Whole grain consumption and the risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality – a systematic review and dose-response meta-analysis of prospective studies

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Dear editor and dear reviewers

Thank you very much for the additional comments and suggestions. We have modified the manuscript according to the comments below. We have also updated the literature search and the statistical analyses as there have been published five additional publications (Shi et al, 2015, Xu et al, 2015, Wang et al, 2016, Bongard et al, 2016, and Helnæs et al, 2016), two of which reported on whole grains and the remaining reporting on total grains, bread, refined grains and breakfast cereals. We hope this is sufficient for the manuscript to be accepted for publication in BMJ.

On behalf of all the co-authors

Yours sincerely

Dagfinn Aune

Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the Editors:

* Please remove calculations about premature deaths avoided if grain intake was increased to 120 g/d (see reviewer 2's comments).

** RESPONSE: We have removed all calculations of attributable risks. **

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers **

Reviewer: 1

Recommendation:

Comments:
I read this revised manuscript about whole grains and all-cause and cause-specific risk and mortality with great interest. I think that the authors did a great job addressing review comments.

** RESPONSE: Thank you very much! **

Besides the few extra comments below, I have no further comments to add.

I think that this meta-analysis addresses a important topic, and that it could have a large and broad public health impact, as many countries are still to focus more on increasing the whole-grain intake of the general population, due to the many health benefits elegantly illustrated in this meta-analysis.

Few extra comments:
- Supplementary tables 3, add a column indicating the actual outcomes under study (e.g. for CVD, indicating that the outcome is incidence of ischemic heart disease). I know that it is mentioned in the table, but it would be more clear, if it had a separate column.
RESPONSE: We have added a separate column to Supplementary Tables 3-6 which indicates whether the outcome is incidence or mortality from the specific outcome. For the remaining outcomes in Supplementary Tables 7-12 all are from mortality.

- First line of the discussion: please avoid priority statements.
RESPONSE: We have modified the sentence so it reads: “This dose-response meta-analysis found an inverse association between whole grain intake and several major chronic disease outcomes, including coronary heart disease, stroke, cardiovascular disease overall, total cancer, all-cause mortality as well as less common causes of death such as mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death.”

Additional Questions:
Please enter your name: Cecilie Kyrø

Job Title: Postdoc

Institution: Danish Cancer Society Research Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests <a href="http://www.bmj.com/sites/default/files/attachments/resources/2011/07/bmjpolicyondeclarationofinterestsdocuments2014.pdf" target="_new">(please see BMJ policy)</a> please declare them here: No, I have no competing interest.

My research is funded by Innovation Fund Denmark (ELIN-B0603-00580B)
Reviewer: 2

Recommendation:

Comments:

I thank the authors for their very detailed replies to comments on the submitted version. While I find such studies very interesting, as I’m sure most of us do, I’m quite sceptical about whether we can draw reliable inferences. In all such studies the risk of residual confounding is considerable. I’m in favour of transparency but I do question whether we need 22 supplementary tables and 95 supplementary figures.

RESPONSE: We agree with the referee that there is a large number of supplementary tables and figures, but think these add important details for particularly interested readers and also better enable readers to assess limitations and strengths. A lot of the material contained in the supplementary appendix is required by the PRISMA guidelines (search strategy, list of excluded studies and exclusion reason, study characteristics, subgroup analyses, study quality assessment, funnel plots, results of sensitivity analyses). Lastly, for consistency with several other meta-analyses on other plant foods and antioxidants and mortality which we have conducted (under review) and for which we used the same format we would prefer to keep this information in the supplement.

Specific comments in response to the authors’ responses:

1. I queries the use of 7 servings a day as optimal. The authors have not changed this. While it is fine to use 7 as the reference the term “optimal” is surely inappropriate. In the context of diet in particular I think this term is unwise.

RESPONSE: The text where the term “optimal” was referred to was deleted together with the calculations of attributable risks.

2. I’d prefer that the authors note that tests for “publication bias” do have low power when there are few studies, not that they may have low power. And note that it is recommended that funnel plots not be used with fewer than 10 studies (Sterne et al BMJ 2011;343:d4002).

RESPONSE: We modified the sentence so it reads: “There was no evidence of publication bias for the remaining outcomes, although the number of studies was moderate and power to detect such bias is low when there are few studies.” We have deleted the funnel plots for analyses with less than 10 studies.

3. The authors present calculations of numbers of deaths saved if grain intake was increased to 120 g/d. Such calculations make very strong assumptions. Apart from the relevance of the actual studies to the general population, no account is taken of other changes to the diet that would occur if someone increased grain intake.

RESPONSE: We have deleted all calculations of attributable risks and the text describing it.

Other comments relating to reading the revised version:

4. PRISMA is not a guide for conducting a systematic review (p176).

RESPONSE: We agree with the reviewer and have amended our sentence referring to the PRISMA criteria so that it now reads: We followed standard criteria (PRISMA criteria) for reporting meta-analyses.(37)

5. Table 1 should explain what the RRrs are and also be explicit that RR<1 favours those with higher intake.

RESPONSE: We added to both table 1 and 2 the following: “RR (95% CI) = relative risk and 95% confidence intervals. RR<1 favours those with higher intake”
6. Figures. It would be good to reduce the size of the black squares in forest plots so that the CIs can be seen.
RESPONSE: We have reduced the size of the black squares so the CIs are visible for most of the studies. However, for a couple of studies the CIs are so narrow that it was not possible to make the CIs visible.

7. How were CIs for splines calculated?
RESPONSE: We added to the statistical methods section: "The 95% CIs were derived from the standard errors of the differences in linear predictors between each given point on the dose-response curve and a stated reference value, computed from the covariate values and the covariance matrix of the estimated coefficients."

8. I don’t really get a good idea from the figures of the range of intakes – I’d find it useful to know what was the range of intakes of each food of most people in the studies. But I’m not sure how easily that can be summarised across studies.
RESPONSE: We have added scatter plots for the nonlinear analyses to the supplement to give an indication of the range of whole grain intake across studies (Supplementary Figures 2, 4, 6, 8, 10, 12, 14, 16, 18, 20).

9. The existence or not of an association is defined by P value. P>0.05 shows lack of evidence of an association – it doesn’t demonstrate lack of association. This is especially so as there are fewer than 10 studies for most analyses and thus low power. So it’s not good to say that there was no association. Of course nor does P<0.05 demonstrate that there is an association. I think that the words used to summarise the results should not be based solely on P values.
RESPONSE: We agree with the reviewer and have modified the sentence in the first paragraph of the discussion so it reads: “There was also a 19%, 36%, 20%, and 21% reduction in the relative risk of mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death, respectively, with a high vs. low intake of whole grains, but no evidence of an association was observed for mortality from nervous system disorders in the high vs. low or linear dose-response analysis.”

Additional Questions:
Please enter your name: Doug Altman
Job Title: Statistician
Institution: Univ of Oxford
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
Funds for a member of staff?: No
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Have you in the past five years been employed by an organisation that may
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Whole grain consumption and the risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality – a systematic review and dose-response meta-analysis of prospective studies

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Key words: Whole grains, cardiovascular disease, cancer, mortality, meta-analysis

Word count (abstract): 391

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Abstract

OBJECTIVE

To quantify the dose-response relationship between whole grain consumption and specific types of grains and the risk of cardiovascular disease, total cancer, and all-cause and cause-specific mortality.

DATA SOURCES

PubMed and Embase were searched up to 3rd of April, 2016.

STUDY SELECTION

Prospective studies reporting adjusted relative risk estimates for the association between intake of whole grains or specific types of grains and cardiovascular disease, total cancer, all-cause or cause-specific mortality were included.

DATA SYNTHESIS

Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model.

RESULTS

Forty five studies (64 publications) were included. The summary RRs per 90 g/d increase in whole grain intake (90 g = 3 servings, e.g. 2 slices of bread and 1 bowl of cereals or 1.5 slice of pita bread from whole grains) was 0.81 (95% CI: 0.75 to 0.87, I²=9%, n=7) for coronary heart disease, 0.88 (95% CI: 0.75 to 1.03, I²=56%, n=6) for stroke, 0.78 (95% CI: 0.73 to 0.85, I²=40%, n=10) for cardiovascular disease, 0.85 (95% CI: 0.80 to 0.91, I²=37%, n=6) for total cancer, 0.83 (95% CI: 0.77 to 0.90, I²=83%, n=11) for all-cause mortality, 0.78 (95% CI:
0.70 to 0.87, $I^2=0\%, n=4$) for respiratory disease mortality, 0.49 (95% CI: 0.23 to 1.05, $I^2=85\%, n=4$) for diabetes mortality, 0.74 (95% CI: 0.56 to 0.96, $I^2=0\%, n=3$) for infectious disease mortality, 1.15 (95% CI: 0.66 to 2.02, $I^2=79\%, n=2$) for nervous system disease deaths, and 0.78 (95% CI: 0.75 to 0.82, $I^2=0\%, n=5$) for all non-cardiovascular, non-cancer causes of death. Reductions in risk were observed up to an intake of 210-225 grams per day (7-7.5 servings per day) for most of the outcomes. Specific types of whole grains including whole grain bread, whole grain breakfast cereals, and added bran, as well as total bread and total breakfast cereals were also associated with reduced risk of cardiovascular disease and/or all-cause mortality, but there was little evidence of an association with refined grains, white rice, total rice, or total grains.

**CONCLUSION**

This meta-analysis provides further evidence that whole grain intake is associated with reduced risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality, and mortality from respiratory disease, infectious disease, diabetes and all non-cardiovascular, non-cancer causes of death. These findings support dietary guidelines that recommend increased whole grain intake to reduce the risk of premature mortality.
What is already known on this topic

A high intake of whole grains has been associated with lower risk of type 2 diabetes, cardiovascular disease and weight gain, however, recommendations for whole grain intake have often been unclear or inconsistent with regard to the amount and types of whole grain foods that should be consumed to reduce chronic disease and mortality risk.

What this study adds

A high intake of whole grains was associated with reduced risk of coronary heart disease, cardiovascular disease, total cancer and all-cause mortality, as well as mortality from respiratory disease, infectious disease, diabetes and all non-cardiovascular, non-cancer causes of death. Reductions in risk were observed up to an intake of 210-225 grams per day (7-7.5 servings/day) and were also observed for whole grain bread, whole grain breakfast cereals, added bran.

The present results provide strong support for dietary recommendations to increase intake of whole grain foods in the general population to reduce risk of chronic diseases and premature mortality.
Introduction

Cardiovascular disease and cancer remain the two most common causes of death and accounted for 25.5 million deaths worldwide in 2013.[1] Grains are one of the major staple foods consumed around the world and provide 56% of the energy and 50% of the protein consumed by humans worldwide, and grains constitute the largest component of recommended daily intake in all dietary guidelines.[2] Because of their important role in most diets around the world, interest in the health effects of grain consumption, and in particular whole grains is increasing.[3, 4] A high intake of whole grains has been associated with reduced risk of type 2 diabetes,[5] coronary heart disease,[6] and obesity.[6] Whole grains contain endosperm, germ, and bran, in contrast to refined grains which have the germ and bran removed during the milling process. Whole grains are good sources of fiber, B-vitamins and some trace minerals such as iron, magnesium and zinc.[7] These nutrients are found in the outer layer of the grains or the bran which functions as a protective shell for the germ and endosperm inside. The germ functions as the nourishment for the seed and contains antioxidants, vitamin E and some B-vitamins, while the endosperm provides carbohydrates, protein and energy.[7] Consumption of whole grains differs considerably between populations [8] with the main source being whole grain bread in Scandinavian countries [9], whole grain bread and breakfast cereals in the US [10], brown rice, unrefined maize and sorghum in some African countries [11], and brown rice in Asia,[12] although most of the rice consumed in Asia is white rice.[13, 14]

Several previous prospective studies found lower risk of coronary heart disease,[4, 9, 15-17] stroke,[16, 18] cardiovascular disease,[4, 19, 20] and all-cause mortality [4, 9, 16, 20-22] with a high intake of whole grains, however, not all studies reported a clear association.[23-27] Some of the current authors have previously reported an inverse association between dietary fiber and whole grain intake and colorectal cancer risk,[28] and a
previous review of mostly case-control studies reported a lower risk of several individual
cancers, mainly of the digestive system, with higher intake of whole grains,[3] but data from
cohort studies are very limited. Whether whole grain consumption is associated with total
cancer risk is not clear and clarifying this question would be important from a public health
point of view. However, epidemiological studies on whole grains and total cancer have
reported mixed results, with some studies suggesting a possible inverse association,[4, 9, 22,
29] while others have shown no clear association.[20, 27] Of the cohort studies on whole
grains and cardiovascular disease or all-cause mortality, some,[16, 20, 22] but not all [4, 15,
17, 21, 29] studies reported a suggestive plateau effect with most of the benefit observed at
relatively low levels of intake. Although two previous meta-analyses suggested an inverse
association between high vs. low intake of whole grains and coronary heart disease,[6, 30] no
dose-response analyses were conducted, thus questions remain about the strength and shape of
the dose-response relationship between whole grains and coronary heart disease and the
amount of whole grains that need to be eaten to reduce risk of coronary heart disease and
other chronic diseases. Whole grain intake has also been inversely associated with other less
common causes of death including deaths from infections,[4, 20, 22] respiratory disease,[4, 9,
20, 22] diabetes,[9, 20, 22] and kidney disease [20] in some studies, but the available data are
limited.

In spite of a growing body of epidemiological evidence for the health benefits of
whole grain consumption, dietary recommendations have often been unclear or inconsistent
with regard to the amount of whole grains that should be eaten to reduce chronic disease risk.
For example in the World Cancer Research Fund 2007 report it was recommended individuals
should "eat relatively unprocessed cereals (grains) and/or pulses with every meal",[31] while
in the United Kingdom there is no specific recommendation other than "choosing whole grain,
brown or high fibre varieties wherever you can", but no specific quantities of whole grains
were recommended.[32] In the USA and Canada the recommendation is that "all adults eat at least half their grains as whole grains" so at least 3 servings of whole grains should be consumed per day.[33] while in the Scandinavian countries at least 75 grams per day of whole grain intake (dry weight) which equals approximately 250 grams per day (~8 servings/day) of whole grain products (fresh weight) is recommended [34]. There may be several reasons for the inconsistent dietary guidelines for whole grain intake including difficulties in measuring whole grain intake, differences in the consumption patterns of whole grains between populations, or lack of data on whole grain intake in some populations, but they may also be because most previous meta-analyses only considered selected disease endpoints and did not conduct dose-response analyses.[6, 30] Some of the current authors found a reduced risk of type 2 diabetes incidence with up to 2-3 servings per day (60-90 g/d) of whole grain intake, but no further reductions in risk with higher intakes,[5] while in a second meta-analysis of whole grain intake and colorectal cancer a linear inverse association was observed up to an intake of 180 g/d.[28] Whether the association is linear or reaches a plateau for other chronic disease outcomes and all-cause mortality, or whether only specific types of whole grains are associated with chronic disease and all-cause mortality would be important to clarify to provide more detailed and consistent dietary recommendations with regard to the amount of whole grains that should be consumed to reduce the risk of chronic disease and premature mortality. Answering this question would also clarify whether there are additional benefits with very high intakes such as those recommended in the Scandinavian guidelines,[34] and whether such high recommendations are justified. Several large cohort studies including >22 000 cardiovascular disease cases and more than 662 000 participants [9, 20, 22, 27, 35] have been published since or were missed [36] by the previous meta-analyses of whole grains and cardiovascular disease.[6, 30] Therefore to provide a more comprehensive, up-to-date and detailed assessment of whole grain intake and a number of health outcomes we conducted a
systematic review and meta-analysis of whole grain consumption in relation to coronary heart
disease, stroke, cardiovascular disease, total cancer and all-cause mortality, as well as less
common causes of mortality including respiratory disease, infectious disease, diabetes,
neurological disease and all non-cardiovascular, non-cancer causes of death combined, and
particularly aimed to clarify the strength and the shape of the dose-response relationship
between whole grain intake and these outcomes. We also summarized data on specific types
of whole grains as well as on refined grains and total grains, however, because of the limited
amount of data the main focus of the current analysis is on whole grains.
Methods

Search strategy and inclusion criteria

We searched the Pubmed and Embase databases from their inception (1966 and 1947, respectively) to 31st of May 2014 and the search was later updated to 3rd of April 2016. Details of the search terms are provided in Supplementary Table 1. Prospective studies of grain intake and incidence or mortality from coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause and cause-specific mortality were included if they reported adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) and for the dose-response analyses a quantitative measure of the intake for at least 3 categories of grain intake or a risk estimate for grain intake on a continuous scale had to be available. We searched the references of the retrieved reports for any additional studies. A list of the excluded studies is provided in Supplementary Table 2. We followed standard criteria (PRISMA criteria) for reporting meta-analyses. [37] The authors of one study [22] were contacted for clarification of the amount of whole grain intake, which was reported in ounces/day in the publication, but was clarified to be in ounces/1000 kcal/day by the authors.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Data extraction

The following data from the studies were extracted into tables: name of first author, publication year, country, the name of the study, follow-up period, sample size and number of
cases or deaths, type of outcome, gender, age, type of grains, amount or frequency of intake, RRs and 95% CIs and variables adjusted for in the analysis. Data were extracted by one author (DA) and checked by another author (DCG) for accuracy.

**Statistical methods**

We calculated summary relative risks of cardiovascular disease, total cancer and mortality for the highest versus the lowest level and 90 grams per day (3 servings/day) (the approximate median range across studies) of grain intake using the random-effects model by DerSimonian and Laird,[38] which takes into account both within and between study variation (heterogeneity). The average of the natural logarithm of the RRs was estimated and the RRs from each study were weighted using random effects weights. When studies reported data separately by gender we pooled the RRs using a fixed effects model before inclusion in the meta-analysis. A two-tailed P<0.05 was considered statistically significant.

We conducted linear dose-response analyses using the method by Greenland and Longnecker [39] to compute study-specific slopes (linear trends) and 95% CIs from the natural logarithm of the RRs across categories of grain intake. For each category of grain intake we used the mean or median if reported in the publication, and the midpoint of the upper and lower bound was estimated for the remaining studies. When extreme categories were open-ended or had extreme upper or lower values we used the width of the adjacent interval to calculate an upper or lower cut-off value. For total grains, whole grains and refined grains we used 30 grams as a serving size (1 slice of bread or one bowl of breakfast cereal) to recalculate studies reporting data in grams per day to servings per day, as in our previous analyses.[5, 28] For intake of pasta we used 150 grams as a serving size while for total rice we used 167.25 grams as a serving size (cooked weight) based on a weighted average of the serving size for white rice (158 g/d) and brown rice (195 g/d), weighted by the proportion of
rice intake of each type (75% white rice and 25% brown rice),[40] unless a serving size was specified in the paper. Separate analyses were conducted for studies reporting on total whole grains and specific subtypes of whole grains. A potential nonlinear dose-response relationship between grain intake and cardiovascular disease, cancer and mortality risks was assessed using restricted cubic splines with 3 knots at 10%, 50%, and 90% percentiles of the distribution which was combined using multivariate meta-analysis.[41, 42] The 95% CIs were derived from the standard errors of the differences in linear predictors between each given point on the dose-response curve and a stated reference value, computed from the covariate values and the covariance matrix of the estimated coefficients [43]. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity.[44]

Heterogeneity between studies was evaluated using Q and $I^2$ statistics.[45] For the Q statistic a P<0.10 was considered to be statistically significant. $I^2$ is the amount of total variation that is explained by between study variation. Subgroup and meta-regression analyses were conducted stratified by study characteristics (duration of follow-up, gender, geographic location, number of cases, whether the dietary assessment method had been validated, study quality and adjustment for confounding factors) to investigate potential sources of heterogeneity. Influence analyses excluding one study at a time from each analysis were conducted to investigate the robustness of the findings. We assessed publication bias with Egger’s test,[46] and funnel plots are provided in analyses with 10 or more studies included. Influence analyses were conducted excluding one study at a time from the analysis. Study quality was assessed using the Newcastle-Ottawa scale which awards 0-9 stars based on the selection, comparability, and outcome assessment.[47] We considered studies with 0-3, 4-6, and 7-9 stars to represent low, medium and high quality studies. Stata, version 12.0 software (StataCorp, Texas, US) was used for the analyses.
Results

Forty five cohort studies (64 publications) [4, 9, 15-27, 29, 35, 36, 40, 48-92] were included in the analyses of grain intake and coronary heart disease, stroke, cardiovascular disease, total cancer, all-cause mortality and other causes of mortality (Supplementary Table 3-12, Figure 1). Twenty studies were from the Europe, sixteen were from the US and 9 were from Asia. The studies included in the analyses of whole grains included 7,068 coronary heart disease cases, 2,337 stroke cases, 26,243 cardiovascular disease cases, 34,346 cancer cases and 100,726 all-cause deaths and the number of participants ranged from 245,012 to 705,253. A summary of the study characteristics is provided in Supplementary Table 3-12. Figure 1 shows a flowchart of the study selection. Figures 2-7 shows the results of the dose-response analyses and Supplementary Figure 1-20 shows the results from the high vs. low analyses and scatter plots from the nonlinear dose-response analyses. Results for specific types of grains, refined grains, and total grains are provided in Supplementary Figures 21-102.

Whole grains and coronary heart disease

Seven cohort studies [4, 9, 15-17, 23, 62] investigated the association between whole grain intake and coronary heart disease risk and included a total of 7,068 cases and 316,491 participants (one additional publication was only included in the subgroup analysis of coronary heart disease incidence [63]). The summary RR for high vs. low intake was 0.79 (95% CI: 0.73 to 0.86, I²=0%, p_heterogeneity=0.63) (Supplementary Figure 1, Table 1). The summary RR per 90 g/day was 0.81 (95% CI: 0.75 to 0.87, I²=9%, p_heterogeneity=0.36) (Figure 2a, Table 1). Although the test for nonlinearity was significant for the association between whole grain intake and coronary heart disease, p_nonlinearity<0.0001, with a slightly steeper reduction in risk up to 3 servings per day than above 3 servings per day, there was a clear
dose-response relationship and there was further reductions in risk up to 210 g/day (Figure 2b, Supplementary Figure 2, Supplementary Table 13).

Subtypes of whole grains including whole grain bread,[9, 15, 29, 50, 51, 59, 61] whole grain breakfast cereals,[9, 15, 50, 52] and added bran [15, 17, 53] were inversely associated with coronary heart disease, but no association was observed for germ,[15, 17] refined grains,[4, 16, 57, 62], white bread,[50, 59] refined grain breakfast cereals,[50, 52] total rice,[40, 55, 58] or total grains,[54, 60-62] while rye was only inversely associated in the high vs. low analysis and not in the dose-response analysis (Supplementary Figures 21-44, Table 2).[9, 48, 56]

Whole grains and stroke

Six cohort studies [4, 9, 16, 18, 24, 62] were included in the analysis of whole grain intake and risk of stroke and included a total of 2 337 cases and 245 012 participants. The pooled RR for high vs. low intake was 0.87 (95% CI: 0.72 to 1.05, I²=32 %, p_heterogeneity=0.21 (Supplementary Figure 3, Table 1). The summary RR per 90 g/day was 0.88 (95% CI: 0.75 to 1.03, I²=56%, p_heterogeneity=0.04) (Figure 2c, Table 1). There was evidence of nonlinearity between whole grain and stroke risk, p_nonlinearity<0.0001, and there was no further reduction in risk above 120-150 g/day (Figure 2d, Supplementary Figure 4, Supplementary Table 13).

No clear association was observed between intake of whole grain bread,[9, 51] whole grain breakfast cereals,[9, 52] refined grains,[4, 16, 18, 24, 62] total rice, [40, 55, 58, 67] or total grains [18, 24, 60, 62, 66, 68] and risk of stroke (Supplementary Figures 45-56, Table 2).

Whole grains and cardiovascular disease

Ten cohort studies (9 publications) [4, 9, 19-22, 26, 27, 62] investigated whole grain intake and cardiovascular disease risk and included a total of 26 243 cases and 704 317 participants. The summary RR for high vs. low intake was 0.84 (95% CI: 0.80 to 0.87, I²=0%,
The summary RR was 0.78 (95% CI: 0.73 to 0.85, $I^2=40\%$, $p_{\text{heterogeneity}}=0.09$) per 90 g/day (Figure 3a, Table 1). There was evidence of a nonlinear association between whole grain intake and cardiovascular disease risk, $p_{\text{nonlinearity}}<0.0001$, with little indication of further reductions in risk above 150-180 g/day (Figure 3b, Supplementary Figure 6, Supplementary Table 13).

Intake of whole grain breads,[9, 29, 36, 51, 61] whole grain breakfast cereals,[9, 52] total breakfast cereals,[36, 52, 70] and bran,[20, 53] but not germ,[20] refined grains,[4, 20, 35, 62] total rice,[40, 55, 58], or total grains,[60, 61, 69] were inversely associated with the risk of cardiovascular disease (Supplementary Figures 57-72, Table 2).

**Whole grains and total cancer**

Six cohort studies (5 publications) [4, 9, 20, 22, 27] were included in the analysis of whole grain intake and total cancer risk and included 34,346 cancer deaths among 640,065 participants. The summary RR for the high vs. the low intake was 0.89 (95% CI: 0.82 to 0.96, $I^2=72\%$, $p_{\text{heterogeneity}}=0.003$) (Supplementary Figure 7, Table 1). The summary RR per 90 g/day was 0.85 (95% CI: 0.80 to 0.91, $I^2=37\%$, $p_{\text{heterogeneity}}=0.16$) (Figure 3c, Table 1). The heterogeneity appeared to be explained by one large American study [22], and when excluded there was no evidence of heterogeneity, $I^2=0\%$, $p_{\text{heterogeneity}}=0.74$, and the association remained similar, summary RR=0.87 (95% CI: 0.83 to 0.92). There was no evidence of a nonlinear association between whole grain intake and total cancer, $p_{\text{nonlinearity}}=0.15$ (Figure 3d, Supplementary Figure 8, Supplementary Table 13).

There was an inverse association between intake of whole grain bread,[9, 29, 36, 51] refined grains[4, 20] and total grains[73, 74] and total cancer in the dose-response analysis, but no association was observed between brown rice,[92] white rice,[92] total breakfast cereals,[36, 70] and total rice [72, 92] and total cancer (Supplementary Figures 73-86, Table 2).
Whole grains and all-cause mortality

Eleven cohort studies (10 publications) [4, 9, 16, 19-22, 25, 27] investigated the association between whole grain intake and all-cause mortality and included 100,726 deaths and 705,253 participants. The pooled RR for high vs. low intake was 0.82 (95% CI: 0.77 to 0.88, $I^2=83\%$, $p_{\text{heterogeneity}}<0.0001$) (Supplementary Figure 9, Table 1). The summary RR was 0.83 (95% CI: 0.77 to 0.90, $I^2=83\%$, $p_{\text{heterogeneity}}<0.0001$) per 90 g/day (Figure 4a, Table 1). The heterogeneity was reduced when excluding two outlying studies [21, 25], $I^2=66\%$, $p_{\text{heterogeneity}}=0.003$, but the association was not substantially altered, summary RR=0.81 (95% CI: 0.76 to 0.86). Although the test for nonlinearity was significant, $p_{\text{nonlinearity}}<0.0001$, and steeper reductions in risk were observed at lower intakes, there was a clear dose-response relationship and the lowest risk was observed at 225 g/day (Figure 4b, Supplementary Figure 10, Supplementary Table 13).

Intakes of whole grain breads,[9, 29, 51, 61, 90] whole grain breakfast cereals,[9, 52, 86] pasta,[79, 88] total bread,[75, 76, 88] and total breakfast cereals,[52, 70, 88] were inversely associated with all-cause mortality, and in addition total grains [60-62, 64, 65, 75, 81-84, 86, 87, 89, 91] was inversely associated with mortality in the high vs. low analysis, but not in the dose-response analysis, while refined grains was weakly inversely associated with mortality in the dose-response analysis, but not in the high vs. low analysis [4, 16, 20, 62] (Table 2). There was no association between intake of oats or oatmeal,[9, 85, 90] and mortality (Supplementary Figures 87-102, Table 2).

Whole grains and other causes of death

Inverse associations were also observed for the association between whole grains and mortality from respiratory disease (Figure 5, Supplementary Figure 11, 12, Table 1),[4, 9, 20, 22] diabetes (Figure 5, Supplementary Figure 13, 14, Table 1),[4, 9, 20, 22] infectious disease
(Figure 6, Supplementary Figure 15, 16, Table 1),[4, 20, 22] and non-cardiovascular, non-
cancer causes of death (Figure 7, Supplementary Figure 19, 20, Table 1).[4, 9, 20, 22, 27], but
not for nervous system disease mortality (Figure 6, Supplementary Figure 17, 18, Table 1).[4,
20] There was evidence of nonlinearity in the analyses or respiratory disease mortality
\( (p_{\text{nonlinearity}} = 0.001) \), diabetes mortality \( (p_{\text{nonlinearity}} < 0.0001) \), infectious disease mortality
\( (p_{\text{nonlinearity}} = 0.003) \), and nervous system disease mortality, \( p_{\text{nonlinearity}} < 0.0001 \), with most of the
reduction in risk observed with intakes up to approximately 60-90 g/day for diabetes and
infectious disease mortality, but with further reductions in risk with higher intakes for
respiratory disease mortality (Figure 5-6, Supplementary Figure 12, 14, 16, 18, 20). The
analysis of nervous system disease mortality showed a slight positive association at low
intakes, but no association at intakes of 90 g/day, while the association with all non-
cardiovascular, non-cancer causes of death showed little evidence of nonlinearity,
\( p_{\text{nonlinearity}} = 0.06 \) (Figure 6-7, Supplementary Table 14).

**Publication bias, subgroup and meta-regression analyses, study quality, and influence
analyses**

There was no evidence of small study bias such as publication bias with Egger’s test for
coronary heart disease, \( p=0.11 \), cardiovascular disease, \( p=0.31 \), total cancer, \( p=0.44 \), and all-
cause mortality, \( p=0.99 \) (Supplementary Figures 103, 104), but some indication for stroke,
\( p=0.01 \) however, there were few studies in these analyses and exclusion of one outlying study
[18] from the analysis attenuated Egger’s test to non-significance, \( p=0.13 \), respectively, and
made the summary estimate significant, 0.82 (95% CI: 0.72 to 0.93). There was little evidence
of heterogeneity between subgroups in subgroup and meta-regression analyses stratified by
study characteristics including duration of follow-up, sex, type of outcome, geographic
location, number of cases or adjustment for confounding factors (Supplementary Table 15 and
16). The association between whole grain intake and coronary heart disease, cardiovascular disease and total cancer was consistent among both American and European studies, while the association with stroke and all-cause mortality was observed only in American studies, however, for all-cause mortality exclusion of one study [25] in which intake of whole grains was extremely low (and which partly explained the heterogeneity), made the summary estimate significant for the European studies as well, summary RR=0.82 (95% CI: 0.79 to 0.85, I^2=0%, p_{heterogeneity}=0.36). In the analysis of whole grain intake and stroke a significant association was observed among studies with stroke mortality as the outcome, among American studies and among studies with a validated dietary assessment, however, there was no significant between these subgroup analyses (Supplementary Table 15). There was also little evidence of heterogeneity in the remaining subgroup analyses (Supplementary Table 15 and 16).

Mean (median) study quality scores for the studies on whole grains were 7.9 (8.0) for coronary heart disease, 7.7 (8.0) for stroke, 7.7 (8.0) for cardiovascular disease, 7.8 (8.0) for total cancer, and 7.9 (8.0) for mortality out of a maximum of 9 points (Supplementary Table 17-21).

In sensitivity analyses excluding one study at a time from each analysis the summary estimates were not substantially altered for coronary heart disease, cardiovascular disease, total cancer, and all-cause mortality, but for stroke there was one study [24] which explained the lack of association (Supplementary Figure 105-109).
Discussion

This dose-response meta-analysis found an inverse association between whole grain intake and several major chronic disease outcomes, including coronary heart disease, stroke, cardiovascular disease overall, total cancer, all-cause mortality as well as less common causes of death such as mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death. There was a 21%, 16%, 11% and 15% reduction in the relative risk of coronary heart disease, cardiovascular disease, total cancer, and all-cause mortality for the highest versus the lowest category of whole grain intake, and in the dose-response analyses there were 19%, 22%, 15% and 17% reductions in the relative risk per 90 g/d (1 serving = 30 grams), while the association for stroke was only significant in the nonlinear dose-response analysis. There was also a 19%, 36%, 20%, and 21% reduction in the relative risk of mortality from respiratory disease, diabetes, infectious disease, and all non-cardiovascular, non-cancer causes of death, respectively, with a high vs. low intake of whole grains, but no evidence of an association was observed for mortality from nervous system disorders in the high vs. low or linear dose-response analysis. There was indication of nonlinearity in several of the dose-response analyses with somewhat steeper reductions in risk at lower levels of intake, however, there were further reductions in the risk of coronary heart disease, and mortality from cancer, respiratory disease, all non-cardiovascular, non-cancer causes of death as well from all-cause mortality up to intakes as high as 210-225 grams per day (7 servings per day). Although current dietary guidelines recommend whole grains rather than refined grains, recommendations have often not quantified the amount of whole grain intake that should be consumed,[31] thus the current analysis provides a considerable improvement of the evidence base for the level of whole grains that should be consumed. Relatively few people may have a whole grain intake of 3 servings per day or higher, however, as indicated by the nonlinear dose-response analysis benefits were observed at an
intake of even 1 or 2 servings per day in relation to most of the outcomes, thus even moderate
increases in whole grain intake could reduce the risk of premature mortality. In addition, a
large part of the population may have a total grain intake of 3 servings per day or more, thus
replacing most or all of the refined grains consumed with whole grains could increase whole
grain intake substantially.

Although there was some evidence of nonlinear associations between whole grain
intake and coronary heart disease, stroke, cardiovascular disease and all-cause mortality, with
stronger reductions in risk observed at lower levels of intake, there was a clear dose-response
relationship with further reductions with intakes up to 7-7.5 servings per day (210-225 grams
per day) in most of the analyses. In addition, there were inverse associations observed for
some subtypes of whole grains or total grains and coronary heart disease (whole grain bread,
whole grain breakfast cereals, added bran), cardiovascular disease (whole grain bread, whole
grain breakfast cereals, bran), total cancer (whole grain bread, total grains), all-cause
mortality (whole grain bread, whole grain cereals, total grains, total bread, pasta), which
supports the findings for whole grain intake overall, but there was no evidence of an
association between intake of refined grains and any of the outcomes, although the number of
studies in the analyses of grain subtypes was low. Given that whole grain consumption differs
substantially between populations both with regard to type and amount and because most of
the current data is from American and European studies it is possible that effect sizes may
differ in other populations.

Limitations of the study

Our meta-analysis has some limitations that should be mentioned. There was high
heterogeneity in the analysis of whole grains and all-cause mortality, however, with the
exception of one study from the Netherlands [25] which had a very small range of whole
grain intake (25th and 75th percentile was 0/0 and 10.6/13.5 g/d in men/women, respectively),
the heterogeneity appeared to be more due to differences in the strength of the association
between studies, than due to differences in the direction of the association. Exclusion of two
outlying studies [21, 25] reduced the heterogeneity in the analysis of all-cause mortality, but
did not substantially alter the summary estimates.

Although we took into account the different amounts and ranges of whole grain intake
between studies in the dose-response analysis, studies may also have differed by the types of
whole grains consumed, by how accurately they measured whole grain intake, or by how they
defined whole grains and this could have contributed to heterogeneity between studies. In
addition, given the diversity of whole grain products available it is difficult to assess whole
grain intake accurately in epidemiological studies and some degree of measurement error is
inevitable. A recent review recommended reporting whole grain intakes as the actual amount
of whole grain intake per dry weight [93]. Since some studies have classified some whole
grain items (breakfast cereals, muesli) as whole grain foods if they have a whole grain content
of ≥25% or >50% of the weight of the product then a grain product could be considered whole
grain if its whole grain content varied between 25-100 or 51-100 grams per 100 grams of the
product. Somebody could consume a product with 24 grams or 50 grams of whole grain per
100 grams of the product and still be considered to eat no whole grain, leading to
misclassification of the exposure. Most of the studies appeared to report whole grain food
intake as the amount or frequency of whole grain food or product intake (fresh weight
including water content), while only two publications [9, 20] reported intakes in actual
amount of whole grain food (dry weight) [9]. However, one study which reported results for
both whole grain products (fresh weight) and actual whole grain intake (dry weight) in
relation to mortality found similar associations for the two [9]. Most of the associations were
similar for different types of whole grains, and in addition most of the American studies
appeared to define whole grains similarly, while few of the European studies provided a
whole grain definition.

Subjects with a high intake of whole grains may have different lifestyles, diets [20, 94]
or socio-economic status [94] than those with a low intake, thus confounding by other
lifestyle factors is a potential source of bias. In subgroup analyses we found that the
associations observed persisted among studies with adjustment for smoking, alcohol, physical
activity, BMI and other dietary factors such as sugar-sweetened beverages, red meat, and fruit
and vegetables. Differences in socio-economic factors or deprivation could also have
influenced the findings, however, both the Nurses’ Health Study and the Health Professionals
Follow-up Study, cohorts where there would be relatively little confounding by socio-
economic status or deprivation, found similar results to the overall analysis and there was no
evidence of heterogeneity in the results when stratified by adjustment for education.
The number of studies that investigated subtypes of whole grains and total or refined grains
was limited, thus, any further studies should try to clarify associations between specific
subtypes of grains and cardiovascular disease, cancer and mortality, as well as less common
causes of mortality. As in any meta-analysis of published studies publication bias could have
influenced the results. We found some indication of small study effects such as publication
bias in the analysis of coronary heart disease and stroke, however, in each of these analyses
exclusion of one outlying study made Egger’s test non-significant, but did not substantially
alter the summary estimates. There was no evidence of publication bias for the remaining
outcomes, although the number of studies was moderate and power to detect such bias is low
when there are few studies.

Strengths of the study
Strengths of the current meta-analysis includes the comprehensive analyses of whole
grain and subtypes of grain intake in relation to a range of chronic disease and mortality
outcomes including high vs. low analyses, linear and nonlinear dose-response analyses, the
detailed subgroup, sensitivity, and influence analyses, the large number of cases or deaths and
participants included, and the high quality of the studies included.

Mechanisms

Several mechanisms might explain the beneficial effect observed between whole grain
intake and coronary heart disease, cardiovascular disease, cancer, and all-cause mortality.
Whole grains are rich in fiber which can reduce the postprandial glucose and insulin
responses leading to better glycemic control.[95] Epidemiological studies have suggested a
lower risk of overweight and obesity [6, 96, 97] and of type 2 diabetes [5, 6] among subjects
with a high whole grain intake. Both adiposity and type 2 diabetes are established risk factors
for cardiovascular disease, cancer and mortality, however, in this analysis all the studies
adjusted for BMI, suggesting an association independent of BMI. One study on whole grains
and coronary heart disease [17] and another study on mortality [9] found very little difference
between BMI-adjusted and BMI-unadjusted hazard ratios, so if anything BMI may mediate
only a small part of the association. Higher whole grain intake has been associated with a
lower prevalence or risk of hypertension or elevated blood pressure,[95, 98, 99]
hypertriglyceridemia,[95, 100] and lower total and LDL-cholesterol levels,[97, 100] which
are important cardiovascular risk factors. Higher fiber intake has been associated with reduced
risk of coronary heart disease,[101] stroke,[102] some cancers,[28, 103] and all-cause
mortality. [104-106] Fiber intake, in particular soluble fiber, may reduce cholesterol levels by
inhibiting bile acid reabsorption and by bacterial fermentation of fiber in the colon which
results in the production of short chain fatty acids which inhibit cholesterol synthesis in the
Dietary fiber can reduce cancer risk by mechanic removal of damaged cells from the digestive tract, increasing stool bulk, diluting carcinogens, decreasing transit time, altering the gut microbiota, and by binding estrogens in the colon and increasing the faecal excretion of estrogens, leading to lower estrogen concentrations. Whole grain consumption has been found inversely associated with mortality due to inflammatory diseases and an intervention study found reduced levels of fasting serum glucose, measures of lipid peroxidation, and homocysteine concentrations among participants fed a whole grain/legume powder supplement. Whole grain intake has been associated with lower levels of inflammatory markers (PAI-1, CRP) and liver enzymes (GGT, ASAT), higher levels of which have been associated with increased cardiovascular, cancer and mortality risk. Whole grain intake has also been associated with higher levels of adiponectin which increases insulin sensitivity and reduces inflammation.

Whole grains also contain a number of other potentially beneficial components which could explain some of the current findings. Further studies are needed to clarify whether there is an underlying mechanism for the nonlinear association between whole grain intake and cardiovascular disease, all-cause mortality, and mortality from respiratory disease, diabetes and infectious diseases. A high intake of whole grains may also reduce risk of chronic disease and mortality indirectly, by displacement of unhealthy foods or drinks, however, the association for cardiovascular disease and mortality persisted in studies that adjusted for intake of red and processed meat and sugar-sweetened beverages.

Policy implications and future research

The current analysis found that a high whole grain intake was associated with reduced risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality as well as mortality due to respiratory disease, infections, diabetes, and all non-cardiovascular, non-
cancer causes of death combined and provides strong evidence that a high intake of whole 
grains is beneficial for several health outcomes in a dose-response manner. In addition, a high 
intake of whole grains has previously been associated with reduced risk of colorectal 
cancer,[28] type 2 diabetes incidence,[5] and with overweight or obesity.[6] Altogether these 
findings have important public health implications as whole grain intake can be modified 
relatively easily by replacing refined grains and could have a large effect on the chronic 
disease burden if adopted in the general population. As shown in the current meta-analysis, a 
high whole grain intake is not only associated with reduced risk of cardiovascular disease and 
diabetes, but also with mortality from cancer, respiratory disease, infectious disease, and all 
non-cancer, non-cardiovascular causes of death combined, thus the current findings strongly 
support existing dietary recommendations to increase whole grain consumption in the general 
population. From a practical angle a whole grain product intake of 90 g/d can be achieved for 
example by eating a portion of whole grain breakfast cereals (30-40 g) at breakfast, and a 
piece of whole grain pita bread for dinner (60 g). The nonlinear analyses suggested that the 
reductions in mortality risk is steepest at the lowest level of whole grain intake (from 0 to 2 
servings/day) and that perhaps targeting subjects with a very low intake might have a greater 
impact, however, further reductions were observed up to 210-225 g/d (7-7.5 servings per day), 
suggesting further benefits with even higher intakes. Most of the studies included in the 
alyses of whole grains were from the US, and only a very few European studies have been 
published so far. Whole grain intake is higher in Northern Europe [34, 122] than in the US 
and these populations may therefore be promising for further studies of the association 
between whole grains and health outcomes, both in terms of examining more extreme intakes 
and specific types of whole grains, but further studies are needed in other geographic 
locations as well. Further studies of specific diseases and less common causes of death and 
incorporating biomarkers of whole grain intake [123] are also needed.
In conclusion our results provide further evidence for the beneficial effects of diets high in whole grains upon the risk of coronary heart disease, cardiovascular disease, total cancer and all-cause mortality, as well as mortality from respiratory disease, infections, diabetes and all non-cardiovascular, non-cancer causes of death combined. Reductions in risk are observed up to 210-225 grams per day or 7-7.5 servings per day and the current findings support dietary recommendations to increase intake of whole grains and as much as possible to choose whole grains rather than refined grains.

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Contribution: DA had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DA, TN. Acquisition, analysis or interpretation of data: DA, NK, EG, LTF, PB, TN, DCG, ER, ST. Checking of data extractions: DCG. Drafting of manuscript: DA. Critical revision of the manuscript for important intellectual content: DA, EG, PB, LTF, NK, TN, DCG, LJV, ER, ST. Statistical analysis: DA, DCG. Obtained funding: DA, LJV, ST, ER. Study supervision: TN. All authors have read and approved the final manuscript. DA is guarantor for the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
Ethical approval: Because the study used already published data, there was no need for ethical approval of the study.

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Data sharing: no additional data available.
Table 1. Total whole grains and coronary heart disease, stroke, cardiovascular disease, total cancer, all-cause mortality, and cause-specific mortality

<table>
<thead>
<tr>
<th></th>
<th>High vs. low analysis</th>
<th>Dose-response analysis</th>
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<tbody>
<tr>
<td></td>
<td>N RR (95% CI) I² p</td>
<td>Dose N RR (95% CI) I² p</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6 0.79 (0.73 to 0.86) 0% 0.63</td>
<td>90 g/d 7 0.81 (0.75 to 0.87) 9% 0.36</td>
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<tr>
<td>Stroke</td>
<td>5 0.87 (0.72 to 1.05) 32% 0.21</td>
<td>90 g/d 6 0.88 (0.75 to 1.03) 56% 0.04</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9 0.84 (0.80 to 0.87) 0</td>
<td>90 g/d 10 0.78 (0.73 to 0.85) 40% 0.09</td>
</tr>
<tr>
<td>Total cancer</td>
<td>6 0.89 (0.82 to 0.96) 72% 0.003</td>
<td>90 g/d 6 0.85 (0.80 to 0.91) 37% 0.16</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>9 0.82 (0.77 to 0.88) 83% &lt;0.0001</td>
<td>90 g/d 11 0.83 (0.77 to 0.90) 83% &lt;0.0001</td>
</tr>
<tr>
<td>Respiratory disease mortality</td>
<td>4 0.81 (0.69 to 0.94) 63% 0.05</td>
<td>90 g/d 4 0.78 (0.70 to 0.87) 0% 0.46</td>
</tr>
<tr>
<td>Diabetes mortality</td>
<td>4 0.64 (0.42 to 0.98) 64% 0.04</td>
<td>90 g/d 4 0.49 (0.23 to 1.05) 85% &lt;0.0001</td>
</tr>
<tr>
<td>Infectious disease mortality</td>
<td>3 0.80 (0.68 to 0.96) 0% 0.68</td>
<td>90 g/d 3 0.74 (0.56 to 0.96) 0% 0.85</td>
</tr>
<tr>
<td>Nervous system disease mortality</td>
<td>2 1.13 (0.89 to 1.43) 29% 0.24</td>
<td>90 g/d 2 1.15 (0.66 to 2.02) 79% 0.03</td>
</tr>
<tr>
<td>Non-cardiovascular, non-cancer causes of mortality</td>
<td>5 0.79 (0.69 to 0.92) 86% &lt;0.0001</td>
<td>90 g/d 5 0.78 (0.75 to 0.82) 0% 0.99</td>
</tr>
</tbody>
</table>

RR (95% CI) = relative risk and 95% confidence intervals. RR<1 favours those with higher intake.
<table>
<thead>
<tr>
<th>Type of grain</th>
<th>High vs. low analysis</th>
<th>Dose-response analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole grain bread</td>
<td>7</td>
<td>0.83 (0.75 to 0.92)</td>
</tr>
<tr>
<td>Whole grain breakfast cereals</td>
<td>4</td>
<td>0.72 (0.64 to 0.82)</td>
</tr>
<tr>
<td>Rye products</td>
<td>2</td>
<td>0.81 (0.70 to 0.94)</td>
</tr>
<tr>
<td>Added bran</td>
<td>3</td>
<td>0.78 (0.63 to 0.95)</td>
</tr>
<tr>
<td>Germ</td>
<td>2</td>
<td>0.73 (0.33 to 1.64)</td>
</tr>
<tr>
<td>Refined grains</td>
<td>4</td>
<td>1.16 (0.84 to 1.59)</td>
</tr>
<tr>
<td>White bread</td>
<td>2</td>
<td>1.07 (0.86 to 1.34)</td>
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<tr>
<td>Refined grain breakfast cereals</td>
<td>2</td>
<td>1.15 (0.79 to 1.67)</td>
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<tr>
<td>Total rice</td>
<td>4</td>
<td>0.98 (0.90 to 1.07)</td>
</tr>
<tr>
<td>Total grains</td>
<td>3</td>
<td>1.07 (0.91 to 1.25)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td>Whole grain bread</td>
<td>2</td>
<td>0.88 (0.75 to 1.03)</td>
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<tr>
<td>Whole grain breakfast cereals</td>
<td>2</td>
<td>0.99 (0.53 to 1.86)</td>
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<tr>
<td>Refined grains</td>
<td>4</td>
<td>0.95 (0.78 to 1.14)</td>
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<tr>
<td>Total rice</td>
<td>4</td>
<td>1.02 (0.94 to 1.11)</td>
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<tr>
<td>Total grains</td>
<td>4</td>
<td>0.89 (0.79 to 1.00)</td>
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<td><strong>Cardiovascular disease</strong></td>
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<tr>
<td>Whole grain bread</td>
<td>4</td>
<td>0.83 (0.75 to 0.92)</td>
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<tr>
<td>Whole grain breakfast cereals</td>
<td>2</td>
<td>0.74 (0.65 to 0.84)</td>
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<tr>
<td>Bran</td>
<td>3</td>
<td>0.82 (0.76 to 0.88)</td>
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<tr>
<td>Germ</td>
<td>2</td>
<td>1.06 (0.97 to 1.16)</td>
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<tr>
<td>Refined grains</td>
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<td>1.02 (0.91 to 1.14)</td>
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<tr>
<td>Total breakfast cereals</td>
<td>2</td>
<td>0.80 (0.70 to 0.90)</td>
</tr>
<tr>
<td>Total rice</td>
<td>3</td>
<td>0.96 (0.90 to 1.03)</td>
</tr>
<tr>
<td>Total grains</td>
<td>3</td>
<td>0.94 (0.84 to 1.06)</td>
</tr>
<tr>
<td><strong>Total cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole grain bread</td>
<td>3</td>
<td>0.89 (0.78 to 1.01)</td>
</tr>
<tr>
<td>Brown rice</td>
<td>3</td>
<td>1.07 (0.91 to 1.26)</td>
</tr>
<tr>
<td>Refined grains</td>
<td>1</td>
<td>0.98 (0.82 to 1.16)</td>
</tr>
<tr>
<td>White rice</td>
<td>3</td>
<td>0.87 (0.76 to 1.01)</td>
</tr>
<tr>
<td>Total breakfast cereals</td>
<td>1</td>
<td>0.90 (0.86 to 0.95)</td>
</tr>
<tr>
<td>Food</td>
<td>RR</td>
<td>95% CI</td>
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<tr>
<td>-----------------------</td>
<td>--------</td>
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</tr>
<tr>
<td>Total rice</td>
<td>0.95</td>
<td>(0.88 to 1.02)</td>
</tr>
<tr>
<td>Total grains</td>
<td>0.92</td>
<td>(0.80 to 1.06)</td>
</tr>
<tr>
<td>Whole grain bread</td>
<td>0.81</td>
<td>(0.74 to 0.88)</td>
</tr>
<tr>
<td>Whole grain breakfast cereals</td>
<td>0.79</td>
<td>(0.72 to 0.86)</td>
</tr>
<tr>
<td>Refined grains</td>
<td>1.02</td>
<td>(0.93 to 1.12)</td>
</tr>
<tr>
<td>Pasta</td>
<td>0.61</td>
<td>(0.26 to 1.45)</td>
</tr>
<tr>
<td>Total bread</td>
<td>0.77</td>
<td>(0.72 to 0.81)</td>
</tr>
<tr>
<td>Total breakfast cereals</td>
<td>0.87</td>
<td>(0.81 to 0.93)</td>
</tr>
<tr>
<td>Total grains</td>
<td>0.91</td>
<td>(0.87 to 0.95)</td>
</tr>
</tbody>
</table>

RR (95% CI) = relative risk and 95% confidence intervals. RR<1 favours those with higher intake.
Reference List


Ref Type: Generic


88. Sluik D, Boeing H, Li K et al. Lifestyle factors and mortality risk in individuals with diabetes mellitus: are the associations different from those in individuals without diabetes? Diabetologia 2014;57:63-72.


98. Steffen LM, Kroenke CH, Yu X et al. Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white


Figure legends

Figure 1. Flow-chart of study selection

Figure 2. Whole grains and coronary heart disease and stroke

Figure 3. Whole grains and cardiovascular disease and total cancer

Figure 4. Whole grains and all-cause mortality

Figure 5. Whole grains and respiratory disease and diabetes mortality

Figure 6. Whole grains and infectious disease and nervous system disease mortality

Figure 7. Whole grains and non-cardiovascular, non-cancer causes of death
Print abstract

Study question: To quantify the dose-response relationship between whole grain consumption and the risk of cardiovascular disease, total cancer, and all-cause and cause-specific mortality.

Methods: PubMed and Embase were searched up to 3rd of April, 2016. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Forty five studies (64 publications) were included.

Study answer and limitations: Higher intake of whole grains was associated with a reduced risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality, and mortality from respiratory disease, diabetes, infectious diseases, and all non-cardiovascular, non-cancer causes of death. Reductions in risk were observed up to an intake of 210-225 grams per day (7-7.5 servings per day) for most of the outcomes.

What this study adds: This meta-analysis suggest that a high intake of whole grains reduces the risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality, and mortality from respiratory disease, diabetes, infectious diseases, and all non-cardiovascular, non-cancer causes of death.

Funding: The project was funded by ‘Olav og Gerd Meidel Raagholt’s Stiftelse for Medisinsk forskning’, the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and the
Imperial College National Institute of Health Research (NIHR) Biomedical Research Centre (BRC).

**Competing interests:** All authors declare no conflicts of interest.

**Data sharing:** No additional data are available.
Figure 1. Flow-chart of study selection

48380 records identified in total:
39741 records identified in the PubMed database
8639 records identified in the Embase database

47049 records excluded based on title or abstract

1331 records given detailed assessment

1185 reported on other exposures than grains

146 reported on intake of grains

82 publications excluded:
18 reviews
14 case-control studies
10 abstract only publications
9 not relevant exposure/outcome
9 meta-analyses
6 duplicates
3 no risk estimates, confidence intervals
2 studies in diabetes subjects only
2 not usable result, no quantities
2 qualitative assessment of grain
1 not original data
1 patients with heart disease
1 crude dietary assessment
1 cross-sectional study
1 ecological study
1 total disease mortality as outcome
1 unadjusted risk estimates

45 cohort studies (64 publications) included

CHD incidence or mortality: 23 studies (25 publications)
Stroke incidence or mortality: 15 studies (15 publications)
CVD incidence or mortality: 19 studies (20 publications)
Total cancer incidence or mortality: 13 studies (14 publications)
All-cause mortality: 30 studies (36 publications)
Respiratory disease mortality: 5 studies (5 publications)
Infectious disease mortality: 4 studies (4 publications)
Diabetes mortality: 5 studies (5 publications)
Nervous system disease mortality: 3 studies (3 publications)
Non-cardiovascular, non-cancer causes of death: 5 studies (4 publications)
Figure 2. Whole grains and coronary heart disease and stroke incidence or mortality

A. Whole grains and coronary heart disease, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.83 (0.57, 1.23)</td>
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<tr>
<td>Johnsen, 2015</td>
<td>0.84 (0.77, 0.93)</td>
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<tr>
<td>Rautiainen, 2012</td>
<td>0.90 (0.78, 1.04)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.72 (0.60, 0.87)</td>
</tr>
<tr>
<td>Jensen, 2004</td>
<td>0.65 (0.46, 0.92)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.75 (0.56, 1.01)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.72 (0.56, 0.93)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.81 (0.75, 0.87)</td>
</tr>
</tbody>
</table>

B. Whole grains and coronary heart disease, nonlinear dose-response

C. Whole grains and stroke, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.80 (0.57, 1.12)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.86 (0.71, 1.04)</td>
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<td>Mizrahi, 2009</td>
<td>1.08 (0.96, 1.22)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.89 (0.67, 1.19)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.70 (0.44, 1.11)</td>
</tr>
<tr>
<td>Liu, 2000</td>
<td>0.69 (0.48, 1.00)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.75, 1.03)</td>
</tr>
</tbody>
</table>

D. Whole grains and stroke, nonlinear dose-response

Best fitting cubic spline
--- 95% confidence interval
Figure 3. Whole grains and cardiovascular disease incidence or mortality and total cancer mortality

**A** Whole grains and cardiovascular disease, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.82 (0.63, 1.05)</td>
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<tr>
<td>Huang, 2015</td>
<td>0.74 (0.68, 0.80)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.85 (0.78, 0.92)</td>
</tr>
<tr>
<td>Sonestedt, 2015</td>
<td>0.86 (0.76, 0.98)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.72 (0.58, 0.90)</td>
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<tr>
<td>Wu, 2015, NHS</td>
<td>0.56 (0.40, 0.79)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.83 (0.40, 1.71)</td>
</tr>
<tr>
<td>Fitzgerald, 2012</td>
<td>0.89 (0.71, 1.11)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.75 (0.63, 0.89)</td>
</tr>
<tr>
<td>Sahyoun, 2006</td>
<td>0.45 (0.21, 0.96)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.73, 0.85)</td>
</tr>
</tbody>
</table>

**B** Whole grains and cardiovascular disease, nonlinear dose-response

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.79 (0.74, 0.84)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.86 (0.81, 0.91)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.90 (0.74, 1.10)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.96 (0.76, 1.21)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.77 (0.43, 1.38)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.92 (0.81, 1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.85 (0.80, 0.91)</td>
</tr>
</tbody>
</table>

**C** Whole grains and total cancer, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.74 (0.70, 0.79)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.88 (0.85, 0.90)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.87 (0.73, 0.97)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.86 (0.75, 0.99)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.70 (0.41, 1.20)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.70 (0.74, 0.81)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.73, 0.83)</td>
</tr>
</tbody>
</table>

**D** Whole grains and total cancer, nonlinear dose-response

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.71 (0.67, 0.76)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.86 (0.82, 0.90)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.86 (0.74, 1.04)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.92 (0.76, 1.11)</td>
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<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.67 (0.38, 1.22)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.75 (0.64, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.76 (0.71, 0.82)</td>
</tr>
</tbody>
</table>
Figure 4. Whole grains and all-cause mortality

### A  Whole grains and all-cause mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.94 (0.80, 1.16)</td>
</tr>
<tr>
<td>Huang, 2015</td>
<td>0.76 (0.73, 0.79)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.82 (0.79, 0.85)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.91 (0.81, 1.02)</td>
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<tr>
<td>Wu, 2015, NHS</td>
<td>0.67 (0.57, 0.77)</td>
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<tr>
<td>Boggs, 2014</td>
<td>0.30 (0.15, 0.60)</td>
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<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.98 (0.67, 1.44)</td>
</tr>
<tr>
<td>van den Brandt, 2011</td>
<td>1.05 (0.95, 1.17)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.82 (0.76, 0.89)</td>
</tr>
<tr>
<td>Sahyoun, 2006</td>
<td>0.80 (0.49, 1.31)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.77 (0.61, 0.96)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.77, 0.90)</td>
</tr>
</tbody>
</table>

### B  Whole grains and all-cause mortality, nonlinear dose-response

Relative Risk (RR) vs. Whole grains (g/day)

- **Best fitting cubic spline**
- **95% confidence interval**
Figure 5. Whole grains and respiratory disease and diabetes mortality

A. Whole grains and respiratory disease mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.82 (0.71, 0.95)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.82 (0.66, 1.03)</td>
</tr>
<tr>
<td>Wu, 2015</td>
<td>0.71 (0.49, 1.02)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.67 (0.53, 0.85)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.70, 0.87)</td>
</tr>
</tbody>
</table>

B. Whole grains and respiratory disease mortality, nonlinear dose-response

C. Whole grains and diabetes mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.42 (0.25, 0.69)</td>
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<td>Johnsen, 2015</td>
<td>1.10 (0.79, 1.52)</td>
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<td>Wu, 2015</td>
<td>0.15 (0.05, 0.40)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.63 (0.31, 1.26)</td>
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<tr>
<td>Overall</td>
<td>0.49 (0.23, 1.05)</td>
</tr>
</tbody>
</table>

D. Whole grains and diabetes mortality, nonlinear dose-response

Best fitting cubic spline
--- 95% confidence interval
Figure 6. Whole grains and infectious disease and nervous system disease mortality

**A** Whole grains and infectious disease mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.71 (0.52, 0.96)</td>
</tr>
<tr>
<td>Wu, 2015</td>
<td>0.89 (0.41, 1.94)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.79 (0.37, 1.70)</td>
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<tr>
<td>Overall</td>
<td>0.74 (0.56, 0.96)</td>
</tr>
</tbody>
</table>

**B** Whole grains and infectious disease mortality, nonlinear dose-response

**C** Whole grains and nervous system disease mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk  (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Wu, 2015</td>
<td>1.53 (1.08, 2.16)</td>
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<td>Jacobs, 2007</td>
<td>0.86 (0.59, 1.26)</td>
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<tr>
<td>Overall</td>
<td>1.15 (0.66, 2.02)</td>
</tr>
</tbody>
</table>

**D** Whole grains and nervous system disease mortality, nonlinear dose-response

- Best fitting cubic spline
- 95% confidence interval
Figure 7. Whole grains and non-cardiovascular, non-cancer causes of death

A  Whole grains and non-cardiovascular, non-cancer causes of death, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.78 (0.68, 0.89)</td>
</tr>
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<td>Johnsen, 2015</td>
<td>0.78 (0.74, 0.83)</td>
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<tr>
<td>Wu, 2015</td>
<td>0.80 (0.68, 0.93)</td>
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<td>Buil-Cosiales, 2014</td>
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<td>Jacobs, 2007</td>
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<td>Overall</td>
<td>0.78 (0.75, 0.82)</td>
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B  Whole grains and non-cardiovascular, non-cancer causes of death, nonlinear dose-response

- Best fitting cubic spline
- 95% confidence interval
### Supplementary Table 1. Search strategy in PubMed and Embase

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<table>
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<td>&quot;cereal fibre&quot;</td>
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<td>&quot;DASH diet&quot;</td>
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91. cohorts
92. prospective
93. longitudinal
94. retrospective
95. “follow-up”
96. “cross-sectional”
97. “population-based”
98. “relative risk
99. “odds ratio”
100 “hazard ratio”
101 “incidence rate ratio”
102 (89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101)
103. 69 AND 88 AND 102
Supplementary Table 2. List of excluded studies and reason for exclusion

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<td>Abstract only publication</td>
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<td>Case-control study</td>
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<td>Cross-sectional study</td>
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<td>Crude dietary assessment</td>
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<td>Diabetes patient population</td>
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<td>Duplicates</td>
<td>(29-34)</td>
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<td>Ecological study</td>
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<td>Meta-analysis</td>
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<td>(45;46)</td>
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<td>No risk estimates</td>
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<td>Not original data</td>
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<td>Not usable result</td>
<td>(49)</td>
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<td>Not relevant exposure</td>
<td>(50;51)</td>
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<td>Not relevant outcome</td>
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<tr>
<td>Patients with heart disease</td>
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<tr>
<td>Qualitative assessment (whole grain vs. refined grains)</td>
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<td>Quantity not provided</td>
<td>(62)</td>
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<td>Review</td>
<td>(63-60)</td>
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<td>Total disease mortality as outcome (not all-cause mortality), quantity not provided</td>
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<tr>
<td>Unadjusted risk estimates</td>
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Reference List


https://mc.manuscriptcentral.com/bmj


<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>CHD incidence or mortality</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
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<tr>
<td>Pietinen P et al, 1996, Finland</td>
<td>Alpha-Tocopherol Beta-Carotene Cancer Prevention Study</td>
<td>1986-1987 -1993, 6.1 years follow-up</td>
<td>21930 smoking men, age 50-69 years: 635 CHD deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 276 food items</td>
<td>Rye products</td>
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<td>1.00 0.87 (0.68-1.10) 0.86 (0.68-1.10) 0.79 (0.61-1.01) 0.75 (0.58-0.98) 1.00 0.94 (0.73-1.21) 0.93 (0.72-1.21) 1.03 (0.79-1.34) 1.05 (0.79-1.40)</td>
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<td>Gartside PS et al, 1998, USA</td>
<td>National Health and Nutrition Examination Follow-up Study 1</td>
<td>1971-1987, 16 years follow-up</td>
<td>5811 men and women, age 40-74 years: 1976 CHD cases</td>
<td>Incidence</td>
<td>NA</td>
<td>Bread</td>
<td>H vs l</td>
<td>1.16, p=0.05</td>
<td>Age, sex, race, geographic region, serum cholesterol, education, physical exercise, physical activity, smoking, BMI, alcohol, fish, dessert, cheese</td>
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<td>Jacobs DR Jr et al, 1998, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986-1995, 8.64 years of follow-up</td>
<td>34492 women, age 55-69 years: 438 ischemic heart disease cases</td>
<td>Incidence</td>
<td>FFQ, 127 food items</td>
<td>Dark bread</td>
<td>0-0.5 serv/wk 1.0-3.0 5.5-7.0 17.5-42.0 0 serv/wk 0.5-1.0 3.0 5.5-7.0 0 serv/wk 0.5-1.0 1.5-5.0 5.5-91.0 0 serv/wk 0.5-1.0 3.0, 7.0-42.0</td>
<td>1.00 0.81 (0.62-1.06) 0.62 (0.46-0.82) 0.67 (0.49-0.91) 1.00 0.82 (0.62-1.08) 0.78 (0.58-1.06) 0.77 (0.56-1.04) 1.00 1.43 (1.01-2.02) 1.17 (0.81-1.68) 1.26 (0.81-1.95) 1.00 0.90 (0.64-1.27) 1.43 (1.08-1.89) 1.24 (0.94-1.64)</td>
<td>Age, total energy, education, marital status, high blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, pack-years, alcohol, use of vitamin supplements, oral contraceptive use, HRT, Keys score, fruit and vegetable intake (except juice), red meat, fish and seafood, sucrose</td>
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<tr>
<td></td>
<td>0 serv/wk</td>
<td>0.5-1.0</td>
<td>3.0</td>
<td>5.5-7.0</td>
<td>0-2.0 serv/wk</td>
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<td>5.5-7.0</td>
<td>7.5-11.0</td>
<td>11.5-143.0</td>
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<td>Refined-grain breakfast cereal</td>
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<td>0.94 (0.70-1.26)</td>
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<tr>
<th>Liu S et al, 1999, USA Nurses' Health Study</th>
<th>1984-1994, 10 years follow-up</th>
<th>75521 women, age 38-63 years: 761 CHD cases</th>
<th>Incidence</th>
<th>Validated FFQ, 126 food items</th>
<th>Whole grain</th>
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<td>Bran</td>
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<td>0.76 (0.59-0.98)</td>
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<td>0.68 (0.44-1.03)</td>
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<td>0.79 (0.57-1.08)</td>
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Age, BMI, cigarette smoking, alcohol, parental or family history of myocardial infarction before age 60, hypertension, hypercholesterolemia, menopausal status, HRT, protein intake, aspirin use, multiple/vitamin E use, vigorous activity, total energy, SFA, PUFA, MUFA, trans-FAs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population</th>
<th>Follow-up</th>
<th>CHD Deaths/Mortality</th>
<th>FFQ Items</th>
<th>Whole Grain</th>
<th>Refined Grain</th>
<th>Total Breakfast Cereals</th>
<th>Incidence</th>
<th>FFQ Validation</th>
<th>Whole Grain</th>
<th>Refined Grain</th>
<th>Total Breakfast Cereals</th>
<th>Adjustment Factors</th>
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<tr>
<td>Jacobs DR et al, 2001, Norway</td>
<td>Norwegian County Study</td>
<td>1977-1993, 14.4 years</td>
<td>33,848 men and women, age 35-56 years: 553 CHD deaths</td>
<td>Mortality</td>
<td>FFQ, 66 food items</td>
<td>Whole grain bread score</td>
<td>0.05-0.60</td>
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<td>0.80-0.93</td>
<td>0.90-0.93</td>
<td>1.35-1.40</td>
<td>1.25-1.30</td>
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<td>Age, energy intake, sex, smoking status, physical activity during leisure, physical activity during work, cod liver oil, multivitamin use, SFA, SBP, serum total cholesterol, BMI</td>
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<tr>
<td>Appleby PN et al, 2002, UK</td>
<td>The Health Food Shoppers Study</td>
<td>1973-1979, 19.8 years</td>
<td>10,741 men and women, age 16-89 years: 605 ischemic heart disease deaths</td>
<td>Mortality</td>
<td>FFQ</td>
<td>Wholemeal bread</td>
<td>Daily vs less</td>
<td>Daily vs less</td>
<td>0.86 (0.72-1.03)</td>
<td>1.13 (0.94-1.35)</td>
<td>Age at recruitment, sex, smoking, fresh fruit, nuts/dried fruit, raw vegetables salads, mutual adjustment: wholemeal bread and bran cereals</td>
<td></td>
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<tr>
<td>Liu S et al, 2003, USA</td>
<td>Physicians’ Health Study</td>
<td>1982-1988, 5.5 years</td>
<td>86,190 men, age 40-84 years: 488 MI cases</td>
<td>Incidence</td>
<td>Validated FFQ</td>
<td>Whole grain breakfast cereals</td>
<td>Rarely</td>
<td>1 serv/wk</td>
<td>2-6/wk</td>
<td>≥1/day</td>
<td>1.00</td>
<td>Age, cigarette smoking, alcohol intake, physical activity, BMI, history of type 2 diabetes, high cholesterol, hypertension, use of multivitamins</td>
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<tr>
<td>Steffen LM et al, 2003, USA</td>
<td>Atherosclerosis Risk in Communities Study</td>
<td>1987-1989, 11 years</td>
<td>11,940 men and women, age 45-64 years: 535 fatal or nonfatal coronary artery disease cases</td>
<td>Incidence</td>
<td>Validated FFQ, 61 food items</td>
<td>Whole grain</td>
<td>0.1 serv/day</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
<td>3.0</td>
<td>0.5 serv/day</td>
<td>1.5</td>
<td>2.0</td>
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<td>Jensen MK et al, 2004, USA</td>
<td>Health Professionals Follow-up Study</td>
<td>1986-2000, 14 years</td>
<td>42,850 men, age 40-75 years: 1818 CHD cases</td>
<td>Incidence</td>
<td>Validated FFQ, 131 food items</td>
<td>Whole grains</td>
<td>3.5 g/d</td>
<td>9.6</td>
<td>16.0</td>
<td>24.7</td>
<td>42.4</td>
<td>0 g/d</td>
<td>1.00</td>
<td>Age, energy, smoking, alcohol, physical activity, family history of MI, use of vitamin E supplements, SFA, PUFA, trans FA, fruit, vegetables, fish, BMI, mutual adjustment between</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Follow-up</td>
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<td>Mink PJ et al, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986-2002, 16 years follow-up</td>
<td>34,489 women, age 55-69 years: 1,329 CHD deaths</td>
<td>Mortality</td>
<td>FFQ, 127 food items</td>
<td>Bran, added to food</td>
<td>0.30 1.40 4.23 11.10 0 g/d 0.20 0.83</td>
<td>whole grains, added bran, and added germ</td>
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<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27,312 women, age 55-69 years: 1,034 CHD deaths</td>
<td>Mortality</td>
<td>FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk 5.6 8.8 14.5 25.6 0-5.75 serv/wk 6-9.5 9.6-13.5 14-22 ≥22.5</td>
<td>Age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, smoking, HRT</td>
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<td>Buckland G et al, 2009, Spain</td>
<td>European Prospective Investigation into Cancer and Nutrition – Spain</td>
<td>1992-1996 – 2004, 10.4 years follow-up</td>
<td>41,078 men and women, age 29-69 years: 609 CHD cases</td>
<td>Incidence</td>
<td>Dietary history interview, validated FFQ, ~600 foods</td>
<td>Cereals</td>
<td>0.7-2.5 g/d &gt;7.25-102.6 &gt;102.6-501.3</td>
<td>Age, sex, center, education, physical activity, BMI, smoking status, diabetes, hypertension, hyperlipidemia, total calories</td>
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<td>Eshak ES et al, 2011, Japan</td>
<td>Japan Collaborative Cohort Study</td>
<td>1988-1990 – 2003, 14.1 years follow-up</td>
<td>83,752 men and women, age 40-79 years: 707 CHD deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 40 food items</td>
<td>Rice, men</td>
<td>280 g/d 420 449 583 711 279 g/d 359 420 453 560</td>
<td>Age, history of hypertension, history of diabetes, BMI, alcohol, smoking status, exercise, walking, education, perceived mental stress, sleep duration, fish, meat, fruit, dairy products, soy, total energy, sodium, Key’s dietary score</td>
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<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Follow-up Period</td>
<td>Number of Participants</td>
<td>Age at Baseline</td>
<td>Incidence and Mortality</td>
<td>Food Items</td>
<td>Whole Grains Consumption</td>
<td>Relative Risk (95% CI)</td>
<td>Nutritional Factors</td>
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<td>Rautiainen S et al, 2012, Sweden</td>
<td>Sweden</td>
<td>Swedish Mammography Cohort</td>
<td>1997-2007, 9.9 years follow-up</td>
<td>32561 women, age 49-83 years: 1114 MI cases</td>
<td>49-83</td>
<td>Incidence, Validated FFQ, 96 food items</td>
<td>≤2.3 serv/d</td>
<td>2.4-3.4 3.4-4.7 ≥4.7</td>
<td>1.00 (0.95 (0.81-1.13) 0.88 (0.74-1.04) 0.89 (0.74-1.07)</td>
<td>Age, education, smoking, BMI, physical activity, hypertension, hypercholesterolemia, family history – MI, aspirin use, HRT, dietary supplement use, total energy, alcohol</td>
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<td>Simila ME et al, 2013, Finland</td>
<td>Finland</td>
<td>Alpha-Tocopherol Beta-Carotene Cancer Prevention Study</td>
<td>1985-1988 – 2004, 19 years follow-up</td>
<td>21995 male smokers, age 50-69 years: 4379 CHD cases</td>
<td>50-69</td>
<td>Incidence, Validated FFQ, 276 food items</td>
<td>Rye Per 100 g/d</td>
<td></td>
<td>1.00 (0.94-1.03)</td>
<td>Age, intervention group</td>
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<td>Du D et al, 2013, China</td>
<td>China</td>
<td>Shanghai Women’s Health Study</td>
<td>1997-2000 – 2009, 9.8 years follow-up</td>
<td>64854 women, age 40-70 years: 120 CHD cases</td>
<td>40-70</td>
<td>Incidence, Validated FFQ, 77 food items</td>
<td>White rice and refined wheat products</td>
<td>250 g/d 274 290 311</td>
<td>0.97 (0.49-1.93) 1.41 (0.69-2.90) 1.53 (0.64-3.68)</td>
<td>Age, birth cohort, education, income, smoking status, alcohol, physical activity, waist-to-hip ratio, hypertension, total energy, SFA, protein</td>
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<td>Du D et al, 2013, China</td>
<td>China</td>
<td>Shanghai Men’s Health Study</td>
<td>2002-2006 – 2009, 5.4 years follow-up</td>
<td>52512 men, age 40-74 years: 189 CHD cases</td>
<td>40-74</td>
<td>Incidence, Validated FFQ, 81 food items</td>
<td>White rice and refined wheat products</td>
<td>253 g/d 290 327 367</td>
<td>1.00 (0.69-1.90) 1.38 (0.76-2.51) 2.01 (0.96-4.23)</td>
<td>Age, birth cohort, education, income, smoking status, alcohol, physical activity, waist-to-hip ratio, hypertension, total energy, SFA, protein</td>
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<td>Eshak ES et al, 2014, Japan</td>
<td>Japan</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>1990/1993 – 2007/2009, 15.2 years follow-up</td>
<td>91223 men and women, age 40-69 years: 1088 IHD cases 605 IHD deaths</td>
<td>40-69</td>
<td>Incidence and mortality, Validated FFQ, 44/52 food items</td>
<td>Rice, CHD incidence</td>
<td>251 g/d 326 377 430 542</td>
<td>1.00 (0.93-0.76-1.14) 0.99 (0.80-1.22) 0.95 (0.77-1.19) 1.08 (0.84-1.38) 1.00</td>
<td>Age, sex, public health center area, hypertension, diabetes, use of lipid-lowering drugs, BMI, smoking status, ethanol intake, leisure-time sports activity, occupation, seafood, meat, fruit, vegetables, soy, SFAs, sodium, total energy, women: HRT, menopausal status</td>
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<td>Rebello SA et al, 2014, Singapore</td>
<td>Singapore</td>
<td>Singapore Chinese Health Study</td>
<td>1993-1998 – 2011, 15 years follow-up</td>
<td>53469 men and women, age 45-74 years: 1660 IHD deaths</td>
<td>45-74</td>
<td>Mortality, Validated FFQ, 165 food items</td>
<td>Whole-wheat bread, men 0.00 slices/d 0.33</td>
<td>1.00</td>
<td>0.93 (0.77-1.2) 0.94 (0.66-1.33) 0.99 (0.78-1.27) 1.00</td>
<td>Age, year of interview, father’s dialect, total energy intake, cigarette smoking, alcohol, physical activity, sleep duration, education, BMI, hypertension, PUFA/SFA ratio, rice, noodles, vegetables, fruit, fish, red meat, poultry, eggs, legumes, soy protein, white bread and whole-</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Participants</td>
<td>Incidence</td>
<td>Methods</td>
<td>White bread, women</td>
<td>Rice, men</td>
<td>Rice, women</td>
<td>Noodles, men</td>
<td>Noodles, women</td>
<td>References</td>
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<td>Muraki I et al, 2014, USA</td>
<td>Nurses' Health Study</td>
<td>1984-2010, 26 years follow-up</td>
<td>73228 women, age 38-63 years: 3060 CAD cases</td>
<td>Validated FFQ, 118-166 food items</td>
<td>0.33, 1.00</td>
<td>0.33, 1.00</td>
<td>0.33, 1.00</td>
<td>0.33, 1.00</td>
<td>0.33, 1.00</td>
<td>Age, sex, cohort, ethnicity, BMI, smoking status, cigarettes per day, alcohol, physical activity, family history – MI, multivitamin use, current aspirin use, prevalent hypertension, prevalent hypercholesterolemia, prevalent diabetes, total energy</td>
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<td>Nurses' Health Study 2</td>
<td>1991-2011, 20 years</td>
<td>92158 women, age 27-44 years: 534 CAD cases</td>
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<td>Study</td>
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<td>Cohort</td>
<td>Follow-up</td>
<td>Design/Methods</td>
<td>Exposure</td>
<td>Outcome</td>
<td>Relative Risk (95% CI)</td>
<td>Additional Factors Considered</td>
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<tr>
<td>Health Professionals Follow-up Study</td>
<td>1986-2010, 24 years follow-up</td>
<td>42170 men, age 40-75 years: 4125 CAD cases</td>
<td>Total rice</td>
<td>≥5 Per 3 serv/wk</td>
<td>0.80 (0.57-1.22)</td>
<td>1.00 (0.91-1.11)</td>
<td>Age, smoking, alcohol, physical activity, cigarette smoking</td>
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<td>Tognon G et al, 2014, Denmark</td>
<td>The 1982-1983 Danish Monitoring trends and determinants of Cardiovascular disease study (MONICA)</td>
<td>1982-2007, 14 years follow-up</td>
<td>Incidence and mortality</td>
<td>Cereals, MI incidence</td>
<td>0.90 (0.66-1.24)</td>
<td>0.69 (0.41-1.16)</td>
<td>Age, sex, BMI, education, physical activity, cigarette smoking</td>
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<td>Atkins JL et al, 2014, United Kingdom</td>
<td>British Regional Heart Study</td>
<td>1998-2010, 11.3 years follow-up</td>
<td>Incidence</td>
<td>Cereals, MI death</td>
<td>1.19 (0.73-1.93)</td>
<td>0.76 (0.18-3.15)</td>
<td>Age, smoking, alcohol, physical activity, social class, BMI, energy intake, diet score without respective components</td>
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<td>Johnsen NF et al, 2015, Norway, Sweden, Denmark</td>
<td>HELGA Cohort (Norwegian Women and Cancer Study, Northern Sweden Health and Disease Study, Danish Diet, Cancer and Health Study – part of the EPIC study)</td>
<td>1992-1998 to 2008-2009, 11.1 years follow-up</td>
<td>Mortality</td>
<td>Whole grain breakfast cereals, women</td>
<td>1.00</td>
<td>0.71 (0.43-1.16)</td>
<td>Age, follow-up time, education, smoking status/years since quit, cigarettes per day, alcohol, BMI, total energy</td>
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<td>Non-white bread</td>
<td>1.00</td>
<td>0.53 (0.37-0.77)</td>
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<td></td>
<td>Crisp bread</td>
<td>1.00</td>
<td>0.45 (0.30-0.61)</td>
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<td></td>
<td>Total whole grain products</td>
<td>1.00</td>
<td>0.59 (0.43-0.81)</td>
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<td>Oat</td>
<td>1.00</td>
<td>0.66 (0.47-0.91)</td>
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Notes: MI = myocardial infarction, CHD = coronary heart disease, CAD = coronary artery disease, FFQ = food frequency questionnaire.
<table>
<thead>
<tr>
<th></th>
<th>Rye</th>
<th>Wheat</th>
<th>Total whole grain types</th>
<th>Whole grain breakfast cereals, men</th>
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<td>18</td>
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<td>22</td>
<td>41</td>
<td>3</td>
<td>0.4 g/d</td>
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<td>0.79 (0.57-1.11)</td>
<td>1.02 (0.75-1.38)</td>
<td>0.69 (0.46-1.05)</td>
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<td>0.59 (0.42-0.82)</td>
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<td>37</td>
<td>0.8 g/d</td>
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<td>0.88 (0.69-1.11)</td>
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<td>20 g/d</td>
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<td>1.23 (0.88-1.71)</td>
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<td>2 g/d</td>
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<td>0.98 (0.81-1.19)</td>
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<td>34 g/d</td>
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<td>0.82 (0.65-1.03)</td>
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<td></td>
<td>7 g/d</td>
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<td>0.81 (0.67-0.97)</td>
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<td>21</td>
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<td>0.88 (0.73-1.07)</td>
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<td>38</td>
<td>0.1 g/d</td>
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<td>0.70 (0.55-0.88)</td>
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<td>38</td>
<td>1 g/d</td>
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<td>38</td>
<td>10</td>
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<td>0.84 (0.65-1.08)</td>
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<td>Danish Diet, Cancer and Health Cohort</td>
<td>1993-1997, 13.6 years follow-up</td>
<td>54871 men and women, age 50-64 years; 2329 MI cases</td>
<td>Incidence</td>
<td>Validated FFQ, 192 food items</td>
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<td>54 g/d</td>
<td>0.80 (0.66-0.97)</td>
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<td>80 g/d</td>
<td>0.74 (0.61-0.91)</td>
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<td>116 g/d</td>
<td>0.83 (0.73-0.95)</td>
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<td>224 g/d</td>
<td>0.77 (0.67-0.89)</td>
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<td>22 g/d</td>
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<td>52 g/d</td>
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<td>74 g/d</td>
<td>0.84 (0.73-0.95)</td>
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<td>25 g/d</td>
<td>0.86 (0.76-0.99)</td>
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<td>63 g/d</td>
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<td>103 g/d</td>
<td>0.88 (0.83-0.93)</td>
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<td>38 g/d</td>
<td>0.83 (0.67-1.02)</td>
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<td>74 g/d</td>
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<td>25 g/d</td>
<td>0.71 (0.56-0.89)</td>
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<td>29 g/d</td>
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<td>42 g/d</td>
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<td></td>
<td>63 g/d</td>
<td>0.86 (0.70-1.06)</td>
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<td>25 g/d</td>
<td>0.77 (0.62-0.95)</td>
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<td>25 g/d</td>
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<td>25 g/d</td>
<td>0.87 (0.78-0.96)</td>
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<tr>
<td>Oatmeal</td>
<td>96 g/d</td>
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<tr>
<td>Crispbread</td>
<td>97 g/d</td>
<td>0.97 (0.81-1.17)</td>
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<tr>
<td>Wheat</td>
<td>96 g/d</td>
<td>0.96 (0.84-1.09)</td>
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<tr>
<td>Rye</td>
<td>96 g/d</td>
<td>0.96 (0.93-0.99)</td>
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<tr>
<td>Oats</td>
<td>93 g/d</td>
<td>0.93 (0.88-0.97)</td>
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<tr>
<td>Rye bread, women</td>
<td>93 g/d</td>
<td>0.93 (0.88-0.98)</td>
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<tr>
<td>Whole grain bread</td>
<td>98 g/d</td>
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<tr>
<td>Oatmeal</td>
<td>89 g/d</td>
<td>1.12 (0.92-1.36)</td>
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</table>

Age, education, smoking status, pack-years, alcohol from beer and spirits, alcohol from wine, sports, menopausal status, HRT, fruit, vegetables, fish, red meat, processed meat, BMI, waist circumference, SBP, hypertension, serum cholesterol, hypercholesterolemia
<table>
<thead>
<tr>
<th>Grains</th>
<th>Per 10 g/d</th>
<th>Per 50 g/d</th>
<th>Per 25 g/d</th>
<th>Wang JB et al, 2016, China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>0.89 (0.70-1.13)</td>
<td>0.96 (0.90-1.01)</td>
<td>0.94 (0.86-1.02)</td>
<td>1.13</td>
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<tr>
<td>Rye</td>
<td>1.00</td>
<td>0.85 (0.75-0.98)</td>
<td>0.85 (0.74-0.98)</td>
<td>0.90</td>
</tr>
<tr>
<td>Oats</td>
<td>0.97 (0.94-1.01)</td>
<td>0.77-1.02</td>
<td>0.77-1.02</td>
<td>0.86-1.02</td>
</tr>
<tr>
<td>Total whole grain</td>
<td>0.94 (0.88-0.99)</td>
<td>0.87 (0.76-0.99)</td>
<td>0.87 (0.76-0.99)</td>
<td>0.76-0.99</td>
</tr>
<tr>
<td>products, men</td>
<td>1.00</td>
<td>0.93 (0.82-1.07)</td>
<td>0.93 (0.82-1.07)</td>
<td>0.82-1.07</td>
</tr>
<tr>
<td>Total whole grains</td>
<td>0.91 (0.85-0.98)</td>
<td>0.88 (0.76-1.02)</td>
<td>0.88 (0.76-1.02)</td>
<td>0.76-1.02</td>
</tr>
<tr>
<td>products, women</td>
<td>1.00</td>
<td>0.72 (0.57-0.91)</td>
<td>0.72 (0.57-0.91)</td>
<td>0.57-0.91</td>
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<tr>
<td>Total whole grains</td>
<td>0.89 (0.80-0.99)</td>
<td>0.79 (0.64-0.98)</td>
<td>0.79 (0.64-0.98)</td>
<td>0.64-0.98</td>
</tr>
<tr>
<td>Rye bread, men</td>
<td>0.98 (0.96-1.01)</td>
<td>0.76 (0.61-0.96)</td>
<td>0.76 (0.61-0.96)</td>
<td>0.61-0.96</td>
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<td>Whole grain bread</td>
<td>1.01 (0.98-1.03)</td>
<td>0.89 (0.82-0.96)</td>
<td>0.89 (0.82-0.96)</td>
<td>0.82-0.96</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>0.93 (0.77-1.11)</td>
<td>0.93 (0.77-1.11)</td>
<td>0.93 (0.77-1.11)</td>
<td>0.77-1.11</td>
</tr>
<tr>
<td>Crispbread</td>
<td>1.03 (0.90-1.17)</td>
<td>0.93 (0.93-1.02)</td>
<td>0.93 (0.93-1.02)</td>
<td>0.90-1.17</td>
</tr>
<tr>
<td>Wheat</td>
<td>0.96 (0.91-1.00)</td>
<td>0.96 (0.91-1.00)</td>
<td>0.96 (0.91-1.00)</td>
<td>0.91-1.00</td>
</tr>
<tr>
<td>Rye</td>
<td>0.93 (0.88-0.98)</td>
<td>0.93 (0.88-0.98)</td>
<td>0.93 (0.88-0.98)</td>
<td>0.88-0.98</td>
</tr>
<tr>
<td>Oats</td>
<td>0.96 (0.88-1.05)</td>
<td>0.88 (0.71-1.14)</td>
<td>0.88 (0.71-1.14)</td>
<td>0.71-1.14</td>
</tr>
<tr>
<td>Wang JB et al, 2016, China</td>
<td>1.00 (0.92-1.09)</td>
<td>1.05 (0.94-1.16)</td>
<td>1.05 (0.94-1.16)</td>
<td>0.94-1.16</td>
</tr>
</tbody>
</table>

Linxian Nutrition Intervention Trial
Mortality FFQ, 64 food items
All grains Non-whole grains
Per 1 time/day Per 1 time/day
Age, sex, commune, smoking, drinking, season, BMI
| cohort | 26 years follow-up | 69 years: 355 heart disease deaths | Whole grains | Per 1 time/day | 0.94 (0.83-1.07) |

BMI; body mass index, CHD; coronary heart disease, FFQ; food frequency questionnaire, H vs l; High vs low, HDL-cholesterol; high-density lipoprotein cholesterol, HRT; hormone replacement therapy, IHD; ischemic heart disease, LDL; low density lipoprotein cholesterol, MI; myocardial infarction, MUFA; monounsaturated fatty acids, NHS2; Nurses’ Health Study 2, PUFA; polyunsaturated fatty acids, SBP; systolic blood pressure, SFA; saturated fatty acids, trans-FA; trans fatty acids
### Supplementary table 4. Whole grains and refined grains and stroke

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Stroke incidence or mortality</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
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</thead>
<tbody>
<tr>
<td>Liu S et al, 2000, USA</td>
<td>Nurses’ Health Study</td>
<td>1984-1996, 12 years follow-up</td>
<td>75521 women, age 38-63 years: 352 ischemic stroke cases</td>
<td>Incidence</td>
<td>Validated FFQ, 126 food items</td>
<td>Whole grains</td>
<td>0.13 serv/day</td>
<td>0.92 (0.42-1.99)</td>
<td>0.89 (0.30-2.57)</td>
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<tr>
<td>Appleby PN et al, 2002, UK</td>
<td>The Health Food Shoppers Study</td>
<td>1973-1979 – 1997, 19.8 years follow-up</td>
<td>10741 men and women, age 16-89 years: 356 cerebrovascular disease deaths</td>
<td>Mortality</td>
<td>FFQ</td>
<td>Wholemeal bread Bran cereals</td>
<td>Daily vs less</td>
<td>0.89 (0.70-1.13)</td>
<td>0.92 (0.73-1.17)</td>
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<td>Liu S et al, 2003, USA</td>
<td>Physicians’ Health Study</td>
<td>1982-1988, 5.5 years follow-up</td>
<td>86190 men, age 40-84 years: 146 stroke cases</td>
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<td>Validated FFQ</td>
<td>Whole grain breakfast cereals</td>
<td>Rarely 1 serv/wk</td>
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<td>0.92 (0.42-1.99)</td>
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<td>Study</td>
<td>Years Follow-up</td>
<td>Participants</td>
<td>Incidence / Mortality</td>
<td>Whole Grain Consumption</td>
<td>Refined Grain Consumption</td>
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<tr>
<td>Atherosclerosis Risk in</td>
<td>1987-1989 -</td>
<td>15792 men</td>
<td>Incidence</td>
<td>0.1 serv/day</td>
<td>0.5 1.0 1.5 3.0 0.5 serv/day 1.5 2.0 3.0 5.0</td>
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<tr>
<td>Communities Study</td>
<td>1999, 11 years</td>
<td>women, age</td>
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<td>0.1 serv/day</td>
<td>0.5 1.0 1.5 3.0 0.5 serv/day 1.5 2.0 3.0 5.0</td>
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<td>45-64 years:</td>
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<td>1.11 (0.75-1.64) 0.79 (0.50-1.21) 0.89 (0.57-1.39) 0.75 (0.46-1.22) 1.00 1.10 (0.71-1.73) 1.00 (0.63-1.58) 0.68 (0.41-1.13) 0.82 (0.48-1.40)</td>
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<td>1.11 (0.75-1.64) 0.79 (0.50-1.21) 0.89 (0.57-1.39) 0.75 (0.46-1.22) 1.00 1.10 (0.71-1.73) 1.00 (0.63-1.58) 0.68 (0.41-1.13) 0.82 (0.48-1.40)</td>
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<td>stroke deaths</td>
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<td>1.00</td>
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<td>Iowas Women’s Health Study</td>
<td>1986 – 2003,</td>
<td>27312 women,</td>
<td>Mortality</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>17 years follow-</td>
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<tr>
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<td>years:</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>414 stroke</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>deaths</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>113 intracranial hemorrhagic stroke deaths</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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<td>stroke deaths</td>
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<td>0.91 (0.67-1.24) 0.84 (0.61-1.15) 0.88 (0.64-1.22) 0.85 (0.60-1.21) 1.00 1.28 (0.68-2.42) 1.33 (0.71-2.49) 1.01 (0.51-1.99) 1.28 (0.64-2.56)</td>
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Age at baseline, race, sex, time-dependent energy intake, education, smoking status, pack-years of smoking, physical activity, alcohol intake, HRT (women), BMI, waist-to-hip ratio, SBP, antihypertensive medication use

Whole grains vs refined grains, mutually adjusted for age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, HRT, multivitamin supplement use, intake of alcohol, alcohol^2, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains.
<table>
<thead>
<tr>
<th>Mizrahi A et al, 2009, Finland</th>
<th>Finnish Mobile Clinic Health Examination Survey</th>
<th>1968-1972 - 1994, 24 years follow-up</th>
<th>3932 men and women, age 40-74 years: 625 stroke cases</th>
<th>Incidence</th>
<th>Dietary history interview</th>
<th>Cereals, cerebrovascular disease</th>
<th>Whole grains</th>
<th>Refined grains</th>
<th>Cereals, ischemic stroke</th>
<th>Whole grains</th>
<th>Refined grains</th>
<th>Cereals, intracerebral stroke</th>
<th>Whole grains</th>
<th>Refined grains</th>
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<td>≥22.5</td>
<td>1.19 (0.72-1.97)</td>
<td>1.00</td>
<td>1.09 (0.87-1.36)</td>
<td>1.09 (0.86-1.39)</td>
<td>1.09 (0.82-1.45)</td>
<td>0.98 (0.78-1.23)</td>
<td>1.18 (0.93-1.48)</td>
<td>1.12 (0.87-1.45)</td>
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<td>0.96 (0.71-1.31)</td>
<td>1.12 (0.81-1.53)</td>
<td>0.97 (0.66-1.43)</td>
<td>1.00</td>
<td>0.81 (0.60-1.10)</td>
<td>0.95 (0.70-1.29)</td>
<td>1.11 (0.81-1.51)</td>
<td>1.06 (0.75-1.50)</td>
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<td>0.85 (0.61-1.19)</td>
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<td>1.72 (0.88-3.36)</td>
<td>0.64 (0.27-1.53)</td>
<td>1.14 (0.47-2.78)</td>
<td>1.00</td>
<td>0.70 (0.36-1.36)</td>
<td>1.01 (0.49-2.08)</td>
<td>1.31 (0.64-2.68)</td>
<td>1.19 (0.53-2.67)</td>
<td>0.66 (0.33-1.33)</td>
<td>0.66 (0.31-1.42)</td>
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<td>Study</td>
<td>Country</td>
<td>Years</td>
<td>Population</td>
<td>Incidence</td>
<td>Cereals, cerebral infarction</td>
<td>Cereals, intracerebral hemorrhage</td>
<td>Cereals, subarachnoid hemorrhage</td>
<td>Mortality</td>
<td>Rice, men, total stroke</td>
<td>Rice, women</td>
<td>Rice, men, ischemic stroke</td>
<td>Rice, women</td>
<td>Rice, men, hemorrhagic stroke</td>
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<td>Larsson SC et al, 2009, Finland</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study</td>
<td>1985-1988 - 2004, 13.6 years follow-up</td>
<td>26556 male smokers, age 50-69 years: 2702 cerebral infarctions 383 intracerebral hemorrhages 196 subarachnoid hemorrhages</td>
<td>Incidence</td>
<td>Validated FFQ, 276 food items</td>
<td>116.4 g/d 165.6 205.2 249.9 327.4</td>
<td>116.4 g/d 165.6 205.2 249.9 327.4</td>
<td>116.4 g/d 165.6 205.2 249.9 327.4</td>
<td>1.00 0.98 (0.87-1.10) 0.97 (0.85-1.10) 0.93 (0.81-1.07) 0.87 (0.74-1.03) 1.00</td>
<td>0.85 (0.63-1.16) 0.88 (0.64-1.22) 0.70 (0.48-1.01) 0.64 (0.41-1.01) 1.00</td>
<td>1.00 0.95 (0.59-1.52) 0.53 (0.26-1.04) 0.84 (0.43-1.62) 1.00 1.47 (0.78-2.79) 1.22 (0.62-2.37) 1.37 (0.64-2.94) 1.00 0.97 (0.51-1.82) 0.84 (0.43-1.62) 1.00 1.53 (0.64-3.68) 1.14 (0.49-2.67) 1.67 (0.69-4.07) 1.00 0.73 (0.35-1.50) 0.39 (0.15-1.00) 0.71 (0.34-1.49) 1.00 0.98 (0.33-2.91) 1.81 (0.71-4.66) 2.36 (0.92-6.03)</td>
<td>Age, supplementation group, cigarettes per day, BMI, SBP, DBP, serum total cholesterol, serum HDL-cholesterol, diabetes, coronary heart disease, leisure-time physical activity, alcohol, total energy</td>
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<td>Oba S et al, 2010, Japan</td>
<td>Takayama Study</td>
<td>1992 – 1999, 7 years follow-up</td>
<td>12561 men and 15301 women, age ≥35 years: 247 stroke deaths 126 ischemic stroke deaths 94 hemorrhagic stroke deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 169 food items</td>
<td>2.3 serv/d (67.6 g) 3.2 3.7 4.0 1.9 serv/d 2.3 2.7 3.2 2.3 serv/d (67.6 g) 3.2 3.7 4.0 1.9 serv/d 2.3 2.7 3.2 2.3 serv/d (67.6 g) 3.2 3.7 4.0 1.9 serv/d 2.3 2.7 3.2</td>
<td>1.00 0.95 (0.59-1.52) 0.53 (0.26-1.04) 0.84 (0.43-1.62) 1.00 1.47 (0.78-2.79) 1.22 (0.62-2.37) 1.37 (0.64-2.94) 1.00 0.97 (0.51-1.82) 0.84 (0.43-1.62) 1.00 1.53 (0.64-3.68) 1.14 (0.49-2.67) 1.67 (0.69-4.07) 1.00 0.73 (0.35-1.50) 0.39 (0.15-1.00) 0.71 (0.34-1.49) 1.00 0.98 (0.33-2.91) 1.81 (0.71-4.66) 2.36 (0.92-6.03)</td>
<td>Age, BMI, smoking status, physical activity, hypertension, education, total energy, alcohol, dietary fiber, salt, total fat</td>
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<td>Study</td>
<td>Country/Cohort</td>
<td>Study Period</td>
<td>Follow-up</td>
<td>Sample Size</td>
<td>Endpoints</td>
<td>FFQ/Food Items</td>
<td>Rice Consumption</td>
<td>Incidence/Mortality</td>
<td>Other Factors</td>
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<tr>
<td>Eshak ES et al, 2011, Japan</td>
<td>Japan Collaborative Cohort Study</td>
<td>1988-1990 – 2003, 14.1 years follow-up</td>
<td>83752 men and women, age 40-79 years: 1640 stroke deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 40 food items</td>
<td>Rice, men 280 g/d 420 449 583 711 279 g/d 359 420 453 560</td>
<td>Rice, women</td>
<td>1.00 0.96 (0.79-1.17) 0.96 (0.76-1.22) 0.78 (0.61-1.00) 1.02 (0.82-1.31) 1.00 0.85 (0.64-1.22) 0.89 (0.72-1.11) 0.89 (0.64-1.26) 0.99 (0.75-1.31)</td>
<td>Age, history of hypertension, history of diabetes, BMI, alcohol, smoking status, exercise, walking, education, perceived mental stress, sleep duration, fish, meat, fruit, dairy products, soy, total energy intake</td>
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<td>Misirili G et al, 2012, Greece</td>
<td>European Prospective Investigation into Cancer and Nutrition: Greece</td>
<td>1994-1999 – 2009, 10.6 years follow-up</td>
<td>23601 men and women, age 25-67 years: 395 incidence cases 196 deaths cerebrovascular disease</td>
<td>Incidence and mortality</td>
<td>FFQ, 150 food items</td>
<td>Cereals, incidence Per 70 g/d 1.02 (0.89-1.16) Cereals, mortality Per 70 g/d 0.97 (0.79-1.19)</td>
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<td>Age, education, smoking status, BMI, physical activity, hypertension, diabetes, total energy intake</td>
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<tr>
<td>Eshak E et al, 2014, Japan</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>1990/1993 – 2007/2009, 15.2 years follow-up</td>
<td>91223 men and women, age 40-69 years: 4395 total strokes 1777 hemorrhagic strokes 2590 ischemic strokes 1153 stroke deaths</td>
<td>Incidence</td>
<td>Validated FFQ, 44/52 food items</td>
<td>Rice, stroke incidence 251 g/d 326 377 430 542 251 g/d 326 377 430 542 251 g/d 326 377 430 542</td>
<td>Rice, hemorrhagic stroke incidence</td>
<td>1.00 1.07 (0.93-1.17) 0.94 (0.85-1.08) 0.93 (0.84-1.13) 1.01 (0.90-1.14) 1.00 1.05 (0.90-1.22) 0.95 (0.81-1.12) 0.95 (0.81-1.11) 0.96 (0.79-1.15) 1.00 1.07 (0.92-1.23) 0.99 (0.81-1.07) 0.99 (0.81-1.16) 1.05 (0.90-1.22) 1.00 1.07 (0.88-1.30) 1.07 (0.88-1.32) 1.00 (0.82-1.23)</td>
<td>Age, sex, public health center area, hypertension, diabetes, use of lipid-lowering drugs, BMI, smoking status, ethanol intake, leisure-time sports activity, occupation, seafood, meat, fruit, vegetables, soy, SFA, sodium, total energy, menopausal status, HRT</td>
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<td>Study</td>
<td>Design and Duration</td>
<td>Participants</td>
<td>Incidence</td>
<td>Exposure</td>
<td>Validation</td>
<td>Carbohydrate Source</td>
<td>Relative Risk (95% CI)</td>
<td>Additional Covariates</td>
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<tr>
<td>Muraki I et al, 2014, USA</td>
<td>Nurses’ Health Study 1984-2010, 26 years follow-up</td>
<td>73228 women, age 38-63 years: 2703 stroke cases</td>
<td>Incidence</td>
<td>White rice</td>
<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.00</td>
<td>Age, ethnicity, BMI, smoking status, alcohol, physical activity, family history of MI, menopausal status, OC use (NHS2), HRT, multivitamin use, current aspirin use, prevalent hypertension, prevalent hypercholesterolemia, prevalent diabetes, total energy intake, alternate Healthy Eating Index score</td>
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<td>Nurses’ Health Study 1991-2011, 20 years follow-up</td>
<td>92158 women, age 27-44 years: 494 stroke cases</td>
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<td>Brown rice</td>
<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>0.97 (0.90-1.03)</td>
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<td>Health Professionals Follow-up Study 1986-2010, 24 years follow-up</td>
<td>42170 men, age 40-75 years: 1475 stroke cases</td>
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<td>Total rice</td>
<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.00</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>0.97 (0.89-1.05)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.25 (0.99-1.57)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.02 (0.94-1.11)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.00</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.03 (0.94-1.14)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.05 (0.92-1.19)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.39 (0.99-1.96)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.11 (0.98-1.26)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>0.94 (0.87-1.01)</td>
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<td></td>
<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>0.98 (0.91-1.06)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.04 (0.89-1.21)</td>
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<td>FFQ, 118-166 food items</td>
<td>&lt;1 serv/wk</td>
<td>1.02 (0.95-1.10)</td>
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<td>Tognon G et al, 2014, Denmark</td>
<td>The 1982-83 Danish Monitoring trends and determinants of Cardiovascular disease study (MONICA)</td>
<td>948 women and 901 men, age NA: 167 stroke cases</td>
<td>Incidence</td>
<td>Cereals, incidence</td>
<td>7 day food record</td>
<td>&gt;median vs. &lt;median</td>
<td>0.82 (0.60-1.11)</td>
<td>Age, sex, BMI, education, physical activity, cigarette smoking</td>
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<td>Cereals, mortality</td>
<td>7 day food record</td>
<td>&gt;median vs. &lt;median</td>
<td>1.00 (0.53-1.89)</td>
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<td>Johnsen NF et al, 2015, Norway, Sweden, Denmark</td>
<td>HELGA Cohort (Norwegian Women and Cancer Study, Northern Sweden Health and Disease Study, Danish Diet, Cancer and Health Study – part of the EPIC study)</td>
<td>120010 men and women, age 30-64 years: 137/143 stroke deaths</td>
<td>Mortality</td>
<td>Whole grain breakfast cereals, women</td>
<td>FFQ, 88 food items</td>
<td>0 g/d</td>
<td>1.00</td>
<td>Age, follow-up time, education, smoking status/years since quit/ cigarettes per day, alcohol, BMI, total energy</td>
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<td>Wang JB et al, 2016, China</td>
<td>Linxian Nutrition Intervention Trial cohort</td>
<td>1984-1991, 19-26 years follow-up</td>
<td>2445 men and women, age 40-69 years; 452 stroke deaths</td>
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<tr>
<td>Jacobs DR et al, 2001, Norway</td>
<td>Norwegian County Study</td>
<td>1977-1983 – 1994, 14.4 years follow-up</td>
<td>33848 men and women, age 35-56 years: 758 CVD deaths</td>
<td>Mortality</td>
<td>FFQ, 66 food items</td>
<td>Whole grain bread score</td>
<td>0.05-0.60 0.83-0.83 0.90-1.13 1.35-1.80 2.25-5.40</td>
<td>1.00 0.93 (0.73-1.18) 0.84 (0.68-1.05) 0.84 (0.66-1.05) 0.77 (0.60-0.98)</td>
<td>Age, energy intake, sex, smoking status, physical activity during leisure, physical activity during work, cod liver oil, multivitamin use, SFA, SBP, serum total cholesterol, BMI</td>
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<td>Appleby PN et al, 2002, UK</td>
<td>The Health Food Shoppers Study</td>
<td>1973-1979 – 1997, 19.8 years follow-up</td>
<td>10741 men and women, age 16-89 years: 1202 circulatory disease deaths</td>
<td>Mortality</td>
<td>FFQ</td>
<td>Wholemeal bread Bran cereals</td>
<td>Daily vs less Daily vs less</td>
<td>0.86 (0.76-0.98) 1.04 (0.92-1.18)</td>
<td>Age at recruitment, sex, smoking, fresh fruit, nuts/dried fruit, raw vegetables salads, mutual adjustment between wholemeal bread and bran cereals</td>
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<tr>
<td>Liu S et al, 2003, USA</td>
<td>Physicians’ Health Study</td>
<td>1982-1988, 5.5 years follow-up</td>
<td>86190 men, mean age 40-84 years: 1381 CVD deaths</td>
<td>Mortality</td>
<td>Validated FFQ</td>
<td>Whole grain breakfast cereals Refined-grain breakfast cereals Total breakfast cereals</td>
<td>Rarely 1 serv/wk 2-6/wk ≥1/day Rarely 1 serv/wk 2-6/wk ≥1/day Rarely 1 serv/wk 2-6/wk ≥1/day</td>
<td>1.00 0.93 (0.75-1.17) 0.82 (0.68-0.98) 0.80 (0.66-0.97) 1.00 1.18 (0.99-1.40) 1.08 (0.89-1.31) 1.04 (0.84-1.27) 1.00 1.04 (0.89-1.22) 0.93 (0.79-1.10) 0.87 (0.74-1.03)</td>
<td>Age, cigarette smoking, alcohol intake, physical activity, BMI, type 2 diabetes, high cholesterol, hypertension, use of multivitamins</td>
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<tr>
<td>Sahyoun NR et al, 2006, USA</td>
<td>NA</td>
<td>1981-1984 – 1995, 12-15 years follow-up</td>
<td>535 men and women, age ≥60 years: 89 CVD deaths</td>
<td>Mortality</td>
<td>3-day food record</td>
<td>Whole grain 0.31 serv/d 0.86 1.49 2.90</td>
<td>1.00 0.77 (0.41-1.43) 0.76 (0.41-1.41) 0.48 (0.25-0.96)</td>
<td>Age, sex, race, education, marital status, smoking, alcohol intake, exercise, BMI, energy intake, SFA, antihypertensive or lipid-lowering therapy</td>
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<tr>
<td>Mink PJ et al, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986-2002, 16 years follow-up</td>
<td>34489 women, age 55-69 years: 2316 CVD</td>
<td>Mortality</td>
<td>Validated FFQ, 127 food items</td>
<td>Bran, added to food 0 serv/wk ≥ 0</td>
<td>1.00 0.86 (0.76-0.97)</td>
<td>Age, energy intake, marital status, education, blood pressure, diabetes, BMI, waist-</td>
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</tbody>
</table>
Deaths to hip ratio, physical activity, smoking, HRT

Jacobs DR, 2007, USA
Iowa Women's Health Study
1986-2003, 17 years follow-up
27312 women, age 55-69 years: 1900 CVD deaths
Mortality
Validated FFQ, 127 food items
Whole grains
1.8 serv/wk
5.6
8.8
14.5
25.6
0-5.75 serv/wk
6-9.5
9.6-13.5
14-22
≥22.5
1.00
0.96 (0.84-1.10)
0.83 (0.72-0.96)
0.83 (0.71-0.96)
0.73 (0.62-0.86)
1.00
0.94 (0.82-1.08)
0.89 (0.76-1.03)
0.75 (0.64-0.88)
0.94 (0.78-1.12)
Age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, HRT, multivitamin supplement use, intake of alcohol, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains

Gardener H et al, 2011, USA
The Northern Manhattan Study
NA – NA, 9 years follow-up
2568 men and women, age >40 years: 314 vascular deaths
Mortality
FFQ
Cereals ≥61 vs. <61 g/d
0.98 (0.79-1.23)
Age, sex, race-ethnicity, education, moderate to heavy physical activity, energy, cigarette smoking

Eshak ES et al, 2011, Japan
Japan Collaborative Cohort Study
1988-1990 – 2003, 14.1 years follow-up
83752 men and women, age 40-79 years: 3514 CVD deaths
Mortality
Validated FFQ, 40 food items
Rice, men
280 g/d
420
449
583
711
279 g/d
359
420
453
560
1.00
0.90 (0.79-1.03)
0.87 (0.74-1.02)
0.79 (0.67-0.93)
0.82 (0.70-0.97)
1.00
0.94 (0.78-1.14)
0.90 (0.77-1.05)
1.20 (0.94-1.51)
1.07 (0.88-1.34)
Age, history of hypertension, history of diabetes, BMI, alcohol smoking status, exercise, walking, education, perceived mental stress, sleep duration, fish, meat, fruit, dairy products, soy, total energy

Fitzgerald KC et al, 2012, USA
Women's Health Study
34827 women, age ≥45 years: 1094 CVD cases
Incidence
Validated FFQ, 133 food items
Whole grains
<0.50 serv/d
0.50-0.93
0.94-1.36
1.40-2.20
≥2.21
1.00
1.01 (0.84-1.21)
1.03 (0.86-1.24)
0.86 (0.71-1.05)
0.96 (0.79-1.17)
Age, randomization status, smoking, postmenopausal status, HRT, alcohol intake, energy, physical activity, cigarettes per day, highest education level

Von Ruesten A et al, 2013, Germany
European Prospective Investigation into Cancer and Nutrition– Potsdam study
1994/1998 – NA, 8 years follow-up
23531 men and women, age 35-65 years: 363 CVD cases
Incidence
Validated FFQ, 148 food items
Whole grain bread
Other bread
Grain flakes, muesli
Corn flakes, crisps
Pasta, rice
Per 50 g/d
Per 50 g/d
Per 50 g/d
Per 50 g/d
Per 100 g/d
0.96 (0.81-1.14)
0.99 (0.85-1.16)
0.54 (0.28-1.01)
1.89 (0.79-4.51)
1.01 (0.44-2.34)
Age, sex, smoking status, pack-years of smoking, alcohol, leisure-time physical activity, BMI, waist-to-hip ratio, prevalent hypertension, high blood lipid levels, education, vitamin supplementation, total...
<table>
<thead>
<tr>
<th>Study</th>
<th>Population Details</th>
<th>Energy, non-consumption of the food group, other food groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eshak E et al, 2014, Japan Public Health Center-based Prospective Study</td>
<td>91223 men and women, age 40-69 years: 2705 CVD deaths</td>
<td>Age, sex, public health center area, hypertension, diabetes, use of lipid-lowering drugs, BMI, smoking status, ethanol intake, leisure-time sports activity, occupation, seafood, meat, fruit, vegetables, soy, SFAs, sodium, total energy, and for women: menopausal status, HRT</td>
</tr>
<tr>
<td>Previención con dieta Mediterránea (PREDIMED) study</td>
<td>7216 men and women, age 55-75 years: 103 CVD deaths</td>
<td>Age, sex, smoking status, diabetes, BMI, SBP, DBP, recruitment center, statins, alcohol, education, physical activity, total energy, vegetables, fruits</td>
</tr>
<tr>
<td>British Regional Heart Study</td>
<td>3328 men, age 60-79 years: 582 CVD cases 327 CVD deaths</td>
<td>Age, smoking, alcohol, physical activity, social class, BMI, energy intake, diet score without respective components</td>
</tr>
<tr>
<td>Nurses' Health Study</td>
<td>73228 women, age 38-63 years: 5763 CVD cases</td>
<td>Age, ethnicity, BMI, smoking status, alcohol, physical activity, family history of MI, menopausal status, oral contraceptive use (NHS2), HRT, multivitamin use, current aspirin use, prevalent hypertension, prevalent hypercholesterolemia, prevalent diabetes, total energy intake, alternate Healthy Eating Index score</td>
</tr>
<tr>
<td>Nurses' Health Study 2</td>
<td>92158 women, age 27-44 years: 1028 CVD cases</td>
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<tr>
<td>Study</td>
<td>Study Period</td>
<td>Follow-up Period</td>
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<tr>
<td>Tognon G et al, 2014, Denmark</td>
<td>1982-1983 – 2007, 14 years</td>
<td>follow-up</td>
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<tr>
<td>Wu H et al, 2015, USA</td>
<td>1984-2010, 26 years</td>
<td>follow-up</td>
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<tr>
<td>Wu H et al, 2015, USA</td>
<td>1986-2010, 24 years</td>
<td>follow-up</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
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<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>74341 women, age 38-63 years: 2989 CVD deaths, 43744 men, age 32-87 years: 3621 CVD deaths</td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>367442 men and women, age 50-71 years: 11283 CVD deaths</td>
</tr>
<tr>
<td>Sonestedt E et al, 2015, Sweden</td>
<td>Malmö Diet and Cancer Study</td>
<td>26445 men and women, age 44-74 years: 2921 ischemic CVD events</td>
</tr>
<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>367442 men and women, age 50-71 years: 11283 CVD deaths</td>
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<tr>
<td>Wang JB et al, 2016, China</td>
<td>Linxian Intervention Trial cohort</td>
<td>1984-1991 - 2010, 19-26 years follow-up</td>
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</tbody>
</table>

1. The original paper reports in ounces/d, after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.

2. Data for heart disease and stroke deaths were pooled using a fixed effects model.

BMI; body mass index, CVD; cardiovascular disease, DBP; diastolic blood pressure, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, SBP; systolic blood pressure, SFA; saturated fatty acids
## Supplementary table 6. Whole grains and refined grains and total cancer

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Total cancer incidence or mortality</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR et al, 2001, Norway</td>
<td>Norwegian County Study</td>
<td>1977-1983 – 1994, 14.4 years follow-up</td>
<td>33848 men and women, age 35-56 years: 870 cancer deaths</td>
<td>Mortality</td>
<td>FFQ, 66 food items</td>
<td>Whole grain bread score</td>
<td>0.05-0.60</td>
<td>0.83-0.83</td>
<td>0.90-1.13</td>
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<tr>
<td>Appleby PN et al, 2002, UK</td>
<td>The Health Food Shoppers Study</td>
<td>1973-1979 – 1997, 19.8 years follow-up</td>
<td>11000 men and women, age 16-89 years: 680 cancer deaths</td>
<td>Mortality</td>
<td>FFQ</td>
<td>Wholemeal bread bran cereals</td>
<td>Daily vs less</td>
<td>Daily vs less</td>
<td>1.01 (0.85-1.20)</td>
</tr>
<tr>
<td>Khan MMH et al, 2004, Japan</td>
<td>The Hokkaido Study</td>
<td>1984-1985 – 2002, 14.3 years follow-up</td>
<td>1524 men and 1634 women, age ≥40 years: 155/89 cancer deaths</td>
<td>Mortality</td>
<td>FFQ, 37 food items</td>
<td>Bread, men Instant noodles Noodles Bread, women Instant noodles Noodles</td>
<td>≥2/wk vs ≥1mo</td>
<td>≥2/wk vs ≥1mo</td>
<td>≥2/wk vs ≥1mo</td>
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<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986-2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 2099 cancer deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains Refined grains</td>
<td>1.8 serv/wk 5.6 8.8 14.5 25.6 0-5.75 serv/wk 6-9.5 9.6-13.5 14-22 ≥22.5</td>
<td>1.00</td>
<td>0.86 (0.75-0.99)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Years Follow-up</td>
<td>Participants</td>
<td>Data Collection</td>
<td>Outcome</td>
<td>Food Group</td>
<td>Per Serving</td>
<td>Odds Ratio</td>
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<tr>
<td>Iso H et al, 2007</td>
<td>Japan</td>
<td>Collaborative Cohort Study</td>
<td>1988-1990-2003, ~12.8 years</td>
<td>42513 men and 57777 women, age 40-79 years; 3579/2138 cancer deaths</td>
<td>FFQ</td>
<td>Mortality</td>
<td>Rice, men</td>
<td>&lt;3/d</td>
<td>1.00</td>
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<td>Rice, women</td>
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<td>&lt;3/d</td>
<td>1.04 (0.91-1.18)</td>
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<td>≥5</td>
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<tr>
<td>Couto E et al, 2011</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>1992-2000-2002-2005, 8.7 years</td>
<td>142605 men and 335873 women, age 25-70 years; 9669/21062 cancer cases</td>
<td>Validated FFQs, 7-day or 14-day record diaries, diet history</td>
<td>Incidence</td>
<td>Cereals</td>
<td>Per 110 g/d</td>
<td>0.97 (0.95-0.98)</td>
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<tr>
<td>Von Ruesten A et al, 2013</td>
<td>Germany</td>
<td>European Prospective Investigation into Cancer and Nutrition–Potsdam study</td>
<td>1994/1998–NA, 8 years</td>
<td>23,531 m &amp; w, age 35–65 years; 844 cancer cases</td>
<td>Validated FFQ, 148 food items</td>
<td>Incidence</td>
<td>Whole grain bread</td>
<td>Per 50 g/d</td>
<td>0.94 (0.84-1.05)</td>
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<td></td>
<td>Other bread</td>
<td>Per 50 g/d</td>
<td>0.98 (0.88-1.09)</td>
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<td></td>
<td>Grain flakes, muesli</td>
<td>Per 50 g/d</td>
<td>0.98 (0.73-1.30)</td>
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<td></td>
<td>Cornflakes, crisps</td>
<td>Per 50 g/d</td>
<td>1.10 (0.57-2.11)</td>
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<td></td>
<td>Pasta, rice</td>
<td>Per 100 g/d</td>
<td>0.84 (0.48-1.48)</td>
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<tr>
<td>Sharma S et al, 2013, USA</td>
<td>Multiethnic Cohort Study</td>
<td>1993-1996 – 2001, NA</td>
<td>146389 men and women, age 45-75 years; 2028/1464 cancer deaths</td>
<td>Mortality</td>
<td>Validated FFQ, 180 food items</td>
<td>Grains, men, all</td>
<td>≤5.6 serv/(d)</td>
<td>5.7-7.8</td>
<td>7.9-10.8</td>
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<td>Grains, African American</td>
<td>≤5.6 serv/(d)</td>
<td>5.7-7.8</td>
<td>7.9-10.8</td>
<td>&gt;10.8</td>
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<td>Grains, Native Hawaiian</td>
<td>≤5.6 serv/(d)</td>
<td>5.7-7.8</td>
<td>7.9-10.8</td>
<td>&gt;10.8</td>
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<td>Grains, Japanese American</td>
<td>≤5.6 serv/(d)</td>
<td>5.7-7.8</td>
<td>7.9-10.8</td>
<td>&gt;10.8</td>
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<td>Grains, Latinos</td>
<td>≤4.5 serv/(d)</td>
<td>4.6-6.4</td>
<td>6.5-8.9</td>
<td>&gt;8.9</td>
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<td>Grains, Caucasian</td>
<td>≤5.6 serv/(d)</td>
<td>5.7-7.8</td>
<td>7.9-10.8</td>
<td>&gt;10.8</td>
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<td>Grains, women, all</td>
<td>≤4.5 serv/(d)</td>
<td>4.6-6.4</td>
<td>6.5-8.9</td>
<td>&gt;8.9</td>
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<td>Grains, African American</td>
<td>≤4.5 serv/(d)</td>
<td>4.6-6.4</td>
<td>6.5-8.9</td>
<td>&gt;8.9</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Grains, Native Hawaiian</td>
<td>≤4.5 serv/(d)</td>
<td>4.6-6.4</td>
<td>6.5-8.9</td>
<td>&gt;8.9</td>
</tr>
</tbody>
</table>

Age, time on study, years of education, energy intake, smoking status, pack-years, BMI, physical activity, diabetes, alcohol, women: HRT, oophorectomy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Mortality</th>
<th>Diet</th>
<th>Whole grains</th>
<th>Energy</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevej-Cosiales P et al, 2014, Spain&lt;br&gt;Prevencion con Dieta Mediterranea (PREDIMED) study</td>
<td>7216 men and women, age 55-75 years: 169 cancer deaths</td>
<td>2003-2009 – 2012, 5.9 years follow-up</td>
<td>Validated FFQ, 137 food items</td>
<td>0 g/d</td>
<td>1.00</td>
<td>0.62 (0.41-0.92)</td>
<td>Age, sex, smoking status, diabetes, BMI, SBP, DBP, recruitment center, statins, alcohol, education, physical activity, total energy, vegetables, fruits</td>
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<tr>
<td>Wu H et al, 2015, USA&lt;br&gt;Nurses’ Health Study</td>
<td>74341 women, age 38-63 years: 5964 cancer deaths</td>
<td>1984-2010, 26 years follow-up</td>
<td>Validated FFQ, 126 food items</td>
<td>4.2 g/d</td>
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<td>0.94 (0.55-1.62)</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since quitting smoking, alcohol, physical activity, family history of diabetes, cancer and heart disease, multivitamin use, aspirin use, hypertension, high cholesterol, diabetes, total energy, healthy eating index (excluding whole grains): women: postmenopausal status, HRT</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Duration</td>
<td>Participants</td>
<td>Follow-up</td>
<td>Age Range</td>
<td>Cancer Deaths</td>
<td>Mortality Validation</td>
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<td>Wu H et al, 2015, USA</td>
<td>USA</td>
<td>1986-2010, 24 years follow-up</td>
<td>43744 men, age 32-87 years: 3921 cancer deaths</td>
<td>Mortality</td>
<td>FFQ, 131 food items</td>
<td>5.9 g/d</td>
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<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
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<td>1984-2010, 26 years follow-up</td>
<td>74341 women, age 38-63 years: 5964 cancer deaths</td>
<td>Mortality</td>
<td>FFQ, 126/131 food items</td>
<td>1 2 3 4 5</td>
<td>0.13 oz/1000 kcal/d</td>
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<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2008, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 19043 cancer deaths</td>
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<td>Validated FFQ, 124 food items</td>
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<td>Non-white bread</td>
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<tr>
<td>Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)</td>
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<td>120010 men and women, age 30-64 years; 1375/1775 cancer deaths</td>
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<tr>
<td>Age, follow-up time, education, smoking status/years since quit/cigaretes per day, alcohol, BMI, total energy</td>
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<thead>
<tr>
<th>Whole grain types</th>
<th>Norway (Norway)</th>
<th>Sweden (Sweden)</th>
<th>Denmark (Denmark)</th>
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<tr>
<td>Oat 0 g/d</td>
<td>0.8</td>
<td>12</td>
<td>50</td>
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<tr>
<td>8 g/d</td>
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<td>113</td>
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<td>31</td>
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<td>2</td>
<td>6</td>
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<tr>
<td>100</td>
<td>56</td>
<td>131</td>
<td>201</td>
</tr>
<tr>
<td>Rye 0 g/d</td>
<td>0.4</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>8 g/d</td>
<td>18</td>
<td>22</td>
<td>41</td>
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<tr>
<td>37</td>
<td>0.4 g/d</td>
<td>3</td>
<td>10</td>
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<td>37</td>
<td>0.4 g/d</td>
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<td>10</td>
</tr>
<tr>
<td>Wheat 0 g/d</td>
<td>20</td>
<td>33</td>
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<td>74</td>
<td>20</td>
<td>33</td>
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<th>Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120010 men and women, age 30-64 years; 1375/1775 cancer deaths</td>
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<tr>
<td>Age, follow-up time, education, smoking status/years since quit/cigarettes per day, alcohol, BMI, total energy</td>
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<table>
<thead>
<tr>
<th>Mortality</th>
<th>Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)</th>
</tr>
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<tbody>
<tr>
<td>120010 men and women, age 30-64 years; 1375/1775 cancer deaths</td>
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<tr>
<td>Age, follow-up time, education, smoking status/years since quit/cigarettes per day, alcohol, BMI, total energy</td>
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## Whole grain breakfast cereals, men

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<tr>
<th>Item</th>
<th>0 g/d</th>
<th>7 g/d</th>
<th>50 g/d</th>
<th>13 g/d</th>
<th>66 g/d</th>
<th>118 g/d</th>
<th>201 g/d</th>
<th>1 g/d</th>
<th>2 g/d</th>
<th>34 g/d</th>
<th>Total whole grain products</th>
<th>64 g/d</th>
<th>107 g/d</th>
<th>156 g/d</th>
<th>222 g/d</th>
<th>Total whole grain types</th>
<th>21 g/d</th>
<th>37 g/d</th>
<th>54 g/d</th>
<th>80 g/d</th>
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</thead>
<tbody>
<tr>
<td>Whole grain</td>
<td>0 g/d</td>
<td>0.8 g/d</td>
<td>7 g/d</td>
<td>50 g/d</td>
<td>13 g/d</td>
<td>66 g/d</td>
<td>118 g/d</td>
<td>201 g/d</td>
<td>1 g/d</td>
<td>2 g/d</td>
<td>34 g/d</td>
<td>64 g/d</td>
<td>107 g/d</td>
<td>156 g/d</td>
<td>222 g/d</td>
<td>21 g/d</td>
<td>37 g/d</td>
<td>54 g/d</td>
<td>80 g/d</td>
<td>0 g/d</td>
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<tr>
<td>Non-white bread</td>
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<tr>
<td>Total whole grain products</td>
<td>1.00</td>
<td>0.99 (0.81-1.21)</td>
<td>0.73 (0.63-0.85)</td>
<td>0.75 (0.64-0.87)</td>
<td>0.92 (0.76-1.12)</td>
<td>0.97 (0.79-1.19)</td>
<td>0.79 (0.64-0.97)</td>
<td>1.00</td>
<td>0.99 (0.85-1.15)</td>
<td>0.92 (0.79-1.07)</td>
<td>0.83 (0.67-1.03)</td>
<td>1.00</td>
<td>0.84 (0.72-0.98)</td>
<td>0.74 (0.64-0.86)</td>
<td>0.70 (0.60-0.81)</td>
<td>1.00</td>
<td>0.84 (0.72-0.98)</td>
<td>0.74 (0.64-0.86)</td>
<td>0.70 (0.60-0.81)</td>
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<tr>
<td>Oat</td>
<td>0 g/d</td>
<td>0.4 g/d</td>
<td>3 g/d</td>
<td>30 g/d</td>
<td>7 g/d</td>
<td>21 g/d</td>
<td>38 g/d</td>
<td>56 g/d</td>
<td>0.1 g/d</td>
<td>1 g/d</td>
<td>5 g/d</td>
<td>21 g/d</td>
<td>37 g/d</td>
<td>54 g/d</td>
<td>80 g/d</td>
<td>21 g/d</td>
<td>37 g/d</td>
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<td>80 g/d</td>
<td>0.1 g/d</td>
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<tr>
<td>Rye</td>
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<td>3 g/d</td>
<td>30 g/d</td>
<td>7 g/d</td>
<td>21 g/d</td>
<td>38 g/d</td>
<td>56 g/d</td>
<td>0.1 g/d</td>
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<td>5 g/d</td>
<td>21 g/d</td>
<td>37 g/d</td>
<td>54 g/d</td>
<td>80 g/d</td>
<td>0.85 (0.73-0.99)</td>
<td>1.00</td>
<td>0.85 (0.73-0.99)</td>
<td>0.58 (0.49-0.69)</td>
<td>0.74 (0.63-0.87)</td>
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<tr>
<td>Wheat</td>
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<tr>
<td>Total whole grain types</td>
<td>1.00</td>
<td>0.99 (0.81-1.21)</td>
<td>0.73 (0.63-0.85)</td>
<td>0.75 (0.64-0.87)</td>
<td>0.92 (0.76-1.12)</td>
<td>0.97 (0.79-1.19)</td>
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<td>0.92 (0.79-1.07)</td>
<td>0.83 (0.67-1.03)</td>
<td>1.00</td>
<td>0.84 (0.72-0.98)</td>
<td>0.74 (0.64-0.86)</td>
<td>0.70 (0.60-0.81)</td>
<td>1.00</td>
<td>0.84 (0.72-0.98)</td>
<td>0.74 (0.64-0.86)</td>
<td>0.70 (0.60-0.81)</td>
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<tr>
<td>Study</td>
<td>Duration</td>
<td>Participants</td>
<td>Incidence</td>
<td>Validation Method</td>
<td>Food Items</td>
<td>Rice Consumption</td>
<td>Odds Ratio (95% CI)</td>
<td>Adjusted Factors</td>
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<tr>
<td>Nurses' Health Study 1, 1984-2010, 26 yrs</td>
<td>26 yrs follow-up</td>
<td>70603 women, age 38-63 yrs: 15673 cancer cases</td>
<td>Incidence</td>
<td>FFQ, 126 food items</td>
<td>Total rice, White rice, Brown rice</td>
<td>&lt;1 serv/wk, 1-2, ≥5 serv/wk</td>
<td>1.00 (1.01-1.05), 1.00 (0.96-1.04), 1.02 (0.93-1.12)</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, physical activity, family history of cancer, multivitamin supplement use, total energy intake, alcohol, fruit, vegetables, red meat, fish, nuts, whole grain (except brown rice), sugar-sweetened beverages, HRT</td>
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<tr>
<td>Nurses' Health Study 2, 1991-2009, 18 yrs</td>
<td>18 yrs follow-up</td>
<td>90264 women, age 27-44 yrs: 5149 cancer cases</td>
<td>Incidence</td>
<td>FFQ, 133 food items</td>
<td>Total rice, White rice, Brown rice</td>
<td>&lt;1 serv/wk, 1-2, ≥5 serv/wk</td>
<td>0.93 (0.93-1.00), 0.96 (0.95-1.05), 0.97 (0.93-1.00)</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, physical activity, family history of cancer, multivitamin supplement use, total energy intake, alcohol, fruit, vegetables, red meat, fish, nuts, whole grain (except brown rice), sugar-sweetened beverages, HRT</td>
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<td>Health Professionals Follow-up Study, 1986-2008, 22 yrs follow-up</td>
<td>22 yrs follow-up</td>
<td>45382 men, age 40-75 yrs: 10833 cancer cases</td>
<td>Incidence</td>
<td>FFQ, 131 food items</td>
<td>Total rice, White rice, Brown rice</td>
<td>&lt;1 serv/wk, 1-2, ≥5 serv/wk</td>
<td>1.00 (0.99-1.04), 1.00 (0.95-1.05), 1.00 (0.93-1.10)</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, physical activity, family history of cancer, multivitamin supplement use, total energy intake, alcohol, fruit, vegetables, red meat, fish, nuts, whole grain (except brown rice), sugar-sweetened beverages</td>
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BMI; body mass index, DBP; diastolic blood pressure, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, SBP; systolic blood pressure, SFA; saturated fatty acids
1 The original paper reports in ounces/d, after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
Supplementary table 7. Whole grains and refined grains and all-cause mortality

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
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<tbody>
<tr>
<td>Kahn HA et al, 1984, USA</td>
<td>Adventist Mortality Study</td>
<td>1960-1980, 21 years follow-up</td>
<td>27530 men and women, age ≥30 years: 5751 deaths</td>
<td>FFQ, 28 food items</td>
<td>Bread, rolls, biscuits</td>
<td>Cereal</td>
<td>&lt;1/wk 1-2 3-4 6-7 &lt;1/wk 1-2 3-6 7</td>
<td>1.00 0.88 (0.80-0.96) 0.81 (0.69-0.95) 0.82 (0.73-0.92) 1.00 0.80 (0.71-0.90) 0.77 (0.67-0.88) 0.84 (0.75-0.94)</td>
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<td>Rotevatn S et al, 1989, Norway</td>
<td>NA</td>
<td>1964-1967 – 1978, 11.5 years follow-up</td>
<td>10187 men, age 35-74 years: 2458 deaths</td>
<td>FFQ</td>
<td>Bread consumption</td>
<td>≥6 vs. &lt;6/d</td>
<td>0.752</td>
<td>Age, physical exercise, cigarette smoking, alcohol</td>
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<td>Trichopoulou A, 1995, Greece,</td>
<td>NA</td>
<td>1988-1990 – 1993-1994, ~3-6 years follow-up</td>
<td>182 men and women, &gt;70 years: 53 deaths</td>
<td>Validated FFQ, 198 food items/beverages</td>
<td>Cereal</td>
<td>20 g/d</td>
<td>1.02 (0.97-1.07)</td>
<td>Age, smoking status, sex</td>
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<tr>
<td>Osler M et al, 1997, Denmark</td>
<td>Euronet SENECA study Denmark</td>
<td>1988-1989 – 1995, NA</td>
<td>202 men and women, mean age 73.4 years: 52 deaths</td>
<td>3-day food record and frequency checklist of foods</td>
<td>Cereals</td>
<td>Per 20 g/d</td>
<td>1.10 (1.03-1.17)</td>
<td>Age, sex, smoking</td>
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<td>Cortes C et al, 2000, Italy</td>
<td>NA</td>
<td>1993-1998, 5 years follow-up</td>
<td>162 men and women, age ≥65 years: 53 deaths</td>
<td>FFQ, 114 food items</td>
<td>Pasta</td>
<td>&lt;1/wk 1-4/wk &gt;4/wk</td>
<td>1.00 0.56 (0.26-1.21) 0.61 (0.26-1.45)</td>
<td>Age, sex, education, BMI, smoking, cognitive function, chronic diseases</td>
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<td>Jacobs DR et al, 2001, Norway</td>
<td>Norwegian County Study</td>
<td>1977-1983 – 1994, 14.4 years follow-up</td>
<td>33848 men and women, age 35-56 years: 2058 deaths</td>
<td>FFQ, 66 food items</td>
<td>Whole grain bread score</td>
<td>0.05-0.60 0.83-0.83 0.90-1.13 1.35-1.80 2.25-5.40</td>
<td>1.00 0.87 (0.75-1.01) 0.80 (0.71-0.92) 0.85 (0.74-0.98) 0.75 (0.65-0.88)</td>
<td>Age, energy, sex, current smoking, past smoking, leisure-time physical activity, occupational physical activity, cod liver oil use, multivitamins, SFA intake, SBP, serum total cholesterol, BMI</td>
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<tr>
<td>Study Details</td>
<td>Study Period</td>
<td>Follow-up Duration</td>
<td>Participants</td>
<td>Mortality</td>
<td>FFQ Details</td>
<td>Exposure Description</td>
<td>HR (95% CI)</td>
<td>Covariates</td>
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<tr>
<td>Appleby PN et al, 2002, UK</td>
<td>1973-1979 - 1997, 19.8 years follow-up</td>
<td>11000 men and women, age 16-89 years: 2529 deaths</td>
<td>FFQ</td>
<td>Wholemeal bread</td>
<td>Daily vs less</td>
<td>0.89 (0.82-0.98)</td>
<td>Age at recruitment, sex, smoking, fresh fruit, nuts/dried fruit, raw vegetables, salads, mutual adjustment between wholemeal bread and bran cereals</td>
<td></td>
</tr>
<tr>
<td>Liu S et al, 2003, USA</td>
<td>1982-1988 - 5.5 years follow-up</td>
<td>86190 men, age 40-84 years: 3114 deaths</td>
<td>Validated FFQ</td>
<td>Whole grain breakfast cereals</td>
<td>Rarely 1 serv/wk 2-6/wk ≥1/day</td>
<td>1</td>
<td>Age, cigarette smoking, alcohol intake, physical activity, BMI, diabetes mellitus, high cholesterol, hypertension, multivitamin use</td>
<td></td>
</tr>
<tr>
<td>Steffen LM et al, 2003, USA</td>
<td>1987-1989 -1999, 11 years follow-up</td>
<td>11940 men and women, age 45-64 years: 867 deaths</td>
<td>Validated FFQ, 61 food items</td>
<td>Whole grain</td>
<td>0.1 serv./day 0.5 1.0 1.5 3.0 0.5 1.0 2.0 3.0 5.0</td>
<td>1.00 0.96 (0.79-1.17) 0.80 (0.65-0.99) 0.87 (0.70-1.08) 0.77 (0.61-0.97) 1.00 0.96 (0.75-1.23) 1.03 (0.81-1.31) 0.97 (0.76-1.23) 1.08 (0.83-1.40)</td>
<td>Age at baseline, race, sex, time-dependent energy intake, education, smoking status, pack-years of smoking, physical activity, alcohol intake, HRT-women, BMI, waist-to-hip ratio, SBP, antihypertensive medication use</td>
<td></td>
</tr>
<tr>
<td>Trichopoulou A et al, 2005, Greece</td>
<td>1992-2000 - 2003, 7.4 years follow-up</td>
<td>74607 men and women, age 60 years: 4047 deaths</td>
<td>Validated FFQs, food records</td>
<td>Cereals</td>
<td>Per 104 g/d</td>
<td>0.94 (0.91-0.98)</td>
<td>Age, sex, country, diabetes, waist-to-hip ratio, BMI, education, smoking status, occupational physical activity, leisure-time physical activity, alcohol, total energy</td>
<td></td>
</tr>
<tr>
<td>Study Authors</td>
<td>Study Name</td>
<td>Study Period</td>
<td>Follow-up</td>
<td>Sample Size</td>
<td>Outcome</td>
<td>Food Group</td>
<td>Serving Level</td>
<td>Hazard Ratio (95% CI)</td>
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<tr>
<td>Hays JC et al, 2005, USA</td>
<td>Established Population for Epidemiologic Studies of the Elderly – Duke University</td>
<td>1992-1993 - 1996, 4 years follow-up</td>
<td>1920 men and women, mean age 76.1 (whites)/ 77.0 (black): 226 deaths</td>
<td>Short interview</td>
<td>Grains, white men, Grains, black men, Grains, white women, Grains, black women</td>
<td>≥2 vs. &lt;2 serv/d</td>
<td>0.34 (0.10-1.19)</td>
<td>Age, lived alone, below poverty threshold, impaired food related activities of daily living, non-dairy protein, dairy, grains, smoking, alcohol, BMI, waist circumference, cognitive status, self-rated health</td>
</tr>
<tr>
<td>Kooops KTB et al, 2006, Europe</td>
<td>Healthy Ageing – a Longitudinal Study in Europe (HALE)</td>
<td>1988-1991 - 2000, 10 years follow-up</td>
<td>2068 men and 1049 women, mean age 73.7 years: 1382 deaths</td>
<td>Dietary history</td>
<td>Grains</td>
<td>≥median vs. &lt;median</td>
<td>0.84 (0.77-0.92)</td>
<td>Age, sex, physical activity, smoking, alcohol, education, BMI, chronic disease at baseline, study centre</td>
</tr>
<tr>
<td>Sahyoun NR et al, 2006, USA</td>
<td>NA</td>
<td>1981-1984 - 1995, 12-15 years follow-up</td>
<td>535 men and women, age ≥60 years: 186 deaths</td>
<td>3-day food record</td>
<td>Whole grain</td>
<td>0.31 serv/d</td>
<td>1.00</td>
<td>Age, sex, race, education, marital status, smoking, alcohol intake, exercise, BMI, energy intake, SFA, antihypertensive or lipid-lowering therapy</td>
</tr>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 5552 deaths</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk</td>
<td>1.00</td>
<td>Age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, HRT, multivitamin supplement use, intake of alcohol, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains</td>
</tr>
<tr>
<td>Iso H et al, 2007, Japan</td>
<td>Japan Collaborative Cohort Study</td>
<td>1988-1990-2003, 12.8 years follow-up</td>
<td>42513 men and 57777 women, age 40-79 years: 9560/6575 deaths</td>
<td>FFQ</td>
<td>Rice, men, Rice, women</td>
<td>&lt;3/d</td>
<td>1.00</td>
<td>Age, area of study</td>
</tr>
<tr>
<td>Trichopoulou A et al, 2009, Greece</td>
<td>European Prospective Investigation into Cancer and Nutrition - Greece</td>
<td>1994-1997 - 2002, 8.5 years follow-up</td>
<td>23349 men and women, age 20-86 years: 1075 deaths</td>
<td>Validated FFQ, 150 food items</td>
<td>Cereals</td>
<td>&lt;median</td>
<td>1.00</td>
<td>Age, sex, education, smoking status, waist-to-hip ratio, BMI, physical activity, total energy intake</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort/Dates/Location</td>
<td>Participants/Duration</td>
<td>Methods/Items</td>
<td>Main Data/Exposure</td>
<td>Main Covariates</td>
<td>Main Outcomes</td>
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<tr>
<td>Buckland G et al, 2011, Spain</td>
<td>European Prospective</td>
<td>40622 men and women,</td>
<td>Validated DHQ, 600 food items</td>
<td>Cereals</td>
<td>Age, sex, centre, BMI, waist circumference, education level, physical activity, smoking status and intensity, total energy intake</td>
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<tr>
<td>European Prospective Investigation into Cancer and Nutrition – Spain cohort</td>
<td>1992/1996 - 2008, 13.4 years follow-up</td>
<td>age 26-69 years: 1855 deaths</td>
<td></td>
<td>151.8 g/d</td>
<td>0.92 (0.82-1.03)</td>
<td>0.91 (0.81-1.03)</td>
<td></td>
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<tr>
<td>Olsen A et al, 2011, Denmark</td>
<td>Diet, Cancer, and Health Study</td>
<td>50290 men and women, age 50-64 years: 4126 deaths</td>
<td>Validated FFQ, 192 food items</td>
<td>Rye bread, men</td>
<td>Age, time under study, smoking status, smoking duration, current tobacco consumption, time since cessation, alcohol, education, participation in sports, time spent in sports per week, BMI, red meat, processed meat, total energy, fish, cabbages, apples and pears, root vegetables</td>
<td></td>
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<tr>
<td>Diet, Cancer, and Health Study</td>
<td>1993-1997 – 2008, 12 years follow-up</td>
<td></td>
<td></td>
<td>63 g/d</td>
<td>0.84 (0.75-0.94)</td>
<td>1.00 (0.82-1.02)</td>
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<tr>
<td>Olsen A et al, 2011, Denmark</td>
<td>Diet, Cancer, and Health Study</td>
<td></td>
<td></td>
<td>&lt;63 g/d</td>
<td>1.00</td>
<td>0.91 (0.80-1.01)</td>
<td>1.00</td>
<td>0.97 (0.84-1.11)</td>
</tr>
<tr>
<td>Van den Brandt PA et al, 2011, Netherlands</td>
<td>Netherlands Cohort Study</td>
<td>120852 men and women, age 55-69 years: 9691 deaths</td>
<td>Validated FFQ, 150 food items</td>
<td>Whole grains, men</td>
<td>Age, cigarette smoking, cigarettes per day, years of smoking, BMI, nonoccupational physical activity, hypertension, education, energy intake</td>
<td></td>
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<tr>
<td>Netherlands Cohort Study</td>
<td>1986-1996, ~11 years follow-up</td>
<td>3576 subcohort members</td>
<td></td>
<td>Per 10.6 g/d</td>
<td>1.01 (0.99-1.02)</td>
<td>1.00 (0.98-1.03)</td>
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<tr>
<td>Van den Brandt PA et al, 2011, Netherlands</td>
<td>Gerontological and Geriatric Population Studies in Gothenburg</td>
<td>1037 men and women, age 70 years: 630 deaths</td>
<td>Dietary history</td>
<td>Whole grains cereals</td>
<td>Age, sex, baseline BMI, waist circumference, physical activity, marital status, smoking status, birth cohort, education</td>
<td></td>
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<tr>
<td>Tognon G et al, 2011, Sweden</td>
<td>Seguimiento Universidad de Navarra Project</td>
<td>15535 men and women, mean age 38 years: 185 deaths</td>
<td>Validated FFQ, 136 food items</td>
<td>Cereals</td>
<td>Age, years of university education, BMI, smoking, physical activity, hours spent watching television, history of depression, hypertension, hypercholesterolemia, total energy, egg intake, potato, adoption of special diets, MUFA/SFA ratio, fruits/nuts, vegetables, legumes, fish, meat/meat products, dairy, alcohol</td>
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<tr>
<td>Tognon G et al, 2011, Sweden</td>
<td>Seguimiento Universidad de Navarra Project</td>
<td></td>
<td></td>
<td>≥median vs. &lt;median</td>
<td>0.83 (0.54-1.27)</td>
<td></td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Follow-up</td>
<td>Participants</td>
<td>Outcomes</td>
<td>Validation</td>
<td>Food Items</td>
<td>Exposure</td>
<td>HR (95% CI)</td>
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<tr>
<td>Sliuk D et al, 2014, Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>1992-2000 - NA, 9.9 years follow-up</td>
<td>265295 men and women, age 30-70 years: 830/12135 deaths (diabetes/no diabetes)</td>
<td>Validated FFQs, food records and questionnaires</td>
<td>Pasta, diabetes</td>
<td>Per 10 g/d</td>
<td>0.93 (0.90-0.96)</td>
<td>Age, centre, sex, prevalence of heart disease, cancer, stroke, education, diabetes medication use, alcohol, smoking behavior, physical activity, underlying dietary patterns</td>
</tr>
<tr>
<td>Li K et al, 2014, Germany</td>
<td>European Prospective Investigation into Cancer and Nutrition - Heidelberg Cohort</td>
<td>1994-1998 - 2009, 11 years follow-up</td>
<td>10235 men and 12234 women, age ≥40 years: 1599 deaths</td>
<td>Validated FFQ, 148 food items</td>
<td>Cereals, men</td>
<td>Low vs. high</td>
<td>1.08 (0.96-1.23)</td>
<td>Age, smoking status, duration and cigarettes per day, BMI, alcohol, leisure-time physical activity, red and processed meat, vegetables and fruits, fish, dairy products</td>
</tr>
<tr>
<td>Tognon G et al, 2014, Denmark</td>
<td>The 1982-1983 Danish Monitoring trends and determinants of Cardiovascular disease study (MONICA)</td>
<td>1982-1983 - 2007, 14 years follow-up</td>
<td>948 women and 901 men, age NA: 553 deaths</td>
<td>7 day food record</td>
<td>Cereals</td>
<td>&gt;median vs. &lt;median</td>
<td>0.97 (0.82-1.15)</td>
<td>Age, sex, BMI, education, physical activity, smoking</td>
</tr>
<tr>
<td>Atkins JL et al, 2014, United Kingdom</td>
<td>British Regional Heart Study</td>
<td>1998-2000 - 2010, 11.3 years follow-up</td>
<td>3328 men, age 60-79 years: 933 deaths</td>
<td>Validated FFQ, 86 food items</td>
<td>Cereals</td>
<td>Daily vs. &lt;1 day/wk</td>
<td>1.15 (0.87-1.52)</td>
<td>Age, smoking, alcohol, physical activity, social class, BMI, energy intake, diet score without respective components</td>
</tr>
<tr>
<td>Buil-Cosiales P et al, 2014, Spain</td>
<td>Prevencion con Dieta Mediterranea (PREDIMED) study</td>
<td>2003-2009 - 2012, 5.9 years follow-up</td>
<td>7216 men and women, age 55-75 years: 425 deaths</td>
<td>Validated FFQ, 137 food items</td>
<td>Whole grains, baseline</td>
<td>0 g/d</td>
<td>1.00</td>
<td>Age, sex, smoking status, diabetes, BMI, SBP, DBP, intervention group, recruitment center, statins, alcohol, education, physical activity, total energy, vegetables, fruits</td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study</td>
<td>1984-2010, 26 years follow-up</td>
<td>74341 women, age 38-63 years: 15106 deaths</td>
<td>Validated FFQ, 126 food items</td>
<td>Whole grains</td>
<td>4.2 g/d</td>
<td>1.00</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since</td>
</tr>
</tbody>
</table>
Wu H et al, 2015, USA
Health Professionals Follow-up Study
1986-2010, 24 years follow-up
43744 men, age 32-87 years: 11814 deaths
Validated FFQ, 133 food items
Whole grains
5.9 g/d
14.4
22.1
31.3
47.8
1.00
1.00 (0.94-1.05)
0.97 (0.91-1.02)
1.01 (0.95-1.07)
0.95 (0.89-1.00)
Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since quitting smoking, alcohol, physical activity, family history of diabetes, cancer and heart disease, multivitamin use, aspirin use, hypertension, high cholesterol, diabetes, total energy, healthy eating index (including fruits, vegetables, nuts and legumes, red or processed meat, sugar-sweetened beverages, alcohol, sodium, trans fat, long-chain n-3 FA, other PUFAs, but excluding whole grains)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
<th>Participants</th>
<th>Methods</th>
<th>Intake Units</th>
<th>HR (95% CI)</th>
<th>Additional Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boggs DA et al, 2015, USA</td>
<td>Black Women’s Health Study</td>
<td>37001 women, age 30-69 years: 1678 deaths</td>
<td>Validated FFQ, 68 food items</td>
<td>Whole grains</td>
<td>0.01 serv/d 0.11 0.22 0.62 1.44</td>
<td>Age, total energy intake, education, marital status, vigorous exercise, TV watching, smoking, alcohol, vegetables, fruits, nuts/legumes, low-fat dairy, red or processed meat, sugar-sweetened beverages, sodium</td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>367442 men and women, age 50-71 years: 46067 deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Whole grains</td>
<td>0.13 oz/1000 kcal/d 0.3 0.47 0.69 1.20</td>
<td>Age, sex, number of cigarettes per day, time of smoking cessation, race/ethnicity, alcohol, education, marital status, health status, BMI, physical activity, red meat, total fruit and vegetables, total energy, HRT (women)</td>
</tr>
<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>367442 men and women, age 50-71 years: 46067 deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Ready-to-eat cereals</td>
<td>0.00 g/d 0.67 3.48 9.33 22.48</td>
<td>Age, sex, smoking status, smoking dose, time since quitting smoking, race/ethnicity, education, marital status, self-rated health status, BMI, physical activity, menopausal hormone therapy, alcohol, red meat, fruits, vegetables, total energy</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Population</td>
<td>Time Period</td>
<td>Follow-up</td>
<td>Deaths</td>
<td>Study Design</td>
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<tr>
<td>Prinelli F et al, 2015, Italy</td>
<td>NA</td>
<td>974 men and women, age 40-74 years: 193 deaths</td>
<td>1991-1995 - 2012, 17.4 years follow-up</td>
<td>FFQ, 158 food items</td>
<td>Cereals &gt;median vs. ≤median</td>
<td>0.91 (0.66-1.26)</td>
</tr>
<tr>
<td>Roswall N et al, 2015, Sweden</td>
<td>Swedish Women’s Lifestyle and Health Cohort</td>
<td>44961 women, age 29-49 years: 1855 deaths</td>
<td>1991-1992 - 2012, 21.3 years follow-up</td>
<td>Validated FFQ, ~80 food items</td>
<td>Whole grain bread &lt;median ≥median</td>
<td>1.00 0.83 (0.76-0.92)</td>
</tr>
<tr>
<td>Johnsen NF et al, 2015, Norway, Sweden, Denmark</td>
<td>HELGA Cohort (Norwegian Women and Cancer Study, Northern Sweden Health and Disease Study, Danish Diet, Cancer and Health Study – part of the EPIC study)</td>
<td>120010 men and women, age 30-64 years: 4181/3658 deaths</td>
<td>1992-1998 – 2008-2009, 11.1 (Norway), 14.2 (Sweden), 11.9 years (Denmark) follow-up</td>
<td>Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)</td>
<td>Whole grain breakfast cereals, women 0 g/d 0.8 0.8 12 25 g/d 50 75 g/d 100 120 g/d</td>
<td>1.00 0.77 (0.67-0.89) 0.79 (0.71-0.88) 0.75 (0.69-0.82)</td>
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<td>3</td>
<td>0.72 (0.65-0.79)</td>
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<td></td>
<td>10</td>
<td>0.65 (0.58-0.72)</td>
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<tr>
<td>Total whole grain types</td>
<td>37</td>
<td>0.63 (0.53-0.74)</td>
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<td>20 g/d</td>
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<td>33</td>
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<td></td>
<td>49</td>
<td>0.74 (0.67-0.81)</td>
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<td>74</td>
<td>0.74 (0.67-0.81)</td>
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<tr>
<td>Whole grain breakfast cereals, men</td>
<td>0 g/d</td>
<td>1.00</td>
<td></td>
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<td></td>
<td>0.8</td>
<td>0.92 (0.82-1.04)</td>
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<td></td>
<td>7</td>
<td>0.82 (0.76-0.89)</td>
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<tr>
<td></td>
<td>50</td>
<td>0.74 (0.68-0.81)</td>
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<tr>
<td>Non-white bread</td>
<td>13 g/d</td>
<td>1.00</td>
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<tr>
<td></td>
<td>66</td>
<td>0.92 (0.83-1.03)</td>
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<tr>
<td></td>
<td>118</td>
<td>0.85 (0.75-0.95)</td>
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<tr>
<td></td>
<td>201</td>
<td>0.78 (0.69-0.88)</td>
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<tr>
<td></td>
<td>1 g/d</td>
<td>1.00</td>
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<tr>
<td>Crisp bread</td>
<td>2</td>
<td>0.97 (0.89-1.06)</td>
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<td>4</td>
<td>0.94 (0.86-1.02)</td>
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<td>34</td>
<td>1.03 (0.90-1.17)</td>
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<tr>
<td></td>
<td>64 g/d</td>
<td>1.00</td>
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<tr>
<td>Total whole grain products</td>
<td>107</td>
<td>0.87 (0.80-0.95)</td>
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<td>156</td>
<td>0.74 (0.68-0.81)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>222</td>
<td>0.75 (0.68-0.81)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oat</td>
<td>0.4</td>
<td>0.87 (0.80-0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.85 (0.77-0.94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.76 (0.69-0.85)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rye</td>
<td>7 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0.91 (0.83-1.00)</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>38</td>
<td>0.82 (0.74-0.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>0.86 (0.78-0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>0.1 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.87 (0.80-0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.76 (0.69-0.84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.71 (0.64-0.78)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total whole grain types</td>
<td>21 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>0.82 (0.75-0.90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>0.72 (0.66-0.78)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>80</td>
<td>0.75 (0.68-0.82)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Description</td>
<td>Follow-up Period</td>
<td>Participants</td>
<td>Outcomes</td>
<td>Dietary Assessments</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>--------------------------------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Shi Z et al, 2015, China</td>
<td>China</td>
<td>Chinese Longitudinal Health Longevity Survey</td>
<td>1998-1999 - 2011, 4.3 years follow-up</td>
<td>8959 men and women, age ≥80 years: 6626 deaths</td>
<td>FFQ, 10 items</td>
<td>Staple food (total grains: rice, corn, wheat, other)</td>
</tr>
<tr>
<td>Wang JB et al, 2016, China²</td>
<td>China</td>
<td>Linxian Nutrition Intervention Trial cohort</td>
<td>1984-1991 - 2010, 19-26 years follow-up</td>
<td>2445 men and women, age 40-69 years: 1501 deaths</td>
<td>FFQ, 64 food items</td>
<td>All grains</td>
</tr>
<tr>
<td>Bongard V et al, 2016, France</td>
<td>France</td>
<td>MONitoring of trends and determinants in CARdiovascular disease (MONICA) Project</td>
<td>1995-1997 - 2010, 14.8 years follow-up</td>
<td>960 men, age 45-64 years: 150 deaths</td>
<td>3-day food record</td>
<td>Cereals</td>
</tr>
</tbody>
</table>

1 The study reported 99% confidence intervals which have been recalculated to 95% confidence intervals.
2 The original paper reports per 10 g/d for bread, but after contact with authors it was confirmed that 100 g/d is correct.
3 The original paper reports in ounces/d, after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
Supplementary table 8. Whole grains and refined grains and respiratory disease mortality

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 569 respiratory disease deaths</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk</td>
<td>5.6 8.8 14.5 25.6</td>
<td>1.00 0.65 (0.51-0.83) 0.65 (0.50-0.84) 0.58 (0.44-0.76) 0.60 (0.46-0.80)</td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>1984-2010, 26 years follow-up 1986-2010, 24 years follow-up</td>
<td>74341 women, age 38-63 years and 43744 men, age 32-87 years: 2016 respiratory disease deaths</td>
<td>Validated FFQ, 126/133 food items</td>
<td>Whole grains</td>
<td>4.2/5.9 g/d (w/m)</td>
<td>9.7/14.4 14.7/22.1 21.1/31.1 33.0/47.8</td>
<td>1.00 0.96 (0.84-1.08) 1.00 (0.87-1.14) 0.88 (0.76-1.02) 0.89 (0.77-1.03)</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort Description</td>
<td>Participants</td>
<td>Follow-up</td>
<td>End Points</td>
<td>Validation Method</td>
<td>Food Items</td>
<td>Whole Grains</td>
<td>Ready-to-eat Cereals</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------</td>
<td>--------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------------------</td>
<td>------------</td>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study 1995-1996 – 2009, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 3796 respiratory disease deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Whole grains</td>
<td>0.13 oz/1000 kcal/d</td>
<td>0.30</td>
<td>0.47</td>
<td>0.69</td>
</tr>
<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study 1995-1996 – 2008, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 3796 respiratory disease deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Ready-to-eat cereals</td>
<td>0.00 g/d</td>
<td>0.67</td>
<td>3.48</td>
<td>9.33</td>
</tr>
</tbody>
</table>
Johnsen NF et al, 2015, Norway, Sweden, Denmark
HELGA Cohort (Norwegian Women and Cancer Study, Northern Sweden Health and Disease Study, Danish Diet, Cancer and Health Study – part of the EPIC study)
120010 men and women, age 30-64 years: 111/125 respiratory disease deaths
Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)
Whole grain breakfast cereals, women
<table>
<thead>
<tr>
<th>Whole grain breakfast cereals, women</th>
<th>0 g/d</th>
<th>0.8</th>
<th>12</th>
<th>50</th>
<th>80</th>
<th>113</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-white bread</td>
<td>0.6 g/d</td>
<td>2</td>
<td>6</td>
<td>31</td>
<td>100</td>
<td>131</td>
<td>201</td>
</tr>
<tr>
<td>Crisp bread</td>
<td>0.6 g/d</td>
<td>2</td>
<td>6</td>
<td>31</td>
<td>100</td>
<td>131</td>
<td>201</td>
</tr>
<tr>
<td>Total whole grain products</td>
<td>56 g/d</td>
<td>100</td>
<td>131</td>
<td>201</td>
<td>1.00</td>
<td>0.56 (0.35-0.89)</td>
<td>0.53 (0.33-0.86)</td>
</tr>
<tr>
<td>Oat</td>
<td>0 g/d</td>
<td>0.4</td>
<td>4</td>
<td>19</td>
<td>1.00</td>
<td>0.56 (0.36-0.88)</td>
<td>0.48 (0.27-0.85)</td>
</tr>
<tr>
<td>Rye</td>
<td>0 g/d</td>
<td>0.4</td>
<td>4</td>
<td>19</td>
<td>1.00</td>
<td>0.56 (0.36-0.88)</td>
<td>0.48 (0.27-0.85)</td>
</tr>
<tr>
<td>Wheat</td>
<td>0 g/d</td>
<td>3</td>
<td>10</td>
<td>37</td>
<td>1.00</td>
<td>0.63 (0.41-0.99)</td>
<td>0.57 (0.34-0.94)</td>
</tr>
<tr>
<td>Total whole grain types</td>
<td>20 g/d</td>
<td>33</td>
<td>49</td>
<td>74</td>
<td>1.00</td>
<td>0.65 (0.40-1.08)</td>
<td>0.64 (0.39-1.04)</td>
</tr>
<tr>
<td>Whole grain breakfast cereals, men</td>
<td>0 g/d</td>
<td>0.8</td>
<td>7</td>
<td>50</td>
<td>1.00</td>
<td>1.50 (0.79-2.82)</td>
<td>1.23 (0.76-1.98)</td>
</tr>
</tbody>
</table>
| Age, follow-up time, education, smoking status/years since quit/ cigarettes per day, alcohol, BMI, total energy
<table>
<thead>
<tr>
<th>Non-white bread</th>
<th>13 g/d</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crisp bread</td>
<td>1 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.77 (0.45-1.32)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.98 (0.59-1.62)</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>1.00 (0.50-2.01)</td>
</tr>
<tr>
<td>Total whole grain products</td>
<td>64 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>1.03 (0.61-1.76)</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>1.05 (0.63-1.77)</td>
</tr>
<tr>
<td></td>
<td>222</td>
<td>0.60 (0.33-1.07)</td>
</tr>
<tr>
<td>Oat</td>
<td>0 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.99 (0.59-1.68)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.87 (0.50-1.51)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.52 (0.28-0.97)</td>
</tr>
<tr>
<td>Rye</td>
<td>7 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>1.16 (0.65-2.10)</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>0.70 (0.32-1.57)</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>1.02 (0.53-1.97)</td>
</tr>
<tr>
<td>Wheat</td>
<td>0.1 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.46 (0.83-2.55)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.40 (0.76-2.56)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.06 (0.57-1.95)</td>
</tr>
<tr>
<td>Total whole grain types</td>
<td>21 g/d</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>0.96 (0.58-1.61)</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>0.65 (0.38-1.11)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.74 (0.42-1.30)</td>
</tr>
</tbody>
</table>

BMI; body mass index, FA; fatty acids, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, PUFA; polyunsaturated fatty acids

1 The original paper reports in ounces/d, but after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
### Supplementary table 9. Whole grains and refined grains and infectious disease mortality

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 59 infectious disease deaths</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk</td>
<td>1.00</td>
<td>Age, energy intake, BMI, waist-to-hip ratio, smoking, education, hypertension, physical activity, HRT, multivitamin supplement use, intake of alcohol, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains</td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>1984-2010, 26 years follow-up 1986-2010, 24 years follow-up</td>
<td>74341 women, age 38-63 years and 43744 men, age 32-87 years: 405 infectious disease deaths</td>
<td>Validated FFQ, 126/133 food items</td>
<td>Whole grains</td>
<td>4.2/5.9 g/d (w/m)</td>
<td>1.00</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since quitting smoking, alcohol, physical activity, family history of diabetes, cancer and heart disease, multivitamin use, aspirin use, hypertension, high cholesterol, diabetes, total energy, healthy eating index (including fruits, vegetables, nuts and legumes, red or processed meat, sugar-sweetened beverages, alcohol, sodium, trans fat, long-chain n-3 FA, other PUFAs, but excluding whole grains), women: postmenopausal status, HRT</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Year, Country</td>
<td>Duration</td>
<td>Population</td>
<td>Follow-up</td>
<td>Validation</td>
<td>Food Item</td>
<td>Whole Grains</td>
</tr>
<tr>
<td>-------</td>
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<td>--------------</td>
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<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2009, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 922 infectious disease deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>0.13 oz/1000 kcal/d</td>
<td>0.30 0.47 0.69 1.20 1.00</td>
<td>0.84 (0.70-1.02) 0.78 (0.64-0.96) 0.79 (0.65-0.97) 0.77 (0.62-0.95)</td>
<td></td>
</tr>
<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2008, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 922 infectious disease deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>0.00 g/d 0.67 3.48 9.33 22.48</td>
<td>1.00</td>
<td>0.97 (0.79-1.20) 0.85 (0.68-1.06) 0.84 (0.68-1.05) 0.97 (0.78-1.21)</td>
<td></td>
</tr>
</tbody>
</table>

BMI; body mass index, FA; fatty acids, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, PUFA; polyunsaturated fatty acids

1 The original paper reports in ounces/d, but after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 60 deaths due to endocrine, nutritional and metabolic disorders (mainly diabetes)</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk 5.6 8.8 14.5 25.6</td>
<td>1.00 0.44 (0.19-1.02) 0.65 (0.31-1.37) 0.46 (0.20-1.08) 0.55 (0.24-1.28)</td>
<td>Age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, HRT, multivitamin supplement use, intake of alcohol, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains</td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>1984-2010, 26 years follow-up 1986-2010, 24 years follow-up</td>
<td>74341 women, age 38-63 years and 43744 men, age 32-87 years: 283 diabetes deaths</td>
<td>Validated FFQ</td>
<td>Whole grains</td>
<td>4.2/5.9 g/d (w/m) 9.7/14.4 14.7/22.1 21.1/31.1 33.0/47.8</td>
<td>1.00 0.59 (0.42-0.83) 0.52 (0.35-0.77) 0.52 (0.34-0.79) 0.50 (0.34-0.75)</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since quitting smoking, alcohol, physical activity, family history of diabetes, cancer and heart disease, multivitamin use, aspirin use, hypertension, high cholesterol, diabetes, total energy, healthy eating index (including fruits, vegetables, nuts and legumes, red or processed meat, sugar-sweetened beverages, alcohol, sodium, trans fat, long-chain n-3 FA, other PUFA, but excluding whole grains), women: postmenopausal status, HRT</td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2009, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 371 diabetes deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Whole grains</td>
<td>0.13 oz/1000 kcal/d</td>
<td>0.30</td>
<td>0.47</td>
</tr>
<tr>
<td>Xu M et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2008, 14 years follow-up</td>
<td>367442 men and women, age 50-71 years: 371 diabetes deaths</td>
<td>Validated FFQ, 124 food items</td>
<td>Ready-to-eat cereals</td>
<td>0.00 g/d</td>
<td>0.67</td>
<td>3.48</td>
</tr>
</tbody>
</table>
Table 1. Whole grain breakfast cereals and diabetes mortality.

<table>
<thead>
<tr>
<th>HELGA Cohort (Norwegian Women and Cancer Study, Northern Sweden Health and Disease Study, Danish Diet, Cancer and Health Study – part of the EPIC study)</th>
<th>1992-1998 – 2008-2009, 11.1 years (Norway), 14.2 years (Sweden), 11.9 years (Denmark) follow-up</th>
<th>120010 men and women, age 30-64 years: 70/24 diabetes deaths</th>
<th>Validated FFQ, 88 food items (Norway), 98 food items (Sweden), 173 food items (Denmark)</th>
<th>Whole grain breakfast cereals, women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 g/d</td>
<td>0.8</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>Non-white bread</td>
<td>25 g/d</td>
<td>0.8 (0.23-2.77)</td>
<td>0.45 (0.13-1.59)</td>
<td>0.28 (0.07-1.04)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>113</td>
<td>180</td>
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</tr>
<tr>
<td>Crisp bread</td>
<td>0.6 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.21 (0.41-3.54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.25 (0.36-4.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>1.09 (0.27-4.43)</td>
<td></td>
<td></td>
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<tr>
<td>Total whole grain products</td>
<td>56 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.41 (0.13-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>131</td>
<td>0.41 (0.13-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>201</td>
<td>0.90 (0.31-2.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oat</td>
<td>0 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.88 (0.34-2.27)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4</td>
<td>0.36 (0.09-1.51)</td>
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</tr>
<tr>
<td></td>
<td>19</td>
<td>0.25 (0.05-1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rye</td>
<td>8 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.93 (0.28-3.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0.46 (0.14-1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>0.70 (0.22-2.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>0.4 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.69 (0.26-1.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.61 (0.20-1.88)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>37</td>
<td>3.17 (0.27-37.59)</td>
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<tr>
<td></td>
<td>20 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>0.77 (0.25-2.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>0.44 (0.14-1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>0.64 (0.20-2.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total whole grain types</td>
<td>20 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>0.77 (0.25-2.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>0.44 (0.14-1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>0.64 (0.20-2.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole grain breakfast cereals, men</td>
<td>0 g/d</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.59 (0.24-1.50)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.31 (0.14-0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.45 (0.23-0.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age, follow-up time, education, smoking status/years since quit/ cigarettes per day, alcohol, BMI, total energy

Note: The table represents the relationship between whole grain breakfast cereals and diabetes mortality in the HELGA Cohort study. The data includes information on the consumption of whole grain breakfast cereals and the risk of diabetes mortality, along with other variables such as age, follow-up time, education, smoking status, alcohol intake, BMI, and total energy intake. The table includes various types of whole grain products, with the consumption levels and corresponding risk ratios presented in a tabular format.
<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white bread</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>66</td>
<td>1.89(0.66-5.41)</td>
<td>1.59(0.52-4.82)</td>
<td>2.30(0.79-6.72)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Crisp bread</td>
<td>2 g/d</td>
<td>1.33(0.68-2.61)</td>
<td>1.07(0.53-2.15)</td>
<td>2.35(1.10-5.03)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Total whole grain products</td>
<td>64 g/d</td>
<td>1.76(0.83-3.74)</td>
<td>1.09(0.49-2.42)</td>
<td>1.67(0.79-3.51)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Oat</td>
<td>0 g/d</td>
<td>1.00</td>
<td>0.60(0.32-1.12)</td>
<td>0.33(0.16-0.72)</td>
<td>0.40(0.20-0.81)</td>
<td></td>
</tr>
<tr>
<td>Rye</td>
<td>7 g/d</td>
<td>1.14(0.53-2.48)</td>
<td>0.40(0.12-1.34)</td>
<td>1.80(0.80-4.05)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>0.1 g/d</td>
<td>0.75(0.37-1.56)</td>
<td>1.07(0.51-2.22)</td>
<td>1.18(0.60-2.34)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Total whole grain types</td>
<td>21 g/d</td>
<td>0.92(0.45-1.87)</td>
<td>0.95(0.49-1.86)</td>
<td>1.18(0.59-2.38)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

BMI; body mass index, FA; fatty acids, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, PUFA; polyunsaturated fatty acids

1 The original paper reports in ounces/d, but after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
### Supplementary table 11. Whole grains and refined grains and nervous system disease mortality

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27,312 women, age 55-69 years: 241 nervous system deaths</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains</td>
<td>1.8 serv/wk</td>
<td>1.00</td>
<td>0.84 (0.53-1.32)</td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>1984-2010, 26 years follow-up; 1986-2010, 24 years follow-up</td>
<td>74,341 women, age 38-63 years and 43,744 men, age 32-87 years: 2044 neurodegenerative disease deaths</td>
<td>Validated FFQ</td>
<td>Whole grains</td>
<td>4.2/5.9 g/d (w/m)</td>
<td>1.00</td>
<td>1.24 (1.08-1.42)</td>
</tr>
</tbody>
</table>
Supplementary table 12. Whole grains and refined grains and non-cardiovascular, non-cancer causes of death

<table>
<thead>
<tr>
<th>Author, publication year, country</th>
<th>Study name</th>
<th>Study period</th>
<th>Number of participants, gender, age, number of cases/deaths</th>
<th>Dietary assessment</th>
<th>Exposure and subgroup</th>
<th>Whole grain consumption frequency or amount</th>
<th>Relative risks (95% confidence intervals)</th>
<th>Adjustment for confounding factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs DR, 2007, USA</td>
<td>Iowa Women’s Health Study</td>
<td>1986 – 2003, 17 years follow-up</td>
<td>27312 women, age 55-69 years: 1072 non-CVD, non-cancer, inflammatory disease deaths 482 non-CVD, non-cancer, non-inflammatory disease deaths</td>
<td>Validated FFQ, 127 food items</td>
<td>Whole grains, non-CVD, non-cancer, inflammatory diseases</td>
<td>1.8 serv/wk</td>
<td>1.00 0.89 (0.57-0.83) 0.79 (0.66-0.95) 0.64 (0.53-0.79) 0.66 (0.54-0.81) 1.00</td>
<td>Age, energy intake, BMI, waist-to-hip ratio, smoking, education, physical activity, HRT, multivitamin supplement use, intake of alcohol, coffee, red meat, fish and seafood, total fruit and vegetables, mutual adjustment between whole grains and refined grains</td>
</tr>
<tr>
<td>Buil-Cosiales P et al, 2014, Spain</td>
<td>Prevencion con Dieta Mediterranea (PREDIMED) study</td>
<td>2003 - 2009 – 2012, 5.9 years follow-up</td>
<td>7216 men and women, age 55-75 years: 153 non-CVD, non-cancer deaths</td>
<td>Validated FFQ, 137 food items</td>
<td>Whole grains</td>
<td>0 g/d</td>
<td>1.00 0.89 (0.49-1.63) 1.03 (0.52-2.02) 1.03 (0.51-2.10) 0.76 (0.38-1.53)</td>
<td>Age, sex, smoking status, diabetes, BMI, SBP, DBP, recruitment center, statins, alcohol, education, physical activity, total energy, vegetables, fruits</td>
</tr>
<tr>
<td>Study</td>
<td>Time Period</td>
<td>Participants</td>
<td>FFQ Validation</td>
<td>Whole Grains</td>
<td>RR (95% CI)</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------------------------------------------------</td>
<td>----------------</td>
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<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu H et al, 2015, USA</td>
<td>Nurses’ Health Study &amp; Health Professionals Follow-up Study</td>
<td>1984-2010, 26 years follow-up</td>
<td>Validated FFQ</td>
<td>Whole grains</td>
<td>4.2/5.9 g/d (w/m) 9.7/14.4 14.7/22.1 21.1/31.1 33.0/47.8</td>
<td>Age, ethnicity, BMI, smoking status, cigarettes per day, pack-years smoked, years since quitting smoking, alcohol, physical activity, family history of diabetes, cancer and heart disease, multivitamin use, aspirin use, hypertension, high cholesterol, diabetes, total energy, healthy eating index (including fruits, vegetables, nuts and legumes, red or processed meat, sugar-sweetened beverages, alcohol, sodium, trans fat, long-chain n-3 FA, other PUFAs, but excluding whole grains), women: postmenopausal status, HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang T et al, 2015, USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>1995-1996 – 2009, 14 years follow-up</td>
<td>Validated FFQ, 124 food items</td>
<td>Whole grains</td>
<td>0.13 oz/1000 kcal/d 0.30 0.47 0.69 1.20</td>
<td>Age, sex, number of cigarettes per day, time of smoking cessation, race/ ethnicity, alcohol, education, marital status, health status, BMI, physical activity, red meat, total fruit and vegetables, total energy, HRT (women)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI; body mass index, DBP; diastolic blood pressure, FA; fatty acids, FFQ; food frequency questionnaire, HRT; hormone replacement therapy, PUFA; polyunsaturated fatty acids, SBP; systolic blood pressure

1 For the Nurses’ Health Study, Health Professionals Follow-up Study, and NIH-AARP Diet and Health Study data were pooled for all non-CVD, non-cancer causes of death (NHS&HPFS: deaths from respiratory disease, neurodegenerative disease, infectious disease, kidney disease, diabetes, and other causes, and NIH-AARP Diet and Health Study: deaths from diabetes, respiratory disease, infections and other/unknown causes) using a fixed effects model.

2 The original paper reports in ounces/d, but after contact with the authors it was confirmed that ounces/1000 kcal/d is correct.
Supplementary Table 13. Relative risks from nonlinear dose-response analysis of whole grains and coronary heart disease, stroke, cardiovascular disease, total cancer, and all-cause mortality

<table>
<thead>
<tr>
<th>Coronary heart disease g/d</th>
<th>RR (95% CI)</th>
<th>Stroke g/d</th>
<th>RR (95% CI)</th>
<th>Cardiovascular disease g/d</th>
<th>RR (95% CI)</th>
<th>Total cancer g/d</th>
<th>RR (95% CI)</th>
<th>All-cause mortality g/d</th>
<th>RR (95% CI)</th>
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<tbody>
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<td>0</td>
<td>1.00</td>
<td>0</td>
<td>1.00</td>
<td>0</td>
<td>1.00</td>
<td>0</td>
<td>1.00</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>15</td>
<td>0.93 (0.92-0.95)</td>
<td>15</td>
<td>0.94 (0.92-0.95)</td>
<td>15</td>
<td>0.93 (0.91-0.94)</td>
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<td>0.97 (0.96-0.98)</td>
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<td>0.95 (0.94-0.96)</td>
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<td>30</td>
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<td>30</td>
<td>0.88 (0.85-0.91)</td>
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<td>0.87 (0.85-0.89)</td>
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<td>0.95 (0.93-0.97)</td>
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<tr>
<td>45</td>
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<td>45</td>
<td>0.83 (0.78-0.87)</td>
<td>45</td>
<td>0.83 (0.81-0.86)</td>
<td>45</td>
<td>0.93 (0.90-0.95)</td>
<td>45</td>
<td>0.87 (0.85-0.89)</td>
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<tr>
<td>60</td>
<td>0.78 (0.75-0.82)</td>
<td>60</td>
<td>0.78 (0.73-0.84)</td>
<td>60</td>
<td>0.81 (0.79-0.84)</td>
<td>60</td>
<td>0.91 (0.88-0.94)</td>
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<td>0.85 (0.82-0.87)</td>
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<td>75</td>
<td>0.75 (0.71-0.79)</td>
<td>75</td>
<td>0.75 (0.69-0.81)</td>
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<td>0.80 (0.77-0.82)</td>
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<td>0.89 (0.86-0.92)</td>
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<td>0.83 (0.80-0.85)</td>
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<td>90</td>
<td>0.72 (0.69-0.76)</td>
<td>90</td>
<td>0.73 (0.66-0.79)</td>
<td>90</td>
<td>0.79 (0.76-0.82)</td>
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<td>0.87 (0.84-0.91)</td>
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<td>0.81 (0.79-0.83)</td>
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<tr>
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<td>105</td>
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<tr>
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<td>0.70 (0.63-0.77)</td>
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<td>0.85 (0.81-0.89)</td>
<td>120</td>
<td>0.78 (0.76-0.81)</td>
</tr>
<tr>
<td>135</td>
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<td>0.69 (0.62-0.77)</td>
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<td>0.83 (0.80-0.87)</td>
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<td>0.69 (0.62-0.77)</td>
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<td>0.76 (0.71-0.82)</td>
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<td>0.82 (0.78-0.86)</td>
<td>150</td>
<td>0.76 (0.73-0.79)</td>
</tr>
<tr>
<td>165</td>
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<td>165</td>
<td>0.69 (0.62-0.77)</td>
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<tr>
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<td>0.75 (0.68-0.82)</td>
<td>180</td>
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<td>180</td>
<td>0.73 (0.70-0.77)</td>
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<td>0.74 (0.67-0.82)</td>
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<td>0.78 (0.73-0.84)</td>
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<td>0.72 (0.68-0.76)</td>
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<td>0.70 (0.62-0.78)</td>
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<td>0.73 (0.66-0.82)</td>
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<td>0.77 (0.72-0.83)</td>
<td>210</td>
<td>0.71 (0.67-0.75)</td>
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<td>0.70 (0.63-0.78)</td>
<td>225</td>
<td>0.76 (0.71-0.82)</td>
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<td>0.70 (0.65-0.75)</td>
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<td>0.70 (0.65-0.75)</td>
</tr>
</tbody>
</table>

P_{nonlinearity} <0.0001  <0.0001  <0.0001  <0.0001  <0.0001
### Supplementary Table 14. Relative risks from nonlinear dose-response analysis of whole grains and

<table>
<thead>
<tr>
<th>Respiratory disease mortality</th>
<th>Diabetes mortality</th>
<th>Infectious disease mortality</th>
<th>Nervous system disease mortality</th>
<th>All noncardiovascular, noncancer causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/d RR (95% CI)</td>
<td>g/d RR (95% CI)</td>
<td>g/d RR (95% CI)</td>
<td>g/d RR (95% CI)</td>
<td>g/d RR (95% CI)</td>
</tr>
<tr>
<td>4.8 1.00</td>
<td>4.8 1.00</td>
<td>4.8 1.00</td>
<td>4.8 1.00</td>
<td>0 1.00</td>
</tr>
<tr>
<td>15 0.93 (0.91-0.96)</td>
<td>15 0.80 (0.77-0.83)</td>
<td>15 0.89 (0.85-0.93)</td>
<td>15 1.15 (1.11-1.18)</td>
<td>15 0.96 (0.95-0.97)</td>
</tr>
<tr>
<td>30 0.88 (0.84-0.92)</td>
<td>30 0.65 (0.61-0.70)</td>
<td>30 0.81 (0.75-0.88)</td>
<td>30 1.26 (1.19-1.33)</td>
<td>30 0.92 (0.90-0.94)</td>
</tr>
<tr>
<td>45 0.83 (0.78-0.88)</td>
<td>45 0.55 (0.50-0.60)</td>
<td>45 0.78 (0.72-0.85)</td>
<td>45 1.28 (1.20-1.37)</td>
<td>45 0.88 (0.86-0.91)</td>
</tr>
<tr>
<td>60 0.79 (0.73-0.85)</td>
<td>60 0.48 (0.43-0.54)</td>
<td>60 0.77 (0.71-0.84)</td>
<td>60 1.23 (1.15-1.33)</td>
<td>60 0.85 (0.83-0.88)</td>
</tr>
<tr>
<td>75 0.76 (0.69-0.82)</td>
<td>75 0.44 (0.39-0.50)</td>
<td>75 0.76 (0.70-0.84)</td>
<td>75 1.14 (1.05-1.25)</td>
<td>75 0.82 (0.79-0.85)</td>
</tr>
<tr>
<td>90 0.73 (0.67-0.80)</td>
<td>90 0.42 (0.37-0.48)</td>
<td>90 0.76 (0.68-0.85)</td>
<td>90 1.05 (0.93-1.17)</td>
<td>90 0.79 (0.77-0.82)</td>
</tr>
<tr>
<td>105 0.71 (0.65-0.78)</td>
<td>105 0.41 (0.35-0.48)</td>
<td>105 0.76 (0.66-0.87)</td>
<td>105 0.95 (0.83-1.10)</td>
<td>105 0.77 (0.74-0.80)</td>
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<tr>
<td>120 0.70 (0.63-0.77)</td>
<td>120 0.41 (0.35-0.48)</td>
<td>120</td>
<td>120</td>
<td>120 0.75 (0.72-0.78)</td>
</tr>
<tr>
<td>135 0.68 (0.61-0.76)</td>
<td>135 0.41 (0.35-0.49)</td>
<td>135</td>
<td>135</td>
<td>135 0.72 (0.69-0.75)</td>
</tr>
<tr>
<td>150 0.67 (0.60-0.75)</td>
<td>150 0.42 (0.35-0.50)</td>
<td>150</td>
<td>150</td>
<td>150 0.70 (0.67-0.73)</td>
</tr>
<tr>
<td>165 0.66 (0.59-0.74)</td>
<td>165 0.43 (0.36-0.52)</td>
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<td>165</td>
<td>165 0.68 (0.65-0.71)</td>
</tr>
<tr>
<td>180 0.65 (0.57-0.73)</td>
<td>180 0.44 (0.36-0.54)</td>
<td>180</td>
<td>180</td>
<td>180 0.66 (0.62-0.69)</td>
</tr>
<tr>
<td>195 0.63 (0.56-0.72)</td>
<td>195 0.45 (0.36-0.56)</td>
<td>195</td>
<td>195</td>
<td>195 0.64 (0.60-0.67)</td>
</tr>
<tr>
<td>210 0.62 (0.54-0.72)</td>
<td>210 0.46 (0.37-0.58)</td>
<td>210</td>
<td>210</td>
<td>210 0.62 (0.58-0.66)</td>
</tr>
<tr>
<td>225 0.62 (0.53-0.71)</td>
<td>225 0.47 (0.37-0.59)</td>
<td>225</td>
<td>225</td>
<td>225 0.60 (0.57-0.64)</td>
</tr>
<tr>
<td>240 0.62 (0.54-0.72)</td>
<td>240 0.47 (0.37-0.59)</td>
<td>240</td>
<td>240</td>
<td>240 0.60 (0.57-0.64)</td>
</tr>
</tbody>
</table>

\[ P_{\text{nonlinearity}} = 0.001 \quad \text{<0.0001} \quad 0.003 \quad \text{<0.0001} \quad 0.06 \]
Supplementary table 15: Subgroup analyses of whole grains and coronary heart disease, stroke, and cardiovascular disease, per 3 servings per day

<table>
<thead>
<tr>
<th></th>
<th>Coronary heart disease</th>
<th>Stroke</th>
<th>Cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR (95% CI)</td>
<td>I²</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 yrs follow-up</td>
<td>1</td>
<td>0.90 (0.78-1.04)</td>
<td>0.24</td>
</tr>
<tr>
<td>≥10 yrs follow-up</td>
<td>1</td>
<td>0.80 (0.74-0.86)</td>
<td>0</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>5</td>
<td>0.84 (0.77-0.92)</td>
<td>33.8</td>
</tr>
<tr>
<td>Mortality</td>
<td>3</td>
<td>0.81 (0.74-0.89)</td>
<td>9.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>0.92 (0.87-0.97)</td>
<td>0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5</td>
<td>0.78 (0.72-0.86)</td>
<td>12.3</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
<td>0.80 (0.60-1.08)</td>
<td>66.1</td>
</tr>
<tr>
<td>Women</td>
<td>4</td>
<td>0.76 (0.66-0.88)</td>
<td>51.8</td>
</tr>
<tr>
<td>Men and women</td>
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<td>0.78 (0.62-0.98)</td>
<td>0</td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>0.86 (0.79-0.93)</td>
<td>0</td>
</tr>
<tr>
<td>America</td>
<td>4</td>
<td>0.72 (0.63-0.81)</td>
<td>0</td>
</tr>
<tr>
<td>Asia</td>
<td>1</td>
<td>0.83 (0.57-1.23)</td>
<td>0</td>
</tr>
<tr>
<td>Australia</td>
<td>6</td>
<td>0.80 (0.74-0.87)</td>
<td>24.0</td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases &lt;500</td>
<td>1</td>
<td>0.83 (0.57-1.23)</td>
<td>0</td>
</tr>
<tr>
<td>Cases 500-1000</td>
<td>2</td>
<td>0.73 (0.61-0.89)</td>
<td>0</td>
</tr>
<tr>
<td>Cases ≥1000</td>
<td>4</td>
<td>0.81 (0.73-0.90)</td>
<td>42.7</td>
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<tr>
<td>Validated dietary assessment</td>
<td>6</td>
<td>0.80 (0.74-0.87)</td>
<td>24.0</td>
</tr>
<tr>
<td>Study quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 stars</td>
<td>0</td>
<td>0.86</td>
<td>0</td>
</tr>
<tr>
<td>4-6</td>
<td>1</td>
<td>0.83 (0.57-1.23)</td>
<td>0</td>
</tr>
<tr>
<td>7-9</td>
<td>6</td>
<td>0.80 (0.74-0.87)</td>
<td>24.0</td>
</tr>
<tr>
<td>Adjustment for confounding factors</td>
<td>Yes</td>
<td>8.9 (0.75-0.87)</td>
<td>0.36</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----</td>
<td>-----------------</td>
<td>------</td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td>0.83 (0.76-0.90)</td>
<td>22.0</td>
</tr>
<tr>
<td>No</td>
<td>0.73 (0.60-0.87)</td>
<td>0.66</td>
<td>0.68</td>
</tr>
<tr>
<td>Education</td>
<td>Yes</td>
<td>0.78 (0.65-0.95)</td>
<td>50.3</td>
</tr>
<tr>
<td>No</td>
<td>0.81 (0.75-0.88)</td>
<td>0.47</td>
<td>0.75</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>Yes</td>
<td>0.81 (0.75-0.87)</td>
<td>8.9</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
<td>0.89 (0.71-1.11)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Yes</td>
<td>0.81 (0.75-0.87)</td>
<td>8.9</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>0.81 (0.75-0.87)</td>
<td>8.9</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1</td>
<td>1.08 (0.96-1.22)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Yes</td>
<td>0.77 (0.69-0.87)</td>
<td>28.0</td>
</tr>
<tr>
<td>No</td>
<td>0.84 (0.77-0.93)</td>
<td>0.93</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>0.82 (0.71-0.95)</td>
<td>24.2</td>
</tr>
<tr>
<td>No</td>
<td>0.79 (0.71-0.88)</td>
<td>20.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypercholesterolemia, serum</td>
<td>Yes</td>
<td>0.83 (0.67-1.01)</td>
<td>51.3</td>
</tr>
<tr>
<td>cholesterol</td>
<td>No</td>
<td>0.80 (0.74-0.87)</td>
<td>0.41</td>
</tr>
<tr>
<td>Coffee, caffeine</td>
<td>Yes</td>
<td>0.72 (0.60-0.87)</td>
<td>0.46</td>
</tr>
<tr>
<td>No</td>
<td>0.83 (0.77-0.89)</td>
<td>0.46</td>
<td>0.79</td>
</tr>
<tr>
<td>Sugar-sweetened beverages</td>
<td>Yes</td>
<td>0</td>
<td>NC</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>0.81 (0.75-0.87)</td>
<td>8.9</td>
</tr>
<tr>
<td>Meat or processed meat</td>
<td>Yes</td>
<td>0.72 (0.60-0.87)</td>
<td>9.0</td>
</tr>
<tr>
<td>No</td>
<td>0.83 (0.77-0.89)</td>
<td>0.46</td>
<td>0.69</td>
</tr>
<tr>
<td>Fish</td>
<td>Yes</td>
<td>0.71 (0.60-0.83)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>0.84 (0.78-0.90)</td>
<td>0.62</td>
<td>0.69</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>Yes</td>
<td>0.71 (0.60-0.83)</td>
<td>0.62</td>
</tr>
<tr>
<td>No</td>
<td>0.84 (0.78-0.90)</td>
<td>0.62</td>
<td>0.85</td>
</tr>
<tr>
<td>Dairy</td>
<td>Yes</td>
<td>0</td>
<td>NC</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>0.81 (0.75-0.87)</td>
<td>8.9</td>
</tr>
<tr>
<td>Energy intake</td>
<td>Yes</td>
<td>0.80 (0.74-0.87)</td>
<td>24.0</td>
</tr>
<tr>
<td>No</td>
<td>0.1</td>
<td>0.83 (0.57-1.23)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* denotes the number of studies.

1 P for heterogeneity within each subgroup,

2 P for heterogeneity between subgroups with meta-regression analysis,

3 P for heterogeneity between men and women (studies with genders mixed were excluded),

NC = not calculable
Supplementary table 16: Subgroup analyses of whole grains and total cancer and all-cause mortality, per 3 servings per day

<table>
<thead>
<tr>
<th></th>
<th>Total cancer</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>I²</td>
</tr>
<tr>
<td>All studies</td>
<td>0.85 (0.80-0.91)</td>
<td>37.0</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 yrs follow-up</td>
<td>0.77 (0.43-1.38)</td>
<td>0.74</td>
</tr>
<tr>
<td>≥10 yrs follow-up</td>
<td>0.86 (0.80-0.92)</td>
<td>49.0</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.87 (0.81-0.93)</td>
<td>51.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.82 (0.75-0.89)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.83 (0.77-0.89)</td>
<td>0.36</td>
</tr>
<tr>
<td>Women</td>
<td>0.92 (0.86-0.98)</td>
<td>0.92</td>
</tr>
<tr>
<td>Men and women</td>
<td>0.79 (0.74-0.84)</td>
<td>0.94</td>
</tr>
<tr>
<td>Geographic location</td>
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<td></td>
</tr>
<tr>
<td>Europe</td>
<td>0.86 (0.81-0.91)</td>
<td>0.72</td>
</tr>
<tr>
<td>America</td>
<td>0.87 (0.78-0.97)</td>
<td>58.5</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases &lt;500</td>
<td>0.77 (0.43-1.38)</td>
<td>0.74</td>
</tr>
<tr>
<td>Cases 500-1000</td>
<td></td>
<td>0.77 (0.61-0.96)</td>
</tr>
<tr>
<td>Cases ≥1000</td>
<td>0.86 (0.80-0.92)</td>
<td>49.0</td>
</tr>
<tr>
<td>Validated dietary assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.85 (0.80-0.91)</td>
<td>37.0</td>
</tr>
<tr>
<td>No</td>
<td>0.92 (0.78-1.10)</td>
<td>0.94 (0.80-1.16)</td>
</tr>
<tr>
<td>Study quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 stars</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>0.85 (0.80-0.91)</td>
<td>37.0</td>
</tr>
<tr>
<td>Adjustment for confounding factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.85 (0.80-0.91)</td>
<td>37.0</td>
</tr>
</tbody>
</table>
| No                     | 0.83 (0.77-0.90) | 82.9               | 0.0001 |}

https://mc.manuscriptcentral.com/bmj
<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>Yes, 6, 0.85 (0.80-0.91), 37.0, 0.16</td>
<td>No, 1, 0.30 (0.15-0.60)</td>
<td>82.2, &lt;0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes, 6, 0.85 (0.80-0.91), 37.0, 0.16</td>
<td>No, 0</td>
<td>82.9, &lt;0.0001</td>
<td>NC</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Yes, 6, 0.85 (0.80-0.91), 37.0, 0.16</td>
<td>No, 0</td>
<td>71.0, &lt;0.0001</td>
<td>0.07</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Yes, 5, 0.86 (0.78-0.95), 45.2, 0.12</td>
<td>No, 1, 0.86 (0.81-0.91)</td>
<td>85.5, &lt;0.0001</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes, 2, 0.93 (0.80-1.08), 0, 0.66</td>
<td>No, 4, 0.84 (0.78-0.90), 51.1, 0.11</td>
<td>85.6, &lt;0.0001</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Yes, 2, 0.93 (0.80-1.08), 0, 0.66</td>
<td>No, 4, 0.84 (0.78-0.90), 51.1, 0.11</td>
<td>90.6, 0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>Coffee</td>
<td>Yes, 1, 0.92 (0.81-1.04), 0, 0.36</td>
<td>No, 5, 0.84 (0.79-0.89), 30.2, 0.22</td>
<td>84.6, &lt;0.0001</td>
<td>0.99</td>
</tr>
<tr>
<td>Sugar-sweetened beverages</td>
<td>Yes, 2, 0.93 (0.80-1.08), 0, 0.66</td>
<td>No, 4, 0.84 (0.78-0.90), 51.1, 0.11</td>
<td>89.0, &lt;0.0001</td>
<td>0.25</td>
</tr>
<tr>
<td>Red or processed meat</td>
<td>Yes, 4, 0.87 (0.78-0.97), 58.5, 0.07</td>
<td>No, 2, 0.86 (0.81-0.91), 0, 0.72</td>
<td>81.7, &lt;0.0001</td>
<td>0.17</td>
</tr>
<tr>
<td>Fish</td>
<td>Yes, 1, 0.92 (0.81-1.04), 0, 0.36</td>
<td>No, 5, 0.84 (0.79-0.89), 30.2, 0.22</td>
<td>84.6, &lt;0.0001</td>
<td>0.99</td>
</tr>
<tr>
<td>Fruit and vegetables</td>
<td>Yes, 5, 0.86 (0.78-0.95), 45.2, 0.12</td>
<td>No, 1, 0.86 (0.81-0.91)</td>
<td>82.7, &lt;0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td>Dairy</td>
<td>Yes, 0</td>
<td>No, 6, 0.85 (0.80-0.91), 37.0, 0.16</td>
<td>82.2, &lt;0.0001</td>
<td>0.51</td>
</tr>
</tbody>
</table>

n denotes the number of studies.
1 P for heterogeneity within each subgroup,
2 P for heterogeneity between subgroups with meta-regression analysis,
3 P for heterogeneity between men and women (studies with genders mixed were excluded).
| NC = not calculable

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Supplementary table 17: Study quality of studies included in the analysis of whole grains and coronary heart disease

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Representativeness</th>
<th>Selection of non-exposed cohort</th>
<th>Exposure-ascertainment(^1)</th>
<th>Demonstration of outcome not present at start</th>
<th>Adjustment for age</th>
<th>Adjustment for any other factor</th>
<th>Assessment of outcome</th>
<th>Long enough follow-up</th>
<th>Adequacy of follow-up(^2)</th>
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\(^1\) 1 point for validated self-reported questionnaires or interview

\(^2\) 1 point for loss-to-follow-up less than 10%
### Supplementary table 18: Study quality of studies included in the analysis of whole grains and stroke

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Represen-tativeness</th>
<th>Selection of non-exposed cohort</th>
<th>Exposure-ascertainment&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Demonstration of outcome not present at start</th>
<th>Adjustment for age</th>
<th>Adjustment for any other factor</th>
<th>Assessment of outcome</th>
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<th>Adequacy of follow-up&lt;sup&gt;2&lt;/sup&gt;</th>
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<sup>1</sup>1 point for validated self-reported questionnaires or interview

<sup>2</sup>1 point for loss-to-follow-up less than 10%
Supplementary table 19: Study quality of studies included in the analysis of whole grains and cardiovascular disease

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Representativeness</th>
<th>Selection of non-exposed cohort</th>
<th>Exposure-ascertainment</th>
<th>Demonstration of outcome not present at start</th>
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<th>Adjustment for any other factor</th>
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<th>Long enough follow-up</th>
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1 1 point for validated self-reported questionnaires or interview
2 1 point for loss-to-follow-up less than 10%
## Supplementary table 20: Study quality of studies included in the analysis of whole grains and total cancer

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<tr>
<th>Author, publication year</th>
<th>Representativeness</th>
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<th>Adjustment for age</th>
<th>Adjustment for any other factor</th>
<th>Assessment of outcome</th>
<th>Long enough follow-up</th>
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\(^1\) 1 point for validated self-reported questionnaires or interview

\(^2\) 1 point for loss-to-follow-up less than 10%
### Supplementary table 21: Study quality of studies included in the analysis of whole grains and all-cause mortality

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<th>Author, publication year</th>
<th>Representativeness</th>
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<th>Demonstration of outcome not present at start&lt;sup&gt;2&lt;/sup&gt;</th>
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<th>Adjustment for any other factor</th>
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<th>Long enough follow-up</th>
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<sup>1</sup> 1 point for validated self-reported questionnaires or interview

<sup>2</sup> 1 point for exclusion of prevalent cardiovascular disease or cancer cases

<sup>3</sup> 1 point for loss-to-follow-up less than 10%
Supplementary Figure 1. Whole grains and coronary heart disease, high versus low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.76 (0.64, 0.90)</td>
</tr>
<tr>
<td>Rautiainen, 2012</td>
<td>0.89 (0.74, 1.07)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.72 (0.57, 0.90)</td>
</tr>
<tr>
<td>Jensen, 2004</td>
<td>0.84 (0.71, 0.98)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.72 (0.53, 0.97)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.75 (0.59, 0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.79 (0.73, 0.86)</td>
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</table>

Supplementary Figure 2. Whole grains and coronary heart disease, scatter plot from nonlinear dose-response analysis

- **X**: Reference categories
- **O**: Relative Risk
Supplementary Figure 3. Whole grains and stroke, high vs. low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.86 (0.61, 1.19)</td>
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<tr>
<td>Mizrahi, 2009</td>
<td>1.12 (0.87, 1.45)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.85 (0.60, 1.21)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.75 (0.46, 1.22)</td>
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<tr>
<td>Liu, 2000</td>
<td>0.69 (0.50, 0.98)</td>
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<tr>
<td>Overall</td>
<td>0.87 (0.72, 1.05)</td>
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Supplementary Figure 4. Whole grains and stroke, scatter plot from nonlinear dose-response analysis

- Reference categories
- Relative Risk

https://mc.manuscriptcentral.com/bmj
Supplementary Figure 5. Whole grains and cardiovascular disease, high vs. low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.83 (0.78, 0.88)</td>
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<td>Johnsen, 2015</td>
<td>0.78 (0.67, 0.91)</td>
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<tr>
<td>Sonestedt, 2015</td>
<td>0.87 (0.77, 0.97)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.84 (0.75, 0.93)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.86 (0.76, 0.96)</td>
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<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.73 (0.34, 1.58)</td>
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<tr>
<td>Fitzgerald, 2012</td>
<td>0.96 (0.79, 1.17)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.73 (0.57, 0.90)</td>
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<tr>
<td>Sahyoun, 2006</td>
<td>0.48 (0.25, 0.96)</td>
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<tr>
<td>Overall</td>
<td>0.84 (0.80, 0.87)</td>
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</table>

Supplementary Figure 6. Whole grains and cardiovascular disease, scatter plot from nonlinear dose-response analysis
Supplementary Figure 7. Whole grains and total cancer, high vs. low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.85 (0.81, 0.89)</td>
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<tr>
<td>Johnsen, 2015</td>
<td>0.78 (0.70, 0.86)</td>
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<td>Wu, 2015, HPFS</td>
<td>0.95 (0.86, 1.05)</td>
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<tr>
<td>Wu, 2015, NHS</td>
<td>0.99 (0.91, 1.07)</td>
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<td>Buil-Cosiales, 2014</td>
<td>0.75 (0.40, 1.41)</td>
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<td>Jacobs, 2007</td>
<td>0.89 (0.77, 1.04)</td>
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<tr>
<td>Overall</td>
<td>0.89 (0.82, 0.96)</td>
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</table>

Supplementary Figure 8. Whole grains and cardiovascular disease, scatter plot from nonlinear dose-response analysis
Supplementary Figure 9. Whole grains and all-cause mortality, high vs. low analysis

Supplementary Figure 10. Whole grains and all-cause mortality, scatter plot from nonlinear dose-response analysis
Supplementary Figure 11. Whole grains and respiratory disease mortality, high vs. low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.89 (0.80, 0.98)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.72 (0.49, 1.05)</td>
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<tr>
<td>Wu, 2015</td>
<td>0.89 (0.77, 1.03)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.60 (0.46, 0.80)</td>
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<tr>
<td>Overall</td>
<td>0.81 (0.69, 0.94)</td>
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</tbody>
</table>

Supplementary Figure 12. Whole grains and respiratory disease mortality, scatter plot from nonlinear dose-response analysis
Supplementary Figure 13. Whole grains and diabetes mortality, high vs. low analysis

Supplementary Figure 14. Whole grains and diabetes mortality, scatter plot from nonlinear dose-response analysis
Supplementary Figure 15. Whole grains and infectious disease mortality, high vs. low analysis

![Relative Risk Diagram]

Relative Risk

(95% CI)

Study

Huang, 2015

0.77 (0.62, 0.95)

Wu, 2015, NHS

0.90 (0.66, 1.23)

Jacobs, 2007

0.68 (0.26, 1.75)

Overall

0.80 (0.68, 0.96)

Supplementary Figure 16. Whole grains and infectious disease mortality, scatter plot from nonlinear dose-response analysis

![Scatter Plot Diagram]

Estimated RR

Whole grains (g/d)

X Reference categories

O Relative Risk
Supplementary Figure 17. Whole grains and nervous system disease mortality, high vs. low analysis

Supplementary Figure 18. Whole grains and nervous system disease mortality, scatter plot from nonlinear dose-response analysis
Supplementary Figure 19. Whole grains and non-cardiovascular, non-cancer causes of death, high vs. low analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, 2015</td>
<td>0.86 (0.78, 0.94)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.67 (0.60, 0.74)</td>
</tr>
<tr>
<td>Wu, 2015</td>
<td>0.91 (0.86, 0.97)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.76 (0.38, 1.53)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.75 (0.63, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.79 (0.69, 0.92)</td>
</tr>
</tbody>
</table>

Supplementary Figure 20. Whole grains and non-cardiovascular, non-cancer causes of death, scatter plot from nonlinear dose-response analysis

[Graph showing relative risk as a function of whole grain intake]
Supplementary Figure 21. Whole grain bread and coronary heart disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.82 (0.64, 1.04)</td>
</tr>
<tr>
<td>Atkins, 2014</td>
<td>0.76 (0.18, 3.15)</td>
</tr>
<tr>
<td>Rebello, 2014</td>
<td>0.79 (0.59, 1.05)</td>
</tr>
<tr>
<td>Appleby, 2002</td>
<td>0.86 (0.72, 1.03)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.76 (0.56, 1.02)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.98 (0.77, 1.25)</td>
</tr>
<tr>
<td>Jacobs, 1998</td>
<td>0.67 (0.49, 0.91)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.75, 0.92)</td>
</tr>
</tbody>
</table>

Supplementary Figure 22. Whole grain bread and coronary heart disease, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.88 (0.78, 0.98)</td>
</tr>
<tr>
<td>Rebello, 2014</td>
<td>0.65 (0.35, 1.23)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.78 (0.61, 1.01)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.81 (0.53, 1.24)</td>
</tr>
<tr>
<td>Jacobs, 1998</td>
<td>0.67 (0.48, 0.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.76, 0.92)</td>
</tr>
</tbody>
</table>
Supplementary Figure 23. Whole grain bread and coronary heart disease, nonlinear dose-response
Supplementary Figure 24. Whole grain breakfast cereal and coronary heart disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.69 (0.58, 0.83)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.71 (0.51, 0.98)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.76 (0.57, 1.00)</td>
</tr>
<tr>
<td>Jacobs, 1998</td>
<td>0.77 (0.56, 1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.72 (0.64, 0.82)</td>
</tr>
</tbody>
</table>

Supplementary Figure 25. Whole grain breakfast cereal and coronary heart disease, per 30 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.84 (0.76, 0.92)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.77 (0.61, 0.97)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.73 (0.55, 0.96)</td>
</tr>
<tr>
<td>Jacobs, 1998</td>
<td>0.75 (0.54, 1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.81 (0.75, 0.88)</td>
</tr>
</tbody>
</table>
Supplementary Figure 26. Whole grain breakfast cereal and coronary heart disease, nonlinear dose-response
Supplementary Figure 27. Rye and coronary heart disease, high vs. low

Study | Relative Risk (95% CI)
--- | ---
Johnsen, 2015 | 0.84 (0.71, 1.00)
Pietinen, 1996 | 0.75 (0.58, 0.98)
Overall | 0.81 (0.70, 0.94)

Supplementary Figure 28. Rye and coronary heart disease, per 30 g/d

Study | Relative Risk (95% CI)
--- | ---
Johnsen, 2015 | 0.92 (0.83, 1.02)
Simila, 2013 | 1.00 (0.98, 1.01)
Overall | 0.97 (0.91, 1.05)
Supplementary Figure 29. Bran and coronary heart disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mink, 2007</td>
<td>0.91 (0.78, 1.06)</td>
</tr>
<tr>
<td>Jensen, 2004</td>
<td>0.72 (0.61, 0.84)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.63 (0.42, 0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.63, 0.95)</td>
</tr>
</tbody>
</table>

Supplementary Figure 30. Bran and coronary heart disease, per 10 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen, 2004</td>
<td>0.76 (0.66, 0.88)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.59 (0.40, 0.87)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.72 (0.58, 0.89)</td>
</tr>
</tbody>
</table>
Supplementary Figure 31. Germ and coronary heart disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen, 2004</td>
<td>0.98 (0.85, 1.12)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.41 (0.15, 1.10)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.73 (0.33, 1.64)</td>
</tr>
</tbody>
</table>

Supplementary Figure 32. Germ and coronary heart disease, per 2 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen, 2004</td>
<td>0.95 (0.68, 1.32)</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.87 (0.73, 1.03)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.76, 1.03)</td>
</tr>
</tbody>
</table>
Supplementary Figure 33. Refined grains and coronary heart disease, high vs. low

![Diagram showing relative risk with 95% CI for different studies.]

- Yu, 2013, SMHS: 2.01 (0.96, 4.23)
- Yu, 2013, SWHS: 1.53 (0.64, 3.68)
- Jacobs, 2007: 0.89 (0.70, 1.14)
- Steffen, 2003: 1.17 (0.82, 1.66)
- Overall: 1.16 (0.84, 1.59)

Supplementary Figure 34. Refined grains and coronary heart disease, per 90 g/d

![Diagram showing relative risk with 95% CI for different studies.]

- Wang, 2016: 1.16 (0.83, 1.56)
- Yu, 2013, SMHS: 1.70 (0.98, 2.97)
- Yu, 2013, SWHS: 2.07 (0.60, 7.15)
- Jacobs, 2007: 0.86 (0.71, 1.05)
- Steffen, 2003: 1.17 (0.94, 1.46)
- Overall: 1.13 (0.90, 1.42)
Supplementary Figure 35. Refined grains and coronary heart disease, nonlinear dose-response
Supplementary Figure 36. White bread and coronary heart disease, high vs. low

Relative Risk

Study

Rebello, 2014
0.98 (0.83, 1.16)

Jacobs, 1998
1.24 (0.94, 1.64)

Overall
1.07 (0.86, 1.34)

Supplementary Figure 37. White bread and coronary heart disease, per 90 g/d

Relative Risk

Study

Rebello, 2014
0.70 (0.49, 1.00)

Jacobs, 1998
1.30 (0.98, 1.72)

Overall
0.96 (0.53, 1.76)
Supplementary Figure 38. Refined grain breakfast cereals and coronary heart disease, high vs. low

Supplementary Figure 39. Refined grain breakfast cereals and coronary heart disease, per 90 g/d

https://mc.manuscriptcentral.com/bmj
Supplementary Figure 40. Total rice and coronary heart disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eshak, 2014</td>
<td>1.08 (0.84, 1.38)</td>
</tr>
<tr>
<td>Muraki, 2014</td>
<td>0.97 (0.86, 1.08)</td>
</tr>
<tr>
<td>Rebello, 2014</td>
<td>1.05 (0.85, 1.29)</td>
</tr>
<tr>
<td>Eshak, 2011</td>
<td>0.81 (0.61, 1.08)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.98 (0.90, 1.07)</td>
</tr>
</tbody>
</table>

Supplementary Figure 41. Total rice and coronary heart disease, per 100 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eshak, 2014</td>
<td>1.03 (0.95, 1.11)</td>
</tr>
<tr>
<td>Muraki, 2014</td>
<td>0.96 (0.77, 1.23)</td>
</tr>
<tr>
<td>Rebello, 2014</td>
<td>1.00 (0.96, 1.05)</td>
</tr>
<tr>
<td>Eshak, 2011</td>
<td>0.94 (0.88, 1.01)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.99 (0.95, 1.03)</td>
</tr>
</tbody>
</table>
Supplementary Figure 42. Total rice and coronary heart disease, nonlinear dose-response

![Graph showing the relationship between rice consumption and coronary heart disease risk.](image-url)
Supplementary Figure 43. Total grains and coronary heart disease, high vs. low

![Relative Risk vs. Study](chart1)

Relative Risk
(95% CI)

Study

Atkins, 2014: 1.19 (0.73, 1.93)
Tognon, 2014: 0.90 (0.66, 1.24)
Buckland, 2009: 1.12 (0.92, 1.38)
Overall: 1.07 (0.91, 1.25)

Supplementary Figure 44. Total grains and coronary heart disease, per 90 g/d

![Relative Risk vs. Study](chart2)

Relative Risk
(95% CI)

Study

Wang, 2016: 1.00 (0.78, 1.30)
Buckland, 2009: 1.19 (0.88, 1.61)
Overall: 1.07 (0.88, 1.30)
Supplementary Figure 45. Whole grain bread and stroke, high vs. low

Study

Johnsen, 2015
0.87 (0.70, 1.09)

Appleby, 2002
0.89 (0.70, 1.13)

Overall
0.88 (0.75, 1.03)
Supplementary Figure 46. Whole grain breakfast cereals and stroke, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.74 (0.54, 1.03)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>1.41 (0.85, 2.34)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.99 (0.53, 1.86)</td>
</tr>
</tbody>
</table>

Supplementary Figure 47. Whole grain breakfast cereals and stroke, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.88 (0.74, 1.05)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>1.37 (0.95, 1.97)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.07 (0.69, 1.64)</td>
</tr>
</tbody>
</table>
Supplementary Figure 48. Refined grains and stroke, high vs. low

Study                     | Relative Risk (95% CI) |
---------------------------|-------------------------|
Mizrahi, 2009             | 0.85 (0.70, 1.04)       |
Jacobs, 2007              | 1.30 (0.88, 1.91)       |
Steffen, 2003             | 0.82 (0.48, 1.40)       |
Liu, 2000                 | 0.97 (0.67, 1.42)       |
Overall                   | 0.95 (0.78, 1.14)       |

Supplementary Figure 49. Refined grains and stroke, per 90 g/d

Study                     | Relative Risk (95% CI) |
---------------------------|-------------------------|
Wang, 2016                 | 0.73 (0.55, 0.94)       |
Mizrahi, 2009              | 0.94 (0.88, 1.02)       |
Jacobs, 2007               | 1.12 (0.83, 1.52)       |
Steffen, 2003              | 0.80 (0.57, 1.11)       |
Liu, 2000                  | 0.92 (0.68, 1.25)       |
Overall                   | 0.91 (0.81, 1.02)       |
Supplementary Figure 50. Refined grains and stroke, nonlinear dose-response
Supplementary Figure 51. Total rice and stroke, high vs. low

Supplementary Figure 52. Total rice and stroke, per 100 g/d
Supplementary Figure 53. Total rice and stroke, nonlinear dose-response
Supplementary Figure 54. Total grains and stroke, high vs. low

![Relative Risk Chart](null)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tognon, 2014</td>
<td>0.82 (0.60, 1.11)</td>
</tr>
<tr>
<td>Larsson, 2009</td>
<td>0.85 (0.73, 0.99)</td>
</tr>
<tr>
<td>Mizrahi, 2009</td>
<td>1.05 (0.84, 1.31)</td>
</tr>
<tr>
<td>Liu, 2000</td>
<td>0.79 (0.54, 1.18)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.89 (0.79, 1.00)</td>
</tr>
</tbody>
</table>

Supplementary Figure 55. Total grains and stroke, per 90 g/d

![Relative Risk Chart](null)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.73 (0.57, 0.91)</td>
</tr>
<tr>
<td>Misirli, 2012</td>
<td>1.03 (0.86, 1.21)</td>
</tr>
<tr>
<td>Larsson, 2009</td>
<td>0.93 (0.88, 0.99)</td>
</tr>
<tr>
<td>Mizrahi, 2009</td>
<td>1.02 (0.93, 1.11)</td>
</tr>
<tr>
<td>Liu, 2000</td>
<td>0.79 (0.61, 1.02)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.93 (0.85, 1.02)</td>
</tr>
</tbody>
</table>
Supplementary Figure 56. Total grains and stroke, nonlinear dose-response

![Graph showing the relationship between total grains (serv/day) and RR]

- **Best fitting cubic spline**
- **--- 95% confidence interval**
Supplementary Figure 57. Whole grain bread and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.82 (0.66, 1.00)</td>
</tr>
<tr>
<td>Atkins, 2014</td>
<td>0.60 (0.22, 1.65)</td>
</tr>
<tr>
<td>Appleby, 2002</td>
<td>0.86 (0.76, 0.98)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.77 (0.60, 0.98)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.75, 0.92)</td>
</tr>
</tbody>
</table>

Supplementary Figure 58. Whole grain bread and cardiovascular disease, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.88 (0.79, 0.97)</td>
</tr>
<tr>
<td>Von Ruesten, 2013</td>
<td>0.93 (0.68, 1.27)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.81 (0.66, 0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.80, 0.95)</td>
</tr>
</tbody>
</table>
Supplementary Figure 59. Whole grain breakfast cereals and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.70</td>
<td>(0.60, 0.82)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.80</td>
<td>(0.66, 0.97)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.74</td>
<td>(0.65, 0.84)</td>
</tr>
</tbody>
</table>

Supplementary Figure 60. Whole grain breakfast cereals and cardiovascular disease, per 30 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.84</td>
<td>(0.78, 0.92)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.83</td>
<td>(0.72, 0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.84</td>
<td>(0.78, 0.90)</td>
</tr>
</tbody>
</table>
Supplementary Figure 61. Bran and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.80 (0.71, 0.90)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.80 (0.70, 0.91)</td>
</tr>
<tr>
<td>Mink, 2007</td>
<td>0.86 (0.76, 0.97)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.82 (0.76, 0.88)</td>
</tr>
</tbody>
</table>

Supplementary Figure 62. Bran and cardiovascular disease, per 10 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.86 (0.80, 0.93)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.81 (0.71, 0.91)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.85 (0.79, 0.90)</td>
</tr>
</tbody>
</table>
Supplementary Figure 63. Germ and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2015, HPFS</td>
<td>1.03 (0.92, 1.16)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>1.11 (0.97, 1.27)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.06 (0.97, 1.16)</td>
</tr>
</tbody>
</table>

Supplementary Figure 64. Germ and cardiovascular disease, per 2 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2015, HPFS</td>
<td>1.03 (0.93, 1.14)</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>1.12 (0.94, 1.34)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.05 (0.96, 1.15)</td>
</tr>
</tbody>
</table>
Supplementary Figure 65. Refined grains and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonestedt, 2015</td>
<td>1.06</td>
<td>(0.95, 1.20)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.94</td>
<td>(0.78, 1.12)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.02</td>
<td>(0.91, 1.14)</td>
</tr>
</tbody>
</table>

Relative Risk

Supplementary Figure 66. Refined grains and cardiovascular disease, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonestedt, 2015</td>
<td>1.04</td>
<td>(0.96, 1.13)</td>
</tr>
<tr>
<td>Wu, 2015</td>
<td>0.97</td>
<td>(0.91, 1.03)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.87</td>
<td>(0.74, 1.03)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.98</td>
<td>(0.90, 1.06)</td>
</tr>
</tbody>
</table>

Relative Risk
Supplementary Figure 67. Total breakfast cereals and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, 2015</td>
<td>0.76 (0.71, 0.81)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.87 (0.74, 1.03)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.80 (0.70, 0.90)</td>
</tr>
</tbody>
</table>

Supplementary Figure 68. Total breakfast cereals and cardiovascular disease, per 30 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, 2015</td>
<td>0.74 (0.69, 0.80)</td>
</tr>
<tr>
<td>von Ruesten, 2013</td>
<td>0.69 (0.47, 1.01)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.90 (0.80, 1.01)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.80 (0.68, 0.93)</td>
</tr>
</tbody>
</table>
Supplementary Figure 69. Total rice and cardiovascular disease, high vs. low

Study | Relative Risk (95% CI)
--- | ---
Eshak, 2014 | 0.97 (0.84, 1.13)
Muraki, 2014 | 0.99 (0.90, 1.08)
Eshak, 2011 | 0.91 (0.80, 1.03)
Overall | 0.96 (0.90, 1.03)

Supplementary Figure 70. Total rice and cardiovascular disease, per 100 g/d

Study | Relative Risk (95% CI)
--- | ---
Eshak, 2014 | 0.99 (0.94, 1.04)
Muraki, 2014 | 1.00 (0.94, 1.07)
Eshak, 2011 | 0.96 (0.93, 1.00)
Overall | 0.98 (0.95, 1.00)
Supplementary Figure 71. Total rice and cardiovascular disease, high vs. low

Supplementary Figure 72. Total grains and cardiovascular disease, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins, 2014</td>
<td>1.13 (0.79, 1.62)</td>
</tr>
<tr>
<td>Tognon, 2014</td>
<td>0.90 (0.78, 1.04)</td>
</tr>
<tr>
<td>Gardener, 2011</td>
<td>0.98 (0.79, 1.23)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.94 (0.84, 1.06)</td>
</tr>
</tbody>
</table>
Supplementary Figure 73. Whole grain bread and total cancer, high vs. low

Supplementary Figure 74. Whole grain bread and total cancer, per 90 g/d
Supplementary Figure 75. Brown rice and total cancer, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2016, HPFS</td>
<td>0.95 (0.77, 1.17)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS</td>
<td>1.07 (0.84, 1.38)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS2</td>
<td>1.28 (0.96, 1.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.07 (0.91, 1.26)</td>
</tr>
</tbody>
</table>

Supplementary Figure 76. Brown rice and total cancer, per 100 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2016, HPFS</td>
<td>0.95 (0.87, 1.04)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS</td>
<td>1.01 (0.92, 1.11)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS2</td>
<td>1.00 (0.88, 1.14)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.98 (0.92, 1.04)</td>
</tr>
</tbody>
</table>
Supplementary Figure 77. Brown rice and total cancer, nonlinear dose-response

![Graph showing the relationship between Brown rice consumption (g/day) and RR (risk ratio). The graph includes a best fitting cubic spline and 95% confidence interval.](https://mc.manuscriptcentral.com/bmj)
Supplementary Figure 78. Refined grains and total cancer, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2015</td>
<td>0.94 (0.91, 1.00)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.98 (0.84, 1.14)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.94 (0.90, 0.99)</td>
</tr>
</tbody>
</table>
Supplementary Figure 79. White rice and total cancer, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2016, HPFS</td>
<td>0.91 (0.79, 1.05)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS</td>
<td>0.96 (0.81, 1.14)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS2</td>
<td>0.73 (0.59, 0.90)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.76, 1.01)</td>
</tr>
</tbody>
</table>

Supplementary Figure 80. White rice and total cancer, per 100 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2016, HPFS</td>
<td>1.01 (0.94, 1.08)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS</td>
<td>1.02 (0.95, 1.09)</td>
</tr>
<tr>
<td>Zhang, 2016, NHS2</td>
<td>0.90 (0.82, 1.00)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.98 (0.92, 1.05)</td>
</tr>
</tbody>
</table>
Supplementary Figure 81. White rice and total cancer, nonlinear dose-response
Supplementary Figure 82. Total breakfast cereals and total cancer, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, 2015</td>
<td>0.88 (0.83, 0.93)</td>
</tr>
<tr>
<td>von Ruesten, 2013</td>
<td>0.99 (0.83, 1.17)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.90 (0.82, 1.00)</td>
</tr>
</tbody>
</table>
Supplementary Figure 83. Total rice and total cancer, high vs. low

Study                      | Relative Risk (95% CI)          |
---------------------------|---------------------------------|
Zhang, 2016, HPFS         | 1.00 (0.93, 1.10)               |
Zhang, 2016, NHS          | 1.02 (0.93, 1.12)               |
Zhang, 2016, NHS2         | 0.83 (0.73, 0.94)               |
Iso, 2007                  | 0.92 (0.86, 0.99)               |
Overall                    | 0.95 (0.88, 1.02)               |

Supplementary Figure 84. Total rice and total cancer, per 100 g/d

Study                      | Relative Risk (95% CI)          |
---------------------------|---------------------------------|
Zhang, 2016, HPFS         | 1.00 (0.95, 1.06)               |
Zhang, 2016, NHS          | 1.01 (0.96, 1.06)               |
Zhang, 2016, NHS2         | 0.89 (0.83, 0.97)               |
Iso, 2007                  | 0.98 (0.97, 1.00)               |
Overall                    | 0.98 (0.95, 1.01)               
Supplementary Figure 85. Total rice and total cancer, nonlinear dose-response
Supplementary Figure 86. Total grains and total cancer, per 90 g/d

- **Study**
  - **Sharma, 2013**
    - Relative Risk: 0.96 (0.91, 1.01)
  - **Couto, 2011**
    - Relative Risk: 0.98 (0.96, 0.98)
  - **Overall**
    - Relative Risk: 0.97 (0.96, 0.99)
Supplementary Figure 87. Whole grains bread and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.75 (0.69, 0.81)</td>
</tr>
<tr>
<td>Roswall, 2015</td>
<td>0.83 (0.76, 0.92)</td>
</tr>
<tr>
<td>Atkins, 2014</td>
<td>0.77 (0.32, 1.90)</td>
</tr>
<tr>
<td>Appleby, 2002</td>
<td>0.89 (0.82, 0.98)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.75 (0.65, 0.88)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.81 (0.74, 0.88)</strong></td>
</tr>
</tbody>
</table>

Supplementary Figure 88. Whole grains bread and all-cause mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.86 (0.82, 0.90)</td>
</tr>
<tr>
<td>Jacobs, 2001</td>
<td>0.81 (0.71, 0.92)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.85 (0.82, 0.89)</strong></td>
</tr>
</tbody>
</table>
Supplementary Figure 89. Whole grain breakfast cereals and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.75 (0.70, 0.79)</td>
</tr>
<tr>
<td>Tognon, 2011</td>
<td>0.85 (0.73, 1.00)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.83 (0.73, 0.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.79 (0.72, 0.86)</td>
</tr>
</tbody>
</table>

Supplementary Figure 90. Whole grain breakfast cereals and all-cause mortality, per 1 serv/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.87 (0.84, 0.90)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.86 (0.79, 0.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.84, 0.90)</td>
</tr>
</tbody>
</table>
Supplementary Figure 91. Oats or oatmeal and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen, 2015</td>
<td>0.77 (0.71, 0.83)</td>
</tr>
<tr>
<td>Roswall, 2015</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>Olsen, 2011</td>
<td>0.93 (0.86, 1.02)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.89 (0.76, 1.04)</td>
</tr>
</tbody>
</table>
Supplementary Figure 92. Refined grains and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs, 2007</td>
<td>1.01 (0.91, 1.12)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>1.08 (0.83, 1.40)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.02 (0.93, 1.12)</td>
</tr>
</tbody>
</table>

Supplementary Figure 93. Refined grains and all-cause mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.88 (0.78, 1.03)</td>
</tr>
<tr>
<td>Wu, 2015</td>
<td>0.94 (0.91, 0.97)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>1.05 (0.90, 1.24)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.95 (0.91, 0.99)</td>
</tr>
</tbody>
</table>
Supplementary Figure 94. Pasta and all-cause mortality, per 1 serv/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sluik, 2014</td>
<td>0.79</td>
<td>(0.68, 0.91)</td>
</tr>
<tr>
<td>Fortes, 2000</td>
<td>0.92</td>
<td>(0.80, 1.06)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.85</td>
<td>(0.74, 0.99)</td>
</tr>
</tbody>
</table>
Supplementary Figure 95. Total bread and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bongard, 2016</td>
<td>0.80 (0.51, 1.26)</td>
</tr>
<tr>
<td>Rotevatn, 1989</td>
<td>0.75 (0.69, 0.79)</td>
</tr>
<tr>
<td>Kahn, 1984</td>
<td>0.82 (0.73, 0.92)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.77 (0.72, 0.81)</td>
</tr>
</tbody>
</table>

Supplementary Figure 96. Total bread and all-cause mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bongard, 2016</td>
<td>0.80 (0.60, 1.07)</td>
</tr>
<tr>
<td>Sluik, 2014</td>
<td>0.83 (0.78, 0.84)</td>
</tr>
<tr>
<td>Kahn, 1984</td>
<td>0.65 (0.46, 0.92)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.80, 0.85)</td>
</tr>
</tbody>
</table>
Supplementary Figure 97. Total bread and all-cause mortality, nonlinear dose-response
Supplementary Figure 98. Total breakfast cereals and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, 2015</td>
<td>0.85 (0.83, 0.88)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.92 (0.82, 1.02)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.81, 0.93)</td>
</tr>
</tbody>
</table>

Supplementary Figure 99. Total breakfast cereals and all-cause mortality, per 30 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, 2015</td>
<td>0.83 (0.81, 0.86)</td>
</tr>
<tr>
<td>Sluik, 2014</td>
<td>0.92 (0.90, 0.93)</td>
</tr>
<tr>
<td>Liu, 2003</td>
<td>0.93 (0.86, 1.01)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.89 (0.83, 0.96)</td>
</tr>
</tbody>
</table>
Supplementary Figure 100. Total grains and all-cause mortality, high vs. low

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bongard, 2016</td>
<td>0.76 (0.48, 1.19)</td>
</tr>
<tr>
<td>Prinelli, 2015</td>
<td>0.91 (0.66, 1.26)</td>
</tr>
<tr>
<td>Shi, 2015</td>
<td>0.91 (0.84, 0.98)</td>
</tr>
<tr>
<td>Atkins, 2014</td>
<td>1.15 (0.87, 1.52)</td>
</tr>
<tr>
<td>Li, 2014</td>
<td>0.94 (0.85, 1.04)</td>
</tr>
<tr>
<td>Tognon, 2014</td>
<td>0.97 (0.82, 1.15)</td>
</tr>
<tr>
<td>Martinez-Gonzalez, 2012</td>
<td>0.83 (0.54, 1.27)</td>
</tr>
<tr>
<td>Buckland, 2011</td>
<td>0.91 (0.81, 1.03)</td>
</tr>
<tr>
<td>Tognon, 2011</td>
<td>1.01 (0.86, 1.19)</td>
</tr>
<tr>
<td>Trichopoulou, 2009</td>
<td>0.99 (0.86, 1.13)</td>
</tr>
<tr>
<td>Knoops, 2006</td>
<td>0.84 (0.77, 0.92)</td>
</tr>
<tr>
<td>Hays, 2005</td>
<td>0.90 (0.61, 1.33)</td>
</tr>
<tr>
<td>Kahn, 1984</td>
<td>0.84 (0.75, 0.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.91 (0.87, 0.95)</td>
</tr>
</tbody>
</table>

Supplementary Figure 101. Total grains and all-cause mortality, per 90 g/d

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bongard, 2016</td>
<td>0.70 (0.44, 1.13)</td>
</tr>
<tr>
<td>Wang, 2016</td>
<td>0.88 (0.80, 1.00)</td>
</tr>
<tr>
<td>Shi, 2015</td>
<td>0.97 (0.95, 1.00)</td>
</tr>
<tr>
<td>Trichopoulou, 2005</td>
<td>0.95 (0.92, 0.98)</td>
</tr>
<tr>
<td>Osler, 1997</td>
<td>1.54 (1.14, 2.03)</td>
</tr>
<tr>
<td>Trichopoulou, 1995</td>
<td>1.09 (0.87, 1.36)</td>
</tr>
<tr>
<td>Kahn, 1984</td>
<td>0.70 (0.50, 0.98)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96 (0.90, 1.02)</td>
</tr>
</tbody>
</table>
Supplementary Figure 102. Total grains and all-cause mortality, nonlinear dose-response
Supplementary Figure 103. Funnel plot of whole grains and cardiovascular disease

Supplementary Figure 104. Funnel plot of whole grains and all-cause mortality
Supplementary Figure 105. Influence analysis of whole grains and coronary heart disease

<table>
<thead>
<tr>
<th>Study omitted</th>
<th>$e^\text{coef.}$</th>
<th>95% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.80325192</td>
<td>0.73750728, 0.87485725</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.78475595</td>
<td>0.70969582, 0.8677547</td>
</tr>
<tr>
<td>Rautiainen, 2012</td>
<td>0.79712176</td>
<td>0.74025631, 0.85835552</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.83140707</td>
<td>0.77479708, 0.89215332</td>
</tr>
<tr>
<td>Jensen, 2004</td>
<td>0.82358283</td>
<td>0.77009189, 0.88078934</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.81029981</td>
<td>0.74506956, 0.88124096</td>
</tr>
<tr>
<td>Liu, 1999</td>
<td>0.81833088</td>
<td>0.75697881, 0.88465548</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td><strong>0.81134143</strong></td>
<td><strong>0.75406713, 0.87296592</strong></td>
</tr>
</tbody>
</table>
Supplementary Figure 106. Influence analysis of whole grains and stroke

<table>
<thead>
<tr>
<th>Study omitted</th>
<th>e^coef.</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.88287657</td>
<td>0.73981452 1.0536033</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.86779642</td>
<td>0.7094658 1.0614616</td>
</tr>
<tr>
<td>Mizrahi, 2009</td>
<td>0.82212949</td>
<td>0.72333467 0.93441796</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.86227262</td>
<td>0.71278179 1.043116</td>
</tr>
<tr>
<td>Steffen, 2003</td>
<td>0.89551038</td>
<td>0.76146871 1.0531474</td>
</tr>
<tr>
<td>Liu, 2000</td>
<td>0.90933239</td>
<td>0.77837229 1.0623263</td>
</tr>
<tr>
<td>Combined</td>
<td>0.87530632</td>
<td>0.74741362 1.0250832</td>
</tr>
</tbody>
</table>
Supplementary Figure 107. Influence analysis of whole grains and cardiovascular disease

<table>
<thead>
<tr>
<th>Study omitted</th>
<th>$e^{\text{coef.}}$</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.78125685</td>
<td>0.72075218 0.84684068</td>
</tr>
<tr>
<td>Huang, 2015</td>
<td>0.80042845</td>
<td>0.7388069 0.86718959</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.76861632</td>
<td>0.70844555 0.83389759</td>
</tr>
<tr>
<td>Sonestedt, 2015</td>
<td>0.77045089</td>
<td>0.71031886 0.83567339</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
<td>0.7903021</td>
<td>0.72978294 0.85584003</td>
</tr>
<tr>
<td>Wu, 2015, NHS</td>
<td>0.79728162</td>
<td>0.74731356 0.85059083</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.78345406</td>
<td>0.72522616 0.84635699</td>
</tr>
<tr>
<td>Fitzgerald, 2012</td>
<td>0.7762832</td>
<td>0.7177375 0.83960456</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.78840691</td>
<td>0.72586286 0.85634005</td>
</tr>
<tr>
<td>Sahyoun, 2006</td>
<td>0.78992122</td>
<td>0.73630428 0.84744245</td>
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<td><strong>0.78494631</strong></td>
<td><strong>0.72913752 0.84502676</strong></td>
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Supplementary Figure 108. Influence analysis of whole grains and total cancer

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<th>e^coef.</th>
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<td>0.86217254</td>
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<td>0.85649318</td>
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Supplementary Figure 109. Influence analysis of whole grains and all-cause mortality

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<td>Sahyoun, 2006</td>
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<td>Steffen, 2003</td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td></td>
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</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
</tr>
</tbody>
</table>
## PRISMA 2009 Checklist

### Synthesis of results

14. Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.

#### RESULTS

### Study selection

17. Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

#### Supplementary Table 3-12

### Study characteristics

18. For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

#### Supplementary Table 15-16

### Risk of bias within studies

19. Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

#### Supplementary Table 15-16, subgroup analyses by study quality

### Results of individual studies

20. For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.

#### 12-16, Figure 2-7

### Synthesis of results

21. Present results of each meta-analysis done, including confidence intervals and measures of consistency.

#### 12-18, Figure 2-7, Table 1, Supplementary Table 13-14, 17, Supplementary Figure 1-84

### Risk of bias across studies

22. Present results of any assessment of risk of bias across studies (see Item 15).

#### 16-17, Supplementary Figure 85-89

### Additional analysis

23. Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

#### Supplementary Table 15-16,
## DISCUSSION

<table>
<thead>
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<th>Item</th>
<th>Page</th>
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<tr>
<td>Summary of evidence</td>
<td>24</td>
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<td>Limitations</td>
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<td>Conclusions</td>
<td>26</td>
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## FUNDING

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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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https://mc.manuscriptcentral.com/bmj
### Whole grains and coronary heart disease

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<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Wang, 2016</td>
<td>0.83 (0.57 to 1.23)</td>
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<tr>
<td>Johnsen, 2015</td>
<td>0.84 (0.77 to 0.93)</td>
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<td>Rautiainen, 2012</td>
<td>0.90 (0.78 to 1.04)</td>
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<tr>
<td>Jacobs, 2007</td>
<td>0.72 (0.60 to 0.87)</td>
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<td>Jensen, 2004</td>
<td>0.65 (0.46 to 0.92)</td>
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<tr>
<td>Steffen, 2003</td>
<td>0.75 (0.56 to 1.01)</td>
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<tr>
<td>Liu, 1999</td>
<td>0.72 (0.56 to 0.93)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.80 (0.74 to 0.87)</strong></td>
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### Whole grains and stroke

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Wang, 2016</td>
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<td>Johnsen, 2015</td>
<td>0.86 (0.71 to 1.04)</td>
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<td>Mizrahi, 2009</td>
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<td>Jacobs, 2007</td>
<td>0.89 (0.67 to 1.19)</td>
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<tr>
<td>Steffen, 2003</td>
<td>0.70 (0.44 to 1.11)</td>
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<tr>
<td>Liu, 2000</td>
<td>0.69 (0.48 to 1.00)</td>
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<td><strong>Overall</strong></td>
<td><strong>0.88 (0.74 to 1.05)</strong></td>
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<tr>
<td>Study</td>
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<td><strong>Whole grains and cardiovascular disease</strong></td>
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<tr>
<td>Wang, 2016</td>
<td>0.82 (0.63 to 1.05)</td>
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<td>Huang, 2015</td>
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<td>Wu, 2015, NHS</td>
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<td>Sahyoun, 2006</td>
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<td><strong>Whole grains and total cancer</strong></td>
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<td>Wu, 2015, HPFS</td>
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<td>Buil-Cosiales, 2014</td>
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<td>Jacobs, 2007</td>
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Whole grains and all-cause mortality

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<td>Wang, 2016</td>
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<td>Johnsen, 2015</td>
<td>0.82 (0.79 to 0.85)</td>
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<tr>
<td>Wu, 2015, HPFS</td>
<td>0.91 (0.81 to 1.02)</td>
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<td>Wu, 2015, NHS</td>
<td>0.67 (0.57 to 0.77)</td>
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<tr>
<td>Boggs, 2014</td>
<td>0.30 (0.15 to 0.60)</td>
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<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.98 (0.67 to 1.44)</td>
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<td>van den Brandt, 2011</td>
<td>1.05 (0.95 to 1.17)</td>
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<td>Jacobs, 2007</td>
<td>0.82 (0.76 to 0.89)</td>
</tr>
<tr>
<td>Sahyoun, 2006</td>
<td>0.80 (0.49 to 1.31)</td>
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<tr>
<td>Steffen, 2003</td>
<td>0.77 (0.61 to 0.96)</td>
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Whole grains and respiratory disease mortality

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<td>Johnsen, 2015</td>
<td>0.82 (0.66 to 1.03)</td>
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<td>Wu, 2015</td>
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<td>Jacobs, 2007</td>
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Whole grains and diabetes mortality

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<td>Johnsen, 2015</td>
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<td>Wu, 2015</td>
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<td>Jacobs, 2007</td>
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<tr>
<td>整体</td>
<td>0.49 (0.23 to 1.05)</td>
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**全谷物与传染病死亡率**

| Huang, 2015  | 0.71 (0.52 to 0.96) |
| Wu, 2015    | 0.89 (0.41 to 1.94) |
| Jacobs, 2007| 0.79 (0.37 to 1.70) |
| Overall     | 0.74 (0.56 to 0.96) |

**全谷物与神经系统疾病死亡率**

| Wu, 2015    | 1.53 (1.08 to 2.16) |
| Jacobs, 2007| 0.86 (0.59 to 1.26) |
| Overall     | 1.15 (0.66 to 2.02) |

**全谷物与非心血管、非癌症死亡原因**

| Huang, 2015  | 0.78 (0.68 to 0.89) |
| Johnsen, 2015| 0.78 (0.74 to 0.83) |
| Wu, 2015     | 0.80 (0.68 to 0.93) |
| Buil-Cosiales, 2014 | 0.77 (0.40 to 1.46) |
| Jacobs, 2007 | 0.78 (0.67 to 0.89) |
| Overall     | 0.78 (0.75 to 0.82) |
Print abstract

Study question: To quantify the dose-response relationship between whole grain consumption and the risk of cardiovascular disease, total cancer, and all-cause and cause-specific mortality.

Methods: PubMed and Embase were searched up to 3rd of April, 2016. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Forty five studies (64 publications) were included.

Study answer and limitations: Higher intake of whole grains was associated with a reduced risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality, and mortality from respiratory disease, diabetes, infectious diseases, and all-noncardiovascular, non-cancer causes of death. Reductions in risk were observed up to an intake of 210-225 grams per day (7-7.5 servings per day) for most of the outcomes.

What this study adds: This meta-analysis suggest that a high intake of whole grains reduces the risk of coronary heart disease, cardiovascular disease, total cancer, all-cause mortality, and mortality from respiratory disease, diabetes, infectious diseases, and all non-cardiovascular, non-cancer causes of death.

Funding: The project was funded by ‘Olav og Gerd Meidel Raagholt’s Stiftelse for Medisinsk forskning’, the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and the
Imperial College National Institute of Health Research (NIHR) Biomedical Research Centre (BRC).

**Competing interests:** All authors declare no conflicts of interest.

**Data sharing:** No additional data are available.
Figure. Whole grains and all-cause mortality

### A

**Whole grains and all-cause mortality, per 90 g/d**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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<tr>
<td>Wang, 2016</td>
<td>0.94 (0.80, 1.16)</td>
</tr>
<tr>
<td>Huang, 2015</td>
<td>0.76 (0.73, 0.79)</td>
</tr>
<tr>
<td>Johnsen, 2015</td>
<td>0.82 (0.79, 0.85)</td>
</tr>
<tr>
<td>Wu, 2015, HPFS</td>
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</tr>
<tr>
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<td>Boggs, 2014</td>
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</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.98 (0.67, 1.44)</td>
</tr>
<tr>
<td>van den Brandt, 2011</td>
<td>1.05 (0.95, 1.17)</td>
</tr>
<tr>
<td>Jacobs, 2007</td>
<td>0.82 (0.76, 0.89)</td>
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<td>Sahyoun, 2006</td>
<td>0.80 (0.49, 1.31)</td>
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<tr>
<td>Steffen, 2003</td>
<td>0.77 (0.61, 0.96)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.83 (0.77, 0.90)</td>
</tr>
</tbody>
</table>

### B

**Whole grains and all-cause mortality, nonlinear dose-response**

- **Best fitting cubic spline**
- **95% confidence interval**