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REVIEW

WILEY

The effect of almond intake on cardiometabolic risk factors, inflammatory markers, and liver enzymes: A systematic review and meta-analysis

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Abstract

Almond intake may be correlated with improvements in several cardiometabolic parameters, but its effects are controversial in the published literature, and it needs to be comprehensively summarized. We conducted a systematic search in several international electronic databases, including MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov until April 2021 to identify randomized controlled trials that examined the effects of almond consumption on cardiometabolic risk factors, inflammatory markers, and liver enzymes. Data were pooled using the random-effects model method and presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Twenty-six eligible trials were analyzed ($n = 1750$ participants). Almond intake significantly decreased diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein (LDL), non-high-density lipoprotein (HDL), and very LDL ($p < 0.05$). The effects of almond intake on systolic blood pressure, fasting blood glucose, insulin, hemoglobin A1c, homeostatic model assessment of insulin resistance, C-peptide, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, C-reactive protein (CRP), hs-CRP (high sensitivity C-reactive protein), interleukin 6, tumor necrosis factor-α, ICAM (Intercellular Adhesion Molecule), VCAM (Vascular Cell Adhesion Molecule), homocysteine, HDL, ox-LDL, ApoA1, ApoB, and lipoprotien-a were not statistically significant ($p > .05$). The current body of evidence supports the ingestion of almonds for their beneficial lipid-lowering and antihypertensive effects. However, the effects of almonds on antiinflammatory markers, glycemic control, and hepatic enzymes should be further evaluated via performing more extensive randomized trials.

KEYWORDS

almond, blood lipids, cardiometabolic, glycemic control, hepatic enzymes, inflammation

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1 | INTRODUCTION

Cardiovascular diseases, diabetes mellitus, and dyslipidemia (obesity) are three of the most frequent cardiometabolic disorders globally (1). They often cluster in an amalgamation of two or more disorders—known as cardiometabolic multimorbidity—and are correlated with amplified risks of considerable morbidity and mortality (Di Angelantonio et al., 2015). Accruing evidence puts forward nutritional habits as pivotal determinants of cardiometabolic disorders (Miranda et al., 2019; Mozaffarian, 2016). Accordingly, in tandem with pharmacotherapy, healthy dietary lifestyles and/or nutritional therapy surface as indispensable elements for management of cardiometabolic disorders (Eckel et al., 2014; Fox et al., 2015; Grundy et al., 2019).

Nuts, including almonds, encompass a diversity of bioactive constituents that orchestrate numerous physiologic and metabolic processes. Hence, nuts increasingly emerge as significant components of healthy dietary habits (Bowen et al., 2019; Williamson, Liu, & Izzo, 2020). Almonds, a distinct kind of tree nut, are rich in vitamins, minerals, and monosaturated and polyunsaturated fatty acids (Jaceldo-Siegl, Sabaté, Rajaram, & Fraser, 2004).

Accumulating body of literature from high-quality meta-analyses depicts almonds as valuable therapeutics for controlling blood pressure, blood glucose, and lipid levels. However, the outcomes of these endpoints are widely contradictory. For instance, with regard to blood pressure control, Li et al. uncovered the beneficial impact of almond consumption on reducing systolic blood pressure (SBP), but not diastolic blood pressure (DBP) (Li et al., 2020). Conversely, Eslampour et al. reported antipodal findings in which almond consumption substantially reduced DBP, but not SBP (Eslampour et al., 2020). Concerning blood lipid control, Musa-Veloso et al. chronicled the favorable outcomes of almond consumption on reducing total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels; high-density lipoprotein (HDL) levels were not significantly impacted (Musa-Veloso, Paulionis, Poon, & Lee, 2016). On the other hand, Lee-Bravatti et al. concluded favorable effects of almond consumption on lowering TC, LDL, and HDL levels; TG levels were not significantly impacted (Lee-Bravatti et al., 2019). Lastly, for glycemic control, Tindall et al. voiced advantageous downregulation of fasting insulin levels with almond consumption; fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c) levels were not significantly impacted (Tindall, Johnston, Kris-Etherton, & Petersen, 2019). On the contrary, Viguiliouk et al. revealed opposite results in which almond consumption correlated with a significant reduction in FBG and HbA1c levels, whereas fasting insulin levels were not significantly impacted (Viguiliouk et al., 2014).

All in all, the discrepancies of these meta-analyses regarding conclusions of efficacy endpoints warrant further investigation. Plausible reasons for this observation may be ascribed to the heterogeneity of the included research participants, for example, the inclusion of a combined population of healthy and diseased subjects. Additional reasons may be attributable to the lack of assessing dose–response effects of almond intake as underestimation or excessive consumption can substantially impact endpoints. Lastly, it should be pinpointed that most studies focused on some blood pressure, lipid, or glycemic parameters, but not all cardiometabolic risk factors together. More rigorous, comprehensive research is needed to augment the generalizability of the findings and solidly inform dietary endorsements concerning almond consumption.

This systematic review aimed to investigate the effectiveness of almond supplementation compared with placebo or no intervention on improving cardiometabolic measures, such as glycemic indices, blood pressure parameters, lipid enzymes, inflammatory markers, and hepatic enzymes in adults.

2 | METHODS

2.1 | Study design

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2010).

2.2 | Study selection

We included randomized controlled trials (RCTs), parallel or crossover, of adults with any health condition. The included trials evaluated some form of almond supplementation (e.g., oil, Baru, extract, snacks, and almond-rich diet) compared with placebo (i.e., non-almond supplementation) or no intervention. Our primary outcomes were FBG, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), C-peptide, and HbA1c levels. Secondary outcomes included TC, TG, HDL, LDL, very LDL (VLDL), non-HDL, ApoA1, ApoB, lipoprotein-a, oxidized LDL (ox-LDL), SBP, DBP, hepatic enzymes (i.e., aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT)), inflammatory markers (i.e., C-reactive protein (CRP), high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), intercellular adhesion

molecule (ICAM), vascular cell adhesion molecule (VCAM)), and homocysteine. No language restrictions were applied.

2.3 | Data sources and searches

We searched several databases and trial registries, including MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform until April 30, 2021. Our search terms were synonyms of "almond supplementation," "cardiometabolic," and "randomized controlled trials." Our complete search strategy can be found in Supporting information Appendix 1. Two reviewers (JH and MM) independently evaluated the titles, abstracts, and full texts of articles retrieved from the abovementioned search. Our database search was supplemented by manual examination of the reference lists of the included studies. Disagreements between the two reviewers were resolved by discussion or consultation with a third reviewer (ABP).

2.4 | Data extraction and quality assessment

We used a standardized data extraction form to obtain trial characteristics (e.g., design, setting, intervention parameters, sample size, age, and body mass index of participants) and outcome data (e.g., FBG, HDL, and LDL levels). We included more than one week's oral interventions. Two reviewers (JRZ and MM) independently extracted the data, compared data extraction forms for each trial, and resolved all disagreements. Corresponding authors of select studies were contacted in cases of missing data.

Two reviewers (ABP and JH) independently rated the risk of bias using the Cochrane Collaborations' risk of bias tool (version 1). Disagreements were resolved by discussion or by consultation with a third reviewer (MM). This instrument evaluates several domains of biases, as follows: selection, performance, detection, reporting, and attrition biases. Each domain was rated as "high," "unclear," or "low" risk of bias.

2.5 | Data analysis

All data were entered into STATA (version 11) for analysis. Entered data were further checked for accuracy by another reviewer (AA). We used a random-effects meta-analysis model (due to differences in almond supplementation across the included trials) to determine the mean treatment effect of almond supplementation on cardiometabolic measures. We obtained a standardized mean difference (SMD) and 95% confidence interval (CI) for all outcomes. SMDs were interpreted as small effects (0.2), medium effects (0.5), and large effects (0.8) (Cohen, 2013). When more than ten trials contributed data to a meta-analysis, we assessed publication bias using a funnel plot and Egger's regression test for funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997). Heterogeneity was assessed using the I^2 statistic and interpreted as follows: 0%–40%, unlikely to be important heterogeneity; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity (Higgins & Thompson, 2002). Subgroup analyses were performed to explore whether our main findings differed according to specific patients' demographics, health status, age, duration/dosage of almond intake, and type of control group. The certainty of evidence was evaluated according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) method. In GRADE method certainty of evidence evaluated according to risk of bias, inconsistence between studies, indirectness, imprecision, and Publication bias. GRADE incorporates results of included studies with explicit consideration of the values and preferences of participants and society at big scale to arrive at recommendations.

3 | RESULTS

3.1 | Study characteristics

Figure 1 presents the flow diagram of the selection process of included articles. The initial search results from PubMed, Web of Science, Scopus, Cochrane Central Register of Controlled Trials, and EMBASE were 108, 48, 110, 23, and 174 studies, respectively. After removing duplicates, 299 records remained for title and abstract screening. Next, 247 records were excluded during the title and abstract screening. After carefully assessing the remaining 52 full-text articles, 26 papers were further excluded. Finally, 26 studies (Abazarfard, Eslamian, Salehi, & Keshavarzi, 2016; Abazarfard, Salehi, & Keshavarzi, 2014; Bento, Cominetti, Simoes, & Naves, 2014; Berryman, West, Fleming, Bordi, & Kris-Etherton, 2015; Bowen et al., 2019; Chen et al., 2015; Chen et al., 2017; Coates et al., 2020; Cohen & Johnston, 2011; de Souza et al., 2019; de Souza, Gomes, de Castro, & Mota, 2018; Dhillon et al., 2018; Dikariyanto et al., 2020; Jamshed, Sultan, Iqbal, & Gilani, 2015; Jenkins et al., 2002; Jenkins et al., 2008a; Jenkins et al., 2008b; Jung, Chen, Blumberg, & Kwak, 2018; Liu et al., 2017; Liu, Hwang, Kim, & Park, 2018; Liu, Liu, Chen, Chang, & Chen, 2013; Palacios et al., 2020; Rajaram, Connell, & Sabate, 2010; Schincaglia et al., 2020; Tan & Mattes, 2013; Zibaeenezhad, Ostovan, Mosavat, Zamirian, & Attar, 2019) met the inclusion criteria and were included in this systematic review and meta-analysis.

3.2 | Study characteristics

The main characteristics of the eligible included trials are presented in Table 1. Included trials were published between 2002 and 2020 and conducted on 1750 participants. The studies were performed in nine countries: Australia (Bowen et al., 2019; Coates et al., 2020; Tan & Mattes, 2013), United Kingdom (Dikariyanto et al., 2020), Brazil (Bento et al., 2014; de Souza et al., 2018; de Souza et al., 2019; Schincaglia et al., 2020), Iran (Abazarfard et al., 2014; Abazarfard et al., 2016; Zibaeenezhad et al., 2019), Canada (Jenkins et al., 2002;

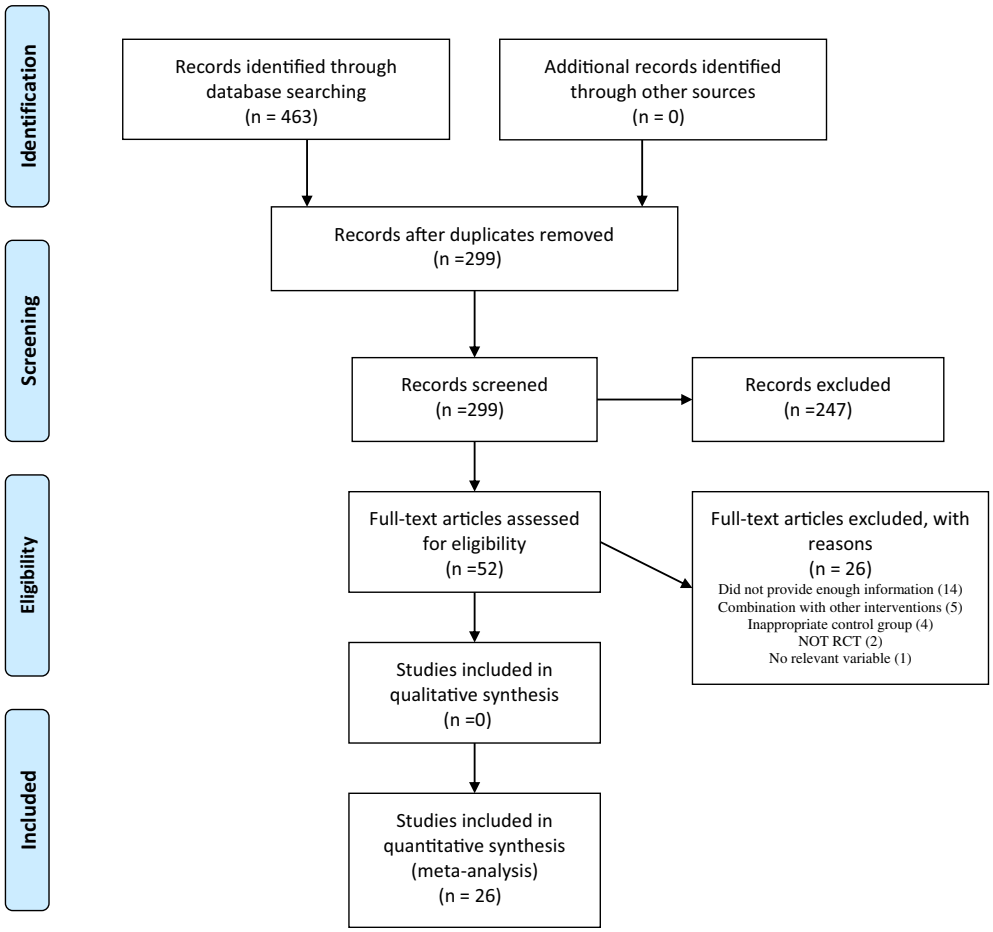

FIGURE 1 PRISMA Flow diagram of study selection

Jenkins et al., 2008a; Jenkins et al., 2008b), South Korea (Jung et al., 2018; Liu et al., 2017; Liu et al., 2018), Pakistan (Jamshed et al., 2015), Taiwan (Chen et al., 2017; Liu et al., 2013), and United States of America (Berryman et al., 2015; Chen et al., 2015; Cohen & Johnston, 2011; Dhillon et al., 2018; Palacios et al., 2020; Rajaram et al., 2010). Of these 26 trials, six studies were conducted on overweight and obese subjects (Abazarfard et al., 2014; Abazarfard et al., 2016; Coates et al., 2020; de Souza et al., 2018; de Souza et al., 2019; Jung et al., 2018), four studies on cardiovascular disease patients (Chen et al., 2015; Dikariyanto et al., 2020; Jamshed et al., 2015; Jenkins et al., 2002), six studies on diabetic subjects (Bowen et al., 2019; Chen et al., 2017; Cohen & Johnston, 2011; Liu et al., 2013; Palacios et al., 2020; Tan & Mattes, 2013), five studies on hyperlipidemic subjects (Bento et al., 2014; Berryman et al., 2015; Jenkins et al., 2008a; Jenkins et al., 2008b; Zibaeenezhad et al., 2019), one study on hemodialysis patients (Schincaglia et al., 2020), and four studies on healthy subjects (Dhillon et al., 2018; Liu et al., 2017; Liu et al., 2018; Rajaram et al., 2010). Fifteen studies were randomized crossover trials, and 11 had a parallel randomized design. Nineteen studies used whole raw almonds as an intervention; four studies used Baru almonds; two studies used roasted almonds; one study used Persian almonds; and one study used an almond-rich diet. Dosage of almond intake ranged between 5 and 85 g/day. The duration of treatment differed among trials and ranged between 4 and 20 weeks. The age of participants in the included studies ranged from 26 to 64 years old.

3.3 | Effect of almond intake on blood pressure

The effects of almond consumption on blood pressure parameters are presented in Figure 2. Meta-analysis of 18 interventional arms did not show a significant change in SBP after almond intake (SMD: −0.06; 95% CI: −0.20, 0.08; $I^2 = 28.3\%$). However, according to sensitivity analysis, dropout of Abazarfard et al. (; Abazarfard et al., 2014) study (Abazarfard et al., 2014) changed the results to a significant outcome in favor of the almond group compared with the control group (SMD: −0.12; 95% CI: −0.24, 0.00; $I^2 = 0\%$). Subgroup analysis according to the age of the participants indicated that almond intake significantly decreased SBP in senior adults (Table 2). Moreover, meta-analysis of 18 interventional arms indicated that almond intake significantly decreased DBP (SMD: −0.17; 95% CI: −0.28, −0.05; $I^2 = 0\%$). Subgroup analysis depicted that almond intake significantly decreased DBP in unhealthy subjects, participants with baseline DBP less than 75 mmHg, participants with more than 50 g/d intake of almond, participants with more than 10 weeks of trial duration, and in studies with a regular diet as the control group type (Table 2).

TABLE 1 Main characteristics of included studies (effect of almond on cardiometabolic parameters: a systematic review and meta-analysis)

Study (ref)	Country	Subjects	Design	Sample size	Amount/day (how and when was ingested)	Almond type	Almond dosage (g/day)	Control type	Duration (week)	Gender (% females)	Age (years)		BMI (kg/m^2)		Main outcomes[a]
											Intervention mean ± SD	Placebo Mean ± SD	Intervention mean ± SD	Placebo Mean ± SD	
Abazarfard et al. (2014)	Iran	Overweight And obese women	RCT	100	Two snacks (25 g almond each)	Raw almond	50	Nut-free diet	12	100	42.36 ± 7.30	42.94 ± 6.82	29.91 ± 1.20	29.37 ± 1.73	↓TC, ↓TG, ↓HDL, ↓FBG, ↓DBP, ↔SBP, ↔LDL
Abazarfard et al. (2016)	Iran	Overweight And obese women	RCT	108	25 g almond twice a day	Raw almond	50	Nut-free diet	12	100	42.36 ± 4.30	42.94 ± 6.82	29.91 ± 1.20	29.37 ± 1.73	↓ALT, ↓AST, ↓GGT
Bento et al. (2014)	Brazil	Mildly hyper cholesterolemic subjects	Randomized crossover trial	20	Once a day (snacks or with meals)	Baru almond	20	Corn starch capsule	12	60	34.9 ± 2.7	34.9 ± 2.7 (SAME GROUP)	23.2 ± 0.6	23.1 ± 0.6	↓TC, ↓LDL, ↓non-HDL, ↔HDL, ↔TG, ↔VLDL
Berryman et al. (2015)	USA	Individuals with elevated LDL-C	Randomized crossover trial	48	One snack between meals	Raw almond	42.5	Muffin	12	54	49.9 ± 9.4	49.9 ± 9.4 (SAME GROUP)	26.2 ± 2.8	NR	↓LDL, ↓non-HDL
Bowen et al. (2019)	Australia	Adults with elevated risk of type 2 diabetes	RCT	76	2 servings daily (28 g each)	Raw almond	56	Sweet biscuits	8	41	60.8 ± 6.6	60.6 ± 8.8	34.4 ± 6.2	33.2 ± 4.9	↓TC/HDL in women, not in men
Chen et al. (2015)	USA	Patients with coronary artery disease	Randomized crossover trial	45	Snacks	Raw almond	85	Nut-free diet	12	60	61.8 ± 8.6	61.8 ± 8.6 (SAME GROUP)	30.2 ± 5.1	30.2 ± 5.1	↔ lipid profile, but improved diet quality
Chen et al. (2017)	Taiwan	Type 2 diabetes mellitus	Randomized cross-over trial	33	Snacks	Roasted almond	60	Nut-free diet	28	60	54.9 ± 10.5	54.9 ± 10.5 (SAME GROUP)	25.4 ± 4.3	25.3 ± 4.1	↔ lipid profile ↓FBG
Coates et al. (2020)	Australia	Old overweight adults	Randomized cross-over trial	128	Snacks	Raw almond	30	Nut-free diet	12	61	64 ± 8	65 ± 8	30.3 ± 3.6	30.5 ± 3.8	↓triglycerides, ↓SBP
Cohen and Johnston (2011)	USA	Well-controlled type 2 diabetes mellitus	Randomized cross-over trial	13	Mealtime	Raw almond	28	Nut-free diet	12	53	66 ± 3	53 ± 3	32.6 ± 2.3	36.7 ± 3.6	↓FBG, ↔ lipid profile
de Souza et al. (2019)	Brazil	Overweight and obese women	RCT	46	Snacks	Baru almond	20	Nut-free diet	8	100	40 ± 11	40 ± 11	32.5 ± 4.3	33.3 ± 4.6	↑GPx, ↔ CAT, SOD, MDA
Dhillon et al. (2018)	USA	Young adults	RCT	73	Morning snack	Raw almond	56.7	Crackers	8	56	34 (97)[b]	38 (100)[b]	25.6 ± 5.0	25.3 ± 4.5	↓HDL, ↑glucose tolerance, ↑insulin sensitivity
Dikariyanto et al. (2020)	UK	Above-average risk of developing CVD	RCT	105	Snacks	Roasted unsalted almond	63	Mini-muffins	6	70	56.3 ± 10.3	56.0 ± 10.7	27.3 ± 4.4	26.7 ± 4.5	↓LDL, ↔ TG, HDL, BP, glucose, insulin, insulin resistance, leptin, adiponectin
Jamshed et al. (2015)	Pakistan	Coronary artery disease patients	RCT	150	Before breakfast	Talwa raw almond	10	Nut-free diet	12	25	32–86[b]	32–86[b]	75 ± 0.2	73.4 ± 0.2	↑HD, ↔ TC, TG, LDL, VLDL
Jenkins et al. (2008)	Canada	Non-diabetic hyperlipidemic subjects	Randomized crossover trial	27	Snacks	Whole almond	73 ± 3	Whole-wheat muffin	12	45	64 ± 9	64 ± 9 (SAME GROUP)	25.7 ± 3.0 (SAME GROUP)	25.7 ± 3.0	↓insulin secretion, ↔ FBG
Jenkins et al. (2008)	Canada	Healthy old hyperlipidemic subjects	Randomized crossover trial	27	Snacks	Whole almond	73 ± 3	Whole-wheat muffins	12	45	64 ± 9	64 ± 9	25.5 ± 4.0	25.5 ± 4.0	↓LDL, ↑HDL
Jenkins et al. (2002)	Canada	Coronary heart disease risk factors	Randomized crossover trial	27	Snacks	Whole almond	73 ± 3	Whole-wheat muffins	12	45	64 ± 9	64 ± 9	25.7 ± 3.0	25.7 ± 3.0	↓LDL, ↑HDL

(Continues)

TABLE 1 (Continued)

Study (ref)	Country	Subjects	Design	Sample size	Amount/day (how and when was ingested)	Almond type	Almond dosage (g/day)	Control type	Duration (week)	Gender (% females)	Age (years)		BMI (kg/m^2)		Main outcomes[a]
											Intervention mean ± SD	Placebo Mean ± SD	Intervention mean ± SD	Placebo Mean ± SD	
Jung et al. (2018)	Korea	Overweight/obese participant	Randomized cross-over trial	84	Snacks	Raw almond	56	Cookies	12	87	52.4 ± 0.6	52.4 0.6	23–29.9[b]	23–29.9[b]	↔ TG, ↓TC, LDL, and non-HDL
Liu et al. (2013)	Taiwan	Type 2 diabetes mellitus	Randomized cross-over trial	20	Snacks	Raw almond	56	Control diet	12	55	58 ± 2	58 ± 2	26.0 ± 0.7	26.0 ± 0.7	↓IL-6, CRP
Liu et al. (2017)	Korea	Healthy adults	Randomized crossover trial	169	Before meals or snack	Raw almond	56	Cookies	16	55	26.33 ± 5.55	26.33 ± 5.55	22.59 ± 3.04	22.59 ± 3.04	↓TCL, LDL, ↔ HDL
Liu et al. (2018) (Liu et al., 2018)	Korea	Free-living healthy adults	RCT	84	Snacks	Raw almond	56	Cookies	20	55	26.96 ± 5.22	26.14 ± 5.40	23 ± 3.17	21.66 ± 3.08	↓TC, TG, LDL, non-HDL
Palacios et al. (2020)	USA	Adults with prediabetes	Randomized crossover trial	33	Snacks	Raw almond	42.5	Iso- caloric CHO-based foods	10	55	48.3 ± 2.2	48.3 ± 2.2	30.5 ± 0.7	30.5 ± 0.7	↔TC, TG, LDL, non-HDL, FBG
Rajaram et al. (2010)	USA	Healthy adults	Randomized crossover trial	25	Snacks	High almond diet	NR	Low almond diet	8	44	40.9 ± 12.8	40.9 ± 12.8	NR	NR	↓CRP
Schincaglia et al. (2020)	Brazil	Hemodialysis patients	RCT	29	After lunch and after diner	Baru almond oil	5	Mineral oil	12	45	49.3 ± 3.4	51.3 ± 3.0	23.8 ± 1.5	25.5 ± 1.4	↔CRP
de Souza et al. (2018)	Brazil	Overweight and obese women	RCT	46	Snacks	Baru almond	20	Nut-free diet	8	100	NR	NR	32.54 ± 4.35	33.34 ± 4.69	↓HDL
Tan and Mattes (2013)	Australia	Increased risk for type 2 diabetes	Randomized crossover trial	137	With breakfast or lunch	Raw almond	43	Nut-free diet	4	67	32.9 ± 11.5	28.7 ± 9.6	28.2 ± 4.8	27.0 ± 4.4	↓ glucose post prandial, ↓hunger
Zibaeenezhad et al. (2019)	Iran	Hyperlipidemic patients	RCT	97	Two times a day (5 mL)	Persian almond oil	10 mL[c]	No intervention	4	NR	49.4 ± 12.02	50.19 ± 9.87	26.475 ± 2.89	28.5 ± 4.18	↓TC, ↓LDL

Bolded values represents the presented 95% CI.

Note: ↓ *Means decreasing variables in the intervention group*, ↑ *means increasing variables in the intervention group, and* ↔ *indicates that there is no difference between the two groups.*

Abbreviation: NR, not reported.

[a]ALT, Alanine aminotransferase; ASP, Aspartate aminotransferase; BP, Blood Pressure; CAT,Catalase; CRP, C-reactive protein; DBP, diastolic blood pressure; FBG, Fasting blood glucose; GGT,Gamma-glutamiltransferase; GPx, Glutathione Peroxidase; HDL, High density lipoprotein; IL-6, Interleukin-6; LDL, Low density lipoprotein; MAD, Malondialdehyde; SBP, Systolic blood pressure; SOD, Superoxide dismutase; TC, Total cholesterol; TG, Triglyceride; VLDL, Very low density lipoprotein.

[b]Range.

[c]Milliliter per day.

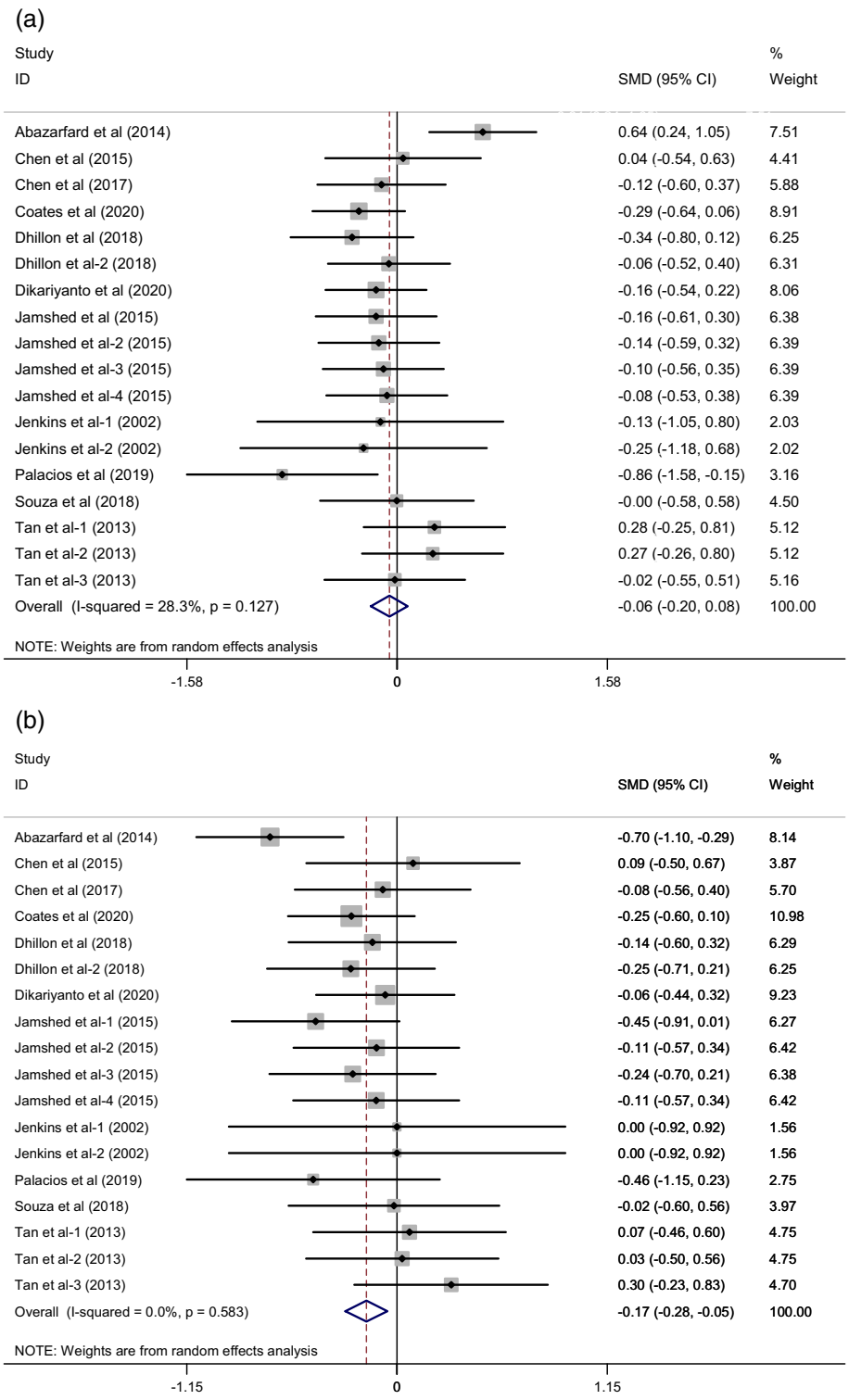

FIGURE 2 Forest plot of the effect of almond intake on SBP (a) and DBP (b)

3.4 | Effect of almond intake on glycemic control

The effects of almond consumption on glycemic parameters are presented in Figure 3. The results of our meta-analysis indicated that almond intake had no significant effect on FBG (15 interventional arms; SMD: 0.02; 95% CI: −0.24, 0.28; $I^2 = 71.9\%$), insulin (12 interventional arms; SMD: 0.19; 95% CI: −0.06, 0.44; $I^2 = 56.8\%$), HbA1c (4 interventional arms; SMD: -0.10; 95% CI: −0.37, 0.18; $I^2 = 00.0\%$), HOMA-IR (6 interventional arms; SMD: 0.07; 95% CI: −0.21, 0.35; $I^2 = 36.9\%$), and C-peptide (3 interventional arms; SMD: 1.42; 95% CI: −0.15, 2.99; $I^2 = 88.1\%$). Subgroup analyses based on diabetic status, health status, trial duration, dose of almond intake, type of control, and age did not show significant changes in the pooled effect sizes of these variables (Table 3).

TABLE 2 Subgroup analysis assessing the effect of almond intake on blood pressure parameters

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
SBP	Baseline levels	≥125 mmHg	10	−0.04	−0.27, 0.18	55.1	**.018**
		<125 mmHg	8	−0.10	−0.28, 0.08	00.0	.851
	Diabetes status	Diabetic	5	−0.04	−0.39, 0.30	48.9	.098
		Non-diabetic	13	−0.07	−0.22, 0.09	23.9	.202
	Health status	Healthy	3	−0.18	−0.43, 0.06	00.0	.696
		Unhealthy	15	−0.03	−0.19, 0.14	35.6	.084
	Duration	≥10 weeks	9	−0.08	−0.32, 0.16	57.4	**.016***
		<10 weeks	9	−0.05	−0.22, 0.13	00.0	.764
	Almond dosage	≥50 g	8	−0.08	−0.38, 0.21	62.0	**.010***
		<50 g	10	−0.07	−0.23, 0.08	00.0	.814
	Control group	Nut free diet	12	−0.08	−0.28, 0.12	42.0	.061
		Regular diet	6	−0.04	−0.23, 0.15	00.0	.127
	Age	Middle aged adults (31–50)	6	0.10	−0.27, 0.48	65.3	.013
		Senior adults (>50)	12	**−0.15**	**−0.30, −0.00***	00.0	.99
DBP	Baseline levels	≥75 mmHg	9	−0.15	−0.38, 0.07	36.4	.141
		<75 mmHg	9	**−0.16**	**−0.31, −0.00***	00.0	.940
	Health status	Healthy	3	−0.14	−0.39, 0.11	00.0	.825
		Unhealthy	15	**−0.17**	**−0.31, −0.04***	4.9	.397
	Duration	≥10 weeks	9	**−0.27**	**−0.43, −0.12***	1.5	.421
		<10 weeks	9	−0.03	−0.20, 0.15	00.0	.947
	Almond dosage	≥50 g	8	**−0.23**	**−0.42, −0.03***	14.8	.314
		<50 g	10	−0.12	−0.27, 0.03	00.0	.730
	Control group	Nut free diet	12	−0.12	−0.37, 0.14	49.6	.064
		Regular diet	6	**−0.18**	**−0.33, −0.03***	00.0	.975

Note: Bolded values represents the presented 95% CI.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SMD, Standardized mean difference.
*Statistically significant.

3.5 | Effect of almond intake on hepatic enzymes

The effects of almond intake on hepatic enzymes are presented in Figure 4. The results of our meta-analysis demonstrated that almond intake did not significantly change ALT (5 interventional arms; SMD: -0.16; 95% CI: −0.43, 0.10; $I^2 = 43.4\%$), AST (4 interventional arms; SMD: -0.20; 95% CI: −0.43, 0.04; $I^2 = 00.7\%$), and GGT (3 intervention arms; SMD: 0.02; 95% CI: −0.28, 0.32; $I^2 = 29.4\%$). Subgroup analyses for ALT are presented in Table 4.

3.6 | Effect of almond intake on inflammatory markers and homocysteine level

Meta-analysis of the included trials showed that almond intake did not significantly impact the CRP (7 interventional arms; SMD: 0.02; 95% CI: −0.20, 0.25; $I^2 = 0\%$), hs-CRP (5 interventional arms; SMD: 0.22; 95% CI: −0.45, 0.02; $I^2 = 00.0\%$), IL-6 (11 interventional arms; SMD: 0.01; 95% CI: −0.31, 0.34; $I^2 = 78.9\%$), TNF-α (4 interventional arms; SMD: 0.86; 95% CI: −0.38, 2.09; $I^2 = 94.9\%$), ICAM (3 interventional arms; SMD: 0.02; 95% CI: −0.25, 0.29; $I^2 = 22.8\%$), VCAM (3 interventional arms; SMD: 0.02; 95% CI: −0.23, 0.26; $I^2 = 0\%$), and homocysteine (3 interventional arms; SMD: 0.08; 95% CI: −0.45, 0.61; $I^2 = 0\%$) levels between almond and control groups (Figure 5). However, sensitivity analysis indicated that, after drop out of de Souza et al. (2019) results (de Souza et al., 2019), almond intake significantly decreased IL-6 levels (10 interventional arms; SMD: −0.20; 95% CI: −0.36, −0.04; $I^2 = 14.3\%$). Due to the limited number of interventional arms, subgroup analyses could not be performed for hs-CRP, TNF-α, ICAM, VCAM, and homocysteine levels. Subgroup analyses for CRP and IL-6 levels are presented in Table 5.

3.7 | Effect of almond intake on blood lipids

The effects of almond intake on hepatic enzymes are presented in Figure 6. Our results indicated that almond intake significantly decreased TC (29 interventional arms; SMD: −0.29; 95% CI: −0.40, −0.18; $I^2 = 33.5\%$), TG (30 interventional arms; SMD: −0.23; 95% CI: −0.32, −0.13; $I^2 = 14.6\%$), LDL (30 interventional arms; SMD: −0.29; 95% CI: −0.39, −0.19; $I^2 = 20.8\%$), non-HDL (14 interventional arms; SMD: -0.36; 95% CI: −0.49, −0.24; $I^2 = 0\%$), and VLDL

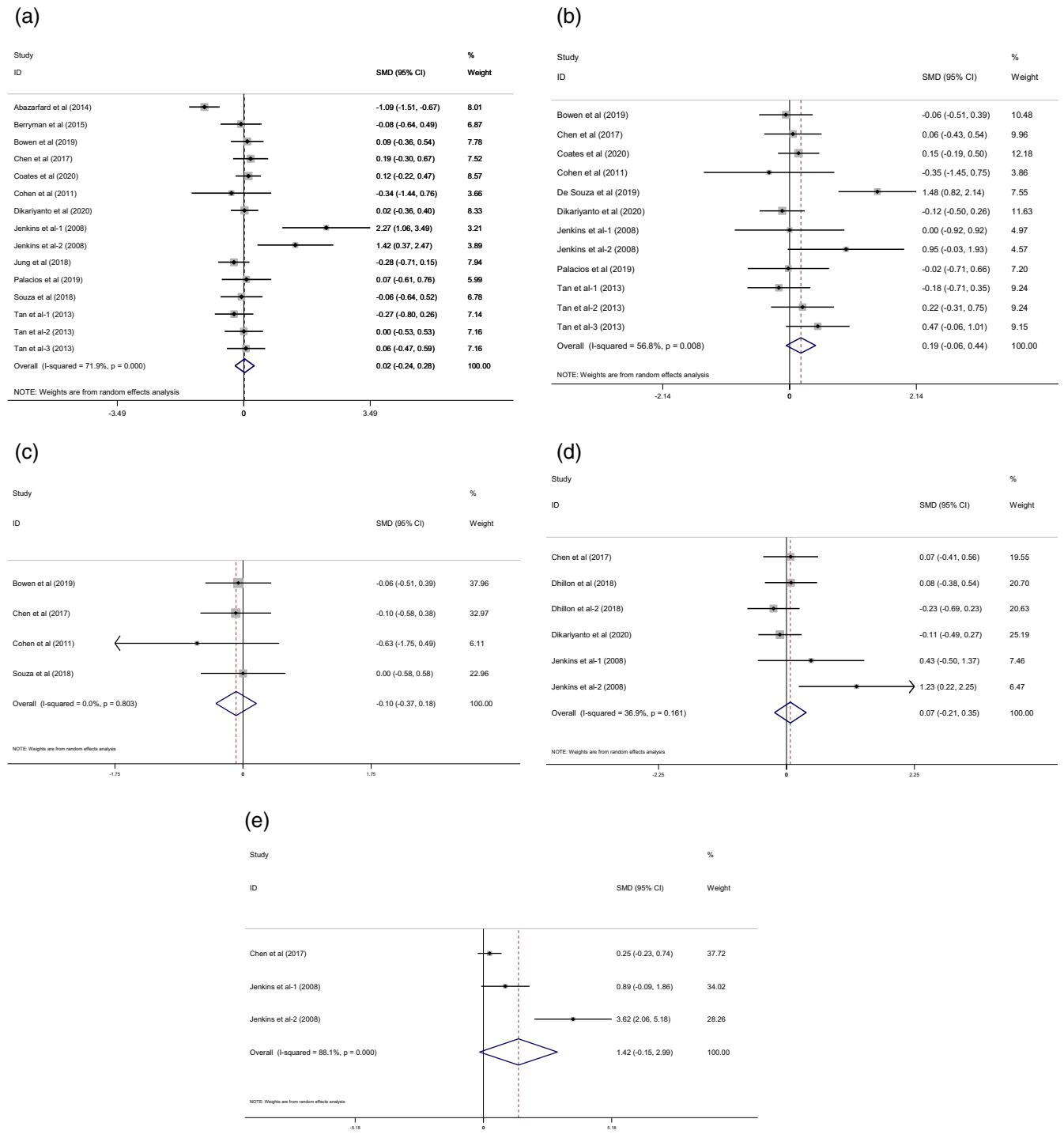

FIGURE 3 Forest plot of the effect of almond intake on FBS (a), Insulin (b), HbA1c (c), HOMA-IR (d) and C-peptide (e)

(14 interventional arms; SMD: −0.23; 95% CI: −0.38, −0.07; $I^2 = 0\%$) levels. When compared with the control group, our results indicated that almond intake did not significantly impact HDL (29 interventional arms; SMD: 0.01; 95% CI: −0.10, 0.13; $I^2 = 39.9\%$), ox-LDL (9 interventional arms; SMD: −0.13; 95% CI: −0.28, 0.02; $I^2 = 00.0\%$), ApoA1 (9 interventional arms; SMD: 0.02; 95% CI: −0.18, 0.22; $I^2 = 00.0\%$), ApoB (8 interventional arms; SMD: −0.14; 95% CI: −0.35, 0.07; $I^2 = 00.0\%$), and lipoprotein-a (3 interventional arms; SMD: 0.10; 95% CI: −0.33, 0.53; $I^2 = 00.0\%$) levels. Subgroup analyses according to participants' baseline blood lipid levels, health status, age, trial duration, dosage of almond intake, and type of control group are presented in Table 6.

3.8 | Quality assessment and publication bias

The quality appraisal report of the included studies is presented in Supporting information Appendix 2. More than 60% of the included

TABLE 3 Subgroup analysis assessing the effect of almond intake on glycemic control parameters

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
FBG	Diabetes status	Diabetic	9	0.10	−0.32, 0.51	83.1	**<.001***
		Non-diabetic	6	−0.00	−0.24, 0.23	00.0	.846
	Health status	Healthy	1	0.02	−0.36, 0.40	-	-
		Unhealthy	14	0.03	−0.26, 0.32	73.8	**<.001***
	Duration	≥10 weeks	6	−0.19	−0.66, 0.29	79.0	**<.001***
		<10 weeks	9	0.14	−0.17, 0.46	65.7	**.003***
	Almond dosage	≥ 50 g	7	0.03	−0.45, 0.52	84.6	**<.001***
		< 50 g	8	0.03	−0.20, 0.26	22.3	.252
	Control group	Nut free diet	8	−0.17	−0.51, 0.17	71.6	**<.001***
		Regular diet	7	0.28	−0.14, 0.70	72.5	**<.001***
Insulin	Diabetes status	Diabetic	6	0.09	−0.14, 0.33	00.0	.559
		Non-diabetic	6	0.34	−0.12, 0.79	76.4	**<.001***
	Duration	≥10 weeks	4	0.08	−0.18, 0.33	00.0	.840
		<10 weeks	8	0.30	−0.08, 0.67	71.0	**<.001***
	Almond dosage	≥ 50 g	5	−0.05	−0.28, 0.18	00.0	.986
		< 50 g	7	0.38	−0.03, 0.79	69.7	**.003***
	Control group	Nut free diet	5	0.30	−0.23, 0.82	75.3	**.003***
		Regular diet	7	0.09	−0.15, −0.32	23.2	.252
	Age	Middle aged adults	5	0.38	−0.15, 0.92	76.3	**.002***
		Senior adults	7	0.04	−0.15, 0.23	00.0	.528
HbA1c	Diabetes status	Diabetic	2	−0.18	−0.63, 0.26	00.0	.395
		Non-diabetic	2	−0.04	−0.40, 0.31	00.0	.863

Note: Bolded values represents the presented 95% CI.
Abbreviations: CI, confidence interval; FBG, fasting blood glucose; HbA1c, Glycated hemoglobin A1c; SMD, Standardized mean difference.
*statisticaly significant.

trials had a low risk of random sequence allocation. Allocation concealment was considered at low risk in about 50% of the included trials. About more than 70% of the included trials had high risk of performance and detection bias. Most studies had an unclear risk of bias for selective reporting and incomplete data. More than 75% of the included trials were judged to be at low risk of bias for other biases. Begg's and Egger's weighted regression tests and visual inspection of funnel plot asymmetry showed no potential publication bias. Funnel plots of selected variables are presented in Supporting information Appendix 3. The certainty of evidence according to the GRADE scale is presented in Supporting information Appendix 4.

4 | DISCUSSION

This systematic review and meta-analysis included 26 studies, enrolling 1750 subjects and assessing the effects of almond ingestion on various cardiometabolic risk factors. Examples of such cardiometabolic risk factors included blood pressure, blood lipids, hepatic enzymes, glycemic markers, and inflammatory parameters. The results of this systematic review and meta-analysis were generated from a very recent bibliographic search that was carried out until April 2021, allowing for inclusion of the most recent published literature on the subject. As far as we know, this is the most comprehensive and largest study on the subject; many factors were analyzed simultaneously, including parameters that are scarcely studied in this context (such as the hepatic enzymes). Overall, the pooled results indicated that almond consumption significantly decreased blood pressure (SBP and DBP, but these were only true for some sub-groups, Table 2) and blood lipid levels (including TC, TG, LDL, non-HDL, and VLDL). Some variables presented significant changes only for particular subgroups as it was the case for ALT (decreased in the sub-group of unhealthy subjects, Table 4), HDL (decreased in the subgroup of young adults, and its level also changed independently of the amount of almond ingested, Table 6), and apoB (decreased in the sub-group of unhealthy participants, Table 6). No significant effects were observed for all analyzed glycemic parameters, inflammatory mediators (CRP, hs-CRP, TNFα, ICAM, and VCAM), homocysteine, certain hepatic enzymes (AST and GGT), and some blood lipids (ox-LDL, lipoprotein-a, and ApoA1).

Almond is a well-known nut that is particularly rich in several relevant macronutrients and micronutrients, including fatty acids (such as MUFAs and PUFAs), vitamins (with high levels of vitamin E), minerals (such as magnesium), fibers, antioxidants, and other bioactive compounds (such as arginine, phytophenols, and phytosterols), which have been associated to play protective roles in human health and promote

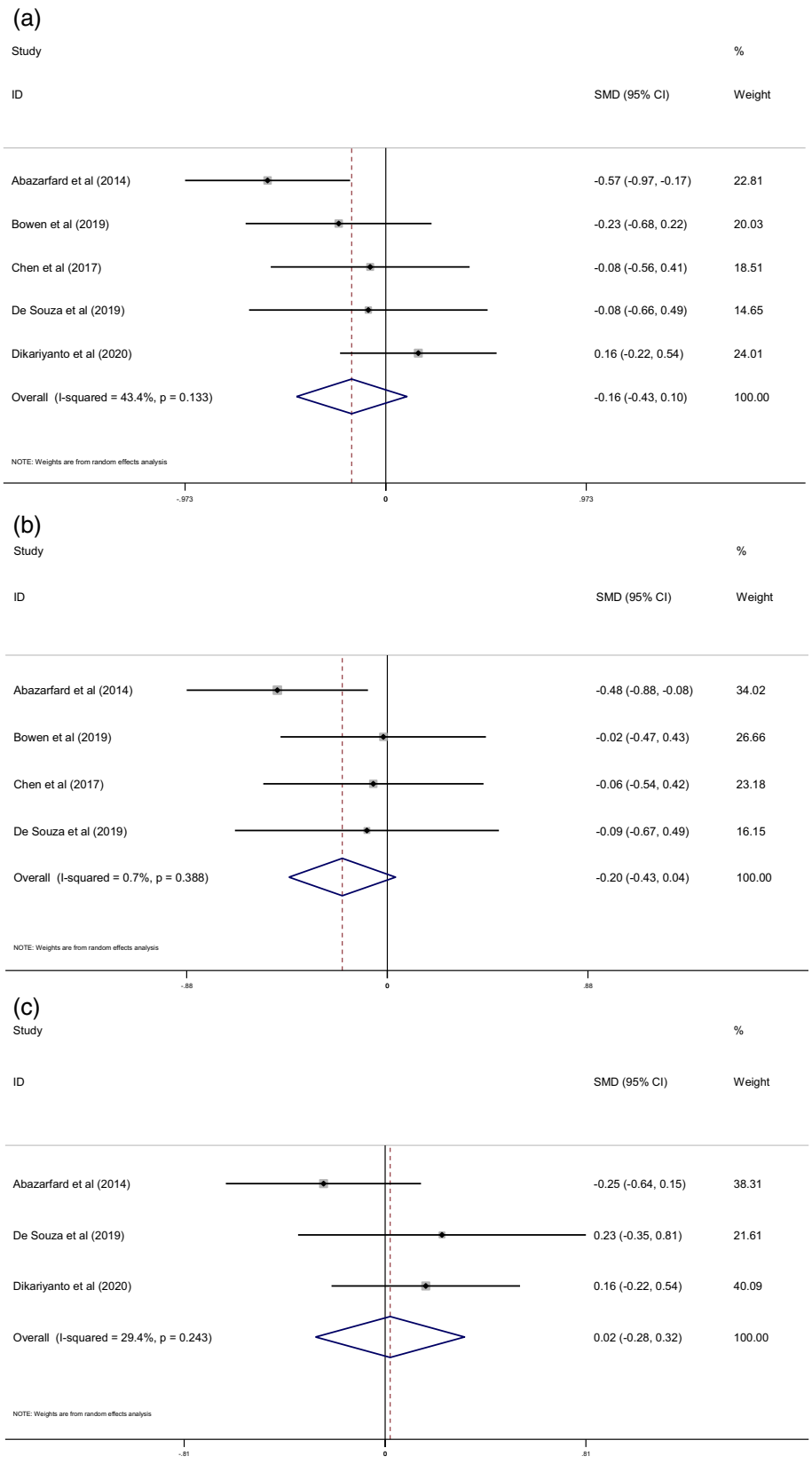

FIGURE 4 Forest plot of the effect of almond intake on hepatic enzymes; ALT (a), AST (b), and GGT (c)

gut microbiota. Almond composition differs based on several factors (such a genetics, climate, soil and cultivation practices, and even type of consumption) (Alasalvar & Bolling, 2015; Barreca et al., 2020; Bolling, Chen, McKay, & Blumberg, 2011; Li et al., 2020; Ros, 2015). For example, most antioxidants present in nuts are found in the skin, and their removal may reduce the antioxidant levels up to more than 90% (Blomhoff, Carlsen, Andersen, & Jacobs Jr., 2006). The available studies on the effect of almond intake are pretty different in terms of the

TABLE 4 Subgroup analysis assessing the effect of almond intake on ALT

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
ALT	Health status	Healthy	1	0.16	−0.22, 0.54	-	-
		Unhealthy	4	**−0.28**	**−0.53, −0.04***	07.2	.357
	Duration	≥10 weeks	2	−0.34	−0.83, 0.14	58.6	.120
		<10 weeks	3	−0.02	−0.28, 0.24	00.0	.424
	Age	Middle age adults	2	−0.38	−0.85, 0.09	46.0	.174
		Senior adults	3	−0.02	−0.27, 0.23	00.0	.423

Note: Bolded values represents the presented 95% CI.
Abbreviations: ALT, alanine aminotransferase; CI: confidence interval; SMD, standardized mean difference.
[a]Statistically significant.

type of almond, form of almond consumption (i.e., raw, roasted, peeled, oil, and powder), dose of almond intake, and duration of almond ingestion; all these factors may have contributed to the discrepancy of the summary results observed between this present investigation and other reported meta-analyses (Lee-Bravatti et al., 2019; Li et al., 2020; Liu et al., 2020; Musa-Veloso et al., 2016). Hence, there is a need for additional, well-controlled trials to deduce solid conclusions regarding the effects of almond intake on the various cardiovascular risk factors.

It is well-established that several nutrients play instrumental roles in regulating blood pressure and modulating the risk of cardiometabolic diseases. Potassium, protein, MUFAs, PUFAs, and tocopherol that are present in almonds are associated with a favorable decrease in blood pressure, while several other nutrients are still controversial in terms of their effects (Lelong et al., 2015; Mazidi, Ofori-Asenso, George, & Vatanparast, 2020; Ros, 2015; Savica, Bellinghieri, & Kopple, 2010). Most lipids present in almonds are MUFAs and PUFAs (Barreca et al., 2020; Ros, 2015), which may be one of the reasons why a decrease in blood pressure is associated with almond consumption, as unsaturated fatty acids and their derivatives have been proven to reduce blood pressure through several mechanisms that include vasodilatation, increasing sodium excretion, and decreasing inflammation (Imig, 2019). Another explanation may be due to the high content of L-arginine in almonds (Barreca et al., 2020; Ros, 2015), which is an important metabolite involved in the endothelial synthesis of nitric oxide, contributing to the regulation of vascular tone (Gambardella et al., 2020; Munteanu & Zingg, 2007). Additionally, tocopherol, which is present in elevated levels in almonds, may also contribute to blood pressure regulation, as it can participate in the regulation of endothelial function through several metabolic processes (Munteanu & Zingg, 2007).

Regarding the effects of almonds on blood lipid levels, the reported studies have depicted contradictory conclusions. Nevertheless, a general trend of improvement in the lipid profile has been observed (Griel & Kris-Etherton, 2006; Lee-Bravatti et al., 2019; Liu et al., 2020; Musa-Veloso et al., 2016). Our results align with the previously reported results as we observed a significant decrease in TC, LDL, and TG levels. Additionally, in our meta-analysis, non-HDL and VLDL levels were significantly decreased with almond intake. Except for some subgroups, no changes were observed in HDL or the remaining parameters assessed (such as apoA1, apoB, lipoprotein-a, and oxidized LDL) (Table 6). The almond nutritional composition of unsaturated fatty acids, phytosterols, antioxidants, and other bioactive compounds may explain the positive impact of almond consumption. This is because it has been shown that these nutrients exert protective effects on cardiovascular health due to the improvements of blood lipid profiles through mechanisms that might include beneficial changes in hepatic cholesterol absorption as well as favorable processing of TGs and lipoproteins (Alasalvar & Bolling, 2015; Bolling et al., 2011; Griel & Kris-Etherton, 2006; Zhao & Schooling, 2019). Moreover, the polyphenolic compounds present in almond skin, together with vitamins C and E, seem to have an essential role in preventing the oxidation of apoB, resulting in a decrease in LDL oxidation and in preventing the formation of atherosclerotic plaques (Chen, Milbury, Chung, & Blumberg, 2007; Jenkins et al., 2008a). Our results show that a significant reduction in apoB levels was induced by almond ingestion in hyperlipidemic subjects.

Regarding the several glycemic parameters assessed in the present meta-analysis, no significant changes were observed with almond intake. However, a previous review reported that tree nut consumption might positively affect diabetic subjects (Viguiliouk et al., 2014). However, in this study, almond consumption was not explicitly evaluated. More recently, another meta-analysis depicted that almond ingestion had no effect on FBG or HbA1c levels, but was associated with a decrease in insulin and HOMA-IR levels (Tindall et al., 2019). These discrepancies may be due to several factors, such as the number of studies included in these earlier meta-analyses and the present meta-analysis.

The effects of almond intake on hepatic enzymes were extensively evaluated in the present meta-analysis. The results suggested that almond intake did not affect these parameters, except for unhealthy subjects, as in this subgroup, a significant reduction of ALT level was detected compared with healthy participants. ALT enzyme is used as an indicator of hepatocellular damage. The effects of almonds on hepatic enzymes are scarcely studied. However, some nutrients present in almond composition (including magnesium, vitamin E, and selenium, for example) have been associated with exhibiting beneficial effects on liver function, by positively affecting hepatic enzyme levels, at least in unhealthy subjects (Galli et al., 2017; Gullestad et al., 1992; Pervez, Khan, Ijaz, & Khan, 2018; Shi et al., 2020). Additionally,

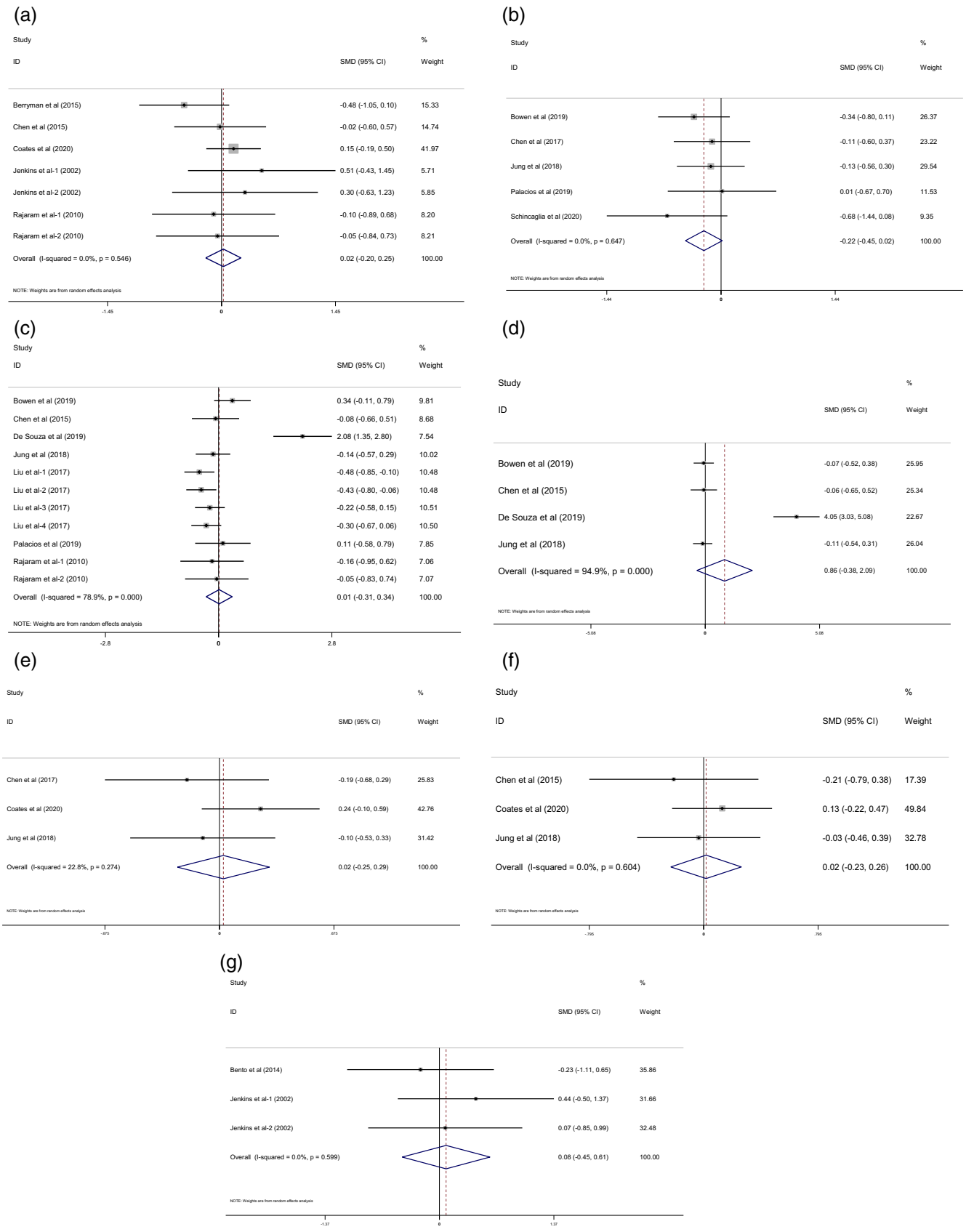

FIGURE 5 Forest plot of the effect of almond intake on inflammatory markers and Homocysteine; CRP (a), hs-CRP (b), IL-6 (c), TNF-α (d), ICAM (e), VCAM (f) and Homocysteine (g)

TABLE 5 Subgroup analysis assessing the effect of almond intake on inflammatory markers

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
CRP	Health status	Healthy	2	−0.08	−0.63, 0.48	00.0	.929
		Unhealthy	5	0.03	−0.25, 0.32	17.2	.305
	Duration	≥10 weeks	3	−0.06	−0.43, 0.31	41.0	.184
		<10 weeks	4	0.12	−0.30, 0.55	00.0	.730
	Almond dosage	≥50 g	3	0.08	−0.34, 0.50	00.0	.598
		<50 g	3	−0.21	−0.64, 0.21	02.7	.358
	Age	Middle age adults	2	−0.08	−0.63, 0.48	00.0	.929
		Senior adults	5	0.03	−0.25, 0.32	17.2	.305
IL-6	Health status	Healthy	6	**−0.33**	**−0.51, −0.15***	00.0	.860
		Unhealthy	5	0.43	−0.24, 1.10	86.3	**<.001**
	Duration	≥10 weeks	4	**−0.27**	**−0.50, −0.05***	00.0	.511
		<10 weeks	7	0.16	−0.34, 0.67	85.7	**<.001**
	Almond dosage	≥50 g	9	**−0.19**	**−0.36, −0.02***	23.7	.232
		<50 g	3	0.96	−1.23, 3.16	94.1	**<.001***
	Control group	Nut free diet	3	0.76	−0.36, 1.87	91.1	**<.001***
		Regular diet	8	**−0.28**	**−0.44, −0.12***	00.0	.795
	Age	Young adults	4	**−0.36**	**−0.54, −0.17***	00.0	.759
		Middle age adults	5	0.50	−0.56, 1.55	87.6	**<.001***
		Senior adults	3	0.05	−0.26, 0.36	20.0	.287

Note: Bolded values represents the presented 95% CI.
Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, Interleukin 6; SMD, Standard mean difference.
*Statistically significant.

almonds are often included in hypocaloric diets for weight loss purposes due to their satiating properties and favorable effects on hepatic enzymes (Abazarfard et al., 2016).

Regarding inflammatory markers, the pooled results showed that ingestion of almonds only significantly impacted IL-6 levels in some subgroups, namely healthy participants, interventions longer than ten weeks, young adults, almond doses equal to or greater than 50 g, and when control groups consumed regular diets (compared with nut-free diets). IL-6, together with other cytokines, is recognized for its role in the pathogenesis of heart failure and broad action on many different cell types. Additionally, the IL-6 signaling pathway has been linked to several age-related changes that lead to a high risk of atherosclerosis, such as declining vascular mitochondrial function (Tyrrell & Goldstein, 2020). The involvement of IL-6 in the process of age-related atherosclerosis and heart failure led to its identification as a potential therapeutic target, although several questions still need to be addressed (Hanna & Frangogiannis, 2020; Tyrrell & Goldstein, 2020).

This review has several strengths; for example, this is the first systematic review and meta-analysis that comprehensively summarized all the major databases of evidence on the effects of almonds on various cardiometabolic risk factors. Overall, the results showed that almond intake had positive effects on improving various health-related parameters, endorsing its formal incorporation into dietary regimens. However, this review also has some limitations. For example, a study protocol was not preregistered in the International Prospective Register of Systematic Reviews (PROSPERO). Although protocol preregistration is not a mandatory requirement by the Cochrane Collaboration, however, this is a concern that might have introduced potential bias to the present investigation. Considering the high caloric value of almonds, it might be essential to define in future studies a narrower dose interval that could ensure a decrease in cardiovascular risk, although some reported results showed that the controlled ingestion of almonds might even contribute to a decrease in body weight (Berryman et al., 2015). The interpretation of the reported results in the published reviews should be cautious, considering that a dose–response relationship between the dose of almond consumed and its effect on cardiometabolic risk has been described and that several factors related to almond ingestion and the overall diet composition, especially for control groups, may affect the outcomes observed (Del Gobbo, Falk, Feldman, Lewis, & Mozaffarian, 2015; Griel & Kris-Etherton, 2006). Moreover, it is notorious that only a few relevant parameters associated with cardiometabolic risks, such as inflammatory parameters and hepatic enzymes, have been studied in a small number of trials. In the 26 studies included in the present meta-analysis, only five studies investigated some of these factors (Abazarfard et al., 2016; de Souza et al., 2019; Liu et al., 2013; Rajaram et al., 2010; Schincaglia et al., 2020). In this context, the available information is not enough to conclude about the actual efficacy of almonds on controlling cardiometabolic risk factors.

Considering the high heterogeneity between the studies included in the present meta-analysis, sensitivity analyses were conducted to

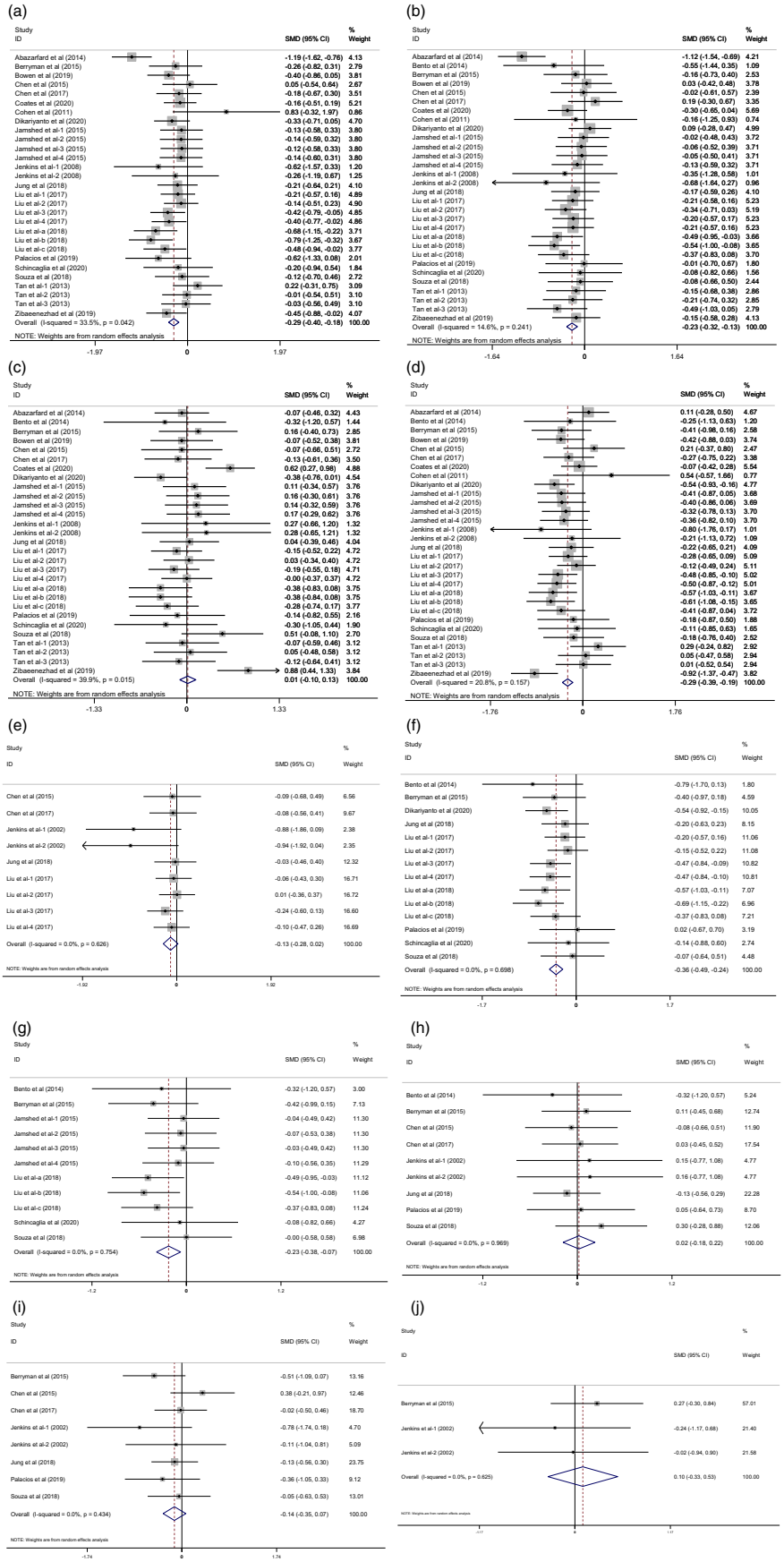

FIGURE 6 Forest plot of the effect of almond intake on blood lipids; TC (a), TG (b), HDL (c), LDL (d), ox-LDL (e), non-HDL cholesterol (f), VLDL (g) ApoA1 (h), ApoB (i) and "Lp(a)" (j)

TABLE 6 Subgroup analysis assessing the effect of almond intake on blood lipids

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
TC	Baseline blood lipid	Hyper-lipidemic	6	**−0.51**	**−0.90, −0.13***	59.7	**.030**
		Normo-lipidemic	23	**−0.25**	**−0.35, −0.15***	04.7	.398
	Health status	Healthy	8	**−0.40**	**−0.54, −0.25***	04.2	.398
		Unhealthy	21	**−0.23**	**−0.38, −0.08***	37.5	**.043**
	Duration	≥10 weeks	16	**−0.30**	**−0.48, −0.13***	52.3	**.008**
		<10 weeks	13	**−0.28**	**−0.41, −0.15***	00.0	.564
	Almond dosage	≥50 g	15	**−0.43**	**−0.58, −0.27***	43.5	**.037**
		<50 g	14	−0.13	−0.27, 0.01	00.0	.899
	Age	Young adults	7	**−0.41**	**−0.58, −0.24***	16.5	.304
		Middle age adults	7	−0.32	−0.71, 0.07	74.5	**.001**
		Senior adults	15	**−0.19**	**−0.32, −0.06***	00.0	.960
	Control group	Nut free diet	13	**−0.41**	**−0.65, −0.18***	57.3	**.005**
		Regular diet	16	**−0.22**	**−0.33, −0.11***	00.0	.898
TG	Baseline blood lipid	Hyper-lipidemic	8	−0.34	−0.71, 0.04	64.9	**.006**
		Normo-lipidemic	22	**−0.20**	**−0.29, −0.10***	00.0	.940
	Health status	Healthy	8	**−0.26**	**−0.40, −0.12***	00.0	.496
		Unhealthy	22	**−0.20**	**−0.33, −0.07***	22.9	.163
	Duration	≥10 weeks	17	**−0.25**	**−0.40, −0.09***	38.3	.055
		<10 weeks	13	**−0.18**	**−0.31, −0.05***	00.0	.837
	Almond dosage	≥50 g	15	**−0.25**	**−0.42, −0.09**	50.9	**.012**
		<50 g	15	**−0.18**	**−0.32, −0.05***	00.0	.988
	Control group	Nut free diet	21	**−0.25**	**−0.38, −0.12***	28.7	.109
		Regular diet	9	**−0.16**	**−0.31, −0.01***	00.0	.780
	Age	Young adults	7	**−0.31**	**−0.47, −0.16***	00.0	.864
		Middle age adults	8	**−0.36**	**−0.66, −0.06***	57.2	**.022**
		Senior adults	15	−0.08	−0.21, 0.04	00.0	.963
HDL	Baseline blood lipid	Hyper-lipidemic	3	0.32	−0.36, 1.00	73.2	**.024**
		Normo-lipidemic	26	−0.02	−0.12, 0.08	18.3	**.203**
	Duration	≥10 weeks	16	0.03	−0.11, 0.16	22.2	.202
		<10 weeks	13	0.02	−0.19, 0.22	55.5	**.008**
	Almond dosage	≥50 g	15	**−0.14**	**−0.26, −0.03***	00.0	.933
		<50 g	14	**0.21**	**0.03, 0.39***	38.7	.069
	Control group	Nut free diet	16	−0.05	−0.20, 0.10	39.7	.051
		Regular diet	13	0.09	−0.08, 0.27	39.7	.069
	Age	Young adults	7	**−0.16**	**−0.32, −0.01***	00.0	.701
		Middle age adults	8	0.13	−0.17, 0.42	57.7	**.021**
		Senior adults	14	0.07	−0.08, 0.23	26.7	.168
LDL	Baseline blood lipid	Hyper-lipidemic	7	**−0.44**	**−0.70, −0.19***	16.6	.303
		Normo-lipidemic	23	**−0.26**	**−0.37, −0.16***	19.1	.204
	Health status	Healthy	8	**−0.42**	**−0.56, −0.28***	00.0	.685
		Unhealthy	22	**−0.21**	**−0.34, −0.09***	21.1	.184
	Duration	≥10 weeks	17	**−0.25**	**−0.37, −0.13***	00.0	.501
		<10 weeks	13	**−0.34**	**−0.51, −0.16***	40.0	.067
	Almond dosage	≥50 g	15	**−0.33**	**−0.45, −0.21***	13.3	.304
		<50 g	15	**−0.24**	**−0.40, −0.07***	28.2	.146
	Control group	Nut free diet	15	**−0.15**	**−0.30, 0.00***	21.7	.212
		Regular diet	15	**−0.40**	**−0.52, −0.29***	00.0	.690

TABLE 6 (Continued)

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
	Age	Young adults	7	**−0.40**	**−0.56, −0.25***	00.0	.628
		Middle age adults	8	0.13	−0.43, 0.17	58.1	**.019**
		Senior adults	15	**−0.29**	**−0.42, −0.16***	00.0	.710
Non-HDL	Health status	Healthy	8	**−0.41**	**−0.55, −0.27***	00.0	.596
		Unhealthy	6	−0.22	−0.46, 0.03	00.0	.755
	Duration	≥10 weeks	8	**−0.37**	**−0.54, −0.19***	00.0	.557
		<10 weeks	6	**−0.36**	**−0.53, −0.19***	00.0	.536
	Almond dosage	≥50 g	10	**−0.38**	**−0.51, −0.24***	00.0	.564
		<50 g	4	−0.29	−0.62, 0.04	00.0	.571
	Control group	Nut free diet	9	**−0.33**	**−0.49, 0.17***	00.0	.485
		Regular diet	5	**−0.41**	**−0.60, −0.22***	00.0	.730
	Age	Young adults	7	**−0.39**	**−0.54, −0.24***	00.0	.534
		Middle age adults	3	−0.18	−0.60, 0.24	08.1	.337
		Senior adults	4	**−0.36**	**−0.60, −0.12***	00.0	.640
Ox-LDL	Health status	Healthy	4	−0.10	−0.28, 0.08	00.0	.831
		Unhealthy	5	−0.21	−0.52, 0.09	21.0	.281
	Duration	≥10 weeks	4	−0.06	−0.27, 0.15	00.0	.979
		<10 weeks	5	−0.22	−0.47, 0.04	24.1	.261
	Age	Young adults	4	−0.10	−0.28, 0.08	00.0	.831
		Senior adults	5	−0.21	−0.52, 0.09	21.0	.281
VLDL	Baseline blood lipid	Hyper-lipidemic	3	−0.30	−0.70, 0.10	00.0	.780
		Normo-lipidemic	8	**−0.22**	**−0.38, −0.05***	00.0	.533
	Health status	Healthy	3	**−0.47**	**−0.73, −0.20***	00.0	.873
		Unhealthy	8	−0.11	−0.29, 0.08	00.0	.974
	Duration	≥10 weeks	9	**−0.21**	**−0.38, −0.04***	00.0	.774
		<10 weeks	2	−0.28	−0.75, 0.20	40.4	.195
	Almond dosage	≥50 g	3	**−0.47**	**−0.73, −0.20***	00.0	.873
		<50 g	8	−0.11	−0.29, 0.08	00.0	.974
	Control group	Nut free diet	7	**−0.18**	**−0.37, 0.00***	00.0	.731
		Regular diet	4	**−0.31**	**−0.58, −0.05***	00.0	.478
	Age	Young adults	3	**−0.47**	**−0.73, −0.20***	00.0	.873
		Middle age adults	2	−0.10	−0.58, 0.39	00.0	.558
		Senior adults	6	−0.11	−0.31, 0.09	00.0	.928
ApoA1	Baseline blood lipid	Hyper-lipidemic	4	−0.05	−0.34, 0.43	00.0	.847
		Normo-lipidemic	5	0.01	−0.23, 0.25	00.0	.826
	Duration	≥10 weeks	5	−0.00	−0.27, 0.27	00.0	.945
		<10 weeks	4	0.05	−0.26, 0.35	40.4	.676
	Almond dosage	≥50 g	5	−0.03	−0.28, 0.22	00.0	.973
		<50 g	4	0.12	−0.22, 0.46	00.0	.724
	Control group	Nut free diet	4	−0.01	−0.30, 0.28	00.0	.867
		Regular diet	5	0.05	−0.23, 0.33	00.0	.822
	Age	Middle age adults	3	0.09	−0.30, 0.49	00.0	.511
		Senior adults	6	−0.00	−0.24, 0.23	21.0	.975
ApoB	Baseline blood lipid	Hyper-lipidemic	3	**−0.48**	**−0.91, −0.04***	00.0	.610
		Normo-lipidemic	5	−0.04	−0.27, 0.20	00.0	.570

(Continues)

TABLE 6 (Continued)

Variable	Sub-grouped by		No. of arms	Effect size (SMD)	95% CI	I^2 (%)	*p* for heterogeneity
	Duration	≥10 weeks	4	−0.11	−0.49, 0.26	41.3	.164
		<10 weeks	4	0.17	−0.48, 0.13	00.0	.628
	Almond dosage	≥50 g	5	−0.09	−0.38, 0.20	21.1	.280
		<50 g	3	−0.25	−0.63, 0.12	00.0	.515
	Control group	Nut free diet	3	−0.05	−0.53, 0.42	55.5	.105
		Regular diet	5	−0.20	−0.48, 0.08	00.0	.742
	Age	Middle age adults	2	−0.18	−0.62, 0.27	00.0	.506
		Senior adults	6	−0.13	−0.41, 0.14	22.7	.264

Note: Bolded values represents the presented 95% CI.
Abbreviations: ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; CI, confidence interval; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; ox-LDL, oxidized LDL; SMD, Standardized mean difference; TC, total cholesterol; TG, triglyceride; VLDL, Very low-density lipoprotein.
*Statistically significant.

assess the effect of each study on the overall results, and changes were only observed in two situations. Different results, both showing a significant decrease, were obtained in the effects of almond intake on SBP and IL-6 levels when the reports of Abazarfard et al. (2014) and de Souza et al. (2019) were removed, respectively. In addition, due to various populations, dietary intake, almond amount, trial duration, and center settings, there was significant heterogeneity between the included studies that might have indirectly affected the results. These observations reinforce that the obtained results should always be carefully interpreted to safeguard the presented conclusions.

In conclusion, the current body of evidence supports the ingestion of almonds for their beneficial lipid-lowering and antihypertensive effects. Moreover, almond intake has potential promising effects on inflammatory markers, glycemic indices, and hepatic enzymes. Nevertheless, due to a lack of rigorous regulation, the need for the nutraceutical manufacturers to prove the efficacy, safety, and quality of the marketed products is less strongly enforced than in the pharmaceutical sectors. Therefore, many available products might be ineffective. However, the results of systematic reviews and meta-analyses are at the top of the hierarchy of clinical evidence (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016; Williamson et al., 2020). Additional trials with well-controlled conditions in terms of almond consumption, number of participants, duration of interventions, and studied outcomes are warranted to allow for more accurate evaluation of the effects of almond intake on the various cardiovascular risk factors.

AUTHOR CONTRIBUTIONS

Mojgan Morvaridzadeh and Javad Heshmati: designed the review; Shima Abdollahi and Ana Beatriz Pizarro: performed the electronic database search and data extraction; Omid Toupchian, Shima Abdollahi, and Joshua R. Zadro: conducted the statistical analysis, evaluated and reported the results; M. Dulce Estêvão, Mostafa Qorbani, Somaye Ziaie and Ahmed Abu-Zaid: wrote the manuscript's draft; and all authors: carefully assessed the final version of the article and approved it.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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