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Review

The Effect of Regular Consumption of Reformulated Breads on Glycemic Control: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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A B S T R A C T

Bread is a major source of grain-derived carbohydrates worldwide. High intakes of refined grains, low in dietary fiber and high in glycemic index, are linked with increased risk for type 2 diabetes mellitus (T2DM) and other chronic diseases. Hence, improvements in the composition of bread could influence population health. This systematic review evaluated the effect of regular consumption of reformulated breads on glycemic control among healthy adults, adults at cardiometabolic risk or with manifest T2DM. A literature search was performed using MEDLINE, Embase, Web of Science and the Cochrane Central Register of Controlled Trials. Eligible studies employed a bread intervention (≥2 wk) in adults (healthy, at cardiometabolic risk or manifest T2DM) and reported glycemic outcomes (fasting blood glucose, fasting insulin, HOMA-IR, HbA1c, and postprandial glucose responses). Data were pooled using generic inverse variance with random-effects model and presented as mean difference (MD) or standardized MD between treatments with 95% CIs. Twenty-two studies met the inclusion criteria (n = 1037 participants). Compared with "regular" or comparator bread, consumption of reformulated intervention breads yielded lower fasting blood glucose concentrations (MD: −0.21 mmol/L; 95% CI: −0.38, −0.03; I^2 = 88%, moderate certainty of evidence), yet no differences in fasting insulin (MD: −1.59 pmol/L; 95% CI: −5.78, 2.59; I^2 = 38%, moderate certainty of evidence), HOMA-IR (MD: −0.09; 95% CI: −0.35, 0.23; I^2 = 60%, moderate certainty of evidence), HbA1c (MD: −0.14; 95% CI: −0.39, 0.10; I^2 = 56%, very low certainty of evidence), or postprandial glucose response (SMD: −0.46; 95% CI: −1.28, 0.36; I^2 = 74%, low certainty of evidence). Subgroup analyses revealed a beneficial effect for fasting blood glucose only among people with T2DM (low certainty of evidence). Our findings suggest a beneficial effect of reformulated breads high in dietary fiber, whole grains, and/or functional ingredients on fasting blood glucose concentrations in adults, primarily among those with T2DM. This trial was registered at PROSPERO as CRD42020205458.

Keywords: glycemic control, bread consumption, carbohydrate staple foods, type 2 diabetes mellitus, metabolic health, systematic review and meta-analysis

Abbreviations: GI, glycemic index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; RCT, randomized clinical trial; SMD, standardized mean difference; T2DM, type 2 Diabetes mellitus.

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Statements of significance

To date, meta-analyses have addressed the effect of whole-grain consumption, dietary fiber, and glycemic index on metabolic health parameters. However, in view of the paradigm shift from nutrient-based guidelines toward food-based dietary guidelines, a direct appraisal on the relevance of modified bread as a food group on glycemic control is warranted. To our knowledge, no other systematic reviews and meta-analyses have been published on this specific topic.

Introduction

Bread is a staple food in countries worldwide and thus is important in global nutrition. The metabolic effect of bread depends on several qualitative aspects ranging from the type of grain, its content of carbohydrates, and other nutrients to the chemical structure and processing. Qualitative aspects of the bread are best captured by its content of dietary fiber, whole grain, kernels, and added sugar [1, 2]. The type of bread traditionally consumed, and its carbohydrate quality, varies greatly between countries, giving this staple food an enormous potential for improvement which may be well tolerated by consumers.

From a public and clinical health perspective, replacing highly processed carbohydrates with less-processed carbohydrates is regarded as an important approach [1, 3–5]. Less-processed and whole-grain cereals are rich in dietary fiber, making bread a good source of these less digestible and more slowly digestible carbohydrates, which are associated with a reduced incidence and mortality from several chronic diseases [3]. In addition, being one of our main sources of dietary fiber, bread is a significant source of whole grain, the consumption of which is associated with reduced risk of chronic diseases, such as type 2 diabetes mellitus (T2DM) [6]. Although whole-grain consumption has been found to improve postprandial glucose and insulin homeostasis compared with refined foods [7, 8], longer-term effects are less conclusive [7, 8]. This may, to some extent, be attributable to the high glycemic index (GI) of many commonly consumed whole-grain products, also including bread [9, 10].

Thus, the metabolic effects of bread are dependent on its composition and the quality of its carbohydrates, including the aspect of food processing [2]. To date, meta-analyses addressed the effects of whole-grain consumption [3, 6–8], dietary fiber [3], and GI [4, 5] on metabolic health parameters, such as glycemic control. However, in view of the paradigm shift from nutrient-based guidelines toward food-based dietary guidelines [11, 12], direct evidence from intervention studies investigating the relevance of bread as a food group on glycemic control is warranted. Also, a number of novel approaches beyond the incorporation of fiber and/or increasing whole grain contents have recently been explored so as to improve the health effects of bread consumption (e.g., functional ingredients, novel plant protein sources). In line with the WHO definition of food reformulation [altering the processing or composition of a food or beverage product, to improve its nutritional profile or to reduce its content of ingredients or nutrients of concern [13]], we use the term "reformulated bread" for all these approaches. Thus, we aimed to investigate the overall effect of regular consumption of reformulated breads on glycemic control in healthy adults, in those at risk of developing cardiometabolic disease (e.g., having hypertension, hyperglycemia, hypercholesterolemia, and/or overweight/obesity), and in those with manifest T2DM, and to assess the certainty of the evidence.

Materials and Methods

This systematic review was reported in accordance with the PRISMA guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020205458).

Search strategy

The electronic databases MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (including unpublished trials from clinicaltrial.gov) were used for the systematic search of current literature. The systematic search was conducted in September 2020 and updated in February 2022. There were no limitations on the year of publication or language. The full search strategy is available in Supplemental Table 1.

Study eligibility criteria

The identified studies were assessed for eligibility by two independent investigators (AMS, IR) using the inclusion and

TABLE 1
Overview of the inclusion and exclusion criteria applied in the selection process of eligible studies

Category	Inclusion criteria	Exclusion criteria
Design	Randomized controlled trials (parallel- and crossover-design), nonrandomized intervention studies, with ≥10 participants per study arm	All other study types, intervention studies with <10 participants per study arm
Participants	Adults without the presence of acute or chronic diseases, except for type 2 diabetes mellitus, overweight/obesity, dyslipidemia, and/or hypertension	Children and adolescents, pregnant and breastfeeding females, presence of acute or chronic diseases, nonhuman subjects
Intervention	Consumption of bread over ≥2 wk, also including bread with functional ingredients. Data on planned and achieved amount of bread consumption should be provided	Studies with interventions other than bread, studies lasting <2 wk, studies with physical activity as an exposure
Comparator	Consumption of control bread, usual bread intake, usual diet, a control diet, or other carbohydrate staple foods over ≥2 wk	No comparators/controls
Outcomes	Fasting blood glucose, HbA1c, postprandial glucose response, fasting insulin, HOMA-IR	No assessment of relevant outcomes

exclusion criteria listed in Table 1. Studies considered eligible were randomized trials (parallel or crossover designs) evaluating the effects of reformulated bread consumption, for a duration of ≥2 wk, on glycemic outcomes in healthy adults, adults at cardiometabolic risk, or adults with T2DM. Included studies were evaluated for ≥1 of the following outcomes: fasting blood glucose, fasting insulin, HOMA-IR, HbA1c, or postprandial glucose response.

Data collection

The selection of studies for the systematic review was performed in duplicate by two independent researchers (AMS, IR). First, a duplicate control was performed in citation management software followed by a manual duplicate control by one of the researchers (IR). Second, the studies identified from the literature search were reviewed using the software Rayyan [14], where two independent researchers blinded to each other performed an initial evaluation of inclusion based on the titles and abstracts. Whenever the abstract did not provide sufficient information according to the inclusion and exclusion criteria, the full text was assessed. Third, the same reviewers independently assessed the full text of the studies identified as eligible from the initial screening (see Figure 1 for an overview of the selection process). Disagreement between the reviewers was resolved by involving a third party (HRR, US).

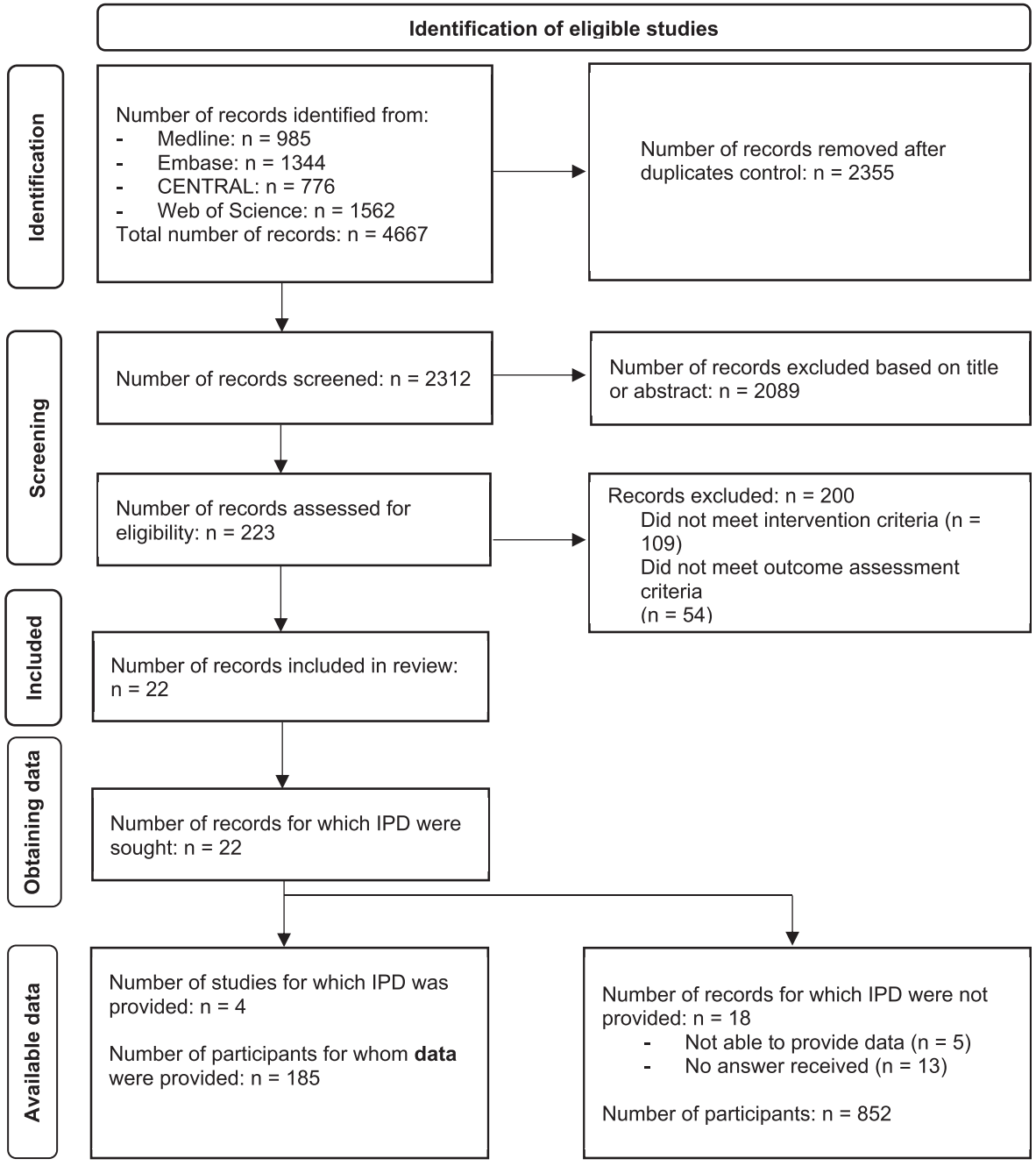

FIGURE 1. PRISMA flow chart of the study identification and selection process for eligible randomized controlled trials. CENTRAL002C the Cochrane Central Register of Controlled Trials; IPD, individual participant data.

TABLE 2
Characteristics of the randomized controlled trials included in the systematic review and meta-analysis[1]

Publication	Study design	*Arms* (n)	*Population* (n)	Intervention	Daily amount (intervention)	Control	*Daily amount* (control)	Duration (washout)	Outcomes
Bajerska et al., 2015 [43]	Parallel, single-blinded	2	44; males ($n = 17$) and females ($n = 27$) with obesity I: $n = 23$; C: $n = 21$	Rye bread with 1.1% green tea extract	Males: 360 g Females: 280 g	Rye bread	Males: 360 g Females: 280 g	12 wk	FBG ↔
Becerra-Tomás et al., 2015 [44]	Crossover, double-blinded	3	30; males ($n = 13$) and females ($n = 17$) with pre- or mild-to-moderate hypertension I: $n = 30$; C: $n = 30$	I: Low-sodium wheat bread with potassium, GABA, and ACE inhibitor peptides II: Low-sodium wheat bread with potassium	120 g	Wheat bread	120 g	4 wk (2 wk)	FBG ↔; INS ↔; HOMA-IR ↔
Dainty et al., 2016 [45]	Crossover, double-blinded	2	24; males ($n = 16$) and postmenopausal females ($n = 8$) at high risk of T2DM I: $n = 24$; C: $n = 24$	Bagel with resistant starch	120 g	Wheat bagel	120 g	8 wk (4 wk)	FBG ↔; INS ↓; HOMA-IR ↓
Frank et al., 2004 [24]	Crossover, double-blinded	2	22; males ($n = 11$) and females ($n = 11$) with moderate hypercholesterolemia I: $n = 22$; C: $n = 22$	Oat bread with high-molecular-weight β-glucan (797 kDa)	120 g (6 g β-glucan)	Oat bread with low-molecular-weight β-glucan (217 kDa)	120 g (6 g β-glucan)	3 wk (2 wk)	FBG ↔; INS ↔
Ghafouri et al., 2019 [46]	Parallel, double-blinded	4	100; males ($n = 57$) and females ($n = 43$) with T2DM I: $n = 75$; C: $n = 25$	I: Lactic acid bread with β-glucans II: Synbiotic bread with β-glucans; Bacillus coagulans, inulin III: Synbiotic+lactic acid bread with β-glucans, Bacillus coagulans, inulin	120 g (3 × 40 g)	Control bread with β-glucan	120 g (3 × 40 g)	8 wk	FBG ↔; INS ↔; HOMA-IR ↔; HbA1c ↓
Hodgson et al., 2010 [22]	Parallel, nonblinded	2	74; males ($n = 26$) and females ($n = 48$) with overweight I: $n = 37$; C: $n = 37$	Lupin flour–enriched bread	15%–20% of EI	White wheat bread	15%–20% of EI	16 wk	FBG ↔; INS ↔; HOMA-IR ↔
Islam et al., 2015 [47]	Parallel	2	30; males ($n = 22$) and females ($n = 8$) with T2DM I: $n = 17$; C: $n = 13$	Composite-flours bread	NS	Wheat bread	NS	4 wk	FBG ↔
Juntunen et al., 2003 [48]	Crossover, blinding not stated	2	20 healthy postmenopausal females I: $n = 20$; C: $n = 20$	High-fiber rye bread	208 g	White wheat bread	170 g	8 wk (8 wk)	FBG ↔; INS ↔
Lappi et al., 2014 [31]	Crossover, blinding not stated	2	21 healthy; males ($n = 9$) and females ($n = 12$) with self-reported gastrointestinal symptoms I: $n = 21$; C: $n = 21$	White wheat bread with rye bran	6–10 slices (25–30 g/slice)	Sourdough whole-grain rye bread	6–10 slices (25–30 g/slice)	4 wk (NS)	FBG ↔; INS ↔
Li et al., 2018 [23]	Crossover, nonblinded	2	37 healthy overweight males (30 completed both intervention periods) I: $n = 28$; C: $n = 28$	Quinoa-enriched bread	160 g (20 g quinoa)	White wheat bread	160 g	4 wk (4 wk)	FBG ↔; INS ↔; $AUC^{4H}_{GLUCOSE}$ ↓
Liatis et al., 2009 [32]	Parallel, double-blinded	2	41; males ($n = 23$) and females ($n = 18$) with T2DM and LDL-C >3.36 mmol/L I: $n = 23$; C: $n = 18$	β-glucan–enriched bread	120 g (4 × 30 g), providing 3 g β-glucan	Wheat bread	Amount not stated but possibly 120 g (4 × 30 g) here as well	3 wk	FBG ↔; INS ↓; HOMA-IR ↓; HbA1c ↔

(*continued on next page*)

TABLE 2 (*continued*)

Publication	Study design	*Arms* (n)	*Population* (n)	Intervention	Daily amount (intervention)	Control	*Daily amount* (control)	Duration (washout)	Outcomes
MacKay et al., 2012 [33]	Crossover, blinding not stated	2	28 normoglycemic and hyperglycemic; males ($n = 20$) and females ($n = 8$) I: $n = 28$; C: $n = 28$	Whole-grain wheat sourdough bread	Males: 163.8 g (7 slices) Females: 136.5 g (6 slices)	White wheat bread	Males: 163.8 g (7 slices) Females: 136.5 g (6 slices)	6 wk (4–5 wk)	FBG ↔; INS ↔; [2]$AUC_{GLUCOSE}$ ↓
Moghaddam et al., 2014 [34]	Crossover, nonblinded	2	30 premenopausal females with T2DM I: $n = 30$; C: $n = 30$	Wheat bread with soybean flour	120 g	Habitual diet	—	6 wk (4 wk)	FBG ↔; INS ↔; HOMA-IR ↔; HbA1c ↔
Mohtashami, 2019 [35]	Crossover, double-blinded	2	54; males ($n = 30$) and females ($n = 21$) with MS (51 analyzed) I: $n = 51$; C: $n = 51$	Bread with Nigella sativa	100 g	Bread without Nigella sativa	100 g	8 wk (2 wk)	FBG ↔
Moreira-Rosário et al., 2019 [25]	Crossover, double-blinded	2	52 healthy; males ($n = 16$) and females ($n = 36$) I: $n = 52$; C: $n = 52$	Wheat bread with wheat germ	100 g (6 g wheat germ)	Wheat bread	100 g	4 wk (5 wk)	FBG ↔; INS ↔; HOMA-IR ↔; HbA1c ↔
Pagliai et al., 2021 [36]	Crossover, double-blinded	2	17; males ($n = 10$) and females ($n = 7$) I: $n = 17$; C: $n = 17$	Sourdough bread with ancient grain "Verna"	150g	Control bread with baker's yeast and ancient grain "Verna"	150g	4 wk (4 wk)	FBG ↔
Sereni et al., 2017 [37]	Crossover, double-blinded	2	45 healthy; males ($n = 32$) and females ($n = 13$) I: $n = 23$; C: $n = 22$	Organic cultivated verna bread	NS	Conventional cultivated verna bread	NS	8 wk (NS)	FBG ↔
Sobhana et al., 2020 [38]	Parallel, nonblinded	2	94; males and females with T2DM I: $n = 47$; C: $n = 47$	Multigrain rotis and standardized curry	135 g roti and 200 g curry	Regular diet	NS	90 d	FBG ↔; INS ↓; HOMA-IR ↓; HbA1c ↓
Tajadadi-Ebrahimi et al., 2014 [39]	Parallel, double-blinded	3	81; males (15) and females (66) with T2DM (76 analyzed) I: $n = 54$; C: $n = 27$	I: Synbiotic bread II: Probiotic bread	120 g (3 × 40 g)	Control bread	120 g (3 × 40 g)	8 wk	*FBG ↔; *INS ↓; *HOMA-IR ↓
Thakur, 2009 [40]	Parallel, blinding not stated	2	120; males ($n = 62$) and females ($n = 58$) with T2DM I: $n = 60$; C: $n = 60$	Wheat chapattis with flax gum	6 chapattis (5 g flax gum)	Wheat bread	6 chapattis	12 wk	FBG ↓; INS ↔; HOMA-IR ↔
Velikonja et al., 2018 [41]	Parallel, double-blinded	2	43; males ($n = 10$) and females ($n = 33$) with or with high risk of MS I: $n = 27$; C: $n = 16$	Wheat bread with barley β-glucan	200 g	Wheat bread	200 g	4 wk	FBG ↔; INS ↔; HOMA-IR ↔; OGTT↔
Yanni et al., 2018 [42]	Parallel, single-blinded	2	30; males and females with T2DM I: $n = 15$; C: $n = 15$	Chromium-enriched whole wheat bread	112 (4 × 28) g	Whole wheat bread	112 (4 × 28) g	12 wk	FBG ↓; INS ↓; HbA1c ↓; OGTT ↓; HOMA-IR ↓

[1] ↔ indicates no difference between the intervention and control groups for the respective outcome of interest. ↓ indicates significant difference (lower values) in the intervention group compared with the control group for the respective outcome of interest.

[2] In the hyperglycemic group. C, control group; FBG, fasting blood glucose; I, intervention group; INS, insulin; MS, metabolic syndrome; NS, not stated; T2DM, type 2 diabetes mellitus.

Data extraction

Data extraction was performed independently by two reviewers (AMS, IR) pertaining to data on methodological aspects, interventions, and outcomes of the included studies using a standardized form. The data extracted included sex, age, health condition (i.e., healthy participants, participants with conditions related to cardiometabolic metabolic health such as hypertension, hyperglycemia, hypercholesterolemia and/or overweight and obesity, participants with manifest T2DM), type of bread, the addition of functional ingredients, amount of bread consumed, duration of the intervention period, study design, number of intervention arms, recruitment, randomization procedure, and the end points analyzed, including fasting blood glucose, fasting insulin, HOMA-IR, postprandial glucose responses, and HbA1c (Supplemental Table 2). Data presented in the graphs were extracted using WebPlotDigitizer version 4.5 [56]. All corresponding authors of the included studies were contacted by mail and requested to contribute individual participant data for the meta-analysis.

The primary end point, which was investigated in all included studies, was mean difference (MD) in fasting blood glucose concentrations between the intervention and control. Secondary end points were MD in fasting insulin concentration, calculated HOMA-IR, and HbA1c percentage, and standardized MD (SMD) in postprandial glucose responses. The units of measurements used were mmol/L for blood glucose concentrations, pmol/L for insulin concentrations, and % for HbA1c. Data not presented in the aforementioned units were converted using the following factors: blood glucose concentrations reported as mg/dL were converted by the factor 1 mg/dL = 0.55 mmol/L, insulin concentrations reported in mU/mL were converted using the factor 1 mU/mL = 6.00 pmol/L [15], and HbA1c reported as mmol/mol was converted using the formula [HbA1c %] = 0.0915 * [HbA1c mmol/mol] + 2.15 [16, 17].

For parallel-design studies with >2 arms, the experimental groups were combined as described in the Cochrane handbook [18]. For crossover-design studies, only data from the most relevant experimental group and the control group were extracted. The selection of the appropriate group to include was based on the characteristics of the intervention and the similarity to the other studies. If not otherwise specified, end-of-study values from all participants in the intervention and control groups were extracted and used in the meta-analyses. A further description of the data used can be found in Supplemental Method 1.

Risk of bias assessment

The risk of bias within the eligible studies was assessed using the Cochrane Risk of Bias 2 tool [19]. The tool identifies the risk of bias by assessing the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results. Bias arising from period and carryover effects were also included when assessing crossover-design studies. Two independent authors (AMS, IR) assessed the risk of bias within the eligible studies separately. Any inconsistencies between the authors were resolved through discussion until consensus.

Rating the certainty of evidence

The certainty of the body of evidence was rated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [20] as either high, moderate, low, or very low. The GRADE approach provides transparency in nutritional research when rating the certainty of evidence [21]. Randomized clinical trials (RCTs) start at high certainty evidence and can then be downgraded based on prespecified criteria: risk of bias (assessed using the Cochrane Risk of Bias 2 tool), inconsistency (substantial and unexplained between-study heterogeneity, $I^2 \geq 50\%$), indirectness (presence of factors that limit the generalization of the results), imprecision [low number of participants in the intervention and control groups ($n < 400$)], and publication bias.

Statistical analyses

Results are presented as MD and SMD for absolute values between treatments with 95% CIs. Because most studies did not report the mean change scores within or between the treatment groups, end-of-study values were used to avoid a large degree of data imputation, as recommended in the Cochrane handbook [18]. In cases where end-of-study values were not reported, change scores within each treatment group were applied. If not provided, SD was obtained from the standard error or the 95% CI according to equations in the Cochrane handbook [18], see Supplemental Method 1 for additional information. Data were extracted from the studies unless individual participant data were available, which was the case for four studies [22–25]. When studies reported multiple follow-ups, the most recent and appropriately reported data were used in the analyses.

A random-effects model applying generic inverse variance was used to pool the effect sizes. The effect sizes are bias-corrected MD and SMD. The heterogeneity of variance τ^2 was calculated using the restricted maximum likelihood estimator [26]. Hartug–Knapp adjustments [27] were applied to calculate the CIs around the pooled effect. Statistical heterogeneity of treatment effects between the studies was assessed by Cochran's Q test and I^2 inconsistency test. Sensitivity analyses were conducted if the I^2 value was >50% or if the P value was <0.10, indicating high heterogeneity. Outliers were identified through influence analyses and the leave-one-out method. If the metrics from the influence analyses provided extreme values, adjusted analyses were performed without the identified outliers. Subgroup analyses were performed for predefined variables such as manifest T2DM (yes/no), type of intervention and control treatment, duration of intervention period, continent of study origin, and study design, assuming an independent τ^2.

To further explore potential explanatory factors, mixed-effects model meta-regressions were applied where the pooled effect estimates from ≥10 studies were available. Covariates in the regression model included the predefined variables T2DM ("yes" or "no"), the continent of study origin ("Europe, North America, and Oceania" or "Asia"), and study duration (in weeks). In addition, univariate meta-regressions were applied to explore the relevance of the content of dietary fiber in the intervention and control treatments (in g/100 g bread) as well as the daily amount of bread (in g/day) consumed by the participants.

Publication bias was assessed for each outcome of interest using visual inspection of contour-enhanced funnel plots and quantified by Egger's test. When SMD was used as effect size, Egger's test applying the Pustejovsky–Rodger's approach was used. In case of evidence of publication bias, the Duval & Tweedie trim-and-fill method was used to adjust funnel plot asymmetry with and without the identified outliers.

The statistical analyses were performed in R, version 4.1.3 (*RStudio Team, 2020)* using the R packages *meta* [28], *metafor* [29], and *metasens* [30]. Additional information on the packages used is available in Supplemental Method 2.

Results

Search results

Of 4667 records identified in the systematic literature search, 223 studies were assessed for eligibility by full-text review (Figure 1). Of these, 22 studies [22–25, 31–48] were eligible for inclusion. One of the studies [33] investigated 2 individual populations (participants with normoglycemia and hyperglycemia) where each population had its own intervention and control group. The two populations were included separately in the meta-analyses, thus the meta-analysis consisted of 22 studies and 23 distinct study populations.

Study characteristics

All studies were RCTs, 12 of which had a crossover design [23–25, 31, 33–37, 44, 45, 48], and 10 had a parallel design [22, 32, 38–43, 46, 47] (Table 2). In total, 1037 participants were included. These provided 669 and 595 data points for intervention and control comparisons, respectively. The study population consisted of 47% males and 53% females. Six studies included healthy participants [25, 31, 33, 36, 37, 48], eight included participants with manifest T2DM [32, 34, 38–40, 42, 46, 47], and nine studies included participants at cardiometabolic risk [22–24, 33, 35, 41, 43–45], such as the metabolic syndrome [35], hypertension [44], hypercholesterolemia [24], hyperglycemia [33], and overweight and obesity [22, 23, 43]. Thirteen studies were from Europe [23–25, 31, 32, 36, 37, 41–45, 48], one was from North America [33], one was from Oceania [22], and seven were from Asia and the Middle East [34, 35, 38–40, 46, 47]. The study duration ranged from 3 to 16 wk, and the washout periods in the crossover studies lasted from 2 to 8 wk.

Eleven studies investigated functional-ingredient bread [21, 22, 25, 30–32, 35, 38, 39, 40, 42], eight studies investigated fiber-enriched or whole-grain breads [32, 33, 38, 40, 41, 45, 47, 48], and three studies investigated high-protein breads with lupin [22], soybean [34], or quinoa [23]. Most studies used wheat bread as a comparator [22, 23, 25, 32, 33, 36, 37, 40, 41, 44, 45, 47, 48], whereas three studies used various types of whole-grain breads [31, 42, 43], two used β-glucan-enriched breads [24, 46], two used habitual diet [34,38], and for two studies, it was unclear which kind of bread was used as the comparator [35, 39]. See Supplemental Table 3 for bread characteristics and nutritional values.

All studies reported fasting blood glucose [22–25, 31–48], 16 studies reported fasting insulin [22–25, 31–34, 38–42, 44–46, 48], 13 reported HOMA-IR [22, 25, 32–34, 38–42, 44–46], six studies reported HbA1c [25, 32, 34, 38, 42, 46], and eight studies reported postprandial glucose responses [25, 31, 33, 41, 42, 45, 47, 48].

Risk of bias

Concern for risk of bias mainly arose from the selection of the reported results as most studies did not have a prespecified analysis plan, which led to the overall judgment of "some concern" for most of the studies (Supplemental Figures 1 and 2). Other sources of bias were missing information on the allocation and randomization process [32, 34, 38, 40, 47], lack of information on the washout period [31, 35], and the study duration being too short to fully assess changes in HbA1c, i.e., lasting ≥8 wk [25, 32, 34]. Studies having ≥3 domains of "some concern" were judged to have a high overall risk of bias [40, 47]. Further information on the risk of bias assessment is provided in Supplemental Figures 1 and 2.

Fasting blood glucose

When considering all eligible studies (22 RCTs, 23 distinct studies), regardless of the type of bread and manifest T2DM (yes/no), the fasting blood glucose concentrations improved with the interventions compared with the controls (MD: −0.21 mmol/L; 95% CI: −0.38, −0.03; moderate certainty of evidence) (Figure 2). The between-study heterogeneity of variance was estimated at τ^2 of 0.09 (95% CI: 0.04, 0.34), with I^2 of 88% (95% CI: 84%, 92%).

Influence analyses identified the data from Mohtashami [35], Tajadadi-Ebrahimi et al. [39], and Thakur et al. [40] (participants with metabolic syndrome or T2DM) to significantly influence the pooled results for fasting blood glucose concentration. Adjusted analyses removing the influential cases changed the pooled effect estimate to −0.05 mmol/L (95% CI: −0.11, 0.02; I^2 = 0%) (Supplemental Table 4).

Subgroup analyses (Supplemental Table 5) revealed that the effect on fasting blood glucose was confined to participants with manifest T2DM, with no significant effect among participants without a manifest T2DM (−0.68 mmol/L; 95% CI: −1.11, −0.36; I^2 = 57% and −0.04 mmol/L; 95% CI: −0.13, 0.05; I^2 = 25%, respectively; $P < 0.001$; Figure 3). Further subgroup analyses by health condition (i.e., healthy compared with at cardiometabolic risk compared with manifest T2DM) corroborated a significant effect for those with manifest T2DM, yet no significant effect among either healthy persons ($P = 0.930$) or persons at cardiometabolic risk ($P = 0.286$), Supplemental Table 5. Subgroup analyses by continent revealed a more pronounced effect on fasting blood glucose concentrations in studies conducted in Asia and the Middle East compared with studies conducted in Europe, North America, and Oceania (MD: −0.84 mmol/L; 95% CI: −1.35, −0.33; $I^2 = 52\%$ and MD: −0.04 mmol/L; 95% CI: −0.10, 0.03; I^2 = 0%, respectively; $P < 0.001$). Further subgroup analyses found that the type of control bread, but not the type of intervention bread, affected the pooled effect estimate of fasting blood glucose concentration ($P = 0.03$), with the largest difference reported in studies not describing the control bread used [35, 39]. The subgroup analyses also revealed that the effect estimate differed by study design, with a more pronounced effect on fasting blood glucose being observed in parallel design compared with crossover-design studies (MD: −0.38 mmol/L; 95% CI: −0.65, −0.10; $I^2 = 90\%$ and MD: −0.01 mmol/L; 95% CI: −0.06, 0.04; $I^2 = 0\%$, respectively; $P = 0.005$). Additional subgroup analyses did not reveal differences by study duration or by type of intervention bread.

Overall, the multivariate meta-regression model including the covariates continent ("Europe, North America, and Oceania" or "Asia"), T2DM ("yes" or "no"), and study duration (in wk), showed a significant association of continent ($\beta = 0.76$; 95% CI: 0.30, 1.22), but not with T2DM ($\beta = -0.19$; 95% CI −0.65, 0.27) or duration ($\beta = 0.00$; 95% CI: −0.2, 0.02) with the magnitude of the difference in fasting glucose concentrations between intervention and control group. The univariate meta-regressions did not find associations between the magnitude of the difference and the dietary fiber content of the intervention and control bread, or the daily amount of bread consumed (data not shown).

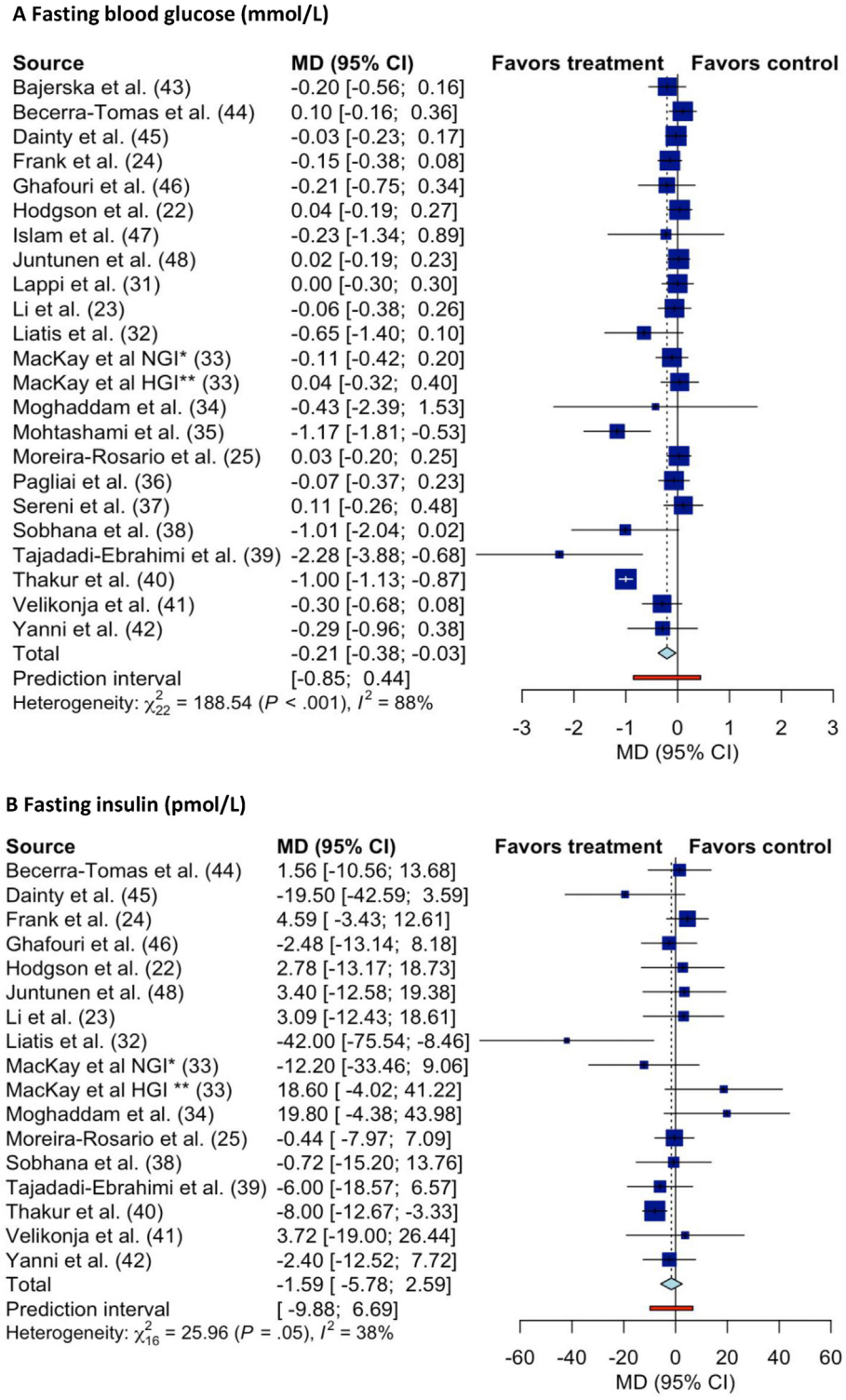

FIGURE 2. Forrest plots showing mean differences (MDs) in (A) fasting blood glucose (mmol/L) and (B) fasting insulin (pmol/L) between regular consumption of reformulated intervention breads and control breads/diets in healthy adults, adults at risk of cardiometabolic disease, and adults with manifest type 2 diabetes mellitus. Negative values show a decrease by the intervention treatment compared with the control treatment.

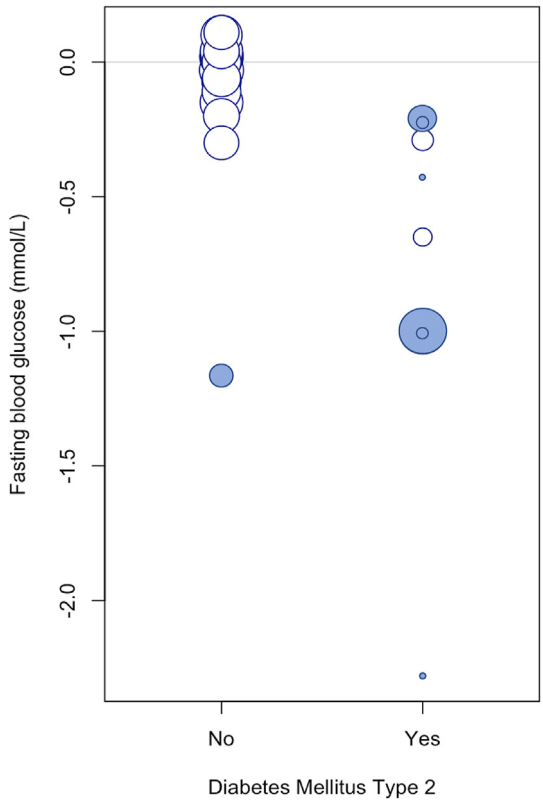

FIGURE 3. Bubble plot showing the mean differences in fasting blood glucose (mmol/L) between intervention and control treatments stratified by manifest type 2 diabetes mellitus status (yes/no). The blue bubbles represent studies from Asia, whereas the white bubbles represent studies from Europe, North America, and Australia.

Fasting insulin

Consumption of the intervention bread did not lower fasting insulin concentrations compared with the control breads (MD: −1.59 pmol/L; 95% CI: −5.78, 2.59; moderate certainty of evidence) (Figure 2). The between-study heterogeneity of variance was estimated at τ^2 of 11.87 (95% CI: 0.00, 118.69), with I^2 of 38% (95% CI: 0.0%, 66%).

Influence analyses identified the data from Liatis et al. [32] (participants with manifest T2DM) to significantly influence the pooled results for fasting insulin concentration. Adjusted analyses removing the influential case did not change the direction or significance level of the pooled effect estimate (−1.17 pmol/L; 95% CI: −4.88, 2.53; I^2 = 27%; Supplemental Table 4).

Subgroup analyses (Supplemental Table 5) found a statistically significant difference in fasting insulin concentrations between participants with manifest T2DM and those without manifest T2DM (i.e., either healthy or at cardiometabolic risk) (−5.45 pmol/L; 95% CI: −12.10, 1.21; I^2 = 45% and 1.52 pmol/L; 95% CI: −2.91, 5.95; I^2 = 0%, respectively; P = 0.038). Additional subgroup analyses did not reveal differences by continent, study duration, study design, type of intervention bread, or control bread. The multivariate meta-regression did not show any associations of continent, manifest T2DM, or study duration with the magnitude of the difference in insulin concentrations between intervention and control group, nor did the univariate meta-regressions reveal a relevance in the amount of dietary fiber in the intervention or control breads or the amount of bread consumed daily (data not shown).

HOMA-IR

Consumption of the intervention breads did not lower HOMA-IR compared with the control breads (MD: −0.09; 95% CI: −0.35, 0.22; moderate certainty of evidence) (Figure 4). The between-study heterogeneity of variance was estimated at τ^2 of 0.05 (95% CI: 0.01, 1.49), with I^2 of 60% (95% CI: 28%, 78%).

Influence analyses identified the data from Liatis et al. [32] to significantly influence the pooled results for HOMA-IR. Adjusted analyses removing the influential case did not change the direction or significance level of the pooled effect estimate (−0.08; 95% CI: −0.31, 0.15; I^2 = 56%; Supplemental Table 4).

Subgroup analyses (Supplemental Table 5) found the type of intervention bread to significantly influence the effect estimates for HOMA- IR, with high-dietary fiber breads having a more pronounced effect on HOMA-IR compared with functional-ingredient breads and protein-rich breads (−0.27; 95% CI: −0.52, −0.01; I^2 = 58% and 0.04; 95% CI: −0.47, 0.27; I^2 = 45% and 0.18; 95% CI: −0.91, 1.29; I^2 = 0%, respectively; P = 0.004). Additional subgroup analyses did not reveal differences by T2DM status (yes/no), continent, study duration, study design, or type of control bread. The multivariate meta-regressions did not show any associations of continent, T2DM status (yes/no), or study duration with the magnitude of the difference in HOMA-IR between intervention and control, nor did the univariate meta-regressions assessing the amount of dietary fiber in the intervention and control breads and the daily amount of bread consumed (data not shown).

HbA1c

Six RCTs [25, 32, 34, 38, 42, 46] reported data on the effect of bread intake on HbA1c. Consumption of intervention bread did not lower HbA1c concentrations compared with the control bread (−0.14; 95% CI: −0.39, 0.10; P = 0.195; very low certainty of evidence, Figure 4). The between-study heterogeneity of variance was estimated at τ^2 of 0.03 (95% CI: 0.0, 0.28) with I^2 of 56% (95% CI: 0.0%, 82%). Influence analyses did not identify any statistically significant influential cases. Subgroup analyses were not carried out because of the low number of trials ($n < 10$) with HbA1c as an outcome.

Postprandial glucose responses

The results of the meta-analysis of the seven RCTs [25, 33, 41, 42, 45, 47, 48] (eight distinct study populations) reporting data on postprandial glucose responses are shown in Figure 4. Data from Lappi et al. [31] were not included as the values from the graph showing postprandial glucose responses could not be extracted. Consumption of intervention bread did not lower the postprandial glycemic response compared with control (−0.46; 95% CI: −1.28, 0.36; P = 0.226; low certainty of evidence). The between-study heterogeneity of variance was estimated at τ^2 of 0.62 (95% CI: 0.2, 4.81), with I^2 of 74% (95% CI: 48%, 87%).

Influence analyses identified the data from Islam et al. [47] to significantly influence the pooled effect for postprandial glucose responses. Adjusted analyses removing the influential case did not change the direction or significance level of the pooled effect estimate (−0.17; 95% CI: −0.45, 0.11; I^2 = 0%; Supplemental

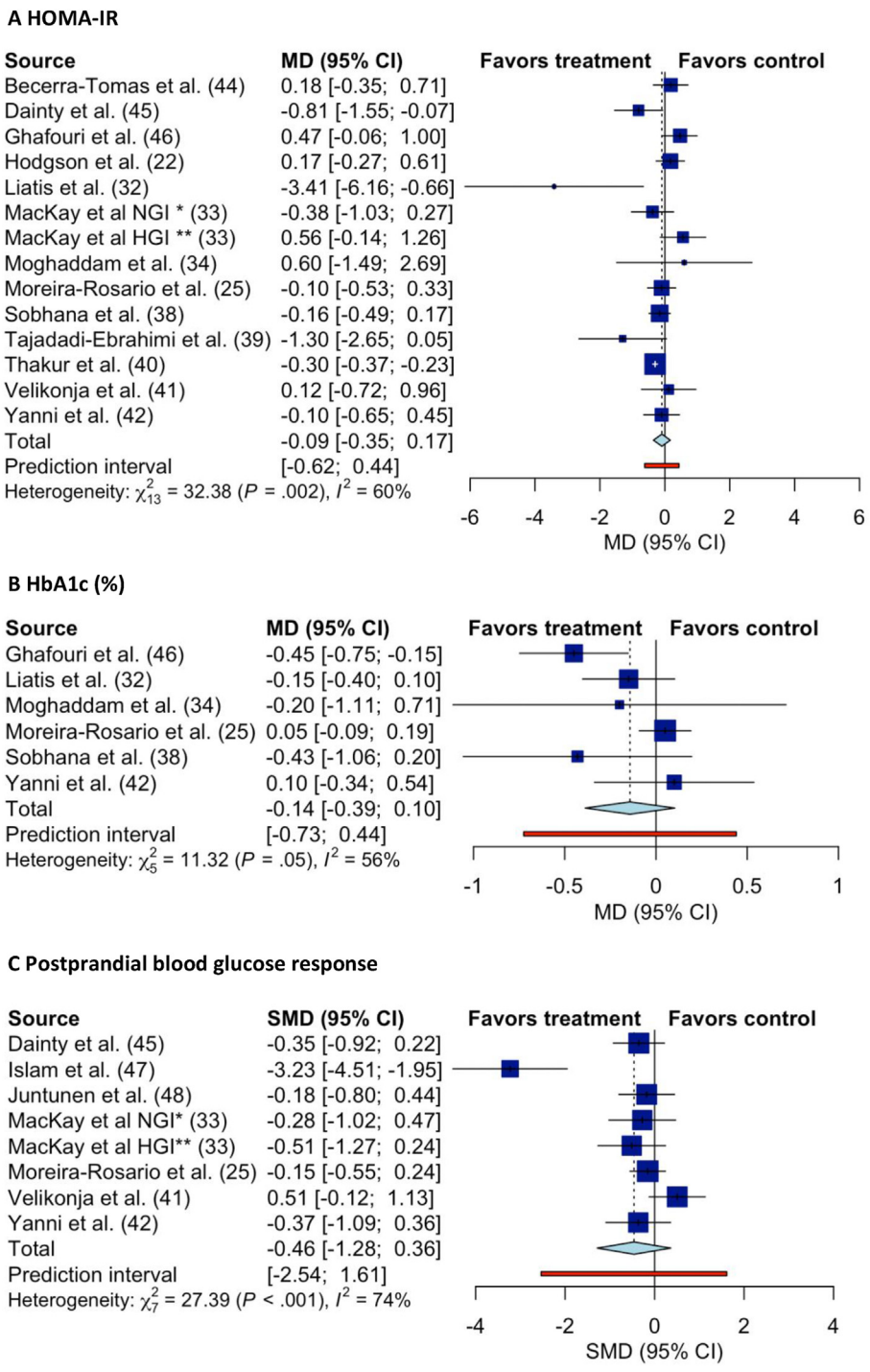

FIGURE 4. Forrest plots showing mean differences (MDs) in (A) HOMA-IR and (B) HbA1c and standardized mean differences (SMDs) in (C) postprandial glucose response between regular consumption of reformulated intervention breads (treatment) and control bread/diets (control) in healthy subjects, subjects at risk of cardiometabolic disease and with manifest type 2 diabetes mellitus. Negative values show a decrease by the intervention treatment compared with the control treatment.

Table 4). Subgroup analyses were not carried out because of the low number of trials (n < 10) with postprandial glucose response as an outcome.

GRADE

The certainty of evidence was moderate for fasting blood glucose, fasting insulin, and HOMA-IR (Supplemental Table 6). The certainty of evidence for fasting blood glucose and insulin was downgraded once because of the substantial risk of bias in the individual studies (Supplemental Figures 1 and 2). The certainty of evidence for fasting blood glucose in subgroups of persons with or without manifest T2DM was low (Supplemental Table 6). The certainty of evidence for HOMA-IR was downgraded once because of a high degree of heterogeneity, which could not be explained by sensitivity analyses. The certainty of evidence was graded as very low for HbA1c and low for postprandial glucose response. Evidence for both outcomes was downgraded because of imprecision [wide 95% CI and low numbers of participants ($n < 400$)] and a substantial risk of bias. The evidence for HbA1c was also downgraded because of a high degree of heterogeneity, which could not be explained by sensitivity analyses (Supplemental Figure 3).

Publication bias analyses

Visual inspection of funnel plots for publication bias showed little evidence of asymmetry or small-study effects for any of the outcomes assessed (Supplemental Figure 4). Egger's tests were not statistically significant for any of the outcomes and did not provide evidence of publication bias (Supplemental Table 7).

Discussion

This review and meta-analysis are, to the best of our knowledge, the first to systematically investigate the effects of regular consumption of reformulated breads, i.e., enriched with dietary fiber, whole grains, or functional ingredients on measures of glycemic control. It summarizes the evidence and the certainty of evidence, of the metabolic effects of regular bread consumption from small-scale intervention studies. Taken together, analyses of data from 1037 participants in 22 RCTs suggest a beneficial effect of reformulated bread variants on fasting blood glucose concentrations. These analyses, however, do not provide evidence for improvement in other measures of glycemic control.

From a mechanistic point of view, it is surprising that benefits were confined to fasting blood glucose, as one would expect that repeated dampening of the acute blood glucose response would lead to a decreased insulin demand, which may ultimately benefit insulin sensitivity. If blood glucose spikes during the day were regularly reduced, one would furthermore expect beneficial effects on the HbA1c concentrations. However, these sustained benefits may require longer intervention periods; yet many of the included studies were of shorter duration than the known half-life for HbA1c turnover. In addition, the type of reformulation of the bread may be an important factor. Improvements in specific outcomes may also be linked to defined groups within populations such as persons with manifest T2DM.

Fasting blood glucose measurements were available from all studies because this was chosen as our primary outcome. This is attributable to practical reasons as fasting blood glucose concentrations are generally reported even in studies not addressing glycemic control as the primary outcome. By contrast, measurements of HOMA-IR or HbA1c, i.e., parameters reflecting the longer-term response to bread consumption, were only available from a few of the included studies. The studies reporting HbA1c used different methods to determine HbA1c concentrations, which might have augmented between-study differences. The standardization of the HbA1c method, as recommended by the WHO as a diagnostic criterion for diabetes mellitus [49], was initiated in 2002, but the implementation of the reference method in clinical laboratories is still ongoing [49, 50]. In addition to the different methods used, the study durations varied between 3 wk to 3 mo, yet HbA1c is considered to reflect average glucose levels of the past 8–12 wk. Of note, three of six studies reporting HbA1c lasted shorter than 8 wk and were thus judged as high risk of bias [25, 32, 34]. Hence, our ability to identify effects on fasting blood glucose may reflect the outcome-specific methodological limitations rather than outcome-specific mechanisms.

Beyond a mismatch between-study duration and captured timespan of HbA1c, a longer study duration may also be needed to elicit changes in markers of insulin resistance. However, it should be noted that our formal stratified analyses by study duration ($\leq$4 wk compared with >4 wk) and the meta-regressions exploring study duration (in wk) did not reveal statistically significant differences for fasting blood glucose or HOMA-IR, and such analyses could not be performed for HbA1c because of the small number of included studies reporting this outcome. Taken together, more longer-term studies (i.e., lasting $\geq$12 wk) are needed to examine the effects of regular consumption of reformulated breads on parameters of longer-term glycemic control, such as HbA1c and HOMA-IR.

The evidence available to date stems mainly from studies investigating the potential benefits of whole-grain intake on glycemic control. In a systematic review and meta-analysis investigating the effect of whole-grain intake on glycemic control among healthy subjects [8], analyses based on acute studies (14 studies examining postprandial responses $\leq$4 hours) supported a beneficial effect of whole grain (compared with diverse controls) on acute postprandial blood glucose responses. In contrast, meta-analyses based on studies with intervention periods lasting 2–16 wk did not report significant effects on fasting blood glucose concentrations or HOMA-IR [8]. Similarly, a meta-analysis including 80 studies comparing intake of whole grain to refined grain [7] confirmed acute improvements in postprandial glycemia and insulinemia, yet also revealed longer-term benefits of whole-grain consumption, which were confined to HbA1c percentage (6 studies with a duration of 4–16 wk) [7]. Contrary to our study, no effects were seen on fasting glucose (22 studies); however—in line with our study—they also reported no effects on fasting insulin (18 studies) or HOMA-IR (10 studies, lasting 6–16 wk) [7]. However, the comparison of our study to these meta-analyses is severely hampered by the fact that both included several whole-grain foods other than bread (e.g., oats, oatmeal, flakes, flours, biscuits, pasta, and rice), with no stratified analyses of studies assessing whole-grain bread intake [7, 8].

Alternatively, the lack of effects of the consumption of reformulated bread on HbA1c and HOMA-IR may be attributable to the great variation in the intervention and control treatments used in the included studies. Bread types, including those reformulated to improve its nutritional profile, differ notably around the world. This is also reflected by differences in the "reformulated variant" used in the included studies: studies from Poland [43] and Finland [48, 51] used rye bread, whereas the study from India [40] employed wheat chapattis. Overall, the rye intervention breads were characterized by higher fiber content than the wheat intervention breads (Supplemental Table 3). In addition, the employed intervention breads also varied in the extent to which they included whole grain. The subgroup analyses found high-fiber intervention breads to have a more pronounced effect than functional-ingredient and protein-rich breads, but this was only found to be statistically significant for HOMA-IR (n = 9, >10 g fiber/100 g). This is in line with the result of another systematic review and meta-analysis investigating the effects of dietary fiber on glycemic control and insulin sensitivity among 911 patients with T2DM [52], based on 22 RCTs, which reported reduced HOMA-IR following consumption of a median of 10 g/d of dietary fiber over a study period of 8 wk.

Contrary to our findings, they reported benefits for HbA1c and fasting insulin in addition to benefits for fasting blood glucose.

The reformulated bread types included and studied in our meta-analysis vary widely in terms of the type of whole grains used, and whole grain and dietary fiber content (Supplemental Table 3). Of note, some reformulations may incur a higher/altered processing, hence reformulated breads as defined here are not synonymous to less-processed breads. In addition, various functional ingredients were used, such as β-glucan [24], green tea extract [43], and sourdough [36]. These functional ingredients may also affect the GI of the breads. Unfortunately, GI was not reported in the studies included in this review, but it is known to be lower in β-glucan–enriched or sourdough breads [53, 54]. In contrast, contrary to popular belief, most commonly consumed whole-grain breads have a medium to high GI [9], whereas most whole-kernel breads have medium to low GI values. Because consumption of diets high in GI (or glycemic load) are known to increase the risk for T2DM [5], it is plausible that the habitual consumption of whole-grain breads with a lower GI (with or without functional ingredients) could beneficially affect longer-term glycemic control.

Overall, heterogeneity was only considerable for the outcome fasting glucose. However, subgroup analysis revealed that the effect of regular consumption of reformulated bread on fasting blood glucose was confined to adults with manifest T2DM, i.e., we could identify a major source of heterogeneity. Persons with T2DM profited concerning their fasting insulin concentrations, whereas no effects were seen among healthy participants or participants merely at cardiometabolic risk. Because of the low number of trials investigating HbA1c and postprandial glucose responses, subgroup analyses were not carried out for these outcomes. However, the certainty of evidence for the relevance of reformulated bread among persons with T2DM is still low, requiring additional studies. Although an average reduction of fasting blood glucose by 0.68 mmol/L among persons with T2DM may appear small compared with 25%–30% reductions following drug treatment [55], it should be judged as substantial from a public health nutrition perspective given that bread is only one—albeit commonly important—component of the everyday diet.

Meta-regression analyses suggest that continent may be more relevant than T2DM, yet this appears to be a chance finding, as continent and presence of T2DM showed a large overlap in our meta-analysis (Figure 3). Although it is plausible that persons with manifest T2DM are particularly receptive to the benefits of breads yielding lower postprandial blood glucose excursions, it remains to be established whether the benefits extend to persons at risk of T2DM. Analyses of the trajectories to manifest T2DM revealed that decreased insulin sensitivity and increased fasting glucose emerges 5 and 3 years before the diagnosis of T2DM, respectively [57]. Hence, bread types requiring lower insulin demand could be of benefit for this relatively large group of persons.

Although publication bias was considered negligible for the studies included in this meta-analysis, the risk of bias assessment revealed that most of the studies had some concerns of risk of bias. This was mostly because studies did not provide a prespecific analysis plan, yet other studies also lacked information on the randomization process and the washout period applied. Hence, future studies should establish a prespecified analysis plan beforehand and clearly describe the applied randomization process and the washout period. Further, the GRADE assessment found the certainty of evidence to be moderate to very low for all included outcomes, suggesting that further studies on the relevance of reformulated bread for glycemic control are needed.

The strengths of this systematic review and meta-analysis include the focus on high-quality intervention studies (i.e., RCTs using either crossover or parallel design) and the inclusion of longer-term studies (≥2 wk) to address the effectiveness of regular bread replacement for glycemic control in everyday life. Similarly, the focus on reformulated, presumably "healthier" bread varieties worldwide allows estimating the benefit of using such breads in our everyday life. We hence excluded acute effect studies, which were considered in other meta-analyses (7, 8). Acute studies may only provide information on the theoretical efficacy, not long-term health effects. Our data provide novel direct evidence for food-based dietary guidelines, which have to date relied on indirect evidence stemming from studies on potentially relevant nutrients in bread. However, the great variety of reformulated bread types can also be seen as a limitation, impeding the identification of ingredients/components potentially of mechanistic relevance. Further limitations include the lack of reported details of the breads, i.e., the content of metabolizable starch or type of dietary fiber, or habitual diets used as control, as well as some of the studies reporting changes in HbA1c had a shorter duration than the period of 8–12 wk HbA1c is considered to reflect. Another source of heterogeneity is the variation in study duration ranging from 3 to 16 wk.

In conclusion, our analysis provides evidence that regular consumption of the reformulated "healthier" bread variants probably exerts beneficial effects on fasting blood glucose concentrations in adults (moderate certainty of evidence). This benefit may be more pronounced among people with manifest T2DM (low certainty of evidence). Our data suggest that bread quality is relevant for metabolic health among adults and that future studies should address its relevance among people at risk of T2DM.

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Author disclosures

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bias, undertaking meta-analyses, and for rating of the certainty of evidence. AM-R, JF, JH, CS: contributed with independent participant data. AM-R, JD, JF, JH, CS: contributed with critical review and input to the article. AEB, HR-R: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2022.10.008.

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