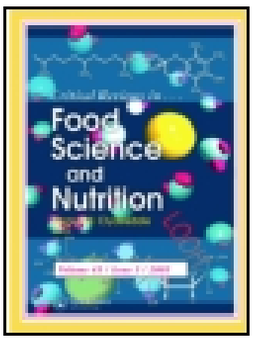

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REVIEW

The effect of dietary (poly)phenols on exercise-induced physiological adaptations: A systematic review and meta-analysis of human intervention trials

Guille Martinez-Negrin, Jarred P. Acton, Stuart P. Cocksedge, Stephen J. Bailey, and Tom Clifford

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ABSTRACT

We performed a systematic review and meta-analysis to determine whether (poly)phenol supplementation augments the physiological adaptations to exercise training. Eligible studies administered a (poly)phenol supplement alongside ≥2 weeks of supervised exercise in adult humans. After screening, 22 studies were included in the analysis. Isoflavones and green tea (poly)phenols were administered most frequently. Quality assessments suggested most studies were free from bias. (Poly)phenols had no effect on training-induced adaptations in muscle strength, peak power output, and $\dot{V}O_{2max}$, but enhanced exercise capacity (SMD: 0.67, 95% CI: 0.25 to 1.09, $p < 0.01$). (Poly)phenols had no overall effect on fat loss (SMD: 0.10, 95% CI: −0.10 to 0.29; $p = 0.97$) or lean mass gains (SMD: 0.06, 95% CI: −0.18 to 0.30, $p = 0.62$) but sub-analysis suggested that isoflavones increased lean mass (SMD: 0.25, 95 CI%: −0.00 to 0.50, $p = 0.05$). Resveratrol impaired adaptations in two studies, although this was a non-statistically significant finding (SMD: −0.54, 95% CI: −1.15 to 0.07, $p = 0.08$). Our results suggest that isoflavones may augment aspects of the adaptive response to exercise training, while resveratrol may compromise training adaptations. More high-quality research is needed to resolve the effects of (poly)phenols on exercise training adaptations.

KEYWORDS

Phytochemicals; phenols; antioxidants; oxidative stress; redox balance; nutrition

Introduction

(Poly)phenols are chemical compounds found in plants and some animal foods (Frank et al. 2020). Structurally, they contain one or more phenolic rings attached to a hydroxyl group (Frank et al. 2020; Bravo 2009). More than 8,000 distinct (poly)phenol structures have been identified and they are typically classified into four major families: lignans, stilbenes, phenolic acids, and flavonoids (Bravo 2009; Crozier et al. 2006). They are particularly abundant in fruits, vegetables, coffee, tea, cocoa, herbs, and spices (Scalbert et al. 2002). A high intake of these (poly)phenol-rich foods is associated with a reduced risk of chronic diseases, including several cancers, cardiovascular disease, and diabetes (Wedick et al. 2012; Knekt et al. 2002; Arts and Hollman 2005). These findings have been ascribed to a myriad of putative physiochemical effects, including antioxidant, anti-inflammatory, anti-atherogenic, anti-carcinogenic, anti-microbial, vasodilation, and chemoprotection, conferred by (poly)phenol-rich foods (Pandey and Rizvi 2009).

There is a growing interest in whether (poly)phenol supplements can augment adaptations evoked by exercise training, such as increased aerobic capacity and muscle strength (Costa et al. 2017; Layne et al. 2017; Gaamouri et al. 2019). These physiological adaptations are not only important for sports performance but also general health. Indeed, low fitness is associated with an increased risk of mortality (Sui et al. 2007; Gander et al. 2011), and a progressive loss in muscle strength is a hallmark of sarcopenia, a condition affecting ∼10% of the global population (Shafiee et al. 2017). Therefore, strategies with the potential to boost exercise-induced adaptations are of great interest to athletes and healthcare practitioners.

Several mechanisms have been proposed to explain how (poly)phenols might augment exercise-induced physiological adaptations; enhanced muscle blood flow (and therefore O_2 delivery during exercise), which may enable greater intensity training to be completed (Morgan, Barton, and Bowtell 2019; Trexler et al. 2014); enhanced mitochondrial biogenesis, resulting from stimulation of key signaling cascades such as peroxisome proliferator-activated receptor coactivator 1 alpha (PGC1-α) (Sandoval-Acuña, Ferreira, and Speisky 2014; Davis et al. 2009); upregulated antioxidant defence, via stimulation of nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the transcription of several antioxidant genes (Christensen and Christensen 2014; Mi et al. 2018) and; accelerated between-workout recovery, owing to a decrease in inflammation and oxidative stress (Doma, Gahreman, and Connor 2020; Wiswedel et al. 2004). Most of these effects are ascribed to the vasodilatory, antioxidant and anti-inflammatory effects of (poly)phenols, which are well-established in vitro (Rice-Evans et al. 1997; Scalbert, Johnson, and Saltmarsh 2005) but more equivocal in humans (Forman, Davies, and Ursini 2014; Hollman

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et al. 2011). Pre-clinical studies also suggested that some (poly)phenols, notably catechins from green tea or cocoa, may also exert thermogenic effects by decreasing catechol-O-methyltransferase (COMT), an enzyme that inhibits norepinephrine and β-oxidation (Dos Santos et al. 2018; Lin and Lin-Shiau 2006). Thus, (poly)phenols may work synergistically with exercise to assist with weight management.

To date, clinical trials combining exercise training and (poly)phenol supplementation have produced equivocal findings. For example, a recent study found that carob (poly)phenols (208 mg·day^{-1}) alongside 6 weeks of taekwondo training increased distance ran during an intermittent shuttle running test (Gaamouri et al. 2019). By contrast, green tea (poly)phenols (573 mg·day^{-1}) combined with 60 min of cycling 3 days·week^{-1} for 10 weeks did not augment maximal aerobic capacity ($\dot{V}O_{2max}$) compared to a placebo in heathy young males (Ichinose et al. 2011). Other studies combining (poly)phenol supplementation and exercise training reported that physiological adaptations were enhanced (Thompson et al. 2018) or unchanged (Sadowska-Krępa et al. 2019; Kuo et al. 2015). In addition, some studies have observed augmented body fat losses when (poly)phenols are consumed alongside an exercise program (Aubertin-Leheudre et al. 2007; Lebon et al. 2014) while others have not (Hill et al. 2007; Choquette et al. 2011).

In contrast to studies reporting positive or no effects of (poly)phenol supplementation on exercise training adaptations, a few studies have observed that (poly)phenol supplementation inhibits some exercise-induced physiological adaptations (Schwarz et al. 2018; Scribbans et al. 2014). The antagonistic effects of (poly)phenol supplements on exercise adaptations has been attributed to their antioxidant and/or anti-inflammatory properties (Schwarz et al. 2018; Scribbans et al. 2014). Exercise generates reactive oxygen and nitrogen species that act as signaling molecules for physiological adaptations, and curbing them with nutritional antioxidants like vitamin C and E has been shown to blunt adaptations in some (Gomez-Cabrera et al. 2008; Paulsen, Cumming et al. 2014) but not all studies (Yfanti et al. 2011; Roberts et al. 2011). However, most (poly)phenols have poor bioavailability (Halliwell 2008) and are not present in the same concentrations as vitamin C and E when consumed orally. For example, (poly)phenol doses of 1000 mg or more may only lead to maximum systemic concentrations of ~7 µM (Habauzit and Morand 2012; Manach et al. 2005), whereas 1000 mg of vitamin C or 440 mg of vitamin E, doses typically given in intervention studies, can lead to plasma concentrations of ≥70 µM (Dimitrov et al. 1991; Close et al. 2006). As such, their in vivo mechanisms of action are likely distinct to antioxidant vitamins and other anti-oxidants (e.g., n-acetyl cysteine); indeed, the current consensus is that at most (poly)phenols only have indirect antioxidant effects (instead of direct scavenger effects) via the stimulation of Nrf2, which is widely regarded as a desirable response (Ursini, Maiorino, and Forman 2016; Cuadrado et al. 2018). Whether (poly)phenols are beneficial or harmful during exercise training may depend on the type of exercise training intervention; the duration, dose, and type of (poly)phenols consumed; habitual (poly)phenol intake, baseline concentrations of (poly)phenols, and redox status (Margaritelis et al. 2020); and the age and sex of the participants. However, the influence of these variables has not yet been systematically investigated.

The equivocal findings in individual studies means there is little consensus as to whether (poly)phenols augment, blunt or have no effects on exercise-induced physiological adaptations. This has important implications for applied practitioners who recommend (poly)phenols to clients, and athlete and patient populations who self-administer (poly)phenols as adjuvant therapies during exercise. Therefore, this study conducted a systematic review and meta-analysis of studies examining the combined effects of (poly)phenol supplementation during exercise-training on physiological adaptations (changes in performance and body composition) in humans, as compared to an exercise only or exercise plus placebo group.

Methods

Search strategy

The protocol was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD201532) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). English language articles from Medline and SPORTDiscus databases were searched from inception to June 20th, 2020. Our search strategy was based on our Population Intervention Comparator Outcome and Study Design (PICOS) framework (Online Supplementary Material). We used Boolean operators, as well as truncation "*" and wildcard "#" terms where appropriate to increase the sensitivity of the search. The full search strategy is available in the Online Supplementary Material. Titles and abstracts were screened for eligibility by two independent reviewers (GMN and TC). The full texts of any articles deemed eligible at this stage were retrieved and checked for inclusion by both authors. The reference list of eligible studies and relevant review articles were screened for additional articles. Both reviewers agreed on the full texts included in the review. Figure 1 provides a flow diagram of the search strategy.

Inclusion criteria

Inclusion criteria were: 1) adult participants ≥ 18 years; 2) studies examining the combined effects of (poly)phenol supplement(s) and a supervised exercise training program of ≥ 2 weeks duration; 3) a comparator group performing the same exercise training program but receiving either an inert placebo supplement or no supplement (i.e., exercise-only group); 4) studies reporting changes in body composition, aerobic/exercise capacity or muscle strength performance; 5) randomized, parallel design, controlled trials in humans. Studies with non-(poly)phenol supplements or that provided

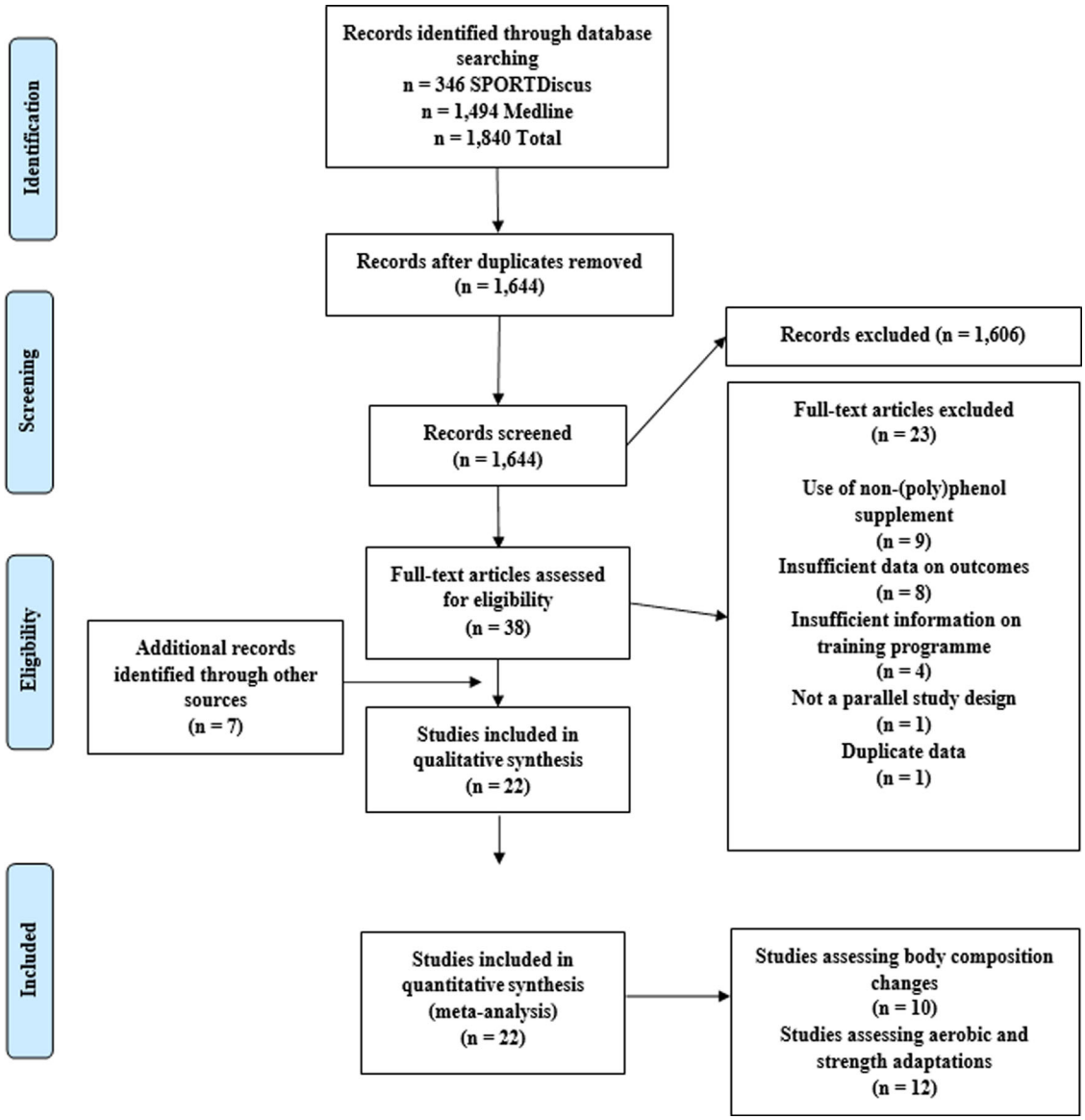

Figure 1. Flow diagram of search strategy.

insufficient information on the supplementation regimen or exercise program were excluded.

Data extraction

Type, age and number of participants, interventions and comparators, exercise program, and mean ± SD for each outcome, were extracted into a Microsoft Excel Spreadsheet. If the standard error of the mean (SEM) was provided, SD was calculated with the following formula: SD = sqrt (n) × SEM, whereby n is the number of subjects (Higgins et al. 2019). For one study (Barsalani et al. 2012), SD were calculated from confidence intervals with the following formula taken from Chapter 6 of the Cochrane Handbook (Higgins et al. 2019): SD = sqrt (n) × (upper limit – lower limit)/X, where X is a divisor generated from a t distribution. Data not available in the text was obtained from authors (n = 1) or using online software (WebPlotDigitizer, Version 3.12) (n = 2).

Heterogeneity, risk of bias, and sensitivity analyses

Heterogeneity was assessed via Chi-square (Chi^2) and I^2 statistics. A Chi^2 test of $p > 0.10$ indicated significant heterogeneity. An I^2 of $< 25\%$ was considered low risk; 25-75% moderate risk; $> 75\%$ high risk (Higgins et al. 2003). The quality of evidence was assessed with the Cochrane risk of bias tool (Higgins and Green 2011). This was conducted independently by two investigators (GMN and JA) and any disagreement resolved by a third investigator (TC). Three separate sensitivity analyses were performed to assess their influence on the meta-analysis: we removed studies with a high risk of bias, that reported mean changes from baseline values, and that contained no placebo control group.

Outcome categorization and subgroup analyses

We performed separate analysis on upper-body and lower-body strength measures. Exercise performance measures were categorized as peak power output, exercise capacity

(time to exhaustion or total distance covered) or timed up and go test. Some studies included several measures of body composition and maximal aerobic capacity. To avoid within-study effect size multiplicity (López-López et al. 2018), we selected one outcome per study for our meta-analysis using a decision rule. If multiple instruments were used to measure the same outcome (e.g., body fat) we selected the most relevant effect size according to a pre-defined hierarchy (see Supplementary material Table S2 for full list) (Bidonde et al. 2017; López-López et al. 2018). Briefly, for body composition, we preferentially extracted whole body measures; for $\dot{V}O_{2max}$, we preferentially selected relative values; for muscle strength, we preferentially extracted isometric and dynamic strength tests. Markers of exercise performance were considered independently. When sufficient studies permitted ($\geq$2 measuring the same outcome), we performed sub-group analysis for age and supplement type (both were pre-specified). Older adults were classified as $\geq$50 years, as this is when physiological decline is proposed to accelerate (Borges et al. 2016; Clifford 2019).

Statistical analyses

Review Manager 5.4 was used to perform the meta-analysis (Cochrane Collaboration, UK). Standardized mean differences (SMDs) were calculated for outcome measures as they were not taken on the same scale. Random effects models were used to account for the heterogeneous study designs. Funnel plots were performed to evaluate publication bias for studies measuring body composition changes (Supplementary material Figure S1). Funnel plots were not calculated for other variables as they contained less than 10 studies and thus the finding may not be valid (Higgins and Green 2011).

Results

Search results

Our search strategy retrieved 1,840 studies, which was reduced to 1,644 after removing duplicates (Figure 1). After screening the title and abstracts, 38 full-text articles were identified for further assessment. A further 7 papers were identified for assessment from the reference lists of relevant review articles (Bowtell and Kelly 2019; Myburgh 2014; Somerville, Bringans, and Braakhuis 2017). After screening the full-texts, 23 studies were excluded (see Figure 1 and Supplementary material Table S3), leaving 22 studies for inclusion in the final meta-analysis.

Study characteristics

Tables 1 and 2 summarize studies assessing the effects of (poly)phenols on exercise induced changes in body composition and performance (n = 16) and performance and strength (n = 6), respectively. Six studies measured body composition and performance (Barbosa et al. 2019; Gaamouri et al. 2019; Gliemann et al. 2013; Orsatti et al. 2010; Kim et al. 2013; Mafi et al. 2019). All studies employed a parallel study design with the intervention and control groups completing an exercise training program equal in duration to the supplementation period. In three studies, the control group performed the same exercise program but were not provided with a placebo supplement (Mafi et al. 2019; Amozadeh, Shabani, and Nazari 2018; Kim et al. 2013). Furthermore, the control group for one study (Thompson et al. 2018) provided potassium nitrate and although this is not an inert placebo, this group was used as the control since potassium nitrate does not contain (poly)-phenol compounds. The interventions ranged from 4 weeks to 12 months, with the average duration being 13 weeks. Only four studies were longer than 13 weeks (Barsalani et al. 2012; Choquette et al. 2011; Lebon et al. 2014; Orsatti et al. 2010).

A total of 646 participants were included in the meta-analysis; 453 were females and 174 males. This is excluding participants from one study who recruited female and male participants but did not specify the numbers of each sex (Schwarz et al. 2018). More than half of the studies (n = 12) recruited adults $\geq$50 years old (n = 444) (Aubertin-Leheudre et al. 2007; Barbosa et al. 2019; Barsalani et al. 2012; Choquette et al. 2011; Gliemann et al. 2013; Lebon et al. 2014; Mafi et al. 2019; Orsatti et al. 2010; Hill et al. 2007; Kim et al. 2013; Wu, Oka, Higuchi, et al. 2006; Giolo et al. 2018). Some participants were classified as obese or overweight (n = 276) (Hill et al. 2007; Bagheri et al. 2020; Amozadeh, Shabani, and Nazari 2018). Others recruited overweight postmenopausal females (n = 162) (Aubertin-Leheudre et al. 2007; Barsalani et al. 2012; Choquette et al. 2011; Lebon et al. 2014; Orsatti et al. 2010); healthy postmenopausal females (n = 124) (Barbosa et al. 2019; Wu, Oka, Higuchi, et al. 2006; Giolo et al. 2018); healthy and recreationally active adults (n = 67) (Ichinose et al. 2011; Schwarz et al. 2018; Thompson et al. 2018; Sadowska-Krępa et al. 2019); healthy but non-active adults (n = 63) (Gliemann et al. 2013; Scribbans et al. 2014; Kuo et al. 2015); sarcopenic adults (n = 93) (Kim et al. 2013; Mafi et al. 2019); and national-level athletes (n = 20) (Gaamouri et al. 2019).

Five different (poly)phenol supplements were assessed: isoflavones (Aubertin-Leheudre et al. 2007; Barbosa et al. 2019; Barsalani et al. 2012; Choquette et al. 2011; Giolo et al. 2018; Lebon et al. 2014; Orsatti et al. 2010; Wu, Oka, Tabata, et al. 2006); (poly)phenols derived from tea, including green tea, green tea extract, tea catechin and epigallocatechin gallate (Amozadeh, Shabani, and Nazari 2018; Bagheri et al. 2020; Hill et al. 2007; Ichinose et al. 2011; Sadowska-Krępa et al. 2019; Kim et al. 2013; Kuo et al. 2015); resveratrol (Gliemann et al. 2013; Scribbans et al. 2014); epicatechin (Mafi et al. 2019; Schwarz et al. 2018); carob extract (Gaamouri et al. 2019) and beetroot juice (Thompson et al. 2018). The exercise programme implemented alongside the supplement intervention varied widely: aerobic exercise (Aubertin-Leheudre et al. 2007; Amozadeh, Shabani, and Nazari 2018; Bagheri et al. 2020; Hill et al. 2007; Ichinose et al. 2011; Kuo et al. 2015; Schwarz et al. 2018; Wu, Oka, Higuchi, et al. 2006), resistance training

Table 1. A summary of the studies included in the systematic review and meta-analysis that measured effects of exercise training and (poly)phenol intake on body composition and performance.

Study	Subjects	Age (years)	(Poly)phenol	Control	Exercise	Duration	Outcomes	Conclusion
Wu et al. (2006)	INT: 31 F CON: 31 F PMW	INT: 54 ± 3 CON: 53 ± 3	ISO (150 mg•day^{-1})	Dextrin	AT 3 × 1 h•week^{-1}	6 months	FM (kg) LBM (kg)	ND for all outcomes
Aubertin-Leheudre et al. (2007)	INT: 11 F CON: 11 F OB/PMW	INT: 57 ± 5 CON: 58 ± 5	ISO (70 mg•day^{-1})	Placebo (source unclear)	AT 3 × 1 h•week^{-1}	6 months[a]	FM (kg) App FFM (kg)	↓ FM with INT ND for FFM
Hill et al. (2007)	INT: 19 F CON: 19 F OB	INT: 45-70 CON: 45-70	EGCG (300 mg•day^{-1})	Lactose	AT 3 × 45 min•week^{-1}	12 weeks	BF (Δ kg) LBM (Δ kg)	ND for all outcomes
Orsatti et al. (2010)	INT: 15 F CON: 18 F OB/PMW	INT: 56 ± 7 CON: 57 ± 9	ISO (100 mg•day^{-1})	Lactose	RT 2 × ≈ 1 h•week^{-1}	9 months	1 RM LE (% Δ) MM (kg) BF (%)	ND for all outcomes
Choquette et al. (2011)	INT: 16 F CON: 18 F OB/PMW	INT: 61 ± 3 CON: 58 ± 6	ISO (70 mg•day^{-1})	Cellulose	Mix 3 × ≈1 h•week^{-1} [b]	6 months	FM (kg) LBM (kg)	ND for all outcomes
Barsalani et al. (2012)	INT: 18 F CON: 21 F OB/PMW	INT: 50-70 CON: 50-70	ISO (280 mg•day^{-1})	Cellulose	Mix 3 × ≈1 h•week^{-1} [b]	6 months	FM (kg) LBM (kg)	ND for all outcomes
Gliemann et al. (2013)	INT: 14 M CON: 13 M H/NA	INT: 65 ± 4 CON: 65 ± 4	RSV (250 mg•day^{-1})	Placebo (no mention of source)	AT 2 × ≈1 h•week^{-1} + CF 1 × ≈1 h•week^{-1}	8 weeks	$\dot{V}O_{2max}$ (mL•min^{-1}•kg^{-1}) BF (kg) LBM (kg)	↓ with INT for $\dot{V}O_{2max}$ ND for other outcomes
Kim et al. (2013)	INT: 32 F CON: 32 F Sarcopenic	INT: 81 ± 4 CON: 80 ± 4	TC (540 mg•day^{-1})	No placebo	RT 2 × 1 h•week^{-1}	3 months	TUG test (min) Grip strength (kg) KE strength (Nm) MM (kg)	ND for all outcomes
Lebon et al. (2014)	INT: 19 F CON: 15 F OB/PMW	INT: 59 ± 6 CON: 60 ± 3	ISO (70 mg•day^{-1})	Cellulose	Mix 3 × 1 h•week^{-1} [b]	6 months	FM (kg) MMI (kg•m^{-2})	↓ FM with INT ND for MMI
Giolo et al. (2018)	INT: 17 F CON: 15 F PMW	INT: 56 ± 22 CON: 53 ± 19	ISO (100 mg•day^{-1})	Corn starch	Mix 3 × ≈1 h•week^{-1} [b]	10 weeks	FM (kg)	ND
Amozadeh, Shabani, and Nazari (2018)	INT: 13 F CON: 13 F OB	INT: 28 ± 7 CON: 27 ± 7	GT (99 mg•day^{-1})	No placebo	AT 3 × 80-90 min•week^{-1}	8 weeks	BF (%)	ND
Barbosa et al. (2019)	INT: 16 F CON: 14 F PMW	INT: 56 ± 6 CON: 53 ± 4	ISO (100 mg•day^{-1})	Corn starch	Mix 3 × ≈1 h•week^{-1} [a]	5 weeks	LBM (%) 1RM LP (kg) 6MWT (min)	ND for all outcomes
Bagheri et al. (2020)	INT: 10 F CON: 10 F OB	INT: 38 ± 2 CON: 40 ± 4	GTE (500 mg•day^{-1})	Chickpea flour	AT 3 × 1 h•week^{-1}	8 weeks	BF (%)	↓ with INT
Gaamouri et al. (2019)	INT: 5 F 6 M CON: 6 F 6 M	INT: 22 ± 1 CON: 22 ± 1	Carob extract (208 mg•day^{-1})	Taste-matched placebo drink	TWD 4 × 45-60 min•week^{-1}	6 weeks	Yo-Yo IR1 (m) BF (%)	↑ with INT for Yo-Yo IR1 ND for BF
Mafi et al. (2019)	INT: 15 M CON: 14 M Sarcopenic	INT: 69 ± 3 CON: 69 ± 2	EPI		(1 mg•kg^{-1}•day^{-1})	No	placebo	RT 3 × 1 h•week^{-1}
8 weeks	1 RM LP (kgΔ) 1 RM CP (kgΔ) TUG (secΔ) AppMMI (kg•m^{2}Δ)	↓ with INT for 1RM strength ND for TUG and AppMMI						
Bagheri et al. (2020)	INT: 15 M CON: 15 M OB	INT: 45 ± 3 CON: 44 ± 3	GTE (500 mg•day^{-1})	Chickpea flour	AT 3 × 1 h•week^{-1}	8 weeks	BF (%)	↓ with INT

INT, intervention; CON, control; F, females; M, males; PMW, postmenopausal; OB, obese; H, healthy;; NA, non-active ISO, isoflavone; mg, milligram; AT, aerobic training; RT, resistance training; h, hour; FM, fat mass; LBM, lean body mass; ND, no difference; App, appendicular; FFM, fat free mass; EGCG, epigallocatechin gallate; EPI, epicatechin; GTE, green tea extract; min, minute; 1RM, 1 repetition maximum; BF, body fat; Δ, delta change from baseline; ≈, approximately; Mix, combination of resistance training and aerobic training; MMI, muscle mass index; ↓, lower; m^2, meters squared; GT, green tea; %, percentage; RSV, resveratrol; $\dot{V}O_{2max,}$ maximal aerobic capacity; Δ, delta change from baseline; KE, knee extension; TWD, taekwondo; 6MWT, 6 minute walk test; CP, chest press; LP, leg press; TUG, timed up and go; Nm, torque; Yo-Yo IR1, Yo-Yo intermittent recovery test; m, meter; m^2, meters squared. Data presented as mean ± SD.

[a]supplementation began 6 months prior to the exercise intervention; [b] time distributed evenly between RT and AT per day.

Table 2. A summary of the studies included in the systematic review and meta-analysis that measured performance adaptations to exercise training and (poly)phenol intake.

Study	Subjects	Age (years)	(Poly)phenol	Control	Exercise	Duration	Outcomes	Conclusion
Ichinose et al. (2011)	INT: 6 M CON: 6 M H/RA	INT: 23 ± 5 CON: 23 ± 5	GTE (573 mg•day^{-1})	Taste-matched placebo drink	AT 3 × 1 h•week^{-1}	10 weeks	$\dot{V}O_{2peak}$ (L•min^{-1})	ND
Scribbans et al. (2014)	INT: 8 M CON: 8 M H/NA	INT: 21 ± 3 CON: 22 ± 3	RSV (150 mg•day^{-1})	Cellulose	SIT 3 × 5 min•week^{-1}	28 days	$\dot{V}O_{2peak}$ (mL•min^{-1}•kg^{-1}) PPO (W)	↓ with INT in all outcomes
Kuo et al. (2015)	INT: 10 M CON: 10 M H/NA	INT: 21 ± 3 CON: 20 ± 3	GTE (207 mg•day^{-1})	Starch	AT			

3 × 20 min•week^{-1}4 weeks$\dot{V}O_{2max}$ (mL•min^{-1}•kg^{-1})
TTE (sec)ND for all outcomesSchwarz et al. (2018)INT: 10 F + M
CON: 9 F + M
H/RAINT: 21 ± 2
CON: 21 ± 2EPI (200 mg•day^{-1})CelluloseAT 4 × 40-60 min•week^{-1}4 weeks$\dot{V}O_{2max}$ (mL•min^{-1}•kg^{-1})
PPO (W)↓ $\dot{V}O_{2max}$ with INT
ND in PPOThompson et al. (2018)INT: 4 F 6 M
CON: 4 F 6 M
H/RAINT: 25 ± 7
CON: 25 ± 3BRJ (6.4 mmol•day^{-1})KNO_3SIT 4 × ≈ 2-5 min•week^{-1}28 days$\dot{V}O_{2peak}$ (L•min^{-1})
TTE (sec)
PPO (W)↑ with INT for $\dot{V}O_{2peak}$ and TTE
ND for PPOSadowska-krępa et al. (2019)INT: 8 M
CON: 8 M
H/RAINT: 23 ± 2
CON: 22 ± 1GTE (490 mg•day^{-1})CelluloseCF 5 × ≈1 h•week^{-1}6 weeks$\dot{V}O_{2peak}$ (mL•min^{-1}•kg^{-1})NDINT, intervention; CON, control; F, female; M, male; H, healthy; RA, recreationally active; NA, non-active; g, grams; ISO, isoflavone; mg, milligram; h, hour; ND, no difference; GTE, green tea extract; AT, aerobic training; $\dot{V}O_{2peak}$, peak oxygen consumption; min, minute; RSV, resveratrol; CF, CrossFit; ≈, approximately; $\dot{V}O_{2max}$, maximal oxygen consumption; mL, milliliter; LBM, lean body mass; ↓, lower; SIT, sprint interval training; PPO, peak power output; W, watts; TTE, time to exhaustion; sec, seconds; EPI, epicatechin; BRJ, beetroot juice; L, liter; mmol, millimole; KNO_3, potassium nitrate; ↑, higher; Data presented as mean ± SD.

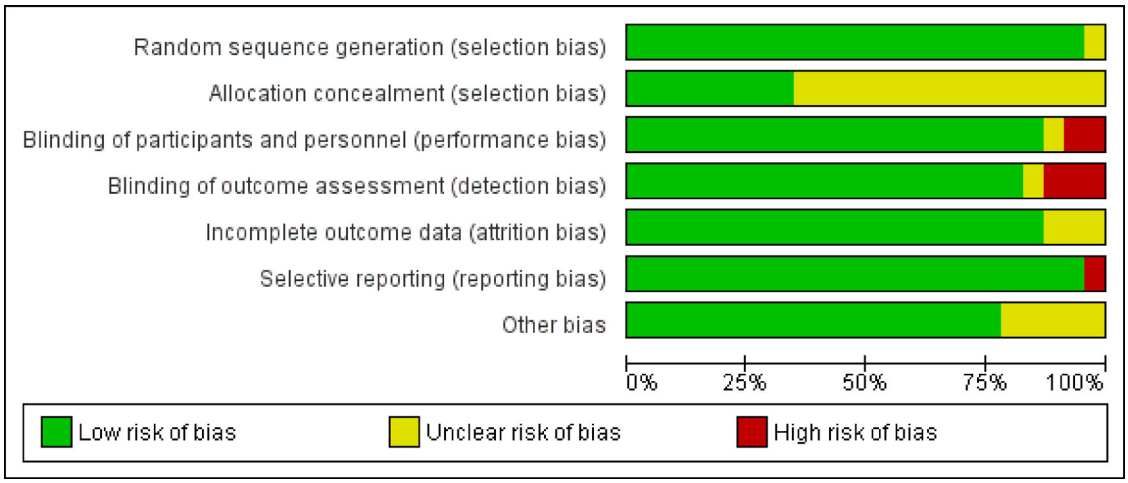

Figure 2. Risk of bias summary.

(Orsatti et al. 2010; Mafi et al. 2019; Kim et al. 2013); a combination of resistance and aerobic training (Barbosa et al. 2019; Barsalani et al. 2012; Choquette et al. 2011; Giolo et al. 2018; Lebon et al. 2014; Gliemann et al. 2013); sprint interval training (Scribbans et al. 2014; Thompson et al. 2018); sport-specific training (Gaamouri et al. 2019; Sadowska-Krępa et al. 2019).

Risk of bias

The quality of evidence was generally high but only three studies had a low risk of bias for all outcomes (Figure 2 and Supplementary material Figure S2). Allocation concealment had an unclear risk of bias in several studies due to insufficient information regarding the concealment protocol (Bagheri et al. 2020; Choquette et al. 2011; Gaamouri et al. 2019; Giolo et al. 2018; Gliemann et al. 2013; Hill et al. 2007; Ichinose et al. 2011; Mafi et al. 2019; Sadowska-Krępa et al. 2019; Schwarz et al. 2018; Scribbans et al. 2014; Kuo et al. 2015; Wu, Oka, Higuchi, et al. 2006). Three studies were considered to have an unclear risk of bias for allocation concealment since the control group did not consume a placebo, only performing exercise (Kim et al. 2013; Amozadeh, Shabani, and Nazari 2018; Mafi et al. 2019). Only one study was considered to have an unclear risk of bias for random sequence generation and high risk for selective reporting (Gliemann et al. 2013). With regards to performance and detection bias, two studies were considered to have a high risk of bias for both outcomes since supplementation was not double-blinded (Amozadeh, Shabani, and Nazari 2018; Sadowska-Krępa et al. 2019). Three studies had an unclear risk of attrition bias as reasons for participant withdrawals were not provided (Barsalani et al. 2012; Gaamouri et al. 2019; Sadowska-Krępa et al. 2019). For "other" bias, four studies were deemed to have an unclear risk of bias as they were funded by a pharmaceutical company and it was unclear what involvement they had on the study design (Aubertin-Leheudre et al. 2007; Hill et al. 2007; Lebon et al. 2014; Orsatti et al. 2010).

The funnel plots for body fat and lean mass gains are symmetrical suggesting minimal evidence for publication bias (Supplementary material Figure S2).

Meta-analysis results

Exercise performance

(Poly)phenols had no effect on training-induced changes in peak power output (SMD: −0.04, 95% CI: −0.57 to 0.49, $p = 0.89$; $Chi^2 = 0.15$, $I^2 = 0\%$, $p = 0.93$) or timed up and go test (SMD: 0.24, 95% CI: −0.17 to 0.64, $p = 0.26$; $Chi^2 = 0.53$; $I^2 = 0\%$, $p = 0.93$) (Figure 3A and C, respectively) but enhanced exercise capacity (SMD: 0.67, 95% CI: 0.25 to 1.09, $p < 0.01$; $Chi^2 = 0.35$, $I^2 = 0\%$, $p = 0.95$) (Figure 3B). Subgroup analyses were not performed due to limited studies measuring these outcomes.

Muscle strength

(Poly)phenols did not alter training-induced adaptations in upper-body strength (SMD: 0.00, 95% CI: −0.41 to 0.40, $p = 0.99$; $Chi^2 = 0.02$, $I^2 = 0\%$, $p = 0.90$) (Figure 3E). No subgroup analyses were conducted as only two studies were included in the main analysis. Similar findings were observed with lower-body strength (SMD: −0.03, 95% CI: −0.35 to 0.28, $p = 0.85$; $Chi^2 = 1.35$, $I^2 = 0\%$, $p = 0.72$) (Figure 3D). Subgroup analysis on isoflavone supplementation showed no significant effect on lower-body strength compared to a CON (SMD: −0.09, 95% CI: −0.65 to 0.47, $p = 0.74$; $Chi^2 = 1.26$, $I^2 = 21\%$, $p = 0.26$) (Supplementary material Figure S3).

$\dot{V}O_{2max}$(1)

(Poly)phenols had no effect on training-induced changes in $\dot{V}O_{2max}$ (SMD: −0.12, 95% CI: −0.47 to 0.23, $p = 0.51$; $Chi^2 = 4.24$, $I^2 = 0\%$, $p = 0.64$) (Figure 4A). In our sub-group analysis, resveratrol (SMD: −0.54, 95% CI: −1.15 to 0.07, $p = 0.08$; $I^2 = 0\%$, $p = 0.64$) (Figure 4B) and tea-derived (poly)phenols did not augment $\dot{V}O_{2max}$

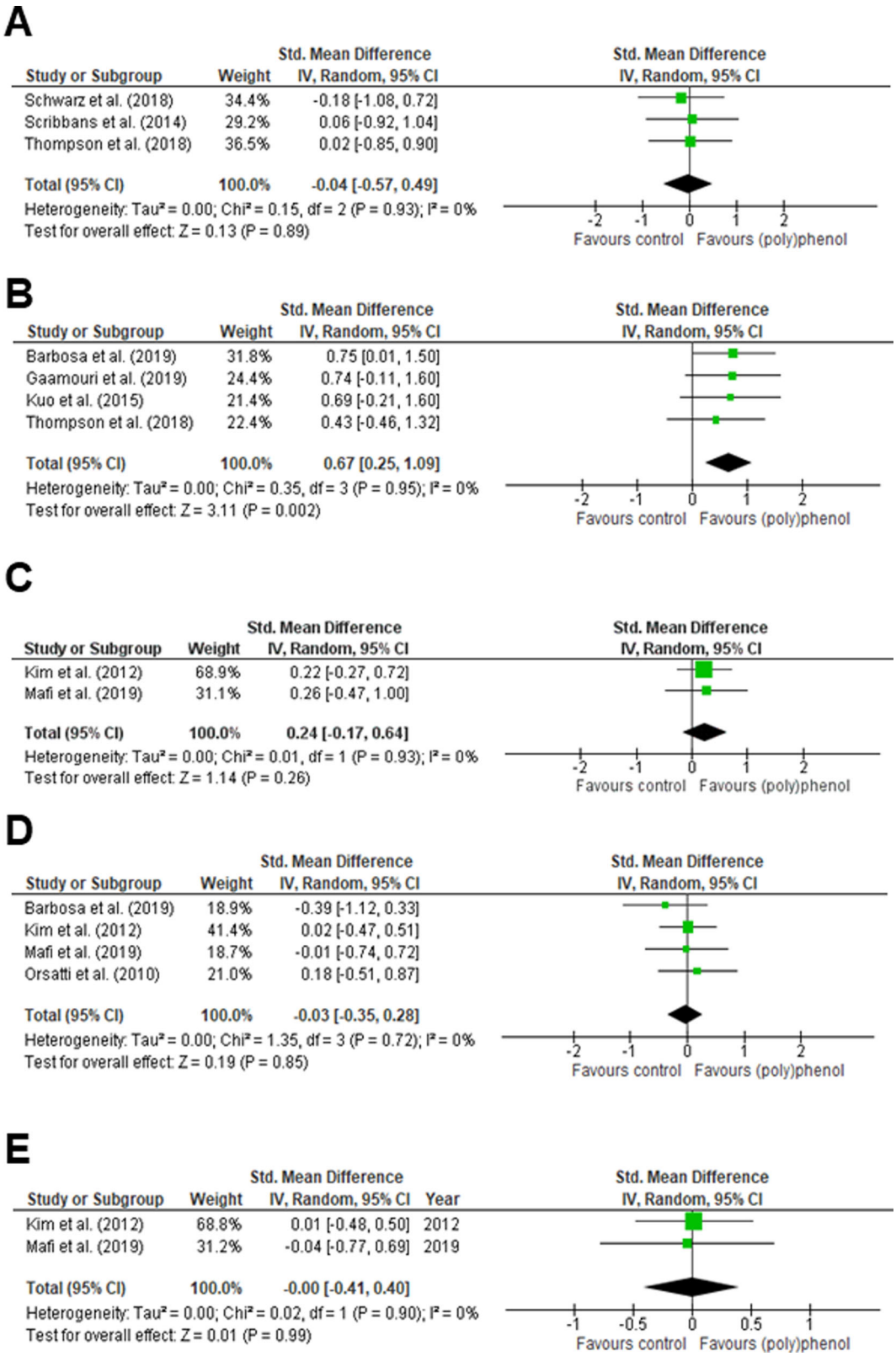

Figure 3. Forest plots for the effects of (poly)phenol supplementation on aerobic peak power output (A), exercise capacity (B), timed up and go test (C), lower-body strength (D), and upper-body strength (E). Data are presented as random effect point estimates (SMD) with 95% confidence intervals (CI) and the diamonds at the bottom of each forest plot corresponds to the overall effect estimate. Data are also presented as MD ± 95% CI (C).

(SMD: 0.25, 95% CI: −0.32 to 0.82, $p = 0.39$; $Chi^2 = 0.09$, $I^2 = 0\%$, $p = 0.96$) (Figure 4B). Only one study (Gliemann et al. 2013) measured changes in $\dot{V}O_{2max}$ in older adults; a sub-group analysis in younger adults showed no effect of (poly)phenols (Supplementary material Figure S4).

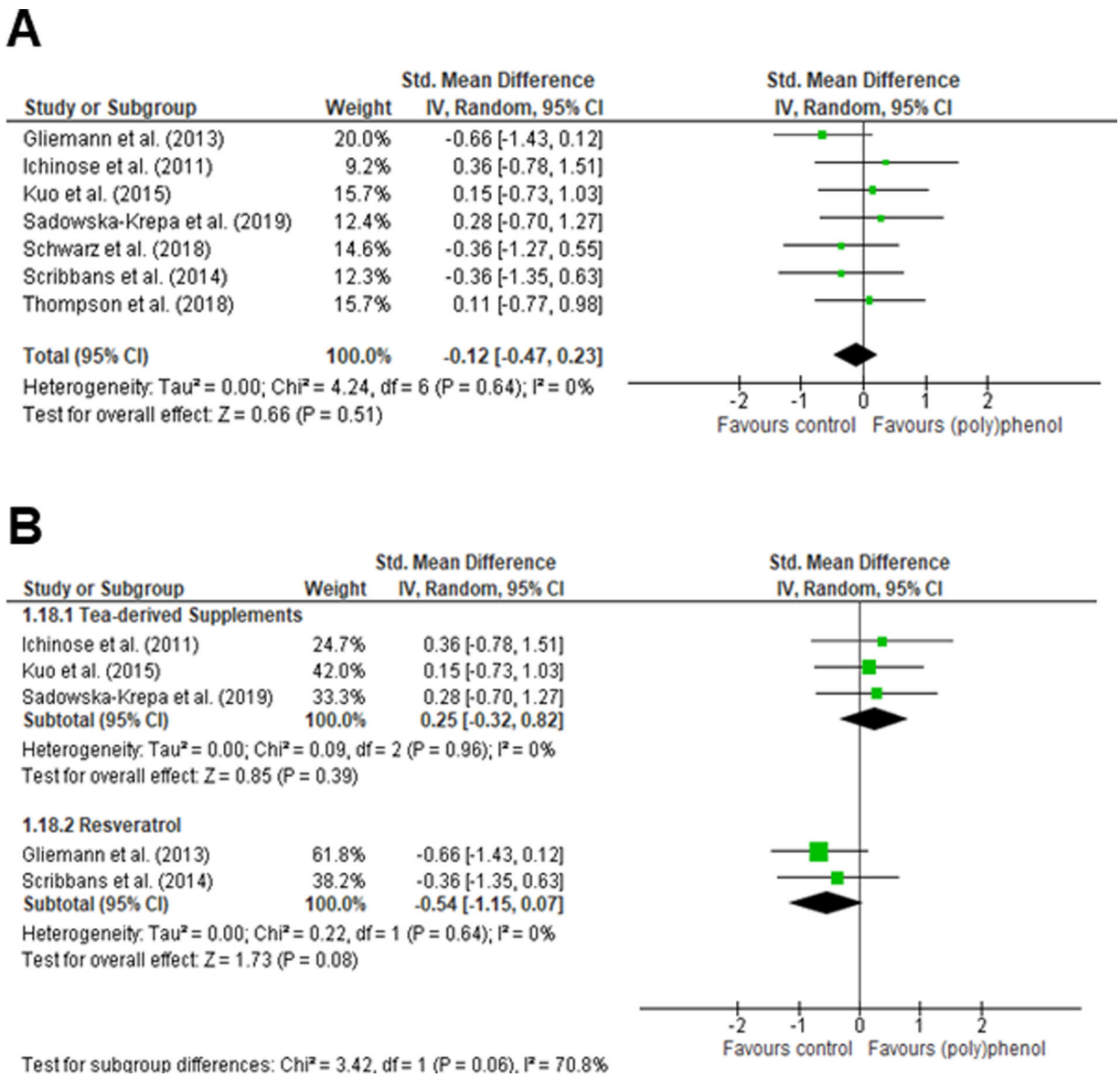

Figure 4. Forest plots for the effects of (poly)phenol supplementation on adaptions to $\dot{V}O_{2max}$ (A); sub-group analysis of supplement type on $\dot{V}O_{2max}$, (B). Data are presented as random effect point estimates (SMD) with 95% confidence intervals (CI) and the diamonds at the bottom of each forest plot corresponds to the overall effect estimate.

Body fat

(Poly)phenols did not augment exercise-induced changes in body fat losses (SMD: 0.10, 95% CI: −0.10 to 0.29, $p = 0.32$; $Chi^2 = 4.67$, $I^2 = 0\%$, $p = 0.97$) (Figure 5A). Sub-group analysis revealed no differences in younger or older adults (SMD: 0.10, 95% CI: −0.12 to 0.32, $p = 0.37$; $Chi^2 = 3.68$, $I^2 = 0\%$, $p = 0.89$) (Figure 5B). Similarly, subgroup analyses in isoflavone (SMD: 0.04, 95% CI: −0.21 to 0.28, $p = 0.77$; $Chi^2 = 1.76$, $I^2 = 0\%$, $p = 0.94$) and tea-derived (poly)phenols (SMD: 0.29, 95% CI: −0.08 to 0.66, $p = 0.12$; $Chi^2 = 1.03$; $I^2 = 0\%$, $p = 0.79$) showed no benefits compared to a placebo (Figure 5C).

(Poly)phenols showed no effect on changes in lean body mass (SMD: 0.06, 95% CI: −0.18 to 0.30, $p = 0.62$; $Chi^2 = 14.73$, $I^2 = 32\%$, $p = 0.14$) (Figure 6A). Isoflavone supplementation appeared to augment lean mass gains (SMD: 0.25, 95 CI%: −0.00 to 0.50, $p = 0.05$; $Chi^2 = 4.91$, $I^2 = 0\%$, $p = 0.56$) but tea-derived (poly)phenols had no effect (SMD: −0.25, 95% CI: −0.64 to 0.14, $p = 0.21$, $Chi^2 = 0.09$, $I^2 = 0\%$, $p = 0.77$) (Figure 6B). All studies were conducted in older adults.

Although not pre-specified, as there was sufficient studies we also performed a sub-group analysis to explore the influence of training type (aerobic training, resistance training, or a mixture of aerobic training and resistance training) on changes on lean mass and body fat with (poly)phenol supplementation. However, this analysis did not yield any significant influence of training mode on these outcome measures (data not shown; all $p > 0$ .05).

Sensitivity analyses

Sensitivity analyses (data not shown), in which studies were removed when they did not provide an inert placebo to the

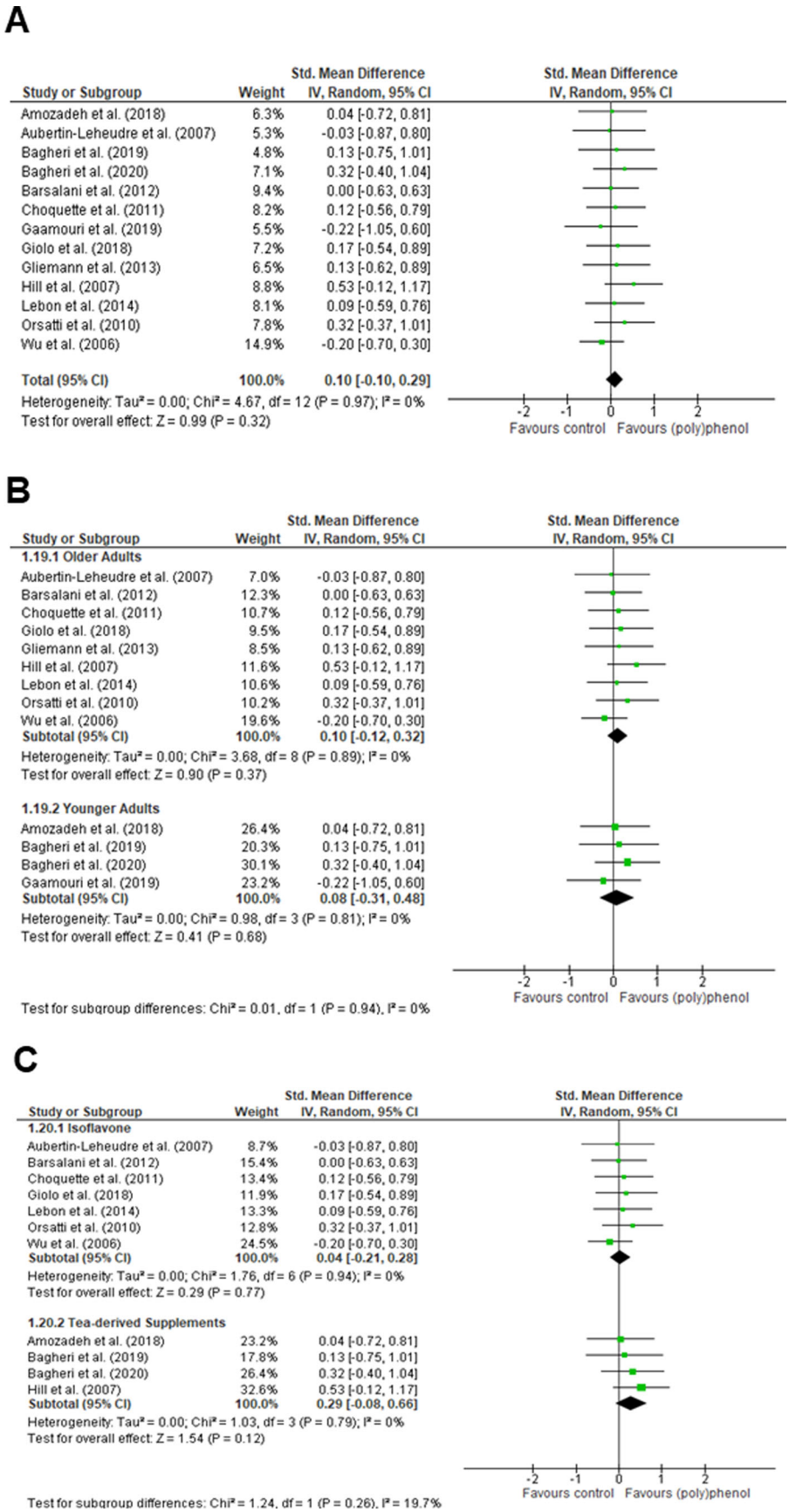

Figure 5. Forest plots for the effects of (poly)phenol supplementation on changes in body fat (A); sub-group analysis of age on body fat, (B); sub-group analysis of supplement type on body fat (C). Data are presented as random effect point estimates (SMD) with 95% confidence intervals (CI) and the diamonds at the bottom of each forest plot corresponds to the overall effect estimate.

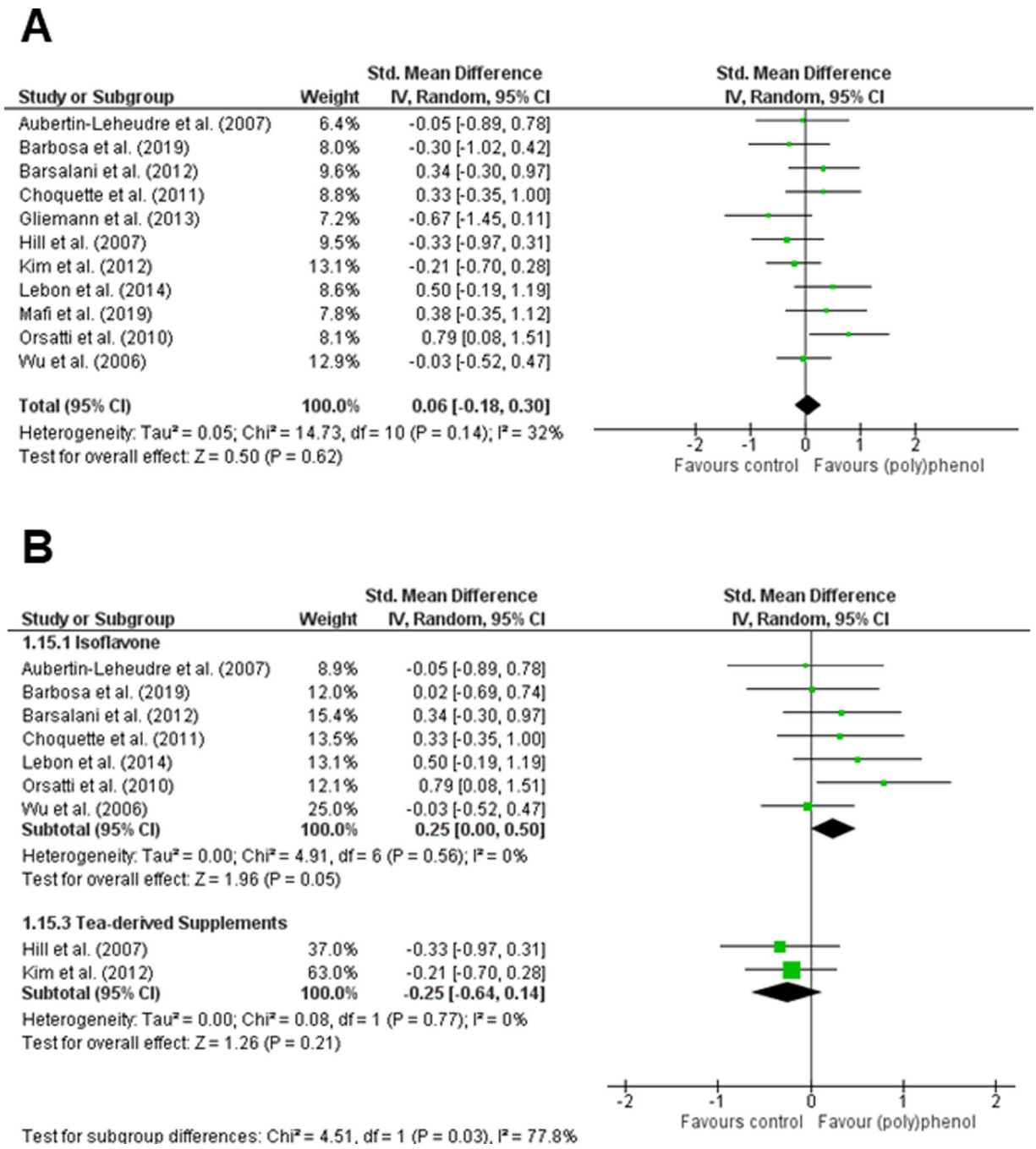

Figure 6. Forest plots for the effects of (poly)phenol supplementation on changes in lean mass (A); sub-group analysis of supplement type on lean mass (B). Data are presented as random effect point estimates (SMD) with 95% confidence intervals (CI) and the diamonds at the bottom of each forest plot corresponds to the overall effect estimate.

control group (i.e., an exercise-only group) or had a high risk of bias, and/or provided data as mean changes from baseline, did not significantly alter the pooled results for lower- body strength (n = 2 removed), $\dot{V}O_{2max}$ (n = 1 removed), body fat (n = 3 removed) and lean body mass (n = 4 removed). We did not perform sensitivity analysis when only two studies were available.

Discussion

The main findings of the present systematic review and meta-analysis are: 1) (poly)phenols do not modulate training-induced improvements in $\dot{V}O_{2max}$, peak power output, or muscle strength, but may augment exercise capacity; 2) (poly)phenols do not stimulate greater body fat losses, but isoflavones may enhance lean mass gains; and 3) resveratrol may blunt aerobic exercise-induced adaptations. Only 5 types of (poly)phenols were examined in the eligible studies, though most were with isoflavones or derived from green tea. Overall, our analysis included a limited number of studies with small sample sizes, making it difficult to draw definitive conclusions about the efficacy of (poly)phenols for stimulating exercise-induced fat loss or physiological adaptations.

The most frequently measured outcome was changes in body composition, either as fat mass losses or lean mass gains. Our pooled analysis suggests (poly)phenols, predominantly isoflavones and green tea extracts, were no better than a placebo for altering body fat or lean mass when combined with exercise. This suggests any effects these (poly)phenols may have on thermogenesis (Lin and Lin-Shiau 2006; Santos et al. 2018) do not translate to greater fat losses during an exercise training program. In contrast, our sub-group analysis suggested isoflavones augmented lean mass gains when taken alongside exercise-training, albeit with a small effect (SMD: 0.25). It is unclear why isoflavones seemed to augment lean mass gains, but the tea-derived (poly)phenols in our other sub-group analysis did not. It could be because there were more studies using isoflavone supplementation and this gave us greater statistical power to detect effects. It is also possible that health status influenced these results; the studies with isoflavone supplementation were all in post-menopausal females. The length of the intervention could have also influenced the results; those with isoflavones tended to be of longer duration ($\geq$6 months) than the studies in tea (poly)phenols (3 months). It might be that a longer training and supplementation period is required to achieve meaningful changes. It is also possible that isoflavones are simply more potent than tea derived (poly)phenols due to their comparatively superior bioavailability, irrespective of dose (Rio et al. 2013). Future studies are required to explore the effects of combing isoflavones and exercise-training in other populations.

Akin to studies with the nutritional antioxidants vitamin C and E (Paulsen, Hamarsland et al. 2014; Gomez-Cabrera et al. 2008), there was evidence from individual studies that (poly)phenols blunted exercise-induced improvements in $\dot{V}O_{2max/peak}$ (Gliemann et al. 2013; Scribbans et al. 2014; Schwarz et al. 2018). Two of these studies administered resveratrol, a stilbenoid found in red wine that has gained attention as an exercise mimetic (Momken et al. 2011; Guerrieri, Moon, and van Praag 2017). In a sub-group analysis, resveratrol had a moderate (SMD: 0.54), albeit non-significant, antagonistic effect on exercise-induced changes in $\dot{V}O_{2max}$. The attenuation in $\dot{V}O_{2max}$ gains in these studies contrasts with animal data, which consistently shows resveratrol augments physiological adaptations associated with exercise (Dolinsky et al. 2012; Lagouge et al. 2006; Hart et al. 2013). The mechanisms by which resveratrol blocks these adaptations in humans is not well-understood. One study suggested that resveratrol may have blunted redox signaling in skeletal muscle, although they did not measure any reactive species or redox changes to confirm this postulate (Gliemann et al. 2013). Scribbans et al. (2014) found that resveratrol blunted the increase in PGC1-α and Sirtuin 1 expression, which could partly explain how resveratrol compromised improvements in $\dot{V}O_{2max}$. Future studies are needed to confirm these findings and determine how resveratrol and other (poly)phenols may disrupt reactive species mediated signaling, and other putative signaling responses, to hinder exercise-induced physiological adaptations.

There was no effect of (poly)phenols on exercise-induced changes in $\dot{V}O_{2max}$, muscle strength, peak power output or timed-up and go test, but a small improvement in exercise performance, as measured by time-to exhaustion and time trial tests, was observed. The studies measuring exercise capacity all used a different (poly)phenol (Table 2), so these results are unlikely related to the type of supplement consumed. Mechanisms to explain these effects are unclear, but combining (poly)phenols with exercise-training has been shown to enhance mitochondrial biogenesis and antioxidant responses, at least in animal models (Davis et al. 2009; Bruns et al. 2018; Sahin et al. 2016). Assuming these changes are reproducible in humans, this could account for enhanced exercise performance after exercise training with concomitant (poly)phenol supplementation. While these findings are promising and warrant further investigation, they should be interpreted cautiously as only 4 studies were included in the analysis and the effect size was moderate (SMD: 0.67).

Ageing is associated with progressive disruption to immune function, redox balance, and protein signaling, all of which attenuate the ability to adapt to an acute stress, such as exercise (Done et al. 2016). As such, older adults may not receive the same physiological benefits from exercise as their younger counterparts. Although not a consistent finding, studies have found reestablishing immune function and redox balance with anti-inflammatory drugs or nutritional antioxidants may augment exercise-induced adaptations in older adults, while having deleterious effects in healthy younger adults (Trappe et al. 2016; 2011; Gomez-Cabrera et al. 2013). Analogously, (poly)phenols may also preferentially benefit older adults, although this has received less attention in the literature. Although the present study intended to assess the potential for an age dependence of (poly)phenol supplementation during training by performing a sub-group analysis of older and younger adults for each outcome, there was only sufficient data to analyze age-related differences for body fat losses, and there was no significant effects in either cohort. The mediating role of age on the efficacy of (poly)phenols and exercise warrants further research.

Few studies assessed the combined effect of (poly)phenols and exercise-training in young athletes. Only one study recruited athletes (national level taekwondo athletes) (Gaamouri et al. 2019) and four studies recruited participants described as healthy or recreationally active ($\dot{V}O_{2max/peak} \leq 50\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$) (Ichinose et al. 2011; Schwarz et al. 2018; Thompson et al. 2018; Sadowska-Krępa et al. 2019). Sub-group analysis of these four studies (data not shown) revealed no effect of (poly)phenol supplementation on any of the outcomes they measured, suggesting training status may not influence the efficacy of (poly)phenols to mediate exercise training adaptations. However, more research is needed to confirm this given the small number of eligible studies. Changes in muscle strength were also only measured in untrained older adults, so the findings of the current study are unlikely to represent changes in younger adults, given strength adaptations are affected by

training status and age (Lemmer et al. 2000; Ahtiainen et al. 2003).

This review had several limitations. Firstly, many of the included studies were hampered by low sample sizes. Only four studies performed a *priori* calculation to ensure sufficient statistical power (Giolo et al. 2018; Bagheri et al. 2020; Barbosa et al. 2019), such that many were probably not adequately powered to detect meaningful changes. Secondly, some studies were of poor quality, since they did not employ a double-blind design (n = 2) or include a placebo control group (e.g., exercise only) (n = 3). Thirdly, due to a lack of homogenous studies, it was not possible to conduct sub analysis to discern the influence of sex, and (poly)phenol dose and duration on the outcomes of the study. It should all be noted that most studies did not state when they provide supplements in relation to the exercise bouts (e.g., 1 h pre or post-exercise) and, thus, we could not assess whether supplement timing influenced the results. We suggest future studies report this information. Finally, as our analysis included only a few types of (poly)phenols, principally isoflavones and those from green tea, our findings are not representative of other (poly)phenols.

Conclusion

This review found no effect of (poly)phenols on exercise-induced changes in body fat, muscle strength and $\dot{V}O_{2max}$. The small benefit of (poly)phenols for exercise capacity warrants further investigation since the observation is limited by the low number of studies. Overall, our findings suggest consuming (poly)phenol supplements alongside exercise training is unlikely to stimulate greater changes in performance or body composition, with the exception perhaps of isoflavones, which may enhance lean mass gains in postmenopausal females. These conclusions are limited by the small number of studies assessing the combined effects of exercise and (poly)phenol supplementation, irrespective of (poly)phenol type and dose. Future studies should employ rigorous study designs and ensure they are adequately powered to detect meaningful group effects. More in vivo research is needed on the combined and independent effects of other commonly consumed (poly)phenol supplements, such as curcumin, cocoa flavanols, and hydroxytyrosol, and the mediating role age and exercise type, to provide greater insight into the potential of (poly)phenol supplements to impact the adaptations to exercise training.

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