Consumption of Whole Grains and Cardiometabolic Health

CONSUMPTION OF WHOLE GRAINS AND CARDIOMETABOLIC HEALTH

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Abstract

Evidence from observational studies and intervention studies has shown inverse associations between whole grain consumption and risk of developing cardiometabolic diseases. Most studies to date have characterized whole grain intake as the sum of whole grain ingredients from all grain-containing foods which may contain diverse contents of whole grains and refined grains. Whether different whole grain foods may exert differential associations with cardiometabolic diseases remains unknown. This dissertation focuses on individual whole grain foods, including whole grain cold breakfast cereal, oatmeal, dark bread, brown rice, popcorn, wheat germ, and added bran, in relation to major cardiometabolic diseases including type 2 diabetes (T2D), coronary heart disease (CHD), and obesity.

The first project investigated the associations between individual whole grain foods and risk of T2D. We conducted a prospective analysis examining the association between the seven individual whole grain foods and risk of T2D. We found higher consumption of total whole grains and most individual whole grain foods were significantly associated with a lower risk of T2D, whereas higher popcorn intake was associated with an increased risk of T2D.

The second project evaluated whether heterogeneous associations existed for CHD risk among individual whole grain foods. We used proportional hazards models to estimate the association between individual whole grain foods and risk of CHD. Our results showed that higher intake of total whole grains and most individual whole grain foods were significantly associated with lower risk of CHD. Popcorn intake was not associated with CHD risk.

The final project examined the change of individual whole grain foods intake in relation to long-term weight change. Multivariable generalized linear regression models were used to

evaluate the association between the change of intake of whole grain foods and 4-year weight change over the same 4-year follow-up interval. Our findings suggested that increased consumption of most individual whole grain foods, especially in replacements of refined grains, was associated with less weight gain.

This dissertation demonstrated overall beneficial associations between individual whole grain foods and risk of developing the cardiometabolic diseases. The data support the current dietary guidelines that encourage increased whole grain intake for better cardiometabolic health.

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Chapter 1. Intake of whole grain foods and risk of type 2 diabetes: results from three prospective cohort studies

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Abstract

Background

Although numerous epidemiological studies have shown an association between higher consumption of total whole grains and lower risk of type 2 diabetes (T2D), less is known for the associations with individual whole grain foods.

Methods

A total of 67,571 women from Nurses' Health Study (NHS, 1984-2012), 88,233 women from NHSII (1991-2013), and 36,861 men from the Health Professionals Follow-Up Study (HPFS, 1986-2012) who were free of major chronic diseases were prospectively followed. Incident cases of T2D were identified through self-reports in follow-up questionnaires and confirmed by a validated supplementary questionnaire. Total whole grains and seven individual whole grain foods were assessed using a validated food frequency questionnaire at baseline and were updated during follow up.

Results

During 4,132,274 person-years of follow-up, 16,622 T2D cases were identified. After adjusting for body mass index (BMI) and other lifestyle and dietary risk factors for diabetes, each additional one serving/day consumption of total whole grains was associated with 13% lower risk of T2D (HR: 0.87; 95% CI: 0.85, 0.89). The pooled hazard ratios (95% CIs) for T2D comparing participants consuming ≥1 servings/d with those consuming < 1 serving/month were 0.76 (0.72, 0.80) for whole grain cold breakfast cereal, 0.93 (0.91, 0.96) for dark bread, and 1.12 (1.03, 1.22) for popcorn. For other whole grain foods with lower overall intake levels, comparing intake level of ≥ 2 servings/week with < 1 serving/month, the pooled hazard ratios (95% CIs) were 0.78 (0.74, 0.82) for oatmeal, 0.88 (0.81, 0.95) for brown rice, 0.82 (0.77, 0.87) for added bran, and 0.84 (0.75, 0.95) for wheat germ. The inverse associations were relatively stronger among lean individuals (P for interaction=0.02),

although they otherwise did not vary significantly across levels of physical activity, family history of diabetes, and smoking status.

Conclusion

Higher consumption of total whole grains and several commonly-consumed whole grain foods including whole grain breakfast cereal, oatmeal, dark bread, brown rice, added bran, and wheat germ are significantly associated with lower risk of T2D. These findings provide further support for the current recommendations of increasing whole grain consumption as part of a healthy diet for the prevention of T2D.

Introduction

Whole grains have been widely recognized as healthy foods due to their high contents of fiber, antioxidants, and phytochemicals.[1] Accumulating epidemiological studies have shown inverse associations between whole grain consumption and risk of developing several major chronic diseases, including type 2 diabetes (T2D), cardiovascular disease (CVD), obesity, and certain types of cancer.[2–4] Meanwhile, multiple clinical intervention trials have demonstrated the potential of a whole grains-enriched diet in reducing fat mass, promoting energy balance, increasing insulin sensitivity, improving lipids profile, and reducing systemic inflammation.[5–12] Most studies to date have characterized whole grain intake as the sum of whole grain ingredients from all grain-containing foods which may contain various contents of whole grains and refined grains.[13] Despite a similar proportion of bran and germ (approximately 13% and 2%, respectively),[14] individual whole grain foods usually contain various contents of dietary fiber, antioxidants, magnesium, and phytochemicals,[15–17] which may result in differential effects of various types of whole grain foods on cardiometabolic health. Several prospective cohort studies have shown favorable associations between certain whole grain foods such as whole grain breakfast cereal and brown rice on T2D risk,[18–20] although associations for other whole grain foods remain to be determined.

In the current study, we aimed to prospectively examine the associations between the consumption of several commonly-consumed whole grain foods, including whole grain cold breakfast cereal, oatmeal, dark bread, brown rice, popcorn, wheat germ, and added bran intake and T2D risk in the Nurses' Health Study (NHS), NHSII and Health Professionals Follow-Up Study (HPFS), three large, well-characterized cohort studies with diet and other characteristics repeatedly assessed over two decades of follow-up.

Methods

Study population

The NHS cohort was established in 1976 when 121,700 female registered nurses aged 30-55 years completed a questionnaire on their medical history and lifestyle characteristics. The NHSII was initiated in 1989 and included 116,340 eligible women aged 25-42 years. A questionnaire similar to that used in NHS was administered at baseline to assess medical history, lifestyle factors, and diet in the NHSII. The HPFS began in 1986 when 51,529 U.S. male health professionals, aged 40-75 years, answered a similar baseline questionnaire. In all three cohorts, similar follow-up questionnaires have been sent to the participants to update information and to identify newly diagnosed T2D and other diseases every two years. The cumulative response rates in three cohorts exceeded 90%.[21,22]

For the current study, study baseline was set at 1984, 1991, and 1986 for the NHS, NHSII, and HPFS, respectively. We excluded participants diagnosed with T2D, CVD, or cancer at baseline, those who did not return semi-quantitative food frequency questionnaires (sFFQs) or had an unusual level of total energy intake (<500 or >3500 kcal/day for the NHS and the NHSII and <800 or >4200 kcal/day for the HPFS) at baseline, those with unconfirmed T2D case status, and those who completed only the baseline questionnaire. After these exclusions, 67,571 NHS participants, 88,233 NHSII participants, and 36,861 HPFS participants were included in the final analysis. The study protocol was approved by the Human Research Committee of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. Completion and return of study questionnaires implied informed consent of the participants.

Assessment of individual whole grain food consumption

In 1984, a 116-item sFFQ was administered to NHS participants to collect information on their usual diet in the previous year. The dietary information was updated in 1986 and every four years thereafter using similar but expanded sFFQs. In the NHSII and HPFS, the same sFFQ has been used to collect and update dietary information quadrennially since 1991 and 1986, respectively. In the sFFQs, participants were asked how often, on average, during the previous year they consumed each food item listed in the sFFQ with a pre-specified, standard portion size. There are nine possible responses that ranged from never or <1 time/month to ≥6 times/day. In the sFFQs, we inquired about intake of several commonly-consumed whole grain foods, including cold breakfast cereals, dark bread, popcorn, oatmeal, bran added to food, wheat germ, and brown rice. Participants were asked to provide information of types and brand names of their cold breakfast cereal, which was used to match with data provided by cereal manufacturers regarding whole grain contents. Cold breakfast cereals with ≥25% whole grain or bran content by weight were deemed to be whole grains. Beginning in 2002 for the NHS and HPFS, and 2003 for the NHSII, we further inquired about intake of regular popcorn and light/fat free popcorn in the sFFQs. Intakes of total whole grains were estimated from all grain-containing foods (rice, bread, pasta, and cold breakfast cereals) according to the dry weight of the whole grain ingredients in each food.[13,23,24] By definition, the following foods and ingredients were considered whole grains: whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal and whole corn flour, whole rye and whole rye flour, whole barley, bulgur, buckwheat, brown rice and brown rice flour, popcorn, amaranth, and psyllium.

Validation studies conducted within the NHS and HPFS have demonstrated reasonable validity and reproducibility of the sFFQ assessments of whole grain foods in these cohorts.[25] The intake levels of whole grain foods assessed using two sFFQs administered 12 months apart were significantly correlated with each other. For example, the Pearson correlation coefficients were 0.57 and 0.71 for dark bread and cold breakfast cereal, respectively. The FFQ assessments were also significantly correlated with those assessed using 7-day diet records; the correlation coefficients were 0.58 for dark bread and 0.73 for cold cereal breakfast.

Assessment of covariates

In the NHS, NHSII and HPFS, we biennially send follow-up questionnaires to collect and update occurrence of diseases and a multitude of lifestyle and demographic risk factors, including smoking status, vitamin supplements use, alcohol consumption, menopausal status, and years of postmenopausal hormone use (NHS and NHSII only), body weight, physician-diagnosed hypertension and hypercholesterinemia, and other variables. Physical activities were repeatedly assessed in three cohorts. A validated questionnaire regarding time spent on up to 10 recreational activities was used to derive metabolic equivalent tasks (METs) in hours/week.[26] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2) to measure overall obesity. A series of validation studies demonstrated the validity of these self-reported variables.[27–31] Finally, we modified the alternative healthy eating index (AHEI) — a diet score reflecting overall diet quality and predictive of major chronic diseases,[32] by removing the whole grain component.

Assessment of outcomes

Self-reported T2D cases were identified through a follow-up questionnaire. Participants who reported having diabetes were sent a supplementary questionnaire to confirm the diagnosis. Before 1998, T2D was confirmed if participants met at least one of the following National Diabetes Data Group criteria[33]:(1) an elevated glucose concentration (fasting plasma glucose of 7.8 mmol/l, random plasma glucose of 11.1 mmol/l, or plasma glucose 11.1 mmol/l ≥ 2 hours after an oral glucose load), and at least one symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger); (2) no symptoms, but elevated glucose concentrations on at least two occasions; or (3) treatment with insulin or other hypoglycemic medication. For cases of T2D identified after 1998, the cut-off point used for fasting plasma glucose concentrations was lowered to 7.0 mmol/l according to the American Diabetes Association criteria.[34] We further considered HbA1c ≥6.5% in the diagnosis criteria for confirming T2D cases identified after January, 2010.[35] A validation study showed that 97% of questionnaire-confirmed self-reported T2D cases were reconfirmed by medical record review.[36,37] We identified deaths by reports from next of kin or postal authorities, or by searching the national death index. [38] More than 97% of deaths can be identified in these cohorts.[39]

Statistical analysis

Baseline characteristics were expressed as mean (SD) or median (interquartile range) for continuous variables, and percentage was used for categorical variables according to quintiles of total whole grain consumption. Person-time for each participant was counted from the return date of the baseline FFQ to the T2D diagnosis date, death date, date of last return of a valid follow-up questionnaire, or the end of follow-up (2012 for NHS and HPFS, 2013 for NHSII), whichever happened first. To better represent long-term intake and to minimize within-person variation, we calculated cumulative averages for total whole grains and each whole grain food since baseline.[40] To minimize potential bias resulting from change of usual diet due to the diagnosis of chronic diseases/conditions, we stopped updating dietary information when participants first reported having myocardial infarction, stroke, cancer, hypertension, or hypercholesterolemia.[41] For these participants, we carried forward the cumulative averages of dietary intake prior to the occurrence of these diseases or symptoms to represent diet for subsequent follow-up. Because the proportion of missing values of covariates was low, ranging from 2.7% for total energy to 8.5% for BMI, we replaced missing values with the valid values in the most recent follow-up cycle and then missing indicators were used to accommodate missing data.

For the primary analysis, a multivariable Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between each individual whole grain food as well as total whole grain intake and risk of T2D. The proportional hazards assumption was evaluated by including an interaction term between whole grain intake and the logarithm of person-time. No evidence of violations of the assumption was detected in each cohort (P>0.05 for all tests). Total whole grain intake was categorized into quintiles and we used pre-specified cutoffs for ranking the intake levels of whole grain foods: < 1 serving/month, 1 serving/month – 1 serving/week and ≥ 2 servings/week. For whole grain cold breakfast cereal, dark bread, and popcorn, we used four categories: < 1 serving/month, 1 serving/month – 1 serving/week, 1 serving/week – 4-6 servings/wk, and ≥ 1 serving/d, because these foods have relatively higher overall intake. The statistical models adjusted for age (month), ethnicity (white, African American, Asian, others), time-varying BMI, smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), family history of diabetes (yes, no), postmenopausal hormone use (women only ; never, former, or current hormone use, or missing), and oral contraceptive use (yes, no; women only). Because the time-varying BMI (<21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥35.0 kg/m^2) could be both confounder and intermediate, we additionally adjusted for it in a separate model. The continuous variable for each exposure was used to calculate the p value for trend and HR of T2D for each serving/day of intake. To evaluate the heterogeneous associations among individual whole grain foods with T2D risk, we performed a Wald test for the joint hypothesis that assumed the beta coefficients were equal for seven individual whole grain foods.

Stratified analyses were performed for BMI, physical activity, smoking status, and family history of diabetes to explore effect modification. P values for interaction were calculated from likelihood ratio tests comparing multivariable-adjusted model with and without product term between dummy variables of total whole grains intake in quintiles and dummy variables of BMI categories. Finally, we evaluated whether the associations between individual whole grain food intake and T2D risk were accounted for by concurrent BMI by comparing the HRs in models with and without adjusting for concurrent BMI.[42,43] In a secondary analysis, we further examined regular or fat-free/light popcorn consumption (assessed since 2002 in NHS and HPFS and 2003 in NHSII), separately, in relation to T2D risk.

To assess the dose-response relationship between total whole grain intake as well as each individual whole grain food and risk of T2D, we combined the data from three cohorts and fitted a cubic spline regression with the same covariates (except for women only variables) adjusted in the primary analysis. Total whole grain intake was converted to servings by dividing a factor of 16 (based on the dry weight estimation of serving size). We conducted several sensitivity analyses to test the robustness of the primary findings. First, we used simply-updated whole grain food intake or baseline intake instead of the cumulative averaged value to repeat the analysis. Second, we conducted a series of latency analyses by modelling individual whole grain food intake with T2D incidence occurred 2, 4, or 6 years after reported intake to examine the possibility of reverse causation bias. Third, since individual whole grain foods might confound the associations of each other, we additionally adjusted for the total intake of all other six whole grain foods when modelling each individual whole grain food. Fourth, we adjusted for baseline BMI only to evaluate the impact of potential over-adjustment of BMI during follow-up, which could operate in the causal pathway. Fifth, we adjusted for individual dietary factors for T2D including polyunsaturated to saturated fat ratio, *trans* fat, red/processed meat, fruits, vegetables, fish, sugar sweetened beverages, coffee, and nuts (all in quintiles) instead of the modified AHEI to further reduce the impact of residual confounding by diet. Sixth, we continued to update dietary intake upon occurrence of certain chronic conditions. Seventh, we stopped updating dietary information until 8 years after occurrence of myocardial infarction, stroke, cancer, hypertension, or hypercholesterolemia to examine whether the associations were robust to our strategies of handling dietary changes after incidence of these conditions. For example, for participants who developed stroke in 1990, we stopped updating diet in 1994 and 1998 and then continued to update diet after 1998. Lastly, because participants with higher whole grain intake tended to have higher degree of health awareness which lead to more frequent examination of blood glucose, we restricted to symptomatic T2D cases to address potential detection bias. Data from each cohort were analyzed separately and were pooled using a random effect model. All statistical tests were 2-sided with significant level of 0.05 and performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

A total of 16,622 T2D cases were identified and confirmed during 4,132,274 person-years of follow-up. In all three cohorts at baseline, participants with higher total whole grain consumption, on average, were slightly older, more likely to be white, leaner, multivitamin users, and more physically active, in comparison with participants with lower intake. They also tended to have a lower prevalence of hypertension and family history of diabetes, higher diet quality, and more frequent screening for fasting glucose (**Table 1.1**).

Table 1.1. Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Total whole grain consumption				
	Q1	Q2	Q3	Q4	Q5
Nurses' Health Study					
Median, servings/d	0.1	0.4	0.7	1.1	2.1
No of participants	13,376	13,696	13,546	13,420	13,533
Age (years)	49.6 (6.9)	49.7 (7.0)	50.1 (7.1)	51.0 (7.2)	52.3 (7.2)
Baseline body mass index (kg/m²)	25.0 (4.9)	25.1 (4.8)	25.0 (4.6)	24.7 (4.4)	24.2 (4.1)
Race					
- White, %	97.0	97.8	98.1	98.1	98.3
- African American, %	0.2	0.2	0.2	0.2	0.3
- Asian, %	1.2	0.7	0.6	0.5	0.4
- Others, %	1.6	1.2	1.1	1.2	1.1
Physical activity(MET-h/wk)[*]	5.20 (2.00-15.4)	6.90 (2.40-16.7)	7.70 (2.90-18.7)	8.50 (3.20-20.2)	10.2 (3.40-21.6)
Hypertension, %	8.9	8.0	7.4	6.9	6.5
High cholesterol, %	2.8	2.8	3.0	3.4	3.9
Current smokers, %	36.5	27.7	23.3	19.0	14.3
Family history of diabetes, %	29.0	28.0	28.4	27.8	27.4
Multivitamin use, %	30.3	33.8	36.8	39.9	44.2
Oral contraceptive use, %	47.3	49.3	50.2	50.2	50.6
Hormone use					
- premenopausal, %	53.4	53.6	54.4	53.8	53.6
- postmenopausal-never, %	26.9	25.2	24.0	22.8	22.0
- postmenopausal-current, %	9.1	10.6	10.9	12.2	13.6
- postmenopausal-past, %	10.7	10.6	10.7	11.2	10.8
Fasting glucose examination[†]					
- Yes, for screening, %	46.3	47.9	49.4	50.0	50.5
- Yes, for symptoms, %	1.3	1.5	1.5	1.1	1.1
- No examination, %	31.3	32.2	32.1	31.7	32.5
- Missing, %	21.1	18.4	17.0	17.1	15.9
Alcohol consumption (g/day)[*]	3.00 (0.50-12.2)	2.70 (0.50-9.90)	2.50 (0.50-9.30)	2.30 (0.40-8.20)	1.70 (0.00-6.80)
Modified alternative healthy eating index	42.8 (9.9)	44.2 (9.6)	45.6 (9.8)	47.0 (10.0)	49.5 (10.6)
Total energy intake (Kcal/d)	1708 (551)	1791 (540)	1782 (540)	1778 (522)	1653 (476)
Nurses' Health Study II					
Median, servings/d	0.3	0.7	1.1	1.6	2.8
No of participants	17,659	17,558	17,678	17,734	17,604
Age (years)	36.5 (4.7)	36.5 (4.7)	36.4 (4.7)	36.4 (4.6)	36.9 (4.6)
Baseline body mass index (kg/m²)	25.0 (5.8)	24.9 (5.5)	24.6 (5.2)	24.3 (4.9)	23.8 (4.5)

Table 1.1. (Continued) Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Race					
- White, %	94.4	96.3	97.2	97.6	97.3
- African American, %	0.5	0.6	0.4	0.4	0.6
- Asian, %	3.1	1.4	1.1	0.9	1.0
- Others, %	2.0	1.7	1.3	1.1	1.1
Physical activity(MET-h/wk)[*]	9.4 (3.4-22.0)	11.3 (4.5-24.6)	12.5 (5.2-25.9)	13.9 (5.9-28.4)	16.5 (7.3-32.7)
Hypertension, %	4.0	3.6	3.1	2.7	2.4
High cholesterol, %	9.8	9.5	9.2	8.8	8.8
Current smokers, %	19.4	14.3	11.1	8.5	7.0
Family history of diabetes, %	35.3	34.2	33.5	33.7	31.5
Multivitamin use, %	36.1	40.6	44.2	47.7	50.7
Oral contraceptive use, %	82.5	84.5	84.6	84.4	83.4
Hormone use					
- premenopausal, %	97.1	96.8	97.1	96.9	96.7
- postmenopausal-never, %	0.2	0.2	0.2	0.2	0.2
- postmenopausal-current, %	2.4	2.8	2.5	2.6	2.8
- postmenopausal-past, %	0.3	0.3	0.2	0.3	0.3
Fasting glucose examination[†]					
- Yes, for screening, %	36.6	39.2	39.8	40.9	41.2
- Yes, for symptoms, %	1.3	1.2	1.3	1.1	1.1
- No examination, %	35.5	35.2	35.5	36.1	36.3
- Missing, %	26.6	24.4	23.4	21.8	21.4
Alcohol consumption (g/day)[*]	0.9 (0-3.6)	1.3 (0-4.0)	1.3 (0-3.9)	1.2 (0-3.7)	1.0 (0-3.4)
Modified alternative healthy eating index	41.6 (9.7)	44.0 (9.5)	45.7 (9.7)	47.2 (9.7)	50.7 (10.0)
Total energy intake (Kcal/d)	1770 (578)	1822 (561)	1824 (551)	1821 (526)	1710 (509)
Health Professionals Follow-Up Study					
Median, servings/d	0.2	0.6	1.1	1.7	3.2
No of participants	7,394	7,388	7,307	7,397	7,375
Age (years)	52.4 (9.2)	51.9 (9.3)	52.3 (9.3)	52.7 (9.5)	53.5 (9.5)
Baseline body mass index (kg/m²)	25.7 (3.3)	25.8 (3.3)	25.5 (3.3)	25.3 (3.2)	24.7 (2.9)
Race					
- White, %	93.2	95.3	95.9	96.8	95.6
- African American, %	2.3	2.2	2.2	1.8	2.3
- Asian, %	3.5	1.3	1.0	0.8	1.2
- Others, %	1.0	1.2	0.9	0.5	0.8
Physical activity(MET-h/wk)[*]	8.70 (2.50-23.9)	10.7 (3.40-26.8)	12.5 (4.30-28.6)	13.8 (4.80-30.4)	16.8 (6.10-35.1)

Table 1.1. (Continued) Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Hypertension, %	21.2	19.8	17.3	17.1	17.4
High cholesterol, %	9.0	9.2	9.6	10.0	12.2
Current smokers, %	17.2	11.8	8.3	5.8	4.2
Family history of diabetes, %	13.0	13.4	12.9	12.9	12.3
Multivitamin use, %	34.7	37.6	41.2	45.1	50.4
Fasting glucose examination[†]					
- Yes, for screening, %	49.9	51.8	52.0	54.7	55.0
- Yes, for symptoms, %	3.6	3.1	3.0	3.0	2.6
- No examination, %	13.5	13.7	14.6	14.0	14.0
- Missing, %	33.0	31.4	30.4	28.3	28.4
Alcohol consumption (g/day)[*]	7.00 (1.00-19.3)	6.70 (1.10-16.6)	6.40 (1.00-16.1)	5.80 (0.90-13.8)	3.90 (0.00-12.2)
Modified alternative healthy eating index	45.9 (10.6)	48.5 (10.3)	49.9 (10.4)	51.5 (10.5)	54.7 (10.3)
Total energy intake (Kcal/d)	1991 (649)	2040 (643.9)	2060 (636)	2023 (594)	1883 (555)

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

[*]Value is median (interquartile range).

[†]The first assessment of fasting glucose examination was conducted in 1998 for the NHS, 2001 for the NHSII, and 2000 for the HFPS.

After adjusting for BMI and other lifestyle and dietary risk factors of diabetes, higher total whole grain consumption was consistently associated with a lower risk of T2D in all three cohorts (**Table 1.2**). In pooled results, comparing extreme quintiles of total whole grain intake, there was a 31% (HR: 0.69, 95% CI: 0.66, 0.73, P for trend < 0.0001) lower risk of T2D. **Table 1.3** shows the associations between consumption of specific whole grain foods and risk of T2D. The pooled HRs (95% CIs) comparing participants consuming ≥1 servings/d with those consuming < 1 serving/month were 0.79 (0.75, 0.83) for whole grain cold breakfast cereal, 0.80 (0.76, 0.84) for dark bread, and 1.12 (1.03, 1.22) for popcorn. For other whole grain foods with lower overall intake levels, comparing intake level of ≥2 servings/week with < 1 serving/month, the pooled hazard ratios (95% CIs) were 0.78 (0.74, 0.82) for oatmeal, 0.88 (0.81, 0.95) for brown rice, 0.82 (0.77, 0.87) for added bran, and 0.84 (0.75, 0.95) for wheat germ. The inverse associations for total whole grains as well as individual whole grain foods were attenuated but remained statistically significant after adjusting for BMI. The non-significant p values for heterogeneity across the cohorts suggested the inverse associations were largely consistent in the three cohorts for most of whole grain foods (**Supplemental table 1.1**). The p values for the joint Wald test was highly significant (NHS: P < 0.0001; NHSII: P < 0.0001; HPFS: P < 0.0001) suggesting potentially heterogeneous associations between individual whole grain foods with T2D risk. In light of the positive association for popcorn intake, we repeated the likelihood ratio test by removing popcorn intake variable and found somewhat attenuated results (NHS: P < 0.0001; NHSII: P = 0.03; HPFS: P = 0.007). For individual whole grain foods, updated BMI explained substantial amount of the inverse associations (> 40%) for most individual whole grain foods (**Supplemental table 1.2**). Fixed effect model resulted in similar pooled estimates for aforementioned analyses.

Table 1.2. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for total whole grains consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Total whole grain consumptions						
	Q1	Q2	Q3	Q4	Q5	P trend	Per one daily serving
NHS							
Cases/person years	2,045/320,442	1,720/321,826	1,487/321,628	1,220/321,241	1,025/322,045		
Age-adjusted model	1.00	0.84 (0.79, 0.89)	0.72 (0.67, 0.77)	0.59 (0.55, 0.63)	0.48 (0.45, 0.52)	<.0001	0.70 (0.67, 0.73)
Multivariable adjusted model[*]	1.00	0.86 (0.81, 0.92)	0.76 (0.71, 0.82)	0.64 (0.60, 0.69)	0.55 (0.50, 0.59)	<.0001	0.75 (0.72, 0.78)
Additional adjusting for BMI[†]	1.00	0.87 (0.82, 0.93)	0.80 (0.74, 0.85)	0.70 (0.65, 0.75)	0.65 (0.60, 0.71)	<.0001	0.82 (0.79, 0.85)
NHSII							
Cases/person years	1,806/355,262	1,343/354,962	1,085/357,183	917/357,289	769/356,825		
Age-adjusted model	1.00	0.77 (0.72, 0.82)	0.62 (0.58, 0.67)	0.52 (0.48, 0.56)	0.43 (0.39, 0.46)	<.0001	0.69 (0.67, 0.72)
Multivariable adjusted model[*]	1.00	0.85 (0.79, 0.91)	0.73 (0.68, 0.79)	0.65 (0.59, 0.70)	0.57 (0.52, 0.62)	<.0001	0.79 (0.76, 0.82)
Additional adjusting for BMI[†]	1.00	0.90 (0.84, 0.97)	0.82 (0.76, 0.88)	0.76 (0.70, 0.82)	0.74 (0.67, 0.81)	<.0001	0.88 (0.85, 0.91)
HPFS							
Cases/person years	883/148,477	711/148,627	617/148,701	534/148,823	460/148,943		
Age-adjusted model	1.00	0.81 (0.74, 0.90)	0.71 (0.64, 0.78)	0.61 (0.54, 0.67)	0.51 (0.46, 0.57)	<.0001	0.81 (0.78, 0.84)
Multivariable adjusted model[*]	1.00	0.85 (0.77, 0.94)	0.77 (0.69, 0.85)	0.68 (0.61, 0.76)	0.59 (0.52, 0.66)	<.0001	0.85 (0.82, 0.89)
Additional adjusting for BMI[†]	1.00	0.84 (0.76, 0.93)	0.82 (0.73, 0.91)	0.75 (0.67, 0.84)	0.72 (0.64, 0.81)	<.0001	0.92 (0.88, 0.95)
Pool results[‡]							
Cases/person years	4,734/824,181	3,774/825,415	3,189/827,512	2,671/827,353	2,254/827,813		
Age-adjusted model	1.00	0.81 (0.77, 0.84)	0.68 (0.65, 0.71)	0.57 (0.54, 0.59)	0.47 (0.45, 0.49)	<.0001	0.73 (0.72, 0.75)
Multivariable adjusted model[*]	1.00	0.86 (0.82, 0.89)	0.75 (0.72, 0.79)	0.65 (0.62, 0.68)	0.56 (0.53, 0.59)	<.0001	0.80 (0.78, 0.81)
Additional adjusting for BMI[†]	1.00	0.88 (0.84, 0.91)	0.81 (0.77, 0.85)	0.73 (0.69, 0.77)	0.69 (0.66, 0.73)	<.0001	0.87 (0.85, 0.89)

[*]Adjusted for age (years), ethnicity (white, African American, Asian, others), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

[†]Additionally adjusted for time-varying BMI (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2).

[‡]Study estimates from three cohorts were pooled using a random effects model.

Table 1.3. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Cases/person-time	6,323/1,264,453	3,644/824,582	4,888/1,456,846	1,767/586,392		
Multivariable adjusted model*	1.00	0.91 (0.87, 0.95)	0.66 (0.64, 0.69)	0.65 (0.61, 0.68)	<.0001	0.61 (0.58, 0.65)
Additional adjusting for BMI†	1.00	0.92 (0.88, 0.95)	0.74 (0.71, 0.77)	0.79 (0.75, 0.83)	<.0001	0.76 (0.72, 0.80)
Dark bread						
Cases/person-time	2,278/444,879	3,671/829,699	5,647/1,523,922	5,026/1,333,774		
Multivariable adjusted model*	1.00	0.94 (0.90, 1.00)	0.77 (0.73, 0.81)	0.79 (0.75, 0.83)	<.0001	0.92 (0.90, 0.94)
Additional adjusting for BMI†	1.00	0.91 (0.86, 0.96)	0.79 (0.75, 0.83)	0.80 (0.76, 0.84)	<.0001	0.93 (0.91, 0.96)
Popcorn						
Cases/person-time	4,076/996,107	8,042/2,081,352	3,667/897,111	837/157,703		
Multivariable adjusted model*	1.00	1.08 (1.04, 1.13)	1.09 (1.04, 1.15)	1.53 (1.41, 1.65)	<.0001	1.28 (1.22, 1.33)
Additional adjusting for BMI†	1.00	0.99 (0.95, 1.03)	0.93 (0.89, 0.98)	1.12 (1.03, 1.22)	<.001	1.09 (1.04, 1.15)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	8,734/2,037,445	6,091/1,504,428	1,797/590,400	-		
Multivariable adjusted model*	1.00	0.95 (0.92, 0.98)	0.68 (0.64, 0.71)	-	<.0001	0.55 (0.49, 0.63)
Additional adjusting for BMI†	1.00	0.96 (0.93, 1.00)	0.78 (0.74, 0.82)	-	<.0001	0.74 (0.65, 0.84)
Brown rice						
Cases/person-time	10,680/2,356,967	5,134/1,495,382	808/279,924	-		
Multivariable adjusted model*	1.00	0.91 (0.88, 0.94)	0.80 (0.74, 0.86)	-	0.0005	0.73 (0.61, 0.87)
Additional adjusting for BMI†	1.00	0.94 (0.91, 0.98)	0.88 (0.81, 0.95)	-	0.09	0.86 (0.72, 1.02)
Added bran						
Cases/person-time	13,772/3,248,707	1,759/507,400	1,091/376,167	-		
Multivariable adjusted model*	1.00	0.87 (0.83, 0.91)	0.71 (0.66, 0.75)	-	<.0001	0.76 (0.70, 0.82)
Additional adjusting for BMI†	1.00	0.91 (0.87, 0.96)	0.82 (0.77, 0.87)	-	<.001	0.87 (0.80, 0.93)
Wheat germ						
Cases/person-time	15,527/3,745,109	811/274,044	284/113,120	-		
Multivariable adjusted model*	1.00	0.81 (0.76, 0.87)	0.67 (0.60, 0.76)	-	<.0001	0.57 (0.47, 0.69)
Additional adjusting for BMI†	1.00	0.90 (0.84, 0.96)	0.84 (0.75, 0.95)	-	0.02	0.80 (0.66, 0.96)

Table 1.3. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

†Additionally adjusted for time-varying BMI (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2).

Study estimates from three cohorts were pooled using a random effects model.

Cubic spline modelling suggested a nonlinear inverse association between total whole grain intake and T2D risk (**Figure 1.1 Panel A;** P value for non-linearity < 0.001). The risk reduction slightly plateaued over two servings per day of total whole grain consumption. Using total whole grains excluding the contribution from popcorn yielded a similar significant p for non-linearity ($P < 0.001$), although the non-linear pattern was less apparent (**Figure 1.1 Panel B**). For individual whole grain foods, non-linear relationships were observed for whole grain breakfast cereal and dark bread intake with T2D risk, for which the risk reduction plateaued approximately at 0.5 serving/d (**Supplemental figure 1.1**). The inverse associations between total whole grain intake and T2D risk appeared to be stronger among lean or overweight participants than obese participants ($P = 0.02$ for interaction) while no significant effect modification found for smoking status, physical activity or family history (**Table 1.4**).

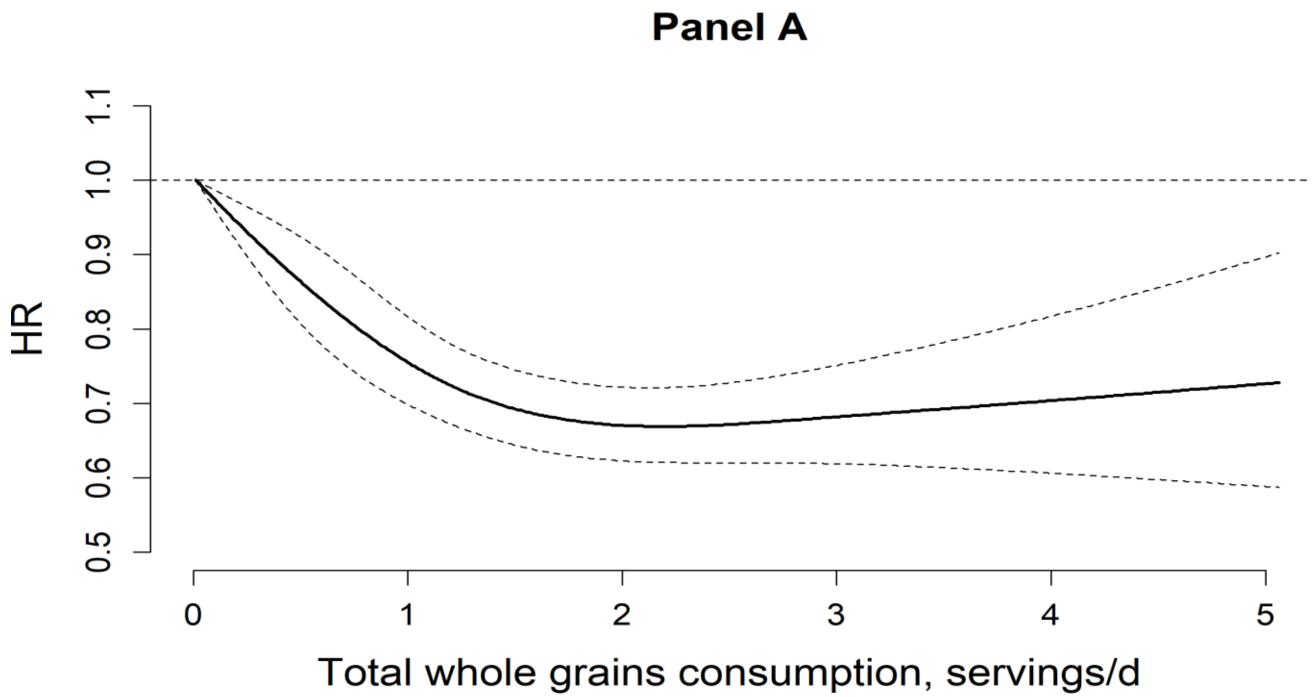

Figure 1.1. Panel A. Non-linear association between total whole grain foods consumption and risk of type 2 diabetes in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), and Health Professionals Follow-Up Study (1986-2012)

Data from three cohorts were combined and truncated at 0.5^{th} -99.5^{th} percentile (0.01-5.1 servings/d).

Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

P values for non-linearity < 0.0001

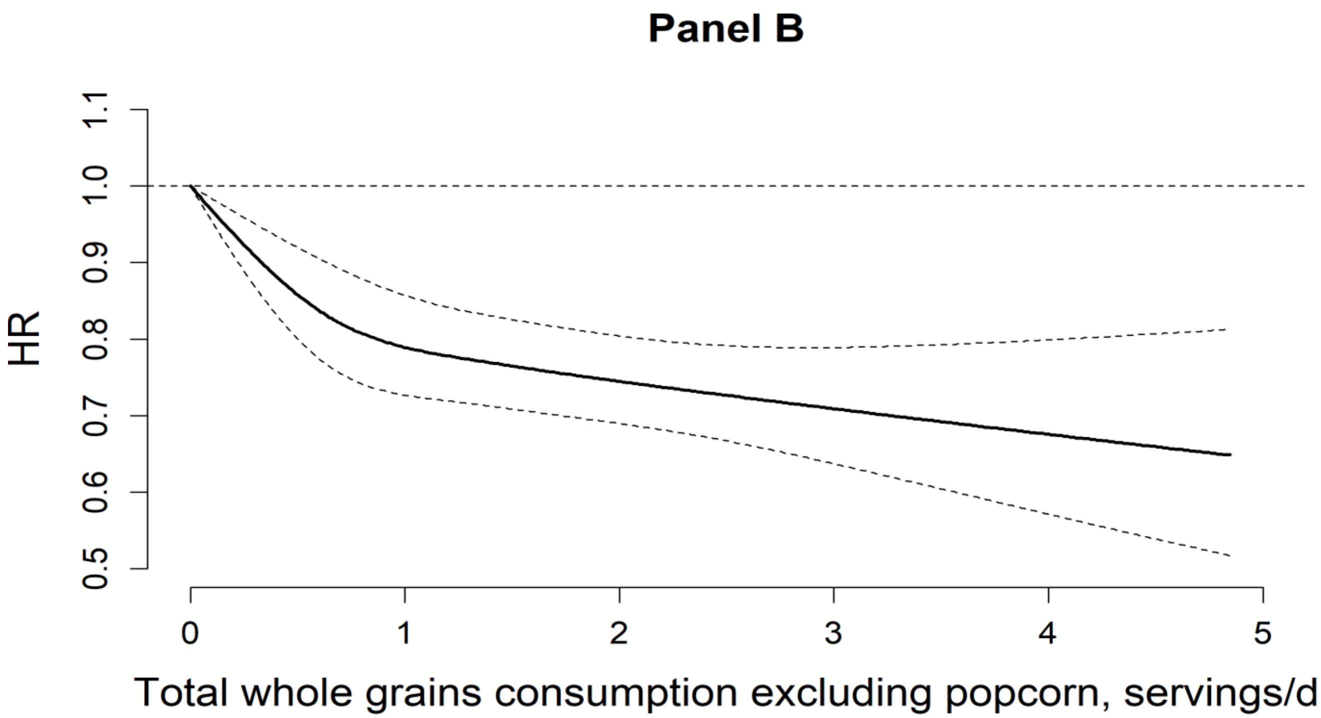

Figure 2.1. Panel B. Non-linear association between total whole grain foods consumption excluding popcorn and risk of type 2 diabetes in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), and Health Professionals Follow-Up Study (1986-2012)

Data from three cohorts were combined and truncated at 0.5th -99.5th percentile (0-4.8 servings/d).

Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

P values for non-linearity 0.002.

Table 1.4. Association between total whole grains and type 2 diabetes risk stratified by body mass index, family history of diabetes, physical activity, and smoking status.

	Total whole grain consumptions					
	Q1	Q2	Q3	Q4	Q5	P for interaction
BMI						0.02
<25 kg/m^2	1.00	0.79 (0.68, 0.91)	0.75 (0.64, 0.87)	0.73 (0.62, 0.85)	0.62 (0.53, 0.73)	
25-30 kg/m^2	1.00	0.84 (0.77, 0.92)	0.77 (0.70, 0.84)	0.63 (0.58, 0.70)	0.64 (0.57, 0.71)	
≥ 30 kg/m^2	1.00	0.93 (0.88, 0.99)	0.86 (0.81, 0.92)	0.81 (0.76, 0.87)	0.77 (0.71, 0.83)	
Physical activity						0.60
Tertile 1	1.00	0.89 (0.83, 0.95)	0.83 (0.77, 0.89)	0.76 (0.70, 0.82)	0.71 (0.66, 0.78)	
Tertile 2	1.00	0.88 (0.81, 0.96)	0.79 (0.72, 0.87)	0.76 (0.69, 0.84)	0.70 (0.62, 0.77)	
Tertile 3	1.00	0.86 (0.77, 0.96)	0.78 (0.69, 0.87)	0.69 (0.61, 0.77)	0.68 (0.60, 0.77)	
Smoking status						0.06
Never smokers	1.00	0.89 (0.83, 0.95)	0.81 (0.76, 0.87)	0.78 (0.72, 0.84)	0.69 (0.64, 0.75)	
Past smokers	1.00	0.84 (0.78, 0.90)	0.80 (0.73, 0.86)	0.69 (0.63, 0.75)	0.66 (0.60, 0.73)	
Current smokers	1.00	0.96 (0.83, 1.12)	0.89 (0.74, 1.06)	0.75 (0.61, 0.93)	0.85 (0.67, 1.08)	
Family history of diabetes						0.97
No	1.00	0.90 (0.84, 0.96)	0.79 (0.74, 0.85)	0.74 (0.69, 0.80)	0.70 (0.65, 0.76)	
Yes	1.00	0.87 (0.81, 0.93)	0.83 (0.77, 0.89)	0.74 (0.69, 0.80)	0.70 (0.64, 0.76)	

Adjusted for same covariates as in main analysis except for the stratification variable.

Continuous BMI and physical activity were adjusted to minimize residual confounding.

In a secondary analysis that examined regular popcorn and light/fat free separately, non-significant positive associations were observed for both regular popcorn and light/fat free popcorn intake (**Supplemental table 1.3**). Comparing participants with consumption greater or equal than two servings/week with those eating less than 1 serving/month, regular popcorn intake was non-significantly associated with 4% (HR: 1.04; 95% CI: 0.91, 1.19; P for trend 0.52) greater risk of T2D and light/fat free popcorn intake was associated with 11% (HR: 1.11; 95% CI: 1.00, 1.23; P for trend 0.03) greater risk of T2D.

In the sensitivity analysis using baseline dietary information only, the associations were slightly attenuated, while using simple updated intake produced similar results (**Supplemental table 1.4**). Latency analyses also yielded similar estimates (**Supplemental table 1.4**). Adjusting for baseline BMI or the sum of other individual whole grain foods did not substantially change the results (**Supplemental table 1.5**). Updating the dietary information regardless of the occurrence of certain chronic conditions yielded similar results except for brown rice for which the inverse association was attenuated to null (**Supplemental table 1.6**). In contrast, stopping updating diet up to 8 years after occurrence of the chronic conditions did not materially change the results (**Supplemental table 1.6**). Finally, restricting to symptomatic T2D cases resulted in similar estimates for most whole grain foods (**Supplemental table 1.7**).

Discussion

Findings from three prospective cohorts showed that higher total whole grain intake was significantly associated with a lower T2D risk. While such inverse associations were also observed for most individual whole grain foods, we also found an elevated increased risk of T2D associated with popcorn consumption. These associations were independent of established and potential T2D risk factors and were substantially accounted for by the concurrent BMI. The inverse association between total whole grain intake and T2D risk was weaker among obese participants while the associations were largely persisted in other sub-groups with various diabetes risk profiles.

The inverse association between higher whole grain consumption and risk of T2D has been found in many previous studies. A dose-response meta-analysis of prospective cohort studies showed that total whole grain consumption was associated with a lower T2D risk, with a potentially non-linear dose-response relationship in that the risk reduction plateaued at three servings per day.[44] Moreover, this meta-analysis also showed that higher intake of several whole grain foods, including whole grain bread, whole grain breakfast cereals, wheat bran, and brown rice, were associated with a similar risk reduction of T2D. However, data for other types of whole grain foods in this meta-analysis are sparse. Individual whole grain foods contain various amounts of dietary fiber, magnesium, antioxidants, and phytochemicals, which all may play important roles in reducing T2D risk.[45] For example, on average, raw oat bran has 15.4 g total dietary fiber per 100 gram dry weight, but 100 gram brown rice only contains 1.6 g fiber.[46] Similarly, magnesium is the richest in raw oat bran (>300 mg/100g) and wheat germ (235mg/100g), and poorest in rye bread (40mg/100g) and brown rice (39mg/100g), with breakfast cereal, oatmeal and popcorn in the middle (100-150mg/100g).[46] In addition, heterogeneous glycemic properties among individual whole grains may also exert different health effects on glucose metabolism as higher glycemic index was associated with an increased risk of T2D.[47] For example, the average glycemic index (GI) is 42 for whole grain cold breakfast cereal, 55 for oatmeal and brown rice, and 27-70 for whole grain bread depending on the ingredients contained (barley, buckwheat, oats, rye, and etc.), whereas popcorn has the highest GI value of 72.[48] In the current study, the goodness of fit test suggested potential heterogeneous effects among individual whole grain foods with T2D risk, although the effect sizes for most whole grain foods were not substantially different from each other. Of note, the highly significant p values for heterogeneity among individual whole grain foods may result from the substantial statistical power in the three cohorts.

The observation that higher popcorn intake was associated with increased T2D risk merits discussion. The fatty acid content might play a role in the positive association between regular popcorn intake and T2D risk. An analysis comparing the change of *trans* fatty acid contents among a variety of foods in the U.S. supermarket in the period 2009-2011 showed that popcorn was one of the food items that had the smallest decline of the *trans* fatty acid content over time.[49] Accordingly, the relatively high content of *trans* fats in popcorn may offset beneficial effects of other ingredients in this whole grain food, given the positive association between *trans* fat intake and T2D risk.[50] However, *trans* fatty acids per se may not fully explain the positive association because light/fat free popcorn tended to be associated with a higher diabetes risk as well. Butter and salt that are often added during cooking or processing of popcorn may also undermine the health effects of whole grain contents of popcorn. Furthermore, studies have shown that microwave popcorn packaging contains perfluoroalkyl substances, anthropogenic chemicals possessing endocrine disrupting properties, which can contaminate popcorn.[51,52] Several recent studies revealed that these compounds were associated with poor glucose metabolism,[53,54] weight gain,[55] and increased T2D risk.[56] Furthermore, higher popcorn intake may represent frequent snacking pattern which is associated with increased risk of T2D risk.[57] Overall, these data underscore the possibility that unhealthful constituents added or introduced during food preparation may modulate the health effects of popcorn, and more research is needed to corroborate our findings and to elucidate potential mechanisms.

An interesting finding in the subgroup analysis demonstrated a relatively weaker inverse association between total whole grains intake and T2D risk among obese participants than lean or overweight participants. It is possible that obese participants have a high-risk profile characterized by chronic inflammation, dyslipidemia, hypertension, and insulin resistance, which may partially offset the beneficial effects of whole grain intake on glucose metabolism. Of note, given the much higher risk of developing T2D among obese individuals, the relatively weaker relative risk may still be translated into substantial reduction of absolute risk in this high-risk group of participants. Moreover, our data showed that obese participants on average consumed more popcorn than their non-obese counterpart (0.15 serving/d, 0.17 serving/d, and 0.20 serving/d for lean, overweight, and obese participants, respectively) while their consumption levels for other whole grain foods were either similar or lower (data not shown). Lastly, given a borderline significant p value and potential multiple testing issue in the stratified analysis, we cannot rule out the possibility of chance finding for this effect modification.

The strengths of our study include the use of data from three large cohort studies with long-term follow-up, comprehensive, repeated assessments of diet, and potential confounders, and high follow-up rates. Potential limitations also warrant consideration. First, although we adjusted for a multitude of lifestyle practices and diet quality, residual or unmeasured confounding cannot be excluded in observational studies. Second, multiple comparisons may result in false positive results because we examined the associations for seven whole grain foods concurrently. However, our main results remained statistically significant for most whole grain foods even after adjusting for the multiplicity using the conservative Bonferroni correction, and the consistent associations across three cohorts made the chance findings less likely. Third, our observations may largely pertain to white health professionals and lack generalizability to other populations with different characteristics. However, it is unlikely that the underlying biological mechanisms differ substantially by race or by socioeconomic status.

In conclusion, higher consumption of total whole grains and most whole grain foods is significantly associated with lower T2D risk. These findings provide further support for current recommendations to increase whole grain consumption as part of a healthy diet for the prevention of T2D.

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Supplemental Material

Supplemental table 1.1. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels					
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d	P trend	Per one daily serving
Cold breakfast cereal						
NHS						
Cases/person-time	3,228/581,979	1,631/320,209	2,120/547,496	518/157,498		
Multivariable adjusted model*	1.00	0.92 (0.86, 0.97)	0.73 (0.69, 0.77)	0.70 (0.64, 0.77)	<.0001	0.65 (0.59, 0.71)
NHSII						
Cases/person-time	1,893/450,577	1,400/371,926	1,909/684,888	718/274,129		
Multivariable adjusted model*	1.00	0.93 (0.86, 0.99)	0.73 (0.69, 0.78)	0.85 (0.78, 0.93)	<.0001	0.82 (0.76, 0.90)
HPFS						
Cases/person-time	1,202/231,897	613/132,447	859/224,462	531/154,765		
Multivariable adjusted model*	1.00	0.89 (0.81, 0.98)	0.77 (0.71, 0.84)	0.82 (0.74, 0.91)	0.0001	0.82 (0.74, 0.91)
P for heterogeneity			<.001			
Dark bread						
NHS						
Cases/person-time	925/158,089	1,599/314,621	2,609/602,442	2,364/532,030		
Multivariable adjusted model*	1.00	0.92 (0.85, 1.00)	0.82 (0.76, 0.89)	0.81 (0.75, 0.88)	0.001	0.94 (0.91, 0.98)
NHSII						
Cases/person-time	906/206,813	1,336/364,402	2,108/690,820	1,570/519,486		
Multivariable adjusted model*	1.00	0.89 (0.82, 0.97)	0.78 (0.72, 0.84)	0.80 (0.73, 0.87)	0.02	0.95 (0.91, 0.99)
HPFS						
Cases/person-time	447/79,977	736/150,676	930/230,660	1,092/282,258		
Multivariable adjusted model*	1.00	0.92 (0.82, 1.04)	0.75 (0.67, 0.84)	0.78 (0.69, 0.87)	<.0001	0.90 (0.86, 0.94)
P for heterogeneity			0.18			
Popcorn						
NHS						
Cases/person-time	2,452/542,997	3,589/757,260	1,253/269,653	203/37,272		
Multivariable adjusted model*	1.00	1.02 (0.96, 1.07)	0.93 (0.87, 1.00)	1.09 (0.94, 1.26)	0.99	1.00 (0.91, 1.10)
NHSII						
Cases/person-time	706/237,057	2,957/965,953	1,804/489,960	453/88,550		

Supplemental table 1.1. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Multivariable adjusted model*	1.00	0.94 (0.87, 1.02)	0.91 (0.83, 1.00)	1.13 (1.00, 1.27)	0.003	1.11 (1.04, 1.19)
HPFS						
Cases/person-time	918/216,053	1,496/358,139	610/137,498	181/31,881		
Multivariable adjusted model*	1.00	0.97 (0.89, 1.06)	0.96 (0.86, 1.07)	1.15 (0.98, 1.36)	0.002	1.15 (1.05, 1.26)
P for heterogeneity			0.10			
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
NHS						
Cases/person-time	4,196/865,968	2,615/544,248	686/196,966	-		
Multivariable adjusted model*	1.00	0.94 (0.89, 0.99)	0.76 (0.70, 0.83)	-	0.002	0.72 (0.59, 0.88)
NHSII						
Cases/person-time	2,651/774,105	2,504/726,014	765/281,401	-		
Multivariable adjusted model*	1.00	1.02 (0.97, 1.08)	0.82 (0.76, 0.89)	-	0.47	0.93 (0.75, 1.14)
HPFS						
Cases/person-time	1,887/397,372	972/234,166	346/112,033	-		
Multivariable adjusted model*	1.00	0.91 (0.84, 0.99)	0.72 (0.64, 0.81)	-	<.0001	0.55 (0.43, 0.70)
P for heterogeneity			0.04			
Brown rice						
NHS						
Cases/person-time	5,465/1,077,416	1,828/460,930	204/68,835	-		
Multivariable adjusted model*	1.00	0.94 (0.89, 0.99)	0.76 (0.66, 0.88)	-	0.002	0.55 (0.38, 0.80)
NHSII						
Cases/person-time	3,479/921,631	2,038/706,757	403/153,133	-		
Multivariable adjusted model*	1.00	0.95 (0.90, 1.01)	0.93 (0.83, 1.03)	-	0.70	1.05 (0.81, 1.38)
HPFS						
Cases/person-time	1,736/357,920	1,268/327,695	201/57,956	-		
Multivariable adjusted model*	1.00	0.94 (0.87, 1.01)	0.92 (0.79, 1.07)	-	0.44	0.88 (0.64, 1.21)
P for heterogeneity			0.02			
Added bran						
NHS						
Cases/person-time	6,160/1,217,646	769/204,140	568/185,396	-		
Multivariable adjusted model*	1.00	0.84 (0.78, 0.91)	0.78 (0.71, 0.85)	-	0.0002	0.79 (0.70, 0.89)
NHSII						

Supplemental table 1.1. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Cases/person-time	5,109/1,481,900	578/203,019	233/96,602	-		
Multivariable adjusted model*	1.00	0.98 (0.90, 1.07)	0.92 (0.81, 1.06)	-	0.85	0.98 (0.83, 1.17)
HPFS						
Cases/person-time	2,503/549,161	412/100,241	290/94,169	-		
Multivariable adjusted model*	1.00	0.96 (0.86, 1.06)	0.81 (0.72, 0.92)	-	0.04	0.89 (0.79, 0.99)
P for heterogeneity			0.46			
Wheat germ						
NHS						
Cases/person-time	6,943/1,436,666	399/115,471	155/55,045	-		
Multivariable adjusted model*	1.00	0.90 (0.81, 1.00)	0.85 (0.72, 1.00)	-	0.08	0.79 (0.61, 1.03)
NHSII						
Cases/person-time	5,621/1,644,227	253/109,144	46/28,150	-		
Multivariable adjusted model*	1.00	0.93 (0.82, 1.05)	0.78 (0.58, 1.05)	-	0.11	0.62 (0.34, 1.12)
HPFS						
Cases/person-time	2,963/664,216	159/49,429	83/29,925	-		
Multivariable adjusted model*	1.00	0.85 (0.72, 0.99)	0.87 (0.70, 1.08)	-	0.26	0.85 (0.64, 1.12)
P for heterogeneity			0.63			

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Supplemental table 1.2. Mediation effects of BMI on associations between whole grain foods consumption and T2D risk*

Whole grains	% (95% CI) of association explained by BMI			
	NHS	**NHSII**	**HPFS**	**Pooled**†
Whole grain breakfast cereal	37.2% (30.6%, 44.4%)	60.8% (46.7%, 73.3%)	30.6% (20.5%, 43.0%)	43.6% (37.7%, 49.7%)
Oatmeal	48.6% (32.1%, 65.4%)	65.2% (18.5%, 94.0%)	No effect	34.0% (23.1%, 46.9%)
Dark bread	No effect	No effect	17.4% (9.6%, 29.4%)	10.8% (4.0%, 26.4%)
Brown rice	37.9% (19.8%, 60.1%)	No effect	No effect	57.1% (24.8%, 84.3%)
Popcorn	94.1% (0%, 100%)	50.1% (34.9%, 65.4%)	22.5% (12.0%, 38.1%)	47.5% (35.1%, 60.2%)
Added bran	41.5% (27.1%, 57.5%)	97.3% (0%, 100%)	28.7% (14.2%, 49.6%)	42.1% (29.5%, 55.8%)
Wheat germ	41.1% (19.0%, 67.4%)	51.0% (27.4%, 74.2%)	41.9% (21.4%, 65.6%)	44.4% (29.9%, 59.8%)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

†Data from three cohorts were combined.

Supplemental table 1.3. Association between regular and light/fat free popcorn intake and risk of type 2 diabetes in Nurses' Health Study (2002-2012), Nurses' Health Study II (2003-2013) and Health Professionals Follow-Up Study (2002-2012)

	Regular popcorn				Light, fat free popcorn			
	<1 serving/month	1 serving/ month– 1 serving/wk	> 2 servings/wk	P trend	<1 serving/month	1 serving/month – 1 serving/wk	> 2 servings/wk	P trend
NHS								
Cases/person-years	1,595/316,003	519/87,906	66/10,387		1,345/278,937	674/110,924	161/24,435	
Multivariable-adjusted model 1*	1.00	1.02 (0.92, 1.13)	1.01 (0.78, 1.30)	0.87	1.00	1.17 (1.06, 1.28)	1.20 (1.01, 1.42)	0.02
Multivariable-adjusted model 2*	1.00	1.02 (0.92, 1.13)	1.01 (0.78, 1.30)	0.94	1.00	1.17 (1.06, 1.28)	1.20 (1.01, 1.42)	0.02
NHSII								
Cases/person-years	1,283/302,159	973/214,156	158/28,670		1,213/269,373	945/222,978	256/52,635	
Multivariable-adjusted model 1*	1.00	0.95 (0.87, 1.03)	1.06 (0.89, 1.26)	0.59	1.00	0.96 (0.88, 1.04)	1.03 (0.90, 1.18)	0.65
Multivariable-adjusted model 2*	1.00	0.95 (0.87, 1.03)	1.05 (0.89, 1.25)	0.60	1.00	0.96 (0.88, 1.05)	1.02 (0.89, 1.17)	0.66
HPFS								
Cases/person-years	292/68,608	232/43,112	30/5,734		368/80,360	150/31,478	36/5,616	
Multivariable-adjusted model 1*	1.00	1.16 (0.97, 1.39)	1.09 (0.74, 1.61)	0.54	1.00	1.02 (0.84, 1.24)	1.37 (0.96, 1.95)	0.08
Multivariable-adjusted model 2*	1.00	1.17 (0.98, 1.40)	1.07 (0.73, 1.58)	0.57	1.00	1.01 (0.83, 1.23)	1.39 (0.98, 1.98)	0.09
Pooled†								
Multivariable-adjusted model 1*	1.00	1.00 (0.94, 1.06)	1.05 (0.92, 1.20)	0.47	1.00	1.04 (0.98, 1.11)	1.12 (1.01, 1.24)	0.02
Multivariable-adjusted model 2*	1.00	1.00 (0.94, 1.06)	1.04 (0.91, 1.19)	0.52	1.00	1.04 (0.98, 1.11)	1.11 (1.00, 1.23)	0.03

*Multivariable-adjusted model 1 adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Multivariable-adjusted model 2 mutually adjusted for regular popcorn and light/fat free

†Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 1.4. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, and latency analysis

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Baseline intake						
Cases/person-time	7873/1728643	3796/907800	2829/773102	2124/722727		
Multivariable adjusted model*	1.00	0.97 (0.93, 1.01)	0.89 (0.86, 0.94)	0.83 (0.79, 0.87)	<.0001	0.84 (0.80, 0.88)
Simple updated intake						
Cases/person-time	6646/1403901	3290/790358	2822/764271	2185/730609		
Multivariable adjusted model*	1.00	0.92 (0.88, 0.96)	0.85 (0.81, 0.89)	0.77 (0.73, 0.81)	<.0001	0.78 (0.74, 0.82)
Lag 2 years						
Cases/person-time	5,823/1,137,378	3,418/739,405	4,538/1,287,561	1,667/529,806		
Multivariable adjusted model*	1.00	0.93 (0.89, 0.97)	0.75 (0.72, 0.78)	0.80 (0.76, 0.85)	<.0001	0.77 (0.73, 0.81)
Lag 4 years						
Cases/person-time	5,389/1,016,891	3,182/658,191	4,223/1,125,215	1,568/476,098		
Multivariable adjusted model*	1.00	0.93 (0.89, 0.98)	0.77 (0.74, 0.80)	0.80 (0.76, 0.85)	<.0001	0.78 (0.74, 0.83)
Lag 6 years						
Cases/person-time	4,968/902,781	2,912/580,535	3,811/966,139	1,466/424,083		
Multivariable adjusted model*	1.00	0.93 (0.89, 0.98)	0.79 (0.75, 0.82)	0.81 (0.76, 0.86)	<.0001	0.79 (0.75, 0.84)
Dark bread						
Baseline intake						
Cases/person-time	2984/639203	4428/1080552	3926/994766	5284/1417753		
Multivariable adjusted model*	1.00	0.91 (0.87, 0.95)	0.91 (0.87, 0.96)	0.85 (0.82, 0.90)	<.0001	0.94 (0.92, 0.96)
Simple updated intake						
Cases/person-time	2557/554852	4084/996707	3686/935805	4724/1241379		
Multivariable adjusted model*	1.00	0.93 (0.89, 0.98)	0.93 (0.88, 0.98)	0.89 (0.85, 0.94)	<.0001	0.95 (0.93, 0.97)
Lag 2 years						
Cases/person-time	2,116/401,703	3,434/747,697	5,237/1,351,047	4,659/1,193,703		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.96)	0.79 (0.75, 0.83)	0.80 (0.76, 0.84)	<.0001	0.93 (0.91, 0.95)
Lag 4 years						
Cases/person-time	1,968/360,180	3,209/669,676	4,866/1,184,875	4,319/1,061,664		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.96)	0.81 (0.76, 0.85)	0.80 (0.76, 0.85)	<.0001	0.92 (0.90, 0.95)
Lag 6 years						
Cases/person-time	1,834/321,108	2,992/595,231	4,406/1,024,150	3,925/933,051		
Multivariable adjusted model*	1.00	0.92 (0.86, 0.97)	0.82 (0.77, 0.86)	0.79 (0.75, 0.84)	<.0001	0.92 (0.90, 0.95)

Supplemental table 1.4. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, and latency analysis

Popcorn						
Baseline intake						
Cases/person-time	4964/1236337	8360/2162389	2242/510462	1056/223084		
Multivariable adjusted model*	1.00	1.02 (0.98, 1.06)	1.09 (1.03, 1.15)	1.11 (1.03, 1.19)	<.001	1.08 (1.03, 1.13)
Simple updated intake						
Cases/person-time	4391/1153501	7677/1955642	2144/461594	938/182432		
Multivariable adjusted model*	1.00	1.04 (1.00, 1.08)	1.14 (1.08, 1.21)	1.16 (1.07, 1.25)	<.001	1.09 (1.04, 1.14)
Lag 2 years						
Cases/person-time	3,661/884,512	7,544/1,870,261	3,456/796,791	785/142,585		
Multivariable adjusted model*	1.00	1.01 (0.97, 1.05)	0.96 (0.91, 1.01)	1.13 (1.04, 1.23)	<.001	1.10 (1.04, 1.15)
Lag 4 years						
Cases/person-time	3,357/782,112	7,069/1,667,196	3,198/698,641	738/128,444		
Multivariable adjusted model*	1.00	1.01 (0.97, 1.05)	0.96 (0.91, 1.01)	1.11 (1.02, 1.21)	0.001	1.09 (1.03, 1.14)
Lag 6 years						
Cases/person-time	3,029/686,632	6,561/1,469,345	2,872/602,608	695/114,956		
Multivariable adjusted model*	1.00	1.03 (0.98, 1.08)	0.97 (0.92, 1.03)	1.13 (1.03, 1.23)	<.01	1.08 (1.02, 1.14)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time						
Baseline intake						
Cases/person-time	9852/2394061	5746/1436021	1024/302190	-		
Multivariable adjusted model*	1.00	1.00 (0.97, 1.04)	0.93 (0.87, 0.99)	-	0.01	0.86 (0.77, 0.97)
Simple updated intake						
Cases/person-time	8375/1991297	5498/1357252	1271/398961	-		
Multivariable adjusted model*	1.00	0.99 (0.95, 1.03)	0.82 (0.77, 0.87)	-	<.0001	0.71 (0.63, 0.79)
Lag 2 years						
Cases/person-time	8,125/1,830,900	5,686/1,347,500	1,635/515,750	-		
Multivariable adjusted model*	1.00	0.96 (0.93, 1.00)	0.77 (0.73, 0.82)	-	<.0001	0.70 (0.62, 0.80)
Lag 4 years						
Cases/person-time	7,583/1,633,759	5,294/1,197,394	1,485/445,240	-		
Multivariable adjusted model*	1.00	0.96 (0.93, 1.00)	0.78 (0.73, 0.82)	-	<.0001	0.73 (0.63, 0.83)
Lag 6 years						
Cases/person-time	6,997/1,445,255	4,837/1,051,234	1,323/377,053	-		
Multivariable adjusted model*	1.00	0.97 (0.93, 1.00)	0.79 (0.75, 0.84)	-	<.0001	0.74 (0.64, 0.85)

Supplemental table 1.4. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, and latency analysis

Brown rice						
Baseline intake						
Cases/person-time	11482/2617628	4609/1343917	531/170729	-		
Multivariable adjusted model*	1.00	0.97 (0.94, 1.01)	0.97 (0.89, 1.06)	-	0.14	0.89 (0.76, 1.04)
Simple updated intake						
Cases/person-time	10108/2280077	4486/1299373	506/162119	-		
Multivariable adjusted model*	1.00	0.96 (0.93, 1.00)	0.94 (0.86, 1.04)	-	0.06	0.84 (0.71, 1.01)
Lag 2 years						
Cases/person-time	9,879/2,109,254	4,810/1,338,099	757/246,799	-		
Multivariable adjusted model*	1.00	0.94 (0.91, 0.98)	0.89 (0.82, 0.96)	-	0.07	0.84 (0.70, 1.01)
Lag 4 years						
Cases/person-time	9,165/1,872,404	4,507/1,187,767	690/216,222	-		
Multivariable adjusted model*	1.00	0.94 (0.91, 0.98)	0.88 (0.81, 0.95)	-	0.07	0.84 (0.69, 1.01)
Lag 6 years						
Cases/person-time	8,383/1,646,631	4,157/1,041,051	617/185,858	-		
Multivariable adjusted model*	1.00	0.95 (0.91, 0.99)	0.87 (0.79, 0.94)	-	0.03	0.80 (0.65, 0.97)
Added bran						
Baseline intake						
Cases/person-time	14230/3408972	1547/439792	845/283509	-		
Multivariable adjusted model*	1.00	0.94 (0.89, 0.99)	0.85 (0.79, 0.92)	-	<.0001	0.87 (0.81, 0.93)
Simple updated intake						
Cases/person-time	13056/3176090	1328/339934	746/232414	-		
Multivariable adjusted model*	1.00	1.05 (0.99, 1.11)	0.93 (0.86, 1.00)	-	0.04	0.93 (0.87, 1.00)
Lag 2 years						
Cases/person-time	12,801/2,904,995	1,637/454,096	1,008/335,060	-		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.96)	0.82 (0.77, 0.88)	-	<.001	0.86 (0.80, 0.93)
Lag 4 years						
Cases/person-time	11,885/2,576,168	1,536/403,907	941/296,318	-		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.96)	0.82 (0.77, 0.88)	-	<.001	0.87 (0.80, 0.94)
Lag 6 years						
Cases/person-time	10,868/2,259,954	1,417/355,100	872/258,486	-		
Multivariable adjusted model*	1.00	0.92 (0.87, 0.97)	0.85 (0.79, 0.91)	-	0.002	0.88 (0.81, 0.95)
Wheat germ						
Baseline intake						
Cases/person-time	15654/3784653	742/265996	226/81626	-		
Multivariable adjusted model*	1.00	0.83 (0.77, 0.90)	0.88 (0.77, 1.00)	-	0.005	0.79 (0.68, 0.93)

Supplemental table 1.4. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, and latency analysis

Simple updated intake						
Cases/person-time	14195/3441547	633/206037	183/64499	-		
Multivariable adjusted model*	1.00	0.92 (0.85, 1.01)	0.97 (0.83, 1.13)	-	0.10	0.86 (0.72, 1.03)
Lag 2 years						
Cases/person-time	14,426/3,346,499	764/246,705	256/100,946	-		
Multivariable adjusted model*	1.00	0.90 (0.83, 0.97)	0.82 (0.73, 0.94)	-	0.008	0.77 (0.63, 0.93)
Lag 4 years						
Cases/person-time	13,420/2,966,502	708/220,527	234/89,364	-		
Multivariable adjusted model*	1.00	0.88 (0.82, 0.95)	0.81 (0.71, 0.92)	-	0.004	0.74 (0.60, 0.91)
Lag 6 years						
Cases/person-time	12,291/2,600,526	650/195,309	216/77,705	-		
Multivariable adjusted model*	1.00	0.86 (0.80, 0.93)	0.83 (0.72, 0.95)	-	0.008	0.75 (0.61, 0.93)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 1.5. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) adjusting for baseline BMI, individual dietary factors or total consumption of all other whole grain foods

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Cases/person-time	6,323/1,264,453	3,644/824,582	4,888/1,456,846	1,767/586,392		
Adjusting for individual dietary factors*	1.00	0.94 (0.90, 0.98)	0.79 (0.76, 0.82)	0.84 (0.79, 0.88)	<.0001	0.81 (0.77, 0.86)
Adjusting for baseline BMI only	1.00	0.92 (0.88, 0.96)	0.74 (0.71, 0.77)	0.77 (0.73, 0.82)	<.0001	0.74 (0.71, 0.79)
Adjusting for total consumption of all other whole grain foods	1.00	0.92 (0.89, 0.96)	0.75 (0.72, 0.78)	0.80 (0.76, 0.85)	<.0001	0.77 (0.73, 0.81)
Dark bread						
Cases/person-time	2,278/444,879	3,671/829,699	5,647/1,523,922	5,026/1,333,774		
Adjusting for individual dietary factors*	1.00	0.93 (0.88, 0.98)	0.83 (0.79, 0.88)	0.84 (0.80, 0.88)	<.0001	0.95 (0.93, 0.97)
Adjusting for baseline BMI only	1.00	0.91 (0.86, 0.96)	0.79 (0.75, 0.83)	0.79 (0.75, 0.83)	<.0001	0.93 (0.91, 0.95)
Adjusting for total consumption of all other whole grain foods	1.00	0.92 (0.87, 0.97)	0.81 (0.77, 0.85)	0.82 (0.78, 0.87)	<.0001	0.94 (0.92, 0.97)
Popcorn						
Cases/person-time	4,076/996,107	8,042/2,081,352	3,667/897,111	837/157,703		
Adjusting for individual dietary factors*	1.00	1.00 (0.96, 1.04)	0.97 (0.92, 1.02)	1.12 (1.03, 1.22)	<.001	1.09 (1.04, 1.15)
Adjusting for baseline BMI only	1.00	1.01 (0.97, 1.05)	0.98 (0.93, 1.03)	1.19 (1.09, 1.29)	<.0001	1.13 (1.08, 1.18)
Adjusting for total consumption of all other whole grain foods	1.00	0.99 (0.95, 1.03)	0.94 (0.90, 0.99)	1.14 (1.05, 1.23)	<.0001	1.10 (1.05, 1.15)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	8,734/2,037,445	6,091/1,504,428	1,797/590,400	-		
Adjusting for individual dietary factors*	1.00	0.99 (0.96, 1.02)	0.82 (0.78, 0.87)	-	<.001	0.81 (0.71, 0.91)
Adjusting for baseline BMI only	1.00	0.96 (0.93, 1.00)	0.77 (0.73, 0.81)	-	<.0001	0.72 (0.64, 0.82)
Adjusting for total consumption of all other whole grain foods	1.00	0.98 (0.95, 1.01)	0.80 (0.75, 0.84)	-	<.0001	0.77 (0.68, 0.87)
Brown rice						
Cases/person-time	10,680/2,356,967	5,134/1,495,382	808/279,924	-		
Adjusting for individual dietary factors*	1.00	0.95 (0.92, 0.99)	0.90 (0.83, 0.97)	-	0.10	0.86 (0.72, 1.03)
Adjusting for baseline BMI only	1.00	0.95 (0.92, 0.99)	0.89 (0.83, 0.96)	-	0.21	0.89 (0.75, 1.07)
Adjusting for total consumption of all other whole grain foods	1.00	0.96 (0.93, 1.00)	0.90 (0.84, 0.97)	-	0.36	0.92 (0.77, 1.10)
Added bran						

Supplemental table 1.5. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) adjusting for baseline BMI, individual dietary factors or total consumption of all other whole grain foods

Cases/person-time	13,772/3,248,707	1,759/507,400	1,091/376,167	-		
Adjusting for individual dietary factors*	1.00	0.93 (0.88, 0.98)	0.84 (0.79, 0.90)	-	0.001	0.88 (0.82, 0.95)
Adjusting for baseline BMI only	1.00	0.92 (0.87, 0.96)	0.82 (0.77, 0.87)	-	<.001	0.87 (0.81, 0.94)
Adjusting for total consumption of all other whole grain foods	1.00	0.93 (0.88, 0.98)	0.85 (0.80, 0.91)	-	0.006	0.90 (0.84, 0.97)
Wheat germ						
Cases/person-time	15,527/3,745,109	811/274,044	284/113,120	-		
Adjusting for individual dietary factors*	1.00	0.92 (0.85, 0.98)	0.88 (0.78, 1.00)	-	0.05	0.84 (0.70, 1.00)
Adjusting for baseline BMI only	1.00	0.89 (0.83, 0.96)	0.83 (0.73, 0.93)	-	0.008	0.78 (0.65, 0.94)
Adjusting for total consumption of all other whole grain foods	1.00	0.93 (0.86, 1.00)	0.90 (0.80, 1.01)	-	0.20	0.89 (0.74, 1.06)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), polyunsaturated to saturated fat ratio, trans fat, red/processed meat, fruits, vegetables, fish, sugar sweetened beverages, coffee, nuts (all in quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 1.6. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) not stop updating or partially stop updating dietary variables upon occurrence of chronic conditions

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Not stop updating diet*						
Cases/person-time	4,096/988,649	3,359/766,492	7,883/1,861,493	1,251/511,259		
Multivariable adjusted model*	1.00	1.00 (0.95, 1.05)	0.92 (0.88, 0.96)	0.84 (0.78, 0.89)	<.0001	0.81 (0.77, 0.86)
Stop updating up to 8 years*						
Cases/person-time	5,692/1,182,734	3,580/809,302	5,717/1,573,192	1,625/565,841		
Multivariable adjusted model*	1.00	0.95 (0.91, 0.99)	0.81 (0.78, 0.84)	0.82 (0.77, 0.87)	<.0001	0.81 (0.76, 0.85)
Dark bread						
Not stop updating diet*						
Cases/person-time	1,426/347,626	2,422/670,543	7,861/1,798,922	4,880/1,310,802		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.98)	0.93 (0.88, 0.99)	0.89 (0.83, 0.94)	0.009	0.97 (0.94, 0.99)
Stop updating up to 8 years*						
Cases/person-time	2,036/417,760	3,311/783,733	6,298/1,602,481	4,969/1,327,095		
Multivariable adjusted model*	1.00	0.92 (0.87, 0.97)	0.85 (0.81, 0.90)	0.84 (0.79, 0.89)	<.0001	0.95 (0.92, 0.97)
Popcorn						
Not stop updating diet*						
Cases/person-time	3,277/910,207	7,142/1,986,213	5,613/1,103,113	557/128,359		
Multivariable adjusted model*	1.00	1.02 (0.98, 1.06)	1.12 (1.07, 1.18)	1.15 (1.05, 1.27)	<.0001	1.13 (1.07, 1.20)
Stop updating up to 8 years*						
Cases/person-time	3,853/973,804	7,750/2,052,143	4,236/956,132	775/148,991		
Multivariable adjusted model*	1.00	1.00 (0.96, 1.04)	1.02 (0.97, 1.07)	1.19 (1.09, 1.29)	<.0001	1.12 (1.06, 1.17)

	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Not stop updating diet*						
Cases/person-time	6,777/1,768,961	6,193/1,496,763	3,619/862,167	-		
Multivariable adjusted model*	1.00	1.04 (1.00, 1.07)	0.97 (0.93, 1.02)	-	0.02	0.86 (0.76, 0.98)
Stop updating up to 8 years*						
Cases/person-time	8,180/1,958,241	6,152/1,504,631	2,282/668,198	-		
Multivariable adjusted model*	1.00	1.00 (0.97, 1.04)	0.86 (0.82, 0.91)	-	<.001	0.81 (0.71, 0.91)
Brown rice						
Not stop updating diet*						

Supplemental table 1.6. (continued) Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) not stop updating or partially stop updating dietary variables upon occurrence of chronic conditions

Cases/person-time	9,813/2,246,149	5,547/1,543,120	1,229/338,624	-		
Multivariable adjusted model*	1.00	0.99 (0.95, 1.02)	1.01 (0.95, 1.08)	-	0.40	0.92 (0.76, 1.12)
Stop updating up to 8 years*						
Cases/person-time	10,462/2,324,940	5,249/1,509,741	903/296,389	-		
Multivariable adjusted model*	1.00	0.95 (0.92, 0.98)	0.90 (0.83, 0.96)	-	0.04	0.82 (0.68, 0.99)
Added bran						
Not stop updating diet*						
Cases/person-time	13,208/3,160,915	1,900/523,755	1,481/443,223	-		
Multivariable adjusted model*	1.00	0.94 (0.89, 0.99)	0.90 (0.85, 0.95)	-	<.0001	0.82 (0.75, 0.90)
Stop updating up to 8 years*						
Cases/person-time	13,607/3,225,103	1,795/511,766	1,212/394,200	-		
Multivariable adjusted model*	1.00	0.93 (0.88, 0.98)	0.87 (0.81, 0.92)	-	<.001	0.87 (0.80, 0.94)
Wheat germ						
Not stop updating diet*						
Cases/person-time	15,474/3,737,688	760/260,714	355/129,489	-		
Multivariable adjusted model*	1.00	0.92 (0.86, 1.00)	0.90 (0.81, 1.00)	-	0.03	0.78 (0.62, 0.98)
Stop updating up to 8 years*						
Cases/person-time	15,526/3,743,052	785/270,141	303/117,876	-		
Multivariable adjusted model*	1.00	0.90 (0.83, 0.96)	0.85 (0.76, 0.96)	-	0.02	0.78 (0.64, 0.95)
Not stop updating diet*						
Cases/person-time	8,180/1,958,241	6,152/1,504,631	2,282/668,198	-		
Multivariable adjusted model*	1.00	1.00 (0.97, 1.04)	0.86 (0.82, 0.91)	-	<.001	0.81 (0.71, 0.91)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

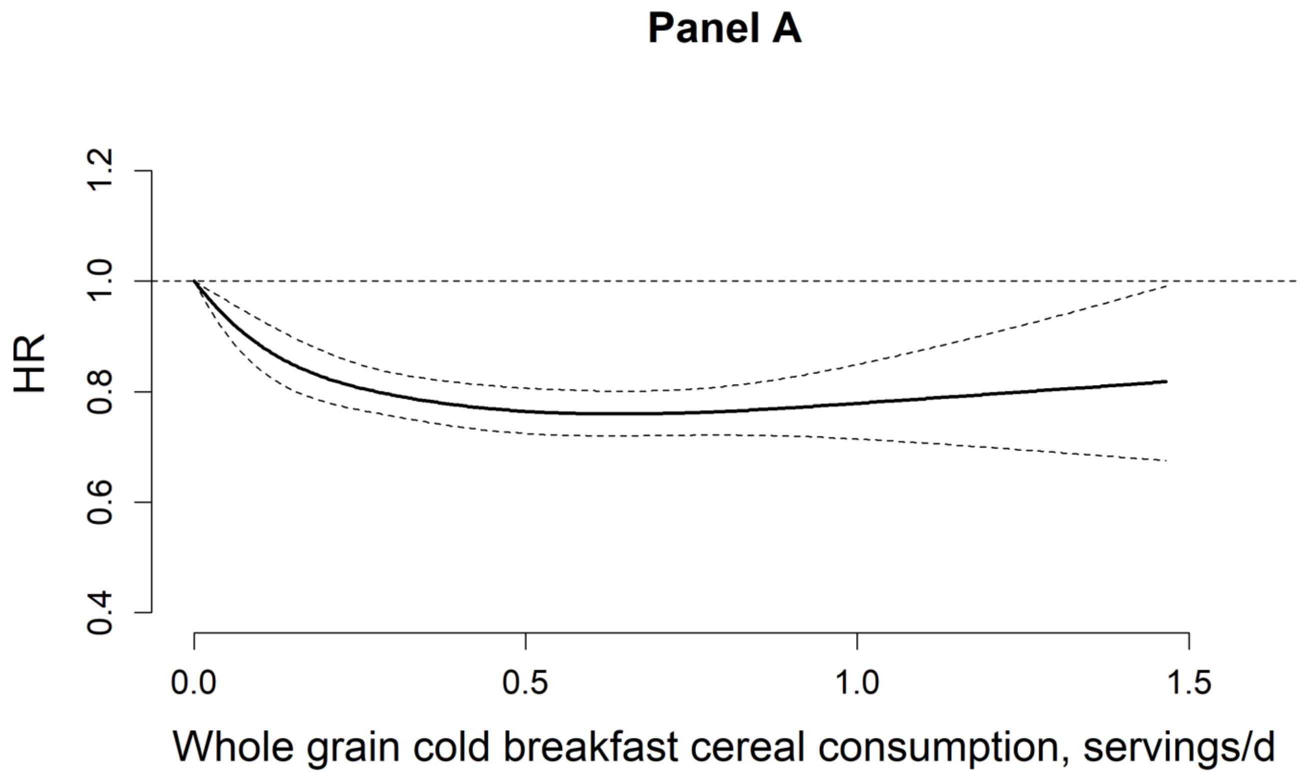
Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 1.7. Pooled hazard ratios (95% confidence intervals) of symptomatic type 2 diabetes for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Cases/person-time	3,958/1,295,412	2,477/840,362	3,211/1,478,309	1,185/594,778		
Multivariable adjusted model*	1.00	0.95 (0.90, 1.00)	0.75 (0.71, 0.78)	0.81 (0.75, 0.86)	<.0001	0.76 (0.71, 0.81)
Dark bread						
Cases/person-time	1,547/454,545	2,421/846,454	3,695/1,547,685	3,168/1,360,178		
Multivariable adjusted model*	1.00	0.91 (0.86, 0.98)	0.80 (0.75, 0.85)	0.81 (0.76, 0.86)	<.0001	0.94 (0.91, 0.97)
Popcorn						
Cases/person-time	2,251/1,018,989	5,324/2,117,985	2,631/910,900	625/160,988		
Multivariable adjusted model*	1.00	1.01 (0.95, 1.06)	0.95 (0.89, 1.01)	1.11 (1.00, 1.22)	0.003	1.09 (1.03, 1.15)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	5,396/2,076,619	4,199/1,532,894	1,236/599,348	-		
Multivariable adjusted model*	1.00	1.01 (0.96, 1.05)	0.82 (0.77, 0.87)	-	0.04	0.86 (0.74, 0.99)
Brown rice						
Cases/person-time	6,807/2,408,303	3,442/1,517,260	582/283,299	-		
Multivariable adjusted model*	1.00	0.91 (0.88, 0.94)	0.80 (0.74, 0.86)	-	0.04	0.86 (0.74, 0.99)
Added bran						
Cases/person-time	9,047/3,310,394	1,144/516,364	640/382,104	-		
Multivariable adjusted model*	1.00	0.96 (0.90, 1.03)	0.89 (0.82, 0.97)	-	0.01	0.88 (0.79, 0.97)
Wheat germ						
Cases/person-time	10,170/3,815,535	510/278,681	151/114,646	-		
Multivariable adjusted model*	1.00	0.90 (0.83, 0.99)	0.85 (0.72, 1.00)	-	0.15	0.84 (0.66, 1.07)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

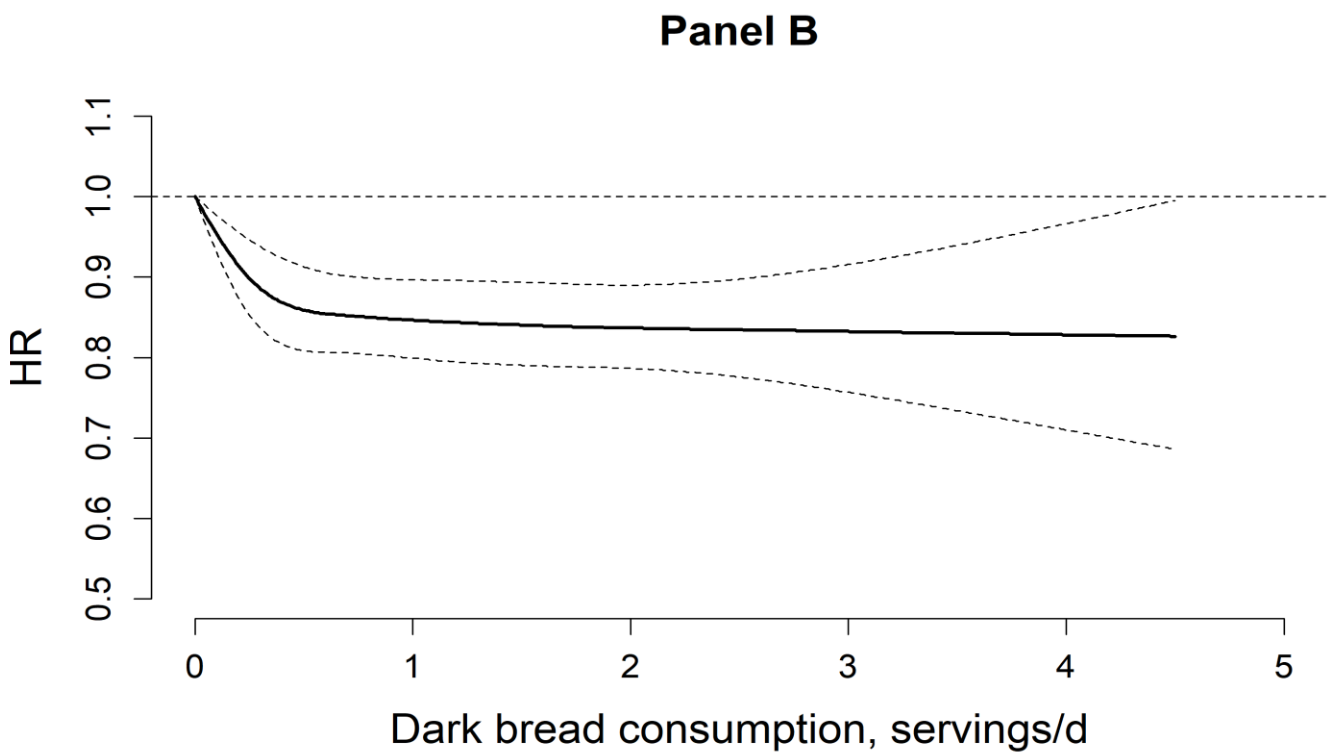
Study estimates from three cohorts were pooled using a random effects model.



Supplemental figure 1.1. Panel A. Non-linear association between whole grain cold breakfast cereal consumption and risk of type 2 diabetes in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), and Health Professionals Follow-Up Study (1986-2012)

Data from three cohorts were combined and truncated at 0.5^{st} -99.5^{th} percentile (0-1.5 servings/d).

Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.



Supplemental figure 1.1. Panel B. Non-linear association between dark bread consumption and risk of type 2 diabetes in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), and Health Professionals Follow-Up Study (1986-2012)

Data from three cohorts were combined and truncated at 0.5^{st} -99.5^{th} percentile (0-4.5 servings/d).

Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles), and family history of diabetes (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Chapter 2. Intake of whole grain foods and risk of coronary heart disease in US men and women

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Abstract

Background

Epidemiological studies have demonstrated a favorable association of whole grain intake with coronary heart disease (CHD) risk, although whether such an inverse association holds true for individual whole grain foods that have diverse nutritional profiles has not been examined.

Methods

We followed 72,025 women from Nurses' Health Study (NHS) since 1986, 90,390 women from NHSII since 1991, and 39,480 men from the Health Professionals Follow-Up Study (HPFS) since 1984, who did not have a history of cardiovascular disease or cancer at baseline. Intake of seven individual whole grain foods was repeatedly assessed using a validated semi-quantitative food frequency questionnaire (sFFQ) every 2-4 years since baseline. Total CHD including nonfatal myocardial infarction and fatal CHD was ascertained through review of medical records or death certificates by physicians who were blinded to exposure status. Deaths were identified through reports from the next of kin, the postal authorities, or by searching the National Death Index (NDI).

Results

We documented 8,041 CHD cases during an average of 23.1 years follow-up. In the multivariable-adjusted model, the pooled hazard ratio (HR) (95% CI) of CHD risk comparing extreme quintiles of total whole grains consumption was 0.77 (0.72, 0.83; p trend <0.0001). Higher consumption of most individual whole grain foods was associated with significantly lower risk of CHD. Comparing participants consuming ≥1 servings/d with those consuming < 1 serving/month, the multivariable-adjusted pooled HRs (95% CIs) of CHD were 0.84 (0.78, 0.90; p trend <0.0001) for whole grain cold breakfast cereal and 0.92 (0.85, 0.99) for dark bread, and the association was null for popcorn intake [HR (95% CI): 1.08 (0.95, 1.23)]. For other whole

grain foods with lower overall intake levels, comparing intake levels of ≥2 servings/week with < 1 serving/month, the pooled hazard ratios (95% CIs) were 0.79 (0.73, 0.84) for oatmeal, 0.79 (0.71, 0.89) for brown rice, 0.83 (0.77, 0.90) for added bran, and 0.82 (0.71, 0.94) for wheat germ. Stratified analyses did not show differential associations by body weight, physical activity, family history of myocardial infarction, or smoking status.

Conclusion

These data suggest that the higher consumption of total whole grains, as well as most individual whole grain foods, were significantly associated with lower CHD risk. This study provides further evidence in support of increasing whole grain intake for the prevention of CHD in U.S. populations.

Introduction

Cardiovascular disease (CVD) remains a leading cause of death in the U.S. Recent national statistics suggested that CVD accounted for 23.4% of total deaths in 2015.[1] Coronary heart disease (CHD) alone leads to over 370,000 pre-mature deaths annually.[2] Meanwhile, CHD is largely preventable through adopting a healthy lifestyle and diet.[3] Of many modifiable dietary factors, whole grains have been extensively examined in relation to risk of CHD. Most epidemiological studies derived total whole grain intake by summing up the whole-grain contents from all food sources.[4] The majority of prospective cohort studies have consistently documented potential benefits of overall whole grain consumption on the prevention of CHD,[5–9] although less is known regarding the relationship between individual whole grain foods and risk of CHD. Given various biochemical compositions of grain species, as well as exogenous ingredients introduced during food preparation,[10] it is likely that different whole grain foods may exert differential associations with cardiovascular outcomes. Therefore it is of great importance to evaluate whether individual whole grain foods are associated with chronic disease risk. Such information will also further refine the guidelines on increasing the consumption of whole grains to facilitate disease prevention. In this regard, a meta-analysis of prospective cohort studies of CHD has demonstrated inverse associations of several whole grain foods including whole grain cold breakfast cereal, whole grain bread, and added bran, while the relationship with other commonly-consumed whole grain foods, such as popcorn and oatmeal, remains largely unknown.

To fill the knowledge gap, the current study systematically evaluated the associations between intake of several commonly-consumed whole grain foods and the risk of CHD in three large prospective cohorts of health professionals.

Methods

Study population

The Nurses' Health Study (NHS) was initiated in 1976, when 121,700 female registered nurses aged 30-55 years answered a mailed questionnaire on their medical history and lifestyle characteristics. A parallel cohort study of younger women, the Nurses' Health Study II (NHSII), was established in 1989 and included 116,340 eligible female nurses aged 25-42 years. A questionnaire similar to that used in NHS was administered at baseline to assess medical history and lifestyle factors. In 1986, the Health Professionals Follow-Up Study (HPFS) was started and recruited 51,529 U.S. male health professionals aged 40-75 years. The HPFS participants completed a baseline questionnaire that was similar to that used in the NHS and NHSII. In all three cohorts, participants were sent questionnaires biennially to update their diet and lifestyle information and identify newly diagnosed CHD and other diseases. The cumulative response rates in three cohorts exceeded 90%.[11,12]

The study baseline was set to be 1984 for NHS, 1991 for NHSII, and 1986 for HPFS, when a comprehensive semi-quantitative food frequency questionnaire (sFFQ) was administered to assess diet. The exclusion criteria included the presence of cardiovascular disease or cancer at baseline, not returning the sFFQ or had unusual total energy intake (<500 or >3500 kcal/day for women and <800 or >4200 kcal/day for men), or completing baseline questionnaire only. The final study population consisted of 71,942 participants in NHS, 90,886 in NHSII, and 39,490 in HPFS.

The study protocol was approved by the Human Research Committee of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. Completion and return of study questionnaires implied informed consent of the participants.

Dietary assessment

In all three cohorts, diet was assessed using a validated sFFQ at baseline and updated every 2-4 years during the follow-up. For each food item listed in the sFFQ, the participants were asked their average consumption frequency of a pre-specified portion size during the previous year. There are nine possible responses for consumption frequencies ranging from never or <1 time/month to ≥6 times/day. In the current analysis, we focused on the consumption of seven commonly-consumed whole grain foods/components, including cold breakfast cereals, dark bread, popcorn, oatmeal, bran added to food, wheat germ, and brown rice. Based on the brand names provided by the participants, we further classified cold breakfast cereal into whole grain-based breakfast cereal and refined grain-based breakfast cereal, depending on the relative contents of whole grain ingredients in the product (containing ≥25% whole grains or bran by weight classified as whole grain cold breakfast cereal). Since 2002 in the NHS and HPFS, and 2003 in the NHSII, an additional question regarding the types of popcorn was added to the sFFQ in which participants were asked whether they consumed regular or light/fat free popcorn. We estimated the total whole grain consumption by summing up the intake of whole grain ingredients from all grain-containing food.[13] Validation studies showed adequate validity of whole grain foods assessments. For example, the FFQ assessments were significantly correlated with those assessed using multiple-day diet records; the correlation coefficients were 0.58 for dark bread and 0.73 for cold breakfast cereal.[14]

Demographic and lifestyle factors assessment

In all three cohorts, a similar follow-up questionnaire was mailed to participants to assess and update information regarding smoking status, vitamin supplements use, alcohol consumption, menopausal status (women only), and years of postmenopausal hormone use (women only), physician-diagnosed hypertension and hypercholesterinemia, and other time-varying variables. Height was reported at baseline, and body weight was updated biennially. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Recreational physical activity was measured with a validated questionnaire asking about the average time spent on 10 common activities. Based on this information, we calculated weekly energy expenditure in metabolic equivalent (METs) hours weighting each activity by its intensity level.[15] Multiple validation studies demonstrated adequate validity of these self-reported variables.[16–20] We used the alternative healthy eating index (AHEI),[21] after removing the whole grain component, to assess overall diet quality independent of whole grains intake.

Assessment of coronary heart disease

Total coronary heart disease (CHD) including nonfatal myocardial infarction (MI) and fatal CHD was the primary disease outcome for the current analysis. In all three cohorts, permission was sought to access medical records of participant who reported having a nonfatal MI on a follow-up questionnaire. Study physicians who were blinded to exposure status reviewed the medical records and confirmed a reported MI according to the WHO criteria, which require the presence of symptoms, and either typical electrocardiographic changes or elevated cardiac enzyme levels.[22,23] Deaths were identified through reports from the next of kin, the postal authorities, or by searching the National Death Index (NDI).[24] Fatal coronary heart disease was confirmed by a review of hospital records or autopsy reports in which CHD was listed as the underlying cause of death or there was evidence of previous CHD available from medical records.[25]

Statistical analysis

Cumulative averages of total whole grains and individual whole grain foods were calculated to represent long-term intake.[26] For each participant, we counted their person-time from the return date of the baseline FFQ to the CHD diagnosis date, death date, date of last return of a valid follow-up questionnaire, or the end of follow-up (2012 for NHS and HPFS, 2013 for NHSII), whichever occurred first. To alleviate the potential reverse causality that participants with existing diseases might change their usual diet intake that is etiologically relevant, we stopped updating dietary information once the participants developed diabetes, stroke, coronary artery bypass graft, hypertension, hypercholesterinemia or cancer during follow-up. The proportion of missing values of covariates ranged from 4.0% for total energy to 10.7% for BMI. We replaced missing values with valid values in the preceding questionnaire for one follow-up cycle, and then created missing indicators to handle subsequent missing values.

A multivariable-adjusted Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between total whole grains as well as individual whole grain foods and risk of CHD. The proportional hazards assumption was evaluated by including an interaction term between each whole grain variable and the logarithm of person-time, and we did not detect violations in any analyses. Total whole grain intake was categorized into quintiles. We used three pre-specified categories (< 1 serving/month, 1 serving/month – 1 serving/week and ≥ 2 servings/week) for oatmeal, brown rice, added bran, and wheat germ which had modest-to-low intake, whereas four pre-specified categories (< 1 serving/month, 1 serving/month – 1 serving/week, 1 serving/week – 4-6 servings/wk, and ≥ 1 serving/d) were used for whole grain cold breakfast cereal, dark bread, and popcorn, for which the consumption level were, on average, higher. Covariates included in the models were age (month), ethnicity (white, African American, Asian, others), time-varying BMI (<21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥30.0 g/d), multivitamin use (yes, no), physical activity (quintiles), modified AHEI (quintiles), family history of myocardial infarction (yes, no), baseline diabetes (yes, no), postmenopausal hormone use (women only ; never, former, or current hormone use, or missing), and oral contraceptive use (yes, no; women only). The median value of each individual whole grain food and total whole grain consumption within each category was modeled as continuous variables to calculate HRs (95%CIs) and p value for trend. Moreover, in the subgroup analysis, we explored the effect modification by several lifestyle factors, including BMI, physical activity, smoking status, and family history of myocardial infarction. In a secondary analysis, we analyzed the associations for regular or fat-free/light popcorn consumption with CHD risk. Data from each cohort were analyzed separately, and results were pooled using a random effect model. To evaluate the heterogeneous associations among individual whole grain foods with CHD risk, we performed a Wald test for the joint hypothesis that assumed the beta coefficients were equal for seven individual whole grain foods.

Several sensitivity analyses were performed. First, because the whole grain food intake might confound the associations of each other, we additionally adjust for the intake of all other whole grain foods when modeling each whole grain food. For example, when oatmeal was modeled, a variable that summed up the intake of all other six foods was additionally adjusted in the same model. Second, because the strategy of stopping updating dietary information upon occurrence of chronic conditions may introduce differential errors in dietary assessments between diseased participants and other participants, we conducted a sensitivity analysis by continuing to update dietary intake upon occurrence of diabetes, stroke, coronary artery bypass graft, hypertension, hypercholesterinemia or cancer. We further tested the robustness of this strategy by resuming to update diet 8 years after the incidence of aforementioned chronic diseases. For example, for participants who developed stroke in 1990, we stopped updating diet in 1994 and 1998 and then continued to update diet after 1998. Finally, to further reduce the impact of residual confounding by diet we adjusted for individual dietary factors including polyunsaturated to saturated fat ratio, intakes of *trans* fat, red/processed meat, fish, sugar sweetened beverages, coffee, and nuts (all in quintiles) instead of the modified AHEI.

All statistical tests were 2-sided with significant level of 0.05 and performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

Table 2.1 presents participants' baseline characteristics according to the total whole grain intake in the three cohorts. In all three cohorts, higher total whole grain intake was correlated with a constellation of healthy lifestyle and dietary factors, including a lower BMI, higher physical activity level, lower prevalence of smoking, higher prevalence of multivitamin use, and better diet quality. Moreover, cross-sectionally, frequent whole grain consumers tended to have a lower prevalence of hypertension and a higher prevalence of hypercholesterolemia except for participants in the NHSII for whom whole grain intake was associated with a lower prevalence of both conditions.

Table 2.1. Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Total whole grain consumption				
	Q1	Q2	Q3	Q4	Q5
Nurses' Health Study					
Median, servings/d	0.1	0.4	0.7	1.0	1.9
No of participants	142,22	14,555	14,426	14,449	14,373
Age (years)	49.7 (6.9)	49.8 (7.0)	50.2 (7.1)	51.1 (7.2)	52.4 (7.2)
Baseline body mass index (kg/m²)	25.2 (5.0)	25.3 (4.9)	25.2 (4.7)	24.9 (4.6)	24.4 (4.3)
Race					
- White, %	96.8	97.8	98.1	98.0	98.2
- African American, %	0.3	0.2	0.2	0.2	0.3
- Asian, %	1.2	0.7	0.6	0.5	0.4
- Others, %	1.8	1.2	1.2	1.2	1.1
Physical activity(MET-h/wk)*	5.1 (1.9-15.2)	6.8 (2.4-16.5)	7.7 (2.9-18.6)	8.4 (3.1-20.2)	10.0 (3.4-21.5)
Hypertension, %	9.2	8.4	7.7	7.2	6.8
High cholesterol, %	3.0	3.0	3.1	3.6	4.0
Baseline diabetes, %	0.9	0.9	0.8	0.9	0.9
Family history of MI , %	19.9	19.8	19.6	18.4	19.4
Current smokers, %	36.3	27.6	23.3	19.0	14.5
Multivitamin use, %	30.2	33.9	36.7	39.7	44.1
Oral contraceptive use, %	46.9	49.0	49.9	50.0	50.4
Hormone use					
- premenopausal, %	52.7	53.0	53.8	53.2	52.9
- postmenopausal-never, %	27.2	25.5	24.3	23.3	22.4
- postmenopausal-current, %	9.1	10.6	11.0	12.2	13.6
- postmenopausal-past, %	11.0	10.8	10.9	11.3	11.1
Alcohol consumption (g/day)*	2.8 (0.4-12.0)	2.5 (0.5-9.7)	2.4 (0.4-9.0)	2.1 (0-8.0)	1.5 (0-6.5)
Total energy intake (Kcal/d)	1707(552)	1791(541)	1783(540)	1776(522)	1652 (476)
Modified alternative healthy eating index	42.7 (9.9)	44.2 (9.6)	45.6 (9.7)	46.9 (10.0)	49.4 (10.6)
Nurses' Health Study II					
Median, servings/d	0.3	0.7	1.1	1.6	2.5
No of participants	18,165	17,986	18,094	18,135	18,010
Age (years)	36.5 (4.7)	36.5 (4.7)	36.5 (4.7)	36.5 (4.6)	36.9 (4.6)
Baseline body mass index (kg/m²)	25.1 (5.9)	25.0 (5.6)	24.7 (5.3)	24.4 (5.0)	23.9 (4.6)
Race					
- White, %	94.3	96.2	97.1	97.6	97.3
- African American, %	0.5	0.6	0.4	0.4	0.6
- Asian, %	3.1	1.5	1.1	0.9	1.0

Table 2.1. (continued) Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

- Others, %	2.1	1.8	1.3	1.2	1.1
Physical activity(MET-h/wk)*	9.3 (3.4-21.8)	11.2 (4.5-24.5)	12.5 (5.2-25.9)	13.9 (5.9-28.2)	16.3 (7.2-32.7)
Hypertension, %	4.4	3.8	3.3	3.0	2.6
High cholesterol, %	10.1	9.8	9.4	9.0	9.0
Baseline diabetes, %	0.7	0.6	0.6	0.5	0.8
Family history of MI, %	44.4	44.1	43.0	42.7	42.7
Current smokers, %	19.4	14.4	11.2	8.5	7.1
Multivitamin use, %	36.1	40.7	44.0	47.7	50.7
Oral contraceptive use, %	82.4	84.5	84.6	84.3	83.2
Hormone use					
- premenopausal, %	97.0	96.7	97.1	96.9	96.6
- postmenopausal-never, %	0.2	0.2	0.2	0.2	0.2
- postmenopausal-current, %	2.4	2.8	2.5	2.6	2.8
- postmenopausal-past, %	0.3	0.3	0.2	0.3	0.3
Alcohol consumption (g/day)*	0.9 (0-3.5)	1.2 (0-4.0)	1.2 (0-3.8)	1.2 (0-3.7)	0.9 (0-3.3)
Total energy intake (Kcal/d)	1772 (578)	1821 (561)	1824 (551)	1820 (527)	1710 (510)
Modified alternative healthy eating index	41.6 (9.7)	44.0 (9.5)	45.7 (9.7)	47.2 (9.7)	50.7 (10.0)
Health Professionals Follow-Up Study					
Median, servings/d	0.2	0.6	1.1	1.7	2.8
No of participants	7,953	7,897	7,818	7,898	7,914
Age (years)	52.6 (9.2)	52.1 (9.3)	52.4 (9.4)	53.0 (9.5)	53.8 (9.6)
Baseline body mass index (kg/m²)	25.8 (3.3)	25.8 (3.3)	25.6 (3.3)	25.4 (3.3)	24.8 (3.0)
Race					
- White, %	92.9	94.9	95.9	96.8	95.4
- African American, %	2.3	2.3	2.1	1.8	2.4
- Asian, %	3.6	1.4	1.0	0.9	1.3
- Others, %	1.1	1.4	0.9	0.5	0.9
Physical activity(MET-h/wk)*	8.3 (2.4-23.1)	10.6 (3.4-26.6)	12.1 (4.1-28.3)	13.5 (4.7-30.1)	16.3 (5.9-34.8)
Hypertension, %	22.2	20.8	18.4	18.0	18.5
High cholesterol, %	9.2	9.5	10.0	10.3	12.8
Baseline diabetes, %	2.1	2.1	2.3	2.4	2.9
Family history of MI , %	12.4	12.3	11.9	11.5	11.9
Current smokers, %	17.1	12.0	8.3	6.0	4.3
Multivitamin use, %	34.7	37.8	41.2	45.1	50.3
Alcohol consumption (g/day)*	6.9 (1.0-18.8)	6.6 (1.1-16.4)	6.3 (1.0-16.1)	5.5 (0.9-13.8)	3.9 (0-12.1)
Total energy intake (Kcal/d)	1987 (647)	2037 (643)	2063 (637)	2021 (596)	1881 (556)
Modified alternative healthy eating index	45.9 (10.6)	48.5 (10.3)	49.8 (10.4)	51.5 (10.5)	54.7 (10.3)

Table 2.1. (continued) Age-standardized characteristics of study participants in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

*Value is median (interquartile range)

During an average follow-up duration of 23.1 years, a total of 8,041 CHD cases were documented, of which 5,267 were nonfatal MI and 3,259 cases were fatal CHD. In all three cohorts, higher total whole grain consumption was associated a significantly lower risk of CHD (**Table 2.2**). Comparing extreme quintiles, the multivariable-adjusted pooled HR was 0.77 (95%CI 0.72, 0.83, p trend <0.0001). The associations between individual whole grain foods and CHD risk were presented in **Table 2.3**. In the pooled results, comparing participants consuming ≥1 servings/d with those consuming < 1 serving/month, the multivariable-adjusted pooled HRs (95% CIs) of CHD were 0.84 (0.78, 0.90; p trend <0.0001) for whole grain cold breakfast cereal, 0.92 (0.85, 0.99) for dark bread, and 1.08 (0.95, 1.23) for popcorn. For other whole grain foods with lower overall intake levels, comparing intake level of ≥2 servings/week with < 1 serving/month, the pooled HRs (95% CIs) were 0.79 (0.73, 0.84) for oatmeal, 0.79 (0.71, 0.89) for brown rice, 0.83 (0.77, 0.90) for added bran, and 0.82 (0.71, 0.94) for wheat germ. Results by cohorts were shown in **Supplemental table 2.1**. The p values for the joint test was 0.05 for the NHS, 0.004 for the NHSII, and 0.01 for the HPFS suggesting potentially heterogeneous associations between individual whole grain foods with CHD risk. The associations were similar for fatal CHD (**Supplemental table 2.2)** and nonfatal MI (**Supplemental table 2.3)** except that the associations with fatal CHD were attenuated for brown rice and wheat germ. In a secondary analysis that examined the associations with regular popcorn and light/fat free popcorn separately, neither type of popcorn was associated with risk of CHD (**Supplemental table 2.4**). Stratified analyses did not show differential associations by body weight, physical activity, family history of myocardial infarction, or smoking status (**Figure 2.1**).

Table 2.2. Pooled hazard ratios (95% confidence intervals) of coronary heart disease for total whole grains consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Total whole grain consumptions						
	Q1	Q2	Q3	Q4	Q5	P trend	Per one daily serving
NHS							
Cases/person years	919/364,584	734/367,404	664/366,701	619/367,559	641/366,885		
Age-adjusted model	1.00	0.80 (0.72, 0.88)	0.70 (0.64, 0.78)	0.62 (0.56, 0. 68)	0.57 (0.51, 0.63)	<.0001	0.80 (0.76, 0.84)
Multivariable adjusted model*	1.00	0.89 (0.81, 0.99)	0.84 (0.76, 0.94)	0.80 (0.72, 0.89)	0.78 (0.70, 0.87)	0.0009	0.92 (0.88, 0.97)
NHSII							
Cases/person years	215/390,279	147/390,984	110/391,745	86/392,866	90/392,008		
Age-adjusted model	1.00	0.72 (0.58, 0.89)	0.55 (0.44, 0.69)	0.42 (0.33, 0.54)	0.42 (0.33, 0.54)	<.0001	0.66 (0.59, 0.73)
Multivariable adjusted model*	1.00	0.84 (0.68, 1.04)	0.73 (0.58, 0.93)	0.60 (0.46, 0.78)	0.66 (0.50, 0.86)	<.0001	0.80 (0.72, 0.89)
HPFS							
Cases/person years	937/173,213	789/173,125	738/174,127	668/174,141	684/174,298		
Age-adjusted model	1.00	0.85 (0.78, 0.94)	0.79 (0.72, 0.87)	0.70 (0.63, 0.77)	0.67 (0.61, 0.74)	<.0001	0.90 (0.87, 0.92)
Multivariable adjusted model*	1.00	0.90 (0.82, 0.99)	0.86 (0.78, 0.95)	0.80 (0.72, 0.88)	0.79 (0.71, 0.88)	<.0001	0.94 (0.91, 0.97)
Pool results†							
Cases/person years	2,071/928,076	1,670/931,513	1,512/932,573	1,373/934,566	1,415/933,191		
Age-adjusted model	1.00	0.81 (0.76, 0.87)	0.73 (0.68, 0.78)	0.64 (0.59, 0.68)	0.60 (0.56, 0.64)	<.0001	0.85 (0.83, 0.88)
Multivariable adjusted model*	1.00	0.89 (0.84, 0.95)	0.84 (0.79, 0.90)	0.78 (0.73, 0.84)	0.77 (0.72, 0.83)	<.0001	0.93 (0.90, 0.95)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

†Study estimates from three cohorts were pooled using a random effects model.

Table 2.3. Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels					
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d	P trend	Per one daily serving
Whole grain cold breakfast cereal						
Cases/person-time	3,259/1,464,778	1,541/934,640	2,094/1,610,015	1,147/650,486		
Multivariable adjusted model*	1.00	0.92 (0.86, 0.98)	0.75 (0.71, 0.79)	0.84 (0.78, 0.90)	<.0001	0.83 (0.78, 0.89)
Dark bread						
Cases/person-time	1,009/517,808	1,755/945,783	2,423/1,693,570	2,854/1,502,759		
Multivariable adjusted model*	1.00	1.05 (0.97, 1.13)	0.87 (0.80, 0.94)	0.92 (0.85, 0.99)	0.28	0.98 (0.96, 1.01)
Popcorn						
Cases/person-time	3,012/1,140,594	3,596/2,336,110	1,157/1,000,616	276/182,600		
Multivariable adjusted model*	1.00	1.00 (0.95, 1.05)	0.92 (0.86, 0.99)	1.08 (0.95, 1.23)	0.99	1.00 (0.92, 1.08)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	4,455/2,312,100	2,618/1,690,160	968/657,660	-		
Multivariable adjusted model*	1.00	0.96 (0.91, 1.01)	0.79 (0.73, 0.84)	-	0.001	0.79 (0.69, 0.91)
Brown rice						
Cases/person-time	5,190/2,682,179	2,509/1,667,141	342/310,601	-		
Multivariable adjusted model*	1.00	0.92 (0.87, 0.96)	0.79 (0.71, 0.89)	-	0.05	0.78 (0.61, 1.00)
Added bran						
Cases/person-time	6,350/3,673,718	911/568,620	780/417,583	-		
Multivariable adjusted model*	1.00	0.91 (0.85, 0.98)	0.83 (0.77, 0.90)	-	0.002	0.89 (0.82, 0.96)
Wheat germ						
Cases/person-time	7,355/4,229,255	468/306,014	218/124,651	-		
Multivariable adjusted model*	1.00	0.97 (0.88, 1.07)	0.82 (0.71, 0.94)	-	0.006	0.77 (0.64, 0.93)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were

Table 2.3. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

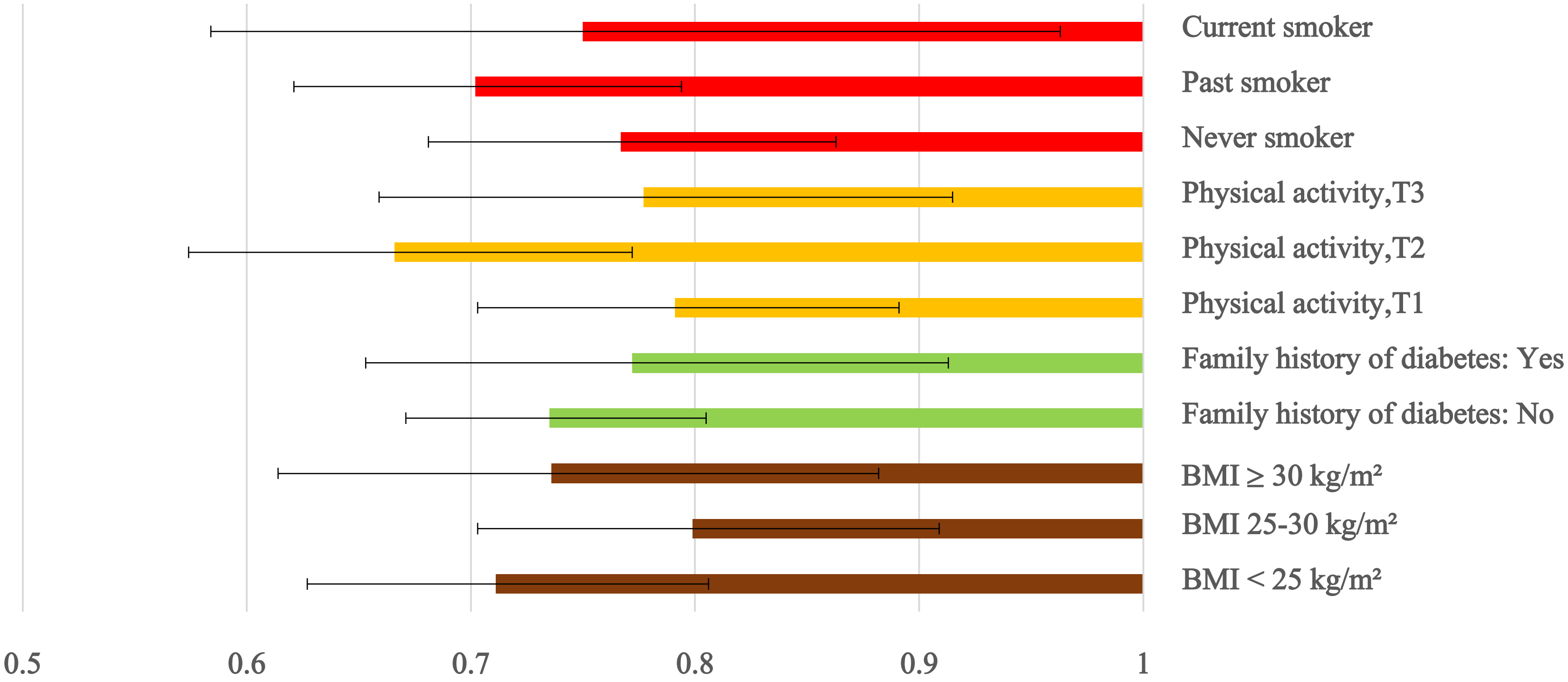

Figure 2.1. Association between total whole grains and coronary heart disease risk stratified by updated body mass index, family history of diabetes, physical activity, and smoking status

Comparing extreme quintiles.

Adjusted for same covariates as in **Table 2.3** except for the stratification variable. Continuous BMI and physical activity were adjusted to minimize residual confounding.

In the sensitivity analysis that used baseline intake only or simply-updated intake, the HRs did not change materially for most individual whole grain foods except popcorn which was associated with an increased risk of CHD (**Supplemental table 2.5**). Including individual dietary factors of the modified AHEI in the model to replace modified AHEI or adjusting for total consumption of all other whole grain foods did not change the results either (**Supplemental table 2.5**). Finally, adjusting for prevalent hypertension and hypercholesterinemia and continuously updating dietary information upon disease occurrence attenuated the results for most whole grain foods (**Supplemental table 2.6**). On the contrary, resuming dietary update after 8 years of chronic diseases occurrence produced comparable estimates as the primary analysis (**Supplemental table 2.6**).

Discussion

In three U.S. cohorts of men and women, during over 20 years of follow-up, we found that higher consumption of total whole grains was associated with significantly lower risk of CHD, and such inverse associations did not vary by physical activity, smoking status, BMI, or family history of MI. Higher consumption of all individual whole grain foods, except popcorn, was also associated with lower risk of CHD.

The epidemiological evidence consistently supports a favorable role of whole grain intake in CHD prevention. A recent meta-analysis of 45 prospective cohort studies estimated that three-serving daily whole grain intake was associated with nearly 20% lower risk of CHD, and there was no evidence of heterogeneity among included studies.[27] In contrast to the abundance of evidence regarding the association between total whole grain intake and health outcomes, there were only a limited number of studies that evaluated associations for individual whole grain foods. The previous investigations in this regard were restricted to whole grain breakfast cereal, whole grain-based bread, or added bran, all of which were associated with a lower risk of CHD in prospective studies.[8,9,28] In the current study, taking advantage of three large cohort studies with over 20 years of follow-up and repeated measurements of several commonly-consumed whole grain foods in the western diet, we were able to perform a comprehensive evaluation for their associations with risk of CHD.

Our observed inverse associations between total whole grain intake and most individual whole grain foods and CHD risk were in line with existing evidence linking whole grain intake with cardiovascular risk factors. A meta-analysis of 18 randomized clinical trials (RCTs) concluded that whole grain-based diet rich in beta-glucan, including whole wheat, oat-based breakfast cereal, oatmeal, and oat bran-supplemented foods, was effective in lowering both systolic and diastolic blood pressure.[29] Another meta-analysis including 28 RCTs examining oat bran-enriched diets showed that adding ≥3 g oat beta-glucan to the diet were able to reduce LDL and total cholesterol.[30] Moreover, comparing with a control diet that was mainly white wheat bread, whole grain meals, including whole wheat cookies, whole grain rye bread or rye porridge, and whole grain wheat or rye kernels, led to lower postprandial glucose and insulin response based on data from 14 short-term feeding trials.[31] Furthermore, comparing with refined grain-based food, whole grain food consumption has been shown to reduce inflammatory markers such as high-sensitive C-reactive protein, intercellular adhesion molecule-1, and tumor necrosis factor-α in several clinical intervention studies.[32,33] Limited evidence from intervention trials also sheds light on the biological mechanisms through which specific whole grain foods exert beneficial effects on cardiometabolic health. Whole wheat consumption may improve cardiovascular health through improving glycemic control,[34] increasing insulin sensitivity,[35] and decreasing inflammatory markers.[36] Oats intake may exert favorable effects on lowering cholesterol[37] and blood pressure,[38] while consumption of rice bran oil has been linked to lower LDL cholesterol levels.[39]

It is known that different grain species may contain various contents of dietary fiber, magnesium, antioxidants, and phytochemicals.[5] According to the USDA food composition database,[40] for example, comparing with 100g rice or oat bran, popcorn contained far less dietary fiber but much higher amount of *trans* fatty acids which can reach as much as 4 g per serving.[41] Moreover, the same amount of rye bread generally contains higher amounts of dietary fiber and vitamins than brown rice. The contents of potentially cardiovascular-protective lignans also vary substantially among whole grain foods with oat products have on average the highest amounts (401 μg/100 g) and maize products have the lowest amounts (23 μg/100 g) in dry weight.[42] Furthermore, of all whole grain foods, rice bran, oat bran, and wheat germ have generally higher contents of magnesium (>200mg/100g), an essential mineral that has been associated with reduced risk of cardiovascular disease.[43] It is worth noting that despite a potential heterogeneity in the profile of various healthy constituents, an inverse association was consistently observed for most whole grain foods, suggesting that the health benefits do not vary substantially across individual whole grain foods.

The inverse associations observed for dark bread in the current analysis was somewhat weaker compared with previous studies.[27] It is likely that participants might wrongly perceive refined grain bread with dark coloring as dark bread. This misclassification may partially explain the weaker associations. Moreover, comparing with participants from European cohorts,[28] the intake level of dark bread in the current study was much lower, and thus we were unable to examine the associations with CHD at high intake levels of whole grain dark bread. In addition to phytochemical composition intrinsic to different whole grain foods, exogenous ingredients introduced during food processing could also modulate the associations. The null association between popcorn intake and CHD risk may at least partially reflect some adverse effects resulting from constituents introduced during cooking. For example, oil-popped popcorn is prepared with butter, partially hydrogenated oil,[41] and salt. Despite a declining trend of *trans* fat in U.S. food products, a U.S. food market survey in 2011 still found that popcorn products contained an average of 1.5g/serving of *trans* fatty acids,[41] which are associated with an elevated risk of cardiovascular disease.[44] Furthermore, recent studies revealed the presence of perfluoroalkyl substances in microwave popcorn packaging.[45,46] In a recent investigation, we observed a significant correlation between popcorn intake and blood levels of these endocrine disrupting chemicals, which were associated with type 2 diabetes risk in the NHSII cohort.[47] These ingredients or contaminants may exert adverse effects on lipid profiles, blood pressure, and insulin resistance, and offset potential beneficial effects of popcorn on cardiovascular health.

The major strengths of the current study include the comprehensive, repeated measurements of several common whole grains foods, large sample size with long follow-up time, and high follow-up rates. Our study has several limitations as well. First, in this observational study, we cannot exclude the possibility of confounding by lifestyle and dietary factors that we did not assess in the follow-up questionnaire and sFFQ or were measured with errors. Second, measurement errors may present in the assessments of individual whole grain foods, particularly for those with low consumptions. However, using the cumulative averages of the individual whole grain foods intake over 10 follow-up cycles helped to minimize random measurement errors and concomitantly provided estimates of long-term intake of these whole grain foods. Moreover, the prospective design renders that the measurement error of dietary assessment was unlikely to be differential with respect to the outcome ascertainment, and thus usually resulted in an attenuated association towards the null. Third, we were unable to analyze the association of other whole grains, such as quinoa, rye, and buckwheat for which the consumption level is low in U.S. populations. Fourth, stopping updating the dietary information upon occurrence of chronic conditions may help alleviate reverse causation due to changes in diet as a result of the diagnosis of the chronic diseases, although this approach may also potentially introduce extraneous heterogeneity in dietary assessments. This is because it can carry forward less updated intake levels during extended follow-up periods especially for some participants who developed diseases at early follow-up, but for others diet was continuously updated and thus subject to less random errors. Nonetheless, in the sensitivity analysis where we stopped updating dietary information until 8 years after occurrence of chronic diseases, the associations were not materially changed, suggesting potentially limited impact of this approach on the associations of interest. Finally, the generalizability of our findings may be limited because the participants were health professionals with higher health awareness and better access to health care resources. However, the underlying mechanisms linking whole grains intake and CHD development are unlikely vary across different ethnic groups.

In conclusion, higher intake of total whole grains, as well as most individual whole grain foods, is associated with significantly lower CHD risk in US men and women. Our data provide further support for the current recommendations to increase consumption of whole grains for the prevention of cardiovascular diseases.

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Supplemental materials

Supplemental table 2.1. Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels					
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d	P trend	Per one daily serving
Cold breakfast cereal						
NHS						
Cases/person-time	1,577/677,721	719/366,140	923/611,220	358/178,053		
Multivariable adjusted model*	1.00	0.95 (0.87, 1.04)	0.74 (0.68, 0.80)	0.89 (0.79, 1.00)	<0.001	0.81 (0.72, 0.91)
NHSII						
Cases/person-time	247/509,405	158/412,036	184/740,798	59/295,643		
Multivariable adjusted model*	1.00	0.83 (0.68, 1.02)	0.60 (0.49, 0.73)	0.57 (0.43, 0.76)	<.0001	0.56 (0.42, 0.74)
HPFS						
Cases/person-time	1,435/277,652	664/156,464	987/257,997	730/176,790		
Multivariable adjusted model*	1.00	0.91 (0.83, 1.00)	0.79 (0.73, 0.86)	0.84 (0.77, 0.92)	0.001	0.87 (0.80, 0.95)
P for heterogeneity			0.02			
Dark bread						
NHS						
Cases/person-time	426/185,635	770/362,027	1,144/676,324	1,237/609,148		
Multivariable adjusted model*	1.00	1.04 (0.92, 1.17)	0.85 (0.76, 0.96)	0.91 (0.81, 1.02)	0.50	0.98 (0.94, 1.03)
NHSII						
Cases/person-time	94/234,629	170/405,070	227/751,003	157/567,181		
Multivariable adjusted model*	1.00	1.16 (0.90, 1.50)	0.91 (0.71, 1.17)	0.90 (0.69, 1.18)	0.42	0.95 (0.84, 1.08)
HPFS						
Cases/person-time	489/97,544	815/178,686	1,052/266,243	1,460/326,430		
Multivariable adjusted model*	1.00	1.03 (0.92, 1.16)	0.87 (0.78, 0.97)	0.92 (0.83, 1.03)	0.51	0.99 (0.95, 1.02)
P for heterogeneity			0.80			
Popcorn						
NHS						
Cases/person-time	1,498/623,861	1,552/861,433	448/304,893	79/42,947		
Multivariable adjusted model*	1.00	0.99 (0.92, 1.07)	0.93 (0.83, 1.04)	1.18 (0.94, 1.48)	0.38	1.07 (0.93, 1.23)
NHSII						
Cases/person-time	80/260,276	359/1,059,076	150/536,998	59/101,533		
Multivariable adjusted model*	1.00	1.13 (0.88,1.44)	0.87 (0.66, 1.15)	1.66 (1.17, 2.35)	0.43	1.09 (0.89, 1.33)
HPFS						

Supplemental table 2.1. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Cases/person-time	1,434/256,457	1,685/415,601	559/158,725	138/38,120		
Multivariable adjusted model*	1.00	0.99 (0.92,1.07)	0.92 (0.83, 1.02)	0.92 (0.77, 1.10)	0.25	0.94 (0.84, 1.05)
P for heterogeneity			0.18			
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
NHS						
Cases/person-time	2,011/989,651	1,207/621,912	359/221,571	-		
Multivariable adjusted model*	1.00	0.99 (0.92, 1.07)	0.80 (0.71, 0.89)	-	0.26	0.87 (0.68, 1.11)
NHSII						
Cases/person-time	332/854,551	250/797,202	66/306,129	-		
Multivariable adjusted model*	1.00	0.87 (0.74, 1.03)	0.64 (0.49, 0.85)	-	0.04	0.47 (0.23, 0.95)
HPFS						
Cases/person-time	2,112/467,898	1,161/271,046	543/129,960	-		
Multivariable adjusted model*	1.00	0.94 (0.87, 1.01)	0.80 (0.72, 0.88)	-	0.006	0.79 (0.66, 0.93)
P for heterogeneity			0.33			
Brown rice						
NHS						
Cases/person-time	2,611/1,238,689	860/517,823	106/76,623	-		
Multivariable adjusted model*	1.00	0.95 (0.87, 1.03)	0.86 (0.71, 1.05)	-	0.22	0.74 (0.46, 1.20)
NHSII						
Cases/person-time	396/1,020,042	208/771,414	44/166,426	-		
Multivariable adjusted model*	1.00	0.82 (0.69, 0.98)	0.87 (0.63, 1.21)	-	0.97	0.99 (0.42, 2.30)
HPFS						
Cases/person-time	2,183/423,448	1,441/377,904	192/67,552	-		
Multivariable adjusted model*	1.00	0.91 (0.85, 0.97)	0.74 (0.64, 0.86)	-	0.01	0.77 (0.57, 1.05)
P for heterogeneity			0.85			
Added bran						
NHS						
Cases/person-time	2,877/1,397,650	380/230,206	320/205,278	-		
Multivariable adjusted model*	1.00	0.89 (0.79, 0.99)	0.79 (0.70, 0.89)	-	0.27	0.92 (0.80, 1.06)
NHSII						
Cases/person-time	569/1,631,234	61/221,613	18/105,036	-		
Multivariable adjusted model*	1.00	0.91 (0.69, 1.19)	0.56 (0.35, 0.90)	-	0.06	0.45 (0.20, 1.02)
HPFS						
Cases/person-time	2,904/644,834	470/116,801	442/107,269	-		

Supplemental table 2.1. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

Multivariable adjusted model*	1.00	0.94 (0.85, 1.04)	0.88 (0.79, 0.98)	-	0.005	0.88 (0.80, 0.96)
P for heterogeneity			0.22			
Wheat germ						
NHS						
Cases/person-time	3,284/1,642,669	206/129,627	87/60,838	-		
Multivariable adjusted model*	1.00	0.95 (0.83, 1.10)	0.80 (0.64, 1.00)	-	0.17	0.79 (0.57, 1.11)
NHSII						
Cases/person-time	624/1,809,524	21/118,432	3/29,926	-		
Multivariable adjusted model*	1.00	0.69 (0.45, 1.08)	0.38 (0.12, 1.18)	-	0.05	0.04 (0.00, 0.98)
HPFS						
Cases/person-time	3,447/777,062	241/57,955	128/33,887	-		
Multivariable adjusted model*	1.00	1.02 (0.89, 1.16)	0.84 (0.70, 1.01)	-	0.03	0.78 (0.62, 0.97)
P for heterogeneity			0.18			

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Supplemental table 2.2. Pooled hazard ratios (95% confidence intervals) of nonfatal myocardial infarction for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

	Consumption levels					
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d	P trend	Per one daily serving
Whole grain cold breakfast cereal						
Cases/person-time	2,108/1,434,946	1,041/913,471	1,420/1,580,720	698/639,699		
Multivariable adjusted model*	1.00	0.92 (0.85, 0.99)	0.76 (0.71, 0.81)	0.82 (0.75, 0.89)	<.0001	0.82 (0.75, 0.89)
P for heterogeneity			0.02			
Dark bread						
Cases/person-time	648/503,605	1,153/924,064	1,628/1,661,393	1,838/1,479,773		
Multivariable adjusted model*	1.00	1.04 (0.94, 1.15)	0.86 (0.79, 0.95)	0.92 (0.84, 1.01)	0.98	1.00 (0.97, 1.03)
P for heterogeneity			0.32			
Popcorn						
Cases/person-time	1,779/1,127,555	2,484/2,285,736	825/978,422	179/177,123		
Multivariable adjusted model*	1.00	1.03 (0.97, 1.10)	0.94 (0.86, 1.02)	1.05 (0.89, 1.24)	0.82	0.99 (0.90, 1.09)
P for heterogeneity			0.10			
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	2,954/2,269,654	1,736/1,654,715	577/644,467	-		
Multivariable adjusted model*	1.00	0.94 (0.89, 1.00)	0.75 (0.69, 0.82)	-	0.01	0.79 (0.66, 0.95)
P for heterogeneity			0.17			
Brown rice						
Cases/person-time	3,403/2,633,647	1,648/1,631,997	216/303,191	-		
Multivariable adjusted model*	1.00	0.90 (0.85, 0.96)	0.76 (0.66, 0.88)	-	0.01	0.65 (0.46, 0.90)
P for heterogeneity			0.51			
Added bran						
Cases/person-time	4,195/3,597,255	579/558,690	493/412,891	-		
Multivariable adjusted model*	1.00	0.90 (0.82, 0.98)	0.87 (0.79, 0.96)	-	0.03	0.89 (0.81, 0.99)
P for heterogeneity			0.39			
Wheat germ						
Cases/person-time	4,844/4,144,363	295/300,806	128/123,665	-		
Multivariable adjusted model*	1.00	0.95 (0.84, 1.07)	0.81 (0.67, 0.97)	-	0.05	0.78 (0.61, 1.00)
P for heterogeneity			0.20			

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9,

Supplemental table 2.2. (continued) Pooled hazard ratios (95% confidence intervals) of nonfatal myocardial infarction for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012)

15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 2.3. Pooled hazard ratios (95% confidence intervals) of fatal coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012) and Health Professionals Follow-Up Study (1986-2012)

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Cases/person-time	1,378/976,318	592/532,761	764/881,967	525/361,731		
Multivariable adjusted model*	1.00	0.94 (0.85, 1.04)	0.69 (0.63, 0.76)	0.86 (0.77, 0.95)	0.0005	0.84 (0.76, 0.92)
P for heterogeneity			0.33			
Dark bread						
Cases/person-time	429/289,352	687/552,144	926/957,574	1,217/953,708		
Multivariable adjusted model*	1.00	1.02 (0.90, 1.15)	0.85 (0.76, 0.96)	0.90 (0.81, 1.01)	0.19	0.97 (0.93, 1.01)
P for heterogeneity			0.99			
Popcorn						
Cases/person-time	1,481/898,766	1,303/1,301,107	370/470,483	105/82,424		
Multivariable adjusted model*	1.00	0.93 (0.86, 1.00)	0.84 (0.75, 0.95)	1.12 (0.91, 1.37)	0.96	1.00 (0.87, 1.14)
P for heterogeneity			0.95			
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time	1,794/1,486,317	1,026/909,645	439/356,818	-		
Multivariable adjusted model*	1.00	0.97 (0.90, 1.05)	0.80 (0.72, 0.90)	-	0.007	0.76 (0.62, 0.93)
P for heterogeneity			0.93			
Brown rice						
Cases/person-time	2,126/1,694,767	989/911,962	144/146,051	-		
Multivariable adjusted model*	1.00	0.92 (0.85, 1.00)	0.85 (0.71, 1.01)	-	0.87	1.03 (0.74, 1.42)
P for heterogeneity			0.70			
Added bran						
Cases/person-time	2,542/2,082,626	379/352,711	338/317,441	-		
Multivariable adjusted model*	1.00	0.93 (0.84, 1.04)	0.78 (0.69, 0.88)	-	0.01	0.87 (0.77, 0.97)
P for heterogeneity			0.77			
Wheat germ						
Cases/person-time	2,947/2,466,312	194/190,540	118/95,928	-		
Multivariable adjusted model*	1.00	0.99 (0.85, 1.14)	0.94 (0.78, 1.14)	-	0.29	0.89 (0.71, 1.11)
P for heterogeneity			0.84			

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline

Supplemental table 2.3. (continued) Pooled hazard ratios (95% confidence intervals) of fatal coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012) and Health Professionals Follow-Up Study (1986-2012)

diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model

Supplemental table 2.4. Association between regular and light/fat free popcorn intake and risk of coronary heart disease in Nurses' Health Study (2002-2012), Nurses' Health Study II (2003-2013) and Health Professionals Follow-Up Study (2002-2012)

	Regular popcorn				Light, fat free popcorn			
	<1 serving/month	1 serving/month – 1 serving/wk	> 2 servings/wk	P trend	<1 serving/month	1 serving/month – 1 serving/wk	> 2 servings/wk	P trend
NHS								
Cases/person-years	756/372,436	164/103,039	18/12,163		673/327,389	225/131,515	40/28,734	
Multivariable-adjusted model 1*	1.00	0.92(0.77,1.10)	0.89(0.55,1.43)	0.45	1.00	1.08(0.92,1.26)	0.98(0.70,1.35)	0.98
Multivariable-adjusted model 2*	1.00	0.91(0.77,1.09)	0.90(0.56,1.44)	0.45	1.00	1.08(0.92,1.27)	0.98(0.71,1.36)	0.94
NHSII								
Cases/person-years	131/327,727	91/233,338	16/31,805		144/293,358	76/242,083	18/57,428	
Multivariable-adjusted model 1*	1.00	0.98(0.75,1.29)	1.22(0.72,2.08)	0.49	1.00	0.72(0.54,0.95)	0.70(0.42,1.15)	0.14
Multivariable-adjusted model 2*	1.00	0.99(0.75,1.31)	1.22(0.72,2.09)	0.42	1.00	0.72(0.54,0.96)	0.69(0.42,1.14)	0.13
HPFS								
Cases/person-years	284/80,244	168/49,753	21/6,874		359/93,502	98/36,655	16/6,714	
Multivariable-adjusted model 1*	1.00	1.12(0.92,1.37)	1.00(0.63,1.58)	0.84	1.00	0.85(0.67,1.07)	0.84(0.51,1.40)	0.34
Multivariable-adjusted model 2*	1.00	1.13(0.93,1.38)	1.00(0.63,1.58)	0.79	1.00	0.84(0.67,1.05)	0.85(0.51,1.42)	0.33
Pooled†								
Multivariable-adjusted model 1*	1.00	1.00 (0.89, 1.13)	1.01 (0.77, 1.34)	0.97	1.00	0.94 (0.84, 1.06)	0.87 (0.69, 1.11)	0.27
Multivariable-adjusted model 2*	1.00	1.00 (0.89, 1.13)	1.02 (0.77, 1.35)	0.90	1.00	0.94 (0.84, 1.06)	0.88 (0.69, 1.11)	0.28

*Multivariable-adjusted model 1 adjusted for age, race (white, African-American, Asian, others), multivitamin use, family history of MI (yes, no), baseline diabetes, alcohol consumption (Abstainer, 0-4.9g/d, 5-9.9g/d, 10-14.9g/d, 15-29.9g/d and ≥ 30g/d), modified alternative healthy eating index with whole grain excluded (quintiles), smoking status (never smoker, past smoker, current 1-14 cigarettes/d, current 15-24 cigarettes/d and ≥ 25 cigarettes/d), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), oral contraceptive use (women only), hormone use (women only, pre-menopausal, post-menopausal with never use, current use and past use) and total energy (quintiles).

Multivariable-adjusted model 2 mutually adjusted for regular popcorn and light/fat free.

†Study estimates from three cohorts were pooled using a random effects model

Supplemental table 2.5. Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, or adjusting for individual dietary factors or adjusting for total consumption of all other whole grain foods

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Baseline intake						
Cases/person-time	3,849/1,974,734	1,545/1,021,687	1,343/863,984	1,304/799,515		
Multivariable adjusted model*	1.00	0.97 (0.93, 1.01)	0.89 (0.86, 0.94)	0.83 (0.79, 0.87)	<.0001	0.84 (0.80, 0.88)
Simple updated intake						
Cases/person-time	3,311/1,586,097	1,397/872,793	1,300/838,678	1,297/794,806		
Multivariable adjusted model*	1.00	0.92 (0.88, 0.96)	0.85 (0.81, 0.89)	0.77 (0.73, 0.81)	<.0001	0.78 (0.74, 0.82)
Adjusting for individual dietary factors						
Cases/person-time	3,259/1,464,778	1,541/934,640	2,094/1,610,015	1,147/650,486		
Multivariable adjusted model*	1.00	0.94 (0.88, 1.00)	0.78 (0.74, 0.83)	0.86 (0.80, 0.92)	<.0001	0.85 (0.80, 0.91)
Adjusting for total consumption of all other whole grain foods						
Cases/person-time	3,259/1,464,778	1,541/934,640	2,094/1,610,015	1,147/650,486		
Multivariable adjusted model*	1.00	0.93 (0.87, 0.99)	0.76 (0.72, 0.80)	0.85 (0.79, 0.91)	<.0001	0.84 (0.78, 0.89)
Dark bread						
Baseline intake						
Cases/person-time	1,242/732,578	2,099/1,219,244	1,815/1,115,553	2,885/1,592,546		
Multivariable adjusted model*	1.00	0.91 (0.87, 0.95)	0.91 (0.87, 0.96)	0.85 (0.82, 0.90)	<.0001	0.94 (0.92, 0.96)
Simple updated intake						
Cases/person-time	1,108/622,331	1,838/1,100,724	1,656/1,030,482	2,652/1,375,431		
Multivariable adjusted model*	1.00	0.93 (0.89, 0.98)	0.93 (0.88, 0.98)	0.89 (0.85, 0.94)	<.0001	0.95 (0.93, 0.97)
Adjusting for individual dietary factors						
Cases/person-time	1,009/517,808	1,755/945,783	2,423/1,693,570	2,854/1,502,759		
Multivariable adjusted model*	1.00	1.07 (0.99, 1.16)	0.91 (0.84, 0.98)	0.96 (0.89, 1.04)	0.90	1.00 (0.97, 1.03)
Adjusting for total consumption of all other whole grain foods						
Cases/person-time	1,009/517,808	1,755/945,783	2,423/1,693,570	2,854/1,502,759		
Multivariable adjusted model*	1.00	1.05 (0.97, 1.14)	0.89 (0.82, 0.96)	0.94 (0.88, 1.02)	0.61	0.99 (0.97, 1.02)
Popcorn						
Baseline intake						

Supplemental table 2.5. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, or adjusting for individual dietary factors or adjusting for total consumption of all other whole grain foods

Cases/person-time	3,423/1,407,663	3,605/2,423,816	705/573,820	308/254,623		
Multivariable adjusted model*	1.00	1.02 (0.98, 1.06)	1.09 (1.03, 1.15)	1.11 (1.03, 1.19)	<.001	1.08 (1.03, 1.13)
Simple updated intake						
Cases/person-time	3,014/1,284,485	3,264/2,153,997	697/512,289	310/205,290		
Multivariable adjusted model*	1.00	1.04 (1.00, 1.08)	1.14 (1.08, 1.21)	1.16 (1.07, 1.25)	<.001	1.09 (1.04, 1.14)
Adjusting for individual dietary factors						
Cases/person-time	3,012/1,140,594	3,596/2,336,110	1,157/1,000,616	276/182,600		
Multivariable adjusted model*	1.00	1.02 (0.97, 1.07)	0.96 (0.89, 1.04)	1.11 (0.97, 1.26)	0.69	1.02 (0.94, 1.10)
Adjusting for total consumption of all other whole grain foods						
Cases/person-time	3,012/1,140,594	3,596/2,336,110	1,157/1,000,616	276/182,600		
Multivariable adjusted model*	1.00	1.00 (0.95, 1.05)	0.93 (0.87, 1.00)	1.09 (0.96, 1.24)	0.96	1.00 (0.93, 1.09)
	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Cases/person-time						
Baseline intake						
Cases/person-time	4,968/2,704,472	2,461/1,613,198	612/342,250			
Multivariable adjusted model*	1.00	1.00 (0.97, 1.04)	0.93 (0.87, 0.99)		0.01	0.86 (0.77, 0.97)
Simple updated intake						
Cases/person-time	4,234/2,213,385	2,350/1,497,994	706/438,620			
Multivariable adjusted model*	1.00	0.99 (0.95, 1.03)	0.82 (0.77, 0.87)		<.0001	0.71 (0.63, 0.79)
Adjusting for individual dietary factors						
Cases/person-time	4,455/2,312,100	2,618/1,690,160	968/657,660			
Multivariable adjusted model*	1.00	0.98 (0.93, 1.03)	0.81 (0.76, 0.87)		0.006	0.82 (0.72, 0.95)
Adjusting for total consumption of all other whole grain foods						
Cases/person-time	4,455/2,312,100	2,618/1,690,160	968/657,660			
Multivariable adjusted model*	1.00	0.97 (0.92, 1.02)	0.80 (0.75, 0.86)		0.004	0.81 (0.71, 0.93)
Brown rice						
Baseline intake						
Cases/person-time	5,503/2,968,068	2,289/1,500,168	249/191,684			
Multivariable adjusted model*	1.00	0.97 (0.94, 1.01)	0.97 (0.89, 1.06)		0.14	0.89 (0.76, 1.04)
Simple updated intake						
Cases/person-time	4,888/2,546,479	2,161/1,418,981	220/177,674			
Multivariable adjusted model*	1.00	0.96 (0.93, 1.00)	0.94 (0.86, 1.04)		0.06	0.84 (0.71, 1.01)

Supplemental table 2.5. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, or adjusting for individual dietary factors or adjusting for total consumption of all other whole grain foods

Adjusting for individual dietary factors					
Cases/person-time	5,190/2,682,179	2,509/1,667,141	342/310,601		
Multivariable adjusted model*	1.00	0.93 (0.88, 0.98)	0.82 (0.73, 0.92)	0.13	0.83 (0.65, 1.06)
Adjusting for total consumption of all other whole grain foods					
Cases/person-time	5,190/2,682,179	2,509/1,667,141	342/310,601		
Multivariable adjusted model*	1.00	0.93 (0.88, 0.98)	0.81 (0.73, 0.91)	0.12	0.82 (0.65, 1.05)
Added bran					
Baseline intake					
Cases/person-time	6,648/3,850,080	791/493,415	602/316,426		
Multivariable adjusted model*	1.00	0.94 (0.89, 0.99)	0.85 (0.79, 0.92)	<.0001	0.87 (0.81, 0.93)
Simple updated intake					
Cases/person-time	6,011/3,517,634	694/378,843	572/256,857		
Multivariable adjusted model*	1.00	1.05 (0.99, 1.11)	0.93 (0.86, 1.00)	0.04	0.93 (0.87, 1.00)
Adjusting for individual dietary factors					
Cases/person-time	6,350/3,673,718	911/568,620	780/417,583		
Multivariable adjusted model*	1.00	0.93 (0.87, 1.00)	0.85 (0.79, 0.92)	0.005	0.89 (0.83, 0.97)
Adjusting for total consumption of all other whole grain foods					
Cases/person-time	6,350/3,673,718	911/568,620	780/417,583		
Multivariable adjusted model*	1.00	0.93 (0.86, 0.99)	0.86 (0.79, 0.93)	0.009	0.90 (0.83, 0.97)
Wheat germ					
Baseline intake					
Cases/person-time	7,426/4,273,814	442/295,093	173/91,014		
	1.00	0.83 (0.77, 0.90)	0.88 (0.77, 1.00)	0.005	0.79 (0.68, 0.93)
Simple updated intake					
Cases/person-time	6,561/3,811,241	376/226,102	141/70,776		
Multivariable adjusted model*	1.00	0.92 (0.85, 1.01)	0.97 (0.83, 1.13)	0.10	0.86 (0.72, 1.03)
Adjusting for individual dietary factors					
Cases/person-time	7,355/4,229,255	468/306,014	218/124,651		
Multivariable adjusted model*	1.00	1.00 (0.90, 1.10)	0.83 (0.73, 0.96)	0.01	0.79 (0.66, 0.95)
Adjusting for total consumption of all other whole grain foods					
Cases/person-time	7,355/4,229,255	468/306,014	218/124,651		
Multivariable adjusted model*	1.00	0.99 (0.90, 1.09)	0.84 (0.73, 0.97)	0.03	0.81 (0.68, 0.98)

Supplemental table 2.5. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) using baseline intake, simple updated intake, or adjusting for individual dietary factors or adjusting for total consumption of all other whole grain foods

[*]Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

Supplemental table 2.6. Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) in analyses that used various strategies to handle dietary data after occurrence of chronic conditions

	Consumption levels				P trend	Per one daily serving
	< 1 serving/month	1 serving/month - 1 serving/week	1 serving/week – 4-6 servings/week	≥1 servings/d		
Whole grain cold breakfast cereal						
Continuously updating diet						
Cases/person-time	2,142/1,129,994	1,363/869,337	3,636/2,094,769	831/558,911		
Multivariable adjusted model*	1.00	0.93 (0.87, 1.00)	0.89 (0.84, 0.94)	0.84 (0.77, 0.91)	<.0001	0.86 (0.80, 0.93)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	3,042/1,376,237	1,510/918,442	2,400/1,736,255	1,078/627,299		
Multivariable adjusted model*	1.00	0.90 (0.85, 0.96)	0.74 (0.70, 0.78)	0.82 (0.77, 0.89)	<.0001	0.82 (0.77, 0.88)
Dark bread						
Continuously updating diet						
Cases/person-time	590/397,895	1,096/755,344	3,485/2,022,683	2,801/1,477,089		
Multivariable adjusted model*	1.00	1.08 (0.97, 1.19)	1.09 (1.00, 1.19)	1.07 (0.98, 1.18)	0.90	1.00 (0.97, 1.03)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	935/487,593	1,624/895,426	2,633/1,780,529	2,838/1,494,686		
Multivariable adjusted model*	1.00	1.05 (0.96, 1.14)	0.87 (0.80, 0.94)	0.91 (0.84, 0.98)	0.19	0.98 (0.95, 1.01)
Popcorn						
Continuously updating diet						
Cases/person-time	2,451/1,031,973	3,438/2,221,907	1,891/1,253,268	192/145,864		
Multivariable adjusted model*	1.00	1.08 (1.03, 1.14)	1.09 (1.02, 1.16)	1.09 (0.94, 1.27)	0.81	1.01 (0.92, 1.11)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	2,938/1,117,158	3,550/2,303,535	1,281/1,064,290	261/173,251		
Multivariable adjusted model*	1.00	1.00 (0.95, 1.05)	0.91 (0.85, 0.98)	1.09 (0.95, 1.24)	0.60	0.98 (0.90, 1.06)

	< 1 serving/month	1 serving/month - 1 serving/week	≥2 servings/week			
Oatmeal						
Continuously updating diet						
Cases/person-time	3,328/1,988,047	2,584/1,681,799	2,060/983,164	-		
Multivariable adjusted model*	1.00	0.99 (0.94, 1.04)	0.98 (0.92, 1.04)	-	0.11	0.90 (0.78, 1.02)

Supplemental table 2.6. (continued) Pooled hazard ratios (95% confidence intervals) of coronary heart disease for individual whole grain food consumption in Nurses' Health Study (1984-2012), Nurses' Health Study II (1991-2013), Health Professionals Follow-Up Study (1986-2012) in analyses that used various strategies to handle dietary data after occurrence of chronic conditions

Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	4,216/2,225,677	2,640/1,690,216	1,174/742,339	-		
Multivariable adjusted model*	1.00	0.96 (0.92, 1.01)	0.80 (0.74, 0.85)	-	<0.001	0.79 (0.68, 0.90)
Brown rice						
Continuously updating diet						
Cases/person-time	4,691/2,549,644	2,735/1,723,940	546/379,428	-		
Multivariable adjusted model*	1.00	1.03 (0.98, 1.08)	1.03 (0.93, 1.13)	-	0.88	1.02 (0.79, 1.31)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	5,107/2,647,476	2,527/1,682,179	396/328,577	-		
Multivariable adjusted model*	1.00	0.92 (0.88, 0.97)	0.85 (0.77, 0.95)	-	0.10	0.81 (0.63, 1.04)
Added bran						
Continuously updating diet						
Cases/person-time	5,850/3,566,402	1,007/589,347	1,115/497,263	-		
Multivariable adjusted model*	1.00	0.97 (0.90, 1.04)	0.94 (0.88, 1.01)	-	0.07	0.93 (0.85, 1.01)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	6,289/3,647,265	903/573,125	838/437,844	-		
Multivariable adjusted model*	1.00	0.89 (0.83, 0.95)	0.83 (0.77, 0.90)	-	<0.001	0.87 (0.80, 0.94)
Wheat germ						
Continuously updating diet						
Cases/person-time	7,258/4,218,526	412/290,995	302/143,491	-		
Multivariable adjusted model*	1.00	0.93 (0.84, 1.03)	0.96 (0.85, 1.08)	-	0.08	0.83 (0.67, 1.02)
Resuming to update diet 8 years after occurrence of diseases						
Cases/person-time	7,339/4,227,137	450/301,138	241/129,959	-		
Multivariable adjusted model*	1.00	0.96 (0.87, 1.06)	0.85 (0.75, 0.97)	-	0.01	0.79 (0.66, 0.95)

*Adjusted for age (years), ethnicity (white, African American, Asian, others), updated body mass index (calculated as weight in kilograms divided by height in meters squared) (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, or ≥ 35.0 kg/m^2), smoking status (never smoked, past smoker, currently smoke 1-14 cigarettes per day, 15-24 cigarettes per day, or ≥ 25 cigarettes per day), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, and ≥ 30.0 g/d), baseline diabetes, multivitamin use (yes, no), physical activity (quintiles), modified alternative healthy eating index (quintiles, whole grain component was excluded) and family history of MI (yes, no). For women, postmenopausal hormone use (never, former, or current hormone use, or missing), and oral contraceptive use were further adjusted.

Study estimates from three cohorts were pooled using a random effects model.

Chapter 3. Changes in whole grain food consumption and body weight in three prospective cohort studies

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Abstract

Background

Total whole grain consumption is associated with lower body weight and less weight gain in observational studies. However, whether the associations persist among individual whole grain foods with various nutritional profiles has not been illustrated.

Methods

We included 137,998 men and women from three prospective cohort studies in this analysis. Whole grain food consumption was evaluated every four years using a validated food frequency questionnaire and body weight was assessed through self-reports biennially. A multivariable-adjusted generalized linear regression model was used to evaluate the association between the changes in whole grain food intake and weight change in each 4-year follow-up interval. Results from three cohorts were pooled using a random-effects meta-analysis.

Results

Each serving per day increased intake of total whole grains was associated with 0.17 kg (95% CI: 0.15, 0.19) less weight gain in concurrent 4-year period. Increased intake of most whole grain foods, including oatmeal, brown rice, added bran, wheat germ, and light/fat-free popcorn, were also associated with less weight gain, whereas null associations were observed for whole grain cold breakfast cereal, dark bread, and regular popcorn. Further analyses showed that replacing refined grain food with the same amount of total whole grains or whole grain foods was significantly associated with lower weight gain. For each serving/day substitution for refined grain foods, the weight change (95% CI) was -0.41 kg (-0.53, -0.28 kg) for total whole grains, -0.25 kg (-0.33,-0.17) for whole grain cold breakfast cereal, -0.23 kg (-0.31, -0.16) for dark bread, -0.64 kg (-0.71, -0.56) for oatmeal, -0.74 kg (-0.89, -0.60) for brown rice, -0.48 kg (-0.71, -0.25) for added bran, -0.42 kg (-0.53, -0.30) for wheat germ, and

-0.50 kg (-0.70, -0.30) for total popcorn. The inverse associations for popcorn were primarily attributed to light/fat free popcorn (-1.27 kg, 95% CI: -1.57, -0.96 kg) and no association was observed for regular popcorn (0.05 kg, 95% CI: -0.93, 0.50kg). Participants with higher BMI had less weight gain when replacing refined grains with the whole grain foods ($p < 0.005$ for interaction for all foods).

Conclusions

Increased consumption of total whole grains and most individual whole grain foods as replacements for refined grains was inversely associated with weight gain. These findings highlight the largely consistent associations of major whole grain foods with body weight maintenance.

Introduction

Obesity has become a major contributor to the global burden of chronic diseases.[1] According to the Centers for Disease Control and Prevention, about 93.3 million U.S. adults were obese in 2015-2016, and the medical cost for people with obesity was $1,429 higher than those of normal weight.[2] As a chronic relapsing disease process, obesity contributes to the development of multiple major chronic diseases, including type 2 diabetes, cardiovascular disease, and certain types of cancer.[3] Of established risk factors of obesity, a poor diet quality characterized by high intake of highly processed foods and animal products as well as low intake of plant-based foods may be a particularly important factor fueling the global obesity epidemic.[4,5]

Abundant evidence from prospective cohort studies has demonstrated that higher total whole grain consumption may help maintain a healthy body weight.[6] In most of these studies, whole grain intake was derived from various food items that contain whole grain ingredients, and few studies have examined individual whole grain foods that are more pertinent to real-world intake of whole grains. Moreover, the diverse nutrient compositions (fibers, proteins, vitamins, magnesium, and other dietary constituents) among whole grain foods may potentially result in differential associations with cardiometabolic health and weight maintenance.[7–9] However, the possibility that individual whole grains may be differentially associated with weight change has not been explicitly explored.

The current study aimed to evaluate changes in intake of several commonly-consumed whole grain foods, including whole grain breakfast cereal, oatmeal, dark bread, brown rice, added bran, wheat germ, and popcorns, in relation to the long-term weight change in three large prospective cohort studies of U.S. men and women.

Methods

Study population

The study population consists of three prospective cohorts of health professions. The Nurses' Health Study (NHS) was established in 1976 when 121,700 female registered nurses aged 30-55 were enrolled. The NHSII cohort was initiated in 1989 and included 116,340 women aged 25-42 years. The Health Professionals Follow-Up Study (HPFS) began in 1986 and enrolled 51,529 male health professionals aged 40-75 years. The cumulative response rates exceeded 90% in each two-year cycle in all three cohorts. Participants were followed biennially through mailed questionnaires inquiring medical and lifestyle information.[10,11]

In the current analysis, the follow-up was set to be from 1986 to 2010 in NHS, from 1991 to 2013 in NHSII, and from 1986 to 2010 in HPFS. To minimize the impacts of disease-related weight change, we excluded participants with cancer, type 2 diabetes, ulcerative colitis, pulmonary embolus, and cardiovascular disease (myocardial infarction, stroke, coronary artery bypass graft surgery, and angina) at baseline. In addition to censoring person-time after incident cardiovascular disease, pulmonary embolus, and diabetes, participants who developed the following diseases 6 years prior to each 4-y follow-up cycle were also censored: chronic obstructive pulmonary disease, ulcerative colitis, tuberculosis, renal disease, amyotrophic lateral sclerosis, multiple sclerosis, system lupus erythematosus (women only), Parkinson's disease, gastric bypass surgery, and cancer.[12] The person-time during which women were pregnant or lactating was also excluded in the NHSII. Participants at age 65 years or older were excluded at baseline and person-time was also censored upon age 65 during the follow-up to minimize the impact of age-related differential loss of lean body mass on the associations of interest. Participants with implausible energy intake (<800 or >4,200 calories for men and <600 or >3,500 calories for women) were excluded at baseline. A total of 43,151 participants from the NHS, 71,650 participants from the NHSII, and 18,996 participants from the HPFS were included in the final analysis.

The study protocol was approved by the Human Research Committee of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. Completion and return of study questionnaires implied informed consent of the participants.

Assessment of diet and lifestyle

In 1986 and every four years thereafter, a 130-item semi-quantitative food frequency questionnaire (sFFQ) was administered among participants to collect information on their usual diet in the previous year in the NHS. The similar sFFQ was used for dietary assessment in the NHSII and HPFS beginning in 1991 and 1986, respectively. Participants were asked regarding the average frequency they consumed each food item listed in the sFFQ during the previous year with a pre-specified, standard portion size. Nine possible responses were available ranging from never or <1 time/month to ≥ 6 times/day. Intake of total whole grains was estimated from all grain-containing foods according to the dry weight of the whole grain ingredients in each food.[13] The current study considered seven whole grain foods including whole-grain cold breakfast cereals, dark bread, popcorn, oatmeal, bran added to food, wheat germ, and brown rice. The cold breakfast cereal was further classified as whole grain-based cereal or refined grain-based cereal, depending on the whole grain proportion in the product determined from the manufacturers' brand,[14] and we focused on whole-grain cold breakfast cereals in the current analysis. Beginning in 2002 for the NHS and HPFS, and 2003 for then NHSII, we further inquired intake of subtypes of popcorn (regular and light/fat free popcorn) in the sFFQ. Validation studies conducted within the NHS and HPFS have demonstrated reasonable validity of the sFFQ assessments for whole grain foods. For example, the Pearson correlation coefficients comparing diet assessment from the sFFQ with multiple 7-d food records were 0.58 for dark bread and 0.73 for cold breakfast cereals.[15]

Assessment of weight change and lifestyles

In each two-year survey cycle, participants in all three cohorts were inquired about current weight, smoking status, and medical history. Information regarding hours of TV watching, hours of sleep, and physical activity was also repeatedly collected during the follow-up. Weight change was calculated as the difference in weight between the beginning and end of each 4-y interval to be aligned with dietary assessments. In these cohorts, a strong correlation (r=0.97) was observed between self-reported and measured body weight in validation studies,[16,17] suggesting that the self-reported body weight was highly accurate in these health professionals.

Statistical analysis

To account for the repeated measurements of body weight during the follow-up, multivariable generalized linear regression models were used to evaluate the association between the change of intake of each whole grain food and 4-year weight change over the same 4-year follow-up interval.[12,18] The generalized linear estimator was used to estimate the empirical variance and the results were averaged across all 4-year interval. The change of weight and dietary variables was truncated at the 0.5^{th} and 99.5^{th} percentile to alleviate the potential impacts of outliers in the linear regression models.

The consumption of total whole grains was converted to servings by dividing 16 grams (estimated dry weight of whole grains in each serving). In the analysis for individual whole grain foods, all seven food items were mutually adjusted in the models. In each model, we adjusted for baseline age, BMI, and change of diet and lifestyle variables including smoking status, physical activity, hours of sitting or watching TV per week, hours of sleep per day, and intake of fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood. The baseline consumption of total whole grains or individual whole grain foods was also adjusted. In a secondary analysis, the change of total energy was additionally adjusted to assess whether the associations were explained by increased or decreased total energy intake resulted from change of whole grain foods intake. Results from three cohorts were pooled using random-effect models.

A stratification analysis by baseline BMI at the beginning of each 4-y interval was performed for total whole grains and individual whole grain foods, and the *p* value for interactions were determined by the Wald test. Finally, we evaluated the association of replacing one daily serving whole grain foods for same amount of total refined grain foods including bagels, English muffins or rolls, white rice, muffins or biscuits, pasta, pancake or waffles, and white bread on weight change. Differences of β coefficients between each whole grain food and total refined grain foods estimated from the same multivariable-adjusted model were used to quantify the substitution associations, and their variances and covariance matrixes were used to derive the 95% CI.[19] To test for effect modification by BMI, for each whole grain food we first calculated beta coefficients for two product terms: one is between whole grain food and BMI, and the other between refined grains and BMI. We then calculated the difference between the two beta coefficients, and the variances and covariance matrixes were used to derive standard errors. The pooled p values for interaction were derived from a random-effect model combining the differences between beta coefficients from three cohorts.

We also investigated the association between the two types of popcorn and weight change. The baseline was reset to 2002 for the NHS and HPFS, and 2003 for the NHSII, when the sFFQ first assessed the types (regular or light/fat free popcorn) of popcorn. The same covariates were included in the models as in the primary analysis and the two types of popcorns were mutually adjusted. Stratification analysis by baseline BMI was also conducted for two types of popcorn.

Several sensitivity analyses were performed to examine the robustness of our findings. First, we excluded participants with baseline BMI greater than 30 kg/m^2 because obese participants tended to intentionally lose weight and therefore inclusion of these participants might distort the associations of interest. Second, to further relieve this concern, instead of examining the concurrent associations within 4 years, we used 4-year changes of whole grain foods intake to predict 8 years weight change (e.g., whole grain foods changes between 1990 and 1994 to predict weight change between 1990 and 1998). Finally, to disentangle the impacts of total energy, we repeated the analysis using the energy-adjusted residuals of all whole grain foods.

All P values presented were two-sided, with statistical significance level of 0.05. Data were analyzed with the use of SAS software, version 9.4

Results

The baseline characteristics and average 4-y lifestyle and diet changes were shown in **Table 3.1.** The baseline BMI was similar among three cohorts even though the NHSII participants were on average 10 years younger than NHS and HPFS participants. The total whole grain consumption was around 1 serving/d in three cohorts at baseline. The most commonly-consumed individual whole grain foods were dark bread, whole grain cold breakfast cereal, and popcorns, ranging from 0.17 serving/d to 0.76 serving/d, and the average consumption of other whole grain foods was less than 1 serving/wk. On average, the whole grain intake during follow-up was stable in these cohorts.

Table 3.1. Baseline (mean ± standard deviation [SD]) characteristics and average 4-y lifestyle and diet changes (mean and 1 to 99th percentile range) of men and women in three prospective cohorts

	HPFS (n=21,304)		NHS (n=43,169)		NHSII (n=73,525)	
	Baseline (1986)	4-y change	Baseline (1986)	4-y change	Baseline (1991)	4-y change
Age (years)	48.9 ± 6.66		51.0 ± 6.25		36.9 ± 4.55	
BMI (kg/m^2)	25.3 ± 3.04		25.0 ± 4.55		24.5 ± 5.18	
Weight (kg)	81.0 ± 11.3	0.98 (-10 to 12.3)	67.2 ± 13.1	1.23 (-14 to 15.9)	66.5 ± 14.8	2.05 (-16 to 20.4)
Physical activity (MET-hr/wk)	22.1 ± 30.2	5.91(-90 to 126)	14.2 ± 20.0	1.60 (-60 to 68.5)	20.8 ± 27.2	0.49 (-62 to 63.8)
Alcohol (grams/d)	11.4 ± 15.1	0.28 (-31 to 30.1)	6.28 ± 10.6	-0.05 (-24 to 22.7)	3.21 ± 6.15	0.63 (-17 to 22.8)
Total whole grains (servings/d)	1.34 ± 1.20	0.21 (-2.9 to 3.59)	0.87 ± 0.82	0.23 (-2.4 to 3.09)	1.28 ± 0.98	0.19 (-2.9 to 3.51)
Whole grain cold breakfast cereal (servings/d)	0.33 ± 0.44	0.01 (-1.0 to 1.00)	0.24 ± 0.36	0.03 (-1.0 to 1.00)	0.29 ± 0.39	0.00 (-1.00 to 1.00)
Dark bread (servings/d)	0.76 ± 1.00	-0.01 (-2.4 to 2.43)	0.64 ± 0.78	0.00 (-2.4 to 2.43)	0.61 ± 0.79	-0.03 (-2.4 to 2.36)
Popcorn (servings/d)	0.17 ± 0.35	0.00 (-0.86 to 0.86)	0.13 ± 0.26	0.00 (-0.86 to 0.86)	0.23 ± 0.37	-0.03 (-0.86 to 0.72)
Oatmeal (servings/d)	0.07 ± 0.20	0.02 (-0.72 to 0.93)	0.06 ± 0.14	0.03 (-0.72 to 0.93)	0.08 ± 0.16	0.02 (-0.72 to 0.86)
Brown rice (servings/d)	0.07 ± 0.15	0.00 (-0.36 to 0.43)	0.04 ± 0.09	0.00 (-0.36 to 0.36)	0.06 ± 0.12	0.00 (-0.36 to 0.43)
Added bran (servings/d)	0.10 ± 0.39	0.00 (-1.1 to 1.43)	0.07 ± 0.28	0.00 (-1.0 to 1.00)	0.05 ± 0.23	-0.01 (-0.72 to 0.43)
Wheat germ (servings/d)	0.03 ± 0.19	0.00 (-0.36 to 0.14)	0.02 ± 0.13	0.00 (-0.29 to 0.29)	0.01 ± 0.09	0.00 (-0.07 to 0.07)
Total fruits (servings/d)	1.47 ± 1.21	0.05 (-2.8 to 3.00)	1.64 ± 1.19	0.01 (-2.9 to 2.94)	1.19 ± 0.94	0.10 (-2.6 to 3.09)
Total vegetables (servings/d)	3.22 ± 1.89	0.17 (-4.6 to 5.22)	3.72 ± 2.10	0.05 (-5.2 to 5.43)	3.07 ± 1.96	0.09 (-5.2 to 5.67)
Whole-fat dairy (servings/d)	0.98 ± 1.01	-0.08 (-2.7 to 2.36)	1.15 ± 1.06	-0.12 (-2.9 to 2.50)	0.79 ± 0.77	-0.07 (-2.7 to 2.64)
Low-fat dairy (servings/d)	0.83 ± 1.01	-0.07 (-2.6 to 2.50)	0.86 ± 0.94	0.09 (-2.5 to 2.93)	1.12 ± 1.05	0.00 (-2.8 to 2.92)
Seafood (servings/d)	0.37 ± 0.31	-0.01 (-0.72 to 0.72)	0.34 ± 0.28	-0.01 (-0.72 to 0.72)	0.27 ± 0.24	-0.01 (-0.65 to 0.65)
Refined grains (servings/d)	1.17 ± 1.02	-0.02 (-2.8 to 2.78)	1.24 ± 0.97	-0.06 (-2.8 to 2.64)	1.54 ± 0.98	-0.09 (-3.0 to 2.86)
Nuts (servings/d)	0.25 ± 0.45	0.02 (-1.4 to 1.71)	0.15 ± 0.30	0.02 (-0.93 to 1.08)	0.06 ± 0.14	0.11 (-1.1 to 2.08)
Sugar-sweetened beverages (servings/d)	0.39± 0.64	-0.02 (-2.0 to 1.93)	0.24 ± 0.51	0.00 (-2.0 to 2.00)	0.46 ± 0.83	-0.03 (-2.5 to 2.43)
Diet soda (servings/d)	0.52 ± 0.96	0.00 (-2.4 to 2.43)	0.54 ± 0.87	-0.02 (-2.5 to 2.50)	1.03 ± 1.41	-0.07 (-3.2 to 2.64)
Juice (servings/d)	0.79 ± 0.83	0.00 (-2.4 to 2.36)	0.81 ± 0.79	-0.03 (-2.3 to 2.16)	0.65 ± 0.78	-0.06 (-2.2 to 1.93)
Fried foods (servings/d)	0.40 ± 0.28	-0.05 (-0.71 to 0.51)	0.27 ± 0.19	-0.02 (-0.50 to 0.43)	0.29 ± 0.21	-0.01 (-0.64 to 0.50)
Fried potatoes (servings/d)	0.28 ± 0.32	-0.02 (-0.79 to 0.72)	0.06 ± 0.09	-0.01 (-0.29 to 0.29)	0.11 ± 0.13	-0.01 (-0.36 to 0.36)
Sweets (servings/d)	1.32 ± 1.29	-0.03 (-3.5 to 3.43)	1.12 ± 1.09	-0.02 (-3.3 to 3.29)	1.14 ± 1.06	-0.09 (-3.0 to 2.65)
Non-processed meats (servings/d)	0.82 ± 0.60	-0.03 (-1.4 to 1.33)	0.76 ± 0.51	-0.04 (-1.3 to 1.15)	0.72 ± 0.51	-0.02 (-1.3 to 1.27)
Processed meats (servings/d)	0.37 ± 0.42	-0.03 (-1.0 to 0.93)	0.30 ± 0.31	-0.02 (-0.80 to 0.72)	0.23 ± 0.26	-0.01 (-0.79 to 0.79)
Trans fat (% of total energy)	1.28 ± 0.50	-0.03 (-1.4 to 1.48)	1.69 ± 0.53	-0.10 (-1.6 to 1.45)	1.65 ± 0.61	-0.22 (-1.5 to 0.88)
Total energy	2,020 ± 619	-6.9 (-1,286 to 1,257)	1,776 ± 523	-4.9 (-1,136 to 1,112)	1,781 ± 544	-4.2 (-1,211 to 1,208)

Table 3.2 presents the associations between total and individual whole grain foods and weight changes within 4-year intervals. Pooled across three cohorts, each serving/d increase of total whole grains was associated with 0.17 kg (95% CI: 0.15, 0.19) less weight gain. Except for whole grain cold breakfast cereal and dark bread for which the association was null, increased consumption of most whole grain foods were associated with significantly less weight gain. On average, each daily serving increase of oatmeal, brown rice, added bran, wheat germ, and popcorn was associated with -0.38 kg (95% CI: -0.46, -0.30 kg), -0.47 kg (95% CI: -0.62, -0.32 kg), -0.22 kg (95% CI: -0.33, -0.11 kg), -0.19 kg (95% CI: -0.30, -0.08 kg), and -0.25 kg (95% CI: -0.37, -0.13 kg) weight change, respectively. The correspondent estimates were 0.00 kg (-0.05, 0.04) for whole grain cold breakfast cereal, and 0.02 kg (-0.02, 0.07) for dark bread. Additional adjustment of changes in total energy did not change the results.

For total whole grains as well as all seven whole grain foods, increasing one serving/d while decreasing same amount of refined grain foods resulted in significantly less weight gain: -0.41 kg (95% CI: -0.53, -0.28) for total whole grains, -0.25 kg (95% CI: -0.33, -0.17 kg) for whole grain cold breakfast cereal, -0.64 kg (95% CI: -0.71, -0.56 kg) for oatmeal, -0.23 kg (95% CI: -0.31, -0.16 kg) for dark bread, -0.74 kg (95% CI: -0.89, -0.60 kg) for brown rice, -0.48 kg (95% CI: -0.71, -0.25 kg) for added bran, -0.42 kg (95% CI: -0.53, -0.30 kg) for wheat germ, and -0.50 kg (95% CI: -0.70, -0.30 kg) for total popcorn (**Figure 3.1**).

Table 3.2. Relationships between changes in intake of total grains and individual whole grain food and weight change over 4 y in three cohorts

	HPFS	NHS	NHSII	Pooled
	Age-adjusted model			
Total whole grains	-0.23 (-0.26, -0.20)	-0.35 (-0.38, -0.31)	-0.35 (-0.38, -0.32)	-0.31 (-0.38, -0.23)
Whole grain cold breakfast cereal	-0.27 (-0.36, -0.19)	-0.09 (-0.16, -0.02)	-0.05 (-0.12, 0.02)	-0.14 (-0.26, -0.01)
Oatmeal	-0.59 (-0.74, -0.44)	-0.67 (-0.80, -0.55)	-0.67 (-0.81, -0.53)	-0.65 (-0.73, -0.57)
Dark bread	-0.04 (-0.08, 0.01)	-0.02 (-0.06, 0.02)	0.04 (0.00, 0.08)	-0.00 (-0.05, 0.04)
Brown rice	-0.76 (-1.1, -0.45)	-0.90 (-1.2, -0.62)	-1.0 (-1.3, -0.82)	-0.92 (-1.09, -0.76)
Added bran	-0.17 (-0.25, -0.10)	-0.29 (-0.38, -0.19)	-0.45 (-0.58, -0.32)	-0.30 (-0.45, -0.15)
Wheat germ	-0.32 (-0.51, -0.13)	-0.17 (-0.36, 0.01)	-0.36 (-0.64, -0.07)	-0.26 (-0.38, -0.14)
Popcorn	-0.18 (-0.30, -0.06)	-0.32 (-0.45, -0.20)	-0.18 (-0.32, -0.05)	-0.23 (-0.33, -0.14)
	Multivariable-adjusted model			
Total whole grains	-0.16 (-0.19, -0.12)	-0.19 (-0.22, -0.16)	-0.17 (-0.20, -0.14)	-0.17 (-0.19, -0.15)
Whole grain cold breakfast cereal	-0.18 (-0.26, -0.10)	0.09 (0.02, 0.16)	0.09 (0.03, 0.16)	0.00 (-0.17, 0.17)
Oatmeal	-0.42 (-0.56, -0.28)	-0.42 (-0.53, -0.30)	-0.29 (-0.43, -0.15)	-0.38 (-0.46, -0.30)
Dark bread	-0.02 (-0.07, 0.02)	0.03 (-0.01, 0.07)	0.06 (0.02, 0.10)	0.02 (-0.02, 0.07)
Brown rice	-0.53 (-0.83, -0.24)	-0.39 (-0.66, -0.11)	-0.49 (-0.70, -0.27)	-0.47 (-0.62, -0.32)
Added bran	-0.12 (-0.20, -0.05)	-0.25 (-0.34, -0.16)	-0.31 (-0.44, -0.19)	-0.22 (-0.33, -0.11)
Wheat germ	-0.28 (-0.45, -0.10)	-0.12 (-0.30, 0.05)	-0.13 (-0.41, 0.14)	-0.19 (-0.30, -0.08)
Popcorn	-0.15 (-0.27, -0.03)	-0.36 (-0.47, -0.24)	-0.23 (-0.35, -0.10)	-0.25 (-0.37, -0.13)
	Additional adjustment of changes in total energy intake			
Total whole grains	-0.17 (-0.20, -0.14)	-0.21 (-0.24, -0.18)	-0.18 (-0.21, -0.16)	-0.19 (-0.21, -0.17)
Whole grain cold breakfast cereal	-0.22 (-0.31, -0.14)	0.05 (-0.03, 0.12)	0.05 (-0.01, 0.12)	-0.04 (-0.21, 0.13)
Oatmeal	-0.45 (-0.59, -0.31)	-0.46 (-0.58, -0.35)	-0.34 (-0.47, -0.20)	-0.42 (-0.50, -0.34)
Dark bread	-0.05 (-0.10, -0.01)	0.00 (-0.04, 0.04)	0.02 (-0.02, 0.07)	-0.01 (-0.05, 0.03)
Brown rice	-0.61 (-0.91, -0.32)	-0.46 (-0.74, -0.18)	-0.54 (-0.76, -0.33)	-0.54 (-0.69, -0.39)
Added bran	-0.13 (-0.20, -0.06)	-0.26 (-0.35, -0.17)	-0.32 (-0.45, -0.20)	-0.23 (-0.34, -0.11)
Wheat germ	-0.29 (-0.47, -0.12)	-0.13 (-0.31, 0.05)	-0.15 (-0.43, 0.13)	-0.20 (-0.31, -0.09)
Popcorn	-0.18 (-0.30, -0.06)	-0.38 (-0.50, -0.27)	-0.27 (-0.39, -0.14)	-0.28 (-0.40, -0.16)

Adjusted for baseline age and BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood.

Baseline individual whole grain foods intake were also adjusted.

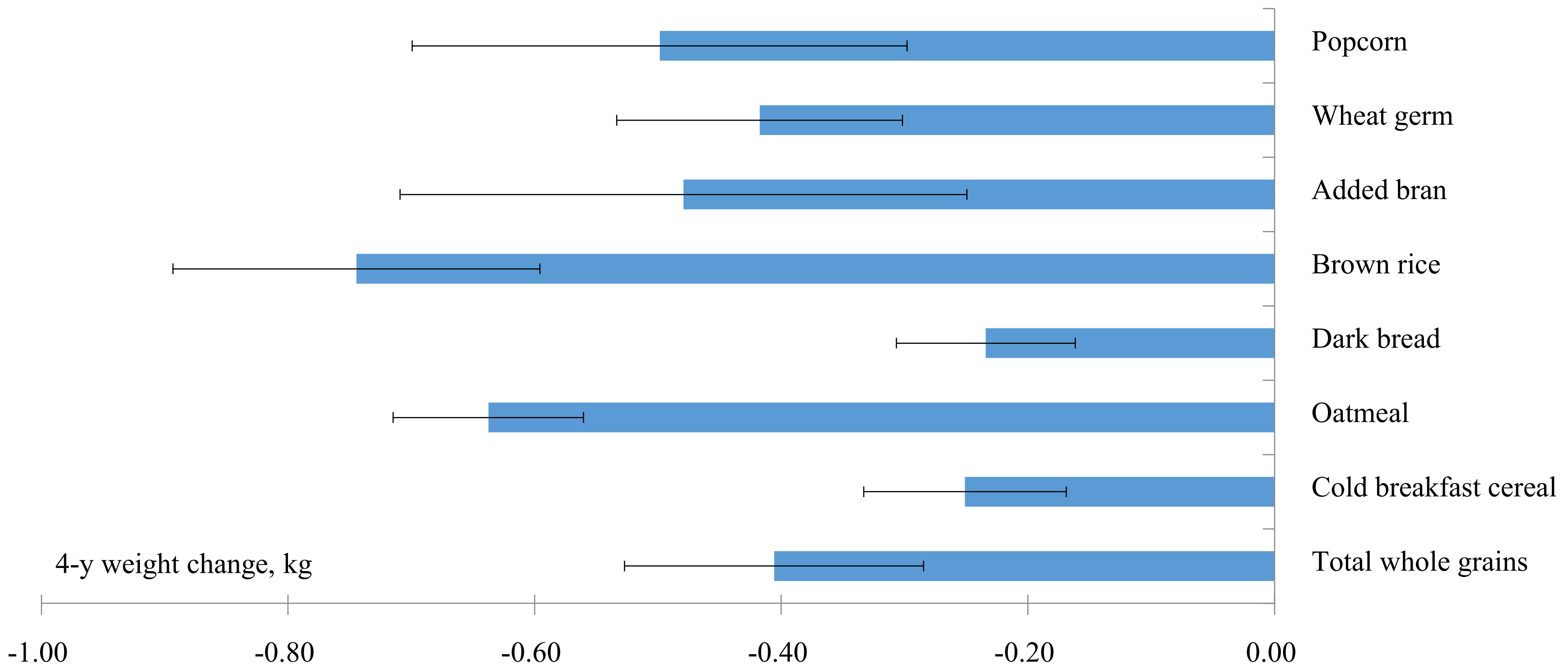

Figure 3.1. Substitution analysis for replacing one serving/d of total whole grains or whole grain foods for same amount refined grain foods.

Refined grain foods included bagels, English muffins or rolls, white rice, muffins or biscuits, pasta, pancake or waffles, and white bread.

Adjusting for the same covariates in **Table 3.2**.

Figure 3.2. Panel A shows the pooled association between whole grain food intake and weight change stratified by baseline BMI. Higher consumption of total whole grains, popcorn, added bran, brown rice, oatmeal, and wheat germ was consistently associated with significantly less weight gain among participants with higher baseline BMI. An opposite pattern was observed for whole grain cold breakfast cereal in that whole grain cold breakfast cereal intake was associated with less weight gain among lean individuals only. No significant effect modifications by baseline BMI was found for dark bread. Moreover, baseline BMI also modified the associations of substituting whole grain foods for refined grains in that participants with higher BMI had less weight gain when replacing refined grains intake with the whole grain foods ($p < 0.005$ for interactions for all foods) (**Figure 3.2 Panel B**).

Panel A

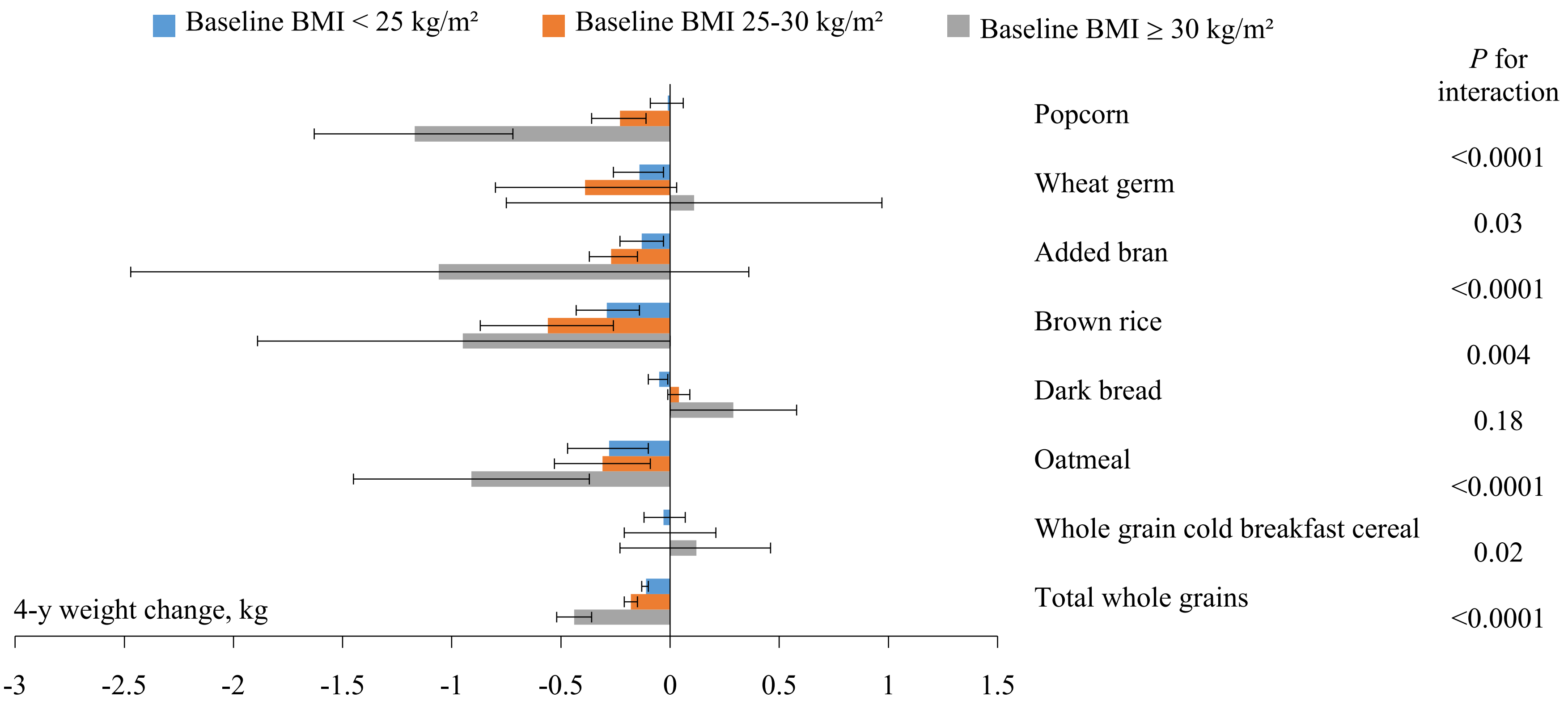

Figure 3.2. Panel A Stratified analysis by baseline BMI for the weight change associated with one daily serving increment of whole grain foods.

Adjusting for the same covariates in **Table 3.2** and change of total energy

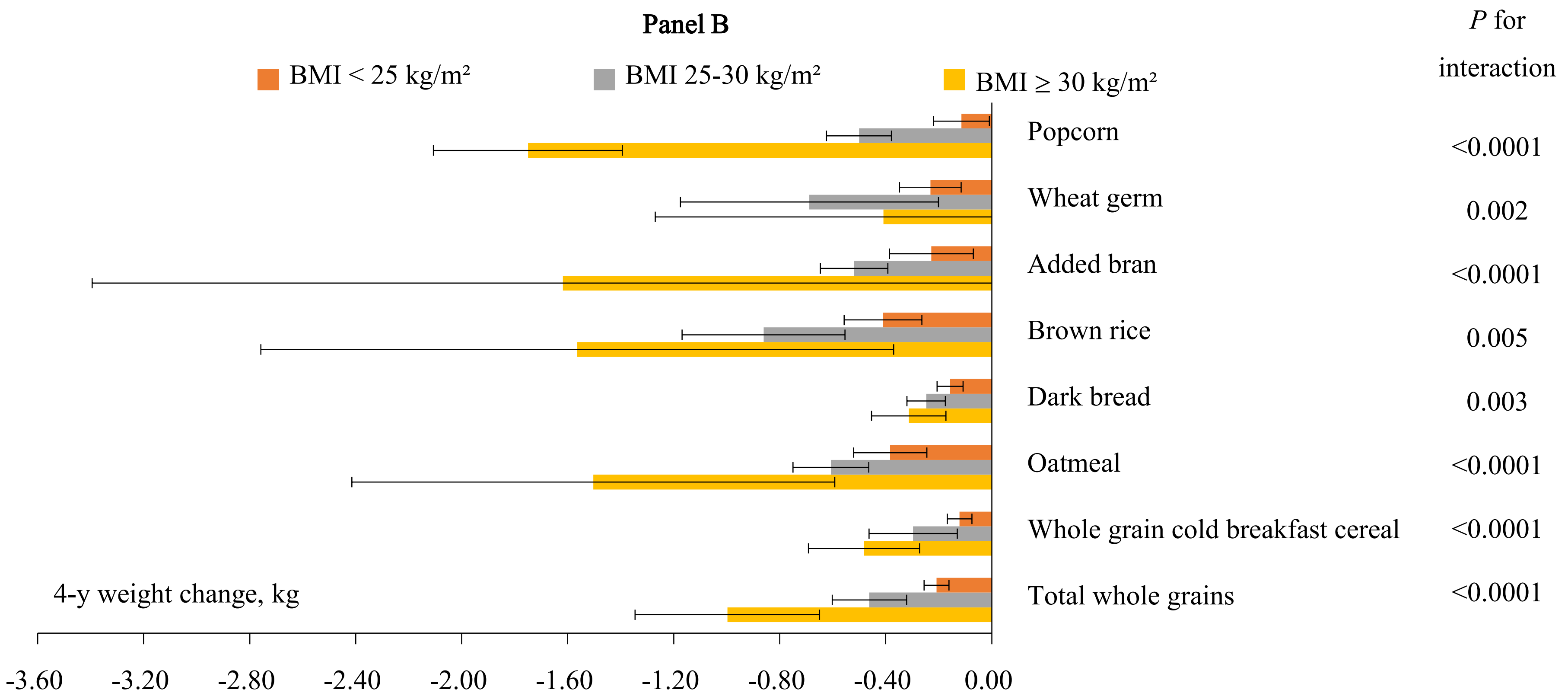

Figure 3.3. Panel B Stratified analysis by baseline BMI for the weight change associated replacing one daily serving of refined grain foods with whole grain foods.

Refined grain foods included bagels, English muffins or rolls, white rice, muffins or biscuits, pasta, pancake or waffles, and white bread.

Adjusting for the same covariates in **Table 3.2.**

When further examining popcorns by types, we found that the inverse associations were primarily driven by the increased intake of light/fat free popcorn (**Table 3.3**). On average, one serving/d increase of regular popcorn consumption was non-significantly associated with 0.52 kg (95% CI: -0.23, 1.28 kg) more weight gain, while each serving increment of light/fat free popcorn was associated with -0.62 kg (95% CI: -0.92, -0.32) weight change within 4 years. Stratified analyses by baseline BMI revealed that the associations between light/fat free popcorn and weight change were more pronounced among participants with higher baseline BMI ($p<0.0001$ for interaction), whereas no significant interactions were detected for regular popcorn intake ($p=0.75$ for interaction). Replacing refined grain foods with light/fat free popcorn was associated with less weight gain (-1.27 kg, 95% CI: -1.57, -0.96 kg), and no substitution effects were found for regular popcorn (0.05 kg, 95% CI: 0.50, -0.93 kg) (**Supplemental figure 3.1**). Moreover, heavier participants experienced significantly less weight gain when replacing refined grain foods with light/fat free popcorn than lean participants ($p <0.0001$ for interaction). Increasing one serving/d light/fat free popcorn for same amount of refined grain foods resulted in weight change of 0.39 kg (95% CI: -0.30, 1.08 kg) among normal weight participants, -1.22 kg (95% CI: -1.72, 0.73 kg) among overweight participants, and -3.11 kg (95% CI: -4.01, -2.21 kg) among obese participants. No interaction was observed for replacing refined grains with regular popcorn.

Table 3.3. Relationships between changes in intake of regular or light/fat free popcorn and weight change over 4 y in three cohorts and stratification analysis by baseline BMI

	HPFS	NHS	NHSII	Pooled
		Overall		
Total popcorn	-0.29 (-1.1, 0.51)	-0.06 (-0.55, 0.44)	-0.31 (-0.62, -0.01)	-0.25 (-0.49, 0.00)
Regular popcorn	0.00 (-0.96, 0.95)	1.30 (0.53, 2.08)	0.24 (-0.34, 0.82)	0.52 (-0.23, 1.28)
Light/fat free popcorn	-0.58 (-1.6, 0.40)	-0.72 (-1.4, -0.10)	-0.59 (-0.96, -0.23)	-0.62 (-0.92, -0.32)
		Baseline BMI < 25 kg/m^2		
Total popcorn	1.24 (-0.60, 3.07)	0.82 (0.29, 1.36)	0.46 (0.09, 0.84)	0.60 (0.30, 0.90)
Regular popcorn	1.04 (-0.85, 2.94)	0.92 (-0.17, 2.02)	0.68 (0.03, 1.34)	0.77 (0.23, 1.31)
Light/fat free popcorn	1.44 (-0.53, 3.40)	0.71 (0.09, 1.32)	0.34 (-0.08, 0.77)	0.49 (0.15, 0.84)
		Baseline BMI 25-30 kg/m^2		
Total popcorn	-1.1 (-2.0, -0.23)	-0.20 (-0.88, 0.48)	-0.19 (-0.68, 0.30)	-0.41 (-0.91, 0.10)
Regular popcorn	-0.88 (-2.1, 0.39)	0.71 (-0.30, 1.72)	0.48 (-0.34, 1.29)	0.20 (-0.65, 1.04)
Light/fat free popcorn	-1.2 (-2.5, 0.08)	-0.72 (-1.7, 0.23)	-0.56 (-1.2, 0.05)	-0.69 (-1.17, -0.21)
		Baseline BMI ≥ 30 kg/m^2		
Total popcorn	-0.87 (-2.9, 1.16)	-0.73 (-2.0, 0.51)	-1.4 (-2.2, -0.59)	-1.17 (-1.82, -0.52)
Regular popcorn	1.26 (-1.6, 4.08)	1.80 (-0.49, 4.10)	-0.88 (-2.2, 0.41)	0.47 (-1.41, 2.36)
Light/fat free popcorn	-2.9 (-5.6, -0.12)	-2.2 (-3.9, -0.64)	-1.6 (-2.8, -0.49)	-1.94 (-2.82, -1.06)

Follow-up started from 2002 in the NHS and from 2003 in the HPFS when the type of popcorn was first assessed. Adjusted for baseline age, BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood.

Baseline popcorns intake were also adjusted.

In the sensitivity analysis that excluded baseline obese participants, the results were slightly attenuated for all individual whole grain foods (**Supplemental table 3.1**). Using 4-year whole grain foods changes to predict 8-year weight change also produced attenuated results, but the associations for most whole grain foods remained statistically significant, except that change of brown rice intake was no longer associated with weight change while increasing popcorn intake was associated significantly more weight gain (**Supplemental table 3.2**). Finally, the results were not materially changed when we used the energy-adjusted residuals of whole grain foods in statistical analyses (**Supplemental table 3.3**).

Discussion

In three prospective cohorts of U.S. men and women, increased intake of several commonly consumed whole grain foods including oatmeal, brown rice, light/fat free popcorn, added bran, and wheat germ was associated with significantly less weight gain during each 4-y follow-up interval. Moreover, decreasing one daily serving refined grain foods while increasing the same amount of whole grain foods, especially brown rice and oatmeal, was associated with significantly less weight gain. These associations were independent of established and potential predictors of weight change and more pronounced among participants with higher baseline BMI.

The association between higher total whole grain intake and less weight change has been demonstrated in prospective cohort studies.[20–22] Data regarding individual whole grain foods and weight change are relatively sparse. With various glycemic properties and different compositions of nutrients such as dietary fiber, magnesium, antioxidant, and phytochemicals, different whole grain foods may have distinct effects on body weight regulation. For example, for the same 100 gram in dry weight, oat bran on average has much higher contents of fiber and magnesium than brown rice.[23] Moreover, popcorn intake leads to the highest GI value compared with other whole grain foods considered in the current analysis.[24] In an early investigation in the HPFS, baseline whole grain breakfast cereal intake was inversely associated with BMI and weight gain during a 13 years of follow-up.[22] Another analysis in the same cohort estimated that each 20g/d increase of added bran (mostly from wheat and oats) was associated with 0.36 kg less weight gain in eight years.[20] In the current analysis that represents the first study evaluating individual food items in relation to long-term weight change, we demonstrated that the relationships with weight change were largely homogenous among individual whole grain foods.

One of interesting findings of the current study was that the two types of popcorn manifested divergent associations with weight change. This implies that constituents other than corn grains may modulate the inverse association for popcorn. According to a report regarding the *trans* fatty acid reduction among U.S. food products, popcorn still remained high in *trans* fatty acid at, on average, more than 1.5 g per serving.[25] It is possible that the high contents of *trans* fatty acid in the regular popcorn might attenuate potential inverse associations, given the positive link between higher intake of *trans* fatty acid and weight gain.[26] In addition, accumulating evidence suggests that popcorn can be contaminated by perfluoroalkyl substances (PFAS) through food packaging.[27,28] In a recent study, higher exposure to these chemicals was associated with faster weight regain and slower regression of resting metabolic rate in an analysis in the weight-loss trial setting.[29] Further studies are warranted to further elucidate the mechanisms explaining the relationship between popcorn intake and weight change.

The mechanisms underlying favorable associations between whole grain intake and less weight gain are not completely understood, although factors including better nutritional profiles of beneficial nutrients, lower glycemic index, lower energy density, and interactions with gut microbiota may come into play for mediating the effects of whole grains intake on body weight regulation.[30] The relative large particle size and rich contents of dietary fiber may decrease subsequent energy intake by enhancing satiety and gastric distention,[31] and reducing postprandial glucose concentration.[32] Moreover, comparing with refined grain foods, whole grain foods have lower energy density due to the high contents of non-fermentable fiber which provide no digestible energy. In addition, recent studies have suggested the gut microbiota may metabolize cereal fiber and produce short-chain fatty acid that can promote glucose and lipid oxidation, stimulate gut hormone secretion, and slow gastrointestinal transit.[33] These mechanisms may also underline the strong inverse associations with weight gain when we modeled the associations of substituting whole grain foods for refined carbohydrates.

It is interesting to observe stronger associations among obese participants than lean participants. These data may suggest whole grain foods can particularly help obese individuals to control weight gain through the aforementioned pathways. At the same time, caution must be taken to interpret these findings in observational studies in that these inverse associations might be confounded by the strong weight loss intention among heavier participants through dieting. Under such circumstance, the observed inverse associations for whole grain foods are less likely to remain beyond 4 years because the weight loss attempt usually lasts for a short period of time and is notoriously difficult to maintain.[34] However, the sensitivity analysis showing that the 4-year change of whole grain foods could still predict significantly less weight change in 8 years suggested our results were not severely confounded by underlying intentional weight loss. Further weight loss trials are needed to further illustrate the role of whole grains in weight changes among individuals with various baseline obesity status.

The strengths of study included a large sample size, comprehensive dietary assessment of commonly consumed whole grain foods, and extended duration of follow-up. Several limitations merit discussion. First, dietary assessments of whole grain foods are subject to measurement errors, although given our prospective study design the measurement errors are likely to be random and attenuate the true associations toward the null. Second, although a multitude of dietary and lifestyle covariates were adjusted for in the models, the sFFQ and follow-up questionnaire might not fully capture the dietary and lifestyle changes within each follow-up period, resulting in residual confounding. Finally, our study participants are predominantly white health professionals, which may limit the generalizability of our findings.

In conclusion, in three large prospective cohort studies of men and women, increased consumption of individual whole grain foods is significantly associated with less weight gain when refined carbohydrates are replaced by these whole grain foods. Overall these results suggest individual whole grains do not differ substantially from each other regarding their inverse associations with body weight, and dietary guidelines shall continue to emphasize substitution of whole grains for refined carbohydrate for better weight control.

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Supplemental Materials

Supplemental table 3.1. Relationships between changes in intake of total grains and individual whole grain food and weight change over 4 y in three cohorts with exclusion of baseline obese participants.

	HPFS	NHS	NHSII	Pool
	Age-adjusted model			
Total whole grains	-0.21 (-0.24, -0.18)	-0.29 (-0.31, -0.26)	-0.29 (-0.31, -0.26)	-0.26 (-0.31, -0.21)
Whole grain cold breakfast cereal	-0.25 (-0.32, -0.17)	-0.07 (-0.13, 0.00)	-0.04 (-0.10, 0.02)	-0.12 (-0.23, -0.00)
Oatmeal	-0.54 (-0.69, -0.40)	-0.57 (-0.68, -0.45)	-0.51 (-0.63, -0.39)	-0.54 (-0.61, -0.47)
Dark bread	-0.05 (-0.09, -0.01)	-0.04 (-0.07, 0.00)	0.00 (-0.04, 0.03)	-0.03 (-0.05, -0.00)
Brown rice	-0.69 (-0.99, -0.40)	-0.84 (-1.1, -0.58)	-0.83 (-1.0, -0.63)	-0.80 (-0.95, -0.66)
Added bran	-0.15 (-0.22, -0.08)	-0.24 (-0.32, -0.16)	-0.32 (-0.43, -0.21)	-0.23 (-0.32, -0.14)
Wheat germ	-0.28 (-0.46, -0.09)	-0.21 (-0.40, -0.03)	-0.44 (-0.70, -0.17)	-0.28 (-0.40, -0.16)
Popcorn	-0.13 (-0.24, -0.01)	-0.07 (-0.17, 0.03)	-0.08 (-0.21, 0.04)	-0.09 (-0.15, -0.02)
	Multivariable-adjusted model			
Total whole grains	-0.15 (-0.18, -0.12)	-0.16 (-0.19, -0.13)	-0.14 (-0.17, -0.12)	-0.15 (-0.17, -0.13)
Whole grain cold breakfast cereal	-0.17 (-0.24, -0.09)	0.09 (0.02, 0.15)	0.08 (0.02, 0.14)	0.00 (-0.15, 0.15)
Oatmeal	-0.39 (-0.52, -0.25)	-0.34 (-0.45, -0.23)	-0.22 (-0.33, -0.10)	-0.31 (-0.41, -0.22)
Dark bread	-0.03 (-0.08, 0.01)	0.00 (-0.04, 0.04)	0.01 (-0.03, 0.05)	-0.01 (-0.03, 0.02)
Brown rice	-0.50 (-0.79, -0.21)	-0.40 (-0.66, -0.14)	-0.38 (-0.57, -0.18)	-0.41 (-0.55, -0.27)
Added bran	-0.11 (-0.17, -0.04)	-0.20 (-0.28, -0.12)	-0.20 (-0.31, -0.09)	-0.16 (-0.23, -0.10)
Wheat germ	-0.25 (-0.42, -0.08)	-0.14 (-0.32, 0.04)	-0.21 (-0.47, 0.05)	-0.20 (-0.31, -0.09)
Popcorn	-0.11 (-0.22, 0.00)	-0.14 (-0.24, -0.05)	-0.16 (-0.28, -0.04)	-0.14 (-0.20, -0.07)
	Additional adjusted for total energy change			
Total whole grains	-0.16 (-0.19, -0.12)	-0.17 (-0.20, -0.14)	-0.15 (-0.18, -0.13)	-0.16 (-0.18, -0.14)
Whole grain cold breakfast cereal	-0.19 (-0.27, -0.12)	0.07 (0.00, 0.13)	0.05 (-0.01, 0.11)	-0.02 (-0.18, 0.13)
Oatmeal	-0.41 (-0.55, -0.27)	-0.37 (-0.47, -0.26)	-0.25 (-0.37, -0.13)	-0.34 (-0.43, -0.25)
Dark bread	-0.05 (-0.10, -0.01)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.03)	-0.03 (-0.05, -0.00)
Brown rice	-0.56 (-0.85, -0.27)	-0.43 (-0.70, -0.17)	-0.42 (-0.62, -0.23)	-0.46 (-0.59, -0.32)
Added bran	-0.11 (-0.18, -0.04)	-0.20 (-0.29, -0.12)	-0.21 (-0.32, -0.10)	-0.17 (-0.24, -0.10)
Wheat germ	-0.26 (-0.43, -0.09)	-0.15 (-0.33, 0.03)	-0.22 (-0.48, 0.04)	-0.21 (-0.32, -0.10)

Supplemental table 3.1. (continued) Relationships between changes in intake of total grains and individual whole grain food and weight change over 4 y in three cohorts with exclusion of baseline obese participants

Popcorn	-0.13 (-0.24, -0.02)	-0.16 (-0.26, -0.06)	-0.19 (-0.31, -0.07)	-0.16 (-0.22, -0.09)

Adjusted for baseline age and BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood.

Baseline individual whole grain foods intake were also adjusted.

Supplemental table 3.2. Relationships between changes in intake of total grains and individual whole grain food and weight change over 8 y in three

	HPFS	NHS	NHSII	Pool
	Multivariable-adjusted model			
Whole grain cold breakfast cereal	-0.19 (-0.29, -0.09)	-0.04 (-0.13, 0.04)	-0.10 (-0.18, -0.02)	-0.11 (-0.19, -0.03)
Oatmeal	-0.26 (-0.42, -0.09)	-0.24 (-0.37, -0.12)	-0.11 (-0.25, 0.04)	-0.20 (-0.29, -0.11)
Dark bread	-0.07 (-0.12, -0.02)	0.01 (-0.04, 0.06)	0.01 (-0.04, 0.05)	-0.02 (-0.07, 0.03)
Brown rice	-0.06 (-0.39, 0.28)	-0.07 (-0.38, 0.23)	-0.18 (-0.48, 0.12)	-0.11 (-0.29, 0.07)
Added bran	-0.09 (-0.22, 0.04)	-0.18 (-0.28, -0.09)	-0.15 (-0.31, 0.01)	-0.15 (-0.22, -0.08)
Wheat germ	-0.35 (-0.69, -0.01)	-0.26 (-0.47, -0.04)	-0.49 (-0.81, -0.16)	-0.33 (-0.49, -0.17)
Popcorn	0.20 (0.04, 0.37)	0.35 (0.22, 0.47)	0.50 (0.35, 0.65)	0.35 (0.19, 0.51)

Adjusted for baseline age and BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood.

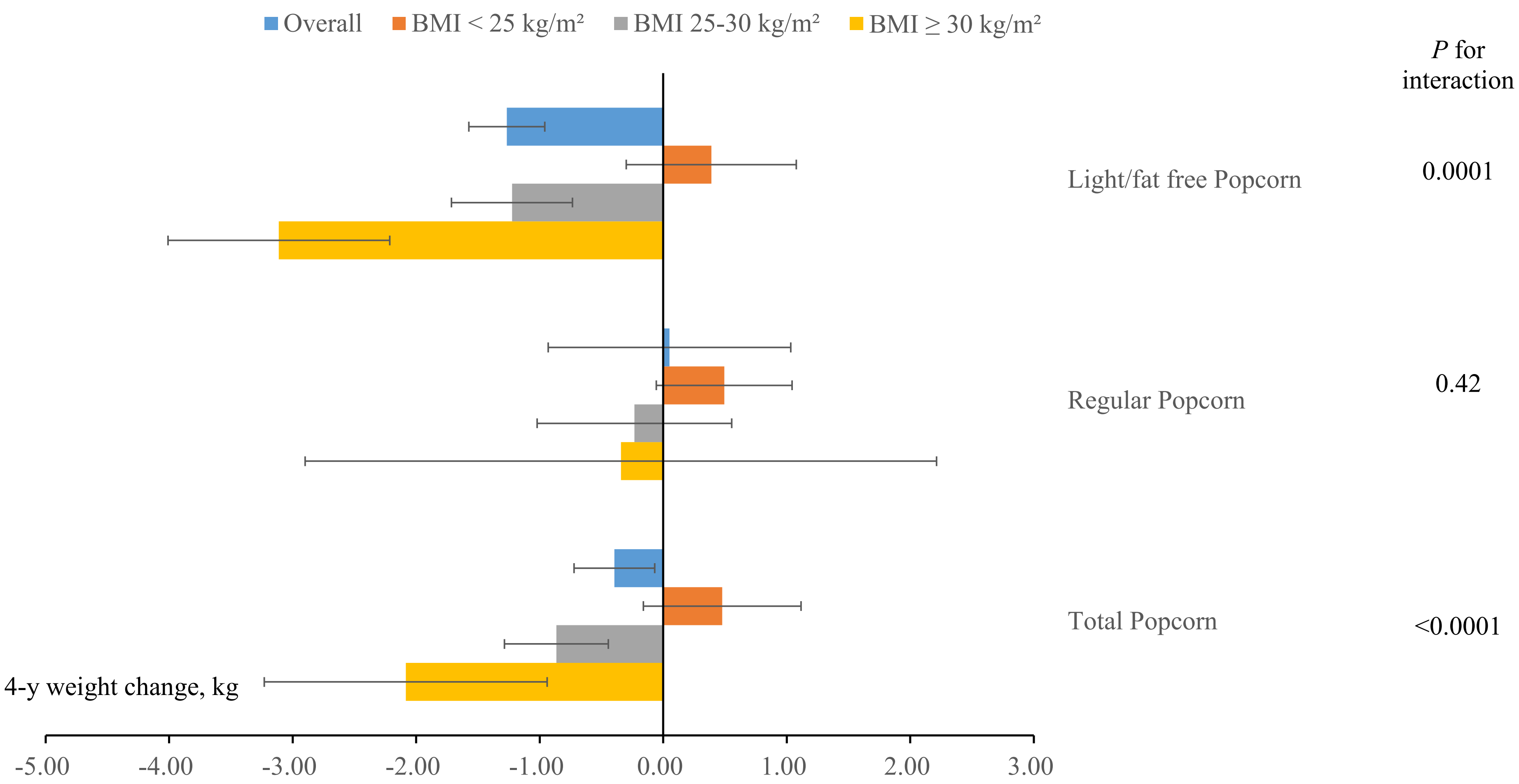
Baseline individual whole grain foods intake were also adjusted.

Supplemental table 3.3. Relationships between changes in intake of total grains and individual whole grain food and weight change over 4 y in three cohorts using energy-adjusted residuals.

	HPFS	NHS	NHSII	Pool
	Multivariable-adjusted model			
Whole grain cold breakfast cereal	-0.23 (-0.32, -0.15)	0.04 (-0.03, 0.11)	0.06 (-0.01, 0.13)	-0.04 (-0.22, 0.13)
Oatmeal	-0.47 (-0.61, -0.32)	-0.48 (-0.60, -0.36)	-0.35 (-0.49, -0.20)	-0.44 (-0.52, -0.35)
Dark bread	-0.06 (-0.11, -0.02)	-0.02 (-0.06, 0.02)	0.01 (-0.03, 0.05)	-0.02 (-0.07, 0.02)
Brown rice	-0.71 (-1.0, -0.41)	-0.63 (-0.93, -0.33)	-0.63 (-0.86, -0.40)	-0.65 (-0.81, -0.49)
Added bran	-0.15 (-0.22, -0.08)	-0.25 (-0.34, -0.16)	-0.37 (-0.50, -0.24)	-0.24 (-0.36, -0.12)
Wheat germ	-0.22 (-0.39, -0.04)	-0.12 (-0.30, 0.06)	-0.09 (-0.31, 0.13)	-0.15 (-0.26, -0.04)
Popcorn	-0.17 (-0.29, -0.05)	-0.43 (-0.55, -0.31)	-0.31 (-0.44, -0.17)	-0.30 (-0.46, -0.15)

Adjusted for baseline age and BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, total fruits, total vegetables, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood.

Baseline individual whole grain foods intake were also adjusted.



Supplemental figure 3.1. Substitution analysis for replacing one serving/d of total popcorn or subtypes of popcorn for same amount refined grain foods*

*Refined grain foods included bagels, English muffins or rolls, white rice, muffins or biscuits, pasta, pancake or waffles, and white bread.

Adjusting for the same covariates in **Table 3.3.**