Associations of cereal grains intake with cardiovascular disease and mortality across 21 countries in Prospective Urban and Rural Epidemiology study: prospective cohort study

Sumathi Swaminathan,[1] Mahshid Dehghan,[2] John Michael Raj,[3] Tinku Thomas,[3] Sumathy Rangarajan,[2] David Jenkins,[4] Prem Mony,[1] Viswanathan Mohan,[5] Scott A Lear,[6] Alvaro Avezum,[7] Patricio Lopez-Jaramillo,[8] Annika Rosengren,[9,10] Fernando Lanas,[11] Khalid F AlHabib,[12] Antonio Dans,[13] Mirac Vural Keskinler,[14] Thandi Puoane,[15] Biju Soman,[16,17] Li Wei,[18] Katarzyna Zatonska,[19] Rafael Diaz,[20] Noorhassim Ismail,[21] Jephat Chifamba,[22] Roya Kelishadi,[23] Afzalhussein Yusufali,[24] Rasha Khatib,[25,26] Liu Xiaoyun,[18] Hu Bo,[18] Romaina Iqbal,[27] Rita Yusuf,[28] Karen Yeates,[29,30] Koon Teo,[2] Salim Yusuf[2]

For numbered affiliations see end of the article.

Correspondence to: M Dehghan Mahshid.dehghan@phri.ca (ORCID 0000-0003-2149-847X)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;372:m4948
http://dx.doi.org/10.1136/bmj.m4948

Accepted: 10 November 2020

ABSTRACT

OBJECTIVE

To evaluate the association between intakes of refined grains, whole grains, and white rice with cardiovascular disease, total mortality, blood lipids, and blood pressure in the Prospective Urban and Rural Epidemiology (PURE) study.

DESIGN

Prospective cohort study.

SETTING

PURE study in 21 countries.

PARTICIPANTS

148 858 participants with median follow-up of 9.5 years.

EXPOSURES

Country specific validated food frequency questionnaires were used to assess intakes of refined grains, whole grains, and white rice.

MAIN OUTCOME MEASURE

Composite of mortality or major cardiovascular events (defined as death from cardiovascular causes, non-fatal myocardial infarction, stroke, or heart failure). Hazard ratios were estimated for associations of grain intakes with mortality, major cardiovascular events, and their composite by using multivariable Cox frailty models with random intercepts to account for clustering by centre.

RESULTS

Analyses were based on 137 130 participants after exclusion of those with baseline cardiovascular disease. During follow-up, 9.2% (n=12 668) of these participants had a composite outcome event. The highest category of intake of refined grains (≥350 g/day or about 7 servings/day) was associated with higher risk of total mortality (hazard ratio 1.27, 95% confidence interval 1.11 to 1.46; P for trend=0.004), major cardiovascular disease events (1.33, 1.16 to 1.52; P for trend<0.001), and their composite (1.28, 1.15 to 1.42; P for trend<0.001) compared with the lowest category of intake (<50 g/day). Higher intakes of refined grains were associated with higher systolic blood pressure. No significant associations were found between intakes of whole grains or white rice and health outcomes.

CONCLUSION

High intake of refined grains was associated with higher risk of mortality and major cardiovascular disease events. Globally, lower consumption of refined grains should be considered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Among cereals that largely contribute to carbohydrate intake, higher consumption of whole grains has been associated with lower risk of total mortality and cardiovascular disease

However, no clear associations have been observed between refined grains and these outcomes

WHAT THIS STUDY ADDS

The Prospective Urban and Rural Epidemiology study includes participants from low, middle, and high income countries, covering broad patterns of diet globally

A higher intake of refined grains was associated with a higher risk of total mortality and major cardiovascular disease

No associations with the outcomes were found for whole grains or white rice

Introduction

Diet may influence the development and progression of chronic diseases.[1 2] Globally, over the past few decades, the consumption of refined grains and added sugars has increased. Positive associations between higher consumption of refined carbohydrates with high glycaemic load and risk factors for cardiovascular disease have been reported.[3]

We previously showed that higher intake of carbohydrate was associated with higher risk of total mortality and cardiovascular disease,[4] which was also reported by Ho et al.[5] Cereal grains contribute approximately 50% of caloric intake across the world, with higher levels in low income and middle income countries, particularly in Africa and South Asia. In these regions, cereal grains contribute about 70% of daily caloric intake.[6] Therefore, a detailed examination of the association between the types of cereal grains and health outcomes is warranted.

Several prospective cohort studies and their meta-analyses have reported that higher consumption of whole grain is associated with a lower risk of mortality and cardiovascular disease.[7-11] The association of refined grains with total mortality and cardiovascular disease has not been clearly defined. Meta-analyses

have found different results, with two showing no association and another a positive association.[12-14]

Previous studies have been conducted mostly in North America and Europe, with limited information from other parts of the world where the amount and types of carbohydrates consumed in the diet vary, as do their contribution to overall calories. Studies in single geographical regions provide information on associations across a relatively limited range of intake. The Prospective Urban Rural Epidemiology (PURE) study has the distinct advantage of examining diets from diverse populations in low, middle, and high income countries in multiple regions across the world. The analysis reported here was conducted to evaluate the association of intake of refined grains, whole grains, and white rice with total mortality, major cardiovascular disease events, blood pressure, and blood lipids.

Methods

Study participants

The PURE study is a large prospective cohort study conducted in countries across the regions of North America and Europe, South America, Africa, the Middle East, South Asia, South East Asia, and China. The design and sampling for the study have been published elsewhere.[15 16] Data on people aged 35 to 70 years at baseline were collected from 21 countries—five low income countries, five lower middle income countries, seven upper middle income countries, and four high income countries, as classified by the World Bank in 2006, covering urban and rural locations. Participants recruited from January 2003 and followed up until July 2019 were included in the analysis.

Data collection procedures

Baseline survey

Individual, household, and community level information was collected through questionnaires, using a standardised protocol across all countries at baseline. Details of demographic factors, socioeconomic status (education, income, employment), lifestyle behaviours (smoking, physical activity, diet, and alcohol intake), personal medical history including self-reported history of diabetes, use of medications, record of comorbidities (hypertension, cardiovascular disease, history of diabetes, etc), and risk factors were obtained. Physical activity was assessed using the long form of the International Physical Activity Questionnaire and categorised as low (<600 MET-minutes per week), moderate (600-3000 MET-minutes per week), and high (≥3000 MET-minutes per week). A standard protocol was used to take physical measurements of blood pressure and anthropometric measurements of weight, height, and waist and hip circumference.[16] Blood samples were collected and blood lipid concentrations measured. Of the 148 858 participants, 129 740 (87%) had fasting blood samples and 3632 had non-fasting blood samples; we were unable to ascertain blood status for the rest.

Follow-up

Follow-up was conducted every three years. Data were collected at the community, household, and individual levels with standardised questionnaires administered by trained staff. Standard case report forms were used to record data on major cardiovascular events and mortality (classified by cause) during follow-up, which were adjudicated centrally in each country by trained physicians using common definitions, according to a standard protocol as previously described.[4] The definitions of events are detailed in the methods section of the supplementary appendix. For this analysis, we included all adjudicated outcome events. The study was coordinated by the Population Health Research Institute (PHRI), Hamilton, Canada.

Dietary assessment

Each participant's food intake was recorded at baseline using country specific (or region specific in India) validated food frequency questionnaires as previously described.[4 17] Typically, the food lists for food frequency questionnaires contained between 98 and 220 food items across the various countries. Interviewers asked participants: "During the past year, on average, how often have you consumed the following foods or drinks." The format of the food frequency questionnaire remained similar for all countries, with options of frequencies ranging from never to more than six times a day. Portion sizes were assigned to each food item on the list. We calculated the daily food intake of each participant by multiplying the daily frequency of intake by the portion size.

Exposures

The main exposures were the consumption of refined grains, whole grains, and white rice. For this analysis, we categorised grains into three groups: refined grains, whole grains, and white rice. We examined white rice separately from all other refined grains because more than 60% of the PURE population reside in Asia where rice is a staple food. The three grain food categories were mutually exclusive. The definitions used for the grain categories were as follows.

We defined refined grains as wheat grain products or flours that have been modified to remove the bran (the aleurone layer) and germ and therefore have a low fibre content. Products in this category are made with refined (white) flour, including white bread, pasta/noodles, breakfast cereals, crackers, and bakery products/desserts containing refined grains. For bakery products and desserts, we counted only the proportion of refined grains. Ready to eat breakfast made from corn was also included in this group.

The whole grains group contained two types of grains. The first was whole grain flours such as those made from wheat, rye, triticale, oats, barley, maize, finger and pearl millet, sorghum, or buckwheat. Wheat products made from flours ideally contain all the components of the intact grain (whole meal). This applies to all flours that are produced as "stone ground flours"—that is, where millstones, the traditional

doi: 10.1136/bmj.m4948 | BMJ 2021;372:m4948 | the bmj

method of making grain flours, are used to grind flours. With the onset of industrialisation, flours were produced by steel roller mills. In this case, a "white" flour is produced and the germ (lipid) and aleurone layer that contains fibre and protein are separated. The germ, containing the lipid, is then heat treated to prevent rancidity. The bran (that is, the aleurone fibre layer), the heat treated germ, and the "white" flour are recombined in various proportions to reflect their proportion in the intact grain (for example, 25%, 50%, 75%, or 100% of the germ and aleurone layer). This percentage is the extraction rate. As the method of processing is unknown (for example, stone mill or steel roller), we refer to all flours with some increased fibre, over and above the "white flour" content, as whole grain flour. The second type of grain in this group is intact or "cracked" whole grains and whole grain porridges—whole grains that are still associated with their fibre, such as pumpernickel breads, cracked wheat, bulgur, steel cut oats, barley, and oat and maize porridges. The whole grain definition also includes whole corn and cornmeal and dark bread but excludes corn products such as popcorn. Intake of popcorn as a snack was recorded only in Brazil and Canada.

In white rice, the grain has been left recognisably intact but processed to remove the protein and fibre aleurone layer and the germ to make it "white" but visually "intact." In other words, it is milled rice from which the husk, bran, and germ have been removed. Ready to eat breakfast made of rice was also included in this group. In the PURE study, we were unable to differentiate between regular white rice and parboiled white rice, which contains more of the nutrients associated with brown rice and is more slowly digested and accordingly has a lower glycaemic index. Brown rice consumption was captured only in Argentina and Brazil, where its intake was very low (2 g/day in Argentina and 16 g/day in Brazil). Therefore, brown rice was not included in any grain group.

For each centre, all food containing grains or mixed dishes with grains were identified. All food frequency questionnaires combined gave a total list of 566 refined grain, 207 whole grain, and 176 white rice items. For mixed dishes, we considered the proportion of grains constituting the cooked portion in a recipe while calculating the grain intake in grams for each person. We grouped participants on the basis of their range of intakes into five categories for refined grains (<50, 50 to <150, 150 to <250, 250 to <350, and ≥350 g/day), four categories for whole grains (0, <50, 50 to <100, and ≥100 g/day), and five categories for white rice (<50, 50 to <150, 150 to <300, 300 to <450, and ≥450 g/day). The categorisation for each grain was based on a 100 g increase, except for white rice, for which an increase of 150 g per day (a cup of cooked rice) was considered. Furthermore, for the categorisation of white rice, as a large proportion of participants reported intakes below 150 g per day, intakes below 150 g were separated into two categories. For refined grains, the highest category of 350 g/day or more represented about seven to 10 servings per day mainly as white bread, whole grain intake of 100 g/day or more represented at least three servings per day, and 450 g/day or more of white rice represented at least six servings of cooked rice per day.

To calculate the raw value of whole grain, we calculated dry matter for whole grain foods at the region level. The calculations for dry weight used a coefficient for the water content. Thus, for North America/Europe, South America, and the Middle East, it was 30%, as the main source of whole grain was whole wheat bread.[18] It was 50% for Africa, with porridges mostly being consumed, 35% for South Asia and South East Asia, and 40% for China (based on some of the main whole grain recipes from these regions). For dry weight, we categorised whole grains as 0, less than 10, 10-19.9, 20-29.9, and at least 30 g/day. The serving sizes for each country were also calculated as per the US Department of Agriculture.

We used the lowest category of intake for refined grain and white rice and the highest category for whole grains as the reference categories. Participants with plausible energy intakes (500-5000 kcal/day) were included in the analysis.[4]

Outcomes

The primary outcome of this analysis was the composite of mortality or major cardiovascular disease events (defined as death from cardiovascular causes, non-fatal myocardial infarction, stroke, or heart failure). Secondary outcomes were total mortality, and major cardiovascular disease (fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, heart failure, and cardiovascular mortality). Other outcomes measured were blood lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, total cholesterol to high density lipoprotein cholesterol ratio, triglycerides, apolipoprotein A1, apolipoprotein B, apolipoprotein B to apolipoprotein A1 ratio) and blood pressure measured at baseline.

Statistical analysis

We summarised continuous measurements by using mean and standard deviation if normally distributed; otherwise, we used medians and interquartile ranges. We present categorical observations as frequency and percentages. We created a wealth index by using information collected on household possessions such as electricity, car, computer, television, and telephone. We created a binary yes/no classification for each item and then used a principal component analysis to extract the component with the largest eigenvalue. We then assigned each household to a score based on factor loadings. We categorised education as none or primary school (first six years), secondary school (seven to 11 years), and college, trade school, or university (>11 years); smoking as never, former, or current; and physical activity as low (<600 MET-min per week), moderate (600-3000 MET-min per week), and high (>3000 MET-min per week) activity.

We evaluated the proportional hazards assumption by visual inspection of log-log plots, which were consistent with proportional hazards. We assessed

the association between types of grain intake and the time to occurrence of events by using a Cox frailty model with random intercepts to account for clustering by centres (which simultaneously adjusts for region and country). We assumed that frailty followed a γ distribution with correlated observations within cluster. We estimated hazard ratios for both the univariate base model and the multivariable adjusted model and presented them as hazard ratios and 95% confidence intervals. We excluded participants with history of cardiovascular disease at baseline. For all analyses on associations, we adjusted total energy intake by using a standard multivariable model, as the study examined the association between food intake and clinical outcomes.[19 20] We identified covariates a priori, on the basis of the literature,[17 21-28] as those that were associated with at least one of the events listed and are potential confounders in the association of grains with events. We also included fruit and vegetable intake as a covariate, as these are a major source of fibre. We used one way analysis of variance to examine the association of wealth index, age, waist to hip ratio, and intakes of total energy, fruits and vegetable, and unprocessed red meat with grain intake. We used Pearson's χ^2 test for categorical variables such as sex, location (urban/rural), education, smoking, physical activity, and history of diabetes (yes/no). As previous food frequency questionnaire validation studies have shown that the error of variance for sodium is high,[29] we did not include dietary sodium as a covariate in our models. However, an analysis with adjustment for saturated fat and sodium is also presented in the supplementary material. We did not include alcohol intake in the model, as this was not captured in five Muslim countries (Bangladesh, Iran, Pakistan, Malaysia, and United Arab Emirates). Soft drink intake in low and middle income countries (except Argentina) was low, so intake of sugar sweetened drinks was not included as a covariate in the models. To evaluate whether history of diabetes could be a mediator, we analysed data with and without diabetes included in the model. Considering the biology and the causal pathway, no colliders were included.

The base model was adjusted for age and sex, with centre considered as a random effect. The minimally adjusted model included the base model with further adjustment for location (urban/rural), education, wealth index, smoking status, waist to hip ratio, physical activity, history of diabetes, energy intake, fruit and vegetable intake, and dairy intake. The fully adjusted model additionally included refined or whole grain intake as appropriate, as grains are eaten in combination. This also allows for adjustment for fibre from other cereal sources. The main results reported are on the basis of the fully adjusted models. We did an additional analysis using the fully adjusted model with medications included (statins and blood pressure lowering drugs). We used restricted cubic splines with four knots (at the 5th, 35th, 65th, and 95th percentiles) to explore the shape of the association of grains with events.

We did a sensitivity analysis of the fully adjusted model by excluding participants who had cardiovascular disease events in the first two years of follow-up to account for possible reverse causation. To account for the clustering of intakes within region, we performed the Cox proportional hazards models with frailty separately within high and low intake regions for refined grains. Low intakes regions were Africa and South Asia, where median intakes were below 100 g, and the remaining regions had high intakes. The whole grain intake in Africa was much higher than in the rest of the regions, so we did a sensitivity analysis that excluded data from Africa and explored the association of whole grains and outcomes. To further account for the clustering of grain intake by region, we estimated hazard ratios by region and obtained an overall estimate by meta-analysis. To examine heterogeneity of the associations of grains with major cardiovascular disease and mortality by geographical region, we did a random effects meta-analysis across all regions. Tests of heterogeneity used the I^2 statistic.

We could not do subgroup analyses for the Africa region for estimate of composite outcome, total mortality, and major cardiovascular disease events for refined grain, whole grain, and white rice consumption and for South East Asia for estimation of total mortality for refined grain consumption alone, as the sample size in these regions was insufficient for hazard ratio estimation. Additionally, we did a subgroup analysis in the Asian regions (South Asia, South East Asia, and China), where consumption of rice was higher than in non-Asian regions. We also present results with serving size per day as a continuous variable for each grain type. We did further subgroup analyses to assess associations of grains with major cardiovascular disease events and mortality by country income level (high, middle, and low income countries), body mass index (<25 and ≥25), and sex, with tests for interaction.

We also analysed whole grains alone with the raw quantities of whole grains calculated for each region. The results of analysis using serving sizes are also reported.

To examine the association of grain intake with blood pressure and blood lipids, we used multilevel linear regression with random effect models adjusted for centre. For all comparisons, the criterion for the P value to be considered significant was at the 5% level. We used Stata version 14 for all analyses.

Patient and public involvement

Patients and the public were not formally involved in setting the research question or the outcome measures; nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. At each site, community leaders were informed about the study plans to motivate their community to participate in the study. Each participating centre provided results of clinical tests such as electrocardiography and spirometry at baseline and follow-up visits along with information about the progress of the study.

Results

Data were available for 148 858 participants. Of these, 11 728 with baseline cardiovascular disease were excluded from analysis, leaving 137 130 for analysis. The rate of follow-up was 94% over the median follow-up duration of 9.5 (interquartile range 8.6-10.9) years. The follow-up period and rate for each country are provided in supplementary table S1. During this period, 10.3% (n=15 251) of participants had a composite outcome event. Of the total of 9279 deaths, 3583 (38.6%) were due to cardiovascular disease. Major cardiovascular disease events (myocardial infarction, stroke, heart failure) were recorded in 8833 (5.9%) participants. The flowchart of recruitment is provided in the supplementary appendix.

The consumption of refined grains was highest in China followed by South East Asia, and intake of white rice was highest in South Asia. Countries in Africa reported the highest intake of whole grains (table 1). All covariates considered were significantly associated with grain intake and were considered in the fully adjusted models (supplementary tables S2-S4; all P<0.001). The models were first tested with and without adjustment of diabetes (supplementary tables S5-S7) for each of the grains, and the results were not different; therefore, we did not consider the presence of diabetes as a mediator in the association between grains and outcome and we included it in multivariable adjustment.

Table 2 shows the association of refined grain consumption and risk of various clinical outcomes. In the fully adjusted model, compared with low intake, a higher level of intake (<50 g/day *v* >350 g/day) was significantly associated with higher risk of the composite outcome (hazard ratio 1.28, 95% confidence interval 1.15 to 1.42; P for trend <0.001), total mortality (1.27, 1.11 to 1.46; P for trend=0.004), non-cardiovascular mortality (1.31, 1.10 to 1.56; P for trend=0.004), major cardiovascular disease events (1.33, 1.16 to 1.52; P for trend <0.001), and stroke (1.47, 1.22 to 1.77; P for trend<0.001). For a 50 g increase in refined grain intake, the hazard ratio for the composite outcome of total mortality and major cardiovascular disease events was 1.02 (1.01 to 1.03). We noted no significant associations with cardiovascular disease mortality, myocardial infarction, and heart failure. These associations were unchanged after adjustment for medications (table 2). We found significant positive associations in high intake regions, but not in low intake regions, for composite events, total mortality, and major cardiovascular disease (fig 1; supplementary table S8; all P for interaction>0.05).

Table 1 | Characteristics of study participants at enrolment overall and by regions (n=137 130). Values are numbers (percentages) unless stated otherwise

Characteristics	Overall (n=137 130)	North America and Europe (n=17 615)	South America (n=21 619)	Africa (n=5817)	Middle East (n=9427)	South Asia (n=29 238)	South East Asia (n=11 818)	China (n=41 596)
Mean (SD) age, years	50.1(9.9)	52.1(9.2)	51.0 (9.6)	49.8 (10.6)	47.5 (9.2)	48.1 (10.2)	51.6 (9.8)	50.5 (9.7)
Male sex	57 101 (41.6)	7572 (43.0)	8318 (38.5)	1760 (30.3)	4553 (48.3)	12 746 (43.6)	4746 (40.2)	17 406 (41.9)
Urban	72 422 (52.8)	12 261 (69.6)	12 243 (56.6)	2884 (49.6)	5448 (57.8)	14 103 (48.2)	5601 (47.4)	19 882 (47.8)
Current smoker	28 478 (20.8)	3123 (17.8)	4533 (21.1)	1385 (24.2)	1388 (14.7)	6708 (23.1)	1824 (15.6)	9517 (23.1)
History of diabetes	9784 (7.1)	1050 (6.0)	1412 (6.5)	261 (4.5)	1395 (14.8)	2662 (9.1)	1436 (12.2)	1568 (3.8)
Physical activity:	(n=127 692)	(n=16 345)	(n=20 648)	(n=3452)	(n=9333)	(n=25 719)	(n=11 193)	(n=41 002)
Low	23 041 (18.0)	1473 (9.0)	2770 (13.4)	695 (20.1)	2956 (31.7)	5520 (21.5)	3271 (29.2)	6356 (15.5)
Moderate	47 833 (37.5)	6053 (37.0)	6609 (32.0)	1283 (37.2)	3966 (42.5)	8784 (34.2)	3850 (34.4)	17 288 (42.2)
High	56 818 (44.5)	8819 (54.0)	11 269 (54.6)	1474 (42.7)	2411 (25.8)	11 415 (44.4)	4072 (36.4)	17 358 (42.3)
Mean (SD) nutrient intake/day:								
Energy, kcal	2155 (819)	2275 (834)	2213 (798)	2042 (950)	2340 (835)	2109 (828)	2521 (1008)	1977 (667)
Energy from carbohydrate, %	61.1 (11.6)	51.7 (8.2)	57.6 (11.4)	61.2 (11.3)	55.7 (6.5)	65.4 (11.3)	54.5 (8.5)	67.0 (9.8)
Energy from fat, %	23.7 (9.4)	31.07 (6.2)	25.2 (7.7)	25.2 (8.9)	28.8 (5.4)	22.7 (10.5)	28.9 (6.5)	17.7 (7.8)
Energy from protein, %	15.2 (3.6)	16.6 (2.7)	17.5 (3.8)	13.79 (3.1)	17.4 (2.7)	11.61 (1.9)	16.7 (3.4)	15.3 (2.8)
Median (IQR) food intake, g/d:								
Refined grains	116 (46-226)	109 (62-184)	124 (72-204)	82 (34-139)	144 (85-195)	30 (8-84)	157 (95-262)	225 (72-455)
Whole grains	35 (2-143)	70 (28 146)	21 (1-7.4)	394 (195-771)	17 (0-72)	53 (11-202)	3 (0-14)	38 (0-163)
White rice	129 (38-401)	23 (8-38)	68 (23-158)	60 (23-96)	108 (74-182)	612 (110-948)	229 (115-389)	200 (59-600)
Fruits	143 (52-313)	334 (201-520)	328 (166-596)	147 (46-313)	320 (210-505)	46 (15-113)	175 (93-281)	84 (41-162)
Vegetables	250 (126-279)	310 (181-498)	287 (163-469)	148 (72-282)	255 (183-339)	122 (64-220)	174 (93-261)	251 (218-257)
Red meat	43 (11-98)	82 (49-120)	90 (46-148)	47 (17-101)	78 (45-126)	1 (0.0-10)	21 (10-42)	52 (22-101)
Events:								
Composite events	12 668 (9.2)	1171 (6.6)	1586 (7.3)	800 (13.8)	378 (4.0)	4139 (14.2)	1105 (9.4)	3489 (8.4)
Total mortality	7821 (5.7)	552 (3.1)	1105 (5.1)	620 (10.7)	155 (1.6)	3046 (10.4)	784 (6.6)	1559 (3.7)
Non-cardiovascular mortality	5406 (3.9)	460 (2.6)	788 (3.6)	496 (8.5)	105 (1.1)	2035 (7.0)	563 (4.8)	959 (2.3)
Cardiovascular mortality	2777 (2)	100 (0.6)	358 (1.7)	210 (3.6)	51 (0.5)	1125 (3.8)	294 (2.5)	639 (1.5)
Major cardiovascular disease	6898 (5.0)	734 (4.2)	800 (3.7)	245 (4.2)	265 (2.8)	1830 (6.3)	496 (4.2)	2528 (6.1)
Myocardial infarction	2999 (2.2)	361 (2.0)	402 (1.9)	48 (0.8)	159 (1.7)	1152 (7.0)	215 (1.8)	662 (1.6)
Stroke	3227 (2.4)	263 (1.5)	272 (1.3)	95 (1.6)	87 (0.9)	566 (14.2)	192 (1.6)	1752 (4.2)
Heart failure	656 (0.5)	114 (0.6)	131 (0.6)	65 (1.1)	32 (0.3)	99 (10.4)	71 (0.6)	144 (0.3)

IQR=interquartile range.

The associations between refined grains and clinical outcomes after grouping of participants into fifths of intake also showed that higher intake of refined grains was associated with higher risk of clinical outcomes (supplementary table S9).

Table 3 shows associations between whole grains and health outcomes. We found non-significant associations between intake of whole grains and risk of mortality or cardiovascular events in the fully adjusted models. In the base model, we observed a higher risk of composite events, total mortality, non-cardiovascular mortality, cardiovascular mortality, major cardiovascular disease, and stroke in participants with no whole grain intake. The association remained the same in the sensitivity analysis with the African region excluded from the analysis (supplementary table S10).

Table 2 | Association between refined grain intake and clinical outcomes in participants (n=135 260) without baseline cardiovascular disease

	Hazard ratio (95% CI)*					
	<50 g/d (n=35 665)†	50 to <150 g/d (n=44 015)‡	150 to <250 g/d (n=25 507)§	250 to <350 g/d (n=12 133)¶	≥350 g/d (n=17 940)**	P for trend
Composite events						
No (%) events	3903 (10.9)	3686 (8.4)	1938 (7.6)	1016 (8.4)	1778 (9.9)	
Base model	1.00 (reference)	0.97 (0.91 to 1.02)	0.93 (0.87 to 0.99)	0.97 (0.89 to 1.05)	1.12 (1.03 to 1.21)	0.05
Minimally adjusted	1.00 (reference)	1.07 (1.01 to 1.15)	1.11 (1.03 to 1.20)	1.16 (1.05 to 1.28)	1.27 (1.14 to 1.41)	<0.001
Fully adjusted	1.00 (reference)	1.07 (1.01 to 1.14)	1.11 (1.03 to 1.21)	1.17 (1.05 to 1.29)	1.28 (1.15 to 1.42)	<0.001
Fully adjusted with medications	1.00 (reference)	1.08 (1.01 to 1.15)	1.12 (1.03 to 1.21)	1.18 (1.06 to 1.30)	1.29 (1.16 to 1.43)	<0.001
Total mortality						
No (%) events	2703 (7.6)	2289 (5.2)	1122 (4.4)	532 (4.4)	878 (4.9)	
Base model	1.00 (reference)	0.91 (0.85 to 0.97)	0.87 (0.80 to 0.95)	0.85 (0.76 to 0.96)	1.08 (0.97 to 1.20)	0.84
Minimally adjusted	1.00 (reference)	1.04 (0.96 to 1.13)	1.08 (0.97 to 1.20)	1.04 (0.91 to 1.19)	1.26 (1.09 to 1.45)	0.006
Fully adjusted	1.00 (reference)	1.04 (0.96 to 1.13)	1.09 (0.98 to 1.21)	1.05 (0.91 to 1.20)	1.27 (1.11 to 1.46)	0.004
Fully adjusted with medications	1.00 (reference)	1.05 (0.96 to 1.14)	1.09 (0.98 to 1.21)	1.05 (0.92 to 1.21)	1.28 (1.11 to 1.47)	0.003
Non-cardiovascular mortality						
No (%) events	1907 (5.4)	1564 (3.6)	812 (3.2)	375 (3.1)	530 (3.0)	
Base Model	1.00 (reference)	0.89 (0.83 to 0.97)	0.89 (0.81 to 0.99)	0.85 (0.74 to 0.97)	1.00 (0.88 to 1.14)	0.49
Minimally adjusted	1.00 (reference)	1.08 (0.98 to 1.19)	1.19 (1.05 to 1.35)	1.1 (0.94 to 1.30)	1.29 (1.08 to 1.53)	0.007
Fully adjusted	1.00 (reference)	1.08 (0.98 to 1.19)	1.19 (1.05 to 1.35)	1.12 (0.95 to 1.31)	1.31 (1.10 to 1.56)	0.004
Fully adjusted with medications	1.00 (reference)	1.08 (0.98 to 1.19)	1.20 (1.05 to 1.35)	1.12 (0.95 to 1.32)	1.31 (1.11 to 1.56)	0.003
Cardiovascular mortality						
No (%) events	904 (2.5)	851 (1.9)	358 (1.4)	179 (1.5)	384 (2.1)	
Base model	1.00 (reference)	0.94 (0.83 to 1.05)	0.8 (0.69 to 0.93)	0.83 (0.69 to 1.01)	1.20 (1.00 to 1.43)	0.32
Minimally adjusted	1.00 (reference)	0.99 (0.86 to 1.14)	0.85 (0.71 to 1.02)	0.91 (0.72 to 1.14)	1.18 (0.94 to 1.47)	0.40
Fully adjusted	1.00 (reference)	0.99 (0.86 to 1.14)	0.85 (0.71 to 1.02)	0.9 (0.72 to 1.13)	1.17 (0.94 to 1.47)	0.44
Fully adjusted with medications	1.00 (reference)	0.99 (0.86 to 1.14)	0.86 (0.71 to 1.02)	0.92 (0.73 to 1.15)	1.18 (0.95 to 1.48)	0.36
Major cardiovascular disease						
No (%) events	1774 (5.0)	2000 (4.5)	1127 (4.4)	654 (5.4)	1233 (6.9)	
Base model	1.00 (reference)	1.08 (1.00 to 1.17)	1.03 (0.94 to 1.13)	1.12 (1.00 to 1.25)	1.25 (1.12 to 1.39)	<0.001
Minimally adjusted	1.00 (reference)	1.11 (1.01 to 1.21)	1.13 (1.02 to 1.26)	1.25 (1.10 to 1.42)	1.32 (1.15 to 1.51)	<0.001
Fully adjusted	1.00 (reference)	1.11 (1.01 to 1.21)	1.13 (1.02 to 1.26)	1.26 (1.10 to 1.43)	1.33 (1.16 to 1.52)	<0.001
Fully adjusted with medications	1.00 (reference)	1.11 (1.02 to 1.21)	1.14 (1.03 to 1.27)	1.27 (1.12 to 1.45)	1.34 (1.17 to 1.53)	<0.001
Myocardial infarction						
No (%) events	874 (2.5)	983 (2.2)	485 (1.9)	229 (1.9)	360 (2.0)	
Base model	1.00 (reference)	1.08 (0.97 to 1.21)	1.01 (0.88 to 1.16)	1.02 (0.85 to 1.22)	1.08 (0.91 to 1.29)	0.66
Minimally adjusted	1.00 (reference)	1.10 (0.96 to 1.25)	1.07 (0.91 to 1.26)	1.13 (0.92 to 1.39)	1.14 (0.92 to 1.42)	0.25
Fully adjusted	1.00 (reference)	1.10 (0.96 to 1.25)	1.07 (0.91 to 1.25)	1.12 (0.91 to 1.38)	1.12 (0.90 to 1.39)	0.35
Fully adjusted with medications	1.00 (reference)	1.10 (0.96 to 1.25)	1.07 (0.91 to 1.26)	1.13 (0.92 to 1.39)	1.13 (0.91 to 1.40)	0.30
Stroke						
No (%) events	751 (2.1)	774 (1.8)	519 (2.0)	369 (3.0)	797 (4.4)	
Base model	1.00 (reference)	1.04 (0.93 to 1.17)	1.02 (0.89 to 1.17)	1.16 (0.99 to 1.36)	1.34 (1.15 to 1.57)	<0.001
Minimally adjusted	1.00 (reference)	1.08 (0.94 to 1.23)	1.13 (0.96 to 1.32)	1.28 (1.07 to 1.54)	1.44 (1.20 to 1.74)	<0.001
Fully adjusted	1.00 (reference)	1.07 (0.94 to 1.22)	1.13 (0.96 to 1.32)	1.29 (1.08 to 1.55)	1.47 (1.22 to 1.77)	<0.001
Fully adjusted with medications	1.00 (reference)	1.07 (0.94 to 1.22)	1.13 (0.97 to 1.32)	1.30 (1.09 to 1.56)	1.47 (1.22 to 1.78)	<0.001
Heart failure						
No (%) events	129 (0.4)	244 (0.6)	150 (0.6)	57 (0.5)	72 (0.4)	
Base model	1.00 (reference)	1.20 (0.94 to 1.52)	1.36 (1.04 to 1.77)	1.19 (0.83 to 1.69)	1.15 (0.81 to 1.65)	0.34
Minimally adjusted	1.00 (reference)	1.21 (0.92 to 1.59)	1.55 (1.13 to 2.12)	1.38 (0.92 to 2.07)	1.1 (0.71 to 1.72)	0.31
Fully adjusted	1.00 (reference)	1.22 (0.93 to 1.61)	1.59 (1.16 to 2.18)	1.43 (0.95 to 2.15)	1.16 (0.74 to 1.82)	0.22
Fully adjusted with medications	1.00 (reference)	1.22 (0.93 to 1.61)	1.60 (1.17 to 2.19)	1.46 (0.97 to 2.19)	1.17 (0.75 to 1.82)	0.19

*Cox frailty model. Base model: adjusted for age and sex, with centre as random effect; minimally adjusted: adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), vegetable and fruits, dairy, and red meats, with centre as random effect; fully adjusted: adjusted as for minimally adjusted plus whole grains, with centre as random effect; fully adjusted with medications: adjusted as for fully adjusted plus medications (statins and antihypertensives), with centre as random effect.
†Median (interquartile range (IQR) intake) 18.5 (7.0-32.9).
‡Median (IQR) intake 92.9 (72.0-118.9).
§Median (IQR) intake 185.9 (165.4-213.9).
¶Median (IQR) intake 300.0 (272.3-319.5).
**Median (IQR) intake 498.4 (450.0-675.0).

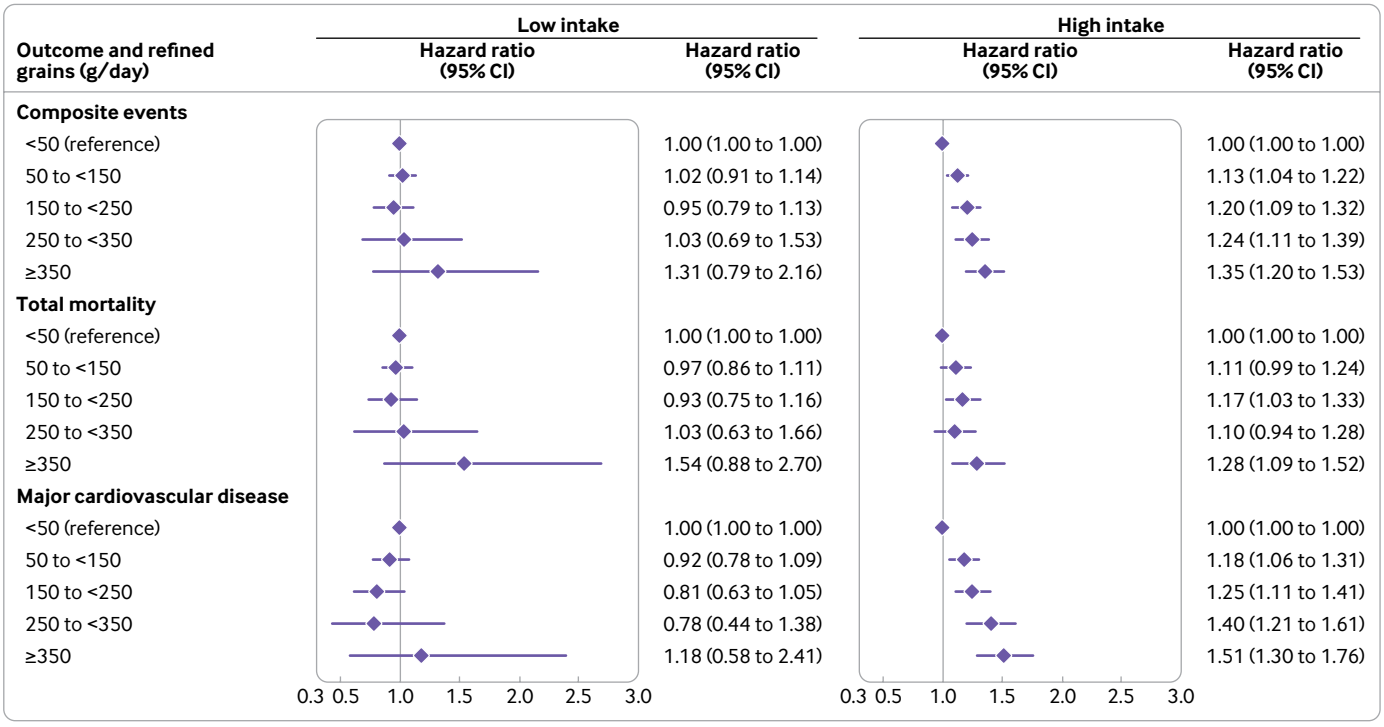

Fig 1 | Association between refined grain intake and clinical outcomes in high (n=102 075) and low (n=33 185) intake regions. Cox frailty model hazard ratios and 95% CIs in model fully adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), whole grains, vegetable and fruits, dairy, and red meats, with centre as random effect

We observed similar results when we used dry weight as measure of whole grain intake (supplementary table S11).

Higher intake of white rice (>450 g/day *v* <150 g/day) was not associated with any of the health outcomes in the fully adjusted models (table 4). Similar neutral associations existed between consumption of white rice and clinical events in Asian (high intake) and non-Asian (low intake) countries (P>0.05 for composite events, total mortality, and major cardiovascular disease; fig 2 and supplementary table 12; P for interaction>0.05). In both the base and minimally adjusted models, higher intakes (≥450 g/day) of white rice were associated with lower risk of composite events, total mortality, non-cardiovascular mortality and major cardiovascular disease.

The inclusion of sodium and saturated fat intake into the models did not change the results for any type of grain (supplementary tables S13-S15). Likewise, excluding participants who had cardiovascular disease events in the first two years of follow-up did not change the results (supplementary tables S16-S18). Multivariable splines showed significant linear associations of higher consumption of refined grains with total mortality but no significant associations between intake of whole grains or white rice and composite events, total mortality, and major cardiovascular disease (fig 3).

When we did a meta-analysis of region specific analyses, the overall associations between refined grain intake and clinical outcomes were not significant (hazard ratio 1.03 (0.96 to 1.09) for composite event (P for heterogeneity=0.001); 1.04 (0.98 to 1.10) for total mortality (P for heterogeneity=0.13); and 1.01 (0.89 to 1.12) for major cardiovascular disease (P for heterogeneity <0.001)), but we observed a significant positive association for all three outcomes for China (supplementary figure S1A). Even when we examined the association for a 50 g increase in intake of refined grain, we saw a positive effect in China for all the three outcomes but not overall for all regions (supplementary figure S1B). Intakes of whole grain and rice were not associated with any of the outcomes (supplementary figure S1C, S1D).

When we examined intakes of refined and whole grains as servings per day (supplementary table S19), we observed similar results for refined grains and whole grains. Stratified analyses by high, middle, and low income countries showed similar associations among all income regions (P for interaction>0.05) (supplementary tables S20-S22). By contrast, we found significant heterogeneity by region for white rice for composite outcome events (P=0.001), total mortality (P=0.02), and major cardiovascular disease (P=0.003), with rice intake associated with events in middle and low income countries but not in high income countries (where there were fewer participants).

In analyses stratified by body mass index (≥25 and <25) (supplementary figures S2-S4), we found stronger associations between refined grain intake and total mortality in the lower body mass index group (<25) than in the group with body mass index of 25 or above (P for interaction=0.001). For whole grains, the risk of total mortality was higher among participants with

Table 3 | Association between whole grain intake and clinical outcomes in participants (n=137 130) without baseline cardiovascular disease

	Hazard ratio (95% CI)*				
	0 (n=31 686)†	<50 g/d (n=45 112)‡	50 to <100 g/d (n=17 016)§	≥100 g/d (n=43 316)¶	P for trend
Composite events					
No (%) events	2717 (8.6)	4484 (9.9)	1455 (8.6)	4012 (9.3)	
Base model	1.15 (1.08 to 1.23)	1.08 (1.02 to 1.14)	1.04 (0.97 to 1.11)	1.00 (reference)	<0.001
Minimally adjusted	1.04 (0.97 to 1.12)	1.02 (0.96 to 1.09)	1.05 (0.98 to 1.13)	1.00 (reference)	0.37
Fully adjusted	1.03 (0.96 to 1.10)	1.01 (0.95 to 1.08)	1.05 (0.98 to 1.13)	1.00 (reference)	0.59
Fully adjusted with medications	1.03 (0.96 to 1.11)	1.01 (0.95 to 1.08)	1.05 (0.98 to 1.13)	1.00 (reference)	0.57
Total mortality					
No (%) events	1518 (4.8)	2892 (6.4)	840 (4.9)	2571 (5.9)	
Base model	1.17 (1.07 to 1.28)	1.06 (0.99 to 1.14)	0.99 (0.91 to 1.08)	1.00 (reference)	<0.001
Minimally adjusted	0.99 (0.90 to 1.09)	0.96 (0.88 to 1.04)	1.01 (0.92 to 1.11)	1.00 (reference)	0.54
Fully adjusted	0.97 (0.88 to 1.07)	0.95 (0.87 to 1.03)	1.00 (0.91 to 1.11)	1.00 (reference)	0.37
Fully adjusted with medications	0.97 (0.88 to 1.07)	0.95 (0.87 to 1.03)	1.00 (0.91 to 1.10)	1.00 (reference)	0.37
Non-cardiovascular mortality					
No (%) events	1030 (3.3)	2023 (4.5)	570 (3.4)	1783 (4.1)	
Base model	1.18 (1.07 to 1.31)	1.05 (0.96 to 1.14)	0.96 (0.86 to 1.06)	1.00 (reference)	0.003
Minimally adjusted	0.96 (0.86 to 1.08)	0.91 (0.83 to 1.00)	0.98 (0.87 to 1.09)	1.00 (reference)	0.25
Fully adjusted	0.94 (0.83 to 1.05)	0.89 (0.81 to 0.98)	0.96 (0.86 to 1.08)	1.00 (reference)	0.11
Fully adjusted with medications	0.94 (0.83 to 1.05)	0.89 (0.81 to 0.98)	0.96 (0.86 to 1.08)	1.00 (reference)	0.10
Cardiovascular mortality					
No (%) events	557 (1.8)	1008 (2.2)	300 (1.8)	912 (2.1)	
Base model	1.17 (1.02 to 1.35)	1.09 (0.96 to 1.23)	1.03 (0.89 to 1.19)	1.00 (reference)	0.03
Minimally adjusted	1.06 (0.91 to 1.24)	1.06 (0.92 to 1.21)	1.02 (0.86 to 1.2)	1.00 (reference)	0.40
Fully adjusted	1.07 (0.91 to 1.26)	1.07 (0.93 to 1.23)	1.02 (0.87 to 1.21)	1.00 (reference)	0.34
Fully adjusted with medications	1.07 (0.91 to 1.26)	1.07 (0.93 to 1.23)	1.02 (0.86 to 1.21)	1.00 (reference)	0.33
Major cardiovascular disease					
No (%) events	1618 (5.1)	2243 (5.0)	853 (5.0)	2184 (5.0)	
Base model	1.11 (1.02 to 1.20)	1.05 (0.98 to 1.13)	1.06 (0.98 to 1.16)	1.00 (reference)	0.03
Minimally adjusted	1.04 (0.95 to 1.14)	1.04 (0.96 to 1.13)	1.07 (0.97 to 1.17)	1.00 (reference)	0.37
Fully adjusted	1.04 (0.95 to 1.14)	1.04 (0.96 to 1.13)	1.07 (0.97 to 1.17)	1.00 (reference)	0.41
Fully adjusted with medications	1.05 (0.95 to 1.15)	1.04 (0.96 to 1.12)	1.06 (0.97 to 1.17)	1.00 (reference)	0.38
Myocardial infarction					
No (%) events	651 (2.1)	1038 (2.3)	392 (2.3)	918 (2.1)	
Base model	1.12 (0.98 to 1.28)	1.03 (0.92 to 1.16)	1.12 (0.98 to 1.28)	1.00 (reference)	0.21
Minimally adjusted	1.12 (0.97 to 1.30)	1.09 (0.96 to 1.23)	1.14 (0.99 to 1.32)	1.00 (reference)	0.16
Fully adjusted	1.12 (0.97 to 1.31)	1.08 (0.95 to 1.23)	1.14 (0.99 to 1.32)	1.00 (reference)	0.18
Fully adjusted with medications	1.13 (0.97 to 1.31)	1.08 (0.95 to 1.23)	1.14 (0.99 to 1.32)	1.00 (reference)	0.18
Stroke					
No (%) events	852 (2.7)	950 (2.1)	383 (2.3)	1042 (2.4)	
Base model	1.14 (1.01 to 1.27)	1.05 (0.94 to 1.16)	1.03 (0.91 to 1.16)	1.00 (reference)	0.04
Minimally adjusted	1.06 (0.93 to 1.20)	1.01 (0.90 to 1.13)	1.02 (0.90 to 1.16)	1.00 (reference)	0.44
Fully adjusted	1.05 (0.93 to 1.19)	1.00 (0.89 to 1.12)	1.01 (0.88 to 1.15)	1.00 (reference)	0.51
Fully adjusted with medications	1.06 (0.93 to 1.19)	1.00 (0.89 to 1.12)	1.01 (0.88 to 1.15)	1.00 (reference)	0.47
Heart failure					
No (%) events	109 (0.3)	243 (0.5)	99 (0.6)	205 (0.5)	
Base model	0.86 (0.65 to 1.14)	1.14 (0.91 to 1.44)	1.21 (0.93 to 1.56)	1.00 (reference)	0.53
Minimally adjusted	0.77 (0.56 to 1.06)	1.18 (0.92 to 1.53)	1.25 (0.94 to 1.66)	1.00 (reference)	0.30
Fully adjusted	0.75 (0.55 to 1.04)	1.19 (0.92 to 1.54)	1.27 (0.95 to 1.69)	1.00 (reference)	0.25
Fully adjusted with medications	0.76 (0.55 to 1.04)	1.19 (0.92 to 1.54)	1.27 (0.95 to 1.69)	1.00 (reference)	0.26

*Cox frailty model. Base model: adjusted for age and sex, with centre as random effect; minimally adjusted: adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), vegetable and fruits, dairy, and red meats, with centre as random effect; fully adjusted: adjusted as for minimally adjusted plus whole grains, with centre as random effect; fully adjusted with medications: adjusted as for fully adjusted plus medications (statins and antihypertensives), with centre as random effect.
†Median (interquartile range (IQR)) intake 0.0 (0.0-0.0).
‡Median (IQR) intake 17.3 (9.2-31.3).
§Median (IQR) intake 73.6 (62.0-84.2).
¶Median (IQR) intake 226.8(154.3-362.2).

higher body mass index (P for interaction=0.043). We found similar associations between grains and events by geographical region and by sex (P for interaction>0.05). Mean systolic and diastolic blood pressure was significantly higher among participants with higher refined grain intake (supplementary tables S23-S25). For lipids, we found no clinically relevant differences in lipid concentrations with higher grain intake.

Table 5 shows the amount of macronutrient provided by white bread, whole wheat bread, cooked rice, and other intact grains. In the PURE study, we found white bread to be the main source of carbohydrates. Mean daily energy intake of PURE participants was about 2100 kcal/day, of which white bread was the main source. Because three servings of white bread contribute about 10% of total daily energy intake, we estimated the effect of a 10%

Table 4 | Association between white rice intake and clinical outcomes in participants (n=137 130) without baseline cardiovascular disease

	Hazard ratio (95% CI)*					
	<50 g/d (n=38 022)†	50-150 g/d (n=35 617)‡	150-300 g/d (n=16 230)§	300-450 g/d (n=16 045)¶	≥450 g/d (n=31 216)**	P for trend
Composite events						
No (%) events	3437 (9.0)	2826 (7.9)	1393 (8.6)	1436 (9.0)	3576 (11.5)	
Base model	1.00 (reference)	0.89 (0.85 to 0.95)	0.84 (0.78 to 0.90)	0.84 (0.78 to 0.92)	0.79 (0.72 to 0.86)	<0.001
Minimally adjusted	1.00 (reference)	1.00 (0.93 to 1.06)	0.97 (0.89 to 1.06)	0.95 (0.86 to 1.04)	0.87 (0.79 to 0.96)	0.01
Fully adjusted	1.00 (reference)	1.01 (0.94 to 1.07)	1.01 (0.93 to 1.11)	0.98 (0.89 to 1.08)	0.97 (0.86 to 1.08)	0.58
Fully adjusted with medications	1.00 (reference)	1.01 (0.95 to 1.08)	1.01 (0.92 to 1.11)	0.98 (0.89 to 1.08)	0.96 (0.86 to 1.08)	0.55
Total mortality						
No (%) events	2114 (5.6)	1698 (4.8)	784 (4.8)	867 (5.4)	2358 (7.6)	
Base model	1.00 (reference)	0.85 (0.79 to 0.91)	0.77 (0.70 to 0.85)	0.81 (0.72 to 0.90)	0.77 (0.69 to 0.86)	<0.001
Minimally adjusted	1.00 (reference)	0.95 (0.87 to 1.04)	0.89 (0.79 to 1.00)	0.91 (0.80 to 1.03)	0.81 (0.71 to 0.93)	0.004
Fully adjusted	1.00 (reference)	0.96 (0.88 to 1.05)	0.93 (0.82 to 1.05)	0.95 (0.83 to 1.08)	0.90 (0.78 to 1.04)	0.18
Fully adjusted with medications	1.00 (reference)	0.96 (0.89 to 1.05)	0.93 (0.82 to 1.05)	0.94 (0.83 to 1.07)	0.90 (0.78 to 1.04)	0.17
Non-cardiovascular mortality						
No (%) events	1527 (4.0)	1191 (3.3)	513 (3.2)	570 (3.6)	1605 (5.1)	
Base model	1.00 (reference)	0.84 (0.77 to 0.91)	0.73 (0.65 to 0.83)	0.80 (0.70 to 0.91)	0.73 (0.64 to 0.83)	<0.001
Minimally adjusted	1.00 (reference)	0.93 (0.84 to 1.03)	0.86 (0.74 to 0.99)	0.87 (0.75 to 1.01)	0.74 (0.63 to 0.86)	<0.001
Fully adjusted	1.00 (reference)	0.94 (0.85 to 1.04)	0.90 (0.78 to 1.04)	0.91 (0.78 to 1.07)	0.82 (0.69 to 0.98)	0.05
Fully adjusted with medications	1.00 (reference)	0.94 (0.85 to 1.04)	0.90 (0.78 to 1.04)	0.91 (0.78 to 1.07)	0.82 (0.69 to 0.98)	0.05
Cardiovascular mortality						
No (%) events	659 (1.7)	605 (1.7)	319 (2.0)	338 (2.1)	856 (2.7)	
Base model	1.00 (reference)	0.86 (0.76 to 0.97)	0.86 (0.74 to 1.01)	0.86 (0.72 to 1.02)	0.91 (0.76 to 1.08)	0.23
Minimally adjusted	1.00 (reference)	1.03 (0.89 to 1.19)	0.99 (0.82 to 1.2)	0.99 (0.81 to 1.21)	1.00 (0.81 to 1.24)	0.97
Fully adjusted	1.00 (reference)	1.04 (0.90 to 1.21)	1.03 (0.84 to 1.25)	1.02 (0.83 to 1.26)	1.09 (0.86 to 1.38)	0.59
Fully adjusted with medications	1.00 (reference)	1.05 (0.91 to 1.22)	1.02 (0.84 to 1.24)	1.02 (0.83 to 1.25)	1.09 (0.85 to 1.38)	0.62
Major cardiovascular disease						
No (%) events	1925 (5.1)	1598 (4.5)	851 (5.2)	824 (5.1)	1700 (5.5)	
Base model	1.00 (reference)	0.93 (0.86 to 1.00)	0.90 (0.81 to 0.99)	0.86 (0.77 to 0.95)	0.79 (0.70 to 0.89)	<0.001
Minimally adjusted	1.00 (reference)	1.01 (0.93 to 1.10)	0.99 (0.89 to 1.11)	0.93 (0.82 to 1.05)	0.87 (0.76 to 0.99)	0.05
Fully adjusted	1.00 (reference)	1.02 (0.94 to 1.11)	1.04 (0.93 to 1.16)	0.98 (0.86 to 1.10)	0.97 (0.84 to 1.13)	0.70
Fully adjusted with medications	1.00 (reference)	1.03 (0.95 to 1.12)	1.03 (0.92 to 1.15)	0.97 (0.86 to 1.10)	0.97 (0.83 to 1.12)	0.63
Myocardial infarction						
No (%) events	832 (2.2)	670 (1.9)	380 (2.3)	337 (2.1)	780 (2.5)	
Base model	1.00 (reference)	0.92 (0.82 to 1.03)	0.98 (0.84 to 1.14)	0.82 (0.69 to 0.97)	0.72 (0.60 to 0.86)	0.001
Minimally adjusted	1.00 (reference)	0.99 (0.87 to 1.13)	1.07 (0.90 to 1.27)	0.86 (0.71 to 1.05)	0.84 (0.69 to 1.04)	0.10
Fully adjusted	1.00 (reference)	0.99 (0.87 to 1.13)	1.06 (0.89 to 1.27)	0.86 (0.70 to 1.04)	0.81 (0.64 to 1.02)	0.08
Fully adjusted with medications	1.00 (reference)	1.00 (0.87 to 1.14)	1.06 (0.89 to 1.26)	0.85 (0.70 to 1.04)	0.81 (0.64 to 1.02)	0.07
Stroke						
No (%) events	891 (2.3)	735 (2.1)	395 (2.4)	407 (2.5)	799 (2.6)	
Base model	1.00 (reference)	0.90 (0.81 to 1.00)	0.81 (0.71 to 0.94)	0.85 (0.73 to 0.99)	0.81 (0.69 to 0.96)	0.008
Minimally adjusted	1.00 (reference)	0.96 (0.86 to 1.08)	0.90 (0.77 to 1.05)	0.91 (0.77 to 1.08)	0.85 (0.71 to 1.02)	0.09
Fully adjusted	1.00 (reference)	0.99 (0.88 to 1.11)	0.98 (0.83 to 1.15)	1.03 (0.86 to 1.22)	1.08 (0.88 to 1.33)	0.57
Fully adjusted with medications	1.00 (reference)	1.00 (0.89 to 1.12)	0.97 (0.83 to 1.14)	1.02 (0.85 to 1.21)	1.08 (0.87 to 1.32)	0.62
Heart failure						
No (%) events	193 (0.5)	198 (0.6)	75 (0.5)	79 (0.5)	111 (0.4)	
Base model	1.00 (reference)	1.20 (0.95 to 1.51)	1.11 (0.80 to 1.53)	1.14 (0.81 to 1.60)	1.03 (0.70 to 1.52)	0.75
Minimally adjusted	1.00 (reference)	1.44 (1.11 to 1.87)	1.26 (0.87 to 1.81)	1.28 (0.88 to 1.86)	1.00 (0.64 to 1.55)	0.73
Fully adjusted	1.00 (reference)	1.46 (1.120 to 1.89)	1.30 (0.90 to 1.88)	1.30 (0.89 to 1.91)	1.11 (0.69 to 1.78)	0.44
Fully adjusted with medications	1.00 (reference)	1.47 (1.13 to 1.92)	1.30 (0.90 to 1.87)	1.30 (0.89 to 1.90)	1.12 (0.70 to 1.79)	0.44

*Cox frailty model. Base model: adjusted for age and sex, with centre as random effect; minimally adjusted: adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), vegetable and fruits, dairy, and red meats, with centre as random effect; fully adjusted: adjusted as for minimally adjusted plus whole grains, with centre as random effect; fully adjusted with medications: adjusted as for fully adjusted plus medications (statins and antihypertensives), with centre as random effect.
†Median (interquartile range (IQR) intake) 20.0 (8.2-28.0).
‡Median (IQR) intake 84.6 (67.7-114.3).
§Median (IQR) intake 200 (171.4-214.3).
¶Median (IQR) intake 395.0 (327.5-400.0).
**Median (IQR) intake 863.1 (608.2-988.8).

increase in refined carbohydrate consumption on risk of mortality and other outcomes. For every 200 kcal increase in carbohydrate, the risk of mortality increased by about 3% (table 6). A 200 kcal increase through consumption of white bread was also associated with a higher risk of mortality.

Discussion

In this large prospective study from 21 countries, we found that higher intakes of refined grains were associated with higher risks of mortality, non-cardiovascular mortality, major cardiovascular disease, stroke, and composite outcomes. We did

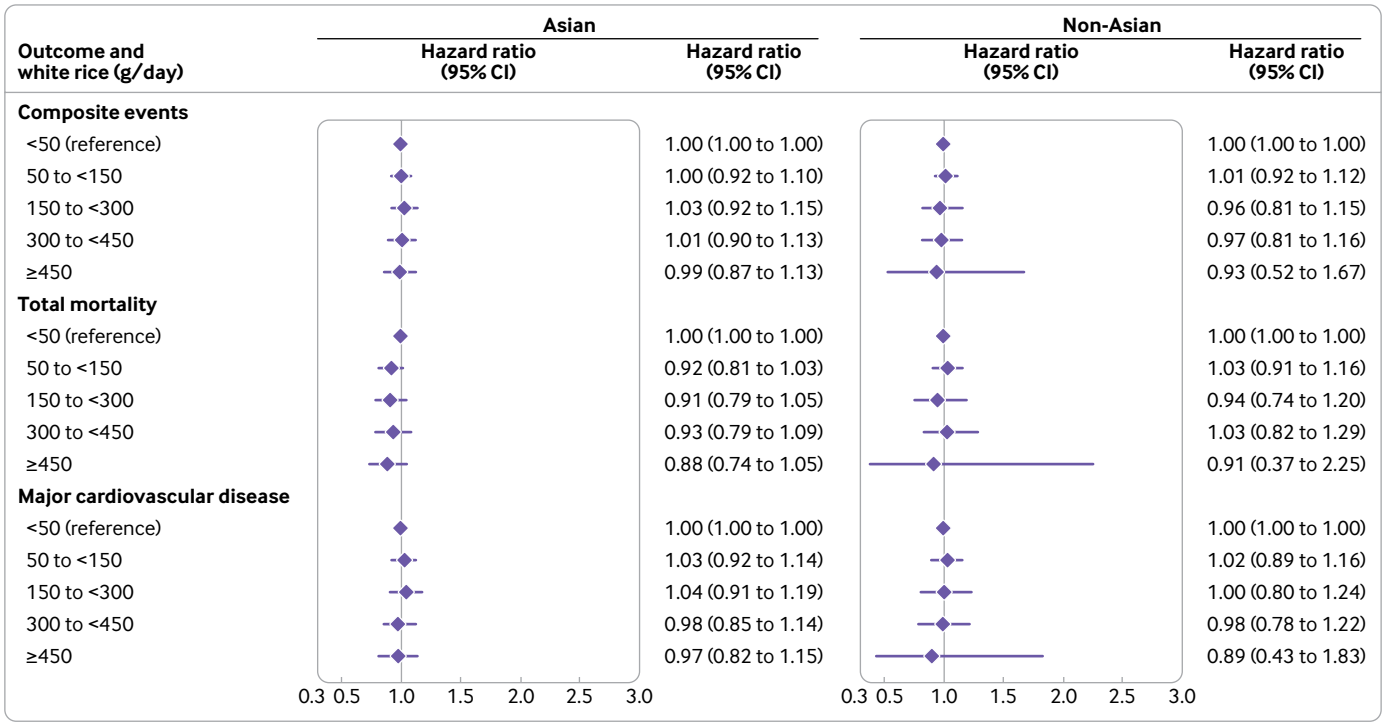

Fig 2 | Association between white rice intake and clinical outcomes in Asian (n=82 652) and non-Asian countries (n=54 478). Cox frailty model hazard ratios and 95% CIs in model fully adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), refined grains, whole grains, vegetable and fruits, dairy, and red meats, with centre as random effect.

not find significant associations of consumption of whole grains or white rice with total mortality and cardiovascular outcomes.

Comparison with other studies

The association of refined grains with outcomes of all cause and cause specific mortality has been explored previously. Schwingshackl et al,[13] in a meta-analysis of four prospective studies with 11 034 mortality events, showed no association of high versus low intake of refined grains (intake range 0-183 g/day) with all cause mortality. The PURE study includes participants with a broad range of intakes, as it included countries across multiple regions. Previous cohort studies have shown an increased risk of coronary heart disease with higher intake of refined grains, and the association was observed in female participants.[14] In a meta-analysis involving 711 728 participants and 16 144 events on the effects of refined grain including white rice, intake varied from 15 g to 540 g/day.[11] Comparing high versus low intakes, this study reported a higher risk of coronary heart disease. Some previous studies have included white rice in the refined grain group, but we did not include rice in the refined grains group in PURE. The fact that a 200 kcal increase through the intake of white bread was associated with a greater risk of cardiovascular mortality in our population reaffirms the findings of our analyses.

Refined grains have lower dietary fibre content, vitamins and minerals, essential fatty acids, and phytochemicals, largely owing to loss of the outer bran layer and the endosperm of the grain being pounded during the process of refining. As a consequence of the refining process, rapid action by digestive enzymes and quick absorption from the small intestines could lead to an increase in post-prandial blood glucose concentrations.[30 31] The rise in glucose concentrations increases the insulin concentrations, which leads to hypoglycaemia, lipolysis, and the stimulation of hunger and food intake.[14] A review that investigated the association of bread intake with obesity and abdominal fat reported that reduction in white bread intake in a Mediterranean-style dietary pattern resulted in lower weight gain and abdominal fat gain. This might have happened as a result of a reduction in intake of a food with higher energy density and glycaemic index and lower dietary fibre,[32] and higher consumption of fruits and vegetables.

When we did a meta-analysis of the PURE data by regions, the association of refined grains with clinical outcomes was apparent in China but not in other regions. This difference might have been due to the highest refined grain intakes in China compared with other regions, along with a wide range of intakes reported. Longitudinal trends have indicated an increase in consumption of refined grains in China.[33 34] A change from a traditional rice based pattern to a modern dietary pattern has been seen, which included increasing wheat intakes. Wheat intake in China has been steadily increasing over two decades (1991-2011) and has been positively associated with risk of cardiovascular disease.[35] The level of refinement of

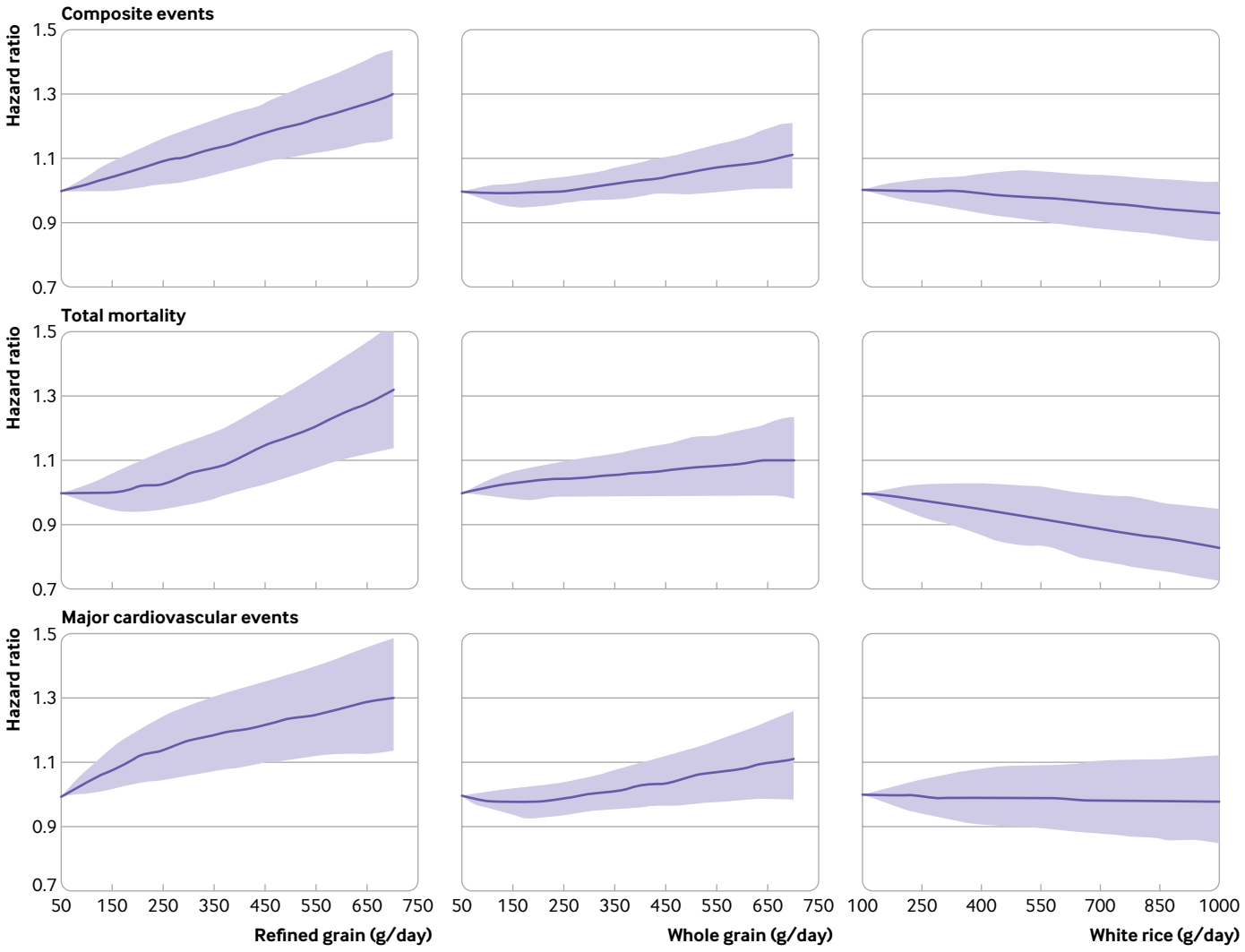

Fig 3 | Association between intake of refined grain (n=135 260), whole grain (n=135 096), and white rice (n=137 130) and clinical outcomes of composite events, total mortality, and major cardiovascular disease for every 50 g increase in intake. Multivariable fully adjusted model adjusted for age, sex, location (urban/rural), wealth index, education, smoking, waist-hip ratio, physical activity, history of diabetes, and daily intakes of energy (kcal), refined grains, whole grains, vegetable and fruits, dairy, and red meats, with centre as random effect

wheat and intake of refined wheat, however, has not been reported in previous studies.

We did not find a significant association between whole grain consumption and health outcomes. In the Atherosclerosis Risk in Communities (ARIC) study,[36] involving 11 940 people and 2539 events (total mortality 867; coronary artery disease 535; stroke 270), whole grain intakes were inversely associated with total mortality and incident coronary artery disease but not with stroke. Also, inverse associations of whole grain intake with total and cardiovascular mortality have been reported in a few meta-analyses[7 9 12 37-42] (the largest involving 1 041 692 participants and 96 710 events). In the meta-analysis by Wei et al,[7] which included 816 599 participants and 89 251 events, each three servings per day increase in whole grain intake was associated with 19% and 26% lower risk of mortality and cardiovascular mortality, respectively. Such associations were not evident in our study.

Several possible reasons exist for the lack of an association between whole grains and cardiovascular disease or mortality observed in our study. Firstly, no standard definition for whole grains exists, and the definition varies between countries. For example, the whole grain breads in different regions in Europe, North America, and South America have different amounts of whole grain added. Most products commercially available in retail stores that are termed whole grain foods are reconstituted or recombined to various extents.[1 36 43] Secondly, whole grains purportedly contain biologically active compounds, such as dietary fibre, vitamins, minerals, antioxidants, and other plant compounds such as lignans and phytosterols, which are removed during processing.[14 43-45] The health benefits are also attributed to their uniqueness in phytochemical composition, with some being in the bound (soluble, conjugated, or insoluble) form and others in the unbound or free form, with the bound form contributing the most to antioxidant

Table 5 | Cooked portions of grains and their relative percentage energy contribution as carbohydrate*

Foods	Portion size (~100 g)	Per 100 g			% energy consumption from carbohydrate in PURE population
		Energy (kcal)	Carbohydrate (g)	Water (g)	
White bread	3-4 slices	263	49	36	35
Whole wheat bread	3-4 slices	240	41	39	11
Other whole grains, cooked	1 cup	160	18	78	8
White rice, cooked	0.5 cup	130	28	69	26

*Values taken from US Department of Agriculture National Nutrient Database for Standard Reference Legacy Release April 2018 (https://data.nal.usda.gov/dataset/usda-national-nutrient-database-standard-reference-legacy-release).

activity, reducing oxidative stress.[1 43] These biological compounds may affect cardiovascular risk by altering glucose homoeostasis, lipids and lipoproteins, endothelial function, and some other mechanisms.[9] The amount of these biological compounds may vary depending on the type of whole grains. Thirdly, plant genetics and a variety of agro-climatic factors influence the content of phytochemicals present in whole grains.[43] Fourthly, the physiological mechanism through which dietary carbohydrates influence health is thought to be via their effect on glycaemic responses,[46] which vary by type of grain and particle size. This indicates that associations between whole grain intake and health outcomes are very complex and could be heterogeneous. Fifthly, whole grains are often consumed with sugar, negating much of the benefit of whole grains.[45] In our study, which was conducted in 21 countries, a variety of whole grains was consumed, and this may have obscured true associations with a specific form of whole grain.

A limited number of studies have examined the association of rice intake with total or cardiovascular mortality or cardiovascular events. A Japanese study showed a protective effect for cardiovascular disease, but only in men.[47] By contrast, in a cohort of 117 366 Chinese men and women, 40-74 years of age, with a mean follow-up of 9.8 years and 309 events, Yu et al reported a hazard ratio of 1.80 (95% confidence interval 1.01 to 3.17) for highest versus lowest quarter of intake of rice and refined wheat grain, as a combined category, for coronary heart disease.[48] In a recent meta-analysis (14 306 mortality events), an inverse association between consumption of rice and mortality among men (relative risk 0.87, 0.81 to 0.94) and a positive association among women were reported.[49] Two other meta-analysis (including 207 556 to 1 777 059 participants and 12 391 to 22 537 events) reported no associations between rice consumption and cardiovascular mortality.[50 51] Muraki et al examined the association between white and brown rice consumption and risk of cardiovascular disease in three US cohorts and reported no association, similar to our findings.[50] One probable reason for a higher risk of cardiovascular disease with higher rice intake was attributed to arsenic content in soil and during irrigation which is probably removed by polishing rice. Our study included participants from several countries where various varieties of rice were eaten. The composition of and physiological responses to different kinds of rice vary. Variations in glycaemic and insulinaemic responses have been reported, which could be due to differences in the characteristics of starch (for example, amylase to amylopectin ratio), in cultivated varieties, and in post-harvest technologies used, as well as the differences in cooking across the world.[52] Another reason for the inconsistent association seen between rice consumption and outcomes may be the effect of complementary dishes that are consumed along with rice.[49] Caution must be exercised, however, so that high intakes of rice are not advocated indiscriminately without ensuring that total carbohydrate intakes are within the limits of the acceptable macronutrient distribution range.

The reason for the different associations observed with refined grains and white rice is not clear. However, refined wheat is uniformly and rapidly digested and raises blood glucose, with none of the health advantages of fibre. Varieties of rice such as long grain rice and especially parboiled white rice may have both a definite glycaemic advantage and an overall nutritional advantage over refined wheat products. Also, depending on the culture and the nature of the rice eaten, rice may be displacing less desirable foods. Other differences in chemical composition and physical properties could exist, which might contribute to the associations seen.

Strengths and limitations of study

Our study has some strengths and some potential limitations. With data from 21 countries across five continents being used for this analysis, diverse patterns of diet and a broad range of consumption have been characterised, and the results are likely to have wider generalisability than those of a study conducted in a single country. We considered extensive covariates during analysis. The addition of medications in the model did not change the results, indicating that our findings were robust. In addition to centre, location

Table 6 | Risk of mortality by 200 kcal increase in energy from various sources of carbohydrate

Foods (100 g)	Portion size	Hazard ratio (95% CI)	P value
% energy from carbohydrate	-	1.03 (1.00 to 1.05)	<0.001
White bread	3 slices	1.05 (1.03 to 1.07)	<0.001
Whole wheat bread	3 slices	1.01 (0.98 to 1.03)	0.15
Rice, cooked	1 cup	0.98 (0.96 to 1.00)	0.12

(urban/rural), and income level of countries, we have controlled for variation in socioeconomic status by adjusting for education and wealth index, which are strong predictors of socioeconomic status (for example, deprivation or poverty), as countries at varying levels of nutrition transition (that is, shifts in diet and physical activity occurring because of demographic, economic, and epidemiological changes and globalisation) participated in the PURE study.

Although we recognise that desserts and pastries include both sugar and cereal grains, the sugar content was not accounted for in mixed dishes. Sweets, however, include other food groups in the recipe, so the effect of added sugars in cereal foods alone cannot be assessed. The intake of the various food groups by the categories of refined and whole grain intake (supplementary tables S26 and S27) does not indicate an increase in added sugar intake with increasing categories of intake. A similar pattern persisted for intake of the other food groups as well. With many known confounders accounted for, the observed associations might still be partly due to residual confounding factors. Furthermore, food frequency questionnaires do not capture absolute intakes, only relative intakes. However, dietary data collected in epidemiological studies provide estimates of food or nutrient intake that are useful for grouping individuals by their relative levels of intake of a food but not their absolute levels. This may underestimate the relation of diet and events. In PURE, diets were recorded comprehensively only at baseline and changes in diet may have occurred over the subsequent years. This would also tend to attenuate the associations with outcomes. However, in a previous analysis of PURE relating the consumption of fruits and vegetables to outcomes, similar associations were obtained by recording diet at baseline and at three years.[17] In the PURE study, data were 99.5% complete for all variables, except for waist to hip ratio and physical activity. The completeness was 94% for waist to hip ratio and 93% for physical activity. We recognise that missingness may introduce bias, reduce power, and/or affect the representativeness of the results. This is unlikely to be the case here, as the percentage with missing data was low for such large cohort study. We did a series of sensitivity analyses to check whether the missing data on these two covariates might have been non-random. Firstly, we excluded waist to hip ratio and physical activity from the multivariable models and found that the estimates for associations of refined grains, whole grains, and rice with outcomes were consistent. Additionally, we excluded the six countries that had missing data exceeding 10% on either of the two covariates and estimates were unchanged. This indicates that the missingness in our study had little effect on our results.

We acknowledge that repeated measures may improve precision of estimates, but we do not have repeated dietary measurements in PURE. Large observational studies have shown that four different approaches for analysing the association of dietary fats with coronary heart disease using repeated dietary measurements (baseline diet only, most recent diet, and two different algorithms for calculating cumulative average diets) yield substantively similar results.[53] On the basis of these data by Hu et al, we are confident that over a relatively short follow-up (<10 years), the substantive estimates would not differ with repeated measures. A further limitation was that the dry weight of whole grain was approximately calculated for each region and not for each food item in the respective country items in the food list. We acknowledge this limitation, which might attenuate the association between whole grain and outcomes. Globally, however, we see that in the culture specific questionnaires, most whole grains are consumed in hydrated form as breads, pancake-like foods, and thick oat and maize porridges.

Conclusions and policy implications

Our study from 21 countries showed that higher intake of refined grains was associated with higher risk of total mortality and major cardiovascular events. We observed no significant association between intake of whole grains or white rice and clinical outcomes. Intakes of a combination of cereal grains with a lower intake of refined wheat products should be encouraged while promoting a higher intake of whole grains. Reduction in quantity and improvement in quality of carbohydrate is essential for better health outcomes.

AUTHOR AFFILIATIONS

[1]St John's Research Institute, Bangalore, India
[2]Population Health Research Institute (PHRI), McMaster University, Hamilton Health Sciences, Hamilton, ON, Canada
[3]St John's Medical College, Bangalore, India
[4]Department of Nutritional Sciences and [4]Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[5]Madras Diabetes Research Foundation and Dr Mohan's Diabetes Specialities Centre, Chennai, India
[6]Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada
[7]International Research Centre, Hospital Alemao Oswaldo Cruz, Sao Paulo, Brazil, Universidade Santo Amaro (UNISA), Sao Paulo, Brazil
[8]Masira Research Institute, Medical School, Santander University (UDES), Colombia
[9]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[10]Sahlgrenska University Hospital, Gothenburg, Sweden
[11]Universidad de La Frontera, Temuco, Chile
[12]Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[13]University of Philippines, Section of Adult Medicine and Medical Research Unit, Manila, Philippines
[14]Department of Internal Medicine, Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey
[15]University of the Western Cape, Bellville, South Africa
[16]Health Action by People, Thiruvananthapuram, Kerala, India
[17]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India
[18]National Centre for Cardiovascular Diseases, Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, China
[19]Wroclaw Medical University, Department of Social Medicine, Wroclaw, Poland
[20]Estudios Clinicos Latinoamerica ECLA, Rosario, Santa Fe, Argentina

[21]Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[22]Physiology Department, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe
[23]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[24]Dubai Medical University, Hatta Hospital, Dubai Health Authority, Dubai, United Arab Emirates
[25]Institute for Community and Public Health, Birzeit University, Birzeit, Palestine
[26]Advocate Research Institute, Advocate Health Care, Illinois, USA
[27]Departments of Community Health Sciences and Medicine, Aga Khan University, Karachi, Pakistan
[28]School of Life Sciences, Independent University, Bangladesh, Dhaka, Bangladesh
[29]Department of Medicine, Queen's University, Kingston, ON, Canada
[30]New York University, College of Global Public Health, NY, USA

We thank all the participants in all countries who have willingly participated in the study and contributed to its results. We appreciate the contributions of Andrew Mente in the final interpretations of the data.

Contributors: SY conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct, and reviewed and commented on the draft. SS drafted and revised the manuscript and interpreted the analyses. MD coordinated the entire nutrition component of the PURE study. SR coordinated the worldwide study and reviewed and commented on drafts. JMR and TT did all data analyses and interpreted the data. All other authors coordinated the study in their respective countries, provided comments on drafts of the manuscript, and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SY is the guarantor.

Funding: SY is supported by the Marion W Burke endowed chair of the Heart and Stroke Foundation of Ontario. The PURE study is an investigator initiated study that is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute (HHSRI), the Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Ontario, with support from the Canadian Institutes of Health Research's Strategy for Patient Oriented Research, through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long term Care, and through unrestricted grants from several pharmaceutical companies (with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier, and GlaxoSmithKline) and additional contributions from Novartis and King Pharma and from various national or local organisations in participating countries. These include Argentina: Fundacion ECLA (Estudios Clínicos Latino America); Bangladesh: Independent University, Bangladesh, and Mitra and Associates; Brazil: Unilever Health Institute, Brazil; Canada: unrestricted grant from Dairy Farmers of Canada and the National Dairy Council (US), Public Health Agency of Canada, and Champlain Cardiovascular Disease Prevention Network; Chile: Universidad de La Frontera (DI13-PE11); China: National Center for Cardiovascular Diseases and ThinkTank Research Center for Health Development; Colombia: Colciencias (grant 6566-04-18062 and grant 6517-777-58228); India: Indian Council of Medical Research; Malaysia: Ministry of Science, Technology and Innovation of Malaysia (grant number: 100-IRDC/BIOTEK 16/6/21 [13/2007], and 07-05-IFN-BPH 010), Ministry of Higher Education of Malaysia (grant number: 600-RMI/LRGS/5/3 [2/2011]), Universiti Teknologi MARA, Universiti Kebangsaan Malaysia (UKM-Hejim-Komuniti-15-2010); occupied Palestinian territory: the United Nations Relief and Works Agency for Palestine Refugees in the Near East, International Development Research Centre, Canada; Philippines: Philippine Council for Health Research and Development; Poland: Polish Ministry of Science and Higher Education (grant number: 290/W-PURE/2008/0), Wroclaw Medical University; Saudi Arabia: Saudi Heart Association, Saudi Gastroenterology Association, Dr Mohammad Alfagih Hospital, the Deanship of Scientific Research at King Saud University, Riyadh, (research group number: RG-1436-013); South Africa: North-West University, Netherlands Programme for Alternative Development, National Research Foundation, Medical Research Council of South Africa, South Africa Sugar Association, Faculty of Community and Health Sciences; Sweden: grants from the Swedish state under the agreement concerning research and education of doctors, the Swedish Heart and Lung Foundation, the Swedish Research Council, the Swedish Council for Health, Working Life and Welfare, King Gustaf V's and Queen Victoria Freemason's Foundation, AFA Insurance; Turkey: Metabolic Syndrome Society, AstraZeneca, Sanofi Aventis; United Arab Emirates: Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences, Dubai Health Authority, Dubai. The external funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. Please refer to the supplementary material for a list of PURE project office staff, national coordinators, investigators, and key staff.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support for the study as detailed above; no financial relationships with any organisations 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: Institutional ethical approvals were obtained at each site. Written informed consent was obtained from all participants.

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of the PURE study are disseminated through press releases issued from each of the participating institutions in each of the 21 countries and through use of social media.

Data sharing: Data described in the manuscript and the analytical code will be made available during PURE study conduct only to the investigators who have participated in/contributed to the study. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by non-contributing individuals three years after the study has been completed (that is, complete recruitment and a minimum of 10 years' follow-up in all) and the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will need to be met by anybody not contributing to the study and requesting analyses.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Adom KK, Liu RH. Antioxidant activity of grains. *J Agric Food Chem* 2002;50:6182-7. doi:10.1021/jf0205099
2 Develaraja S, Reddy A, Yadav M, Jain S, Yadav H. Whole grains in amelioration of metabolic derangements. *J Nutrit Health Food Sci* 2016;4:1-11. doi:10.15226/jnhfs.2016.00173
3 Anand SS, Hawkes C, de Souza RJ, et al. Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. *J Am Coll Cardiol* 2015;66:1590-614. doi:10.1016/j.jacc.2015.07.050
4 Dehghan M, Mente A, Zhang X, et al, Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 2017;390:2050-62. doi:10.1016/S0140-6736(17)32252-3
5 Ho FK, Gray SR, Welsh P, et al. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. *BMJ* 2020;368:m688. doi:10.1136/bmj.m688
6 Kearney J. Food consumption trends and drivers. *Philos Trans R Soc Lond B Biol Sci* 2010;365:2793-807. doi:10.1098/rstb.2010.0149
7 Wei H, Gao Z, Liang R, Li Z, Hao H, Liu X. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: a meta-analysis of prospective cohort studies. *Br J Nutr* 2016;116:514-25. doi:10.1017/S0007114516001975
8 Benisi-Kohansal S, Saneei P, Salehi-Marzijarani M, Larijani B, Esmaillzadeh A. Whole-Grain Intake and Mortality from All Causes, Cardiovascular Disease, and Cancer: A Systematic Review and

Dose-Response Meta-Analysis of Prospective Cohort Studies. *Adv Nutr* 2016;7:1052-65. doi:10.3945/an.115.011635
9 Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. *Nutr Metab Cardiovasc Dis* 2008;18:283-90. doi:10.1016/j.numecd.2006.12.008
10 Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* 2019;393:434-45. doi:10.1016/S0140-6736(18)31809-9
11 Bechthold A, Boeing H, Schwedhelm C, et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr* 2019;59:1071-90. doi:10.1080/10408398.2017.1392288
12 Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;353:i2716. doi:10.1136/bmj.i2716
13 Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2017;105:1462-73. doi:10.3945/ajcn.117.153148
14 Chen M, Li J, Li W, Sun X, Shu H. Dietary refined grain intake could increase the coronary heart disease risk: Evidence from a meta-analysis. *Int J Clin Exp Med* 2017;10:12749-55.
15 Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J* 2013;166:636-646.e4. doi:10.1016/j.ahj.2013.04.019
16 Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, PURE Investigators-Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J* 2009;158:1-7.e1. doi:10.1016/j.ahj.2009.04.019
17 Miller V, Mente A, Dehghan M, et al, Prospective Urban Rural Epidemiology (PURE) study investigators. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *Lancet* 2017;390:2037-49. doi:10.1016/S0140-6736(17)32253-5
18 Ross AB, Kristensen M, Seal CJ, Jacques P, McKeown NM. Recommendations for reporting whole-grain intake in observational and intervention studies. *Am J Clin Nutr* 2015;101:903-7. doi:10.3945/ajcn.114.098046
19 Farvid MS, Cho E, Eliassen AH, Chen WY, Willett WC. Lifetime grain consumption and breast cancer risk. *Breast Cancer Res Treat* 2016;159:335-45. doi:10.1007/s10549-016-3910-0
20 Tong TYN, Appleby PN, Bradbury KE, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. *BMJ* 2019;366:l4897. doi:10.1136/bmj.l4897
21 Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health* 2017;2:e000298. doi:10.1136/bmjgh-2017-000298
22 Gao Z, Chen Z, Sun A, Deng X. Gender differences in cardiovascular disease. *Med Nov Technol Devices* 2019;4:1-6.
23 Rosengren A, Subramanian SV, Islam S, et al, INTERHEART Investigators. Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study. *Heart* 2009;95:2014-22. doi:10.1136/hrt.2009.182436
24 Liu S, Manson JE, Lee IM, et al. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr* 2000;72:922-8. doi:10.1093/ajcn/72.4.922
25 Kaluza J, Akesson A, Wolk A. Processed and unprocessed red meat consumption and risk of heart failure: prospective study of men. *Circ Heart Fail* 2014;7:552-7. doi:10.1161/CIRCHEARTFAILURE.113.000921
26 Zhong VW, Van Horn L, Greenland P, et al. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. *JAMA Intern Med* 2020;180:503-12. doi:10.1001/jamainternmed.2019.6969
27 Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* 2017;390:2643-54. doi:10.1016/S0140-6736(17)31634-3
28 Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *Lancet Glob Health* 2019;7:e748-60. doi:10.1016/S2214-109X(19)30045-2
29 Day N, McKeown N, Wong M, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. *Int J Epidemiol* 2001;30:309-17. doi:10.1093/ije/30.2.309
30 Liu S. Intake of refined carbohydrates and whole grain foods in relation to risk of type 2 diabetes mellitus and coronary heart disease. *J Am Coll Nutr* 2002;21:298-306. doi:10.1080/07315724.2002.10719227
31 Lafiandra D, Riccardi G, Shewry PR. Improving cereal grain carbohydrates for diet and health. *J Cereal Sci* 2014;59:312-26. doi:10.1016/j.jcs.2014.01.001
32 Serra-Majem L, Bautista-Castaño I. Relationship between bread and obesity. *Br J Nutr* 2015;113(Suppl 2):S29-35. doi:10.1017/S0007114514003249
33 Batis C, Mendez MA, Sotres-Alvarez D, Gordon-Larsen P, Popkin B. Dietary pattern trajectories during 15 years of follow-up and HbA1c, insulin resistance and diabetes prevalence among Chinese adults. *J Epidemiol Community Health* 2014;68:773-9. doi:10.1136/jech-2013-203560
34 Batis C, Sotres-Alvarez D, Gordon-Larsen P, Mendez MA, Adair L, Popkin B. Longitudinal analysis of dietary patterns in Chinese adults from 1991 to 2009. *Br J Nutr* 2014;111:1441-51. doi:10.1017/S0007114513003917
35 Shi Z, Ganji V. Dietary patterns and cardiovascular disease risk among Chinese adults: a prospective cohort study. *Eur J Clin Nutr* 2020;74:1725-35. doi:10.1038/s41430-020-0668-6
36 Steffen LM, Jacobs DRJr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2003;78:383-90. doi:10.1093/ajcn/78.3.383
37 Zhang B, Zhao Q, Guo W, Bao W, Wang X. Association of whole grain intake with all-cause, cardiovascular, and cancer mortality: a systematic review and dose-response meta-analysis from prospective cohort studies. *Eur J Clin Nutr* 2018;72:57-65. doi:10.1038/ejcn.2017.149
38 Huang T, Xu M, Lee A, Cho S, Qi L. Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals. *BMC Med* 2015;13:59. doi:10.1186/s12916-015-0294-7
39 Kelly SA, Hartley L, Loveman E, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017;8:CD005051. doi:10.1002/14651858.CD005051.pub3
40 Li B, Zhang G, Tan M, et al. Consumption of whole grains in relation to mortality from all causes, cardiovascular disease, and diabetes: Dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)* 2016;95:e4229. doi:10.1097/MD.0000000000004229
41 Zong G, Gao A, Hu FB, Sun Q. Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Meta-Analysis of Prospective Cohort Studies. *Circulation* 2016;133:2370-80. doi:10.1161/CIRCULATIONAHA.115.021101
42 Johnsen NF, Frederiksen K, Christensen J, et al. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. *Br J Nutr* 2015;114:608-23. doi:10.1017/S0007114515001701
43 Belobrajdic DP, Bird AR. The potential role of phytochemicals in wholegrain cereals for the prevention of type-2 diabetes. *Nutr J* 2013;12:62. doi:10.1186/1475-2891-12-62
44 Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* 2019;393:434-45. doi:10.1016/S0140-6736(18)31809-9
45 Kyrø C, Tjønneland A. Whole grains and public health. *BMJ* 2016;353:i3046. doi:10.1136/bmj.i3046
46 Jenkins DJA, Wolever TMS, Jenkins AL. Starchy foods and glycemic index. *Diabetes Care* 1988;11:149-59. doi:10.2337/diacare.11.2.149
47 Eshak ES, Iso H, Date C, et al, JACC Study Group. Rice intake is associated with reduced risk of mortality from cardiovascular disease in Japanese men but not women. *J Nutr* 2011;141:595-602. doi:10.3945/jn.110.132167
48 Yu D, Shu XO, Li H, et al. Dietary carbohydrates, refined grains, glycemic load, and risk of coronary heart disease in Chinese adults. *Am J Epidemiol* 2013;178:1542-9. doi:10.1093/aje/kwt178
49 Saneei P, Larijani B, Esmaillzadeh A. Rice consumption, incidence of chronic diseases and risk of mortality: meta-analysis of cohort studies. *Public Health Nutr* 2017;20:233-44. doi:10.1017/S1368980016002172
50 Muraki I, Wu H, Imamura F, et al. Rice consumption and risk of cardiovascular disease: results from a pooled analysis of 3

U.S. cohorts. *Am J Clin Nutr* 2015;101:164-72. doi:10.3945/ajcn.114.087551
51 Krittanawong C, Tunhasiriwet A, Zhang H, et al. Is white rice consumption a risk for metabolic and cardiovascular outcomes? A systematic review and meta-analysis. *Heart Asia* 2017;9:e010909. doi:10.1136/heartasia-2017-010909
52 Boers HM, Seijen Ten Hoorn J, Mela DJ. A systematic review of the influence of rice characteristics and processing methods on postprandial glycaemic and insulinaemic responses. *Br J Nutr* 2015;114:1035-45. doi:10.1017/S0007114515001841
53 Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 1999;149:531-40. doi:10.1093/oxfordjournals.aje.a009849

Web appendix: Supplementary materials