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Effects of whole grain intake on glycemic control: A meta-analysis of randomized controlled trials

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ABSTRACT

Aims/Introduction: Although mounting evidence has suggested an inverse association between the intake of whole grains and glycemic control, findings from randomized controlled trials are still conflicting. The current study was carried out to evaluate the effect of medium/long-term whole grain intake on glycemic control in metabolic syndrome and healthy populations.

Materials and Methods: A literature search was carried out to identify qualified studies up to July 2021. The effects of whole grain consumption on glycemic control were calculated using a fixed effects model. Subgroup analysis was used to study whether grouping factors were important influencing factors of heterogeneity between research results.

Results: A total of 32 randomized controlled trials with 2,060 participants were included in the analyses. Whole grain consumption showed a significant inverse regulatory effect on fasting glucose concentration, but no significant effect was found for other glycemic measures, such as fasting insulin, homeostatic model assessment for insulin resistance, glycated hemoglobin and 2-h glucose, in the pooled analysis. Through subgroup analyses, a significant decrease in fasting glucose concentration was observed for studies with a higher whole grain dose, with participants of normal glycemia, and with mixed types of whole grain.

Conclusions: Medium-/long-term whole grain intake reduced the fasting glucose concentration compared with similar refined foods. Appropriate intervention dose and accurate population selection might be the key links for whole grain consumption to exert its glycemic control effect.

INTRODUCTION

Glycemic control, as a basic physiological function of the body, is important to maintain individual health[1]. However, for metabolic disorders, glycemic homeostasis is usually impaired and brings undesired hazards. Diabetes is considered to be a group of metabolic disorders as a result of the lack of insulin secretion, insulin activity, or both[2]. According to epidemiological research data, approximately 422 million people suffer from diabetes worldwide, and this figure has risen sharply[3]. The ensuing complications lead to numerous deaths and a heavy burden on medical systems. Recently, dietary intervention strategies have attracted increasing attention in diabetes treatment, because compared with hypoglycemic drugs, dietary intervention strategies have fewer side-effects and are more cost-effective[4–6].

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Among the existing dietary adjustment strategies, increasing intake of whole grains has been widely investigated for glycemic control[7]. A recent meta-analysis including cohort studies suggested that increased whole grain food intake could reduce the risk of diabetes[8]. Evidence from another observational study also showed an inverse dose–response relationship between whole grain consumption and the incidence rate of type 2 diabetes mellitus[9]. It is worth noting that most studies have emphasized that the observed effect of whole grain intake is an increased sensitivity of insulin rather than a decrease in postprandial glycemia[10]. However, several recent studies suggest that whole grains can directly bring changes to postprandial blood glucose[11,12]. Thus, data on whether whole grains improve glucose control and the detailed mechanism of this effect remain conflicting. Although the results of a meta-analysis have been reported, that study only included populations with specific health statuses and did not set the duration of the whole grain intervention. As a supplementary study with better evidence, the current study was carried out to evaluate the effect of medium-/long-term (≥2 weeks) whole grain intake on glycemic control in metabolic syndrome and healthy populations by including randomized controlled studies.

MATERIALS AND METHODS

Search strategy

PubMed (up to July 2021; http://www.ncbi.nlm.nih.gov/pubmed/), Embase (up to July 2021; http://www.embase.com/search/advanced/) and the Cochrane Library (up to July 2021; http://www.cochrane.org/) were searched in all fields with the following terms: wholegrain, whole grain, whole meal, wheat, whole wheat, rice, wild rice, brown rice, oat, maize, rye, barley, corn, millet, triticale, sorghum, amaranth, canary seed, quinoa and buckwheat, paired with the following words: glucose, glycemic control, glycemic, glucose control, insulin sensitivity and insulin. Two researchers independently screened each report, and any discrepancies were resolved by consensus and arbitration by a third investigator.

Study selection

We selected studies that met the following criteria: (i) medium-/long-term treatment duration ≥2 weeks; (ii) parallel or cross-over designed randomized controlled studies with human participants; (iii) availability of end-point values for blood glucose, fasting insulin, homeostatic model assessment for insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c) with standard error or standard deviation or 95% confidence intervals (CIs) for the control and intervention groups; (iv) participants received whole grain diet or product intervention; (v) inclusion of an isoenergetic control group with lower levels or no whole grain content; (vi) sole difference between observational groups of intervention of whole grains, and distinguishability of the effect value; (vii) examining lack of examination of the effects of individual grain components; and (viii) no special restrictions on the health status of the participants.

Risk of bias and quality of evidence

We used the Cochrane risk of bias tool to evaluate the quality of the literature. The assessment tool mainly divides bias into the following aspects: selection bias, implementation bias, measurement bias, follow-up bias, reporting bias and other bias[13]. The evaluation was completed independently by two researchers. Any discrepancies were resolved with the participation of another coauthor. Trials were classified as being at a high risk of bias if one or more items were evaluated with a high bias risk, and at a low risk of bias if all of the items were evaluated with low bias risk, and all other trials were classified as being at unclear risk of bias.

Data extraction

The following study characteristics were extracted: (i) study characteristics, including publication year, author information, study design, treatment duration and sample size; (ii) population characteristics, including age, percentage of female subjects, body mass index (BMI) and participant health status; (iii) baseline and post-treatment values in fasting glucose, plasma insulin, HOMA-IR, HbA1c and 2-h glucose; and (iv) dietary information/foods provided in the intervention group and control group. The study values were converted to unified measuring units for data standardization.

Statistical analysis

We carried out the present meta-analysis using Stata version/SE 14.2 software (StataCorp, College Station, TX, USA). The postintervention values of anthropometric measures in the control and treatment groups were used to calculate the effect size. The outcomes of treatments were estimated using weighted mean differences (WMDs). The baseline and outcome values are shown in Table S1. The I^2 statistic and P-value were used to determine the study heterogeneity. The random effects model was chosen if significant heterogeneity was detected, and otherwise, the fixed effects model was chosen.

In the meta-analysis, we divided the research into subgroups according to the research characteristics of study design, treatment duration, type of whole grain, dose of whole grain, baseline mean BMI, glycemic condition, weight change and risk of bias. The purpose of subgroup analysis was to study whether the effect values were different in different populations or conditions. Funnel plots, Egger's regression test and sensitivity analyses were carried out. P-values <0.05 were considered statistically significant.

RESULTS

Results of the literature search

The flow chart of the search strategy and study selection is shown in Figure 1. In total, 5,710 articles were initially identified. A total of 5,565 articles were excluded, because they were irrelevant to the present meta-analysis or were duplicate publications. Of the 145 remaining articles, an additional 113 were excluded for the following reasons: the participants of 12

studies used treatment of individual grain components, 42 studies had an uncontrolled study design, 16 studies had incomplete data, 10 studies had a non-randomized study design, 22 studies lasted <2 weeks and for 11 studies the data could not be extracted. Thus, 32 articles were finally included in the present meta-analysis[14–45].

Study characteristics

A summary of the article characteristics is presented in Table 1. In total, 2,060 participants were included in the 32 included studies (18 parallel design and 14 cross-over design studies), and the number of participants in each study ranged from 11 to 206. A total of 13 randomized controlled studies were mixed whole grain interventions, and the other 19 trials examined the effects of individual whole grains. The intervention dose ranged from 45 to 301 mg/day (not reported in 8 studies), and the duration of treatment ranged from 3 to 16 weeks (median 8 weeks). According to the baseline mean BMI, 11 studies had obese populations (≥30 kg/m^2), and the other 21 studies had non-obese populations (<30 kg/m^2). A total of 25 studies included participants with normal glycemia, whereas the other seven studies included participants with hyperglycemia.

Risk of bias

The risk of bias of the studies included in the present meta-analysis was rated as moderate or low. Overall, 11 studies had a low risk of bias for random sequence generation, and two had a high risk of bias for allocation concealment. Three studies had a high risk of bias on blinding, and two were at high risk of bias on blinding of outcome assessment. Most articles were at low risk of incomplete outcome data, selective reporting and other biases. Specific details of this part of the work are presented in Table S2.

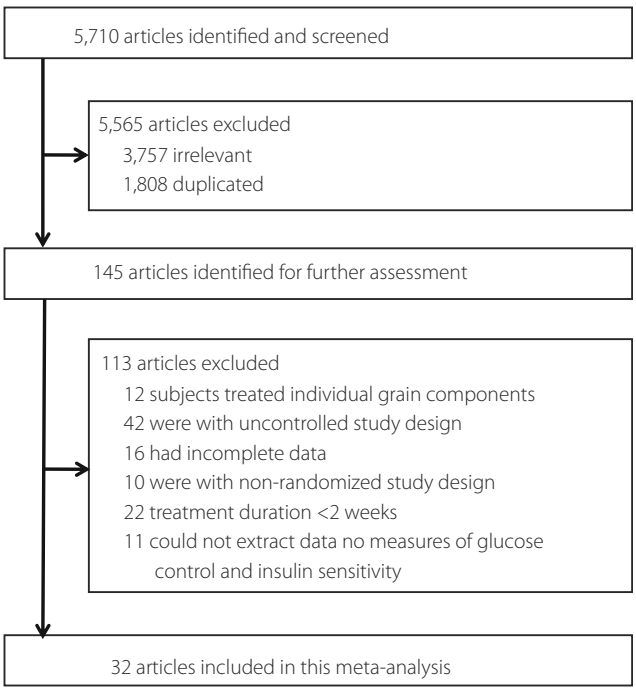

Figure 1 | Flow diagram showing the number of citations retrieved in individual searches of articles included in the review.

Effects of whole grain consumption on glycemic control and insulin sensitivity

As shown in Figure 2 and Table S3, a significant reduction in fasting glucose concentration was observed in participants supplemented with whole grain (WMD −0.05 mmol/L, 95% CI −0.10, −0.01 mmol/L) when compared with control participants. In addition, there were 27 studies investigating fasting insulin concentration change after whole grain consumption, but no significant differences were observed (WMD −0.12 mIU/mL, 95% CI −0.52, −0.29 mIU/mL; Figure 3 and Table S3). Furthermore, no positive effect of whole grain on HOMA-IR, HbA1c or 2-h glucose was observed by the pooled analysis (Figure S1 and S2, and Table S3). No significant between-study heterogeneity in the effects of whole grain intake on these measures was observed (Table S3).

Subgroup analysis was carried out by categorizing treatment duration into shorter- (<8 weeks) and longer-term subgroups (≥8 weeks). The dose of whole grain was divided into a higher dose (≥102.5 g/day) and a lower dose (<102.5 g/day). The baseline mean BMI was categorized as obese (≥30 kg/m^2) or not obese (<30 kg/m^2; Table 2). A significant reduction in fasting glucose concentration was observed for studies with higher whole grain doses (WMD −0.08 mmol/L, 95% CI −0.15, −0.02 mmol/L), and the subgroup analyses showed that whole grain consumption significantly lowered fasting glucose in mixed types of whole grain (WMD −0.10 mmol/L, 95% CI −0.17, −0.03 mmol/L; Table 2). Additionally, we found a significant reduction in insulin concentration for studies with only a cross-over design (WMD −0.74 mIU/mL, 95% CI −1.39, −0.08 mIU/mL; Table 2). Sensitivity analysis showed that the comprehensive effect of whole grain consumption on fasting blood glucose and insulin concentration did not change after interpolation with a correlation coefficient of 0.5. Finally, the systematic deletion of each trial during sensitivity analysis did not significantly change the overall effect of whole grain consumption on fasting blood glucose or insulin concentration.

Publication bias

The funnel plots were symmetrical, and Egger's test showed no significant publication bias in the meta-analysis of fasting insulin, fasting glucose, HOMA-IR or HbA1c (Figures S3–S6; Egger's test: P = 0.39, 0.89, 0.53 and 0.06, respectively).

DISCUSSION

The present study suggested that whole grain consumption effectively reduced fasting glucose concentration in metabolic syndrome and healthy populations, but the inverse regulation effect was not observed on other glucose-related measures, such

Table 1 | Characteristics of eligible studies

Author, year, country	Study design	No. participants	Duration (weeks)	Dose (g/day)	Age, years (mean)	BMI	Female (%)	Population	Whole grain group	Control group
Ampatzoglou, 2014, UK[14]	R, C	33	6	>80	48.8	27.9	63.6	Healthy	Mixed whole grain	Refined grain products
Andersson, 2007, Sweden[15]	R, C	30	6	112	59	28.3	26.7	Overweight and obesity	Mixed whole grain	Refined grain products
Charlton, 2012, Australia[16]	R, P	87	6	137	51	27.3	56.7	Hypercholesterolemia without diabetes mellitus	Oats	Refined grain products
Connolly, 2016, UK[17]	R, C	15	6	45.0	42	26.4	63.3	Risk of developing cardiometabolic disease	Oats	Refined grain products
Giacco, 2013, Finland/Italy[18]	R, P	123	12	185	40–65	31.6	52.8	Metabolic syndrome	Mixed whole grain	Refined grain products
Giacco, 2014, Finland/Italy[19]	R, P	54	12	136	57.2	31.7	57.4	Metabolic syndrome	Mixed whole grain	Refined grain products
Giacco, 2009, Finland/Italy[20]	R, C	15	3	NR	54.5	27.4	20	Healthy	Wheat	Refined grain products
Jackson, 2014, USA[21]	R, P	48	12	163–301	46.4	32.9	50	Overweight and obesity	Mixed whole grain	Refined grain products
Karl, 2017, USA[22]	R, P	80	6	207	54.5	25.7	39.5	Overweight and obesity	Mixed whole grain	Refined grain products
Katcher, 2008, USA[23]	R, P	50	12	NR	46	35.5	50	Metabolic syndrome	Mixed whole grain	Refined grain products
Kazemzadeh, 2014, Iran[24]	R, C	35	6	150	32.6	29.8	100	Overweight and obesity	Brown rice	Refined grain products
Kikuchi, 2019, Japan[25]	R, P	49	12	88.4	47.7	27.4	34.7	Obesity	Wheat	Refined grain products
Kirwan, 2016, USA[26]	R, C	33	8	93	39	33.1	51.5	Overweight and obesity	Mixed whole grain	Refined grain products
Kondo, 2016, Japan[27]	R, P	28	8	150	66.7	24.6	55.6	Type 2 diabetes	Brown rice	Refined grain products
Kristensen, 2012, Denmark[28]	R, P	72	12	105	59.7	30.2	100	Overweight	Wheat	Refined grain products
Liatis, 2009, Greece[29]	R, P	41	3	NR	63	28.5	43.9	Type 2 diabetes	Oats	Refined grain products
Liu, 2018, China[30]	R, P	110	5	<69 >69	58	26.5	54.5	Type 2 diabetes	Wheat	Refined grain products
Malik, 2019, USA[31]	R, C	166	12	127.5	37.1	28.1	45	Overweight	Brown rice	Refined grain products
Malin, 2019, USA[32]	R, C	13	8	100	37.2	33.6	76.9	Overweight and obesity	Mixed whole grain	Refined grain products
McIntosh, 2003, Australia[34]	R, C	28	4	NR	40–65	30	0	Overweight	Wheat Rye	Refined grain products
Pereira, 2002, USA[35]	R, C	11	6	NR	41.6	30.2	54.5	Overweight and obesity	Mixed whole grain	Refined grain products
Pick, 1998, Canada[36]	R, C	11	12	NR	51	27.4	0	Type 2 diabetes	Barley	Refined grain products
Pins, 2002, USA[37]	R, P	88	12	60	48.6	30.9	48.9	Hypertension without diabetes mellitus	Oats	Refined grain products
Roager, 2017, Denmark[38]	R, C	50	8	179	20–65	29	36.0	Metabolic syndrome	Mixed whole grain	Refined grain products
Schutte, 2018, Netherlands[39]	R, P	50	12	98	61	27.8	62	Overweight with mildly elevated levels of plasma total cholesterol	Wheat	Refined grain products
Shimabukuro, 2013, Japan[40]	R, C	27	8	NR	NR	26·7	0	Obese and metabolic syndrome	Brown rice	Refined grain products
Steven, 2017, USA[33]	R, C	14	8	90.5	38	34	78.6	Overweight and obesity	Mixed whole grain	Refined grain products
Tighe, 2010, UK[41]	R, P	206	12	100–120	51.8	28	50.4	Overweight	Mixed whole grain wheat	Refined grain products
Vitaglione, 2015, Slovenia[42]	R, P	68	8	70	38.6	29.8	66.2	Overweight and obesity	Wheat	Refined grain products
Wang, 2013, USA[43]	R, P	57	12	NR	52.5	25.8	66.7	Prediabetes	Brown rice	Refined grain products
Zhang, 2011, China[44]	R, P	202	16	100	49.7	25.7	46.5	Diabetes or high risk for diabetes	Brown rice	Refined grain products
Zhang, 2012, China[45]	R, P	166	6	100	53.2	25.5	38.6	Hypercholesterolemia	Oats	Refined grain products

BMI, body mass index; BP, blood pressure; C, cross-over; CVD, cardiovascular disease; NR, not reported; P, parallel; R, random; WG, whole grain.

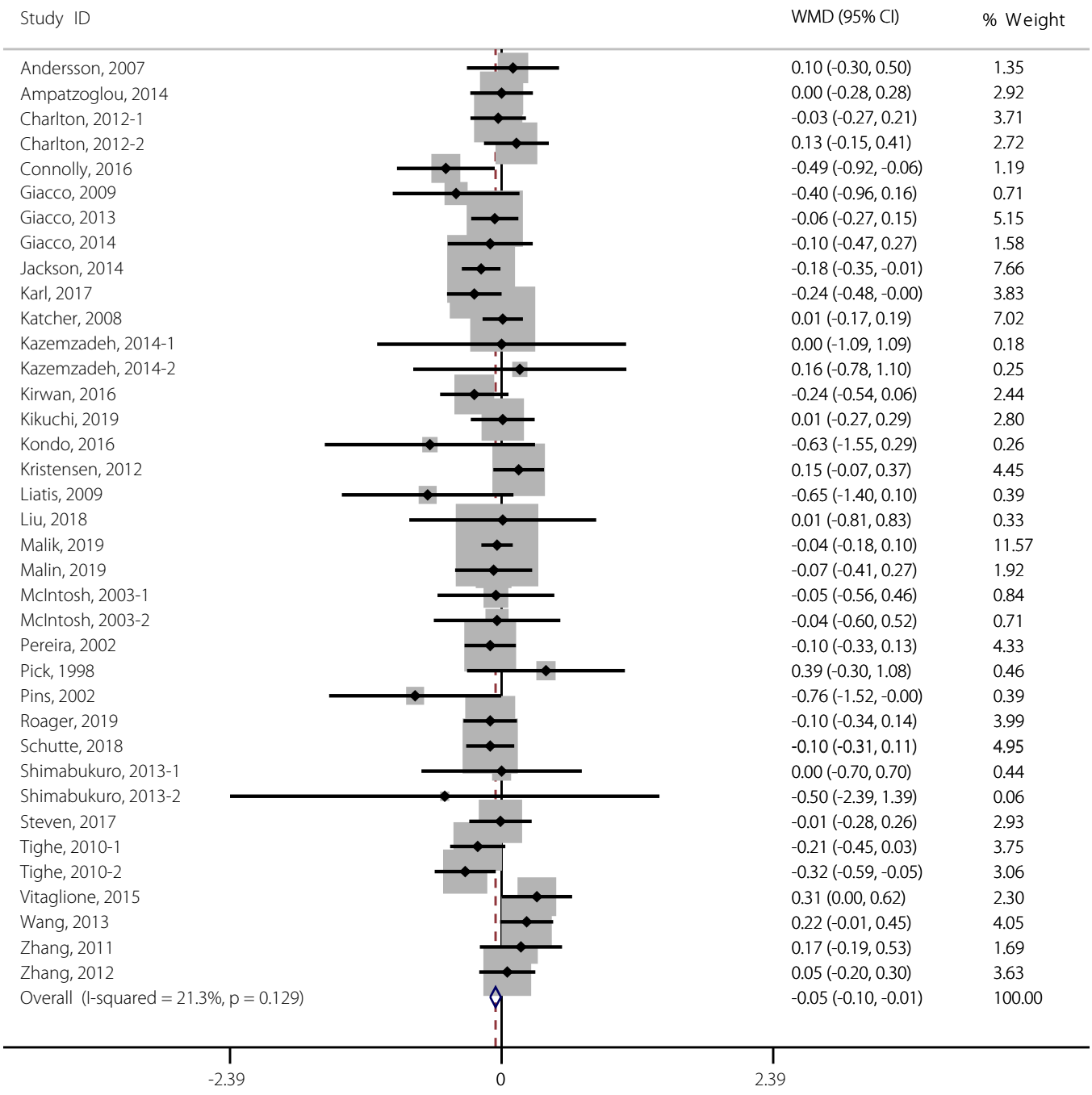

Figure 2 | Meta-analysis of the effects of whole grain on fasting glucose concentration. Weight was assigned with Stata (version 14.2; StataCorp, College Station, TX, USA) by using the number of participants and the standard deviation. Sizes of the data markers show the weight of each study in this analysis. The diamond represents the overall estimated effect and the result was obtained from a fixed effects model. WMD, weighted mean difference.

as fasting insulin consumption, HOMA-IR, HbA1c or 2-h glucose level. Furthermore, subgroup analysis showed that fasting blood glucose concentration was significantly decreased in studies with higher whole grain doses, participants with normal glycemic baseline or mixed types of whole grains.

Consistent with the present results, several studies confirmed the regulatory effect of whole grain on blood glucose levels. In a meta-analysis including 14 trials, Marventano *et al.*[11] explored the acute effects of whole grain intake on glucose control, and their results showed that whole grain intake significantly

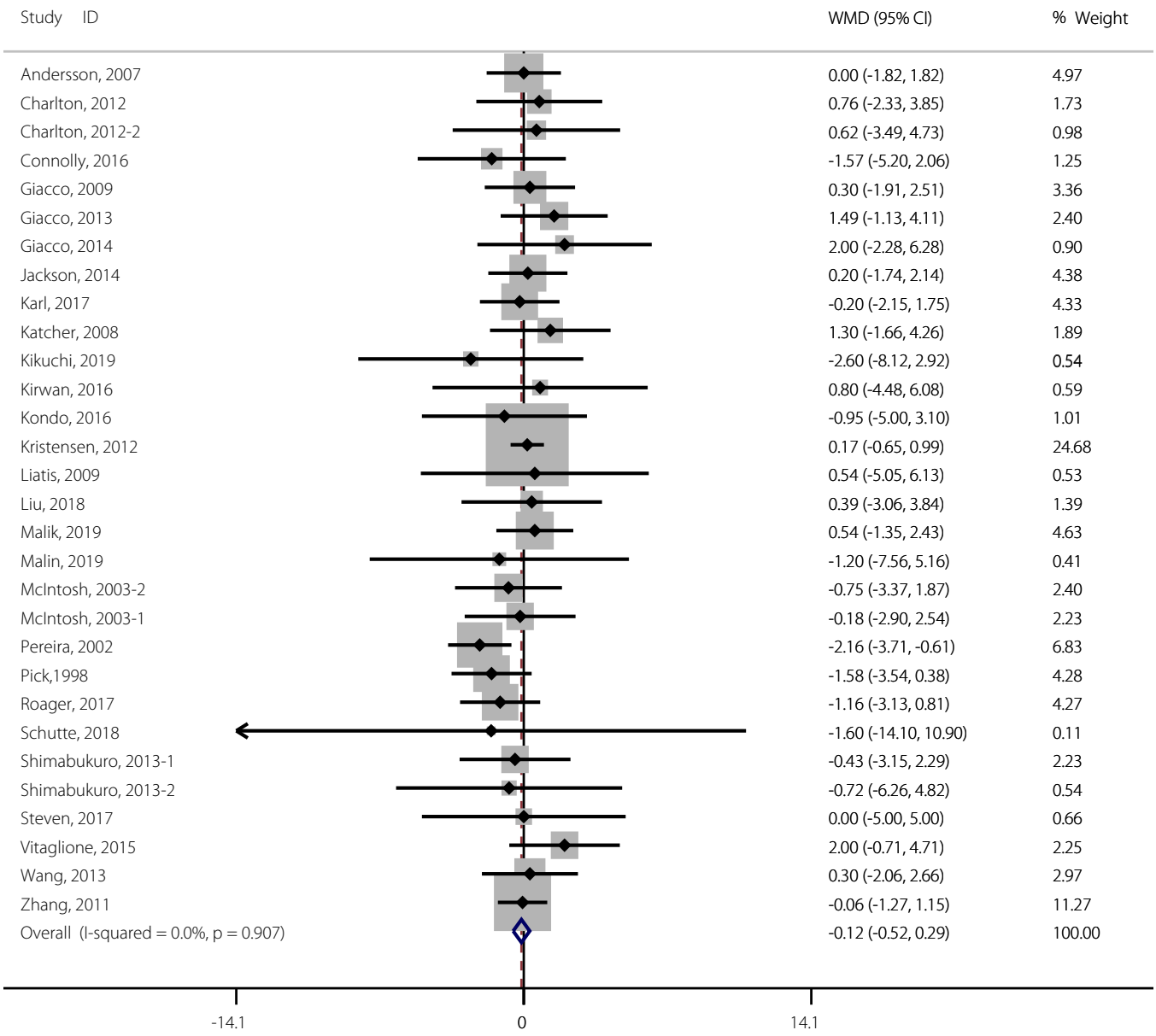

Figure 3 | Meta-analysis of the effects of whole grain on fasting insulin concentration. Weight was assigned with Stata (version 14.2; StataCorp, College Station, TX, USA) by using the number of participants and the standard deviation. Sizes of the data markers show the weight of each study in this analysis. The diamond represents the overall estimated effect, and the result was obtained from a fixed effects model. WMD, weighted mean difference.

reduced the postprandial glucose values by 29.71 mmol min/L. In another 12-week intervention study, the effects of different dietary carbohydrate sources on blood glucose concentrations were compared, and the blood glucose level in the unrefined carbohydrate group was improved significantly[12]. Of note, there was no significant association between the improvement of glucose-related measures and whole grain food consumption, suggesting that an effect on insulin sensitivity might be slight or none. This finding is supported by Andersson's research results; in healthy and moderately overweight adults, replacing refined grain products with whole grains did not show a beneficial effect on the sensitivity of insulin or other inflammation markers[15]. The underlying mechanism of the observed effects of whole grain consumption might involve the following aspects: (i) whole grains are a better source of fiber and nutrients, and generally have a lower glycemic index/load than refined grains[46]; (ii) multiple aspects of habitual consumption of whole grains seem to impact the effects of whole grain

Table 2 | Subgroup analyses of fasting glucose and insulin concentrations stratified by previously defined study characteristics

Variables	Fasting glucose				Fasting insulin			
	No. trials	Net change (95% CI) (mmol/L)	Test of heterogeneity†		No. trials	Net change (95% CI) (mIU/mL)	Test of heterogeneity†	
			P	I^2 (%)			*P*	I^2 (%)
Study design								
Parallel	18	−0.07 (−0.10, 0.02)	0.012	46.3	15	0.28 (−0.24, 0.80)	0.985	0.0
Cross-over	14	−0.07 (−0.15, 0.00)	0.874	0.0	12	−0.74 (−1.39, −0.08)	0.832	0.0
Duration of intervention								
<8 weeks (lower than median)	19	−0.06 (−0.14, 0.01)	0.443	1.3	16	−0.45 (−1.08, 0.18)	0.892	0.0
≥8 weeks (higher than median)	11	−0.05 (−0.11, 0.01)	0.038	50.6	11	0.13 (−0.41, 0.66)	0.762	0.0
Type of whole grain								
Mixed	13	−0.10 (−0.17, −0.03)	0.837	0.0	11	−0.38 (−1.10, 0.35)	0.370	7.8
Others	19	−0.01 (−0.07, 0.06)	0.057	33.6	19	−0.01 (−0.49, 0.50)	0.979	0
Dose of whole grain								
Higher	12	−0.08 (−0.15, −0.02)	0.293	14.3	10	0.15 (−0.40, 0.70)	0.936	0.0
Lower	12	−0.03 (−0.12, 0.06)	0.117	34.1	9	0.04 (−0.90, 0.99)	0.857	0.0
Baseline mean of BMI								
Obese (≥30 kg/m^2)	11	−0.07 (−0.14, 0.01)	0.368	8.0	10	−0.09 (−0.68, 0.50)	0.364	8.4
Non-obese (<30 kg/m^2)	21	−0.06 (−0.14, 0.02)	0.055	33.3	17	−0.14 (−0.70, 0.42)	0.959	0.0
Weight change								
Yes	12	−0.01 (−0.08, 0.07)	0.254	17.8	11	−0.16 (−0.40, 0.72)	1.00	0.0
No	15	−0.06 (−0.12, 0.01)	0.307	13.1	12	−0.27 (−0.95, 0.41)	0.241	20.6
Glucose								
Normal glycemia	25	−0.05 (−0.10, −0.003)	0.165	20.4	21	−0.03 (−0.49, 0.42)	0.771	0.0
Hyperglycemia	7	−0.07 (−0.30, 0.17)	0.160	33.6	6	−0.42 (−1.30, 0.46)	0.907	0.0
Risk of bias								
High	8	−0.07 (−0.11, 0.02)	0.759	0.0	7	−0.03 (−0.93, 0.99)	0.800	0.0
Others	24	−0.06 (−0.10, 0.11)	0.049	21.3	20	−0.15 (−0.60, 0.30)	0.907	0.0

†*P* for heterogeneity was assessed by using Cochran's test, and $P < 0.1$ was considered to show significant heterogeneity across studies. The I^2 statistic was calculated by using Cochran's test, and $I^2 > 50\%$ was considered to show significant heterogeneity across studies.

consumption, such as the low energy density of whole grains and the fermentation products of indigestible carbohydrates; (iii) in view of the aforementioned characteristics, whole grains directly affect the early postprandial blood glucose response, but do not cause significant changes in late blood glucose levels through hormonal (mainly insulin and glucagon) or metabolic (free fatty acid) mechanisms; and (iv) the intervention time of 6 weeks might be relatively short to have a significant effect on insulin sensitivity[15].

For the present meta-analysis, study design, duration of intervention, type of whole grain, dose of whole grain, baseline mean BMI, weight change and basal blood glucose status were potential factors that might influence the results. To evaluate these influences, we carried out detailed subgroup analysis and found only a few positive results, suggesting that the present study results are relatively stable. Subgroup analyses suggested that a higher dose of whole grain intake, but not a lower dose, was associated with improved glycemic control. This implies that the regulatory effect might be dose-dependent. Chanson *et al.*[47] reported a significant inverse association between whole grain intake and the occurrence of type 2 diabetes mellitus, with a slope of −0.000293; an overall reduction of 0.3% in the incidence of type 2 diabetes mellitus for each additional 10 g of whole grain ingredients consumed per day was observed. Another study confirmed the non-linear negative relationship between whole grains and the risk of type 2 diabetes mellitus. When the intake of whole grains increased to 60 g/day, most of the reductions were observed[48]. Although further original research is necessary to discover the underlying mechanisms of the observed non-linear associations, the present study shows that a proper increase in daily whole grain intake might be beneficial for glucose control.

The present meta-analysis showed that whole grain consumption significantly reduces fasting glucose in participants with normal basal fasting glucose levels. In contrast, whole grain intake did not significantly affect glucose control in the hyperglycemia subgroup. This phenomenon was supported by two recent meta-analyses. A meta-analysis found that the consumption of whole grain foods acutely improved postprandial glucose compared with controls in healthy participants[11], but the inverse association disappeared when the included participants were prediabetes and type 2 diabetes mellitus patients from the research of Rahim's *et al.*[49] Furthermore, animal studies also showed that the intake of whole grain has no significant effect on glycemic measures in diabetic rodents. However, the underlying mechanisms remain unclear. A possible explanation is that non-diabetic participants have normal blood glucose homeostasis, which is more sensitive to the regulatory effect of whole grains than the abnormal blood glucose homeostasis of prediabetes and type 2 diabetes mellitus patients. In contrast, for hyperglycemic patients with impaired function and decreased compensatory capacity, the protective effect from whole grains would not be observed. This potential effect needs to be evaluated through better designed animal experiments or high-quality randomized controlled studies. The present results might be of great value in guiding the inclusion of populations that are suitable for whole grain intake.

This is the first meta-analysis to evaluate the effect of medium-/long-term whole grain intake on glycemic control in metabolic syndrome and healthy populations. The results further enhance the understanding of the value of whole grain intake on glucose control. The present meta-analysis also had several limitations. First, the lack of a clear definition of the concept of whole grain food, as well as different properties of dietary whole grain sources, might lead to some bias. A separate survey of designated types of whole grain foods produced by different crops might help to reduce heterogeneity, but due to the insufficient number of original studies, a meta-analysis cannot be implemented. Second, our work increased the amount of evidence of the hypoglycemic effect from whole grain consumption, but we did not analyze the dose-dependent relationship, and we were unable to further explain the hypoglycemic mechanisms. Third, the present study systematically focused on the medium-term effect of whole grain consumption on blood glucose regulation, because most of the study durations were <1 year, and we could not investigate the protective effect of longer duration whole grain intake on health. Fourth, the studies included in the meta-analysis mainly came from developed countries in Asia, North America and Europe. To better understand the effect of whole grains on human blood glucose control, further research in other regions is still required.

In conclusion, the present results of our meta-analysis suggested that intake of whole grain foods could reduce the fasting glucose concentration compared with intake of similar refined foods. Appropriate intervention dose and accurate population selection might be the key links for whole grain intake to exert the effect of blood glucose regulation. To explain the underlying mechanism by which whole grain products have a positive impact on glucose regulation, it is necessary to carry out better designed studies on different groups of people using different forms of whole grain foods with different structures.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: This network meta-analysis was registered at www.crd.york.ac.uk/PROSPERO as CRD42019131128.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline and outcome data used in the meta-analysis.

Table S2 | Judgments of review authors for each risk of bias item according to the Cochrane risk of bias assessment tool.

Table S3 | Pooled effects of whole grain consumption on glucose control and insulin sensitivity.

Figure S1 | Meta-analysis of the effects of whole grain on homeostatic model assessment for insulin resistance.

Figure S2 | Meta-analysis of the effects of whole grain on glycated hemoglobin.

Figure S3 | Funnel plots for the studies of the association of whole grain and fasting glucose concentrations.

Figure S4 | Funnel plots for the studies of the association of whole grain and fasting insulin concentrations.

Figure S5 | Funnel plots for the studies of the association of whole grain and homeostatic model assessment for insulin resistance.

Figure S6 | Funnel plots for the studies of the association of whole grain and glycated hemoglobin.