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Dietary polyphenols and the risk of metabolic syndrome: a systematic review and metaanalysis

Pushpamala Ramaiah¹, Kamilya Jamel Baljon¹, Ahmed Hjazi², Maytham T. Qasim³, Ornar Abu, Jwahid Salih Al-ani⁴, Shad Imad⁵, Beneen M. Hussien⁶, Ali Alsalamy⁷ and Nazila Garousi^{8*}

Abstract

Background Accumulating evidence has suggested that dietary poly suggested that diet syndrome (MetS); however, the available evidence is contradictory. The virin or this meta-analysis was to assess the association between dietary intake of polyphenols and the odds of Mets

Methods The PubMed and Scopus databases were systematical, searched to obtain eligible studies. The risk of MetS for the highest versus the lowest intakes of total, subclasses, and includual polyphenols were examined by pooling odds ratios (OR) and 95% confidence intervals (95%C) using the random effects model.

Results A total of 14 studies (6 cohort and 8 cross-schonal) tudies) involving a total of 50,366 participants with 10,879 cases of MetS were included. When various poly, and compounds were pooled, they were significantly related to a 22% decreased odds of MetS (([studies]; OR: 0.78; 95%CI: 0.72–0.85). Higher intakes of total flavonoids (([9 studies]; OR: 0.78; 95%Cl: 0.72–0.85) navan-3-0, ([2 studies]; OR: 0.64; 95%Cl: 0.43–0.94), isoflavones (([3 studies]; OR: 0.84; 95%Cl: 0.75–0.93), stilbenes (4 studies]; OR: 0.86; 95%Cl: 0.76–0.97), flavones (([2 studies]; OR: 0.79; 95%Cl: 0.71–0.89), and quercetin (([2 studies]; 2.0.62,95%Cl: 0.43–0.93) were also significantly associated with a decreased risk of MetS. The associations we not mouthed by the age of the participants. No association was found for total polyphenols, phenolic acids, lignans, and nocyanins, and flavonols.

Conclusion The results on his meta-analysis supported that higher polyphenol intake can lower the risk of MetS.

Keywords Metabolics, closed Flavonoids, Polyphenols, Meta-analysis



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Background

Metabolic syndrome (MetS) is a multifactorial and complex complication featured by a cluster of metabolic aberrations, comprising hypertension, adnominal obesity, impaired glucose metabolism, and dyslipidemia [1, 2]. The prevalence of MetS is increasing globally and has become a main public health issue, as it dramatically increases the odds of chronic diseases, such as cardiovascular disease (CVD), type 2 diabetes mellitus as well as mortality [3]. Thus, recognizing amendable risk factors of MetS is of extreme significance to develop preventive strategies to reduce its related pathologies [4].

Among the leading contributing factors, sedentary lifestyles and unhealthy dietary patterns have been frequently identified to be responsible for the etiology of this disease [5]. Evidence has revealed that high-quality diets, including the Mediterranean diet and plant-based diets such as the vegetarian dietary pattern, have protective effects against MetS or could even recover the MetS phenotype [6, 7]. These diets are rich in plants and their beneficial effects are partly attributed to polyphenols, the most widely distributed secondary metabolites in dietary sources which are available in plant-based food such as nuts, whole grains, vegetables, beverages, fruits, cocoa products [8, 9]. Polyphenols are a diverse group of bioactive antioxidants belonging to the four chien lasses, including lignans, phenolic acids, flavone is, and tilbenes [10]. Due to the antioxidant, an i-inflammatory, and antihyperglycemic properties as we as their positive impacts on metabolic pathways and guincrobiota [11-13], polyphenols have received considerable attention for their potential to exert prot ctive effects against the development of Met^S con ponen 3. Despite promising effects on single om, and of MetS [14], epidemiological studies 1 ve yield inconclusive results for the association be ween the intakes of total polyphenols and main subclasses and the risk of MetS phenotype. The prospective c hort study by Sohrab et al. on 1265 adults, identified no significant relationship between total polyphen 'co sumption and other subclasses with MetS [15], while higher intakes of total polyphenols, phenolic acid, and h. vonoids were linked to reduced odds of MetS in a Danish cohort [9]. The disagreement in the results of the previous studies may be due the differences in study design, sample size, or geographic region.

To the best of our knowledge, no systematic review or meta-analysis has yet focused on the association of polyphenols with MetS by pooling the results of observational studies. However, some systematic reviews and meta-analyses on clinical trials have reported that supplementation with polyphenols could improve some individual components of metabolic syndrome [16, 17]. A recent systematic review identified that supplementation with flavonoids can significantly modulate several metabolic parameters, such as lipid profile, blood pressure, and blood glucose, while no significant effect was reported on body weight and body mass index [18]. In contrast, another systematic review did not find a positive effect for grape polyphenols on the component of MetS [19]. Currently, it is not known whether the consumption of polyphenols can play a role in the preention of MetS. Due to the contradiction in the results of observational studies that investigated the relationship between polyphenols and MetS and the lack of a metaanalysis in this field, the presentation of the polyphenol intake and their subclasses and the risk of MetS by conducting a meta-analysis.

Methods

The Preferred Repo. ing Items for Systematic Reviews and Meta-analysis (FRISMA) guidelines were followed to present the restarts of this meta-analysis [20] (Supplementary Appendix 1). The protocol of the study was registered in PROSPERO (CRD42023451126).

Sea. h strategy

A systematic search PubMed Scoin and r as was conducted to obtain pertinent publications published from commencement to July 2023 with the use of the following search strategy: OR "Flavonols"[Mesh]) (((((((((("Flavonoids"[Mesh] OR "Flavanones" [Majr]) OR "Isoflavones" [Mesh]) OR "Flavones" [Mesh]) OR "Anthocyanins" [Majr]) OR "Anthocyanins" [Mesh]) OR "Catechin" [Mesh]) OR "Proanthocyanidins"[Mesh]) OR "Quercetin"[Mesh]) OR "Polyphenols"[Majr]) OR "Apigenin" [Majr]) OR "Luteolin"[Majr]) OR OR noids[Title/Abstract]) (flavanones[Title/ Abstract])) OR (isoflavones[Title/Abstract])) OR (isoflavonoids[Title/Abstract])) OR (flavones[Title/ Abstract])) OR (flavan-3-ols[Title/Abstract])) OR (flavanols[Title/Abstract])) OR (flavonols[Title/ Abstract])) OR (anthocyanidins[Title/Abstract])) OR (anthocyanins[Title/Abstract])) OR (catechins[Title/ Abstract])) OR (proanthocyanidins[Title/Abstract])) OR (quercetin[Title/Abstract])) OR (polyphenols[Title/ Abstract])) OR (kaempferol[Title/Abstract])) OR (isorhamnetin[Title/Abstract])) OR (apigenin[Title/ Abstract])) OR (luteolin[Title/Abstract])) OR (phenolics[Title/Abstract]))) AND ((("Metabolic Syndrome"[Mesh]) OR (metabolic syndrome))). No language restriction was considered for the literature search. The full electronic search strategy is presented in Table S1. Additionally, the references of the pertinent publications were manually reviewed to find any unrecognized studies.

Eligibility criteria and study selection

Initially, all retrieved publications were compiled in the EndNote reference manager software (version 7) [21]. Two researchers (PR and NG) independently were involved in title/abstract screening and full-text screening of the papers and discrepancies were solved by a discussion with a third reviewer. Studies were included based on the following criteria: (1) studies that assessed the relation of the intakes of various dietary polyphenols (exposure) to MetS (outcome), (2) studies were observational in design (cohort, case-control, cross-sectional), (3) studies that provided risk estimates (relative risk (RR), odds ratio (OR), or hazard ratio (HR) along with 95% confidence intervals (CI); when a publication reported more than one effect size for subgroups (e.g. men and women), all effect sizes were extracted. We extracted risk estimates from the most adjusted models. Review studies, letters, book chapters, animal studies, molecular studies on gene expression, studies with inappropriate exposure/outcome, and studies with unextractable data were all excluded from the analysis.

Data extraction and quality assessment

The following data were gathered from each inc. led article with the use of a standardized extraction shee The name of the first author, publication year geder and age of participants, study design, country total smple size, number of cases with MetS, criteria used for the definition of MetS, dietary assessment tool, risk estimates (OR, RR, or HR) and 95%CI for the associations, type of polyphenols or their subclasses, inc. poriates adjusted for in the analyses. In most of the audies included in the meta-analysis, effect si es v ere reported for polyphenols and its subclass s, so trace, For these studies, we extracted all effect izes and ported the results for different polyphen. Is in ubgroup analysis. For example, in the study by Heiazi et a [22], effect sizes were reported separately, r total flavonoids, anthocyanins, flavones, isoflaveres, a. Pavonols, resulting in multiple effect size in ne present meta-analysis. The process of data extracion was independently conducted by two investigators and differences were resolved by a group discussion. The quality of the included studies was scored by the Newcastle-Ottawa Scale (NOS), which ranges from 0 to 9 and scores 0–3, 4–6, and 7–9 are representative of low, moderate, and high quality, respectively [23].

Statistical analysis

ORs with 95%CIs were used as the measure of the association of polyphenols and individual classes with MetS for the highest categories of exposure, compared to the lowest exposure. Meta-analysis was carried out when there were at least 2 effect sizes with a common exposure. Heterogeneity across the publications was measured using the Cochrane Q and I-squared statistics, and heterogeneity was defined as $I^2 > 50\%$ and p < 0.05 [24]. Because of the anticipated heterogeneity, the random-effects model proposed by DerSimonian and Laird (DL) [25] was applied to pool the effect sizes, since it con ders both within-study and between-study variations. Sproup analysis by study design, polyphenol s bclasses, cfinition of MetS, and dietary assessment tool vas conducted only in the case when the hetercgeneity we significant with the aim to explore the source's of heterogeneity, and when the number of include stude in the meta-analysis was at least 10. A sersicivity nalysis was carried out by exclusion of individu articles from the overall analysis step by step to invest, the stability of findings. Moreover, we carried out a meta-regression analysis to check whether the station of polyphenols consumption with MetS is odified by the age of participants. Publication. was evaluated by inspecting asymmetry in funnel p c is a id Egger's test [26]. All statistical analyses were dor 2 with the use of Stata MP 14.0 (Stata Corp., Colic \rightarrow Station, TX, USA).

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iterature search and characteristics of studies

The systematic literature search abstained a total of 2,895 papers. When duplicates were excluded, 2,225 studies remained. Of which, 2182 publications were removed based on the titles/abstracts and 43 studies underwent full-text evaluation. In this stage, 29 additional studies were excluded according to the inclusion criteria. Finally, a total of 14 publications [9, 10, 15, 22, 27-36], including a total of 50,366 participants and 10,879 MetS cases, examining the relation between polyphenol intake and the risk of MetS were included in the meta-analysis. In most of the studies included in the meta-analysis, effect sizes were reported for polyphenols and its subclasses, separately. For these studies, we extracted all effect sizes, resulting in multiple effect sizes (43 effect sizes) in the present meta-analysis. The process of study selection is explained in Fig. 1. The analyzed studies were published from 2012 to 2023. The sample sizes of the included studies ranged between 223 and 9,108 participants. The ages of subjects were between 27.0 ± 3.9 and 67.4 ± 7.80 years. Six publications applied a prospective cohort [9, 15, 22, 28, 30, 34] and 8 publications used a cross-sectional study design [10, 27, 29, 31-33, 35, 36]. Five studies reported effect sizes for total polyphenols intake [9, 10, 15, 27, 36], 9 for total flavonoids [9, 10, 15, 22, 27, 28, 30, 32, 33], 4 for lignans [9, 10, 15, 27], 4 for stilbenes [9, 10, 15, 27], 4 for phenolic acids [9, 10, 15, 27], 3 for isoflavones [22, 30, 34], 2 for flavan-3-ols [30, 35], 2 for anthocyanins [22, 30], 2 for flavones [22, 30], 2 for flavonols [22, 31], and 2 studies for quercetin [28, 29]. Dietary assessment tools for measuring the intake was food-frequency questionnaire

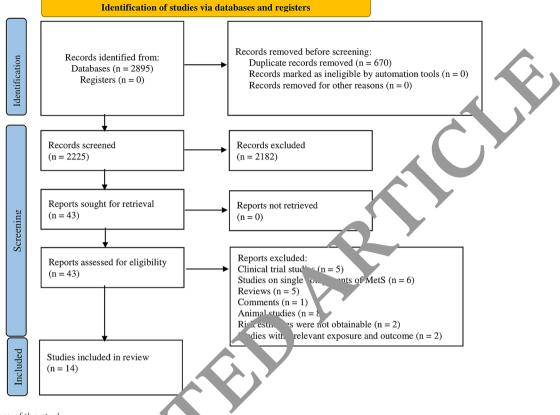


Fig. 1 Flow diagram of the study

(FFQ) in 9 studies [10, 15, 22, 27-30, 3, 34] an I 24-hour dietary recalls in 5 publications [9, 31, 5, 36]. The criteria used for the definition of N. Twere applied by the International Diabetes Federa on (IDF) in 4 studies [9, 27, 28, 32], the Adult Tre. ment Panel III (ATP III) in 4 studies [10, 15, 34 35], 'e juit Interim guidelines in 3 studies [22, 30 3], the A derican Heart Association and the Nationa. Hea. Lung, and Blood Institute (AHA/ NHLBI) in one study [1,], the Korean diabetes association in one tury [1], and the IDF and AHA/NHLBI in one study [36 Except for the study by Oh et al. [31] wh[;] h in luded only women as the study population, all other the other the other other the other ders. The results of all included studies had been adjusted for the potential covariates. Based on the NOS, the quality of all included studies was rated as high with scores ranging from 7 to 9 (Table S2). The characteristics of the studies are presented in Table 1.

Meta-analysis

Meta-analysis of a total of 43 effect sizes from 14 studies [9, 10, 15, 22, 27–36] regarding the association between the intake of various polyphenolic compounds and MetS identified that higher intakes of various polyphenolic compounds are significantly related to 22% decreased odds of MetS (OR: 0.78; 95% CI: 0.72–0.85), with a

significant heterogeneity across the studies ($I^2=79.9\%$, P < 0.001) (Fig. 2). The results of the subgroup analysis revealed no difference in the pooled effect size when subgroup analysis was performed according to the study design and dietary assessment toll, but there was a significant difference in the pooled effect size across the subgroups of polyphenol subclasses and definitions of MetS (Table 2). The results of subgroup analysis based on the polyphenol subclasses are reported in Fig. 3; Table 2. A reduced risk of MetS for higher intakes of total flavonoids (OR: 0.78; 95% CI: 0.72-0.85), flavan-3-ols (OR: 0.64; 95% CI: 0.43-0.94), isoflavones (OR: 0.84; 95% CI: 0.75-0.93), stilbenes (OR: 0.86; 95% CI: 0.76-0.97), flavones (OR: 0.79; 95% CI: 0.71-0.89), and quercetin (OR: 0.63; 95% CI: 0.43-0.93) was identified in the subgroup analysis. No significant association was found for total polyphenols, phenolic acids, lignans, anthocyanins, and flavonols (Table 2). The sensitivity analysis by removing publications by turns revealed that the pooled effect size for the association of various polyphenolic compounds with MetS was not remarkably charged by any individual study, showing the reliability of the findings.

For single compounds with one effect size, kaempferol (OR: 0.56; 95% CI: 0.34–0.93), isorhamnetin (OR: 0.58; 95% CI: 0.35–0.96), luteolin (OR: 0.49; 95% CI: 0.32–0.76), favonols (OR: 0.66; 95% CI: 0.58–0.75), and

Lanuza 2023 Dermark Prospective co- hort (12 months 3.9 Oth 676 80 DF Grosso 2017 Poland Cross-sectional 58.5±7.0 Both 88.21 0 DF Hejazi 2021 Iran Prospective 58.5±7.0 Both 88.21 0 DF Ho 2021 Iran Prospective 36.5±13.3 Both 1915 591 the Jointh Jin 2021 Iran Prospective 3.6.5±13.3 Both 1915 591 the Jointh Jin 2021 China Prospective 51 80.4 171.5 90.4	as	Dietary Exposure assessment		n (95% npari- reme	Adjustment
SS0 2017 Poland Cross-sectional 58.5 ± 7.0 Both 8821 0 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 azi 2021 China Prospective 36.5 ± 13.3 Both 6417 1283 azi 2021 China Prospective 51 Both 6417 1283		24-hour di- Total etary recalls polyphenols	•	1.32-1.05)	Age, sex and time origin, physical activity, smoking,
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350 2017 Poland Cross-sectional 58.5.±7.0 Both 88.21 6.0 201 Iran Prospective 36.5.±13.3 Both 1915 591 202 Iran Prospective 51 Both 1915 591 2021 China Prospective 51 65.3% 6417 1283 2021 China Prospective 51 651.3% 651.3% 6317 1283		Phenolic acids			of saturated fats,
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sso 2017 Poland Cross-sectional 58.5 ± 7.0 Both 821 6 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 azi 2021 Iran Prospective 36.5 ± 13.3 Both 1915 591 2021 Cohort (8.9 years) 36.5 ± 13.3 Both 1915 591 2021 China Prospective 51 6.5.3% 6.417 1283 2021 China Prospective 51 Both 6417 1283 2021 China Prospective 51 Both 653.3% 6.5.3% 1283		Tyrosol			energy, consumption of red meat, processed meat, fish, soft drinks, and salt
 ^{azi} 2021 Iran Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years cohort (8.9 years follow-up) ²⁰²¹ China Prospective 51 Both 6417 1283 follow-up) 	IDF FFQ	Q Phenolic acids		0.78 (0.67–0.91)	Age, gender, educa- tion, occupation, phys-
 ^{azi} 2021 Ian Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years cohort (8.9 years follow-up) ²⁰²¹ China Prospective 51 Both 6417 1283 follow-up) 		Total fla	Total flavonoids	0.88 (0.73-1)	ical activity, smoking
azi 2021 Iran Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years (53.5%) (53.5%) 1915 591 follow-up) 2021 China Prospective 51 Both 6417 1283 follow-up)		Lignans	5		status, alcohol drink-
azi 2021 Iran Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years follow-up) follow-up) 51 Both 6417 1283 2021 China Prospective 51 Both 6417 1283 follow-up)		Stilbenes			ing, body mass index,
azi 2021 Iran Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years (53.5%) (53.5%) 591 follow-up) 2021 China Prospective 51 Both 6417 1283 follow-up) follow-up)		Total		0.74 (0.64–0.86)	total energy intake, and other polyphenol
azi 2021 Iran Prospective 36.5±13.3 Both 1915 591 cohort (8.9 years (53.5%) (53.5%) follow-up) follow-up) 2021 China Prospective 51 Both 6417 1283 follow-up) follow-up)		polypnenols	enois		quartiles of intake
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)	the Joint Interim guidelines	Total fla	Total flavonoids 0.	0.77 (0.62–0.95)	Age, gender, smok- ing, physical activity, education levels, oc-
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)		Flavano		1.04 (0.85–1.28)	cupational status, total
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)		Anth	yah ⁱ ns 0.	0.92 (0.74–1.14)	energy intake, fiber
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)		F' O	0		intake, iamiiy nistory of diabetes, familv his-
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)		Fleva	nes	1.1 (0.9–1.34)	tory of cardiovascular
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)		Isoflav pres		0.83 (0.68–1.01)	disease and body
2021 China Prospective 51 Both 6417 1283 cohort (5.3 years (65.3%) follow-up)					mass index
follow-up)	IDF FFQ	Quercetin		.55 (0.34–0.88)	Age, sex, drinking, smoking, physical
		2			activity, body mass
		Kaempterol	C	56 (0.34-0.93	index, iai, protein, carbohydrate, fiber
		Apigenin	ellu	50) 20	and total energy
		Luteolin		2-2	

Table 1 (continued)	CUTUTI											
Author	year	year Country	Study design	ieàn age, y	Gender (% women)	Total sample size	Cases with MetS	MetS definition	Dietary assessment	Exposure	Association (95% Cl) for compari- son of extreme quantiles	Adjustment
ee	2016	2016 Korea	Cross-sectional	98. 720	-oth (46.1)	428	203	AHA/NHLBI	FFQ	Quercetin	0.83 (0.42–1.61)	Age, sex, educational level, history of heart disease, pack-years of smoking, total energy intake, marital status, ethanol intake, red meat intake, dairy food intake, and body
ЧO	2014	2014 Korea	Cross-sectional	27.0±3.9	Females (100%)	223	57	Korean Diabetes A sociation	24-hour di- etary recalls	Flavonols	0.11 (0.02–0.62)	Agent and the second
Ŋ	2018	2018 China	Cross-sectional	54.17±9.34	Both (62.9%)	9108	2635		FFQ	Total flavonoids	0.77 (0.66–0.9)	Sex, age, body mass index, drinking, smoking, and physical activitiv
Sebastian	2022	USA	Cross-sectional	47.7	Both (54.9%)	828 (males) 1009 (females)	233 382	guidelines	4-hour di- etary calls	Total flavonoids Total flavonoids	0.62 (0.53–0.71) 1.22 (0.92–1.61)	accurs, Race, poverty status, age, education level, smoking status, literacy, menopause status (women only), health status, and
Sohrab	2013 Iran	Iran	Cross-sectional	41.5±14.8	Both (56%)	2618	К Х	ATP III	FFQ	Tota Total wonoids Phenc ic acids Stilbenes	0.92 (0.7–1.22) 0.25 (0.19–0.34) 1.06 (0.81–1.4) 0.1 (0.69–1.22)	Age, gender, physical activity, smoking sta- activity, smoking sta- tus, educational levels, study center and total energy intake
Sohrab	2018 Iran	ue	Prospective cohort (6.2 years follow-up)	36.6±0.58	Both (56.6%)	1265	276	АТР III	ĘŦQ	Total polyphenols Phenolic acids Stilbenes Lignans	0.097 (0.63 v 1.31) 0.097 (0.63 v 1.31) 0.097 (0.65 v 1.31) 1.13 (0.81–1.64)	Age, gender, physical activity, total energy intake, total fiber in- take, total cholesterol intake and body mass index

Table 1	Table 1 (continued)										
Author	year Country	y Study design	Mean-age.y	Genr * (° omen)	Total sample s e	Cases with MetS	MetS definition	Dietary assessment	Exposure	Association (95% CI) for compari- son of extreme quantiles	Adjustment
Moslehi	2019 Iran	Prospective cohort (5.4 years follow-up)	33.8±12.4	Both (67.4%)		368	the Joint Interim guidelines	Q.	Total flavonoids Flavan-3-ols Favonols Flavones favanones Anthocyanins	0.5 (0.42-0.59) 0.48 (0.4-0.57) 0.66 (0.58-0.75) 0.76 (0.67-0.87) 0.78 (0.66-0.91) 0.85 (0.73-0.98) 0.9 (0.79-1.02)	Age, gender, baseline body mass index (BMI), BMI-change, and energy intake
Moo	2019 Korea	Prospective cohort (3.6 years folow-up)	61.0±10.2	Both (60%)	2204 (males) 3305 (females)	312 553	ANII	Q.	Isoflavones Isoflavones	0.93 (0.67–1.28) 0.98 (0.75–1.28)	Age, education, regu- lar exercise, current smoking, total energy intake, calcium intake, fiber intake, egg con- sumption, soda drink consumption and diet quality index
Yang	2012 Korea	Cross-sectional	50.5±11.4		1,827 (males) 2,918 (females)	541 688	АТР III АТР III	24-hou di- etary recalls	Flavan₌3-ols Fla i-3-ol	0.92 (0.62–1.34) 0.64 (0.45–0.91)	Age, body mass index, education, current smoking, regular ex- ercise, functional food use, intakes of total energy, fat, and fiber
Zujko	2018 Korea	Cross-sectional	50.08 ± 16.44	Both (55.11%)	2554 (males) 3136 (females)	1000 1028	IDF and AHA/NHLBI	24-hour di- etary recalls	Total polyphenols Total polyphenols	0.95	Age, body mass index, educational level, leisure time physical activity, smoking, and alcohol intake
IDF: Internai mass index	ational Diabetes Fer	IDF: International Diabetes Federation, ATP III: Adult Treatment Panel III report, AHA/NHLBI: The American Heart Association and the National Heart, Lung, and Blood Institute, Fl mass index	reatment Panel III	l report, AHA	/NHLBI: The A	merican H	leart Association and th	ie National Heart	Lung, and Blood Inst	food freq.	cyquestionnaire, BMI: body

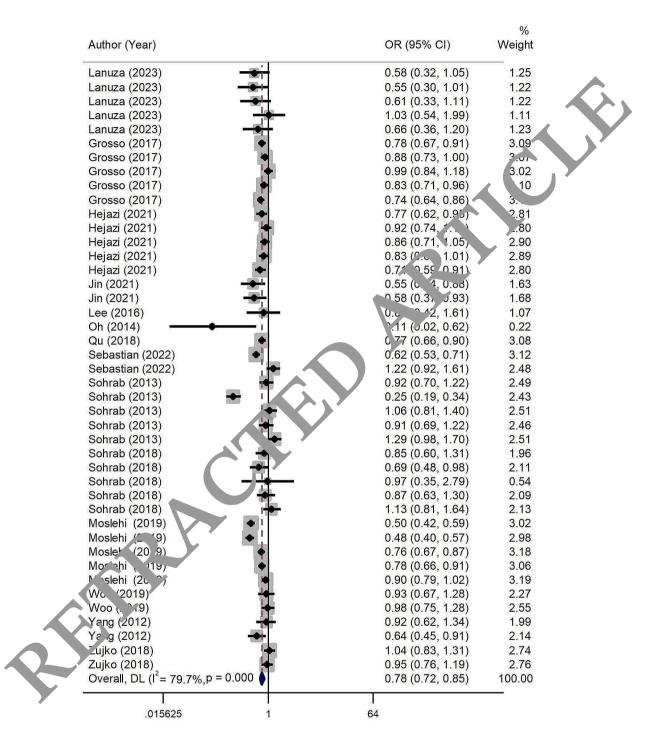


Fig. 2 Meta-analysis of the association between various polyphenolic compounds and risk of MetS. DL: DerSimonian and Laird random effects model

favanones (OR: 0.85; 95% CI: 0.73–0.98) showed protective relations to MetS susceptibility, but, no significant association was recognized for alkylphenols, tyrosol, flavanols, flavanones, and apigenin (Table 2).

Meta-regression and publication bias

Meta-regression analysis according to the age of participants detected that the relation of various polyphenolic compounds to MetS was not modified by the age (p=0.25) (Fig. 4). Furthermore, no evidence of publication bias was observed based on the Egger's test (t=-0.14, p=0.88) (Fig. 5).

			Test of	association	Heteroge	eneity	_	Pub lica- tion
Subgroup	Subgroups	Effect sizes (N)	OR	95%Cl	l ² (%)	Ρ	P value crusubgroup any vsis	bias P
	Overall (all polyphenolic compounds)	43 (14)	0.78	0.72–0.85	79.9	< 0.001		0.88
Study design	Prospective cohort	24 (6)	0.75	0.68-0.84	71.0	< 0.001	0.41	
	Cross-sectional	19 (8)	0.81	0.70-0.93	85.9	< 0.01		
Dietary assessment	FFQ	31 (9)	0.78	0.71-0.86	82.1	- 2001	0.87	
	24-hour recalls	12 (5)	0.77	0.60-0.98	74.2	< 0.001		
Definition of MetS	IDF	13 (4)	0.79	0.73-0.86	32.0	ι ⁻	0.02	
	The joint interim guidelines	12 (3)	0.75	0.65–0.86	0.80	< 0.0		
	ATP III	14 (4)	0.83	0.66-1.05	85	< 0.001		
	AHA-NHLBI	1 (1)	0.83	0.42-1.63		-		
	Korean diabetic association	1 (1)	0.11	0.02–0.61		-		
	IDF and AHA-NHLBI	2 (1)	0.99	0-95-1.17	0.0	0.57		
Polyphenol subclasses	Total polyphenols	6 (5)	0.86	0.75 0	45.8	0.10	0.008	0.84
	Total flavonoids	10 (9)	0.64	0.51-8	90.1	< 0.001		0.64
	Flavan-3-ols	3 (2)	0.64	3 0.94	79.6	0.007		0.22
	Isoflavones	4 (3)	0.8 +	0.75-0.93	0.0	0.47		0.08
	Lignans	4 (4)	1.5	0.87–1.28	40.7	0.16		0.82
	Stilbenes	(4,	0.8	0.76-0.97	0.0	0.88		0.08
	Phenolic acids	4 (4)	0.85	0.68-1.06	37.2	0.18		0.23
	Anthocyanins	2 (2)	0.91	0.81-1.01	0.0	0.86		-
	Flavones	2 (2)	0.79	0.71-0.89	5.7	0.30		-
	Flavonols	.2)	0.34	0.06-2.04	77.6	0.03		-
	Quercetin	2 (2)	0.63	0.43-0.93	0.0	0.32		-

Table 2 Meta-analysis of main results of all polyphenolic compounds and subgroups

OR, odd ratio; CI, confidence interval. N: numbe va stucies

Discussion

This meta-analysis dentifies that a higher dietary intake of total polyphenols, tilbenes, phenolic acids, and total flavonoids, with some or its subclasses including flavones, quercetin, it wan-3- ils, isoflavones, flavones, and quercetin, is accociantly with lower risk of MetS. No significant association was revealed for total polyphenols, phenolic acids, mans or other subclasses of flavonoids (anthocyanins, an flavonols) probably because of the small number of analyzed studies for these groups.

Edible plants and beverages provide generous amounts of polyphenols in the human diet [37]. Accumulating evidence from preclinical, clinical, and observational studies suggests that polyphenols might prevent or delay MetS development by improving blood pressure, blood glucose, body weight, and lipid metabolism [14, 18, 38]. Nevertheless, epidemiological studies have reported inconsistent findings for the relation of polyphenols to MetS. The cross-sectional study by Wisnuwardani et al. [39] showed no association between the intake of total polyphenols, polyphenol classes, individual polyphenols and MetS risk in adolescents. In agreement with our meta-analysis, the Framingham Offspring Study demonstrated that a high intake of phytoestrogens, a class of phenolic compounds, is linked to a favorable metabolic cardiovascular risk profile and MetS score in postmenopausal women [40]. Plasma phytoestrogen concentrations have been also shown to be negatively associated with MetS risk in the Chinese population [41]. However, Kim et al. [42] identified no significant differences in dietary intake of isoflavones, daidzein, and genistein between patients with and without MetS. In contrast, Popiolek-Kalisz el al [43]. measured differences in habitual consumption of flavonols between patients with MetS and healthy population and found that the intake of isorhamnetin, total flavonols, quercetin, and kaempferol is significantly lower in MetS patients, and a moderate reverse correlation was detected between total flavonols, kaempferol, quercetin, isorhamnetin and MetS stage. The controversy in the results of the previous studies may be due to differences in main food sources, dietary assessment method, study design, definition of MetS, and genetic background of various

subscr (rest) A) Total polyphends CP (DSC) Weight Verg (DS) Source (SS) D) Inflavours D(DSC) Normality Lancas (2023)				%				%
Lanca (bb) Corres (Corr) Corr (O = 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,	author (year)	A) Total polyphenols	OR (95% CI)	Weight	author (year)	F) Isoflavones	OR (95% CI)	
	Lanuza (2023)	*	0.58 (0.32, 1.05)	5.21	Hejazi (2021)		0.83 (0.68, 1.01)	29.08
Sorenta DC015) 0.22 (0.70, 1.22) 16.17 0.92 (0.70, 1.22) 16.17 Zupio (2016) 0.56 (0.60, 1.31) 0.02 0.56 (0.60, 1.31) 0.02 Zupio (2016) 0.56 (0.60, 1.10) 0.03 (0.76, 1.10) 0.03 0.04 (0.11) <t< td=""><td>Grosso (2017)</td><td></td><td>0.74 (0.64, 0.86)</td><td>28.00</td><td></td><td></td><td></td><td></td></t<>	Grosso (2017)		0.74 (0.64, 0.86)	28.00				
Schene (2016) 0.65 (0.60, 1.31) 10.27 Zujio (2016) 0.66 (0.61, 1.31) 20.50 Jujio (2016) 0.66 (0.75, 1.10) 20.50 Junca (2023) 0.56 (0.75, 1.10) 100.00 Jantara (2023) 0.56 (0.75, 1.10) 100.00 Junca (2023) 0.56 (0.30, 1.01) 6.45 Genes (0.17) 0.56 (0.30, 1.01) 6.46 Miler (rear) 0.57 (0.30, 1.01) 6.46 Grass (0.27) 0.56 (0.30, 1.01) 6.46 Miler (Cold) 0.57 (0.30, 0.01) 6.46 Grass (0.17) 0.58 (0.73, 1.00) 1.33 Schele (0.21) 0.57 (0.50, 0.01) 1.35 Schele (0.21) 0.52 (0.31, 0.21) 1.13 Schele (0.21) 0.67 (0.42, 0.59) 1.35 Schele (0.21) 0.67 (0.42, 0.59) 1.35 Schele (0.21) 0.67 (0.42, 0.59) 1.13 Modeli (0.21) 0.67 (0.42, 0.59) 1.12 Oreal (0.47, 1.90, 0.51, 0.51) 0.67 (0.50, 1.13) 0.58 (0.75, 1.09) Schele (0.21) 0.67 (0.50, 01) 0.67 (0.50, 01) Jactr (rear) 0.67 (0.50, 01) <td< td=""><td>Sohrab (2013)</td><td></td><td>0.92 (0.70, 1.22)</td><td>16.17</td><td></td><td></td><td></td><td></td></td<>	Sohrab (2013)		0.92 (0.70, 1.22)	16.17				
Lipic (2018) 1.04 (0.28, 1.51) 20.05 Zujic (2018) 0.95 (0.76, 1.19) 20.35 Overall, DL (* 44.8%, p = 0.100) 0.95 (0.76, 1.19) 20.35 Jathor (war) B) Total Revendes OR (65%, C) Weight Lanca (2023) 0.55 (0.76, 1.19) 0.55 (0.77, 1.10) 1.00 Lanca (2023) 0.55 (0.76, 1.10) 0.64 0.55 (0.77, 1.13) 0.55 (0.77, 1.13) Lip (221) 0.77 (0.22, 0.58) 0.83 (0.77, 1.08) 0.82 0.05 (0.57, 1.13) 0.00 (0.54, 1.28) 0.00 (0.54, 1.28) 1.00 (0.56, 0.57) Lip (222) 0.55 (0.77, 0.23) 0.62 (0.50, 0.71) 1.13 (0.81, 1.64) 2.057 0.000 (0.54, 1.28) 1.000 (0.56, 0.57) 1.13 (0.81, 1.64) 2.057 Lip (221) 0.55 (0.73, 0.28) 0.62 (0.50, 0.71) 1.14 (0.56, 0.57) 1.15 (0.57, 0.57) 0.000 (0.56, 1.28) 1.000 (0.56, 1.28) 1.000 (0.56, 1.28) 1.000 (0.56, 0.27) 1.01 (1.40, 0.51) 0.07 (0.55, 0.27) 1.02 (0.51, 0.51) 1.02 (0.54, 1.59) 1.55 (0.56, 0.57) 1.13 (0.51, 0.51) 0.000 (0.56, 0.28) 1.01 (1.40, 0.75) 0.55 (0.54, 0.27) 1.01 (1.40, 0.51) 0.07 (0.56, 0.27) 1.02 (0.56, 0.27) 1.05 (0.56, 0.27)	Sohrab (2018)		0.85 (0.60, 1.31)	10.27				
Zujic (2018) 0.85 (0.72, 1.19) 20.35 0.86 (0.72, 1.10) 100.00 2.3 4 % 1 1.68 (0.72, 1.10) 100.00 2.3 4 % 1 1.68 (0.72, 1.10) 100.00 0.98 (0.75, 1.10) 100.00 1.4mca (2023) 0.67 (0.95% CI) Weight 1.4mca (2023) 0.68 (0.73, 1.00) 1.4mca (2023) 0.98 (0.84, 1.18) 42.53 Solvab (2013) 0.57 (0.20, 1.9) 0.58 (0.30, 0.10) 6.45 Solvab (2013) 1.29 (0.08, 1.70) 22.53 1.4mca (2023) 0.77 (0.82, 0.99) 10.83 0.56 (0.80, 1.11) 1.29 (0.84, 1.18) 42.53 Solvab (2013) 0.77 (0.82, 0.99) 10.83 0.77 (0.82, 0.99) 1.29 (0.08, 1.70) 2.57 1.4 0.62 (0.50, 0.71) 1.141 2.29 (0.48, 1.99) 1.25 0.64 (0.51, 0.81) 10.05 Solvab (2013) 0.59 (0.42, 0.59) 1.22 (0.02, 1.81) 0.75 (0.87, 0.97) 0.83 (0.71, 0.49) 8.55 Solvab (2019) 0.59 (0.42, 0.59) 1.23 (0.42, 0.59) 1.23 (0.42, 0.59) 1.28 (0.42, 0.59) 0.58 (0.20, 0.57) 25 1 0.59 (0.50, 0.50)	Zujko (2018)		1.04 (0.83, 1.31)	20.00	overam, be (r = 0.070, p = 0.471)		0.04 (0.10,	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Zujko (2018)		0.95 (0.76, 1.19)	20.35	.6666667	1	1.5	Ň
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Overall, DL (l ² = 45.8%, p = 0.100)		0.86 (0.75, 1.00)	100.00	author (year)	G) Lignans	OR (S CI)	
author (year) b) Total flavenoids $OR (85K C)$ Weight Lanuza (2023) Lanuza (2023) $OP = 0.035, 1.20$ $OP = 0.035, 0.27, 1.035$ $OP = 0.035, 0.27, 1.035, 1.105$ $OP = 0.035, 0.27, 1.035, 1.105$ $OP = 0.035, 0.27, 1.035, 0.25, 0.27, 1.035, 0.25, 0.$.25	1	4	%				
Linnaz Greeso (2017) D.96 (0.84, 1.16) 4.25.5 Linnaz (2023) 0.55 (0.30, 1.01) 6.46 Sohrab (2013) 1.29 (0.96, 1.70) 27.59 Migaz (2021) 0.77 (0.62, 0.95) 10.83 Overall, DL (1 ² = 40.7%, p = 0.169) 1.06 (0.87, 1.28) 100000 Jun (2021) 0.58 (0.37, 0.03) 8.02 0.62 (0.53, 0.07) 1.41 3.55 Sohrab (2015) 0.22 (0.9, 0.34) 10.01 0.68 (0.44, 1.94) 3.55 Sohrab (2015) 0.62 (0.53, 0.71) 1.41 3.55 3.56 Modeleh (2016) 0.69 (0.42, 0.59) 1.123 0.68 (0.51, 0.51) 10.01 Jost (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	author (year)	D) T. (19	OR (95% CI)		Lanuza (2023)		0 8 (0.36, 1.20)	9.00
Lancz (223) Crosso (2017) Hejaz (2021) Cu (2018) Cu (2018) C		B) Total flavonoids		Weight	Grosso (2017)		0.99 (0.84, 1.18)	42.53
Grosso (2017) 0.88 (0.73, 1.00) 11.33 Sohrab (2018) 1.13 (0.81, 1.64) 20.57 Heijaz (2021) 0.77 (0.62, 0.85) 10.83 Overall, DL ($f = 40.7\%$, p = 0.168) 1.06 (0.87, 1.28) 10000 Grosso (2017) 0.58 (0.37, 0.93) 8.83 Overall, DL ($f = 40.7\%$, p = 0.168) 1.06 (0.87, 1.28) 10000 Grosso (2017) 0.62 (0.53, 0.71) 11.41 author (year) 10) Stilbenes OR (65%, C) Weight Sohrab (2018) 0.57 (0.62, 0.85) 11.23 0.68 (0.87, 1.28) 10.03 (0.54, 1.59) 3.58 Grosso (2017) 0.58 (0.48, 0.88) 9.24 0.50 (0.42, 0.59) 11.23 0.51 (0.54, 1.59) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.08) 0.58 (0.57, 1.28) 1.05 (0.58, 1.20) 1.15 (0.58, 1.20) 1.55 (0.58, 1.20) 0.58 (0.58, 1.20) 1.55 (0.58, 1.20) 1.55 (0.58, 1.20) 1.55 (0.58, 1.20) 1.55 (0.58, 1.20) 1.56 (0.53, 1.11) 0.58 (0.53, 1.11)	Lanuza (2023)	*	0.55 (0.30, 1.01)	6.45	Sohrab (2013)		1.29 (0.98, 1.70)	27.89
Hejad (2021) 0.77 (0.82, 0.95) 10.83 Jin (2021) 0.77 (0.82, 0.95) 10.83 Qu (2018) 0.77 (0.86, 0.90) 11.35 Schasten (2022) 0.27 (0.86, 0.90) 11.35 Schasten (2022) 0.22 (0.9, 1.61) 10.13 Schasten (2022) 0.25 (0.19, 0.34) 10.01 Schrab (2018) 0.56 (0.42, 0.58) 12.23 Overall, DL (² = 40.7%, p = 0.084) 0.88 (0.76, 0.89) 12.24 Woshel (2019) 0.50 (0.42, 0.59) 11.23 0.86 (0.48, 0.89) 9.24 Moshel (2019) 0.50 (0.42, 0.59) 11.25 0.84 (0.51, 0.81) 100.00 $\frac{1}{25}$ $\frac{1}{4}$ 0.88 (0.76, 0.97) 10.8 (0.67, 1.28) 10.8 (0.67, 0.27) author (year) C) Flavan-3-obs CR (95% C) Weight 0.88 (0.76, 0.97) 0.08 (0.76, 0.97) 10.9 (0.81, 1.22) 16.89 Overall, DL (² = 90.1%, p = 0.000) 0.88 (0.76, 0.97) 0.88 (0.76, 0.97) 0.08 (0.76, 0.97) 0.08 (0.76, 0.97) 10.000 Moshir (2019) 0.9 (9.68, C1) Weight 0.9 (9.68, C1) Weight 1.60 (0.61, 1.40) 1.60 (0.61, 0.43) 1.51 (0.60, 0.61, 0.43) <td></td> <td></td> <td></td> <td></td> <td>Sohrab (2018)</td> <td></td> <td>1.13 (0.81, 1.64)</td> <td>20.57</td>					Sohrab (2018)		1.13 (0.81, 1.64)	20.57
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hejazi (2021)			10.83	Overall, DL (l ² = 40.7%, p = 0.168)		1.06 (0.87, 1.28)	100.00
Gu (2018) 0.77 (0.66, 0.89) 11.35 58 Sebastian (2022) 0.62 (0.53, 0.71) 11.41 Sohrab (2013) 0.25 (0.19, 0.34) 10.01 Sohrab (2018) 0.25 (0.19, 0.34) 10.01 Overall, DL (² = 90.1%, p = 0.000) 0.64 (0.51, 0.81) 100.00 225 1 4 Author (year) C) Flavan-3-ob OR (65% Cl) Oreall, DL (² = 20.6%, p = 0.067) 0.84 (0.45, 0.97) 1.02 1 0.54 (0.40, 51) 1.00.00 225 1 4 Author (year) C) Flavan-3-ob OR (65% Cl) Weight Overall, DL (² = 20.6%, p = 0.067) 0.48 (0.47, 0.97) 1.00.00 3 0.55 (0.42, 0.59) 1.00.00 0.55 (0.1, 0.81) 0.00.00 4 0.55 (0.1, 0.81) 0.00.00 0.55 (0.1, 0.81) 0.08 (0.76, 0.57) 10.000 3 0.48 (0.47, 0.97) 1.02 1.02 (0.49, 0.97) 1.02 1.02 (0.49, 0.97) 1.02 Yang (2012) 0.48 (0.47, 0.97) 1.02 0.55 (0.1, 0.97) 0.06 (0.51, 0.49) 0.51 (7.1, 0.1, 0.90) 0.51 (7.1, 0.1, 0.90) 0.51 (7.	Jin (2021) —		0.58 (0.37, 0.93)	8.02				
Sebastian (2022) 1 22 (0.92, 1.61) 10.13 0.5 0.13 0.5 0.14 (0.61, 0.91) 1.03 (0.54, 1.99) 3.55 Sohrab (2013) 0.50 (0.42, 0.59) 11.23 0.55 (0.42, 0.59) 11.23 0.64 (0.51, 0.81) 100.00 0.68 (0.67, 0.97) 0.83 (0.71, 0.96) 66.35 Overall, DL (¹ = 90.1%, p = 0.000) 0.64 (0.51, 0.81) 100.00 0.64 (0.51, 0.81) 100.00 0.66 (0.68, 1.22) 18.59 Solvab (2012) 0.64 (0.51, 0.81) 100.00 0.68 (0.76, 0.97) 0.68 (0.76, 0.97) 100.00 Author (year) C) Flavan-3-ols OR (95% Cl) Weight .5 1 2 Moslehi (2019) 0.48 (0.47, 67) 3.00 .5 .5 1 2 Yang (2012) 0.51 (0.23, 1.14) 20.71 .5 1 2 % Author (year) D) Authocyanins OR (95% Cl) Weight .5 .5 .66 (0.81, 1.40) 33.18 Overall, DL (¹ = 20.5%, p = 0.684) 0.97 (0.82, 1.79) 4.15 .5 .68 (0.86, 0.81, 0.8) 100.00 3 0.91 (0.81, 1.01) 0.90 (0.73, 1.22) 74.98 .	Qu (2018)	-2-	0.77 (0.66, 0.90)	11.35		1 2		%
Sebastar (2022) 1 22 (0.92, 1.61) 10.13 Schrab (2013) 0.25 (0.19, 0.34) 10.01 Moslehi (2019) 0.50 (0.42, 0.59) 11.23 Overall, D. (2 = 90.1%, p = 0.000) 0.64 (0.51, 0.81) 100.00 25 1 4 Sohrab (2013) 0.91 (0.84, 1.09) 3.55 Overall, D. (2 = 90.1%, p = 0.000) 0.64 (0.51, 0.81) 100.00 25 1 4 Author (year) C) Flavan-3-ols OR (65% Cl) Weight Also (212) 0.64 (0.43, 1.34) 23.7 Yang (2012) 0.64 (0.43, 1.34) 23.7 Sohrab (2018) 0.67 (0.53, 1.14) 25.91 Overall, D. (2 = 79.5%, p = 0.007 0.62 (0.74, 1.14) 25.91 Author (year) D) Anthocyanins OR (65%, Cl) Weight Hejazi (2021) 0.91 (0.81, 1.01) 100.00 .75 1 1.33333 % author (year) D) Anthocyanins 0.91 (0.81, 1.01) 100.00 .75 1 1.33333 % 25 1 4 Sohrab (2018) 0.91 (0.81, 1.01) </td <td>Sebastian (2022)</td> <td></td> <td>0.62 (0.53, 0.71)</td> <td>11.41</td> <td>author (year)</td> <td>H) Stilbenes</td> <td>OR (95% CI)</td> <td>Weight</td>	Sebastian (2022)		0.62 (0.53, 0.71)	11.41	author (year)	H) Stilbenes	OR (95% CI)	Weight
Sohrab (2018) 0.69 (0.48, 0.98) 9.24 1.63 (0.41, 1.99) 3.35 Moslehi (2019) 0.50 (0.42, 0.59) 11.23 0.64 (0.51, 0.81) 100.00 25 1 4 0.68 (0.42, 0.59) 11.23 author (year) C) Flavan-3-ols OR (95% C) Weight 0.51 (0.51, 1.39) 15.5 Moslehi (2019) 0.48 (0.97, 57) 0.48 (0.97, 57) 0.48 (0.97, 57) 0.48 (0.97, 57) Yang (2012) 0.97 (625, 1.34) 9.72 5 1 2 Yang (2012) 0.97 (625, 1.34) 9.73 0.64 (0.97, 57) 0.64 (0.97, 57) 0.64 (0.97, 57) Yang (2012) 0.97 (625, 1.34) 9.72 5 1 2 % author (year) D) Anthocyanins OR (95% () Weight 0.61 (0.33, 1.11) 10.89 Gorsso (2017) 0.76 (0.67, 0.91) 51.77 50 rab (2013) 0.61 (0.33, 1.11) 10.89 Ocreati, DL (² = 79.6%, p = 0.084) 0.97 (0.55, 279) 4.15 0.50 (0.81, 1.40) 33.18 othor (year) D) Anthocyanins OR (95% () Weight 0.51 (0.11, 100) 0.51 (0.21, 100) 0.55	Sebastian (2022)		1.22 (0.92, 1.61)	10.13		Tij Stubenes		
Moslehi (2019) $0.50 (0.42, 0.59)$ 11.23 $0.50 (0.42, 0.59)$ 11.23 Overall, DL (2 = 90.1%, p = 0.000) $0.64 (0.51, 0.81)$ 100.00 $0.64 (0.51, 0.81)$ 0.000 author (year) C) Flavan-3-ols OR (95% Cl) Weight $0.64 (0.51, 0.81)$ 0.000 Moslehi (2019) $0.44 (0.51, 0.81)$ 0.000 $0.86 (0.76, 0.97)$ $0.86 (0.76, 0.97)$ Yang (2012) $0.44 (0.45, 0.57)$ $0.64 (0.33, 0.11)$ 0.50 $0.61 (0.33, 1.11)$ 100.89 Yang (2012) $0.91 (0.61, 1.22)$ $0.61 (0.33, 1.11)$ $0.80 (0.76, 0.97)$ $0.61 (0.33, 1.11)$ 10.89 Weight $0.91 (0.62, 1.22)$ $0.93 (0.62, 1.34)$ 29.7 $64 (0.90 (0.91)$ 31.30 Overall, DL (2 = 79.6%, p = 0.007 $0.93 (0.78, 1.02)$ 74.09 $0.61 (0.33, 1.11)$ 10.89 Moslehi (2019) $0.91 (0.81, 1.01)$ $0.92 (0.74, 1.14)$ 25.91 4.5 $0.97 (0.35, 2.79)$ 4.15 Moslehi (2019) $0.92 (0.74, 1.14)$ 25.91 4.5 $0.61 (0.33, 1.11)$ $0.80 (0.79, 1.02)$ 74.09 $0.91 (0.81, 1.00)$ $0.97 (0.35, 2.79)$ 4.15 $0.$	Sohrab (2013)		0.25 (0.19, 0.34)	10.01	Lanuza (2023)	*	1.03 (0.54, 1.99)	3.55
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Fig. 3 Meta-analysis of the association between various polyphenol subclasses and risk of MetS. DL: DerSimonian and Laird random effects model

studied popul, ior.s. The present meta-analysis reduced the in onsistencies by increasing the pooled sample size a crecognized a significant protection of polyphenols against MetS.

This meta-analysis found that the majority of polyphenol compounds were significantly related to decreased odds of MetS, but no association was found for total polyphenols, phenolic acids, lignans, anthocyanins, and flavonols. These differences may be due to the multifaceted nature of MetS, variations in the bioavailability and metabolism of polyphenols, and the complex interactions between different polyphenol compounds and metabolic pathways [44]. The complex nature of MetS involves multiple interconnected factors such as obesity, insulin resistance, hypertension, and dyslipidemia [1, 2]. Different polyphenol compounds have different mechanisms of action and may have varying effects on these components, leading to a lack of uniform association with MetS [45]. For example, some polyphenols may have a greater impact on blood glucose levels, while others may be more effective in reducing blood pressure or body weight [44]. In addition, these compounds are presented in a wide variety of foods, and the specific foods and amounts consumed by the people may have varied widely, which could have affected the results [9]. The observed differences may also be due to the fact that the bioavailability and metabolism of polyphenols are different [46]. The protective functions of polyphenol compounds may only become effective through frequent and sustained intake over the long term, as part of a healthy and diversified diet [27]. Additionally, the composition of polyphenolrich foods is complex and they may have additive or

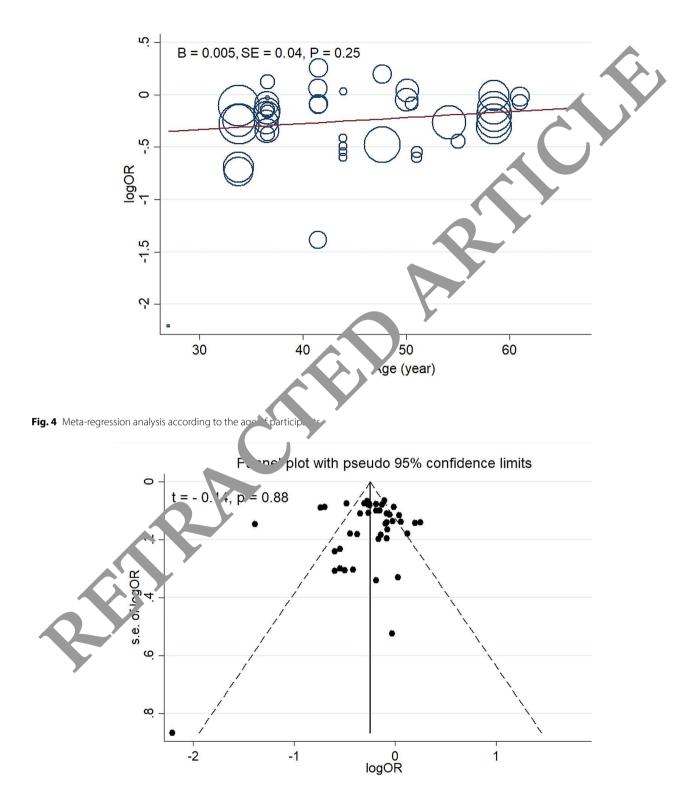


Fig. 5 Funnel plot for publication bias

synergistic effects, making it challenging to isolate their individual effects on MetS [44]. This suggests that the association between polyphenols and MetS may not be universally observed and could vary based on the specific polyphenol compounds and their interactions with the complex metabolic pathways involved in MetS.

Overall, the biological mechanisms of various polyphenols in preventing MetS are multifaceted and involve modulation of metabolic parameters, regulation of gene expression, modulation of gut microbiota, anti-inflammatory effects, improvement of insulin resistance, and antioxidant effects [15, 47]. Flavonoids can significantly improve several metabolic parameters, such as lipid profile, blood pressure, and blood glucose levels, which are individual components of MetS [18]. Polyphenols have been found to exert regulatory effects on gene expression in metabolic pathways, including glucose and lipid metabolism, and energy expenditure. This can lead to improved insulin sensitivity and glucose uptake, which are important for preventing MetS [27]. They can also reduce oxidative stress and inflammation by affecting the genes involved in the controlling of the pro-inflammatory nuclear factor kappa-lightchain-enhancer of activate a B cells (NF-K β) and the anti-inflammatory nuclear κ to erythroid 2-related factor 2 (Nrf2) pathways, which turn can scavenge free radicals, inhibit lipid *r* erc idation and downregulate the pro-inflammatory protein, such as toll-like receptor 4 (TLR4) [22], ir terleukin 1b (IL-1b), and IL-6, and tumor necrosis factor-alphe (TNF- α) [48]. Lastly, it has been well-identified a polyphenol intake might influence gut microb. which through the modulation of inflammation nay affect CVD risk biomarkers [49]. These 'ndi gs hay important implications for public healt' sec is to provide evidence-based recommendations for diet. / interventions targeting MetS prevention. Acordingly, adherence to a diet with high conten's of polyp, enol-rich foods such as vegetables, nuts, ic.s, fluits, virgin olive oil, and seasonings with aromatic plants are recommended as a potential app back to makage MetS.

To the best of our knowledge, this is the first metaanalysis avestigating the relationship between dietary intake of polyphenols and their main subclasses to MetS. This study has several strengths, as (i) it comprehensively analyzed various polyphenolic compounds/subclasses with a relatively high sample size for the included studies; (ii) no time or language limitations were considered for the search and no evidence of publication bias was detected; (iii) the reliability of the findings was confirmed by the sensitivity analysis. However, some limitations of the present analysis should be acknowledged. First, there was significant heterogeneity in some analyzes. We applied a random effects model for the analysis to reduce the effect of the observed heterogeneity on the pooled effect sizes. Moreover, a stratified analysis was done to detect the possible sources of the heterogeneity. Subgroup analysis revealed that the identified heterogeneity was explainable by differences in polyphenol successes and the definition used for the diagnosis of M/ S. Second, analyzed studies were observational, and cau -effect association cannot be fully assessed; the efore, the usults might suffer from reverse causation an unm asured/ residual confounding. Neverthele s, all inclu .d publications controlled the results for the potential covariates. Third, exposure assessmer, vas , "f med using the retrospective dietary questionners, which are at risk of recall and measurement iases. Lestly, the small number of the included studies for vbclasses of polyphenols did not allow for cor.du, ing sub_roup analyses for individual was conducted for soverall analysis, which included all polyphencus mpounds.

Conclusion -

In schmary, the present meta-analysis proposes that olyphenol intake has the potential to reduce the odds on MetS. Plant-based diets with food items rich in polyphenols may represent a potential preventive approach against the rising trend of MetS. Additional studies, particularly clinical trials and prospective studies are required to demonstrate these findings.

Abbreviations

MetS	Metabolic syndrome
RR	relative risk
OR	odds ratio
HR	hazard ratio
95%CI	95% confidence interval
CVD	cardiovascular disease
NOS	Newcastle-Ottawa Scale
FFQ	food-frequency questionnaire
IDF	International Diabetes Federation
ATP III	Adult Treatment Panel III report
AHA/NHLBI	The American Heart Association and the National Heart, Lung,
	and Blood Institute
TLR4	toll-like receptor 4
IL-1b	interleukin 1b
IL-6	interleukin – 6
TNF- α	tumor necrosis factor-alpha

Supplementary Information

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Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
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Author contributions

Pushpamala Ramaiah: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Investigation. Kamilya Jamel Baljon: Investigation, Writing - original draft, Data curation. Ahmed Hjazi: Investigation, Methodology, Writing - original draft. Maytham T. Qasim: Validation, Methodology, Writing - review & editing. Omar Abdulwahid Salih Al-ani: Methodology, Validation, Writing - review & editing. Shad Imad: Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Project administration. Beneen M. Hussien: Conceptualization, Resources, Writing – original draft. Ali Alsaalamy: Methodology, Validation, Writing – review & editing, Resources, Validation. Nazila Garousi: Project administration, Formal analysis, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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