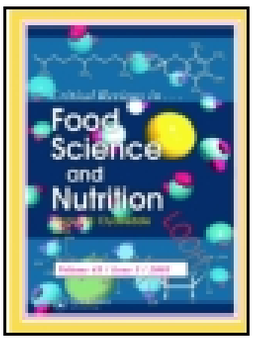

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REVIEW

Effects of coffee consumption on arterial stiffness and endothelial function: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background: Endothelial function (EF) and arterial stiffness (AS) are predictors of cardiovascular disease. As previous research concerning the effect of coffee intake on EF and AS was controversial, we conducted a systematic review and meta-analysis to synthesize research.

Methods: We performed a systematic search in PubMed, Scopus and Web of Science to find clinical trials investigating the effect of coffee intake on EF or AS up to March 2020.Random-effects models were used to estimate the pooled weighted mean difference (WMD) between intervention and control groups for randomized controlled trials (RCTs). Between study heterogeneity was estimated using Cochran's Q and the I^2-inconsistency index. Internal validity of included randomized trials was determined with the Cochrane Collaboration's tool for assessing the risk of bias.

Results: Twenty-three articles were included for qualitative and 11 articles for quantitative synthesis. Meta-analysis of 14 RCTs (nine articles) indicated a positive short-term (postprandial) effect of coffee intake on flow-mediated dilation (FMD) as a measure of EF (WMD: 1.93%[95% CI: 1.10–2.75]; I^2= 97.9%). Meta-analysis of three long-term RCTs(two articles) found no such effect on FMD (WMD: −0.08% [−3.82 to 3.66]; I^2= 61.4%).Most short-term information was from studies at low or unclear risk of bias, while the proportion of long-term information from studies at high risk of bias was considerable.

Conclusion: The results from this meta-analysis suggest a beneficial short-term effect of coffee intake on EF as measured by FMD. Base on systematic review results acute and chronic intake of coffee products may exerts an unfavorable effect on AS. While we found no such effect concerning long-term coffee intake, this latter finding must be interpreted cautiously as the number of studies were low and included studies had a considerable risk of bias.

KEYWORDS
Coffee; caffeine; arterial stiffness; endothelial function; meta-analysis

Introduction

Cardiovascular diseases (CVDs)is a leading cause of mortality and morbidity worldwide (Bowen et al. 2018). Impairment of vascular function, vascular rigidity and endothelial dysfunction have been described as markers of CVD, and they are independent predictors of cardiovascular risk (Vlachopoulos et al. 2004; Maruhashi et al. 2018). Noninvasive vascular function tests have been developed to measure endothelial function (EF) and vasoreactive vascular changes (Maruhashi et al. 2018). These procedures have a pivotal role in the early diagnosis of arteriosclerosis and cardiovascular events (Ochiai et al. 2004). Flow-mediated dilation (FMD) is a typically used measure of EF (Matsuzawa et al. 2015), while pulse wave velocity (PWV) and augmentation index (AIx) are typically used measures of arterial stiffness (AS) (Maruhashi et al. 2018; Vlachopoulos, Panagiotakos, et al. 2005; Vlachopoulos et al. 2007; Burlá et al. 2019; Deanfield, Halcox, and Rabelink 2007; Solanki et al. 2019). Both AS and endothelial dysfunction are considered an initial stage of arteriosclerosis (Ochiai et al. 2004; Suzuki et al. 2019). In addition, some studies have found an association between AS and hypertension (Shirwany and Zou 2010), cognitive function (Pase et al. 2012), and increased damage to blood vessels particularly in the brain and kidneys (Mitchell 2008).

Effective strategies to prevent CVDs are dearly needed, and diet is a well-known modifiable factor with impact on morbidity and mortality. Nowadays studies have revealed that diet is an important factor for preventing or controlling various CVD related outcomes (Daneshzad et al. 2019; Sepidarkish et al. 2020). Recently, we have shown in a meta-analysis that cocoa-based products consumption had beneficial effect on arterial stiffness parameters in adults (Jafari Azad, et al. 2020). Also, coffee is widely drunk throughout the world and in the most of countries is consumed by people every day. It contains a complex mixture of compounds

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including caffeine, antioxidants, vitamin B_3, magnesium, potassium and polyphenols like chlorogenic acids (Nieber 2017).The particular profile is dependent on the form of coffee bean, roasting and processing (Nieber 2017).Several studies have assessed the effects of coffee intake on various diseases such as type 2 diabetes (Ding, Bhupathiraju, Satija, et al. 2014), liver dysfunction (Liu et al. 2015) and inflammatory diseases (Andersen et al. 2006).

Previous evidence of the effects of coffee intake on EF and AS was inconclusive. Researchers have found coffee consumption to be related with endothelial dysfunction (Papamichael et al. 2005; Shechter et al. 2011), aortic stiffness and wave reflections (Vlachopoulos, Panagiotakos, et al. 2005). Some studies indicated that coffee consumption might increase AS (Washio, Sasaki, and Ogoh 2017; Vlachopoulos 2003; Mahmud and Feely 2001); others found coffee to improve EF (Suzuki et al. 2019; Kajikawa et al. 2019). Another study reported a decrease in FMD after coffee intake (Buscemi et al. 2010), but in yet other studies, coffee intake was not found to have a significant effect on PWV (Echeverri et al. 2017) and FMD (Papamichael et al. 2005).

These contradictory findings from prior research are the reason for which we conducted a systematic review and meta-analysis to synthesize evidence concerning coffee intake and its effects on AS and EF.

Methods

This study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher 2009), however, it was not protocolized beforehand due to time constraints.

Search strategy

To provide a comprehensive assessment of all available evidence, we searched three main international data sources: PubMed, Scopus and Web of Science (March 2020). Search strings can be found in the Appendix. To prevent missing related studies, we also checked the references of included papers. Two investigators (BJA and JH) judged the eligibility of articles and any non-agreement was resolved by a third researcher (ED).

Eligibility criteria

Clinical trials, published in English, that assessed the effect of different forms of coffee intake on AS or EF were eligible. Studies were included if they met the following criteria: Study design being a clinical trial (for qualitative synthesis) or randomized controlled trial (RCT; either parallel or crossover design; for meta-analysis); conducted in adult subjects (>18 years); reporting mean and standard derivation (SD) of their outcomes at baseline and end of study (or mean changes) for the intervention and the control group.

Data extraction

Consumption of coffee-derived products was considered to be the intervention.AS and EF measures were included as outcomes. The following characteristics were extracted from each included study: study first author, type of study, year of publication, number of intervention and control groups, population, participant gender, participant age, study design, study location, duration of intervention; and dosage, means and SD of AS and EF measure before and after intervention. Studies were dichotomized into investigations of short-term (postprandial) or long-term effects.

Assessment of study quality

A systematic assessment of risk of bias was performed for trials included in the meta-analysis with the Cochrane Collaboration's risk of bias tool (Higgins et al. 2011). Two authors (BJA and JH) independently evaluated the quality of included articles.

Data synthesis and statistical analysis

Mean changes in AS and EF measures were defined as our dependent variables. The following formula was used to calculate missing SDs for studies that did not report SD of the mean difference: SD_{change}= square root [($SD_{baseline}^2$+SD_{final}^2) − (2 × R × $SD_{baseline}$× SD_{final})].We used a correlation coefficient of 0.9 as *R*-value of the above-mentioned formula (Borenstein, et al. 2009). For studies that reported standard error instead of standard deviation, we estimated the SD by (SD = SE * $\sqrt{n}$), *n* being the number of participants. If a study reported the outcome in graphic form, data extraction was performed using GetData Graph Digitizer 2.24 (Fedorov 2002). Assessment of publication bias was performed by visual inspection of funnel plots along with Egger's regression tests.

Random-effects meta-analysis estimated the pooled weighted mean difference (WMD) between intervention and control groups (RCTs only). We performed subgroup analyses to determine sources of heterogeneity. Further sensitivity analysis was carried out to investigate the effect of each study on the overall analysis (leave-one-out approach).

Results

Study selection

Overall, 2601 potential records were identified in the databases and by hand search, and 23 articles were finally included in our qualitative analysis. Eleven articles provided randomized evidence and were included in quantitative synthesis (meta-analysis). The study selection flow chart is presented in Figure 1.

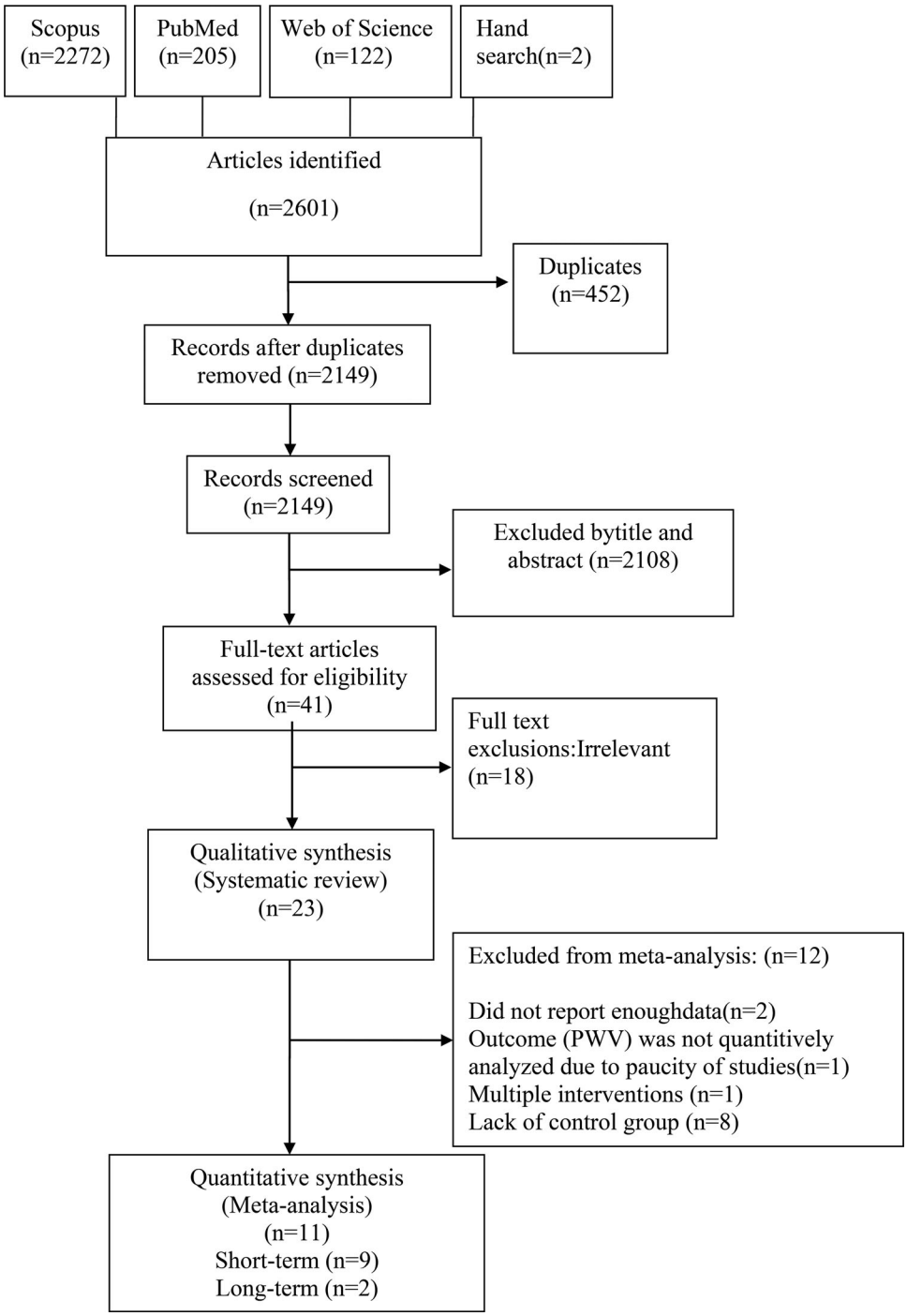

Figure 1. Study selection flow chart.

Study characteristics

The general characteristics of all studies included in our qualitative analysis are shown in Table 1. Short-term data were finally pooled from nine eligible articles including 483 subjects (42.9% males), 246 subjects in the treatment group and 237 subjects in the control group. These RCTs were published from 2011 to 2019, were carried out in Europe (Mills et al. 2017), Asia (Shechter et al. 2011; Kajikawa et al. 2019; Jokura et al. 2015; Ochiai et al., 2015) and Australia (Boon et al. 2017; Mubarak et al. 2012; Ward et al. 2016), and used different doses of coffee ranging from 18 ml/d to 600 ml/d (except one which used less than 10 ml/d) (Mills et al. 2017). The treatment duration ranged from 60 to 300 min. Individuals in 85.7% of short-term studies were healthy subjects. Two studies enrolled patients with hypertension (Kajikawa et al. 2019) and coronary artery disease (Shechter et al. 2011). The age of subjects in short term-studies was between 26 and 59 years. All included studies were crossover in design.

Concerning long-term intake, data were pooled from two eligible articles including 115 subjects (57 subjects in the treatment group, 58 subjects in the control group). These RCTs were published in 2016 and 2019. One study was

Table 1. Characteristics of studies included for qualitative synthesis.

Author (Year), Country	Study design	Population	In/Cn Sex (age)	Duration	Dose (ml/d)	Outcome	Group	
							Intervention	Control
Short-term (minutes)								
Buscemi et al. (2009) Italy.	crossover	Healthy Subjects	15/15 Both (29 ± 11.6)	60	50	⊠FMD	(50 ml) two cups decaffeinated espresso coffee (10 mg caffeine)	(25 ml) one cup decaffeinated espresso coffee (5 mg caffeine).
Buscemi et al. (2010) Italy.	Crossover	Healthy Subjects	20/20 Both (31 ± 8.9)	60	25	⊠FMD	(25 ml) one cup of caffeinated (CC) Italian espresso coffee (caffeine:130 mg)	(25 ml) one cup of decaffeinated (DC) Italian espresso coffee (caffeine: 5 mg)
Shechter et al. (2011) (a) Israel.	Crossover	subjects without CAD	40/40 Both (53 ± 6)	60	375	⊠FMD	capsules containing caffeine 200 mg (2.5 cups of coffee)	placebo capsules
Shechter et al. (2011) (b) Israel.	Crossover	subjects with CAD	40/40 Both (53 ± 8)	60	375	⊠FMD	capsules containing caffeine 200 mg , (2.5 cups of coffee)	placebo capsules
Echeverri et al. (2017) Colombia.	crossover	Healthy Subjects	30/30 Both (46.2 ± 10.4)	60	14	⊠PWV ⊠ AIx	Caffeinated excelso-coffee (caffeine-151.2 mg)	Decaffeinated excelso-coffee (caffeine-3.92 mg)
Washio, Sasaki, and Ogoh (2017) Japan.	crossover	Healthy Subjects	10/10 Males (21 ± 0.3)	60	250	⊠baPWV	Caffeinated Coffee (containing 150 mg of caffeine)	Placebo: (decaffeinated coffee containing 4.5 mg of caffeine
Ioakeimidis et al. (2018)(a) Greece.	crossover	Healthy Subjects (Non-habitual Consumers)	13/13 Both (31 ± 9)	60	25	⊠cfPWV ⊠ AIx	Coffee espresso (caffeine:80 mg)	Placebo (hot water) volume was similar to that of coffee
Ioakeimidis et al. (2018) (b) Greece.	crossover	Healthy Subjects (habitual Consumers)	11/11 Both (34 ± 9)	60	25	⊠cfPWV ⊠ AIx	Decaffeinated coffee Espresso(caffeine:3mg)	Placebo (hot water) volume was similar to that of coffee
Ioakeimidis et al. (2018) (c) Greece.	crossover	Healthy Subjects (habitual Consumers)	11/11 Both (34 ± 9)	60	25	⊠cfPWV ⊠AIx	Coffee espresso (caffeine:80 mg)	Placebo (hot water) volume was similar to that of coffee
Ioakeimidis et al. (2018) (d) Greece.	crossover	Healthy Subjects (Non-habitual Consumers)	13/13 Both (31 ± 9)	60	25	⊠cfPWV ⊠AIx	Decaffeinated coffee Espresso(caffeine:3mg)	Placebo (hot water) volume was similar to that of coffee
Mahmud and Feely (2001) Ireland.	crossover	healthy subjects	7/7 Both (26 ± 6)	90	250	⊠cf.PWV ⊠AIx	freshly brewed caffeinated (150 mg) coffee.	freshly brewed decaffeinated (<2 mg) coffee.
Vlachopoulos et al. (2004) Greece.	crossover	Healthy Subjects Smoker	10/10 Both (33 ± 3)	90	300	⊠cf.PWV ⊠AIx	caffeine (200 mg, equivalent to 2 cups of coffee) + smoking one standard cigarette 60 min after coffee intake,(2 cups of coffee)	smoking one standard cigarette 60 min after placebo intake
Papamichael et al. (2005) Greece.	crossover	Healthy Subjects	17/17 Both (28.9 ± 3)	120	150	⊠FMD	a cup of caffeinated coffee (80 mg of caffeine), (1 cup of coffee)	decaffeinated coffee (<2 mg of caffeine)
Kajikawa et al. (2019) Japan.	crossover	patients with stage 1 HTN	9/9 Both (56 ± 15)	120	185	⊠FMD	Coffee with a high content of CGAs and low content of HHQ (CGAs: 412 mg, HHQ:0.11 mg, and caffeine: 69 mg)	placebo (CGAs: 0 mg, HHQ: 0.1 mg, and caffeine: 59 mg) Coffee flavored agents

Karatzis et al. (2005) Greece.	crossover	Healthy Subjects	16/16 Both (29 ± 3.2)	120	240	⊠ AIx	Caffeinated coffee (80mg of caffeine)	decaffeinated coffee
Mubarak et al. (2012) Australia.	crossover	Healthy Subjects	23/23 Both (52.3 ± 10.6)	120	300	⊠FMD	Coffee (400 mg CGAs), (2 cups of coffee)	Water
Vlachopoulos, Hirata, and O'rourke (2003) Australia	crossover	healthy subjects	20/20 Both (50 ± 16)	180	375	⊠cf.PWV ⊠ AIx	caffeine (250 mg) a dose equivalent to 2.5 cups of coffee	placebo
Ward et al. (2016)(a) Australia.	crossover	Healthy subjects	14/14 Both (59.9 ± 8.2)	240	300	⊠baFMD	CGA-enriched coffee (CGA :450mg + 1 g maltodextrin), (2 cups of coffee)	1 g maltodextrin
Ward et al. (2016)(b) Australia	crossover	Healthy subjects	14/14 Both (59.9 ± 8.2)	240	600	⊠baFMD	CGA-enriched coffee (CGA :900mg + 1 g maltodextrin). (4 cups of coffee)	1 g maltodextrin
Jokura et al. (2015) Japan.	crossover	Healthy Subjects	19/19 Males (38.1 ± 8.4)	240	185	⊠FMD ⊠FMD	Coffee polyphenol extract containing beverage(355 mg of CGAs and 54.9 mg of caffeine)	Placebo (coffee-flavored , Free CGAs and 54.9 mg of caffeine)
Ochiai et al. (2015) Japan.	crossover	Healthy Subjects	13/13 Males (44.9 ± 5.0)	240	300	⊠FMD	Coffee bean polyphenols beverage (600 mg of CGAs = two cups of coffee)	Placebo: no coffee bean polyphenols beverage
Boon et al. (2017) (a) Australia.	crossover	Healthy Subjects	12/12 Both (59.4 ± 6.4)	240	18	⊠FMD	caffeinated coffee (300mg CGA in 200mL of hot water)	200ml of hotwater
Boon et al. (2017) (b). Australia.	crossover	Healthy Subjects	12/12 Both (59.4 ± 6.4)	240	18	⊠FMD	decaffeinated coffee (287mg CGA in 200mL of hot water)	200ml of hot water
Jokura et al. (2015) (a) Japan.	crossover	Healthy Subjects	10/10 Males (32.6 ± 6.7))	240	185	⊠FMD	coffee polyphenol extract beverage with HHQ (contained 300 mg of CGAs and 0.7 mg of HHQ)	placebo,(not contain CGAs or HHQ)
Jokura et al. (2015) (b) Japan.	crossover	Healthy Subjects	10/10 Males (32.6 ± 6.7))	240	185	⊠FMD	coffee polyphenol extract beverage without HHQ (contained 306 mg of CGAs and 0.1 mg of HHQ)	placebo,(not contain CGAs or HHQ)
Mills et al. (2017) (a) U.K.	crossover	Healthy Subjects	15/15 Males (26.3 ± 1.6)	300	3.6	⊠FMD	coffee (CGAs:310 mg and 110 mg of caffeine)	110 mg caffeine and 0 mg CGA in hot water
Mills et al. (2017) (b) U.K.	crossover	Healthy Subjects	15/15 Males (26.3 ± 1.6)	300	3.6	⊠FMD	coffee, (CGAs: 89 mg and 110 mg of caffeine)	110 mg caffeine and 0 mg CGA in hot water
Long-term(weeks)								
Suzuki et al. (2019) Japan.	Parallel	Healthy Subjects	8/8 Males (44.6 ± 5.3)	2	100	⊠FMD	CGAs-enriched green coffee bean extract (≈300 mg as CGAs) (included sweetener, acidulant and flavouring.)	Placebo (cGCE was not added to the placebo beverage) (included sweetener, acidulant and flavouring.)
Ochiai et al. (2009) Japan.	Parallel	Subjects with mild HTN	9/12 Both) 30–64(	8	184	⊠FMD	Hydroxyhydroquinone-reduced coffee (CGAs= 300 mg)	Hydroxyhydroquinone-reduced coffee (CGAs =0mg)
Agudelo-Ochoa et al. (2016) (a). Colombia.	Parallel	Healthy Subjects	24/25 Both (20–60)	8	400	⊠FMD	coffee containing high CGAS:780 mg	no coffee consumption

(*continued*)

Table 1. Continued.

Author (Year), Country	Study design	Population	In/Cn Sex (age)	Duration	Dose (ml/d)	Outcome	Group	
							Intervention	Control
Agudelo-Ochoa et al. (2016) (b) Colombia.	Parallel	Healthy Subjects	25/25 Both (20–60)	8	400	⊠FMD	coffee containing a medium CGAs (MCCGA; 420 mg)	no coffee consumption
Ochiai et al. (2004). Japan.	Parallel	Healthy subjects	10/10 Males (36)	16	125	⊠baPWV	green coffee bean extract drink (chlorogenic acid 140 mg/day)	placebo drink

Abbreviations: PWV, pulse wave velocity; baPWV, Brachial-ankle pulse wave velocity; AIx, augmentation index ⊠, no change; ⊠, decrease; ⊠, increase; HTN: Hypertension; CGAs: Chlorogenic acids; CAD: Coronary artery disease; HHQ: Hydroxyhydroquinone.

carried out in Asia (Suzuki et al. 2019), the other in the United States (Agudelo-Ochoa et al. 2016). They used different doses of coffee ranging from 100 ml/d to 400 ml/d. The duration of treatment ranged from 2 to 8 weeks. The average age of subjects was 42.3 years. All participants were healthy subjects. These studies were parallel in design.

Qualitative synthesis

Coffee and endothelial function

Eight studies did not find any significant effect on FMD (Jokura et al. 2015; Ochiai et al. 2015; Boon et al. 2017; Mubarak et al. 2012; Ward et al. 2016; Agudelo-Ochoa et al. 2016; Ochiai et al. 2009), four articles revealed a significant reduction in FMD (Papamichael et al. 2005; Buscemi et al. 2010; Jokura et al. 2015) and six studies indicated a positive effect on FMD (Suzuki et al. 2019; Shechter et al. 2011; Kajikawa et al. 2019; Mills et al. 2017; Ward et al. 2016; Buscemi et al. 2009).

Coffee and arterial stiffness

Three studies did not report a significant effect on PWV (Echeverri et al. 2017; Ochiai et al. 2004; Ioakeimidis et al. 2018) and five articles reported positive effects (Washio, Sasaki, and Ogoh 2017; Mahmud and Feely 2001; Ioakeimidis et al. 2018; Vlachopoulos, Hirata, and O'rourke 2003; Vlachopoulos et al. 2004). Six studies found a positive effect on AIx (Mahmud and Feely 2001; Echeverri et al. 2017; Ioakeimidis et al. 2018; Vlachopoulos, Hirata, and O'rourke 2003; Vlachopoulos et al. 2004; Karatzis et al. 2005), while one study indicated that coffee consumption had no effect on this factor (Ioakeimidis et al. 2018).

Effects of caffeinated and decaffeinated coffee

Among the six articles that compared acute effects of caffeinated and decaffeinated coffee (healthy subjects), three studies indicated that AS was significantly increased after consuming 250 ml caffeinated coffee compared with decaffeinated coffee (Washio, Sasaki, and Ogoh 2017; Mahmud and Feely 2001; Karatzis et al. 2005). Another study found that after consumption 14 g of caffeinated coffee for 60 min, aortic-AIx level was significantly increased; however, it found no effect on the PWV (Echeverri et al. 2017). Two studies showed that intake of one cup of caffeinated coffee exerts an unfavorable effect on EF (Papamichael et al. 2005; Buscemi et al. 2010).

Effects of coffee on consumers with specific habits

One study examined the acute effect of coffee on aortic stiffness and wave reflections in non-habitual compared to habitual coffee consumers. Caffeinated and decaffeinated coffee led to significantly increased in PWV and AIx in non-habitual consumers, while just caffeinated coffee had a significant effect on AS factors in habitual consumers. In other words, caffeinated and decaffeinated coffee consumption is associated with a more potent effect on AS in non-

Table 2. Risk of bias assessment.

Study (Year)	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Short-term						
Shechter et al. (2011)	U	L	L	L	L	U
Jokura et al. (2015)	U	U	U	L	L	U
Ochiai et al. (2015)	U	L	L	L	L	U
Boon et al. (2017)	U	U	U	L	L	U
Jokura et al. (2015)	U	U	U	L	L	U
Mills et al. 2017	L	U	L	L	L	U
Kajikawa et al. (2019)	L	L	L	L	L	L
Mubarak et al. (2012)	L	L	L	L	U	U
Ward et al. (2016)	L	L	L	L	L	L
Long-term						
Agudelo-Ochoa et al. (2016)	U	H	H	L	L	U
Suzuki et al. (2019)	U	L	L	U	L	U

L, low risk of bias; H, high risk of bias; U, unclear risk of bias

habitual than habitual coffee consumers (Ioakeimidis et al. 2018). One article investigated smoking along with 200 mg of caffeine (equivalent to two cups of coffee). It found that the combination exerts a synergistic, unfavorable effect on aortic stiffness (Vlachopoulos et al. 2004).

Effects of coffee polyphenols

Three articles examined the effect of a drink containing coffee bean polyphenol extract in healthy males (duration: 240 min). They reported that consumption of 185 ml of polyphenol coffee extract (equivalent to 2 cups of coffee) with high chlorogenic acid (CGA) content (more than 300 mg) had no significant effect on FMD (Jokura et al. 2015; Ochiai et al., 2015). One short-term study demonstrated that FMD levels increased significantly after coffee intake (containing 89–310 mgCGA) for five hours (Mills et al. 2017). Consuming 400 ml coffee containing a high and medium dose of CGA (420–700 mg) did not have a significant effect on FMD in healthy subjects after eight weeks (Agudelo-Ochoa et al. 2016). Another study, on the other hand, reported that intake of 100 ml CGA-enriched green coffee bean extract (≈300 mg CGA) for two weeks increased the FMD in healthy males (Suzuki et al. 2019). In addition, one study observed that 240 min after consumption of 4 cups of a CGA-enriched coffee (900 mg CGA), FMD levels increased in healthy subjects compared to controls (Ward et al. 2016). A different study found that consumption of 184 ml hydroxyhydroquinone (HHQ)-reduced coffee for 8 weeks, containing 300 mg CGA, did not exert significant effects on EF compared with placebo in subjects with mild hypertension (Ochiai et al. 2009). However, 185 ml of coffee with a high content of CGA (412 mg) and low content of HHQ (0.11 mg) had a positive effect on EF in patients with stage 1 hypertension after 120 min (Kajikawa et al. 2019). Contrarily, in another study coffee polyphenol extract beverage with 0.7 mg of HHQ and 300 mg of CGA decreased FMD significantly after 240 min compared with a placebo beverage in healthy males (Jokura et al. 2015).

Meta-analyses

Risk of bias

The risk of bias assessment of the 11 articles (randomized trials only) included in our meta-analyses is presented in Table 2. Most information concerning the short-term effects of coffee intake was from trials at low or unclear risk of bias. The proportion of information from trials at high risk of bias was considerable in the meta-analysis of studies investigating long-term effects.

Short-term (postprandial)

We only analyzed data concerning FMD (measure of EF) as there was not enough data for other variables to be analyzed quantitatively. Meta-analysis including nine articles (14 studies with 246 cases and 237 controls), showed that coffee intake had a positive effect on FMD (WMD: 1.93%; 95% CI: 1.10–2.75, $p < 0.0001$) ($I^2 = 97.9\%$, $p < 0.0001$) (Figure 2).

Sensitivity analysis (leave-one-out approach) indicated that no single study had an especially pronounced impact on the pooled FMD (Figure 3). Evaluation of publication bias by visual inspection of a funnel plot yielded no confirmation of publication bias (Figure 4). This finding is supported by Egger's test ($p = 0.212$). Since dosage, duration of intervention, type of intervention, population, age of participants, and participants' gender might affect the changes in FMD, we performed further subgroup analyses. The results are summarized in Table 3. According to dose-response evaluation, coffee consumption had stronger effects at a dose of more than 400 ml per day (p(nonlinearity) = 0.019; Figure 5 A). Moreover, duration of consumption showed a significant but non-linear relationship with FMD (p(nonlinearity) <0.0001) (Figure 5B).

Long-term

The pooled estimate (two articles, three studies, including 57 cases and 58 controls) showed no significant effect of coffee intake on FMD in the long term (WMD: −0.08%; 95% CI: −3.82 to 3.66, $p = 0.968$) ($I^2 = 61.4\%$, $p = 0.075$) (Figure 6).

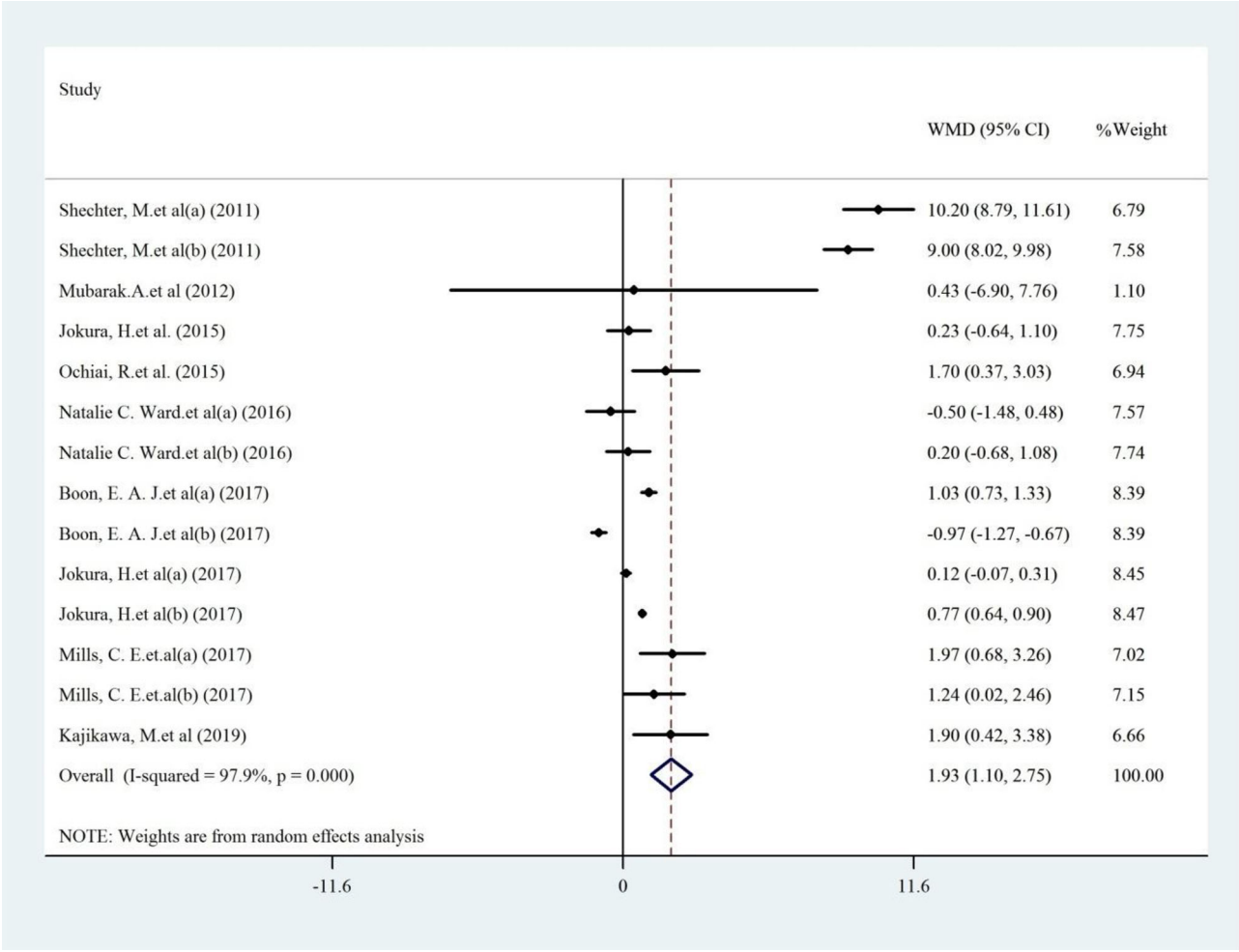

Figure 2. Forest plot of the acute effect of coffee consumption on FMD.

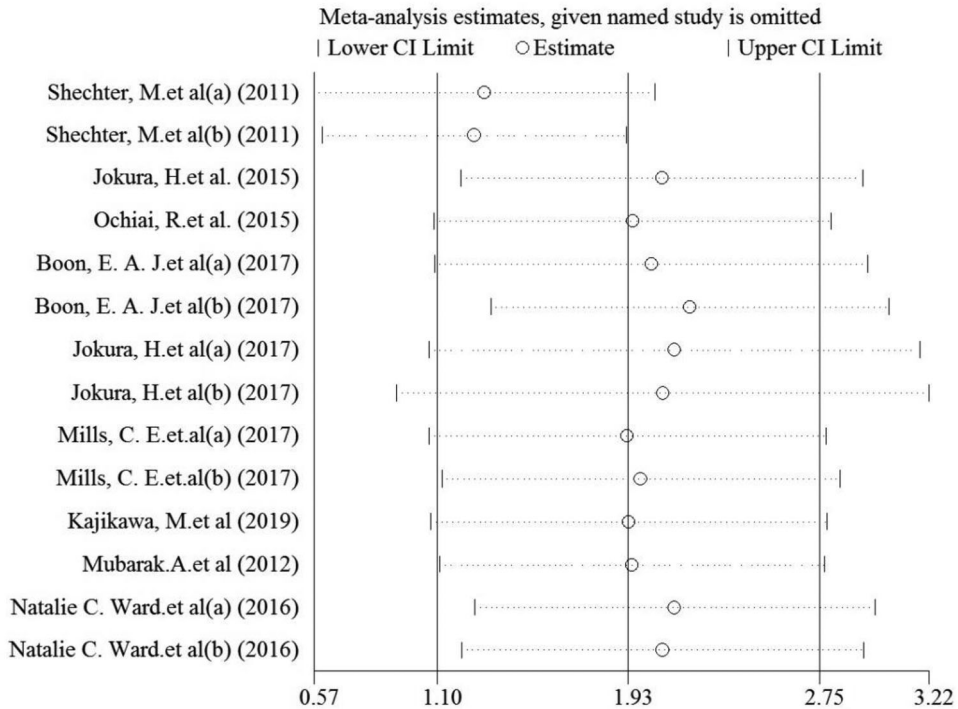

Figure 3. Results of an influence analysis (sensitivity analysis) in which the meta-analysis of FMD is re-estimated omitting each long-term study in turn.

Discussion

The results of our systematic review and meta-analysis suggest a beneficial short-term effect of coffee intake on EF as measured by FMD. Long-term consumption was not associated with a change in FMD; however, the latter analysis was limited by a low number of studies with a high risk of bias. Outcomes concerning AS could not be assessed. Qualitative synthesis suggests that coffee intake increases AS in healthy subjects in the short term–especially in non-habitual consumers. However, this finding must be interpreted with caution because of great heterogeneity between studies; the lack of studies with in of long-term evaluations; and missing quantitative analysis due to a paucity of comparable data.

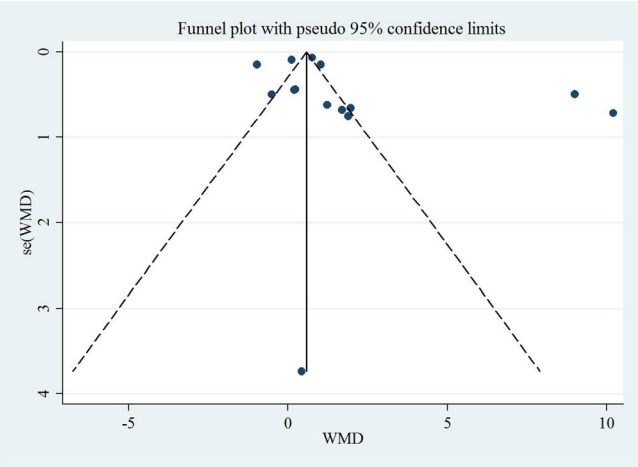

Figure 4. Funnel plot of the weighted mean difference (WMD) versus the S.E. of the weighted mean difference (WMD) for studies that investigated the FMD directly after coffee consumption.

In accordance with our results, previous systematic reviews and meta-analyses revealed that coffee consumption was inversely associated with the risk of type 2 diabetes (Huxley 2009) (in a dose–response manner (Ding, Bhupathiraju, Satija, et al. 2014)) and the risk of metabolic syndrome (Marventano et al. 2016). Furthermore, moderate coffee consumption seems to be inversely associated with CVD risk while heavy coffee consumption was not associated with increased CVD risk (Ding, Bhupathiraju, Satija, et al. 2014).

On the other hand, some studies have shown that long-term coffee consumption is not associated with a change of risk in CVD (Sofi et al. 2007) or hypertension (Steffen et al. 2012). Results of subgroup analysis conform: Coffee consumption in hypertensive individuals was not found to exert an effect on EF. Conversely, in some studies, high coffee consumption has been associated with an increased risk of hypertension (Zhang et al. 2011). Possible explanations for the differing findings in these studies may be the presence of confounders when it comes to the development of arterial hypertension or CVDs. Another possibility is that relationships might be U-shaped or J-shaped as found for the association between coffee consumption and the risk of myocardial infarction and stroke (de Koning Gans et al. 2010; Bonita et al. 2007).

Coffee is a widely drunk beverage. It contains several chemical active ingredients such as caffeine, HHQ, cafestol, CGA, kahweol, anthocyanin and others (O'Keefe, DiNicolantonio, and Lavie 2018; Yamagata 2018). Of these compounds, caffeine has attracted the most attention.

Table 3. Subgroup analyses of short-term effects of coffee and FMD.

Subgroup	Number of studies	Effect size (95% CI)	I^2 (%)	P Heterogeneity[a]	P Within[b]	P Between[c]
Overall	14	1.93(1.10, 2.75)	97.9%	<0.0001	<0.0001	
Country						<0.0001
Asia	7	0.72(0.61, 0.83)	98.8%	<0.0001	<0.0001	
Australia	5	0.02(−0.18, 0.22)	95.4%	<0.0001	0.869	
Europe	2	1.58(0.70, 2.47)	0.0%	0.421	<0.0001	
Population						<0.0001
Healthy subjects	12	0.49(0.40, 0.59)	96.7%	<0.0001	<0.0001	
CAD	1	9.00(8.02, 9.98)	.	.	<0.0001	
HTN	1	1.90(0.42, 3.38)	.	.	0.012	
Gender						0.843
Both	8	0.60(0.40, 0.79)	98.8%	<0.0001	<0.0001	
Male	6	0.57(0.47, 0.68)	87.1%	<0.0001	<0.0001	
Age(year)						0.843
<50	6	0.57(0.47, 0.68)	87.1%	<0.0001	<0.0001	
>50	8	0.60(0.40, 0.79)	98.8%	<0.0001	<0.0001	
Type						<0.0001
1-caffeinated coffee	3	2.05(1.77, 2.33)	99.5%	<0.0001	<0.0001	
2-decaffeinated coffee	1	−0.97(−1.27, −0.67)	.	.	<0.0001	
3-coffee polyphenol extract	4	0.56(0.45, 0.67)	91.0%	<0.0001	<0.0001	
4-coffee containing high CGAs	5	0.53(−0.01, 1.07)	68.8%	0.012	0.057	
5-coffee containing low CGAs	1	1.24(0.02, 2.46)	.	.	0.046	
Dose (ml/day)						<0.0001
<150	4	0.11(−0.09, 0.32)	96.9%	<0.0001	0.278	
>150	10	0.70(0.59, 0.81)	98.2%	<0.0001	<0.0001	
Duration(Minutes)						<0.0001
≤120	4	7.61(6.91, 8.32)	96.3%	<0.0001	<0.0001	
>120	10	0.45(0.35, 0.54)	93.9%	<0.0001	<0.0001	

Abbreviations: HTN, hypertension; CAD, Coronary artery disease; CGAs: Chlorogenic acids.
[a]P Heterogeneity, differences in heterogeneity effect across subgroups.
[b]P Within, source of heterogeneity ($P < 0.1$).
[c]P Between, difference between subgroups mean.

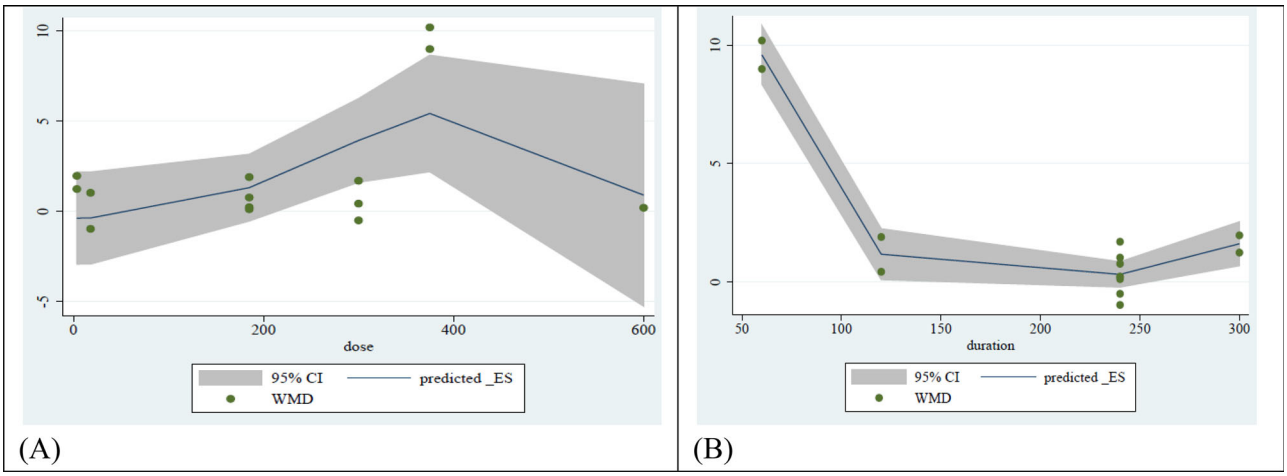

Figure 5. **(A and B).** Non-linear dose-responses between acute intake of coffee and unstandardized mean difference in FMD,(A). Non-linear duration-responses between acute intake of coffee and unstandardized mean difference in FMD, (B).

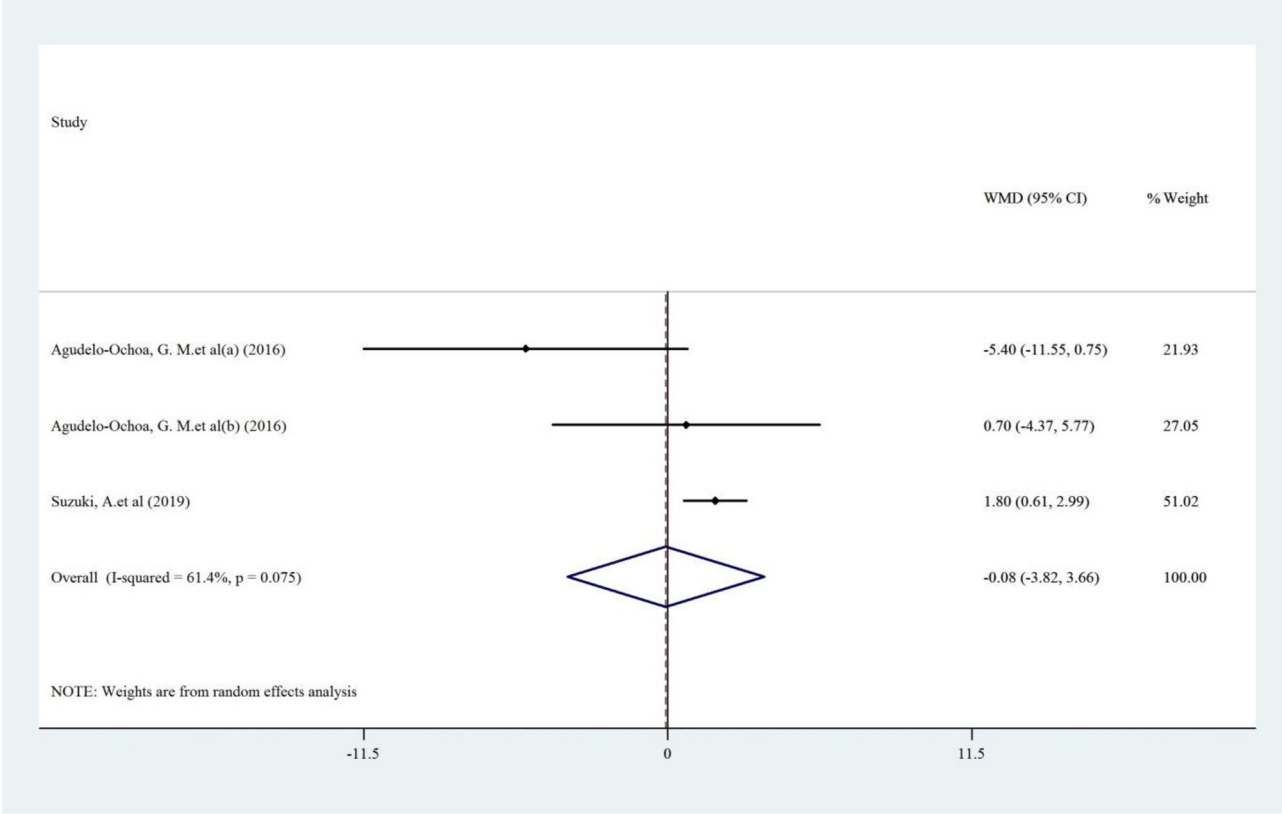

Figure 6. Forest plot of the effect of coffee consumption on FMD in long-term studies.

However, the effects of caffeine on blood pressure (Noordzij et al. 2005; Hartley, Lovallo, and Whitsett 2004) and CVDs (Kleemola et al. 2000; Happonen, Voutilainen, and Salonen 2004) are still controversial. The results of our study suggest that coffee consumption can improve EF in the short term, possibly due to caffeine, but the effects of coffee are usually also attributed to other active ingredients such as the pro-oxidant substance HHQ and the anti-oxidant substance CGA. Endothelial-modulating properties of coffee might be due to complex interrelated effects.

Oxidative stress is usually induced by an imbalance of NO-levels and overproduction of reactive oxygen species (ROS). Generally, it is well known that oxidative stress is a major risk factor of endothelial dysfunction through a decrease in NO bioavailability (Cao et al. 2005). The role of caffeine in EF is complex–it is thought to regulate NO metabolism and homeostasis. The potential beneficial impacts of coffee intake on NO levels may be related to changes in the metabolism of asymmetric dimethyl-arginine (ADMA). ADMA is an endogenous suppressor of nitric oxide synthase (NOS) and metabolized and reduced by the enzyme Dimethyl arginine Dimethyl amino hydrolase 1(DDAH1). Caffeine is associated with elevated amount of DDAH1 and decreased ADMA (Powers and Gallaher 2015).

Several studies have reported that caffeine is a direct and strong antagonist of adenosine receptors (Smits, Lenders, and Thien 1990; Lopes, Pliássova, and Cunha 2019). Vasoconstrictory effects of adenosine are caused by a reduction of NO release from endothelial cells through activation of the adenosine A_1 receptor (Headrick et al. 2013). Caffeine has been reported to elevate NO generation via inhibition of the adenosine receptor A_1 (Chen et al. 2017). In addition, caffeine increases NO production in the endothelium via activation of the ryanodine-sensitive calcium channel and release of calcium from the endoplasmic reticulum (Hatano et al. 1995).

CGA is also found in coffee. It plays a role in ROS scavenging due to its antioxidant properties (Kwon et al. 2010). Several studies showed that CGA ameliorated oxidative-stress-induced endothelial dysfunction by induction of heme oxygenase-1 (HO-1) (Yun, Kang, and Lee 2012). HO is a critical enzyme breaking down pro-oxidative heme to unconjugated bilirubin, ferrous iron and carbon monoxide. Carbon monoxide and unconjugated bilirubin themselves have been revealed to have anti-oxidative and anti-inflammatory proprieties (Otterbein et al. 2000). HO-1 gene expression is increased by the metabolic pathway of nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (Abraham and Kappas 2008). CGA regulates both Nrf2 nuclear translocation and gene expression of antioxidant-response-element (Boettler, Sommerfeld, et al. 2011). Moreover, recent in vivo studies also found CGA to increase NO generation in a dose-dependent manner (Jiang et al. 2016). CGA remarkably protects the cells from H_2O_2-mediated oxidative damages (Yao et al. 2019). Mechanistic studies showed that a main mechanism of CGA antioxidant activities was upregulation of a panel of phase II cytoprotective species, including glutathione, NAD(P)H: quinoneoxido reductase 1, and thioredoxin 1 (Kim et al. 2012). As mentioned before, CGA has been introduced as an activator of the Nrf2-ARE-signaling pathway to perform several cytoprotection mechanisms in various types of cells (Boettler, Sommerfeld, et al. 2011; Bao et al. 2018). In oxidative stress circumstances, CGA may lead to protection against endothelial dysfunction through HO-1/NO/eNOS pathway. CGA scavenges ROS directly and activates eNOS, contributing to amelioration of EF (Li et al. 2013). Inflammation also plays a pivotal role regarding EF (Libby, Ridker, and Maseri 2002), and coffee-CGA has been found to exert robust anti-inflammatory effects (Fukushima et al. 2009).

Adenosine monophosphate-activated protein kinase (AMPK) is present in different type of tissues and regulates multiple pathways of cellular energy homeostasis (Shirwany and Zou 2014). At the same time, AMPK is a critical enzyme for vascular homeostasis and regulation (Sun et al. 2014). Recent findings showed that coffee-CGA increases the phosphorylation of AMPK in human umbilical vein endothelial cells (HUVEC). Intervention with CGA improved mitochondrial dysfunction and decreased oxidized low-density-lipoprotein-induced oxidative damage in HUVEC through activation of the AMPK/peroxisome proliferator-activated receptor γ coactivator-1 pathways and elevation of Sirt-1 function (Tsai et al. 2018). AMPK activation has several beneficial effects on the EF: e.g., it phosphorylates the serine residue of eNOS, which activates eNOS, leading to increased generation of NO from endothelial cells (Hu et al. 2008). In summary, these mechanisms suggest that coffee-CGA probably improves EF by means of an elevation in NO levels via the dual manner of increasing NO generation and reducing NO deactivation.

This systematic review and meta-analysis has several limitations. First, the included studies had rather small sample sizes. Second, the search for studies was limited to English-language articles. However, this search was not only systematic but also comprehensive: Three large databases were searched. In addition, coffee contains hundreds of compounds that might affect outcomes. The effect of additives (sugar and milk) and the different ways of coffee preparation may possibly also account for these discrepancies. In this regard, endothelial function deteriorates after glucose ingestion. However, most included studies have mentioned "No added sugar or milk was permitted" and a lack of additives in the intervention. So, we cannot rule out these limitations in this work. Also, in some studies, the reported dosage of coffee was imprecise due to unscientific measures ("cups"), possibly leading to heterogeneity between studies. Indeed, heterogeneity was considerable in both short-term and long-term analyses. While the long-term analyses must be interpreted with caution not only due to the low number of studies, but also because of the low quality of included trials, all short-term studies except one had the same direction with regard to treatment effects, and most short-term trials' risk of bias was low or unclear. Furthermore, we conducted random-effects meta-analyses, which incorporated between-study variability (as opposed to fixed-effects models), and performed subgroup analyses to search for populations which might benefit more than others.

Conclusion

Our findings suggest a beneficial short-term effect of different form of coffee intake on EF as measured by FMD. However, base on systematic review results acute and chronic intake of coffee products does not appear to have a favorable effect on AS factors. While we found no such effect concerning long-term coffee intake, this latter finding must be interpreted cautiously as the number of studies was low and included studies had a considerable risk of bias. Additional long-term studies with larger sample sizes should be performed to approve our findings.

Disclosure statement

All authors declare that they have no conflict of interest.

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Appendix

((((((((((((((Coffee) OR "Coffee"[Mesh]) OR caffeine) OR "Caffeine"[Mesh]) OR "Chlorogenic acid") OR "green coffee"[Title/Abstract]) OR "green coffee extract"[Title/Abstract]) OR CGA[Title/Abstract]) OR "caffeic acid"[Title/Abstract]) OR "ferulic acid"[Title/Abstract]) OR beverages[Title/Abstract])))) AND ((((((((((((((((("Vascular Function"[Title/Abstract]) OR "Endothelial Function"[Title/Abstract]) OR "Vascular stiffness"[Title/Abstract]) OR "arterial stiffness"[Title/Abstract]) OR "arterial compliance"[Title/Abstract]) OR "endothelium dysfunction"[Title/Abstract]) OR endothelium[Title/Abstract]) OR endothelial[Title/Abstract]) OR "Vascular Reactivity"[Title/Abstract]) OR "flow mediated dilatation") OR "flow mediated dilation") OR "flow-mediated vasodilatation") OR FMD) OR "Pulse wave velocity") OR "Pulse Wave Analysis"[Mesh]) OR "Pulse Wave Analysis") OR PWV) OR "augmentation index")) AND ((((((((((("Intervention Studies"[Title/Abstract]) OR intervention[Title/Abstract]) OR "controlled trial"[Title/Abstract]) OR randomized[Title/Abstract]) OR randomized[Title/Abstract]) OR random*[Title/Abstract]) OR placebo[Title/Abstract]) OR assignment[Title/Abstract]) OR Trial*[Title/Abstract]) OR "randomised controlled trial"[Title/Abstract]))