Perspective: Refined Grains and Health: Genuine Risk, or Guilt by Association?

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ABSTRACT

Refined grain intake is widely assumed to be associated with adverse health outcomes, including increased risk for cardiovascular disease (CVD), type 2 diabetes (T2D), and obesity. The 2015 Dietary Guidelines Advisory Committee recommended that to improve dietary quality, the US population should replace most refined grains with whole grains. This recommendation was based largely on results from studies that examined dietary patterns, not separate food groups. A Western dietary pattern typically includes red and processed meat, sugar-sweetened foods and beverages, French fries, and high-fat dairy products, as well as refined grains, and has been linked to increased risk of many chronic diseases. However, when evaluated as a distinct food category, 11 meta-analyses of prospective cohort studies, which included a total of 32 publications with data from 24 distinct cohorts, demonstrated that refined grain intake was not associated with all-cause mortality, T2D, CVD, coronary heart disease (CHD), stroke, hypertension, or cancer. By contrast, consumption of red and processed meat was consistently associated with increased risk of these same health outcomes. Refined grain consumption up to 6–7 servings/d (1 serving = 30 g) was not associated with higher risk of CHD, T2D, hypertension, or all-cause mortality. Moreover, total grain intake was not associated with risk of CVD, CHD, stroke, or cancer, but was associated with lower risk of all-cause mortality. Consequently, the recommendation to reduce refined grain intake based on results from studies linking a Western dietary pattern to numerous adverse health outcomes is contrary to a substantial body of published scientific evidence. Future research needs to better define refined grain intake to distinguish between staple grain foods and indulgent grain foods, and to better design randomized controlled trials to resolve discrepancies between results from observational studies and such trials with regard to determining the benefits of whole grains compared with refined grains. *Adv Nutr* 2019;10:361–371.

Keywords: whole grains, white rice, Western dietary pattern, red and processed meat, cardiovascular disease, stroke, diabetes, all-cause mortality, obesity, hypertension

Introduction

Current US dietary guidelines consider grains as part of a healthy eating pattern and recommend that at least one-half of grain consumption come from whole grains (1). The health benefits of whole grains are well established from the results of many prospective cohort studies (2–9). Unfortunately, only 2–7% of Americans meet the recommendation to consume at least one-half of total grains from whole grains (10, 11), and <1% of the population consumes ≥3 servings/d (1 serving = 1 oz-equivalent) of whole grains (11).

Among US children and adults whole-grain intake averages <1 serving/d and refined grain intake averages 5–6 servings/d (12). Because epidemiologic research suggests that substantial reductions in the risk of type 2 diabetes (T2D), cardiovascular disease (CVD), and all-cause mortality can be obtained by increasing intake of whole grains to just 2–3 servings/d (2–4, 6, 13) (1 serving = 30 g in these studies), the case for increasing whole-grain consumption is clear cut. To achieve the recommended balance of whole and refined grains would require increasing whole-grain intake and simultaneously decreasing the intake of refined grains. In fact, the 2015 Dietary Guidelines Advisory Committee (DGAC) recommended that "to improve dietary quality, the US population should replace most refined grains with whole grains" (12). This recommendation was reiterated in the dietary advice of the American Heart Association (14).

The rationale for recommending a reduced intake of refined grains was based on the DGAC's conclusion that

there was "strong" evidence that a dietary pattern lower in refined grains was associated with lower risk of CVD, and "moderate" evidence that a reduced intake of refined grains was associated with lower risk of T2D and obesity (12). It is important to note that the DGAC relied almost exclusively on results from studies that examined dietary patterns, and not separate food groups. For example, in addition to emphasizing that vegetables, fruits, whole grains, low-fat or nonfat dairy, seafood, legumes, and nuts were key components of a healthy dietary pattern, the DGAC also asserted that a healthy dietary pattern is "lower in red and processed meat, and low in sugar-sweetened foods and drinks and refined grains."

The inclusion of refined grains in an unhealthy dietary pattern is quite common in the nutrition literature. This unhealthy, or Western, dietary pattern typically includes red and processed meat, sugar-sweetened foods and beverages, French fries, high-fat dairy products, and refined grains, and has been linked to an increased risk of a number of chronic diseases (12, 15–19). An important question is whether each of the food groups in this dietary pattern is culpable for the increased disease risk. For example, is refined grain consumption associated with higher risk for CVD, T2D, and obesity, as asserted by the DGAC? Or is it possible that the higher risk is not due to consumption of refined grain foods categorically, but is instead a consequence of "guilt by association" with foods that are the real culprits?

The objective of this Perspective is to briefly summarize the published research on refined grain intake and associations with CVD, coronary heart disease (CHD), stroke,

T2D, cancer, BMI, and all-cause mortality. The discussion relies primarily on meta-analyses of relevant literature in which refined grain intake was analyzed separately, and not as part of a Western dietary pattern. The Institute for Scientific Information's Web of Science was utilized to identify relevant meta-analyses of prospective cohort studies and randomized controlled trials (RCTs). Additionally, articles were identified through the use of the key words "refined grain intake" and each disease outcome. Finally, reference lists and citation records of all identified articles were searched for additional studies not cited in meta-analyses.

CVD/CHD

Five meta-analyses were identified that evaluated the association between refined grain intake and either CVD (2, 5) or CHD (2, 4, 20) (Table 1). Collectively, these meta-analyses included a total of 12 publications (21–32). In both meta-analyses for CVD (2, 5) and in 2 of the 3 meta-analyses for CHD (2, 4), no association was observed between refined grain intake and either outcome measure in comparisons of highest with the lowest intake groups and in dose-response analyses. Aune et al. (2) also reported no association between intake of white bread or refined grain breakfast cereals and CHD risk.

In the meta-analysis of Chen et al. (20), refined grain intake was associated with a 9.4% higher risk of CHD (which included studies of CHD, CVD, myocardial infarction, and ischemic heart disease). However, this meta-analysis is flawed because the wrong outcome variable (metabolic syndrome rather than CHD) was used for 1 of the studies included in

TABLE 1 Refined grain intake and relative risk of CVD, CHD, stroke, hypertension, heart failure, T2D, cancer, and all-cause mortality: results from meta-analyses of prospective cohort studies[1]

| Meta-analysis reference | Highest vs lowest intakes | | Dose response[2] | | |
	Number of cohorts included	Relative risk (95% CI)	Number of cohorts included	Relative risk (95% CI)	Outcome
Aune et al. (2)	4	1.16 (0.84, 1.59)	5	1.13 (0.90, 1.42)	CHD
Aune et al. (2)	2	1.02 (0.91, 1.14)	3	0.98 (0.90, 1.06)	CVD
Bechthold et al. (4)	5	1.11 (0.99, 1.25)	4	1.01 (0.99, 1.04)	CHD
Mellen et al. (5)	3	1.07 (0.94, 1.22)	—	—	CVD
Chen et al. (20)[3]	8	1.09 (1.01, 1.19)	—	—	CVD/CHD/MI
Aune et al. (2)	4	0.95 (0.78, 1.14)	5	0.91 (0.81, 1.02)	Stroke
Bechthold et al. (4)	6	1.02 (0.94, 1.11)	4	1.00 (0.98, 1.01)	Stroke
Chen et al. (33)	5	0.99 (0.84, 1.16)	5	0.95 (0.86, 1.03)	Stroke
Wu et al. (34)	10	1.02 (0.93, 1.10)	10	0.98 (0.93, 1.03)	Stroke
Schwingshackl et al. (35)	3	0.95 (0.88, 1.03)	3	0.99 (0.96, 1.02)	Hypertension
Bechthold et al. (4)	1	0.83 (0.58, 1.19)	1	0.86 (0.68, 1.09)	Heart failure
Aune et al. (3)	6	0.94 (0.82, 1.09)	6	0.95 (0.88, 1.04)	T2D
Schwingshackl et al. (13)	15	1.01 (0.92, 1.10)	14	1.01 (0.99, 1.03)	T2D
Aune et al. (2)	1	0.98 (0.82, 1.16)	2	0.94 (0.90, 0.99)	Total cancer
Schwingshackl et al. (36)	2	1.27 (1.02, 1.57)	—	—	Colon cancer
Schwingshackl et al. (36)	1	0.82 (0.48, 1.40)	—	—	Rectal cancer
Schwingshackl et al. (36)	2	1.46 (0.80, 2.67)	—	—	Colorectal cancer
Aune et al. (2)	2	1.02 (0.93, 1.12)	4	0.95 (0.91, 0.99)	All-cause mortality
Schwingshackl et al. (6)	4	0.99 (0.94, 1.05)	4	0.99 (0.97, 1.01)	All-cause mortality

[1]CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes.
[2]In dose-response analyses, relative risks are per 90 g/d in Aune et al. (2, 3) and Chen et al. (20); and per 30 g/d in Bechthold et al. (4) and Schwingshackl et al. (6, 13, 35).
[3]In this meta-analysis an incorrect outcome variable (metabolic syndrome rather than CHD) was used for one of the studies (27) included in the meta-analysis. See text for discussion.

the meta-analysis (27). In this study (27), no association was observed between refined grain intake and CVD mortality. In fact, of the 12 studies included in the 5 meta-analyses, 11 reported no association between refined grain intake and risk of either CVD or CHD (21–31). The only study that reported an increased CHD risk associated with refined grain intake included Chinese adults who had very high total carbohydrate intake, primarily from white rice (32). This is not a consistent finding because white rice intake was not associated with CVD or coronary artery disease (CAD) in an analysis of 3 large US cohorts (37).

In addition to these meta-analyses, refined grain was not associated with progression of CAD over a 3.2-y follow-up in postmenopausal women (38). Also, the only study to date on refined grain intake and heart failure found no association between refined grain breakfast cereal intake and incident heart failure (39) .

By comparison, with few exceptions meta-analyses have demonstrated that consumption of red meat and processed meat is associated with greater risk of CHD (4, 40), CVD (41, 42), and heart failure (4). The relationship for processed meat intake is the most consistent, with all meta-analyses reporting significantly higher risk (15–42%) both when comparing the highest with the lowest intakes (4, 41, 42) and in dose-response analyses (4, 40, 42).

Stroke

Four meta-analyses have been published on the association between refined grain intake and stroke risk, and all reported no association both when comparing the highest with the lowest intake groups and in dose-response analyses (2, 4, 33, 34) (Table 1). It is important to note that of the 12 studies included in these 4 meta-analyses, 11 found no association between refined grain intake and stroke risk (21, 22, 24, 25, 28, 29, 37, 43–46), and 1 actually demonstrated a 10% lower risk of stroke associated with nonwhole-grain intake (30).

The lack of association between refined grain intake and stroke is consistent with the lack of association between refined grain intake and hypertension. A meta-analysis that included 3 studies found no association between refined grain intake and incident hypertension both when comparing the highest with the lowest intake groups and in dose-response analyses (35) (Table 1). In 1 of the studies, refined grain intake of ≥6 servings/d was not associated with increased risk of hypertension (47). In another, refined grain breakfast cereal intakes of 2–6 servings/wk and ≥7 servings/wk were associated with a 14% reduced risk of hypertension (48).

By contrast, meta-analyses have reported increased risk of stroke associated with consumption of red and processed meat both when comparing the highest with the lowest intake groups (4, 49) and in dose-response analyses (4). One meta-analysis reported no significantly greater stroke risk associated with either red or processed meat intake, but intake of total meat was associated with higher stroke risk in a dose-response analysis (40). Furthermore, the risk of hypertension was also shown to be higher in a meta-analysis

comparing the highest and lowest intake groups for both red and processed meat consumption (50).

T2D

Two meta-analyses have been published on the association between refined grain intake and risk of T2D, and both demonstrated no association both when comparing the highest with the lowest intake groups and in dose-response analyses (3, 13) (Table 1). Of the 12 publications included in these 2 meta-analyses, 5 reported no association between refined grain intake and T2D (51–55) and 3 reported a reduced risk of T2D associated with refined grain intake (56–58). In the Women's Health Initiative Observational Study, the reduced risk of T2D associated with refined grain intake in fully adjusted models was comparable to that for whole-grain intake (57).

Four of the studies included in the meta-analyses reported mixed findings, all pertaining to white rice intake (59–62). One reported that in comparing the highest with the lowest intakes, white rice consumption was not associated with T2D risk in the Health Professionals Follow-up Study and Nurses' Health Study I, but was associated with increased risk in the Nurses' Health Study II and in pooled analysis of all 3 cohorts (62). Another showed that white rice intake was associated with T2D risk in only 1 of 2 Iranian cohorts studied (59). White rice intake was associated with T2D risk in Japanese women but not in Japanese men, whereas intakes of bread and noodles were not associated with T2D risk in either sex (61). In the Melbourne Collaborative Cohort study of middle-aged men and women, white rice and pasta intake were not associated with risk of T2D, but white bread intake was (60).

Two meta-analyses have been published on the association between white rice intake and risk of T2D (3, 63) (**Table 2**). Aune et al. (3) reported no association in comparison of highest with lowest intake groups, but a 23% higher risk of T2D in the dose-response analysis. The meta-analysis of Hu et al. (63) indicated that white rice intake was associated with increased T2D risk in 3 Asian cohorts but not in 4 Western cohorts. It should also be noted that in a Spanish cohort white rice consumption was associated with a reduced risk of T2D (58).

The results from most of the studies included in these meta-analyses (3, 13), i.e., that refined grain intake is not associated with increased T2D risk, are consistent with the finding that refined grain intake was shown to be unrelated to insulin resistance, as assessed by the HOMA-IR, and weakly inversely associated with glycated hemoglobin concentrations in the Framingham Offspring Study (64, 65). Additionally, refined grain intake was not associated with development of the metabolic syndrome (66).

By contrast, 2 meta-analyses reported that intake of processed meat was associated with 19–37% higher risk of T2D in dose-response analyses (13, 40) and in highest with lowest intake group comparisons (13). Intake of red (13) and total (40) meat were also associated with higher T2D risk. Sugar-sweetened beverages, also included in the Western

TABLE 2 White rice intake and relative risk of T2D and cancer: results from meta-analyses of prospective cohort studies[1]

Meta-analysis reference	Highest vs lowest intakes		Dose response[2]		Outcome
	Number of cohorts included	Relative risk (95% CI)	Number of cohorts included	Relative risk (95% CI)	
Aune et al. (3)	7	1.17 (0.93, 1.47)	6	1.23 (1.15, 1.31)	T2D
Hu et al. (63)	4 (Western)	1.12 (0.94, 1.33)	—	—	T2D
Hu et al. (63)	3 (Asian)	1.27 (1.04, 1.54)	—	—	T2D
Aune et al. (2)	3	0.87 (0.76, 1.01)	3	0.98 (0.95, 1.05)	Total cancer

[1]T2D, type 2 diabetes.
[2]In dose-response analyses, relative risks are per 90 g/d in Aune et al. (2, 3).

dietary pattern, have been reported to be associated with higher risk of T2D in most (13, 67–69), but not all (70), meta-analyses. This illustrates that the increased risk of T2D associated with a Western dietary pattern (15) is more likely attributable to consumption of red and processed meat, and possibly sugar-sweetened beverages, than to consumption of refined grains.

Cancer

Two meta-analyses on the association between refined grain intake and cancer risk have been published (2, 36) (Table 1). Both meta-analyses are limited by inclusion of few studies. In 1 of these analyses, a weak inverse association between refined grain intake and total cancer mortality in dose-response analysis was reported, but no association was found when comparing the highest and lowest intake groups (2). In the other, refined grain intake was not associated with risk of rectal or colorectal cancer risk, but refined grain intake was associated with a 27% higher risk of colon cancer (36). White rice intake was not associated with total cancer incidence in the meta-analysis of Aune et al. (2), both when comparing the highest and lowest intake groups and in dose-response analysis (Table 2). In addition to the studies used in these meta-analyses, several other analyses from cohort studies have demonstrated no increased cancer risk associated with refined grain intake (30, 71–75).

By contrast, meta-analyses have shown higher total cancer mortality when comparing highest and lowest intake groups for consumption of processed meat (41, 42), red meat (42), and total meat (41), and higher total cancer mortality in dose-response analyses for both processed and red meat consumption (42). A 2018 meta-analysis reported that consumption of red meat and processed meat was associated with significantly greater colon and colorectal cancer risk both when comparing the highest and lowest intake groups and in dose-response analyses, and greater rectal cancer risk in dose-response analyses (36).

All-Cause Mortality

Six studies have been published on the relationship between refined grain intake and all-cause mortality, 5 of which reported no association between refined grain intake and all-cause mortality (22, 25, 27, 29, 30), and 1 that reported a slight, but statistically significant, inverse association between refined grain intake and mortality (31). Two meta-analyses have been published that included 5 of these studies in their analyses (2, 6) (Table 1). Not surprisingly, both reported no association when comparing the highest and lowest intakes. In the dose-response analysis, 1 reported no association (6), whereas Aune et al. (2) reported a 5% lower all-cause mortality risk for each 90-g/d intake of refined grains.

By contrast, the meta-analysis of Schwingshackl et al. (6) demonstrated that all-cause mortality was significantly related to consumption of red meat and processed meat both when comparing the highest and lowest intake groups and in dose-response analyses. Collectively, these studies show that mortality risk associated with the Western dietary pattern (76) is more likely attributable to consumption of red and processed meat, and not to intake of refined grains.

Obesity

No meta-analyses on the association between refined grain intake and measures of body weight or body fat have been performed. Three systematic reviews reported no consistent relationship between refined grain intake and BMI or measures of adiposity (77–79). Most cohort studies show no association between refined grain intake and BMI (23, 25, 27, 29, 52, 57, 65, 71, 80–85). Although some studies indicate a positive association between refined grain intake and BMI (47, 73, 83, 86–89) or body fat (87), the magnitude of the difference between extremes of refined grain intake is typically very small. For example, in the Nurses' Health Study (86), over a 12-y period the difference in weight gain between the lowest and highest quintiles of changes in refined grain intake (–0.91 compared with +0.86 servings per 1000 kcal/d) was only 0.43 kg, or ∼0.036 kg/y (i.e., <0.02 lb/y). Although statistically significant, the clinical relevance of this is not obvious.

Definitions of Refined Grain Intake May Confound Interpretation of Findings

As reviewed above, meta-analyses consistently show that refined grain intake is not associated with increased risk of major chronic diseases and all-cause mortality. It is necessary to interpret these results from the perspective of how refined grains have been defined in most of the studies included

in these meta-analyses. In addition to staple grain foods such as bread, cereals and pasta, most of the studies that have examined refined grain intake separate from a Western dietary pattern have defined refined grains to include such foods as cookies (29, 38, 55, 65, 83), cakes (25, 29, 31, 38, 44, 47, 52, 53, 55, 65, 86), donuts (29, 83), brownies (29, 83), muffins (25, 31, 38, 44, 47, 53, 64, 71, 84, 86), sweet rolls or buns (25, 31, 44, 52, 53, 55, 83, 86), sweets or desserts made with grains (23, 24, 54, 73), and pizza (23–25, 31, 38, 44, 47, 52–54, 73, 83, 84, 86, 87). These foods frequently contain high amounts of fat or sugar (or both), consumption of which may offset any beneficial effects of staple grain foods. Thus the generally neutral findings in most of the cohort studies of refined grain intake on health outcomes may be biased against yielding positive results.

Total Grain Intake and Chronic Disease

Meta-analyses have shown that total grain consumption is associated with reduced risk of T2D (3), total cancer (2), and all-cause mortality (2) (**Table 3**). Although meta-analyses indicate that total grain intake is not associated with risk of CHD (2), CVD (2), or stroke (2, 33), all relative risks for CVD and stroke (0.83–0.97) are actually suggestive of a benefit (Table 3). It should be noted that in both meta-analyses of grain intake and stroke risk (2, 33), the association between whole-grain intake and stroke risk was also not statistically significant.

Only 1 meta-analysis has reported on the association between total grain intake and all-cause mortality (2). In this analysis total grain intake was associated with a 9% lower risk of all-cause mortality when comparing the highest and lowest intake groups, which included 13 cohorts. The dose-response analysis, which included only 7 cohorts, produced a nonsignificant relative risk of 0.96 (Table 3).

These results for total grain intake are not surprising in view of the consistently beneficial associations between whole-grain intake and chronic disease risk (2–9) and the largely neutral findings for refined-grain intake (Table 1).

Whole Compared with Refined Grains: The Conundrum of Randomized Controlled Trial Results

Despite the consistent superiority of whole grains reported in observational studies, RCTs have not consistently produced expected findings. Four meta-analyses of RCTs comparing whole and refined grains have been published, with mixed results (7, 90–92) (**Table 4**). These meta-analyses have included studies that determined the effects of diets higher in whole-grain foods compared with diets higher in refined-grain foods, or usual diet. Studies included in these meta-analyses were relatively short duration (2–16 wk).

In 1 meta-analysis (92), increased consumption of whole-grain foods had no effect on body weight or waist circumference compared with nonwhole-grain foods, but percentage body fat was reduced by 0.48% more after eating more whole-grain foods. The significance of a decrease in body fat of such small magnitude is questionable. In a Cochrane review and meta-analysis (90), diets higher in whole-grain foods had no significant effect on body weight, BMI, total cholesterol, LDL cholesterol, HDL-C, triglycerides, or blood pressure. Similarly, a meta-analysis of RCTs found no effect of whole-grain foods on fasting glucose and insulin, or HOMA-IR (91). The only meta-analysis of RCTs showing a superiority of whole-grain foods reported lower fasting glucose, total cholesterol, and LDL-C, and a trend for a reduction in fasting insulin, but no significant effect on blood pressure or body weight (7) (Table 4). The difference in findings for glucose and insulin (7, 91) and total cholesterol and LDL cholesterol (7, 90) could be due in large part to the different studies included in each of the meta-analyses.

The short duration of the studies (none lasted >16 wk, and most were between 4 and 6 wk) may have contributed to the lack of differences between the diets. If the differences apparent in observational studies are truly due to whole-grain intake, it may reflect habitual intake over years. In addition, the reduced risk of chronic diseases associated with whole-grain intake may be attributable to novel biomarkers of cardiometabolic health not measured in the RCTs. Alternatively, the superior health benefits of whole-grain foods may be due in large part to their postprandial effects. A meta-analysis

TABLE 3 Total grain intake and relative risk of CVD, CHD, stroke, T2D, cancer, and all-cause mortality: results from meta-analyses of prospective cohort studies[1]

| Meta-analysis reference | Highest vs lowest intakes | | Dose response[2] | | |
	Number of cohorts included	Relative risk (95% CI)	Number of cohorts included	Relative risk (95% CI)	Outcome
Aune et al. (2)	3	1.07 (0.91, 1.25)	2	1.07 (0.88, 1.30)	CHD
Aune et al. (2)	3	0.94 (0.84, 1.06)	1	0.83 (0.70, 1.00)	CVD
Aune et al. (2)	4	0.89 (0.79, 1.00)	5	0.93 (0.85, 1.02)	Stroke
Chen et al. (33)	8	0.97 (0.83, 1.14)	6	0.97 (0.90, 1.03)	Stroke
Aune et al. (3)	4	0.74 (0.58, 0.93)	4	0.83 (0.75, 0.91)	T2D
Aune et al. (2)	1	0.92 (0.80, 1.06)	2	0.97 (0.96, 0.99)	Total cancer
Aune et al. (2)	13	0.91 (0.87, 0.95)	7	0.96 (0.90, 1.02)	All-cause mortality

[1]CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes.
[2]In dose-response analyses, relative risks are per 90 g/d for all studies.

TABLE 4 Effects of whole-grain foods compared with refined-grain foods (or usual diet) on cardiovascular risk markers, blood pressure, body weight, and body fat: results from meta-analyses of randomized controlled trials[1]

Outcome	Meta-analysis reference	Number of trials included	Mean difference (95% CI)
Intervention studies			
Fasting glucose, mmol/L	Ye et al. (7)	13	−0.93 (−1.65, −0.21)
	Marventano et al. (91)	15	−0.04 (−2.26, 0.04)
Fasting insulin, pmol/L^{-1}	Ye et al. (7)	12	−0.29 (−0.59, 0.01)
	Marventano et al. (91)	14	−2.26 (−6.58, 2.06)
HOMA-IR	Marventano et al. (91)	7	−0.18 (−0.48, 0.13)
Fasting cholesterol, mmol/L	Ye et al. (7)	20	−0.83 (−1.23, −0.42)
	Kelly et al. (90)	7	0.07 (−0.07, 0.21)
Fasting LDL cholesterol, mmol/L	Ye et al. (7)	19	−0.82 (−1.31, −0.33)
	Kelly et al. (90)	8	0.06 (−0.05, 0.16)
Fasting HDL cholesterol, mmol/L	Kelly et al. (90)	8	−0.02 (−0.05, 0.01)
Fasting triglycerides, mmol/L	Kelly et al. (90)	8	0.03 (−0.08, 0.13)
Body weight, kg	Ye et al. (7)	12	−0.18 (−0.54, 0.18)
	Pol et al. (92)	31	0.06 (−0.09, 0.20)
	Kelly et al. (90)	5	−0.41 (−1.04, 0.23)
Body mass index, kg/m^2	Kelly et al. (90)	5	−0.12 (−0.24, 0.01)
Body fat, %	Pol et al. (92)	9	−0.48 (−0.95, −0.01)
Waist circumference, cm	Pol et al. (92)	11	−0.15 (−0.51, 0.22)
Systolic blood pressure, mm Hg	Ye et al. (7)	7	−0.06 (−0.21, 0.10)
	Kelly et al. (90)	8	0.04 (−1.67, 1.75)
Diastolic blood pressure, mm Hg	Ye et al. (7)	7	−0.05 (−0.21, 0.11)
	Kelly et al. (90)	7	0.16 (−0.89, 1.21)
Acute feeding studies			
iAUC glucose 120, mmol · min · L^{-1}	Marventano et al. (91)	23	−29.71 (−43.57, −15.85)
iAUC glucose 180, mmol · min · L^{-1}		8	−15.40 (−31.52, 0.73)
iAUC insulin 120, mmol · min · L^{-1}		7	−2.01 (−2.88, −1.14)
iAUC insulin 180, mmol · min · L^{-1}		13	−3.64 (−5.00, −2.28)
Maximum postprandial glucose, mmol/L		11	−0.25 (−0.43, −0.06)
Maximum postprandial insulin, pmol/L		8	−73.78 (−108.56, −38.99)

[1] iAUC, incremental area under the curve.

of RCTs demonstrated clear superiority of whole grains for producing lower maximal postprandial responses and incremental area under the curve for glucose and insulin (91) (Table 4). Elevated nonfasting blood glucose concentration is a risk factor for CVD (93), and postprandial hyperglycemia has been reported to better predict CVD than fasting blood glucose (94).

Replace Refined Grains with Whole Grains, or Just Eat More Whole Grains?

Despite persistent efforts to encourage Americans to eat more whole-grain foods (1), consumption of whole grains remains well below recommended amounts (10–12). Because the health properties of food have a lower priority than taste, convenience, or price (95), it is not surprising that the US population mean whole-grain consumption remains <1 serving/d (12). It is important to note that even though the 2015 DGAC recommended that dietary quality would improve if Americans replaced most refined grains with whole grains, the committee's report also acknowledged that, based on food modeling, consumption of all grains as whole grains, without including any enriched grain products, would result in nutrient shortfalls (12). Consumption of refined grain foods that have been enriched or fortified can help alleviate shortfalls of nutrients, including folic acid, iron, thiamin, niacin, and riboflavin (96, 97). Folic acid is essential

for women of childbearing age to help prevent neural tube birth defects, and enriched grains are the largest contributor of folic acid in the American diet (98). The rate of neural tube defects in the United States has decreased by 35% since the fortification of enriched grains began in 1998 (99).

Grain foods contribute 54.5% of all fiber in the American diet (100). Of this, ∼72% of the grain contribution to total fiber intake comes from refined grains (100). Thus ∼39% of dietary fiber intake among Americans comes from refined grains. The contributions of both whole and refined grains to total fiber intake are important because >90% of adults and children fall short of dietary fiber recommendations (101). Cereal fiber intake has been associated with reduced risk of chronic disease (102), and meta-analyses demonstrate that cereal fiber intake has a stronger association with reduced T2D than fiber from fruits and vegetables (103). In these studies the sources of cereal fiber were not separated into whole- or refined-grain foods. Given the fact that most cereal fiber in the US diet comes from refined grains, it would be unreasonable to conclude that the benefits of cereal fiber are exclusively due to whole grains. For example, in the NIH-AARP study, fiber from grains (without distinction between whole and refined), but not other sources, was associated with significant reduction in all-cause, CVD, and cancer mortality (104). Thus refined grain intake may provide an important source of cereal fiber in the US diet. Consequently,

reducing intake of refined grains may have unintended consequences.

Conclusion

Eleven systematic reviews and meta-analyses of prospective cohort studies have assessed the association between refined-grain intake and all-cause mortality, T2D, CVD, CHD, stroke, hypertension, and cancer (Table 1). Collectively, they included a total of 32 publications with data from 24 distinct cohorts. These meta-analyses essentially show that refined grain intake is not associated with the chronic diseases widely assumed to be moderately or strongly linked to refined grain consumption (12, 14). The results are remarkably consistent, with virtually all of the 32 publications indicating no higher risk associated with refined grain intake. There is some evidence that white rice consumption is associated with increased risk of T2D, but this appears to be limited primarily to Asian populations, in which white rice consumption is much higher than in Western populations (63).

By contrast, 9 published meta-analyses consistently show increased risk of these same chronic diseases and all-cause mortality associated with intake of red and processed meat (4, 6, 13, 40–42, 49, 50, 36), key components of the Western dietary pattern. Thus it is inaccurate to attribute the adverse health outcomes associated with the Western dietary pattern to refined-grain intake (12, 14). It is possible that the higher risk associated with red and processed meat intake could be related in part to the fact that diets high in either red or processed meat may be lower in overall diet quality, including lower intakes of fruits and vegetables (105, 106). However, not all studies have reported lower intakes of fruits and vegetables among high consumers of red and processed meat (107–109). Moreover, data from the European Prospective Investigation into Cancer and Nutrition study indicated that the higher all-cause mortality risk associated with processed meat consumption was evident in participants who fell both below and above median consumption of fruits and vegetables (106), and results from 2 large Swedish cohorts demonstrated that the higher hazard ratios for all-cause and CVD mortality associated with total red meat consumption were significant, and of similar magnitude, across all categories (low, medium, high) of fruit-and-vegetable intake (107).

Although recommendations to increase whole-grain consumption are scientifically supported, because total grain consumption is unrelated to risk of CHD, CVD, and cancer, and is associated with reduced risk of T2D and all-cause mortality (Table 3), the recommendation to reduce consumption of refined grains (1, 12, 14) is contrary to a substantial body of published scientific evidence.

Refined grain consumption up to 6–7 servings/d is not associated with higher risk of chronic disease or all-cause mortality (3, 4, 47, 48, 56). Also, enriched/refined grains contribute meaningfully to reduce gaps in certain shortfall nutrients (96, 97), including dietary fiber (100). Consequently, the most scientifically sound recommendation may be to encourage increased consumption of whole grains without specific recommendations for reducing refined grain intake. Benefits of whole-grain consumption are most apparent with consumption of 2–3 servings/d (60–90 g, or ∼2–3 oz, per day) (2–4, 6, 13). Current average US intake for whole grains is <1 serving/d. Thus a recommendation to increase whole-grain consumption, by as little as 1–2 servings/d, may be the most uncomplicated, as well as scientifically justified, approach.

It could be argued that increasing whole-grain consumption without recommending a reduction in refined-grain consumption could contribute to greater positive energy balance, thus adversely affecting weight control efforts. However, the lack of any consistent association between refined-grain intake and BMI (23, 25, 27, 29, 52, 57, 65, 71, 77–85) suggests that this should not be a serious concern. Furthermore, prospective cohort studies consistently show an inverse relationship between carbohydrate intake and BMI (77). It must also be noted that in studies showing a positive association between refined-grain intake and either BMI or weight gain, the definition of refined grains in these studies included foods such as cookies, brownies, donuts, sweet rolls, scones, croissants, hush puppies, ice cream bread, muffins, coffee cakes, and pizza (47, 73, 83, 86–89). Thus it is impossible to determine from these studies the separate contributions to body weight and body fat of staple grain foods (i.e., bread, cereals, pasta) compared with indulgent grain foods. Indulgent grain foods have a higher fat and sugar content, and lower fiber content and nutrient density (96, 97).

Therefore, it would be prudent, both in terms of public health recommendations and in future research, to make clear distinctions between health impacts of staple grain foods and indulgent grain foods. As described herein, most published reports have failed to make such distinctions. Benefits of whole grains are based on studies of grain foods that are primarily staple grains, whereas studies on refined grains, mainly prospective cohort studies, include both staple and indulgent grain foods in the definition of refined grains. Another important research gap is to resolve the discrepant findings of observational studies and RCTs with respect to health effects of whole-grain and refined-grain foods. Results from RCTs do not indicate a consistent benefit of whole-grain foods compared with refined-grain foods. This is a dilemma that needs resolution.

Finally, this literature analysis illustrates a pitfall of attributing health risks to specific food groups based primarily on analysis of dietary patterns (12, 15–19). With regard to refined grains, a large and consistent body of evidence from meta-analyses of prospective cohort studies (2–6, 13, 20, 33, 34, 35, 36) suggests that the assumed health risks are largely a consequence of guilt by association with other foods within the Western dietary pattern, and not to refined grains per se.

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