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Impact of soy milk consumption on cardiometabolic risk factors: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Soy milk contains some beneficial components such as isoflavones which can exert favorable effects on the cardiovascular health. The current study aimed to comprehensively evaluate the potential effects of soy milk consumption on cardiometabolic risk factors in adults.

Methods: Relevant articles published up to June 2020 were systematically retrieved from SCOPUS, PubMed/MEDLINE, EMBASE, and Web of Science databases. In our study, we included all the randomized controlled trials (RCTs) investigating the impact of soy milk consumption on various cardiometabolic risk factors in adults (age $\geq$ 18 years). A *meta*-analysis of the eligible studies was performed using the random-effects model.

Results: The quantitative *meta*-analysis of 18 eligible RCTs (665 participants, age range 18–65 years) demonstrated that the consumption of soy milk significantly reduced systolic ($P < 0.001$) and diastolic ($P = 0.002$) blood pressure, total ($P = 0.001$) and low-density lipoprotein ($P = 0.041$) cholesterol, waist circumference ($P = 0.005$), C-reactive protein ($P < 0.001$), and tumor necrosis factor-alpha ($P = 0.016$). Significant between-study heterogeneity was found for the pooled effect sizes of blood pressure and low-density lipoprotein cholesterol. In addition, the subgroup analyses indicated that the decrease in systolic blood pressure (SBP) was more pronounced when soy milk was consumed for $\leq$ 4 weeks. However, there were no significant differences between soy milk and control groups for the other factors, namely body weight, body mass index (BMI), high-density lipoprotein cholesterol, triglycerides, fasting blood glucose (FBG), and fasting insulin, interleukin-6, and fibrinogen.

Conclusions: The current systematic review and *meta*-analysis revealed that incorporating soy milk into the diet might favorably affect several cardiometabolic risk factors in both healthy and unhealthy individuals.

Abbreviations: DBP, diastolic blood pressure; ES, effect size; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; T2D, type 2 diabetes; RCT, randomized controlled trials; WC, Waist circumference.

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1. Introduction

Cardiometabolic disorders affect large numbers of subjects worldwide and are recognized as one of the leading causes of death (de Magalhães Cunha et al., 2018; Rao, 2018). More than 60% of the deaths from chronic kidney disease, diabetes, and cardiovascular disorders are linked to the presence of cardiometabolic risk factors, such as dyslipidemia, inflammation, hypertension, and obesity (Danaei et al., 2014). Moreover, these risk factors are associated with a significant increase in medical expenditures as well as loss of productivity (McQueen et al., 2016). Thus, many researchers have focused on unravelling non-pharmacological approaches to the management of cardiometabolic risk factors (O'Keefe, Gheewala, & O'Keefe, 2008). Indeed, lifestyle changes involving modification of dietary habits are increasingly emerging as key steps in the management of cardiometabolic risk factors (Micha et al., 2017; Dariush Mozaffarian, Wilson, & Kannel, 2008).

Soy milk, which is derived from whole soybeans, is one of the most popular functional beverages (Wang et al., 2013). Due to its high nutritional value, soy milk is a suitable milk-substitute for vegans/vegetarians and those who suffer from milk allergy or lactose intolerance. It is also regarded as a low-cost and high-quality source of protein and energy for malnourished subjects, as well as in populations with an insufficient supply of cow milk (Mazumder & Begum, 2016; Sethi, Tyagi, & Anurag, 2016). Soy milk contains some beneficial components such as isoflavones and polyphenols which can exert favorable effects on the cardiovascular health (Takatsuka et al., 2000). Moreover, as a rich source of isoflavones, soy milk intake is associated with a lower incidence of cancer, osteoporosis, menopausal symptoms, and cardiovascular diseases (Woodside, Brennan, & Cantwell, 2016).

The potential health-promoting effects of soy milk consumption on several cardiometabolic risk factors have been examined in several interventional studies (Azadbakht & Nurbakhsh, 2011; Beavers, Serra, Beavers, Cooke, & Willoughby, 2009; Eslami et al., 2019; SH Faghih, Abadi, Hedayati, & Kimiagar, 2011). However, there are discrepancies in the reported results. Some randomized controlled trials (RCTs) have reported on the beneficial effects of soy milk on several cardiometabolic risk factors, that is, blood pressure, glycemic profile, and inflammatory markers in non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus patients (Maleki et al., 2019; Miraghajani, Esmaillzadeh, Najafabadi, Mirlohi, & Azadbakht, 2012). However, several studies have reported contradictory results (Beavers et al., 2009; Nourieh, Keshavarz, HosseinzadehAttar, & Azadbakht, 2012).

To our knowledge, there is no systematic review and *meta*-analysis regarding the impact of soy milk on cardiometabolic risk factors. Hence, we sought to conduct a systematic review and *meta*-analysis of RCTs to assess the overall impact of soy milk consumption on cardiometabolic risk factors.

2. Methods

2.1. Search strategy

The current systematic review was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement criteria (Moher et al., 2015). The study protocol has been previously registered with the PROSPERO database (ID number: **219486**). The relevant articles were retrieved from four online databases: PubMed/MEDLINE, SCOPUS, Web of Science, and EMBASE. The literature was systematically searched from February 1994 until July 2020 using the following Medical Subject Headings (MeSH) and text keywords: ("Soya Milk" OR "Soy Milk" OR "Soy drink" OR "Soy beverage") AND ("RCT" OR "Intervention" OR "Trial" OR "Control*" OR "Clinical" OR "Random*" OR "Placebo" OR "Assignment" OR "Allocation"). No language limitation was imposed to the literature search. Moreover, we hand-searched the references of any identified review papers to detect other potentially relevant articles.

2.2. Study selection

The studies were selected for full-text review using the EndNote software if they met the following PICOS evidence-based criteria: 1) **P**atients: adult male or female participants (aged $\geq$ 18 years), 2) **I**ntervention: soy milk consumption, 3) **C**omparator: placebo or cow milk, 4) **O**utcomes: reported sufficient data on at least one of the outcomes of interest, namely body weight, body mass index (BMI), waist circumferences (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting blood glucose (FBG), insulin, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and fibrinogen, and 5) **S**tudy design: RCTs. We excluded non-randomized trials, studies without appropriate control groups, animal studies, review articles, unpublished studies (inclusive of conference abstracts and high quality RCTs), and studies that administered soy milk in combination with other compounds such as phytosterols. The primary outcomes of this study included TC, LDL-C, HDL-C, TG, SBP, DBP, WC, FBG, and CRP concentrations. Body weight, BMI, insulin, TNF-α, IL-6, and fibrinogen were considered as secondary outcomes.

2.3. Data extraction

Eligible studies were independently reviewed by two authors (Mh.S. and A.L.) and the following data were extracted: first author's name, study location, publication year, RCT design (cross-over or parallel), sample size (intervention and control groups) participant characteristics (gender, age, and health status), duration of intervention, the amount of soy milk consumed, and the means and standard deviations (SDs) of the intended outcomes at baseline, post-intervention and/or changes between baseline and post-intervention.

2.4. Quality assessment

The details of the quality assessment of the included studies are presented in Table 2. The quality of the RCTs was methodologically evaluated based on the Cochrane risk of bias criteria (JPT Higgins & Wells, 2011). Two authors independently (S.F. and Mh.S.) rated each study as having a low, high, or unclear risk of bias based on the following potential sources of bias: blinding of outcome assessment; allocation concealment; blinding of participants and personnel; random sequence generation; incomplete outcome data; selective reporting; and other bias. Any discrepancies were resolved via discussion with a third author (F.S.).

2.5. Statistical analysis

Data were analyzed using STATA version 12.0 software. Standard formulas were applied to convert different formats of data to the mean and standard deviations (SDs) (JP Higgins, 2011; Hozo, Djulbegovic, & Hozo, 2005). For instance, in the absence of SDs of the change, we calculated it through the following formula: SD changes = square root [(SD baseline^2 + SD final^2) - (2 × R × SD baseline × SD final)]. Also, we converted the standard error of the mean (SEM) to the SD using the following formula: SD = SEM × $\sqrt{n}$, where "n" is the number of subjects in each group. Heterogeneity among studies was appraised using the I-squared (I^2) statistic (J. P. Higgins, Thompson, Deeks, & Altman, 2003). The random-effects model was used for *meta*-analysis of study outcomes. The weighting of studies was done using the generic inverse variance method. In case of multiple evaluations in a single study group, the values belonging to the longest time point were used for the analyses. The effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). Moreover, in order to determine the potential sources of heterogeneity, subgroup analyses based on dose, country, and duration of intervention was performed. The sensitivity

analysis was also done to assess the impact of every individual study on the pooled effect size. The publication bias was examined using the formal Egger's test (Egger, Smith, Schneider, & Minder, 1997)

3. Results

3.1. Study selection

Fig. 1 depicts the literature search and selection process. In the primary systematic search, 865 studies were detected. After removing the duplicate records, a total of 475 publications remained. Thereafter, two investigators (Mh.S. and S.F.) independently and blindly screened the titles/abstracts of the retrieved studies and excluded 446 articles which did not meet the inclusion criteria. After secondary review of full-texts (Mh.S. and S.F.), 29 studies remained of which 11 were excluded due to different reasons. Finally, 18 studies (Azadbakht & Nurbakhsh, 2011; Beavers et al., 2009; Eslami et al., 2019; SH Faghih et al., 2011; S Faghih, Hedayati, Abadi, & Kimiagar, 2009; Gardner, Messina, Kiazand, Morris, & Franke, 2007; Keshavarz, Nourieh, Attar, & Azadbakht, 2012; Lukaszuk, Luebbers, & Gordon, 2007; Maleki et al., 2019; Miraghajani et al., 2012; Miraghajani et al., 2013; Mitchell & Collins, 1999; Mohammad-Shahi, Mowla, Haidari, Zarei, & Choghakhori, 2016; Nourieh et al., 2012; Önning, Åkesson, Öste, & Lundquist, 1998; Onuegbu, Olisekodiaka, Onibon, Adesiyan, & Igbeneghu, 2011; Rivas, Garay, Escanero, Cia Jr, et al., 2002; Takatsuka et al., 2000) with 19 treatment arms were eligible for inclusion in the present *meta*-analysis. Five studies provided data for FBG (Gardner et al., 2007; Keshavarz et al., 2012; Maleki et al., 2019; Miraghajani et al., 2013; Önning et al., 1998), four articles for insulin (29,30,32, 35), seven trials for body weight (Azadbakht & Nurbakhsh, 2011; Eslami et al., 2019; SH Faghih et al., 2011; Keshavarz et al., 2012; Lukaszuk et al., 2007; Miraghajani et al., 2013; Mohammad-Shahi et al., 2016), six studies for BMI (Azadbakht & Nurbakhsh, 2011; Eslami et al., 2019; S Faghih et al., 2009; Keshavarz et al., 2012; Lukaszuk et al., 2007; Mohammad-Shahi et al., 2016), five trials for WC (Azadbakht & Nurbakhsh, 2011; Eslami et al., 2019; S Faghih et al., 2009; Keshavarz et al., 2012; Lukaszuk et al., 2007), five articles for blood pressure (Azadbakht & Nurbakhsh, 2011; Keshavarz et al., 2012; Maleki et al., 2019; Miraghajani et al., 2013; Rivas, Garay, Escanero, Cia Jr, et al., 2002), four studies for CRP (Eslami et al., 2019; Miraghajani et al., 2012; Mohammad-Shahi et al., 2016; Nourieh et al., 2012) and IL-6 (Beavers et al., 2009; Miraghajani et al., 2012; Mohammad-Shahi et al., 2016; Nourieh et al., 2012), and three trials for TNF-α (Beavers et al., 2009; Miraghajani et al., 2012; Mohammad-Shahi et al., 2016) and fibrinogen (Keshavarz et al., 2012; Maleki et al., 2019; Miraghajani et al., 2012). Eight trials reported the effect of soy milk on TG (Eslami et al., 2019; Gardner et al., 2007; Miraghajani et al., 2013; Mitchell & Collins, 1999; Nourieh et al., 2012; Önning et al., 1998; Onuegbu et al., 2011; Takatsuka et al., 2000), and seven trials reported the data on LDL-C, HDL-C, and TC (Eslami et al., 2019; Gardner et al., 2007; Miraghajani et al., 2013; Mitchell & Collins, 1999; Nourieh et al., 2012; Önning et al., 1998; Onuegbu et al., 2011; Takatsuka et al., 2000).

3.2. Study characteristics

The characteristics of the eligible RCTs are displayed in Table 1. Ten studies were conducted in Iran (Azadbakht & Nurbakhsh, 2011; Eslami et al., 2019; SH Faghih et al., 2011; S Faghih et al., 2009; Keshavarz et al., 2012; Maleki et al., 2019; Miraghajani et al., 2012; Miraghajani et al., 2013; Mohammad-Shahi et al., 2016; Nourieh et al., 2012) and

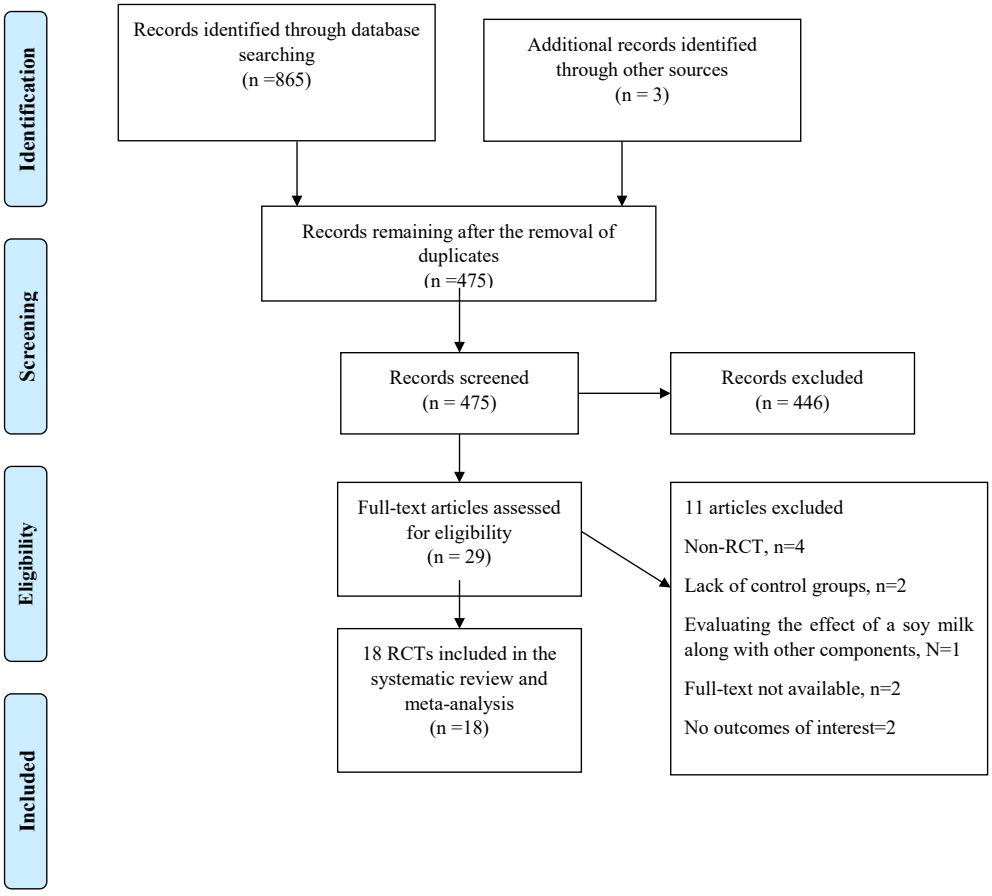

Fig. 1. Flow diagram demonstrating the study selection process for the *meta*-analysis (PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] diagram). RCTs, randomized controlled trials.

Table 1
Characteristics of the randomized controlled trials included in this *meta*-analysis.

Study ID	Country	Study design	Participants/ Sex	Sample size Intervention/ control	Mean age or range age	Intervention group (components milk or diet)	Control group (components milk or diet)	Measure or range of Intervention group	Duration (weeks)	Outcomes
Keshavarz et al 2012	Iran	Cross-over	Overweight and obese Subjects/Female	24/24	37.7	soy milk + reduced 200 to 500 kcal/ day (CHO: 3.5, Fat: 1 , Pro: 2.5 g/ 100 ml) CHO: 50–60% Fat: <30% Pro: 15–20%	cow's milk + reduced 200 to 500 kcal/ day (CHO: 4.9, Fat: 1.5 , Pro: 3.3 g/ 100 ml) CHO: 50–60% Fat: <30% Pro: 15–20%	240 ml	4	Fasting blood sugar Fasting insulin Systolic blood pressure Diastolic blood pressure Weight BMI Fibrinogen WC
Malekiet al. 2019	Iran	Parallel	NAFLD patients/Male and Female	31/31	45.89	soy milk + 500-kcal deficit diet (CHO: 9.15, Fat: 4 , Pro: 6.75 g /per serving) CHO: 55% Fat: 30% Pro: 15%	500-kcal deficit diet: CHO: 55% Fat: 30% Pro: 15%	240 ml	8	Fasting blood sugar Fasting insulin Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure Fibrinogen
Miraghajaniet al. 2012 and 2013	Iran	Cross-over	Diabetic nephropathy patients/ Male and Female	25/25	51	soy milk (CHO: 3.5, Fat: 1, Pro: 2.5 per 100 g)	cow's milk (CHO: 4.9, Fat: 1.5, Pro: 3.3 per 100 g)	240 ml	4	Fasting blood sugar Fasting insulin Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure Weight CRP TNF-α IL-6 Fibrinogen
Gardner et al., 2007	USA	Parallel	Hypercholesterolemic adults/ Male and Female	12/12	52	1)soy milk (CHO: 39, Fat: 9.5, Pro: 25 Amount Consumed/ Day) 2) whole soy milk (CHO: 40, Fat: 13.2, Pro: 25 Amount Consumed/ Day)	dairy milk (CHO: 35, Fat: 5.8, Pro:25 Amount Consumed/ Day)	828 ml	4	Fasting blood sugar Fasting insulin HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure
Önning et al 1998	Sweden	Parallel		12/12	31.7			875 ml	4	

(*continued on next page*)

Table 1 (*continued*)

Study ID	Country	Study design	Participants/ Sex	Sample size Intervention/ control	Mean age or range age	Intervention group (components milk or diet)	Control group (components milk or diet)	Measure or range of Intervention group	Duration (weeks)	Outcomes
			Healthy subjects/ Male and Female			soy milk (CHO: 40, Fat: 20, Pro: 30 per liter)	cow's milk (CHO: 49, Fat: 17, Pro:34 per liter)			Fasting blood sugar Fasting insulin Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure Weight
Nourieh et al 2012	Iran	Cross-over	overweight and obese subjects/ Female	24/24	37.7	soy milk + reduced 200 to 500 kcal/ day (Fat: 1 g/ 100 ml) CHO: 50–60% Fat: <30% Pro: 15–20%	cow's milk + reduced 200 to 500 kcal/ day (Fat: 1.5 g/100 ml) CHO: 50–60% Fat: <30% Pro: 15–20%	240 ml	4	Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure CRP IL-6
Eslami et al., 2019	Iran	Parallel	NAFLD patients/ Female	24/24	45.7	soy milk + 500-kcal deficit diet (CHO: 9.15, Fat: 4 , Pro: 6.75 g /per serving) CHO: 55% Fat: 30% Pro: 15%	500-kcal deficit diet: CHO: 55% Fat: 30% Pro: 15%	240 ml	8	Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure CRP Weight BMI WC
Azadbakht et al 2011	Iran	Cross over	overweight and obese subjects/ Female	23/23	22.2	soy milk + reduced 200 to 500 kcal/ day (CHO: 3.5, Fat: 1 , Pro: 2 g/100 ml) CHO: 50–60% Fat: <30% Pro: 15–20%	cow's milk + reduced 200 to 500 kcal/ day CHO: 50–60% Fat: <30% Pro: 15–20%	240 ml	6	Systolic blood pressure Diastolic blood pressure Weight BMI WC
Mohammad-Shahi et al., 2016	Iran	Cross-over	rheumatoid arthritis patients/ Female	24/24	45.72	soy milk (CHO: 7.5, Fat: 1, Pro: 2.4 per 100 g)	cow's milk (CHO: 4.9, Fat: 1.5, Pro: 3.3 per 100 g)	240 ml	4	Fasting blood sugar Fasting insulin HOMA-IR Triglycerides HDL cholesterol LDL cholesterol Total cholesterol

(*continued on next page*)

Table 1 (*continued*)

Study ID	Country	Study design	Participants/ Sex	Sample size Intervention/ control	Mean age or range age	Intervention group (components milk or diet)	Control group (components milk or diet)	Measure or range of Intervention group	Duration (weeks)	Outcomes
										Systolic blood pressure Diastolic blood pressure CRP TNF-α IL-6 Weight BMI
Faghih et al 2009 and 2011	Iran	Parallel	overweight and obese subjects/ Female	21/20	35	soy milk(low fat milk 1.5%) + 500-kcal deficit diet: CHO: 55% Fat: 27% Pro: 18%	500-kcal deficit diet: CHO: 55% Fat: 27% Pro: 18%	720 ml	8	Fasting blood sugar Fasting insulin HOMA-IR Triglycerides HDL cholesterol LDL cholesterol Total cholesterol Systolic blood pressure Diastolic blood pressure Weight BMI WC
Beavers et al 2009	USA	Parallel	Healthy postmenopausal women/ Female	16/15	50	soy milk (CHO: 19, Fat: 4 , Pro: 6 g /per serving)	dairy milk (CHO: 12, Fat: 4.5 , Pro: 8 g /per serving)	740 ml	4	TNF-α IL-6
Takatsuka et al 2000	Japan	Parallel	Healthy premenopausal women/ Female	27/25	26.5	soy milk (CHO: N/A, Fat: 2.3 , Pro: 4.3 g /per serving)	Usual diet	400 ml	8	Triglycerides HDL cholesterol LDL cholesterol Total cholesterol
Onuegbu et al 2011	Nigeria	Parallel	Healthy subjects/ Male and Female	42/40	20–35	soy milk (CHO: N/A, Fat: 2.3 , Pro: 4.3 g /per serving)	Did not consume soymilk	500 ml	3	Triglycerides HDL cholesterol LDL cholesterol Total cholesterol
Mitchell et al 1999	UK	Parallel	Healthy subjects/ Male	4/3	20–50	soy milk	dairy milk	1000 ml	4	Triglycerides Total cholesterol
Rivas et al 2002	Spain	Parallel	Hypertensive patients/ Male and Female	20/20	N/A	soy milk (CHO: 25, Fat: 10.5, Pro: 18 gr/liter)	cow's milk (CHO: 13.5, Fat: 1.5, Pro: 15.5 gr/liter)	1000 ml	12	Systolic blood pressure Diastolic blood pressure
Lukaszuk et al 2007	USA	Parallel	Overweight/ Female	7/7	31.5	soy milk + 500-kcal deficit diet	skimmed milk + 500-kcal deficit diet	720 ml	8	Weight BMI WC

NAFLD, non-alcoholic fatty liver disease. Pro, protein. CHO, carbohydrates. LDL, low-density lipoprotein. HDL, high-density lipoprotein. CRP, C-reactive protein. TNF-α, tumour necrosis factor α. IL-6, interleukin 6. BMI, body mass index. WC, waist circumference. HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

Table 2
Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool.

Study, Year (reference)	Random sequence generation	Allocation concealment	Blinding of participantsand personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overallassessment of risk of bias
Keshavarz et al 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Malekiet al. 2019	Low	Unclear	Unclear	Low	Low	Low	Unclear
Miraghajaniet al. 2012 and 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gardner et al., 2007	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Önning et al 1998	Low	Unclear	Low	Low	Low	Unclear	Unclear
Nourieh et al 2012	Low	Low	Unclear	Low	Low	Low	Unclear
Eslami et al., 2019	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Azadbakht et al 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mohammad-Shahi et al., 2016	Low	Low	Unclear	Low	Unclear	Low	Unclear
Faghih et al 2009 and 2011	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Beavers et al 2009	Low	Low	Low	Low	Low	Low	Low
Takatsuka et al 2000	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Onuegbu et al 2011	Low	Unclear	Low	Low	Low	Unclear	Unclear
Mitchell et al 1999	Low	Low	Unclear	Low	Low	Low	Unclear
Rivas et al 2002	Low	Low	Unclear	Low	Low	Low	Unclear
Lukaszuk et al 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

three studies in the United States of America (USA) (Beavers et al., 2009; Gardner et al., 2007; Lukaszuk et al., 2007). The rest of the studies were carried out in Sweden (Önning et al., 1998), Japan (Takatsuka et al., 2000), Nigeria (Onuegbu et al., 2011), United Kingdom (Mitchell & Collins, 1999), and Spain (Rivas, Garay, Escanero, Cia Jr, et al., 2002). These studies were published between the years 1998–2019. The age of the participants ranged from 18 to 65 years. Respectively, ten and one study were performed on women and men, and the rest on both sexes. Twelve RCTs had a parallel design (Beavers et al., 2009; Eslami et al., 2019; SH Faghih et al., 2011; S Faghih et al., 2009; Gardner et al., 2007; Lukaszuk et al., 2007; Maleki et al., 2019; Mitchell & Collins, 1999; Önning et al., 1998; Onuegbu et al., 2011; Rivas, Garay, Escanero, Cia Jr, et al., 2002; Takatsuka et al., 2000), whereas the remaining had a cross-over design (Azadbakht & Nurbakhsh, 2011; Keshavarz et al., 2012; Miraghajani et al., 2012; Miraghajani et al., 2013; Mohammad-Shahi et al., 2016; Nourieh et al., 2012). The duration of the intervention varied from 4 to 8 weeks and the amount of soy milk administered ranged between 240 and 1000 ml/day among the analyzed studies. Eight trials administered soy milk with a reduced-calorie (200–500 kcal) diet (Azadbakht & Nurbakhsh, 2011; Eslami et al., 2019; SH Faghih et al., 2011; S Faghih et al., 2009; Keshavarz et al., 2012; Lukaszuk et al., 2007; Maleki et al., 2019; Nourieh et al., 2012). Six studies were conducted on healthy overweight/obese individuals (Azadbakht & Nurbakhsh, 2011; SH Faghih et al., 2011; S Faghih et al., 2009; Keshavarz et al., 2012; Lukaszuk et al., 2007; Nourieh et al., 2012), and the other studies enrolled patients with non-alcoholic fatty liver disease (NAFLD) (Eslami et al., 2019; Maleki et al., 2019), diabetic nephropathy (Miraghajani et al., 2012; Miraghajani et al., 2013), hypercholesterolemia (Gardner et al., 2007), rheumatoid arthritis (Mohammad-Shahi et al., 2016), or hypertension (Rivas, Garay, Escanero, Cia Jr, et al., 2002). In addition, five RCTs enrolled healthy individuals (Beavers et al., 2009; Mitchell & Collins, 1999; Önning et al., 1998; Onuegbu et al., 2011; Takatsuka et al., 2000).

3.3. Meta-analysis

3.3.1. The effect of soy milk on fasting blood glucose and fasting insulin

Based on a random-effects statistical model, the *meta*-analysis of the RCTs detected no significant impact of soy milk on FBG (weighted mean difference, WMD: −0.15 mg/dL, 95% CI: −2.19, 1.89, P = 0.88) and fasting insulin (WMD: 0.61 μU/mL, 95% CI: −1.35, 2.56, P = 0.54). No evidence of heterogeneity was observed among the analyzed studies for FBG (Cochran Q test, P = 0.97, I^2 = 0.0%). However, the between-study heterogeneity for fasting insulin was significantly high (Cochran Q test, P = 0.014, I^2 = 71.8%) (Fig. 2). In the subgroup analysis, the dose and the duration of the intervention were considered as heterogeneity factors on the overall effect size for fasting insulin (**Supplementary** Figure 1). As the number of articles in each subgroup was small, the results were not reportable.

3.3.2. The effect of soy milk on the lipid profile

The pooled results from the random-effects model revealed that soy milk consumption resulted in a significant reduction of TC (WMD: −8.97 mg/dL, 95% CI: −14.29, −3.65, P = 0.001) and LDL-C (WMD: −9.30 mg/dL, 95% CI: −18.20, −0.40, P = 0.041) concentration. However, soy milk intake did not reduce serum TG (WMD: −1.60 mg/dL, 95% CI: −14.15, 10.94, P = 0.80) and also did not affect serum HDL-C (WMD: 1.43 mg/dL, 95% CI: −2.07, 4.94, P = 0.42) concentration. No significant heterogeneity was observed between these trials for TC (Cochran Q test, P = 0.73, I^2 = 0.0%) and HDL-C (Cochran Q test, P = 0.07, I^2 = 50.9%). However, a significant heterogeneity was seen for LDL-C (Cochran Q test, P = 0.008, I^2 = 65.3%) and TG (Cochran Q test, P = 0.008, I^2 = 65.2%) (Fig. 3). In the subgroup analysis for LDL-C and TG, we found that the duration and the dose of the intervention could explain this heterogeneity. However, the subgroup analysis based on these factors did not show a significant effect of soy milk consumption on TG, HDL-C or LDL-C (**Supplementary** Figure 2, 3, 4).

3.3.3. The effect of soy milk on body composition

The *meta*-analysis of seven eligible RCTs for body weight and of six RCTs for BMI showed no significant difference in body weight (WMD: −0.74 kg, 95% CI: −1.65, 0.17, P = 0.11) and BMI (WMD: −0.21 kg/m^2, 95% CI: −0.51, 0.09, P = 0.176) following the consumption of soy milk. However, the quantitative *meta*-analysis displayed that soy milk lowered WC in a significant manner compared with the control group (WMD: −1.61 cm, 95% CI: −2.74, −0.48, P = 0.005). There was no evidence of significant between-study heterogeneity (Cochran Q test, P = 1.00, I^2 = 0.0% for weight; Cochran Q test, P = 1.00, I^2 = 0.0% for BMI; Cochran Q test, P = 0.84, I^2 = 0.0% for WC) in the current *meta*-analysis (Fig. 4).

3.3.4. The effect of soy milk on SBP and DBP

The pooled effect sizes from five RCTs indicated that soy milk significantly decreased SBP (WMD: −7.38 mmHg; 95% CI: −10.87, −3.88, P < 0.001) and DBP (WMD: −4.36 mmHg; 95% CI: −7.06, −1.66, P = 0.002). However, for SBP and DBP, the detected heterogeneity was significantly high (Cochran Q test, P < 0.001, I^2 = 89.9% for

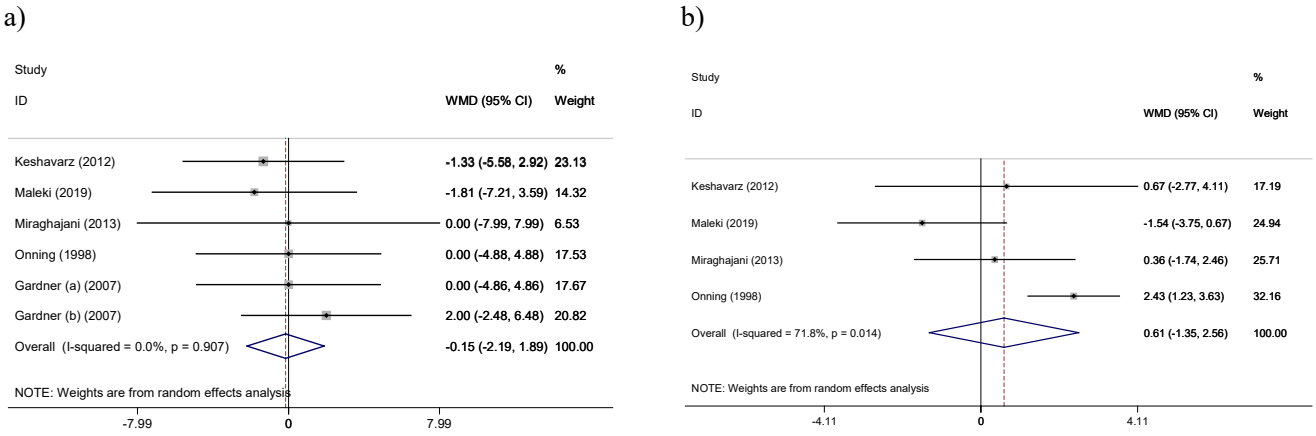

Fig. 2. Forest plots from the *meta*-analysis of clinical trials investigating the effects of soy milk supplementation on (a) fasting blood glucose and (b) fasting insulin. WMD: weighted mean difference. CI: confidence intervals.

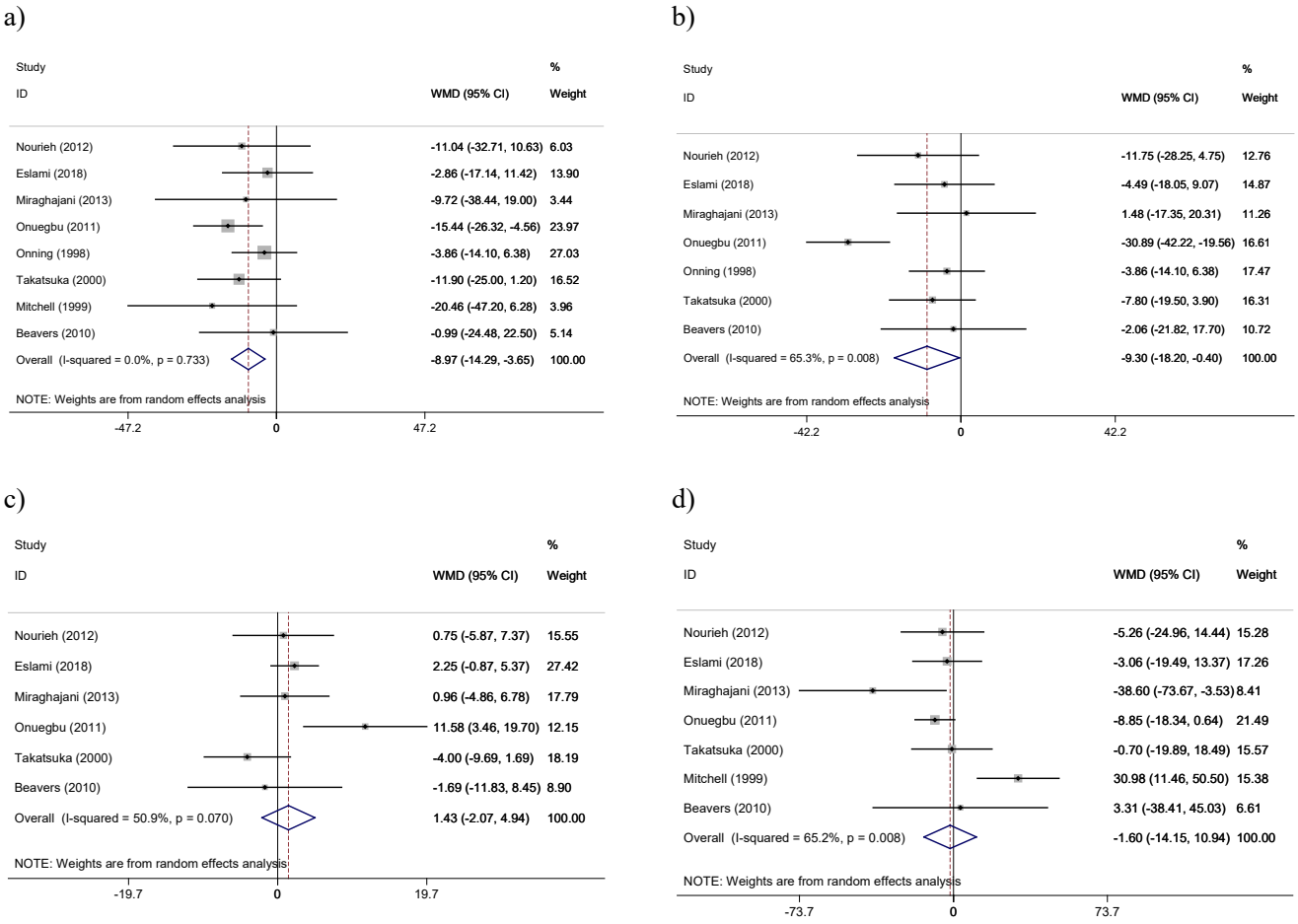

Fig. 3. Forest plots from the *meta*-analysis of clinical trials investigating the effects of soy milk supplementation on (a) total cholesterol, (b) LDL-C, c) HDL-C and d) TG. WMD: weighted mean difference. CI: confidence intervals. LDL-C: low-density lipoprotein cholesterol. HDL-C: high-density lipoprotein cholesterol. TG: triglycerides.

SBP and Cochran Q test, $P < 0.001$, $I^2 = 89.0\%$ for DBP), respectively (Fig. 5). The health status of the participants (healthy versus unhealthy) was considered as the heterogeneity factor on the overall effect size for blood pressure. When the studies were categorized based on their durations, soy milk decreased SBP in a more notable manner when it was administered for $\leq$ 4 weeks (WMD: −8.79 mmHg, 95% CI: −16.80, −0.78). However, no significant effect of soy milk on DBP was observed in the subgroup analysis based on the duration of the intervention. (**Supplementary** Figure 5, 6).

3.3.5. *Effect of soy milk on CRP, IL-6, TNF-α and fibrinogen*

Four and three studies reported data for serum CRP and TNF-α as outcome measures, respectively. The results from our *meta*-analysis indicate a significant reduction of CRP (WMD: −1.07, mg/L, 95% CI:

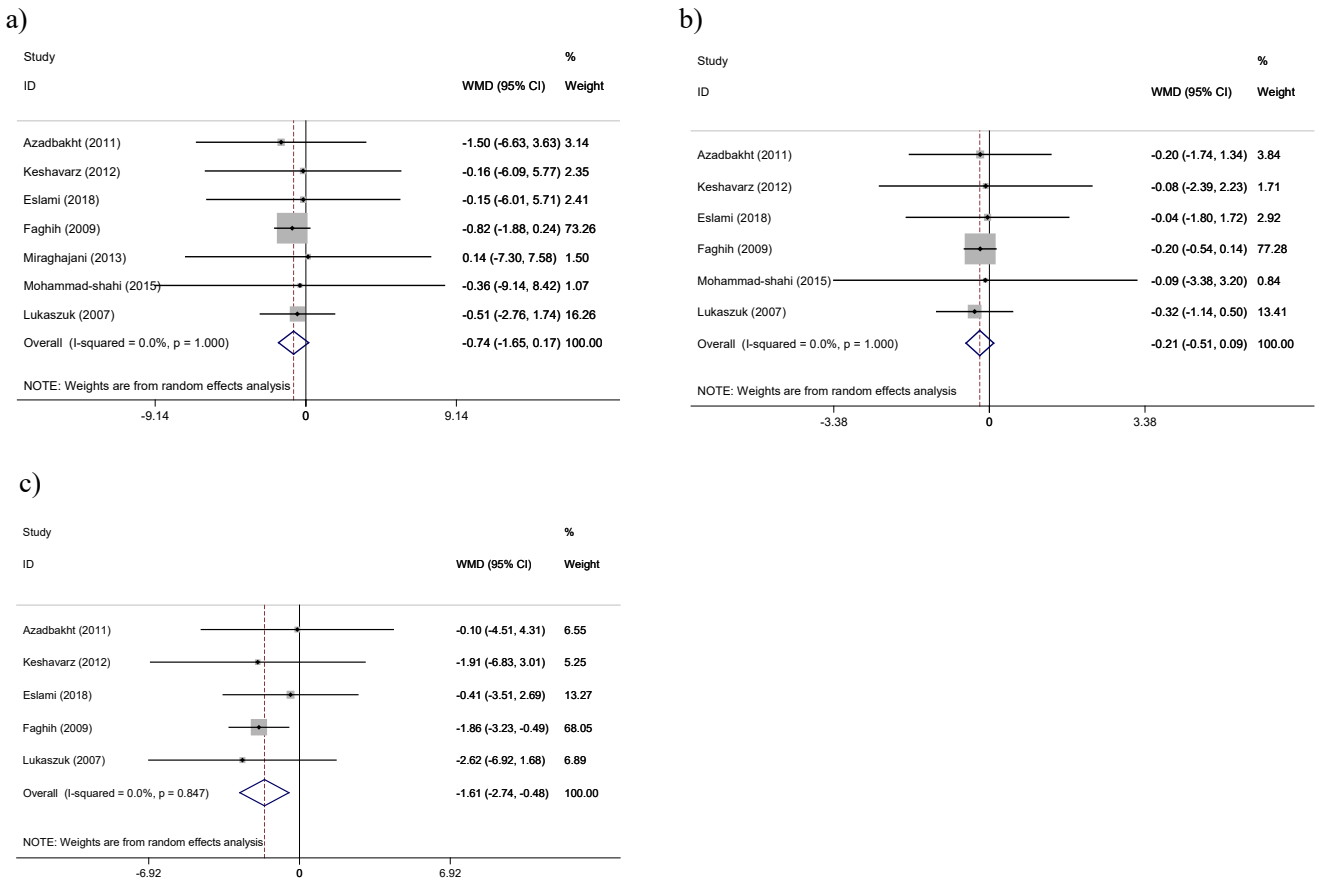

Fig. 4. Forest plots from the *meta*-analysis of clinical trials investigating the effects of soy milk supplementation on (a) body weight, (b) body mass index (BMI), c) waist circumference (WC). WMD: weighted mean difference. CI: confidence intervals.

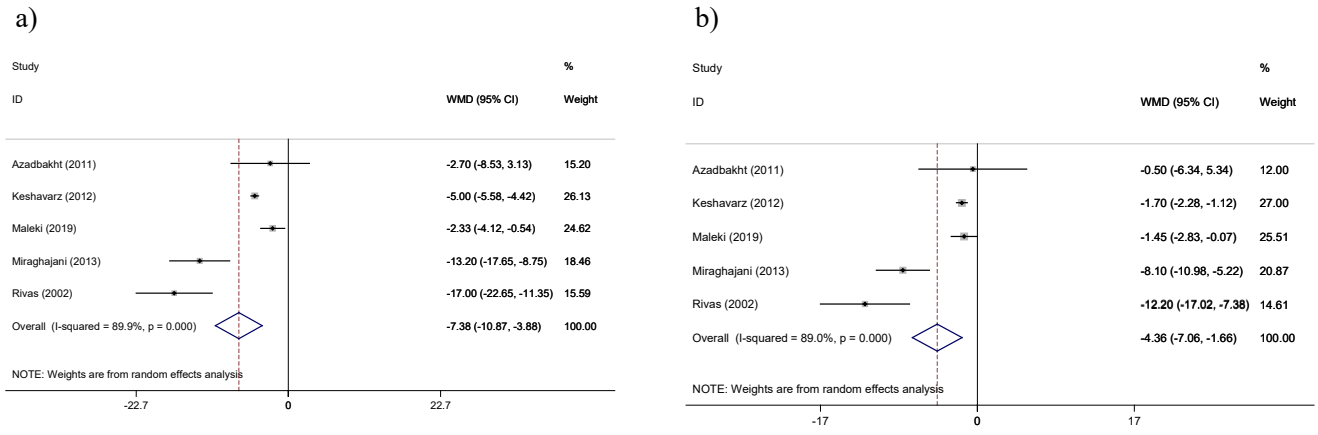

Fig. 5. Forest plots from the *meta*-analysis of clinical trials investigating the effects of soy milk supplementation on (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP). WMD: weighted mean difference. CI: confidence intervals.

−1.13, −1.01, P < 0.001) and TNF-α (WMD: −0.30, pg/mL, 95% CI: −0.55, −0.06, P = 0.016) levels following soy milk consumption. In addition, a significant heterogeneity was not noted among the analyzed studies for CRP (Cochran Q test, P = 0.93, I^2 = 0.0%) and TNF-α (Cochran Q test, P = 0.42, I^2 = 0.0%). However, the pooled results showed no significant effect on IL-6 (WMD: 0.09 pg/ml, 95% CI: −0.22, 0.39, P = 0.57) and fibrinogen (WMD: −6.07 mg/dL, 95% CI: −20.58, 8.44, P = 0.41). Moreover, no evidence of heterogeneity was shown for the RCTs evaluating IL-6 (Cochran Q test, P = 0.401, I^2 = 0.0%) and fibrinogen (Cochran Q test, P = 0.765, I^2 = 0.0%) (Fig. 6).

3.3.6. *Sensitivity analysis*

The leave-one-out method was applied to evaluate the influence of each individual study on the pooled effect size (Kocaguneli & Menzies, 2013). The results remained robust after the sequential elimination of RCTs for all outcomes **(Supplementary Figure 7, 8, 9, 10, 11).**

3.3.7. *Publication bias*

The visual inspection of the funnel plots and the Egger's test revealed no evidence of publication bias in the present study for weight (P = 0.25), BMI (P = 0.59), WC (P = 0.54), SBP (P = 0.48), DBP (P = 0.21),

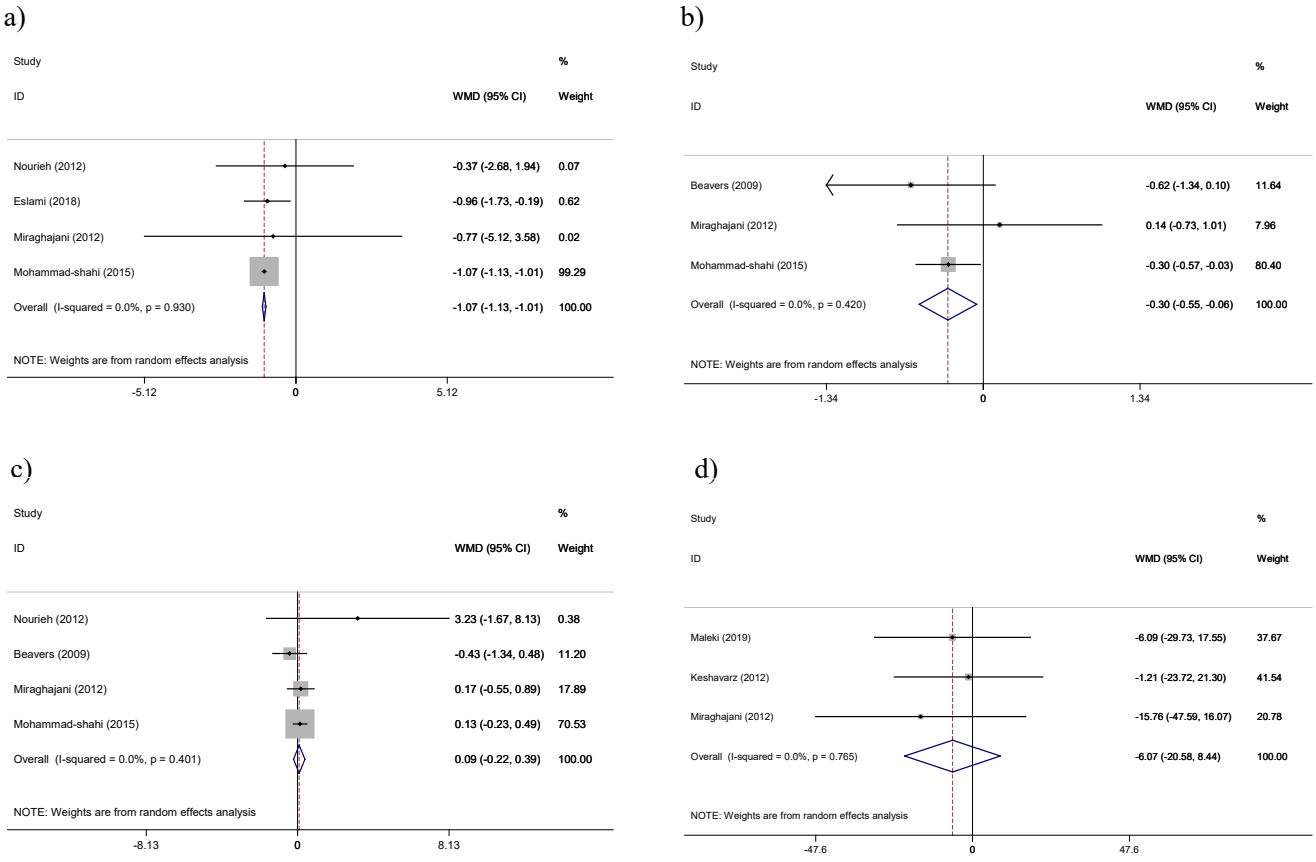

Fig. 6. Forest plots from the *meta*-analysis of clinical trials investigating the effects of soy milk supplementation on (a) C-reactive protein (CRP), (b) tumour necrosis factor α (TNF-α), c) interleukin 6 (IL-6) and d) fibrinogen. WMD: weighted mean difference. CI: confidence intervals.

TC (P = 0.79), LDL-C (P = 0.48), HDL-C (P = 0.98), TG (P = 0.80), FBG (P = 0.87), fasting insulin (P = 0.23), TNF-α (P = 0.91), IL-6 (P = 0.68), fibrinogen (P = 0.17), and CRP (P = 0.13) levels (**Supplementary Figure 12, 13, 14, 15, 16**).

3.3.8. Discussion

In this systematic review and *meta*-analysis, we evaluated the effects of the consumption of soy milk on various anthropometric indices and cardiometabolic risk factors. We included all the relevant RCTs (n = 18), which included both healthy and subjects diagnosed with several cardiometabolic diseases, to powerfully consolidate the conclusions and overcome the contradictory and sample size limitations of individual RCTs. Overall, the included RCTs had a low to unclear risk of bias and comprised a total of 665 individuals (336 and 329 individuals received soy milk and dairy milk/control diet, respectively). Our findings depicted beneficial effects of soy milk consumption on blood pressure and several serum lipids, inflammation markers and anthropometric indices. Specifically, soy milk consumption reduced SBP, DBP and WC. Moreover, it lowered TC and LDL-C. Lastly, soy milk administration decreased CRP and TNF-α. On the other hand, soy milk consumption did not exert any effects on FBG, fasting insulin, TG, several inflammatory markers (IL-6 and fibrinogen), and body composition indices (body weight and BMI). Overall, our results reinforce that soy milk should be integrated in the diet, owing to its favorable outcomes on blood pressure, serum lipids, inflammatory markers and anthropometric parameters. Recent publications have also reported that soy products, for example soy nuts or soy milk, exhibit positive effects on cardiovascular risk factors. Whole soy, due to its composition in phytosterols, essential fats, plant amino acids, and isoflavones, might positively impact the human health (Azadbakht & Nurbakhsh, 2011; Steinberg, 2007). Pure phytoestrogens or isolated soy protein alone do not appear to be as effective as combinations of soy with proteins, fatty acids, and phytoestrogens (Azadbakht et al., 2007). Several researchers have assessed the effects of different soy products by comparing the pharmacokinetics of isoflavones from soymilk (liquid matrix) with those from textured vegetable proteins (solid matrix). They discovered that, despite equivalent doses per kilogram body weight, soymilk yielded higher maximal plasma isoflavone concentrations and total areas under the curve, which implies that the matrix of food can influence its effects on the human health (Cassidy et al., 2006).

Cardiometabolic disorders, namely obesity, diabetes mellitus and hypertension, are major concerns to the public healthcare worldwide ("Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017," 2018). They commonly bundle together, being referred to as cardiometabolic multimorbidity, and are associated with extensive rates of disability and death (Di Angelantonio et al., 2015). An extensive body of literature underscores the significance of dietary patterns as crucial determinants in the development of cardiometabolic disorders (Miranda et al., 2019; D. Mozaffarian, 2016). Moreover, in addition to pharmacotherapy, nutritional habits are considered key elements in both the management and prevention of these disease (Miranda et al., 2019; D. Mozaffarian, 2016). In this context, the consumption of soy products has been reported to exhibit positive effects on the human health, particularly in patients with cardiovascular and metabolic disorders, including a reduction of the cancer-related or cardiovascular-related risk of death (Nachvak et al., 2019; Ramdath, Padhi, Sarfaraz, Renwick, & Duncan, 2017; Soltanipour, Hasandokht, Soleimani, Mahdavi-Roshan, & Jalali, 2019). It has been advocated that the consumption of whole soy, rather than its selective components, is preferable as it is associated with more health benefits (Reinwald, Akabas, & Weaver, 2010). Distinctively, soy

milk and whole soy are rather equivalent, as both virtually encompass the same beneficial components, for example essential fatty acids, soy isoflavones, inositols, healthy cholesterol, and phytosterols (Reinwald et al., 2010).

Our pooled analysis demonstrated that subjects who received soy milk experienced a decrease in their SBP and DBP. The blood pressure-lowering effects of soy milk can be largely attributed to its composition in isoflavonoids, namely genistein and equol as a metabolite of daidzein, both of which have exerted vasorelaxant and diuretic activities in *in vivo* studies (Gimenez et al., 1997; Giménez et al., 1998; Mishra et al., 2000). Moreover, soy milk contains bioactive peptides that counteract the activity of the angiotensin-converting enzyme (ACE) and stimulate the activity of bradykinin, decreasing thus blood pressure (Maleki et al., 2019). Based on our findings, soy milk reduced SBP and DBP and we may hypothesize that it can be combined with conventional antihypertensive drugs in clinical practice in order to manage hypertension. It is relevant to underscore that even a reduction of 2 mmHg in SBP and DBP can decrease ischemic heart disease-related and stroke-related mortality by 7% and 10%, respectively (Khalesi, Sun, Buys, & Jayasinghe, 2014; Lewington, Clarke, Qizilbash, Peto, & Collins, 2003).

The greater effect of soy milk consumption on lowering blood pressure during less than or equal to 4 weeks of intervention in this study may be due to the effects of soy on microbiota composition. Evidence has shown that soy in the long run causes an imbalance of intestinal microbiota by reducing the relative abundance of beneficial intestinal bacteria as well as increasing the production of trimethylamine-N-oxide, which may not be beneficial to intestinal health(Ashaolu, 2020; Huang, Krishnan, Pham, Yu, & Wang, 2016). Previous studies have shown an association between microbiota imbalance and impaired blood pressure regulation(Jama, Kaye, & Marques, 2019; Toral et al., 2019). It has also been shown that the metabolic components of soy, such as genistein, which are responsible for the antihypertensive effects, have a very short half-life that loses its beneficial effects in the long run(Rivas, Garay, Escanero, Cia, et al., 2002). In addition, soy milk in the long run reduces the absorption of micronutrients useful in lowering blood pressure, such as magnesium (Rivas, Garay, Escanero, Cia, et al., 2002).

Soy proteins are approved by the United States Food and Drug Administration (FDA) and other similar governing bodies from various countries, particularly for their clinical utility in decreasing LDL-C levels (Xiao, 2008). The molecular mechanisms and beneficial cholesterol-lowering effects of soy proteins are well-documented in the literature, including evidence from several high-quality *meta*-analyses of RCTs (Blanco Mejia et al., 2019; Reynolds et al., 2006). However, the magnitude of LDL-C reduction remains a point of controversy ranging from as low as 5% (Zhan & Ho, 2005) to as high as 13% (Anderson, Johnstone, & Cook-Newell, 1995), yet none of the studies that have reported these results have specifically examined the efficacy of soy milk versus dairy milk on various anthropometric parameters and cardiometabolic risk factors. On one hand, our results demonstrated that soy milk consumption lowered TC and LDL-C. On the other hand, the impact of soy milk on HDL-C and TG levels was not significant. An accumulating body of evidence highlights that the lipid-lowering effects of soy milk on LDL-C levels are more notable in subjects diagnosed with hypercholesterolemia rather than individuals who do not suffer from dyslipidemia (Anderson & Bush, 2011; Tokede, Onabanjo, Yansane, Gaziano, & Djoussé, 2015; Zhan & Ho, 2005). This observation supports, to a larger degree, the use of soy milk in selected individuals (for example, dyslipidemic subjects) in order to attain maximum therapeutic benefits.

Inflammation, marked by an increased expression of pro-inflammatory cytokines such as TNF-α (Zhang et al., 2009) and IL-6 (Volpato et al., 2001), is a key feature in the initiation and progression of cardiovascular diseases, in addition to its ability to forecast mortality. Soy isoflavones intrinsically harbor estrogen-like actions which interfere with the generation of TNF-α (Ito et al., 2001) and IL-6 (Miyamoto et al., 1999). The anti-inflammatory activity of soy isoflavones has been previously documented in various *in vitro* and in vivo studies (Chacko et al., 2005; Sadeghalvad, Mohammadi-Motlagh, Karaji, & Mostafaie, 2019). Our findings demonstrated that individuals who consume soy milk exhibit a significant decrease in TNF-α and CRP levels. Whether the magnitude of reduction is enough to cause a physiological benefit remains a point for further research. However, soy milk consumption did not alter IL-6 concentrations. Soy milk and goat milk contain oligosaccharides that reduce intestinal inflammation and the concentrations of pro-inflammatory cytokines (Lara-Villoslada et al., 2006; Tsangalis & Shah, 2004). In addition, several studies have shown that soy isoflavones may reduce CRP and pro-inflammatory cytokine concentrations by inhibiting the nuclear factor kappa B (NF-κB) as a major regulator of pro-inflammatory mediator synthesis (Fanti, Asmis, Stephenson, Sawaya, & Franke, 2006; Mohammad-Shahi et al., 2016).

Soy isoflavones ameliorate insulin sensitivity and glucose homeostasis *via* several mechanisms, namely by decreasing the activity of the intestinal alpha-glucosidase (Hanhineva et al., 2010) and the glucose transporter type-4 (Ha et al., 2012). Nonetheless, in our study, while soy milk supplementation favorably increased and decreased fasting insulin and glucose levels, respectively, these effects were not statistically significant. These findings were in agreement with the results of two *meta*-analyses which revealed that soy consumption did not lead to clinically meaningful effects on various indices of glycemic control in healthy individuals or in patients diagnosed with cardiometabolic disorders, for example diabetes mellitus (Liu, Chen, & Ho, 2011; Soltanipour et al., 2019). Further research is needed to explore in which subjects soy milk may show increased benefits and whether the administration of this product should be tailored according to certain clinical features or demographics, for example glycemic status.

With regard to anthropometric parameters, our findings revealed a significant reduction in WC following soy milk consumption. However, in the current *meta*-analysis, no significant changes were observed for other anthropometric indices, such as body weight or BMI. A recent *meta*-analysis revealed that the administration of soy foods and isoflavones did not alter weight and WC in a significant fashion (Akhlaghi, Zare, & Nouripour, 2017). However, the subgroup analyses underpinned that this effect could vary based on the age, the gender of the participants, the consumption dose, the type of soy products employed, the duration of the intervention, as well as the anthropometric indices at baseline (Akhlaghi et al., 2017). Therefore, such differences might explain the conflicting inter-study results regarding the impact of soy on anthropometric indices. On the other hand, a *meta*-analysis of 43 RCTs that examined the effects of soy protein and soy isoflavones on anthropometric parameters detected no statistically significant changes of these variables following the intervention (Mu et al., 2019). Various studies with high sample sizes have shown that large waist sizes in men and women are significantly associated with low HDL-C and high levels of fasting triacylglycerol, insulin, FBG, LDL-C, as well as elevated blood pressure, all of which are markers of cardiovascular risk (Dobbelsteyn, Joffres, MacLean, & Flowerdew, 2001; Seidell, Pérusse, Després, & Bouchard, 2001). Increased WC reflects an elevated accumulation of visceral fat and an overexposure of the liver to fatty acids, and can be involved in the development of insulin resistance and endothelial dysfunction, as well as influence the lipid profile (Gans, 2006).

Our study has several strengths. To the best of our knowledge, this is the first systematic review and *meta*-analysis that scrutinized the impact of soy milk consumption specifically, as opposed to other soy products, on cardiometabolic risk factors. The design of our study, that is systematic review and *meta*-analysis, is advantageous and enable us to draw solid conclusions and to overcome the contradictions as well as sample size limitations of individual RCTs. We included only papers with high-quality study designs (RCTs) and excluded non-RCTs papers. We analyzed a comprehensive panel of biochemical markers and anthropometric indices, namely blood pressure and glycemic, lipid, inflammatory, and anthropometric indices. The *meta*-analysis of the RCTs evaluating changes in the SBP and DBP was marked by heterogeneity

and thus we attempted to resolve this drawback by employing subgroup analyses based on the duration of the intervention and the health status of the participants. The other assessed variables were homogeneous (except for the lipid profile), reflecting no substantial inter-study variations of the outcomes. Moreover, we employed leave-one-out sensitivity analyses which reinforced the robustness of the findings and we did not identify publication biases in our study outcomes.

Nonetheless, our study has some limitations that ought to be recognized. Notably, the small number of included RCTs and their sample sizes constitute a major limitation. The included studies mostly recruited women, hence the results might not be generalizable to men. Moreover, another limitation of our paper is that, due to the small number of studies in each group in terms of study populations, it was not possible to perform subgroup analysis based on the health status of the participants, which could have affected the interpretation of our results. In addition, we discovered that the quality of most of the analyzed RCTs was heterogeneous. Furthermore, the adherence/compliance to the soy milk intervention was not quantitatively verified by examining the serum or urinary levels of soy isoflavones.

3.3.9. Conclusions

According to the available evidence, soy milk consumption can exert favorable effects on blood pressure, several components of the lipid profile and certain anthropometric and inflammatory markers as compared to controls. However, further research on larger samples is warranted to confirm these findings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2021.104499.

References

Akhlaghi, M., Zare, M., & Nouripour, F. (2017). Effect of Soy and Soy Isoflavones on Obesity-Related Anthropometric Measures: A Systematic Review and Meta-analysis of Randomized Controlled Clinical Trials. *Adv Nutr, 8*(5), 705–717. https://doi.org/10.3945/an.117.015370.

Anderson, J. W., & Bush, H. M. (2011). Soy protein effects on serum lipoproteins: A quality assessment and meta-analysis of randomized, controlled studies. *J Am Coll Nutr, 30*(2), 79–91. https://doi.org/10.1080/07315724.2011.10719947.

Anderson, J. W., Johnstone, B. M., & Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med, 333*(5), 276–282. https://doi.org/10.1056/nejm199508033330502.

Ashaolu, T. J. (2020). Soy bioactive peptides and the gut microbiota modulation. *Applied Microbiology and Biotechnology*, 1–9.

Azadbakht, L., Kimiagar, M., Mehrabi, Y., Esmaillzadeh, A., Hu, F. B., & Willett, W. C. (2007). Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes care, 30*(4), 967–973.

Azadbakht, L., & Nurbakhsh, S. (2011). Effect of soy drink replacement in a weight reducing diet on anthropometric values and blood pressure among overweight and obese female youths. *Asia Pacific journal of clinical nutrition, 20*(3), 383.

Beavers, K. M., Serra, M. C., Beavers, D. P., Cooke, M. B., & Willoughby, D. S. (2009). Soymilk supplementation does not alter plasma markers of inflammation and oxidative stress in postmenopausal women. *Nutrition research, 29*(9), 616–622.

Blanco Mejia, S., Messina, M., Li, S. S., Viguiliouk, E., Chiavaroli, L., Khan, T. A., & Kris-Etherton, P. (2019). A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *The Journal of nutrition, 149*(6), 968–981.

Cassidy, A., Brown, J. E., Hawdon, A., Faughnan, M. S., King, L. J., Millward, J., & Setchell, K. D. (2006). Factors affecting the bioavailability of soy isoflavones in humans after ingestion of physiologically relevant levels from different soy foods. *The Journal of nutrition, 136*(1), 45–51.

Chacko, B. K., Chandler, R. T., Mundhekar, A., Khoo, N., Pruitt, H. M., Kucik, D. F., & Patel, R. P. (2005). Revealing anti-inflammatory mechanisms of soy isoflavones by flow: Modulation of leukocyte-endothelial cell interactions. *Am J Physiol Heart Circ Physiol, 289*(2), H908–H915. https://doi.org/10.1152/ajpheart.00781.2004.

Danaei, G., Lu, Y., Singh, G. M., Carnahan, E., Stevens, G. A., Cowan, M. J., & Rao, M. (2014). Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: A comparative risk assessment. *Lancet Diabetes & Endocrinology*.

Cunha, C.d. M., Costa, P. R. F., de Oliveira, L. P. M., Queiroz, V. A.d. O., Pitangueira, J. C. D., & Oliveira, A. M. (2018). Dietary patterns and cardiometabolic risk factors among adolescents: Systematic review and meta-analysis. *British Journal of Nutrition, 119*(8), 859–879.

Di Angelantonio, E., Kaptoge, S., Wormser, D., Willeit, P., Butterworth, A. S., Bansal, N., & Danesh, J. (2015). Association of Cardiometabolic Multimorbidity With Mortality. *Jama, 314*(1), 52. https://doi.org/10.1001/jama.2015.7008.

Dobbelsteyn, C., Joffres, M., MacLean, D. R., & Flowerdew, G. (2001). A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. *International journal of obesity, 25*(5), 652–661.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj, 315*(7109), 629–634.

Eslami, O., Shidfar, F., Maleki, Z., Jazayeri, S., Hosseini, A. F., Agah, S., & Ardiyani, F. (2019). Effect of soy milk on metabolic status of patients with nonalcoholic fatty liver disease: A randomized clinical trial. *Journal of the American College of Nutrition, 38*(1), 51–58.

Faghih, S.h., Abadi, A. R., Hedayati, M., & Kimiagar, S. M. (2011). Comparison of the effects of cows' milk, fortified soy milk, and calcium supplement on weight and fat loss in premenopausal overweight and obese women. *Nutrition, Metabolism and Cardiovascular Diseases, 21*(7), 499–503.

Faghih, S., Hedayati, M., Abadi, A., & Kimiagar, M. (2009). Comparison of the Effects of Cow' s Milk, Fortified Soy Milk, and Calcium Supplement on Plasma Adipocytokines in Overweight and Obese Women. Iranian Journal of Endocrinology and Metabolism, 11(6), 692-698.

Fanti, P., Asmis, R., Stephenson, T. J., Sawaya, B. P., & Franke, A. A. (2006). Positive effect of dietary soy in ESRD patients with systemic inflammation—correlation between blood levels of the soy isoflavones and the acute-phase reactants. *Nephrology Dialysis Transplantation, 21*(8), 2239–2246.

Gans, R. O. B. (2006). The metabolic syndrome, depression, and cardiovascular disease: Interrelated conditions that share pathophysiologic mechanisms. *Medical Clinics, 90*(4), 573–591.

Gardner, C. D., Messina, M., Kiazand, A., Morris, J. L., & Franke, A. A. (2007). Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *Journal of the American College of Nutrition, 26*(6), 669–677.

Gimenez, I., Lou, M., Vargas, F., Alvarez-Guerra, M., Mayoral, J. A., Martinez, R. M., & Alda, J. O. (1997). Renal and vascular actions of equol in the rat. *J Hypertens, 15*(11), 1303–1308. https://doi.org/10.1097/00004872-199715110-00015.

Giménez, I., Martinez, R. M., Lou, M., Mayoral, J. A., Garay, R. P., & Alda, J. O. (1998). Salidiuretic action by genistein in the isolated, perfused rat kidney. *Hypertension, 31*(2), 706–711. https://doi.org/10.1161/01.hyp.31.2.706.

Ha, B. G., Nagaoka, M., Yonezawa, T., Tanabe, R., Woo, J. T., Kato, H., & Yagasaki, K. (2012). Regulatory mechanism for the stimulatory action of genistein on glucose uptake in vitro and in vivo. *J Nutr Biochem, 23*(5), 501–509. https://doi.org/10.1016/j.jnutbio.2011.02.007.

Hanhineva, K., Törrönen, R., Bondia-Pons, I., Pekkinen, J., Kolehmainen, M., Mykkänen, H., & Poutanen, K. (2010). Impact of dietary polyphenols on carbohydrate metabolism. *Int J Mol Sci, 11*(4), 1365–1402. https://doi.org/10.3390/ijms11041365.

Higgins, J. (2011). Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration. www. cochrane-handbook. org.

Higgins, J., & Wells, G. (2011). Cochrane handbook for systematic reviews of interventions.

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). *Measuring inconsistency in meta-analyses. Bmj, 327*(7414), 557–560.

Hozo, S. P., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology, 5*(1), 13.

Huang, H., Krishnan, H. B., Pham, Q., Yu, L. L., & Wang, T. T. Y. (2016). Soy and gut microbiota: Interaction and implication for human health. *Journal of agricultural and food chemistry, 64*(46), 8695–8709.

Ito, A., Bebo, B. F., Jr., Matejuk, A., Zamora, A., Silverman, M., Fyfe-Johnson, A., & Offner, H. (2001). Estrogen treatment down-regulates TNF-alpha production and reduces the severity of experimental autoimmune encephalomyelitis in cytokine knockout mice. *J Immunol, 167*(1), 542–552. https://doi.org/10.4049/jimmunol.167.1.542.

Jama, H. A., Kaye, D. M., & Marques, F. Z. (2019). The gut microbiota and blood pressure in experimental models. *Current opinion in nephrology and hypertension, 28*(2), 97–104.

Keshavarz, S. A., Nourieh, Z., Attar, M. J. H., & Azadbakht, L. (2012). Effect of soymilk consumption on waist circumference and cardiovascular risks among overweight and obese female adults. *International journal of preventive medicine, 3*(11), 798.

Khalesi, S., Sun, J., Buys, N., & Jayasinghe, R. (2014). Effect of probiotics on blood pressure: A systematic review and meta-analysis of randomized, controlled trials. *Hypertension, 64*(4), 897–903.
Kocaguneli, E., & Menzies, T. (2013). Software effort models should be assessed via leave-one-out validation. *Journal of Systems and Software, 86*(7), 1879–1890.
Lara-Villoslada, F., Debras, E., Nieto, A., Concha, A., Gálvez, J., López-Huertas, E., & Xaus, J. (2006). Oligosaccharides isolated from goat milk reduce intestinal inflammation in a rat model of dextran sodium sulfate-induced colitis. *Clinical Nutrition, 25*(3), 477–488.
Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2003). Age-specific relevance of usual blood pressure to vascular mortality. *The Lancet, 361*(9366), 1391–1392.
Liu, Z. M., Chen, Y. M., & Ho, S. C. (2011). Effects of soy intake on glycemic control: A meta-analysis of randomized controlled trials. *Am J Clin Nutr, 93*(5), 1092–1101. https://doi.org/10.3945/ajcn.110.007187.
Lukaszuk, J. M., Luebbers, P., & Gordon, B. A. (2007). Preliminary study: Soy milk as effective as skim milk in promoting weight loss. *Journal of the American Dietetic Association, 107*(10), 1811–1814.
Maleki, Z., Jazayeri, S., Eslami, O., Shidfar, F., Hosseini, A. F., Agah, S., & Norouzi, H. (2019). Effect of soy milk consumption on glycemic status, blood pressure, fibrinogen and malondialdehyde in patients with non-alcoholic fatty liver disease: A randomized controlled trial. *Complementary Therapies in Medicine, 44*, 44–50.
Mazumder, M. A. R., & Begum, A. A. (2016). Soy milk as source of nutrient for malnourished population of developing country: A review. *International Journal of Advanced Scientific and Technical Research, 5*(6), 192–203.
McQueen, R. B., Ghushchyan, V., Olufade, T., Sheehan, J. J., Nair, K. V., & Saseen, J. J. (2016). Incremental increases in economic burden parallels cardiometabolic risk factors in the US. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 9*, 233.
Micha, R., Peñalvo, J. L., Cudhea, F., Imamura, F., Rehm, C. D., & Mozaffarian, D. (2017). Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *Jama, 317*(9), 912–924.
Miraghajani, M. S., Esmaillzadeh, A., Najafabadi, M. M., Mirlohi, M., & Azadbakht, L. (2012). Soy milk consumption, inflammation, coagulation, and oxidative stress among type 2 diabetic patients with nephropathy. *Diabetes care, 35*(10), 1981–1985.
Miraghajani, M. S., Najafabadi, M. M., Surkan, P. J., Esmaillzadeh, A., Mirlohi, M., & Azadbakht, L. (2013). Soy milk consumption and blood pressure among type 2 diabetic patients with nephropathy. *Journal of Renal Nutrition, 23*(4), 277–282.e1.
Miranda, J. J., Barrientos-Gutiérrez, T., Corvalan, C., Hyder, A. A., Lazo-Porras, M., Oni, T., & Wells, J. C. K. (2019). Understanding the rise of cardiometabolic diseases in low- and middle-income countries. *Nat Med, 25*(11), 1667–1679. https://doi.org/10.1038/s41591-019-0644-7.
Mishra, S. K., Abbot, S. E., Choudhury, Z., Cheng, M., Khatab, N., Maycock, N. J., & Aaronson, P. I. (2000). Endothelium-dependent relaxation of rat aorta and main pulmonary artery by the phytoestrogens genistein and daidzein. *Cardiovasc Res, 46*(3), 539–546. https://doi.org/10.1016/s0008-6363(00)00049-3.
Mitchell, J. H., & Collins, A. R. (1999). Effects of a soy milk supplement on plasma cholesterol levels and oxidative DNA damage in men–a pilot study. *European Journal of Nutrition, 38*(3), 143–1138.
Miyamoto, N., Mandai, M., Suzuma, I., Suzuma, K., Kobayashi, K., & Honda, Y. (1999). Estrogen protects against cellular infiltration by reducing the expressions of E-selectin and IL-6 in endotoxin-induced uveitis. *J Immunol, 163*(1), 374–379.
Mohammad-Shahi, M., Mowla, K., Haidari, F., Zarei, M., & Choghakhori, R. (2016). Soy milk consumption, markers of inflammation and oxidative stress in women with rheumatoid arthritis: A randomised cross-over clinical trial. *Nutrition & Dietetics, 73*(2), 139–145.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews, 4*(1). https://doi.org/10.1186/2046-4053-4-1.
Mozaffarian, D. (2016). Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. *Circulation, 133*(2), 187–225. https://doi.org/10.1161/circulationaha.115.018585.
Mozaffarian, D., Wilson, P. W. F., & Kannel, W. B. (2008). Beyond established and novel risk factors: Lifestyle risk factors for cardiovascular disease. *Circulation, 117*(23), 3031–3038.
Mu, Y., Kou, T., Wei, B., Lu, X., Liu, J., Tian, H., & Cui, W. (2019). Soy products ameliorate obesity-related anthropometric indicators in overweight or obese asian and non-menopausal women: A meta-analysis of randomized controlled trials. *Nutrients, 11*(11), 2790.
Nachvak, S. M., Moradi, S., Anjom-Shoae, J., Rahmani, J., Nasiri, M., Maleki, V., & Sadeghi, O. (2019). Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *J Acad Nutr Diet, 119*(9), 1483–1500.e1417. https://doi.org/10.1016/j.jand.2019.04.011.
Nourieh, Z., Keshavarz, S., HosseinzadehAttar, M., & Azadbakht, L. (2012). Effect of soymilk consumption on Inflammatory markers and lipid profiles among non-menopausal overweight and obese female adults. *Journal of Research in Medical Sciences, 17*(4), 1.
O'Keefe, J. H., Gheewala, N. M., & O'Keefe, J. O. (2008). Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *Journal of the American College of Cardiology, 51*(3), 249–255.
Önning, G., Åkesson, B., Öste, R., & Lundquist, I. (1998). Effects of consumption of oat milk, soya milk, or cow's milk on plasma lipids and antioxidative capacity in healthy subjects. *Annals of nutrition and metabolism, 42*(4), 211–220.
Onuegbu, A. J., Olisekodiaka, J. M., Onibon, M. O., Adesiyan, A. A., & Igbeneghu, C. A. (2011). Consumption of soymilk lowers atherogenic lipid fraction in healthy individuals. *Journal of medicinal food, 14*(3), 257–260.
Ramdath, D., Padhi, E., Sarfaraz, S., Renwick, S., & Duncan, A. (2017). Beyond the Cholesterol-Lowering Effect of Soy Protein: A Review of the Effects of Dietary Soy and Its Constituents on Risk Factors for Cardiovascular Disease. *Nutrients, 9*(4), 324. https://doi.org/10.3390/nu9040324.
Rao, G. H. (2018). Prevention or reversal of cardiometabolic diseases. *Journal of Clinical and Preventive Cardiology, 7*(1), 22. https://doi.org/10.4103/JCPC.JCPC_41_17.
Reinwald, S., Akabas, S. R., & Weaver, C. M. (2010). Whole versus the piecemeal approach to evaluating soy. *J Nutr, 140*(12), 2335s–2343s. https://doi.org/10.3945/jn.110.124925.
Reynolds, K., Chin, A., Lees, K. A., Nguyen, A., Bujnowski, D., & He, J. (2006). A meta-analysis of the effect of soy protein supplementation on serum lipids. *The American journal of cardiology, 98*(5), 633–640.
Rivas, M., Garay, R. P., Escanero, J. s. F., Cia Jr, P., Cia, P., & Alda, J. O. (2002). Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. The Journal of nutrition, 132(7), 1900-1902.
Sadeghalvad, M., Mohammadi-Motlagh, H. R., Karaji, A. G., & Mostafaie, A. (2019). In vivo anti-inflammatory efficacy of the combined Bowman-Birk trypsin inhibitor and genistein isoflavone, two biological compounds from soybean. Journal of biochemical and molecular toxicology, 33(12), e22406.
Seidell, J. C., Pérusse, L., Després, J.-P., & Bouchard, C. (2001). Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: The Quebec Family Study. *The American Journal of Clinical Nutrition, 74*(3), 315–321. https://doi.org/10.1093/ajcn/74.3.315.
Sethi, S., Tyagi, S. K., & Anurag, R. K. (2016). Plant-based milk alternatives an emerging segment of functional beverages: A review. *Journal of food science and technology, 53*(9), 3408–3423.
Soltanipour, S., Hasandokht, T., Soleimani, R., Mahdavi-Roshan, M., & Jalali, M. M. (2019). Systematic Review and Meta-Analysis of the Effects of Soy on Glucose Metabolism in Patients with Type 2 Diabetes. *Rev Diabet Stud, 15*(1), 60–70. https://doi.org/10.1900/RDS.2019.15.60.
Steinberg, F. M. (2007). Soybeans or soymilk: does it make a difference for cardiovascular protection? Does it even matter? : Oxford University Press.
Takatsuka, N., Nagata, C., Kurisu, Y., Inaba, S., Kawakami, N., & Shimizu, H. (2000). Hypocholesterolemic Effect of Soymilk Supplementation with Usual Diet in Premenopausal Normolipidemic Japanese Women. *Preventive Medicine, 31*(4), 308–314. https://doi.org/10.1006/pmed.2000.0714.
Tokede, O. A., Onabanjo, T. A., Yansane, A., Gaziano, J. M., & Djoussé, L. (2015). Soya products and serum lipids: A meta-analysis of randomised controlled trials. *Br J Nutr, 114*(6), 831–843. https://doi.org/10.1017/s0007114515002603.
Toral, M., Robles-Vera, I., de la Visitación, N., Romero, M., Yang, T., Sánchez, M., & Duarte, J. (2019). Critical role of the interaction gut microbiota–sympathetic nervous system in the regulation of blood pressure. *Frontiers in physiology, 10*. https://doi.org/10.3389/fphys.2019.00231.
Tsangalis, D., & Shah, N. P. (2004). Metabolism of oligosaccharides and aldehydes and production of organic acids in soymilk by probiotic bifidobacteria. *International journal of food science & technology, 39*(5), 541–554.
Volpato, S., Guralnik, J. M., Ferrucci, L., Balfour, J., Chaves, P., Fried, L. P., & Harris, T. B. (2001). Cardiovascular disease, interleukin-6, and risk of mortality in older women: The women's health and aging study. *Circulation, 103*(7), 947–953. https://doi.org/10.1161/01.cir.103.7.947.
Wang, J., Wu, R., Zhang, W., Sun, Z., Zhao, W., & Zhang, H. (2013). Proteomic comparison of the probiotic bacterium Lactobacillus casei Zhang cultivated in milk and soy milk. *Journal of dairy science, 96*(9), 5603–5624.
Woodside, J. V., Brennan, S., & Cantwell, M. (2016). Are Soy-Milk Products Viable Alternatives to Cow's Milk? Beverage Impacts on Health and Nutrition (pp. 151-162): Springer.
Xiao, C. W. (2008). Health effects of soy protein and isoflavones in humans. *J Nutr, 138*(6), 1244s–1249s. https://doi.org/10.1093/jn/138.6.1244S.
Zhan, S., & Ho, S. C. (2005). Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr, 81*(2), 397–408. https://doi.org/10.1093/ajcn.81.2.397.
Zhang, H., Park, Y., Wu, J., Chen, X., Lee, S., Yang, J., & Zhang, C. (2009). Role of TNF-alpha in vascular dysfunction. *Clin Sci (Lond), 116*(3), 219–230. https://doi.org/10.1042/cs20080196.