Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies

Guo-Chong Chen, Xing Tong, Jia-Ying Xu, Shu-Fen Han, Zhong-Xiao Wan, Jia-Bi Qin, and Li-Qiang Qin

ABSTRACT

Background: The potential role of whole grain in preventing various mortality outcomes has been inconsistently reported in a wealth of prospective observational studies.

Objective: We evaluated the relations between whole-grain intake and risks of dying from any cause, cardiovascular disease (CVD), and cancer through a meta-analytic approach.

Design: Relevant studies were identified by searching PubMed and EMBASE databases and bibliographies of retrieved full publications. Summary RRs with 95% CIs were calculated with a random-effects model.

Results: Thirteen studies on total mortality (104,061 deaths), 12 on CVD mortality (26,352 deaths), and 8 on cancer mortality (34,797 deaths) were included. Three studies reported whole-grain intake, and the remaining studies reported whole-grain product intake. In the dose-response analysis in which the intake of whole-grain products was converted to the amount of whole grain, the summary RRs for an increment in whole-grain intake of 50 g/d were 0.78 (95% CI: 0.67, 0.91) for total mortality, 0.70 (95% CI: 0.61, 0.79) for CVD mortality, and 0.82 (95% CI: 0.69, 0.96) for cancer mortality. A similar reduction was observed for the mortality from ischemic heart disease (RR: 0.68; 95% CI: 0.55, 0.84) but not from stroke (RR: 0.93; 95% CI: 0.54, 1.62). There was evidence of nonlinear associations of whole-grain intake with total (P-nonlinearity < 0.001) and CVD mortality (P-nonlinearity < 0.001), but not with cancer mortality (P-nonlinearity = 0.12), with the curves for the associations appearing slightly steeper at lower ranges (<35 g/d) of the intake than at higher ranges.

Conclusions: Our findings suggest significant inverse relationships between whole-grain intake and mortality due to any cause, CVD, or cancer. The findings support the recommendation of increasing whole-grain intake to improve public health.

Keywords: whole grain, cardiovascular disease, cancer, mortality, meta-analysis

INTRODUCTION

Whole grains are among the nutrient-dense plant-based foods that are an important part of a healthy dietary pattern (1). Whole grains consist of 3 parts—namely, bran, germ, and starchy endosperm. The bran and germ, which are removed during the refining process, are rich in micronutrients, dietary fiber, and phytochemicals, and these components may exert favorable effects on health because of their potential anticancerogenic and cardioprotective properties by multiple mechanisms, such as reduction of inflammation and immune protection (2–4). For several decades, intake of whole-grain products has been suggested to be protective against a range of chronic diseases, such as type 2 diabetes (5), ischemic heart disease (IHD) (3), and certain cancers (e.g., colorectal cancer) (6), and their potential risk factors, such as obesity (7), hypertension (8, 9), and elevated fasting glucose, insulin, and LDL-cholesterol concentrations (10). This evidence base has prompted several national organizations to recommend that people eat more whole grains as part of a healthy diet (11, 12).

Despite these potential benefits, the role of whole-grain intake in preventing premature death remains uncertain. The effects of whole-grain intake on mortality outcomes reflect the effects on both disease development and progress and may be more relevant to the public when compared with the effects on a specific disease. Among a wealth of prospective observational studies (13–26) that examined the risk of mortality associated with whole grain or whole-grain product intake, although risk reductions have been frequently reported, some studies have found no association with total (13, 23, 25), cardiovascular disease (CVD) (13, 18, 21), or cancer mortality (13, 15, 16, 18, 26). The disparate findings may be ascribed to the differences in the measurement and/or definition of whole grain, statistical adjustment, baseline exclusion criteria, or some other varieties in study and population characteristics across individual studies. Hence, to systematically and quantitatively assess the survival benefits of whole grain is of both scientific and public health
significance. In an attempt to quantify the relations between whole-grain intake and risk of dying from any cause, CVD, and cancer, a systematic review and meta-analysis of prospective studies were performed. We hypothesized that whole-grain intake would be associated with reduced risk of mortality.

METHODS

Literature search

The study was planned, conducted, and reported in adherence to the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (27). A literature search was performed on PubMed and EMBASE databases through 30 June 2015, with the use of the search strategy reported in Supplemental Table 1, with the core search involving total and individual whole grain (e.g., wheat, corn, rye, and oats) and mortality outcomes combined with specific terms for study design. No language restrictions were imposed. The bibliographies of retrieved full publications and related reviews were also carefully hand searched for any further study. We did not contact relevant authors of the retrieved publications for additional information.

Study selection

Studies that met the following criteria were considered: 1) the study design was prospective; 2) the exposure of interest was intake of whole grain or whole-grain products; 3) the outcome of interest was total mortality, CVD mortality, or cancer mortality; and 4) RRs with corresponding 95% CIs were reported or could be calculated. When multiple publications from the same study were available, the one with the largest number of events was included. Studies that investigated mortality risk in patients with a specific disease (e.g., cancer or heart failure) were excluded.

Data extraction and quality assessment

With the use of a standardized data-collection form, the following data were extracted from each included study: the first author’s last name, publication year, country, study name, years of follow-up, participant age, participant sex, number of deaths and participants, types of intake (whole-grain products or whole grain), levels of intake in each category, definition of whole grain or whole-grain products, methods for diet assessment, prevalent diseases excluded at baseline, adjusted RR with 95% CI for each category of whole-grain intake, and potential confounders adjusted for in the statistical models.

The study quality was evaluated with the use of the 9-star Newcastle-Ottawa Scale (28). A quality score was calculated on the basis of 3 major components of included studies: selection of the study groups (0–4 stars), adjustment for known confounding factors (0–2 stars), and ascertainment of the outcome of interest (0–3 stars). A higher score represented better methodologic quality. Literature selection, data extraction, and quality assessment were conducted independently by 2 authors (G-CC and L-QQ), with any disagreement resolved by consensus.

Statistical analysis

The RR was used as the effect size across studies, and the HRs and incidence rate ratios were deemed equivalent to RR. In general, risk estimates that reflected the greatest degree of adjustment for potential confounders were used in the meta-analysis. For the NIH-AARP Diet and Health Study (14), we extracted multivariable-adjusted estimates without adjustment for dietary fiber intake to avoid overadjustment, because whole grain is a major source of dietary fiber, which may causally lower mortality. We used a random-effects model (29), which considers both within- and between-study variation to calculate the summary risk estimates. For studies that separately reported results by sex (17) or CVD subtype (17, 18) (IHD and stroke) without presenting overall estimates, we pooled the results with a fixed-effects model and included the combined results in the main analyses to maintain the correct df for heterogeneity tests. We conducted stratified analyses to explore the potential sources of heterogeneity according to geographic region, sex, duration of follow-up, methods for exposure assessment, the types of intake (whole-grain products compared with whole grain), quality scores, exclusion of prevalent disorders at baseline, and adjustment for potential confounders. Further sensitivity analyses were carried out by omitting one study at each turn while pooling results from the remaining studies.

Given the distinct cutoff points across studies, dose-response analyses were conducted with the use of the method of Greenland and Longnecker (30) and Orsini et al. (31). The method requires the number of cases and person-years and the risk estimates with their variance for ≥3 quantitative exposure categories. For studies that did not provide the number of cases or person-years in each exposure category, the data were estimated from the total number of cases/person-years. For each study, the median or mean level of intake for each category was assigned to each corresponding risk estimate. When the median or mean intake per category was not provided, the midpoint of the upper and lower boundaries in each category was assigned as a mean intake. If the highest category was open ended, we assumed the width of the interval to be the same as in the second-highest category. Three studies from 2 publications (17, 26) reported the amount of whole-grain intake, and the other included studies reported the amount or frequency of whole-grain products. According to recent recommendations by Ross et al. (32), we converted the intake of whole-grain products into the intake of whole grain as follows: for studies (14, 15, 19, 21, 23, 24) reporting the frequency of whole-grain products, the intake was converted into the amount of whole grain by using 16 g as a serving size, and for studies (13, 20, 25) in which whole-grain products were reported in grams, the weights were multiplied by 0.57 (28 g of whole-grain products approximates 16 g of whole grain) to estimate the intake of whole grain. The results of linear dose-response in the forest plots were presented for a 50-g/d increment, which approximates the intake level (3 servings/d) recommended by diet guidelines (11, 12). Potential nonlinear relationships between whole-grain intake and mortality were examined by modeling exposure levels with the use of restricted cubic splines with 3 kn at percentiles 10%, 50%, and 95% of the distribution (33, 34). A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

Heterogeneity tests were performed with the use of Q and F² statistics (35). For the Q statistic, P < 0.1 was considered statistically significant. For the F² statistic, the following cutoff points were used: <30% (little or no heterogeneity), 30–75% (moderate heterogeneity), and >75% (high heterogeneity). Potential publication bias was investigated with both Egger regression and Begg
correlation tests (36, 37). All statistical analyses were performed with the use of STATA software, version 11.0 (STATA Corp.). All P values were 2-sided, and the level of significance was at <0.05, unless explicitly stated.

RESULTS

Literature selection

A flowchart of the study screening and selection process is shown in Figure 1. Briefly, a total of 921 independent citations were identified after duplicate exclusion, of which 63 were retrieved for more detailed reviews. A total of 49 full reports were excluded after further evaluations. Most of these reports were excluded because the exposure or outcome of interest was not relevant to the topic studied. The Iowa Women’s Health Study; the Nurses’ Health Study; and the Diet, Cancer and Health study had 4 (15, 38–40), 3 (26, 41, 42), and 2 (17, 43) overlapping publications, respectively, and we included the reports (15, 17, 26) with the largest number of events. One report (44) was excluded because the association was investigated in participants with heart failure. Further excluded was one report (45) in which whole-grain bread was compared with white bread. Finally, a total of 15 independent prospective studies from 14 publications (13–26) were included, consisting of 13 studies (13–19, 22–26) on total mortality (104,061 total deaths), 12 studies (13–21, 23, 26) on CVD mortality (26,352 CVD-related deaths), and 8 studies (13–18, 26) on cancer mortality (34,797 cancer-related deaths) in relation to whole grain or whole-grain product intake.

Study characteristics

Table 1 summarizes the characteristics of the included studies. The studies were published between 1996 and 2015. They were mainly from the United States (14, 15, 19, 23, 24, 26) or Europe (13, 16–18, 20, 22, 25) in addition to one cohort (21) of Singapore Chinese. The study duration ranged between 5.5 and 26 y, with all but 3 studies (13, 19, 20) being followed up for ≥10 y. Except for the 2 Harvard cohorts that reported whole grain, and 1 European cohort in which both whole grain and whole-grain products were reported, most of the included studies reported whole-grain product intake, with some merely investigating individual whole-grain products, such as whole-grain bread (16, 18, 21, 22), rye products (20), and whole-grain breakfast cereals (19). Most studies (13–16, 18, 20–26) excluded prevalent CVD and/or cancer at baseline, and some (14, 15, 20–25) further excluded prevalent diabetes. Supplemental Table 2 reports the potential confounders adjusted for in the original studies. Age and smoking were adjusted for in all cohorts. Other commonly considered potential confounders included alcohol, BMI, physical activity, energy intake, educational levels, and history of diabetes, hypertension, and hypercholesterolemia.

Supplemental Table 3 summarizes the definition and measurement of whole grain or whole-grain products and reported results from individual studies. Whole-grain foods were mostly defined as those containing ≥25% of whole grain and/or bran by weight among studies that reported the definition. Dietary information was collected with self-administered food frequency questionnaires, with the exceptions of 3 studies (13, 21, 24) in which interviews were performed and one study (23) in which a 3-d food record was applied. In a Norwegian cohort, Jacobs et al. (16) developed a whole-grain bread score by multiplying the number of slices of bread eaten per day by the proportion of whole-grain flour. We also included this study because the score could be an indicator of the amount of whole grain consumed. Supplemental Table 4 presents the details of quality assessment according to the 9-star Newcastle-Ottawa Scale.

Whole-grain intake and total mortality

High compared with low intake

Twelve studies (13–19, 22–24, 26) were included in the analysis of high compared with low whole-grain (3 studies) or whole-grain product (9 studies) intake and total mortality. The summary RR was 0.83 (95% CI: 0.80, 0.88), with moderate heterogeneity (P < 0.001, I² = 70.6%) (Supplemental Figure 1A).
<table>
<thead>
<tr>
<th>First author (ref), year</th>
<th>Location</th>
<th>Study name, duration</th>
<th>Participants</th>
<th>Deaths, n</th>
<th>Type of intake</th>
<th>Baseline diseases excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key (18), 1996</td>
<td>UK</td>
<td>NR, 18.8 y</td>
<td>10,977 men and women aged 16–79 y</td>
<td>1343 total, 350 IHD, 147 stroke, and 451 cancer</td>
<td>Whole-meal bread</td>
<td>Cancer</td>
</tr>
<tr>
<td>Pietinen (20), 1996</td>
<td>Finland</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 6.1 y</td>
<td>21,930 male smokers aged 50–69 y</td>
<td>635 IHD</td>
<td>Rye products</td>
<td>CVD, diabetes, and exercise-related chest pain</td>
</tr>
<tr>
<td>Jacobs (16), 2001</td>
<td>Norway</td>
<td>Norwegian County Study, 14.4 y</td>
<td>33,848 men and women aged 35–56 y</td>
<td>2058 total, 758 CVD, 553 IHD, and 870 cancer</td>
<td>Whole-grain bread</td>
<td>CVD</td>
</tr>
<tr>
<td>Steffen (24), 2003</td>
<td>US</td>
<td>Atherosclerosis Risk in Communities Study, 11 y</td>
<td>11,940 men and women aged 45–64 y</td>
<td>867 total</td>
<td>Whole-grain products</td>
<td>CVD, diabetes, and cancer</td>
</tr>
<tr>
<td>Liu (19), 2003</td>
<td>US</td>
<td>Physicians’ Health Study, 5.5 y</td>
<td>86,190 men aged 40–84 y</td>
<td>314 total, 1381 CVD, 488 MI, and 146 stroke</td>
<td>Whole-grain breakfast cereals</td>
<td>CVD and cancer</td>
</tr>
<tr>
<td>Sahyoun (23), 2006</td>
<td>US</td>
<td>NR, 14 y</td>
<td>535 men and women aged 60–98 y</td>
<td>185 total and 89 CVD</td>
<td>Whole-grain products</td>
<td>Insulin or oral glycemic agent users</td>
</tr>
<tr>
<td>Jacobs (15), 2007</td>
<td>US</td>
<td>Iowa Women’s Health Study, 17 y</td>
<td>27,312 postmenopausal women aged 55–69 y</td>
<td>5552 total, 1900 CVD, 1034 IHD, 414 stroke, and 2099 cancer</td>
<td>Whole-grain products</td>
<td>CVD, cancer, diabetes, chronic colitis, and liver cirrhosis</td>
</tr>
<tr>
<td>van den Brandt (25), 2011</td>
<td>Netherlands</td>
<td>Case-cohort within the Netherlands Cohort Study, 10 y</td>
<td>13,267 men and women aged 55–69 y</td>
<td>9691 total</td>
<td>Whole-grain products</td>
<td>CVD, cancer, and diabetes</td>
</tr>
<tr>
<td>Buil-Cosiales (13), 2014</td>
<td>Spain</td>
<td>PREDIMED study, 5.9 y</td>
<td>7216 men (55–75 y) and women (60–69 y) at high CVD risk</td>
<td>425 total, 103 CVD, and 169 cancer</td>
<td>Whole-grain products</td>
<td>CVD</td>
</tr>
<tr>
<td>Rebello (21), 2014</td>
<td>Singapore</td>
<td>Singapore Chinese Health Study, 15 y</td>
<td>53,469 men and women aged 45–74 y</td>
<td>1660 IHD</td>
<td>Whole-wheat bread</td>
<td>CVD, cancer, and diabetes</td>
</tr>
<tr>
<td>Huang (14), 2015</td>
<td>US</td>
<td>NIH-AARP Diet and Health Study, 14 y</td>
<td>367,442 men and women aged 50–71 y</td>
<td>46,067 total, 11,283 CVD, and 19,043 cancer</td>
<td>Whole-grain products</td>
<td>CVD, cancer, diabetes, and end-stage renal disease</td>
</tr>
<tr>
<td>Wu (26), 2015</td>
<td>US</td>
<td>Nurses’ Health Study, 26 y</td>
<td>74,341 female nurses aged 30–55 y</td>
<td>15,106 total, 2985 CVD, and 5964 cancer</td>
<td>Whole grain</td>
<td>CVD and cancer</td>
</tr>
<tr>
<td>Wu (26), 2015</td>
<td>US</td>
<td>Health Professionals Follow-Up Study, 24 y</td>
<td>43,744 male professionals aged 32–87 y</td>
<td>11,814 total, 3621 CVD, and 3921 cancer</td>
<td>Whole grain</td>
<td>CVD and cancer</td>
</tr>
<tr>
<td>Roswall (22), 2015</td>
<td>Sweden</td>
<td>Swedish Women’s Lifestyle and Health cohort, 21.3 y</td>
<td>44,961 women aged 29–49 y</td>
<td>1855 total</td>
<td>Whole-grain bread and oatmeal</td>
<td>CVD, cancer, and diabetes</td>
</tr>
<tr>
<td>Johnsen (17), 2015</td>
<td>Norway, Denmark, and Sweden</td>
<td>HELGA cohort, 11.1–14.2 y</td>
<td>120,010 men and women aged 30–64 y</td>
<td>7832 total, 11,56 IHD, 280 stroke, and 3150 cancer</td>
<td>Both whole-grain products and whole grain</td>
<td>None</td>
</tr>
</tbody>
</table>

\(^1\text{CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; NR, not reported; PREDIMED, Prevención con Dieta Mediterránea; ref, reference.}\)
Dose-response analysis

Ten studies (13–15, 17, 19, 23–26) were included in the dose-response analysis. Seven (13–15, 19, 23–25) of these studies reported whole-grain product intake, and for these studies we converted the intake into the amount of whole grain. The summary RR for an increase in whole-grain intake of 50 g/d was 0.78 (95% CI: 0.67, 0.91), with considerable heterogeneity ($P < 0.001$, $I^2 = 94.3\%$) (Figure 2A). There was no evidence of publication bias ($P$-Egger = 0.81 and $P$-Begg = 1.00). There was evidence of a nonlinear relation between whole-grain intake and total mortality, with further but more moderate decreases in risk after the intake of 35 g/d ($P$-nonlinearity $< 0.001$) (Figure 2B and Supplemental Table 5).

Whole-grain intake and CVD mortality

High compared with low intake

Twelve studies (13–21, 23, 26) were included in the analysis of high compared with low whole-grain (3 studies) or whole-grain product (9 studies) intake and CVD mortality. The summary RR was 0.82 (95% CI: 0.78, 0.85), with no heterogeneity ($I^2 = 0\%$) (Supplemental Figure 1B). Excluding 2 studies (20, 21) that involved only IHD death, the summary RR was 0.82 (95% CI: 0.79, 0.85), with no heterogeneity ($I^2 = 0\%$). The summary RRs were 0.75 (95% CI: 0.69, 0.83) for IHD mortality [Supplemental Figure 2A; 7 studies (15–21)] and 0.96 (95% CI: 0.75, 1.22) for stroke mortality [Supplemental Figure 2B; 4 studies (15, 17–19)].

Dose-response analysis

Ten studies (13–15, 17, 19–21, 23, 26) were included in the dose-response analysis, among which we converted the intake of whole-grain products to the amount of whole grain for 7 studies (13–15, 19–21, 23). The summary RR for each 50-g/d increase in whole-grain intake was 0.70 (95% CI: 0.61, 0.79), with moderate heterogeneity ($P = 0.002$, $I^2 = 64.8\%$) (Figure 3A). There was no evidence of publication bias ($P$-Egger = 0.14 and $P$-Begg = 0.37). There was evidence of a nonlinear association ($P$-nonlinearity $< 0.001$) (Figure 3B, Supplemental Table 5), with additional but more moderate reductions in risk after the intake of 35 g whole grain/d. The summary RRs were 0.68 (95% CI: 0.55, 0.84) for IHD mortality [Supplemental Figure 2C, 5 studies (15, 17, 19–21)] and 0.93 (95% CI: 0.54, 1.62) for stroke mortality [Supplemental Figure 2D; 3 studies (15, 17, 19)]. There was a nonlinear association with IHD mortality (Supplemental Figure 2E; $P$-nonlinearity = 0.03) but not with stroke mortality (Supplemental Figure 2F).

Whole-grain intake and cancer mortality

High compared with low intake

Eight studies (13–18, 26) were included in the analysis of high compared with low whole-grain (3 studies) or whole-grain product (5 studies) intake and cancer mortality. The summary RR was 0.89 (95% CI: 0.84, 0.95), with moderate heterogeneity ($P = 0.04$, $I^2 = 53.6\%$) (Supplemental Figure 1C).

Dose-response analysis

Six studies (13–15, 17, 26) were eligible for the dose-response analysis, and the intake of whole-grain products was converted to whole-grain intake for 3 studies (13–15). The summary RR for whole-grain intake of 50 g/d was 0.82 (95% CI: 0.69, 0.96), with substantial heterogeneity ($P < 0.001$, $I^2 = 85.3\%$) (Figure 4A). There was no evidence of publication bias ($P$-Egger = 0.75 and $P$-Begg = 0.71). No evidence of a nonlinear relation was observed (Figure 4B).

Subgroup and sensitivity analyses

Results of subgroup analyses for the association of whole-grain or whole-grain product intake (high compared with low) and risk of mortality are shown in Supplemental Table 6. All estimates, despite disparate magnitudes, were in the same direction, and most were highly statistically significant. When stratifying the analyses by the types of intake (whole-grain products compared with whole grain), the risks of total mortality and CVD mortality were significantly and inversely associated with both of the intakes, and the risk of cancer mortality was significantly inversely associated with the intake of whole-grain products rather than whole grain, but the differences between strata were not statistically significant. There was evidence that adjustment for education significantly strengthened the associations with total mortality ($P$-difference $= 0.05$) and cancer mortality ($P$-difference $= 0.02$), whereas adjustment...
intake of whole grain was associated with reduced risk of total mortality and death from CVD and cancer. High compared with low intake of whole grain or whole-grain products was significantly associated with 11–18% lower risk of total or cause-specific mortality. In the linear dose-response analyses in which the intake of whole-grain products was converted to the amount of whole grain, each 50-g/d increase in whole-grain intake was associated with 22%, 30%, and 18% lower risk of dying from any cause, CVD, and cancer, respectively. Furthermore, the curves for the associations with total mortality and CVD mortality appeared steeper at lower ranges of the intake than at higher ranges.

Our findings are consistent with the evidence from prospective studies that showed protections of whole-grain intake on a variety of chronic diseases. A 2012 meta-analysis (10) of 10 prospective cohort studies reported 21% decreased CVD risk (fatal and/or nonfatal) for high compared with low whole-grain intake. Another meta-analysis (5) of 10 cohort studies showed a 32% reduction in the incidence of type 2 diabetes for whole-grain intake of 3 servings/d, which was in line with the findings of subsequent studies (14, 17) showing reduced diabetes mortality in habitual whole-grain consumers. Other conditions that were shown to be inversely associated with whole-grain intake include obesity (7),

DISCUSSION

In this large systematic review and meta-analysis of prospective studies involving >104,000 incident deaths, we found that a high

FIGURE 3 Meta-analysis of whole-grain intake and cardiovascular mortality. The summary risk estimates were calculated with a random-effects model. HPFS, Health Professionals Follow-Up Study; NHS, Nurses’ Health Study.

FIGURE 4 Meta-analysis of whole-grain intake and cancer mortality. HPFS, Health Professionals Follow-Up Study; NHS, Nurses’ Health Study.
the metabolic syndrome (23, 46), hypertension (8, 9), colorectal cancer (6), and inflammatory and respiratory diseases (15, 17, 18). Few prospective studies also showed significant inverse associations between whole-grain intake and mortality in individuals with specific diseases such as heart failure (44) and type 2 diabetes (41).

Whole-grain products are a major source of dietary fiber. An accumulation of evidence shows that dietary fiber intake is associated with lower risk of specific diseases (6, 47–50) and total mortality (51). Apart from dietary fiber, whole grain also contains a wide array of other potentially beneficial constituents, such as folate, B-group vitamins, minerals, and phytochemicals that may independently or jointly exert a favorable effect on health (3). Evidence from randomized controlled trials (RCTs) shows that supplementation with whole grain can favorably affect metabolic intermediate risk factors. In a pooled analysis of 21 RCTs (10), participants receiving whole-grain interventions, regardless of formulation and dosage, had significantly reduced fasting glucose and insulin concentrations, reduced total and LDL-cholesterol concentrations, lower systolic and diastolic blood pressure, and less weight gain when compared with control subjects. In the subgroup analyses of the current study, we found that the association of whole-grain intake with total mortality was significantly modified by adjustment for hypertension, and the association with cancer mortality was modified by the adjustment for hypertension and hypercholesterolemia. These differences, although they may be chance findings due to multiple subanalyses performed, nonetheless suggest that the benefits of whole grain may partly be mediated by its effects on blood pressure and/or cholesterol concentrations, and controlling for these potential mediators may represent overadjustments, thereby leading to attenuated estimates.

Several limitations should be acknowledged when interpreting the findings of this study. First, a meta-analysis of observational studies is subject to the problems with confounding factors that could be inherent in the selected studies. A higher intake of whole grain often clusters with overall healthier lifestyle behaviors, such as a higher physical activity, greater intakes of fruit and vegetables, and less smoking and processed red meat consumption. However, our stratified analyses by those factors that were known to confound the whole grain–mortality association supported the robustness of the summary estimates. Second, potential impacts of exposure misclassification need to be addressed. There were several sources of exposure misclassification, including the distinct definition of whole grain, the single collection of dietary information at baseline [in all but 3 studies (13, 26)], and the use of mostly self-administered food-frequency questionnaires to assess whole-grain intake. It may be difficult to consistently define and precisely estimate the intake of whole grain in observational studies, and some of the difficulties have been pointed out by Ross et al. (32). In cohort studies, misclassification of exposure would most likely be nondifferential, thus leading to an underestimation of the magnitude of the associations. In this respect, the observed reductions in mortality associated with whole-grain intake may be conservative estimates. Furthermore, reverse causality also merits consideration, because participants (in particular those whose dietary intakes were collected after the approval of the health claims for whole-grain intake) with high-risk conditions (e.g., hypertension and hypercholesterolemia) or diagnosed chronic diseases (e.g., diabetes, cancer, and CVD) may have changed their dietary habits. However, these participants would likely increase their intakes of whole grain and other potentially beneficial foods given the widely recommended intake of such foods, and including them would lead to a tendency of attenuated rather than exaggerated associations.

Despite the fact that increasing the intake of whole-grain foods has been recommended in several health claims, the amount of consumption remains relatively low. It is estimated that <10% of British adults and only 4.8% of American adults aged 19–50 y consumed ≥3 servings whole-grain foods/d (52, 53). In China, the daily intake of coarse grains, including whole grains and some legumes, reduced from 104 g/person in 1982 to 24 g/person in 2002, leading the 2007 Dietary Guidelines for Chinese to recommend coarse grain intake of ≥50 g/d for adults (54). Our dose-response analysis showed nonlinear relations between whole-grain intake and mortality, with the most important risk reductions at the lower ranges of the intake. These observations should be cautiously interpreted because of measurement errors and other methodologic issues in the original studies and also because of potential new measurement errors occurring when estimating the amount of whole-grain intake in the dose-response analyses. Nevertheless, these observations may highlight the necessity of further promoting the recommendation to increase whole-grain intake, in particular among low-intake populations, to improve public health. The issues encountered in trying to estimate whole-grain intake also highlighted the need for future studies to identify biomarkers for whole-grain intake, which would considerably reduce the likelihood of measurement errors and enhance the accuracy of the risk estimates.

In summary, our findings indicate significant inverse associations of whole-grain intake with total mortality, CVD mortality, and cancer mortality, which support the recommendation of increasing whole-grain intake to improve public health. Additional prospective studies with consistent, improved methods of estimating the intake are warranted to investigate whether the associations differ by specific types of whole grain, and future well-designed RCTs, such as those conducted among high-risk populations, are also warranted for definite conclusions.

The authors’ responsibilities were as follows—G-CC and L-QQ: designed the study and completed the literature search and data extraction; G-CC and XT: drafted the manuscript; G-CC and J-BQ: performed the statistical analyses; J-YX, S-FH, and Z-XW: critically revised the manuscript for important analyses; J-YX, S-FH, and Z-XW: critically revised the manuscript for important

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