Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study[1–3]

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ABSTRACT

Background: Although current dietary guidelines for Americans recommend increased intake of grain products to prevent coronary heart disease (CHD), epidemiologic data relating whole-grain intake to the risk of CHD are sparse.

Objective: Our objective was to evaluate whether high whole-grain intake reduces risk of CHD in women.

Design: In 1984, 75 521 women aged 38–63 y with no previous history of cardiovascular disease or diabetes completed a detailed, semiquantitative food-frequency questionnaire (SFFQ) and were followed for 10 y, completing SFFQs in 1986 and 1990. We used pooled logistic regression with 2-y intervals to model the incidence of CHD in relation to the cumulative average diet from all 3 cycles of SFFQs.

Results: During 729 472 person-years of follow-up, we documented 761 cases of CHD (208 of fatal CHD and 553 of nonfatal myocardial infarction). After adjustment for age and smoking, increased whole-grain intake was associated with decreased risk of CHD. For increasing quintiles of intake, the corresponding relative risks (RRs) were 1.0 (reference), 0.86, 0.82, 0.72, and 0.67 (95% CI comparing 2 extreme quintiles: 0.54, 0.84; *P* for trend < 0.001). After additional adjustment for body mass index, postmenopausal hormone use, alcohol intake, multivitamin use, vitamin E supplement use, aspirin use, physical activity, and types of fat intake, these RRs were 1.0, 0.92, 0.93, 0.83, and 0.75 (95% CI: 0.59, 0.95; *P* for trend = 0.01). The inverse relation between whole-grain intake and CHD risk was even stronger in the subgroup of never smokers (RR = 0.49 for extreme quintiles; 95% CI: 0.30, 0.79; *P* for trend = 0.003). The lower risk associated with higher whole-grain intake was not fully explained by its contribution to intakes of dietary fiber, folate, vitamin B-6, and vitamin E.

Conclusions: Increased intake of whole grains may protect against CHD. *Am J Clin Nutr* 1999;70:412–9.

KEY WORDS Diet, whole grain, refined grain, coronary heart disease, women, myocardial infarction, smoking, risk factors, Nurses' Health Study, food-frequency questionnaire

INTRODUCTION

Current dietary guidelines for Americans recommend increased consumption of grain products to prevent coronary heart disease (CHD), but the amount of whole grains to be consumed is not specified (1, 2). These recommendations are mainly derived from the belief that replacing fats with carbohydrates may reduce risk of CHD by improving plasma lipids (2). Moreover, in addition to being a source of carbohydrates, whole grains, especially wheat, rice, and oats, provide protein and essential fatty acids and may have unique and beneficial combinations of many micronutrients, antioxidants, phytochemicals, and fiber (3). The influence of whole-grain consumption on CHD risk and possibly other chronic diseases may well depend on the presence or absence of many constituents and their interactions. However, most of the grain products consumed in the United States are highly refined (3); the bran (outer layer) and germ (inner layer) are separated from the starchy endosperm (middle layer) during milling, which leads to the loss of many nutrients and fiber (4, 5).

A clear understanding of the relation of whole-grain consumption to CHD risk will not only yield insights into the diet-CHD relation but may also provide practical dietary guidance. Yet, few studies have specifically examined the association between intakes of whole-grain foods and risk of CHD. The first study to comprehensively assess whole-grain intake was conducted recently by Jacobs et al (6). In 34 492 postmenopausal women followed for 6 y, a greater intake of whole grain was associated with a reduced risk of CHD death; the multivariate-adjusted relative risk was 0.67 (95% CI: 0.48, 0.92) when the highest quintile was compared with the lowest quintile of intake. However, nonfatal myocardial infarctions were not documented in that study so that the relation of whole-grain intake to incidence of CHD remains uncertain.

To test further the hypothesis that greater intake of whole grain reduces risk of CHD, we analyzed prospective data from the

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Nurses' Health Study collected from 1984 to 1994 using repeated dietary measurements. Specifically, we examined *1*) the dose-response relations of intake of total whole grain and its major source foods to CHD risk and *2*) whether the relation of whole-grain intake to CHD risk can be attributed to its constituents such as vitamin E, vitamin B-6, fiber, and folate, which have individually been associated with lower risk of CHD in other studies.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study was initiated in 1976 when 121 700 female registered nurses 30–55 y of age answered a mailed questionnaire on their medical history and lifestyle. The cohort has since been followed every 2 y to assess potential risk factors and incident diseases. In 1980, we assessed diet with a 61-item semiquantitative food-frequency questionnaire (SFFQ; 7). In 1984, the SFFQ was expanded to include 126 items. Because the expanded questionnaires contained additional food items that are important for assessing details of carbohydrate intake, we considered 1984 as the baseline for the current analysis. We excluded respondents to the 1984 questionnaires who did not satisfy the a priori criteria of reported daily energy intake between 2514 kJ (600 kcal) and 14 665 kJ (3500 kcal) and those with previously diagnosed diabetes, angina, myocardial infarction, stroke, or other cardiovascular diseases because these diagnoses may have led to a recent change in diet. The final baseline population consisted of 75 521 women aged 38–63 y in 1984.

Assessment of whole-grain consumption

Measurements of whole grain and refined-grain foods along with other aspects of diet were repeated in 1986 and 1990 by using SFFQs similar to that used in 1984. For each food, a commonly used unit or portion size (eg, 1 slice of bread) was specified, and the subject was asked how often, on average, during the previous year she had consumed that amount. Nine responses were possible, ranging from "never" to "six or more times per day." Type and brand of breakfast cereal were also assessed. We used a procedure developed by Jacobs et al (6) to classify foods as whole or refined grains. Specifically, whole-grain foods included dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (eg, bulgar, kasha, and couscous). Refined grain included sweet rolls, cake desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereal, white rice, pancakes or waffles, and pizza. The list of breakfast cereals reported in the SFFQ was evaluated for whole grain and bran content; breakfast cereals with ≥25% whole grain or bran content by weight were classified as whole grain. A full description of the SFFQs and data on reproducibility and validity in this cohort were reported previously (7). The performance of the SFFQ in assessing the individual grain products has been documented to be high (8). For example, between the SFFQ and detailed diet records in a sample of the participants, correlation coefficients were 0.75 for cold breakfast cereal, 0.71 for white bread, and 0.77 for dark bread. Overall, these data indicate that the SFFQ provides reasonably valid measures of average long-term dietary intakes.

Outcomes

The primary endpoint for this analysis was incident CHD, which included fatal CHD and any nonfatal myocardial infarction that occurred during the 10-y period between the return of the 1984 questionnaire and June 1, 1994. On a biennial follow-up questionnaire, we requested permission to review the medical records of women who reported having a nonfatal myocardial infarction. The diagnosis was confirmed by physicians who were unaware of questionnaire data and were using criteria proposed by the World Health Organization—ie, symptoms plus either typical electrocardiographic changes or elevation of cardiac enzymes (9). Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17%). All confirmed and probable cases were included in the current analyses because the results were almost identical when probable cases were excluded. Fatal CHD was confirmed by hospital records, by autopsy, or if CHD was listed as the cause of death on the certificate and evidence of previous CHD was available. With use of all sources combined, mortality follow-up was >98% complete (10). We designated as "presumed CHD" those cases in which CHD was the underlying cause on the death certificate, but no records were available. These cases constituted 14.7% of fatal CHD cases. Analyses limited to confirmed cases yielded very similar although less precise results. We also included sudden death within 1 h of onset of symptoms in women with no other plausible cause (other than coronary disease), which was 12.3% of fatal CHD.

Data analysis

Person-time for each participant was calculated from the date of return of the 1984 questionnaire to the date of first coronary event, death, or June 1, 1994. Before data analysis, we examined distributions of individual foods to create categories of consumption with adequate person-time at risk in each category. We then calculated incidence rates by dividing the number of events by person-time in each category. The relative risks (RR) were then estimated as the rate of coronary events in a specific category of intake of whole grain or refined grain divided by the rate in the lowest category. Tests of linear trend across increasing categories of grain consumption were conducted by assigning the medians of intakes to categories (servings/d) that were treated as a continuous variable.

To reduce within-person variation and best represent long-term diet, we used a cumulative average method with repeated measures of diet during the follow-up. Details of this method were reported elsewhere (11). Briefly, we used pooled logistic regression with 2-y intervals (12), which is asymptotically equivalent to the Cox-proportional-hazard regression (13, 14), to model the incidence of CHD in relation to the cumulative average diet from all 3 cycles of SFFQs. For example, incidence of CHD from 1984 to 1986 was related to intakes of whole grain or refined grain and other dietary variables assessed on the 1984 questionnaire, incidence from 1986 to 1990 was related to the average intake reported in 1984 and 1986, and incidence from 1990 to 1994 was related to the average intake from all 3 dietary questionnaires. Some intermediate endpoints occurred during the follow-up, including angina, hypercholesterolemia, diabetes, and hypertension, which could lead to changes in diet and may therefore confound the associations between diet and disease. Hence, we stopped updating information on diet at the beginning of the interval during which those conditions were diagnosed in a participant. On average, 83% of the respondents to the 1984 baseline SFFQ also completed the 1986 and 1990 SFFQs during the follow-up.

TABLE 1
Baseline characteristics according to quintiles of whole grain intake in 75 521 female US nurses aged 38–63 y in 1984[1]

	Quintile of whole-grain intake				
Variable	1: 0.13 (0–0.26)[2]	2: 0.43 (0.27–0.56)	3: 0.85 (0.57–1.06)	4: 1.31 (1.07–1.76)	5: 2.70 (1.77–17.86)
Subject characteristics (% of group)					
Parental MI before age 60 y	15	15	14	14	14
Vigorous activity ≥1 time/wk	36	41	44	47	50
Current smoker	35	28	23	18	16
Multivitamin use	30	34	37	40	44
Vitamin E supplement use	12	15	17	19	24
Current hormone replacement therapy postmenopause	20	22	23	26	27
Hypertension	22	22	22	20	19
Hypercholesterolemia	7	7	8	8	9
Body mass index (kg/m^2)	25 ± 5[3]	25 ± 5	25 ± 5	25 ± 4	25 ± 4
Food intake by category					
Carbohydrate (g/d)	178 ± 35	180 ± 35	185 ± 3	190 ± 28	195 ± 30
Polyunsaturated fat (g/d)	12 ± 3	12 ± 3	12 ± 3	12 ± 3	12 ± 3
Monounsaturated fat(g/d)	24 ± 5	23 ± 5	22 ± 4	22 ± 4	21 ± 4
Saturated fat (g/d)	23 ± 5	23 ± 5	22 ± 4	21 ± 4	20 ± 4
trans-Fatty acids (g/d)	4 ± 1	4 ± 1	3 ± 1	3 ± 1	3 ± 1
Cholesterol (mg/d)	292 ± 111	293 ± 93	289 ± 90	281 ± 88	269 ± 92
Protein (g/d)	69 ± 14	70 ± 12	72 ± 12	72 ± 12	73 ± 12
Dietary fiber (g/d)	14 ± 4	15 ± 4	16 ± 4	18 ± 4	20 ± 5
Cereal fiber (g/d)	3 ± 1	3 ± 1	4 ± 1	5 ± 2	6 ± 2
Alcohol (g/d)	8 ± 13	8 ± 12	7 ± 11	7 ± 10	6 ± 10
Dietary vitamin E (mg/d)	6 ± 3	6 ± 3	6 ± 3	7 ± 4	7 ± 4
Folate (μg/d)	334 ± 225	359 ± 223	384 ± 226	414 ± 228	432 ± 237
Fruit (servings/d)[4]	1.6 ± 1.2	1.9 ± 1.3	2.1 ± 1.3	2.4 ± 1.4	2.7 ± 1.5
Vegetables (servings/d)[4]	2.9 ± 1.7	3.3 ± 1.7	3.6 ± 1.9	3.9 ± 2.0	4.2 ± 2.3
Red meat (servings/d)[5]	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.6	0.9 ± 0.6	0.9 ± 0.6
Intake of individual foods (servings/d)					
Dark bread	0.05	0.24	0.44	0.64	1.73
Whole grain					
Breakfast cereal	0.04	0.14	0.30	0.44	0.55
Brown rice	0.01	0.02	0.03	0.04	0.06
Wheat germ	0.00	0.00	0.01	0.02	0.09
Bran	0.00	0.01	0.02	0.07	0.30
Other grains	0.00	0.00	0.01	0.01	0.02
Cooked oatmeal	0.01	0.03	0.05	0.08	0.11
Popcorn	0.03	0.07	0.10	0.13	0.21

[1] Whole grain includes dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (eg, bulgar, kasha, couscous). Breakfast cereals with ≥25% whole-grain or bran content by weight were classified as whole grain. MI, myocardial infarction.

[2] Quintile number, quintile median, and range of servings/d of quintile in parentheses.

[3] $\bar{x}$ ± SD.

[4] A composite score of 6 fruit and 28 vegetables.

[5] A composite score of the following foods: beef, pork, or lamb, as a main dish; beef, pork, or lamb as a sandwich or mixed dish; hamburger; hot dog; processed meat, and bacon.

Missing data indicators were created for those who had missing dietary data for 1986 or 1990 and the last available value was carried forward. Age, smoking status, body mass index, postmenopausal hormone replacement therapy (HRT), alcohol intake, and multivitamin and vitamin E supplement use were also updated biennially. Aspirin use was assessed in 1984 and 1988. Vigorous exercise was assessed in 1980. All of these covariates, including total energy intake, were adjusted for in the multivariate models.

In additional analyses, we examined the possibility that specific dietary components found in whole grains—which have been shown or hypothesized to be associated with CHD—may explain any association observed between whole grains and CHD. For these analyses, several dietary components of whole grains, including dietary fiber, folate, vitamin B-6, and vitamin E were simultaneously included with whole grain in the same multivariate model.

We conducted alternative analyses limited to those women who never smoked, were less active, and did not receive HRT or use multivitamin or vitamin E supplements to minimize residual confounding because participants with high intakes of whole grains also tended to smoke less, tended to exercise more, and were more likely to receive HRT and use multivitamin or vitamin E supplements.

RESULTS

At baseline in 1984, the mean daily intake of whole-grain foods was 1.12 servings/d, with dark bread contributing 55% of

these servings and whole-grain breakfast cereal the second largest proportion (16%). The median intake of whole grain ranged from virtually none in the lowest quintile to nearly 3 servings/d in the highest quintile (**Table 1**).

Women with high intakes of whole-grain foods smoked less, exercised more, and were more likely to receive postmenopausal HRT or use supplements of multivitamins or vitamin E. Greater whole-grain intake was also associated with higher intakes of carbohydrates, proteins, dietary fiber, cereal fiber, and folate, but lower intakes of fat, cholesterol, and alcohol (Table 1). BMI and history of parental myocardial infarction before 60 y of age did not vary appreciably across quintiles of whole-grain intake.

During a 6-y period from 1984 to 1990, the mean intakes of whole grain increased from 1.12 servings/d to 1.43 serving/d. The correlation coefficients between any 2 dietary assessments ranged from 0.49 to 0.60, depending on the time between assessments (**Table 2**).

There was a strong inverse association between whole-grain intake and risk of CHD (**Table 3**). The age-adjusted RR of CHD was 0.51 (95% CI: 0.41, 0.64; $P < 0.0001$ for trend) for women in the highest compared with the lowest quintiles. The inverse relation between whole-grain intake and CHD risk was observed for both nonfatal (RR = 0.51; 95% CI: 0.39, 0.66; P for trend < 0.0001) and fatal CHD (RR = 0.51; 95% CI: 0.33, 0.80; P for trend < 0.001). In multivariate models of whole-grain intake and CHD risk, smoking was the strongest confounding factor. The RR for whole grain was 0.67 (95% CI: 0.54, 0.84) after smoking was added to the model and was further attenuated to 0.74 (95% CI: 0.58, 0.94) after other CHD risk factors were adjusted for (**Table 4**). With adjustment for the same covariates in an analysis of the overall trend considering intake of whole grain as a continuous variable, we found an RR of 0.91 (95% CI: 0.85, 0.97) for CHD risk for each additional daily serving of whole-grain foods. The reduction in risk associated with a greater intake of whole grain was similar when either baseline measures of intake (1984) or updated cumulative average of whole-grain intake (1984, 1986, and 1990) were used.

Intake of whole grains was positively associated with intakes of its constituents, such as dietary fiber (Spearman $r = 0.55$), folate (Spearman $r = 0.32$), vitamin B-6 (Spearman $r = 0.29$), and vitamin E (Spearman $r = 0.34$), which may reduce CHD risk. Therefore, these factors should not be adjusted for if one wants to assess the full effect of whole grains on CHD risk. Yet, it is useful to determine whether the relation of whole-grain intake to CHD risk could be attributed to these constituents. After adjustment for dietary fiber intake, folate, vitamin B-6, and vitamin E, the association of whole-grain intake with risk of CHD was modestly attenuated (RR = 0.79; 95% CI: 0.62, 1.01 for a comparison of the highest with the lowest quintiles; $P = 0.07$ for trend) (Table 4).

To address concerns that high intake of whole-grain products may be a marker for healthy behaviors and that there may be residual confounding effects of smoking, physical inactivity, and postmenopausal HRT, we further examined the relation between whole-grain intakes and CHD risk in subgroups of women who were never smokers, were nondrinkers, did not receive HRT, or reported no regular vigorous physical activity. The reduction in risk of CHD associated with a high intake of whole grain was even stronger among never smokers (RR = 0.49; 95% CI: 0.30, 0.79; $P = 0.003$ for trend), and remained essentially unchanged among nondrinkers, those who did not receive HRT or use vitamin E or other multivitamin supplements, and those who were less likely to engage in vigorous physical activity (Table 4).

The relation of whole-grain intake to CHD risk was independent of refined-grain intake. The Spearman correlation coefficient between whole-grain intake and refined-grain intake was -0.1 and the reduction in risk of CHD for increasing intakes of whole grain was not attenuated when intake of refined grain was added to the models. We also conducted a sensitivity analysis that excluded CHD cases that occurred in the first 4 y of follow-up to avoid potential change in diet due to preclinical conditions; the RRs for CHD were essentially unchanged although the CIs became wider because of fewer cases (data not shown).

To understand these relations further, we examined the individual foods that contributed to whole-grain consumption in relation to CHD risk. After adjustment for total energy intake and known CHD risk factors except diet, significant inverse associations with CHD were observed for whole-grain breakfast cereals, brown rice, popcorn, and bran (**Table 5**).

We also examined the relations between lifestyle factors and intake of refined grain. As opposed to whole grains, findings were generally reversed for women who had higher intakes of refined grains. However, we found little evidence of an association between refined-grain intake and risk of CHD. The age and smoking-adjusted RRs from the lowest to the highest quintiles of intake were 1.00, 1.06, 1.11, and 0.87 (NS). Higher intake of refined grains appeared to be associated with greater risk of CHD in never smokers (RR = 1.46 for the highest compared with the lowest quintiles; $P = 0.09$ for trend), but this relation was attenu-

TABLE 2
Mean and median intakes of whole grain and refined grain assessed in 1984, 1986, and 1990 with food-frequency questionnaires and their Spearman correlation coefficients in 75 521 female US nurses[1]

	Correlation coefficient			Servings per day		
Variable	1984 × 1986	1986 × 1990	1984 × 1990	1984	1986	1990
Whole grain	0.60	0.52	0.49	1.12 ± 1.12	1.24 ± 1.17	1.43 ± 1.21
				0.85 (0.29–1.49)	0.99 (0.43–1.64)	1.14 (0.57–1.92)
Refined grain	0.62	0.55	0.52	2.12 ± 1.56	1.98 ± 1.50	2.04 ± 1.50
				1.70 (1.04–2.82)	1.61 (0.97–2.55)	1.68 (1.04–2.62)

[1] Whole grain includes dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains (eg, bulgar, kasha, and couscous). Refined grain includes sweets rolls and cakes or desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereal, white rice, pancakes or waffles, and pizza. A brand name or generic cereal specified was coded for whole-grain content; breakfast cereals with ≥25% whole-grain or bran content by weight were classified as whole grain. The correlation coefficient between whole grain and refined grain intakes was -0.10.

[2] $\bar{x}$ ± SD; median with 25th–75th percentile range in parentheses.

TABLE 3
Cohort data, adjusted relative risk, and 95% CIs 1984–1994 of coronary heart disease (CHD) according to quintile of whole-grain intake in 75 521 female US nurses aged 38–63 y at baseline

	Quintile of whole-grain intake					
	1 (lowest)	2	3	4	5 (highest)	*P* for trend
Full cohort						
Cases of CHD	191	162	152	129	127	
Person-years of follow-up	143 564	148 431	145 628	146 262	145 588	
Relative risk						
Age and smoking adjusted	1.00	0.87 (0.70, 1.07)[1]	0.82 (0.67, 1.02)	0.72 (0.58, 0.90)	0.67 (0.54, 0.84)	<0.001
Multivariate adjusted[2]	1.00	0.91 (0.74, 1.14)	0.91 (0.74, 1.14)	0.82 (0.65, 1.03)	0.74 (0.58, 0.94)	0.01
After additional adjustment for fats[3]	1.00	0.92 (0.75, 1.14)	0.93 (0.75, 1.15)	0.83 (0.66, 1.05)	0.75 (0.59, 0.95)	0.01
After additional adjustment for fats, dietary fibers, folate, vitamin B-6, and vitamin E	1.00	0.93 (0.74, 1.14)	0.94 (0.75, 1.16)	0.86 (0.68, 1.09)	0.79 (0.62, 1.01)	0.07
Never Smokers						
Cases of CHD	46	32	47	29	30	
Person-years of follow-up	64 089	64 007	63 824	63 901	63 818	
Relative risk						
Age and smoking adjusted	1.00	0.67 (0.43, 1.05)	0.87 (0.58, 1.30)	0.51 (0.32, 0.81)	0.48 (0.30, 0.76)	0.002
Multivariate adjusted[2]	1.00	0.73 (0.46, 1.15)	0.91 (0.60, 1.38)	0.54 (0.34, 0.87)	0.49 (0.30, 0.79)	0.003
After additional adjustment for fats[3]	1.00	0.75 (0.47, 1.18)	0.94 (0.62, 1.43)	0.56 (0.34, 0.91)	0.50 (0.31, 0.83)	0.007
After additional adjustment for fats, dietary fibers, folate, vitamin B-6, and vitamin E	1.00	0.73 (0.46, 1.15)	0.89 (0.58, 1.37)	0.52 (0.31, 0.87)	0.47 (0.27, 0.79)	0.006

[1] Relative risk; 95% CI in parentheses.

[2] The multivariate models were simultaneously adjusted for age (5-y categories), body mass index (6 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), alcohol intake (4 categories), parental or family history of myocardial infarction before the age of 60 y, self-reported history of hypertension or hypercholestoremia, menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), protein intake (in quintiles), aspirin use (4 categories), use of multiple vitamin or vitamin E supplements, vigorous activity (≥1 time/wk), and total energy intake (in quintiles).

[3] Dietary fats included saturated, polyunsaturated, monounsaturated, and *trans* fats (all in quintiles).

ated after adjustment for known CHD risk factors, and further attenuated when whole-grain intake was added to the model (RR = 0.97 for comparisons between the extreme quintiles; $P = 0.78$ for trend).

DISCUSSION

In this large, prospective study of adult US women followed for 10 y, we found a strong inverse association between intake of whole grain and risk of CHD. This association was independent of both dietary and nondietary coronary risk factors and, to a large degree, was not explained by the constituents of whole grain thought to be protective.

Because our study was observational, we considered several alternative explanations for these findings. First, the association between CHD and whole grain may be explained by other healthy lifestyle factors in women in the highest quintile of whole-grain intake. However, the apparently protective effect of whole-grain consumption persisted in multivariate models accounting for known coronary risk factors. Further, the reduction in risk of CHD associated with high intake of whole grain was even stronger in never smokers and remained essentially unchanged in those who did not receive postmenopausal HRT or those women who reported no regular vigorous physical activity. Second, some intermediary events, including angina, hypercholesterolemia, diabetes, and hypertension could have led to changes in diet and may therefore have confounded the associations between whole-grain intake and CHD risk. However, any confounding effects from these indications would tend to attenuate the protective effect of whole grain because the tendency would be for women to increase their intake of whole-grain foods if they perceived themselves to be at elevated risk of CHD. In addition, similar findings were observed when women with those conditions at baseline in 1984 were excluded from the main analysis.

Because whole-grain intake was reported through a self-administered food-frequency questionnaire, misclassification of intake was another major concern. Assessment of whole-grain foods by the questionnaires used in this study had relatively high accuracy ($r > 0.70$ compared with a dietary record for most whole-grain foods). Also, we measured diet 3 times in 10 y to reduce within-person variation and better represent participants' long-term average dietary intakes. However, it is difficult to distinguish the effects of different grains within the whole or refined-grain category because our questionnaires cannot assess the specific types of grains used in the foods typically eaten. For example, the category of "dark bread" may have included refined-grain products such as pumpernickel and other breads with a tough crust because such products might have been wrongly perceived as whole-grain products by some participants in our study. However, any measurement error in assessing whole-grain intake was likely to be unrelated to CHD outcome in a prospective setting, and would thus tend to weaken any association between whole-grain intake and CHD risk. Therefore, the 30% reduction in risk associated with high intake of whole grain observed in our study may be a conservative estimate.

TABLE 4
Cohort data, adjusted relative risk (RR), and 95% CIs 1984–1994 of coronary heart disease (CHD) according to quintile of whole-grain intake in subgroups of 75 521 female US nurses aged 38–63 y at baseline[1]

	Quintile of whole-grain intake					
Subgroup	1 (lowest)	2	3	4	5 (highest)	*P* for trend
No hypercholesterolemia						
Cases of CHD	167	134	126	98	107	
Person-years of follow-up	132 969	136 981	135 967	133 184	135 061	
RR (95% CI)	1.00	0.87 (0.69, 1.10)	0.87 (0.69, 1.10)	0.73 (0.57, 0.96)	0.72 (0.54, 0.91)	0.01
No multivitamin use						
Cases of CHD	100	77	82	72	61	
Person-years of follow-up	76 359	74 267	77 199	77 031	75 845	
RR (95% CI)	1.00	0.93 (0.69, 1.26)	1.02 (0.75, 1.37)	0.90 (0.65, 1.23)	0.73 (0.52, 1.02)	0.05
No vitamin E supplement use						
Cases of CHD	101	80	77	68	72	
Person-years of follow-up	78 334	79 073	78 082	76 591	77 776	
RR (95% CI)	1.00	0.92 (0.68, 1.24)	0.92 (0.68, 1.25)	0.88 (0.64, 1.21)	0.83 (0.60, 1.15)	0.32
No alcohol use						
Cases of CHD	69	55	55	40	45	
Person-years of follow-up	45 170	44 564	44 818	44 686	44 710	
RR (95% CI)	1.00	0.83 (0.58, 1.20)	0.88 (0.61, 1.28)	0.75 (0.51, 1.11)	0.72 (0.49, 1.06)	0.07
No vigorous physical activity						
Cases of CHD	110	87	78	89	75	
Person-years of follow-up	73 607	73 693	73 226	73 972	73 513	
RR (95% CI)	1.00	0.84 (0.64, 1.11)	0.88 (0.66, 1.16)	0.92 (0.68, 1.24)	0.74 (0.54, 1.02)	0.11
No hormone replacement therapy						
Cases of CHD	106	102	90	66	68	
Person-years of follow-up	94 026	98 124	96 757	96 782	96 381	
RR (95% CI)	1.00	1.04 (0.80, 1.36)	1.08 (0.82, 1.42)	0.65 (0.46, 0.91)	0.75 (0.54, 1.04)	0.02

[1] The multivariate models were simultaneously adjusted for age (5-y categories), body mass index (6 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), alcohol intake (4 categories), parental or family history of myocardial infarction before the age of 60 y, self-reported history of hypertension or hypercholestoremia, menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), protein intake (in quintiles), aspirin use (4 categories), use of multiple vitamin or vitamin E supplements, vigorous activity (≥1 time/wk), and total energy intake (in quintiles).

Two previous prospective cohort studies of women also examined whether intake of whole grains was related to CHD morbidity and mortality. In the Adventist Health Study, Fraser et al (15) reported an inverse association between intake of whole-wheat bread and risk of myocardial infarction. The inverse association was especially evident for nonfatal myocardial infarction. The relative risk was 0.56 (95% CI: 0.35, 0.89) for nonfatal myocardial infarction when consumption of whole-wheat bread was compared with intake of white bread in 31 208 white Seventh-day Adventists in California. However, no comparisons were made related to the quantity and frequency of consumption, and dose-response relations were not examined in that study (15). Using the same dietary questionnaire used in the Nurses' Health Study, Jacobs et al (6) reported a lower risk of coronary death associated with higher intake of whole grain in 34 492 postmenopausal women. CHD mortality as an endpoint could reflect survival or better treatment rather than direct effects of whole grains. However, our results were generally consistent with these previous findings. In addition, we found that the reduction in risk associated with higher whole-grain intake was almost identical for fatal and nonfatal CHD.

The biological mechanisms whereby whole-grain foods may exert their protective effects are not clear but are likely to be multiple (3, 5). Greater intakes of many constituents of whole grains, including dietary fiber, vitamin E, and folate, have been independently associated with reduced risk of CHD (16, 17). Even after adjustment for these components of whole-grain foods thought to be protective in the current study, a significant inverse relation of whole-grain intake to CHD risk was still evident, suggesting additional protective effects of other constituents or their interactions. Reduced insulin demand may be another protective mechanism associated with higher intake of whole grain. In general, because of their physical form and high content of viscous fiber, whole-grain products tend to be slowly digested and absorbed and thus have relatively low glycemic indexes. In some metabolic studies of both diabetic and nondiabetic subjects, high intake of low-glycemic-index foods has been associated with lower concentrations of LDL (18), glycated hemoglobin, and urinary C-peptide excretion (a marker for β cell insulin production; 19). We recently reported that dietary glycemic load—the total glycemic effect of dietary carbohydrate—is positively associated with risk of CHD (20, 21), especially in women with greater adiposity, a major marker of insulin resistance.

The Food Guide Pyramid of the US Department of Agriculture recommends consumption of 6–11 servings of grain products/d, but the amount of whole grains is not specified (1). A survey of 4000 households in the United States (22) suggests that the average consumption of whole-grain products is only about one-half serving per day per person. In our cohort, women in the top quintile of whole-grain consumption consumed only a median of 2.5 servings/d, yet experienced a >30% lower risk of CHD than the lowest quintile (median 0.13 servings/d). Because the relation

TABLE 5
Cohort data and adjusted relative risk (RR) of coronary heart disease (CHD) 1984–1994 according to intake of specific whole-grain foods in 75 521 female US nurses aged 38–63 y at baseline[1]

	Category of consumption[2]					
Whole-grain food	Almost never	<1 serving/wk	2–4 servings/wk	5–6 servings/wk	≥1 serving/d	*P* for trend
Dark bread (servings/d)	0	0.07	0.43	0.71	1.30	
Cases of CHD	108	198	170	96	189	
Person-years of follow-up	46 831	86 368	94 301	52 832	91 359	
RR (95% CI)	1.00	1.13 (0.89, 1.43)	0.92 (0.72, 1.18)	0.97 (0.74, 1.29)	0.98 (0.77, 1.25)	0.43
Whole-grain breakfast cereal (servings/d)	0	0.07	0.22	0.43	0.93	
Cases of CHD	404	110	81	105	61	
Person-years of follow-up	155 897	59 785	58 647	60 950	36 412	
RR (95% CI)	1.00	0.89 (0.72, 1.10)	0.72 (0.56, 0.92)	0.82 (0.66, 1.02)	0.76 (0.57, 1.00)	0.007
Popcorn (servings/d)	0	0.07	0.33	0.62	1.0	
Cases of CHD	381	310	56	6	9	
Person-years of follow-up	136 093	181 881	39 418	9349	4950	
RR (95% CI)	1.00	0.86 (0.74, 1.01)	0.88 (0.66, 1.18)	0.42 (0.18, 0.92)	0.92 (0.45, 1.87)	0.27
Cooked oatmeal (servings/d)	0	0.07	0.33	0.67	1.0	
Cases of CHD	471	239	36	10	5	
Person-years of follow-up	210 903	129 344	26 107	3448	1889	
RR (95% CI)	1.00	0.92 (0.79, 1.08)	0.70 (0.49, 0.98)	1.41 (0.75, 2.66)	1.10 (0.45, 2.68)	0.68
Brown rice (servings/d)	0	0.07	0.31	0.79	—	
Cases of CHD	571	175	14	1	—	
Person-years of follow-up	253 637	106 223	10 557	1274	—	
RR (95% CI)	1.00	0.86 (0.72, 1.02)	0.77 (0.45, 1.32)	0.45 (0.06, 3.20)	—	0.04
Wheat germ (servings/d)	0	0.07	0.36	0.93	—	
Cases of CHD	717	27	13	4	—	
Person-years of follow-up	330 539	29 761	6335	5056	—	
RR (95% CI)	1.00	0.55 (0.37, 0.81)	1.11 (0.64, 1.93)	0.41 (0.15, 1.10)	—	0.01
Bran (servings/d)	0	0.07	0.36	1.0	—	
Cases of CHD	644	70	23	24	—	
Person-years of follow-up	287 273	47 844	17 798	18 776	—	
RR (95% CI)	1.00	0.76 (0.59, 0.98)	0.68 (0.44, 1.03)	0.63 (0.42, 0.95)	—	0.001
Other grains (servings/d)	0	0.07	—	—	—	
Cases of CHD	721	40	—	—	—	
Person-years of follow-up	341 661	30 030	—	—	—	
RR (95% CI)	1.00	0.79 (0.57, 1.08)	—	—	—	0.16

[1] The multivariate RRs were adjusted for body mass index (6 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), alcohol intake (4 categories), parental or family history of myocardial infarction before the age of 60 y, self-reported history of hypertension or hypercholestoremia, menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), aspirin use (4 categories), use of multiple vitamin or vitamin E supplements, vigorous activity (≥1 time/wk), and total energy intake.

[2] Each category was defined as it was originally queried in the questionnaire; categories without CHD events were combined with adjacent categories.

between greater consumption of whole-grain foods and lower risk of CHD in this cohort appeared to be continuous and without an apparent threshold, increasing the frequency of consumption of whole-grain foods should be feasible and is likely to have significant benefits in reducing the risk of CHD. Although most of the grains consumed in the United States are processed and refined, whole-grain products are readily available from many sources (23). Even though the health effects of different grain products may differ from one another, it is unlikely that the protective effect on CHD risk is limited to only one specific source of whole grain. In our cohort, protective effects of whole grain were derived from several different sources, including whole-grain breakfast cereal, brown rice, and bran.

In conclusion, higher intakes of whole-grain foods were associated with lower risks of both fatal and nonfatal CHD in this large population of women. The inverse association was independent of known coronary risk factors and components of whole-grain foods currently believed to be beneficial. These findings support the notion that increasing intakes of whole grains may help reduce the incidence of CHD.

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