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Adherence to the mediterranean diet: Microbiota and non-communicable diseases

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Adherence to the mediterranean diet: Microbiota and non-communicable diseases

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Editorial: Adherence to the Mediterranean diet: microbiota and non-communicable diseases

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Mediterranean diet, non-communicable diseases, microbiota, dietary habit, lifestyle

Editorial on the Research Topic
Adherence to the Mediterranean diet: microbiota and non-communicable diseases

Effects of diet have long been associated with non-communicable diseases, which have exhibited a dramatic worldwide increased prevalence within the last decade (1). Special attention has been given to the Mediterranean diet (MD) because of its protective effects against type 2 diabetes, cancer, inflammatory diseases, metabolic syndrome, liver diseases or cardiovascular diseases (CVD) (2, 3). Although that some associations have been well established, research on the causal influence of such dietary pattern on health outcomes yielded inconsistent findings because of the emerging role of dietary-based microbiota composition in the progression of the diseases (4). It is therefore important to gain more comprehensive understandings of the association between the levels of the adherence to the Mediterranean diet (AMD) and co-morbidities among various population based on their age and/or groups gender and/or ethnicity and their cross-talk with gut microbiome.

This Research Topic includes the contribution of 54 authors from 9 articles presenting studies made in China, Iran, Iraq, Luxembourg, Spain, United States and New Zealand and treating recent findings on the aspects covered above.

The work of Al Kudsee et al. evaluated the association between the Alternative healthy eating index (AHEI) and the Mediterranean diet score (MDS), and the odds of metabolic syndrome (MetS) from 1,404 adults of the nationwide cross-sectional ORISCAV-LUX2 study in Luxembourg used to assess CVDs and their risk factors. Interestingly, the study demonstrated that CVD components of the MetS and the continuous MetS severity score was inversely correlated with the two dietary indices AHEI and MDS. These results highlight the importance of high AMD as preventive measure against MetS.

Chen et al. investigated the associations of adherence to MD pattern with incident rosacea through a prospective cohort study of government employees in China, in the absence of literature regarding the role of diet on rosacea. Results suggested that adherence MD pattern might reduce the risk of incident rosacea among non-overweight individuals.

The study of Liu and Lu discussed the research patterns, existing state, and possible hotspots in implementing the MD for the prevention and treatment of cancer using bibliometrics between 2012 and 2021. Results stressed on the value of the MD as a good regimen for lowering the risk of cancer and suggested that more research focusing on molecular mechanisms and clinical studies are required since the topic is receiving continuously a special attention.

A community-based cohort study conducted by Yiannakou et al. examined the associations between adherence to four established MD indices and breast cancer risk in women in the Framingham Offspring Study. Higher adherence to the MD was associated with a lower risk of breast cancer incidence. Findings suggest that the methodology and the composition of MD indices influence their ability to assess conformity to this specific diet pattern and predict disease risk. Similarly, the work performed by Sadeghi et al. evaluated the association between adherence to a MD and breast cancer among 350 Iranian women. Results reveal a significant inverse association between the MD and breast cancer and that adherence to Mediterranean dietary pattern was associated with reduced odds of breast cancer.

The study done by Melguizo-Ibáñez, Zurita-Ortega et al. showed that male adolescents in Spain were more prone to adhere adequately to the MD in contrast to teenager female, who exhibited higher consumption of alcohol beverage. Such lifestyle habits in youth male contributed to a better quality of life. These findings may serve as reference to investigate further risk factor for NCD in this group population. Another study conducted by the same authors Melguizo-Ibáñez, González-Valero et al. examined the association between the adherence to MD and self-concept and anxiety as a function of weekly physical activity in higher education context. Results show that students having low adherence to MD had higher levels of anxiety compared to those having a high degree of adherence. The same group reported high scores in the different dimensions of self-concept. Findings show that active lifestyle demonstrates improvement in the effect of a healthy dietary pattern on the different dimensions of self-concept and anxiety.

Fateh et al. conducted a clinical randomized control trial and provided evidence that a 12-week intervention based on a 250 ml daily intake of beetroot from Iranian adults significantly potentize beneficial effect of MD on lipid profile by lowering levels of cholesterol, triglycerides and LDL and by decreasing specific liver enzymatic markers contributing to reduction of steatosis, a conditions of fatty liver diseases.

Lithander et al. tested whether an intervention including a Mediterranean dietary pattern incorporating high quality New Zealand foods (NZMedDiet pattern) and behavior change science can improve the metabolic health of 200 participants and their household. Authors have demonstrated that the approach of both a household/whanau based intervention and the provision of food for a whole diet intervention is acceptable and culturally relevant for people in Aotearoa New Zealand.

Altogether, the results presented in this Research Topic shed light on the importance of MD in the prevention of NCD and its potential impact on microbiota modulation. These findings contributed to the understanding of the influence of some components of the MD on NCD outcomes, and may serve as guidelines for nutritional intervention or as guide for future works on the field.

Author contributions

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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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High adherence to the Mediterranean diet and Alternative Healthy Eating Index are associated with reduced odds of metabolic syndrome and its components in participants of the ORISCAV-LUX2 study

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Background: Metabolic syndrome (MetS) is a major risk factor for cardiometabolic complications. Certain dietary patterns play a pivotal role in improving MetS components. The aim of this investigation was to study associations between the Mediterranean Diet Score (MDS) and the Alternative Healthy Eating Index (AHEI) and the odds of MetS and its components in adults living in Luxembourg.

Methods: Data from 1,404 adults participating in the cross-sectional ORISCAV-LUX2 study were analyzed by a self-reported questionnaire, anthropometric measures, a food frequency questionnaire (174 items), and blood/urine samples.

Results: A significant association of dietary indices and MetS was not found except when expressing MetS as a score (continuous variable, log-transformed), based on the weighting of compounds using exploratory factor analysis with the MDS (β = −0.118, 95% CI: −0.346, −0.120) and AHEI (β = −0.133, 95% CI: −0.059, −0.019). Fully adjusted linear regression models further showed significant inverse associations between components of MetS and MDS (all as log-transformed variables), including body mass index (BMI) (β = −0.0067, 95% CI: −0.0099, −0.0036), waist-circumference (WC) (β = −0.0048, 95% CI: −0.0072, −0.0024), systolic blood pressure (SBP) (β = −0.0038, 95% CI: −0.0061, −0.0016), and diastolic blood pressure (DBP) (β = −0.0035, 95% CI: −0.0060, −0.0009). Similarly, significant inverse associations between AHEI and components of MetS (log-transformed) included BMI (β = −0.0001, 95% CI: −0.0016, −0.0002), WC (β = −0.0007, 95% CI: −0.0011, −0.0002), SBP (β = −0.0006, 95% CI: −0.0010, −0.0002), and DBP (β = −0.0006, 95% CI: −0.0011, −0.0001).

Conclusion: Higher adherence to a Mediterranean diet and following healthy eating guidelines were associated with reduced odds of MetS and several of its components in Luxembourgish residents, highlighting that balanced and healthy eating patterns are a crucial cornerstone in the fight against MetS.

KEYWORDS

inflammation, oxidative stress, heart disease, type 2 diabetes, hypertension, dietary indices

Introduction

Metabolic syndrome (MetS) is a metabolic and public health-related condition that burdens the life of people and also the healthcare system globally. It is a major risk factor for cardiometabolic complications, affecting over a billion people worldwide (1), with a prevalence of 28% in adults in Luxembourg (2). MetS is a multi-faceted disorder characterized by a cluster of interrelated risk factors for coronary heart disease (CHD), cardiovascular diseases (CVD), and type 2 diabetes (T2D) (1). There are various definitions and diagnostic criteria for MetS. The most generally used and documented criteria are based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (3). MetS is diagnosed when three or more of the following five main components are fulfilled: dyslipidemia, elevated arterial blood pressure (BP), dysregulated glucose homeostasis, abdominal obesity, and/or insulin resistance (4).

One of the most important aspects of MetS is that it aids in screening individuals at high risk of developing CVD, T2D, hypertension, and atherosclerosis, together with increased disease mortality (5). MetS is linked to a 1.5-fold increase in all-cause mortality and a 2-fold elevation of CVD risk (6). In order to decrease the risk of CVD, T2D, and other complications, drug therapy for metabolic components is considered in some cases (7). However, early prevention measures for this condition are more effective when employed on a population-wide scale rather than drug therapy treatment. Nutrition is among the most significant modifying lifestyle factors influencing cardio-metabolic health (8). Modest weight reduction by lifestyle modification, including a healthy diet and sufficient physical activity, are a practical and effective means that can improve all five components of MetS, as lifestyle modification controls the entire metabolic profile of individuals with MetS and selectively mobilizes the abdominal visceral fat (9, 10).

Despite the widespread occurrence and significance of MetS, there is no consensus about the contribution of individual dietary risk factors to MetS. However, several meta-analyses investigating risk factors for MetS have shown that a healthy diet can significantly reduce the (pooled relative) risk of developing MetS (by 15%) and CVD (by 31%) (8, 11, 12). For example, it has been shown that dietary patterns such as a diet low in saturated fat (13), low in simple sugars (14), and reduced meat consumption (15) but high in fruits and vegetables (16) can reduce the risk of MetS. However, rather than focusing only on individual dietary aspects, more integrative and comprehensive approaches that investigate the entirety of food items consumed are sought that characterize dietary properties in a more holistic approach. Such approaches have the primary goal of synthesizing a significant quantity of dietary data (a food item or a nutrient) into an overall score that can be used to evaluate potential risk factors or relate to a health outcome. Two such prominent indices include the Alternative Healthy Eating Index (AHEI) and the Mediterranean Diet Score (MDS).

The AHEI is an index developed by researchers at the Harvard School of Public Health as an alternative measure of diet quality, focused on absolute food intake rather than nutrient density, to identify the future risk of diet-related chronic disease. The AHEI is a valuable tool that measures adherence to dietary guidelines and evidence-based recommendations for nine food groups or aspects, including vegetables, fruits, nuts, and soy protein, the ratio of white to red meat, fiber, trans-fatty acids, the ratio of PUFA/SFA, multivitamin supplement intake, and alcohol (17). A multiethnic Cohort found that better diet quality—as assessed by AHEI, was associated with an 18–26% lower risk of all-cause and CVD mortality; meta-analyses also confirmed these results (18, 19). Several mechanisms for how a higher AHEI may relate to cardiometabolic diseases have been described, such as the direct effects of fibers in reducing cholesterol absorption, the impact of polyphenols in reducing oxidative stress and inflammation, as well as their indirect effects through gut microbiota (20). The MDS is based on solid epidemiologic evidence and evaluates adherence to the Mediterranean diet (MD) based on the consumption of selected foods, especially considering fish intake in addition to legumes, vegetables, fruits, and grains as an advantageous group, and dairy products, red meat, lipids, and alcohol as an adverse health food group (21). High MDS (indicating adherence to an MD) is characterized by high consumption of fish and seafood, olive oil as the primary fat, vegetables, fruits, whole grains, legumes, and nuts, with a high MUFA/SFA ratio; and low consumption of red meat and meat products is related to a lower risk of cardiometabolic diseases. The high amounts of unsaturated fats (MUFA and PUFA), fiber, and polyphenols in this diet and other factors, such as the low intake of SFA, contribute to its beneficial effects in reducing the risk of such diseases, including MetS (22). In addition, recently, the regulatory role of nutritional components of the MD on the gut microbiota and the immune system and the relation to non-communicable diseases, including obesity, T2D, CVD, MetS, and some types of cancer, has been emphasized (23). Evidence suggests that MD adherence was able to modulate the gut microbiota and increases its diversity, which has been related to increased short-chain fatty acid (SCFA) production, among others (24).

It has been shown that assessing overall diet quality, rather than specific nutrients or food components, is more successful in predicting a relationship between diet and disease (25). According to our knowledge, no previous study has used MDS and AHEI together for estimating the risk of MetS. Since these two indicators somehow complement each other (in terms of components) and surveys using them together are limited, a combined investigation was felt appropriate. In addition, no association between dietary indices such as MDS and AHEI with MetS and its components among residents of Luxembourg, a country characterized by a high rate of risk factors such as obesity and high blood pressure (26) and quite diverse dietary habits/culinary landscape (due its almost 50% foreign residents), has been reported on thus far. Therefore, it is important to shed light on this area with the aim of better controlling MetS. This study strives to derive a more recent estimation of this association by determining the relation between MDS, AHEI score, and MetS and its components among residents of Luxembourg.

Materials and methods

Study protocol and design

This analysis is based on the national survey "Observation of Cardiovascular Risk Factor in Luxembourg (ORISCAV-LUX 2)," which is the second wave of a cross-sectional study, carried out between January 2016 and January 2018 to assess risk factors of CVD in the Luxembourgish adult population (27). In the original ORISCAV-LUX survey (2007–2008), n = 1,432 participants were included by a systematic random sampling procedure. In the following ORISCAV-LUX 2 survey, participants were retained by an initial baseline and complimentary sampling. A total of 660 individuals participated in both studies. In the present analysis, the participants were randomly selected based on sociodemographic attributes, including the district of residence, age, and gender. A full description of the sampling procedure in the first and second waves has already been published elsewhere (28). This study was approved by the National Research Ethics Committee (CNER, No 201-505/12) and the National Commission for Data Protection (CNPD).

A total of 1,558 Luxembourg residents between the ages of 25 and 81 were recruited for the ORISCAV-LUX2 study (27). Of the 1,558 participants, 127 were excluded from the analysis due to missing FFQ information or missing data, 26 due to receiving extreme values of energy, and 1 due to age over 80 years. Overall, 1,404 participants were included in our research question (descriptive analyses), with a complete dataset of nutritional characteristics and having at least one of the MetS components. When crucial data for our analysis, such as results of the five main components of MetS, were missing, it was considered an incomplete metabolic profile; thus, these cases (60 participants) were excluded. Therefore, participants with incomplete metabolic profiles were excluded from correlation and regression analyses, and 1,344 cases were considered for such analysis, as represented in the flowchart in **Figure 1**.

Data collection

Participation in ORISCAV-LUX 2 research entailed three primary steps: completing a self-reported questionnaire (including socio-demographic variables), clinical and anthropometric measures by trained nurses per the standardized operating procedures, and collecting blood, urine, and hair samples in a commercial accredited Laboratory (Ketterthill, Luxembourg).

The data were obtained from questionnaires related to sociodemographic and anthropometric aspects, lifestyle, and self-reported health conditions, including a validated food frequency questionnaire (FFQ) with 174 items (29). The participants, with the assistance of a trained nurse, indicated the frequency and portion size of all consumed food items and beverages on a scale ranging from "never or rarely," "two or more times/day," "once a day," "3–5 times/week," "1–2 times/week," and "1–3 times/month" over the previous year. The macro- and micronutrient intake was calculated by multiplying each food item's consumption frequency by the specific nutrient content of each portion. A photo album covering portion size images of all the consumed food and beverage items was used to accurately identify the portion sizes and determine the amount of intake. The macronutrient and micronutrient intakes were calculated by translating foods and beverages into nutrients using the French Ciqual food database, which lists nutritional information for over 3,100 food items (30). Furthermore, The MDS score and its quartiles were calculated based on the FFQ and Ciqual database; the same was done regarding the AHEI. Demographics, socioeconomic factors, and details about the anthropometric and clinical measurement are all explained in more detail previously, similar to the dietary assessment (27).

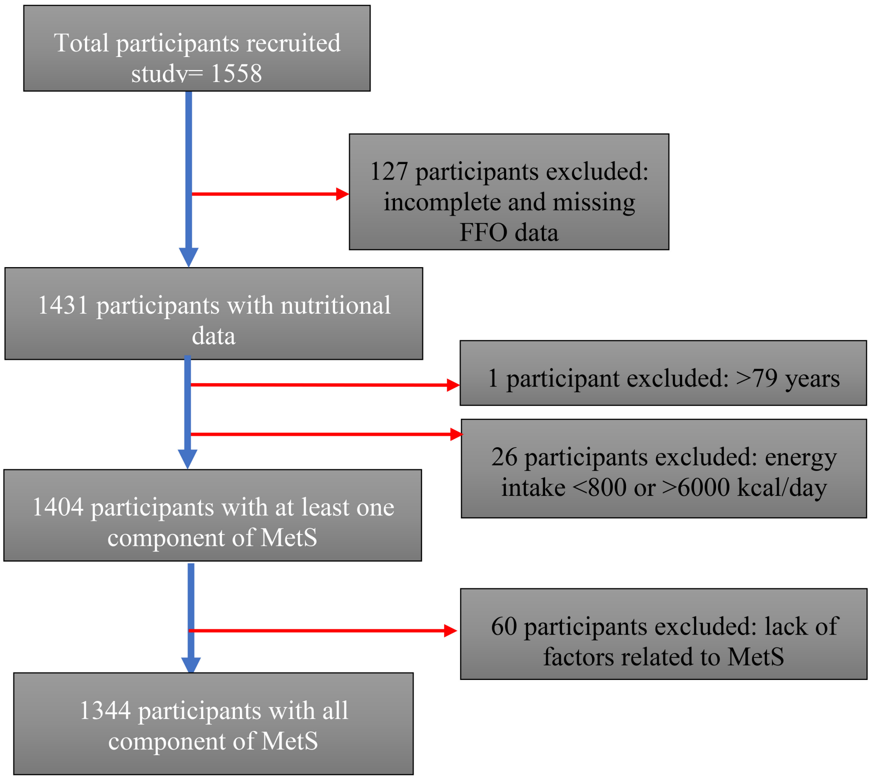

FIGURE 1
Participant sample progression.

Calculation of MetS scores

The MetS as a categorical variable was defined based on the NCEP ATP III definition (**Supplementary Table 1**). Accordingly, the participant was considered to have MetS if he/she had three or more of the following main components: dyslipidemia, elevated arterial BP, dysregulated glucose homeostasis, abdominal obesity, and/or insulin resistance, according to the NCEP ATP III criteria (3).

However, as there is no validated tool to calculate the MetS score as a continuous variable, previous research reports have employed several methods to quantify it. We used three different standard methods in our approach to quantify the MetS.

First, we calculated the MetS score based on the weighting of its component by using the exploratory factor analysis (EFA). The scoring MetS based on EFA (MetSEFA) was calculated by subtracting the total mean of each component of MetS from values for each person and then dividing it by the total SD multiplied by the EFA coefficient for each component (31). MetSEFA = [(total mean of FBG-individuals FBG/total SD) * EFA coefficient for FBG] + [(total mean of triglyceride (TG)-individuals TG/total SD) * EFA coefficient for TG] + [(total mean of waist circumference (WC)-individuals WC/total SD) * EFA coefficient for WC] + [(total mean of SBP-individuals SBP/total SD) * EFA coefficient for SBP] + [(total mean of HDL-individuals HDL/total SD) * EFA coefficient for HDL], with FBG being fasting blood glucose, SD being standard deviation, and SBP being systolic blood pressure.

The second method (siMS score) was based on a previously published method (32), with the following equation: (2 * WC/height) + (FBG/5.6) + (TG/1.7) + (SBP/130) − (HDL/1.28 or 1.02 for women or men) with values for TG, HDL, and FBG in mmol/L, height and WC in cm.

The third quantifying method was calculated based on regression modules (MetSR) using logistic regression, and the final equation was: −19.94 + (WC * 0.072) + (FBG * 0.052) + (TG * 0.008) + (HDL * − 0.037) + (SBP * 0.025) + (gender * 1.188 or −1.188 for men or women, respectively) + (age * 0.009 or * 0.067 for men or women, respectively), with values for HDL, TG, and FBG in mg/dL.

Calculation of Mediterranean diet score and alternative healthy eating index

Mediterranean diet score

The MDS was chosen in this study to assess the association of the MD diet with MetS. To calculate the MDS for this study, the intake of required food groups was obtained from the completed FFQ data. Then, the median intake of the entire population investigated was found for each food group, and after that, each participant's food consumption was compared with the median. The MDS ranged from zero (low adherence to MD) to nine (high adherence to MD) and was calculated by combining all component ratings (33). In the end, MDS quartiles were calculated.

Alternative healthy eating index

The AHEI was used in this study to assess the association between a healthy diet and MetS. The AHEI uses nine nutritional components to assess food quality and may be used to offer dietary advice for healthy eating (**Supplementary Table 2**). Moreover, it is considered more detailed and specific compared to its predecessor, the healthy eating index (HEI), because it includes more items than the HEI, such as protein sources, red-to-white meat ratio, polyunsaturated to saturated fat, and fibers, rather than the broader categories, such as grains and all meats combined as used in the HEI. In addition, attention to the duration of multivitamin usage is also one element that distinguishes the AHEI from the original HEI and other indices (17), though we could not include it here. To construct the AHEI score for this study, relevant food items on the FFQ were allocated to their relevant food categories of each completed FFQ. The nutritional database CIQUAL was used to compute the ratio of PUFA to SFA and cereal fiber intake. The trans-fatty acid information was not available. Therefore, it was not considered in the AHEI scoring, and the AHEI was calculated for this study with only eight components. The amount of each food group was calculated in grams, and grading was done by using the highest-scoring point as a cut-off point. Each component is worth a minimum of zero and a maximum of 10 points, except for the multivitamin component (5 points is the maximum). A total AHEI score, ranging from zero (worst/unhealthy) to 75 (best/healthy), was calculated by combining all component ratings (**Supplementary Table 2**). In the end, the four AHEI quartiles were calculated.

Statistical analyses

Descriptive and correlations analyses

Statistical analyses were performed using SPSS (IBM, Chicago, IL, USA) v. 25. The normality of data distribution and equality of variance was tested by both Q-Q normality plots and the Kolmogorov–Smirnov test. Log-transformation was undertaken to obtain normal distribution when original data did not meet the normality criteria. These values were reported as median and interquartile ranges (IR), and the categorical variables were reported as numbers and percentages. For continuous data, *t*-tests were utilized (log-transformation was used for all the continuous variables), while the chi-square test was employed for categorical variables. Distributions of demographics, anthropometric and socioeconomic characteristics of participants based on gender were reported, also based on the MDS and its quartiles and the AHEI and its quartiles. In addition, the distribution of the MDS, the AHEI, and the selected nutrients of participants were reported based on gender and metabolic syndrome status. The *p*-values below 0.05 (2-tailed) were considered statistically significant.

For correlations, as our data were not normally distributed, the non-parametric correlation was performed using Spearman correlations (bivariate correlations) to assess the correlation of the dietary indices MDS and AHEI with cardiometabolic biomarkers.

Linear regression models were performed to assess the association of each component of MetS with MDS and AHEI. The dietary indices' scores and the quartiles were analyzed in models A, B, and C.

Model A: the dependent variable was one of the components, and the independent variable was one of the indices, either as the continuous score or as quartiles.

Model B: Model A + adjusted for age groups and gender as confounding factors.

Model C: Model B + additionally adjusted for all sociodemographic variables and selected anthropometric variables (education, job, income, marital status, country of birth, physical activity, currently smoking, and total energy intake).

Logistic regression models were also performed to analyze the association of MetS (as a categorical variable) with the MDS and AHEI with three models (all dependent variables were entered in the regression models log-transformed):

Model A: the dependent variable was MetS as a categorical variable, and the independent variable is one of the indices (AHEI score, AHEI quartiles, MDS score, MDS quartiles).

Model B: Model A + adjusted for age groups and gender as confounding factors.

Model C: Model B + additionally adjusted for all sociodemographic variables and selected anthropometric variables (education, job, income, marital status, country of birth, physical activity, currently smoking, and total energy intake).

In addition, *linear regression models* were performed to assess MetS scores' (as a continuous variable) association with MDS and AHEI. The score and the dietary indices' quartiles were analyzed in three models A, B, and C, as the following (all dependent variables were entered in the regression models log-transformed):

Model A: the dependent variable was one of MetS scores (MetSEFA, siMS score, and MetSR), and the independent variable was one of the indices (MDS and AHEI), either as the continuous score or as quartiles.

Model B: Model A + adjusted for age groups and gender as confounding factors.

Model C: Model B + additionally adjusted for all sociodemographic variables and selected anthropometric variables (education, job, income, marital status, country of birth, physical activity, currently smoking, and total energy intake).

Results

Descriptive analyses

Demographic and socioeconomic distribution analyses are given in **Table 1**. There were significant differences between participants with MetS and participants without MetS regarding age, BMI, education, job, income, and marital status (**Table 1**).

Also, there were significant differences in dietary patterns between the participants who did have MetS and participants who did not have MetS, according to plant-based protein, docosapentaenoic acid (DPA), carbohydrates, sugar, salt, zinc, sodium, potassium, dairy products, fruits, red meat, nuts and soy products and starchy vegetables (**Table 2**).

In addition, a comparison of dietary intakes based on categories of MetS components are represented in **Table 3**. The results of the in-depth investigation showed that participants with SBP higher than the ATP III cut-off (≥130) significantly consumed more energy, red meat, grains, starchy vegetables, total fat, SFA, sodium, simple sugars, alcohol, and less fish and DHA than participants with SBP lower than the cut-off (<130). Similar findings were encountered for DBP. Regarding other components, participants with WC higher than the cut-off [≥102 (men) and ≥88 (women)] consumed significantly more red meat, starchy vegetables, dairy products, cholesterol, sodium, and alcohol comparing participants with WC lower than the cut-off [<102 (men) and <88 (women)]. Similar results were obtained comparing participants based on FBG and TG and in the reverse for HDL categories.

Correlation analyses

The correlation analyses between MDS and cardiometabolic markers revealed statistically significant inverse correlations with BMI, waist circumference (WC), TG, SBP, and DBP. Furthermore, a moderate positive correlation was observed between the MDS and the AHEI. The AHEI showed no statistically significant correlation with cardiometabolic markers (**Table 4**); however, significant results were observed in regression models adjusted for confounding factors.

Regression models

Linear regression analyses of MDS and AHEI with MetS components in final models revealed statistically significant negative associations between MDS and BMI, WC, SBP, and DBP (**Table 5**, model C). Similar findings were observed for MDS when investigated by quartiles. Regarding the AHEI score, negative associations were observed with the BMI, WC, fasting blood glucose (FBG), SBP, and DBP. For the AHEI quartiles, negative associations were found with BMI, WC, and SBP only (**Supplementary Table 3**).

The final model (C) of logistic regression analysis revealed no statistically significant association between MetS and the dietary indices MDS and AHEI, neither when presented as scores nor as quartiles (**Supplementary Table 4**).

Linear regression analyses of MetS scores (based on the EFA scoring model; MetSEFA) with MDS (as a score and as quartiles) in the three models revealed statistically significant negative associations; similar findings were observed regarding MetS scores (based on the regression scoring model; MetSR) and MDS. Moreover, linear regression analyses of the MetS score presented as the siMS score with the MDS revealed statistically significant negative associations only in model A (**Table 6**).

The linear regression analyses between the MetSEFA score and the AHEI (both the score and the quartiles) in model B and C show a significant negative association. Regarding the MetSR, there was a significant negative association with the AHEI in model C. However, there was no significant association between AHEI and MetS score as a siMS score with the AHEI (**Table 6**; **Supplementary Table 5**).

Discussion

In this nationwide cross-sectional study, we investigated the association between two prominent dietary indices, the MDS and AHEI, with MetS (both as a categorical and continuous outcome) and its components. Logistic regression models did not reveal significant associations between the MDS or AHEI and the odds of MetS (as a categorical variable). However, when employing MetS as a continuous variable, inverse associations between MDS and AHEI and MetS were found partly in the fully adjusted models. Furthermore, based on the final adjusted linear regression models, the MetS components BMI, WC, SBP, and DBP were significantly inversely associated with the MDS, and BMI, WC, SBP, DBP, and FBG with the AHEI.

The inverse associations of the MDS with BMI and WC are well-aligned with the findings from previous studies and with meta-analyses (3, 34). As noted earlier, MD has been reported to positively affect central adiposity in persons with MetS (3, 34). The MD's high intake of fruits, vegetables, fibers, whole grains, and unsaturated fatty acids (MUFA and PUFA) characteristics has been reported to decrease adiposity,

TABLE 1 Distribution of demographics, anthropometric and socioeconomic characteristics of participants based on gender and MetS status, presented as frequency, percentage, and *P*-values, comparing women vs. men and participants without MetS vs. participants with MetS.

Variable	Total (*n* = 1,404)[e]		Women (*n* = 750)		Men (*n* = 652)		*P*-value[†]	Total (*n* = 1,344)[f]		Participant without MetS (*n* = 977)		Participant with MetS (*n* = 367)		*P*-value[†]
	n	%	n	%	n	%		n	%	n	%	n	%	
Age group (years)														
25–34.99	162	11.5	85	11.3	77	11.8	0.954	147	10.9	142	14.5	5	1.3	<**0.001**
35–44.99	315	22.4	163	21.7	152	23.2		302	22.4	266	27.2	36	9.8	
45–54.99	381	27.1	207	27.6	174	26.6		362	26.9	278	28.4	84	22.8	
55–64.99	352	25.1	191	25.5	161	24.6		342	25.4	208	21.2	134	36.5	
65–79	194	13.8	104	13.9	90	13.8		191	14.2	83	8.5	108	29.4	
BMI (kg/m^2)														
Normal (<24.99)	649	46.2	416	55.5	233	35.6	<**0.001**	616	45.8	559	57.2	57	15.5	<**0.001**
Overweight (25–29.99)	493	35.1	218	29.1	275	42.0		476	35.4	330	33.7	146	39.7	
Obesity (>30)	262	18.7	116	15.5	146	22.3		252	18.7	88	9.0	164	44.6	
Education														
No diploma*	182	13.0	105	14.0	77	11.8	0.168	171	12.7	97	9.9	74	20.1	<**0.001**
Certified**	251	17.9	135	18.0	116	17.7		238	17.7	154	15.7	84	22.8	
Diploma***	321	22.9	158	21.1	163	24.9		311	23.1	227	23.2	84	22.8	
Tertiary****	526	37.5	277	36.9	249	38.1		506	37.6	422	43.2	84	22.8	
Did not answer	124	8.8	75	10.0	49	7.5		118	8.8	77	7.8	41	11.1	
Job														
Employed, maternal leave	918	65.4	467	62.3	451	69.0	<**0.001**	877	65.2	720	73.4	157	42.7	<**0.001**
Unemployed[c]	153	10.9	126	16.8	27	4.1		144	10.7	96	9.8	48	13.1	
Retired, Long leave[d]	316	22.5	147	19.6	169	25.8		308	22.9	151	15.4	157	42.7	
Did not answer	17	1.2	10	1.3	7	1.1		15	1.1	10	1.1	5	0.8	
Income (€/month)														
Less than 750	4	0.3	1	0.1	3	0.5	<**0.001**	4	0.3	2	0.2	2	0.5	**0.006**
750–1,499	22	1.6	14	1.9	8	1.2		18	1.3	13	1.3	5	1.3	
1,500–2,249	49	3.5	31	4.1	18	2.8		45	3.3	25	2.5	20	5.4	
2,250–2,999	78	5.6	55	7.3	23	3.5		76	5.6	53	5.4	23	6.2	
30,000–4,999	335	23.9	170	22.7	165	25.2		319	23.7	225	26.1	94	25.6	
5,000–10,000	482	34.3	235	31.3	247	37.8		469	34.9	361	36.9	108	29.4	
More than 10,000	115	8.2	47	6.3	68	10.4		109	8.1	89	10.1	20	5.4	
Did not answer	319	22.7	197	26.3	122	18.7		304	22.6	209	21.4	95	25.8	

(Continued)

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TABLE 1 (Continued)

Variable	Total (*n* = 1,404)[e]		Women (*n* = 750)		Men (*n* = 652)		*P*-value[†]	Total (*n* = 1,344)[f]		Participant without MetS (*n* = 977)		Participant with MetS (*n* = 367)		*P*-value[†]
	n	%	n	%	n	%		n	%	n	%	n	%	
Marital status														
Married	1,047	74.6	526	70.2	521	79.8	**<0.001**	1,002	74.5	705	72.1	297	80.9	**0.001**
Widow	164	11.7	86	11.5	78	11.9		157	11.6	131	13.4	26	7.1	
Divorced[b]	155	11.0	102	13.6	53	8.1		148	11.1	117	11.9	31	8.4	
Single[a]	36	2.6	35	4.7	1	0.2		36	2.6	23	2.3	13	3.5	
Country of birth														
Luxembourg	832	59.3	443	59.1	389	59.5	0.192	794	59.0	568	58.1	226	61.5	0.328
Portugal	110	7.8	59	7.9	51	7.8		109	8.1	79	8.1	30	8.1	
Other European countries	336	23.9	170	22.7	166	25.4		323	24.0	236	24.1	87	23.7	
Non-European country	126	9.0	78	10.4	48	7.3		118	8.7	94	9.6	24	6.5	
Physical activity	Total = 903		Women = 464		Men = 439		0.830	Total = 868		Without MetS = 656		With MetS = 212		0.452
Inactive	124	13.7	62	13.4	62	14.1		219	25.2	164	25.0	55	25.9	
Moderately active	229	25.4	121	26.1	108	24.6		530	61.0	407	62.0	123	58.0	
Active	550	60.9	281	60.6	269	61.3		119	13.7	85	13.0	34	16.0	

[†]Chi-square test was performed to find the *P*-values; Significant values are given in bold.
*Pre-primary and primary education; **CATP, Certificate of Technical and Professional Aptitude; CITP, Certificate of Technical and Professional Initiation; CCM, Certificate of Manual Capability, Diploma for Completion of Secondary Technical Studies, Diploma for Completion of Secondary General Studies; ***Technician diploma, Bac + 2 (BTS), Bac + 3 (Bachelors/Degree), Diploma from a Grande Ecole, an Engineering School; ****Bac + 4 (Masters), Bac + 5, and more (3rd Cycle, DEA, DESS, MBA, Masters, Ph.D., etc.).
[a]Single, never married, and never in a registered partnership.
[b]Divorced, separated, separated but still legally married.
[c]In school, university or training, at home, unemployed, or in search of employment.
[d]Retired or in early retirement, on long-term leave.
[e]Number of participants having at least one component of MetS assessed.
[f]Number of participants having all components of MetS assessed.

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TABLE 2 Distribution of AHEI, MDS, and selected nutrient intakes of participants per day based on gender and MetS status.

Variable[a]	Participant without MetS						Participant with MetS						*P*-value* T *vs.* T
	Women (*n* = 554)	IR	Men (*n* = 423)	IR	Total (*n* = 977)	IR	Women (*n* = 159)	IR	Men (*n* = 208)	IR	Total (*n* = 367)	IR	
AHEI	35.0	15.1	37.0	14.1	36.0	14.0	37.1	15.2	36.1	14.4	37.0	14.0	0.967
MDS	5.01	2.01	4.00	3.01	5.00	2.00	5.00	31.03	5.00	2.00	5.00	3.00	0.273
Total energy (kcal)	2,118	897.1	2,683	1,182	2,328	1,120	2,171	1,048	2,619	1,116	2,426	1,155	0.072
Proteins (g)	78.4	36.3	100.8	267.0	87.8	44.2	83.4	36.3	98.2	52.7	90.1	46.1	**0.003**
Lipids (g)	59.9	49.8	65.9	57.2	61.7	52.6	57.4	45.1	62.2	49.3	59.6	46.5	0.936
SFA to MUFA ratio	0.54	0.27	0.52	0.25	0.53	0.25	0.52	0.29	0.52	0.23	0.53	0.25	0.246
Total fat (g)	108.0	56.1	129.0	65.2	115.0	64.2	108.0	58.2	123.0	68.5	114.0	65.9	0.907
PUFA (g)	19.5	12.4	22.9	13.2	20.8	13.4	20.1	14.1	20.6	15.9	20.5	14.0	0.643
EPA (g)	0.18	0.23	0.26	0.25	0.20	0.23	0.19	0.22	0.20	0.21	0.20	0.21	0.333
DHA (g)	0.26	0.32	0.31	0.37	0.29	0.32	0.27	0.30	0.28	0.29	0.28	0.30	0.488
DPA (mg)	713	683	887	749	791	687	825	651	868	652	818	672	**0.039**
Fibers, total (g)	22.5	11.6	24.1	12.8	23.1	12.2	23.7	11.8	22.8	12.3	23.1	11.7	0.479
Soluble fibers (g)	4.7	2.4	4.8	2.4	4.7	2.4	5.0	2.6	4.4	2.4	4.7	2.4	0.404
Carbohydrates (g)	194	86	243	124	214	111	210	114	233	98	225	98	**0.013**
Vegetables (g)	226	187	210	161	220	176	229	197	192	157	211	171	0.191
Simple sugars (g)	94.8	55.2	106.7	61.1	98.7	60.1	107.0	58.1	106.0	54.5	107.0	56.8	**0.041**
Sugary beverages (ml)	75.5	250.0	70.7	225.0	70.7	233.0	51.4	214.0	53.5	229.0	53.5	214.0	0.307
Non-caloric beverages (ml)	1,680	896	1,700	1,073	1,696	991	1,660	872	1,579	1,148	1,633	1,046	0.458
Vitamin C (mg)	149	102	141	100	145	99.5	159	110	141	109	145	115	0.158
Vitamin D (μg)	4.76	4.44	5.73	4.96	5.13	4.69	5.15	4.29	5.30	4.76	5.17	4.68	0.344
Vitamin E (mg)	16.8	10.0	21.0	13.6	18.5	12.0	17.1	8.65	18.5	11.9	18.0	10.3	0.133
β-Carotene (μg)	5,170	4,509	4,947	3,969	5,057	4,096	5,464	4,052	4,479	3,595	4,842	3,758	0.166
Energy (kcal)	2,118	897	2,683	1,182	2,328	1,120	2,171	1,048	2,619	1,116	2,426	1,155	0.063
Water (ml)	3,002	1,074	3,122	1,365	3,072	1,196	3,041	1,279	3,118	1,392	3,080	1,342	0.826
Alcohol (ml)	3.82	7.65	9.33	15.40	5.86	11.00	2.88	7.74	9.22	16.3	5.64	12.3	0.575
Zinc (mg)	10.90	4.84	14.29	6.24	12.10	6.19	11.50	4.77	13.2	7.22	12.4	6.47	**0.009**
Selenium (μg)	86.0	35.2	103.4	43.8	92.3	40.0	85.3	44.1	95.7	48.8	92.1	45.2	0.299
Sodium (mg)	2,882	1,511	3,855	2,135	3,261	1,909	3,044	1,748	3,797	1,976	3,416	1,942	**0.012**
Potassium (mg)	3,338	1,405	3,714	1,587	3,472	1,503	3,606	1,474	3,665	1,679	3,643	1,553	**0.006**
Grains (g)	109	91	136	111	117	96	116	106	131	115	121	113	0.156
Dairy products (g)	169	199	170	177	170	186	199	193	178	220	189	207	**0.010**
Fruits (g)	286	256	275	261	281	261	335	308	304	260	316	303	**0.006**
Legumes (g)	6.6	21.4	10.0	13.3	6.67	21.4	6.67	13.3	6.6	13.3	6.6	13.3	0.664

(Continued)

TABLE 2 (Continued)

Variable[a]	Participant without MetS						Participant with MetS						*P*-value* T *vs.* T
	Women (*n* = 554)	IR	Men (*n* = 423)	IR	Total (*n* = 977)	IR	Women (*n* = 159)	IR	Men (*n* = 208)	IR	Total (*n* = 367)	IR	
Red meat (g)	100	93	154	105	121	112	106	70	159	137	131	124	**0.004**
Nuts and soya (g)	1.67	10.70	0.99	10.70	1.67	10.70	0.99	10.70	0.99	6.67	0.99	10.0	**0.039**
Fish (g)	64.6	65.3	78.14	72.0	70.8	68.2	64.1	63.2	73.8	70.7	70.1	68.6	0.880
Polyphenols (mg)	2,511	1,659	2,575	1,620	2,539	1,656	2,626	1,332	2,484	1,743	2,504	1,601	0.463
Fast food[b] (g)	72	86	120	10	92	100	85	88	107	122	98.2	112	0.199
Protein-rich food (g)	184	124	245	162	209	139	185	119	236	176	214	866	0.117
Starchy vegetables (g)	49.7	59.9	62.8	60.7	55.4	61.3	56.9	73.3	70.9	77.2	64.2	77.14	**<0.001**

Shown by the median and interquartile range (IR), and *P*-value compares total participants without MetS vs. participants with MetS.

*Log of the variables was used for the independent sample *t*-test.

[a]Median and interquartile ranges were reported for all the variables because these were not normally distributed.

[b]Fast foods and ready-to-eat meals.

AHEI, alternative healthy eating index; MDS, Mediterranean diet score; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; IR, interquartile range; T *vs.* T, comparing total participants without MetS with total participants with MetS. *Significant values are given in bold.

leading to improvements in BMI and, thus also, WC. The mechanistic aspects involved may include antioxidant, anti-inflammatory, and also prebiotic-like effects (35), all of which having metabolic advantages on the cardiovascular system. The influence of the MD on the human gut microbiota has been met recently with increased interest, suggesting that the gut microbiota of people following a Mediterranean-type diet was significantly different in terms of diversity and richness (e.g., *F. prausnitzii* and *B. cellulosilyticus*) from people on a Western-type diet (36). Suggested possible mechanisms included bacterial metabolic effects in the colon, including plant-derived polysaccharide degradation, SCFA production out of dietary fiber, and increased excretion of secondary bile acids (36). However, our present knowledge of the cause-effect associations between gut microbiota and the risk of diseases is incomplete and requires further controlled intervention trials to understand the causal relationship between gut microbiota and dietary patterns, including the MD. In addition, direct effects *via* reduced energy intake are also plausible. For example, due to their high protein content, the nuts included in the MD may positively affect satiety, leading to a decreased caloric intake and, thus, a reduction in BMI (37). In the present study, participants with MetS vs. without MetS–in addition to consuming fewer nuts–also consumed more salt, red meat, and simple sugars (**Table 2**), which are all characteristics of a more Western-type diet but are typically low in the MD (14), and which could negatively affect MetS (8, 14). Especially simple sugars, due to their pro-inflammatory aspects and impacting insulin sensitivity (38, 39), have been related to the risk of MetS (40), and red meat, due to its high heme-iron content and less favorable fatty acid profile, have also been related to MetS (41). However, it was also observed that persons with MetS consumed more fruits and starchy vegetables (mostly potatoes) than persons without MetS, but of course, reverse causality (persons with MetS being more prudent with their dietary habits) cannot be excluded from our study.

Regarding the association of the odds of MetS and the MDS and the AHEI, the logistic regression results were surprising, as they revealed a non-significant association between MetS and the MDS or the AHEI, even in the final adjusted models. This may be due to the fact that MetS was reported as a categorical variable with a bivariate outcome (yes, no), which likely decreased statistical power compared to continuous variables such as the individual components. Accordingly, in future analyses, it would be recommendable to extend analyses and to study the effects of dietary indices on a "MetS score," e.g., the Metabolic Syndrome Severity Score as a continuous variable that allows for better powered statistical analyses. Indeed, such MetS scores have been proposed (32, 42); however, no validated or globally accepted, or recommended single score exists. When using MetS as a continuous variable, the EFA-based score and especially the MetSR score resulted in a significant inverse association with a high regression coefficient

TABLE 3 Comparison (median and IR) of intake of food groups and selected nutrients based on MetS components.[a]

Variable	SBP (mmHg)			DBP (mmHg)			WC (cm)			HDL (mg/dL)			FBG (mg/dL)			Triglycerides (mg/dL)		
	≥130	<130	*P*-value	≥85	<85	*P*-value	≥102 (men) ≥88 (women)	<102 (men) <88 (women)	*P*-value	<40 (men) <50 (women)	≥40 (men) ≥50 (women)	*P*-value	≥100	<100	*P*-value	≥150	<150	*P*-value
Total energy (kcal/d)	2,507 (1,115)	2,289 (1,096)	<**0.001**	2,471 (1,137)	2,330 (1,103)	0.114	4,208 (1,143)	2,361 (1,112)	0.268	2,501 (1,116)	2,327 (1,102)	0.188	2,551 (1,367)	2,357 (1,098)	**0.029**	2,656 (1,196)	2,310 (1,097)	<**0.001**
Fish group (g/d)	66.3 (64.1)	73.1 (68.9)	**0.005**	68.1 (63.1)	71.3 (69.3)	0.222	72.7 (69.5)	70.3 (68.4)	0.704	70.2 (66.5)	73.4 (76.8)	0.559	69.9 (67.3)	84.1 (70.5)	0.178	70.9 (76.9)	70.8 (67.8)	0.857
Red meat (g/d)	131.1 (118.1)	120.2 (118.8)	**0.024**	135.6 (126.5)	120.6 (115.8)	**0.003**	138.7 (127.7)	118.7 (110.5)	<**0.001**	145.5 (123.6)	119.8 (112.9)	**0.001**	143.8 (134.7)	119.7 (113.2)	**0.003**	165.5 (125.4)	118.3 (106.1)	<**0.001**
Fruits (g/d)	296.5 (288.7)	289.8 (271.9)	0.171	283.1 (281.6)	300.1 (276.3)	0.122	309.8 (280.4)	282.2 (274.7)	0.200	292.2 (282.1)	296.5 (273.5)	0.335	310.0 (244.2)	289.5 (277.2)	0.401	285.3 (298.9)	296.1 (271.1)	0.792
Vegetables (g/d)	215.1 (177.6)	217.3 (166.1)	0.507	194.8 (175.1)	221.3 (167.9)	**0.017**	217.7 (175.7)	216.7 (170.1)	0.870	213.4 (179.0)	219.3 (171.1)	0.740	226.9 (202.6)	216.4 (168.2)	0.582	220.0 (181.2)	217.6 (172.6)	0.398
Starchy veg (g/d)	67.1 (79.5)	53.5 (59.0)	<**0.001**	62.8 (76.0)	56.1 (59.0)	**0.045**	64.2 (76.3)	56.1 (57.9)	**0.013**	62.8 (75.3)	56.1 (60.7)	**0.013**	64.2 (66.9)	56.1 (62.6)	**0.002**	62.8 (72.5)	56.1 (62.6)	**0.010**
Fast foods[b] (g/d)	96.6 (109.1)	92.2 (98.9)	0.096	95.6 (117.2)	93.9 (99.1)	0.758	99.9 (106.3)	92.0 (101.1)	0.385	110.0 (116.8)	87.4 (100.3)	**0.001**	102.5 (116.6)	92.0 (99.0)	0.352	121.2 (134.5)	90.1 (95.8)	<**0.001**
Grains (g/d)	126.2 (101.2)	115.9 (100.4)	**0.012**	120.2 (111.9)	119.2 (98.7)	0.710	115.8 (106.3)	120.7 (99.1)	0.414	132.3 (117.2)	117.1 (97.1)	**0.041**	134.0 (113.2)	117.5 (98.9)	0.072	129.2 (89.9)	117.6 (102.8)	0.146
Dairy (g/d)	179.7 (205.7)	175.6 (199.0)	0.178	186.3 (198.0)	175.1 (199.8)	0.296	189.7 (215.0)	171.4 (186.5)	**0.009**	182.5 (215.0)	174.5 (194.6)	0.932	180.1 (208.6)	175.0 (196.0)	0.605	184.5 (199.9)	174.5 (198.5)	0.338
Total fiber (g/d)	23.6 (12.5)	22.9 (11.8)	0.051	22.6 (12.2)	23.5 (12.1)	0.281	23.2 (12.3)	23.2 (12.1)	0.987	23.6 (12.5)	23.0 (11.9)	0.518	24.0 (12.8)	23.0 (11.9)	0.235	22.8 (11.9)	23.2 (12.2)	0.894
Soluble fiber (g/d)	4.8 (2.5)	4.7 (2.4)	0.054	4.5 (2.6)	4.8 (2.4)	0.198	4.7 (2.6)	4.7 (2.4)	0.456	4.8 (2.4)	4.7 (2.4)	0.449	4.8 (2.7)	4.7 (2.4)	0.199	4.5 (2.5)	4.8 (2.4)	0.807
Total fat (g/d)	119.9 (64.1)	114.6 (63.4)	**0.025**	119.7 (66.1)	115.0 (63.5)	0.243	118.2 (63.6)	115.6 (65.4)	0.492	121.0 (66.3)	115.3 (64.3)	0.464	119.6 (74.1)	115.6 (63.8)	0.454	124.6 (64.9)	114.5 (64.7)	**0.003**
EPA (g/d)	0.18 (0.21)	0.20 (0.23)	0.158	0.18 (0.21)	0.20 (0.23)	0.584	0.19 (0.22)	0.20 (0.23)	**0.045**	0.19 (0.23)	0.20 (0.23)	0.878	0.20 (0.27)	0.19 (0.23)	0.069	0.20 (0.22)	0.19 (0.23)	0.493
DHA (g/d)	0.25 (0.29)	0.30 (0.32)	**0.037**	0.26 (0.29)	0.29 (0.32)	0.248	0.30 (0.31)	0.27 (0.32)	0.093	0.28 (0.32)	0.28 (0.31)	0.895	0.29 (0.40)	0.28 (0.31)	0.106	0.28 (0.33)	0.28 (0.31)	0.618
MUFA (g/d)	48.9 (25.1)	46.1 (26.3)	0.074	48.2 (26.7)	46.4 (26.3)	0.464	47.3 (25.3)	46.5 (26.8)	0.399	48.5 (27.0)	46.7 (26.5)	0.349	49.0 (32.7)	46.5 (26.0)	0.249	50.6 (27.1)	46.3 (26.3)	**0.004**

(Continued)

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TABLE 3 (Continued)

Variable	SBP (mmHg)			DBP (mmHg)			WC (cm)			HDL (mg/dL)			FBG (mg/dL)			Triglycerides (mg/dL)		
	≥130	<130	*P*-value	≥85	<85	*P*-value	≥102 (men) ≥88 (women)	<102 (men) <88 (women)	*P*-value	<40 (men) <50 (women)	≥40 (men) ≥50 (women)	*P*-value	≥100	<100	*P*-value	≥150	<150	*P*-value
PUFA (g/d)	21.5 (13.5)	20.3 (13.5)	0.270	21.4 (13.4)	20.5 (13.4)	0.851	20.7 (13.3)	20.8 (13.5)	0.782	20.8 (13.8)	20.8 (13.3)	0.938	21.0 (16.8)	20.8 (13.5)	0.893	21.4 (14.6)	20.7 (13.6)	0.114
SFA (g/d)	41.8 (24.5)	38.8 (21.8)	**0.001**	42.4 (24.8)	39.1 (21.8)	**0.030**	40.0 (23.4)	39.4 (22.4)	0.285	40.9 (24.6)	39.3 (22.4)	0.960	40.2 (23.9)	39.4 (22.3)	0.495	44.4 (21.8)	38.8 (22.3)	**<0.001**
Cholesterol (mg/d)	372.8 (214.9)	349.8 (197.1)	0.058	367.9 (220.8)	353.5 (198.8)	0.126	371.5 (215.3)	348.1 (206.5)	**<0.001**	381.8 (199.2)	349.8 (201.4)	**0.035**	376.7 (342.2)	351.1 (196.2)	**0.005**	402.9 (230.0)	344.7 (192.8)	**<0.001**
Phenolics (mg/d)	2,678 (1,474)	2,480 (1,707)	0.190	2,691 (1,667)	2,506 (1,642)	0.877	2,562 (1,754)	2,538 (1,617)	0.380	2,382 (1,627)	2,575 (1,616)	0.098	2,584 (1,465)	2,522 (1,659)	0.088	2,448 (1,790)	2,553 (1,632)	0.486
Beta-carotene (μg/d)	5,071 (4,451)	4,966 (4,004)	0.609	4,854 (4,111)	5,042 (4,027)	0.169	4,977 (3,990)	4,994 (4,143)	0.951	4,697 (4,122)	5,047 (3,959)	0.781	5,045 (3,977)	4,992 (4,095)	0.982	4,695 (3,774)	5,044 (4,112)	0.590
Sodium (mg/d)	3,512 (2,037)	3,193 (1,821)	**<0.001**	3,526 (2,156)	3,236 (1,830)	**0.005**	3,460 (1,940)	3,229 (1,936)	**0.003**	3,581 (1,840)	3,239 (1,918)	**0.001**	3,642 (2,248)	3,267 (1,891)	**0.008**	3,911 (2,201)	3,225 (1,842)	**<0.001**
Simple sugars (g/d)	107.6 (60.2)	98.7 (59.6)	**0.001**	101.6 (56.0)	100.6 (60.4)	0.602	101.6 (62.1)	100.5 (59.2)	0.717	98.5 (59.0)	101.4 (58.7)	0.813	99.8 (68.2)	100.9 (57.7)	0.603	107.7 (60.34)	99.7 (58.3)	**0.024**
Alcohol (g/d)	7.7 (13.8)	5.1 (10.1)	**0.001**	7.5 (14.7)	5.27 (11.1)	**0.001**	4.6 (11.1)	6.4 (12.0)	**0.028**	4.4 (8.2)	6.4 (12.2)	**0.004**	9.0 (16.8)	5.5 (11.0)	**0.002**	8.9 (17.1)	5.4 (10.9)	**<0.001**

Significant values are given in bold.

[a]All *P*-values are reported based on log-transformed data using the *t*-test.

[b]Fast foods and ready-to-eat meals.

IR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HDL, high-density lipoprotein cholesterol; FBG, fasting blood glucose levels; TG, triglycerides; Veg, vegetables; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; Phenolics, total phenolics.

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TABLE 4 Correlation of dietary indices MDS and AHEI with cardiometabolic biomarkers.

Variables	MDS		AHEI	
	CC	*P*-value*	CC	*P*-value*
BMI(kg/m^2)	−0.118	<**0.001**	−0.043	0.115
Insulin(μg/L)	−0.031	0.252	0.024	0.373
HbA1c(%)	0.020	0.462	0.046	0.093
HOMA-IR	−0.040	0.143	0.020	0.471
TG(mg/dL)	−0.068	**0.013**	−0.019	0.496
Total cholesterol(mg/dL)	−0.012	0.667	−0.014	0.614
LDL(mg/dL)	0.001	0.975	0.018	0.500
MDS			0.473	<**0.001**
AHEI	0.473	<**0.001**		

Presented as correlation coefficient (CC) and *P*-value.
*Spearman test, non-parametric correlation.
Significant values are given in bold.
Correlation is significant at the 0.05 level (2-tailed).
AHEI, alternative healthy eating index; MDS, Mediterranean diet score; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose levels; HbA1c, glycated hemoglobin; HOMA, homeostatic model assessment of insulin resistance; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

TABLE 5 Association of the dietary indices MDS and AHEI with MetS components, as derived by linear regression (beta non-standardized, 95% CI, *P*-value**, and strength of linear association R).

Dependent[a]/ Independent variable	Model-A					Model-B					Model-C Full				
	Beta	95% CI		*P*-value	*R*	Beta	95% CI		*P*-value	*R*	Beta	95% CI		*P*-value	*R*
BMI*/MDS	−0.0054	−0.0080	−0.0027	<**0.001**	0.106	−0.0050	−0.0075	−0.0024	<**0.001**	0.308	−0.0067	−0.0099	−0.0036	<**0.001**	0.375
WC/MDS	−0.0048	−0.0071	−0.0026	<**0.001**	0.113	−0.0039	−0.0059	−0.0020	<**0.001**	0.517	−0.0048	−0.0072	−0.0024	<**0.001**	0.559
FBG/MD	−0.0017	−0.0039	0.0005	0.136	0.041	−0.0015	−0.0036	0.0005	0.138	0.384	−0.0004	−0.0027	0.0017	0.673	0.427
TG/MD	−0.0095	−0.0170	−0.0020	**0.013**	0.068	−0.0071	−0.0142	−0.00006	**0.048**	0.335	−0.0026	−0.0115	0.0063	0.565	0.396
HDL/MDS	0.0017	−0.0021	0.0056	0.376	0.024	−0.0009	−0.0043	0.0025	0.596	0.476	−0.0001	−0.0043	0.0041	0.957	0.536
SBP/MDS	−0.0034	−0.0054	−0.0013	**0.001**	0.087	−0.0030	−0.0048	−0.0012	**0.001**	0.510	−0.0038	−0.0060	−0.0016	**0.001**	0.530
DBP/MDS	−0.0036	−0.0058	−0.0015	**0.001**	0.091	−0.0033	−0.0053	−0.0013	**0.001**	0.335	−0.0034	−0.0060	−0.0009	**0.008**	0.344
BMI*/AHEI	−0.0001	−0.0005	0.0002	0.460	0.020	0.0001	−0.001	0.0005	0.139	0.294	−0.0001	−0.002	−0.0002	**0.001**	0.263
WC/AHEI	0.0001	−0.0001	0.0005	0.351	0.025	−0.00003	−0.0003	0.0002	0.809	0.508	−0.0007	−0.0011	−0.0002	**0.002**	0.559
FBG/AHEI	−0.00008	−0.0004	0.0002	0.631	0.013	0.0002	−0.0005	0.00008	0.143	0.384	−0.0005	−0.0009	−0.00009	**0.017**	0.436
TG/AHEI	−0.0006	−0.0017	0.0005	0.297	0.028	−0.0010	−0.0020	0.00006	0.064	0.334	−0.0008	−0.0025	0.0008	0.324	0.359
HDL/AHEI	−0.0004	−0.0010	0.0001	0.123	0.042	−0.0002	−0.0007	0.0002	0.333	0.477	−0.00003	−0.0008	0.0007	0.933	0.506
SBP/AHEI	−0.00007	−0.0003	0.0002	0.634	0.013	−0.0002	−0.0005	0.000007	0.056	0.506	−0.0006	−0.0010	−0.0002	**0.004**	0.533
DBP/AHEI	−0.0003	−0.0006	−0.00009	**0.044**	0.054	−0.0004	−0.0007	−0.0001	**0.003**	0.333	−0.0005	−0.0010	−0.00009	**0.021**	0.345

[a]All dependent variables were entered in the models as log-transformed.
Model A: the dependent variable was one of the components, and the independent variable was one of the indices as the continuous score.
Model B: the dependent variable was one of the components, and the independent variables were one of the indices as the continuous score, in addition to age groups and gender as confounding factors.
Model C: the dependent variable was one of the components, and the independent variable was one of the indices as the continuous score, and the confounding factors were age group, gender, and all sociodemographic variables and selected anthropometric variables (education, job, income, marital status, and country of birth, physical activity, currently smoking, and total energy intake).
AHEI, alternative healthy eating index; MDS, Mediterranean diet score; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose levels; TG, triglycerides; HDL, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*The BMI is not a component of the MetS and is analyzed for additional information.
**Significant values are given in bold.

(Table 6) between both the MDS and the AHEI and MetS, which is more in line with the results of the MetS components. Both the MDS and AHEI were similarly associated with MetS regarding the regression coefficient and beta.

Our findings regarding blood pressure (BP) measurements are in line with previous research studies and meta-analysis outcomes that also showed an inverse association of the MDS with both SBP and DBP (43, 44). The effects of MD on BP may have several reasons. For instance, the MD is rich in polyphenols such as flavonoids that can improve the formation of nitric oxide, which can enhance vasodilation and endothelial function (45). Carotenoids, another group of secondary plant metabolites, could have anti-inflammatory factors that are also important for vessel health (46). In addition to acting in an antioxidant and anti-inflammatory fashion *via* transcription factors, this can also improve vessel health (47). The intake of fruits and vegetables and less processed foods lowers the burden of sodium intake, which has been strongly associated with BP (48). As in our study, polyphenol and also carotenoid intake did not differ between persons with and without MetS; perhaps the higher salt intake in persons with MetS could have rather been playing a more important role. Though not all studies found significant effects of MD on BP, e.g., in the study of Thomopoulos et al., it was argued that even a marginal effect could contribute to improved CVD risk, as 1 mm Hg improvement in BP can lead to a 2% improvement of CVD risk (49).

Regarding blood lipids, such as triglycerides and HDL-C, our results did not reveal an inverse association in our final adjusted model. Our finding is in line with the results by Godos et al., who found a non-significant association between MDS and TG (3). Other studies, though, have shown a significant inverse association between adherence to MD and TG (34). However, a systematic review concluded that the MD significantly influences HDL-C functionality (antioxidant and anti-inflammatory properties), size, and composition. Specifically, there was an expressed need to clarify MD-derived modulations of HDL-C regarding the determination of HDL-C subgroups, some of which are rather pro- (e.g., HDL2) and some anti-inflammatory (e.g., HDL3) (50). Therefore, our study's lack of significant results could be due to the lack of insights into relevant HDL-C subgroups, differing by size and lipid composition. In addition, it is likely that population differences and additional possible confounders, such as genetic background or environmental variables, might account for these differences in findings.

Fasting blood glucose, another hallmark component of MetS, did also not associate significantly with MD. This outcome is, on one side, similar to the findings of previous meta-analyses (3, 34). On the other side, Shah et al., in their meta-analysis, described the MD as the best anti-diabetic diet, as it significantly decreased the risk of T2D (51), which has been emphasized in the general literature, as reviewed previously (20). It is possible that FBG exhibited too high variability in the present study, and other markers, such as HbA1C, would have been a more suitable predictor of blood glucose status. FBG is also strongly influenced by physical activity (51), as are blood lipids; however, as we took it into account as a possible confounder, we do not think this perturbed our analysis.

Regarding the AHEI, our investigations found significant inverse associations between the AHEI and BMI, WC, FBG, and BP. These results are largely in accordance with previous findings from meta-analyses and research studies (52–56). Such results are not surprising because increasing the intake of healthy food groups, including fruits, vegetables, and unsaturated fat, and avoiding unhealthy food groups, such as red meat and saturated fat, can supply the body with vitamins and secondary plant metabolites such as polyphenols (e.g., flavonoids) and carotenoids that can improve vascular function, insulin sensitivity, thrombosis, and inflammation (57).

Comparing the association of the MDS and the AHEI with MetS components, it was found that the MDS had a similar association with all MetS components than the AHEI. For instance, improving both scores by one-third, i.e., 3 units in MDS score would reduce WC by 1.43%, and an increase in 25 units of AHEI would reduce WC by 1.74%. However, there are some differences in the scoring algorithm between MDS and the AHEI, such as the fish group that only exists in the MDS. Fish is rich in anti-inflammatory omega-3 fatty acids, which can improve the MetS and its components (58), while the AHEI scoring algorithm reflects the fatty acid as a ratio of MUFA to SFA. In this case, MDS may be more capable of capturing the benefit of fatty acids regarding the MetS thanks

TABLE 6 Association of MetS scores with MDS and AHEI, as calculated by linear regression (beta non-standardized, 95% CI, *P*-value*, and strength of linear association R).

Models	Dependent[a]/ Independent variable	Beta	*P*-value	95%CI		*R*
Model A	siMS/MDS	−0.062	**0.023**	−0.211	−0.016	0.062
	siMS/AHEI	−0.025	0.366	−0.021	0.008	0.025
	EFA/MDS	−0.125	<**0.001**	−0.365	−0.148	0.125
	EFA/AHEI	−0.047	0.085	−0.031	0.002	0.047
	MetSR/MDS	−0.086	**0.002**	−0.309	−0.073	0.086
	MetSR/AHEI	0.031	0.258	−0.008	0.028	0.031
Model B	siMS/MDS	−0.049	0.061	−0.184	0.004	0.277
	siMS/AHEI	−0.041	0.115	−0.026	0.003	0.276
	EFA/MDS	−0.122	<**0.001**	−0.344	−0.156	0.518
	EFA/AHEI	−0.079	<**0.001**	−0.038	−0.010	0.510
	MetSR/MDS	−0.054	<**0.001**	−0.189	−0.051	0.814
	MetSR/AHEI	−0.020	0.205	−0.017	0.004	0.812
Model C	siMS/MDS	−0.028	0.370	−0.176	0.066	0.384
	siMS/AHEI	−0.054	0.152	−0.037	0.006	0.385
	EFA/MDS	−0.118	<**0.001**	−0.346	−0.120	0.534
	EFA/AHEI	−0.133	<**0.001**	−0.059	−0.019	0.533
	MetSR/MDS	−0.053	**0.004**	−0.197	−0.039	0.848
	MetSR/AHEI	−0.056	**0.010**	−0.033	−0.004	0.848

[a]All dependent variables were entered in the models as log-transformed.
Model A: the dependent variable was one of the MetS Score, and the independent variable was one of the indices, as the continuous score.
Model B: the dependent variable was one of the MetS Score, and the independent variables were one of the indices as the continuous score, in addition to age groups and gender as confounding factors.
Model C: the dependent variable was one of the MetS Score, and the independent variable was one of the indices as the continuous score, and the confounding factors were age group, gender, and all sociodemographic variables and selected anthropometric variables (education, job, income, marital status, and country of birth, physical activity, currently smoking, and total energy intake).
*Significant values are given in bold.
siMS: MetS score; EFA: Exploratory factor analysis; MetSR: MetS based on regression models.

to its scoring algorithm that includes the fish group. Although fish intake did not differ between persons with MetS and those without, this differs when focusing on components of MetS. For example, participants with SBP higher than the ATP III cut-off (≥130) significantly consumed less fish and DHA than participants with SBP lower than the ATP III cut-off (<130) (**Table 3**). However, the intake of some food groups, such as fruits and vegetables, and in line with these, the intake of beta-carotene and polyphenols between people with and without MetS, as well as its components, were not significantly different.

The present study has limitations. First, it was a cross-sectional study; thus, no causality can be inferred from such epidemiological studies. This may be overcome in the future by prospective cohort studies or even randomized controlled trials. Second, our data was not fully representative of the Luxembourg population regarding age, BMI, and place of residence. Accordingly, the results cannot be generalized to the general population. This may be amended by future larger trials with superior stratification designs.

Moreover, Luxembourg's geographical location may influence the MD's operational definition and whether it can accurately reflect the typical Mediterranean dietary pattern in its original location. Therefore, there may be a need for an adapted MDS for non-Mediterranean countries (59). Last but not least, diet scores that adapt for energy as part of the scoring algorithm, namely "the relative MDS," may provide a stronger insight into how MD diet composition is related to body weight, which is—*via* WC—a core component of MetS. Still, we have selected to assess the more commonly used unadjusted scores. The same applies to the AHEI.

Strengths of the study include that a trained nurse collected the FFQ, which was not a self-ported questionnaire; thus, measurement bias was reduced. Moreover, using the FFQ as a tool for reporting dietary intake is more appropriate and precise than some other techniques, such as food records. The FFQ also contained a large number of food items (174 items), and it was matched with a local food composition database (Ciqual from France) to estimate nutrient intake. Finally, we had anthropometric measurements rather than relying on self-reported measures often used in similar large data sets, and a commercially accredited laboratory in Luxembourg carried out the biological measurements.

Conclusion

According to our knowledge, this is the first study to observe an association of the MDS and the AHEI with MetS and its components across Luxembourgish residents. Our study found significant inverse associations between MDS and BMI, WC, and blood pressure as components of MetS and, similarly, inverse associations between the AHEI and MetS components (BMI, WC, FBG, and blood pressure). It was also shown that a MetS severity score that is continuous was more aligned with findings from the components than the classical categorical definition. Accordingly, results support that adherence to the MD or healthy eating patterns can improve cardiovascular disease risk factors, including MetS. Further research is needed to examine the association of MDS and AHEI in more detail and focus on additional biomarkers of MetS components, such as markers of inflammation and/or oxidative stress. Finally, to validate that the MD and the AHEI might be taken as a first option for the primary prevention of MetS, more research on high-risk patients is needed, preferably within the frame of intervention studies.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by CNER–Comité National d'Ethique de Recherche. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FV and KA performed the statistical analyses, interpreted the data, and drafted the manuscript. FV and TB provided expertise and oversight on the intellectual content. TB was involved in critically reviewing the manuscript. 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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2022.1087985/full#supplementary-material

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Associations of adherence to Mediterranean-like diet pattern with incident rosacea: A prospective cohort study of government employees in China

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Background: Despite of growing evidence on gastrointestinal comorbidities of rosacea, there was a lack of literatures regarding the role of diet on rosacea.

Objectives: To investigate the relationship between adherence to a Mediterranean-like diet pattern and the risk of incident rosacea.

Methods: This was a prospective cohort study of government employees aged >20 years conducted between January 2018 and December 2021 from five cities of Hunan province of China. At baseline, participants completed a food frequency questionnaire and participated in a skin examination. Presence of rosacea was determined by certified dermatologists. Subsequent skin examinations during follow-up were performed every one-year interval since the entry of the study. The Mediterranean diet score (MDS) was generated based on seven food groups (whole grains, red meats, fish, raw vegetables, legumes, fruits and nuts). Binary logistic regression models adjusted for potential confounders were used to estimate risks for incident rosacea.

Results: Of the 3,773 participants who completed at least two consecutive skin examinations, 3,496 were eligible for primary analyses. With a total follow-up of 8,668 person-years, we identified 83 incident rosacea cases. After full adjustments for covariates, the MDS was associated a decreased risk of incident rosacea (aOR: 0.84, 95% CI: 0.72, 0.99; $P_{trend} = 0.037$ for 1-point increment of MDS). In subgroup analyses by body mass index (BMI), this inverse association was consistently observed in the lowest and medium tertiles of BMI (<24.5 kg/m^2), but not in the highest tertile of BMI (≥24.5 kg/m^2), with a significant interaction effect ($P < 0.001$).

Conclusions: Our results suggested that adherence to a Mediterranean-like diet pattern might reduce the risk of incident rosacea among non-overweight individuals.

KEYWORDS

rosacea, Mediterranean diet, incidence rate, diet pattern analysis, anti-inflammatory

Introduction

Rosacea is recognized as a common chronic inflammatory skin syndrome encompassing a variety of signs or symptoms, which affects 5.46% of the general population over the world (1, 2). Although the exact pathogenesis of rosacea still remains unclear, it's found that both genetic and environmental factors contributed to development of the disease (3). In one survey conducted by the National Rosacea Society, several dietary factors including heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related, were reported as rosacea triggers by patients (4), which suggested the diet might play an important role in rosacea. What's more, epidemiological studies have demonstrated that compared to healthy subjects, patients with rosacea had a higher prevalence of gastrointestinal (GI) disease, such as *Helicobacter pylori* infection (HPI), small intestinal bacterial overgrowth (SIBO), and irritable bowel syndrome (IBS) (5, 6). These findings further emphasized the importance of carrying out dietary interventions to decrease the risk of GI comorbidities. However, there was a lack of literatures regarding the role of dietary factors on the development of rosacea, (4) with few studies only focusing on effects of single nutrients or food groups (7, 8).

The Mediterranean diet (MD) is a healthy diet pattern characterized as high intake of fruits, vegetables, whole grains, fish, legumes, and nuts; moderate consumption of alcohol; low intake of red or processed meats, and using olive oil as the main source of fat (9, 10). A meta-analysis has shown that greater adherence to MD was associated with decreased incidence of many chronic diseases (e.g., cancer, Parkinson's disease, and Alzheimer's disease) (11, 12). Epidemiology studies also demonstrated that adherence to the MD pattern reduced the mortality caused by a series of metabolic diseases, such as cardiovascular disease and type 2 diabetes (13–15). The underlying mechanisms could partially be explained by the anti-inflammatory capacity of MD (16). Meanwhile, the MD pattern had also shown protective roles on severity or development of certain inflammatory skin disorders like acne and psoriasis (17–20). Similarly, higher levels of pro-inflammatory serum markers like C-reaction protein (CRP) in rosacea patients indicated the involvement of both cutaneous and systemic inflammation in the pathogenesis of rosacea (21–23).

Combining this evidence, we hypothesized that MD might also have an effect on the onset of rosacea. The objective of the current study was therefore to investigate the relationship between a score reflecting adherence to MD and the risk of incident rosacea in a prospective cohort of government employees. The traditional MD score was mainly applied in Mediterranean countries like Greece or for samples of elderly participants (24). To adapt the score to Chinese population, we selected the alternate Mediterranean Diet (aMed) score established by Fung et al. to evaluate adherence to MD in our study (25).

Materials and methods

Study design and population

This was a population-based prospective cohort study conducted from January 2018 to December 2021 in five cities (Changsha, Zhuzhou, Xiangtan, Huaihua, and Changde) of Hunan province, China. On the basis of informed consent, a total of 11,523 government employees aged >20 years from 25 organizations were enrolled. At baseline, they completed a questionnaire collecting information on demographic, socioeconomic, and lifestyle behaviors and participated in a dermatological physical examination at the same time. Subsequent skin examinations were performed every one-year interval since their enrollment of the study to update their skin health status during the follow-up period.

The follow up began on the date the questionnaires were returned or the first physical examinations were performed (baseline). Participants contributed person-time from baseline until the date of the first-time rosacea diagnosis during follow-up or the date of last-time physical examination (due to loss to follow up or the end of the study), whichever came first.

In the current study, we only included participants who completed at least two consecutive dermatological physical examinations ($n = 3773$). Thus, the follow-up time of participants ranged from 1 to 4 years. The study procedures were approved by the institutional research ethics boards of Xiangya School of Public Health, Central South University (XYGW-2016-10).

Outcome ascertainment

The presence of rosacea was determined by certified dermatologists from local tertiary hospitals in each dermatological physical examination. In the field survey, clinical manifestation, disease history, and family history of participants were inquired, and dermatologists made an accurate diagnosis of rosacea based on the diagnostic criteria established by the National Rosacea Society Expert Committee in 2017 (at least 1 diagnostic or 2 major phenotypes were required) (2).

Dietary assessment and Mediterranean diet score calculation

The weekly average frequency of dietary intake for different food groups over the preceding year of enrollments was assessed by a self-reported semi-quantitative food frequency questionnaire (FFQ) at baseline. Each food groups had 5 possible frequency of intake responses in the FFQ: rarely, <1 time/week, 1–3 days/week, 4–6 days/week and every day. The Mediterranean diet score (MDS) applied in this study was adopted from the aMed score posted by Fung et al. (25). As alcohol drinking was associated with increased risks of incident rosacea even under low doses of daily intake, it was not included in the MDS calculation (26). Due to the availability of data, ratio of monounsaturated to saturated fat was also excluded. Eventually, our MDS consisted of seven components of food groups: whole grains, red meats, fish, raw vegetables, legumes, fruits, and nuts. Each component was assigned with point 0 or 1 using sex-specific medians of food intake frequency categories as cut-offs. For presumed beneficial food groups (whole grains, fish, raw vegetables, legumes, fruits, and nuts), participants whose intake was below the median categories received a point of 0, and a point of 1 otherwise. For presumed detrimental food groups (red meats), participants whose intake was below the median categories received a point of 1, and a point of 0 otherwise. Thus, the possible MDS ranged from 0 to 7, with higher score representing closer adherence to the

Mediterranean diet pattern. We additionally separated participants by approximately tertiles of MDS into three groups: low (0–3), medium (4–5), and high (6–7).

Covariates

Information on socioeconomic characteristics (education level, annual household income) and behaviors (smoking status, alcohol drinking status, frequency of sunbath, frequency of physical exercise) was collected by questionnaires at baseline. New variables were created when including cigarette smoking and alcohol drinking for adjustments in multivariable models by further including information on daily average consumption of cigarettes and frequency of drinking per week in current smokers and drinkers. The body mass index (BMI) was calculated by dividing individuals' weight in kilograms by the square of their height in meters which were obtained from physical examination.

Statistical analysis

Descriptive statistics were performed to summarize participants' characteristics at baseline stratified by categories of MDS. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as number (%). Between-group differences were tested by ANOVA or chi-square test for continuous and categorical variables. We used binary logistic regression models to assess the association between incident rosacea and variables of interests and calculated the odds ratio (OR) and 95% confidence interval (CI).

First, we evaluated the association of incident rosacea with each component of food groups in the MDS separately. Those food intake frequency groups with small sample sizes were merged into one group where appropriate to achieve approximately tertiles and the lowest tertiles were treated as reference groups. Then, we investigated the association of MDS with risks of incident rosacea using MDS categories with lowest (0–3) adherence to MD as reference. A *P*-value for trend across MDS categories was calculated by treating MDS as a continuous variable. We also applied natural cubic splines to examine potential non-linear or linear relationships between MDS and incidence of rosacea. As the obesity was reported as a risk factor for incident rosacea in previous study, (27) we additionally tested effect modification by BMI by adding an interaction term between MDS and BMI into logistic models. We then stratified the analyses by tertiles of BMI. Subgroup analyses by other potential covariates were also performed.

To test the robustness of the primary analyses, we performed sensitivity analyses by (1) excluding participants who made significant changes on dietary or lifestyle habits last year before the entry of the study, or (2) excluding participants with prevalent or incident acne vulgaris, contact dermatitis or seborrheic dermatitis which were considered as differential diagnoses of rosacea for patients with skin of color (28).

We used principal component analysis (PCA) to extract components of intake frequency of other dietary factors not associated with calculation of MDS in our FFQ (rice, pasta, poultry, eggs, dairy products, pickles, deserts, and marinated or smoked fish) with eigenvalues >1, for the purpose of addressing the collinearity issues among dietary factors when being included in multivariate models. All basic models were adjusted by age and sex, and the fully adjusted models were further adjusted by education level, annual household income, BMI, cigarette smoking, alcohol drinking, sunbath, physical exercise, and specially, the principal components of other dietary factors not associated with calculation of MDS to reduce residual confounding. Participants with missing data on dietary intake frequency associated with calculation of MDS was eliminated, while missing data on covariates was imputed by multiple imputation.

All statistical analyses were performed using R software (version 4.1.3). A $P < 0.05$ was considered significant.

Results

Baseline characteristics stratified by MDS categories

After excluding participants with unavailable follow-up time ($n = 68$), prevalent rosacea ($n = 51$), and missing data on dietary intake frequency ($n = 158$), there were a total of 3,496 participants included in the primary analyses (Supplementary Figure S1). During a median follow-up of 2 years (interquartile range: 2–3 years; 8,668 total person-years), we identified 83 incident rosacea cases (incidence rate: 9.58 per 1,000 person-years). The baseline characteristics of participants stratified by MDS categories were shown in Table 1. Among 3,496 eligible participants, 23.3, 45.8, and 30.9% of them were categorized into low, medium, and high adherence to Mediterranean diet pattern groups. Compared to participants with either low or medium adherence to MD, those in the high adherence group had older age, higher education level, annual household income, and frequency of physical exercise, and lower rate of current smokers (all *p*-values <0.05). We extracted three components from other dietary factors not associated with calculation of MDS, accounting for 33.6, 16, and 13% of the total variance, respectively (Supplementary Figure S2).

Food groups and incident rosacea

Associations between intakes of each food groups from MDS and incident rosacea were reported in Table 2. Taken individually, we observed that the intake of whole grains with ≥4 days/week was associated with a decreased risk of incident rosacea compared to the lowest intake frequency group (<1 time/week) in both basic model and fully adjusted model (aOR: 0.37; 95%CI: 0.17, 0.84). However, no significant association was found for other food groups in fully adjusted models.

Mediterranean diet score and risks of incident rosacea

In the whole study population, we observed an inverse association between MDS and the risk of incident rosacea in both basic and fully-adjusted models (aOR: 0.84, 95%CI: 0.72, 0.99; $P_{trend} = 0.037$ for 1-point increment of MDS) (Table 3). Cubic splines revealed

TABLE 1 Baseline characteristics of the study population according to MDS categories ($n = 3496$).

Characteristics	Mediterranean diet score			*P*-value	Missing value
	Low (0-3)	Medium (4-5)	High (6-7)		
Participants, *n* (%)	816 (23.3)	1602 (45.8)	1078 (30.9)		
Age (year), mean ± SD	38.05 ± 9.08	38.50 ± 9.25	39.53 ± 9.30	0.001	
Sex, *n* (%)				0.072	
Male	354 (43.4)	676 (42.2)	416 (38.6)		
Female	462 (56.6)	926 (57.8)	662 (61.4)		
BMI (Kg/m^2), mean ± SD	23.39 ± 3.75	23.46 ± 3.58	23.47 ± 3.71	0.866	1
Annual household income (CNY), *n* (%)				<0.001	1
<50,000	121 (14.8)	177 (11.0)	119 (11.0)		
50,000 ∼ 100,000	241 (29.6)	398 (24.8)	269 (25.0)		
100,000 ∼ 200,000	286 (35.1)	617 (38.5)	392 (36.4)		
>200,000	167 (20.5)	410 (25.6)	298 (27.6)		
Education level, *n* (%)				<0.001	384
High school and below	55 (7.7)	77 (5.4)	45 (4.6)		
Undergraduate degree	461 (64.3)	772 (54.3)	507 (52.2)		
Postgraduate degree and above	201 (28.0)	574 (40.3)	420 (43.2)		
Smoking status, *n* (%)				0.003	193
Non-smoker	640 (83.4)	1307 (86.4)	918 (89.6)		
Current smoker	109 (14.2)	175 (11.6)	85 (8.3)		
Past smoker	18 (2.3)	30 (2.0)	21 (2.1)		
Alcohol drinking status, *n* (%)				0.242	
Non-drinker	700 (85.8)	1413 (88.2)	961 (89.1)		
Current drinker	108 (13.2)	173 (10.8)	107 (9.9)		
Past drinker	8 (1.0)	16 (1.0)	10 (0.9)		
Frequency of physical exercise, *n* (%)				<0.001	263
Rarely	456 (61.3)	719 (48.1)	359 (36.1)		
1–2 times/week	176 (23.7)	396 (26.5)	316 (31.8)		
≥ 3 times/week	112 (15.1)	380 (25.4)	319 (32.1)		

CNY, Chinese Yuan; MDS, Mediterranean diet score; SD, standard deviation.

a negative linear relationship between MDS and the incidence of rosacea (Figure 1).

Subgroup analysis

Since an interaction effect between BMI and MDS was detected ($P_{interaction} < 0.001$), we further stratified the analyses by tertiles of BMI shown in Table 4 (two participants eliminated with missing value or extremely low value on BMI). Among participants in tertile 1 (BMI < 21.8) and tertile 2 (BMI range: 21.8–24.5), we consistently found inverse associations between MDS and incident rosacea in fully-adjusted models ($P_{trend} = 0.018$ and 0.023, respectively). However, no significant protective effects of MDS were observed in those with highest tertile of BMI (tertile 3: BMI ≥ 24.5) in both the basic model and fully-adjusted model. Subgroup analysis by other covariates was presented in Figure 2.

Sensitivity analysis

The results of primary analyses remained stable when excluding participants with significant lifestyle or dietary modifications over the preceding year, or excluding participants with skin disorders that were differential diagnoses of rosacea (Supplementary Table S1).

Discussion

In this population-based prospective cohort of Chinese government employees, we observed an inverse association between adherence to MD and risks of incident rosacea. This association was consistently present in groups with lowest and medium tertiles of BMI (BMI < 24.5 Kg/m^2), but not in group with highest tertile of BMI (BMI ≥ 24.5 Kg/m^2). To our knowledge, this was the first study to report a positive association between MD and rosacea.

TABLE 2 Associations of each food groups from MDS with incident rosacea ($n = 3496$).

	Total no. of participants	No. of cases of rosacea/person-years	Incidence rate (per 1000 person-years)	Model 1		Model 2	
				aOR (95%CI)	P	aOR (95%CI)	P
Total	3,496	83/8668	9.58				
Whole grains							
<1 time/week	1,489	44/3711	11.86	Reference		Reference	
1–3 days/week	1,308	31/3243	9.56	0.73 (0.46, 1.17)	0.190	0.73 (0.45, 1.18)	0.196
≥4 days/week	699	8/1714	4.67	0.37 (0.17, 0.79)	0.011	0.37 (0.17, 0.84)	0.017
Red meats							
≤3 days/week	1,164	35/2907	12.04	Reference		Reference	
4-6 days/week	878	15/2199	6.82	0.60 (0.32, 1.11)	0.102	0.67 (0.35, 1.26)	0.209
Everyday	1,454	33/3562	9.26	0.83 (0.51, 1.34)	0.438	0.96 (0.55, 1.67)	0.892
Fish							
Rarely	506	18/1222	14.73	Reference		Reference	
<1 time/week	1,378	33/3483	9.47	0.62 (0.34, 1.12)	0.111	0.69 (0.37, 1.27)	0.235
≥1 day/week	1,612	32/3963	8.07	0.54 (0.30, 0.97)	0.041	0.61 (0.32, 1.17)	0.137
Raw vegetables							
≤3 days/week	457	15/1182	12.69	Reference		Reference	
4-6 days/week	681	19/1719	11.05	0.89 (0.44, 1.77)	0.732	0.90 (0.44, 1.84)	0.781
Everyday	2,358	49/5767	8.50	0.64 (0.35, 1.19)	0.158	0.68 (0.35, 1.33)	0.259
Legumes							
<1 time/week	877	26/2147	12.11	Reference		Reference	
1–3 days/week	1,659	40/4150	9.64	0.77 (0.46, 1.27)	0.305	0.77 (0.46, 1.31)	0.343
≥4 days/week	960	17/2371	7.17	0.58 (0.31, 1.08)	0.084	0.59 (0.29, 1.21)	0.149
Fruits							
≤3 days/week	1,512	36/3720	9.68	Reference		Reference	
4-6 days/week	779	15/1947	7.70	0.66 (0.36, 1.22)	0.182	0.73 (0.39, 1.37)	0.322
Everyday	1,205	32/3001	10.66	0.89 (0.54, 1.45)	0.628	1.05 (0.61, 1.80)	0.854
Nuts							
<1 time/week	1,324	36/3249	11.08	Reference		Reference	
1-3 days/week	1,459	29/3643	7.96	0.66 (0.40, 1.08)	0.096	0.72 (0.43, 1.22)	0.222
≥4 days/week	713	18/1776	10.14	0.85 (0.47, 1.52)	0.575	1.00 (0.51, 1.98)	0.990

Model 1: Adjusted by age and sex. Model 2: Further adjusted by education level, annual household income, BMI (continuous), cigarette smoking (never, past, or current smoking of 1–14, 15–20, or >20 cigarettes/d), alcohol drinking (rarely, past, or current drinking of 1, 2-4, or ≥ 5 times/week), sunbath (rarely, sometimes, and frequently), frequency of physical exercise, and principal components of other dietary factors.

In this study, the incidence rate of rosacea was 9.58 per 1,000 person-years. Previously, only one study from U.K.-based General Practice Research Database had reported an incidence rate of rosacea (1.65 per 1,000 person-years), which was notably lower than our study (1, 29). However, the ascertainment of rosacea from this database was performed by general practitioners in primary care and diagnoses were primarily based on visible symptoms due to lacking diagnostic guidelines, thus leading to underestimate of the incidence rate for missing cases with mild rosacea (29). By contrast, presence of rosacea in this study was determined by certified dermatologists in field survey for all enrolled participants based on the latest diagnostic criteria combining presenting cutaneous signs and personal history, which allowed us to assume a higher diagnostic accuracy (2). Moreover, to address the concern of misdiagnosis, we also performed sensitivity analysis by excluding participants with skin disorders that were considered as differential diagnoses of rosacea.

As mentioned before, prior studies investigating the role of diet on rosacea mainly focused on single nutrients or food components. For instance, a case-control study with 1,347 rosacea patients and 1,290 controls reported a positive correlation between high-frequency intake of fatty food and tea and risks of rosacea, while high-frequency intake of dairy products showed a negative correlation (7). In our analyses of single food components, we only observed a significant inverse association between intakes of whole grains and incident rosacea. However, there seemed to be a negative but non-significant correlation between higher intake frequency of other

TABLE 3 Associations of Mediterranean diet score with incident rosacea (*n* = 3496).

	Mediterranean diet score			Per 1-point increment of MDS	*P-value* for trend
	Low (0-3)	Medium (4-5)	High (6-7)		
No. of Cases of Rosacea/Person-Years	29/2029	33/3974	21/2665		
Incidence Rate (Per 1000 Person-years)	14.29	8.30	7.88		
Age- and sex-adjusted OR (95% CI)	Reference	0.56 (0.34, 0.94)	0.52 (0.29, 0.92)	0.83 (0.72, 0.96)	0.010
Multivariate adjusted OR (95% CI) *	Reference	0.58 (0.34, 1.00)	0.55 (0.28, 1.06)	0.84 (0.72, 0.99)	0.037

*Models were further adjusted by education level, annual household income, BMI (continuous), cigarette smoking (never, past, or current smoking of 1–14, 15–20, or >20 cigarettes/d), alcohol drinking (rarely, past, or current drinking of 1, 2-4, or ≥ 5 times/week), sunbath (rarely, sometimes, and frequently), frequency of physical exercise, and principal components of other dietary factors.

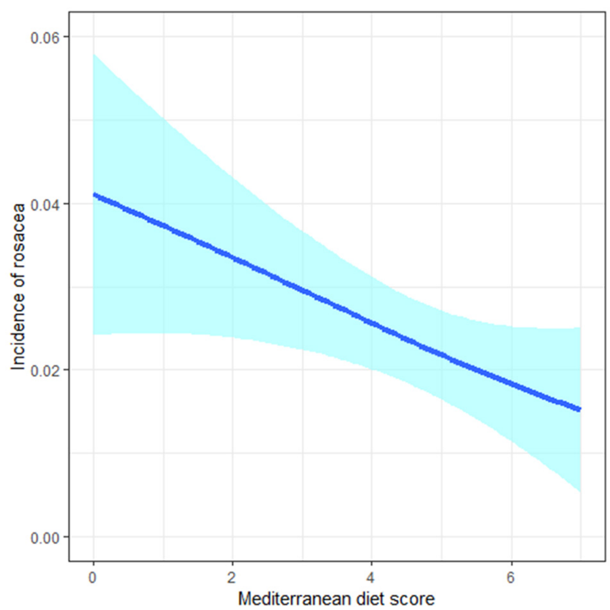

FIGURE 1
The negative linear relationship between the Mediterranean diet score and incidence of rosacea in cubic splines.

beneficial components of MD and the incidence of rosacea. This could partially be explained that the effect of single food components might be too small to detect among individuals, while a dietary pattern approach examining cumulative effects of multiple nutrients or food components was feasible to identify overall effects. What's more, dietary pattern analysis considered the issues of complex interactions and correlations among nutrients (30).

Although the mechanism of health benefits of MD had not been fully understood, several hypotheses could be considered when interpreting our results. First, the MD exerted antioxidative properties. It's known that oxidative stress plays a role in the pathogenesis of rosacea. Individuals with rosacea were confirmed to have higher serum peroxide levels and lower serum antioxidative potential levels (31). Takci et al. (32) also demonstrated that rosacea patients had decreased activity of Paraoxonase-1 (PON1), an antioxidant enzyme, and higher levels of serum lipid hydroperoxide (32). Multiple components of MD, including nuts, fruits, and vegetables, have been proven effective in increasing PON1 activity and reducing lipid peroxidation (33). Second, the MD pattern exhibited an anti-inflammatory capacity. The elevated levels of chemokines and CRP in serum (21, 34). and pro-inflammatory cytokines (IL-8, IL-1β, TNF-α) in skin lesions implied that rosacea was not only a cutaneous inflammatory skin disorder but also with low-grade systemic inflammation (22, 35). Interestingly, diet intervention studies revealed inverse associations between MD and almost all inflammatory biomarkers which indicated the capacity of MD to reduce low-grade inflammation (36). This was potentially mediated by modulation of the gastrointestinal (GI) microbiota. Altered GI microbiota, a pivotal element of gut-skin axis, has been observed by emerging studies in rosacea and might be responsible for increased risks of GI comorbidities in rosacea (37, 38). Multiple nutrients from MD, including polyphenols, polyunsaturated fatty acids (PUFAs) and fiber, contribute to modulations of the gut microbiota both in the aspects of diversity and inflammatory response (39). For example, the ω-3 PUFAs, rich in fish and nuts, could induce increases of several short-chain fatty acid-producing intestinal bacteria thus leading to suppression of inflammation, (40, 41) and was reported effective in the treatment of ocular rosacea (42). In addition, the MD was also associated with an increased abundance of fiber-degrading bacteria in GI microbiota and lower levels of intestinal inflammation (43). We hypothesized that a chronic subclinical inflammation caused by obesity might counterbalance the anti-inflammatory capacity of MD, which could explain the interaction effects between BMI and MDS (16, 27).

Our study encompassed several strengths and limitations. The strengths included the prospective study design, the dermatologists-based rosacea diagnoses, annually-renewable skin health status, and the availability of various epidemiological factors which allowed us to adjust for potential confounders and performed sensitivity analyses based on multiple conditions. In the meanwhile, we also acknowledged the existence of several limitations in our study. First, this study had a high rate of loss to follow-up (referring to those excluded for only attending skin examinations at baseline) and this population represented a lower level of education and income compared to those included in primary analyses (Supplementary Table S2). As a result, even though we adjusted the models with education, income and lifestyle factors, the selection bias was inevitable, and it should be interpreted with caution when generalizing our results to the public population. Second, our study was limited by short periods of follow-up and few cases of incident rosacea. However, a short-time study duration ensured the stability of dietary habits of participants during follow-up. Moreover, we also applied sensitivity analyses by excluding participants with dietary modifications to minimize the measurement error of dietary intake by FFQ. Third, it's worth noting that due to the availability of data, our MDS didn't include the variable of monounsaturated fat (MUFA) to

TABLE 4 Subgroup analysis for the associations of MDS with incident rosacea by tertiles of BMI ($n = 3494$).

	Total no. of participants	No. of cases of rosacea/person-years	Incidence rate (per 1000 person-years)	Model 1		Model 2	
				aOR (95%CI)	*P*	aOR (95%CI)	*P*
Tertile 1 (<21.8)	1,164	36/2993	12.03				
Low (0–3)	278	14/730	19.18	Reference		Reference	
Medium (4–5)	539	17/1388	12.25	0.60 (0.29, 1.23)	0.163	0.66 (0.30, 1.48)	0.318
High (6–7)	347	5/875	5.71	0.26 (0.09, 0.74)	0.012	0.31 (0.10, 0.99)	0.047
Per 1-point increment of MDS				0.72 (0.58, 0.89)		0.74 (0.58, 0.95)	
P_{trend}				0.002		0.018	
Tertile 2 (21.8-24.5)	1,165	26/2843	9.15				
Low (0–3)	268	11/651	16.90	Reference		Reference	
Medium (4–5)	512	9/1255	7.17	0.42 (0.17, 1.02)	0.056	0.36 (0.14, 0.95)	0.038
High (6–7)	385	6/937	6.40	0.36 (0.13, 0.99)	0.047	0.27 (0.08, 0.91)	0.035
Per 1-point increment of MDS				0.76 (0.59, 0.96)		0.71 (0.53, 0.95)	
P_{trend}				0.022		0.023	
Tertile 3 (≥24.5)	1,165	21/2826	7.43				
Low (0–3)	270	4/648	6.17	Reference		Reference	
Medium (4–5)	549	7/1325	5.28	0.79 (0.23, 2.76)	0.717	0.93 (0.25, 3.45)	0.912
High (6–7)	346	10/853	11.72	1.77 (0.54, 5.76)	0.345	2.35 (0.62, 8.97)	0.210
Per 1-point increment of MDS				1.26 (0.90, 1.75)		1.36 (0.95, 1.93)	
P_{trend}				0.175		0.090	

Model 1: Adjusted by age and sex. Model 2: Further adjusted by education level, annual household income, cigarette smoking (never, past, or current smoking of 1–14, 15–20, or >20 cigarettes/d), alcohol drinking (rarely, past, or current drinking of 1, 2-4, or ≥ 5 times/week), sunbath (rarely, sometimes, and frequently), frequency of physical exercise, and principal components of other dietary factors.

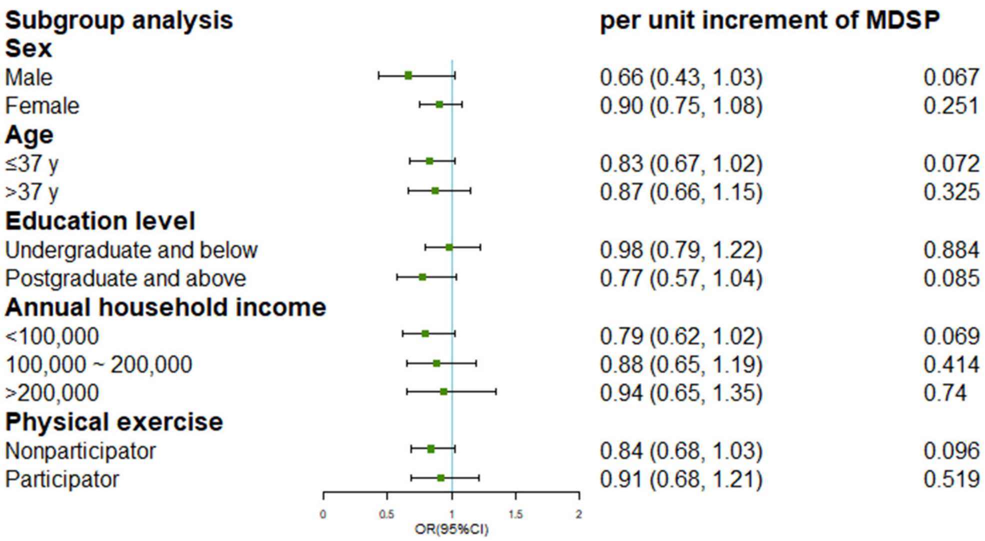

FIGURE 2
Subgroup analysis for the association of Mediterranean diet score and incident rosacea by potential covariates.

saturated fat (SFA) ratio thus only representing a Mediterranean-like diet pattern. Nevertheless, this parameter could partially be reflected by the intakes of nuts and meat products which were rich in MUFA and SFA, respectively (44, 45). The efficacy of unsaturated fat in rosacea treatment also allowed us to assume an underestimate of protective effects of the Mediterranean diet on rosacea (42).

Conclusion

In summary, this study indicated that adherence to a Mediterranean-like diet pattern was associated with lower risks of incident rosacea among non-overweight individuals. Our results needed to be verified in other population-based prospective cohort studies with larger sample sizes, longer follow-up periods and quantitative measurement on foods or nutrients intake.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xiangya Hospital, Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PC drafted the manuscript and analyzed the data. ZY, ZF, BW, YT, YX, DL, and SX participated in the field investigation. MS and HX designed the study. MS, HX, XC, and JL obtained the funding. All authors participated in the data collection, critically revised the manuscript, and gave final approval to the version submitted 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1092781/full#supplementary-material

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A bibliometric analysis of Mediterranean diet on cancer from 2012 to 2021

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Background: Numerous studies have demonstrated the value of the Mediterranean diet (MD) as a nutritious eating regimen for lowering the risk of cancer. This study aims to discuss the research patterns, existing state, and possible hotspots in implementing the MD for the prevention and treatment of cancer using bibliometrics.

Methods: The Web of Science Core Collection (WoSCC) was searched for articles on cancer that were related to the MD. CiteSpace, VOSviewer, Microsoft Excel 2019, and R software were utilized for bibliometric analysis and data visualization.

Results: There were 1,415 articles and reviews published from 2012 to 2021. Annual publication volume showed a continuous upward trend. Italy and Harvard University were the country and institution, respectively, with the highest number of publications on this topic. Nutrients ranked first in the number of documents, number of citations, and the *H*-index. James R. Hebert was the most productive writer, and Antonia Trichopoulou was the most co-cited author. "Alcohol consumption," "oleic acid," and "low density lipoprotein" were keywords used in earlier publications, while more recent hotspots focused on "gut microbiota," "older adult," and "polyphenol."

Conclusion: Over the past decade, research on the MD in the field of cancer has received increasing attention. To improve the level of evidence for the beneficial effects of the MD on a range of cancers, more research on molecular mechanisms and better clinical studies are required.

KEYWORDS
Mediterranean diet, cancer, bibliometric analysis, VOSviewer, CiteSpace

1. Introduction

Cancer is one of the leading causes of death worldwide, accounting for roughly 10 million deaths in 2020, or nearly one-sixth of all deaths. By 2040, there are expected to be 28.4 million instances of cancer worldwide (1, 2), accounting for an increasing impact and burden of cancer on public health at a global scale (3). Numerous studies have demonstrated that people are becoming increasingly aware of the positive effects of diet on cancer (4, 5). The Mediterranean diet (MD) was first proposed by Keys (6), who later identified that the monounsaturated fatty acids in the MD are effective in lowering mortality due to coronary heart disease. After decades of development, the MD has become defined as a comprehensive lifestyle that includes daily physical activity and that is based on a diet that includes a higher intake of whole grains, vegetables, and fruits. The MD includes olive oil as the main source of fat and fish and white meat as the main sources of protein. It also encourages the consumption of nuts and a small amount of red wine (7). Studies have become increasingly concentrated on the beneficial effects of the MD on cancer (8).

The beneficial effects of the MD on breast cancer (BC) (9, 10), colorectal cancer (CRC) (11, 12), lung cancer (13, 14), prostate cancer (15–17), and other cancers have been confirmed.

American bibliographer Pritchard (18) originally introduced the concept of bibliometrics in 1969. Bibliometrics uses philological, mathematical, and statistical methods to quantitatively investigate the macroscopic rules of literature and can swiftly establish the current state and future potential development trends and hotspots of a research field by processing information such as countries/regions, institutions, journals, authors, references, and keywords (19).

Despite the large number of studies on the impact of the MD on cancer, the general developmental process, current state, hotspots, and future trends in this field are unknown. This study carefully synthesizes pertinent research over the last 10 years using bibliometrics to correctly depict and analyze the entire breath of research on the MD in the field of cancer.

2. Materials and methods

2.1. Data source and search strategy

Data was obtained from the Science Citation Index Expanded (SCI-EXPANDED) edition in the Web of Science Core Collection (WoSCC). To avoid errors caused by WoS database upgrades, all data searches and exports were performed on 7 December 2022. The search strategy was as follows: #1 Topic = (cancer*) OR (its synonyms); #2: Topic = ("MD") OR (its synonyms); and incorporation of #1 AND #2. From 2012 to 2021, the language was limited to English. Article type was limited to original research and review articles. The detailed search strategy and data filtering process are shown in **Figure 1**.

2.2. Data analysis, visualization, and analysis index

Full records and cited references were downloaded for all documents obtained from WoSCC, which were received in TXT or BibTeX format. The bibliometrix package (20) in the R software (version 4.1.0) was used for extraction and statistical analysis of data (e.g., count/citation, title, abstract, publication year, source, author, country/region, and keyword). Microsoft Excel 2019 was used for data statistics that examined the volume of annual publications and their trends.

VOSviewer and CiteSpace are commonly used bibliometric and visualization software platforms (21, 22). VOSviewer (version 1.6.18) (23) is utilized for visual analysis of co-occurrence networks of countries/regions and institutions. CiteSpace (5.8.R3) (24) was developed by Professor Chaomei Chen and was originally designed for co-citation analysis and later extended to a variety of other functions. CiteSpace was employed for author and reference co-citation analysis, author co-authorship network analysis and visualization, keyword-related analysis and visualization, and dual-map overlap analysis of journals (25). Additionally, the R software circlize package (26) and ComplexHeatmap package (27) were used to partially show the country/region distribution of publications and collaborations. The number of documents or citations is indicated by the node size in CiteSpace and VOSviewer, with a larger node indicating more publications or citations. Relationships of collaboration, co-occurrence, or co-citation are represented by lines connecting the nodes. In CiteSpace, different node colors indicate different years; circles with a range of colors from the inside to the outside represent the years 2012 to 2021. The outermost purple ring indicates that the node has a very high centrality, which is usually regarded as a turning point between distinct yields. Impact factor (IF) and quartiles were obtained from the Journal Citation Report (JCR) 2021 and Quartile List as significant indicators of the study's scientific worth. The *H*-index (28) was defined as the number of citations of at least *h* papers greater than *h* by an independent individual. It is used as an effective indicator to evaluate the academic influence for assessing both the quantity and quality of independent individuals such as countries/regions, institutions, journals, and authors.

3. Results

3.1. Annual publication volume and trend

Our search strategy identified a total of 1,415 papers, including 989 articles (68.99%) and 426 reviews (30.11%), related to the MD and cancer. The annual publication volume and trends in the field of the MD on cancer are illustrated in **Figure 2**. It is clear that over the past 10 years, the number of publications in this field has gradually increased, rising from 69 in 2012 to 219 in 2021. The overall trend in this area continues to rise, demonstrating that research on the effect of MD on cancer is at a stage of sustained positive development, and there will likely be a significant number of relevant studies in the future.

3.2. Distribution of countries/regions and institutions

A total of 77 different countries and 2,123 institutions participated in the study of the effects of the MD on cancer. **Table 1** lists the top 10 countries/regions for scientific research production. Most publications were produced in Italy (428), followed by the United States (414), Spain (268), the United Kingdom (138), and Greece (98). **Figure 3A** displays the geographical distribution of publications by countries/regions. The top five countries/regions' trajectory from 2012 to 2021 is shown in **Figure 3B**. Italy had the highest annual output and the fastest growth, while the United States and Spain have consistently maintained high output levels. **Figure 3C** depicts the cooperation between countries/regions. Italy was the country with the most active international cooperation, and the most common cooperation occurred between Italy and the United States. **Figure 4A** displays the network of international cooperation between countries/regions and the average publication time. Iran, Singapore, and the Republic of Korea have produced publications in this field in recent years (yellow nodes). **Table 1** lists the top 10 research institutions by production, with Harvard University in the United States ranking first, followed by the University of Milan, Barcelona University, University of Navarre, and Granada University. With four institutions each in Italy and Spain, Italy and Spain housed the most institutions among the top 10 research institutions

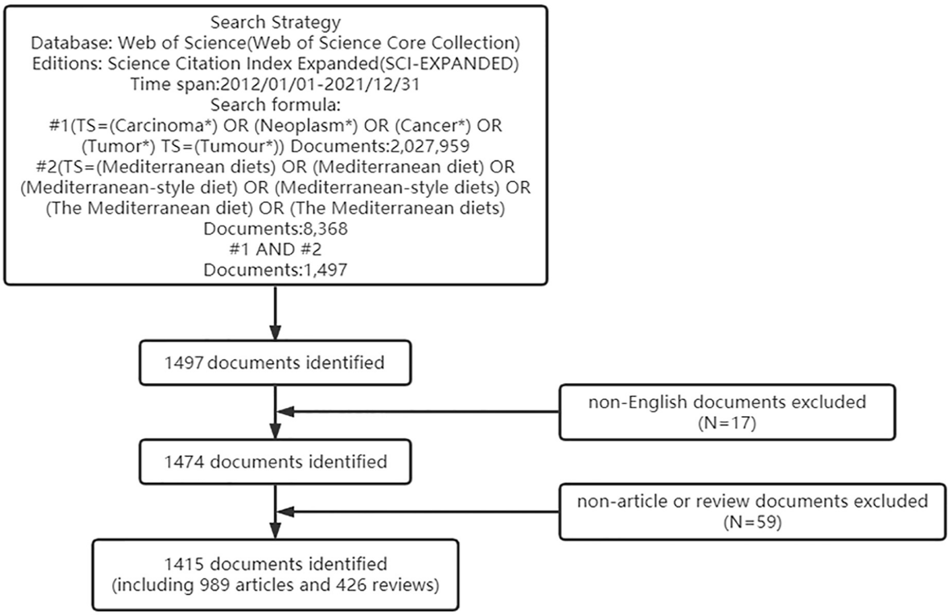

FIGURE 1
Search strategy and data filtering process.

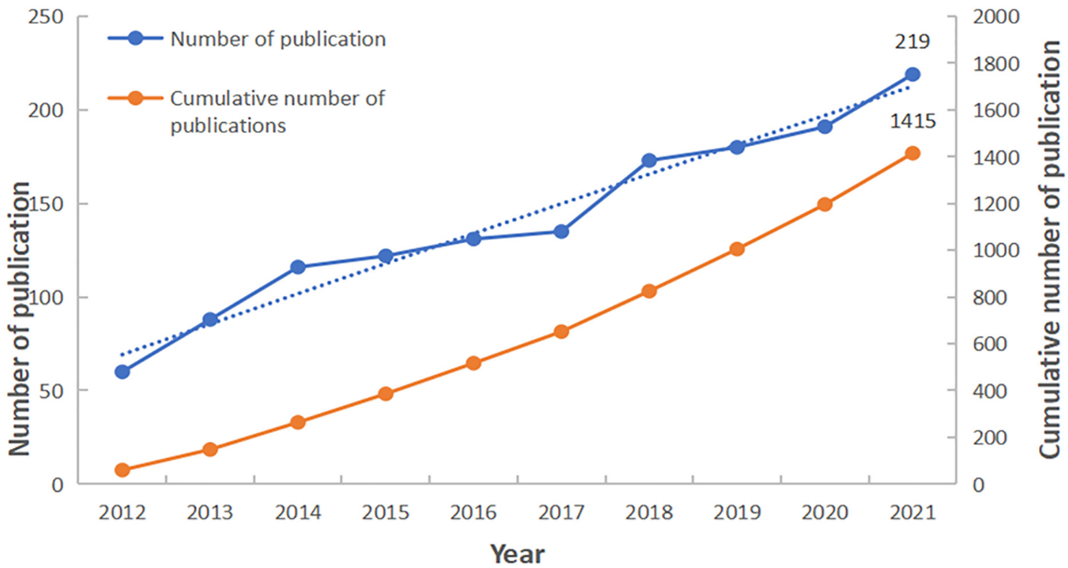

FIGURE 2
The annual volume and trend of publications on the Mediterranean diet (MD) on cancer.

researching the MD and cancer. Co-authorship between institutions and the average publication time of research is shown in Figure 4B. Harvard University was the hub of inter-agency cooperation, and the University of South Carolina has published some studies in this field most recently.

3.3. Journals

The 1,415 papers included were published in 450 different journals. The top 10 journals by publication volume are shown in Table 2, with *Nutrients* having the greatest volume with 158 papers (11.17%), followed by the *British Journal of Nutrition* (44, 3.11%), *European Journal of Nutrition* (41, 2.90%), *American Journal of Clinical Nutrition* (34, 2.40%), and *Journal of Nutrition* (33, 2.33%). When ranked by the number of citations, the top five journals were *Nutrients* (4,927), *Journal of Nutrition* (1,798), *British Journal of Nutrition* (1,795), *International Journal of Molecular Sciences* (1,748), and *American Journal of Clinical Nutrition* (1,716). According to the magnitude of the *H*-index, the top journal was *Nutrients* (37), and the *British Journal of Nutrition* (23) and *American Journal of Clinical Nutrition* (23) were tied for second place. A total of 80% of the top 10 journals were in Q1 and Q2, with 40% in the United States and 30% in Switzerland. These publications

TABLE 1 Top 10 productive countries/regions and top 10 productive institutions related to the Mediterranean diet (MD) on cancer.

Rank	Country/region	Count	Percentage (*N*/1,415)	Rank	Institution	Count	Location
1	Italy	428	30.25	1	Harvard University	229	USA
2	USA	414	29.26	2	University of Milan	112	Italy
3	Spain	268	18.94	3	Barcelona University	100	Spain
4	England	138	9.75	4	University of Navarre	100	Spain
5	Greece	98	6.93	5	Granada University	96	Spain
6	Germany	90	6.36	6	Carlos III Health Institute	92	Spain
7	Australia	83	5.87	7	University of Catania	89	Italy
8	France	83	5.87	8	University of Athens	80	Greece
9	Sweden	72	5.09	9	University of Florence	75	Italy
10	Netherlands	67	4.73	10	University of Naples Federico II	72	Italy

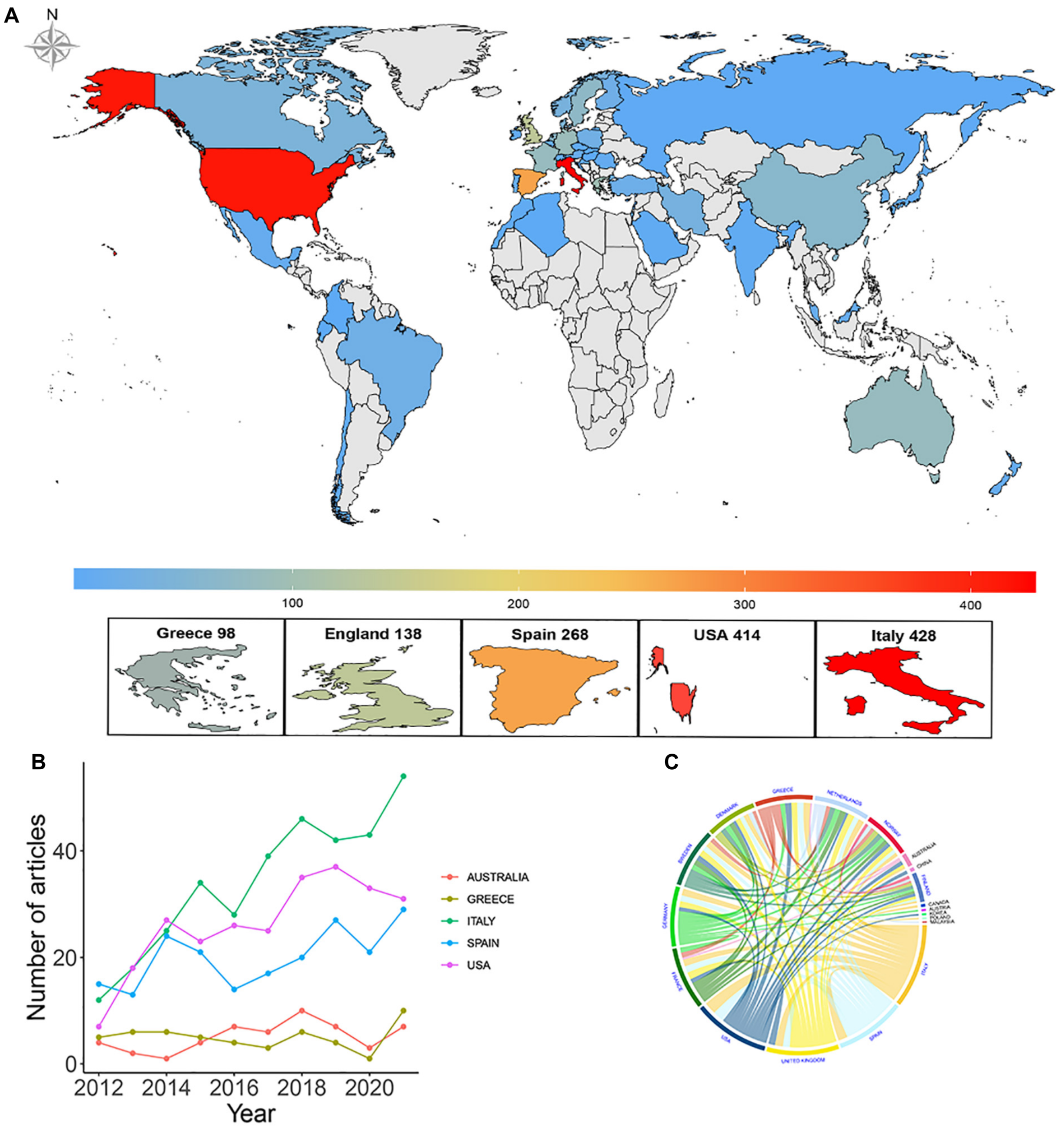

FIGURE 3
(A) Geographical distribution of the countries/regions in terms of publications. **(B)** The trends of publications by top five countries from 2012 to 2021. **(C)** The chord diagram of cooperation among countries/regions.

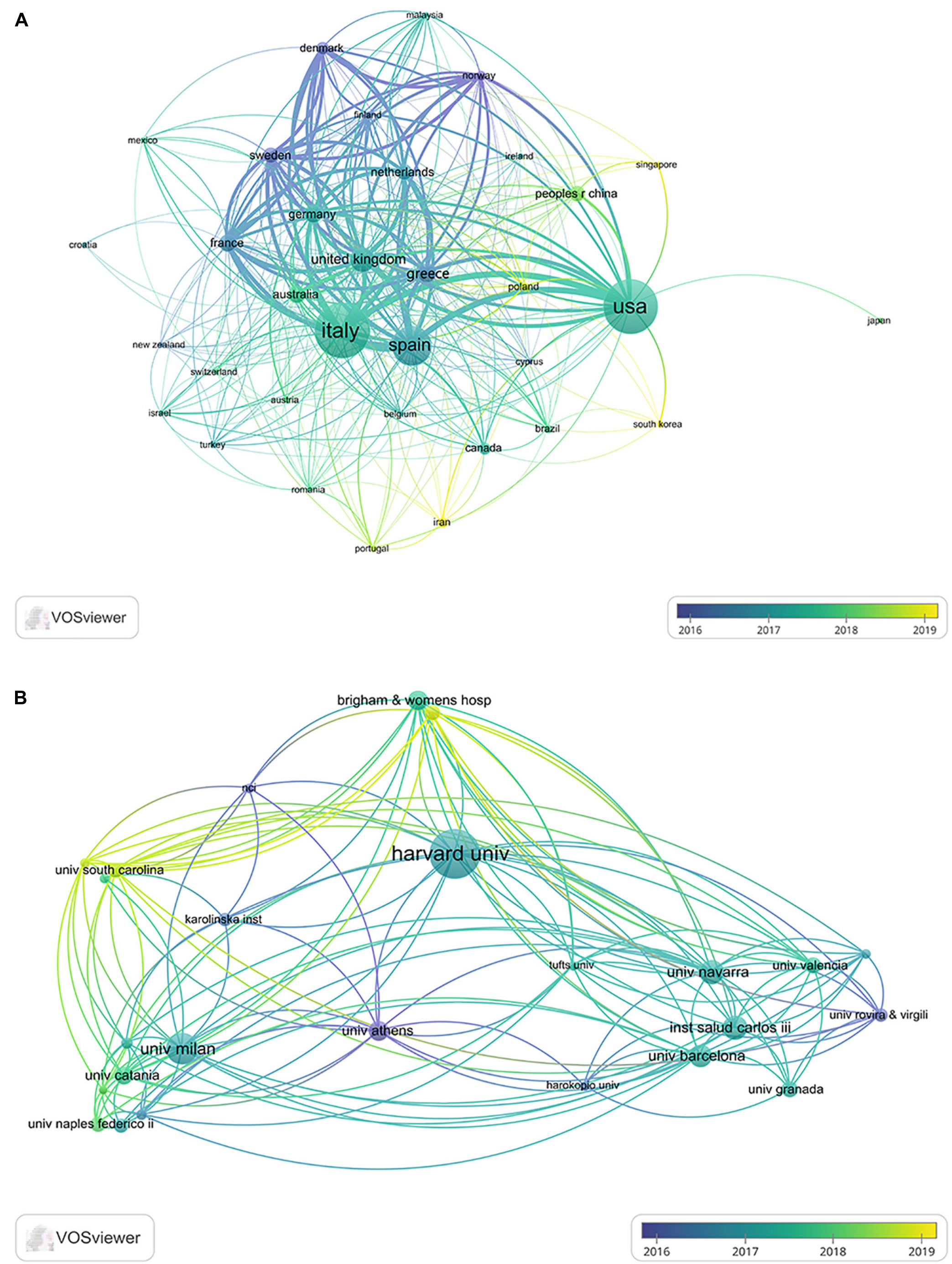

FIGURE 4
The co-authorship network diagram of panel **(A)** the countries/regions and **(B)** institutions. The size of the nodes represents the number of publications, the lines represent cooperation, and the color of the nodes represents the time.

ranged in IF (2021) from 2.816 to 8.472. Figure 5 shows the dual-map overlap of journals with publications on the MD and cancer. The distribution of subjects between citing journals (left part) and cited journals (right part) is illustrated in Figure 5. As shown in Figure 5, the three most significant relationship bands demonstrate that the pertinent research in this field was mainly published in journals belonging to Medicine/Medical/Clinical or Molecular/Biology/Immunology subjects. Furthermore, these studies were mainly based on research published in journals belonging to Molecular/Biology/Genetic or Health/Nursing/Medicine subjects.

3.4. Authors and co-cited authors

In all, 7,275 authors contributed to the literature on the MD and cancer. The top 10 authors by number of publications and citations are listed in Table 3. Based on the number of publications, the top five authors were James R. Hebert (27), Carlo La Vecchia (24), Nitin Shivappa (24), Antonia Trichopoulou (21), and Anne Tjonneland (19). As shown by the co-authorship network (Figure 6A), many scholars had a centrality greater than 0.1 (purple outer ring), with James R. Hebert (0.54) having the highest centrality, followed by

TABLE 2 Top 10 productive journals related to the Mediterranean diet (MD) on cancer.

Journal	Count (%)	Citation	*H*-index	IF (2021)	JCR	Country
Nutrients	158 (11.17)	4,927	37	6.706	Q1	Switzerland
British Journal of Nutrition	44 (3.11)	1,795	23	4.125	Q3	England
European Journal of Nutrition	41 (2.90)	801	17	4.865	Q2	Germany
American Journal of Clinical Nutrition	34 (2.40)	1,716	23	8.472	Q1	USA
Journal of Nutrition	33 (2.33)	1,798	21	4.687	Q2	USA
International Journal of Cancer	32 (2.26)	1,187	18	7.316	Q1	Switzerland
International Journal of Molecular Sciences	25 (1.77)	1,748	18	6.208	Q1	Switzerland
PLoS One	24 (1.70)	816	16	3.752	Q2	USA
Nutrition and Cancer-An International Journal	20 (1.41)	282	10	2.816	Q3	USA
European Journal of Clinical Nutrition	18 (1.27)	830	14	4.884	Q2	England

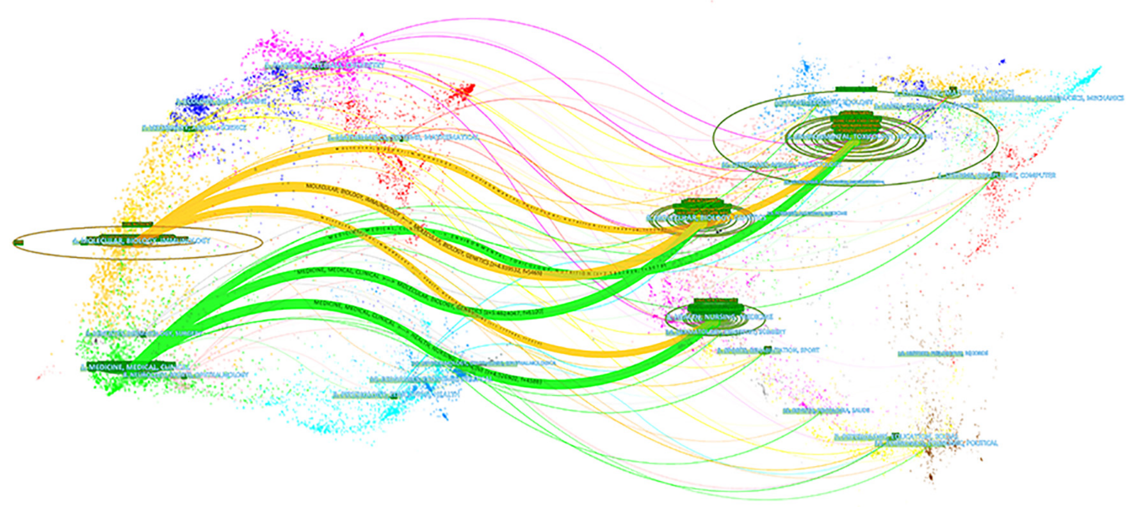

FIGURE 5
A dual-map overlap of journals of Mediterranean diet (MD) on cancer. The left is the cited journal and the right is the cited journal, the longer transverse diameter of the ellipse represents more publications in the corresponding journal.

Carlo La Vecchia (0.50) and Antonia Trichopoulou (0.49). These data reveal that these scholars' studies serve as a pivot point for the various fields studying the MD and cancer. In terms of co-citations (Table 1), Antonia Trichopoulou had the most citations, reaching 501. Ramon Estruch (310) was second, followed by Francesco Sofi (307), Lukas Schwingshackl (303), and Miguel A. Martinez Gonzalez (271). If two articles were cited by the same document, a co-citation relationship existed between the two articles (29). Figure 6B displays the network of connections between co-cited authors, with the top three centrality scholars including Teresa T. Fung (0.82), Antonia Trichopoulou (0.53), and Frank B. Hu (0.52).

3.5. References

In total, 62,468 references were cited in 1,415 included papers. Table 4 lists the top 10 cited references. The most cited reference was authored by Estruch (30) and had 159 citations, followed by Schwingshackl (31) (88 citations) and Toledo (9) (86 citations). Five of the top 10 cited references had centralities greater than 0.1, with Estefania Toledo's study having the highest centrality (0.29), followed by Ramón Estruch's (0.26), and Lukas Schwingshackl's (0.15). These data show that these references, especially the reference authored by Estefania Toledo, are key points that connect different fields studying the MD and its effects of cancer. The co-citation relationship of these references is presented in Figure 7A. To cluster these references and display temporal trends, a timeline plot was constructed (Figure 7B). In Figure 7B, there are a total of nine clusters that show that the initial research in the area of the MD primarily focused on olive oil (including #3 olive oil intake, #4 olive oil phenol), and that the "diet quality score" was the longest-lasting theme. Additionally, these data showed that BC and CRC were recent research hotspots.

3.6. Keywords

Keywords summarize the core material of a paper in great detail. Cluster analysis and co-occurrence analysis of keywords is depicted in Figure 8A. After clustering, a total of 12 clustering

TABLE 3 Top 10 productive authors and top 10 co-cited authors related to the Mediterranean diet (MD) on cancer.

Rank	Authors	Count	Centrality	Co-cited author	Citation	Centrality
1	James R. Hebert	27	0.54	Antonia Trichopoulou	501	0.53
2	Carlo La Vecchia	24	0.50	Ramon Estruch	310	0.49
3	Nitin Shivappa	24	0.01	Francesco Sofi	307	0.49
4	Antonia Trichopoulou	21	0.49	Lukas Schwingshackl	303	0.00
5	Anne Tjonneland	19	0.22	Miguel A. Martinez Gonzalez	271	0.10
6	Kim Overvad	16	0.22	Teresa T. Fung	264	0.82
7	Walter C. Willett	16	0.08	Genevieve Buckland	225	0.00
8	Miguel A. Martinez Gonzalez	14	0.34	Walter C. Willett	194	0.02
9	Dolores Corella	13	0.16	Frank B. Hu	170	0.52
10	Frank B. Hu	13	0.13	Katherine Esposito	161	0.14

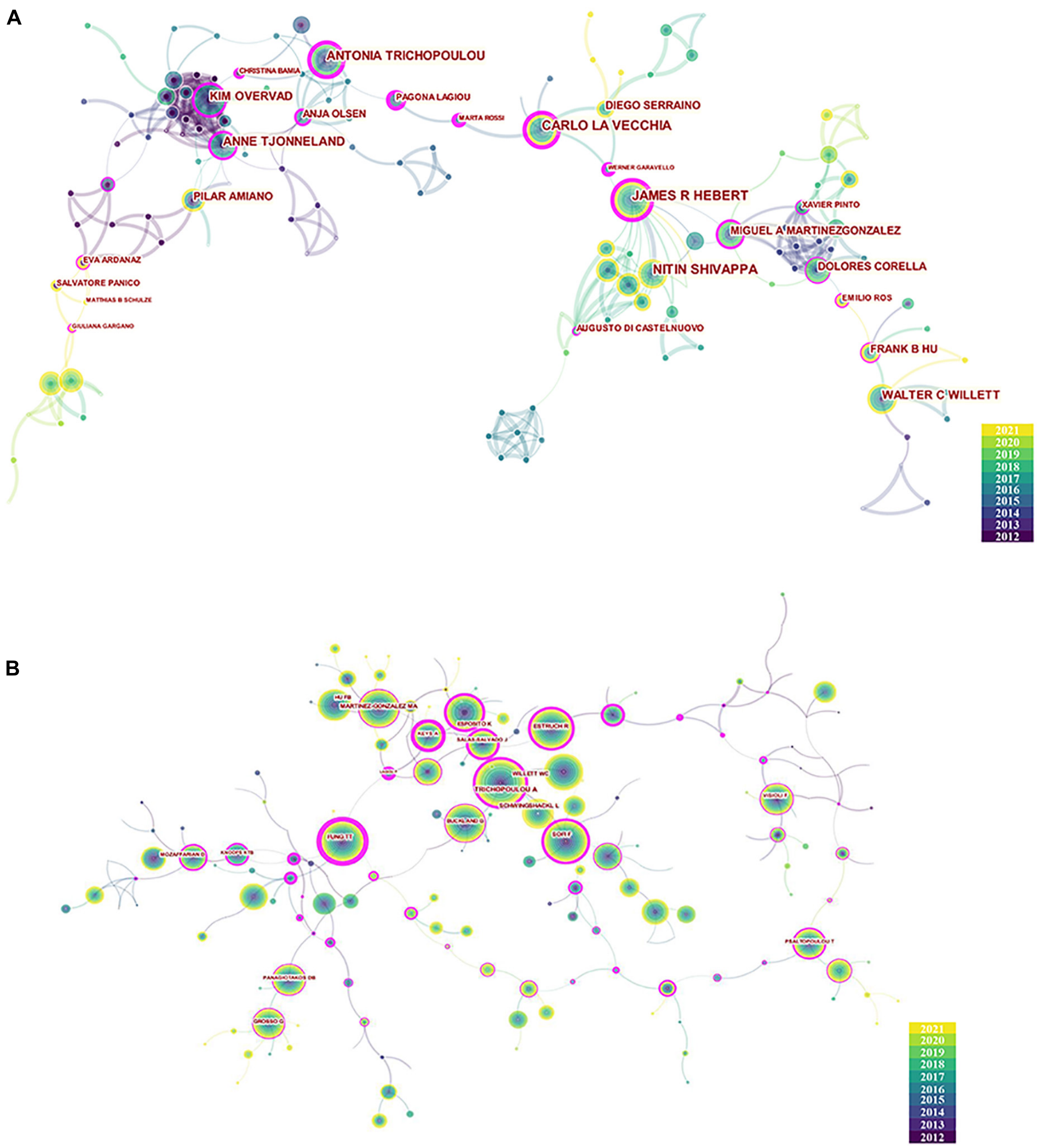

FIGURE 6
The collaboration map of panel **(A)** authors and **(B)** co-cited authors.

labels were produced, which were divided into three main categories: nutrition-related (e.g., #3 nutrition study, #5 nutrition therapy, #6 nutritional genomics inflammation), diet-related (e.g., #0 red meat consumption, #2 olive oil, #7 index-based dietary pattern), and cancer-related (including #1 post-menopausal BC and #8 pancreatic cancer) keywords. Notably, cancer-related keywords such as CRC and prostate cancer were also included in cluster eight. Since 2012, a total of 26 keywords have undergone a sudden burst. The results of burst detection are shown in **Figure 8B**. Keywords like gut microbiota, older adult, and polyphenol have increased since 2019, proving that research in these keyword-related areas is currently a hot topic and represent future developmental trends in the field of the MD and cancer research. The burst strength of the gut microbiota was 8.06, the highest among the burst keywords. Thus, research in the area of the gut microbiota in relation to the MD and cancer deserves strong attention.

4. Discussion

Research on the MD and cancer has increased over the past decade (2012–2021), with the total number of studies exceeding 200 (219) in 2021. This is more than three times that of 2012 and is partly due to cancer already being a focus and hotspot of interest (32). Another more significant reason that research on the MD and cancer has increased in recent years is due to the recently discovered beneficial effects of diet on cancer (33). The rise in studies confirms that the field of the MD on cancer has a promising prospect and requires more attention and in-depth study.

Italy is the country with the most publications in this research area, and together with Spain, Greece, France, and other southern European countries on the Mediterranean coast, it leads the forefront of research on the MD in the cancer field in the world. This is not surprising given its geographical location and dietary habits. In addition to Italy, only the United States has published more than 400 articles on the MD and cancer, which may be a result of the favorable acceptance of the MD and strong scientific research strength in the United States (34). Among scientific research institutions, Harvard University in the United States had the most publications worldwide, which also shows that the United States has a strong scientific research base in the field of the MD and cancer. The majority of the top 10 institutions conducting research on the MD and cancer were located in Italy and Spain, which is consistent with national publishing numbers and trends. In terms of cooperation, Italy and the United States had the highest levels of reciprocal cooperation, independent of whether Italy, Spain, Greece, or France were used as the representatives of the MD countries. The United States, the United Kingdom, Germany, and other countries also showed international cooperation. Collectively, these data suggest that research on the MD and cancer is a field of global cooperation. In addition, some countries/regions need to strengthen international exchanges and cooperation.

Nutrients published the most articles in the field of the MD and cancer and was the only journal to include more than 10% of the total of all published research in the area. In addition to this, *Nutrients* ranked first in terms of total citations and *H*-index, indicating that *Nutrients* included a large number of high-quality articles. In conclusion, *Nutrients* is the most authoritative journal on the MD and cancer as a Q1 nutrition journal. The majority of the top 10 journals were nutrition-related, however, a small number of journals in the fields of oncology, biology, and comprehensive journals also published research on the MD and cancer. Research centers in the field were mainly focused on nutrition, and it is foreseeable that more oncology research will appear in the future. According to the dual-map overlap of journals and disciplines, it was found that the current research is mostly centered on Medicine/Medical/Clinical subjects and mainly based on Molecular/Biology/Genetic subjects. Furthermore, the clinical transformation of basic research represents the current research state and trend. In addition, research in the Molecular/Biology/Immunology fields were inseparable from the contributions from the Molecular/Biology/Genetic fields. Some basis of clinical transformation comes from Health/Nursing/Medicine, suggesting that Health/Nursing is also an important source and direction for clinical transformation.

The number of articles published by the author was used in the current study to represent the contribution of the author to the research field, and the number of citations of the co-cited author reflected the influence of the author. The authors Antonia Trichopoulou, Miguel A. Martinez Gonzalez, and Frank B. Hu were within the top 10 contributing authors, both in terms of the number of publications and number of citations. These data indicate that the scientific output and influence of these authors are wide-reaching. Among the top 10 highly cited references, Ramón Estruch, Francesco Sofi, and Lukas Schwingshackl all authored more than two articles. These three authors have all been cited more than 300 times, ranking them among the top five co-cited authors. The most cited reference was published in the *New England Journal of Medicine* (NEJM) and was authored by Ramón Estruch. It was a randomized controlled trial (RCT) that confirmed that the MD reduces the incidence of adverse cardiovascular events in people with high cardiovascular disease risk (30). As an RCT study published in a high-impact journal, with 159 citations, this speaks volumes about the extremely high quality of the study. This study provided further evidence of the cardiovascular benefits of the MD, making its high rate of citation by MD-related research understandable. References related to the MD and cancer mainly included meta-analyses (31, 35–37). Notably, of these meta-analyses, the most cited study (88 citations) was written by Lukas Schwingshackl and was published in *Nutrients*. This meta-analysis was conducted on the adherence of subjects to the MD and their risk of cancer and evaluated 83 studies and 2,130,753 subjects. The results of the study confirmed that higher MD adherence was strongly associated with lower cancer mortality and lower risk of CRC, BC, gastric cancer (GC), liver cancer, head and neck cancer, and prostate cancer. The study published in 2017 was more recently published compared with other references but had a large number of citations, indicating that the study had a strong focus on the MD and cancer and that it was a high quality article. Within the cancer references, a large emphasis was on BC (9, 37, 38). For instance, an RCT study conducted by Estefania Toledo and published in *JAMA Internal Medicine* confirmed the positive significance of the MD on BC in women with high cardiovascular risk. This article also had the highest centrality (0.29), likely because it discussed the effects of the MD on both cardiovascular disease and cancer. The timeline plot visually depicts the development of each MD topic based on references. As a representative of the MD, the intake of olive oil (39, 40), the primary active ingredient of olive oil, and olive oil phenols

TABLE 4 Top 10 high-cited references related to the Mediterranean diet (MD) on cancer.

Rank	References	First Authors	Citation	Centrality	Journal	JCR	IF (2021)
1	Primary prevention of cardiovascular disease with a MD	Estruch et al. (30)	159	0.26	New England Journal of Medicine	Q1	176.077
2	Adherence to MD and risk of cancer: an updated systematic review and meta-analysis	Schwingshackl et al. (31)	88	0.11	Nutrients	Q1	6.706
3	MD and invasive breast cancer (BC) risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial	Toledo et al. (9)	86	0.29	JAMA Internal Medicine	Q1	44.411
4	Accruing evidence on benefits of adherence to the MD on health: an updated systematic review and meta-analysis	Francesco Sofi (93)	77	0.15	American Journal of Clinical Nutrition	Q1	8.4722
5	MD and health status: an updated meta-analysis and a proposal for a literature-based adherence score	Francesco Sofi (94)	66	0.02	Public Health Nutrition	Q2	4.539
6	Adherence to MD and risk of cancer: an updated systematic review and meta-analysis of observational studies	Schwingshackl and Hoffmann (35)	62	0.15	Cancer Medicine	Q2	4.711
7	Adherence to MD and risk of cancer: a systematic review and meta-analysis of observational studies	Schwingshackl and Hoffmann (36)	61	0.03	International Journal of Cancer	Q1	7.316
8	Primary prevention of cardiovascular disease with a MD supplemented with extra-virgin olive oil or nuts	Estruch et al. (30)	60	0.05	New England Journal of Medicine	Q1	176.077
9	MD adherence and risk of post-menopausal BC: results of a cohort study and meta-analysis	van den Brandt and Schulpen (37)	54	0.09	International Journal of Cancer	Q1	7.316
10	Adherence to the MD and risk of BC in the European prospective investigation into cancer and nutrition cohort study	Buckland et al. (38)	51	0.09	International Journal of Cancer	Q1	7.316

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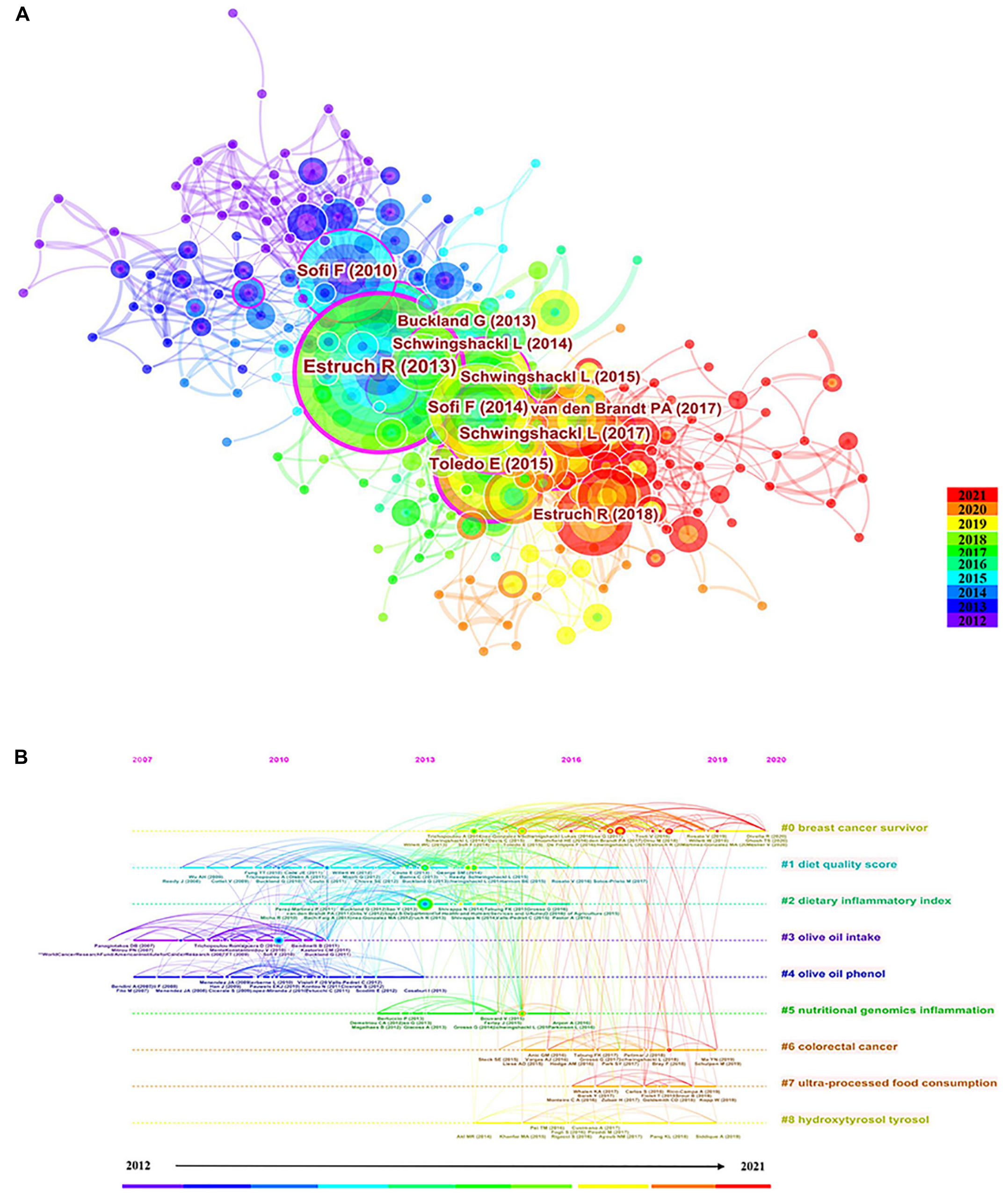

FIGURE 7
(A) The co-occurrence map of references. **(B)** The timeline plot of references. The texts on the right are the topics.

(41, 42), were the foci of early research. Olive oil phenols exert anticancer effects by inhibiting the proliferation of cancer cell lines that represent leukemia, CRC, and BC and by promoting apoptosis of cancer cells. Recent investigations have focused on hydroxytyrosol, oleocanthal, and other major components in olive oil polyphenols. Hydroxytyrosol as an important phenolic compound unique to olive oil that exerts chemopreventive and treatment effects in cancer. Hydroxytyrosol is a strong antioxidant that reduces the risk of cancer by reducing oxidative DNA damage. Oleocanthal inhibits the growth, proliferation, migration, and angiogenesis of cancer cells, such as those in melanoma, BC, liver cancer, and colon cancer. Oleocanthal also induces apoptosis of tumor cells by increasing reactive oxygen species generation (43, 44). BC is a persistent and hot topic in cancer, and the beneficial influence of the MD on BC is definite, as the MD has been showed to be effective as a means of primary prevention for BC and to lower the incidence of BC (45, 46). Another cancer-related topic covers digestive system tumors and is represented by CRC. The MD is negatively correlated with the risk of CRC and reduces the incidence of CRC (47, 48). The MD is a protective factor for GC and esophageal cancer, and higher MD adherence is linked with a lower incidence of GC and esophageal cancer (49–52).

Keywords can summarize the characteristics and focus of a research field. Clustering results of keywords are comparable to those for references. In addition to nutrition and diet-related clustering, the cancer-related cluster pointed to a protective effect of the MD on pancreatic cancer and prostate cancer (53, 54). Current cancer research frontiers and hotspots were identified by keyword burst

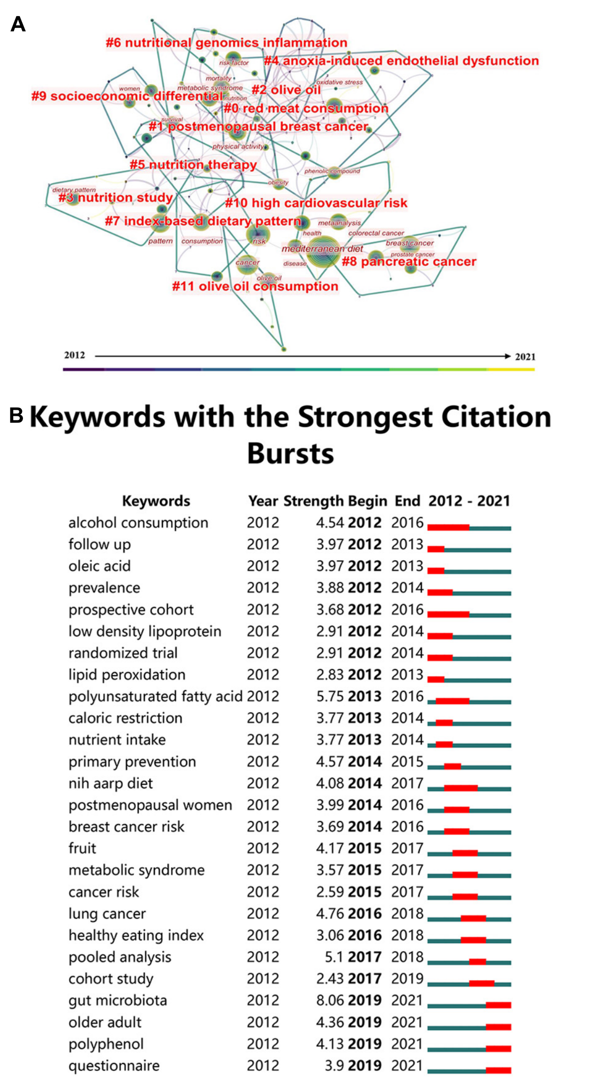

FIGURE 8
(A) Cluster and collaboration map of keywords. **(B)** Bursts detection map of keywords.

detection. The strongest keyword identified was the gut microbiota, which has been a hotspot since 2019. Interestingly, the MD has been shown to cause changes in the gut microbiome (55–57). Regulating the gut microbiota and its corresponding metabolites enhances the effects of anti-tumor therapies and further helps in the investigation of new tumor prevention strategies (58, 59). Such a promising and potential field has inspired researchers, leading to the hypothesis that the MD can prevent and inhibit the development of CRC by regulating the gut microbiota, by maintaining intestinal barrier function, and by reducing inflammation. The MD may increase anti-inflammatory microbiota and simultaneously inhibit pro-inflammatory microbiota that alter intestinal barrier function to improve the dysregulated intestinal ecology (60, 61). Another significant keyword identified in the current study was polyphenols. Olive oil polyphenols are the primary active ingredients of olive oil, whose consumption is encouraged in the MD. Research on olive oil polyphenols has expanded our understanding of their beneficial effects on cancer. The beneficial impact of the MD on tumors may be due to the interaction between olive oil polyphenols and the gut microbiota. For example, olive oil polyphenols can regulate the composition and activity of intestinal microbiota, which transforms the intestinal microbiome to include more protective bacteria. These gut microbiota can produce active metabolites with additional chemopreventive effects through the degradation of polyphenols and other components in olive oil (62, 63).

The MD is a healthy dietary pattern, and cancer is an important factor affecting the security of global public health. The publication of 1,415 related studies in the past decade and the ongoing rise of research in this area have proved the necessity and significance of the MD in cancer research. The current research field illustrates the importance of international cooperation. At present, the field is more focused on the benefits connected to BC. With the support of RCTs and meta-analysis, a high degree of evidence for implementing the MD in the prevention of BC exists. Additionally, the MD has been shown to be beneficial for gastrointestinal cancers, such as CRC, GC, esophageal cancer, and pancreatic cancer. However, the level of evidence for implementing the MD diet for these cancers is relatively low. In the future, more high-quality, multi-center, rigorously designed, high-level, evidence-based medical research is needed to improve the credibility of these research conclusions. Lung cancer and prostate cancer-related research utilizing the MD also exists. However, these non-digestive systems cancer need further attention and in-depth study. Currently, study of the MD and its effects on the gut microbiota is the most popular research direction. The beneficial effects of the MD on tumors is closely related to the gut microbiota, and CRC, specifically in the intestine, has drawn the most attention. In addition to studying the effects of MD on CRC, scholars should put effort into studying the potential benefits of the MD on other gastrointestinal tumors, including esophageal cancer, GC, and pancreatic cancer *via* modulation of the gut microbiota in the future. Research on the primary components of the MD, such as olive oil and polyphenols, particularly hydroxytyrosol, and their mechanisms of action in the prevention and treatment of cancer have been studied. There are relatively a large number of studies on polyphenols, which are of great promise and significance (64). However, the beneficial effects of the MD, either due to a single component or as a synergistic effect of multiple nutrients, is controversial. Olive oil is beneficial to CRC with its effects being opposite to those of red meat. For example, when red meat consumption is used as a keyword cluster, high intakes of red meat and processed meat, and alcohol have been shown to increase the risk of CRC (65). Conversely, increased intake of dietary fiber lowers the risk of CRC (66). High dietary fiber intake is also a part of the MD. According to some researchers, obesity and cancer are related (67), and the healthy MD greatly reduces the probability of obesity thereby preventing some cancers. These studies have indicated that the mechanism by which the MD regulates cancer must be the result of numerous factors, so the identification of the key components of its effects on different cancers and a further in-depth grasp of the molecular mechanisms important for the beneficial effects of the MD is imperative (68). The role of the MD on tumors is mainly reflected in cancer prevention, preventing the occurrence of cancer at its root is the most effective measure to reduce the burden of cancer, which is similar to the old Chinese proverb, "Excellent doctor preventive treatment of disease."

For advanced cancer, anti-tumor treatments that utilize immunotherapy has become more prevalent and significant (69). The MD is considered a feasible intervention to enhance the effectiveness of immunotherapy by modulating the gut microbiota

(70, 71). Therefore, the MD has great potential as an adjunct to immunotherapy. In addition to prevention, the interaction of the MD with anti-tumor therapy may improve the quality of life and promote recovery after surgery. These potential effects and interactions of the MD with other anti-tumor treatments require further research.

The MD is popular with students, adults, and the elderly (72–74). The extensive research of the MD in the field of cancer demonstrates its enormous potential for both cancer prevention and treatment. In addition to the MD, many other dietary patterns may be beneficial for cancer. The Dietary Approaches to Stop Hypertension (DASH) diet originated from a large-scale hypertension prevention and treatment program launched in the United States in 1997. The DASH diet has been found to be effective not only in preventing high blood pressure but also in reducing cancer risk. Studies have confirmed that the DASH diet can significantly reduce the risk of CRC, BC, colorectal adenoma, and other cancers (75–77). The ketogenic diet is a dietary pattern characterized by high fat, low protein, and very low carbohydrate intake. The ketogenic diet promotes metabolism of fats and produces ketones, such as acetoacetate and β-hydroxybutyrate, which may exhibit anti-tumor activities by inhibiting the aerobic glycolytic metabolic pathways in cancer cells (78–80). Numerous studies have also confirmed that the ketogenic diet enhances the therapeutic effects of chemotherapy and radiotherapy and reduces the side effects of chemotherapy and radiotherapy in BC, lung cancer, pancreatic cancer, and others (81–84). The relationship between fasting, such as can be found as part of intermittent fasting and in fasting-mimicking diets (FMDs), and cancer has attracted much attention. Fasting affects the living environment of cancer cells by reducing levels of insulin, blood glucose, etc., and improves the clinical outcome of patients with cancer. Fasting also increases the immunity of normal cells and activates a portion of the immune cell population to improve anti-tumor immunity and lessen the toxic side effects of radiotherapy and chemotherapy (85–87). The mechanisms responsible for the inhibitory effects of fasting on cancers such as CRC and triple-negative BC and the ability of fasting to enhance the anti-tumor effects of chemotherapy have been studied (88–90). Numerous clinical studies have confirmed that a diet that mimics fasting can improve the efficacy of neoadjuvant therapy in patients with HER2-negative BC and improve the quality of life of patients with ovarian cancer and BC who receive chemotherapy (91, 92). This evidence fully illustrates the great potential of dietary patterns represented by the MD for cancer prevention and treatment.

This study is the first to comprehensively summarize and analyze the research foundation, development process, current hotspots, and future trends of the MD on cancer using bibliometrics. The use of CiteSpace, VOSviewer, and R packages to visually analyze results allows researchers to swiftly sort out previous research results and identify hotspots and frontiers in specific research fields of interest. The current study inevitably has intrinsic limitations due to the bibliometric analysis utilized. First, this study only included literature retrieved from the WoS database, as the WoS database provides complete information on research articles and their corresponding citations, both of which are required for bibliometrics. Second, there was a certain degree of language prejudice due to the screening methods used, which allowed only those publications written in English to be included in the analysis. In addition, in terms of search strategy, to optimize the inclusion of pertinent research, this paper adopted a relatively broad topic search. Although a comprehensive search formula has been adopted, some studies may still have been missed.

5. Conclusion

Overall, the current study analyzed and summarized the development of the MD and cancer-related research, current hotspots in the field, and future directions. Research on the role of the MD in cancer prevention and treatment is receiving more and more attention. At present, numerous in-depth studies have described the positive effects of the MD on BC, CRC, GC, lung cancer, etc., with research on other cancers being insufficient. Exploration of the mechanisms of interaction between the MD and the gut microbiota, the impact of these interactions on various cancers, and the discovery of the main active ingredients of the MD, mainly represented by olive oil polyphenols, are the current hotspots and future research directions. Scientific advancement is based on the investigation of mechanisms, and clinical trials are intuitive means to confirm efficacy. The effects of the MD on a range of cancers urgently needs more high-quality clinical studies to provide high-level, evidence-based medical evidence and more in-depth molecular mechanistic studies to provide a theoretical basis for the implementation of the MD in preventing and treating various cancers.

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.

Author contributions

YL was responsible for data collection, data analysis, completing the writing, figures, and tables. JL was responsible for checking data and analysis results and reviewing and revising articles. Both authors contributed to the article, designed the study, and approved the final version of the submitted manuscript.

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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Indices of Mediterranean diet adherence and breast cancer risk in a community-based cohort

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Introduction: A Mediterranean-style dietary pattern is believed to have cancer-protective effects. We compared the prospective associations between adherence to four established Mediterranean diet indices and breast cancer risk (including total, postmenopausal, and hormone receptor positive cases) in women in the Framingham Offspring Study.

Methods: The four indices used two different approaches to measuring adherence to a Mediterranean diet: (a) scores based on the population-specific median intakes of Mediterranean diet-related foods in a given population (i.e., alternate Mediterranean Diet (aMED) index and Mediterranean Diet Score (MDS) index), and (b) scores based on compliance with recommended intakes of relevant foods from the Mediterranean diet pyramid [i.e., Mediterranean Diet (MeDiet) index and Mediterranean Style Dietary Pattern (MSDP) index]. Dietary data were derived from semiquantitative food frequency questionnaires collected in 1991-95. Participants included 1579 women aged $\leq$30 years who were free of prevalent cancer. Women were followed through 2014, and Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for various confounders.

Results: During a median follow-up of approximately 18 years, 87 breast cancer cases were documented. Women in the highest (vs. lowest) score category of the pyramid-based scores (i.e., MeDiet or MSDP) had approximately 45% statistically significantly lower breast cancer risks. These effects were even stronger for any hormone receptor positive cases using the MeDiet index (highest vs. lowest score categories: HR = 0.45, 95% CI: 0.22–0.90). Neither of the median intake-based scores (i.e., aMED, MDS) was associated with breast cancer risk.

Discussion: Our results suggest that the methodology and the composition of Mediterranean diet indices influence their ability to assess conformity to this specific diet pattern and predict breast cancer risk.

KEYWORDS

breast cancer, Mediterranean diet, dietary index, prospective cohort study, diet quality, hormone receptor status

1. Introduction

Dietary guidelines in the US recommend the Mediterranean diet as a healthy dietary pattern for the prevention of chronic disease risk, including cancer (1). The Mediterranean diet is a well-balanced plant-based diet. However, its specific definition varies somewhat due to the variations in culture, religion, ethnicity, and socio-economic status among and within the different Mediterranean countries (2). Nevertheless, a Mediterranean diet is commonly characterized by frequent consumption of non-refined grains, vegetables, fruits, nuts, olive oil, and dairy products, and moderate intakes of fish, poultry, potatoes, legumes, eggs, and sweets. Finally, moderate intake of red wine during meals and increased physical activity are important components of the Mediterranean lifestyle (3, 4).

Various *a priori* criterion-based dietary indices have been developed over the years to assess a population's conformity to the Mediterranean diet (5, 6) and examine the cancer-protective effects of this dietary pattern. Evidence from some observational studies suggests that higher adherence to the Mediterranean diet is protective against breast cancer (7), especially in postmenopausal women (8–10), although evidence on molecular subtypes (defined by hormone receptor status) is very limited and inconsistent (11–14).

Mediterranean diet indices are designed to assess conformity to a single dietary pattern, but they often have different dietary components, use different methodologies for assigning points and scoring the diet, and apply different weighting strategies (5, 6, 15). These differences may influence the ability of a given index to assess conformity to the diet and predict disease risk.

Over the last decades, more than 25 Mediterranean diet indices with different scoring methods were developed. Historically, the first Mediterranean diet index was created by Trichopoulou and her colleagues in 1995 (16). Then Trichopoulou and colleagues created a modified index in 2003 called the Mediterranean Diet Score (MDS) that excluded potatoes, added fish, and changed the alcohol score (17). Shortly thereafter, in 2005, an alternative index was created called the alternate Mediterranean Diet (aMED) index (18). The differences between the MDS and aMED were mainly in the selection of food groups (e.g., inclusion or exclusion of dairy, whole grains, fruit, and nuts). In our comparison of Mediterranean diet indices for this study, we propose first to examine these two indices of Mediterranean diet adherence that have similar scoring systems based on population-specific median intakes of Mediterranean diet-related foods in a given population. Since these scores may perform differently in non-Mediterranean populations who consume very different amounts of Mediterranean-style foods, we chose to compare these indices with two additional indices that base their scoring on adherence to recommended intakes of foods from the traditional Mediterranean diet pyramid (19). Thus, for these analyses, we chose to additionally evaluate the Mediterranean Diet (MeDiet) index developed by Panagiotakos and his colleagues in 2006 (20), as well as another index developed for use in the Framingham Study in 2009, called the Mediterranean Style Dietary Pattern (MSDP) index (21). These latter indexes may address some of the limitations of previous indices when used in non-Mediterranean populations. Whether these pyramid-based indices better predict disease risk than those based on population-specific median intakes has not been previously examined within the same study population.

This study aims to compare the prospective associations between adherence to four established Mediterranean diet indices and breast cancer risk in adult females in the Framingham Offspring Study (FOS). The four indices represent two different approaches to measuring adherence to the diet pattern: (a) scores based on the population-specific median intakes (i.e., MDS and aMED); and (b) scores based on compliance with recommended intakes (i.e., MeDiet and MSDP). In addition, since diet may act differently in preventing certain cancer subtypes (e.g., based on hormone receptor status) (22), we also propose to assess the associations between Mediterranean diet adherence and breast cancer risk stratified by hormone receptor status.

2. Material and methods

2.1. Study sample

In 1971, the Framingham Offspring Study enrolled the offspring and spouses of the original cohort members who had been followed for approximately four decades (23). Participants were asked to complete questionnaires on medical, demographic, diet, and other lifestyle information approximately every 4 years. The first complete food frequency questionnaire (FFQ) was administered at examination visit 5 (1991–1995), and that visit will serve as the baseline for these analyses; follow-up will continue until 2013, the last year with available cancer follow-up data. From a total of 3,712 subjects attending the fifth examination, we excluded the following subjects: (a) missing or invalid FFQ data (e.g., reported energy intakes $<$600 kcal/d or $>$4,000 kcal/d) or 12 blank food items or missing data on calorie contribution from each food item (n = 362); (b) history of prevalent cancer, except non-melanoma skin cancer cases (n = 147); (c) age $<$30 years (n = 4); (d) males (n = 1,496); and (e) missing covariates (n = 124). For analyses of estrogen or progesterone receptor (ER/PR) positive breast cancer cases, we additionally excluded 12 cases missing information on hormone receptor status (study sample used = 1,567). The Institutional Review Board of Boston University School of Medicine approved the Framingham Offspring Study data collection and these analyses (Protocols H-32086 and H-32132).

2.2. Assessment of adherence to the Mediterranean diet

Dietary data were collected *via* the Harvard 126-food item semiquantitative FFQ (24). The FFQ consists of a list of foods with standardized serving sizes and assesses the frequency of consumption during the previous year, ranging from "never or $<$one serving/month" to" $\geq$six servings/day." Separate questions allowed subjects to add up to 3 additional foods usually consumed regularly that were not listed on the FFQ, as well as types of cold breakfast cereals and cooking oils usually used.

Abbreviations: aMED, alternate Mediterranean diet score; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; ER/PR, estrogen receptor or progesterone receptor; FFQ, food frequency questionnaire; FOS, Framingham offspring study; HR, hazard ratio; ICD, International Classification of Diseases; MDS, Mediterranean diet score; MeDiet, Mediterranean diet score; MET, metabolic equivalents; MSDP, Mediterranean-style dietary pattern; Mono, monounsaturated fat; Srvg, serving; WHtR, waist-to-height ratio.

TABLE 1 Standards for maximum scores on each Mediterranean diet index.

	Standards for maximum scores			
	Median intake-based scores		Pyramid-based scores	
Individual components	MDS index[a]	aMED index[a]	MeDiet index[b]	MSDP index[c]
Vegetables except potatoes	≥median (svgs/day)[d]	≥median (svgs/day)[d]	≥33 svgs/week[e]	6 svgs /day
Potatoes	—	—	≥4 svgs/week[e]	3 svgs/week
Legumes	≥median (svgs/day)[d]	≥median (svgs/day)[d]	≥6 svgs/week[e]	—
Olives, pulses, and nuts	—	—	—	4 svgs/week
Fruits, fruit juice and nuts	≥median (svgs/day)[d]	—	—	—
Fruits and fruit juice	—	≥median (svgs/day)[d]	≥22 svgs/week[e]	3 svgs/day
Nuts	—	≥median (svgs/day)[d]	—	—
Cereals	≥median (svgs/day)[d]	—	—	—
Wholegrains	—	≥median (svgs/day)[d]	—	8 svgs/day
Wholegrains, nuts, and seeds	—	—	≥32 svgs/week[e]	—
Dairy (low and full fat)	<median (svgs/day)[d]	—	—	2 svgs/day
Full fat dairy products	—	—	≤10 svgs/week	—
Fish	≥median (svgs/day)[d]	≥median (svgs/day)[d]	≥6 svgs/week[e]	6 svgs/week
Meat and meat products	<median (svgs/day)[d]	—	—	—
Red and processed meats	—	<median (svgs/day)[d]	—	1 svg/week
Red, processed meats and eggs	—	—	≤1 svgs/week	—
Poultry	—	—	≤3 svgs/week[e]	4 svgs/week
Eggs	—	—	—	3 svgs/week
Alcohol (grams/day)	5–25 grams/day (females)	5–15 grams/day	—	—
Alcoholic beverages	—	—	1–<3 svgs/day[f]	—
Wine	—	—	—	1.5 svgs/day (females)
Mono:saturated fat ratio	≥median ratio	—	—	—
Mono:saturated fat ratio[g]	—	≥median ratio	—	—
(energy-adj)				
Olive oil	—	—	Olive oil only[h]	Olive oil only[i]
Sweets	—	—	—	3 svgs/week
Total score	0–9	0–9	0–55	0–100

MDS, Mediterranean Diet Score index by Trichopoulou et al., (17); aMED, Alternate Mediterranean Diet index by Fung et al., (18); MeDiet, Mediterranean Diet index by Panagiotakos et al., (20); MSDP, Mediterranean-Style Dietary Pattern index by Rumawas et al., (21); svgs, servings; mono, monounsaturated, and adj, adjusted.
[a]1 point for meeting criteria, 0 points if not.
[b]Standards reflect recommended intakes. Each component has 6 recommended intake categories (22), except the olive oil component, which has 3. The scoring for each component ranges from 0 to 5.
[c]Standards reflect recommended intakes. Each of the 13 food items except olive oil was scored from 0 to 10 depending on the degree of correspondence with the % of the recommended intake of that item. Then a penalty for overconsumption and a weighting factor for consumption of non-Mediterranean foods were applied.
[d]Servings were as listed on the food-frequency questionnaire.
[e]Servings were adjusted based on the food guide pyramid recommendations (5).
[f]1 serving of alcoholic beverage consists of 12 % ethanol.
[g]Dietary fats were adjusted for energy intake by adding residuals from linear regression models to overall median intake values.
[h]Olive oil consumption was classified into three categories: a) exclusive use of olive oil (score 5), use of olive oil along with other vegetable oils (score 3), or no olive oil (score 0).
[i]Exclusive use of olive oil score was given a score of 10 while the use of olive oil plus other vegetable oils received a score of 5, and no use of olive oil, a score of 0.

The MDS and aMED indices were chosen for these analyses as two of the most frequently used instruments that rely on median food intakes in the population. The MeDiet and MSDP indices were chosen as two indices reflecting adherence to recommended intakes of relevant foods from the Mediterranean diet pyramid. The food items included in each score component are shown in Supplementary Table S1, while the scoring standards and points to be assigned for these four indices are shown in Table 1. The serving sizes used for dietary variables in the two earlier indices (aMED and MDS) are taken from the FFQ. Serving sizes for the components in the MeDiet index were adjusted to match the recommended servings of the food guide pyramid (19).

2.2.1. Mediterranean Diet Score index (MDS)

The nine components of the MDS index (17), as shown in Table 1, are each assigned a value of 0 or 1. For the intake of vegetables (except potatoes), legumes, fruit, fruit juice and nuts, cereals, and fish, those participants whose intake was at or above the sex-specific median received a score of 1 (vs. a score of 0 for intakes below the median). Similarly, having a monounsaturated to saturated fat ratio ≥median (vs. <median) was also given a score of 1. For components believed to be less healthy (i.e., dairy and meat), subjects whose intake was below the median were assigned a value of 1 (vs. a score of 0 for ≥median). Subjects (females only in this study) with alcohol intake of 5–25 g/day were assigned a value of 1, while both lower and higher intakes received a score of 0. The total MDS ranged from 0 to 9.

2.2.2. Alternate Mediterranean Diet index (aMED)

The aMED index (18) is a modified version of the MDS index (17). The aMED index separates fruits and nuts into two groups, eliminates the dairy group, includes whole grains instead of all cereals, and replaces all meats with red and processed meats. Further, alcohol intake for women was limited to 5–15 g/day to receive 1 point. Finally, the monounsaturated to saturated fat ratio was adjusted for energy using the residual method. The possible scores on the aMED index ranged from 0 to 9.

2.2.3 Mediterranean Diet index (MeDiet)

The MeDiet score created by Panagiotakos et al. (20) ranges from 0 to 55 points, with up to 5 points being given for each of 11 items. Foods derived from mixed dishes and foods listed by participants were also assigned to the appropriate component scores. Scores of 0 to 5 were assigned to intakes of each healthy food component. For example, intakes of fruit (and fruit juice) in the following categories of weekly intake were given scores of 0–5, respectively: never, 1–4, 5–8, 9–15, 16–21, and ≥22 servings/week. Similar scoring was used for intakes of the following: 1) vegetables (except potatoes), 2) potatoes, 3) legumes, 4) wholegrain, nuts, and seeds, and 5) fish. Scores were reversed for full-fat dairy products, poultry, and red and processed meats (including eggs). For alcohol consumption, a score of 5 was assigned to drinkers with intakes of 1-<3 servings (each serving is equal to 12 g of ethanol) per day and a score of 0 for <1 or ≥3 servings per day. We modified the original scoring of olive oil due to the absence of information about the quantity of oil consumed on our FFQ. We classified olive oil consumption into three categories: a) exclusive use of olive oil (score 5), use of olive oil along with other vegetable oils (score 3), or no olive oil (score 0).

2.2.4 Mediterranean-Style Dietary Pattern index (MSDP)

The fourth index used in this study is the MSDP (21) which is based on the recommended intake of 13 foods shown in a traditional Mediterranean diet pyramid (Table 1). All items on the FFQ, including mixed dishes, were evaluated to determine whether the item fits into one of the score components. Some foods (e.g., yams) were not traditionally consumed in Mediterranean regions. Still, if other similar foods (e.g., other potatoes) were consumed, the item (yams) was added to the score component (potatoes). Each of the 13 components except olive oil was scored from 0 to 10 depending on the degree of correspondence with the percent of the recommended intake of that item (e.g., consuming 40% of the recommended servings would result in a score of 4). Exceeding the recommendations resulted in a lower score proportional to the degree of overconsumption (e.g., exceeding the recommendation by 40% would result in a score of 6). A negative score due to more than 100% overconsumption was given a score of zero. Exclusive use of olive oil was given a score of 10, while the use of olive oil plus other vegetable oils received a score of 5, and no use of olive oil a score of 0. The sum of the 13 component scores was standardized on a scale of 0–100 and weighted (from 0 to 1) by the proportion of energy intake attributed to the consumption of foods included in the Mediterranean diet pyramid (e.g., if 45% of energy was derived from foods not included in the Mediterranean diet pyramid, the calculated weighting factor would be 0.55). The final total MSDP score has a theoretical range of 0–100.

2.3. Cancer outcomes

Framingham investigators used standardized protocols (25) to detect cancer cases using information from self-reports, surveillance of local hospital admissions, and searches of the state health department's death records and the National Death Index. The cancer diagnosis and ER/PR status for cases were validated based on information from pathology reports and, in a few instances, from medical records. Breast cancer cases were defined using the International Classification of Diseases (ICD-O-3). In total, there were 87 first primary-site malignant breast cancer cases.

2.4. Potential confounders

We assessed several potential confounders at baseline, including age, cigarette smoking, alcohol intake, supplement use, energy intake, parity, body mass index (BMI), waist-to-height ratio (WHtR), and type 2 diabetes mellitus (T2DM). We also used information from all the examination visits to determine age at menopause and estrogen use. Self-reported information about education level was derived from the first exam in FOS and used to classify participants as having a college or graduate degree vs. less. An index for moderate and vigorous physical activity (in metabolic equivalents per hour) was created previously based on self-reported data (26) at every exam except exam 6. Because the index distribution at baseline exam (exam 5) was highly skewed to the right compared to the rest exams, we used the mean of physical activity index from exams 4 and 7. Participants were diagnosed with T2DM at each exam based on standardized Framingham criteria as described previously (27). For baseline anthropometric measures, a standard beam balance (with a stadiometer) was used to measure weight and height with the subject dressed in a hospital gown with no shoes. Because of the natural height loss occurring after age 60, we calculated the average of all height measures for adults up to age 60. Waist circumference was measured at the level of the umbilicus during mid-respiration to the nearest 0.25 inch with a cloth tape. Waist circumference was divided by average height measure to calculate WHtR (with missing values at exam 5 substituted using the mean values from exams 4 and 6).

Postmenopausal women were asked to report their age at menopause directly. In addition, at each exam, women were asked about their current menopausal status and estrogen use. For those missing self-reported age at menopause, we took the age at the exam at which a woman first reported being postmenopausal to be her age at menopause. Otherwise, we took the age at which a woman first reported using estrogen (typically for perimenopausal symptoms) and added 1 year to estimate the age at menopause. For non-estrogen users aged <50 years old, we substituted age at menopause with the median age of natural menopause in this cohort (50 years). Lastly, for non-estrogen users who were ≥50 years old, we took the age at menopause to be the age at the exam at which a woman last reported being premenopausal plus 1 year.

Estrogen use was treated as a time-dependent variable and classified as never or ever use (prior to, at baseline, or during the follow-up period). Women with missing information on estrogen use who reported no use at any other exams were treated as non-users for the missing exams.

2.5. Statistical analysis

Descriptive statistics were used to describe the total score distribution of each index. Pearson correlation coefficients were computed to compare total scores on the four Mediterranean diet indices. As previously done (17), we classified total scores of both MDS and aMED indices to reflect low, moderate, and high categories of adherence to the Mediterranean diet as follows: 0–3, 4–5, and 6–9 points, respectively. Sensitivity analyses and the score distributions were used to determine the cut-off values for classifying the final two indices into three categories: MeDiet index (low: 14–28; moderate: 29–34; and high: 35–53) and MSDP index (low: 4.0–19.0; moderate: 19.1–25.0; high: 25.1–50.9). The lowest category was used as the referent group for all analyses.

Breast cancer outcomes included total incident cases, postmenopausal cases, and any ER or PR positive cases (including ER-/PR+, ER+/PR-, ER+/PR+). Incidence rates for breast cancer were computed in each diet score category using person-years of follow-up calculated from exam 5 to the first of the following events: occurrence of incident breast cancer, loss of follow-up, date of the last exam, or date of death. Survival analyses were conducted to examine the association between adherence to each of the four Mediterranean diet indices and breast cancer risk. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HRs) and 95% CIs for the occurrence of first breast cancer cases. Tests for linear trends across categories of scores were performed using the category-specific medians in each score category.

The basic model for each index was adjusted for age (in years) and total calorie intake; except MSDP adjusted for age only because MSDP score accounts for calorie intake in its scoring system. Next, we examined a list of potential confounders and evaluated how they altered the basic model-parameter estimates by approximately 10% or more. We adjusted for WHtR, cigarette smoking (pack years), physical activity (METs/hour), diabetes status, supplement use, and age at menopause. Factors that were found not to confound the association between adherence to the Mediterranean diet and breast cancer risk were not included in the final model, i.e., alcohol intake and educational level. Lastly, highly collinear variables were not included together in the model, i.e., age at menopause and estrogen use. Finally, the proportional hazards assumptions were tested by using an interaction term with time in the models. No violations of the assumption were found. Statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

3. Results

3.1. Descriptive information

All Mediterranean diet scores were normally distributed in the FOS cohort. The mean (standard deviation, SD) scores for the MDS and aMED were very similar, 4.2 (1.7) and 4.3 (1.9) out of the possible maximum score of 9, respectively. Mean scores (SD) for MeDiet and MSDP scores were 32.1 (5.2) out of a hypothetical maximum possible score of 55 and 23.4 (7.2) out of a hypothetical maximum score of 100, respectively.

Table 2 shows the baseline characteristics of the participants according to the score categories for each Mediterranean diet index. Overall, women in the highest score category for all indices were older, more frequently had a high school degree or above, were more active, and smoked fewer cigarettes compared with those in the lowest category. Further, women with higher adherence to the Mediterranean diet (higher score categories) consumed more calories and were more likely to take dietary supplements.

Correlations between the four Mediterranean diet scores are shown in Supplementary Table S2. The strongest correlation was between the two scores based on the population-specific median intakes, MDS and aMED ($r = 0.83$). There were moderate to high correlations between MeDiet and all other scores ($r = 0.57–0.61$). Lastly, the MSDP score was only weakly correlated with MDS ($r = 0.39$) and moderately correlated with aMED ($r = 0.54$).

3.2. Adherence to the Mediterranean diet and breast cancer

Table 3 shows the associations between two median intake-based indices and two pyramid-based Mediterranean diet scores with the risk of breast cancer. Those in the high pyramid-based score categories of MeDiet and MSDP indices had the lowest cancer incidence rate, 2.42 and 2.46 per 1,000 person-years of follow-up, respectively. After adjusting for multiple confounders, women in the highest (vs. lowest) category

TABLE 2 Baseline characteristics[a] across the score categories of Mediterranean diet indices in women of the Framingham Offspring Study.

Mediterranean diet indices	Age (years)	BMI (kg/m^2)	Waist (cm)	Cigarettes (pack years)	Calorie intake (kcals/day)	Supplement use, %	Physical activity (METs/hour)	Age at menopause[b] (years)	Estrogen users[c], %	Prevalent diabetes, %	≥High school, %
Median intake-based scores											
MDS index											
Low (0–3)	52.2 (9.4)	26.9 (5.8)	87.6 (15.2)	15.4 (1.0)	1,614.8 (534.6)	27.0	13.5 (7.7)	47.9 (5.8)	45.1	4.3	20.4
Moderate (4–5)	54.7 (9.6)	26.7 (5.5)	87.1 (14.7)	12.2 (0.8)	1,766.2 (592.1)	33.1	14.3 (7.3)	48.0 (6.3)	47.0	5.4	29.6
High (6–9)	56.4 (9.0)	25.9 (4.8)	86.0 (13.4)	9.6 (0.9)	1,929.1 (532.7)	39.7	15.2 (7.3)	48.5 (5.3)	48.7	4.6	30.8
aMED index											
Low (0–3)	53.1 (9.5)	26.9 (5.9)	87.6 (15.5)	16.4 (1.1)	1,566.6 (549.9)	27.1	13.8 (7.9)	47.8 (5.9)	44.5	5.1	20.1
Moderate (4–5)	54.2 (9.7)	26.6 (5.2)	87.0 (13.9)	11.6 (0.8)	1,746.3 (538.9)	32.2	13.7 (7.0)	48.1 (6.2)	47.4	4.3	28.4
High (6–9)	55.5 (9.2)	26.2 (5.1)	86.2 (14.3)	9.6 (0.8)	1,993.3 (547.5)	39.8	15.4 (7.5)	48.5 (5.6)	48.7	5.1	32.6
Pyramid-based scores											
MeDiet index											
Low (15–28)	53.3 (9.8)	27.2 (5.6)	88.9 (15.6)	17.2 (1.3)	1,597.8 (601.5)	27.4	13.7 (8.2)	47.9 (5.7)	41.0	4.0	21.5
Moderate (29–34)	54.2 (9.5)	26.7 (5.5)	87.3 (14.4)	13.6 (0.8)	1,726.7 (545.3)	31.4	13.9 (7.1)	47.7 (6.3)	48.4	6.3	24.9
High (35–51)	54.8 (9.2)	25.9 (5.2)	85.2 (13.9)	8.8 (0.7)	1,901.6 (540.7)	37.9	15.0 (7.4)	48.8 (5.4)	48.9	3.4	32.9
MSDP index											
Low (4.0–19.0)	52.8 (9.4)	26.5 (5.7)	87.0 (14.9)	17.7 (1.2)	1,591.6 (595.3)	25.8	13.4 (7.9)	47.7 (5.9)	46.4	5.2	21.3
Moderate (19.1–25.0)	54.6 (9.9)	26.8 (5.3)	87.6 (14.6)	12.7 (0.9)	1,777.6 (569.9)	27.9	14.1 (7.2)	48.1 (5.7)	42.9	4.2	25.7
High (25.1–50.9)	54.8 (9.2)	26.5 (5.4)	86.6 (14.4)	9.6 (0.7)	1,836.1 (529.4)	40.7	14.8 (7.3)	48.3 (6.1)	49.8	5.1	30.9

BMI, body mass index; SE, standard error; METs, metabolic equivalents; MDS, Mediterranean Diet Score index by Trichopoulou et al., (17); aMED, Alternate Mediterranean Diet index by Fung et al., (18); MeDiet, Mediterranean Diet index by Panagiotakos et al., (20); MSDP, Mediterranean-Style Dietary Pattern index by Rumawas et al., (21).

[a]Values for continuous variables are arithmetic means (standard deviation) except for cigarette smoking which is a geometric mean.

[b]Including natural and non-natural menopause.

[c]Percent of women ever using estrogen from exams 1 to 8, of which 256 were missing information. Sample used is 1,323 women.

TABLE 3 Hazard ratios for breast cancer associated with Mediterranean diet indices.

Mediterranean diet indices	*N*	Cases	Rate per 1,000 PY	Age and calorie-adjusted HR (95% CI)[a]	Multivariable HR (95% CI)[b]
Median intake-based scores					
MDS index					
Low (0–3)	578	32	3.15	1 (Ref)	1 (Ref)
Moderate (4–5)	631	31	2.80	0.83 (0.51–1.38)	0.85 (0.51–1.41)
High (6–9)	370	24	3.75	1.08 (0.62–1.87)	1.15 (0.65–2.01)
P-trend[c]				*0.70*	*0.55*
aMED index					
Low (0–3)	568	33	3.33	1 (Ref)	1 (Ref)
Moderate (4–5)	581	30	2.94	0.91 (0.68–2.21)	0.89 (0.53–1.47)
High (6–9)	430	24	3.19	0.93 (0.67–1.29)	0.91 (0.51–1.60)
P-trend[c]				*0.58*	*0.71*
Pyramid-based scores					
MeDiet index					
Low (15–28)	401	30	4.31	1 (Ref)	1 (Ref)
Moderate (29–34)	682	36	3.01	0.67 (0.41–1.09)	0.68 (0.42–1.12)
High (35–51)	496	21	2.42	0.52 (0.29–0.91)	0.55 (0.31–0.97)
P-trend[c]				*0.02*	*0.04*
MSDP index					
Low (4.0–19.0)	442	32	4.21	1 (Ref)	1 (Ref)
Moderate (19.1–25.0)	506	27	3.05	0.69 (0.50–0.94)	0.71 (0.43–1.19)
High (25.1–50.9)	631	28	2.50	0.71 (0.53–0.95)	0.56 (0.33–0.94)
P-trend[c]				*0.03*	*0.03*

PY, person-years; MDS, Mediterranean Diet Score index by Trichopoulou et al., (17); aMED, Alternate Mediterranean Diet index by Fung et al., (18); MeDiet, Mediterranean Diet index by Panagiotakos et al., (20); MSDP, Mediterranean-Style Dietary Pattern index by Rumawas et al., (21).
[a]Model adjusted for age and total calorie intake. MSDP score analysis was adjusted for age only.
[b]Model was additionally adjusted for waist-to-height ratio, cigarette smoking (pack-years), physical activity, diabetes status, supplement use, and age at menopause.
[c]Derived from the test for linear trend, modeling the median value for each category as a continuous variable. Two-sided *P*-values <0.05 indicated statistical significance.

of these two pyramid-based scores had approximately 45% lower breast cancer risks, both with statistically significant trends. We found no association between median intake-based scores (i.e., MDS and aMED scores) and breast cancer risk.

We further analyzed the associations between the four Mediterranean diet indices and breast cancer risk among postmenopausal women only (Table 4). Due to insufficient power, we could not analyze premenopausal breast cancer separately, as there were only 6 cases of premenopausal breast cancer. Both pyramid-based scores (MeDiet and MSDP indices) were inversely associated with postmenopausal breast cancer risk; however, the results did not reach statistical significance. Once again, neither the MDS nor the aMED scores were associated with postmenopausal breast cancer risk.

Lastly, we examined the prospective associations between the four Mediterranean diet indices and the risk of any ER/PR positive breast cancer (Table 5). The highest MeDiet score category was strongly and inversely associated with any positive ER/PR breast cancer risk compared with the lowest category (HR: 0.45, 95% CI: 0.22–0.90). Results for the MSDP were weaker. We observed no association between the median intake-based scores and any ER/PR positive breast cancer risk.

4. Discussion

In this prospective cohort study of middle-aged women in a non-Mediterranean population, we examined the association between four different Mediterranean diet indices and breast cancer risk over approximately 18 years of follow-up. These four indices represent two different approaches to measuring adherence to a Mediterranean diet: (a) scores based on the population-specific median intakes of Mediterranean diet-related foods (i.e., aMED and MDS indices), and (b) scores based on compliance with recommended intakes of relevant foods from the Mediterranean diet pyramid (i.e., MeDiet and MSDP indices). We found that higher adherence to MeDiet and MSDP indices was protectively

TABLE 4 Hazard ratios for postmenopausal breast cancer associated with Mediterranean diet indices.

Mediterranean diet indices	*N*	Cases	Rate per 1,000 PY	Age and calorie-adjusted HR (95% CI)[a]	Multivariable HR (95% CI)[b]
Median intake-based scores					
MDS index					
Low (0–3)	578	29	2.85	1 (Ref)	1 (Ref)
Moderate (4–5)	631	28	2.52	0.80 (0.47–1.36)	0.81 (0.48–1.38)
High (6–9)	370	24	3.75	1.13 (0.64–1.98)	1.18 (0.66–2.09)
P-trend[c]				*0.55*	*0.46*
aMED index					
Low (0–3)	568	29	2.92	1 (Ref)	1 (Ref)
Moderate (4–5)	581	28	2.74	1.04 (0.59–1.84)	0.92 (0.54–1.57)
High (6–9)	430	24	3.19	0.93 (0.53–1.61)	0.99 (0.55–1.77)
P-trend[c]				*0.86*	*0.96*
Pyramid-based scores					
MeDiet index					
Low (15–28)	401	27	3.86	1 (Ref)	1 (Ref)
Moderate (29–34)	682	33	2.75	0.67 (0.40–1.12)	0.68 (0.41–1.15)
High (35–51)	496	21	2.42	0.56 (0.32–1.01)	0.58 (0.32–1.06)
P-trend[c]				*0.05*	*0.07*
MSDP index					
Low (4.0–19.0)	442	28	3.67	1 (Ref)	1 (Ref)
Moderate (19.1–25.0)	506	26	2.94	0.77 (0.45–1.31)	0.76 (0.45–1.31)
High (25.1–50.9)	631	27	2.41	0.62 (0.36–1.05)	0.59 (0.34–1.02)
P-trend[c]				*0.08*	*0.06*

PY, person-years, MDS, Mediterranean Diet Score index by Trichopoulou et al., (17); aMED, Alternate Mediterranean Diet index by Fung et al., (18); MeDiet, Mediterranean Diet index by Panagiotakos et al., (20); MSDP, Mediterranean-Style Dietary Pattern index by Rumawas et al., (21).
[a]Model adjusted for age and total calorie intake. MSDP score analysis was adjusted for age only.
[b]Model was additionally adjusted for waist-to-height ratio, cigarette smoking (pack-years), physical activity, diabetes status, supplement use, and age at menopause.
[c]Derived from the test for linear trend, modeling the median value for each category as a continuous variable. Two-sided *P*-values <0.05 indicated statistical significance.

associated with incident breast cancer. The risk estimates from the pyramid-based scores were associated with more than a 40% reduction in risk of total breast cancer as well as postmenopausal breast cancer. Results for hormone-receptor positive breast cancer were similar for MeDiet. Neither of the scores based on the population-specific median intakes (i.e., MDS and aMED indices) was associated with incident breast cancer risk.

Previous studies conducted in non-Mediterranean populations have frequently used Mediterranean diet scores based on median intakes when examining breast cancer risk. Studies using the MDS or aMED indices showed no association between adherence to the Mediterranean diet and breast cancer risk (10, 11, 14, 28–32), results that are consistent with the present study. Although the original authors who developed the aMED index in the Nurses' Health Study found that higher scores were protective against several inflammatory biomarkers (18) and cardiometabolic diseases (33)—mechanisms that may be linked with the development of cancer—the scores were not predictive of postmenopausal breast cancer risk (14). However, they did find that aMED scores were inversely associated with ER- breast cancer risk among postmenopausal women in a non-linear fashion. Contrary to our results, analyses in two cohort studies in US women showed that higher aMED scores (without alcohol in the index) were associated with somehow lower total risks of ER+ (12) and postmenopausal breast cancer (9, 10) but these results did not reach statistical significance. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, which recruited 335,062 women from a mix of the Mediterranean and non-Mediterranean countries, showed that higher scores on a modified version of aMED index (excluding alcohol and some food groups) were associated with lower risk of postmenopausal but not premenopausal breast cancer (13).

We are the first to report on associations between pyramid-based scores (i.e., MSDP and MeDiet indices) and breast cancer risk in a non-Mediterranean population. We found that both of these two indices were inversely associated with breast cancer risk in this mainly American Caucasian population. The evidence using these scores to predict breast cancer risk in Mediterranean populations has been limited, and results were inconsistent, possibly due to the limitations associated with a case-control

TABLE 5 Hazard ratios for any ER/PR positive breast cancer associated with Mediterranean diet indices.

Mediterranean diet indices	*N*	Cases	Rate per 1,000 PY	Age and calorie-adjusted HR (95% CI)[a]	Multivariable HR (95% CI)[b]
Median intake-based scores					
MDS index					
Low (0–3)	575	25	2.46	1 (Ref)	1 (Ref)
Moderate (4–5)	624	21	1.90	0.73 (0.40–1.31)	0.75 (0.41–1.35)
High (6–9)	368	18	2.81	1.04 (0.55–1.96)	1.13 (0.59–2.16)
P-trend[c]				*0.78*	*0.60*
aMED index					
Low (0–3)	565	26	2.62	1 (Ref)	1 (Ref)
Moderate (4–5)	575	22	2.16	1.37 (0.71–2.63)	0.83 (0.46–1.49)
High (6–9)	427	16	2.12	1.08 (0.56–2.08)	0.77 (0.39–1.50)
P-trend[c]				*0.33*	*0.42*
Pyramid-based scores					
MeDiet index					
Low (15–28)	398	23	3.29	1 (Ref)	1 (Ref)
Moderate (29–34)	675	28	2.35	0.68 (0.39–1.19)	0.70 (0.40–1.22)
High (35–51)	494	13	1.49	0.42 (0.21–0.83)	0.45 (0.22–0.90)
P-trend[c]				*0.01*	*0.02*
MSDP index					
Low (4.0–19.0)	438	24	3.15	1 (Ref)	1 (Ref)
Moderate (19.1–25.0)	502	19	2.15	0.67 (0.36–1.22)	0.67 (0.37–1.23)
High (25.1–50.9)	627	21	1.88	0.57 (0.32–1.03)	0.57 (0.31–1.04)
P-trend[c]				*0.07*	*0.07*

ER/PR, estrogen receptor or progesterone receptor; PY, person-years; MDS, Mediterranean Diet Score by Trichopoulou et al., (17); aMED, Alternate Mediterranean Score by Fung et al., (18); MeDiet, Mediterranean Diet Score by Panagiotakos et al., (20); and MSDP, Mediterranean–Style Dietary Pattern Score by Rumawas et al., (21).

[a]Model adjusted for age and total calorie intake. MSDP score analysis was adjusted for age only.

[b]Model was additionally adjusted for waist-to-height ratio, cigarette smoking (pack-years), physical activity, diabetes status, supplement use, and age at menopause.

[c]Derived from the test for linear trend, modeling the median value for each category as a continuous variable. Two-sided *P*-values <0.05 indicated statistical significance.

design (34, 35). Nevertheless, previous findings showed that higher adherence to these pyramid-based scores might prevent the development of metabolic dysfunction and, as a result, prevent the development of obesity-related cancers, including breast cancer. Previous prospective cohort analysis in the Framingham Study showed that individuals without prevalent diabetes who had higher MSDP scores had less metabolic dysfunction, as evidenced by a lower waist circumference, lower fasting plasma glucose, lower triglyceride levels, less insulin resistance, and higher HDL cholesterol levels, compared with those who had lower scores (36). Further, an analysis among US adults from the NHANES study showed that higher MeDiet scores were associated with lower adiposity measures, inflammatory markers, and glucose and lipoprotein a levels after multivariable adjustment (37). Moreover, the present study found that higher MeDiet scores were strongly and inversely associated with any hormone receptor (ER/PR) positive breast cancer risk. This could be due to effects of certain bioactive compounds (e.g., anti-oxidants and flavonoids) in the Mediterranean diet that have been shown to reduce endogenous estrogen production and increase sex-hormone binding globulin levels, thus decreasing circulating levels of estrogen (13).

Methodological differences in the composition of different indices may explain the inconsistency between studies with respect to the cancer-protective effects of the Mediterranean diet (15). Specifically, it may be that scores based on median cut-off values may perform differently in Mediterranean and non-Mediterranean populations as they consume different amounts of traditional Mediterranean-style foods. In contrast, scores that are based on recommended intakes of relevant foods may be more appropriately applied in different non-Mediterranean populations because the standards for assigning points do not change based on the intake distributions. Further, the foods considered to be Mediterranean foods differ between indices (e.g., potatoes are excluded from the MDS and aMED indices and dairy from the aMED). There are other differences between these indices as well. The MSDP score has a penalty for overconsumption and takes into account the consumption of non-Mediterranean foods of a similar type. However, these features make the score more computationally complex. Comparing the MeDiet and MSDP indices, the overconsumption penalty and the weighting strategies used to account for total energy intake in the MSDP index may explain the generally lower adherence (the maximum observed score in this study was 50.9 out of a possible maximum of 100 points) to the Mediterranean diet pattern with this index. In contrast, the MeDiet index applied in the same study population generally produced much higher adherence scores (a maximum of 51 out of a possible maximum of 55 points). Moreover, the standard for assigning the maximum points for each MSDP component score was based on a single recommended intake value, making it difficult for most individuals to be fully adherent to each component.

A systematic review comparing 28 Mediterranean diet indices concluded that the MeDiet index was one of the very few scores that provided strong construct and content validity, internal consistency, and evidence for an association with biological markers. The MSDP and MDS indices did not perform as well on these psychometric properties, and the aMED index was not evaluated (36). A more recent review comparing 8 different Mediterranean diet indices concluded that those indices whose scoring scheme was based on a single threshold (e.g., MDS), thus yielding a dichotomous score for each food item, provided less accurate measures of adherence to the diet pattern compared with others that assign scores proportional to the degree of concordance. While each index has strengths and limitations, the current findings suggest that the scores based on population-specific median intakes may not be as appropriate as the pyramid-based scores for measuring adherence to the Mediterranean diet in a non-Mediterranean population.

Some of the strengths of this study include the direct comparison of four established Mediterranean diet indices within the same non-Mediterranean study population to predict the same outcome. We used a prospective design and a thorough adjudication of cancer cases using standardized procedures. In addition, confounding effects were minimized as much as possible, given the careful, systematic collection of various variables. For example, adiposity, an important risk factor for breast cancer, was directly measured rather than self-reported. Nonetheless, residual confounding is always a possibility.

There are several limitations in this study as well. The dietary information was derived from FFQs, which have been associated with measurement errors. However, earlier validation studies of the Harvard FFQ showed that many of the foods included in these indices were adequately captured on the FFQ based on correlations with diet records (38). Another important limitation of this study is the limited power associated with small numbers of subjects, especially for the analysis of breast cancer subtypes. Further, although the use of oral contraceptives is a traditional breast cancer risk factor; these data were not available in this dataset. Lastly, the FOS cohort consists of exclusively Caucasian individuals, and therefore more studies are needed to confirm these results in other non-Mediterranean populations.

5. Conclusion

In this prospective study of middle-aged American Caucasian women, we found that higher adherence to the Mediterranean diet, as assessed by scores based on compliance with recommended intakes of relevant foods (MeDiet and MSDP indices) from the Mediterranean diet pyramid, was associated with a lower risk of incident breast cancer. This was not the case for scores based on population-specific median intakes of Mediterranean diet-related foods (MDS and aMED indices). In conclusion, our results suggest that the methodology and the composition of Mediterranean diet indices influence their ability to assess conformity to this specific diet pattern and predict disease risk. Specifically, indices based on median intakes may not predict cancer risk as well as scores based on traditional Mediterranean diet pyramid recommendations when used in non-Mediterranean populations. The heterogeneity in these indices and their use in different study populations may explain some of the differences in results between existing studies of the Mediterranean diet pattern and risk of breast cancer and other chronic diseases.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found upon request at https://biolincc.nhlbi.nih.gov/studies/framoffspring/ (accessed on 13 September 2022).

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Boston University School of Medicine which approved the Framingham Offspring Study data collection and these analyses (Protocols H-32086 and H-32132). The participants provided their written informed consent to participate in this study.

Author contributions

LLM and IY designed the analysis and wrote the manuscript. IY analyzed the data. MRS curated the data. IY, MRS, and LLM participated in interpreting the results and editing the manuscript. All authors read and approved the final 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1148075/full#supplementary-material

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A case–control study on the association between adherence to a Mediterranean-style diet and breast cancer

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Background: Previous studies on the association between diet and breast cancer are mostly from Western populations, and data from Middle East countries are scarce, where the prevalence of breast cancer is high; therefore, it ranks first among other cancers. This population-based case–control study aimed to investigate the relationship between a Mediterranean-style diet and breast cancer among Iranian women.

Methods: In the current study, 350 new cases of breast cancer and 700 age- and socioeconomic status-matched controls were enrolled. We evaluated the dietary intakes of participants by using a 106-item Willett-format semi-quantitative dish-based food frequency questionnaire (SQ-FFQ). We calculated the Mediterranean diet score according to the dietary intakes of participants. In addition, using pre-tested questionnaires, we collected information on potential confounding variables.

Results: In this study, we found a significant inverse association between the Mediterranean diet and breast cancer so that after controlling for potential confounders, individuals in the highest tertile of the Mediterranean diet score compared with those in the lowest tertile were 57% less likely to have breast cancer [odds ratio (OR): 0.43, 95% confidence interval (CI): 0.28–0.67]. Such an inverse association was also observed for postmenopausal women. Similarly, after controlling for potential confounding variables, high adherence to the Mediterranean dietary pattern was associated with lower odds of breast cancer (OR: 0.37, 95% CI: 0.23–0.60). However, this relationship was not significant among premenopausal women.

Conclusion: We found that adherence to Mediterranean dietary pattern was associated with reduced odds of breast cancer. Studies with prospective design are needed to further examine this association.

KEYWORDS
Mediterranean diet, breast cancer, case–control study, food frequency questionnaire, diet

Introduction

Mediterranean dietary pattern is one of the healthy dietary patterns which is associated with high intakes of plant foods, olive oil, fish, and sea foods, low-to-moderate consumption of milk and dairy products, low consumption of poultry, red and processed meat, and moderate consumption of wine (during meals) (1, 2). This dietary pattern is rich in fiber, antioxidants, omega-3 polyunsaturated fatty acids (PUFAs), vitamins B and E, and minerals such as magnesium (3, 4). Previous studies have shown that these nutrients have beneficial effects on chronic diseases such as cardiovascular diseases (CVDs), hypertension, and some cancers (5–7). For instance, in the UK Women's Cohort Study, the Mediterranean dietary pattern was inversely associated with colorectal cancer risk (8). In addition, it has been shown that the Mediterranean diet has protective effects against prostate, gastric, and pancreatic cancers (9–11).

Given the anti-inflammatory effects of the Mediterranean diet, it may have a benefit for the prevention of cancers such as breast cancer. However, the Mediterranean dietary pattern is rich in phytoestrogens that may adversely affect breast cancer incidence (12). In addition, the findings from previous studies on the relationship between adherence to the Mediterranean dietary pattern and the risk of breast cancer are conflicting. In a systematic review in 2015, Farsinejad et al. reported that there is no sufficient data to reach a definite conclusion about the effect of the Mediterranean diet on the risk of breast cancer in premenopausal and postmenopausal women (13). However, in the PREDIMED trial, it has been shown that adherence to the Mediterranean dietary pattern combined with extra-virgin olive oil has beneficial effects on the prevention of breast cancer (14). In addition, a case–control study reported an inverse association between the Mediterranean diet and breast cancer (15). However, in a prospective cohort study in Sweden, no significant association between the Mediterranean dietary pattern and the risk of breast cancer was reported (16). In addition to discrepant findings, most studies on the association between the Mediterranean diet and the risk of breast cancer have been conducted in Western countries, whereas no study is available on the Middle Eastern population where the incidence of breast cancer is estimated to be high. In Iran, the prevalence of breast cancer is high, and its incidence rate is 35.8 per 100,000 population (17). In Mediterranean countries, adherence to the Mediterranean dietary pattern is common; however, adherence to a Mediterranean-style diet may have beneficial effects on the Middle Eastern population. Therefore, our study aimed to investigate the relationship between adherence to the Mediterranean dietary pattern and breast cancer in Iranian women.

Materials and methods

Study population

We conducted a population-based case–control study on women older than 30 years living in Isfahan, Iran. In this study, breast cancer cases were diagnosed by mammography findings and physical examination within the last 6 months at most. From July 2013 to July 2015, cases of breast cancer were recruited from patients who were referred to private clinics or hospitals in Isfahan, Iran. By considering that an unhealthy diet might enhance the risk of breast cancer by 1.5 times and the type I error of 5%, the study power of 80%, the common ratio of 0.25 and 2 for the ratio of controls to cases, we required 350 cases of breast cancer and 700 healthy controls for the current study. Cases were undergoing surgical resection of breast tumors, chemotherapy, radiotherapy, or all of them. In the current study, cases were those who had a primary breast tumor with aggressive behavior, and its histology was available and accessible in patients' medical records. We did not include patients who had a history of neoplastic lesions or cysts (except current breast cancer), and those patients who had a history of hormone replacement therapy. In addition, patients who had a special diet were not included. Using the cluster method sampling, age (±5 year) adjusted controls were randomly selected from healthy women who had no relationship with breast cancer patients and had no family history of breast cancer. In addition to age, we did our best to match controls in terms of their place of residence as a proxy measure of socioeconomic status (SES) with the cases. In this study, controls were Iranian women who had no history of malignancy, medical disorder, cysts, and hormone replacement therapy and who did not have a special diet from the general adult population. Finally, 350 cases and 700 controls were included in this study. An informed consent form was provided to participants, and they were asked to sign it. The Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran has ethically approved the present study.

Assessment of dietary intakes

In this study, the dietary intakes of participants were collected by using a 106-item Willett-format semi-quantitative dish-based food frequency questionnaire (SQ-FFQ). This questionnaire has been specifically designed and validated for the Iranian population (18). Information on the design and validity of this questionnaire has been reported elsewhere (19). In the current study, a trained nutritionist completed the questionnaires through a face-to-face interview. Participants reported their dietary intake of foods and mixed dishes according to 9 multi-choice frequency response categories ranging from "never or less than once per month" to "≥ 12 times per day." For the food list, categories of frequency response ranged from 6 to 9 choices. For low-consumption foods, we eliminated the high-frequency categories, while for high-consumption foods, the number of multiple-choice categories was increased. Finally, for all food items, we calculated daily intakes and then using household measures converted them to grams per day (20). We computed daily values for all food items according to the composition of foods, average frequency of food consumption, and portion size of foods. We computed nutrient intake by summing up the nutrients of all foods. In this study, we obtained nutrient intake by using Nutritionist IV software, which was modified for Iranian foods.

Construction of the Mediterranean diet score

Based on the methodology by Trichopoulou (21, 22), we computed scores of the Mediterranean diet based on nine components [positive components: fish, fruits, vegetables, legumes, nuts, and ratio of monounsaturated fatty acids (MUFAs) to saturated fatty acids (SFAs) and negative components: grains, dairy, and meats (poultry, red meat, and processed meat)]. If participants were at the top median intakes of positive components and bottom median intakes of negative components, they received a score of 1. Participants received a score of 0 if they were at the top median intakes of negative components and bottom median intakes of positive components. By summing up the score of each component, we obtained the total score for the Mediterranean diet.

Assessment of breast cancer

All breast cancer patients were Iranian women who were recently diagnosed with breast cancer (stages I–IV). For all of them, the local or invasive status of breast cancer was determined by using mammography and physical examination. Mammography is an imaging method using X-ray that is used to diagnose diseases related to the breast (23). The adverse side effects of exposing breasts to radiation with this method are very low and can be ignored. To perform mammography, patients were placed in standing, vertical, and horizontal situations. For a few seconds, the breast was pressed between pages, and then, the photograph was taken.

Evaluation of other variables

By using a pre-tested questionnaire, we collected information about participants' age, education, marital status, menopausal status, region, family history of breast cancer, smoking, consumption of alcohol, and disease history. This questionnaire was completed for all participants through face-to-face interviews. Regarding anthropometric assessments, participants' weight was measured using a digital scale to the nearest 100 grams. Weight measurements were taken while the participants were minimally clothed and without shoes. By using a tape meter that was mounted on the wall, we measured the height of participants to the nearest 0.5 cm. Height measurement was performed while the participants were standing normally without shoes. In addition, we calculated body mass index (BMI) according to the following formula: "weight (kilograms)/height (meters squared)." In the current study, a short form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate the physical activity level of the participants. Participants were classified as physically inactive (having <1 h of moderate physical activity per week) or physically active (having 1 h or more of moderate physical activity per week).

Statistical analysis

At first, by using an independent sample *t*-test and chi-square test, cases and controls were compared in terms of general characteristics. Then, participants were classified according to tertile cutoff points of the Mediterranean diet score. To investigate the differences of continuous variables across tertiles of the Mediterranean diet score, we used one-way ANOVA. In addition, to evaluate categorical variable distribution across tertiles of the Mediterranean diet score, the chi-square test was employed. To determine the relationship between adherence to the Mediterranean diet and breast cancer, we used binary logistic regression in adjusted models. Age and energy intake were considered in the first model. In the second model, we made further adjustments for participants' education (non-educated/educated), marital status (single/married), menopausal status (premenopausal/postmenopausal), region (rural/urban), family history of breast cancer (no/yes), smoking (non-smoker/smoker), consumption of alcohol (no/yes), physical activity, socioeconomic scores (continuous), and disease history (no/yes). In addition, the final model was adjusted for BMI, to remove the confounding effect of obesity from the relationship between the Mediterranean diet and breast cancer. In all analyses, the reference group was those who were in the first tertile of the Mediterranean diet score. In the current study, to obtain the overall trend of odds ratios of breast cancer across tertiles of the Mediterranean diet score, we considered these categories as an ordinal variable. In addition, the analysis of logistic regression was stratified according to menopausal status (premenopausal/postmenopausal). By using SPSS software (version 18), we performed all statistical analyses. In this study, the significance level was P-value < 0.05.

Results

Table 1 presents the general characteristics of cases and controls. Compared with the control group, cases are more likely to be older, single, postmenopausal, smoker, non-educated, and have a lower BMI and family history of breast cancer. We found no other significant differences between cases and controls.

Table 2 shows the general characteristics of participants across tertiles of the Mediterranean diet score. Women with the highest tertile of the Mediterranean diet score were more likely to be younger, married, educated, alcohol consumers, living in urban areas, having a higher BMI and socioeconomic score and were less likely to be postmenopausal and have a history of disease compared with those in the lowest category. There was no other significant difference in this regard.

Table 3 indicates the dietary intakes of women across tertiles of the Mediterranean diet score. Compared with women in the bottom tertile of the Mediterranean diet score, those in the top tertile had higher intakes of fish, legumes, nuts, fruits, vegetables, MUFAs, PUFAs, and fiber and lower intakes of grains, dairy products, and SFAs. In addition, the ratio of MUFAs-to-SFAs was different across tertiles of the Mediterranean diet score. We found no other significant differences in this regard.

TABLE 1 General characteristics of cases and controls.

Variables	Cases (n = 350)	Controls (n = 700)	P-value*
Age (year)	65.2 ± 11.2	61.0 ± 10.3	<0.001
Social economic status	12.8 ± 5.2	13.4 ± 5.5	0.09
BMI (kg/m^2)	21.8 ± 4.8	25.5 ± 5.0	<0.001
Region (urban) (%)	36.0	36.1	0.96
Marital status (single) (%)	25.1	11.3	<0.001
Education (educated) (%)	17.4	28.9	<0.001
Disease history (yes) (%)	10.3	8.7	0.40
Physical activity (inactive) (%)	31.7	34.4	0.38
Family history of breast cancer (yes) (%)	9.4	3.4	<0.001
Menopausal status (postmenopausal) (%)	88.3	77.4	<0.001
Smoking (smoker) (%)	17.4	13.0	0.05
Alcohol (alcoholic) (%)	4.6	7.4	0.07

Data are presented as mean (SD) or percent.
BMI, body mass index.
*Obtained from independent sample t-test or chi-square, where appropriate.

TABLE 2 General characteristics of the study participants across tertiles (T) of Mediterranean diet scores.

	T_1	T_2	T_3	P*
Age (year)	65.31 ± 10.06	61.78 ± 11.01	60.66 ± 10.80	<0.001
BMI (kg/m^2)	23.25 ± 5.27	24.49 ± 5.44	25.14 ± 4.90	<0.001
Socioeconomic score	11.41 ± 4.48	12.76 ± 4.94	15.72 ± 6.16	<0.001
Region (urban) (%)	24.7	33.7	51.0	<0.001
Marital Status (single) (%)	21.6	15.4	11.0	0.009
Education (Educated) (%)	16.6	19.8	41.3	<0.001
Disease history (yes) (%)	12.2	9.5	6.0	0.03
Physical activity (inactive) (%)	37.5	32.6	31.0	0.20
Family history of breast cancer (yes) (%)	7.8	5.3	3.3	0.06
Menopausal status (post) (%)	88.5	79.3	76.3	<0.001
Smoking (smoker) (%)	17.2	13.9	12.7	0.25
Alcohol consumption (yes) (%)	1.4	5.7	12.7	<0.001

Data are presented as mean (SD) or percent.
BMI, body mass index.
*Obtained from one-way analysis of variance (ANOVA) or chi-square, where appropriate.

Table 4 illustrates multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer across tertiles of the Mediterranean diet score. We found a significant inverse association between the Mediterranean diet and breast cancer (OR: 0.34, 95% CI: 0.23–0.48). Such association was also seen after adjusting for demographic variables, menopausal status, energy intake, physical activity, and BMI; such that women in the top tertile of the Mediterranean diet score compared with those in the bottom tertile had 57% lower odds of breast cancer (OR: 0.43, 95% CI: 0.28–0.67). Such association was also observed for postmenopausal women; such that after controlling for potential confounding variables, postmenopausal women in the highest tertile of the Mediterranean diet score compared with those in the lowest tertile were 63% less likely to have breast cancer (OR: 0.37, 95% CI: 0.23–0.60). However, among premenopausal women, we found no significant association in this regard.

Discussion

In the present study, we found a significant inverse relationship between the Mediterranean diet and the odds of breast cancer. After controlling for potential confounders, this association remained significant. Among postmenopausal women, a significant inverse association was found, while among premenopausal women, this

TABLE 3 Dietary intakes of study participants across tertiles (T) of Mediterranean diet scores.

	T_1	T_2	T_3	P^*
Food groups (g/d)				
Fruits	131.4 ± 161.1	150.6 ± 135.5	219.2 ± 160.3	<0.001
Vegetables	44.6 ± 38.4	76.1 ± 59.0	124.0 ± 92.8	<0.001
Legume	8.9 ± 8.9	13.8 ± 11.2	21.9 ± 20.8	<0.001
Nuts	0.3 ± 1.0	2.0 ± 4.7	4.7 ± 8.2	<0.001
Fish	3.9 ± 11.2	10.6 ± 44.7	12.4 ± 16.0	0.002
Grains	441.2 ± 155.2	440.5 ± 163.0	409.0 ± 148.6	0.01
Dairy products	251.0 ± 186.1	211.5 ± 138.2	242.5 ± 143.0	0.001
Meat	89.3 ± 73.3	89.8 ± 87.7	88.8 ± 66.2	0.98
Nutrients				
Energy (kcal/d)	2,301 ± 715	2,286 ± 712	2,265 ± 637	0.81
Protein (g/d)	77.7 ± 27.2	76.8 ± 30.3	78.3 ± 27.3	0.77
Carbohydrate (g/d)	314.4 ± 112.2	318.6 ± 110.9	318.0 ± 97.0	0.86
Fat (g/d)	87.4 ± 35.3	84.3 ± 36.9	82.1 ± 31.1	0.17
SFA (g/d)	52.7 ± 26.4	48.0 ± 29.3	41.4 ± 19.5	<0.001
MUFA (g/d)	19.4 ± 7.7	20.0 ± 8.2	21.5 ± 8.8	0.004
PUFA (g/d)	8.4 ± 4.2	9.5 ± 5.0	12.4 ± 10.6	<0.001
MUFA/SFA	0.4 ± 0.1	0.5 ± 0.2	0.6 ± 0.3	<0.001
Fiber (g/d)	20.6 ± 7.4	22.2 ± 7.9	24.2 ± 7.9	<0.001

Data are presented as mean (SE).
SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; g/d, gram/day; kcal/d, kcal/day.
*Obtained from one-way ANOVA.

TABLE 4 Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CI) for breast cancer across tertiles (T) of Mediterranean diet scores.

	Mediterranean diet scores		
	T_1	T_2	T_3
Total			
Crude	1	0.65 (0.48–0.88)	0.34 (0.23–0.48)
Model 1	1	0.73 (0.53–1.01)	0.38 (0.26–0.56)
Model 2	1	0.74 (0.53–1.03)	0.42 (0.28–0.63)
Model 3	1	0.78 (0.54–1.12)	0.43 (0.28–0.67)
Premenopausal women			
Crude	1	0.68 (0.29–1.58)	0.51 (0.22–1.17)
Model 1	1	0.76 (0.31–1.83)	0.61 (0.25–1.44)
Model 2	1	0.88 (0.33–2.35)	0.76 (0.28–2.06)
Model 3	1	1.45 (0.43–4.83)	1.94 (0.57–6.54)
Postmenopausal women			
Crude	1	0.64 (0.46–0.89)	0.33 (0.22–0.49)
Model 1	1	0.69 (0.49–0.98)	0.35 (0.23–0.52)
Model 2	1	0.70 (0.49–1.00)	0.37 (0.24–0.58)
Model 3	1	0.73 (0.50–1.07)	0.37 (0.23–0.60)

Data are presented as OR and 95% CI.
Model 1: adjusted for age and energy.
Model 2: additionally, adjusted for region, marital status, education, disease history, physical activity, family history of breast cancer, menopausal status, smoking, alcohol consumption, and socioeconomic status.
Model 3: additional adjustment for BMI.
ORs were obtained from binary logistic regression.

association was not significant. To the best of our knowledge, this is the first study on the Middle Eastern population that examined the relationship between the Mediterranean dietary pattern and breast cancer.

Breast cancer is one of the most common cancers among women (24, 25). Previous studies on diet–breast cancer relationships revealed that diet as a modifiable risk factor has an important contribution to the etiology of cancers such as breast cancer (24–27). Recent studies have mainly investigated the relationship between individual food groups or nutrients with breast cancer, and the influence of a whole diet has less been studied (28). In the current study, an inverse association was found between the Mediterranean dietary pattern and the odds of breast cancer. Our findings were aligned with the findings from a case–control study conducted by Turati et al. in Switzerland in which adherence to the Mediterranean diet was inversely associated with the risk of breast cancer (15). The findings from a prospective cohort study conducted by Brandt et al. showed an inverse association between adherence to the Mediterranean dietary pattern and receptor-negative breast cancer (29). However, in the Swedish Women's Lifestyle and Health cohort study that was performed on 49,258 women aged 30–49 years, Couto et al. showed that the Mediterranean dietary pattern did not decrease breast cancer risk (16). Different findings of Couto et al. study might be due to the different age range participants compared with previous studies and also ours. Couto et al. recruited young women (30–49 years) and all of them are probably premenopausal women. It seems that the association between the Mediterranean diet and breast cancer is different between pre- and postmenopausal women; such that evidence of the inverse association among postmenopausal women is more than premenopausal ones. Moreover, in the current study, we found a significant inverse relationship between the Mediterranean diet and breast cancer among postmenopausal women but not among premenopausal women. In addition, different adjustments for confounding variables are another reason for the observed controversy.

The observed disparity between premenopausal and postmenopausal women might be explained by internal estrogen in premenopausal women. Internal estrogen can increase breast cancer risk by increasing reactive oxygen species (ROS) production in the breast (30, 31). In addition to causing genotoxicity through an indirect increase in genomic instability, excess ROS can stimulate breast carcinogenesis by triggering a redox–associated signaling pathway (32). Overall, the non-significant relationship between the Mediterranean dietary pattern and breast cancer in premenopausal women might be due to the interference of endogenous estrogenic effects with the beneficial effects of the Mediterranean diet.

Although the exact mechanisms through which the Mediterranean diet contributes to the prevention of breast cancer are unclear, this protective effect might be due to its nutrient content. Mediterranean diet contains a high amount of MUFAs and omega-3 fatty acids that have anti-inflammatory properties (21, 33). Inflammation is an important risk factor in the incidence of breast cancer (34). Mediterranean diet is rich in dietary fiber, lignans, flavonoids, and other compounds that are known to support estrogen metabolic pathways and have estrogen-modulatory effects which are protective against breast cancer among premenopausal and postmenopausal women (35–37). Antioxidant-rich foods such as fruits and vegetables are other components of the Mediterranean diet that can have protective effects against breast cancer by reducing the production of oxidant species (38).

This study has several strengths. First, we investigated the relationship between adherence to the Mediterranean dietary pattern and breast cancer in the Middle East. In addition, we controlled our analyses for many confounding variables. We presented a subgroup analysis based on menopausal status which is an important confounder in diet–cancer relationships. Furthermore, to collect data, we used validated questionnaires, which can support the accuracy of our findings. However, some limitations should be taken into account. Since selection and recall bias are common in case–control studies, our findings are subjected to these two types of bias. In addition, due to the use of FFQ, misclassification of study participants is inevitable. In this study, although we controlled our analyses for several confounding variables, we cannot exclude the potential effects of remaining confounding variables. In addition, since the dietary intakes of the Middle East nations are different from the Western population, caution should be taken in generalizing these findings to other populations.

Conclusion

In conclusion, we found that adherence to a Mediterranean-style diet was associated with reduced odds of breast cancer in the Middle Eastern population. Such finding was also seen among postmenopausal women but not among premenopausal women. To confirm these findings, more studies should be conducted in diverse populations. In addition, future studies should determine this association for receptor-negative and receptor-positive breast cancer patients separately.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the Isfahan University of Medical Sciences, Isfahan, Iran. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AE, SB-K, and LA contributed to the conception, design, and data collection. SB-K contributed to data preparation. OS, NE, and AE contributed to data analysis and manuscript drafting. AE supervised the study. All authors read and approved the final 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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Mediterranean diet adherence on self-concept and anxiety as a function of weekly physical activity: an explanatory model in higher education

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Introduction: Scientific literature has now demonstrated the benefits of an active lifestyle for people's psychological health. Based on the above statement, the aim was to (a) evaluate and adjust a structural equation model containing the variables anxiety, self-concept, and Mediterranean diet adherence and (b) contrast the proposed theoretical model by studying the differences between the variables according to the level of weekly physical activity in a sample of 558 university students.

Methods: A non-experimental, exploratory, cross-sectional investigation has been proposed. Instruments such as the PREDIMED Questionnaire, the Beck Anxiety Inventory, the International Physical Activity Questionnaire, and the Form 5 Self-Concept Questionnaire were used to collect data.

Results and discussion: The results illustrate that students showing low adherence to the Mediterranean diet had higher levels of anxiety (M = 0.95) than those showing a high degree of adherence (M = 0.75). It is also observed that young people with a high degree of adherence to the Mediterranean diet report higher scores in the different dimensions of self-concept compared to young people with a low degree of adherence. In conclusion, it is affirmed that young people who show a high degree of adherence to this dietary pattern show lower levels of anxiety and greater recognition of the different areas of their self-concept.

KEYWORDS

Mediterranean diet (MD), self-concept, anxiety, physical self-concept, university students

1. Introduction

The undergraduate educational stage is assumed to be a time period in which critical changes in dietary patterns (1, 2) and time spent in physical activity occur (3, 4). It has been observed that during this academic period, there is a decrease in the intake of healthy foods as well as less time devoted to physical exercise (5). Mainly, the intake of healthy foods is reduced due to the high academic load that young university students have (5), opting directly for precooked dishes that have a high caloric level (4, 5).

In terms of following and adhering to a healthy dietary pattern, numerous research studies have shown that the Mediterranean diet has health benefits for individuals (6). These benefits are not only due to the type of food but also to the quality, cooking, and nutrient supply of the food (7, 8). This dietary model is characterized by the ingestion of fresh, seasonal, and local products, as well as a diet low in animal fats and refined sugars (9). On the other hand, the consumption of fruits, vegetables, cereals, and legumes predominates higher consumption of oily fish, eggs, and foods rich in omega-3 fatty acids (6–9). Although there are many variations on this model, it is agreed that more than half of the micronutrient intake comes from carbohydrates (9). Regarding the quality of fats, it is observed that most of the fatty acids are monounsaturated (8, 9). Specifically, a low degree of adherence to the Mediterranean diet has been observed in the university population (5, 6). Studies have shown that positive adherence to the Mediterranean diet has health benefits for young people (10). Knight et al. (10) noted that positive follow-up helps increase the quality of life and reduces the risk of cardiovascular disease, as well as various types of cancer. Likewise, it has been observed that a positive follow-up to this dietary pattern, together with an adequate level of physical activity, provides benefits to the cognitive and emotional areas of young people (6).

Another element that provides numerous benefits for physical and mental health is the practice of regular physical activity (11). Physical activity is defined as any bodily movement performed by skeletal muscles, which involves significant energy expenditure (12). Currently, for the practice of physical activity to be beneficial, the World Health Organization (13) has established different time ranges depending on the age range. In terms of time, that organization (13) states that people between 18 and 64 years of age should perform between 150 and 300 min of moderate aerobic physical activity per week. Regarding the type of physical activity, the World Health Organization (13) states that if the physical activity is aerobic and vigorous, it should be between 75 and 150 min per week. In addition, if moderate aerobic physical activity exceeds 300 min and vigorous aerobic physical activity exceeds 150 min per week, additional mental health benefits are obtained (11). Being active from the physical point of view denotes improvements at the organic level, such as improved muscular and cardiorespiratory fitness, improved functional and bone health, reduced risk of hypertension, and prevention of different types of cancer (13). Regarding the psychological area, it has been observed that the regular practice of physical exercise brings benefits to the mental conception that the subject has of himself (14).

Self-concept is defined as the mental representation that a person creates of himself/herself as he/she interacts with and relates to the different environments of his/her daily life (15). Initially, this construct was conceived in a unidimensional way (16), but a multidisciplinary view of it has been constructed (17). The study model proposed by Shavelson et al. (18) differentiates self-concept into two subdimensions, namely, academic and non-academic. The latter is made up of physical, emotional, family, and social dimensions (18). This view has been studied in numerous investigations (19, 20), as it does not focus exclusively on academic elements but also on areas closely related to physical and mental wellbeing. One of the dimensions that gains more strength within the study of self-concept is the physical area (17). In this area, it has been observed that many young people show dissatisfaction with their physical condition (17). If this dissatisfaction is prolonged over time, disorders related to physical appearance may develop, directly affecting the emotional area (15).

Poor attention to mental health can lead to mental illnesses such as anxiety (21). This state is characterized by the association of symptoms such as muscle tension, a high degree of irritability, and a high state of worry (21). The study by Dasinger and Solmon (22) found that regular physical activity helps to reduce this state due to the release of neurotransmitters (4). Likewise, Marchena et al. (23) and Trigueros et al. (24) developed the idea that a healthy food intake and a positive adherence to a healthy diet have a positive effect on mental health, helping to prevent the occurrence of disturbing states. Likewise, it has been observed that young people who show poorer adherence to the Mediterranean diet and a sedentary lifestyle show higher levels of anxiety (24). It has been found that the university population shows high levels of anxiety about the academic environment (23). Despite this, many young people show a process of emotional overeating consisting of uncontrolled food intake to palliate the effects of anxiety (23, 24).

Once the problems that are evident in this study have been contextualized, this study aimed to (a) evaluate and fit a structural equation model containing the variables anxiety, self-concept, and Mediterranean diet adherence and (b) contrast the proposed theoretical model by studying the differences between the variables according to the level of weekly physical activity in a sample of 558 university students.

2. Material and methods

2.1. Sample and design

An exploratory, cross-sectional, and *ex post facto* study of 558 Spanish university students has been proposed. The sample is made up of university students in educational sciences. Focusing attention on the sociodemographic variables, the students' ages were between 18 and 31 years (25.09 ± 6.22). Regarding the distribution of the sample according to sex, three-quarters of the population (75%) belonged to the female sex, and one-quarter (25%) belonged to the male sex. Convenience sampling was employed to collect the data. Likewise, responses from participants who did not meet the inclusion criteria have been eliminated (studying a degree related to educational sciences).

2.2. Variables and instruments

The variables that make up the study and the instruments used for data collection are detailed below.

Own elaboration Questionnaire: It was used to collect age and sex (male/female). This instrument was used to add complementary data to the study sample.

Beck Anxiety Inventory: It has been used to collect the anxiety variable. It was initially settled by Beck et al. (25). According to the sample size of this research, the version adapted by Sanz and Navarro (26) has been used. The reason why the version of Sanz and Navarro (26) was used is because this version is adapted for university students. It consists of 21 items (For the past month I have felt unable to relax) that are answered through a 4-level Likert scale (0 = Not at all; 3 = Severely). This questionnaire has shown a high degree of reliability with a value of α = 0.939 in this study. It was decided to use this instrument because of its high degree of reliability. Likewise, this questionnaire offers an analysis of anxiety as studied in this research.

Self-Concept Questionnaire Form 5: It was designed and adapted to Spanish by García and Musitu (27). It consists of 30 items (I do my school work well) that are answered on a Likert scale. The reliability analysis showed in this research a value of α = 0.889. This instrument assesses self-concept under the theory developed by Shavelson et al. (18). This allows for a multidimensional view, wherein each self-concept variable can be studied as an independent variable.

Predimed Questionnaire: It was elaborated by Schöder et al. (28). The version by Álvarez-Álvarez et al. (29) was used due to the characteristics of the sample under study. The reason for using the version of Álvarez et al. (29) is due to the high degree of reliability and the adaptation of this instrument to the population under study. It consists of 14 items (e.g., Do you use olive oil as your main culinary fat? and How many sweet or carbonated beverages do you drink per day?) which are answered dichotomously and indicate consumption amounts. Once all the items had been answered and according to the final score, the responses were categorized into low, medium, and high adherence. The reliability analysis showed in this research a value of α = 0.830. This questionnaire has been used because it is a very reliable one to measure adherence to the Mediterranean diet. In addition, this version is the one proposed for the adult population.

International Physical Activity Questionnaire: It has been employed in the Spanish version adapted for university students (30). This questionnaire evaluates through time and frequency the type of physical activity performed in the last week (how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling in the last 7 days?). The responses are classified into three levels, namely, low, moderate, and high. The reliability analysis showed in this research a value of α = 0.815. This instrument was used for this study due to its high level of internal consistency. It is also a very useful questionnaire.

2.3. Procedure

The process related to the preparation of this study is described below. At an initial moment, once the initial idea was presented, a bibliographic search was carried out. This was carried out to determine the most reliable instruments to collect the data.

Once the design of the study was conceived at the University of Granada, specifically at the Faculty of Education Sciences, the questionnaire began to be sent to the different young people. The research was publicized through the different social networks of the Department of Didactics of Musical, Plastic, and Corporal Expression to try to contact as many students as possible. Before students were given access to the questionnaire, they were asked to participate on a voluntary basis. They were also assured that the data would be treated anonymously and exclusively for scientific purposes. Once this was done, students were given access to the questionnaire they had created. Due to the COVID-19 health crisis, to establish the least contact with the participants, the data were collected virtually. For this purpose, the questionnaire was registered on the Google Forms platform. Prior to creating this questionnaire, the research group agreed to duplicate two questions. The reason for this decision was to avoid registering participants who responded randomly. This resulted in the discarding of a total of 78 participants.

For the ethical aspects of the research, the ethical criteria registered in the Declaration of Helsinki were followed. In addition, to ensure greater ethical rigor, this study was continuously supervised by an ethics committee of the University of Granada (2966/CEIH/2022).

2.4. Statistical analysis

The IBM SPSS 25.0 statistical program was used for the comparative analysis. Initially, the homogeneity degree of the results was studied through the Kolmogorov-Smirnov test. The aforementioned test showed a normal distribution of the results. Subsequently, for the purpose of this research, a single-factor ANOVA was used. Cohen's standardized *d* (31) was used to study the effect size.

The IBM SPSS AMOS 26.0 software was employed to evaluate and adjust the structural equation models (Figure 1). The models are made up of endogenous and exogenous variables. The variable adherence to the Mediterranean diet serves as an exogenous variable, while all the dimensions of self-concept and anxiety act as endogenous variables. For endogenous variables, causal explanations have been carried out. These have been carried out based on the association between the indicator and the degree of measurement reliability. Hence, it has been possible to introduce the observation error. Likewise, the unidirectional arrows symbolize the regression weight between the latent and observed variables and are interpreted as regression weights. For the comparative and exploratory analyses, the significance level was established at a 95% confidence interval.

Based on the criteria established to adjust the equation models, attention will be focused on the values of the following indices (32, 33). The first one is related to the chi-square test, where non-significant values show a good fit (32). The comparative fit index, incremental reliability index, goodness of fit index, and root mean square approximation (33) will also be used. For the first three indices, the values must be higher than 0.900 (33). For the root mean square approximation, the value must be lower than 0.100 (32, 33). In addition to focusing attention on the size and susceptibility of the sample (34), attention should be paid to other adjustment indices such as the Tucker-Lewis index (34). For this index, the values must be >0.900 (34). Finally, with respect to the sampling error, a sampling error of 3.81% was obtained for a confidence level of 97%.

3. Results

Table 1 shows the comparative analysis of the data. For the anxiety variable, it was observed that participants who showed

TABLE 1 Comparative analysis of variables according to the level of Mediterranean diet adherence.

		N	M	SD	*F*	*P*	ES (d)	95% CI
ANX	High adherence	221	0.75	0.61	2.659	≥0.05	(–)	(–)
	Needs to improve	263	0.77	0.64				
	Low adherence	73	0.95	0.65				
AC	High adherence	221	4.06	0.65	12.058	≤0.05[a,b]	0.343[a]	[0.163; 0.523][a]
	Needs to improve	263	3.81	0.79			0.648[b]	[0.378; 0.918][b]
	Low adherence	73	3.62	0.76				
SO	High adherence	221	3.46	0.35	7.213	≤0.05[b]	0.543[b]	[0.275; 0.811][b]
	Needs to improve	263	3.44	0.41				
	Low adherence	73	3.27	0.35				
EM	High adherence	221	3.04	0.80	0.364	≥0.05	(–)	(–)
	Needs to improve	263	3.10	0.78				
	Low adherence	73	3.06	0.88				
FA	High adherence	221	3.49	0.37	4.276	≤0.05[b]	0.397[b]	[0.131; 0.664][b]
	Needs to improve	263	3.41	0.47				
	Low adherence	73	3.34	0.40				

[a]Differences between high adherence and needs to improve.
[b]Differences between high adherence and low adherence.
[c]Differences between needs to improve and low adherence.
N, Number of participants; M, mean value; SD, standard deviation; F, F-test; P, significance level; ES, effect size; 95% CI, 95% confidence interval; ANX, Anxiety; AC, academic self-concept; SO, social self-concept; EM, emotional self-concept; FA, family self-concept; PH, physical self-concept; PA, physical activity.

optimal adherence (M = 0.75) reflected lower levels of anxiety than those who showed low adherence (M = 0.95). Continuing with the self-concept, it is observed that young people who show a high degree of adherence to the Mediterranean diet obtain greater recognition in the academic, social, family, and physical areas (M = 4.06; M = 3.46; M = 3.49; M = 3.33) compared to those showing a low level of adherence (M = 3.62; M = 3.27; M = 3.34; M = 2.79; M = 1.97). Very different results are observed for the emotional self-concept, showing a greater recognition of participants who need to improve adherence to this dietary pattern (M = 3.10). For this dimension of self-concept, higher scores are observed for participants who show a low degree of adherence (M = 3.06) compared to those who show a high degree of adherence (M = 3.04). With regard to the practice of physical activity, higher levels were observed for participants who showed a high degree of adherence to the Mediterranean diet (M = 2.43).

The model presented for the participants who showed a low physical activity level evidenced a good fit. A non-significant value was obtained (X^2 = 51.612; df = 15; pl = 0.000) for the chi-square test. The values obtained for the fit indices are shown below. The Comparative Fit Index (CFI), the Normalized Fit Index (NFI), the Incremental Fit Index (IFI), and the Tucker-Lewis Index (TLI) obtained values of 0.968, 0.961, 0.969, and 0.929 for each one. The root mean square error of approximation analysis (RMSEA) was 0.025.

Figure 2 and Table 2 evidence the regression weights of the proposed theoretical model for participants showing a low level of physical activity. Mediterranean diet adherence was positively associated with social self-concept ($p < 0.05$; β = 0.217), emotional self-concept (β = 0.048), family self-concept (β = 0.093), physical domain (β = 0.161), and anxiety (β = 0.498). A negative effect was observed in the academic area (β = −0.041).

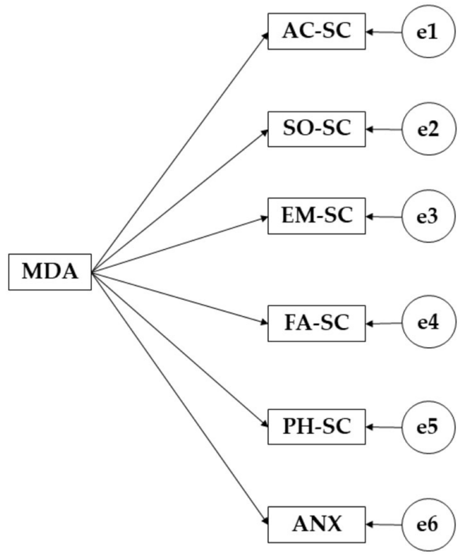

FIGURE 1
Research base model.

The structural equation model presented for the students who evidenced a moderate level of physical activity was a good fit. A non-significant value was obtained (X^2 = 55.289; df = 15; *p*l = 0.000) for the chi-square test. The values obtained for the fit indices are shown below. The Comparative Fit Index (CFI), the Normalized

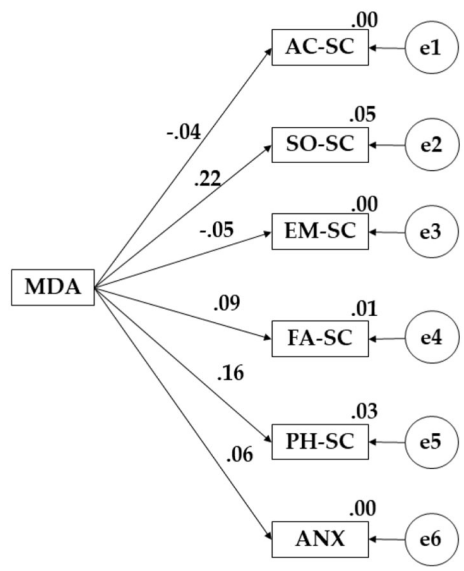

FIGURE 2
Proposed model for low-level PA.

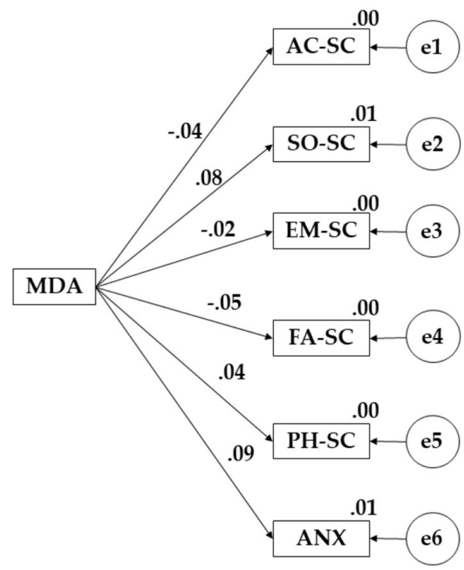

FIGURE 3
Proposed model for moderate levels of PA.

TABLE 2 Standardized regression weights obtained for participants with a low level of PA.

Effect direction	RE.WE				ST.RE.WE
	EST	ES.ERR	CR.RA	*P*	EST
AC ←MDA	−0.272	0.587	−0.464	0.643	−0.041
SO ←MDA	0.728	0.291	2.503	< 0.05	0.217
EM ←MDA	0.311	0.570	0.545	0.586	0.048
FA ←MDA	0.308	0.294	1.049	0.294	0.093
PH ←MDA	0.875	0.477	1.836	0.066	0.161
ANX ←MDA	0.322	0.476	0.677	0.498	0.060

ANX, Anxiety; AC, academic self-concept; SO, social self-concept; EM, emotional self-concept; FA, family self-concept; PH, physical self-concept; PA, physical activity; MDA, Mediterranean diet adherence; RE.WE, Regression weights; ST.RE.WE, standardized regression weights; ES.ERR, estimation error; CR.RA, critical ratio; EST, estimation.

Fit Index (NFI), the Incremental Fit Index (IFI), and the Tucker-Lewis index (TLI) obtained values of 0.924, 0.961, 0.918, and 0.905, respectively. The value obtained by root mean square error of approximation analysis (RMSEA) was 0.030.

Figure 3 and Table 3 evidence the regression weights of the proposed theoretical model. Mediterranean diet adherence was positively associated with social self-concept (β = 0.082), physical self-concept (β = 0.045), and anxiety (β = 0.085). In contrast, negative relationships were observed with academic domain (β = −0.036), emotional area (β = −0.020), and family self-concept (β = 0.047).

The structural equation model presented for the participants who showed a high level of physical activity evidenced a good fit. A non-significant value was obtained (X^2 = 54.892; df = 15; pl = 0.000) for the chi-square test. The values obtained for the fit indices are shown below. The Comparative Fit Index (CFI), the Normalized Fit Index (NFI), the Incremental Fit Index (IFI), and the Tucker-Lewis Index (TLI) obtained values of 0.947, 0.958, 0.950, and 0.910, respectively. On the contrary, the value obtained by root mean square error of approximation analysis (RMSEA) was 0.040.

It is evidenced in Table 4 and Figure 4 that the Mediterranean diet has a positive effect on academic self-concept (β = 0.109), social self-concept (β = 0.038), family self-concept (β = 0.064), physical self-concept (β = 0.146), and anxiety (β = 0.024). On the contrary, Mediterranean diet adherence was negatively associated with emotional self-concept (β = −0.132).

The previous tables (Tables 2–4) show the differences found according to the models proposed. Considering the relationship between adherence to the Mediterranean diet and self-concept, a greater effect was observed for participants with a high level of physical activity (β = 0.109). Higher scores are observed in the relationship between adherence to the Mediterranean diet and social self-concept (β = 0.217), adherence to the Mediterranean diet and emotional self-concept (β = 0.048), adherence to the Mediterranean diet and family self-concept (β = 0.093), and between adherence to the Mediterranean diet and the practice of physical activity (β = 0.161) for participants who show a low level of physical activity. Finally, participants showing a high level of physical activity evidenced a better relationship between adherence to the Mediterranean diet and anxiety (β = 0.024).

4. Discussion

Once the relationship between the variables has been analyzed, the Discussion Section aims to compare the results found with those of other studies similar to this one. In this case, a comparative and exploratory analysis of the variables, namely anxiety, adherence to the Mediterranean diet, self-concept, and physical activity

TABLE 3 Standardized regression weights obtained for participants with a moderate level of PA.

Effect direction	RE.WE				ST.RE.WE
	EST	ES.ERR	CR.RA	*P*	EST
AC ←MDA	−0.224	0.473	−0.473	0.636	−0.036
SO ←MDA	0.237	0.221	1.072	0.284	0.082
EM ←MDA	−0.127	0.481	−0.265	0.791	−0.020
FA ←MDA	−0.163	0.267	−0.609	0.542	−0.047
PH ←MDA	0.240	0.413	0.581	0.561	0.045
ANX ←MDA	0.388	0.350	1.110	0.267	0.085

ANX, Anxiety; AC, academic self-concept; SO, social self-concept; EM, emotional self-concept; FA, family self-concept; PH, physical self-concept; PA, physical activity; MDA, Mediterranean diet adherence; RE.WE, Regression weights; ST.RE.WE, standardized regression weights; ES.ERR, estimation error; CR.RA, critical ratio; EST, estimation.

TABLE 4 Standardized regression weights obtained for the participants with a high level of PA.

Effect direction	RE.WE				ST.RE.WE
	EST	ES.ERR	CR.RA	*P*	EST
AC ←MDA	0.688	0.392	1.757	0.079	0.109
SO ←MDA	0.136	0.223	0.611	0.541	0.038
EM ←MDA	−0.994	0.462	−2.150	0.032	−0.132
FA ←DA	0.258	0.249	1.037	0.300	0.064
PH ←MDA	1.119	0.471	2.373	< 0.05	0.146
ANX ←MDA	0.143	0.367	0.389	0.697	0.024

ANX, Anxiety; AC, academic self-concept; SO, social self-concept; EM, emotional self-concept; FA, family self-concept; PH, physical self-concept; PA, physical activity; MDA, Mediterranean diet adherence; RE.WE, Regression weights; ST.RE.WE, Standardized regression weights; ES.ERR, estimation error; CR.RA, critical ratio; EST, estimation.

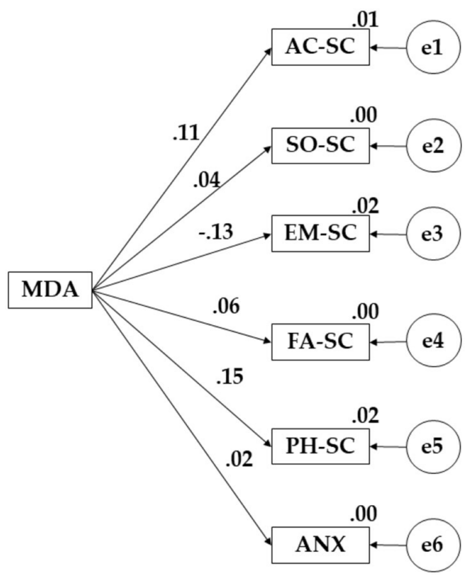

FIGURE 4
Proposed model for high-level PA.

practice has been presented. The exploratory analysis was presented using a multigroup structural equation model.

The comparative analysis shows that young people who show a high degree of adherence to the Mediterranean diet have lower levels of anxiety. The study by Marchena et al. (23) conducted in the university population found a negative relationship between anxiety and adherence to the Mediterranean diet. This research (23) also found that low adherence to the Mediterranean diet is associated with emotional problems and higher levels of negative emotions such as anxiety and stress. Given the appearance of these negative states in the university population, the studies by Marchena et al. (23) and Trigueros et al. (24) found positive relationships between eating behavior problems and the appearance of anxiety or stress.

This analysis then shows that a high degree of adherence to the Mediterranean diet has a beneficial effect on the different dimensions of self-concept. In view of these findings, the research carried out by Melguizo-Ibáñez et al. (35) on a population of university students of educational sciences found that the Mediterranean diet acts beneficially on all dimensions of self-concept. In line with the previous study, Ubago-Jiménez et al. (5) found in the university population benefits of a positive adherence to the Mediterranean diet, such as a better conception of fitness and notable improvements in the dimensions of interpersonal intelligence, which is positively related to self-concept. Similarly, the study conducted by Marchena et al. (23) also found that university students with a high adherence to the Mediterranean diet show a better conception of all dimensions of self-concept and self-esteem. The Mediterranean diet has been shown to be emotionally, socially, and physically beneficial due to the types of foods that make up this dietary pattern (5, 23, 35).

Likewise, the comparative analysis illustrates that participants who show high adherence to the Mediterranean diet obtain a higher level of physical activity. The research carried out by López-Gil et al. (36) found that from the early ages of human development, a positive link should be created toward an active and healthy lifestyle. Likewise, in the adult population, an increase in the practice of physical activity has been found, as well as a greater consumption of foods present in the Mediterranean diet (37). In view of the above statement, it has been found that a healthy diet together with an active lifestyle helps to increase the life expectancy of young women and to prevent cardiorespiratory and cardiovascular diseases (37).

Next, the exploratory analysis reveals the associations between adherence to the Mediterranean diet and the various dimensions of self-concept based on the type of physical activity performed.

Regarding the relationship between academic self-concept and adherence to the Mediterranean diet, it was found that greater exercise intensity improved the relationship between these variables. In this case, the research developed by Melguizo-Ibáñez et al. (35) in a sample of students of educational sciences found a significant improvement between a higher intensity of physical activity and academic self-concept. In view of these findings, the research carried out by López-Gil et al. (36) found that the practice of physical activity at a moderate or vigorous level reports improvements in executive functions, improving attention and concentration.

Continuing with the results of the relationship between adherence to the Mediterranean diet and social self-concept, a better relationship is observed for lighter physical activity. Research conducted by Laiou et al. (37) in an adult population concluded that the practice of any type of physical activity helps promote socialization among people. Similarly, Zhang et al. (38) found that being physically active helps to have a better social image as well as increase the degree of socialization among peers. Regarding the type of physical activity, it has been found that low-intensity sports practice allows a higher degree of interaction among peers (37, 38).

Regarding the emotional domain and adherence to the Mediterranean diet, a worsening of both variables was obtained as the intensity of physical exercise increased. The study conducted by Melguizo-Ibáñez et al. (39) in an adolescent population found that in the academic stages prior to university, positive relationships are found between the emotional, physical, and health domains. Furthermore, this research (39) found that the development of these patterns in the early stages of development favors the persistence of these behaviors into adulthood. Likewise, González-Valero et al. (40) found that within the university student environment, the practice of physical exercise helps to improve attention, clarity, and emotional repair. In addition, Trigueros et al. (41) found that positive adherence to a healthy dietary pattern contributes to improving the cognitive sphere, which is directly affected by emotions.

Focusing on the family sphere of self-concept, it was found that university students who practice physical activity at a lower intensity reflect better results in the family sphere and adherence to a healthy dietary pattern. In view of these findings, Melguizo-Ibáñez et al. (42) found that in the early stages of adolescent development, the family environment plays a key role in the creation of an active and healthy lifestyle. Likewise, this research (42) affirms that families with a low socioeconomic level show less concern for the development of healthy and active behaviors in their infants. Within the university setting, Marco-García et al. (43) found that young people acquire a greater degree of dependence and therefore show a detachment from the nuclear family. Likewise, the development of active behavior may be affected by the academic environment (43).

Regarding the physical dimension of self-concept, it was found that participants with a low level of physical activity showed a better effect of the Mediterranean diet in this area. Given such findings, Melguizo-Ibáñez et al. (44) found that in adolescents and young adults, there is a greater concern for the care of body appearance. Likewise, the study carried out by Fernández-Bustos et al. (45) found a higher level of self-concept for young people who show a moderate or vigorous level of physical activity.

Finally, it is observed that for the relationship between adherence to the Mediterranean diet and anxiety, participants who practice vigorous physical activity obtain better results. Similar results were obtained by Marchena et al. (23), whereas Jayo-Montoya et al. (46) affirm that the practice of physical activity together with a healthy dietary pattern helps to reduce the disruptive states generated during daily life due to the segregation of neurotransmitters.

4.1. Limitations and future perspectives

Once the objectives of this research have been answered, it is necessary to mention its limitations. The first of these is related to the study population. Despite having obtained a significant sample, generalizations cannot be made. This is mainly because the sample is not significant at the national or regional level. The next aspect related to the sample is the degree of homogeneity of the sample. The sample for this study is made up mostly of female participants. Another limitation would also be the research design since only one data collection can be interpreted at the time the data were collected. This means that the data should be interpreted with caution. Considering the prospects, this research can be used as a starting point to develop an intervention program with a longitudinal design.

Several practical applications have emerged from this research. The first of these is related to the physical and nutritional training that students receive. It would be necessary that during the last stages of Compulsory Secondary Education, students receive information related to the benefits of an active and healthy lifestyle. Likewise, this research can be considered a pilot study that will shed light on an intervention program for the training of future teachers. Another possible practical application would be the need to carry out a greater number of intervention programs aimed at improving the health status of young people.

5. Conclusion

The comparative analysis shows that young people who demonstrate a high degree of adherence to the Mediterranean diet show lower levels of anxiety. It is also observed that a high degree of adherence to the Mediterranean diet brings benefits in the family, academic, social, and physical dimensions of self-concept. In addition, participants with a high degree of adherence show a greater level of physical activity.

The exploratory analysis shows that a high level of weekly physical activity shows a better effect of the Mediterranean diet on the academic areas of self-concept and anxiety. Young people who practice a low level of weekly physical exercise show a better effect of the Mediterranean diet on the social and family dimensions. Finally, negative effects of the Mediterranean diet on emotional, family, and academic areas of self-concept were observed.

Finally, this study concludes that an active lifestyle demonstrates improvements in the effect of a healthy dietary pattern on the different dimensions of self-concept and anxiety.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee 2966/CEIH/2022 of the University of Granada approved the present research. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

EM-I, LPA, JA-V, PP-M, and GB conceived and designed the experiments. EM-I, GG-V, JA-V, PP-M, GB, and FHY performed the experiments and wrote the article. EM-I, GG-V, JA-V, PP-M, GB, and LPA analyzed and interpreted the data. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Comparing effects of beetroot juice and Mediterranean diet on liver enzymes and sonographic appearance in patients with non-alcoholic fatty liver disease: a randomized control trials

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Background: In both developed and developing countries, non-alcoholic fatty liver disease (NAFLD) has lately risen to the top of the list of chronic liver illnesses. Although there is no permanent cure, early management, diagnosis, and treatment might lessen its effects. The purpose of conducting the current study is to compare the effects of beetroot juice and the Mediterranean diet on the lipid profile, level of liver enzymes, and liver sonography in patients with NAFLD.

Methods: In this randomized controlled trial, 180 people with a mean age of (45.19 ± 14.94) years participated. Participants ranged in age from 19 to 73. The mean weight before intervention was (82.46 ± 5.97) kg, while the mean weight after intervention was roughly (77.88 ± 6.26) kg. The trial lasted for 12 weeks. The participants were split into four groups: control, a Mediterranean diet with beet juice (BJ + MeD), Mediterranean diet alone (MeD), and beetroot juice (BJ). The Mediterranean diet included fruits, vegetables, fish, poultry, and other lean meats (without skin), sources of omega-3 fatty acids, nuts, and legumes. Beetroot juice had 250 mg of beetroot. Data analysis was done using SPSS software (version 26.0). $p < 0.05$ is the statistical significance level.

Results: Following the intervention, Serum Bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), serum cholesterol (CHOL), triglyceride (TG), and low-density lipoprotein (LDL) levels were significantly decreased in the BJ + MeD, BJ, and MeD groups ($p = 0.001$). Also, high-density lipoprotein (HDL) significantly increased in the BJ + MeD, BJ, and MeD groups ($p = 0.001$), while decreasing in the Control group ($p = 0.001$).

Conclusion: The research findings indicate a significant reduction in hepatic steatosis among the groups receiving beetroot juice (BJ) and beetroot juice combined with the Mediterranean diet (BJ + MeD). This suggests that beetroot juice holds potential as an effective treatment for non-alcoholic fatty liver disease (NAFLD) in adults. Furthermore, the combination of beetroot juice with the Mediterranean diet showed enhanced efficacy in addressing NAFLD.

Clinical trial registration: ClinicalTrials.gov, identifier NCT05909631.

KEYWORDS

mediterranean diet, beetroot juice, nonalcoholic fatty liver, RCT, NAFLD

Introduction

Non-alcoholic fatty liver disease (NAFLD) has recently become the most common chronic liver disease in both industrialized and developing countries (1). It is characterized by the deposit of fat in the liver, which is not caused by alcohol consumption and is frequently linked to other metabolic diseases such as hyperlipidemia, cardiovascular disease, hepatocellular carcinoma, type 2 diabetes, and obesity (2–5). According to studies, NAFLD and its link to obesity will considerably increase liver-related morbidity and mortality by 2030 (6). The prevalence of NAFLD varies among different populations, with the Middle East having the highest rates (32% of the population is thought to be affected), followed by the United States and South America (30%). The estimated prevalence for other regions, including Asia, Europe, and Africa, ranges from 27 to 13% (7). As the prevalence of NAFLD rises, the search for effective and accessible treatment options becomes more important. The conventional management of NAFLD involves lifestyle modifications, including dietary changes and physical activity (8).

Recently, there has been an increase in interest in the efficacy of specific dietary components in the management of NAFLD, such as beetroot supplementation and the Mediterranean diet (MeD). Beetroot, which is high in bioactive compounds such as betaine, nitrates, and antioxidants, is one such supplement that has received attention for its potential health benefits (9). And also have a hepatoprotective effect and it effectively keeps away fat from depositing in the liver. This is probably due to the presence of betaine in beetroot which is a methyl group donor in the liver transmethylation process (10). Studies have examined the effects of beetroot supplementation on NAFLD, and the results have been encouraging (11). On the other hand, the Mediterranean diet (MeD) is defined as "a plant-based diet characterized by a high ratio of mono-unsaturated fatty acids (MUFA) to saturated fatty acids (SFA)" with a total fat accounting for 30–40% of daily energy consumption. The MeD is rich in olive oil, which is the main source of added fat together with nuts, has a high percentage of fibers, mainly obtained from vegetables, whole grains, and legumes, and is rich in fish and seafood, while meat and dairy products are consumed in a lower percentage. It is therefore a high-fat diet, with fat comprising 35–45% of the total energy intake, at least half of which should be from MUFAs. Carbohydrates constitute 35–40% and protein 15–20% of the energy intake (12).

According to research, the Mediterranean diet is good for several health outcomes, including liver function. Studies show that the MIND diet may improve liver health and reduce the risk of NAFLD (13–15).

Due to the continuous increase in the prevalence of NAFLD and its related risk factors in recent decades, the prevalence of unhealthy dietary patterns that follow them, we aimed to compare the effects of beetroot juice and the Mediterranean diet on lipid profile, level of liver enzymes and the liver sonography in patients with NAFLD.

Method and materials

Participants and study design

This Randomized Control Trial was conducted in Kalar City, Kurdistan region, Iraq. The Ethics Committee of Sulaimani Polytechnic University, Kalar technical college approved the study. It was also registered in ClinicalTrials.gov: (NCT05909631). Informed consent had been obtained from all participants before the start of the study and was approved by Sulaimany Polytechnic University, Kalar Technical College ethics committee, and the consent process was documented in their medical records.

All methods were carried out by relevant guidelines and regulations. All methods were carried out by relevant guidelines and regulations. This study was conducted by the Declaration of Helsinki.

Patients with NAFLD were identified and enrolled for this research at the PAR hospital in the Kurdistan Region of Iraq. Based on eligibility requirements, the participants were chosen by purposive sampling. Patients had to be between the ages of 19 and 73, and they had to have NAFLD as their main diagnosis. For a NAFLD diagnosis, ultrasound proof of fatty liver (stage I or above) and an elevated level of liver enzymes were required. An experienced radiologist did the ultrasonography. The grade of fatty liver was determined based on hepatic parenchymal brightness by ultrasound, and established methods were used to test the liver's biochemical profile (16).

The following factors were used as exclusion criteria: a history of diseases like cardiovascular, liver, chronic hepatitis C, and kidney disease; supplement use within the previous 6 months; hormone therapy; use of drugs like amiodarone, methotrexate, and corticosteroids; cases of starvation or inadequate nutrition; pregnancy; metabolic disorders like Wilson disease and glycogen storage disease; a history of liver irradiation; and a refusal to continue the study protocol. We selected 180 participants for this study because they all met the requirements for inclusion. Finally, eligible participants were divided equally into four groups; a control group ($n = 45$) and three groups for the intervention group: $n = 45$ for beetroot juice plus Mediterranean diet (BJ + MeD), beetroot juice (BJ), and Mediterranean diet (MeD) via simple randomization. Then, the sequence of groups was drawn up by coin tossing.

For 12 weeks, for the group members who were receiving the MeD, we recommended consuming Mediterranean foods like fish, poultry, sources of omega-3, vegetables and colored fruits, legumes and nuts, and low-fat goods while avoiding inflammatory foods like high-fat foods, processed meats, fast food, simple sugars, chips, and soft drinks.

At baseline, the participants' demographic and anthropometric information, including gender, age, weight, height, smoking status, location of residence, and physical activity, were recorded.

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Nutrients and bioactive compounds of beetroot

Beetroot is consisting of multiple biologically active phytochemicals including betalains (9) (e.g., betacyanins, and betaxanthins), flavonoids, polyphenols, Saponins (9) and inorganic Nitrate (NO3); it also a rich source of diverse minerals such as potassium, sodium, phosphorous, calcium, magnesium, copper, iron, zinc, and manganese (17). It is commonly consumed in the form of supplemental juice, powder, bread, gel, boiled, oven-dried, pickled, pureed, or jam-processed across different food cultures (18, 19). As shown in Table 1, 100 mL of beetroot juice is comprised of 95 Kcal energy, 22.6 g carbohydrates, 0.70 g proteins, 0.16 g total lipids, 0.91 g total dietary fiber, and 12 g total sugars. As such, the micro nutritional composition of 100 mL beetroot juice is estimated as 8.8 g sucrose, 0.86 g fructose, and 2.5 g glucose (9).

Moreover, various commercial organic and conventional beetroot juices, are reported to contain total sugar, vitamin C, and total flavonoids within a range of 1.73–7.85 g, 10.75–20.36 mg, and 2.02–2.36 mg (per 100 g), respectively (20). Betalains make up to ~70–100% of the phenolic composition of beetroot, limited to 0.8–1.3 g/L of fresh beetroot juice (about 60% betacyanins and 40% betaxanthins) (21).

Beetroot is classified as one of the ten plants with the highest antioxidant activity (9). It is believed to be the main commercial source of betalains, in concentrated forms, powder, or natural dyes in gelatins, confectionery, dairy, meat, and poultry-derived products (9). According to Baião et al., flavonoids change vegetable processing while polyphenols remain active after *in vitro* digestion, yet found in the highest ratio in beetroot gel than other conformations including beetroot juice (9).

TABLE 1 Nutrient composition of beetroot and its byproducts (per 100 g or L).

	Raw	Cooked, boiled	Canned	Fresh juice
Water, g	87.58	87.6	90.96	–
Energy, kcal	43	44	31	30
Protein, g	1.61	1.68	0.91	1.02
Total fats, g	0.17	0.18	0.14	–
Carbohydrate, g	9.56	9.96	7.21	6.6
Fiber, g	2.8	2	1.8	0
Sugars, g	6.76	7.96	5.51	6.6
Calcium, mg	16	16	15	–
Iron, mg	0.8	0.79	1.82	0
Magnesium, mg	23	23	17	–
Phosphorus, mg	40	38	17	–
Potassium, mg	325	305	148	–
Sodium, mg	78	77	194	93
Zinc, mg	0.35	0.35	0.21	–
Vitamin C, mg	4.9	3.6	4.1	0
Thiamin, mg	0.031	0.027	0.01	–
Riboflavin, mg	0.04	0.04	0.04	–
Niacin, mg	0.334	0.331	0.157	–
Folate, µg	109	80	30	–
Total phenolic content[a]	255	238	192	225
Total flavonoid content[b]	260	261	173	126

[a]As mg gallic acid equivalent (GAE)/100 g.
[b]As mg rutin equivalent (RE)/100 g sample.

Dietary intake

To eliminate potential confounding variables, we matched the four groups according to sex, degree of physical activity, and caloric consumption. Participants conduct a 24 h dietary recall once a week to assess MeD compliance. Other groups received a 3 day food record questionnaire at the start and conclusion of the trial (1 day off and 2 days non-off). Using the Modified Nutritionist IV Software, the calorie, macronutrient, micronutrient, and water intakes were calculated (version 3.5.2, First Data-Bank; Hearst Corp., San Bruno, CA).

Monitoring and follow-up

To control adherence to the MeD, patients complete a 24 h recall (weekly consumption data). Patients were also followed up every week by telephone to be aware of possible side effects and to ensure the use of beetroot juice.

Nutritional intervention

250 mL of concentrated beetroot juice, 250 mL of a placebo (red carmoisine food color and a little quantity of a sweetener diluted in water), and beetroot juice were given to participants in the BJ groups and BJ + MeD groups (subjects swirled 250 mL of concentrated beetroot juice orally). This was carried out in the morning, 30 min before breakfast, and on an empty stomach.

Fatty liver index

FLI was first presented by Bedogni et al. in 2006 with thirteen variables (including age, gender, ethanol intake, AST, ALT, GGT, WC, BMI, the sum of four skinfolds, Insulin, glucose, TG, and cholesterol), four of which remained as predictors in the equation (22, 23).

$$\mathrm{FLI} = \left(e^{0.953*\mathrm{loge}(\mathrm{triglycerides})+0.139*\mathrm{BMI}+0.718*\mathrm{loge}(\mathrm{ggt})+0.053*\mathrm{waist\ circumference}-15.745}\right) / \left(1+e^{0.953*\mathrm{loge}(\mathrm{triglycerides})+0.139*\mathrm{BMI}+0.718*\mathrm{loge}(\mathrm{ggt})+0.053*\mathrm{waist\ circumference}-15.745}\right) \times 100.$$

According to the area under the receiver operator characteristic curve (AUROC), the FLI's fatty liver detection accuracy was 0.83 (95% CI: 0.825 to 0.842). The FLI scores are between 0 and 100. Thus, with a high degree of diagnostic accuracy, FLI scores of 30 and 60 indicated the absence or presence of fatty liver, respectively (22).

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Physical activity

The BEACK Questionnaire was used to assess the degree of physical activity among the patients (24) at the start of the investigation.

Biochemical parameter measurements

After fasting for 10–12 h, 10 mL of whole blood was drawn from each participant at the beginning and end of the study. After centrifuging the samples, the serum was extracted. The serum was kept at −80°C for upcoming experiments. The levels of All biochemical investigations including liver function tests (ALT, AST, ALP, and S. Bilirubin), lipid profile tests (serum triglyceride (TG), cholesterol (Chol), cholesterol LDL and cholesterol HDL), and the grade of fatty liver were also assessed. Hence, COBASE C111 fully automated analyzer was used for analysis.

Liver ultrasound

The ultrasound examination was performed by two experienced radiologists with more than 15 years of experience in the field. The machines used for the scanning were the GE Logiq7 and Philips HD11, both equipped with a 2–5 MHz curved probe.

The diagnosis of fatty liver was based on parenchymal brightness, liver-to-kidney contrast, bright vessel walls, gallbladder wall definition, and diaphragmatic definition (25).

The fatty disease was graded and labeled as mild, moderate, or severe, or grades 0 to 3 (with 0 being normal) based on the degree of parenchymal brightness.

Grade 0 (normal liver): the liver and renal cortex are of similar echogenicity (Figure 1A).

Grade 1 (mild): slight diffuse increase in the fine echoes of liver parenchyma with appreciable periportal and diaphragmatic echogenicity (Figure 1B).

Grade 2 (moderate): moderately diffuse increase in fine echoes of the liver parenchyma obscuring periportal echogenicity, but diaphragmatic echogenicity is still appreciable.

Grade 3 (severe): marked increase in fine echoes of liver parenchyma with poor or no visualization of the intrahepatic vessel borders, diaphragm, and posterior portion of the right lobe of the liver.

When the discrepancy between the grades of fatty liver developed between the two radiologists, the final decision was made by consensus.

Data analysis

SPSS software (version 26.0) was used to analyze the data, also data were presented as means and standard deviations for continuous variables and frequencies, and Categorical data were expressed as counts and percentages. The Kolmogorov–Smirnov test and histogram were applied to ensure the normal distribution of variables. Chi-square was used for the sociodemographic characteristics of the subjects and differences between qualitative. Paired *t*-test and one-way analysis of variance (ANOVA) were applied to determine differences between continuous variables. Statistical significance was considered when $p < 0.05$ was used.

Results

Participants' characteristics

A total of 180 participants of different ages were enrolled in the current study and were randomly assigned to one of the four groups (total = 180 cases; $n = 45$). According to the following chart in Figure 2, all participants completed the study, and their data were entered into the final analysis. Sociodemographic characteristics are minimized in Table 2. As shown in Table 2, no age differences are observed between the groups. There was no difference in BMI between the groups at the beginning of the study, but after the study, statical differences were observed in each group before and after the study.

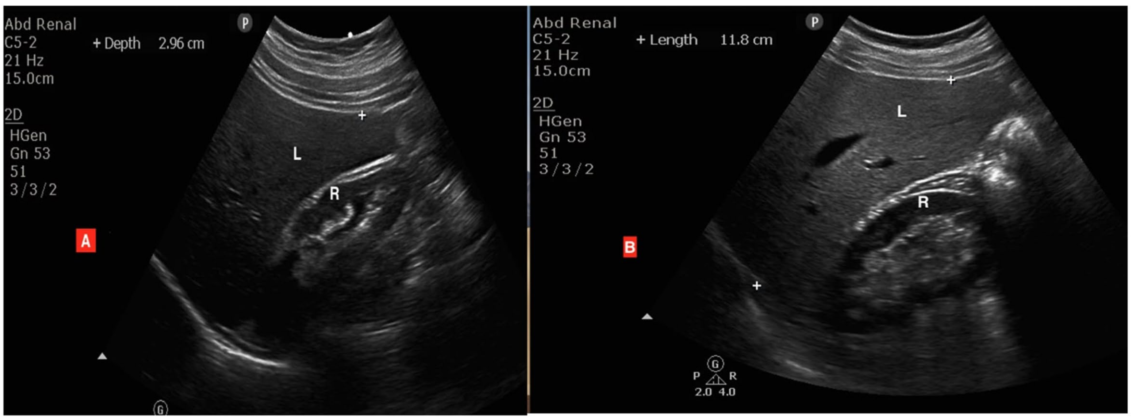

FIGURE 1
Ultrasound images of two different cases: **(A)** a normal liver with similar brightness of the liver (L) and renal cortex (R), while **(B)** is a patient with grade 1 (mild) fatty changes showing the liver (L) is brighter than the renal cortex (R) but the wall of the intrahepatic vessels is still clearly seen.

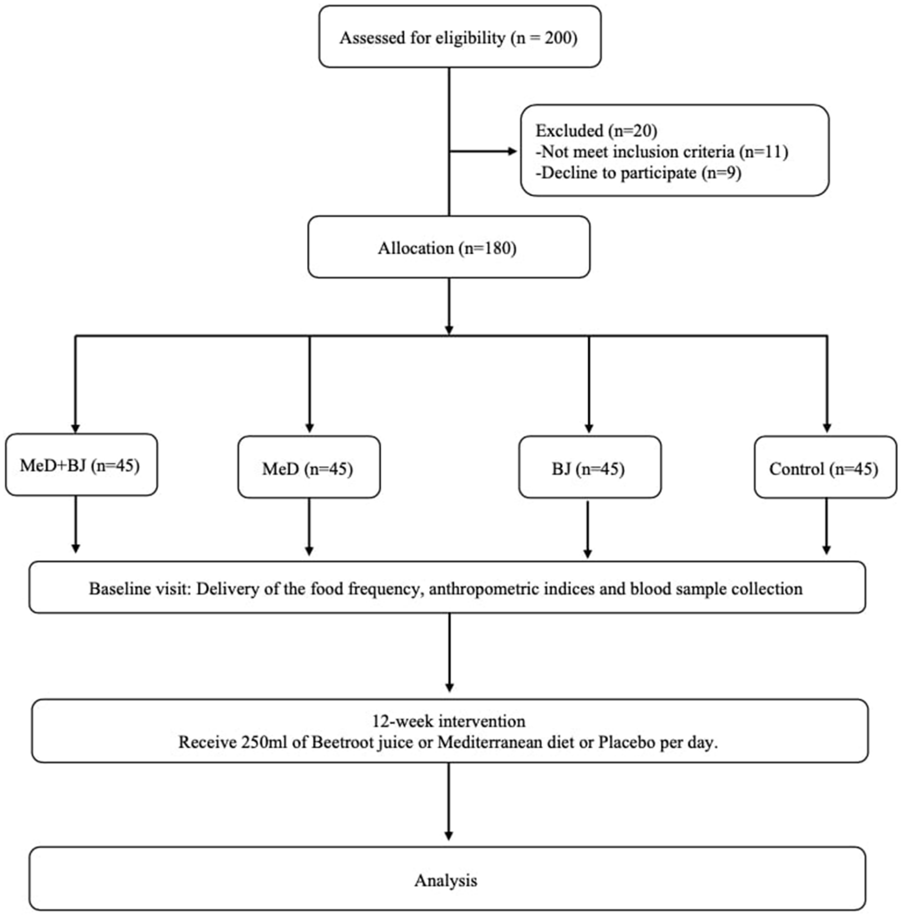

FIGURE 2
Follow chart of the study. Med plus BJ; Med; BJ and Control.

Liver enzymes

Table 3 shows the results for the liver enzyme test at the end of the study were as follows; T.S.B. in the intervention groups was significantly decreased as compared with that of the control group ($p < 0.001$). Further, a comparison of the intergroup revealed that at the end of the current study, the T.S.B. in groups BJ + MED ($p < 0.001$), and BJ ($p < 0.001$) in comparison with the beginning of the study, had decreased significantly. Furthermore, no significant differences in serum AST levels were found between the intervened groups and the control group at the end of the study, whereas the intergroup comparison for serum AST levels revealed that at the end of the current study, the amount of serum AST in the BJ (p.001) and MED ($p < 0.001$) groups was significantly lower than at the start of the study. In the case of ALT, there is a significant decrease in the concentration of ALT in the intervened groups as compared with that of the control group ($p < 0.001$). Further, a comparison of the intergroup data revealed that the concentration of serum ALT at the end of the study was significantly lower in the MED ($p < 0.001$) and BJ + MED ($p < 0.001$) groups. Finally, the results for serum ALP concentration showed that the concentration of serum ALP at the end of the study in the intervention groups was significantly lower in comparison with that of the control group. Besides, the intergroup comparison for serum ALP at the beginning and end of the study revealed a significant decrease in serum ALP concentration in the BJ + MED ($p < 0.001$) and BJ ($p < 0.001$) groups at the end of the current study.

Lipid profile

The assessment of the lipid profile at the end of the study was as follows: the results for serum TG concentration in the intervention groups were significantly reduced in comparison with that of the control group ($p < 0.001$). Further, the intragroup comparison revealed that at the end of the current study, the concentrations of serum TG in the BJ + MED ($p < 0.001$), MED ($p < 0.001$), and BJ ($p < 0.001$) groups were significantly decreased in comparison with the beginning of sample collection. Further, serum cholesterol concentrations in the intervention groups were significantly reduced in comparison with those of the control group ($p < 0.001$). In addition, the intergroup comparison revealed that serum cholesterol concentrations in the BJ + MED ($p < 0.001$), MED ($p < 0.001$), and BJ ($p < 0.001$) groups had been significantly reduced at the end of the current study. Besides, the concentration of serum LDL in the intervention groups was significantly decreased at the end of the study as compared with that of the control group ($p < 0.001$), and the intragroup comparison

TABLE 2 Baseline characteristics in the four groups.

Variables		BJ + MeD	MeD	BJ	Control	*p value
		Mean ± SD/n (%)				
Age (year)		44.49 ± 15.73	47.31 ± 15.75	44.91 ± 15.24	44.04 ± 13.2	0.736
Gender n (%)	Male	17 (9.4)	23 (12.8)	28 (15.6)	28 (15.6)	0.062
	Female	28 (15.6)	22 (12.2)	17 (9.4)	17 (9.4)	
Smoker n (%)	No	40 (22.2)	35 (19.4)	33 (18.3)	28 (15.6)	0.031
	Yes	5 (2.8)	10 (5.6)	12 (6.7)	17 (99.4)	
Physical activity (Met h/day)	Light	8 (4.4)	17 (9.4)	14 (7.8)	15 (8.3)	0.516
	Moderate	22 (12.2)	16 (8.9)	16 (8.9)	17 (9.4)	
	High	15 (8.3)	12 (6.7)	15 (8.3)	13 (7.2)	
Living Place n (%)	Rural	21 (11.7)	21 (11.7)	14 (7.8)	22 (12.2)	0.294
	Urban	24 (13.3)	24 (13.3)	31 (17.2)	23 (12.8)	
BMI kg/m^2	Before	29.96 ± 2.77	29.19 ± 3.94	28.01 ± 2.55	28.62 ± 3.84	0.042
	After	27.30 ± 3.45	27.75 ± 3.74	26.46 ± 2.56	27.82 ± 3.36	0.191
	**p value	<0.001	<0.001	<0.001	0.037	
Waist circumference (cm)	Before	90.25 ± 5.74	91.34 ± 4.53	91.72 ± 6.99	92.33 ± 4.89	0.354
	After	87.59 ± 5.14	89.91 ± 4.77	90.17 ± 6.69	91.54 ± 4.89	0.008
	**p value	<0.001	<0.001	<0.001	0.032	

Data presented as Mean ± SD/n (%), *obtained by Chi square test and **obtained by paired t-test. BJ + MeD, beetroot juice and Mediterranean diet; MeD, Mediterranean diet; BJ, beetroot juice.

revealed that the concentration of serum LDL in all four groups was significantly reduced at the end of the study ($p < 0.001$). Finally, there were significant differences in serum HDL concentration between the intervention groups and the control group at the end of the study. However, as shown in the intragroup comparison, we notice that the concentration of serum HDL in the BJ + MED ($p < 0.001$), MED ($p < 0.001$), and BJ ($p < 0.001$) groups was significantly increased in Table 3.

Nutritional assessment

Structural and cross-sectional questionnaires were carried out for all groups regarding the baseline at the end of the intervention for Mediterranean diet components. Significant differences were reported between groups in variables within vegetables, legumes, nuts and seeds, low-fat dairy, red and processed meats, poultry and fish, and MUFA/SFA ($p < 0.001$) while no significant differences were reported in other variables: total cereal, fermented dairy, and fruits (Table 4). Additionally, significant changes ($p < 0.001$) were reported within groups regarding total cereal, low-fat dairy, and MUFA/SFA in the control group, fermented dairy legumes, nuts, and seeds; low-fat dairy, red and processed meats, poultry, fish; and fruits in the BJ + Med, group; and red and processed meats, fish, and MUFA/SFA in the MeD group, while only MUFA/SFA was reported as a significant variable in the BJ group. According to daily energy intake, at the beginning of the study, the highest daily energy intake was for the BJ + Med group (2,278 ± 76.37 kcal/d), and the lowest was the control group (2,116 ± 59.28 kcal/d). At the end of the study, there was a change in the daily energy intake of all groups, with the greatest amount of change in the BJ + Med group.

Fatty liver status assessment

Currently, our results show a significant decrease in fatty liver accumulation. Especially in the BJ + MeD and BJ groups during the study. This reduction was reported at a higher level in the BJ + MeD group (one-degree reduction: 48%; and 2-degree decreasing: 35%, while in the BJ group, one-degree decreasing: 51%; and 2-degree decreasing: 22%, also, 71% of the control group showed no change in their liver fat accumulation; Figure 3).

As shown in Figure 4, the FLI of study participants according to groups Figure 4A, is the beginning of the study and there is no difference between the FLIs of the participants and all participants have high FLIs. However, Figure 4B shows the end of our study and tells us that the BJ + MD group had a significantly lower FLI. There was a difference between all groups before and after the study.

Discussion

To our knowledge, in this area, this is the first randomized controlled trial observing the comparing Effects of Beetroot juice and the Mediterranean diet on the level of liver enzymes and sonography in those cases with NAFLD. We found that consumption of 250 mL of red beetroot juice for 12 weeks, parallel to the Mediterranean diet, had a significant beneficial impact on some liver enzymes and lipid profiles (S. Bilirubin, ALT, ALP, TG, Cholesterol, LDL, and HDL). Flavonoids, dietary nitrate, and Saponin are the three main components of beetroot (26). Saponin was previously reported to be a significant contributor to lowering cholesterol activity (27) and dietary nitrate, which can increase the production of nitric oxide in the body. Nitric oxide has been shown

TABLE 3 Comparisons of the changes from baseline to the end of the intervention for biochemical parameters.

Variables		BJ + MeD	MeD	BJ	Control	**p value
		Mean ± SD				
Liver Enzymes						
S. Bilirubin	Before	1.46 ± 0.3	1.27 ± 0.4	1.15 ± 0.2	1.44 ± 0.3	<0.001
	After	0.87 ± 0.1	1.16 ± 0.2	0.72 ± 0.1	1.50 ± 0.3	<0.001
	*p value	<0.001	0.155	<0.001	0.431	
AST	Before	63.53 ± 8.80	61.32 ± 7.79	61.43 ± 8.85	63.85 ± 8.78	0.349
	After	59.16 ± 7.34	58.63 ± 7.87	58.18 ± 6.33	61.11 ± 6.93	0.014
	*p value	0.150	<0.001	<0.001	0.101	
ALT	Before	46.75 ± 6.61	44.44 ± 7.18	37.63 ± 3.45	46.89 ± 5.71	<0.001
	After	42.87 ± 6.50	38.06 ± 7.30	36.61 ± 5.87	44.50 ± 6.56	<0.001
	*p value	0.010	<0.001	0.320	0.059	
ALP	Before	121.8 ± 5.7	119.3 ± 6.5	119.0 ± 8.5	120.2 ± 3.1	<0.001
	After	114.8 ± 6.8	117.4 ± 6.3	113.6 ± 7.6	122.0 ± 3.6	<0.001
	*p value	<0.001	0.316	<0.001	<0.001	
Lipid Profile						
S.TG	Before	243.1 ± 14.3	240.4 ± 13.3	233.5 ± 14.1	173.8 ± 12.6	<0.001
	After	175.5 ± 10.6	217.9 ± 10.6	217.6 ± 11.6	175.7 ± 14.6	<0.001
	*p value	<0.001	<0.001	<0.001	0.494	
S. Cholesterol	Before	244.9 ± 28.8	232.5 ± 19.4	228.9 ± 6.2	224.6 ± 16.8	<0.001
	After	188.8 ± 15.8	219.6 ± 5.3	210.5 ± 3.7	221.1 ± 16.7	<0.001
	*p value	<0.001	<0.001	<0.001	0.304	
LDL	Before	142.4 ± 9.2	143.5 ± 11.0	140.2 ± 9.2	147.1 ± 11.2	<0.001
	After	128.8 ± 6.3	130.7 ± 5.4	132.2 ± 5.8	135.7 ± 9.7	<0.001
	*p value	<0.001	<0.001	<0.001	<0.001	
HDL	Before	30.2 ± 5.1	33.1 ± 4.8	29.8 ± 3.9	30.9 ± 3.9	<0.001
	After	41.5 ± 3.2	39.8 ± 3.8	36.6 ± 4.2	28.8 ± 4.01	<0.001
	*p value	<0.001	<0.001	<0.001	<0.001	

Data presented as Mean ± SD, *p* value obtained by *Paired *t*-test and **One-way Anova. BJ + MeD, beetroot juice and Mediterranean diet; MeD, Mediterranean diet; BJ, beetroot juice.

to have beneficial effects on the liver, including reducing inflammation and improving blood flow (28). Also, fibers are one of the major components of beetroot and the Mediterranean diet. Insoluble fibers can decrease the level of lipid profile since they do not absorb in the intestine, so they can bind to the cholesterol and remove it from the body Soluble fibers have been shown to increase the rate of bile excretion, therefore reducing serum total and LDL cholesterol (27).

In this study, a significant decrease in BMI was observed in the BJ, BJ + MeD, and MeD groups after 12 weeks of intervention. Likewise, a meta-analysis including seven observational reports and six randomized clinical trials revealed that adherence to MeD can significantly decrease BMI (effect size = −1.23 kg/m^2; 95% CI − 2.38 to −0.09 kg/m^2), weight (effect size = −4.13 kg; 95% CI − 8.06 to −0.20 kg) (29).

Our results showed that the level of TC, TG, LDL-C, and HDL-C after intervention was reduced in the BJ + MeD group compared to the BJ or MeD groups. Both beetroots juice and the Mediterranean diet have been studied for their effects on lipid profiles, specifically serum triglyceride (TG) concentrations. In the current study, serum TG levels were significantly affected. Furthermore, the intergroup comparison revealed that at the end of the study, serum TG concentrations in the BJ + MeD, MeD, and BJ groups were significantly lower than at the start of sample collection within daily feed intake. Besides, serum cholesterol concentrations in the intervention groups were significantly lower than in the control group. A cohort study by Baratta et al. revealed that adherence to MeD had a preventive effect on NAFLD (OR: 0.801, $p = 0.018$) (30). Kaliora et al. (2019) shows that adherence to the Med diet can reduce the concentration of serum triglycerides (effect size = −33.01 mg/dL; 95% CI − 52.84 to −13.18 mg/dL), and the total cholesterol (effect size = −6.89 mg/dL; 95% CI − 14.90 to 1.12 mg/dL), which can be theoretically translated to protective effects in NAFLD (31).

A 2022 published review found that drinking beetroot juice for 4 weeks significantly reduced serum TG concentrations in healthy adults (32). In a conducted study by de Castro et al. (33), Dyslipidemia overweight subjects used freeze-dried red beet leaves (2.8 g) for 4 weeks, which resulted in lower LDL-C, especially in intervention groups but not in control groups. Another study revealed that female soccer players reported a significant reduction in the concentration of

TABLE 4 Comparisons of the changes from baseline to the end of the intervention for Mediterranean diet components.

Variables		BJ + MeD	MeD	BJ	Control	**p value
		Mean ± SD				
Daily energy intake (kcal/day)	Before	2,278 ± 76.37	2,143 ± 35.14	2,199 ± 62.63	2,116 ± 59.28	<0.001
	After	2096 ± 24.19	2,127 ± 32.75	2,152 ± 32.94	2,102 ± 52.13	<0.001
	*p value	<0.001	0.019	<0.001	0.765	
MeD component						
Vegetables (g/d)	Before	307.6 ± 118.1	308 ± 104.8	315.5 ± 109.1	296.4 ± 130.9	0.891
	After	366.6 ± 145 ± 7	329.3 ± 126.2	320.6 ± 116.4	248.3 ± 113.4	<0.001
	*p value	0.053	0.424	0.810	0.106	
Total cereal (g/d)	Before	295.5 ± 83.6	297.2 ± 90.9	286.3 ± 70.3	316.9 ± 80.0	0.341
	After	313.6 ± 92.8	295.2 ± 101.1	293.0 ± 64.1	264.4 ± 80.5	0.059
	*p value	0.307	0.922	0.629	<0.001	
Fermented dairy (g/d)	Before	452.8 ± 76.1	442.8 ± 89.6	461.3 ± 87.9	459.1 ± 84.9	0.732
	After	497.4 ± 97.8	460.4 ± 83.6	475.9 ± 90.8	458.4 ± 77.4	0.131
	*p value	<0.001	0.337	0.457	0.969	
Legume, nut and seed (g/d)	Before	38.6 ± 20.3	38.4 ± 15.4	36.7 ± 18.2	40.0 ± 17.4	0.854
	After	60.1 ± 23.0	39.2 ± 22.9	38.2 ± 16.4	371 ± 14.4	<0.001
	*p value	<0.001	0.834	0.661	0.374	
Low fat dairy(g/d)	Before	127.9 ± 40.6	121.1 ± 40.8	110.9 ± 51.4	127.0 ± 25.7	0.068
	After	106.6 ± 37.9	111.2 ± 39.4	104.9 ± 44.3	90.9 ± 55.6	<0.001
	*p value	<0.001	0.262	0.589	<0.001	
Red and processed meats (g/d)	Before	34.5 ± 15.5	26.7 ± 16.8	41.6 ± 16.7	37.4 ± 17.5	<0.001
	After	24.9 ± 14.2	19.1 ± 10.8	36.8 ± 17.7	33.8 ± 13.4	<0.001
	*p value	<0.001	<0.001	0.175	0.271	
Poultry (g/d)	Before	109.3 ± 44.4	110 ± 39.9	98 ± 46.1	118 ± 48.4	0.214
	After	137.7 ± 48.9	120.5 ± 41.4	108.6 ± 43.9	117.3 ± 45.0	<0.001
	*p value	<0.001	0.243	0.248	0.946	
Fish (g/d)	Before	36.7 ± 9.46	34.6 ± 7.4	37.1 ± 9.3	37.1 ± 10.8	0.542
	After	47 ± 9.6	42.7 ± 10.9	39.5 ± 10.9	39.3 ± 9.5	<0.001
	*p value	<0.001	<0.001	0.333	0.317	
Fruits (g/d)	Before	302.9 ± 56.1	295.3 ± 54.6	308.5 ± 51.6	289.8 ± 56.3	0.385
	After	329.6 ± 66.3	305.9 ± 67.7	301.6 ± 60.6	296.3 ± 60.7	0.072
	*p value	<0.001	0.444	0.575	0.613	
MUFA/SFA (g/d)	Before	0.78 ± 0.13	0.71 ± 0.12	0.90 ± 0.11	0.91 ± 0.17	<0.001
	After	0.90 ± 0.17	0.86 ± 0.11	0.92 ± 0.13	0.79 ± 0.17	<0.001
	*p value	0.382	<0.001	<0.001	<0.001	

Data presented as Mean ± SD, *p* value obtained by *Paired *t*-test and **One-way Anova. BJ + MeD, beetroot juice and Mediterranean diet; MeD, Mediterranean diet; BJ, beetroot juice.

LDL-C in the test group who consumed 200 mL of beetroot juice 2 h before their training (34). However, consuming powder beetroot for 12 weeks reduced the level of lipid profile and liver enzymes. Amnah and Alushaibani (2013) reported in their study that, when done on rats that consume biscuits prepared with beetroot powder, they can significantly reduce liver enzymes, cholesterol, and total lipids in cases compared to controls (35). Nouri et al. (2017) observed that male Wistar rats with liver illnesses had lower liver enzyme levels after consuming beetroot juice (36).

Combining beetroot juice and the Mediterranean diet may have even greater effects on lipid profiles. A 2020 study published in the Journal of Functional Foods found that combining beetroot juice and the Mediterranean diet for 12 weeks significantly reduced serum TG concentrations in overweight and obese adults (37). Sigh et al. (2015) conducted a human study that revealed that consuming beetroot juice reduced the lipid profile, including LDL, triglycerides, and total cholesterol levels, while also significantly increasing HDL levels in physically active individuals (38).

Hence, our finding showed that the bilirubin level in participants in the intervention groups was considerably lower than in the control groups. Additionally, the total bilirubin level in groups BJ + MeD and BJ had considerably decreased. Several studies have found that beetroot juice can improve liver enzyme levels in people with liver disease. For example, a 2017 study published in the World Journal of Gastroenterology found that drinking beetroot juice for 12 weeks significantly reduced levels of liver enzymes in people with non-alcoholic fatty liver disease (39).

Moreover, there were no discernible differences in serum AST levels between the baseline and end of the intervention in the BJ + MeD group. However, an intragroup comparison of AST showed that the amounts of AST in the BJ and MeD groups had significantly decreased from the study's start to the end. When compared to the control group, the percentage of ALT in the intervention groups significantly decreased.

Integration of BJ the key liver disease biomarkers, AST and ALP, was considerably reduced in the NAFLD patients' treatment regimen compared to the standard of care. Because NAFLD patients have greater degrees of fibrosis and increased AST (40), a possible strategy to stop the advancement of liver fibrosis is to enhance AST. The interaction between time and groups showed that BJ's influence on ALT increased over time, even though BJ could not have a significant impact on ALT in this study. Future research should assess BJ's impact on ALT over a longer period than 6 months. In a different study, the hepatoprotective effects of beetroot juice on liver damage in male Sprague Dawley rats were assessed. It was discovered that beetroot juice had dose-dependent hepatoprotective effects on liver damage (41). This finding supports our hypothesis about the discrepancy between our results and the study by Srivastava and colleagues. Moreover, Ozsoy-Sacan et al. (42) in their study assessed the *Beta vulgaris* extract effect on the liver of diabetic rats and found that the level of ALT, AST, and ALP significantly reduced in the intervened group, as compared to the placebo or control group.

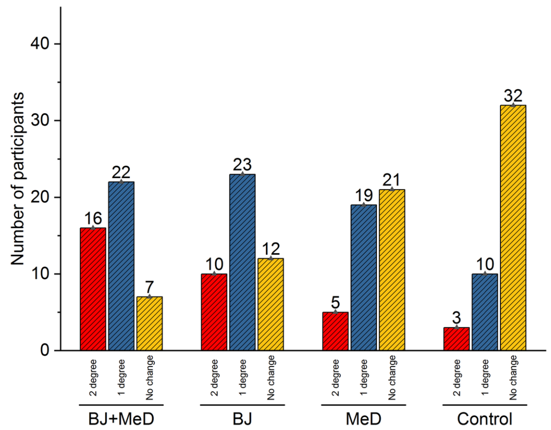

FIGURE 3
Fatty liver grade change after at the end of intervention.

On NAFLD, MeD, which primarily consists of higher intakes of fruits, vegetables, whole-grain cereals, plant-based proteins (legumes and nuts), micronutrients like potassium, calcium, and vitamin C, dietary fiber, omega-3 fatty acids, and monounsaturated fatty acids, as well as polyphenols and other antioxidant agents, has been linked to several beneficial outcomes (43). Currently, strong evidence-based supports the advantages of healthy dietary patterns in controlling most of the risk factors for NAFLD (44); for instance, Dorosty et al. reported that consuming whole grains for 12 weeks, independent of weight loss, beneficially affected concentration of liver enzymes, and fatty liver in the patients with NAFLD (45).

Consuming a healthy diet that contains sufficient amounts of vegetables and fruits (about 400 g/day) prevents the incidence of non-communicable diseases (30). Because it is high in fiber, antioxidants, and essential minerals, beetroot juice is one of the best homemade remedies for fatty liver. Its nutrients help to detoxify the liver and improve the processes of fat elimination. In mammals, the main sources of nitrate are diet (particularly leafy green vegetables) and endogenous synthesis (46). According to a new study co-authored by Harvard T.H. Chan School of Public Health researchers, a Mediterranean diet that includes more green plant matter may cut the risk of non-alcoholic fatty liver disease in half (14).

The main finding of the current study was a significant reduction in liver steatosis in BJ and BJ + MeD groups. It was also observed that this reduction in hepatic steatosis in the group members receiving Beetroot juice was increasingly more significant than that in the Mediterranean diet group. The results of this study were supported by

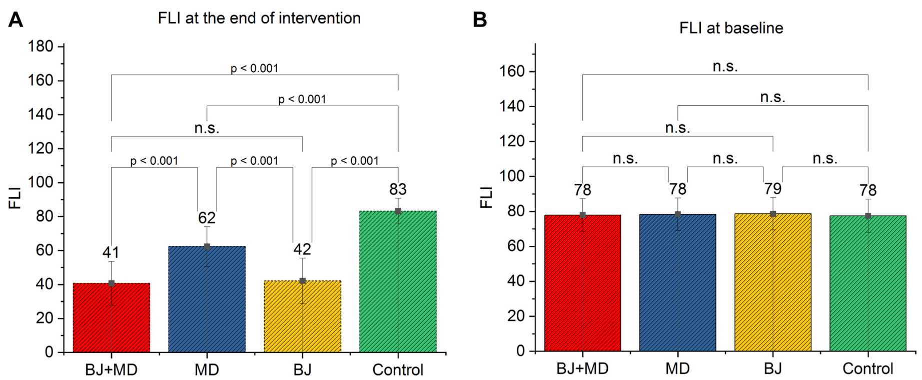

FIGURE 4
FLI of study participants according to groups: **(A)** FLI at the end of intervention, while **(B)** FLI at the baseline of intervention.

Srivastava et al. (2019) (34). And these effects may be due to the presence of dietary nitrate or antioxidant properties.

Finally, based on the comparison between the intervention groups in this study, it was concluded that beetroot juice (BJ group) is more effective than the Mediterranean diet (MeD group) in the treatment of NAFLD. By contrast, taking the Mediterranean diet (MeD group) and beetroot juice (BJ group) together (BJ + MeD group) is even more effective than taking either beetroot juice or the Mediterranean diet alone. The strength of the current study is that it is the first to estimate the effect of two intervened groups alone and together on the NAFLD. However, there are some limitations, such as the lack of complete adherence to a diet by some participants.

Conclusion

Red beetroot stands out as one of the most nutritionally dense foods found in the plant kingdom, containing a wealth of essential nutrients such as vitamins, minerals, phenols, carotenoids, nitrate, ascorbic acids, and betalains. Notably, both beetroot juice and the Mediterranean diet have demonstrated promising advantages for liver well-being. Nevertheless, additional research is necessary to comprehensively grasp their impact on liver enzyme levels and liver sonography. Future studies must examine any potential adverse effects that may arise from the consumption of beetroot juice.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Kalar technical college ethic commite. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HF designed the study and analyzed the data. HF, SR, SM, SA-J, and AA prepared the 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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Are there differences between Mediterranean diet and the consumption of harmful substances on quality of life?—an explanatory model in secondary education regarding gender

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Background: Adolescence is a key life stage in human development. It is during this stage of development that healthy and physical behaviors are acquired that will last into adulthood. Gender differences in the acquisition of these behaviors have been observed. This research aims to (a) study the levels of Mediterranean diet adherence, quality of life and alcohol and tobacco consumption as regarding the gender of the participants and (b) study the effects of the variable adherence to the Mediterranean diet, alcohol consumption and tobacco consumption on quality of life as a function of the gender of the participants.

Methods: A non-experimental, cross-sectional, exploratory study was carried out in a sample of 1,057 Spanish adolescents (Average Age = 14.19; Standard Deviation = 2.87).

Results: The comparative analysis shows that the male teenagers shows a higher Mediterranean diet adherence compared to the male adolescents ($p \leq 0.05$) and a higher consumption of alcoholic beverages ($p \leq 0.05$). On the contrary, adolescent girls show a higher consumption of alcoholic beverages than male participants ($p \leq 0.05$). The exploratory analysis indicates that for boys, alcohol consumption has a beneficial effect on the quality of life of adolescents ($\beta = 0.904$; $p \leq 0.001$).

Conclusion: In this case, participants show differences in the levels of Mediterranean diet adherence, consumption of harmful substances and quality of life according to gender. Likewise, there are different effects between the variables according to gender. Therefore, gender is a key factor to consider during adolescence.

KEYWORDS

Mediterranean diet adherence, quality of life, alcohol, tobacco, gender

Background

The current area of study of human development focuses on expanding knowledge of the different phases of the human life cycle (1) and understanding the different changes that occur at each stage (2). Specifically, the adolescent stage takes place between the ages of fourteen and twenty-one and is divided into three phases: Early Adolescence (11–14 years), Middle Adolescence (15–17 years) and Late Adolescence (18–21 years) (3). Variations in the physical and health pattern of adolescents have been observed during the different stages that make up adolescence (3). During adolescence, young people tend to be more sedentary and have a higher intake of high-calorie ready meals (4). Gender differences have also been observed during this stage of human development (5). This has meant that gender is a key factor in understanding physical-healthy behaviors during adolescence (5). Studies have found that there are gender differences in adolescence when it comes to leading an active and healthy lifestyle (6, 7). These differences are often due to changes in food and physical preferences that originate in adolescence (7).

There are numerous variations in the dietary pattern followed during adolescence (8). Throughout the 21st century, unhealthy eating habits have become increasingly prevalent (9). This is mainly due to the easy access adolescents have to this type of high-calorie fast food (9). This results in increased rates of overweight and obese adolescents (10). This concern has led to an increase in the number of adults with metabolic and cardiovascular diseases (10). In terms of nutritional patterns, it has been observed that males are more likely to develop negative behavior toward following a healthy dietary pattern (11). Specifically, within the Mediterranean area, it has been observed that European adolescents show a worse Mediterranean diet adherence (12). A positive follow-up to the Mediterranean diet has reported numerous benefits in health such as reduced prevalence of metabolic syndrome, improved high-density lipoprotein cholesterol among others (13). Psychological improvements have also been observed, such as improvements in executive functions and improvements in the different dimensions of self-concept (13, 14). This dietary pattern is branded by the intake of foods characteristic of the Mediterranean area such as olive oil, vegetables, fruits, oily fish and dairy products (13). In addition, it offers a low intake of processed red meat, saturated fats and low consumption of alcoholic drinks (13).

An intensification in the consumption of alcoholic drinks in the adolescent population has been observed for both males and females (15). The main reason for increased drinking in the adolescent population is related to social recognition (16). A shift in drinking trends has been observed to be taking place (16). This is related to lifestyle, as many adolescents tend to consume alcoholic beverages after physical-recreational activity (17). Physical-recreational activities are becoming a justified cause for drinking alcoholic beverages (18). Regular consumption of alcoholic beverages during adolescence has been shown to lead to decreased academic performance, impaired executive functions and damage to brain cells (18). It has also been observed that young people who drink alcoholic beverages at an early age tend to develop a dependence process toward this substance (19). It has been observed that the consumption of alcoholic beverages can act as a catalyst for the consumption of other harmful substances (19), such as tobacco. It has been found that young people who regularly drink alcoholic beverages show higher tobacco consumption (20). Research has shown that the main reasons why adolescents smoke are pleasure, family influence and social recognition (21). Regular tobacco use has been shown to cause laryngeal cancer, oropharyngeal cancer, lung cancer, myocardial infarction, and stroke (20). This is why regular tobacco and alcohol consumption puts young people's adult life at risk and worsens their quality of life (21).

Quality of life has been studied under a multidimensional view relating to the social, emotional, mental and physical domains (22). In view of the new patterns of life, it is necessary to study the quality of life of adolescents, as this variable is positively related to the state of health of individuals and to higher academic performance (23). Studies show that the acquisition and promotion of healthy attitudes that are positively related to quality of life are associated with adolescents' educational attainment (23). This is why education based on the benefits of an active and healthy lifestyle can help to improve the quality of life of adolescents.

Thus, the different implications of this research study in relation to future lines of research focusing on the implementation of health promotion strategies during adolescence stand out. Several descriptive studies have been conducted examining adherence to the Mediterranean diet, quality of life and alcohol and tobacco consumption (9, 11, 17, 20, 22, 23). Despite this, little research has been found that focuses on studying the effects of these variables through multigroup equation modeling. That is why this study aims:

- To study the levels of adherence to the Mediterranean diet, quality of life and alcohol and tobacco consumption according to the gender of the participants.
- To study the effects of the variable adherence to the Mediterranean diet, alcohol consumption and tobacco consumption on quality of life according to the sex of the participants.

Methods

Design and participants

In line with the proposed objectives, the design of this research is non-experimental (*ex post facto*), comparative, exploratory and cross-sectional (only a single measurement was taken). It should be noted that the socio-economic level of the families is moderate and that half of the parents have a university education.

Moving on to the research participants, the sample of this study consists of 1,057 (Average Age = 14.19; Standard Deviation = 2.87) secondary school students. The population consists of 547 boys (51.75%) and 510 girls (48.25%). Following Byrnes et al. (24) and Melguizo-Ibáñez et al. (25), adolescence is made up of three stages: Early adolescence (11–14 years), middle adolescence (15–17 years) and late adolescence (18–21 years). According to this classification, 918 belong to early adolescence, 139 belong to middle adolescence and none to late adolescence. Continuing with the study of the sampling error, for a confidence level of 95.0%, a level of less than 5.0% was obtained.

Instruments

The following instruments were used to collect the data:

Own sociodemographic questionnaire: It was employed to collect sociodemographic data like age and gender (male/female).

Alcohol Use Disorders Identification Test (AUDIT) (26): It has been used the Spanish version (27). It is made up of 10 items. The first eight are assessed using a 5-choice Likert scale (0 = Never; 4 = Daily). The last items are assessed using a 3-option Likert scale. Regarding the reliability analysis, a value of α = 0.749 was obtained.

Fagerström Test for Nicotine Dependence (FTND) (28): Due to the characteristics of the sample, the Spanish version was used (29). This questionnaire provides information on the number of cigarettes smoked by the subject, the urge to smoke and the degree of dependence on nicotine. It consists of 6 items. Cronbach's alpha obtained a value of α = 0.916.

Mediterranean Diet Adherence Test (KIDMED) (30): This questionnaire is used to determine the degree of adherence to the Mediterranean diet. This questionnaire is made up of 16 questions. These questions are answered positively or negatively. The instrument presents four questions written in a negative way, so that if they are answered positively, they are valued with −1 point. The twelve questions, if answered positively, are rated with +1 point. Cronbach's alpha evidenced a value of $\alpha = 0.702$.

Quality of Life: The short version of the SF-36 questionnaire (31) was used to measure this variable. Specifically, we used the version adapted to Spanish (32). This instrument examines two distinct areas. The first dimension assesses the dimensions of bodily pain, general health, role and physical function. The second assesses the areas of vitality, social function and emotional role. Cronbach's alpha obtained a value of $\alpha = 0.916$.

Procedure

Initially, a reading of the different research on this subject was carried out. Based on these readings, the most reliable instruments were selected and this study was theoretically contextualized. In order to carry out the fieldwork, three secondary schools were randomly selected. The schools were then contacted and informed of the aims of the study. Once informed, the schools sent an informative letter to the different teenagers' legal guardians. Once the legal guardians were informed of the research objectives, they were asked to sign the informed consent form, authorizing their children to participate. In this informed consent, the legal guardians were notified that data would be processed scientifically and in an anonymized form.

During data collection, the researchers were always present to answer any questions. All data were collected during physical education classes. This was done so as not to interrupt the teaching of other subjects.

With regard to the ethical aspects related to research ethics, this study followed the criteria redacted in the Declaration of Helsinki. Likewise, throughout the research process, the study was supervised by an ethics committee of the University of Granada (2966/CEIH/2022).

Data analysis

Initially, the normality of the data was checked with the Kolmogorov–Smirnov test with Lillieforts correction. Homoscedasticity was measured using Lev's test. The variables followed a non-normal distribution. The analyses were carried out using non-parametric tests. For the comparative analysis, the Mann–Whitney U test was used. The significance level was set at $p \leq 0.05$. The statistical program IBM SPSS 25.0 for Windows was used to perform all the above.

Continuing with the exploratory analysis, the theoretical model (Figure 1) consists of twelve variables. Ten variables play an endogenous role and two variables act as exogenous variables. For the variables acting as endogenous, causal explanations have been made. These have been done by taking into account the observed associations between the degree of reliability of the measurement process and the indicators. This allows measurement error to be included in the different models. Furthermore, measurement error can be controlled and interpreted as multivariate regression coefficients. The direction of the arrows refers to the direction in which the effect occurs. In this case the significance level was set at $p \leq 0.05$ and $p \leq 0.001$. IBM SPSS Amos 26.0 (IBM Corp., Armonk, NY, USA) was used to develop the theoretical model.

To assess the fit of the theoretical model, the established criteria have been followed (33, 34). Initially, the fit of the Chi-Square test should be taken into account. When non-significant values are obtained, a good fit is evident. The following indices should also be considered: Comparative Fit Index (CFI), Goodness of Fit Index (GFI) and Incremental Fixity Index (IFI). The values must be higher than 0.90 to obtain a good fit. Also, the Root Mean Square Approximation (RMSEA) value must be taken into account. For this index values should be less than 0.100. Following the criteria established by Tenembaum and Eklund (35), sample size and susceptibility should be considered. Therefore, the Tucker Lewis Index has been included, which should be equal to or greater than 0.900.

The proposed model for the male adolescents obtained a non-significant value (Chi-Square = 78.760; Degrees of Freedom = 19; Probability Level = 0.002). The fit indices obtained an excellent fit (CFI = 0.965; IFI = 0.974; TLI = 0.952; RMSEA = 0.068). The proposed model for the female population obtained a non-significant value (Chi-Square = 32.726; Degrees of Freedom = 20; Probability Level = 0.008). The fit indices obtained an excellent fit (CFI = 0.976; IFI = 0.964; TLI = 0.939; RMSEA = 0.081).

Results

Table 1 shows the results obtained from the comparative analysis. It is observed that males shows higher levels in physical functionality (PF) (2.9653 ± 0.09468 vs. 2.9394 ± 0.14593; $p \leq 0.05$), physical role (PR) (1.9073 ± 0.25821 vs. 1.9016 ± 0.26382), social function (SF) (3.4672 ± 0.43987 vs. 3.4173 ± 0.53364; $p \leq 0.05$) emotional role (ER) (1.8728 ± 0.28883 vs. 1.8163 ± 0.36541; $p \leq 0.05$), mental health (MH) (3.9092 ± 0.37755 vs. 3.8693 ± 0.38740), Mediterranean diet adherence (0.8008 ± 0.08255 vs. 0.7930 ± 0.07939; $p \leq 0.05$) and tobacco consumption (1.5450 ± 0.74462 vs. 1.402929 ± 0.71684; $p \leq 0.05$). On the contrary, female teenagers show higher scores in bodily pain (2.0551 ± 1.02591 vs. 1.8957 ± 0.98256), general health (GH) (3.0110 ± 0.39626 vs. 2.9703 ± 0.35236; $p \leq 0.05$), vitality (VT) (3.4350 ± 0.48306 vs. 3.4258 ± 0.51263) and alcohol consumption (4.0661 ± 0.57752 vs. 4.0235 ± 0.59279; $p \leq 0.05$).

Table 2 together with Figure 2 show the standardized regression weights for boys. Regarding the relationship between adherence to the Mediterranean diet (MDA) and alcohol consumption (AC), a negative effect is observed ($\beta = -0.025$). There was also a negative effect of

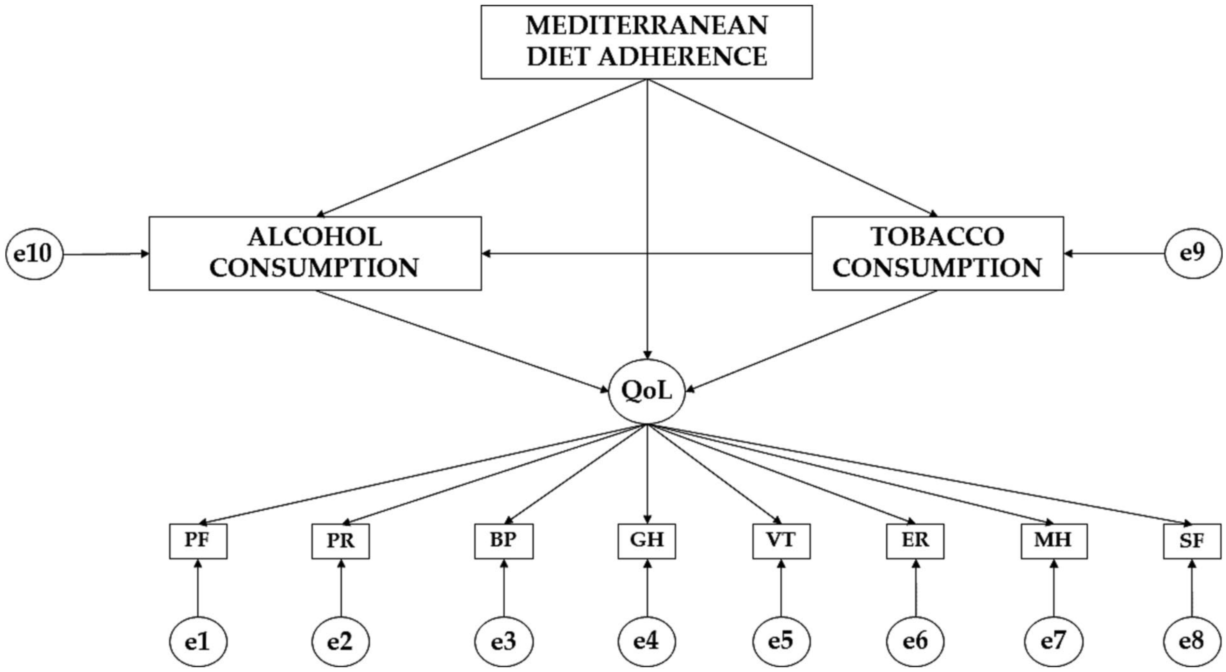

FIGURE 1
Theoretical model proposed. PF, physical function; PR, physical role; BP, bodily pain; GH, general health; VT, vitality; SF, social function; ER, emotional role; MH, mental health.

TABLE 1 Comparative analysis of the sample.

		N	*M* ± S.D	*P*
Physical function	Female	127	2.9394 ± 0.14593	0.007
	Male	930	2.9653 ± 0.09468	
Physical role	Female	127	1.9016 ± 0.26382	0.817
	Male	930	1.9073 ± 0.25821	
Bodily pain	Female	127	2.0551 ± 1.02591	0.880
	Male	930	1.8957 ± 0.98256	
General health	Female	127	3.0110 ± 0.39626	0.029
	Male	930	2.9703 ± 0.35236	
Vitality	Female	127	3.4350 ± 0.48306	0.089
	Male	930	3.4258 ± 0.51263	
Social function	Female	127	3.4173 ± 0.53364	0.025
	Male	930	3.4672 ± 0.43987	
Emotional role	Female	127	1.8163 ± 0.36541	0.039
	Male	930	1.8728 ± 0.28883	
Mental health	Female	127	3.8693 ± 0.38740	0.087
	Male	930	3.9092 ± 0.37755	
Mediterranean diet adherence	Female	127	0.7930 ± 0.07939	0.039
	Male	930	0.8008 ± 0.08255	
Alcohol consumption	Female	127	4.0661 ± 0.57752	0.043
	Male	930	4.0235 ± 0.59279	
Tobacco consumption	Female	127	1.4029 ± 0.71684	0.039
	Male	930	1.5450 ± 0.74462	

Mediterranean diet adherence (MDA) on tobacco consumption (TC) ($\beta = -0.120$; $p \leq 0.05$). A positive effect of alcohol consumption (AC) on tobacco consumption (TC) was observed ($\beta = 0.004$). Continuing with the effect of alcohol consumption (AC) on quality of life (QoL), a positive impact is obtained ($\beta = -0.904$; $p \leq 0.001$). Likewise, a positive effect of Mediterranean diet adherence (MDA) on quality of life (QoL) is obtained ($\beta = 0.245$). In contrast, a negative impact of tobacco consumption (TC) on quality of life (QoL) was obtained ($\beta = -0.344$; $p \leq 0.05$).

Considering the variables that make up the Quality-of-Life (QoL) variable, a negative effect of this variable on vitality (VT) ($\beta = -0.050$) and bodily pain (BP) ($\beta = -0.159$; $p \leq 0.001$) is obtained. On the contrary, a positive effect of Quality-of-Life (QoL) on mental health (MH) ($\beta = 0.107$), emotional role (ER) ($\beta = 0.083$; $p \leq 0.05$), social function (SF) ($\beta = 0.022$), general health (GH) ($\beta = 0.017$), physical role (PR) ($\beta = 0.084$; $p \leq 0.05$) and physical function (PF) ($\beta = 0.005$) is observed.

Table 3 together with Figure 3 show the standardized regression weights for girls. In this case, Mediterranean diet adherence (MDA) has a negative effect on alcohol consumption (AC) ($\beta = -0.072$) and tobacco consumption (TC) ($\beta = -0.011$) consumption. Similarly, alcohol consumption (AC) has a negative effect on tobacco consumption (TC) ($\beta = -0.055$) and quality of life (QoL) ($\beta = -0.208$). In contrast, Mediterranean diet adherence (MDA) has a positive effect on quality of life (QoL) ($\beta = -0.425$). Continuing with the variables that make up quality of life (QoL), it is observed a negative effect of this variable on emotional role (ER) ($\beta = -0.036$), social function (SF) ($\beta = -0.018$) and physical role (PR) ($\beta = -0.087$). In contrast, quality of life (QoL) exerts a positive effect on vitality (VT) ($\beta = 0.155$), general health (GH) ($\beta = -0.072$), bodily pain (BP) ($\beta = 0.145$) and personal role (PR) ($\beta = 0.101$).

TABLE 2 Male standardized regression weights.

Effect direction	Regression weights				Standardized regression weights
	Estimations	Estimation error	Critical Ratio	*p*	Estimations
AC ← MDA	−0.176	0.236	−0.748	0.454	−0.025
TC ← MDA	−1.084	0.294	−3.689	**	−0.120
TC ← AC	0.005	0.041	0.119	0.905	0.004
QoL ← AC	0.061	0.019	3.191	***	0.904
QoL ← TC	−0.019	0.009	−2.029	**	−0.344
QoL ← MDA	0.119	0.076	1.569	0.117	0.245
MH ← QoL	1.000				0.107
ER ← QoL	0.598	0.298	2.007	**	0.083
SF ← QoL	0.238	0.366	0.651	0.515	0.022
VT ← QoL	−0.642	0.462	−1.390	0.164	−0.050
GH ← QoL	0.145	0.291	0.499	0.618	0.017
BP ← QoL	−3.895	1.432	−2.721	***	−0.159
PR ← QoL	0.536	0.267	2.012	**	0.084
PF ← QoL	0.011	0.077	0.145	0.885	0.005

**$p < 0.05$.

***$p < 0.001$.

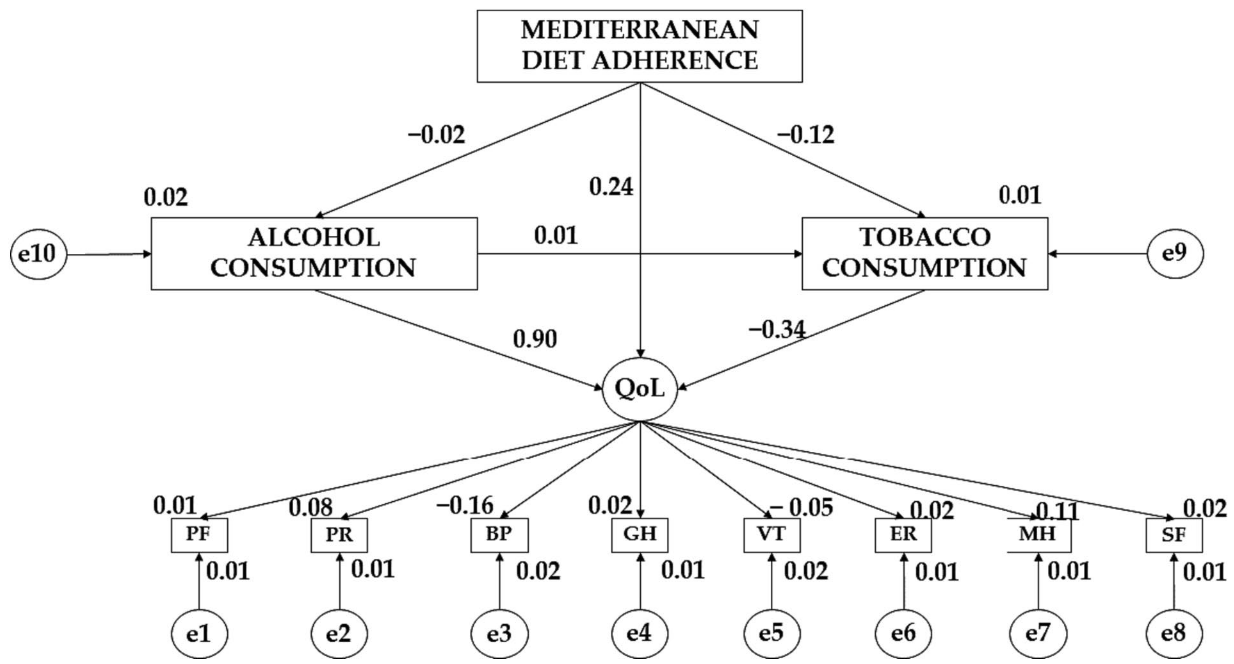

FIGURE 2
Theoretical model together with standardized regression weights for the male gender.

Discussion

The aims of this research are to study the levels of Mediterranean diet adherence, quality of life and alcohol and tobacco consumption according to the gender of the participants and to study the effects of the variable adherence to the Mediterranean diet, alcohol consumption and tobacco consumption on quality of life according to the gender of the participants. Once the relevant data analysis has been carried out to meet these objectives, the discussion aims to compare the results obtained with those of other similar studies.

With regard to the comparative analysis, it is observed that boys show greater adherence to the Mediterranean diet. Despite these results, research indicates that the male adolescents show a greater degree of complexity when it comes to following a healthy dietary pattern (36). Studies have found that there are no statistically significant differences between adherence to the Mediterranean diet

TABLE 3 Female standardized regression weights.

Effect direction	Regression weights				Standardized regression weights
	Estimations	Estimation error	Critical Ratio	Estimations	Estimation error
AC ← MDA	−0.527	0.646	−0.815	0.415	−0.072
TC ← MDA	−0.103	0.805	−0.127	0.899	−0.011
TC ← AC	−0.069	0.111	−0.622	0.534	−0.055
QoL ← AC	−0.011	0.021	−0.533	0.594	−0.208
QoL ← AC	−0.038	0.043	−0.885	0.376	−0.882
QoL ← MDA	0.165	0.216	0.763	0.445	0.425
MH ← QoL	1.000				0.080
ER ←QoL	−0.429	1.159	−0.370	0.711	−0.036
SF ← QoL	−0.305	1.579	−0.193	0.847	−0.018
VT ← QoL	2.429	3.042	0.798	0.425	0.155
GH ← QoL	0.925	1.540	0.601	0.548	0.072
BP ← QoL	4.842	6.150	0.787	0.431	0.145
PR ← QoL	−0.746	1.127	−0.662	0.508	−0.087
PF ← QoL	0.478	0.678	0.704	0.482	0.101

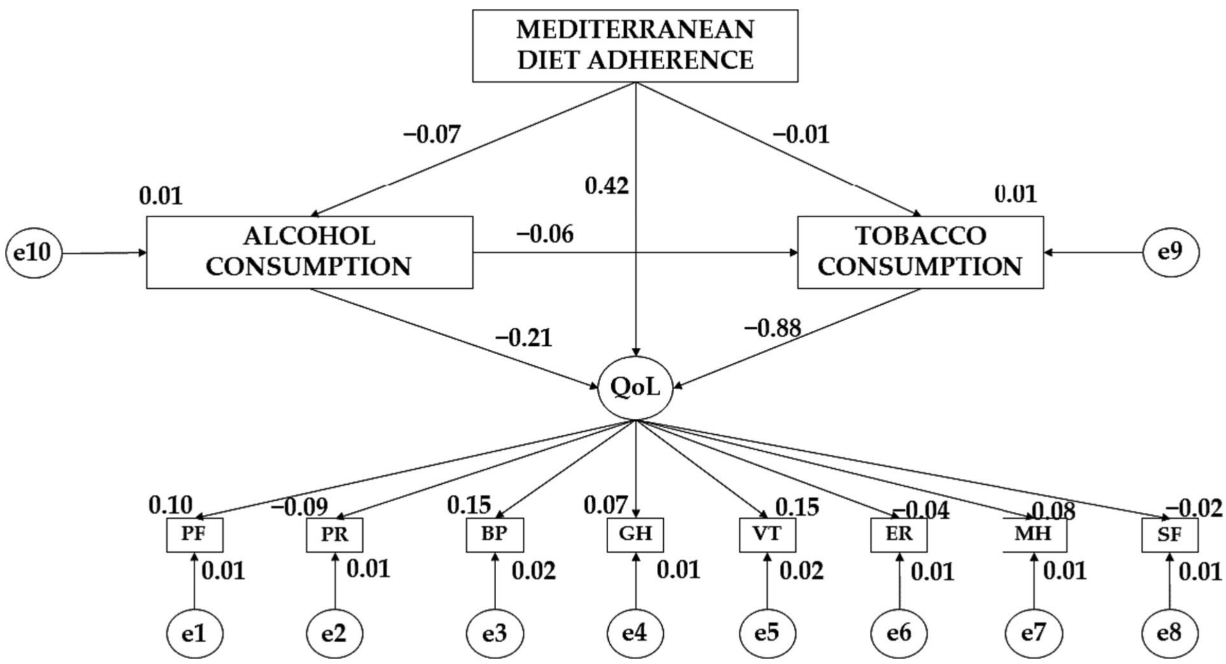

FIGURE 3
Theoretical model together with standardized regression weights for the female gender.

and gender (37, 38). It has been observed that women tend to pay more attention to the type of food they eat and how it is cooked (38). A decline in adherence to the Mediterranean diet has also been observed in adolescents in Greece, Italy and Spain (39). This is due to new food trends where, through new food apps, speed is prioritized over food quality and cooking (39). There are also factors that condition the degree of adherence to the Mediterranean diet, such as the socioeconomic level of families and the parents' level of education (40).

Continuing with the consumption of alcohol and tobacco, it is observed that female teenagers show a higher consumption of alcohol and the boys show a higher consumption of tobacco. In view of these findings, it has been pointed out that in Europe a higher intake of harmful substances is taking place at earlier ages of human development (16). Research similar to the present study found no statistically significant differences according to gender (17). Despite these findings, it has been found that males are more likely to exhibit positive alcohol and tobacco behaviors throughout adolescence (17).

Alcohol and tobacco use data have been positively related to social recognition and peer image (41). It has been shown that males attach greater importance to social recognition during adolescence, thus favoring unhealthy behaviors (17).

Continuing with the quality of life, it is observed that the male population shows higher scores in physical function, physical role, social function, emotional role, and mental health. In contrast, males show higher scores in vitality and general health. It has been observed that during adolescence the female gender shows a lower weekly physical activity time (17, 38). Studies indicate that males are more active than females during adolescence (17, 38). It has been observed that regular physical exercise has benefits for the physical function of the body, emotional control, social and mental health (13). In the physical area, physical activity helps to reduce body mass index, burn fat and improve aerobic capacity (13). In terms of emotional control and improved mental health, physical activity promotes the release of neurotransmitters such as serotonin and dopamine (42). It has also been observed that an active lifestyle helps to prevent the onset of body aches and pains resulting from physical inactivity (4, 13). Physical activity helps to improve general health (4). However, there are elements that have a negative impact on vitality and general health, such as alcohol, tobacco and cannabis consumption (17). In this case, it has been observed that the girls are reluctant to ingest these substances (17).

The exploratory analysis shows a negative effect of adherence to the Mediterranean diet on alcohol and tobacco consumption for male and female population. In this case, the Mediterranean diet has been found to be a dietary pattern that provides health benefits (13). This dietary pattern is characterized by a low intake of alcoholic beverages (13). Tobacco use has been reported to have negative effects on the health of individuals, irrespective of gender (16, 18). It has been observed that the boys are more prone to the intake of these substances as they help in acquiring greater social recognition from their peers (17).

Continuing with the effect of alcohol consumption on tobacco consumption and quality of life, the female teenagers show a negative effect. In contrast, males show an effect of alcohol consumption on tobacco consumption and quality of life. Studies indicate that alcohol consumption at an early age favors the use of tobacco and other psychoactive substances (17, 19, 20). The study by Jacobs et al. (43) states that girls show a greater rejection of alcohol and tobacco use. Regular consumption of alcoholic beverages is shown to worsen the quality of life of young people (43). However, there is an increasing intake of alcoholic beverages at younger and younger ages (43, 44). This may be due to a lack of awareness of the effects of alcohol on quality of life (44). It has also been reported that alcohol is used as a socializing element, thus encouraging socializing among peers (17, 44).

There is also a positive effect of adherence to the Mediterranean diet on quality of life for both men and women. Positive adherence to this dietary pattern has been observed to have benefits in different spheres of the human being (13). In this case, benefits have been observed at the organ level, such as reduced blood pressure and increased life expectancy (13). At the mental level, improvements in executive functions and improvements in self-concept have been found (45).

Strengths and limitations

In terms of the strengths of this study, it is worth noting its applicability. This research offers totally reliable data through various analyses where the current state of the variables is described and where the effect of these variables is analyzed according to gender. In this case, this study highlights the existing differences between the male and female sexes when it comes to leading a healthy lifestyle. When designing intervention programs, the motivations between men and women should be taken into account.

Finally, this research is not without limitations. The first of these is related to the design of the study. Being a cross-sectional study, data were only collected once. Although the instruments have been validated and adapted by the scientific community, they have an intrinsic measurement error. For future research it would be interesting to add new study variables. It would be advisable to add variables related to the socio-economic level of the families. It would also be advisable to add variables related to academic performance.

Conclusion

The conclusions obtained from this research are shown below.

In terms of objective one, it is concluded that boys show a greater adherence to the Mediterranean diet and a higher consumption of tobacco. On the other hand, the female adolescents show a higher consumption of alcoholic beverages. In terms of quality of life, the male teenagers show higher levels in the variables that make up this variable.

Continuing with the second objective, it is concluded that there are considerable differences in the relationship between the effect of the Mediterranean diet and the consumption of alcohol and tobacco on quality of life according to the gender of the participants.

As a general conclusion, this study shows that during adolescence, gender is a key factor when it comes to leading a healthy lifestyle.

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 study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board and approved by the Ethics Committee of University of Granada under Statement Number 2966/CEIH/2022. Written informed consent was obtained from all individual participants included in the study.

Author contributions

EM-I: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FZ-O: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JU-J: Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. GB: Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FY: Supervision, Validation, Writing – original draft, Writing – review & editing. GG-V: Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. LPA: Supervision, Validation, Writing – original draft, Writing – review & editing. PP-M: Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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He Rourou Whai Painga, an Aotearoa New Zealand dietary pattern for metabolic health and whānau wellbeing: protocol for a randomized controlled trial

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Background: Cardiometabolic diseases are highly prevalent in Aotearoa New Zealand. Dietary intake is a modifiable risk factor for such diseases and certain dietary patterns, specifically the Mediterranean diet (MedDiet), are associated with improved metabolic health. This study aims to test whether an intervention including a Mediterranean dietary pattern incorporating high quality New Zealand foods (NZMedDiet pattern) and behavior change science can improve the metabolic health of participants and their household/whānau.

Methods and analysis: This is a multi-center, three-stage trial with two parallel group superiority randomized controlled trials (RCTs), and a longitudinal cohort study embedded within the trial design. The first RCT (RCT 1) is a comparison of the NZMedDiet pattern compared to usual diet for 12 weeks. The Behavior Change Wheel was used to select and implement strategies to support participant adherence to the NZMedDiet, such as web-based nutrition education on healthy shopping and cooking. The second (RCT 2) compares online social support to no online social support for 12 weeks, administered to participants immediately following RCT 1. The third stage is a longitudinal cohort study where all participants are followed from the beginning of their start of the active intervention for 12 months in total. The primary outcome measure for each stage is the metabolic syndrome severity score (MetSSS). The duration of enrolment is 12–15 months. The total recruitment target is 200 index participants and their household/whānau members who participate with them, and the primary analyses will be intention to treat on index participants.

Discussion: The trial will test whether the NZMedDiet pattern and behavior change support improves the cardiometabolic health of people in Aotearoa New Zealand.

Clinical trial registration: https://www.anzctr.org.au/Default.aspx, identifier ACTRN12622000906752 and https://www.isrctn.com/, identifier ISRCTN89011056 (Spirit 2).

KEYWORDS

metabolic syndrome, dietary pattern, mediterranean diet, cardiometabolic, metabolic syndrome severity score, behavior change support, household/family intervention

Introduction (Spirit 6a)

Cardiometabolic diseases, including type 2 diabetes (T2DM) and cardiovascular disease, are common. In 2017, one in three deaths were caused by cardiovascular disease in Aotearoa New Zealand (1). Diet is an important modifiable risk factor for cardiovascular disease (2), and certain dietary patterns such as the Mediterranean diet (MedDiet) are associated with a reduced risk of cardiometabolic disease (3, 4). The MedDiet is rich in minimally processed plant-based foods and legumes; low in saturated fat and red meat; and a distinguishing feature is its use of olive oil (3). Nutrition knowledge regarding the benefits of adopting a dietary pattern such as the MedDiet does not always translate into a change in dietary behavior. Dietary change can be affected by barriers to behavior change such as cost, acceptability, time, dietary knowledge, nutrition competence and cultural practices (5).

Recent research from our group, and others, reports that the use of, and adherence to, a MedDiet pattern in Aotearoa New Zealand is low (6, 7). To promote a MedDiet pattern in countries such as Aotearoa New Zealand, attention should be given to optimizing a dietary intervention, taking into consideration the behavioral and social structures that decrease barriers to adherence (8, 9). Studies of interventions aimed at improving dietary patterns in community living individuals report that barriers to a healthier diet include the "good taste" of unhealthy food, inconvenience and difficulties in enjoying non-fatty food (5, 10). Individual choice, cultural norms and taste preferences of the study population are important to consider when adapting a dietary pattern into a population. Studies recruiting Māori, who are indigenous New Zealanders, and young adults of various ethnicities, report that the provision of meal preparation support and financial assistance for the use of healthy diets, may be useful to support changes in dietary patterns (11, 12). Food provision, barriers to which may have otherwise prevented dietary change, such as the lack of prior exposure, uncertainty about how to prepare the food, and cost, is a potential intervention that may enable the uptake of a healthier diet (13). The social context of sharing and consuming meals within a household/whānau is an important aspect of many cultures and takes into consideration that all the household/whānau members within a dietary intervention may facilitate ongoing dietary change for all (12, 14, 15). The provision of food and related education is reported to support adherence to a healthy diet, and lower the burden associated with food preparation, particularly when applied on a household/whānau basis (16). The behavior change wheel framework is underpinned by the Capability, Opportunity and Motivation Behavior (COM-B) theory and facilitates consideration of the aforementioned barriers to adopting the desired dietary pattern (17, 18). Consequently, this framework will be used to identify effective and feasible strategies to overcome these and support participant adherence.

The primary objective of this trial is to evaluate if a Mediterranean dietary pattern incorporating high quality New Zealand foods (NZ MedDiet pattern), delivered in a household/whānau setting and underpinned by behavior science can improve the cardiometabolic health of people in Aotearoa New Zealand. We have chosen to do this through the metabolic syndrome severity score (MetSSS). The metabolic syndrome (MetS) refers to the clustering of several risk factors including hypertension, obesity, dyslipidemia and insulin resistance, which identifies individuals at greater risk of CVD and T2DM (19). MetS is commonly classified in a dichotomous fashion, as having or not having MetS. An alternative approach, which gives a continuous and more nuanced description, is the Metabolic Syndrome Severity Score (MetSSS) which quantifies the value of MetS latent factors for an individual, and the resulting score behaves like a Z-score in that it is normally distributed in a population. The MetSSS has been shown to predict future cardiometabolic disease and can be modified by diet, exercise, and pharmacological intervention to estimate change in cardiometabolic disease risk, and is therefore a useful tool in assessing the impact of a dietary intervention (19). It has been validated in a New Zealand population and has been shown to be responsive to diet and lifestyle interventions in people with pre-diabetes (19–21).

A secondary objective of this study is to evaluate the effectiveness of continued online social support (Spirit 7).

Methods and analysis

This protocol is reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidance (22). In preparation for this trial, a feasibility study was conducted to test the recruitment and screening strategy, retention, acceptability of the method of delivery of a component of the intervention, and to collect relevant data to refine the power calculation for this study (23).

Trial design (Spirit 8)

This is a multi-center, three-stage trial, with two randomized controlled trials (RCTs); both parallel group superiority trials, and a longitudinal cohort study. The first RCT (RCT 1) compares the effect of Mediterranean dietary pattern incorporating high quality New Zealand foods (NZMedDiet pattern) to usual diet on MetSSS, a marker of cardiometabolic health for 12-weeks. The intervention in RCT 1 includes elements of behavior change science including the provision of food, recipes, weekly meal plans, access to web-based nutrition education and opt-in online social support. From here on

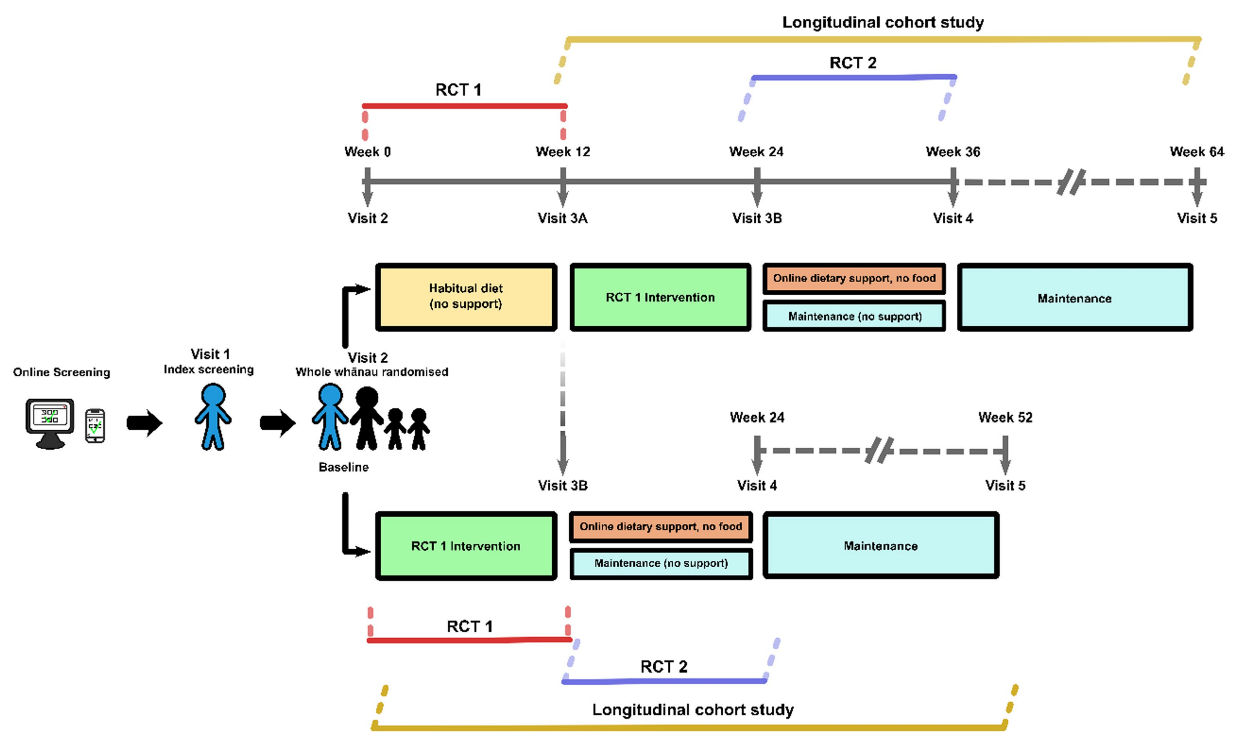

FIGURE 1
Study design.

within the manuscript 'RCT 1 intervention' is referred to as a package including these described aspects. The second RCT (RCT 2) compares the opt-in online social support, to no online social support with an outcome assessment 12 weeks after the second randomization (Figure 1). Those participants who were originally randomized to the control group in RCT 1 will be given the RCT 1 intervention before the second randomization. After the second randomization, both groups continue to have access to the bespoke study website housing nutrition information and education. The third stage is a longitudinal cohort study where all participants are followed for 12 months from the start of the dietary intervention. The trial design is summarized in Figure 1 (Spirit 8).

Trial setting (Spirit 9)

The trial settings are four centers in Aotearoa New Zealand: two based at university research units (University of Auckland and University of Otago, Christchurch), one at a community-based traditional Māori meeting place (Tū Kotahi Māori Asthma and Research Trust at Kōkiri Marae in Lower Hutt, Wellington), and the other based at a hospital-based research unit (the Center for Endocrine Diabetes and Obesity Research (CEDOR) in Wellington).

Eligibility criteria (Spirit 10)

Index participants and their household/whānau members will be recruited through the four trial sites. Multiple recruitment strategies will be used to recruit participants to the study. Advertising to the public through television, newspaper and radio advertisements, study posters, study information sessions, and other hardcopy and online media, including targeted social media, and institutional mailing lists will be used. Participants will be recruited from the local populations of the area of each study center. An important element of recruitment for research in Aotearoa New Zealand is to enhance Māori capacity and capability for research, and to include Māori and their whānau as research participants. This will be enabled by the close relationship between CEDOR and Kōkiri Marae to support the staff at Kōkiri Marae and oversee the running of the trial at that site (Figure 2).

Tables 1, 2 show the eligibility criteria for both index participants and household/whānau participants. Screening will occur consistent with our feasibility study (23). Potential participants who respond to advertisements or who otherwise contact researchers will be directed to the trial website[1] and an on-line questionnaire to complete as step one of the two step screening process. The website provides information about the trial and the questionnaire includes contact information and questions to enable calculation of the AUSDRISK (24). If this score is greater than 12, potential participants will be invited to a second step of screening which is conducted in-person at one of the study sites. This will include a fasting blood sample and anthropometric measurements to enable the calculation of the MetSSS. If they have a fasted MetSSS greater than 0.35, they will be the index participant. Once identified, and having given written consent for participating, household/whānau members of the index participant will also be invited to participate in the trial. Between one and five household/whānau members per index participant will be invited. The food provision intervention (see

1 www.hrwp.co.nz

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Male:

-5.4559 + (0.0125 × Waist Circumference (cm)) - (0.0251 × HDL (mmol/L) ×38.67) + (0.0047 × Systolic Blood Pressure) + (0.8244 × log(TAG (mmol/L) ×88.57)) + (0.0106 × Glucose (mmol/L) ×18)

Female:

-7.2591 + (0.0254 × Waist Circumference (cm)) - (0.0120 × HDL (mmol/L) ×38.67) + (0.0075 × Systolic Blood Pressure) + (0.5800 × log(TAG (mmol/L) ×88.57)) + (0.0203 × FPG1×18)

FIGURE 2
Formulae used for the calculation of the MetSSS.

TABLE 1 Inclusion and exclusion criteria for index participants.

Inclusion criteria	Exclusion criteria
18–70 years	Previous bariatric surgery, or pre-existing Type 1, or Type 2 diabetes. Where a previous diagnosis of T2DM is uncertain, this will be defined as ever having had two consecutive HbA1c results ≥50 mmol/mol that are at least three months apart
Metabolic syndrome severity Score (MetSSS) >0.35	Total cholesterol ≥8 mmol/L
1–5 household/whānau members agree to participate*	Chronic severe renal disease (eGFR <30 mL/min/1.72m^2)
Participants and their whānau are planning to live together for the duration of the study	Current pregnancy or breastfeeding, or planning to conceive during the study (due to impact on interpreting outcome measures)
Access to the internet at home	Unstable body weight (active weight loss/gain >5 kg in prior three months)
Able and willing to attend all site visits	Gastrointestinal disorder that alters the digestion and absorption of nutrients (e.g., ulcerative colitis, Crohn's disease, coeliac disease, an ileostomy or colostomy).
Willing to adhere to local health and safety regulations	Severe food allergies (anaphylaxis) in any household/whānau member
For the consumer insights study, there needs to be a willingness to be interviewed	Medication use – current use of medications that modify blood sugar levels, or anticipated regular use of oral or injected steroids
	Does not agree to refrain from donating blood for three months prior to each study visit (due to impact on HbA1c)
	Is participating in, or has recently participated in another research study involving an intervention which may alter outcomes of interest to this study
	Any other condition or situation, which in the view of investigators would affect the compliance or safety of the individual taking part

*Additional whānau/household members, if they are eligible and interested, may also be enrolled as an index participant.

below) will be calculated based on the total number of people in the household, for up to 6 members. All household/whānau members who qualify for inclusion will complete age-appropriate questionnaires (Table 3), will be invited to undertake clinical measurements and to provide blood samples if aged 11 years and over. If an index participant and household/whānau participant were to separate over the course of the trial, attempts would be made to gather data from those who continue living in the same building as the index participant.

Who will take informed consent (Spirit 26a)

Written informed consent will be obtained from index participants at Visit 1 by a member of the study team and from whānau/household participants at Visit 2 (Figure 1). Assent and parental/caregiver consent will be collected from household/whānau participants who are aged less than 16 years. However, if a 14- or 15-year-old child demonstrates an understanding of what the study involves at Visit 2, they will be invited to complete consent. Additional written consent will be requested from index participants at visit 1 for several sub-studies. These include (1) participation in a mixed meal tolerance test at two timepoints (2) participation in a sub-study around the measurement of dietary intake using a phone application. In addition, at visit 1, index participants will be asked if they wish to learn more about a qualitative study that runs in parallel with the current study. If so, their contact details will be passed to a qualitative researcher who will contact them by phone with further details and will take consent, as applicable.

TABLE 2 Inclusion criteria for household/whānau participants and exclusion criteria for household/whānau participants who provide a blood sample.

Living in the same household as the index individual	Age ≤ 11 years
Consent/assent to consume the intervention food	Pre-existing Type 1 diabetes.
	Chronic severe renal disease (eGFR <30 mL/min/1.72m^2)
	Current pregnancy or breastfeeding, or planning to conceive during the study (due to impact on interpreting outcome measures)
	Unstable body weight (active weight loss/gain >5 kg in prior three months)
	Gastrointestinal disorder that alters the digestion and absorption of nutrients (e.g., ulcerative colitis, Crohn's disease, coeliac disease, an ileostomy or colostomy).
	Medication use – current use of medications that modify blood sugar levels, or anticipated regular use of oral or injected steroids
	Does not agree to refrain from donating blood for three months prior to each study visit (due to impact on HbA1c)
	Is participating in, or has recently participated in another research study involving an intervention which may alter outcomes of interest to this study
	Any other condition or situation, which in the view of investigators would affect the compliance or safety of the individual taking part
	Children living in the household but who do not have a legal guardian also living in the household

TABLE 3 Summary of questionnaires.

	How administered	What it measures	Which participants
Otago short-form FFQ (25)	On REDCap	Habitual dietary intake	All index participants and household/whānau participants aged 11y and over
Three factor eating questionnaire or child version (26)	Emailed survey which will be linked to REDCap	Cognitive restraint uncontrolled eating and emotional eating	All index participants and household/whānau participants aged 11y and over
24h Food recall	On intake 24 website (https://intake24.co.uk/info/recall)	Dietary intake in previous 24h	All index participants and household/whānau participants aged 11y and over
IPAQ Physical activity (27)	On REDCap	Habitual physical activity	All index participants and household/whānau participants aged 11y and over
SF 36 (28)	On REDCap	Quality of life	All index participants and household/whānau participants aged 11y and over
Kaupapa Māori Wellbeing questionnaire	On REDCap	Covering the four realms of Te Whare Tapa Whā to determine quality of life from a Māori perspective	Any Māori participants aged 11y and over
Gastrointestinal symptom rating scale (29)	On REDCap	Gastrointestinal symptoms	All index participants and household/whānau participants aged 11y and over
Self-evaluation COM Questionnaire (30)	On REDCap	Evaluates the process; assesses participant perceptions of barriers and enablers throughout the study to see if the behavior change support is working as it is intended	Index participants
Impact Evaluation for Nutrition and Behavior Change Support (31)	On REDCap	Assesses how the behavior change support impacts participants (including engagement, satisfaction, and perception of impact)	Index participants

FFQ, food frequency questionnaire; IPAQ, international physical activity questionnaire; COM, capability opportunity motivation.

Additional consent provisions for collection and use of participant data and biological specimens (Spirit 26b)

Participants will be given the option to provide written consent for their blood samples and related meta-data to be included in an anonymous manner in a biobank.

Intervention for RCT 1 (Spirit 6b and 11a)

The two arms in RCT 1 are: (a) the intervention arm, which is a package that includes food provision designed to supply the majority of estimated energy requirements for participants, combined with recipes, weekly meal plans, access to web-based nutrition education and opt-in online social support; and (b) the control arm, which is usual dietary intake and lifestyle, i.e., usual care.

The food provision will comprise food delivery to the participants' homes for 12 weeks and is provided free of charge. The food will be assembled and delivered by two commercial companies, one of which is a meal kit home delivery service and the other is a grocery provider. The meal kit home delivery service will deliver food and recipes for five evening meals and fruit, and the grocery provider will deliver food that can be used for breakfast, lunch and snacks.

The food from both companies will be predominantly plant-based and rich in fruit and vegetables, grains, legumes, seafood, nuts, with some meat and dairy. The five New Zealand food groups used as the basis of the food provision are: vegetables; fruit; grain foods; legumes, nuts, seeds, fish and other seafood, eggs, poultry or red meat with fat removed; and reduced-fat milk and milk products. The amount of food provided is designed to provide approximately 75% of estimated energy requirements for the index participant and up to five members of their household/whānau. The food provided will align with a Mediterranean dietary pattern and when combined with the remaining ~25% energy requirements provided by participants themselves, will aim to fall within the acceptable total energy and macronutrient reference ranges for fat, carbohydrate and protein (32). Further details on the estimated energy, macronutrient distribution and food provided will be published separately. If a participant and their household/whānau go on holiday during the 12-week intervention period, the food delivery will be temporarily paused and will resume when they return home. During this time, they will be encouraged to adhere to the dietary pattern and will continue to have access to the education and social support resources.

The meal kit home delivery service and the grocery provider deliver food that has come from two sources; food provided in-kind to the study by New Zealand food and beverage (F&B) companies and food that is purchased by the research team. The food provided in-kind will be transported from the F&B companies directly to the meal kit home delivery service and the grocery provider, and then distributed to study participants. The involvement of the F&B companies was such that a nationwide call was made by the funding body (High Value Nutrition National Science Challenge) to F&B companies in New Zealand who wished to partner in the research study. The researchers assessed whether their foods align with the dietary pattern and if so, agreed on the quantity of food to be provided. The F&B companies had no direct role in the design or composition of the dietary pattern. Regular communication will take place between the researchers and the F&B companies who provide food.

The meal kit home delivery service will deliver meals that will have been pre-selected on behalf of the participants by a study dietitian. These meals will be either vegetarian, fish-based, or contain lean meat wherever possible. There are three grocery boxes that will be provided weekly by the grocery provider which have been developed by the research team to align with weekly breakfast, lunch and snack suggestions and recipes. These will be rotated over three weeks to provide variety, with each box being provided four times over the 12-weeks. An additional 'Starter Box' of products will be provided at the beginning of the 12-week period. The 'Starter Box' will include items that participants can use either immediately or throughout the entire 12-week period such as macadamia nuts, dried fruit, fish oil dressing, honey and seaweed snacks. Examples of the items in the other three boxes that are provided in a rotating manner are breakfast cereal, reduced-fat milk, seeds, rice cakes, olive oil, tuna, nuts, beans, lentils and fruit. The menu plans and recipes will be accessible through the study website.

The implementation of the dietary intervention incorporates elements of behavior change science which will be delivered by a multidisciplinary team including trained research staff and allied health care professionals including dietitians. Each site will have one research assistant and a doctoral student to support the clinic visits and arrange for the provision of food. The site staff will also make participants aware of the website and social media support options available to them and will play the website video titled "Introduction to the diet" so participants will be aware of what the dietary pattern entails. The behavioral aspects of the trial aim to support adherence to the NZMedDiet pattern and will include private Facebook groups and Facebook Messenger chats with a dietitian and peer support (online social support) which will be managed by one doctoral student who is a registered dietitian; a behavior change contract signed by participants prior to beginning RCT 1; and educational and motivational resources hosted on a participant facing website and YouTube channel. The website will be developed prior to the trial starting and will have six tabs covering: 1. Research Team, 2. Industry partners, 3. Nutrition support 4. Industry products, 5. Participant frequently asked questions and 6. Contact Us. The Nutrition Support section will link to short videos which will cover an introduction to the diet, goal setting, sample menus and recipes. The Nutrition support will also include multiple one-minute videos recorded by members of the research team, such as those entitled "Planning your shopping," "Meal Planning," "Getting to know your ingredients," "Cooking" and "What to do with leftover food/ kai," "Understanding your health data," "Keeping motivated" and "Healthy Holiday Tips." The behavior change wheel was used to design these resources to overcome identified barriers to the behavior, such as time and cost (17, 18). The participants will be able to interact with the website and online social support as little or as much as they chose.

Control arm for RCT 1; usual dietary intake and lifestyle

Participants allocated to the control arm will continue their usual lifestyle and diet for 12-weeks. Nutritional education and social support will not be provided. At the end of this 12-week period, they will receive the intervention package described above, for 12-weeks.

Intervention for RCT 2 (Spirit 6b and 11a)

At the end of the 12-weeks of RCT 1, participants randomized to the RCT 1 intervention will immediately be randomized to continuing the opt-in online social support or stopping it. Participants randomized initially to the RCT 1 control will then receive the RCT 1 intervention package described above for 12-weeks and will then be randomized to RCT 2 to either continuing the opt-in online social support or stopping it (Figure 1). All participants will continue to have access to the bespoke study website housing nutrition information.

Criteria for discontinuing or modifying allocated interventions (Spirit 11b)

Enrolled participants from either arm can withdraw from the study at any time during the study. The reason for withdrawal will be captured.

Strategies to improve adherence to the intervention (Spirit 11c)

Ongoing support will be provided by a member of the research team which includes the development and provision of additional short videos for the study website containing strategies around adhering to the intervention during holiday periods such as Christmas and New Year. Participants will also receive ongoing bespoke individualized support from the same team member in response to barriers they may encounter and queries they may have. Measurements and outcomes (Spirit 12).

Outcomes for RCT1 and RCT2

The primary outcome for RCT 1 and RCT 2 is MetSSS in index participants. Secondary outcome measures for RCT 1 and RCT 2 for index and household/whānau participants are listed in Table 4. The behavior change elements of the trial are designed to support adherence to the dietary intervention and will be assessed using the Food Frequency Questionnaire (FFQ) and the Mediterranean adherence diet score which is taken from the FFQ data. While online engagement metrics as count scores will be assessed, these have little to no clinical relevance and will be used as modifying factors in the analysis.

Outcomes for longitudinal cohort study

The primary outcome measure for the longitudinal cohort study is MetSSS in index participants 52 weeks after the start of the RCT 1 intervention package, whether that be at the beginning of the trial for those randomized to this arm initially, or after the initial 12-week control period for those randomized to the usual care arm of RCT 1. Secondary outcome measures for index and household/whānau participants are also listed in Table 4.

Details of outcome measures

Clinical assessment including anthropometry, blood sample provision and bioelectrical impedance (BIA) or dual x-ray absorptiometry (DXA) scans will be carried out at the research sites as described in Table 5. Height (cm) will be measured using a wall mounted stadiometer and weight (kg) will be measured using electronic scales. Body composition to include fat mass and lean mass in kg and as %body weight will be measured using either DXA and/or BIA, depending on what is available at the site. Waist circumference (cm) will be measured using a non-stretch tape and blood pressure (BP) (mmHg) will be measured using an automated blood pressure machine. The mean of three measurements of height, weight and waist circumference will be used for these outcome variables. For BP, three measurements will be recorded and the mean of the second and third measurements will be used. Adherence to the dietary pattern will be measured during the intervention period using a 24-h dietary recall and a FFQ (25). The FFQ includes additional questions specifically related to the dietary pattern of interest. The dietary pattern will be assessed using the FFQ data to create a Mediterranean diet adherence score based on the number of serves of olive oil, vegetables, fruit, breads & cereals, legumes, nuts, fish and seafood, eggs, poultry, dairy foods, red meat and sweets that the participants consume (33). A fecal sample will be collected from index participants for future microbiome analysis (Table 5).

A number of sub-studies may be undertaken which include consumer insights including that of Pacific island participants; mixed meal tolerance tests; use of a phone application for the measurement of dietary intake; fecal microbiome analyses. Details of these sub-studies will not be described in this paper.

Participant timeline (Spirit 13)

The duration of the study is 52-weeks after the intervention component of RCT 1.

Sample size (Spirit 14)

The sample size uses a clinically important difference of 0.4 for the MetSSS score based on detecting a 'moderate' effect size. This is because the MetSSS score was designed to represent the total number of standard deviations different for an overall risk factor profile for poor cardiovascular outcomes (19, 34). The standard deviation for the MetSSS for the calculation, 0.83, was derived from a large Auckland-based cohort study of these risk factors in a similar sample to that for recruitment (20). A t-test based sample size calculation used 90% power and a two-sided type I error rate of 0.05 was for 184 total participants and increased to 200 index participants to allow for a 10% non-completion rate. A smaller effect size is likely to be detectable by using baseline MetSSS as a co-variate in an ANCOVA.

Assignment of interventions

Allocation sequence generation in RCT 1 and in RCT 2 (Spirit 16a)

Index participants and their household/whānau will be block randomized into RCT 1 at site level to either start the intervention package or continue usual dietary intake for 12 weeks. If there is a second person within the household/whānau who meets the criteria for an index participant, they will be allocated to the same arm as the first index participant, where applicable. Index participants will be randomized using a computer-generated sequence. Household/whānau members will be randomized to the same arm as their corresponding index participant. Index and household/whānau participants will all be randomized once their data have been collected at Visit 2. It is not possible to blind index participants or their household/whānau members to the intervention in RCT 1. Nor is it practical to blind study staff

TABLE 4 Primary and secondary outcome measures for RCT1, RCT2 and the longitudinal cohort study for index participants and for household/whānau members.

Outcome variables	RCT 1	RCT 2	LCS	Proposed analysis
Primary outcome				
MetSSS	X	X	X	ANCOVA with baseline measurements as covariate, see text for details of sensitivity analysis confounders and sub-group
Secondary outcomes				
Weight	X	X	X	ANCOVA with baseline measurements as covariate
Body mass index	X	X	X	ANCOVA with baseline measurements as covariate, consideration of logarithm transformation
Lean mass (FFM calculated from BIA and DXA measurements)	X	X	X	ANCOVA with baseline measurements as covariate
Fat mass (calculated from BIA and DXA Measurements)	X	X	X	ANCOVA with baseline measurements as covariate
Dietary pattern measured using Food Frequency Questionnaire	X	X	X	
Individual components of MetSSS				
Glucose	X	X	X	ANCOVA with baseline measurements as covariate
Triglycerides	X	X	X	ANCOVA with baseline measurements as covariate, consideration of logarithm transformation
HDL cholesterol	X	X	X	ANCOVA with baseline measurements as covariate
Systolic blood pressure	X	X	X	ANCOVA with baseline measurements as covariate
Waist circumference	X	X	X	ANCOVA with baseline measurements as covariate
HbA1c	X	X	X	ANCOVA with baseline measurements as covariate
Insulin	X	X	X	ANCOVA with baseline measurements as covariate, consideration of logarithm transformation
HOMA	X	X	X	ANCOVA with baseline measurements as covariate, consideration of logarithm transformation
Total cholesterol	X	X	X	ANCOVA with baseline measurements as covariate
LDL cholesterol	X	X	X	ANCOVA with baseline measurements as covariate
Diastolic BP	X	X	X	ANCOVA with baseline measurements as covariate
hsCRP	X	X	X	Mann–Whitney test with Hodges Lehmann estimator
Quality of life				
SF36 (MCS and PCS and all dimensions)	X	X	X	ANCOVA with baseline measurements as covariate
Kaupapa Māori Wellbeing questionnaire	X	X	X	Analyzed and reported separately
Online engagement metrics	X	X		*Count scores*
Self-evaluation COM Questionnaire	X	X	X	*Count scores*
Impact evaluation	X	X	X	*Qualitative thematic analysis*

LCS, longitudinal cohort study; MetSSS, metabolic syndrome severity score; FFM, fat free mass; BIA, bioelectrical impedance; DXA, dual-energy X-ray absorptiometry; HDL, high density lipoprotein; HOMA, homeostatic model assessment; LDL, low density lipoprotein; hsCRP, high sensitivity C reactive protein; MCS, mental component summary; PCS, physical component summary.

collecting data, however the principal investigator, study statistician and the laboratory team will remain blinded throughout the study and analysis period. Participants will be informed of which arm of RCT 2 they are randomized to after they have completed the RCT 1 intervention.

Concealment mechanism (Spirit 16b)

Participants will be randomized after eligibility and written consent has been confirmed at visit 1 and baseline measurements have been completed (index participants) and visit 2 (household/ whānau participants).

Implementation (Spirit 16c)

A member of the study team will log into the online system to seek randomization. The allocated arm will be recorded in the participant's file and in the Site File.

Assignment of interventions: blinding

Who will be blinded (Spirit 17a)

The Principal investigator, laboratory technicians and study statistician will be blinded.

TABLE 5 Schedule of measurements for index participants.

Study period timepoints	Eligibility	Enrolment	Intervention and follow up					
	Visit 1 Screening	Visit 2 Baseline Enrolment	Phone contact	Email Contact	Visit 3a Control only	Visit 3b	Visit 4	Visit 5
RCT1 control group		Week 0			Week 12	Week 24	Week 36	Week 64
RCT1 intervention group			Week 2	Week 6		Week 12	Week 24	Week 52
Eligibility screen	✓							
Informed consent	✓							
Medical history	✓							
Education about RCT 1 and RCT 2		✓						
Questionnaires								
Otago short-form FFQ		✓			✓	✓	✓	✓
24 h dietary recall		✓		✓	✓	✓	✓	✓
IPAQ Physical activity		✓			✓	✓	✓	✓
Kaupapa Māori Wellbeing questionnaire		✓			✓	✓	✓	✓
Three factor eating questionnaire		✓			✓	✓	✓	✓
Gastrointestinal symptom rating scale		✓			✓	✓	✓	✓
Self-Evaluation COM questionnaire		✓			✓	✓	✓	✓
Impact evaluation for nutrition and behavior change support					✓	✓	✓	✓
SF-36 quality of life		✓			✓	✓	✓	✓
Assessments								
Height	✓							
Clinical measurements[a]	✓	✓			✓	✓	✓	✓
Body composition		✓			✓	✓	✓	✓
Current medications	✓	✓		✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓	✓
Fasting blood samples [b]	✓	✓			✓	✓	✓	✓
Fecal sample		✓			✓	✓	✓	˘

[a]Weight, waist circumference, height, blood pressure in triplicate. [b]HbA1c, fasting glucose, lipids and metabolites and hormones related to metabolic health Household/whanau members will attend visits 2, 3a/3b, 4, and 5.

10.3389/fnut.2023.1298743

Procedure for unblinding if needed (Spirit 17b)

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes (Spirit 18a)

In addition to clinical measurements and blood samples, data will also be collected using participant-completed questionnaires on paper and/or electronically through the study period (Table 5). Data will be collected during interviewer-led assessments at the relevant timepoints, and during the phone calls. Body composition using a DXA scan and/or BIA will be measured in index participants only.

Plan to promote participant retention and complete follow-up (Spirit 18b)

If randomized to the intervention, participants may opt out of intervention activities that are offered but remain enrolled in the study and continue with clinical assessments, complete questionnaires and allow researchers access to their medical records. Index and household/whānau participants will receive phone, text message or email reminders regularly to complete the questionnaires, depending on their preference.

Data management (Spirit 19)

When an index participant consents to take part, they will be allocated a unique participant identification number. A corresponding household/whānau participant will be allocated a unique participant identification number which connects to the identification number of their corresponding index participant. Consent forms and other paperwork containing personal identifiable data including completed paper questionnaires will be stored in a locked filing cabinet or password protected computer at each site. Data collected on REDCap will be stored within the REDCap system. Dietary intake data collected on Intake 24 is stored on that platform. Personal and research data entered directly onto a computer by participants or by a member of the research team will only be accessible to members of the research team. Participant details will be anonymized in all publications and other means of dissemination that result from the trial.

Confidentiality (Spirit 27)

The principles of confidentiality will be adhered to. Data will be collected and retained in accordance with the Privacy Act 2020 and the National Ethics Advisory Committee National Ethical Standards for Health and Disability Research and Quality Improvement. Personal data will be kept only for as long as it is required. All data analysis will take place on encrypted, password-protected computers. No data will be released to any unauthorized third party without the written approval of Principal Investigator. Data will be available for monitoring by the Health and Disability Ethics Committee or regulatory agencies if requested. An archiving plan will be developed for all study materials in accordance with the Sponsor's archiving policy, and study materials will be archived for 10 years from the end of the trial. Access to the protocol, data and the statistical code will be available through application to the Principal Investigator once the primary manuscripts have been submitted.

Plans for collection, laboratory evaluation and storage of biological specimen for genetic or molecular analyses in this trial/future use

Analysis of blood samples will be limited to analytes that will give information on the cardiometabolic health of participants. This will include but are not limited to HbA1c, lipids, glucose, insulin and high sensitivity C reactive protein. Participants will be given the option to provide consent for their blood and fecal samples to be included in an anonymous manner in a biobank.

Statistical analyses

The primary analysis will be conducted according to the intention to treat principle. Appropriate data descriptions and plots will be used for all variables. Change from baseline variables will also be described as paired differences but, in general, baseline values of response variables will be used as covariates in analyses rather than analyzing change from baseline. For RCT 1 and RCT 2 and for the index participants, the primary analysis for the primary outcome variable will be Analysis of Covariance (ANCOVA) with the baseline value of the MetSSS as a continuous covariate and the randomized treatment as the main explanatory variable. This strategy will also be used for all continuous outcome variables with the appropriate baseline value of any specific outcome variable as the covariate. The baseline measurement will be just before the relevant randomization. Normal distribution assumptions for residuals will be checked for models of continuous outcome variables and if these are badly violated transformations, such as a logarithm transformation, will be used. For some variables, outlined in Table 4, it is already established that the logarithm transformation is likely to be appropriate. Where appropriate transformations cannot be identified a rank-based procedure, the Mann–Whitney test with the Hodges-Lehmann estimator of location difference, will be used. For the primary outcome variable, the MetSSS, a sensitivity analysis will be a secondary analysis adjusting for possible confounding by important explanatory variables that may have not been evenly distributed by the randomization. These will be as a composite categorical variable for whether medication was changed for any of blood pressure control, glucose management, or lipid control; and separately, for physical activity assessed by the international physical activity questionnaire score. Analysis will be by ANCOVA with these confounding variables in addition to the baseline MetSSS and randomized treatment. Another secondary analysis will be to explore if randomized treatment allocation is associated with different effects in subgroups; using an appropriate treatment by subgroup interaction models. These subgroups are: age, sex, baseline diet adherence score, household size, and whether a household has children. For the continuous variables the analysis of the interaction will be on the continuous scale but for illustrative purposes, and for use in a Forest-like plot, will also be estimated for the first and third quartile of the continuous predictor distribution. Another important secondary analysis will be of all participants treating each household as a cluster and using a Mixed Linear model with baseline measurement and randomized treatment as fixed effects, and household clusters as random effects. If in the event there are very few clusters, the random effect may not be estimable and then this will be equivalent to ANCOVA. The Intraclass correlation coefficient for the clustering effect will be estimated directly from the variance components in the mixed linear models, should a cluster effect be estimable. Categorical and ordinal variables will be analyzed by logistic regression, the latter corresponding to ordinal regression, for the individual participant analysis, and by a Generalized Mixed Linear Model for all participants. There may be other effect modifiers that we will consider but these will be outlined in the Statistical Analysis Plan.

For the longitudinal cohort study stage, a similar ANCOVA strategy will be used for the final measurement of the continuous outcomes. A mixed linear model will also be used to examine linear trends in changes in outcomes by accounting for correlation between measurements in the same participants as well as the clustering effect for an analysis of all participants.

SAS version 9.4 will be used for analyses.

Oversight and monitoring

Composition of the coordinating center and the trial steering committee (Spirit 5d)

The study is led by a Senior Leadership Team who meet every two weeks and will be responsible for the oversight of the trial. It is composed of the Principal Investigator and senior members of the research team. The Operations Team meets every two to four weeks and will be responsible for the day-to-day running of the trial. In addition, author FEL operates as research program manager and works closely with all sites and with food providers. The trial also has an independent Māori advisory committee providing oversight to support the research team, Māori researchers and Māori participants.

Safety

As per standard procedure, any changes to the protocol or serious adverse events will be communicated to the Health and Disability Ethics Committee. Any significant changes in the protocol will be notified to participants by study staff, and any changes to the informed consent will be actioned at the next scheduled study visit. There is no Data Monitoring Committee for this trial and The Sponsor is responsible for monitoring the conduct of the trial.

Discussion

This trial has been designed to investigate the effect of the Mediterranean dietary pattern incorporating high quality New Zealand foods, implemented using elements of behavior science, on the cardiometabolic health of people in Aotearoa New Zealand. The trial has a number of strengths, the first of which relates to the trial design which is an efficient way to answer three separate but linked important questions which is important in the reduction of participant burden and overall research costs. It comprises two RCTs and a longitudinal cohort study which allows the effect of the 12-week combined intervention package (RCT 1) and then subsequent ongoing online social support (RCT 2) to be tested. This is then followed by testing of whether any dietary changes and effects on cardiometabolic health are maintained at 12 months through a longitudinal cohort study.

The inclusion of household/whānau participants, including any children over 5 years in the household/whānau is important when considering the impact of the dietary intervention on cardiometabolic health, where shared genetics and/or environmental factors influence health outcomes. Not only do household/whānau participants receive the study food, which is likely to improve uptake and adherence for the index participant, but the household/whānau participants are also included in the measurements, allowing an assessment of whether their health status can also be improved. Furthermore, in this study we are providing a substantive proportion of the whole household/whānau weekly food requirements in order to reduce barriers to change from cost and availability, and to increase the opportunity for trying new foods and facilitate change in dietary pattern. While other studies have provided food to facilitate adherence to an intervention (13, 35), the current study provides up to 75% of estimated energy requirements across all food groups in a way that aligns with the NZMedDiet pattern. We have demonstrated that the approach of both a household/whānau based intervention and the provision of food for a whole diet intervention is acceptable and culturally relevant for people in Aotearoa New Zealand in our feasibility study (23).

The current trial has also taken a broad collaborative approach in a significant partnership between academia and the food industry and aims to provide locally produced food. The study team has established relationships with over thirty food companies and negotiated the provision of food that aligns with the dietary pattern. Importantly, although contributing foods and beverages that align with the NZMedDiet pattern, the food industry has not been involved with or influenced the trial design and will not be involved with the data analysis or reporting of the trial findings. The goal of the funding body, High Value Nutrition National Science Challenge, is to bring together academics and the food industry to grow science excellence and knowledge to deliver food to the world which is associated with positive health outcomes. The relationships built are important and demonstrate an ability for academics and industry to work together for better health for communities. Food grown and produced in Aotearoa New Zealand is known to be nutritious and of high quality, and foods which align with the MedDiet dietary pattern can be predominantly sourced in Aotearoa New Zealand. In this trial, engagement and partnership with the local food industry to provide food for the participants allows the provision of locally sourced, seasonable and fresh food.

Another key component of this trial is the importance of Māori as the indigenous New Zealanders across the trial. This includes Māori as co-investigators on the Science Leadership Team, one study site being based at Kokiri Marae where Māori participants will be recruited using local protocols for engagement. The trial includes Māori research staff, Māori F&B companies and Māori participants in the study. The trial also has an independent Māori committee providing oversight to support the research team, Māori researchers and Māori participants.

The use of the MetSSS as the primary outcome measure was carefully considered as the dietary intervention may have small but collectively important effects on multiple risk factors for cardiometabolic disease. Therefore, a composite outcome measure which incorporates several of these, rather than choosing one specific risk factor, is attractive. MetSSS is a continuous variable derived from the traditional components of the metabolic syndrome (20, 36). The MetSSS has been shown to predict future cardiometabolic disease and can be modified by lifestyle including diet and exercise, and pharmacological interventions to corresponding change in cardio-metabolic disease risk. It is therefore a useful tool in assessing the impact of a dietary intervention on metabolic health (19). In an Aotearoa New Zealand population, the MetSSS positively associated with impaired glucose regulatory status and history of cardiovascular disease for all ethnic groups (20, 21). This places it in a good position to have utility as a tool to quantify an individual's cardiometabolic disease risk within the multi-ethnic population of Aotearoa New Zealand (20).

There are several challenges faced by the study team to effectively deliver this trial. The feasibility study has shown that it is possible to recruit individuals and household/whānau to a whānau-based intervention. It also showed that the two-step screening process was effective and efficient and that the commercial meal kit home delivery service was acceptable. However, in the current trial we also need to bring together F&B providers, co-ordinate collection and delivery of these foods integrated into the dietary pattern and further enable and facilitate adoption and adherence to this. Informed by the feasibility study we have incorporated more behavior change support and further information on how to prepare or use foods which participants may not have encountered before. One particular challenge will be to maintain participants in the trial after the provision of food has finished and adoption of the dietary pattern when they are purchasing all of their own food. This is one of the important research questions being addressed; whether substantive food provision and support enables subsequent sustained dietary pattern change.

In summary, this trial combines two RCTs and a longitudinal cohort study to investigate whether a household/whānau-based dietary intervention incorporating high quality whole foods from New Zealand, consistent with a Mediterranean dietary pattern, combined with dietary change support, improves the cardiometabolic health of New Zealanders.

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 approval was granted by the New Zealand Health and Disability Ethics Committee – Northern B branch – reference 2022 FULL 12045. Dissemination is planned in a series of journal articles, conference abstracts and presentations; reports and presentations to industry partners; communication with study participants and the wider community.

Author contributions

FL: Writing – original draft, Writing – review & editing. AP: Writing – original draft, Writing – review & editing. AB: Writing – original draft, Writing – review & editing. AW: Writing – review & editing, Writing – original draft. MF: Writing – review & editing. AR: Writing – review & editing. CD: Writing – review & editing. JM: Writing – review & editing. CR: Writing – review & editing. DC: Writing – review & editing. TM: Writing – review & editing. RG: Writing – review & editing. MW: Writing – review & editing. JK: Writing – original draft, Writing – review & editing.

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Conflict of interest

MF was employed by Edible Research Ltd. DC was employed by the New Zealand Institute for Plant & Food Research Ltd.

The remaining 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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