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Environmental factors implicated in obesity

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Environmental factors implicated in obesity

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Editorial: Environmental factors implicated in obesity

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Editorial on the Research Topic
Environmental factors implicated in obesity

The prevalence of obesity has considerably grown in the past few decades globally. Several environmental and behavioral risk factors could explain, at least in part, this observed increase. Obesity predisposes to several comorbidities and a higher risk of mortality. In particular, Cai et al. found that adiposity was associated with a higher risk for all-cause mortality, assessed with the novel index termed the weight-adjusted waist index (WWI). Modern lifestyles are characterized by a variety of potential factors contributing to the development of obesity, such as poor diet quality due to increased exposure to junk food and the scarcity of healthy alternatives, especially in some places (so-called food deserts), but also higher levels of stress resulting from modern life (1). People living in food deserts may rely on unhealthy, processed, and high-calorie foods readily available in convenience stores and fast-food restaurants. This limited access to healthy food options and reliance on unhealthy foods can contribute to the development of obesity and diet-related chronic diseases. The absence of availability of nutritious dietary alternatives can lead to a diet high in calories, saturated fats, and added sugars, which can result in weight gain and the development of obesity. Moreover, food deserts are often found in low-income communities, where residents may face additional barriers, such as transportation difficulties and financial constraints, that limit their ability to access healthy food (2). These factors can lead to a higher reliance on unhealthy meals and play a role in increasing obesity rates.

Furthermore, the transition from healthy dietary patterns, characterized by a preference for plant-based foods, to a Western-style diet, marked by high consumption of nutrient-poor and energy-dense ultra-processed foods such as sugar-sweetened drinks (SSBs), has been identified as a possible cause (3, 4). Ultra-processed foods are typically high in calories and low in nutrients and have been linked to an increased risk of type 2 diabetes, obesity, and other chronic conditions (5). Their consumption has been on the rise globally, and this trend has been associated with adopting Western-style dietary patterns. These diets frequently contain little vegetables, fruits, and whole grains and are dominated by high consumption of high-fat snacks, processed fast foods, and SSBs. The high availability and low cost of ultra-processed foods and aggressive marketing strategies have contributed to their widespread consumption. Therefore, reducing their intake is essential to promoting healthy dietary patterns. Interventions to reduce the consumption of ultra-processed foods can include policies that limit the marketing and availability of these products, education campaigns that promote the consumption of whole, minimally processed foods, and initiatives that improve access to healthy foods in low-income

communities. By addressing the role of ultra-processed foods in unhealthy dietary patterns, we can help promote healthier eating habits and reduce the burden of chronic diseases.

The link between diet quality and obesity is quite complex and most likely multidimensional, involving other aspects of lifestyle (e.g., level of physical activity, feeding times, chronotype, smoking, and alcohol consumption habits, etc.) as well as certain genetic predispositions (6). Of note, the genetics and genomics of nutrition are tools that form the basis for understanding the genetic pathways that are influenced by diet and lead to an increased predisposition to obesity. In addition to hormonal imbalances, alterations in the gut microbiota (GM) and obesity are also studied to unravel the mechanisms underlying the relationship between genetics, environment, GM, and obesity (4). Finally, the ever-increasing trends of obesity-related malignancies make this disease spectrum a public health priority (7). Research on this Research Topic is multidisciplinary. Therefore, future interventions for obesity will increasingly have to consider the numerous environment-obesity interactions. In this Research Topic, there are 10 papers covering the aspects mentioned above.

Food insecurity (FI), the lack of regular access to enough food for a healthy diet, has been the subject of two studies. Although the relationship between FI, poor diet quality, and obesity is widely established, more analysis of the underlying mechanisms and risks is required. Carvajal-Aldaz et al. noted that there are yet no mechanisms explaining this phenomenon. They concluded that although much evidence suggests a link between FI and obesity, this association has only been consistently seen in women from high-income countries, particularly the US. Future research must be adequately planned to shed light on the possible processes underlying this association. The same subject was covered by Fonseca-Pérez et al.; however, they focused on sarcopenic obesity. They reported that diet and aging-related impairments mediate the link between FI and sarcopenic obesity. Additionally, nutrition quality, a significant modifiable risk factor for the development of sarcopenia and obesity, can be influenced by FI. Noteworthy is the inverse relationship between diet quality and FI.

In the context of poor diet quality, SSBs, which contribute to excessive daily energy and sugar intake, are widespread worldwide. Mainly, SSB intake has been related to a higher risk of several health issues, including obesity, diabetes, and cardiovascular disease. Interesting research was conducted by AlFaris et al. on the consumption rates of weekly and daily SSBs in a multi-ethnic middle-aged men group and the relationships between obesity and sociodemographic factors. They discovered that nationality and obesity predicted both weekly and daily consumption of SSBs.

During the COVID-19 pandemic, Abril-Ulloa et al. investigated stress, another element linked to diet quality, among Ecuadorian adults. They demonstrated that higher stress levels were linked to worse diet quality and that the relationship between stress and diet quality was inverse and non-linear.

Thus, new public health measures in places (food deserts) where food insecurity predominates or at critical times (e.g., pandemics) are needed to improve the population's lifestyle and eating habits, which are well-known driving factors for obesity. In this regard, Limone et al.'s notable research has made a major contribution to the current state of information in serious games as a strategy to solve the problem of unhealthy eating behavior. They demonstrated that several serious game projects are effective interventions to modify the eating behavior of children and adults to address the risks of obesity and overweight in these populations.

Also, modern technologies can come to the rescue. In the future, it is intended to achieve personalized customization of the nutritional requirements of different populations and individuals based on the genetic inheritance of variants, ethnicity, and gene expression. The review by Guevara-Ramírez et al. synthesizes dietary practices in Latin America and the relationships between genes and single nucleotide polymorphisms (SNPs) linked to obesity, including the risk allele frequencies. They concluded that several genes and their SNPs had been associated with obesity and obesity-related issues. The risk alleles have been correlated with the deterioration of the lipid profile, and high-fat dietary behaviors were found to induce gene expression profiles related to several metabolic alterations. In addition, in the last few years, increasing evidence linking obesity to GM has been reported. GM management has become a new method of obesity treatment. Sarmiento-Andrade et al. have summarized the biology and physiology of GM in obesity, its role in the pathophysiology of several obesity-related disorders, and the emerging therapeutic applications of prebiotics, probiotics, and fecal microbiota transplantation. Instead, Mayorga-Ramos et al. focused their research on the exciting role of butyrate (a short-chain fatty acid produced by GM) in obesity and diabetes. The authors, after an exhaustive review of the literature, point out that efforts are still needed to decipher well the determination of the best conditions and food sources for butyrate production by the GM *in situ*, the absorption of dietary and microbially produced butyrate under different physiological and pathological conditions, the regulatory mechanisms of butyrate at the cellular and systemic level, and the potential for use as a therapeutic alternative in specific obesity-related disorders. Overall, the connection between genetics, gut microbiota, and obesity related-environmental factors is complex and interrelated. While genetics play a role in determining an individual's susceptibility to obesity, environmental factors such as diet, physical activity, and exposure to endocrine disruptors can influence the gut microbiota and contribute to the development of obesity.

Finally, starting from the evidence that the Mediterranean diet (MD) is a healthy diet effective in tackling obesity and its consequences, Barrea et al. demonstrated that low adherence to the MD was also associated with the presence of nodular thyroid disease and in particular with those at high risk of malignancy in a cohort of subjects with overweight/obesity. These results underscore the importance of promoting healthy dietary habits and adherence to MD as a preventative measure against cancers and associated health risks.

In summary, the reviews and studies mentioned earlier represent a broad amount of new relevant data on the environmental and behavioral factors involved in the etiology, pathophysiology, and treatment of obesity. The articles included in this Research Topic demonstrate that many parts of the

issue still need to be defined and understood, despite all the research and data that already exist on this crucial subject. After reading this Research Topic, some topics, such as environmental factors involved in the development and treatment of obesity, will appear more clear/evident to the reader and strengthen the conviction that environmental intervention is a fundamental part of obesity prevention and treatment.

Author contributions

LV wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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.

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ORIGINAL RESEARCH
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Association of the Weight-Adjusted-Waist Index With Risk of All-Cause Mortality: A 10-Year Follow-Up Study

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Background: To explore the relationship between weight-adjusted-waist index (WWI) and the risk of all-cause mortality in one urban community-dwelling population in China.

Methods: This is a prospective cohort study with a sample of 1,863 older adults aged 60 years or over in Beijing who completed baseline examinations in 2009–2010 and a 10-year follow-up in 2020. WWI was calculated as waist circumference (cm) divided by the square root of weight (kg). Cox regression analysis was performed to investigate the significance of the association of WWI with all-cause mortality. The area under the receiver operating characteristic (ROC) curves were used to compare the ability of each obesity index to predict mortality.

Results: During a median follow-up of 10.8 years (1.0 to 11.3 years), 339 deaths occurred. After adjusted for covariates, the hazard ratios (HRs) for all-cause mortality progressively increased across the tertile of WWI. Compared with the lowest WWI category (tertile1 $<$10.68 cm/$\sqrt{}$kg), with WWI 10.68 to 11.24cm/$\sqrt{}$kg, and$\geq$11.25 cm/$\sqrt{}$kg, the HRs (95% confidence intervals (CIs)) for all-cause mortality were 1.58 (1.12–2.22), and 2.66 (1.80–3.92), respectively. In stratified analyses, the relationship between WWI and the risk of all-cause mortality persisted. The area under ROC for WWI was higher for all-cause mortality than BMI, WHtR, and WC.

Conclusion: WWI was associated with a higher risk for all-cause mortality, and the association was more robust with the highest WWI category.

Keywords: weight-adjusted waist index, all-cause mortality, obesity, older people, 10-year follow-up

INTRODUCTION

Globally, obesity is a significant health challenge as it greatly increases the risk of developing diseases such as metabolic disease, hypertension, stroke, myocardial infarction, osteoarthritis, Alzheimer's disease, depression, and several cancers, resulting in a reduction in life expectancy, with an estimated loss of 5–20 years (1–3). The incidence of obesity is on the rise worldwide. The global prevalence of obesity has almost tripled since the 1980s and continues to grow rapidly (4–6).

Body mass index (BMI) is a widely used measure of obesity. While BMI measures an individual's health, it is flawed. Its assessment of body fat in older adults is not as accurate as of that in younger adults. It doesn't distinguish visceral fat from fat in other areas, such as the buttocks (7). The accumulation of visceral fat, rather than subcutaneous fat, has been strongly associated with insulin resistance, high blood pressure, and dyslipidemia; excess visceral fat is more harmful to an individual's health than fat elsewhere (8–10). Much evidence indicated a linear association between BMI and the risk of hypertension, type 2 diabetes, and cardiovascular diseases (CVD) (11). However, inconsistent or inverse associations between BMI and mortality in various populations have contributed to the "obesity paradox" (12–14). Waist circumference (WC) has been proposed as a high association with CVD risk factors and mortality (15, 16). However, the "obesity paradox" was also found when WC was used to measure obesity (17). Moreover, WC is highly correlated with BMI and is thus limited as an independent measure of mortality risk (16, 18, 19). Waist-to-Height Ratio (WHtR) appears superior in assessing obesity but remains controversial in predicting obesity-related CVD risk and mortality (20–22).

A new adiposity index termed the "weight-adjusted-waist index" was proposed in this context (23). WWI has been proposed to assess obesity (24). Studies on about 1 million Korean adults found that WWI was positively correlated with CVD mortality; unlike BMI, WC, and waist-to-hip ratio, WWI was best at predicting the risk of cardiometabolic disease and death (23). However, the relationship between WWI and all-cause mortality in older Chinese is unclear. Therefore, this study aimed to investigate the association between WWI and all-cause mortality in elderly Chinese.

METHODS

Study Population

Our research program and sampling details have been described above (25–27). In brief, this community-based study was conducted in the Wanshou Road Community of Haidian District in Beijing from September 2009 to June 2010. A two-stage stratified cluster sampling selected community residents aged 60 or above as a representative sample. We excluded cancer patients at baseline. Most cancers are chronic wasting diseases, resulting in weight loss and a reduction in WC (28, 29), there will be an impact on the primary study indicators. A total of 2,162 subjects (female:60.1%) completed the survey. Of the study population, 19 subjects were excluded due to lack of anthropometric data, 280 were lost during the follow-up period from 2010 to 2020, and 1,863 were finally available for statistical analysis. As previously mentioned, all participants in this study were recruited in a community-based cross-sectional survey. Therefore, we retrospectively divided the subjects into three groups to calculate the test power, applied sample size, hazard ratio, overall probability of event, proportion of sample in group, power value was 0.85 and 0.99 and concluded that the difference was statistically significant.

The study protocol was reviewed and approved by the ethical committees of the Chinese PLA General Hospital. The research procedures followed the ethically normative criteria. Written informed consent was acquired from all subjects. All investigators were trained at the Chinese PLA General Hospital and qualified for the post.

Outcome Measures

The outcomes in the present study were all-cause mortality. All-cause death is defined as death from any cause. Follow-up ended in December 2020, and survival was defined as the number of months from recruitment to death or the end of observation (December 31, 2020). Information about vital status was determined through telephone interviews with family members or other caregivers. Respondents' identities were verified by information such as name, age, and gender.

Data Collection

Using standard questionnaires, the researchers assessed the demographics of all participants through face-to-face interviews, including a range of demographic factors, medical history, and lifestyle. Lifestyle includes drinking and smoking. Alcohol consumption and smoking were considered dichotomous variables for never/former and current. Height, weight, WC, and blood pressure were measured according to standardized protocols. Anthropometric measurements were taken by specially trained researchers on subjects wearing light clothes and no shoes. Weight and height were measured twice to the nearest 0.1 kg and 0.1 cm, respectively. We measured the WC of the standing subjects with a piece of soft tape located between the lowest rib and the iliac crest (to the nearest 0.1 cm). WWI was calculated as WC (cm) divided by the square root of weight (kg) (23). BMI was calculated as weight in kilograms divided by the square of height in meters.

Two blood pressure recordings (5-min intervals) were obtained from participants' right arms in a sitting position after 30 min of rest. The blood pressure was measured using a sphygmomanometer, and the average of the two was used for analysis.

Fasting blood samples were taken from all subjects in the morning (after fasting for at least 12 h). An automatic biochemical analyzer measured serum lipids, glucose, routine blood tests, and creatinine. All biochemical analyses were performed in the Department of Biochemistry of the Chinese People's Liberation Army General Hospital.

Participants with fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose ≥11.1 mmol/l after oral glucose tolerance test or blood glucose ≥11.1 mmol/L at any time or those receiving anti-diabetic medications were diagnosed with diabetes mellitus (30, 31). The study population included patients with type 2 diabetes.

Abbreviations: WWI, weight-adjusted-waist index; ROC, receiver operating characteristic; BMI, body mass index; WHO, World Health Organization; CVD, cardiovascular diseases; WC, waist circumference; WHtR, Waist-to-Height Ratio; SBP, systolic Blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, Triglycerides; SUA, serum uric acid; Scr, Serum creatinine; CHD, Coronary heart disease; HTN, hypertension; SD, Standard deviation; HRs, hazard ratios; 95%CIs, 95% confidence intervals.

TABLE 1 | Baseline characteristics of study participants by weight-adjusted waist index.

Characteristics	Weight-adjusted waist index(cm/$\sqrt{}$kg)			*P*-value
	Tertile1(<10.68)	Tertile2(10.68-11.24)	Tertile3(≥11.25)	
N	621	617	625	
Age (years)	68.56 ± 6.78	70.68 ± 6.70	73.81 ± 6.61	< 0.001
Males (%)	288(46.4)	278(45.1)	192(30.7)	< 0.001
BMI (kg/m2)	24.20 ± 3.11	25.11 ± 3.38	25.58 ± 3.64	< 0.001
WC (cm)	81.96 ± 8.48	88.69 ± 7.44	93.49±8.45	< 0.001
SBP (mmHg)	135.05 ± 17.04	138.51 ± 19.44	141.18 ± 20.77	< 0.001
DBP (mmHg)	76.51 ± 9.20	77.57 ± 9.98	77.33 ± 9.96	0.132
FPG (mmol/L)	5.83 ± 1.23	6.01 ± 1.45	6.26 ± 1.84	< 0.001
TC (mmol/L)	5.22 ± 0.99	5.23 ± 1.02	5.28 ± 1.01	0.544
TG (mmol/L)	1.53 ± 0.90	1.66 ± 0.80	1.76 ± 0.98	0.005
HDL-C (mmol/L)	1.46 ± 0.40	1.39 ± 0.35	1.40 ± 0.40	0.007
LDL-C (mmol/L)	3.23 ± 0.84	3.24 ± 0.86	3.21 ± 0.87	0.896
SCr (μmol/L)	74.53 ± 19.13	74.01 ± 20.43	74.39 ± 22.16	0.911
SUA(μmol/L)	300.34 ± 79.68	308.79 ± 92,78	318.33 ± 91.74	0.002
Smokers (%)	183(29.5)	201(32.6)	180(28.8)	0.300
Drinkers (%)	176(28.3)	153(24.8)	140(22.4)	0.052
CHD, *n* (%)	130(20.9)	146(23.7)	160(25.6)	0.148
HTN, *n* (%)	299(48.1)	349(56.6)	368(58.9)	< 0.001
Diabetes, *n* (%)	86(13.8)	113(18.3)	143(22.9)	< 0.001
Stroke, *n* (%)	61(9.8)	82(13.3)	89(14.2)	0.045

BMI, body mass index; WC, waist circumference; SBP, systolic Blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, Triglycerides; SUA, serum uric acid; Scr, Serum creatinine; CHD, Coronary heart disease; HTN, hypertension.

TABLE 2 | Cox regression analyses for the association between all-cause mortality and weight-adjusted waist index.

WWI (cm/$\sqrt{}$kg)	Cases/participants	HR (95% CI)					
		Model 1	*P*-value	Model 2	*P*-value	Model 3	*P*-value
Tertile1(<10.68)	66/621	1 (References)		1 (References)		1 (References)	
Tertile2(10.68–11.24)	108/617	1.71(1.26–2.32)	0.001	1.51(1.11–2.05)	0.009	1.58(1.12–2.22)	0.009
Tertile3(≥11.25)	165/625	2.74(2.06–3.65)	<0.001	2.45(1.83–3.29)	<0.001	2.66(1.80–3.92)	<0.001

Values are n or HR (95% CI).
HR, hazard ratio; CI, confidence interval.
Model 1: Unadjusted.
Model 2: Adjusted for sex, age.
Model 3: Adjusted for age, sex, BMI, WC, SBP, DBP, FPG, TC, HDL, LDL, TG, SUA, SCr, smoking, alcohol drinking, CHD, HTN, diabetes, stroke.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software (version 26.0) was used for data management and statistical analysis. Continuous variables were reported as mean ± standard deviation (SD) and categorical variables as percentages. WWI (cm/$\sqrt{}$kg) was classified by tertile as follows: tertile 1 (<10.68 cm/$\sqrt{}$kg), tertile 2 (10.68–11.24 cm/$\sqrt{}$kg), and tertile 3 (≥11.25 cm/$\sqrt{}$kg). Baseline characteristics between subjects in different groups were compared using the $\chi 2$ test and analysis of variance. We investigated the all-cause mortality according to the WWI categories, with the lowest WWI category (<10.68 cm/$\sqrt{}$kg) as the reference. Cox proportional hazards models were used to estimate the association between all-cause mortality risk and WWI, estimating HRs and 95% CIs. We developed three models to adjust for potential confounders and plotted survival curves. Model 1: unadjusted; Model 2: adjusted for sex, age; Model 3: adjusted for age, sex, BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), serum uric acid (SUA), Serum creatinine (Scr), smoking, alcohol drinking, coronary heart disease (CHD), hypertension (HTN), diabetes, stroke, Subgroup analyses were stratified by sex (men or women), age (<75 or ≥75 years), smoking status (smoking or no smoking), drinking status (alcohol drinking or no alcohol drinking), BMI (<24 kg/m² or 24 kg/m²). Findings were recorded by HRs and 95% CIs. The area under the ROC curves were used to compare the ability of obesity indexes to

predict mortality. All statistical tests were 2-sided, with $P < 0.05$ considered statistically significant.

RESULTS

Baseline Characteristics

Among 1,863 participants (40.69% males), the median follow-up time was 10.8 years (1.0 to 11.3 years), and 339 deaths occurred. The cumulative incidence of death during follow-up was 18.2%. **Table 1** shows the baseline characteristics of participants by WWI categories: As compared with the lowest WWI category (<10.68 cm/$\sqrt{}$kg), the highest WWI category (≥11.25 cm/$\sqrt{}$kg) had higher BMI, WC, SBP, DBP, FPG, TG, SUA, but lower HDL-C; were more likely to be older and probably had a higher rate of diabetes, HTN, and stroke (all $P < 0.05$).

Association Between WWI and All-Cause Mortality

Table 2 and **Figure 1** show the association between WWI and the risk of all-cause mortality. For all models, the WWI category was positively associated with all-cause mortality. Univariate analysis (model 1), after adjustment for age and sex (model 2), and further for BMI, WC, SBP, DBP, FPG, TC, HDL, LDL, TG, SUA, Scr, smoking, alcohol drinking, CHD, HTN, diabetes, stroke (model 3), the HRs for all-cause mortality remained progressively increased across tertile of WWI. Specifically, as compared with the lowest WWI category (<10.68 cm/$\sqrt{}$kg), a WWI of 10.68 to 11.24 cm/$\sqrt{}$kg increased the probability of all-cause mortality (HR 1.58, 95% CI 1.12–2.22), as did the highest WWI category (≥11.25 cm/$\sqrt{}$kg) (HR 2.66, 95% CI 1.80–3.92).

Subgroup Analyses for Association Between WWI and All-Cause Mortality

The association between the highest WWI category (≥11.25 cm/$\sqrt{}$kg) and the risk of all-cause mortality was evaluated by the subgroups sex, age, smoking status, drinking status, BMI, with the lowest WWI category (<10.68 cm/$\sqrt{}$kg) as the reference. After controlling for all covariates except for the stratified variable, the association between WWI and the risk of all-cause mortality remained in nearly every subgroup analysis, but the association was not significant at age ≥75 years (**Figure 2**).

ROC Curves of Each Obesity Indices

Figure 3 shows the area under the ROC curve with its 95% CI to identify all-cause mortality by each obesity indices. According to the ROC analyses, WWI AUC value: 0.636, WC: 0.553, WHtR:0.568. However, the AUC of BMI had no statistical significance for all-cause mortality (AUC <0.5).

DISCUSSION

In this large prospective study of an older Chinese population with a 10-year follow-up cohort, we suggested that WWI, a new adiposity index, was significantly associated with an increased risk of all-cause mortality. The association was independent of sex, age, lifestyle factors, BMI, WC, and various cardiovascular and cerebrovascular risk factors. The highest WWI category (≥11.25 cm/$\sqrt{}$kg) was 2.66-fold associated with all-cause mortality as compared with the lowest WWI category (<10.68 cm/$\sqrt{}$kg). These results were essentially consistent in subgroup analyses. The association between WWI and all-cause mortality in older people (≥75years) disappeared. This result

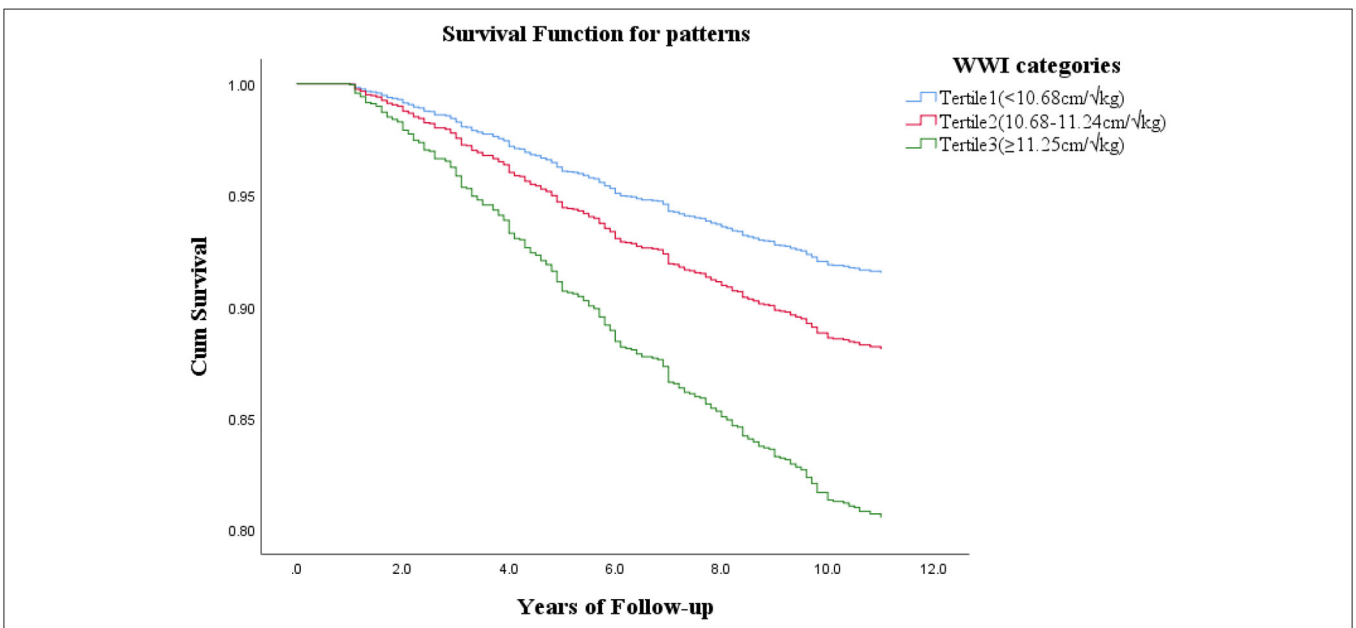

FIGURE 1 | Cox proportional hazards after adjusted for age, sex, BMI, WC, SBP, DBP, FPG, TC, HDL, LDL, TG, SUA, SCr, smoking, alcohol drinking, CHD, HTN, diabetes, stroke.

may be due to differences in body fat distribution between the older and the younger. In addition, there are more risk factors for death in the elderly population. Furthermore, this inconsistent result may also be due to the limited statistical power of this study. Finally, our findings showed that WWI was superior to BMI, WC, and WHtR in predicting all-cause mortality.

Obesity is caused by a chronic energy imbalance between eating too many calories and burning too few (32). Other studies have suggested that obesity may be an inherited disorder of energy homeostasis (33). Hormonal, nutritional, and metabolic factors, energy expenditure, psychological factors, and sedentary behavior play a role in the pathophysiology of obesity (34). Obesity prevalence increases year by year and has become the number one lifestyle-related risk factor for premature death (5). Several studies have demonstrated that obesity increases the risk of all-cause mortality (35–39).

In 1993, WHO defined obesity as a BMI≥30 kg/m² (40). However, subsequent evidence suggests that Asians with lower BMIs are more likely to develop diabetes than European-American (41). Well-known, death rates are highest in those who have had diabetes for a long time (42). A recent large study found that the risk of diabetes in Chinese people with a BMI of 26.9 kg/m²was the same as that of European-American populations with a BMI of 30 kg/m², which remained after controlling for socioeconomic status and smoking status (41, 43). It is unclear whether the lower threshold for BMI in Asians is due to differences in body composition, biochemical characteristics, lifestyle, or genetics. However, what is clear is that Asian populations need to intervene with weight change earlier.

Stratified Variables	WWI (cm/√kg)	HR (95% CI)		*P* for interaction
Sex	**Men**			0.157
	Tertile2(10.68-11.24)	1.77(1.13-2.77)	0.012	
	Tertile3(≥11.25)	2.73(1.61-4.63)	<0.001	
	Women			
	Tertile2(10.68-11.24)	1.19(0.69-2.05)	0.536	
	Tertile3(≥11.25)	2.20(1.21-4.00)	0.010	
Age	**Age <75 years**			0.133
	Tertile2(10.68-11.24)	1.84(1.08-3.14)	0.025	
	Tertile3(≥11.25)	2.63(1.31-5.27)	0.007	
	Age ≥ 75 years			
	Tertile2(10.68-11.24)	1.03(0.65-1.64)	0.900	
	Tertile3(≥11.25)	1.36(0.82-2.25)	0.230	
Smoking Status	**non-smoking**			0.211
	Tertile2(10.68-11.24)	1.78(1.13-2.79)	0.012	
	Tertile3(≥11.25)	3.06(1.90-4.94)	<0.001	
	smoking			
	Tertile2(10.68-11.24)	1.50(0.91-2.47)	0.115	
	Tertile3(≥11.25)	2.73(1.56-4.77)	<0.001	
drinking Status	**non-drinking**			0.073
	Tertile2(10.68-11.24)	1.35(0.90-2.00)	0.143	
	Tertile3(≥11.25)	2.78(1.81-4.28)	<0.001	
	drinking			
	Tertile2(10.68-11.24)	2.88(1.55-5.37)	0.001	
	Tertile3(≥11.25)	3.38(1.71-6.68)	<0.001	
BMI	**BMI<24**			0.540
	Tertile2(10.68-11.24)	2.07(1.27-3.37)	0.004	
	Tertile3(≥11.25)	4.18(2.46-7.11)	<0.001	
	BMI ≥ 24			
	Tertile2(10.68-11.24)	1.20(0.75-1.90)	0.445	
	Tertile3(≥11.25)	1.72(1.03-2.88)	0.037	

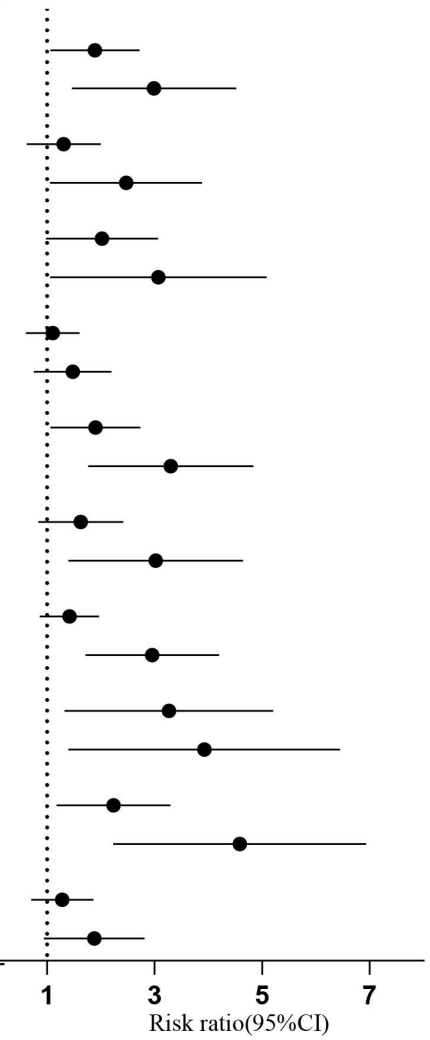

FIGURE 2 | Subgroup analyses for the association between all-cause mortality and WWI categories. Adjusted for age, sex, BMI, WC, SBP, DBP, FPG, TC, HDL, LDL, TG, SUA, smoking, alcohol drinking, CHD, HTN, diabetes, stroke, except for the stratified variable. The stratified analysis was performed according to the boundaries of the bolded values.

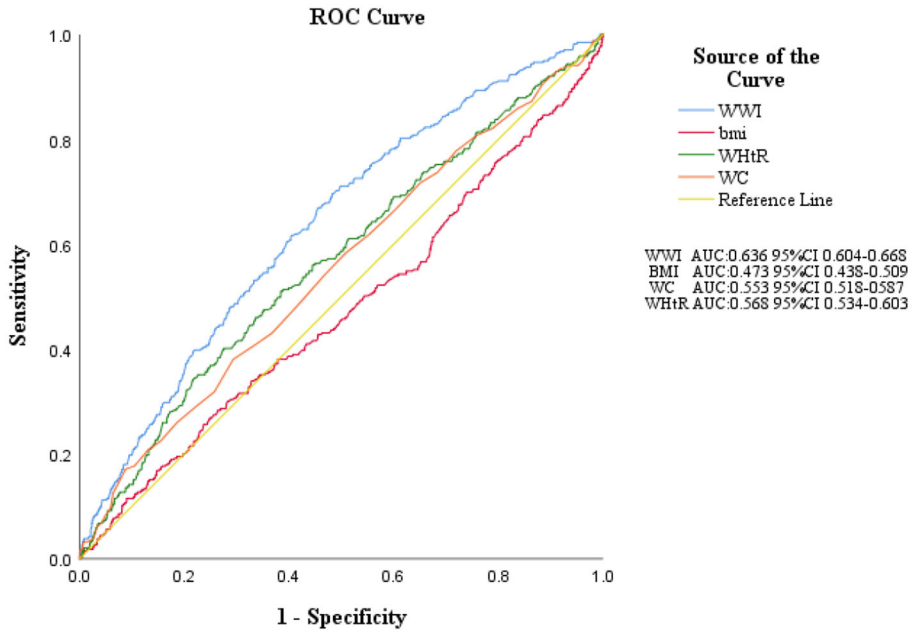

FIGURE 3 | ROC curves of each obesity indices. WWI, weight-adjusted-waist index; BMI, body mass index; WHtR, waist-to-height ratio; WC, waist circumference; ROC, receiver operating characteristic; AUC, area under the curve.

Unfortunately, current mainstream guidelines do not make clear racial distinctions, which ignores east-west differences and other factors such as economics. In addition, whether BMI is the best predictor of future health is debatable, so more detailed studies are urgently needed to guide clinical practice.

WWI is a new obesity index based on weight and WC, which has a good predictive ability for cardiometabolic morbidity and mortality in the Korean population (23). Li et al. recently reported in a rural Chinese cohort study that the highest WWI category was significantly associated with an increased risk of HTN (44). A recent study on WWI reflecting fat and muscle mass in the opposite direction in older adults showed that WWI was positively correlated with fat mass and negatively correlated with muscle mass (24). WWI is a novel obesity index developed in recent years, and there are few related studies. Our study further verified the association of this indicator with all-cause mortality in the Chinese elderly population. The indicator is easy to operate and economical. It can be applied to medical and health institutions at all levels, especially in areas where medical standards are lacking or large-scale data research is required. Therefore, for the high WWI population, early assessment of target organ damage and initiation of treatment can reduce the risk of cardiovascular and cerebrovascular diseases and improve prognosis.

The present study has some limitations. Firstly, our sample did not include young adults, and more research is needed to validate our results for the general population. Secondly, confounding variables not included in the current analyses, such as socioeconomic status and some drugs possibly affecting mortality. All individuals were chosen from the Wanshoulu Community, and their socioeconomic status is relatively balanced. However, some drugs were not included in the study due to their wide variety and low usage rate. Finally, the association between WWI and cause-specific mortality could not be determined because death registration details were unavailable.

CONCLUSION

In this study, high levels of WWI were positively associated with all-cause mortality in older Chinese people. This study may provide evidence that WWI as an indicator of obesity is an independent risk factor for all-cause mortality, suggesting that WWI may be an intervention indicator to reduce all-cause mortality in the elderly.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants and was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chinese PLA General Hospital. Informed written consent to participate in the study

was obtained from all participants. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SW, PZ, and SC designed the research. SC, BC, and AZ collected the data. SC, LZ, and YuZ wrote the manuscript. JS, ML, YS, YaZ, SM, and QB help optimize the research and proofread the manuscript. All authors read and approved the final manuscript.

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Adherence to the Mediterranean Diet as a Modifiable Risk Factor for Thyroid Nodular Disease and Thyroid Cancer: Results From a Pilot Study

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Iodine deficiency is the most important established nutritional risk factor for the development of thyroid nodular disease. Nevertheless, to the best of our knowledge, to date no study focused on the association between the adherence to the Mediterranean diet (MD) and thyroid nodular disease. Adherence to the MD was evaluated using the PREvención con DIetaMEDiterránea (PREDIMED) questionnaire. Physical activity, smoking habits, and anthropometric parameters were studied. PREDIMED was used to evaluate the degree of adherence to the MD. Evaluation of fine needle aspiration cytology of thyroid lesions based on 2013 Italian thyroid cytology classification system. Cytology of thyroid nodules was carried out through sonography-guided fine-needle aspiration and patients were divided into 5 categories: TIR2, TIR3a, TIR3b, TIR4, and TIR5. The study population consisted of 794 subjects (554 females, 69.8%), aged 18–65 years, with BMIs ranging from 19.4 to 55.3 kg/m^2. Thyroid nodular disease was present in 391 participants (49.2%), and the most frequent cytological categories was TIR2 (18.3 %), followed by a TIR4 (8.9 %). The presence of thyroid nodules was also significantly associated with the lowest adherence to the MD (OR 6.16, $p < 0.001$). Patients with TIR5 had the lower adherence to the MD (2.15 ± 1.12 score) compared to other TIRs ($p < 0.001$). The cytological category with high-risk of malignancy (TIR4/TIR5) was significantly associated with the lowest adherence to the MD (OR 137.55, $p < 0.001$) and PREDIMED score (OR = 0.33, $p < 0.001$, 95% IC = 0.26–0.41, $R^2 = 0.462$). At multiple regression analysis, PREDIMED score was the main predictor of both the presence of nodules ($p < 0.001$) and the cytological category with high-risk of malignancy ($p < 0.001$). At ROC analysis PREDIMED score ≤ 5 and ≤ 4 ($p = 0.001$) were the values that predicted the presence of thyroid nodular disease and cytological category with high-risk of malignancy, respectively. In conclusion, our study demonstrated that the low adherence to the MD is associated with the presence of thyroid nodular disease and in particular with those at high-risk of malignancy.

Keywords: Mediterranean diet (MD), thyroid nodular disease, thyroid cancer, FNA, Tir, PREvención con DIeta MEDiterránea (PREDIMED), nutritionist, fine needle aspiration (FNA)

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INTRODUCTION

Iodine deficiency represents the most important established nutritional risk factor for the development of thyroid nodular diseases (1). Furthermore, iodine intake is also a risk factor for thyroid cancer (2), with a U-shaped association between iodine consumption and thyroid diseases, indicating that either high or a low iodine intake will lead to thyroid diseases (3). A number of different modifying and non-modifying factors could account for the increased incidence of benign/malign thyroid nodular disease (4). In particular, unhealthy dietary pattern could contribute to the pathogenesis of thyroid nodular disease, although there are not sufficient studies to establish if this was due to a direct effect of unhealthy nutrition or mediated by obesity, insulin resistance, and inflammation that are usually a consequence of unhealthy nutrition (1).

Along with obesity, the incidence of both benign and malign thyroid nodular disease is increasing worldwide (5). However, the association between obesity epidemic and benign thyroid nodular disease or thyroid cancer is still debated (6, 7). In particular, there is conflicting evidence on the association between obesity and differentiate thyroid cancer, the most common endocrine malignancy, and differentiate thyroid cancer aggressiveness (8).

In this regard, the inflammatory potential and insulin resistance related to unhealthy dietary pattern are well-known (9, 10). In particular, inflammation (11) and insulin resistance (12, 13) have gained growing interest in promoting thyroid cell hyperplasia, thus facilitating the prevalence and malignant growth in thyroid nodular disease. To increase the knowledge on nutritional factors might be of crucial importance for organizing thyroid nodular disease prevention strategies (14–16).

Indeed, rarely the record of the consumption of some single foods, including red meat, and nut intake, alcohol drinking, has been included in the clinical evaluation of thyroid nodular disease (17, 18). In particular, Yao et al. reported that red meat consumption was an independent risk factor of thyroid nodular disease, while nut consumption was an independent protective factor (18).

Some nutritional patterns, together with excessive weight, seem to also play a relevant role in thyroid cancer carcinogenesis, although a clear association between dietary factors and thyroid cancer has not been defined so far (1, 19). In particular, different single foods have been reported to have protective effects on thyroid cancer risk, including fish (1, 20), vegetables (21), mainly cruciferous intake (1, 22), fruit (21). Nevertheless, the studies were conducted only in Western country population (23), and their results were globally inconsistent (24).

In addition, diet is a complex and synergistic combination of single foods, which are not individually consumed (25). For this reason, in free-living populations, it is challenging, to separate the effect of single foods from others (26). In this context, the evaluation of a healthful dietary pattern, as Mediterranean diet (MD), in patients with thyroid nodular disease and grouped according to their cytological classification has been never investigated previously.

The Mediterranean-style dietary pattern has demonstrated to represent as the dietary pattern that globally reflects the characteristics of a healthy diet effective in tackling obesity epidemic (27) and obesity-related consequences, including cardiovascular diseases (28), and cancer (29). The anti-inflammatory and anti-oxidant properties exerted by the MD is widely recognized (30, 31).

According to current guidelines, management of thyroid nodular disease is primarily based on morphologic classification of the cytological samples obtained by fine-needle aspiration (FNA) complemented by clinical history, imaging findings, and molecular markers test results (32–34). Nevertheless, the nutritional aspects of patients with thyroid nodular disease have generally been unexplored.

A primary aim of this study was to investigate the association between adherence to the MD and presence of thyroid nodular disease in a large cohort of adult population, providing a detailed information about single MD food items in patients with thyroid nodule presence. As second aim, in the subset of the study participants who have undergone FNA, we have evaluated adherence to the MD according to the cytological classification of thyroid nodules.

MATERIALS AND METHODS

This monocentric study was carried out in patients attending the Obesity Unit (C.I.B.O. and EASO center) at the Unit of Endocrinology, Clinical Medicine and Surgery Department, University "Federico II" of Naples from January 2015 to January 2021. Federico II Ethical Committee approved this study protocol (n. 239/11). This study was carried out in accordance with the Declaration of Helsinki (Code of Ethics of the World Medical Association) for experiments that involved humans. Part of the participants were also recruited during the OPERA prevention project for details see "The opera prevention project" (35). All participants were informed about the study design and aim and gave informed consent. This study included 794 participants, coming from the same geographical area around Naples metropolitan area, Campania, Italy.

Thyroid Assessments

In all participants, thyroid nodular disease was evaluated at the Endocrinology Unit of Federico II Hospital (Naples, Italy). In the subset of the study participants with thyroid nodular disease, the cytological samples obtained by FNA, have been analyzed of the Pathology Department, according to the Italian consensus for the classification and reporting of thyroid cytology (36). Based on this classification, patients were divided into 5 categories: TIR2, non-malignant/benign; TIR3a, low-risk indeterminate lesion; TIR3b, high-risk indeterminate lesion; TIR4, suspicious of malignancy, and TIR5, malignant. In particular, in this study we grouped the patients into two different risk categories, low risk or uncertain risk of malignancy (TIR2, TIR3a, and TIR3b) and high risk of malignancy (TIR4/TIR5). Thyroid nodular disease with TIR1 cytology were excluded from this study.

Physical Activity and Smoking Habits

Physical activity levels and smoking habits were evaluated in all participants through the administration of a standard questionnaire, as already reported in other studies (37, 38). Subjects who practiced at least 30 min of daily aerobic physical activity were classified as active (YES). Similarly, when participants smoking at least one cigarette per day were classified as current smokers (YES), as we reported earlier (39, 40).

Anthropometric Measurements

All anthropometric measurements, including weight and height were done after an overnight fast, between 9 and 10 a.m. in all participants who wore light clothing and were without shoes. In particular, a wall-mounted stadiometer to the nearest 1 cm and a calibrated balance beam scale was used to the nearest 50 g (Seca 711; Seca, Hamburg, Germany) were used for height and weight measurement, respectively. Body mass index (BMI) was calculated by weight (kg) and height squared (m^2) and subjects were classified into five BMI classes: normal weight, overweight, grade I obesity, grade II obesity, and grade III obesity (BMI: 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, and $\geq$40.0 kg/m^2, respectively), as previously reported (41) and in accordance with the WHO's criteria WHO (42).

Adherence to the MD

A previously validated of 14-item questionnaire PREvention with MEDiterranean Diet (PREDIMED) (43) questionnaire, was assessed for evaluated adherence to the MD (43), as we reported earlier (44–46). This questionnaire was performed by a certified clinical nutritionist through a face-to-face interview with all the enrolled participants. Scores of zero (No) and one (Yes), were given for questions of PREDIMED questionnaire. From the sum of the 14 questions of the PREDIMED questionnaire, PREDIMED score was calculated. From the totalized PREDIMED score values, participants we divided into three categories of adherence to the MD: highest adherence, average adherence, and lowest adherence to the MD (PREDIMED score $\geq$10, 6–9, and 0–5, respectively) (44–46).

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate the data distribution and the abnormal data were normalized by logarithm. Skewed variables were back-transformed for presentation in tables and figures. The chi-square (χ^2) test was used to determine the statistically significant differences in the frequency distribution, including sex, lifestyle characteristics, anthropometric measurements, nutritional and thyroid parameters. The differences in continuous variables between nodules presence/absence were compared using the Student's unpaired *t*-test, while the differences in multiple groups (cytology categories based on 2013 Italian thyroid cytology classification system) were analyzed by ANOVA test followed by the Bonferroni *post-hoc* test. A multinomial logistic regression model, odds ratio (OR), *p*-value, 95% interval confidence (IC), R^2, and χ^2, were performed to assess the association among nodules presence/absence and cytology categories (TIR2, TIR3a, TIR3b vs. TIR4, and TIR5) with categorical variables included in this study. To the bivariate proportional OR model performed to assess the association among the nodules presence/absence and cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) with continuous variables included in this study (*p*-value, 95% CI, and R^2). In addition, two multiple linear regression analysis models (stepwise method), expressed as R^2, Beta (β) and *t*, with the nodules presence/absence as a dependent variable were used to estimate the predictive value of: sex, lifestyle characteristics, BMI categories, and PREDIMED scores (Model 1), and each item included in PREDIMED questionnaire and PREDIMED score (Model 2). Further two multiple linear regression analysis models (stepwise method), expressed as R^2, Beta (β), and *t*, with the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) as a dependent variable were used to estimate the predictive value of: sex, lifestyle characteristics, BMI categories, and PREDIMED scores (Model 1), and each item included in PREDIMED questionnaire and PREDIMED score (Model 2). Receiver operator characteristic (ROC) curves analysis were performed to determine area under the curve (AUC), criterion, sensitivity and specificity, standard error, and 95% IC as well as cut-off values for PREDIMED score in detecting presence of thyroid nodules and the high-risk of malignancy (TIR4/TIR5). Variables with a variance inflation factor (VIF) >10 were excluded to avoid multicollinearity. The *p*-values below 5% were considered statistically significant. Data were analyzed using the IBM SPSS Statistics Software (PASW Version 21.0, SPSS Inc., Chicago, IL, USA) and MedCalc® package (Version 12.3.0 1993–2012 MedCalc Software bvba—MedCalc Software, Mariakerke, Belgium).

RESULTS

The study population consisted of 794 subjects, 240 males (30.2%) and 554 females (69.8%), aged 18–65 years, with BMIs ranging from 19.4 to 55.3 kg/m^2. There were 215 current smokers (27.1%), while there were 416 physically active subject (52.4%). Regarding BMI classes, the most common was grade III obesity (170 patients, 21.4%). In addition, based on PREDIMED categories, the majority of subjects had an average adherence to the MD (49.4%), while only 15.7% of the study population showed a high adherence to the MD. Thyroid nodular disease were present in 391 (49.2%) participants, with a clear gender difference in thyroid nodular disease prevalence ($\chi^2 = 90.06$; $p < 0.001$). The descriptive characteristics, including gender, age, lifestyle characteristics, anthropometric measurements, nutritional, and thyroid parameters of the study population are given in **Table 1**.

Table 2 showed the same characteristics reported in **Table 1** of the study population according to presence/absence of thyroid nodular disease. In particular, there were no sex, age, and BMI differences in the two categories. Contrariwise, participants with thyroid nodular disease were more frequently smokers ($p < 0.001$) and practiced less physical activity ($p < 0.001$) than to those without thyroid nodular disease. In addition, patients with thyroid nodular disease had a lower adherence to the MD ($p < 0.001$) compared to those without thyroid nodular disease.

TABLE 1 | The descriptive characteristics, including gender, age, lifestyle characteristics, anthropometric measurements, nutritional, and thyroid parameters of the study population.

Parameters	Mean ± SD or *n*, % *n*. 794
Sex (Male)	240 (30.2%)
Age (Years)	43.13 ± 11.98
Lifestyle characteristics	
Smoking (Yes)	215 (27.1%)
Physical activity (Yes)	416 (52.4%)
Anthropometric measurements	
Weight (kg)	93.33 ± 25.88
Height (m)	1.68 ± 0.09
BMI (kg/m^2)	32.86 ± 7.94
Normal weight (*n*, %)	166 (20.9%)
Overweight (*n*, %)	161 (20.3%)
Grade I obesity (*n*, %)	157 (19.8%)
Grade II obesity (*n*, %)	140 (17.6%)
Grade III obesity (*n*, %)	170 (21.4%)
Nutritional parameters	
PREDIMED score	6.61 ± 2.86
Low adherence to the MD	277 (34.9%)
Average adherence to the MD	392 (49.4%)
High adherence to the MD	125 (15.7%)
Thyroid nodules	
Presence	391 (49.2%)
Absence	403 (50.8%)

SD, Standard deviations; BMI, Body mass index; PREDIMED, Prevención con Dieta Mediterránea; MD, Mediterranean Diet.

TABLE 2 | The descriptive characteristics, including gender, age, lifestyle characteristics, anthropometric measurements, nutritional, and thyroid parameters of the study population according to presence/absence of thyroid nodular disease.

Parameters	Nodules presence *n*. 391 (49.2%)	Nodules absence *n*. 403 (50.8%)	*p-value
Sex			
Males (*n*, %)	110 (28.1%)	130 (32.3%)	$\chi^2 = 1.41$, $p = 0.235$
Females (*n*, %)	281 (71.9%)	273 (67.7%)	
Age (Years)	42.83 ± 13.59	43.43 ± 10.19	0.480
Lifestyle characteristics			
Smoking (Yes)	155 (39.6)	60 (14.9%)	$\chi^2 = 60.33$, $p < 0.001$
Physical activity (Yes)	143 (36.6)	273 (67.7%)	$\chi^2 = 76.05$, $p < 0.001$
Anthropometric measurements			
BMI (kg/m^2)	33.27 ± 8.08	32.45 ± 7.79	0.145
Normal weight (*n*, %)	70 (17.9%)	96 (23.8%)	$\chi^2 = 3.85$, $p = 0.066$
Overweight (*n*, %)	90 (23.0%)	71 (17.6%)	$\chi^2 = 3.25$, $p = 0.071$
Grade I obesity (*n*, %)	76 (19.4%)	81 (20.1%)	$\chi^2 = 0.02$, $p = 0.884$
Grade II obesity (*n*, %)	70 (17.9%)	70 (17.4%)	$\chi^2 = 0.01$, $p = 0.917$
Grade III obesity (*n*, %)	85 (21.7%)	85 (21.1%)	$\chi^2 = 0.02$, $p = 0.892$
Nutritional parameters			
PREDIMED score	5.27 ± 2.62	7.90 ± 2.44	<0.001
Low adherence to the MD	212 (54.2%)	65 (16.1%)	$\chi^2 = 125.09$, $p < 0.001$
Average adherence to the MD	158 (40.4%)	234 (58.1%)	$\chi^2 = 24.05$, $p < 0.001$
High adherence to the MD	21 (5.4%)	104 (25.8%)	$\chi^2 = 60.95$, $p < 0.001$

*BMI, Body mass index; PREDIMED, Prevención con Dieta Mediterránea; MD, Mediterranean Diet. *A significant difference ($p < 0.05$).*

Analyzing the response frequency of items included in the PREDIMED questionnaire in detail, according to presence/absence of thyroid nodular disease, we found that the patients with thyroid nodular disease consumed less healthy foods of MD including extra-virgin olive oil ($p < 0.001$), vegetables ($p < 0.001$), and fish ($p < 0.001$), and more non-Mediterranean foods, including red/processed meats ($p < 0.001$) and butter ($p = 0.004$) as compared with the subjects without thyroid nodular disease; **Table 3**.

Figure 1 showed the percentage of the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system. Most of the participants presented a TIR2 (18.3%), followed by a TIR4 (8.9%).

Table 4 reported gender, age, lifestyle characteristics, anthropometric measurements, and nutritional parameters of the study population according to the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system. Patients with TIR5 were mostly male ($p < 0.001$) and were younger than subjects with TIR2 ($p < 0.001$). In addition, a higher percentage of smokers and sedentary were present in patients with TIR5 compared to the other TIR categories ($p < 0.001$). In addition, a higher percentage of patients with grade III obesity (41.7%) were present in patients with TIR5 compared to other TIRs ($p < 0.001$). With respect to nutritional parameters, patients with TIR 5 had the lowest adherence to the MD (2.15 ± 1.12 score) and had the highest percentage of the low adherence to this dietary pattern (98.3%) than other TIRs ($p < 0.001$; **Table 4**).

In **Table 5** we reported the responses of each item included in PREDIMED questionnaire in the study population grouped according to the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system. As showed in the **Table 5**, the participants with TIR5 exhibited significant differences compared with other TIRs in terms of the consumption of all PREDIMED items, except for poultry meat ($p = 0.096$).

Table 6 reported the results of a multinomial logistic regression to assess the association between the thyroid nodules presence/absence and categorical variables included in this study. The presence of thyroid nodular disease was significantly

TABLE 3 | Response frequency of dietary components included in the PREDIMED questionnaire according to presence/absence of thyroid nodular disease.

Questions of PREDIMED questionnaire	Nodules presence		Nodules absence			
	n	%	*n*	%	χ^2	**p*-value
Use of extra virgin olive oil as main culinary lipid	273	69.8	341	84.6	66.22	<0.001
Extra virgin olive oil >4 tablespoons	177	45.3	218	54.1	5.84	0.016
Vegetables ≥2 servings/day	130	33.2	247	61.3	61.46	<0.001
Fruits ≥3 servings/day	100	25.6	286	71.0	110.67	<0.001
Red/processed meats <1/day	129	33.0	305	75.7	144.22	<0.001
Butter, cream, margarine <1/day	234	59.8	200	49.6	7.96	0.004
Soda drinks <1/day	184	47.1	199	49.4	0.34	0.559
Wine glasses ≥7/week	95	24.3	162	40.2	22.20	<0.001
Legumes ≥3/week	146	37.3	228	56.6	28.70	<0.001
Fish/seafood ≥3/week	79	20.2	329	81.6	297.37	<0.001
Commercial sweets and confectionery ≤2/week	123	31.5	182	45.2	15.18	0.001
Tree nuts ≥3/week	89	22.8	151	37.5	19.66	<0.001
Poultry more than red meats	177	45.3	210	52.1	6.64	0.010
Use of sofrito sauce ≥2/week	121	30.9	161	40.0	3.45	0.063

*PREDIMED, Prevención con Dieta Mediterránea. *A significant difference ($p < 0.05$).*

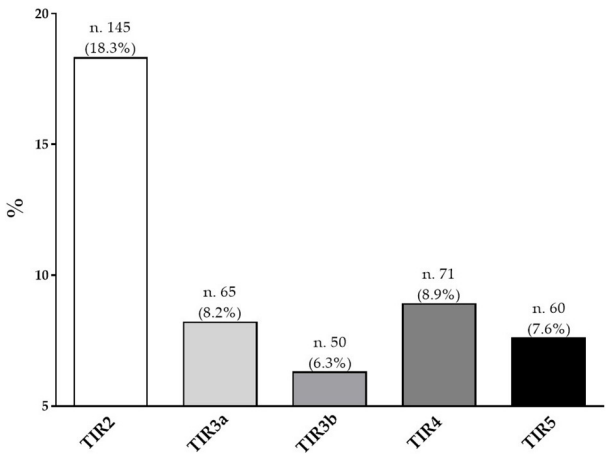

FIGURE 1 | Percentage of the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system.

associated with all categorical variables ($p < 0.001$), except gender ($p = 0.206$) and grade I obesity ($p = 0.815$). In particular, the presence of thyroid nodular disease was associated with smoking (OR 3.76, $p < 0.001$), physically inactive subjects (OR 0.28, $p < 0.001$), the BMI classes, and the lowest adherence to the MD (OR 6.16, $p < 0.001$).

To the bivariate proportional OR model performed to assess the association between the thyroid nodules presence/absence and continuous variables, included age (OR = 0.99, $p = 0.480$, 95% CI = 0.98–1.01, $R^2 = 0.001$), BMI (OR = 1.01, $p = 0.145$, 95% CI = 0.99–1.03, $R^2 = 0.003$), and PREDIMED score (OR = 0.67, $p < 0.001$, 95% CI = 0.63–0.72, $R^2 = 0.208$).

Table 7 summarized the results of a multinomial logistic regression to assess the association between the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) and categorical variables included in this study. The TIR4/TIR5 category was significantly associated with all categorical variables ($p < 0.001$), except grade I obesity (OR 1.29, $p = 0.339$). In particular, the TIR4/TIR5 category were associated with smoking (OR 9.94, $p < 0.001$), physically inactive subjects (OR 0.09, $p < 0.001$), the BMI classes, and the lowest adherence to the MD (OR 137.55, $p < 0.001$; **Table 7**).

To the bivariate proportional OR model performed to assess the association between the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) and continuous variables, included age (OR = 0.96, $p < 0.001$, 95% CI = 0.94–0.97, $R^2 = 0.076$), BMI (OR = 1.15, $p < 0.001$, 95% CI = 1.12–1.19, $R^2 = 0.021$), PREDIMED score (OR = 0.33, $p < 0.001$, 95% CI = 0.26–0.41, $R^2 = 0.462$).

Table 8 showed the bivariate proportional OR model performed to assess the association between the nodules presence/absence and the responses of each item included in PREDIMED questionnaire. In particular, the presence of thyroid nodules was associated with all items included in PREDIMED questionnaire, except for soda drinks ($p = 0.513$) and use of sofrito sauce ($p = 0.054$; **Table 8**).

Table 9 reported the bivariate proportional OR model performed to assess the association between the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) and the responses of each item included in PREDIMED questionnaire. TIR4/TIR5 category was associated with all items included in PREDIMED questionnaire, except for wine glasses ≥7/week ($p = 0.298$; **Table 9**).

To compare the relative predictive power of sex, smoking, physical activity, BMI categories, PREDIMED score, and each item included in PREDIMED questionnaire associated with thyroid nodules presence/absence, we performed two multiple regression analysis. The first model included sex, lifestyle characteristics, BMI categories, and PREDIMED scores. In this

TABLE 4 | Gender, age, lifestyle characteristics, anthropometric measurements, and nutritional parameters of the study population according to the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system.

Parameters	TIR2 *n*. 145 (18.3%)	TIR3a *n*. 65 (8.2%)	TIR3b *n*. 50 (6.3%)	TIR4 *n*. 71 (8.9%)	TIR5 *n*. 60 (7.6%)	*p-value
Sex						
Males (*n*, %)	26 (17.9%)	13 (20.0%)	14 (28.0%)	24 (33.8%)	33 (55.0%)	$\chi^2 = 32.14$, $p < 0.001$
Females (*n*, %)	119 (82.1%)	52 (80.0%)	36 (72.0%)	47 (66.2%)	27 (45.0%)	
Age (Years)	48.73 ± 11.29	44.69 ± 13.80	37.32 ± 11.98	37.25 ± 13.86	37.71 ± 13.31	<0.001
Lifestyle characteristics						
Smoking (Yes)	22 (15.2%)	17 (26.2%)	19 (38.0%)	40 (56.3%)	57 (95.0%)	$\chi^2 = 126.40$, $p < 0.001$
Physical activity (Yes)	81 (55.9%)	30 (46.2%)	21 (42.0%)	7 (9.9%)	4 (6.7%)	$\chi^2 = 71.44$, $p < 0.001$
Anthropometric measurements						
BMI (kg/m^2)	27.80 ± 6.06	29.94 ± 7.33	39.64 ± 5.08	38.34 ± 5.44	38.77 ± 6.72	<0.001
Normal weight (*n*, %)	52 (35.9%)	15 (23.1%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	$\chi^2 = 71.36$, $p < 0.001$
Overweight (*n*, %)	55 (37.9%)	22 (33.8%)	0 (0.0%)	8 (11.3%)	5 (8.3%)	$\chi^2 = 56.18$, $p < 0.001$
Grade I obesity (*n*, %)	20 (13.8%)	15 (23.1%)	12 (24.0%)	17 (23.9%)	12 (20.0%)	$\chi^2 = 5.10$, $p = 0.278$
Grade II obesity (*n*, %)	11 (7.6%)	7 (10.8%)	16 (32.0%)	20 (28.2%)	16 (26.7%)	$\chi^2 = 27.74$, $p < 0.001$
Grade III obesity (*n*, %)	7 (4.8%)	6 (9.2%)	21 (42.0%)	26 (36.6%)	25 (41.7%)	$\chi^2 = 65.66$, $p < 0.001$
Nutritional parameters						
PREDIMED score	7.49 ± 1.76	6.28 ± 2.02	4.04 ± 1.54	3.31 ± 1.10	2.15 ± 1.12	<0.001
Low adherence to the MD	21 (14.5%)	24 (36.9%)	38 (76.0%)	70 (98.6%)	59 (98.3%)	$\chi^2 = 212.99$, $p < 0.001$
Average adherence to the MD	105 (72.4%)	39 (60.0%)	12 (24.0%)	1 (1.4%)	1 (1.7%)	$\chi^2 = 159.88$, $p < 0.001$
High adherence to the MD	19 (13.1%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	$\chi^2 = 28.01$, $p < 0.001$

*BMI, Body mass index; PREDIMED, Prevención con Dieta Mediterránea; MD, Mediterranean Diet. *A significant difference ($p < 0.05$).*

model, PREDIMED score was entered at the first step ($p < 0.001$), followed by the BMI ($p < 0.001$). Results were reported in **Table 10**. The second model included each item included in PREDIMED questionnaire and PREDIMED score. In this model, fish consumed was entered at the first step ($p < 0.001$).

To compare the relative predictive power of sex, smoking, physical activity, BMI categories, PREDIMED score, and each item included in PREDIMED questionnaire associated with the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5), we performed two multiple regression analysis. The first model included sex, lifestyle characteristics, BMI categories, and PREDIMED scores. In this model, PREDIMED score was entered at the first step ($p < 0.001$), followed by the smoking ($p < 0.001$). Results were reported in **Table 11**. The second model included each item included in PREDIMED questionnaire and PREDIMED score. In this model, PREDIMED score consumed was entered at the first step ($p < 0.001$; **Table 11**).

To determine the cut-off values of PREDIMED score that were predictive of the presence of thyroid nodules and TIR4/TIR5 cytology category, two ROC analysis were performed. In the first ROC analysis the threshold values of adherence to the MD predicting the presence of thyroid nodules were found at PREDIMED score ≤ 5 ($p = 0.001$, AUC 0.758, standard error 0.017, 95% CI = 0.725–0.791; **Figure 2**).

In the second ROC analysis the threshold values of adherence to the MD that was predictive of the presence of TIR4/TIR5 cytology category was found at PREDIMED score ≤ 4 ($p = 0.001$, AUC 0.921, standard error 0.013, 95% CI = 0.896–0.947; **Figure 3**).

DISCUSSION

In this study, we evaluated the association of adherence to the MD with the thyroid nodular disease and the cytological classification in a large cohort of adult population. As novel finding, we reported that adherence to the MD was reduced in patients with thyroid nodular disease and in particular in those with cytological category with high-risk of malignancy, independently of BMI.

TABLE 5 | Responses of each item included in PREDIMED questionnaire in the study population grouped according to the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system.

Questions of PREDIMED questionnaire	TIR2 *n*. 145 (18.3%)		TIR3a *n*. 65 (8.2%)		TIR3b *n*. 50 (6.3%)		TIR4 *n*. 71 (8.9%)		TIR5 *n*. 60 (7.6%)			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	χ^2	**p*-value
Use of extra virgin olive oil as main culinary lipid	136	93.8	58	89.2	29	58.0	30	42.3	20	33.3	117.99	<0.001
Extra virgin olive oil >4 tablespoons	95	65.5	38	58.5	17	34.0	19	26.8	8	13.3	65.64	<0.001
Vegetables ≥2 servings/day	73	50.3	24	36.9	16	32.0	13	18.3	4	6.7	45.77	<0.001
Fruits ≥3 servings/day	47	32.4	20	30.8	17	34.0	15	21.1	1	1.7	25.11	<0.001
Red/processed meats <1/day	92	63.4	14	24.5	16	32.0	7	9.9	0	0.0	111.47	<0.001
Butter, cream, margarine <1/day	122	84.1	55	84.6	13	26.0	21	29.6	23	38.3	114.66	<0.001
Soda drinks <1/day	113	77.9	36	55.4	17	34.0	15	21.1	3	5.0	126.56	<0.001
Wine glasses ≥7/week	24	16.6	24	36.9	11	22.0	21	29.6	15	25.0	11.60	0.021
Legumes ≥3/week	76	52.4	34	52.3	13	26.0	17	23.9	6	10.0	47.67	<0.001
Fish/seafood ≥3/week	59	40.7	6	9.2	6	12.0	8	11.3	0	0.0	63.39	<0.001
Commercial sweets and confectionery ≤2/week	59	40.7	26	40.0	18	36.0	13	18.3	7	11.7	25.00	0.001
Tree nuts ≥3/week	63	43.4	10	15.4	5	10.0	9	12.7	2	3.3	58.93	<0.001
Poultry more than red meats	36	24.8	22	33.8	12	24.0	27	38.0	24	40.0	7.89	0.096
Use of sofrito sauce ≥2/week	88	60.7	41	63.1	12	24.0	20	28.2	16	26.7	48.13	<0.001

*PREDIMED, Prevención con Dieta Mediterránea. * A significant difference ($p < 0.05$).*

TABLE 6 | The results of a multinomial logistic regression to assess the association between the thyroid nodules presence/absence and categorical variables included in this study.

Parameters	OR	**p*-value	95% CI	R^2	χ^2
Sex					
Males/Females	1.22	0.206	0.90–1.65	0.002	1.60
Lifestyle characteristics					
Smoking	3.76	<0.001	2.67–5.28	0.076	63.17
Physical activity	0.28	<0.001	0.21–0.37	0.094	78.59
Anthropometric measurements					
Normal weight	0.69	0.041	0.49–0.99	0.005	4.22
Overweight	1.40	0.050	0.98–1.98	0.005	3.59
Grade I obesity	0.96	0.815	0.67–1.36	0.001	0.55
Grade II obesity	0.66	0.018	0.46–0.93	0.007	5.66
Grade III obesity	1.76	0.003	1.21–2.55	0.011	8.99
Nutritional parameters					
Low adherence to the MD	6.16	<0.001	4.42–8.58	0.153	131.68
Average adherence to the MD	0.49	<0.001	0.37–0.65	0.031	24.88
High adherence to the MD	0.16	<0.001	0.10–0.27	0.081	67.48

*MD, Mediterranean diet; OR, odds ratio; CI, confidence interval. *A significant difference ($p < 0.05$).*

Thyroid Nodular Disease and Mediterranean Diet

A PREDMED score ≤5 was reported in more than 50% of patients with thyroid nodules vs. 16% of those without thyroid nodules. Analyzing the single items of the PREDIMED questionnaire, it was evident that the consumption of almost all the Mediterranean healthy foods was lower in patients with thyroid nodules. At multiple regression analysis, the low consumption of fish and fruits, and the high consumption of red meats were associated with the presence of thyroid nodules. At regression analysis, the low adherence to the MD entered before than BMI as the best predictor of the presence of thyroid nodules. In the context of the accurate clinical evaluation of thyroid nodular disease, the PREDIMED score ≤5 could be served as an adjunctive predictor for helping in characterizing patients with presence of thyroid nodules.

Previous studies have mainly focused on the correlation between adherence to the MD and reduced risk of several cancer types and mortality (47). In addition, several studies have been carried out on the intake of single nutrients and foods and the risk of thyroid cancer, summarized in a recent narrative review (1). In particular, evidence reported that many foods typical of the MD,

TABLE 7 | Results of a multinomial logistic regression to assess the association between the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) and categorical variables included in this study.

Parameters	OR	*p-value	95% CI	R^2	χ^2
Sex					
Males/Females	0.33	<0.001	0.21–0.53	0.55	22.32
Lifestyle characteristics					
Smoking	9.94	<0.001	6.10–16.18	0.224	99.12
Physical activity	0.09	<0.001	0.05–0.17	0.180	77.57
Anthropometric measurements					
Normal weight	0.04	<0.001	0.01–0.18	0.115	47.95
Overweight	0.26	<0.001	0.14–0.49	0.053	21.22
Grade I obesity	1.29	0.339	0.77–2.17	0.002	0.90
Grade II obesity	2.52	0.001	1.49–4.26	0.030	11.74
Grade III obesity	4.24	<0.001	2.56–7.01	0.080	32.63
Nutritional parameters					
Low adherence to the MD	137.55	<0.001	33.22–269.47	0.389	192.89
Average adherence to the MD	0.01	<0.001	0.01–0.043	0.331	156.90
High adherence to the MD	0.25	<0.001	0.18–0.51	0.044	17.73

*MD, Mediterranean diet; OR, odds ratio; CI, confidence interval. *A significant difference ($p < 0.05$).*

TABLE 8 | The bivariate proportional OR model performed to assess the association between the thyroid nodule presence/absence and the responses of each item included in PREDIMED questionnaire.

Questions of PREDIMED questionnaire	OR	*p-value	95% CI	R^2	χ^2
Use of extra virgin olive oil as main culinary lipid	0.42	<0.001	0.29–0.59	0.031	25.08
Extra virgin olive oil >4 tablespoons	0.70	0.013	0.53–0.93	0.008	6.19
Vegetables ≥2 servings/day	0.32	<0.001	0.24–0.42	0.077	63.46
Fruits ≥3 servings/day	0.14	<0.001	0.10–0.19	0.193	169.92
Red/processed meats <1/day	0.16	<0.001	0.11–0.22	0.173	150.83
Butter, cream, margarine <1/day	1.51	0.004	0.14–2.00	0.010	8.38
Soda drinks <1/day	0.91	0.513	0.69–1.20	0.001	0.43
Wine glasses ≥7/week	0.48	<0.001	0.35–0.65	0.029	23.13
Legumes ≥3/week	0.46	<0.001	0.34–0.61	0.037	29.67
Fish/seafood ≥3/week	0.06	<0.001	0.04–0.08	0.334	322.25
Commercial sweets and confectionery ≤2/week	0.56	<0.001	0.42–0.75	0.020	15.83
Tree nuts ≥3/week	0.49	<0.001	0.36–0.67	0.026	20.54
Poultry more than red meats	0.67	0.008	0.50–0.90	0.009	7.04
Use of sofrito sauce ≥2/week	0.76	0.054	0.58–1.00	0.005	3.72

*PREDIMED, Prevención con Dieta Mediterránea; OR, odds ratio; CI, confidence interval. *A significant difference ($p < 0.05$).*

including fish and iodine-rich foods, fruits and vegetables, might exert protective effects on the reduction of thyroid cancer risk. Conversely, alcohol intake (48, 49) and red meat consumption (50) exert negative effects on thyroid cancer risk. Indeed, it is well-known that an approach based on studying a single food does not take into account the synergistic and/or antagonistic interactions existing among nutrients and foods, and it probably has a suboptimal statistical power to assess associations with the risk of cancer (51). Yet, no study to date has attempted to investigate the association of adherence to the MD or single foods of MD and thyroid nodular disease.

Previous evidence investigated the association between obesity and thyroid nodular disease, indicating that patients with obesity were more likely to have thyroid nodules disease compared to normal weight individuals (6, 52). In particular, obesity has been linked to higher serum thyroid stimulating hormone (TSH) concentrations (53, 54), which consequently leads to higher thyroid volume (55) being the TSH a stimulating factor potentially contributing to the development of thyroid nodular disease and thyroid cancer (56).

Of interest, as found by Panagiotou et al. the nodule size was associated also with body fat percentage (57). In our study, we did not measure body composition; nevertheless, we found that patients with obesity had a higher prevalence of thyroid nodules compared with normal weight individuals. Studies showed that hyperglycaemia, insulin resistance and type 2

TABLE 9 | The bivariate proportional OR model performed to assess the association between the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) and the responses of each item included in PREDIMED questionnaire.

Questions of PREDIMED questionnaire	OR	*p-value	95% CI	R^2	χ^2
Use of extra virgin olive oil as main culinary lipid	0.10	<0.001	0.06–0.17	0.210	91.93
Extra virgin olive oil >4 tablespoons	0.19	<0.001	0.12–0.31	0.122	50.98
Vegetables ≥2 servings/day	0.20	<0.001	0.11–0.34	0.098	40.19
Fruits ≥3 servings/day	0.29	<0.001	0.16–0.52	0.050	20.21
Red/processed meats <1/day	0.06	<0.001	0.03–0.14	0.189	81.81
Butter, cream, margarine <1/day	0.18	<0.001	0.12–0.29	0.135	56.66
Soda drinks <1/day	0.09	<0.001	0.05–0.16	0.217	95.59
Wine glasses ≥7/week	1.29	0.298	0.79–2.09	0.003	1.07
Legumes ≥3/week	0.24	<0.001	0.14–0.39	0.086	35.29
Fish/seafood ≥3/week	0.17	<0.001	0.08–0.37	0.070	28.42
Commercial sweets and confectionery ≤2/week	0.28	<0.001	0.16–0.47	0.064	25.87
Tree nuts ≥3/week	0.21	<0.001	0.011–0.42	0.065	26.26
Poultry more than red meats	1.73	0.016	0.11–2.70	0.015	5.77
Use of sofrito sauce ≥2/week	0.32	<0.001	0.20–0.50	0.064	25.91

*PREDIMED, Prevención con Dieta Mediterránea; OR, odds ratio; CI, confidence interval. *A significant difference ($p < 0.05$).*

TABLE 10 | Multiple regression analysis models (stepwise method) with the thyroid nodules presence/absence as a dependent variable to estimate the predictive value of sex, lifestyle characteristics, BMI categories, PREDIMED scores, and each item included in PREDIMED questionnaire.

Parameters	Multiple regression analysis			
	R^2	β	t	*p-value
Model 1				
PREDIMED score	0.211	−0.461	−14.61	<0.001
BMI categories	0.287	−0.334	−9.24	<0.001
Model 2				
Fish/seafood ≥3/week	0.377	−0.614	−21.92	<0.001
Fruits ≥3 servings/day	0.431	−0.255	−8.77	<0.001
Red/processed meats <1/day	0.455	−0.173	−7.43	<0.001
PREDIMED score	0.462	−0.094	−3.54	<0.001

*PREDIMED, Prevención con Dieta Mediterránea; BMI, Body mass index. *A significant difference ($p < 0.05$).*

TABLE 11 | Multiple regression analysis models (stepwise method) with the cytology categories (TIR2, TIR3a, TIR3b vs. TIR4/TIR5) as a dependent variable to estimate the predictive value of sex, lifestyle characteristics, BMI categories, PREDIMED scores, and each item included in PREDIMED questionnaire.

Parameters	Multiple regression analysis			
	R^2	β	t	*p-value
Model 1				
PREDIMED score	0.626	−0.792	−25.55	<0.001
Smoking	0.664	0.224	6.70	<0.001
BMI categories	0.669	0.104	2.63	0.009
Model 2				
PREDIMED score	0.626	−0.792	−25.55	<0.001
Use of extra virgin olive oil as main culinary lipid	0.639	−0.144	−4.24	<0.001
Red/processed meats <1/day	0.653	−0.142	−4.12	<0.001

*PREDIMED, Prevención con Dieta Mediterránea; BMI, Body mass index. *A significant difference ($p < 0.05$).*

diabetes conditions that often coexist in patients with obesity, and represent risk factors for thyroid cancer independent of obesity. The proposal mechanism for this association was the activation of insulin and insulin-like growth factor pathway, which share affinity with insulin receptor and that could be over activated by compensatory hyperinsulinemia to insulin resistance (58). In addition, considering that the body size affects the iodine requirements, obesity is also considered one condition of relative iodine deficiency, which could predispose to thyroid nodular disease (59).

Thyroid Nodule Cytology and Mediterranean Diet

The management of thyroid nodular disease is primarily based on morphologic classification of cytological samples obtained by FNA, complemented by clinical history of the nodule, imaging findings, and molecular markers test results (60). Nevertheless, ∼25% of all FNAs falls into the indeterminate category, possibly resulting in unnecessary thyroid surgery (61). To increase the characterization of the cytological category with high-risk of malignancy by including the evaluation of modifiable risk factors, such as unhealthy foods and dietary patterns, could add an additional criterion to help the clinicians in the management of thyroid nodular disease. To our knowledge, this is the first study investigating the association between adherence to the MD according to the cytological classification of thyroid nodular disease in the subset of the study participants who have undergone FNA.

According to the five diagnostic cytology categories based on 2013 Italian thyroid cytology classification system, more than

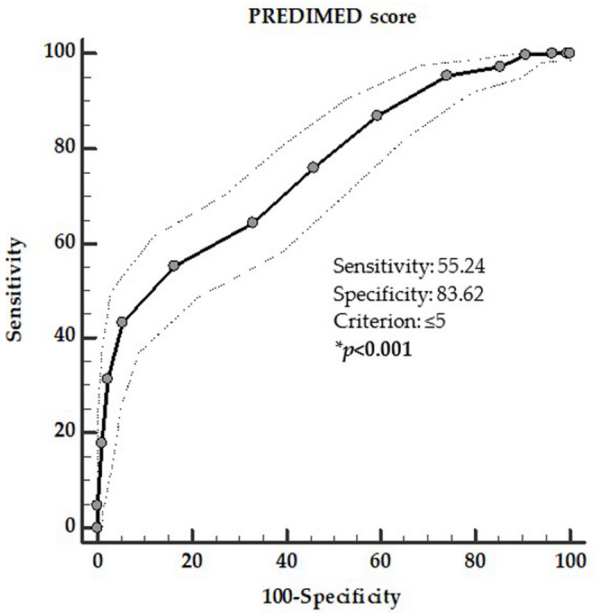

FIGURE 2 | ROC for predictive values of PREDIMED score in detecting the presence of thyroid nodules. A PREDIMED score ≤ 5 ($p = 0.001$, AUC 0.758, standard error 0.017, 95% CI 0.725–0.791) predicted the presence of thyroid nodules. *A significant difference ($p < 0.05$).

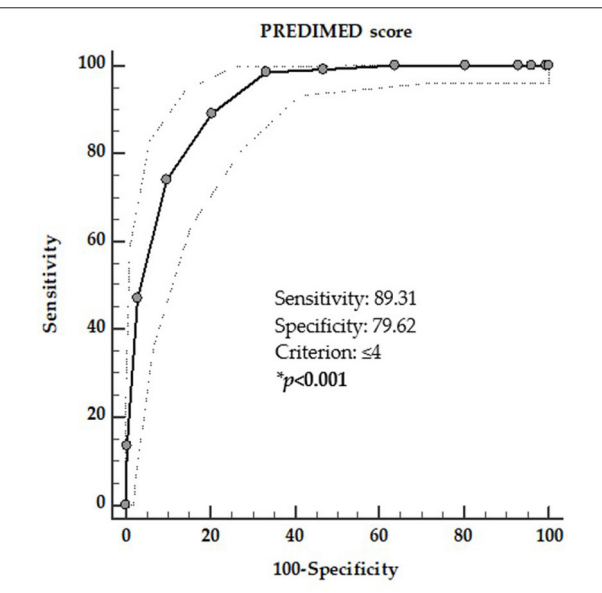

FIGURE 3 | ROC for predictive values of PREDIMED score in detecting the presence of TIR4/TIR5 cytology category. A PREDIMED score ≤ 4 ($p = 0.001$, AUC 0.921, standard error 0.013, 95% CI 0.896–0.947) predicted the presence of TIR4/TIR5 cytology category. *A significant difference ($p < 0.05$).

18% of the study participants presented TIR2, while ∼9 and 8% of the participants had high-risk categories, TIR4 and TIR5, respectively. The high-risk category (TIR4/TIR5) increased along the BMI categories. In particular, in class II obesity 54.9% of patients had high-risk categories (TIR4 28.2% and TIR5 26.7%), while 7.6% had TIR2; in class III obesity 78.3% of patients had high-risk categories (TIR4 36.6% and TIR5 41.7%), while 4.8% had TIR2. Consistently, the high-risk categories increased along with the reduction to adherence to the MD. In particular, up to 98% of patients with TIR5 had a low adherence to the MD.

Analyzing the single items of the PREDIMED questionnaire in relation with cytological categories, the consumption of almost all Mediterranean healthy foods was lower in patients with the high-risk category compared to patients with the low-risk category of malignancy. In particular, the low consumption of extra virgin olive oil, and the high consumption of red meats were associated with the high-risk category of malignancy. In addition, considering lifestyles (smoking and physical activity), BMI, and score of adherence to the MD, at multiple regression analysis, the PREDIMED score entered before smoking and BMI as predictor of high-risk category and a PREDIMED score ≤ 4 could help to characterize patients with high-risk category of malignancy.

Earlier evidence has mainly evaluated the association between single foods and differentiated thyroid cancer, nevertheless only few researches have been carried out studies to investigate the relationship between differentiated thyroid cancer and dietary patterns (21, 62–64).

In a case control study Sangsefidi et al. conducted among 309 individuals in northeast of Iran, authors investigated the association among four major dietary patterns including traditional dietary pattern, western dietary pattern, transitional dietary pattern, and healthy dietary pattern with the risk of having or developing thyroid cancer (64). The study results showed that only Western diet, characterized by high consumption of meat, eggs, refined cereals, cakes, sweet drinks, and alcohol intake, was associated with increased risk of thyroid cancer (64).

In contrast with results of Sangsefidi et al. (64) and Clero et al. (62) conducted in French Polynesia a case-control study in 229 cases of thyroid cancer and 371 controls, evaluating two different dietary patterns: Western diet and traditional Polynesian dietary pattern. The traditional Polynesian diet included specific foods of Pacific islands, including taro, cassava, tubers, sweet potato, fish and seafood, and fruits (as banana, mango, and pawpaw). Authors concluded that in French Polynesia there was no association between a Western diet and the risk of thyroid cancer. Conversely, the traditional Polynesian diet led to a weak reduced risk of thyroid cancer (62).

Results similar to ours were reported by Markaki et al. in a Greek population (63). This case-control study has been conducted in 113 patients with histologically verified thyroid cancer and 138 healthy controls, age, and sex-matched. The study results showed that dietary patterns characterized by the high consumption of fish, vegetables and fruits, led to a reduced risk for all thyroid cancers. In particular, high fish and vegetable intakes led to an increased risk of follicular thyroid cancer (63).

Moreover, in another study Liang J et al. in a case-control study of 390 historically confirmed incident thyroid cancer cases and 436 population controls conducted in Connecticut (2010–2011), examined the association between thyroid cancer risk and dietary pattern (21). The dietary patterns analyzed in this study

were three: high protein and fat, starchy foods and desserts, and fruits and vegetables. The results of this study showed that the fruits and vegetables dietary pattern was significantly correlated with a reduced risk of overall thyroid cancer. Contrariwise, the starchy foods and desserts dietary pattern was positively associated with an overall thyroid cancer risk among men (21).

All the above-mentioned studies supported the link between specific foods characteristic of the MD and reduced thyroid cancer risk, although the exact mechanisms through which MD might affect thyroid cancer risk are still unclear. In particular, the low adherence to the MD is characterized by high consumption of red meat and low consumption of fish. Evidence indicated that processing of red meat or its cooking at a high temperature, is associated with the production of carcinogenic compounds, including polycyclic aromatic hydrocarbons, heterocyclic amines, and N-nitroso compounds. These compounds *via* increasing the proliferation of cells can promote carcinogenesis and result in increasing of overall cancer risk (65, 66). In this context, in 2002 Memon et al. showed a positive association between the high consumptions of mutton and lamb with thyroid cancer (67). Two very recent review summarized the role of individual foods on thyroid cancer risk concluding that to date, no definite association among dietary patterns, including MD and thyroid cancer, and its clinical severity and aggressiveness have been found (1, 68). Albeit the association between single foods and thyroid cancer is difficult to examine, the high consumption of vegetables, fruits, and fish foods, might exert protective effects on thyroid cancer risk. These foods, for the presence of essential nutrients including omega-3 polyunsaturated fatty acids, vitamins (retinol, vitamin D, and vitamin E), and minerals, have an anti-inflammatory properties and have been reported to be a protective factor in some types of tumors, including breast cancer (69, 70), neuroendocrine tumors (71, 72), and thyroid cancer (50, 73, 74).

Despite the attention that has been paid to the relation between diet and thyroid cancer risk, it is tempting to speculate that the beneficial anti-inflammatory effects of MD could be extended to the complex pathogenesis of thyroid nodular disease. However, although it has been reported that different foods and vitamins supplementation were differently associated with benign breast disease and diet, the relationship between adherence to the MD and thyroid nodular disease is an unexplored field, and associative clinical studies are still lacking (75). In particular, to the best of our knowledge the association between adherence to the MD and the cytological classification of thyroid nodular disease has not investigated previously.

Several studies supported the link between the low adherence to the MD and inflammation (31, 76). Indeed, cytokines, activating molecules in chronic inflammation, has been reported to facilitate the prevalence of thyroid nodular disease directly causing thyroiditis, playing a critical role in widely regulating cellular functions and promoting cellular proliferation, hyperplasia, differentiation, and survival (11). In this context, a recent study has been reported that the inflammation promotes the development of thyroid nodular disease, probably due to its indirect effect through inhibiting the synthesis of thyroid hormones, which results in the elevation of TSH levels (11). Furthermore, chronic inflammation is also associated with the malignant growth in thyroid nodular disease (77). In particular, the elevated TSH levels was implied of the development of thyroid nodular disease through the growth and proliferation of thyroid cell in different ways, thus leading to the formation to the goiter and thyroid nodular disease (11, 78). These results suggest that chronic inflammation, which coexists

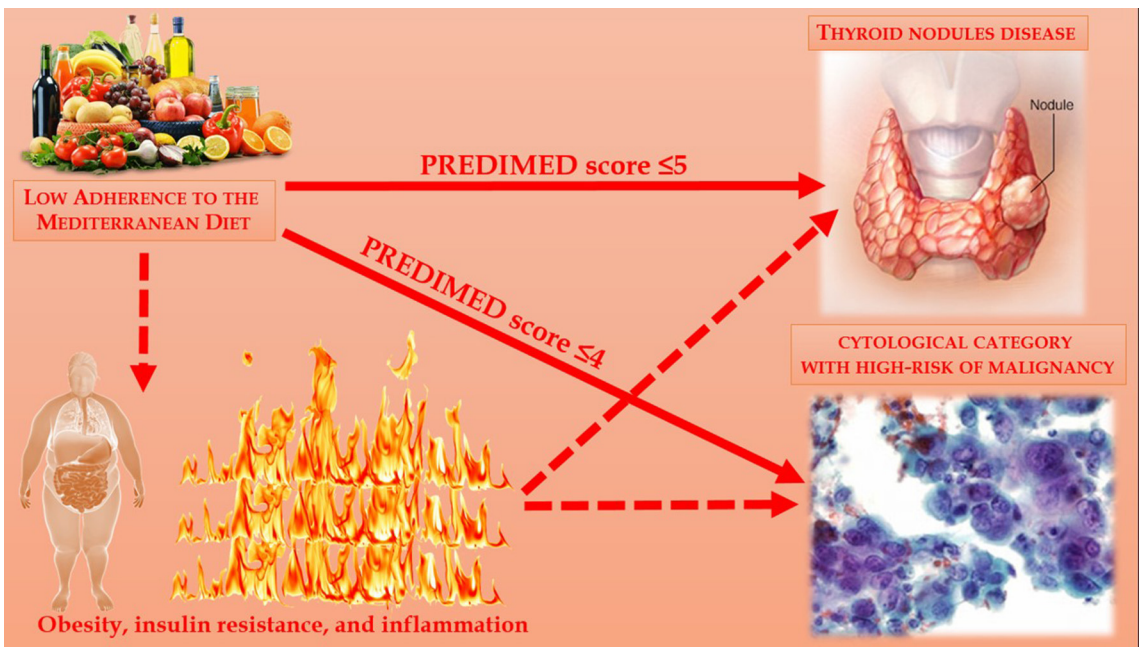

FIGURE 4 | Association between adherence to the MD and thyroid nodular disease and cytological category with high-risk of malignancy were carried out.

with the elevated TSH levels, in involved in the pathogenesis of thyroid nodular disease (11).

Limitations

Despite these novel results, we are aware that our study presented several limitations. First, the observational design of this study does not allow any causal interpretation of the findings. In fact, the main limitation of this study is represented by the by the cross-sectional experimental design, which, although showing the association of the adherence to the MD with thyroid nodular disease and thyroid cancer malignancy, fails to provide any explanation of the causality of this association. Further, the study participants were not investigated by a medical history, including familiarity for thyroid nodular disease, exposure to radiation, and iodine intake. Second, data on thyroid function and additional ultrasound characteristics of thyroid nodular disease are lacking. Indeed, the relationship between adherence to the MD and thyroid function has been previously investigated in a cohort of subjects with overweight and obesity (79). In this cohort study, the Authors demonstrated that the higher adherence to the MD was independently associated to a slightly reduced thyroid function, and attributed this due to increase in the tissue and organ sensitivity to thyroid hormones and the reduction of thyroid hormones could be associated with the reduced formation of thyroid nodular disease (79). Third, we did not analyse inflammatory markers. Nevertheless, on the one side the anti-inflammatory and antioxidant effects of the MD is well-known (31, 80); on the other side it has reported that chronic inflammation promotes the development of thyroid nodular disease, probably due to its indirect effect *via* inhibiting the synthesis of thyroid hormone, which results in the elevation of TSH (11). A further important limitation in this study is that cytological data were not confirmed by histopathology. Finally, the proposed cut-off points of PREDIMED score for helping in characterizing patients with presence of thyroid nodules and cytological categories with high risk of malignancy (TIR4 and TIR5) should be validated in different population samples by further clinical trials.

Strengths

This study has several strengths. The single-center study design of this research, although it could represent a selection bias due to the limits the generalizability of our findings, allowed us to increase the homogeneity of the sample. In particular, all participants included were came from the same geographical area, thus possibly sharing overall similar food availability. Moreover, we adjusted our data for a wide range of confounding factors that might have influence on thyroid nodular disease and thyroid cancer, including sex, age, physical activity, smoking, and BMI. The questionnaire of adherence to the MD used in this study, PREDIMED questionnaire was recently validated in different Mediterranean countries, including Italy (81). This questionnaire was not self-reported, but face-to-face administered by a certified Nutritionist, to reduce any bias related to the filling in of this questionnaire. Furthermore, the results of nutritional research using overall dietary patterns, such as MD compared to the study of the single food or nutrient is more amenable to translation into clinical practice (51, 82).

CONCLUSIONS

Thyroid nodular disease is common in general population. To the best of our knowledge, no study to date that reported the association of adherence to the MD with thyroid nodular disease and cytological category with high-risk of malignancy were carried out. Even if the mechanisms underlying these observed associations remain largely speculative, the evaluation of adherence to the MD could represent an adjunctive tool in helping clinicians to better characterize patients with thyroid nodular disease and with cytological category with high-risk of malignancy. In this context, there is a strong rationale to support the inclusion of the evaluation to adherence to the MD into disease-specific dietary guidelines for the management of thyroid nodular disease, in order to reduce the inflammation that paves the way for insulin resistance and, consequently, the increased risk of developing thyroid nodular disease with high-risk category of malignancy; **Figure 4**. Further clinical studies on the associations between the prevalence of nodular thyroid disease and potential lifestyle characteristics, as dietary pattern including the MD, are warranted to confirm our observations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Università Federico II di Napoli. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LB and SS: conceptualization. LB, GM, FF, and GT: methodology. CV: formal analysis. GM, TP, LV, and SA: investigation. GA: data curation. LB and GA: writing—original draft preparation. LB, GA, and GM: writing—review and editing. AC and SS: visualization and supervision. All authors have read and agreed to the published version of the manuscript.

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Stress and Diet Quality Among Ecuadorian Adults During the COVID-19 Pandemic. A Cross-Sectional Study

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Background: Stress has been associated with food habits. Stress changes eating patterns and the salience and consumption of hyperpalatable foods. During the lock-down due to the COVID-19 pandemic, stress was very common.

Objective: We investigated the association between stress and diet quality in Ecuadorian adults during the COVID-19 pandemic.

Design: A cross-sectional study.

Setting: Data was collected using a self-administered online survey. Stress was measured using the Perceived Stress Scale (PSS-14), and diet quality was evaluated using the Global Diet Index (GDI). A linear regression model with restrictive cubic splines was used to investigate the association between stress and diet quality.

Participants: Participants were recruited by convenience sampling, including a total of 2602 individuals. Most participants were female (68.57%) and had university education (78.52%), with a median age of 25 (IQR: 25, 37).

Results: Stress was reported by 26.06% of participants. The majority of individuals (75.79%) reported having a diet that needed changes or an unhealthy diet. Independently from biological sex, age, level of education, people/room ratio, economic allowance, and expenses for food, stress was statistically significantly associated with diet quality ($p = 0.035$). The association between stress and diet quality was inverse and non-linear; higher stress levels were associated with poorer diet quality. The consumption of palatable foods was not statistically significant associated with stress.

Conclusions: Stress is associated with poorer diet quality. Public health measures to improve the mental health and lifestyle of the population are needed during the lock-down of the pandemic.

Keywords: COVID-19 pandemic, stress, diet quality, palatable foods, Ecuadorian adults

INTRODUCTION

At the end of 2019, the Coronavirus pandemic begins. In January 2020, the World Health Organization declared a health emergency due to the high number of infected people and the high death rate due to the disease caused by the coronavirus (COVID-19) (1, 2). This situation has had an impact on the family and world economy, on people's lifestyles and mental health, with reports of stress, changes in eating habits, and physical activity in several studies (3). Eating well helps maintain health and physical activity (4), thus improving the enjoyment of life. Good diets and eating habits are critical for proper growth and development and disease prevention. Some different health problems are caused by poor diet and nutrition (5).

Most humans experience altered eating behaviors under stress, with approximately 40% eating more and 40% eating less than usual. In addition, under stress, most people report increased intake of highly palatable foods, regardless of hyperphagia or hypophagia. The consumption of processed products is related to overweight and obesity in all age groups, leading to the development of chronic non-communicable diseases that are a severe public health problem (3, 6).

Unhealthy eating habits are related to stress, anxiety, and depression (7). Some studies show the relationship between the consumption of processed foods and simple carbohydrates with psychological problems, including depression (8, 9). For example, acute stress is associated with loss of appetite, resulting in insufficient consumption. In contrast, chronic stress is associated with a greater preference for appetizing foods rich in sugar and fat (10).

Regarding the quality of the diet, some studies have found a significant relationship between the quality of the diet and the presence of stress. And other studies in which this association has not been found (7, 11). Park et al. (12), showed changes in eating habits in 1 out of 2 adults, they reported consuming more unhealthy snacks and desserts during the initial phase of the COVID-19 pandemic. Consumption of these less healthy foods was higher in younger adults. Dietary changes to less healthy foods can affect long-term metabolic health. In general, during this time of the COVID-19 pandemic, the quality of the diet has decreased, and psychological illnesses, such as stress, anxiety, and depression, have increased. To improve these psychological illnesses, consuming foods rich in omega 3 and reducing the consumption of simple sugars and saturated fats are recommended (13, 14). This research aimed to analyze the relationship between perceived stress and the global quality index of food.

METHODOLOGY

Design and Context

The present work is an observational cross-sectional study. It is part of a project called EFRICA, currently being carried out in Ecuador. Data collection took place between January and February 2020. At that time, confinement in Ecuador was mandatory. To collect the data, a self-administered survey was used.

Sample

Individuals of both genders over 18 years old were invited to participate in the study. A non-probabilistic convenience sampling was implemented to recruit participants. Participation invitations were sent through different platforms and social networks, including Facebook, Instagram, Twitter, and WhatsApp. Participation is voluntary and self-selected. In total, 2602 adults voluntarily agreed to participate.

The Survey

The online self-administered survey was reviewed by four health and nutrition experts participating in the project EFRICA. The survey was first applied to 30 Ecuadorian adults (15 men and 15 women, between 18 and 64 years old) to check for errors and inconsistencies. After corrections were implemented, the survey was distributed through social networks using Google Forms. The survey had four sections: Section 1 included a presentation, objectives, and an informed consent form; Section 2 was meant to collect socio-demographic data; Section 3 included questions regarding diet quality, and Section 4 had questions to assess perceived stress. Diet quality and perceived stress were evaluated using validated questionnaires (15).

Variables

Diet Quality

The global diet index was used to measure the quality of the diet. This instrument contains 12 variables, which include the frequency of daily or weekly consumption of group (a) 5 groups of healthy foods: fruits, vegetables, fish, legumes, and milk or derivatives; group (b) 4 unhealthy foods: fried foods, sugary drinks, cakes/cookies/pastries/sweets and sugar, and group (c) main meals: breakfast, lunch, and dinner.

For each of these variables, the following alternatives were considered: 2 or more times a day, 1 time a day, 4–6 times a week, 2–3 times a week, once a week, and occasionally or never. Based on this information, scores were assigned, with 10 being the ideal value and a score of 1 being the least healthy for each index parameter. The maximum score with the 12 parameters studied was 120, classified according to the following criteria: Healthy eating: 90–120 points; a diet that needs changes: 60–89 points; unhealthy eating: <60 points.

Stress

The experience of stress was assessed using the perceived stress scale (PSS), which evaluates the degree to which situations in one's life are experienced as stressful (15). The PSS consists of 14 questions with five possible answers and scores: never = 0, hardly ever = 1, occasionally = 2, often = 3, always = 4, and items, each of which respondents are ranked from 0 (never) to 4 (very often). Questions 4, 5, 6, 7, 9, and 10 are "positive" and therefore scored inversely. PSS-14 scores range from 0 to 56. The higher the overall score, the higher the level of perceived stress. A cut-point corresponding to the group's median was established for group participants as having or not experiencing stress.

Statistical Analysis

Categorical variables were summarized by frequency and percentages. Median and interquartile ranges (IQR) were used to summarize numerical variables since all were non/normally distributed. Association between categorical variables and stress was tested using the Chi^2 test. Association between numerical variables and stress was tested using the rank-sum test. The association between diet quality and stress was analyzed by implementing a linear regression model with restrictive cubic splines (RCS) to model non-linearity. In this model, the score of diet quality (GDI) was included as the outcome variable and that of Stress (PSS) as an explanatory variable. The model was adjusted by age (male, female), age (years), level of education (No education/primary/secondary, university), economic allowance (yes, no), and expenses per month in food (<$400, $400–$800, >$800). The RCS regression model determined the shape of the relationship between diet quality and stress without any prior assumption. RCSs fitted a smooth continuous curve of adjusted means with 95% confidence intervals (95% CIs) across PEE levels. RCSs allowed for changes in the function at defined knot points and restricted the splines to linear relationships at the tail ends. Knot points were located at percentiles 5, 27.5, 50, 72.5, and 95 altitudes, as previously recommended to avoid forcing curvature or inflections (16). R version 3.6.3 (2020-02-29) and related packages, including rms were used to analyze the data (16, 17).

RESULTS

Sample Characterization

The sample included 2602 adults, of whom 1776 (68.57%) were female and 814 (31.43%) were male, with a median age of 25 (IQR: 25, 37). Most participants had a university education (n = 2043, 78.52%). They did not receive any economic allowance from the government to cover their expenses (n = 2463, 96.32%). The median ratio between the number of people living at home and the number of rooms was 1.4 (IQR: 1, 2). From the participants 48.82% (n = 1059) reported spending <$400 per month, 47.30% ($n$ = 1025) between $400 and $800 per month and 3.87% (n = 83) > $800 per month in food. Sample characteristics are summarized by having or not experiencing Stress in **Table 1**.

The median score of PSS was 18 (IQR: 15, 22), and 26.01% (n = 678) reported having experienced stress. The median score of GDI was 76.50 (IQR: 65.00, 88.50). The majority of participants (n = 1972, 75.79%) reported having a poor diet quality [needed changes, n = 1,558 (59.88%); unhealthy, n = 414 (15.91%)]. It was observed that those who reported having experienced stress also reported a worse diet quality (**Table 1**).

Association Between Stress and Diet Quality

To study the association between stress and diet quality, we implemented a linear regression model with RCS (see Methods). We found that independently of biological sex, age, level of education, the ratio of people/room, economic allowance, and expenses in food, stress was statistically significantly associated with diet quality (F = 2.88, df = 3, p = 0.035). The association between stress and diet quality was inverse and non-linear. That is, higher levels of stress (measured by PSS) were associated with lower diet quality (measured by GDI) (**Figure 1**). Predicted GDI means for different PSS values are shown in **Table 2**.

Diet quality was also significantly associated with age (F = 5.65, df = 1, p = 0.018), biological sex (F = 13.64, df = 1, p

TABLE 1 | General characteristics of the sample by level of stress.

		No stress (n = 1924, 73.94%)	Stress (n = 678, 26.06%)	Missing n (%)	Test	*P value*
Biological sex	Female	1210 (63.22)	566 (83.73)	12 (0.00)	Chisq. (1 df) = 97.51	< 0.001
	Male	704 (36.78)	110 (16.27)			
Age (years)	Median (IQR)	26 (21.00, 38.00)	23 (20.00, 30.00)	22 (0.84)	Ranksum test	< 0.001
Level of education	No	392 (20.37)	167 (24.63)	0 (0.00)	Chisq. (1 df) = 5.39	0.020
	education/primary/ secondary University	1532 (79.63)	511 (75.37)			
Overcrowding	Median(IQR)	1.33 (1.00, 2.00)	1.5 (1.00, 2.00)	44 (1.69)	Ranksum test	< 0.001
Economical allowance	No	1816 (96.19)	647 (96.71)	45 (1.73)	Chisq. (1 df) = 0.39	0.535
	Sí	72 (3.81)	22 (3.29)			
Expenses per month	< 1 basic salary	796 (49.08)	263 (48.08)	433 (16.64)	Chisq. (2 df) = 4.00	0.136
	1-3 basic salaries	756 (46.61)	270 (49.36)			
	> 3 basic salaries	70 (4.32)	14 (2.56)			
Diet quality	Median (IQR)	77.5 (66.50, 90.00)	73.75 (60.50, 85.88)	0 (0.00)	Ranksum test	< 0.001
	Healthy	498 (25.88)	132 (19.47)		Chisq. (2 df) = 33.41	< 0.001
	Need changes	1164 (60.50)	394 (58.11)			
	Not healthy	262 (13.62)	152 (22.42)			

Sample included 2602 adults. Having or not experiences stress was measured using the perceived stress scale. Diet quality was measured using the global diet index. Symbology and abbreviations: IQR, interquartil range; GDI, general diet index; df, degrees of freedom; n, number; %, percentage.

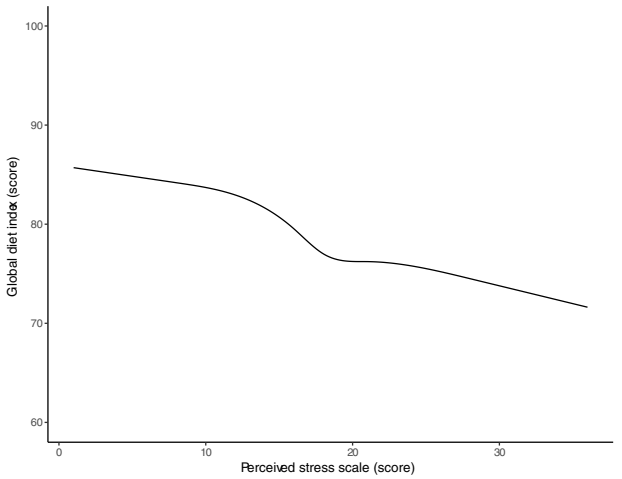

FIGURE 1 | Association between diet quality and stress. Predicted means of GDI and respective 95% confidence intervals are shown for different levels of stress. An inverse nonlinear association between diet quality and stress is shown in that, a worse diet quality is associated with higher levels of stress. Data was modeled using linear regression with resctrictive cubic splines (see Methods section).

TABLE 2 | Predicted means of GDI.

Variable		Mean	LCI	UCI
PES	1Q (15)	80.72	78.77	82.66
	Median (18)	77.01	75.05	78.98
	3Q (22)	76.16	74.22	78.10
Biological sex	Female	77.01	75.05	78.98
	Male	74.12	71.98	76.26
Age (years)	1Q (18)	76.49	74.44	78.53
	Median (25)	77.01	75.05	78.98
	3Q (37)	77.92	75.88	79.96
Ratio person/room	1Q (1)	79.51	77.49	81.54
	Median (1.4)	77.01	75.05	78.98
	3Q (6)	70.75	63.97	77.54
Economical allowance	No	77.01	75.05	78.98
	Yes	73.25	69.24	77.27

Adjusted predicted means and their confidence intervals are showed for stress (quartiles), sex, age (quartiles), ratio number of persons/room (quartiles), economical allowance. Symbology and abbreviations: 1Q, first quartil; 3Q, third quartil; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

< 0.001), rario people/room ($F = 3.83$, df $= 3$, $p = 0.001$), and economical allowance ($F = 4.06$, df $= 1$, $p = 0.044$), but not to level of education ($F = 0.85$, df $= 1$, $p = 0.357$) or expenses in food ($F = 0.95$, df $= 2$, $p = 0.388$). In this way, a worse quality of diet was evident in young compared to old people, in males compared with females, in people living in overcrowding, and among those receiving an economical allowance from the government. Predicted means of GDI for significantly associated covariates are shown in **Table 2**.

Palatable Foods and Stress

There was not a statistically significant association between different palatable foods and stress, with the exception of consumption of cookies (**Supplementary Table 1**). In this way, a higher consumption of cokies was associated with 0.013 points reduction on the stress score.

DISCUSSION

Stress and Lockdown

People's mental health is severely affected during pandemics, and this has already been observed, for example, in the SARS pandemic, where it was observed that episodes of anxiety (18) and stress (19) were common among people.

The increase in mental health problems in the COVID-19 pandemic has been evidenced in numerous scientific studies, including several meta-analyses (20, 21). In this sense, it has been observed that the highest risk groups are health professionals (22), women, young adults, and people with low incomes (23, 24). Moreover, the World Health Organization (25) has issued public interest guidelines to address psychological problems that may arise in times of pandemics.

Our data indicates that 26.01% of people experienced stress during the pandemic. Studies on the Ecuadorian population have also shown an increase in stress in the population (24) and a relationship between stress and increased depression (26). Statistics alert public health systems to create emerging policies supported by health professionals to generate actions to protect mental health (27). However, the actual consequences in the medium and long term of increasing mental health problems in the population are a projection and should continue to be studied.

Diet Quality and Lockdown

People are social beings, and confinement has had several consequences. Staying home for days with little or no contact with other people has caused some people to overeat or more frequently as a mechanism to reduce fear and anxiety (28). In addition, limited access to groceries led many people to have little access to fresh foods such as fruits and vegetables. The most convenient for them was to buy processed products, junk food, and ready-to-eat cereals rich in fat, sugar, and salt (29). This situation could lead to an increase in sweets, fats, and alcohol (30), salty snacks, and fast foods every day that is very dangerous for the health (31).

Our study found that 75.79% of the participants had a poor-quality diet. It could be due to little access to fresh food and money available for food during the month. It has been reported that the socioeconomic level influences the quality of food, finding that at the low socioeconomic levels, the consumption of fruits and vegetables is lower (32). On the other hand, social determinants such as loss of employment or few job opportunities and lack of access to recreational activities due to confinement impacted the diet quality, negatively affecting the most vulnerable groups (33).

These findings may be in contrast to what has been found in other studies where it has been found that during

confinement, the consumption of fruits, vegetables, and organic foods improved, which may be related to cultural and economic factors (29, 33). It is also necessary to consider that food insecurity and food quality before the COVID-19 pandemic could worsen during confinement, affecting the most vulnerable groups (33).

It is necessary to carry out studies that allow knowing the determining factors of these changes in eating habits in the Ecuadorian population to promote an accessible and sustainable healthy diet. On the other hand, almost all the studies during confinement were carried out online. It would be essential to know how people's eating habits with little or no access to the internet changed because these groups possibly show other consumption patterns.

Diet Quality and Stress

Stressful situations stemming from the COVID-19 pandemic have been linked to unhealthy habits (34). One of the concerns of health professionals corresponds to the unhealthy changes that the stressed population can have in their diet (34).

Stress can lead to emotional overeating and high energy food craving (35). In general, bad eating habits are related to the presence of stress (7). In this sense, there has been an increase in palatable foods and alcohol consumption and a decrease in the consumption of fruit and vegetables in various countries (36). Also, in studies, a relationship has been found between the consumption of simple meat hydrates and processed foods with psychological problems (7). It should be mentioned that there is no single validated index that allows measuring the quality of the diet in all countries. However, our work will give us a global perspective on diet quality in the study subjects (37). Our results show a relationship between increased stress, unhealthy diet, and health problems. Similar findings show that mental health is directly related to food consumption, so it must be considered in dietary prescriptions and public health policies (38).

Prolonged stress causes the release of cortisol, which increases the feeling of appetite. It has been reported that stress due to the COVID 19 pandemic has been able to influence the increase in food consumption (52% of people), including energy-rich products and snacks after dinner, which in turn could have an impact on the increase in weight that is a risk for obesity; it affects people's health and well-being (35, 39).

The decrease in the consumption of fruits, vegetables, and a variety of foods, can also impact the immune system, making it more sensitive to infections and diseases. Therefore, ensuring adequate intake of vitamins, minerals, and micronutrients through food is essential to strengthen the immune system and maintain good health (40). In addition to promoting healthy eating, it is essential to promote mental health care as a priority for the population's well-being, even more so with the evidence that stress has a negative impact on people's physical and mental health (41).

Strengths and Limitations of the Study

This study had some limitations. First, a virtual survey was used to collect the information that, although true, allowed us to obtain the data in a relatively short time. Second, we work with a non-representative sample, so we cannot determine the generalizability of the results. Third, it is possible that as a cross-sectional virtual survey self-reported survey data, the results potentially suffer from recall and reporting bias. Fourth, we could not evaluate food and beverage consumption before the COVID-19 outbreak. Fifth, although we tried to reach more male participants, sex distribution is not balanced. Also, we do not consider BMI for the adjustment because the body image was reported. The strength of this study is that, to our knowledge, this is the first study to evaluate stress.

Although this study recognizes some limitations, including the lower participation of men compared to women, it is important to indicate that the number of participants at the national level is relatively high and allows the identification of cardiovascular risk factors that can have a strong impact on the Ecuadorian population. Nevertheless, factors such as stress and diet may differ between genders; the information obtained is the first report in the country and serves as the basis for the formulation of new studies focused not only on identifying these and other cardiovascular risk factors at the population level but also promoting healthy lifestyles and improving quality of life. All of these actions are in order to avoid negative impacts on the health of the Ecuadorian population in the medium and long term.

Perspectives and Future Studies

They are finding in this study the relationship between food and stress. The diet of these people should be taken into account. New studies should also be done on diet and psychological illnesses.

It could be interesting to analyze these factors in different socioeconomic strata to have a better understanding of the variability o similarities that could show people and in the future design interventions with a focus on public health considering several determinants that could affect the health.

CONCLUSIONS

Our results suggest that higher stress levels (measured by PSS) were associated with lower diet quality (measured by GDI). The consumption of palatable foods associated with stress was not statistically significant. Recent research has analyzed possible associations to stress-related eating. Although the data suggest potentially addictive properties of hyper-palatable foods, there is a debate about food addiction. The lockdown is an excellent strategy to stop the spread of the virus. However, it is essential to consider that physical inactivity, weight gain, behavioral food changes, and social isolation exist during this process, depending on the intensity of stress and environmental factors. By describing several substances involved in appetite regulation and weight control, identifying all centers involved in eating behavior demonstrates the complexity of studying this phenomenon and, consequently, energy homeostasis. Understanding the associations and interactions between stress and diet is essential in developing effective prevention.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The present study has been approved by the University of Cuenca Bioethical Committee (UC-COBIAS-2020-078) and Research Institute (IDI) of Escuela Superior Politécnica de Chimborazo. All participants signed a written informed consent before being considered in the study.

AUTHOR CONTRIBUTIONS

VA-U, SS, YM-T, and MV-V: conception and design, analysis and interpretation of data, and drafting of the article. VA-U, SS, MV-V, YM-T, and AE-F: final approval of the version to be published. AE-F: writing. MV-V and AE-F: critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Sugar-sweetened beverages consumption in a multi-ethnic population of middle-aged men and association with sociodemographic variables and obesity

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Background: Adults frequently consume sugar-sweetened beverages. These products are linked to negative health effects such as obesity. Our study was carried out to assess rates of weekly and daily sugar-sweetened beverages consumption in a multi-ethnic population of middle-aged men and association with sociodemographic variables and obesity.

Methods: A sum of 1,800 middle-aged men (36–59 years) living in Riyadh, KSA, participated in this cross-sectional study. Sociodemographic variables and the frequency of sugar-sweetened beverages consumption were gathered from participants using face to face interviews. Weekly and daily consumption of sugar-sweetened beverages were the two binary outcome variables applied in this research. Weight and height were measured following standard procedures.

Results: In this study, 93.8 and 32.6% of participants consumed sugar-sweetened beverages weekly and daily, respectively. The weekly and daily sugar-sweetened beverages consumption was predicted by nationality. Subjects from Pakistan (99.3%) and Yemen (60.0%) reported the greatest rates of weekly and daily consumption, respectively, while Bangladeshi and Sudanese subjects reported the lowest rates of weekly (87%) and daily (2.9%) consumption, respectively. Another factor that predicted weekly sugar-sweetened beverages consumption was obesity. Obese subjects had a significantly greater odds ratio of weekly sugar-sweetened beverages intake than non-obese individuals (OR = 3.80, $P = 0.003$).

Conclusion: Consumption of sugar-sweetened beverages is common among middle-aged men who live in KSA. Results show connecting sugar-sweetened beverages intake with specific sociodemographic variables and obesity.

KEYWORDS

sugar-sweetened beverages, multi-ethnic, middle-aged men, sociodemographic, obesity

Introduction

Globally, a widespread intake of sugar-sweetened beverages (SSBs) has been documented in adults (1). Common SSBs include regular soda, fruit drinks, and energy drinks. Most of SSBs are manufactured by adding high amounts of various types of free sugars such as sucrose and fructose (2). Consumption of SSBs contributes to daily energy intake due to their high added sugar content (3). Thus, SSBs intake may decline overall diet quality and lower daily intake of essential micronutrients (4). Consumption of SSBs is linked to a greater risk of numerous health problems like obesity, diabetes, cardiovascular disease and dental caries (5–7). Subsequently, SSBs intake has been considered an important public health issue (8). This situation motivated the WHO to create guidelines encouraging adults to limit added sugar intake to 5–10% of typical day calories (9). As SSBs consumption is very common among adults, it is vital to investigate patterns of SSBs intake and related sociodemographic variables to create efficient wellbeing promotion initiatives to minimize their use (10, 11).

In the Kingdom of Saudi Arabia (KSA), adult obesity is a serious health issue accompanied by unhealthy lifestyle choices such as physical inactivity and poor diet, including high consumption of SSBs (12–16). Indeed, KSA is the top oil producer in the Middle East region, and its economy is rising quickly. It should be no surprise that KSA hires people from all over the world. In fact, KSA had a workforce of about 50% foreigners, and 90% of the private sector occupations were held by foreigners (17). About one-third of the people in this country are non-Saudi residents, with men making up roughly three-fourths of them (18). Immigrants from various ethnic backgrounds make exploring the disparities in food habits and connections to wellness and illness in a diverse population exciting. Therefore, the objectives of this study were to determine the rates of weekly and daily SSBs consumption in a population of middle-aged men from various ethnic groups and the association with socioeconomic variables and obesity.

Abbreviations: KSA, Kingdom of Saudi Arabia; BMI, Body Mass index; OR, odds ratio.

Methods

Study sample and design

The data for this study were derived from a research project named the Relationship between Obesity, physical Activity, and Dietary pattern among men in KSA (ROAD-KSA) (15, 16, 19–22). It is a cross-sectional research project that took place in Riyadh, KSA, from February to June 2019. The study sample was randomly drawn from Riyadh public areas using a stratified clustered sampling technique. The eligible subjects were middle-aged men aged 36–59 years, living in Riyadh city, without any physical disability (the disability nature may affect body weight and height, which could bias the outcome of obesity diagnosis, and may affect food habits, including SSBs intake which could bias the outcome of SSBs consumption frequency), and having citizenship from one of these countries: KSA, Egypt, Yemen, Syria, Jordan, Sudan, Turkey, Pakistan, Afghanistan, India, Bangladesh, and the Philippines. Before taking part in our study, informed consent was collected from subjects in agreement with the Helsinki Declaration. The present study was authorized by the research ethics committee of Princess Nourah bint Abdulrahman University.

Sociodemographic data

Professional research team gathered sociodemographic data following face to face interviews. The collected data were nationality, age, residency period in KSA, household type, marital status, educational level, and monthly income.

Body mass index

Professional research team measured weight and height of subjects while wearing minimal clothes and no slippers in a complete standup situation. Weight was measured to the closest 0.1 kg using a weight balance (Seca 802, Hamburg, Germany), whilst height was measured to the closest 0.1 cm using a portable stadiometer (Seca 213, Hamburg, Germany). Weight (kg) was divided by height (m^2) to find body mass index (BMI) value. Obesity is determined as a BMI $\geq$ 30 (23).

Sugar-sweetened beverages intake

The frequency of SSBs intake was determined using a valid and reliable questionnaire. The questionnaire's face validity was assessed using an objective evaluation from five skilled researchers. A test-retest pilot study with a 14 days' time lag was used to judge the questionnaire's reliability. Data were collected by a skilled research team using face to face interviews. In this study, SSBs were defined as artificial beverages with free sugars that are not recognized as diet or low-calorie, excluding coffee, tea, dairy, and alcoholic beverages (11). Consequently, SSBs were classified into three subtypes: regular soda, fruit drinks and energy drinks. Regular soda refers to carbonated beverages with added sugar. Fruit drinks are artificial fruit juices with free sugars, excluding natural fruit juices. Energy drinks are any carbonated beverage with added sugar and a high level of stimulating ingredients such as caffeine. To determine the frequency of SSBs consumption, the participants were questioned about the number of servings (on average 12 fl oz can or bottle) from each SSBs subtype they usually drink per week or day during the preceding year. The frequency of weekly and daily consumption for total SSBs and each SSBs subtype were computed based on replies. Drinking at least one serving per week was considered weekly consumption, while drinking at least one serving per day was considered daily consumption (24).

Statistical analysis

Data analysis was managed using Statistical Package for the Social Sciences (SPSS) software for Windows, version 26.0 (SPSS Inc., Armonk, NY, USA). This study uses two binary outcome variables: weekly and daily consumption of SSBs. Categorical variables were analyzed using the Chi-square test, and the results were displayed as frequencies and percentages. After adjusting for studied sociodemographic variables and obesity, a multivariate logistic regression analysis was done to investigate variables linked to weekly and daily SSBs consumption. Two-tailed testing was used to determine *P*-values. Statistical significance was recognized when $P < 0.05$.

Results

The study subjects came from twelve different countries who lived in KSA. The mean age of study participants was 40.9 ± 3.8 years, and the mean BMI was 26.6 ± 3.6. Table 1 displays the prevalence of weekly SSBs consumption among subjects by sociodemographic variables and obesity. Weekly SSBs consumption was reported in 93.8% of the full study sample, while weekly consumption rates for regular soda, fruit drinks, and energy drinks were 81.9, 58.1, and 32.1%, respectively. When participants were divided into subgroups depending on their nationality, significant differences ($P < 0.001$) in weekly SSBs consumption rates were observed. The participants from Pakistan have the highest rate of SSBs intake per week (99.3%), while the subjects from Bangladesh have the lowest rate (87%). The highest prevalence of regular soda drinking per week (89.8%) was observed among Afghani subjects, while the lowest prevalence (71.8%) was observed among Jordanian subjects. While Filipino subjects have the highest weekly consumption rates of fruit drinks (85.9%) and energy drinks (53.5%). The lowest rates of fruit drinks (24.0%) and energy drinks (17.8%) were reported among subjects from Bangladesh and Sudan, respectively. Participants who have lived in KSA for more than 5 years had a significantly higher prevalence of weekly SSBs intake (94.4%) than those who have been there for 5 years or less (91.3%). Living within non-family households was correlated with a significantly greater rate of weekly SSBs intake (95.8%) than living within family households (90.5%). Single subjects have significantly higher weekly consumption rates of SSBs (95.5%) and regular soda (88.8%) than married participants (93.4 and 81.2%, respectively). A low education level was correlated with a significantly greater weekly SSBs intake rate (95.9%) than high education level (90.0%). Likewise, low monthly income was connected with a significantly greater weekly consumption rate of SSBs (95.9%) than high monthly income (91.6%). Lastly, obese participants have a significantly greater prevalence of weekly SSBs consumption (97.7%) than non-obese subjects (93.2%).

Table 2 shows the prevalence of daily SSBs consumption among study participants by sociodemographic variables and obesity. Daily consumption of SSBs was reported in 32.6% of the full study sample, whereas the rates for regular soda, fruit drinks, and energy drinks were 11.7, 2.6, and 0.8%, respectively. When participants are subdivided depending on their nationality, significant variations ($P < 0.001$) in daily intake rates of SSBs, regular soda and fruit drinks are identified. Yemeni subjects have the highest rates of daily SSBs intake (60.0%) and regular soda (20.9%). In comparison, the highest rates of daily intake of fruit drinks and energy drinks were seen among Filipino (12.7%) and Afghan (2.7%) subjects, respectively. In contrast, the lowest rates of daily consumption of SSBs (2.9%) and regular soda (0.6%) were reported among Sudanese and Jordanian subjects, respectively. However, daily consumption of fruit drinks was not observed among Sudanese, Pakistani, Indian, and Bangladeshi subjects, while daily consumption of energy drinks was not observed among Egyptian, Jordanian, Sudanese, and Bangladeshi subjects. The daily SSBs consumption rates among participants with 5 years or less and more than 5 years of residency in KSA were 36.4 and 31.7%, respectively ($P > 0.05$). Similarly, the daily SSBs consumption rates among participants who live within non-family and family households were 33.0 and 31.9%, respectively. The daily SSBs consumption rates among single and married participants were 37.4 and 32.0%, respectively. The daily SSBs consumption rates among

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TABLE 1 Prevalence of weekly sugar-sweetened beverages (SSBs) consumption among study participants ($n = 1,800$) stratified by sociodemographic variables and obesity.

Variables	Total SSBs	Regular soda	Fruit drinks	Energy drinks
All Participants	1,689 (93.8%)	1,475 (81.9%)	1,045 (58.1%)	578 (32.1%)
Nationality				
Saudi	144 (89.4%)	126 (78.3%)	112 (69.6%)	30 (18.6%)
Egyptian	153 (95.0%)	138 (85.7%)	123 (76.4%)	47 (29.2%)
Yemeni	114 (99.1%)	97 (84.3%)	97 (84.3%)	48 (41.7%)
Syrian	141 (89.8%)	118 (75.2%)	110 (70.1%)	65 (41.4%)
Jordanian	148 (87.1%)	122 (71.8%)	125 (73.5%)	40 (23.5%)
Sudanese	162 (93.1%)	140 (80.5%)	49 (28.2%)	31 (17.8%)
Turkish	237 (96.0%)	208 (84.2%)	112 (45.3%)	87 (35.2%)
Pakistani	143 (99.3%)	129 (89.6%)	75 (52.1%)	46 (31.9%)
Afghan	145 (98.6%)	132 (89.8%)	75 (51.0%)	65 (44.2%)
Indian	147 (96.1%)	124 (81.0%)	82 (53.6%)	51 (33.3%)
Bangladeshi	87 (87.0%)	84 (84.0%)	24 (24.0%)	30 (30.0%)
Filipino	67 (94.4%)	57 (80.3%)	61 (85.9%)	38 (53.5%)
P-value*	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Residency Period in KSA				
1–5 years	303 (91.3%)	259 (78.0%)	198 (59.6%)	105 (31.6%)
6 years or more	1,386 (94.4%)	1,216 (82.8%)	847 (57.7%)	473 (32.2%)
P-value*	**0.031**	**0.039**	0.517	0.834
Household Type				
Non-family household	1,088 (95.8%)	969 (85.3%)	572 (50.4%)	410 (36.1%)
Family household	601 (90.5%)	506 (76.2%)	473 (71.2%)	168 (25.3%)
P-value*	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Marital status				
Single	208 (97.2%)	187 (87.4%)	126 (58.9%)	69 (32.2%)
Married	1,481 (93.4%)	1,288 (81.2%)	919 (57.9%)	509 (32.1%)
P-value*	**0.029**	**0.028**	0.795	0.965
Education level				
Low (high school or less)	1,133 (95.9%)	1,005 (85.0%)	596 (50.4%)	394 (33.3%)
High (college or more)	556 (90.0%)	470 (76.1%)	449 (72.7%)	184 (29.8%)
P-value*	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Monthly income				
Low (<1,000 USD)	954 (95.6%)	838 (84.0%)	535 (53.6%)	359 (36.0%)
High (≥1,000 USD)	735 (91.6%)	637 (79.4%)	510 (63.6%)	219 (27.3%)
P-value*	**0.001**	**0.013**	**<0.001**	**<0.001**
Obesity (BMI ≥ 30)				
No	1,431 (93.2%)	1,257 (81.8%)	887 (57.7%)	513 (33.4%)
Yes	258 (97.7%)	218 (82.6%)	158 (59.8%)	65 (24.6%)
P-value*	**0.004**	0.773	0.523	**0.005**

*Categorical variables were analyzed by using Chi-squared test and expressed as numbers and percentages. Significant values (*P*-value < 0.05) were presented in Bold type.

participants with low and high education levels were 32.3 and 33.2%, respectively. The daily SSBs consumption rates among participants with low and high monthly income were 32.0 and 33.4%, respectively. Finally, the daily SSBs consumption rates among obese and non-obese participants were 28.8 and 33.3%, respectively.

Table 3 demonstrates the odds ratios for weekly and daily SSBs consumption among participants for sociodemographic variables and obesity. Nationality was found to be a predictor of weekly and daily SSBs consumption. Compared to Bangladeshi participants, subjects from Egypt, Yemen, Turkey, Pakistan, Afghanistan, and India had significantly greater odds ratios

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TABLE 2 Prevalence of daily sugar-sweetened beverages (SSBs) consumption among study participants (n = 1,800) stratified by sociodemographic variables and obesity.

Variables	Total SSBs	Regular soda	Fruit drinks	Energy drinks
All participants	587 (32.6%)	210 (11.7%)	46 (2.6%)	14 (0.8%)
Nationality				
Saudi	41 (25.5%)	14 (8.7%)	2 (1.2%)	1 (0.6%)
Egyptian	96 (59.6%)	33 (20.5%)	10 (6.2%)	0 (0.0%)
Yemeni	69 (60.0%)	24 (20.9%)	10 (8.7%)	3 (2.6%)
Syrian	58 (36.9%)	20 (12.7%)	3 (1.9%)	2 (1.3%)
Jordanian	49 (28.8%)	1 (0.6%)	6 (3.5%)	0 (0.0%)
Sudanese	5 (2.9%)	5 (2.9%)	0 (0.0%)	0 (0.0%)
Turkish	75 (30.4%)	50 (20.2%)	4 (1.6%)	1 (0.4%)
Pakistani	40 (27.8%)	7 (4.9%)	0 (0.0%)	1 (0.7%)
Afghan	61 (41.5%)	23 (15.6%)	2 (1.4%)	4 (2.7%)
Indian	45 (29.4%)	27 (17.6%)	0 (0.0%)	1 (0.7%)
Bangladeshi	11 (11.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)
Filipino	37 (52.1%)	4 (5.6%)	9 (12.7%)	1 (1.4%)
P-value*	**<0.001**	**<0.001**	**<0.001**	0.074
Residency Period in KSA				
1–5 years	121 (36.4%)	49 (14.8%)	13 (3.9%)	1 (0.3%)
6 years or more	466 (31.7%)	161 (11.0%)	33 (2.2%)	13 (0.9%)
P-value*	0.099	0.052	0.082	0.274
Household type				
Non-family household	375 (33.0%)	168 (14.8%)	24 (2.1%)	10 (0.9%)
Family household	212 (31.9%)	42 (6.3%)	22 (3.3%)	4 (0.6%)
P-value*	0.636	**<0.001**	0.119	0.517
Marital status				
Single	80 (37.4%)	38 (17.8%)	9 (4.2%)	1 (0.5%)
Married	507 (32.0%)	172 (10.8%)	37 (2.3%)	13 (0.8%)
P-value*	0.113	**0.003**	0.103	0.582
Education level				
Low (high school or less)	382 (32.3%)	170 (14.4%)	19 (1.6%)	8 (0.7%)
High (college or more)	205 (33.2%)	40 (6.5%)	27 (4.4%)	6 (1.0%)
P-value*	0.714	**<0.001**	**<0.001**	0.5
Monthly income				
Low (<1,000 USD)	319 (32.0%)	124 (12.4%)	29 (2.9%)	7 (0.7%)
High (≥1,000 USD)	268 (33.4%)	86 (10.7%)	17 (2.1%)	7 (0.9%)
P-value*	0.514	0.264	0.294	0.681
Obesity (BMI ≥ 30)				
No	511 (33.3%)	179 (11.7%)	38 (2.5%)	12 (0.8%)
Yes	76 (28.8%)	31 (11.7%)	8 (3.0%)	2 (0.8%)
P-value*	0.151	0.967	0.597	0.968

*Categorical variables were analyzed by using Chi-squared test and expressed as numbers and percentages. Significant values (*P*-value < 0.05) were presented in Bold type.

of SSBs consumption per week [odds ratio (OR) ranged from 2.96 to 29.19, $P < 0.05$]. Likewise, compared to subjects from Sudan, subjects from the remaining countries had significantly greater odds ratios of daily SSBs consumption (OR ranging from 3.72 to 103.15, $P < 0.05$). Furthermore, increasing age was significantly associated with lower odds ratios of weekly (OR = 0.88, $P < 0.001$) and daily (OR = 0.95, $P < 0.001$) SSBs consumption. Subjects who lived in family households had a significantly lower odds ratio of daily SSBs consumption than those who lived in non-family households (OR = 0.41, $P < 0.001$). Highly educated subjects had a significantly lower odds ratio of daily SSBs consumption than those with low education

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TABLE 3 Odds ratios of weekly and daily sugar-sweetened beverages (SSBs) consumption among study participants for sociodemographic variables and obesity.

Variables	Weekly SSBs consumption		Daily SSBs consumption	
	Odds ratio (95% CI)*	*P*-value	Odds ratio (95% CI)*	*P*-value
Nationality				
Saudi	2.40 (0.79–7.30)	0.122	31.41 (11.29–87.38)	**<0.001**
Egyptian	3.35 (1.12–9.99)	**0.03**	89.76 (33.83–238.19)	**<0.001**
Yemeni	29.19 (3.38–252.28)	**0.002**	103.15 (37.58–283.17)	**<0.001**
Syrian	2.39 (0.81–7.02)	0.113	47.94 (17.55–130.92)	**<0.001**
Jordanian	1.94 (0.68–5.57)	0.216	28.50 (10.37–78.31)	**<0.001**
Sudanese	1.73 (0.71–4.22)	0.226	1	
Turkish	3.81 (1.40–10.36)	**0.009**	12.52 (4.85–32.35)	**<0.001**
Pakistani	16.40 (2.00–134.20)	**0.009**	14.69 (5.54–38.94)	**<0.001**
Afghan	9.81 (2.05–46.93)	**0.004**	25.19 (9.66–65.69)	**<0.001**
Indian	2.96 (1.05–8.38)	**0.041**	12.59 (4.83–32.81)	**<0.001**
Bangladeshi	1		3.72 (1.25–11.11)	**0.019**
Filipino	3.14 (0.84–11.76)	0.09	57.05 (20.13–161.68)	**<0.001**
Age (years)	0.88 (0.84–0.93)	**<0.001**	0.95 (0.92–0.98)	**<0.001**
Residency period in KSA				
1–5 years	1		1	
6 years or more	1.33 (0.79–2.22)	0.283	0.94 (0.70–1.26)	0.665
Household type				
Non-family household	1		1	
Family household	0.66 (0.30–1.48)	0.314	0.41 (0.28–0.61)	**<0.001**
Marital status				
Single	1		1	
Married	1.11 (0.44–2.82)	0.82	1.35 (0.94–1.93)	0.102
Education level				
Low (high school or less)	1		1	
High (college or more)	0.67 (0.32–1.38)	0.274	0.60 (0.42–0.86)	**0.006**
Monthly income				
Low (<1,000 USD)	1		1	
High (≥1,000 USD)	0.81 (0.42–1.57)	0.527	1.35 (1.01–1.80)	**0.044**
Obesity (BMI ≥ 30)				
No	1		1	
Yes	3.80 (1.60–9.05)	**0.003**	0.72 (0.52–1.00)	0.052

*Multivariate logistic regression analysis was used after adjusting for subjects' sociodemographic variables and obesity. Differences were considered statistically significant at *P*-value < 0.05, and significant values were presented in Bold type.

(OR = 0.60, $P = 0.006$). Subjects with a high monthly income had a significantly higher odds ratio of daily SSBs consumption than those with low monthly income (OR = 1.35, $P = 0.044$). Finally, obese subjects had a significantly higher odds ratio of weekly SSBs consumption than non-obese subjects (OR = 3.80, $P = 0.003$).

Discussion

This study explored weekly and daily SSBs consumption rates in a multi-ethnic population of middle-aged men. Our results disclosed that most subjects (93.8%) were weekly consumers of SSBs and about one-third (32.6%) were daily consumers of SSBs. The prevalence of SSBs consumption among adults has been investigated in several studies. According to a recent nationally representative survey from KSA, 71.2% of adults consumed SSBs weekly, while 35.5% consumed SSBs daily. In addition, 65% of middle-aged adults (35–54 years) were weekly SSBs consumers (24). In a national survey of Australian adults, 55.9 and 19.3% of men consumed SSBs weekly and daily, respectively. The rates of weekly and daily SSBs intake in adults aged 31–45 years were 54.7% and 16.3, respectively, while the rates of weekly and daily SSBs

intake in adults aged 46–60 years were 41.1 and 12.5%, respectively (10). A Norwegian study reported that SSBs intake rate among adults was 34% (25). Another study indicated that 63.9% of American adults drank SSBs daily. Moreover, the daily consumption rates of regular soda, fruit drinks, and energy/sport drinks were 21, 6.6, and 5.7%, respectively (26). The rate of daily SSBs consumption among British adults was 20.4% (27). Finally, research from New York City reported that 27.5% of adults were daily consumers of SSBs (28).

This study's data showed that participants from different countries consumed SSBs at significantly different rates. This outcome is in line with several earlier research that found a substantial difference in SSBs intake across adults from various countries, regions, or ethnic origins (26, 29, 30). A study that compared the consumption of SSBs across 187 countries spread over 21 global geographical areas discovered significant variation in SSBs consumption. The difference between the top and lowest regional consumption levels was over ten times. East Asia had the lowest intake of SSBs, while the Caribbean had the highest (30). The consumption of SSBs and SSBs subtypes in the United States differed according to where people lived. Adults in the Northeast, South, West, and Midwest consumed daily SSBs at rates of 68.4, 66.7, 61.2, and 58.8%, respectively. According to findings from this study, adults in the Northeast were much more likely (OR = 1.13) to report consuming SSBs on a daily basis than adults in the South, while those in the Midwest (OR = 0.70) and the West (OR = 0.78) were noticeably less likely to do so (26). In another American study, SSBs intake varies depending on ethnicity. Blacks and Hispanic middle-aged and older adults were more likely than Whites to drink SSBs (29). The causes of these differences in SSBs consumption rates by nationality are still unconfirmed. The potential explanations include differences in the ecological factors such as availability and accessibility to SSBs that adults experienced in their original countries during the preceding age stages (31, 32). Other reasons include variations in how they reacted to SSBs marketing advertisements in the country where they lived caused by disparities in language and cultural standards (10, 33). Nevertheless, when initiatives to lower SSBs consumption are developed, disparities in SSBs consumption rates by nationality should be taken into account (34).

Linking SSBs consumption among adults to sociodemographic factors is widely discussed in previous studies (27, 29). Our results observed significant relationships between weekly or daily SSBs consumption and age, household type, education level and monthly income. Our findings agreed with findings from previous studies that reported a higher likelihood of SSBs consumption was linked to younger age (10, 24, 28, 35, 36), living within non-family households (37), and lower education levels (27, 29). Contrarily, our findings conflict with an earlier study which stated that SSBs consumption did not seem to differ between university students living in their family households and those living in non-family households (38), and earlier studies reported that a higher likelihood of SSBs consumption was linked to lower monthly income (27, 29).

Interestingly, our findings supported the link between consuming SSBs every week and obesity. Many adults are affected by obesity, a costly condition with high morbidity and mortality rates (39, 40). Numerous studies support the relationship between SSBs consumption and adulthood obesity and other obesity-related conditions like diabetes and coronary heart disease (6, 41, 42). Several theories have been established to elucidate the relationship between SSBs use and obesity (43). Adults who usually drink SSBs consume significantly more calories, which causes a positive energy balance (44, 45). On any given day, around 50% of United States adults have one or more SSBs servings, and nearly 7% of their daily caloric intake is derived from SSBs (46). Possible mechanisms include decreased satiety, fast fructose absorption, and after-meal hyperglycemia. The absorption of glucose can cause after-meal hyperglycemia when SSBs are drunk, which reduces the carbohydrate-related elevation in serum glucose level (47). Postprandial hyperglycemia causes a cascade of changes, including hyperinsulinemia, glucose uptake by insulin-sensitive tissues, concurrent hypoglycemia to levels lower than fast values, greater appetite driven by the lack of available fuel, and overeating (48). Furthermore, fructose is processed largely in the liver. Fast fructose absorption from SSBs may overload hepatic metabolic processes, promote lipogenesis, and result in physiological abnormalities such as insulin resistance and excessive fat accumulation (49). Fructose consumption switch on hepatic *de novo* lipogenesis through stimulating two master transcriptional regulators: SREBP-1c and ChREBP. As this process is independent of insulin secretion, fructose consumption can encourage hepatic lipid buildup even in the presence of insulin resistance. Furthermore, fructose intake causes ATP depletion and suppresses the oxidation of fatty acids in the hepatocytes' mitochondria, promoting fat accumulation in the liver and secreting triglycerides-rich VLDL particles. Overall, fructose intake promotes dyslipidemia, cardiometabolic risk factors and insulin resistance, and elevates visceral fat deposit in overweight and obese adults (50, 51).

Several environmental and governmental modifications need to be made to lower SSBs use in the community (11). Limiting the availability of these foods in public places and reducing exposure to SSBs commercial advertisements in the media may help reduce SSBs consumption (10). Moreover, raising public knowledge of the harmful health effects of SSBs use through public health education initiatives may aid efforts to restrict overall SSBs intake (8). In addition, campaigns that encourage substituting SSBs with energy-free liquids like water should be considered (52). Global public health organizations have encouraged governments to intervene due to the widespread and fast increases in SSBs intake.

Taxing the price of SSBs is one practical solution to decrease SSBs intake (53, 54).

Few limitations apply to our study. The significant associations between outcome measures and their predictors could not be used to infer causality because of the cross-sectional design. Moreover, women were not involved in the present study. Another drawback was using a self-reported frequency approach to collect consumption data, which relied on participants' memories. Compared to evaluating the consumption using a 24-h recall method, this approach can result in an underestimated SSBs intake. The definition of SSBs is diverse across studies limiting the opportunity to compare our results with previous studies. Finally, this study could not account for calorie intake when analyzing the relationship between SSBs consumption and obesity due to a lack of energy intake data. Despite these limitations, this study still presents valuable data about the rates of SSBs consumption and associated determinants.

Conclusions

According to this study, middle-aged men who live in KSA consumed SSBs at relatively high rates. The results demonstrated that middle-aged men from different countries who reside in KSA drink SSBs at noticeably varied rates. The findings also show a connection between SSBs consumption, certain sociodemographic variables, and obesity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee at Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RIA, RAA, NAls, and NAlF: conceptualization. MA, HA, and JA: methodology. NAlK, RIA, and MA: software. MA and MB: validation. HA and NAls: formal analysis. RAA and NAlK: investigation. NAlF and MB: resources. RAA, HA, and NAls: data curation. NAlF, NAlK, JA, and RIA: writing—original draft preparation. RAA, MB, NAls, and HA: writing—review and editing. JA, MA, and MB: visualization. NAlF: supervision. JA: project administration. RIA and NAlK: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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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.

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Serious games and eating behaviors: A systematic review of the last 5 years (2018–2022)

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Background: Serious game intervention has emerged over the years as a popular strategy for solving the problem of unhealthy eating behavior. This has prompted several scholars to explore its significant impact on eating behaviors, identifying its positive effect on nutritional knowledge and eating behaviors. However, since this research field is yet nascent, an update in knowledge is required to further inform the real-world practice as an alternative intervention for instating healthy eating behavior. Therefore, this current research utilized a systematic review method to reveal the latest state of this concept of a serious game and eating behavior, to identify the position of the literature and shed light on under-researched and emerging areas by recommending future investigations.

Method: To achieve the object of this research, four electronic databases- Science Direct, Web of Science (WoS), APA PsycINFO, and Emerald- were searched using predefined keywords (search string) relating to the review topic. A total of 15,107 results were retrieved from the databases. After title, abstract, and full-text screening, 15 studies were included following inclusion criteria.

Key findings: The result of this research demonstrated that various designs of serious games comprise an effective intervention for changing eating behavior in both children and adults and addressed the risks of childhood obesity and overweight. The findings also show that the design of the games is co-designed by different specialists such as a nutritionist, psychologist and developer, among others, as either single or multiple players. The effectiveness of the games was attributed to behavior techniques (BT), cognitive theories (CT), and socio-cognitive theories (SCT) of behavior change technique (BCT), incorporating an element of implicit learning in serious games. Feedback and reward were the most reported influencing strategies and self-reporting the evaluation approach.

Conclusion: This research contributed significantly to the body of knowledge in the field of serious games as the most recent review of evidence in the research area. Evidence from 93.33% of the included studies confirmed the effectiveness of serious games in addressing eating behavior. This study concludes that serious games are an effective intervention for improving healthy eating behavior and decreasing unhealthy eating behavior and that various elements of behavior change techniques are essential components of implicit nutritional learning through the games. In addition, it is concluded that

the risk of childhood obesity and overweight can be reduced or prevented by leveraging the strength of these games. The need for future research in this field was also pointed out by this study.

KEYWORDS

eating behavior, serious games, review—systematic, unhealthy, game for health

Introduction

The negative effects of unhealthy eating behaviors

Obesity is now a disease developed all over the world. The World Health Organization (WHO) has defined obesity as a pathological clinical condition that manifests itself with the increase and excess of fat mass both at the subcutaneous and visceral levels, and is equally defined as a multifactorial disease, given by a combination of several factors, including excessive intake of unhealthy foods, reduced physical activity, altered microbiome, congenital alterations, genetic susceptibility, and epigenetic alterations (1). In recent years, this condition has reached quite high levels. A phenomenon in strong growth after the COVID-19 pandemic, as the introduction of blockades and other containment measures has significantly changed the lifestyle and eating behavior of citizens (2). The difficulty in following a balanced diet, the increased consumption of "comfort food" able to reduce stress by increasing the production of serotonin which has a positive effect on mood and reducing physical activity with a consequent increase in sedentary behavior, led to an average weight gain of 4 kg per citizen, mostly in women (about 24% compared to 22% of men) and with a prevalence in the under 30s of 21% compared to the general population (3).

For healthy growth and development, the importance of eating behavior has received significant attention over the years. This is due to the increasing incidence of chronic disease and illness that result from unhealthy eating behavior (4, 5). Several studies have shown that unhealthy eating behavior, especially during young age, is a significant risk factor in causing long-term chronic disease. This pattern of unhealthy eating behavior negates the standard eating behavior, consequently increasing the risk of excess weight gain and obesity (6, 7). This may be why Lobstein et al. (8) and Williams et al. (9) rued the drastic increase in the child obesity rate in the past decades and emphasized the necessity for proper guidance for healthy eating behavior.

A Mexican study found that 35.6% of children of the school-age are obese due to unhealthy eating behavior, and as a result may suffer severe emotional and physical health issues (10). To prevent the negative consequences, Nishtar et al. (11) suggested that the intake of healthy food must be encouraged, and unhealthy eating behavior discouraged, especially the consumption of unsaturated fatty foods, which are consumed by over 70% of the people. Ogden et al. (12) argued that while several factors have led to the increase in the rate of obesity, eating behavior has contributed significantly. The increased incidence of obesity due to unhealthy eating behavior has been reported not only in Mexico but across regions. Instituto Brasileiro de Geografia e Estatística (13) research also revealed an exponential growth in the rate of overweight people in Brazil, again attributing it to diet decisions. Another research found that Brazilian adolescent consumption of all kinds of saturated fats and sugar exceeds the standard recommendation for consumption level, falling short of the recommended intake of other essential minerals needed for growth and development (14). Mendes (15) point out that addressing these challenging public issues is quite difficult because several factors such as social, cultural, etc. predict eating behaviors.

The role of serious games intervention in reducing unhealthy eating behavior

According to literature, the most effective interventions for reducing unhealthy eating behaviors are represented by those interventions that foster a non-sedentary lifestyle and healthy eating habits by improving health quality, reducing weight, and preventing weight gain (16). Specifically, among them, we can find diet and lifestyle interventions (17), drugs for weight reduction (18), balancing prescription of medications that cause weight gain (18) and surgical intervention (19). Among these interventions, research has shown that serious games could influence people to be more active, promoting non-sedentary lifestyles (20).

Serious games can be defined as games designed for other purpose that pure entertainment (21) and the emergence of serious games intervention has become popular over the years in solving the problem of unhealthy eating behavior. Baranowski et al. (22) describe the serious games intervention as an emerging and complementary intervention approach to accomplish that need through exciting, innovative, and enticing approaches for luring attention, enlightening and enhancing attitudes and

human behavior change. Long before Baranoskwi and Shrum (23) described the games as a "rule-based system" with different outcomes depending on the individual performance of the players. Earlier, the author indicated that due to this rule-based system, players must overcome the physical or mental challenges posed along the line of the games to accomplish the goal of the game, and as such become emotionally connected to the outcome.

Unlike the aforementioned interventions used to reduce and prevent obesity, this approach has been established to identify unhealthy eating behavior and train people in healthy eating behaviors through exciting and innovative attraction, without preforming the player. These games are interactive mechanisms that encourage a flexible association with the content, and as a result, the players become familiar with the learning process. Rabin (24) and Schell (25) described long back that the main contribution of this game lies in the players' understanding of the focus, process of design, and impact of the game. Emphasis was placed on how interactive the game is with the player.

In addition, several authors have discussed the positive effect of serious games on nutritional knowledge and eating behaviors (22). Jonhson-Glenberg and Heckler (26) using the Video game Allien health intervention on children, revealed that children who underwent intervention with this game had increased understanding of nutritional knowledge and good eating behavior, vis-a-vis the standard of MyPlate guideline by the US Department of Agriculture, compared to other children. A similar and recent study by Hermans et al. (27) revealed that playing the game for just an hour increases children's knowledge of the most important macronutrients of food. Playing Fit, Food, and Fun Video games by young children was reported by Holzmann et al. (28) to increase children's nutritional knowledge of food intake. Likewise, Matchetti et al. (29) confirmed, with a sample of children above 14 playing videos, the other scholars' position regarding increased nutritional knowledge resulting from the game (30).

Some other scholars describe the game as an educational tool for changing eating behaviors. The educational learning approach is based on implicit and explicit strategies. According to DeSmet et al. (31), it uses explicit educational strategies, e.g., provision of an answer, feedback, and suggestion to the game players, while the implicit learning strategies educate the player with prior awareness (32). The significant attention attracted by this field is proportional to the increase in the number of mobile games and serious games for health and educational purposes. Likewise, its potential benefits in terms of stimulating players' behavior account for its increasing popularity. This game is reported to stimulate players' brain function through the improvement of their behavior and cognitive performance (33). Several scholars have posited that serious games bring about positive effects. Charlier et al. (34) found serious games to be an effective and positive intervention for enhancing children's healthy eating behavior. Moreover, several scholars have reported positive results of the serious games intervention in healthy eating behavior. Majumdar et al. (35) found that children between 11 and 13 playing the serious video game creature 101 had an increase in nutritional knowledge, which eventually lead to a drastic decrease in the consumption of high-sugar beverages and processed snacks by the children after introducing the intervention. A similar study by Sharwama et al. revealed positive results of video game intervention. The study reported that children playing Quest to Lava Mount serious video games for 6 weeks increased their nutritional behavior and reduced consumption of sugar.

Although research in this area is still scarce, serious games interventions seem to be promising interventions to influence healthy eating habits such as non-sedentary lifestyle or modifications of eating patterns, promoting behavioral changes in users (36).

Characteristics of effective serious games interventions

The process and design of the games were revealed as a moderator of the player's experience, and as such, the predictor of outcomes. Savi and Ulbricht (37) highlight that for the effectiveness of the game through a more engaging learning experience for the player, the game should be designed in such a way that the gameplay, rules of the game, interactions of the key elements, adaptations, actions, feedback mechanisms, winning, conflicts, resolutions, and understanding in terms of interpretation should all have interaction in the design. This is because these associated parameters will bring about increasing player pleasure from the game, due to interactive experience, which is considered an intrinsic driver of the player for playing serious games. All these unique features are expected to enhance an interactive player's experience. These moments of enjoyment experienced by the players while playing serious games can be channeled into an implicit learning message. This may be why games are regarded as lean-forward media, as opposed to the radio and television traditional approach, regarded as lean-back media (38). Hence, serious games are highly effective in attracting and retaining children's attention, and are therefore a good tool in communication, inducing healthy eating behavior by increasing the players' sensitivity to food intake (39).

The current study

While much is known about the significance of serious games, there seems to be limited research that has distinctively reviewed findings on how serious games can change eating behaviors, although a recent and similar review has been conducted by Ifeoma (40). The research was on serious games and nutritional behavior. To avoid repeating these, the present

research aims to remove the limitation of the study and further update the body of knowledge. The fact that this research focuses more on serious game design and the review of findings between 2015 and 2020 affords it insights into identifying unhealthy eating behavior and moderated solutions resulting from serious games in the last 5 years. The research coverage, though originally up to 2020, was extended to 2022, as it is believed that in the space of 2 years (2020–2022) more findings might have been revealed. Furthermore, Ifemoa's research, as also highlighted in their limitations, did not cover relevant database and do not provide a rigors assessment of the included studies using theoretical frameworks that guide the realization of review studies such as the PRISMA method. *Therefore, the present study aims to provide a systematic review of how serious games can change eating behavior, in the last 5 years, with an emphasis on eating behavior.*

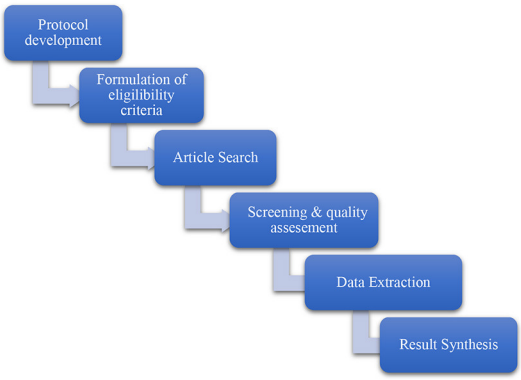

FIGURE 1
Flow diagram explaining the stages to the identification of relevant studies.

Method and methodology

Since this research aims to synthesize evidence-based information from existing publications on how serious games impact eating behaviors, it has been decided to proceed with a systematic literature review (SLR) approach. According to literature, indeed, this method is significant in terms of evidence synthesis that will aid decision-making and policymaking in real-time (41–44).

This review utilized qualitative information of secondary data following the guidelines suggested by Petersen et al. (45), to gather and synthetise information from high-quality scientific studies relevant to the topic. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols were utilized, in incongruence with Moher et al. (46). This helped to manage the identifications of relevant studies as part of the search process, which allowed us to develop eligibility criteria for inclusion and exclusion during the screening process of studies. Only references that met the inclusion criteria were included in the study. The methodology consisted of several stages. The first stage of the study was the protocol development, followed by the inclusion and exclusion criteria. We performed literature research for studies from the database. The studies were screened by two authors. The screening process covered the abstract, title and full-text screening, followed by data extraction and lastly, a synthesis of the previous findings. A flow diagram showing the stages is presented in Figure 1.

The research protocol

The protocol is the first stage of the research and establishes the main research question that guides the article search, selection of papers, the data sources and search string, the inclusion and exclusion criteria, as well as the results section (47). With the aid of the research questions, quality studies were identified from four different databases.

Inclusion criteria

The selection process for the inclusion of papers follows the inclusion criteria to detect the overall validity of the literature review; studies were eligible for the research only if they focused on the research topic, which is the impact of a serious game and eating behaviors. Papers were selected from 2018 up to 2022 to retrieve the latest research information in the context of the review topic. Serious games' development processes rapidly change and update. For this reason, this review focus on studies published in the last 5 years to identify the most current trends, in order to present and analyze the most up-to-date interventions. We included papers written in the English language since most of the published peer-reviewed papers are in English and other reviewers too confine their search to English studies to save time and resources and reduce the shortcomings of non-English papers (48, 49). Studies reflecting the search keywords (Serious games and eating behaviors), and original articles were considered as opposed to review papers, for the reliability of synthesis evidence. Likewise, only research fields related to the review topic were considered and articles as the document type were alone included.

Exclusion criteria

Due to the quality of the current research, we excluded studies not written in English, systematic literature review studies, dissertations, magazines, conference papers, notes,

letters, and observational studies. Likewise, publications not falling within the 2018–2022 period were excluded. Since this study concentrated on serious games and eating behaviors, studies that digressed from the scope of the topic and papers were excluded, as also research papers without a clear explanation of serious games.

Search strategy

The Science Direct, Web of Science (WoS), APA PsyclNFO, and Emerald databases were searched for the publication period of 2018–2022. The appropriateness of these databases is due to their specificity and diversity across domains. For instance, WoS is considered a leading database globally for the search for scientific citations and is diversified across research fields (50). The scope of the literature search was based on the inclusion and exclusion criteria. The database was queried using pre-formed search keywords or strings within the title and abstract of the databases using the Boolean operator ("AND" and "OR").

The literature search was performed using the following keywords: *"Serious games" AND "eating behaviors" OR "feeding behaviors" OR "Eating habits" OR "feeding habits" OR "Healthy eating" OR "Healthy feeding" OR "Nutrition."*

The process of screening using eligibility criteria is shown in the PRISMA flow diagram in Figure 2.

Study selection and screening process

After applying the keywords to the Science Direct, Web of Science (WoS), APA Psyclnfo, and Emerald databases, 15,107 results were retrieved. The result was then exported into excel software version 12.0. The raw data was cleaned, arranged, sorted and finally, 7,351 duplicates were removed. Then, two independent reviewers scrutinized the title and abstracts of the studies to identify those related to the research, those not within the scope of the paper, and those that did not focus on the serious game and eating behaviors. This led to the omission of 7,691 results.

Differences between the results of the two reviewers were resolved through discussion and engagement. Title and abstract screening were also performed using an excel sheet. Ae full-text screening was performed on the remaining 65 eligible studies to evaluate each study's research questions, method and methodology, data analysis, result presentation, and logical conclusion to see confirm its relationship to the scope of the current study. In this process, 50 papers were excluded because the results of the study were not properly presented, an inappropriate methodology was adopted, no logical conclusions were arrived at, etc. The full-text screening left us with 15 studies to be included in the systematic review. The full-text screening of these was independently performed by the same two reviewers. A consensus was reached on the differences between the two reviewers through discussion. The process of screening using eligibility is shown in the PRISMA flow diagram in Figure 2.

Quality assessment and data extraction

The quality of the included studies was accessed using the grading of recommendation assessment, development and evaluation (GRADE) by the formulation of certain quality assessment questions and a scoring system of 1–10, similar to the method described by Kitchenham and Stuart (51). The questions are listed in Supplementary Table 1. Each research study accepted as part of the literature was further broken down as per the research topic by applying these questions. Each question represented one point, so each research study had a score ranging from 0 to 10 points. This gave us the opportunity to assess the quality of each included study. In addition, each of the 26 included studies was evaluated based on the formulated questions. The results of the quality assessment are reported in Table 1. The total score across all was rated as "Very Poor" if the total score was <2, "Poor" for scores between 3 and 4, "Good" for scores between 5 and 7, "Very Good" for scores between 8 and 9, and "Excellent" if the total was 10.

Data extraction

A pre-defined sheet was used to gather the following information from the included studies: the Author ID, the author's first name, type of study, year of publication, country of publication, sample size, and main findings.

Results

Overview of the included studies

Analysis of the last 5 years' publications (2018–2022) shows that the research field experienced increased publication during 2020; since then, the publication rate has shown a downward trend. All the 15 included studies were published across eight countries. Germany and The Netherlands lead in the number of publications, having three papers each. Brazil, Canada, and Mexico had two each, while Denmark, Sweden, and the USA had one publication each. The result of the quality assessment of the 15 studies revealed that five were excellent in quality rating [S1, S2, S4, S9, S11], seven very good [S3, S5, S6, S7, S8, S10, S15], while three studies were good [S12, S13, S14], as shown in Supplementary Table 2.

Different methods were adopted by the studies. Randomized control trial (RCT) and randomized (R) studies were the most prominent methods. Each method was adopted by five studies

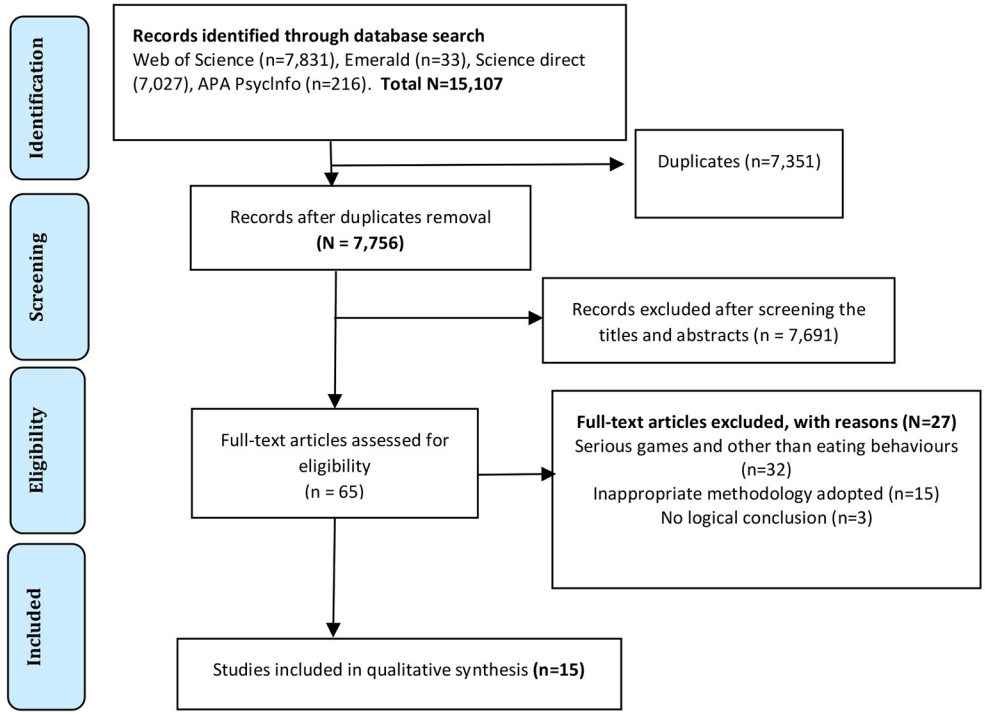

FIGURE 2
PRISMA flowchart showing the screening process for the identification of relevant studies.

[RCT: S1, S2, S3, S4, S14; R: S5, S6, S10, S11, S12]. Two of the studies were pilot studies [S8, S9], while the remaining two [S7 and S15] were randomized control pilot and quasi-experimental mixed-methods studies, respectively. The studies adopted different sample sizes, with most of the studies (13 studies) focusing more on children between the ages of 7–15 years while some used parents along with their children as a post-test or feedback for the effectiveness of the serious game intervention on the children. Three studies including a sample composed by the adult population (>18 years old) were found. One study [S10] which included participants aged more than 18 years [S12] with a sample who had a mean age of 37.6, and [S13] for people aged 23–30 years old, as shown in Supplementary Table 3.

None of the studies reported gender bias in the sample population. The studies adopted different serious game types, as the games were differently designed to focus on their research objective, although all the studies reported similar research objectives, viz., eating or nutritional behaviors. This was the reason they are included in this review. All these serious games were designed around foods such as fruits and vegetables, drinks, snacks, whole grains, and varying types of junk foods (Supplementary Table 3). In the game design, 67% or 10 studies adopted a single design of the serious game and 20% or 3 studies adopted a multiplayer game design, while the remaining studies did not report the player design approach. The theoretical framework adopted by the studies uses behavior change techniques (BCT). Varying numbers of days, weeks, and months of playing the games with accustomed minutes of playing time were adopted by the studies. However, 1–2 weeks were the most reported play days. Interestingly, all the included studies confirmed the effectiveness of serious games on eating behaviors except [S1], which found no moderate effect as shown in Table 1.

Discussion

Evidence from this systematic literature review of the last 5 years on serious games and eating behavior includes fifteen studies, which is not many. However, this is not surprising since this is an emerging research field, but interestingly, the present research identified that field is becoming under-researched in the last 2 years (2021–2022). This is good evidence to draw the attention of scholars to this research area.

TABLE 1 Evidence table.

A/C	Authors, YOP	Type of game	Description and framework	BCT techniques	Number of players	Game intervention focus	Duration	Outcome
S1	Frans et al. (52)	Garfield vs. Hotdog	The game was designed in collaboration with scientific researchers based on a behavior change technique theoretical framework (BCT)	Self-control; Regular and balanced diet; Recognition of healthy and unhealthy foods; Feedbacks on decision	Single	Attitude toward eating, drinks, and snacks	1 week	Not effective
S2	Ismael et al. (53)	FoodRateMaster	Behavioral change theories and techniques were adopted. It included a set of BCTs in the gameplay elements of FoodRateMaster to create a stimulating and engaging environment in which key aspects of healthy behaviors and behavior-specific knowledge were promoted and strengthened It focuses on helping players understand the differences in the nutritional properties of healthy and unhealthy food, as well as the recommended ranges for food nutrients that can help them determine whether they should reduce or maintain the intake of certain foods Behavioral theory (BT), cognitive theory (CT), social cognitive theory (SCT)	BT: Shaping, Behavioral repetition and substitution, stimulus control, learning by consequence e.g., reward CT: Cognitive restructuring SCT: Self-efficacy, self-evaluation, self-observation, and self-reaction	Single	Improve knowledge of healthy and unhealthy foods, increase intake of healthy foods, and reduce intake of ultra-processed food	6 weeks	Effective
S3	Yi-Chin et al. (54)	Fooya vs. Uno	Fooya is a pediatric dietary mobile game with implicit learning components on food choices. It also quantifies children's heterogeneous gameplay patterns using game telemetry and determines the effects of these patterns on players' food choices Uno is a board game without dietary education	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Choice of food	NR	Effective

(Continued)

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TABLE 1 (Continued)

A/C	Authors, YOP	Type of game	Description and framework	BCT techniques	Number of players	Game intervention focus	Duration	Outcome
S4	Mack et al. (55)	Bursting Bubble Game, Kangaroo-Turtle Race, Liquid Rankings on the Sugar Scale, Foods Under the Microscope, Balloon Game, Relaxation story	Balloon food game: This game deals with the food pyramid and its food groups Food Under Microscope induces satiety, which is the volume of food i.e., dietary energy density (DED) Rankings on the Sugar Scale is a questionnaire scale Kangaroo-Turtle Race: In this game, the player has to apply knowledge about DED without having much time to think. A kangaroo (the computer) races against a turtle (the player) Bursting Bubble Game: This game provides information about eustress, distress, and coping strategies Relaxation Story: This task begins with an introduction about eustress and distress and strategies to cope with stress	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Influence of KOP on dietary energy density principle (DED-P) concerning nutrition	2 weeks	Effective
S5	Ismael et al. (56)	Helperfriend	Was developed by a multidisciplinary team that included nutritionists, psychologists, physical activity experts, human-computer interaction experts, and software engineers, based on published design methodology. It is a vicarious experiential video game designed to promote 3 lifestyle behaviors among young children: physical activity, healthy eating, and socio-emotional wellness Several BCT were adopted-Behavioral, Cognitive, and Social cognitive theories	Providing information about health consequences, behavioral practice, behavioral substitution, incentives and rewards, goal setting, reviewing behavioral goals, monitoring behaviors, providing feedback on behavior, discrepancies between current behaviors and goals, monitoring emotional consequences, and prompts or cues	NR	Physical activity, healthy eating, and socioemotional wellness	4 weeks	Effective

(Continued)

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TABLE 1 (Continued)

A/C	Authors, YOP	Type of game	Description and framework	BCT techniques	Number of players	Game intervention focus	Duration	Outcome
S6	Chagas et al. (57)	Rango Cards	A digital game developed for an adequate and healthy diet using simple information in a playful context	Implicit learning; psychoeducation; shaping behavior (modeling)	Multiple	Use of digital games to promote healthy dietary practices	NR	Effective
S7	Froome et al. (58)	Foodbot vs. My Salad Shop Bar	Support school children in learning about Canada's Food Guide; however, its impacts on nutrition knowledge	Feedback and monitoring, social support, shaping knowledge, natural consequences, reward, and threat, quizzes and sub-games requiring a user to catch food and sort food	NR	To see whether the digital game improves children's knowledge of Canada's Food Guide	5 days	Effective
S8	Viggiano et al. (59)	Kaledo	This is an educational board game to improve nutritional knowledge and a healthy lifestyle	Implicit learning; psychoeducation; shaping behavior (modeling)	Multiple	To modify dietary behavior	7 days	Effective
S9	Skouw et al. (60)	The Kingdom of Taste	A game which unites fitting motivators, a fitting social situation, and mere exposure to novel or disliked foods through sensory interactions, to encourage food exploration and possibly change eating behavior in families	Implicit learning; psychoeducation; shaping behavior (modeling)	Multiple	To improve food behavior in families	3 weeks	Effective
S10	Alblas et al. (61)	Skyland	A 2D strategic game in which players have to fight an adversary located at a ground level, who is trying to take down floating islands by forcing unhealthy 156 food upon the inhabitants The healthy game is based on the EC paradigm	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Food choice behavior	NR	Effective
S11	Hermans et al. (27)	Alien Heart Game: Force choice game, Quick sort game, Build a meal game, Ship runner game, Super shopper	A nutritional healthy video game designed to change food choices	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Short term effectiveness on nutrition and healthy food choices	2 weeks	Effective
S12	Langlet et al. (62)	HTC VIVE VR system (HTC)	The HTC VIVE VR system (HTC) is an immersive VR technology in this study, consists of a headset (connected to a computer) through which the VR environment can be viewed, two hand controllers that enable interaction with the VR environment, and two base stations that enable motion tracking	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Virtual game on eating disorders	NR	Effective

(Continued)

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TABLE 1 (Continued)

A/C	Authors, YOP	Type of game	Description and framework	BCT techniques	Number of players	Game intervention focus	Duration	Outcome
S13	Rodrigues et al. (63)	VR	This is a virtual reality game that combines the serious game concept for treating eating disorder	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Eating disorder	1 week	Effective
S14	Weiland et al. (64)	Kid Obesity Game (KOP)	A type of serious game designed to change the nutritional behavior of children and parents	Implicit learning; psychoeducation; shaping behavior (modeling)	Single	Nutritional behavior	2 weeks	Effective
S15	Brown et al. (65)	Foodbot factory	It is an app game that incorporates BCT	Feedback and monitoring, social support, shaping knowledge, natural consequences, and reward and threat	Single	Eating behavioral change	NR	Effective

AC, article code; YOP, year of publication; NR, not reported.

Research outcomes: The positive association between serious games and healthy eating behaviors

Overall, the serious games developed by all the included studies were embedded with various nutritional information, properties, and consequences of healthy and unhealthy foods. The success of players at every stage of the games was developed to depend on either eating or cooking healthy foods. According to the results, indeed, 14 of the 15 included studies, showed positive associations between playing serious games over time and changing in eating behaviors. In this regard, evidence from Ismael et al. (53) confirmed FoodRateMaster, a serious game, as a viable tool for intervening with people, especially 8–10-year-old children, toward healthy eating behaviors. The game was proven to enhance nutritional knowledge and the rate of food intake behavior of the children who play the game, toward healthy eating behavior. The study also confirmed these from the parents of the children after the intervention, as most of them reported positive feedback for the game in terms of reducing their children's positive attitude toward the consumption of unhealthy foods. Also, Mack et al. (55) proved through the development of different serious games, that these games increase the nutritional knowledge of the player, enhancing the positive attitude toward healthy food intake and their coping ability. In the same way, Chagas et al. (57) developed Helperfriend, a serious game based on behavior change techniques (BCT) to moderate physical activities, eating behavior and socio-emotional behavior. In line with previous scholars, their study confirmed the effectiveness of games in improving the dietary knowledge of the player and food intake behavior. Another serious game developed by Yi-Chin et al. (54) confirmed the significant positive effect of a game named Fooya on children's food choices. Similar to previous research, they also posited that players show a negative attitude toward eating unhealthy food after playing the game. The study iterated that the positive outcome observed in the game is due to the implicit learning behavior embedded in it, which tends to increase the players' nutritional knowledge, haven experience the consequence of unhealthy and healthy eating behavior through the game.

Contrasting findings were reported only by one study (52) who failed to confirm previous findings using the Grafield serious game developed to persuade children to eat fruits as opposed to Hotfdog game for energy-dense food. They found no positive attitude toward eating behavior in the children who played the Grafield game and no negative attitude to eating unhealthy energy-dense food. The food intake behavior was not different between those who played the game and non-players i.e., those who played the game did not eat healthier or unhealthier food than those who did not play. The non-effective result of Frans et al. (52) may be related to the design

and approach of the game. Or maybe specifically the game playing time.

The role of game design

According to the result of this review, a central feature that bring together all the analyzed serious games is the game design. In all the studies, the game design incorporated behavior change techniques (BCT). These techniques aim at moderating the psychology of the game players around eating behavior. The techniques were reported to exist in three major frameworks, including behavioral technique (BT), cognitive theory (CT), and social cognitive theory (SCT). Most of the game designs were around these theoretical frameworks. This element of BCT theoretical constructs induced in the game is said to create a stimulating and interactive environment for players, which in turn may have psychological interaction with the players' brains, thus stimulating their behaviors. The construct is centered on self-control, stimulus control, recognition, repetitive behaviors, social support, feedback, monitoring, shaping of nutritional knowledge, and most importantly, learning by consequence i.e., rewards, threats, and consequences of unhealthy eating (66).

With regard to the single-player o multiplayer design of the serious game, instead, with both the format positive outcomes were found. For example, the Kaledo board game developed by Viggiano et al. (59) is a multiple player serious game proven to make players live a healthy lifestyle by instigating healthy eating behavior. Likewise, the Kid Obesity program Game (KOP) and FoodBotFactory are single-player serious games designed by Weiland et al. (64) and Brown et al. (65). Both games demonstrate how serious games maintain high nutritional knowledge in children who play the game. The game was reported to be interactive and full of fun, which was the key reason for its acceptability among children. KOP helps change even parents' nutritional behavior and can reduce the rate of obesity which mostly increases amongst kids due to unhealthy eating and lifestyles. Virtual reality is another version of a serious game observed to be effective for instigating eating behavioral change (67). Rodrigues et al. (63) and Langlet et al. (62) confirmed how the VR serious games version could be used as an effective intervention for treating an eating disorder.

Although the number of articles reviewed in this study is only 15, results from this review could usually inform future serious games interventions for promoting healthy eating behaviors. Results indicated that it is important to take into account different field of disciplines and experts when designing the serious game's contents (education, psychology, nutrition, human-computer interaction, user experience, engineering). Moreover, they highlighted the importance of adapting the interventions' content to individual differences, to create interventions as tailored as possible for users, to improve their efficacy.

Limitations

Critical issues arise from this review. First of all, no standards in terms of the evaluation of the efficacy of these interventions based on serious games seem to have been reached. For example, while some interventions were evaluated in terms of pre- and post-performance of participants in both intervention and control groups, other interventions compared only participants' performance over time. Secondly, the majority of studies present interventions that use serious games developed with a one-size-fits-all approach instead of tailoring the games taking to account the peculiar differences and characteristics of individuals or groups to increase their efficacy. Furthermore, most of the studies do not include in their research design a long-term evaluation of the intervention efficacy in order to verify the generalization and consolidation of the learned behaviors. Finally, only three studies have been found with the adult population. These studies showed similar findings in terms of efficacy with studies conducted on children and adolescents. Further studies on the adult population are needed to corroborate these similarities.

The findings of this review should also be interpreted in light of the limitations of our own work. The small number of included studies reviewed by this current research is one of the few limitations of this study. However, this is because of the five-year (2018–2022) inclusion criteria to review the latest trend in serious games and eating behavior knowledge in the emerging research area. This study is also limited in its consideration of databases, as some other relevant studies may have been omitted during the search. Although the four databases searched may also overlap with other databases, considering too many databases may predispose the search to excessive unjustifiable duplicates of searched results. Instead of these, this research identifies the need for future research to employ broader search terms to retrieve and review more studies on serious games and eating behavior. Also, this study identifies the need for more research in this area, as the studies have demonstrated limited publications in this research field.

Conclusion

The result of this review demonstrated the present state of research on serious games and eating behavior. The synthesized evidence confirmed how serious games can significantly change people across different age groups toward healthy eating behavior and actual food intake. Increased nutritional knowledge due to the game helps to maintain a healthy choice of food and as such, increases negative attitudes toward unhealthy food choices such as sugared, junk, and fatty-related foods. The majority of the games developed by the included studies reported successful outcomes and are designed using behavior techniques, cognitive theories, and socio-cognitive theories of

behavior change techniques. The games were co-designed by several specialists. The effectiveness of the game was observed in children, adults >18, and parents, with the effectiveness of the playtime varying from 5 days to 6 months; feedbacks and rewards were the most frequently adopted influencing strategies and a self-reporting evaluation approach was confirmed across all studies.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Author contributions

GM: introduction. PL: research and discussion. GT: conclusion. All authors contributed to the article and approved the submitted version.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.978793/full#supplementary-material

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Food insecurity as a risk factor for obesity: A review

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Obesity is considered a 21st-century epidemic and it is a metabolic risk factor for Non-Communicable Diseases such as cardiovascular diseases, type 2 diabetes, metabolic syndrome, hypertension, some types of cancer, among others. Thus, its prevention and treatment are important public health concerns. Obesity within the context of food insecurity adds an additional layer of complexity to the current obesity epidemic. Efficient policies and interventions ought to take into consideration the effects of food insecurity on the risks of developing obesity among food insecure households. This review aims to analyze the recent available evidence around the obesity – food insecurity paradox. Most of the literature has consistently shown that there is a significant association between food insecurity and obesity, specifically in women of high-income countries. However, mechanisms explaining the paradox are still lacking. Even though researchers have tried to analyze the issue using different individual and societal variables, these studies have failed to explain the mediatory mechanisms of the food insecurity–obesity relationship since the proposed mechanisms usually lack strength or are purely theoretical. The research focus should shift from cross-sectional models to other research designs that allow the exploration of pathways and mechanisms underlying the food insecurity and obesity relationship, such as longitudinal studies, which will hopefully lead to consecutive research testing the effectiveness of different approaches and scale up such interventions into diverse contexts among those affected by obesity and the different degrees of food insecurity.

KEYWORDS

obesity, food insecurity, paradox, food access, overweight

Introduction

In recent years, food insecurity (FI) has been exacerbated because of the COVID-19 pandemic and the increase of conflicts between nations, which affect food affordability worldwide. FI not only refers to the lack of access to acquire food (1), but itincludes its nutritional quality and food safety. In 2021, it was estimated that about 41 percent of the world population suffered some degree of FI, ranging from moderate to severe (2). Poverty is a key factor that contributes to FI and directly triggers the consumption of unhealthy diets among the low- and middle-income populations. Poverty strikes mainly African, Latin American, and Caribbean populations (2). Moreover, the Middle East, North Africa and Latin America are the low- and middle-income regions with the highest rate of obesity (3). Consequently, FI and poverty not only contribute to the rise of undernutrition, but it can also increase the prevalence of obesity.

The understanding of the coexistence of both food insecurity and obesity, although it might seem contradictory, is relevant for generating further public health actions. Obesity is considered a 21st-century epidemic (4), thus it is an important public health concern (5). This multifactorial chronic disease is influenced by social and environmental factors and not only by an altered nutritional behavior or a genetic disorder (6). Obesity is a metabolic risk factor for Non-Communicable Diseases (NCD) like type 2 diabetes, cardiovascular diseases, metabolic syndrome, hypertension, some types of cancer, among others (7). The treatment of these NCD that are associated with obesity is expensive (8) and it is estimated that obese individuals have a 30 percent higher medical expenses compared to individuals with a normal weight (9). The obese population is concentrated mainly in low- and middle-income countries (10).

Obesity within the context of FI adds an additional layer of complexity to the current obesity epidemic. Efficient policies and interventions ought to take into consideration the effects of FI on the risks of developing obesity among food insecure households. Therefore, this review aims to analyze the recent available evidence around the obesity - FI paradox.

Food insecurity

Several reasons have interfered with attaining world hunger Sustainable Development Goals (SDGs) and diminishing malnutrition in all its forms by 2030 (11). Moreover, the impact of the COVID-19 pandemic has emphasized the need for contemplating how to address the major influencers of the global FI and malnutrition situation and its consequences on the population's health (2).

Food security has been defined by the Rome Declaration on World Food Security 1996 as as a state in which "all individuals, always, have physical, social, and economic access to sufficient, safe, and nutritious food to meet their dietary needs and food preferences for an active and healthy life" (12) whereas FI is the state where there is limited, inadequate, or unreliable availability or access to obtain nutritionally sufficient and safe foods in socially acceptable ways (1, 13, 14). This may be due to financial or social reasons, poverty, urbanization, environmental changes, and agricultural policy (15). FI around the world shows persistent regional disparities, Africa being the most affected region with 20 percent of its population facing hunger in 2021 compared to 9.1 percent in Asia, 8.6 percent in Latin America and the Caribbean, 5.8 percent in Oceania, and <2.5 percent in Northern America and Europe, respectively (2).

As for 2021, the prevalence of moderate FI has remained somewhat unaffected in comparison to 2020. However, the prevalence of severe FI increased, this suggests that those who were already facing moderate FI deteriorated their situation because of the COVID-19 pandemic (11). In 2021, around29.3 was moderately food insecure, and 11.7 percent was severely food insecure (2). FI has been linked to chronic diseases, such as obesity, diabetes, pulmonary diseases, cardiovascular diseases, resulting in a decrease in quality of life, mental health issues, and increased mortality rates (16, 17).

According to Food Insecurity Experience Scale (FIES), FI can be experienced at different levels of severity. Moderate food insecurity characterizes by reduced accessibility to either quality and/or quantity of food, due to lack of financial resources or other resources. It can increase the risk of stunting in children, micronutrient deficiencies, or obesity in adulthood (18). On the other hand, severe food insecurity is at the extreme of the scale, meaning that people who fall into this categoryhave no food consumption for at least a day or more. This group are those called the "hungry" (19). Approximately 702–828 million people in the world faced hunger in 2021 (20).

Poverty

If there are not enough resources to cover the necessities of life such as food, clean water, shelter, clothing, healthcare, education, and even transportation, that could put well-being at risk (19). Specifically, it could lead to even more people finding healthy diets unaffordable. To define poverty, the World Bank and FAO use extreme poverty as a reference to measure the situation. Those living on less than USD 1.90 a day (2011 PPP prices) in a country each year are considered to be extremely poor (2, 21) while people living on between $1.90-$3.10 per day are moderately poor (2).

The COVID-19 pandemic and the war in Ukraine have influenced on food prices, food supply chains and are affecting the economic recovery among countries. Poverty has increased specifically in Sub-Saharan Africa, Latin America, and the Caribbean (2). The poorest countries are not the only ones being affected but also households with 60 percent lower global income distribution (2). Pre-COVID-19 calculations estimated that daily per capita household incomes would grow from $7.15 in 2019 to $7.44 in 2021 (22).

Obesity

The rise in obesity and other forms of malnutrition could partly be a result of moderate FI. Highly energy-dense processed foods that are high in saturated fats, sugars, and sodium are consumed more often than micronutrient-dense quality foods (23). Energy-dense foods may help meet daily caloric requirements, but essential nutrients are missing. Therefore, in many countries, undernutrition and obesity coexist and both can be consequences of FI (24).

The relationship between obesity and FI has been studied since its prevalence has been increasing worldwide. Weight gain happens when individuals ingest more energy than they expend. Adipose tissue accumulation is an adaptive strategy used

to defend themselves against periods when food is unavailable (16, 24). Consequently, the optimal level of body fat relies on access to food. Obesity is a chronic, relapsing, multifactorial disease, that starts early in life, and childhood obesity is now a growing public health concern where early prevention is crucial (10). From an epidemiological perspective, the most widely used method to identify obesity is body mass index. In adults, a BMI of $\geq$30 kg/m2 is used to define the prevalence of obesity (24).

By 2030, 1 in five women and one in seven men, will be obese. Nations will not only fail to achieve the 2025 WHO target to halt the rise in obesity at 2010 levels, but the number of individuals living with obesity is on its course to a 2-fold increase worldwide (10). The highest prevalence of obesity is found in low- and middle-income countries, with numbers steeply increasing compared to 2010 (10). A new measure called the Obesity-Non-Communicable Disease Preparedness Index indicates that all of the 30 most prepared countries are high-income countries, whereas the 30 least prepared countries are all low- and middle-income countries (10).

Therefore, additional studies are needed to better understand underlying mechanisms, associated risks, and effective strategies to mitigate these public health concerns.

The obesity – food insecurity paradox

The coexistence of both obesity and FI has drawn the attention of researchers since it seems contradictory that people with limited access to food can become obese. In the last 5 years, a few articles have been published related to this topic.

One of the plausible mechanisms that could explain this paradox is that FI leads to a low dietary quality which emphasizes the consumption of energy dense foods. Kowaleski-Jones and colleagues aimed to explain the association between obesity and FI through potential mediating risk factors such as lack of access to healthy foods, physical activity, energy intake, stress, access to healthcare and marital status using the data obtained from the 2007–2008 National Health and Examination Surveys NHANES (25). Even though the aforementioned variables were significantly associated, none of them served as mediators of the relationship between FI and obesity after being tested using multiple regression techniques. The positive association between FI and elevated BMI was true only in women, this finding is consistent with other studies (16, 26–28).

On the other hand, Potochnick et al. explored the health implications that FI has among Hispanic/Latino youth living in the US using the data from the Hispanic Community Children's Health/Study of Latino Youth. They found that the prevalence of FI was high, 46%, which was double the national average and that youth living in those food insecure households had a higher mean BMI and depression scores than their food secure peers. This was attributed to greater familial acculturative stress, greater economic stress and a weakened family support system that was more prevalent in food insecure households. It is worth noting that food insecure youth within the lowest household income was associated with greater BMI. Therefore, the authors suggested that poor diet quality and weight gain might only be associated with FI within the context of low income (29). This finding harmonizes with the work done by Oberle et al. (30) where children found to be food insecure had significantly higher BMI percentiles, although household income was not measured.

Most studies have found that the paradox is present only in women and not in men. For this reason, Taylor and colleagues conducted a study to explore the factors that may explain this gender disparity and recruited a total of 25 food insecure mother-father pairs in Connecticut, USA. Participants were interviewed individually using the United States Department of Agriculture Household Food Security Module, Center for Epidemiological Studies Depression Scale, and Coping Strategies Index. Although they did not find significant associations between BMI, FI and depression, this study offered a possible explanation for why women seem to be the only ones getting affected. They found that it was significantly more likely for mothers to sacrifice their diet quality to feed their children than fathers. The authors argued that this tendency may be attributed to social constructs were, at least in traditional gender roles, men have the place of breadwinner and providers so mothers might prioritize the needs of their husbands and children over their own needs (31).

Research has mostly focused on explaining the paradox at a household level. Farrell and colleagues reviewed the literature pertaining to low- and middle-income countries and focused on the bigger picture, that is, analyzing the issue at an individual, household, community, and country level. They proposed 5 context-mechanisms factors that could modify the association between an individual's food insecurity and obesity risk: affordability of energy dense, processed foods, quantity & diversity of food consumed, spatial temporal access to nutritious food, interpersonal distribution of food and non-dietary behavior. Nevertheless, affordability of energy dense foods was identified as the main mechanism since the authors had limited evidence to support the other mechanisms (26). Other authors have proposed that social support can also play a role since they found that food insecure women who reported lower levels of social support were more likely to be obese (28).

To the best of our knowledge, literature regarding the obesity and FI paradox in Latin American countries has not been published in recent years.

Discussion

The present mini review had the purpose of examining the literature that has been published within the last 5 years

regarding the FI– obesity paradox with the aim of improving our understanding of the topic.

As of now, most of the literature has consistently shown that there is a significant association between FI and obesity, specifically in women of high-income countries (16, 25–28, 31, 32). It is worth noting that unlike previous years, emerging studies have aimed to analyze the issue in children, adolescents, young adults, and the elderly. These studies have found the FI– obesity relationship to be true in children and adolescents (29, 30) but not in young adults (33) and the elderly (34). However, there is not enough information to draw strong conclusions in these segments of the population.

Mechanisms explaining the paradox are still lacking. Even though researchers have tried to analyze the issue using different individual and societal variables, these studies have failed to explain the mediatory mechanisms of the food insecurity–obesity relationship since the proposed mechanisms usually lack strength (25, 26) or are purely theoretical (16). This could be partly explained by the nature of their methodology; most studies used a cross-sectional model analyzing data drawn from other research that did not have the purpose of directly studying the phenomenon, for instance, data from large national health surveys.

Until now, studies have suggested that food insecure populations are more likely to have access to high-energy, processed foods (because of their affordability), thereby increasing their likelihood of becoming obese. Although being a sound argument, there is no strong evidence to support this claim since there are no studies which have measured food intake, household income and living expenses at the same time so to demonstrate that in fact a healthier diet could be more expensive. Perhaps is not that they lack the resources but the knowledge or abilities to make better food choices.

There are several research barriers and challenges regarding the paradox. For instance, there is no gold standard when it comes to measuring food insecurity, since there are instruments that range from a single question to 10 – 18 items questionnaires and there is no clear way of categorizing the severity and duration of such insecurity (acute vs. chronic) (35). In addition, when selecting study populations, factors such as physical activity, sex, age, height and eating behaviors ought to be considered for they affect energy balance. Another challenge is that in order to examine how FI could lead to obesity, there is the need for longitudinal studies.

In conclusion, although much of the literature supports the idea that FI is associated with obesity, it has only been consistent in women from high income countries, particularly from the U.S. The research focus should shift from cross-sectional models to other research designs that allow the exploration of pathways and mechanisms underlying the FI and obesity relationship, which will hopefully lead to consecutive research testing the effectiveness of different approaches and scale up such interventions into diverse contexts among those who experience obesity and the varying degrees of food insecurity.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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.

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Gut microbiota and obesity: New insights

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Obesity is a pathology whose incidence is increasing throughout the world. There are many pathologies associated with obesity. In recent years, the influence of the microbiota on both health and pathological states has been known. There is growing information related to changes in the microbiome and obesity, as well as its associated pathologies. Changes associated with age, exercise, and weight changes have been described. In addition, metabolic changes associated with the microbiota, bariatric surgery, and fecal matter transplantation are described. In this review, we summarize the biology and physiology of microbiota in obese patients, its role in the pathophysiology of several disorders associated, and the emerging therapeutic applications of prebiotics, probiotics, and fecal microbiota transplantation.

KEYWORDS

obesity, gut, microbiota, microbiome, overweight

Introduction

Chronic disease conditions such as cancer, hypertension, type 2 diabetes (T2D), and obesity are well known as common causes of disease burden worldwide. Obesity is often the initial pathophysiological mechanism of these pathologies and is currently defined for adults by the World Health Organization (WHO) as a body mass index (BMI) $\geq$30.0 kg/m^2 or a waist-hip ratio of more than 0.90 for men and more than 0.85 for women (1, 2). Additionally, underweight is defined as having a body mass index (BMI) $<$ 18.5 kg/m^2, and overweight as having a BMI between 25.0 and 29.9 kg/m^2 inclusive (1, 2). Overweight/obese people comprise more than 2.1 billion of the worldwide population (3). Although BMI might be considered an approximate guide because it may not correspond to the same degree of obesity in different individuals, it is the same for both sexes and all ages of adults, thus, it provides the best measure at the population-level, of overweight and obesity. However, when defining overweight and obesity for children, age needs to be considered (4). Studies that have compared BMI with other measures of adiposity have found that, at higher BMI classifications, using BMI gives similar results to other approaches, such as dual-energy x-ray absorptiometry (5).

Pathogenesis of obesity is multifactorial, but one of the most interesting factors being studied during recent decades is the influence of gut microbiota. It has been suggested that some issues related to the gut microbiome, such as its composition, diversity index, relative levels, and functional pathways, may predispose adults toward obesity (6). Microbiota is defined as the community of microorganisms in a specific habitat, and the microbiome as its function in that environment (7). This includes a collection of trillions of microorganisms interacting with human hosts, with effects ranging from beneficial to pathogenic (7). One of the first hypotheses about this association between microbiota and BMI proposed that certain groups of bacteria were efficient in absorbing nutrients and energy and then, through rapid metabolism of nutrients, boosting calories absorbed, leading to an increase in BMI (8). It must be considered that overgrowth of bacteria of the phylum *Firmicutes*, accompanied by reduction of bacteria from phylum *Bacteroidetes*, was a characteristic of obese mice and human intestines (9). However, recent data has not confirmed the differences in the Bacteroidetes/Firmicutes ratio between lean and obese humans (9–11). This issue suggests instead another implicated mechanism, such as the high number of bacteria belonging to the *Bacteroidetes* phylum that significantly affects glucose intolerance caused by the consumption of a high-fat diet (9). Other proposed ways of microbiota contributing to obesity are through the anorexigenic gut GLP-1 and, especially, dysregulation of bile acid (BA) signaling mediated by gut microbiota, which could be a promising strategy for obesity therapy (9, 12). The aim of this review is to elucidate recent reports associating gut microbiota with obesity.

Changes in the microbiota in the obese

Due to massive sequencing techniques (shotgun sequencing), it has been possible to identify the profile of the intestinal microbiota and how its composition affects human metabolism, playing a fundamental role in the development of this disease (12–14). Several studies have observed a difference in the number of bacteria in obese subjects compared to people with normal weight and although 90% of the intestinal microbiota is composed of *Firmicutes* and *Bacteroides*, there is controversy regarding the relative abundance of these bacteria and their causal relationship (15).

Abbreviations: BA, Bile Acid; BF%, Body Fat Percentage; BMI, Body Mass Index; CR, Caloric Restriction; CVD, Cardiovascular Disease; EUT, eutrophic; FIAF, Fasting-Induced Adipose Factor; F/B, *Firmicutes/Bacteroides;* GM, Gut Microbiota; LPS, Lipopolysaccharide (LPS); NAFLD, Non-Alcoholic Fatty Liver Disease; PPAR-y, Peroxisome Proliferator-Activated Receptor-y; RYGB, Roux-Y Gastric Bypass; SCFAs, Short-Chain Fatty Acids; SG, Sleeve Gastrectomy; SIBO, Small Intestinal Bacterial Overgrowth; T2D, Type 2 Diabetes; VSG, Vertical Sleeve Gastrectomy; WHO, World Health Organization.

Microbiota, obesity, and age

States of overweight and obesity are most often observed in increasingly younger populations, including gestational obesity, which may be associated with the composition of the intestinal microbiota (Figure 1) (16). Gestational obesity modifies the intestinal microbiota, with elevated levels of *Bacteroides* in the third trimester; this condition doubles the risk of neonatal obesity due to changes in the microbial composition of the infant's intestine. This is demonstrated by the population in a cohort study of 935 mother-baby couples where 7.5% of newborns of obese mothers presented obesity at 1 year (OR 3.80; 95% CI 1.88–7.66) and 3 years of age (OR 3.79; 95% CI 2.10–6.84); these children had a greater wealth of *Firmicutes* $P < 0.05$ (17). Although it is not yet clearly defined, it is known that the microbiota increases during the first year of life and is modified with age (16). As confirmed in the study with 12 twins whose microbiota composition was measured and it was observed that both normal weight and obese children had a predominance of *Veillonella, Klebsiella Akkermansia, Streptococcus, or Staphylococcus* at 1 month of age while at 6 months *Bifidobacteria, Lachnospiracea incertae sedis, Escherichia and Shigella* predominated without a significant difference in terms of diversity ($P > 0.05$) and richness of bacterial species of these groups (*P*-value for Chao index was 0.849) (16).

Also, microbial compositions were identified in 96 female adolescents (14–19 years) divided into three groups: eutrophic (EUT) with adequate body fat percentage (BF%), high EUT and BF%, and obese with high BF%, where the last group had a predominance of *Firmicutes* (median 5.5 IQ 2.5–10.5) with respect to the other groups, without statistical significance ($P = 0.384$) (14).

Microbiota, obesity, and weight

The relationship between microbiota and body weight control has been investigated, without a specific causality or association between these two factors (18), and it is thought that the composition of bacterial species varies according to the presence or not of obesity (14). In Iran, the composition of gut bacteria of 50 normal-weight people was compared with 50 obese people, and it was shown that patients with obesity had an increase in the *Firmicutes/Bacteroides (F/B)* ratio ($p = 0.002$) (19). The same relationship was observed in 61 adult individuals from Ukraine, where the *F/B* ratio increased as BMI values increased (OR = 1.23; 95% CI 1.09–1.38) (18). Similarly, in a Chinese population of children aged between 3 and 18 years, it was identified that the relative abundance of

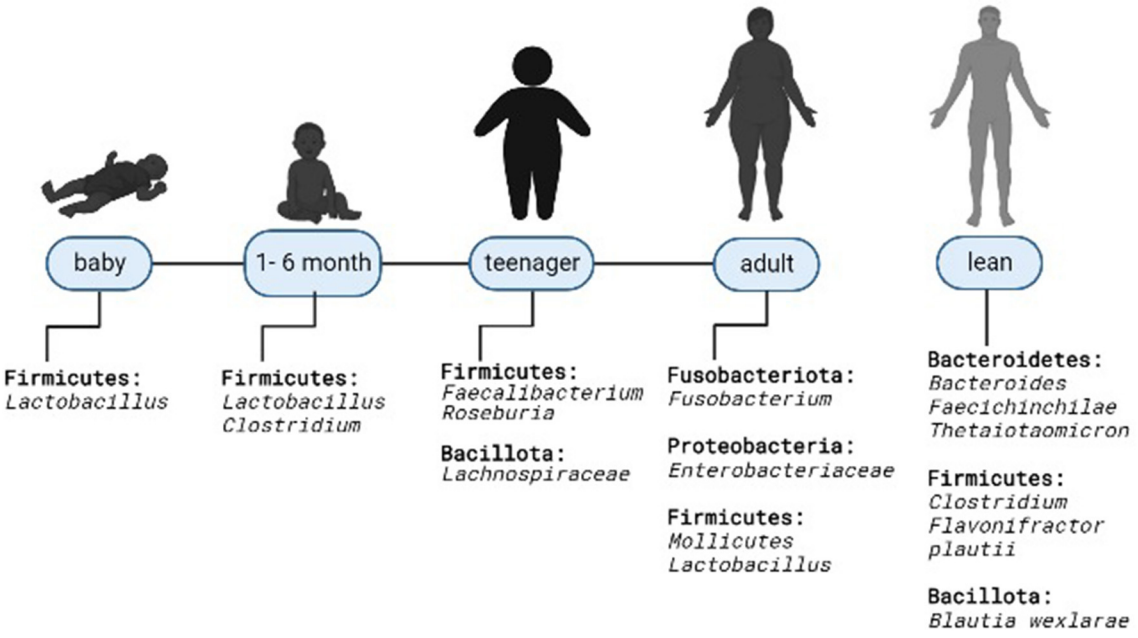

FIGURE 1
Microbiota modification in overweight and obese humans. Predominant microbiota composition at the phylum and genus level in relation to thin.

F/B was significantly higher in obese people compared to non-obese (20). These results are contrasted with the observational study of 163 healthy young people, divided into three groups (overweight, normal weight, and low weight), which did not show significant differences in the phylum ($p = 0.55$), family ($p = 0.10$) or gender ($p = 0.12$) and in all three *Firmicutes* and *Bacteroidetes* predominated (11). Although, this study demonstrated the higher abundance of the genus *Firmicutes* in the overweight group compared to low weight group ($P = 0.002$), and diversity was significantly lower in the group with the overweight ($P = 0.007$ for Shannon index and $P = 0.009$ for the Ace index) and low weight ($p = 0.05$ for the Shannon index and $p = 0.08$ for the Ace index) (11). Similarly, in the study of the intestinal bacterial composition of 1 and 6 months old lactating twins, there was also no significant difference in the diversity of species between subjects of normal weight and obese ($P > 0.05$); even in 1-month-old infants with normal weight there was a greater abundance of *Lactobacillus* and in the obese *Rhomboutsia* predominated and in the obese 6 months old, *Clostridium sensu stricto* (16).

Microbiota obesity and bile acids

The intestinal microbiota acts in the metabolism of BA through processes of deconjugation and dehydroxylation in the intestinal lumen (21). They transform primary BA into secondary: cholate into deoxycholate and chenodeoxycholate into lithocolate (LCA) (22). This action is due to bile salt hydrolase enzymes present mainly in the phyla of *Firmicutes and Bacteroidetes*, especially in the genera Clostridium clusters (22).

On the other hand, in the enterocytes of the colon, the BA that will be reabsorbed binds to the farnesoid X receptors. This action stimulates the production of fibroblast growth factor-19 (FGF19) and decreases the hepatic synthesis of BA; in addition, this BA activates the G protein-coupled plasma membrane bile acid receptor (TGR5) by increasing the production of GLP-1. This hormone modulates glucose homeostasis, energy metabolism (23, 24), and the synthesis, conjugation, and transport of BA (21). When the enzymatic action of the microbiota is altered, the composition of the BA does so, facilitating the absorption of fat and causing obesity (12). This was corroborated in a recent study evaluating 183 subjects with high BMI (121 metabolically healthy and 62 metabolically unhealthy), the unhealthy obese subjects had a significantly lower proportion of secondary BA compared to primary ones (OR 1.129, IC 95%: 1.083–1.176, $P < 0.01$); being a predictor in healthy subjects with high BMI (AUC = 0.87, IC 95%: 0.82–0.93, $P < 0.01$, a cut-off value of 66.1 with a sensitivity of 78.5% and a specificity of 91.9%) suggesting that the altered composition of BA may be involved in different metabolic states of obesity (12).

In parallel, a study was conducted on rodents to identify changes in BA metabolism and its association with the gut

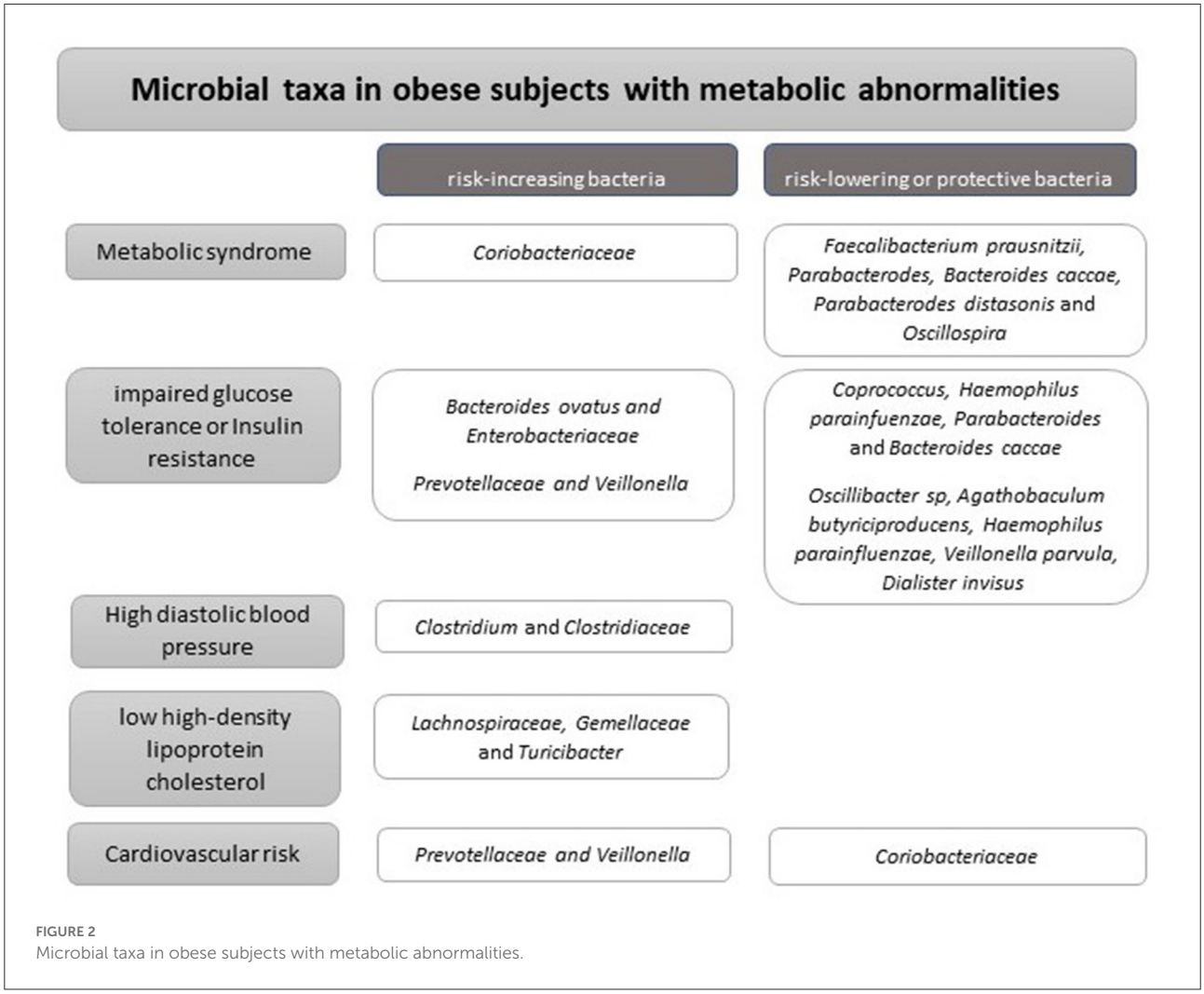

FIGURE 2
Microbial taxa in obese subjects with metabolic abnormalities.

microbiota, where the group of rodents fed with high-fat diets was divided into a group prone to obesity and another group resistant to it (12). It was observed that the composition of the microbiota did not vary significantly in both groups. However, the genus was abundant in *Clostridium scindens* and *Clostridium hylemonae* in rodents prone to obesity. Due to their high capacity for bioconversion, these bacteria modify the metabolism of the BA and promote obesity. This conclusion was reaffirmed by findings in this same group of rodents of a decrease in secondary BA and an increase in primary ones (12).

Microbiota, obesity, and exercise

The microbiota can be modified with physical activity, improving the metabolic profile and immune response, an already demonstrated effect in animal and human studies (25). These temporary modifications differ between normal weight and individuals with obesity. This difference was demonstrated in 32 subjects (18 thin and 14 with obesity) who, after performing physical activity, the microbiota composition showed a variation of the genus of bacteria with a predominance of *Bacteroides* in those with obesity and *Faecalibacterium and Lachnospira* in normal weight subjects (26). Also, showed that microbiota composition differed from pre-exercise, and these changes remitted after exercise cessation (26). Similar results were observed in 27 sedentary obese people who, after moderate and intense physical activity, reduced the *F/B* ratio ($P = 0.04$) with an increase in *Bacteroides* ($p = 0.03$) and a reduction in *Blautia* ($P = 0.05$) and *Clostridium* ($P = 0.04$) (27). Similarly, the research on 40 premenopausal women with BMI 20–25Kg/m^2 (19 active and 21 sedentary) did not detect significant differences in alpha and beta diversity or the *Firmicutes*/*Bacteroidetes* relationship ($p = 0.115$) between the two groups. Nevertheless, there was more presence of *Firmicutes* ($p = 0.085$) and lower presence of *Bacteroidetes* ($p = 0.076$) in active women (28).

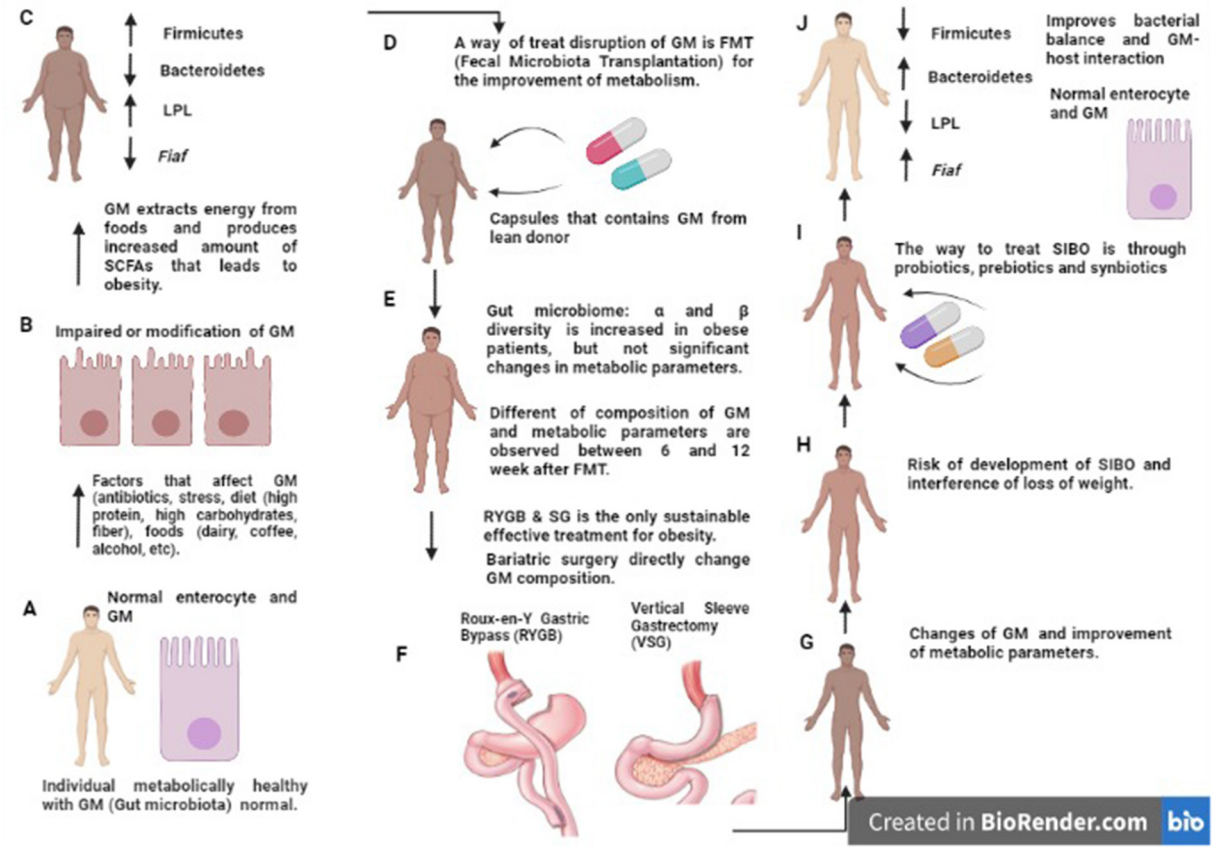

FIGURE 3
Disruption in intestinal microbiota composition and treatment by FMT, BS, probiotics, prebiotics and synbiotics. Schematic representation of altered GM composition in obesity and MS. In people metabolically healthy, the GM and enterocyte are normal **(A)**. In obesity, altered GM composition (diet, drugs, stress, etc.) inhibits Fiaf in epithelial cells and increases LPL activity; this leads to increased synthesis of triglycerides, fatty acids, and fat storage in adipocytes **(B,C)**; the opposite effect can be seen after treatment (RYGB, VSG) **(D–F)** in which the amount of Fiaf inhibits LPL [described in **(J)**]. However, there is a risk of SIBO **(G,H)**. Prebiotics, probiotics, and synbiotics are an alternative to treatment and have been described to achieve a balanced gut microbiota and lead to a healthy metabolic state **(I,J)**. MS, Metabolic Syndrome; GM, Gut microbiota; Fiaf, Fasting-Induced Adipose Factor or Angptl4; LPL, Lipoprotein lipase; RYGB, Roux-en-Y Gastric Bypass; VSG, Vertical Sleeve Gastrectomy; SIBO, Small Intestinal Bacterial Overgrowth.

Microbiota and pathologies associated with obesity

Obesity is a source of chronic low-level inflammation in various tissues, associated with metabolic defects (29), such as glucose intolerance, insulin resistance (30–32), and cardiovascular diseases (Figure 2) (33–38). An important risk factor for metabolic defects associated with diabetes, metabolic syndrome, and cardiovascular disease is inflammation. The interaction between the host and a certain microbiota pattern has been related to a different profile of interleukin expression (39). For example, lower levels of anti-inflammatory cytokines, including IL-4, IL-13, and IL-10, have been found in obese subjects with metabolic syndrome compared to those without metabolic syndrome (40).

On the other hand, the gut microbiota can influence glucose metabolism and host hormone regulation by producing various metabolites, such as short-chain fatty acids and BA (41–43). Furthermore, elevated levels of bacterial lipopolysaccharide (LPS) have been found among subjects with obesity induced by a high-fat diet (44, 45). Changes in the intestinal microbiota cause an increase in intestinal porosity, an immune response of the mucosa, and, consequently, an increase in intestinal permeability. It appears that the microbiota releases LPS but favors their translocation, possibly leading to metabolic endotoxemia and insulin obstruction (44, 45). Meanwhile, hyperglycemia increases intestinal permeability causing the translocation of some bacterial products, such as LPS, to the systemic circulation, which contributes to chronic inflammation of the liver and adipose tissue associated with impaired glucose or insulin resistance as well as metabolic syndrome (46).

A matter of great importance is that bacterial LPS has been reported not to be necessary for impaired glucose or insulin tolerance (47). The association between bacterial LPS and insulin resistance was reported in gnotobiotic mice, where the authors found that the presence of gut bacteria caused impaired glucose metabolism and increased accumulation and polarization of macrophages toward the pro-inflammatory M1 phenotype in white adipose tissue and, consequently, the development of insulin resistance (47). Although the gut microbiota induced LPS-dependent macrophage accumulation in white adipose tissue, the altered systemic glucose metabolism was not LPS-dependent (47). These results also indicate that macrophage accumulation in white adipose tissue does not always correlate with impaired glucose metabolism (47).

On the other hand, in 68 children with obesity, patients with insulin resistance and higher blood pressure had reduced bacterial richness. Also, different associations were found between higher pressure levels and the presence of *Clostridium and Clostridiaceae*, lower LDL cholesterol and *Lachnospiraceae, Gemellaceae, Turicibacter*, higher metabolic syndrome risk, and the presence of *Coriobacteriaceae* meanwhile *Faecalibacterium prausnitzii, Parabacterodes, Bacteroides caccae, Oscillospira, Parabacteroides distasonis, Coprococcus, and Haemophilus parainfluenzae* were associated lower metabolic syndrome score, fasting glucose, and HOMA_IR (48). A cross-sectional non-controlled study in 21 children with obesity found no significant differences in the abundance of bacterial phyla across different insulin resistance profiles, but a lower microbiome diversity related to children with higher insulin resistance (49). Interestingly, the decrease in microbiome diversity was more pronounced in obese children with a higher degree of insulin resistance (49). Consonantly, a cross-sectional study on normal-weight, overweight adults and those with obesity found that younger subjects have lower inflammation, lower total and visceral adiposity, and lower levels of indicators linked to cardiovascular risk and insulin resistance (50). In that study, subjects with high inflammation scores were associated with a reduced microbiota diversity and bacterial taxa as the family *Prevotellaceae* and the genus *Veillonella*, in contrast, the family *Coriobacteriaceae* seemed to exert a protective effect against the proinflammatory phenotype (50).

Furthermore, some specific bacterial species are associated with a lower level of insulin resistance in the context of obesity. In a nematode, the supplementation with *Pediococcus acidilactici* neutralized the effect of high glucose levels, apparently by modulation of the insulin/IGF-1 signaling pathway (51). Similarly, in obese and lean Asian subjects, a negative correlation has been found between the intestinal abundance of *Akkermansia muciniphila* and the risk of increased severity of insulin resistance (52).

Microbiota, weight loss, and metabolic changes

The microbiota is maintained thanks to an appropriate intestinal environment, although its survival can be modified by dietary composition, lifestyle, and the use of prebiotics, probiotics, and antibiotics. This understanding offers a new approach to treating metabolic alterations (53). As has been pointed out, the gut microbiota plays a role in the pathogenesis of obesity and associated diseases, and research about interventions with probiotics, prebiotics, and synbiotics (prebiotic and probiotic components) is ongoing to evaluate if these interventions could correct the alteration of the microbiota in obesity and inflammation (54–56).

Dysbiosis, given by the interruption of the healthy symbiotic relationship of the microbiota with the intestine, has been proposed as a contributing factor to obesity and its consequences: T2D, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and cancer (57, 58). This dysbiosis increases the release of LPS, an endotoxic molecule of the outer membrane of Gram-negative bacteria, which alters immunity and the intestinal mucosal barrier causing "leaky gut" and inflammatory pathways activation (59). Marel Roberfroid defined Prebiotics in 1995 (60) as "a selective ingredient that allows changes in composition and activity in the intestinal microbiota and confers wellbeing and health in the host" (60). Prebiotics are non-digestible fibers and can be fermented by gut microbiota (61). Fructans and arabinoxylans (dietary fiber) are the most studied. The intestinal microbiota ferments them into short-chain fatty acids (SCFAs: acetate, propionate, butyrate), CO2, H+, CH4, and other metabolites that regulate metabolic processes (62). Several studies have found contradictory effects on metabolic parameters, describing both neutral (63–65) and positive effects (66–68), and another one has shown influence on the reduction of inflammatory parameters (69). These randomized controlled trials have been developed including, different populations of obese, pre-diabetic, and T2D people.

Most probiotics belong to species with similar functions to the symbiotic microbiota. Probiotics have presented the ability to hydrolyze bile salts, reduce fat accumulation, and reduce systemic inflammation and leptin values, in addition to negatively regulating the expression of "peroxisome proliferator-activated receptor-y (PPAR-y)" at the hepatic level; however, more research is required (70). Research has shown similar controversy with prebiotics. Łagowska and Drzymała-Czyz, in an randomized controled trial (RCT) with overweight/obese women with polycystic ovary syndrome (PCOS), found no additional beneficial effects on SCFA levels, selected gut bacteria abundance, or lipid profile (71). Another study on overweight and obese pregnant Australian women found that the probiotics used (*Lactobacillus rhamnosus* and *Bifidobacterium animalis subspecies lactis*) did not prevent gestational diabetes mellitus

(GDM) (72). On the other hand, in Korean obese individuals, a *Lactobacillus plantarum* K50 (LPK) supplementation for 12 weeks significantly reduced the total cholesterol and triglyceride levels with an increase in *L. plantarum* and a decrease in *Actinobacteria*, both correlated with changes in visceral adiposity (73). In postmenopausal women, the effects of a multi-species probiotics intervention altered the influence of microbiota on biochemical, physiological, and immunological parameters without affecting its diversity and taxonomic composition (74).

A recent study found an association between a decrease in blood glucose over time and an increase in *Lactobacillus* abundance with a symbiotic supplement. However, the decrease in BMI, waist circumstance, and body fat mass was associated with a decrease in *Bifidobacterium* abundance over time, supporting the idea that the synbiotic supplement used in this clinical trial modulates human gut microbiota by increasing the abundance of potentially beneficial microbial species (54). Two randomized clinical trials in Thailand have reported an association between gut microbiota and anthropometric and metabolic parameters. The first one compared symbiotic supplementation and placebo groups in Thai obese adults (BMI $\geq$ 25 kg/m^2) according to the Asia-Pacific criteria, aged 18–65 years (75). After 12 weeks of supplementation, in the synbiotic group, significant differences ($P < 0.05$) were observed in body weight, BMI, body fat, waist circumference, waist/hip ratio, HDL-C, LDL-C, IL-6, IL-10, IL-1β, TNF-α, IgA, LPS, and zonulin values compared to the baseline values, meanwhile in placebo group no significant changes were obtained (75). In the second study, in older adults, probiotics were indicated. As a result, they achieved an improved intestinal barrier function (up to 48%), a significant increase in the high-density lipoprotein cholesterol (HDL-C), better obesity-related anthropometric biomarkers, and an improvement of short-chain fatty acid levels in human subjects (76). Another study reported that specific metabolite changes following synbiotic intervention might suggest some advantage in providing *Bifidobacterium lactis* in combination with fructooligosaccharide in a low-energy diet, rather than probiotics or diet alone (77).

The clinical effects on body fat regulation seem more significant when probiotics are administered. The intervention combining the probiotic (B420) with prebiotic (refined ultra polydextrose or LU) in overweight and obese adult patients compared to B420, LU, demonstrated that the gut microbiota was modified for all groups compared to placebo (78). The 6-month intervention showed that the group of patients receiving B420 had a higher abundance of *Akkermansia* ($P < 0.01$) and *Streptococcus* ($P < 0.01$) compared to the placebo (78). The intervention with B420+LU increased the abundance of *Akkermansia*, *Christensenellaceae*, and *Methanobrevibacter*, while there was a reduction of *Paraprevotella*. This species correlates positively with fat body mass and suggests that its increase in abundance may be detrimental to metabolic health. In addition, a negative correlation of the *Family Christensenellaceae* with waist-hip index, energy consumption, and hip body fat mass was demonstrated (78).

Bariatric surgery

Currently, bariatric surgery is considered the only sustainable, efficient treatment for obesity (79). Surgical procedures such as Roux-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG) facilitate a 50–70% decrease in body weight and fat mass (79). In addition, it leads to a decrease in caloric intake or malabsorption and metabolic changes, improves glucose metabolism, and produces changes in gut microbiota (79).

The role of altered host-microbiota interactions is not fully understood. A significant association has been shown between changes in the microbiota and clinical markers of patients undergoing bariatric surgery (RYGB, SG) (79). The increase in bilirubin is associated with the increase in *Prevotellaceae*, *Bacteroidales*, and *Peptococcaceae* taxa; the increase in iron is associated with an increase in *Pasteurellaceae*; the decrease in HbA1c is associated with a decrease in *Coriobacteriacea* and the increase in *Clostridiales* taxa. The most pronounced positive association is described between *Lachnospiraceae* and *Coriobacteriaceae* taxa in the reduction of cholesterol levels; however, the associations described correspond to the sequential impact of a crash diet followed by RYGB and SG, in which progressive weight loss and changes in the composition of the microbiota of patients with morbid obesity have been demonstrated (79). The changes in the microbiota that persist after surgery suggest an anatomical and physiological adaptation, as well as reduced acid production, elevated oxygen content, and altered concentration of bile acids. The effects of the crash diet are associated with an increase in *Bifidobacteriaceae* and a decrease in *Streptococcaceae*, while the effect of surgery shows an increase in *Streptococcaceae* and a decline in *Bifidobacteriaceae* (79).

The crash diet causes changes in the diversity and composition of the microbiota, while surgical procedures (RYBG, SG) prevent early changes in the composition and restoration of the microbial diversity that probably contributes to weight loss (79). The elevated pH resulting from RYGB has been shown to ensure the survival of probiotic bacteria, making surgical patients a therapeutic target for probiotic therapy (80). In addition, patients undergoing these surgical procedures may develop small intestinal bacterial overgrowth (81), a condition that interferes with weight loss and increases the risk of micronutrient deficiency (vitamins and essential elements) that appears to impair and affect the configuration and composition of the intestinal microbiota (Figure 3) (82, 83). Specific interventions to correct the microbial balance and improve microbiota-host interactions are necessary after

surgery (84). One of these strategies is probiotic therapy which contributes to weight loss, reduction of small intestinal bacterial overgrowth (SIBO), improvement of the synthesis of micronutrients, and optimization of the metabolic state (Figure 3) (85).

Roux-en-Y Gastric Bypass (RYGB) surgery improves plasma glucose with a long-lasting effect in patients withT2D. Although the mechanism is unclear, RYGB increases the secretion of GLP-1 and improves insulin resistance (86). Obese patients with type 1 and 2 diabetes mellitus (T1D, T2D) undergoing bariatric surgery [RYGB, Omega Loop, sleeve gastrectomy (SG)] have a very different microbiome composition compared to patients with a "normal" microbiome, and the more weight they lose, the more the microbiome differs (Figure 3), and in general, the metabolic status of patients improves significantly (BMI, glucose, HbA1c, triglycerides, etc.) (87). While the effects of bariatric surgery on obesity are widespread, there are also adverse effects: nausea, vomiting, infections, neuropathy due to nutritional deficiency, and eating disorders (depression, anxiety) (88). Regarding BS, gastric banding (GB), RYGB, and microbiota, there is a decrease in *Firmicutes* (Figure 3) and an increase in *Proteobacteria* and *A. muciniphila*. The latter seems to be associated with weight reduction and insulin sensitivity in patients with severe obesity, despite a certain level of abundance of *A. muciniphila* may be required for metabolic benefits (89).

Restrictive diet

The adequate caloric restriction (CR) advised for patients with metabolic alterations and healthy adults imply a reduction of 40% of the daily recommendation and allows for the observation of changes in the microbial composition, patients with *Prevotella* enterotypes exhibit a significant weight reduction compared to individuals enterotype *Bacteroides* (89). CR can delay the development of metabolic alterations and is associated with changes in the composition and metabolic function of the microbiota (90). A study conducted on overweight and obese women suggests that the intervention with CR of 800 Kcal has allowed achieving a reduction in body weight, adiposity, hyperglycemia, microbial diversity, and abundance of SCFAs effective in weight reduction (91). In addition, the microbiota after CR (post-CR) was characterized by a lower capacity in the extraction of energy from the diet (91). Despite the benefits of the very-low-calorie diets (VLCDs), metabolic alterations could reverse when normal consumption of calories is restarted (92). This configuration of the microbiota is known as the "yo-yo effect", and the mechanisms of this phenomenon have yet to be investigated (93). In addition, some modifications in the composition of the microbiota are not normalized even if the reduction of body weight has been achieved (93). A study about the effect of CR in women with obesity described that the intervention of 4 weeks of CR led to a significant weight loss and also reduced systemic inflammation, and improved the integrity of the intestinal barrier, instead a microbial alteration could be due to a high protein or high gluten diet (94).

Fecal microbiota transplantation

Another current hypothesis about the usefulness of the gut microbiota in weight loss is the one that refers to the possible regulation of glycemia and body weight through the manipulation of the intestinal microbiota (Figure 3). Previous studies have shown that fecal microbiota transplantation (FMT) from lean individuals to individuals with obesity and metabolic syndrome transiently reduced peripheral insulin sensitivity, among other metabolic outcomes: total cholesterol (−0.6 mmol/l), HbA1c (−0.2%), and plasma glucose (−0.6 mmol/l) (95). Donor and recipient microbiomes can vary in graft diversity and composition, so neither all of them are effective, nor are all recipients responsive to microbiome therapy (95). Future research should explore whether donor and recipient preselection or specifically designed microbial composition can optimize changes in the microbiota and whether the use of the microbiome in conjunction with exercise and diet could synergistically improve metabolism in patients with obesity (95).

Fecal microbiota transplantation from lean donors to patients with obesity and metabolic syndrome (MS) has shown significant improvement in insulin sensitivity after 6 weeks with FMT from a lean donor (allogeneic) vs. FMT autologous or aFMT (96). In addition, aFMT based on self-administration of microbiota from a beneficial state to an altered state has been shown to induce rapid recovery from antibiotic-produced dysbiosis (97). aFMT is also associated with attenuation in weight regain, and administration of aFMT capsules is associated with long-term weight maintenance (98). This personalized treatment is considered an alternative to allogeneic transplantation, has greater efficacy, and presents fewer side effects (99). It is described that when trying to relate FMT, diet, and exercise in mice, effects such as reducing fat mass and food efficacy intake may be transmissible *via* FMT and suggest a therapeutic potential for treating individuals with obesity. FMT has also shown efficacy in the treatment of ulcerative colitis (UC). It has been described that after 1 week of treatment with anaerobic FMT from a donor, it results in a high probability of remission at 8 weeks (100). Still, if FMT can transmit beneficial effects of diet and exercise to alter metabolic profiles has not yet been investigated (101).

Conclusion

Some GM processes have been better studied through intensive research that associates GM with obesogenic mechanisms. One is related to its participation in the BA's metabolism that finally contributes, in different ways, to

increase the GLP-1 production, leading to more efficient glucose homeostasis, decreased insulin resistance, reduced fat absorption, and weight gain risk.

Another way that GM may affect bodyweight control is through its effects depending on modifications to other metabolic processes related to immune function, mainly due to elevated levels of bacterial LPS, which have been found among subjects with obesity induced by a high-fat diet. These changes might cause an immune response of the mucosa and, consequently, an increase in intestinal permeability, even though it is not LPS dependent. Otherwise, hyperglycemia may also increase intestinal permeability, causing the translocation of LPS to the systemic circulation, which contributes to chronic inflammation of the liver and adipose tissue associated with the development of impaired glucose or insulin resistance, as well as metabolic syndrome.

Studies have been conducted about the influence of physical activity (PA) on GM to improve body weight control. PA improves the metabolic profile and immune response, at least temporarily, probably by incrementing *Bacteroidetes* proportion in GM.

Nevertheless, there are still many gaps in the underlying mechanisms that GM exerts around body weight control. One poorly understood mechanism is related to how specific GM composition and function are associated with body weight dysregulation and related pathologies. Even though most of the research indicates that the ratio of *Firmicutes/Bacteroides* is higher in the obese gut, other researchers indicate the opposite or no association with this ratio.

On the other hand, there is still much controversy regarding the benefits, dosage, ideal composition, time of administration, side effects, and feasibility studies concerning pre-pro and symbiotic use in humans, as well as the real benefits of FMT in the prevention and management of obesity. Nonetheless, most research has found a more significant benefit in using symbiotics than prebiotics or probiotics administered individually. Besides, the aFMT has been associated with attenuation in weight regain and administration of aFMT capsules with long-term weight maintenance, but assessment and focus on individual response to intervention are needed.

Therefore, despite the evidence supporting that GM induces favorable changes in the intestine of the subject with obesity, research on maintaining the long-term effects of therapeutics for the prevention and treatment of metabolic disorders associated with obesity is still lacking.

Author contributions

RS, YS-A, BQ, and KG wrote the paper. SC conceived the draft, supervised the writing, and corrected the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Food insecurity as a risk factor of sarcopenic obesity in older adults

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Sarcopenic obesity is characterized by the loss of muscle strength, mass and muscle functionality and increased adipose tissue (obesity) according to different criteria and cut-off points. The prevalence of sarcopenic obesity among older adults is growing worldwide, and many factors are involved in its development. Diet and food security have been described as the main contributors to the development of obesity and sarcopenia. Food insecurity consists of limited or uncertain access to adequate and nutritious foods. This narrative review aims to summarize the existing data on food insecurity as a risk factor for sarcopenic obesity in the elderly.

KEYWORDS

food insecurity, low food security, sarcopenic obesity, sarcopenia, older adults

Introduction

It is widely recognized that aging and obesity are common public health issues worldwide. According to the World Population Prospect of the United Nations, in 2017, adults older than 65 involved almost 13% of the global population. This percentage is increasing at a more rapid rate compared to the portion of any other age group, and it is due to recent changes in the increase in life expectancy (1). Along with aging comes a loss of skeletal muscle mass and function, commonly accompanied by body fat (BF) gain.

Obesity is considered a worldwide pandemic (2), and is usually diagnosed by body mass index (BMI) above 30 kg/m^2. Currently, some factors have been identified as contributors to obesity, such as genetic predisposition and unhealthy lifestyle, especially sedentary habits and excess of caloric intake (3).

Not only obesity is linked to metabolic syndrome, type 2 diabetes (T2D), and some cardiovascular events, as well as the development of drastic personal, social, economic, and healthcare tasks. Obese individuals are at higher risk of chronic and acute diseases, including end-stage organ failures, cancer, and infections, which can lead to complications and hospitalizations. Indeed, the rising rates of obesity have contributed to the coexistence of this disease with other comorbidities like sarcopenia (4).

The European Working Group on Sarcopenia in Older People (EWGSOP) in 2018 redefined the operational definition of sarcopenia as the presence of low muscle mass and strength, and severe sarcopenia if low physical performance is confirmed (5). Sarcopenia is considered as a syndrome with a multifactorial etiology whose prevalence increases with age (6). Several conditions in older adults have been described that may contribute to the development of sarcopenia, like lack of physical activity and dietary habits, which are similar to obesity-related risk factors (7). The term "sarcopenic obesity" (SO) was introduced to define a clinical and functional condition described by the conjunction of obesity and sarcopenia (6, 7).

Despite well-known risk factors for sarcopenia and obesity, growing evidence has shown that bad eating habits are one of these factors and can cause food insecurity. For example, in the United States, food insecurity increased significantly from 5.5 to 12.4% in the last ten years among older adults, and they have been related to obesity and sarcopenia (8–10). However, there is no scientific evidence exploring food insecurity as a risk factor for SO in aged people. For this reason, it is essential to describe how food insecurity may contribute to SO in older adults.

This narrative review aims to summarize the existing data on food insecurity as a risk factor for SO in the elderly. To accomplish this and contribute to the field, we will describe the presence of obesity and sarcopenia in older adults and the conjunction of both pathologies, food insecurity, and dietary intake as risk factors for SO.

Materials and methods

A comprehensive search was carried out through PubMed and Web of Science for papers published until August 2022. We reviewed studies focusing on SO and its determinants, the relationship better obesity and food insecurity, and sarcopenia and food insecurity.

Body composition changes in older adults

The aging process causes many changes in body composition (BC) of the elderly population, regardless of metabolic and physiological functions, resulting in a decrease in lean mass, also called fat-free mass (FFM) (11). Related to fat mass (FM), there is an increase in adiposity and a redistribution of fat from subcutaneous regions to intra-abdominal, intrahepatic, and intramuscular areas, characteristics associated with diseases such as diabetes and cardiovascular disease (12).

Older adults have more body fat percentages (BFP) than their younger counterparts, and there are gender differences in anthropometric measures and BFP. For example, women showed higher values of BMI, subcutaneous fat, and BFP; older men are prone to show more weight and lean mass (13).

Due to these BC changes, aging is linked with obesity and probably with sarcopenia or both of them. These conditions could aggravate disability and frailty, increasing morbidity and mortality rates (14).

Sarcopenia and Obesity have to be measured by using validated methods for measuring body composition, like whole-body Dual-energy X-ray Absorptiometry (DXA), bioelectrical impedance analysis (BIA), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) to diagnose obesity, sarcopenia, or both of them (5) DXA evaluates bone mineral density and is considered a method to assess whole-body and regional soft-tissue composition, which provides good data about the total amount of FM and FFM by body segments (13). BIA is an adequate and low cost method to measure total water and FFM. CT has accurate and reproducible data for FM, FFM, and visceral fat. MRI identifies changes in muscle structure (5). Using these methods, measurements of FM and FFM can properly make an accurate diagnosis against traditional anthropometric measurements.

Obesity in older adults

The World Obesity Federation in 2017 stated that obesity is a chronic disease. There is a link between FM and the vulnerability of the host, making it significant as a health problem (15). There has been an increase of obesity at all ages on the past decade. In older adults, the prevalence of obesity on both sexes has been found at 37.5 and 39.4%, respectively (16). The association between excess of body fat in older adults and the whole or specific disease mortality is still under debate (17). Obesity is defined, regardless of age, as a BMI greater than or equal to 30 kg/m^2. There is no consensus regarding the best measure of obesity in the older population. BMI is an easy tool that correlates with the percentage of body fat in young and middle-aged adults. However, physiological changes in BC render BMI less accurate with aging.

The changes in age-related BC, specially fat distribution, could assist in perceiving the link between adiposity, morbidity, and mortality in older adults. Recent data suggest that the distribution of FM, visceral fat, and reduction of FFM would be

more relevant than BMI seeking health problems associated with obesity in older adults (17).

In 2007, the Spanish Society of Parenteral and Enteral Nutrition published the following BMI cohort points to identify overweight and obesity in older adults: 27.0–29.9 kg/m^2 (overweight); 30.0-34.9 kg/m^2 (obesity class I); 35.0–39.9 kg/m^2 (obesity class II); 40.0–49.9 kg/m^2 (obesity class II); and 50 kg/m^2 (obesity class IV) (18).

Sarcopenia in older adults

Sarcopenia is a progressive and generalized skeletal muscle disturbance (5). The prevalence range may differ depending on the clinical scenario, and the main difference can be the method proposed for the description. Peterman-Rocha et al. found that the prevalence of sarcopenia varies significantly in the systematic (10–27%) vs. a narrative review (0.2–86.5%), regardless of the differences in the methodology and cut-off points (19). These differences can be due to the scientific criteria of the selection of the studies. The classification systems most usually used are EWGSPOP and the Asian Working Group on Sarcopenia (AWSP) (19). In 2019, Rodriguez-Rejón et al. found that despite the methodology used to diagnose sarcopenia, the results did not change in frequency (20).

Primary sarcopenia occurs with aging, and secondary sarcopenia develops due to physical inactivity, malnutrition, and diseases, such as neurodegenerative disease, endocrine disease, or malignancies (5).

This condition is associated with increased adverse outcomes, including falls, functional decline, frailty, and mortality. At first, sarcopenia was an age-related process in older people (21); nowadays, evidence shows it can be present across the lifespan and is influenced by lifestyle risk factors (22), genetics, and also secondary to disease (23).

In order to assess sarcopenia, revised guidelines suggest measuring muscle functionality and validating strength, which is better at predicting unfavorable outcomes (24). Actually, EWGSOP2 valued low muscle strength as a leading parameter of sarcopenia and an adequate measure of muscle function. However, sarcopenia is probably when low muscle strength is present. The diagnosis is made when the low muscle quantity is registered, and severe sarcopenia when quality is confirmed (5).

Sarcopenic obesity

Sarcopenic obesity (SO) was first described by Baumgartner in 2000 as a clinical and functional condition characterized by the presence of obesity and the diagnosis of sarcopenia (7, 25, 26). Both conditions, loss of MM and muscle capability and gaining body fat, may increase the risk for non-communicable diseases like diabetes and cardiovascular disease and increase the chances of adverse health outcomes such as disability or impairment, cardiometabolic diseases, other comorbidities, and mortality more than sarcopenia or obesity individually (5, 26).

Sarcopenia and obesity share pathological factors, including aging, changes in BC, inflammation, and hormones (27). The aging process carries a low metabolic rate and metabolic adaptations, including adaptive thermogenesis and changes in oxidative capacity; this process favors the development and onset of SO (28). Changes in BC related to age are the main risk factor for SO. Studies have shown that FM increases with age, especially between 60 and 75 years old (27–29). Muscle mass and strength decline progressively around 30, accelerating after 60 years. In addition, there are changes in fat accumulation with aging; visceral fat and intramuscular fat tend to increase, while subcutaneous fat in other body regions declines. Fat infiltration is associated with lower muscle strength and leg performance capacity (29).

Another associated risk is low physical activity, a well-known risk factor of obesity, low muscle strength, muscle atrophy, and reduced metabolic rate (30).

Inflammation also contributes to SO (31). The adipose tissue produces pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and adipokines such as leptin and adiponectin, which regulate the inflammatory response (32, 33). Obese subjects have a pro-inflammatory state which may be one of the key factors in decreasing muscle strength, creating a vicious cycle (33).

Obese individuals have muscle catabolism because insulin has no anabolic function due to insulin resistance (34). Insulin resistance correlates independently with poor muscle strength, and older patients with diabetes show accelerated loss of leg muscle strength and quality (34). Indeed, low levels of sex-specific hormones are an important factor related to SO (34). After menopause, a decline in estrogen levels can result in increased body weight and FM as well as shifts in the accumulation of fat from subcutaneous to visceral deposits. In older men, total lower levels of testosterone are associated with sarcopenia and may contribute to muscle impairment in obese individuals (35, 36).

On the other hand, obesity can independently lead to loss of muscle mass and function due to the negative impact of adipose tissue, which causes metabolic alterations that include oxidative stress, inflammation, and insulin resistance. All of them negatively affect muscle mass (37).

In addition, diet is a risk factor that affects sarcopenia and obesity by different mechanisms. Generally, sarcopenia is associated with an insufficient nutritional intake, whereas obesity is an outcome of excessive energy intake, leading to an imbalance between energy intake and energy expenditure (38).

Due to the clinical and epidemiologic importance of assessing SO, screening tools and diagnostic criteria for this condition have been published recently (5). However, despite the classification, the method used for screening and diagnosing

sarcopenia is critical for appropriate and prompt interventions in older adults.

Screening and diagnosis of sarcopenic obesity

Screening of SO is based on elevated BMI or waist circumference and indicators of sarcopenia such as clinical symptoms and risk factors or the use of SARC-F. The clinical symptoms and risk factors include age >65 years, chronic diseases, recent acute disease or nutritional alterations, repeated falls, weakness, exhaustion, fatigue, and movement limitations (**Table 1**) (6).

To diagnose sarcopenia and obesity, MM and FM body can be assessed by diverse techniques, such as anthropometry, BIA, and medical imaging. Anthropometry includes BMI diagnosis, skin-fold thickness, and body circumferences. Despite some studies of cut-off points for older adults, the limitation is the lack of precision in evaluating the MM and the high probability of error (39, 40).

BIA measures MM and FM established on electrical conduction through tissues; limitations include hydration levels, exercise, and food or liquid intake. Medical imaging has an advantage for diagnosing and grading sarcopenia and obesity. It is an accurate and reliable method and can be applied for longitudinal changes in clinical trials and as a treatment assessment tool (41).

SO, as other clinical conditions, require standardization and cut-off points for diverse populations or ethnicity, especially due to dissimilarity regardless of body type, adiposity, and lifestyles of the worldwide population, mainly for the Asian and Latin American populations.

Diagnosis of SO should include altered skeletal muscle functional parameters and altered BC (42). For skeletal muscle functional parameters, hand grip strength and knee strength can be used (43). For BC, DEXA or BIA are recommended, and if possible, TC (44).

The staging of SO should be based on the presence or absence of complications. The screening, diagnosis, and staging summary are presented in **Table 1**, adapted from the Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement (6).

TABLE 1 Screening, diagnosis, and staging of sarcopenic obesity.

Screening of SO	• High BMI and WC • Clinical symptoms, clinical suspicion SARC-F • If conditions present, go to Diagnosis
Diagnosis of SO	• HGS, Chair stand test if positive, go to body composition. • Increased Fat mass, reduced muscle mass using medical imaging, BIA, calf circumference • Items 1 and 2 must be present.
Staging of SO	Based on the presence of complications resulting from high FM and low ASMM • Stage I: No complications • Stage II: presence of at least one complication attributable to SO: metabolic diseases, functional disabilities, cardiorespiratory diseases,

SO, sarcopenic obesity; BMI, body weight index; WC, waist circumference; HGS, hand grip strength; BIA, bioelectrical impedance analysis; FM, fat mass; ASMM, appendicular skeletal muscle mass. Adapted from the Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement (6).

Food insecurity

Food insecurity is a severe global public health concern. Around 2,300 million people worldwide were affected by moderate or severe food insecurity in 2021 due mainly to conflicts, meteorological phenomena, and socio-economic perturbations (45). There should be an update of food and agricultural policies to make healthy diets more affordable. Food insecurity is defined as limited or uncertain access to adequate and nutritious foods due to many factors, especially financial resources (46).

Food insecurity and hunger are concepts that could seem like synonyms. Nevertheless, food insecurity is a household-level economic and social condition limiting access to food, and hunger is an individual-level physiological condition resulting from food insecurity (47). In addition, The United States Department of Agriculture (USDA) classifies food insecurity as reduced quality, variety, or desirability of the diet with little or no indication of reduced food intake and very low food security as multiple indications of disrupted eating patterns and reduced food intake (48).

It has been reported that food insecurity increases have affected people of all ages, particularly those in vulnerable situations (48). Older adults are exposed to many conditions that increase their vulnerability. Food insecurity has been well described as a critical factor that leads to health issues in the aged population, mainly affecting those primarily alone, who have fixed incomes and chronic health concerns (49, 50). Consequently, the prevalence of chronic diseases, poor management of chronic diseases, and decreased health-related quality of life in older adults are associated with food insecurity (49, 51).

One of the main ways that food insecurity can be a determinant of health and diseases is its impact on diet quality.

Food insecurity and diet quality

Diet quality (DQ) can be determined by many indicators such as specific nutrient quantitative and qualitative content or by designed tools that assess an individual's overall diet quality (52, 53).

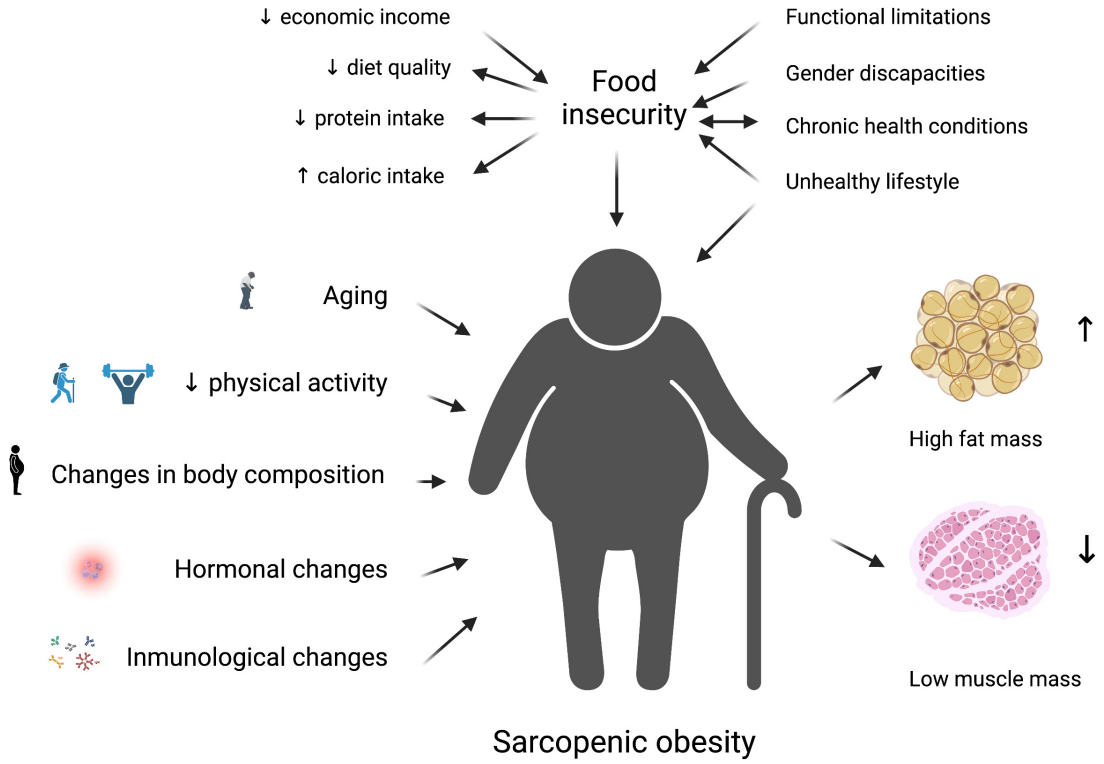

FIGURE 1
The interrelation between food insecurity and sarcopenic obesity in older adults is related to low economic income, impacting a low-quality diet with a small protein intake with a high energy offer. This scenario is worsened by unhealthy lifestyles and the presence of comorbidities, and body composition alteration due to hormonal and immunological changes, resulting in low muscle mass and high-fat mass. This image was created using Biorender.com.

Poor DQ is a direct and preventable cause of death globally. Food insecurity has been associated with lower DQ (54), particularly with more than 50 adverse associations with differences according to sex and ethnicity (55, 56).

The decline in diet quality has been observed in cohorts that aged from middle to older adulthood, especially in response to drastic changes derived from social or health issues (57, 58). The proportion of US older adults with poor diet quality significantly increased from 50.9 to 60.9% between 2001 to 2018, with a significant decreasing trend in diet scores among both sexes and all age groups (59).

DQ can also impact nutritional status. Carrier et al. found that diet quality was associated with malnutrition in older adults living in long-term care. In this cohort, several individual nutrients were associated with low calf circumferences (<31 cm). In the same study, older adults with better dietary quality and habits were more likely to have better nutritional status. In addition, a US longitudinal study showed that malnutrition was significantly associated with poorer diet quality and lower energy and protein intake (60).

It is important to mention that sarcopenia could increase the risk of inadequate diets. For example, in long-term care homes in Spain, the risk of a poorer diet was higher in females and residents with sarcopenia (61). In community-dwelling older adults, diet quality has been associated with the number of comorbidities and baseline risk of malnutrition (62). In contrast, prospective associations of poor DQ with long-term incidence of protein-energy malnutrition have not been found (63).

Those differences could result from the method to assess DQ, the definition of malnutrition or risk of malnutrition, and institutional or community-dwelling older adults' location.

On the contrary, a recent systematic review and meta-analysis describe a significant association between healthy dietary patterns and maintenance of gait speed with age, an indicator of sarcopenia risk (64).

Food insecurity and obesity in older adults

Obesity and food insecurity are both public health concerns influenced by social disparities that impact the quality of life in older adults (64). Social and economic transitions in low and middle-income countries are contributing to an increase in the aging population and, together with the added burden of poverty and inequities, increase food insecurity, obesity, and

associated comorbidities (65). Food insecurity is paradoxically associated with obesity in high-income countries. The first hypothesis of whether food insecurity causes obesity was published 27 years ago (66).

Explaining the link between food insecurity and body weight is a complex issue to the fact that it is not well understood what mechanisms cause it. One of the most studied hypotheses describes that food insecurity can cause obesity due to the high calorie and palatable food consumed by low food secure populations such as older adults could be (67). Also, the food insecure population could have limited knowledge about nutrition and resources to follow a healthy lifestyle, so they might have fewer opportunities to keep healthy eating and exercise to prevent and treat obesity (68). Furthermore, older adults' nutrition knowledge can influence positively or negatively their health status and quality of life (69).

The resource scarcity hypothesis suggests that perceived food insecurity in a permissive environment with access to high-calorie foods may cause positive energy balance in individuals of low social status or socially vulnerable populations (70).

Physical limitations can also be a potential risk factor for food insecurity and the food insecurity-obesity paradox in older adults (71). However, some hypotheses suggest a bidirectional association between food insecurity and physical limitations (72).

In particular, the association between food insecurity and obesity has shown mixed findings by age and gender. This association appears not to be present in older men even though food insecurity and obesity coexist among low-income, older women due to differences in household income, educational attainment, and social networks (73–77).

Food insecurity and sarcopenia in older adults

Not long ago, it was found that individuals who experienced food insecurity had lower muscle mass strength and physical performance (78, 79). On the contrary, functional limitations are significantly associated with increasing food insecurity in older adults, and these associations could be influenced by ethnicity (80). Currently, food insecurity is strongly associated with sarcopenia (81–84). Prevalence of sarcopenia in older adults with food insecurity has been described in 24,4% in low- and middle-income countries; indeed, severe food insecurity was associated with 2.05 times higher odds for sarcopenia (84). **Figure 1** illustrates the previously described interaction between food insecurity and SO in older adults.

The double burden of malnutrition has been proposed as a term that can describe a scenery where critical nutrients are poor independently of excess energy intake. In this sense, the excess FM can lead to sarcopenia and, consequently, SO (85).

Against these conditions, improve food insecurity (86), healthy eating patterns such as the Mediterranean, and physical activity (87), have been described as strategies to achieve healthy aging and reduce the risk of obesity and sarcopenia.

Conclusion

Sarcopenia and obesity share pathological factors, including aging and changes in BC. Changes in BC are the leading risk factor for SO. That is why SO needs to be screened and diagnosed adequately. The relationship between food insecurity and SO is mediated mainly by diet and disabilities associated with aging. Food insecurity can determine diet quality which is an important modifiable risk factor in the development of sarcopenia and obesity.

Author contributions

All authors have conceptualized this narrative review, analyzed current literature, wrote the original draft, reviewed the final version, and agreed to the published version of this manuscript.

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Conflict of interest

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Protective role of butyrate in obesity and diabetes: New insights

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Studies in human microbiota dysbiosis have shown that short-chain fatty acids (SCFAs) like propionate, acetate, and particularly butyrate, positively affect energy homeostasis, behavior, and inflammation. This positive effect can be demonstrated in the reduction of butyrate-producing bacteria observed in the gut microbiota of individuals with type 2 diabetes (T2DM) and other energy-associated metabolic alterations. Butyrate is the major end product of dietary fiber bacterial fermentation in the large intestine and serves as the primary energy source for colonocytes. In addition, it plays a key role in reducing glycemia and improving body weight control and insulin sensitivity. The major mechanisms involved in butyrate regulation include key signaling pathways such as AMPK, p38, HDAC inhibition, and cAMP production/signaling. Treatment strategies using butyrate aim to increase its intestine levels, bioavailability, and improvement in delivery either through direct supplementation or by increasing dietary fiber in the diet, which ultimately generates a higher production of butyrate in the gut. In the final part of this review, we present a summary of the most relevant studies currently being carried out in humans.

KEYWORDS

butyrate, obesity, fiber, short-chain fatty acid (SCFA), diabetes

Introduction

The World Health Organization (WHO) defines obesity as an abnormal fat accumulation that may impair health (1). The evidence of the relationship between the gut microbiome and the development of obesity and type 2 diabetes mellitus (T2DM) has been rising for the last decade (2). The gut microbiota plays a pivotal role in regulating energy homeostasis. Among other host factors, this balance between energy intake and expenditure relies on the microorganisms and their metabolites, helping in

nutrient processing, nutrient access regulation, and storage in the body by secreting hormones and mediators of energy homeostasis (3). Some glycemic alterations that cause a detrimental cascade effect have also been linked to chronic inflammation, cardiovascular diseases, and gut dysbiosis, where the loss of several butyrate-producing bacteria has been observed (4).

The short-chain fatty acids (SCFAs) are ingested through diet or produced by fermentation of non-digestible fiber by gut microbiota; the three major SCFAs produced are butyrate, propionate, and acetate (5). After production or consumption, butyrate, the SCFA with the most important systemic effects, is absorbed rapidly in the gut and acts as a source of energy and a signaling molecule in numerous cell types (6). It has been reported to have metabolic effects on obesity and glucose homeostasis. In a recent study, individuals with obesity and T2DM showed a decreased abundance of butyrate-producing bacteria and downregulation of genes related to butyrate production (7). Despite these findings, its exact role remains unclear since obese individuals present higher fecal butyrate concentrations than the control group, with similar diet consumption (8, 9). Restoration of butyrate-producing bacteria and butyrate levels by ingesting butyrate-rich foods or dietary fibers that lead to butyrate production might provide new treatment options for T2DM and obesity-related metabolic diseases (5). Here we review the basic mechanisms that explain the role of butyrate in this context.

Sources of butyrate in food

SCFAs, including butyrate, are present in high amounts in milk and milk derivatives from different mammals. Bovine fat milk and its derivatives are a great source of butyric acid, e.g., butter (∼3 g/100 g), goat's cheese (∼1–1.8 g/100 g), parmesan (∼1.5 g/100 g), whole cow's milk (∼0.1 g/100 g) (10). Human milk (HM) has also been reported as a source of butyrate, where the concentration measured in HM samples from healthy women fluctuates between 0.15 and 1.93 mM in colostrum and 0.16–1.97 mM in mature milk. Considering a median butyrate concentration of 0.75 mM in mature HM, a breastfed infant could receive a daily dose of butyrate of approximately 30 mg/kg body weight (11).

Salatrims, a fat calorie replacer commonly used in the food industry, is also a source of dietary butyrate. Salatrim has triglyceride mixtures in which butyric acid is inter-esterified with a long-chain fatty acid moiety such as stearic acid (12, 13). Since butyrate is esterified at the α(sn-3) position (14, 15), pancreatic lipase can cleave triacylglycerols releasing free fatty acids (FFA) in the small intestine (16, 17). To prevent digestion -and absorption- in the upper part of the gastrointestinal tract, butyrate might be esterified to a dietary fiber such as butyrylated or tributyrin, in which butyrate is esterified to triglycerides; as a result, these esterificated form of butyrate have also been shown to increase colonic butyrate concentrations (18, 19).

In most human clinical and rodent studies focused on obesity and diabetes, butyrate is supplied orally as sodium butyrate, which has an unpalatable flavor and odor. Novel strategies have been developed recently to improve palatability and the release and absorption of butyrate in the digestive tract (20). Coating sodium butyrate with cellulose-based capsules has been one approach to delay the release in the intestinal tract (21). According to pharmacological and clinical data from the literature, butyric acid is considered a safe drug. Therapeutic doses (150–300 mg) have shown no clinical side effects (22). Even when higher doses up to 2,000 mg/day, no adverse reactions have been observed (22, 23)

On the other hand, dietary fiber is used by some bacteria in the gut microbiota for butyrate production in two different ways: (I) Direct, where fiber acts as a substrate for bacterial fermentation producing butyrate, (II) Indirect since bifidogenic fibers help to increase the abundance of bifidobacteria, which increase butyrate production indirectly (24).

Maybe, the most efficient way to influence the composition of intestinal and colon microbiota is by ingestion of dietary fibers such as inulin-type fructans, xylooligosaccharides, arabinoxylans, arabinoxylan oligosaccharides, β-glucans, and oligofructose (25–28). Important foods to increase intestinal butyrate are complex polysaccharides not easily digested by saliva and pancreatic amylases. For instance, resistant starch, a group of molecules that resist digestion, may be added or fortified into bread and cereals (29) but is also found naturally occurring in some legumes, cooked potatoes, and unripened bananas. Studies have shown that resistant starch potentiates butyrate production and yields more butyrate than non-starch polysaccharides (30, 31). Other non-easily digested polysaccharides producing butyrate include cereal breakfasts, such as barley and oats, containing β-glucans, which are also naturally present in edible mushrooms and seaweed (32). Finally, inulin, on the other hand, is mainly found in artichokes, onion, and chicory roots (33) are also good foods to increase intestinal butyrate.

A high-fiber diet can cause gastrointestinal discomforts, such as gas, bloating, and constipation in patients with Crohn's disease, irritable bowel syndrome, or ulcerative colitis. This is why a gradual increase in fiber intake is recommended for everyone (34).

Biosynthesis and butyrate absorption

Although butter is the most abundant source of dietary butyrate (up to 3 g per 100 g), the best way to increase the amount of intestinal butyrate is by consuming non-digestible carbohydrates (complex polysaccharides) to

increase *in situ* production by human gut microbiota (35). Intestinal butyrate is produced by obligate anaerobic bacteria through fermentation (36). Most human butyrate producers belong to the *Firmicutes* phylum including species such as *Clostridium butyricum, Clostridium kluyveri, Faecalibacterium prausnitzii, Butyrivibrio fibrisolvens, Eubacterium limosum* (37–39).

Although several routes for the production of butyrate have been described, in human gut microbiota, butyrate is mainly synthesized from acetyl-coenzyme A (Ac-CoA) obtained from the breakdown of complex carbohydrates (e.g., xylan, starch) as a precursor (18, 37). Subsequently, two molecules of AcCoA condense into acetoacetyl CoA, and after several consecutive steps, it is transformed into butyrate (40). The final step in butyrogenesis is the conversion of butyryl-phosphate into butyrate by butyrate kinase encoded by the *buk* gene or butyryl-CoA to butyrate by butyryl-CoA: acetate-CoA transferase, encoded by the *but* gene (41). In addition to the colonization of the colon by butyrogenic bacteria, it has been proposed that cross-feeding interactions between *Bifidobacterial* strains and *F. prausnitzii* may ultimately enhance butyrate production (42).

Whether butyrate is ingested through the diet or produced locally in the intestine from dietary fiber, it is absorbed into the enterocytes by diffusion and delivered through the portal vein into the liver and systemic circulation (43, 44). Due to its size and hydrophobicity, butyrate, like propionate and acetate, are absorbed through a non-ionic diffusion across the apical membrane of colonocytes (45, 46). Sodium-coupled monocarboxylate transporter 1 (SCMT1) utilizes colonic concentration of Na^+ to internalize SCFAs within colonocytes. It has been described that SCMT1 transports propionate acetate at a slower rate compared to butyrate transport. The solute carrier family 5 member 8 (SLC5A8) is considered the primary butyrate transporter across the apical membrane of the colonocytes (47, 48).

Butyrate and liver metabolism

The liver is the master organ for regulating energy homeostasis, particularly for lipid and glucose metabolism regulation. The liver plays a central role in the development of obesity-associated metabolic alterations. It is, therefore, highly relevant to outline the effect of butyrate on regulating lipid metabolism and liver function. Recent studies showed that butyrate supplementation reduced serum triglyceride levels and the respiratory exchange ratio in high-fat diet (HFD)-fed animals compared to controls with HFD only, suggesting that butyrate may exert its effect by promoting fatty acid oxidation (49–53). In addition, butyrate also reduced lipid content in brown adipose tissue (BAT) and, to a lesser extent, in the liver and muscle (51). Additionally, demonstrating its protective role, butyrate supplementation in animals with HFD resulted in a significant reduction of proinflammatory serum markers (TNF-α, MCP-1, and IL-1β) compared to the markers of animals with HFD only (50).

Although butyrate mechanisms of action are unclear, previous studies show that butyrate modulates the AMP/ATP ratio activating the AMPK pathway to promote oxidative metabolism (decrease lipid synthesis and increase lipid oxidation) in the liver and adipose tissue (53). In addition, butyrate increases the percentage of oxidative type fibers (actively using lipid oxidation for ATP biosynthesis) in skeletal muscle by activating AMPK and p38 (54) and increases mitochondrial function in skeletal muscle (49) and liver (50).

Butyrate as a regulator of body weight

In addition to its well-known effects on intestine function (55), butyrate is a critical link between gut microbiota and the regulation of host energy homeostasis. Results from several groups have provided evidence supporting this role. For instance, chronic sodium butyrate supplementation in food (49, 51, 53, 54, 56) or orally delivered *via* gavage (50, 57–59) reduces body weight gain and fat mass of mice fed with a HFD compared to mice fed with an HFD alone, suggesting that butyrate can prevent or contribute for the treatment of diet-induced obesity (DIO). Also in agreement with this regulating role, intraperitoneal (IP) injection of sodium butyrate for ten consecutive weeks reduced body weight gain of rats treated with butyrate (60). A mechanism explaining the effect of butyrate on reducing body weight and fat mass is the activation of lipid oxidation initiated by butyrate in BAT and the liver (51). In addition to the increased energy expenditure and lipid oxidation, reduced food intake, also described as an effect of oral butyrate supplementation but not an intravenous injection, may contribute to decreased body weight gain induced by butyrate and reduced fat mass (51). The lack of effect of intravenous injection of butyrate suggests a role of this SCFA in regulating the gut-brain circuit.

Although there is evidence that sodium butyrate supplementation in standard diet-fed rats reduced weight gain (55), the effects of butyrate under chow diet-fed conditions remain controversial. There are contradicting results from other studies claimed that a chow diet plus 1% or 5% butyrate did not significantly affect body weight in mice (50, 61) and even that offspring rats of

TABLE 1 Therapeutic interventions with butyrate supplementation.

Population	Type (concentration)	Design approach	Trial details	Metabolic effects	Study
Obesity and metabolic syndrome					
– Children with obesity (n = 48)	Sodium butyrate (20 mg/kg body-weight per day)	Randomized controlled trial	Duration: 6 months administration: oral doses: 1 per day (no schedule specified)	– Decrease in waist circumference and BMI – Significant reduction of fasting insulin, HOMA-index, and LDL – Significant downregulation of peripheral miR-221 expression and a significant decrease of fasting serum ghrelin	(90)
– Healthy lean males (n = 9) -males with obesity (n = 10)	Sodium butyrate (4 g per day)	Clinical trial	Duration: 4 weeks administration: oral doses: 2 per day (no schedule specified)	– Males with obesity exhibit decreased oxLDL-induced trained immunity. – No effect observed in the counts of neutrophils, lymphocytes, or monocytes	(91)
– Patients with metabolic syndrome (n = 24)	Sodium butyrate (4 g per day) + autologous fecal transplantation	Randomized clinical trial	Duration: 4 weeks administration: oral doses: 1 per day (no schedule specified)	– Decrease in HbA1c, total cholesterol and triglycerides – No effects in BMI, hepatic and peripheral insulin sensitivity, fasting insulin and fasting glucose	(87)
– Healthy lean males (n = 9) -males with metabolic syndrome (n = 10)	Sodium butyrate (4 g per day)	Clinical trial	Duration: 4 weeks administration: oral doses: 2 per day (no schedule specified)	– Healthy lean males exhibit improvements in peripheral and hepatic insulin sensitivity – No effect observed in individuals with metabolic syndrome	(89)
Diabetes					
– Patients with T2DM (n = 42)	Sodium butyrate (3.6 g per day)	Randomized controlled trial	Duration: 6 weeks administration: oral doses: 6 per day (before and after 3 main meals)	– Decrease in systolic and diastolic blood pressure – Slight decrease in blood sugar 2-h postprandial but no statistically significant difference with placebo group	(85)
– Patients with T1DM (n = 53)	Sodium butyrate (3.6 g per day)	Randomized controlled trial	Duration: 12 weeks administration: oral doses: 2 per day (no schedule specified)	– No effects in inflammatory markers, kidney parameters, HbA1c, metabolites or gastrointestinal symptoms	(92)
– Patients with T2DM (n = 60)	Sodium butyrate (600 mg per day) + inulin (10 g per day)	Randomized controlled trial	Duration: 45 days administration: oral doses: 2 per day (no schedule specified)	(2017) – Decrease in diastolic blood pressure – Decrease in fasting blood sugar and hip-to-waist ratio during combined (sodium butyrate + inulin) administration (2020) – Downregulation of genes: TLR2/4, NF-κB1, Caspase-1, NLRP3, IL-1β and IL-18 (related to pyroptosis cell death)	(86, 93)
– Patients with T1DM (n = 30)	Sodium butyrate (4 g per day)	Crossover randomized controlled trial	Duration: 4 weeks administration: oral doses: 2 per day (no schedule specified)	– No effects in BMI, energy intake, fasting glucose or total insulin dose – No effects in β-cells autoimmunity or innate immunity regulation	(88)

BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-Index, homeostatic model assessment for insulin resistance; IL-1β, Interleukin-1β; IL-18, Interleukin-18; NF-κB1, Nuclear factor κB1; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; oxLDL, oxidized low density lipoprotein; TLR2/4, Toll-like receptors 2/4; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

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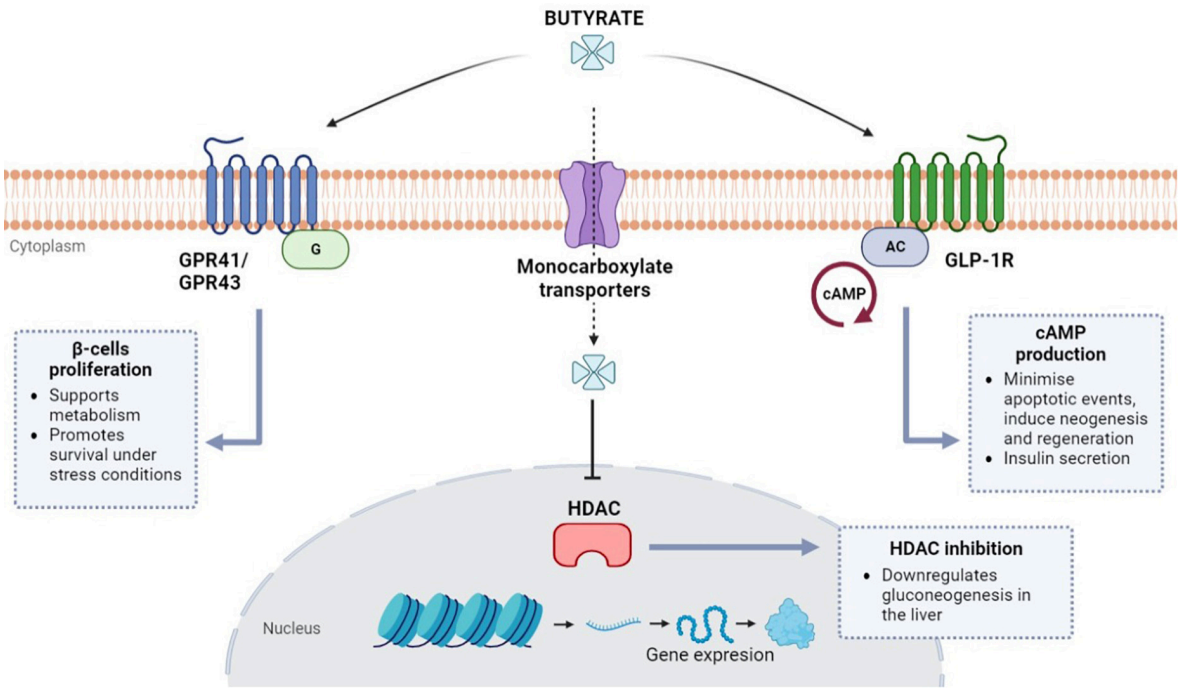

FIGURE 1
Butyrate regulation pathways in β-cells (pancreatic islets). Butyrate is involved in β-cells metabolism *via* G protein-coupled receptors (GPRs) GPR41 and GPR43. Butyrate can also enter the cells via monocarboxylate transporters and inhibit histone deacetylases (HDAC) which are thought to be involved in gluconeogenesis signaling. Butyrate can also regulate the cAMP signaling for insulin secretion *via* glucagon-like peptide-1 receptors (GLP-1R).

mothers fed a 1% butyrate in a chow diet had higher body weight (62). Major milestones of butyrate action and results from key therapeutic trials are summarized in **Table 1**.

Butyrate and diabetes

As it has been extensively documented in the literature, insulin resistance can be attributed to a decrease in receptor sensitivity together with the functional impairment of β-cells in the pancreatic islets (63). Histological studies of human islet tissue have shown that butyrate has a protective effect against oxidative and mitochondrial stress promoting the survival of β-cells *in vitro* (64, 65). Remarkably, initial analysis of the conditions associated with β-cells autoimmunity in children at risk of type-1 diabetes mellitus (T1DM) found a reduction in the average population of butyrate-producing bacteria (66, 67). There is evidence that butyrate is involved in the metabolism of β-cells in the pancreatic islets due to its interaction with G-protein coupled receptors (GPR) like free fatty acid receptors FFAR3 (GPR41) and FFAR2 (GPR43), as seen in **Figure 1** (64, 68, 69). In light of this association, one study suggested that butyrate could be responsible for a proliferative effect during *in vitro* mouse intestinal organoid development due to its interactions with GPR41 and 43 receptors (70).

Animal data in obese mice have shown that butyrate administration rapidly decreased fasting insulin levels (50, 71). As a result, aside from its protective role in β-cells, butyrate has been proposed as a direct regulator of insulin secretion *via* GPR-mediated signaling. However, this direct role remains unconfirmed and controversial (72). Nevertheless, recent findings suggest sodium-butyrate treatment can indirectly enhance insulin secretion by repressing β-cell key functional genes in rat islets (73). More evidence about the indirect role of butyrate during insulin secretion has emerged after studies reported its involvement with glucagon-like peptide-1 (GLP-1) secretion from intestinal L-cells (74, 75). Activation of the GLP-1R (receptor) genes, also present in β-cell, and subsequent GLP-1 release can also be induced by butyrate (76). GLP-1 has the potential to minimize apoptotic events and induce neogenesis and regeneration of β-cells *via* cAMP (cyclic adenosine monophosphate) upregulation (77). Production of cAMP can also elicit postprandial-like insulin secretion by accelerating the glucose-dependent closure of ATP-regulated potassium channels (77–79).

On the other hand, the inhibitory activity of butyrate toward histone deacetylases (HDAC) has also been extensively described in literature due to HDAC involvement in transcriptional regulation, metabolism, metastasis, oncogenesis, and ischemic brain events (80, 81). HDACs have also been linked to hyperglycemia by promoting gluconeogenesis in the liver; therefore, becoming an important target to regulate glucose levels *via* the administration of HDAC inhibitors like metformin (a first-line antihyperglycemic drug for T2DM treatment) (82, 83). Type-2 diabetic animal studies have revealed that butyrate has similar effects to metformin in reducing insulin resistance and other T2DM-associated conditions (60). In addition, the role of butyrate-mediated HDAC inhibition has been described as an enhancer in the differentiation and maturation of β-cells in neonatal porcine islets (84). Altogether, there is strong evidence about the crucial role of butyrate and its interactions with insulin-secreting β-cells. The potential regulation of gluconeogenesis *via* HDAC and the robust induction of insulin secretion *via* GLP-1 appoint butyrate administration as a potential target for research in diabetes treatment.

Consequently, several therapeutic interventions have already been conducted to assess the effects of butyrate supplementation in diabetic patients and patients with obesity and metabolic syndrome (**Table 1**). Some trials reported a positive outcome after treatment with oral butyrate with a reduction in the patient's blood pressure and blood sugar levels (85, 86). In addition, other trials also found significant reductions in HbA1c (hemoglobin-A1c: glucose linked to hemoglobin in red blood cells), total cholesterol, and triglycerides (87). On the other hand, several studies contradict some of these findings and report no significant effects on sugar levels, insulin sensitivity, and secretion (87, 88). One study suggests that butyrate therapy benefits healthy individuals, but this outcome is not reflected in patients with metabolic syndrome (89). Overall, there are still some limitations on these data, which may prevent direct comparisons and conclusions. Some of these trials may be conditioned by the short duration of butyrate administration, small sample size, lack of placebo control, and variability within the target population. Moreover, butyrate combination therapies with other potential antidiabetic drugs are still unexplored, so further research is encouraged.

Concluding remarks

In addition to the described effects on intestinal function and metabolic control, the system-level impacts of butyrate remain elusive, and the detailed molecular mechanisms responsible for butyrate action in host and microbial cells are still a very active research field. On the other hand, to detail the effects of butyrate on host metabolism and further promote butyrate as a therapeutic approach for designing novel clinical trials, it is critical to identify its effects on different animals and humans and evaluate different doses, treatment times and delivery methods. In addition, although many studies support the role of butyrate as an essential mediator in host metabolic control, some of its effects remain controversial.

Highly relevant questions in this exciting field are still awaiting elucidation. They should be decoded, including but not limited to determining the best conditions and food sources for butyrate production by gut microbiota *in situ*, absorption of dietary and microbially produced butyrate under different physiological and pathological conditions, the regulatory mechanisms of butyrate at a cellular and systemic levels and the potential of using it as a therapeutic alternative in some obesity-associated metabolic alterations.

Author contributions

CB-O and LG: conceptualization and research/investigation. AM-R, DS-R, and CB-O: writing—original draft preparation. LG and DS-R: writing—review and editing. LG: supervision. All authors contributed to the article and approved the submitted version.

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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.

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Genetics, genomics, and diet interactions in obesity in the Latin American environment

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Obesity is a chronic disease characterized by abnormal or excessive fat accumulation that could impact an individual's health; moreover, the World Health Organization (WHO) has declared obesity a global epidemic since 1997. In Latin America, in 2016, reports indicated that 24.2% of the adult population was obese. The environmental factor or specific behaviors like dietary intake or physical activity have a vital role in the development of a condition like obesity, but the interaction of genes could contribute to that predisposition. Hence, it is vital to understand the relationship between genes and disease. Indeed, genetics in nutrition studies the genetic variations and their effect on dietary response; while genomics in nutrition studies the role of nutrients in gene expression. The present review represents a compendium of the dietary behaviors in the Latin American environment and the interactions of genes with their single nucleotide polymorphisms (SNPs) associated with obesity, including the risk allele frequencies in the Latin American population. Additionally, a bibliographical selection of several studies has been included; these studies examined the impact that dietary patterns in Latin American environments have on the expression of numerous genes involved in obesity-associated metabolic pathways.

KEYWORDS

obesity, nutrigenetics, nutrigenomic, Latin America, SNPs

Introduction

Obesity is a chronic disease characterized by abnormal or excessive fat accumulation that could impact an individual's health. The World Health Organization (WHO) defines adult obesity as when the body mass index (BMI) is equal to or greater than 30 kg/m^2. Moreover, the WHO declared obesity a global epidemic in 1997 (1).

Additionally, obesity is considered one of the principal causes of morbidity and mortality in most countries. Worldwide, the prevalence of obesity has increased during the last decades; about 13% of the adult population was obese in 2016 (1). If this

increasing trend continues, it is expected that the majority of the adult population will be obese by 2030 (2).

Obesity has become a health concern in Latin America, reporting a 24.2% of the region's adult population was obese in 2016 (3). The highest prevalence was found in Argentina (28.3%), and the lowest was in Peru (19.7%). The data showed that the southern part of South America is more obese than the north (2, 4–6). Besides, the studies suggested that by 2030 up to 81.9% of the Latin American adult population may be obese or overweight (7).

The adverse impacts of obesity increase the risk for many diseases and health conditions, such as type 2 diabetes, high cholesterol, coronary heart disease, breathing problems, hypertension, stroke, and depression, among others (8–10). These conditions could cause disability and even premature death. Due to the lack of effective interventions for obesity prevention and management, the increase in obesity is not surprising, even with the socioeconomic disparities, because the incidence has gradually shifted to the lower-income population (11).

Genes could define susceptibility to a condition or disease, and the environmental factor or specific behaviors like dietary intake or physical activity could determine the development of that condition or illness (12). Studies of dietary patterns have been performed in North Americans and Europeans, but there is still a lack of evidence of food intake in Latin America (13). Latin American countries have been experiencing a change in eating habits, which has meant that the prevalence of undernutrition is declining, while the prevalence of overweight and obesity is increasing (7).

Moreover, a study published by Sepulveda said that the caloric intake varies from 1,880 to 2,170 calories/day, with an average animal protein consumption of 496 calories (14). In contrast, nowadays, the diet has changed; for example, a study by Kovalskys et al. reported 1,959 kcal/d divided into 54% carbohydrate, 30% fat, and 16% protein. Also, they described that the dietary intake of Latin Americans is based on grains, pasta, bread, meat, eggs, oils, fats, non-alcoholic beverages, and ready-to-drink beverages. Additionally, they reported that 25% of the energy intake comes from food rich in sugar and fat; meanwhile, 13% comes from fiber and micronutrients (13).

Nutrigenetics and nutrigenomics provide data related to the mechanism of nutrients and genes interactions, approaches for precision nutrition, and their relation to disease risk (**Figure 1**). Indeed, nutrigenetics studies genetic variations and their effect on dietary response (12). The genetic variations are DNA sequence differences between individuals or populations, including single nucleotide polymorphisms (SNPs) and copy number variations (CNV). Those genetic variants could modify the effects of dietary intake, affect food metabolism, and influence food preferences. Meanwhile, nutrigenomics studies the role of nutrients in gene expression (15). As a matter of fact, diet intake could directly affect gene expression and genome stability, leading to diseases or adverse phenotypes in any life stage (16).

The Latin American population constitutes a mixed population of Native American, European, and African descendants (17). Ethnicity could influence the genetic predisposition to obesity and dietary intake could affect gene expression. The present study constitutes a complete review of the dietary behavior in the Latin American environment related to obesity. It is divided into two main sections, the first one "the genetics in obesity in the Latin American population," which describes the genetic variants associated with food intake in Latin America; and the second section "Genomics and diet interaction in obesity in the Latin American environment" that presents how nutrition could impact the gene expression influencing the incidence of obesity in the population.

Genetics in obesity in the Latin American population

As described in the introduction, genetics in nutrition is the science that studies the interactions between genetic variations and how the body processes nutrients, associating the variation with human health and disease, including obesity (18, 19). Moreover, obesity is increasing worldwide, and Latin America is no exception (4). Hence, it is vital to understand the interaction between genetic variation and obesity in the Latin American population due to the differences in ethnicity with other regions.

The present section represents a compendium of genes and their SNPs associated with obesity (**Figure 2**). Moreover, the Latin American population's reference and alternative allele frequencies were retrieved from the ALFA: Allele Frequency Aggregator and The Population Architecture using Genomics and Epidemiology (PAGE) Study. The ALFA: Allele Frequency Aggregator is a database that contains over two million subjects, from different ancestral backgrounds, including African, Asian, European, Latin American, and others (20). Similarly, The PAGE Study is another database that contains allele frequencies; however, this project is focused on describing the genetic components of underrepresented minorities (21). The terms included in the review included Latin American, South American, and Native American. Additionally, to describe the function of each gene, its association with environment, and obesity, the GO (Gene Ontology) Biological processes were included.

Table 1 describes the allele frequencies, in Latin America, of SNPs associated with obesity. Even though most of the studies correlating SNPs and obesity predisposition have been performed on Asian and European populations, identifying the frequency of these risk alleles, in Latin America, is of the utmost importance to understand obesity and its association with the complex genetic architecture of the region.

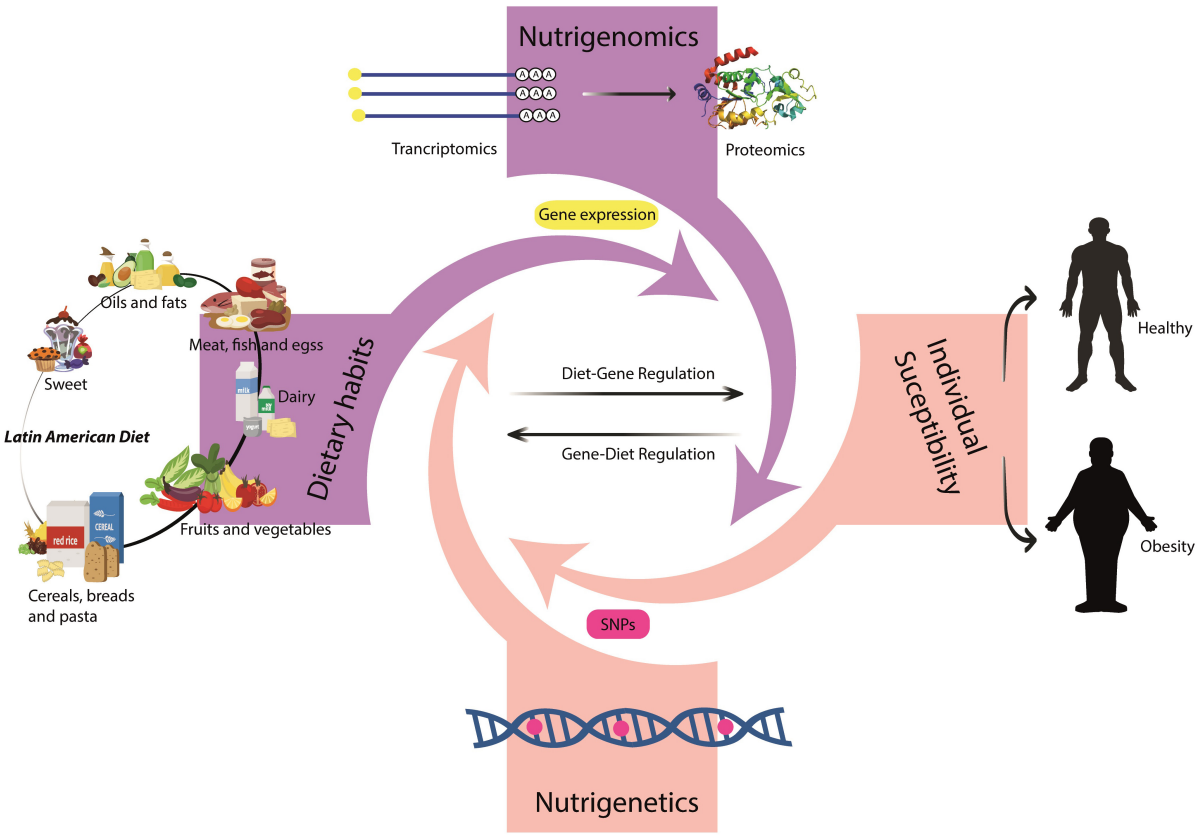

FIGURE 1
Nutrigenetics, nutrigenomics, dietary habits, and individual susceptibility. Nutrigenetics studies genetic variations (SNPs) and their effect on dietary response. Nutrigenomics studies the role that the nutrients have on gene expression with a focus on the Latin American environment. Collectively, these three factors could increase or decrease an individual's susceptibility to develop obesity in Latin America.

Single nucleotide polymorphisms associated with obesity and the frequencies in Latin America

ADRB2 is a protein-coding gene that encodes a beta-2-adrenergic receptor, a member of the G protein-coupled receptor superfamily (22). The receptor's primary function is the catecholamine-induced activation of adenylate cyclase (23). Moreover, The GO: Biological Process in which *ADRB2* is involved encompasses regulation of systemic arterial blood pressure by norepinephrine-epinephrine, diet-induced thermogenesis, G protein-coupled receptor signaling pathway, positive regulation of MAPK cascade, and adenylate cyclase-activating adrenergic receptor signaling pathway (24).

Furthermore, SNPs on *ADRB2* have been reported to be related to obesity. For example, reports regarding the SNP rs1042713 have described that carriers of the G allele were associated with higher insulin resistance, total cholesterol/high-density lipoprotein (HDL) ratio, total cholesterol, and low-density lipoprotein (LDL) than individuals with an AA genotype (25). The presence of the G allele in Latin America is higher, with an overall of 0.54, whereas the A allele is 0.46 (20, 21). Hence, the Latin American population may have an obesity predisposition and should avoid high-cholesterol foods.

Similarly, *ADRB3* is a protein-coding gene that modulates the catecholamine-induced activation of adenylate cyclase by the action of G proteins (22). The protein transcribed is part of the beta-adrenergic receptors family and is involved in lipolysis and thermogenesis regulation (23). Obesity has been associated with SNPs in this gene (22). The GO: Biological processes include diet-induced thermogenesis, eating behavior, positive regulation of cold-induced thermogenesis, generation of precursor metabolites and energy, norepinephrine-epinephrine-mediated vasodilation involved in the regulation of systemic arterial blood pressure, and carbohydrate metabolic process (24).

Moreover, an SNP (rs4994) in the *ADRB3* gene has been associated with obesity in different populations. For example, Xie et al. found an increased risk of childhood and adolescent obesity in individuals carrying the C allele in the East Asia population (26). Similarly, Daghestani et al. reported an association between rs4994 and the development of obesity and increased levels of insulin, leptin, glucose, and lipids in a Saudi

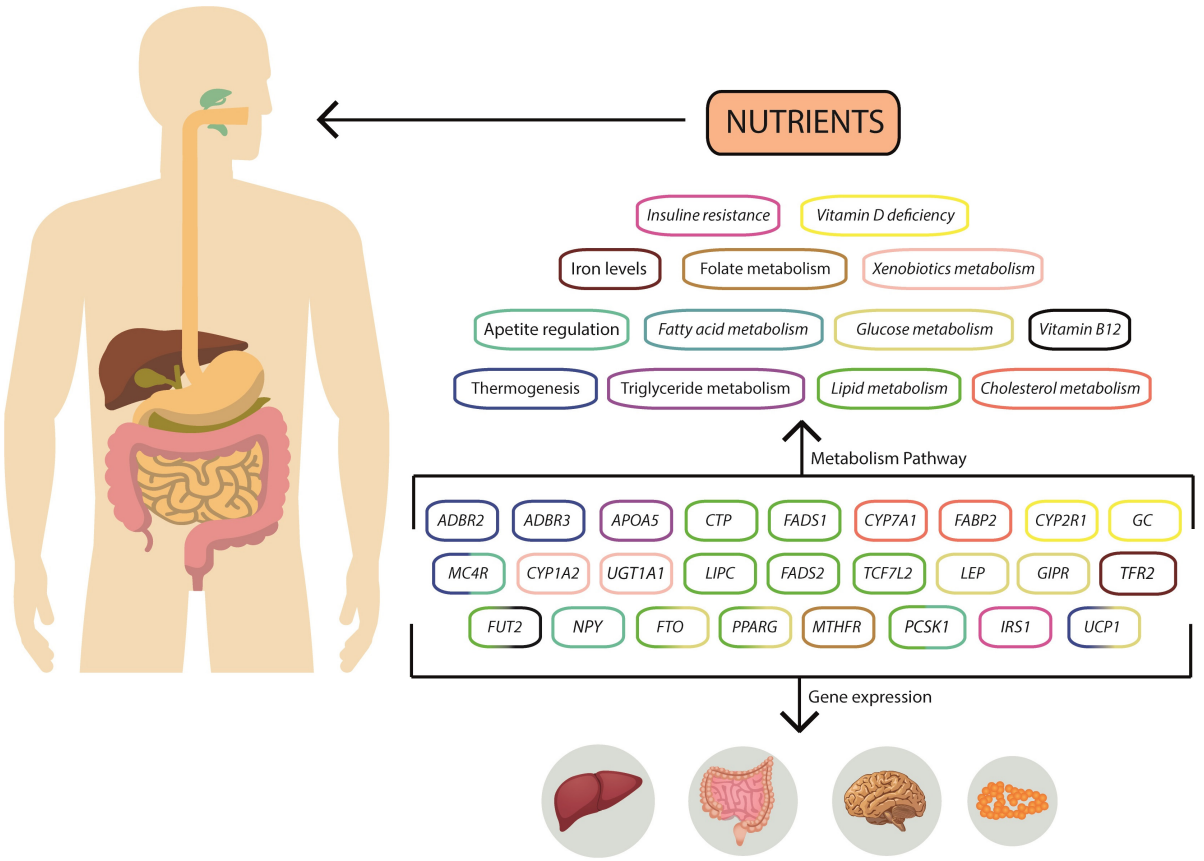

FIGURE 2
Overview of gene interactions and gene expression in nutritional metabolism pathways. Diet can influence gene expression in several ways, and nutrients can be metabolized through various pathways, altering the concentration of substrates or intermediates that influence gene expression. Changes in gene expression can impact the liver, hypothalamus, and adipose tissue. These nutrient-gene interactions can be detrimental, increasing the risk of obesity.

population (27). The presence of the C allele in Latin America represents a 0.14, whereas the T allele is 0.86 (20, 21). Further studies are needed to determine the role of the SNP in the Latin American population by performing case-control studies.

APOA5 is a protein-coding gene that encodes an apolipoprotein with a vital role in plasma triglyceride level regulation (22). The GO: Biological process encompasses the triglyceride metabolic process, lipid transport, cholesterol biosynthetic process, triglyceride catabolic process, regulation of intestinal cholesterol absorption, and triglyceride homeostasis (24). Mutations in *APOA5* have been correlated with hyperlipoproteinemia and hypertriglyceridemia (22).

Single nucleotide polymorphisms in *APOA5* have been associated with lower HDL and higher triglyceride levels (28–30). For instance, the SNP rs964184, in individuals with metabolic syndrome carrying the G allele, has been correlated with higher triglyceride levels and lower HDL in serum (28). Similarly, Qiu et al. found an association between the G allele in rs964184 and higher triglyceride concentration in Maonan and Han populations (29). In Latin America, the G allele has a frequency of 0.24, and the C allele, 0.76 (20, 21). Likewise, in the SNP rs662799, the allele C on the *APOA5* gene has been correlated with increased plasma lipids levels and higher total cholesterol levels (31). The frequency of the C allele in Latin America is 0.14, whereas, of the T allele, it is 0.86 (20, 21). Even though the frequencies of the associated SNP alleles are low, the Latin American population should be aware of the risk that consuming alcohol, fats, carbohydrates, and sugars has on human health (32).

CETP is a protein-coding gene located on chromosome 16. The protein encoded in this gene is involved in the transfer of neutral lipids, such as cholesteryl ester from HDL to other lipoproteins. Additionally, CETP regulates reverse cholesterol transport, sending the excess cholesterol to the liver for elimination (22, 23). Diseases associated with CETP encompass familial hyperlipidemia and hyperalphalipoproteinemia 1. The GO: Molecular functions of CETP are lipid, cholesterol, triglyceride, phosphatidylcholine binding, phospholipid transporter activity, and cholesterol transfer activity (24).

TABLE 1 Latin American frequencies of SNPs associated with obesity, including South and Native American.

Gene	SNP	Frequency of reference allele			Frequency of alternative allele			Association
		ALFA Latin American	PAGE Study South American	PAGE Study Native American	ALFA Latin American	PAGE Study South American	PAGE Study Native American	
ADRB2	rs1042713	***G* = 0.55**	***G* = 0.52**	***G* = 0.54**	*A* = 0.44	*A* = 0.48	*A* = 0.46	Higher cholesterol levels
ADRB3	rs4994	*T* = 0.86	*T* = 0.83	*T* = 0.88	***C* = 0.14**	***C* = 0.17**	***C* = 0.12**	Increased levels of insulin, leptin,glucose, and lipids
APOA5	rs964184	***G* = 0.25**	***G* = 0.34**	***G* = 0.20**	*C* = 0.75	*C* = 0.66	*C* = 0.80	Lower HDL and higher triglyceride levels
	rs662799	***C* = 0.14**	***C* = 0.18**	***C* = 0.09**	*T* = 0.85	*T* = 0.82	*T* = 0.90	Higher levels of total cholesterol
CETP	rs3764261	***C* = 0.66**	***C* = 0.66**	***C* = 0.65**	*A* = 0.33	*A*−0.33	*A* = 0.35	Lower HDL
CYP1A2	rs762551	***C* = 0.33**	***C* = 0.22**	***C* = 0.30**	*A* = 0.67	*A* = 0.78	*A* = 0.70	Higher caffeine consumption
CYP2R1	rs10741657	*A* = 0.36	NA	NA	***G* = 0.64**	NA	NA	Vitamin D deficiency
CYP7A1	rs3808607	*C* = 0.35	*C* = 0.30	*C* = 0.42	***A* = 0.65**	***A* = 0.70**	***A* = 0.58**	Cholesterol levels
FABP2	rs1799883	***T* = 0.26**	***T* = 0.27**	***T* = 0.26**	*C* = 0.74	*C* = 0.73	*C* = 0.74	Fatty acid uptake
FADS1	rs174545	*C* = 0.49	*C* = 0.39	*C* = 0.61	***G* = 0.51**	***G* = 0.61**	***G* = 0.39**	Fatty acid metabolism
	rs174561	*T* = 0.51	NA	NA	***C* = 0.49**	NA	NA	
FADS2	rs174583	*C* = 0.48	*C* = 0.36	*C* = 0.57	***T* = 0.52**	***T* = 0.64**	***T* = 0.43**	Triglyceride levels
FTO	rs8050136	*C* = 0.67	*C* = 0.76	*C* = 0.65	***A* = 0.33**	***A* = 0.23**	***A* = 0.35**	Obesity predisposition
	rs9939609	*T* = 0.66	*T* = 0.76	*T* = 0.64	***A* = 0.34**	***A* = 0.24**	***A* = 0.34**	
FUT2	rs601338	***G* = 0.64**	NA	NA	*A* = 0.36	NA	NA	Vitamin B12 levels
GC	rs2282679	*A* = 0.77	NA	NA	***C* = 0.23**	NA	NA	Vitamin D deficiency
GIPR	rs2287019	***C* = 0.85**	***C* = 0.89**	***C* = 0.83**	*T* = 0.15	*T* = 0.11	*T* = 0.17	Obesity predisposition
IRS1	rs1522813	*G* = 0.68	NA	NA	***A* = 0.32**	NA	NA	Increased levels of glucose
LEP	rs7799039	*G* = 0.69	NA	NA	***A* = 0.31**	NA	NA	Food intake regulation
LIPC	rs1800588	*C* = 0.60	*C* = 0.48	*C* = 0.63	***T* = 0.40**	***T* = 0.52**	***T* = 0.37**	Higher LDL levels
MC4R	rs17782313	*T* = 0.82	*T* = 0.88	*T* = 0.81	***C* = 0.18**	***C* = 0.12**	***C* = 0.19**	Energy homeostasis and appetite regulation
	rs11872992	*G* = 0.86	*G* = 0.84	*G* = 0.88	***A* = 0.14**	***A* = 0.16**	***A* = 0.12**	
	rs8093815	*C* = 0.68	NA	NA	***T* = 0.32**	NA	NA	
	rs17066856	*T* = 0.82	NA	NA	***C* = 0.18**	NA	NA	
	rs1943218	*T* = 0.70	NA	NA	***C* = 0.30**	NA	NA	
	rs17066829	*T* = 0.65	NA	NA	***A* = 0.35**	NA	NA	
	rs9966412	*G* = 0.79	NA	NA	***A* = 0.21**	NA	NA	
	rs17066859	*G* = 0.87	NA	NA	***A* = 0.13**	NA	NA	
MYRF	rs174537	*G* = 0.61	*G* = 0.39	*G* = 0.61	***T* = 0.39**	***T* = 0.61**	***T* = 0.39**	LDL and cholesterol levels
MTHFR	rs1801133	*C* = 0.63	*C* = 0.58	*C* = 0.71	***T* = 0.37**	***T* = 0.42**	***T* = 0.29**	Folate deficiency
NOS3	Rs1799983	***T* = 0.24**	NA	NA	*G* = 0.76	NA	NA	Obesity predisposition

(Continued)

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TABLE 1 (Continued)

Gene	SNP	Frequency of reference allele			Frequency of alternative allele			Association
		ALFA Latin American	PAGE Study South American	PAGE Study Native American	ALFA Latin American	PAGE Study South American	PAGE Study Native American	
NPY	rs16147	**T = 0.40**	**T = 0.32**	**T = 0.44**	C = 0.60	C = 0.68	C = 0.56	Higher obesity risk
PCSK1	rs6234	G = 0.76	G = 0.79	G = 0.75	**C = 0.24**	**C = 0.21**	**C = 0.56**	Obesity predisposition
	rs236918	C = 0.93	C = 0.77	C = 0.82	**G = 0.07**	**G = 0.23**	**G = 0.18**	Lower HDL levels
PPARG	rs1801282	C = 0.96	C = 0.89	C = 0.88	**G = 0.04**	**G = 0.11**	**G = 0.12**	Obesity predisposition
TCF7L2	rs7903146	C = 0.72	C = 0.81	C = 0.74	**T = 0.28**	**T = 0.19**	**T = 0.26**	Increased diabetes risk
TFR2	rs7385804	**C = 0.31**	**C = 0.25**	**C = 0.34**	A = 0.69	A = 0.75	A = 0.66	Iron deficiency
UCP1	rs1800592	A = 0.60	A = 0.52	A = 0.65	**G = 0.40**	**G = 0.48**	**G = 0.35**	Obesity predisposition
UGT1A1	rs6742078	G = 0.69	G = 0.63	G = 0.65	**T = 0.31**	**T = 0.37**	**T = 0.35**	Bilirubin serum level

The obesity-associated risk alleles are in in bold.

Moreover, an SNP (rs3764261) in the *CETP* has been associated with low HDL; individuals carrying the C allele have a strong risk factor for low HDL, which has been correlated with obesity (33, 34). In observational studies, significant interactions between diet and rs3764261 have been described. For example, in a study of 4,700 Iranian participants, a correlation between higher fish intake and a decrease in total cholesterol in individuals carrying the A allele was found (35). The frequency of the C allele in the Latin American population is 0.66, whereas for the A allele is 0.34 (20, 21). The C allele, associated with low HDL, is high in Latin America, increasing the obesity predisposition; hence, fish intake should be one of the principal components in the Latin American diet.

CYP1A2 is a protein-coding gene located on chromosome 15. It encodes a cytochrome P450 monooxygenase, part of the cytochrome P450 superfamily of enzymes. These enzymes are involved in the metabolism of substrates such as steroids, cholesterol, and vitamins (22, 23). Reports have described the role of the CYP1A2 protein in the metabolism of carcinogenic intermediates from polycyclic aromatic hydrocarbons (PAHs) (22). Moreover, caffeine, aflatoxin B1, and acetaminophen have been reported as xenobiotics substrates of the enzyme (22). The GO: Biological process encompasses fatty acid, cholesterol, estrogen metabolic process, steroid catabolic and metabolic process, and cellular aromatic compound metabolic process (24).

An SNP (rs762551) in the *CYP1A2* gene has been reported to influence caffeine metabolism. For instance, studies have described that individuals carrying the A allele have a fast caffeine metabolism. On the other hand, the C allele was correlated with a slow metabolism and a higher risk of myocardial infarction (36, 37). Moreover, higher coffee consumption has been reported in rapid (A allele) compared to slow metabolizers (C allele), leading to a lower dietary fat intake (38). The frequency of the A allele in the Latin American population is 0.71, whereas, of the C allele, the frequency is 0.29 (20, 21). Latin America has a high coffee consumption, and based on those above; this could lead to a decrease in the fat intake in the region. However, further studies should be performed to understand the effect of caffeine on health.

Similarly, *CYP2R1* is a protein-coding gene located on chromosome 11. It encodes a cytochrome P450 monooxygenase, part of the cytochrome P450 superfamily of enzymes, which has an essential role in vitamin D precursors activation (22, 23). Additionally, CYP2R1 is involved in steroids, cholesterol, and other lipids synthesis. Diseases associated with this gene include rickets due to vitamin D deficiency (39). The GO: Biological processes include lipid, vitamin, and xenobiotic metabolic processes (24).

An SNP (rs1041657) in the *CYP2R1* gene has been correlated with vitamin D differences in serum. For instance, studies have reported that individuals carrying the G allele had lower vitamin D levels in serum, concluding that the rs1041657 has a vital role

in determining vitamin D levels (40, 41). The frequency of the G allele in Latin America is 0.64, whereas for the A allele is 0.36 (20). Vitamin D levels have been associated with a preventive role in obesity, where individuals with low levels had a higher obesity predisposition (42). Based on this SNP frequency and vitamin D role, the diet in Latin America should aim for a high vitamin D intake.

Another member of the cytochrome P450 superfamily of enzymes is CYP7A1. The protein is a cytochrome P450 monooxygenase that has a crucial role in the metabolism of steroids, cholesterol, and other lipids. Moreover, the protein catalyzes the initial reaction of the cholesterol catabolic pathway in the synthesis of bile acids (22, 23). Hypercholesterolemia has been correlated with *CYP7A1* (22). The GO: Biological process of this gene encompasses lipid, steroid, sterol, cholesterol metabolic process, bile acid biosynthetic process, cholesterol catabolic process, response to organic cyclic compound, bile acid and bile salt transport, bile acid signaling pathway, cholesterol homeostasis, positive regulation of cholesterol biosynthetic process, and negative regulation of fatty acid biosynthetic process (24).

Furthermore, an SNP (rs3808607) in the *CYP7A1* gene has been correlated with serum cholesterol levels. For example, Iwanicki et al. found that individuals carrying the A allele in rs3808607 presented the highest total cholesterol concentration, whereas the C allele carriers had the lowest (43). The frequency of the A allele in the Latin American population is 0.65, while the C allele is 0.35 (20, 21). Thus, Latin American people may have a predisposition to high cholesterol, given the high frequency of the A allele. A balanced diet with low cholesterol intake should be followed.

FABP2 is a protein-coding gene located on chromosome 4 (24). The protein encoded plays a vital role in the intracellular transport, metabolism, and uptake of fatty acids (FAs); moreover, FABP2 has a high affinity for binding saturated long-chain FAs (22, 23). The GO: Biological process includes fatty acid transport, metabolic process, and intestinal lipid absorption (24).

An SNP (rs1799883) in the *FABP2* gene has been associated with obesity. For example. Han, T-K and So, W-Y. described that carriers of the T allele had an increased incidence of central obesity and obesity-related metabolic syndrome in Korean women (44). Similarly, Kops et al. described that individuals carrying the T allele showed higher anthropometric profiles than individuals with the C allele (45). The frequency in Latin America of the T allele is 0.26, and for the C allele is 0.74 (20, 21).

FADS1 is a protein-coding gene located on chromosome 11. The function of the protein encoded by *FADS1* is to introduce *cis* double bonds between carbons of the fatty acyl chain to regulate the unsaturation of FAs. It is also involved in the biosynthesis of highly unsaturated FAs and plays a role in the metabolism of inflammatory lipids (22, 23). Lipid metabolism disorder has been associated with *FADS1* (22). The GO: Biological process of FADS1 includes lipid, phospholipid, and fatty acid metabolic process, cell-cell signaling, cellular response to starvation, linoleic acid metabolic process, and regulation of cell differentiation (24).

Single nucleotide polymorphisms in *FADS1* have been correlated with fatty acid metabolism. For instance, carriers of the G allele in the rs174545 have been associated with higher triglyceride levels than C allele carriers (46). Mathias et al. described a significant association between rs174545 and alpha-linoleic, stearidonic, eicosanoic, and docosapentaenoic acids (47). The frequency of the C allele in Latin America is 0.49, and the G allele is 0.51 (20, 21). Similarly, the SNP rs174561 in the *FADS1* gene has been correlated with differences in polyunsaturated fatty acids (PUFA) ω-6 plasma concentrations in pregnant women, where carriers of the C allele showed higher concentrations of PUFA ω-6, in comparison with homozygotes with the TT genotype (48). In the Latin American population, the frequency of the C allele is 0.49, and for the T allele is 0.51 (20). Given the frequency of the risk alleles, the diet in Latin America should aim for a low fatty acid intake to prevent obesity.

The *FADS2* gene encodes a protein member of the fatty acid desaturase (FADS) family (24). The protein function includes the regulation of the unsaturation of FAs by introducing double bonds in the fatty acyl chain. Moreover, it has an important role in the biosynthesis of highly unsaturated FAs (22, 23). The GO: Biological processes include alpha-linolenic acid, lipid, fatty acid metabolic process, unsaturated, fatty acid biosynthetic process, and cellular biosynthetic process (24). Hyperlipoproteinemia has been associated with *FADS2* (22).

An SNP (rs174583) has been correlated with different triglyceride levels. For instance, Khodarahmi et al. reported significant differences in the atherogenic index of plasma and triglyceride levels. The carriers of the T allele had higher triglyceride concentrations than the carriers of the C allele (49). Similarly, Mazoochian et al. described increased triglyceride levels in individuals with the TT genotype (50). The T allele frequency in Latin America is 0.53, and the C allele is 0.47 (20, 21). Similar to *FADS1*, given the high frequency of the risk allele, a diet with low triglyceride levels should be followed in Latin America.

The *FTO* gene is located on chromosome 16. It encodes a nuclear protein involved in the demethylation of RNA. However, further studies are required to identify the specific physiological function. Glucose/energy metabolism is one of the FTO-related pathways (22, 23). FTO plays a role in the regulation of body fat accumulation and body size. Moreover, it is involved in adipocyte differentiation into brown or white fat cells (23). The GO: Biological processes include temperature homeostasis, DNA dealkylation involved in DNA repair, regulation of lipid storage, oxidative single-stranded DNA and RNA demethylation, adipose tissue development,

regulation of white fat cell proliferation, and regulation of brown fat cell differentiation (24).

Single nucleotide polymorphisms in the *FTO* gene have been described as having a role in obesity. For example, Ahmad et al. reported that individuals carrying the A allele in the rs8050136 have a greater risk of obesity, higher BMI, and obesity-related conditions; however, by modifying the lifestyle and physical activity of the participants, the effect of the SNP was almost entirely blunted (51). The frequency of the A allele in Latin America is 0.31, and for the C allele is 0.69 (20, 21). Similarly, for the rs9939609, Sonestedt et al. reported that carriers of the A allele with low physical activity and a high-fat diet may be more predisposed to obesity (52). The frequency of the A allele in Latin America is 0.32, whereas, for the T allele is 0.68 (20, 21). Given the frequency of the risk alleles, the diet in Latin America should focus on low-fat intake, and daily physical activity.

FUT2 is a protein-coding gene that encodes the galactoside 2-L-fucosyltransferase enzyme. The protein catalyzes the transfer of L-fucose to glycans chains on the cell surface; the resulting epitope is involved in different cellular processes, such as cell-cell interaction, and cell proliferation (22, 23). The gene is located on chromosome 19 and has been associated with differences in Vitamin B12 plasma levels (22). The GO: Biological processes include regulation of endothelial cell proliferation, carbohydrate and lipids metabolic process, protein glycosylation, and L-fucose catabolic process (24).

An SNP (rs601338) in the *FUT2* gene has been associated with vitamin B12 levels. The SNP rs601338 has been correlated with plasma vitamin B12 levels. Reports describe that individuals carrying the A allele have a higher vitamin B12 plasma concentration. This is in line with what has been found in different ethnic groups, correlating the frequency of the A allele with vitamin B12 plasma concentration. For instance, in the Indian population, the frequency of individuals carrying the G allele is higher than those carrying the A allele; hence, a lower vitamin B12 concentration is expected (53–56). The frequency of the A allele in Latin America is 0.36, and for the G allele is 0.64 (20). Reports have described low vitamin B12 concentrations in Latin America (57), which is in line with the frequency of the G allele in the region.

Moreover, studies have found an inverse correlation, associating low vitamin B12 levels with higher obesity predisposition (58). Thus, the Latin American population should increase their vitamin B12 intake to avoid an increased obesity risk. However, further studies should be performed to correlate the Latin American genotype with the vitamin B12 concentration.

GC is a protein-coding gene located on chromosome 4 (24). The protein encoded has a role in vitamin D binding and transport. Moreover, *GC* is part of the steroid and vitamin D metabolism pathways (22). The GO: Biological processes are vitamin D metabolic process, vitamin transport, and transmembrane transport (24).

Different SNPs in the *GC* gene have been associated with different vitamin D concentrations. For instance, Cheung et al. reported a correlation between the C allele in the SNP (rs2282679) and vitamin D deficiency in a Chinese population (59). Wang et al. reported that the rs2282679 was correlated with lower vitamin D levels (60). The frequency of the C allele in Latin America is 0.23, and of the A allele is 0.77 (20). Obesity and its genetic predisposition are complex; specific alleles could increase the obesity risk, and others may decrease it. Therefore, despite the genetic background, healthy food consumption should be the principal diet.

The *GIPR* gene encodes a G-protein coupled receptor for the gastric inhibitory polypeptide, which has been reported to stimulate insulin release. The GO: Biological processes encompass desensitization of the G protein-coupled receptor signaling pathway, generation of precursor metabolites and energy, signal transduction, G protein-coupled receptor signaling pathway, activation of adenylate cyclase activity, positive regulation of cytosolic calcium ion concentration, response to nutrients, calcium ions, FAs, and glucose (24).

The SNP rs2287019 has been associated with obesity and a higher BMI. For example, Speliotes et al. described a correlation between rs2287019 and an increased risk of developing obesity in individuals carrying the C allele (61). The frequency of the C allele in Latin America is 0.85, and the T allele is 0.15 (20, 21). The high frequency in Latin America is a matter of concern since obesity is now considered a significant health challenge in the region; hence, Latin America should aim to develop a healthier lifestyle to overcome this problem (4).

IRS1 is a protein-coding gene located on chromosome 2. The protein encoded by this gene has been associated with the control of various cellular processes when phosphorylated by the insulin receptor tyrosine kinase. Type 2 diabetes has been correlated with IRS1 (22, 23). The GO: Biological processes encompass positive regulation of cell population proliferation, insulin receptor signaling pathway, positive regulation of glucose metabolic process, positive regulation of fatty acid beta-oxidation, cellular response to insulin stimulus, positive regulation of glycogen biosynthetic process, regulation of insulin receptor signaling pathway (24).

Single nucleotide polymorphisms in the *IRS1* gene have been associated with diabetes and higher glucose levels. For instance, He et al. reported an increased risk of developing diabetes in women carriers of the A allele of the SNP rs1522813, compared to carriers of the G allele (62). The frequency of the A allele in Latin America is 0.32, and of the G allele, 0.68 (20). Similarly, Ohshige et al. reported a significant association between the C allele and the risk of type 2 diabetes in a Japanese population (63); this is in line with what was reported in a European population (64). The frequency of the C allele in Latin America is 0.75 and of the T allele 0.25 (20, 21).

Moreover, diabetes has been associated with obesity in both ways, with obesity increasing the risk of diabetes, and vice versa

(65). In diabetes, the glucose does not enter the cell; it remains in the blood, where it is converted into FAs, and stored as fat (65). The high frequency of the C allele in the Latin American population is alarming, so public policies should consider the genetic information of the region.

The *LEP* gene encodes a protein called leptin which plays a role in energy homeostasis regulation. The protein binds to its receptor in the hypothalamus, activating signaling pathways that promote energy consumption and inhibit feeding. The protein also regulates the secretion of hormones in the brain. Mutations in the *LEP* gene have been significantly associated with obesity. Diseases correlated to LEP include leptin deficiency and overnutrition (22, 23). The GO: Biological processes include regulation of protein phosphorylation, response to dietary excess, glucose metabolic process, energy reserve metabolic process, regulation of blood pressure, and adult feeding behavior (24).

An SNP (rs7799039) in the *LEP* gene has been associated with obesity. For instance, Zayani et al. found a significant association between obesity and carriers of the A allele (66). This agrees with what Bains et al. found in an Indian population (67). The frequency of the G allele in Latin America is 0.69, and for the A allele is 0.31 (20). Overeating is one of the principal causes of obesity; however, the origin of overeating may be in the person's genetic information (68). Based on the high frequency of the A allele, obesity in Latin America could be predisposed by SNPs in the *LEP* gene. Thus, genetic studies should be part of the diagnosis and obesity treatment.

The *LIPC* gene encodes a hepatic triglyceride lipase, which catalyzes phospholipid and triglyceride hydrolysis. The protein is involved in the triacylglycerol biosynthesis pathway (22, 23). The GO: Biological processes include lipid and cholesterol metabolic process, fatty acid biosynthetic process, cholesterol transport, lipoprotein particle remodeling, and cholesterol and triglyceride homeostasis (24).

An SNP (rs1800588) in the *LIPC* gene has been associated with LDL cholesterol and triglyceride levels. Carriers of the T allele had higher LDL cholesterol and triglyceride levels than carriers of the C allele (69). The frequency of the C allele in the Latin American population is 0.57, and for the T allele, 0.43 (20, 21). Based on the frequency of the SNP, the diet in Latin America should be focused on a low LDL and triglycerides intake.

The *MC4R* gene is located on chromosome 18 and encodes a membrane-bound receptor, part of the melanocortin receptor family. The protein plays a crucial role in somatic growth and energy homeostasis. Moreover, mutations causing a deficiency in the MC4R protein have been associated with obesity (22, 24). The GO: Biological processes encompass diet-induced thermogenesis, energy reserve metabolic process, G protein-coupled receptor signaling pathway, feeding behavior, regulation of the metabolic process, and regulation of eating behavior (24).

Several SNPs in *MC4R* have been correlated with obesity since the protein encoded by it plays a vital role in weight control, energy balance, and food intake. Thus, loss-of-function mutations will disrupt the pathways where MC4R is involved (70). For example, Yu et al. reported an association between the C allele in the rs17782313 and a higher risk of developing obesity (71). The frequency of the C allele in Latin America is 0.17, and for the T allele is 0.83 (20, 21). Moreover, more SNPs in the *MC4R* have been associated with alterations in energy balance and food intake, including rs11872992, rs8093815, rs17066856, rs1943218, rs17066829, rs9966412, and the rs17066859 (61, 70–73). On the other hand, gain-of-function mutations have been negatively correlated with obesity (72).

The gene *MTHFR* encodes a protein that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Moreover, it has been highly associated with folate (22, 23). Among its related pathways, the metabolism of glucose is included. Mutations in this gene have been associated with homocystinuria, and neural tube defects (22). The GO: Biological processes correlated with *MTHFR* include neural tube closure, metabolic process, response to vitamin B2, tetrahydrofolate interconversion, and response to folic acid (24).

Single nucleotide polymorphisms in the gene *MTHFR* have been associated with folate deficiency (74, 75). For example, for the SNP rs1801133, individuals with the genotype CT had an enzyme activity of 67%, and individuals with the TT genotype had 25% activity (74). Similarly, reports have found that carriers of the T allele have lower folate levels (76). Moreover, folate deficiency has been identified as an obesity risk factor (77). The frequency of the C allele in Latin America is 0.64, whereas the T allele is 0.36 (20, 21). Based on the allele frequency of the SNP and the association of folate with obesity, an appropriate folate intake is vital for maintaining good health.

The gene *MYRF* encodes a transcription factor involved in the myelination of the central nervous system. The protein promotes the expression of myelin production genes (22, 23). The GO: Biological processes associated with *MYRF* include regulation of transcription, proteolysis, oligodendrocyte development, and central nervous system myelination. Moreover, SNPs in this gene have been associated with obesity (24).

An SNP (rs174537) in the *MYRF* gene has been correlated with different levels of LDL and cholesterol. For example, Tanaka et al. described that carriers of the G allele had higher LDL and cholesterol levels in serum than individuals with the T allele (78). The frequency of the G allele in Latin America is 0.50, the same for the T allele (20, 21). Given the high frequency of the risk allele in the Latin American population, a diet with low LDL and cholesterol should be followed.

The *NOS3* gene is a protein-coding gene located on chromosome 7. The protein encoded is a nitric oxide synthase 3 involved as a biological mediator in different processes.

L-arginine is used as a precursor for nitric oxide synthesis (22). Nitric oxide is related to vascular smooth muscle relaxation, angiogenesis, and blood clotting. Moreover, diseases correlated with *NOS3* are Alzheimer's, stroke, and obesity (22, 23, 79).

The SNP (rs1799983) in the *NOS3* gene has been associated with obesity. For instance, Nasr et al. described an association between rs1799983 and obesity, individuals carrying the T allele had a higher obesity predisposition than carriers of the G allele (79). Similarly, Pawlik et al. found a correlation between the T allele and higher obesity-related parameters, such as a higher BMI (80). The frequency of the T allele in Latin America is 0.24, whereas the G allele is 0.76. Hence, regarding the *NOS3* gene, only a small proportion of the Latin American population may be predisposed to obesity. However, maintaining a balanced diet is crucial to avoid obesity.

The gene *NPY* encodes a neuropeptide associated with several physiological processes, such as circadian rhythms, cardiovascular function, stress response, and food intake (22). The GO: Biological processes of the gene include the neuropeptide signaling pathway, chemical synaptic transmission, feeding behavior, positive regulation of appetite, dopamine metabolic process, and eating behavior. Diseases associated with the *NPY* gene are eating disorders (24).

Moreover, SNPs in the *NPY* have been associated with obesity. For example, Zain et al. described that carriers of the T allele in the SNP (rs16147) were correlated with high obesity parameters such as BMI, triglyceride levels, and body fat percentage, and increased obesity risk in comparison with carriers of the C allele (81). Lin et al. reported similar obesity-associated findings; however, the effects of rs16147 were blunted by a low-fat diet (82). The frequency of the T allele in Latin America is 0.40, whereas, of the C allele, the frequency is 0.60 (20, 21). Based on the high frequency of the T allele, the diet in Latin America should be focused on a low-fat intake.

The gene *PCSK1* is a protein-coding gene located on chromosome 5. The protein encoded by *PCSK1* is part of the subtilisin-like proprotein convertase family, which is involved in the protein and peptide precursors trafficking. Moreover, the protein participates in the activation of neuropeptide precursors and polypeptide hormones (22). Mutations in *PCSK1* have been associated with obesity predisposition (39).

Single nucleotide polymorphisms in the *PCSK1* gene have been correlated with obesity predisposition. For instance, Benzinou et al. described an association between the presence of the C allele in rs6234 and an increased risk of developing severe obesity in a European population (83). Similarly, Nead et al. found that the C allele not only predisposes the carrier to severe obesity but increases the risk of common obesity and higher BMI (84); with a frequency of the C allele in Latin America of 0.23, and for the G allele, 0.77 (20, 21).

PPARG is a protein-coding gene located on chromosome 3. The protein encoded by *PPARG* is a nuclear receptor, part of the peroxisome proliferator-activated receptor subfamily of nuclear receptors. After ligand binding, the protein modulates the peroxisomal beta-oxidation pathway of FAs, glucose homeostasis, and adipocyte differentiation (22, 23). Mutations in the *PPARG* gene have been associated with diseases such as atherosclerosis, diabetes, and obesity (22, 39).

An SNP in *PPARG* has been correlated with obesity. Li et al. described an association between the G allele in the SNP rs1801282 and higher levels of BMI, and total cholesterol, increasing obesity predisposition and hypercholesterolemia, in comparison with CC homozygotes (85). The frequency of the C allele in Latin America is 0.92, and for the C allele is 0.08 (20, 21). Although the risk allele frequency is low, a balanced diet should be followed for a healthy lifestyle.

The *TCF7L2* gene encodes a transcription factor that participates in the Wnt signaling pathway, regulating MYC expression by repressing or activating its transcription. Mutations in the *TCF7L2* gene have been associated with increased blood glucose levels, and diabetes (22, 39). The GO: Biological processes associated include the Wnt signaling pathway, positive regulation of insulin secretion, glucose homeostasis, canonical Wnt signaling pathway, and fat cell differentiation (24).

Furthermore, SNPs in the *TCF7L2* gene have been associated with obesity and diabetes. For example. Wrzosek et al. found that the T allele in the rs7903146 was associated with an increased risk of developing diabetes compared to carriers of the C allele (86). Similarly, Yazdi et al. described a significant association between the T allele in the rs7903146 and type 2 diabetes (87). The frequency of the C allele in Latin America is 0.76, and of the T allele is 0.24 (20, 21). Even though the risk allele frequency is not high in the region, the diet should be focused on a healthy intake of micro and macronutrients.

TFR2 is a protein-coding gene located on chromosome 7. The protein encoded by *TFR2* is a single-pass type II transmembrane protein, part of the transferrin receptor-like family. The protein participates in the cellular uptake of transferrin-bound iron. Hemochromatosis is a disease associated with *TFR2* (22, 23). The GO: Biological processes include iron ion transport and homeostasis, transferrin transport, cellular response to iron ions, and positive regulation of peptide hormone secretion (24).

Moreover, SNPs in *TFR2* have been associated with dysregulations in iron levels. For instance, An et al. found that carriers of the C allele in the SNP rs7385804 correlated with lower serum ion levels, compared to A allele carriers (88). Furthermore, low iron levels have been associated with obesity and anemia (89). The frequency of the C allele in Latin America is 0.3, while of the A allele is 0.7 (20, 21). In Latin America, iron deficiency is a problem; hence, the diet should be focused on reaching the iron requirements and avoiding health issues, such as anemia (90).

The gene *UCP1* is a protein-coding gene located on chromosome 6. The protein encoded is part of the

mitochondrial uncoupling proteins, which are involved in separating oxidative phosphorylation from ATP synthesis, producing heat in this process (22, 23). Moreover, the protein participates in the reduction of the mitochondrial membrane potential in mammalian cells. The *UCP1* gene is only expressed in brown adipose tissue, specialized in heat production (22, 23). The GO: Biological processes associated include diet-induced thermogenesis, mitochondrial transport, response to temperature stimulus, response to nutrient levels, brown fat cell differentiation, and adaptive thermogenesis (24).

Furthermore, SNPs in the *UCP1* gene have been associated with obesity. For instance, carriers of the G allele in the SNP rs1800592 have been correlated with an increased risk of developing moderate obesity in comparison with the A allele. Thus, the SNP could play a role in the initial stages of obesity (91). The frequency of the G allele in the Latin American population is 0.41, whereas the A allele is 0.59 (20, 21). The high frequency of the risk allele in Latin America could be associated with the increasing obesity tendency in the region (4); hence the diet should include an adequate caloric intake. Further studies should be performed in Latin America to understand the extent of the SNP in obesity.

UGT1A1 is a protein-coding gene located on chromosome 2. The protein encoded by *UGT1A1* is a UDP-glucuronosyltransferase, which participates in the transformation of lipophilic molecules, such as hormones, steroids, and bilirubin, into excretable metabolites. However, the enzyme has a higher affinity for bilirubin (22). UGT1A1 is involved in the elimination of endogenous compounds, xenobiotics, and drugs (23). Diseases associated with *UGT1A1* include Gilbert syndrome and dysregulation of bilirubin (22, 39).

Moreover, SNPs in the *UGT1A1* gene have been associated with different bilirubin levels. For example, Abbasi et al. described a correlation between the T allele in the SNP rs6742078 and higher bilirubin levels, in comparison with the G allele (92). Moreover, high bilirubin levels have been related to a higher risk of developing diabetes (93). The frequency of the G allele in Latin America is 0.66, whereas the T allele is 0.34 (20, 21). Thus, the diet in Latin America should include foods that could reduce the bilirubin levels, such as flavonoid-rich fruits and vegetables (94).

Genomics and diet interaction in obesity in the Latin American environment

The application of omics sciences, such as genomics, has facilitated the study of genetic variants in diseases such as obesity. Genetic and environmental factors contribute to obesity. Therefore, it is crucial to analyze the interaction between factors such as gene expression and food intake to implement dietary guidelines. These diets could modify gene expression at the pre-, post-transcriptional, or translational level and reduce the risk of developing diseases (12, 15).

The nutrition effects on metabolic pathways or oxidative and inflammatory stress are the subject of several nutrigenomic investigations worldwide. Carbohydrates, proteins, fats, and vitamins are essential for body's normal function. Various genes have been associated with the absorption of nutrients (95).

Ignatieva et al. designed a compendium comprising 578 human genes controlling feeding behavior and body weight. This compilation included genes from the scientific literature, such as *ADRB2*, *LEP*, *NPY*, *PCSK1*, *PPARG*, *UCP1*, *APOA5*, *IRS1*, and others. Moreover, they found that genes from the compendium list were expressed in seven tissues or organs: adipose tissue, breast tissue, adrenal gland, pituitary gland, pancreas, liver, and whole brain. Each of the tissues and organs plays an essential role in metabolism; for example, the adrenal and pituitary glands control metabolism through humoral signals. Adipose tissue and the breast are related to lipid storage. The liver is essential for lipogenesis, gluconeogenesis, and cholesterol metabolism. Finally, the brain regulates eating behavior through sensory signals such as taste, smell, and texture of food. (95–97).

In this section, a bibliographical selection of several studies that examined the impact of diet on the gene expression of numerous genes involved in various metabolic pathways has been selected. The studies were related to obesity, weight loss, metabolism related to insulin resistance, and elevated lipid and carbohydrate levels.

Table 2 includes a list of dietary factors that influence gene expression of genes involved in various metabolic pathways. This information reveals different comparative approaches, such as (a) The difference between after (post) and before (pre) any intervention (bariatric surgery); (b) the variation between groups consuming distinct types of diet; (c) many studies were performed in small groups of individuals; (d) nine studies used animal models in their research; and (e) some of the studies were published decades ago.

Influence of ADBR2 and ADBR3 on thermogenesis

Obesity is characterized by a long-term imbalance in energy homeostasis, which is influenced by adaptive thermogenesis. The sympathetic nervous system regulates thermogenesis and is produced in muscle and brown adipose tissue. Adipose tissue contains adrenergic receptors like the beta-3 adrenergic receptor (*ADRB3*) and the beta-2 adrenergic receptor (*ADRB2*). Both *ADRB2* and *ADRB3* are receptors for thermogenesis and lipolysis regulation, which provides free FAs for thermogenesis (98).

TABLE 2 Influence of dietary factors in gene expression of genes associated with obesity.

Dietary factors	Target genes	Regulation up or down	Potential health effects	Type sample	References
Lipid metabolism and insulin	ADRB2	Down	The expression of ADRB2 was significantly lower in the adipose tissues of obese patients than in tissues of normal-weight individuals	Adipose tissues	(98)
Lipid metabolism	ADRB3	Down	ADRB3 expression levels in adipocytes were downregulated before the onset of obesity, indicating that reduced ADRB3 expression might be the cause of obesity.	Mature adipocytes and adipose tissue stromal vascular cells	(136)
Triglyceride metabolism	APOA5	Down	The amount of apoA5 was significantly reduced by 69% in the obese group as compared with the non-obese group	Human subcutaneous abdominal adipose tissues	(137)
HDL metabolism	CETP	Up	HDL concentration and CETP expression are correlated; if HDL concentration is higher, CETP expression is also higher.	Subcutaneous abdominal adipose tissue	(138)
Xenobiotic metabolism	CYP1A2	Down	The high-fat diet curtailed the activity and the expression the CYP1A2 in obese male and female mice.	Liver tissue	(139)
Vitamin D deficiency	CYP2R1	Down	Obesity represses CYP2R1 expression in human adipose tissue.	Adipose tissue	(110)
Cholesterol metabolism	CYP7A1	Up	Relative to the high fat diet fed group, the low fat diet fed animals showed reductions in the hepatic expression of CYP7A1.	Hepatic tissue	(140)
Free fatty acid metabolism	FABP2	Down	FABP2 expression was intermediate in the duodenum, highest in the ileum, and close to zero in the colon.	Duodenal, ileum, and colon biopsy samples	(132)
Lipid metabolism	FADS1	Down	FADS1 gene expression was lower in duodenum and jejunum 3 months following Roux-en-Y gastric bypass, compared to before surgery.	Mucosa from stomach, duodenum, jejunum and ileum	(141)
Lipid metabolism	FADS2	Down	FADS1 and FADS2 mRNA levels were significantly reduced in the TT carriers compared with the CC and TT carriers.	Visceral adipose tissues	(142)
Glucose and lipid metabolism	FTO	Up	The relative gene expressions in overweight/obese were significantly decreased at the end of Ramadan intermittent fasting.	Whole blood sample	(121)
Lipid metabolism and vitamin B12 levels	FUT2	Up	Fut2 mRNA had significantly lower expression after Western diet feeding for 20 weeks in an obese mouse model.	Ileum and colon tissue	(143)
Glucose and fat metabolism	GIPR	Down	GIPR expression was downregulated in human adipose tissue from obese patients and correlated negatively with body mass index, waist circumference, systolic blood pressure, and glucose and triglyceride levels.	Human sc adipose tissue	(144)
Insuline resistance	IRS1	Down	The reduced expression of IRS-1 in visceral adipose tissue of morbidly obese people suggests that IRS-1 expression plays a prognostic role in visceral adipose tissue's insulin responsiveness.	Visceral adipose tissue	(145)
Glucose metabolism	LEP	Up	An increased expression of LEP was detected in the subcutaneous fat of the obese group compared to control.	Subcutaneous fat tissue	(146)
Lipid metabolism	LIPC	Down	High-fat diet feeding significantly decreases hepatic lipase activity (LIPC) in mice	Liver tissue	(147)
Appetite regulation	MC4R	Down	They found a significant decrease in MC4R mRNA expression in rats fed a high-fat diet compared to expression levels in rats fed a normal diet.	Adipose tissue	(148)
Folate metabolism	MTHFR	Up	MTHFR expression was directly correlated with severe obesity.	Visceral adipose tissue	(149)

(Continued)

TABLE 2 (Continued)

Dietary factors	Target genes	Regulation up or down	Potential health effects	Type sample	References
Omega 3	MYRF	Up	Several genes were associated with the progression of obesity-associated type 2 diabetes mellitus. Inconclusive results for MYRF.	GEO database: GPL20301 dataset	(150)
Lipid metabolism and obesity	NOS3	Up	Increased gene expression of NOS3 may cause decreased lipolysis of subcutaneous adipose tissue in obesity.	Adipose tissue.	(151)
Appetite regulation	NPY	Up	NPY overexpression in the paraventricular nucleus causes obesity by increasing food intake, whereas NPY knockdown in the hypothalamus promotes energy expenditure.	Hypothalamus rats	(152)
Lipid and cholesterol metabolism appetite regulation	PCSK1	Down	Inconclusive study	Pancreatic tissue of mice	(153)
Lipid and carbohydrates metabolism	PPARG	Up	PPARG mRNA expression is most abundant in serum of obese patients both diabetic and non-diabetic.	Serum	(154)
Insuline resistance	TCF7L2	Down	Obesity was associated with reduced TCF7L2 transcript levels in whole subcutaneous abdominal AT but paradoxically increased expression in adipose progenitor cells.	Subcutaneous abdominal adipose tissue	(155)
Iron levels	TFR2	Up	Increased tfR2 expression and the presence of iron.	Adipose tissues from obese mice	(156)
Glucose and energy balance	UCP1	Up	UCP1 mRNA expression in had significant negative correlations with obesity-related markers.	Abdominal visceral adipose tissue	(157)
Non-alcoholic fatty liver disease Bilirubin levels	UGT1A1	Up	These data demonstrated obesity- and fasting-induced UGT1A1 increased expression in mouse liver.	Liver tissue	(158)

Defective expression of ADRBs on the cell surface or their altered signaling can result in decreased lipolysis and thermogenesis, which may contribute to obesity. *ADRB3* is found primarily on the surface of visceral and brown adipose cells and stimulates sympathetic nerves to release noradrenaline in response to cold temperatures or food consumption. *ADRB2* regulates catecholamine function and may be important in obesity because catecholamines contribute to energy expenditure and lipolysis (99). Research in mice reported that *ADRB2* is also expressed in hypothalamic neurons, confirming its role in the central regulation of eating behavior (100).

CYP1A2

Morbid obesity and changes in body weight and composition are parameters that can influence cytochrome P450 (CYP) superfamily activities and, consequently, drug metabolism. The liver is the main organ responsible for the metabolization and detoxification of xenobiotic molecules, such as caffeine, exogenous toxins, and drugs. The CYP family are drug heme-metabolizing enzymes and play an essential role in protecting the body against both endogenous and exogenous toxic compounds. These enzymes are involved in the metabolism of drugs and phase I toxins, which contributes to the target compounds being more hydrophilic and more easily excreted in the bile or urine. In addition, the dietary composition can alter the expression and activity of many CYP proteins, influencing drug metabolism and disease prevalence. CYP1A2 is one such enzyme, and it is responsible for about 5% of drug metabolism in humans.

Vitamin D deficiency related to *CYP2R1* and *GC*

Certain studies indicate that obesity-related disorders or excess body fat could be associated with vitamin D deficiency (101). Vitamin D is an active prohormone necessary for bone tissue maintenance and calcium and phosphorus homeostasis. Ergocalciferol, often known as vitamin D2, and cholecalciferol, known as vitamin D3, are the two natural forms of vitamin D. D3 is derived from a diet rich in oily fish, liver, egg yolk, and fortified foods such milk, bread, and margarine. In contrast, D2 comes from the conversion of ergosterol, a plant sterol obtained from a diet that includes only plant foods such as yeast and mushrooms (102).

Vitamin D (both D2 and D3 forms) from food is absorbed by bile salts action in the distal part of the small intestine and then transported by vitamin D–Binding Protein (GC), albumin, or LDL to different tissues and organs. When vitamin D enters the liver, it undergoes its first hydroxylation at carbon-25 *via* the enzyme 25-hydroxylase (CYP2R1), making 25-hydroxyvitamin D [25(OH)D], or calcidiol that is biologically inactive (103). The 25(OH)D needs to undergo a second hydroxylation at carbon-1 by the enzyme 1α-hydroxylase (CYB27B1), which is mainly found in the kidneys and produces 1,25-dihydroxy vitamin D [1,25(OH)2D] or calcitriol, to become active. Finally, calcitriol binds to the nuclear vitamin D receptor and regulates calcium homeostasis and bone metabolism (104). This has led to the routine use of measuring the plasma concentration of 25(OH)D to identify people at risk of vitamin D insufficiency.

At the level of Latin America, vitamin D deficiency was classified as a mild, moderate, or severe public health problem, depending on the subgroups evaluated in each country. For example, in Mexico, a 10% prevalence of vitamin D insufficiency was found (25 -hydroxyvitamin D < 50 nmol/L) in adults (102). In addition, a study evaluated the diet in different regions of Latin America, currently obtaining a diet pattern based on total fats, an increase in animal products, and a decrease in the consumption of cereals, fruits, and some vegetables (105). In this sense, Sharifan et al. suggested that a diet characterized by high consumption of fruits, green leafy vegetables, honey, dairy products, olive oil, nuts, legumes, and low consumption of sugar and solid fats was associated with better serum concentrations of 25(OH)D (106). Consequently, the diet could influence the regulation of vitamin D bioavailability. Nevertheless, other studies report that the deficiency of this vitamin is attributed to the lack of exposure to the sun, especially in obese people who, due to their weight, limit their movement and prefer to cover their bodies (107).

Research has shown that obesity suppresses CYP2R1 expression. Studies in mice showed that obesity inhibited the expression of CYP2R1 in mouse livers, which was linked to a decrease in enzyme 25-hydroxylation activity, influencing fluctuations in the levels of 25-OH-D in the blood (108, 109). It shows that decreased vitamin D hydroxylation could play a role in obesity-induced vitamin D deficiency. Another study analyzed CYP2R1 expression from abdominal adipose tissue samples from four female patients who underwent gastric bypass surgery, suggesting that obesity represses CYP2R1 expression in human adipose tissue and that weight loss restores CYP2R1 (110). Decreased CYP2R1 expression could be due to high fat intake affecting the amount of vitamin D absorbed from food. Several studies have reported that vitamin D metabolites can be retained by excess body fat. Likewise, cholecalciferol can be largely sequestered by body fat before being transported to the liver due to its reduced hydrophobicity (107).

Another critical factor affecting 25-OH-D levels is vitamin D binding protein (VDBP) and the GC gene codes for VDBP. The lower plasma concentrations of 25-OH-D may be due to decreased hepatic synthesis of VDBP. In one study they found that, unlike CYP2R1, there is insufficient evidence that obesity influences VDBP expression in mouse liver, suggesting that these two crucial indicators of vitamin D status are controlled differently (110).

CYP7A1 and cholesterol

Cholesterol is a structural component of cell membranes and a precursor of steroid hormones and bile acids. Cholesterol is converted to bile acids in the liver, removing it from the active cholesterol pool and leading to an increase in hepatic LDL receptors and a decrease in plasma cholesterol levels. Bile acids are also excreted into the small intestine, where they act as detergents to aid in the absorption of dietary cholesterol, lipids, and fat-soluble vitamins. Bile acids are reabsorbed in the distal ileum and returned to the liver, but only once per cycle. Thus, cholesterol removal from the body is facilitated by conversion to bile acids, which may also influence plasma cholesterol levels (111).

Dietary cholesterol regulates the expression of many genes in the liver. Cholesterol 7-hydroxylase (Cyp7a1) is a candidate gene for this function. CYP7A1 is a rate-limiting enzyme in the bile acid synthesis pathway; bile acids influence energy expenditure and glucose and lipid metabolism. CYP7A1 is found in the endoplasmic reticulum (ER) of hepatocytes (112).

The research evaluated the effects of diets with 0.0 and 0.5% cholesterol in different mice. They showed that transgenic mice overexpressing Cyp7a1 in the liver were resistant to obesity, fatty liver, and high-fat diet-induced insulin resistance. These results suggest that Cyp7a1 regulation could be an important determinant of plasma cholesterol responsiveness (113).

FADS1 and *FADS2* are regulated by polyunsaturated fatty acids

Polyunsaturated fatty acids are widely acknowledged to have a significant impact on human health. PUFAs have been linked to various clinical outcomes, including obesity and metabolic syndrome. Fatty acid desaturase 1 (*FADS1*) and fatty acid desaturase 2 (*FADS2*) have been studied as candidate genes for endogenous conversion of 18-carbon PUFAs into very long-chain FAs such as arachidonic acid, docosahexaenoic acid, and eicosapentaenoic acid. The lipogenic transcription factors SREBP1c and peroxisome proliferator-activated receptors (PPARs) regulate gene expression of the FADS1 and FADS2, primarily in the liver but also in adipose tissue (114). Several studies have found that high-fat diets reduce the expression of Fads1 and Fads2 in a variety of hepatic models, ranging from human HepG2 cells treated with different PUFAs

to mice and baboons. Furthermore, PUFA-mediated decreases in Fads expression are mirrored in liver fatty acid content (115, 116).

One study evaluated FADS1 and FADS2 expression in adipocytes treated with α-linolenic, linoleic, eicosapentaenoic, or arachidonic acid. They observed reductions in the expression of the FADS2 protein gene but not in FADS1. Concluding that these adipocytes have a functional FADS pathway that can be regulated by PUFA (117).

Relationship of glycogenesis and lipogenesis with *FTO*

Alpha-ketoglutarate-dependent dioxygenase (FTO) is the gene with the most significant impact on obesity. FTO acts as a cellular sensor for some nutrients like lipids and glucose (118, 119). FTO regulates the expression of hepatic gluconeogenic genes such as G6PC (Glucose-6-phosphatase) and PCK (Phosphoenolpyruvate carboxykinase) by altering the activity and interaction with transcription factors such as STAT30 (Signal Transducers and Activators of Transcription 3), CREB (protein cAMP-responsive element binding), and ATF4 (activating transcription factor 4) (120). Increased FTO expression causes increased transcription of genes encoding gluconeogenic enzymes, leading to increased gluconeogenesis, while decreased FTO expression causes the opposite effect (121). For example, Doaei et al. report that the FTO expression level in peripheral blood mononuclear cells increased in obese individuals (122). Furthermore, FTO regulates hepatic lipid metabolism by changing the methylation status of genes involved in fatty acid oxidation, lipolysis, and *de novo* lipogenesis. Increased FTO expression decreases CPT1, LIPE, and ATGL mRNA expression, resulting in decreased fatty acid oxidation and lipolysis. It also raises ATF4 expression, which stimulates the expression of lipogenic genes, resulting in increased *de novo* lipogenesis in the liver (120).

FUT2

Vitamin B12 is obtained from food or synthesized by microorganisms in the gut in humans. Three proteins in the body are responsible for its absorption, transport, and cellular uptake: haptocorrin, intrinsic factor, and Transcobalamin II (123). Vitamin B12 is essential for many processes, including the formation of red blood cells, DNA synthesis, and the maintenance of the myelin nerve sheath. Variations in the FUT2 gene may increase the risk of Helicobacter pylori (H. pylori) infection and the associated gastric-induced vitamin B12 malabsorption. Infections with H. pylori in the human intestine have been shown to inhibit the release of intrinsic factors, required for vitamin B12 absorption (124).

A study reported that the association between genetically low vitamin B12 concentrations and cardio-metabolic traits could be modified by dietary intake. They evaluated in a Brazilian population, the metabolism and concentration of vitamin B12. As a result, they showed a significant interaction between dietary carbohydrate and protein intake on LDL cholesterol and homocysteine concentrations in obese individuals (125).

Leptin

Imbalanced expenditure of energy leads to excess body fat. The leptin (LEP) hormone plays a significant role in the energy balance and control of body weight. Levels high of leptin are associated with obesity. Furthermore, obese patients with insulin resistance have a higher concentration of circulating leptin than normal-weight people (126). Insulin resistance is facilitated by leptin, a negative regulator of insulin.

Leptin is also involved in other physiological processes, such as glucose metabolism. Thus, through activation of its LEPR receptor, leptin reaches numerous brainstem regions, including the hypothalamus, helping regulate glucose and energy balance. Another way to reverse the high glucose levels or increase insulin sensitivity is indirect hypoglycemia, where glucose binds to the liver's leptin receptor to regulate hepatic glucose metabolism (109). When leptin is present, the body's tissues can absorb more insulin and glucose. Therefore, if there are alterations in leptin receptor expression or inhibition of the activator of transcription-3 (*STAT-3*), the leptin signaling pathway will not be activated (127, 128).

Dietary factors, such as overeating, including fats or sugars, can generate molecular mechanisms that lead to leptin resistance (129). For example, dietary sugar and saturated fat elevate plasma triglycerides, and several animal and human studies demonstrate how particular macronutrient patterns correlate with circulating leptin levels. In a study of healthy women, an increase in carbohydrate intake (bread, rice, and sugar) led to plasma leptin levels increasing by 28% and an increase in energy expenditure of 7%. Therefore, fructose removal from high-fat diets can reverse leptin resistance (130).

Proprotein convertase subtilisin/kexin type 1

Obesity is associated with changes in the melanocortin pathway, a crucial factor in energy homeostasis. The central melanocortin system regulates food intake and energy expenditure through pro-opiomelanocortin (POMC) neurons. POMC is cleaved sequentially by two prohormone convertases, PC1/3, and PC2, and processed by three enzymes to at least three melanocortin peptides. These peptides are essential

melanocortins involved in the regulation of appetite and body weight (37).

Prohormone convertase 1/3 (PC1/3) is encoded by the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene. Various human genetics studies have associated PCSK1 with metabolic phenotypes such as early onset obesity, intestinal malabsorption, gastrointestinal complications, diabetes, and reactive hypoglycemia (38, 39). The availability of various PCSK1 mouse models made it possible to investigate its function and expression in different tissues (brain, brainstem, pancreas, intestine, stomach, and immune cells) (40, 41).

TCF7L2

TCF7L2 encodes a protein that acts as a transcription factor and participates in the formation of pancreatic β-cells needed to reduce blood sugar (97). One study evaluated the association between TCFL2, obesity, and diabetes in adipose tissue, reporting that TCFL2 expression decreased in rats fed a 60% fat diet compared to a 10% fat diet. Based on these findings, the researchers suggest that reduced TCFL2 expression in adipocytes could lead to reduced glucose or lipid metabolism due to a high-fat diet (42). A study conducted on Chileans, the world's largest consumers of sugar-sweetened beverages, suggested adverse effects in individuals who consume at least two sugar supplies per day. In addition, their findings link obesity, diabetes and genetic susceptibility involving the TCF7L2 and MTNR1B genes. The role of TCF7L2 in the development of these conditions may be because this gene influences the regulation of glucose metabolism through the WNT signaling pathway (43).

Other genes related to obesity and metabolic pathways

The FABP2 gene codes for a protein that binds to FAs in the intestine and promotes active transport across the intestinal wall membrane; only the epithelial cells of the small intestine contain the intracellular protein. Hydrophobic FAs are transported from the plasma membrane to the ER *via* the aqueous cytosol by FABP2. In the ER, FAs are esterified with glycerol-3-phosphate (G3P) to form triglycerides. The triglycerides are packaged into chylomicrons, which circulate in the plasma. (131). A study confirmed that deletion of the FABP2 gene in mice results in weight gain and higher circulating triglyceride concentrations compared to wild-type mice (132).

PPARG and *CET* are two other genes involved in lipid metabolism. The PPARG gene encodes the nuclear receptor, which induces the proliferation of peroxisomes that regulate the transcription of several genes involved in the human body's metabolism of lipids and carbohydrates, and inflammatory processes (133). The *CETP* gene is essential in lipid metabolism because it encodes the cholesterol ester transporter protein, which converts HDL cholesterol into LDL. High cholesterol levels and dietary fat intake cause an increase in CETP mRNA and protein concentration (134).

Finally, apolipoprotein A5 is the protein encoded by the *APOA5* gene. It plays a crucial role in regulating the level of triglycerides in the blood plasma (135).

Future perspectives

The accelerated increase in the prevalence of obesity in Latin America makes it essential to develop nutrition-focused intervention strategies for the region focus on their eating patterns. Genetics and genomics in nutrition are tools that constitute the basis of understanding the genes pathways that are being affected due to nutrition leading to a greater susceptibility to obesity. In the future, it is intended to achieve personalized customization of the nutritional requirements of different populations and individuals based on the genetic inheritance of variants, ethnicity, and gene expression.

In this context, most of the studies in genetics, genomics, and epigenetics interactions with diet have been developed in European or North American countries. Therefore, association studies of genetic predisposition to obesity in the region are required. Moreover, the Latin American population is genetically different, marked by a mix of ethnic groups. Population in which the dietary improvements could potentially prevent deaths caused by obesity and the potential development of chronic diseases.

Furthermore, personalized medicine must be based on genetic evidence and environmental analysis as tools to prevent chronic diseases like obesity. Integrating new techniques or data obtained from genetics and genomics approaches in obesity could achieve a better quality of life and prompt response in the population of Latin America.

Lastly, nutrition programs should be promoted in Latin American environments where processed food and sugary drinks are a fundamental part of the diet. With the aim to make the population understand the relevance of healthy nutrition from an early age. Meanwhile, there are package labeling systems in several Latin American countries. However, it is still necessary to implement other measures that directly reach the consumer and create healthcare awareness through healthy eating.

In conclusion, several genes and their SNPs have been associated with obesity and obesity-related issues; however, only 7 of the 39 risk alleles have high frequencies in the mixed Latin American population. The risk alleles have been correlated with high total cholesterol, low HDL, vitamin D and B12 deficiency,

and obesity predisposition. Furthermore, high-fat dietary behaviors could induce gene expression profiles related to insulin intolerance, lipolysis dysregulation, imbalanced energy expenditure, glucose dysregulation, and vitamin deficiency. Although the Latin American genetic background may not have an increased obesity genetic risk, the population should be aware of the dietary behavior in their environment to include all the necessary nutrients and avoid high-fat foods.

Author contributions

PG-R, SC-U, and AZ: conceptualization and writing – review and editing. EP-C, RT-T, and VR-P: research. AZ and DS-R: supervision and conceptualization. All authors contributed to the article and approved the submitted version.

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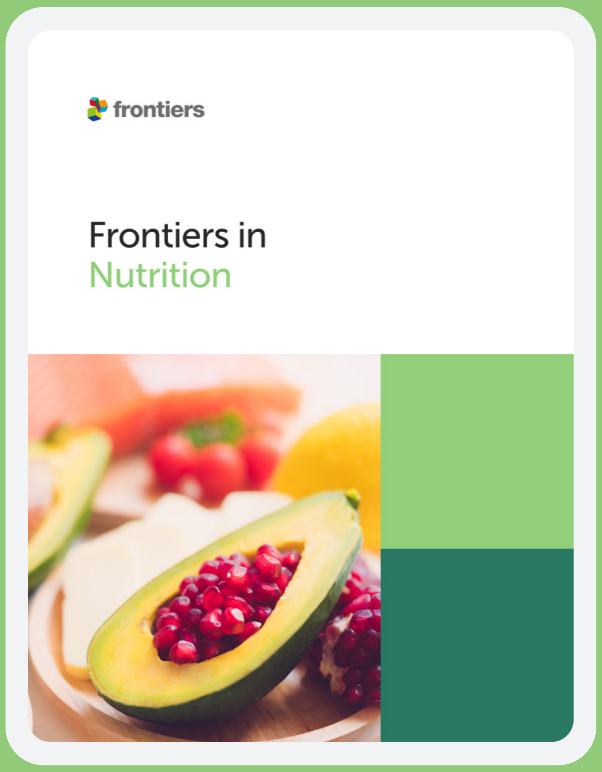

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