid[1], Noelle Lyn C. Santos[1], Julianne Janine V. Carrillo[1], Mikko Glen Fernandez[1] and Gerard Bryan L. Gonzales[2,3]

[1]Department of Science and Technology – Food and Nutrition Research Institute (DOST-FNRI), Taguig, Philippines, [2]Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, Netherlands, [3]Department of Public Health and Primary Care, Faculty of Medicine and Health Science, Ghent University, Ghent, Belgium

Introduction: Managing nutrition and lifestyle practices, nutrition phenotypes, and the genome forms the foundation of precision nutrition. Precision nutrition focuses on metabolic variability among individuals, and one approach to achieving its goals is to integrate gene-based nutrition and lifestyle recommendations in nutrition practice. However, scientific evidence proving the effectiveness of such recommendations is limited. This study will examine whether providing nutrition and lifestyle recommendations based on individual genotype can lead to better weight loss, along with reduction in body mass index (BMI), waist circumference, and body fat percentage among overweight and obese adults.

Methods and analysis: A parallel group, single-blind, randomized controlled trial will be conducted. Sixty-two overweight/obese individuals aged 19–59 years old will be recruited. Participants will be randomly allocated to either the intervention ($n = 31$) or the control arm ($n = 31$). Participants in the intervention group will receive the MyGeneMyDiet® Recommendation for Weight Management, a gene-based nutrition and lifestyle recommendation that was developed based on existing evidence of the effects of *FTO* rs9939609 on body weight, BMI, and physical activity; *UCP1* rs1800592 on calorie intake; and *TCF7L2* rs7903146 on dietary fat intake. Participants in the control group will receive the standard recommendations for weight management. The primary outcomes will be the differences in weight, BMI, waist circumference, and body fat percentage between arms in both the active phase (6 months) and inactive phase (last 6 months) of the trial. Participants in both arms will be evaluated at baseline and in months 3, 6, 9, and 12.

Discussion: To the best of our knowledge, this will be the first gene-based intervention that will adopt a phase of intensive nutrition counseling, followed by a simulation of a free-living state to determine adherence to a gene-based recommendation. This study will contribute to the future implementation of precision nutrition interventions by providing evidence on the effectiveness of a gene-based nutrition and lifestyle recommendation for weight loss.

Clinical trial registration: clinicaltrials.gov, identifier [NCT05098899].

KEYWORDS

genotype, lifestyle genomics, nutrigenomics, nutritional genomics, obesity, overweight

1. Introduction

Genetics is one of the factors that influence the variability of responses to weight-loss interventions (1). Certain genetic polymorphisms are believed to affect an individual's tendency toward obesity and other-related aspects such as appetite control and energy balance (2–4). For instance, the risk allele of *FTO* rs9939609 closely relates to obesity and other related phenotypes in various populations (5–9). Earlier studies have observed the influence of physical activity in this genetic variant, as demonstrated by the significantly higher obesity risk among physically inactive carriers of the risk allele (8–10), and the reduction of such risk among the physically active risk allele carriers (9, 11). On the other hand, mutations in the *UCP1* gene contribute to the development of obesity by reducing energy expenditure modulating the thermogenic function on brown adipose tissue (12, 13). The variant rs1800592 (also known as the -382A/G mutation) is associated with resistance to weight loss in response to energy restriction (14). Carriers of the risk allele for this variant demonstrated lesser weight loss from controlled-energy diet regimen (14, 15), even when exercise is an added regimen to the energy-restricted diet (16). Obese women carrying the ht3 [GAG] haplotype showed accelerated reduction of waist-to-hip ratio and body fat mass when a very low-calorie diet (700 kcal/day) was given to them (17). Moreover, it is becoming apparent that obesity mediates the strong association of *TCF7L2* rs7903146 with type 2 diabetes (18). This variant is associated with obesity risk (19), obesity phenotype (20–22), and several obesity comorbidities such as impaired glucose homeostasis and increased lipid and C-reactive protein levels (23). Dietary intake of saturated fat appears to augment the risk of metabolic syndrome (20) as individuals who carry the risk allele of rs7903146 have better responses to weight loss when fed with a low-fat diet (18). High dietary saturated fat intake accentuates the effect of the variant, implying that dietary fatty acid consumption potentially modifies genetic susceptibility toward metabolic syndrome (20).

Earlier studies have shown that dietary advice based on genetic information resulted in specific changes in the intake of sodium and dietary fat (24, 25). However, substantial research showing the effectiveness of gene-based nutrition recommendations for improving weight and obesity-related outcomes are rather limited. Available evidence showed none or modest improvements in weight, lifestyle, and dietary behavior when advice was linked to genetic profiles (24, 26–28) or when genetic risks were disclosed to the participants (24, 25, 29, 30).

To expand the existing knowledge about the effects of gene-based nutrition and lifestyle recommendations, this randomized controlled trial aims to determine if the provision of the MyGeneMyDiet® Recommendation for Weight Management and disclosure of genetic risk can help overweight/obese individuals achieve 5–10% weight loss in a 12-month trial when compared with the standard advice for weight management. Other primary outcomes include reduction in BMI, waist circumference, and body fat percentage.

2. Methods and analysis

2.1. Study design

The MyGeneMyDiet® study is a parallel-group, single-blind, randomized controlled trial (Figure 1). Sixty-two overweight or obese adults will be recruited through waves of study enrollment. The 12-month trial will entail an "active" phase (first 6 months), followed by an "inactive" phase from months 7–12. During months 1–6, all participants will receive three sessions of nutrition counseling, including general health and information presented in nutrition modules designed for the study. A simulation of a "free-living state" will be applied to the participants during months 7–12. During this period, a follow-up data collection on month 9 and the nutrition counseling session at the end of the study on month 12 will be initiated. The inactive phase will determine whether the participants continue to adhere to the dietary and lifestyle recommendations given to them during the active phase.

2.2. Recruitment and informed consent processes

Invitation letters, social media promotions, and snowball sampling will be employed to recruit participants. Social media promotional materials will contain electronic links and contact information of the research team. Orientation sessions will be conducted via videoconferencing platforms such as Zoom webinars. Details of the study protocol and the informed consent form, including an open forum to tackle the rights and privileges of the participants, will be discussed during these sessions. The informed consent form will be emailed to the prospective study participants after the orientation.

10.3389/fnut.2023.1238234

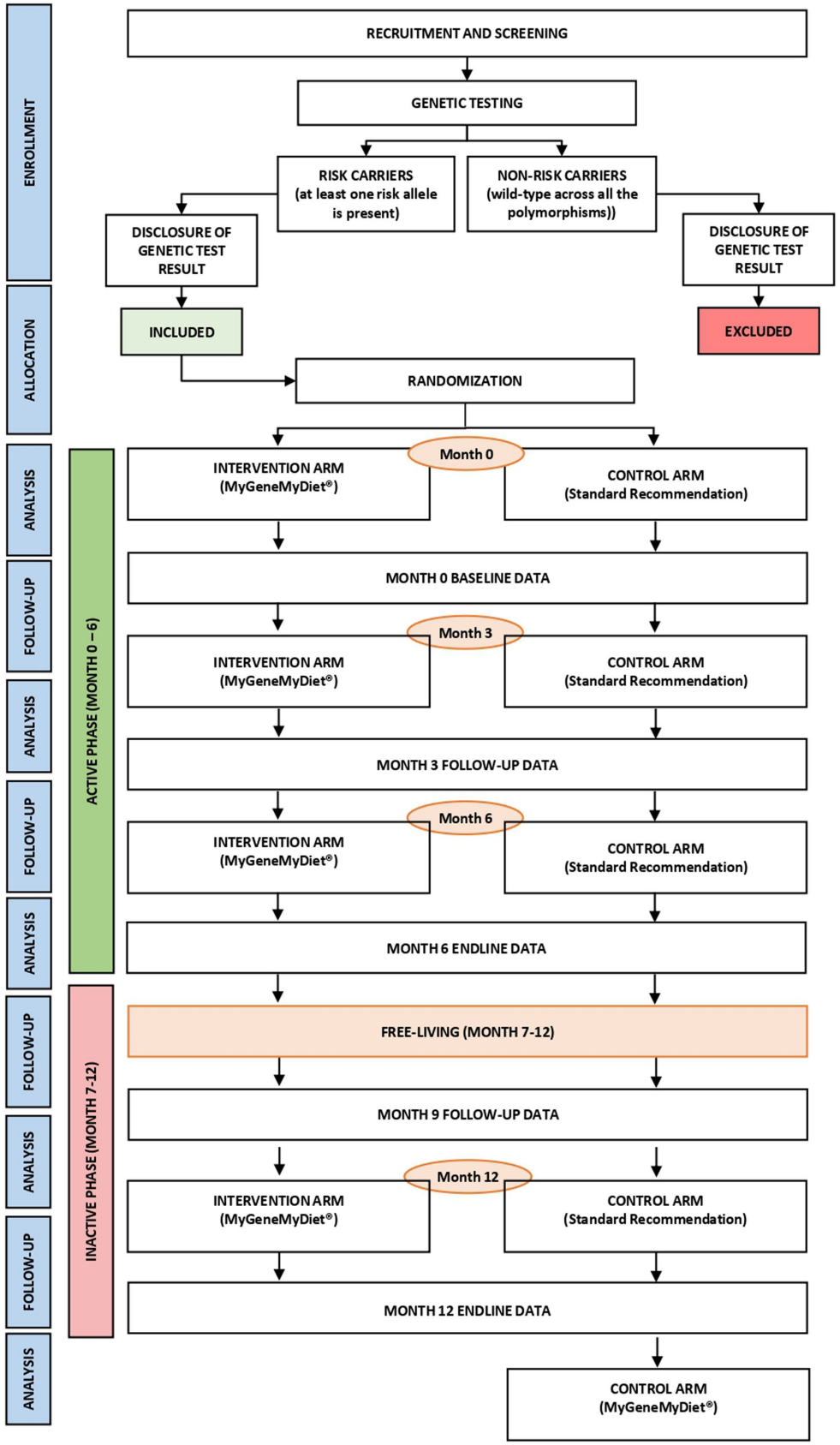


FIGURE 1
The design of the MyGeneMyDiet® Study.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

The trial targets overweight or obese individuals aged between 19 and 59, who indicate willingness to participate in the study. Their BMI should be equal to or greater than 25 but not more than 40 kg/m^2. They should also have normal to pre-disease state level of fasting blood glucose, lipid profile, and blood pressure, and blood cortisol and thyroid hormone levels. They should carry at least one of the risk alleles of the three target genetic polymorphisms: A allele for *FTO* rs9939609, T allele for *TCF7L2* rs7903146, and G allele for *UCP1* rs1800592.

2.3.2. Exclusion criteria

The exclusion criteria are as follows: individuals with elevated levels of fasting blood glucose, lipids, blood pressure, thyroid, and cortisol; self-reported history of heart disease; participation in a weight-loss program; adherence to a restrictive/therapeutic diet in the past 3 months; self-reported weight changes (greater than 3.0 kg); planned or recent bariatric surgery; consumption of weight altering medications and/or nutritional supplements that provide weight gain/loss in the past 6 months; clinical diagnosis of any mental disorder; current use of mental health medications; for females, pregnant, nursing, or with self-declared intention to become pregnant during the trial; and, current and anticipated enrollment in another research study.

The self-declared items in the exclusion criteria will be obtained using a questionnaire that will be provided during the registration to the trial. A licensed physician will be present during the screening visits to determine if a prospective participant is eligible to join the trial.

2.4. Genetic counseling

All participants, regardless of whether they will soon be randomized to either the intervention or control arm, will undergo pre-and post- genetic test counseling sessions. A genetic counselor will meet with the participants for a two-part, interactive, one-on-one virtual counseling. The pre-genetic test counseling will be scheduled a few days after the DNA sample collection and before genotyping of the samples. During this session, the genetic counselor will provide genetic education to the participants, with topics such as basic information about genes, chromosomes, genetic mutations, environmental and genetic interactions, and genetic testing procedures. The genetic counselor will also discuss the impact and potential emotional and psychological concerns that may arise from the result of the genetic test.

The post-genetic test counseling session will be conducted 2 weeks after the pre-test genetic counseling, in time for the release of the genetic testing results of the participants. The genetic counselor will disclose the genotyping results to the participants, along with psychosocial counseling to assist the participants in adapting the new information.

2.5. Sample size calculation

To address the primary research question, at least 52 participants ($n = 26$ per group) are needed to detect a clinically meaningful difference of 5% weight loss after 6 months of intervention, assuming 80% power, an alpha of 5%, and a 0.25 SD in the main outcome variable (31). We aim to recruit 62 participants ($n = 31$ per group) to account for the potential dropout rate of 20%.

2.6. Intervention

2.6.1. Intervention arm

Participants in the intervention arm will receive the MyGeneMyDiet® Recommendations. It is a gene-based nutrition and lifestyle recommendation developed by the research team by incorporating genetic information based on the result of a genetic test into the standard recommendations for weight management. The MyGeneMyDiet® Recommendations are customized diet and lifestyle advice that will be based on the participant's anthropometric data (BMI, waist circumference, body fat percentage), biochemical test results, dietary intake, physical activity level, and genetic risk profile.

Decision trees and coded messages were generated by simulating possible genotypes, anthropometric data, results of clinical tests, dietary intake, and physical activity level (Supplementary Table S1; Supplementary Figures S1–S4). A Scientific Advisory Board consisting of nutrition and dietetic professionals, genetic counselors, and a lifestyle medicine physician guided the team in developing the recommendations. The overview of the weight management recommendations among carriers of the risk alleles for *FTO* rs9939609, *UCP1* rs1800592, and *TCF7L2* rs7903146 is described in Table 1.

Should the participant in the intervention group have more than one genetic polymorphism, all the corresponding MyGeneMyDiet® recommendations (based on the risk alleles they carry) will be given.

The intervention will be delivered by trained and registered nutritionist-dietitians who will meet with the participants during online counseling sessions in months 0, 3, 6, and 12. These sessions will track the compliance with the meal and exercise plan, and to adjust the caloric and weight loss goals of the participants.

2.6.2. Control arm

Participants in the control arm will be provided with the standard recommendations for weight management. For this study, the standard recommendations are based on the Philippines' Nutrition Practice Guidelines (NPG) for the Screening and Management of Obesity, and other population-based recommendations including the 2012 Nutritional Guidelines for Filipinos (37), the *Pinggang Pinoy* (Filipino food plate model) dietary recommendations (38), and the WHO 2020 Guidelines on Physical Activity. Except for the customized recommendation based on alleles for *FTO* rs9939609, *UCP1* rs1800592, and *TCF7L2* rs7903146, the advice for the control arm will be based on the participant's anthropometric data, biochemical test results, dietary intake, and physical activity level.

Participants in the control arm will also receive online nutrition counseling from trained and registered nutritionist-dietitians in months 0 (baseline), 3, 6, and 12. As part of the after-trial care, participants in the control arm will receive the corresponding MyGeneMyDiet® Recommendation for Weight Management after the month 12 visit.

TABLE 1 Overview of the MyGeneMyDiet® recommendations.

Outcomes	Genetic polymorphisms	Standard recommendations (control arm)	MyGeneMyDiet® recommendations (Inervention arm)
Weight, BMI, and physical activity	*FTO* rs9939609	Achieve and maintain a normal BMI 20–40 min of daily moderate-intensity aerobic physical activity (32)	Achieve and maintain a normal BMI. 30–60 min of daily moderate-intensity aerobic physical (33)
Calorie requirement	*UCP1* rs1800592	Follow the recommended daily caloric intake based on desirable body weight (DBW) and physical activity level (PAL) (34)	Reduce 150 kcal from the recommended daily caloric intake (35)
Dietary fat intake	*TCF7L2* rs7903146	25–30% of the recommended caloric intake from fat (36)	15–20% of the recommended caloric intake from fat (18)

2.7. Outcomes

The primary outcomes will be the difference in weight, BMI, waist circumference, and body fat percentage between the arms after both the active and inactive phases. Secondary outcomes will include improvement in dietary intake, eating behavior, physical activity levels, glycated hemoglobin, and blood lipid profile. In addition, stages and motivation for weight loss and the knowledge and perceptions in nutrigenomics and genetic testing will be evaluated.

2.8. Randomization and allocation

All participants will be stratified by BMI using the World Health Organization (WHO) cutoff. Overweight (BMI of 25–30 kg/m^2) and obese (BMI of >30 kg/m^2) adults will be randomly distributed into blocks of 4, 6, and 8. Within these blocks, each participant will be randomly allocated to the intervention group (MyGeneMyDiet®) or control (standard weight management recommendation) using a Random Allocation Software.[1] Two research staff will perform the randomization.

During randomization, 62 identical (31 for each treatment) sequentially numbered, opaque sealed envelopes (SNOSE) will be prepared. The sequential numbering will be synchronized with the online registration and will be used to designate participant study numbers. The randomization allocation will be concealed from the participants and the rest of the researchers involved in the month 0 visit.

2.9. Data collection methods

Study outcomes will be assessed at five time points: baseline (month 0), and months 3, 6, 9, and 12. Table 2 provides an overview of data collection and outcome measures.

The research team will conduct the screening and subsequent data collection sessions at the Food and Nutrition Research Institute, Taguig City, Philippines. Pre-session visits will be conducted 2 weeks before the online nutrition counseling sessions.

2.9.1. Anthropometric measurements

Body weight and body fat percentage will be determined using a body composition analyzer (Tanita-MC78U, Tanita Corporation, Japan). Height will be measured using a stadiometer (Seca 217, Seca, Germany) while waist and hip circumference will be obtained using a non-stretchable tape measure (Seca 203, Seca, Germany). Anthropometric measurements will be done twice following a standard procedure. A third measurement will be taken if the difference between the two measurements is greater than 0.3 kg for weight, 0.5 cm for height, and 0.5 cm for waist circumference. The average of all the readings will be taken as the final estimated value of the measurement. BMI will be derived by dividing the weight in kilograms by height in meters squared. The percent body fat (BF%) will be assessed according to the chart by Gallagher et al. (39).

2.9.2. Dietary intake

On a monthly basis, participants will be asked to complete a three-day food diary to estimate their mean energy and macronutrient intake while enrolled in the trial. The food record will consist of two non-consecutive weekdays and one weekend. In total, the participants will accomplish 12 sets of food diaries during the trial.

Proper recording of food and beverage intake and estimating food portion sizes will be explained to the participants during the orientation session. The food diary must reflect all the food and beverages consumed by the participants within the specified periods, the description of each food items (type, variety, brand name), amounts, the time of the day the meal is taken, cooking method (e.g., boiled, fried, broiled), and the source of the food (e.g., home-cooked or takeaway). A food diary form (printed or in electronic form, depending on the participant's preference) will be distributed during the pre-session visits or approximately 2 weeks before the online follow-up sessions.

Checking and verification to ensure the completeness and correctness of the recorded intake will be done by the nutritionists of the research team, 2 weeks before the online nutrition counseling session. This will provide sufficient time for the nutritionists to analyze the dietary intake of the participants. Energy and macronutrients will be computed using the Philippine Food Composition Tables (FCT).

1 https://www.random-allocation-software.software.informer.com/2.0/

TABLE 2 MyGeneMyDiet® study data collection and outcome measures.

Outcome measures	Active phase			Inactive phase	
	Baseline (Month 0)	Month 3	Month 6	Month 9	Month 12
Demographic information	X				
Anthropometry (weight, BMI, waist circumference, hip circumference, percent body fat)	X	X	X	X	X
Dietary intake (3-day food record)*	X	X	X	X	X
Blood chemistry analysis (glycated hemoglobin, lipid profile)	X	X	X	X	X
Physical activity level (IPAQ-SF)	X	X	X	X	X
Eating behavior (TFEQ R-18)	X	X	X	X	X
Motivation for weight loss (SP-Weight Loss)	X	X	X	X	X
Knowledge and perception of nutrigenomics	X		X		X

*Monthly 3-day food records are also collected from the participants, in addition to the food records collected on months 0, 3, 6, 9, and 12.

Other foreign FCTs will be used for the items not found in the local FCT.

2.9.3. Biochemical data

Blood samples will be collected during the specified time points (months 0, 3, 6, 9, and 12). The participants will be asked to undergo 10–12 h of fasting before specimen collection. A phlebotomist will collect approximately 5 mL of blood for the analysis of glycated hemoglobin and lipid profile.

2.9.4. Physical activity

The International Physical Activity Questionnaire – Short Form (IPAQ-SF) will be used to measure the level of physical activity of the participants. The short version has seven questions to assess the type and intensity of physical activity that individuals do as part of their daily lives and to estimate the total physical activity in metabolic equivalent (ME).

2.9.5. Eating behavior

The Three-Factor Eating Behavior Questionnaire (TFEQ-R18) (40) will evaluate the eating behavior of the participants. The questionnaire will capture the current dietary practices and aspects of eating behavior such as cognitive restraint eating (conscious restriction of food intake), uncontrolled eating (tendency to eat more than usual due to loss of control over intake accompanied by subjective feeling of hunger), and emotional eating (inability to resist emotional cues).

2.9.6. Level of motivation to change

The Stages (S-Weight) and Process (P-Weight) of Change for Weight Loss Questionnaire will be used to assess the participants' motivation to lose weight. The S-Weight consists of five mutually exclusive items that will allocate the participants to one of the five stages of change: pre-contemplation, contemplation, preparation, action, and maintenance (41, 42). The P-Weight is a 34-item questionnaire that measures the four processes of change: emotional re-evaluation, weight management actions, environmental restructuring, and weight consequences evaluation (41–44).

2.9.7. Knowledge and perceptions on genetic testing and nutrigenomics

Participants will be asked to complete a survey designed to assess awareness, perceptions, and self-efficacy toward genetic testing and nutrigenomics. Written permission from the main author of the questionnaire (45) was sought before using it for this study.

2.10. Statistical analysis plan

Outcome data will be reported following the Consolidated Standard Reporting Trials (CONSORT) guidelines (46). An intention-to-treat analysis will be employed.

The mean and standard deviation (SD) will be used to report continuous variables while percentages will be used for categorical variables. Estimates of the different sources of attrition bias will be conducted using two-way analysis of variance (ANOVA) models. Student *t*-test will be used to compare the differences in means between the intervention and the control group for the primary and secondary outcome measures. One-way ANOVA will be used if the comparison of multiple subclasses is warranted, with Dunn's multiple comparisons *post-hoc* test. Linear mixed models will be used to

determine changes from baseline among the different study outcomes, with participant number retained as random effect. A two-sided alpha of 0.05 will be used for hypothesis testing.

2.11. Monitoring

Adverse events and withdrawals will be monitored by the research team. Any adverse events and deviations will be reported to the FNRI Institutional Ethics Review Committee and included in the continuing ethics review of the trial.

3. Discussion

This trial aims to provide evidence to support a strategy of gene-based nutrition lifestyle intervention to manage weight loss. It will incorporate disclosure of genetic risk and recommendations based on the genetic profile of the participants.

To the best of our knowledge, this will be the first gene-based nutrition and lifestyle intervention that will adopt an intensive gene-based nutrition counseling, followed by an "inactive" period of 6 months where a "free-living" state is simulated. Along with the goals of evaluating the effectiveness of gene-based nutrition and lifestyle advice, this trial will also raise the awareness of the Filipino population regarding nutritional genomics. It acknowledges the vital role of genetic counselors in guiding the population in making informed choices upon learning their genetic risks, particularly so that all participants are carriers of at least one (or a combination) of the risk alleles for *FTO* rs9939609, *UCP1* rs1800592, and *TCF7L2* rs7903146. This trial will play an important role in leveraging a unique multidisciplinary approach to weight management that involves nutrition professionals and genetic experts.

Limitations of the study include (1) limited applicability of the findings to other populations since the trial will be conducted among overweight/obese Filipino adults only; (2) the recommendations are based only on three genetic polymorphisms, and it is likely that there are other genetic loci that may pose risks to unhealthy weight gain that will not be tackled in this study, and; (3) the intervention will only entail counseling/education and no standardized meals will be given.

4. Ethics and dissemination

4.1. Research ethics approval

This protocol was approved by the Food and Nutrition Research Institute (FNRI) Institutional Ethics Review Committee (FIERC-2021-001). In case protocol amendments are required, approval from the FIERC will be obtained before applying any changes. The current version of the protocol is version 7 (dated 2022-04-18).

4.2. Confidentiality

Substitute codes will be used to protect the identity of participants. A designated secured cabinet and password-protected central database will be used to store the trial documents. All recorded video conversations on Zoom will be downloaded immediately after each session and will be deleted from the Cloud once the recording is assured to have been saved in a password-protected external drive. Only the research team members who performed the randomization and allocation have access to the data collection and storage devices.

4.3. Dissemination policy

The research findings will be submitted to and published in peer-reviewed journals.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the FNRI Institutional Ethics Review Committee (FIERC-2021-001). The participants provided their written informed consent to participate in this study.

Author contributions

JN wrote the manuscript and the primary investigator of this study. JN, JL, and DR designed the trial. JN and MR provide overall administrative support to the study. JN, MR, GG, and DR spearhead the clinical and genomic aspects of the trial. RF, MM, NS, and JL spearhead the nutrition and dietary components of the study. AD, RF, MM, NS, JC, and MF contributed to the development of the trial protocol. All authors will be involved in the collection of data. All authors contributed to the critical review of this manuscript for intellectual content and approved the submitted version. All authors substantially revised, read, and approved the final manuscript.

Funding

The MyGeneMyDiet® trial is part of the Interventions using Genomics-based Strategies (InGeSt) Research Program of the Department of Science and Technology – Food and Nutrition Research Institute funded through the Locally Funded Project (LFP) of the Philippines' Department of Budget and Management (DBM).

Acknowledgments

The authors thank the Scientific Advisory Board of the MyGeneMyDiet® Recommendations: Celeste C. Tanchoco, Liezl M. Atienza, Ma-am Joy R. Tumulak, Zenaida F. Velasco, Peter James

B. Abad, Jan Paolo P. Dipasupil, and Hon. Virgith B. Buena. Likewise, the authors would like to acknowledge the support of Fränzel van Duijnhoven of Wageningen University & Research, Imelda Angeles-Agdeppa, Mario V. Capanzana, Rosemarie G. Garcia, Michael E. Serafico, and Robby Carlo A. Tan of DOST-FNRI for the administrative and technical guidance to the trial.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1238234/full#supplementary-material

References

1. Lamiquiz-Moneo I, Mateo-Gallego R, Bea AM, Dehesa-García B, Pérez-Calahorra S, Marco-Benedí V, et al. Genetic predictors of weight loss in overweight and obese subjects. *Sci Rep*. (2019) 9:10770. doi: 10.1038/s41598-019-47283-5

2. Schlauch KA, Read RW, Lombardi VC, Elhanan G, Metcalf WJ, Slonim AD, et al. A comprehensive genome-wide and phenome-wide examination of BMI and obesity in a northern Nevadan cohort. *G3 (Bethesda)*. (2020) 10:645–64. doi: 10.1534/g3.119.400910

3. Jiang L, Penney KL, Giovannucci E, Kraft P, Wilson KM. A genome-wide association study of energy intake and expenditure. *PLoS One*. (2018) 13:e0201555. doi: 10.1371/journal.pone.0201555

4. Dougkas A, Yaqoob P, Givens DI, Reynolds CK, Minihane AM. The impact of obesity-related SNP on appetite and energy intake. *Br J Nutr*. (2013) 110:1151–6. doi: 10.1017/s0007114513000147

5. Tan JT, Dorajoo R, Seielstad M, Sim XL, Ong RT, Chia KS, et al. FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. *Diabetes*. (2008) 57:2851–7. doi: 10.2337/db08-0214

6. Mehrdad M, Fardaei M, Fararouei M, Eftekhari MH. The association between FTO rs9939609 gene polymorphism and anthropometric indices in adults. *J Physiol Anthropol*. (2020) 39:14. doi: 10.1186/s40101-020-00224-y

7. da Fonseca ACP, Abreu GM, Zembrzuski VM, Campos Junior M, Carneiro JRI, Nogueira Neto JF, et al. The association of the fat mass and obesity-associated gene (FTO) rs9939609 polymorphism and the severe obesity in a Brazilian population. *Diabetes Metab Syndr Obes*. (2019) 12:667–84. doi: 10.2147/dmso.S199542

8. Cho HW, Jin HS, Eom YB. The interaction between FTO rs9939609 and physical activity is associated with a 2-fold reduction in the risk of obesity in Korean population. *Am J Hum Biol*. (2021) 33:e23489. doi: 10.1002/ajhb.23489

9. Chermon D, Birk R. FTO common obesity SNPs interact with actionable environmental factors: physical activity, sugar-sweetened beverages and wine consumption. *Nutrients*. (2022) 14:4202. doi: 10.3390/nu14194202

10. Rana S, Nawaz H. Interactive effects of FTO rs9939609 and obesogenic behavioral factors on adiposity-related anthropometric and metabolic phenotypes. *Nucleosides Nucleotides Nucleic Acids*. (2023) 42:637–56. doi: 10.1080/15257770.2023.2182886

11. Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. (2011) 8:e1001116. doi: 10.1371/journal.pmed.1001116

12. Chathoth S, Ismail MH, Vatte C, Cyrus C, Al Ali Z, Ahmed KA, et al. Association of Uncoupling Protein 1 (UCP1) gene polymorphism with obesity: a case-control study. *BMC Med Genet*. (2018) 19:203. doi: 10.1186/s12881-018-0715-5

13. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev*. (2004) 84:277–359. doi: 10.1152/physrev.00015.2003

14. Nagai N, Sakane N, Kotani K, Hamada T, Tsuzaki K, Moritani T. Uncoupling protein 1 gene −3826 a/G polymorphism is associated with weight loss on a short-term, controlled-energy diet in young women. *Nutr Res (New York, NY)*. (2011) 31:255–61. doi: 10.1016/j.nutres.2011.03.010

15. Fumeron F, Durack-Bown I, Betoulle D, Cassard-Doulcier AM, Tuzet S, Bouillaud F, et al. Polymorphisms of uncoupling protein (UCP) and beta 3 adrenoreceptor genes in obese people submitted to a low calorie diet. *Int J Obes Relat Metab Disord*. (1996) 20:1051–4.

16. Kogure A, Yoshida T, Sakane N, Umekawa T, Takakura Y, Kondo M. Synergic effect of polymorphisms in uncoupling protein 1 and beta3-adrenergic receptor genes on weight loss in obese Japanese. *Diabetologia*. (1998) 41:1399. doi: 10.1007/s001250051084

17. Fogelholm M, Valve R, Kukkonen-Harjula K, Nenonen A, Hakkarainen V, Laakso M, et al. Additive effects of the mutations in the beta3-adrenergic receptor and uncoupling protein-1 genes on weight loss and weight maintenance in Finnish women. *J Clin Endocrinol Metab*. (1998) 83:4246–50. doi: 10.1210/jcem.83.12.5339

18. Grau K, Cauchi S, Holst C, Astrup A, Martinez JA, Saris WH, et al. TCF7L2 rs7903146-macronutrient interaction in obese individuals' responses to a 10-wk randomized hypoenergetic diet. *Am J Clin Nutr*. (2010) 91:472–9. doi: 10.3945/ajcn.2009.27947

19. Bride L, Naslavsky M, Lopes Yamamoto G, Scliar M, Pimassoni LH, Sossai Aguiar P, et al. TCF7L2 rs7903146 polymorphism association with diabetes and obesity in an elderly cohort from Brazil. *PeerJ*. (2021) 9:e11349. doi: 10.7717/peerj.11349

20. Phillips CM, Goumidi L, Bertrais S, Field MR, McManus R, Hercberg S, et al. Dietary saturated fat, gender and genetic variation at the TCF7L2 locus predict the development of metabolic syndrome. *J Nutr Biochem*. (2012) 23:239–44. doi: 10.1016/j.jnutbio.2010.11.020

21. Muller YL, Hanson RL, Piaggi P, Chen P, Wiessner G, Okani C, et al. Assessing the role of 98 established loci for BMI in American Indians. *Obesity (Silver Spring)*. (2019) 27:845–54. doi: 10.1002/oby.22433

22. Al-Daghri NM, Alkharfy KM, Al-Attas OS, Krishnaswamy S, Mohammed AK, Albagha OM, et al. Association between type 2 diabetes mellitus-related SNP variants and obesity traits in a Saudi population. *Mol Biol Rep*. (2014) 41:1731–40. doi: 10.1007/s11033-014-3022-z

23. Abadi A, Alyass A, Robiou du Pont S, Bolker B, Singh P, Mohan V, et al. Penetrance of polygenic obesity susceptibility loci across the body mass index distribution. *Am J Hum Genet*. (2017) 101:925–38. doi: 10.1016/j.ajhg.2017.10.007

24. Nielsen DE, El-Sohemy A. Disclosure of genetic information and change in dietary intake: a randomized controlled trial. *PLoS One*. (2014) 9:e112665. doi: 10.1371/journal.pone.0112665

25. Horne J, Gilliland J, O'Connor C, Seabrook J, Madill J. Enhanced long-term dietary change and adherence in a nutrigenomics-guided lifestyle intervention compared to a population-based (GLB/DPP) lifestyle intervention for weight management: results from the NOW randomised controlled trial. *BMJ Nutr Prev Health*. (2020) 3:49–59. doi: 10.1136/bmjnph-2020-000073

26. Coletta AM, Sanchez B, O'Connor A, Dalton R, Springer S, Koozehchian MS, et al. Alignment of diet prescription to genotype does not promote greater weight loss success in women with obesity participating in an exercise and weight loss program. *Obes Sci Pract*. (2018) 4:554–74. doi: 10.1002/osp4.305

27. Doets EL, de Hoogh IM, Holthuysen N, Wopereis S, Verain MCD, van den Puttelaar J, et al. Beneficial effect of personalized lifestyle advice compared to generic advice on wellbeing among Dutch seniors - an explorative study. *Physiol Behav*. (2019) 210:112642. doi: 10.1016/j.physbeh.2019.112642

28. Celis-Morales C, Marsaux CF, Livingstone KM, Navas-Carretero S, San-Cristobal R, Fallaize R, et al. Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial. *Am J Clin Nutr*. (2017) 105:1204–13. doi: 10.3945/ajcn.116.145680

29. Marsaux CF, Celis-Morales C, Livingstone KM, Fallaize R, Kolossa S, Hallmann J, et al. Changes in physical activity following a genetic-based internet-delivered personalized intervention: randomized controlled trial (Food4Me). *J Med Internet Res*. (2016) 18:e30. doi: 10.2196/jmir.5198

30. O'Donovan CB, Walsh MC, Forster H, Woolhead C, Celis-Morales C, Fallaize R, et al. The impact of MTHFR 677C→T risk knowledge on changes in folate intake: findings from the Food4Me study. *Genes Nutr*. (2016) 11:25. doi: 10.1186/s12263-016-0539-x

31. Frankwich KA, Egnatios J, Kenyon ML, Rutledge TR, Liao PS, Gupta S, et al. Differences in weight loss between persons on standard balanced vs Nutrigenetic diets in a randomized controlled trial. *Clin Gastroenterol Hepatol*. (2015) 13:1625–32.e1. doi: 10.1016/j.cgh.2015.02.044

32. World Health Organization. *WHO guidelines on physical activity and sedentary behaviour*. Geneva: World Health Organization (2020).

33. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes*. (2008) 57:95–101. doi: 10.2337/db07-0910

34. Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI). *Food exchange lists for meal planning. 4th* ed. Taguig City: Food and Nutrition Research Institute (DOST-FNRI) (2019).

35. Nagai N, Sakane N, Tsuzaki K, Moritani T. UCP1 genetic polymorphism (−3826 a/G) diminishes resting energy expenditure and thermoregulatory sympathetic nervous system activity in young females. *Int J Obes*. (2011) 35:1050–5. doi: 10.1038/ijo.2010.261

36. Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI). *Philippine dietary reference intakes*. Taguig City: Food and Nutrition Research Institute (DOST-FNRI) (2015).

37. Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI). *Nutritional Guidelines for Filipinos, Revised 2012*. Taguig City: (2015).

38. Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI). *Pinggang Pinoy: A healthy plate for a well-nourished nation*. Taguig City: Guide for Nutrition Professionals (2016).

39. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr*. (2000) 72:694–701. doi: 10.1093/ajcn/72.3.694

40. de Lauzon B, Romon M, Deschamps V, Lafay L, Borys JM, Karlsson J, et al. The three-factor eating questionnaire-R18 is able to distinguish among different eating patterns in a general population. *J Nutr*. (2004) 134:2372–80. doi: 10.1093/jn/134.9.2372

41. Andrés A, Saldaña C, Gómez-Benito J. Establishing the stages and processes of change for weight loss by consensus of experts. *Obesity (Silver Spring)*. (2009) 17:1717–23. doi: 10.1038/oby.2009.100

42. Andrés A, Saldaña C, Gómez-Benito J. The transtheoretical model in weight management: validation of the processes of change questionnaire. *Obes Facts*. (2011) 4:433–42. doi: 10.1159/000335135

43. Andrés A, Saldaña C, Beeken RJ. Assessment of processes of change for weight management in a UK sample. *Obes Facts*. (2015) 8:43–53. doi: 10.1159/000373900

44. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. *Am J Psychol*. (1992) 47:1102–14. doi: 10.1037//0003-066x.47.9.1102

45. Nielsen DE, El-Sohemy A. A randomized trial of genetic information for personalized nutrition. *Genes Nutr*. (2012) 7:559–66. doi: 10.1007/s12263-012-0290-x

46. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. (2010) 340:c332. doi: 10.1136/bmj.c332

frontiers | Frontiers in Nutrition

TYPE Mini Review
PUBLISHED 26 October 2023
DOI 10.3389/fnut.2023.1241017

OPEN ACCESS

EDITED BY
Claudia Ojeda-Granados,
University of Catania, Italy

REVIEWED BY
Jose Geraldo Mill,
Federal University of Espirito Santo, Brazil

*CORRESPONDENCE
Ana Karina Zambrano
anazambrano17@hotmail.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 June 2023
ACCEPTED 12 October 2023
PUBLISHED 26 October 2023

CITATION
Zambrano AK, Cadena-Ullauri S, Guevara-Ramírez P, Ruiz-Pozo VA, Tamayo-Trujillo R, Paz-Cruz E, Ibarra-Rodríguez AA and Doménech N (2023) Genetic diet interactions of *ACE*: the increased hypertension predisposition in the Latin American population.
Front. Nutr. 10:1241017.
doi: 10.3389/fnut.2023.1241017

Genetic diet interactions of *ACE*: the increased hypertension predisposition in the Latin American population

Ana Karina Zambrano[1*†], Santiago Cadena-Ullauri[1†], Patricia Guevara-Ramírez[1], Viviana A. Ruiz-Pozo[1], Rafael Tamayo-Trujillo[1], Elius Paz-Cruz[1], Adriana Alexandra Ibarra-Rodríguez[2] and Nieves Doménech[3]

[1]Centro de Investigación Genética y Genómica, Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE, Quito, Ecuador, [2]Grupo de investigación identificación genética-IdentiGEN, FCEN, Universidad de Antioquia, Medellin, Colombia, [3]Instituto de Investigación Biomédica de A Coruña (INIBIC)-CIBERCV, Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidad da Coruña (UDC), La Coruña, Spain

Hypertension is one of the primary risk factors associated with cardiovascular diseases (CVDs). It is a condition that affects people worldwide, and its prevalence is increasing due to several factors, such as lack of physical activity, population aging, and unhealthy diets. Notably, this increase has primarily occurred in low and middle-income countries (LMICs). In Latin America, approximately 40% of adults have been diagnosed with hypertension. Moreover, reports have shown that the Latin American genetic composition is highly diverse, and this genetic background can influence various biological processes, including disease predisposition and treatment effectiveness. Research has shown that Western dietary patterns, which include increased consumption of red meat, refined grains, sugar, and ultra-processed food, have spread across the globe, including Latin America, due to globalization processes. Furthermore, a higher than recommended sodium consumption, which has been associated with hypertension, has been identified across different regions, including Asia, Europe, America, Oceania, and Africa. In conclusion, hypertension is a multifactorial disease involving environmental and genetic factors. In Latin America, hypertension prevalence is increasing due to various factors, including age, the adoption of a "Westernized" diet, and potential genetic predisposition factors involving the *ACE* gene. Furthermore, identifying the genetic and molecular mechanisms of the disease, its association with diet, and how they interact is essential for the development of personalized treatments to increase its efficacy and reduce side effects.

KEYWORDS

***ACE*, nutrigenetics, traditional diet, cardiovascular disease, genetic adaptation, polymorphism, Latin America**

Introduction

Hypertension (high blood pressure) is one of the primary risk factors associated with cardiovascular diseases (CVDs). It is defined as blood pressure (BP) of ≥140/90 mmHg (1). The prevalence of hypertension is increasing worldwide due to several factors, including lack of physical activity, population aging, and unhealthy diets, especially those with high

saturated fat and sugar intake and low in fruits, vegetables, and whole grains (2, 3).

Moreover, the increase in hypertension prevalence has primarily occurred in low and middle-income countries (LMICs), whereas high-income countries (HICs) experienced a decrease in hypertension prevalence (3, 4). In Latin America, approximately 40% of adults have been diagnosed with hypertension (5). Furthermore, the consumption of fast and processed foods has increased in the region, leading to a higher risk of chronic diseases such as diabetes, hypertension, and CVDs (3). A study by Defagó et al. (6) analyzed the dietary patterns in South America and their correlation with hypertension. The authors found that one of the predominant diets in the region contained a high intake of sweets, refined grains, processed meats, and snacks. In addition, they identified that this type of diet was positively associated with hypertension (6).

Hypertension is considered a polygenic disease with more than 150 genes associated with it (7). The renin-angiotensin system (RAS) (Supplementary Figure S1) is an associated factor that plays a central role in BP regulation by maintaining sodium and water homeostasis (8). Moreover, the RAS participates in intracrine, autocrine, paracrine, and endocrine signaling, suggesting it influences intra-and extracellular processes (9). The studies on the RAS and its genes aim to establish a relationship to the development of cardiovascular pathology like hypertension (10). Furthermore, RAS polymorphisms have been associated with protective and pathogenic effects on hypertension (9).

The angiotensin-converting enzyme gene (*ACE*), part of the RAS pathway, has been correlated with high BP. *ACE* gene encodes an enzyme that plays a crucial role in BP regulation and electrolyte balance. The primary function of the enzyme is to convert angiotensin I into angiotensin II, a vasoconstrictor and aldosterone–stimulating peptide that regulates blood pressure and fluid-electrolyte balance. This enzyme inactivates bradykinin, thereby increasing blood pressure. Genetic polymorphisms in the *ACE* gene strongly influence the serum level of *ACE* and blood pressure (11, 12). For instance, one common variant associated with the enzyme's activity is the rs4343 (c.2328G > A), located in the 17 exon of the *ACE* that results in a synonymous variant (13). The variant has been related to increased susceptibility to migraine (13), hypertension due to a high saturated fat diet (14), *ACE* activity (15), salt-sensitive hypertension risk (8, 16), hypertension (17, 18), atherosclerosis (19), adiposity and blood pressure (20), among others.

Reports have shown that the Latin American genetic composition is highly heterogenic (21–23). Moreover, this genetic background is associated with several biological processes, including disease predisposition, treatment effectiveness, and how the people in the region respond to different dietary patterns, among others. For instance, Ogunniyi et al. (24) described high disparities in hypertension prevalence due to race and ethnicity. The authors mentioned that Hispanic and Black adults have an increased risk of developing hypertension, which is correlated with higher mortality and morbidity rates (24).

The present mini review aims to provide an overview of the complex relationships between diet, *ACE* polymorphisms, and hypertension, focusing on how these interactions affect diverse populations. By doing so, it aims to contribute to the understanding of hypertension and the implication for clinical practice and public health.

Impact of dietary patterns on *ACE*

Recent studies have investigated the impact of dietary patterns on *ACE*, focusing on their potential to modulate *ACE* activity. This section aims to review the existing research on diet and its influence on *ACE*, with a particular emphasis on comparative studies that explore the effects of specific foods (Figure 1). For instance, Schüler et al. (14) studied forty-six Caucasian non-obese healthy twins with a median age of 31 ± 14 years. The researchers evaluated the effects of a high-saturated-fat (HF) diet under isocaloric conditions, compared to a diet rich in carbohydrates and low-fat, over a period of 6 weeks each. As a result, the authors found that the group that underwent a HF diet, had a 15% increase in circulating *ACE* concentrations and higher *ACE* expression in adipose tissue (14).

Furthermore, a study by Ogawa et al. (25) analyzed the impact of a 10% alpha-linolenic acid-rich flaxseed oil diet compared with high oleic safflower oil (control) on *ACE*. The research identified a significant decrease in *ACE* mRNA expression levels and *ACE* activity in the group that consumed the alpha-linolenic acid-rich diet compared to the control group (25). This study provides valuable information on the potential of alpha-linolenic acid-rich flaxseed oil as an *ACE* regulator, suggesting possible benefits in hypertension management.

Moreover, research by Tejpal et al. (26) described the association between *ACE* expression and activity with weight loss. The study included 32 participants from the University of Warsick, who were 18 years old or older, and not taking any medication. The mean BMI of the subjects was 28.4 ± 4.8 kg/m^2 and 78% were females, and 22% males. The participants followed a 1,200 KCal calorie-restricted diet, and recorded physical activity, food intake, and urine collection. The authors identified that the *ACE* levels correlated with weight loss in patients with obesity and decreased during calorie restriction (26). Similarly, in a study by Harp et al. (27), the effects of dietary weight loss on *ACE* activity were analyzed. The project included 16 adults with obesity and a mean BMI of 35.7 ± 4.3 kg/m^2. The researchers found that dietary weight loss decreased by 23% ± 12% *ACE* activity (27).

Emerging research suggests that dietary patterns and specific foods can modulate *ACE* gene expression and activity. Diets with an increased intake of potassium, soy protein, alpha-linolenic acid, and low in sodium have been shown to decrease *ACE* activity, potentially reducing the risk of hypertension (25, 28–30). Furthermore, similar studies have demonstrated the impact of diet on *ACE* function (27, 31). However, further investigation is required to elucidate the underlying mechanisms of this interaction and use this information to develop personalized dietary strategies that consider the *ACE* gene.

Influence of the *ACE* polymorphisms on hypertension in response to the diet

As previously described, the *ACE* gene has been strongly associated with hypertension (7, 32). Moreover, single nucleotide polymorphisms (SNPs) within the gene have also been correlated with disease risk to varying degrees based on factors such as diet, individual traits, race, and region (7). Table 1 shows several risk alleles of *ACE* gene polymorphisms that have been associated with hypertension and

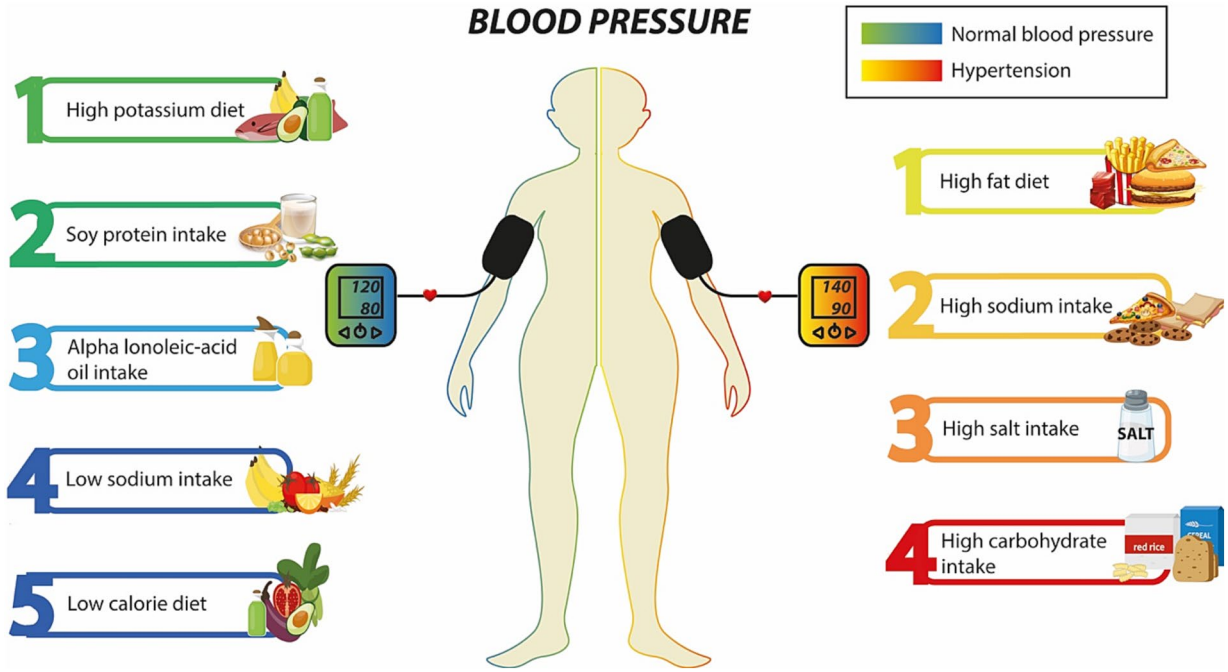


FIGURE 1
Dietary patterns associated with blood pressure. On the left side, the components correlated with a normal blood pressure are depicted; whereas on the right side, the factors related to hypertension are shown.

TABLE 1 Reported hypertension risk allele frequencies in Latin America, Europe, Asia, and Africa (33).

ACE polymorphism	Risk allele frequency in Latin America	Risk allele frequency in Europe	Risk allele frequency in Asia	Risk allele frequency in Africa
rs4290	C = 1	C = 1	C = 1	C = 0.89
rs4291	T = 0.36	T = 0.39	T = 0.33	T = 0.35
rs4305	A = 0.48	A = 0.45	A = 0.36	A = 0.81
rs4335	G = 1	G = 0.63	G = 0.78	G = 0.66
rs4343	A = 0.57	A = 0.46	A = 0.65	A = 0.74
rs4344	G = 0.53	G = 0.55	G = 0.36	G = 0.66
rs4353	A = 0.53	A = 0.54	A = 0.38	A = 0.64
rs4362	T = 0.48	T = 0.53	T = 0.38	T = 0.47
rs4363	G = 0.46	G = 0.53	G = 0.37	G = 0.43
rs1799752	NA	NA	NA	NA
rs7213516	A = 0.02	A = 0.001	A = 0	A = 0.16
rs7214530	G = 0.04	G = 0.001	G = 0	G = 0.21

the reported frequency of each SNP in Latin America, Europe, Asia, and Africa.

Jeong et al. (16) conducted a Mendelian randomization study on a sample of 51,034 adults from Korea to investigate the association between sodium intake, hypertension, and genetic polymorphisms. The authors analyzed 1,282 alleles and found that the A allele of rs4343 increased the hypertension risk by more than 2.1-fold, and this risk was further amplified by high sodium intake (16).

Similarly, Wang et al. (34) analyzed 32 SNPs of the *ACE* gene in 1,024 hypertensive and 956 control participants. The authors reported that rs4343 was a risk factor for high pulse pressure levels associated with arterial elasticity and hypertension (34). Additionally, in the province where the study was performed, the diet included a high salt intake, and when the participants were overweight, the risk increased, suggesting a correlation between diet, obesity, and hypertension (34). These results align with those of Wang et al. (32), where a correlation between a high-salt diet and increased hypertension prevalence was described (32). More studies regarding the impact of rs4343 have been performed for different populations, including samples from Europe, and Asia, with similar outcomes, associating rs4343 with an increased hypertension risk (35). Furthermore, Schüler et al. found that the rs4343 *ACE* polymorphism was a biomarker correlated with higher

ACE levels and a higher risk of hypertension (14). Similarly, in another study by the same group, the authors again observed increased *ACE* levels in response to a high-fat diet, which was associated with rs4343 and an increased risk of developing type 2 diabetes (36).

Furthermore, Martínez-Rodríguez et al. (37) analyzed the correlation between five *ACE* SNPs (rs4363, rs4362, rs4353, rs4344, rs4335, and rs4291) and essential hypertension in Mexican Mestizo individuals. The authors found that, under a dominant model, all the polymorphisms were associated with an increased hypertension risk. Moreover, by including the polymorphisms in haplotypes, one specific haplotype (*GGATG*) was related to a higher hypertension risk (37). Interestingly, the association remained significant even after considering factors such as smoking, age, gender, alcohol consumption, BMI, and triglycerides. Similarly, Ji et al. (38) described an association between rs4305 and hypertension in the Han Chinese population. Additionally, they found a correlation between *ACE* serum levels and BMI, triglycerides, and total cholesterol (38).

Likewise, Pachocka et al. (39) analyzed the correlation between *ACE*, environmental factors, and hypertension. The study included 73 adults (31 males and 42 females) with a BMI of >25 kg/m^2. The authors described an association between rs1799752, hypertension, and carbohydrate intake. Individuals with the DD allele had a higher carbohydrate intake and an increased hypertension predisposition compared to those carrying the ID and II alleles. Moreover, they showed that people carrying the DD allele had an increased salt intake of more than 5 g/day, which may also be associated with a higher risk of hypertension (39). There are no reports of this SNP in the Latin American region.

Moreover, *ACE* variants in specific tissues has also been associated with cardiovascular phenotypes. For instance, Johnson et al. (40) evaluated *ACE* mRNA expression in heart tissues and genotyped the *ACE* locus. The study included the left-ventricle tissue from 65 heart transplant patients, including African American patients, at the Ohio State University. The authors found that three SNPs (rs7214530, rs4290, and rs7213516) affected *ACE* expression. Moreover, the SNPs rs4290 and rs7213516 were correlated with adverse cardiovascular outcomes, with an odds ratio of 6.16 for rs7213516 (40). In Latin America, the frequencies of rs7214530 and rs7213516 have been reported, whereas there are no reports of rs4290 (33).

In conclusion, *ACE* polymorphisms have been previously associated with an increased hypertension risk; hence, they could serve as biomarkers for hypertension predisposition. However, further studies are necessary to fully understand the interaction between genetic composition, hypertension, and diet.

Discussion

Hypertension incidence is growing worldwide, and factors such as population aging, obesity, and an unhealthy diet, further increase the issue (7, 41). Furthermore, the genetic composition of a population could also significantly increase hypertension predisposition (32), highlighting the importance of gene–environment interactions involved in this disease. Moreover, LMICs are the most affected by the increase in hypertension prevalence, with more than 1.04 billion people living with this disease in these regions (42). Understanding the association between genetic factors and environmental influences is crucial for developing targeted disease management strategies.

Historically, the diet in Latin America has been primarily plant-based. For instance, the Maya culture consumed high quantities of corn, avocado, tomatoes, beans, and sweet potato. This diet was complemented by hunting, fishing, and turkey farming. Similarly, in the Inca civilization, their diet predominantly consisted of potatoes, which constituted a great source of carbohydrates, protein, and potassium. Meat consumption was rare, as cattle were mainly used for leather. Likewise, several other Latin American civilizations had similar plant-based diets (43). It is important to mention that these dietary patterns were prevalent before the colonization processes, which drastically changed the diet. However, based on genetic background analysis, most Latin American people still have a higher Native American ancestral proportion, which could still influence diet interactions and metabolism in the region (44).

Furthermore, Western dietary patterns, which include increased consumption of red meat, refined grains, sugar, and ultra-processed food, have spread across the globe, including Latin America, due to globalization processes (45, 46). For instance, according to the Pan American Health Organization (PAHO), the intake of high-saturated fats has increased in Latin America. The region has gone from consuming 53,458 kilotons of ultra-processed foods in 2000 to 79,108 kilotons in 2013, which may be correlated with increased hypertension prevalence (47).

Additionally, excessive salt consumption, which has been correlated with an increased hypertension risk, is also a common problem in the region. According to PAHO, the recommended daily salt intake is 5 grams, equivalent to 2 grams of sodium per day (48). However, studies have found that sodium intake is higher than recommended in the Latin American region. For example, in Brazil, sodium intake is 4.11 g/day; in Chile, it is 3.93 g/day; in Mexico, it is 3.1 g/day; and in El Salvador, it is 3.6 g/day (49–55).

Similarly, dysregulations in RAS have also been described as key factors correlated with hypertension pathogenesis (32). The RAS regulates blood pressure by modulating sodium concentration in plasma and can act locally or systematically through the action of the kidneys (9, 56). Notably, overactivity of the classical RAS pathway has been correlated with hypertension, while alternative pathways involving peptides, such as alamandine, and angiotensin, acting as antagonists of the classical RAS, have been associated with antihypertensive effects (57–59).

The most studied *ACE* polymorphism is rs4343, which, although a synonymous mutation resulting in the same amino acid (Thr776Thr), has been associated with a higher hypertension risk in both healthy and obese subjects (7, 16, 34, 36). Hypotheses suggest that the polymorphism could still influence gene expression by altering mRNA folding, leading to increased *ACE* protein synthesis (60, 61). In Latin America, databases report a risk allele frequency of 0.57 for rs4343 (Table 1) (33, 62), while, for the African population, the frequency is 0.74 (33, 62).

Table 1 presents several SNPs associated with hypertension in different regions. By analyzing the table, comparisons between populations can be made. For example, the frequency of risk alleles in Latin America is similar to the European population. However, Europe, comprised mostly of high-income countries (HIC), has lower hypertension rates compared to Latin America. In contrast, when comparing Latin America with Asia, the former carries more hypertension risk alleles, which aligns with

hypertension rates in both regions. For instance, the Republic of Korea, and China are among the countries with the lowest hypertension prevalence for women, while Paraguay and the Dominican Republic are among the countries with the highest hypertension prevalence (3, 63).

On the other hand, the African population carries the highest number of hypertension risk alleles compared to Europe, Asia, and Latin America. Significantly, the World Health Organization (WHO) states that the African continent has the highest hypertension prevalence at 27% (64). Nevertheless, hypertension rates in Africa cannot be solely attributed to *ACE* SNPs, since hypertension is a multifactorial disease with a strong environmental component, including diet and physical activity. Thus, more research is needed to understand the genetic and environmental factors contributing to the condition.

Moreover, LMICs, including countries in Latin America, face another problem, which is limited healthcare access (3). According to PAHO, Latin America and the Caribbean are the most unequal regions in terms of health care access. For instance, only 7.7% of hypertension patients in LMICs have their BP under control (3). Furthermore, Horowitz et al. (65) conducted a study to analyze the perspectives of hypertension minority patients regarding diet modifications as part of their treatment. They found that patients have difficulties following the recommendations due to the costs, social situations, and withdrawal from their traditional diets, which could increase the risk and prevalence of hypertension (65).

In conclusion, hypertension is a multifactorial disease that comprises environmental and genetic factors. In Latin America, hypertension prevalence is increasing due to several factors, including aging, a "Westernized" diet, and possible genetic predisposition factors involving the *ACE* gene. Furthermore, understanding the genetic and molecular mechanisms of the disease, its association with diet, and how they interact is essential for the development of personalized treatments to increase its efficacy and reduce side effects.

Future perspectives

Further research is required regarding the diet, hypertension, and genetic background. For instance, it is essential to continue with the genetic characterization of the Latin American populations and understand how they are associated with hypertension and other diseases. Moreover, functional analyses correlating the current Latin American diet with *ACE* activity should be conducted to elucidate the role of this diet on *ACE* activity.

Author contributions

AZ and SC-U: conceived the idea, design, and writing. PG-R, VR-P, RT-T, EP-C, AI-R, and ND: written edition. All authors contributed to the article and approved the submitted version.

Funding

The publication fee of this article will be funded by Universidad UTE.

Acknowledgments

The authors are grateful to Universidad UTE for their support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1241017/full#supplementary-material

References

1. The Lancet Regional Health-Americas. Latin America and Caribbean's path to improve hypertension control: time for bolder, tougher actions. *Lancet Reg Health Am*. (2022) 9:100278. doi: 10.1016/j.lana.2022.100278

2. Guevara-Ramírez P, Cadena-Ullauri S, Ruiz-Pozo VA, Tamayo-Trujillo R, Paz-Cruz E, Simancas-Racines D, et al. Genetics, genomics, and diet interactions in obesity in the Latin American environment. *Front Nutr*. (2022) 9:1063286. doi: 10.3389/fnut.2022.1063286

3. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. (2020) 16:223–37. doi: 10.1038/s41581-019-0244-2

4. Zhou B, Bentham J, Di Cesare M, Bixby H, Danaei G, Cowan MJ, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet*. (2017) 389:37–55. doi: 10.1016/S0140-6736(16)31919-5

5. Ruilope LM, Chagas ACP, Brandão AA, Alcalá JJA, Paris JV, Cerda JJO. Hypertension in Latin America: current perspectives. *Hipertens Riesgo Vasc*. (2016) 34:50–6. doi: 10.1016/j.hipert.2016.11.005

6. Defagó MD, Mozaffarian D, Irazola VE, Gutierrez L, Poggio R, Serón P, et al. Dietary patterns and blood pressure in southern cone of Latin America. *Nutr Metab Cardiovasc Dis*. (2021) 31:3326–34. doi: 10.1016/j.numecd.2021.08.048

7. Wang L, Song TT, Dong CW. Association between interactions among ACE gene polymorphisms and essential hypertension in patients in the Hefei region, Anhui, China. *J Renin Angiotensin Aldosterone Syst*. (2023) 2023:1159973. doi: 10.1155/2023/1159973

8. Gu D, Kelly TN, Hixson JE, Chen J, Liu D, Chun CJ, et al. Genetic variants in the renin-angiotensin-aldosterone system and salt-sensitivity of blood pressure. *J Hypertens*. (2010) 28:1210–20. doi: 10.1097/HJH.0b013e3283383655

9. Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system – focus on eye. *Open Ophthalmol J*. (2017) 11:122–42. doi: 10.2174/1874364101711010122

10. Azova M, Timizheva K, Aissa AA, Blagonravov M, Gigani O, Aghajanyan A, et al. Gene polymorphisms of the renin-angiotensin-aldosterone system as risk factors for the development of in-stent restenosis in patients with stable coronary artery disease. *Biomolecules*. (2021) 11:763. doi: 10.3390/biom11050763

11. Zhang L, Miyaki K, Araki J, Song Y, Kimura T, Omae K, et al. Interaction of angiotensin I-converting enzyme insertion-deletion polymorphism and daily salt intake influences hypertension in Japanese men. *Hypertens Res*. (2006) 29:751–8. doi: 10.1291/hypres.29.751

12. Dengel DR, Brown MD, Ferrell RE, Supiano MA. Role of angiotensin converting enzyme genotype in sodium sensitivity in older hypertensives. *Am J Hypertens*. (2001) 14:1178–84. doi: 10.1016/S0895-7061(01)02204-X

13. Abedin-Do A, Pouriamanesh S, Kamaliyan Z, Mirfakhraie R. Angiotensin-converting enzyme gene rs4343 polymorphism increases susceptibility to migraine. *CNS Neurosci Ther*. (2017) 23:698–9. doi: 10.1111/cns.12712

14. Schüler R, Osterhoff MA, Frahnow T, Seltmann AC, Busjahn A, Kabisch S, et al. High-saturated-fat diet increases circulating angiotensin-converting enzyme, which is enhanced by the rs4343 polymorphism defining persons at risk of nutrient-dependent increases of blood pressure. *J Am Heart Assoc*. (2017) 6:1–11. doi: 10.1161/JAHA.116.004465

15. Chung CM, Wang RY, Chen JW, Fann CSJ, Leu HB, Ho HY, et al. A genome-wide association study identifies new loci for ACE activity: potential implications for response to ACE inhibitor. *Pharmacogenomics J*. (2010) 10:537–44. doi: 10.1038/tpj.2009.70

16. Jeong S, Kim JY, Cho Y, Koh SB, Kim N, Choi JR. Genetically, dietary sodium intake is causally associated with salt-sensitive hypertension risk in a community-based cohort study: a Mendelian randomization approach. *Curr Hypertens Rep*. (2020) 22:45. doi: 10.1007/s11906-020-01050-4

17. Yang YL, Mo YP, He YS, Yang F, Xu Y, Li CC, et al. Correlation between renin-angiotensin system gene polymorphisms and essential hypertension in the Chinese Yi ethnic group. *J Renin Angiotensin Aldosterone Syst*. (2015) 16:975–81. doi: 10.1177/1470320315598697

18. Niu W, Qi Y, Gao P, Zhu D. Association between angiotensin converting enzyme G2350A polymorphism and hypertension risk: a meta-analysis. *J Renin Angiotensin Aldosterone Syst*. (2011) 12:8–14. doi: 10.1177/1470320310375859

19. Jia EZ, Chen ZH, An FH, Li LH, Guo CY, Gu Y, et al. Relationship of renin-angiotensin-aldosterone system polymorphisms and phenotypes to mortality in Chinese coronary atherosclerosis patients. *Sci Rep*. (2014):4:4600. doi: 10.1038/srep04600

20. Eisenmann JC, Sarzynski MA, Glenn K, Rothschild M, Heelan KA. ACE I/D genotype, adiposity, and blood pressure in children. *Cardiovasc Diabetol*. (2009) 8:14. doi: 10.1186/1475-2840-8-14

21. Zambrano AK, Gaviria A, Vela M, Cobos S, Leone PE, Gruezo C, et al. Ancestry characterization of Ecuador's Highland mestizo population using autosomal AIM-INDELs. *Forensic Sci Int Genet Suppl Ser*. (2017) 6:e477–8. doi: 10.1016/j.fsigss.2017.09.191

22. Zambrano AK, Gaviria A, Cobos-Navarrete S, Gruezo C, Rodríguez-Pollit C, Armendáriz-Castillo I, et al. The three-hybrid genetic composition of an Ecuadorian population using AIMs-InDels compared with autosomes, mitochondrial DNA and Y chromosome data. *Sci Rep*. (2019) 9:1–8. doi: 10.1038/s41598-019-45723-w

23. Toscanini U, Gaviria A, Pardo-Seco J, Gómez-Carballa A, Moscoso F, Vela M, et al. The geographic mosaic of Ecuadorian Y-chromosome ancestry. *Forensic Sci Int Genet*. (2018) 33:59–65. doi: 10.1016/j.fsigen.2017.11.011

24. Ogunniyi MO, Commodore-Mensah Y, Ferdinand KC. Race, ethnicity, hypertension, and heart disease: JACC focus seminar 1/9. *J Am Coll Cardiol*. (2021) 78:2460–70. doi: 10.1016/j.jacc.2021.06.017

25. Ogawa A, Suzuki Y, Aoyama T, Takeuchi H. Dietary-alphalinolenic-acid-inhibits-angiotensinconverting-enzyme-activity-and-mrna-expression-levels-in-the-aorta-of-spontaneously-hypertensive-rats. *J Oleo Sci*. (2009) 360:355–60. doi: 10.5650/jos.58.355

26. Tejpal S, Sanghera N, Manoharan V, Planas-Iglesias J, Bastie CC, Klein-Seetharaman J, et al. Angiotensin converting enzyme (ACE): a marker for personalized feedback on dieting. *Nutrients*. (2020) 12:660. doi: 10.3390/nu12030660

27. Harp JB, Henry SA, DiGirolamo M. Dietary weight loss decreases serum angiotensin-converting enzyme activity in obese adults. *Obes Res*. (2002) 10:985–90. doi: 10.1038/oby.2002.134

28. Vio CP, Gallardo P, Cespedes C, Salas D, Diaz-Elizondo J, Mendez N, et al. Dietary potassium downregulates angiotensin-I converting enzyme, renin, and angiotensin converting Enzyme 2. *Front Pharmacol*. (2020) 11:920. doi: 10.3389/fphar.2020.00920

29. Yang HY, Chen JR, Chang LS. Effects of soy protein hydrolysate on blood pressure and angiotensin-converting enzyme activity in rats with chronic renal failure. *Hypertens Res*. (2008) 31:957–63. doi: 10.1291/hypres.31.957

30. Hamming I, Van Goor H, Turner AJ, Rushworth CA, Michaud AA, Corvol P, et al. Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats. *Exp Physiol*. (2008) 93:631–8. doi: 10.1113/expphysiol.2007.041855

31. Jayasooriya AP, Mathai ML, Walker LL, Begg DP, Denton DA, Cameron-Smith D, et al. Mice lacking angiotensin-converting enzyme have increased energy expenditure, with reduced fat mass and improved glucose clearance. *Proc Natl Acad Sci U S A*. (2008) 105:6531–6. doi: 10.1073/pnas.0802690105

32. Wang Z, Hou J, Zheng H, Wang D, Tian W, Zhang D, et al. Genetic and phenotypic frequency distribution of ACE, ADRB1, AGTR1, CYP2C9*3, CYP2D6*10, CYP3A5*3, NPPA and factors associated with hypertension in Chinese Han hypertensive patients. *Medicine*. (2023) 102:e33206. doi: 10.1097/MD.0000000000033206

33. Phan L, Jin Y, Zhang H, Qiang W, Shekhtman E, Shao D, et al. (2020). *ALFA: allele frequency aggregator*. Bethesda, United States of America: National Center for Biotechnology Information, U.S. National Library of Medicine, p. 1–4.

34. Wang N, Li X, Zhang Q, Zhang H, Zhou L, Wu N, et al. Association of angiotensin-converting enzyme gene polymorphism with pulse pressure and its interaction with obesity status in Heilongjiang province. *Clin Exp Hypertens*. (2018) 41:70–4. doi: 10.1080/10641963.2018.1445749

35. Sousa AC, dos Reis RP, Pereira A, Borges S, Freitas AI, Guerra G, et al. Genetic polymorphisms associated with the onset of arterial hypertension in a Portuguese population. *Acta Medica Port*. (2018) 31:542–50. doi: 10.20344/amp.9184

36. Schüler R, Osterhoff MA, Frahnow T, Möhlig M, Spranger J, Stefanovski D, et al. Dietary fat intake modulates effects of a frequent ACE gene variant on glucose tolerance with association to type 2 diabetes. *Sci Rep*. (2017) 7:1–7. doi: 10.1038/s41598-017-08300-7

37. Martínez-Rodríguez N, Posadas-Romero C, Villarreal-Molina T, Vallejo M, Del-Valle-Mondragón L, Ramírez-Bello J, et al. Single nucleotide polymorphisms of the angiotensin-converting enzyme (ACE) gene are associated with essential hypertension and increased ACE enzyme levels in Mexican individuals. *PLoS One*. (2013) 8:e65700. doi: 10.1371/journal.pone.0065700

38. Ji L, Cai X, Zhang L, Fei L, Wang L, Su J, et al. Association between polymorphisms in the renin-angiotensin-aldosterone system genes and essential hypertension in the Han Chinese population. *PLoS One*. (2013) 8:4–9. doi: 10.1371/journal.pone.0072701

39. Pachocka L, Włodarczyk M, Kłosiewicz-Latoszek L, Stolarska I. The association between the insertion/deletion polymorphism of the angiotensin converting enzyme gene and hypertension, as well as environmental, biochemical and anthropometric factors. *Rocz Panstw Zakl Hig*. (2020) 71:207–14. doi: 10.32394/rpzh.2020.0119

40. Johnson AD, Gong Y, Wang D, Langaee TY, Shin J, Cooper-Dehoff RM, et al. Promoter polymorphisms in ACE (angiotensin I-converting enzyme) associated with clinical outcomes in hypertension. *Clin Pharmacol Ther*. (2009) 85:36–44. doi: 10.1038/clpt.2008.194

41. Liu M, Yi J, Tang W. Association between angiotensin converting enzyme gene polymorphism and essential hypertension: a systematic review and meta-analysis. *J Renin Angiotensin Aldosterone Syst*. (2021) 22:1470320321995074. doi: 10.1177/1470320321995074

42. OECD, World Bank Group. *Health at a glance: Latin America and the Caribbean 2020*. Paris, France: OECD Publishing (2020).

43. Acosta Navarro JCA, Cārdenas Prado SM, Cārdenas PA, Santos RD, Caramelli B. Pre-historic eating patterns in latin america and protective effects of plant-based diets on cardiovascular risk factors. *Clinics*. (2010) 65:1049–54. doi: 10.1590/s1807-59322010001000022

44. Yam P, Albright J, VerHague M, Gertz ER, Pardo-Manuel de Villena F, Bennett BJ. Genetic background shapes phenotypic response to diet for adiposity in the collaborative cross. *Front Genet*. (2021) 11:615012. doi: 10.3389/fgene.2020.615012

45. Azzam A. Is the world converging to a "Western diet"? *Public Health Nutr*. (2021) 24:309–17. doi: 10.1017/S136898002000350X

46. da Costa GG, da Conceição NG, da Silva PA, Simões BFT. Worldwide dietary patterns and their association with socioeconomic data: an ecological exploratory study. *Global Health*. (2022) 18:1–12. doi: 10.1186/s12992-022-00820-w

47. Moubarac JCPan American Health Organization, World Health Organization. (2015). *Ultra-processed food and drink products in Latin America: trends, impact on obesity, policy implications*. Pan American Health Organization World Health Organization: Washington, DC, USA, p. 1–58.

48. Aparicio A, Rodríguez-Rodríguez E, Cuadrado-Soto E, Navia B, López-Sobaler AM, Ortega RM. Estimation of salt intake assessed by urinary excretion of sodium over 24 h in Spanish subjects aged 7–11 years. *Eur J Nutr*. (2017) 56:171–8. doi: 10.1007/s00394-015-1067-y

49. World Health Organization. (2012). *Guideline: sodium intake for adults and children*. Geneva, Switzerland: World Health Organization, 1–56.

50. OPS/OMS. Organizacion Mundial de la Salud. (2014). *La OPS/OMS insta a los países a reducir el consumo de sal para prevenir la hipertensión y las enfermedades cardíacas*. Washington D.C., United States of America:Pan American Health Organization.

51. Félix PV, De Castro MA, Nogueira-de-Almeida CA, Fisberg M. Prevalence of excess sodium intake and their corresponding food sources in adults from the 2017–2018 Brazilian National Dietary Survey. *Nutrients*. (2022) 14:4018. doi: 10.3390/nu14194018

52. Blanco-Metzler A, Vega-Solano J, Franco-Arellano B, Allemandi L, Larroza RB, Saavedra-Garcia L, et al. Changes in the sodium content of foods sold in four latin american countries: 2015 to 2018. *Nutrients*. (2021) 13:1–12. doi: 10.3390/nu13114108

53. Global Nutrition Report. (2018). *Nutrition country profile – El Salvador*. Available at: https://globalnutritionreport.org/documents/174/El_Salvador.pdf (Accessed Jul 11, 2023).

54. Campos-Nonato I, Vargas Meza J, Nieto C, Ariza AC, Barquera S. Reducing sodium consumption in Mexico: a strategy to decrease the morbidity and mortality of cardiovascular diseases. *Front Public Health*. (2022) 10:1–7. doi: 10.3389/fpubh.2022.857818

55. Valentino G, Hernández C, Tagle R, Orellana L, Adasme M, Baraona F, et al. Urinary sodium-to-potassium ratio and body mass index in relation to high blood pressure in a national health survey in Chile. *J Clin Hypertens*. (2020) 22:1041–9. doi: 10.1111/jch.13904

56. Martyniak A, Tomasik PJ. A new perspective on the renin-angiotensin system. *Diagnostics (Basel)*. (2023) 13:16. doi: 10.3390/diagnostics13010016

57. Kittana N. Angiotensin-converting enzyme 2–angiotensin 1-7/1-9 system: novel promising targets for heart failure treatment. *Fundam Clin Pharmacol*. (2018) 32:14–25. doi: 10.1111/fcp.12318

58. Chaszczewska-Markowska M, Sagan M, Bogunia-Kubik K. UKład renina-angiotensyna-aldosteron (RAA) – fizjologia i molekularne mechanizmy funkcjonowania. *Postepy Hig Med Dosw*. (2016) 70:917–27. doi: 10.5604/17322693.1218180

59. Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the brain: the renin angiotensin system. *Int J Mol Sci*. (2018) 19:1–23. doi: 10.3390/ijms19030876

60. Heera SB, Mahwish UN, Rahman F, Sayeeduddin S. Synonymous variant of ACE gene (rs4343) is coupled with early age at onset and diminished diabetic duration in south Indian diabetic nephropathy patients. *Genet Mol Res*. (2019) 1. doi: 10.4238/gmr16039954

61. Turner JM, Kodali R. Should angiotensin-converting enzyme inhibitors ever be used for the management of hypertension? *Curr Cardiol Rep*. (2020) 22:95. doi: 10.1007/s11886-020-01352-8

62. Carlson CS, Matise TC, North KE, Haiman CA, Fesinmeyer MD, Buyske S, et al. Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE study. *PLoS Biol*. (2013) 11:e1001661. doi: 10.1371/journal.pbio.1001661

63. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. More than 700 million people with untreated hypertension. *Lancet*. (2021) 398:957–80. doi: 10.1016/S0140-6736(21)01330-1

64. World Health Organization. Fact Sheets Hypertension WHO. (2023). *Hypertension*. Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension.

65. Horowitz CR, Tuzzio L, Rojas M, Monteith SA, Sisk JE. How do urban African Americans and Latinos view the influence of diet on hypertension? *J Health Care Poor Underserved*. (2004) 15:631–44. doi: 10.1353/hpu.2004.0061

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 16 November 2023
DOI 10.3389/fnut.2023.1274662

OPEN ACCESS

EDITED BY
Omar Ramos-Lopez,
Universidad Autónoma de Baja California, Tijuana, Mexico

REVIEWED BY
Karina Gonzalez-Becerra,
Universidad de Guadalajara, Mexico
Elisa Barron-Cabrera,
Autonomous University of Sinaloa, Mexico

*CORRESPONDENCE
Gustavo Torres De Souza
✉ gustavo.torres@fagrongenomics.com

†These authors have contributed equally to this work

RECEIVED 08 August 2023
ACCEPTED 24 October 2023
PUBLISHED 16 November 2023

CITATION
Mera-Charria A, Nieto-Lopez F, Francès MP, Arbex PM, Vila-Vecilla L, Russo V, Silva CCV and De Souza GT (2023) Genetic variant panel allows predicting both obesity risk, and efficacy of procedures and diet in weight loss. *Front. Nutr.* 10:1274662. doi: 10.3389/fnut.2023.1274662

Genetic variant panel allows predicting both obesity risk, and efficacy of procedures and diet in weight loss

Alejandra Mera-Charria[1†], Francisco Nieto-Lopez[1,2†], Manel Pacareu Francès[3†], Priscila Marques Arbex[4†], Laura Vila-Vecilla[5], Valentina Russo[5], Carolina Costa Vicente Silva[6] and Gustavo Torres De Souza[5*]

[1]Dorsia Clinics, Madrid, Spain, [2]Catedra UCAM Dorsia, Catholic University San Antonio of Murcia, Guadalupe, Spain, [3]Independent Researcher, Barcelona, Spain, [4]Fagron Genomics US, LLC, Austin, TX, United States, [5]Fagron Genomics, Barcelona, Spain, [6]Fagron (Netherlands), Rotterdam, Netherlands

Purpose: Obesity is a multifactorial condition with a relevant genetic correlation. Recent advances in genomic research have identified several single nucleotide polymorphisms (SNPs) in genes such as FTO, MCM6, HLA, and MC4R, associated with obesity. This study aimed to evaluate the association of 102 SNPs with BMI and weight loss treatment response in a multi-ethnic population.

Methods: The study analyzed 9,372 patients for the correlation between SNPs and BMI (dataset A). The correlation between SNP and weight loss was accessed in 474 patients undergoing different treatments (dataset B). Patients in dataset B were further divided into 3 categories based on the type of intervention: dietary therapy, intragastric balloon procedures, or surgeries. SNP association analysis and multiple models of inheritance were performed.

Results: In dataset A, ten SNPs, including rs9939609 (FTO), rs4988235 (MCM6), and rs2395182 (HLA), were significantly associated with increased BMI. Additionally, other four SNPs, rs7903146 (TCF7L2), (rs6511720), rs5400 (SLC2A2), and rs7498665 (SH2B1), showed sex-specific correlation. For dataset B, SNPs rs2016520 (PPAR-Delta) and rs2419621 (ACSL5) demonstrated significant correlation with weight loss for all treatment types. In patients who adhered to dietary therapy, SNPs rs6544713 (ABCG8) and rs762551 (CYP1A2) were strongly correlated with weight loss. Patients undergoing surgical or endoscopic procedures exhibited differential correlations with several SNPs, including rs1801725 (CASR) and rs12970134 (MC4R), and weight loss.

Conclusion: This study provides valuable insights into the genetic factors influencing BMI and weight loss response to different treatments. The findings highlight the potential for personalized weight management approaches based on individual genetic profiles.

KEYWORDS

obesity, weight loss, genetics, single nucleotide polymorphism, bariatric surgery

1 Introduction

Obesity is a complex condition resulting from an imbalance between energy intake and expenditure. Affecting over 2 billion people worldwide, it has significant negative impacts on quality of life and health, including an increased risk of numerous comorbidities such as type 2 diabetes, cardiovascular disease, and cancer. It is important to also consider the intricate interplay between the increase in adipose tissue and the modifications in it that contribute to the development of insulin resistance and type 2 diabetes (1, 2). Obesity treatment necessarily involves lifestyle changes; however, surgical and endoscopic procedures may also be necessary. Understanding the multifactorial causes of obesity, including genetic and environmental factors, is crucial for effective treatment and prevention strategies (3). The genomic markers related to the development of obesity are essential in understanding and predicting this condition. Nevertheless, there is also evidence showing that there are loci related to weight loss in response to the treatment of choice (3–6).

Nutrigenomics is an interdisciplinary field that examines the intricate interactions between genetic and dietary factors on health outcomes. By combining genetics, nutrition, and molecular biology, researchers aim to understand how individual genetic variations influence a person's response to nutrients, food components, and dietary patterns. The goal of nutrigenomics research is to provide personalised dietary recommendations and promote optimal health outcomes. This emerging field has significant potential for improving health and preventing chronic diseases such as type 2 diabetes, obesity, and cardiovascular diseases by tailoring dietary interventions to the specific patient genotype (7–11).

This approach has garnered considerable attention in clinical research due to its potential for personalising nutritional recommendations based on an individual's genetic profile. For instance, individuals with variations in the FTO gene have been found to be more susceptible to obesity and may benefit from personalised dietary interventions (8, 12, 13). Nutrigenetic testing has also been employed to identify individuals at risk of developing lactose intolerance, coeliac disease, and phenylketonuria, providing them with tailored dietary management. These examples illustrate the potential of nutrigenetics to improve clinical outcomes by enabling more targeted and effective nutritional interventions (7, 11).

A genome-wide association study (GWAS) conducted on over 21,000 subjects from the Taiwan Biobank identified several significant adiposity-associated trait-loci pairs. Among these genes, RALGAPA1 was found to be a specific genetic predisposing factor for high BMI in the Taiwanese population. Additionally, the study detected a moderate genetic correlation between waist-hip ratio (WHR) and BMI, indicating that different genetic determinants exist for abdominal adiposity and overall adiposity. Intriguingly, the study also uncovered the importance of neural pathways that might influence body fat percentage (BF%), waist circumference (WC), and WHR in the Taiwanese population. These findings suggest that multiple genetic factors contribute to obesity and BMI in the Taiwanese population, necessitating further research to better understand the specific pathways involved (14).

In a study by Locke et al., the researchers investigated the heterogeneity of BMI-associated SNPs' effects, observing stronger effects in women for two SNPs near SEC16B and ZFP64 and significant heterogeneity between European and African-descent samples for two SNPs near NEGR1 and PRKD1, as well as between European and East Asian individuals for an SNP near GBE1. The majority of BMI-associated SNPs demonstrated comparable effects across ancestries and sexes. Utilizing LD differences across populations, the study fine-mapped association signals, revealing that the inclusion of non-European individuals in the meta-analysis refined the genomic region or reduced the credible set's SNPs for 10 of the 27 BMI loci fine-mapped on Metabochip (5, 6, 15).

Examining the combined effects of lead SNPs at 97 loci in an independent European-descent sample ($n = 8,164$), the study found an average increase of 0.1 BMI units per BMI-increasing allele and a significant mean BMI difference between individuals with the most and least BMI-increasing alleles. Additionally, incorporating genetic risk scores into a model with age, sex, and four genotype-based principal components marginally yet significantly enhanced obesity prediction accuracy (5, 6, 15).

Subsequent evaluations analyzed the association between BMI and approximately 2.8 million SNPs in up to 123,865 individuals, confirming 14 known obesity susceptibility loci and identifying 18 new loci, including a copy number variant near GPRC5B. Notably, several loci were situated near hypothalamic energy balance regulators (e.g., MC4R, POMC, SH2B1, BDNF) and an incretin receptor (GIPR), potentially providing novel insights into human body weight regulation (16). Overall, these findings suggest that obesity is a complex trait influenced by a combination of genetic and environmental factors. Nevertheless, there is clear genetic contribution to the development of obesity and alterations in body composition. Therefore, finding and employing genomic markers to predict and better understand this pathology might be of great help in dealing with patients presenting this condition.

Genetic variants seem to play a crucial role in the outcomes of bariatric surgeries, such as Roux-en-Y gastric bypass (RYGB). A diverse range of weight loss responses has been observed among patients, and several genes have been associated with these differences. The 15q26.1 locus near ST8SIA2 and SLCO3A1 has been significantly linked to weight loss after RYGB, with the expression of ST8SIA2 in omental fat at baseline correlating with post-surgery weight loss. Additionally, genes such as PKHD1, HTR1A, NMBR, and IGF1R have been identified as potential contributors to the variation in weight loss outcomes after RYGB. However, genetic risk scores (GRSs) for adiposity and the rs1358980-T risk allele in the VEGFA locus did not predict weight loss after gastric bypass surgery in one study. The association between a GRS for abdominal obesity and the response to bariatric surgery may be dependent on the association between the GRS and baseline BMI. Overall, these findings highlight the importance of considering genetic factors when evaluating weight loss outcomes following bariatric surgeries, as they may significantly influence individual responses (17–19).

While there have been previous studies that investigate the impact of genetic factors on the efficacy of surgical and endoscopic interventions for obesity, these studies often involve limited sample sizes or narrow scopes. Consequently, there remains a significant need for comprehensive evaluations that encompass larger, multi-ethnic populations. The identification of specific genetic variations associated with obesity and the predisposition to respond favourably to various therapeutic approaches serves a dual purpose. Firstly, it aids in elucidating the underlying biological mechanisms that contribute to weight loss following therapeutic interventions. Secondly, it provides

valuable insights that could facilitate personalized medical decision-making, enabling clinicians to predict patient response to different treatments with greater accuracy. In this context, our study aims to fill the existing gaps in the literature by providing a broader evaluation of the role of genetic variations in influencing the effectiveness of weight loss therapies.

Additionally, it is significant to emphasise that there are numerous factors which ought to be taken into consideration when deciding upon the clinical approach to a patient, whether through a reversible procedure, such as an intragastric balloon, or a non-temporary one, like bariatric surgery or endoscopic interventions. While guidelines exist for the selection of patients for each type of procedure, several of the clinical markers overlap, thus posing a considerable challenge in evaluating the risk versus benefit ratio (20, 21). In the current study, the efficacy of each type of procedure was correlated with the genotypes present in several genomic markers with the aim to enhance the decision-making process for the choice between temporary and non-temporary procedures (20–22).

Therefore, comprehending the genetic factors involved in obesity, high BMI, and the weight loss process is crucial for a more in-depth understanding of these processes and determining optimal management strategies. In this study, we analysed two patient databases, which were genotyped for a panel of 102 SNPs. These SNPs were identified as significant in various energy metabolism pathways, as well as genes implicated in the behavioural aspects of eating.

2 Methods

2.1 Study design

We analysed two distinct databases containing matched genotypes of patients for the 102 SNPs examined, in relation to either their BMI at a single time point or weight loss and BMI changes in patients who underwent weight loss treatment. The complete data comprised two sets of patient information: (A) 9,372 patients whose genotypes were matched to their BMI at the time of DNA collection; (B) 474 patients who were both genotyped and had their weight and BMI assessed before and after follow-up for dietary treatment, endoscopic intragastric balloon procedures, or surgical interventions.

The datasets are composed of patients who had been previously genotyped as part of their nutritional counselling, *as per* request of the patient for the treatment offered to them, and had their BMI and anthropometric data recorded on their medical record in a fully anonymised database. Only the genotype and BMI data were recovered with no identifiable features associated. Both datasets were fully anonymised before any data processing, ensuring that only the BMI, weight loss, and genotype for each patient were compiled, according to the dataset. These patients had their genotypes and clinical data stored as medical records within a repository, which included individuals from a diverse range of ethnic backgrounds.

2.2 Genotyping procedure

Briefly, all the genotyping assays were performed by qPCR from genomic DNA previously collected from the patients. The DNA was extracted with the automated bead-based method using the KingFisher system (Thermo Fisher). Nucleic acid were quantified with the RNAseP method in order to ensure sample quality control. The SNPs analysed are summarized on Table 1. All SNP genotyping was done with the Taqman probe assay designed on the Genotyping software offered by the Thermo Fisher platform, the raw qPCR amplification data was updated to the cloud service to ensure genotyping to be performed automatically.

2.3 Association analyses and statistical framework

The association between genotype and clinical features was analysed according to the data group. In dataset A, patients' genotypes were associated with their BMI at the time of DNA collection. The dataset B was composed of patients who were treated with one of the weight loss therapeutic interventions studied. The patients were categorised into groups based on clinical, surgical, or endoscopic interventions for weight loss. Subsequently, the genotypes were associated with weight and BMI loss. Additional data were also evaluated for significance; in dataset B, the follow-up duration until the last weight measurement was assessed, patients were not enrolled to the studied, as it was a retrospective medical record analysis, therefore, there was no information related to the beginning of the intervention. The baseline BMI information was employed to infer weight loss when comparing to the final results. For dataset A, SNP association was tentatively performed for subsets of male and female patients; however, since no relevant data were found, this will not be discussed further.

Statistical analyses were performed using R (version 4.2.2) as the computational environment. The SNPassoc package was chosen for the necessary calculations (23). We evaluated the genotype–phenotype association without restrictions to the dominance model and applied Bonferroni correction. The dominance models applied were: (1) codominance, in which alleles exhert effect; (2) dominance, SNP allele is dominant in determining the phenotype; (3) recessive, SNP allele is recessive the determination of the phenotype; (4) overdominant, heterozygous does not determine a phenotype within the two homozygous possibilities; and (5) additive, neither allele is dominant. The p-values reported are the ones depicting the highest statistical correlation. We aimed to assess the clinical and molecular significance according to the specific study of each SNP. Statistical significance was defined as $p < 0.01$.

3 Results

3.1 Association between SNPs and BMI

An SNP association analysis was conducted to correlate BMI with genotype for the studied SNPs. Upon analysing the 9,372 patients belonging to dataset A, ten SNPs demonstrated statistically significant correlations with increased BMI. Since the raw genotype data were generated by qPCR for a limited number of SNPs, the genotyping rate for all SNPs was 100%, as only patients with complete genotypes were considered for this study. Table 2 summarises the p-values found for each SNP under the evaluated model of genotype association and Figure 1 displays the Manhattan Plot for visualization of the results.

TABLE 1 Summary of genomic information of the SNPs analysed in patients included in datasets A and B.

SNP	Chromosome	Gene or region involved	SNP	Chromosome	Gene or region involved	SNP	Chromosome	Gene or region involved
rs671	12	ALDH2	rs7498665	16	SH2B1	rs2383208	9	CDKN2A, CDKN2B
rs1050450	3	GPX1	rs7903146	10	TCF7L2	rs7756992	6	CDKAL1
rs1800566	16	NQO1	rs9939609	16	FTO	rs7901695	10	TCF7L2
rs4680	22	COMT	rs1121980	16	FTO	rs12970134	18	MC4R
rs4880	6	SOD2	rs1800588	15	LIPC	rs17782313	18	MC4R
rs1051168	15	NMB	rs7799039	7	LEP	rs4788102	16	SH2B1
rs1726866	7	TAS2R38	rs1800546	9	ALDOB	rs1395479	4	AGA
rs1800497	11	DRD2	rs76917243	9	ALDOB	rs891684	17	SLC39A11
rs2229616	18	MC4R	rs17700633	18	MC4R	rs2025804	1	LEPR
rs6277	11	DRD2	rs10811661	9	CDKN2A/B	rs5400	3	SLC2A2
rs1801282	3	PPAR-Y	rs676210	2	APOB	rs2241201	12	MMAB
rs662799	11	APOA5	rs12740374	1	CELSR2	rs3846663	5	HMGCR
rs2016520	6	PPARD	rs2650000	12	HNF1A	rs12934922	16	BCMO1
rs713598	7	TAS2R38	rs6511720	19	LDLR	rs7501331	16	BCMO1
rs2470893	15	CYP1A1	rs6544713	2	ABCG8	rs1279683	20	SLC23A2
rs762551	15	CYP1A2	rs2395182	6	HLA	rs33972313	5	SLC23A1
rs10766197	11	CYP2R1	rs4713586	6	HLA	rs10741657	11	CYP2R1
rs2282679	4	GC	rs7454108	6	HLA	rs12785878	11	NADSYN1, DHCR7
rs1550532	2	DGKD	rs7775228	6	HLA	rs2060793	11	CYP2R1
rs1570669	20	CYP24A1	rs182549	2	MCM6	rs3829251	11	NADSYN1, DHCR7
rs17251221	3	CASR	rs4988235	2	MCM6	rs12272004	11	INTERGENIC
rs1801725	3	CASR	rs1800562	6	HFE	rs964184	11	ZNF259, LOC100128347, APOA5, SIK3, BUD13
rs7481584	11	CARS	rs3811647	3	TF	rs1042714	5	ADRB2
rs780094	2	GCKR	rs4820268	22	TMPRSS6	rs1801133	1	MTHFR
rs11577390	1	AMY1-AMY2	rs10850219	12	KCTD10	rs4343	17	ACE
rs4244372	1	AMY1	rs11144134	9	TRPM6	rs4654748	1	NBPF3
rs1799883	4	FABP2	rs13146355	4	SHROOM3	rs602662	19	FUT2
rs17300539	3	ADIPOQ	rs3925584	11	DCDC5	rs8177253	3	TF
rs1805134	1	LEPR	rs4072037	1	MUC1	rs9770242	7	NAMPT
rs2289487	15	PLIN1	rs1056836	2	CYP1B1	rs1501299	3	ADIPOQ
rs2419621	10	ACSL5	rs1048943	15	CYP1A1	rs2241766	3	ADIPOQ
rs5883	16	CETP	rs1695	11	GSTP1	rs1800629	6	TNF-α
rs490683	3	GHSR	rs174547	11	FADS1	rs1800795	7	IL-6
rs5082	1	APOA2	rs2237892	11	KCNQ1	rs1800896	1	IL-10

3.2 Correlation between SNPs and female patients

Interestingly, four additional SNPs were found to have statistically significant associations only among the female population of dataset A. Among female patients, SNPs in the LDL receptor (LDLR), transcription factor TCF7L2, glucose transporter protein SLC2A2, and SH2B1 were positively associated. The following *p*-values were found for the SNPs under all different models of inheritance: rs7903146 (TCF7L2) $p = 0.0027$, rs6511720 (LDLR) $p = 0.003$, rs5400 (SLC2A2) $p = 0.003$, and rs7498665 (SH2B1) $p = 0.008$.

TABLE 2 *p* values obtained upon statistic evaluation of the association between BMI (phenotype) to the 102 SNPs analysed.

SNP	Genic region	*p* value for codominant model	*p* value for dominant model	*p* value for recessive model	*p* value for overdominant model	Log-additive
rs9939609	FTO	2.114E-13	1.3648E-06	6.9133E-13	0.3409127	6.1171E-13
rs1121980	FTO	4.6083E-13	2.6843E-06	1.1519E-12	0.1531425	9.2509E-13
rs4988235	MCM6	8.2181E-05	0.00466017	3.782E-05	0.5219651	3.9791E-05
rs182549	MCM6	0.0006154	0.10589411	0.0001213	0.11425821	0.00161272
rs2395182	HLA	0.00063581	0.00187173	0.00239678	0.05458373	0.00023214
rs10850219	KCTD10	0.00167209	0.5343385	0.00162645	0.0202502	0.4217869
rs3829251	NADSYN1	0.01063817	0.77429347	0.00541801	0.12041572	0.44187628
rs3846663	HMGCR	0.01149159	0.04712569	0.00548761	0.92405252	0.0047282
rs2470893	CYP1A1	0.01441176	0.10656919	0.00510184	0.8942208	0.01444574
rs1050450	GPX1	0.0193709	0.03977497	0.26727718	0.00532972	0.30002542
rs2229616	MC4R	0.0280324	0.011384	0.22106289	0.01769627	0.00857146

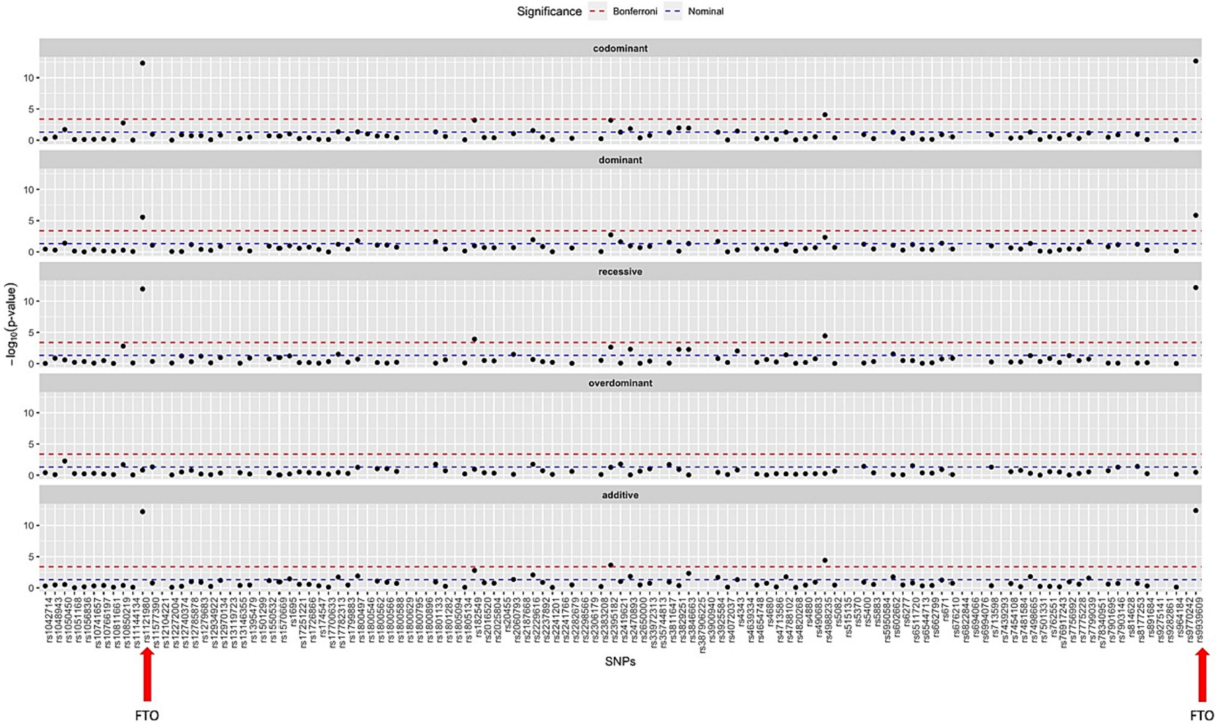


FIGURE 1
Manhattan plot summarizing the statistic results for all SNPs studied under all models of association to the BMI as phenotype. The SNPs studied in the FTO gene, found to be the most significant ones, are marked with a red arrow.

3.3 Follow-up length of patients under weight loss therapy

In dataset B, which comprised patients who underwent either dietary therapy or surgical or endoscopic procedures, these patients were monitored to assess weight loss. The overall mean follow-up time for the patients in dataset B was 188.72 days. Among patients exclusively receiving dietary intervention, the mean time was 123.97 days. However, for patients monitored for their diet, 58 were assigned zero days of follow-up in the dataset, indicating that there was no adherence to the treatment at all. Consequently, the rate of adherence to the follow-up program for patients previously tested with this panel of SNPs was 78.27%.

3.4 SNPs on the PPAR-delta and ACSL5 genes predict weight loss in all patients accompanied

When considering all patients in dataset B, who were treated for weight loss, including those who underwent dietary intervention, intragastric balloon procedures, or surgeries, the SNPs rs2016520 and

rs2419621 demonstrated significant correlation between genotype and weight loss using the recessive model. Figure 2 summarises the data found for this dataset.

3.5 Response to diet therapy

Weight loss was documented in patients in dataset B who followed appropriate dietary management and were monitored by nutrition professionals. The difference in BMI and weight was strongly correlated with the genotypes of two SNPs: rs6544713 ($p = 0.00001$) and rs762551 ($p = 0.00033$). It is also worth noting that the SNP studied in the COMT enzyme, rs4680, exhibited some degree of correlation when using the recessive model of association, with a p-value of 0.02.

3.6 SNP-association to the weight loss in patients subject to surgical or endoscopic procedures

Weight loss in patients undergoing surgical or endoscopic procedures was greater, as expected and supported by the literature (24, 25). Moreover, several SNPs could also be differentially correlated with these procedures.

Patients who underwent intragastric balloon procedures demonstrated a positive correlation between weight loss and the genotype of the following SNPs: rs1801725 (CASR gene) $p = 0.00131$, rs4820268 (TMPRSS6) $p = 0.002$, rs17300539 (ADIPOQ) $p = 0.003$, and rs17251221 (CASR) $p = 0.007$.

The difference in weight before and after endoscopic sleeve or POSE procedures exhibited a high degree of statistical significance with 5 SNPs. The genotypes of the following SNPs were correlated using a recessive model to the amount of weight lost: rs12970134 (MC4R) $p = 0.00003$, rs17782313 (MC4R) $p = 0.00003$, rs4072037 (MUC1) $p = 0.00052$, rs1550532 (ACE) $p = 0.001$, and rs1550532 (DGKD) $p = 0.00078$. It is also worth mentioning that rs4343, in the leptin gene, showed a p-value of 0.02. Furthermore, the PPAR-delta SNP rs2016520 has been associated with weight loss in patients who underwent all types of procedures, including balloon, endoscopic sleeve, i.e., and POSE.

4 Discussion

In this study, we analysed two groups of patients, separate into: dataset A (9,372 patients), and dataset B (474 patients). We aimed to investigate the association between selected SNPs and BMI, as well as their potential role in predicting weight loss response to various treatments in a diverse population. Our findings revealed that several of the studied SNPs were significantly correlated with BMI. We also identified a subset of SNPs that were uniquely associated with BMI in female patients. Moreover, we observed that specific SNPs were significantly linked to weight loss outcomes in patients undergoing different weight loss treatments. These results highlight the complex interplay between genetic factors and obesity, as well as the response to weight loss interventions.

Furthermore, the difference in potential genomic markers that predict increased BMI and weight loss in different procedures highlights the importance of nutrigenetics in the management of patients to control obesity and its comorbidities (7). By understanding the genetic predispositions and individual responses to weight loss interventions, we can develop personalized treatment approaches that optimize weight loss outcomes and overall health. Table 3 summarises the findings.

Moreover, the strong interaction between the two SNPs on the FTO gene, rs9939609 and rs1121980, and increased BMI as a phenotype reinforces the importance of the FTO gene in the development of obesity, as previously reported in the literature (26–28). FTO has been associated with leptin concentration, as well as alterations in HDL and triglyceride levels (29, 30). These SNPs have also been linked to dietary intake, leptin levels, and body mass distribution (31, 32). However, our study did not find any association between these SNPs and weight loss in any of the intervention groups. This finding suggests that while the FTO gene may play a significant role in the development of obesity, its involvement in weight loss response might be limited or influenced by other factors. Our results warrant further investigation to better understand the underlying mechanisms.

The process of losing weight involves creating a caloric deficit to restore the energy balance. However, biochemical and psychological factors can determine the success of sustaining the caloric deficit to achieve significant weight loss. This has led to the search for genomic markers to predict the ideal type of diet based on individual factors.

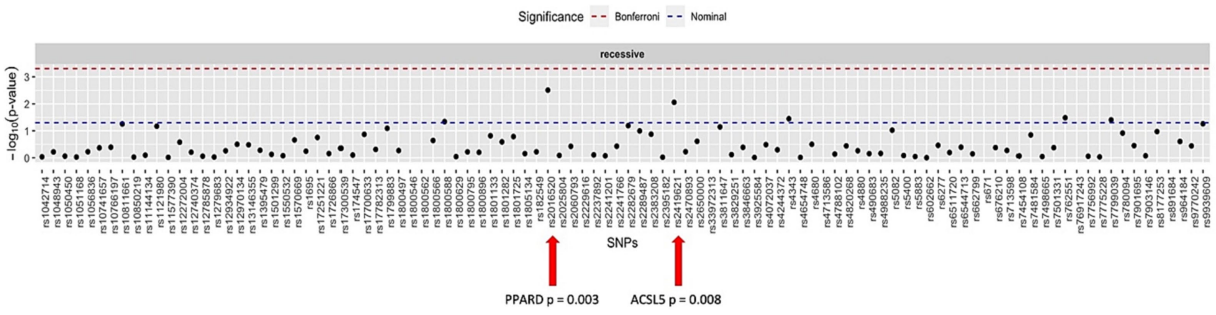


FIGURE 2
Manhattan plot showing the distribution of p-values for the association between the genotypes and weight loss in all patients.

TABLE 3 Summary of the *p*-values found for the association between genotypes and the phenotypes.

BMI (all patients)			BMI (female patients)			Weight loss (all patients)			Weight loss (diet group)			Weight loss (balloon group)			Weight loss (sleeve or POSE group)			Weight loss (sleeve, POSE or balloon group)		
SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value	SNPid	Gene Regio	*p*-value
rs9939609	FTO	6.9133E-13	rs7903146	TCF7L2	0.0027	rs2016520	PPARD	0.00309	rs6544713	ABCG8	0.00874	rs1801725	CASR	0.00131	rs12970134	MC4R	0.00003	rs2016520	PPARD	0.00840
rs1121980	FTO	4.6083E-13	rs6511720	LDLR	0.003	rs2419621	ACSL5	0.00874	rs762551	CYP1A2	0.00001	rs4820268	TMPRSS6	0.002	rs17782313	MC4R	0.00003			
rs4988235	MCM6	3.782E-05	rs5400	SLC2A2	0.003				rs4680	COMT	0.00033	rs17300539	ADIPOQ	0.003	rs4072037	MUC1	0.00052			
rs182549	MCM6	0.0001213	rs7498665	SH2B1	0.008							rs17251221	CASR	0.007	rs1550532	ACE	0.001			
rs2395182	HLA DQ2.2	0.00187173													rs1550532	DGKD	0.00078			
rs10850219	KCTD10	0.00162645													rs4343	LEP	0.02			
rs3829251	NADSYN1	0.00541801																		
rs3846663	HMGCR	0.00548761																		
rs2470893	CYP1A1	0.00510184																		
rs1050450	GPX1	0.00532972																		
rs2229616	MC4R	0.011384																		

Personalising the diet through nutrigenomics could be a successful approach to improving weight loss outcomes (4).

The relevance of genetics in predicting diets and weight loss has become increasingly apparent, as recent advances in genomics have enabled researchers to uncover key genes that influence individual responses to specific dietary interventions. Understanding these genetic factors can help tailor personalised nutrition plans, ultimately leading to more effective weight loss and better overall health outcomes. Among the most significant genes related to diet and weight loss are FTO, MC4R, and PPARγ, which have been implicated in the regulation of appetite (4, 33), energy expenditure, and fat metabolism. Studies employing Mendelian randomisation have further strengthened the causal links between these genes, dietary patterns, and obesity risk. As our understanding of the complex interplay between genetics and diet continues to grow, nutrigenomic approaches will likely play an increasingly important role in developing effective, personalised weight loss strategies (4, 34).

Apart from the dietary and life-style approach, surgical and endoscopic methods do also play an important role in aiding patients achieve significative weight loss. Nevertheless, the efficacy of those methods is also variable, which has to be balanced with the risks involved in the procedures (24, 25). Therefore, the search for genomic markers of success related to surgical, endoscopic, and dietary interventions seem an interesting possibility to guide the decisions.

In this study, SNPs rs1050450 (GPX1) and rs2229616 (MC4R) have been associated with increased BMI and body weight. Both genes have previously been linked to obesity (35), and it is noteworthy that MC4R is involved in appetite regulation (36–38). Although the GPX1 gene does not show any apparent functional connection to weight gain, our results support previous findings. The presence of variations in the melanocortin receptor could serve as a crucial marker for determining patient management, as it indicates both the risk of obesity and a predisposition to poor appetite control. Consequently, appropriate nutritional intervention may be guided by the genotype.

In the female population, the SNP rs5400 (SLC2A2) was associated with increased BMI. In addition to corroborating previous studies (39), this finding offers valuable insights for designing nutrigenomic diets for both weight loss and type 2 diabetes management. This SNP indicates that individuals may have altered sensitivity to sugar, leading to higher sugar intake (40, 41). The rs7498665 in the SH2B1 gene has also been found to be associated with BMI in our female subset (31, 42–44).

Apart from variations previously associated with BMI, we also found a positive correlation between BMI and SNPs previously linked to alterations in lipid and lipoprotein levels: rs10850219 (KCTD10) (45, 46); rs3846663 (HMGCR) (33, 47, 48); and rs6511720 (LDLR) (49–51).

The SNP rs2470893, which influences the function of the CYP1A1 enzyme, has also been found to be associated with an increase in BMI. Although there appears to be no direct mechanistic link, a previous study has shown this polymorphism to be associated with both alterations in coffee consumption and BMI. Researchers speculated that this connection might be due to differences in appetite control, including variations in circulating levels of asprosin (52).

Another intriguing correlation of interest was discovered in the MCM6 gene. The two SNPs studied in this gene, rs4988235 and rs182549, were strongly linked with alterations in body mass, in our study. Variants in the lactase gene are widely known to cause lactose intolerance, which, *per se*, has no direct correlation to weight gain

(53). A few studies have shown the rs4988235 SNP to be linked to changes in body composition and lipid concentrations (35, 54). The rs182549 has also been correlated with changes in food consumption patterns (55) These previous findings, combined with the strong connection to BMI increase observed in our data, suggest that this is a relevant target for nutrigenetic management. Variations in the MCM6 also drive changes in the microbiota, which can potentially be therapeutically manipulated (56).

With regards to the genotype–phenotype correlations discovered in dataset B of this study, we identified several genomic markers capable of determining predispositions for success under specific therapeutic approaches to weight loss. Variations in the ABCG8 and COMT genes (SNPid rs6544713), previously linked to cholesterol levels (57), and in the COMT gene, widely recognised for its relevance in the behavioural aspects of eating (58, 59), have been associated with weight loss in patients exclusively undergoing dietary therapy. By understanding the implications of alterations in eating patterns, dietitians may be able to further tailor diets for patients presenting alterations in the COMT gene, who are predisposed to behavioural changes.

Among the SNPs associated with success in intragastric balloon procedures, the genotypes of rs17300539 in the adiponectin gene were positively correlated. Variations in the adiponectin gene have been previously linked to obesity, likely due to altered expression of this marker (60, 61). In our study, we identified the SNP rs17300539 as a novel genomic marker correlated with weight loss. In patients undergoing sleeve or POSE surgery, SNPs in the melanocortin receptor were strongly associated with the capacity to lose weight. This finding offers both an interesting target for nutrigenetic management and a mechanistic understanding of weight gain and loss in light of the central regulation of appetite. In addition, the rs4343 in the leptin gene, previously associated with weight gain and satiety (62, 63), was a novel finding related to weight loss in patients undergoing these procedures.

The discovery of markers linked to the success of treating patients via either a temporary procedure, i.e., the intragastric balloon, or a definitive surgical or endoscopic intervention, contributes significantly to the existing body of literature. It offers the potential to more effectively guide physicians in determining the optimal therapeutic approach. From a biological perspective, it is noteworthy that polymorphisms in the adiponectin gene were correlated with success in patients treated with the intragastric balloon. This association could potentially be attributed to the role of adiponectin in mediating signals from adipose tissue, which is involved in insulin resistance, glucose level regulation, and ultimately, energy metabolism (64–66). Previous studies have linked other adiponectin gene polymorphisms to the response to aerobic exercise (67).

Simultaneously, polymorphisms in the melanocortin-4 receptor and leptin genes were linked to successful outcomes in non-temporary procedures, namely surgical or endoscopic interventions. This suggests an inherent correlation between the response to these procedures and the central mechanisms of appetite control. In light of these novel findings, the utilisation of genomic markers could supplement the clinical data used in the decision-making process to determine the most appropriate type of procedure (3, 68).

In addition to the findings related to genetic analysis, we also observed interesting results regarding the overall utility of this approach. In dataset B, 78.27% of patients demonstrated a global adherence to dietarian changes, which is considerably higher compared to studies with non-genotyped patients (1, 2, 69, 70). This suggests that nutrigenetic tools might also impact the efficacy of diet due to increased adherence.

5 Conclusion

This study sheds light on the complex interplay between genetic factors and obesity, as well as the response to weight loss interventions. The identification of significant correlations between specific SNPs and BMI, along with SNPs uniquely associated with BMI in female patients, underscores the importance of considering personalized treatment approaches based on individual genetic profiles. The findings also reveal the potential of nutrigenetics in guiding patient management by targeting key genes, such as FTO, GPX1, MC4R, SLC2A2, and SH2B1. These results contribute to our understanding of the genetic predispositions and individual responses to weight loss interventions, enabling the development of tailored treatment strategies to optimize weight loss outcomes and overall health.

Moreover, the study highlights the potential impact of nutrigenetic tools on the efficacy of diet due to increased adherence. The higher global adherence to diet observed among genotyped patients suggests that incorporating genetic information into weight loss interventions may lead to improved patient engagement and success. As obesity and its comorbidities continue to pose significant public health challenges, the insights gained from this research pave the way for more targeted and effective approaches to weight management, ultimately leading to better health outcomes for patients.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies involving humans because the whole study was conducted solely with data obtained from a database of medical records and genetic data from patients previously collected. All the data is anonymised completely so as to comply with not needing ethical approval. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AM-C: Writing – original draft, Writing – review & editing. FN-L: Conceptualization, Data curation, Writing – original draft. MF: Conceptualization, Writing – review & editing. PA: Conceptualization, Formal analysis, Supervision, Writing – original draft. LV-V: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. VR: Formal analysis, Investigation, Methodology, Writing – original draft. CS: Investigation, Validation, Writing – review & editing. GS: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

AM-C and FN-L are affiliated with Dorsia Clinics, Medical Department, Madrid, Spain, with FN-L also affiliated with Universidad Católica San Antonio de Murcia (UCAM), Murcia, Spain. MF is employed by Fagron Ibérica, Barcelona, Spain. PA is employed by Gx Sciences, Austin, Texas, United States. LV-V, VR, and GS are employed by Fagron Genomics, Barcelona, Spain. CS is employed by Fagron BV, Rotterdam, Netherlands.

Despite these affiliations and employments with commercial entities, the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We would like to reiterate that although the authors are associated or employed by industry or commercial entities, we declare no conflict of interest as the data generated is not intended for commercial use. Rather, the aim is to utilise data acquired to corroborate and contribute to the existing basic literature, thereby enhancing the quality of health care and contributing to scientific knowledge in the field.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Selvam J, Thangaraj P, Hemalatha K, Subbian P. Diet adherence and factors associated with nonadherence among type 2 diabetics at an urban health center in Tamil Nadu, India. *Int J Acad Med*. (2023) 9:25. doi: 10.4103/ijam.ijam_10_22

2. Ayele AA, Emiru YK, Tiruneh SA, Ayele BA, Gebremariam AD, Tegegn HG. Level of adherence to dietary recommendations and barriers among type 2 diabetic patients: a cross-sectional study in an Ethiopian hospital. *Clin Diabetes Endocrinol*. (2018) 4:21. doi: 10.1186/s40842-018-0070-7

3. González-Muniesa P, Mártinez-González M-A, Hu FB, Després J-P, Matsuzawa Y, Loos RJF, et al. Obesity. *Nat Rev Dis Primers*. (2017) 3:17034. doi: 10.1038/nrdp.2017.34

4. Chen M, Chen W. Single-nucleotide polymorphisms in medical nutritional weight loss: challenges and future directions. *J Transl Int Med*. (2022) 10:1–4. doi: 10.2478/jtim-2022-0002

5. Zaitlen N, Kraft P, Patterson N, Pasaniuc B, Bhatia G, Pollack S, et al. Using extended genealogy to estimate components of heritability for 23 quantitative and dichotomous traits. *PLoS Genet*. (2013) 9:e1003520. doi: 10.1371/journal.pgen.1003520

6. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. *Mol Cell Endocrinol*. (2014) 382:740–57. doi: 10.1016/j.mce.2012.08.018

7. Roosan D, Wu Y, Tran M, Huang Y, Baskys A, Roosan MR. Opportunities to integrate nutrigenomics into clinical practice and patient counseling. *Eur J Clin Nutr*. (2023) 77:36–44. doi: 10.1038/s41430-022-01146-x

8. Ghosh D, Skinner MA, Laing WA. Pharmacogenomics and nutrigenomics: synergies and differences. *Eur J Clin Nutr*. (2007) 61:567–74. doi: 10.1038/sj.ejcn.1602590

9. Robinson K, Rozga M, Braakhuis A, Ellis A, Monnard CR, Sinley R, et al. Effect of incorporating genetic testing results into nutrition counseling and care on dietary intake: An evidence analysis center systematic review—part I. *J Acad Nutr Diet*. (2021) 121:553–581.e3. doi: 10.1016/j.jand.2020.04.001

10. Trujillo E, Davis C, Milner J. Nutrigenomics, proteomics, metabolomics, and the practice of dietetics. *J Am Diet Assoc*. (2006) 106:403–13. doi: 10.1016/j.jada.2005.12.002

11. Barrea L, Annunziata G, Bordoni L, Muscogiuri G, Colao A, Savastano S. Nutrigenetics—personalized nutrition in obesity and cardiovascular diseases. *Int J Obes Suppl*. (2020) 10:1–13. doi: 10.1038/s41367-020-0014-4

12. Merritt DC, Jamnik J, El-Sohemy A. FTO genotype, dietary protein intake, and body weight in a multiethnic population of young adults: a cross-sectional study. *Genes Nutr*. (2018) 13:4. doi: 10.1186/s12263-018-0593-7

13. Santos KD, Rosado EL, da Fonseca ACP, Belfort GP, da Silva LBG, Ribeiro-Alves M, et al. FTO and ADRB2 genetic polymorphisms are risk factors for earlier excessive gestational weight gain in pregnant women with Pregestational diabetes mellitus: results of a randomized Nutrigenetic trial. *Nutrients*. (2022) 14:1050. doi: 10.3390/nu14051050

14. Wong HS-C, Tsai S-Y, Chu H-W, Lin M-R, Lin G-H, Tai Y-T, et al. Genome-wide association study identifies genetic risk loci for adiposity in a Taiwanese population. *PLoS Genet*. (2022) 18:e1009952. doi: 10.1371/journal.pgen.1009952

15. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. (2015) 518:197–206. doi: 10.1038/nature14177

16. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. (2010) 42:937–48. doi: 10.1038/ng.686

17. Rinella ES, Still C, Shao Y, Wood GC, Chu X, Salerno B, et al. Genome-wide Association of Single-Nucleotide Polymorphisms with Weight Loss Outcomes after Roux-en-Y Gastric Bypass Surgery. *J Clin Endocrinol Metab*. (2013) 98:E1131–6. doi: 10.1210/jc.2012-3421

18. Hatoum IJ, Greenawalt DM, Cotsapas C, Daly MJ, Reitman ML, Kaplan LM. Weight loss after gastric bypass is associated with a variant at 15q26.1. *Am J Hum Genet*. (2013) 92:827–34. doi: 10.1016/j.ajhg.2013.04.009

19. Aasbrenn M, Svendstrup M, Schnurr TM, Lindqvist Hansen D, Worm D, Balslev-Harder M, et al. Genetic markers of abdominal obesity and weight loss after gastric bypass surgery. *PLoS One*. (2021) 16:e0252525. doi: 10.1371/journal.pone.0252525

20. Bawahab MA, Abbas KS, El MWMA, Abdelgadir RS, Altumairi K, Alqahtani AR, et al. Factors affecting weight reduction after Intragastric balloon insertion: a retrospective study. *Healthcare*. (2023) 11:600. doi: 10.3390/healthcare11040600

21. Eisenberg D, Shikora SA, Aarts E, Aminian A, Angrisani L, Cohen RV, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of obesity and metabolic disorders (IFSO): indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. (2022) 18:1345–56. doi: 10.1016/j.soard.2022.08.013

22. Stavrou G, Shrewsbury A, Kotzampassi K. Six intragastric balloons: which to choose? *World J Gastrointest Endosc*. (2021) 13:238–59. doi: 10.4253/wjge.v13.i8.238

23. González JR, Armengol L, Solé X, Guinó E, Mercader JM, Estivill X, et al. SNPassoc: an R package to perform whole genome association studies. *Bioinform*. (2007) 23:654–55. doi: 10.1093/bioinformatics/btm025

24. Kang JH, Le QA. Effectiveness of bariatric surgical procedures. *Medicine*. (2017) 96:e8632. doi: 10.1097/MD.0000000000008632

25. Vantanasiri K, Matar R, Beran A, Jaruvongvanich V. The efficacy and safety of a Procedureless gastric balloon for weight loss: a systematic review and Meta-analysis. *Obes Surg*. (2020) 30:3341–6. doi: 10.1007/s11695-020-04522-3

26. Hinney A, Nguyen TT, Scherag A, Friedel S, Brönner G, Müller TD, et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS One*. (2007) 2:e1361. doi: 10.1371/journal.pone.0001361

27. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. (2007) 447:661–78. doi: 10.1038/nature05911

28. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. (2007) 316:889–94. doi: 10.1126/science.1141634

29. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al. Discovery and refinement of loci associated with lipid levels. *Nat Genet*. (2013) 45:1274–83. doi: 10.1038/ng.2797

30. Yaghootkar H, Zhang Y, Spracklen CN, Karaderi T, Huang LO, Bradfield J, et al. Genetic studies of leptin concentrations implicate leptin in the regulation of early adiposity. *Diabetes*. (2020) 69:2806–18. doi: 10.2337/db20-0070

31. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet*. (2019) 28:166–74. doi: 10.1093/hmg/ddy327

32. Goh Y, Choi J-H. Genetic variation rs1121980 in the fat mass and obesity-associated gene (FTO) is associated with dietary intake in Koreans. Food. *Nutr Res*. (2022):66. doi: 10.29219/fnr.v66.8059

33. Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature*. (2019) 570:514–8. doi: 10.1038/s41586-019-1310-4

34. Pirastu N, McDonnell C, Grzeszkowiak EJ, Mounier N, Imamura F, Merino J, et al. Using genetic variation to disentangle the complex relationship between food intake and health outcomes. *PLoS Genet*. (2022) 18:e1010162. doi: 10.1371/journal.pgen.1010162

35. Huang LO, Rauch A, Mazzaferro E, Preuss M, Carobbio S, Bayrak CS, et al. Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities. *Nat Metab*. (2021) 3:228–43. doi: 10.1038/s42255-021-00346-2

36. Geller F, Reichwald K, Dempfle A, Illig T, Vollmert C, Herpertz S, et al. Melanocortin-4 receptor gene variant I103 is negatively associated with obesity. *Am J Hum Genet*. (2004) 74:572–81. doi: 10.1086/382490

37. Ahituv N, Kavaslar N, Schackwitz W, Ustaszewska A, Martin J, Hébert S, et al. Medical sequencing at the extremes of human body mass. *Am J Hum Genet*. (2007) 80:779–91. doi: 10.1086/513471

38. Heid IM, Vollmert C, Kronenberg F, Huth C, Ankerst DP, Luchner A, et al. Association of the MC4R V103I polymorphism with the metabolic syndrome: the KORA study. *Obesity*. (2008) 16:369–76. doi: 10.1038/oby.2007.21

39. Hwang L-D, Lin C, Gharahkhani P, Cuellar-Partida G, Ong J-S, An J, et al. New insight into human sweet taste: a genome-wide association study of the perception and intake of sweet substances. *Am J Clin Nutr*. (2019) 109:1724–37. doi: 10.1093/ajcn/nqz043

40. Gaulton KJ, Willer CJ, Li Y, Scott LJ, Conneely KN, Jackson AU, et al. Comprehensive association study of type 2 diabetes and related quantitative traits with 222 candidate genes. *Diabetes*. (2008) 57:3136–44. doi: 10.2337/db07-1731

41. Eny KM, Wolever TMS, Fontaine-Bisson B, El-Sohemy A. Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. *Physiol Genomics*. (2008) 33:355–60. doi: 10.1152/physiolgenomics.00148.2007

42. Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med*. (2019) 25:1390–5. doi: 10.1038/s41591-019-0563-7

43. Kichaev G, Bhatia G, Loh P-R, Gazal S, Burch K, Freund MK, et al. Leveraging polygenic functional enrichment to improve GWAS power. *Am J Hum Genet*. (2019) 104:65–75. doi: 10.1016/j.ajhg.2018.11.008

44. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. (2009) 41:18–24. doi: 10.1038/ng.274

45. Junyent M, Parnell LD, Lai C-Q, Lee Y-C, Smith CE, Arnett DK, et al. Novel variants at KCTD10, MVK, and MMAB genes interact with dietary carbohydrates to modulate HDL-cholesterol concentrations in the genetics of lipid lowering drugs and diet network study. *Am J Clin Nutr*. (2009) 90:686–94. doi: 10.3945/ajcn.2009.27738

46. Chen Y, Zhu J, Lum PY, Yang X, Pinto S, MacNeil DJ, et al. Variations in DNA elucidate molecular networks that cause disease. *Nature*. (2008) 452:429–35. doi: 10.1038/nature06757

47. Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet*. (2009) 41:56–65. doi: 10.1038/ng.291

48. Noordam R, Bos MM, Wang H, Winkler TW, Bentley AR, Kilpeläinen TOet al. Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration. *Nat Commun*. (2019) 10:5121. doi: 10.1038/s41467-019-12958-0

49. Trompet S, de Craen AJ, Postmus I, Ford I, Sattar N, Caslake M, et al. Replication of LDL GWAs hits in PROSPER/PHASE as validation for future (pharmaco)genetic analyses. *BMC Med Genet*. (2011) 12:131. doi: 10.1186/1471-2350-12-131

50. Middelberg RPS, Heath AC, Madden PAF, Montgomery GW, Martin NG, Whitfield JB. Evidence of differential allelic effects between adolescents and adults for plasma high-density lipoprotein. *PLoS One*. (2012) 7:e35605. doi: 10.1371/journal.pone.0035605

51. Mohlke KL, Boehnke M, Abecasis GR. Metabolic and cardiovascular traits: an abundance of recently identified common genetic variants. *Hum Mol Genet*. (2008) 17:R102–8. doi: 10.1093/hmg/ddn275

52. Gkouskou KG, Georgiopoulos G, Vlastos I, Lazou E, Chaniotis D, Papaioannou TG, et al. CYP1A2 polymorphisms modify the association of habitual coffee consumption with appetite, macronutrient intake, and body mass index: results from an observational cohort and a cross-over randomized study. *Int J Obes*. (2022) 46:162–8. doi: 10.1038/s41366-021-00972-6

53. Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, et al. Genetic signatures of strong recent positive selection at the lactase gene. *Am J Hum Genet*. (2004) 74:1111–20. doi: 10.1086/421051

54. Hoffmann TJ, Choquet H, Yin J, Banda Y, Kvale MN, Glymour M, et al. A large multiethnic genome-wide association study of adult body mass index identifies novel loci. *Genetics*. (2018) 210:499–515. doi: 10.1534/genetics.118.301479

55. Cole JB, Florez JC, Hirschhorn JN. Comprehensive genomic analysis of dietary habits in UK biobank identifies hundreds of genetic associations. *Nat Commun*. (2020) 11:1467. doi: 10.1038/s41467-020-15193-0

56. Qin Y, Havulinna AS, Liu Y, Jousilahti P, Ritchie SC, Tokolyi A, et al. Combined effects of host genetics and diet on human gut microbiota and incident disease in a single population cohort. *Nat Genet*. (2022) 54:134–42. doi: 10.1038/s41588-021-00991-z

57. Schroor MM, Mokhtar FBA, Plat J, Mensink RP. Associations between SNPs in intestinal cholesterol absorption and endogenous cholesterol synthesis genes with cholesterol metabolism. *Biomedicine*. (2021) 9:1475. doi: 10.3390/biomedicines9101475

58. Avsar O, Kuskucu A, Sancak S, Genc E. Are dopaminergic genotypes risk factors for eating behavior and obesity in adults? *Neurosci Lett*. (2017) 654:28–32. doi: 10.1016/j.neulet.2017.06.023

59. Kring SII, Werge T, Holst C, Toubro S, Astrup A, Hansen T, et al. Polymorphisms of serotonin receptor 2A and 2C genes and COMT in relation to obesity and type 2 diabetes. *PLoS One*. (2009) 4:e6696. doi: 10.1371/journal.pone.0006696

60. Warodomwichit D, Shen J, Arnett DK, Tsai MY, Kabagambe EK, Peacock JM, et al. ADIPOQ polymorphisms, monounsaturated fatty acids, and obesity risk: the GOLDN study. *Obesity*. (2009) 17:510–7. doi: 10.1038/oby.2008.583

61. Cauchi S, Nead KT, Choquet H, Horber F, Potoczna N, Balkau B, et al. The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications for association studies. *BMC Med Genet*. (2008) 9:45. doi: 10.1186/1471-2350-9-45

62. Mohamed AA, Alrohaimi AH, Sayed Abdelgeliel A, Albogami S, Jafri I, Fayad E, et al. The impact of LEP rs7799039 polymorphism and obesity on the severity of coronavirus Disease-19. *Diabetes Metab Syndr Obes*. (2023) 16:515–22. doi: 10.2147/DMSO.S391869

63. Martins MC, Trujillo J, Farias DR, Kac G. Polymorphisms in the leptin (rs7799039) gene are associated with an increased risk of excessive gestational weight gain but not with leptin concentration during pregnancy. *Nutr Res*. (2017) 47:53–62. doi: 10.1016/j.nutres.2017.09.003

64. Kaur H, Badaruddoza B, Bains V, Kaur A. Genetic association of ADIPOQ gene variants (−3971A>G and +276G>T) with obesity and metabolic syndrome in north Indian Punjabi population. *PLoS One*. (2018) 13:e0204502. doi: 10.1371/journal.pone.0204502

65. Uddin MS, Rahman MM, Sufian MA, Jeandet P, Ashraf GM, Bin-Jumah MN, et al. Exploring the new horizon of AdipoQ in obesity-related Alzheimer's dementia. *Front Physiol*. (2021) 11:567678. doi: 10.3389/fphys.2020.567678

66. Truong S, Tran NQ, Ma PT, Hoang CK, Le BH, Dinh T, et al. Association of ADIPOQ single-nucleotide polymorphisms with the two clinical phenotypes type 2 diabetes mellitus and metabolic syndrome in a Kinh Vietnamese population. *Diabetes Metab Syndr Obes*. (2022) 15:307–19. doi: 10.2147/DMSO.S347830

67. Leońska-Duniec A, Grzywacz A, Jastrzębski Z, Jażdżewska A, Lulińska-Kuklik E, Moska W, et al. ADIPOQ polymorphisms are associated with changes in obesityrelated traits in response to aerobic training programme in women. *Biol Sport*. (2018) 35:165–73. doi: 10.5114/biolsport.2018.72762

68. Greenhill C. Link between MC4R mutations and adiposity. *Nat Rev Endocrinol*. (2021) 17:449–9. doi: 10.1038/s41574-021-00524-y

69. Del Corral P, Chandler-Laney PC, Casazza K, Gower BA, Hunter GR. Effect of dietary adherence with or without exercise on weight loss: a mechanistic approach to a global problem. *J Clin Endocrinol Metab*. (2009) 94:1602–7. doi: 10.1210/jc.2008-1057

70. Mousavi H, Karandish M, Jamshidnezhad A, Hadianfard AM. Determining the effective factors in predicting diet adherence using an intelligent model. *Sci Rep*. (2022) 12:12340. doi: 10.1038/s41598-022-16680-8

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 30 November 2023
DOI 10.3389/fnut.2023.1287312

OPEN ACCESS

EDITED BY
Claudia Ojeda-Granados,
University of Catania, Italy

REVIEWED BY
Erika Cione,
University of Calabria, Italy
Bianca Castiglioni,
National Research Council (CNR), Italy

*CORRESPONDENCE
Silvia Lorente-Cebrián
✉ slorentec@unizar.es
Fermín I. Milagro
✉ fmilagro@unav.es

RECEIVED 01 September 2023
ACCEPTED 06 November 2023
PUBLISHED 30 November 2023

CITATION
Díez-Sainz E, Lorente-Cebrián S, Aranaz P, Amri E-Z, Riezu-Boj JI and Milagro FI (2023) miR482f and miR482c-5p from edible plant-derived foods inhibit the expression of pro-inflammatory genes in human THP-1 macrophages. *Front. Nutr.* 10:1287312. doi: 10.3389/fnut.2023.1287312

miR482f and miR482c-5p from edible plant-derived foods inhibit the expression of pro-inflammatory genes in human THP-1 macrophages

Ester Díez-Sainz[1], Silvia Lorente-Cebrián[2,3,4]*, Paula Aranaz[1,5], Ez-Zoubir Amri[6], José I. Riezu-Boj[1,5] and Fermín I. Milagro[1,5,7]*

[1]Department of Nutrition, Food Science and Physiology/Center for Nutrition Research, Faculty of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain, [2]Department of Pharmacology, Physiology and Legal and Forensic Medicine, Faculty of Health and Sport Science, University of Zaragoza, Zaragoza, Spain, [3]Instituto Agroalimentario de Aragón-IA2, Universidad de Zaragoza-CITA, Zaragoza, Spain, [4]Aragón Health Research Institute (IIS-Aragon), Zaragoza, Spain, [5]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain, [6]CNRS, Inserm, iBV, Université Côte d'Azur, Nice, France, [7]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain

Background: Edible plants can exert anti-inflammatory activities in humans, being potentially useful in the treatment of inflammatory diseases. Plant-derived microRNAs have emerged as cross-kingdom gene expression regulators and could act as bioactive molecules involved in the beneficial effects of some edible plants. We investigated the role of edible plant-derived microRNAs in the modulation of pro-inflammatory human genes.

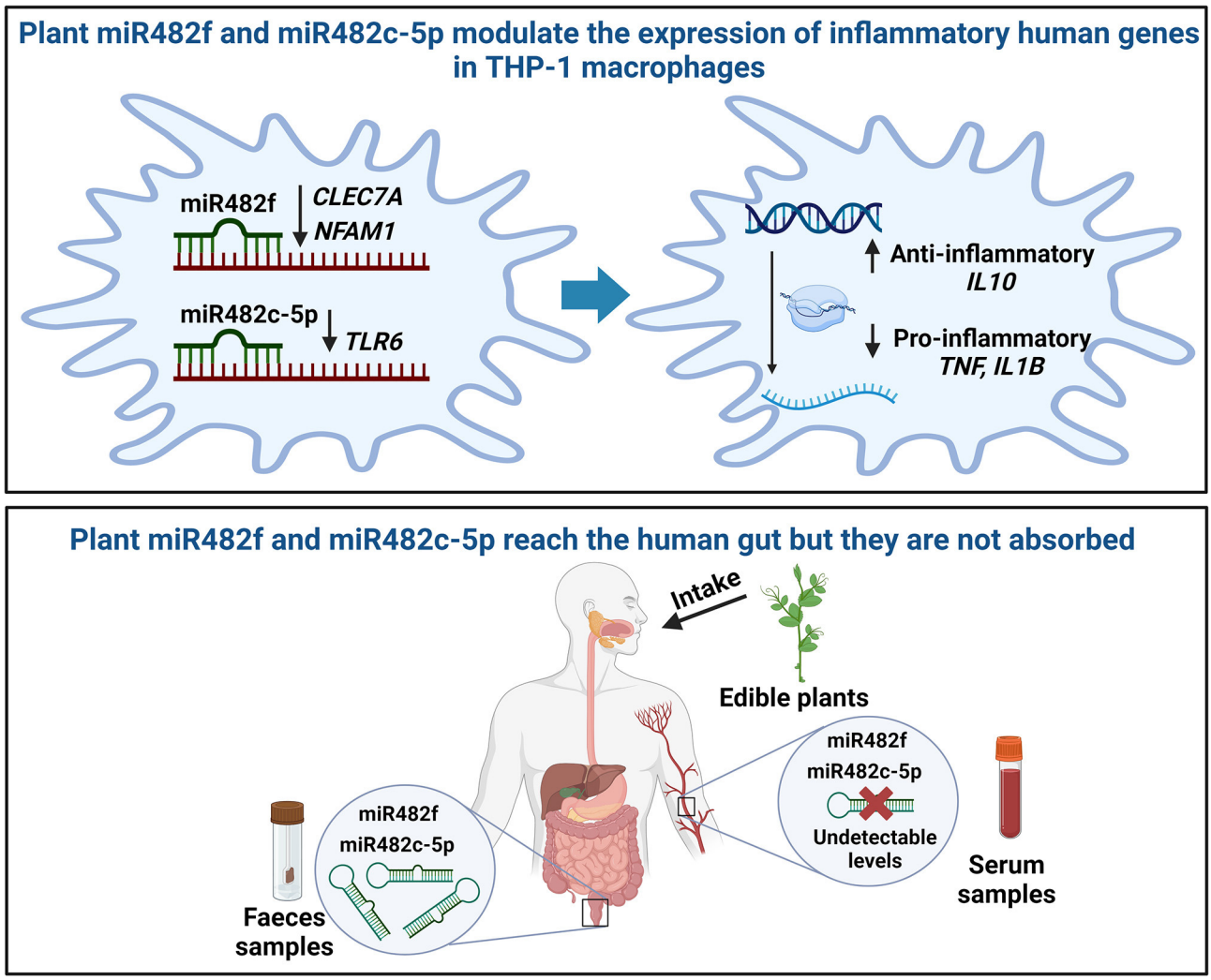
Methods: MicroRNAs from plant-derived foods were identified by next-generation sequencing. MicroRNAs with inflammatory putative targets were selected, after performing *in silico* analyses. The expression of candidate plant-derived miRNAs was analyzed by qPCR in edible plant-derived foods and their effects were evaluated in THP-1 monocytes differentiated to macrophages. The bioavailability of candidate plant miRNAs in humans was evaluated in feces and serum samples by qPCR.

Results: miR482f and miR482c-5p are present in several edible plant-derived foods, such as fruits, vegetables, and cooked legumes and cereals, and fats and oils. Transfections with miR482f and miR482c-5p mimics decreased the gene expression of *CLEC7A* and *NFAM1*, and *TRL6*, respectively, in human THP-1 monocytes differentiated to macrophages, which had an impact on gene expression profile of inflammatory biomarkers. Both microRNAs (miR482f and miR482c-5p) resisted degradation during digestion and were detected in human feces, although not in serum.

Conclusion: Our findings suggest that miR482f and miR482c-5p can promote an anti-inflammatory gene expression profile in human macrophages *in vitro* and their bioavailability in humans can be achieved through diet, but eventually restricted at the gut level.

KEYWORDS

***CLEC7A*, *NFAM1*, *TLR6*, microRNA, cross-kingdom regulation, diet, inflammation, xenomiRs**



GRAPHICAL ABSTRACT
Image designed with BioRender.

1 Introduction

Chronic inflammation is associated with the development of several comorbidities, such as cardiovascular diseases, cancer, autoimmune disorders, metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease, which altogether are the leading causes of mortality worldwide (1–4). Among the factors that could trigger long-term inflammation are obesity, chronic infections, gut microbiota dysbiosis, social, lifestyle, and environmental factors (1). The mechanisms underlying inflammation are complex and comprise several signaling pathways, including the nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways (5). Factors that could regulate these inflammatory pathways include Toll-like receptors (TLRs), microbial products, and pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (5).

Plant-based diets have been associated with the improvement of inflammation. Reported evidence has shown that consumption of nuts, fruits, vegetables, grains, and olive oil promotes an anti-inflammatory profile (6–11). However, the role of plant-based diets in inflammation in humans is currently under investigation; in particular, the identification of all bioactive molecules and their specific mechanisms of action. Among the plant bioactive compounds with anti-inflammatory activities are the phytochemicals, vitamins, minerals, and oil compounds, such as phenolics and triterpenoids found in fruits and vegetables; lectins and peptides in legumes; fiber, polyphenols, phytosterols, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), vitamin E, selenium, and copper in nuts and peanuts; and polyphenols and fiber in cereals (6, 12–14). Notably, microRNAs (miRNAs) have recently emerged as new key bioactive molecules in plants (15, 16).

miRNAs are non-coding RNA molecules of approximately 22 nucleotides that exert post-transcriptional gene expression regulation by interacting with messenger RNAs (mRNAs) (17).

Plant-derived miRNAs are crucial components of the biology of plants, playing a part in a wide range of functions, such as stress responses, development, and metabolism (18). Increasing evidence shows that edible plant-derived miRNAs could also modulate mammalian gene expression, influencing their physiology, for which they have become cross-kingdom gene expression regulators, and they stand for as therapeutic tools to treat human diseases (15, 16, 19, 20). Plant-derived miRNAs could modulate host metabolism, cell proliferation, apoptosis, and viral infections by interacting with diverse cell types, such as adipocytes, hepatocytes, enterocytes, and tumoral cells (21–27). However, there are controversial findings about the bioavailability of edible plant-derived miRNAs in the host (28). While some authors have found plant-derived miRNAs in animal tissues and blood samples, others have reported undetectable levels of these molecules in the host (29, 30). Further investigation is mandatory in order to clarify whether miRNAs could be relevant bioactive components of edible plants in modulating host physiology.

The general aim of the present study was to identify miRNAs in edible plant-based foods that could regulate the expression of human genes associated with inflammation. For this purpose, we selected several food types, including fruits, vegetables, legumes, cereals, and fats and oils, that have been previously associated with beneficial anti-inflammatory effects (6–11). The first objective consisted of identifying miRNAs in edible plant-based products that could display anti-inflammatory effects through modulation of human genes, by performing next-generation sequencing (NGS) and bioinformatic analysis to predict potential human target genes. The second objective was to evaluate the role of candidate edible plant-derived miRNAs in the modulation of inflammation-related human genes in human THP-1 macrophages. The third objective was to determine if candidate edible plant-derived miRNAs with potential anti-inflammatory effects could reach the gastrointestinal tract, being detected in human feces and serum samples.

2 Materials and methods

2.1 Total RNA isolation from samples of edible plant-derived foods

Plant fruits (apples, oranges, and pears), vegetables and greens (green peppers, spinaches, green beans, lettuces, and tomatoes), fats and oils (walnuts and olives), legumes (chickpeas and lentils), and cereals (rice) were purchased at local supermarkets. Plant-origin products were considered as different food types or groups: fruits ($n = 3$), vegetables/greens ($n = 5$), fats and oils ($n = 2$), and cooked legumes/cereals ($n = 3$). Green beans were heat treated in boiling water for 4.5 min in a pressure cooker. Legumes were soaked in water (lentils for 2 h and chickpeas for 12 h) and cooked in a pressure cooker (lentils for 15 min and chickpeas for 30 min). Rice was cooked in water for 20 min in a casserole. Other food elements were used as raw products (non-heat treated).

Total RNA was isolated using the miRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany) as follows: 0.1 g of fruits, legumes, vegetables, and greens, 0.05–0.1 g of fats and oils (0.05 g of walnut and 0.1 g of olive), and 0.2 g of cereals were added to 1 ml of QIAzol Lysis Reagent and grounded at the highest speed, on ice, using Ultra-Turrax T25 Basic (Basic IKA-Werke, Staufen, Germany) between 1 min (fruits, fats and oils, vegetables, and greens) and 2 min (legumes and cereals). Samples were centrifuged at 12,000 *g* between 5 min (fruits, walnuts, legumes, and cereals) and 15 min (olives, vegetables, and greens) at 4°C to remove cell debris and insoluble material. The upper-fat layer of olive samples was removed, and olive samples were centrifuged again at 12,000 *g* for 5 min at 4°C. The supernatants were collected, and RNA purification was concluded following the manufacturer's instructions. For the plant-based food samples used for quantitative real-time PCR (qPCR) assays, 1 μl of spike-in controls (RNA Spike-In Kit, for RT, Qiagen) was added to each sample. RNA for NGS or qPCR was isolated from one sample per type of plant-based food product.

2.2 Next-generation sequencing of miRNAs derived from samples of edible plant-based foods and bioinformatic analysis

NGS was performed in total RNA derived from plant-based products, which were selected for their suitability for small RNA-sequencing (small RNA-seq) after conducting quality controls: 0.1 g of fruits (apple, orange, and pear), 0.1 g of vegetables (spinach and tomato), and 0.05–0.1 g of fats and oil nuts (0.05 g of walnut and 0.1 g of olive). One sample was used for each type of plant-based food product. Libraries were prepared using the NEBNext® Small RNA Library Prep Set for Illumina® kit (New England Biolabs, Ipswich, MA, USA) according to the manufacturer's protocol. Briefly, RNAs were subjected to 3′ and 5′ adaptor ligation and first-strand cDNA synthesis. PCR selectively enriched those DNA fragments that had adapter molecules on both ends. Library amplification was performed by PCR using NEBNext® Multiplex Oligos for Illumina (Index Primers Set 1–4) (New England Biolabs). Purification after PCR was performed using AgenCourt AMPure XP beads (Beckman Coulter, Brea, CA, USA), and libraries were analyzed using Agilent Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) to estimate the quantity and check size distribution. The samples underwent bead-based purification to remove big fragments: the samples were incubated with AgenCourt AMPure XP beads at a ratio of 1.3×, and the beads were then discarded. New beads were added to the supernatant for a final ratio of 3.7×, and all material left was recovered. Final libraries were quantified by qPCR using the KAPA Library Quantification Kit (KAPA Biosystems Inc., Wilmington, MA, USA) before amplification with Illumina's cBot. Libraries were sequenced $1 \times 50 + 8$ bp on Illumina's HiSeq2500.

The bioinformatic analyses to identify miRNA sequences were carried out as follows: the adapter from raw data was removed using a skewer (31), and reads with a size ranging from 15 to 30 bases were aligned to a plant-based reference genome (*Prunus persica*, NCBIv2, and annotation NCBIv2.52 restricted to miRNAs) (hhttps://plants.ensembl.org/Prunus_persica/Info/Index; https://mirbase.org/results/?query=prunus+persica), with

miRNA annotation from miRBase (version 22) using ShortStack (32), allowing a maximum of two mismatches in the seed area. Mapped tags were counted using Htseq-count (33), considering the strand information. Raw reads were normalized with DESeq2. Sequencing data were deposited in NCBI's Gene Expression Omnibus (34): GEO series accession number GSE234786 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE234786).

2.3 Bioinformatic target gene prediction analysis

The RNA target analysis servers psRNATarget scoring schemas V1 and V2 (https://www.zhaolab.org/psRNATarget/) (35) and TAPIR (http://bioinformatics.psb.ugent.be/webtools/tapir/) (36) were used to predict human putative target genes of all the plant-derived miRNAs identified by NGS.

The cDNA library chosen for both psRNATarget and TAPIR servers was the "*Homo sapiens* (human), transcript, Human genomic sequencing project," available at psRNATarget, and the bioinformatic predictions were performed with the default parameters. Applying psRNATarget scoring schemas V1 and V2, the following parameters for each output were reported: target accession number of the putative target gene, expectation (penalty for the mismatches), mRNA target aligned fragment, and the inhibitory effect (cleavage or translation inhibition) (35). The scoring Schema V1 also showed the unpaired energy (UPE), which is the energy required to open a mRNA secondary structure (35). The results showed applying the TAPIR program includes the score (penalty for mismatches, gaps, and G-U pairs), the minimum free energy (MFE) ratio, which is a ratio between the free energy of the miRNA–mRNA duplex vs. the free energy of this duplex with perfect matches, and the mRNA target aligned fragment (36). The GeneCodis4 program (https://genecodis.genyo.es/) was used to perform the Gene Ontology (GO) biological process analysis of candidate putative target genes.

2.4 miRNA miR482f and miR482c-5p expression analysis

Expression of miR482f and miR482c-5p was analyzed using qPCR in total RNA isolated from 0.1 g of fruits (apple, orange, and pear), 0.1 g of vegetables and greens (green pepper, spinach, raw and cooked green beans, lettuce, and tomato), 0.05–0.1 g of fats and oils (0.05 g of walnut and 0.1 g of olive), 0.1 g of cooked legumes (chickpeas and lentils), 0.2 g of cooked cereals (rice), biological (serum and feces) human samples (described in MM Section 2.8), and cell culture samples (described in MM Section 2.5). Expression of the spike-in UniSp4 was used as a positive control in plant-derived food, and human samples to determine that short RNA fragments/miRNAs were unaffected by RNA isolation and expression analysis. miR-141-3p and miR-103a-3p were used as human (internal) controls to determine the quality of serum and feces samples and the reliability of the results. Previous evidence has reported consistent presence and stability of miR-141-3p and miR-103a-3p in the feces and serum of mammals, including humans (37–40).

Total RNA (4 µl) was reverse transcribed in 10 µl of final volume reaction with miRCURY LNA RT Kit (Qiagen). Reactions were performed in a MyCycler Thermal Cycler (Bio-Rad, Hercules, CA, USA) at 42°C for 60 min and 95°C for 5 min. cDNA from plant-derived food samples was centrifuged for 1 min at maximum speed, and the supernatant was collected for qPCR.

qPCR was performed with cDNA diluted 1/10 using the miRCURY LNA SYBR Green PCR Kit (Qiagen) and miRCURY LNA miRNA PCR Assays (Qiagen). The sequences of the PCR assays are described in Table 1. qPCR was performed in a CFX384 Touch Real-Time PCR Detection System (Bio-Rad) with the following cycling conditions: 95°C for 2 min, 40 cycles at 95°C for 10 s, and 56°C for 1 min. Non-template control samples were added to each qPCR reaction. qPCR duplicates were made for each sample.

2.5 Cell culture and edible plant-derived miRNA mimic transfection

Human monocytic leukemia cell line THP-1 was purchased from the American Type Culture Collection (ATCC® TIB-202™; Manassas, VA, USA). THP-1 cells were maintained in RPMI-1640 medium (Gibco, Thermo Fisher Scientific Inc.) supplemented with 10% fetal bovine serum (FBS; Gibco) and 1% penicillin–streptomycin solution (P/S; Gibco) and incubated at 37°C and 5% CO_2.

For the experiments, THP-1 cells were seeded in 12-well plates (200,000 cells/well) for gene and miRNA expression assays and 48-well plates (50,000 cells/well) for cytotoxicity assays. The cells were seeded in RPMI-140 medium supplemented with 10% FBS, 1% P/S, and phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich, San Luis, MO, USA) at a final concentration of 50 ng/ml to induce the differentiation of THP-1 monocytes into macrophages. The cells were incubated for 48 h.

After differentiation, the cells were forward transfected with Lipofectamine RNAiMAX Reagent (Thermo Fisher Scientific Inc., Waltham, MA, USA) and 60 nM of mirVana™ miRNA mimics (Thermo Fisher Scientific Inc.): miR482f (5′-UCUUUCCUACUCCACCCAUUCC-3′), miR482c-5p (5′-GGAAUGGGCUGUUUGGGAUG-3′), and a scramble control (mirVana™ miRNA mimic, negative control #1). Cell medium was changed to RPMI-140 supplemented with 10% FBS, without antibiotics (1 ml/well of 12-well plates, 250 µl/well of 48-well plates). MiRNA mimics and Lipofectamine were diluted in Opti-MEM I Reduced Serum Medium (Gibco), mixed in a 1:1 ratio, and incubated for 5 min at room temperature. miRNA mimic–Lipofectamine complexes were added to each well (100 µl/well of 12-well plates and 25 µl/well of 48-well plates). The volumes of Lipofectamine used were: 2.5 µl per well of 12-well plates (on a volume of 1,100 µl) and 0.625 µl per well of 48-well plates (on a volume of 275 µl). The cells were incubated for 6 h to evaluate the transfection efficiency (detection of transfected miRNAs in cell cultures) or 48 h for gene expression and cytotoxicity assays.

TABLE 1 Assays used for qPCR miRNA expression analyses.

miRNA name	miRBase accession number	Assay reference (GenGlobe ID)	Assay sequence (5′-3′)
hsa-miR-141-3p	MIMAT0000432	YP00204504	5′-UAACACUGUCUGGUAAAGAUGG-3′
hsa-miR-103a-3p	MIMAT0000101	YP00204063	5′-AGCAGCAUUGUACAGGGCUAUGA-3′
ppe-miR482f	MIMAT0031512	YP02105458	5′-UCUUUCCUACUCCACCCAUUCC-3′
ppe-miR482c-5p	MIMAT0027283	YP02114485	5′GGAAUGGGCUGUUUGGGAUG-3′
UniSp4	N/A	YP00203953	N/A

MiRNA names, accession number, and sequences of miRCURY LNA miRNA PCR Assays (Qiagen). N/A, non-applicable.

2.6 Gene expression analysis

Cells were frozen on dry ice and stored at −80°C. For miRNA expression analysis experiments, before freezing, the cells were washed with PBS. Total RNA was isolated with TRIzol Reagent (Thermo Fisher Scientific Inc.), according to the manufacturer's instructions. RNA quantity and purity (260/280 ratio) were determined in a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific Inc.). miRNA miR482f and miR482c-5p expression analyses were performed as described in MM Section 2.4.

For mRNA expression analysis, RNA (1 μg) was treated with DNA-free™ DNA Removal Kit (Invitrogen. Thermo Fisher Scientific Inc.) following the manufacturer's protocol. DNA-free RNA was reverse transcribed into cDNA with dNTP Mix (Bioline, Luckenwalde, Germany), Random Primers (Invitrogen. Thermo Fisher Scientific Inc.), Recombinant RNAsin Ribonuclease Inhibitor (Promega, Madison, WI, USA), and M-MLV Reverse Transcriptase (Invitrogen). All the reactions were performed in a GeneAmp PCR System 2700 (Applied Biosystems. Thermo Fisher Scientific Inc.). qPCR was performed with cDNA diluted 1/1.5 using iTaq™ Universal Probes Supermix (Bio-Rad) and specific TaqMan® Gene Expression Assays (Thermo Fisher Scientific Inc.) and Predesigned qPCR Assays from Integrated DNA Technologies (Coralville, IA, USA) described in Table 2. Amplification reactions were performed in a CFX384 Touch Real-Time PCR Detection System (Bio-Rad) as follows: 50°C for 2 min, 95°C for 10 min, 40 cycles at 95°C for 15 s, and 60°C for 1 min. Non-template control samples were added to each qPCR reaction. Gene expression levels (Cq) were normalized (ΔCq) with the housekeeping gene TATA box binding protein (*TBP*). The $2^{-\Delta\Delta Cq}$ method (41) was used to determine the relative gene expression of genes, through comparisons between the plant-derived miRNA mimic treatments and the scramble control. At least, two independent experiments were conducted, and qPCR was run in triplicates for each sample.

2.7 Cytotoxicity assays

Cell viability and proliferation after miRNA treatments were determined with the (3-4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) assay (CellTiter 96® Aqueous One Solution Cell Proliferation Assay. Promega) in THP-1 macrophages. Cells were incubated with MTS reagent (20 μl of reagent per 100 μl of culture medium) for 2.5 h at 37°C. The absorbance was measured at 490 nm in an absorbance microplate reader Agilent BioTek 800 TS (Agilent Technologies). The cell viability was expressed as the % relative viability; calculated as the mean percentage of each experimental group relative to the mean of the scramble control. Four independent experiments were conducted.

TABLE 2 Assays used for qPCR gene expression analyses.

Gene name	Assay ID	Accession number (RefSeq)
NFAM1	[1]Hs.PT.58.45296389	NM_145912(1)
CLEC7A	[1]Hs.PT.58.3686547.g	NM_022570(6)
TLR6	[1]Hs.PT.58.26737272.g	NM_006068(1)
BCL2L12	[1]Hs.PT.58.4708679	NM_001040668(2)
IL10	[2]Hs00961622_m1	NM_000572.2
TNF	[2]Hs00174128_m1	NM_000594.3
IL1B	[2]Hs01555410_m1	NM_000576.2 XM_017003988.1
TBP	[2]Hs00427620_m1	NM_001172085.1 NM_003194.4

Gene names, assay IDs, and accession numbers of Integrated DNA technologies Predesigned qPCR Assays[1] and TaqMan® Gene Expression Assays[2].

2.8 Detection of edible plant-derived miR482f and miR482c-5p in biological human samples

Plant-derived miRNA analyses from serum and fecal samples were performed as a proof of concept from anonymous volunteers (>18 yr), who qualitatively consumed plant-based products. The samples were donated by nine volunteers (five men and four women) anonymously, and no personal data were collected from these subjects. Specifically, volunteers usually consumed these plant-based food groups: legumes, fruits, vegetables, cereals, and fats and oils, in the variety and proportion they preferred.

Blood samples were collected through a venous puncture in BD Vacutainer® SST™ II Advance tubes (BD Vacutainer Systems, Plymouth, United Kingdom). Samples were kept at room temperature for 30 min and centrifuged at 2,000 *g* for 15 min at 4°C. Serum was collected and centrifuged at 16,000 *g* for

10 min at 4°C. Total RNA was extracted from 200 μl of serum samples using miRNeasy Serum/Plasma Advanced Kit (Qiagen). Fecal samples were collected in stool nucleic acid collection and preservation tubes (Norgen Biotek Corp., ON, Canada) according to the manufacturer's instructions. Total RNA was isolated using the RNeasy PowerMicrobiome Kit (Qiagen) from 250 μl of feces following the manufacturer's protocol. Overall, 1 μl of spike-in controls (Qiagen) was added to the serum and fecal samples before RNA extraction. MiRNA miR482f and miR482c-5p expression analyses were performed as described in MM Section 2.4.

2.9 Statistical analysis

The statistical analyses were performed using GraphPad Prism 6.0 for Windows (GraphPad Software Inc., La Jolla, CA, USA). For *in vitro* studies, comparisons between the miRNA negative control and the experimental groups were performed using Student's *t*-test. Student's *t*-test was selected because the aim was to determine differences between plant-derived miR482f and miR482c-5p with the negative control, as independent studies, and not to establish a comparison between the three groups. Statistical significance was considered at p-value <0.05.

3 Results

3.1 Plant-derived miRNAs are present in edible plant-based products, and miR482f and miR482c-5p could potentially inhibit the expression of pro-inflammatory human genes

We performed NGS analysis to identify miRNAs in edible plant-based foods, including fruits (apple, orange, and pear), vegetables (spinach and tomato), and fats and oils (walnut and olive). After the alignment of the reads with the peach genome, as a reference genome, 176 miRNAs were identified in the overall pool of plant-based food samples analyzed (Supplementary Table S1).

The bioinformatic analysis with psRNATarget and TAPIR predicted potential human target genes of the 176 miRNAs detected in the plant-based food samples (data not shown). In the present study, we only focused on miR482f (Ensembl gene: ENSRNA049996209) and miR482c (Ensembl gene ENSRNA049996546) because human gene prediction analyses revealed their potential role in targeting inflammation-related human genes.

The alignment of the miR482f mature sequence with the human transcriptome revealed that 6 (psRNATarget scoring schema V1), 24 (psRNATarget scoring schema V2), and 5 (TAPIR) transcripts could be putative targets (Supplementary Table S2). Altogether, 26 different transcripts (corresponding to 22 different genes) were predicted as putative targets of miR482f. Only three transcripts appeared in the three algorithms. These were as follows: the transcript NM_145912, which codifies for NFAT activating protein with ITAM motif 1 (NFAM1), and the transcripts NM_197949 and NM_022570, which codify for two isoforms of the C-type lectin domain containing 7A (CLEC7A) protein (Supplementary Table S2, Supplementary Figure S1).

The alignment of the plant-derived miR482c-5p mature sequence and the human transcriptome reported that 2 (psRNATarget scoring schema V1), 24 (psRNATarget scoring schema V2), and 5 (TAPIR) transcripts could be putative target genes (Supplementary Table S3). A total of 27 different transcripts (22 different genes) were identified as putative targets of plant-derived miR482c-5p. The only common targets of the three prediction programs were the transcript NM_001160332 of the neurofascin (NFASC) protein and the transcript NM_006068, which encodes for the Toll-like receptor 6 (TLR6) (Supplementary Table S3, Supplementary Figure S2).

According to the bibliography, the combination of psRNATarget and TAPIR programs gives highly accurate predictions (42). Therefore, we selected for subsequent analyses the common target genes to psRNATarget (schemas V1 and V1) and TAPIR: *NFAM1* and *CLEC7A* as putative target genes of miR482f, and *NFASC* and *TLR6* as putative target genes of miR482c-5p.

To explore the biological functions shared between the predicted target genes, we performed Gene Ontology (GO) biological process analysis with GeneCodis4 (Supplementary Figure S3). For the miR482f potential targets, the results revealed that both *NFAM1* and *CLEC7A* participate in the inflammatory response and in the positive regulation of DNA-binding transcription activity (Supplementary Figure S3A). GeneCodis4 associated *TLR6* with a wide variety of functions related to the immune system, such as macrophage activation, and pro-inflammatory cytokines production (Supplementary Figure S3B). We did not delve into the study of the potential role of miR482c-5p in shaping the *NFASC* gene expression since the aim of the present study was to evaluate the impact of plant-derived miRNAs on inflammation. *NFASC* main functions are related to the nervous system (43). According to Protein Atlas (https://www.proteinatlas.org/ENSG00000163531-NFASC/subcellular), its expression is negligible in THP-1 monocytes, which was the *in vitro* model selected in this study to achieve the abovementioned objective.

Regarding miR482f, we identified 220.38 normalized reads in the walnut sample, which were also detected in the tomato, orange, olive, and pear samples (Table 3). miR482c, which comprises−5p and−3p sequences, was mostly detected in the walnut and pear samples (655.13 and 266.26 normalized reads, respectively) as well as in the apple, orange, spinach, and olive samples (Table 3), although in lower copy read numbers.

We next sought to qualitatively complement the small RNA-seq results using qPCR analysis in different food matrices, including a greater range of edible plant-derived foods: fruits (apples, oranges, and pears), vegetables and greens (green pepper, spinach, raw and cooked green beans, lettuce, and tomato), fats and oils (walnuts and olives), cooked legumes (chickpeas and lentils), and cooked cereals (rice) (Figure 1). miR482f was detected in fruits (orange and pear), vegetables and greens (raw and cooked green beans, lettuce, spinach, green pepper, and tomato), legumes (cooked lentils), cereals (cooked rice), and fats and oils (olive) (Figure 1A). Regarding miR482c, we validated that the sequence corresponding to the transcript miR482c-5p. miR482c-5p was present in all

10.3389/fnut.2023.1287312

TABLE 3 Detection of miR482f and miR482c in plant-based foods by next-generation sequencing.

Gene ID	miRNA name	Normalized reads						
		Walnut	Tomato	Orange	Pear	Apple	Olive	Spinach
gene:ENSRNA049996209	miR482f	220.38	78.09	45.35	0.10	U	0.41	U
gene:ENSRNA049996546	miR482c	655.13	U	0.60	266.26	67.70	0.28	0.27

Small RNA-seq was performed with total RNA isolated from 0.05 to 0.1 g of fats and oils and 0.1 g of fruits and vegetables. Reads were mapped to the *Prunus persica* genome (annotation NCBIv2.52). Results correspond to the normalized reads of a single sample per plant-based product. U, undetectable.

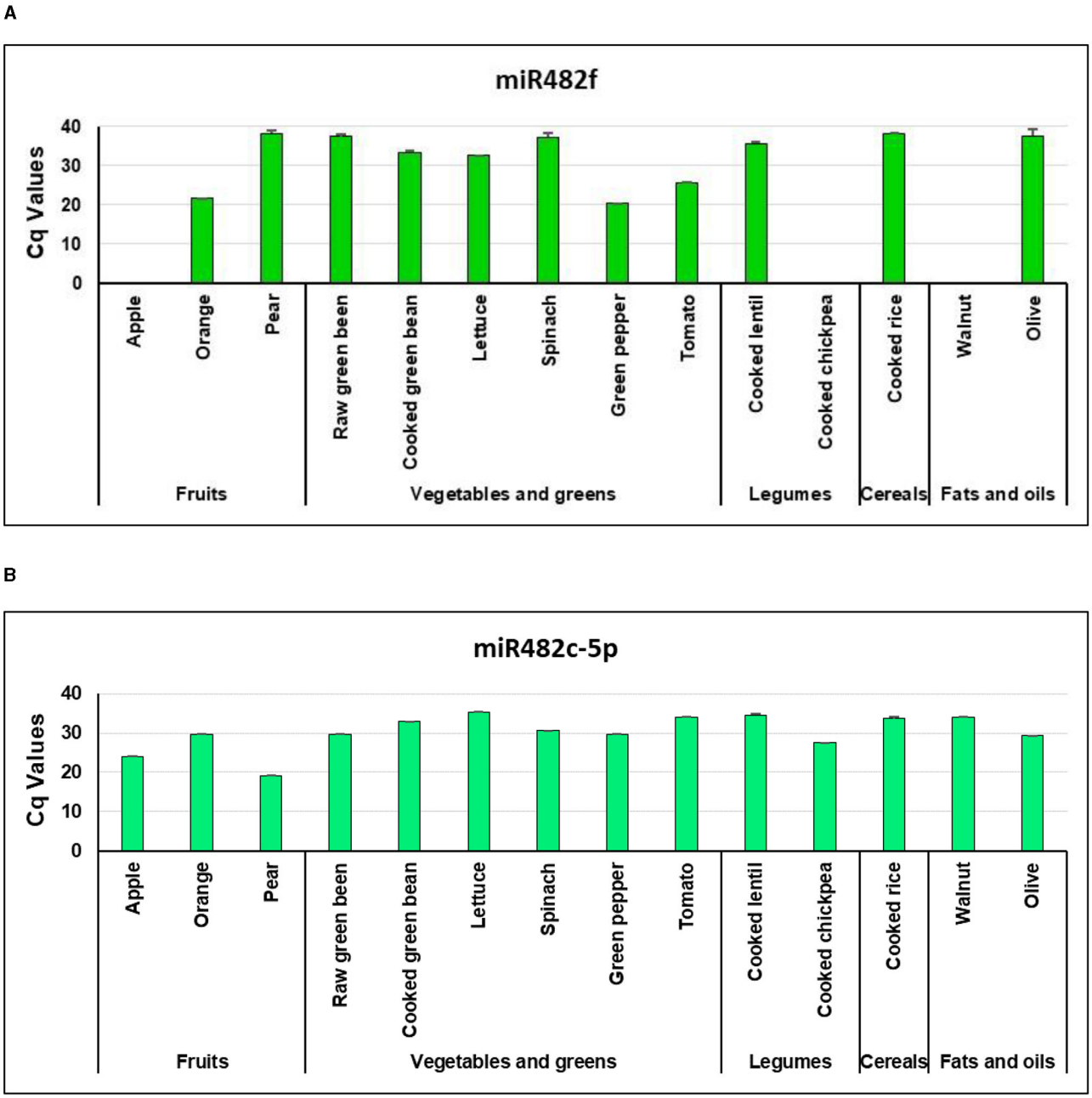


FIGURE 1
Detection of miR482f and miR482c-5p in plant-based foods by qPCR. Cq values of **(A)** miR482f (5′-UCUUUCCUACUCCACCCAUUCC-3′) and **(B)** miR482c-5p (5′-GGAAUGGGCUGUUUGGGAUG-3′) with RNA isolated from 0.1 g of fruits (apple, orange, and pear), 0.1 g of vegetables and greens (green pepper, spinach, raw and cooked green beans, lettuce, and tomato), 0.05–0.1 g of fats and oils (0.05 g of walnut and 0.1 g of olive), 0.1 g of cooked legumes (chickpea and lentil), and 0.2 g of cooked cereals (rice). Results are the mean ± standard error of the mean (SEM) (one sample per type of food product and duplicates for qPCR).

the selected edible plant-derived foods (Figure 1B). The objective of this analysis was to determine the presence or absence of miRNAs, rather than comparing their abundance between samples. Therefore, data were not normalized to any small RNA sequence (housekeeping) as usually performed for qPCR methods, providing that (1) our aim required only a qualitative measurement and (2) no standardized normalization method has been established for plant-derived miRNA quantification. Positive detection of the spike-in UniSp4 was achieved in all food-based samples, which confirmed the accurate isolation and detection of miRNAs (data not shown).

Overall, miR482f and miR482c-5p were present in the different raw and cooked plant-derived foods that were analyzed. The miRNA target gene prediction algorithms and the Genecodis4 GO biological processes analyses, suggest that miR482f and miR482c-5p could potentially inhibit the expression of genes involved in inflammation. Therefore, we delved into the study of the potential role of miR482f and miR482c-5p modulating the expression of their putative target genes (*NFAM1* and *CLEC7A*, and *TLR6*, respectively), and their potential impact on the expression profile of anti- and pro-inflammatory cytokines, in an *in vitro* model of human macrophages.

3.2 Plant-derived miR482f and miR482c-5p mimics are present in human macrophage-like THP-1 cells after transfection

Human monocytes THP-1 cells differentiated to macrophages were transfected with miRNA mimics miR482f and miR482c-5p, and a scramble control at a concentration of 60 nM. To determine the effectiveness of transfections, we performed qPCR analysis to detect the miRNAs after 6 h of transfection (Supplementary Figure S4). miR482f and miR482c-5p were present in THP-1 cells transfected with each of these mimics (Cq values between 12 and 13). The plant-derived miRNA sequences were not detected in negative control-transfected cells, suggesting that miR482f and miR482c-5p have no human homologous miRNAs in the THP-1 cells.

3.3 Impact of plant-derived miR482f and miR482c-5p mimics on macrophage-like THP-1 viability and/or proliferation

The viability/proliferation of THP-1 macrophage-like cells was evaluated with MTS at 48 h of transfection with 60 nM of plant-derived miR482f, miR482c-5p mimics, and a scramble sequence as a control (Figure 2). miR482f mimic did not induce any change in cell viability or proliferation (Figure 2A), whereas miR482c-5p mimic decreased 13.5 ± 3.6% of the viability/proliferation of THP-1-like macrophages in comparison with the control cells (Figure 2B).

3.4 Plant-derived miR482f and miR482c-5p modulate gene expression of predicted target genes and inflammation-related biomarkers in THP-1 cells

We validated the human target gene bioinformatic predictions (*NFAM1* and *CLEC7A* for miR482f; and *TLR6* for mi482c-5p) in the transfected THP-1 macrophage-like cells. Gene expression profile of anti- and pro-inflammatory biomarkers (interleukin 10, *IL10*; tumor necrosis factor, *TNF*; interleukin 1 Beta; and *IL1B*) and the Bcl-2-like protein 12 (*BCL2L12*) was evaluated.

miR482f mimic downregulated the gene expression of the putative targets *NFAM1* (35.2% ± 3.0; $p < 0.0001$) and *CLEC7A* (37.7% ± 4.2; $p < 0.0001$) (Figure 3A) after 48 h of miRNA transfection. miR482f mimic increased the mRNA levels of the anti-inflammatory cytokine *IL10* (31.5% ± 13.3, $p < 0.05$) and reduced the mRNA levels of the pro-inflammatory cytokine *TNF* (26.0% ± 7.2, $p < 0.01$) (Figure 3B). No significant changes were detected for *IL1B*, *TRL6*, and *BCL2L12* gene expression (Figure 3B). A trend was observed for *IL1B* mRNA decrease (21.9 % ± 10.7, $p = 0.0708$).

The transfection of miR482c-5p mimic reduced the mRNA levels of the putative target gene *TLR6* (40.5% ± 7.6 %, $p < 0.001$) at 48 h of transfection (Figure 4A). miR482c-5p downregulated gene expression of the pro-inflammatory genes *TNF* (29.6% ± 7.5, $p < 0.01$), *NFAM1* (45.4% ± 3.4, $p < 0.0001$), *CLEC7A* (14.7% ± 4.4 $p < 0.01$), *IL1B* (28.4% ± 10.93 $p < 0.05$), and *BCL2L12* (27.39% ± 8.2, $p < 0.01$), but it did not induce significant changes in the expression of the anti-inflammatory cytokine *IL10* (Figure 4B).

3.5 Plant-derived miRNAs miR482f and miR482c-5p are detected in human feces but not in serum

To determine whether miR482f and miR482c-5p derived from plant-based foods could reach the gastrointestinal tract, resist degradation during digestion, and potentially be absorbed, we collected feces and serum samples from healthy volunteers who usually consume edible plant-based products. The positive expression of the spike-in UniSp4 in both serum and feces samples confirmed the accuracy of the experimental procedure (RNA isolation and expression analysis) (data not shown).

We measured expression levels of plant-derived miR482f and miR482c-5p using qPCR in nine fecal samples (Figure 5). Both miR482f and miR482c-5p were detected in all the samples, suggesting that plant-derived miRNAs are present in the gastrointestinal tract and resist digestion. The expression of the human hsa-miR-141-3p was used as an endogenous control to determine the quality of the fecal samples.

We analyzed the levels of plant-derived miR482f and miR482c-5p in serum samples from the same volunteers in which the two plant-derived miRNAs were present in feces. Neither miR482f nor miR482c-5p were detected in serum samples in any of the volunteers (data not shown). To further confirm the reliability of the results, we used the human miR-103a-3p as an endogenous

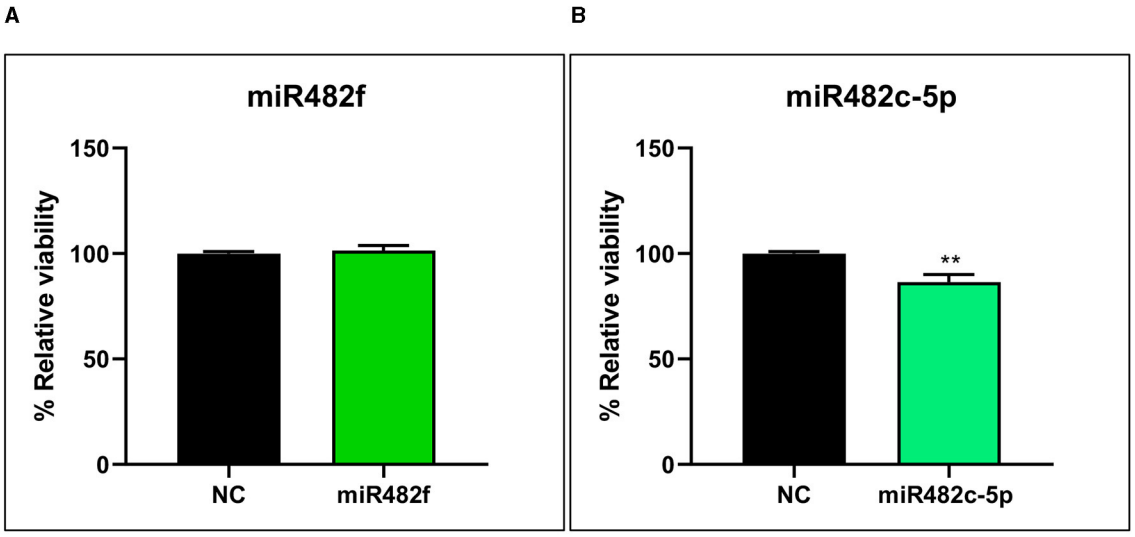


FIGURE 2
Evaluation of the effect of plant-derived miRNA mimics **(A)** miR482f and **(B)** miR482c-5p on the viability/proliferation of THP-1 macrophage-like cells. THP-1 monocytes differentiated to macrophages for 48 h were transfected with 60 nM of miRVana mimics miR482f (5′-UCUUUCCUACUCCACCCAUUCC-3′), miR482c-5p (5′-GGAAUGGGCUGUUUGGGAUG-3′), and a scramble sequence as a negative control (NC). Cell viability/proliferation was evaluated in THP-1 macrophage-like cells after 48 h of transfections. Results are the mean percentage ± standard error of the mean (SEM) relative to the cells transfected with the scramble sequence (negative control) ($n = 4$ independent experiments; NC: $n = 13$; miR482f: $n = 13$; miR482c-5p: $n = 13$). NC, negative control. Significance refers to the effect of miR482f or miR482c-5p with respect to the negative control. p-value: ** $p < 0.01$.

control. hsa-miR-103a-3p was detected in all the serum samples analyzed (Cq values between 24 and 28), suggesting that the lack of detection of plant-derived miR482f and miR482c-5p could be due to their very low or inexistent quantity to be detected by qPCR and not because of the serum sample quality.

4 Discussion

The present study aimed to identify miRNAs from edible plant-derived foods that could modulate the expression of human genes associated with inflammation. The rationale of this hypothesis is mainly based on the evidence supporting (1) the role of plant-based diets in alleviating inflammation, and (2) the recent discovery of miRNAs as bioactive molecules of plants and cross-kingdom gene expression regulators (19, 44).

We selected five groups of plant-derived foods (fruits, vegetables and greens, legumes, cereals, and fats and oils) based on previous evidence that unveiled their anti-inflammatory properties (8–11). Although we identified a wide variety of miRNAs in edible plants, miR482f and miR482c-5p were selected for their potential role in targeting inflammatory human genes. We found that these miRNAs are present in the five groups of foods. We used the *Prunus Persica* genome as a reference to annotate plant-derived miRNA sequences of edible plants detected by NGS. As regards our results, both NGS and qPCR, there is a high degree of conservation of these miRNAs in the plant kingdom or at least among the plant-origin food products analyzed in this study. The results revealed that original plant-derived miR482f and miR482c withstand standard heat-treatment (cooking) processes. In agreement with our findings, other authors have also reported that harsh conditions such as storage, processing, and cooking do not compromise plant-derived miRNA survival (45). For some plant-based food samples, we detected miR482f or miR482c by NGS and not by qPCR and vice versa. For instance, we detected miR482f in walnuts only by NGS and in spinach only by qPCR. The miR482c were detected in tomato only by qPCR. The results obtained with both techniques are complementary, given that the nature of the sample might determine the suitability for either NGS and/or qPCR. However, the NGS hits that could not be validated by qPCR should be taken with caution. Reliable conclusions can only be drawn about the presence or absence of miR482f and miR482c in each plant-based product (verified by two independent methods). The relative abundance between different types of plant-based products cannot be compared since there is no reliable and universal endogenous plant-derived miRNA normalization method established yet. Our *in silico* analysis predicted that our miRNA candidates (miR482f and miR482c-5p) would eventually bind specific mRNA targets associated with inflammation. Providing that the mechanism of action of miRNA usually links to mRNA inhibition (target repression), plant-derived miR482f and miR482c-5p could eventually downregulate inflammation-related genes. To eventually validate this hypothesis, we used differentiated human THP-1 macrophages, an *in vitro* cell model widely used in the study of the antioxidant and anti-inflammatory bioactive properties of chemical compounds and derived food products (46–48).

Using differentiated human THP-1 macrophages, we have demonstrated for the first time that plant-derived miR482f and miR482c-5p can achieve efficient inhibition of their predicted targets (*CLEC7A* and *NFAM1* and *TLR6*, respectively) and

10.3389/fnut.2023.1287312

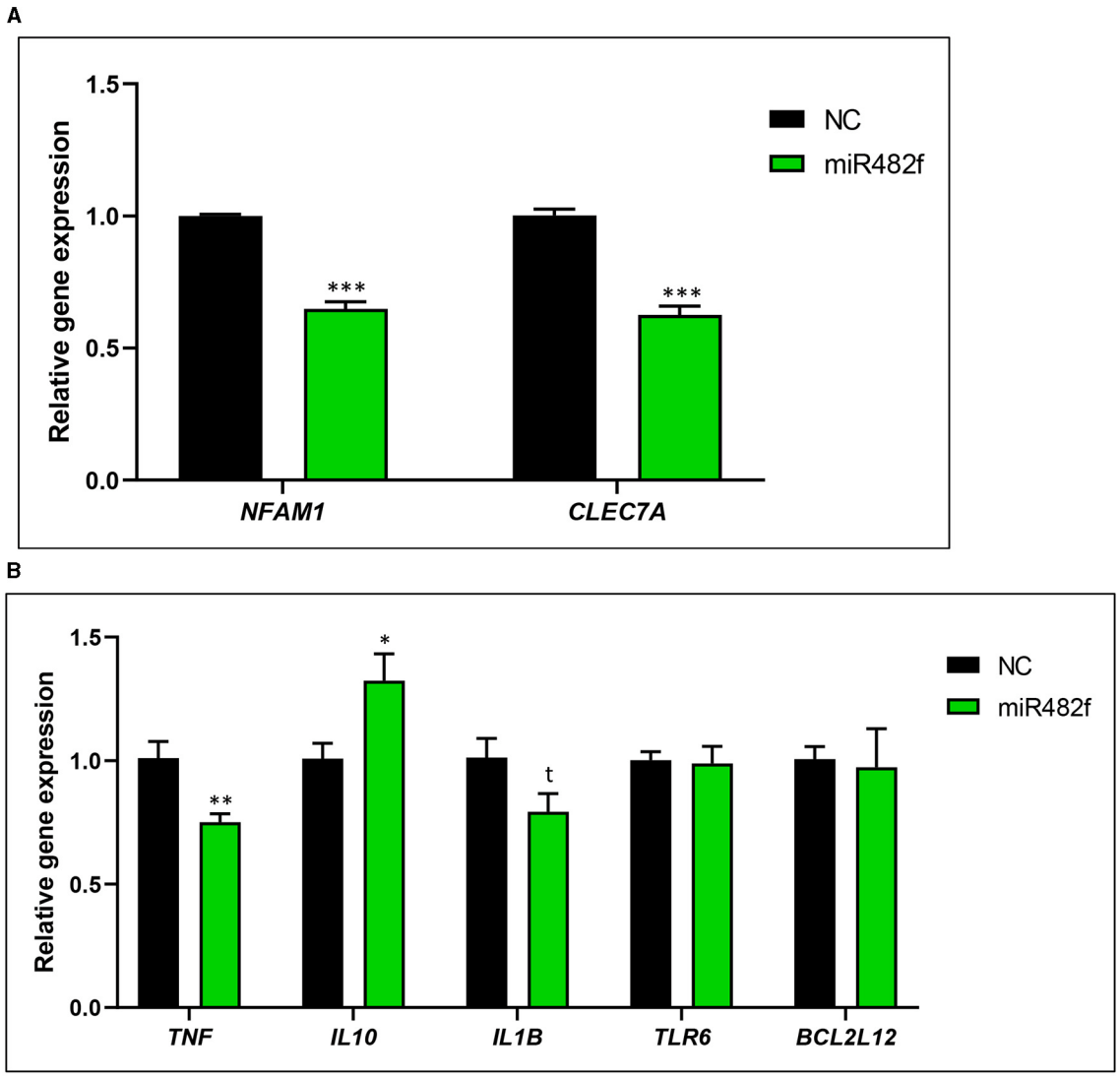


FIGURE 3
Gene expression analysis of THP-1 macrophage-like cells transfected with plant-derived miR482f mimic. **(A)** mRNA levels of putative targets *NFAM1* and *CLEC7A*. **(B)** Gene expression levels (mRNA) of pro-inflammatory (*TNF*, *IL1B*, and *TLR6*) and anti-inflammatory (*IL10*) biomarkers and *BCL2L12*. THP-1 macrophage-like cells were transfected with 60 nM of miRVana mimic miR482f (5′-UCUUUCCUACUCCACCCAUUCC-3′) and a scramble sequence as a negative control. Gene expression levels were measured at 48 h of transfection by qPCR. Results are the gene expression levels of each gene normalized to the housekeeping gene *TBP* and calculated by the $2^{-\Delta\Delta Ct}$ method, establishing comparisons with the negative control. NC, negative control. The results are presented as mean percentage ± standard error of the mean (SEM) ($n = 2$ independent experiments, run in triplicate; NC: $n = 5$; miR482f: $n = 6$). p-value: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, t = 0.0708.

induce significant changes in other (functional) inflammation-related genes. As regards our results, plant-derived miR482f and miR482c-5p stand out as bioactive molecules from dietary sources with the potential to manage inflammation-associated genes. However, specific differences (in direct targets and in functional genes) between both miRNAs exist and could suggest different but complementary mechanisms of action for each plant-derived miRNA. miR482f and miR482c-5p direct targets had previously been linked to immune system function (49–52) and production of pro-inflammatory cytokines (such as TNF-α, IL1-β, and IL-6) (53–56), suggesting that their inhibition could have a therapeutic approach. The finding that miR482c-5p also reciprocally downregulated *CLEC7A* and *NFAM1* gene expression as its counterpart (miR482f) is of relevance since a positive correlation between *TLR6* and *CLEC7A* expression has also been reported (57). On the other hand, while miR482f reciprocally upregulated anti-inflammatory (*IL10*) and downregulated pro-inflammatory factors (*TNF*), miR482c-5p only downregulated pro-inflammatory genes (*TNF*, *IL1B*). Whether these changes at the mRNA expression level translate to functional (i.e., protein secretion) modifications remains to be established in future studies.

Interestingly, it has been documented that TLRs could modulate the expression of anti-apoptotic Bcl-2 family proteins, and TLR6 could protect cells from apoptosis (58–61). This evidence could explain the slight decrease in the viability/proliferation that we detected upon the inhibition of *TLR6* by miR482c-5p.

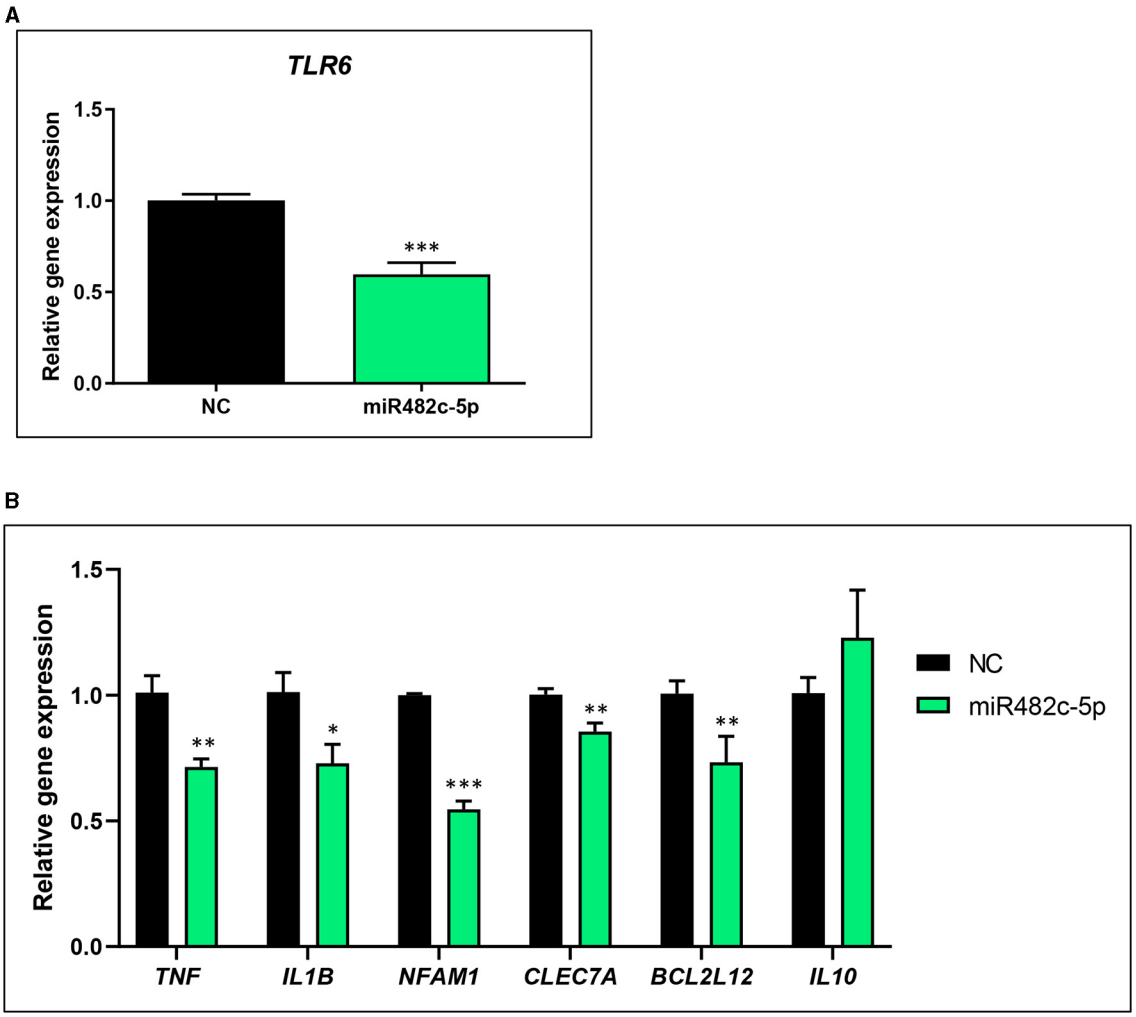


FIGURE 4
Gene expression analysis of THP-1 macrophage-like cells transfected with plant-derived miR482c-5p mimic. **(A)** mRNA levels of putative target *TLR6*. **(B)** Gene expression levels (mRNA) of pro-inflammatory (*TNF*, *IL1B*, *TLR6*) and anti-inflammatory (*IL10*) biomarkers and *BCL2L12*. THP-1 macrophage-like cells were transfected with 60 nM of miRVana mimic miR482c-5p (5′-GGAAUGGGCUGUUUGGGAUG-3′) and a scramble sequence as a negative control. Gene expression levels were measured at 48 h of transfection by qPCR. Results are the gene expression levels of each gene normalized to the housekeeping gene *TBP* and calculated by the $2^{-\Delta\Delta Ct}$ method, establishing comparisons with the negative control. NC, negative control. The results are presented as mean percentage ± standard error of the mean (SEM) ($n = 2$ independent experiments, run in triplicate; NC: $n = 5$; miR482f: *NFAM1*, *TNF*, $n = 5$; *CLEC7A*, *BCL2L12*, *IL10*, *IL1B*, $n = 6$). p-value: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Plant-derived miRNAs miR482f and miR482c-5p are detected in human feces but not in serum.

In concordance, the downregulation of the anti-apoptotic gene *BCL2L12* (62, 63), in miR482c-5p treated cells suggests that this miRNA could be interfering with the viability of macrophages. We hypothesize that, since in miR482c-5p-treated cells the *TLR6* levels decrease, these cells are less protected against pro-apoptotic stimuli than other (scramble control and miR482f-treated) cells in which the expression of *TLR6* was not affected. We speculate that *TLR6* inhibition might not decrease cell viability in physiological conditions absent of potentially harmful events (i.e., transfection procedure). In any case, we consider that the decrease in macrophage viability (10%) is very low to be considered biologically relevant.

The role of plant-derived miRNAs as cross-kingdom immune-modulatory agents has recently been documented. This could be mediated through plant-derived miRNA interaction with viral, bacteria, and mammalian cell genes (64–68). In the present study, we reported a direct interaction between plant-derived miRNAs with immunomodulatory properties and mammalian genes, which has been also documented by other studies (67, 68). Indeed, we found that plant-derived miRNAs could interact with immune system cells, in particular with human macrophages, and regulate gene expression. Although the mechanism underlying the interactions between plant-derived miRNAs and immune system cells described in our study relies mainly on gene expression regulation, we do not exclude the involvement of other additional/complementary mechanisms (i.e., involving indirect target gene interactions) (68).

A crucial but controversial aspect of the plant-derived miRNA cross-kingdom gene expression regulation hypothesis is the bioavailability in the host. Interestingly, edible plant-derived

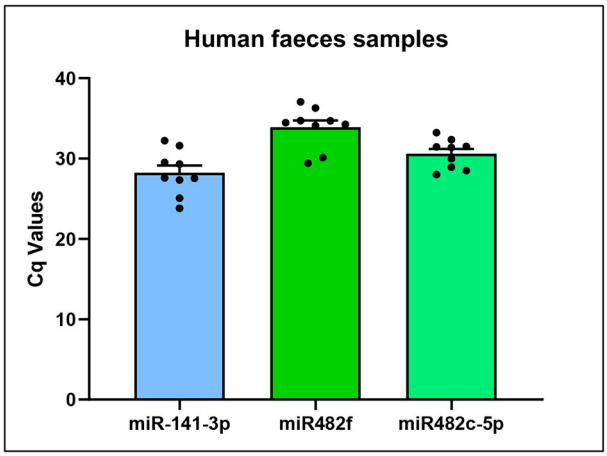


FIGURE 5
Detection of plant-derived miR482f and miR482c-5p in human feces of healthy volunteers using qPCR. Cq values of plant-derived miR482f (5′-UCUUUCCUACUCCACCCAUUCC-3′), miR482c-5p (5′-GGAAUGGGCUGUUUGGGAUG-3′), and human miR-141-3p (5′-UAACACUGUCUGGUAAAGAUGG-3′) as an endogenous control, in nine human feces samples (qPCR duplicates for each sample) from healthy volunteers. Results are the mean ± standard error of the mean (SEM) ($n = 9$).

miRNAs could be present in extracellular vesicles (EVs) (69, 70), which could be a key determinant of absorption (16, 71, 72). Nevertheless, bioactive activities upon the absorption by mammalian cells have been reported *in vivo* after the administration of plant-derived miRNAs in a free form (68, 73). This evidence suggests that either in a free form or encapsulated in EVs, plant-derived miRNAs could have a cross-kingdom functional impact. In the present study, we verified that plant-derived miR482f and miR482c-5p were detected in human feces but not in the serum of healthy individuals who usually consumed plant-based products. These results demonstrate that plant-derived miRNAs (miR482f and miR482c-5p) resist physical (cooking and digestive motility) and chemical treatments (digestive enzymes) but is rather unlikely that they could reach physiological levels in the bloodstream. We do not rule out completely the possibility that miR482f and miR482c-5p could be absorbed since it is quite reasonable that their bioavailability might be lower (or beyond that) the detection level of standard methods and conditions used for addressing small RNA expression. It could be worthy to analyze their presence in serum in other experimental conditions since the bioavailability of miRNAs might depend on dietary intake levels (74), gut permeability variability (16), and the sensitivity of the techniques used for its detection. Interestingly, it has been suggested that technical limitations, artifacts, contaminations, inter-individual variability in gut permeability, and dietary abundance and stability of plant-derived miRNAs could explain the disparity of the results reported between studies (75, 76). Importantly, plant-derived miRNAs could potentially modulate inflammation at the local (gut) level through the modulation of tissue-resident immune cells (macrophages, lymphocytes) and/or gut microbiota. Although some previous evidence supports this hypothesis (66), intimate mechanisms of this cross-kingdom communication remain to be established; especially, the direct interaction of plant-derived miRNAs with gut immune cells should be confirmed in future *in vivo* and/or clinical studies. The abundance of plant-derived miR482f and miR482c-5p in fecal samples suggests that they reach the gastrointestinal tract (and move forward throughout the intestinal lumen). As regards our findings, plant-derived miRNAs are physically present and stable in the gastrointestinal tract. Whether their presence in host organisms fully translates into physiological changes (at cellular/tissue level) remains to be established in future experiments since it would require additional resources (methodologies, ethical) or invasive procedures (biopsies) and this was out of our scope. Although *in vivo* approaches would eventually contribute to clarify this, important inter-species differences arise. For instance, *in silico* plant-derived miR482f and miR482c-5p predictions are biologically different in human vs. mouse (according to their respective mRNA sequence) and thus prevent the implementation of animal models in the context of our study.

This article is not free of limitations. Additional research would be necessary to explore the role of plant-derived miR482f and miR482c-5p on inflammation beyond the regulation of gene expression levels. To determine if plant-derived miR482f and miR482c-5p effects at the gene level could translate to physiological events such as cytokine protein expression changes, we evaluated IL-10 secretion levels in conditioned media, as a first preliminary (proof of concept) approach. We found that these miRNAs modulated IL-10 secretion levels (data not shown), concordantly to reported gene expression changes. However, depth investigations will be required to evaluate the overall impact of plant-derived miR482f and miR482c-5p on the protein secretion levels of the whole cytokines panel presented in this study (a secretome analysis). Thus, whether the modulation of inflammatory-associated genes promoted by plant-derived miR482f and miR482c-5p fully translate to physiologically relevant events remains to be established in future studies. This could determine whether these miRNAs might potentially be important therapeutic agents to shape immune system responses.

5 Conclusion

We show here that miR482f and miR482c-5p are present in standard plant-based foods (legumes, vegetables, greens, fruits, cereals, and fats and oils), resist physical–chemical degradation during cooking and digestion, and reach the human gut, although eventually, they are not absorbed. *In vitro*, these plant-derived miRNAs modulate the gene expression profile of inflammation-associated biomarkers in human macrophages. A better understanding of the cross-talk between plant-derived miR482f and miR482c-5p and the immune system could help to determine their therapeutic potential as bioactive molecules with anti-inflammatory properties.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE234786.

Ethics statement

The studies involving humans were approved by University of Navarra, Pamplona, Spain. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ED-S: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. SL-C: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. PA: Methodology, Writing – review & editing. E-ZA: Writing – review & editing. JR-B: Funding acquisition, Project administration, Writing – review & editing. FM: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition (CIBERobn, grant No. CB12/03/30002), Ministerio de Asuntos Económicos y Transformación Digital (PID2022-141766OB-I00, RTI2018-102205-B-I00, and BFU2015-65937-R projects), and a Center for Nutrition Research pre-doctoral grant awarded to ED-S.

Acknowledgments

The authors thank the Centre for Genomic Regulation (CRG) for performing the next-generation sequencing of miRNAs derived from plant-based samples and bioinformatic analyses to identify plant-derived miRNA sequences.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1287312/full#supplementary-material

References

1. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med.* (2019) 25:1822–32. doi: 10.1038/s41591-019-0675-0

2. Rajendran P, Chen YF, Chen YF, Chung LC, Tamilselvi S, Shen CY, et al. The multifaceted link between inflammation and human diseases. *J Cell Physiol.* (2018) 233:6458–71. doi: 10.1002/jcp.26479

3. Zhao H, Shang Q, Pan Z, Bai Y, Li Z, Zhang H, et al. Exosomes from adipose-derived stem cells attenuate adipose inflammation and obesity through polarizing m2 macrophages and beiging in white adipose tissue. *Diabetes.* (2018) 67:235–47. doi: 10.2337/db17-0356

4. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity.* (2022) 55:31–55. doi: 10.1016/j.immuni.2021.12.013

5. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget.* (2018) 9:7204–18. doi: 10.18632/oncotarget.23208

6. Grosso G, Laudisio D, Frias-Toral E, Barrea L, Muscogiuri G, Savastano S, et al. Anti-inflammatory nutrients and obesity-associated metabolic-inflammation: state of the art and future direction. *Nutrients.* (2022) 14:1137. doi: 10.3390/nu14061137

7. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials. *Obes Rev.* (2016) 17:1067–79. doi: 10.1111/obr.12439

8. Xiao Y, Xia J, Ke Y, Cheng J, Yuan J, Wu S, et al. Effects of nut consumption on selected inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Nutrition.* (2018) 54:129–43. doi: 10.1016/j.nut.2018.02.017

9. Hosseini B, Berthon BS, Saedisomeolia A, Starkey MR, Collison A, Wark PAB, et al. Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. *Am J Clin Nutr.* (2018) 108:136–55. doi: 10.1093/ajcn/nqy082

10. Juárez-Chairez MF, Meza-Márquez OG, Márquez-Flores YK, Jiménez-Martínez C. Potential anti-inflammatory effects of legumes: a review. *Br J Nutr.* (2022) 128:2158–69. doi: 10.1017/S0007114522000137

11. Milesi G, Rangan A, Grafenauer S. Whole grain consumption and inflammatory markers: a systematic literature review of randomized control trials. *Nutrients.* (2022) 14:374. doi: 10.3390/nu14020374

12. Majdan M, Bobrowska-Korczak B. Active compounds in fruits and inflammation in the body. *Nutrients.* (2022) 14:2496. doi: 10.3390/nu14122496

13. Rajaram S, Damasceno NR, Braga RA, Martinez R, Kris-Etherton P, Sala-Vila A. Effect of nuts on markers of inflammation and oxidative stress: a narrative review. *Nutrients.* (2023) 15:1099. doi: 10.3390/nu15051099

14. Awika JM, Rose DJ, Simsek S. Complementary effects of cereal and pulse polyphenols and dietary fiber on chronic inflammation and gut health. *Food Funct.* (2018) 9:1389–409. doi: 10.1039/C7FO02011B

15. Li D, Yang J, Yang Y, Liu J, Li H, Li R, et al. A timely review of cross-kingdom regulation of plant-derived MicroRNAs. *Front Genet.* (2021) 12:613197. doi: 10.3389/fgene.2021.613197

16. Díez-Sainz E, Lorente-Cebrián S, Aranaz P, Riezu-Boj JI, Martínez JA, Milagro FI. Potential mechanisms linking food-derived microRNAs, gut microbiota and intestinal barrier functions in the context of nutrition and human health. *Front Nutr.* (2021) 8:586564. doi: 10.3389/fnut.2021.586564

17. Bartel DP. Metazoan MicroRNAs. *Cell.* (2018) 173:20–51. doi: 10.1016/j.cell.2018.03.006

18. Dong Q, Hu B, Zhang C. MicroRNAs and their roles in plant development. *Front Plant Sci.* (2022) 13:824240. doi: 10.3389/fpls.2022.824240

19. Li Z, Xu R, Li N. MicroRNAs from plants to animals, do they define a new messenger for communication? *Nutr Metab (Lond).* (2018) 15:68. doi: 10.1186/s12986-018-0305-8

20. Saiyed AN, Vasavada AR, Johar SRK. Recent trends in miRNA therapeutics and the application of plant miRNA for prevention and treatment of human diseases. *Futur J Pharm Sci.* (2022) 8:24. doi: 10.1186/s43094-022-00413-9

21. Chen T, Ma F, Peng Y, Sun R, Xi Q, Sun J, et al. Plant miR167e-5p promotes 3T3-L1 adipocyte adipogenesis by targeting β-catenin. *Vitr Cell Dev Biol Anim.* (2022) 58:471–9. doi: 10.1007/s11626-022-00702-w

22. Zhang L, Hou D, Chen X, Li D, Zhu L, Zhang Y, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res.* (2012) 22:107–26. doi: 10.1038/cr.2011.158

23. Li M, Chen T, He J-J, Wu J-H, Luo J-Y, Ye R-S, et al. Plant MIR167e-5p inhibits enterocyte proliferation by targeting β-Catenin. *Cells.* (2019) 8:1385. doi: 10.3390/cells8111385

24. Akao Y, Kuranaga Y, Heishima K, Sugito N, Morikawa K, Ito Y, et al. Plant hvu-MIR168-3p enhances expression of glucose transporter 1 (SLC2A1) in human cells by silencing genes related to mitochondrial electron transport chain complex I. *J Nutr Biochem.* (2022) 101:108922. doi: 10.1016/j.jnutbio.2021.108922

25. Marzano F, Caratozzolo MF, Consiglio A, Licciulli F, Liuni S, Sbisà E, et al. Plant miRNAs reduce cancer cell proliferation by targeting MALAT1 and NEAT1: a beneficial cross-kingdom interaction. *Front Genet.* (2020) 11:552490. doi: 10.3389/fgene.2020.552490

26. Zhou Z, Li X, Liu J, Dong L, Chen Q, Liu J, et al. Honeysuckle-encoded atypical microRNA2911 directly targets influenza A viruses. *Cell Res.* (2015) 25:39–49. doi: 10.1038/cr.2014.130

27. Minutolo A, Potestà M, Gismondi A, Pirrò S, Cirilli M, Gattabria F, et al. Olea europaea small RNA with functional homology to human miR34a in cross-kingdom interaction of anti-tumoral response. *Sci Rep.* (2018) 8:12413. doi: 10.1038/s41598-018-30718-w

28. Sundaram GM. Dietary non-coding RNAs from plants: Fairy tale or treasure? *Non-coding RNA Res.* (2019) 4:63–8. doi: 10.1016/j.ncrna.2019.02.002

29. Huang F, Du J, Liang Z, Xu Z, Xu J, Zhao Y, et al. Large-scale analysis of small RNAs derived from traditional Chinese herbs in human tissues. *Sci China Life Sci.* (2019) 62:321–32. doi: 10.1007/s11427-018-9323-5

30. Huang H, Davis CD, Wang TTY. Extensive degradation and low bioavailability of orally consumed corn miRNAs in mice. *Nutrients.* (2018) 10:215. doi: 10.3390/nu10020215

31. Jiang H, Lei R, Ding S-W, Zhu S. Skewer: a fast and accurate adapter trimmer for next-generation sequencing paired-end reads. *BMC Bioinformatics.* (2014) 15:182. doi: 10.1186/1471-2105-15-182

32. Axtell MJ. ShortStack: comprehensive annotation and quantification of small RNA genes. *RNA.* (2013) 19:740–51. doi: 10.1261/rna.035279.112

33. Anders S, Pyl PT, Huber W. HTSeq–a Python framework to work with high-throughput sequencing data. *Bioinformatics.* (2015) 31:166–9. doi: 10.1093/bioinformatics/btu638

34. Edgar R, Domrachev M, Lash AE. Gene expression omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res.* (2002) 30:207–10. doi: 10.1093/nar/30.1.207

35. Dai X, Zhao PX. psRNATarget: a plant small RNA target analysis server. *Nucleic Acids Res.* (2011) 39:W155–9. doi: 10.1093/nar/gkr319

36. Bonnet E, He Y, Billiau K, Van de Peer Y. TAPIR a web server for the prediction of plant microRNA targets, including target mimics. *Bioinformatics.* (2010) 26:1566–8. doi: 10.1093/bioinformatics/btq233

37. Moloney GM, Viola MF, Hoban AE, Dinan TG, Cryan JF. Faecal microRNAs: indicators of imbalance at the host-microbe interface? *Benef Microbes.* (2018) 9:175–83. doi: 10.3920/BM2017.0013

38. Wohnhaas CT, Schmid R, Rolser M, Kaaru E, Langgartner D, Rieber K, et al. Fecal MicroRNAs show promise as noninvasive crohn's disease biomarkers. *Crohn's Colitis.* (2020) 2:otaa003. doi: 10.1093/crocol/otaa003

39. Liu H, Bian Q-Z, Zhang W, Cui H-B. Circulating microRNA-103a-3p could be a diagnostic and prognostic biomarker for breast cancer. *Oncol Lett.* (2022) 23:38. doi: 10.3892/ol.2021.13156

40. Wanhainen A, Mani K, Vorkapic E, De Basso R, Björck M, Länne T, et al. Screening of circulating microRNA biomarkers for prevalence of abdominal aortic aneurysm and aneurysm growth. *Atherosclerosis.* (2017) 256:82–8. doi: 10.1016/j.atherosclerosis.2016.11.007

41. Rao X, Huang X, Zhou Z, Lin X. An improvement of the 2^(-delta delta CT) method for quantitative real-time polymerase chain reaction data analysis. *Biostat Bioinforma Biomath.* (2013) 3:71–85.

42. Srivastava PK, Moturu TR, Pandey P, Baldwin IT, Pandey SP. A comparison of performance of plant miRNA target prediction tools and the characterization of features for genome-wide target prediction. *BMC Genomics.* (2014) 15:348. doi: 10.1186/1471-2164-15-348

43. Zonta B, Tait S, Melrose S, Anderson H, Harroch S, Higginson J, et al. Glial and neuronal isoforms of Neurofascin have distinct roles in the assembly of nodes of Ranvier in the central nervous system. *J Cell Biol.* (2008) 181:1169–77. doi: 10.1083/jcb.200712154

44. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol.* (2006) 48:677–85. doi: 10.1016/j.jacc.2006.03.052

45. Philip A, Ferro VA, Tate RJ. Determination of the potential bioavailability of plant microRNAs using a simulated human digestion process. *Mol Nutr Food Res.* (2015) 59:1962–72. doi: 10.1002/mnfr.201500137

46. Chanput W, Mes JJ, Wichers HJ. THP-1 cell line: an in vitro cell model for immune modulation approach. *Int Immunopharmacol.* (2014) 23:37–45. doi: 10.1016/j.intimp.2014.08.002

47. Siegel PM, Sander L, Fricke A, Stamm J, Wang X, Sharma P, et al. P(2)Y(12) receptor blockers are anti-inflammatory drugs inhibiting both circulating monocytes and macrophages including THP-1 cells. *Sci Rep.* (2021) 11:17459. doi: 10.1038/s41598-021-95710-3

48. Al-Nasser MM, Al-Dosari MS, Parvez MK, Al-Anazi MR, Alkahtane AA, Alothaid H, et al. The potential effects of Indigofera coerulea extract on THP-1 human cell line. *J King Saud Univ - Sci.* (2021) 33:101446. doi: 10.1016/j.jksus.2021.101446

49. Juchem KW, Gounder AP, Gao JP, Seccareccia E, Yeddula N, Huffmaster NJ, et al. NFAM1 promotes pro-inflammatory cytokine production in mouse and human monocytes. *Front Immunol.* (2021) 12:773445. doi: 10.3389/fimmu.2021.773445

50. Tang C, Kamiya T, Liu Y, Kadoki M, Kakuta S, Oshima K, et al. Inhibition of dectin-1 signaling ameliorates colitis by inducing lactobacillus-mediated regulatory T cell expansion in the intestine. *Cell Host Microbe.* (2015) 18:183–97. doi: 10.1016/j.chom.2015.07.003

51. Pedro AR V, Lima T, Fróis-Martins R, Leal B, Ramos IC, Martins EG, et al. Dectin-1-mediated production of pro-inflammatory cytokines induced by yeast β-glucans in bovine monocytes. *Front Immunol.* (2021) 12:689879. doi: 10.3389/fimmu.2021.689879

52. Castoldi A, Andrade-Oliveira V, Aguiar CF, Amano MT, Lee J, Miyagi MT, et al. Dectin-1 activation exacerbates obesity and insulin resistance in the absence of MyD88. *Cell Rep.* (2017) 19:2272–88. doi: 10.1016/j.celrep.2017.05.059

53. Ozinsky A, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, et al. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc Natl Acad Sci U S A.* (2000) 97:13766–71. doi: 10.1073/pnas.250476497

54. Joosten LAB, Abdollahi-Roodsaz S, Dinarello CA, O'Neill L, Netea MG. Toll-like receptors and chronic inflammation in rheumatic diseases: new developments. *Nat Rev Rheumatol.* (2016) 12:344–57. doi: 10.1038/nrrheum.2016.61

55. Zou M, Yang W, Niu L, Sun Y, Luo R, Wang Y, et al. Polydatin attenuates Mycoplasma gallisepticum (HS strain)-induced inflammation injury via inhibiting the TLR6/MyD88/NF-κB pathway. *Microb Pathog.* (2020) 149:104552. doi: 10.1016/j.micpath.2020.104552

56. Arias-Loste MT, Iruzubieta P, Puente Á, Ramos D, Santa Cruz C, Estébanez Á, et al. Increased expression profile and functionality of TLR6 in peripheral blood mononuclear cells and hepatocytes of morbidly obese patients with non-alcoholic fatty liver disease. *Int J Mol Sci.* (2016) 17:1878. doi: 10.3390/ijms17111878

57. Moreira AP, Cavassani KA, Ismailoglu UB, Hullinger R, Dunleavy MP, Knight DA, et al. The protective role of TLR6 in a mouse model of asthma is mediated by IL-23 and IL-17A. *J Clin Invest.* (2011) 121:4420–32. doi: 10.1172/JCI 44999

58. Abrahams VM, Aldo PB, Murphy SP, Visintin I, Koga K, Wilson G, et al. TLR6 modulates first trimester trophoblast responses to peptidoglycan. *J Immunol.* (2008) 180:6035–43. doi: 10.4049/jimmunol.180.9.6035

59. Garg M, Potter JA, Abrahams VM. Identification of microRNAs that regulate TLR2-mediated trophoblast apoptosis and inhibition of IL-6 mRNA. *PLoS ONE.* (2013) 8:e77249. doi: 10.1371/journal.pone.0077249

60. Jablonska E, Garley M. TLRs and Bcl-2 family proteins in neutrophils of oral cavity cancer patients. *Folia Histochem Cytobiol.* (2009) 47:615–9. doi: 10.2478/v10042-008-0118-8

61. Parker LC, Whyte MKB, Dower SK, Sabroe I. The expression and roles of Toll-like receptors in the biology of the human neutrophil. *J Leukoc Biol.* (2005) 77:886–92. doi: 10.1189/jlb.1104636

62. Stegh AH, Kim H, Bachoo RM, Forloney KL, Zhang J, Schulze H, et al. Bcl2L12 inhibits post-mitochondrial apoptosis signaling in glioblastoma. *Genes Dev.* (2007) 21:98–111. doi: 10.1101/gad.1480007

63. Li M-G, Liu X-Y, Liu Z-Q, Hong J-Y, Liu J-Q, Zhou C-J, et al. Bcl2L12 contributes to Th2-biased inflammation in the intestinal mucosa by regulating CD4(+) T cell activities. *J Immunol.* (2018) 201:725–33. doi: 10.4049/jimmunol.1800139

64. Teng Y, Xu F, Zhang X, Mu J, Sayed M, Hu X, et al. Plant-derived exosomal microRNAs inhibit lung inflammation induced by exosomes SARS-CoV-2 Nsp12. *Mol Ther.* (2021) 29:2424–40. doi: 10.1016/j.ymthe.2021.05.005

65. Minutolo A, Potestà M, Roglia V, Cirilli M, Iacovelli F, Cerva C, et al. Plant microRNAs from moringa oleifera regulate immune response and HIV infection. *Front Pharmacol.* (2020) 11:620038. doi: 10.3389/fphar.2020.620038

66. Teng Y, Ren Y, Sayed M, Hu X, Lei C, Kumar A, et al. Plant-derived exosomal micrornas shape the gut microbiota. *Cell Host Microbe.* (2018) 24:637–652.e8. doi: 10.1016/j.chom.2018.10.001

67. Hou D, He F, Ma L, Cao M, Zhou Z, Wei Z, et al. The potential atheroprotective role of plant MIR156a as a repressor of monocyte recruitment on inflamed human endothelial cells. *J Nutr Biochem.* (2018) 57:197–205. doi: 10.1016/j.jnutbio.2018.03.026

68. Cavalieri D, Rizzetto L, Tocci N, Rivero D, Asquini E, Si-Ammour A, et al. Plant microRNAs as novel immunomodulatory agents. *Sci Rep.* (2016) 6:25761. doi: 10.1038/srep25761

69. Xiao J, Feng S, Wang X, Long K, Luo Y, Wang Y, et al. Identification of exosome-like nanoparticle-derived microRNAs from 11 edible fruits and vegetables. *PeerJ.* (2018) 6:e5186. doi: 10.7717/peerj.5186

70. Baldrich P, Rutter BD, Karimi HZ, Podicheti R, Meyers BC, Innes RW. Plant extracellular vesicles contain diverse small RNA species and are enriched in 10- to 17-Nucleotide "Tiny" RNAs. *Plant Cell.* (2019) 31:315–24. doi: 10.1105/tpc.18.00872

71. Del Pozo-Acebo L, López de Las Hazas M-C, Margollés A, Dávalos A, García-Ruiz A. Eating microRNAs: pharmacological opportunities for cross-kingdom regulation and implications in host gene and gut microbiota modulation. *Br J Pharmacol.* (2021) 178:2218–45. doi: 10.1111/bph.15421

72. Urzì O, Gasparro R, Ganji NR, Alessandro R, Raimondo S. Plant-RNA in extracellular vesicles: the secret of cross-kingdom communication. *Membranes.* (2022) 12:352. doi: 10.3390/membranes12040352

73. Li M, Chen T, Wang R, Luo J-Y, He J-J, Ye R-S, et al. Plant MIR156 regulates intestinal growth in mammals by targeting the Wnt/β-catenin pathway. *Am J Physiol Cell Physiol.* (2019) 317:C434–48. doi: 10.1152/ajpcell.00030.2019

74. Yang J, Farmer LM, Agyekum AAA, Elbaz-Younes I, Hirschi KD. Detection of an abundant plant-based small RNA in healthy consumers. *PLoS ONE.* (2015) 10:e0137516. doi: 10.1371/journal.pone.0137516

75. Kang W, Bang-Berthelsen CH, Holm A, Houben AJS, Müller AH, Thymann T, et al. Survey of 800+ data sets from human tissue and body fluid reveals xenomiRs are likely artifacts. *RNA.* (2017) 23:433–45. doi: 10.1261/rna.059725.116

76. Witwer KW. Alternative miRNAs? Human sequences misidentified as plant miRNAs in plant studies and in human plasma. *F1000Research.* (2018) 7:244. doi: 10.12688/f1000research.14060.1

frontiers | Frontiers in Nutrition

TYPE Review
PUBLISHED 04 April 2024
DOI 10.3389/fnut.2024.1379785

OPEN ACCESS

EDITED BY
Katia Petroni,
University of Milan, Italy

REVIEWED BY
Ali Sheikhy,
Tehran University of Medical Sciences, Iran
Marco Bucci,
University of Studies G. d'Annunzio Chieti and Pescara, Italy

*CORRESPONDENCE
Claudia Ojeda-Granados
✉ claudiaojedagranados@hotmail.com

RECEIVED 31 January 2024
ACCEPTED 22 March 2024
PUBLISHED 04 April 2024

CITATION
Ojeda-Granados C, Campisi E, Barchitta M and Agodi A (2024) Genetic, lifestyle and metabolic factors contributing to cardiovascular disease in the Italian population: a literature review.
Front. Nutr. 11:1379785.
doi: 10.3389/fnut.2024.1379785

Genetic, lifestyle and metabolic factors contributing to cardiovascular disease in the Italian population: a literature review

Claudia Ojeda-Granados*, Elisabetta Campisi, Martina Barchitta and Antonella Agodi

Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy

Cardiovascular diseases (CVD) represent a major health problem worldwide. In Italy, despite the decline in CVD mortality and disability-adjusted life years recently observed, CVD remains the leading cause of death. The development of CVD has a complex and multifactorial etiology that involves environmental, lifestyle/behavioral (e.g., unhealthy diet, physical inactivity, smoking, and alcohol abuse), metabolic, and genetic factors. Although a large number of CVD susceptibility genetic variants have been identified, some seem to confer risk according to the genetic background or ethnicity of the population. Some CVD-associated polymorphisms with appreciable frequency in the Italian population may be important contributors to the development and progression of the most prevalent CVD in the population. This literature review aims to provide an overview of the epidemiology of CVD in Italy, as well as to highlight the main genetic, lifestyle/behavioral, and metabolic factors contributing to CVD risk in this population.

KEYWORDS

chronic disease, genetic risk, susceptibility, molecular epidemiology, lifestyle, diet

1 Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality, morbidity, and disability in Europe, accounting for 45% of total deaths (1, 2). In Italy, although a decline in the CVD mortality rate has been evidenced over the last three decades, CVD remains the leading cause of mortality, morbidity, and disability (2). CVD comprises a group of heart and blood vessel disorders, including coronary heart disease (CHD) (also called ischemic heart disease –IHD or coronary artery disease –CAD), cerebrovascular disease, and peripheral artery disease, among others (3). The etiology of CVD is complex, with multiple environmental, lifestyle/behavioral (e.g., unhealthy diet, physical inactivity, smoking, and alcohol abuse), and genetic factors contributing to its development and progression (4). Lifestyle/behavioral factors often contribute to the well-known metabolic risk factors, including high systolic blood pressure, elevated total cholesterol, elevated fasting glucose, and increased body mass index (5). Genetic risk factors, on the other hand, generally comprise the presence of genetic variants or risk alleles that confer susceptibility to the development of CVD (6). A wide variety of genetic polymorphisms associated with an increased risk of CVD have been identified to date, findings

that have been replicated in association studies conducted in different populations (7). However, the risk conferred by some genetic variants may be closely related to the genetic ancestry or ethnicity of the population (8). When multiple risk factors are present, they may have a synergetic or multiplicative effect on the risk of developing CVD, rather than merely an additive effect (1). Prevention of this complex disease should be based on an integrated, multidisciplinary approach to manage and control CVD risk factors and their interactions (9). Evidence suggests that simultaneous and comprehensive treatment of all cardiovascular risk factors, rather than a single factor alone, is linked to CVD burden reduction (9). Specifically, in Italy, a considerable proportion of the population smokes, is physically inactive, has a modest adherence to their traditional Mediterranean diet (MedDiet), and suffers from overweight/obesity, hypertension, dyslipidemia or type 2 diabetes mellitus (T2DM) (1, 10). Given the complexity of this disease, knowing the population-specific risk factors that contribute to their CVD risk could help to design preventive, treatment, and surveillance strategies tailored to their particular context. This review aimed to provide an overview of the epidemiology of CVD in Italy, as well as to highlight the main genetic, lifestyle/behavioral, and metabolic factors contributing to the CVD risk in this population.

2 Epidemiology of CVD in the Italian population

2.1 CVD prevalence and incidence

According to the European Cardiovascular Disease Statistics 2017, during the last two decades the absolute number of CVD cases has increased in Europe (5). In Italy, the overall crude prevalence of CVD is nearly 2 fold higher than the global prevalence (12.9% vs. 6.6%) based on epidemiological estimates derived from the Global Burden of Disease Injuries and Risk Factors Study 2017 (11). IHD and stroke are responsible for the most important CVD burden in Italy (11). More specifically, IHD and stroke show a crude prevalence of 3.6 and 1.3%, with corresponding global estimates of 1.7 and 1.4%, respectively (11). Hypertensive heart disease is also frequent in the Italian population, with a crude prevalence of 0.7% as opposed to a global prevalence of 0.2% (11). Considering instead high-risk population groups, the CAPTURE project study that integrates data on T2DM adults from 13 different European countries reports an estimated overall weighted prevalence of CVD in 2018–19 of 34.8%, while 38.8% for the Italian population (12, 13). Considering only the Italian CAPTURE cohort, atherosclerotic CVD reached a frequency of 33.1%, with CHD being the most prevalent subtype (20.8%), followed by carotid artery disease/stenosis (13.2%), cardiac arrhythmia and conduction abnormalities (7.0%), and cerebrovascular disease (5.4%) (13). In detail, the most frequent CHD types included myocardial infarction (MI), angina, coronary artery stenosis, and heart failure, while the most frequent forms of cerebrovascular disease comprised ischaemic stroke and transient ischaemic attack (13, 14).

On the other hand, according to the European Society of Cardiology (ESC) CVD 2021 statistics, middle-income ESC member countries show the highest burden of CVD, with 30% higher incidence rates compared with high-income countries (10). In fact, incidence estimates for IHD and stroke have decreased by more than 25% over the past 30 years, especially in high-income countries (10). Overall, IHD is twice as high in males than in females, while stroke has similar incidence rates in both genders (10). In Italy, the crude incidence of CVD is higher than the global incidence (0.6% vs. 0.2%) (11). In particular, IHD and stroke have crude incidence estimates of 0.07 and 0.04% in Italy, whereas the corresponding global estimates are 0.03 and 0.03% (11).

2.2 CVD mortality and morbidity

CVD caused 45% of all deaths in Europe and represents the leading cause of death among men in countries considered by the European Statistics on Cardiovascular Diseases 2017 (5). Similarly, according to the ESC – CVD 2021 report, CVD remains the most common cause of death, accounting for 45 and 39% of all deaths in women and men, with IHD and stroke representing the first and second most common causes of death (10). In Italy, CVD represents the leading cause of death, contributing to 34.8% of all deaths in 2017, although a decline of −53.8% in the CVD mortality rate has been recorded since 1990 (2). Compared to global estimates, CVD mortality and morbidity are lower in Italy (11). In fact, CVD accounted for 31.8% of deaths globally while 34.8% in Italy, also showing a lower age-standardized mortality rate compared to the global one (113/100,000 vs. 233.01/100,000) (11). Also in Italy, IHD and stroke represented the first and second leading cause of total CVD death contribution in 2017 (2). Specifically, IHD accounted for 15.5% of deaths and its impact on morbidity was 6.8%, whereas stroke accounted for 9.5% of deaths and its impact on morbidity was 4.3% (11). Mortality rates from IHD and stroke in Italy have been reported to be higher in men than in women (2).

3 Genetic determinants of CVD

3.1 Genetic background and susceptibility to CVD

Regarding genetic risk factors, genome-wide association studies (GWAS), genetic association studies, and high-throughput DNA sequencing technologies have led to the identification of variants in candidate genes or genomic regions associated with susceptibility for some CVD (7). For example, it has been estimated that 40–60% of the interindividual variations in CAD susceptibility are related to heritability, with specific genetic variants playing a key role in CAD pathogenesis (15, 16). The association between particular genetic variants and certain CVD has been replicated in various studies and populations. Still, some of them seem to confer risk in relation to the population's genetic background or ethnicity (8). For instance, the association of single nucleotide polymorphisms (SNPs) at the 9p21.3 locus with CAD and MI represents one of the most replicated among diverse populations (17, 18). However, linkage disequilibrium (LD) between SNPs (e.g., rs9632884, rs10757274, rs2383206, rs1333042, rs1333040, and rs1333049) in this genomic region varies according to genetic ancestry, resulting in different SNPs being associated or not with CVD for each population (18). The rs10757274 and rs2383206 have been found to be in strong LD in Caucasians and associated with CAD in risk allele carriers (17). Interestingly, both risk alleles were

also found with appreciable frequencies but not associated with CAD in a subgroup of African Americans, indicating that genetic variants may also require a specific environment to come into effect (16, 17). In individuals of European descent, the probability of carrying one or two CAD risk-associated alleles at the 9p21.3 locus is 50 and 25%, respectively (16). The association of SNPs at this locus with CAD has been confirmed even when adjusting for potential confounding covariates (e.g., age, sex, lipid levels, blood pressure, T2DM, etc.), suggesting that risk-associated alleles have an effect independent of traditional CVD risk factors (16, 17).

Besides SNPs with no apparent direct relationship to traditional risk factors, other variants with more evident relationships to gene function, influence on cardiovascular risk factors, and CVD risk have also been identified. SNPs at the 1p13.3 locus consistently associated with low-density lipoprotein cholesterol (LDL-C) levels represent an example of such a direct relationship whose association with CAD has been replicated by several studies (19, 20). The rs599839 representative of this locus has been associated with elevated LDL-C levels and CAD particularly in Caucasian European and Asian populations, but not in African Americans, in whom the A-risk allele is rare (19–22). The following section of the review describes the CVD-associated genetic variants that have been identified in a population of European ancestry, particularly in the Italian population.

3.2 Candidate genes and variants associated with CVD in the Italian population

CVD-associated polymorphisms with appreciable frequency in the Italian population have generally been identified in genes or regions involved in different processes such as cell adhesion, inflammation, and cellular stress processes, hemodynamic regulation, lipid traits, insulin signaling, and glucose homeostasis, thus contributing to the risk of the most prevalent CVD through different mechanisms (Table 1). The allele and genotypic frequencies of these polymorphisms in the Italian population are presented in Supplementary Table 1.

3.2.1 Genes involved in cell adhesion, inflammation, and cellular stress processes

Most of the polymorphisms for CVD susceptibility in the Italian population have been identified in genes that play an important role in cellular adhesion, inflammation, and cellular stress processes. The adhesion of circulating cells to the arterial surface represents an early detectable process of atherogenesis (31). Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), involved in leukocyte transmigration and angiogenesis, is also implicated in plaque formation, thrombosis, and the development of atherosclerosis (31). In the Italian population, the *PECAM1* V125L and N563S polymorphisms, as well as the 53 G > A variant located in the 5′ untranslated region of the gene, were associated with CAD (31). In particular, the 125 V/V, 563 N/N, and 53 G/G genotypes were associated with CAD independently of conventional risk factors (31). The *eNOS* also represents a candidate gene implicated in CAD risk. Nitric oxide (NO) can inhibit several key steps in atherosclerosis, including the adhesion of platelets and leukocytes to the endothelium (36). Therefore, *eNOS* genetic variants may influence susceptibility to atherosclerosis by altering the amount of NO produced by the vascular endothelium (37). The *eNOS* Glu298Asp (rs1799983) and T786C (rs2070744) variants were significantly associated with the occurrence and severity of CAD among Italian people (36, 37). CAD risk was increased in subjects homozygous for the 786C allele independently of other common risk factors. Moreover, individuals with the Glu2983 Asp/Asp genotype and at least one 786C allele had an increased risk of CAD (36, 37).

Inflammation is also a key factor in the development of CVD. A possible role of the *TNF* −308 G/A (rs1800629) SNP in the predisposition to the development of CAD in Italians has been evidenced (32). A significantly higher frequency of the *TNF* -308A allele was found in patients with CAD, suggesting a genetic predisposition to produce higher amounts of this proinflammatory cytokine and to develop a stronger inflammatory response contributing to CAD development (32). Additional genes involved in inflammation and cellular adhesion mechanisms include *IL6* and *ICAM1*. Polymorphisms in these genes have been associated with several atherosclerotic and ischemic disorders. In Italian patients, an increased risk of stroke was found in carriers of both the *IL6*–174GG and *ICAM1* 469E/E genotypes of the *IL6*–174 G > C (rs1800795) and *ICAM1* 469 E > K (rs5498) polymorphisms (34). Genetic variants in the *MTHFR* and *CYBA* genes have also been shown to have a role in chronic inflammatory processes and tissue stress related to CAD development (33, 35). The *MTHFR* C677T SNP (rs1801133) is widely known to impact serum homocysteine levels, a marker of inflammation, especially in inadequate folate intake (35). In Italian subjects, a gene-nutrient interaction defining an increased risk of CAD determined by folate levels below specific thresholds was evidenced among carriers of the *MTHFR* 677 T allele (35). On the other hand, CYBA (p22phox), an essential component for NADPH oxidase assembly and activation and, consequently, a relevant player in oxidative stress, was found to be associated with CAD. There is evidence that the *CYBA* C242T variant (rs4673) significantly reduces vascular NADH/NADPH oxidase activity. A significantly increased risk of early CAD and coronary stenosis progression was found in Italian 242 T allele carriers (33).

In addition, the *TP53* Arg72Pro (rs1042522) polymorphism, affecting the biochemical and functional properties of the p53-encoded protein, has shown a significant relationship with cardiac function, evidenced by a lower left ventricular ejection fraction (LVEF) in Italians carrying the *Pro allele (28). Unlike the *Arg variant with apoptosis-inducing properties, the *Pro variant results in a stronger transcriptional activator that could aggravate local coronary inflammatory lesions with a negative effect on cardiac function particularly in subjects with CAD (28).

3.2.2 Genes with hemodynamic regulation function

A genetic variant (−55 C > A) in the promoter region of the *NPR3* gene, having an important role in the regulation of blood volume and pressure, has been found to influence susceptibility to cerebrovascular disease in the Italian population (26). In a cohort of Italian individuals with early-onset ischemic stroke, a significant association of the −55 AA genotype with stroke was observed independently of common risk factors (i.e., age, gender, hypertension, hypercholesterolemia, smoking habit, and T2DM) (26). Furthermore, polymorphisms in the *ACE* and *AGTR1* genes, also involved in blood pressure regulation, were found

TABLE 1 Candidate genes and variants associated with cardiovascular disease risk in the Italian population.

Gene/locus	SNP names	rs number	Study population	Key findings	References
CELSR2 (1p13.3 locus)	G > T	rs629301	Italian cohort of 2,429 patients undergoing coronary angiography	T allele associated with extension and severity of CAD, ↑ LDL-C, non-HDL-C, apoB, apoE, and apoCIII levels, ↓ HDL-C levels, independently of common risk factors	(23)
CDKN2A-CDKN2B (9p21.3 locus)	C > G	rs1333049	711 Italian CAD patients and 755 controls	↓ risk of CAD in G allele carriers independently of common risk factors	(8)
APOC3 *MMP3* *SELE* 9p21.3 locus	−482C > T 1,171 5A > 6A G98T C > G	rs2854117 rs3025058 rs1805193 rs1333049	114 patients with early onset of IHD 384 patients with late onset of IHD	SNPs associated with early onset of IHD. Strong interaction for the presence of rs2854117 and rs1333049 with HTG. ↑ risk of early IHD in patients in the top tertile of multilocus GRS considering risk alleles vs. those in the bottom tertile	(24)
LRP8		rs7546246, rs2297660, rs3737983, R952Q rs5177	Three European-ancestry cohorts including and Italian cohort (248 MI patients +308 controls) and one Asian cohort	TACGC risk haplotype was significantly associated with familial MI in the European-ancestry cohorts including the Italian cohort. The CATAG risk haplotype was also identified among Italians	(25)
NPR3	−55C > A		Italian cohort of 368 early-onset ischemic stroke cases and 335 controls	Significant association of the −55 AA genotype with stroke independently of common risk factors	(26)
TCF7L2	T > C C > T G > T	rs7901695 rs7903146 rs12255372	Italian cohort of 154 T2DM patients and 171 healthy controls	All three SNPs associated with T2DM susceptibility, both at genotypic and at allelic level, as well as with diabetic complications (diabetic retinopathy, CVD and CAD). Carriers of CTT risk-allele haplotype showed ↑ risk of T2DM	(27)
TP53	Arg72Pro	rs1042522	198 Italian subjects with CAD and 129 with CVD without CAD	Significant relationship of *Pro variant with cardiac function, measured as LVEF, in subjects with CAD	(28)
ENPP1	K121Q	rs1044498	Prospective study (≈37 months) considering 3 Italian cohorts (330 subjects with T2DM and CAD, 141 with MI, and 266 with end-stage renal disease)	↑ hazard ratio for incidence of cardiovascular events in KQ + QQ carriers versus KK carriers considering the three cohorts combined. Polymorphism is an independent predictor of major cardiovascular events in high-risk individuals	(29)
9p21.3 locus	C > T	rs1333040	Italian cohort of 1,508 patients hospitalized for a first MI before 45y age, followed up for the occurrence of cardiovascular events	SNP significantly influenced the hazard ratio of coronary revascularization (1.38; 95% CI: 1.17–1.63 for CT and 1.90; 95% CI: 1.36–2.65 for TT carriers). It also significantly influenced the angiographic endpoint of coronary atherosclerosis progression	(30)
PECAM1	V125L N563S G670R 53 G > A	rs281865545 – rs1131012 –	431 Italian CAD patients and 119 controls	125 V/V, 563 N/N, and 53 G/G genotypes were associated with CAD independently of common risk factors	(31)
TNF	−308 G/A	rs1800629	248 Italian CAD patients and 241 controls	Significantly ↑ frequency of −308A allele in CAD patients vs. controls	(32)
CYBA	C242T (Tyr72His)	rs4673	276 CAD patients and 218 controls	↑ risk of early CAD and coronary stenosis progression in 242 T allele carriers	(33)
IL6 ICAM1	−174 G > C 469 E > K	rs1800795 rs5498	119 patients with history of ischemic stroke and 133 controls	IL-6 -174 GG and ICAM-1469 E/E genotypes were significantly associated with history of ischemic stroke. ↑ risk of stroke in subjects carrying both genotypes	(34)

(Continued)

10.3389/fnut.2024.1379785

TABLE 1 (Continued)

Gene/locus	SNP names	rs number	Study population	Key findings	References
MTHFR	677 C>T	rs1801133	655 subjects, with (433) or without (222) angiographically documented CAD	↑ risk of CAD determined by folate levels below specific thresholds combined with carrying T allele	(35)
eNOS (NOS3)	Glu298Asp T786 C	rs1799983 rs2070744	415 subjects undergoing coronary angiography	298Asp and 786C variants were significantly associated with occurrence and severity of CAD	(36, 37)
APOB *APOE* *LIPC*	XbaI E2/E3/E4 T202T (C>G)	rs693 rs429358 and rs7412	102 CAD subjects and 104 controls	ApoB XbaI and ApoE4 variants associated with various markers of dyslipidemia and CAD Independent role observed for the LIPC T202T variant	(38)
ACE (17q23) *AGTR1*	I/D 287-bp A1166C	rs1799752 rs5186	205 CAD patients and 209 controls	↑ risk of CAD in the presence of ACE DD and *AGTR1* CC genotypes independently of other risk factors; stronger association with MI in ACE DD and *AGTR1* C allele carriers	(39)
ACE	I/D 250-bp	rs1799752	388 patients with CAD and 290 healthy subjects	*ACE* D allele was the strongest risk factor for atherosclerosis, and significantly associated with the risk of MI	(40)

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SNP, single nucleotide polymorphisms; IHD, ischemic heart disease; GRS, genetic risk scores; MI, myocardial infarction; T2DM, type 2 diabetes; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction.

to be associated with risk for hypertension, MI, and CAD, possibly with a synergic effect (39, 40). These include the *ACE* insertion/deletion (I/D) polymorphism (rs1799752) involving a 287-bp Alu repeat sequence in intron 16 of the gene, and the A1166C (rs5186) SNP in the *AGTR1* gene (39, 40). In Italian patients, an increased risk of CAD was observed among *ACE* DD and *AGTR1* CC genotype carriers, independently of other risk factors (39). A strong association with MI was also observed in carriers of the *ACE* DD genotype and the *AGTR1* C allele, suggesting that the *ACE* D variant is associated with the development of coronary artery stenosis and the occurrence of MI and that the *AGTR1* C allele contributes synergistically to the risk of MI (39, 40).

3.2.3 Genes involved in lipid traits

Polymorphisms in genes modulating serum lipid levels have been associated with an increased risk of CAD/IHD, stroke, and MI in the Italian population. In particular, the rs629301 SNP located in the intergenic region between *PSRC1* and *CELSR2* genes at 1p13.3 locus was associated with the extension and severity of CAD independently from other CVD risk factors (23). The T/T genotype correlated with higher levels of LDL-C, non-HDL cholesterol, apoB, apoE, and apoCIII, and lower HDL-C (23). Also, the *APOC3*–482 C>T (rs2854117) SNP which has shown a significant interaction with hypertriglyceridemia, has been found to be associated with early onset of IHD (24). In addition, a risk haplotype (TACGC) in the *LRP8* gene identified among cohorts of European ancestry participants, including an Italian cohort, was significantly associated with familial and early-onset CAD and MI (25). Homozygous subjects (TACGC/TACGC) showed significantly higher LDL-C levels than heterozygotes (25). Specifically, in Italians, another risk haplotype (CATAG) associated with familial MI was identified. Other genetic variants in the *APOB*, *APOE,* and *LIPC* genes have also been associated with CAD in the Italian population (38). In particular, the *APOB* XbaI (rs693) and the *APOE* ε4 variants were associated with diverse markers of dyslipidemia and CAD, while an independent role was observed for the *LIPC* T202T variant (38). Given that apolipoprotein B (ApoB) is the main component of LDL particles, *APOB* polymorphisms often contribute to CAD due to their role in regulating LDL metabolism and utilization (38). Instead, common SNPs (rs429358 and rs7412) in *APOE*, result in the main ε2, ε3 and ε4 alleles widely known for their lower, normal, and higher affinity to the LDL receptor, respectively. An increased plasma LDL-C has been associated with the Apoε4 variant and can therefore be considered potentially atherogenic. The LIPC 202G polymorphism may also be associated with higher triglyceride and lower HDL levels (38).

3.2.4 Genes involved in insulin signaling and glucose homeostasis

Genetic variants in the Italian population that have been associated with CVD through the modulation of insulin signaling and glucose homeostasis have been found in the *TCF7L2* and *ENPP1* genes (27, 29). Three *TCF7L2* SNPs (rs7901695, rs7903146, and rs12255372) have shown a strong association with impaired insulin secretion, susceptibility to T2DM, and some T2DM complications (i.e., diabetic retinopathy, CVD, and CAD), both at the genotypic and allelic levels (27). Furthermore, carriers of the *TCF7L2* CTT risk-allele haplotype showed an increased risk of T2DM, compared with subjects carrying the wild-type (TCG) haplotype (27). A strong correlation was

particularly found between the rs7903146 and the presence of cardiac autonomic neuropathy (27). A nonsynonymous polymorphism in the *ENPP* gene (K121Q, rs1044498), which results in inhibition of insulin receptor signaling, has been associated with insulin resistance in several but not all studies. In Italians, this variant constituted an independent predictor of major cardiovascular events in T2DM individuals carrying the KQ or QQ genotypes, an effect that was exacerbated by the presence of obesity (29).

3.2.5 The 9p21.3 locus

SNPs at the 9p21.3 locus that have been studied in the Italian population include rs1333040 (C > T) and rs1333049 (C > G), the latter with variable results. In a cohort of Italian patients with early-onset MI, the presence of the rs1333040 T allele significantly influenced the progression of coronary atherosclerosis and the likelihood of coronary artery revascularization during long-term follow-up (30). On the other hand, the G allele of the rs1333049 SNP was associated with a significantly lower risk of CAD, independently of common risk factors (8). However, in a study evaluating the effect of diverse CAD and/or MI high-risk SNPs, the rs1333049 variant resulted among those strongly associated with the risk of premature IHD, suggesting that it may synergically cooperate with other cardiovascular risk factors such as hypertriglyceridemia and smoking (24). Specifically, the simultaneous presence of the risk allele and hypertriglyceridemia doubled the risk of early IHD, while the presence of smoking led to a 1.5-fold increased risk of early IHD (24).

3.3 Genetic risk scores for CVD

Genetic risk scores (GRS) can provide important information about the genetic component contributing to disease susceptibility, especially when considering those variants with relevant frequency per population. A study in Italian patients with early and late onset of IHD, considered a general set of 44 CAD and/or MI high-risk SNPs, identifying four genetic variants (*APOC3*–482 C > T, *MMP3* 1,171 5A > 6A, *SELE* G98T, and 9p21.3 locus rs1333049 C > G) as independent predictors of early onset of IHD (24). The combined effect of these SNPs was assessed by a GRS evidencing that the presence of high-risk alleles conferred an additive effect on cardiovascular events (24). Specifically, each risk allele was associated with a 1.3-fold higher risk of premature onset of IHD, with a gradual decrease in patients' age as the number of risk alleles carried increased (24).

4 Lifestyle/behavioral factors contributing to CVD

More than 80% of the CVD burden can be attributed to potentially modifiable lifestyle/behavioral risk factors, such as diet, alcohol consumption, physical activity, and smoking (2, 41). It has been reported that only 7.3% of men and 13.0% of women in Italy have a healthy lifestyle, involving a combination of healthy dietary habits, the practice of physical activity, and the absence of smoking (1). A higher prevalence of a healthy lifestyle in both genders, with greater adherence in women than in men, is observed especially among subjects with a high educational level compared to those with a low educational level (1).

4.1 Diet and alcohol use

Dietary habits make the largest contribution to the risk of CVD mortality worldwide and CVD disability-adjusted life years (DALYs) across Europe (5, 10). Recent evidence suggests that dietary factors may influence mortality from CHD with one in five premature deaths being preventable with healthy dietary habits (10). In Italy, dietary habits represented the CVD risk factor with the second largest proportion of attributable CVD DALYs, preceded only by high systolic blood pressure (1). In fact, elevated systolic blood pressure and dietary habits together accounted for the largest proportion of age-standardized attributable CVD DALYs, whereas the burden of alcohol consumption declined over the last decades (1). In ESC member countries, the risk of CVD increased according to dietary habits, with a higher risk of CVD observed in high-income countries, characterized by a higher intake of sugar, trans-fatty acids, and sugar-sweetened beverages, while a lower consumption of fruits and vegetables (10). Likewise, diets rich in trans-fatty acids and red meat were associated with CHD risk and mortality, whereas substitution with polyunsaturated fats reduced CVD risk by 13% (10). High intakes of sugars and fats, especially trans and saturated fatty acids, increase the risk of atherosclerosis, while high intake of sodium increases the risk of hypertension, thus contributing to the development of CVD (10). Furthermore, high alcohol consumption, especially binge drinking, increases CVD risk by raising blood pressure and serum triglyceride levels (5). According to the WHO Global Health Observatory, the prevalence of binge drinking is considerably higher in males than females across 51 European countries (5). However, among European countries, heavy drinking was less prevalent in Italy in both genders, with a prevalence of 9% in males and 0.6% in females (5). In particular, according to the Health Examination Survey (HES) 2018–2019 within the CUORE Project of the Istituto Superiore di Sanità, more than two-thirds of the evaluated men and women had an alcohol consumption within the recommended limits according to sex and age (42).

On the contrary, dietary patterns rich in fruits, vegetables, legumes, whole grains, and lean protein sources, with low consumption of processed foods, trans-fats, sugar-sweetened beverages, sodium, and alcohol have proven cardioprotective effects (9, 10, 43). The MedDiet, rich in fruits, vegetables, legumes, nuts, whole grains, and unsaturated fatty acids, is a dietary model widely known for its positive effects on health, including CVD prevention (1, 9, 10). In the populations of the Mediterranean basin, including the Italian population, good adherence to the MedDiet is associated with a 9% reduction in CVD mortality (9, 10). In Italy, despite the strong link with gastronomic tradition, adherence to the MedDiet is rather modest (44). Considering a nationally representative sample, 31.4% of Italian adults have demonstrated low adherence, 31.3% low-to-moderate, 24% moderate-to-high, and only 13.3% high adherence to the MedDiet (45). Analysis of CVD risk markers shows that good adherence to this dietary pattern has beneficial effects on blood pressure, lipid profile, inflammation, oxidative stress, and carotid atherosclerosis (46, 47). In addition, it also influences the expression of proatherogenic genes involved in thrombosis and vascular events (46). In fact, nutritional genomic studies have demonstrated interactions between MedDiet and some genetic variants, such as the *TCF7L2* rs7903146, by reducing their adverse effect on CVD risk (46).

4.2 Physical activity

Regular physical activity and/or aerobic training are important preventive factors for CVD development. Evidence shows that a sedentary lifestyle raises CVD risk by increasing the risk of hypertension, high triglycerides, low HDL plasma level, T2DM, and obesity (5). One-third of adults living in ESC member countries are physically inactive, especially in high-income countries compared with middle-income ones (10). According to the Eurobarometer survey on physical activity, participation in exercise or sport is relatively low across the EU (5). On average, 42% of respondents reported never exercising or practicing sports and only 8% reported doing so at least five times a week. In Italy, 60% of respondents reported never exercising or practicing sports, and 50% reported not participating in informal physical activities either (5). In 2020, only 36.6% of Italians reported practicing any sport in their free time, of which 27.1% reported practicing it frequently, while 9.5% do it occasionally (48). On the other hand, those who only engage in some physical activity accounted for 28.1% of the population, while 35.2% reported being sedentary (48). Similarly, according to data from the Italian HES 2018–2019—CUORE Project, sedentary lifestyle during leisure time was 34 and 45% among men and women aged 35–74 years (42).

4.3 Smoking

Smoking is a major modifiable risk factor for CVD. Smoking may raise the risk of IHD by increasing the tendency of the blood to clot and raising blood pressure, as well as favoring atherosclerosis due to its inflammatory action on arteries. It can also decrease plasma HDL levels and exercise tolerance (5). Over the past three decades, the prevalence of smoking among men has decreased in almost all European countries (5). Across ESC member countries, CVD mortality rates decreased according to smoking prevalence reduction (10). In fact, a smaller reduction in deaths attributable to CVD has been observed in middle-income countries characterized by a high proportion of male smokers (10). In 2015, in Italy, smoking prevalence among adults aged ≥15 years was 24.8% in males and 15.1% in females (5). In 2018–2019 according to the CUORE Project HES, total cigarette current smokers were 23 and 19% of men and women aged 35–74 years (42). Furthermore, smoking was primarily responsible for the increased risk of CVD among Italians aged 40–49 years (26% smokers) in a population sample participating in the 2015 World Hypertension Day survey (49). Although smoking is dangerous at any age, the associated risk of developing CVD is closely related to the age of onset (9). Smoking cessation can reduce the risk of death due to CVD (2, 5). In particular, among heavy smokers, smoking cessation has been associated with a significantly lower CVD risk within 5 years compared with current smokers (50). However, compared with never-smokers, the risk of former smokers remained significantly elevated beyond 5 years after smoking cessation (50). Smoking cessation without subsequent weight gain is also associated with a reduced risk of CVD and mortality (51). Weight gain that may occur following smoking cessation may attenuate the reduction in CVD risk but does not attenuate the beneficial effect of smoking cessation for mortality (52).

4.4 Self-care management

Self-care management requires people to have adequate knowledge of health-related behavior and lifestyle, as well as awareness and perception of the risk of developing diseases. For example, optimal nutrition knowledge among the Italian adult population, as assessed by the Italian Nutrition Knowledge Questionnaire, has resulted in increased adherence to the MedDiet (45). Individuals showing high adherence to the MedDiet corresponded to those with the highest nutritional knowledge and, conversely, those with low adherence showed the lowest nutritional knowledge (45). However, greater knowledge or awareness of cardiovascular health and main CVD factors does not always translate into better self-care or risk perception, as demonstrated by a pilot observational study conducted on cardiovascular specialists during the 2022 National Conference of the Italian Society of Hypertension (53). Among 62 study participants, 19.4% were smokers, 17.7% had dyslipidemia, 26.3% had high blood pressure, and 11.3% had hypertension, of which 57.1% was uncontrolled (53). A non-adherence to guidelines-directed preventive measures for cardiovascular health was also evidenced (53). A multicenter cross-sectional observational study to assess the perception and knowledge of cardiovascular risk among Italian women also showed that good knowledge of the major cardiovascular risk factors was not associated with better recognition of CVD as a leading cause of death, and less than 10% of respondents perceived themselves as being at high CVD risk (54). However, increased CVD risk perception was associated with older age, a higher frequency of cardiovascular risk factors and disease, and a poorer self-rated health status (54).

5 Metabolic risk factors for CVD

Modifiable lifestyle/behavioral factors often contribute to common metabolic CVD risk factors, including high systolic blood pressure, elevated total cholesterol, elevated fasting glucose, and increased body mass index (5). The metabolic risk factors for CVD that are more prevalent among the Italian population are hypertension, dyslipidemias, T2DM and excess body weight (3).

5.1 Hypertension

Hypertension is a major contributor to the global burden of CVD and related mortality (55). In Italy, hypertension is quite frequent in the population. According to a nationwide opportunistic cross-sectional survey promoted by the Italian Society of Hypertension During the XVII World Hypertension Day in 2021, 42.3% of 1,354 volunteer participants aged 18–91 years reported being hypertensive (55). Among the hypertensive participants, 41.4% were taking medication and of these, 26.9% had controlled blood pressure (55). The prevalence of self-reported hypertension was higher in men (47.5%) than in women (38.4%), and increased with age (55). A similar survey organized in 2017 by the International Society of Hypertension in Italy consisting in 1 month of blood pressure screening in a larger number of participants found instead that 30.8% of the 10,076 volunteers aged ≥18 years were hypertensive (56). Of

note is the decline in the prevalence of hypertension in the Italian population observed in the last two decades (57). Comparing data from HESs of adults aged 35–74 years conducted in Italy in 1998–2002, 2008–2012, and in 2018–2019 within the CUORE Project of the Istituto Superiore di Sanità, it was evidenced that systolic and diastolic blood pressure in men (136/86 mm Hg, 132/84 mm Hg; and 132/78 mm Hg) and in women (132/82 mm Hg, 126/78 mm Hg; and 122/73 mm Hg) significantly reduced (57). The same was observed for both the prevalence of raised blood pressure (50, 40, and 30% in men, and 39, 25, and 16% in women) and hypertension (54, 49, and 44% in men, and 45, 35, and 32% in women) with consistent trends according to age and educational level (57). In 2018–2019, hypertensive men and women with controlled blood pressure were 27 and 41%, but a significant favorable trend was also observed (57).

5.2 Abnormal lipid profile

Abnormal blood cholesterol is highly prevalent among the Italian population. According to data from the Longevity check-up 7+ (Lookup 7+) project, an initiative of health promotion campaigns conducted throughout Italy between 2016 and 2017, 64.5% of 3,040 participants (aged 18–98 years) had abnormal cholesterol levels, with no differences between women and men (34% vs. 36%) (58). Specifically, more than 40% of subjects had cholesterol levels between 200 and 240 mg/dL, and about 10% had cholesterol levels >240 mg/dL (58). Prevalence of abnormal cholesterol was higher among individuals aged 45–64 years (55% 200–240 mg/dL; 18% >240 mg/dL), and considering this age group the prevalence was higher in women than in men (77% vs. 62%) (58). Another study conducted between 2019 and 2020 involving subjects of a similar age range (45–59 y) from a population in central Italy, evidenced that both total cholesterol/HDL ratio (4.1 ± 1.1. vs. 3.5 ± 1.1) and triglycerides were higher in men than in women (129.1 ± 91.6 vs. 105.4 ± 62.8 mg/dL) (59). According to the 2008–2012 HES within the CUORE Project of the Istituto Superiore di Sanità, among 8,141 Italian subjects aged 35–74 years, 35.8% had hypercholesterolemia (34.7% of men and 36.8% of women) (1). The frequency of elevated LDL-C and hypertriglyceridemia reached approximately 68 and 23% among the population, with 67.8% of men and 67.6% of women having elevated LDL-C and 30.2% of men and 15.5% of women having hypertriglyceridemia (1).

5.3 Diabetes

The prevalence of T2D in Italy has increased over time consistent with population aging and in relation to the increase in obesity (60). Diabetes is one of the main cardiovascular risk factors and CVD is the leading cause of death among people with T2D in Italy (12). In the general Italian population, prevalence has increased from 3.8% in 2000 to 5.3% in 2016, or from 4.1 to 4.9% considering standardized prevalence controlled for the effect of population aging (60). Fasting blood glucose, hyperglycemia, and T2D prevalence have been shown to be related to educational level, which represents a proxy indicator of socioeconomic status (1, 60). For example, among women and men aged 65–74 years with a high school degree or higher, T2D prevalence was 6.8 and 13.2%. In contrast, among women and men of the same age and a lower educational level, it increased to 13.8 and 16.4%, respectively (60). On the other hand, T2D incidence in Italy is ~5 per 1,000 person-years. Incident cases of T2D accounted for ~10% of all cases detected in 2018. Incidence is higher in women than in men aged 11–40 years, but higher in men than in women >40 years (61).

5.4 Overweight and obesity

Considering data from the 2017–2018 TackSHS survey, the estimated overall prevalence of overweight and obesity in Italian adults aged ≥18 years was 44.0%, with overweight prevalence being 36.5% and obesity prevalence 7.5% (62). Similar prevalences were observed with data from the multiscope survey "Aspects of daily life" of the Italian National Institute of Statistics (ISTAT) conducted in 2015 on a representative sample of nearly 46,000 subjects, from which it emerged that 35.3% of the population had overweight and 9.8% had obesity (63). The 2020 version of the survey, although conducted with mixed survey technique (Computer Assisted Web Interviewing/Computer Assisted Personal Interviewing/Paper And Pencil Interviewing), confirmed that 36.1% of the adult population had overweight and 11.5% has obesity. Overall, 47.6% of the Italian population aged ≥18 years are overweight/obese (64). Excess weight was higher among men (64). In fact, 43.9% of men vs. 28.8% of women were overweight and 12.3% of men vs. 10.8% of women were obese. Both men and women aged 65–74 years showed the highest proportions of excess weight (64).

6 Conclusion and future direction

CVD remains the leading cause of mortality, morbidity, and disability in the Italian population, with IHD/CAD and stroke accounting for the most important CVD burden. Considering the multifactorial nature of CVD, major environmental, lifestyle/behavioral, metabolic and genetic risk factors involved in the development of the disease should be considered to establish effective prevention, treatment, and screening measures. Furthermore, given the pleiotropic effect of candidate genes, genetic variants with important frequency in each population should be considered to better assess CVD susceptibility, e.g., through population-targeted genetic risk scores (16, 46). Differences in CVD risk observed between populations may thus vary also according to genetic heterogeneity, making it important to consider population-specific interactions between frequent risk alleles, and environmental and cultural factors (8, 65, 66). Future studies should be focused on the identification of polymorphisms as prognostic and predictive biomarkers in CVD (67). Further research is also needed to shed light on the unclear mechanisms and processes underlying the interactions between the diverse CVD risk factors.

Author contributions

CO-G: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. EC: Investigation, Writing – original draft, Writing – review & editing. MB: Conceptualization, Validation, Visualization, Writing – review & editing. AA: Conceptualization, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was partially funded within the framework of the "UNICT University Research Program 2020-22, PIAno di inCEntivi per la RIcerca (PIACERI) di Ateneo 2020/2022".

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1379785/full#supplementary-material

References

1. Giampaoli S, Palmieri L, Donfrancesco C, Lo Noce C, Pilotto L, Vanuzzo D, et al. Cardiovascular health in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: osservatorio epidemiologico cardiovascolare/health examination survey 1998–2012. *Eur J Prev Cardiol*. (2015) 22:9–37. doi: 10.1177/2047487315589011

2. Cortesi PA, Fornari C, Madotto F, Conti S, Naghavi M, Bikbov B, et al. Trends in cardiovascular diseases burden and vascular risk factors in Italy: the global burden of disease study 1990–2017. *Eur J Prev Cardiol*. (2021) 28:385–96. doi: 10.1177/2047487320949414

3. Tragni E, Filippi A, Casula M, Favato G, Brignoli O, Cricelli C, et al. Risk factors distribution and cardiovascular disease prevalence in the Italian population: the CHECK study. *Open J Epidemiol*. (2012) 2:90–100. doi: 10.4236/ojepi.2012.24014

4. Poulter N. Coronary heart disease is a multifactorial disease. *Am J Hypertens*. (1999) 12:92–5. doi: 10.1016/S0895-7061(99)00163-6

5. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, et al. *European cardiovascular disease statistics 2017*. Belgium: European Heart Network (2017).

6. Sitinjak BDP, Murdaya N, Rachman TA, Zakiyah N, Barliana MI. The potential of single nucleotide polymorphisms (SNPs) as biomarkers and their association with the increased risk of coronary heart disease: a systematic review. *Vasc Health Risk Manag*. (2023) 19:289–301. doi: 10.2147/VHRM.S405039

7. Nikpay M, Goel A, Won H-H, Hall LM, Willenborg C, Kanoni S, et al. A comprehensive 1000 genomes–based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. (2015) 47:1121–30. doi: 10.1038/ng.3396

8. Pignataro P, Pezone L, di Gioia G, Franco D, Iaccarino G, Iolascon A, et al. Association study between coronary artery disease and rs1333049 polymorphism at 9p21.3 locus in Italian population. *J Cardiovasc Transl Res*. (2017) 10:455–8. doi: 10.1007/s12265-017-9758-9

9. Volpe M, Battistoni A, Gallo G, Rubattu S, Tocci G. Executive summary of the 2018 joint consensus document on cardiovascular disease prevention in Italy. *High Blood Pressure Cardiovasc Preven*. (2018) 25:327–41. doi: 10.1007/s40292-018-0278-8

10. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, de Smedt D, et al. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J*. (2022) 43:716–99. doi: 10.1093/eurheartj/ehab892

11. SAGLIETTO A, MANFREDI R, ELIA E, D'ASCENZO F, de FERRARI GM, BIONDI-ZOCCAI G, et al. Cardiovascular disease burden: Italian and global perspectives. *Minerva Cardiol Angiol*. (2021) 69:231–40. doi: 10.23736/S2724-5683.21.05538-9

12. Mosenzon O, Alguwaihes A, Leon JLA, Bayram F, Darmon P, Davis TME, et al. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. *Cardiovasc Diabetol*. (2021) 20:154. doi: 10.1186/s12933-021-01344-0

13. Russo GT, Corigliano G, Arturi F, Cavallo MG, Bette C, Mannucci E. CAPTURE: a cross-sectional study on the prevalence of cardiovascular disease in adults with type 2 diabetes in Italy. *Nutr Metab Cardiovasc Dis NMCD*. (2022) 32:1195–201. doi: 10.1016/j.numecd.2022.01.026

14. Atella V, Piano Mortari A, Kopinska J, Belotti F, Lapi F, Cricelli C, et al. Trends in age-related disease burden and healthcare utilization. *Aging Cell*. (2019) 18:e12861. doi: 10.1111/acel.12861

15. Zdravkovic S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, de Faire U. Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J Intern Med*. (2002) 252:247–54. doi: 10.1046/j.1365-2796.2002.01029.x

16. Schunkert H, Erdmann J, Samani NJ. Genetics of myocardial infarction: a progress report. *Eur Heart J*. (2010) 31:918–25. doi: 10.1093/eurheartj/ehq038

17. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science*. (2007) 316:1488–91. doi: 10.1126/science.1142447

18. Lu X, Wang L, Chen S, He L, Yang X, Shi Y, et al. Genome-wide association study in Han Chinese identifies four new susceptibility loci for coronary artery disease. *Nat Genet*. (2012) 44:890–4. doi: 10.1038/ng.2337

19. Samani NJ, Braund PS, Erdmann J, Götz A, Tomaszewski M, Linsel-Nitschke P, et al. The novel genetic variant predisposing to coronary artery disease in the region of the PSRC1 and CELSR2 genes on chromosome 1 associates with serum cholesterol. *J Mol Med Berl Ger*. (2008) 86:1233–41. doi: 10.1007/s00109-008-0387-2

20. Muendlein A, Geller-Rhomberg S, Saely CH, Winder T, Sonderegger G, Rein P, et al. Significant impact of chromosomal locus 1p13.3 on serum LDL cholesterol and on angiographically characterized coronary atherosclerosis. *Atherosclerosis*. (2009) 206:494–9. doi: 10.1016/j.atherosclerosis.2009.02.040

21. Wallace C, Newhouse SJ, Braund P, Zhang F, Tobin M, Falchi M, et al. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. *Am J Hum Genet*. (2008) 82:139–49. doi: 10.1016/j.ajhg.2007.11.001

22. Bressler J, Folsom AR, Couper DJ, Volcik KA, Boerwinkle E. Genetic variants identified in a European genome-wide association study that were found to predict incident coronary heart disease in the atherosclerosis risk in communities study. *Am J Epidemiol*. (2010) 171:14–23. doi: 10.1093/aje/kwp377

23. Noto D, Cefalù AB, Martinelli N, Giammanco A, Spina R, Barbagallo CM, et al. rs629301 CELSR2 polymorphism confers a ten-year equivalent risk of critical stenosis assessed by coronary angiography. *Nutr Metab Cardiovasc Dis*. (2021) 31:1542–7. doi: 10.1016/j.numecd.2021.01.018

24. Vecoli C, Adlerstein D, Shehi E, Bigazzi F, Sampietro T, Foffa I, et al. Genetic score based on high-risk genetic polymorphisms and early onset of ischemic heart disease in an Italian cohort of ischemic patients. *Thromb Res*. (2014) 133:804–10. doi: 10.1016/j.thromres.2014.03.006

25. Shen G-Q, Girelli D, Li L, Rao S, Archacki S, Olivieri O, et al. A novel molecular diagnostic marker for familial and early-onset coronary artery disease and myocardial infarction in the LRP8 gene. *Circ Cardiovasc Genet*. (2014) 7:514–20. doi: 10.1161/CIRCGENETICS.113.000321

26. Rubattu S, Giusti B, Lotta LA, Peyvandi F, Cotugno M, Stanzione R, et al. Association of a single nucleotide polymorphism of the NPR3 gene promoter with early onset ischemic stroke in an Italian cohort. *Eur J Intern Med*. (2013) 24:80–2. doi: 10.1016/j.ejim.2012.09.002

27. Ciccacci C, di Fusco D, Cacciotti L, Morganti R, D'Amato C, Novelli G, et al. TCF7L2 gene polymorphisms and type 2 diabetes: association with diabetic retinopathy and cardiovascular autonomic neuropathy. *Acta Diabetol*. (2013) 50:789–99. doi: 10.1007/s00592-012-0418-x

28. Gloria-Bottini F, Saccucci P, Magrini A, Bottini E, Banci M, Papetti F, et al. p53 codon 72 polymorphism and coronary artery disease: evidence of association with left ventricular ejection fraction. *Am J Med Sci*. (2012) 343:127–30. doi: 10.1097/MAJ.0b013e318223ac71

29. Bacci S, Rizza S, Prudente S, Spoto B, Powers C, Facciorusso A, et al. The ENPP1 Q121 variant predicts major cardiovascular events in high-risk individuals: evidence for interaction with obesity in diabetic patients. *Diabetes*. (2011) 60:1000–7. doi: 10.2337/db10-1300

30. Ardissino D, Berzuini C, Merlini PA, Mannuccio Mannucci P, Surti A, Burtt N, et al. Influence of 9p21.3 genetic variants on clinical and angiographic outcomes in

early-onset myocardial infarction. *J Am Coll Cardiol*. (2011) 58:426–34. doi: 10.1016/j.jacc.2010.11.075

31. Listì F, Caruso C, di Carlo D, Falcone C, Boiocchi C, Cuccia M, et al. Association between platelet endothelial cellular adhesion molecule-1 polymorphisms and atherosclerosis: results of a study on patients from northern Italy. *Rejuvenation Res*. (2010) 13:237–41. doi: 10.1089/rej.2009.0940

32. Sbarsi I, Falcone C, Boiocchi C, Campo I, Zorzetto M, de Silvestri A, et al. Inflammation and atherosclerosis: the role of TNF and TNF receptors polymorphisms in coronary artery disease. *Int J Immunopathol Pharmacol*. (2007) 20:145–54. doi: 10.1177/039463200702000117

33. Nasti S, Spallarossa P, Altieri P, Garibaldi S, Fabbi P, Polito L, et al. C242T polymorphism in CYBA gene (p22phox) and risk of coronary artery disease in a population of Caucasian Italians. *Dis Markers*. (2006) 22:167–73. doi: 10.1155/2006/458587

34. Pola R, Flex A, Gaetani E, Flore R, Serricchio M, Pola P. Synergistic effect of −174 G/C polymorphism of the interleukin-6 gene promoter and 469 E/K polymorphism of the intercellular adhesion molecule-1 gene in Italian patients with history of ischemic stroke. *Stroke*. (2003) 34:881–5. doi: 10.1161/01.STR.0000062346.70983.DF

35. Girelli D, Martinelli N, Pizzolo F, Friso S, Olivieri O, Stranieri C, et al. The interaction between MTHFR 677 C-->T genotype and folate status is a determinant of coronary atherosclerosis risk. *J Nutr*. (2003) 133:1281–5. doi: 10.1093/jn/133.5.1281

36. Colombo MG, Paradossi U, Andreassi MG, Botto N, Manfredi S, Masetti S, et al. Endothelial nitric oxide synthase gene polymorphisms and risk of coronary artery disease. *Clin Chem*. (2003) 49:389–95. doi: 10.1373/49.3.389

37. Colombo MG, Andreassi MG, Paradossi U, Botto N, Manfredi S, Masetti S, et al. Evidence for association of a common variant of the endothelial nitric oxide synthase gene (Glu298-->asp polymorphism) to the presence, extent, and severity of coronary artery disease. *Br Heart J*. (2002) 87:525–8. doi: 10.1136/heart.87.6.525

38. Baroni MG, Berni A, Romeo S, Arca M, Tesorio T, Sorropago G, et al. Genetic study of common variants at the Apo E, Apo AI, Apo CIII, Apo B, lipoprotein lipase (LPL) and hepatic lipase (LIPC) genes and coronary artery disease (CAD): variation in LIPC gene associates with clinical outcomes in patients with established CAD. *BMC Med Genet*. (2003) 4:8. doi: 10.1186/1471-2350-4-8

39. Fatini C, Abbate R, Pepe G, Battaglini B, Gensini F, Ruggiano G, et al. Searching for a better assessment of the individual coronary risk profile. The role of angiotensin-converting enzyme, angiotensin II type 1 receptor and angiotensinogen gene polymorphisms. *Eur Heart J*. (2000) 21:633–8. doi: 10.1053/euhj.1999.1738

40. Arbustini E, Grasso M, Fasani R, Klersy C, Diegoli M, Porcu E, et al. Angiotensin converting enzyme gene deletion allele is independently and strongly associated with coronary atherosclerosis and myocardial infarction. *Br Heart J*. (1995) 74:584–91. doi: 10.1136/hrt.74.6.584

41. Monasta L, Abbafati C, Logroscino G, Remuzzi G, Perico N, Bikbov B, et al. Italy's health performance, 1990–2017: findings from the global burden of disease study 2017. *Lancet Public Health*. (2019) 4:e645–57. doi: 10.1016/S2468-2667(19)30189-6

42. Donfrancesco C, Buttari B, Marcozzi B, Sieri S, di Lonardo A, Lo Noce C, et al. Nutrition, physical activity and smoking habit in the Italian general adult population: CUORE project health examination survey 2018–2019. *Healthcare*. (2024) 12:475. doi: 10.3390/healthcare12040475

43. Diab A, Dastmalchi LN, Gulati M, Michos ED. A heart-healthy diet for cardiovascular disease prevention: where are we now? *Vasc Health Risk Manag*. (2023) 19:237–53. doi: 10.2147/VHRM.S379874

44. Vitale M, Giosuè A, Vaccaro O, Riccardi G. Recent trends in dietary habits of the Italian population: potential impact on health and the environment. *Nutrients*. (2021) 13:476. doi: 10.3390/nu13020476

45. Aureli V, Rossi L. Nutrition knowledge as a driver of adherence to the Mediterranean diet in Italy. *Front Nutr*. (2022) 9:804865. doi: 10.3389/fnut.2022.804865

46. Ros E, Martínez-González MA, Estruch R, Salas-Salvadó J, Fitó M, Martínez JA, et al. Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. *Adv Nutr*. (2014) 5:330S–6S. doi: 10.3945/an.113.005389

47. Rees K, Takeda A, Martin N, Ellis L, Wijesekara D, Vepa A, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. (2019) 2019:CD009825. doi: 10.1002/14651858.CD009825.pub3

48. Osservatorio Nazionale sulla salute nelle regioni italiane. *Rapporto Osservasalute 2021. Stato di salute e qualià dell'assistenza nelle regioni italiane*. Italy: Com (2021).

49. Torlasco C, Faini A, Makil E, Ferri C, Borghi C, Veglio F, et al. Cardiovascular risk and hypertension control in Italy. Data from the 2015 world hypertension day. *Int J Cardiol*. (2017) 243:529–32. doi: 10.1016/j.ijcard.2017.03.151

50. Duncan MS, Freiberg MS, Greevy RA, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA*. (2019) 322:642–50. doi: 10.1001/jama.2019.10298

51. Liu G, Hu Y, Zong G, Pan A, Manson JAE, Rexrode KM, et al. Smoking cessation and weight change in relation to cardiovascular disease incidence and mortality in people with type 2 diabetes: a population-based cohort study. *Lancet Diabetes Endocrinol*. (2020) 8:125–33. doi: 10.1016/S2213-8587(19)30413-9

52. Sahle BW, Chen W, Rawal LB, Renzaho AMN. Weight gain after smoking cessation and risk of major chronic diseases and mortality. *JAMA Netw Open*. (2021) 4:e217044. doi: 10.1001/jamanetworkopen.2021.7044

53. Agabiti Rosei C, del Pinto R, Grassi G, Muiesan ML, Ferri C. Prevalence of cardiovascular risk factors and related medical and lifestyle interventions among Italian cardiovascular specialists: a proof-of-concept study. *High Blood Press Cardiovasc Prev*. (2023) 30:255–64. doi: 10.1007/s40292-023-00578-1

54. Maffei S, Meloni A, Deidda M, Sciomer S, Cugusi L, Cadeddu C, et al. Cardiovascular risk perception and knowledge among Italian women: lessons from IGENDA protocol. *J Clin Med*. (2022) 11:1695. doi: 10.3390/jcm11061695

55. del Pinto R, Grassi G, Muiesan ML, Borghi C, Carugo S, Cicero AFG, et al. World hypertension day 2021 in Italy: results of a Nationwide survey. *High Blood Press Cardiovasc Prev*. (2022) 29:353–9. doi: 10.1007/s40292-022-00519-4

56. Torlasco C, Faini A, Makil E, Bilo G, Pengo M, Beaney T, et al. Nation-wide hypertension screening in Italy: data from may measurements month 2017—Europe. *Eur Heart J Suppl*. (2019) 21:D66–70. doi: 10.1093/eurheartj/suz058

57. Donfrancesco C, di Lonardo A, Lo Noce C, Buttari B, Profumo E, Vespasiano F, et al. Trends of blood pressure, raised blood pressure, hypertension and its control among Italian adults: CUORE project cross-sectional health examination surveys 1998/2008/2018. *BMJ Open*. (2022) 12:e064270. doi: 10.1136/bmjopen-2022-064270

58. Marzetti E, Calvani R, Picca A, Sisto A, Tosato M, Martone AM, et al. Prevalence of dyslipidaemia and awareness of blood cholesterol levels among community-living people: results from the longevity check-up 7+ (lookup 7+) cross-sectional survey. *BMJ Open*. (2018) 8:e021627. doi: 10.1136/bmjopen-2018-021627

59. Altobelli E, Marzi F, Angeletti PM, Galassi F, Guercache AK, Profeta VF, et al. The burden of modifiable cardiovascular risk factors in a population of Central Italy: a pilot study. *Healthcare*. (2023) 11:1473. doi: 10.3390/healthcare11101473

60. Istituto Nazionale di Statistica. *Diabetes in Italy*. Italy: ISTAT (2017).

61. Bonora E, Cataudella S, Marchesini G, Miccoli R, Vaccaro O, Fadini GP, et al. Incidence of diabetes mellitus in Italy in year 2018. A nationwide population-based study of the ARNO diabetes observatory. *Nutr Metab Cardiovasc Dis*. (2021) 31:2338–44. doi: 10.1016/j.numecd.2021.04.017

62. Stival C, Lugo A, Odone A, van den Brandt PA, Fernandez E, Tigova O, et al. Prevalence and correlates of overweight and obesity in 12 European countries in 2017-2018. *Obes Facts*. (2022) 15:655–65. doi: 10.1159/000525792

63. Istituto Nazionale di Statistica. *Fattori di rischio per la salute: fumo, obesità, alcol e sedentarietà - Anno 2015*. Italy: ISTAT (2016).

64. Istituto Nazionale di Statistica. *Fattori di rischio per la salute: fumo, obesità, alcol e sedentarietà - Anno 2021*. Italy: ISTAT (2022).

65. Razieh C, Zaccardi F, Miksza J, Davies MJ, Hansell AL, Khunti K, et al. Differences in the risk of cardiovascular disease across ethnic groups: UK biobank observational study. *Nutr Metab Cardiovasc Dis*. (2022) 32:2594–602. doi: 10.1016/j.numecd.2022.08.002

66. Ho FK, Gray SR, Welsh P, Gill JMR, Sattar N, Pell JP, et al. Ethnic differences in cardiovascular risk: examining differential exposure and susceptibility to risk factors. *BMC Med*. (2022) 20:149. doi: 10.1186/s12916-022-02337-w

67. Tuttolomondo A, Simonetta I, Daidone M, Mogavero A, Ortello A, Pinto A. Metabolic and vascular effect of the Mediterranean diet. *Int J Mol Sci*. (2019) 20:4716. doi: 10.3390/ijms20194716

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 05 April 2024
DOI 10.3389/fnut.2024.1359989

OPEN ACCESS

EDITED BY
Claudia Ojeda-Granados,
University of Catania, Italy

REVIEWED BY
Berenice Palacios-Gonzalez,
National Institute of Genomic Medicine (INMEGEN), Mexico
Hong Chen,
Sichuan Agricultural University, China

*CORRESPONDENCE
Wenzhi Guo
✉ guowz66@163.com
Jiacheng Zhang
✉ aster65@163.com

RECEIVED 22 December 2023
ACCEPTED 20 March 2024
PUBLISHED 05 April 2024

CITATION
Zhang J, Hu B, Deng X, Sun R, Zhang R, Chen K and Guo W (2024) Multiomics analysis investigating the impact of a high-fat diet in female Sprague–Dawley rats: alterations in plasma, intestinal metabolism, and microbial composition.
Front. Nutr. 11:1359989.
doi: 10.3389/fnut.2024.1359989

Multiomics analysis investigating the impact of a high-fat diet in female Sprague–Dawley rats: alterations in plasma, intestinal metabolism, and microbial composition

Jiacheng Zhang[1,2,3]*, Binhong Hu[4], Xin Deng[4], Rong Sun[4], Rong Zhang[5], Kuo Chen[6] and Wenzhi Guo[1,3,7]*

[1]Department of Hepatobiliary, Pancreatic and Liver Transplantation Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]Henan Key Laboratory of Digestive Organ Transplantation, Zhengzhou, China, [3]Open and Key Laboratory of Hepatobiliary and Pancreatic Surgery and Digestive Organ Transplantation at Henan Universities, Zhengzhou, China, [4]College of Chemistry and Life Sciences, Chengdu Normal University, Chengdu, China, [5]School of Physical Science and Technology, ShanghaiTech University, Shanghai, China, [6]Department of Breast Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [7]Henan Research Centre for Organ Transplantation, Zhengzhou, China

Introduction: With improvements in living conditions, modern individuals exhibit a pronounced inclination towards a high-fat diet, largely because of its distinctive gustatory appeal. However, the association between high-fat diets and metabolic complications has largely been ignored, and metabolic diseases such as obesity and non-alcoholic fatty liver disease now constitute a major public health concern. Because high-fat diets increase the risk of metabolic diseases, a thorough investigation into the impact of high-fat diets on gut microbiota and metabolism is required.

Methods: We utilize 16S rRNA sequencing and untargeted metabolomics analysis to demonstrate that SD rats fed a high-fat diet exhibited marked alterations in gut microbiota and plasma, intestinal metabolism.

Results: Changes in gut microbiota included a decreased abundance at phylum level for Verrucomicrobiota, and a decreased abundance at genus level for *Akkermansia, Ralstonia, Bacteroides*, and *Faecalibacterium*. Additionally, significant changes were observed in both intestinal and plasma metabolite levels, including an upregulation of bile acid metabolism, an upregulation of glucose-lipid metabolism, and increased levels of metabolites such as norlithocholic acid, cholic acid, D-fructose, D-mannose, fructose lactate, and glycerophosphocholine. We also investigated the correlations between microbial communities and metabolites, revealing a significant negative correlation between *Akkermansia* bacteria and cholic acid.

Discussion: Overall, our findings shed light on the relationship between symbiotic bacteria associated with high-fat diets and metabolic biomarkers, and they provide insights for identifying novel therapeutic approaches to mitigate disease risks associated with a high-fat diet.

KEYWORDS

high fat diet, gut microbiota, metabolome, *Akkermansia*, bile acids

1 Introduction

Long-term consumption of a high-fat diet (HFD) is a significant risk factor for a diverse range of public health diseases, including obesity, inflammatory bowel disease, and reproductive damage. HFD consumption has also been shown to gradually impair function in multiple organs (1–4). Other consequences include dyslipidemia and an alteration in lipid and plasma transaminase profiles (5). During the development of these lipid disorders, the body typically encounters adaptive barriers to nutrition and to the environment. These changes include modifications to molecular mechanisms associated with metabolic damage. For instance, HFD significantly promotes hepatic lipid droplet accumulation while modulating SIRT-1/AMPK pathways and influence gene expression related to lipid synthesis and degradation (5, 6).

Gut microbiota dysbiosis is also closely associated with long-term HFD consumption. Studies of the relationship between diet-related diseases and microbiota have progressively shifted from correlation studies to inquiries on causality and interactions (7–9). Because HFD modulates the composition of gut microbial communities, the integrity of the intestinal barrier is compromised (7, 10). Moreover, the resulting damage to the intestinal mucosa and increase in lipopolysaccharide (LPS) production stimulate systemic inflammation and metabolic disorders, which are factors in the development of obesity and type 2 diabetes (T2DM) (11, 12). In addition, fatty acids derived from microbes exacerbate diet-induced obesity and further compromise intestinal epithelial integrity (13). Disordered intestinal microbiota and its metabolites can promote inflammation, for example, the enrichment of arachidonic acid and lipopolysaccharide biosynthetic pathways found in the feces of young adults on a high-fat diet (14). Therefore, it is necessary to understand the mechanism of intestinal microbiota mediating HFD, and then design personalized dietary strategies by regulating intestinal microbiota (15, 16).

Understanding the impact of long-term HFD consumption on metabolism is crucial for elucidating the interaction between host metabolism and microbiota. In HFD-fed mice, supplementation of medium-chain and long-chain triglycerides (MLCT) improved energy utilization, enhanced regulation of glucose and lipid metabolism, and inhibited inflammation (17). HFD consumption is also known to activate fatty acid oxidation processes that mediate intestinal stemness and tumorigenicity (18). Bile acids (BAs) are synthesized endogenously in the liver, and they subsequently circulate to distal organs such as the intestine where they exert profound effects (19). These essential metabolic products play an important role in liver diseases. Gut microbiota also produce short-chain fatty acids and BAs that promote hepatic homeostasis through their interaction with mitochondria (20). Modulation of the BA signaling pathway along the "gut-liver axis" has emerged as a novel approach for ameliorating obesity and metabolic disorders. Supporting evidence for this approach comes from the observation that primary BAs and dietary fat intake supplementation can improve metabolic disorders (21). Notably, intestinal BA levels are significantly elevated in diet-induced obese mice (22). Despite these advances, a comprehensive understanding of the dynamic characteristics induced by long-term HFD consumption is lacking, and further elucidation of HFD-induced changes may facilitate the identification of effective intervention strategies.

In the present study, we aim to investigate the impacts of long-term HFD consumption on the interaction between microbiota and metabolites using 16S rRNA sequencing and untargeted metabolomics approaches. Our objectives include the detection of potential symbiotic bacteria, the identification of biomarkers associated with HFD consumption, and an elucidation of the underlying mechanisms linking gut microbiota and host metabolism.

2 Materials and methods

2.1 Animal models

All animal experiments were approved by the Ethics Office of the First Affiliated Hospital of Zhengzhou University, China (no. 2023-KY-0658), and conducted in accordance with the ARRIVE guidelines and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. The 24 female Sprague Dawley (SD) rats (3–4 weeks of age) (23) were purchased from Yuchi Experimental Animal Co. Ltd., China. The rats were housed in a controlled environment (temperature, 25 ± 3°C; humidity, 75 ± 5%), under a 12-h light/dark cycle, and provided with sufficient food and water. The rats were separately randomly divided into two groups ($n = 12$): CON (normal diet) and HFD (60% fat, 20% protein, and 20% carbohydrates). These experimental groups were then maintained for a duration of 60 days. For the sample sequencing, we employed a method of combining two microbiota samples and conducted a pooled treatment of four samples within each metabolic group to ensure biological replicability.

2.2 Blood index detection

At the end of the experimental period, 0.5 mL of blood was collected from SD rat through the tail vein ($n = 6$). All blood samples were then incubated for 15 min, and the serum was isolated by centrifugation at 2000 ×*g* for 10 min. Serum levels of estradiol (E2), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were analyzed using specific enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The blood samples were paired and subjected to testing using a kit.

2.3 Oral glucose tolerance test

After the 60-day intervention, rats were given a glucose load (2 g/kg) by oral gavage. Blood glucose levels were measured using a glucose oxidase reagent strip 30, 60, 90, and 120 min before and after glucose administration (24).

2.4 16S rRNA sequencing

Colorectal contents of SD female rats were collected from 6 per group for 16S rRNA sequencing. FLASH (V1.2.11) (25) was used to assemble the sample reads to obtain the Raw Tags. These were subjected to quality control using fastp. The Clean Tags obtained after quality control were compared with the Silva database, and chimeras

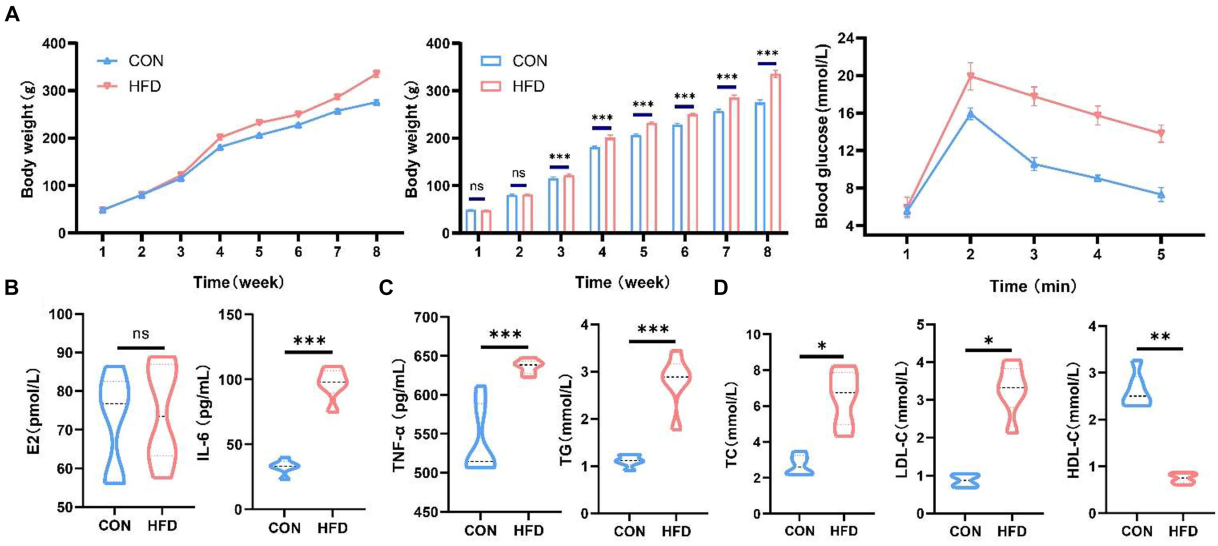


FIGURE 1
High-fat diet induces weight gain and dyslipidemia in female SD rats. **(A)** Changes in body weight and oral glucose tolerance test in rats on normal or high-fat diets. **(B)** Serum estradiol levels in female rats. **(C)** Serum IL-6 and TNF-α levels in female rats. **(D)** Serum TG, TC, HDL-C and LDL-C levels in female rats. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

were detected and removed using Vsearch (25). DADA2 (by default) or deblur in QIIME2 (Version QIIME2-202006) (26, 27) were used for denoising, and sequences with relative abundance less than 5% in the total microbial profile were filtered out (28) to obtain the final amplicon sequence variants (ASVs) and feature table. The species in each sample were annotated using the Silva database through QIIME2 software.

2.5 Metabolomics analysis

Plasma samples (100 µL) and colorectal contents (60 mg) from SD female rats were further processed for metabolomics analysis. First, 300 µL of the protein precipitation agent methanol-acetonitrile (V:V = 2:1, containing L-2-chlorophenylalanine 2 µg/mL) and 600 µL of methanol–water (V:V = 4:1, containing L-2-chlorophenylalanine 4 µg/mL) was added to each sample of plasma and colorectal contents, respectively. Next, the mixture was vortexed and ultrasonically extracted. The resulting solution was filtered through a 0.22 µm organic phase pinhole filter for LC–MS analysis. LC was performed on an ACQUITY UPLC column (150 mm × 2.1 mm, 1.8 µm) using water (containing 0.1% formic acid) as solvent A and acetonitrile as solvent B (flow rate, 0.35 mL/min; injection volume, 5 µL). The positive and negative ion scanning modes were both employed for relative quantitative analysis of samples using Progenesis QI v2.3 software.

2.6 Statistical analysis

All data were presented as mean ± standard deviation. GraphPad Prism 8.0 was used for all statistical analyses. A two-tailed *t*-test was used to compare differences between two groups, and one-way analysis of variance (ANOVA) was used to compare multiple groups. Differences with a $p < 0.05$ were considered statistically significant. Correlation between genus-level flora and inflammatory factors, TG, TC, LDL-C, HDL-C was assessed using Spearman's rank correlation coefficient.

3 Results

3.1 Consumption of a high-fat diet induces weight gain, upregulates inflammatory factors, and disrupts lipid metabolism in female Sprague–Dawley rats

HFD consumption induced an increase in body weight in SD rats (Figure 1A). Oral glucose tolerance test demonstrating changes in blood glucose concentration in each group (Figure 1A). We investigated the changes in estradiol levels in female rats and found no difference in estradiol levels between normal female rats and rats in the HFD group (Figure 1B). Moreover, consumption of an HFD by SD female rats resulted in elevated inflammatory factor levels and disrupted lipid metabolism (Figures 1C,D). While levels of TG, TC, and LDL-C were elevated, HDL-C levels were markedly decreased.

3.2 High-fat diets lead to changes in the composition of the gut microbiota

After data merging and quality control of the raw sequencing data, we successfully obtained a total of 59,442–68,217 high-quality sequence reads of the 16S rRNA gene from 12 samples of intestinal content. Analysis of these reads reveals no statistically significant difference in the α-diversity of gut microbiota between rats fed a normal diet and rats fed an HFD. The top ten bacterial taxa are presented in a species bar chart at both phylum level (Figure 2A) and genus level (Figure 2B).

10.3389/fnut.2024.1359989

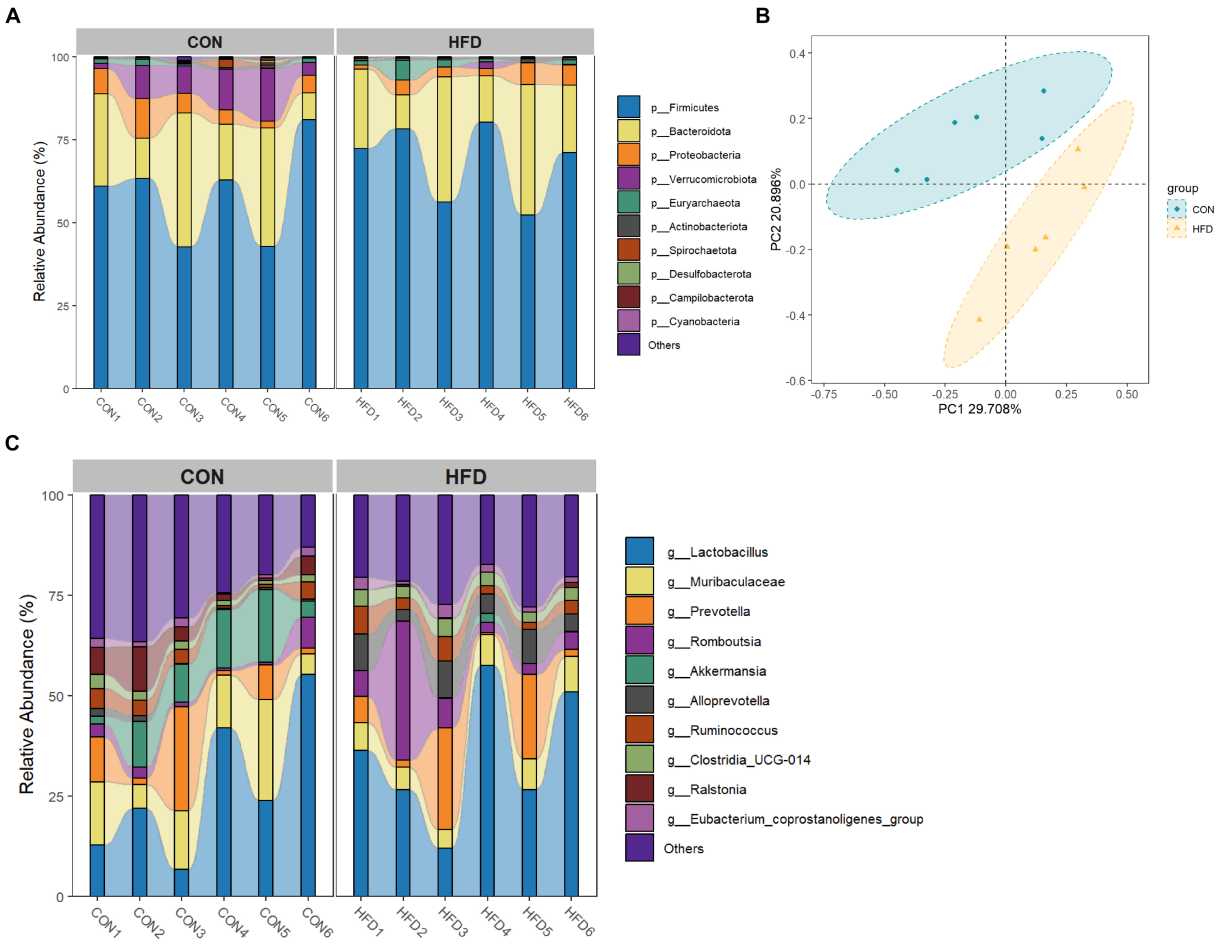


FIGURE 2
High-fat diet-induced changes in the gut microbiota of rats. **(A)** Phylum level bar chart. **(B)** Genus level bar chart. **(C)** PCoA analysis based on Bray Curtis dissimilarity index.

At the phylum level, Firmicutes, Bacteroidota, Proteobacteria, Verrucomicrobiota, and Euryarchaeota were predominant. At the genus level, *Lactobacillus*, *Muribaculaceae*, *Prevotella*, *Romboutsia*, and *Akkermansia* were predominant. Principal co-ordinates analysis (PCoA) was employed to compare microbial community distribution among the different groups (Figure 2C), revealing a noticeable disparity in gut microbiota composition between rats fed on normal diet and rats fed on HFD.

3.3 Rats fed a high fat diet exhibit a different microbial composition

A Venn plot showing shared and unique ASVs obtained from rats fed a normal diet and rats fed a HFD is presented in Figure 3A. Linear discriminant analysis Effect Size (LEfSe) analysis indicated that at the phylum level, Verrucomicrobiota dominated in the CON group. At the genus level, *Akkermansia*, *Ralstonia*, *Bacteroides*, and *Faecalibacterium* were dominant in the CON group, whereas *Alloprevotella*, *Commensalibacter*, *Clostridia_UCG_014*, and *Candidatus_Soleaferrea* were dominant in the HFD group (Figure 3B). The above findings demonstrate marked alterations in gut microbiota composition in rats fed a HFD. In addition, the associations of intestinal flora with the expression of inflammatory factors and dyslipidemia were calculated based on spearman correlation analysis (Figure 3C).

3.4 A high-fat diet elicits modifications in the composition of intestinal contents and plasma metabolites

OPLS score charts for intestinal contents (Figure 4A) and plasma samples (Figure 4B) illustrate the changes in metabolite distribution between the CON group and HFD group. In total, 104 different metabolites were identified in intestinal content samples (R2Y = 0.991, Q2 = 0.606) with 64 up-regulated and 40 down-regulated metabolites detected in positive and negative ion modes, respectively. In addition, 148 differential metabolites were identified in plasma samples (R2Y = 0.999, Q2 = 0.91) with 79 up-regulated and 69 down-regulated in positive and negative ion modes, respectively. To facilitate their identification, the screened differential metabolites ($p < 0.05$ and VIP > 1.0) were visualized in Volcano plots (Figures 4C,D).

In addition, heat maps were used to identify differences in the TOP50 metabolites between the CON and HFD groups (for intestinal

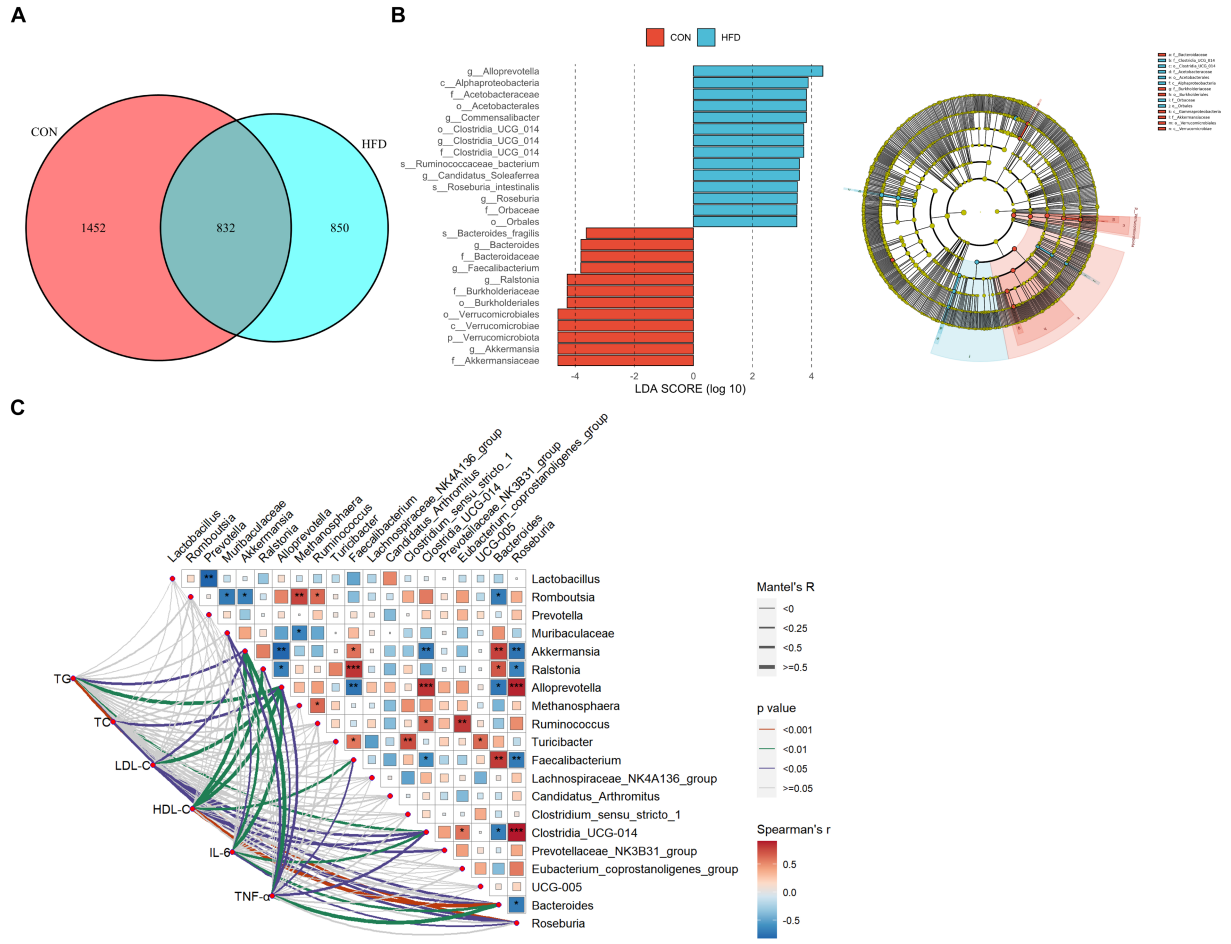


FIGURE 3
The gut microbiota of rats fed a high-fat diet exhibited significant differences compared to the gut microbiota of rats fed a normal diet. **(A)** Venn chart. **(B)** LEfSe analysis and evolutionary branch chart. Intergroup comparisons were conducted using the Wilcoxon rank sum test (LDA, 3.5). **(C)** Heatmap of mantel test correlation.

contents, Figure 5A; for plasma samples, Figure 5C). The key metabolites were subsequently identified from these differential metabolites. Significant differences in the metabolites between experimental groups ($p < 0.05$) were confirmed using a two-tailed t-test (for intestinal contents, Figure 5B; for plasma samples, Figure 5D). For the intestinal contents, the key metabolites included norlithocholic acid, cholic acid, taurodeoxycholic acid, and hyaluronan biosynthesis precursor-1 (Figure 5B). For the plasma samples, the upregulated key metabolites included L-isoleucine, cholic acid, isoursodeoxycholic acid, taurocholic acid, 12-Ketodeoxycholic acid, D-Fructose, D-mannose, fructose lactate, and glycerophosphocholine, and the down-regulated key metabolites were D-lysine and D-glutamine (Figure 5D). Pearson correlation analysis showed the correlation of colorectal contents with plasma lipid metabolism-related metabolites (Figure 5E).

3.5 High-fat diets induce alterations in metabolic pathways within the intestinal tract and plasma

To further elucidate the impact of HFD consumption on metabolic pathways, we performed KEGG analyses. For the intestinal contents, significantly enriched upregulated pathways were predominantly associated with "bile secretion" and "primary bile acid biosynthesis" (Figure 6A). For the plasma samples, the significantly enriched upregulated pathways included "bile secretion," "valine, leucine and isoleucine biosynthesis and degradation," and "primary bile acid biosynthesis," while the significantly enriched downregulated pathways included "Lysine degradation" and "D-Glutamine and D-glutamate metabolism" (Figure 6B). Notable alterations in "choline metabolism in cancer" were also observed. Collectively, these findings provide evidence that HFD consumption is associated with perturbations in amino acid metabolism, energy metabolism, and bile acid metabolism.

3.6 Correlation between gut microbiota and metabolites

Pearson correlation analysis revealed negative correlations between *Akkermansia* and the intestinal contents metabolites cholic acid, berkeleylactone G, tetradecanedioic acid, N-Acetylmuramate, and valeant. Conversely, our analysis also revealed positive correlations between *Akkermansia* and the intestinal contents metabolites

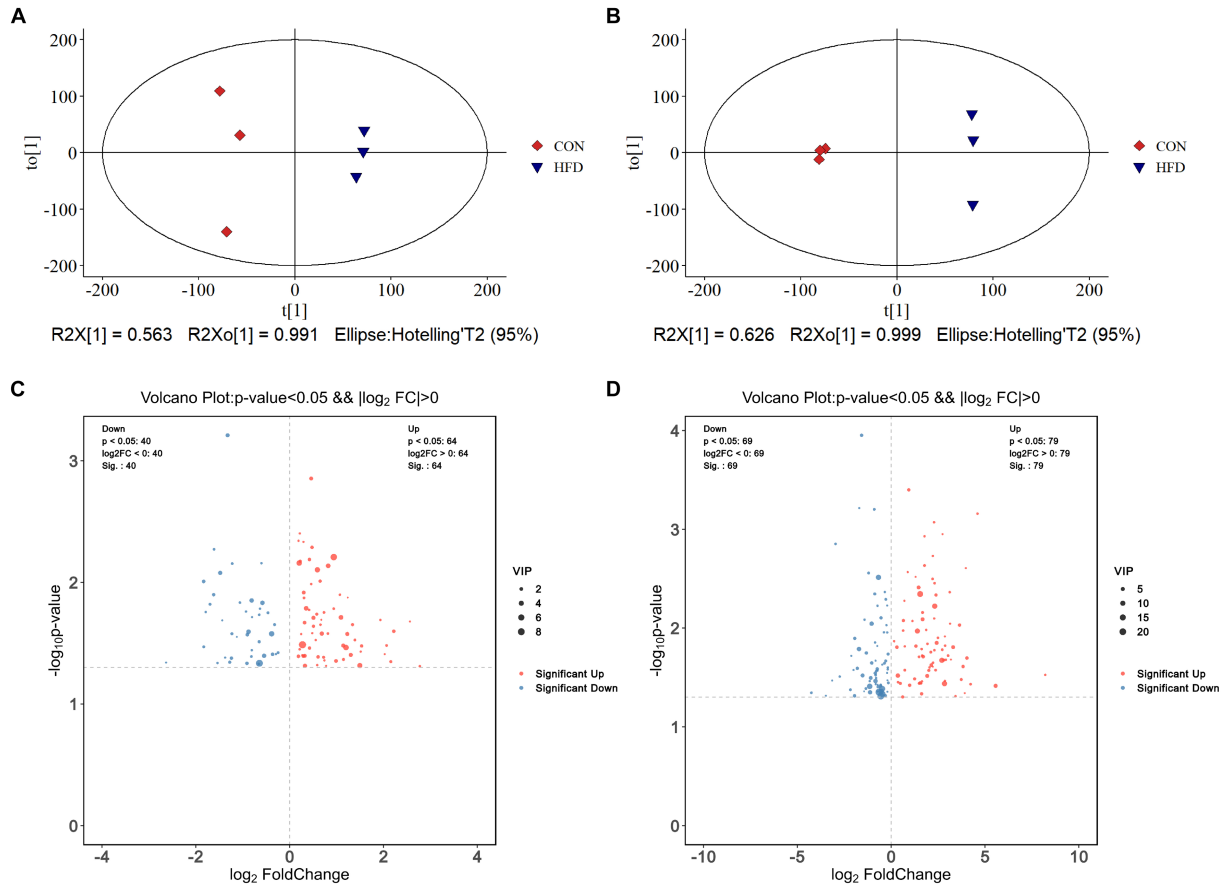


FIGURE 4
High-fat diet-induced alterations in colorectal contents metabolites and plasma metabolites. **(A)** OPLS-DA score plot of colorectal contents metabolites. **(B)** OPLS-DA score plot of plasma metabolites. **(C)** Volcano plot demonstrating changes in colorectal contents metabolites. **(D)** Volcano plot demonstrating changes in plasma metabolites.

N-Acetylneuraminic acid and camonagrel (Figure 7A). In addition, Pearson correlation analysis revealed negative correlations between *Akkermansia* and the plasma metabolites cholic acid, 3b-hydroxy-5-cholenoic acid, 3-amino-3-methylbutanoic acid, D-fructose and L-isoleucine. Conversely, our analysis also revealed positive correlations between *Akkermansia* and the plasma metabolites GM4 (d18:1/16:0) and LysoPC (0:0/18:1(9Z)) (Figure 7B). Analysis of the correlation between *Akkermansia* and bile acids (Figure 7C), showed a negative correlation.

4 Discussion

Animal models fed HFD are commonly utilized to investigate different metabolic diseases, e.g., non-alcoholic fatty liver disease, hypercholesterolemia, and obesity (5, 29, 30), and these diseases are closely associated with dysbiosis of gut microbiota. Diet is known to be a crucial factor influencing alterations of gut microbiota (31). An unhealthy diet (such as long-term HFD consumption) not only leads to unfavorable metabolic outcomes, but it also induces changes in microbiota composition, which consequently increases intestinal permeability, allowing toxic bacterial metabolites to enter the circulatory system, ultimately promoting systemic inflammation (32).

In the present study, we observed an increased secretion of pro-inflammatory factors in the blood of HFD-fed rats (in comparison with control rats), along with alterations in the composition of their gut microbiota. Specifically, at the phylum level, there was a decrease in the abundance of microorganisms other than Verrucomicrobiota within the HFD group. At the genus level, we noted a reduction in *Akkermansia*, *Ralstonia*, *Bacteroides*, and *Faecalibacterium* abundance. Conversely, *Alloprevotella*, *Commensalibacter*, *Clostridia_UCG_014*, and *Candidatus_Soleaferrea* exhibited an increase in abundance. It is noteworthy that individuals with gastrointestinal-related diseases or abnormalities often exhibit decreases in the levels of *Faecalibacterium* and *A. muciniphila* — two species primarily responsible for butyric acid production — and this is contrary to what is typically observed in a healthy human gut (33, 34). *A. muciniphila* also influences mucin production, and its abundance in the flora is reduced in cases of obesity and mild inflammation (35). Indeed, supplementation with *A. muciniphila* alone can loss weight and improve metabolic disorders (35). Furthermore, *A. muciniphila* converts mucin into beneficial by-products, contributing to the regulation of intestinal homeostasis and the maintenance of intestinal barrier integrity (36). In conclusion, the decrease in *A. muciniphila* levels observed in HFD may be closely associated with intestinal damage and metabolic disorders. The abundance levels of Bacteroides, which secrete bile acid hydrolase

10.3389/fnut.2024.1359989

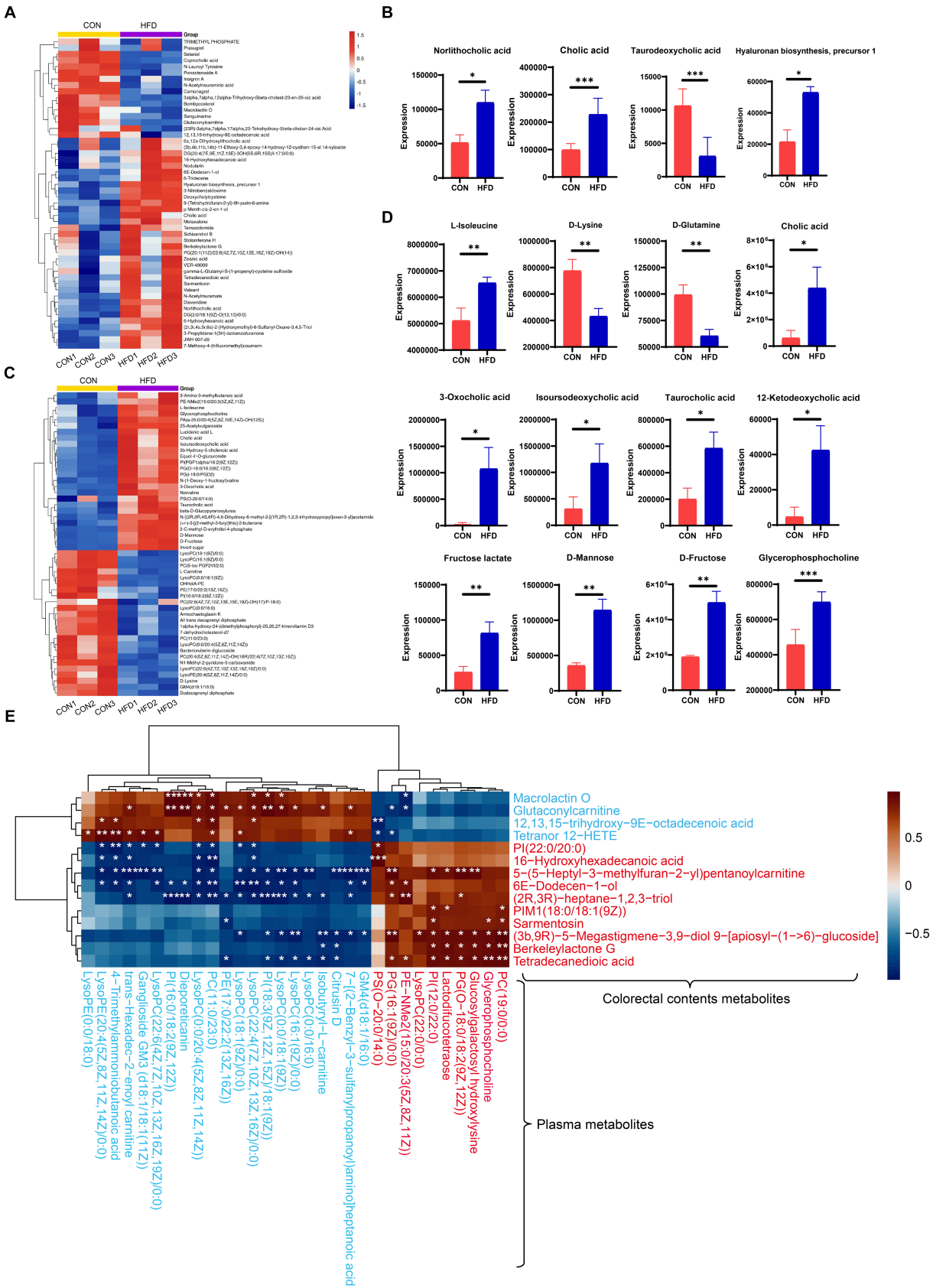


FIGURE 5
Analysis of alterations in gut content metabolites and plasma metabolites. **(A)** Heatmap displaying the top 50 metabolites present in the gut. **(B)** Identification of key metabolites within the gut. **(C)** Heatmap displaying the top 50 metabolites present in plasma. **(D)** Identification of key metabolites within plasma. **(E)** Correlation heatmap depicting differential metabolites associated with lipid metabolism. The blue text denotes downregulation of these metabolites in the HFD group compared to the control, while the red font indicates upregulation. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

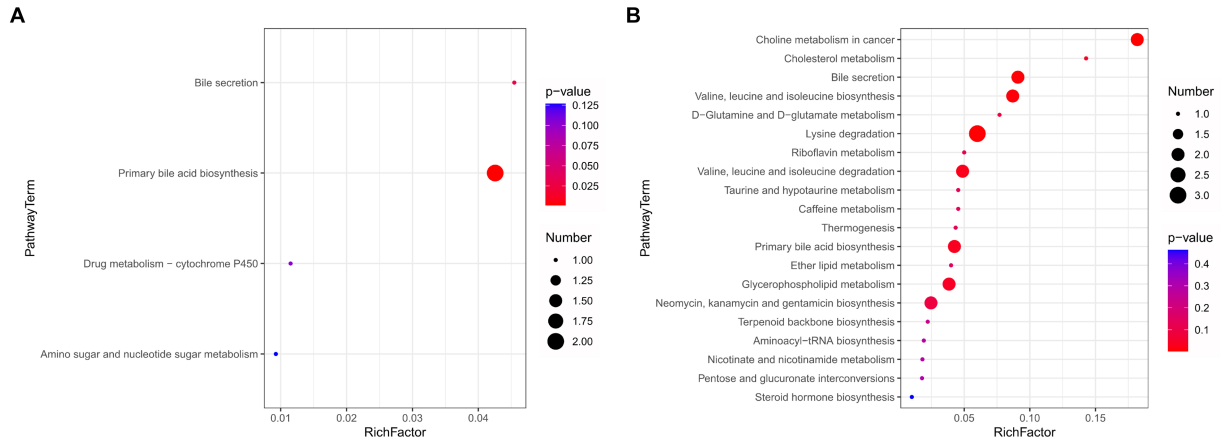


FIGURE 6
High-fat diet-induced changes in top 20 metabolic pathways. **(A)** Enrichment map of metabolic pathways for intestinal contents. **(B)** Enrichment map of metabolic pathways for plasma samples.

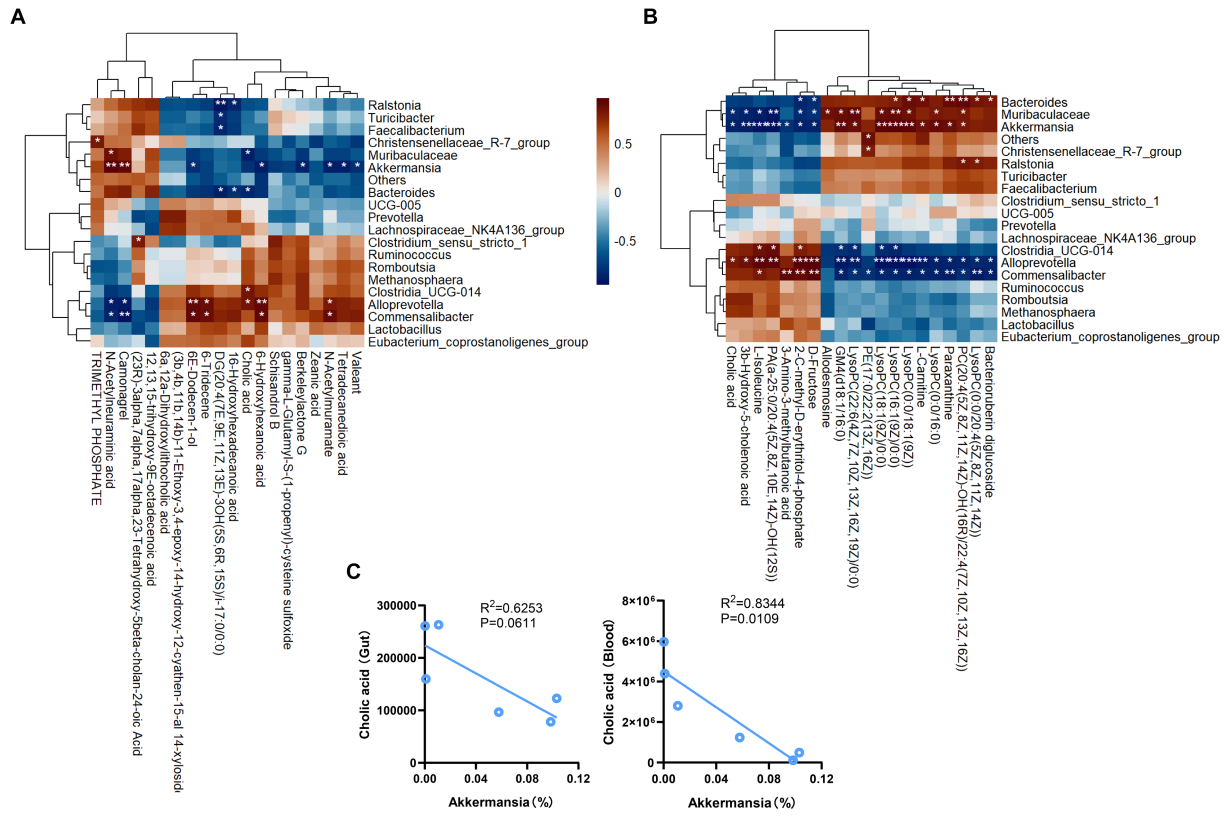


FIGURE 7
Pearson correlation analyses between gut microbiota and various metabolic products. **(A)** The relationship between gut content metabolism and gut microbial community. **(B)** The relationship between plasma metabolism and gut microbial community. **(C)** Correlation analysis. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

(37), are also down-regulated in rats fed an HFD. Some similar observations were previously reported in study on T2DM and long-term HFD (22, 33).

Under normal dietary conditions, there exists a robust temporal and spatial correlation among metabolites, enabling metabolic communication and coordination across multiple tissues and organs. However, long-term HFD consumption disrupts these intricate metabolic networks (38). In the present study, we employed non-targeted metabolomics approaches to evaluate the impact of an HFD on plasma and intestinal metabolic profiles. We observed changes in lipid metabolism-related metabolites, and Pearson analysis demonstrated a correlation

between lipid metabolism-related metabolites in colorectal contents and plasma. Among the plasma metabolites, two LysoPEs and seven LysoPCs were downregulated in the HFD group relative to control. Consistent with our study, significant reductions in plasma LysoPCs levels were also found in obese and T2DM patients (39). Importantly, in the group fed an HFD, we observed a significant elevation in cholic acid levels in both the plasma and within the gut. It is already well-established that HFD consumption induces an increase in BA concentrations within the liver, stool, and plasma (40). In samples of intestinal contents, we observed an HFD-induced increase in the levels of norlithocholic acid, taurodeoxycholic acid, hyaluronan biosynthesis precursor-1, and other metabolites. In plasma samples, we observed elevations in the levels of isoursodeoxycholic acid, taurocholic acid, and 12-ketode oxycholic acid. BAs are known to play a crucial role in regulating intestinal function (22, 41), and their concentrations are strongly influenced by dietary factors and alterations in gut microbiota (42). A reduction in BA levels can alleviate changes in gut microbiome induced by HFD and subsequently mitigate obesity phenotypes (22). Of the symbiotic gut bacteria influenced by HFD consumption, *A. muciniphila* appears to be particularly involved in bile acid-host metabolism. Previous studies have demonstrated that most bile salts (including cholic acid) inhibit the growth of *A. muciniphila* (43). Indeed, we observed a significant negative correlation between *A. muciniphila* and cholic acid content. Furthermore, *A. muciniphila* has the potential to modulate BA production, leading to an inhibition of systemic inflammation, a reduction in blood glucose levels, and an improvement in glucose homeostasis (44, 45). Consequently, we postulate that a liver-BA-gut microbiome metabolic axis exists within the body, and that HFD-induced changes result in substantial alterations in both BA levels and microbiome composition, ultimately contributing to metabolic disorders. Therefore, a combined intervention targeting *A. muciniphila* and BA holds promise as an innovative approach for mitigating disease risk associated with HFD.

Estradiol levels are closely associated with the development of disorders related to glucose and lipid metabolism, such as diabetes and obesity (46, 47). Some studies have reported a reduction in estradiol levels following a high-fat diet (23), while others have not observed significant differences in estradiol levels among female rats under an HFD, consistent with our findings (46, 48). This discrepancy may be attributed to variations in glycolipid metabolism; however, the precise relationship remains unclear. Given the crucial role of estradiol in regulating metabolism and body weight homeostasis (49), further investigations are warranted to elucidate the association between estradiol levels and a HFD.

Metabolic disorders resulting from excessive fat consumption increase an individual's susceptibility to disease occurrence, particularly by disrupting glucose and lipid metabolism (50). Long-term HFD consumption impacts serum levels of total cholesterol, low-density LDL-C, and HDL-C (51). In our present study, we also report increased plasma concentrations of D-fructose, D-mannose, lactate fructose, and choline glycerophosphate after HFD consumption. Thus far, elevated levels of glycerophosphocholine have been regarded as an indicator of aberrant choline metabolism in cancer (52). In summary, our study demonstrates significant HFD-induced alterations in metabolite levels in SD rats, especially in the levels of metabolites within BA metabolism and glycolipid metabolism pathways. We observed alterations in both plasma and intestinal bile acid levels, alongside changes in glucolipid metabolism among plasma metabolites, suggesting that plasma metabolites may serve as more suitable indicators for assessing the nutritional status of organisms on a HFD. To date, metabolic patterns have not been utilized to predict the health effects and underlying mechanisms of HFDs. Therefore, further investigation is warranted to elucidate specific metabolic signatures associated with nutrient/ microbiome interactions for intervention strategies, diagnostic purposes, and a comprehensive understanding of the impact of nutrition on the quantitative composition of healthy gut microbiota.

5 Conclusion

Our research findings demonstrate that long-term HFD consumption induces dyslipidemia in rats, leading to perturbations in gut microbiota and metabolism. In particular, we observed a reduction in the abundance of *A. muciniphila* and an elevation in BA levels among rats receiving an HFD. Correlation analysis revealed an inverse association between *A. muciniphila* and BA levels, both in the intestines and in plasma. In summary, our study elucidates the underlying mechanisms responsible for the deleterious effects of an HFD on organisms, and it also identifies potentially impacted metabolic pathways, specifically "bile acid metabolism" and "glucose-lipid metabolism".

Data availability statement

Original datasets are available in a publicly accessible repository: The original contributions presented in the study are publicly available. This data can be found here: [https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA1067806/PRJNA1067806].

Ethics statement

The animal study was approved by the Ethics Office of the First Affiliated Hospital of Zhengzhou University, China (no. 2023-KY-0658). The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

JZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Software, Writing – original draft, Writing – review & editing. BH: Data curation, Software, Writing – original draft. XD: Data curation, Formal analysis, Methodology, Software, Writing – original draft. RS: Formal analysis, Methodology, Software, Writing – original draft. RZ: Data curation, Software, Writing – original draft. KC: Project administration, Writing – original draft. WG: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by the National Natural Science Foundations of China (82170648, 82370646, and 32300081), Henan Medical Science and Technology Joint Construction Project (LHGJ20220387 and LHGJ20220319).

Acknowledgments

The authors thank the investigators and staff of the Shanghai Luming Biotechnology Co., Ltd. for technical support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Gulhane M, Murray L, Lourie R, Tong H, Sheng YH, Wang R, et al. High fat diets induce colonic epithelial cell stress and inflammation that is reversed by IL-22. *Sci Rep*. (2016) 6:28990. doi: 10.1038/srep28990

2. Hao Y, Feng Y, Yan X, Chen L, Ma X, Tang X, et al. Gut microbiota-testis Axis: FMT mitigates high-fat diet-diminished male fertility via improving systemic and testicular metabolome. *Microbiol. Spectrum*. (2022) 10:e0002822–2. doi: 10.1128/spectrum.00028-22

3. Song Z, Xie W, Chen S, Strong JA, Print MS, Wang JI, et al. High-fat diet increases pain behaviors in rats with or without obesity. *Sci Rep*. (2017) 7:10350. doi: 10.1038/s41598-017-10458-z

4. Di Berardino C, Peserico A, Capacchietti G, Zappacosta A, Bernabò N, Russo V, et al. High-fat diet and female fertility across lifespan: a comparative lesson from mammal models. *Nutrients*. (2022) 14:4341. doi: 10.3390/nu14204341

5. Sun S-F, Zhong H-J, Zhao Y-L, Ma X-Y, Luo J-B, Zhu L, et al. Indole alkaloids of *Alstonia scholaris* (L.) R. Br. Alleviated nonalcoholic fatty liver disease in mice fed with high-fat diet. *Nat. Prod. Bioprospect.* (2022) 12:14. doi: 10.1007/s13659-022-00335-2

6. Liou C-J, Lee Y-K, Ting N-C, Chen Y-L, Shen S-C, Wu S-J, et al. Protective effects of *Licochalcone* a ameliorates obesity and non-alcoholic fatty liver disease via promotion of the Sirt-1/AMPK pathway in mice fed a high-fat diet. *Cells*. (2019) 8:447. doi: 10.3390/cells8050447

7. Zeng N, Wu F, Lu J, Li X, Lin S, Zhou L, et al. High-fat diet impairs gut barrier through intestinal microbiota-derived reactive oxygen species. *Sci China Life Sci*. (2023). doi: 10.1007/s11427-022-2283-4 [Epub ahead of print].

8. Zhao L. The gut microbiota and obesity: from correlation to causality. *Nat Rev Microbiol*. (2013) 11:639–47. doi: 10.1038/nrmicro3089

9. Newman TM, Shively CA, Register TC, Appt SE, Yadav H, Colwell RR, et al. Diet, obesity, and the gut microbiome as determinants modulating metabolic outcomes in a non-human primate model. *Microbiome*. (2021) 9:100. doi: 10.1186/s40168-021-01069-y

10. Han L, Li Q, Du M, Mao X. Bovine milk osteopontin improved intestinal health of high-fat diet pregnant rats through improving bile acid metabolism. *J Dairy Sci*. (2023) 107:24–39. doi: 10.3168/jds.2023-23802

11. Rodrigues ELR, Fang H, Robin N, Bhatwa A, Marko DM, Schertzer JD. Microbiota and nod-like receptors balance inflammation and metabolism during obesity and diabetes. *Biom J*. (2023) 46:100610. doi: 10.1016/j.bj.2023.100610

12. Chen X, Wu J, Fu X, Wang P, Chen C. Fructus mori polysaccharide alleviates diabetic symptoms by regulating intestinal microbiota and intestinal barrier against TLR4/NF-κB pathway. *Int J Biol Macromol*. (2023) 249:126038. doi: 10.1016/j.ijbiomac.2023.126038

13. Takeuchi T, Kameyama K, Miyauchi E, Nakanishi Y, Kanaya T, Fujii T, et al. Fatty acid overproduction by gut commensal microbiota exacerbates obesity. *Cell Metab*. (2023) 35:361–375.e9. doi: 10.1016/j.cmet.2022.12.013

14. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. *Gut*. (2019) 68:1417–29. doi: 10.1136/gutjnl-2018-317609

15. Zhang XY, Chen J, Yi K, Peng L, Xie J, Gou X, et al. Phlorizin ameliorates obesity-associated endotoxemia and insulin resistance in high-fat diet-fed mice by targeting the gut microbiota and intestinal barrier integrity. *Gut Microbes*. (2020) 12:1842990–18. doi: 10.1080/19490976.2020.1842990

16. Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, et al. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut*. (2014) 63:727–35. doi: 10.1136/gutjnl-2012-303839

17. Shi J, Wang Q, Li C, Yang M, Hussain M, Zhang J, et al. Effects of the novel LaPLa-enriched medium- and long-chain Triacylglycerols on body weight, glycolipid metabolism, and gut microbiota composition in high fat diet-fed C57BL/6J mice. *Molecules*. (2023) 28:722. doi: 10.3390/molecules28020722

18. Mana MD, Hussey AM, Tzouanas CN, Imada S, Barrera Millan Y, Bahceci D, et al. High-fat diet-activated fatty acid oxidation mediates intestinal stemness and tumorigenicity. *Cell Rep*. (2021) 35:109212. doi: 10.1016/j.celrep.2021.109212

19. Leung H, Xiong L, Ni Y, Busch A, Bauer M, Press AT, et al. Impaired flux of bile acids from the liver to the gut reveals microbiome-immune interactions associated with liver damage. *NPJ Biofilms Microbiomes*. (2023) 9:35. doi: 10.1038/s41522-023-00398-0

20. Bellanti F, Lo Buglio A, Vendemiale G. Hepatic mitochondria-gut microbiota interactions in metabolism-associated fatty liver disease. *Meta*. (2023) 13:322. doi: 10.3390/metabo13030322

21. Just S, Mondot S, Ecker J, Wegner K, Rath E, Gau L, et al. The gut microbiota drives the impact of bile acids and fat source in diet on mouse metabolism. *Microbiome*. (2018) 6:134. doi: 10.1186/s40168-018-0510-8

22. Zheng X, Huang F, Zhao A, Lei S, Zhang Y, Xie G, et al. Bile acid is a significant host factor shaping the gut microbiome of diet-induced obese mice. *BMC Biol*. (2017) 15:120. doi: 10.1186/s12915-017-0462-7

23. Patel R, Shah G. High-fat diet exposure from pre-pubertal age induces polycystic ovary syndrome (PCOS) in rats. *Reproduction*. (2018) 155:141–51. doi: 10.1530/REP-17-0584

24. Kowluru RA. Retinopathy in a diet-induced type 2 diabetic rat model and role of epigenetic modifications. *Diabetes*. (2020) 69:689–98. doi: 10.2337/db19-1009

25. Magoč T, Salzberg SL. FLASH: fast length adjustment of short reads to improve genome assemblies. *Bioinformatics (Oxford)*. (2011) 27:2957–63. doi: 10.1093/bioinformatics/btr507

26. Bokulich NA, Kaehler BD, Rideout JR, Dillon M, Bolyen E, Knight R, et al. Optimizing taxonomic classification of marker-gene amplicon sequences with QIIME 2's q2-feature-classifier plugin. *Microbiome*. (2018) 6:90. doi: 10.1186/s40168-018-0470-z

27. Bolyen E, Rideout JR, Dillon MR, Bokulich NA, Abnet CC, Al-Ghalith GA, et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. *Nat Biotechnol*. (2019) 37:852–7. doi: 10.1038/s41587-019-0209-9

28. Li M, Shao D, Zhou J, Gu J, Qin J, Chen W, et al. Signatures within esophageal microbiota with progression of esophageal squamous cell carcinoma. *Chin. J. Cancer Res.* (2020) 32:755–67. doi: 10.21147/j.issn.1000-9604.2020.06.09

29. Lu M, Sun J, Zhao Y, Zhang H, Li X, Zhou J, et al. Prevention of high-fat diet-induced hypercholesterolemia by *Lactobacillus reuteri* Fn041 through promoting cholesterol and bile salt excretion and intestinal mucosal barrier functions. *Front Nutr*. (2022) 9:851541. doi: 10.3389/fnut.2022.851541

30. Morinaga H, Mohri Y, Grachtchouk M, Asakawa K, Matsumura H, Oshima M, et al. Obesity accelerates hair thinning by stem cell-centric converging mechanisms. *Nature*. (2021) 595:266–71. doi: 10.1038/s41586-021-03624-x

31. Barrea L, Muscogiuri G, Frias-Toral E, Laudisio D, Pugliese G, Castellucci B, et al. Nutrition and immune system: from the Mediterranean diet to dietary supplementary through the microbiota. *Crit Rev Food Sci Nutr*. (2021) 61:3066–90. doi: 10.1080/10408398.2020.1792826

32. Malesza IJ, Malesza M, Walkowiak J, Mussin N, Walkowiak D, Aringazina R, et al. High-fat, Western-style diet, systemic inflammation, and gut microbiota: a narrative review. *Cells*. (2021) 10:3164. doi: 10.3390/cells10113164

33. Zhang X, Shen D, Fang Z, Jie Z, Qiu X, Zhang C, et al. Human gut microbiota changes reveal the progression of glucose intolerance. *PLoS One*. (2013) 8:e71108. doi: 10.1371/journal.pone.0071108

34. Martín R, Rios-Covian D, Huillet E, Auger S, Khazaal S, Bermúdez-Humarán LG, et al. Faecalibacterium: a bacterial genus with promising human health applications. *FEMS Microbiol Rev*. (2023) 47:39. doi: 10.1093/femsre/fuad039

35. Kobyliak N, Falalyeyeva T, Kyriachenko Y, Tseyslyer Y, Kovalchuk O, Hadiliia O, et al. *Akkermansia muciniphila* as a novel powerful bacterial player in the treatment of metabolic disorders. *Minerva Endocrinol (Torino)*. (2022) 47:242–52. doi: 10.23736/s2724-6507.22.03752-6

36. Aggarwal V, Sunder S, Verma SR. Disease-associated dysbiosis and potential therapeutic role of *Akkermansia muciniphila*, a mucus degrading bacteria of gut microbiome. *Folia Microbiol (Praha)*. (2022) 67:811–24. doi: 10.1007/s12223-022-00973-6

37. Guzior DV, Quinn RA. Review: microbial transformations of human bile acids. *Microbiome*. (2021) 9:140. doi: 10.1186/s40168-021-01101-1

38. Dyar KA, Lutter D, Artati A, Ceglia NJ, Liu Y, Armenta D, et al. Atlas of circadian metabolism reveals system-wide coordination and communication between clocks. *Cell*. (2018) 174:1571–1585.e11. doi: 10.1016/j.cell.2018.08.042

39. Barber MN, Risis S, Yang C, Meikle PJ, Staples M, Febbraio MA, et al. Plasma lysophosphatidylcholine levels are reduced in obesity and type 2 diabetes. *PLoS One*. (2012) 7:e41456. doi: 10.1371/journal.pone.0041456

40. Li H, Perino A, Huang Q, Von Alvensleben GVG, Banaei-Esfahani A, Velazquez-Villegas LA, et al. Integrative systems analysis identifies genetic and dietary modulators of bile acid homeostasis. *Cell Metab*. (2022) 34:1594–1610.e4. doi: 10.1016/j.cmet.2022.08.015

41. van Best N, Rolle-Kampczyk U, Schaap FG, Basic M, Olde Damink SWM, Bleich A, et al. Bile acids drive the newborn's gut microbiota maturation. *Nat Commun*. (2020) 11:3692. doi: 10.1038/s41467-020-17183-8

42. Majait S, Nieuwdorp M, Kemper M, Soeters M. The black box Orchestra of gut Bacteria and Bile Acids: who is the conductor? *Int J Mol Sci*. (2023) 24:1816. doi: 10.3390/ijms24031816

43. Hagi T, Geerlings SY, Nijsse B, Belzer C. The effect of bile acids on the growth and global gene expression profiles in *Akkermansia muciniphila*. *Appl Microbiol Biotechnol*. (2020) 104:10641–53. doi: 10.1007/s00253-020-10976-3

44. Xie J, Li H, Zhang X, Yang T, Yue M, Zhang Y, et al. *Akkermansia muciniphila* protects mice against an emerging tick-borne viral pathogen. *Nat Microbiol*. (2023) 8:91–106. doi: 10.1038/s41564-022-01279-6

45. Zhang J, Ni Y, Qian L, Fang Q, Zheng T, Zhang M, et al. Decreased abundance of *Akkermansia muciniphila* leads to the impairment of insulin secretion and glucose homeostasis in lean type 2 diabetes. *Adv Sci (Weinh)*. (2021) 8:e2100536. doi: 10.1002/advs.202100536

46. Stranahan AM, Guo DH, Yamamoto M, Hernandez CM, Khodadadi H, Baban B, et al. Sex differences in adipose tissue distribution determine susceptibility to Neuroinflammation in mice with dietary obesity. *Diabetes*. (2023) 72:245–60. doi: 10.2337/db22-0192

47. Maric C. Sex, diabetes and the kidney. American journal of physiology-renal. *Physiology*. (2009) 296:F680–8. doi: 10.1152/ajprenal.90505.2008

48. Wen X, Han Z, Liu SJ, Hao X, Zhang XJ, Wang XY, et al. Phycocyanin improves reproductive ability in obese female mice by restoring ovary and oocyte quality. *Front Cell Dev Biol*. (2020) 8:595373. doi: 10.3389/fcell.2020.595373

49. Krause WC, Rodriguez R, Gegenhuber B, Matharu N, Rodriguez AN, Padilla-Roger AM, et al. Oestrogen engages brain MC4R signalling to drive physical activity in female mice. *Nature*. (2021) 599:131–5. doi: 10.1038/s41586-021-04010-3

50. Song Y, Shen H, Liu T, Pan B, De Alwis S, Zhang W, et al. Effects of three different mannans on obesity and gut microbiota in high-fat diet-fed C57BL/6J mice [10.1039/D0FO03331F]. *Food Funct*. (2021) 12:4606–20. doi: 10.1039/D0FO03331F

51. Hu Q, Niu Y, Yang Y, Mao Q, Lu Y, Ran H, et al. Polydextrose alleviates adipose tissue inflammation and modulates the gut microbiota in high-fat diet-fed mice. *Front Pharmacol*. (2021) 12:795483. doi: 10.3389/fphar.2021.795483

52. Sonkar K, Ayyappan V, Tressler CM, Adelaja O, Cai R, Cheng M, et al. Focus on the glycerophosphocholine pathway in choline phospholipid metabolism of cancer. *NMR Biomed*. (2019) 32:e4112. doi: 10.1002/nbm.4112

frontiers | Frontiers in Nutrition

TYPE Review
PUBLISHED 09 May 2024
DOI 10.3389/fnut.2024.1379364

OPEN ACCESS

EDITED BY
Katia Petroni,
University of Milan, Italy

REVIEWED BY
Félix Gómez-Gallego,
Rey Juan Carlos University, Spain
Luis Rodrigo Macias Kauffer,
Universität zu Lübeck, Germany

*CORRESPONDENCE
Arturo Panduro
✉ apanduro@prodigy.net.mx;
✉ apanduro53@gmail.com

RECEIVED 31 January 2024
ACCEPTED 01 April 2024
PUBLISHED 09 May 2024

CITATION
Panduro A, Roman S, Mariscal-Martinez IM, Jose-Abrego A, Gonzalez-Aldaco K, Ojeda-Granados C, Ramos-Lopez O and Torres-Reyes LA (2024) Personalized medicine and nutrition in hepatology for preventing chronic liver disease in Mexico. *Front. Nutr.* 11:1379364. doi: 10.3389/fnut.2024.1379364

Personalized medicine and nutrition in hepatology for preventing chronic liver disease in Mexico

Arturo Panduro[1]*, Sonia Roman[1], Irene M. Mariscal-Martinez[1], Alexis Jose-Abrego[1], Karina Gonzalez-Aldaco[1], Claudia Ojeda-Granados[2], Omar Ramos-Lopez[3] and Luis A. Torres-Reyes[1]

[1]Department of Genomic Medicine in Hepatology, Civil Hospital of Guadalajara, Fray Antonio Alcalde, Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico, [2]Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia", University of Catania, Catania, Italy, [3]Medicine and Psychology School, Autonomous University of Baja California, Tijuana, Baja California, Mexico

Chronic liver disease is a global health issue. Patients with chronic liver disease require a fresh approach that focuses on the genetic and environmental factors that contribute to disease initiation and progression. Emerging knowledge in the fields of Genomic Medicine and Genomic Nutrition demonstrates differences between countries in terms of genetics and lifestyle risk factors such as diet, physical activity, and mental health in chronic liver disease, which serves as the foundation for the implementation of Personalized Medicine and Nutrition (PerMed-Nut) strategies. Most of the world's populations have descended from various ethnic groupings. Mexico's population has a tripartite ancestral background, consisting of Amerindian, European, and African lineages, which is common across Latin America's regional countries. The purpose of this review is to discuss the genetic and environmental components that could be incorporated into a PerMed-Nut model for metabolic-associated liver disease, viral hepatitis B and C, and hepatocellular carcinoma in Mexico. Additionally, the implementation of the PerMed-Nut approach will require updated medicine and nutrition education curricula. Training and equipping future health professionals and researchers with new clinical and investigative abilities focused on preventing liver illnesses in the field of genomic hepatology globally is a vision that clinicians and nutritionists should be concerned about.

KEYWORDS

Mexico, genetics, diet-related adaptive genes, hepatopathogenic diet, Genomex diet, nutrients, training, genomic medicine in hepatology

1 Introduction

Modern humans, taxonomically known as *Homo sapiens sapiens*, emerged in Africa 200,000 years ago and began the migration out-of-Africa to colonize the globe between 50,000 and 70,000 years ago (1, 2). Studies on human evolutionary history relate that most of the world's populations have descended from 19 ancestral human ethnic groups (Figures 1A,B) (2, 4). However, the human genome, which is constantly evolving, is a melting pot of past, present, and even future genetic signs of adaptations to diverse environmental niches, and it appears that they are not always

10.3389/fnut.2024.1379364

FIGURE 1
Peopling of the world. **(A)** Migration of the 19 ancestral human populations from which Native Americans made their way to the Americas. **(B)** Peopling and main settlements of the Americas in pre-Colombian times by the ancestral Native American component. kya, kilo years ago. Reproduced from references (1–3).

meant to create life-threatening disorders (5, 6). These differences are explained by genetic variants including single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and deletion or insertion (Del/Ins) polymorphisms (7). Other non-genetic mechanisms, such as transgenerational plasticity and cultural evolution, were undoubtedly additional powerful forces that contributed to human adaptation (8). However, discrete changes in the nature and frequency of specific genetic variants might influence health triggered by environmental factors (9). Such variants have been revealed with the completion of the Human Genome Project's mapping of the human haploid reference genome (10) and the incorporation of other worldwide genomic databases (11) so that the understanding of the genetic basis of human disease and, ultimately, the prevention of many diseases may be achieved (12).

Currently, the paradigm shift in medicine from reactive to predictive is focused in providing models of prevention strategies based on the population's genetic makeup and the risk factors that contribute to the emergence of chronic diseases, whether infectious or non-communicable (13). Clinicians need to reconsider their traditional approach to managing major diseases (such as hypertension, heart disease, type 2 diabetes, cancer, renal, and liver disease) from a bench to bedside/translational perspective, combining novel omics data with pathological clinical phenotypes in search of an individualized therapy (14). This has resulted in a multitude of terms, including Predictive Medicine, Individualized Medicine, Personalized Medicine, and Precision Medicine (15, 16), all of which acknowledge that each person is unique but still shares ancestral genetic variants based on ethnicity and environmental circumstances. These characteristics may explain why certain people are susceptible or prone to diseases when exposed to risky conditions or behaviors, but others in similar circumstances (i.e., family members) are unaffected (17). Personalized Medicine "omics" techniques have been proposed for nearly all medical fields including Nutrition, where Genomic Nutrition, Personalized Nutrition, and Precision Nutrition are becoming increasingly important (18).

The Personalized Medicine and Nutrition (PerMed-Nut) approach in Hepatology will inevitably include managing the main etiologies that cause chronic liver disease worldwide (19), such as alcohol persistence, chronic viral hepatitis B and C infections, metabolic-associated steatotic liver disease, hepatotoxicity (drugs or toxins), and auto-immune conditions. However, the prevalence of these etiologies varies greatly between countries due to genetic, environmental, and cultural differences in the host populations (20). As a result, the extent of liver damage might be immediate and self-limiting, or it can progress to chronic phases in which the inflammatory process of injury causes fibrosis, cirrhosis, and, in rare cases, hepatocellular carcinoma (HCC).

How can we begin using the PerMed-Nut approach as a strategy to prevent chronic liver diseases? Firstly, it is essential to understand the impact of genes and the environment at a regional level to develop measures to prevent liver damage. Hence, this work aims to define these factors for the prevention and management of liver illnesses using a PerMed-Nut model and the need for training in genomic education. We will address some polymorphic genes associated with the clinical outcomes of liver diseases as well as sociocultural features of the Mexican population in the sections that follow.

2 Mexico's genetic ancestry and sociodemographic background

Studies examining the genetic ancestry of the Latin American (LATAM) populations including Mexico have revealed heterogeneous

proportions of three main ancestral lineages: Amerindian, European, and African. As shown in Table 1, most LATAM countries contain all three with some having a higher degree of African (21, 28) and Native American (22, 27, 29, 30) ancestry than European (3, 23–26, 29). The indigenous people of Mexico are part of the third Native American migration wave that crossed the Bering Strait to the American continent around 20,000 years ago (2) (Figure 1B, blue arrow). These Native Americans settled primarily in Mexico (Tenochtitlan) and Peru (Cuzco) followed by Brazil, the United States, Bolivia, Columbia, and in lesser proportions Argentina, Venezuela, Ecuador, Canada, and Alaska (31). The current 68 ethnic groups of Mexican Amerindians are descendants of the original First Nations who followed either a nomadic or agricultural lifestyle, primarily in Aridoamerica and Mesoamerica, respectively (3, 32). During the Spanish colony (from 1521 to 1826), a genetic and cultural admixture occurred among Mexican Amerindians, Spaniards, and enslaved Africans (21). The Spanish Catholic Church recognized new births using a caste system, with Amerindian and Black heritage overlooked that has marked the social distribution of the ancestral lineages since colonial up until modern times.

Most Mexicans are admixed containing practically half of the main lineages (24, 25). However, as illustrated in Table 2, the degree of admixture varies across the country. Northern Mexico has a higher rate of European trait carriers (33, 34) and intermediate rates in the Central Region (35–37), contrasting with Southern Mexico, who are more likely to be carriers of Amerindian traits (35, 39) including the true Native Americans *per se* (38). African ancestry is present in varying quantities among the admixed general population and Afro-Mexicans who reside along the South Pacific and the Gulf of Mexico coastal communities (40). Further genetic studies show indigenous mitochondrial DNA as the maternal source of inheritance, while Y-STR analysis tracks European paternal lineage (37, 41).

Among the Genome-Wide Association Study (GWAS) database catalog, a total of 284 studies related to liver diseases have been conducted, identifying 1,546 associations in over 606 genes (42, 43). They are mainly reported in European, Asian, and African populations and scarcely in Native American ancestry (Figure 2A). However, one GWAS using the Mexican Biobank have shown 25 associations in 15 genes involved in lipid metabolism and transportation, vitamin A metabolism, protein folding, regulation of gene expression, cellular signaling, embryonic development, and heart development (Figure 2B). Among the most important clinical associations are hypercholesterolemia, hyper triglyceridemia, body weight, creatinine levels, hypertension, and arthritis. Furthermore, this study confirmed earlier findings of the north–south gradient of European-Amerindian ancestry (44).

Overall, the underlying genetic heterogeneity of most LATAM populations including Mexico constitutes a key aspect that makes sub-structure analysis and GWAS combined important tools to reveal which lineage is carrying the disease-related genetic polymorphisms and, consequently, the genetic foundation of disease vulnerability (17, 45). As shown in Figure 3A, regional variations in the ancestral component carrying the genetic variants as well the interactions with environmental and lifestyle factors support the need of regional PerMed-Nut strategies to address these differences (46).

3 Environmental changes and evolutionary genetic mismatch

One important factor in the gene–environment interaction equation is diet. The domestication of endemic wild plants and animals by the prehispanic groups of ancient Mexico, approximately

TABLE 1 Distribution of the ancestral components among LATAM populations.

Country/(Reference)	GAM	Ancestry (%)			
		Native American	European	African	Asian
Argentina (3)	AIM	27.7–32.3	65.6–68.4	2–3.8	-
Barbados* (21)	Y-DNA	1	-	87	-
Bolivia (22)	AIM	77–86	13–21	2	-
Brazil (23)	AIM	17.3	59.7	23	-
Chile (24)	SNP	43	55	2	-
Colombia (25)	CODIS	25.22	64.75	9.01	1.03
Cuba (26)	mtDNA	4	70	26	-
Dominican Republic (26)	mtDNA	6	56	38	-
Ecuador (27)	HLA	53–63	29–47	19	-
Haiti (28)	STR	0	4	96	-
Mexico (24)	SNP	51	46	3	-
Mexico (25)	CODIS	44.52	43.26	4.8	4.45
Paraguay (29)	mtDNA	33.8	55.4	10.8	-
Peru (29)	CODIS	73.76	20.36	3.01	2.87
Puerto Rico (29)	CODIS	12.82	71.5	15.01	0.67
Uruguay (30)	SNP	27	30–70	7	-

GAM, Genetic ancestry marker. *Afroamericans; Y-DNA, Y chromosome inheritance; AIM, Ancestry informative marker; SNP, Single nucleotide polymorphisms; CODIS, Combined DNA index system; mtDNA, Mitochondrial DNA; HLA, Human leukocyte antigens; and STR, Short tandem repeats.

TABLE 2 Distribution of the Mexican ancestral lineages throughout the country.

Region/Reference	GAM	Ancestry (%)			
		Native American	European	African	Asian
North					
Chihuahua (33)	STR	38	50	12	-
Northeast (34)	AIM	38	56	6	-
Nuevo Leon (34)	AIM	40	55	5	-
Central					
Jalisco (35)	STR	53	31	16	-
Zacatecas (36)	AIM	51	46	3	-
Mexico City (37)	Y-DNA	66.6	23.3	6.6	3.5
South					
Yucatan (35)	STR	70	19	11	-
Puebla (35)	STR	72	17	11	-
Guerrero (35)	AIM	95	4	1	-
Native Amerindian					
Yaquis (38)	AIM	72	28	-	-
Huicholes (38)	AIM	92	8	-	-
Seris (38)	AIM	92	8	-	-
Teenek (38)	AIM	98	2	-	-
Zapoteco (38)	AIM	98.1	1.9	-	-

GAM, Genetic ancestry marker; Y-DNA, Y chromosome inheritance; AIM, Ancestry informative marker DNA; and STR, Short tandem repeats.

6,000 years ago, is a historic milestone for the peopling and development of the Aztec civilization and other ethnic groups because it provided the primary source of nutrients for the indigenous communities (47). Mexico is noted for three staple plants: maize, beans, and chili, along with squash, tomato, amaranth, and chia growing in an eco-agricultural style known as "milpa" using the "chinampas" system (48). The inverted Mesoamerican food pyramid contains edible leafy green vegetables and wild fruits at the top, cereals/grains at the middle, and animal meat at the bottom, implying that it was consumed in smaller quantities because animal rearing was uncommon. The exposure to this diet over millennia may have exerted positive selective pressure on the Mexican genome, favoring the dominance of diet-related adaptive gene (DRAG) polymorphisms that regulate essential energy, immunological, and nutritional pathways (47). Based on the earlier environmental conditions, the adaptive allele, which was selected over the wild allele, is a risk allele for disease in unfavorable conditions such as the occurring globalized nutrition transition (48–50). Different allelic frequencies of these DRAGs may influence the risk of complex diseases among populations based on interactions with dietary contexts, such as the current obesity endemic. For example, the cholesterol transporter ATP-binding cassette transporter A1 (*ABCA1*) gene variant (R230C, rs9282541) is unique to Native American individuals and has been associated with low high-density lipoprotein cholesterol (HDL-C) levels, obesity and type 2 diabetes in admixed Mexicans (51, 52). The positive selection of the C allele among the Native American population may be related to energy-saving processes among the ancient Mesoamericans. Overall, the current frequency of the *ABCA1* 230RC + CC genotypes ranges from 6 to 20% (46) and studies performed in central west Mexico have shown that up to 41% of Native American individuals who are carriers of the *ABCA1* C allele have low HDL-c levels compared to admixed Mexicans in 7% (53), suggesting the need of targeted strategies among the population.

In this sense, populations that maintain their historical staple foods are less likely to develop nutrition-related disorders (54). However, when combined with imbalanced modern diets, these adaptive genes may generate pathological processes. In Mexico, globalization and urbanization have driven the nutrition transition, leading to a shift toward a hepatopathogenic diet containing ultra-processed foods, unhealthy dietary habits, and an imbalance in essential fatty acids, vitamins, and minerals (48, 55) (Figure 3B). Notably, a recent study analyzing data from the National Health and Nutrition Survey (2018–2019) revealed that 68% of the Mexican population consumes a western dietary pattern high in processed foods compared to only 7% of those following a traditional Mexican diet (56). Currently, 72.1% of the Mexican population is overweight or obese; this risk factor, in combination with genetic vulnerability, has increased the incidence of cardiovascular disease, type 2 diabetes, cerebrovascular events, hepatopathologies, and cancer (breast and prostate) (57). Thus, understanding the ancestral and historical transitions is the foundation for developing a regionalized PerMed-Nut approach to address the dynamic interplay between genetic and environmental features that could affect the outcome of liver diseases in this region.

4 Managing chronic liver disease using a PERMED-NUT approach

4.1 Metabolic-associated liver disease

Genetic susceptibility (Figure 2) and the consumption of an unhealthy diet are the two most important risk factors related to

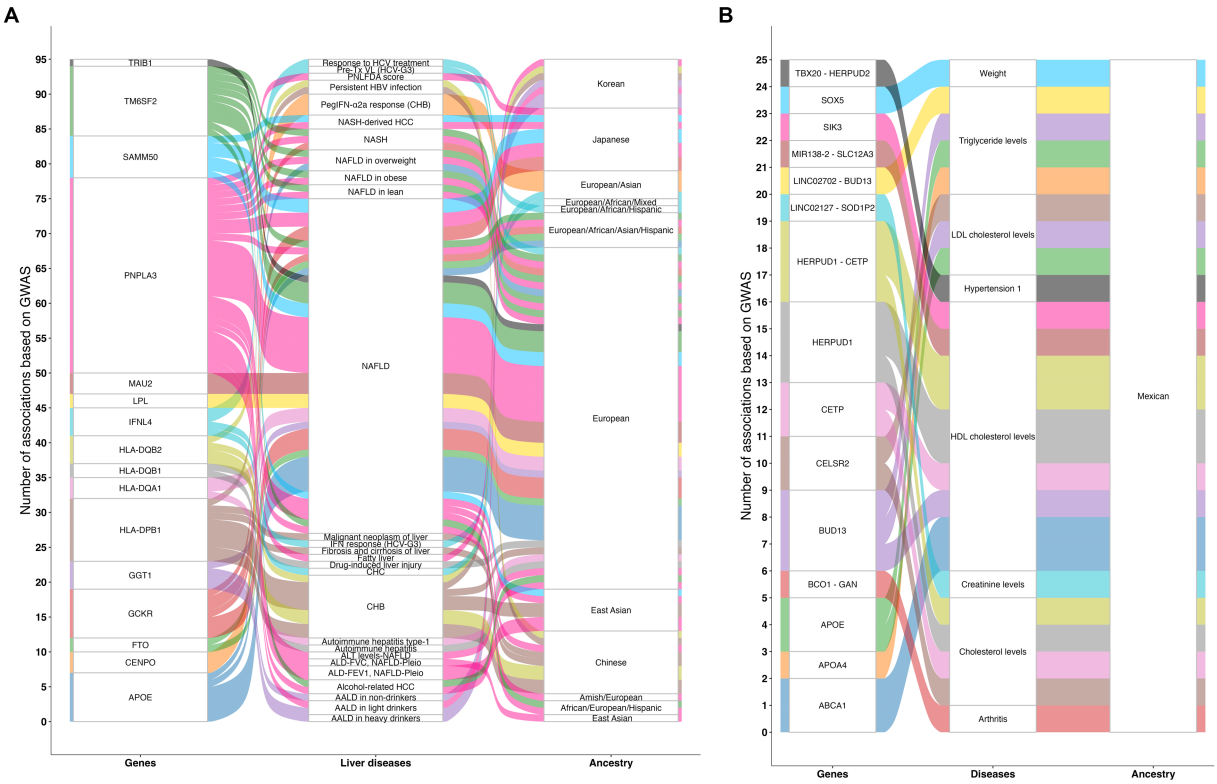


FIGURE 2
Genomic studies related to liver diseases. **(A)** Illustration of 284 GWAS related to liver diseases that have been conducted, identifying 1,546 associations in over 606 genes that involve the regulation of body weight and fat mass, glucose metabolism, peptide metabolism, lipid metabolism and transport, centromere structure and function, immune system, response to viral infections, meiotic cell division, mitochondrial membrane protein assembly, and cellular proliferation. **(B)** Illustration of the results of the Mexican Biobank analysis showing 25 associations in 15 genes involved in lipid metabolism and transport, vitamin A metabolism, protein folding, regulation of gene expression, cellular signaling, embryonic development, and heart development. Among the most important clinical associations are hypercholesterolemia, hyper triglyceridemia, body weight, creatinine levels, hypertension, and arthritis. The lines on the chart indicate the number of associations found between each gene, disease, and ancestral group. GWAS, Genome-wide association study; ALD-FEV1, NAFLD-Pleio, Accelerated lung function decline (FEV1) and worsened/persistent change in fatty liver (pleiotropy); ALD-FVC, NAFLD-Pleio, Accelerated lung function decline (FVC) and worsened/persistent change in fatty liver (pleiotropy); ALT levels-NAFLD, Alanine aminotransferase levels in non-alcoholic fatty liver disease; AALD in heavy drinkers, Alcohol-associated liver disease in heavy drinkers; AALD in light drinkers, Alcohol-associated liver disease in light drinkers; AALD in non-drinkers, Alcohol-associated liver disease in non-drinkers; Alcohol-related HCC, Alcohol-related hepatocellular carcinoma; Autoimmune hepatitis, Autoimmune hepatitis in primary sclerosing cholangitis; Autoimmune hepatitis type-1, Autoimmune hepatitis type-1; CHB, Chronic hepatitis B infection; CHC, Chronic hepatitis C infection; Drug-induced liver injury, Drug-induced liver injury (amoxicillin-clavulanate); Fatty liver, Fatty liver; Malignant neoplasm of liver: ICD10 C22, Malignant neoplasm of liver and intrahepatic bile ducts; Fibrosis and cirrhosis of liver: ICD10 K74, Fibrosis and cirrhosis of liver; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; NASH-derived HCC, Nonalcoholic steatohepatitis-derived hepatocellular carcinoma; PNLFDA score, Pediatric non-alcoholic fatty liver disease activity score; PegIFN-α2a response (CHB), Peginterferon alfa-2a treatment response in chronic hepatitis B infection; Persistent HBV infection, Persistent hepatitis B virus infection; Pre-Tx VL (HCV-G3), Pre-treatment viral load in hepatitis C virus genotype 3; Response to HCV treatment, Response to hepatitis C treatment; IFN response (HCV-G3), Response to interferon treatment in hepatitis C virus genotype 3. Source: GWAS catalog liver diseases, licensed under CC0. Summary statistics were downloaded on March 11, 2024 from the NHGRI-EBI GWAS Catalog. Accession ID: EFO_0001421.

metabolic-associated steatotic liver disease (MASLD) (formerly known as non-alcoholic fatty liver disease, NAFLD), which encompasses fatty liver or steatosis and metabolic-associated steatohepatitis (MASH) (formerly non-alcoholic steatohepatitis, NASH). Hence, a PerMed-Nut approach for the management of MAFLD would require knowledge of the allele/genotype frequency of several genes involved in food preferences and lipid/carbohydrate metabolism.

Food preference genes may partially explain the risk of abnormal lipid parameters and liver damage among the Mexican population. In this regard, some candidate-gene studies have been performed one example is the A allele (rs1761667) of the class B scavenger (*CD36*) receptor gene, which was found to be associated with higher fat intake and hypercholesterolemia in overweight individuals and more instances of liver damage in chronic hepatitis C patients (58, 59). Moreover, Mexicans carrying the Val allele (rs35874116) of the sweet taste receptor (*TAS1R2*) gene consumed more carbohydrates and had increased serum triglyceride levels (60). Furthermore, the novel AVV haplotype of the bitter taste receptor (*TAS2R38*) gene was first identified in the Mexican population and was associated with high alcohol intake (61). However, because genome structure corrections were not performed in these studies, further research is required to confirm these results.

Apolipoprotein E (APO E) is a plasma protein that transfers lipids from circulating lipoproteins to tissues through binding membrane receptors (62). The *APOE* gene encodes three major protein isoforms, E2, E3, and E4 with differential binding receptor affinities (63). The frequency of the *APOE* alleles differs worldwide (64). Recently, we identified a differential distribution of lipid genes among several ethnic groups showing that the *E4* allele associated with hypercholesterolemia was more frequent in Mexican Amerindians,

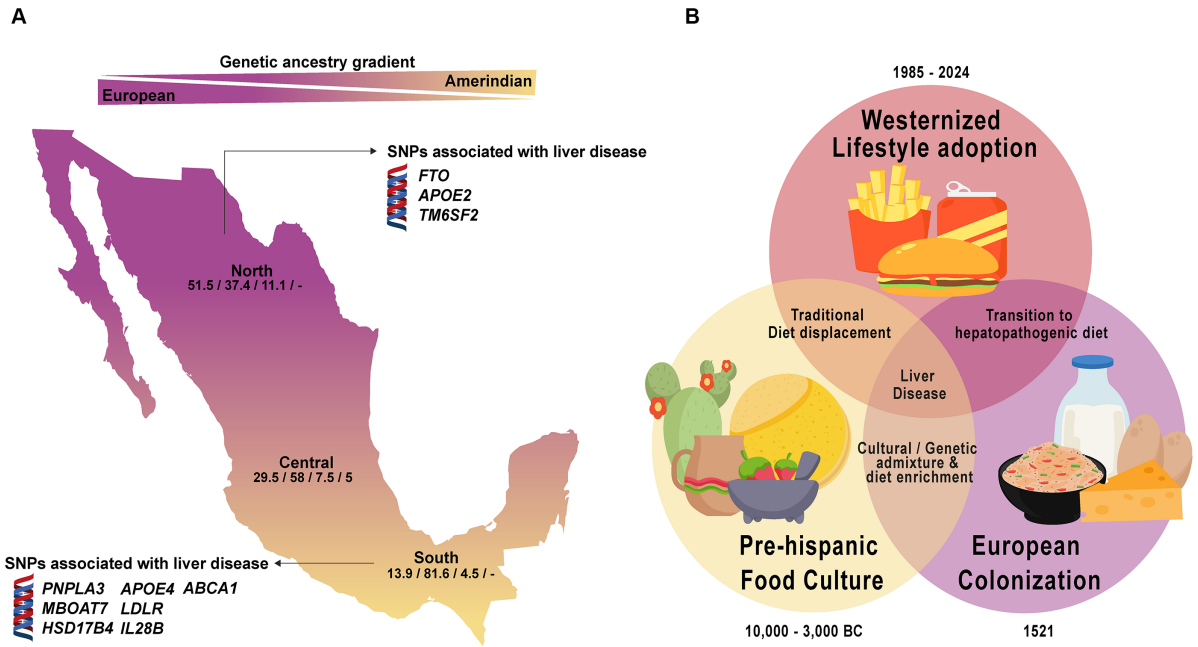


FIGURE 3
Ancestral genetic gradient and nutrition transition in Mexico. **(A)** Contemporary Mexicans show a tripartite ancestry admixture with predominant European ancestry in the North and increasing Amerindian ancestry towards the southern region. Genetic variants linked to liver disease vary based on population ancestry. Numbers in the map represent the average percentage of the European/Amerindian/African/Asian component. **(B)** Dietary transition in Mexico reflects a shift from traditional to a westernized hepatopathogenic diet, contributing to a higher liver disease prevalence in the population.

whereas those associated with hypertriglyceridemia such as *E2* are common among European populations ancestry (53).

Another functional gene is the Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) I148M (rs738409 C>G) variant, one of the most studied genetic determinants implicated in liver damage associated with the generation of a pro-inflammatory environment and oxidative stress (65, 66). This variant has shown a geographic relationship with the prevalence of MASH and it has been documented that the *PNPLA3* risk G allele (148 M) highly prevails in Mexican Amerindians compared to admixed populations (67). This variant has been strongly associated with elevated alanine transaminase (ALT) levels in normal weight and overweight/obese Mexican children suggesting that it may be a risk factor for liver damage (68). Furthermore, the Transmembrane 6 superfamily 2 (*TM6SF2*) gene is involved in plasma lipid regulation by influencing triglyceride secretion and hepatic lipid droplet content. The *TM6SF2* E167K (rs58542926) polymorphism has been associated with impaired hepatic lipid synthesis in NAFLD patients (69). Additionally, the fat mass and obesity (*FTO*) associated gene encoding the 2-oxoglutarate dependent DNA/RNA methylase interacts with lifestyle factors. The A allele of the *FTO* A>T (rs9939609) polymorphism in interaction with modifiable lifestyle factors has been associated with energy homeostasis, eating behavior, and appetite with an impact on body weight. Notably, some populations with European lineage have shown a higher risk allele frequency, thus predisposing them to extreme obesity (70).

Therefore, screening these genetic variants could be useful to identify genetically susceptible groups and prescribe tailored genome-based nutritional advice under a regionalized and personalized scope. On the other hand, the nutritional composition of the hepatopathogenic diet may lead to dyslipidemia (including hypertriglyceridemia), insulin resistance, oxidative stress, and the induction of a pro-inflammatory state, which jointly may contribute to the development of liver damage. In this context, a high prevalence of MASH and abnormal liver stiffness was reported in young Mexicans with obesity, even in normal-weight individuals consuming a high-fat/high-sugar diet (71). Altogether, these data reveal that among the admixed population of Mexico, the interaction between genes and lifestyle factors such as diet significantly impact liver health. Preventing the onset and progression of liver injury should be a priority by healthcare providers to avoid further disease. In this context, intervention studies have been conducted to avoid plausible diet-related chronic diseases. By using a genome-based nutrigenetic strategy, a Genomex diet was implemented to provide a resource for managing patients with a risk of chronic disease (72). This diet provided the appropriate recommended daily allowances of macro-, and micronutrients considering the staple foods and culture of the Mexican population and was based on the prevalence of some adaptive alleles that are predominant among the population. In this manner, patients who had altered metabolic parameters were normalized in 24 weeks with a significant reduction in body weight, BMI, insulin resistance, hypertriglyceridemia, and VLDL levels. Although this was a quasi-experimental study evaluating the effect on metabolic and clinical parameters before and after the Genomex intervention, a randomized trial evaluating the effect of a dietary intervention integrating some Mexican staples vs. a habitual diet on metabolic syndrome parameters yielded similar results. Only patients on the Mexican food-enriched diet decreased their triglyceride levels, glucose

intolerance, and area under the curve for insulin, in addition, carriers of the *ABCA1* 230C variant showed greater weight loss and increased serum adiponectin (73).

4.2 Alcoholic liver disease

Alcoholic liver disease (ALD) is a chronic condition that requires a multidisciplinary approach involving medical, nutritional, and psychosocial interventions, which are key to avoiding disease recurrence and managing complications. Early intervention and adherence to treatment plans are crucial for improving outcomes in patients with ALD (74). The development of the disease is multifactorial, involving interactions between genetic susceptibility and lifestyle factors, such as alcohol consumption. Thus, PerMed-Nut strategies could be beneficial to tailor patient's needs based on genetic and environmental factors.

Genes involved in alcoholism and the risk for chronic liver disease include taste receptors, neurotransmitter receptors, alcohol-metabolizing enzymes, and steatotic genes that are highly polymorphic worldwide (75, 76). Notably, some of these genes overlap with the risk for MAFLD and HCC. In a Mexican cohort, a 36% *TAS2R38* AVV haplotype homozygosity (non-taster phenotype) was found among drinkers compared to non-drinkers (61). Additionally, the *DRD2/ANKK1* Taq1A1 (rs1800497) polymorphism involved in addictive behaviors ranges up to 67% among the Amerindian subpopulations compared to 47% in the admixed groups (77). Likewise, a cohort of subjects displaying unhealthy food choices and altered biochemical parameters showed a high prevalence of this genetic variant (78). Thus, the riskier *TAS2R38/DRD2/ANKK1* genetic profile (affecting bitter taste perception and food reward, respectively) predisposes one to consume significantly more calories (alcohol or high-dense food), which may enhance hepatic damage. However, these associations need to be explored in other regions across Mexico and even in other populations worldwide.

Additionally, the genetic profile of the alcohol-oxidizing liver enzymes among the Mexicans reveals a high rate of the A1 allele (rs1229984) of the alcohol dehydrogenase 1B (*ALD1B*) gene, contrasting with a low rate of the protective A2 allele (rs671) of the aldehyde dehydrogenase (*ALDH2*) gene whereas the cytochrome P450 2E1 (*CYP2E1*) C2 allele (rs2031920) is highly present in the Amerindian populations (79). It is noteworthy to mention that despite a high-risk genetic profile tending toward liver damage, the peril will depend on both the specific combination of the risk or protective alleles (slow, intermediate, or fast metabolizers) and the pattern of alcohol consumption influenced by socio-cultural factors (75).

In this sense, the history of alcohol consumption among the Mexicans has evolved over the centuries in which distilled liquor was not regularly consumed by the Mesoamericans until the arrival of the Europeans. Most alcoholic beverages were fermented and obtained mainly from maize (tesgüino) or fruits (pulque from the agave plant), and mostly nobles (emperors or priests) had access to them. Only in circumstances such as illness o festivities were the laypeople allowed to consume alcoholic beverages. In contrast, the national alcohol consumption is currently an average of 4.4 L/*per capita* in young adults who begin to drink at early ages during the weekends despite public health warning measures, and eventually, alcohol intake increases (79). Thus, risk scores containing both the genetic and social factors involved in alcohol consumption should be taken into account to devise preventive strategies.

4.3 Hepatitis B infection

The first step in using PerMed-Nut strategies in the management of hepatitis B patients is to make an appropriate diagnosis. Personalized therapy is highly dependent on the patient's genetic features and HBV genotype (80). HBV is divided into 10 HBV genotypes (A-J) based on the whole genome, each with a unique global distribution and clinical outcomes based on the interactions between the host and the virus (81). To date, five HBV genotypes may be significant for PerMed-Nut in Mexicans with different clinical implications. Among these, HBV genotypes H is predominant followed by G, F, A, and D which circulate in patients according to genetic and sociodemographic backgrounds (82, 83). Based on molecular epidemiology data, HBV genotypes A and D discovered in Mexico are deemed exotic when compared to the Americas' prevalent H and F. Indeed, phylogenetic examination of those genotypes suggested that A2 originated in Europe and D4 in Africa. These findings are consistent with the demographic history of the Mexican population, as previously stated.

Regarding the clinical result, HBV genotypes A and D have been identified in individuals with chronic infection, but genotype H is common in occult hepatitis B cases and exhibits a high degree of adaptation among the local people (82). Interestingly, sub-genotype F1b native to South America and linked to HCC in Native Alaskans (84) and Native Peruvians (85) has been found in Mexican patients (86). However, the potential association of liver cancer in patients acutely infected with F1b has not been tested due to its low incidence (87). Nonetheless, among HIV or men who have sex with men (MSM) individuals, the presence of three HBV genotypes (in various combinations) increased the likelihood of severe liver fibrosis by 15-fold compared to dual-mixtures or single HBV genotype infections (88). As a result, in these populations, early diagnosis of the HBV genotype may help determine the risk of liver injury. Likewise, chronic hepatitis B patients often remain asymptomatic until decompensation, making late diagnosis of cirrhosis a challenge (89). Genetic markers could improve early diagnosis and prevent end-stage liver disease. Genome-wide association (Figure 2) and SNP studies reveal associations with clinical outcomes (90).

Pharmacological treatment is the primary target for managing chronic liver disease, considering mutations in the reverse transcriptase domain of the polymerase. The use of lamivudine should be avoided in samples with M204V/I or L180M + M204V mutations, and tenofovir should be monitored when quadruple mutation CYEI is detected (91). The main mutations associated with resistance to adefovir are A181T/V/S and N236T (92). Also, response to long-term lamivudine may be decreased in patients with genotype A since it is more susceptible to YMDD motif mutations (93).

Together with pharmacological treatment, adjuvant nutritional support, including vitamins and bioactive components like resveratrol, vitamin E, lactoferrin, selenium, curcumin, luteolin-7-O-glucoside, moringa extracts, chlorogenic acid, and epigallocatechin-3-gallate showing *in vitro* and *in vivo* anti-HBV activity may be beneficial for managing chronic hepatitis B patients. These nutrients are accessible and found in native American foods (94). The effectiveness of

nutritional therapy will depend on the patient's capacity to absorb anti-HBV nutrients, HBV genotype, and population ancestry.

4.4 Hepatitis C infection

4.4.1 Immune response

PerMed-Nut strategies should include early detection of patients at risk of chronic HCV infection. Next-generation sequencing-based studies have identified human variants that predispose to susceptibility or are associated with self-resolution (95, 96). Some genetic markers are associated with HCV infection outcome, as they influence the immune response and lipid metabolic pathways. The interleukin 28-B (*IFNL3*) gene belonging to the type III IFN-β family is one of the best predictors of HCV infection outcome and induces antiviral and antitumor states through innate and adaptive immune responses (97, 98). The polymorphism, rs12979860 C/T, is located 3 kb upstream of the *IFNL3* gene. Patients homozygous for the CC genotype are more likely to achieve a sustained virological response (SVR) following a PEG-IFN-β plus ribavirin than CT and TT genotypes (99). The rs12979860-CC genotype, associated with spontaneous clearance in white, African, and Hispanic HCV patients, was found to be proportional to the SVR rate across ethnic groups (100, 101). In Mexico, the C allele has a frequency of 56.5% in admixed patients and was associated with self-clearance and less liver damage (101). Similarly, a polymorphism in the *IFNL4* rs368234815 (TT) gene was also associated with HCV clearance in Mexican mestizo patients. When these polymorphisms were analyzed in haplotype with the *IFNL3* rs8099917 SNP, the beneficial haplotype C/T/TT (rs12979860, rs8099917, and rs368234815) was associated with spontaneous clearance and less liver damage in Mexican patients (101).

4.4.2 Lipid metabolism

APOE has several ligands in the hepatocyte, including low-density lipoprotein receptor (LDLR), syndecan-1 and syndecan-2, and heparan sulfate proteoglycans (102). APOE is also a structural component of the HCV envelope and mediates virion entry, assembly, and production (62). The *E4* allele is protective against HCV, as carriers have a higher chance of spontaneous recovery after infection and treatment with interferon plus ribavirin (103, 104). The *E2* allele protects against chronic infection, while the *E3* is associated with chronic infection (105). In Mexico, the *E4* allele has been associated with spontaneous clearance and less liver damage, while *E3* was associated with advanced fibrosis in chronic patients, which is present in 85% of the mestizo population (72), however, the *E2* allele exerted no effect (106). Therefore, there is a higher risk of developing advanced liver damage induced by HCV.

Clustering differentiation 36 (CD36) is a candidate receptor involved in the gustatory detection of lipids. Evidence suggests that genetic variation in the *CD36* gene can modulate the uptake of fatty acids. A promoter polymorphism -31118G > A, rs1761667 was studied among admixed Mexican HCV patients. It was demonstrated that the AA genotype had higher values of total fat and saturated fatty acids than non-GG genotypes. Additionally, AA genotype increased AST and liver fibrosis among chronic HCV-infected patients (59). It is known that the AA genotype decreases fat taste perception, thus, AA carriers could need an increased amount of fat to reach satiety. Thus, triggering the onset of fat liver accumulation that in conjunction with HCV infection potentializes liver damage among HCV patients.

The low-density lipoprotein receptor (LDLR) is a protein involved in the trafficking of lipoproteins containing APOE, such as VLDL and chylomicrons (107, 108). The rs688 C/T polymorphism protects against infection development, affects cholesterol levels and mRNA splicing, and decreases receptor surface expression levels. This makes LDLR less capable of lipid uptake, making it less susceptible to HCV.

As mentioned above, nutrition also plays a crucial role in HCV infection because it can modify serum lipid components and provide anti-HCV micronutrients. *In vitro* studies have shown the effect of certain nutrients with anti-HCV properties on the outcome of HCV infection, but no potential diet intervention has been performed in patients (55). A recent study in Mexican patients revealed that adherence to a fish-rich diet, mainly consisting of fish, seafood, and vegetable oils, had low viral loads and significant consumption of PUFAs ≥4.9% (109). Therefore, diets rich in anti-HCV macro- and micronutrients may affect HCV infection outcomes. Further dietary interventions are needed to clarify the role of diet in the management of HCV infection.

4.5 Hepatocellular carcinoma

Hepatocellular carcinoma seen as the end-stage outcome of chronic liver disease is influenced by various gene–environment interactions that vary depending on the population (81). In Mexico, HCC is low in prevalence which may be due to the population's immune response to the HBV/H genotype, despite the high rate of occult HBV infection (82). Nonetheless, the influence of the emergent F1b, A, and D genotypes on the natural history of HCC has not been thoroughly studied (86).

Genetic variations involved in the development of HCC are very diverse, and each example correlates with specific susceptibility. The aforementioned *PNPLA3* I148M allele associated with MAFLD/MASH has been linked to the development of HCC in patients with obesity (65, 110). In Europe, individuals with the *PNPLA3* GG genotype, particularly those with severe obesity, have a higher risk of developing HCC (111, 112). In Japan, patients with obesity/MAFLD or chronic hepatitis C infection have a higher frequency of the GG genotype, making them more susceptible to HCC (113, 114). Furthermore, association of rs738409 *PNPLA3* and rs58542926 *TM6SF2* as a risk factor for HCC was reported in patients with different liver disease etiologies (115), suggesting that underlying altered lipid metabolism influences the outcome of chronic liver disease.

The Membrane-bound O-acyltransferase domain containing 7 (MBOAT7), also known as lysophosphatidylinositol acyltransferase 1 is involved in the remodeling phospholipid chains and controlling cell membrane desaturation (116). The reduced expression of the *MBOAT7* rs641738 T allele is associated with altered cell membranes and plasma composition, including cell fat accumulation, pro-inflammatory environment, MAFLD, MASH, severe fibrosis, and HCC (117–121). An Italian cohort showed an 80% increased risk of

HCC due to the presence of the *MBOAT7* rs641738 T allele, contributing to the evolution of liver disease (118). However, the rs641738 T allele was not associated neither with HCC risk nor HBV infection in Chinese patients. (122).

Likewise, the hydroxysteroid 17-Beta dehydrogenase 13 protein encoded by the *HSD17B13* gene is involved in the metabolism of steroid hormones, prostaglandins, lipids, xenobiotics, and retinoids (123). This liver lipid droplet-associated enzyme is markedly upregulated in patients with MAFLD (124). HSD17B13 expression has been linked to steatosis, MASH, type 2 diabetes, and liver cancer (125) and was shown to be downregulated in an HCC model (126). Some *HSD17B13* variants such as the rs72613567 T > A have been associated with a protective effect in cirrhotic and HCC patients (127) as well as in European patients with ALD (128, 129) and HCV patients (130). In a recent study, this polymorphism was detected in patients with extreme obesity and MASH among other gen variants related to HCC (131). However, further genetic studies are also needed for LATAM populations, including Mexico, to confirm these associations.

Finally, a healthy diet can be potentially protective against HCC. Recent studies have identified nutrients, dietary patterns, and food groups with reduced, neutral, and high risk of developing HCC (132, 133). The nutrients reducing the risk of HCC are monounsaturated fatty acids, vitamin E, vitamin B9, beta-carotene, manganese, and potassium. Conversely, sodium, processed red meat, and sugar-sweetened beverages increase the risk. Currently, Mexicans consume a hepatopathogenic diet (48) with a potentially high risk of developing MAFLD/MASH setting the scenario that HCC may be underdiagnosed or increase in the future years (71, 134). The Genomex diet, containing a high content of protective nutrients has been implemented to prevent developing chronic liver disease (72). Furthermore, it has been reported that the treatment of alkaline-brined corn dough used to make the widely consumed Mexican tortillas can potentially protect against aflatoxin-induced HCC (135). However, further studies are needed to validate the role of diet in patients at risk of HCC, given the current prevalence of overweight and obesity.

5 Genomic education

Medical specialties and subspecialties, in their first stage of scientific medicine focused more on the complications of chronic disease, prolonging the patients' life and improving their quality of life, but do not prevent in all cases disease remission (136). Faced with this situation, PerMed-Nut approaches based on genomic medicine/nutrition need to integrate medical, nutritional, sociocultural, and emotional/spiritual aspects of health (137). However, new medical education and training for medical professionals are required (138, 139). In LATAM and Mexico, updating the medical and other health sciences education curriculum both at the undergraduate and graduate levels must be considered a priority. This curriculum needs to integrate the so-called basic subjects: Biochemistry, Cell Biology, Genetics/Genomics, and Molecular Biology at different levels with bioinformatics, technological/digital strategies (Telemedicine) and novel clinical approaches focused on preventing chronic diseases and long-term complications (140). These basic subjects can be integrated sequentially during the first years of schooling, not independently, as in the past. In the last century, most medical specialties and careers in Nutrition were created separately. However, with this new understanding, physicians/clinicians need to integrate nutrition, while the nutritionist should handle the knowledge of disease the same way as the doctors work (141).

Likewise, hepatology was not born when most medical specialties were created (142). Although some hepatology postgraduate courses have been sponsored by the associations for the study of the liver to update medical specialists, pre-graduate doctors and nutritionists need to understand the molecular physiology of the liver, while more postgraduate courses in MedPer-Nut are required to advance in Genomic Hepatology (143). Furthermore, the capability to analyze hundreds or thousands of these genes simultaneously leads us to large-scale data management (Big Data) and specialized bioinformatics (machine learning and other artificial intelligence methods), together with advanced omics biotechnologies (epigenetics, metagenomics, proteomics, lipidomics, and metabolomics), digital media, and electronic medical records (144). These applications are not the Medicine of the future, they are the present Medicine that will require training and re-constructing health career curriculums.

Lastly, the major benefit of re-engineering the educational curriculum is to promote the formation of researchers in LATAM and Mexico, thus creating novel knowledge in the field of MedPer-Nut in this region (145). In this sense, transforming the present clinical practice guidelines is an ongoing challenge because most recommendations are based on studies carried out in foreign populations (146). As illustrated in Figure 4, the genetic profile interacting with the environmental factors that concur in Mexico, may not replicate in other regions and vice versa. Thus, the vision is to prevent the onset and progression of chronic liver disease using MedPer-Nut approaches concordant with the genetic and environmental characteristics of the population (147).

6 Discussion

In the field of Medicine, we are now moving toward a new landscape of what exactly health means and how the pathological process begins. A primary goal is to avoid the onset of chronic diseases such as obesity, type 2 diabetes, and cardiovascular and liver diseases with their associated complications in the advanced stages. Reaching this goal will require detecting the genetic susceptibility to such diseases at young ages or at early stages, avoiding the pathology's development as is the case of liver cirrhosis due to alcohol, viral hepatitis, or MASLD. Such studies are the beginning of the pathway toward the new age of PerMed-Nut in liver diseases.

In perspective, 20 years ago, it was commonly said that genes and environment interact with each other, but it was not clear how such interactions took place, nor which were the main environmental factors. Currently, it is recognized that at least three environmental factors constantly interact with our genes: diet (micro and macronutrients), physical activity (exercise), and emotions (stressors) (137). Human adaptability to these elements lies in the genetic variations gained through evolution that mark the differences between individuals or populations at the genomic

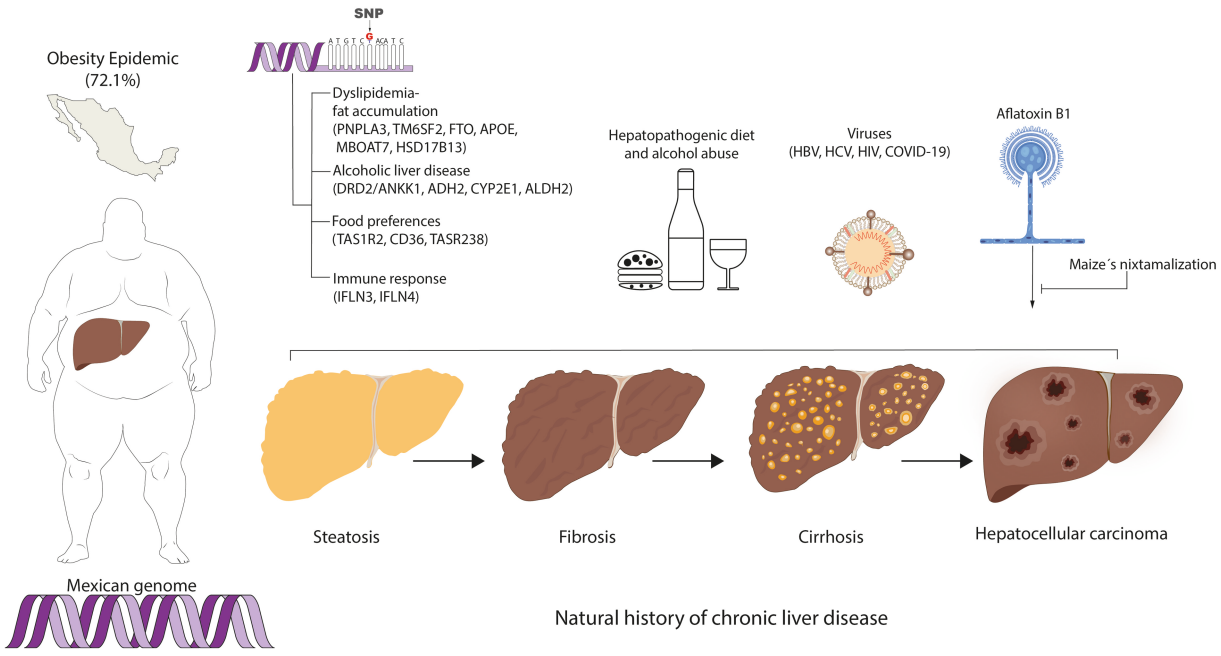


FIGURE 4
Personalized medicine and nutrition in hepatology among the Mexican population. The concurring genetic and environmental factors involved in chronic liver disease among the Mexican population are components to consider for the implementation of regionalized prevention strategies for chronic liver disease.

and cultural levels (47, 148, 149). As shown in this review, within LATAM, despite having a common social history of the peopling of the continent, a wide spectrum of ancestral inter-variability is notable as well a distinct environmental conditions (24, 25, 28, 33). In the case of Mexico, it has been shown that the North–South gradient of the European-Amerindian ancestry impacts importantly in the distribution of the several genes with biomedical implications for the risk of chronic liver diseases (Tables 2, 3; Figure 3) (32, 44, 45, 153). More so, this pattern of distribution could also be replicated intra-regionally in light of the social-demographic movements that occurred over time as in the case of the *ABCA1* polymorphism (46). This feature is the reason for further studies regarding the plausible association of certain genetic alleles with the clinical outcomes to tailor preventive strategies.

The diet-related alleles that have been studied to date among the Mexican population are key elements in the development of chronic illnesses including liver disease. As shown in Table 3, some polymorphisms are related to high food preferences for carbohydrates or lipids, altered food behaviors (excessive alcohol consumption), and dyslipidemias that can partly explain the increasing onset of MAFLD among the Mexican population. Interestingly, several genomic studies in Mexican Amerindian and admixed cohorts have identified the signature of positive selection of some serum lipid-modulating gene traits involved in cardiovascular diseases (150–152) that plausibly could overlap with the natural history of MAFLD. Overall, these genes can be useful for the development and validation of polygenic risk scores testing for the susceptibility in liver diseases among the Mexican population in the context of the tripartite ancestry (154–156). On the other hand, the impact of nutrition in patients with chronic viral hepatitis, specifically hepatitis B and C is an opportunity of exploration since patients with these pathologies have unmet needs in terms of their nutrition care to prevent further liver damage due to genetic susceptibility and harmful eating habits. Ultimately, understanding the molecular basis of these pathologies and the interactions that take place with the environment will derive in the making of a PerMed-Nut strategy appropriate for the Mexican population focused on the implementation of preventive strategies based on nutrition, exercise, and mental health instead of treating advanced diseases (157).

7 Conclusion

LATAM including Mexico shares a common ancestry in terms of genetics and culture that have an impact on health. However, further research regarding the distribution of genetic risk alleles and the interaction with environmental factors is required in this region. PerMed-Nut strategies based on these factors are the forthcoming trend in the field of Genomic Hepatology and other fields of medical specialties for preventing and managing chronic liver diseases. Knowledge of the genetic and lifestyle factors involved in the onset and progression of the major etiologies of chronic liver diseases needs to be generated by local researchers to provide regional clinical practice guidelines concordant with the features of the population. Achieving this PerMed-Nut approach is not without challenges since updated Medicine and Nutrition education curriculums are required. Training and preparing future health professionals and

TABLE 3 Summary of genetic variants related to etiologies of liver conditions or disease based on ancestry.

Gene	Polymorphism	Risk/ Protective allele	Nutritional/Clinical association	Statistical value*	Ancestry**	Reference
Metabolic-associated steatotic liver disease						
CD36	−31118 G>A rs1761667	A	Higher fat intake and hypercholesterolemia	2.75 (1.33–2.75) $p = 0.005$	Admixed Mexican	(58)
TAS1R2	Ile191Val rs35874116	Val	High carbohydrate intake and hypertriglyceridemia	2.61 (1.12–6.07) $p = 0.02$	Admixed Mexican	(60)
APOE	rs429358/rs7412	E4	High prevalence of hypercholesterolemia	$p = 0.047$	Amerindian	(53)
		E2	High prevalence of hypertriglyceridemia	$p = 0.045$	Admixed Mexican	
PNPLA3	Ile148Met (C > G) rs738409	Met	High ALT serum levels	3.7 (2.3–5.9) $p = 3.7 \times 10^{-8}$	Amerindian Admixed Mexican	(68)
SIK3	G > A rs139961185	A	High triglycerides levels after a high-fat meal	1.44 (1.27–1.63) $p = 1.15 \times 10^{-12}$	Admixed Mexican	(150)
SIDT2	G > A rs17120425	A	High HDL-C levels	2.92 (0.98) $p = 0.005$	Admixed Mexican	(151)
APOA5	G > C rs964184	G	High triglycerides levels	$p = 5.32 \times 10^{-37}$ BETA = 0.289	Admixed Mexican	(152)
Alcoholic liver disease						
TAS2R38	A49P rs13598	AVV haplotype	High consumption of alcohol	1.79 (1.13–2.84) $p < 0.05$	Admixed Mexican	(61)
	V262A rs1726866					
	I296V rs10246939					
DRD2/ANKK1	Taq1A A1 > A2 rs1800497	A1	High consumption of alcohol	4.09 (1.56–10.68) $p = 0.0021$	Admixed Mexican	(77)
ADH1B	Arg48His rs1229984	Arg (A1)	Low frequency of protective allele (A2)	ND	Admixed	(79)
					Amerindian	
ALDH2	Glu504Lys rs671	Glu (A1)	Low frequency of protective allele (A2)	ND	Amerindian	
CYP2E1	−1055C > T rs2031920	T (C2)	High frequency of risk allele	ND	Amerindian	
Hepatitis C infection						
IFLN3	rs12979860/	C/T/TT haplotype	Spontaneous clearance and less liver damage	0.46 (0.22–0.95) $p = 0.03$ and 0.32 (0.10–0.97), $p = 0.04$	Admixed Mexican	(101)
IFLN4	rs8099917/rs368234815					
APOE	rs429358/rs7412	E4	Spontaneous clearance and less liver damage	0.55 (0.31–0.98) $p = 0.042$ and 0.091 (0.01–0.75) $p = 0.020$	Admixed Mexican	(106)
		E3	Severe fibrosis (F3-F4)	2.99 (1.13–7.87) $p = 0.02$	Admixed Mexican	
CD36	−31118 G > A rs1761667	A	High-fat intake, serum AST values, and advanced liver fibrosis	3.60 (1.16–11.15) $p = 0.02$	Admixed Mexican	(58)
Hepatocellular carcinoma						
PNPLA3	Ile148Met	Met	Development of HCC in patients with obesity, viral infection, and ALD	5.88 (1–45–23.80) $p = 0.013$	Caucasian	(110)
				2.62 (1.15–5.96) $p = 0.0218$	Japanese	(114)
				3.91 (2.52–6.06) $p = 1.14 \times 10^{-9}$	Caucasian	(115)
MBOAT7	rs641738	T	HCC risk	2.18 (1.30–3.63) $p = 0.003$	Caucasian	(118)
			Liver fat	0.034 (0.018–0.051) $p = 4.8 \times 10^{-5}$		(121)
			Fibrosis	1.21 (1.03–1.45) $p = 0.021$		
HSD17B13	rs72613567	A	Reduced HCC risk in HCV and ALD	0.71 (0.60–0.85) $p = 0.002$	Caucasian	(128)
				0.73 (0.65–0.82) $p \leq 0.0001$		

Source: Data extracted from the indicated references. *Figures are OR (95% CI), p value or p value alone when compared to opposing genotypes/alleles or study group. **Data regarding hepatocellular carcinoma and specified genes has not been studied in Mexican population. ND, not determined.

researchers with new clinical and investigative skills focused on preventing liver diseases in the field of Genomic Hepatology globally is a vision that clinicians and nutritionists should be concerned about.

Author contributions

AP: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. SR: Conceptualization,

Investigation, Visualization, Writing – original draft, Writing – review & editing. IM-M: Investigation, Visualization, Writing – review & editing. AJ-A: Investigation, Visualization, Writing – review & editing. KG-A: Investigation, Visualization, Writing – review & editing. CO-G: Investigation, Visualization, Writing – review & editing. OR-L: Investigation, Visualization, Writing – review & editing. LT-R: Investigation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Shriner D, Tekola-Ayele F, Adeyemo A, Rotimi CN. Genome-wide genotype and sequence-based reconstruction of the 140,000 year history of modern human ancestry. *Sci Rep*. (2014) 4:6055. doi: 10.1038/srep06055

2. Shriner D, Tekola-Ayele F, Adeyemo A, Rotimi CN. Ancient human migration after out-of-Africa. *Sci Rep*. (2016) 6:26565. doi: 10.1038/srep26565

3. Adhikari K, Chacón-Duque JC, Mendoza-Revilla J, Fuentes-Guajardo M, Ruiz-Linares A. The genetic diversity of the Americas. *Annu Rev Genomics Hum Genet*. (2017) 18:277–96. doi: 10.1146/annurev-genom-083115-022331

4. Harcourt AH. Human phylogeography and diversity. *Proc Natl Acad Sci USA*. (2016) 113:8072–8. doi: 10.1073/pnas.1601068113

5. Fan S, Hansen MEB, Lo Y, Tishkoff SA. Going global by adapting local: a review of recent human adaptation. *Science*. (2016) 354:54–9. doi: 10.1126/science.aaf5098

6. Fu W, Akey JM. Selection and adaptation in the human genome. *Annu Rev Genomics Hum Genet*. (2013) 14:467–89. doi: 10.1146/annurev-genom-091212-153509

7. National Institute of Health. National Human Genome Research Institute Human Genomic Variation (2024). Available at: https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation (Accessed March 10, 2024)

8. O'Dea RE, Noble DWA, Johnson SL, Hesselson D, Nakagawa S. The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps. Environ. *Epigenetics*. (2016) 2:dvv014. doi: 10.1093/eep/dvv014

9. Ottman R. Gene-environment interaction: definitions and study designs. *Prev Med*. (1996) 25:764–70. doi: 10.1006/pmed.1996.0117

10. Chial H. (2024). Human Genome Project: Sequencing the Human Genome | Learn Science at Scitable. Available at: http://www.nature.com/scitable/topicpage/dna-sequencing-technologies-key-to-the-human-828 (Accessed January 24, 2024).

11. Lathe W., Williams J., Mangan M., Karolchik D. (2024). Genomic Data Resources: Curation, Databasing, and Browsers | Learn Science at Scitable. Available at: https://www.nature.com/scitable/topicpage/genomic-data-resources-challenges-and-promises-743721/# (Accessed March 8, 2024).

12. Gonzaga-Jauregui C, Lupski JR, Gibbs RA. Human genome sequencing in health and disease. *Annu Rev Med*. (2012) 63:35–61. doi: 10.1146/annurev-med-051010-162644

13. Golubnitschaja O, Baban B, Boniolo G, Wang W, Bubnov R, Kapalla M, et al. Medicine in the early twenty-first century: paradigm and anticipation—EPMA position paper 2016. *EPMA J*. (2016) 7:23. doi: 10.1186/s13167-016-0072-4

14. Goldblatt EM, Lee W-H. From bench to bedside: the growing use of translational research in cancer medicine. *Am J Transl Res*. (2010) 2:1–18.

15. Roth SC. What is genomic medicine? *J Med Libr Assoc*. (2019) 107:442–8. doi: 10.5195/jmla.2019.604

16. Pokorska-Bocci A, Stewart A, Sagoo GS, Hall A, Kroese M, Burton H. "Personalized medicine": what's in a name? *Pers Med*. (2014) 11:197–210. doi: 10.2217/pme.13.107

17. Romero-Hidalgo S, Flores-Rivera J, Rivas-Alonso V, Barquera R, Villarreal-Molina MT, Antuna-Puente B, et al. Native American ancestry significantly contributes to neuromyelitis optica susceptibility in the admixed Mexican population. *Sci Rep*. (2020) 10:13706. doi: 10.1038/s41598-020-69224-3

18. Ramos-Lopez O, Milagro FI, Allayee H, Chmurzynska A, Choi MS, Curi R, et al. Guide for current nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition involving the prevention and management of chronic diseases associated with obesity. *J Nutr*. (2017) 10:43–62. doi: 10.1159/000477729

19. Cheemerla S, Balakrishnan M. Global epidemiology of chronic liver disease. *Clin Liver Dis*. (2021) 17:365–70. doi: 10.1002/cld.1061

20. Teng ML, Ng CH, Huang DQ, Chan KE, Tan DJ, Lim WH, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol*. (2023) 29:S32–42. doi: 10.3350/cmh.2022.0365

21. Rotimi CN, Tekola-Ayele F, Baker JL, Shriner D. The African diaspora: history, adaptation and health. *Curr Opin Genet Dev*. (2016) 41:77–84. doi: 10.1016/j.gde.2016.08.005

22. Heinz T, Álvarez-Iglesias V, Pardo-Seco J, Taboada-Echalar P, Gómez-Carballa A, Torres-Balanza A, et al. Ancestry analysis reveals a predominant native American component with moderate European admixture in Bolivians. *Forensic Sci Int Genet*. (2013) 7:537–42. doi: 10.1016/j.fsigen.2013.05.012

23. Coelho AVC, Moura RR, Cavalcanti C, Guimarães RL, Sandrin-Garcia P, Crovella S, et al. A rapid screening of ancestry for genetic association studies in an admixed population from Pernambuco, Brazil. *Genet Mol Res*. (2015) 14:2876–84. doi: 10.4238/2015.March.31.18

24. Norris ET, Wang L, Conley AB, Rishishwar L, Mariño-Ramírez L, Valderrama-Aguirre A, et al. Genetic ancestry, admixture and health determinants in Latin America. *BMC Genomics*. (2018) 19:861. doi: 10.1186/s12864-018-5195-7

25. Hughes CE, Algee-Hewitt BFB, Konigsberg LW. Population identifiability from forensic genetic markers: ancestry variation in Latin America. *Hum Biol*. (2018) 90:161–75. doi: 10.13110/humanbiology.90.3.03

26. Fernandes DM, Sirak KA, Ringbauer H, Sedig J, Rohland N, Cheronet O, et al. A genetic history of the pre-contact Caribbean. *Nature*. (2021) 590:103–10. doi: 10.1038/s41586-020-03053-2

27. Galarza JM, Barquera R, Álvarez AMT, Hernández Zaragoza DI, Sevilla GP, Tamayo A, et al. Genetic diversity of the HLA system in human populations from the Sierra (Andean), Oriente (Amazonian) and costa (coastal) regions of Ecuador. *Hum Immunol*. (2018) 79:639–50. doi: 10.1016/j.humimm.2018.06.004

28. Salzano FM, Sans M. Interethnic admixture and the evolution of Latin American populations. *Genet Mol Biol*. (2014) 37:151–70. doi: 10.1590/S1415-47572014000200003

29. Simão F, Ribeiro J, Vullo C, Catelli L, Gomes V, Xavier C, et al. The ancestry of eastern Paraguay: a typical south American profile with a unique pattern of admixture. *Gene*. (2021) 12:1788. doi: 10.3390/genes12111788

30. Spangenberg L, Fariello MI, Arce D, Illanes G, Greif G, Shin J-Y, et al. Indigenous ancestry and admixture in the Uruguayan population. *Front Genet*. (2021) 12:733195. doi: 10.3389/fgene.2021.733195

31. Andrey E. (2024). Civilizaciones Prehispanicas de America. Available at: https://www.academia.edu/19510611/Osvaldo_Silva_Galdames_Civilizaciones_Prehispanicas_de_America (Accessed January 24, 2024).

32. García-Ortiz H, Barajas-Olmos F, Contreras-Cubas C, Reynolds AW, Flores-Huacuja M, Snow M, et al. Unraveling signatures of local adaptation among indigenous groups from Mexico. *Gene*. (2022) 13:2251. doi: 10.3390/genes13122251

33. Chacón-Duque J-C, Adhikari K, Fuentes-Guajardo M, Mendoza-Revilla J, Acuña-Alonzo V, Barquera R, et al. Latin Americans show wide-spread converso ancestry and imprint of local native ancestry on physical appearance. *Nat Commun*. (2018) 9:5388. doi: 10.1038/s41467-018-07748-z

34. Martinez-Fierro ML, Beuten J, Leach RJ, Parra EJ, Cruz-Lopez M, Rangel-Villalobos H, et al. Ancestry informative markers and admixture proportions in northeastern Mexico. *J Hum Genet*. (2009) 54:504–9. doi: 10.1038/jhg.2009.65

35. Rubi-Castellanos R, Anaya-Palafox M, Mena-Rojas E, Bautista-España D, Muñoz-Valle JF, Rangel-Villalobos H. Genetic data of 15 autosomal STRs (Identifiler kit) of three Mexican mestizo population samples from the states of Jalisco (west), Puebla (Center), and Yucatan (southeast). *Forensic Sci Int Genet*. (2009) 3:e71–6. doi: 10.1016/j.fsigen.2008.07.006

36. Silva-Zolezzi I, Hidalgo-Miranda A, Estrada-Gil J, Fernandez-Lopez JC, Uribe-Figueroa L, Contreras A, et al. Analysis of genomic diversity in Mexican mestizo populations to develop genomic medicine in Mexico. *Proc Natl Acad Sci USA*. (2009) 106:8611–6. doi: 10.1073/pnas.0903045106

37. González-Sobrino BZ, Pintado-Cortina AP, Sebastián-Medina L, Morales-Mandujano F, Contreras AV, Aguilar YE, et al. Genetic diversity and differentiation in urban and indigenous populations of Mexico: patterns of mitochondrial DNA and Y-chromosome lineages. *Biodemography Soc Biol*. (2016) 62:53–72. doi: 10.1080/19485565.2015.1117938

38. Granados-Silvestre MA, Ortiz-López MG, Granados J, Canizales-Quinteros S, Peñaloza-Espinosa RI, Lechuga C, et al. Susceptibility background for type 2 diabetes in eleven Mexican indigenous populations: HNF4A gene analysis. *Mol Genet Genom*. (2017) 292:1209–19. doi: 10.1007/s00438-017-1340-2

39. Bonilla C, Gutiérrez G, Parra EJ, Kline C, Shriver MD. Admixture analysis of a rural population of the state of Guerrero, Mexico. *Am J Phys Anthropol*. (2005) 128:861–9. doi: 10.1002/ajpa.20227

40. Torre-Cantalapiedra E, Sánchez-Soto G, Torre-Cantalapiedra E, Sánchez-Soto G. Afro-descendants and social stratification in Mexico. New evidence from the 2015 intercensal survey. *Papeles Poblac*. (2019) 25:273–302. doi: 10.22185/24487147.2019.100.20

41. López-Ramírez YL, Aguilar-Velázquez JA, López-Armenta M, Ruiz-Hernández M, Rangel-Villalobos H. Paternal lineages and forensic parameters based on 23 Y-STRs (Powerplex® Y23) in mestizo males from Mexico City. *Int J Legal Med*. (2020) 134:199–202. doi: 10.1007/s00414-019-02183-1

42. GWAS (2024). Catalog. Available at: https://www.ebi.ac.uk/gwas/efotraits/EFO_0001421 (Accessed March 9, 2024).

43. Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res*. (2019) 47:D1005–12. doi: 10.1093/nar/gky1120

44. Sohail M, Palma-Martínez MJ, Chong AY, Quinto-Cortés CD, Barberena-Jonas C, Medina-Muñoz SG, et al. Mexican biobank advances population and medical genomics of diverse ancestries. *Nature*. (2023) 622:775–83. doi: 10.1038/s41586-023-06560-0

45. Moreno-Estrada A, Gignoux CR, Fernández-López JC, Zakharia F, Sikora M, Contreras AV, et al. Human genetics. The genetics of Mexico recapitulates native American substructure and affects biomedical traits. *Science*. (2014) 344:1280–5. doi: 10.1126/science.1251688

46. Ojeda-Granados C, Panduro A, Gonzalez-Aldaco K, Sepulveda-Villegas M, Rivera-Iñiguez I, Roman S. Tailoring nutritional advice for Mexicans based on prevalence profiles of diet-related adaptive gene polymorphisms. *J Pers Med*. (2017) 7:16. doi: 10.3390/jpm7040016

47. Ojeda-Granados C, Abondio P, Setti A, Sarno S, Gnecchi-Ruscone GA, González-Orozco E, et al. Dietary, cultural, and pathogens-related selective pressures shaped differential adaptive evolution among native Mexican populations. *Mol Biol Evol*. (2021) 39:msab290. doi: 10.1093/molbev/msab290

48. Roman S, Ojeda-Granados C, Ramos-Lopez O, Panduro A. Genome-based nutrition: an intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis. *World J Gastroenterol*. (2015) 21:3449–61. doi: 10.3748/wjg.v21.i12.3449

49. Shetty P. Nutrition transition and its health outcomes. *Indian J Pediatr*. (2013) 80:S21–7. doi: 10.1007/s12098-013-0971-5

50. Popkin BM, Gordon-Larsen P. The nutrition transition: worldwide obesity dynamics and their determinants. *Int J Obes Relat Metab Disord J Int Assoc Study Obes*. (2004) 28:S2–9. doi: 10.1038/sj.ijo.0802804

51. Acuña-Alonzo V, Flores-Dorantes T, Kruit JK, Villarreal-Molina T, Arellano-Campos O, Hünemeier T, et al. A functional ABCA1 gene variant is associated with low HDL-cholesterol levels and shows evidence of positive selection in native Americans. *Hum Mol Genet*. (2010) 19:2877–85. doi: 10.1093/hmg/ddq173

52. Villarreal-Molina T, Aguilar-Salinas C, Rodríguez-Cruz M, Barros D, Villalobos-Comparan M, Coral R, et al. The ATP-binding cassette transporter A1 R230C variant affects HDL cholesterol levels and BMI in the Mexican population association with obesity and obesity-related comorbidities. *Diabetes*. (2007) 56:1881–7. doi: 10.2337/db06-0905

53. Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K, Panduro A. Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among native American and mestizo Mexicans. *World J Hepatol*. (2022) 14:1408–20. doi: 10.4254/wjh.v14.i7.1408

54. Aguilar CA, Talavera G, Ordovas JM, Barriguete JA, Guillén LE, Leco ME, et al. The apolipoprotein E4 allele is not associated with an abnormal lipid profile in a native American population following its traditional lifestyle. *Atherosclerosis*. (1999) 142:409–14. doi: 10.1016/S0021-9150(98)00251-2

55. Roman S, Rivera-Iñiguez I, Ojeda-Granados C, Sepulveda-Villegas M, Panduro A. Genome-based nutrition in chronic liver disease In: RR Watson and VR Preedy, editors. *Dietary Interventions in Liver Disease*: Academic Press, Elsevier, USA (2019). 3–14.

56. Guibrunet L, Ortega-Avila AG, Arnés E, Mora AF. Socioeconomic, demographic and geographic determinants of food consumption in Mexico. *PLoS One*. (2023) 18:e0288235. doi: 10.1371/journal.pone.0288235

57. Barquera S, Rivera JA. Obesity in Mexico: rapid epidemiological transition and food industry interference in health policies. *Lancet Diabetes Endocrinol*. (2020) 8:746–7. doi: 10.1016/S2213-8587(20)30269-2

58. Ramos-Lopez O, Panduro A, Martinez Lopez E, Fierro Nora A, Ojeda-Granados C. Genetic variant in the CD36 gene (rs1761667) is associated with higher fat intake and high serum cholesterol among the population of West Mexico. *J Nutr Food Sci*. (2014) 5:1000353. doi: 10.4172/2155-9600.1000353

59. Ramos-Lopez O, Roman S, Martinez-Lopez E, Fierro NA, Gonzalez-Aldaco K, Jose-Abrego A, et al. CD36 genetic variation, fat intake and liver fibrosis in chronic hepatitis C virus infection. *World J Hepatol*. (2016) 8:1067–74. doi: 10.4254/wjh.v8.i25.1067

60. Ramos-Lopez O, Panduro A, Martinez-Lopez E, Roman S. Sweet taste receptor TAS1R2 polymorphism (Val191Val) is associated with a higher carbohydrate intake and hypertriglyceridemia among the population of West Mexico. *Nutrients*. (2016) 8:101. doi: 10.3390/nu8020101

61. Ramos-Lopez O, Roman S, Martinez-Lopez E, Gonzalez-Aldaco K, Ojeda-Granados C, Sepulveda-Villegas M, et al. Association of a novel TAS2R38 haplotype with alcohol intake among Mexican-mestizo population. *Ann Hepatol*. (2015) 14:729–34. doi: 10.1016/S1665-2681(19)30768-9

62. Qiao L, Luo GG. Functional characterization of apolipoproteins in the HCV life cycle. *Methods Mol Biol*. (2019) 1911:235–46. doi: 10.1007/978-1-4939-8976-8_16

63. Seripa D, D'Onofrio G, Panza F, Cascavilla L, Masullo C, Pilotto A. The genetics of the human APOE polymorphism. *Rejuvenation Res*. (2011) 14:491–500. doi: 10.1089/rej.2011.1169

64. Eisenberg DTA, Kuzawa CW, Hayes MG. Worldwide allele frequencies of the human apolipoprotein E gene: climate, local adaptations, and evolutionary history. *Am J Phys Anthropol*. (2010) 143:100–11. doi: 10.1002/ajpa.21298

65. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. (2008) 40:1461–5. doi: 10.1038/ng.257

66. Pingitore P, Pirazzi C, Mancina RM, Motta BM, Indiveri C, Pujia A, et al. Recombinant PNPLA3 protein shows triglyceride hydrolase activity and its I148M mutation results in loss of function. *Biochim Biophys Acta*. (2014) 1841:574–80. doi: 10.1016/j.bbalip.2013.12.006

67. Panduro A, Sepulveda-Villegas M, Andrea P, Guevara-Gonzalez AP, Milan RG, Gonzalez-Aldaco K, et al. Influence of ancestry on the FTO, PNPLA3, and TM6SF2 risk alleles and their association with metabolic abnormalities in admixed Mexicans with NASH and extreme obesity. *Hepatology*. (2022) 76:S1–S1564. doi: 10.1002/hep.32697

68. Larrieta-Carrasco E, León-Mimila P, Villarreal-Molina T, Villamil-Ramírez H, Romero-Hidalgo S, Jacobo-Albavera L, et al. Association of the I148M/PNPLA3 variant with elevated alanine transaminase levels in normal-weight and overweight/obese Mexican children. *Gene*. (2013) 520:185–8. doi: 10.1016/j.gene.2013.03.038

69. Xue W-Y, Zhang L, Liu C-M, Gao Y, Li S-J, Huai Z-Y, et al. Research progress on the relationship between TM6SF2 rs58542926 polymorphism and non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol*. (2022) 16:97–107. doi: 10.1080/17474124.2022.2032661

70. Chermon D, Birk R. FTO common obesity SNPs interact with actionable environmental factors: physical activity, sugar-sweetened beverages and wine consumption. *Nutrients*. (2022) 14:4202. doi: 10.3390/nu14194202

71. Sepulveda-Villegas M, Roman S, Rivera-Iñiguez I, Ojeda-Granados C, Gonzalez-Aldaco K, Torres-Reyes LA, et al. High prevalence of nonalcoholic steatohepatitis and abnormal liver stiffness in a young and obese Mexican population. *PLoS One*. (2019) 14:e0208926. doi: 10.1371/journal.pone.0208926

72. Ojeda-Granados C, Panduro A, Rivera-Iñiguez I, Sepúlveda-Villegas M, Roman S. A regionalized genome-based Mexican diet improves anthropometric and metabolic parameters in subjects at risk for obesity-related chronic diseases. *Nutrients*. (2020) 12:645. doi: 10.3390/nu12030645

73. Guevara-Cruz M, Tovar AR, Aguilar-Salinas CA, Medina-Vera I, Gil-Zenteno L, Hernández-Viveros I, et al. A dietary pattern including nopal, chia seed, soy protein, and oat reduces serum triglycerides and glucose intolerance in patients with metabolic syndrome. *J Nutr*. (2012) 142:64–9. doi: 10.3945/jn.111.147447

74. Dugum M, McCullough A. Diagnosis and Management of Alcoholic Liver Disease. *J Clin Transl Hepatol*. (2015) 3:109–16. doi: 10.14218/JCTH.2015.00008

75. Panduro A, Rivera-Iñiguez I, Ramos-Lopez O, Roman S. Chapter 50—genes and alcoholism: taste, addiction, and metabolism In: VR Preedy, editor. *Neuroscience of Alcohol*: Academic Press, Elsevier, USA (2019). 483–91.

76. Trépo E, Valenti L. Update on NAFLD genetics: from new variants to the clinic. *J Hepatol*. (2020) 72:1196–209. doi: 10.1016/j.jhep.2020.02.020

77. Panduro A, Ramos-Lopez O, Campollo O, Zepeda-Carrillo EA, Gonzalez-Aldaco K, Torres-Valadez R, et al. High frequency of the DRD2/ANKK1 A1 allele in Mexican native Amerindians and mestizos and its association with alcohol consumption. *Drug Alcohol Depend*. (2017) 172:66–72. doi: 10.1016/j.drugalcdep.2016.12.006

78. Rivera-Iñiguez I, Panduro A, Ramos-Lopez O, Villaseñor-Bayardo SJ, Roman S. DRD2/ANKK1 TaqI A1 polymorphism associates with overconsumption of unhealthy foods and biochemical abnormalities in a Mexican population. *Eat Weight Disord*. (2019) 24:835–44. doi: 10.1007/s40519-018-0596-9

79. Roman S, Zepeda-Carrillo EA, Moreno-Luna LE, Panduro A. Alcoholism and liver disease in Mexico: genetic and environmental factors. *World J Gastroenterol*. (2013) 19:7972–82. doi: 10.3748/wjg.v19.i44.7972

80. Lok AS. Personalized treatment of hepatitis B. *Clin Mol Hepatol*. (2015) 21:1–6. doi: 10.3350/cmh.2015.21.1.1

81. Jose-Abrego A, Roman S, Laguna-Meraz S, Panduro A. Host and HBV interactions and their potential impact on clinical outcomes. *Pathogens*. (2023) 12:1146. doi: 10.3390/pathogens12091146

82. Panduro A, Roman S, Laguna-Meraz S, Jose-Abrego A. Hepatitis B virus genotype H: epidemiological, molecular, and clinical characteristics in Mexico. *Viruses*. (2023) 15:2186. doi: 10.3390/v15112186

83. Roman S, Jose-Abrego A, Fierro NA, Escobedo-Melendez G, Ojeda-Granados C, Martinez-Lopez E, et al. Hepatitis B virus infection in Latin America: a genomic medicine approach. *World J Gastroenterol*. (2014) 20:7181–96. doi: 10.3748/wjg.v20.i23.7181

84. Hayashi S, Khan A, Simons BC, Homan C, Matsui T, Ogawa K, et al. An association between Core mutations in hepatitis B virus genotype F1b and hepatocellular carcinoma in Alaskan native people. *Hepatol Baltim*. (2019) 69:19–33. doi: 10.1002/hep.30111

85. Cerapio JP, Marchio A, Cano L, López I, Fournié J-J, Régnault B, et al. Global DNA hypermethylation pattern and unique gene expression signature in liver cancer from patients with indigenous American ancestry. *Oncotarget*. (2021) 12:475–92. doi: 10.18632/oncotarget.27890

86. Jose-Abrego A, Panduro A, Fierro NA, Roman S. High prevalence of HBV infection, detection of subgenotypes F1b, A2, and D4, and differential risk factors among Mexican risk populations with low socioeconomic status. *J Med Virol*. (2017) 89:2149–57. doi: 10.1002/jmv.24913

87. Panduro A, Roman S, Fierro NA, Rebello-Pinho JR. Viral kinetics of an acute hepatitis B virus subgenotype F1b infection in a Mexican subject. *Clin Liver Dis*. (2022) 19:41–8. doi: 10.1002/cld.1178

88. Jose-Abrego A, Roman S, Rebello Pinho JR, de Castro VFD, Panduro A. Hepatitis B virus (HBV) genotype mixtures, viral load, and liver damage in HBV patients co-infected with human immunodeficiency virus. *Front Microbiol*. (2021) 12:640889. doi: 10.3389/fmicb.2021.640889

89. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician*. (2006) 74:756–62.

90. Zhang Z, Wang C, Liu Z, Zou G, Li J, Lu M. Host genetic determinants of hepatitis B virus infection. *Front Genet*. (2019) 10:696. doi: 10.3389/fgene.2019.00696

91. Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatol Baltim*. (2018) 67:1560–99. doi: 10.1002/hep.29800

92. Park E-S, Lee AR, Kim DH, Lee J-H, Yoo J-J, Ahn SH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. *J Hepatol*. (2019) 70:1093–102. doi: 10.1016/j.jhep.2019.02.006

93. Kobayashi M, Suzuki F, Akuta N, Suzuki Y, Arase Y, Ikeda K, et al. Response to long-term lamivudine treatment in patients infected with hepatitis B virus genotypes a, B, and C. *J Med Virol*. (2006) 78:1276–83. doi: 10.1002/jmv.20701

94. Jose-Abrego A, Rivera-Iñiguez I, Torres-Reyes LA, Roman S. Anti-hepatitis B virus activity of food nutrients and potential mechanisms of action. *Ann Hepatol*. (2023) 28:100766. doi: 10.1016/j.aohep.2022.100766

95. Vergara C, Duggal P, Thio CL, Valencia A, O'Brien TR, Latanich R, et al. Multi-ancestry fine mapping of interferon lambda and the outcome of acute hepatitis C virus infection. *Genes Immun*. (2020) 21:348–59. doi: 10.1038/s41435-020-00115-3

96. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology*. (2010) 138:1345.e1–7. doi: 10.1053/j.gastro.2009.12.056

97. Prokunina-Olsson L. Genetics of the human interferon lambda region. *J Int Soc Interferon Cytokine Res*. (2019) 39:599–608. doi: 10.1089/jir.2019.0043

98. Bruening J, Weigel B, Gerold G. The role of type III interferons in hepatitis C virus infection and therapy. *J Immunol Res*. (2017) 2017:7232361. doi: 10.1155/2017/7232361

99. Hayes CN, Kobayashi M, Akuta N, Suzuki F, Kumada H, Abe H, et al. HCV substitutions and IL28B polymorphisms on outcome of peg-interferon plus ribavirin combination therapy. *Gut*. (2011) 60:261–7. doi: 10.1136/gut.2010.223495

100. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. (2009) 461:798–801. doi: 10.1038/nature08463

101. Gonzalez-Aldaco K, Rebello Pinho JR, Roman S, Gleyzer K, Fierro NA, Oyakawa L, et al. Association with spontaneous hepatitis C viral clearance and genetic differentiation of IL28B/IFNL4 haplotypes in populations from Mexico. *PLoS One*. (2016) 11:e0146258. doi: 10.1371/journal.pone.0146258

102. Wilsie LC, Gonzales AM, Orlando RA. Syndecan-1 mediates internalization of apoE-VLDL through a low density lipoprotein receptor-related protein (LRP)-independent, non-clathrin-mediated pathway. *Lipids Health Dis*. (2006) 5:23. doi: 10.1186/1476-511X-5-23

103. Gomaa HE, Mahmoud M, Saad NE, Saad-Hussein A, Ismail S, Thabet EH, et al. Impact of apo E gene polymorphism on HCV therapy related outcome in a cohort of HCV Egyptian patients. *J Genet Eng Biotechnol*. (2018) 16:47–51. doi: 10.1016/j.jgeb.2017.10.008

104. Mueller T, Fischer J, Gessner R, Rosendahl J, Böhm S, van Bömmel F, et al. Apolipoprotein E allele frequencies in chronic and self-limited hepatitis C suggest a protective effect of APOE4 in the course of hepatitis C virus infection. *Liver Int Off J Int Assoc Study Liver*. (2016) 36:1267–74. doi: 10.1111/liv.13094

105. Price DA, Bassendine MF, Norris SM, Golding C, Toms GL, Schmid ML, et al. Apolipoprotein epsilon3 allele is associated with persistent hepatitis C virus infection. *Gut*. (2006) 55:715–8. doi: 10.1136/gut.2005.079905

106. Gonzalez-Aldaco K, Roman S, Torres-Valadez R, Ojeda-Granados C, Torres-Reyes LA, Panduro A. Hepatitis C virus clearance and less liver damage in patients with high cholesterol, low-density lipoprotein cholesterol and APOE ε4 allele. *World J Gastroenterol*. (2019) 25:5826–37. doi: 10.3748/wjg.v25.i38.5826

107. Syed GH, Tang H, Khan M, Hassanein T, Liu J, Siddiqui A. Hepatitis C virus stimulates low-density lipoprotein receptor expression to facilitate viral propagation. *J Virol*. (2014) 88:2519–29. doi: 10.1128/JVI.02727-13

108. Go G-W, Mani A. Low-density lipoprotein receptor (LDLR) family orchestrates cholesterol homeostasis. *Yale J Biol Med*. (2012) 85:19–28.

109. Ojeda-Granados C, Panduro A, Gonzalez-Aldaco K, Rivera-Iñiguez I, Campos-Medina L, Roman S. Adherence to a fish-rich dietary pattern is associated with chronic hepatitis C patients showing low viral load: implications for nutritional management. *Nutrients*. (2021) 13:3337. doi: 10.3390/nu13103337

110. Li J-F, Zheng E-Q, Xie M. Association between rs738409 polymorphism in patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene and hepatocellular carcinoma susceptibility: evidence from case-control studies. *Gene*. (2019) 685:143–8. doi: 10.1016/j.gene.2018.11.012

111. Liu Y-L, Patman GL, Leathart JBS, Piguet A-C, Burt AD, Dufour J-F, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. *J Hepatol*. (2014) 61:75–81. doi: 10.1016/j.jhep.2014.02.030

112. Burza MA, Pirazzi C, Maglio C, Sjöholm K, Mancina RM, Svensson P-A, et al. PNPLA3 I148M (rs738409) genetic variant is associated with hepatocellular carcinoma in obese individuals. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. (2012) 44:1037–41. doi: 10.1016/j.dld.2012.05.006

113. Takeuchi Y, Ikeda F, Moritou Y, Hagihara H, Yasunaka T, Kuwaki K, et al. The impact of patatin-like phospholipase domain-containing protein 3 polymorphism on hepatocellular carcinoma prognosis. *J Gastroenterol*. (2013) 48:405–12. doi: 10.1007/s00535-012-0647-3

114. Nakaoka K, Hashimoto S, Kawabe N, Nitta Y, Murao M, Nakano T, et al. PNPLA3 I148M associations with liver carcinogenesis in Japanese chronic hepatitis C patients. *Springerplus*. (2015) 4:83. doi: 10.1186/s40064-015-0870-5

115. Yang J, Trépo E, Nahon P, Cao Q, Moreno C, Letouzé E, et al. PNPLA3 and TM6SF2 variants as risk factors of hepatocellular carcinoma across various etiologies and severity of underlying liver diseases. *Int J Cancer*. (2019) 144:533–44. doi: 10.1002/ijc.31910

116. Gijón MA, Riekhof WR, Zarini S, Murphy RC, Voelker DR. Lysophospholipid acyltransferases and arachidonate recycling in human neutrophils. *J Biol Chem*. (2008) 283:30235–45. doi: 10.1074/jbc.M806194200

117. Mancina RM, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, et al. The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of European descent. *Gastroenterology*. (2016) 150:1219–1230.e6. doi: 10.1053/j.gastro.2016.01.032

118. Donati B, Dongiovanni P, Romeo S, Meroni M, McCain M, Miele L, et al. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. *Sci Rep*. (2017) 7:4492. doi: 10.1038/s41598-017-04991-0

119. Meroni M, Longo M, Fracanzani AL, Dongiovanni P. MBOAT7 down-regulation by genetic and environmental factors predisposes to MAFLD. *EBioMedicine*. (2020) 57:102866. doi: 10.1016/j.ebiom.2020.102866

120. Pelusi S, Baselli G, Pietrelli A, Dongiovanni P, Donati B, McCain MV, et al. Rare pathogenic variants predispose to hepatocellular carcinoma in nonalcoholic fatty liver disease. *Sci Rep*. (2019) 9:3682. doi: 10.1038/s41598-019-39998-2

121. Teo K, Abeysekera KWM, Adams L, Aigner E, Anstee QM, Banales JM, et al. rs641738C>T near MBOAT7 is associated with liver fat, ALT and fibrosis in NAFLD: a meta-analysis. *J Hepatol*. (2021) 74:20–30. doi: 10.1016/j.jhep.2020.08.027

122. Wang P, Li Y, Li L, Zhong R, Shen N. MBOAT7-TMC4 rs641738 is not associated with the risk of hepatocellular carcinoma or persistent hepatitis B infection. *Front Oncol*. (2021) 11:639438. doi: 10.3389/fonc.2021.639438

123. Marchais-Oberwinkler S, Henn C, Möller G, Klein T, Negri M, Oster A, et al. 17β-hydroxysteroid dehydrogenases (17β-HSDs) as therapeutic targets: protein structures, functions, and recent progress in inhibitor development. *J Steroid Biochem Mol Biol*. (2011) 125:66–82. doi: 10.1016/j.jsbmb.2010.12.013

124. Su W, Wang Y, Jia X, Wu W, Li L, Tian X, et al. Comparative proteomic study reveals 17β-HSD13 as a pathogenic protein in nonalcoholic fatty liver disease. *Proc Natl Acad Sci USA*. (2014) 111:11437–42. doi: 10.1073/pnas.1410741111

125. Su W, Mao Z, Liu Y, Zhang X, Zhang W, Gustafsson J-A, et al. Role of HSD17B13 in the liver physiology and pathophysiology. *Mol Cell Endocrinol*. (2019) 489:119–25. doi: 10.1016/j.mce.2018.10.014

126. Chen J, Zhuo J-Y, Yang F, Liu Z-K, Zhou L, Xie H-Y, et al. 17-beta-hydroxysteroid dehydrogenase 13 inhibits the progression and recurrence of hepatocellular carcinoma. *Hepatobil Pancreat Dis Int*. (2018) 17:220–6. doi: 10.1016/j.hbpd.2018.04.006

127. Gellert-Kristensen H, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. High risk of fatty liver disease amplifies the alanine transaminase-lowering effect of a HSD17B13 variant. *Hepatol Baltim*. (2020) 71:56–66. doi: 10.1002/hep.30799

128. Yang J, Trépo E, Nahon P, Cao Q, Moreno C, Letouzé E, et al. A 17-Beta-hydroxysteroid dehydrogenase 13 variant protects from hepatocellular carcinoma development in alcoholic liver disease. *Hepatol Baltim*. (2019) 70:231–40. doi: 10.1002/hep.30623

129. Stickel F, Lutz P, Buch S, Nischalke HD, Silva I, Rausch V, et al. Genetic variation in HSD17B13 reduces the risk of developing cirrhosis and hepatocellular carcinoma in alcohol misusers. *Hepatol Baltim*. (2020) 72:88–102. doi: 10.1002/hep.30996

130. De Benedittis C, Bellan M, Crevola M, Boin E, Barbaglia MN, Mallela VR, et al. Interplay of PNPLA3 and HSD17B13 variants in modulating the risk of hepatocellular carcinoma among hepatitis C patients. *Gastroenterol Res Pract*. (2020) 2020:4216451. doi: 10.1155/2020/4216451

131. Torres-Reyes LA, Gonzalez-Aldaco K, Panduro A, Jose-Abrego A, Roman S. Whole-exome sequencing identified olfactory receptor genes as a key contributor to extreme obesity with progression to nonalcoholic steatohepatitis in Mexican patients: olfactory receptor genes in obese NASH patients. *Ann Hepatol*. (2022) 27:100767. doi: 10.1016/j.aohep.2022.100767

132. Wiseman MJ. Nutrition and cancer: prevention and survival. *Br J Nutr*. (2019) 122:481–7. doi: 10.1017/S0007114518002222

133. George ES, Sood S, Broughton A, Cogan G, Hickey M, Chan WS, et al. The association between diet and hepatocellular carcinoma: a systematic review. *Nutrients*. (2021) 13:172. doi: 10.3390/nu13010172

134. Ramos-Lopez O, Martinez-Lopez E, Roman S, Fierro NA, Panduro A. Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico. *World J Gastroenterol*. (2015) 21:11552–66. doi: 10.3748/wjg.v21.i41.11552

135. Gomez-Quiroz LE, Roman S. Influence of genetic and environmental risk factors in the development of hepatocellular carcinoma in Mexico. *Ann Hepatol*. (2022) 27:100649. doi: 10.1016/j.aohep.2021.100649

136. Cassel CK, Reuben DB. Specialization, subspecialization, and Subsubspecialization in internal medicine. *N Engl J Med*. (2011) 364:1169–73. doi: 10.1056/NEJMsb1012647

137. Panduro A, Rivera-Iñiguez I, Sepulveda-Villegas M, Roman S. Genes, emotions and gut microbiota: the next frontier for the gastroenterologist. *World J Gastroenterol*. (2017) 23:3030–42. doi: 10.3748/wjg.v23.i17.3030

138. Slade I, Subramanian DN, Burton H. Genomics education for medical professionals—the current UK landscape. *Clin Med Lond Engl*. (2016) 16:347–52. doi: 10.7861/clinmedicine.16-4-347

139. Simpson S, Seller A, Bishop M. Using the findings of a National Survey to inform the work of England's genomics education programme. *Front Genet*. (2019) 10:1265. doi: 10.3389/fgene.2019.01265

140. Roman S, Panduro A. Genomic medicine in gastroenterology: a new approach or a new specialty? *World J Gastroenterol*. (2015) 21:8227–37. doi: 10.3748/wjg.v21.i27.8227

141. Donini LM, Leonardi F, Rondanelli M, Banderali G, Battino M, Bertoli E, et al. The domains of human nutrition: the importance of nutrition education in academia and medical schools. *Front Nutr*. (2017) 4:2. doi: 10.3389/fnut.2017.00002

142. Bacon BR, Adams PC. Hepatology as a distinct specialty—born in the USA? *Can J Gastroenterol*. (2007) 21:421. doi: 10.1155/2007/320986

143. Panduro A. Training in hepatology: from medical school to a Ph.D. and clinical specialty program. *Ann Hepatol*. (2022) 27:100682. doi: 10.1016/j.aohep.2022.100682

144. Panduro A. Viruses and the liver 2020: before COVID-19 and the beginning of a new age in medicine. *Ann Hepatol*. (2021) 20:100293. doi: 10.1016/j.aohep.2020.100293

145. Panduro A, Roman S. Personalized medicine in Latin America. *Pers Med*. (2020) 17:339–43. doi: 10.2217/pme-2020-0049

146. Panduro A, Roman S. Advancements in genomic medicine and the need for updated regional clinical practice guidelines in the field of hepatology. *Ann Hepatol*. (2020) 19:1–2. doi: 10.1016/j.aohep.2019.12.002

147. Ojeda-Granados C, Roman S. Mediterranean diet or genome-based nutrition diets in Latin America's clinical practice guidelines for managing chronic liver diseases? *Ann Hepatol*. (2021) 20:100291. doi: 10.1016/j.aohep.2020.100291

148. Alt KW, Al-Ahmad A, Woelber JP. Nutrition and health in human evolution–past to present. *Nutrients*. (2022) 14:3594. doi: 10.3390/nu14173594

149. Benton ML, Abraham A, LaBella AL, Abbot P, Rokas A, Capra JA. The influence of evolutionary history on human health and disease. *Nat Rev Genet*. (2021) 22:269–83. doi: 10.1038/s41576-020-00305-9

150. Ko A, Cantor RM, Weissglas-Volkov D, Nikkola E, Reddy PMVL, Sinsheimer JS, et al. Amerindian-specific regions under positive selection harbour new lipid variants in Latinos. *Nat Commun*. (2014) 5:3983. doi: 10.1038/ncomms4983

151. León-Mimila P, Villamil-Ramírez H, Macías-Kauffer LR, Jacobo-Albavera L, López-Contreras BE, Posadas-Sánchez R, et al. Genome-wide association study identifies a functional SIDT2 variant associated with HDL-C (high-density lipoprotein cholesterol) levels and premature coronary artery disease. *Arterioscler Thromb Vasc Biol*. (2021) 41:2494–508. doi: 10.1161/ATVBAHA.120.315391

152. Below JE, Parra EJ, Gamazon ER, Torres J, Krithika S, Candille S, et al. Meta-analysis of lipid-traits in Hispanics identifies novel loci, population-specific effects, and tissue-specific enrichment of eQTLs. *Sci Rep*. (2016) 6:19429. doi: 10.1038/srep19429

153. García-Ortiz H, Barajas-Olmos F, Contreras-Cubas C, Cid-Soto MÁ, Córdova EJ, Centeno-Cruz F, et al. The genomic landscape of Mexican indigenous populations brings insights into the peopling of the Americas. *Nat Commun*. (2021) 12:5942. doi: 10.1038/s41467-021-26188-w

154. Serra-Burriel M, Juanola A, Serra-Burriel F, Thiele M, Graupera I, Pose E, et al. Development, validation, and prognostic evaluation of a risk score for long-term liver-related outcomes in the general population: a multicohort study. *Lancet*. (2023) 402:988–96. doi: 10.1016/S0140-6736(23)01174-1

155. Nature (2024). Polygenic risk: What's the score? Available at: https://www.nature.com/articles/d42473-019-00270-w (Accessed March 12, 2024).

156. Busby GB, Kulm S, Bolli A, Kintzle J, Domenico PD, Bottà G. Ancestry-specific polygenic risk scores are risk enhancers for clinical cardiovascular disease assessments. *Nat Commun*. (2023) 14:7105. doi: 10.1038/s41467-023-42897-w

157. Roman S. Genome-based nutritional strategies to prevent chronic liver disease. *Ann Hepatol*. (2019) 18:537–8. doi: 10.1016/j.aohep.2019.05.005

frontiers | Frontiers in Nutrition

TYPE Perspective
PUBLISHED 24 May 2024
DOI 10.3389/fnut.2024.1370595

OPEN ACCESS

EDITED BY
Claudia Ojeda-Granados,
University of Catania, Italy

REVIEWED BY
Venkata Saroja Voruganti,
University of North Carolina at Chapel Hill,
United States

*CORRESPONDENCE
Sonia Roman
✉ sonia.roman@academicos.udg.mx

RECEIVED 15 January 2024
ACCEPTED 13 May 2024
PUBLISHED 24 May 2024

CITATION
Roman S, Campos-Medina L and Leal-Mercado L (2024) Personalized nutrition: the end of the one-diet-fits-all era. *Front. Nutr.* 11:1370595. doi: 10.3389/fnut.2024.1370595

Personalized nutrition: the end of the one-diet-fits-all era

Sonia Roman[1,2]*, Liliana Campos-Medina[1,2,3] and Leonardo Leal-Mercado[1,2,3]

[1]Department of Genomic Medicine in Hepatology, Civil Hospital of Guadalajara, Fray Antonio Alcalde, Guadalajara, Jalisco, Mexico, [2]Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico, [3]Doctoral Program in Molecular Biology in Medicine, Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico

Personalized Nutrition emerged as a new trend for providing nutritional and food advice based on the individual's genetic composition, a field driven by the advancements in the multi-omic sciences throughout the last century. It intends not only to tailor the recommended daily allowances of nutrients and functional foods that a person may need but also to maintain the principles of sustainability and eco-friendliness. This principle implies the implementation of strategies within the healthcare system to advocate for the ending of the one-diet-fits-all paradigm by considering a personalized diet as an ally to prevent diet-related chronic diseases. In this Perspective, we highlight the potential benefits of such a paradigm within the region of Latin America, particularly Mexico, where the genetic admixture of the population, food biodiversity, and food culture provide unique opportunities to establish personalized nutrigenetic strategies. These strategies could play a crucial role in preventing chronic diseases and addressing the challenges confronted in the region.

KEYWORDS

genes, polymorphisms, ancestry, Genomex diet, hepatopathogenic diet, food culture, Latin America, Mexico

1 Introduction

The field of Genomic Nutrition, also known as Nutritional Genomics, is rapidly advancing with the integration of multi-omic analyses in nutritional science (1, 2). This discipline mainly encompasses two subfields, Nutrigenomics and Nutrigenetics, which explore the bidirectional interactions between genes, diet (nutrients), and health outcomes (3, 4). Nutrigenetics focuses on how a specific polymorphism (allele/genotype) or genetic profile affects the body's metabolic responsiveness to foods (nutrients) (5). Nutrigenomics studies the impact of nutrients and bioactive food compounds on gene expression, specifically in transcriptomics, proteomics, and metabolomics, regardless of the inherited genotype (6). In addition, the emerging fields of Nutri-epigenetics and Nutri-metagenomics widen our understanding of gene expression modulation at the chromatin level (7, 8) and the signaling between the gut microbiota, considered our "second genome," and the host's organs/tissues (9, 10), respectively. Other interacting environmental factors to consider are physical activity, psychosocial context (stress, emotions), and contaminants (11). Together, they provide the scientific basis for designing more effective dietary interventions that consider genetic diversity, gut microbiota, and lifestyle to design personalized nutrition strategies that align with an individual's unique needs.

Research in Nutritional Genomics and its practical application in personalized nutrition have incited two interconnected aspects. On the one hand, much enthusiasm

has risen due to the potential to predict nutritional recommendations based on individual genetic profiles, leading to improved health outcomes (12). In addition, understanding the genomic landscape contributing to the risk of chronic diseases in a specific population has advantages. It allows for proactive measures to prevent these diseases rather than relying solely on reactive healthcare (13, 14). On the other hand, the inception of personalized nutrition based on multi-omic data has sparked a significant debate among health experts regarding the interpretation of this data and ethical and privacy concerns surrounding it (15). These controversies have led to the establishment of standardized definitions, regulations, and ethical delivery of nutritional care (16). Although crucial for ensuring professional clinical practices, these aspects go beyond the scope of this Perspective. Nonetheless, it is undeniable that personalized nutrition, indicating the right food for all, is an ongoing trend in our society (17, 18) that will inherently lead to the end of the universal approach of the "one-diet-fits-all era".

Herein, we examine our rationale and the implications of implementing personalized nutrition in Latin America, particularly Mexico. The population's varying genetic backgrounds, food diversity, and cultural traditions present a potential for tailoring regionalized nutritional genomic strategies to move away from a "one-diet-fits-all" to fight chronic illnesses.

2 Evolution of the human diet and mismatch between genes and nutrients

Gene-nutrient interactions are highly dynamic. Firstly, there have been significant evolutionary changes in how humans obtain nutrients from the environment and how these needs are regulated by genes (19). Dietary patterns have substantially changed across different regions throughout history (20). Currently, numerous societies are amid a shift from pre- and post-globalization movements. This transition has resulted in detrimental effects on food quality and quantity, as well as an increase in chronic diseases due to greater food processing and accessibility (21, 22). Likewise, humans have experienced different stages of evolutionary adaptation through exposure to various environments and selective pressures. The genome of modern humans has been shaped by the availability of nutrients in different environments, leading to multiple locally positively selected gene variations (23). While advantageous in one setting, these adaptations can become problematic when faced with a changing nutritional landscape, such as in the current epidemiological transition (24–26). The significant shifts in lifestyle factors, such as reduced physical activity, increased stress levels, and exposure to environmental pollutants, are causing an evolutionary mismatch that contributes to the development of chronic illnesses (26).

From a nutritional standpoint, some societies maintain a historically traditional diet, while others have adopted either an imported traditional diet or a more modern diet (27). Unfortunately, this does not suggest that our overall health surpasses that of our ancestors or previous generations. The prevalence of obesity-related chronic diseases has increased globally, affecting individuals of all economic backgrounds. This trend is particularly evident among children, adolescents, and adults residing in urban areas where ultra-processed foods have surged alongside the acculturation process (28, 29).

In contrast, sustaining or reintroducing indigenous food knowledge and protecting traditional cultural food practices worldwide positively impacts social-cultural well-being and substantially reduces the likelihood of developing chronic diseases (30). The composition of traditional diets, which refers to the predominant diet consumed for many generations and comprises a higher share of natural staple foods, reflects earlier phases of food evolution before industrialization (31). Hence, personalized nutrition should focus on reintroducing the main staple foods that have influenced human DNA in the past. However, these foods are not universal and will vary significantly according to geography, the population's ethnicity, and cultural practices.

3 Personalized nutrition to prevent diet-related chronic diseases

In the early days before the genomics era, Dr. Richard O. Brennan introduced the concept of nutrigenetics in 1977. He used this term to describe the notion that diet could alleviate hypoglycemia, which is linked to genetics (32). In addition, newborns that inherit single-gene inborn metabolism errors and diseases require personalized nutritional support to address these diseases at early stages (33). However, the boom of personalized nutrition, as we recognize it today, occurred during the post-genomic era (6). The Human Genome Project gained significant attention because it became clear that most common chronic disease phenotypes derive from the complex interplay between multiple genetic variations, (single nucleotide polymorphisms (SNPs), number copy variations and insertion-deletion polymorphisms) and environmental factors such as diet, containing nutrients and bioactive compounds (34, 35). The Human Microbiome Project was subsequently established to disseminate knowledge, resources, and discoveries that connect human-microbiome interactions and health-related outcomes (36).

Personalized nutrition or precision nutrition multi-omic technologies have ultimately revolutionized healthcare strategies by recognizing the unique nature of individuals and the need for tailored dietary recommendations. Nevertheless, it is crucial not to disregard a fundamental principle. Personalized nutrition should consider the occurrence of the diseases it aims to prevent, which are, in turn, shaped by genetic and cultural factors specific to the target population (37, 38). Hence, it is not only the inheritance of "risk alleles" that is important, but also the traditions and history (food culture) that shaped that genome, so diets should not be recommended indiscriminately. Developing personalized nutrition plans is and will be a complex task, but it is feasible due to the growing scientific research, societal acceptance, political backing, and health and economic policies (39, 40).

4 The one-diet-fits-all saga

Good nutrition is fundamental in sustaining a healthy lifestyle across all stages of human development (41). Preventing chronic diseases is crucial because life expectancy has increased, and living disease-free enhances the quality of the aging process (42–44). In the past, mothers

had an important role in feeding, and nourishment was delivered by moms' dietary approaches, which influenced the food environment and shaped our eating patterns within the family (45, 46). Family recipes, influenced by the geographic availability of food resources, transmit wisdom to the younger generations by guiding the consumption of essential foods and nutrients and cooking practices (food culture).

Maintaining good habits throughout life can contribute to one's overall health. It is worth noting that prior to industrialization, most individuals' primary cause of death was infectious diseases rather than nutrition-related chronic diseases (47). While there may be some overlap between undernutrition and overnutrition, human dietary habits have culturally shifted regarding the types, locations, and quantities of food we consume, which differs from the biological needs encoded in our genes. Following "mom's advice" has become increasingly difficult due to shifts in the food system, insufficient personalization of dietary recommendations, and the promotion of non-regional cuisines.

The convergence of multiple tendencies may have endorsed the one-diet-fits-all regimen. First, globalization of the food supply facilitated the importation of highly or ultra-processed products into underdeveloped countries or their targeted marketing to underprivileged sectors, chiefly because of their affordability and widespread availability (48). Globalization has increased the likelihood of societies to prefer "globalized" food that may differ in quality from locally produced foods. Secondly, several health organizations in the United States reached a consensus on the recommended guidelines for essential nutrients such as carbohydrates, proteins, fats, vitamins, antioxidants, minerals, and fiber to prevent atherosclerosis, cancer, diabetes, and obesity (49). As previously stated, the need to reverse the growing prevalence of chronic diseases led to the unification of standard dietary guidelines for the clinical management of chronic-diseased patients without considering genetic or cultural factors, endorsing a one-diet-fits-all approach (50). Thirdly, the recommendation to adopt traditional diets such as the "Mediterranean diet," "Japanese diet," or "Nordic diet" (51–53) to lower the onset of chronic disease outside their region of origin overlooks the equally beneficial nutritional and economic advantages of local diets (54). All things considered, one type of local diet is not healthier or better than any other, and trying to adapt specific diets to resemble, for example, the Mediterranean diet as a universal diet to treat chronic disease (55, 56) is against the required food system, food culture, or a personalized nutrition approach.

Furthermore, when incorporated into national clinical practice guidelines, these exotic dietary programs may not be practical for most people or suitable for their genetic composition (57). Furthermore, parallel to the criticism against the one-diet-fits-all trend, there is a need for tailored "normal" cut-off values of health indicators regarding body mass index, glucose levels, liver function tests, or fat percentage to account for the variability in human body measurements. Thus, in a broader sense, the personalized nutrition movement is an opportunity to provide real-life population-based or regionalized recommendations for societies seeking to prevent chronic diseases based on their characteristics.

5 Shaping the basis of personalized nutrition in Mexico

Research has revealed that human populations possess genetic variations that enable them to withstand better extreme climates, high altitudes, infectious diseases, or varying levels of nutrient availability. As mentioned before, these adaptations are specific to local environments (23). However, there is limited knowledge regarding the nutritional adaptations of Latin American populations, including Mexico, and the mechanisms behind their development. Thus, our research has focused on developing a comprehensive biocultural model of genome-based nutrition integrating the individual's or population's genetic background with their food culture to create personalized nutritional recommendations or interventions (58, 59).

The genetic history of Mexico traces back to the arrival of the Amerindians or First Nations People, who exploited the rich ambient biodiversity of the region. The early events after the Spanish conquest involved the introduction of European and African genes, which now form the mixed genetic pool of the present population. Additionally, there was an exchange of Old and New World foods, leading to the development of a distinct regional food culture heritage and subsequent food preferences. However, before European colonialism, the Amerindian tribes inhabited distinct ecological regions. Aridoamerica, located in the northern part of Mexico, was the land of nomadic hunter-gatherers, and Mesoamerica, spanning from central Mexico to part of Nicaragua, was home to sedentary/agricultural ethnic groups (60). Recent studies reveal that the Mexican Indigenous people exhibit signatures of local adaptations resulting from their specific dietary and cultural practices. These adaptations have influenced their biological networks, substrate metabolism, and disease susceptibility (61, 62).

Figure 1 illustrates the transformative changes in Mexico's genetics and food culture throughout the last five centuries. These transitions have played a crucial role in shaping dietary preferences and impacting the population's vulnerability to infectious and chronic diseases. The period of Spanish rule led to the admixture of the European, Amerindian, and African lineages with a gradient shift in the ancestral components from north to south (63). This feature translates into the fact that North Mexicans with mixed ancestry could benefit from tailored recommendations based on their higher European heritage, contrasting with individuals from the South with Amerindian ancestry, as discussed later (64–66).

The Mesoamerican food system constitutes the foundation of the traditional Mexican diet, primarily consisting of plant-based foods such as maize, beans, chili, squash, tomato, chia, pumpkin seeds, amaranth, prickly pears, and cacao. Research has shown that this diet is associated with a reduced risk of metabolic disorders and is nutritionally well-balanced and culturally acceptable (67). Nevertheless, the Mexican population is immersed in an obesogenic environment, consuming a hepatopathogenic diet that causes dyslipidemias, insulin resistance, steatosis, and metabolic-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD) (65, 68–70). As shown in Figure 1, the transition from a state of evolutionary concordance to a mismatch between the nature of our ancestral genes and the environment is part of the current health problem. Based on this evidence, a comprehensive approach was developed to address the prevalent health issues within the Mexican population.

6 The Genomex diet: benefits and challenges

The evidence mentioned above is substantial enough to establish a framework for implementing a public health policy that considers

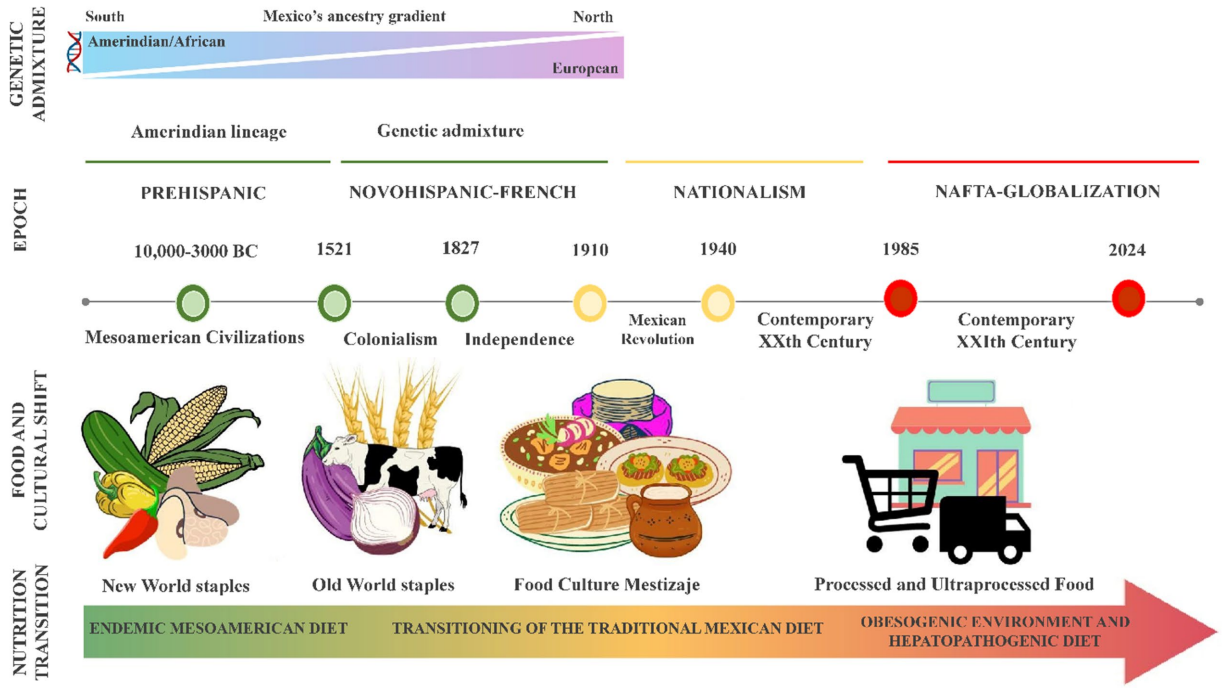


FIGURE 1
Genetic and alimentary evolution of the Mexican population. Mexico's population genetics and food culture have undergone significant shifts with each economic/historical period (herein marked illustratively), shaping dietary preferences and influencing susceptibility to infectious and chronic diseases. This timeline highlights the shift from harmony with the environment to a growing mismatch between genes and the modern diet. The endemic Mesoamerican diet, rich in plant-based staples like maize, beans, and chili, was historically linked to lower metabolic risk factors. However, this has been replaced by a highly palatable, energy-dense diet dominated by processed and ultra-processed foods, poor nutritional quality, and promoting metabolic diseases. In this obesogenic environment, Mexico faces an obesity epidemic among its young and adult population, fueled by dietary patterns that result in metabolic disturbances like dyslipidemia, insulin resistance, diabetes, and metabolic-associated steatotic liver disease (MASLD). NAFTA, North American Free Trade.

the balance between ancestral genes and our food options. Paradoxically, the battle against the prevailing Westernized diet and its detrimental effects is fought by advocating for the "gold standard" Mediterranean diet as if it were *the silver bullet*. Almost all major clinical practice guidelines in Mexico, endorsed by the medical associations, recommend adopting the Mediterranean diet to prevent chronic diseases and overlook the fundamental national dietary recommendations (71). With this attitude, we fail to seize the valuable opportunity to offer nutritious, environmentally friendly, and sustainable food choices to a population immersed in an obesity epidemic and with financial constraints that prevent them from purchasing expensive non-local ingredients regularly.

Even though the traditional Mediterranean and Mexican diets are culturally inherited eating patterns that consist of distinct recipes made using locally sourced ingredients and are highly valued in each society, they are not head-to-head comparable (72). Established initially on earlier agricultural and rural models, the Mediterranean diet reflects the illustrious history of culinary and cultural exchanges that have occurred in the countries surrounding the Mediterranean Basin for millennia (73). This diet contains wheat-based (bread, pasta, or couscous) foods, a wide range of plant-based foods, and virgin olive oil as the primary source of fat. It also includes a moderate intake of red wine, seafood, fermented dairy products, poultry, and eggs and a low consumption of red and processed meat and sweets (74, 75). On the contrary, the traditional Mexican dietary regimen predominantly comprises Mesoamerican staples cultivated in this area. These include maize and its by-products, such as "tortillas," legumes (beans), high amounts of vegetables (e.g., dark-green leafy vegetables named "quelites," squash, tomato, chile, and prickly pears), and plant-based fats obtained from avocado, chia, pumpkin seeds, and amaranth. Complementary foods include fruits, beverages (e.g., "cacao," "pulque," and "tesgüino" fermented beverages), fish and seafood, small wild animal meat, herbs, and condiments (76). Therefore, it is worth noting that Mexico can potentially promote the components of the Mesoamerican diet and the traditional postcolonial dishes as healthy dietary options (67), whereas the Mediterranean diet is not entirely feasible.

Furthermore, the traditional Mexican diet received the prestigious recognition of the Intangible Cultural Heritage in 2010 (77). This distinction is valuable for educating the public about this cultural legacy's significance rather than merely being displayed on a wall. The healthcare community frequently stigmatizes the typical Mexican diet as being high in fat and contributing to weight gain. However, the root issue lies in the overconsumption of modern, non-native, calorie-dense processed foods and the lack of nutrition education.

Genomic analyses conducted on Mexicans have provided valuable insights into the influence of ancestry on the population's health (62, 66, 78) and the potential consequences of not implementing preventive measures to mitigate disease risks. In light of the significant rise in unhealthy eating habits in Mexico and the growing prevalence of obesity and associated co-morbidities, we set forth to develop a

strategy to prevent and address the metabolic alterations driven by the gen-environment mismatch.

To this end, the next step was to create a genome-based nutrition program aligning with the Mexican population's genetic background and food culture, denoted as the Genomex diet. Despite its trendy name, the diet is not meant to be a fad diet because it adheres to the principles of a correct diet, and it seeks to promote the consumption of nutritious staples that are culturally accepted while considering regional genetic and culinary variations. The Genomex diet combines the nutritional advantages of traditional local dishes, which contain Mesoamerican staple foods rich in nutrients and bioactive components that are prepared in a healthy manner and align with the Mexican population's functional nutrigenetic and nutrigenomic characteristics (58).

Table 1 provides an overview of the genetic polymorphisms and their evolutionary mismatch, which the Genomex diet intends to counteract, highlighting the adaptive alleles that become "risk alleles" due to unhealthy eating habits. For example, the high frequency of the *MTHFR* 677 T allele among the Amerindian population is consistent with their historical dietary habits of consuming folate-rich leafy greens (64). In addition, admixed subpopulations with a higher percentage of Amerindian ancestry are more likely to carry the 677 T allele than those with European ancestry, predominantly carriers of the 677C allele. Furthermore, a correlation has been observed between the 677 T risk allele and the presence of liver steatosis and other co-morbidities (79). Therefore, encouraging the inclusion of sufficient quantities of green leafy foods in a balanced diet aligns with the genetic background of most individuals while preserving the traditional intake of these foods (80) and minimizing the risk of chronic disease.

Another interesting example is the highly prevalent *TAS2R38* AVV haplotype that encodes the non-taster phenotype (81). This genetic trait aligns with the ability to tolerate bitter taste tolerances and the abundance of endemic bitter leafy vegetables mentioned before. Conversely, this haplotype is a risk factor for a higher consumption of alcohol among the Mexican population in modern times, which culturally has revolutionized over the centuries.

Similarly, when studying lipid-transporter genes, it is important to consider the differential allele distribution, within the admixed population (Table 1) (64). For example, the *ApoE* e2 and e4 alleles (65, 69), have been associated with hyperglyceridemia and hypercholesteremia, respectively. Thus, consuming chia, pumpkin seeds, and amaranth can offer a plant-based supply of mono-unsaturated fatty acids (MUFA) and poly-unsaturated fatty acids (PUFA) while inhibiting anti-inflammatory cell-signaling pathways that are frequently triggered in various chronic diseases (58). In line with these features, a recent study assessed the impact of specific nutrigenetic recommendations for 11 genetic variants associated with dyslipidemias, reducing blood lipids and low-grade inflammation in adults with excess weight (82).

Regarding carbohydrate metabolism, most Mexicans have inherited the lactose-intolerant trait, which is consistent with dairy animals not being part of the Mesoamerican ambient until after

TABLE 1 Gene polymorphisms and their evolutionary mismatch among the admixed Mexican population.

Gene/allele	Lineage of allele predominance	Mesoamerican food culture	Evolutionary mismatch/disease
High prevalence of MTHFR 677 T risk allele and TAS2R38/AVV bitter non-tasters			
MTHFR/T (rs1801133)	Amerindian	High consumption of folate-rich bitter dark leafy greens	Low consumption of folate-rich foods
TAS2R38/AVV	Amerindian	Null consumption of distilled alcoholic beverages	High consumption of alcohol
Differential prevalence of risk alleles for dyslipidemias			
CD36/A (rs1761667)	Amerindian	A plant-based diet, high in complex carbohydrates, rich in MUFA and PUFA, and low in animal fat. Staple foods: maize, beans, chili, squash, tomato, chia, pumpkin seeds, amaranth, prickly pears, and cacao. No animal protein from cattle, pork, goat, or sheep.	High consumption of fatty-processed food
APOE/e2	European		High risk of hypertriglyceridemia and type II diabetes
APOE/e4	Amerindian		High risk of hypercholesterolemia
ABCA1/C (rs9282541)	Amerindian		High risk of hypoalphalipoproteinemia
Carbohydrate metabolism			
LCT/T-Lactase non-persistence (rs4988235)	Amerindian	No dairy products	High risk of hypertriglyceridemia
AMYA1 copy number	Amerindian/European	High consumption of complex carbohydrates: maize and beans	High consumption of simple sugars
High prevalence of Taq A1 risk allele and addictive behaviors			
DRD2/ANKK1/A1 (rs1800497)	Amerindian	Endemic food is high in complex carbohydrates, low in fats and sodium	Hepatopathogenic diet containing high calories, simple sugars, saturated fats, and sodium

MTHFR, Methylenetetrahydrofolate reductase; TAS2R38, Taste 2 Receptor Member 38; CD36, cluster of differentiation 36; APOE, Apolipoprotein E; ABCA1, Member 1 of the ATP-binding cassette transporter; LCT, lactase; DRD2/ANKK1, dopamine receptor D2/ ankyrin repeat and kinase-domain containing 1.

Spanish colonialization. Likewise, regulating the intake of complex carbohydrates from maize-based foods and legumes supports glucose homeostasis through enhanced insulin sensitivity based on the population's average number of six *AMY1* copies. Also, the starch-resistant properties of these foods contribute to maintaining a healthy gut microbiota (64). Finally, the high prevalence of the DRD2/ANKK1 A1 allele has been associated with unhealthy food choices among the population (83). In conjunction, this information can help tailor nutrigenetic recommendations to address the prevalent dyslipidemias among Mexicans based on their unique genetic profiles.

Recently, the Genomex diet, containing most of the food staples of Mexico, was tested during a 6-month intervention nutrigenetic study, normalizing the anthropometric and biochemical profile of the study group (84) and improving auto-efficacy to maintain adherence to the nutritional plan (85). One significant effect was the 50% reduction of the HOMA-IR value after 3 months, which can be attributed to the components of the above dietary pattern. These results suggest that adherence to the Genomex diet decreases the risk of nutrition-related chronic diseases based on the millenary genetic adaptations that the Mexicans have inherited. Finally, an important feature of the Genomex diet is that the population culturally recognizes the recipes used to support this dietary program. Thus, nutritional recommendations based on the genetic profile of the population can be endorsed by "mom's advice" by asking family members about the recipes of the food dishes comprising the staple indigenous foods.

In the same line of thought, studies carried out in East Asian populations where wild rice or other millet were consumed before their cultivation have revealed biological adaptations against the detrimental side effects of consuming high amounts of polished rise compared to other Asian populations (86). Thus, maintaining legendary dietary patterns may be the answer to preventing the risk of chronic diseases while conserving the local culinary culture.

Developing the genome-based nutrition strategy in Mexico has been challenging. The road to incorporating the principles of the Genomex diet into the Mexican clinical practice guidelines has faced skepticism from medical and nutrition associations. Another challenge is the food industry's marketing consistently advocating for high-calorie ultra-processed foods and external dietary alternatives that impede food sovereignty and are not aligned with the Mexican population's genetic makeup and food traditions. A marked rise in the consumption of ultra-processed foods in Mexico has been reported in the last three decades. Concurrently, there has been a decrease in the acquisition of unprocessed or minimally processed foods and processed culinary ingredients (87). Reversing this situation will require training and education in Genomic Nutrition to adequately prepare frontline clinicians, nutritionists, and other medical specialists to fight against these external factors and promote better eating patterns (88–92). In addition, research in complementary fields, including population genetics, food anthropology, social sciences, and evolutionary medicine studies, is crucial to provide an integrated framework defining the biological and cultural basis of a personalized or regionalized nutrition approach.

7 Conclusion

Will there be a time for the era of one-diet-fits-all to come to an end? We believe that the principles of the Genomex diet can aid in recovering and eating the traditional Mexican dietary ingredients while providing the nutrients that keep our adaptive genes healthy. Our mission is to educate health professionals and the general population on how to keep themselves nutritionally healthy, given our genetic legacy, regional food biodiversity, and food culture compatible with the Mexican population. Nonetheless, extrapolating the results throughout Mexico will require adjustments due to intraregional genetic and cultural differences, as mentioned before. In addition, implementing this approach in other Latin American countries will also require analyzing the regional prevalence of chronic diseases, prevailing risk alleles/traits, food culture, and other lifestyle factors (93–97) despite sharing a similar historical background of colonialism and globalization as Mexico. In this "weakness" lies the strength of eluding the one-diet-fits-all scheme and avoiding foreign alternatives while promoting entrepreneurism toward national eco-friendly agricultural and food industries aiming to contribute toward the world's Sustainable Development Goals (98). Further research, training, teaching, and advocacy activities are required to advance toward a compelling personalized nutrition approach in Mexico to reclaim the benefits of a healthy diet.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SR: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. LC-M: Investigation, Writing – review & editing, Visualization. LL-M: Investigation, Writing – review & editing, Visualization.

Funding

The author(s) declare no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

To the members of the Nutrigenetic team for their dedication and willingness to bring alive the Genomex Diet project.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Ordovas JM, Corella D. Nutritional genomics. *Annu Rev Genomics Hum Genet*. (2004) 5:71–118. doi: 10.1146/annurev.genom.5.061903.180008

2. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French T-AC, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *J Nutrigenet Nutrigenomics*. (2011) 4:69–89. doi: 10.1159/000327772

3. Mutch DM, Wahli W, Williamson G. Nutrigenomics and nutrigenetics: the emerging faces of nutrition. *FASEB J*. (2005) 19:1602–16. doi: 10.1096/fj.05-3911rev

4. Kussmann M, Fay LB. Nutrigenomics and personalized nutrition: science and concept. *Pers Med*. (2008) 5:447–55. doi: 10.2217/17410541.5.5.447

5. El-Sohemy A. Nutrigenetics. *Forum Nutr*. (2007) 60:25–30. doi: 10.1159/000107064

6. Simopoulos AP. Nutrigenetics/nutrigenomics. *Annu Rev Public Health*. (2010) 31:53–68. doi: 10.1146/annurev.publhealth.031809.130844

7. Feinberg AP. The key role of epigenetics in human disease prevention and mitigation. *N Engl J Med*. (2018) 378:1323–34. doi: 10.1056/NEJMra1402513

8. Huo M, Zhang J, Huang W, Wang Y. Interplay among metabolism, epigenetic modifications, and gene expression in Cancer. *Front Cell Dev Biol*. (2021) 9:793428. doi: 10.3389/fcell.2021.793428

9. Wang W-L, Xu S-Y, Ren Z-G, Tao L, Jiang J-W, Zheng S-S. Application of metagenomics in the human gut microbiome. *World J Gastroenterol*. (2015) 21:803–14. doi: 10.3748/wjg.v21.i3.803

10. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med*. (2016) 22:1079–89. doi: 10.1038/nm.4185

11. Shyam S, Lee KX, Tan ASW, Khoo TA, Harikrishnan S, Lalani SA, et al. Effect of personalized nutrition on dietary, physical activity, and health outcomes: a systematic review of randomized trials. *Nutrients*. (2022) 14:4104. doi: 10.3390/nu14194104

12. Van Karnebeek CDM, Wortmann SB, Tarailo-Graovac M, Langeveld M, Ferreira CR, Van De Kamp JM, et al. The role of the clinician in the multi-omics era: are you ready? *J Inherit Metab Dis*. (2018) 41:571–82. doi: 10.1007/s10545-017-0128-1

13. Bloss CS, Jeste DV, Schork NJ. Genomics for disease treatment and prevention. *Psychiatr Clin North Am*. (2011) 34:147–66. doi: 10.1016/j.psc.2010.11.005

14. Waldman SA, Terzic A. Healthcare evolves from reactive to proactive. *Clin Pharmacol Ther*. (2019) 105:10–3. doi: 10.1002/cpt.1295

15. Derecho CMP. Regulations and ethical considerations in nutrigenomics research In: G Dable-Tupas and C Egbuna, editors. *Role of nutrigenomics in modern-day healthcare and drug discovery. Drug discovery update*. Netherlands: Elsevier (2023). 557–65.

16. Camp KM, Trujillo E. Position of the academy of nutrition and dietetics: nutritional genomics. *J Acad Nutr Diet*. (2014) 114:299–312. doi: 10.1016/j.jand.2013.12.001

17. Sales NMR, Pelegrini PB, Goersch MC. Nutrigenomics: definitions and advances of this new science. *J Nutr Metab*. (2014) 2014:202759:1–6. doi: 10.1155/2014/202759

18. Wang F, Zheng J, Cheng J, Zou H, Li M, Deng B, et al. Personalized nutrition: a review of genotype-based nutritional supplementation. *Front Nutr*. (2022) 9:992986. doi: 10.3389/fnut.2022.992986

19. Soloway PD. Gene nutrient interactions and evolution. *Nutr Rev*. (2006) 64:S52–4. doi: 10.1301/nr.2006.may.s52-s54

20. Jew S, AbuMweis SS, Jones PJH. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food*. (2009) 12:925–34. doi: 10.1089/jmf.2008.0268

21. Alt KW, Al-Ahmad A, Woelber JP. Nutrition and health in human evolution-past to present. *Nutrients*. (2022) 14:3594. doi: 10.3390/nu14173594

22. Münster A, Knipper C, Oelze VM, Nicklisch N, Stecher M, Schlenker B, et al. 4000 years of human dietary evolution in Central Germany, from the first farmers to the first elites. *PLoS One*. (2018) 13:e0194862. doi: 10.1371/journal.pone.0194862

23. Rees JS, Castellano S, Andrés AM. The genomics of human local adaptation. *Trends Genet*. (2020) 36:415–28. doi: 10.1016/j.tig.2020.03.006

24. Benton ML, Abraham A, LaBella AL, Abbot P, Rokas A, Capra JA. The influence of evolutionary history on human health and disease. *Nat Rev Genet*. (2021) 22:269–83. doi: 10.1038/s41576-020-00305-9

25. Kennedy ET. The global face of nutrition: what can governments and industry do? *J Nutr*. (2005) 135:913–5. doi: 10.1093/jn/135.4.913

26. Corbett S, Courtiol A, Lummaa V, Moorad J, Stearns S. The transition to modernity and chronic disease: mismatch and natural selection. *Nat Rev Genet*. (2018) 19:419–30. doi: 10.1038/s41576-018-0012-3

27. Sproesser G, Ruby MB, Arbit N, Akotia CS, Alvarenga Dos S, Bhangaokar R, et al. Understanding traditional and modern eating: the TEP10 framework. *BMC Public Health*. (2019) 19:1606. doi: 10.1186/s12889-019-7844-4

28. Templin T, Hashiguchi TCO, Thomson B, Dieleman J, Bendavid E. The overweight and obesity transition from the wealthy to the poor in low- and middle-income countries: a survey of household data from 103 countries. *PLoS Med*. (2019) 16:e1002968. doi: 10.1371/journal.pmed.1002968

29. Popkin BM, Ng SW. The nutrition transition to a stage of high obesity and noncommunicable disease prevalence dominated by ultra-processed foods is not inevitable. *Obes Rev*. (2022) 23:e13366. doi: 10.1111/obr.13366

30. Olstad DL, Nejatinamini S, Blanchet R, Moubarac J-C, Polsky J, Vanderlee L, et al. Protecting traditional cultural food practices: trends in diet quality and intake of ultra-processed foods by indigenous status and race/ethnicity among a nationally representative sample of adults in Canada. *SSM Popul Health*. (2023) 24:101496. doi: 10.1016/j.ssmph.2023.101496

31. Trichopoulou A, Soukara S, Vasilopoulou E. Traditional foods: a science and society perspective. *Trends Food Sci Technol*. (2007) 18:420–7. doi: 10.1016/j.tifs.2007.03.007

32. Brennan RO, Mulligan WC. *Nutrigenetics: new concepts for relieving hypoglycemia*. New York, NY: Evans. (1975). Available at: https://www.ncbi.nlm.nih.gov/nlmcatalog?cmd=PureSearch&term=7603392%5Bnlmid%5D (Accessed November 18, 2023).

33. Bernstein LE, Rohr F, Helm JR *Nutrition management of inherited metabolic diseases*. Lessons from Metabolic University | Springer: Cham. Available at: https://link.springer.com/book/10.1007/978-3-030-94510-7 (Accessed November 18, 2023).

34. Davies K. The era of genomic medicine. *Clin Med (Lond)*. (2013) 13:594–601. doi: 10.7861/clinmedicine.13-6-594

35. Auffray C, Griffin JL, Khoury MJ, Lupski JR, Schwab M. Ten years of genome medicine. *Genome Med*. (2019) 11:7. doi: 10.1186/s13073-019-0618-x

36. Proctor LM, Creasy HH, Fettweis JM, Lloyd-Price J, Mahurkar A, Zhou W, et al. The integrative human microbiome project. *Nature*. (2019) 569:641–8. doi: 10.1038/s41586-019-1238-8

37. Gurdasani D, Barroso I, Zeggini E, Sandhu MS. Genomics of disease risk in globally diverse populations. *Nat Rev Genet*. (2019) 20:520–35. doi: 10.1038/s41576-019-0144-0

38. Dries DL. Genetic ancestry, population admixture, and the genetic epidemiology of complex disease. *Circ Cardiovasc Genet*. (2009) 2:540–3. doi: 10.1161/CIRCGENETICS.109.922898

39. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Food and Nutrition Board; Food Forum. *Challenges and opportunities for precision and personalized nutrition: Proceedings of a workshop—In brief*. AE Callahan, editor. Washington (DC): National Academies Press (US). (2021). Available at: http://www.ncbi.nlm.nih.gov/books/NBK575794/ (Accessed November 18, 2023).

40. Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. *The. BMJ*. (2018) 361:bmj.k2173. doi: 10.1136/bmj.k2173

41. Kimokoti RW, Millen BE. Nutrition for the prevention of chronic diseases. *Med Clin North Am*. (2016) 100:1185–98. doi: 10.1016/j.mcna.2016.06.003

42. Willett WC, Koplan JP, Nugent R, Dusenbury C, Puska P, Gaziano TA. "Prevention of chronic disease by means of diet and lifestyle changes.," In: DT Jamison, JG Breman, AR Measham, G Alleyne, M Claeson and DB Evanset al. editors. *Disease control priorities in developing countries*. Washington (DC): The International Bank for Reconstruction and Development / The World Bank (2006) Available at: http://www.ncbi.nlm.nih.gov/books/NBK11795/ (Accessed November 18, 2023).

43. Gropper SS. The role of nutrition in chronic disease. *Nutrients*. (2023) 15:664. doi: 10.3390/nu15030664

44. Li Y, Schoufour J, Wang DD, Dhana K, Pan A, Liu X, et al. Healthy lifestyle and life expectancy free of cancer, cardiovascular disease, and type 2 diabetes: prospective cohort study. *BMJ*. (2020) 368:l6669. doi: 10.1136/bmj.l6669

45. Dietert RR. Dietary approaches from moms, farms, and nature to overcome chronic diseases and the Pharmacracy. *Nutrients*. (2023) 15:3965. doi: 10.3390/nu15183965

46. Laila A, Leme AC, Hou S, Ma DWL, Haines J. Perceived challenges and strategies to achieve Canada's food guide recommendation to "cook more often": findings from parents of young children. *Appetite*. (2023) 182:106413. doi: 10.1016/j.appet.2022.106413

47. Shaw-Taylor L. An introduction to the history of infectious diseases, epidemics and the early phases of the long-run decline in mortality. *Econ Hist Rev*. (2020) 73:E1–E19. doi: 10.1111/ehr.13019

48. Barquera S. Intersection of public health, nutrition, and mental health: challenges to progress. *Salud Ment*. (2022) 45:211–2. doi: 10.17711/sm.0185-3325.2022.027

49. Deckelbaum RJ, Fisher EA, Winston M, Kumanyika S, Lauer RM, Pi-Sunyer FX, et al. Summary of a scientific conference on preventive nutrition: pediatrics to geriatrics. *Circulation*. (1999) 100:450–6. doi: 10.1161/01.CIR.100.4.450

50. Tanne JH. One diet fits all. *BMJ*. (1999) 318:1646. doi: 10.1136/bmj.318.7199.1646d

51. D'Innocenzo S, Biagi C, Lanari M. Obesity and the Mediterranean diet: a review of evidence of the role and sustainability of the Mediterranean diet. *Nutrients*. (2019) 11:1306. doi: 10.3390/nu11061306

52. Abe S, Zhang S, Tomata Y, Tsuduki T, Sugawara Y, Tsuji I. Japanese diet and survival time: the Ohsaki cohort 1994 study. *Clin Nutr*. (2020) 39:298–303. doi: 10.1016/j.clnu.2019.02.010

53. Olsen A, Egeberg R, Halkjær J, Christensen J, Overvad K, Tjønneland A. Healthy aspects of the Nordic diet are related to lower total mortality. *J Nutr*. (2011) 141:639–44. doi: 10.3945/jn.110.131375

54. Burt KG, College L. The whiteness of the Mediterranean diet: a historical, sociopolitical, and dietary analysis using critical race theory. *J Crit Diet*. (2021) 5:41–52. doi: 10.32920/cd.v5i2.1329

55. Phokaewvarangkul O, Kantachadvanich N, Buranasrikul V, Phoumindr A, Phumphid S, Jagota P, et al. From evidence to the dish: a viewpoint of implementing a Thai-style Mediterranean diet for Parkinson's disease. *J Mov Disord*. (2023) 16:279–84. doi: 10.14802/jmd.23021

56. Figueroa C, Echeverría G, Villarreal G, Martínez X, Ferreccio C, Rigotti A. Introducing plant-based Mediterranean diet as a lifestyle medicine approach in Latin America: opportunities within the Chilean context. *Front Nutr*. (2021) 8:680452. doi: 10.3389/fnut.2021.680452

57. Ojeda-Granados C, Roman S. Mediterranean diet or genome-based nutrition diets in Latin America's clinical practice guidelines for managing chronic liver diseases? *Ann Hepatol*. (2021) 20:100291. doi: 10.1016/j.aohep.2020.100291

58. Roman S, Ojeda-Granados C, Ramos-Lopez O, Panduro A. Genome-based nutrition: an intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis. *World J Gastroenterol*. (2015) 21:3449–61. doi: 10.3748/wjg.v21.i12.3449

59. Panduro A, Roman S. Personalized medicine in Latin America. *Pers Med*. (2020) 17:339–43. doi: 10.2217/pme-2020-0049

60. García-Ortiz H, Barajas-Olmos F, Contreras-Cubas C, Cid-Soto MÁ, Córdova EJ, Centeno-Cruz F, et al. The genomic landscape of Mexican indigenous populations brings insights into the peopling of the Americas. *Nat Commun*. (2021) 12:5942. doi: 10.1038/s41467-021-26188-w

61. Ojeda-Granados C, Abondio P, Setti A, Sarno S, Gnecchi-Ruscone GA, González-Orozco E, et al. Dietary, cultural, and pathogens-related selective pressures shaped differential adaptive evolution among native Mexican populations. *Mol Biol Evol*. (2021) 39:msab290. doi: 10.1093/molbev/msab290

62. García-Ortiz H, Barajas-Olmos F, Contreras-Cubas C, Reynolds AW, Flores-Huacuja M, Snow M, et al. Unraveling signatures of local adaptation among indigenous groups from Mexico. *Genes*. (2022) 13:2251. doi: 10.3390/genes13122251

63. Ongaro L, Scliar MO, Flores R, Raveane A, Marnetto D, Sarno S, et al. The genomic impact of European colonization of the Americas. *Curr Biol*. (2019) 29:3974–3986.e4. doi: 10.1016/j.cub.2019.09.076

64. Ojeda-Granados C, Panduro A, Gonzalez-Aldaco K, Sepulveda-Villegas M, Rivera-Iñiguez I, Roman S. Tailoring nutritional advice for Mexicans based on prevalence profiles of diet-related adaptive gene polymorphisms. *J Pers Med*. (2017) 7:16. doi: 10.3390/jpm7040016

65. Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K, Panduro A. Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among native American and mestizo Mexicans. *World J Hepatol*. (2022) 14:1408–20. doi: 10.4254/wjh.v14.i7.1408

66. Moreno-Estrada A, Gignoux CR, Fernández-López JC, Zakharia F, Sikora M, Contreras AV, et al. Human genetics. The genetics of Mexico recapitulates native American substructure and affects biomedical traits. *Science*. (2014) 344:1280–5. doi: 10.1126/science.1251688

67. Valerino-Perea S, Armstrong MEG, Papadaki A. Adherence to a traditional Mexican diet and non-communicable disease-related outcomes: secondary data analysis of the cross-sectional Mexican National Health and nutrition survey. *Br J Nutr*. (2022) 129:1266–79. doi: 10.1017/S0007114522002331

68. Sepulveda-Villegas M, Roman S, Rivera-Iñiguez I, Ojeda-Granados C, Gonzalez-Aldaco K, Torres-Reyes LA, et al. High prevalence of nonalcoholic steatohepatitis and abnormal liver stiffness in a young and obese Mexican population. *PLoS One*. (2019) 14:e0208926. doi: 10.1371/journal.pone.0208926

69. Gonzalez-Aldaco K, Roman S, Torres-Reyes LA, Panduro A. Association of Apolipoprotein e2 allele with insulin resistance and risk of type 2 diabetes mellitus among an admixed population of Mexico. *Diabetes Metab Syndr Obes*. (2020) 13:3527–34. doi: 10.2147/DMSO.S268329

70. Moreno-Altamirano L, García-García JJ, Salvatore P, Soto-Estrada G, Hernández-Montoya D. Metabolic syndrome: changes in mediterranean and mesoamerican diet due to socioeconomic factors in Mexico and Italy. *Mediterr J Nutr Metab*. (2017) 10:49–59. doi: 10.3233/MNM-16124

71. SSA, INSP, GISAMAC, UNICEF. Guias alimentarias saludables y sostenibles para la población mexicana 2023. Mexico. Available at: http://www.gob.mx/promosalud/articulos/que-son-las-guias-alimentarias?idiom=es (Accessed January 8, 2024).

72. Ojeda-Granados C, Barchitta M, La Rosa MC, La Mastra C, Roman S, Panduro A, et al. Evaluating dietary patterns in women from southern Italy and Western Mexico. *Nutrients*. (2022) 14:1603. doi: 10.3390/nu14081603

73. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr*. (2011) 14:2274–84. doi: 10.1017/S1368980011002515

74. Royo C, Soriano JM, Alvaro F. *Wheat: a crop in the bottom of the Mediterranean diet pyramid | IntechOpen*. (2017). Available at: https://www.intechopen.com/chapters/55480 (Accessed May 8, 2024).

75. Donini LM, Serra-Majem L, Bulló M, Gil Á, Salas-Salvadó J. The Mediterranean diet: culture, health and science. *Br J Nutr*. (2015) 113:S1–3. doi: 10.1017/S0007114515001087

76. Valerino-Perea S, Lara-Castor L, Armstrong MEG, Papadaki A. Definition of the traditional Mexican diet and its role in health: a systematic review. *Nutrients*. (2019) 11:2803. doi: 10.3390/nu11112803

77. UNESCO – Traditional Mexican cuisine – ancestral, ongoing community culture, the Michoacán paradigm. Available at: https://ich.unesco.org/en/RL/traditional-mexican-cuisine-ancestral-ongoing-community-culture-the-michoacan-paradigm-00400 (Accessed January 8, 2024).

78. Sohail M, Palma-Martínez MJ, Chong AY, Quinto-Cortés CD, Barberena-Jonas C, Medina-Muñoz SG, et al. Mexican biobank advances population and medical genomics of diverse ancestries. *Nature*. (2023) 622:775–83. doi: 10.1038/s41586-023-06560-0

79. Raghubeer S, Matsha TE. Methylenetetrahydrofolate (MTHFR), the one-carbon cycle, and cardiovascular risks. *Nutrients*. (2021) 13:4562. doi: 10.3390/nu13124562

80. Díaz-José J, Guevara-Hernández F, Morales-Ríos V, López-Ayala J. Traditional knowledge of edible wild plants used by indigenous communities in Zongolica, Mexico. *Ecol Food Nutr*. (2019) 58:511–26. doi: 10.1080/03670244.2019.1604340

81. Panduro A, Rivera-Iñiguez I, Ramos-Lopez O. Roman S. Chapter 50 – genes and alcoholism: taste, addiction, and metabolism In: VR Preedy, editor. *Neuroscience of alcohol*. Academic Press (2019). 483–91.

82. Pérez-Beltrán YE, González-Becerra K, Rivera-Iñiguez I, Martínez-López E, Ramos-Lopez O, Alcaraz-Mejía M, et al. A Nutrigenetic strategy for reducing blood lipids and low-grade inflammation in adults with obesity and overweight. *Nutrients*. (2023) 15:4324. doi: 10.3390/nu15204324

83. Rivera-Iñiguez I, Panduro A, Ramos-Lopez O, Villaseñor-Bayardo SJ, Roman S. DRD2/ANKK1 TaqI A1 polymorphism associates with overconsumption of unhealthy foods and biochemical abnormalities in a Mexican population. *Eat Weight Disord*. (2019) 24:835–44. doi: 10.1007/s40519-018-0596-9

84. Ojeda-Granados C, Panduro A, Rivera-Iñiguez I, Sepúlveda-Villegas M, Roman S. A regionalized genome-based Mexican diet improves anthropometric and metabolic parameters in subjects at risk for obesity-related chronic diseases. *Nutrients*. (2020) 12:645. doi: 10.3390/nu12030645

85. Rivera-Iñiguez I, Panduro A, Villaseñor-Bayardo SJ, Sepulveda-Villegas M, Ojeda-Granados C, Roman S. Influence of a Nutrigenetic intervention on self-efficacy, emotions, and rewarding behaviors in unhealthy eating among Mexicans: an exploratory pilot study. *Nutrients*. (2022) 14:213. doi: 10.3390/nu14010213

86. Landini A, Yu S, Gnecchi-Ruscone GA, Abondio P, Ojeda-Granados C, Sarno S, et al. Genomic adaptations to cereal-based diets contribute to mitigate metabolic risk in some human populations of east Asian ancestry. *Evol Appl*. (2020) 14:297–313. doi: 10.1111/eva.13090

87. Marrón-Ponce JA, Tolentino-Mayo L, Hernández-F M, Batis C. Trends in ultra-processed food purchases from 1984 to 2016 in Mexican households. *Nutrients*. (2018) 11:45. doi: 10.3390/nu11010045

88. Roman S, Panduro A. Genomic medicine in gastroenterology: a new approach or a new specialty? *World J Gastroenterol*. (2015) 21:8227–37. doi: 10.3748/wjg.v21.i27.8227

89. Roman S. Genome-based nutritional strategies to prevent chronic liver disease. *Ann Hepatol*. (2019) 18:537–8. doi: 10.1016/j.aohep.2019.05.005

90. Panduro A, Roman S. Advancements in genomic medicine and the need for updated regional clinical practice guidelines in the field of hepatology. *Ann Hepatol*. (2020) 19:1–2. doi: 10.1016/j.aohep.2019.12.002

91. Roman S, Ramos-Lopez O, Panduro A. Genomic medicine in hepatology: towards personalized medicine in obesity and chronic liver disease. *Ann Hepatol*. (2023) 28:100875. doi: 10.1016/j.aohep.2022.100875

92. Panduro A, Roman S, Mariscal-Martinez IM, Jose-Abrego A, Gonzalez-Aldaco K, Ojeda-Granados C, et al. Personalized medicine and nutrition in hepatology for preventing chronic liver disease in Mexico. *Front Nutr*. (2024) 11:1379364. doi: 10.3389/fnut.2024.1379364

93. Elena R-IM, Gabriela G-D, Arnulfo G-C, Enrique CA. Studying the gut microbiome of Latin America and Hispanic/Latino populations. Insight into obesity and diabetes: systematic review. *Curr Diabetes Rev*. (2019) 15:294–301. doi: 10.2174/1573399814666180730124817

94. Biruete A, Leal-Escobar G, Espinosa-Cuevas Á, Mojica L, Kistler BM. Dieta de la Milpa: a culturally-concordant plant-based dietary pattern for Hispanic/Latine people with chronic kidney disease. *Nutrients*. (2024) 16:574. doi: 10.3390/nu16050574

95. Ruz M, Solomons NW. A vision for nutritional research for the Latin American region. *Food Nutr Bull*. (2019) 40:14–25. doi: 10.1177/0379572119832780

96. Zambrano AK, Cadena-Ullauri S, Guevara-Ramírez P, Ruiz-Pozo VA, Tamayo-Trujillo R, Paz-Cruz E, et al. Genetic diet interactions of ACE: the increased hypertension predisposition in the Latin American population. *Front Nutr*. (2023) 10:1241017. doi: 10.3389/fnut.2023.1241017

97. Fernández-Rhodes L, Graff M, Buchanan VL, Justice AE, Highland HM, Guo X, et al. Ancestral diversity improves discovery and fine-mapping of genetic loci for anthropometric traits—the Hispanic/Latino anthropometry consortium. *HGG Adv*. (2022) 4:100149. doi: 10.1016/j.xhgg.2022.100149

98. THE 17 GOALS | sustainable development. Available at: https://sdgs.un.org/goals (Accessed November 20, 2023).

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 28 May 2024
DOI 10.3389/fnut.2024.1373578

OPEN ACCESS

EDITED BY
Omar Ramos-Lopez,
Universidad Autónoma de Baja California, Tijuana, Mexico

REVIEWED BY
Daniela Abigail Navarro,
Ariel University, Israel
Nanette Steinle,
United States Department of Veterans Affairs, United States

*CORRESPONDENCE
Sonia Roman
✉ soniamariaroman@hotmail.com

†These authors have contributed equally to this work and share first authorship

‡PRESENT ADDRESS
Ingrid Rivera-Iñiguez,
Department of Pediatrics, University of California San Diego School of Medicine, San Diego, CA, United States

RECEIVED 20 January 2024
ACCEPTED 18 April 2024
PUBLISHED 28 May 2024

CITATION
Rivera-Iñiguez I, Hunot-Alexander C, Sepúlveda-Villegas M, Campos-Medina L and Roman S (2024) Relationship between energy balance and reward system gene polymorphisms and appetitive traits in young Mexican subjects.
Front. Nutr. 11:1373578.
doi: 10.3389/fnut.2024.1373578

Relationship between energy balance and reward system gene polymorphisms and appetitive traits in young Mexican subjects

Ingrid Rivera-Iñiguez[1,2†‡], Claudia Hunot-Alexander[2†], Maricruz Sepúlveda-Villegas[1], Liliana Campos-Medina[1,3] and Sonia Roman[1*]

[1]Department of Genomic Medicine in Hepatology, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico, [2]Department of Human Reproduction Clinics, Infant Growth and Development, Institute of Human Nutrition, Health Sciences Center, Guadalajara, Jalisco, Mexico, [3]Doctoral Program in Molecular Biology in Medicine, Health Sciences Center, University of Guadalajara, Guadalajara, Jalisco, Mexico

Introduction: Appetitive traits are influenced by the interplay between genetic and environmental factors. This study aimed to explore the relationship between gene polymorphisms involved in the regulation of energy balance and food reward and appetitive traits in young Mexican subjects.

Methods: This cross-sectional study involved 118 university freshman undergraduates who completed the Adult Eating Behaviour Questionnaire for Spanish speakers (AEBQ-Esp) to assess their appetitive traits. A real-time PCR system was employed to determine gene polymorphisms involved in energy balance (*LEP* rs7799039, *MC4R* rs17782313, *FTO* rs9939609, *GHRL* rs696217), and reward system (*DRD2/ANKK1* Taq1A rs1800497 and *COMT* rs4680).

Results: The mean age of participants was 20.14 ± 3.95 years, 71.2% were women and their mean BMI was 23.52 ± 4.05 kg/m^2. *COMT* Met allele carriers presented a significantly higher "Emotional overeating" mean score than Val allele carriers (2.63 ± 0.70 vs. 2.23 ± 0.70, $p = 0.028$). The *MC4R* CC + CT genotype correlated positively with "Emotional overeating" (Phi = 0.308, $p = 0.01$). The *COMT* MetMet+MetVal genotype correlated with higher "Emotional overeating" ($r = 0.257$, $p = 0.028$; Phi = 0.249, $p = 0.033$). The protective genotype *FTO* TT correlated positively with "Emotional undereating" (Phi = 0.298, $p = 0.012$). Carriers of the risk genotype *MC4R* CC + CT presented a higher risk of "Emotional overeating" than TT carriers (OR = 2.4, 95% CI 1.3–4.8, $p = 0.034$). Carriers of the risk genotype *COMT* MetMet+MetVal (OR = 3.4, 95% CI 1.1–10.3, $p = 0.033$), were associated with a higher risk of "Emotional overeating" than ValVal carriers. The protective *FTO* genotype TT was associated with "Emotional undereating" (OR = 1.8, 95% CI 1.1–9.1, $p = 0.014$).

Discussion: The study found a relationship between the protective genotypes of *FTO* TT and "Emotional undereating" and risk genotypes of *COMT* Met/Met+Met/Val and *MC4R* CC + CT with "Emotional overeating." These genetic factors may increase weight gain by enhancing hedonic food consumption and reducing satiety control. Future studies should focus on replication studies in ethnically diverse young adults and life stages to explore the relationship between polymorphisms and appetitive traits and weight. This will help tailor personalized nutrigenetic strategies to counteract disordered eating patterns leading to obesity and associated co-morbidities.

KEYWORDS

polymorphisms, AEBQ, appetitive traits, young adults, personalized nutrition, tailoring, eating patterns

1 Introduction

Western societies and countries with emerging market economies such as Mexico are immersed in an environment conducive to the development of obesity (1). Given this rise, the "Behavioral Susceptibility Theory" (BST) proposes that some individuals are more sensitive to external food cues or "Food Responsiveness" and less responsive to internal cues for satiety or "Satiety Responsiveness," therefore, increasing the risk of obesity (2, 3). The BST suggests that human body weight and appetitive traits are influenced by the interaction between genetic factors with the surrounding environment (4–6). "Food approach" and/or "food avoidance" appetitive traits, can be measured using psychometric questionnaires such as the Adult Eating Behavior Questionnaire (AEBQ) and its validated Spanish version (AEBQ-Esp) (7, 8). These traits are linked to higher body weight changes spanning from infancy to adulthood (5, 7).

Twin studies and Genome-Wide Association Studies (GWAS) have explained how genetic susceptibility to obesity is influenced by appetite; having a heightened sensitivity to internal hunger and fullness signals ("Satiety responsiveness") and enjoying food ("Enjoyment of food"), as well as wanting to eat in response to the sight, smell, or taste of food ("Food responsiveness"), with heritability estimates of 63 and 75%, respectively (9). In the Gemini cohort, appetitive traits such as "Slowness in eating" (84%) and "Satiety responsiveness" (72%) were found to be highly genetically determined, while a moderate effect was associated with "Food responsiveness" (59%) and "Enjoyment of food" (53%) (10). Several extensive adult cohorts spanning the UK, the US, Canada, France, and Finland consistently reveal associations between genetic susceptibility and appetitive traits related to "Food responsiveness" such as "External eating," "Uncontrolled eating" and "Disinhibition" (11–14). Notably, a longitudinal study of 2,464 British adults from the Whitehall II cohort demonstrated that "Disinhibition" mediated 34% of the association between a polygenic risk score (PRS) for obesity (comprising 97 genetic variants) in 20-year BMI trajectories during midlife (15).

Responsiveness to food cues, refers to the desire to eat when encountering food-related stimuli like the appearance, aroma, or taste of food (3). This aspect is linked to hedonic processes associated with pleasure and reward (16) regulated in the brain reward system. Gene polymorphisms related to the reward system such as the Dopamine Receptor 2 (*DRD2/ANKK1*) gene and Catechol-O-methyltransferase (*COMT*) seem to influence appetitive traits, by promoting hedonic food consumption and reducing satiety control (17). The A1 allele from the *DRD2/ANKK1 TaqIA1* (rs1800497) polymorphism contributes to decreased DRD2 receptor density and increases L-DOPA activity, impairing the reward system. The A1 allele is highly prevalent in Mexicans and contributes to detrimental dietary quality and metabolic disturbances (18). The *COMT* gene regulates emotional, cognitive, and appetitive processes (19, 20). The rs4680 (Val158Met) polymorphism in the *COMT* gene has been related to appetite conditioning (19).

Internal satiety signals such as hunger and fullness are regulated by hormones in the energy balance system (21). Three genes encode important components related to energy intake and energy expenditure balance such as Leptin (*LEP*), ghrelin (*GHRL*), melanocortin-4-receptor (*MC4R*), and the fat mass and obesity-associated gene (*FTO*) (22, 23). Leptin, the hormone that regulates fullness is codified by the Leptin (*LEP*) gene and the G allele from the −2548G > A, rs7799039 polymorphism of this gene has been linked with lower levels of postprandial fullness (24). The rs696217 polymorphism (Leu72Met) of the *GHRL* gene affects hunger and satiety. Individuals with the Met72Met genotype exhibit greater consumption of sugars and bread compared to carriers of the Leu72Leu genotype (25). There is evidence that individuals showing genetic risk factors exhibit varying scores related to "food approach" and "food avoidant" appetitive traits, as observed among 180 young Mexican subjects, where circulating IgG autoAbs reacting to ghrelin and leptin were evaluated (26). Additionally, *MC4R* regulates energy homeostasis and appetite signals (27, 28). The C allele from the −188 kb T > C, rs17782313 *MC4R* polymorphism is associated with higher BMI (29) and higher appetite (30). In a study with 221 obese Chilean children, the rs17782313 variant was associated with "Satiety responsiveness" and "Enjoyment of food" scores (31). This variant may be linked to childhood obesity, impacting factors such as "Enjoyment of food" and "Satiety responsiveness" and possibly "Eating in the absence of hunger" according to a case–control study involving 139 normal-weight and 238 obese children aged 6–12 years (32). The T > A, rs9939609 *FTO* gene polymorphism expressed in the hypothalamus, regulating food intake and energy expenditure is known to be related to higher BMI. Studies in children examining the relationship between appetitive traits and *FTO* reveal that those with the AA genotype are more prone to overweight or obesity. This inclination is attributed to lower "Satiety responsiveness," heightened "Food responsiveness," and increased "Enjoyment of food" in children and adolescents (33, 34).

Studies indicate that young adults, especially university students, undergoing a transitional life stage face challenges such as balancing work and study responsibilities, as well as managing stress (35). These stressors can adversely affect their eating behaviors, putting them at a heightened risk of developing disordered eating patterns (36, 37) and the development of obesity (38). However, little is known of the relationship that exists between different polymorphisms that participate in the regulation of food consumption and appetitive traits in young people, which could serve to tailor intervention in this age group and move toward a more personalized medicine and nutrition approach. Therefore, this study aimed to explore the relationship between polymorphisms of genes involved in energy balance (*LEP* rs7799039, *MC4R* rs17782313, *FTO* rs9939609, *GHRL* rs696217), and reward system (*DRD2/ANKK1* rs1800497 and *COMT* rs4680) and appetitive traits subscales of the AEBQ-Esp in young Mexican subjects.

2 Materials and methods

2.1 Participants and procedure

This study was carried out at the Department of Genomic Medicine in Hepatology from January 2018–2019. Due to the 2019 COVID pandemic, research activities were postponed and resumed from July to December 2022. The study involved primarily freshman undergraduates selected from the Health Sciences Center (*Centro Universitario de Ciencias de la Salud, CUCS*) at the Universidad de Guadalajara, a public non-fee-paying university. Students who did not have Spanish as their first language were not included in the research. Researchers initiated contact with university administrators, who, in turn, approached lecturers responsible for undergraduate courses, seeking their willingness to involve their classes in the study. The researchers secured informed consent from the students before commencing data collection. Ethical approval (number CI-08218) was obtained by the Institutional Review Board.

2.2 Measurement of appetitive traits

Appetitive traits were assessed using the AEBQ-Esp, a 30-item self-report questionnaire known for its validity and reliability in measuring seven distinct appetitive traits (8). The three "food approach" traits consisted of "Food responsiveness" (four items, e.g., I am always thinking about food), "Emotional overeating" (five items, e.g., I eat more when I'm angry), and "Enjoyment of food" (three items, e.g., I love food). Four "Food avoidance" traits included: "Satiety responsiveness" (four items, e.g., I get full up easily), "Emotional undereating" (five items, e.g., I eat less when I'm upset), "Food fussiness" (five items, e.g., I enjoy tasting new foods) and "Slowness in eating" (four items, e.g., I eat slowly). All participants responded to a 5-point Likert scale, ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Mean scores were calculated for each subscale and classified as dichotomous variables, as "high-score" for "food approach" traits if their score on each subscale was greater than three, likewise, they were classed as "low-score" for "food avoidance" traits if their score for each subscale was less than three.

2.3 DNA extraction and genotyping

A peripheral blood sample was obtained to perform the genomic DNA extraction from leukocytes with a modified Salting Out technique (39); a quantified concentration of 20 ng/μl with Nanodrop 2000c was stored at −70°C. A real-time PCR system was performed with predesigned TaqMan Single Nucleotide Polymorphism (SNP) Genotyping Assays (Applied Biosystems, Life Technologies, Camarillo, CA, USA) for the determination of *LEP* rs7799039 (C___1328079_10), *MC4R* rs17782313 (C__32667060_10), *FTO* rs9939609 (C__30090620_10), *GHRL* rs696217 (C___3151003_20), *DRD2/ANKK1* Taq1A rs1800497 (C___7486676_10) and *COMT* rs4680 polymorphisms (C__25746809_50) using a 96-well plate and then read on a Step One Plus thermocycler (Applied Biosystems). Thermal cycling conditions were the following: activation stage at 95°C for 10 min, denaturation stage of 40 cycles at 95°C for 15 s. And the annealing/extension stages at 60°C for 1 min.

2.4 Sociodemographic data

Participants reported their age, university, work status (full-time job; part-time job; self-employed; not working), marital status (not married; married; lives with partner), living status (at home; away from home), both parents' work (full-time job; part-time job; self-employed; has different jobs; unemployed; does not have a father or mother) and both parents' education (primary school; GCSE levels; A levels; bachelors; postgraduate). The latter information was used as a proxy for socioeconomic status (data not shown) (40).

2.5 Anthropometry

Height was measured without shoes to the nearest 0.1 cm (Seca stadiometer); weight was measured in kilograms to the nearest 100 g (Tanita weighing scale); and body mass index (BMI) was the ratio of weight (kg), by height (m^2). BMI cut-off points were as follows: healthy weight (18.5–24.9 kg/m^2) overweight (25–29.9 kg/m^2), and obesity (>30 kg/m^2).

2.6 Statistical analyses

The Kolmogorov–Smirnov test was applied to know the distribution of the analyzed data. Continuous variables were presented as mean ± standard deviations (SD), and categorical variables as percentages where appropriate. Cronbach's alpha was performed to test internal reliability among the AEBQ-Esp subscales, considering an acceptable value of greater than 0.7. Comparisons were conducted using the T-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. Correlation analyses were conducted using point biserial correlations for normally distributed data, Kendall's correlation for non-normally distributed data, and the Phi-Coefficient was also calculated. The association of genotypes with the subscales was estimated with an odds ratio (OR) test and a 95% confidence interval (CI). A p-value of <0.05 was considered significant. Statistical analysis was conducted with SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA), significance level of $p < 0.05$. The Hardy–Weinberg equilibrium (HWE) was obtained with the Arlequin software for Windows (version 3.1; Berne, Switzerland).

3 Results

3.1 Population's descriptive characteristics

Demographic, clinical, and genetic characteristics are presented in Table 1. In this study, 118 young adults (20.14 ± 3.95 years) were evaluated (71.2% women). The mean BMI was 23.52 ± 4.05 kg/m^2.

Most subjects were healthy weight (61%), followed by 33.1% of excess weight, and 5.9% were underweight.

3.2 Descriptive data for appetitive traits and AEBQ-Esp internal validation

The means and standard deviations of the seven appetitive traits of the AEBQ-Esp subscales and their internal reliability are shown in

10.3389/fnut.2024.1373578

TABLE 1 Population demographics and clinical characteristics ($n = 118$).

Characteristic	Mean ± SD
Age (years)	20.14 ± 3.95
Gender	
Female (n, %)	(84, 71.2)
Male (n, %)	(34, 28.8)
Weight (kg)	63.68 ± 14.14
BMI (Kg/m^2)	23.52 ± 4.05
Underweight (n/%)	7 (5.9)
Healthy weight (n/%)	72 (61)
Overweight (n/%)	31 (26.3)
Obesity (n/%)	8 (6.8)

BMI, Body Mass Index.

TABLE 2 AEBQ-Esp subscales and internal reliability.

AEBQ-Esp subscales	Mean ± SD	Internal reliability (Cronbach's alpha)
Food approach subscales		
Food responsiveness (FR)	2.99 ± 0.70	0.744
High (%)	55	
Low (%)	45	
Emotional overeating (EOE)	2.63 ± 0.78	0.779
High (%)	36	
Low (%)	64	
Enjoyment of food (EF)	4.21 ± 0.70	0.734
High (%)	96	
Low (%)	4	
Food approach subscales		
Satiety responsiveness (SR)	2.55 ± 0.77	0.748
High (%)	81	
Low (%)	19	
Emotional undereating (EUE)	3.07 ± 0.81	0.806
High (%)	53	
Low (%)	47	
Food fussiness (FF)	3.17 ± 0.60	0.423
High (%)	33	
Low (%)	67	
Slowness in eating (SE)	2.86 ± 0.70	0.518
High (%)	67	
Low (%)	33	

Table 2. Cronbach's alpha value >0.7 demonstrated good internal reliability in five of the seven traits, only the "Food fussiness" and "Slowness in eating" subscales were < 0.5.

3.3 Allele and genotype frequencies of the analyzed gene polymorphism

The allele and genotype distribution of the analyzed gene polymorphisms are shown in Table 3. All analyzed polymorphisms were in Hardy–Weinberg equilibrium (HWE) ($p > 0.05$). A different number of samples were analyzed for each polymorphism. For the *MC4R*, the T allele was more prevalent in the population (88%), and the absence of the genotype CC was observed. The frequency of the G allele was higher in the genes *LEP*, *COMT*, and *DRD2*; also in these groups, the heterozygote (AG/GA) was the most frequent genotype. In the *FTO* gene, the frequency of the T allele was 70%, and 48% of homozygotes. In the case of the *GHRL* gene, the G allele had a frequency of 85%, while the TT genotype was present in only one subject. All analyzed polymorphisms were in Hardy–Weinberg equilibrium (HWE) ($p > 0.05$).

3.4 Appetitive traits according to gene polymorphisms

The means and SD of the AEBQ-Esp subscales according to the dominant model of the studied gene polymorphisms are presented in Table 4. There was a tendency toward carriers of the *MC4R* C allele to have lower "Emotional overeating" (2.42 ± 0.65, $p = 0.08$). Similarly, *LEP* G allele carriers (2.87 ± 0.65, $p = 0.06$) tended to present lower "Slowness in eating." *FTO* carriers tended to have higher "Emotional undereating" (3.11 ± 0.79, $p = 0.061$). Met allele carriers from the *COMT* gene tended to present higher "Food fussiness" (3.40 ± 0.37, $p = 0.06$) and presented significantly higher "Emotional overeating" (2.63 ± 0.70, $p = 0.028$) than Val allele carriers. No other significant differences were found.

3.5 Correlations between gene polymorphisms and appetitive traits

The correlation analysis between genetic models and mean appetitive trait values is listed in Table 5, and correlations between gene polymorphisms and appetitive traits as dichotomous variables can be found in Table 6. In terms of "food approach" subscales, there was a tendency toward a positive correlation between the *MC4R* CC + CT genotype and "Emotional overeating" mean scores ($r = 0.211$, $p = 0.082$, Table 5), as well as with the categorical variable (Phi = 0.308, $p = 0.010$, Table 6). Similarly, the *COMT* MetMet+MetVal genotype correlated with higher "Emotional overeating" mean scores ($r = 0.257$, $p = 0.028$; Phi = 0.249, $p = 0.033$). Carriers of the higher risk genotype MetMet+MetVal were positively correlated with all "food approach" traits (Phi = 0.378, $p = 0.002$, Table 6). There was a tendency toward a correlation of the high-risk genotype *LEP* GG + AG with higher "Enjoyment of food" mean scores ($r = 0.209$, $p = 0.082$, Table 6).

As part of the relationships between gene polymorphism and "food avoidant" traits, we found that the protective genotype *LEP* AA was positively correlated with "Satiety responsiveness" ($r = 0.209$, $p = 0.085$). In contrast, there was a tendency toward a negative correlation between the risk genotype *DRD2* A1A1 + A1A2 with lower "Satiety responsiveness" ($r = -0.213$, $p = 0.08$). The high-risk genotype *FTO* AA+AT was negatively correlated to "Emotional undereating"; however, it was not significant ($r = -0.190$, $p = 0.061$). There was a significant positive correlation between the protective *FTO* genotype with "Emotional undereating" as a categorical variable (Phi = 0.298, $p = 0.012$). In this study there were only correlation tendencies with "Food fussiness" and gene polymorphisms; *COMT* high-risk genotype MetMet+MetVal and

TABLE 3 Alleles and genotypes frequency of the gene polymorphisms.

Genes	n	HWE	Alleles n (%)		Genotypes n (%)		
MC4R T > C, (rs17782313)	69	0.276	T	C	TT	CT	CC
			122 (88)	16 (12)	53 (77)	16 (23)	0
LEP G > A, (rs7799039)	69	0.297	A	G	AA	AG	GG
			51 (39)	79 (61)	8 (12)	35 (54)	22 (34)
FTO T > A, (rs9939609)	71	0.653	A	T	AA	AT	TT
			39 (30)	93 (70)	5 (8)	29 (44)	32 (48)
COMT Val158Met, (rs4680)	93	0.419	Val	Met	ValVal	ValMet	MetMet
			116 (62)	70 (38)	38 (41)	40 (43)	15 (16)
DRD2/ANKK1 Taq1A (rs1800497)	61	0.868	A2	A1	A2A2	A2A1	A1A1
			76 (62)	46 (38)	24 (39)	28 (46)	9 (15)
GHRL Leu72Met, (rs696217)	109	0.302	G	T	GG	GT	TT
			186 (85)	32 (15)	78 (72)	30 (27)	1 (1)

HWE, Hardy Weinberg Equilibrium. Allele and genotype frequencies are expressed as percentage.

"Food fussiness" ($r = 0.216$, $p = 0.066$), and the protective genotype *DRD2* A2A2 ($r = -0.235$, $p = 0.60$).

3.6 Association between gene polymorphisms and appetitive traits

Carriers of the risk genotype *MC4R* CC + CT presented a higher risk of "Emotional overeating" than TT carriers (OR = 2.4, 95% CI 1.3–4.8, $p = 0.034$). Similarly, carriers of the risk genotype *COMT* MetMet+MetVal, were associated with a higher risk of "Emotional overeating" than Val carriers (OR = 3.4, 95% CI 1.1–10.3, $p = 0.033$). The protective genotype TT from *FTO* was associated with higher "Emotional undereating" (OR = 1.8, 95% CI 1.1–9.1, $p = 0.014$) (Data not shown).

4 Discussion

Mexico presents one of the highest rates of obesity worldwide, and there is limited data in the Mexican population related to appetitive traits and genetic risk factors that contribute to obesity. This appears to be the first study that explores the relationship between gene polymorphisms related to energy balance, hunger, satiety, and reward with scores of "food approach" and "food avoidant" appetitive trait subscales in young healthy weight (BMI: 23.52 ± 4.05) Mexican adults. To determine the appetitive traits in this population, the AEBQ-Esp was used, which has previously been validated in the Mexican population (8). In this study, the results reveal that the AEBQ-Esp with the exclusion of the "Food fussiness" and "Slowness in eating" subscales, were internally reliable (0.734–0.906); therefore, we recommend care be taken with regards to results interpreted using these two subscales. These results differ from the original validation of the AEBQ-Esp, where alpha Cronbach values were 0.70 and 0.91, respectively, for these subscales (8). Lower internal reliability values have also been found when mothers of children (41) and toddlers (42) complete the AEBQ-Esp questionnaire, in samples of Mexican subjects. This could be due to the size of the population obtained in this sample.

In the present study, we found important relationships between the analyzed gene polymorphisms with scores of "food approach" ("Emotional overeating" and "Enjoyment of Food") and "food avoidant" ("Satiety responsiveness," "Food fussiness" and "Emotional undereating") appetitive traits. In terms of "Emotional overeating," *MC4R* has been related to obesity by disrupting energy homeostasis and appetite signals (27, 28). Specifically, the rs17782313 polymorphism of *MC4R* has been previously associated with higher BMI and higher appetite (30). Moreover, when C carriers are exposed to unhealthy eating patterns, the risk of developing depressive feelings increases (43). Our analysis revealed a tendency toward a correlation between the *MC4R* (rs17782313) CC + CT genotype and "Emotional overeating" mean value ($r = 0.211$, $p = 0.082$) and as a categorical variable (Phi = 0.308, $p = 0.010$). Moreover, carriers of the risk genotype *MC4R* CC + CT presented a higher risk of "Emotional overeating" than TT carriers (OR = 2.4, 95% CI 1.3–4.8, $p = 0.034$). This is similar to what was found in an Iranian cross-sectional study in adults overweight and obese, where obese individuals carriers of the C risk allele of *MC4R* (rs17782313) exhibited a higher mean score of "Emotional eating" assessed with the self-report Emotional Eating Questionnaire (EEQ). In that study, *MC4R* rs17782313 was also associated with appetite, energy intake, nutrients, stress, ghrelin, and cortisol levels (44). In contrast, in a study with adults with obesity from Chile, "Uncontrolled eating" and "Emotional eating" measured using the Three-Factor Eating Questionnaire-R18, showed that carriers of the risk allele rs17782313 presented higher scores of "Emotional undereating" compared to non-carriers (45).

The *COMT* gene plays a key role in the reward system, where it regulates emotional, cognitive, and appetite processes (19, 20). Moreover, it is important to highlight that in the Mexican population, a higher prevalence of the Met allele (63%) has been reported (46), which contrasts with the prevalence in other populations. The Met allele has been reported to be associated with a personality trait such as "worrier" and with impulsivity and negative emotions (47, 48). In line with this, in the present study, we found that the high-risk genotype *COMT* (rs4680) MetMet+MetVal was positively correlated with the mean scores ($r = 0.257$, $p = 0.028$), and categorical variables of "Emotional overeating" (Phi = 0.249, $p = 0.033$). In addition,

10.3389/fnut.2024.1373578

TABLE 4 Appetitive traits according to gene polymorphisms.

AEBQ	*MC4R*		*LEP*		*FTO*		*COMT*		*DRD2/ANKK1*		*GHRL*	
	TT	CC + CT	AA	GG + AG	TT	AA + AT	ValVal	MetMet + MetVal	A2A2	A1A1 + A1A2	GG	TT + GT
FR	2.98 ± 1.03	2.95 ± 0.68	2.96 ± 0.62	2.95 ± 0.79	2.94 ± 0.69	2.99 ± 0.78	2.96 ± 0.69	2.93 ± 0.79	2.89 ± 0.74	2.88 ± 0.75	3.00 ± 0.71	2.98 ± 0.71
EOE	2.78 ± 0.91	2.42 ± 0.65*	2.46 ± 0.67	2.52 ± 0.74	2.42 ± 0.73	2.55 ± 0.73	2.26 ± 0.70	2.63 ± 0.70**	2.34 ± 0.67	2.48 ± 0.73	2.65 ± 0.81	2.60 ± 0.73
EF	4.02 ± 0.82	4.19 ± 0.73	4.13 ± 0.77	4.12 ± 0.77	4.04 ± 0.77	4.24 ± 0.72	4.16 ± 0.69	4.11 ± 0.79	4.01 ± 0.66	4.11 ± 0.81	4.1 ± 0.67	4.19 ± 0.77
SR	2.78 ± 0.80	2.71 ± 0.75	2.91 ± 0.92	2.63 ± 0.65	2.82 ± 0.78	2.63 ± 0.72	2.84 ± 0.87	2.69 ± 0.69	2.96 ± 0.67	2.63 ± 0.79	2.54 ± 0.78	2.60 ± 0.81
EUE	3.26 ± 0.88	3.05 ± 0.80	3.26 ± 0.86	3.06 ± 0.77	3.15 ± 0.62	3.11 ± 0.79*	3.24 ± 0.98	3.10 ± 0.66	3.23 ± 0.82	3.16 ± 0.82	3.06 ± 0.83	3.22 ± 0.77
FF	3.38 ± 0.34	3.30 ± 0.36	3.36 ± 0.29	3.30 ± 0.39	3.31 ± 0.32	3.34 ± 0.38	3.24 ± 0.29	3.40 ± 0.37 *	3.43 ± 0.34	3.26 ± 0.36	3.16 ± 0.59	3.12 ± 0.66
SE	3.04 ± 0.74	2.99 ± 0.61	3.16 ± 0.56	2.87 ± 0.65*	3.04 ± 0.56	2.93 ± 0.66	2.93 ± 0.62	3.03 ± 0.63	2.99 ± 0.55	2.94 ± 0.68	2.86 ± 0.74	2.82 ± 0.58

FR, Food responsiveness; EOE, Emotional overeating; EF, Enjoyment of food; SR, Satiety responsiveness; EUE, Emotional undereating; FF, Food fussiness; SE, Slowness in eating. Results are presented as means and standard deviations. Comparisons were conducted using the *T*-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data (EF, EUE and GHRL). ***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

we only found that carriers of the higher risk genotype MetMet+MetVal were positively correlated with "food approach" traits (Phi = 0.378, $p = 0.002$). In contrast, in a cross-sectional study of 3-4-year-old children conducted in Brazil, results showed that the *COMT* Val158Met polymorphism contributed to a higher intake of palatable food. That study revealed that carriers of the Val allele presented a higher intake of fats when compared to MetMet homozygotes (49).

In terms of "food avoidant" traits, we found that the protective genotype *LEP* AA was positively correlated with "Satiety responsiveness" ($r = 0.209$, $p = 0.085$) and a tendency toward a negative correlation between the risk genotype *DRD2* A1A1 + A1A2 and "Satiety responsiveness" ($r = -0.213$, $p = 0.08$). Valladares found that carriers of the class II allele from the non-translatable hypervariable region at the 3′ end of the gene *LEP* (TTTC)n, had higher scores of "Slowness in eating" vs. non-carriers (31). It has been reported previously, that rs7799039 is associated with higher consumption of energy intake (50). These studies so far, highlight that there is a need for more studies to determine whether polymorphisms of *LEP* could be influencing emotional overeating.

Moreover, in this study, we found a tendency toward a negative correlation between the high-risk genotype *FTO* AA+AT and "Emotional undereating" ($r = -0.190$, $p = 0.061$). There was a significant positive correlation between the protective genotype from the *FTO* with "Emotional undereating" as a categorical variable (Phi = 0.298, $p = 0.012$). The protective *FTO* genotype TT was associated with higher "Emotional undereating" (OR = 1.8, 95% CI 1.1–9.1, $p = 0.014$). In contrast, Valladares and colleagues, in their study conducted among Chilean children with obesity, did not find any relationships between "Emotional undereating" and the genetic polymorphisms studied in that population (31).

On the other hand, "Food fussiness" is a "food avoidance" trait, that refers to the reluctance to eat both new and familiar foods, pickiness of the flavor and texture of foods, and it has been mostly explored among children (51, 52). Interestingly, although not significant, in this study, we found a tendency toward the presence of the *COMT* high-risk genotype MetMet+MetVal and higher "Food fussiness" ($r = 0.216$, $p = 0.066$), and the protective genotype *DRD2* A2A2 with lower "Food fussiness" ($r = -0.235$, $p = 0.60$). However, care should be taken not to put too much weight on these results, as the "Food fussiness" "subscale was not reliable." The genes that contribute to "Food fussiness" have not been identified yet. However, it has been previously reported that "Food fussiness" is highly heritable (53). Potentially a larger sample size study that explores the role of the *COMT* and *DRD2* genes and "Food fussiness" would be necessary. According to data from the Gemini twin study, genetic correlations have been observed between "Food fussiness" and preferences for vegetables and fruits (54). It would be worth analyzing if the *COMT* and *DRD2* genes influence the intake of fruits and vegetables in a larger population.

Finally, in the context of the global obesity epidemic including in Mexico, these results show the importance of moving toward a more personalized medicine and nutrition approach, toward assessing risk, and finding novel ways to prevent and treat diseases (55). Furthermore, the presence of the respective risk alleles among the studied genes underscores the need for preventive strategies against further weight gain among the population (56). In the present study, 61% of participants presented healthy weight and the prevalence of

TABLE 5 Correlations between gene polymorphisms and appetitive traits mean values.

Genetic dominant models	FR mean	EOE mean	EF mean	SR mean	EUE mean	FF mean	SE mean
MC4R TT vs. CC + CT	0.011	0.211*	0.069	−0.038	−0.066	−0.087	−0.31
LEP AA vs. GG + AG	0.012	0.022	0.019	0.209*	0.160	0.166	0.225
FTO TT vs. AA + AT	0.036	0.089	0.129	−0.123	−0.190*	0.055	−0.088
COMT MetMet + MetVal vs. ValVal	0.015	0.257**	0.004	−0.096	−0.063	0.216*	0.076
DRD2/ANKK1 A1A1 + A1A2 vs. A2A2	0.001	0.097	0.092	−0.213*	−0.047	−0.235*	−0.042
GHRL GG vs. TT + GT	0.068	0.002	0.026	−0.006	−0.070	−0.020	0.047

FR, Food responsiveness; EOE, Emotional overeating; EF, Enjoyment of food; SR, Satiety responsiveness; EUE, Emotional undereating; FF, Food fussiness; SE, Slowness in eating. Correlation analyses were conducted using point biserial correlations for normally distributed data and Kendall's correlation for non-normally distributed data (EF, EUE and GHRL). ***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

TABLE 6 Correlations between gene polymorphisms and appetitive traits as dichotomous variable.

Genetic dominant models	Food approach (FA)				Food avoidance (FV)				
	FR cat	EOE cat	EF cat	FA cat	SR cat	EUE cat	FF cat	SE cat	FV cat
MC4R TT vs. CC + CT	0.077	0.308**	0.158	1.22	−0.014	0.093	0.014	−0.018	0.082
LEP AA vs. GG + AG	0.011	0.020	0.209*	0.378**	−0.204	−0.212	−0.157	−0.083	0.052
FTO TT vs. AA + AT	0.068	0.042	0.017	0.055	0.107	0.298**	0.089	0.054	−0.063
COMT MetMet + MetVal vs. ValVal	0.129	0.249**	0.072	0.087	0.164	0.085	−0.120	−0.100	0.089
DRD2/ANKK1 A1A1 + A1A2 vs. A2A2	0.035	0.117	0.196	0.016	0.168	0.005	0.165	−0.008	0.042
GHRL GG vs. TT + GT	0.079	0.026	0.153	−0.027	−0.013	0.067	−0.046	−0.029	0.079

FR, Food responsiveness; EOE, Emotional overeating; EF, Enjoyment of food; SR, Satiety responsiveness; EUE, Emotional undereating; FF, Food fussiness; SE, Slowness in eating. Correlation analyses were conducted using Phi-Coefficient. ***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

overweight and obesity was 33.1%. Therefore, a future perspective could be including a bigger sample size to perform analysis according to participant's BMI. Also, appetitive traits can be targeted to create behavioral strategies for weight reduction when personalized profiles are generated for individuals (57). Also, appetitive traits reflect the relationship that individuals have with food and response to food cues in the environment, which initiate in childhood and continue until adolescence as a risk factor for the development of eating disorders (58) is a further complication in this age group.

Our results need to be considered in view of several limitations. We recognize that in a cross-sectional study, it is complex to infer causal relationships because it only involves a one-time measurement, and we did not consider previous individual environmental factors that might influence appetitive traits including the 2019 COVID pandemic. Similarly, the pandemic affected our ability to conduct research activities, but we resumed activities and finalized the data analysis in 2022. Young adults may tend to under-report certain traits perceived as less desirable, such as higher "Food responsiveness," while potentially over-reporting traits considered more favorable, like higher "Satiety responsiveness." Conversely, it's worth noting that social desirability tends to increase with age and be more prevalent in females (59). In addition, in this study, we had higher participation of female than male students. These young adults were recruited from the Health Sciences Center at the Universidad de Guadalajara, in which more than 60% of the students are females, specifically students enrolled in Nutrition are within a healthy BMI. We recognize that the characteristics and size of this sample may limit generalizing the results and detecting further associations. Including more male participants may allow us to identify associations related to gender. However, it has been suggested that certain appetitive traits influence young females to be more susceptible to develop overweight or obesity (60). We also did not evaluate physical activity levels which seems to have a modifying effect on certain SNPs such as the rs993609 *FTO* polymorphism (61, 62) and it is possible that individuals who engage in higher physical activity levels could have lesser levels of stress or negative emotions that influence emotional overeating. Despite the limitations of this study, it is important to recognize that young university adults experience a drastic transition in their lifestyles, which together with their genetic background may influence certain appetitive traits that could increase the risk of overweight and obesity. Multiple environmental factors and genes are involved in eating behavior, so there is a need to continue to expand the number of genes related to energy balance, appetite, satiety, and food reward and conduct longitudinal studies in different populations.

5 Conclusion

In this study the risk genotypes of *COMT* Met+Met and *MC4R* TT correlated with higher "Emotional overeating" and the protective *FTO* genotype TT was also associated with higher "Emotional undereating." These results may facilitate understanding the genetic influence of weight gain by promoting hedonic food consumption and reductions in satiety regulation and could signal the need for more tailored strategies, including personalized medicine, personalized nutrition, or behavior-based treatment strategies that can help improve eating behaviors in young subjects. Similarly, identifying individuals at a higher risk of presenting appetite traits that facilitate cravings and food overconsumption could help prevent the development of obesity at earlier stages, even starting as early as

childhood. These results may also help decision-makers to create public health recommendations and policy changes related to environmental factors that could be triggers of these high-risk appetitive traits. These findings require replication in different culturally diverse young adults, as well as in different stages of the life course. Future studies should also examine the prospective relationship between polymorphisms and appetitive traits and explore how these associations may relate to changes in weight and how engagement in healthy lifestyle behaviors could help modulate these associations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comités de Investigación, Ética en Investigación y Bioseguridad del Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IR-I: Conceptualization, Project administration, Resources, Visualization, Writing – review & editing, Formal analysis, Funding acquisition, Investigation, Writing – original draft. CH-A: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing, Resources. MS-V: Formal analysis, Investigation, Visualization, Writing – review & editing. LC-M: Formal analysis, Investigation, Visualization, Writing – review & editing. SR: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. CH-A was funded by the Programa para el Desarrollo Profesional Docente [PRODEP (UDG-EXB-684)] – Secretaría de Educación Pública (SEP) – Mexico.

Acknowledgments

We would like to thank administrators and Faculty at the Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, for allowing us to collect the data presented in this study. We would also like to thank students from the Instituto de Nutrición Humana, CUCS, Universidad de Guadalajara, and from the Departamento de Medicina Genómica en Hepatologia, Hospital Civil de Guadalajara, "Fray Antonio Alcalde," who helped with the data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor OR-L declared a past co-authorship with the author SR.

Publisher's note

References

1. García-Chávez CG, Monterrubio-Flores E, Ramírez-Silva I, Aburto TC, Pedraza LS, Rivera-Dommarco J. Food contribution to total daily energy intake in the Mexican population older than five years. *Salud Publica Mex*. (2020) 62:166–80. doi: 10.21149/10636

2. Carnell S, Wardle J. Appetite and adiposity in children: evidence for a behavioral susceptibility theory of obesity. *Am J Clin Nutr*. (2008) 88:22–9. doi: 10.1093/ajcn/88.1.22

3. Llewellyn CH, Fildes A. Behavioural Susceptibility Theory: Professor Jane Wardle and the Role of Appetite in Genetic Risk of Obesity. *Curr Obes Rep*. (2017) 6:38–45. doi: 10.1007/s13679-017-0247-x

4. Llewellyn C, Wardle J. Behavioral susceptibility to obesity: gene-environment interplay in the development of weight. *Physiol Behav*. (2015) 152:494–501. doi: 10.1016/j.physbeh.2015.07.006

5. Kininmonth A, Smith A, Carnell S, Steinsbekk S, Fildes A, Llewellyn C. The association between childhood adiposity and appetite assessed using the child eating behavior questionnaire and baby eating behavior questionnaire: a systematic review and meta-analysis. *Obes Rev*. (2021) 22:e13169. doi: 10.1111/obr.13169

6. Llewellyn CH, Kininmonth AR, Herle M, Nas Z, Smith AD, Carnell S, et al. Behavioural susceptibility theory: the role of appetite in genetic susceptibility to obesity in early life. *Philos Trans R Soc Lond Ser B Biol Sci*. (2023) 378:20220223. doi: 10.1098/rstb.2022.0223

7. Hunot C, Fildes A, Croker H, Llewellyn CH, Wardle J, Beeken RJ. Appetitive traits and relationships with BMI in adults: development of the adult eating behaviour questionnaire. *Appetite*. (2016) 105:356–63. doi: 10.1016/j.appet.2016.05.024

8. Hunot-Alexander C, Arellano-Gómez LP, Smith AD, Kaufer-Horwitz M, Vásquez-Garibay EM, Romero-Velarde E, et al. Examining the validity and consistency of the Adult Eating Behaviour Questionnaire-Español (AEBQ-Esp) and its relationship to BMI in a Mexican population. *Eat Weight Disord*. (2022) 27:651–63. doi: 10.1007/s40519-021-01201-9

9. Carnell S, Haworth CMA, Plomin R, Wardle J. Genetic influence on appetite in children. *Int J Obes*. (2008) 32:1468–73. doi: 10.1038/ijo.2008.127

10. Llewellyn CH, van Jaarsveld CHM, Johnson L, Carnell S, Wardle J. Nature and nurture in infant appetite: analysis of the Gemini twin birth cohort. *Am J Clin Nutr*. (2010) 91:1172–9. doi: 10.3945/ajcn.2009.28868

11. Jacob R, Drapeau V, Tremblay A, Provencher V, Bouchard C, Pérusse L. The role of eating behavior traits in mediating genetic susceptibility to obesity. *Am J Clin Nutr*. (2018) 108:445–52. doi: 10.1093/ajcn/nqy130

12. Konttinen H, Llewellyn C, Wardle J, Silventoinen K, Joensuu A, Männistö S, et al. Appetitive traits as behavioural pathways in genetic susceptibility to obesity: a population-based cross-sectional study. *Sci Rep*. (2015) 5:14726. doi: 10.1038/srep14726

13. Cornelis MC, Rimm EB, Curhan GC, Kraft P, Hunter DJ, Hu FB, et al. Obesity susceptibility loci and uncontrolled eating, emotional eating and cognitive restraint behaviors in men and women. *Obesity*. (2014) 22:E135–41. doi: 10.1002/oby.20592

14. de Lauzon-Guillain B, Clifton EA, Day FR, Clément K, Brage S, Forouhi NG, et al. Mediation and modification of genetic susceptibility to obesity by eating behaviors. *Am J Clin Nutr*. (2017) 106:996–1004. doi: 10.3945/ajcn.117.157396

15. Brunner EJ, Maruyama K, Shipley M, Cable N, Iso H, Hiyoshi A, et al. Appetite disinhibition rather than hunger explains genetic effects on adult BMI trajectory. *Int J Obes*. (2021) 45:758–65. doi: 10.1038/s41366-020-00735-9

16. Blundell JE, Finlayson G. Is susceptibility to weight gain characterized by homeostatic or hedonic risk factors for overconsumption? *Physiol Behav*. (2004) 82:21–5. doi: 10.1016/j.physbeh.2004.04.021

17. Salgado-Pineda P, Delaveau P, Blin O, Nieoullon A. Dopaminergic contribution to the regulation of emotional perception. *Clin Neuropharmacol*. (2005) 28:228–37. doi: 10.1097/01.wnf.0000185824.57690.f0

18. Rivera-Iñiguez I, Panduro A, Ramos-Lopez O, Villaseñor-Bayardo SJ, Roman S. DRD2/ANKK1 TaqI A1 polymorphism associates with overconsumption of unhealthy foods and biochemical abnormalities in a Mexican population. *Eat Weight Disord*. (2019) 24:835–44. doi: 10.1007/s40519-018-0596-9

19. Klucken T, Kruse O, Wehrum-Osinsky S, Hennig J, Schweckendiek J, Stark R. Impact of COMT Val158Met-polymorphism on appetitive conditioning and amygdala/prefrontal effective connectivity. *Hum Brain Mapp*. (2015) 36:1093–101. doi: 10.1002/hbm.22688

20. Vai B, Riberto M, Poletti S, Bollettini I, Lorenzi C, Colombo C, et al. Catechol-O-methyltransferase Val(108/158)Met polymorphism affects fronto-limbic connectivity during emotional processing in bipolar disorder. *Eur Psychiatry*. (2017) 41:53–9. doi: 10.1016/j.eurpsy.2016.10.002

21. Harrold JA, Dovey TM, Blundell JE, Halford JCG. CNS regulation of appetite. *Neuropharmacology*. (2012) 63:3–17. doi: 10.1016/j.neuropharm.2012.01.007

22. Krashes MJ, Lowell BB, Garfield AS. Melanocortin-4 receptor-regulated energy homeostasis. *Nat Neurosci*. (2016) 19:206–19. doi: 10.1038/nn.4202

23. Speakman JR. FTO effect on energy demand versus food intake. *Nature*. (2010) 464:E1; discussion E2. doi: 10.1038/nature08807

24. Dougkas A, Yaqoob P, Givens DI, Reynolds CK, Minihane AM. The impact of obesity-related SNP on appetite and energy intake. *Br J Nutr*. (2013) 110:1151–6. doi: 10.1017/S0007114513000147

25. Sanchez-Murguia T, Torres-Castillo N, Magaña-de la Vega L, Rodríguez-Reyes SC, Campos-Pérez W, Martínez-López E. Role of Leu72Met of GHRL and Gln223Arg of LEPR variants on food intake, subjective appetite, and hunger-satiety hormones. *Nutrients*. (2022) 14:2100. doi: 10.3390/nu14102100

26. Espinoza-García AS, Hunot-Alexander C, Martínez-Moreno AG, Vázquez-Solorzano R, Porchas-Quijada M, Reyes-Castillo Z. IgG antibodies reacting with ghrelin and leptin are correlated with body composition and appetitive traits in young subjects. *Appetite*. (2022) 168:105685. doi: 10.1016/j.appet.2021.105685

27. Baldini G, Phelan KD. The melanocortin pathway and control of appetite-progress and therapeutic implications. *J Endocrinol*. (2019) 241:R1–R33. doi: 10.1530/JOE-18-0596

28. Yeo GSH, Chao DHM, Siegert AM, Koerperich ZM, Ericson MD, Simonds SE, et al. The melanocortin pathway and energy homeostasis: from discovery to obesity therapy. *Mol Metab*. (2021) 48:101206. doi: 10.1016/j.molmet.2021.101206

29. Lombard Z, Crowther NJ, van der Merwe L, Pitamber P, Norris SA, Ramsay M. Appetite regulation genes are associated with body mass index in black South African adolescents: a genetic association study. *BMJ Open*. (2012) 2:e000873. doi: 10.1136/bmjopen-2012-000873

30. Hammad MM, Abu-Farha M, Hebbar P, Cherian P, al Khairi I, Melhem M, et al. MC4R variant rs17782313 associates with increased levels of DNAJC27, ghrelin, and visfatin and correlates with obesity and hypertension in a kuwaiti cohort. *Front Endocrinol*. (2020) 11:437. doi: 10.3389/fendo.2020.00437

31. Valladares M, Obregón AM, Weisstaub G, Burrows R, Patiño A, Ho-Urriola J, et al. Association between feeding behavior, and genetic polymorphism of leptin and its receptor in obese Chilean children. *Nutr Hosp*. (2014) 31:1044–51. doi: 10.3305/nh.2015.31.3.8049

32. Ho-Urriola J, Guzmán-Guzmán IP, Smalley SV, González A, Weisstaub G, Domínguez-Vásquez P, et al. Melanocortin-4 receptor polymorphism rs17782313: association with obesity and eating in the absence of hunger in Chilean children. *Nutrition*. (2014) 30:145–9. doi: 10.1016/j.nut.2013.05.030

33. Emond JA, Tovar A, Li Z, Lansigan RK, Gilbert-Diamond D. FTO genotype and weight status among preadolescents: assessing the mediating effects of obesogenic appetitive traits. *Appetite*. (2017) 117:321–9. doi: 10.1016/j.appet.2017.07.009

34. Wardle J, Llewellyn C, Sanderson S, Plomin R. The FTO gene and measured food intake in children. *Int J Obes*. (2009) 33:42–5. doi: 10.1038/ijo.2008.174

35. Hill D, Conner M, Clancy F, Moss R, Wilding S, Bristow M, et al. Stress and eating behaviours in healthy adults: a systematic review and meta-analysis. *Health Psychol Rev*. (2022) 16:280–304. doi: 10.1080/17437199.2021.1923406

36. Quick VM, Byrd-Bredbenner C. Disturbed eating behaviours and associated psychographic characteristics of college students. *J Hum Nutr Diet*. (2013) 26:53–63. doi: 10.1111/jhn.12060

37. Stice E, Desjardins CD, Rohde P, Shaw H. Sequencing of symptom emergence in anorexia nervosa, bulimia nervosa, binge eating disorder, and purging disorder and relations of prodromal symptoms to future onset of these disorders. *J Abnorm Psychol*. (2021) 130:377–87. doi: 10.1037/abn0000666

38. Carnell S, Benson L, Pryor K, Driggin E. Appetitive traits from infancy to adolescence: using behavioral and neural measures to investigate obesity risk. *Physiol Behav*. (2013) 121:79–88. doi: 10.1016/j.physbeh.2013.02.015

39. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res*. (1988) 16:1215. doi: 10.1093/nar/16.3.1215

40. INEGI. *Censos Económicos 2019*. Mexico: INEGI (2020).

41. Hunot-Alexander C, Curiel-Curiel CP, Romero-Velarde E, Vásquez-Garibay EM, Mariscal-Rizo A, Casillas-Toral E, et al. Intergenerational transmission of appetite: associations between mother-child dyads in a Mexican population. *PLoS One*. (2022) 17:e0264493. doi: 10.1371/journal.pone.0264493

42. Hunot-Alexander C, González-Toribio J, Vásquez-Garibay EM, Larrosa-Haro A, Casillas-Toral E, Curiel-Curiel CP. Validity and reliability of the baby and child eating behavior questionnaire, toddler version (BEBQ-Mex and CEBQ-T-Mex) in a low sociodemographic sample recruited in a Mexican hospital. *Behav Sci*. (2021) 11:168. doi: 10.3390/bs11120168

43. Hajmir MM, Mirzababaei A, Clark CCT, Ghaffarian-Ensaf R, Mirzaei K. The interaction between MC4R gene variant (rs17782313) and dominant dietary patterns on depression in obese and overweight women: a cross sectional study. *BMC Endocr Disord*. (2023) 23:83. doi: 10.1186/s12902-023-01335-0

44. Rahati S, Qorbani M, Naghavi A, Pishva H. Association and interaction of the MC4R rs17782313 polymorphism with plasma ghrelin, GLP-1, cortisol, food intake and eating behaviors in overweight/obese Iranian adults. *BMC Endocr Disord*. (2022) 22:234. doi: 10.1186/s12902-022-01129-w

45. Vega JA, Salazar G, Hodgson MI, Cataldo LR, Valladares M, Obregón AM, et al. Melanocortin-4 receptor gene variation is associated with eating behavior in Chilean adults. *Ann Nutr Metab*. (2016) 68:35–41. doi: 10.1159/000439092

46. González-Castro TB, Tovilla-Zárate C, Juárez-Rojop I, Pool García S, Genis A, Nicolini H, et al. Distribution of the Val108/158Met polymorphism of the COMT gene in healthy Mexican population. *Gene*. (2013) 526:454–8. doi: 10.1016/j.gene.2013.05.068

47. Bieliński M, Jaracz M, Lesiewska N, Tomaszewska M, Sikora M, Junik R, et al. Association between COMT Val158Met and DAT1 polymorphisms and depressive symptoms in the obese population. *Neuropsychiatr Dis Treat*. (2017) 13:2221–9. doi: 10.2147/NDT.S138565

48. Stein DJ, Newman TK, Savitz J, Ramesar R. Warriors versus worriers: the role of COMT gene variants. *CNS Spectr*. (2006) 11:745–8. doi: 10.1017/S1092852900014863

49. Galvão ACS, Krüger RC, Campagnolo PDB, Mattevi VS, Vitolo MR, Almeida S. Association of MAOA and COMT gene polymorphisms with palatable food intake in children. *J Nutr Biochem*. (2012) 23:272–7. doi: 10.1016/j.jnutbio.2010.12.004

50. Crovesy L, Rosado EL. Interaction between genes involved in energy intake regulation and diet in obesity. *Nutrition*. (2019) 67-68:110547. doi: 10.1016/j.nut.2019.06.027

51. Russell CG, Russell A. Biological and psychosocial processes in the development of children's appetitive traits: insights from developmental theory and research. *Nutrients*. (2018) 10:692. doi: 10.3390/nu10060692

52. Kininmonth AR, Herle M, Tommerup K, Haycraft E, Farrow C, Croker H, et al. Parental feeding practices as a response to child appetitive traits in toddlerhood and early childhood: a discordant twin analysis of the Gemini cohort. *Int J Behav Nutr Phys Act*. (2023) 20:39. doi: 10.1186/s12966-023-01440-2

53. Smith AD, Herle M, Fildes A, Cooke L, Steinsbekk S, Llewellyn CH. Food fussiness and food neophobia share a common etiology in early childhood. *J Child Psychol Psychiatry*. (2017) 58:189–96. doi: 10.1111/jcpp.12647

54. Fildes A, van Jaarsveld CHM, Cooke L, Wardle J, Llewellyn CH. Common genetic architecture underlying young children's food fussiness and liking for vegetables and fruit. *Am J Clin Nutr*. (2016) 103:1099–104. doi: 10.3945/ajcn.115.122945

55. Roman S, Ramos-Lopez O, Panduro A. Genomic medicine in hepatology: towards personalized medicine in obesity and chronic liver disease. *Ann Hepatol*. (2023) 28:100875. doi: 10.1016/j.aohep.2022.100875

56. Panduro A, Roman S, Milán RG, Torres-Reyes LA, Gonzalez-Aldaco K. Personalized nutrition to treat and prevent obesity and diabetes In: Z Cheng, editor. *Nutritional signaling pathway activities in obesity and diabetes*. Burlington House, Piccadilly, London, W1J 0BA: The Royal Society of Chemistry. (2020).

57. Hunot-Alexander C, Croker H, Fildes A, Johnson F, Beeken RJ. Brief 'Appetitive Trait Tailored Intervention': development in a sample of adults with overweight and obesity. *Behav Chang*. (2022) 39:106–22. doi: 10.1017/bec.2021.22

58. Herle M, Stavola BD, Hübel C, Abdulkadir M, Ferreira DS, Loos RJF, et al. A longitudinal study of eating behaviours in childhood and later eating disorder behaviours and diagnoses. *Br J Psychiatry*. (2020) 216:113–9. doi: 10.1192/bjp.2019.174

59. Soubelet A, Salthouse TA. Influence of social desirability on age differences in self-reports of mood and personality. *J Pers*. (2011) 79:741–62. doi: 10.1111/j.1467-6494.2011.00700.x

60. Campos-Nonato I, Galván-Valencia Ó, Hernández-Barrera L, Oviedo-Solís C, Barquera S. Prevalencia de obesidad y factores de riesgo asociados en adultos mexicanos: resultados de la Ensanut 2022. *Salud Publica Mex*. (2023) 65:s238–47. doi: 10.21149/14809

61. Andersen MK, Ängquist L, Bork-Jensen J, Jonsson AE, Stinson SE, Sandholt CH, et al. Physical activity and insulin sensitivity independently attenuate the effect of FTO rs9939609 on obesity. *Diabetes Care*. (2023) 46:985–92. doi: 10.2337/dc22-2078

62. Chermon D, Birk R. FTO common obesity SNPs interact with actionable environmental factors: physical activity, sugar-sweetened beverages and wine consumption. *Nutrients*. (2022) 14:4202. doi: 10.3390/nu14194202

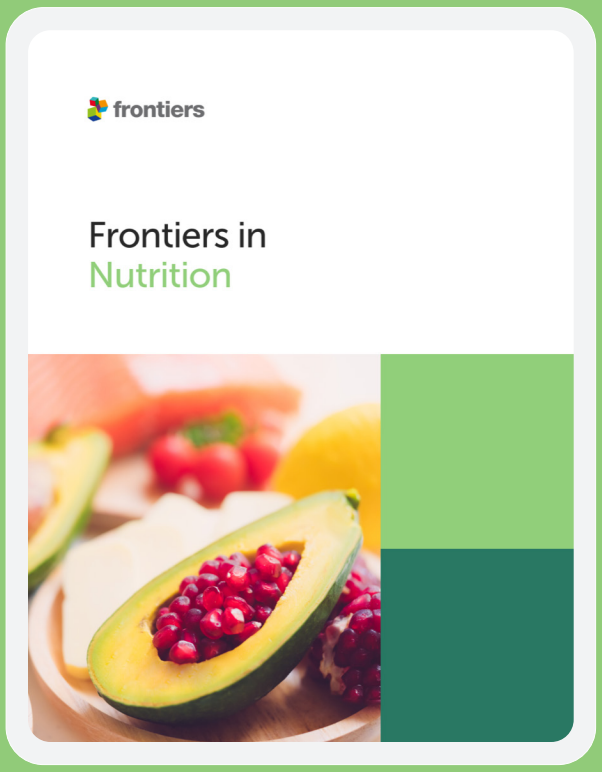
Frontiers in Nutrition

Explores what and how we eat in the context of health, sustainability and 21st century food science

A multidisciplinary journal that integrates research on dietary behavior, agronomy and 21st century food science with a focus on human health.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact