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SYSTEMATIC REVIEWS AND META-ANALYSES

Flavanols are potential anti-obesity agents, a systematic review and meta-analysis of controlled clinical trials

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Body fat percentage

Abstract *Background:* The anti-obesity potential of flavonoids has been shown by animal and human studies. In this meta-analysis, we systematically reviewed controlled clinical trials and quantified the effects of flavonoids and flavonoid subclasses on obesity-related anthropometric measures.

Methods and results: PubMed, EMBASE, Scopus, Web of Science, and ProQuest databases were searched to identify trials examining the effect of flavonoids on body mass index (BMI), waist circumference, and body fat percentage. Fifty eight trials passed the eligibility process. Analysis endpoints were calculated as the mean difference between baseline and post-treatment. Flavonoids were in subclasses of flavanols, flavonols, isoflavones, flavanones, anthocyanins, and proanthocyanidins. They were mostly in the form of supplements and dosages varying from 40 to 1300 mg/day. Among flavonoid subclasses, flavanols showed potential for decreasing BMI, in the overall population (mean difference (MD) = −0.28 kg/m^2, P = 0.04; n = 21) and in the subgroups of Asians (MD = −0.42 kg/m^2; P = 0.046; n = 13), ages < 50 years (MD = −0.50 kg/m^2; P = 0.008; n = 14), BMI ≥ 25 kg/m^2 (MD = −0.30 kg/m^2; P = 0.049; n = 15), and at doses ≥ 500 mg/day (MD = −0.36 kg/m^2; P = 0.049; n = 12). Isoflavones also decreased BMI of non-Asian populations (MD = −0.26 kg/m^2; P = 0.035; n = 13) and doses ≥ 75 mg/day (MD = −0.34 kg/m^2; P = 0.027; n = 8). In the overall assessment, flavanols also decreased waist circumference (MD = −0.60 cm; P = 0.02; n = 18) but had no significant effect on body fat percentage. The available trials did not reveal significant effects from flavonols, flavanones, and anthocyanins on the specified anthropometric measures.

Conclusions: Overall results of this meta-analysis showed that flavanols have potential against obesity.

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Introduction

Obesity is a global health problem [1] that affects all age and gender groups in both developing and developed countries [2]. In the past three decades, the global prevalence of overweight and obesity has increased from 29% to 38% [2]. The high rate of obesity causes extensive morbidity and mortality and inflicts a high economic burden on nations [3]. The relationship between obesity and the occurrence or progression of a variety of diseases including cardiovascular diseases [4], insulin resistance and diabetes [5], non-alcoholic fatty liver disease [6], gallstone disease [7], pancreatitis [7], esophageal reflux [8], inflammatory bowel disease [9], chronic kidney disease [10], polycystic ovary syndrome [11], neurological diseases [12], and various types of cancer [13] has been the focus of recent investigations. Most of these morbidities are caused by chronic oxidative stress and low-grade inflammation resulting from excessive adipose tissue [14].

Flavonoids are a widespread group of plant polyphenols which share in the basic phenyl-benzopyran structure [15]. Flavonoids are divided into main subclasses of flavanols, including flavanol monomers (flavan-3-ols) and flavanol polymers (called proanthocyanidins), flavonols, flavanones, flavones, isoflavones, and anthocyanins [16]. Well-known for their antioxidant activity, flavonoids have many other capabilities, including anti-inflammatory, vasorelaxant, anticoagulant, cardio protective [15,17], anti-obesity and anti-diabetic [18], chemoprotective [19], neuroprotective [20], and antidepressant [21] properties that are gradually being elucidated.

The anti-obesity potential of flavonoids has been acknowledged in the last decade. A 14-year cohort on 4280 males and females aged 55–69 years showed that females with the highest flavonoid intake had a lower body mass index (BMI) elevation over time than females with the lowest flavonoid intake [22]. In addition, a cross sectional study on 2734 female twins indicated that higher habitual intake of anthocyanins, flavonols, flavanols, and proanthocyanidins was associated with lower fat mass [23]. Nevertheless, due to an abundance of confounding factors that cannot be easily controlled and limitations that exist in dietary assessment methods and food composition tables, the results of observational studies need to be confirmed by intervention trials. However, a common weak point of clinical trials is low sample size which reduces the power of studies and necessitates caution in interpreting results. On the other hand, clinical trials that investigated the effect of flavonoids on weight have produced contradictory results. Hence, a meta-analysis may lead to a better conclusion on this issue. This systematic review and meta-analysis was performed on controlled clinical trials to assess the effects of flavonoids and flavonoid subclasses on obesity-related anthropometric parameters, including BMI, waist circumference, and body fat percentage in adults.

Methods

Search strategy

PubMed, Embase, Scopus, Web of Science, and ProQuest were searched to identify controlled clinical trials examining the effect of flavonoids on BMI, waist circumference, and body fat percentage on apparently healthy adults through August 2017. The search was performed by a single investigator (SG). Search terms included: flavonoids, flavonols, flavanols, flavan-3-ols, flavanones, flavones, isoflavones, anthocyanins, proanthocyanidins, anthocyanidin, cyanidin, delphinidin, malvidin, pelargonidin, catechins, epicatechin, epigallocatechin, gallocatechin, theaflavins, thearubigins, quercetin, kaempferol, myricetin, isorhamnetin, galangin, morin, fisetin, luteolin, apigenin, hesperetin, naringenin, naringin, hesperidin, isoflavonoid, genistein, and daidzein. Search terms for obesity-related anthropometric measures included: obesity, obese, overweight, weight, “body mass index”, BMI, waist, “waist circumference”, adipose, abdominal fat, fat, and fat mass. There was no limitation on date and language in the search.

Data extraction and quality assessment

Two authors (MM and ZG) independently screened the articles by title and abstract and assessed the full-texts to qualify for eligibility. Disagreements were resolved through discussion (MM, ZG, and MA). Following information was extracted from each article: first author’s name, year of publication, location of study, study design, sample size, number of participants in case and control groups, age and gender, health status, BMI, intervention duration, type, dosage, and form of flavonoids, and means and standard deviations (or standard errors) of the anthropometric measurements (BMI, waist circumference, and body fat percentage). Quality of articles was determined by Jadad scale based on randomization (0–2 points), blinding (0–2 points), and a statement on dropouts (0–1 point) [24].

Study selection

Controlled clinical trials were included in the analysis if they met the following criteria: 1) human clinical trials; 2) participants’ age of >18 years; 3) consumption of flavonoids in the form of supplements or foods with specified amounts of flavonoids and devoid of other active ingredients; 4) intervention length of ≥ 3 weeks; 5) sufficient information regarding the mean and standard deviation (or standard error) for baseline and final values or the net change of at least one of the outcomes (BMI, waist circumference, and body fat percentage). Trials were excluded if there was 1) insufficient information for the dosage, type of flavonoids used, and duration of the intervention; 2) using a mixture of different flavonoids instead of using a single type; 3) no appropriate placebo or

control group; 4) including participants with weight-affecting diseases, such as diabetes mellitus, or medications, such as corticosteroids; 5) weight-affecting ingredients in the supplements if the corresponding placebo did not contain the same compounds; 6) repeated publications.

Statistical analyses

All analyses were performed with STATA software version 13.0 (StataCorp, Texas, USA). Analysis endpoints were calculated as the mean difference between baseline and final measurement. Also, standard deviation of the mean change was calculated by pooled standard deviation. Standard error was calculated from standard deviation divided by square root of the sample size ($\sqrt{n}$). Results were presented as mean difference (MD) with 95% confidence interval [25]. The percentage of heterogeneity between trials was assessed by using I^2 statistics. Because of differences in the treatment effect between studies, the random effect model was applied to assume a random sample from all studies for estimation of the pooled effect [26]. The visual inspection of funnel plots and Egger's regression test was used to explore potential publication bias [27]. The trim-and-fill analysis was employed to adjust any significant publication bias detected. Sensitivity analysis was conducted by using One Study Removed method to assess the extent to which analyses might depend on a particular study.

Subgroup analysis for all flavonoids was performed based on the type of flavonoids (flavanols, isoflavones, flavonols, anthocyanins, flavanones, and proanthocyanidins). Subgroup analysis for flavanols was conducted based on age (<50 *vs.* ≥ 50 years), BMI (<25 *vs.* ≥ 25 kg/m^2), study location (Asia *vs.* other continents), and treatment dose (<500 *vs.* ≥ 500 mg/day). Subgroup analysis for isoflavones was performed based on BMI (<25 *vs.* ≥ 25 kg/m^2), study location (Asia *vs.* other continents), and treatment dose (<75 *vs.* ≥ 75 mg/day). Isoflavones were not stratified based on age because all but one of isoflavone trials was conducted on individuals older than 50 years. The age of 50 years was chosen because it is the midpoint between adulthood and late adulthood. BMI was categorized based on the cutoff point for overweight/obesity. The basis for dose categorization was the median. A P value of <0.05 was considered as statistically significant.

Results

Search and study selection

The result of the study selection process is shown in Fig. 1. We identified 8936 articles from the literature search. Through hand searching and reference checking of included publications and review and meta-analysis articles, 4 trials were identified for detailed evaluation. One hundred and twenty eight trials were identified for assessing inclusion criteria, and after complete assessment, 58 trials were included in the final systematic review and meta-analysis.

Study characteristics

The main characteristics of the selected trials are presented in Table 1. Flavanols and isoflavones with 24 [28–51] and 18 [52–69] trials, respectively, comprised the largest number of trials, followed by flavonols with 6 trials [70–73], anthocyanins with 5 trials [74–78], flavanones with 4 trials [79–82], and proanthocyanidins with 1 trial [83]. The studies were conducted in different parts of the world from Asia [29–31,36–38,40–45,47,51,58,61,67,69,70,73,74,77,81–83], to Europe [32,39,46,48,52–54,56,57,62,68,71,75,78–80], Australia [33,35,49,76], and America [28,34,50,55,59,60,63–66,72]. But flavanol trials were mostly conducted in Asia [29–31,36–38,40–45,47,51]. Participants were either healthy normal weight [31,35,36,39,41–43,45–47,53–55,57,61,63–69,71,78,79,83], overweight/obese [28–30,32–34,37,38,40,44,48–52,59,60,62,70,72,73,75–77,80,81], or with medical conditions not affecting weight [56,58,74,82].

A total of 4341 subjects aged 19–70 years were included in the meta-analysis from all 58 trials. Duration of the intervention ranged from 3 weeks to 36 months. Daily dosage ranged from 40 to 1344 mg (flavanols 128 mg to 1344 mg, isoflavones 40 mg to 300 mg, flavonols 100 mg to 1000 mg, anthocyanins 160 mg to 500 mg, flavanones 210 mg to 600 mg, and proanthocyanidins 400 mg) which was received in various forms including tablet, capsule, or drinks. Of 58 articles included in the meta-analysis, 53, 31, and 16 articles reported the effect of flavonoids on BMI, waist circumferences, and body fat percentage, respectively. Two studies were used in the analysis twice: one had two distinct intervention groups with different apolipoprotein E isoforms [71] and the other evaluated the effect of quercetin separately on hypertensive and prehypertensive subjects [72]. Based on Jadad scoring system, 52 and 6 trials were scored with ≥ 3 (high quality) and ≤ 2 points (low quality), respectively.

Effect of flavonoid subgroups on BMI

There was an overall significant effect from all flavonoids on BMI (mean difference (MD) = -0.23 kg/m^2; 95% CI: -0.37, -0.10 kg/m^2; P = 0.001) (Fig. 2). Among the subclasses of flavonoids, flavanols showed a significant reduction in BMI (MD = -0.28 kg/m^2; 95% CI: -0.55, -0.01 kg/m^2; P = 0.04). There was also a trend towards lower BMI in isoflavone subclass (MD = -0.16 kg/m^2; 95% CI: -0.38, 0.06 kg/m^2; P = 0.15). Flavonols, anthocyanins, and flavanones did not show an effect. There was no heterogeneity between trials in the overall effect (I^2 = 0.0%, P = 0.9) or different flavonoid subclasses (I^2 = 0.0–0.3%, P = 0.1–1.0).

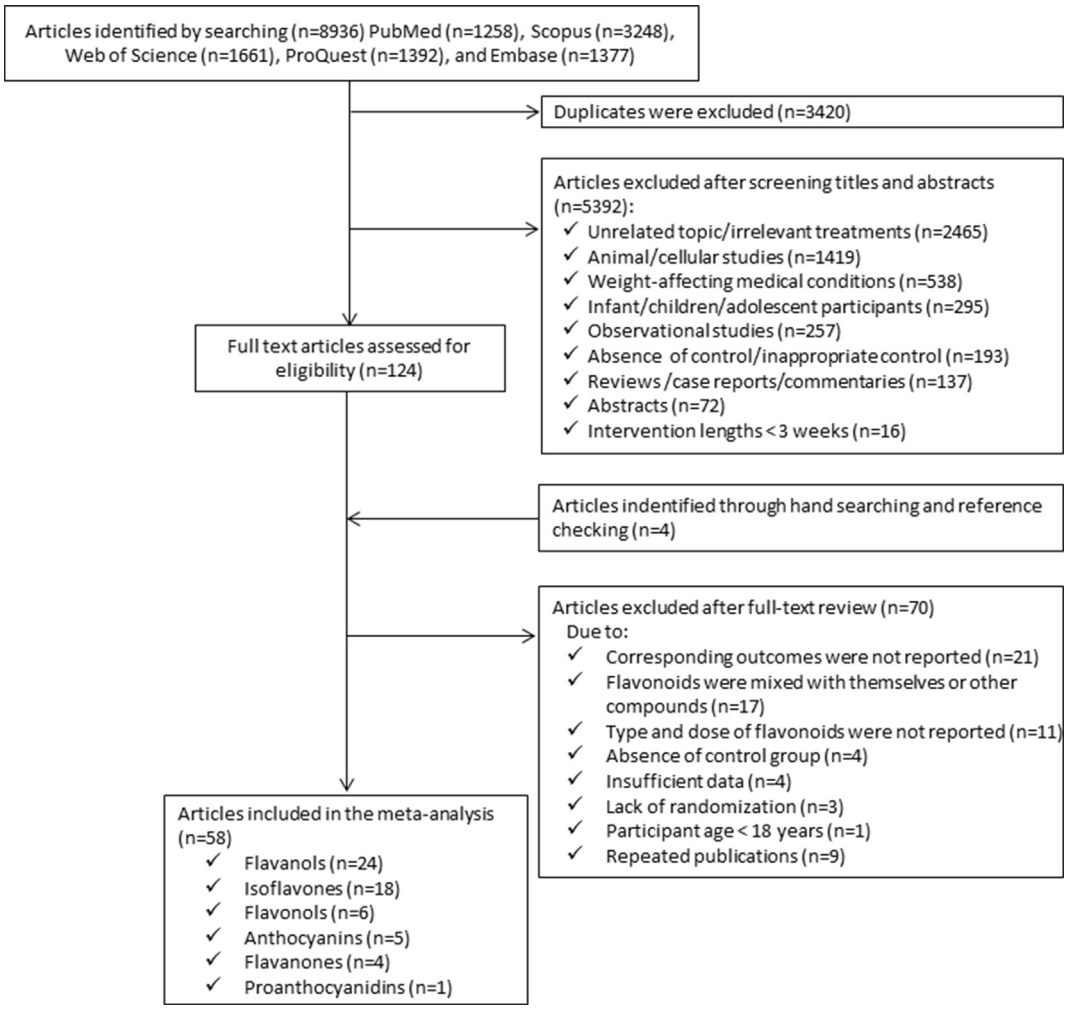

Figure 1 Flowchart of the study selection process.

Subgroup analysis of the effect of flavanols on BMI based on age, BMI, study location, and dosage

Flavanols showed significant effect on BMI in subgroups of ages <50 years (MD = −0.50 kg/m^2; 95% CI: −0.87, −0.13 kg/m^2; P = 0.008), BMI ≥ 25 kg/m^2 (MD = −0.30 kg/m^2; 95% CI: −0.60, −0.00 kg/m^2; P = 0.049), studies conducted in Asia (MD = −0.42 kg/m^2; 95% CI: −0.82, −0.01 kg/m^2; P = 0.046), and dosages ≥ 500 mg/day (MD = −0.36 kg/m^2; 95% CI: −0.72, −0.00 kg/m^2; P = 0.049) (Fig. 3-A–D). No significant heterogeneity was found in any of the stated subgroups.

Subgroup analysis of the effect of isoflavones on BMI based on BMI, study location, and dosage

Although isoflavones did not show a significant overall effect on BMI, in subgroups of studies conducted in non-Asian countries (MD = −0.26 kg/m^2; 95% CI: −0.51, −0.02 kg/m^2; P = 0.035) and doses ≥ 75 mg/day (MD = −0.34 kg/m^2; 95% CI: −0.64, −0.04 kg/m^2; P = 0.027) they demonstrated significant effect decreasing BMI (Table 2). No significant effect was observed in BMI subgroups. The age subgroup was not performed because only one study was conducted on subjects younger than 50 years. No heterogeneity was observed in any of the subgroups except for BMI <25 kg/m^2 which showed a 71.0% heterogeneity (P = 0.004).

Effect of flavonoid subgroups on waist circumference and body fat percentage

Flavonoids showed a significant effect decreasing waist circumference (MD = −0.53 cm; 95% CI: −0.87, −0.19 cm; P = 0.002) (Table 3). Among flavonoid subgroups, only flavanols demonstrated a significant effect (MD = −0.60 cm; 95% CI: −1.11, −0.08 cm; P = 0.02). No effect was observed from flavonoids in total or in flavonoid subgroups on body fat percentage. There was no heterogeneity between results of different studies overall or in any of the subgroups.

Table 1 Characteristics of the clinical trials included in the meta-analysis of the effect of Effect of flavonoids and flavonoid subclasses on obesity-related anthropometric measures.

First author (year) (ref)	Country	Study design	Total N (case/control) (sex)	Population	Age (y)[a]	BMI (kg/m^2)[b]	Intervention duration	Flavonoid (mg)	Flavonoid Subclasses	Flavonoid Form	Outcomes	Results	Quality score
Stendell-Hollis et al. (2010) [28]	USA	P—B—R	23/16 (M/F)	Overweight/obese	57.1	30.1	6 months	Green tea EGCG (128 mg)	Flavanols	Tea	BMI, WC, BF	No change	5
Hsu et al. (2008) [29]	Taiwan	P—B—R	41/37 (M/F)	Obese	43.4	30.9	3 months	Green tea catechins (204 mg)	Flavanols	Capsule	BMI, WC	No change	5
Kobayashi et al. (2016) [30]	Japan	P—B—R	42/40 (M/F)	Moderately obese	44.7	27.4	3 months	Green tea catechins (245.5 mg)	Flavanols	Tea	BMI, WC, BF	No change	4
Sone et al. (2011) [31]	Japan	P—B—R	25/26 (M/F)	Healthy	45.7	24.6	2 months	Green tea catechins (300 mg)	Flavanols	Beverage	BMI, WC	No change	5
Mielgo-Ayuso et al. (2014) [32]	Spain	P—B—R	43/40 (F)	Obese	19—49	34	3 months	Green tea EGCG (300 mg)	Flavanols	Supplement	BMI, WC	No change	5
Hill et al. (2007) [33]	Australia	P—R	19/19 (F)	Overweight/obese	45—70	31.1	3 months	Green tea EGCG (300 mg)	Flavanols	Capsule	BMI, WC, BF	No change	2
Basu et al. (2011) [34]	USA	P—B—R	13/12 (M/F)	Metabolic syndrome	42.5	36.1	2 months	Green tea catechins (400 mg)	Flavanols	Tea	WC	No change	4
Bohn et al. (2014) [35]	Australia	P—B—R	38/39 (M/F)	Healthy	55.7	24.9	6 months	Green tea catechins (429 mg)	Flavanols	Tea	BMI, WC	No change	5
Yoneda et al. (2009) [36]	Japan	P	77/57 (M)	Healthy	43.6	24.5	12 months	Green tea catechins (462 mg)	Flavanols	Beverage	BMI, WC	BMI changed	2
Nagao et al. (2007) [37]	Japan	P—B—R	123/117 (M/F)	Abdominally obese[c]	41.7	26.8	3 months	Green tea catechins (487 mg)	Flavanols	Tea	BMI, WC, BF	Changed	4
Pezeshki et al. (2016) [38]	Iran	P—B—R	35/36 (M/F)	Non-alcoholic fatty liver disease	20—50	34.3	3 months	Green tea catechins (500 mg)	Flavanols	Capsule	BMI	Changed	5
Roberts et al. (2015) [39]	UK	P—B—R	7/7 (M)	Healthy	21.4	—	1 month	Green tea catechins (521.2 mg)	Flavanols	Capsule	BF	Changed	3
Zhang et al. (2012) [40]	China	P—B—R	51/53 (M/F)	Abdominally obese[c]	45.0	30.6	3 months	Green tea catechins (522 mg)	Flavanols	Tea	BMI, BF	No change	5
Nirengi et al. (2016) [41]	Japan	P—B—R	10/11 (F)	Healthy	20.7	21	3 months	Green tea catechins (540 mg)	Flavanols	Beverage	BMI, BF	No change	4
Miyazaki et al. (2013) [42]	Japan	P—B—R	25/25 (M/F)	Healthy	69.1	22.7	3.5 months	Green tea catechins (542 mg)	Flavanols	Tea	BMI, WC	No change	3
Ota et al. (2016) [43]	Japan	C—B—R	14 (M)	Healthy	33.9	22.4	2 months	Green tea catechins (570 mg)	Flavanols	Tea	BF	No change	4
Fukuzawa et al. (2014) [44]	Japan	P—R	26/12 (M/F)	Non-alcoholic steatohepatitis	51.2	29.9	6 months	Green tea catechins (600 mg)	Flavanols	Tablet	BMI, WC	Changed	2
Kajimoto et al. (2005) [45]	Japan	P—B	64/66 (M/F)	Healthy	43.0	24.8	3 months	Green tea catechins (624 mg)	Flavanols	Tea	BMI, WC	Changed	2
Frank et al. (2009) [46]	UK	P—B—R	17/16 (M)	Healthy	40.9	26.1	3 weeks	Green tea catechins (625 mg)	Flavanols	Capsule	BMI	No change	3
Nagao et al. (2005) [47]	Japan	P—B	17/18 (M)	Healthy	24—46	25	3 months	Green tea catechins (668 mg)	Flavanols	Tea	BMI, WC	Changed	3
Brown et al. (2009) [48]	UK	P—B—R	42/46 (M)	Overweight/obese	51.4	31.1	2 months	Green tea EGCG (800 mg)	Flavanols	Capsule	BMI, WC, BF	No change	4

(*continued on next page*)

Table 1 (*continued*)

First author (year) (ref)	Country	Study design	Total N (case/control) (sex)	Population	Age (y)[a]	BMI (kg/m^2)[b]	Intervention duration	Flavonoid (mg)	Flavonoid Subclasses	Flavonoid Form	Outcomes	Results	Quality score
Davison et al. (2008) [49]	Australia	P–B–R	12/11 (M/F)	Overweight/obese	44.9	33.7	3 months	Cocoa flavanols (866 mg)	Flavanols	Cocoa drink	BMI, WC, BF	No change	5
Dostal et al. (2016) [50]	USA	P–B–R	117/120 (F)	Overweight/obese	60.8	28.2	12 months	Green tea catechins (1315 mg)	Flavanols	Capsule	BMI, WC	No change	5
Chen et al. (2016) [51]	Taiwan	P–B–R	39/38 (F)	Abdominally obese[c]	44.5	31	3 months	Green tea catechins (1344 mg)	Flavanols	Capsule	BMI, WC	No change	5
Llaneza et al. (2010) [52]	Spain	P–R	46/44 (F)	Insulin resistance	56.4	30.2	24 months	Soy isoflavones (40 mg)	Isoflavones	Supplement	BMI, WC	No change	3
Atkinson et al. (2004) [53]	UK	P–B–R	83/88 (F)	Healthy	55.2	25.3	12 months	Red clover isoflavones (43.5 mg)	Isoflavones	Tablet	BMI, BF	No change	5
Villa et al. (2009) [54]	Italy	P–R	28/15 (F)	Healthy	53.9	27.2	6 months	Soy genistein (50 mg)	Isoflavones	Tablet	BMI	No change	3
Weickert et al. (2006) [55]	Multi-center	C–B–R	34 (F)	Healthy	59	24.7	2 months	Soy isoflavones (50 mg)	Isoflavones	Enriched snack	BMI	No change	3
Atteritano et al. (2007) [56]	Italy	P–B–R	198/191 (F)	Osteopenic	54.5	25.1	24 months	Soy genistein (54 mg)	Isoflavones	Tablet	BMI	No change	4
Colacurci et al. (2005) [57]	Italy	P–R	29/28 (F)	Healthy	55.2	25.9	6 months	Soy isoflavones (60 mg)	Isoflavones	Tablet	BMI	No change	3
Liu et al. (2013) [58]	China	P–B–R	90/90 (F)	Pre-hypertensive	58.1	23.5	6 months	Soy daidzein (63 mg)	Isoflavones	Powder	BMI, WC, BF	No change	5
Lebon et al. (2014) [59]	Canada	P–B–R	19/15 (F)	Overweight/obese	59.5	29.9	6 months	Soy isoflavones (70 mg)	Isoflavones	Capsule	BMI, WC, BF	No change	4
Barsalani et al. (2013) [60]	Canada	P–B–R	18/21 (F)	Overweight/obese	50–70	30.1	6 months	Soy isoflavones (70 mg)	Isoflavones	Capsule	BMI, WC	WC changed	4
Wu et al. (2006) [61]	Japan	P–B–R	33/33 (F)	Healthy	54.4	21.1	6 months	Soy isoflavones (75 mg)	Isoflavones	Capsule	BMI	No change	4
Llaneza et al. (2012) [62]	Spain	P–R	33/32 (F)	Normal/overweight/ obese	56.7	30.6	24 months	Soy isoflavones (80 mg)	Isoflavones	Supplement	BMI, BF	BMI changed	3
Hidalgo et al. (2005) [63]	Ecuador	C–B–R	53 (F)	Healthy	51.3	26.6	3 months	Red clover isoflavones (80 mg)	Isoflavones	Capsule	BMI	No change	5
Han et al. (2002) [64]	Brazil	P–B–R	40/40 (F)	Healthy	48.5	24.9	4 months	Soy isoflavones (100 mg)	Isoflavones	Capsule	BMI	No change	4
Delmanto et al. (2013) [65]	Brazil	P–B–R	32/34 (F)	Healthy	55.7	29.1	10 months	Soy isoflavones (100 mg)	Isoflavones	Capsule	BMI, WC	No change	4
Garrido et al. (2006) [66]	Chile	P–B–R	15/14 (F)	Healthy	53.5	27	3 months	Soy isoflavones (100 mg)	Isoflavones	Capsule	BMI	No change	4
Mori et al. (2004) [67]	Japan	P–B–R	34/36 (F)	Healthy	49.8	22	6 months	Soy isoflavones (100 mg)	Isoflavones	Tablet	BMI	Changed	2
Engelbert et al. (2016) [68]	Germany	P–B–R	85/85 (F)	Healthy	59.5	25.2	3 months	Soy isoflavones (117.4 mg)	Isoflavones	Capsule	BF	No change	5
Cheng et al. (2015) [69]	Taiwan	P–B–R	41/41 (F)	Healthy	57.6	23	12 months	Soy isoflavones (300 mg)	Isoflavones	Tablet	BMI	No change	3
Choi et al. (2015) [70]	Korea	P–B–R	34/28 (M/F)	Overweight/obese	43.1	26.6	3 months	Quercetin (100 mg)	Flavonols	Capsule	BMI	Changed	4

Pfeuffer et al. (2013) [71]	Germany	C–B–R	19 (M)	Healthy APOE genotype 3	59.5	26.2	2 months	Quercetin (150 mg)	Flavonols	Capsule	BMI, WC	WC changed	3
			30 (M)	Healthy APOE genotype 4	59.4	26.5	2 months	Quercetin (150 mg)	Flavonols	Capsule	BMI, WC	No change	3
Edwards et al. (2007) [72]	USA	C–B–R	19 (M/F)	Pre-hypertensive	47.8	29.7	1 month	Quercetin (730 mg)	Flavonols	Tablet	BMI	No change	3
			22 (M/F)	Hypertensive	49.2	29.4	1 month	Quercetin (730 mg)	Flavonols	Tablet	BMI	No change	3
Rezvan et al. (2017) [73]	Iran	P–B–R	42/40 (F)	Polycystic ovary syndrome	29.8	29	3 months	Quercetin (1000 mg)	Flavonols	Capsule	BMI	No change	5
Qin et al. (2009) [74]	China	P–B–R	60/60 (M/F)	Dyslipidemic	40–65	26.1	3 months	Anthocyanins (160 mg)	Anthocyanins	Supplement	BMI, WC	No change	2
Davinelli et al. (2015) [75]	Italy	P–B–R	26/16 (M/F)	Overweight	45–65	28.7	1 month	Anthocyanins (162 mg)	Anthocyanins	Capsule	BMI, WC	No change	4
Thompson et al. (2017) [76]	Australia	C–B–R	26 (M/F)	Overweight/obese	39	30.7	1 month	Anthocyanins (320 mg)	Anthocyanins	Capsule	BMI	No change	3
Zhang et al. (2016) [77]	China	P–B–R	73/73 (M/F)	Hypercholesterolemic	40–65	26.6	6 months	Anthocyanins (320 mg)	Anthocyanins	Capsule	BMI, WC	No change	3
Curtis et al. (2009) [78]	UK	P–B–R	26/26 (F)	Healthy	58.2	24.7	3 months	Anthocyanins (500 mg)	Anthocyanins	Capsule	BMI	No change	3
Habauzit et al. (2015) [79]	France	C–B–R	48 (F)	Healthy	57.8	25.7	6 months	Naringenin (210 mg)	Flavanones	Beverage	BF	No change	5
Rizza et al. (2011) [80]	Italy	C–B–R	24 (M/F)	Metabolic syndrome	52	34.7	3 weeks	Hesperidin (500 mg)	Flavanones	Capsule	BMI, WC	No change	4
Ohara et al. (2016) [81]	Japan	P–B–R	15/14 (M/F)	Overweight	49.2	26.2	3 months	Hesperidin (500 mg)	Flavanones	Tablet	BMI, WC	No change	4
Haidari et al. (2015) [82]	Iran	P–B–R	38/37 (M/F)	Myocardial infarction	55.5	26.4	1 month	Hesperidin (600 mg)	Flavanones	Capsule	BMI, WC	No change	4
Sano et al. (2007) [83]	Japan	P–B–R	17/18 (M/F)	Healthy	53.1	24.3	3 months	Proanthocyanidins (400 mg)	Proanthocyanidins	Tablet	BMI	No change	3

[a] Age data is presented as the Mean or age range.
[b] BMI is the Mean.
[c] Abdominally obese is defined by high waist circumference as described in the corresponding publications. Abbreviations: APOE, apolipoprotein E; B, blinded; BF, body fat percentage; BMI, body mass index; C, crossover; EGCG, epigallocatechin gallate; F, females; M, males; P, parallel; R, randomized; WC, waist circumference.

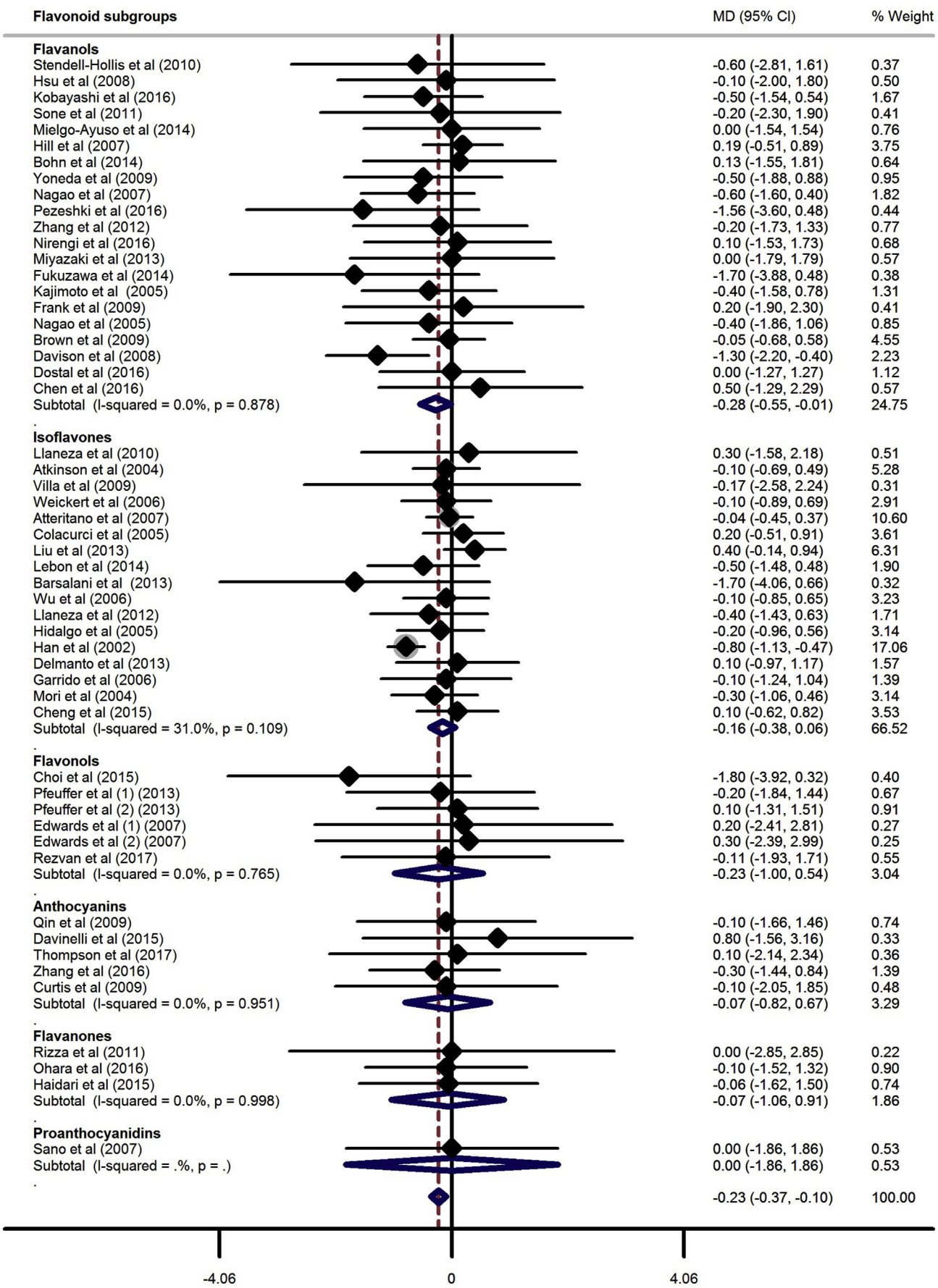

Figure 2 Forest plot of pooled estimate effects of flavonoids on body mass index (BMI) stratified by the type of flavonoids. Data are presented as mean difference (MD) between treatment and control groups with 95% CIs.

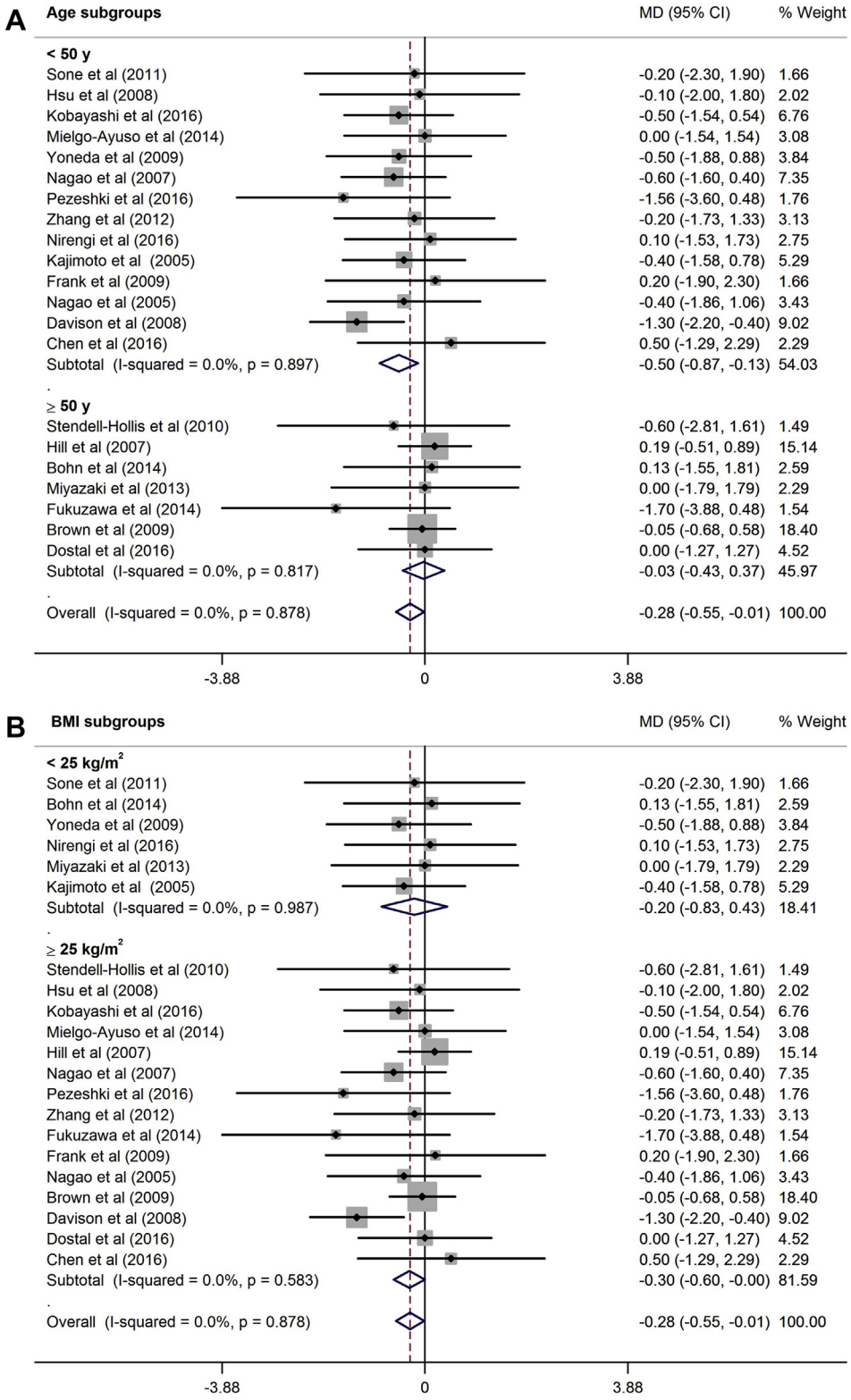

Figure 3 Forest plot of pooled estimate effects of flavanols on body mass index (BMI) stratified by participants' age (A) and BMI (B), study location (C), and flavanol dosage (D). Data are presented as mean difference (MD) between treatment and control groups with 95% CIs.

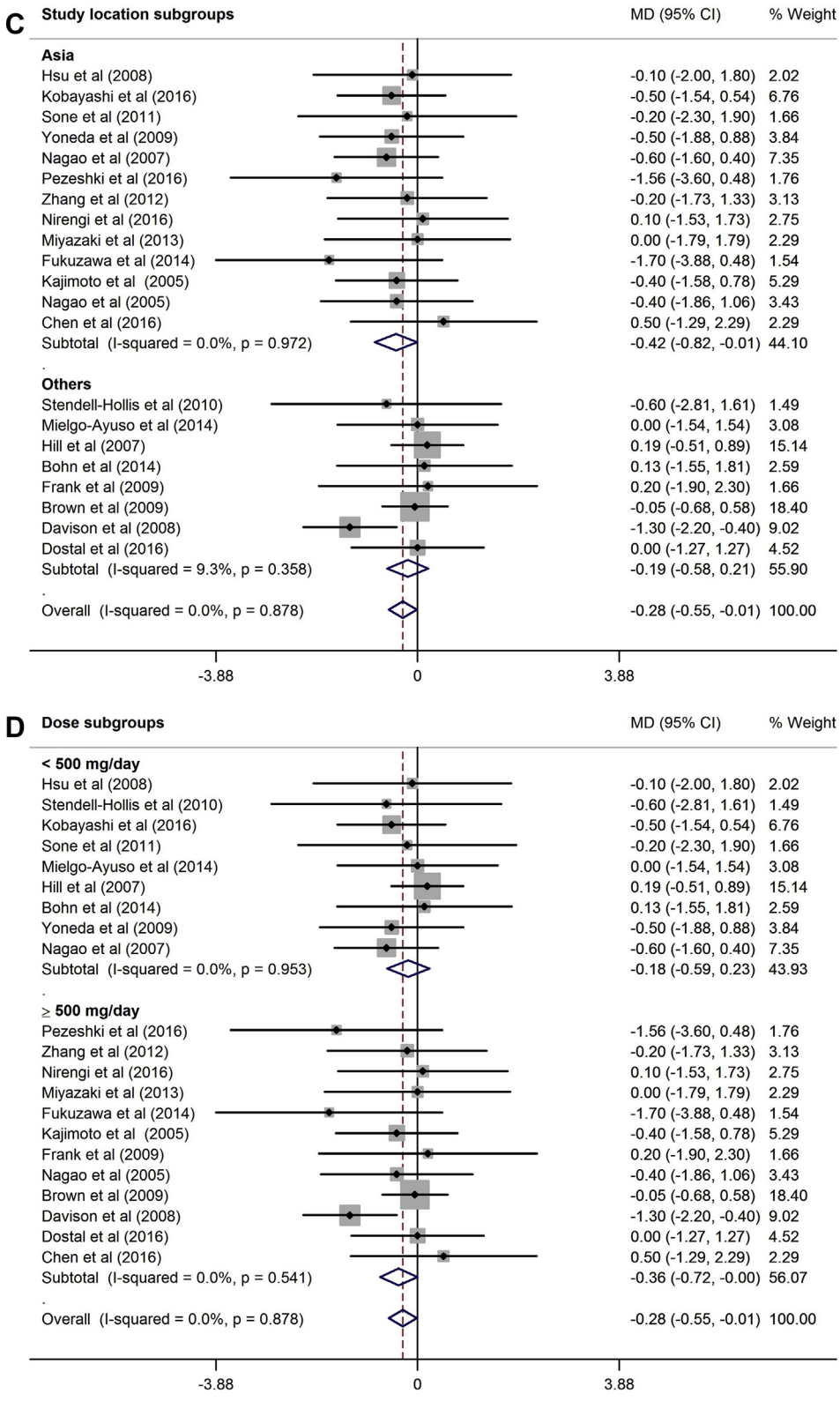

Figure 3 (*continued*)

Sensitivity analysis and publication bias

Sensitivity analysis revealed that the effect of flavonoids on obesity-related anthropometric measures was not substantially modified by excluding a particular study. Visual inspection of funnel plots did not suggest a significant potential publication bias in the meta-analysis of flavonoids on BMI and waist circumference but a

Table 2 Subgroup analysis of the effect of isoflavones on BMI.

Subgroup categorization	Studies (n)	Case/control (n)	Mean difference (95% CI)	P value	Heterogeneity	P for heterogeneity
BMI						
<25 kg/m^2	6	272/274	−0.16 (−0.62, 0.30)	0.7	71.0%	0.004
≥25 kg/m^2	11	554/535	−0.10 (−0.34, 0.15)	0.8	0	1
Study location						
Asia	4	198/200	0.10 (−0.23, 0.43)	0.6	0	0.5
Other continents	13	628/609	−0.26 (−0.51, −0.02)	0.04	23.8%	0.2
Dosage						
<75 mg/day	9	545/526	0.02 (−0.22, 0.26)	0.9	0	0.7
≥75 mg/day	8	281/283	−0.34 (−0.64, −0.04)	0.027	26.2%	0.2

Mean difference and its standard deviation (SD) of control and intervention groups were used to calculate pooled

Table 3 Effects of flavonoid subcategories on waist circumference and body fat percentage.

Subgroups	Studies (n)	Case/control (n)	Mean difference (95% CI)*	P value	Heterogeneity	P for heterogeneity
Waist circumference (cm)						
Flavanols	18	786/739	−0.60 (−1.11, −0.08)	0.02	26.2%	0.15
Isoflavones	5	205/204	0.56 (−0.76, 1.88)	0.4	0	0.6
Flavonols	2	49/49	−0.80 (−2.66, 1.06)	0.4	0	0.4
Anthocyanins	3	159/149	−0.47 (−1.93, 1.00)	0.5	0	0.6
Flavanones	3	77/75	−0.10 (−1.74, 1.55)	0.9	0	0.9
Overall	31	1276/1216	−0.53 (−0.87, −0.19)	0.002	0	0.4
Body fat percentage (%)						
Flavanols	10	343/334	−0.12 (−0.54, 0.30)	0.6	0	0.6
Isoflavones	5	310/310	−0.27 (−1.24, 0.69)	0.6	0	1
Flavanones	1	48/48	−0.10 (−1.81, 1.61)	0.9	–	–
Overall	16	701/692	−0.14 (−0.51, 0.24)	0.5	0	0.9

Mean difference and its standard deviation (SD) of control and intervention groups were used to calculate pooled effects (expressed as mean difference and 95% confidence interval). Statistical heterogeneity was assessed by I^2 test using random inverse-variance heterogeneity. CI: confidence interval.

publication bias was found for body fat percentage. These observations were confirmed by Egger's linear regression test (for BMI: intercept = 0.14; SE = 0.23; 95% CI: −0.33, 0.60; t = 0.59; P = 0.6; for waist circumference: intercept = 0.37; SE = 0.32; 95% CI: −0.29, 1.03; t = 1.14; P = 0.3; for body fat percentage: intercept = −0.70; SE = 0.37; 95% CI: −1.49, 0.08; t = −1.92; P = 0.08). Duval and Tweedie 'trim-and-fill' correction resulted in the imputation of 14 potentially missing studies for BMI with an adjusted effect size of −0.37 (95% CI: −0.50, −0.25) and imputation of 7 potentially missing studies for waist circumference with an adjusted effect size of −0.82 (95% CI: −1.26, −0.38). No study was imputed for body fat percentage.

Discussion

This meta-analysis assessed the anti-obesity potential of flavonoids in healthy individuals or overweight/obese individuals with medical conditions not affecting their weight using controlled clinical trials. Flavanols showed potential for decreasing BMI, in the overall estimate and in subgroups of Asians, ages <50 years, BMI ≥25 kg/m^2, and doses ≥500 mg/day. Isoflavones did not show a significant overall effect on BMI but the pooled analyses indicated their effectiveness on BMI of non-Asian populations and doses ≥75 mg/day. In the overall assessment, flavanols also decreased waist circumference but their effect on body fat percentage was not statistically significant. Isoflavones, however, were not effective on either waist circumference or body fat percentage. The available trials did not reveal a significant effect from flavonols, flavanones, and anthocyanins on the specified anthropometric measures.

The results of this meta-analysis for flavanols are in line with a recent meta-analysis by Gonzales et al. [84] who collected and analyzed data of clinical trials on the effect of flavanol-containing tea, cocoa, and apple products on BMI and waist circumference and found a significant beneficial effect on BMI in the overall estimate and also in subgroup of individuals with BMI ≥25 kg/m^2. We similarly found a significant overall effect following consumption of flavanols and a trend towards lower BMI in the subgroup of individuals with BMI ≥25 kg/m^2 (P = 0.057). In contrast, a previous meta-analysis by Phung et al. [85] did not show benefits of green tea catechins on BMI and waist circumference. It seems that recent clinical trials on the issue have changed the pooled results.

In this meta-analysis, flavanols revealed a significant effect on BMI in studies from Asia but not from other continents. In contrast, isoflavones showed effectiveness

on BMI in trials from other parts of the world but not from Asia. This contrariwise nation-dependent difference in the effect of flavanols and isoflavones may be the result of dietary patterns specific to each region. For instance, high habitual caffeine intake in Western countries can inhibit the beneficial effect of green tea catechins on weight loss and weight maintenance [85,86]. Similarly, the lack of the effectiveness of isoflavones in Asia may be due to traditional soy consumption in this population compared to Western countries [87] which results in routine isoflavone intake and weakening the impact of isoflavones in clinical interventions. The possible ethnic-dependent effect of flavanols in Asian populations may also be due to the existence of the catechol-*O*-methyltransferase (COMT) polymorphism. There are two major polymorphisms of the COMT enzyme: Val/Val polymorphism which has a high activity COMT enzyme (COMTH) and Met/Met polymorphism which has a low activity COMT (COMTL) [88]. Asians are known to have a high frequency of COMTH while Europeans have an equal frequency of both COMTH and COMTL alleles [88]. It has been reported that following ingestion of catechins, subjects with COMTH polymorphism increase energy expenditure and fat oxidation while COMTL carriers do not [89]. Likewise, the plausible ethnic-dependent effect of isoflavones in non-Asian populations is suggested to be the result of a higher frequency of UDP-glucuronosyltransferase 1A3 alleles that produce flavonoid metabolites with high-biological activity [90].

In subgroup analysis, flavanols showed more benefit on BMI when subjects of younger ages (<50 years) were recruited. In this regard, an animal study demonstrated that compared to young rats, adult rats had reduced flavanol absorption rate and phase 2 enzyme metabolism, indicating that rats of young ages may have higher plasma concentration of flavanols after intake [91]. Also, in a study on Malaysian men, plasma concentrations of the isoflavones, daidzein and genistein, were lower in men aged 45–67 years compared to men in 18–34 and 35–44 years age groups [92]. Higher plasma concentrations may explain the significant effect of flavanols on BMI in younger ages.

We found a dose-dependent effect which varied between flavanols and isoflavones: while isoflavone doses ≥75 mg/day proved to be effective, doses as high as ≥500 mg/day were needed to show significant benefits for flavanols. This variation in the dose-dependent effect between flavanols and isoflavones may come from the variation in their bioavailability and absorption rates. Among flavonoid subclasses, isoflavones have the best bioavailability, followed respectively by flavanols, flavanones, flavonols, and anthocyanins [93]. Therefore, flavanols may need to be consumed in higher quantities than isoflavones in order to reveal beneficial effects.

The mechanisms of anti-obesity potential of flavanols are well investigated. Green tea and its flavanols have shown a thermogenic effect that increases fat oxidation and sympathetic nervous system activity [94–96]. They are, additionally, able to downregulate expression of enzymes involved in fat synthesis [97,98]. Similar to flavanols, isoflavones inhibit lipogenesis and increase fatty acid β-oxidation [99]. Furthermore, as phytoestrogens, isoflavones exert anti-obesity activity of estrogens by preventing lipid accumulation and regulating food intake and energy balance [100]. Isoflavones also stimulate catecholamine synthesis and increase energy expenditure [101].

Although this meta-analysis did not show any effectiveness for other flavonoid subclasses, there are reports from animal studies demonstrating anti-obesity effects of other flavonoids, including flavonols [102–104], flavanones [105–107], flavones [108,109], anthocyanins [110–113], and proanthocyanidins [114,115]. Epidemiological studies have also shown anti-obesity effects of these flavonoid classes. Three prospective cohorts indicated that higher intake of foods rich in flavanols, flavonols, anthocyanins, and proanthocyanidins was inversely associated with weight change over 4-year time intervals [116]. The lack of the effect by other subclasses of flavonoids such as anthocyanins and flavonols in this meta-analysis could be due to the limited number of clinical trials in these subclasses.

Due to large molecular weight and ubiquitous existence in foods, proanthocyanidins constitute the major flavonoid subclass in the diet with a mean daily intake of 242 mg, followed by flavanol monomers with a mean daily intake of 102 mg, flavanones 34 mg, anthocyanins 27 mg, flavonols 27 mg, flavones 5 mg, and isoflavones 1 mg [117]. The dosage of flavanols used in most of the trials of this meta-analysis was relatively high, i.e. 300–900 mg/day, on average equivalent to 2–4 cups of green tea per day [118]. Similarly, the dosages of isoflavones used in the trials of this meta-analysis (>40 mg/day) were higher than the average amounts of isoflavones consumed by different nations (Asians 25–50 mg/day and Western countries < 1 mg/day) [119]. Therefore, the dosages that are generally ingested through the diet may not be high enough to exert a potent impact on weight control. To observe biological properties of flavanols and isoflavones against obesity, higher than usual dietary quantities of these compounds need to be consumed in the form of supplements.

Although flavanols showed significant efficacy on BMI and waist circumference and isoflavones revealed significant beneficial effect on BMI in non-Asian populations and dosages ≥75 mg/day, the observed effect size seems to be too small to be clinically important (on average, for flavanols −0.28 kg/m^2 and −0.60 cm for BMI and waist circumference, respectively, and for isoflavones −0.26 and −0.34 kg/m^2 in non-Asians and doses ≥75 mg/day, respectively). However, it is not unlikely that this small effect becomes epidemiologically important in prevention of metabolic syndrome and cardiovascular diseases in large scale populations, as supported by epidemiological investigations [22,23].

Although our meta-analysis had the strength of inclusion of flavonoids from five subclasses, the limited number of trials on flavonols, flavanones, anthocyanins, and proanthocyanidins prevented us from making firm conclusions about these subclasses. Fewer trials assessed waist circumference and body fat percentage compared to BMI, making

conclusions on these parameters uncertain. Also, we could not subgroup the data based on gender because most of the investigators did not report data separately for each gender. Isoflavone trials were mostly conducted on postmenopausal females. Therefore, in isoflavone category, subgroup analysis based on age was not also possible.

Conclusion

Overall results of this study showed that flavanols may be effective in weight control and obesity prevention. Isoflavones were only effective on BMI in non-Asian populations or dosages $\geq$75 mg/day.

Conflict of interest

None.

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