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REVIEW

WILEY

The effect of almond intake on glycemic control: A systematic review and dose–response meta-analysis of randomized controlled trials

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Abstract

Number trials have evaluated the effect of almond intake on glycemic control in adults; however, the results remain equivocal. Therefore, the present meta-analysis aims to examine the effectiveness of almond intake on glycemic parameters. Online databases including PubMed, Scopus, ISI web of science, Embase, and Cochrane Library were searched up to August 2021 for trials that examined the effect of almond intake on glycemic control parameters including fasting blood sugar (FBS), insulin, HOMA-IR, and HbA1C. Treatment effects were expressed as mean difference (MD) and the standard deviation (*SD*) of outcomes. To estimate the overall effect of almond intake, we used the random-effects model. In total, 24 studies with 31 arms were included in our analysis. The meta-analysis revealed that almond intake did not significantly change the concentrations of FBS, HbA1c, insulin levels, and HOMA-IR. In conclusion, there is currently no convincing evidence that almonds have a clear beneficial effect on glycemic control. Future studies are needed before any confirmed conclusion could be drowned.

KEYWORDS
almond, glycemic control, meta-analysis, nuts, systematic review

1 | INTRODUCTION

Controlling glycemic response is important to improve clinical outcomes and quality of life in patients with metabolic disorders including overweight (Gerich, 2005; Livesey, Taylor, Hulshof, & Howlett, 2008; Ramzan et al., 2019). Failure to achieve glycemic response goals is associated with serious consequences and substantial costs (Goel, Grover, Sharma, & Bae, 2018; Livesey et al., 2008).

Foods vary in their ability to provoke a glycemic response (Clar et al., 2017). Due to this, strategies to handle glycemic response through dietary factors are of great clinical importance and may contribute to reducing the various complications from metabolic disease (Bozzetto et al., 2016; Mahmoudian-Sani, Luther, Asadi-Samani, Saeedi-Boroujeni, & Gholamian, 2017; Ramzan et al., 2019). These factors are important, not only because they have been linked to the glycemic response and metabolic disease, but also because they can be modified (Bozzetto et al., 2016; Dehghan-Shahreza, Beladi-Mousavi, & Rafieian-Kopaei, 2016; Ramzan et al., 2019).

Among the vast quantity of effective food with beneficial health effects on cardiovascular risk factors and glycemic response (Cicero, Fogacci, & Colletti, 2017; Hadi, Pourmasoumi, Mohammadi, Symonds, & Miraghajani, 2018; Sahebkar et al., 2016; Tavafi, 2013; Williamson, Liu, & Izzo, 2020), nuts such as almonds have aroused curiosity among the scientific community (Gulati, Misra, & Pandey, 2017; Tindall, Johnston, Kris-Etherton, & Petersen, 2019). Almonds are a nutrient and non-nutrients dense food (Alasalvar & Bolling, 2015; Llorach et al., 2010), in which all have potential favorite effects on glycemic response. With these positive effects of almonds, there have been continuous arguments whether regular consumption of almonds, as a fatty food, may increase the body weight. Because obesity is a major public health problem and a risk factor for hyperglycemia and related factors (Kane et al., 2019; Kawasaki et al., 2018), several questions would be pondered about advising to consume almonds.

In this field, a previous systematic review and meta-analysis had assessed the effects of almonds intake on cardiovascular disease risk factors including FBS and HbA1c (Lee-Bravatti et al., 2019). Although, there was no significant change in FBS in the main analysis, it decreased by almond consumption in high doses. Other meta-analyses carried out which had examined the effects of nuts intake include almonds on glycemic control. There appears to be suggestive evidence of benefit of consumption of tree nuts on HOMA-IR and fasting insulin (Tindall et al., 2019). Due to different types of nutrients and antioxidants (M. Wien, Sabate, Ikle, Cole, & Kandeel, 2003), in mentioned studies, it is not possible to estimate the true effect of almonds on glycemic control. Previous studies showed that despite high calories content of almond; up to 56 g/d of almond consumption did not lead to weight gain according to observational and clinical studies (Fraser, Bennett, Jaceldo, & Sabaté, 2002; Rajaram & Sabaté, 2006; Salas-Salvadó et al., 2008). Almonds despite high fat content are with low-glycemic index and could alter the glycemic index of co-consumed foods (Jenkins et al., 2006; Josse, Kendall, Augustin, Ellis, & Jenkins, 2007). Effect of almond consumption on glycemic indices however were not consistent in previous studies (Casas-Agustench et al., 2011; Scott et al., 2003; Tapsell et al., 2009). Magnesium, fiber, unsaturated fatty acids, and polyphenols in almonds are potential underlying mechanism for improvement of glycemic indices (Paniagua et al., 2007; Tierney & Roche, 2007).

So, we have aimed to include all randomized and controlled clinical trials to summarize current findings on the effect of almonds intake on glycemic control in adult humans. Results from such investigations can produce the evidence with a greater clarity in the applicability of almonds in glycemic control and enable health professionals to make specific recommendations for incorporating almonds into the habitual diets in this context.

2 | METHODS

This systematic review and meta-analysis were carried out and reported in conformity to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009). The *P*opulation (aged >18 years old), *I*ntervention (almond intake), *C*omparison (matched control group), *O*utcome (glycaemic indices) (PICOS) model was used and included FBS, HbA1c, insulin and HOMA-IR measures that were conducted as randomized controlled trials (RCT).

2.1 | Search strategy

PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), ISI Web of Science (http://www.webofscience.com), and Cochrane library (http://www.cochranelibrary.com) databases were searched from time of inception until August 2021, using the following MeSH terms: (almond OR Prunus amygdalus OR P. amygdalus OR Prunus dulcis OR P.dulcis) AND (Intervention OR "Intervention Study" OR "Intervention Studies" OR "controlled trial" OR randomized OR randomized OR random OR randomly OR placebo OR "clinical trial" OR Trial OR "randomized controlled trial" OR "randomized clinical trial" OR RCT OR blinded OR "double blind" OR "double blinded" OR trial OR "clinical trial" OR trials OR "Pragmatic Clinical Trial" OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR parallel OR "parallel study" OR "parallel trial"). No language restriction was considered while searching the mentioned databases. The references of original articles and relevant reviews were also scrutinized for additional articles. All searched articles were exported into EndNote software (version X7, for Windows, Thomson Reuters, Philadelphia, PA) to merge retrieved citations, eliminate duplicated publications, and simplify the review process.

2.2 | Study selection

Upon completion of the searches, titles and abstracts of the identified articles were separately screened by two authors (O.A. and E.E.) to exclude articles that were obviously irrelevant. The full texts of the remaining articles were retrieved, and all relevant studies were identified in this manner. Inclusion criteria were: (a) being a randomized controlled trial (RCT) (either parallel or crossover design); (b) investigating the impact of almond on glycemic markers including fasting blood sugar (FBS), homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin, and glycated hemoglobin; and (c) having a suitable controlled design, that is, the only difference

between the control and treatment groups was almond. Exclusion criteria were as follows: studies that included children, adolescence, pregnant or lactating women, trails with follow-up less than 2 weeks; and articles without sufficient data for meta-analysis. If there was a duplication or overlap of the study group, the study that best met the inclusion criteria or had better quality was included. Any discrepancies were settled via a panel discussion.

2.3 | Data extraction

Data extraction was carried out independently on all studies by two authors (O.A. and E.E.), with disagreements managed by consensus. The following data were extracted: (a) study characteristics (first author's name, year of publication, location of the study, and study design); (b) participants' information (gender, mean age, mean body mass index [BMI], and health status); (c) intervention details (sample size, duration of follow up, form and dose of almond and control); and (d) mean and standard deviation (SD) of change in serum FBS, insulin, glycated hemoglobin, and HOMA-IR levels in each group of intervention and control. In case outcome data was missing, attempts were made to obtain it by contacting the authors via email (2 times).

2.4 | Quality assessment

Study quality was assessed using the Cochrane Collaboration's tool (Higgins et al., 2011). The following methodological domains were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. Each item was scored as a low, unclear, or high risk of bias. Moreover, each scope was further classified into three classes: low risk, high risk, and unclear risk of bias. According to the guidelines, the general quality of each study was considered as good (low risk for more than two cases), fair (low risk for two cases), or weak (low risk for less than two cases). Two authors (O.A. and E.E.) conducted the quality assessment, while any difference was resolved by consensus of the third reviewer (E.G.).

2.5 | Statistical analysis

The whole process of statistical analyses was carried out using the STATA software (version 11.0; Stata Corporation). All data were collected as means ± SD for each variable in similar unit to estimate the pooled effects. In this regard, information in FBS, and insulin were gathered or changed in mg/dl, and μU/ml, respectively. In studies that mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. In addition, SD for the net changes was assigned based on the Follmann method (Follmann, Elliott, Suh, & Cutler, 1992). In studies where the standard error (SE) was reported, SD was calculated as follows: SD = SE × sqrt (n), where n is the number of participants in each group. Weighted mean differences (WMDs) and 95% confidence intervals with forest plots were calculated for our outcome measures. To account for the potential heterogeneity in study designs we employed a random effects model. Heterogeneity between studies was examined using the I-squared (I^2) index. If the I^2 test exhibited >50%, it indicated that heterogeneity existed between the included trials. Subgroup analyses were done based on baseline serum FBS, trial duration, participant's age, almond dose, health status, obesity status, and quality assessment to explore the source of heterogeneity. Sensitivity analysis was also performed to evaluate the potential bias and robustness of the overall effect estimate by omitting one study at a time. Additional sensitivity analysis in studies with good quality was also performed. According to above-mentioned explanations studies with good quality included; then studies deleted one-by-one to show possible effect of each study. Begg's rank-correlation methods were run to assess the presence of publication bias. The non-linear potential effects of almond dosage (g/day) and treatment duration (weeks) were explored using fractional polynominal modeling (Mitchell, 2012). $p < .05$ was considered as statistically significant.

3 | RESULTS

3.1 | Study selection

We found 2,071 articles from PubMed-MEDLINE, Scopus, ISI web of science, and the Cochrane Library out of which 225 were duplicates and therefore removed. After screening based on title and abstract of the remaining articles, 1,800 publication were excluded. Thereafter, 46 articles were eligible for full-text evaluation and we excluded 22 clinical trials due to not having the desired data ($n = 19$) and non-randomization ($n = 3$) (Abbey, Noakes, Belling, & Nestel, 1994; Choudhury, Clark, & Griffiths, 2014; Jaceldo-Siegl, Sabaté, Batech, & Fraser, 2011). Finally, 24 RCTs consist of 31 arms were included in our meta-analysis (Abazarfard, Salehi, & Keshavarzi, 2014; C. E. Berryman, West, Fleming, Bordi, & Kris-Etherton, 2015; Bowen et al., 2019; Chen et al., 2017a; Coates et al., 2020; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza, Gomes, de Castro, & Mota, 2018; Dhillon, Tan, & Mattes, 2016; Dhillon et al., 2018; Dikariyanto et al., 2020, 2020; Hou et al., 2018; Jenkins et al., 2008; Jung, Chen, Blumberg, & Kwak, 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Madan et al., 2021; Richmond, Williams, Mann, Brown, & Chisholm, 2012; Sabaté, Haddad, Tanzman, Jambazian, & Rajaram, 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003) (Figure 1). Twenty three studies with 30 arms reported FBG (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Coates et al., 2020; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017;

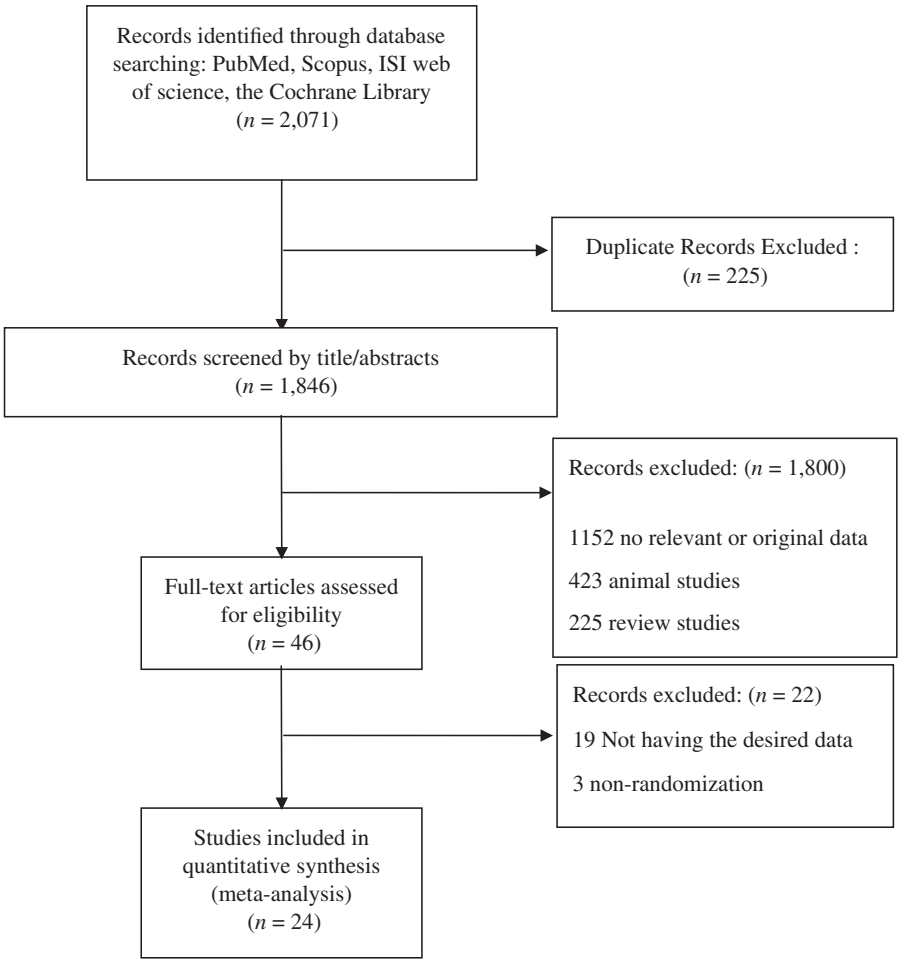

FIGURE 1 Flowchart of study selection for inclusion trials in the systematic review

Li et al., 2011; Madan et al., 2021; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003), nine studies reported HbA1C (Bowen et al., 2019; Chen et al., 2017a; Cohen & Johnston, 2011; de Souza et al., 2018; Hou et al., 2018; Kalgaonkar et al., 2011; Madan et al., 2021; Richmond et al., 2012; M. Wien et al., 2010), 16 studies with 22 arms reported insulin (Bowen et al., 2019; Chen et al., 2017a; Coates et al., 2020; Cohen & Johnston, 2011; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Jenkins et al., 2008; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Madan et al., 2021; Richmond et al., 2012; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003) and 11 trials with 12 effect sizes reported HOMA-IR (Chen et al., 2017a; Coates et al., 2020; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Jenkins et al., 2008; Kalgaonkar et al., 2011; Madan et al., 2021; M. Wien et al., 2010; M. Wien et al., 2003).

3.2 | Systematic review and study characteristics

Most of the studies were conducted in the USA (C. E. Berryman et al., 2015; Cohen & Johnston, 2011; Dhillon et al., 2016; Dhillon et al., 2018; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003) and other studies conducted in the Canada (Jenkins et al., 2008), UK (Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020), Taiwan (Chen et al., 2017a; Li et al., 2011), Spain (Damasceno et al., 2011), New Zealand (Richmond et al., 2012), Iran (Abazarfard et al., 2014), China (Hou et al., 2018), Brazil (de Souza et al., 2018), India (Madan et al., 2021), and Australia (Bowen et al., 2019; Coates et al., 2020). The design of the 13 studies was cross-over (C. E. Berryman et al., 2015; Chen et al., 2017a; Damasceno et al., 2011; Jenkins et al., 2008; Jung et al., 2018; Lee et al., 2017; Li et al., 2011; Richmond et al., 2012; Sabaté et al., 2003) and other was parallel (Abazarfard et al., 2014; Bowen et al., 2019; Coates et al., 2020; Cohen & Johnston, 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Kalgaonkar et al., 2011; Madan et al., 2021; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003). Twenty-seven trials were conducted on both sexes (C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Coates et al., 2020; Cohen & Johnston, 2011; Damasceno et al., 2011; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Lee et al., 2017; Li et al., 2011; Madan et al., 2021; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien

et al., 2003) and four trials on female (Abazarfard et al., 2014; de Souza et al., 2018; Kalgaonkar et al., 2011; Richmond et al., 2012). The eligible trials were published between 2003 and 2020 (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Coates et al., 2020; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Madan et al., 2021; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003). The duration of the interventions varied between 3 and 24 weeks. The age of the individuals ranged from 18 to 70 years. The dose of almond intake ranged from 20 to 76 g/day. These trials performed on healthy (Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Jenkins et al., 2008; Madan et al., 2021; Sabaté et al., 2003) overweight and obese (Abazarfard et al., 2014; Chen et al., 2017a; Coates et al., 2020; de Souza et al., 2018; Dhillon et al., 2016; Jenkins et al., 2008; Jung et al., 2018; Lee et al., 2017; M. Wien et al., 2003) individuals and patients with polycystic ovarian syndrome (Kalgaonkar et al., 2011), hypercholesterolemic (C. E. Berryman et al., 2015; Damasceno et al., 2011), pre-diabetes (Tan & Mattes, 2013; M. Wien et al., 2010), type 2 diabetes (Bowen et al., 2019; Chen et al., 2017a; Cohen & Johnston, 2011; Hou et al., 2018; Li et al., 2011; Richmond et al., 2012) and adults at above-average risk of cardiovascular disease (Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020). The BMI of the subjects ranged from 18 to 39 kg/m^2. The sample size ranged from 13 to 219 (Table 1).

3.3 | Quality assessment

All of the included studies were randomized, however, 10 studies mentioned method of randomization (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Dhillon et al., 2016; Lee et al., 2017; Richmond et al., 2012; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003). And 10 trials had low-risk of bias regarding allocation concealment (C. E. Berryman et al., 2015; Bowen et al., 2019; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Jung et al., 2018; Lee et al., 2017; Tan & Mattes, 2013; M. Wien et al., 2003) and nine studies had high-risk of bias (Abazarfard et al., 2014; Chen et al., 2017a; Damasceno et al., 2011; Hou et al., 2018; Jenkins et al., 2008; Kalgaonkar et al., 2011; Richmond et al., 2012; Sabaté et al., 2003; M. Wien et al., 2010) and other studies had unclear- risk of bias (Cohen & Johnston, 2011; Li et al., 2011). All of the eligible studies were not reported blinding of participants personnel (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003). Most of the studies had high risk of bias (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Hou et al., 2018; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003) in related with blinding of outcome assessors and other had unclear-risk of bias (Chen et al., 2017a; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Jenkins et al., 2008). All studies had low-risk of bias about incomplete outcome data and other sources of bias (Abazarfard et al., 2014; C. E. Berryman et al., 2015; Bowen et al., 2019; Chen et al., 2017a; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Kalgaonkar et al., 2011; Lee et al., 2017; Li et al., 2011; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010; M. Wien et al., 2003). Regarding to Selective outcome reporting only three trials had low-risk of bias (Chen et al., 2017a; Kalgaonkar et al., 2011; M. Wien et al., 2003) and other studies had high-risk of bias (Abazarfard et al., 2014; Claire E Berryman et al., 2015; Bowen et al., 2019; Cohen & Johnston, 2011; Damasceno et al., 2011; de Souza et al., 2018; Dhillon et al., 2016; Dhillon et al., 2018; Dikariyanto, Berry, et al., 2020; Dikariyanto, Smith, et al., 2020; Hou et al., 2018; Jenkins et al., 2008; Jung et al., 2018; Lee et al., 2017; Li et al., 2011; Richmond et al., 2012; Sabaté et al., 2003; Tan & Mattes, 2013; M. Wien et al., 2010). The quality and risk of bias of the eligible trials are reported in Table 2.

3.4 | Meta-analysis results

3.4.1 | The effect of almond intake on FBS level

Thirty arms, with a total of 1,896 individuals (cases = 1,045, control = 851), described FBS as a result measure. The pooled outcomes from the random-effects model specified that almond intervention did not alter FBS level significantly (MD: 0.20 mg/dl, 95% CI: [−0.90 to 1.30, $p = .720$]), with significant heterogeneity across the studies ($I^2 = 83.6\%$, $p < .001$) (Figure 2). However, subgroup analysis demonstrated that almond intake has significant effects on increasing FBS in participants older than 50 years, unhealthy and obese subjects, and studies with quality of fair (Table 3).

3.4.2 | The effect of almond intake on A1C

Moreover, nine effect sizes, including a total of 585 individuals (cases = 291, control = 294), presented data for A1C as an outcome evaluation. The combined results from the random-effects model

TABLE 1 Characteristic of included studies in meta-analysis

Author	Country	Study design	Participant	Sex	Trial duration (week)	Means age		Means BMI		Intervention			Number of participants		Main outcome
						IG	CG	IG	CG	Treatment group	Almond dose (g)	Control group	IG	CG	
Sabaté et al. (2003)	USA	Randomized, crossover	Healthy subjects	M/F	4	Group 1: 41 Group 2: 41	41	Group 1: < 30 Group 2: < 30	< 30	Almonds	Group 1: 20% Group 2: 10%	Step I diet	Group 1: 25 Group 2: 25	25	FBG
M.A. Wien et al. (2003)	USA	Randomized, parallel	Overweight and obese adults	M/F	24	53	57	39	37	Unsalted almonds	84	Self-selected complex carbohydrates (CHO-LCD)	32	33	FBG, insulin, HOMA-IR
Jenkins et al. (2008)	Canada	Randomized, crossover	Healthy hyperlipidemic men and postmenopausal women	M/F	4.28	64	64	25.7	25.7	Whole almonds	Group 1: 73 ± 3 Group 2: 36.5 ± 3	Whole-wheat muffins	27	27	FBG, insulin, HOMA-IR
Li et al. (2011)	Taiwan	Randomized, crossover	Patients with type 2 diabetes mellitus	M/F	4	48	48	26	26	Almond	60	Control National Cholesterol Education Program step II diet	20	20	FBG, insulin, HOMA-IR
M. Wien et al. (2010)	USA	Randomized, parallel	Individuals with prediabetes	M/F	16	53	54	29.3	29	Raw or dry roasted almonds	56	Nut-free	32	33	FBG, HbA1C, insulin, HOMA-IR
Cohen and Johnston (2011)	USA	Randomized, parallel	Individuals with well-controlled type 2 diabetes mellitus	M/F	12	66	66	32.6	36.7	Almond	29	Cheese	6	7	FBG, HbA1C, insulin
Damasceno et al. (2011)	Spain	Randomized, crossover	Hypercholesterolemic patients	M/F	4	56	56	25.7	25.7	Almonds	50–75	Virgin olive oil	18	18	FBG
Kalgaonkar et al. (2011)	USA	Randomized, parallel	PCOS patients	F	6	36.2	31.2	35.1	35.2	Almonds	46	Walnuts	14	17	FBG, HbA1C, insulin, HOMA-IR
Richmond et al. (2012)	New Zealand	Randomized, crossover	Postmenopausal women with type 2 diabetes	F	3	62	62	29.16	29.24	Almond	30	Sunfower kernels	22	22	FBG, HbA1C, insulin
Tan and Mattes (2013)	USA	Randomized, parallel	Participants with increased risk for type 2 diabetes	M/F	4	18–60	18–60	18.5–24.9	18.5–24.9	Almonds	43	Snack or no almonds	Group 1: 28 Group 2: 28 Group 3: 28 Group 4: 26	27	FBG, insulin
Abazarfard et al. (2014)	Iran	Randomized, parallel	Overweight and obese females	F	12.85	42.36	42.94	29.91	29.37	Raw almond	50	Balanced hypocaloric nut-free diet (NFD)	50	50	FBG
C. E. Berryman et al. (2015)	USA	Randomized, crossover	Adults with elevated LDL-cholesterol	M/F	6	49.9	49.9	26.2	26.2	Almond	43	An identical diet with an isocaloric muffin substitution	48	48	FBG
Dhillon et al. (2016)	USA	Randomized, parallel	Overweight or obese adults	M/F	12	33.6	34.9	30.3	30.6	Dry roasted almonds	15%energy	Nut-free diet (NFD)	23	27	FBG, insulin

TABLE 1 (Continued)

Author	Country	Study design	Participant	Sex	Trial duration (week)	Means age		Means BMI		Intervention			Number of participants		Main outcome
						IG	CG	IG	CG	Treatment group	Almond dose (g)	Control group	IG	CG	
Lee et al. (2017)	USA	Randomized, crossover	Overweight and obese individuals	M/F	4	Group 1: 46.3 Group 2: 46.3 Group 3: 46.3	46.3	Group 1: 29.6 Group 2: 29.6 Group 3: 29.6	29.6	Raw almonds	Group 1: 42.5 Group 2: 42.5 Group 3: 42.5	Group 1: Cocoa and dark chocolate Group 2: Chocolate diet Group 3: No treatment foods (average American diet)	Group 1: 31 Group 2: 31 Group 3:31	31	FBG, insulin
Jung et al. (2018)	USA	Randomized, crossover	Overweight/obese participants	M/F	4	45–69	45–69	23–29.9	23–29.9	Almond	56	Isocaloric cookies	84	84	FBG
Chen et al. (2017a)	Taiwan	Randomized, crossover	Patients with better controlled type 2 diabetes	M/F	12	54.9	54.9	25.6	25.3	Almonds	60	NCEP step II diet	33	33	FBG, HbA1C, insulin, HOMA-IR
Hou et al. (2018)	China	Randomized, single blind, parallel	Patients with type 2 diabetes mellitus	M/F	12.85	70.86	68	24.08	22.84	Almonds	55 for M and 45 F	Peanuts	14	11	FBG, HbA1C
de Souza et al. (2018)	Brazil	Randomized, parallel	Overweight and obese women	F	8			32.54	33.34	Roasted baru almonds	20	Baru almond-free diet (BAFD)	24	22	FBG, HbA1C
Dhillon et al. (2018)	USA	Randomized, parallel	Young adults	M/F	8	18–19	18–19	25.6	25.3	Almond	56.7	Cracker	38	35	HOMA-IR
Bowen et al. (2019)	Australia	Randomized, parallel	Elevated risk of type 2 diabetes (T2D) or T2D	M/F	8	60.7	60.7	33.8	33.8	Almonds	56	Biscuit snack	39	37	FBG, HbA1C, insulin,
Dikariyanto, Berry, et al. (2020); Dikariyanto, Smith, et al. (2020)	UK	Randomized, parallel	Adults at moderate risk of CVD	M/F	6	30–70	30–70			Whole roasted almonds	20% TEE	Sweet and savoury mini-muffins	53	49	FBG, insulin, HOMA-IR
Coates et al. (2020)	Australia	Randomized, parallel	Older overweight adults	M/F	12	64	65	30.3	30.5	Almond-enriched diet	15% TEE	Isocaloric nut-free diet	63	65	FBG, insulin, HOMA-IR
Dikariyanto, Berry, et al. (2020); Dikariyanto, Smith, et al. (2020)	UK	Randomized, parallel	Adults at above-average risk of CVD	M/F	6	56.3	56	27.3	26.7	Whole roasted almonds	20% TEE	Mini-muffins	56	51	FBG, insulin, HOMA-IR
Madan et al. (2021)	India	Randomized, parallel	Adolescents and young adults	M/F	12.85	16–25	16–25	23.7	22.4	Almonds	56	Iso-caloric cereal-pulse based snack	107	112	FBG, HbA1C, insulin, HOMA-IR

Abbreviations: CG, control group; CO, controlled; DB, double-blinded; F, Female; HbA1C, hemoglobin A1C; HOMA-IR, homeostatic model assessment for insulin resistance; IG, intervention group; M, Male; NR, not reported; NR, not reported; PC, placebo-controlled; RA, randomized; SB, single-blinded.

TABLE 2 Quality assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	General quality
Sabaté et al. (2003)	U	H	H	H	L	H	L	Fair
M. Wien et al. (2003)	L	L	H	H	L	H	L	Good
Jenkins et al. (2008)	U	H	H	U	L	H	L	Fair
Li et al. (2011)	U	U	H	H	L	H	L	Fair
M. Wien et al. (2010)	L	H	H	H	L	L	L	Good
Cohen and Johnston (2011)	U	U	H	U	L	H	L	Fair
Damasceno et al. (2011)	U	H	H	H	L	H	L	Fair
Kalgaonkar et al. (2011)	U	H	H	H	L	L	L	Good
Richmond et al. (2012)	L	H	H	H	L	H	L	Good
Tan and Mattes (2013)	L	L	H	U	L	H	L	Good
Abazarfard et al. (2014)	L	H	H	H	L	H	L	Good
C. E. Berryman et al. (2015)	L	L	H	H	L	H	L	Good
Dhillon et al. (2016)	L	L	H	H	L	H	L	Good
Lee et al. (2017)	L	L	H	U	L	H	L	Good
Jung et al. (2018)	U	L	H	H	L	H	L	Good
Chen et al. (2017a)	L	H	H	U	L	L	L	Good
Hou et al. (2018)	U	H	H	H	L	H	L	Fair
de Souza et al. (2018)	U	L	H	H	L	H	L	Good
Dhillon et al. (2018)	U	L	H	H	L	H	L	Good
Bowen et al. (2019)	L	L	H	H	L	H	L	Good
Dikariyanto, Berry, et al. (2020); Dikariyanto, Smith, et al. (2020)	U	L	H	U	L	H	L	Good
Coates et al. (2020)	L	L	H	H	L	H	L	Good
Dikariyanto, Berry, et al. (2020); Dikariyanto, Smith, et al. (2020)	L	L	H	H	L	H	L	Good
Madan et al. (2021)	L	L	H	H	L	H	L	Good

Abbreviations: L, low-risk of bias; U, unclear-risk of bias; H, high-risk of bias.

reported that almond intake had not significant effect on A1C (MD: 0.02%, 95% CI: (−0.15 to 0.20%, $p = .758$), with a significant heterogeneity across the studies ($I^2 = 51.3\%$, $p = .037$) (Figure 3). There were no significant differences for the subgroup analysis in HbA1C except in participants with normal weight (Table 3).

3.4.3 | The effect of almond intake on insulin level

Twenty-two intervention arms, with a total of 1,349 individuals (cases = 757, control = 592), described insulin level as a result measure. The combined outcomes from the random-effects model demonstrated that almond intake had not significant effect on insulin level (MD: −0.06 μU/ml, 95% CI: −0.53 to 0.40, $p = .787$), with significant heterogeneity across the studies ($I^2 = 90.2\%$, $p < .001$) (Figure 4). Also, subgroup analysis showed that almond intake had no significant effect on decreases insulin level (Table 3).

3.4.4 | The effect of almond intake on HOMA-IR

Analysis of the 12 intervention arms, with a total of 978 individuals (cases = 502, control = 476), demonstrated that almond intake did not show any significant effect on HOMA-IR (MD: −0.01, 95% CI: −0.16 to 0.14, $p = .900$), with significant heterogeneity across the studies ($I^2 = 97.2\%$, $p < .001$) (Figure 5). Subgroup analysis showed that almond intake significantly improved HOMA-IR in shorter duration, low dose of almond, healthy subjects, and participants younger

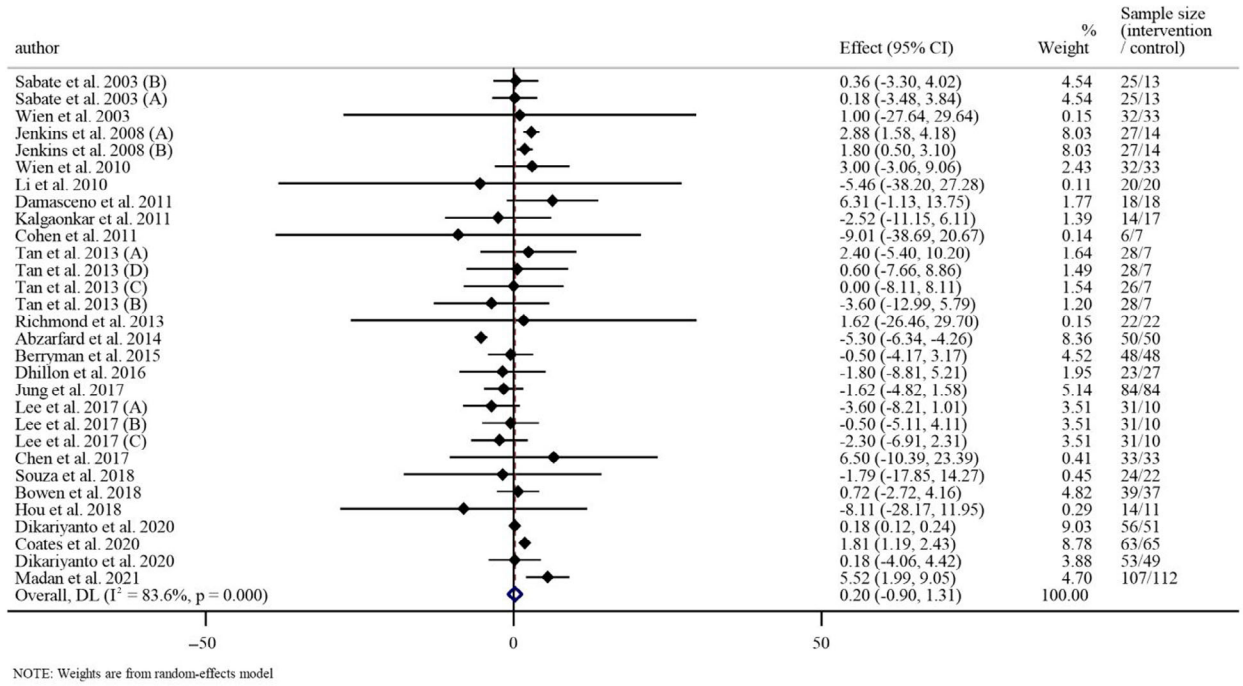

FIGURE 2 Forest plot of randomized controlled trials investigating the effects of almond on fasting blood glucose [Colour figure can be viewed at wileyonlinelibrary.com]

than 50 years. However, as heterogeneity in this variable is under 50%, subgroup analysis must be interpreted with caution.

3.4.5 | Hartung-Knapp adjustment

Due to small number of studies additional analysis based on Hartung-Knapp adjustment method also has been reported (Table 4).

3.5 | Publication bias

The evaluation of the publication bias by Egger's regression test (number of studies less than 10) or Begg's test (number of studies more than 10) and visual examination of the funnel plots did not detect any publication bias for the effect of almond intake on FBS level (Begg's test: $p = .422$), HOMA-IR (Begg's regression test: $p = .244$) and A1C (Egger's regression test: $p = .050$), However, there was a significant publication bias for insulin level (Begg's test: $p = .016$). (Figure 6–9).

3.6 | Trim and fill analysis

Due to evidence of publication bias for insulin level, trim and fill analysis was performed. The trim and fill sensitivity method were estimated from 1 theorized negative unpublished studies. The corrected effect size did not change (MD: -0.09, 95% CI: −0.56 to 0.37) and was statistically non-significant ($p = .685$).

3.7 | Sensitivity analysis

To explore the impact of each single effect size on the overall effect size, we excluded each study from the analysis, step by step. We found no significant effect of any individual study on the overall effect sizes of HOMA-IR level, A1C, and insulin level. However, sensitivity analysis for FBS showed that the overall estimates were influenced by elimination of study conducted by Abzarfard et al. (Abazarfard et al., 2014) (MD: 0.91 mg/dl, 95% CI: 0.07 to 1.76) (weight = 8.36%).

Also, we performed a sensitivity analysis including only the high quality RCTs (those classified as good quality studies). The results of sensitivity analysis for FBS A1c, insulin, and HOMA-IR did not affect by removing each study.

Non-linear dose–responses between dose of almond consumption on glycemic indices components:

Dose–response analysis showed that almond consumption did not change any of measured outcomes in a dose–response fashion. Following are the obtained data in this regard; FBS: (r = −0.052, *p*-nonlinearity = .446) in non-linear fashion. HbA1C (r = −8.02, *p*-nonlinearity = .112), HOMA-IR (r = −0.604, *p*-nonlinearity = .407) and insulin (r = −0.086, *p*-nonlinearity = .221) (Figures S1–S4).

Linear dose-responses between dose of almond consumption on glycemic indices components:

Dose–response analysis demonstrated that almond intake did not alter any of measured outcomes in a dose–response fashion. Meta-regression analysis did indicate a linear relationship between dose absolute changes in FBS (Coef. = 1.25, *p*-linear = .148), A1C (Coef. = 7.46, *p*-linear = .751), insulin (Coef. = −1.36, *p*-linear = .189) and HOMA-IR (Coef. = −3.47, *p*-linear = .148). (Figures S5–S8).

TABLE 3 Subgroup analyses of almond intake on glycemic indices

	NO	WMD (95%CI)	*p*-value	*p* heterogeneity	I^2	Heterogeneity between sub-groups
Subgroup analyses of almond intake on FBS.						
Overall effect	30	0.20 (−0.90, 1.30)	.720	<.001	83.6%	
Baseline serum FBS						
<100 mg/dl	18	0.73 (−0.31, 1.78)	.170	.001	57.7%	0.406
≥100 mg/dl	11	−0.44 (−4.66, 3.78)	.838	<.001	92.6%	
Trial duration (week)						
<6	15	0.72 (−0.51, 1.96)	.251	.124	30.7%	0.001
≥6	15	0.03 (−1.64, 1.70)	.972	<.001	90.4%	
Participant's age						
<50	13	−0.76 (−2.98, 1.46)	.501	<.001	90.0%	<0.001
≥50	10	1.96 (1.45, 2.47)	**<.001**	.777	0.0%	
Almond dose (g)						
<45	13	0.78 (−0.24, 1.81)	.134	.624	0.0%	0.001
≥45	15	0.54 (−2.36, 3.45)	.715	<.001	88.4%	
Health status						
Heathy	15	−0.06 (−2.08, 1.95)	.950	<.001	91.7%	0.187
Unhealthy	15	0.18 (0.12, 0.23)	**<.001**	.947	0.0%	
Obesity status (based on baseline BMI) (kg/m^2)						
Normal (18.5–24.9)	6	2.36 (−0.85, 5.58)	.150	.316	15.3%	<0.001
Over weight (25–29.9)	16	−0.17 (−1.80, 1.46)	.839	<.001	89.2%	
Obese (>30)	7	1.71 (1.10, 2.32)	**<.001**	.810	0.0%	
Quality assessment						
Fair	8	2.13 (1.27, 2.99)	**<.001**	.486	0.0%	<0.001
Good	22	−0.35 (−1.71, 1.00)	.606	<.001	86.0%	
Subgroup analyses of almond intake on hemoglobin A1C.						
Overall effect	9	0.02 (−0.15, 0.20)	.758	51.3%	0.037	
Baseline A1C						
<6.5%	5	0.08 (−0.15, 0.32)	.498	.004	73.8%	0.471
≥6.5%	4	−0.14 (−0.47, 0.17)	.379	.886	0.0%	
Trial duration (week)						
<6	1	0.05 (−0.69, 0.79)	.895	-	-	0.831
≥6	8	0.02 (−0.16, 0.21)	.787	.022	57.2%	
Participant's age						
<50	3	−0.08 (−0.21, 0.04)	.209	.315	13.4%	0.008
≥50	5	0.10 (−0.18, 0.39)	.489	.127	44.3%	
Almond dose (g)						
<45	3	−0.16 (−0.60, 0.26)	.444	.749	0.0%	0.522
≥45	6	0.05 (−0.15, 0.27)	.593	.009	67.6%	
Health status						
Heathy	2	−0.13 (−0.24, −0.01)	.023	.899	0.0%	0.005
Unhealthy	7	0.09 (−0.08, 0.28)	.297	.213	28.3%	
Obesity status (based on baseline BMI) (kg/m^2)						
Normal (18.5–24.9)	2	−0.13 (−0.24, −0.01)	**.022**	.831	0.0%	0.004
Over weight (25–29.9)	3	0.18 (−0.16, 0.53)	.289	.166	44.3%	
Obese (>30)	4	0.02 (−0.17, 0.21)	.841	.652	0.0%	

TABLE 3 (Continued)

Subgroup analyses of almond intake on hemoglobin A1C.						
Quality assessment						
Fair	2	−0.30 (−0.84, 0.23)	.268	.922	0.0%	0.313
Good	7	0.05 (−0.13, 0.25)	.558	.017	61.0%	
Subgroup analyses of almond intake on insulin.						
Overall effect	22	−0.06 (−0.53, 0.40)	.787	90.2%	<0.001	
Baseline insulin						
<25 μIU/ml	19	−0.10 (−0.57, 0.37)	.679	91.4%	<0.001	0.171
≥25 μIU/ml	1	−10.00 (−23.84, 3.84)	.157	-	-	
Trial duration (week)						
<6	11	0.10 (−0.07, 0.28)	.239	.820	0.0%	<0.001
≥6	11	−0.49 (−1.38, 0.40)	.280	<.001	94.5%	
Participant's age						
<50	9	−0.14 (−0.59, 0.29)	.511	.001	68.1%	<0.001
≥50	8	0.14 (−0.35, 0.63)	.573	<.001	73.1%	
Almond dose (g)						
<45	10	0.14 (−0.06, 0.36)	.173	.630	0.0%	0.284
≥45	10	−0.74 (−1.96, 0.47)	.230	.045	47.8%	
Health status						
Heathy	10	0.19 (−0.06, 0.45)	.137	.011	58.0%	<0.001
Unhealthy	12	−0.81 (−2.03, 0.40)	.190	.114	34.5%	
Obesity status (based on baseline BMI) (kg/m^2)						
Normal (18.5–24.9)	5	1.79 (−0.08, 3.68)	.061	.746	0.0%	<0.001
Over weight (25–29.9)	10	−0.12 (−0.54, 0.29)	.550	<.001	85.6%	
Obese (>30)	6	−1.22 (−3.55, 1.11)	.305	.121	42.7%	
Quality assessment						
Fair	18	−0.08 (−0.67, 0.50)	.781	<.001	91.2%	<0.001
Good	4	0.12 (−0.22, 0.47)	.487	.234	29.7%	
Subgroup analyses of almond intake on HOMA-IR.						
Overall effect	12	−0.01 (−0.16, 0.14)	.900	<.001	97.2%	
Trial duration (week)						
<6	3	0.07 (0.00, 0.15)	**.042**	.393	0.0%	<0.001
≥6	9	−0.05 (−0.25, 0.13)	.560	<.001	97.8%	
Participant's age						
<50	6	−0.16 (−0.17, −0.14)	**<.001**	.479	0.0%	<0.001
≥50	5	0.06 (−0.02, 0.15)	.139	.036	61.1%	
Almond dose (g)						
<45	1	0.12 (0.01, 0.22)	**.028**	-	-	0.199
≥45	9	0.03 (−0.11, 0.18)	.661	.145	34.1%	
Health status						
Heathy	7	0.08 (0.06, 0.10)	**<.001**	.428	0.0%	<0.001
Unhealthy	5	−0.29 (−0.71, 0.11)	.158	.243	26.8%	
Obesity status (based on baseline BMI) (kg/m^2)						
Normal (18.5–24.9)	1	0.80 (−0.27, 1.87)	.145	-	-	
Over weight (25–29.9)	7	−0.03 (−0.22, 0.14)	.673	<.001	86.8%	<0.001
Obese (>30)	3	0.05 (−0.40, 0.50)	.827	.342	6.8%	

(Continues)

TABLE 3 (Continued)

Subgroup analyses of almond intake on HOMA-IR.						
Quality assessment						
Fair	9	−0.05 (−0.25, 0.13)	.560	<.001	97.8%	<0.001
Good	3	0.07 (0.00, 0.15)	.042	.393	0.0%	

Abbreviations: BMI, body mass index; CI, confidence interval; FBS, fasting blood sugar; WMD, weighted mean differences.
Bold indicate significant values ($p > .05$).

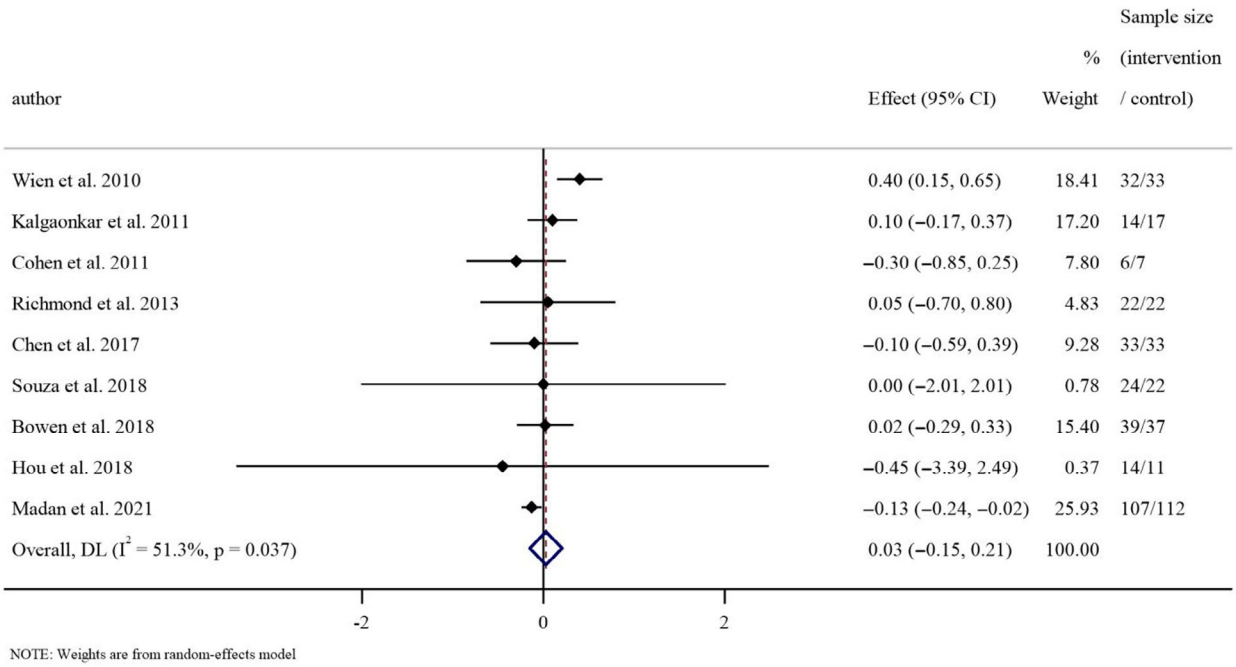

FIGURE 3 Forest plot of randomized controlled trials investigating the effects of almond on hemoglobin A1C [Colour figure can be viewed at wileyonlinelibrary.com]

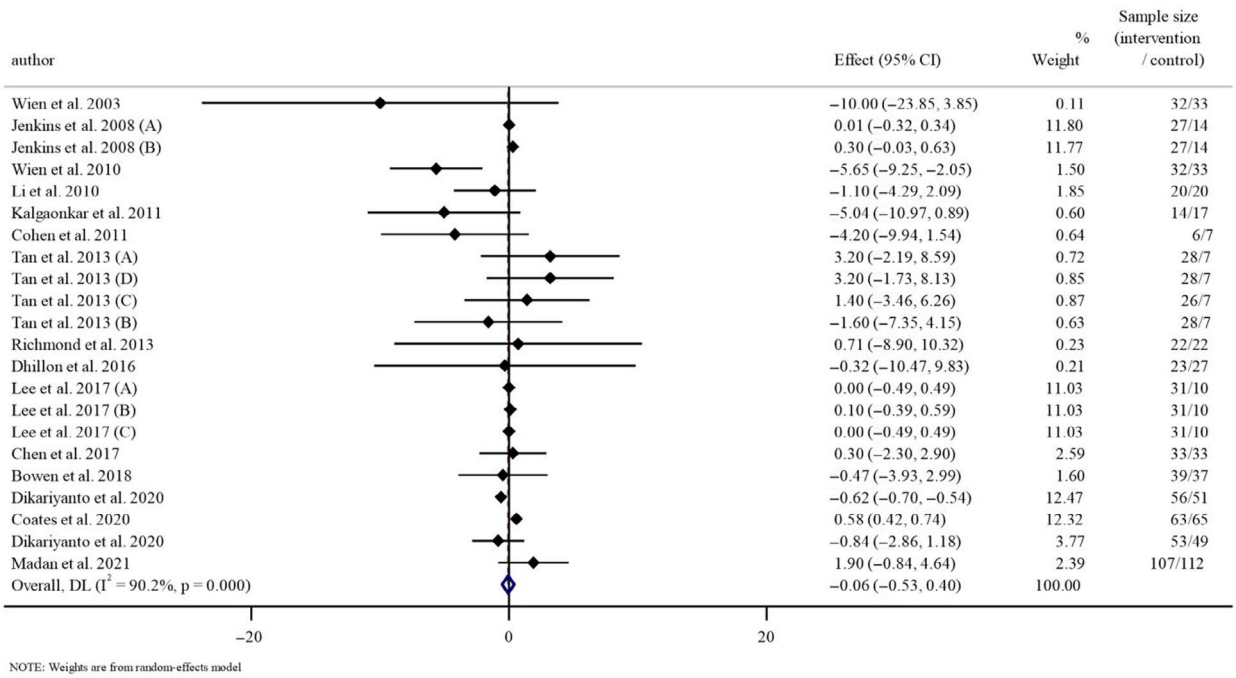

FIGURE 4 Forest plot of randomized controlled trials investigating the effects of almond on insulin level [Colour figure can be viewed at wileyonlinelibrary.com]

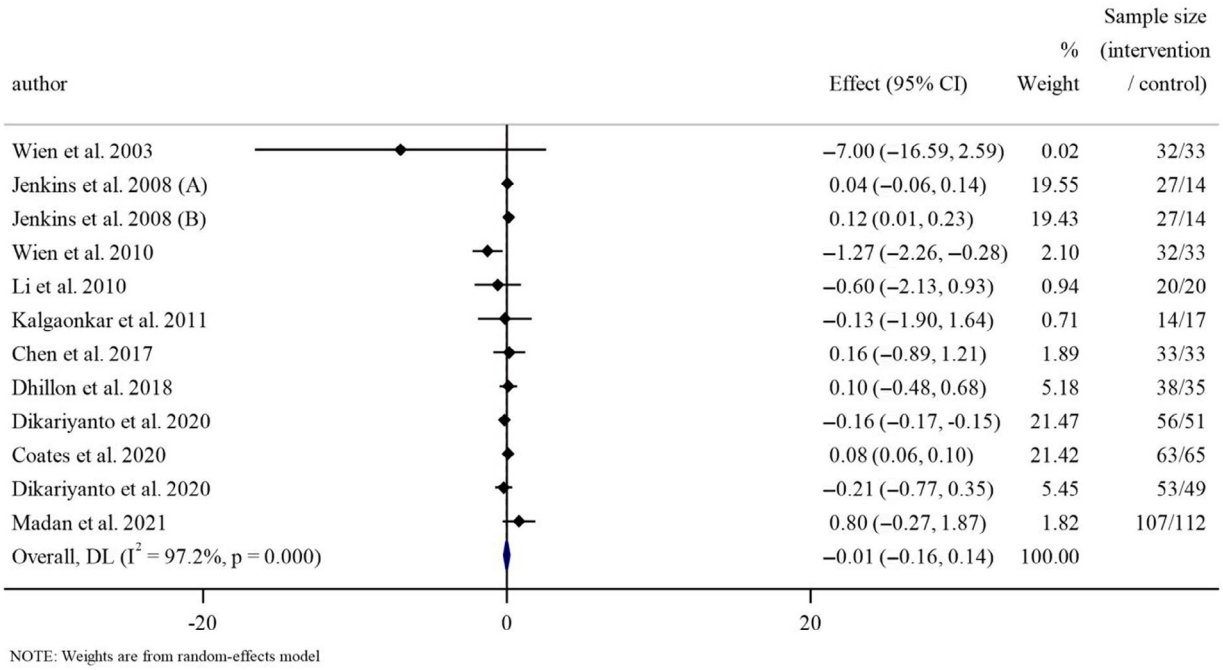

FIGURE 5 Forest plot of randomized controlled trials investigating the effects of almond on homeostatic model assessment for insulin resistance [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Random-effects model restricted maximum likelihood (REML) method and standard error (SE) Knapp-Hartung adjustment

			Confidence interval	
Estimate	**Standard error**	***p* value**	**Lower**	**Upper**
FBS				
−0.288	0.577	0.597	−1.39	0.817
HbA1c				
−0.288	0.537	0.597	−1.39	0.81
Insulin				
−0.288	0.537	0.597	−1.39	0.817
HOMA-IR				
−0.288	0.537	0.597	−1.39	0.81

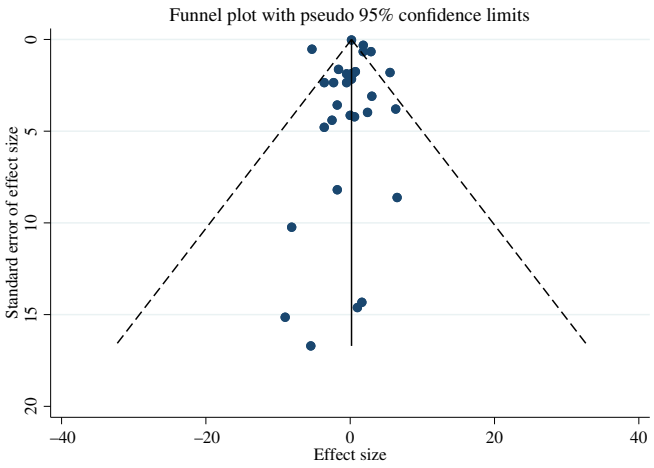

FIGURE 6 Funnel plot of studies evaluate FBS [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Previous studies investigated the effect of different nut consumption on several cardiovascular risk factors and also glycemic control; but those studies evaluated whole nuts and not specifically on definite nuts (Mejia et al., 2014; Ntzouvani, Antonopoulou, & Nomikos, 2019; Viguiliouk et al., 2014). As described, recent meta-analyses examining tree nuts, including almonds on glycemic control in adults. There appears to be suggestive evidence of benefit of consumption of tree nuts on HOMA-IR and fasting insulin (Tindall et al., 2019). There was no significant effect of nut consumption on fasting blood glucose or HbA1C (Tindall et al., 2019). As, nuts contain different types of nutrients and antioxidants (M. Wien et al., 2003), in mentioned studies, it is not possible to estimate the true effect of almonds on glycemic control. Another meta-analysis carried out which had assessed the effects of almonds intake on cardiovascular disease risk factors including FBS and HbA1C (Lee-Bravatti et al., 2019). Although, there was no significant change in FBS in the main analysis, it decreased with almond consumption in high doses. Qualitative review of 2 trial showed neither study found a difference in HbA1C between groups (Lee-Bravatti et al., 2019). In this study other researches as well, other glycemic indices were not considered.

We undertook this meta-analysis to examine evidence on the effects of almonds on glycemic control from randomized controlled trials

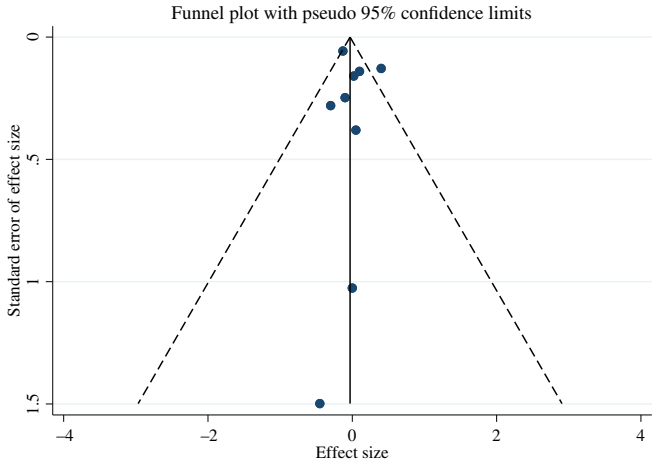

FIGURE 7 Funnel plot of studies evaluate hemoglobin A1C [Colour figure can be viewed at wileyonlinelibrary.com]

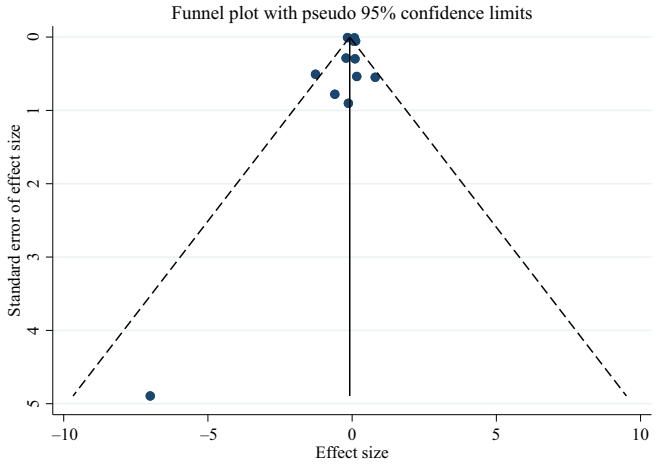

FIGURE 9 Funnel plot of studies evaluate homeostatic model assessment for insulin resistance [Colour figure can be viewed at wileyonlinelibrary.com]

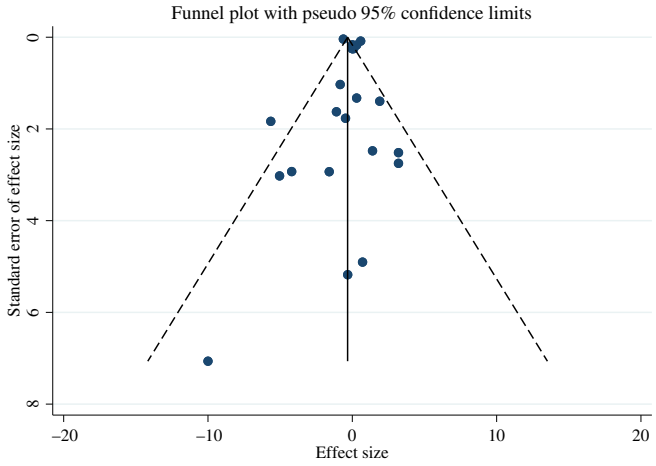

FIGURE 8 Funnel plot of studies evaluate insulin [Colour figure can be viewed at wileyonlinelibrary.com]

to produce the evidence with a greater clarity in the applicability of almonds in the glycemic control. As we know recent trends have grown increasingly for using herbal foods (Williamson et al., 2020). Such results enable health professionals to make specific recommendations for incorporating almonds into the habitual diets in this context.

Our meta-analysis indicated that almonds did not alter FBS level while, subgroup analysis reached a significant reduction in patients who were younger than 50. Other significances could not be reported due to statistical points (between-group significancy). Similarly, a non-significant effect was observed in insulin level. Due to the low percentage of heterogeneity, it was expectable that subgroups were not significant. For HOMA-IR no effect was seen. Subgroup analysis based on health and BMI status has been performed; results showed that there were no significant differences between healthy and unhealthy subjects and different status of BMI in any of variables; Due to number of studies this finding must be interpreted with caution albeit the exact mechanism in this classification needs to be proved.

Indeed, once β-cell function decreases, glycemic control is no longer able to take place, and HbA1C rise (Hitt, Velasquez-Mieyer, Neira, & Cowan, 2016). So, *HbA1C* level provides a reliable measure of chronic hyperglycemia and the inability of the β-cells to compensate poor glycemic control; although in present study any effect was not seen. Some studies have been reported to increase HbA1C test results by iron deficiency and iron deficiency anemia (Cavagnolli, Pimentel, Freitas, Gross, & Camargo, 2015; Hitt et al., 2016). Other factors, such as structural hemoglobinopathies, severe hypertriglyceridemia and hyperbilirubinemia, medications such as salicylates, and opioids, and ingestion of vitamin C can either falsely raise test (Herman, 2009; Radin, 2014). Previous meta-analyses in nuts showed that nut consumption decreased FBS; other meta-analysis also evaluated the effect of different nuts in patients with diabetes; consumption of 56 g/d of nuts significantly lowered HbA1c and FBS; but no significant effects were observed for insulin and HOMA-IR. Other study checked intake of different effect of nuts and seeds in adults with prediabetes; intake of 60 g/day almonds for 4 months improved FBS and insulin, insulin resistance in these patients at risk of diabetes.

Insulin levels demonstrated a significant reduction when almonds were given for a long period of time.

It should be noted that factors affecting glycemic control often manifest differently among racial and ethnic groups, and can have individual variations across a person lifespan (Harris, Eastman, Cowie, Flegal, & Eberhardt, 1999). Differences in the different dietary compliance and calorie intake (An & Yoon, 2019), gut microbiom (Sreng et al., 2019), life style factors and medications (Chrvala, Sherr, & Lipman, 2016; Lipska, Krumholz, Soones, & Lee, 2016; Pai et al., 2016), glycemic index and rate of intestinal digestion and absorption of carbohydrate (Clar et al., 2017) and diversified used approaches for glycemic measurements (Herman, 2009) may contribute to the different clinical response. Moreover, different timing of almonds intake (Liu et al., 2017), mastication and bioavailability factors (C. E. Berryman, Preston, Karmally, Deckelbaum, & Kris-Etherton, 2011), the discrepancy in the context of almonds varieties

(Askin, Balta, Tekintas, Kazankaya, & Balta, 2007), geographical and botanical almonds' origin (Xie, Roto, & Bolling, 2012), harvest time and storage conditions (Kazantzis, Nanos, & Stavroulakis, 2003) and processing (Gebauer, Novotny, Bornhorst, & Baer, 2016) which greatly influence the biological activity of almonds, could affect the results. Also, the diversified used methods for anthropometric measurements and measurement error may contribute to the different clinical response (Sebo, Haller, Pechere-Bertschi, Bovier, & Herrmann, 2015). These factors might lead to the conclusion that in our study favorable effects on glycemic control provided by almonds were not seen.

Almond contains several active compounds, although processing effect could affect some of them (Additional information outlined in Table 5 [Barreca et al., 2020; Franklin & Mitchell, 2019; Grundy, Lapsley, & Ellis, 2016; Lipan et al., 2019]). The mechanisms explored by which almonds may have a favorable alternation in glycemic control are diverse due to large number of almonds' compounds. They are rich in unique nutrients and bioactive component like mono- and polyunsaturated fatty acids, vitamins, minerals, fiber, plant sterols/stanols, and polyphenolic compounds and antioxidants (Alasalvar & Bolling, 2015; Chen et al., 2017a; Heshmati et al., 2019; Llorach et al., 2010; Sepidarkish et al., 2019; Sepidarkish et al., 2019). In fact, by decreasing the generation of damaging reactive oxygen species (ROS) produced in the mitochondria in response to glucose surges could improve glycemic responses (Jenkins et al., 2006). These compositional properties confer almonds as the potential to beneficially influence glycemic control (Chen et al., 2017a; Gulati et al., 2017; Heshmati et al., 2019; Sepidarkish, Akbari-Fakhrabadi, et al., 2019). In addition, it could improve the reducing glycemic index value of co-consumed food (Chen et al., 2017b). The mechanism responsible for these beneficial effects may relate to the slow absorption of carbohydrate typically seen with the use of low GI foods, viscous fibers and Acarbose, the alpha-glucoside hydrolase inhibitor (Augustin et al., 2015). Others could be insulinogenic effects of certain AA and/or stimulation of incretins, reduced gastric emptying rate, increased C-peptide clearance (Augustin et al., 2015).

4.1 | Side effects

Some studies mentioned some adverse effects. The most well-known adverse effect of consumption of almonds is an allergic reaction (Gorji, Moeini, & Memariani, 2018; Martin, Germano, Hartley, Adler, & Rees, 2015). Furthermore, increased almonds consumption as a nut might be believed to cause of weight gain (Martin et al., 2015). In addition, high oxalate content in nuts such as almonds might be one of contributing factors for kidney stone formation in some individuals (Gorji et al., 2018).

4.2 | Study strengths and limitations

The present meta-analysis had several limitations. The effects of main confounding variables including, genetic background, lifestyle modification, medications, dietary patterns, and almonds' varieties on the efficacy of almonds remained unclear. So, mentioned bias makes the overall interpretation of the results difficult. Next, included studies has different quality; although all of them were controlled trials but they were conducted in different countries with different quality study thus it can affect results. Therefore, it must be acknowledged as one of the limitations. In addition, present study has not been registered in the PROSPERO, this could be considered as a limitation as well. On the whole, maybe majority of included studies discussed here have been not performed according to recent consensus document providing a perspective in best practice in pharmacological research on bioactive preparations from plants (Heinrich et al., 2020).

The strength of the current study was the subgroup analysis and assessment of the baseline glycemic indices, duration, dose, age, health, and obesity status on the overall effect sizes. Also, we ran analysis depending on between-group's mean changes that are more accurate than within-group changes leading to find greater effect sizes, favoring intervention. In addition, we tried to minimize any biases in the review process by performing a comprehensive search of the literature and also by conducting and reporting the review by adhering to the PRISMA guidelines. On the other hand, dose–response analysis was one of the other strengths of the present study; as we performed both linear and non-linear analysis.

4.3 | Implications for practice

The exact almond consumption has not been evaluated around the world. Based on last information almond consumption per capita per year showed increasing trend form 190.5 g to 1,070 g between 1980 and 2018. Despite this remarkable increase this per-capita consumption only encompasses daily intake of 2.93 g of almond per day. According to FDA-qualified health claims about 42.5 g needed for meeting daily intake; but this intake meets only ~7% of the FDA-qualified. In that case almond consumption per capita is truly under the FDA-recommended daily serving size of tree nuts (Michelle A Lee-Bravatti et al., 2019). A serving of almond is about 42.5 g of it or 35 almond which contain 246 cal and 9 g of protein, 21 g of fat (13 g from monounsaturated, 5 g from polyunsaturated, 2 g from saturated), 9 g of carbohydrates and 5 g of fiber (Michelle A Lee-Bravatti et al., 2019).

Here is currently no convincing evidence that almonds have a clear beneficial effect on glycemic control. However, subgroup analyses demonstrated almonds in large doses and for a long period of time are effective. It seems, it could be encouraged as part of a healthy diet in order to glycemic control. It should be noted that results cannot be generalized to those with other health presentations such as liver disease and cancer that were not included in this analysis.

4.4 | Implications for research

Future large, long duration, high-quality trials should be designed to ensure low risk of bias and to meet current reporting standards for

TABLE 5 Table of chemical, nutritional properties of almonds and effect of different processing treatments

Nutritional value nutrient content (per 100 g) of different varieties of almonds			
Macronutrients	Protein		16–23
	Lipid		44–61
		SFA	3–4
		MUFA	31–35
		PUFA	11–12
	CHO		15.7–27
		Sugar	4–6
		Fibers	11–14
	Ash		2.5–3.7
Micronutrients	Minerals	Calcium	264–300
		Magnesium	230–268
		Zinc	3.0–4.1
		Manganese	1.2–1.8
	Vitamins	Riboflavin	1.0–1.32
		Vitamin E	25–29.9
		Niacin	2.2–3.72
	Total phenolic compound		260–235
Effect of different processing on treatments			
Roasting	Water loss		
	Damage of cell wall and cytoplasmic network		
	Decreased oil body integrity		
	Millard reaction and browning		
	Increase in		
		Free fatty acids	
	Decrease in		
		Total phenol content	
		Total flavonoids	
		Carbohydrate	
Blanching	Alteration in cytoplasmic network		
	Loss of micronutrients		
	Water uptake		
	Suppression of total polyphenol		
Oil extraction	Loss in oil body integrity		
	Degradation of almond tissue		
Pasteurization	Polyphenol content reduction		
	Flavonoid content reduction		

TABLE 5 (Continued)

Chemical characteristics		
Volatile compounds	Acid	Acetic acid
		Hexanoic acid
	Alcohol	Butanol
		Hexanol
		Nonanol
	Aldehyde	Heptanal
		Hexanal
	Pyrazine	
	Terpene	
	Alkane	

clinical trials. Daily dosing regimen ideally should be tailored to the individual to improve the evidence in this field. As, we mentioned previously, other factors that can affect results, such as different dietary compliance of subjects, life style factors, production process, storage, and geographical and botanical almonds' origin, also need to be considered. Another important point is that about pitfalls in HbA1C measurements and its false-positive results. In situations where HbA1C may not accurately reflect glycemic control, using other alternative indexes include fructosamine, glycated albumin, 1,5-anhydroglucitrol (1,5-AG), and continuous glucose monitoring (CGM) are desirable (Radin, 2014).

5 | CONCLUSION

Here is currently no convincing evidence that almonds have a clear beneficial effect on glycemic control. However, subgroup analyses demonstrated almonds in longer period of time showed weak promising effects but findings are not referrable until future studies showed confirming results. Present study focused on dose and duration; in fact, future studies in specific populations is needed.

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CONFLICTS OF INTEREST

All the authors declared that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ehsan Ghaedi and Azadeh Neisi contributed to the design of study; Omid Asbaghi and Elham Eslampour contributed to screening of

obtained data; Elham Eslampour extracted available data according to pre-designed forms; Maryam Miraghajani and Azadeh Neisi prepared the primary draft of the article; Ehsan Ghaedi and Maryam Miraghajani checked the last edition of article for approval. Finally, all authors approved the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.

DATA AVAILABILITY STATEMENT

Desirable data for readers will be available on responsible request.

ETHICS STATEMENT

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors. This article does not contain any studies with human participants or animals performed by any of the authors. *Consent for publication*: Present study does not contain any studies of human or animals which needs consent for publication.

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