**Title page**

**Association between the Dietary Flavonoid Intake and Metabolic Obesity Phenotypes**

Jiayu Zhang 1#, Guoli Ma 1#, Yinshuang Yao1, Chao Ren2\*, Junlan Qiu3\*, Xiaochen Shu1, 4, 5\*

1 Department of Epidemiology, School of Public Health, Suzhou Medical College of Soochow University, Suzhou, 215123, China.

2 Department of Neurology and Shandong Provincial Key Laboratory of Neuroimmune Interaction and Regulation, Yantai Yuhuangding Hospital, Qingdao University, Yantai, 264000, China.

3 Department of Oncology and Hematology, the Affiliated Suzhou Hospital of Nanjing University Medical School, Suzhou, 215153, China.

4 Jiangsu Key Laboratory of Preventive and Translational Medicine for Major Chronic Non-communicable Diseases, Suzhou Medical College of Soochow University, Suzhou, Jiangsu, 215123, China.

5 MOE Key Laboratory of Geriatric Diseases and Immunology, Suzhou Medical College of Soochow University, Suzhou, Jiangsu, 215123, China.

# Jiayu Zhang and Guoli Ma contributed equally to this work and share first authorship.

\* Joint correspondence

**Author contact information:**

Jiayu Zhang, MPH

Department of Epidemiology, School of Public Health, Suzhou Medical College of Soochow University, Suzhou, 215123, China. E-mail: [jyuzhang1222@163.com](mailto:jyuzhang1222@163.com). ORCID: 0009-0002-0569-2539

Guoli Ma, MPH

Department of Epidemiology, School of Public Health, Suzhou Medical College of Soochow University, Suzhou, 215123, China. E-mail: [guoli20000@gmail.com](mailto:guoli20000@gmail.com). ORCID: 0009-0006-5559-0580

Yinshuang Yao, MPH

Department of Epidemiology, School of Public Health, Suzhou Medical College of Soochow University, Suzhou, 215123, China. E-mail: [20225247081@stu.suda.edu.cn](mailto:20225247081@stu.suda.edu.cn). ORCID: 0009-0002-6058-8005

**Corresponding authors:**

Xiaochen Shu, MD, PhD, Professor

Department of Epidemiology, School of Public Health, Suzhou Medical College of Soochow University, Suzhou, 215123, China. Tel: 86-512-65883323. Fax: 86-512-65883323. E-mail: [xcshu@suda.edu.cn](mailto:xcshu@suda.edu.cn). ORCID: 0000-0002-4933-5851

Chao Ren, MD, PhD, Physician

Department of Neurology, Yantai Yuhuangding Hospital, Qingdao University, Yantai, Shandong Province, 264000, China. Tel: 86-0535-6691999. Fax: 86-0535-6240341. E-mail: [renchaotg@126.com](mailto:renchaotg@126.com). ORCID: 0000-0002-5418-3354

Junlan Qiu, MD, PhD, Chief Physician, Director

Department of Oncology and Hematology, the Affiliated Suzhou Hospital of Medical School, Nanjing University, China. Tel: 0512-69588791. Fax: 0512-69588791. E-mail: [qiujunland@163.com](mailto:qiujunland@163.com). ORCID: 0000-0002-2058-5427

**Running title:** Flavonoid & Metabolic Obesity Phenotypes

**Keywords:** Flavonoid, Obesity, Metabolic; phenotypes, BMI, NHANES

**Abbreviations:**

Adenosine monophosphate-activated protein kinase (AMPK), Analysis of variance (ANOVA), Body mass index (BMI), Blood Pressure (BP), Cardiovascular disease (CVD), Confidence intervals (CI), C-reactive protein (CRP), Carnitine palmitoyltransferase-1 (CPT-1), Diastolic blood pressure (DBP), Food and Nutrient Database for Dietary Studies (FNDDS), Fasting Plasma Glucose (FPG), High-Density Lipoprotein Cholesterol (HDL), Metabolically healthy obesity (MHO), Metabolically unhealthy obesity (MUO), Metabolically healthy non-obesity (MHNO), Metabolically unhealthy non-obesity (MUNO), Metabolic syndrome (MetS), Standard deviation (SD), National Health and Nutrition Examination Survey (NHANES), National Center for Health Statistics (NCHS) , Non-Communicable Diseases (NCDs), Odds ratios (OR), Poverty income ratio (PIR), Physical activity (PA), Peroxisome proliferator-activated receptor alpha (PPARα), Restricted cubic spline regression (RCS), Systolic blood pressure (SBP), Sirtuin 1 (SIRT1), Tumor necrosis factor-α (TNF-α), Triglycerides (TG), Weighted Quantile Sum (WQS), World Health Organization (WHO)

# **Abstract**

This study explored the association between dietary flavonoid intake and metabolic obesity phenotypes using data from 29,940 participants in the National Health and Nutrition Examination Survey (NHANES 2007-2008, 2009-2010, and 2017-2018). Based on metabolic health status (ATP III criteria) and body mass index (BMI), these participants were categorized into four groups: metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), metabolically healthy non-obesity (MHNO), and metabolically unhealthy non-obesity (MUNO). Multivariate logistic regression analyses demonstrated that higher total dietary flavonoid intake was inversely associated with the odds of both MHO (OR = 0.63, 95% CI: 0.44-0.90) and MUO (OR = 0.73, 95% CI: 0.58-0.99). Weighted quantile sum (WQS) regression further revealed that the combined effect of flavonoid subclasses significantly decreased the odds of MHO (OR = 0.66, 95% CI: 0.67-0.90, p < 0.01) and MUO (OR = 0.79, 95% CI: 0.68-0.90, p < 0.01), with anthocyanidins and flavanones being the primary contributors. However, no significant association was observed between flavonoid intake and metabolically unhealthy non-obesity (MUNO). Higher dietary flavonoid intake, particularly of anthocyanins, flavanones, and flavan-3-ols, was associated with metabolic obesity phenotypes. This discovery provided an important potential target for nutritional intervention strategies aimed at obese populations.

**Introduction**

Obesity, a chronic complex disease, is defined by The World Health Organization (WHO) as “excessive fat deposits that can impair health”.[[1](#_ENREF_1" \o "Piche, 2020 #88)] Worldwide adult obesity has more than doubled since 1990, significantly increasing the public health burden. It is estimated that by 2030, more than half of the U.S. population will be affected by obesity. At the same time, metabolic syndrome has become a major health hazard among Non-Communicable Diseases **(**NCDs). Therefore, preventive strategies are imminently needed to mitigate the corresponding adverse outcomes. Previous studies have reported that obesity is closely associated with metabolic syndrome (MetS), but obesity and metabolic abnormalities do not always coexist. In addition, BMI cannot distinguish muscle from fat and metabolic status, so it is unreasonable to lump individuals with diverse metabolic profiles together based on BMI classification alone. Our study divided participants into four groups based on metabolic health status (ATP III criteria) and body mass index (BMI): metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), metabolically healthy non-obesity (MHNO), and metabolically unhealthy non-obesity (MUNO).[[2](#_ENREF_2" \o "van Vliet-Ostaptchouk, 2014 #90), [3](#_ENREF_3" \o "Expert Panel on Detection, 2001 #23)]

Flavonoids are a group of natural substances with variable phenolic structures.(4) According to their molecular structure, flavonoids could be classified into different categories, including flavonols (i.e. quercetin, kaempferol, resveratrol, and myricetin), flavanones (i.e. hesperetin, naringenin and naringin), isoflavones (i.e. daidzin, genistin and glycitein), flavones (i.e. apigenin and luteolin), flavan-3-ols (i.e. catechins and epigallocatechin gallate), and anthocyanins (i.e.cyanidin and Apigenidin).[[4](#_ENREF_4" \o "Kawser Hossain, 2016 #10), [5](#_ENREF_5" \o "Serafini, 2010 #56)]

The body gets most of the flavonoids from berries, citrus fruits, and vegetables. Flavonoids have diverse and extensive health advantages, especially in anti-inflammatory, antioxidant, antiviral, anticancer, and anti-obesity activity.[[5](#_ENREF_5" \o "Serafini, 2010 #56), [6](#_ENREF_6" \o "Panche, 2016 #13)]Several studies have reported that increased intake of total flavonoids is associated with a reduced risk of type 2 diabetes mellitus,[[7](#_ENREF_7" \o "Liu, 2014 #12)] and enhanced consumption of anthocyanins and flavan-3-ols may diminish cardiovascular disease risk.[[8](#_ENREF_8" \o "Micek, 2021 #17)]

Dietary intervention is the most convenient and inexpensive method. Eating more foods rich in flavonoids can prevent obesity and metabolic-related diseases due to the anti-inflammatory and antioxidant properties of flavonoids.[[9](#_ENREF_9" \o "Gentile, 2018 #18)] However, current studies have focused on analyzing the association between dietary flavonoids and diseases such as simple obesity or diabetes, but have not yet systematically explored the differences in their specific roles across different metabolic obesity phenotypes.

This study aims to explored the potential relationship between dietary flavonoid intake and different metabolic obesity phenotypes utilizing data derived from the nationally representative and comprehensive National Health and Nutrition Examination Survey (NHANES) with MHNO individuals as the reference group.

**Methods and materials**

**Data source**

The subjects for this study were derived from NHANES. The NHANES is a comprehensive and nationally representative survey conducted by the National Center for Health Statistics (NCHS) intended to monitor the public health and nutritional status of the US population through a complex and multi-stage probability sampling design. Study procedures received approval from the NCHS Ethics Review Board and all participants provided written informed consents. The original data and additional details are available on the NHANES website and the USDA FNDDS website.

**Study participants**

Due to the availability of data on dietary flavonoid intake, this study synthesized the NHANES continuous datasets from 2007 to 2008, 2009-2010, and 2017-2018. We excluded (1) individuals with age < 20 (n = 11329); (2) Participants who were pregnant (n = 138); (3) individuals with incomplete data on flavonoids intake and extreme energy intake (n = 4144); (4) individuals with missing data about metabolic obesity phenotypes (n = 8585). Finally, a total of 5744 participants were included for further analysis (**Figure 1**)

**Assessment of covariates**

Trained investigators collected participants' baseline data through questionnaires, including age groups (20-45, 46-68, and ≥ 69 years old), gender (Female and Male), race (Non-Hispanic White, Mexican American, Non-Hispanic Black, Other Hispanic, and Other Race), educational level (Less than high school graduate, High school graduate, and College or above), the ratio of family income to poverty threshold (0-1.3, 1.4-3.5, and > 3.5 PIR), and energy intake( kcal). Healthy Eating Index(HEI-2015) score (range 0-100) was categorized as inadequate (<50), average (50–70), and optimal (>70)[[10](#_ENREF_10)]. Alcohol use was classified into never (< 12 drinks in lifetime), current ≥ 12 drinks and currently drinking), and former (no drink last year but ≥ 12 drinks in lifetime). Smoking status included former (≥ 100 cigarettes but not currently smoking), current ≥ 100 cigarettes and currently smoking), and never (< 100 cigarettes in lifetime). Physical activity (PA in MET-h/wk) including no physical activity group (< 1MET-h/wk), low-intensity physical activity group (1-48MET-h/wk), and high-intensity physical activity group (> 48MET-h/wk), was calculated by multiplying the MET values corresponding to different activity types (e.g. 8 MET for vigorous activity, 4 MET for moderate activity) by the weekly frequency and the duration of each activity (PA = MET × frequency × duration). [[10](#_ENREF_10), [11](#_ENREF_11)] The disease history was defined as hypertension (Yes or No) or Cardiovascular Disease (Yes or No) diagnosed by the physician.

**Assessment of dietary flavonoid intake**

The dietary flavonoid intake data used in this study was extracted from the United States Department of Food and Nutrient Database for Dietary Studies (FNDDS).[[12](#_ENREF_12)] The trained interviewers used two 24-hour food recall interviews to collect detailed information on the flavonoid content of foods and beverages.[[12](#_ENREF_12)] Then utilize a comprehensive flavonoid database, sourced from FNDDS, to calculate the flavonoid content of each food item. The Flavonoid Database includes 29 different types of flavonoids, which can generally be grouped into six major categories, including anthocyanidins, flavanones, flavan-3-ols, flavones, isoflavones, and flavonols. In this study, we used the sum of the mean values of these six subclasses as the total flavonoid intake.[[13](#_ENREF_13)] Detailed information can be found in **Table S1** and **Table S2**.

BMI was calculated as weight in kilograms divided by height in meters squared. According to the current WHO, obesity was defined as having a BMI  ≥  30 kg/m2. [[14-17](#_ENREF_14)]

**Definitions of metabolic obesity phenotypes**

Metabolic abnormality was defined as having two or more metabolic risk factors based on the revised NCEP ATP III definition national Cholesterol Education P: (1) Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or antihypertensive drug treatment; (2) Elevated fasting blood glucose: fasting glucose ≥5.6 mmol/L or use of glucose-lowering drugs, or history/diagnosis of type 2 diabetes; (3) Reduced HDL-C: HDL-cholesterol < 1.03 mmol/L in men or < 1.30 mmol/L in women or use of lipid-modifying drugs; and (4) Elevated TG: triglyceride ≥  1.70 mmol/L, or use of lipid-modifying drugs.[[3](#_ENREF_3)] Therefore, we can divide the participants into the following four categories: metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), metabolically healthy non-obesity (MHNO), and metabolically unhealthy non-obesity (MUNO). The waist circumference(WC) was excluded from the diagnostic criteria for metabolic status because of the covariance of the obesity index BMI and WC in this study.[[18](#_ENREF_18)] All models were analyzed using MHNO as the reference group.

**Statistical analysis**

All statistical analyses followed the NHANES analytic and reporting guidelines. Considering the complex multistage probability sampling design used in the NHANES database, all analyses use sampling weights. The dietary two-day sample weight (WTDR2D) was divided by three as the final weights because this study combined three survey cycles.

First, continuous variables were represented by Mean ± standard deviation (Mean ± SD), and categorical variables were represented by N (%). The one-way analysis of variance (ANOVA) or non-parametric test for continuous variables and the Chi-Square test for categorical variables were used to assess the demographic characteristics of the participants. Flavonoid intake was classified into four levels according to quartiles (Q1, Q2, Q3, Q4) as categorical variables.

Additionally, weighted multivariate logistic regression analysis was used to investigate the association between dietary intake of total flavonoids as well as flavonoid subclasses and different metabolic obesity phenotypes in adults. Three models were utilized, with no covariates in model 1. Model 2 adjusted for age, gender, race, the family poverty ratio, and educational level. Model 3 further included smoking status, alcohol use, CVD, and Physical activity. Potential non-linear relationships between dietary flavonoid subclasses, total flavonoids, and metabolic obesity phenotypes were explored through RCS analysis.

Then, a weighted quantile sum (WQS) regression, using the “gWQS” package, was used to assess the association between six flavonoid mixtures in the adult diet and different metabolic obesity phenotypes.[[19](#_ENREF_19" \o "Renzetti, 2023 #98), [20](#_ENREF_20" \o "Yu, 2022 #99)] The dataset was randomly partitioned into two subsets, with 40% used for the training set and the remaining 60% as the validation set. The model evaluates the mixed effects of the flavonoid mixtures and calculates the contribution of each flavonoid subclass to the WQS index to identify the subclass that plays a significant role. For more details on the WQS calculation methodology, please refer to the literature.[[21](#_ENREF_21" \o "Wei, 2021 #25)]

Finally, stratified analyses were conducted by age, gender, race, and other subgroups to investigate the association between dietary flavonoid intake and metabolic obesity phenotypes, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. The statistical significance of differences between groups was evaluated through interaction tests (P values).

A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed in package R (Version 4.4.2), and R studio software.

**Results**

**Basic Characteristics of Participants**

A total of 5,744 participants were included in this study, with 2,122 being MHNO (36.94%), 820 being MHO (14.28%), 1,439 being MUO (25.05%), and1,363 being MUNO (23.73%). There were differences in the demographic characteristics of different obesity metabolic phenotypes: compared to metabolically healthy individuals, the metabolically unhealthy phenotype was more likely to be older, previous smokers and drinkers, have metabolic risk factors, and participate in less physical activity. (**Table** [**1**](https://pmc.ncbi.nlm.nih.gov/articles/PMC10898189/#Tab1))

**Association between Dietary Flavonoid Intake and metabolic obesity phenotypes**

**Table 2** presents the results of the weighted multivariate logistic regression analyses examining the associations between total flavonoid intake and metabolic obesity phenotypes In the crude model, a significant inverse association was observed between flavonoid intake and the odds of MHO for participants in the second (Q2 vs. Q1: OR = 0.62, 95% CI: 0.46-0.84) and third (Q3 vs. Q1: OR = 0.56, 95% CI: 0.40-0.79) quartiles. In Model 2 (adjusted for age, gender, race, PIR, and educational level), the odds ratios for Q2 and Q3 were 0.62 (95% CI: 0.45–0.84) and 0.57 (95% CI: 0.40-0.81), respectively. After further adjustment for all potential confounders in Model 3, the inverse association persisted (Q2: OR = 0.66, 95% CI: 0.48-0.90; Q3: OR = 0.63, 95% CI: 0.44-0.90). Notably, the association was attenuated and became non-significant in the highest quartile (Q4) across all three models.

A similar pattern of inverse association was observed for MUO, with significantly reduced odds in the second and third quartiles across all models, which also attenuated in the highest quartile. In contrast, no significant associations were found between flavonoid intake and the odds of MUNO in any model.

Given the significant findings for MHO and MUO but not for MUNO, subsequent analyses focused on exploring the association between total flavonoid intake and these two phenotypes.

**Associations between six flavonoid subclasses intake and metabolic obesity phenotypes**

As shown in **Table 3**, a higher intake of anthocyanidins, flavan-3-ols, and flavanones was significantly inversely associated with both MHO and MUO across all three models.

After full adjustment for covariates, anthocyanidins demonstrated the most robust inverse association with MHO, particularly in the third (Q3: OR = 0.61, 95% CI: 0.44-0.84) and fourth (Q4: OR = 0.44, 95% CI: 0.20-0.64) quartiles. Significant inverse associations were also observed for flavanones (Q4: OR = 0.65, 95% CI: 0.49-0.87) and flavan-3-ols (Q3: OR = 0.64, 95% CI: 0.49-0.84).The inverse association between flavones and MHO observed in the crude model became statistically non-significant after adjustment for covariates. No significant associations were found between isoflavones or flavonols and MHO in any model.

For MUO, a higher intake of flavanones was significantly associated with reduced odds of MUO in the second (Q2: OR = 0.70, 95% CI: 0.51-0.96), third (Q3: OR = 0.56, 95% CI: 0.38-0.82), and fourth (Q4: OR = 0.66, 95% CI: 0.47-0.93) quartiles.. Similarly, flavan-3-ols (Q2: OR = 0.76, 95% CI: 0.60-0.96; Q3: OR = 0.72, 95% CI: 0.53-0.96) and anthocyanidins (Q3: OR = 0.67, 95% CI: 0.48-0.92; Q4: OR = 0.62, 95% CI: 0.41-0.92) were also inversely associated with MUO. However, the initial associations observed for flavones, isoflavones, and flavonols in the crude model did not persist after further adjustment.

RCS analyses were conducted to explore nonlinear connections between total flavonoid intake and subclasses (flavanones, flavan-3-ols, and anthocyanidins) and metabolic obesity phenotypes (MHO/MUO) (**Figure S1**). After adjusting for socio-demographic, behavioral, and health characteristics, total flavonoids, anthocyanins, and flavanones were associated with MHO an MUO in a J-shaped non-linear association (overall and non-linear P-values < 0.05). This suggested that flavan-3-ols is associated with MUO within a specific intake range (5.09-165.82 mg).

**Mixed effect of Six Dietary Flavonoid Intake on the metabolic obesity phenotypes (MHO/MUO)**

The WQS model indicated that the mixed effect of dietary flavonoid intake was negatively associated with the odds of MHO (OR = 0.66, 95% CI: 0.67-0.90). The estimated weights are shown in **Figure 2**, the flavonoid subclasses with the highest weights were anthocyanidins (35.25%), followed by flavanones (29.31%), flavan-3-ols (22.02%), isoflavones (11.69%), flavonols (1.51%), and flavones (0.24%). The mixed effect was negatively associated with the prevalence of MUO (OR = 0.79, 95% CI: 0.68-0.90), with the largest effect coming from anthocyanidins (37.88%), followed by flavanones (25.54%), flavan-3-ols (23.78%), isoflavones (10.56%), flavonols (1.97%) and flavones (0.28%). In addition, 29 types of flavonoid mixing effects were derived for MHO and MUO with the highest contribution of malvidin (18.92%) and delphinidin (15.94%).

**Subgroup analysis**

Subgroup analysis (**Figure 3**) presents the association between total flavonoid intake and metabolic obesity phenotypes (MHO/MUO) in different subgroups stratified by age, gender, race, educational level, property income ratio (PIR), and lifestyle factors. For MHO, the inverse association was most apparent among individuals of Other Hispanic ethnicity (OR = 0.76, 95% CI: 0.59-0.96), former smokers (OR = 0.80, 95% CI: 0.64-1.00), and those with moderate dietary quality (HEI-2015 score 50-70; OR = 0.80, 95% CI: 0.67-0.95). Interaction tests indicated no statistically significant effect modification across these subgroups (all P for interaction > 0.05), suggesting a consistent association between flavonoid intake and MHO/MUO phenotypes regardless of these demographic and lifestyle factors.

**Discussion**

This study utilized data from NHANES (2007-2008, 2009-2010, and 2017-2018) to evaluate the association between dietary flavonoid intake and metabolic obesity phenotypes in US adults. Findings suggested that an increased consumption of total flavonoids and their subclasses (flavanones, anthocyanins, and flavan-3-ols) were associated with a lower likelihood of MHO and MUO[[22](#_ENREF_22" \o "Landberg, 2011 #85), [23](#_ENREF_23" \o "Cassidy, 2015 #86)], whereas no significant association was observed with MUNO. WQS further corroborates this result.

Flavonoids have been shown to be potentially relevant in the prevention of unhealthy metabolic obesity phenotypes through their antioxidant,[[24](#_ENREF_24" \o "Kumar, 2013 #45)] anti-inflammatory,[[5](#_ENREF_5" \o "Serafini, 2010 #56)]anti-mutagenic,[[25](#_ENREF_25" \o "Snijman, 2007 #31)] and lipid and blood pressure regulation mechanisms.[[26](#_ENREF_26" \o "Koch, 2019 #32)] A cross-sectional study of Dutch subjects can support our results. It is well known that flavonoids are widely present in vegetables, citrus fruits, beans, tea, and berries. Slagter et al.[[27](#_ENREF_27" \o "Slagter, 2018 #29)] have demonstrated that people who follow a diet high in vegetables and fruits are beneficial for improving obesity and metabolic risks. A randomized controlled trial conducted by the University of Rome found that flavonoids improve metabolic syndromeby stimulating the production of nitric oxide in endothelial cells and improving endothelial function.[[28](#_ENREF_28" \o "Rizza, 2011 #36)] Marranzano et al.[[29](#_ENREF_29" \o "Marranzano, 2018 #37)] found that consumption of 900 mg of flavonoid-rich foods per day for 12 weeks in patients with obesity inhibited lipid peroxidation, reduced oxidative stress, decreased C-reactive protein (CRPs) in serum, prevented inflammation, and ameliorated metabolic syndrome. All the above studies confirm that flavonoids have a role in promoting metabolic health.[[30](#_ENREF_30" \o "Penczynski, 2018 #35)] Flavonoids also have anti-obesity activity and can prevent obesity and related comorbidities by reducing adipose tissue mass, thereby reducing intracellular free radical formation, increasing antioxidant defense, and attenuating inflammatory signaling pathways.[[9](#_ENREF_9" \o "Gentile, 2018 #18)] For example, genistein modulates obesity-related inflammation and oxidative stress in pancreatic β cells.[[31](#_ENREF_31" \o "Behloul, 2013 #33)] Furthermore, supplying quercetin to dietary can reduce weight gain by modulating adenosine monophosphate-activated protein kinase (AMPK) α1 phosphorylation and silencing of the sirtuin 1 (SIRT1) pathway and improve insulin sensitivity and glucose tolerance while inhibiting adipose tissue macrophage infiltration and inflammation.[[32](#_ENREF_32" \o "Dong, 2014 #34)] However, to date, studies on the heterogeneous effects of flavonoids and their subclasses on different metabolic obesity phenotypes remain scarce.

The present study demonstrated that flavonoids exerted a more pronounced effect on individuals with MHO compared to those with MUO, across various combinations of metabolic status and obesity, using MHNO individuals as a reference group. This finding remained consistent before and after adjustments for socioeconomic factors, demographic characteristics, and behavioral variables. This may be because the metabolic function of MHO individuals is normal, and they have higher insulin sensitivity, lower levels of inflammatory markers, and normal adipose tissue function,[[29](#_ENREF_29" \o "Marranzano, 2018 #37), [33](#_ENREF_33" \o "Stefan, 2017 #100)] whereas MUO individuals already have higher metabolic disorders and struggle to respond better to dietary interventions. In addition, we did not find a significant association between flavonoid intake and MUNO individuals. This may be attributed to the fact that non-obese individuals generally exhibit lower levels of inflammatory markers compared to people with obesity, and no significant elevation of inflammatory markers was observed in MUNO individuals.[[34](#_ENREF_34" \o "Hansen, 2010 #101), [35](#_ENREF_35" \o "Boutari, 2023 #102)] However, flavonoids usually ameliorate obesity-related metabolic complications by modulating inflammatory markers secreted by adipokines and factors such as fibrinogen activator inhibitor-1, tumor necrosis factor-α (TNF-α), interleukin-6, resistin, and lipocalin.[[36](#_ENREF_36" \o "Bastard, 2006 #48)]

Analysis of different subclasses of flavonoids showed that anthocyanins, flavanones, and flavan-3-ols have important roles in the development of MHO and MUO among individuals. In population-based studies, a higher habitual intake of several flavonoids, including anthocyanins was associated with a lower level of inflammation.[[22](#_ENREF_22" \o "Landberg, 2011 #85)] Flavanones, predominantly derived from citrus fruits, exhibit potent antioxidant and anti-inflammatory properties.[[36](#_ENREF_36" \o "Bastard, 2006 #48)] These compounds ameliorate metabolic dysregulation primarily through modulating AMPK activation, regulating peroxisome proliferator-activated receptor alpha (PPARα) signaling, enhancing carnitine palmitoyltransferase-1 (CPT-1)-mediated lipid utilization, and preserving mitochondrial function mitochondrial function.[[37](#_ENREF_37" \o "Pu, 2012 #39)] Structurally related flavonoids such as anthocyanins and flavan-3-ols have also demonstrated comparable regulatory effects on metabolic pathways. The protective effect of flavanones in MUO (OR = 0.58) was slightly weaker than that of MHO, but it was still statistically significant. The lack of significant effect of the remaining three subclasses (flavones, flavonols, isoflavones) may be due to geographical location, dietary habits(e.g. flavonols are mainly derived from Onions and apples), and bioavailability in the body affecting the type and intake of flavonoid subclasses ultimately influencing their effects.[[38](#_ENREF_38" \o "Rothwell, 2013 #41)]

Although the overall tests for interaction did not reach statistical significance, differences in point estimates observed in certain subgroups remain noteworthy. For instance, the protective effect appeared more pronounced among individuals with moderate diet quality (HEI-2015 score 50–70) and other Hispanic. have ed[[39](#_ENREF_39" \o "Mirmiran, 2020 #42)], and our study suggests that flavonoids may act synergistically with an overall healthy dietary pattern rather than in isolation.[[40](#_ENREF_40" \o "Bondonno, 2023 #87)]

This research employed a multi-stage sampling approach to weight data, ensuring that our outcomes are reflective of the general adult population in the United States. Throughout the study, we applied several statistical analysis models, such as logistic regression, RCS, WQS, and subgroup analysis, to thoroughly investigate the connection between dietary flavonoid consumption and metabolic obesity phenotypes from various angles which have reinforced the robustness and stability of our results. Furthermore, to the best of our knowledge, this is the first study dedicated to exploring the association between flavonoids and different metabolic obesity phenotypes in a nationally representative population. The current research results provide new insights into the precise intervention of people with different metabolic obesity phenotypes.

However, there are some limitations to this study. Due to the constraints of the cross-sectional design, the causality between flavonoids and metabolic obesity phenotypes remains unclear. In addition, even though participants with incomplete data on flavonoid intake were excluded, recall bias may have existed because the data were based on a 24-hour dietary recall interview, and it was also difficult to differentiate among sources of flavonoids. Despite adjusting for traditional risk factors, there may still be unrecognized confounders that may affect the accuracy of effect estimates. Finally, this study was conducted on Americans only, caution is needed in generalizing the findings to other populations. Therefore, future studies should employ a prospective cohort design, incorporate biomarker detection (such as flavonoid metabolites in plasma or urine), enhance the accuracy of intake measurements, and utilize multi-omics techniques to uncover the molecular mechanisms of flavonoid action to verify its applicability across diverse populations.

**Conclusion**

Our results have shown that the intake of three flavonoid subclasses (anthocyanins, flavanones, and flavan-3-ols) is negatively correlated with the metabolic obesity phenotypes (MHO, MUO) in a significant way.

**Acknowledgements**

Jiayu Zhang and Xiaochen Shu designed the research (project conception, development of the overall research plan, and study oversight); Jiayu Zhang, Guoli Ma conducted the research (data collection); Jiayu Zhang, Guoli Ma, and Yinshuang Yao analyzed data and performed statistical analysis; Jiayu Zhang, Guoli Ma, and Yinshuang Yao, Chao Ren, Junlan Qiu, Xiaochen Shu and wrote the paper. Xiaochen Shu had primary responsibility for the final content. All authors have read and approved the final manuscript.

**Data Availability:** Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval from the National Health and Nutrition Examination Survey (<https://www.cdc.gov/nchs/nhanes>).

**Funding:** This work was jointly supported by the Scientific Research Foundation for Talented Scholars in Soochow University, China (Q413900215); the Social Development – Clinical Frontier Technology Project of the Science and Technology Department of Jiangsu Province (Project number: BE2018669); the Suzhou Medical and Industrial Integration Collaborative Innovation Research Project (Project number: SL J202012); the Suzhou Clinical Trial Institution Capacity Enhancement Project (Project number: SLT202003); the Nuclear Energy Development Project, China (Project number: 2016-1295); a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions, China; the Taishan Scholar Project (No.tsqn202312392) the Outstanding Young Talents Project in Health of Qilu and the youth talent training program from Qingdao medical college of Qingdao University (No. RZ2300002690); Suzhou Applied Basic Research Program (Medical and Health Care) - Science and Technology Innovation Project (Second Batch, Guided Project), Project Number: SYWD2024098; Wu Jieping Medical Foundation - Clinical Research Special Grant, Project Number: 320.6750.2022-10-9; Open Research Project of Jiangsu Engineering Research Center for Small Molecule Targeted Therapy and Companion Diagnostics in Oncology, Project Number: SGK1202411. The funding sources had no role in study design, data collection/analysis, manuscript writing, or decision to submit for publication.

**Declaration of interests:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Declaration of Generative AI and AI-assisted technologies in the writing process**: During the preparation of this work, the author(s) used ChatGPT to check for grammatical errors. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

**References**

1. Piche ME, Tchernof A, Despres JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res. 2020;126(11):1477-500; doi: 10.1161/CIRCRESAHA.120.316101.

2. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014;14:9; doi: 10.1186/1472-6823-14-9.

3. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97; doi: 10.1001/jama.285.19.2486.

4. Kawser Hossain M, Abdal Dayem A, Han J, Yin Y, Kim K, Kumar Saha S, et al. Molecular Mechanisms of the Anti-Obesity and Anti-Diabetic Properties of Flavonoids. Int J Mol Sci. 2016;17(4):569; doi: 10.3390/ijms17040569.

5. Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. Proc Nutr Soc. 2010;69(3):273-8; doi: 10.1017/S002966511000162X.

6. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47; doi: 10.1017/jns.2016.41.

7. Liu YJ, Zhan J, Liu XL, Wang Y, Ji J, He QQ. Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Clin Nutr. 2014;33(1):59-63; doi: 10.1016/j.clnu.2013.03.011.

8. Micek A, Godos J, Del Rio D, Galvano F, Grosso G. Dietary Flavonoids and Cardiovascular Disease: A Comprehensive Dose-Response Meta-Analysis. Mol Nutr Food Res. 2021;65(6):e2001019; doi: 10.1002/mnfr.202001019.

9. Gentile D, Fornai M, Pellegrini C, Colucci R, Blandizzi C, Antonioli L. Dietary flavonoids as a potential intervention to improve redox balance in obesity and related co-morbidities: a review. Nutr Res Rev. 2018;31(2):239-47; doi: 10.1017/S0954422418000082.

10. Ran J, Zhang Y, Han L, Sun S, Zhao S, Shen C, et al. The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents. Environ Int. 2021;156:106645; doi: 10.1016/j.envint.2021.106645.

11. Chen L, Cai M, Li H, Wang X, Tian F, Wu Y, et al. Risk/benefit tradeoff of habitual physical activity and air pollution on chronic pulmonary obstructive disease: findings from a large prospective cohort study. BMC Med. 2022;20(1):70; doi: 10.1186/s12916-022-02274-8.

12. Sebastian RS, Wilkinson Enns C, Goldman JD, Martin CL, Steinfeldt LC, Murayi T, Moshfegh AJ. A New Database Facilitates Characterization of Flavonoid Intake, Sources, and Positive Associations with Diet Quality among US Adults. J Nutr. 2015;145(6):1239-48; doi: 10.3945/jn.115.213025.

13. Sebastian RS, Fanelli Kuczmarski MT, Goldman JD, Moshfegh AJ, Zonderman AB, Evans MK. Usual Intake of Flavonoids Is Inversely Associated with Metabolic Syndrome in African American and White Males but Not Females in Baltimore City, Maryland, USA. Nutrients. 2022;14(9); doi: 10.3390/nu14091924.

14. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63(25 Pt B):2985-3023; doi: 10.1016/j.jacc.2013.11.004.

15. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016;22 Suppl 3:1-203; doi: 10.4158/EP161365.GL.

16. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obes Facts. 2015;8(6):402-24; doi: 10.1159/000442721.

17. Brauer P, Gorber SC, Shaw E, Singh H, Bell N, Shane ARE, et al. Recommendations for prevention of weight gain and use of behavioural and pharmacologic interventions to manage overweight and obesity in adults in primary care. CMAJ. 2015;187(3):184-95; doi: 10.1503/cmaj.140887.

18. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J. 2015;36(9):551-9; doi: 10.1093/eurheartj/ehu123.

19. Renzetti S, Gennings C, Calza S. A weighted quantile sum regression with penalized weights and two indices. Front Public Health. 2023;11:1151821; doi: 10.3389/fpubh.2023.1151821.

20. Yu L, Liu W, Wang X, Ye Z, Tan Q, Qiu W, et al. A review of practical statistical methods used in epidemiological studies to estimate the health effects of multi-pollutant mixture. Environ Pollut. 2022;306:119356; doi: 10.1016/j.envpol.2022.119356.

21. Wei MH, Cui Y, Zhou HL, Song WJ, Di DS, Zhang RY, et al. Associations of multiple metals with bone mineral density: A population-based study in US adults. Chemosphere. 2021;282:131150; doi: 10.1016/j.chemosphere.2021.131150.

22. Landberg R, Sun Q, Rimm EB, Cassidy A, Scalbert A, Mantzoros CS, et al. Selected dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in U.S. women. J Nutr. 2011;141(4):618-25; doi: 10.3945/jn.110.133843.

23. Cassidy A, Rogers G, Peterson JJ, Dwyer JT, Lin H, Jacques PF. Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults. Am J Clin Nutr. 2015;102(1):172-81; doi: 10.3945/ajcn.115.108555.

24. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. ScientificWorldJournal. 2013;2013:162750; doi: 10.1155/2013/162750.

25. Snijman PW, Swanevelder S, Joubert E, Green IR, Gelderblom WC. The antimutagenic activity of the major flavonoids of rooibos (Aspalathus linearis): some dose-response effects on mutagen activation-flavonoid interactions. Mutat Res. 2007;631(2):111-23; doi: 10.1016/j.mrgentox.2007.03.009.

26. Koch W. Dietary Polyphenols-Important Non-Nutrients in the Prevention of Chronic Noncommunicable Diseases. A Systematic Review. Nutrients. 2019;11(5); doi: 10.3390/nu11051039.

27. Slagter SN, Corpeleijn E, van der Klauw MM, Sijtsma A, Swart-Busscher LG, Perenboom CWM, et al. Dietary patterns and physical activity in the metabolically (un)healthy obese: the Dutch Lifelines cohort study. Nutr J. 2018;17(1):18; doi: 10.1186/s12937-018-0319-0.

28. Rizza S, Muniyappa R, Iantorno M, Kim JA, Chen H, Pullikotil P, et al. Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. J Clin Endocrinol Metab. 2011;96(5):E782-92; doi: 10.1210/jc.2010-2879.

29. Marranzano M, Ray S, Godos J, Galvano F. Association between dietary flavonoids intake and obesity in a cohort of adults living in the Mediterranean area. Int J Food Sci Nutr. 2018;69(8):1020-9; doi: 10.1080/09637486.2018.1452900.

30. Penczynski KJ, Remer T, Herder C, Kalhoff H, Rienks J, Markgraf DF, et al. Habitual Flavonoid Intake from Fruit and Vegetables during Adolescence and Serum Lipid Levels in Early Adulthood: A Prospective Analysis. Nutrients. 2018;10(4); doi: 10.3390/nu10040488.

31. Behloul N, Wu G. Genistein: a promising therapeutic agent for obesity and diabetes treatment. Eur J Pharmacol. 2013;698(1-3):31-8; doi: 10.1016/j.ejphar.2012.11.013.

32. Dong J, Zhang X, Zhang L, Bian HX, Xu N, Bao B, Liu J. Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: a mechanism including AMPKalpha1/SIRT1. J Lipid Res. 2014;55(3):363-74; doi: 10.1194/jlr.M038786.

33. Stefan N, Schick F, Haring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017;26(2):292-300; doi: 10.1016/j.cmet.2017.07.008.

34. Hansen D, Dendale P, Beelen M, Jonkers RAM, Mullens A, Corluy L, et al. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to non-obese, type 2 diabetes patients. European Journal of Applied Physiology. 2010;109(3):397-404; doi: 10.1007/s00421-010-1362-5.

35. Boutari C, Hill MA, Procaccini C, Matarese G, Mantzoros CS. The key role of inflammation in the pathogenesis and management of obesity and CVD. Metabolism. 2023;145:155627; doi: 10.1016/j.metabol.2023.155627.

36. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

37. Pu P, Gao DM, Mohamed S, Chen J, Zhang J, Zhou XY, et al. Naringin ameliorates metabolic syndrome by activating AMP-activated protein kinase in mice fed a high-fat diet. Arch Biochem Biophys. 2012;518(1):61-70; doi: 10.1016/j.abb.2011.11.026.

38. Rothwell JA, Perez-Jimenez J, Neveu V, Medina-Remon A, M'Hiri N, Garcia-Lobato P, et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database (Oxford). 2013;2013:bat070; doi: 10.1093/database/bat070.

39. Mirmiran P, Moslehi N, Hosseinpanah F, Sarbazi N, Azizi F. Dietary determinants of unhealthy metabolic phenotype in normal weight and overweight/obese adults: results of a prospective study. Int J Food Sci Nutr. 2020;71(7):891-901; doi: 10.1080/09637486.2020.1746955.

40. Bondonno NP, Liu YL, Zheng Y, Ivey K, Willett WC, Stampfer MJ, et al. Change in habitual intakes of flavonoid-rich foods and mortality in US males and females. BMC Med. 2023;21(1):181; doi: 10.1186/s12916-023-02873-z.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table1.** Participant characteristics stratified by metabolic obesity phenotypes. | | | | | | | | | | | | |
| Variables | | | MHNO (N = 2122) | | MHO (N = 820) | | *P* Value | MUO (N = 1439) | | *P* Value | MUNO (N = 1363) | *P* Value b |
| Age, (years) a | | | 42 (15.47) | | 41 (14.48) | | 0.642 | 54(15.04) | | <0.001 | 58 (15.77) | <0.001 |
| Gender, n (%) a | | |  | |  | | 0.866 |  | | 0.571 |  | <0.001 |
| Female | | | 1152 (54.06%) | | 473 (54.62%) | |  | 794 (52.43%) | |  | 592 (42.70%) |  |
| Male | | | 970 (45.94%) | | 347 (45.38%) | |  | 645 (47.57%) | |  | 771 (57.30%) |  |
| Race, n (%) | | |  | |  | | <0.001 |  | | 0.003 |  | 0.195 |
| Non-Hispanic White | | | 983 (70.39%) | | 302 (59.59%) | |  | 668 (69.64%) | |  | 689 (72.62%) |  |
| Non-Hispanic Black | | | 336 (8.59%) | | 205 (15.96%) | |  | 315 (12.47%) | |  | 211 (8.46%) |  |
| Mexican American | | | 363 (8.01%) | | 175 (11.85%) | |  | 231 (7.86%) | |  | 188 (6.21%) |  |
| Other Hispanic | | | 245 (5.51%) | | 94 (6.82%) | |  | 141 (4.14%) | |  | 135 (4.56%) |  |
| Other Race | | | 195 (7.51%) | | 44 (5.79%) | |  | 84 (5.88%) | |  | 140 (8.15%) |  |
| PIR, n (%) | | |  | |  | | 0.004 |  | | 0.015 |  | 0.004 |
| ≤1.3 | | | 601 (19.25%) | | 250 (22.73%) | |  | 436 (21.20%) | |  | 394 (18.34%) |  |
| 1.4-3.5 | | | 801 (33.95%) | | 346 (39.95%) | |  | 595 (38.92%) | |  | 554 (40.57%) |  |
| >3.5 | | | 720 (46.79%) | | 224 (37.31%) | |  | 408 (39.88%) | |  | 415 (41.09%) |  |
| Educational level, n (%) | | |  | |  | | 0.287 |  | | <0.001 |  | <0.001 |
| High school | | | 452 (21.24%) | | 181 (21.51%) | |  | 356 (29.64%) | |  | 372 (30.30%) |  |
| College or above | | | 1,219(66.36%) | | 455 (63.92%) | |  | 678 (51.73%) | |  | 631 (53.34%) |  |
| Less than high school | | | 451(12.40%) | | 184 (14.58%) | |  | 405 (18.62%) | |  | 360 (16.35%) |  |
| Smoking status, n (%) | | |  | |  | | 0.018 |  | | <0.001 |  | 0.002 |
| Never | | | 1,239(57.45%) | | 512 (62.05%) | |  | 737 (52.33%) | |  | 705 (50.82%) |  |
| Former | | | 432 (22.29%) | | 170 (23.84%) | |  | 456 (31.87%) | |  | 418 (30.97%) |  |
| Now | | | 451 (20.26%) | | 138 (14.11%) | |  | 246 (15.80%) | |  | 240 (18.22%) |  |
| Alcohol use, n (%) | | |  | |  | | 0.107 |  | | <0.001 |  | <0.001 |
| Never | | | 770 (33.09%) | | 276 (31.11%) | |  | 473 (28.85%) | |  | 482 (32.64%) |  |
| Former | | | 241 (9.54%) | | 129 (13.17%) | |  | 304 (18.30%) | |  | 272 (18.10%) |  |
| Now | | | 1,111(57.37%) | | 415 (55.73%) | |  | 662 (52.85%) | |  | 609 (49.26%) |  |
| Hypertension | | |  | |  | | 0.050 |  | | <0.001 |  | <0.001 |
| No | | | 1,797 (88.16%) | | 674 (84.37%) | |  | 295 (22.27%) | |  | 300 (26.07%) |  |
| Yes | | | 325 (11.84%) | | 146 (15.63%) | |  | 1,144 (77.73%) | |  | 1063 (73.93%) |  |
| PA levels, n (%) | | |  | |  | | 0.103 |  | | <0.001 |  | <0.001 |
| No | | | 399 (15.52%) | | 192 (19.45%) | |  | 502 (29.15%) | |  | 579 (45.11%) |  |
| Low | | | 944 (46.38%) | | 340 (43.50%) | |  | 572 (44.12%) | |  | 358 (31.08%) |  |
| High | | | 779 (38.10%) | | 288 (37.05%) | |  | 365 (26.72%) | |  | 426 (23.81%) |  |
| CVD (%) | | |  | |  | | 0.476 |  | | <0.001 |  | <0.001 |
| No | | | 2043 (97.17%) | | 778 (96.66%) | |  | 1149 (83.14%) | |  | 1095 (82.79%) |  |
| Yes | | | 79 (2.83%) | | 42 (3.34%) | |  | 290 (16.86%) | |  | 268 (17.21%) |  |
| BMI (kg/m2) | | | 24.44 (3.13) | | 34.94 (4.75) | | <0.001 | 36.32 (5.88) | | <0.001 | 25.97 (2.73) | <0.001 |
| WC (cm) | | | 88 (9.66) | | 111 (11.45) | | <0.001 | 116 (12.85) | | <0.001 | 95 (8.95) | <0.001 |
| HEI-2015(mean, SD) | | | 51.85 (12.25) | | 48.71 (11.29) | | <0.001 | 49.35 (11.63) | | <0.001 | 52.28 (11.95) | 0.446 |
| Total calories (kcal/d) | | | 2,152 (847.65) | | 2,088(782.52) | | 0.211 | 2,075 (827.33) | | 0.085 | 2,051 (808.18) | 0.018 |
| Total Flavonoids (mg) | | | 223 (357.31) | | 221 (363.50) | | 0.022 | 224 (377.67) | | 0.116 | 231 (371.61) | 0.870 |
| Isoflavones (mg) | | | 2.8 (12.13) | | 2.3 (10.33) | | 0.040 | 1.19 (6.48) | | <0.001 | 1.29 (10.25) | <0.001 |
| Flavonols (mg) | | | 19 (17.51) | | 17 (15.62) | | 0.034 | 18 (17.27) | | 0.104 | 19 (16.03) | 0.635 |
| Flavan-3-ols (mg) | | | 172 (339.54) | | 181 (349.72) | | 0.059 | 179 (362.23) | | 0.083 | 182 (354.04) | 0.840 |
| Flavanones (mg) | | | 12 (25.05) | | 10 (22.58) | | <0.001 | 11 (22.49) | | 0.001 | 14 (24.53) | 0.415 |
| Flavones (mg) | | | 1.06 (2.64) | | 0.78 (0.89) | | 0.006 | 0.90 (1.26) | | 0.007 | 0.86 (1.24) | 0.125 |
| Anthocyanidins (mg) | | | 15 (29.48) | | 10 (23.97) | | <0.001 | 13 (34.32) | | <0.001 | 15 (32.69) | 0.770 |
| Abbreviations: BMI, body mass index; CVD, cardiovascular disease; MHNO, metabolically healthy non-obesity; MUNO, metabolically unhealthy non-obesity; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; PIR, poverty income ratio; PA, physical activity; WC, Waist Circumference.  a Data are presented as mean or percent with standard error. Categorical variables are presented as numbers (percentages).  b P values derived from one-way ANOVA (continuous) or χ² test (categorical), with MHNO as reference. | | | | | | | | | | | | |

| **Table 2.** Association between dietary flavonoid intake and metabolic obesity phenotypes | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | Model1 a | | Model2 b | | Model3 c | |
| Characteristic | OR (95% Cl) | *P* Value | OR (95% Cl) | *P* Value | OR (95% Cl) | *P* Value |
| MHO | | | | | | |
| Total Flavonoids (mg) | —  — | | | | | |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.62 (0.46, 0.84) | 0.003 | 0.62 (0.45, 0.84) | 0.003 | 0.66 (0.48, 0.90) | 0.011 |
| Q3 | 0.56 (0.40, 0.79) | 0.001 | 0.57 (0.40, 0.81) | 0.003 | 0.63 (0.44, 0.90) | 0.012 |
| Q4 | 0.74 (0.53, 1.01) | 0.061 | 0.80 (0.57, 1.12) | 0.192 | 0.83 (0.57, 1.21) | 0.321 |
| MUO | | | | | | |
| Total Flavonoids (mg) |  | | | | | |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.66 (0.52, 0.83) | <0.001 | 0.62 (0.48, 0.81) | <0.001 | 0.69 (0.54, 0.89) | 0.006 |
| Q3 | 0.67 (0.52, 0.89) | 0.004 | 0.65 (0.49, 0.86) | 0.004 | 0.73 (0.58, 0.99) | 0.050 |
| Q4 | 0.81 (0.62, 1.06) | 0.120 | 0.78 (0.59, 1.04) | 0.091 | 0.83 (0.60, 1.13) | 0.223 |
| MUNO | | | | | | |
| Total Flavonoids (mg) |  | | | | | |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.86 (0.69, 1.08) | 0.192 | 0.81 (0.61, 1.09) | 0.168 | 0.85 (0.63, 1.14) | 0.270 |
| Q3 | 0.91 (0.70, 1.19) | 0.491 | 0.85 (0.61, 1.17) | 0.304 | 0.93 (0.69, 1.25) | 0.604 |
| Q4 | 1.00 (0.80, 1.27) | 0.969 | 0.97 (0.71, 1.33) | 0.851 | 1.02 (0.74, 1.40) | 0.922 |
| Abbreviations: CI, Confidence Interval; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; OR = Odds Ratio.  a Model 1 Adjusted for no covariates.  b Model 2 Adjusted for age, gender, race, family poverty income ratio, educational level.  c Model 3 Adjusted for age, gender, race, family poverty income ratio, educational level, smoking status, alcohol use, cardiovascular disease, physical activity level, total calories, HEI-2015.  Analytic method: weighted multivariate logistic regression  The analysis was conducted with metabolically healthy non-obesity (MHNO) as the reference group. | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table3.** Associations between Flavonoid subclasses intake and metabolically obesity phenotypes (MHO and MUO). | | | | | | |
|  | Model11 | | Model22 | | Model333 | |
| Flavonoids | OR (95% Cl) | *P* Value | OR (95% Cl) | *P* Value | OR (95% Cl) | *P* Value |
| MHO | | | | | | |
| Flavanones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.93 (0.65, 1.34) | 0.695 | 0.97 (0.65, 1.45) | 0.889 | 0.99 (0.68,1.56) | 0.959 |
| Q3 | 0.70 (0.49, 0.99) | 0.051 | 0.71 (0.48, 1.04) | 0.079 | 0.76 (0.55,1.17) | 0.148 |
| Q4 | 0.62 (0.47, 0.82) | 0.001 | 0.59 (0.43, 0.81) | 0.002 | 0.65 (0.52,0.95) | 0.006 |
| *P* for trend |  | 0.001 |  | <0.001 |  | <0.001 |
| Flavones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.98 (0.73, 1.32) | 0.911 | 0.99 (0.74, 1.35) | 0.996 | 1.04 (0.76, 1.42) | 0.825 |
| Q3 | 0.80 (0.56, 1.13) | 0.201 | 0.85 (0.60, 1.22) | 0.371 | 0.92 (0.63, 1.34) | 0.650 |
| Q4 | 0.66 (0.49, 0.89) | 0.008 | 0.71 (0.52, 0.98) | 0.038 | 0.81 (0.57, 1.15) | 0.231 |
| *P* for trend |  | 0.009 |  | 0.047 |  | 0.611 |
| Flavonols (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.99 (0.71, 1.36) | 0.924 | 1.01 (0.73, 1.39) | 0.952 | 1.10 (0.80, 1.52) | 0.540 |
| Q3 | 0.73 (0.52, 1.03) | 0.073 | 0.76 (0.54, 1.08) | 0.120 | 0.85 (0.61, 1.18) | 0.314 |
| Q4 | 0.71 (0.49, 1.03) | 0.073 | 0.80 (0.55, 1.12) | 0.243 | 0.92 (0.62, 1.36) | 0.670 |
| *P* for trend |  | 0.024 |  | 0.096 |  | 0.577 |
| Flavan-3-ols (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.72 (0.54, 0.96) | 0.026 | 0.72 (0.54, 0.97) | 0.031 | 0.77 (0.57,1.02) | 0.069 |
| Q3 | 0.56 (0.41, 0.77) | 0.001 | 0.58 (0.43, 0.79) | 0.001 | 0.64 (0.49,0.84) | 0.003 |
| Q4 | 0.77 (0.57, 1.05) | 0.092 | 0.85 (0.62, 1.16) | 0.284 | 0.86 (0.61, 1.20) | 0.360 |
| *P* for trend |  | 0.972 |  | 0.581 |  | 0.583 |
| Isoflavones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.94 (0.66, 1.34) | 0.725 | 0.97 (0.76, 1.66) | 0.843 | 0.98 (0.68, 1.43) | 0.919 |
| Q3 | 1.03 (0.76, 1.41) | 0.834 | 1.01 (0.74, 1.40) | 0.915 | 1.08 (0.77, 1.52) | 0.634 |
| Q4 | 0.77 (0.59, 1.00) | 0.053 | 0.82 (0.61, 1.10) | 0.174 | 0.89 (0.66, 1.21) | 0.448 |
| *P* for trend |  | 0.057 |  | 0.139 |  | 0.372 |
| Anthocyanidins (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.74 (0.54, 1.02) | 0.069 | 0.72 (0.51, 1.00) | 0.052 | 0.73 (0.51,1.05) | 0.087 |
| Q3 | 0.60 (0.45, 0.81) | 0.001 | 0.58 (0.47, 0.80) | 0.001 | 0.61 (0.44,0.84) | 0.004 |
| Q4 | 0.39 (0.28, 0.54) | <0.001 | 0.40 (0.29, 0.57) | <0.001 | 0.44 (0.30,0.64) | <0.001 |
| *P* for trend |  | <0.001 |  | <0.001 |  | <0.001 |
| MUO | | | | | | |
| Flavanones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.63 (0.48, 0.81) | 0.001 | 0.66 (0.50, 0.87) | 0.004 | 0.70 (0.51, 0.96) | 0.028 |
| Q3 | 0.49 (0.35, 0.68) | <0.001 | 0.52 (0.36, 0.74) | 0.001 | 0.56 (0.38, 0.82) | 0.004 |
| Q4 | 0.66 (0.52, 0.85) | 0.002 | 0.61 (0.45, 0.82) | 0.002 | 0.66 (0.47, 0.93) | 0.021 |
| *P* for trend |  | 0.418 |  | 0.112 |  | 0.515 |
| Flavones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.92 (0.72, 1.19) | 0.525 | 0.95 (0.74, 1.23) | 0.701 | 1.01 (0.76, 1.32) | 0.973 |
| Q3 | 0.75 (0.61, 0.93) | 0.010 | 0.82 (0.64, 1.04) | 0.102 | 0.92 (0.68, 1.24) | 0.555 |
| Q4 | 0.70 (0.52, 0.94) | 0.019 | 0.72 (0.52, 1.01) | 0.054 | 0.83 (0.57, 1.21) | 0.314 |
| *P* for trend |  | 0.007 |  | 0.022 |  | 0.461 |
| Flavonols (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.95 (0.72, 1.26) | 0.738 | 0.96 (0.71, 1.30) | 0.786 | 1.07 (0.79, 1.45) | 0.631 |
| Q3 | 0.75 (0.56, 1.00) | 0.049 | 0.81 (0.59, 1.11) | 0.177 | 0.95 (0.69, 1.31) | 0.740 |
| Q4 | 0.81 (0.58, 1.11) | 0.181 | 0.83 (0.60, 1.15) | 0.245 | 0.98 (0.70, 1.36) | 0.882 |
| *P* for trend |  | 0.102 |  | 0.164 |  | 0.768 |
| Flavan-3-ols (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.75 (0.60, 0.95) | 0.017 | 0.69 (0.53, 0.88) | 0.004 | 0.76 (0.60, 0.96)  .) | 0.024 |
| Q3 | 0.64 (0.49, 0.84) | 0.002 | 0.64 (0.49, 0.85) | 0.003 | 0.72 (0.53, 0.96) | 0.029 |
| Q4 | 0.82 (0.63, 1.06) | 0.128 | 0.78 (0.60, 1.02) | 0.068 | 0.82 (0.61, 1.09) | 0.163 |
| *P* for trend |  | 0.937 |  | 0.801 |  | 0.869 |
| Isoflavones (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 1.22 (0.95, 1.58) | 0.121 | 1.33 (1.01, 1.74) | 0.045 | 1.37 (1.01, 1.86) | 0.041 |
| Q3 | 0.92 (0.69, 1.23) | 0.570 | 1.05 (0.77, 1.43) | 0.737 | 1.12 (0.80, 1.57) | 0.482 |
| Q4 | 0.63 (0.47, 0.84) | 0.002 | 0.78 (0.57, 1.05) | 0.100 | 0.86 (0.62, 1.19) | 0.333 |
| *P* for trend |  | <0.001 |  | 0.036 |  | 0.187 |
| Anthocyanidins (mg/d) |  |  |  |  |  |  |
| Q1 | ref | — | ref | — | ref | — |
| Q2 | 0.84 (0.65, 1.09) | 0.195 | 0.79 (0.59, 1.05) | 0.105 | 0.81 (0.60, 1.08) | 0.144 |
| Q3 | 0.68 (0.53, 0.87) | 0.003 | 0.61 (0.46, 0.81) | 0.001 | 0.67 (0.48, 0.92) | 0.016 |
| Q4 | 0.61 (0.45, 0.82) | 0.002 | 0.54 (0.38, 0.77) | 0.001 | 0.62 (0.41, 0.92) | 0.021 |
| *P* for trend |  | <0.001 |  | 0.001 |  | 0.072 |

|  |
| --- |
| Abbreviations: CI, Confidence Interval; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; OR = Odds Ratio.  a Model 1 Adjusted for no covariates.  b Model 2 Adjusted for age, gender, race, family poverty income ratio, educational level.  c Model 3 Adjusted for age, gender, race, family poverty income ratio, educational level, smoking status, alcohol use, cardiovascular disease, physical activity level, total calories, HEI-2015.  Analytic method: weighted multivariate logistic regression  The analysis was conducted with metabolically healthy non-obesity (MHNO) as the reference group. |

**Figure Legend**

**Figure. 1.** Flowchart of the sample selection from NHANES 2007–2010 and 2017–2018.

Abbreviations: Body mass index (BMI), Blood Pressure (BP), Fasting Plasma Glucose (FPG), High-Density Lipoprotein Cholesterol (HDL), Triglycerides (TG)

**Figure.2**. Weights from weighted quantile sum regression (WQS) for mixture of dietary flavonoids in relation to metabolic obesity phenotypes in adults.

Models are adjusted for age, gender, and race, educational level, PIR, smoking status, alcohol use, CVD, and PA levels.

Abbreviations: CVD, cardiovascular disease; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; PIR, poverty income ratio; PA, physical activity

(A)(B) MHO, dietary flavonoid intake; (C)(D) MUO, dietary flavonoid intake.

**Figure.3**. Association between dietary flavonoids intake and metabolic obesity phenotypes in different subgroups.

Abbreviations: CVD, cardiovascular disease; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; PIR, poverty income ratio; PA, physical activity

1. Piche ME, Tchernof A, Despres JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res. 2020;126(11):1477-500; doi: 10.1161/CIRCRESAHA.120.316101.

2. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014;14:9; doi: 10.1186/1472-6823-14-9.

3. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97; doi: 10.1001/jama.285.19.2486.

4. Kawser Hossain M, Abdal Dayem A, Han J, Yin Y, Kim K, Kumar Saha S, et al. Molecular Mechanisms of the Anti-Obesity and Anti-Diabetic Properties of Flavonoids. Int J Mol Sci. 2016;17(4):569; doi: 10.3390/ijms17040569.

5. Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. Proc Nutr Soc. 2010;69(3):273-8; doi: 10.1017/S002966511000162X.

6. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47; doi: 10.1017/jns.2016.41.

7. Liu YJ, Zhan J, Liu XL, Wang Y, Ji J, He QQ. Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Clin Nutr. 2014;33(1):59-63; doi: 10.1016/j.clnu.2013.03.011.

8. Micek A, Godos J, Del Rio D, Galvano F, Grosso G. Dietary Flavonoids and Cardiovascular Disease: A Comprehensive Dose-Response Meta-Analysis. Mol Nutr Food Res. 2021;65(6):e2001019; doi: 10.1002/mnfr.202001019.

9. Gentile D, Fornai M, Pellegrini C, Colucci R, Blandizzi C, Antonioli L. Dietary flavonoids as a potential intervention to improve redox balance in obesity and related co-morbidities: a review. Nutr Res Rev. 2018;31(2):239-47; doi: 10.1017/S0954422418000082.

10. De La Cruz N, Shabaneh O, Appiah D. The Association of Ideal Cardiovascular Health and Ocular Diseases Among US Adults. Am J Med. 2021;134(2):252-+; doi: 10.1016/j.amjmed.2020.06.004.

11. Ran J, Zhang Y, Han L, Sun S, Zhao S, Shen C, et al. The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents. Environ Int. 2021;156:106645; doi: 10.1016/j.envint.2021.106645.

12. Chen L, Cai M, Li H, Wang X, Tian F, Wu Y, et al. Risk/benefit tradeoff of habitual physical activity and air pollution on chronic pulmonary obstructive disease: findings from a large prospective cohort study. BMC Med. 2022;20(1):70; doi: 10.1186/s12916-022-02274-8.

13. Sebastian RS, Wilkinson Enns C, Goldman JD, Martin CL, Steinfeldt LC, Murayi T, Moshfegh AJ. A New Database Facilitates Characterization of Flavonoid Intake, Sources, and Positive Associations with Diet Quality among US Adults. J Nutr. 2015;145(6):1239-48; doi: 10.3945/jn.115.213025.

14. Sebastian RS, Fanelli Kuczmarski MT, Goldman JD, Moshfegh AJ, Zonderman AB, Evans MK. Usual Intake of Flavonoids Is Inversely Associated with Metabolic Syndrome in African American and White Males but Not Females in Baltimore City, Maryland, USA. Nutrients. 2022;14(9); doi: 10.3390/nu14091924.

15. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014;63(25 Pt B):2985-3023; doi: 10.1016/j.jacc.2013.11.004.

16. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016;22 Suppl 3:1-203; doi: 10.4158/EP161365.GL.

17. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obes Facts. 2015;8(6):402-24; doi: 10.1159/000442721.

18. Brauer P, Gorber SC, Shaw E, Singh H, Bell N, Shane ARE, et al. Recommendations for prevention of weight gain and use of behavioural and pharmacologic interventions to manage overweight and obesity in adults in primary care. CMAJ. 2015;187(3):184-95; doi: 10.1503/cmaj.140887.

19. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J. 2015;36(9):551-9; doi: 10.1093/eurheartj/ehu123.

20. Renzetti S, Gennings C, Calza S. A weighted quantile sum regression with penalized weights and two indices. Front Public Health. 2023;11:1151821; doi: 10.3389/fpubh.2023.1151821.

21. Yu L, Liu W, Wang X, Ye Z, Tan Q, Qiu W, et al. A review of practical statistical methods used in epidemiological studies to estimate the health effects of multi-pollutant mixture. Environ Pollut. 2022;306:119356; doi: 10.1016/j.envpol.2022.119356.

22. Wei MH, Cui Y, Zhou HL, Song WJ, Di DS, Zhang RY, et al. Associations of multiple metals with bone mineral density: A population-based study in US adults. Chemosphere. 2021;282:131150; doi: 10.1016/j.chemosphere.2021.131150.

23. Landberg R, Sun Q, Rimm EB, Cassidy A, Scalbert A, Mantzoros CS, et al. Selected dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in U.S. women. J Nutr. 2011;141(4):618-25; doi: 10.3945/jn.110.133843.

24. Cassidy A, Rogers G, Peterson JJ, Dwyer JT, Lin H, Jacques PF. Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults. Am J Clin Nutr. 2015;102(1):172-81; doi: 10.3945/ajcn.115.108555.

25. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. ScientificWorldJournal. 2013;2013:162750; doi: 10.1155/2013/162750.

26. Snijman PW, Swanevelder S, Joubert E, Green IR, Gelderblom WC. The antimutagenic activity of the major flavonoids of rooibos (Aspalathus linearis): some dose-response effects on mutagen activation-flavonoid interactions. Mutat Res. 2007;631(2):111-23; doi: 10.1016/j.mrgentox.2007.03.009.

27. Koch W. Dietary Polyphenols-Important Non-Nutrients in the Prevention of Chronic Noncommunicable Diseases. A Systematic Review. Nutrients. 2019;11(5); doi: 10.3390/nu11051039.

28. Slagter SN, Corpeleijn E, van der Klauw MM, Sijtsma A, Swart-Busscher LG, Perenboom CWM, et al. Dietary patterns and physical activity in the metabolically (un)healthy obese: the Dutch Lifelines cohort study. Nutr J. 2018;17(1):18; doi: 10.1186/s12937-018-0319-0.

29. Rizza S, Muniyappa R, Iantorno M, Kim JA, Chen H, Pullikotil P, et al. Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. J Clin Endocrinol Metab. 2011;96(5):E782-92; doi: 10.1210/jc.2010-2879.

30. Marranzano M, Ray S, Godos J, Galvano F. Association between dietary flavonoids intake and obesity in a cohort of adults living in the Mediterranean area. Int J Food Sci Nutr. 2018;69(8):1020-9; doi: 10.1080/09637486.2018.1452900.

31. Penczynski KJ, Remer T, Herder C, Kalhoff H, Rienks J, Markgraf DF, et al. Habitual Flavonoid Intake from Fruit and Vegetables during Adolescence and Serum Lipid Levels in Early Adulthood: A Prospective Analysis. Nutrients. 2018;10(4); doi: 10.3390/nu10040488.

32. Behloul N, Wu G. Genistein: a promising therapeutic agent for obesity and diabetes treatment. Eur J Pharmacol. 2013;698(1-3):31-8; doi: 10.1016/j.ejphar.2012.11.013.

33. Dong J, Zhang X, Zhang L, Bian HX, Xu N, Bao B, Liu J. Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: a mechanism including AMPKalpha1/SIRT1. J Lipid Res. 2014;55(3):363-74; doi: 10.1194/jlr.M038786.

34. Stefan N, Schick F, Haring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017;26(2):292-300; doi: 10.1016/j.cmet.2017.07.008.

35. Hansen D, Dendale P, Beelen M, Jonkers RAM, Mullens A, Corluy L, et al. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to non-obese, type 2 diabetes patients. European Journal of Applied Physiology. 2010;109(3):397-404; doi: 10.1007/s00421-010-1362-5.

36. Boutari C, Hill MA, Procaccini C, Matarese G, Mantzoros CS. The key role of inflammation in the pathogenesis and management of obesity and CVD. Metabolism. 2023;145:155627; doi: 10.1016/j.metabol.2023.155627.

37. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.

38. Pu P, Gao DM, Mohamed S, Chen J, Zhang J, Zhou XY, et al. Naringin ameliorates metabolic syndrome by activating AMP-activated protein kinase in mice fed a high-fat diet. Arch Biochem Biophys. 2012;518(1):61-70; doi: 10.1016/j.abb.2011.11.026.

39. Rothwell JA, Perez-Jimenez J, Neveu V, Medina-Remon A, M'Hiri N, Garcia-Lobato P, et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database (Oxford). 2013;2013:bat070; doi: 10.1093/database/bat070.

40. Mirmiran P, Moslehi N, Hosseinpanah F, Sarbazi N, Azizi F. Dietary determinants of unhealthy metabolic phenotype in normal weight and overweight/obese adults: results of a prospective study. Int J Food Sci Nutr. 2020;71(7):891-901; doi: 10.1080/09637486.2020.1746955.

41. Bondonno NP, Liu YL, Zheng Y, Ivey K, Willett WC, Stampfer MJ, et al. Change in habitual intakes of flavonoid-rich foods and mortality in US males and females. BMC Med. 2023;21(1):181; doi: 10.1186/s12916-023-02873-z.