

## SYSTEMATIC REVIEWS AND META-ANALYSES

# Use of ancient grains for the management of diabetes mellitus: A systematic review and meta-analysis



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**Abstract** *Aims:* A systematic review and meta-analysis of published randomized controlled trials was conducted to collate evidence from studies implementing ancient grains and investigate the impact of ancient grain consumption on health outcomes of patients with Diabetes Mellitus (DM).

*Data synthesis:* Twenty-nine randomized controlled trials were included, and 13 were meta-analyzed. Interventions ranged from 1 day to 24 weeks; most samples were affected by DM type 2 ( $n = 28$  studies) and the ancient grains used were oats ( $n = 10$  studies), brown rice ( $n = 6$  studies), buckwheat ( $n = 4$  studies), chia ( $n = 3$  studies), Job's Tears ( $n = 2$  studies), and barley, Khorasan and millet ( $n = 1$  study). Thirteen studies that used oats, brown rice, and chia provided data for a quantitative synthesis. Four studies using oats showed a small to moderate beneficial effect on health outcomes including LDL-c ( $n = 717$ , MD: 0.30 mmol/l, 95% CI: 0.42 to  $-0.17$ ,  $Z = 4.61$ ,  $p < 0.05$ ,  $I^2 = 0\%$ ), and TC ( $n = 717$ , MD: 0.44 mmol/l, 95% CI: 0.63 to  $-0.24$ ,  $Z = 4.40$ ,  $p < 0.05$ ,  $I^2 = 0\%$ ). Pooled analyses of studies using chia and millet did not show significant effects on selected outcomes.

*Conclusions:* For adults affected by DM type 2, the use of oats may improve lipidic profile. Further experimental designs are needed in interventional research to better understand the effects of ancient grains on diabetes health outcomes.

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**Abbreviations:** DM, Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; LDL-c: Low Density Lipoprotein cholesterol, HDL-c: High Density Lipoprotein cholesterol; TG, Triglycerides; TC, Total Cholesterol; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; SD, Standard Deviation; iAUC, incremental Area Under the Curve; PPBG, Postprandial Plasma Blood Glucose; BMI, Body Mass Index.

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## 1. Introduction

Diabetes Mellitus (DM) is a chronic metabolic condition associated with a relevant increase in morbidity and mortality [1]. The prevalence of DM has doubled globally in the past 30 years, making it the seventh leading cause of death and disability [2]. It is estimated that by 2045, approximately 700 million people will have diabetes, of which 68 million only in Europe, with a 50% increase of prevalence [1,3].

Among the interventions to manage DM, diet represents the cornerstone of therapy together with glucose-lowering drugs. According to the American Diabetes Association, dietary interventions aim at preventing and/or delaying chronic complications of diabetes, through the maintenance of a proper body weight and glycemic profile [4]. Notably, dietary interventions could be more cost-effective and better tolerated than many pharmacologic treatments for diabetes [5].

Grains are prominent components of the daily dietary intake of DM patients. Current guidelines recommend a balanced diet, with a sufficient intake of carbohydrates, preferring those with a lower glycemic index [6–8]. Since grains are the principal source of carbohydrates in human diets, interest in the health effects of grain consumption is increasing [9].

Recently, there has been renewed interest in ancient grain varieties for their possible enhanced health benefits in DM [10,11]. Ancient grains represent an important category of ancient cereals that have not undergone human breeding or genetic modification, thus preserving their inherent genetic features [10]. The genetic diversity of these ancient crops not only offers a variety of food options but also represents a valuable genetic heritage to be preserved [12,13]. Furthermore, the preservation of these species and varieties, which have maintained their characteristics over the centuries, can contribute to biodiversity conservation and provide significant benefits in terms of food security and agricultural sustainability [13,14].

There is a wide range of heterogeneous information derived from utilization of ancient grains in patients with DM. It has been reported that ancient grains, compared with newer commercial varieties (which are defined as those selected and cultivated after the Green Revolution, i.e., after the 1960s [15]), have higher levels of several phytochemicals [16,17], and fiber [18]. Some of these phytochemicals, such as phytosterols, phenolic compounds (like ferulic acid and lignans), flavonoids, and carotenoids [16], have been associated with potential health benefits. These compounds have antioxidant and anti-inflammatory properties, and could influence glucose metabolism, insulin sensitivity, and overall glycemic control [19,20]. Ancient grains, such as spelt, einkorn, and emmer, are frequently known for their elevated fiber content compared to the specific varieties of modern wheat, which enhances nutritional density [21]. Although this generalization holds true, the precise fiber composition varies among different varieties, and is influenced by factors such as growing conditions, agricultural practices, and specific grain types [15,18].

Furthermore, these ancient grains are rich in beta-glucan, a type of soluble fiber that has been shown to improve insulin sensitivity, thereby aiding in the reduction of postprandial glucose response [22].

Notably, while some studies suggest that the use of ancient grains has a positive effect on blood glucose [11,17,23–27], to date there is still ongoing debate about effectiveness of substituting newer varieties with ancient grains in the management of diabetes [10,28,29].

### 1.1. Aim

This systematic review aims to collate evidence from studies that investigate the impact of ancient grain consumption on patients with DM. We specifically sought to address the following inquiries:

1. Does a diet based on ancient grains improve glycemic control and prevent the onset and progression of complications associated with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)?
2. Which types of ancient grains have been studied in relation to DM?
3. Which types of health outcomes have been studied to ascertain the effectiveness of an ancient-grain-based diet for controlling T1DM and T2DM?

## 2. Methods

This study was conducted in accordance with the Protocol Statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [30,31]. The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023422386).

### 2.1. Search strategy

The research question was framed using the PICOS method (P = Population, I = Intervention, C = Comparison, O = Outcome, S = Study design and context); P = patients with T1DM and T2DM; I = ancient grain diet; C = no comparator; O = effectiveness on health outcomes; S = experimental study. We operationalized patients with DM as individuals who had received a confirmed diagnosis of either T1DM or T2DM. We excluded cases of pre-diabetes, gestational diabetes, and unspecified types of diabetes, due to the transient and uncertain nature of their disease. We operationalized ancient grains according to the taxonomy of herbaceous crops [32] and the three main grains' categories (cereals, minor cereals and pseudocereals) [12]. Effectiveness on health outcomes was intended as the enhancement of any clinical, economic, and psychological outcome in the context of DM management. We evaluated all articles that adopted randomized controlled designs, as they are considered the gold standard for the evaluation of health interventions.

Four electronic databases (PubMed, CINAHL, Cochrane, Web of Science) were searched for pertinent papers, from

inception to May 2023. A detailed search strategy and PICOS method used for all electronic databases are reported in [Supplementary Tables 1–2](#).

## 2.2. Study eligibility criteria

The identified studies were assessed for eligibility by two independent authors (CEM, PI). Studies were considered eligible when reporting experimental designs (randomized controlled trials) and investigating the following outcomes: survival, long-term morbidity (e.g., microvascular and macrovascular diabetic complications), symptoms of diabetes, glycemic control (e.g., glycated hemoglobin, fasting blood glucose), direct and indirect costs, cost-effectiveness, psychological factors (e.g., anxiety, depression, stress), satisfaction for quality of care, access to care, equity, and organization of care. Studies using single extracted components of grains (e.g., beta glucans), and those written in languages other than English were excluded.

## 2.3. Study selection

The references obtained from each database were exported and entered into Endnote v.x9 [33], where duplicates were removed. The final list of references was then uploaded into Rayyan [34], where initial screening of titles and abstracts was conducted. Finally, the remaining records were examined in full text, and data extraction was conducted for the papers meeting the eligibility criteria. Agreement between the authors (CEM and PI) was reached through consensus discussions; in case of persistent disagreement, a third author (LR) was involved to make the final decision regarding inclusion.

## 2.4. Data extraction

Data extraction was performed independently by two authors (CEM and PI). The data extracted included first author, publication date, title, country, study design, treatment arms, aim(s), population, sample details, ancient grains used, comparator, intervention duration and washout (if crossover design was adopted), type of outcomes, results. In case of mixed populations, the study was included if data were presented separately for DM patients. We planned to contact the authors of any included study in case important data was missing.

## 2.5. Risk of bias assessment

Risk of bias of eligible studies was evaluated using the Cochrane Risk of Bias 2 tool [35]. This instrument assesses risk of bias by examining the randomization process, deviations from the intended intervention, missing outcome data, outcome measurement, and selection of reported results. For crossover studies, bias arising from period and carryover effects was also evaluated. For each study, risk of bias was assessed for the primary outcome measure. Studies having  $\geq 3$  domains of “some concern” were judged to have a high overall risk of bias. Assessments

were performed by two independent authors (CEM and PI), and any discrepancy resolved through discussion until consensus was reached.

## 2.6. Statistical analyses

Rev-Man v.5 was used to conduct the metaanalyses. Data included in the software were author and year of publication, sample size, mean and standard deviation (SD) for each randomization group. We calculated the mean difference between the mean change of the outcome measures with their 95% confidence intervals (CIs). For crossover studies, we relied on data from the first period due to the absence of information on within-patient differences. The measurements used were mmol/L for fasting blood glucose (FBG), % for glycated hemoglobin (HbA1c), mg/dl for total cholesterol (TC), high density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), and triglycerides (TG), kg/m<sup>2</sup> for BMI, and kg for body weight. If data were not reported in these measurement units, they were converted using the following formulas: for FBG expressed as mg/dl, conversion was performed considering that 1 mg/dl equals 0.55 mmol/l [36]. If HbA1c was reported as mmol/mol, conversion was performed using the formula  $[\text{HbA1c \%}] = 0.0915 * [\text{HbA1c mmol/mol}] + 2.15$  [36]. If lipid profile (TC, HDL-c, LDL-c, TG) was reported as mmol/L, conversion was performed by multiplying the value of TC, HDL-c, and LDL-c by 38.67 for, and multiplying 88.5 for TG [37]. If not provided, SD was extracted from SE through the equation provided by the Cochrane handbook [38]. When feasible, the SDs for changes were also extracted with the formula provided by Cochrane. In case the correlation coefficient between the baseline and final values was not reported, a value of 0.5 was estimated [39]. A fixed effects model was preferred if heterogeneity was low (<25%) or absent [40], otherwise, random-effects models were conducted.

Significance of heterogeneity between the studies was determined by Cochran's Q test and  $I^2$  inconsistency test, with a  $I^2$  value > 50% and a p value < 0.05 denoting significant heterogeneity. Subgroup analyses were planned in case of a significant number of studies included per outcome (>10) [41]. Leave-one-out sensitivity analyses were planned in case of one or more studies had serious risk of bias [42,43], and funnel plots were planned in case of a sufficient number of studies (>10) [41]. Forest plots are presented for each metaanalysis. Publication bias was evaluated through funnel plots and Egger's regression symmetry test when appropriate [44].

## 3. Results

### 3.1. Search results

In total, 2634 potentially relevant records were retrieved from the four databases. Out of these, 1001 were duplicates, thus leaving 1633 records to examine. After reviewing the titles and abstracts, 64 papers were selected and screened in full text. Finally, 29 papers met the eligibility criteria and were included in the systematic review.

An overview of the study selection process is displayed in the PRISMA flowchart (Fig. 1).

### 3.2. Study characteristics

A detailed description of the characteristics of the studies is reported in Table 1. Briefly, of the 29 studies included in this review, 17 (58.6%) were conducted in Asia, 6 (20.7%) in Europe, five (17.2%) North America, and one study (3.5%) in Oceania. Fourteen studies (48.3%) adopted a crossover design, while 15 (51.7%) were parallel trials. Study duration

ranged from 1 day to 24 weeks, and the washout period in the crossover studies lasted from 2 days to 40 weeks.

In total, the studies enrolled 1809 participants (range = 8–298; males:  $n = 998$ , 55.2%) with a mean age of 55.6 years (range = 32–66). One study (3.4%) included only females and two studies (6.9%) included only males. Most studies ( $n = 28$ , 96.6%) included patients with T2DM whereas one study (3.4%) only recruited T1DM patients. The average duration of DM diagnosis was 14.3 years (range 3.1–23) and was mainly treated with both oral hypoglycemic agents and subcutaneous insulin ( $n = 9$

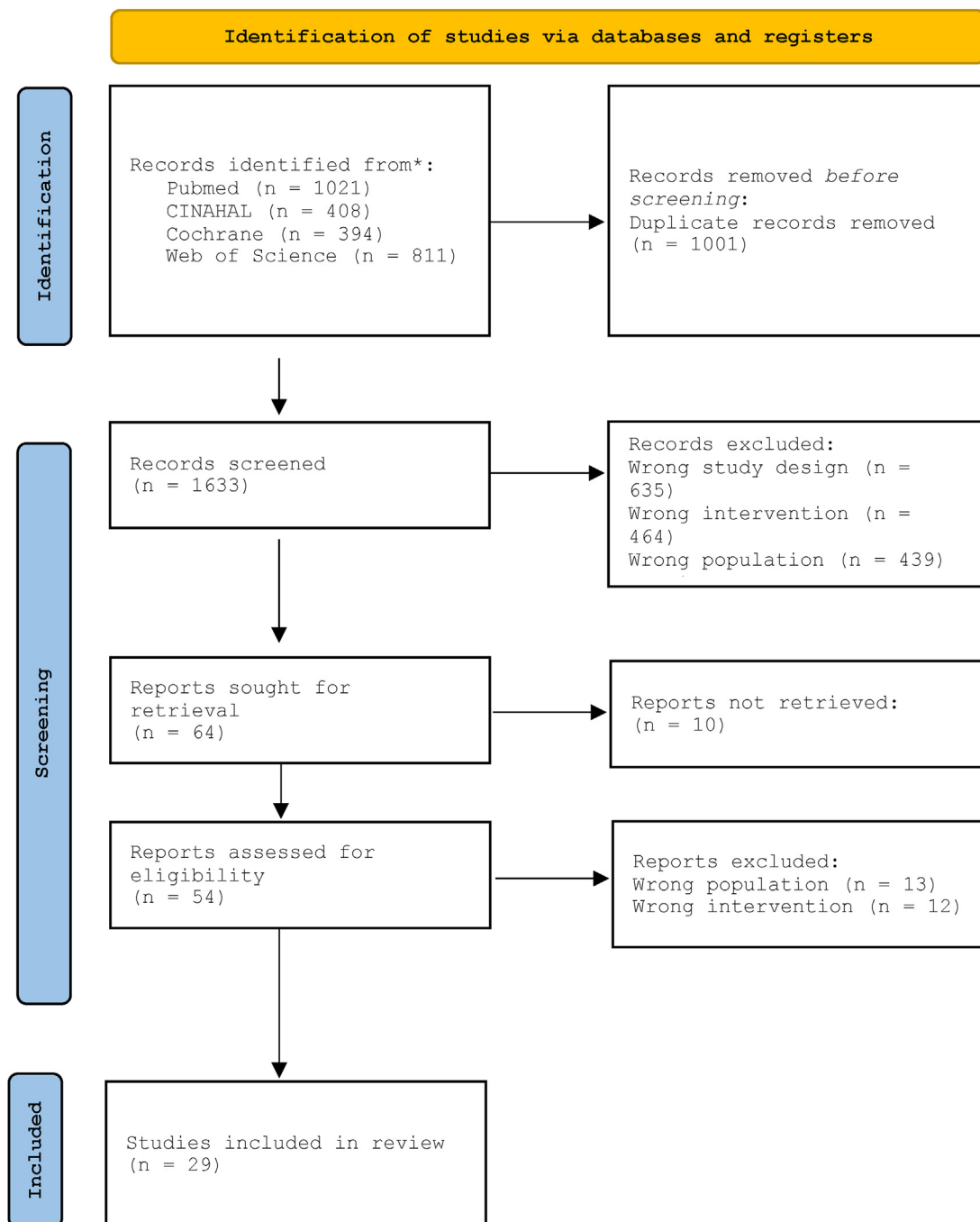


Figure 1 PRISMA flow diagram.

**Table 1** Characteristics of the randomized controlled trials included in the systematic review and meta-analysis.

Author, Year	Country	Study design	Arms	Aim(s)	Population (n)	Sample details (I/C)	Ancient grain used	Daily amount of ancient grain	Comparator	Intervention duration (washout)	Types of outcomes	Results
AlFaris, 2020	Saudi Arabia	Parallel, blinding not stated	6	Evaluate the effects of a low-energy diet with and without oat bran and olive oil supplements on BMI, BP and serum lipids	Nonpregnant or lactating women with T2DM, overweight or obese, without symptoms (n = 78). I: n = 13/group; C: n = 13 DM management: none.	Data not reported separately for the two groups Mean age not reported Age range: 25–39 years (26%), 40–50 years (37.4%), 51–60 years (36.6%) 78 (100%) females	Oats	10 g	Usual meals	12wk	Height, weight, BP, BMI, TG, cholesterol (total, LDL, HDL)	Low energy meals (with oat bran enriched diet) improved BMI, BP, TC and TG
Cai, 2022	China	Parallel, blinding not stated	2	Evaluate the effects of oat on the blood glucose and lipid metabolism	Free-living elderly patients with T2DM (n = 98) I: n = 52; C: n = 46 DM management: none.	I (n = 52): mean age 56.6 years, 20 (38.5%) females, 32 (61.5%) males C (n = 46): mean age 55.7 years, 19 (41.3%) females, 27 (58.7%) males	Oats	40 g	Usual meals	12wk	FBG, PPBG, insulin, GSP, C-peptide, HOMA-IR, HOMA-beta, height, waist circumference, hip circumference, weight, BMI, cholesterol (total, LDL, HDL), TG, AST, ALT, HbA1C, adverse event	Oats enriched diet improved TC and LDL-c
Delgado, 2019	Germany	Two-way crossover, nonblinded	2	Evaluate the effect of two days of oatmeal on daily insuline requirement, glycated hemoglobin, insuline resistance, C-reactive protein, lipid profile	Adults with uncontrolled T2DM (n = 15) I: n = 10; C: n = 5 DM management: none.	Data not reported separately for the two groups Mean age 58.6 years, age range: 41–75 years, 7 (46.7%) females, 8 (53.3%) males	Oats	100 g	Usual meals	2 days (22wk)	Daily insuline requirement, Hb1AC, insuline resistance, PCR, cholesterol (total, LDL, HDL), TG, pre-prandial blood glucose	Oats enriched diet improved insuline requirement and Hb1AC (4 weeks after the intervention)
Delgado, 2020	Germany	Two-way crossover, nonblinded	2	Evaluate the effect of two days of oatmeal on bile acid concentration	Adults with uncontrolled T2DM (n = 15) I: n = 10; C: n = 6 DM management: none.	Data not reported separately for the two groups Mean age 58.6 years, age range: 41–75 years, 7 (46.7%) females, 8 (53.3%) males	Oats	100 g	Usual meals	3 days (22wk)	Bile acid concentration (taurine, glycine conjugates), lipoproteins (VLDL, LDL, HDL), cholesterol (TC, FC), TG	Oat meal enriched diet improved total BA, GCA and proinsulin
Li, 2016	China	Parallel, blinding not stated	4	Evaluate the short- and long-term effects of oat intake on weight, blood glucose and lipid-profile	Adults overweight with T2DM (n = 298) I1: n = 79; I2: n = 80; I3: n = 79; C: n = 60 DM management: oral therapy (n = 167), injection therapy (n = 54), oral and injection therapy (n = 53).	I1: Healthy diet group (n = 79): mean age 59.7 years, 37 (46.8%) females, 42 (53.2%) males I2: 50 g-oats group (n = 80): mean age 59.7 years, 39 (48.7%) females, 41 (51.3%) males I3: 100 g-oats group (n = 79): mean age 59.4 years, 46 (58.2%) females, 33 (41.8%) males C (n = 60): mean age 59.0 years, 21 (35%) females, 39 (65%) males	Oats	I2: 50 g I3: 100 g	Usual meals	4wk	Weight, height, waist circumference, hip circumference, BP, body fat percentage, visceral fat index, FPG, 2-h PPG, Hb1AC, fasting plasma insulin, 2-h postprandial plasma insulin, TC, LDL, HDL, TG, HOMA-IR	Oats enriched diet improved blood glucose, blood lipid, and weight

Ma, 2013	China	Parallel, single-blinded	4	Evaluate the effect and effective doses of naked oat on HbA1c and insulin resistance	Adults with T2DM meeting MetS criteria (overweight) (n = 260) I1: n = 61; I2: n = 65; I3: n = 71; C: n = 63 DM management: not stated.	I1: diet group (n = 61, mean age 59.3), 33 (50.5%) females, 28 (49.5%) males I2: 50 g-ONOG group (n = 65, mean age 59.4 years), 38 (58.5%) females, 27 (41.5%) males I3: 100 g-ONOG group (n = 71, mean age 60.3 years), 45 (63.4%) females, 26 (36.6%) males C: Usual care group (n = 63, mean age 58.4 years), 32 (50.8%) females, 31 (49.2%) males	Oats	I2: 50 g I3: 100 g	Usual meals	4wk	Weight, height, waist circumference, hip circumference and blood pressure, FPG, 2-h PPG, TG, TC, HDL-c, LDL-c, HbA1c, hs-CRP, fasting insulin, insulin resistance, complete blood count, blood biochemical examination, routine urine tests, liver and renal function (serum alanine transaminase, aspartic transaminase, blood urea nitrogen and serum creatinine)	Organic naked oat with whole germ enriched diet improved glycemia, and lipid profile control
McGeoch, 2013	United Kingdom	Two-way crossover, blinding not stated	2	Evaluate the effect of an oat-enriched diet on glycaemic control, postprandial glycaemia, inflammation and oxidative stress	Free-living adults with T2DM (n = 27) I, C: not stated DM management: diet and lifestyle (n = 27).	Data not reported separately for the two groups Mean age 60.9 (46–71) years, 9 (33.3%) females, 18 (66.7%) males	Oats	100 g	Usual meals	16wk (none)	Weight, height, BMI, waist circumference, blood pressure, TC, LDL, HDL, TG, fasting plasma glucose, insulin concentrations, glucose, insulin concentrations, HOMA-IR, HOMA-B, HbA1c, inflammatory markers (CRP, adiponectin, IL-6, IL-18, TNF-alpha), measures of antioxidant capacity and oxidative stress in plasma (ORAC, MDA, fasting oxidized LDL, urinary isoprostane).	Oats enriched diet improved moderately lipid profile (TC and postprandial adiponectine concentration)
Pick, 1996	Canada	Two-way crossover, blinding not stated	2	Evaluate the long-term effects of oat bran concentrate bread products	Free-living adults with T2DM (n = 8) I: n = 4; C: n = 4 DM management: oral therapy and diet (n = 3), diet (n = 5).	Data not reported separately for the two groups mean age 45 years, 8 (100%) males	Oats	40 g	White bread	24wk (none)	Dietary intake, blood glucose, insulin, lipid parameters, FBG, PPBG, insulin, lipid profile, body weight	Oat bran enriched diet improved mean glycemic and insulin response areas under the curve, total cholesterol and LDL-c levels
Tapola, 2005	Finland	Parallel, blinding not stated	2	Evaluate the effects of oat bran flour on postprandial glucose response following an oral glucose load	Free-living adults with T2DM (n = 12) I, C: not stated DM management: diet (n = 12).	Data not reported separately for the two groups mean age 66 years, 5 (41.7%) females, 7 (58.3%) males	Oats	Not reported	Oats	1 day	Height, weight, blood glucose concentrations, blood samples for routine laboratory measurements, AUC, FBG, PPBG	Oat bran flour enriched diet improved glycemic response and postprandial glycemic response
Hsu, 2008	Japan	Two-way crossover, blinding not stated	2	Evaluate the effects of pre-germinated brown rice (PGBR) on blood glucose and lipid levels	Free-living adults with T2DM (n = 11) I: n = 5; C: n = 6 DM management: oral therapy (n = 10), injection therapy (n = 1).	Data not reported separately for the two groups mean age: 51.5 years, 5 (45.5%) female, 6 (54.5%) males	Brown rice	540 g	White rice	6 wk (2wk)	Weight, height, body fat, BMI, BP, TP, Alb, insulin, TC, TG, HDL, LDL, FBG, fructosamine	PGBR enriched diet improved TC, TG, HDL-c, FBG, and fructosamine

(continued on next page)

**Table 1** (continued)

Author, Year	Country	Study design	Arms	Aim(s)	Population (n)	Sample details (I/C)	Ancient grain used	Daily amount of ancient grain	Comparator	Intervention duration (washout)	Types of outcomes	Results
Kim, 2011	Korea	Parallel, double-blinded	2	Evaluate the effects of lees of brown rice on waist metabolic and endocrinologic parameters	Free-living adults with T2DM (n = 30) I: n = 15; C: n = 15 DM management: not stated.	I (n = 15): mean age 50.1 years, 7 (46.7%) females, 8 (53.3%) males C (n = 15): mean age 49.5 years, 7 (46.7%) females, 8 (53.3%) males	Brown rice	40 g	Mixed-grain dietary product	12wk	Weight, height, waist circumference, hip circumference, BMI, total body fat, urea nitrogen, creatinine, glucose, uric acid, calcium, protein, albumin, alkaline phosphatase, total bilirubin, AST, ALT, inorganic phosphates, cholesterol (total, LDL, HDL), TG, CRP, HOMA-IR, HbA1c, GLP-1, insulin, C-peptide, glucose, free fatty acid, chemokines (IL-10, IL-6, MCP-1, TNF-alpha, CRP)	LB enriched diet improved waist circumference, hip circumference, AST, ALT
Kondo, 2017	Japan	Parallel, nonblinded	2	Evaluate the effects of a fiber-rich diet with brown rice on endothelial function	Adults with T2DM (n = 28) I: n = 14; C: n = 14 DM management: glucose lowering therapy not specified (n = 25).	I (n = 14): mean age 65.2 years, 5 (35.7%) females, 9 (64.3%) males C (n = 14): mean age 68.1 years, 5 (35.7%) females, 9 (64.3%) males	Brown rice	Not reported	White rice	8wk	Weight, height, BMI, body fat, BP, fasting plasma glucose, fasting plasma insulin, glycoalbumin, HOMA-IR, HOMA-beta, cholesterol (total, LDL, HDL), TG, insulin resistance, Hb1AC, total adiponectin, hs-CRP, urine 8-isoprostane, PPBG, markers of oxidative stress and inflammation	Brown rice improved endothelial function and high-sensitivity C-reactive protein level tended to improve compared to white rice diet
Lee, 2016	Korea	Parallel, nonblinded	2	Evaluate the effect of a brown rice based-diet on glycemic control and other cardiovascular risk factors	Adults with T2DM (n = 93) I: n = 46; C: n = 47 DM management: oral therapy (n = 70), injection therapy (n = 15).	I (n = 46): mean age 57.5 years, 40 (87%) females, 6 (13%) males C (n = 47): mean age 58.3 years, 35 (74.5%) females, 12 (25.5%) males	Brown rice	Not reported	Usual meals	12wk	Hb1AC, body weight, height, waist circumference, BP, TG, cholesterol (total, LDL, HDL)	Brown rice enriched diet improved waist circumference, and Hb1AC
Na, 2023	China	Parallel, nonblinded	2	Evaluate the effect of germinated brown rice (GBR) on fatty acids metabolism and glucose parameters	Free-living adults with T2DM (n = 85) I: n = 42; C: n = 43 DM management: oral therapy (n = 56), injection therapy (n = 21).	I (n = 42): mean age 64.9 years, 24 (57.1%) females, 18 (42.9%) males C (n = 43): mean age 66.7 years, 27 (62.8%) females, 16 (37.2%) males	Brown rice	100 g	Usual meals	12wk	Weight, height, BMI, waist circumference, hip circumference, blood samples: FBG, HbA1c, FINS, TG, TC, HDL, LDL	GBR enriched diet improved anti-inflammatory profile

Nakayama, 2017	Japan	Two-way crossover, nonblinded	2	Evaluate the effects of glutinous brown rice (GBBR) on glycemic control	Adults with T2DM (n = 16) I: n = 8; C: n = 8 DM management: injection therapy (n = 6), oral and injection therapy (n = 10).	Data not reported separately for the two groups Mean age 64 years, 4 (25%) females, 12 (75%) males	Brown rice	Not reported	White rice	8wk (none)	HbA1c, glycoalbumin, 1,5-anhydroglucitol, plasma glucose, active GLP-1, PYY, s-CPR, iAUC	GBR enriched diet improved HbA1c, glycoalbumin, 30-min postprandial plasma glucose level (PPB) and incremental area under the concentration vs time curve of serum C-peptide (PG, CPR)
Qiu, 2016a	China	Parallel, nonblinded	2	Evaluate the effects of tartary buckwheat on UACR and UN	Adults with T2DM (n = 104) I: n = 52; C: n = 52 DM management: oral therapy (n = 89).	I (n = 52): mean age 59.5 years, 34 (65.4%) females, 18 (34.6%) males C (n = 52): mean age 58.1 years, 29 (55.8%) females, 23 (44.2%) males	Buckwheat 100 g		White rice or wheat flour	4wk	Weight, height, BMI, BP, HbA1c, GA, plasma glucose, SCr, blood UA, and blood UN, UACR, urinary albumin to creatinine ratio, urea nitrogen, serum creatinine, uric acid	Tartary buckwheat enriched diet improved the urinary albumin to creatinine ratio and urea nitrogen
Qiu, 2016b	China	Parallel, nonblinded	2	Evaluate the effects of tartary buckwheat on the risk factors of T2DM	Adults with T2DM (n = 165) I: n = 80; C: n = 85 DM management: oral therapy (n = 101), injection therapy (n = 9), oral and injection therapy (n = 12), none (n = 41).	I (n = 80): mean age 57.0 years, 48 (60%) females, 32 (40%) males C (n = 85): mean age 56.7 years, 50 (58.8%) females, 35 (41.2%) males	Buckwheat 150 g		White rice or wheat flour	4wk	Weight, height, BMI, BP, plasma glucose, TC, HDL-c, LDL-c, TG, HbA1c, serum insulin, insulin resistance, FBG	Tartary buckwheat enriched diet improved fasting insulin, total cholesterol, and LDL-c
Stringer, 2013	Canada	Two-way crossover, single-blinded	2	Evaluate the effect of buckwheat on gastrointestinal hormones, fasting blood glucose, lipids and apolipoproteins	Well-controlled T2DM adults (n = 12) DM management: not stated.	Data not reported separately for the two groups mean age 60.8 years, 7 (58.3%) females, 5 (41.7%) males	Buckwheat	Not reported	White rice	1wk (not stated)	Post-prandial glucagon-like peptide-1, glucose-dependent insulinotropic peptide and pancreatic polypeptide, insulin, C peptide, FBG, PPBG, lipid profile, apolipoproteins	Buckwheat enriched diet improved gastrointestinal satiety hormones
Vetrani, 2019	Italy	Two-way crossover, blinding not stated	2	Evaluate the acute effects of fibre-enriched buckwheat pasta on postprandial blood glucose	Adults with T1DM and celiac disease (n = 10) I, C: not stated DM management: injection therapy (n = 10).	Data not reported separately for the two groups mean age 32 years, 8 (80%) females, 2 (20%) males	Buckwheat 100 g		Corn	2wk (1wk)	Continuous glucose monitoring, plasma glucose concentration, FBG, PPBG	Buckwheat enriched diet improved postprandial profile and glycemic response after 3 h
Alwosais, 2021	Kuwait	Parallel, nonblinded	2	Evaluate the effects of chia on FBG, insulin, HbA1c, BP, lipid profile, body weight, and C-reactive protein	Free-living adults with T2DM (n = 42) I: n = 20; C: n = 22 DM management: not stated.	I (n = 20): mean age 51.8 ± 8.9 years, 12 (60%) females, 8 (40%) males C (n = 22): mean age 52.7 ± 7.3 years, 8 (36.4%) females, 14 (63.6%) males	Chia	40 g	Usual meals	12wk	Height, weight, BMI, heart rate, BP, HbA1C, FBG, insulin, cholesterol (total, LDL, HDL)	Chia enriched diet improved systolic BP

(continued on next page)



Table 1 (continued)

Author, Year	Country	Study design	Arms	Aim(s)	Population (n)	Sample details (I/C)	Ancient grain used	Daily amount of ancient grain	Comparator	Intervention duration (washout)	Types of outcomes	Results
Vuksan, 2007	Canada	Two-way crossover, single-blinded	2	Evaluate the effects of Salba ( <i>Salvia hispanica</i> L.) on major and emerging cardiovascular risk factors	Free-living adults with T2DM (n = 20) I, C: not stated DM management: oral therapy (n = 10), injection therapy (n = 10).	Data not reported separately for the two groups mean age 64 years, 9 (45%) females, 11 (55%) males	Chia	Not reported	Wheat bran	12wk (4–6wk)	BP, C-reactive protein, vonWillebrand factor, Hb1AC, weight, lipid profile, FBG, PPBG, insulin, fibrinogen, liver and renal function markers	Chia enriched diet improved systolic BP, C-reactive protein, vonWillebrand factor, Hb1AC and fibrinogen
Vuksan, 2017	Canada	Parallel, double-blinded	2	Evaluate the effects of Salba-chia on body weight, visceral obesity and obesity-related risk factors	Overweight and obese adults with T2DM (n = 58) I: n = 27; C: n = 31 DM management: glucose lowering therapy not specified (n = 45), diet (n = 13).	I (n = 27): mean age 60 years, 20 (74%) females, 7 (26%) males C (n = 31): mean age 60 years, 20 (65%) females, 11 (35%) males	Chia	30 g	Oats	24wk	Weight, waist circumference, HbA1c, fasting glucose, percentage body fat, body composition, satiety-related hormones (ghrelin and adiponectin), and plasma fatty acids, hs-CRP, urea, creatinine, ALT, PT	Chia enriched diet improved weight, waist circumference, C-reactive protein, adiponectin
Djaja, 2019	Indonesia	Parallel, blinding not stated	2	Evaluate the effects of Job's tears-enriched yoghurt on weight, FBG, GLP-1, and CP feces	Adults with T2DM (n = 60) I: n = 30; C: n = 30 DM management: oral therapy (n = 34).	I (n = 30): mean age 43.4 years, 19 (63.3%) females, 11 (36.7%) males C (n = 30): mean age 44.9 years, 14 (46.7%) females, 16 (53.3%) males	Job's tears	Not reported	Yoghurt without Job's tears	20wk	Height, weight, BMI, GLP-1, FBG, fecal CP	Job's tears enriched diet improved weight and FBG
Djaja, 2022	Indonesia	Parallel, blinding not stated	2	Evaluate the effects of Job's tears with probiotics on lipid profile, and glycated albumin	Adults with T2DM (n = 60) I: n = 30; C: n = 30 DM management: oral therapy (n = 34).	I (n = 30): mean age 43.4 years, 17 (56.7%) females, 13 (43.3%) males C (n = 30): mean age 45.7 years, 16 (53.3%) females, 14 (46.7%) males	Job's tears	250 g	Yoghurt without Job's tears	20wk	Height, weight, BMI, food intake assessment, glycated albumin, cholesterol (TC, LDL, HDL), TG	Job's tears enriched diet improved HDL-c
Pick, 1998	Canada	Two-way crossover, blinding not stated	2	Evaluate the effects of incorporating high beta-glucan barley bread or bread protucts in the everyday diet	Adults with T2DM (n = 11) I: n = 6; C: n = 5 DM management: oral therapy and diet (n = 7), diet (n = 4).	Data not reported separately for the two groups mean age 51 years, 11 (100%) males	Barley	Not reported	White bread	24wk (none)	Day profiles (8-h for blood glucose/insulin levels), FBG, PPBG, insulin, Hb1AC, oral hypoglycemics dosage	Barley enriched diet improved glycemic response and reduced the dose of oral hypoglycemics
Whittaker, 2017	Italy	Two-way crossover, double-blinded	2	Evaluate the effects of Khorasan on glucose, insulin, lipid and inflammatory risk factors	Adults with T2DM (n = 21) I, C: not stated DM management: oral therapy (n = 10).	Data not reported separately for the two groups mean age 64.4 years, 14 (66.7%) females, 7 (33.3%) males	Khorasan	62 g	Modern wheat flour	16wk (8wk)	BMI, BP, TC, LDL, HDL, TG, glycemia, insulin, FBG, PPBG, HOMA index, HbA1c, potassium, magnesium, iron, TBARS, L-derived ROS, M-derived ROS, interleukin-1ra, 4, 6, 8, 10, 12, 17, INF-gamma, MCP-1, MIP-1 beta, TNF-alpha, VEGF	Khorasan enriched diet improved TC, LDL-c, insulin, blood glucose, ROS production, and inflammatory risk factors

Narayanan, India 2016	Two-way crossover, blinding not stated	2	Evaluate the effects of a millet-based dosa (foxtail dosa) on postprandial level of glucose	Adults with T2DM (n = 105) I: n = 52; C: n = 53 DM management: not stated.	Data not reported separately for the two groups Mean age: 49.3 years, 36 (34,3%) females, 69 (65,7%) males	Foxtail millet	290 g	White rice	4 days (2 days)	Body weight, height, BMI, waist and hip circumference, blood glucose concentrations, iAUC, FBG, orghanoleptic rating scale, PPBG	Millet enriched diet improved post-prandial glucose level
Aberg, 2020 New Zealand	Two-way crossover, double-blinded	2	Evaluate the effects of whole-grain milling processing on glycemic control	Free-living adults with T2DM (n = 31) I: n = 16; C: n = 15 DM management: oral therapy(n = 19), injection therapy (n = 9), diet (n = 3).	Data not reported separately for the two groups Mean age: 63 years Age range not reported 14 (45%) females, 17 (55%) males	Oats and brown rice	Not reported	Oats and brown rice	2wk (2wk)	Height, weight, BMI, body fat, BP, HbA1c, cholesterol (total, LDL, HDL), TG, PCR, alpha-1-acid glycoprotein, fasting insulin, FBG, PPBG, glycemia (interstitial glucose), alkylresorcinols, iAUC	Less-processed whole grain enriched diet improved glycemic variability and weight
Hajifaraji, Iran 2012	Two-way crossover, double-blinded	2	Evaluate the effects of oat and barley bread on lipid profiles and blood glucose	Adults with T2DM and dyslipidemia (n = 36) I: n = 13; C: n = 23 DM management: none.	Gender data not reported separately for the two groups: 28 (77%) females, 8 (23%) males Group A (n = 13): mean age 52 years Group B (n = 23): mean age 53 years	Barley and oats	Not reported	Barley and oats	3 wk (3wk)	Height, weight, waist circumference, hip circumference, BMI, blood pressure, glucose, insulin, cholesterol (total, LDL, HDL), TG, PPG	Both barley and oats enriched diet improved anthropometric (weight, BMI) and metabolic indicators (TC). Oat enriched diet improved more HDL-c, FBS, and PPG 2h

**Legend.** ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; C, control; FBG, fasting blood glucose; FINS, fasting insulin; GCA, glycocholic acid; GLP-1, glucagon-like peptide 1; GSP, glycosylated serum protein; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA, homeostasis model assessment; hs-CRP, hypertensive C-reactive protein; I, intervention; iAUC, incremental area under the curve; LDL, low density lipoprotein; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MIP, macrophage inflammatory protein; ORAC, oxygen radical antioxidant capacity; PCR, protein-C reactive; PPBG, post prandial blood glucose; ROS, reactive oxygen species; TBARS, thiobarbituric acid reactive species; TG, triglycerides; VEGF, vascular endothelial growth factor; VFI, visceral fat index; VLDL, very low density lipoprotein.

studies, 31%), or oral hypoglycemic agents alone ( $n = 4$  studies, 13.8%). Ancient grains used included oats ( $n = 9$ , 31.1%), brown rice ( $n = 6$ , 20.7%), buckwheat ( $n = 4$ , 13.9%), chia ( $n = 3$ , 10.4%), Job's Tears ( $n = 2$ , 6.9%), and barley, Khorasan and millet ( $n = 1$ , 3.4%). Two studies contain mixed grains oats and brown rice (3.4%), and oats and barley (3.4%). In seven studies (24.2%) the grains employed were not refined.

Furthermore, when reported, the daily number of ancient grains ranged from 10 to 100 g of oats, from 40 to 540 g of brown rice, from 100 to 150 of buckwheat, from 30 to 40 of chia, and 250 g of Job's tears.

### 3.3. Qualitative findings

All the studies included in this review analyzed cardiovascular risk factors including glycemic, lipid, and anthropometric profile, and other indicators. [Supplementary Table 3](#) reports the statistically significant outcomes per each study.

### 3.4. Glycemic profile

Most of the included studies ( $n = 28$ , 96.5%) reported the effectiveness of ancient grains on glycemic profile, including several outcomes such as insulin, HbA1c, fasting blood glucose (FBG), glycemia, incremental area under the curve (iAUC), postprandial plasma blood glucose (PPBG), and medicaments. However, a significant improvement in the glycemic profile was observed in 20 studies, of which 14 reported significant outcomes related to blood glucose profile, five associated with the insulin axis, and two reported medication effects. Notably, positive effects on glycemic regulation, glucose metabolism, and diabetes treatment were observed following the consumption of oats ( $n = 6$ , 30.0%), brown rice ( $n = 5$ , 25.0%), buckwheat ( $n = 2$ , 10.0%), barley ( $n = 1$ , 5.0%), millet ( $n = 1$ , 5.0%), Job's tears ( $n = 1$ , 5.0%), Khorasan ( $n = 1$ , 5.0%), chia ( $n = 1$ , 5.0%), and mixed ancient grain combinations such as oats and brown rice ( $n = 1$ , 5.0%), and barley and oats ( $n = 1$ , 5.0%). In addition, the study that included patients T1DM [45] observed a positive effect on PPBG related to the glycemic profile. Ancient grains were associated with lower HbA1c [46–51], PPBG [45,48,50,52–54], FBG [48,49,55–57], glycemic variability [54,58–61], iAUC [50,58,59,62], glycated albumin [50], and fructosamine [57] in comparison with modern grains. Ancient grains also influenced the insulin axis, including the production of insulin [61] and proinsulin [63], as well as the effect of fasting insulin on the body [52,56,64]. Furthermore, a few studies suggested that the consumption of ancient grains reduced the need for oral hypoglycemic medication [60] and insulin [46].

### 3.5. Lipid profile

More than half of the included studies ( $n = 22$ , 75.9%) reported the effectiveness of ancient grains on the lipid profile, including fatty acids, TG, transaminase, TC, HDL-c, and LDL-c. A significant beneficial effect on the lipid

profile was observed in 14 studies using oats ( $n = 6$ , 42.9%), brown rice ( $n = 3$ , 21.5%), job's tears ( $n = 1$ , 7.1%), chia ( $n = 1$ , 7.1%), Khorasan ( $n = 1$ , 7.1%), buckwheat ( $n = 1$ , 7.1%), and mixed ancient grains with barley and oats ( $n = 1$ , 7.1%). The improvements in the lipid profile were in specific on adiponectin [65,66], n-3 fatty acid metabolites [49], TG [49,52,57,67], transaminase [68], and cholesterol metabolism including TC [48,52,56,57,59,61,64,65,69], HDL-c [49,56,70], and LDL-c [48,52,59,61,64,69].

### 3.6. Anthropometric profile

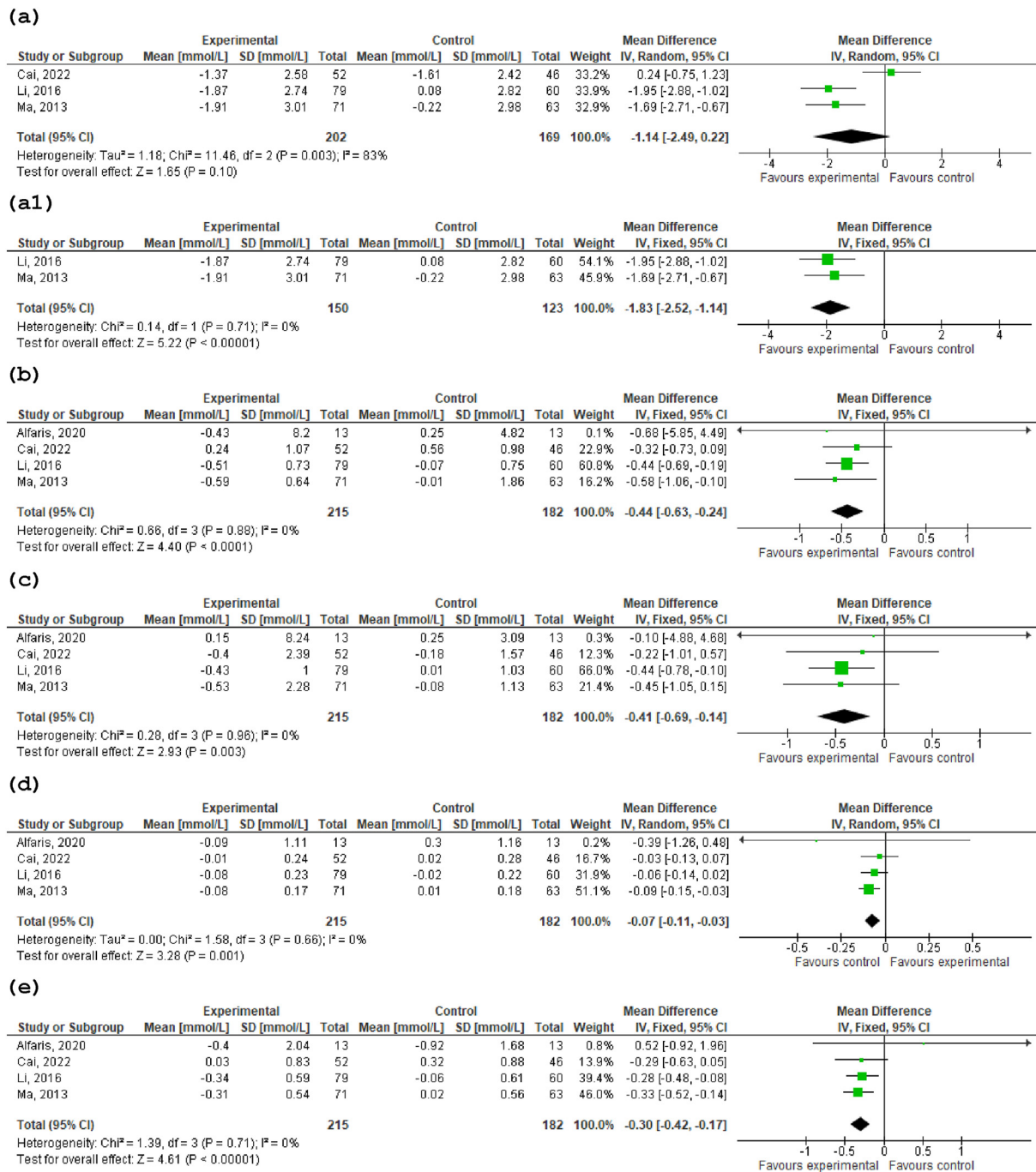
Most studies ( $n = 23$ , 79.3%) investigated anthropometric variables such as body mass index (BMI), weight, waist, and hip circumference. A significant beneficial impact on these outcomes was observed in only six (26.1%) studies; specifically, brown rice ( $n = 2$ , 33.6%), chia ( $n = 1$ , 16.6%), job's tears ( $n = 1$ , 16.6%), oats ( $n = 1$ , 16.6%), and mixed ancient grains with oats and brown rice ( $n = 1$ , 16.6%) had a positive effect on body weight [55,58,66], waist circumference [47,66,68], BMI [58,67], and hip circumference [68].

### 3.7. Other indicators

Other studies ( $n = 9$ , 31.0%) focused on a variety of different outcomes, including vital signs and anti-inflammatory indices. Specifically, chia ( $n = 3$ , 33.4%), oats ( $n = 2$ , 22.2%), buckwheat ( $n = 2$ , 22.2%), Khorasan ( $n = 1$ , 11.1%), and brown rice ( $n = 1$ , 11.1%) have been found to improve blood pressure [51,71], gastrointestinal satiety hormone [72], and renal [73], and liver function [63]. Other improvements were reported for C-reactive protein [48,51,62,66], von Willebrand factor [51], reactive oxygen species, inflammatory factors [61], fibrinogen [51] and endothelial function [62].

### 3.8. Metanalysis findings

Thirteen studies using oats ( $n = 4$ ), brown rice ( $n = 4$ ), chia ( $n = 3$ ), and millet ( $n = 2$ ), provided sufficient data to be combined for a quantitative analysis among clinical outcomes (such as FBG, TC, TG, HDL-c, LDL-c, HbA1c, BMI, body weight). The meta-analysis of the studies comparing oats with conventional diet [48,52,67,69] showed a small to moderate beneficial effect on TC (MD: 0.44 mmol/l, 95% CI: 0.63 to -0.24,  $Z = 4.40$ ,  $p < 0.001$ ,  $I^2 = 0\%$ ) (Fig. 2b), TG (MD: 0.41 mmol/l, 95% CI: 0.69 to -0.14,  $Z = 2.93$ ,  $p = 0.003$ ,  $I^2 = 0\%$ ) (Fig. 2c), and LDL-c (MD: 0.30 mmol/l, 95% CI: 0.42 to -0.17,  $Z = 4.61$ ,  $p < 0.001$ ,  $I^2 = 0\%$ ) (Fig. 2e). There was a negative effect of oats on HDL-c (MD: 0.07 mmol/l, 95% CI: 0.11 to -0.03,  $Z = 3.28$ ,  $p = 0.001$ ,  $I^2 = 0\%$ ) (Fig. 2d). The effects of oats on FBG were not statistically significant ( $p = 0.10$ ,  $I^2 = 83\%$ ); however, there was a high heterogeneity due to the study by Cai et al. (2022), whose effect size was towards the control group. The removal of this study changed the pooled effect to significant in absence of heterogeneity between studies (MD: 1.83 mmol/l, 95% CI: 2.52 to -1.14,  $Z = 5.22$ ,  $p < 0.001$ ,  $I^2 = 0\%$ ) (Fig. 2a1).

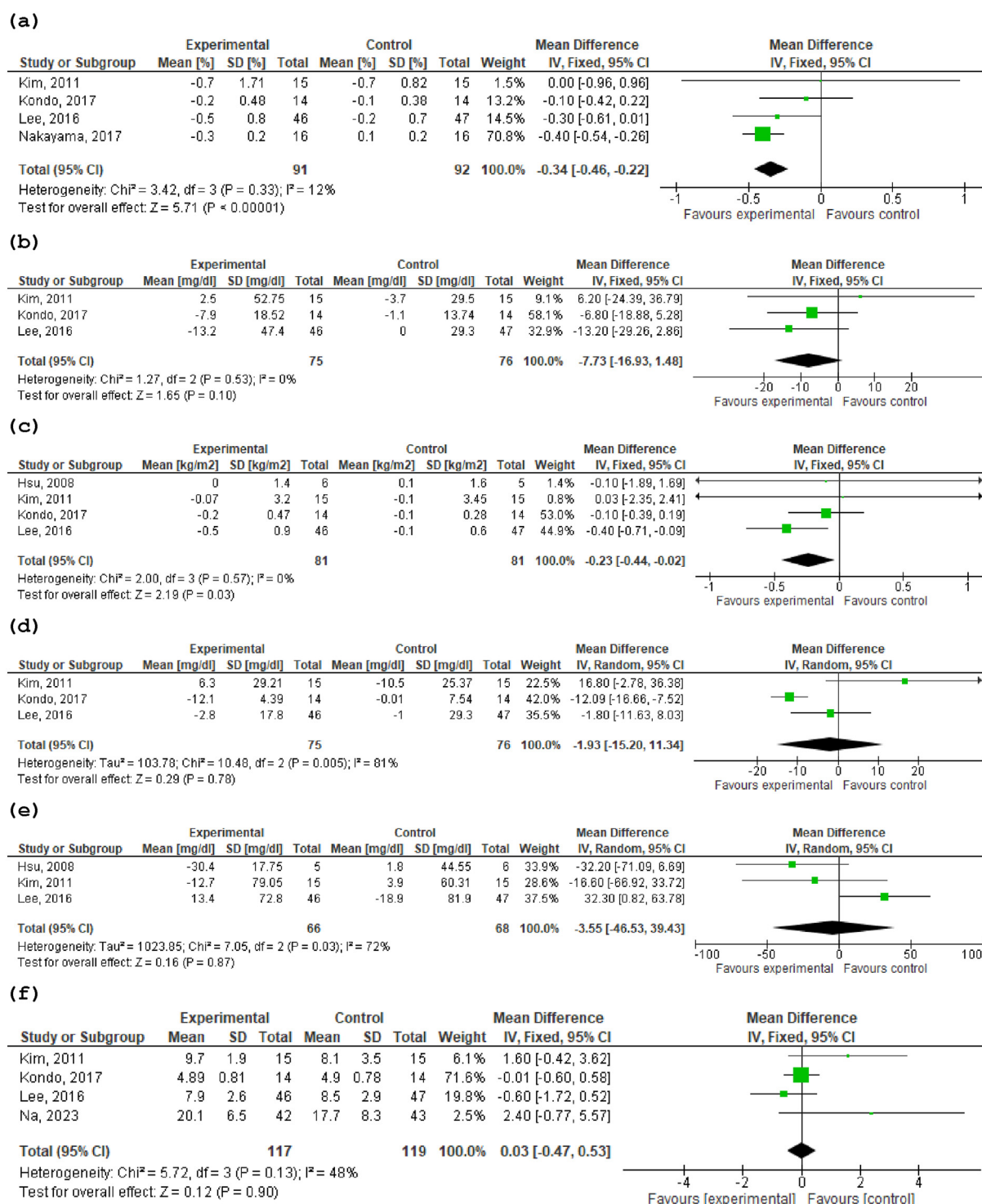


**Figure 2** Forest plots showing mean differences (MD) and 95% CI across studies using oats for (a) fasting blood glucose and (a1) related sensitivity analysis, (b) total cholesterol, (c) triglycerides, (d) HDL cholesterol, and (e) LDL cholesterol.

The meta-analysis of the studies comparing brown rice with white rice [43,50,55], conventional diet [47], showed a small to moderate beneficial effect on HbA1c (MD: 0.34%, 95% CI: 0.46 to -0.22,  $Z = 5.71$ ,  $p < 0.001$ ,  $I^2 = 12\%$ ) (Fig. 3a), and BMI (MD: 0.23 kg/m<sup>2</sup>, 95% CI: 0.44 to -0.02,  $Z = 2.19$ ,  $p = 0.03$ ,  $I^2 = 0\%$ ) (Fig. 3c). The effects of brown rice on FBG, LDL-c, TG, and TC were not statistically significant ( $p = 0.10$ ,  $I^2 = 0\%$ ,  $p = 0.78$ ,  $I^2 = 81\%$ ,  $p = 0.87$ ,  $I^2 = 72\%$ , and  $p = 0.90$ ,  $I^2 = 48\%$ , respectively) (Fig. 3b, d,

3e, 3f) and leave-one out sensitivity analysis did not change the results (data not shown).

The meta-analysis on the studies comparing chia with conventional diet [71], wheat bran [51], and oats [66] did not highlight significant effects on FBG ( $p = 0.57$ ,  $I^2 = 0\%$ ) and HbA1c ( $p = 0.11$ ,  $I^2 = 0\%$ ) in absence of heterogeneity (Fig. 4). Pooled effects of millet [55,70] on body weight was significant in absence of heterogeneity (MD: 0.69 kg/m<sup>2</sup>, 95% CI: 1.25 to -0.14,  $Z = 2.46$ ,  $p = 0.01$ ,  $I^2 = 0\%$ ) (Fig. 5).



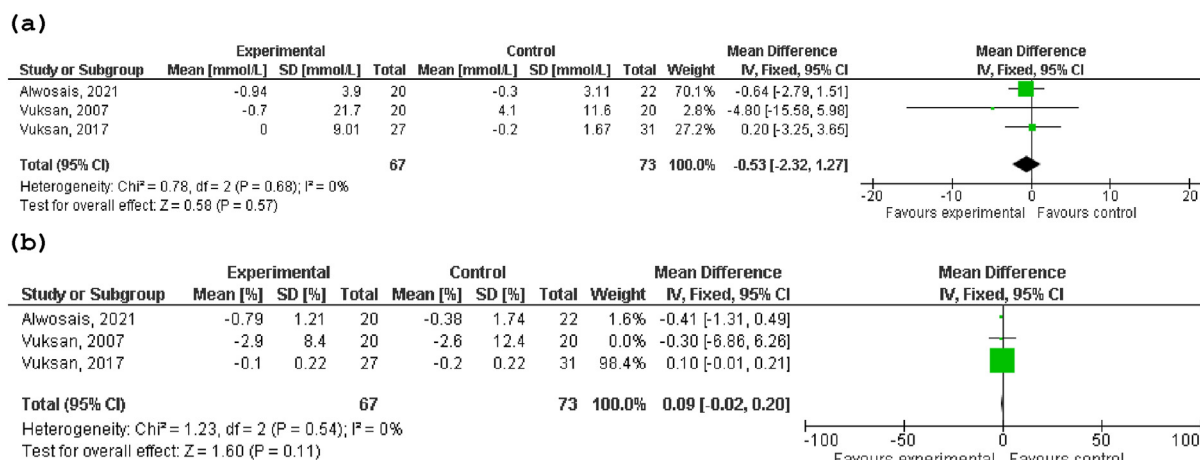
**Figure 3** Forest plots showing mean differences (MD) and 95% CI across studies using brown rice for (a) glycated hemoglobin, (b) fasting blood glucose, (c) body mass index, (d) LDL cholesterol, (e) triglycerides, and (f) total cholesterol. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Given the scarce number of studies available per outcome, subgroup analyses were not performed. Moreover, since the studies per grain were  $<10$ , we had very low statistical power to perform the Begg's and Egger's test for publication bias [38].

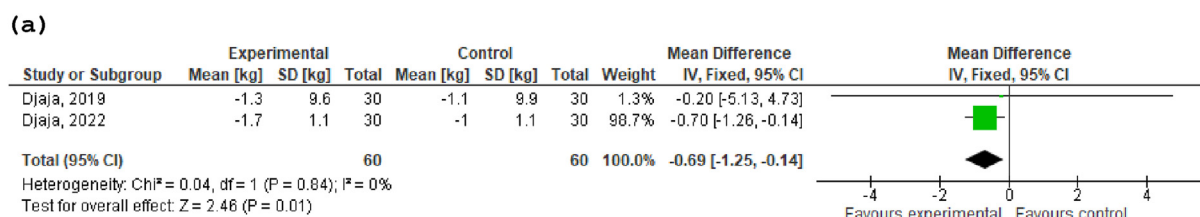
### 3.9. Risk of bias

Risk of bias was high for most studies ( $n = 16$ , 55.2%), of some concerns for eleven studies (37.9%), and low for two studies (6.9%). Main issues identified were the potential





**Figure 4** Forest plots showing mean differences (MD) and 95% CI across studies using chia for (a) fasting blood glucose, and (b) glycated hemoglobin.



**Figure 5** Forest plot showing mean differences (MD) and 95% CI across studies using millet on (a) body weight.

selection of reported results, missing information on allocation concealment and randomization process, and, only for crossover studies, bias arising from period and carryover effects. Other aspects, such as adherence to the intended interventions, outcome data, and measurement of the outcome, were less susceptible to the risk of bias. Further information on risk of bias assessment is provided in Figs. 6 and 7.

#### 4. Discussion

This systematic review and meta-analysis aimed to synthesize available evidence from studies using ancient grains and their impact on patients with DM. Oats, brown rice, buckwheat and chia were the most prevalent grains studied for their potential effects on patients with DM, reporting data on a variety of health outcomes, including body weight, glycemic control, and lipid profile. On the other hand, some outcomes which are very relevant for clinical decisions on treatments, such as treatment satisfaction, well-being, and cost-effectiveness, were not reported in available studies.

To the best of our knowledge, this review and meta-analysis is the first to systematically investigate the effects of ancient grain consumption on the management of DM in patients with either T1DM or T2DM. Through a comprehensive analysis of available studies, this paper could offer an overview of the current evidence regarding the use and effectiveness of ancient grains in managing DM. Almost all

available studies were performed in patients with T2DM. The only trial in T1DM [45] showed that the acute consumption of buckwheat may have clinically relevant effects on postprandial blood glucose in individuals with T1DM. However, due to the small-scale of this study, the findings should be approached with caution as they may not provide conclusive evidence. The paucity of available data on T1DM is not surprising, considering that its prevalence is considerably lower than that of T2DM. On the other hand, patients with T1DM without residual endogenous insulin secretion could represent an interesting model for assessing differences in glycemic response to products derived by either modern or ancient grains.

The distribution of ancient grains prevalence in our studies reflects the quality of their nutritive components. For example, oats, which are the most prevalent among investigated grains, are also the most promising in terms of nutritional composition, because they are rich in proteins, carbohydrates, soluble fibers, phenolic compounds, and minerals, [28]. Selection of specific cereals above others may not only reflect their nutritional properties, but also their diffusion; for example, buckwheat, which is rich in proteins, fibers, and flavonoids, is also widely cultivated and consumed worldwide due to its low cost [74].

Our qualitative findings suggest that consuming ancient grains like chia, barley, millet, Khorasan, buckwheat, and brown rice could have positive effects on a variety of health outcomes in patients with T2DM. However, the type

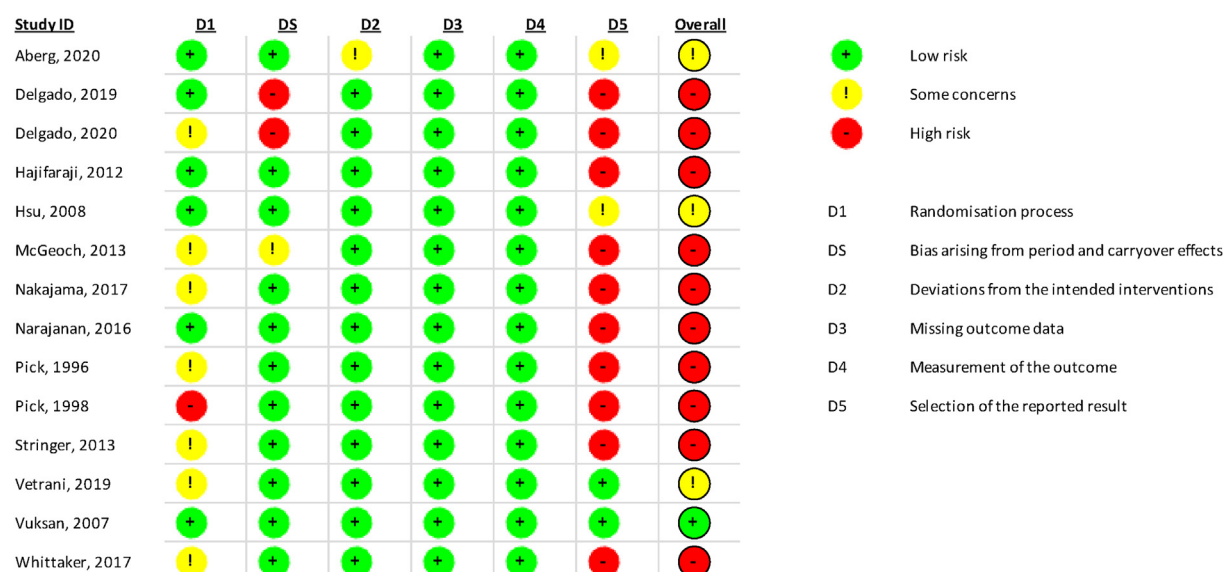


Figure 6 Risk of Bias assessment (crossover studies).



Figure 7 Risk of Bias assessment (parallel studies).

of design and heterogeneity in outcomes prevented their inclusion in a quantitative synthesis.

In our quantitative synthesis, we found that oats can improve lipid profile (except for a statistically significant but clinically trivial reduction of HDL-c) and FBG in patients with T2DM. To our knowledge, only one review was conducted to understand the effects of oats on T2DM, which was consistent with our findings [75]. However, the previous review included, together with RCTs, also observational studies, which are aggravated by a greater risk of

bias, and it also included studies investigating the effects of extracts of oats (e.g., betaglucans) eliminating other potentially interesting nutritional components of the oats, especially those in the outer layer of the grain. The assessment of the effect of oats on FBG is affected by the deviant results of one study [69], in which the description of the diet in the control arm was unclear, and adherence was derived by self-report.

In our meta-analysis we found statistically significant effects of brown rice on HbA1c and BMI, but not on other

glycemic and lipid markers. This result is partly discordant from a systematic review by Golzarand et al. [76], reporting that brown rice had weight-reducing effects with no benefits on blood glucose and lipid profile. The previous review also examined the effect of pre-germinated brown rice, which, contrary to standard brown rice, improved not only body weight, but also lipid profile and FBG. There was heterogeneity in the types of brown rice used in our studies; for example, Hsu et al. [57] tested pre-germinated brown rice, whereas Kim et al. [68] used lees of brown rice. To augment palatability, Nakayama et al. [50] used glutinous brown rice. The poverty of studies included prevented subgroup analyses; thus, our results should be generalized with caution. Another possible factor affecting results is the heterogeneity of the control diets tested. For example, Kim et al. [68] used mixed grains mostly composed of white rice, but in minor parts also by brown rice, millet, and barley. Kondo et al. [62] used only white rice, and Lee et al. [47] used a conventional diabetic diet.

We also did not find any significant effect of chia on outcomes in patients with T2DM. This is in line with a systematic review by Teoh et al. [77], who did not find any statistical difference, although their subgroup analyses suggested that in a mixed population of healthy and ill individuals, high doses of chia could at least lower postprandial blood glucose, HDL-c and diastolic blood pressure. Because of the limited size of included samples, this meta-analysis did not reach a sufficient statistical power to detect small effects of chia on diabetes-related outcomes.

Finally, our meta-analysis indicated a significant effect of millet on body weight. Again, this result should be interpreted with caution, since in the two studies included in the analysis yoghurt was administered in both treatment arms; thus, it is possible that the prebiotics included in the meals, which have the properties of reducing BMI in the general population, had biased the pooled effect of chia.

#### **4.1. Strength and limitations**

Some limitations in this review should be considered when interpreting its results. Firstly, it is possible that the significance of ancient grain variety may not always be fully recognized by researchers, leading to the omission of this information in their studies. However, it is advisable to incorporate the specific ancient grain variety in future research to thoroughly investigate the effects of individual varieties, rather than relying solely on the broader grain species category. Secondly, the presence of a wide range of ancient grain types, and the heterogeneity of dietary products derived from each grain type tested in clinical trials, complicates identification of specific ingredients or components that could be mechanistically relevant. Third, there was high heterogeneity in terms of dosage, frequency, and observed outcomes between studies, which challenges the comparability of evidence. Fourth, the

quality of reporting of statistical data was not always optimal; the most important issue was the unavailability of SD of within differences, which led us to substitute them by means of specific formulas provided by the Cochrane Handbook [74]. Unfortunately, this approach may have introduced bias in the results. Five, due to the limited number of studies available for each outcome, subgroup analyses were not conducted. Therefore, we were not able to explain the amount of heterogeneity caused by potential confounders, such as age, gender, and body composition of participants. Finally, the limited number of trials, the small size of enrolled samples, and the relatively short duration of follow-up all limit the reliability of results on clinical outcomes. Strengths of this review are the strict protocol followed to review and extract data, and the inclusion of RCTs only, which are subjected to lower risk of bias in comparison to observational studies.

#### **5. Conclusions**

A variety of ancient grains have been tested on patients with T2DM, with potentially positive results on health outcomes at least for oats, and possibly brown rice and millet. However, these findings lack the strength needed to formulate dietary recommendations, primarily due to heterogeneity across studies, limited sample sizes, and suboptimal methodological quality of some trials. Further emphasis should be placed in designing future RCTs with better definition of dietary interventions, adequate sample sizes for relevant clinical outcomes, and sufficient duration of treatment. Furthermore, studies specifically designed for patients with T1DM should be implemented.

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#### **Declaration of competing interest**

The authors of this paper have no conflict of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.numecd.2024.03.005>.

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