Review

Association of dietary phytochemical index with cardiometabolic risk factors

Editor's Choice

A systematic review and meta-analysis on observational studies

Sanaz Mehranfar[1], Yahya Jalilpiran[2,3], Hanieh-Sadat Ejtahed[4,5], Ehsan Seif[6], Ehsan Shahrestanaki[6,7], Armita Mahdavi-Gorabi[8], Mohammad Esmaeili-Abdar[9], Bagher Larijani[5], and Mostafa Qorbani[6,10]

1 Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Iran
2 Student Research Committee, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Iran
3 Students' Scientific Research Center, Tehran University of Medical Sciences, Iran
4 Obesity and Eating Habits Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Iran
5 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Iran
6 Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
7 Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
8 Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran
9 Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran
10 Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Iran

Abstract: *Objective(s):* Cardio-metabolic risk factors are becoming a global health concern. To address this problem, one of the proposed ways is to focus on phytochemical-rich foods consumption. Therefore, we aimed to summarize the results of observational studies (cohorts, case-control, and cross-sectional) that investigated the association between dietary phytochemical index (PI) as a new index for evaluating phytochemical-rich food intake and various risk factors of cardio-metabolic disorders. *Methods:* We conducted a comprehensive systematic review through PubMed, Scopus, and Web of Science databases. The literature search was performed up to August 2021 with no publication year restriction on observational studies investigating the association between PI and cardiometabolic risk factors on adults and children. A random-effect meta-analysis was used. *Results:* Overall, 16 articles (cross-sectional, case-control, cohort) were eligible for this systematic review and 8 studies with 99771 participants were included in the meta-analysis. Random effect meta-analysis showed that adherence to higher dietary PI decrease the odds of abdominal obesity (OR: 0.73, 95% CI: 0.58, 0.88, I^2: 84.90), generalized obesity (OR: 0.84, 95% CI: 0.69, 0.98, I^2: 68.10), hypertriglyceridemia (OR: 0.81, 95% CI: 0.73, 0.89, I^2: 0.00), hypertension (OR: 0.86, 95% CI: 0.73, 0.99, I^2: 7.02), and MetS (OR: 0.79, 95% CI: 0.69, 0.88, I^2: 84.90). However, results considering the associations between dietary PI with glycemic indices, and low high-density lipoprotein cholesterol (HDL-C) were not significant ($p<0.05$). *Conclusion:* Evidence showed adverse associations between dietary PI and some cardio-metabolic risk factors such as obesity, hypertriglyceridemia, hypertension and metabolic syndrome.

Keywords: Cardio-metabolic risk factors, metabolic syndrome, phytochemical index, meta-analysis

Introduction

As a global health challenge, non-communicable diseases (NCDs) comprising a variety of disorders such as cardiovascular diseases, diabetes, and cancer [1, 2] impose an economic burden on developed and developing countries [3, 4, 5]. Moreover, mortality caused by cardio-metabolic diseases has increased [6, 7] and prevalence of diabetes as one of the major cardio-metabolic diseases has increased worldwide [8, 9]. Obesity, hypertension, air pollution,

https://doi.org/10.1024/0300-9831/a000763

sedentary life-style, socioeconomic status, smoking, and unhealthy dietary intake [10, 11, 12] are among the most important risk factors for cardio-metabolic diseases. Considering dietary factors, several epidemiological studies have revealed that the consumption of phytochemical-rich foods may potentially reduce the risk of developing cardiovascular and metabolic diseases [13, 14, 15, 16, 17]. Indeed, phytochemicals are substances of plant origin providing a wide variety of health benefits [18, 19, 20, 21, 22]. Generally, phytochemicals are defined as bioactive non-nutrient compounds which have been classified into different categories based on their chemical structures and characteristics [23, 24]. These chemical compounds can be found abundantly in fruits, vegetables, whole grains, nuts, and other plant-based foods [25, 26, 27, 28]. Moreover, phytochemical compounds can offer protection against a number of disorders such as insulin resistance, abnormal glucose, and lipid disturbances by balancing the inflammation and free radical scavenging abilities [29, 30, 31, 32]. Accordingly, the reason for the necessity of consideration of plant foods intake when addressing the risk of obesity and NCDs is mainly due to the fact that these foods contain high amounts of antioxidants and phytochemicals. In this regard, the phytochemical index (PI) was developed as a new dietary index, to evaluate the benefits of phytochemical-rich food intake through population-based epidemiologic studies [14, 15, 33, 34, 35, 36, 37]. Actually, PI has been defined by McCarty as the percentage of dietary calories derived from phytochemical-rich foods; (DPI=(daily energy derived from phytochemical-rich foods (kcal)/total daily energy intake (kcal))× 100) [37]. Foods high in phytochemicals include fruits, vegetables (except tomatoes), legumes, nuts, seeds, and whole grains. Fruit and vegetable juices are often rich in phytochemicals, and are counted in the index. Moreover, Soy is usually a good source of isoflavones and is counted as well.

Although this index has some limitations, but it has many clinical uses. For instance, it is an easy method for clinical nutritionists to estimate the quality of diets, as well as following up the effects of dietary modification [37]. However, there are other scores, such as the prudent diet score and the Mediterranean scores [38], which focus on meats and fish. Based on existing evidence, incorporation of plant-based foods/drinks with Western-style diets can reduce the oxidative mechanisms [39]. In comparison with other scores requiring separate scoring for individual foods, the PI is a simple ratio value between the energy consumed as phytochemical-rich foods compared to the overall energy intake.

Indeed, this index is a simple method for assessing phytochemical intake which can display the quality of diet [37, 40] and epidemiological studies can use PI as an index for relating healthier diets to health consequences and providing evidence to encourage the consumption of more protective foods.

In this regard, some studies revealed that the prevalence of abdominal obesity and lipid disorders was lower in those individuals who had higher PI values [40, 41, 42, 43, 44, 45]. Moreover, it seems that higher PI can decrease the risk of prediabetes [46] and also has potential protective effects against development of insulin resistance [47].

Since there is no meta-analysis to summarize and interpret earlier findings in this regard, in the current systematic review and meta-analysis, we have chiefly focused on summarizing the emerging data proposing the roles of phytochemical-rich foods assessed by dietary PI in reducing the risk of metabolic syndrome, its components and other cardio-metabolic risk factors among both adults and children.

Methods

Search strategy

PubMed, Scopus, and Web of Science databases were searched for all relevant observational published articles up to August 2021 including cross-sectional, case-control, or prospective studies investigating the associations of dietary PI with cardio-metabolic risk factors. Only articles published in English were considered in this systematic review and meta-analysis. A structured search strategy using a combination of keywords regarding "dietary phytochemical index" and cardio-metabolic risk factors was carried out to identify records in the aforementioned databases. Finally, 16 relevant papers were included in this systematic review and meta-analysis. The population, intervention, comparison and outcome (PICO) question was as follows: P; children and adults, I; phytochemical index, C; comparing higher intake of phytochemical-rich foods with lower intake evaluated by the phytochemical index, O; cardiometabolic risk factors such as metabolic syndrome, high blood pressure, dyslipidemia, hyperglycemia, insulin resistance, and overweight, obesity, and abdominal obesity. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Furthermore, the protocol of the present systematic review has been registered in PROSPERO (Number: CRD42021257083).

Selection of studies

Inclusion criteria

All identified documents were exported to Endnote software. SM and YJ screened documents independently through three steps including refinement of titles, abstracts, and the full text in order to select relevant publications according to the inclusion and exclusion criteria.

Disagreements between the two investigators were resolved by discussion and consensus with a third person.

Studies were eligible for inclusion if they fulfilled the following criteria: (1) assessment of dietary phytochemical index; (2) study design: observational studies (cross-sectional, case-control, cohort); (3) the population of interest: adults and children; (4) outcomes: metabolic syndrome, high blood pressure, dyslipidemia, glycemic disorders, insulin resistance, abdominal obesity, obesity and over-weight. There was no publication year restriction.

Exclusion criteria

We excluded studies if: (1) phytochemical intake was not analyzed by dietary PI; (2) articles were duplicated, review, interventional studies, conference papers, letters to the editor, abstracts and unrelated studies.

Data extraction

SM and YJ extracted data from included articles independently and any disagreement was discussed by HSE. The following information was recorded: the first author's name, the year of publication, study design, sample characteristics, instruments for assessing dietary food intake and PI evaluation, confounding factors, measured outcomes, and the methods by which outcomes were measured. We considered ORs and their 95% CIs as the main effect size measures in the meta-analysis.

Quality assessment

The Newcastle–Ottawa Scale was used [48] for assessing the risk of bias in observational studies including cross-sectional, case-control, and cohorts. This scale uses a star system (with a maximum of nine stars) to evaluate studies in three domains: selection of (cohorts/case and controls/samples), comparability of study groups, and the assessment of outcomes (in case of cohort and cross-sectional studies) and exposure (in case of case control studies). We judged studies that received a score of nine or eight stars to be at low risk of bias; studies that scored seven, six or five stars to be at medium risk; and those which scored four or less stars to be at high risk of bias. SM and YJ performed quality assessment independently and any disagreement was discussed by HSE.

Statistical analysis

Odds Ratios (ORs) and their 95% confidence intervals (CI) were used to calculate the pool effect size. Heterogeneity between studies was assessed using Cochran's Q test and I^2 statistics. Considering the existence of study heterogeneity, a random-effect model was used to estimate the pooled ORs. Moreover, for depicting the result of the meta-analysis schematically forest plot was also used. Sensitivity analysis was done to examine the effect of each study on the pooled estimate. Publication bias was assessed by visual inspection of Begg's funnel plots. A formal statistical assessment of funnel plot asymmetry was performed by Egger's regression asymmetry test. Statistical analyses were performed using STATA version 11.2 (Stata Corp, College Station, TX). P values were considered significant at the level of <0.05. It should be noted that if in a study the analyses were performed in males and females separately, we considered two effect sizes for it in our analysis.

Results

Literature search

An initial systematic search in databases (PubMed, Web of Science, and Scopus) resulted in 249 articles (Figure 1). A total of 41 duplicates were removed, and then by screening the titles and abstracts 23 full-text articles were identified for further consideration. Of those, seven articles were not considered in our systematic review because four studies investigated the associations between PI and risk of cancer [49, 50, 51], one study investigated mental health as outcome [52], and one study used a phytonutrient index, but not PI as an exposure [53], and full text of another one was not available. Finally, 16 articles were eligible to include in this systematic review and meta-analysis [40, 41, 42, 43, 44, 45, 46, 47, 54, 55, 56, 57, 58, 59, 60, 61]. Based on various outcomes different articles [41, 42, 44, 56, 57, 58, 59, 61] were included in the meta-analysis. In this regard, we evaluated abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia, low HDL, and metabolic syndrome as potential outcomes.

Characteristics of studies

Table 1 shows the characteristics of the included studies. Accordingly, in the current systematic review and meta-analysis, one case-control [46], five longitudinal [43, 45, 47, 54, 55], and 10 cross-sectional [40, 41, 42, 44, 56, 57, 58, 59, 60, 61] studies with a range of 54–57940 participants were included. These studies were from the USA [40], Korea [42, 57], and Iran [41, 43, 44, 45, 46, 47, 54, 55, 56, 58, 59, 60, 61]. Two studies were conducted on children and students [44, 56] and 14 studies on adults ($\geq$18 y) [40, 41, 42, 43, 45, 46, 47, 54, 55, 57, 58, 59, 60, 61]. All studies included both sexes. Most of the studies were conducted on non-diabetic subjects, however, the population of some studies was people with Type 1 diabetes [58], Type 2 diabetes [60], and pre-diabetes [46]. The outcomes of interest

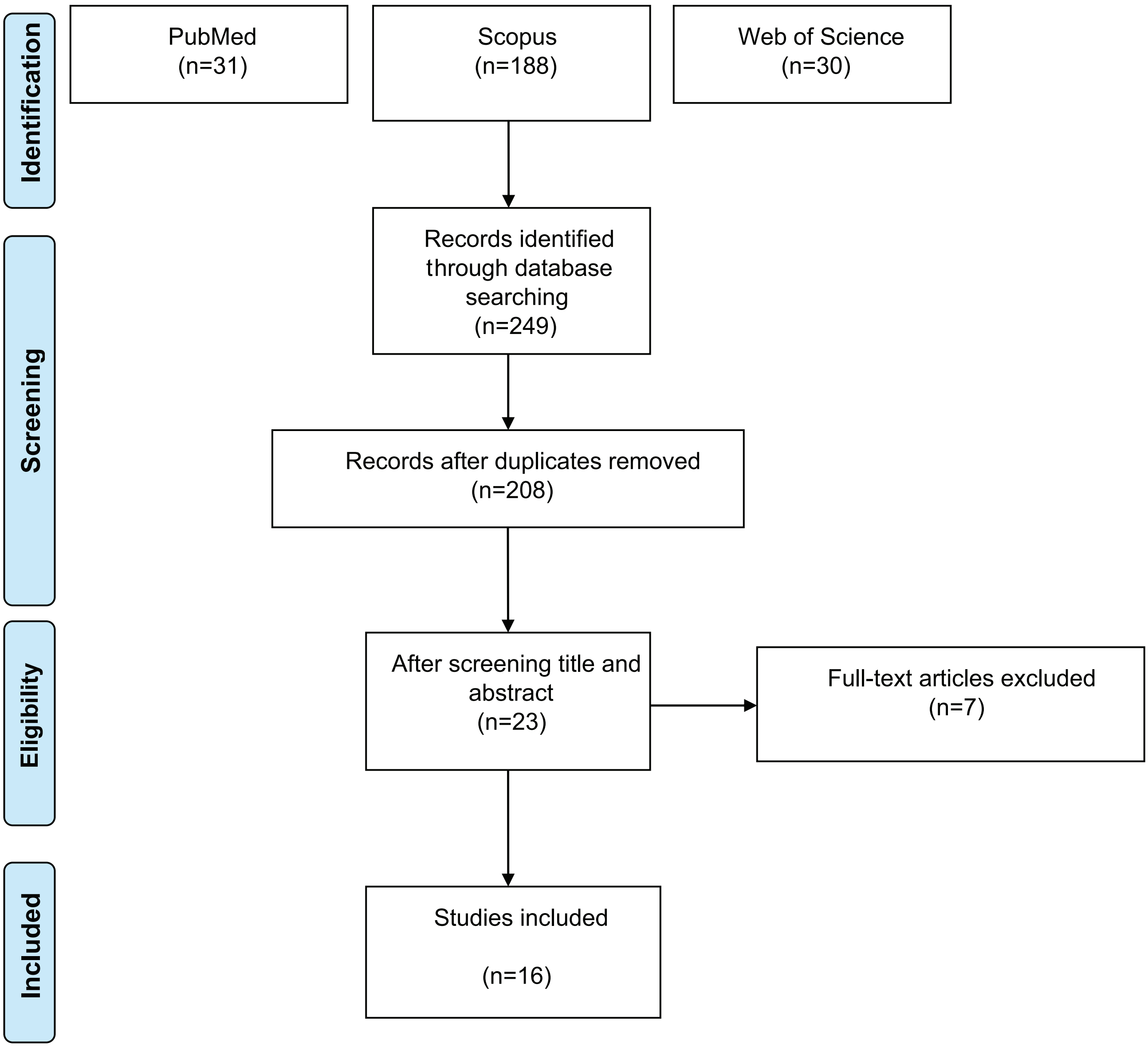

Figure 1. PRISMA flow chart describing the process of study selection.

of these studies were diverse by focusing on various cardiometabolic risk factors and metabolic syndrome. Participant's dietary intakes were assessed using food frequency questionnaire (FFQ) [41, 43, 44, 45, 46, 47, 54, 55, 56, 58, 59, 61], 24-hour recall [42, 57, 60], and three-day dietary records [40]. All studies have calculated the PI based on the method proposed by McCarty (2004). Fruits and vegetables, legumes, whole grains, seeds, nuts, natural fruit and vegetable juices, olive oil, and soy products were all identified as foods with high phytochemical content in all of the investigations. Nevertheless, in some studies, tea [55], wine, beer and cider [40], and seaweed [42, 57], were also classified as phytochemical-rich foods.

The finding of studies comparing participants according to different categories of PI showed higher PI in women [41, 42, 43, 45, 47, 54, 55, 59], and older participants [41, 42, 43, 45, 47, 54, 55, 58]. Furthermore, individuals with lower levels of physical activity had a considerably lower PI [42, 46]. In some studies, subjects in the higher quartiles of PI had a significantly larger intake of dietary fiber [44, 45, 54, 55]. Total energy intake also decreased significantly across quartiles of PI [41, 43, 45, 47, 55, 59, 61], while dietary intake of vitamin C as well as carbohydrates, increased [41, 43, 45, 47, 55]. However, in two studies the carbohydrate intake decreased across quartiles of PI [59, 61]. In the upper quartile of PI, participants had lower dietary fat intake

Table 1. Characteristics of the included studies in this systematic review

								Exposure characteristics/PI			Outcome characteristics
Study first author	Year	Country	Design	Population	Sample size	Age	Sex (M/F)	Definition	Measurements	Foods included	Type
S. Delshad Aghdam	2021	Iran	Cross-sectional	Type 1 Diabetes-Adult	261	18–35	Both	McCarty	FFQ-147	Fruits, vegetables (except potatoes), whole grains, legumes, fruit and vegetable juice, soy products, nuts, seeds, olive and olive oil.	Hyperglycemia, Low HDL-C, High LDL-C, Hypercholesterolemia, High LDL-C/HDL-C, High HbA1c, Overweight or obesity, Abdominal obesity, High systolic blood pressure
F. Dehghani Firouzabadi	2021	Iran	Cross-sectional	Adult	850	18–65	Both	McCarty	FFQ-168	Fruits, vegetables, fruit and vegetable juice, legumes, whole grains, soy products, nuts, seeds, olive, and olive oil. Potatoes were not included.	MetS, Low HDL, Central obesity, Hyperglycemia, Hypertriglyceridemia, Hypertension
R. Sadat Ziaee	2021	Iran	Cross-sectional	Type 2 Diabetes-Adult	235	30–65	Both	McCarty	24-hour recall	Fruits and vegetables, legumes, whole grains, seeds, nuts, natural fruit and vegetable juices, olive oil, and soy products. Potatoes were not included.	BMI, BP-systolic, BP-diastolic, TG, Insulin, TC, LDL-C, HDL-C, HbA1c, Insulin resistance, FBS
E. Asgari	2021	Iran	Cross-sectional	Adult	844	18–59	Both	McCarty	FFQ-168	Fruits, vegetables, legumes, whole grains, nuts, soy products, seeds, and olive oil.	WC, WHR, WHtR, BMI
M. Kim	2020	Korea	Cross-sectional	Adult	31319	≥19 years	Both	McCarty	24-hour recall	Whole grains, vegetables, fruits, legumes, nuts and seeds, and soy products, olive oil, seaweed, fresh fruit and vegetable juices.	Metabolic Syndrome, Abdominal obesity, Hyperglycemia, High blood pressure, Hypo-HDL, Hypertriglyceridemia
O. Eslami	2020	Iran	Cross-sectional	Children	356	7–10 years	Both	McCarty	FFQ-168	Whole grains, fruits, vegetables, soy products, legumes, nuts, seeds, as well as olive oil, tomato sauces, and pure fruit and vegetable juices. Potatoes were not included.	Overweight/Obesity
F. Azizi-Soleiman	2020	Iran	Nationwide cross-sectional	Children	4296	6–18	Both	McCarty	FFQ-168	Fruits, vegetables, legumes, whole grains, nuts, soy products, olives and olive oil	Some obesity indicators (linear regression) Obesity or overweight and Abdominal obesity (logistic regression)
J Im	2020	Korea	large-scale cross-sectional	Adult	57940	≥19 years	Both	McCarty	FFQ-168	Fruits, vegetables, legumes, whole grains, nuts, soy products, olives and olive oil.	Obesity, abdominal obesity
M. Abshirini	2018	Iran	Case-control	Prediabetes	300	35–65	Both	McCarty	FFQ-168	Fruits and vegetables, (except potatoes), legumes, whole grains, nuts, seeds, olive and olive oil.	Fasting blood glucose or 2–h Orale Glucose Tolerantie Test

Table 1. Characteristics of the included studies in this systematic review (Continued)

								Exposure characteristics/PI			Outcome characteristics
Study first author	Year	Country	Design	Population	Sample size	Age	Sex (M/F)	Definition	Measurements	Foods included	Type
M. Golzarand	2015	Iran	Prospective study/3 years	Adult	1546	20–70	Both	McCarty	FFQ-168	Whole grains (whole wheat bread, oat and bulgur), fruits (red, Yellow and orange fruits), vegetables (dark green vegetables, red/orange vegetables, starchy vegetables and other vegetables), natural fruit and vegetable juices, tomato sauces, soy products (soy bean), nuts (peanut, almond, walnut, pistachio and hazelnut), legumes (lentil, beans, chickpea, split bean, mung bean and vicia faba), olive and olive oil. Potato was not included.	Hypertension
Z. Bahadoran	2015	Iran	Longitudinal study	Adult	1141	20–70	Both	McCarty	FFQ-168	Fruits and vegetables, legumes, whole grains, nuts, soy products, olives, and olive oil. Natural fruit and vegetable juices as well as tomato sauces. Potatoes were not included.	Hyperinsulinemia, Insulin resistance, b-Cell dysfunction, Insulin insensitivity
M. Golzarand	2014	Iran	Longitudinal study	Adult	1983	19–70	Both	McCarty	FFQ-168	Fruits and natural fruit juices, vegetables and natural vegetables juices, whole grains, legumes, nuts, seeds, olives, and olive oil.	Lipid profile
A. Mottaghi	2015	Iran	Longitudinal study	Adult	1552	19–70	Both	McCarty	FFQ-168	Fruits and vegetables, legumes, whole grains, nuts, soy products, tea, olives and olive oil. Natural fruit and vegetable juices as well as tomato sauces. Potatoes were not included.	waist circumference and lipid profile
Z. Bahadoran	2013	Iran	Cross-sectional	Adult	2567	19–70	Both	McCarty	FFQ-168	Fruits and vegetables, legumes, whole grains, seeds, nuts, natural fruit and vegetable juices, olive oil and soy products.	WC, FBS, TG, HDL, SBP, DBP

Table 1. Characteristics of the included studies in this systematic review (Continued)

Study first author	Year	Country	Design	Population	Sample size	Age	Sex (M/F)	Exposure characteristics/PI			Outcome characteristics
								Definition	Measurements	Foods included	Type
P.Mirmiran	2012	Iran	Longitudinal study	Adult	2567	19–70	Both	McCarty	FFQ-168	Fruits and vegetables, legumes, whole grains, nuts, soy products, olives and olive oil. Natural fruit and vegetable juices as well as tomato sauces. Potatoes were not included.	Weight change, Waist circumference change, body adiposity change
H. K. Vincent	2010	USA	Cross-sectional	Adult	54	18–30	Both	McCarty	Three-day dietary records	Fruits and vegetables (and prepared foods derived from these), legumes, whole grains, seeds, nuts, fruit or vegetable juices, olive oil, soy sources, wine, beer and cider.	Adiposity (BMI, body fat, waist circumference), weight gain within the last year, oxidative stress measures (PEROX, TAS) and blood cholesterol subfractions, glucose and HbA1c

[41, 43, 45, 59, 61] and higher protein intake [41, 43, 45], except for three studies that showed decreased protein consumption [55, 59, 61]. In the highest quartile of PI, dietary intakes of whole grains, fruits, vegetables, seeds, nuts, and olive oil were considerably greater than in the lowest quartile. [40, 41, 43, 45, 47, 54, 59, 61]. Regarding quality assessment, only one study was categorized as being at high risk of bias [40], supplementary Table E1 in the electronic supplementary material (ESM) 1.

Findings from systematic review

Phytochemical index and anthropometric measures

Our review of eligible articles showed that four studies have investigated the relationship between PI and anthropometric measurements [40, 45, 55, 60]. In a longitudinal study dietary PI was inversely linked with 3-year changes in waist circumference (WC) ($\beta=-0.08$, $P<0.01$), among the Iranian population [55]. Secondary analysis of these data revealed a significant adverse relationship between the highest quartile of dietary PI and 3-year changes in body weight and body adiposity index (BAI), but not in WC [45]. In another cross-sectional study among American overweight young adults (18–30 years old), significant negative correlations were found between dietary PI and body weight ($r=-0.417$), body mass index (BMI) ($r=-0.421$), WC ($r=-0.418$), waist-to-hip-ratio ($r=-0.358$), and body fat percentage ($r=-0.323$) (all $P<0.05$) [40] as well as an Iranian study which showed same associations with BMI [60] (Table 2).

Phytochemical index and lipid profile

Five articles have investigated the correlation between PI and lipid profiles [40, 43, 55, 58, 60]. In a longitudinal study among the Iranian population, the authors found inverse associations between dietary PI and changes in triglycerides (TG) and total cholesterol (TC) in men but not in women [43]. Furthermore, dietary PI was found to be inversely related to 3-year changes in lipid accumulation product ($\beta=-0.09$, $P<0.01$) and 0.07 mg/dl reduction in blood triglycerides ($P<0.01$) in the 1552 Iranian population in another longitudinal investigation [55]. In another study, after adjustment for potential confounders participants in the highest tertiles of the dietary phytochemical index (DPI), showed a 98% lower chance of low-density lipoprotein/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio compared with those in the lowest tertiles [58]. In an Iranian study, results showed that there was a significant positive correlation between PI and HDL ($r=0.129$, $P=0.04$) but not with LDL, TC, and TG [60]. Finally, Vincent et al. did not find any correlation between PI and serum cholesterol subtractions in a low sample size cross-sectional study of overweight young adults in the USA [40] (Table 2).

Table 2. The results of the included studies

Author	Outcome	PI Categories	Measure	Result	Covariate
S. Delshad Aghdam	Hyperglycemia	Highest tertiles/ Lowest tertiles	OR (CI)	0.12 (0.02, 0. 82)	Age, sex, total energy intake, physical activity, BMI, diabetes duration (year), total insulin dose, education and dietary supplement intake.
	L-HDL			0.19 (0.04, 0.86)	
	H-LDL			0.40 (0.11, 1.44)	
	Hypercholesterolemia			1.20 (0.20, 7.29)	
	High LDL-C/HDL-C			0.02 (0.001, 0.89)	
	High HbA1c			1.12 (0.60, 2.08)	
	Overweight or obesity			0.73 (0.37, 1.48)	
	Abdominal obesity			0.47 (0.14, 1.55)	
	High systolic blood pressure			4.15 (0.36, 48.06)	
F. Dehghani Firouzabadi	Women	Highest quartile/ Lowest quartile	OR(CI)		Age and energy intake, marital status, education status, occupation, physical activity, and smoking status.
	Metabolic syndrome			0.86 (0.50, 1.49)	
	HDL			0.76 (0.44, 1.29)	
	Central obesity			0.54 (0.29, 1.00)	
	Hyperglycemia			0.76 (0.45, 1.28)	
	Hypertriglyceridemia			0.95 (0.55, 1.63)	
	Hypertension			1.51 (0.81, 2.81)	
	Men				
	Metabolic syndrome			1.57 (0.64, 3.84)	
	HDL			1.25 (0.47, 3.36)	
	Central obesity			1.21 (0.54, 2.73)	
	Hyperglycemia			1.02 (0.49, 2.11)	
	Hypertriglyceridemia			0.66 (0.32, 1.36)	
	Hypertension			0.78 (0.35, 1.72)	
R. Sadat Ziaee	BMI	–	R, PV	−0.131, P=0.045	–
	BP-systolic			−0.032, P=0.63	
	BP-diastolic			−0.095, P=0.15	
	TG (mg/dl)			−0.098, P=0.14	
	Insulin (μU/ml)			−0.098, P=0.13	
	TC (mg/dl)			−0.014, P=0.83	
	LDL-C (mg/dl)			−0.046, P=0.48	
	HDL-C (mg/dl)			0.129, P=0.045	
	HbA1c (%)			−0.002, P=0.98	
	Insulin resistance			0.093, P=0.10	
	FBS (mg/dl)			−0.090, P=0.17	
E. Asgari	Women	Highest quartile/ Lowest quartile	OR (CI)		Age, energy intake, marriage status, physical activity, smoking status, occupation, menopausal status and education.
	Central obesity (WC)			0.54 (0.29, 1.00)	
	Central Obesity (WHR)			0.73 (0.42, 1.24)	
	Central Obesity (WHtR)			0.41 (0.19, 0.90)	
	General obesity (BMI)			0.56 (0.29, 1.06)	
	Men				
	Central obesity (WC)			1.21 (0.54, 2.73)	
	Central Obesity (WHR)			1.15 (0.41, 3.26)	
	Central Obesity (WHtR)			0.77 (0.26, 2.26)	
	General obesity (BMI)			1.48 (0.62, 3.54)	
M. Kim	Metabolic syndrome	Highest quintiles/ Lowest quintiles	OR (CI)	0.78 (0.69, 0.88)	Age, sex, education level, household income, smoking status, alcohol consumption, and physical activity level.
	Abdominal obesity			0.90 (0.81, 0.99)	
	Hyperglycemia			0.83 (0.74, 0.94)	
	High blood pressure			0.82 (0.73, 0.93)	
	Hypo-HDL cholesterolemia			1.04 (0.94, 1.15)	
	Hypertriglyceridemia			0.84 (0.75, 0.94)	

Table 2. The results of the included studies (Continued)

Author	Outcome	PI Categories	Measure	Result	Covariate
O. Eslami	Overweight and obesity	Highest quartile/ Lowest quartile	OR (CI)	0.47 (0.25, 0.87)	Age, sex, energy intake and physical activity.
M. Abshirini	Prediabetic	Highest quartile/ Lowest quartile	OR (CI)	0.09 (0.03, 0.25)	BMI, physical activity, education, total energy intake, dietary fiber, Dietary carbohydrate, fat, and protein.
M. Golzarand	HTN	Highest quartile/ Lowest quartile	OR (CI)	0.52 (0.32, 0.84)	Age, sex and lifestyle factors (smoking status, physical activity, socioeconomic status and body mass index.), energy intake, total fiber, sodium, potassium, vitamins A, C and E.
Z. Bahadoran	Hyperinsulinemia	Highest quartile/ Lowest quartile	OR (CI)	0.14 (0.07, 0.29)	Age at baseline, gender, smoking status, physical activity, body mass index at baseline, and mean energy intake.
	Insulin resistance			0.48 (0.25, 0.93)	
	b-Cell dysfunction			0.64 (0.34, 1.10)	
	Insulin insensitivity			0.11 (0.05, 0.24)	
M. Golzarand	Men	Highest quartile/ Lowest quartile	B (CI)		Age, total energy intake, dietary carbohydrate, fat, protein, saturated fatty acid, mono-saturated fatty acid and poly-saturated fatty acid.
	Triglycerides			−13.7 (−24.6, −2.8)	
	Total cholesterol			−5.6 (−9.3, −1.8)	
	HDL-C			−3.6 (−7.7, 0.4)	
	LDL-C			−4.9 (−10.7, 0.8)	
	Total cholesterol/HDL-C			−2.3 (−6.7, 1.9)	
	LDL-C/HDL-C			−2.2 (−8.2, 3.7)	
	Triglyceride/HDL-C			−10.7 (−22.7, 1.3)	
	Women				
	Triglycerides			−4.3 (−12.9, 4.3)	
	Total cholesterol			−1.7 (−5.1, 1.73)	
	HDL-C			−0.2 (−4.8, 4.3)	
	LDL-C			0.7 (−4.5, 5.8)	
	Total cholesterol/HDL-C			−1.2 (−5.3, 2.9)	
	LDL-C/HDL-C			1.0 (−4.9, 7.0)	
	Triglyceride/HDL-C			−4.1 (−13.9, 5.7)	
A. Mottaghi	LAP INDEX (Lipid Accumulation Product Index)	–	B, PV	−0.09, P<0.01	Age, weight at baseline and dietary energy intake.
	Serum triglycerides	–	B, PV	−0.07, P<0.01	
	Changes in waist circumference	–	B, PV	−0.08, P<0.01	
Z. Bahadoran	Abdominal obesity	Highest quartile/ Lowest quartile	OR (CI)	0.34 (0.25, 0.52)	Sex, age, physical activity, educational levels, energy intake and smoking.
	Hypertriglyceridaemia			0.69 (0.49, 0.87)	
	Low HDL-C			1.01 (0.77, 1.41)	
	Hyperglycaemia			1.33 (0.86, 2.24)	
	Hypertension			1.04 (0.73, 1.41)	
P. Mirmiran	Weight change	Highest quartile/ Lowest quartile	B (CI)	−1.41 (−2.33, −0.48)	Sex, age at baseline, BMI, education Q85, smoking, physical activity, total energy intake, dietary carbohydrate, fat and protein.
	Waist circumference change			−0.05 (−1.15, 1.06)	
	Body adiposity change			−1.49 (−2.41, −0.56)	
H. K. Vincent	BMI	–	R, PV	−0.421, P<0.05	–
	Weight	–	R, PV	−0.417, P<0.05	
	Waist circumference	–	R, PV	−0.418, P<0.05	
	Waist-to-hip ratio	–	R, PV	−0.358, P<0.05	
	Body fat percentage	–	R, PV	−0.323, P<0.05	
	Weight gain over the last year	–	R, PV	−0.369, P<0.05	

Table 2. The results of the included studies (Continued)

Author	Outcome	PI Categories	Measure	Result	Covariate
F. Azizi-Soleiman	Underweight	–	B, PV		Age, gender, residency (rural or urban), total energy, and PA per week.
	Wrist circumference			0.006, P=0.38	
	NC			0.020, P=0.26	
	BMI			−0.0005, P=0.0.98	
	WC			0.004, P=0.88	
	HC			0.020, P=0.61	
	Normal weight				
	Wrist circumference			−0.002, P=0.003	
	NC			−0.006, P=0.38	
	BMI			−0.010, P=0.33	
	WC			−0.019, P=0.20	
	HC			−0.010, P=0.61	
	Over weight and obese				
	Wrist circumference			−0.010, P=0.61	
	NC			−0.032, P=0.01	
	BMI			−0.077, P=0.002	
	WC			−0.100, P=0.006	
	HC			−0.119, P=0.003	
	Obesity or overweight	Highest quartile/ Lowest quartile	OR (CI)	0.91 (0.74, 1.11)	–
	Abdominal Obesity			0.87 (0.69, 1.09)	
J. Im	Men	Highest quintile/ Lowest quintile	OR (CI)		Age, education, household income, smoking status, alcohol consumption, physical activity, and intake levels of total energy, meat and meat products, sweets and dairy products.
	Obesity			1.05 (0.94, 1.17)	
	Abdominal			0.90 (0.81, 1.01)	
	Women				
	Obesity			0.86 (0.78, 0.94)	
	Abdominal Obesity			0.81 (0.73, 0.90)	

Phytochemical index and indices of glucose homeostasis

Four studies have explored the associations between PI and glucose homeostasis indices [40, 46, 47, 60]. In this regard, a case-control study conducted among Iranian individuals revealed that participants in the higher quartiles of DPI had lower fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) as well as higher physical activity. Moreover, in this study, the DPI score was inversely related to prediabetes. This means that participants in the upper quartile had lower OR for prediabetes in comparison to those in the lowest quartile (OR: 0.09, 95% CI: 0.03, 0.25) (P-trend<0.001) [46]. Accordingly, following a high-PI diet was associated with a lower risk of hyperinsulinemia (OR: 0.14, 95% CI: 0.07, 0.29), insulin resistance (OR: 0.48, 95% CI: 0.25, 0.93), and insulin insensitivity (OR: 0.11, 95% CI: 0.05, 0.24) in longitudinal research among Iranian communities, but not with a marker of B-cell dysfunction (OR: 0.64, 95% CI: 0.34, 1.10) [47]. In contrast, dietary PI was not significantly correlated with the levels of hemoglobin A1c (HbA1C) and blood glucose in a small sample size study of overweight young adults in the USA [40] which is in line with the results of another study [60] (Table 2).

Phytochemical index and blood pressure

The associations between dietary PI and systolic and diastolic blood pressure (SBP, DBP) were investigated by two studies. In a cross-sectional study conducted by Delshad Aghdam et al. the highest tertiles of PI were not significantly linked with high systolic blood pressure as compared to the lowest tertiles [58]. In this study, researchers could not calculate the OR for high DBP because all participants had DBP lower than 90 mmHg. Similarly, another study did not find any significant correlation between the PI and SBP or DBP in an Iranian population in cross-sectional research [60] (Table 2).

Findings from meta-analysis

Total findings of meta-analyses are reported in Table 3. Publication bias was not detected by funnel plots and Egger's regression asymmetry test in this meta-analysis.

Table 3. Meta-analysis of the association between phytochemical index and cardio-metabolic risk factors

	All studies			Heterogeneity assessment		
Risk factors	Number of studies	Sample size	Pooled OR (95% CI)	I^2%	Q^2 test	P-value
Abdominal obesity	7	98,072	0.73 (0.58, 0.88)	84.90	59.62	<0.001
Obesity	5	63,691	0.84 (0.69, 0.98)	68.10	18.82	<0.001
Hypertension	3	34,736	0.86 (0.73, 0.99)	7.02	8.45	0.36
Hyperglycemia	4	34,997	0.75 (0.41, 1.08)	71.50	14.03	0.01
Hypertriglyceridemia	3	34,736	0.81 (0.73, 0.89)	0.00	2.49	0.48
Low HDL-C	4	32,430	0.81 (0.48, 1.13)	76.10	16.72	<0.001
Metabolic syndrome	2	32,169	0.79 (0.69, 0.88)	0.00	1.02	0.6

Abdominal obesity

The association of abdominal obesity with PI is shown in (Figure 2A). Overall, 10 effect sizes from 7 studies [41, 42, 56, 57, 58, 59, 61] were extracted for this association including 98,072 participants. The pooled odds ratio (OR) showed a significant reverse association between adherence to PI and the risk of abdominal obesity (OR: 0.73, 95% CI: 0.58, 0.88). However, after subgrouping based on gender, such association remained significant in women (OR: 0.69, 95% CI: 0.48, 0.89), but disappeared in men (OR: 0.95, 95% CI: 0.80, 1.00). Since the test of heterogeneity was significant (P<0.001), by doing sensitivity analysis we excluded studies performed on type 1 diabetes (OR: 0.74, 95% CI: 0.58, 0.90) [58] or children (OR: 0.70, 95% CI: 0.54, 0.88) [56] and the observed association remained significant.

Obesity

Considering 7 effect sizes from 5 studies [44, 56, 57, 58, 61] including 63,691 individuals, our results illustrated that adherence to higher PI is associated with a 16% lower risk of obesity (OR: 0.84, 95% CI: 0.69, 0.98) (Figure 2B). However, between-study heterogeneity was seen (P<0.001). When we performed sensitivity analysis and excluded diabetic participants (OR: 0.84, 95% CI: 0.69, 0.98) [58] the association was still significant but when we removed children [44, 56], no significant association was seen (OR: 0.88 95% CI: 0.72, 1.05).

Hyperglycemia

With regard to the association between the risk of hyperglycemia and adherence to PI, we did not find any significant association (OR: 0.75, 95% CI: 0.41, 1.08) (Figure 2C). For this assessment, we included 5 effect sizes from 4 studies [41, 42, 58, 59] with 34,997 participants. As between-study heterogeneity in this regard was significant (P=0.01), we excluded one study performing on Type 1 diabetes (T1D) [58]. After removing this study, we observed a 17% lower risk of hyperglycemia by adhering to high dietary PI (OR: 0.83, 95% CI: 0.74, 0.93).

Hypertriglyceridemia

For evaluating the associations between PI and hypertriglyceridemia, we included 4 effect sizes from 3 studies with a sample size of 34,736 participants [41, 42, 59] (Figure 2D). The results showed that adherence to high PI can reduce the risk of hypertriglyceridemia by about 19% (OR: 0.81, 95% CI: 0.73, 0.89). The test of heterogeneity was not significant in this regard (P=0.48).

Low HDL

Regarding the relationship between low-HDL level and PI, 5 effect sizes from 4 studies [41, 42, 58, 59] with 32,430 participants were included in the analysis (Figure 2E). The results did not show any significant association (OR: 0.81, 95% CI: 0.48, 1.13). Considering the significant heterogeneity between studies (P<0.001), the association still remained non-significant (OR: 1.02, 95% CI: 0.92, 1.20) after removing the study on T1D participants [58].

Hypertension

After combining 4 estimates from 3 eligible studies [41, 42, 59] the results showed a 14% reduced risk of hypertension by adhering to high dietary PI (OR: 0.86, 95% CI: 0.72, 0.99) (Figure 2F). Moreover, between-study heterogeneity in this regard was non-significant (P=0.36). In this analysis, a total of 34,736 participants were included.

Metabolic syndrome

The results of evaluating the associations between PI and metabolic syndrome demonstrated a reverse significant association (OR: 0.79, 95% CI: 0.69, 0.88). For assessing such a relationship, 3 effect sizes from 2 [42, 59] studies were included (Figure 2G). It should be noted that the heterogeneity test was non-significant (P=0.6).

Discussion

The results of the current systematic review and meta-analysis revealed that greater adherence to PI can protect against overweight and obesity. Regarding obesity, after

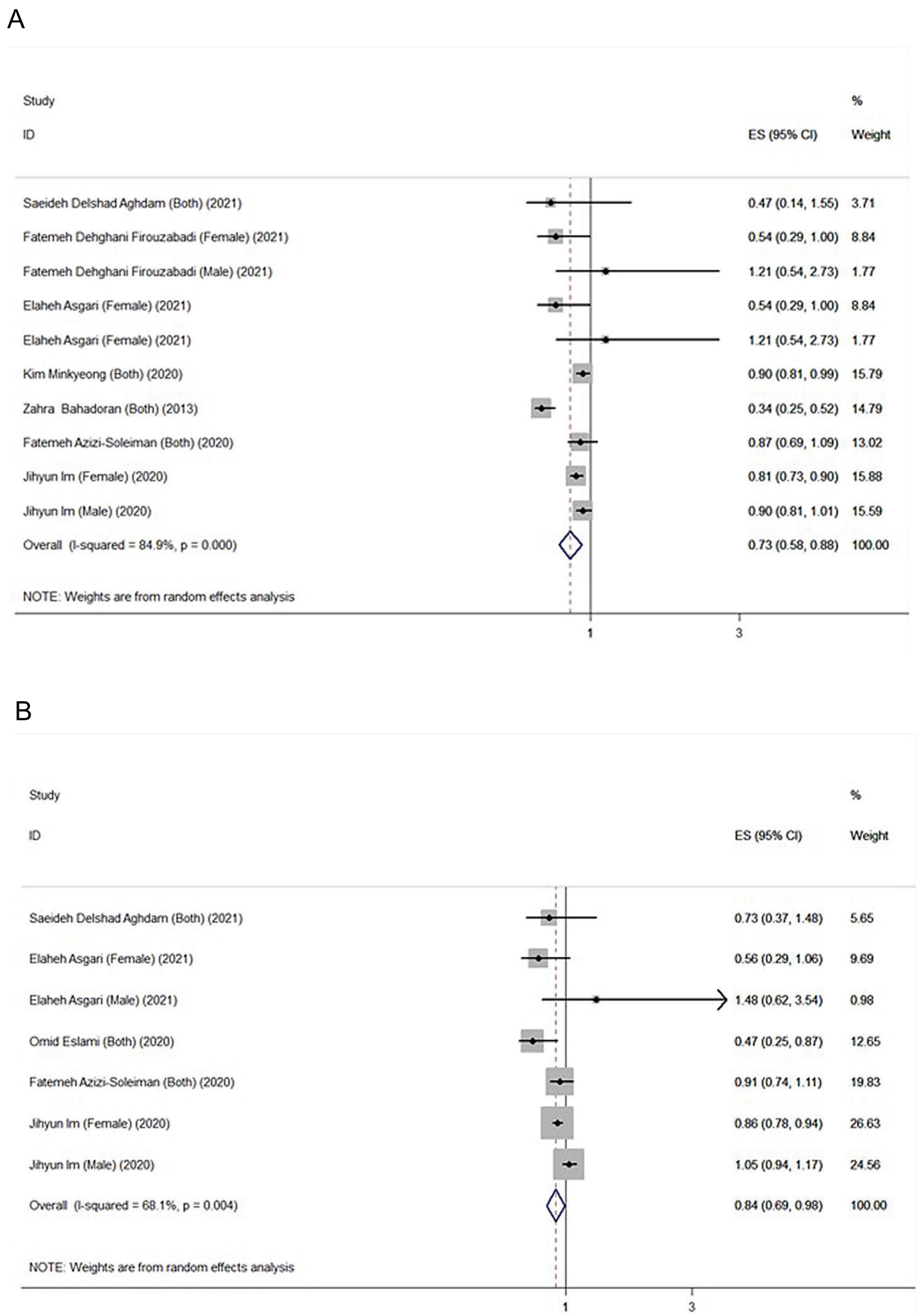

Figure 2. (A) Association between dietary phytochemical index (PI) and abdominal obesity. (B) Association between PI and obesity. (C) Association between PI and hyperglycemia. (D) Association between PI and hypertriglyceridemia. (E) Association between PI and low-HDL-C. (F) Association between PI and hypertension. (G) Association between PI and metabolic syndrome.

excluding participants under 18 years old the significant association disappeared. Although we found that dietary PI is associated with serum TG levels, its relation with other lipid profiles was not significant. The results of our meta-analysis did not prove any significant association between HDL-C and PI, while a study involved in a systematic review showed a significant positive correlation between PI and HDL but not with LDL, TC, and TG. Moreover, in our meta-analysis after removing samples with T1D, a lower risk of hyperglycemia was seen by adhering to high dietary PI. Considering high blood pressure, we observed a reduced risk of hypertension by adhering to higher PI. Finally, we observed a reverse significant association between metabolic syndrome and PI adherence as high dietary PI decreased the risk of metabolic syndrome by 21%.

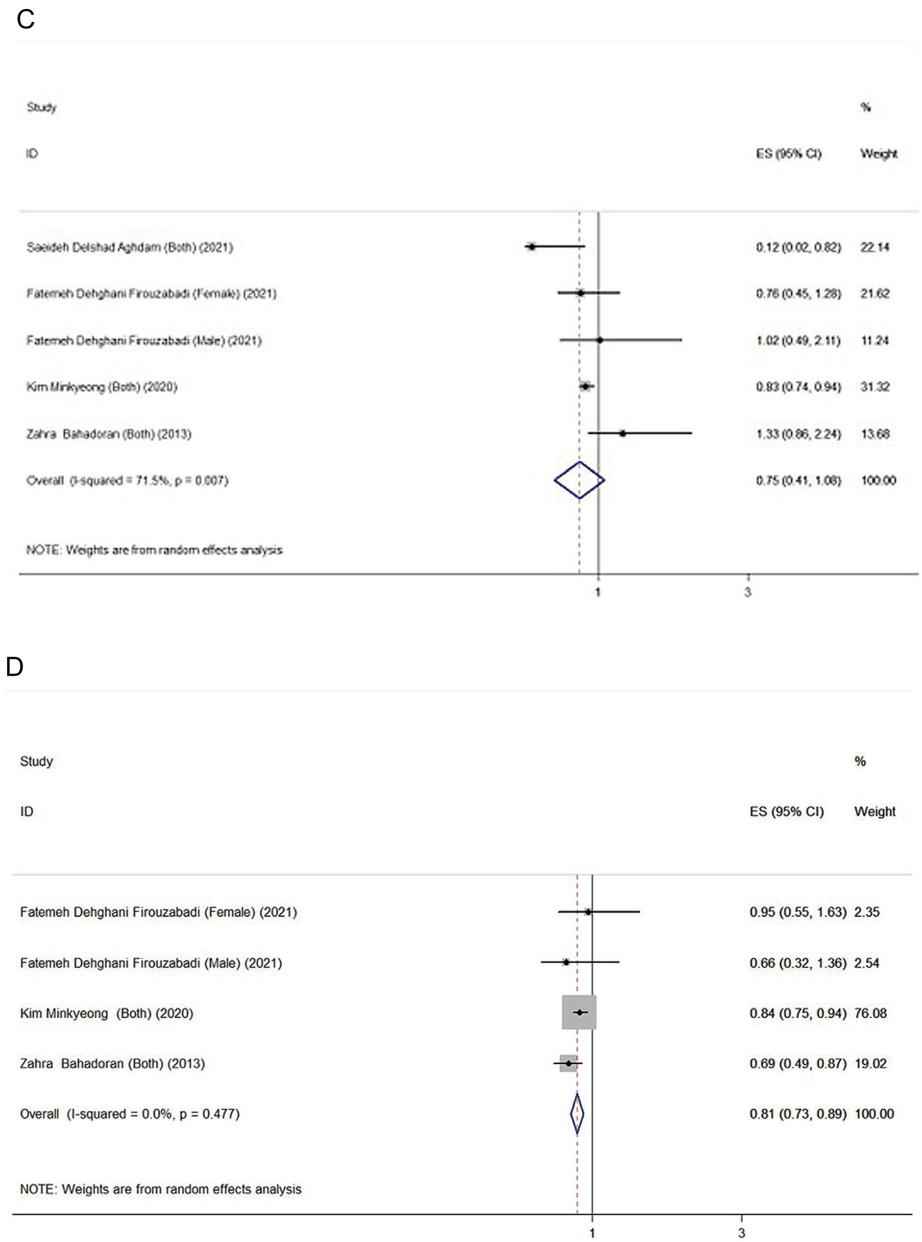

Figure 2. (Continued)

In line with our findings, some previous studies have suggested that older individuals as well as women are more likely to consume higher phytochemical-rich foods. The reason which aforementioned groups have higher PI may be that being more attentive to their health, and they usually use a greater amount of vegetables and phytochemical-rich foods in their diet followed by lower processed meals and fast foods [62, 63].

According to anthropometric findings, the mechanisms by which PI may affect body weight are not clear. However, some evidence derived from in vitro and in vivo studies revealed that phytochemicals may reduce adiposity and body fat in various ways some of which include targeting adipocyte lifecycle such as higher induction of apoptosis and inhibiting proliferation [46], elevating lipolysis and insulin sensitivity followed by a reduction in lipogenesis and angiogenesis as well as decreasing pro-inflammatory mediators in adipocytes [64]. In addition, according to longitudinal evidence, it is suggested that consuming nearly 40% of dietary energy intake from phytochemical-rich foods could be protective against weight gain [45]. Accordingly, it seems that adherence to higher PI is related to lower dietary fat intake [41, 43, 45], higher dietary fiber [44, 45, 54, 55] and protein [41, 43, 45] as well as reduced total

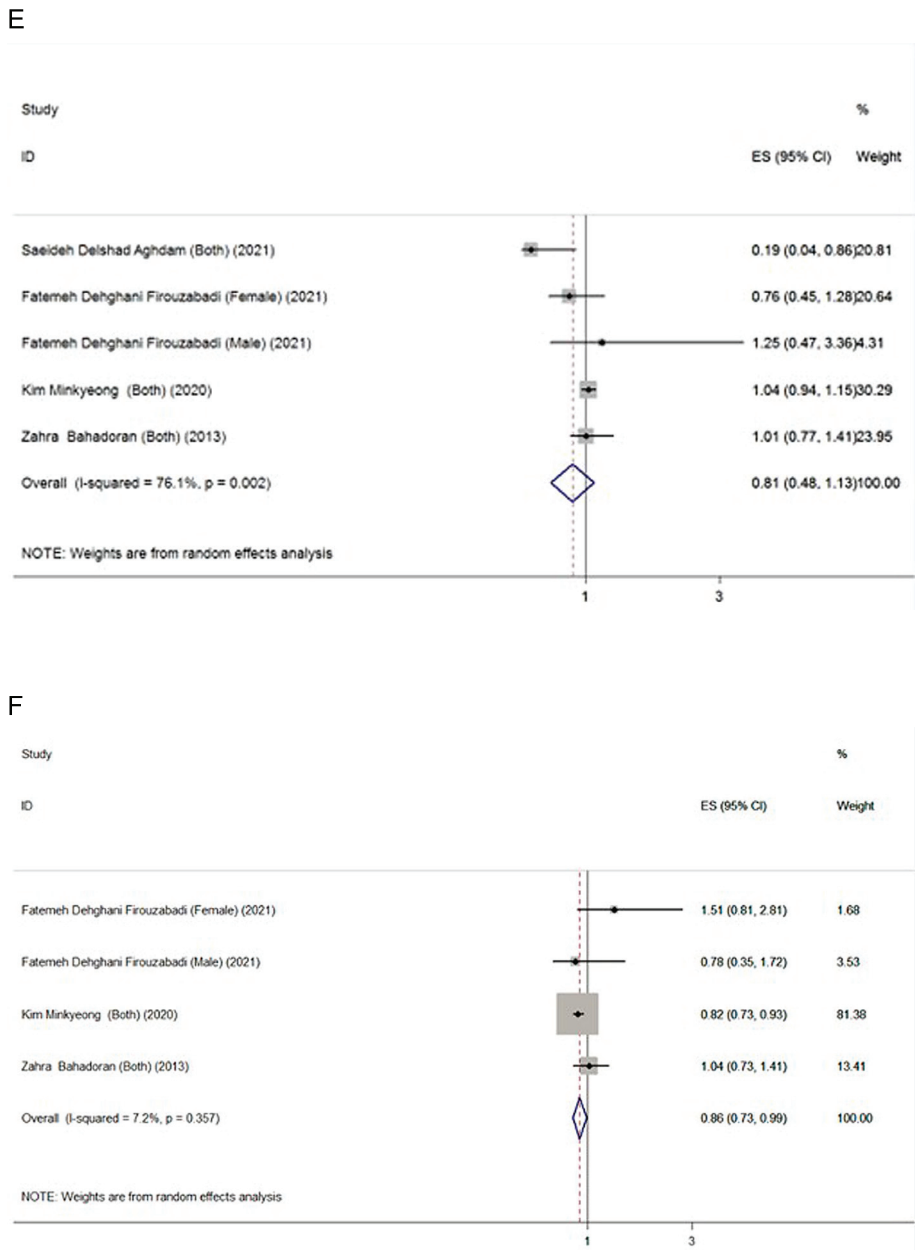

Figure 2. (Continued)

dietary energy intake [41, 43, 45, 47, 55]. Also, another explanation for reducing the risk of obesity through a high intake of phytochemical-rich foods could be its lower glycemic index [36, 37, 46]. So apparently higher dietary PI might be effective in an individual's weight management.

Regarding lipid profile, as the results of the present study showed, there would be an association between PI and TG. Totally, it has been proposed that phytosterols as a subclass of phytochemicals are responsible for phytochemical-related lipid reduction. According to previous studies, dietary products enriched by phytosterols could positively affect lipid profile [65, 66]. Competing with cholesterol for micellar incorporation, phytosterols can lower cholesterol levels. Although these components can inhibit intestinal cholesterol uptake, the reduction of LDL-C is unknown [67]. On the other hand, some phytochemicals can be considered a potent ligand for lipid metabolism regulatory receptors such as peroxisome proliferator-activated receptors. By upregulating genes involved in fatty acid transport and peroxisomal and mitochondrial oxidation, these receptors can modulate lipid metabolism. [68].

Some researchers have attributed the serum lipid reduction to flavonoids, such as quercetin [69, 70]. The synthesis of triglyceride (TG) can be inhibited by quercetin at the

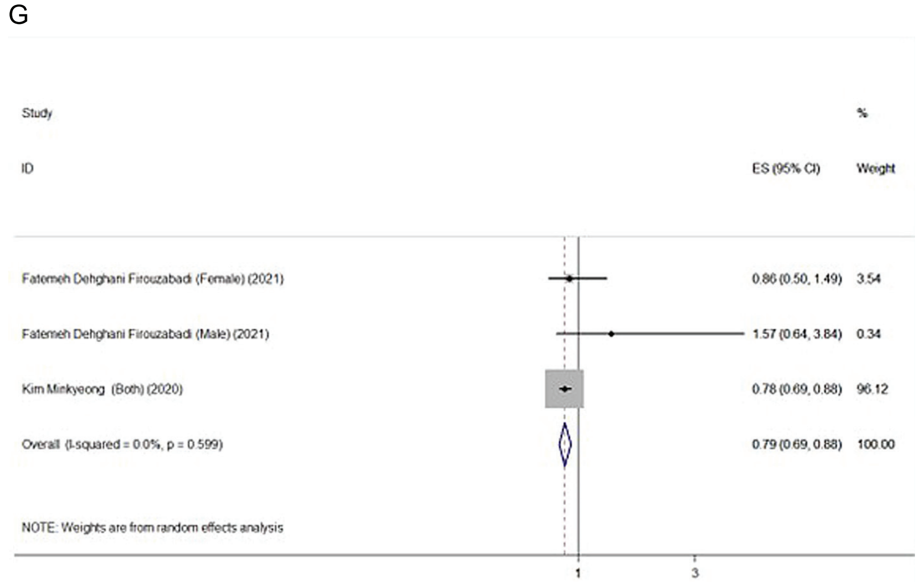

Figure 2. (Continued)

human intestinal CaCo-2 cell line, through inhibiting the secretion of apoB-100 and apoB-48 [71]. Moreover, galangin, another type of flavonoids, can reduce serum lipid levels, lipid peroxidation, and hepatic lipid accumulation such as TGs [72]. Due to the lack of evidence about other lipid profile such as total cholesterol, it is not possible to make a general conclusion.

As mentioned earlier, there is contradictory evidence regarding the association of dietary PI with glucose homeostasis. Nevertheless, some evidence showed that phytochemicals, especially polyphenols can improve insulin resistance by regulating insulin production and secretion as well as pancreatic β-cells protection [73, 74]. Likewise, these phytochemicals derived from plant foods have been highlighted as a potential therapeutic factor for enhancing the uptake of insulin-dependent glucose transporter 4 (GLUT4) [73, 75, 76, 77]. It is thought that eating more fruits with high polyphenol content, such as whole fruits like blueberries, grapes, and apples, is linked to a lower risk of type 2 diabetes [73, 78].

With regard to high blood pressure, as a risk factor for cardio-metabolic disorders in the current study, we observed a negative association between this factor and PI. In this regard, several probable mechanisms have been suggested for the antihypertensive properties of phytochemicals. An increasing body of evidence revealed that the etiology of hypertension is complicated by oxidative stress, which results in excessive production of reactive oxygen species (ROS) [79]. Phytochemicals are the key components of the diet that have antioxidant properties, which reduce oxidative stress and help to prevent hypertension (HTN) [80, 81]. The augmentation of endothelial nitric oxide synthase activity and inhibition of NADPH oxidase activity, which results in vascular smooth muscle tone relaxation, is another underlying mechanism by which phytochemicals can ameliorate HTN [82, 83, 84, 85].

This systematic review has some strengths, such as conducting a comprehensive search strategy through three databases and evaluating different variables as well as large sample size. Moreover, in order to increase the generalizability of the results, we did not exclude any age group or disease. However, in sensitivity analysis, we excluded studies with abovementioned conditions for a more detailed interpretation.

On the other side, the present study has some limitations. For instance, there is small number of researches on this topic, and only three countries had performed such a study, nevertheless included studies had a large sample size. Moreover, there is heterogeneity between the methods that studies used for dietary assessment, but we could not perform subgroup analysis due to the small number of studies.

It is worth mentioning that the PI has also some limitations, such as the non-inclusion of phytochemical-rich non-caloric beverages. Besides, some phytochemicals have potentially more beneficial effects compared to others and the index is not able to take into account these considerations and cannot demonstrate the quality, bioavailability, bio-accessibility, and effect of phytochemicals.

Finally, we showed in this systematic review and meta-analysis that eating foods high in phytochemicals and high dietary PI is linked to decreased weight, WC, and TG as well as reduced risk of metabolic syndrome and hypertension. However, large-scale prospective cohort studies and randomized clinical trials are needed to corroborate our findings due to the scarcity of publications on this topic, as well as the paucity of clinical trial investigations.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000763

ESM 1. The quality assessment of the included studies by Newcastle–Ottawa scale (Table E1).

References

1. Horton R. Offline: Time to radically rethink non-communicable diseases. The Lancet. 2019;393(10184):1922.
2. Nugent R, Fottrell E. Non-communicable diseases and climate change: linked global emergencies. Lancet. 2019;394(10199):622–3.
3. Heller O, Somerville C, Suggs LS, Lachat S, Piper J, Aya Pastrana N, et al. The process of prioritization of non-communicable diseases in the global health policy arena. Health Policy Plan. 2019;34(5):370–83.
4. Miranda JJ, Barrientos-Gutiérrez T, Corvalan C, Hyder AA, Lazo-Porras M, Oni T, et al. Understanding the rise of cardiometabolic diseases in low- and middle-income countries. Nat Med. 2019;25(11):1667–79.
5. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. Circulation. 2005;112(23):3547–53.
6. Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and medical care to cardiovascular mortality trends. Nat Rev Cardiol. 2015;12(9):508.
7. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1–25.
8. Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. The Lancet. 2016;387(10027):1513–30.
9. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. Lancet Diabetes Endocrinol. 2016;4(6):537–47.
10. Organization WH, Global status report on road safety 2015. World Health Organization. 2015.
11. Benziger CP, Roth GA, Moran AE. The global burden of disease study and the preventable burden of NCD. Global heart. 2016;11(4):393–7.
12. Kanjilal S, Gregg EW, Cheng YJ, Zhang P, Nelson DE, Mensah G, et al. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971–2002. Arch Intern Med. 2006;166(21):2348–55.
13. Liu S, Manson JE, Stampfer MJ, Rexrode KM, Hu FB, Rimm EB, et al. Whole grain consumption and risk of ischemic stroke in women: a prospective study. JAMA. 2000;284(12):1534–40.
14. Wang PY, Fang JC, Gao ZH, Zhang C, Xie SY. Higher intake of fruits, vegetables or their fiber reduces the risk of type 2 diabetes: A meta-analysis. J Diabetes Investig. 2016;7(1):56–69.
15. Juan J, Liu G, Willett WC, Hu FB, Rexrode KM, Sun Q. Whole grain consumption and risk of ischemic stroke: results from 2 prospective cohort studies. Stroke. 2017;48(12):3203–9.
16. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med. 2016;14(1):1–14.
17. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, et al. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. Arch Intern Med. 2001;161(21):2573–8.
18. Martinez KB, Mackert JD, McIntosh MK. Polyphenols and intestinal health. Nutrition and functional foods for healthy aging. Elsevier; 2017. p. 191–210.
19. Weng CJ, Yen GC. Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. Cancer Treat Rev. 2012;38(1):76–87.
20. Kocyigit A, Guler EM, Dikilitas M. Role of antioxidant phytochemicals in prevention, formation and treatment of cancer. Reactive Oxygen Species (ROS) in Living Cells London. InterchOpen. 2018;21–45.
21. Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr. 2004;134(12):3479S–85S.
22. Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Curr Opin Food Sci. 2016;8:33–42.
23. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727–47.
24. Han X, Shen T, Lou H. Dietary polyphenols and their biological significance. Int J Mol Sci. 2007;8(9):950–88.
25. Potter JD, Steinmetz K. Vegetables, fruit and phytoestrogens as preventive agents. IARC Sci Publ. 1996;139:61–90.
26. Tucci SA. Phytochemicals in the control of human appetite and body weight. Pharmaceuticals. 2010;3(3):748–63.
27. Ricordi C, Garcia-Contreras M, Farnetti S. Diet and inflammation: possible effects on immunity, chronic diseases, and life span. J Am Coll Nutr. 2015;34(sup1):10–3.
28. Joseph SV, Edirisinghe I, Burton-Freeman BM. Fruit polyphenols: A review of anti-inflammatory effects in humans. Crit Rev Food Sci Nutr. 2016;56(3):419–44.
29. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol. 2003;23(3):434–9.
30. Hanhineva K, Törrönen R, Bondia-Pons I, Pekkinen J, Kolehmainen M, Mykkänen H, et al. Impact of dietary polyphenols on carbohydrate metabolism. Int J Mol Sci. 2010;11(4):1365–402.
31. Kahleova H, Matoulek M, Malinska H, Oliyarnik O, Kazdova L, Neskudla T, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. Diabet Med. 2011;28(5):549–59.
32. Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, et al. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules. 2015;20(12):21138–56.
33. Parker ED, Liu S, Van Horn L, Tinker LF, Shikany JM, Eaton CB, et al. The association of whole grain consumption with incident type 2 diabetes: the Women's Health Initiative Observational Study. Ann Epidemiol. 2013;23(6):321–7.
34. Villegas R, Shu XO, Gao Y-T, Yang G, Elasy T, Li H, et al. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. J Nutr. 2008;138(3):574–80.

35. Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. Arch Intern Med. 2002;162(12): 1382–7.
36. Misirli G, Benetou V, Lagiou P, Bamia C, Trichopoulos D, Trichopoulou A. Relation of the traditional Mediterranean diet to cerebrovascular disease in a Mediterranean population. Am J Epidemiol. 2012;176(12):1185–92.
37. McCarty MF. Proposal for a dietary "phytochemical index". Med Hypotheses. 2004;63(5):813–7.
38. Schröder H, Marrugat J, Vila J, Covas MI, Elosua R. Adherence to the traditional mediterranean diet is inversely associated with body mass index and obesity in a spanish population. J Nutr. 2004;134(12):3355–61.
39. Pérez DD, Strobel P, Foncea R, Díez MS, Vásquez L, Urquiaga I, et al. Wine, diet, antioxidant defenses, and oxidative damage. Ann N Y Acad Sci. 2002;957:136–45.
40. Vincent HK, Bourguignon CM, Taylor AG. Relationship of the dietary phytochemical index to weight gain, oxidative stress and inflammation in overweight young adults. J Hum Nutr Diet. 2010;23(1):20–9.
41. Bahadoran Z, Golzarand M, Mirmiran P, Saadati N, Azizi F. The association of dietary phytochemical index and cardiometabolic risk factors in adults: Tehran Lipid and Glucose Study. J Hum Nutr Diet. 2013;26:145–53.
42. Kim M, Park K. Association between phytochemical index and metabolic syndrome. Nutr Res Pract. 2020;14(3):252–61.
43. Golzarand M, Mirmiran P, Bahadoran Z, Alamdari S, Azizi F. Dietary phytochemical index and subsequent changes of lipid profile: a 3-year follow-up in Tehran lipid and glucose study in Iran. ARYA atherosclerosis. 2014;10(4):203.
44. Eslami O, Khoshgoo M, Shidfar F. Dietary phytochemical index and overweight/obesity in children: a cross-sectional study. BMC Res Notes. 2020;13(1):1–5.
45. Mirmiran P, Bahadoran Z, Golzarand M, Shiva N, Azizi F. Association between dietary phytochemical index and 3-year changes in weight, waist circumference and body adiposity index in adults: Tehran Lipid and Glucose study. Nutr Metab. 2012;9(1):1–9.
46. Abshirini M, Mahaki B, Bagheri F, Siassi F, Koohdani F, Sotoudeh G. Higher intake of phytochemical-rich foods is inversely related to prediabetes: a case-control study. Int J Prev Med. 2018;9.
47. Bahadoran Z, Mirmiran P, Tohidi M, Azizi F. Dietary phytochemical index and the risk of insulin resistance and β-cell dysfunction: a prospective approach in Tehran lipid and glucose study. Int J Food Sci Nutr. 2015;66(8):950–5.
48. Wells GA, Shea B, Da O'Connell, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.
49. Aghababayan S, Sheikhi Mobarakeh Z, Qorbani M, Abbasvandi F, Tiznobeyk Z, Aminianfar A, et al. Dietary phytochemical index and benign breast diseases: a case-control study. Nutr Cancer. 2020;72(6):1067–73.
50. Bahadoran Z, Karimi Z, Houshiar-Rad A, Mirzayi H-R, Rashidkhani B. Dietary phytochemical index and the risk of breast cancer: a case control study in a population of Iranian women. Asian Pac J Cancer Prev. 2013;14(5):2747–51.
51. Alam I, Alam W, Aljuraiban GS, Abulmeaty M, Shivappa N, Razak S. Nutritional, immunological and antioxidant defense status of outpatients diagnosed with colorectal cancer–a case–control study of the little-studied population. Nutr Cancer. 2020;72(8):1307–20.
52. Mofrad MD, Siassi F, Guilani B, Bellissimo N, Azadbakht L. Association of dietary phytochemical index and mental health in women: a cross-sectional study. Br J Nutr. 2019;121(9): 1049–56.
53. Orgeron R II, Pope J, Green V, Erickson D. Phytonutrient intake and body composition: Considering colors. Funct Foods Health Dis. 2019;9(2):108–22.
54. Golzarand M, Bahadoran Z, Mirmiran P, Sadeghian-Sharif S, Azizi F. Dietary phytochemical index is inversely associated with the occurrence of hypertension in adults: a 3-year follow-up (the Tehran Lipid and Glucose Study). Eur J Clin Nutr. 2015;69(3):392–8.
55. Mottaghi A, Bahadoran Z, Mirmiran P, Mirzaei S, Azizi F. Is dietary phytochemical index in association with the occurrence of hypertriglyceridemic waist phenotype and changes in lipid accumulation product index? A prospective approach in Tehran Lipid and Glucose Study. Int J Pharmacog & Phytochem Res. 2015;7(1):16–21.
56. Azizi-Soleiman F, Khoshhali M, Heidari-Beni M, Qorbani M, Pourmirzaei MA, Kelishadi R. Higher dietary phytochemical index is associated with anthropometric indices in children and adolescents: the weight disorders survey of the CASPIAN-IV study. Int J Vitam Nutr Res. 2020.
57. Im J, Kim M, Park K. Association between the phytochemical index and lower prevalence of obesity/abdominal obesity in Korean ADULTS. Nutrients. 2020;12(8):2312.
58. Aghdam SD, Siassi F, Esfahani EN, Qorbani M, Rajab A, Sajjadpour Z, et al. Dietary phytochemical index associated with cardiovascular risk factor in patients with type 1 diabetes mellitus. BMC Cardiovasc Disord. 2021;21(1):1–11.
59. Firouzabadi FD, Jayedi A, Asgari E, Farazi M, Noruzi Z, Djafarian K, et al. The association of dietary phytochemical index with metabolic syndrome in adults. Clin Nutr Res. 2021;10(2):161.
60. Ziaee RS, Keshani P, Salehi M, Ghaem H. Diet Quality indices and their correlation with glycemic status and lipid profile in patients with type 2 diabetes. Adv Prev Med. 2021;2021.
61. Asgari E, Jayedi A, Firouzabadi FD, Noruzi Z, Farazi M, Djafarian K, et al. Association of the dietary phytochemical index with general and central obesity in a sample of Iranian adults. J Funct Foods. 2021;83:104546
62. León-Muñoz LM, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. BMC Med. 2015;13(1):1–9.
63. Schröder H, Marrugat J, Covas M, Elosua R, Pena A, Weinbrenner T, et al. Population dietary habits and physical activity modification with age. Eur J Clin Nutr. 2004;58(2): 302–11.
64. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis. 2011;217(2):492–8.
65. Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R, et al. editors. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc; 2003: Elsevier.
66. Demonty I, Ras RT, van der Knaap HC, Duchateau GS, Meijer L, Zock PL, et al. Continuous dose-response relationship of the LDL-cholesterol – lowering effect of phytosterol intake. J Nutr. 2009;139(2):271–84.
67. Hallikainen MA, Sarkkinen ES, Uusitupa MI. Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner. J Nutr. 2000;130(4):767–76.
68. Ko JK, Lee SS, Martin H. Phytochemicals as modulators of PPARs and RXRs. Hindawi. 2010.

69. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. Metabolism. 2009;58(4):460–8.
70. Esmaillzadeh A, Mirmiran P, Azizi F. Whole-grain consumption and the metabolic syndrome: a favorable association in Tehranian adults. Eur J Clin Nutr. 2005;59(3):353–62.
71. Casaschi A, Wang Q, Richards A, Theriault A. Intestinal apolipoprotein B secretion is inhibited by the flavonoid quercetin: potential role of microsomal triglyceride transfer protein and diacylglycerol acyltransferase. Lipids. 2002; 37(7):647–52.
72. Kumar S, Alagawadi K. Anti-obesity effects of galangin, a pancreatic lipase inhibitor in cafeteria diet fed female rats. Pharm Biol. 2013;51(5):607–13.
73. Bahadoran Z, Mirmiran P, Azizi F. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. J Diabetes Metab Disord. 2013;12(1):1–9.
74. Zhang B, Kang M, Xie Q, Xu B, Sun C, Chen K, et al. Anthocyanins from Chinese bayberry extract protect β cells from oxidative stress-mediated injury via HO-1 upregulation. J Agric Food Chem. 2011;59(2):537–45.
75. Kim Y, Keogh JB, Clifton PM. Polyphenols and glycemic control. Nutrients. 2016;8(1):17.
76. Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, et al. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. J Nutr. 2008;138(9):1671–6.
77. Park CE, Kim M-J, Lee JH, Min B-I, Bae H, Choe W, et al. Resveratrol stimulates glucose transport in C2C12 myotubes by activating AMP-activated protein kinase. Exp Mol Med. 2007;39(2):222–9.
78. Muraki I, Imamura F, Manson JE, Hu FB, Willett WC, van Dam RM, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. BMJ. 2013;347.
79. Moline J, Bukharovich I, Wolff M, Phillips R. Dietary flavonoids and hypertension: is there a link? Med Hypotheses. 2000; 55(4):306–9.
80. Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensive effects of the flavonoid quercetin. Pharmacol Rep. 2009;61(1):67–75.
81. Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr. 2012;51(6):637–63.
82. Loke WM, Hodgson JM, Proudfoot JM, McKinley AJ, Puddey IB, Croft KD. Pure dietary flavonoids quercetin and (–)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. Am J Clin Nutr. 2008;88(4):1018–25.
83. Olszanecki R, Gebska A, Kozlovski V, Gryglewski R. Key words: flavonoids, nitric oxide synthase, macrophages. J Physiol Pharmacol. 2002;53(4):571–84.
84. Steffen Y, Gruber C, Schewe T, Sies H. Mono-O-methylated flavanols and other flavonoids as inhibitors of endothelial NADPH oxidase. Arch Biochem Biophys. 2008;469(2):209–19.
85. Steffen Y, Schewe T, Sies H. (–)-Epicatechin elevates nitric oxide in endothelial cells via inhibition of NADPH oxidase. Biochem Biophys Res Commun. 2007;359(3):828–33.

History
Received March 18, 2022
Accepted August 4, 2022
Published online August 26, 2022

Conflict of interest
The authors declare that there are no conflicts of interest.

Author contributions
MQ and HSE equally contributed to the conception and design of this research; AMG, MEA and BL contributed to the interpretation of the data; MQ and ES performed statistical analysis. SM, HSE and YJ extracted the data and drafted the manuscript; all authors critically revised the manuscript and read and approved the final manuscript.

ORCID
Bagher Larijani
https://orcid.org/0000-0001-5386-7597

Dr. Hanieh-Sadat Ejtahed
Endocrinology and Metabolism Research Center
Endocrinology and Metabolism Clinical Sciences Institute
Tehran University of Medical Sciences
North Kargar Ave, 1411413137
Tehran, Iran
haniejtahed@yahoo.com

