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New insights on the management of obesity with nutrition and physical activity

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New insights on the management of obesity with nutrition and physical activity

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Editorial: New insights on the management of obesity with nutrition and physical activity

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Editorial on the Research Topic
New insights on the management of obesity with nutrition and physical activity

Introduction

Obesity is a rampant global epidemic that is associated with excessive accumulation of body fat, with psychological, social and somatic consequences affecting the quality of life (1–4). The World Health Organization (WHO) classified obesity as a chronic disease in 1997, declaring it as "the first non-infectious epidemic in history and a major problem in the world" (5). Obesity-related health concerns affecting children, adolescents, and adults have reached epidemic levels in both industrialized and developing countries (3, 4). The health risks and health care costs of childhood, adolescent, and adult obesity are considerable and include metabolic disorders, earlier puberty and menarche in girls, type 2 diabetes, hypertension, sleep apnea, adulthood obesity, and higher rates of mortality in young adults (6). Overweight and obesity among children, adolescents and adults are likely to be the result of complex interactions between genes, lifestyles, dietary habits, and socioeconomic factors. There is limited data on the determinants such as lifestyle behaviors, psycho-physiological factors, dietary habits, and familial factors leading to obesity and overweight (6).

An unhealthy lifestyle, including low levels of physical activity and increased intake of calorie-rich foods, is a key factor accelerating obesity (7). Implementation of appropriate nutrition and physical activity in individuals with overweight and/or obesity may improve the health of patients, especially those with adverse health consequences due to increased fat mass and adiposopathic metabolic consequences (8). Nutrition education and/or appropriate physical activity are important components in the management of individuals with obesity (9). However, despite the fact that a good diet and physical activity are known to confer protection against obesity, the molecular and cellular mechanisms that mediate the metabolic benefits of nutrition and/or physical activity remain unclear.

To clarify the effects of various aspects and interventions (nutrition, physical activity and others) in managing overweight and obesity in children, adolescents and adults, we launched a Frontiers Research Topic entitled "*New insights on the management of obesity with nutrition and physical activity*". Accordingly, the goal of this Research Topic was to provide findings from original research and or review articles on the effects of physical activity and/or nutrition on the treatment of obesity.

Summary of selected articles from this Research Topic

Twenty-three manuscripts were received for this Frontiers Research Topic. After rigorous review, nine articles were finally accepted for publication. The contributing 58 authors were from five countries, including Canada, China, Portugal, Spain and Saudi Arabia. This Research Topic received more than 11,000 views and downloads as of September 2023. The key contents and findings of each paper are as follows:

Alsulami et al.

In this study, Alsulami et al., evaluated obesity prevalence, physical activity, and dietary practices among Saudi adults in the Makkah region of the Kingdom of Saudi Arabia (KSA).

The authors used a validated questionnaire, Arab Teens Lifestyle Study (ATLS), to evaluate the physical activities, sedentary behaviors, and nutritional habits in addition to demographic data. Their results show that overweight and obesity was prevalent in 32.8 and 23% of the population, respectively, and that sociodemographic factors were associated with obesity. However, focused intervention strategies are needed to overcome the prevalence of obesity in KSA.

Chen et al.

The study by Chen et al. explored the associations of different types of unsaturated fatty acids (FAs) with overweight/obesity risk among the Chinese population. The study enrolled 8,742 subjects free of overweight/obesity at entry in the China Health and Nutrition Survey (CHNS) that were followed until 2015. Dietary unsaturated FAs were assessed by 3-day 24-h recalls with a weighing method in each wave. Cox regression models were used to obtain the hazard ratios (HRs) and 95% confidence intervals (CIs) for overweight/obesity risk associated with unsaturated FAs. The results demonstrated that higher dietary intake of monounsaturated FAs was associated with a lower overweight/obesity risk, which was mainly driven by dietary oleic acid from either plant or animal sources. Intakes of α-linolenic acid, n-6 polyunsaturated FAs and linoleic acid were related to a higher risk of overweight/obesity. The authors concluded that their results support consuming more monounsaturated FAs for maintaining a healthy body weight among the Chinese population.

Lages et al.

The study of Lages et al. from Center for Innovative Care and Health Technology based in Polytechnic of Leira (Portugal) characterized the chronotype and determine its relation to the phenotype and dietary patterns of healthy patients and those with obesity.

The characterization of the chronotype and the circadian system as a phenotype is innovative and should be taken into consideration in patient-specific forms of obesity in order to develop targeted nutritional interventions. Dietary intake and sleep quality was assessed using validated questionnaires. Body composition was also assessed and blood samples taken to quantify circadian and metabolic biomarkers. This study has helped improve our understanding of the complex mechanisms underlying obesity.

Ma et al.

The study by Ma et al. investigated how Chinese adolescents' lifestyles clustered into different lifestyle patterns, and analyzed the correlation between these patterns and adolescent overweight and obesity. The investigated respondents included 13,670 adolescents aged 13–18 from various administrative regions in China. The studied demonstrated that there was a coexistence of healthy behaviors and health-risk behaviors in the lifestyle clustering of Chinese adolescents. Low physical exercise and high intake of snacks and carbonated beverages were the most common. Physical exercise and health consciousness were the protective factors of overweight and obesity in adolescents.

Salas-González et al.

The health risks of sedentary lifestyles are of increasing global concern, particularly in growing children. Many children and young adults seem addicted to electronic devices, are less likely to actively participate in sports and end up with less quality sleep, and it is likely that these traits will persist in adulthood. A study of Spanish primary school children from five geographic regions ($n = 839$ from 22 schools, aged 8–13 years, 51.1% girls) examined the relationship between 24 h movement guidelines (jointly self-reported by parents and children) and insulin resistance (calculated using the HOMA index). Plasma glucose and insulin levels were also measured. Those children (particularly girls) with insulin resistance had more sedentary lifestyles, while those who were more active had improved metabolic parameters—about half of the study group did not meet recommended movement guidelines, with better adherence to recommended total sleep times for this age group. A strength of the report by Salas-González et al. is studying a multitude of lifestyle factors (e.g., screen time, sleep time, movement), showing the importance of understanding the role of a combination of these coexisting choices.

Shengyu et al.

The report by Shengyu et al. from Department of Economics and Management based in Changsha University (China) identified some risk factors affecting exercise behavior among overweight and obese people in China. This large-scale study of over 3,300 individuals considered the lifestyles of obese people. The study showed that the proportion of active physical activity among obese people was 25%. Groups with better sexual and reproductive health, higher levels of education and income were more likely to take part in sport. Obese people who lived in rural areas, were single or divorced, or in the 35–40 age bracket, had a significantly lower percentages of engagement in active physical activity. Health promotion programs for those who are obese need to be further strengthened and targeted to get closer to WHO recommendations.

Tu et al.

The study by Tu et al., explored changes in physical characteristics in preschool children from 2000 to 2020, and forecast development trends over the next 10 years. The results show that the growth and nutritional status of Chinese preschoolers improved dramatically over the past 20 years, but that overweight and obesity remains. Overweight and obesity rates are expected to continue to increase rapidly over the next 10 years, particularly among boys, and effective measures should be taken to control the obesity epidemic.

Wang et al.

The report by Manda Wang from Shunchang Li's group based in Chengdu Sport University adds to their other studies on the metabolic effects of MOTS-c, an endogenously produced regulator of metabolic homeostasis that stimulates glucose uptake and increases insulin sensitivity. The cardiovascular effects of MOTS-c include improved endothelial function, a hallmark of diabetes in humans and animal models. The study by Wang et al. reports on the cardiac structural and functional benefits of treating a rat model of type 2 diabetes with MOTS-c. Levels of endogenous MOTS-c are reduced in diabetes, and the results this study indicates that restoring MOTS-c levels with exogenously administered MOTS-c (i) repaired mitochondrial damage, (ii) restored cardiac systolic and diastolic function, (iii) improved gene regulation of fatty acid metabolism, immunoregulation, angiogenesis and apoptosis. These data provide the first molecular evidence that MOTS-c improves cardiovascular function in diabetes.

Yu et al.

Yu et al. conducted a systematic review and network meta-analysis (NMA) by comparing adjuvant therapy with different nutritional supplements for overweight and obese adults, so as to provide a reference for clinical practice. The study show that nutritional supplementation lowered cardiovascular disease risk factors in overweight and obese patients. Probiotic supplementation might be the best intervention for blood glucose control; Vitamin D, probiotic + omega-3 have a better impact on improving lipid metabolism.

The editors of this volume are extremely grateful to the authors for their contributions and hard work sharing their research insights. We hope the readers of these papers will benefit from this Frontiers Research Topic and utilize the information herein to advance their scientific pursuits.

Author contributions

HZ: Conceptualization, Writing—original draft, Writing—review and editing. CT: Conceptualization, Writing—original draft, Writing—review and editing. KJ: Conceptualization, Writing—original draft, Writing—review and editing. IL: Conceptualization, Writing—original draft, Writing—review and editing.

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Correlation between lifestyle patterns and overweight and obesity among Chinese adolescents

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Lifestyles such as physical exercise, sedentary behavior, eating habits, and sleep duration are all associated with adolescent overweight and obesity. The purpose of this study was to investigate how Chinese adolescents' lifestyles clustered into different lifestyle patterns, and to analyze the correlation between these patterns and adolescent overweight and obesity. The investigated respondents included 13,670 adolescents aged 13–18 from various administrative regions in China. Latent class analysis was employed to cluster the lifestyles of adolescents, $\chi 2$ test and Logistic regression were used to explore the relationship between lifestyle patterns and overweight and obesity in adolescents. The results identified 6 types of Chinese adolescents' lifestyle patterns, as well as the significant differences in gender and age. The adolescents with high exercise-high calorie diet had the lowest risk of overweight and obesity, and the adolescents with low consciousness-low physical activity and low consciousness-unhealthy had the highest risk of overweight and obesity, which were 1.432 times and 1.346 times higher than those with high exercise-high calorie diet, respectively. The studied demonstrated that there was a coexistence of healthy behaviors and health-risk behaviors in the lifestyle clustering of Chinese adolescents. Low physical exercise and high intake of snacks and carbonated beverages were the most common. Physical exercise and health consciousness were the protective factors of overweight and obesity in adolescents.

KEYWORDS

overweight and obesity, lifestyle, dangerous behavior, physical exercise, adolescent

Introduction

In the recent decades, overweight and obesity have been highly prevalent among children and adolescents populations, and moreover, it has proved to be a major challenge of global health (1). The related data indicated that it was expected that the global obesity of children and adolescents would increase by 60% in the future 10 years, and the total number would reach 250million by 2030, which would undoubtedly put great pressure on the world public health system (2). With the improvement of social development and economic level, the lifestyle and dietary pattern of Chinese adolescents have undergone tremendous changes (3, 4). In the recent 40 years, the height and weight of Chinese teenagers has presented an upward trend, at the same time, the overweight and obesity rate of teenagers has also continued to rise. According to Report on Nutrition and Chronic Diseases of Chinese Residents (5), the overweight and obesity rate of children and adolescents aged 6 to 17 in China has reached 19%, and the growth rate of children's overweight and obesity from 2002 to 2012 was 3.44 times that of adults. Obesity has seriously affected the physical and mental health development of children and adolescents (6).

Overweight and obesity in adolescence would significantly increase the morbidity rate of metabolic disorders, insulin resistance and diabetes, cardiovascular disease, nonalcoholic steatohepatitis, musculoskeletal and psychological disorders. In the meanwhile, it was significantly associated with the health status in their adulthood periods (7–10). In view of the complexity and long-term properties of overweight and obesity in the process of occurrence and development, as well as the immaturity of adolescents' physical and mental development, improving lifestyle-related behaviors and environments has been a scientific method characteristics with safety and economy (11). Under the described background, many studies have been conducted in the aspect of the interaction between overweight and obesity with a variety of lifestyle factors such as physical exercise, sedentary behavior, eating habits and sleep duration. The results illustrated that lifestyle had a direct impact on adolescent overweight and obesity (12, 13). In addition, health-risk behaviors are not isolated as a major contributor to overweight obesity in adolescents, and these behaviors may gradually stabilize or increase further in adulthood (14). Therefore, assessing the lifestyle characteristics of adolescents can identify important factors that contribute to obesity, thereby determining their risk of overweight obesity and developing interventions. In addition, it can also provide a reference for determining the clinical manifestations of cardiometabolic diseases and the clinical manifestations in the subclinical inflammatory process.

In the current status, limited to objective conditions and reality, most studies put more emphasis on the impact of a single behavioral factor on overweight and obesity in adolescents. Although the related factors have been controlled, the explanatory power for complicated interactions was limited (15). It has been demonstrated that when a single negative health behavior and various positive health behaviors occurred simultaneously, lifestyle behaviors were not necessarily associated with negative health outcomes (16). In fact, human behavior is inherently multivariate and interactive. For example, physical activity, sedentary behaviors, and eating habits may behave in more complex ways, with cumulative effects on obesity development in adolescents (17). In this regard, cluster analysis and other "individual-centered" research paradigms were employed to analyze the lifestyles of adolescents, so as to restore the daily lifestyle more comprehensively. Current research has focused on clustering analysis of physical activity, sedentary behavior and eating behavior in adolescents. Other components of lifestyle, such as sleep habits and health awareness, are also significant variables affecting adolescent obesity, so future research should be analyzed from a multifactorial perspective of adolescent lifestyle behavior. In addition, the vast majority of such surveys were conducted in high-income countries, with a lack of research in middle- and low-income countries (18). The lifestyle patterns that lead to adolescent obesity are more complex, and are significantly related to factors such as race, culture, and social psychology, and more research support is still needed.

In the present paper, the lifestyles of adolescents such as physical exercise, sedentary behavior, eating habits, sleep duration were taken as a whole. The subgroups of Chinese adolescents' lifestyles were analyzed through latency class analysis to understand the accumulation of dangerous health behaviors in their lifestyles. Moreover, the differences of overweight and obesity among the adolescents with different lifestyle patterns were compared and analyzed to explore the correlation between lifestyle patterns and overweight and obesity. The present work aims to provide a theoretical basis for the individualized intervention of overweight and obesity, so as to effectively reduce the risk of overweight and obesity among the adolescents.

Methods

Study design and participants

According to the six administrative regions (East China, North China, Central South China, Northwest China, Southwest China, and Northeast China) regulated by Chinese traditional administrative regions, about 200 male and 200 female students in each grade of junior high school were selected by the class cluster sampling method, following the ratio of about 1:1 for men and women, urban and rural areas, and north and south regions. From September to November 2019, in the cities of Nanjing, Datong, Wuhan, Lanzhou, Kunming, and Changchun, respectively, through the Adolescent Living Habits Questionnaire, the basic information and lifestyles of nearly 15,000 children and adolescents in China were collected. Eventually, a total of 13,670 valid data were obtained, including 6,911 boys and 6,759 girls aged from 13 to 18 years.

Before starting the investigation, the research group conducted unified training on the specific requirements of the test for the participating investigators. In the survey, the investigators used the time of the class meeting class or self-study class, accompanied by the class teacher or the classroom teacher, to explain the questionnaire content, fill in the precautions and answer questions on the spot. Students fill out the questionnaire themselves after obtaining informed consent.

Investigators distributed and collected questionnaires on the spot, and eliminated questionnaires with logical contradictions.

BMI and lifestyle related behavior measures

1) Classification criteria of body mass index (BMI). During the test, the participate is required to wear barefoot and single clothes and pants on the instrument, and measure the height and weight of children and adolescents in accordance with the requirements of physical health standards (19). BMI = weight (kg)/[height (m)]^2, and the classification standard is in accordance with the WHO standard (20): ≥1 s to 2 s represents overweight, and >2 s represents obesity.
2) Health consciousness (21): Emphasis on health and physical exercise consciousness are ordinal level variables with 5 categories. According to the respondents' answers, we assign 1 to "not important," 2 to "generally important," 3 to "relatively important," 4 to "important," 5 to "very important." "Very important" and "important" are defined as healthy, while the others are defined as unhealthy.
3) Physical activity (22, 23): The Physical Activity Level Assessment Questionnaire for children and adolescents aged 7 to 18 years in China was used to investigate the PA status. Exercise time survey: mainly investigated the amount of time testers engaged in physical activity per day, classified as healthy (>60 m/d) or unhealthy (≤60 m/d). Video Screen Time Survey: The survey mainly investigated the amount of time testers spent watching TV, playing games and browsing mobile phones per day, classified as healthy (<2 h/d) defined or unhealthy (≥2 h/d). Mode of travel to and from school survey: The survey mainly investigated the mode taken by the testers to travel to and from school each day, defining regular walking and cycling as healthy and others as unhealthy.
4) Sleep duration (24): The actual daily sleep duration was used to assess the sleep duration of adolescents, which was classified as healthy (≥6 h/d) or unhealthy definite (<6 h/d).
5) Eating behavior (25): The frequency of breakfast, snacks and carbonated beverages was investigated, with "mostly eat/drink" being ≥4 times per week, "occasionally eat/drink" being 2–3 times per week, and "hardly eat/drink" being ≤1 time per week. Breakfast intake≥4 times/week is defined as healthy, and <4 times/week is defined as unhealthy. Snack intake <2 times/week is defined as healthy, and ≥2 times/week is defined as unhealthy. Carbonated beverage intake <2 times/week is defined as healthy, and ≥2 times/week is defined as unhealthy.

Statistical analysis

Firstly, Mplus 8.3 software was used to cluster 10 variables related to lifestyle by latent class analysis, and the lifestyle pattern was determined according to the model fitting index. A stepwise regression method was used to fit the latent classification model. The study carried out fitting from the potential states 1–7, and the optimal model was selected based on the fitting index value of each model. The evaluation of model fitting degree was mainly based on Log (L) (Log Likelihood), AIC (Akaike information criteria), BIC (Bayesian information criteria), aBIC (Adjusted Bayesian information criteria) values, etc. The smaller the value was, the better the model fitting degree would be, in which BIC was the optimal indicator (26). On the basis of the indicators of the fitting model and the principle of model category simplicity, six categories of latent models were finally selected in this study.

Secondly, SPSS 24.0 statistical software was employed to compare the category probability of different lifestyle patterns of adolescents, and then the gender and age differences in lifestyle patterns were analyzed through multiple logistic regression analysis. Finally, chi-square test was employed to compare the detection rates of overweight and obesity among the adolescents with different lifestyle patterns, and the correlation was analyzed by binary logistic regression analysis, with the test level $\alpha = 0.05$.

Results

Descriptive characteristic of the sample

The final study sample consisted of male (82.3%; n = 6911) and female (82.6%; n = 6759), with a mean age of 15.50 years (SD = 1.705 year), and 17.5% reported their nutritional status as "overweight and obesity". Participant characteristics and lifestyle-related behavior are outlined in Table 1.

Latent class descriptions

The study selected the optimal model based on the values of each model fitting index and the fitting results are shown in Table 2.

Based on the fitting results, six categories of potential models were finally selected for this study. Each class was named according to the conditional probabilities of 10 variables of 6 classes of the latent model.

In Class 1, among the variables of the emphasis of health, physical exercise consciousness, physical exercise time, video time, weekend leisure mode, etc., the probability of negative health behavior was relatively higher. Therefore, class 1 was named as "low consciousness-low physical activity" class.

TABLE 1 Basic characteristics of the sample.

Variable	Variable description	Male	Female	Overall
Sample size	*n*	6911	6759	13670
Nutritional status	Normal	82.3%	82.6%	82.5%
	Overweight and obesity	17.7%	17.4%	17.5%
Age	Years	15.49 ± 1.708	15.50 ± 1.703	15.50 ± 1.705
School age	Junior high school	50.1%	49.8%	49.9%
	Senior high school	49.9%	50.2%	50.1%
Place of residence	Large and medium-sized cities	37.6%	35.2%	36.4%
	Small cities	37.8%	39.5%	38.7%
	Villages and towns	24.5%	25.3%	24.9%
Regions	East China	16.6%	16.8%	16.7%
	North China	16.6%	16.3%	16.4%
	South central	16.7%	16.6%	16.6%
	Northwest	16.9%	16.4%	16.6%
	Southwest	16.6%	17.2%	16.9%
	Northeast	16.7%	16.8%	16.8%
Emphasis on health	Healthy	46.8%	38.6%	42.7%
	Unhealthy	53.2%	61.4%	57.3%
Physical exercise consciousness	Healthy	82.4%	78.1%	80.3%
	Unhealthy	17.6%	21.9%	19.7%
Physical exercise time	>60 m/d	20.6%	8.6%	14.7%
	≤60 m/d	79.4%	91.4%	85.3%
Video time	<2 h/d	82.1%	85.2%	83.6%
	≥2 h/d	17.9%	14.8%	16.4%
Sleep duration	≥6 h/d	80.9%	80.2%	80.5%
	<6 h/d	19.1%	19.8%	19.5%
Way of going and leaving school	Positive	53.9%	48.5%	51.2%
	Negative	46.1%	51.5%	48.8%
Weekend leisure mode	Time outside ≥ time at home	45.6%	36.6%	41.1%
	Time outside< time at home	54.4%	63.4%	58.9%
Breakfast intake	≥4 times/week	78.4%	79.3%	78.8%
	<4 times/week	21.6%	20.7%	21.2%
Snacks intake	<2 times/week	21.7%	13.2%	17.5%
	≥2 times/week	78.3%	86.8%	82.5%
Carbonated drinks intake	<2 times/week	27.2%	36.1%	31.6%
	≥2 times/week	72.8%	63.9%	68.4%

The result in the table is percentage /% or mean ± standard deviation.

In Class 2, the subjects tended to have positive health behaviors in the probability of 9 explicit variables except physical exercise, which was named as "moderate exercise-balanced" class.

In Class 3, the subjects tended to have negative health behaviors in physical exercise, snacks and carbonated beverage intake, so they were named as "low exercise- high calorie diet" class.

In Class 4, the subjects tended to have negative health behaviors in the explicit variables, and they were named as "low consciousness-unhealthy" class.

In Class 5, the subjects tended to have negative health behaviors in the three variables related to diet, so they were named as "low diet behavior" class.

In Class 6, the positive health behaviors of the research subjects were the most obvious, physical exercise time, and the intake of snacks and carbonated beverages tended to be negative health behaviors. Therefore, they were named as "high exercise-high calorie diet" class.

The conditional probabilities of the 6 latent classes are shown in Figure 1.

TABLE 2 Fitting results of lifestyle latent class analysis (LCA).

Model	K	AIC	BIC	aBIC	Entropy	BLRT	LMR
1-Class	10	150625.393	150700.623	150668.843			
2-Class	21	149144.943	149302.925	149236.89	0.381	**	**
3-Class	32	148311.419	148552.154	148450.461	0.505	**	**
4-Class	43	147914.335	148237.822	148101.172	0.488	**	*
5-Class	54	147693.925	148100.165	147928.558	0.432	**	**
6-Class	65	147548.694	148037.686	147831.122	0.490	**	**
7-Class	76	147493.559	148065.304	147823.783	0.536	**	

*Represents $P < 0.05$, **Represents $P < 0.01$.

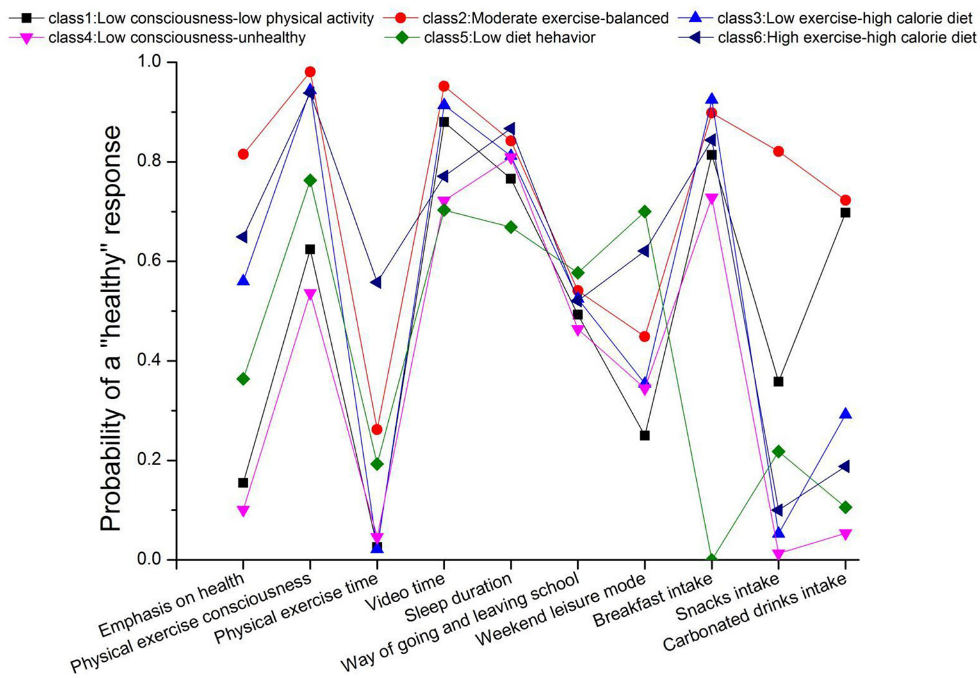

FIGURE 1
Description of the patterns of healthy lifestyle preferences. X-axis, indicators of lifestyle preferences (i.e., emphasis on health, physical exercise consciousness); y-axis, probability of a "healthy" response to each lifestyle preferences conditional on latent class membership.

Descriptive statistics of adolescents' lifestyle patterns

The class probabilities of adolescents' lifestyle patterns were listed as follows: "low consciousness-low physical activity" class (class 1) 13.4%, "moderate exercise-balanced" class (class 2) 7.2%, "low exercise-high calorie diet" class (class 3) 43.4%, "low consciousness-unhealthy" class (class 4) 16.1%, "low diet behavior" class (class 5) 8.2% and "high exercise-high calorie diet" class (class 6) 11.8%. Then, chi square test was employed to compare the class probability of lifestyle patterns among different groups. The results indicated that there were significant differences in the class probability of lifestyle patterns in the groups with different ages and genders ($P < 0.01$).

The logistic regression analysis was carried out with gender and age as the predictive variables, and 6 lifestyle patterns as the dependent variables. The results indicated that compared with "low consciousness-low physical activity" class (class 1), female students were less possible to enter "high exercise-high calorie diet" class (class 6) (OR = 0.335, 95%CI = 0.291–0.386), "moderate exercise-balanced" class (class 2) (OR = 0.449, 95% CI = 0.383–0.527) and "low diet behavior" class (class 5) (OR = 0.616, 95% CI = 0.530–0.715). Compared with the "high exercise-high calorie diet" class (class 6), the junior high

TABLE 3 Class probability of lifestyle patterns.

	Class 1: Low consciousness-low physical activity type	Class 2: Moderate exercise-balanced type	Class 3: Low exercise - high calorie diet type	Class 4: Low consciousness - unhealthy type	Class 5: Low diet behavior type	Class 6: High exercise - high calorie diet type
Overall	13.4%	7.2%	43.4%	16.1%	8.1%	11.8%
Gender						
Male	11.8%	9.1%	39.2%	14.4%	9.2%	16.4%
Female	15.0%	5.3%	47.7%	17.8%	7.2%	7.0%
Value of χ^2			451.968			
Value of P			0.000			
OR (95% CI)	1	0.449 (0.383–0.527)	–	–	0.616 (0.530–0.715)	0.335 (0.291–0.386)
Age group						
Junior high school	12.5%	8.1%	41.6%	16.6%	7.8%	13.4%
Senior high school	14.2%	6.3%	45.2%	15.5%	8.6%	10.2%
Value of χ^2			66.890			
Value of P			0.000			
OR (95% CI)	0.699 (0.608–0.803)	–	0.743 (0.662–0.833)	0.846 (0.740–0.966)	0.719 (0.614–0.814)	1

Gender is based on male students; age group is based on high school, and the results of other related variables are omitted.

school group was less likely to enter the "low consciousness-low physical activities" class (class 1) (OR = 0.699, 95% CI = 0.608–0.803), "low exercise-high calorie diet" class (class 3) (OR = 0.743, 95% CI = 0.662–0.833), "low consciousness-unhealthy" class (class 4) (OR = 0.846, 95% CI = 0.740–0.966) and "low diet behavior" class (class 5) (OR = 0.719, 95% CI = 0.614–0.814), all of which reached significant statistical ($P < 0.05$). The results are shown in Table 3.

Comparison of detection rate of overweight and obesity among adolescents' lifestyle patterns

It can be seen from Table 4 that there were significant differences in the detection rate of overall overweight and obesity among the adolescents with 6 lifestyle patterns ($P < 0.01$), in which, the detection rate of "high exercise-high calorie diet" class (class 6) was the lowest (15.9%), and the detection rate of "low consciousness-low physical activity" class (class 1) was the highest (20.9%). In the junior high school group, the "high exercise-high calorie diet" class (class 6) had the lowest detection rate of overweight and obesity (15.6%), and the "low consciousness-low physical activity" class (class 1) had the highest detection rate (22.0%). In contrast, in the senior high school group, the "low exercise-high calorie diet" class (class 3) had the lowest detection rate of overweight and obesity (14.9%), and the "low consciousness-low physical activity" class (class 1) had the highest detection rate (19.9%), all of the above detection rate were statistically significant ($P < 0.01$).

At the level of 6 lifestyle patterns of adolescents of different genders, there was only a statistically significant difference in the detection rate of overweight and obesity among male students ($P < 0.05$). The detection rate of "high exercise-high calorie diet" class (class 6) was the lowest (15.7%), and the detection rate of "low consciousness- low physical activity" class (class 1) was the highest (20.7%). The detection rate of overweight and obesity in the female students of junior high school group, senior high school group and overall group were statistically significant ($P < 0.01$). The lowest detection rates of overweight and obesity were "low exercise-high calorie diet" class (class 3) (17.2%), "moderate exercise-balanced" class (class 2) (12.8%) and "low exercise-high calorie diet" class (class 3) (15.1%), respectively. Alternatively, the highest detection rates of overweight and obesity were "low consciousness-low physical activity" class (class 1) (junior high school group: 24.9%; senior high school group: 18.0%; overall group: 21.1%).

Logistic regression analysis on the influencing factors of overweight and obesity detection rate

As can be seen from Table 5, age group was the independent influencing factor of overweight and obesity among Chinese adolescents ($P < 0.01$), and the overweight and obesity

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TABLE 4 Comparison of overweight and obesity detection rates of adolescents' lifestyle patterns.

Gender	Class	Statistical value	Junior high school		Senior high school		Total	
			Number of people	Number of detected persons	Number of people	Number of detected persons	Number of people	Number of detected person
Male	Class 1: Low consciousness-low physical activity class		399	75 (18.8)	414	93 (22.5)	813	168 (20.7)
	Class 2: Moderate exercise-balanced class		347	69 (19.9)	285	49 (17.2)	632	118 (18.7)
	Class 3: Low exercise-high calorie diet class		1279	221 (17.3)	1428	242 (16.9)	2707	463 (17.1)
	Class 4: Low consciousness-unhealthy class		490	94 (19.2)	502	99 (19.7)	992	193 (19.5)
	Class 5: Low diet behavior class		300	46 (15.3)	333	58 (17.4)	633	104 (16.4)
	Class 6: High exercise-high calorie diet class		646	94 (14.6)	488	84 (17.2)	1134	178 (15.7)
		Value of χ^2		7.681		8.005		11.892
		Value of P		0.175		0.1565		0.036
Female	Class 1: Low consciousness-low physical activity class		454	113 (24.9)	560	101 (18.0)	1014	214 (21.1)
	Class 2: Moderate exercise-balanced class		206	41 (19.9)	149	19 (12.8)	355	60 (16.9)
	Class 3: Low exercise-high calorie diet class		1563	269 (17.2)	1662	217 (13.1)	3225	486 (15.1)
	Class 4: Low consciousness-unhealthy class		646	155 (24.0)	557	95 (17.1)	1203	250 (20.8)
	Class 5: Low diet behavior class		231	48 (20.8)	255	37 (14.5)	486	85 (17.5)
	Class 6: High exercise-high calorie diet class		266	48 (18.0)	210	30 (14.3)	476	78 (16.4)
		Value of χ^2		21.530		11.497		31.897
		Value of P		0.001		0.042		0.000
Total	Class 1: Low consciousness-low physical activity class		853	188 (22.0)	974	194 (19.9)	1827	382 (20.9)
	Class 2: Moderate exercise-balanced class		553	110 (19.9)	434	68 (15.7)	987	178 (18.0)
	Class 3: Low exercise-high calorie diet class		2842	490 (17.2)	3090	459 (14.9)	5932	949 (16.0)
	Class 4: Low consciousness-unhealthy class		1136	249 (21.9)	1059	194 (18.3)	2195	443 (20.2)
	Class 5: Low diet behavior class		531	94 (17.7)	588	95 (16.2)	1119	189 (16.9)
	Class 6: High exercise-high calorie diet class		912	142 (15.6)	698	114 (16.3)	1610	256 (15.9)
		Value of χ^2		24.760		17.193		38.175
		Value of P		0.000		0.004		0.000

The number in the brackets is the detection rate /%.

probability of junior high school group was 1.16 times that of senior high school group (1/OR senior high school). Compared with the "high exercise-high calorie diet" class (class 6), the "low consciousness-low physical activity" class (class 1) and "low consciousness-unhealthy" class (class 4) were 1.432 times and 1.346 times higher than the "high exercise-high calorie diet" class (class 6), respectively.

Discussion

Analysis of adolescents' lifestyle patterns

The results indicated that the adolescents' lifestyle patterns can be divided into the class of "low consciousness-low physical activity" class (class 1), "moderate exercise-balanced" class (class 2), "low exercise-high calorie diet" class (class 3), "low consciousness-unhealthy" class (class 4), "low diet behavior" class (class 5) and "high exercise-high calorie diet" class (class 6).

Among the above types, the adolescents with "low exercise-high calorie diet" class (class 3) accounted for the highest proportion. In the recent decades, tremendous changes had taken place in the aspects of economic development, social and cultural changes, food safety and built environment, resulting in significant changes in the lifestyle of adolescents (27, 28). The main manifestation focused on the continuous reduction of sleep duration, lack of interest in exercise, increase in irregular diet, as well as the more time spent on video (29). Adolescence is a key stage in the development of a healthy lifestyle, which is closely linked to its time and will develop along with the economic and social development. At present, the Internet has penetrated into the lives and studies of Chinese adolescents, bringing them convenience but also becoming an important factor affecting their health. The excessive use of the Internet and electronic devices has led to a reduction in outdoor activities and sleep time for young people, which in turn has led to metabolic disorders or disturbances in their biological clocks, and has even affected their psychological health, thus adversely affecting their healthy lifestyles (23). In addition, the behaviors such as unhealthy diet, low physical exercise would also affect the development of a variety of health-risk behaviors, and moreover, the factors including self-control level and family environment were also important predictors (30).

The results of the present study demonstrated that the males were inclined to enter the "high exercise-high calorie diet" class (class 6) and "moderate exercise-balanced" class (class 2). The previous results reported that the females were more prone to exhibit low exercise and sedentary behavior, as compared to males (18), which was consistent with the results of this study. The main reason causing females' physical exercise was usually less active than that of males lied in the gender difference of perception barriers, in which, lack of exercise energy and willpower were listed as the main factors (31). Besides, it was also influenced by the phenomenon of gender inequality (32, 33). The results also illustrated that the junior high school group was less likely to enter the class of "low consciousness-low physical exercise" (class 1), "low exercise-high calorie" (class 3), "low consciousness-unhealthy" (class 4) and "low diet behavior" (class 5). This may be attributed to the fact that junior high school students were constrained and regulated by their families and schools in the aspects of daily routine, eating habits, physical exercises, etc., which has also been confirmed by Ji Gang et al. (34). On the other hand, with the increase of age, adolescents' autonomy and the interaction with their peers also enhanced, which would exert an impact on adolescents' lifestyle (35).

Analysis on the clustering characteristics of adolescents' lifestyle

The results indicated that in the clustering of various factors of adolescents' lifestyle, the clustering of low physical exercise and high intake of snacks and carbonated beverages was more common. The clustering of these health-risk behaviors may be related to a series of variations in individual, social and environmental factors induced by China's rapid economic development in recent decades.

Under the influence of various factors such as educational needs (36), Chinese teenagers have been overburdened in their studies and spent less time in extracurricular activities. Moreover, physical education was mainly conducted based on the principle of safety, it was difficult to achieve effective exercise loads and frequency in physical education, and leading limited effect of cultivating students' physical exercise habits (37). Furthermore, due to the influence of family economic level, parents' support attitude, and surrounding sports resources, Chinese adolescents had a relatively low probability to participate in paid sports activities (38, 39). Besides, the natural environment such as air pollution and noise pollution, as well as the built environment such as the suitability of physical exercise in the community, would affect the participation of adolescents in physical exercise (40). These above mentioned factors would affect the training of adolescents' interest in exercise, skill mastery, exercise motivation and psychological simulation, and thereby limiting the subjective initiative and spontaneity of the participation in physical exercise.

According to the survey of the China Health and Nutrition Survey (CHNS) project conducted by the China Center for Disease Control and Prevention and the Population Center of the University of North Carolina in the United States, the proportion of unhealthy snack consumers with high salt, high fat and high energy among Chinese children and adolescents presented a upward trend (41), because of the increasing number of high-income families and economically developed regions. With the improvement of the economic level, the dietary

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TABLE 5 Multivariate logistic regression analysis of overweight and obesity.

Independent variable		*B*	Standard error	*OR*	*OR* value 95%CI	*P*
Gender	Female			1.00		
	Male	0.041	0.046	1.042	0.952–1.140	0.370
Age group	Junior high school			1.00		
	Senior high school	−0.153	0.045	0.858	0.786–0.938	0.001
Regions	East			1.00		
	Middle	0.100	0.055	1.106	0.993–1.231	0.067
	West	−0.045	0.056	0.956	0.857–1.067	0.421
Classes	Class 1: High exercise-high calorie diet type			1.00		
	Class 2: Low consciousness-low physical activity type	0.359	0.090	1.432	1.200–1.708	0.000
	Class 3: Moderate exercise-balanced type	0.155	0.107	1.168	1.168–0.946	0.149
	Class 4: Low exercise-high calorie diet type	0.033	0.078	1.034	0.888–1.204	0.670
	Class 5: Low consciousness-unhealthy type	0.297	0.087	1.346	1.134–1.598	0.001
	Class 6: Low diet behavior type	0.089	0.105	1.093	0.889–1.343	0.400

The gender is based on girls, the age group is based on junior high school, and the region is based on the east; the lifestyle pattern is based on high exercise-high calorie diet type.

consumption behavior and motivation of the teenagers have transformed. People began to pursue experience and satisfaction in delicious food, instead of just having warm clothing and adequate food (42). Meanwhile, under the influence of more and more advertisements concerning high-calorie and low-nutrition foods, the adolescents tended to consume such kind of foods. On the other hand, it could be found from the 2015 survey data of the Chinese General Social Surver (CGSS), the phenomenon of grandparents upbringing existed in 38.35% of Chinese adolescents. It should be noted that the health literacy of middle-aged and elderly groups were obviously lower, and the generation gap and the transfer of consumption rights would aggravate the consumption behavior of unhealthy diets among adolescents (43).

Relationship between overweight and obesity and lifestyle patterns in adolescents

In the comparison of lifestyle patterns of overweight and obesity, it was found that the detection rate of overweight and obesity among adolescents with “high exercise-high calorie diet” class (class 6) was the lowest. In contrast, the risk of overweight and obesity prominently increased in the “low consciousness-low physical activity” class (class 1) and the “low consciousness-unhealthy” class (class 4).

Although the adolescents with “high exercise-high calorie diet” class (class 6) had higher intake of snacks and carbonated beverages, the detection rate of overweight and obesity was still the lowest. For the adolescents in the growing stage, higher levels of physical exercise could effectively facilitate energy metabolism and offset the risk of nutritional status caused by high calorie intake. Moreover, as an important approach to prevent and intervene overweight and obesity, physical exercise could not only reduce the biochemical markers of obesity, but also contribute to individual’s mental health (44) and self-regulation (45). To a certain extent, good mental health, emotion/behavior, and social adaptation could also contribute to a healthier nutritional status (46–48). Moreover, organized physical exercise could promote more healthy behaviors in adolescents (49), and thus exhibiting more positive performance on the individual’s nutritional status. Similar results could be found in the present study, with “high exercise-high calorie diet” class (class 6) adolescents trending toward positive health behaviors in both health consciousness and sleep duration. As a result, regular physical exercise is conducive to building a positive environment and lifestyle for teenagers.

Compared with the "high exercise-high calorie diet" class (class 6), the "low consciousness-low physical activity" class (class 1) and "low consciousness-unhealthy" class (class 4) adolescents had a higher risk of overweight and obesity. It has been reported that health consciousness could help adolescents identify positive healthy behaviors in their lifestyles, thereby helping them change health-risk behaviors to maintain a good living condition, which would be beneficial to effectively promote individuals to live in a healthy nutritional status (50). The following conclusions could be drawn after integrating various personal health behavior variation theories: health consciousness may affect the distal consciousness of behaviors through attitude and self-efficacy, and served as an important factor in the pre-motivation stage (51). Therefore, it can be deduced that low health consciousness could lead to a series of health-risk behaviors such as low physical exercise and poor diet, thereby increasing the risk of overweight and obesity. Additionally, a certain lifestyle of adolescents may trigger the development of a variety of health-risk behaviors (52), increase the interaction performance of health-risk behaviors, and thus elevating the hazard of overweight and obesity.

In this study it was also found that health risk behaviors among adolescents did not occur in isolation, but rather a mixture of healthy and unhealthy behaviors. Evidence suggests that adolescents' lifestyles are often combined with non-modifiable and modifiable covariates into different lifestyle patterns (53). One explanation may include the theory of problem behavior, which suggests that an underlying behavioral syndrome causes adolescents to engage in multiple problem behaviors, possibly caused by an imbalance of risk factors in relation to protective factors in the personality and socio environmental domains (54). Longitudinal studies demonstrated that screen time could, to a large extent, drive adolescents to produce behaviors including poor diet, reduced physical activity and sleep disorders, resulting in an increased risk of obesity (55, 56). Nevertheless, lifestyle patterns in this study tended to be positive healthy behaviors in video time, which may be correlated with the influence of family and school constraints and academic pressure from Chinese middle school. At present, there are few studies on the relationship between lifestyle patterns and individual invariant covariates and their changing trends, and the direct relationship between health behaviors remains to be clarified.

In conclusion, the clustering types of adolescents' lifestyles are relatively complicated. In the future, more characteristics of the investigators, including mental health, whether they live in school, and family environment, should be considered to better explain the potential confounding factors. Considering that the cumulative effect of adolescents' lifestyles on health is relatively sophisticated, in-depth research on the development and changes of adolescents' lifestyle patterns should be further investigated, so as to more scientifically explore the relationship between lifestyles and overweight 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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Conceptualization: YM and HW. Methodology: JS. Software: JinW. Validation: JiaW, JS, and YH. Formal analysis and writing—original draft preparation: YM. Investigation: HW, JinW, and YH. Resources, supervision, project administration, and funding acquisition: HW. Data curation: YM and JiaW. Writing—review and editing: HW, JS, and YH. Visualization: JiaW and JinW. 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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MOTS-c repairs myocardial damage by inhibiting the CCN1/ERK1/2/EGR1 pathway in diabetic rats

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Cardiac structure remodeling and dysfunction are common complications of diabetes, often leading to serious cardiovascular events. MOTS-c, a mitochondria-derived peptide, regulates metabolic homeostasis by accelerating glucose uptake and improving insulin sensitivity. Plasma levels of MOTS-c are decreased in patients with diabetes. MOTS-c can improve vascular endothelial function, making it a novel therapeutic target for the cardiovascular complications of diabetes. We investigated the effects of MOTS-c on cardiac structure and function and analyzed transcriptomic characteristics in diabetic rats. Our results indicate that treatment with MOTS-c for 8-week repaired myocardial mitochondrial damage and preserved cardiac systolic and diastolic function. Transcriptomic analysis revealed that MOTS-c altered 47 disease causing genes. Functional enrichment analysis indicated MOTS-c attenuated diabetic heart disease involved apoptosis, immunoregulation, angiogenesis and fatty acid metabolism. Moreover, MOTS-c reduced myocardial apoptosis by downregulating CCN1 genes and thereby inhibiting the activation of ERK1/2 and the expression of its downstream EGR1 gene. Our findings identify potential therapeutic targets for the treatment of T2D and diabetic cardiomyopathy.

KEYWORDS

MOTS-c, type 2 diabetes, mitochondrial, myocardium, transcriptome

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by persistent hyperglycemia caused by insulin resistance (IR) or insulin deficiency (1), and has a worldwide prevalence of nearly 300 million (2). Persistent hyperglycemia damages the structure and function of the myocardium in patients with DM, resulting in cardiac diastolic dysfunction that can lead to heart failure and myocardial infarction (3–6).

Mitochondrial derived peptides are small bioactive peptides produced by the short open reading frame region of mtDNA, but which does not possess the traditional characteristics of protein-coding genes (7). The mitochondrial open-reading-frame of the 12s rRNA-c (MOTS-c) inhibits the folate cycle, purine biosynthesis, and activates 5'AMP activated protein kinase (AMPK) (8). MOTS-c regulates the expression of nuclear genes related to metabolism, including the antioxidant response element (ARE) that protects against metabolic stress (9, 10). Serum levels of MOTS-c are reduced in patients with type 2 diabetes (11).

The functional activity of MOTS-c has not been widely studied, but in cell culture and animal models suggest that MOTS-c affects mitochondrial metabolism and insulin sensitivity (12), accelerates glucose uptake (8, 12) and regulates glucose production in liver (13, 14). Insulin-dependent protein kinase B (AKT) is activated by MOTS-c in mouse skeletal muscle cells (13). Treatment with MOTS-c activates the AMPK pathway and increases GLUT4 expression in skeletal muscle (8), suggesting that exogenous MOTS-c could lower hyperglycemic levels in patients with diabetes and thereby enhance cardiac function. Our preliminary study reported that exogenous MOTS-c increased the levels of endogenous MOTS-c protein expression in the myocardium (15). More importantly, our findings also demonstrated that MOTS-c prevented myocardial ultrastructural damage and improved cardiac function in non-diabetic rats (15).

We studied the effects of treatment with MOTS-c on cardiac structure and function of rats with diabetes by examining the myocardial transcriptome using the RNA-Seq technology. Our findings could help to identify novel potential therapeutic targets in the management of cardiac complications in diabetes.

2. Materials and methods

2.1. Animal care

Experiments were approved by the Academic Committee of Chengdu Sport Institute (No: 2021-07). Male Sprague Dawley (SD) rats (n = 40) were obtained from Chengdu Da-shuo Experimental Animals Co., Ltd. (Chengdu, China). All rats were housed in a pathogen-free animal room at Chengdu Sports University with relative humidity of 50~60%, ambient temperatures of 21-23°C, and a 12-h dark/light cycle. The body weights (BW) of rats were measured once a week.

2.2. Induction of type 2 diabetes

Rats were randomly divided into control (C, n = 10) and pre-diabetic (PD, n = 30) groups. Rats in the PD group were fed a high-fat diet containing 67% normal pellets, 10% lard, 20% sucrose, 2% cholesterol, and 1% sodium cholate (16) for 7 weeks, and the insulin resistance index (HOMA-IRI) was determined for the rats. During the first 7 weeks of feeding with a high-fat diet, the pre-diabetic rats were given a single intraperitoneal injection of STZ (30 mg/kg) (Sigma-Aldrich, St Louis, MO) dissolved in sodium citrate buffer (0.1 mol/L, pH 4.4) (17, 18). Diabetes was confirmed when the blood glucose measurements were greater than 16.7 mmol/L (**Table 1**). Diabetic rats were randomly divided into two groups: (1) diabetes group (untreated) (D), (2) diabetic rats treated with MOTS-c (M).

2.3. MOTS-c treatment protocol

MOTS-c is synthesized *in vitro* according to its amino acid sequence and spatial structure by GL Biochem (Shanghai) Ltd. (Chengdu, China). Diabetic rats in group M were injected with MOTS-c (0.5 mg/kg/day, i.p.) for 7 days/week for 8 weeks, while rats in groups C and D were injected with normal saline in the same way (**Table 1**).

2.4. Assessment of plasma glucose, insulin, and HOMA-IR indexes

Plasma glucose levels were estimated with a glucometer (On·Call, China). Insulin levels were measured with ELISA kits for rat insulin (Immuno Way, USA) with a plate reader (SpectraMax M5 from Thermo Scientific, USA) at 450 nm. The HOMA-IR was calculated as: HOMA-IR = Fasting blood glucose (FBG) (mmol/L) × Fasting insulin (FINS) (mU/L)/22.5 (19).

2.5. Measurement of cardiac structure and function

2.5.1. Transmission electron microscopy (TEM)

Cardiac tissues were pre-fixed in 3% glutaraldehyde and post fixed in 1% osmium tetroxide, and then dehydrated in acetone and successively infiltrated with a dehydrating agent

TABLE 1 Timeline of interventions.

Timeline	Weeks 1-7	Week 8	Weeks 9-15
Interventions	High-fat diet (group PD) Normal diet (group C)	① Single intraperitoneal injection of STZ for group PD ② Test HOMA-IR and blood glucose to confirm diabetes	MOTS-c treatment for group M and saline for groups C and D

and epoxy resin at ratios of 3:1, 1:1, 1:3, and 30 to 60 min per step. The infiltrated samples were placed into molds, irrigated with embedding solution, then warmed and allowed to form polymerized embedding blocks. Ultrathin sections (~50 nm thickness) were made using an ultramicrotome. After staining with uranyl acetate followed by lead citrate, images of cells were acquired using a JEM-1400PLUS TEM (JEOL, Japan).

2.5.2. Echocardiography

Small animal echocardiography (Philips, CX50) was used to detect changes in ejection fraction (EF), left ventricular posterior wall diastole (LVPWd), early diastolic transmitral flow velocity (E wave), late (atrial) diastolic transmitral flow velocity (A wave) and early to late diastolic transmitral flow velocity (E/A). We measured the long axis image of the left ventricle and the short axis image of the middle part of the left ventricle by M-mode echocardiograms.

2.6. Construction of transcriptome

The cDNA library of samples was sequenced using sequencing by synthesis (SBS) technology with Illumina high-throughput sequencing platform; the low-quality reads containing splices were removed to ensure high-quality reads. HISAT2 (20) and StringTie (21) were used to compare transcriptome data with a reference genome sequence, and the reading distribution on the reference gene was calculated and the coverage was determined. Fragments per kilobase of transcript per million fragments mapped (FPKM) (22) was used as an index to measure transcripts or gene expression levels, and gene expression was analyzed quantitatively. Finally, three transcriptome libraries (C, D, M) were constructed.

EdgeR (23) was used for differential expression analysis of samples to obtain differential expression gene sets under variable experimental bconditions. The p-values were adjusted by applying a false discovery rate (FDR) to control false discovery rates. Genes were expressed differentially when the corrected p-value was < 0.05 and fold change was ≥ 1.5. The purity, concentration and integrity of RNA samples were confirmed to ensure the use of appropriate samples for transcriptome sequencing (Biomarker technologies Co. Ltd.).

2.7. Functional enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of differentially expressed genes (DEGs) were carried out using Cytoscape (version 3.8.2) plug-in ClueGO (version 2.5.7). The KEGG pathway enrichment analysis of DEGs was implemented using R software (Version 3.4.1); KEGG pathways and GO terms were considered significantly enriched with an adjusted p-value < 0.05. ClueGO and R software was also used for clustering GO terms and visualization by Sankey diagrams.

2.8. Quantitative real-time PCR (qRT-pCR) for validation

Total RNA from left ventricles were extracted using Animal Total RNA Isolation Kit and the 5 × All-In-One MasterMix (with AccuRT Genomic DNA Removal kit) (ABM, China). The extraction steps of total RNA were according to the kit instructions. The EvaGreen Express 2 × qPCR MasterMix-No Dye (ABM, China) was used to prepare the qRT-PCR reaction mixture. RT-PCR was performed using a SLAN-96S Real-Time PCR system (Shanghai, China) with an amplification procedure of 95°C for 10 min, 40 cycles of 95°C for 10 s and 60°C for 30 s. The cycle threshold (Ct) value was used to perform calculations. The relative mRNA expression levels were calculated using the ΔCt method (where ΔCt value is obtained by subtracting the Ct value of internal reference mRNA (GAPDH) from that RNAs of selected genes). The ratios of relative expression were expressed as $2^{-\Delta\Delta\ Ct}$. Specific primers were designed by Sangon Biotech Co., Ltd (Chengdu, China) and presented in **Table 2**.

2.9. Western blotting

Total protein was extracted from the left ventricle, and processed total protein samples were separated by electrophoresis using SDS-PAGE and then transferred to PVDF membranes. Blocking incubation was performed with 5% non-fat dry milk for 1.5 h at room temperature. After washing for 30 s, the proteins were incubated within the diluted primary antibodies against CCN1, ERK1/2, EGR1, PGC-1α and

TABLE 2 The primers of qRT-PCR.

mRNA (GenBank no)	Primer	Size (bp)
CCN1 (83476)	Forward: GCCAGTTCCACCGCTCTGAAAG	146
	Reverse: CAGCCCACAGCACCGTCAATAC	
ERK1 (50689)	Forward: GGACCTCATGGAGACGGACCTG	90
	Reverse: CGGAGGATCTGGTAGAGGAAGTAGC	
ERK2 (116590)	Forward: TGAAGACACAGCACCTCAGCAATG	131
	Reverse: GGTGTTCAGCAGGAGGTTGGAAG	
EGR1 (24330)	Forward: GCCAGGAGTGATGAACGCAAGAG	117
	Reverse: GGATGGGTAGGAAGAGAGGGAAGAG	
GAPDH (24383)	Forward: ACAGCAACAGGGTGGTGGAC	226
	Reverse: TTTGAGGGTGCAGCGAACTT	

GAPDH at 4°C for 24 h. After three washes with TBST buffer, the membranes were incubated with horse-radish peroxidase-conjugated secondary antibodies (Proteintech Group Inc., Wuhan, China) for 1h at room temperature. Bands were quantified by ECL luminescence reagent and analyzed by Image J. Primary antibodies against CCN1, EGR1, PGC-1α and GAPDH were purchased from HuaBio Co., Ltd. (Hangzhou, China); antibodies against ERK1/2 were purchased from Abcam (UK).

2.10. Citrate synthase (CS) activity assay

Left ventricular tissues were homogenized in homogenate medium and centrifuged for 10 min at 3,000-4,000 rpm and 4°C. The supernatants were prepared as 10% tissue homogenates for assay. A CS kit (Nanjing Jiancheng Bioengineering Institute, China) was used to measure CS activity levels according to the manufacturer's instructions.

2.11. Statistics

Data were analyzed using SPSS26.0. The Shapiro–Wilk normality test was used to determine the normal distribution of variables and a one-way ANOVA test to compare changes between three groups. GraphPad prism 8.0.1 was used for statistical analysis. Statistically significant differences were set at $p < 0.05$. The results for indexes are presented as the mean ± standard deviation of the mean (SD).

3. Results

3.1. Type 2 diabetic rat model

20 rats in the pre-diabetic group met the criteria for type 2 diabetes, as indicated by polydipsia, polyphagia, polyuria, and blood glucose values of ≥ 16.7 mmol/L. Diabetic rats were randomly divided into group D and M of ten rats per group.

3.2. Blood glucose and insulin resistance

Rats in the D and M groups weighed less than those in group C after 8-weeks of treatment with MOTS-c ($p < 0.05$) (Figures 1A, E). The most rapid weight loss was observed in rats with MOTS-c application, which may account for the ability of MOTS-c to increase energy metabolism (24). Fasting glucose levels were reduced in rats from group M compared with those in group D

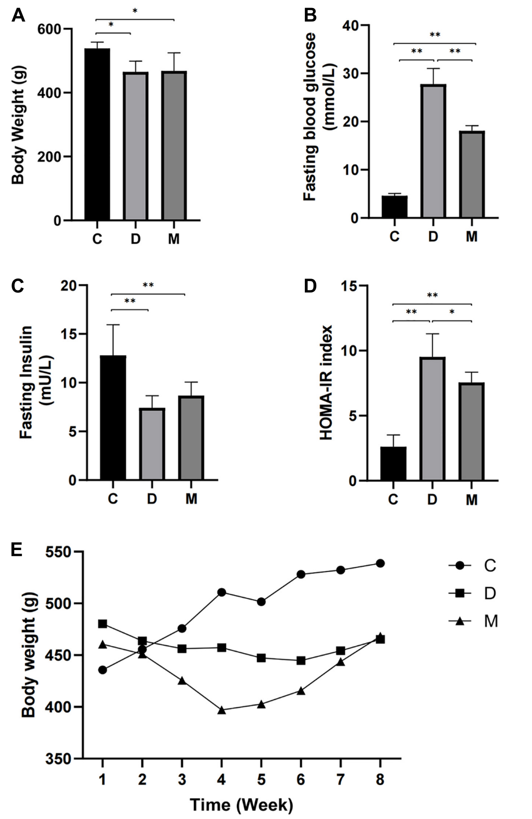

FIGURE 1
Body weight, fasting blood glucose, fasting insulin, and HOMA-IR after 8 weeks of MOTS-c treatment. **(A)** Rats in groups D and M had lower body weights compared with rats in group C ($p < 0.01$). **(B)** Rats in groups D and M had higher FBG compared with rats from group C ($p < 0.01$). Values for FBG in M were significantly lower than that in group D ($p < 0.01$). **(C)** Rats from groups D and M groups had lower FINS compared with rats from group C ($p < 0.01$). **(D)** Rats from groups D and M had higher HOMA-IR values compared with group C ($p < 0.01$). Values of HOMA-IR in group M were significantly lower than in group D ($p < 0.05$). **(E)** The weekly body weight of rats in groups C, D and M. Data are expressed as mean ± SD; n = 10 rats per group; $^*p < 0.05$, $^{**}p < 0.01$; C, non-diabetic control group; D, diabetic control group; M, diabetic MOTS-c injection group.

($p < 0.01$), indicating that treatment with MOTS-c alleviated hyperglycemia (Figure 1B). Furthermore, insulin levels in rats from groups D and M were decreased (both $p < 0.01$) compared with those in group C, with no significant differences between groups D and M (both $p > 0.05$) (Figure 1C). The changes in fasting glucose and fasting insulin were in accordance with the results expected from the induction of type 2 diabetes by high-fat diet plus a low-dose of STZ (25).

HOMA-IR indices were calculated to assess insulin resistance. A higher HOMA-IR index was observed in rats from group D compared with rats in group C ($p < 0.01$), indicating insulin resistance. The HOMA-IR index of rats in group M were decreased in comparison with that of group D ($p < 0.05$), with significant differences between groups M and C ($p < 0.01$) (Figure 1D).

3.3. Cardiac structural and functional indices

We determined the effects of MOTS-c on diabetic myocardial ultrastructure using transmission electron microscopy. Diabetes caused cardiac myofiber disarrangement and abnormal changes of mitochondrial structure, including irregular arrangement, disrupted cristae, swelling and vacuolation of cardiac cells. Treatment of diabetic rats with MOTS-c significantly reduced myocardial mitochondrial damage, with improvements in myocardial fibers and mitochondrial structure. Moreover, we observed an obviously increase in the number of mitochondria (Figure 2).

The activity of CS was measured to determinate mitochondrial function. CS is a the rate-limiting enzyme of the tricarboxylic acid (TCA) cycle and a common biomarker of mitochondrial oxidative capacity (26). CS activity was decreased significantly in rats of group D compared with control rats ($p < 0.05$), and no difference was observed between groups C and M ($p > 0.05$) (Figure 3G), implying recovery of mitochondrial function in diabetic rats after treatment with MOTS-c.

Representative M-mode echocardiographic images from all experimental groups are shown in Figure 3. The LVPWd value of rats in group D was significantly increased, suggesting lesions in the left ventricle ($p < 0.01$) (Figure 3D). Values of EF in rats from group D were decreased compared with rats from group C ($p < 0.01$) (Figure 3B), indicating impaired cardiac systolic function of diabetic rats. We also determined that peak E-waves and A-waves of diabetic rats in group D were decreased ($p < 0.05$), and that the A-wave decreased more rapidly ($p < 0.05$), so increasing the E/A ratio ($p < 0.05$) (Figures 3C, E, F). There were no differences in EF, E/A, LVPWd, peak E-waves and A-waves from groups M and C ($p > 0.05$) (Figures 3B-F), indicating that MOTS-c targeted cardiac diastolic and systolic function.

3.4. Identification of differentially expressed genes

The transcriptome of cardiac tissues from rats in groups C, D and M of rats were profiled to explore the mechanisms involved in the adaptive responses to MOTS-c in diabetic rats. We compared cardiac tissue from D vs. C to explore pathogenic genes of diabetes, and compared M vs. D to determine DEGs in diabetic rats after 8 weeks of treatment with MOTS-c. The overlapping DEGs in the comparisons D vs. C and M vs. D were analyzed to identify the genes improved by MOTS-c as illustrated by a Venn diagram (Figure 4A). The expression patterns of the overlapping DEGs were obtained using hierarchical clustering and are presented in a heatmap (Figure 4B).

Treatment with MOTS-c for 8 weeks resulted in the differential expression of 47 genes when comparing D vs. C and M vs. D; of these, 24 genes were upregulated while 23 genes were downregulated. Among these DEGs, the gene expression of rats in group D group tended to be the opposite of rats in group C, while that of rats in groups M and C were similar.

3.5. Functional enrichment analysis of DEGs

GO describes gene products associated biological processes (BP), cellular components (CC), and molecular functions (MF). The 47 overlapping DEGs in the comparisons D vs. C and M vs. D were enriched in 195 GO terms, of which 188, 2 and 5 terms were enriched in BP, CC,

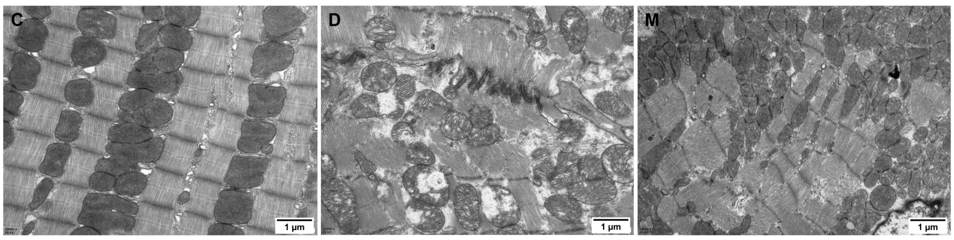

FIGURE 2
Electron micrographs of myocardium in groups C, D, M. The myocardium of rats from group C maintained continuous regular sarcomeres and constituted myofibrils, with mitochondria distributed between myofibrils that were structurally intact. The myofibrils of the myocardium in rats from group D were fragmented and disorganized, and the mitochondria were arranged in a disorganized manner with broken cristae, and with inner membranes that were swollen and appeared vacuolated or ruptured. The arrangement of myocardial sarcomeres in rats from the M group were regular, with intact mitochondrial structure with limited swelling and vacuoles.

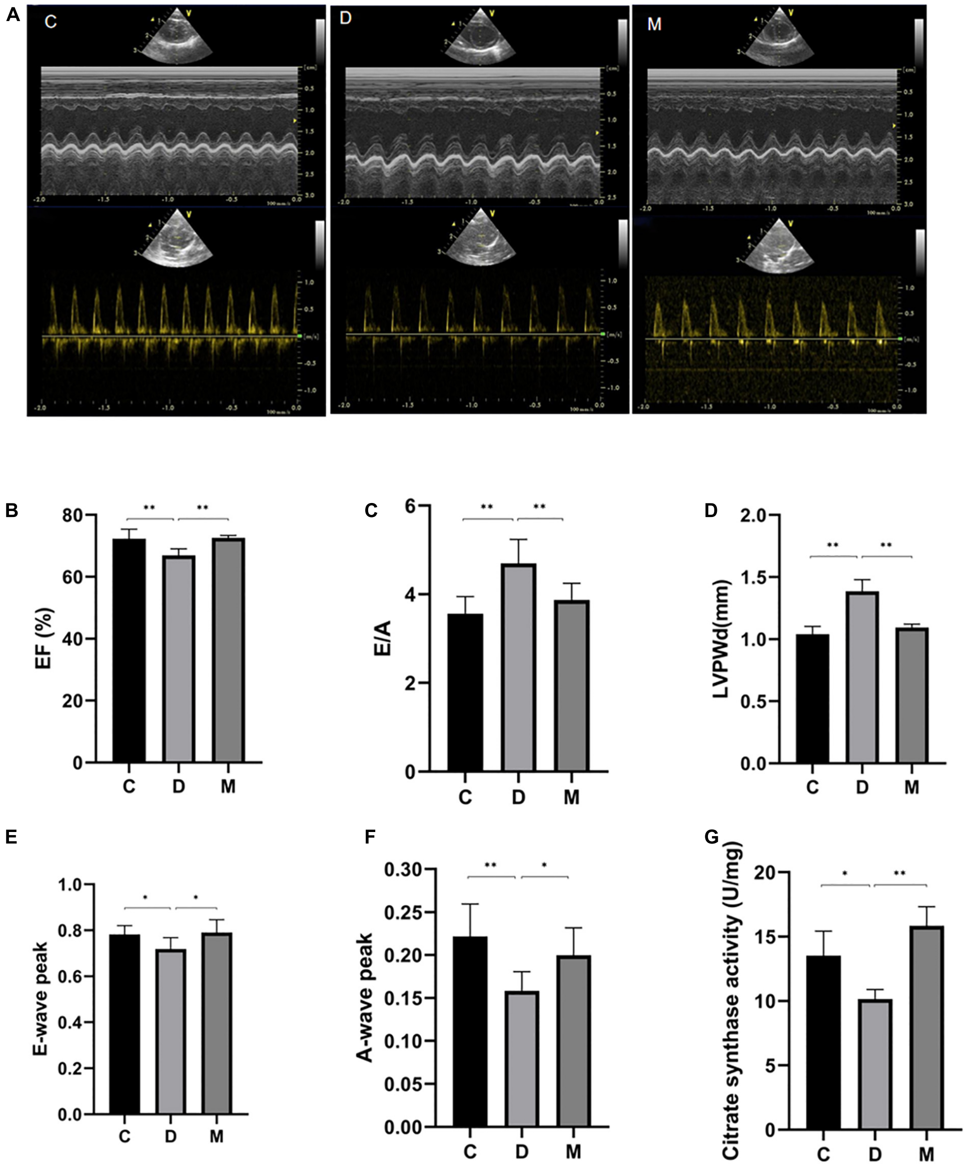

FIGURE 3
Cardiac function after 8 weeks of treatment with MOTS-c. **(A)** M-mode echocardiographic images and echocardiographic doppler color flow images from rats in groups C, D and M. **(B)** Rats from groups C and M had greater EF values compared with rats from groups D ($p < 0.01$), with no significant differences in EF between rats from groups M and C ($p > 0.05$). **(C,D)** The E/A ratio and LVPWd were increased in rats from group D compared with rats from group C ($p < 0.01$). While the E/A ratios and LVPWd in rats from group M were decreased compared with rats from group D ($p < 0.05$), there were no differences from rats in group C ($p > 0.05$). **(E)** The E-wave peak was decreased in rats in group D compared with the C group ($p < 0.05$). Rats from group M had higher E-wave peak values compared with rats from group D ($p < 0.05$), with no significant differences between rats from groups M and C ($p > 0.05$). **(F)** The A-wave peak in rats from group D was decreased compared with rats from groups C and M ($p < 0.01$, $p < 0.05$). **(G)** Citrate synthase activity in left ventricle from rats in groups C, D, and M. Data are expressed as mean ± SD; $n = 10$ rats in each group; *$p < 0.05$, **$p < 0.01$; C, non-diabetic control group; D, diabetic control group; M, diabetic MOTS-c injection group.

and MF, respectively. After clustering, the GO terms were mostly related to angiogenesis, regulation of the apoptotic process, regulation of the MAPK cascade, positive regulation of protein kinase activity, fatty acid metabolic process, regulation of phagocytosis, positive regulation of protein kinase B signaling, regulation of ERK1/2 (extracellular regulated protein kinases) cascade, gliogenesis, and interleukin-1 beta production (Figure 5A). A KEGG pathway enrichment analysis indicated significant enrichment of 18 KEGG pathways (Figure 5B). Five signaling pathways (ErbB signaling pathway, complement and coagulation cascades, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway and AGE-RAGE signaling pathway

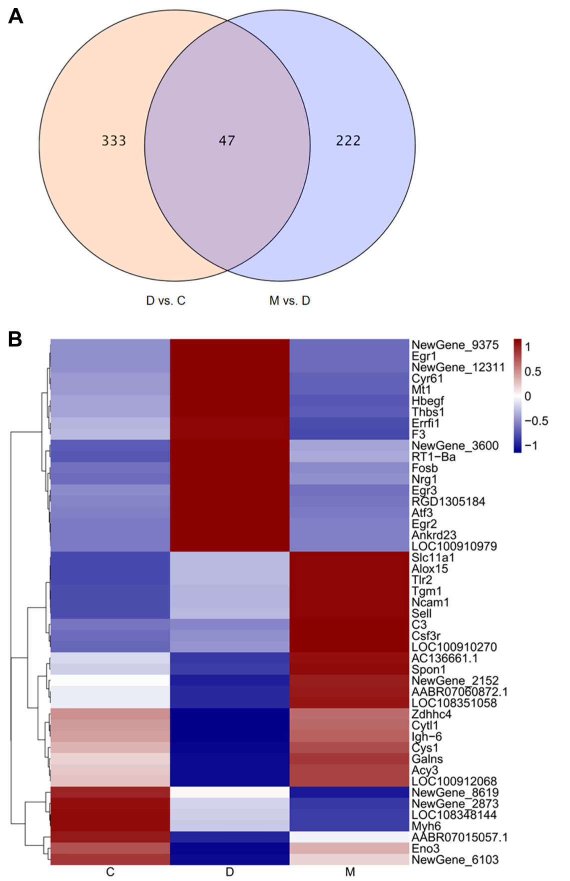

FIGURE 4
Changes in gene expression profiles. **(A)** The overlap of DEGs in the comparison D vs. C and M vs. D presented as a Venn diagram. **(B)** Heatmap representing the relative expression levels of the overlapping DEGs in the comparisons D vs. C and M vs. D. In the heatmap, red and blue represent up regulation and down regulation respectively, and white represents no change.

in diabetic complications) related to immunity, apoptosis and glycometabolism were also enriched. Among the genes associated with functional annotation, ALOX15 (arachidonic acid 15-lipoxygenase-1), ATF3 (activating transcription factor 3), CCN1 (cell communication network factor 1), EGR1 (early growth response 1), EGR3 (early growth response 3), ERRFI1 (ERBB receptor feedback inhibitor 1), THBS1 (thrombospondin-1), TLR2 (toll-like receptor 2) and NRG1 (neuregulin-1) appeared at a higher frequency in the diabetic myocardium.

3.6. The effects of MOTS-c on CCN1/ERK1/2/EGR1 signaling pathway

3.6.1. RT-PCR for validation

Genes for CCN1 and EGR1 were highly expressed and appeared in the apoptosis related terms and CCN1 was included

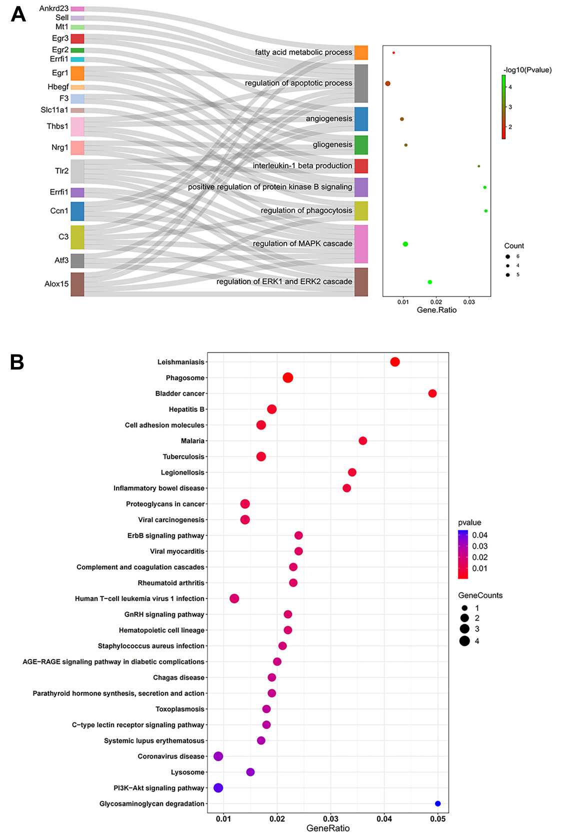

FIGURE 5
Functional enrichment analysis by GO and KEGG. **(A)** Sankey diagram based on analysis of significantly enriched GO terms of the overlapping DEGs in the comparisons D vs. C and M vs. D. DEGs were analyzed using plug-in ClueGO of Cytoscape to determine significantly enriched GO terms. Sankey diagram visualized GO terms and the genes annotated within, where only the most significant terms per group is presented.
(B) Significantly enriched KEGG pathways of the overlapping DEGs in the comparisons D vs. C and M vs. D. In bubble chart, the color and size of the points were scaled with respect to adjusted *p*-values and the number of related DEGs. Gene ratio refers to the proportion of DEGs in each pathway.

in the ERK1/2 cascade with the greatest enrichment. To explore the molecular mechanism by which MOTS-c improves cardiac function in diabetes, we performed transcript analysis of the highly expressed CCN1, ERK1, ERK2, and EGR1 genes by qRT-PCR. The gene expression of CCN1, ERK1/2 and EGR1 in the myocardium of diabetic rats were decreased after MOTS-c treatment ($p < 0.01$) (**Figure 6**).

3.6.2. Western blotting for validation

To further support increases in mitochondrial biogenesis by MOTS-c, we measured PPARγ coactivator-1α (PGC-1α) protein (a mitochondrial biogenesis markers (27)) by western blotting. PGC-1α protein expression was significantly decreased in the myocardium of diabetic rats ($p < 0.05$) and increased after treatment with MOTS-c ($p < 0.01$) (**Figure 7B**).

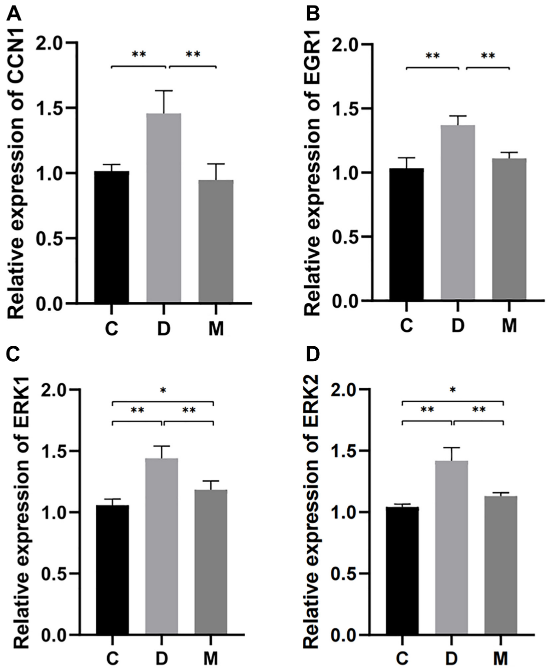

FIGURE 6
Gene expression of CCN1, EGR1, ERK1, and ERK2 in ventricular cardiomyocytes from rats in C, D, and M groups. **(A–D)** The mRNA expression of CCN1, EGR1, ERK1, and ERK2 were decreased in rats from group M compared with C and D groups ($p < 0.01$). Data are expressed as mean ± SD; *$p < 0.05$, **$p < 0.01$; C, non-diabetic control group; D, diabetic control group; M, diabetic MOTS-c injection group.

To further understand the molecular details, we measured protein expression levels of CCN1 ($p < 0.01$) and EGR1 ($p < 0.05$) in diabetic rats. MOTS-c treatment could nearly restore to these changes to normal levels (all $p < 0.01$) (**Figures 7C**, **E**). However, the levels of ERK1/2 protein expression did not differ between the groups ($p > 0.05$) (**Figure 7D**).

4. Discussion

There are disturbances in calcium balance and mitochondrial function in diabetes (28, 29). Metabolic stress causes Ca^{2+} overload, leading to opening of the mitochondrial permeability transition pore and subsequent cardiomyocyte autophagy and cardiac necrosis (30). Changes in the mtDNA copy number can protect mitochondria from oxidative damage in T2D (31). The newly identified mtDNA encoded polypeptide MOTS-c improves insulin sensitivity, regulates glycolipid metabolism, and affects mitochondrial metabolism (8, 32), leading to suggestions that MOTS-c could be a new treatment for diabetes, and for reducing myocardial damage in diabetes (33).

We used a rat model of T2D to explore the effects of MOTS-c on diabetic myocardial structure and function, and used transcriptomics to better characterize the molecular mechanisms involved. Our findings show that high-fat diet combined with STZ-induced produced diabetic rats as also reported in others (34, 35). Treatment with MOTS-c for 8 weeks improved the structure and function of cardiac myofibers and mitochondria in diabetic rats. Moreover, treatment with MOTS-c increased the protein expression level of PGC-1α. PGC-1α is a master coregulator in mitochondrial biogenesis. Upon phosphorylation, PGC-1α translocates from the cytoplasm to the nucleus to trigger mitochondrial biogenesis (27). In consideration of the improved mitochondrial morphology and function in our results, it is possible that MOTS-c exerts its effects on mitochondrial biogenesis. Moreover, transcriptomic analysis indicated that ATF3 and THBS1 genes were overexpressed in diabetic rats, and decreased after MOTS-c treatment. ATF3 is a member of the ATF/cAMP response element-binding (CREB) family (36). Overexpression of ATF3 results in accumulation of depolarized mitochondria, and increased mitochondrial ROS production (37). In addition, Zhao et.al (38) reported that overexpression of THBS1 stimulated mitochondrial Ca^{2+} levels and decreased mitochondrial membrane potential (MMP) levels, leading to mitochondrial dysfunction. These data strongly suggests that MOTS-c improves mitochondrial function.

Functional enrichment analysis indicated that the main mechanisms by which MOTS-c improved diabetic heart function involved changes in fatty acid metabolism, immunoregulation, angiogenesis and apoptosis, with altered regulation of the MAPK and ERK1/2, protein kinase B and ErbB signaling pathways as indicated by functional annotation.

CCN1 and EGR1 genes, as GO terms related to apoptosis, were highly expressed in transcriptomics analysis. CCN1 was annotated in the ERK1/2 cascade pathway with the highest enrichment; ERK1/2 alleviates cardiomyocyte apoptosis by regulating EGR1 (39). Hence, we propose that CCN1/ERK1/2/EGR1 is important for reducing myocardial injury in diabetes, as supported by our findings with RT-PCR and western blotting analysis indicating that MOTS-c reduced mRNA expression levels of CCN1, ERK1/2 and EGR1, and protein expression levels of CCN1 and EGR1 in the hearts of diabetic rats, but without affecting ERK1/2 total protein expression (**Figures 6**, **7**).

Levels of the matricellular protein CCN1 are increased in the cardiomyocytes of a stressed heart to promote cardiomyocyte apoptosis (40). CCN1 is overexpressed in the myocardium of diabetic rats, which can stimulate autophagy and decrease myocardial function (41). Although there were no reports on the targeting of CCN1, AMPK, some studies indicate reduced expression of CCN1 by its ectopically expressed siRNA (42). It is possible that AMPK links MOTS-c to CCN1. CCN1 triggers ROS accumulation and mitochondrial outer membrane

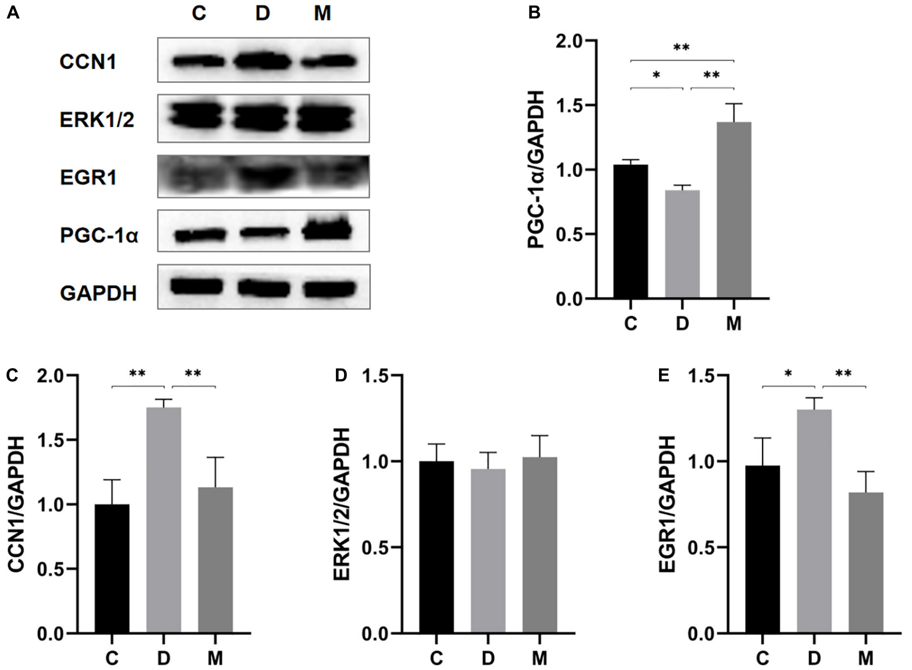

FIGURE 7
Protein expression levels of PGC-1α, CCN1, ERK1/2, and EGR1 in ventricular cardiomyocytes from rats in C, D, and M groups. **(A–E)** Western blot analysis of PGC-1α, CCN1, ERK1/2, and EGR1. Data are expressed as mean ± SD; *$p < 0.05$, **$p < 0.01$; C, non-diabetic control group; D, diabetic control group; M, diabetic MOTS-c injection group.

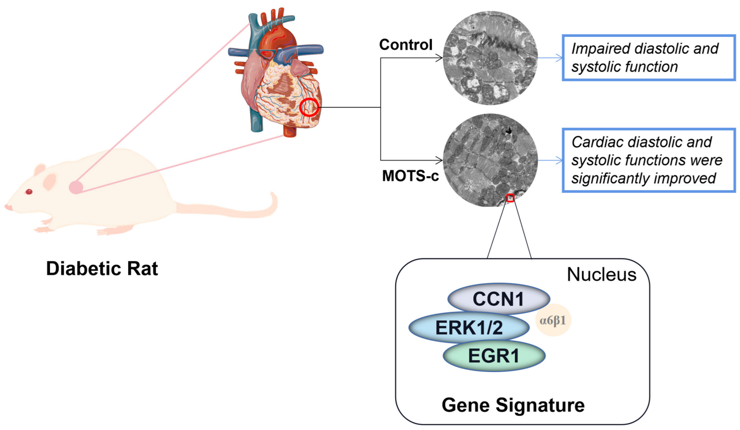

FIGURE 8
A conceptual model of MOTS-c improving myocardial injury in diabetic rats by inhibiting CCN1/ERK/EGR1 expression. Change: Cardiac diastolic and systolic functions were significantly improved to: Improved cardiac diastolic and systolic function.

permeabilization (MOMP) by binding to integrin α6β1 and activation of ERK and JNK to target ubiquitinated mitochondria and stimulate autophagy (43). MOTS-c enhanced mitochondrial homeostasis by decreasing ROS production (44), and CCN1 inhibition may play an important role in this process.

CCN1 also increases levels of the myocardial apoptotic molecule Fas ligand (FasL), which activates the ERK1/2 pathway, leading to dilated cardiomyopathy and advanced heart failure (43, 45, 46). ERKs are a widely conserved family of serine/threonine protein kinases that are implicated in many cellular programs such as cell proliferation, differentiation and apoptosis. MOTS-c participates in various physiological activities by regulating levels of activated ERK1/2 (47, 48). Some studies indicate that MOTS-c administration was without effect on total ERK1/2 protein expression (47, 48), which is consistent with our data. Activation of ERK1/2 mediates cardiac hypertrophy and dysfunction, and in addition to its anti-apoptotic effects in the myocardium (49, 50). The ERK/EGR1 signaling pathway has a critical role in the process of apoptosis in multiple organs (39, 51, 52). Inhibition of ERK1/2 kinase expression downregulates EGR1 expression, thereby reducing myocardial ischemia-reperfusion induced apoptosis and autophagy (39). Our findings suggest that MOTS-c reduces myocardial apoptosis and repairs myocardial mitochondrial injury by inhibiting the overexpression of CCN1 and the downstream activation of ERK1/2, and decreasing the expression of EGR1.

The expression of the tricarboxylic acid (TCA) cycle substrate–dependent mitochondrial calcium uptake 1(MICU1) protein is mediated by the transcription factor EGR1 (53). MICU1 is up-regulated during nutrient deficiency and EGR1 is required for nutrient stress-induced MICU1 upregulation for control of mitochondrial Ca^{2+} uptake (53). Decreased cardiomyocyte function is in part mediated by abnormal mitochondrial calcium handling and a decreased levels of free matrix calcium levels (54), implying that MOTS-c most likely regulates mitochondrial calcium ion homeostasis imbalance by inhibiting EGR1 expression.

4.1. Study limitations

Our study has some limitations: (1) We only measured coding RNA (mRNA) levels and did not investigate the role of non-coding RNA in MOTS-c induced improvements in diabetic heart disease by MOTS-c; (2) We did not investigate the transcriptomic profiling characters of the effects of different MOTS-c treatment protocols such as: different concentration, route and frequency of administration on the diabetic myocardium.

5. Conclusion

An eight-week treatment with MOTS-c treatment reduced cardiac dysfunction in diabetes, which was related to changes in 47 genes involved in fatty acid metabolism, immunoregulation, angiogenesis and apoptosis. Signaling by CCN1/ERK1/2/EGR1 may play an important role in MOTS-c inhibiting myocardial apoptosis. Thus, MOTS-c not only inhibits the development of diabetes and attenuates diabetic myocardial lesions by multiple pathways, including attenuation of mitophagy, reducing mitochondrial damage, and inhibiting myocardial apoptosis through the CCN1/ERK/EGR1 pathway, as illustrated in **Figure 8**. Our findings provide the first experimental evidence of the molecular mechanisms of improvements in cardiac function after treatment of diabetic rats with MOTS-c, and indicate new strategies in the prevention and treatment of diabetic cardiac dysfunction in diabetes.

Data availability statement

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

Ethics statement

This animal study was reviewed and approved by experiments were approved by the Academic Committee of Chengdu Sport Institute (No.: 2021-07).

Author contributions

MW and SL: conceptualization. MW: methodology, writing—original draft preparation, and visualization. MW, XP, and JM: software. XP, YP, and JY: validation. YF: formal analysis. MW and JM: data curation. GW, SL, and IL: writing—review and editing. SL: supervision, project administration, and funding acquisition. All authors 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1060684/full#supplementary-material

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Obesity prevalence, physical activity, and dietary practices among adults in Saudi Arabia

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Introduction: The current study evaluated obesity prevalence, physical activity, and dietary practices among Saudi adults in the Makkah region of the Kingdom of Saudi Arabia (KSA). The current survey was accomplished between November 2021 and March 2022.

Method: A validated questionnaire, Arab Teens Lifestyle Study (ATLS), was used to evaluate all participants' physical activities, sedentary behaviors, and nutritional habits in addition to demographic data.

Result: A total of 2,115 people [1,238 (58.5%) women and 877 (41.5%) men] participated in this survey. Being overweight was prevalent in 32.8% of the population (41% of men and 28.9% of women), obesity was prevalent in 23% of the population (males 23.1% and females 24.2%). Obese people consumed more soft drinks, and overweight people did not consume enough vegetables (fresh/cooked). Obese people consumed fast food (e.g., burgers, sausage, pizza, or Arabic shawarma) over three times each week. The mean (SD) number of days of practice walking was 2.51 (2.05) vs. 1.3 (1.87) ($p < 0.001$) for lean and obese individuals, respectively. In addition, individuals with normal BMI had more days of jogging, moderate and high-intensity exercise, dancing, and strength training than those with obesity. The odds of being obese increased with age (OR: 1.07; $p < 0.001$), in males (OR: 2.16; $p < 0.001$), in participants earning <5,000 SR/month (1.3 thousand $) and 10–15 thousand SR/month (1.34–2.66 thousand $) (OR: 2.36; $P = 0.01$). Obesity was inversely associated with moderate-intensity exercise (OR: 0.802; $p = 0.009$), and regular walking (OR: 0.685; CI: 0.624–0.752; $p < 0.001$).

Discussion: Overweight and obesity were prevalent in 32.8% and 23% of the population, respectively. Sociodemographic factors associated with obesity. Focused intervention strategies are needed to overcome the obesity issue.

KEYWORDS

obesity, overweight and obesity, physical activity, dietary habits, lifestyle factors

Introduction

Scientific discoveries have made every facility available at our fingertips, causing us to adopt sedentary lifestyles and physical inactivity. The advancement of technology, on the one hand, provided relief, conveniences, and pleasures and improved quality of life; on the other hand, being overweight and obese is one of its banes. Obesity has nearly tripled globally since 1975 (1). This is almost a 50-year period when scientific progress is at its peak and enveloped our physical activities. In the recent era, it has become a global epidemic issue.

Globally, over 1.9 billion adult individuals (39%) were overweight, and over 650 million people (13%) were obese (10.8% of men and 14.9% of women) in 2016 (2). The World Health Organization (WHO) reported that the overweight and obesity prevalence in KSA is 68.2% (women 69.2% and men 67.5%) and 33.7% (women 39.5% and men 29.5%), respectively (3). A recent large survey collected data from all regions of KSA and revealed a 24.7% obesity prevalence (4).

Weight status is often thought to result from bad eating habits, a sedentary lifestyle, or a mix of both, given its rising frequency among youngsters (5). Obesity is a complex multidimensional issue influenced by numerous modifiable and non-modifiable elements, including hereditary, demographic, and lifestyle factors (6). It has grown into a huge public health issue because of the increased probability of acquiring type 2 diabetes mellitus, hypertension, cardiovascular disease, obstructive sleep apnea, gall stones, hyperlipidemia, fatty liver disease, osteoarthritis, and psychosocial consequences (4, 7, 8). The current global expenses of obesity are projected to be more than US $2 trillion each year, combining direct healthcare costs and lost economic output, which amounts to 2.8% of global GDP (9).

There is growing evidence linking obesity with vicissitudes in eating practices, primarily because of consuming low quantities of vegetables, fruits, and grains; a constant rise in processed foods intake; increased consumption of sugary beverages and other sugary items, and dining away from home. These changes dramatically boost energy, resulting in a significant shift in metabolic health (10, 11). Most Asian people have a positive energy balance because of lower physical activity at their jobs due to automation, improved transportation, and spending most of their time watching television (12, 13). Many experts attributed obesity as a transfer from indigenous eating habits to western diet habits consisting of ultra-processed foods; therefore, it is considered a legacy of society's modernization (14, 15). These changes have permeated the societies of the Middle East region during the last few decades.

Obesity is a mounting public health issue in the KSA, as it is in the rest of the globe. Several studies have been published concerning the relationship between Saudi adult populations' lifestyle patterns and demographic features with overweight and obesity in various regions of the Kingdom; however, several campaigns have been launched at the governmental level in the recent past to alleviate the Kingdom's alarming rates of overweight and obesity (7, 15). The Makkah region was chosen for this study because it has a high prevalence of obesity among its inhabitants (7). Furthermore, it is one of the top five obesity and overweight regions in the KSA (4).

Because food patterns and physical activities do not remain constant. These are always changing based on age, gender, and responsibilities. Such studies aid in identifying the state of the problem and recommending some adopting steps to control and manage the problem. As a result, the current study will bring the latest updates on the topic in the existing literature, bridging the gap in research and guiding the future management of obesity.

Obesity, which has a significant impact on persons' quality of life in KSA, can be avoided by following correct eating patterns and engaging in regular exercise. Individuals' physical activities and dietary practices can assist to identify their risk for specific diseases, such as diabetes mellitus, and motivate them to adjust their lifestyle habits and care for their bodies and health. Several research investigated weight, nutritional, and physical activity concerns among KSA residents and reported mixed results.

Furthermore, the general public's apathy and lack of initiative in obesity prevention may be due to a lack of cognizance. The cornerstones of preventive and early intervention to tackle the obesity pandemic in KSA include adequate knowledge, optimism, and a proactive commitment to healthy behavior. The study hypothesized that the prevalence of obesity is high in this region and that various dietary, demographic, and lifestyle factors contribute to this high prevalence.

Considering the preceding observations, the current study sought to explore changes in obesity-related indicators among residents of the Makkah region. Therefore, the current survey's objectives were to investigate obesity prevalence, physical activity, and dietary practices among adults in the Makkah region of the KSA.

Methods

The present analytical investigation was carried out in KSA's western region between November 2021 and March 2022 using a cross-sectional design. The ethical approval was taken from "the Biomedical Ethics Research Committee of King Abdulaziz University, Jeddah" (Reference No. 471-21). The current research was carried out in line with the Helsinki Declaration. All data were collected after taking informed consent from all the study participants. The inclusion criteria were people aged 18 years or more, who are residing in the Makkah region, and who agreed to take part in the survey. People who had any disability or suffering from any chronic disease were excluded. A total of 2,115 people were randomly chosen from various public places such as universities, parks, and shopping malls to complete a self-administered questionnaire, and no monetary or any other benefit was offered to them, and their participation was completely voluntary. The first section of the questionnaire consisted of demographic information such as age, gender, educational level, monthly income, and place of residence. Self-reported anthropometric measurements such as height, weight, and most recently measured blood pressure were included in the second section. "The BMI was computed by dividing the weight in kilograms by the square of the individual's height in meters (kg/m^2) and divided into four groups according to the WHO criteria; (a) underweight (BMI 18.5 kg/m^2), (b) normal weight (BMI 18.5–24.9 kg/m^2), (c) overweight (BMI 25–29.9 kg/m^2), and (d) obese (BMI 30 kg/m^2 or more)" (16).

Research instrument

ATLS questionnaire was used to obtain data about the participants' lifestyles (17). It is a 47-item survey. The first five items were related to age, height, weight, waist circumference, and education level, and the remaining were related to physical and sedentary activities and eating practices. The questions were scored using a Likert scale.

TABLE 1 General characteristics of the study participants ($n = 2,115$).

Variables	Mean (SD)
Age (years)	33.52 (13.124)
Mean weight (kg)	70.01 (17.844)
Mean BMI (kg/m^2)	26.23 (6.184)
Waist circumference (cm)	76.20 (18.162)
Systolic BP (mmHg)	122.39 (13.759)
Diastolic BP (mmHg)	79.03 (9.125)
Variables	**Number (percentages)**
Gender	
Male	877 (41.5%)
Female	1,238 (58.5%)
Nationality	
Saudi	1,765 (83.5%)
Non-Saudi	350 (16.5%)
Living place	
Jeddah	1,019 (48.2%)
Rabigh	546 (25.8%)
Other cities	550 (26.0%)
Social status	
Married	1,066 (50.4%)
single	945 (44.7%)
Widow	30 (1.4%)
Divorce	74 (3.5%)
Educational level	
illiterate	34 (1.6%)
High school or below	639 (30.1%)
Bachelor	1,260 (59.3%)
Postgraduate studies	182 (8.6%)%)
Living with	
Family	1,829 (86.5%)
Separate	197 (9.3%)
Friends	67 (3.2%)
Others	22 (1.0%)
Monthly income (in Saudi Riyals)	
<5 thousand	818 (38.7%)
5–10 thousand	498 (23.5%)
10–15 thousand	392 (10.0%)
15–20 thousand	212 (18.5%)
More than 20 thousand	195 (9.2%)
BMI categories	
Underweight	160 (7.5%)
Normal	712 (33.5%)
Overweight	698 (32.8%)
Obese	488 (23.0%)

Physical activities assessment

In total, 29 items (6–34) were related to physical activities such as exercise, swimming, light, moderate, and high-intensity sports activities, participation in traditional dancing, and housework. The original questionnaire has already been found to have good reliability "[intraclass correlation coefficient (ICC) = 0.85; 95% confidence limits (CL), 0.70–0.93] (18) and satisfactory validity ($r = 0.37$, $p < 0.001$) vs. the pedometer-measured level of physical activity" (19).

Sedentary behaviors assessment

Three items of sedentary behavior questions (35–37) were designed to elicit essential information from adults about their average daily time devoted to sedentary activities, such as watching TV, playing video games, and benefiting from computers and the Internet. Individuals were enquired to affirm their average daily work hours, regardless of whether they worked during the week or on weekends.

Eating habits assessment

The ALTS questionnaire assessed eating habits by 10 items (38–47). "Participants were asked frequency of breakfast, fizzy drinks (including soft drinks), vegetables, fruits, and dairy products, donuts and cakes, candy and chocolate, energy drinks, and fast foods per week. In this perspective, fast foods contained examples from both Western fast meals and Arabic fast foods, such as shawarma (grilled meat or chicken on pita bread with some salad)." These questions focused on both good and bad eating habits.

Statistical analysis

Excel spreadsheets and SPSS version 20 were used to enter and process all data. Means and standard deviations for BMI were compiled. By using the chi-square test at the 95% level of significance, the basic relationship between sociodemographic factors and body weight status was examined. An independent t-test was employed to compare continuous variables between lean and obese groups. To evaluate obesity-related factors, multiple logistic regression analyses were performed. The model included age, gender, educational achievement, social position, numerous physical activities, and varied food habits as independent factors, and the odds ratio (OR) was computed. A level of significance of $p < 0.05$ was judged statistically significant.

Results

Overall, 2,115 people [1,238 (58.5%) women and 877 (41.5%) men] participated in this survey. The mean age (SD) was 33.52 (13.12). Being overweight was prevalent in 32.8% of the population (41% of men and 28.9% of women), obesity was prevalent in

TABLE 2 Correlation of dietary habits with different BMI categories (normal, overweight, and obese).

Dietary habits	Normal	Overweight	Obese	*p*-value
	N (%)	*N* (%)	*N* (%)	
Eating breakfast				
Do not eat	69 (31.4%)	71 (32.3%)	61 (27.7%)	0.789
Eating regularly	335 (35.4%)	316 (33.4%)	221 (23.3%)	
Eating sometimes	299 (34.6%)	299 (34.6%)	202 (23.4%)	
Drinking soft drinks				
Do not drink	219 (35.9%)	198 (32.5%)	138 (22.6%)	0.070
1–3 times/week	373 (35.3%)	362 (34.2%)	241 (22.8%)	
More than 3 times/week	108 (30.5%)	121 (34.2%)	105 (29.7%)	
Eating vegetables (fresh or cooked)				
Do not eat	57 (29.1%)	78 (39.8%)	45 (23.0%)	
Eating 1–3 times/week	407 (34.0%)	401 (33.5%)	298 (24.9%)	0.399
Eating more than 3 times/week	225 (36.9%)	202 (33.1%)	136 (22.3%)	
Eating fruits				
Do not eat	106 (30.9%)	116 (33.8%)	88 (25.7%)	0.256
Eating 1–3 times/week	447 (35.4%)	428 (33.9%)	306 (24.2%)	
Eating more than 3 times/week	136 (35.5%)	129 (33.7%)	83 (21.7%)	
Consuming diary product				
Do not eat	71 (30.9%)	73 (31.7%)	65 (28.3%)	0.397
Eating 1–3 times/week	357 (34.4%)	363 (35.0%)	248 (23.9%)	
Eating more than 3 times/week	252 (35.6%)	236 (33.3%)	162 (22.9%)	
Consuming fast food				
Do not eat	184 (35.8%)	161 (31.3%)	117 (22.8%)	0.05
Eating 1–3 times/week	419 (34.6%)	422 (34.8%)	285 (23.5%)	
Eating more than 3 times/week	80 (31.5%)	87 (34.3%)	74 (29.1%)	
Consuming French fries/potato chips				
Do not eat	221 (36.5%)	198 (32.7%)	139 (23.0%)	0.312
Eating 1–3 times/week	410 (35.1%)	390 (33.4%)	283 (24.2%)	
Eating more than 3 times/week	52 (26.5%)	75 (38.3%)	53 (27.0%)	
Eating cakes/biscuits/donuts				
Do not eat	172 (35.8%)	164 (34.1%)	105 (21.8%)	0.845
Eating 1–3 times/week	412 (34.2%)	407 (33.8%)	295 (24.5%)	
Eating more than 3 times/week	94 (32.3%)	97 (33.3%)	77 (26.5%)	
Sweats/chocolate				
Do not eat	143 (34.4%)	140 (33.7%)	94 (22.6%)	0.717
Eating 1–3 times/week	412 (34.8%)	407 (34.4%)	282 (23.8%)	
Eating more than 3 times/week	123 (33.5%)	119 (32.4%)	95 (25.9%)	
Energy drinks				
Do not drink	523 (34.9%)	505 (33.7%)	356 (23.7%)	0.899
Drinking 1–3 times/week	125 (33.4%)	128 (34.2%)	89 (23.8%)	
Drinking more than 3 times/week	29 (33.7%)	29 (33.7%)	24 (27.9%)	

TABLE 3 Comparison of demographic factors with different BMI categories (normal, overweight, and obese).

Factors	Normal *N* (%)	Overweight *N* (%)	Obese *N* (%)	*p*-value
Gender				
Male	255 (29.9%)	350 (41.0%)	197 (23.1%)	**0.00**
Female	457 (38.0%)	348 (28.9%)	291 (24.2%)	
Nationality				
Saudi	622 (36.2%)	523 (30.5%)	428 (24.9%)	**0.00**
Non-Saudi	90 (26.3%)	175 (51.2%)	60 (17.5%)	
Social status				
Married	253 (24.3%)	431 (41.3%)	321 (30.8%)	**0.00**
Single	431 (47.0%)	238 (26.0%)	129 (14.1%)	
Widow	8 (28.6%)	9 (32.1%)	10 (35.7%)	
Divorced	20 (28.6%)	20 (28.6%)	28 (40.0%)	
Educational level				
Illiterate	8 (26.7%)	13 (43.3%)	6 (20.0%)	**0.00**
Secondary and below	229 (37.2%)	192 (31.2%)	150 (24.4%)	
Bachelor student	435 (35.2%)	401 (32.5%)	293 (23.7%)	
Postgraduate	40 (22.6%)	92 (52.0%)	39 (22.0%)	
Occupation				
Health care worker	48 (34.5%)	55 (39.6%)	30 (21.6%)	**0.00**
Government	112 (24.7%)	179 (39.5%)	152 (33.6%)	
Private	71 (27.7%)	107 (41.8%)	59 (23.0%)	
Free work	33 (34.4%)	41 (42.7%)	21 (21.9%)	
Housewife	96 (27.7%)	117 (33.7%)	120 (34.6%)	
Unemployed	43 (38.4%)	29 (25.9%)	21 (18.8%)	
Student	309 (47.2%)	170 (26.0%)	85 (13.0%)	
Monthly income				
<5 thousand	312 (39.5%)	204 (25.9%)	172 (21.8%)	**0.00**
5–9.9 thousand	168 (34.6%)	178 (36.6%)	111 (22.8%)	
10–14.9 thousand	103 (26.9%)	148 (38.6%)	118 (30.8%)	
15–20 thousand	68 (32.5%)	83 (39.7%)	49 (23.4%)	
Above 20 thousand	61 (31.9%)	85 (44.5%)	38 (19.9%)	

All values in bold are statistically significant.

23% of the population (men 23.1% and women 24.2%), and being underweight was prevalent in 7.5% of the population. A total of 1,260 (59.3%) participants have a bachelor's degree and 1,829 (86.5%) live with their families (Table 1).

There were no discernible changes in fresh fruit, dairy products, or sweet consumption between BMI categories. Overweight people did not consume enough vegetables (fresh/cooked) and ate fast food (e.g., burgers, sausage, pizza, or Arabic shawarma) on more than three occasions every week. People with normal weight consume more fresh fruit than those who are obese or overweight. Similarly, participants of normal weight ate breakfast regularly, even though the p-value was not significant ($p = 0.789$) (Table 2).

Many government employees were overweight or obese. Sociodemographic factors such as gender, nationality, social status, educational level, occupation status, and monthly income had a significant impact. Men were more overweight compared to women; on the other hand, more women were obese compared to men. Interestingly, obesity was more prevalent among housewives. Among Saudi and non-Saudi participants, obesity rates are 24.9% and 17.5% and overweight rates are 30.5% and 51.2%, respectively. Obesity is influenced by monthly income; 44.5% of people earning more than SR 20,000 are overweight. On the other hand, 39.5% of people earning <SR 5,000 per month (1.3 thousand $) are of normal weight (Table 3).

The mean (SD) number of days of practice walking was 2.51 (2.058) vs. 1.30 (1.871); $p < 0.001$ for normal and obese individuals, respectively. In addition, individuals with normal BMI had more days of jogging, moderate and high-intensity exercise, dancing, and strength training than those with obesity (Table 4).

The odds of being obese increased with age (OR: 1.07; $p < 0.001$), in men (OR: 2.16; $p < 0.001$), and in participants' earning <5,000 SR/month (1.3 thousand $) (OR: 1.037; $p = 0.001$) and earning 10–15 thousand SR/month (1.34–2.66 thousand $) (OR: 2.36; $p = 0.01$). Obesity was inversely associated with moderate-intensity exercise (OR: 0.802; $p = 0.009$) and regular walking (OR: 0.685; $p < 0.001$) (Table 5).

Discussion

Obesity has generally become a huge point of concern on a global scale, and in the KSA, its mounting prevalence among children, adolescents, and adults has made it a major worry. According to the current study findings, 32.8% of the population was overweight, 23% were obese, and 7.5% were underweight. A bigger percentage of men than women were overweight, but a greater percentage of women than men were obese.

Our overweight and obesity prevalence results corroborate with Saudi, Iraqi, and Brazilian studies (4, 20, 21). However, Iraqi and Brazilian studies have reported a lower incidence of underweight individuals, 1.5% and 3.6%, respectively (20, 21), while a Saudi survey reported a much higher incidence of 21.7% (4). Several KSA studies have shown the varying prevalence of obesity and overweight (7, 22, 23). The actual prevalence of obesity may be more in KSA than in the present study findings. The possible reason could be our study participants' low mean age (33.5 years). Few studies have demonstrated that obesity and overweight increase with age (24–26). Male obesity has been linked to infertility due to a drop in sex hormone levels (27), and it induces polycystic ovarian syndrome in women by interacting with adipokine and steroid hormones (28). Obesity has a deleterious impact on female fecundity as well as fetuses and embryos *via* oxidative processes (29).

TABLE 4 Comparison of different types of physical activity in lean and obese subjects.

Types of physical activities	Lean (BMI = 18.5–24.9 kg/m^2)	Obese (BMI ≥ 30 kg/m^2)	*p*-value
	Mean (SD)	Mean (SD)	
How many days per week do you exercise walking?	2.51 (2.058)	1.30 (1.871)	**0.00**
How many days a week do you regularly exercise (jogging or running or both), whether on the ground or a treadmill? (days/week)	1.24 (1.872)	0.63 (1.429)	**0.00**
How many days a week do you regularly ride a regular bike, stationary bike, or both? (days/week)	0.39 (1.156)	0.28 (0.965)	0.094
How many days a week do you swim regularly? (days/week)	0.29 (0.944)	0.23(0.945)	0.330
How many days a week do you regularly practice moderate-intensity, non-strenuous sports activities other than the activities (such as volleyball, table tennis, bowling, badminton, etc.) (days/week)	0.58 (1.306)	0.31 (0.983)	**0.00**
How many days a week do you do high-intensity and physically strenuous sports other than the activities (such as basketball, handball, football, tennis, squash, CrossFit, etc.) (days/week)	0.51 (1.373)	0.29 (0.956)	**0.002**
How many days a week do you regularly? practice self-defense sports such as (judo, karate, taekwondo)? (days/week)	0.19 (0.850)	0.17 (0.769)	0.686
How many times per week do you regularly do strength training (weight training or body building or calisthenics exercise)? (days/week)	0.70 (1.569)	0.50 (1.286)	**0.017**
How many times per week do you do traditional dancing (whether alone or with your friends)? (days/week)	0.99 (1.734)	0.71 (1.473)	**0.016**
How many times per week do you engage in household work (e.g., gardening, vacuuming, washing, car cleaning)? (days/week)	2.26 (2.575)	2.05 (2.576)	0.192
Average sleeping time (hours)	7.04 (1.853)	6.86 (1.971)	0.110

Mean days of practicing specific physical activity (SD). All values in bold are statistically significant.

The present study results indicate the ineffectiveness of educational campaigns against obesity prevention in the region. Moreover, obesity and its consequences also have a negative impact on the healthcare budget. Therefore, the health ministry's continual campaign on social and mass media is much needed regarding this issue.

The high frequency of overweight among men (41%) is alarming. It needs immediate remedial steps because all these overweight people are at risk of becoming obese. These individuals are needed to change their dietary patterns and adopt healthy lifestyles. It is suggested that walking and other moderate-intensity exercises may help in reducing the risk of obesity (30).

Our investigations revealed that obesity is more widespread in women than men, which conforms with the results of prior investigations (20, 31, 32). Women are more obese for a variety of reasons, including their parity and biological factors such as hormonal shifts and usage of contraceptive pills (33), the less physical effort required in their employment, more household work, less spare time, and imbalance of excessive calorie intake and insufficient activities (11, 31, 34, 35). A prior study demonstrated that the female gender, old age, and reduced physical activity were all major obesity risk elements in South Asian people (36).

It is challenging to interpret why there were no significant variations in fresh fruit, dairy products, or sweet consumption across BMI categories among the current study participants. However, the overweight/obese individuals probably have some realization of their increasing weight, thus they were avoiding the consumption of too many sweets; another probability is that they underestimated their consumption of sweets.

Similar to the present study, a previous Saudi study used the same ATLS questionnaire and found no significant differences in most lifestyle-related patterns between lean and overweight/obese women (22). According to a Saudi survey, the majority of university students drank soft/energy drinks more than once a day, ate fast food daily, and spent 3–4 h per day on their screens (37).

There is emerging evidence linking dietary preferences to body weight. Few studies identified a link between bad dietary habits and being overweight or obese (38–40), but an Iraqi study found no link (21). Few studies have reported that body weight was positively linked with fast food (38) and sweetened beverages (39), and inversely linked with eating fruits, vegetables, legumes, and nuts (40). Several studies in the general population found that greater adherence to healthy eating patterns was related to a decreased incidence of obesity (44, 45).

The current study noted that obese people consumed more soft drinks and fast food such as burgers, sausages, pizza, or Arabic shawarma. There is a need to make them aware that consuming junk food is not good for their health and positively impacts weight gain. Such food also contains more saturated fats, trans-fatty acids, and decreased micronutrients that cause several health issues. As a result, consuming these items regularly may result in excess of daily calorie intake, resulting in a higher frequency of overweight and obesity and more probability of getting chronic non-communicable illnesses such

TABLE 5 Association of demographic characteristics and other variables with different BMI.

Characteristics		B	Obese	
			OR 95% CI	*p*-value
Age		0.074	1.077 (1.057–1.098)	**0.000**
Gender	Male	0.771	2.162 (1.540–3.036)	**0.000**
	Female		Reference	
Social status	Married	0.063	1.433 (0.700–2.933)	0.764
	Single	−0.277	0.758 (0.345–1.664)	0.237
	Widow	−0.388	0.679 (0.182–2.533)	0.686
	Divorce		Reference	
Occupation	Health care worker	0.473	1.298 (0.637–2.648)	0.057
	Government	0.659	1.156 (0.608–2.200)	0.368
	Private	0.646	1.15 (0.631–2.103)	0.087
	Free	0.461	0.730 (0.315–1.688)	0.794
	Housewife	0.234	1.474 (0.778–2.792)	0.158
	Unemployed	0.784	1.106 (0.539–2.268)	0.410
	Student		Reference	
Place of living	Jeddah	−0.058	0.944 (0.665–1.341)	0.748
	Rabigh	−0.044	0.957 (0.639–1.435)	0.833
	Other cities		Reference	
Monthly income	<5 thousand	1.073	2.925 (1.526–5.606)	**0.001**
	5–9.9 thousand	0.432	1.540 (0.808–2.936)	0.981
	10–14.9 thousand	0.861	2.366 (1.233–4.539)	**0.010**
	15–20 thousand	0.277	1.319 (0.946–2.684)	0.444
	More than 20 thousand		Reference	
Educational level	No grade completed	−1.273	0.280 (0.059–1.332)	0.110
	Secondary or below	−0.259	0.772 (0.402–1.482)	0.436
	Bachelor's	−0.210	0.810 (0.446–1.471)	0.490
	Postgraduate		Reference	
Walking		−0.378	0.685 (0.624–0.752)	**0.000**
Moderate intensity exercise		−0.220	0.802 (0.680–0.946)	**0.009**
Consumption of fast food	I don't eat	0.153	1.165 (0.641–2.118)	0.616
	1–3times/week	0.041	1.042 (0.639–1.699)	0.968
	More than 3 times/week		Reference	
Drinking sugary drinks/soft drinks e.g., Coke, Pepsi	I don't drink	−0.421	0.884 (0.53–1.455)	0.627
	1–3 times/week	−0.171	0.843 (0.547–1.298)	0.438
	More than 3 times/week		Reference	

Reference category: normal BMI. All values in bold are statistically significant.

as T2DM, CVD, hypertension, and others. Therefore, providing nutritional counseling and intervention concerning healthy eating is essential.

The present study results indicated that obese individuals were less active, and several sociodemographic factors were associated with obesity. Moderate-intensity exercise and walking were protective factors against obesity, and people who did not take soft drinks were less likely to be obese. Contrary to our findings, a few investigations discovered no association between demographic and lifestyle variables with overweight or obesity (7, 20). A Brazilian study observed sociodemographic characteristics (such as the mother's education level, age range, and gender) were linked to inappropriate eating situations at breakfast and/or dinner (46). Our results are compatible with several studies (20, 47). Our study found that married individuals had probability to be obese than unmarried individuals. It is because married people are older and body weight usually increases with age. Housewives had a higher prevalence of obesity, and it could be because they stay at home, and in KSA, people's socioeconomic conditions are good, and most of them have several servants and maids who perform all house chores. Because of this good socioeconomic condition, they dine outside the home more frequently and are more prone to sedentary behavior. So, this sedentary behavior tends to increase obesity among them.

Similar to our results, an Iraqi study reported that obesity and physical exercise have an inverse relationship (21). Several pieces of research have shown a relationship between physical inactivity and obesity (19, 48, 49). Our findings showed that men had more probability to be obese compared to women. This is consistent with few studies (19, 21) and contradictory with few studies that found its connection with the female gender (7, 22, 50, 51). Physical activities such as moderate exercise and regular walking contribute to the reduction of obesity. This observation could be attributed to the fact that physical activities usually burn calories, and burning more calories is beneficial for maintaining a healthy weight. Regular walking and moderate exercise improve body endurance and fitness level, as well as have a positive impact on all physiological systems. Some of the benefits of physical activity include increased mitochondrial function, better vasculature, and the production of myokines from skeletal muscle that support or enhance cardiovascular function (52). When physical activity is prolonged and muscle glycogen stores are depleted, fat metabolism may become a more important source of energy. As a result, weight loss is attainable (53). Therefore, people should take time out of their hectic lives to improve their health.

Obesity is a big issue in the KSA, and it urgently requires preventative strategies to address an increase in obesity prevalence. People must forsake sedentary behaviors and exercise regularly and eliminate extra fatty and sugar-containing foods from their regular menu to live a healthy life. There is a need to establish more walking tracks and sports centers across the city. The use and assessment of evidence-based therapies are strongly encouraged (7).

Cattafesta et al. (20) have suggested that because obesity has various causes, coping solutions must be multifaceted, intersectoral, and interdisciplinary. Implementing preventive measures, such as programs promoting a healthy diet, proper food policy, encouraging physical activity and discouraging sedentary behavior, and community awareness programs may help reduce obesity (21).

We believe that obesity can be culminated by modifying dietary patterns and providing healthier dining situations for individuals while honoring traditional culinary culture besides promoting physical activity, particularly leisure activities. Obesity interventions can be strengthened by focusing on men, the aged, those with lower and higher socioeconomic status, and physical activities and dietary patterns. It would be better to start awareness campaigns in schools and colleges, thus the new generation knows the consequences of being overweight and obese and its preventive strategies, and they can modify their dietary patterns, physical activities, and lifestyle accordingly.

Limitations

The present study being cross-sectional cannot determine causality. Second, because height and weight are self-reported, they may be underestimated or overstated. Third, because our dietary instrument was designed to offer information about the number of times specific food items were ingested rather than the number of individual food items, we were unable to control the effect of the number of specific food items. Fourth, in the present study, the convenient sampling method was used in which the generalization of the results is compromised. The study's findings can be extrapolated to the population of Saudi Arabia's Makkah region but not the entire country. The likelihood of recall bias in reporting all lifestyle behaviors cannot be ruled out. Fifth, the questionnaire section on food frequency items did not consider portion size, and this factor could have altered the correlations between food habits and being overweight or obese.

Conclusion

Being overweight and obese were prevalent in 32.8% and 23% of the population, respectively. The current study found few sociodemographic and lifestyle factors related to obesity that could be useful targets for preventing and managing obesity among Saudi inhabitants. Focused intervention strategies are needed to deal with the obesity epidemic. Obesity prevention through active lifestyles and a healthy diet should be a national public health priority. Future research should also focus on implementing a healthy lifestyle and assessing its impact on obesity. Furthermore, government agencies and research organizations must maintain ongoing surveillance of overweight 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 ethical approval was taken from the Biomedical Ethics Research Committee of King Abdulaziz University, Jeddah, Saudi Arabia (Reference No. 471-21). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SA contributed to the conceptualization, design, and analysis of the study. MB and TA contributed to the study design, analysis, and preparation of the manuscript. NA, EH, RA, MA, SA, and TA helped in study design, data collection, and interpretation. All authors contributed significantly and approved the submitted version for publication.

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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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Nutritional supplements improve cardiovascular risk factors in overweight and obese patients: A Bayesian network meta-analysis

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Background: Overweight and obesity are considered as one of the major risk factors for cardiovascular diseases (CVD). At present, many studies have proved that multiple nutritional supplements play an active role in metabolic diseases. However, the comparative efficacy of different nutritional supplements in improving indicators of cardiometabolic risk in obese and overweight patients is uncertain.

Methods: Cochrane Library, PubMed, Embase, and Web of Science were searched for the period from January 1990 to March 2022. A random-effect model was built in the Bayesian network meta-analysis. The surface under the cumulative ranking analysis (SUCRA) and clustering rank analysis was performed for ranking the effects.

Results: The study included 65 RCTs with 4,241 patients. In terms of glucose control, probiotic was more conductive to improve FBG (MD: −0.90; 95%CrI: −1.41 to −0.38), FINS (MD: −2.05; 95%CrI: −4.27 to −0.02), HOMA-IR (MD: −2.59; 95%CI −3.42 to −1.76). Probiotic (MD: −11.15, 95%CrI −22.16 to −1.26), omega-3 (MD: −9.45; 95%CrI: −20.69 to −0.93), VD (MD: −17.86; 95%CrI: −35.53 to −0.27), and probiotic +omega-3 (MD: 5.24; 95%CrI: 0.78 to 9.63) were beneficial to the improvement of TGs, TC and HDL-C, respectively. The SUCRA revealed that probiotic might be the best intervention to reduce FBG, FINS, HOMA-IR; Simultaneously, α-lipoic acid, VD, and probiotic + omega-3 might be the best intervention to improve TGs, TC, and HDL-C, respectively. Cluster-rank results revealed probiotic had the best comprehensive improvement effect on glucose metabolism, and probiotic + omega-3 may have a better comprehensive improvement effect on lipid metabolism (cluster-rank value for FBG and FINS: 3290.50 and for TGs and HDL-C: 2117.61).

Conclusion: Nutritional supplementation is effective on CVD risk factors in overweight and obese patients. Probiotic supplementation might be the best intervention for blood glucose control; VD, probiotic + omega-3 have a better impact on improving lipid metabolism. Further studies are required to verify the current findings.

KEYWORDS

obesity, nutritional supplement, cardiovascular risk factors, body composition, probiotics, Bayesian network meta-analysis

1. Introduction

The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that may damage health (1). Obesity is a threat to global population health in terms of prevalence and disease burden. In recent research, 2 billion people was diagnosed with overweight or obesity (2). In obese and overweight patients, the active metabolism of adipose tissue induces metabolic changes, such as increased production of reactive oxygen species, oxidative stress and inflammation, leading to type 2 diabetes mellitus (T2DM), arterial hypertension and dyslipidemia, which are the most important precursor risk factors for cardiovascular diseases (CVD) (3). Cardiometabolic biomarkers, such as blood glucose, insulin resistance and lipid profiles, are important risk indicators of subclinical disease and a valuable tool for monitoring CVD (4–6). Therefore, improving the metabolic status of overweight and obese patients is an important preventive strategy to prevent the development of more serious metabolic diseases.

Since most of the drugs used to treat obesity have been withdrawn from the market due to improper use or side effects, lifestyle change and diet control are the safest and most cost-effective interventions for obese and overweight people to control their weight (7–9). Some nutrients not only have antioxidant, anti-inflammatory and immune-enhancing biological activities, but also have greater safety compared with drugs. Currently available nutritional supplements such as vitamins, minerals, fatty acids, and plant compounds have been shown to improve obesity by improving carbohydrate metabolism, increasing lipolysis or energy expenditure, and reducing hunger (10). Therefore, they have attracted extensive attention in the treatment of metabolic diseases. According to previous meta-analysis, resveratrol, Vitamin D (VD)/VD + calcium (Ca), probiotics, α-lipoic acid, omega-3, curcumin, and magnesium (Mg) were used to improve multiple comorbidities of metabolic disorders (11–17). While most RCTs and meta-analysis to date have proved the beneficial effect of nutritional supplements on metabolism diseases patients, limited data are available regarding their effects on other indicators of CVD risk, i.e., metabolic syndrome (MetS) (18), elevated blood pressure (19), endothelial function (20), and in other at-risk populations. Obesity, particularly intra-abdominal obesity, predisposes people to several modifiable risk factors of CVD and T2DM, i.e., cardiometabolic risk (21). Furthermore, it is difficult to determine the comprehensive efficiency of different nutritional strategies using pair-wise meta-analysis.

The effect of different nutritional supplements for overweight and obesity patients on cardiovascular risk factors, as well as which intervention is most effective, remain to be verified. Therefore, in this study, we aimed to conduct systematic review and network meta-analysis (NMA) by comparing the adjuvant therapy of different nutritional supplements for overweight and obese adults, so as to provide reference for clinical practice.

Abbreviations: CVD, Cardiovascular disease; VD, Vitamin D; Ca, Calcium; Mg, Magnesium; WC, Waist circumference; BMI, Body mass index; FBG, Fasting blood glucose; FINS, Fasting insulin level; HOMA-IR, Homeostatic model assessment of insulin resistance; HbA1c, Hemoglobin A1c; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TGs, Triglycerides; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

2. Methods

This systematic review was prepared according to the preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (22) as well as the PRISMA extension statement for network meta-analysis (23) (Supplementary File 1) and was registered at the international Prospective Register of Systematic Reviews (CRD42022371086).

2.1. Search strategy

Two independent researchers searched PubMed, EMBASE, Web of Science and Cochrane Library from the inception of each database to March 20, 2022, and the search strategy was based on the standards established by the Cochrane Collaboration. The search was limited to human subjects' studies and English language publications. We use both medical subject heading (MeSH) and extensive free-text keywords, and search terms included: random*, adults, obesity, overweight, supplementation, nutrition, resveratrol, Vitamin D, probiotics, α-lipoic acid, omega-3, curcumin, magnesium. The search strategy is shown in Supplementary File 2.

2.2. Eligibility criteria

In this network meta-analysis, randomized controlled trials (RCTs) which fulfilled the following criteria for participants, interventions, comparisons, outcomes, and study design (PICOS) were included: (1) Participants: We included studies of overweight or obese adults and excluded studies of other cardiovascular diseases (i.e., type 2 diabetes, insulin resistance, non-alcoholic fatty liver disease, hyperlipemia, hypertension), children, adolescents or pregnant women. Overweight and obesity are defined as body mass index (BMI) ≥ 25 and 30 kg/m^2, respectively. (2) Intervention: The intervention group used at least one of the following seven nutrition supplements: resveratrol, VD, probiotics, α-lipoic acid, omega-3, curcumin, Mg. The duration was at least 4 weeks. (3) Comparisons: Control, including groups that received placebo or those who received any nutrition supplements on the basis of nutritional treatment or maintaining the usual diet. (4) Outcomes: The parameters in the research results include at least two of the following parameters: cardiovascular risk factors [including systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), fasting insulin level (FINS), homeostatic model assessment of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)] and body composition [including Weight, Waist circumference (WC), and BMI]. (5) Study design: Parallel or cross-over design.

2.3. Data extraction

Two researchers (D.Z. and Z.Y.) independently screened and assessed the titles and abstracts according to the prespecified criteria. The full texts of articles that potentially met the eligibility criteria were reviewed and data extracted using the same standardized data extraction methods. If more than one article from the same study was found, only the article with more detailed information was selected to avoid data duplication. The data was independently extracted and cross-checked by two researchers (D.Z. and Z.Y.), and any disagreement was resolved by the judgment of the third researcher (X.L.).

Information about study design was extracted, including study-level characteristics (i.e., first author name, year of publication, and geographic location), participant-level characteristics (i.e., age, proportion of male participants, and diet control or daily exercise), program-level characteristics (i.e., study design, sample size in each group, type and dose of nutritional supplementation, and outcome data). We extracted the preintervention/postintervention (pre/post) change data to conduct this NMA. Regarding the RCTs with multiple time points, only the last time point was considered and intermediary time points were omitted.

2.4. Quality assessment

Assessment of risk of bias in randomized trials was performed using the Cochrane Risk of Bias Tool for RCTs (24) by two investigators independently (Z.Y. and D.Z.), and studies were assessed from the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was classified as low risk of bias, high risk of bias, or unclear risk of bias. Any disagreement was resolved by discussions with the third author (X.L.).

2.5. Data synthesis and statistical analyses

For continuous data, mean and standard deviation (SD) were extracted. For studies presenting median and interquartile range, mean was estimated by (first quartile + third quartile)/2, and SD was estimated by (third quartile − first quartile)/1.35 (25). For studies presenting 95% confidence intervals (CIs), standard error (SE) was estimated by (upper limit − lower limit)/3.92 and SD was calculated as $SE \times \sqrt{n}$ (26). After data extraction, we unified the unit of the outcomes previously reported, and the FBG, FINS, and the lipid markers levels (i.e., TGs, TC, HDL-C, LDL-C) were encoded in mmol/L, μIU/mL, and mg/dL, respectively.

2.5.1. Pair-wise meta-analysis

First, we performed a pairwise meta-analysis for every intervention comparison. Continuous data were analyzed using Weighted mean differences (WMDs) and 95% CIs to express the effect size and I^2 statistic and Q test were used to assess the heterogeneity of the treatment effect which was deemed significant when P was <0.05 or I^2 was more than 50%. In this analysis, heterogeneity was present, thus, all results were reported using the random-effect model.

2.5.2. Network meta-analysis

Second, network meta-analysis was performed using a random effects model based on the Bayesian framework and this model using the Markov-chain Monte Carlo (MCMC) method to obtain the non-informative uniform and normal prior distributions (27). Four iteration chains, with 50,000 iterations per chain, were set to fit the model and calculate the posterior distributions of model parameters. The thinning interval was set at 10 and the burn-ins at 1,000 for each chain. In this NMA, mean differences (MDs) with 95% credible intervals (CrIs) were generated from the posterior distribution medians, which did not contain 0 indicating significant differences between interventions. Deviance information criterion (DIC) was obtained from consistency and inconsistency models for each endpoint and difference between each pair of DICs (dDIC) were calculated to assess global inconsistency. A value of dDIC < 10 was deemed to have no appreciable global inconsistency. A node-split model was used to check the consistency assumption of direct evidence and indirect evidence with $p < 0.05$ indicating significant local inconsistency (28). The consistency model was adopted only if global inconsistency tests and node-split tests both reported no significant inconsistency. We performed meta-regression analysis to evaluate the potential impact of confounding factors (e.g., age, life style, proportion of male, total number of participants and intervention duration) on the model based on non-negligible differences in participant baseline characteristics (29). Surface under the cumulative ranking curve analysis (SUCRA) derived from posterior probabilities was used to rank the relative efficacy of interventions with larger SUCRA value indicating better interventions (30). Clustered-ranking plots were used for the determination of the most comprehensive intervention choice.

Stata software (version 12.0, StataCorp, College Station, TX) were used to produce the network evidence relationship plot and comparison-adjusted funnel plots. R software (version 3.6.2, MathSoftCorp, AT&T Bell Laboratories) with GeMTC (version 0.8-8) and JAGS packages (version 4.1.0, https://sourceforge.net/projects/mcmc-jags/files/) was used to perform the pairwise and network meta-analysis.

3. Results

3.1. Literature selection and study characteristics

Of the 3,863 publications retrieved *via* literature search, 2,233 records left after removing duplicates. After reviewing the title and abstract, 81 studies were selected for further review. Then 16 studies were excluded (8 included patients with other cardiovascular diseases, 4 were without control group, and 4 did not meet our inclusion criteria). Finally, a total of 65 studies (31–95) and 4,241 obesity or overweight patients were ultimately included in this NMA, with 2,395 in the experimental group and 1,846 in the control group. The detailed selection process is described in Figure 1. All 65 included studies consist of 55 two-arms, 3 three-arms and 8 four-arms and were published between 2005 and 2022. The intervention duration of all studies was more than 4 weeks. The average age of the participants was 43.1 years and the percentage of male patients was about 40.7%. the average BMI of subjects is more than 30 kg/m^2. Table 1 details the study characteristics.

Figure 2 shows the network plots of the included studies. We included 13 kinds of nutritional supplementations in our NMA: resveratrol, VD, probiotics, probiotics + VD, VD + Ca, α-lipoic acid,

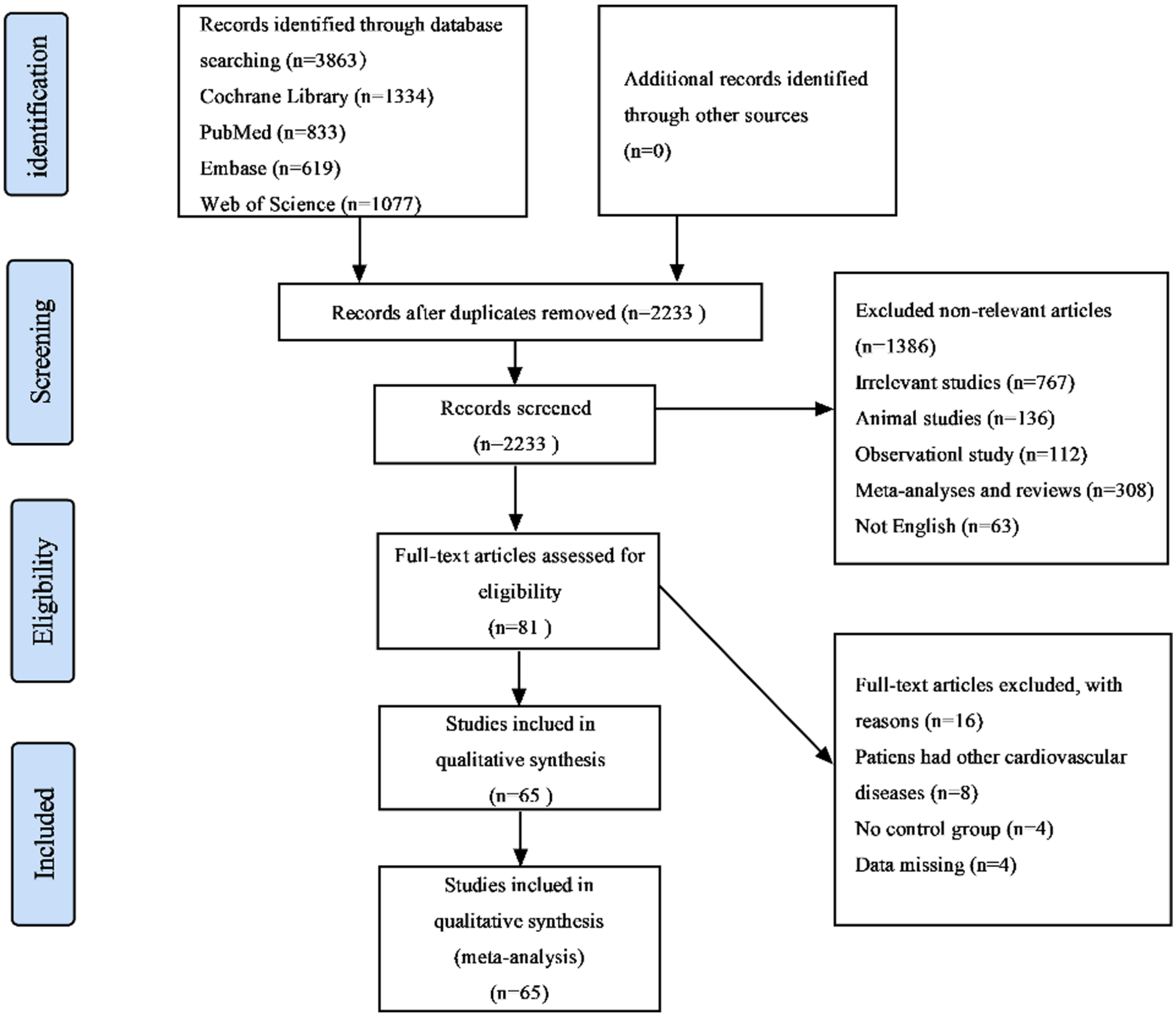

FIGURE 1
PRISMA flow diagram of selection of studies from search to final inclusion.

omega-3, omega-3 + α-lipoic acid, probiotics + α-lipoic acid, curcumin, probiotics + omega-3, Mg, and placebo.

3.2. Risk of bias and data quality

The results of quality assessment were summaries in Supplementary Figure S1. The revised Cochrane Risk-of bias Tool for RCTs (RoB 2.0) was used to assess the quality of 65 included RCTs. All eligible RCTs mentioned randomization and were classified as "low risk." 28 articles showed "unclear risk" and 1 article showed "high risk" in adequate allocation concealment. Six articles showed "unclear risk" and 4 articles showed "high risk" in blinding of participants and personnel. 28 articles showed "unclear risk" and 1 article showed "high risk" in terms of adequate allocation concealment. Six articles showed "unclear risk" and 6 articles showed "high risk" in the aspect of blinding of outcome assessment. For complete outcome assessment and selective reporting, 22 articles were deemed as "unclear risk" in complete data, whereas 65 articles showed no selecting outcomes to report. The 22 articles were considered as "unclear risk" in other bias.

3.3. Exploration of inconsistency

Across all primary and secondary outcomes, model fit and iteration convergence were both good. All the dDIC value of the outcomes are less than 5 and the I^2 value of all outcomes were less than 25%, indicating that there is no significant difference between the global consistency model and inconsistency model (Supplementary Table S2). There are some closed-loop network structures in the comparison of Weight, WC, BMI, FBG, FINS, TGs, TC, HDL-C, LDL-C, and no inconsistency between direct and indirect evidence was found by node-splitting method (all $p > 0.05$ in Supplementary Table S3). Network meta-regression showed no association among our all outcomes and life styles, proportion of male, total number of participants and intervention duration; however, we found some potential heterogeneity in the mean age of the patients with respect to weight and WC (Supplementary Figure S2).

TABLE 1 Characteristics of studies included in the network meta-analysis.

Row	Study	Year	Country	Sample size T	Sample size C	Age mean (SD)/range	Male (%)	Intervention	Exercise	Diet control	Duration (week)	Outcomes
1	Arzola-Paniagua et al. (31)	2016	Mexico	15	24	33.7 (11.9) 38.8 (9.6)	15.4	Placebo vs. Resveratrol (300 mg) q.d.	NO	NO	24	a,b,c,d,e,j
2	Batista-Jorge et al. (32)	2020	Brazil	13	9	30–60	100	Placebo vs. Resveratrol (250 mg) q.d.	Yes	Yes	12	a,b,c,e,g,j,k,l,m
3	Kantartzis et al. (33)	2018	Germany	52	53	18–70	100	Placebo vs. Resveratrol (75 mg) b.i.d	NA	NA	12	d,f,g,h,i,j,k,l,m
4	Morten M (34)	2013	Denmark	11	14	44.7 (3.5) 31.9 (2.9)	100	Placebo vs. Resveratrol (500 mg) q.d.	No	No	4	d,e,f,g,j,k,l,m
5	Timmers et al. (35)	2011	Netherlands	11	11	52.5 (2.1) 52.5 (2.1)	100	Placebo vs. Resveratrol (150 mg) q.d.	No	No	4	d,e,h,i,j
6	Sanne M et al. (36)	2015	Italy	45	45	60.0 (7.0) 60.0 (7.0)	55.6	Placebo vs. Resveratrol (150 mg) q.d.	No	No	4	c,d,h,i,j,k
7	Wong et al. (37)	2013	Australia	15	13	61.0 (1.8) 60.8 (1.8)	42.9	Placebo vs. Resveratrol (75 mg) q.d.	No	No	6	a,h,i
8	Al-Bayyari et al. (38)	2018	Jordan	50	48	23.8 (0.6) 23.3 (0.8)	50	Placebo vs. VD (50,000 IU) q.w.	No	No	8	a,c
9	Carrillo et al. (39)	2013	America	10	13	26.2 (4.7) 26.0 (4.5)	47.8	Placebo vs. VD (4,000 IU) + Ca (500 mg) q.w.	Yes	No	12	d,e,f
10	Chandler et al. (40)	2014	America	81/83	81	51.1 (12.4) 50.3 (11.0) 51.3 (10.8) 50.7 (10.3)	NA	Placebo vs. VD (1,000 IU) vs. VD (2000 IU) q.d.	No	Yes	24	a,c
11	Cheshmazar et al. (41)	2020	Iran	30	25	38.3 (9.3) 36.8 (7.7)	33.9	Placebo vs. VD (2,000 IU) q.d.	Yes	Yes	8	a,b,c,d,j,k,l,m
12	Ebadi et al. (42)	2021	Iran	32	32	39.6 (12.7) 37.0 (10.6)	32.8	Placebo vs. VD (50,000 IU) q.w.	NA	NA	8	d,e,f,j,k,l,m
13	Farag et al. (43)	2018	Iran	21	25	40.4 (5.9) 42.6 (5.6)	56.5	Placebo vs. VD (200 IU) q.d.	Yes	No	12	a,b,c,d,h,i,j,k,l,m
14	Hajipoor (44)	2020	Iran	28/30/30	31	40.9 (6.8) 48.4 (9.7) 36.4 (21.1) 35.37 (11.69)	40	Placebo vs. VD (1,000 IU) vs. Probiotics (4×10^7 CFU) vs. VD (1,000 IU) + Probiotics (4×10^7 CFU) q.d.	Yes	Yes	10	a,b,c,j,k,l,m

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TABLE 1 (Continued)

Row	Study	Year	Country	Sample size T	Sample size C	Age mean (SD)/range	Male (%)	Intervention	Exercise	Diet control	Duration (week)	Outcomes
15	Lithgow et al. (45)	2018	United Kingdom	10	10	34.0 (9.3) 34.0 (10)	70	Placebo vs. VD (4,000 IU) q.d.	Yes	No	6	a,b,c,d,e,f,h,i,j,k,l,m
16	Mai et al. (46)	2015	Italy	12	12	38.0 (2.4) 37.0 (3.0)	54.2	Placebo vs. VD (600,000 IU) at beginning	Yes	Yes	4	a,c,d,e,f,g
17	Major et al. (47)	2006	Canada	30	33	43.6 (5.0) 41.6 (6.1)	0	Placebo vs. VD (200 IU) + Ca (600 mg) b.i.d	No	Yes	15	a,b,c,d,e,h,i,j,k,l,m
18	Mason et al. (48)	2014	America	94	94	60.0 (5.3) 59.6 (5.1)	0	Placebo vs. VD (2,000 IU) q.d.	Yes	Yes	48	a,b,c
19	Rajaie et al. (49)	2018	Iran	20/21	19	39.3 (5.9) 39.1 (6.1) 39.8 (5.5)	50	Placebo vs. VD (200 IU) vs. VD (200 IU) + Ca (500 mg) b.i.d	No	Yes	8	a,b,c
20	Rajaie et al. (50)	2021	Iran	20/21	19	39.3 (5.9) 39.1 (6.1) 39.8 (5.5)	50	Placebo vs. VD (200 IU) vs. VD (200 IU) + Ca (500 mg) b.i.d	No	Yes	8	j,k,l,m
21	Makariou et al. (51)	2019	Greece	25	25	53.0 (7.0) 52.0 (15.0)	50	Placebo vs. VD (2,000 IU) q.d.	No	Yes	12	a,b,c
22	Makariou et al. (52)	2017	Greece	25	25	52.0 (9.0) 51.0 (12.0)	42	Placebo vs. VD (2,000 IU) q.d.	No	Yes	12	d,g,h,i,k,l,m
23	Salehpour et al. (53)	2012	Iran	39	38	38.0 (7.0) 37.0 (8.0)	0	Placebo vs. VD (25 μg) q.d.	Yes	No	12	a,b,c,h,i,j,k,l,m
24	Salekzamani et al. (54)	2016	Iran	35	36	40.5 (5.0) 40.5 (5.0)	100	Placebo vs. VD (5,000 IU) q.w.	NA	NA	16	a,b,c,d,e,f,h,i,j,k,l,m
25	Zittermann et al. (55)	2009	Germany	82	83	47.4 (10.3) 43.7 (10.0)	32.7	Placebo vs. VD (3,332 IU) q.d.	No	Yes	48	a,b,c,d,g,h,i,k,l,m
26	Huerta et al. (96)	2015	Spain	16/19/17	21	38.0 (7.0) 38.0 (8.0) 39.0 (7.0) 39.0 (8.0)	0	Placebo vs. α-lipoic acid (300 mg) vs. EPA (1,300 mg) vs. α-lipoic acid (300 mg) + EPA (1,300 mg) q.d.	No	Yes	10	a,c,d

(Continued)

TABLE 1 (Continued)

Row	Study	Year	Country	Sample size		Age mean (SD)/range	Male (%)	Intervention	Exercise	Diet control	Duration (week)	Outcomes
				T	C							
27	Nasiri et al. (57)	2021	Iran	22/21/22	21	37.3 (7.6) 34.7 (5.0) 34.9 (5.7) 34.3 (7.3)	NA	Placebo vs. α-lipoic acid (600 mg) vs. Probiotics ($2*10^{11}$ CFU) vs. α-lipoic acid (600 mg) + Probiotics ($2*10^{11}$ CFU) q.d.	No	Yes	8	a,b,c,g,h
28	Romo-Hualde et al. (58)	2018	Spain	16/15/15	19	39.3 (6.6) 37.2 (8.1) 38.1 (7.0) 39.0 (8.0)	0	Placebo vs. α-lipoic acid 300 (mg) vs. EPA (1,300 mg) vs. α-lipoic acid (300 mg) + EPA (1,300 mg) q.d.	No	Yes	10	b,c,f,j,k,l
29	Bateni et al. (59)	2021	Iran	22	21	50.0 (9.0) 54.0 (7.0)	23.3	Placebo vs. Curcumin (80 mg) q.d.	No	No	12	a,b,c,d,e,f,g,l,i,g,k,l,m
30	Campbell et al. (60)	2019	America	10	10	18–35	100	Placebo vs. Curcumin (500 mg) q.d.	No	No	12	d,e,h,i
31	Cicero et al. (61)	2020	Italy	40	40	54.0 (3.0) 53.0 (5.0)	60.1	Placebo vs. Curcumin (800 mg) q.d.	Yes	Yes	8	b,c,d,e,f,h,i,j,k,l,m
32	Dolati et al. (62)	2020	Iran	10	10	38.9 (5.4) 40.8 (3.6)	0	Placebo vs. Curcumin (500 mg) q.d.	Yes	No	8	a,b,c,d,e,f,j,k,l,m
33	Javandoost et al. (63)	2018	Iran	36	36	18–35	NA	Placebo vs. Curcumin (100 mg) q.d.	No	Yes	6	e,j,k,l,m
34	Karandish et al. (64)	2021	Iran	21	20	37.0 (7.2) 34.2 (7.0)	31.7	Placebo vs. Curcumin (500 mg) q.d.	Yes	Yes	12	a,b,d,e,g
35	Mohammadi et al. (65)	2013	Iran	15	15	18–52	20	Placebo vs. Curcumin (1 g) q.d.	NA	NA	4	a,b,c,k,j,l,m
36	Yang et al. (66)	2014	China	30	29	59.3 (10.1) 59.6 (14.0)	46.8	Placebo vs. Curcumin (1,890 mg) q.d.	No	No	12	a,b,d,g,j,k,l,m
37	Abbott et al. (67)	2020	Australian	38	32	50.9 ± 12.7	63.2	Placebo vs. DHA (860 mg) + EPA (120 mg) q.d.	No	No	12	a,b,c,d,e,f,j,k,l,m
38	Baxheinrich et al. (68)	2012	Germany	40	41	52.3 (10.6) 50.3 (9.8)	31.6	Placebo vs. α-linolenic acid q.d.	No	Yes	26	a,b,c,d,e,h,i,j,k,l,m
39	Browning et al. (69)	2007	United Kingdom	18	18	NA	0	Placebo vs. DHA (2.9 g) + EPA (1.3 g) q.d.	No	No	12	d,e,h,i,j,k,l,m

(Continued)

TABLE 1 (Continued)

Row	Study	Year	Country	Sample size		Age mean (SD)/range	Male (%)	Intervention	Exercise	Diet control	Duration (week)	Outcomes
				T	C							
40	de Luis et al. (70)	2016	Spain	14	15	47.4 (9.1) 44.3 (11.7)	41.4	Placebo vs. DHA (500 mg) q.d.	Yes	Yes	24	a,b,c,d,e,f,j,k,l,m
41	DeFina et al. (71)	2011	America	64	64	47.4 (9.1) 44.3 (11.7)	31.3	Placebo vs. DHA (2,500 mg) + EPA (500 mg) q.d.	Yes	Yes	24	a,b,c,d,e,h,i,j,l,m
42	Gammelmark et al. (72)	2012	Denmark	25	25	58.0 (7.4) 55.4 (9.5)	48	Placebo vs. DHA (480 mg) + EPA (640 mg) q.d.	No	No	6	b,c,d,g,j,k,l,m
43	Jaacks et al. (73)	2018	America	10	9	40–65	26.7	Placebo vs. DHA/EPA (1.8 g) q.d.	No	No	8	a,c,d,e,j,k,l,m
44	Kratz et al. (74)	2008	America	13	13	37.5 (14.0) 37.8 (13.6)	38.5	Placebo vs. Fish oil (diet) q.d.	No	Yes	16	a,d,e,f
45	Munro et al. (75)	2012	Australia	18	14	40.5 (10.9) 42.3 (9.10)	19.4	Placebo vs. DHA (1.62 g) + EPA (0.42 g) q.d.	No	Yes	14	a,b,c,d,j,k,l,m
46	Munro et al. (76)	2013	Australia	15	15	44.7 (2.7) 47.1 (2.5)	23.1	Placebo vs. DHA (1.62 g) + EPA (0.42 g) q.d.	No	Yes	8	a,b,c,d,j,k,l,m
47	Neale et al. (77)	2013	Australia	14	14	41.9 (11.7) 42.0 (13.3)	32.1	Placebo vs. DHA (744.9 mg) + EPA (1055.1 mg) q.d.	No	Yes	4	a,b,c,d,e
48	Rajkumar et al. (78)	2014	India	15/15/15	15	40–60	50	Placebo vs. DHA (120 mg) + EPA (180 mg) vs. Probiotics (112.5×10^9 CFU) vs. DHA (120 mg) + EPA (180 mg) + Probiotics (112.5×10^9 CFU) q.d.	No	No	6	d,j,k,l,m
49	Romo-Hualde et al. (79)	2016	America	10	10	30.0 (10.1)	100	Placebo vs. EPA (2.45 g) + DHA (1.61 g) + other n-3 (500 mg) q.d.	Yes	No	6	d,e,j,k,l,m
50	Sjoberg et al. (80)	2010	Australia	16/17/17	17	53.6 (2.5) 63.4 (2.2) 54.0 (2.1) 54.0 (1.6)	51	Placebo vs. DHA (0.52 g) vs. DHA (1.04 g) vs. DHA (1.56 g) q.d.	No	No	12	c,h,i
51	Anggeraini et al. (81)	2021	India	8	8	20.3 (0.7) 20.3 (0.7)	50	Placebo vs. Probiotics ($1*10^9$ CFU) q.d.	No	No	8	a,c,d
52	Eslamparast et al. (82)	2014	Iran	19	19	47.5 (9.1) 46.1 (10.1)	39.4	Placebo vs. Probiotics ($1*10^8$ CFU) q.d.	Yes	Yes	28	d,j,k,l,m

(Continued)

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TABLE 1 (Continued)

Row	Study	Year	Country	Sample size		Age mean (SD)/range	Male (%)	Intervention	Exercise	Diet control	Duration (week)	Outcomes
				T	C							
53	Hadi et al. (83)	2019	Iran	30	29	34.5 (6.0) 36.6 (7.3)	66.1	Placebo vs. Probiotics (2*10^9 CFU) q.d.	Yes	Yes	8	a,b,c,d,e,h,i,j,k,l,m
54	Hess et al. (84)	2020	Denmark	59	57	48.9 (8.6) 48.2 (9.0)	45.3	Placebo vs. probiotics (1*10^8 CFU) b.i.d	Yes	Yes	12	a,b,c,d,e,f,g,h,i,j,k,l,m
55	Rabiei et al. (85)	2019	Iran	20	20	57.1 (1.5) 60.8 (1.6)	26.1	Placebo vs. Probiotics (2*10^8 CFU) q.d.	Yes	Yes	12	a,c,d,e,f,j,k,l,m
56	Rahayu et al. (86)	2021	Indonesia	30	30	44.1 (6.2) 44.7 (5.7)	40	Placebo vs. Probiotics (2*10^9 CFU) q.d.	No	No	12	a,c,j,k,l,m
57	Szulińska et al. (87)	2018	Poland	23/24	24	55.2 (6.9) 56.4 (6.6) 58.7 (7.3)	0	Placebo vs. Probiotics (1*10^{10}CFU) vs. Probiotics (2.5*10^9CFU) q.d.	No	No	12	a,b,c,d,e,f,j,k,l,m
58	Tripolt et al. (88)	2013	Austria	13	15	51.0 (11.0) 55.0 (9.0)	35.7	Placebo vs. Probiotics (1.95*10^{10}CFU) q.d.	No	No	12	c,d,e,f
59	Chacko et al. (89)	2011	America	7	7	47.0 (13.8) 41.9 (12.7)	69.2	Placebo vs. Mg (500 mg) q.d.	No	No	4	d,e,j
60	Joris et al. (90)	2016	Netherlands	26	25	62.0 (5.0) 62.0 (6.0)	47.1	Placebo vs. Mg (350 mg) q.d.	No	No	24	h,i
61	Joris et al. (91)	2017	Netherlands	26	25	62.0 (5.0) 62.0 (5.0)	47.1	Placebo vs. Mg (350 mg) q.d.	No	No	24	d,e,f,j,k,l,m
62	Lee et al. (92)	2009	Korea	75	80	39.6 (7.9) 40.5 (7.3)	49.7	Placebo vs. Mg (300 mg) q.d.	No	Yes	12	d,e,f,h,i,j,k,l,m
63	Mooren et al. (93)	2011	Germany	25	22	30–70	0	Placebo vs. Mg (365 mg) q.d.	No	No	24	c,d,e,f,h,i,j,k,l,m
64	Rodríguez-Moran et al. (94)	2014	Mexico	24	23	31.9 (5.6) 39.5 (8.3)	0	Placebo vs. Mg (382 mg) q.d.	No	Yes	16	b,c,d,e,f,h,i,j,l
65	Solati et al. (95)	2019	Iran	35	35	40.7 (11.9) 40.7 (12.7)	48.6	Placebo vs. Mg (300 mg) q.d.	No	No	24	c,d,e,f,j,k,l,m

T, Trail group; C, Control group; SD, Standard deviation; VD, vitamin D; Ca, calcium; Mg, magnesium.
Outcomes: a, Weight; b, Waist circumference (WC); c, Body mass index (BMI); d, Fasting blood glucose (FBG); e, Fasting insulin level (FINS); f, Homeostatic model assessment of insulin resistance (HOMA-IR); g, Hemoglobin A1c (HbA1c); h, Systolic blood pressure (SBP); i, Diastolic blood pressure (DBP); j, Triglycerides (TGs); k, Total cholesterol (TC); l, High-density lipoprotein cholesterol (HDL-C); m, Low-density lipoprotein cholesterol.

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3.4. Cardiovascular risk factors

3.4.1. Blood pressure

The change in blood pressure was recorded in 7 studies with 1787 patients. Pairwise meta-analysis and NMA results both revealed that there was no significant difference in SDP and DBP change in all the 9 interventions and placebo (Supplementary Tables S1, S4). The rankings were shown in Table 2 and Supplementary Figures S3A,B.

3.4.2. Glucose and lipid metabolism

FBG was measured in 39 studies and involved 2,731 patients. The pairwise meta-analysis revealed that compared with placebo, probiotics + omega-3 (WMD: −5.55 mmol/l; 95%CI: −6.69 to −4.40) resulted in a significant reduction in FBG (Supplementary Table S1). However, in NMA (Table 3), compared with placebo (MD: −0.90 mmol/L; 95%CrI: −1.41 to −0.38), VD (MD: −0.75 mmol/L; 95%CrI: −1.47 to −0.01), and omega-3 (MD: −0.84 mmol/L; 95%CrI: −0.20 to −1.47), probiotics resulted in a greater reduction in FBG. According to the SCURA values, probiotics (SUCRA 90.4%) may be the best intervention for decreasing FBG (Table 2; Supplementary Figure S3C).

FINS was measured in 37 studies involving 1936 patients. The pairwise meta-analysis revealed that compared with placebo, α-lipoic acid + probiotics (WMD: −2.51 μIU/mL; 95%CI: −3.33 to −1.69) and probiotics + omega-3 (WMD: −4.04 μIU/mL; 95%CI: −4.94 to −3.14) resulted in a significant reduction in FINS (Supplementary Table S1). However, NMA revealed that probiotics might be more effective than placebo (MD: −2.05 μIU/mL; 95%CrI: −4.27 to −0.02) and probiotics + omega-3 (MD: −8.72 μIU/mL; 95% CrI: −4.61 to −12.92; Table 3). According to the SCURA values, probiotics (SUCRA 90.5%) may be the best intervention to reduce FINS (Table 2; Supplementary Figure S3D).

HOMA-IR was measured in 25 studies involving 1,436 patients. The pairwise meta-analysis revealed that compared with placebo, α-lipoic acid + probiotics (WMD: −2.59; 95%CI: −3.42 to −1.76) and curcumin (WMD: −0.41; 95%CI: −0.74 to −0.08, $I^2 = 0\%$; $p = 0.60$) resulted in a greater benefit in improving HOMA-IR (Supplementary Table S1). However, NMA showed that probiotics might be more effective than placebo (MD: −1.43; 95%CrI: −2.46 to −0.31) and omega-3 (MD: −1.92; 95%CrI: −0.20 to −3.55; Supplementary Table S5). According to the SCURA values, probiotics (SUCRA 93.4%) may be the best intervention to improve HOMA-IR (Table 4; Supplementary Figure S3E).

HbA1c was reported in 12 studies involving 724 patients. The pairwise meta-analysis revealed that only curcumin (WMD: −0.36; 95%CI: −0.70 to −0.01; $I^2 = 16\%$; $p = 0.30$) resulted in a significant reduction in HbA1c compared to placebo (Supplementary Table S1). However, there was no significant difference between all interventions and placebo in NMA (Supplementary Table S5).

TGs was measured in 43 studies involving 2,795 patients. The pairwise meta-analysis revealed that compared with placebo, probiotics (WMD: −0.21 mg/dL; 95%CI −0.39 to −0.04; $I^2 = 49\%$; $p = 0.10$), omega-3 (WMD: −0.29 mg/dL; 95%CI −0.46 to −0.13;

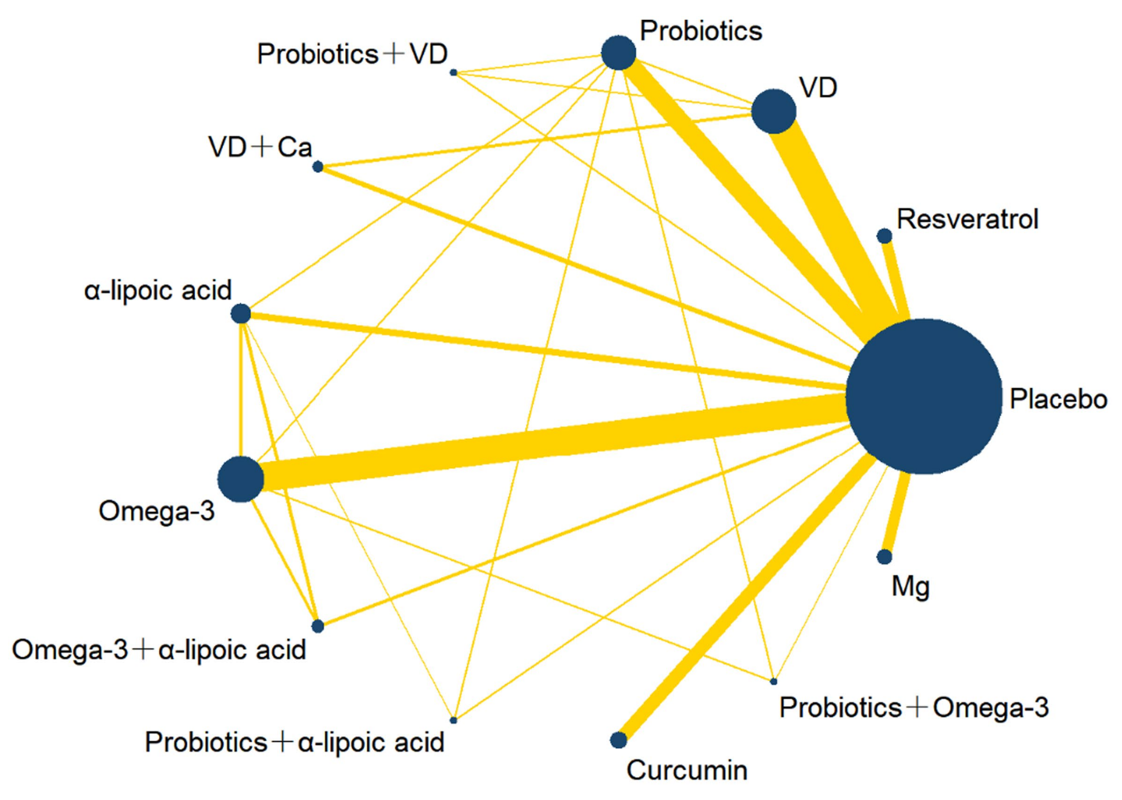

FIGURE 2
Network plot of different nutrition supplements for overweight and obese treatment. The width of the line is directly proportional to the number of treatments for each pair; the area of the circle represents the cumulative number of patients per intervention. VD, Vitamin D; Ca, Calcium; Mg, Magnesium.

TABLE 2 Surface under the cumulative ranking curve and ranking probability of different nutrition supplements on each outcome.

Interventions	SBP		DBP		FBG		FINS		HOMA-IR		HbA1c	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
Placebo	26.5	10	47.1	7	33.0	11	33.0	11	35.9	7	49.5	4
Resveratrol	34.4	8	50.9	5	40.5	8	40.6	8	39.2	6	43.8	5
VD	39.1	7	48.6	6	48.1	4	48.3	4	53.9	4	28.3	7
Probiotics	57.0	4	61.8	3	***90.4***	1	***90.5***	1	***92.4***	1	***73.4***	1
Probiotics + VD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
VD + Ca	42.8	6	47.1	8	41.3	7	41.4	7	NA	NA	NA	NA
α-lipoic acid	67.8	3	59.4	4	36.0	10	35.8	10	32.3	8	NA	NA
Omega-3	69.7	2	11.3	10	39.74	9	39.7	9	18.7	9	51.4	3
Omega-3 + α-lipoic acid	NA	NA	NA	NA	47.14	5	46.9	5	51.2	5	NA	NA
Probiotics + α-lipoic acid	***79.3***	1	***67.7***	1	NA	NA	NA	NA	NA	NA	NA	NA
Curcumin	34.3	9	38.7	9	45.67	6	45.6	6	66.4	2	71.6	2
Probiotics + omega-3	NA	NA	NA	NA	79.85	2	79.8	2	NA	NA	NA	NA
Mg	44.6	5	67.4	2	48.40	3	48.5	3	59.9	3	32.0	6

Interventions	TGs		TC		HDL-C		LDL-C		Weight		WC		BMI	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
Placebo	13.7	12	35.7	9	34.8	9	69.4	2	27.9	10	37.9	9	40.1	11
Resveratrol	31.2	11	40.8	7	22.6	11	35.8	10	49.8	7	51.6	5	45.1	6
VD	39.1	9	***81.2***	1	65.9	4	67.6	3	50.6	5	53.1	4	45.3	5
Probiotics	57.0	5	59.8	3	51.2	5	36.4	9	67.1	2	69.6	2	49.0	4
Probiotics + VD	51.9	7	53.63	5	47.2	6	32.9	11	53.9	4	26.4	12	42.4	9
VD + Ca	58.5	4	61.5	2	47.1	7	40.8	8	44.9	8	35.1	11	44.0	7
α-lipoic acid	***75.2***	1	NA	NA	22.0	12	52.6	5	57.6	3	35.2	10	84.8	2
Omega-3	50.5	8	38.7	8	33.9	10	***77.2***	1	26.7	11	43.1	8	11.8	12
Omega-3 + α-lipoic acid	66.7	3	NA	NA	43.2	8	50.8	6	50.5	6	47.7	6	***90.7***	1
Probiotics + α-lipoic acid	NA	NA	NA	NA	NA	NA	NA	NA	***79.4***	1	***83.5***	1	62.9	3
Curcumin	34.9	10	25.8	10	74.5	2	66.5	4	41.6	9	69.5	3	42.47	8
Probiotics + omega-3	67.3	2	57.1	4	***90.1***	1	21.2	12	NA	NA	NA	NA	NA	NA
Mg	54.1	6	45.8	6	67.5	3	49.0	7	NA	NA	47.3	7	41.44	10

Bold and inclined: the SUCRA is relatively higher when compared with other interventions. Ranking: the probability of being the best, the second best, or the third best treatment, and so on, among all treatments. Rank 1 is the best, and Rank N is the worst. SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; FINS, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, hemoglobin A1c; TGs, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference; BMI, body mass index; SUCRA, surface under the cumulative ranking curve; VD, vitamin D; Ca, calcium; Mg, magnesium.

$I^2 = 0\%$; $p = 0.89$) and probiotics + omega-3 (WMD: −0.60 mg/dL; 95%CI: −1.12 to −0.09) all resulted in a significant reduction in TGs (Supplementary Table S1). Similarly, NMA revealed that probiotics (MD: −11.15 mg/dL; 95%CrI: −22.16 to −1.26) and omega-3 (MD: −9.45 mg/dL; 95%CrI: −20.69 to −0.93) might be more effective than placebo (Table 4). According to the SCURA values, α-lipoic acid (SUCRA 75.2%) may be the best intervention to reduce TGs (Table 4; Supplementary Figure S3G).

TC was measured in 37 studies involving 2,379 patients. The pairwise meta-analysis showed that compared with placebo, probiotics (WMD: −0.36 mg/dL; 95%CI: −0.57 to −0.15; $I^2 = 23\%$; $p = 0.24$), α-lipoic acid + probiotics (WMD: −2.51 mg/dL; 95%CI: −3.33 to −1.69), and probiotics + omega-3 (WMD: −0.94 mg/dL; 95%CI: −1.48 to −0.41) all resulted in a significant reduction in TC (Supplementary Table S1). However, NMA revealed that only VD (MD: −17.86 mg/dL; 95%CrI: −35.53 to −0.27) might be more effective than placebo (Table 4). According to the SCURA

TABLE 3 Results of the network meta-analysis of FINS (lower-left quadrant) and FBG (upper-right quadrant).

	FBG												
	Placebo	−0.06 (−0.74, 0.62)	−0.15 (−0.67, 0.37)	**−0.90 (−1.41, −0.38)**	—	−0.02 (−1.54, 1.50)	0.07 (−1.28, 1.41)	−0.06 (−0.47, 0.35)	−0.14 (−1.49, 1.21)	—	−0.12 (−0.73, 0.49)	−0.82 (−2.07, 0.43)	−0.16 (−0.8, 0.48)
	−0.31 (−2.81, 2.11)	**Resveratrol**	−0.09 (−0.95, 0.77)	−0.84 (−1.69, 0.02)	—	0.04 (−1.62, 1.72)	0.13 (−1.39, 1.64)	0.00 (−0.79, 0.79)	−0.08 (−1.60, 1.43)	—	−0.06 (−0.98, 0.85)	−0.76 (−2.19, 0.66)	−0.1 (−1.03, 0.83)
	−0.17 (−2.68, 2.27)	0.14 (−3.35, 3.62)	**VD**	**−0.75 (−1.47, −0.01)**	—	0.13 (−1.47, 1.74)	0.22 (−1.23, 1.66)	0.09 (−0.57, 0.76)	0.01 (−1.44, 1.46)	—	0.03 (−0.78, 0.83)	−0.67 (−2.03, 0.69)	−0.01 (−0.83, 0.82)
	−2.05 (−4.27, −0.02)	−1.73 (−5.06, 1.44)	−1.88 (−5.17, 1.31)	**Probiotics**	—	0.88 (−0.72, 2.47)	0.96 (−0.48, 2.40)	**0.84 (0.20, 1.47)**	0.76 (−0.69, 2.20)	—	0.77 (−0.03, 1.57)	0.08 (−1.21, 1.36)	0.74 (−0.08, 1.55)
	—	—	—	—	**Probiotics + VD**	—	—	—	—	—	—	—	—
	−0.39 (−5.89, 5.09)	−0.08 (−6.08, 5.95)	−0.22 (−6.22, 5.79)	1.64 (−4.17, 7.63)	—	**VD + Ca**	0.09 (−1.94, 2.11)	−0.04 (−1.61, 1.54)	−0.13 (−2.18, 1.9)	—	−0.11 (−1.74, 1.53)	−0.81 (−2.77, 1.16)	−0.15 (−1.79, 1.5)
FINS	—	—	—	—	—	—	**α-lipoic acid**	−0.13 (−1.47, 1.23)	−0.21 (−1.75, 1.34)	—	−0.19 (−1.68, 1.29)	−0.89 (−2.72, 0.94)	−0.23 (−1.72, 1.27)
	−0.52 (−2.25, 1.14)	−0.21 (−3.2, 2.78)	−0.35 (−3.34, 2.64)	1.54 (−0.95, 4.17)	—	−0.10 (−5.85, 5.62)	—	**omega-3**	−0.08 (−1.43, 1.27)	—	−0.07 (−0.8, 0.67)	−0.76 (−2.04, 0.51)	−0.1 (−0.86, 0.65)
	—	—	—	—	—	—	—	—	**omega-3 + α-lipoic acid**	—	0.02 (−1.46, 1.5)	−0.68 (−2.5, 1.16)	−0.02 (−1.51, 1.47)
	—	—	—	—	—	—	—	—	—	**Probiotics + α-lipoic acid**	—	—	—
	−0.97 (−3.41, 1.92)	−0.66 (−4.02, 3.22)	−0.79 (−4.20, 3.11)	1.08 (−2.09, 4.87)	—	−0.56 (−6.44, 5.76)	—	−0.46 (−3.38, 2.98)	—	—	**Curcumin**	−0.7 (−2.09, 0.7)	−0.04 (−0.92, 0.85)
	6.68 (2.65, 10.63)	**7.00 (2.29, 11.68)**	**6.86 (2.15, 11.54)**	**8.72 (4.61, 12.92)**	—	**7.09 (0.28, 13.82)**	—	**7.20 (3.06, 11.25)**	—	—	**7.66 (2.51, 12.19)**	**Probiotics + omega-3**	0.66 (−0.74, 2.06)
	−0.63 (−2.84, 1.46)	−0.32 (−3.61, 2.91)	−0.46 (−3.76, 2.78)	1.41 (−1.59, 4.48)	—	−0.23 (−6.16, 5.63)	—	−0.13 (−2.90, 2.58)	—	—	0.33 (−3.41, 3.50)	**−7.32 (−11.89, −2.75)**	**Mg**

Data are reported as mean difference (95% credible intervals) and indicate column-to-row differences (i.e., compared with placebo, prebiotic reduces FBG by 0.90 mmol/l). Statistically significant differences are in bold and inclined formats (p-values < 0.05). FBG, Fasting blood glucose; FINS, Fasting insulin level; VD, Vitamin D; Ca, Calcium; Mg, Magnesium. Statistically significant effects are shown in bold and underline.

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TABLE 4 Results of the network meta-analysis of TC (lower-left quadrant) and TGs (upper-right quadrant).

	TGs												
	Placebo	−4.01 (−18.50, 11.34)	−6.39 (−19.11, 5.69)	**−11.15 (−22.16, −1.26)**	−10.63 (−42.58, 21.49)	−12.9 (−37.04, 11.16)	−21.44 (−52.74, 9.12)	**−9.45 (−20.69, −0.93)**	−16.99 (−47.27, 12.45)	—	−4.70(−23.13, 9.62)	−14.94 (−35.44, 3.63)	−11.14 (−25.30, 7.47)
	−0.74 (−28.19, 26.54)	**Resveratrol**	−2.40 (−22.61, 16.46)	−7.20 (−26.38, 10.19)	−6.65 (−42.23, 28.37)	−8.95 (−37.64, 19.07)	−17.4 (−52.62, 16.25)	−5.52 (−25.16, 11.22)	−12.90 (−47.20, 19.66)	—	−0.78(−25.41, 19.25)	−11.00 (−36.87, 12.21)	−7.14 (−27.48, 16.53)
	−17.86 (−35.53, −0.27)	−17.14 (−49.64, 15.42)	**VD**	−4.82 (−20.57, 10.89)	−4.26 (−36.47, 28.88)	−6.53 (−31.34, 18.85)	−15.00 (−48.28, 18.16)	−3.08 (−19.49, 11.74)	−10.59 (−42.92, 21.55)	—	1.67 (−20.15, 20.05)	−8.74 (−31.83, 14.04)	−4.66 (−23.32, 18.61)
	−8.26 (−25.29, 8.78)	−7.55 (−39.48, 24.88)	9.59 (−13.89, 33.28)	**Probiotics**	0.64 (−31.91, 33.58)	−1.65 (−27.56, 24.77)	−10.29 (−42.63, 22.07)	1.83 (−12.43, 14.04)	−5.77 (−37.18, 25.36)	—	6.61 (−14.52, 23.66)	−3.89 (−24.20, 16.17)	0.07 (−16.85, 22.37)
	−7.12 (−49.72, 35.57)	−6.41 (−56.69, 44.45)	10.81 (−32.48, 54.18)	1.09 (−42.40, 44.56)	**Probiotics + VD**	−2.28 (−41.97, 37.15)	−10.79 (−55.43, 33.21)	1.09 (−33.12, 33.98)	−6.36 (−50.51, 37.37)	—	5.8 (−31.93, 40.87)	−4.53 (−41.94, 31.93)	−0.22 (−35.19, 37.08)
	−10.83 (−46.44, 24.42)	−10.11 (−55.03, 34.80)	7.01 (−30.47, 44.46)	−2.61 (−41.91, 36.35)	−3.77 (−58.74, 50.90)	**VD + Ca**	−8.50 (−47.93, 30.28)	3.38 (−23.55, 28.45)	−3.94 (−42.64, 33.83)	—	8.21 (−22.68, 35.42)	−2.20 (−33.59, 28.16)	1.88 (−25.69, 32.92)
TC	—	—	—	—	—	—	**α-lipoic acid**	11.90 (−19.65, 42.29)	4.51 (−32.06, 40.78)	—	16.65 (−19.71, 50.13)	6.26 (−29.60, 42.18)	10.44 (−22.96, 47.62)
	−0.56 (−18.49, 17.47)	0.20 (−32.22, 33.05)	17.32 (−7.77, 42.41)	7.70 (−15.90, 31.55)	6.58 (−39.46, 52.75)	10.29 (−29.38, 50.19)	—	**omega-3**	−7.43 (−36.61, 22.89)	—	4.91 (−14.63, 21.80)	−5.96 (−24.61, 15.12)	−1.42 (−18.39, 21.44)
	—	—	—	—	—	—	—	—	**omega-3 + α-lipoic acid**	—	12.19(−23.09, 44.64)	1.77 (−32.98, 36.70)	5.97 (−26.47, 42.48)
	—	—	—	—	—	—	—	—	—	**Probiotics + α-lipoic acid**	—	—	—
	5.39 (−16.84, 27.37)	6.14 (−29.00, 41.42)	23.26 (−5.00, 51.53)	13.61 (−14.34, 41.46)	12.49 (−35.29, 60.1)	16.26 (−25.59, 57.97)	—	5.95 (−22.66, 34.44)	—	—	**Curcumin**	−10.80 (−33.33, 16.90)	−6.11 (−27.15, 21.72)
	−9.21 (−51.53, 33.41)	−8.51 (−58.83, 42.4)	8.67 (−37, 54.7)	−0.95 (−44.19, 42.53)	−2.13 (−61.73, 57.69)	1.64 (−53.31, 57.06)	—	−8.65 (−52.08, 34.86)	—	—	−14.55 (−62.30, 33.58)	**Probiotics + omega-3**	3.82 (−18.52, 32.83)
	−2.94 (−29.3, 23.75)	−2.21 (−40.05, 36.09)	14.96 (−16.72, 46.85)	5.34 (−26.07, 37.17)	4.16 (−45.99, 54.31)	7.91 (−36.04, 52.31)	—	−2.34 (−34.52, 29.74)	—	—	−8.29 (−42.65, 26.33)	6.30 (−43.67, 56.44)	**Mg**

Data are reported as mean difference (95% credible intervals) and indicate column-to-row differences. Statistically significant dif [illegible] bold and inclined formats (*P*-values < 0.05). TGs, Triglycerides; TC, Total cholesterol; VD, Vitamin D; Ca, Calcium; Mg, Magnesium. Statistically significant effects are shown in bold and underline.

values, VD (SUCRA 81.2%) may be the best intervention to reduce TC (Table 2; Supplementary Figure S3H).

HDL-C was reported in 43 studies involving 2,804 patients. The pairwise meta-analysis demonstrated that curcumin (WMD: 0.35 mg/dL; 95%CI: 0.12 to 0.57; $I^2 = 0\%$; $p = 0.70$) and probiotics + omega-3 (WMD: 3.07 mg/dL; 95%CI: 2.31 to 3.83) resulted in a significant increase in HDL-C compared to placebo (Supplementary Table S1). Likewise, NMA revealed that probiotics + omega-3 might be more effective than placebo (MD: 5.09 mg/dL; 95%CrI: 0.77 to 9.38), resveratrol (MD: 6.36 mg/dl; 95%CrI: 0.92 to 11.58) and omega-3 (MD: 5.24 mg/dL; 95%CrI 0.78 to 9.63; Supplementary Table S6). According to the SCURA values, probiotics + omega-3 (SUCRA 90.1%) may be the best intervention to increase HDL-C (Table 2; Supplementary Figure S3I).

LDL-C was reported in 42 studies involving 2,737 patients. The pairwise meta-analysis described that compared with placebo, probiotics (WMD: −0.32 mg/dL; 95%CI: −0.52 to −0.12; $I^2 = 25\%$; $p = 0.22$) and probiotics + omega-3 (WMD: −1.37 mg/dL; 95%CI: −1.94 to −0.80) resulted in a significant reduction in LDL-C (Supplementary Table S1). However, there was no significant difference between all interventions and placebo in NMA (Supplementary Table S6).

According to the cluster-rank results in Figure 3, probiotics ranked highest in decreasing the FBG and FINS and was the optimum strategy (cluster-rank value = 3290.50); probiotics + omega-3 ranked highest in decreasing the TGs meanwhile increasing the HDL-C and has the greatest potential to be the optimum strategy (cluster-rank value = 2117.61).

3.5. Body composition

In this NMA, body weight, WC and BMI were reported in 38, 33, and 45 studies, respectively. The results of this NMA showed that there was no significant difference in weight loss and WC reduction among all interventions. The effect of omega-3 + α-lipoic acid (MD: −6.70 Kg/m²; 95%CI: −13.13 to −0.24) on reducing BMI was significantly better than that of placebo (Supplementary Table S8). According to the SCURA values, α-lipoic acid + probiotics might be the best intervention to reduce body weight (SUCRA 79.4%) and WC (SUCRA 83.5%), and omega-3 + α-lipoic acid (SUCRA 90.7%) might be the best intervention to reduce BMI (Table 2; Supplementary Figures S3K–M).

3.6. Comparison-adjusted funnel plot

Comparison-adjusted funnel plot was showed in Supplementary Figure S4. All studies on the funnel plot were symmetrically distributed on either side of the vertical line of $X = 0$, indicating that there was no significant small sample effects or publication bias.

4. Discussion

At present, nutritional supplements have been shown to be effective as a complementary therapy to improve glucose and lipid metabolism in patients with metabolic diseases (97, 98). However, the effects of common nutritional supplements on improving cardiometabolic risk factors in overweight and obese patients are inconsistent. Network meta-analysis can directly and indirectly compare the efficacy of various nutritional supplements to determine the best nutritional strategy (99).

Overall, among the interventions we included in the comparison, probiotic showed significantly higher efficacy in reducing FBG, FINS, and HOMA-IR than placebo and other interventions; probiotic and omega-3 seemed to be more effective than placebo and other nutrients

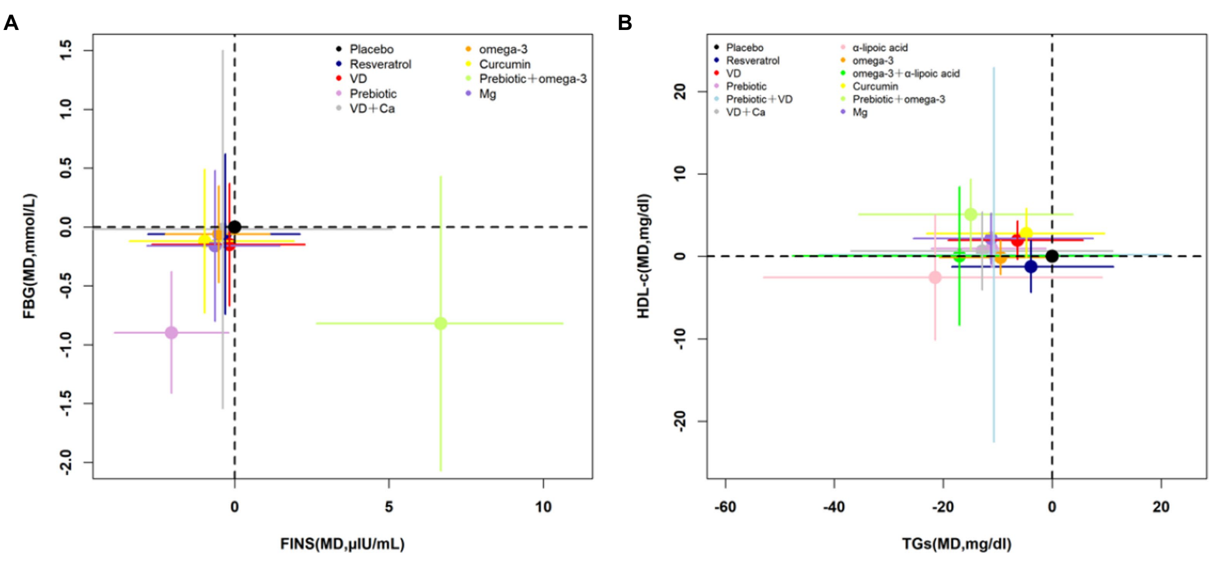

FIGURE 3
Cluster-rank plots. **(A)** The cluster-rank plot of FBG and FINS. **(B)** The cluster-rank plot of HDL-C and TGs. (The cluster-rank value is the product of the abscissa and ordinate of each treatment.) FBG, fasting blood glucose; FINS, fasting insulin level; TGs, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; VD, vitamin D; Ca, calcium; Mg, magnesium.

in reducing TGs; probiotic + omega-3 seemed to be more effective than placebo and other nutrients in increasing HDL-C; however, none of the interventions had a significant impact on body weight, WC, and BMI.

In terms of blood glucose metabolism, SUCRA shows that probiotic was the best way for improving the FBG, FINS, and HOMA-IR. The result is inconsistent with Zarezadeh, who believes that probiotics supplementation does not reduce glucose metabolism in patients with metabolic syndrome and obesity (97). We believe that this is mainly due to the difference in intervention dose and duration. The study intervention included in our meta lasted 8 weeks, and were all medium dose probiotics (more than 10^8 or 10^9 CFU). Our NMA also provides compelling evidence for the benefits of probiotics in improving blood glucose metabolism. Different studies have explained the potential hypoglycemic mechanisms of probiotics, and most studies believe that it may be related to gut bacteria, increasing satiety and reducing appetite (13, 100–102). A variety of probiotics, such as *Bifidobacterium and Lactobacillus,* were used in the included studies. These composite probiotics can decrease the number of harmful bacteria such as *Acinobacteria*, *Escherichina*, and *Gram-negative bacteria*, and promote the growth of short chain fatty acids (SCFAs) (103). SCFAs play an important role in regulating glucose storage in the muscle, adipose tissue, and liver (104). Moreover, probiotics can improve insulin signaling pathway (105).

In terms of lipid metabolism, NMA shows that probiotic and omega-3 seemed to be more effective than placebo in reducing TGs, however, the SUCRA shows that α-lipoic acid might be the most successful intervention among these treatments. This research showed that α-lipoic acid reduced triglycerides to a greatest extent. α-lipoic acid is a potent antioxidant and free radical scavenger, but the mechanism of its regulation of blood lipids is still unclear (106). Butler et al. found that α-lipoic acid offset the rise of TGs in blood and liver by inhibiting liver lipogenic gene expressions, and stimulate clearance of TG-rich lipoproteins by lowering the secretion of hepatic TGs (107). Lee WJ 's experimental study showed that α-lipoic acid decreased lipid accumulation in skeletal muscle and hepatic steatosis by activating AMP-activated kinase (AMPK) (108). The SCURA shows that VD was the best for decreasing TC. Makariou (51) and Jiang XJ (109) found a significant negative correlation between VD supplementation and TC. Jorde et al. found that vitamin D 40,000 IU/wk. did not significantly improve serum lipids and other cardiovascular risk factors compared with placebo (110). In contrast, Ramiro-Lozano and Calvo-Romero presented that oral vitamin D 16,000 IU/wk. showed a reduction in TC but not LDL-C and TGs in type 2 diabetes participants (111). In this NMA, the doses of vitamin D in most studies exceeded 2,000 IU/d, which may prove that high VD levels were associated with a favorable serum lipid profile. With regard to cholesterol level, Major's experiment study showed that vitamin D may increase calcium intestinal absorption and insoluble calcium-fatty soap formation in the gut, resulting in reduced fatty acid absorption and increased fecal fatty acids (47). The effect of probiotics +omega-3 on HDL-C was significant, and SCURA shows that probiotics +omega-3 might be the most successful intervention. The results on HDL-C increasing are compatible with those of Jone's (112) and Venturini's (113) experiment studies, but discordant with those of Chang's (114, 115), possibly owing to the different proportions and dose of omega-3. The effect of omega-3 on HDL cholesterol has been well established (116), but the mechanism of synergistic effect in combination with probiotics remains unclear.

This study comprehensively analyzed the effect of intervention on blood glucose control and lipid metabolism, and the results of cluster rank analysis were consistent with those of SUCRA. Probiotic was found to have statistically significant advantages in decreasing FBG and FINS simultaneously. For the effect of lowering TGs and improving HDL-C, the cluster rank analysis showed that omega-3 + probiotics might be the most effective intervention. Previous meta-analysis results showed different nutrients have different effects on body composition in obese and overweight patients (117, 118). In this NMA, no effective change was found in body weight, WC, and BMI, however, meta-regression shows that age may be a source of heterogeneity in the results of body weight and WC. A low-calorie diet and regular physical exercise were also important ways to improve cardiometabolic indicators in the early prevention of overweight and obesity patients, but meta-regression indicated that the results were consistent, and no matter the daily exercise or a low-calorie diet alone or a combination of the two life styles had no significant effect on the outcomes.

In this review, chronic cardiovascular diseases with complex pathogenesis are excluded, only overweight and obese patients are included, which reduces clinical heterogeneity to some extent and improves the comparability of results. A comprehensive search of treatment strategies for common nutritional supplements in adjuvant therapy was conducted, including a sufficient number of RCT experiments and nutrients were compared as much as possible. The statistical stability and reliability of network meta-analysis depends on the uniform standards of similarity, homogeneity and consistency. No inconsistency was observed in this NMA through consistency test and node splitting method, and the NMA results are robust. Based on SCURA and cluster rank analysis, the results of this NMA will be useful for clinical decision making.

5. Limitations

There are also some limitations shown in the study. First, we did not perform further subgroup analysis. On the one hand, subgroups could not include all supplements in this study. On the other hand, this meta-regression showed the reported results have good consistency, which was not affected by the imputation models. Second, although all the included studies are RCTs, the most common; used is a placebo as a control. Due to the variety of interventions, a small number of direct comparisons of some treatments impairs the robustness of the final results. Third, although SCURA ranking has been widely used to give clinically significant results, due to the minimum absolute difference between the highest rank and others rankings, cautious interpretation is required.

6. Conclusion

Nutrition supplements might be positive efficacious intervention from which patients with overweight or obesity will derive benefit in improving some CVD risk factors. Probiotics supplementation might be potentially the preferred the intervention for glycemic control. VD, α-lipoic acid, probiotic + omega-3 have a better impact on lipid metabolism. Further studies are required to verify the current findings.

Data availability statement

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

Author contributions

XL, ZY, and DZ conceived and designed the research, analyzed the data, interpreted the data, and wrote the first draft. ZY and DZ retrieved the literature and identified eligible studies. XL and DZ extracted the data and checked the statistical methods. XL and ZY reviewed the manuscript and revised the important content. 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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1140019/full#supplementary-material

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Linking dietary intake, circadian biomarkers, and clock genes on obesity: A study protocol

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Background: The prevalence of obesity continues to rise, and although this is a complex disease, the screening is made simply with the value of the Body Mass Index. This index only considers weight and height, being limited in portraying the multiple existing obesity phenotypes. The characterization of the chronotype and circadian system as an innovative phenotype of a patient's form of obesity is gaining increasing importance for the development of novel and pinpointed nutritional interventions.

Objective: The present study is a prospective observational controlled study conducted in Portugal, aiming to characterize the chronotype and determine its relation to the phenotype and dietary patterns of patients with obesity and healthy participants.

Methods: Adults with obesity (study group) and healthy adults (control group), aged between 18 and 75, will be enrolled in this study. Data will be collected to characterize the chronotype, dietary intake, and sleep quality through validated questionnaires. Body composition will also be assessed, and blood samples will be collected to quantify circadian and metabolic biomarkers.

Discussion: This study is expected to contribute to a better understanding of the impact of obesity and dietary intake on circadian biomarkers and, therefore, increase scientific evidence to help future therapeutic interventions based on chronobiology, with a particular focus on nutritional interventions.

KEYWORDS

obesity, circadian rhythms, chrononutrition, nutrigenetics, genes, biomarkers, metabolism

1. Introduction

The prevalence of obesity continues to rise, predicted to become the biggest epidemic in history. According to the World Health Organization, around 2 billion adults are overweight; 50 million have obesity. Most of the world's population lives in countries where obesity and overweight kill more people than underweight (1). Obesity is characterized by an excess of body fat, which can be measured by body composition analysis. Nevertheless, clinical obesity is classified based on the body mass index (BMI), expressed as the ratio of body weight in kilograms divided by the height in square meters (2, 3). Large population studies described the relationship between a higher BMI and increased mortality/morbidity risk (2, 4, 5). The BMI has been used to stratify patients into risk categories and to monitor changes in adiposity since it is an easy, affordable, and quick tool for clinical use, despite its limitations (6, 7).

Different obesity phenotypes are associated with additional cardiovascular risk (8, 9). Some of the phenotypes described in the literature are Metabolically Healthy Obesity, in which a high BMI is associated with an apparently healthy metabolic profile, lower visceral adipose tissue, high values of lean mass, and high cardiorespiratory fitness. This phenotype may transition to metabolically unhealthy obesity and is associated with an increased risk of cardiovascular diseases. Another phenotype is described as Metabolic Obesity with Normal Weight, in which individuals, despite having normal weight, present high values of visceral adipose tissue, lower insulin sensitivity, hyperinsulinemia, dyslipidemia, and increased plasma levels of pro-inflammatory cytokines. Normal weight obesity syndrome presents values of body fat mass above 30% with BMI values within the healthy range. Lastly, there is the Sarcopenic Obesity phenotype, characterized by low skeletal mass and increased fat mass percentage (10). Considering these different phenotypes, the BMI classification is insufficient to adequately stratify patients with obesity regarding types of adiposity, cardiovascular risk or adequacy of therapeutic interventions. In addition to the BMI, clinical practice guidelines suggest associating the measurement of the waist circumference as a reference for abdominal fat (11, 12), however, this measure does not differentiate subcutaneous from visceral fat deposition.

The knowledge regarding the etiology of obesity is still evolving; however, some gaps remain, since the translation of this knowledge into the treatment and management of this disease is yet to be successful in large-scale clinical programs (13). Obesity is a complex condition, therefore not to be considered a homogenous state, considering the noticeable heterogeneity observed among people that meet the current medical diagnostic criteria for obesity (BMI $\geq 30\,kg/m^2$).

Obesity classes I and II encompass different health risks associated with factors that include body fat distribution, overall nutritional quality, physical activity levels, and cardiorespiratory fitness (14). Some people, although they have obesity, eat a nutritionally balanced diet and are physically active (15). Other individuals only show moderate obesity, however, when accompanied by visceral obesity, they can exhibit features of metabolic syndrome (16). These remarks underline the idea that BMI alone might not be sufficient to assess health risks, characterize, and diagnose obesity. Piché and colleagues (2) recently proposed that the singular term "obesity" does not properly define the diverse types of obesities, regarding adipose tissue type and function, body fat distribution, and patient lifestyle habits. These authors suggest that the concept of different "obesities" is more adequate to the clinical reality and to the distinct treatment challenges associated with different categories of obesity.

Current evidence indicates that there is a reciprocal interaction between metabolism and the circadian system. Primarily, a comprehensive neural network connects the suprachiasmatic nucleus (SCN) of the hypothalamus to the energetic centers implicated in, for example, food intake, sleep/wakefulness and energy expenditure (17). The effect of the circadian system on metabolism, mediated by the SCN and peripheral clocks, is reflected in the circadian fluctuations exhibited by several metabolically significant hormones (17, 18). Changes in hormonal rhythms might lead to internal malfunction and are related to metabolic dysfunctions that predispose the development of metabolic diseases such as obesity (18–22). While the SCN is mainly synchronized by light/dark cycles, peripheral clocks are entrained by feeding/fasting cycles (23, 24). Besides meal timing, nutrients can also induce phase shifts in the peripheral circadian clock. Hirao and colleagues found that a combination of carbohydrates and protein is necessary to change the mouse liver clocks (25). As reviewed by Oike and colleagues (26), nutrients such as glucose and amino acids quickly alter the expression of clock genes, particularly Per2 and Rev-erbα (27–30). Skipping breakfast or having a lower food intake in the first meal of the day alongside with high-caloric dinners impairs peripheral clock gene expression and results in higher daily glucose excursions in animals (31–33). A study conducted by Jakubowicz and colleagues on individuals with type 2 diabetes showed that calories consumed at breakfast or dinner affected the daily rhythm of postprandial glycaemic excursion and insulin levels (34). These authors also reported that skipping breakfast negatively affected clock and clock-controlled gene expression (35).

Despite the contribution in elucidating important mechanisms in chronobiology, the majority of the studies do not account for differences of circadian rhythmicity among individuals. Distinct chronotypes reflect different timings of circadian behavior, physiology, and even patterns of clock genes expression. Besides regulating sleep, the chronotype can have a major influence on appetite. Thus, the characterization of individual chronotypes (expression of circadian rhythmicity), as part of a patient phenotype, is gaining increasing importance for the development of novel and pinpointed nutritional interventions. A randomized clinical trial showed that a chronotype-adjusted diet was more effective than the traditional hypocaloric diet in the improvement of anthropometrical parameters in patients with obesity (36). Individual circadian variations may be valuable, and a critical first step, for providing information to design therapeutic strategies and to help "fine-tune" chronobiology interventions, including chrononutrition approaches (37). Research in this field is currently hindered by the fact that only a few studies assessed simultaneously the chronotype and nutrient intake and timing during the interventions. Furthermore, there is no standard method to objectively define chronotypes. Usually, this is determined by a combination of questionnaires, evaluation of clock genes expression and/or protein levels, determination of non-invasive clock outputs, such as core body temperature, and heterogeneous pools of biomarkers that act as readouts of the intrinsic circadian rhythms (38–41). Although there is an increasing interest in chronotype, as a novel dimension of nutrition and health, there is still a lack of consistent evidence regarding its relation to obesity and metabolic disturbances (42, 43). Researchers in this field highlight the need for more research and proper characterization of clock gene expression and circadian biomarkers in obesity. Furthermore, most studies have a high risk of bias and do not evaluate parameters related to metabolic dysfunction such as adiponectin, leptin, and insulin (42, 44).

The relationship between circadian rhythm disruption and obesity is complex and not fully understood. More studies are necessary to assess the role of meal schedules and dietary composition in the regulation and/or deregulation of peripheral clocks, especially including the biological differences in the circadian system through the assessment of individual chronotypes.

The present study aims to conduct an observational study on chronotype, and its relation to phenotype and dietary intake in patients with obesity, compared with healthy individuals. This study will contribute with scientific evidence to help future interventions based on chronobiology, specially chrononutrition.

2. Methods and analysis

2.1. Study design

NutriClock is a prospective observational study involving adults with obesity (study group) and healthy adults (control group). The study protocol was developed based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (45).

2.2. Participant selection

Participants will be recruited from healthcare centers in Leiria, Portugal. The study will also be disseminated through social networks and institutional emails, in an attempt to reach more participants.

The eligibility of the participants will be assessed on the first visit by the assessment of inclusion and exclusion criteria after the potential participants signed the informed consent. The observational study will be conducted on adults and recruitment will be gender-independent. Obesity will be defined according to the criteria of the World Health Organization (1). The detailed participant inclusion and exclusion criteria are listed in Table 1.

TABLE 1 Inclusion and exclusion criteria for the participants in both study groups.

Inclusion criteria
■ Adults aged ≥ 18 and ≤ 75 years. ■ BMI ≥ 30 kg/m² (study group). ■ BMI ≥ 18.5 and < 25.0 kg/m² (control group).
Exclusion criteria
■ Individuals unwilling or unable to give their informed consent. ■ Severe psychiatric conditions and/or inability to understand and engage in the study. ■ Night or rotating shift workers, or individuals that crossed more than two times zones in the 2 weeks before the beginning of the study. ■ Diagnosed sleep disorders, including severe Obstructive Sleep Apnea. ■ Pregnant women[1]. ■ Individuals with an electronic medical device/implant[1]. ■ Infection 4 weeks before baseline assessment. ■ Regular use (equal to or greater than weekly) of the following medications: - Wakefulness-promoting agents modafinil, amphetamine derivates, methylphenidate. - Sedatives including benzodiazepines, Z-drugs (zopiclone, zolpidem and zaleplon). - Melatonin, including circadian and melatonin analogs. - Clonazepam and other drugs for nocturnal movement disorders. - Probiotics. - Anti-obesity drugs (orlistat, liraglutide). - Glucocorticoids.

[1]Assessment of body composition with the bioelectrical impedance analysis (BIA) equipment is not possible in these conditions.

2.3. Sample size

The sample size was estimated using the following formula (46):

$$n\left(each\ group\right) = \frac{\left(p_0 q_0 + p_1 q_1\right)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\left(p_1 - p_0\right)^2}$$

- α is the value of alpha, conventionally 0.05 (two-sided).
- β is the value of beta, conventionally 0.20.
- p_0 is the expected proportion of controls with exposure.
- p_1 is the proportion of cases with exposure.
- $q_0 = (1 - p_0)$.
- $q_1 = (1 - p_1)$.

The prevalence of obesity in the Portuguese adult population was reported as being 17.7% in 2019 (47). Strong evidence suggest that circadian misalignment contributes to obesity and that the metabolic disorders' genetic components underlie the large interindividual variation in body weight. Studies have highlighted that the genetic component can contribute for 40%–70% of obesity cases (48). Considering that the chronotype is related to clock gene expression, we assumed that an average of 55% of individuals with obesity will have a clock gene-mediated genetic contribution to the obesity phenotype. Based on these assumptions:

- p_0 = proportion of controls with obesity = 0.18.
- p_1 = proportion of obesity cases with chronotype misalignment = 0.55.
- $q_0 = (1 - p_0) = 1–0.18 = 0.82$.
- $q_1 = (1 - p_1) = 1–0.55 = 0.45$.
- $z_{(1-\alpha/2)} = 1.96$ (value of the standard normal distribution corresponding to a significance level of alpha [1.96 for a 2-sided test at the 0.05 level]).
- $z_{(1-\beta)} = 0.84$ (value of the standard normal distribution corresponding to the desired level of power –80%).

The sample size necessary for this study is of 46 participants (23 cases and 23 controls). Having into consideration an attrition rate of 40% for visits 2 and 3, the minimum sample size estimated is 64 (32 for each group), to prevent and account for the potential high drop-out rate, incomplete data, and consent withdrawal.

2.4. Data collection timeline

Data collection is expected to be conducted from January 2023 to September 2023, though, this period may be extended to ensure a sufficient sample number, if necessary. Once recruitment begins, all potential participants will be invited to enter the observational study. The study aims and procedures will be explained in detail and in a simple and understandable manner to the potential participants, so that they can make an informed decision, on whether to accept or decline to participate. When a potential participant agrees to join the study, they are required to provide written informed consent. Only after this initial step will data be collected to assess the eligibility of participants.

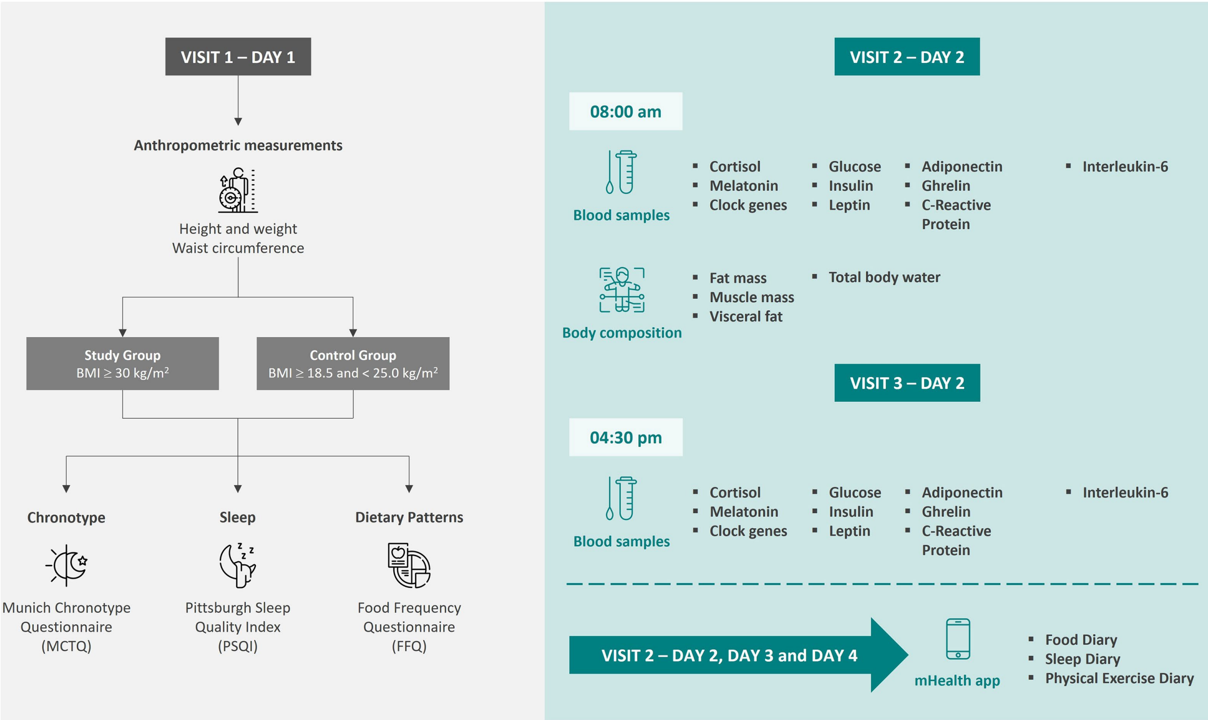

FIGURE 1
Data collection time points and sample collections for the participants of the observational study. Icons made by Freepik from www.flaticon.com. Icons made by iconixar from www.flaticon.com. Icons made by Sweetline from www.flaticon.com.

Data will be collected from eligible adults in three visits, each one with an expected duration of about 1 h. Figure 1 summarizes the study design, including the data and samples to be collected at each time point of the observational study.

2.5. Measurements

2.5.1. Anthropometric and body composition assessments

Participants' body weight, height, and waist circumference will be measured according to the Portuguese Directorate General of Health guidelines for anthropometric procedures in adults (49). Body mass index (BMI; kg/m^2) will be calculated and categorized according to the age and sex-specific BMI cut-offs for adults (50). Fat mass (FM), visceral adipose tissue (VAT), fat-free mass (FFM), and skeletal muscle mass (SMM) for arms, legs, torso, and whole body will be assessed using the bioimpedance equipment seca mBCA 525 (Bacelar, Porto, Portugal).

2.5.2. Biochemical assessments

Peripheral blood samples (15–20 mL) will be collected from the participants at 08:00 a.m., after overnight fasting, and 04:30 p.m. on the same day, and aliquoted into EDTA tubes following safety standards, by certified healthcare professionals. Another blood sample (2.5 mL) will be collected from volunteers to PAXgene® Blood RNA Tubes (BD Biosciences), to obtain total RNA from whole blood.

For the total RNA from peripheral blood mononuclear cells (PBMC), blood samples will be diluted in 25 mL of Phosphate Buffered Saline (PBS) 1 × and added to 50 mL falcon tubes with 10 mL of Histopaque, density 1.077 g/mL. Samples will be centrifugated at 20°C to 22°Cand plasma will be immediately aliquoted and stored at −80°C. The interface bands, which contain the PBMC, will be aspirated into new 50 ml falcon tubes and washed with PBS 1 ×, followed by centrifugation at 21°C–25°C. Supernatants will be discarded and PBMC aliquots will be stored at −80°C until the analysis.

For the total RNA from whole blood, PAXgene® Blood RNA tubes will be centrifuged at 20 to 22°C and the supernatant removed. To the pellet, RNase-free water will be added and the samples vortexed until the pellet dissolution, followed by a centrifugation at 20°C to 22°C. After removal of the supernatant, a lysis buffer will be added, the sample vortexed and transferred to a 1.5 mL microcentrifuge tube where 40 μL of proteinase K will be added. After incubation, the sample will be transferred to a spin column of the Macherey Nagel RNA extraction kit, according to the manufacturer's instructions. RNA concentration and purity will be determined using a spectrophotometer. Samples will be stored at −80°C until the analysis.

RNA samples will then be converted into cDNA and the mRNA levels of the clock genes (BMAL1, CLOCK, PER1-3, CRY1-2, CSNK1ε, REV-ERBα, REV-ERBβ, and DEC1) will be assessed using real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Relative gene expression will be calculated according to the ΔCT method (51, 52).

Plasma levels of insulin, leptin, adiponectin, ghrelin, c-reactive protein, and interleukin-6 will be quantified using ELISA kits, according to the manufacturer's instructions. Glucose will be assessed using the hexokinase method with a commercial kit.

2.5.3. Clinical data

Participants will register in the NutriClock mobile application, specifically designed for this observational study by a multidisciplinary team, including computer engineers, nutritionists, physiologists, and psychologists (53). The NutriClock mobile application and backoffice were designed and developed to comply with ethical standards and the General Data Protection Regulation. The research team and authorized healthcare professionals will have access to the information that each participant introduces in the mobile application *via* the backoffice platform.

The clinical history information may be entered voluntarily by the participant when creating the account. Participants can also add or edit information in their profile after they are registered, at any time point. Healthcare professionals can also complete the information about the participant in the NutriClock backoffice. The information that will be collected includes sociodemographic data, diagnosed pathologies, and current medication.

2.5.4. Dietary intake assessments

Dietary intake will be assessed using two methodologies: a 3-day food diary included in the NutriClock app (53) and a Food Frequency Questionnaire (FFQ). To ensure equal access and opportunity to participate in the research study, regardless of the socioeconomic level, availability of a smartphone, and/or ability to use it, participants can opt to complete the 3-day food diary in the traditional pen-and-paper format.

The participants will start filling out the 3-day food diary on the day of their visit to the research center to collect biological samples (Visit 2, Figure 1). All foods, including drinks, beverages, and dietary supplements consumed during the 3 days should be registered. Participants will also be required to register the meal time and type (breakfast, lunch, dinner or snack). Food portions will be estimated using either a photographic method (participants can take a picture of their meal through the mobile application), using the weight or volume, pre-determined household measures, and/or default mean portions where the participants cannot quantify a specific food item.

The conversion of food into energy and nutrients will be based on the Portuguese Food Composition Table (54), incorporated into the app and, if necessary, other food composition tables. In the app's food diary section, participants can also upload pictures of the nutritional information/food labeling of the food items being consumed, if available. In the backoffice, it is possible to continuously adapt and complete the information on the Portuguese Food Composition Table by adding nutritional information for new food items or meals. The Portuguese Food Frequency Questionnaire (FFQ) is a validated semi-quantitative instrument that assesses dietary intake, reporting the previous 12 months. This tool will be used to collect information on the consumption of less frequently eaten foods and, therefore, minimize interferences with the day-to-day variation of food intake (55). The Portuguese FFQ includes a pre-determined list of 86 food items or groups, and nine frequency categories ranging from "Never or less < 1 per month" to "6+ per day" (56). Food consumption is quantified by multiplying the reported intake frequency by the food item or group average standard portion, and by a seasonal variation factor for items consumed only in a specific season. The conversion to nutrients will be supported by a compilation of databases on the nutritional food composition, including the Portuguese Food Composition Table (54).

The data collected with the FFQ will be mainly used to perform a global characterization of the participants' dietary intake in the previous 12 months. The data collected using the 3-day food diary will be used to correlate dietary intake and circadian biomarkers.

2.5.5. Questionnaires

To complete the participant's characterization and data, a set of validated questionnaires and instruments will be used.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-items (plus 5 additional items, in case the responder has a roommate or bed partner, that do not contribute to the total score) self-reported questionnaire, designed to subjectively assess global sleep quality based on the participant's retrospective evaluation (considers the usual sleep habits over the past one-month period). The items of the PSQI are divided into seven components, namely, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, each weighted equally on a scale from 0 to 3. The global PSQI score ranges from 0 to 21, corresponding to the sum of the seven components. A global PSQI score greater than 5 indicates major difficulties in at least two components or moderate difficulties in more than three components (57, 58). This instrument has been validated for the Portuguese population (59).

The Munich Chronotype Questionnaire (MCTQ) was developed by Roenneberg and colleagues to assess the circadian phase of entrainment, which is considered a quantifiable biological phenotype (41, 60). The questions aim to evaluate sleep behavior on workdays and work-free days, separately, since this distinction is essential to determine the participant's chronotype. The chronotype resultant from the MCTQ is expressed in local time and it is based on the Mid-Sleep time in Free days (MSF) after correction for potential compensatory sleep (MSF_{sc}) (60). The midpoint of sleep has been considered one of the most accurate behavioral markers to determine the circadian phase (60, 61). However, to account for the sleep debt as a cofounder, it is necessary to calculate the average sleep duration of the entire week and correct MSF by subtracting half of the oversleep. According to the results of the MCTQ database, Roenneberg and colleagues identified seven groups based on MSF_{sc}, namely, extremely early, moderately early, slightly early, intermediate, slightly late, moderately late and extremely late (60). This instrument has already been validated for the Portuguese population (62).

2.6. Statistical analysis

Statistical analysis will be performed using the IBM SPSS Statistics software version 28.0.1. (IBM Corp., Warrington, United Kingdom) and GraphPad Prism version 8 (GraphPad Software, Inc.; San Diego, United States). Continuous variables will be presented as the mean ± standard deviation (SD), median, and interquartile range [Q1–Q3]. Categorical variables will be presented in frequency and percentage. The normality of continuous variables will be tested using the Shapiro–Wilk test if $n < 50$ or the Kolmogorov–Smirnov test if $n \geq 50$. Parametric tests (Independent Sample *t*-test) will be used to compare the differences between the study and the control groups if the data has a normal distribution, otherwise, non-parametric tests (Mann–Whitney *U*-tests) will be performed. According to the normality or non-normality of data distribution, Spearman's rank-order correlation (ρ) or Pearson's correlation coefficient (r) will be performed to calculate and assess the strength of correlations between the study variables. Statistical significance will be set at $p < 0.05$.

3. Discussion

In recent decades, there have been breakthroughs in obesity care and treatment. However, despite these advances, there is a major remaining challenge: improving the understanding of the heterogeneity of obesity. This knowledge is essential to determine the best approaches to screen, assess risk, and select personalized and individualized treatments. The findings of this study will provide a better understanding of obesity phenotypes in regard to their chronotype, dietary intake (including meal time and nutrient intake), and circadian and metabolic biomarkers.

The circadian system regulates metabolism through the secretion of hormones, such as cortisol and melatonin (63). Alterations in melatonin and cortisol rhythms, or their blunted secretion, are important attributes of circadian misalignment (64, 65). Melatonin is a major regulator of circadian rhythm, namely sleep–wake cycles and hormone secretion (66). The levels of this hormone typically rise at night and fall during the day, in synchrony with the body's circadian rhythm. Studies have shown that melatonin can help regulate glucose homeostasis by improving insulin sensitivity and reducing insulin resistance (67, 68). In addition, melatonin has been shown to improve lipid metabolism by reducing the levels of triglycerides and cholesterol in the blood. It may also play a role in regulating appetite and body weight (68–70). Disruptions to the body's circadian rhythm can lead to alterations in melatonin secretion patterns which can have negative effects on metabolism and overall health, as disrupted melatonin secretion has been associated with an increased risk of metabolic disorders such as type 2 diabetes and obesity. Cortisol is tightly regulated by the circadian system, showing an anti-phasic pattern of secretion compared to melatonin (71). Disturbances in the normal circadian patterns can promote alterations in cortisol secretion patterns, which might have a deleterious effect on metabolism. Cortisol is a catabolic hormone with several essential functions in the body, including the mobilization of glucose from glycogen, amino acids and fats in response to other hormonal signals (71). Prolonged cortisol release can promote insulin resistance and obesity can promote abnormal cortisol levels (66).

Circadian oscillations of gene expression also regulate whole-body metabolism (72). For example, Gaspar et al. showed that patients with obstructive sleep apnea, which is strongly related to obesity (73, 74), have different patterns of clock gene expression compared with healthy individuals (51), further highlighting the importance of assessing the circadian features in disease.

The importance of determining the circadian rhythm has been extensively reported; although it started more focused on pharmacological studies (40), this relevance has extended to nutrition. From this, the concept of chrononutrition emerged, mostly because peripheral circadian clocks are mainly synchronized by food intake (24, 31). Furthermore, the circadian clock also regulates nutrient challenges, through transcription factors that modulate the expression of genes with regulatory roles in nutrient pathways (37, 75) Therefore, there is the potential to improve metabolic homeostasis by coordinating behavioral changes with the body's daily rhythm. The identification of genetic patterns and signatures in response to dietary intake may guide the advance of new therapeutic approaches.

Designing dietary interventions that account for the quality, quantity and timing of food intake could be an approach to modulate the circadian rhythm and clock-controlled genes and optimize the synchronization of central and peripheral clocks, with a positive impact on overall metabolism. Therefore, the characterization of circadian and dietary makers is a critical first step to underpin therapeutic strategies and to support the adjustment of chrononutritional approaches for the management of chronic diseases such as obesity. In the present study, caloric intake, macronutrients (proteins, carbohydrates, and lipids), and meal times (time of the first meal of the day, time of last meal of the day and overnight fasting period) will be evaluated, in order to assess the impact of dietary intake (timing and nutrients) on circadian rhythm markers.

The research protocol has the advantage of simultaneously evaluating dietary intake, circadian rhythm biomarkers, and metabolic biomarkers in blood samples, of both individuals with obesity and healthy individuals. Taking into account circadian rhythm dysfunction in obesity, a better understatement of the circadian clock might provide important clues regarding overall metabolism and disease progression, helping to design more fitting treatment approaches. Based on previous studies, we expect to find differences in the expression of circadian clock genes between the two groups, particularly, in the expression of BMAL1, PER2, CRY2, and REV-ERBα (51, 76–79).

To minimize the number of visits by participants to the study center, and to attempt to increase study adherence, the food diary, sleep diary, and physical exercise registry will be filled out through the mobile application NutriClock. Previous studies have shown increased satisfaction and preference for mobile applications for reporting dietary intake, compared with conventional methods (80), which is a particularly important observation supporting the methodology of our study. Also, as the data is collected through the NutriClock mobile application, it is immediately available to the researchers, preventing the participant from having to go to the study center to deliver the forms in paper format. Furthermore, if data is not being inputted into the mobile application, the participants receive notifications with reminders of the importance of the diaries. In the backoffice, the researcher is also able to detect immediately, through a color system, if the participants are not collecting data and can contact them, if necessary. The records inserted by participants are evaluated on a daily basis, and the system assigns one of four color levels to each component completed, such as the food or sleep diary. This evaluation is based on two criteria: the time elapsed since the start of registration and the number of registrations made. If the number of registrations exceeds 75% of the total days, the component is marked with a green tab. If the number is between 50% and 75%, the tab is yellow, while an orange tab indicates a number between 25% and 50%. A red tab is assigned if the number of registrations is less than 25%.

Some limitations of this study should be considered, including a potential low acceptance of the protocol, causing difficulties in recruitment, and a high drop-out rate. Therefore, a percentage of 20% of drop-out was taken into consideration when calculating the sample size. This anticipated difficulty in recruitment and acceptance of the study protocol is mostly related to the multiple sample collections, and the requirement of filling out a 3-day food diary, which could potentially be a burden for some participants. Initially, recruitment will be promoted in the Leiria (Portugal) area but may be extended to other areas of the central region of Portugal if necessary. Recruiting participants only in the Leiria area, although more convenient for logistical reasons, could also be considered a limitation, given that all study participants will represent the same geographical area and, therefore, we must be cautious in interpreting and extrapolating data. In addition, to mitigate drop-out, participants who complete the observational study will have the opportunity to have a nutrition education session with a registered nutritionist. Also, participants will have permanent access to all the data that they will introduce in the mobile application. Another potential limitation is related to social bias in the self-reporting questionnaires, especially, in the food diaries, which could lead to an underestimation of food intake (81, 82). The assessment of clock gene expression only at two-time points during the day also represents a pitfall of the study. The circadian rhythm integrity has been previously evaluated by looking at clock gene expression at four-time points in hospitalized patients, allowing a more robust interpretation of the results (50). This protocol is based on outpatient recruitment and collection of blood samples at two different time points during the day for outpatient volunteers carries a significant risk of increasing attrition of the study. To mitigate the risk of misinterpreting the data on circadian rhythm based on two-time point serum biomarkers and clock gene assessment, the Pittsburgh Sleep Quality Index and the Munich Chronotype Questionnaire were added to the protocol to broaden the information obtained by serological analysis.

In conclusion, this study will characterize and compare circadian rhythm biomarkers of healthy individuals and people with obesity, associating this information with dietary intake. The results of this study might provide new evidence to develop more targeted and personalized interventions for nutritionists, endocrinologists, and other healthcare professionals, for the treatment and prevention of obesity and its associated complications.

4. Ethics and dissemination

This is a research project that falls under the scope of Portuguese Law no. 21/2014 April 16 that covers all research with humans, including observational studies. This study will be carried out on adults over the age of 18 years. Adults who are unable to provide their informed consent will not be included in the study.

The research project was approved by the Ethics Committee of the Centre's Regional Health Administration (ARS Centro) on 29th January 2021 (Proc no. 67-2020). The research will be carried out in strict compliance with the ethical principles of the Helsinki Declaration and obeying international, European, and national legislation, including the General Data Protection Regulation (Regulation (EU) 2016/679). The principles of autonomy, nonmaleficence and beneficence, fairness, and clear informed consent will be strictly respected. The researcher will assure that the informed consent document will be available to the volunteers before starting any procedure of the study. The recruitment will be gender-independent to minimize gender bias.

Biological samples will be protected by the principle of non-commercialization, commercial use, patenting, or any financial gain, and the principle of the non-susceptibility of patenting human genetic heritage. The samples will be used exclusively to support this research initiative and will be destroyed immediately after use.

The participants will not be identified by any of their data, to ensure the confidentiality and anonymity of the collected data, a unique ID number will be assigned to each participant. Only the Principal Investigator will have access to the list with the match between the participant's ID and their data. This list will be in electronic format, with restricted access to its content and secured with a password, preventing confidential information from being accessed, printed, forwarded, or copied by an unauthorized person(s). Personal data collected in the context of this study, and shared between team members, will be kept in secure files, with restricted access, be they electronic or physical, and kept after the conclusion of this study, for the time defined by law.

Participants have the right to withdraw from the study at any time, without the need to provide a reason, if they wish not to do so. Participants will be assured that if they wish to withdraw from the study, their medical care will not be affected. Except if the participant indicates otherwise, any data collected up to the point of withdrawing consent will be included in the final analysis.

The results will be disseminated in group data, and individual results that might identify the participant will never be shown to the public. The results and deliverables of this research project will be available in academic health-related publications and through presentations in international scientific meetings.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Centre's Regional Health Administration. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ML, RB, SC-S, and MG conceived and designed the study, contributed to the protocol development, and contributed to the manuscript by revising it critically for intellectual content. ML wrote the first draft of 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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Associations of specific dietary unsaturated fatty acids with risk of overweight/obesity: population-based cohort study

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Background: The role of specific unsaturated fatty acids (FAs) in the development of overweight/obesity remains unclear in the general population. Here, we aimed to explore the associations of different types of unsaturated FAs with overweight/obesity risk among the Chinese population.

Methods: Eight thousand seven hundred forty-two subjects free of overweight/obesity at entry in the China Health and Nutrition Survey (CHNS) were followed up until 2015. Dietary unsaturated FAs were assessed by 3-day 24-h recalls with a weighing method in each wave. Cox regression models were used to obtain the hazard ratios (HRs) and 95% confidence intervals (CIs) for overweight/obesity risk associated with unsaturated FAs.

Results: During a median follow-up of 7 years, 2,753 subjects (1,350 males and 1,403 females) developed overweight/obesity. Consuming more monounsaturated FAs (MUFAs) was associated with a lower risk of overweight/obesity (highest vs. lowest quartile: HR 0.80, 95% CI 0.67–0.96; *P*-trend=0.010). Similar inverse associations were observed for plant-MUFAs (HR_{Q4vsQ1} 0.83, 95% CI: 0.73–0.94; *P*-trend=0.003) and animal-MUFAs (HR_{Q4vsQ1} 0.77, 95% CI: 0.64–0.94; *P*-trend=0.004), total dietary oleic acid (OA) (HR_{Q4vsQ1} 0.66, 95% CI: 0.55–0.79; *P*-trend <0.001), plant-OA (HR_{Q4vsQ1} 0.73, 95% CI: 0.64–0.83; *P*-trend <0.001) and animal-OA (HR_{Q4vsQ1} 0.68, 95% CI: 0.55–0.84; *P*-trend <0.001). In addition, the intakes of n-3 polyunsaturated FAs (PUFAs) (HR_{Q4vsQ1} 1.24, 95% CI: 1.09–1.42; *P*-trend=0.017) and α-linolenic acid (ALA) (HR_{Q4vsQ1} 1.22, 95% CI: 1.07–1.39; *P*-trend=0.039) but not marine n-3 PUFAs were positively linked to overweight/obesity risk. Consumption of n-6 PUFAs (HR_{Q4vsQ1} 1.13, 95% CI: 0.99–1.28; *P*-trend=0.014) and linoleic acid (LA) (HR_{Q4vsQ1} 1.11, 95% CI: 0.98–1.26; *P*-trend=0.020) had marginal and positive relationships with the incidence of overweight/obesity. N-6/n-3 PUFA ratio ranging from 5.7 to 12.6 was related to higher risk of overweight/obesity.

Conclusion: Higher dietary intake of MUFAs was associated with lower overweight/obesity risk, which was mainly driven by dietary OA from either plant or animal sources. Intakes of ALA, n-6 PUFAs and LA were related to higher risk of overweight/obesity. These results support consuming more MUFAs for maintaining a healthy body weight among the Chinese population.

KEYWORDS

unsaturated fatty acids, obesity, overweight, prospective study, China health and nutrition survey

Introduction

Overweight and obesity are a great burden to the world, with the events of overweight and obesity tripling to 1.6 billion in 2016 compared to 1975s (1). Notably, overweight and obesity are vital risk factors for noncommunicable diseases including cardiovascular disease and cancer, which are leading causes of death (2, 3). China is also threatened by the epidemic of overweight and obesity. The latest data from the Chinese Residents Chronic Disease and Nutrition Surveillance (2020) highlighted that the prevalence of overweight and obesity has rapidly increased to approximately over 50% among Chinese adults (4).

Dietary habits are key modifiable factors to prevent a large fraction of overweight and obesity (5). Among them, different types of dietary fatty acids (FAs) have received great attention in human health (6). Dietary guidelines recommend reducing saturated FA (SFA) intake while increasing the intake of polyunsaturated FAs (PUFAs) and monounsaturated FAs (MUFAs) (7). However, these guidelines are based on cardiovascular benefits and fail to focus on specific FAs that could have divergent effects on body size. Previous studies summarized that the chain length, degree of unsaturation, and position and stereoisomeric configuration of the double bonds of FAs might affect FA oxidation rate thereby influencing body weight (8). Our previous study assessed the association of different chain-length SFA intake with overweight/obesity in the Chinese population, which indicated heterogeneous effects among SFAs with different chain lengths (9). In terms of unsaturated FAs, previous studies suggested that dietary oleic acid (OA) and long-chain n-3 PUFAs had a protective effect on body weight or composition (10, 11), while dietary intake of n-6 PUFAs including linoleic acid (LA) and arachidonic acid (AA) were supported to promote weight gain (12). Earlier studies have revealed different effects of MUFAs from animal and plant sources on human health (13–15). However, prospective studies assessing the effects on the development of overweight/obesity are lacking. Chinese adults have higher consumption of OA and LA, but lower intake of palmitoleic acid (PA), α-linolenic acid (ALA) and marine n-3 PUFAs including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (16). The current level of unsaturated FA consumption in relation to overweight/obesity development has not been assessed at a nationwide level in China.

To provide further evidence and advance the field, we investigated the diverse associations of different unsaturated FA intakes with the risk of overweight and obesity among 8,742 Chinese adults enrolled in the China Health and Nutrition Survey (CHNS).

Methods

Study population

CHNS is an ongoing cohort using multistage cluster random sampling to draw a sample of 30,000 individuals from 15 provinces and municipal cities in China. The CHNS was initiated in 1989. Subsequently, the surveys were conducted in 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011, and 2015. Detailed procedures have been described elsewhere (17, 18). Given that only adults aged 20–45 y were included in the 1989 round and the food codes from 1991 to 1993 round did not match the food codes in the Chinese Food Composition Table (FCT), participants in the current analysis were recruited from 1997 to 2011 round. We further excluded the participants aged under 20 years old ($n = 8,706$), without complete dietary data based on a 3-day 24-h dietary recall ($n = 720$), had a history of cardiovascular disease (CVD) or cancer at baseline ($n = 550$), with extreme energy intake (< 800 or > 4,200 kcal/day for men and < 600 or > 3,500 kcal/day for women, $n = 181$), without follow-up or with overweight/obesity at baseline ($n = 8,005$), and without BMI data during the follow-up ($n = 2,572$). Finally, 8,742 participants were selected in the present analyzes (Supplementary Figure S1).

Dietary assessment and covariates

In the CHNS, dietary assessments consist of a 3-day 24-h dietary recall for individuals and a weighing inventory for household food consumption at the same 3 days. Other details on dietary data collection have been described elsewhere (17). Nutrient intakes from various foods were calculated using FCT (19–21). The 1991 version of FCT was used in 1997 and 2000 to obtain dietary information, and the 2002 and 2004 versions were combined for other surveys. Cumulative mean values were computed for each nutrient to represent long-term consumption and reduce within-individual heterogeneity. In addition, demographic and lifestyle information was collected as well, including age, sex, physical activity, marital status, nationality, education level, household income, smoking, alcohol consumption, and history of hypertension and diabetes.

Ascertainment of overweight and obesity

The height and weight of each participant in each interview were measured by well-trained staffs with the use of standard protocol and instruments. BMI was calculated as body weight (kg) divided by height squared (m^2). The ascertainment of overweight and obesity was according to the Chinese Criteria of Weight for Adults (WS/T 428–2013): participants with a range of 24 kg/m^2 ≤ BMI < 28 kg/m^2 were considered as overweight, while a BMI ≥ 28 kg/m^2 was considered as obesity.

Statistical analyzes

Intakes of individual unsaturated FAs were expressed as percentages of total energy intake and then divided into quartiles (22). The baseline characteristics of participants were expressed as the means ± standard errors for continuous variables, while categorical variables were expressed as the percentages (%). To compare proportions or means of baseline characteristics among quartiles of MUFA or PUFA intake, chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables were applied. The follow-up duration of each participant was calculated from the baseline year to the year of developing overweight/obesity or the date of their last assessment. Multivariable Cox proportional hazards regression models were conducted to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for overweight/obesity risk with the first category of unsaturated FAs as the reference. Tests for trends were assessed by calculating the median values in each quartile as continuous variables. Three stepwise models were established with potential confounders considered as covariates: model 1 was a crude model adjusted for age and gender; model 2 was further adjusted for BMI (in kg/m^2: < 18.5, 18.5–23.9, 24–27.9 or ≥ 28), nationality (Han or non-Han), education (less than high school, high school, some college or at least college), deprivation index (quartile), marital status (never married, married or living as married, widowed/divorced/separated, or unknown), household income (quartile), physical activity (no regular activity, low to moderate activity, or vigorous activity), smoking (never, former, current, or unknown), alcohol drinking status (non-drinker or drinker), history of hypertension (yes, no, or unknown) and diabetes (yes, no, or unknown); model 3 was additionally adjusted for the intake of total energy, percentages of energy from protein, SFAs and remaining FAs where appropriate. For the possible dose–response relationship between individual FAs and overweight/obesity, restricted cubic spline regression was performed with 4 knots at prespecified locations according to the percentiles of FAs.

Subgroup analyzes were conducted stratified by gender, age, smoking status, alcohol consumption, physical activity, education level, household income, and history of hypertension and diabetes. In sensitivity analysis, to test the robustness of models, we further adjusted for cholesterol intake, occupation and alternative healthy eating index (AHEI) (23), excluded participants with extreme BMI (< 18.5 kg/m^2), and excluded participants with hypertension or diabetes at baseline.

All these analyzes were performed with the use of SAS version 9.4 (SAS Institute, Cary, NC, United States). Two-sided probability values <0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of 8,742 participants according to quartiles of total MUFA and PUFA intakes are shown in Table 1. Participants who consumed more MUFA or PUFA were older (*p* value <0.001) and women (*p* value <0.001). Furthermore, they had higher household income (*p* value <0.001), higher education levels (*p* value <0.001), higher intake of SFAs (*p* value <0.001) and cholesterol (*p* value <0.001), and higher prevalence of diabetes (*p* value = 0.005 for MUFA, *p* value <0.001 for PUFA). On the contrary, they smoked (*p* value <0.001) and drank alcohol (*p* value <0.001) less frequently, and had less physical activity (*p* value <0.001) and total energy intake (*p* value <0.001).

MUFA intake and risk of overweight and obesity

Over a median of 7-year follow-up, 1,350 males and 1,403 females developed overweight/obesity. In model 3 with potential confounders fully adjusted, participants in the highest quartile of MUFA intake presented a significant reduction of 20% in the risk of overweight/obesity (HR_{Q4vsQ1} 0.80, 95% CI: 0.67–0.96; *P*-trend = 0.010; Table 2). The inverse association was also observed for OA intake (HR_{Q4vsQ1} 0.66, 95% CI: 0.55–0.79; *P*-trend <0.001), whereas PA intake was not associated with the risk of overweight/obesity (HR_{Q4vsQ1} 1.15, 95% CI: 0.96–1.37; *P*-trend = 0.132; Table 2). In terms of dietary source of MUFAs, both animal-derived (HR_{Q4vsQ1} 0.77, 95% CI: 0.64–0.94; *P*-trend = 0.004) and plant-derived MUFAs (HR_{Q4vsQ1} 0.83, 95% CI: 0.73–0.94; *P*-trend = 0.003) had inverse associations with overweight/obesity development (Table 3). The results of OA derived from animal (HR_{Q4vsQ1} 0.68, 95% CI: 0.55–0.84; *P*-trend <0.001) and plant sources (HR_{Q4vsQ1} 0.73, 95% CI: 0.64–0.83; *P*-trend <0.001) exhibited similar association patterns (Supplementary Table S1). However, the adjusted HRs and 95% CIs suggested a detrimental association for plant-PA (HR_{Q4vsQ1} 1.29, 95% CI: 1.14–1.47; *P*-trend = 0.002) but not animal-PA consumption (HR_{Q4vsQ1} 0.86, 95% CI: 0.71–1.05; *P*-trend = 0.132; Supplementary Table S1). Restricted cubic spline regression produced similar findings for these MUFAs (Figure 1; Supplementary Figure S2).

PUFA intake and risk of overweight and obesity

Total dietary PUFA intake was related to an increased risk of overweight/obesity in fully adjusted model 3 (HR_{Q4vsQ1} 1.24, 95% CI: 1.10–1.39; *P*-trend <0.001; Table 2). Participants in the highest quartiles of n-3 PUFAs (HR_{Q4vsQ1} 1.24, 95% CI: 1.09–1.42; *P*-trend = 0.017) and ALA (HR_{Q4vsQ1} 1.22, 95% CI: 1.07–1.39; *P*_trend = 0.039) but not marine n-3 PUFAs (HR_{Q4vsQ1} 0.83, 95% CI: 0.68–1.02; *P*-trend = 0.176) had increased overweight/obesity risk compared to the lowest quartiles (Supplementary Table S2). N-6 PUFA intake was marginally and positively correlated with the risk of overweight/obesity (HR_{Q4vsQ1} 1.13, 95% CI: 0.99–1.28; *P*-trend = 0.014), which was primarily owing to LA (HR_{Q4vsQ1} 1.11, 95% CI: 0.98–1.26; *P*-trend = 0.020) but not AA (HR_{Q4vsQ1} 0.96, 95% CI: 0.82–1.13; *P*-trend = 0.515) intake (Supplementary Table S2). Compared with the lowest quartile, the highest quartile of the n-6/n-3 PUFA ratio was not significantly associated with the incidence of overweight/obesity (HR_{Q4vsQ1} 0.94, 95% CI: 0.84–1.06), but higher risk was observed for the n-6/n-3 PUFA ratio ranging from 5.7 to 12.6 (Table 2). Similar results for these PUFAs were demonstrated by restricted cubic spline regressions (Figure 1; Supplementary Figure S3).

Subgroup and sensitivity analyzes

Subgroup analyzes showed that the inverse associations of overweight/obesity incidence with total dietary MUFA intake were

TABLE 1 Characteristics of the participants at baseline classified by the quartiles of MUFA and PUFA intakes.

	MUFA intake (percentage of energy, %)					PUFA intake (percentage of energy, %)				
	Q1(≤ 8.7)	Q2(8.7–11.4)	Q3(11.4–14.1)	Q4(≥ 14.1)	*P* value	Q1(≤ 5.2)	Q2(5.2–7.0)	Q3(7.0–9.1)	Q4(≥ 9.1)	*P* value
N	2,185	2,186	2,186	2,185		2,185	2,186	2,186	2,185	
Age (years)	41.3 ± 0.3	42.3 ± 0.3	43.3 ± 0.3	44.8 ± 0.3	<0.001	42.0 ± 0.3	42.8 ± 0.3	43.2 ± 0.3	43.8 ± 0.3	<0.001
Body mass index (kg/m^2)	21.0 ± 0.04	21.0 ± 0.04	21.0 ± 0.04	21.0 ± 0.04	0.250	20.8 ± 0.04	20.9 ± 0.04	21.0 ± 0.04	21.2 ± 0.04	<0.001
Household income (yuan/yr)	19,353.2 ± 556.1	27,425.5 ± 697.7	31,293.9 ± 806.8	34,929.0 ± 888.9	<0.001	24,297.2 ± 647.7	29,075.0 ± 751.3	29,129.1 ± 814.2	30,472.7 ± 800.0	<0.001
Male (%)	52.5	47.9	45.8	41.4	<0.001	54.2	49.1	45.0	39.2	<0.001
Han (%)	85.7	84.9	87.4	89.2	<0.001	74.8	86.1	91.7	94.5	<0.001
Married (%)	84.0	85.9	84.2	82.0	<0.001	84.3	84.5	83.8	83.6	<0.001
Greater than high school (%)	5.4	12.5	15.6	17.6	<0.001	7.3	12.5	13.9	17.4	<0.001
Moderate-to-vigorous activity (%)	70.8	57.8	44.4	37.0	<0.001	68.3	54.0	48.4	38.3	<0.001
Current drinker (%)	37.3	37.5	32.8	31.4	<0.001	37.9	36.0	33.9	31.1	<0.001
Current smoker (%)	37.8	31.5	28.7	26.5	<0.001	37.2	31.9	29.6	25.8	<0.001
History of hypertension (%)	9.8	10.2	10.9	10.3	0.712	10.3	10.3	10.8	9.8	0.701
History of diabetes (%)	1.1	1.9	2.5	3.2	0.005	0.9	2.4	2.0	2.5	<0.001
Dietary intake										
Total energy (kcal/day)	2,130.1 ± 11.3	2,108.4 ± 10.5	2,077.6 ± 10.2	2,060.2 ± 11.2	<0.001	2,111.0 ± 11.1	2,128.4 ± 11.0	2,083.5 ± 10.7	2,053.4 ± 10.5	<0.001
Protein (%)	12.1 ± 0.1	12.5 ± 0.1	12.8 ± 0.1	13.1 ± 0.1	<0.001	12.3 ± 0.1	12.8 ± 0.1	12.8 ± 0.1	12.6 ± 0.1	<0.001
Saturated fatty acids (%)	4.7 ± 0.03	6.9 ± 0.03	8.4 ± 0.03	11.3 ± 0.2	<0.001	7.1 ± 0.07	7.7 ± 0.07	7.6 ± 0.06	8.9 ± 0.24	<0.001
Cholesterol (mg/day)	198.8 ± 3.9	285.2 ± 4.9	339.2 ± 4.6	391.2 ± 4.8	<0.001	231.0 ± 4.4	296.5 ± 4.4	328.8 ± 4.9	358.0 ± 5.0	<0.001
AHEI score	53.8 ± 0.2	51.1 ± 0.2	49.7 ± 0.2	48.2 ± 0.2	<0.001	46.8 ± 0.2	48.8 ± 0.2	52.2 ± 0.2	55.0 ± 0.2	<0.001

Values are means ± SE or percentages unless stated otherwise. Q, quartiles; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; AHEI, Alternative healthy eating index.

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TABLE 2 HRs (95% CIs) for the overweight/obesity risk according to MUFA and PUFA consumption.

	Quartiles of dietary fatty acids (% of total energy)				*P*-trend*
	Q1	Q2	Q3	Q4	
MUFAs					
Range	≤ 8.7	8.7–11.4	11.4–14.1	≥ 14.1	
Median	6.9	10.2	12.7	16.1	
Cases/person-years	728/19,665	723/15,302	695/15,302	607/13,110	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.05 (0.94–1.16)	1.05 (0.95–1.17)	1.02 (0.92–1.14)	0.656
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	0.97 (0.87–1.08)	0.92 (0.82–1.03)	0.87 (0.77–0.98)	0.016
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, PUFAs	1.00 (ref.)	0.95 (0.84–1.08)	0.86 (0.73–1.00)	0.80 (0.67–0.96)	0.01
OA					
Range	≤ 6.6	6.6–9.0	9.0–11.6	≥ 11.6	
Median	5.1	7.8	10.2	13.8	
Cases/person-years	713/15,295	730/15,302	707/15,302	603/15,295	
Model					
1.Overweight/obesity ~ Age, sex	1.00 (ref.)	1.05 (0.95–1.17)	1.06 (0.96–1.18)	0.95 (0.85–1.06)	0.396
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	0.99 (0.89–1.10)	0.95 (0.85–1.07)	0.81 (0.72–0.92)	< 0.001
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, PUFAs, PA	1.00 (ref.)	0.93 (0.82–1.06)	0.83 (0.71–0.96)	0.66 (0.55–0.79)	< 0.001
PA					
Range	≤ 0.3	0.3–0.4	0.4–0.6	≥ 0.6	
Median	0.2	0.4	0.5	0.7	
Cases/person-years	687/19,665	714/19,674	741/15,302	611/13,110	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.07 (0.97–1.19)	1.21 (1.09–1.34)	1.14 (1.02–1.27)	0.005
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	1.03 (0.93–1.15)	1.10 (0.99–1.23)	0.98 (0.86–1.10)	0.755
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, PUFAs, OA	1.00 (ref.)	1.06 (0.93–1.19)	1.16 (1.00–1.35)	1.15 (0.96–1.37)	0.132
PUFAs					
Range	≤ 5.2	5.2–7.0	7.0–9.1	≥ 9.1	
Median	4	6.1	7.9	11.1	
Cases/person-years	641/19,665	659/15,302	734/15,302	719/15,295	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.09 (0.98–1.21)	1.27 (1.14–1.41)	1.35 (1.22–1.51)	<0.001

(Continued)

TABLE 2 (Continued)

	Quartiles of dietary fatty acids (% of total energy)				*P*-trend*
	Q1	Q2	Q3	Q4	
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	1.03 (0.92–1.15)	1.15 (1.03–1.29)	1.20 (1.07–1.34)	<0.001
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, MUFAs	1.00 (ref.)	1.05 (0.94–1.18)	1.17 (1.04–1.31)	1.24 (1.10–1.39)	<0.001
n-6 PUFAs					
Range	≤ 4.1	4.1–5.6	5.6–7.5	≥ 7.5	
Median	3.1	4.8	6.5	9.6	
Cases/person-years	636/15,295	658/15,302	731/19,674	728/15,295	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.02 (0.91–1.13)	1.13 (1.01–1.25)	1.28 (1.15–1.43)	<0.001
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	0.96 (0.86–1.07)	1.03 (0.92–1.15)	1.14 (1.02–1.28)	0.004
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, MUFAs, n-3 PUFAs	1.00 (ref.)	0.94 (0.84–1.05)	1.02 (0.91–1.14)	1.13 (0.99–1.28)	0.014
n-3 PUFAs					
Range	≤ 0.4	0.4–0.7	0.7–1.1	≥ 1.1	
Median	0.3	0.5	0.9	1.4	
Cases/person-years	590/19,665	705/13,116	737/15,302	721/15,295	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.49 (1.33–1.66)	1.40 (1.25–1.56)	1.37 (1.22–1.52)	<0.001
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	1.42 (1.27–1.58)	1.32 (1.18–1.47)	1.28 (1.14–1.43)	0.003
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, MUFAs, n-6 PUFAs	1.00 (ref.)	1.40 (1.25–1.57)	1.30 (1.16–1.46)	1.24 (1.09–1.42)	0.017
n-6/n-3 PUFA ratio					
Range	≤ 5.7	5.7–7.9	7.9–12.6	≥ 12.6	
Median	4.4	7	9.2	20.5	
Cases/person-years	655/19,665	758/15,302	729/15,302	611/19,665	
Model					
1. Overweight/obesity ~ Age, sex	1.00 (ref.)	1.26 (1.13–1.40)	1.25 (1.12–1.39)	0.93 (0.83–1.04)	<0.001
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	1.21 (1.08–1.34)	1.22 (1.09–1.36)	0.93 (0.83–1.04)	0.002
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, MUFAs	1.00 (ref.)	1.20 (1.07–1.35)	1.22 (1.08–1.37)	0.94 (0.84–1.06)	0.003

HRs, hazard risks; CIs, confidence intervals; Q, quartile; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; OA, oleic acid; PA, palmitoleic acid. **P*-trend was assessed by calculating the median values in each quartile as continuous variables.

TABLE 3 HRs (95% CIs) for the overweight/obesity risk according to MUFAs from plant and animal sources.

	Quartiles of dietary fatty acids (% of total energy)				*P*-trend*
	Q1	Q2	Q3	Q4	
P-MUFAs					
Range	≤ 3.4	3.4–4.9	4.9–7.1	≥ 7.1	
Median	2.5	4.2	6	9.2	
Cases/person-years	610/10,925	712/15,302	754/19,674	677/19,665	
Model					
1.Overweight/obesity ~ Age, sex	1.00 (ref.)	0.95 (0.86–1.06)	0.97 (0.87–1.08)	0.89 (0.80–1.00)	0.056
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	0.96 (0.86–1.07)	0.99 (0.89–1.11)	0.90 (0.80–1.01)	0.081
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, PUFAs, A-MUFAs	1.00 (ref.)	0.93 (0.83–1.04)	0.94 (0.84–1.05)	0.83 (0.73–0.94)	0.003
A-MUFAs					
Range	≤ 2.9	2.9–5.0	5.0–7.2	≥ 7.2	
Median	1.5	4	6	9.1	
Cases/person-years	718/19,665	757/19,674	696/15,302	582/13,110	
Model					
1.Overweight/obesity ~ Age, sex	1.00 (ref.)	1.11 (1.00–1.22)	1.05 (0.94–1.16)	1.03 (0.92–1.15)	0.79
2. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes	1.00 (ref.)	1.01 (0.91–1.13)	0.93 (0.83–1.04)	0.86 (0.76–0.97)	0.005
3. Overweight/obesity ~ Age, sex, BMI, marital status, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, PUFAs, P-MUFAs	1.00 (ref.)	0.99 (0.86–1.12)	0.84 (0.72–0.99)	0.77 (0.64–0.94)	0.004

HRs, hazard risks; CIs, confidence intervals; Q, quartile; P-MUFA, plant-monounsaturated fatty acid; A-MUFA, animal-monounsaturated fatty acid. **P*-trend was assessed by calculating the median values in each quartile as continuous variables.

only significant in women (*P*-interaction = 0.041), non-drinkers (*P*-interaction <0.001), and those with higher education level (*P*-interaction = 0.012) and lower physical activity level (*P*-interaction = 0.040). Moreover, the positive associations of PUFA intake with the risk of overweight/obesity only appeared in participants with lower household income (*P*-interaction = 0.007; Supplementary Table S3). In sensitivity analyzes, the associations between unsaturated FA intake and overweight/obesity incidence were not materially changed after further adjustment for dietary cholesterol intake, occupation and AHEI, excluding participants with extremely lower BMI (BMI < 18.5 kg/m^2) or those with hypertension or diabetes at baseline (Supplementary Tables S4, S5).

Discussion

To our knowledge, this prospective study is the first to assess the associations of specific dietary unsaturated FA intake with overweight/obesity development among the Chinese population. After adjustment for major potential risk factors, we found that total MUFA, plant-MUFA, animal-MUFA, plant-OA and animal-OA intake was consistently and inversely associated with the risk of overweight/obesity, while ALA, n-6 PUFA and LA intake was positively related to overweight/obesity risk.

OA is the most common type of MUFAs and is mainly consumed from vegetable oil and pork by the Chinese people (14). The beneficial effect of OA on preventing overweight/obesity was supported by several mechanistic studies. First, an OA-rich diet could increase the fat oxidation rate compared to a high SFA diet (24). In addition, the derivative of OA, oleoylethanolamide (OEA) plays a role in appetite modulation and energy intake (25). Although studies on OA biomarkers came to the contrary conclusion that serum OA concertation was positively linked with incident obesity (26). The difference may be due to the fact that serum OA is not an appropriate biomarker for dietary intake but for *de novo* lipogenesis in humans. The accessible regulator of lipogenic gene expression of endogenously synthesized OA and dietary OA was not similar (27). Due to accumulating epidemiology evidence highlighting the importance of

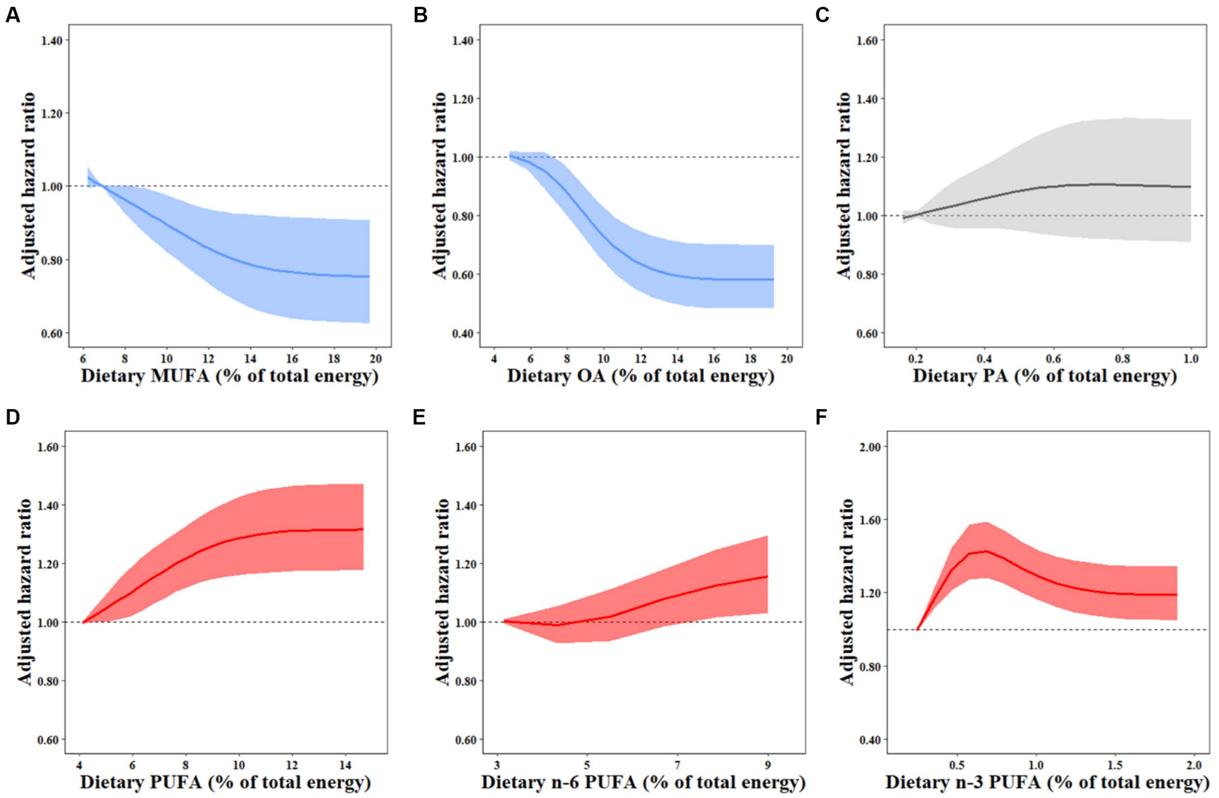

FIGURE 1
Dose–response relationships between dietary FAs and overweight/obesity risk. HRs for the overweight/obesity risk associated with dietary MUFAs **(A)**, OA **(B)**, PA **(C)**, PUFAs **(D)**, N-6 PUFAs **(E)**, and N-3 PUFAs **(F)** were estimated by restricted cubic-spline regression adjusted for age and sex, marital status, BMI, household income, urbanization index, nationality, education, physical activity, smoking, alcohol drinking status, history of hypertension and diabetes, total energy intake, percentages of energy intake from protein, SFAs, and remaining fatty acids where appropriate. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; OA, oleic acid; PA, palmitoleic acid.

food sources of MUFAs on health (13–15), we further assessed the associations of animal and plant sources of MUFAs/OA with the risk of overweight/obesity and found that both sources in CHNS were consistently associated with a reduced risk of overweight/obesity. Moreover, plant-MUFAs seemed less protective than animal-MUFAs in our study, which could be explained by the common cooking method such as stir-frying and griddling applied to vegetable oils in the daily life of the Chinese. Frying vegetable oil may increase the energy density and trans-FA (TFA) formation (28).

PA is another type of MUFAs and has been evidenced to be beneficial for weight maintenance (29). However, the low intake level of PA consumed in the current analyzes resulted in a null association of total PA or animal-PA with incident overweight/obesity, whereas dietary plant-PA intake was linked to overweight/obesity development. The main source of plant-PA in China was soybean oil (14), which was considered more obesogenic than coconut oil and fructose in mice (30). In addition, the cooking methods of the Chinese may also explain this detected adverse association.

Previous epidemiological studies have confirmed the positive correlation between LA intake and incident overweight/obesity that we identified. A cohort including 20,049 participants with a median of 6.5 years of follow-up concluded that dietary LA intake was positively related to weight gain (31). Similarly, another prospective study conducted in Germany found that the baseline level of erythrocyte LA was associated with a higher overweight/obesity risk in middle-aged and older women during a mean of 10.4-y follow-up (32). Besides, several animal experiments also validated the current findings that dietary n-6 PUFA intake was adipogenic (12, 33). The metabolites of dietary LA, such as anandamide and 2-arachidonyl glycerol, which promoted energy intake and weight gain by reducing hypothalamic satiety signaling and skeletal muscle glucose uptake, and increasing accumulation of lipid droplets in the liver, may be responsible for the effect of LA on body size (12). Moreover, prostacyclin converted from dietary LA could stimulate adipocyte differentiation through several pathways, including activating the peroxisome proliferator-activated receptor (PPAR) family and the CCAAT-enhancer binding protein family (CEBPβ and CEBPδ) (12). For AA, a previous study reported that AA promoted adipogenesis (33), which contradicted the existing conclusion that AA intake was not significantly associated with overweight/obesity development. This discrepancy may mainly be due to the overall low consumption of AA (mean intake: 0.02% kcal/d) in the Chinese population.

ALA is an essential n-3 PUFA and mostly accounted for the positive association of n-3 PUFAs in the current analysis. A cross-sectional study based on the National Health and Nutrition Examination Survey and the What We Eat in America found that the relationship of ALA intake was stratified by some sociodemographic groups as a positive association of ALA with BMI was detected among non-Hispanic black individuals (34). Furthermore, ALA in vegetable oils can be transformed into harmful trans-ALA during stir-frying (35), which may account for the adverse relationship as stir-frying was commonly used for ALA-rich vegetable oils among Chinese people. In addition, ALA-enriched diacylglycerol (ALA-DAG) was more prone to weight gaining compared to ALA-enriched triacylglycerol (ALA-TAG) (36). However, we did not divide ALA into ALA-DAG and ALA-TAG, which may also to some extent explain the harmful association for ALA intake. Although we failed to detect an association between marine n-3 PUFA intake and overweight/obesity risk, the *in vivo* studies have demonstrated that fish oil supplementation, which contained high concentrations of EPA and DHA, could offset weight gain induced by a high-fat diet (11, 37). The mechanism of long-chain n-3 PUFAs could be briefly proposed as stimulating lipid oxidation (38), enhancing satiety (39), and inducing browning of white adipose tissue (40). The extremely low consumption of long-chain n-3 PUFAs in our study has a large gap to the 250 mg/d as international dietary guideline recommends, which probably biased the associations toward the null.

The competition on the same enzyme of LA and ALA during the production of AA and EPA/DHA provided a basic theory of the n-6/n-3 PUFA ratio (41). Previous studies focusing on the ratio of n-6 to n-3 PUFAs summarized a positive association between dietary n-6/n-3 PUFA ratio and overweight/obesity incidence (42), which was generally consistent with our results. However, we found divergent associations between dietary LA and AA, and the difference was also observed between ALA and marine n-3 PUFAs. Our findings indicate that the n-6/n-3 PUFA ratio may not be a proper measurement linking unsaturated FA intake to incident overweight/obesity, whereas specific types of unsaturated FAs should be considered when increasing the intake of unsaturated FAs.

In subgroup analyzes, the association of overweight/obesity with total dietary MUFA intake was only significant in women, non-drinkers, and those with higher education levels and lower physical activity levels. These interactions may due to the higher intake levels of MUFAs among persons with the above characteristics. Other detected interactions remain to be elucidated in future studies.

The current study has some strengths. First, the large population and long-term follow-up could reduce the probability of reverse causation. In addition, cumulative intake of unsaturated FAs was used to represent a long-term diet, and within-individual heterogeneity could be reduced as well. Furthermore, this study systematically assessed the associations of different types of unsaturated FAs from diet with overweight/obesity risk. Despite these strengths, some limitations should also be recognized in the current study. First, measurement bias could not be controlled completely, but using the cumulative average intake of nutrients helped to reduce measurement errors. Second, although we adjusted for many potential confounders in models, unmeasured factors still remained and may influence observed results. Third, dietary TFAs was not adjusted in models due to unavailable data. However, the consumption of dietary TFAs was very low in China (43), which may not significantly change our documented results. Fourth, the findings may not apply to other populations because the cooking style and dietary patterns were unique to the Chinese population. Finally, it was not sufficient to establish causality due to the observational nature of this study.

In conclusion, the current findings supported that total dietary MUFA intake was inversely associated with the risk of overweight/obesity, which was mainly driven by dietary OA from both plant and animal sources. ALA and LA had strong positive associations with overweight/obesity risk. Our findings emphasize the importance of increasing the consumption of MUFAs, especially OA, in overweight/obesity prevention among the Chinese population.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cpc.unc.edu/projects/china/data/. 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 the institutional review boards at the University of North Carolina, Chapel Hill and the National Institute of Nutrition and Food Safety from the Chinese Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ, WZ, and JJ conceived and designed the study. YA, XHL, and PZ did the data cleaning, analysis and interpretation. YA wrote the manuscript. WC, YA, XCL, YL, HY, PZ, YZ, and JJ were involved in data acquisition. JJ is the guarantor. All authors contributed to the interpretation of the data and critical revision of the manuscript for important intellectual content and approved the final draft.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1150709/full#supplementary-material

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Identifying risk factors affecting exercise behavior among overweight or obese individuals in China

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Background: The disease burden caused by obesity has increased significantly in China. Less than 30% of those who are obese meet the weekly physical activity standards recommended by the WHO. Risk factors that influence exercise behavior in people with obesity remain unclear.

Methods: Based on the survey from the Chinese General Social Survey program (CGSS) in 2017, 3,331 subjects were identified and enrolled in the univariate and multiple probit regression models. We aimed to identify the association between SRH and the exercise behavior of obese people and further explore the influencing factors of active physical activity in this group of people.

Results: The proportion of active physical activity in obese people was 25%. Groups with better SRH, higher education and income were more likely to participate in sports. Obese people who lived in rural areas, were unmarried or divorced, or fell within the age range of 35–40 had a significantly lower percentage of engagement in active physical activity.

Conclusions: The proportion of people with obesity who meet the WHO recommendation for physical activity in China is not ideal. Health promotion programs for those who are obese need to be further strengthened and targeted, especially for rural areas, low-income families, and middle-aged obese people.

KEYWORDS

obesity, exercise behavior, risk factors, overweight, self-rated health

Introduction

Obesity has become an important public health problem around the world and has a significant impact on quality of life (1). Many scholars have conducted studies on the side effects of obesity, and increasing evidence has confirmed that obesity is significantly associated with the occurrence of some diseases, including hypertension (2), diabetes (3), coronary heart disease (CHD) (4), cancer (5), and stroke (6). According to a retrospective study based on a large number of samples in Britain, obesity may be an important risk factor for premature death (7).

Chinese scholars have also conducted studies that focused on several aspects. First, they described the distribution characteristics of people who are overweight and obese in the Chinese population and also analyzed the changing trends in the burden of being overweight and obese in the country (8, 9).

Second, these researchers explored the influencing factors and related mechanisms of obesity through animal experiments and population surveys (10, 11). Another important research direction was to explore how to diminish the incidence of obesity and reduce the burden of obesity-related diseases based on the previous two aspects (12). Although these studies have played an important role in controlling obesity in China, the disease burden of obesity in China has been showing a rapid growth trend. It is estimated that more than half of the adults in China are overweight or obese, which has become one of the most serious public health concerns in this country (13). Thus, reducing the disease burden caused by obesity has become a major problem affecting the realization of the Healthy China 2030 strategy.

The World Health Organization (WHO) has launched a guideline to prevent and control obesity. The most effective measures to reduce the disease burden of obesity are non-pharmaceutical interventions (NPI), including dietary intervention (reducing nutrient intake) and exercise intervention (increasing fat reduction). For the latter, evidence-based recommendations are provided on the volume of exercise needed to keep fit. For adults, for example, they should get at least 150–300 min of moderate-intensity aerobic exercise per week or participate in no <75–150 min of high-intensity aerobic activity. Moreover, considering the effects of exercise on the health of humans, the population was divided into four groups: (1) inactive group, who have no aerobic physical activity or who seldom take part in exercise; (2) insufficiently active group, who are involved in some aerobic activity each week but less than the aerobic guideline (150–300 min of moderate-intensity exercise); (3) active group (AG), who meet the guideline of participating in aerobic exercise for 300 min per week; (4) sufficiently active group (SAG), who exceed the aerobic guideline of >300 min per week.

The Chinese local government has launched a series of health policies and actions to promote active physical activity (14). However, such policies and actions are not followed by all adults. Previous investigations by our team have found that the proportion of people actively participating in sports every week is not ideal. Some factors, such as culture (15), environment (16), family (17), and community facilities (18), may have a significant impact on the exercise behavior of residents. The recognition of obesity may also be an important risk factor. The Chinese have traditionally viewed obesity as a symbol of wealth. Many of them do not consider obesity an unhealthy condition or disease. In addition, there is not a significant impact on the quality of life in the early stages of being overweight or obese, and the self-rated health of obese individuals may also be a factor that motivates them to participate actively in sports.

The Chinese General Social Survey (CGSS) program was a nationally representative study (19). With data from CGSS 2017, we first compared the exercise behavior of obese individuals and normal-weight groups, and there was no significant difference between the two groups (detailed results are shown in Table 1, Figure 1).

Therefore, our attention was drawn to a question: Although exercise is the best way to stay healthy, why do people with obesity not like to take part in it?

Moreover, previous studies on exercise behavior among obese individuals have mainly focused on the effects of exercise on weight loss (20–23). However, limited studies have focused on the distribution of exercise behavior in overweight and obese individuals, and the risk factors of regular exercise among this special group remain unclear. Therefore, this situation constitutes a significant gap between action assessment and available data, which may affect the precise regulation of health promotion policies.

The main purpose of this study is to describe the distribution characteristics of exercise behavior and explore the factors that affect the exercise behavior of this group. Thus, we can provide guidance to policymakers and other researchers in identifying the important problems of obesity intervention in China at the current stage and enacting proactive measures to promote the exercise participation behavior of obese people.

We also hypothesized that self-rated health might influence the exercise behavior of those who are obese. By verifying the hypothesis and exploring the influencing factors of the exercise behavior of those who are obese, we intended to provide a scientific basis for the improvement of obesity intervention strategies in China.

Methods

The data for this study were derived from the program CGSS2017, which is a nationally representative study containing a multi-stage random sampling across the country. The detailed study design and procedures of this program were previously reported in the original study documentation (19). Data from CGSS2017 were first made public in 2020, and 8,999 samples were included in the program. All data were downloaded publicly (http://cgss.ruc.edu.cn/) in January 2021. Samples were excluded based on the following criteria: (1) Some quantitative variables, such as family income and age, were not answered accurately, such as an income of 0 and an age of more than 120; (2) missing values >5% for family factors and other important variables were excluded from the study; and (3) according to the height and weight of each sample, we first calculated the BMI of each sample, and this study only included the samples whose BMI was >24.

Independent variable

In this study, the quantitative evaluation of sports among those who are obese was considered the independent variable. A question about exercise behavior was asked in the survey: "In the past 12 months, you have engaged in physical activity that usually lasts up to 30 minutes and causes you to sweat. If yes, how many times a week?" Based on the guidelines of the WHO (adults should get at least 150–300 min of moderate-intensity aerobic exercise per week or participate in no <75–150 min of high-intensity aerobic activity), the included samples were divided into two groups: the active group and the inactive group (24).

TABLE 1 Distribution characteristics of exercise behavior of people with different ages and BMI index.

Age	BMI <24		24 < BMI < 28		BMI > 28		χ^2	*p*-value
	n	*n*.sport	*n*	*n*.sport	*n*	*n*.sport		
All	5,668	2,109 (37.21%)	2,543	931 (36.61%)	774	257 (33.20%)	9.75	0.007**
<24	276	141 (51.08)	104	53 (50.96)	30	18 (60.0)	0.89	0.64
24–30	400	154 (38.5)	192	65 (33.85)	49	16 (32.65)	1.57	0.45
31–35	447	143 (32.0)	176	37 (21.02)	49	15 (30.61)	6.66	0.03*
36–40	425	160 (37.65)	185	60 (32.43)	57	16 (28.07)	4.04	0.13
41–45	437	148 (33.87)	181	67 (37.01)	64	21 (32.81)	0.66	0.71
46–50	567	201 (35.45)	250	86 (34.4)	78	22 (28.20)	1.59	0.45
51–55	622	214 (34.40)	262	92 (35.11)	71	16 (22.53)	4.33	0.11
56–60	518	202 (39.0)	237	91 (38.39)	79	31 (39.24)	0.03	0.98
61–65	646	275 (42.57)	286	119 (41.60)	95	35 (36.84)	1.12	0.57
>65	1,330	471 (35.41)	670	261 (38.95)	202	67 (33.16)	7.52	0.02*

*means $p < 0.05$, **means $p < 0.001$.

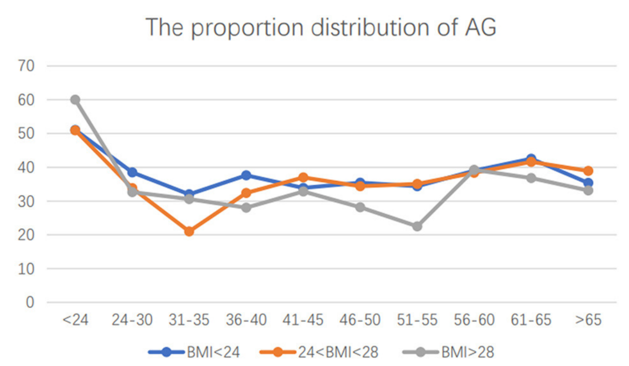

FIGURE 1
The proportion of AG in overweight, obese, and normal-weight samples.

Dependent variable

In this study, self-rated health (SRH) is the variable that contains self-perceived physical health, self-perceived depression, and the impact of health on life. A question referred to self-perceived physical health: "How do you feel about your current physical health?" Options include "very unhealthy," coded as 1, "less healthy," coded as 2, "general," coded as 3, "healthy," coded as 4, and "very healthy," coded as 5, respectively. The average score for this variable in different populations was assessed as a separate variable to evaluate the level of self-perceived physical health. Another item referred to the frequency of depression during the past 4 weeks ("How often have you felt depressed in the past 4 weeks?"). Responses to the question were coded as a quantity range from "1" to "5" ("always" = 1, "frequently" = 2, "sometimes" = 3, "seldom" = 4, or "never" = 5). The question "How often in the past 4 weeks have health problems affected your work or other daily activities?" referred to the impact of health on life. The score of this item was also 1–5. In this study, the SRH score ranged from 5 to 15, with higher scores indicating higher levels of SRH.

Covariate variables

In this study, age was an important factor that was divided into 10 groups. We compared the exercise behaviors of different ages, hoping to provide precise guidance for health intervention.

BMI (body mass index), which is used to measure how fat a person is and whether they are healthy, was calculated using the following formula: BMI = weight (kg)/height^2 (m).

The World Health Organization (WHO) defines being overweight as a BMI of >25 and obesity as a BMI of >30. However, the more common standard in China for being overweight was a BMI of >24, and for being obese, a BMI of >28 (25, 26).

Regarding family income, a question in the questionnaire asked: "What level do you think family income belongs to in the local area?" The answers were "1-below the average line," "2-above the average line," and "3-above the average line."

Educational background categories were as follows: elementary school and below, middle school, high school, and college and above.

Owing to the significant development gap among different areas in China, all the included samples were divided into urban and rural groups according to the Hukou variable.

Statistical analysis

Data analyses were performed using R software (3.5.2), and frequencies and percentages of factors were calculated for descriptive analysis. For numerical variables, bivariate analyses were performed using Pearson's chi-square test, and the association between variables and exercise was assessed using univariate and multinomial logistic regression models. Binary logistic regression analysis with the "enter" method was first used to examine dependent correlates of exercise, with exercise as a dependent variable and those with significant differences in univariate analyses as independent variables. The association between variables and exercise behavior was described with an odds ratio (OR) and 95% confidence interval (CI). The level of significance was set at a p-value of <0.05 (two-tailed t-test).

Results

Descriptive analysis

A total of 8,999 random national samples were included in the CGSS 2017 program, and according to the inclusion and exclusion criteria, 3,331 samples (2,543 overweight and 788 obese) with high BMIs were included in this study. Overall, the proportion of overweight people meeting the recommended physical activity standards of the WHO was lower than that of people of healthy weight. The compliance rates of the healthy population, overweight group, and obesity group are shown in Table 1.

To explore the differences in physical activity between those who were overweight or obese and the general population, we stratified the samples by age and subdivided them into 10 groups. Table 1 shows the proportion of those who meet the WHO recommendation on physical activity. Ideally, those who are overweight or obese should have higher rates of physical activity than the general population. However, the results showed that the proportion of participation in sports was significantly different only in two age groups (31–35 and >65). Moreover, it is particularly important to note that the proportion of obese people was significantly lower than that of normal-weight people at the age of 31–35, which indicates that the low proportion of regular exercise among those who are overweight or obese in China is an important public health problem (Figure 1). The basic descriptive statistics of those who are overweight or obese are shown in Table 2. Among those who are overweight or obese, the proportion of women who meet the exercise standard was higher than that of men (women: 39.02%, men:32.0%), the proportion of people in the married group (34.1%) was higher than that of the those in the divorced group (28.9%), and the proportion of urban residents (42.45%) was higher than that of rural residents (21.88%).

Univariate analysis

The results of the univariate analysis indicated that obese men are less active than women, and significant differences existed in exercise participation among obese people of different ages. Overweight individuals in two age groups (<24 and 60–65 years) had a higher proportion of exercise participation, and the proportion of exercise reaching the standard (amount of exercise) was more than 50%. The minimum proportion of exercise that reached the standard was in the 30–35 age group (25.94%). There was no significant difference in exercise behavior between the overweight and obese groups (36.61 and 33.88%), but a significant difference in exercise behavior was found between the urban and rural groups (42.45 and 21.88%). Educational background also had a significant impact on the exercise behavior of obese people, and the result of the analysis showed that education level was positively correlated with active participation in sports. The samples with a college education or above had the highest proportion of exercise participation behavior (50.41%). Additionally, the three dimensions of self-rated health had a significant relationship with regular exercise ($p < 0.05$). The results of the univariate analysis also showed that sex ($p < 0.00$), family income ($p < 0.00$), hukou ($p < 0.00$), and marital status ($p = 0.01$) were also significantly related to the exercise behavior of those who are overweight. Detailed results are shown in Table 2.

Multivariate analysis

To identify the association between self-rated health and exercise behavior, variables that were significant in the univariate analysis were further incorporated into the multivariate models, and the results indicated that better physical health (OR = 1.14, 95% CI: 1.03–1.19) might significantly improve the exercise behavior of those who are overweight or obese, while poor mental health may reduce the likelihood of participation in sports (OR = 0.95, 95% CI: 0.93–0.98). As shown in Table 3, other variables, such as education, family income, hukou, and marital status, were also significantly related to the exercise behavior of obese people in the multivariate model.

Discussion

Obesity has become an important challenge that needs an urgent response in China. The WHO has recommended exercise guidelines for different groups. However, many of them do not follow the guidelines. Based on the data from the CGSS 2017 program, we sought to explore the related factors that affect the exercise behavior of obese people, especially the influence of self-perceived health (SRH) on exercise.

Exercise behavior in overweight and obese people needs to be promoted

One major finding of this study was that the proportion of AG in overweight and obese people was not ideal and even lower than in people of healthy weight. Previous studies have explained the reasons for this phenomenon mainly from two angles: individual factors and environmental factors (27, 28). The former holds that factors such as personal health literacy and cognition of obesity will have an important impact on exercise participation behavior. Better health literacy helps them to participate more in sports, and those who were aware of the serious medical consequences of obesity were more likely to engage in exercise (29). At present, the Healthy China 2030 strategy is being vigorously promoted, and one of its main purposes is to improve people's health literacy and promote healthy behavior (30, 31).

This study found that age was another important individual factor. The exercise behavior of those who are obese in middle age should be given special attention, especially in the 31–40 and

TABLE 2 Demographic and sociological characteristics and univariate analysis of exercise behavior of overweight people.

Variables	Group	*n*	*n*.sport	%	χ^2	*p*-value
Gender	Male	1,586	507	32.0	20.32	6.528e-06
	Female	1,745	681	39.02		
Age	<24	134	71	52.98	212.18	<2.2e-16
	24–30	241	81	33.60		
	31–35	239	62	25.94		
	36–40	242	76	31.40		
	41–45	245	88	35.92		
	46–50	328	108	32.92		
	51–55	333	108	32.43		
	56–60	316	122	38.60		
	61–65	281	154	54.80		
	>65	872	328	37.61		
BMI	24–28	2,543	931	36.61	1.82	0.17
	>28	788	267	33.88		
Physical health	Good	1,878	756	40.25	67.59	2.10e-15
	General	855	302	35.32		
	Bad	598	140	23.41		
Mental health	Good	2,264	795	36.84	3.76	0.04
	Bad	1,067	409	38.33		
Impact of health on life	Seldom	1,406	258	18.34	55.43	9.196e-13
	Sometimes	969	350	36.11		
	Frequent	956	590	61.71		
Education	1	984	237	24.08	142.77	<2.2e-16
	2	1,000	329	32.90		
	3	627	269	42.90		
	4	720	363	50.41		
Marriage	Divorced	730	211	28.90	6.73	0.01
	Married	2,601	887	34.10		
Income	Subaverage	723	71	9.82	277.3	<2.2e-16
	Average	2,437	1,064	43.66		
	Above average	171	63	36.84		
Hukou	City	2,280	968	42.45	131.2	
	Rural	1,051	230	21.88		

*means $p < 0.05$, **means $p < 0.001$, ***means $p < 0.0001$.

46–50 age groups. The health status of middle-aged people is attracting great attention from scholars and public health experts. In the past, it was believed that the health status of this population was better than other groups, but more and more studies have shown that the peak incidence of some noncommunicable diseases (NCDS) is shifting to the population (32, 33). The rate of sudden death at this age is also increasing rapidly (34, 35). There may be two possible reasons: first, the traditional view is that this group is the backbone of society, subject to more work and pressure, and has less time and opportunity to exercise or relax. Second, compared with older people (>60), this group does not feel physically uncomfortable and has a good level of SRH in the early stages of some NCDS, which will also affect their health behaviors.

TABLE 3 Multivariate analysis of exercise behavior in obese people.

Variables	*B*	SD	*Wald* χ^2	*p*-value	OR	95%CI	
						Lower	Upper
Hukou (Ref = city)							
Rural	−0.52	0.04	−12.99	<2e−16 ***	0.59	0.54	0.64
Gender (ref = male)							
Female	−0.05	0.03	−1.28	0.19	0.95	0.88	1.02
	−0.07	0.03	−1.56	0.11	0.93	0.85	1.01
Age (ref = <24)							
24–30	−0.26	0.11	−2.36	0.01*	0.76	0.61	0.95
31–35	−0.38	0.11	−3.39	0.0006***	0.68	0.54	0.85
36–40	−0.30	0.11	−2.67	0.007**	0.73	0.59	0.92
41–45	−0.21	0.11	−1.86	0.06	0.80	0.64	1.01
46–50	−0.24	0.10	−2.25	0.02*	0.78	0.63	0.96
51–55	−0.21	0.10	−1.94	0.052	0.81	0.65	1.00
56–60	−0.06	0.10	−0.62	0.53	0.93	0.75	1.15
61–65	0.08	0.10	0.76	0.44	1.08	0.88	1.34
>65	0.04	0.10	0.41	0.68	1.04	0.85	1.26
Physical health (ref = bad)							
General	0.04	0.02	1.69	0.09	1.04	0.99	1.09
Good	0.13	0.02	4.85	0.0001***	1.14	1.03	1.19
Self-health (ref = frequent)							
Sometimes	0.02	0.02	1.04	0.29	1.02	0.97	1.04
Seldom	0.03	0.02	1.45	0.14	1.03	0.98	1.06
Mental health (ref = health)							
Unhealth	−0.04	0.01	−2.91	0.003**	0.95	0.93	0.98
Income (ref = below)							
General	0.12	0.01	7.27	<0.000***	1.13	1.09	1.17
Above	0.22	0.03	6.90	<0.000***	1.25	1.17	1.34
Education (ref = 1)							
2	0.04	0.01	2.73	<0.000***	1.04	1.01	1.08
3	0.07	0.01	3.87	<0.000***	1.07	1.03	1.11
4	0.12	0.01	6.54	<0.000***	1.13	1.08	1.17
Marriage (ref = married)							
Divorced	−0.04	0.01	−3.00	0.002**	0.95	0.92	0.98

* <0.05.
** <0.001.
*** <0.0001.

SRH is significantly associated with the health behaviors of those who are overweight or obese

In this study, SRH was defined as a subjective evaluation of health based on which people may adopt different health behaviors (36, 37). Whether SRH has any effect on health behaviors, such as exercise among those who are obese, remains unclear. Previous studies have proven that obesity is a statistically significant predictor of reduced SRH. A similar conclusion was observed not only in adults but also in children and adolescents (38). In China, obesity is traditionally regarded as a sign of wealth or beauty, which may affect the correct perception of obesity. Moreover, the results of this study showed that SRH did have a significant effect on the exercise behavior of obese individuals; those with a better SRH are more likely to participate in sports. Meyer et al. (39) found that

SRH is critical for tailoring interventions and designing programs that can promote physical activity, which is consistent with the conclusion of our study.

From the perspective of public health, reversing the rapid increase in obesity among young and middle-aged people is also an important measure to reduce the disease burden caused by obesity in China.

Environmental factors have a significant influence on the health behavior of those who are overweight or obese

Consistent with some important research (40, 41), this study found that environmental factors such as income, educational background, residential community, and marriage have an important impact on physical activity. Poor income levels and lower education are negatively associated with physical activity, which was highly consistent with the results of this study. The underlying mechanism may be that higher educational background and income are associated with greater social capital, which significantly improves the health literacy of humans (42).

In China, hukou is an important variable that divides urban and rural residents into different communities, and we found that the proportion of those who engage in regular exercise in rural areas was significantly lower than that of urban residents. Rural areas have witnessed rapid development in the past decades, and the food supply for the masses is abundant. However, another problem is that the rate of obesity has also increased significantly, and the increase is greater than the overall population. In recent years, China has promoted the rural revitalization strategy to reduce the huge gap between urban and rural areas. The gap between urban and rural areas includes not only the economic gap but also the gap in health literacy and health behavior of urban and rural residents (43). Only by reducing the health gap between urban and rural residents can rural revitalization be truly realized. Thus, this study can provide important guidance for improving public health services in rural areas.

Limitations

Several major limitations of this study should be noted. First, although the samples in this study are fairly representative, and the latest data are available, the data in this study reflect the situation in 2017, and the conclusions may be different from the current situation in China. Second, this is a cross-sectional study, so any conclusions are only understood as statistically significant but do not provide conclusive causality. Another limitation was that this was an observational study based on public data, and owing to the absence of specific variables such as lifestyle, we could not fully understand the risk factors affecting exercise behavior among those who were obese. Therefore, future studies need to gather more variables in this area so that higher-value scientific evidence can be provided to reduce the disease burden of obesity.

Conclusions

In summary, there is a high incidence of obesity in China, and only <30% of the population meets the recommended guidelines of the WHO regarding the amount of physical activity. Among those who are overweight, those aged 31–35 years were the least physically active, and the proportion of rural residents participating in exercise was significantly lower than that of urban residents. Lower SRH scores, family income, divorce, and educational background significantly negatively affected exercise behavior in obese people.

Suggestions

Interventions should be developed to help those who are overweight or obese based on the findings of this study.

First, health education on obesity should be improved. The proportion of overweight and obese people who reached the target of physical activity was lower than that of normal-weight people, which indicated that many of them do not correctly understand the important impact of obesity on health. According to the theory of planned behavior (TBP), only by changing the wrong perception of obesity can their exercise behavior be increased. Therefore, the existing contents of health education need to be incorporated to emphasize the understanding that “obesity is a disease.” Moreover, it is also worth advocating online health education. More sports guidance videos should be launched on APPs, TikTok, Twitter, and other platforms.

Second, the health literacy of rural residents needs to be further improved. There is a significant difference in the proportion of obese people participating in exercise between urban and rural areas. Based on the analysis of relevant big data, more targeted health promotion services should be provided to rural residents.

Finally, more sports spaces and facilities should be built for communities. For example, sports venues in many Chinese cities are commercialized and open only to those who can afford them, which may limit the enthusiasm of other groups. Community sports resources should be co-managed to help all residents accept and use them by providing exercise guidelines and financial subsidies (reducing the cost of participation).

Data availability statement

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

Author contributions

GS: conceptualization, methodology, and writing. FL and QW: data analysis. 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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Adherence to 24-h movement guidelines in Spanish schoolchildren and its association with insulin resistance: a cross-sectional study

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Introduction: Being more active, being less sedentary, and sleeping enough are associated with adequate body weight and adiposity in children. However, few researchers have analyzed these different lifestyle behaviors and the adherence to 24 h movement guidelines with respect to insulin resistance (IR) at school age. Therefore, we aimed to analyse the association between the adherence to 24 h movement guidelines (physical activity, sedentary time, sleep) and IR in Spanish schoolchildren.

Methods: A cross-sectional study of 839 children (8–13 years, 51.1% girls) were studied. Anthropometric, biochemical, and lifestyle behavioral data were collected. IR was defined as HOMA-IR>3.16. Compliance with the 24 h movement guidelines were defined as ≥60 min/day of moderate and/or vigorous physical activity, <120 min/day of screen time, and 9–11 h/day of sleep time. Associations between adherence to the 24 h movement guidelines and IR were performed by multivariate logistic regression analyses.

Results: The IR in our sample was 5.0%, being higher in girls. Compliance with physical activity or screen time, but not with sleep recommendations, was associated with lower fasting glucose, fasting insulin, and HOMA-IR values. A low adherence to 24 h movement guidelines was associated with a higher risk of IR (odds ratio (95% CI): 2.150 [1.089–4.247]), especially in girls (odds ratio (95% CI): 2.800 [1.180–6.645]).

Conclusion: Higher physical activity levels and lower screen times were associated with a lower risk of IR in schoolchildren, underlining the importance of adhering to as many healthy lifestyle recommendations as possible.

KEYWORDS

insulin resistance, children, schoolchildren, lifestyle behaviors, 24-h movement guidelines

1. Introduction

Insulin resistance (IR) plays an important role in the pathogenesis of comorbid diseases associated with obesity, such as type 2 diabetes mellitus, coronary heart disease, and metabolic syndrome (1). IR has been reported as early as childhood and has been associated in children with alterations in other health parameters, such as dyslipidaemia or elevated blood pressure (2, 3).

There is a growing body of evidence to show the positive associations between different aspects related to the movement [sufficient physical activity (4), limited screen time (5), and appropriate sleep duration (6)] with the children and adolescent health.

Several studies have linked moderate and/or vigorous physical activity (MVPA) with a higher quality of life, better health status, and a lower prevalence of cardiometabolic diseases during school age and adolescence (4, 7–10).

Although an increased sedentary lifestyle has typically been associated with a lack of physical activity, the two can coexist dependently or independently (11). Regardless of physical activity, sedentary behavior has been associated with leading causes of mortality and risk of chronic diseases such as cardiovascular disease and type 2 diabetes mellitus (12, 13). Finally, sedentary behaviors such as TV watching, computer use and general screen time are common behaviors in childhood and adolescence, which are associated with increased body weight and alterations in lipid and glycemic profile (8).

Moreover, associations have been found between sleep deprivation and decreased insulin sensitivity, unhealthy eating habits, sedentary lifestyles, and overweight or obesity (6, 14, 15). Similarly, good sleep habits have also been shown to be a fundamental aspect of human health during all periods of life (16).

MVPA, decreased sedentary activities and adequate sleep duration and quality have been associated in adult reviews and meta-analyses with better weight status, lower RI, lower likelihood of type 2 diabetes mellitus and even lower mortality in several types of cardiovascular disease (17, 18). Furthermore, the relationship between these three aspects of lifestyle and body weight status and adiposity in children and adolescents is well-established (19–21).

Based on the evidence on child health, some organizations such as the World Health Organization have proposed recommendations on physical activity for children and adolescents (at least 60 min of moderate and/or vigorous physical activity) (22). The American Academy of Sleep Medicine has also proposed recommendations on adequate sleep for proper health (9–12 h per day for schoolchildren aged 6–12 years and 8–10 h per day for adolescents aged 13–18 years) (23). Moreover, Tremblay et al. (24) developed 24-h movement guidelines for children and youth, which integrated recommendations of three patterns: physical activity (at least 60 min of MVPA), sedentary time (<120 min/day of screen time), and sleep duration (9–11 h/day) (24). Adherence to these guidelines has been associated with lower cardiometabolic risk (25) and overall health in children and adolescents (26, 27).

Abbreviations: IR, Insulin resistance; HOMA-IR, Homeostasis model of insulin resistance; MVPA, Moderate and/or vigorous physical activity; BMI, Body mass index; zBMI, BMI z-score; X, Mean; SD, Standard deviation.

However, the relationship between different lifestyle patterns, separately and especially in combination, and IR at school-age has not been sufficiently studied, and the relationship remains unclear. Therefore, our aim with this study was to evaluate the lifestyle patterns of a group of Spanish schoolchildren and to analyze the association between the adherence to specific 24 h movement guidelines or a combination of them and IR at school age in order to contribute knowledge in this area and to evaluate the association between lifestyle and IR at school age.

2. Methods

2.1. Study sample

The cross-sectional observational study included a convenience sample of schoolchildren aged 8–13 years from five Spanish provinces (A Coruña, Barcelona, Madrid, Sevilla, and Valencia) (Figure 1). In each province, we randomly selected schools from a list of primary schools with at least two classes per grade. We contacted the management teams of 55 schools by telephone, and we arranged an interview to explain the characteristics and objectives of the study. Once we had obtained permission from the management teams (22 schools), we called the families of the children with ages in the target age range to a meeting to explain the aim and details of the study and to resolve any doubts they might have. Subsequently, we asked the parents or legal guardians of the schoolchildren to sign a written consent for their children to participate in the study.

The inclusion criteria were children aged between 8 and 13 years in the 4th, 5th, or 6th grade of primary school; written informed consent signed by the children's parents and/or guardians; and acceptance of all study conditions.

The exclusion criteria were presenting any disease that could modify the results of the study: metabolic or chronic diseases (diabetes, renal pathologies, etc.); impossibility of attending school on the days agreed for the tests; and receiving pharmacological treatment that could interfere with the results of the study. Measurements were made between February 2005 and June 2009.

Our potential sample included 3,850 schoolchildren. This potential sample size was calculated based on the number of schools that had agreed to participate (22 schools), that each school could have from 1 to 3 different grade levels (4th, 5th, and/or 6th grade), that in some schools there is more than one classroom of the same level, and that the average number of students in each classroom is 25. Of these, 1,035 obtained written consent from their parents or guardians to participate in the study, so the approximate acceptance rate was 27%. Finally, 839 children had a complete daily activities questionnaire and valid biochemical data (Figure 2).

The participating children underwent a socio-demographic, lifestyle, anthropometric and biochemical study at the school by qualified research staff.

We conducted this study in accordance with the guidelines established in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Human Research Review Committee of the Faculty of Pharmacy of the Complutense University of Madrid (PI060318, approved on 17 March 2006).

FIGURE 1
Sample distribution. Modified from "https://d-maps.com/carte.php?num_car=5672&lang=es".

2.2. Socio-demographic data

We used a self-completed survey by the parents/guardians of the children, including questions related to the demographic characteristics of the schoolchildren (sex, date of birth, and maximum level of education attained by the parents).

2.3. Anthropometric data

Anthropometric measurements (weight and height) were recorded by qualified personnel. The study was conducted in the schools during morning hours and following the standards established by the WHO (28). For the measurements, the subjects were barefoot and wore only underwear.

Weight and height were determined with a digital electronic scale (range: 0.1–150 kg, accuracy: 100 g; SECA ALPHA, GMBH, Igny, France) and a Harpenden digital stadiometer (range: 70–205 cm, accuracy: 1 mm; Pfifter, Carlstadt, NJ, USA). We calculated the body mass index (BMI) of the subjects using the formula weight (kg)/height^2 (m^2). Subsequently, we calculated the BMI z-score (zBMI) according to WHO growth standards (29).

2.4. Biochemical data

Blood samples were collected by venipuncture between 08:00 and 09:00 after 12 h of fasting. The nursing staff verified the adequacy of the fasting period before collecting the blood. Samples were collected at the school.

We colourimetrically determined plasma glucose levels by the glucose oxidase–peroxidase method (30) (Vitros GLU Slides, Rochester, NY, USA; CV = 2–8%). We measured insulin levels with an immunochemiluminometric assay (31) (Abbott Diagnostics, Madrid, Spain; CV = 4.8%). We used the homeostasis model assessment value (HOMA-IR) to reflect the degree of IR (32, 33): HOMA-IR = [basal glucose (mmol/L) × basal insulin (μU/mL)]/22.5. We considered IR present when the HOMA-IR was >3.16 (34).

2.5. The 24-h movement guidelines

We assessed lifestyle behaviors with an adapted daily activities questionnaire recording the children's usual daily activities, which had to be jointly completed by parents and children (35) and which has been used in previous studies (36–38). The questionnaire asked about the time spent on different activities usually carried out during the day: sleeping; being in class; studying; eating at different meals; playing sedentary games (PC, video game consoles) or watching TV; actively playing in the street and at home; in gymnastics or other sports activities at school; at recess and in extracurricular activities; and traveling between home and school and other activities, and the mode of transport used.

We then grouped the time spent on the different activities into the following categories: sleeping, very light activities (activities that

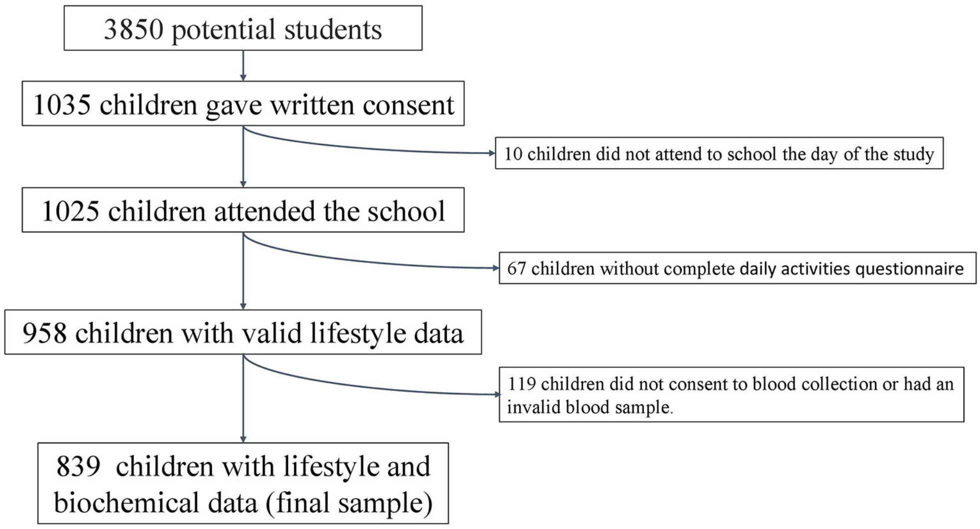

FIGURE 2
Flow chart of the selection process.

are performed lying down, sitting, or standing, such as painting, playing an instrument, cooking, etc.); light activities (equivalent to walking on a flat surface at 4–5 km/h, such as cleaning the house, golf, table tennis, etc.); and moderate and/or vigorous activities (physical activities that require more energy expenditure such as cycling, skiing, tennis, dancing, basketball, football, rugby, running, etc.).

We classified children according to the 24 h movement guidelines (24) as "non-sedentary" if they restricted screen time to < 2 h/day (24) and as "physically active" if they performed at least 60 min of MVPA per day (24). We considered adequate sleep time if the child slept between 9 and 11 h (24).

The percentage of children complying with one, two, three or none of the recommendations of the 24 h movement guidelines was calculated. Schoolchildren were classified according to their adherence to a healthy lifestyle as follows: "low adherence", if they complied with one or none of the recommendations of the 24 h movement guidelines, and "high adherence" if they complied with two or three recommendations.

2.6. Statistical analysis

Descriptive data are expressed as means and standard deviations for continuous variables and as percentages for categorical variables. We compared the data according to sex, lifestyle, and presence or absence of IR. We used the Kolmogorov–Smirnov test to determine the normality of the data. For comparison of means, we used the Mann–Whitney U-test if the distribution of variables was not normal and Student's t-test for normal distributions as well as the two-way ANOVA test. We compared categorical variables using the chi^2 test and the Z-test of proportions. We calculated Spearman correlation coefficients between the hours spent on the different activities and HOMA-IR. We performed logistic regression analysis to identify risk or protective factors for IR, and we report odds ratios (OR) and 95% confidence intervals (CI). We considered a p-value of < 0.05 statistically significant. We performed all calculations with IBM SPSS Statistics for Windows, version 28.0 (Armonk, NY: IBM Corp, published in 2021).

2.7. *Post-hoc* power calculation

Post-hoc power analysis was calculated with G*Power (v. 3.1.9.6, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) using an alpha error of 0.05, a sample size (n1= 367 and n2= 472) and an effect size of 0.35 to detect differences on HOMA-IR values according to adherence to the 24-h movement guidelines.

3. Results

These children were previously studied in another context (37, 38). The potential initial sample size was approximately 3,850 participants, which was calculated considering the number of schools that agreed to participate ($n = 22$), number of students per classroom ($n = 25$), and number of classrooms per grade (between two and three). Subsequently, 1,035 schoolchildren (49.2% boys) obtained written consent from their parents or guardians to participate in the study. Ten children were not in school on the day of the anthropometric study. We obtained valid lifestyle data from 958 schoolchildren (49.3% boys) and valid blood samples from 890 subjects (48.4% boys). The final sample was 839 individuals (48.9% boys) with complete biochemical and lifestyle data (Figure 2).

Table 1 shows the sociodemographic, anthropometric, biochemical, and lifestyle data of the total sample and by sex. We found no differences in age or parental education by sex. Boys had a higher zBMI and fasting glucose values than girls, but lower fasting

TABLE 1 Anthropometric, biochemical, sociodemographic, and lifestyle parameters according to sex.

		Total ($n = 839$)	Girls ($n = 429$)	Boys ($n = 410$)
Age and anthropometric data - X ± SD				
Age (years)		10.1 ± 0.9	10.1 ± 0.9	10.1 ± 0.9
Weight (kg)		39.4 ± 9.3	39.5 ± 9.37	39.2 ± 9.3
Height (cm)		143.4 ± 0.1	144.0 ± 0.1	142.7 ± 0.1*
BMI (kg/m^2)		19.0 ± 3.1	18.9 ± 3.0	19.1 ± 3.3
zBMI #		0.69 ± 1.13	0.56 ± 1.05	0.82 ± 1.20*
Biochemical data - X ± SD				
Glucose (mg/dL)		84.4 ± 9.7	83.4 ± 10.0	85.5 ± 9.2*
Insulin (mcU/mL)		6.2 ± 4.3	7.0 ± 4.8	5.5 ± 3.7*
HOMA-IR		1.31 ± 0.96	1.46 ± 1.07	1.16 ± 0.80*
Insulin Resistance [%(n)]		5.0 (42)	6.8 (29)	3.2 (13)*
Parents' level of education [%(n)]				
Father's highest level of education	No schooling or primary education	24.8 (208)	23.1 (99)	26.6 (109)
	Secondary education	34.7 (291)	35.2 (151)	34.1 (140)
	University studies	30.2 (253)	28.9 (124)	31.5 (129)
	Not determined	10.4 (87)	12.8 (55)	7.8 (32)*
Mother's highest level of education	No schooling or primary education	21.0 (176)	21.2 (91)	20.7 (85)
	Secondary education	39.7 (333)	39.2 (168)	40.2 (165)
	University studies	34.1 (286)	33.6 (144)	34.6 (142)
	Not determined	5.2 (44)	6.1 (26)	4.4 (18)
Daily activities - X ± SD				
Sleep (h/day)		9.31 ± 0.74	9.31 ± 0.75	9.32 ± 0.74
Very Light Physical Activity (h/day)		11.18 ± 1.64	11.17 ± 1.68	11.19 ± 1.61
Screen time (h/day)		1.81 ± 1.07	1.70 ± 1.06	1.92 ± 1.08*
TV (h/day)		1.42 ± 0.86	1.37 ± 0.87	1.48 ± 0.85*
PC (h/day)		0.33 ± 0.47	0.28 ± 0.44	0.39 ± 0.49*
Video games (h/day)		0.05 ± 0.20	0.04 ± 0.19	0.05 ± 0.21
Light Physical Activity (h/day)		2.64 ± 1.49	2.73 ± 1.55	2.53 ± 1.42
MVPA (h/day)		0.81 ± 0.48	0.73 ± 0.47	0.89 ± 0.48*
Adherence to recommendations of 24h-movement guidelines [%(n)]				
Screen time <2 h/day		50.5 (424)	55.0 (236)	45.9 (188)*
MVPA ≥1 h/day		31.9 (268)	23.1 (99)	41.2 (169)*
Sleep between 9 and 11 h/day		82.4 (691)	82.5 (354)	82.2 (337)
Number of complied recommendations	0	9.1 (76)	9.3 (40)	8.8 (36)
	1	34.7 (291)	35.9 (154)	33.4 (137)
	2	38.6 (324)	39.6 (170)	37.6 (154)
	3	17.6 (148)	15.2 (65)	20.2 (83)
Adherence to 24-h movement guidelines	Low adherence	43.7 (367)	45.2 (194)	42.2 (173)
	High adherence	56.3 (472)	54.8 (235)	57.8 (237)

X, mean; SD, standard deviation; BMI, body mass index; MVPA, moderate and/or vigorous physical activity. Low adherence to 24 h movement guidelines: complied with one or none of recommendations; high adherence to 24 h movement guidelines: complied with two or three recommendations. Most variables followed nonparametric distribution; variables with normal distribution are marked (#). We used Mann–Whitney U-test for comparison of means if distribution of variables was not normal and Student's t-test for normal distribution. We analyzed associations between categorical variables with the χ^2 test and the Z-test of proportions. Differences between sexes are indicated by asterisks ($^*p < 0.05$).

TABLE 2 Anthropometric, sociodemographic, and lifestyle parameters according to sex and HOMA-IR.

		Total		Girls		Boys	
		HOMA-IR ≤ 3.16 ($n = 797$)	HOMA-IR > 3.16 ($n = 42$)	HOMA-IR ≤ 3.16 ($n = 400$)	HOMA-IR > 3.16 ($n = 29$)	HOMA-IR ≤ 3.16 ($n = 397$)	HOMA-IR$>$3.16 ($n = 13$)
Age and anthropometric data - X ± SD							
Age (years)		10.1 ± 0.9	10.5 ± 1.0*	10.1 ± 0.9	10.4 ± 1.0	10.1 ± 0.9	10.5 ± 1.0
Weight (kg) – I		38.9 ± 9.0	47.7 ± 9.9*	39.0 ± 9.1	47.0 ± 9.1*	38.9 ± 9.0	49.2 ± 11.8*
Height (cm)# – I		143.1 ± 0.1	148.0 ± 0.1*	143.6 ± 0.1	149.2 ± 0.1*	142.6 ± 0.1	1454 ± 0.1
BMI (kg/m^2) – IS		18.8 ± 3.0	21.7 ± 3.7*	18.7 ± 2.9	21.0 ± 2.9*	18.9 ± 3.1	23.2 ± 4.8*
zBMI – IS		0.64 ± 1.12	1.48 ± 1.12#*	0.51 ± 1.05	1.22 ± 0.83*	0.78 ± 1.17	2.04 ± 1.49#*
Parents' level of education [%(n)]							
Father's highest level of education	No schooling or primary education	24.7 (197)	26.2 (11)	22.8 (91)	27.6 (8)	26.7 (106)	23.1 (3)
	Secondary education	34.0 (271)	47.6 (20)	34.3 (137)	48.3 (14)	33.8 (134)	46.2 (6)
	University studies	30.7 (245)	19.0 (8)	29.5 (118)	20.7 (6)	32.0 (127)	15.4 (2)
	Not determined	10.5 (84)	7.1 (3)	13.5 (54)	3.4 (1)	7.6 (30)	15.4 (2)
Mother's highest level of education	No schooling or primary education	21.0 (167)	21.4 (9)	21.5 (86)	17.2 (5)	20.4 (81)	30.8 (4)
	Secondary education	39.0 (311)	52.4 (22)	38.0 (152)	55.2 (16)	40.1 (159)	46.2 (6)
	University studies	34.8 (277)	21.4 (9)	34.3 (137)	24.1 (7)	35.3 (140)	15.4 (2)
	Not determined	5.3 (42)	4.8 (2)	6.3 (25)	3.4 (1)	4.3 (17)	7.7 (1)
Daily activities - X ± SD							
Sleep (h/day)		9.32 ± 0.74	9.24 ± 0.79	9.31 ± 0.75	9.28 ± 0.76	9.32 ± 0.74	9.15 ± 0.88
Very Light Physical Activity (h/day) – I		11.13 ± 1.64	12.06 ± 1.49*	11.09 ± 1.68	12.25 ± 1.28#*	11.17 ± 1.60	11.64 ± 1.87#
Screen time (h/day)– I		1.78 ± 1.06	2.29 ± 1.18*	1.66 ± 1.04	2.26 ± 1.21*	1.90 ± 1.07	2.36 ± 1.18
TV (h/day)		1.41 ± 0.86	1.65 ± 0.85	1.35 ± 0.87	1.61 ± 0.90	1.47 ± 0.86	1.74 ± 0.74
PC (h/day)– I		0.32 ± 0.45	0.59 ± 0.70*	0.26 ± 0.41	0.59 ± 0.73*	0.38 ± 0.48	0.57 ± 0.64
Video games (h/day)		0.05 ± 0.20	0.05 ± 0.15	0.04 ± 0.19	0.05 ± 0.15	0.05 ± 0.21	0.05 ± 0.14
Light Physical Activity (h/day)– I		2.67 ± 1.49	1.99 ± 1.40*	2.79 ± 1.56	1.89 ± 1.17*	2.55 ± 1.41	2.21 ± 1.85
MVPA (h/day) – S		0.81 ± 0.48	0.69 ± 0.48*	0.74 ± 0.47	0.57 ± 0.42*	0.89 ± 0.48	0.95 ± 0.50
Adherence to recommendations of 24-h movement guidelines [%(n)]							
Screen time <2 h/day		51.3 (409)	35.7 (15)*	56.5 (226)	34.5 (10)*	46.1 (183)	38.5 (5)
MVPA ≥1 h/day		32.7 (261)	16.7 (7)*	24.3 (97)	6.9 (2)*	41.3 (164)	38.5 (5)
Sleep between 9 and 11 h/day		82.9 (661)	73.8 (31)	82.8 (331)	79.3 (23)	83.1 (330)	61.5 (8)*
Number of complied recommendations	0	8.9 (71)	11.9 (5)	9.3 (37)	10.3 (3)	8.6 (34)	15.4 (2)
	1	33.6 (268)	54.8 (23)*	34.0 (136)	62.1 (18)*	33.2 (132)	38.5 (5)
	2	39.1 (312)	28.6 (12)	40.8 (163)	24.1 (7)	37.5 (149)	38.5 (5)
	3	18.3 (146)	4.8 (2)*	16.0 (64)	3.4 (1)	20.7 (82)	7.7 (1)
Adherence to 24-h movement guidelines	Low adherence	42.5 (339)	66.7 (28)*	43.3 (173)	72.4 (21)*	41.8 (166)	53.8 (7)
	High adherence	57.5 (458)	33.3 (14)*	56.8 (227)	27.6 (8)*	58.2 (231)	46.2 (6)

X, mean; SD, standard deviation; BMI, body mass index; MVPA, moderate and/or vigorous physical activity. Low adherence to 24 h movement guidelines: complied with one or none of recommendations; high adherence to 24 h movement guidelines: complied with two or three recommendations. Most variables followed nonparametric distribution; variables with normal distribution are marked (#). We used Mann–Whitney U-test for comparison of means if the distribution of variables was not homogeneous, and Student's t-test for homogeneous distributions. We analyzed associations between categorical variables with χ^2 test and Z-test of proportions. Significant differences are indicated by asterisks (*$p < 0.05$). Two-way ANOVA analysis: S: differences by sex; I: differences by insulin resistance (IR) score; R: interaction between sex and IR.

TABLE 3 Biochemical parameters according to sex and lifestyle parameters.

	Total		Girls		Boys	
Screen time						
	≥ 2h/day ($n = 415$)	< 2 h/day ($n = 424$)	≥ 2 h/day ($n = 193$)	< 2 h/day ($n = 236$)	≥ 2 h/day ($n = 222$)	< 2 h/day ($n = 188$)
Glucose (mg/dL) – S	84.8 ± 9.7	83.5 ± 9.4*	83.3 ± 10.7	83.0 ± 9.1	86.1 ± 8.4	84.1 ± 9.6*
Insulin (mcU/mL) – SA	6.9 ± 4.8	5.8 ± 4.8*	7.9 ± 5.7	6.6 ± 5.5*	6.1 ± 3.7	4.8 ± 3.5*
HOMA-IR – SA	1.46 ± 1.07	1.17 ± 0.81*	1.65 ± 1.29	1.30 ± 0.82*	1.29 ± 0.80	1.00 ± 0.76*
MVPA						
	< 1 h/day ($n = 571$)	≥ 1 h/day ($n = 268$)	< 1 h/day ($n = 330$)	≥ 1 h/day ($n = 99$)	< 1 h/day ($n = 241$)	≥ 1 h/day ($n = 169$)
Glucose (mg/dL) – SA	84.7 ± 8.9	83.0 ± 10.8*	83.9 ± 9.7	80.6 ± 10.0*	85.8 ± 7.4	84.4 ± 11.0
Insulin (mcU/mL) – SA	6.7 ± 4.5	5.5 ± 5.3*	7.4 ± 5.0	6.4 ± 7.3*	5.8 ± 3.6	5.0 ± 3.6*
HOMA-IR – SA	1.42 ± 1.01	1.09 ± 0.79*	1.55 ± 1.13	1.15 ± 0.79*	1.24 ± 0.80	1.05 ± 0.79*
Sleep time						
	< 9 h/day or >11 h/day ($n = 148$)	9–11 h/day ($n = 691$)	< 9 h/day or >11 h/day ($n = 75$)	9–11 h/day ($n = 354$)	< 9 h/day or >11 h/day ($n = 73$)	9–11 h/day ($n = 338$)
Glucose (mg/dL) – S	85.3 ± 10.1	84.3 ± 9.6	84.1 ± 11.6	83.2 ± 9.7	86.5 ± 8.2	85.3 ± 9.4
Insulin (mcU/mL) – S	6.4 ± 4.5	6.2 ± 4.3	6.9 ± 4.6	7.0 ± 4.8	5.9 ± 4.3	5.4 ± 3.5
HOMA-IR – S	1.37 ± 0.99	1.30 ± 0.95	1.47 ± 1.04	1.45 ± 1.08	1.26 ± 0.92	1.14 ± 0.77
Adherence to 24-h movement guidelines						
	Low adherence ($n = 367$)	High adherence ($n = 472$)	Low adherence ($n = 194$)	High adherence ($n = 235$)	Low adherence ($n = 173$)	High adherence ($n = 237$)
Glucose (mg/dL) – SA	85.1 ± 9.3	83.4 ± 9.6*	84.0 ± 10.7	82.4 ± 9.1	86.3 ± 7.4	84.4 ± 10.1*
Insulin (mcU/mL) – SA	7.1 ± 5.0	5.7 ± 4.7*	7.9 ± 5.7	6.5 ± 5.5*	6.2 ± 3.8	5.0 ± 3.5*
HOMA-IR – SA	1.50 ± 1.12	1.16 ± 0.78*	1.67 ± 1.30	1.28 ± 0.80*	1.32 ± 0.83	1.04 ± 0.76*

Data are shown as mean ± standard deviation; MVPA: moderate and/or vigorous physical activity. Low adherence to 24 h movement guidelines: complied with one or none of recommendations. High adherence to 24 h movement guidelines: complied with two or three recommendations. Two-way ANOVA analysis: S: differences according to sex; A: differences according to adherence to lifestyle recommendations; R: interaction between sex and adherence to lifestyle recommendations. No variable followed a normal distribution. For within-sex differences between IR and non-IR, we used Mann–Whitney U-test. Significant differences are shown with asterisks (*$p < 0.05$).

insulin and HOMA-IR values. Of the children, 5% presented IR, the percentage being higher in girls (6.8 vs. 3.2%, $p < 0.05$). Boys spent more hours in front of the TV and computer, so they had more screen time than girls. Boys performed more MVPA than girls. 50.5% of schoolchildren spend <2 h in front of the screen and only 31.9% of schoolchildren spend more than 1 h of MVPA per day. Overall, boys adhered less to screen time recommendations (45.9 vs. 55.0% for girls, $p < 0.05$) and more to physical activity recommendations (41.2 vs. 23.1%, $p < 0.05$) than girls. In addition, the recommendation on sleep is the one most frequently complied with by both sexes (82.4%), no differences between sex groups were seen.

Table 2 shows age, sociodemographic, anthropometric, and lifestyle data according to sex and presence of IR. We found no differences in age or parents' educational level according to IR status. Girls with IR spent more time on computers and screens in general and in very light activities, and they spent less time on light activities and MVPA than girls without IR. Therefore, fewer girls with IR met the 24 h movement guidelines for screen time (34.5 vs. 56.5%, $p < 0.05$) and physical activity (6.9 vs. 24.3%, $p < 0.05$) compared with girls without IR, with no difference in sleep time. In boys, we found no differences in their lifestyles based on having IR, except that boys with IR were less compliant with sleep recommendations than boys without IR (61.5 vs. 83.1%, $p < 0.05$).

Because only two children with IR complied with all three lifestyle recommendations, we decided to group subjects into low adherence (adherence to one or none of the recommendations) and high adherence (adherence to two or three recommendations) for statistical analysis. A lower percentage of girls with IR had high adherence to the 24 h movement guidelines compared with girls without IR (27.6 vs. 56.8%, $p < 0.05$). We observed no significant differences based on the presence of IR in the boys.

Table 3 shows the different biochemical parameters and IR according to adherence to the 24 h movement guidelines. Children who did not follow the recommendations for screen time or physical activity and those with lower adherence to the 24 h movement guidelines had higher fasting insulin levels and HOMA-IR values. We found no significant differences according to the sleep recommendations for either sex.

HOMA-IR directly and significantly correlated with screen time and very light physical activity, and indirectly correlated with light physical activity, MVPA, sleep time, and the number of recommendations met. These associations were maintained when boys and girls were separately analyzed, except for the sleep time (Table 4).

The results of logistic regression analysis showed that low adherence to 24 h movement guidelines was associated with increased risk of IR both in the total sample and in girls. In girls, non-adherence to screen time or physical activity recommendations was associated with an increased risk of IR in the crude model, but the association disappeared when corrected for age and zBMI. There was no association with sleep time. In addition, no significant association was found in boys (Table 5).

TABLE 4 Correlations between lifestyle variables and HOMA-IR.

	Total (839)	Girls (429)	Boys (410)
Sleep (h/day)	−0.074*	−0.086	−0.067
Very Light Physical Activity (h/day)	0.256*	0.273*	0.251*
Screen time (h/day)	0.213*	0.215*	0.267*
TV (h/day)	0.147*	0.138*	0.194*
PC (h/day)	0.192*	0.239*	0.199*
Video games (h/day)	0.137*	0.098*	0.180*
Light Physical Activity (h/day)	−0.207*	−0.217*	−0.231*
MVPA (h/day)	−0.158*	−0.127*	−0.136*
Number of recommendations complied of the 24-h movement guidelines	−0.182*	−0.174*	−0.185*

Data shown are Spearman's rho. MVPA: moderate and/or vigorous physical activity. Significance is shown with asterisks (* $p < 0.05$).

4. Discussion

Our findings showed that schoolchildren with IR had a less active lifestyle in general and had higher levels of screen time than those without IR, especially girls. Children who met the recommendations for physical activity or screen time or had higher adherence to 24 h movement guidelines had lower fasting glucose, fasting insulin, and HOMA-IR levels. Finally, increased adherence to lifestyle recommendations was associated with a lower risk of IR.

In our study, 43.7% of schoolchildren had low adherence to 24 h movement guidelines (complying with only one or none of the recommendations), similar to that reported in another Spanish child population (39.2%) (39) and lower than that reported in an international study (62.9%) (40). The low adherence to lifestyle recommendations in our study was mainly due to the low adherence to physical activity recommendations, because it was lower than the adherence to sleep and screen time recommendations.

About half of our schoolchildren adhered to the screen time guidelines, spending <2 h in front of a screen. This figure is difficult to compare with those in other studies as the percentage of children meeting screen time recommendations widely varies from 8.1 to 98.4% in the 6–12 years age group, as shown by a recent meta-analysis (41). However, approximately half of the sample dedicated more hours to sedentary leisure than is recommended.

The time devoted by our population to MVPA was 49 min, being higher in boys. These data are similar to those published in a study on Spanish children aged 7 to 11 years (44 min) (39) and are lower than those reported in a Finnish child population aged 3–6 years (1 h 25 min) (42). Only 31.9% of the sample spent at least 1 h on MVPA, and this figure was even lower for girls.

In our study and in the bibliography, schoolchildren spend too much time on sedentary leisure (41) and less time than recommended on physical activity (39, 40). This indicates that, in general, schoolchildren are sedentary and inactive, and policies should be strengthened to reverse this situation, which can lead to serious health problems. Moreover, boys and girls have different lifestyles, with boys being more active but more sedentary. Therefore, recommendations and interventions should be tailored to sex to ensure greater adherence.

The recommendation of the 24 h movement guidelines most followed by our schoolchildren was for sleep time, as observed in other studies (36, 42). The children in our study slept an average of 9 h 19 min, lower than that reported in Spanish children in the ALADINO-2019 study (10 h 17 min) (43), but similar to that of a U.S. study of children aged 9–10 years (44) and in a Swedish study of children 10 to 12 years old (9 h) (45). Sleep recommendations were not met by 17.5% of children, a figure higher than that of other European countries (46). This is surprising because, according to the COSI strategy, Spanish children are among those who spend more time sleeping compared with other European countries (47), although this difference may be due to the COSI strategy being applied in children aged 6–9 years, an age somewhat younger than ours, and children sleep less as they age (48).

Regarding the relationship of compliance with the 24 h movement guidelines to IR, sedentary schoolchildren in our study (≥2 h/day of screen time) had higher HOMA-IR values. This result is consistent with those of the European IDEFICS study of children aged 2–17 years (49) and in English (7–13 years) (50) and Spanish schoolchildren (5–14 years) (51). This potential relationship between sedentary lifestyles and IR may have been due to less muscle activity and energy expenditure, causing alterations in homeostasis. Spending more time in sedentary activities may result in a lower rate of glucose processing in skeletal muscle, accompanied by less inhibition of glucose production in the liver (52).

In addition, our schoolchildren who performed more than 60 min of MVPA per day had lower HOMA-IR values. In a study of Indian children, physical activity during early adolescence was found to play a protective role against IR (53). The IDEFICS study assessed cross-sectional associations between physical activity and the clustering of cardiometabolic risk factors (such as IR), and moderate activity time negatively correlated with cardiometabolic risk score (54). Physical activity can influence IR through various potential mechanisms, one of which is the absence of skeletal muscle contractions being associated with reduced blood flow, which decreases circulating glucose transport to muscle (55). MVPA is associated with increased

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TABLE 5 Associations between lifestyle parameters and IR by sex. Logistic regression analysis.

	Total (839)		Girls (429)		Boys (410)	
	Model 1 OR 95% CI	Model 2 OR 95% CI	Model 1 OR 95% CI	Model 2 OR 95% IC	Model 1 OR 95% CI	Model 2 OR 95% CI
Sreen time						
< 2 h/day	1	1	1	1	1	1
≥ 2 h/day	1.897 (0.994–3.621)	1.499 (0.763–2.946)	2.468 (1.119–5.442)*	1.850 (0.810–4.224)	1.368 (0.440–4.255)	1.128 (0.345–3.690)
MVPA						
≥ 1 h/day	1	1	1	1	1	1
< 1 h/day	2.435 (1.067–5.555)*	2.029 (0.845–4.874)	4.322 (1.009–18.506)*	3.914 (0.884–17.317)	1.126 (0.362–3.504)	1.236 (0.371–4.121)
Sleep time						
9–11 h/day	1	1	1	1	1	1
< 9 h/day or >11 h/day	1.725 (0.846–3.516)	1.423 (0.672–3.014)	1.251 (0.491–3.188)	0.978 (0.370–2.588)	3.078 (0.977–9.701)	3.487 (0.996–12.214)
Adherence to 24-h movement guidelines						
High adherence	1	1	1	1	1	1
Low adherence	2.702 (1.401–5.211)*	2.150 (1.089–4.247)*	3.444 (1.490–7.962)*	2.800 (1.180–6.645)*	1.623 (0.536–4.919)	1.529 (0.481–4.861)

Model 1. Crude model. Model 2. Adjusted for age, sex (in total sample) and zBMI. MVPA: moderate and/or vigorous physical activity. Low adherence to 24 h movement guidelines: complied with one or none of recommendations. High adherence to 24 h movement guidelines: complied with two or three recommendations. Significance is shown with asterisks (*$p < 0.05$).

glucose uptake by skeletal muscle, leading to a decrease in blood glucose (56).

Considering sleep as part of a healthy lifestyle to prevent IR is important, as a lack of sleep is associated with elevated stress levels as well as hypothalamic–pituitary–adrenal regulation, which may lead to neuroendocrine disruption, which in turn may cause dysregulation in glucose–insulin metabolism (57). However, the results of studies on the relationship between sleep and IR in children and adolescents are controversial. In our study, sleep duration was not associated with IR, as observed in the IDEFICS study, conducted on children aged 2–15 years (58), and in the HELENA study, conducted on adolescents aged 12.5–17.5 years (59). However, this differs from the results of the ABCD Growth Study, conducted in Brazil on adolescents aged 11–18 years, where this component was the only one related to HOMA-IR (60). A narrative review in a pediatric population concluded that the relationship between sleep and HOMA-IR is not yet clearly established, although "convincing evidence" exists of an association between sleep duration and biomarkers of type 2 diabetes mellitus (including HOMA-IR) (61). The lack of association in our study could be explained by the high percentage of children who adhered to the sleep recommendation, which was the most followed guideline.

Similar to our results, Werneck et al. found that having several inappropriate lifestyle behaviors, or low adherence to recommendations, increases the risk of elevated HOMA-IR, although in this study, in addition to the lifestyle behaviors we analyzed, skipping breakfast was also considered (60).

Therefore, our study agrees with other studies in the relationship between screen time and physical activity with lower IR (49–51, 53, 54). While on the relationship between sleep duration and IR, the results remain controversial, with some studies finding a relationship (60, 61), and others, such as ours and other studies (58, 59), finding no association.

However, to our knowledge, only Werneck et al. (60) and ourselves have jointly assessed these parameters in relation to IR and we have both observed that adherence to various lifestyle factors is more robustly related to IR. Therefore, this is one of the first studies to assess a possible closer relationship by jointly assessing these lifestyle parameters in association with IR.

As other authors have pointed out, our results showed that examining the relationship between a single lifestyle behavior and health is not appropriate. Therefore, different lifestyle recommendations should be combined to further examine the relationship between lifestyle and health outcomes, such as cardiometabolic risk or IR (25–27).

Since this is one of the first studies to jointly assess lifestyle in relation to IR in children. And the results suggest that analyzing lifestyle factors separately may not address the problem of IR, a pooled analysis should be conducted to analyze the risk of IR. In addition, physical activity and sedentary time seem to be more related to IR than sleep in this study sample.

Given that IR is related not only to obesity but also to other comorbidities since childhood and based on the results of our work.

It is important to carry out health policies, recommendations and studies that are not limited to including increased physical activity or decreased sedentary lifestyle, but should be comprehensive, including more physical activity, less sedentary leisure (such as screens nowadays) and correct sleep habits, as these activities should be approached as a whole.

One of the main strengths of our study is the large sample size, although the sample is a convenience one and therefore not representative of the Spanish population.

One of the main limitations was that being a large study, we could not perform Tanner's clinical staging and did not obtain information on the pubertal status of the participants, which could have influenced the prevalence of IR. Moreover, as we used a questionnaire to measure lifestyle and no other methods, such as accelerometers, the data may have been overestimated. Another possible limitation was that, as only a small sample followed all the recommendations, they had to be arbitrarily grouped for the analysis. Ethnicity was not collected in the study, and approximately half of the subjects did not answer about their country of origin, although the majority of those who reported were Spanish. Finally, our study had a cross-sectional design that highlighted the existence of associations but cannot demonstrate causal relationships and the sample studied is a convenience one, so the conclusions of our study should be confirmed in future research. Furthermore, although the sample size was not calculated a priori, a *post hoc* power analysis was performed and showed that our study had a high power (99%) to detect differences in mean HOMA-IR values according to adherence to 24 h movement patterns. Nevertheless, it would have been desirable to determine the sample size a priori and to use a probability sampling method.

Future lines of research are based on carrying out an intervention study in Spanish schoolchildren of the same age to verify the results obtained. In this study we intend to use an accelerometer in addition to the lifestyle questionnaire, in order to validate the questionnaire and to have non-self-reported lifestyle data.

In conclusion, we found that about half of the schoolchildren had low adherence to the 24 h movement guidelines. Sleep time was the most followed recommendation, and physical activity was the least. Girls were less physically active but also spent less time on screens. Our study showed that higher adherence to recommended lifestyle patterns was inversely associated with IR, especially in girls and when several lifestyle factors were combined. Intervention studies are needed that can confirm the possible protective effect of increasing adherence to the 24 h movement guidelines on IR in schoolchildren.

Data availability statement

The datasets analysed for this study are available upon reasonable request from MDS-G (masala06@ucm.es).

Ethics statement

The present study protocol was reviewed and approved by the Ethics Committee of the Faculty of Pharmacy of the Complutense University of Madrid, in Spain (PI060318, approved on 17 March 2006). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AML-S and RMO contributed to conception and design of the study. MDS-G, LMB, MCL-E, and LGG-R collected and processed data. MDS-G performed the statistical analysis and wrote the first draft of 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.

Publisher's note

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Trends and predictions in the physical shape of Chinese preschool children from 2000 to 2020

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Objective: To explore physical shape changes in preschool children from 2000 to 2020, and forecast development trends over the next 10 years.

Method: The grey GM (1,1) prediction model was used to fit the physical shape indicators of preschool children in China from 2000 to 2020, and then the longitudinal change trend of physical shape was compared and analyzed. Finally, the development trend of physical shape in China in 2025 and 2030 was predicted.

Results: (1) During the period from 2000 to 2020, the height, weight and chest circumference of Chinese preschool children all increased rapidly. Specifically, the weight of male and female children increased by 1.8 kg and 1.6 kg, their chest circumference increased by 1.6 cm and 1.5 cm, respectively, and both their heights increased by 3.6 cm. Among these indicators, the older the age, the greater the growth rate. It is expected that all the indicators will continue to grow rapidly over the next 10 years, but the growth rate will slow. (2) From 2000 to 2020, the growth rate of weight was higher than that of height, and BMI showed an increasing trend. The obesity detection rates in boys and girls increased by 5.6 and 2.8%, respectively. Over the next 10 years, the incidence of obesity is expected to increase by 3.8% in boys and 2.8% in girls. (3) Improvement in the growth and development of preschool children in China has a certain correlation with the rapid growth of China's economy,less physical activity, education and other factors.

Conclusion: Over the past 20 years, the growth and nutritional status of Chinese preschoolers have improved dramatically, but overweight and obesity remain. Overweight and obesity rates are expected to continue to increase rapidly over the next 10 years, particularly among boys, and effective measures should be taken to control the obesity epidemic.

KEYWORDS

preschool children, physical shape, GM (1, 1) model, overweight and obesity, longitudinal

1. Introduction

Since China acceded to the World Trade Organization (WTO) in 2001, its economy has grown rapidly, living conditions of its residents have improved dramatically, the level of nutrition has improved, and the growth and development of children has increased (1). However, the rates of overweight and obesity have increased significantly (2, 3). Obesity is a serious public health problem threatening children in many countries and regions (4). Research shows that from 1975 to 2016, the average BMI of boys and girls aged 5–19 increased by 0.40 kg/m^2 and 0.32 kg/m^2 per decade in worldwide (5), respectively. In a study of American children and adolescents,Odgen pointed out that the obesity rate of children aged 2–5 years increased from 7.2% in the 1988–1994 period to 13.9% in the 2003–2004 period, then dropped to 12.1% in the 2009–2010 periodand 9.4% in the 2013–2014 period, showing a downward trend (6). Globally, the growth rate of obesity in developed countries is decreasing, whereas the number of obese children and adolescents in developing countries continues to increase (7). China is a typical developing country in which preschool children are facing a severe obesity epidemic (8).

Preschool is a fundamental stage in the development of good physical fitness, and the level of growth and development during this period has an important impact on adolescence, adulthood, and old age (9–11). Exploring changes and trends in growth and development can provide references for preschool children to improve their physical fitness and health and prevent chronic diseases. At present, Chinese scholars' research on the growth and development of preschool children mainly focuses on cross-sections, and longitudinal research only focuses on individual cities; most longitudinal research methods are simple comparisons or linear regression analyses of different ages (12, 13). However, there has been no in-depth nationwide research on the longitudinal dynamic changes and predictions of body shape and obesity. The grey model GM (1, 1) is an effective model for fuzzy long-term descriptions of the development of things (14, 15). Since its establishment in 1982, the gray model has been widely used in many fields such as medicine (16), economy (17), agriculture (18), and sports (19); successfully solving a large number of practical problems in production, life, and scientific research.

China attaches great importance to the physical health of children. Since 2000, China has implemented a national physical fitness surveillance program, and established a five-year cycle of institutional and systematic national physical fitness surveillance systems. The country has conducted five national physical fitness surveys (in 2000, 2005, 2010, 2014, and 2020) covering 31 provinces (autonomous regions and municipalities). This national physical fitness surveillance includes physical shape indicators such as height, weight, chest circumference, and BMI of children aged 3–6 years. These surveys provide important data for studying children's growth and development in China.

Based on the body shape data of preschool children obtained from five national fitness surveys, this study established a grey prediction model GM (1, 1) for body shape series indicators to explore the internal laws and trends of the growth and development of Chinese school-age children. and to provide the scientific basis for government departments, kindergartens, and families to formulate targeted intervention measures to improve the growth and development level of preschool children and curb the epidemic of overweight and obesity in China.

2. Materials and methods

2.1. Research subjects

The participants were preschool children aged 3–6 years in China. The data was derived from five China national physical fitness surveillances (CNPFS) (20–24). Each survey selected a nationally representative sample of civilians. The sampling scheme is as follows: the first stage covered all 31 provinces, autonomous regions, and municipalities in mainland China. In the second stage, three cities were randomly selected from each province according to their economic condition assessed by GDP; in the third stage, three districts (for urban area) and three counties (for rural area) from each city; in the fourth stage, three streets/towns from each district/county; in the fifth stage, two kindergarten from each street/town. The last stage adopts the method of systematic sampling; they were divided into eight groups according to gender and age, and each group spot tests 100 (2000 is 80 people) in each province. Assuming a response rate of 100/130 with expected enrollment of 1,600 (2020 is 1,280 people) for each province, a total of 52,687, 53,966, 50,546, and 49,667 boys and girls between age 3 ~ 6 were surveyed in 2000, 2005, 2010, 2014, and 2020, respectively; and total of 247,088 valid samples were obtained in altogether.

2.2. Measurement method

All tests were conducted at the same location with the same brand of testing equipment (Jianmin II, Beijing)and the same testing methods. Height was measured to the nearest 0.1 cm using a calibrated height measurement instrument. Weight was measured with a corrected weight measurement instrument, accurate to 0.1 kg. Chest circumference measurements were taken horizontally, and the lower margin of the nylon tape ruler on the chest along the upper margin of the nipple was accurate to 0.1 cm. BMI = weight/(height × height) (kg/m^2). Parents or guardians were given a sports medicine questionnaire before they were tested, on the promise that parents had learned, consented, and signed the consent forms. The tester checked the subjects who participated in this experiment actively, and excluded children with diseases of the heart, lungs, liver, kidneys, and other major organs (such as a history of heart disease, asthma, hyperthyroidism, or other physical disabilities) or other children who were not suitable to participate in more strenuous sports.

2.3. Research method

The main research method of this study uses the data obtained from previous monitoring as time-series data, constructs the grey GM (1, 1) model, develops the fitted curves of growth and development indicators, analyzes the dynamic changes in growth and development during the 20 years from 2000 to 2020, and finally predicts the values of each indicator in 2025 and 2030,The grey GM (1, 1) model is described as follows:

2.3.1. Introduction to the grey model GM (1,1)

Grey systems theory, established by Professor Julong Deng in 1982, is a relatively newmethodology that focuses on the study of problems involving small data and poorinformation (14), Grey system theory is one of the three new uncertainty theories (fuzzy mathematics, grey system, and rough set) in the second half of the 21st century (15). The two SCI regional journals "Grey Systems Theory and Application" and "Journal of Grey System" established by the Institute of Grey Systems provide an important platform for the exchange and development of this theory in the past 40 years, grey system theory has been developed rapidly (25). A large number of scholars, such as LotfiA Zadeh, founder of fuzzy mathematics, Robert Valee, president of the World Organization for Systems and Control, have highly praised the research on grey systems. German Chancellor Angela Merkel praised China's original grey system theory in a speech at Huazhong University of Science and Technology in 2019, believing that the theory and related work has "profoundly affected the world" (25, 26).

GM (1, 1) model is a prediction model of grey system theory and an important branch of grey system theory with the most classic results (27). GM (1, 1) represents a Grey Model of a first-order differential equation with one variable, where G represents grey and M represents Model, the first 1 in parentheses represents the first-order differential equation, and the second 1 represents the equation with only one independent variable, GM (1, 1) has the characteristics of "less series data," "isochronous" and "time series," and the time series of no less than 4 data can build the prediction model (28). The modeling principle of GM (1, 1) is to first process the existing gray information extraction, processing, generation and other information, mining the internal change law of the system, and then make a quantitative prediction of the future trend. The model parameter development coefficient a ≥ − 0.3 can be used for short and medium term prediction, and has a high accuracy (15).

The method and results of this study are reliable and repeatable. A computer software on GM (1, 1) can be downloaded from the web site of Institute for Grey System Studies of Nanjing University of Aeronautics and Astronautics[1] for free (29).

2.3.2. Model building process

The main process of the grey GM (1, 1) model construction is to generate equidistant time-series data, establish a prediction model, test the model, and obtain the fitted and predicted values (15). The height of a 3-year-old male child was used as an example to illustrate the modeling prcess.

The five national monitoring heights in 2000, 2005, 2010, 2014, and 2020 were 99.1 cm, 100.2 cm, 101.3 cm, 102.1 cm and 101.9 cm, respectively. According to the same time intervals modeling requirements, 102.1 cm in 2014 was adjusted to 102.3 cm in 2015 by interpolation. Since the first data of the modeled series does not affect the predicted values and development coefficients of the model (16), an arbitrary value "10" is added before this time series in order to make full use of the original data and to improve the accuracy and reliability of the predictions. Therefore, the initial vector of modeling is (10,99.1, 100.2, 101.3, 102.3, 101.9). The specific steps are described as follows:

1 http://igss.nuaa.edu.cn

1. The initial vector is:

$$X^{(0)}(m) = (10, 99.1, 100.2, 101.3, 102.3, 101.9)$$

2. Accumulating Generation Operator (1-AGO) for the initial vector:

$$X^{(1)}(m) = [10, 109.1, 209.3, 310.6, 412.9, 514.8]$$

3. 1-AGO generates the adjacent mean of the sequence

$$W^{(0)}(m) = [59.55, 159.20, 259.95, 361.75, 463.85]$$

4. Generate the coefficient matrix B and Y (n):

$$B = \begin{bmatrix} -59.55 & 1 \\ -159.20 & 1 \\ -259.95 & 1 \\ -361.75 & 1 \\ -463.85 & 1 \end{bmatrix}, Y(n) = [99.1,100.2,101.3,102.3,101.9].$$

5. Least squares method to solve for the grey model development coefficients a and constant b:

$$\begin{pmatrix} \text{a} \\ \text{b} \end{pmatrix} = \left(B^T B\right)^{-1} BY^T = \begin{pmatrix} -0.00760 \\ 98.97662 \end{pmatrix}$$

6. After substituting a and b into the response function, derivation is obtained and the prediction model is restored:

$$Y^{(0)}(m) = \left(1 - e^{a}\right)\left(X^{(0)}(1) - \frac{b}{a}\right)e^{-a(m-1)} = 98.6772\text{e}^{0.0076(m-1)}$$

7. The calculated average simulation relative error is 0.36764%, the average relative precision is 99.63236% (See Table 1), and the mean square error ratio C is 0.37 (see Table 2); This shows that the effectiveness is good (Level 2).

3. Research result

3.1. Sample characteristics

The main physical shape indicators were height, weight, and chest circumference. The results showed that the growth and development levels of all the age groups increased with age. From age 3 to 6, the greatest increase was observed in weight. All indicators were higher in boys than in girls across all age groups (see Table 3).

3.2. Dynamic changes and prediction of body morphology from 2000 to 2020

Using the Grey model GM (1, 1) to predict the body shape indicators of 3-, 4-, 5-, and 6-year-old children, the parameters, fitting values, and predicted values of the prediction model were obtained. The value of the development coefficient of the model parameter "a"

TABLE 1 Statistical list of the relative error between predicted simulated and original value in this study.

Annual	Original value	Fit values, Predicted values	Residual	Precision of fitting
2000	99.1	99.4	−0.3	99.7%
2005	100.2	100.2	0.1	99.9%
2010	101.3	101.0	0.3	99.7%
2015	102.3	101.7	0.6	99.4%
2020	101.9	102.5	−0.6	99.4%
2025	/	103.3	/	/
2030	/	103.8	/	/

TABLE 2 A list of testing standards for the grey forecasting model in this study.

Model fit rank	Ratio C of mean squared variance	Small error probability P	Average relative accuracy
Excellent (level 1)	<3.5e-01	>9.5e-01	>99.0%
Good (level 2)	<5.0e-01	>8.0e-01	>95.0%
Qualified (Level 3)	<6.5e-01	>7.0e-01	>90.0%
Nonconforming standard (Level 4)	<8.0e-01	>6.0e-01	≤90.0%

reflects the intrinsic development trend of the time series data; if "a" is "negative," it means the increasing trend of the series, if "a" is "positive," it indicates a decreasing trend. The size of the absolute value of "a" indicates the magnitude of increase or decrease; and the smaller the absolute value, the smaller the magnitude of change in the time series, and vice versa (15, 30).

3.2.1. Height

According to the relevant parameters of the height grey model GM (1, 1) (see Table 4), the average error of the fitting curve for each age is 0.14% ~ 0.43%, and the accuracy of the models is above 99.5%, indicating that the established models are highly effective. The development coefficient a of all age groups was negative, and the values of $|a|$ were 5 years >6 years >3 years >4 years. (1) From 2000 to 2020, the height of boys aged 3, 4, 5, and 6 increased by 3.1 cm, 2.9 cm, 4.1 cm and 4.1 cm, respectively; with an average increase of 3.6 cm (an annual increase of 0.16%). The height of girls increased by 3.1 cm, 3.0 cm, 4.1 cm and 4.2 cm, respectively; with an average increase of 3.6 cm (an annual increase of 0.17%). It can be seen that the growth rate of 5- and 6-year-olds is higher than that of 3- and 4-year-olds, with no gender difference. (2) It is predicted that during 2020 to 2030, the height of boys aged 3, 4, 5, and 6 will increase by 1.3 cm, 1.2 cm, 1.9 cm and 1.7 cm, respectively, with an average increase of 1.5 cm (an annual increase of 0.14%). The height of girls will increase by 1.4 cm, 1.4 cm, 2.0 cm and 1.8 cm, respectively, with an average increase of 1.7 cm (an

TABLE 3 Characteristic values of samples of children aged 3 to 6 in China from 2000 to 2020.

Annual	Indicators	Boys				Girls			
		3 years old	4 years old	5 years old	6 years old	3 years old	4 years old	5 years old	6 years old
	Height	99.1 ± 5.4	105.2 ± 5.5	111.0 ± 5.9	115.6 ± 5.9	98.0 ± 5.4	104.0 ± 5.5	109.9 ± 5.8	114.4 ± 5.8
2000	Weight	15.5 ± 2.0	17.2 ± 2.4	19.0 ± 3.0	20.6 ± 3.3	14.9 ± 2.0	16.5 ± 2.3	18.2 ± 2.7	19.6 ± 3.0
	C-C	51.7 ± 2.9	53.2 ± 3.0	54.8 ± 3.4	56.0 ± 3.6	50.5 ± 3.1	51.8 ± 3.1	53.2 ± 3.3	54.4 ± 3.6
	BMI	15.8 ± 1.5	15.5 ± 1.4	15.4 ± 1.6	15.3 ± 1.6	15.5 ± 1.5	15.2 ± 1.5	15.0 ± 1.4	14.9 ± 1.5
	Height	100.2 ± 5.3	106.3 ± 5.2	112.4 ± 5.9	117.5 ± 5.6	99.1 ± 5.3	105.1 ± 5.2	111.0 ± 5.7	116.1 ± 5.5
2005	Weight	16.0 ± 2.3	17.7 ± 2.7	19.7 ± 3.4	21.6 ± 3.9	15.4 ± 2.1	16.9 ± 2.4	18.8 ± 3.0	20.5 ± 3.5
	C-C	51.8 ± 2.9	53.2 ± 3.2	55.1 ± 3.6	56.6 ± 4.2	50.7 ± 3.0	51.8 ± 3.1	53.3 ± 3.7	54.7 ± 4.0
	BMI	15.9 ± 1.6	15.6 ± 1.6	15.5 ± 1.7	15.5 ± 1.5	15.6 ± 1.5	15.3 ± 1.5	15.2 ± 1.7	15.1 ± 1.8
	Height	101.3 ± 5.0	107.1 ± 5.3	113.7 ± 5.5	118.5 ± 5.7	99.9 ± 5.2	105.9 ± 5.1	112.4 ± 5.4	117.0 ± 5.6
2010	Weight	16.4 ± 2.4	18.1 ± 2.9	20.5 ± 3.6	22.5 ± 4.3	15.7 ± 2.2	17.4 ± 2.7	19.5 ± 3.2	21.1 ± 3.6
	C-C	52.5 ± 3.0	54.0 ± 3.4	56.0 ± 3.9	57.5 ± 4.4	51.3 ± 3.0	52.6 ± 3.3	54.2 ± 3.6	55.5 ± 4.1
	BMI	16.0 ± 1.7	15.7 ± 1.7	15.8 ± 1.8	15.9 ± 2.1	15.7 ± 1.6	15.5 ± 1.7	15.3 ± 1.7	15.3 ± 1.8
	Height	102.1 ± 5.4	107.8 ± 5.2	114.0 ± 5.4	119.7 ± 5.5	100.8 ± 5.2	106.5 ± 5.2	112.7 ± 5.3	118.1 ± 5.5
2014	Weight	16.6 ± 2.4	18.3 ± 2.8	20.6 ± 3.5	23.0 ± 4.4	15.9 ± 2.1	17.5 ± 2.6	19.6 ± 3.2	21.6 ± 3.6
	C-C	52.9 ± 3.1	54.5 ± 3.4	56.3 ± 3.9	58.2 ± 4.5	51.8 ± 3.0	53.1 ± 3.2	54.6 ± 3.7	56.2 ± 3.9
	BMI	15.8 ± 1.6	15.7 ± 1.6	15.8 ± 1.9	16.0 ± 2.1	15.6 ± 1.5	15.4 ± 1.6	15.4 ± 1.8	15.4 ± 1.8
	Height	101.9 ± 5.2	108.0 ± 5.0	115.3 ± 5.3	119.6 ± 5.4	100.9 ± 5.2	107.0 ± 5.1	114.1 ± 5.2	118.5 ± 5.4
2020	Weight	16.4 ± 2.3	18.4 ± 2.5	21.4 ± 2.9	23.1 ± 3.2	15.8 ± 2.4	17.7 ± 2.5	20.2 ± 2.8	21.9 ± 3.1
	C-C	52.3 ± 3.1	54.1 ± 3.5	56.3 ± 3.7	58.1 ± 4.1	51.2 ± 3.2	52.7 ± 3.5	54.6 ± 3.7	56.1 ± 4.0
	BMI	15.8 ± 1.6	15.8 ± 1.8	16.1 ± 1.7	16.2 ± 1.9	15.8 ± 1.5	15.5 ± 1.7	15.5 ± 1.7	15.6 ± 1.8

TABLE 4 Parameters, fitting and predicted values of GM (1, 1) for height of preschool children in China, 2000–2030.

Parameter and annual	Boys				Girls			
	3 years old	4 years old	5 years old	6 years old	3 years old	4 years old	5 years old	6 years old
10-3a	−7.6	−6.8	−9.1	−8.8	−7.7	−7.2	−9.1	−8.9
b	99.0	105.0	110.7	115.6	97.8	103.8	109.5	114.1
Fitting error	0.4%	0.3%	0.2%	0.4%	0.3%	0.2%	0.1%	0.3%
2000	99.4	105.5	111.3	116.2	98.2	104.2	110.0	114.8
2005	100.2	106.2	112.3	117.2	99.0	105.0	111.0	115.8
2010	101.0	106.9	113.3	118.2	99.8	105.7	112.0	116.9
2015	101.7	107.6	114.3	119.3	100.6	106.5	113.0	117.9
2020	102.5	108.4	115.4	120.3	101.3	107.2	114.1	119.0
2025	103.3	109.1	116.4	121.4	102.1	108.0	115.1	120.0
2030	103.8	109.6	117.3	122.0	102.7	108.6	116.1	120.8
2020–2000	3.1(3.1%)	2.9(2.7%)	4.1(3.7%)	4.1(3.5%)	3.1(3.2%)	3.0(2.9%)	4.1(3.7)	4.2(0.3.7%)
2030–2020	1.3(1.3%)	1.2(1.1%)	1.9(1.6%)	1.7(1.4%)	1.4(1.4%)	1.4(1.3%)	2.0(1.8%)	1.8(1.5%)

TABLE 5 Parameters, fitting and predicted values of GM (1, 1) for weight of preschool children in China, 2000–2030.

Parameter and annual	Boys				Girls			
	3 years old	4 years old	5 years old	6 years old	3 years old	4 years old	5 years old	6 years old
10-3a	−14.7	−17.2	−28.1	−29.4	−14.7	−17.4	−24.8	−27.6
b	15.4	17.0	18.6	20.3	14.8	16.3	14.8	19.1
Fitting error	1.2%	0.7%	0.6%	1.3%	1.0%	0.5%	0.6%	0.8%
2000	15.7	17.3	19.1	20.9	15.1	16.6	18.3	19.8
2005	15.9	17.6	19.7	21.5	15.3	16.9	18.8	20.4
2010	16.2	18.0	20.2	22.2	15.5	17.2	19.2	20.9
2015	16.4	18.3	20.8	22.8	15.8	17.5	19.7	22.5
2020	16.7	18.6	21.4	23.5	16.0	17.8	20.2	22.1
2025	16.9	18.9	22.0	24.2	16.2	18.1	20.7	22.7
2030	17.0	19.1	22.5	24.7	16.3	18.4	21.2	23.2
2020–2000	1.0(6.4%)	1.3(7.5%)	2.3(12.0%)	2.6(12.4%)	0.9(6.0%)	1.2(7.2%)	1.9(10.4%)	2.3(11.6%)
2030–2020	0.3(1.8%)	0.5(2.7%)	1.1(5.1%)	1.2(5.1%)	0.3(1.9%)	0.6(3.4%)	1.0(5.0%)	1.1(5.0%)

annual increase of 0.15%). As a result, the height of Chinese preschool children will continue to increase over the next 10 years, but the annual growth rate will be slightly lower than that of the previous 10 years.

3.2.2. Weight

According to the relevant parameters of the weight gray model GM (1, 1) (see Table 5), the average error of the fitting curve of each age is 0.5% ~ 1.3%, and the accuracy of the models is above 98.5%, indicating that the established models are highly effective. The development coefficient a of all age groups was negative, and the values of |a| were 6 years >5 years >4 years >3 years. (1) From 2000 to 2020, the weight of boys aged 3, 4, 5, and 6 increased by 1.0 kg, 1.3 kg, 2.3 kg, and 2.6 kg, respectively; with an average increase of 1.8 kg (an annual increase of 0.46%). The weight of girls increased by 0.9 kg, 1.2 kg, 1.9 kg, and 2.3 kg, respectively; with an average increase of 1.6 kg (an annual increase of 0.4%). The growth rate of boys was higher than that of girls; and the older the age, the faster the rate of weight gain. (2) It is predicted that during 2020–2030, the weight of boys aged 3, 4, 5 and 6 will increase by 0.3 kg, 0.5 kg, 1.1 kg, and 1.2 kg, respectively, with an average increase of 0.8 kg (an annual increase of 0.4%). The weight of girls will increase by 0.3 kg, 0.6 kg, 1.0 kg, and 1.1 kg, respectively, with an average increase of 0.7 kg (an annual increase of 0.4%). As a result, the weight of Chinese preschool children will continue to increase over the next 10 years, but the annual growth rate will be slightly lower than that of the previous decade.

3.2.3. Chest circumference

According to the relevant parameters of the chest circumference gray model GM (1, 1) (see Table 6), the average error of the fitting curve of each age is 0.4% ~ 0.8%, and the accuracy of the models is above 99.0%, indicating that the established models are highly

TABLE 6 Parameters, fitting and predicted values of GM (1, 1) for chest circumference of preschool children in China, 2000–2030.

Parameter and annual	Boys				Girls			
	3 years old	4 years old	5 years old	6 years old	3 years old	4 years old	5 years old	6 years old
10-3a	−4.6	−5.9	−7.7	−10.5	−5.3	−6.1	−8.0	−9.0
b	51.6	53.0	54.6	55.7	50.4	51.6	52.9	54.1
Fitting error	0.8%	0.5%	0.4%	0.5%	0.6%	0.5%	0.4%	0.4%
2000	51.8	53.2	54.9	56.1	50.6	51.8	53.2	54.4
2005	52.0	53.5	55.3	56.7	50.9	52.1	53.6	54.9
2010	52.3	53.8	55.7	57.3	51.1	52.4	54.0	55.4
2015	52.5	54.1	56.1	57.9	51.4	52.7	54.4	55.9
2020	52.7	54.5	56.6	58.5	51.7	53.1	54.9	56.4
2025	53.0	54.8	57.0	59.1	52.0	53.4	55.3	56.9
2030	53.2	55.1	57.4	59.7	52.2	53.7	55.8	57.4
2020–2000	0.9(1.7%)	1.3(2.4%)	1.7(3.1%)	2.4(4.3%)	1.1(2.2)	1.3(2.5)	1.7(3.2)	2.0(3.7)
2030–2020	0.5(1.0%)	0.6(1.1%)	0.8(1.4%)	1.2(2.1%)	0.5(1.0%)	0.6(1.1%)	0.9(1.6)	1.0(1.8%)

effective. The development coefficient a of all age groups is negative, and the value of |a| is 6 years >5 years >4 years >3 years. (1) From 2000 to 2020, the chest circumference of boys aged 3, 4, 5, and 6 increased by 0.9 cm, 1.3 cm, 1.7 cm, and 2.4 cm, respectively; with an average increase of 1.6 cm (an annual increase of 0.14%). The chest circumference of girls increased by 1.1 cm, 1.3 cm, 1.7 cm, and 2.0 cm respectively; with an average increase of 1.5 cm (an annual increase of 0.1%). It can be seen that the growth rate of 5- and 6-year-olds is higher than that of 3- and 4-year-olds. (2) It is predicted that during 2020–2030, the chest circumference of boys aged 3, 4, 5, and 6 will increase by 0.5 cm, 0.6 cm, 0.8 cm, and 1.2 cm, respectively, with an average increase of 0.8 cm (an annual increase of 0.1%). The chest circumference of girls will increase by 0.5 cm, 0.6 cm, 0.9 cm, and 1.0 cm, respectively, with an average increase of 0.8 cm (an annual increase of 0.1%). As a result, the chest circumference of Chinese preschool children will continue to increase over the next 10 years, with the same annual growth rate as in the last decade.

3.2.4. BMI

According to the relevant parameters of the BMI gray model GM (1, 1) (see Table 7), the average error of the fitting curve of each age is 0.2% ~ 0.4%, and the accuracy of the models is above 99.5%, indicating that the established models are highly effective. The development coefficient a of all age groups is negative, and the value of |a| is 6 years >5 years >4 years >3 years. (1) From 2000 to 2020, the BMI of boys aged 3, 4, 5, and 6 increased by −0.1, 0.3, 0.6, and 0.9%, respectively, with an average increase of 0.4 (annual increase of 0.14%), while that of girls increased by 0.2, 0.3, 0.4, and 0.7%, respectively, with an average increase of 0.4 (annual increase of 0.13%). It can be seen that the growth rate of 6- and 5-year-olds were higher than that of 4- and 3-year-olds. (2) Between 2020 and 2030, the BMI of boys aged 3, 4, 5, and 6 years are predicted to increase by 0, 0.2, 0.4, and 0.5, respectively, with an average increase of 0.3 (an annual increase of 0.17%). The BMI of girls will increase by 0.1, 0.1, 0.2, and 0.4, respectively, with an average increase of 0.2 (an annual increase of 0.13%). As a result, the BMI of Chinese preschool children will continue to increase in the next 10 years, and the annual growth rate will be higher for boys than in the previous decade.

4. Discussion

4.1. Preschool children body shape change characteristics and trend prediction

In this research, we found that the level of growth of Chinese Preschool Children improved evidently from 2000 to 2020; each indication continued to grow rapidly, and the average annual increase was 0.12% ~ 0.44% in height, weight, and chest circumference. Comparison of the average increase is as follows: weight > height > chest circumference. After stratification by age, it was found that the older the age, the greater the growth rate. In terms of development trends, both male and female children's body shape indicators will continue to keep growing from 2020 to 2030; but the annual increase will be slightly lower than that from 2000 to 2020. For example, for 6-year-old boys, the height increased by 2.0 cm, 2.1 cm, and 1.5 cm per decade from 2000 to 2010, 2010–2020, and 2020–2030, respectively; and the weight increased by 1.3 kg, 1.3 kg, and 1.2 kg. Tracing the relevant studies before 2000, starting from 1975, the Chinese Ministry of Health organized a physical survey of children aged 0–7 years in nine major cities every 10 years, [13]its conclusion shows that the height of 6-year-old children increased by 1.7 cm and 2.1 cm, and their weight increased by 0.4 kg and 1.1 kg per decade in the 1975–1985 and 1985–1995 periods, respectively. It can be seen that during 1975–2020, height and weight went from medium growth (1975–1985) to high growth (1985–2020) and will continue to grow at a medium rate in the next 10 years (2020–2030).

4.2. Analysis of causes of changes in growth and development

Since its reform and opening up in 1978, China's economy has undergone rapid development, with its *per capita* GDP growing from 385 yuan in 1978 to 71,828 yuan by 2020. From 2000 to 2020, China's per-capita GDP increased from 7,942 yuan to 71,828 yuan (an increase of 8.0 times), the disposable income of residents increased from 3,721

TABLE 7 Parameters, fitting and predicted values of GM (1, 1) for BMI of preschool children in China, 2000–2030.

Parameter and annual	Boys				Girls			
	3 years old	4 years old	5 years old	6 years old	3 years old	4 years old	5 years old	6 years old
10-3a	−0.4	−4.7	−10.6	−14.2	−3.4	−4.4	−7.5	−11.2
b	15.8	15.4	15.2	15.0	15.5	15.2	14.9	14.7
Fitting error	0.4%	0.2%	0.4%	0.2%	0.4%	0.3%	0.3%	0.2%
2000	15.9	15.5	15.4	15.3	15.5	15.2	15.1	14.9
2005	15.9	15.6	15.5	15.6	15.6	15.3	15.2	15.1
2010	15.9	15.7	15.7	15.8	15.6	15.4	15.3	15.2
2015	15.8	15.7	15.9	16.0	15.7	15.4	15.4	15.5
2020	15.8	15.8	16.0	16.2	15.7	15.5	15.5	15.6
2025	15.8	15.9	16.2	16.5	15.8	15.6	15.6	15.8
2030	15.8	16.0	16.4	16.7	15.8	15.6	15.7	16.0
2020–2000	−0.1(−0.6%)	0.3(1.9%)	0.6(3.9%)	0.9(5.9%)	0.2(1.3%)	0.3(2.0%)	0.4(2.7%)	0.7(4.7%)
2030–2020	0.0(0.0%)	0.2(1.3%)	0.4(2.5%)	0.5(3.1%)	0.1(0.6%)	0.1(0.7%)	0.2(1.3%)	0.4(2.6%)

yuan to 32,189 yuan (an increase of 7.7 times), and the Engel coefficient decreased from 42.2 to 29.3%. Economic development has resulted in increased living standards and changes in dietary structure (more abundant foods that promote physical growth and development, such as meat, eggs, and milk). The correlation analysis between the growth values of height and weight and national economic data (31) from 2000 to 2020 shows that the correlation coefficients of height with GDP *per capita* (12, 32), disposable income *per capita* and Engel index are 0.22, 0.23 and − 0.46, respectively; and the correlation coefficients of weight with the same are 0.45, 0.42 and − 0.38, respectively. Therefore, growth and development are correlated with socioeconomic and consumption structures, and domestic studies have shown that body shape is positively correlated with GDP. Since the 1950s, there has been a significant increase in the height, weight, and chest circumference of children in most developed countries, such as Korea and Japan. Korea's GDP *per capita* increased from $87 in 1962 to $10,548 in 1996, and the height of children increased by 5 cm between 1965 and 2005 (an average annual increase of 0.13 cm); further segmentation shows that Korean children's height increased rapidly from 1965 to 1996, while it maintained a low growth rate from 1997 to 2005 (33). The Japanese economy went through periods of high growth (1955–1973), moderate growth (1974–1991), and stagnation (after 1992); and child growth and development also went through periods of high, moderate, and low stability. For example, the height of 6-year-old children in Japan increased by 2.2 cm, 1.5 cm, and 0.6 cm per decade from 1963 to 1993, respectively; but most of the increase occurred before 1980, while there was little change from 1993 to 2010 (12, 34). suggesting that the long-term trend in height has stopped. It can be seen that in the past few decades, Japan, Korea, and China have experienced rapid economic development, which corresponds to a significant increase in child growth and development, showing that the changes in growth and development levels are related to the factors of economic development levels, but also that the impact of socio-economic changes on physical morphological development shows stages; when growth and development reach a certain level, its growth rate is bound to slow down or even stagnate. Moreover, records show that the mean height in the Netherlands has increased since 1858; however, this growth stopped after 1997 (35). Our study predicts a slowdown in height growth in China over the next 10 years, similar to the slowdown after high growth in countries such as Japan, Korea, and the Netherlands. Therefore, when economic development is at a higher level, its impact on children's growth and development gradually decreases.

4.3. Prevalence of obesity among preschool children in China

This study found that from 2000 to 2020, preschool children gained more weight than height, with BMI increasing by 0.4 kg/m^2 (0.14% annual increase) and 0.4 kg/m^2 (0.13% annual increase), respectively, and body fullness increasing. For the forecast period 2020–2030, BMI is predicted to increase by 0.43 kg/m^2 (0.17% *per annum*) and 0.2 kg/m^2 (0.13% *per annum*) for boys and girls, respectively.

Increased growth and development has been accompanied by an obesity epidemic. To further analyze the changes and trends in the body shape of preschool children over the past 20 years, a study was conducted on the detection rates of overweight and obesity over time. First, by referring to the standards of overweight and obesity thresholds for young children aged 3–6 years in China (19), the author counted the detection rates of overweight and obesity for children in this age group in China in 2000, 2005, 2010 and 2014 (see Table 8). The results showed that the overweight detection rates over the years for male children were 9.6, 10.3, 12.0, and 12.1%, and the obesity rates were 5.4, 7.5, 8.8, and 9.5%, respectively. Overweight detection rates over the years for girls were 7.0, 8.2, 9.1, and 9.6%, and obesity rates were 3.4, 4.7, 5.2, and 5.7%, respectively. Second, based on the above historical monitoring data, predictions using the GM (1, 1) model show that the overweight and obesity rates in 2030 will be 14.7 and 14.1% for male children, and 12.8 and 7.4% for female children, respectively. Finally, between 2000 and 2020, the rates of overweight and obesity increased by 3.5 and 5.6% for male children, and 3.8 and 2.8% for female children, respectively.

TABLE 8 Overweight and obesity detection rate of 3 ~ 6-year-old children in China, 2000–2030 (%).

Project	2000	2005	2010	2014	2020	2025	2030	2020–2000	2030–2020
Overweight rate of boys	9.6	10.3	12.0	12.1	13.1	14.0	14.7	3.5	1.6
Obesity rate of boys	5.4	7.5	8.8	9.5	11.0	12.5	14.1	5.6	3.1
Overweight rate of girls	7.0	8.2	9.1	9.6	10.9	11.8	12.8	3.8	1.9
Obesity rate of girls	3.4	4.7	5.2	5.7	6.2	6.7	7.4	2.8	1.2

From 2020 to 2030, the overweight and obesity rates are projected to increase by 1.6 and 3.1% for males and 1.9 and 1.2% for females, respectively. The rate of overweight and obesity among preschool children will continue to increase at a faster rate, with preschool children facing an increasingly serious obesity situation. The results of a survey in nine large Chinese cities (the study referred to WHO criteria for overweight and obesity) (36) showed that an epidemic of childhood obesity had not yet developed in China in the 1980s, but there has been a growing trend since the 1990s. In 1996, the obesity detection rates for boys and girls aged 0–7 years were 2.12 and 1.38%, respectively. In 2006, the obesity detection rates for boys and girls aged 0–7 years were 3.82 and 2.48%, respectively. This study suggests that overweight and obesity rates among preschool children will continue the increasing trend, observed since the 1990s, in the 2020–2030 period.

The obesity epidemic among preschool children is caused by several factors maybe. First, it is related to the growth of the economy; first, the improvement of life conditions leads to consuming large amounts of high-calorie foods; second, there is less time for physical activity and preschool children lead a lifestyle of less activity, with more time spent on TV, video games and computers, and participating in training courses for mathematics, foreign languages, and painting. An imbalance in energy intake and consumption caused by these changes may be an important cause of obesity. Preschool children have a relatively limited autonomous choice of diet and lifestyle owing to their young age, and external factors such as family income, parental education, and educational environment play a more significant role (37). Preschool is critical for preventing and healing obesity (38). Thus, parents and kindergartens should actively contribute to curbing the obesity epidemic in preschool children.

5. Conclusion

Our data from five waves of large-scale surveys (CNPFS) over a 20-year period, which included 247,088 nationally representative sample, has a large sample size with strong representativeness. The growth and development level of preschool children greatly improved during the period from 2000 to 2020, and will continue to maintain relatively fast growth in the next 10 years, but the growth rate is slightly lower than that of the previous 20 years. At the same time, if the increase in weight is greater than that in height,BMI will continue to increase in the next 10 years, and the detection rate of overweight and obesity will continue to increase. So the government should scientifically study and judge the development direction of the work related to the growth and development of preschool children, and rationally plan and deploy the work priorities,and Families and kindergartens should focus on the nutritional balance of preschool children and guide them to increase physical activity and reduce resting behavior, to development level of preschool children and curb the epidemic of overweight and obesity in China.

Data availability statement

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

Ethics statement

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) were observed by the authors.

Author contributions

CT did the overall trial management. CJ conceived and designed the study. QP, YT, and SZ contributed to the study analysis plan and data analysis. 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.

Publisher's note

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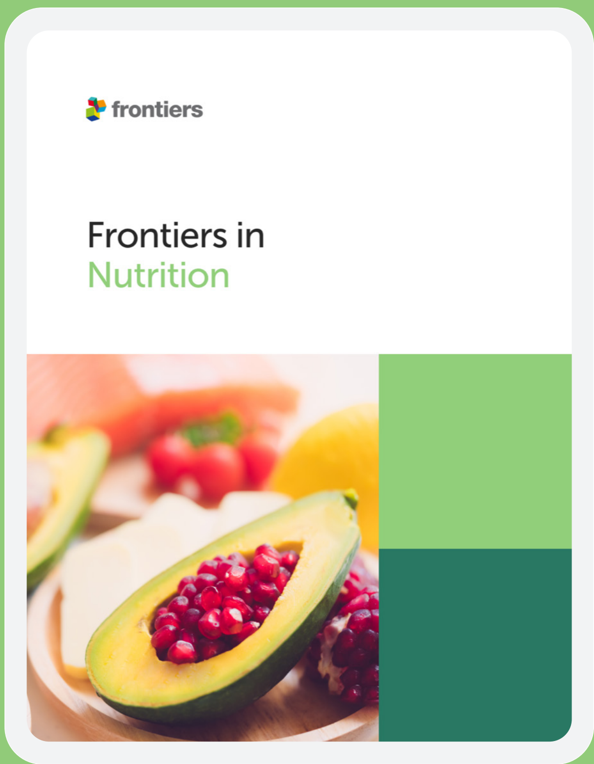

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