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Greater Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes, Cardiovascular Disease, and Weight Gain[1–3]

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Abstract

Whole-grain and high fiber intakes are routinely recommended for prevention of vascular diseases; however, there are no comprehensive and quantitative assessments of available data in humans. The aim of this study was to systematically examine longitudinal studies investigating whole-grain and fiber intake in relation to risk of type 2 diabetes (T2D), cardiovascular disease (CVD), weight gain, and metabolic risk factors. We identified 45 prospective cohort studies and 21 randomized-controlled trials (RCT) between 1966 and February 2012 by searching the Cumulative Index to Nursing and Allied Health Literature, Cochrane, Elsevier Medical Database, and PubMed. Study characteristics, whole-grain and dietary fiber intakes, and risk estimates were extracted using a standardized protocol. Using random effects models, we found that compared with never/rare consumers of whole grains, those consuming 48–80 g whole grain/d (3–5 serving/d) had an ~26% lower risk of T2D [RR = 0.74 (95% CI: 0.69, 0.80)], ~21% lower risk of CVD [RR = 0.79 (95% CI: 0.74, 0.85)], and consistently less weight gain during 8–13 y (1.27 vs 1.64 kg; $P = 0.001$). Among RCT, weighted mean differences in post-intervention circulating concentrations of fasting glucose and total and LDL-cholesterol comparing whole-grain intervention groups with controls indicated significantly lower concentrations after whole-grain interventions [differences in fasting glucose: −0.93 mmol/L (95% CI: −1.65, −0.21), total cholesterol: −0.83 mmol/L (−1.24, −0.42); and LDL-cholesterol: −0.72 mmol/L (−1.34, −0.11)]. Findings from this meta-analysis provide evidence to support beneficial effects of whole-grain intake on vascular disease prevention. Potential mechanisms responsible for whole grains' effects on metabolic intermediates require further investigation in large intervention trials. J. Nutr. 142: 1304–1313, 2012.

Introduction

Type 2 diabetes (T2D)[10] and cardiovascular disease (CVD) are the most prevalent diseases of our time. Although dietary modification is critical for the prevention of these vascular disorders and related risk factors, including obesity, specific food groups that may be beneficial for vascular health remain to be clarified. Several national and international authorities recommend whole grains for the maintenance of vascular health (1–4). Whole grains are defined as intact, ground, cracked, or flaked fruit of grains in which all components of the kernel, i.e., the bran, germ, and endosperm, are present in the same relative proportions as in the intact grain. Examples of whole grains include whole wheat, dark bread, oats, brown rice, rye, barley, and bulgur. Increased whole-grain intake may lower the risk of weight gain/obesity (5–7), T2D (8–13), and CVD (14–20), although specific bioactive components responsible for whole grains' protective effect remain uncertain (21). Potential biological mechanisms are not fully elucidated but may be linked to improvements in glucose metabolism due to the slower digestion and absorption of whole-grain foods or an increased rate of gastric emptying and enhanced postprandial glucose and insulin response after dietary fiber intake. However, despite the vast literature available concerning whole-grain and fiber intakes in relation to risk of T2D, CVD, and weight gain, no study has comprehensively reviewed and summarized the available research on this topic to inform recommendations and determine the risk-benefit balance.

Therefore, we undertook this systematic review and meta-analysis to comprehensively assess and synthesize findings from: *1*) prospective cohort studies investigating the association between

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[3] Supplemental Tables 1–3 and Figures 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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[10] Abbreviations used: CVD, cardiovascular disease; RCT, randomized controlled trial; T2D, type 2 diabetes.

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both whole-grain and fiber intake and risk of T2D, CVD, and weight gain; and *2*) randomized controlled trials (RCT) investigating changes in metabolic intermediates that can be more readily measured in the short duration of randomized settings, including fasting glucose, insulin, total and LDL-cholesterol, blood pressure, and weight gain.

Materials and Methods

Data sources and literature search. We conducted a comprehensive literature search for: *1*) prospective cohort studies examining the association of whole-grain and fiber intakes in relation to T2D, CVD, and weight gain; and *2*) RCT investigating metabolic intermediate risk factors for these outcomes, including fasting glucose, insulin, total and LDL-cholesterol, and blood pressure. We searched several databases, including the Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Elsevier Medical Database, and MEDLINE. A standard search protocol was followed in all databases. Specifically, we used the keywords whole grain, dietary fiber, diabetes, CVD, weight gain, obesity, insulin, glucose, blood pressure, and cholesterol and restricted the search to articles published in English from 1966 to February 2012. CVD was defined to include stroke, myocardial ischemia, cardiovascular death, atrial fibrillation, coronary heart disease, coronary artery disease, and myocardial infarction. We retrieved additional studies by cross-checking relevant references in articles identified in the initial search.

Study selection. In our first round of searching, we identified 3642 articles from the Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Registry of Controlled Trials, Elsevier Medical Database, and MEDLINE. After a review of titles and abstracts, we excluded 3520 articles. We reviewed the full text of the remaining 122 articles and after final exclusions, 66 studies were included in the final analysis (**Supplemental Fig. 1**). Prospective cohort studies included in this study satisfied the following criteria: *1*) free-living humans; *2*) outcome as T2D, CVD, or weight gain; *3*) explicit description of the quantitative methodology used in assessing whole grain and/or dietary fiber intake; *4*) effect size measures, including RR, OR, or HR for disease endpoints; and *5*) detailed descriptions of multivariable adjustments. Relevant RCT included: *1*) interventions including whole grains with detailed descriptions of intake during the intervention period; and *2*) mean changes in fasting insulin, fasting glucose, systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, or weight gain. Studies examining intake from supplements were excluded.

Data extraction and quality assessment. Three investigators (S.A.C., Q.Y., and M.K.) extracted and tabulated all data for prospective cohort studies and RCT, including lead author, publication year, country of origin, sample size, sex, race, and age of participants. For prospective cohort studies, additional data extracted included date of enrollment, length of follow-up, method of dietary intake assessment, median levels of whole-grain intake in highest and lowest categories, outcome assessment, case ascertainment, adjustment for potential confounders, diagnostic criteria of diabetes [National Diabetes Data group 1979 (22) or WHO 1985 cutpoint $\geq$7.8 mmol/L (23) vs. American Diabetes Association 1997 (24) or WHO 1999 cutpoint of $\geq$7.0 mmol/L (25)], total number of cases, RR of event comparing groups with the highest and lowest levels of intake, and CI and *P* values. For RCT, study design, duration, health status, number of treatment and control groups, post-treatment means in fasting insulin, glucose, total and LDL-cholesterol, systolic and diastolic blood pressure, weight gain, and differences in means between intervention and controls were extracted.

Statistical analysis. Multivariable-adjusted RR, OR, and HR estimates were pooled via DerSimonian and Laird random effects models (26) to determine summary measures of association from prospective cohort studies. Participants in the highest category of whole-grain and dietary fiber intakes [median whole-grain intake = 44.4 g/d (2.75 serving/d); median fiber intake = 25.4 g/d] were compared with those in the lowest category of intake (rare/never consumers). When estimates were presented based on continuous dietary intake (e.g., increase in risk per g/d), we multiplied the estimate in the log scale by a constant, approximating the difference between the highest and lowest category and exponentiated back to the original scale. For RCT, weighted mean differences between treatment (whole grains) and control (refined or normal diet) groups were combined via random effects models to estimate the size of intervention effects on metabolic intermediates, including fasting glucose, insulin, total and LDL-cholesterol, blood pressure, and weight gain. Randomized trials comparing the effects of specific grains or fibers without a refined or normal diet control were excluded.

To explore potential sources of heterogeneity across studies and examine the impact on final summary estimates, we conducted a series of prespecified subgroup analyses according to sex, study quality, health status, study duration, level of dietary intake, and method of outcome measurement. We also formally tested between-study heterogeneity using the Cochrane's χ^2 test (Q test) and the I^2 statistic. Publication bias was evaluated using funnel plots in which the RR was plotted on a logarithmic scale against its corresponding SE. The power for formal tests for publication bias was limited due to the small number of studies for each outcome. All statistical analyses were conducted using STATA 12.0 (StataCorp); $P < 0.05$ was considered significant.

Results

We identified a total of 66 articles that met the inclusion criteria, including 45 prospective cohort studies and 21 RCT (Supplemental Fig. 1). Of the 45 prospective cohort studies, 16 examined the relation between whole-grain intake and risk of T2D and CVD (**Tables 1** and **2**), 26 examined dietary fiber intake with respect to T2D and CVD risk (**Tables 3** and **4**), and *5* assessed the relation of whole-grain and fiber intake to weight gain (**Supplemental Tables 1** and **2**). A total of 21 RCT were identified that examined the effects of a whole-grain intervention on metabolic intermediate endpoints for T2D and CVD (**Supplemental Table 3**).

Prospective cohort studies

Whole-grain intake and risk of T2D. We identified 6 prospective cohort studies (8–13) that investigated the relation of whole-grain intake to T2D risk (Table 1). Studies were primarily conducted in the US with the exception of one Finnish study (12) and comprised 2,919,482 person-years of follow-up. The overall estimated multivariable-adjusted RR of T2D comparing the highest with the lowest level of intake was RR = 0.74 (95% CI: 0.69, 0.80) (**Fig. 1***A*). No significant heterogeneity between studies was observed. After excluding one study with a substantially higher median intake of fiber in the highest category than other included studies (12), we observed no significant difference in the overall summary estimate. No evidence of publication bias was apparent.

Whole-grain intake and risk of CVD. We identified 10 prospective cohort studies that directly investigated whole-grain intake in relation to CVD risk including 4,336,411 person-years of follow-up (14–20,27–29) (Table 2). All studies were conducted in the US. Compared with the lowest category of whole-grain intake, the highest category of intake was associated with a 21% reduction in CVD risk [RR = 0.79 (95% CI: 0.74, 0.85)] after adjustment for known CVD risk factors (Fig. 1*B*). No significant heterogeneity among studies was observed, although we did observe slight asymmetry in the funnel plot (Begg's test *P* = 0.03), indicating possible publication bias.

TABLE 1 Characteristics of prospective cohort studies of whole-grain intake and risk of T2D[1]

Author (reference)	Sex	Age, *y*	*n*	Follow-up, *y*	Exposure measurement	Exposure categorization	T2D outcome ascertainment	Adjustments
Meyer (11)	F	55–69	35,988	6	FFQ	Quintiles	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity
Liu (10)	F	38–63	75,521	10	FFQ	Quintiles	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication
Fung (9)	M	40–75	42,898	12	FFQ	Quintiles	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication, dietary factors
Montonen (12)	47% M, 53% F	40–69	4316	10	Diet history	Quartiles	Self-report	Age, sex, geographic area, energy intake, BMI, smoking, dietary factors
Van Dam (13)	F	21–69	41,186	8	FFQ	4 groups	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity, history of diabetes, dietary factors
De Munter (8)	F	26–46	88,410	12	FFQ	Quintiles	Self-report	Age, energy intake, BMI, smoking, alcohol, physical activity, history of T2D, dietary factors

[1] T2D, type 2 diabetes.

Dietary fiber and risk of T2D. We identified 11 prospective cohort studies that examined the relation of total dietary and/or cereal fiber intake to T2D risk (11,12,30–38) encompassing 3,202,850 person-years (Table 3). The overall estimate of the multivariable-adjusted RR of T2D comparing the highest and lowest category of fiber intake was 0.84 (95% CI: 0.76, 0.93) for total dietary fiber (**Fig. 2***A*) and 0.87 (95% CI: 0.81, 0.94) for total cereal fiber (**Fig. 3***A*). However, we observed borderline significant heterogeneity across studies (dietary fiber: I^2 = 44.1%, P = 0.04; cereal fiber: I^2 = 73.6%, $P < 0.001$). Subgroup analyses in men and women revealed a slightly more protective association among men [dietary fiber: RR = 0.80 (95% CI: 0.65, 0.98); cereal fiber: RR = 0.77 (95% CI: 0.59, 1.01)] than among women [RR = 0.86 (95% CI: 0.72, 1.03); RR = 0.80 (95% CI: 0.65, 1.00)] with no significant heterogeneity, indicating the original heterogeneity may have been

TABLE 2 Characteristics of prospective cohort studies of whole grain intake and risk of CVD outcomes[1]

Author (reference)	Sex	Age, *y*	*n*	Follow-up, *y*	Exposure measurement	Exposure categories	CVD outcome ascertainment	Adjustments
Jacobs (14)	F	55–69	34,492	9	FFQ	Quintiles	Ischemic heart disease mortality (death certificate)	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication, dietary factors, diabetes, hypertension
Jacobs (15)	F	55–90	38,740	9	FFQ	Quintiles	CVD mortality (death certificate)	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication, dietary factors, diabetes, hypertension, cancer, heart disease
Liu (19)	F	38–63	75,521	10	FFQ	Quintiles	CHD (medical records)	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication, dietary factors, diabetes, history of hypertension/high cholesterol
Liu (17)	F	38–63	75,521	12	FFQ	Quintiles	Ischemic stroke (medical records)	Age, energy intake, BMI, education, smoking, alcohol, physical activity, use of medication, dietary factors, diabetes, history of hypertension/high cholesterol
Liu (18)	M	40–84	86,190	5.5	FFQ	Quartiles	CVD mortality (death certificate)	Age, BMI, smoking, alcohol, physical activity, use of multivitamins, history of T2D, high cholesterol, hypertension
Steffen (20)	F	45–64	11,940	11	FFQ	Quintiles	CAD (medical records/registry)	Age, race, sex, energy intake, education, smoking, alcohol, physical activity, hormone use
Jensen (16)	M	45–75	42,850	14	FFQ	Quintiles	CHD (medical records)	Age, energy intake, smoking, alcohol, physical activity, dietary factors, history of hypertension/high cholesterol/ diabetes/MI
Djousse (27)	M	40–86	21,376	19.6	FFQ	Four categories	Heart failure (self-report)	Age, smoking, alcohol, physical activity, dietary factors, use of multivitamins, history of CVD
Nettleton (28)	F	45–64	14,153	13.3	FFQ	—	Heart failure (medical records/ death certificates)	Age, race, sex, education, smoking, alcohol, physical activity, CVD/diabetes/hypertension
He (29)	F	30–55	7822	26	FFQ	Quintiles	CVD mortality (death certificate)	Age, energy intake, smoking, alcohol, physical activity, dietary factors, hormone use, menopausal status, diabetes duration

[1] CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes.

TABLE 3 Characteristics of prospective cohort studies of total dietary and cereal fiber intake and risk of T2D[1]

Author (reference)	Sex	Age, *y*	*n*	Follow-up, *y*	Exposure measurement	Exposure categories	T2D outcome ascertainment	Adjustments
Meyer (11)	F	55–69	35,988	6	FFQ	Quintiles	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity
Stevens (35)								Age, sex, BMI, education, physical activity
White	M/F	45–64	9529	9	FFQ	—[2]	Self-report/exam	
African American	M/F	45–64	2722	9	FFQ	—	Self-report/exam	
Montonen (12)								Age, energy intake, BMI, geographic area, smoking, dietary factors
Men	M	40–69	2286	10	Diet history	Quartiles	Self-report/exam	
Women	F	40–69	2030	10	Diet history	Quartiles	Self-report/exam	
Hodge (31)	F	40–69	31,641	4	FFQ	—	Self-report	Age, sex, BMI, education, physical activity
Schulze (33)	F	24–44	91,249	8	FFQ	Quintiles	Self-report	Age, BMI, energy intake, smoking, alcohol, physical activity, use of medication, family history of T2D, history of hypertension/high cholesterol, dietary factors
Barclay (30)	M/F	49+	2123	10	FFQ	—	Self-report	Age, sex, physical activity, family history of T2D, smoking, triglycerides, HDL-cholesterol
Krishnan (38)	F	21–69	40,078	8	FFQ	Quintiles	Self-report	Age, energy intake, BMI, education, smoking, alcohol, physical activity, family history of T2D, dietary factors
Schulze (34)	39% M 61% F	35–65	25,067	7	FFQ	Quintiles	Self-report	Age, sex, energy intake, education, smoking, alcohol, physical activity, dietary factors
Wannamethee (36)	M	60–79	34,248	7	7-d recall FFQ	Quartiles	Self-report/medical records	Age, energy intake, waist circumference, smoking, alcohol physical activity, SES, stroke, MI, use of statins
Hopping (32)								Age, ethnicity, energy intake, BMI, physical activity, education
Men	M	45–75	36,256	14	FFQ	5 groups	Self-report/medical records	
Women	F	45–75	39,256	14	FFQ	5 groups	Self-report/medical records	
Slujis (37)	26% M 74%F	21–70	37,846	10	FFQ	—	Self-report	Age, BMI, waist circumference, education, smoking, alcohol, physical activity, family history of T2D, dietary factors

[1] MI, myocardial infarction; SES, socioeconomic status; T2D, type 2 diabetes.
[2] Categorical data not provided.

explained by this sex difference. We observed no evidence of publication bias.

Dietary fiber intake and risk of CVD. Fifteen prospective cohort studies (39–53) comprising 9,129,408 person-years of follow-up, reported an association between total dietary fiber and/or cereal fiber intake with CVD risk (Table 4). In pooled analyses, the overall multivariable-adjusted RR of CVD comparing the highest with the lowest category of total dietary fiber intake was 0.81 (95% CI: 0.77, 0.86) (Fig. 2*B*) and 0.80 (95% CI: 0.73, 0.88) for total cereal fiber intake (Fig. 3*B*). No significant heterogeneity was observed between studies included in the total dietary fiber analyses [dietary fiber intake (I^2 = 21%, P = 0.19)]; however, we did observe significant heterogeneity between studies assessing cereal fiber intake (I^2 = 61.3%, P = 0.003). Subgroup analyses (data not shown) did not change the magnitude or direction of the overall estimate. We also observed borderline significant evidence of publication bias (Begg's test P = 0.04), potentially related to other sources of heterogeneity across these studies.

Whole-grain and dietary fiber intake and weight gain. We identified 3 prospective cohort studies investigating whole-grain intake and weight gain (5–7) and 2 examining the relation between dietary fiber intake and weight gain (6,7) (**Supplemental Tables 3** and **4**). Although the small number of studies combined with the lack of available data on numbers within categories limited our ability to pool the data, the findings generally indicated an inverse association between whole-grain and dietary fiber intakes and weight gain over time. Among 74,091 apparently healthy female nurses followed for 12 y, those with the greatest increase in whole-grain intake over time gained less weight than those with lower increases (ranging from 1.52 kg in the lowest quintile of intake to 1.23 kg in the highest quintile) every 2–4 y (7). In the same cohort, women in the highest quintile of whole-grain intake had a 23% lower risk of major weight gain [OR = 0.77 (95% CI: 0.59, 1.01)]; those in the highest quintile of dietary fiber intake had a 49% lower risk of weight gain [OR = 0.51 (95% CI: 0.39, 0.67)] (7). In another prospective study of 27,082 men aged 40–75 y at baseline, a 40-g/d increase in whole-grain intake was associated with reduced long-term weight gain by 0.49 kg during 8 y of follow-up (6). Among 17,881 male physicians, weight gain was 0.35 kg lower among participants who consumed at least 16 g/d of whole-grain cereals (1 serving/d) compared with those who rarely or never consumed whole-grain cereals during 8 y of follow-up (5). Of the

TABLE 4 Characteristics of prospective cohort studies of total dietary and cereal fiber intake and risk of CVD outcomes[1]

Author (reference)	Sex	Age, *y*	*n*	Follow-up, *y*	Exposure measurement	Exposure categories	CVD outcome ascertainment	Adjustments
Khaw (39)							Ischemic heart disease mortality (death certificate)	Age, sex, BMI, systolic blood pressure, cholesterol, fasting glucose, smoking
Men	M	50–79	356	12	24-h recall	Tertiles		
Women	F	50–70	503	12	24-h recall	Tertiles		
Pietinen (40)	M	50–69	21,930	6.1	Diet history	Quintiles	Coronary event (registry/death certificate)	Age, energy intake, smoking, alcohol, BMI, blood pressure, education, physical activity, dietary factors
Todd (41)							CHD (medical records)	Age, energy intake, BMI, alcohol, physical activity, metabolic risk factors
Men	M	40–59	5754	7.7	FFQ	Quartiles		
Women	F	40–59	5875	7.7	FFQ	Quartiles		
Wolk (42)	F	37–64	68,782	10	FFQ	Quintiles	CHD (medical records)	Age, BMI, smoking, physical activity, menopausal status, aspirin use, multivitamin use, hypertension, family history of MI, dietary factors
Liu (43)	F	38–63	39,876	6	FFQ	Quintiles	CVD (medical records)	Age, energy intake, smoking, exercise, alcohol, hormone use, BMI, multivitamin use, history of hypertension/high cholesterol/diabetes, dietary factors
Bazzano (44)	M/F	25–74	9776	19	24-h recall	Quartiles	CVD (medical records/death certificate)	Age, sex, race, BMI education, physical activity, systolic blood pressure, total cholesterol, diabetes, alcohol, smoking, dietary factors
Merchant (45)	M	40–75	46,032	12	FFQ	Quintiles	Peripheral arterial disease (medical record)	Age, smoking, BMI, alcohol, physical activity, hypertension, high cholesterol, family history of heart disease
Mozaffarian (46)	M/F	> 65	3588	8.6	FFQ	Quintiles	CVD (medical record)	Age, sex, education, diabetes, smoking, physical activity, alcohol, cereal, fruit, and vegetable fiber intake
Oh (47)	F	30–55	78,779	18	FFQ	Quintiles	Stroke (medical record)	Age, BMI, energy intake, smoking, alcohol, physical activity, history of MI/hypertension/high cholesterol/ diabetes, menopausal status, use of medication, multivitamins
Eshak (48)							CVD mortality (death certificate)	Age, BMI, history of hypertension, diabetes, alcohol, smoking, education, physical act, dietary factors
Men	M	40–79	23,119	14	FFQ	Quintiles		
Women	F	40–79	35,611	14	FFQ	Quintiles		
Shen (50)		62 ± 10	4526	4	FFQ	Quartiles	Atrial fibrillation (medical records)	Age, sex, BMI, systolic blood pressure, hypertension, ECG, PR interval[2], heart murmur, heart failure
Kokubo (49)							CVD (medical records)	Age, sex, smoking, alcohol, BMI, history of diabetes, medication for hypertension/hypercholesterolemia, physical activity, dietary factors
Men	M	45–65	40,046	10.4	FFQ	Quintiles		
Women	F	45–65	46,341	10.4	FFQ	Quintiles		
Park (51)							CVD mortality (death certificate)	Age, race, total energy intake, education, marital status, health status, BMI, physical activity, smoking, alcohol, dietary factors
Men	M	50–71	219,123	9	FFQ	Quintiles		
Women	F	50–71	168,999	9	FFQ	Quintiles		
Larsson (52)	M	50–69	26,556	13.6	FFQ	Quintiles	Stroke (hospital registry)	Age, energy intake smoking, BMI, blood pressure, cholesterol, history of T2D and CHD, physical act, alcohol, total dietary factors
Streppel (53)	M	49–83	1373	40	Diet history	—	CHD mortality (death certificate)	Age, energy intake, alcohol, smoking, BMI, SES, dietary factors

[1] CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; SES, socioeconomic status.
[2] PR interval, the time from the onset of the P wave to the beginning of the QRS complex in electrocardiograms.

3 prospective studies investigating whole-grain consumption and risk of weight gain, whole-grain intake was associated with a reduction in weight gain ranging from 0.4 to 1.5 kg during 8–13 y.

RCT

Whole-grain interventions and metabolic intermediates. We identified 21 RCT that directly investigated the effects of whole-grain interventions on metabolic intermediate risk factors, including fasting insulin, fasting glucose, systolic and diastolic blood pressure, circulating total and LDL-cholesterol, and weight gain (54–74). Interventions ranged from 4 to 16 wk (9 parallel in design and 12 crossover studies) (Supplemental Table 3). Participants were either healthy or had one or more major risk factors for T2D or CVD, including hyperinsulinemia, hypercholesterolemia, hypertension, or overweight. Characteristics of the whole-grain interventions, control groups, duration, and design varied widely across studies. On average, we observed significantly lower concentrations of fasting glucose, insulin, total and LDL-cholesterol, lower systolic and diastolic blood

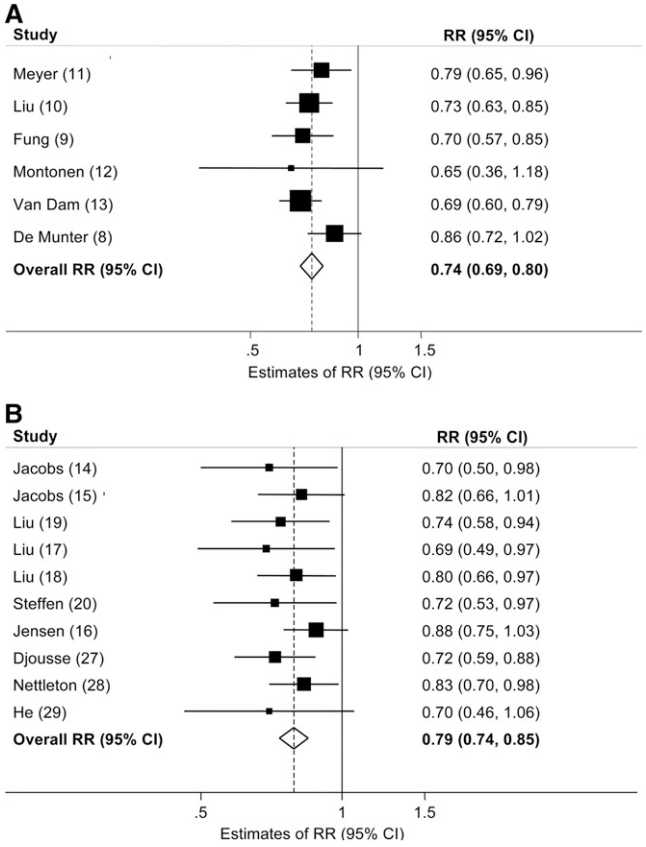

FIGURE 1 Multivariable-adjusted RR of T2D (*A*) and CVD (*B*) comparing the highest and lowest categories of whole-grain intake in prospective cohort studies. Squares indicate the RR estimate in each study. The size of the square is proportional to the weight of each study in the overall random effects estimate. The horizontal line represents the 95% CI. The overall summary estimate and its 95% CI are indicated by the open diamond. I^2 = 0.0%, P = 0.44 for T2D; I^2 = 0.0%, P = 0.82 for CVD. CVD, cardiovascular disease; T2D, type 2 diabetes.

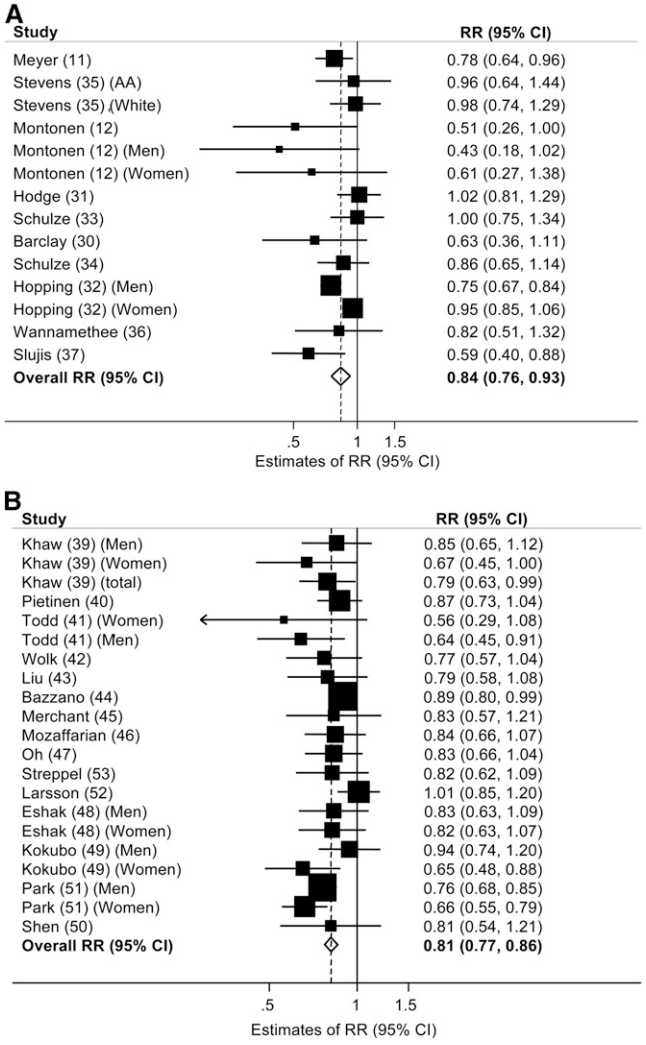

FIGURE 2 Multivariable-adjusted RR of T2D (*A*) and CVD (*B*) comparing the highest and lowest categories of dietary fiber intake in prospective cohort studies. Squares indicate the RR estimate in each study. The size of the square is proportional to the weight of each study in the overall random effects estimate. The horizontal line represents the 95% CI. The overall summary estimate and its 95% CI are indicated by the open diamond. I^2 = 44.1%, P = 0.04 for T2D; I^2 = 21.0%, P = 0.19 for CVD. CVD, cardiovascular disease; T2D, type 2 diabetes.

pressure, and less weight gain after whole-grain interventions compared with controls regardless of formulation and dosage (**Table 5**; **Supplemental Fig. 2***A–G*). Weighted mean differences in post-intervention concentrations of fasting glucose and total and LDL-cholesterol between whole-grain intervention groups compared with controls indicated significantly lower concentrations after the whole-grain interventions [differences in fasting glucose: −0.93 mmol/L (95% CI: 1.65, −0.21), total cholesterol: −0.83 mmol/L (95% CI: −1.24, −0.42); and LDL-cholesterol: −0.72 mmol/L (95% CI: −1.34, −0.11)]. We observed heterogeneity across trials ($P < 0.05$), which remained significant in subgroups after stratification by duration, study quality, and health status.

Discussion

Findings from this comprehensive meta-analysis indicate that intake of whole grains is inversely associated with risk of T2D and CVD risk. Compared with those who rarely or never consume whole grains, those reporting an average of 48–80 g/d of whole grain (3–5 serving/d) had a 26% reduction in T2D risk and a 21% reduction in CVD risk, independent of known CVD risk factors. We also observed an inverse association between whole-grain intake and weight gain, with consistently less weight gain observed in those consuming 48–80 g/d of whole grain (3–5 servings/d) compared with never/rare consumers (1.27 vs. 1.64 kg) during 8–13 y of follow-up.

Whole-grain foods are a rich source of vitamins, minerals, phytochemicals, and lignans (21). Compared with refined grains, whole grains generally have a lower glycemic index because of their intact structure (75,76). Constituents of whole grains, including magnesium and antioxidants such as vitamin E, phytic acid, and selenium, may help to maintain glucose and insulin homeostasis (21) and reduce CVD risk (77). In addition to this rich source of phytochemicals, whole grains contain 20–50% of soluble fiber, which can lower serum cholesterol, LDL-cholesterol, and apoB concentrations (78,79). It has also been reported that the presence of undigested carbohydrates in whole grains can increase fecal weight and shorten the intestinal transit time and may reduce risk of weight gain (21). Dietary fiber may be one important component of whole grains responsible for their reported beneficial effects on T2D and CVD risk driven in part by increased gastric emptying and macronutrient absorption

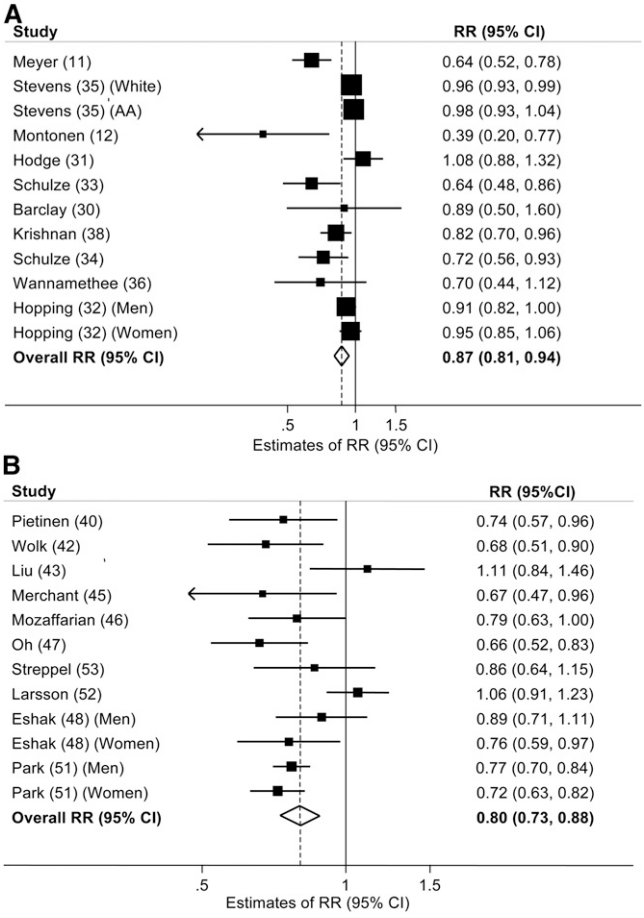

FIGURE 3 Multivariable-adjusted RR of T2D (*A*) and CVD (*B*) comparing the highest and lowest categories of dietary cereal fiber intake in prospective cohort studies. Squares indicate the RR estimate in each study. The size of the square is proportional to the weight of each study in the overall random-effects estimate. The horizontal line represents the 95% CI. The overall summary estimate and its 95% CI are indicated by the open diamond. $I^2 = 73.6\%$, $P < 0.001$ for T2D; $I^2 = 61.3\%$, $P = 0.003$ for CVD. CVD, cardiovascular disease; T2D, type 2 diabetes.

and an improved postprandial glucose response (80–82). Findings from this meta-analysis suggest that greater intake of total dietary and cereal fiber were significantly and inversely associated with risk of T2D and CVD, although substantial heterogeneity across studies was observed.

Relatively few well-controlled and long-term randomized trials have directly examined the effects of whole-grain interventions on metabolic intermediaries for T2D and CVD, including weight gain, fasting blood glucose, insulin, and lipids and blood pressure, and trials to date have been of short duration with small sample sizes. Although we observed substantial heterogeneity across trials likely stemming from variability in study duration, types of whole-grain foods included in each intervention, comparison groups, and sample sizes, our overall findings suggest that higher levels of whole-grain intake were associated with lower levels of fasting glucose, total and LDL-cholesterol, systolic and diastolic blood pressure, and weight gain. Consistent with prior studies (83), our meta-analysis indicated that increased intake of whole grains for 4–16 wk significantly improved an individual's lipid profile, reducing total cholesterol by 0.83 mmol/L and LDL-cholesterol by 0.72 mmol/L. Given the varied whole-grain dosages in these trials, further randomized trials should further investigate these intermediates to explore possible mechanistic explanations for the consistently reported observation that whole grains may be beneficial for these intermediate risk factors for vascular disease.

Several limitations of this meta-analysis should be noted. First, although known confounders were comprehensively considered in most studies, residual confounding remains a possibility. Inadequate or incomplete adjustment for lifestyle and dietary factors may potentially overestimate the strength of the inverse association observed in these studies. Nevertheless, the consistent inverse associations observed across multiple cohort studies, in addition to supportive mechanistic investigation of whole-grain intake and metabolic intermediaries from randomized trials, reduce the likelihood of these biases. Second, the majority of studies were conducted among Caucasians in the US, limiting the generalizability of our findings to ethnic groups with differing dietary practices. Heterogeneity of trials combined with small sample sizes and short intervention periods highlight the importance of adopting a consistent strategy for study design in future trials guided by observations from prospective studies. Adopting a standardized method in identifying and classifying dietary carbohydrates as proposed by Englyst et al. (84) on behalf of the WHO's expert committee would help distinguish fiber from whole grain, intact grains from processed flours and various viscous fiber sources for future studies. Addressing these issues in future RCT may help to establish potential causal relations between whole-grain intake and intermediate metabolic biomarkers as well as uncover other mechanisms not yet recognized.

In conclusion, our systematic review and meta-analysis of 45 prospective cohorts and 21 randomized intervention trials indicates that increased intake of whole grain and fiber may lower the risk of T2D, CVD, and weight gain. Our findings support current recommendations stating that consumption of at least 48 g whole grains/d (approximately 3 servings/d) may

TABLE 5 Weighted mean difference in post-treatment metabolic biomarker concentrations comparing whole-grain intervention groups to controls

Metabolic biomarkers	Studies, *n*	Weighted mean difference (95% CI)
Fasting insulin, *pmol/L*	10	−0.29 (−0.59, 0.01)
Fasting glucose, *mmol/L*	11	−0.93 (−1.65, −0.21)
Total cholesterol, *mmol/L*	16	−0.83 (−1.24, −0.42)
LDL-cholesterol, *mmol/L*	15	−0.72 (−1.34, −0.11)
Systolic blood pressure, *mm Hg*	6	−0.06 (−0.21, 0.10)
Diastolic blood pressure, *mm Hg*	6	−0.05 (−0.21, 0.11)
Weight gain, *kg*	9	−0.18 (−0.54, 0.18)

offer beneficial effects for weight maintenance and the prevention of vascular disease (85). To further elucidate mechanisms underlying the potential beneficial effects of whole-grain intake for the prevention of chronic diseases, long-term RCT seem warranted.

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