Whole- and refined-grain intakes and the risk of hypertension in women[1–3]

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ABSTRACT

Background: Prospective studies linking whole- and refined-grain intakes with the risk of hypertension, a major cardiovascular disease risk factor, remain limited.

Objective: We aimed to determine whether baseline intake of whole or refined grains is associated with subsequent development of hypertension.

Design: We conducted a prospective cohort study in 28 926 female US health professionals aged ≥45 y who were free of baseline cardiovascular disease, cancer, and hypertension in 1992. Baseline whole- and refined-grain intakes were assessed from semiquantitative food-frequency questionnaires. We identified 8722 incident cases of hypertension from annual questionnaires during 10 y of follow-up.

Results: After adjustment for known hypertension risk factors, the relative risks (RRs) (and 95% CIs) of incident hypertension were 1.00 (reference), 0.96 (0.89, 1.03), 0.95 (0.88, 1.02), 0.92 (0.85, 0.99), and 0.89 (0.82, 0.97) across the increasing quintiles of baseline whole-grain intake (P for trend = 0.007). When functional cutoffs were used, women who consumed 0.5 to <1, 1 to <2, 2 to <4, and ≥4 whole-grain servings/d had multivariate RRs (95% CIs) of 0.93 (0.87, 1.00), 0.93 (0.87, 0.99), 0.92 (0.85, 0.99), and 0.77 (0.66, 0.89), respectively, compared with those who consumed <0.5 whole-grain servings/d. In contrast, refined-grain intake was not associated with the risk of hypertension. The multivariate RRs of hypertension across the increasing quintiles of refined-grain intake were 1.00, 0.97, 0.94, 0.99, and 0.97 (P for trend = 0.80).

Conclusion: Higher whole-grain intake was associated with a reduced risk of hypertension in middle-aged and older women, which suggests a potential role for increasing whole-grain intake in the primary prevention of hypertension and its cardiovascular complications. *Am J Clin Nutr* 2007;86:472–9.

KEY WORDS Dietary intake, whole grains, refined grains, hypertension, epidemiology

INTRODUCTION

Whole grains contain a myriad of vitamins, minerals, phytochemicals, and other nutrients in the outer (bran) and inner (germ) layers (1). The bran and germ are both removed during the refining process, which makes refined grains more energy dense but less nutrient rich than are whole grains. A greater intake of whole grains has been shown to prevent cardiovascular disease (CVD) (2–7), whereas intake of refined grains had no effect or adverse effects on the risk of CVD (2, 5–7). The effects of whole- and refined-grain intakes in the development of CVD are attributable, in part, to the induced changes in blood pressure (BP). However, epidemiologic evidence regarding the association of whole- and refined-grain intakes with the risk of developing hypertension remains limited.

Cross-sectional studies have found an association between higher whole-grain intake and a lower prevalence of hypertension (2, 3, 6). We are aware of only 2 cohort studies on the prospective association. In a large cohort of US women, intakes of some individual whole-grain foods were inversely associated with self-reported systolic BP (SBP) and diastolic BP (DBP) during follow-up (8). More recently, a study in young adults showed an inverse association between baseline whole-grain intake and the incidence of elevated BP (9). Small trials have evaluated the effects of selected whole-grain foods in reducing BP; the results are inconclusive, but they suggest potential benefits (10–15). The large study of dietary intervention for BP control, the Dietary Approaches to Stop Hypertension (DASH) Trial, showed that a healthy dietary pattern that emphasized whole-grain cereal products (16) substantially lowered BP in subjects with and without hypertension (17). Preliminary findings on the association of refined-grain intake with BP or risk of hypertension are much less consistent than those for whole-grain intake; positive associations, inverse associations, and no association have all been reported for refined grains (8, 9).

To further clarify the specific effects of the type and amount of grains in the diet on hypertension development, we used data from an existing prospective cohort of 39 876 middle-aged and older women to examine the association between baseline whole- and refined-grain intakes and the development of incident hypertension during 10 y of follow-up. To investigate the potential benefit of replacing refined grains with whole grains when the

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total grain intake stays constant, we also calculated the proportion of whole grains in total grain intake and assessed the association of that proportion with the development of hypertension.

SUBJECTS AND METHODS

Study population

The Women's Health Study (WHS) was a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial evaluating the effects of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer (18). A third component, β-carotene, was initially included in the trial but was terminated on 18 January 1996, after a median treatment duration of 2.1 y (19).

From September 1992 to May 1995, a total of 39 876 female US health professionals aged ≥ 45 y who were free of a history of myocardial infarction, stroke, transient ischemic attack, and cancer (except nonmelanoma skin cancer) were randomly assigned to the WHS. Of these 39 876 women, 39 310 provided detailed baseline dietary information by completing a 131-item validated semiquantitative food-frequency questionnaire (SFFQ) (20). Among them, 829 women were excluded because of insufficient completion of the SFFQ (>70 items left blank) or an implausible mean energy intake of <600 or ≥3500 kcal/d, 17 women were excluded because of insufficient data from which to calculate the consumption of whole and refined grains, and 37 women were excluded because of prerandomization CVD or cancer.

For the current analysis, we further excluded 10 317 women with baseline self-reported hypertension, defined as having a physician diagnosis of hypertension, self-reported SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or current or past treatment for high BP. Baseline SBP was reported in 1 of 9 ordinal categories ranging from <110 to ≥180 mm Hg, and DBP was reported in 1 of 7 ordinal categories ranging from <65 to ≥105 mm Hg. Self-reported BP in health professionals has been shown to be strongly correlated with measured SBP ($r = 0.72$) and DBP ($r = 0.60$) (21). After all of these nonmutual exclusions, a baseline population of 28 926 women remained for analysis.

Written informed consent was obtained from all participants. The study was approved by the institutional review board of Brigham & Women's Hospital (Boston, MA).

Intakes of whole grains, refined grains, other food groups, and nutrients

For each food, a commonly used unit or portion size was specified on the SFFQ. Participants were asked how often, on average, they had consumed that amount of the food during the previous year. Nine possible responses ranging from "never or less than once/mo" to ">6 times/d" were recorded. The average daily intake of an individual food item was calculated by multiplying the intake frequency by the portion size of the specific item. Intakes of food groups such as whole and refined grains, fruit and vegetables, meat, and dairy products were calculated by summing the intake of individual food items. Nutrient intake was computed by multiplying the intake frequency of each unit of food by the nutrient content of the specified portion size according to food-composition tables from the Harvard University School of Public Health (Boston, MA; 22). All nutrients were adjusted for total energy intake with the use of the residual method (23). The validity and reproducibility of the SFFQ used in the WHS has been described previously (20).

The classification of whole- and refined-grain foods has been widely used in other studies (2–4, 7). Specifically, whole-grain foods included dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, wheat germ, brown rice, bran, and other grains. Refined-grain foods included sweet rolls and cakes or desserts, white bread, pasta, English muffins, muffins or biscuits, refined-grain breakfast cereal, white rice, pancakes or waffles, and pizza. The type and brand of breakfast cereal were reported in the SFFQ and evaluated for whole-grain and bran content on the basis of data provided by the package labels. Breakfast cereals with ≥25% whole-grain or bran content by weight were considered as "whole grains." As documented in previous validation studies (24, 25), Pearson correlations comparing the intake of an individual grain food estimated from the SFFQ with the intake from 7-d detailed dietary records were mostly >0.60, and correlations comparing grain-food intake estimates from 2 SFFQs administered 1 y apart were mostly >0.50.

Other baseline variables

On the baseline questionnaire, women provided self-reports of age (in y), weight and height [which were used to calculate body mass index (BMI; in kg/m^2)], smoking status (never, former, or current), alcohol use (rarely or never, 1–3 drinks/mo, 1–6 drinks/wk, or ≥1 drink/d), vigorous exercise (rarely or never or <1, 1–3, or ≥4 times/wk), parental history of myocardial infarction before age of 60 y (no or yes), menopausal status (no, yes, or uncertain), postmenopausal hormone use (never, former, or current), multivitamin use (never, former, or current), history of diabetes (no or yes), and hypercholesterolemia (no or yes). Hypercholesterolemia was defined as physician diagnosis, self-reported cholesterol concentrations of ≥240 mg/dL, or current treatment for high cholesterol.

Ascertainment of incident hypertension

As reported previously (26), incident cases of hypertension were defined by the meeting of ≥1 of 4 criteria from annual follow-up questionnaires: self-reports of a new physician diagnosis of hypertension, self-reports of newly initiated antihypertensive treatment, self-reported SBP ≥ 140 mm Hg, or self-reported DBP ≥ 90 mm Hg. Women reporting a new physician diagnosis of hypertension also stated the month and year of that diagnosis. A missing date for a physician diagnosis or hypertension defined by other criteria was assigned a date of incident hypertension by random selection of a date between the current and the previous annual questionnaires. The subjects developing major CVD—including myocardial infarction and stroke, the management of which may have effect on BP—were censored at the date of that diagnosis. On the basis of this definition, 8722 cases of incident hypertension were identified during follow-up of the cohort for a mean of 10 y (maximum: 10.9 y).

Statistical analyses

Statistical analyses were performed by using SAS software (version 8.0l; SAS Institute, Cary, NC). Whole- and refined-grain intakes were categorized into quintiles on the basis of overall distribution. The proportion of whole grains in the total grain intake, calculated by dividing absolute intake of whole grains by the sum of whole and refined grains, was also divided

into quintiles. Mean values or proportions of hypertension risk factors at baseline were compared according to quintiles of whole- and refined-grain intakes. The incidence rates of hypertension were calculated for each grain intake category by dividing the number of cases by the person-years of follow-up. Follow-up time was calculated as the time from randomization to the date of incident hypertension, the last day the person was in the study, or 31 March 2004, whichever came first. After testing of the proportional hazards assumption, Cox regression models were used to estimate the relative risk (RR) and 95% CI of developing hypertension across quintiles of whole-grain intake, refined-grain intake, and proportion of whole grains in total grains, with the lowest quintile used as the reference category. First, models were adjusted only for age, race, total energy intake, and randomized treatment assignment. Second, models were also adjusted for lifestyle factors, including smoking, alcohol use, exercise, menopausal status, postmenopausal hormone use, multivitamin use, and family history of myocardial infarction, which were potential confounding factors. Third, models were also adjusted for clinical factors, including BMI and a history of diabetes and hypercholesterolemia, which could be confounding factors or intermediate factors in the causal pathway between grain intake and development of hypertension. Fourth, models were also adjusted for dietary intakes of other food groups, including fruit and vegetables, meats (except fish), and dairy products (all in quintiles). Nutrients known to be contained in whole grains—eg, fiber, folate, potassium, and magnesium—were added separately into multivariate models to explore the specific contribution of each nutritional factor. A linear trend across increasing quintiles was tested by using the median value of each quintile as an ordinal variable.

We further repeated the Cox regression analyses by using functional cutoffs. Whole-grain intake was categorized a priori into <0.5, 0.5 to <1.0, 1.0 to <2.0, 2.0 to <4.0, and ≥4.0 servings/d, and refined-grain intake was categorized into <1.0, 1.0 to <2.0, 2.0 to <4.0, 4.0 to <6.0, and ≥6.0 servings/d. Whole- and refined-grain intakes were also modeled as continuous variables, and a curvilinear trend was tested by adding a quadratic term in the linear model. Finally, the analyses were stratified a priori by major hypertension risk factors, including BMI (<25 or ≥25), vigorous exercise (none or any), smoking status (current smoker or never or former smoker), and alcohol consumption (none or any). Interactions were tested by using the Wald chi-square test.

RESULTS

In 28 926 women with a mean (±SD) age of 53.8 ± 6.6 y in 1992, the intake of whole grains ranged from 0 to 15.3 (median: 1.13) servings/d. The major contributors to whole-grain intake in this population included dark bread (50.1%), popcorn (17.2%), and whole-grain cold breakfast cereal (16.2%). The intake of refined grains ranged from 0 to 24.5 (median: 1.85) servings/d. The major contributors to refined grains included white bread (19.3%), cookies (17.2%), English muffins (11.7%), and pasta (11.6%). The proportion of whole grains in total grain intake ranged from 0% to 100% (median: 36.7%). Whole- and refined-grain intakes were only weakly correlated ($r = 0.05$, $P < 0.05$).

Participants' characteristics and hypertension risk factors for the 1st (lowest), 3rd, and 5th quintiles of whole-grain and refined-grain intakes are shown in **Table 1**. Compared with women in the lowest quintile of whole-grain intake, those in higher quintiles were significantly less likely to be current smokers and heavy alcohol drinkers, but they were significantly more likely to exercise vigorously and take multivitamins ($P < 0.0001$ for all). The proportions of postmenopausal women, postmenopausal hormone users, and women with a history of diabetes or hypercholesterolemia were significantly higher among women who consumed more whole grains ($P < 0.0001$ for all except history of diabetes: $P = 0.0009$). BMI and parental history of myocardial infarction at <60 y of age did not significantly differ across quintiles of whole-grain intake. Regarding other dietary factors, higher whole-grain intake was directly associated with higher intakes of fruit and vegetables, meat, and dairy products. Dietary fiber, folate, potassium, and magnesium were all progressively higher with increasing whole-grain consumption. The associations of refined-grain intake with most lifestyle, clinical, and dietary factors were opposite to those for whole-grain intake, except the similar inverse associations with smoking and alcohol use and positive associations with total energy intake and intakes of other food groups. Finally, both whole- and refined-grain intakes were positively associated with baseline SBP but not with baseline DBP. The associations with SBP were only modest, albeit significant ($P = 0.003$ for whole grains and $P = 0.005$ for refined grains), which reflects the large number of subjects in the study.

There were 8722 cases of incident hypertension over a mean duration of 10 y. Whole-grain intake was associated with a modest but significant reduction in the risk of hypertension (**Table 2**). Compared with women in the lowest quintile of whole-grain intake, the age-, race-, total energy intake–, and randomized treatment– adjusted RRs (95% CIs) of incident hypertension were 0.96 (0.90, 1.03), 0.92 (0.86, 0.99), 0.90 (0.84, 0.97), and 0.86 (0.80, 0.93) across the increasing quintiles (P for linear trend < 0.0001). The inverse association was only slightly attenuated and remained significant with further adjustment for lifestyle factors (P for trend = 0.001), clinical factors (P for trend = 0.0009), and the intake of other food groups (P for trend = 0.007). When nutrients contained in whole grains were individually added to the multivariate model, the RRs and the linear trends were essentially unchanged except those for dietary fiber, for which RRs (95% CIs) after adjustment were 1.00, 0.97 (0.90, 1.04), 0.97 (0.90, 1.05), 0.95 (0.87, 1.03), and 0.93 (0.85, 1.01), respectively, across increasing quintiles (P for trend = 0.11). In contrast with whole-grain intake, refined-grain intake was not associated with the risk of hypertension (Table 2). In the age-, race-, total energy intake–, and randomized treatment–adjusted model, the RRs of incident hypertension across increasing quintiles of refined-grain intake were 1.00, 0.99, 0.95, 0.97, and 0.98 (P for linear trend = 0.84). The RRs did not materially change after adjustment for lifestyle, clinical, or dietary factors. The associations of the proportion of whole grains in total grain intake and of the frequency of intake of whole grains with the risk of hypertension were similar (Table 2). Women in the highest quintile of the proportion of whole-grain intake (≥58% of total grains as whole grains) had a multivariate RR of hypertension of 0.90 (95% CI: 0.84, 0.98) compared with those in the lowest quintile (≤18% total grains as whole grains) (P for trend = 0.002). The linear trend across quintiles of proportion of whole-grain intake remained significant ($P = 0.03$) after additional adjustment for dietary fiber.

Table 1
Baseline characteristics of 28 926 women free of baseline hypertension according to quintile (Q) of whole- and refined-grain intake

	Whole grains				Refined grains			
	Q1 (n = 5514)	Q3 (n = 5541)	Q5 (n = 5817)	P^1	Q1 (n = 5808)	Q3 (n = 5800)	Q5 (n = 5784)	P^1
Median intake (servings/d)	0.21	1.13	3.07		0.76	1.85	4.06	
Age (y)	53.0 ± 6.3[2]	53.7 ± 6.6	54.6 ± 6.9	<0.0001	54.9 ± 7.0	53.4 ± 6.4	53.4 ± 6.6	<0.0001
BMI (kg/m^2)	25.1 ± 4.6	25.2 ± 4.3	25.2 ± 4.6	0.42	25.0 ± 4.3	25.1 ± 4.4	25.5 ± 4.7	<0.0001
White (%)	92.7	96.6	96.8	<0.0001	94.6	95.9	95.7	<0.0001
Current smoker (%)	21.2	12.3	8.7	<0.0001	15.7	11.8	13.6	<0.0001
Exercise (%)				<0.0001				<0.0001
Rarely or never	46.4	34.8	31.3		36.7	33.7	39.9	
< 1 time/wk	20.0	20.5	18.7		18.8	20.3	21.1	
1–3 times/wk	25.2	33.7	35.3		31.7	34.1	29.8	
≥4 times/wk	8.4	11.0	14.7		12.8	11.9	9.2	
Alcohol use (%)				<0.0001				<0.0001
Rarely or never	44.9	41.1	45.6		45.1	41.9	45.3	
1–3 drinks/mo	13.2	13.3	13.0		11.9	13.4	13.1	
1–6 drinks/wk	30.3	34.9	32.8		30.9	34.2	34.0	
≥1 drinks/d	11.6	10.7	8.6		12.1	10.5	7.6	
Postmenopausal (%)	48.1	50.4	55.0	<0.0001	55.2	49.8	49.8	<0.0001
Postmenopausal hormone use (%)	37.2	40.2	42.4	<0.0001	43.9	41.0	36.2	<0.0001
Multivitamin use (%)	26.2	29.9	31.0	<0.0001	32.1	30.1	26.2	<0.0001
History of diabetes (%)	1.2	1.4	1.8	0.0009	1.9	1.3	1.1	0.0003
History of hypercholesterolemia (%)	22.5	24.6	27.2	<0.0001	25.6	24.2	25.2	0.14
Family history of myocardial infarction (%)	12.6	12.5	12.8	0.20	12.2	12.6	13.5	0.09
Dietary factors								
Total energy intake (kcal/d)	1457 ± 487	1696 ± 490	2026 ± 508	<0.0001	1325 ± 405	1689 ± 417	2183 ± 515	<0.0001
Fruit and vegetables (servings/d)	4.55 ± 2.78	6.00 ± 3.11	7.59 ± 4.77	<0.0001	5.31 ± 3.21	6.07 ± 3.47	6.83 ± 4.48	<0.0001
Meats (servings/d)	1.07 ± 0.67	1.15 ± 0.67	1.21 ± 0.77	<0.0001	0.89 ± 0.55	1.11 ± 0.57	1.47 ± 0.87	<0.0001
Dairy products (servings/d)	1.82 ± 1.59	2.14 ± 1.44	2.52 ± 1.61	<0.0001	1.80 ± 1.41	2.15 ± 1.48	2.56 ± 1.78	<0.0001
Fiber (g/d)[3]	15.7 ± 5.0	19.1 ± 5.4	21.9 ± 6.5	<0.0001	20.5 ± 7.5	19.0 ± 5.6	17.5 ± 4.8	<0.0001
Folate (μg/d)[3]	386 ± 238	440 ± 227	451 ± 205	<0.0001	471 ± 281	431 ± 216	388 ± 174	<0.0001
Potassium (mg/d)[3]	3021 ± 644	3240 ± 563	3298 ± 561	<0.0001	3453 ± 655	3212 ± 548	2950 ± 500	<0.0001
Magnesium (mg/d)[3]	302 ± 72	341 ± 70	369 ± 74	<0.0001	364 ± 88	339 ± 72	314 ± 58	<0.0001
Blood pressure at baseline (%)				0.003				0.005
Systolic								
< 110 mm Hg	22.3	19.0	19.5		20.8	21.2	18.5	
110–119 mm Hg	36.1	38.2	37.0		36.8	37.5	37.5	
120–129 mm Hg	28.5	29.6	29.7		28.4	28.7	29.3	
130–139 mm Hg	13.1	13.2	13.8		14.0	12.6	14.7	
Diastolic (%)				0.13				0.16
< 65 mm Hg	12.3	11.2	12.4		12.9	11.9	11.2	
65–74 mm Hg	40.1	42.1	40.5		40.8	41.9	39.9	
75–84 mm Hg	39.7	38.2	39.3		38.4	38.0	40.4	
85–89 mm Hg	7.9	8.5	7.8		7.9	8.2	8.5	

[1] Trend test for continuous variables and chi-square test for categorical variables.
[2] $\bar{x}$ ± SD (all such values).
[3] Adjusted for energy by using the residual method.

We further estimated the RRs of hypertension across functional categories of whole-grain intake defined in servings per day. Compared with women who consumed <0.5 whole-grain servings/d, those who consumed 0.5 to <1, 1 to <2, 2 to <4, and ≥4 servings/d had RRs (95% CIs) of hypertension of 0.93 (0.87, 1.00), 0.93 (0.87, 0.99), 0.92 (0.85, 0.99), and 0.77 (0.66, 0.89), respectively, in the multivariate-adjusted model (**Figure 1**). The substantially reduced risk of hypertension in women consuming ≥4 whole-grain servings/d remained significant after adjustment for dietary fiber (RR: 0.80; 95% CI: 0.69, 0.93). The results of analyses stratified by BMI (<25 or ≥25), vigorous exercise (none or any), cigarette smoking status (current smoker or never or former smoker), and alcohol use (none or any) were similar to the overall results (**Table 3**). The differences in the multivariate RRs of hypertension in the subgroups were only modest (P for interaction > 0.05 for all). Refined-grain intake was also examined by using functional categories. There was no association of refined-grain intake with the risk of hypertension either in overall analyses (Figure 1) or in the stratified analyses (data not shown). When modeled as continuous variable, each 1-serving/d increase in whole-grain intake was associated with a 4% (95% CI: 1%, 6%) reduction in hypertension risk after multivariate adjustment, whereas the same increase in refined-grain intake was not associated with the risk of hypertension.

Table 2
Relative risks (and 95% CIs) of hypertension according to quintile (Q) of whole- and refined-grain intake

	Q1	Q2	Q3	Q4	Q5	*P* for linear trend[1]
Whole grains						
Servings/d	0.21 (0 to <0.49)[2]	0.64 (0.49 to <0.924)	1.13 (0.924 to <1.35)	1.64 (1.35 to <2.14)	3.07 (2.14–15.3)	
Cases/person-years	1688/44 030	1886/49 663	1647/44 563	1769/47 522	1732/46 985	
Age-, race-, energy-, and treatment-adjusted[3]	1.00 (reference)	0.96 (0.90, 1.03)[4]	0.92 (0.86, 0.99)	0.90 (0.84, 0.97)	0.86 (0.80, 0.93)	<0.0001
Also adjusted for lifestyle factors[5]	1.00 (reference)	0.96 (0.89, 1.03)	0.93 (0.86, 1.00)	0.90 (0.83, 0.97)	0.88 (0.81, 0.95)	0.001
Also adjusted for lifestyle and clinical factors[6]	1.00 (reference)	0.95 (0.88, 1.02)	0.93 (0.87, 1.01)	0.90 (0.84, 0.97)	0.87 (0.81, 0.95)	0.0009
Also adjusted for lifestyle, clinical, and dietary factors[7]	1.00 (reference)	0.96 (0.89, 1.03)	0.95 (0.88, 1.02)	0.92 (0.85, 0.99)	0.89 (0.82, 0.97)	0.007
Refined grains						
Servings/d	0.76 (0 to <1.057)	1.33 (1.057 to <1.61)	1.85 (1.61 to <2.18)	2.55 (2.18 to <3.12)	4.06 (3.12–24.5)	
Cases/person-years	1800 / 46347	1737 / 46422	1677 / 47178	1723 / 46743	1785 / 46072	
Age-, race-, energy-, and treatment-adjusted[3]	1.00 (reference)	0.99 (0.92, 1.06)	0.95 (0.88, 1.01)	0.97 (0.91, 1.05)	0.98 (0.91, 1.07)	0.84
Also adjusted for lifestyle factors[5]	1.00 (reference)	0.97 (0.91, 1.05)	0.93 (0.86, 1.00)	0.96 (0.89, 1.04)	0.96 (0.88, 1.04)	0.46
Also adjusted for lifestyle and clinical factors[6]	1.00 (reference)	0.97 (0.90, 1.05)	0.94 (0.88, 1.02)	1.00 (0.92, 1.08)	0.99 (0.91, 1.08)	0.80
Also adjusted for lifestyle, clinical, and dietary factors[7]	1.00 (reference)	0.97 (0.90, 1.04)	0.94 (0.87, 1.01)	0.99 (0.91, 1.07)	0.97 (0.89, 1.06)	0.80
Proportion of whole grains in total grains						
Percentage (%)	10 (0 to <18)	25 (18 to <31)	37 (31 to <43)	50 (43 to <58)	69 (58–100)	
Cases/person-years	1775/46 037	1800/45 987	1713/46 965	1718/47 034	1715/46 685	
Age-, race-, energy-, and treatment-adjusted[3]	1.00 (reference)	1.01 (0.94, 1.07)	0.93 (0.87, 0.99)	0.92 (0.86, 0.99)	0.89 (0.83, 0.95)	<0.0001
Also adjusted for lifestyle factors[5]	1.00 (reference)	1.02 (0.95, 1.10)	0.95 (0.89, 1.02)	0.95 (0.88, 1.02)	0.90 (0.84, 0.97)	0.0007
Also adjusted for lifestyle and clinical factors[6]	1.00 (reference)	1.01 (0.94, 1.09)	0.94 (0.88, 1.01)	0.93 (0.87, 1.00)	0.88 (0.82, 0.95)	0.0001
Also adjusted for lifestyle, clinical, and dietary factors[7]	1.00 (reference)	1.02 (0.95, 1.10)	0.95 (0.89, 1.03)	0.95 (0.88, 1.02)	0.90 (0.84, 0.98)	0.002

[1] Linear trends were tested by using the median value of each category as an ordinal variable.
[2] Median; range in parentheses (all such values).
[3] Model was adjusted for age (continuous), race (white, black, or other), total energy intake (continuous), and randomized treatment assignment (aspirin, vitamin E, β-carotene, or placebo).
[4] Relative risk; 95% CI in parentheses (all such values).
[5] Model was also adjusted for smoking (never, former, or current), alcohol use (rarely or never or 1–3 drinks/mo, 1–6 drinks/wk, or ≥1 drink/d), exercise (rarely or never or <1, 1–3, or ≥4 times/wk), family history of myocardial infarction (yes or no), postmenopausal (yes, no, or uncertain), postmenopausal hormone use (never, former, or current), and multivitamin use (never, former, or current).
[6] Model was also adjusted for BMI (continuous), history of diabetes (yes or no), and history of hypercholesterolemia (yes or no).
[7] Model was also adjusted for dietary intake of fruit and vegetables, meats, and dairy products (in quintiles).

Because the women with a history of diabetes, hypercholesterolemia, or obesity had, on average, a higher risk of developing hypertension and CVD than did those without such a history, and, because the former group may have changed their diet after perceiving these conditions, we repeated all analyses while excluding women with these indications at baseline. For the same reason, we also repeated the analyses with the women who developed those intermediate diseases during the follow-up censored at the time of diagnoses. None of these supplemental analyses altered the conclusions.

DISCUSSION

In this large, prospective, cohort study, whole-grain intake was inversely associated with the subsequent risk of hypertension. The association was modest but dose related and independent of known risk factors for hypertension. In contrast, we found no association between refined-grain intake and the risk of hypertension.

Previous epidemiologic studies of the association between whole- and refined-grain intakes and the risk of hypertension are limited. An inverse association between whole-grain intake and the prevalence of hypertension was observed in cross-sectional analyses (2, 3, 6). In a large cohort of US female nurses, intakes of selected whole-grain foods were inversely associated with self-reported SBP and DBP after a 4-y follow-up (8). A more recent study found an inverse association between baseline whole-grain intake and the risk of elevated BP—defined as incident SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or the use of antihypertensive medication—during a 15-y follow-up of 4304 young adults (9). Improvements in BP reduction with whole-grain foods have been observed in some (10, 11, 14) but not all (12, 13, 15) small trials. The DASH diet, consisting of whole-grain products and other healthy foods (17), substantially lowered BP in 459 adults with baseline SBP ≤ 160 mm Hg and DBP 80–95 mm Hg (16). The present study agrees with these earlier findings from observational and interventional studies and provides further evidence for the potential benefits of whole-grain intake in hypertension prevention. The inverse association across increasing whole-grain intake was modest but consistent among most analyses. Furthermore, the reduction in hypertension risk in women who consumed a fair amount of whole grains (eg, ≥4 servings/d) was large and highly significant.

Although multiple nutritional components of whole grains may explain the beneficial effects with respect to hypertension development, the biological pathways remain incompletely understood (27). Dietary fiber, folate, potassium, and magnesium are all commonly found in whole grains and are inversely associated with BP in large cohort studies (28–30), although clinical trials of supplements with these nutrients have shown small and inconsistent effects in lowering BP (31–35). In our analyses, only adjustment for fiber attenuated the inverse association between whole-grain intake and the risk of hypertension, which suggests that the protective effects of whole grains in the development of

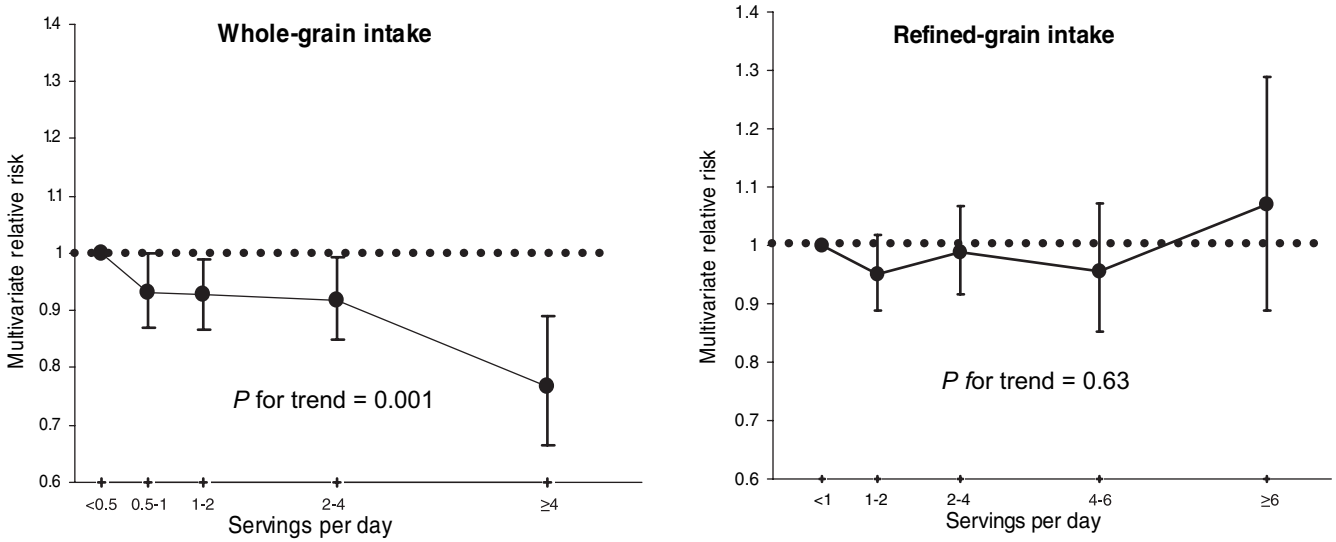

FIGURE 1. Relative risks of hypertension across functional categories of whole- and refined-grain intake. The number of cases/total number of women across the increasing categories of whole-grain intake were 1984/6440, 1888/6287, 2880/9656, 1682/5473, and 288/1070. The number of cases/total number of women across the increasing categories of refined-grain intake were 1591/5142, 3201/10 810, 2978/9933, 711/2331, and 241/710. The model was adjusted for the lifestyle, clinical, and dietary factors defined in Table 2. Relative risks were plotted on the median of each intake category. Error bars indicate 95% CIs. *P* for trend was tested by using the median value of each category as an ordinal variable.

hypertension may be partly due to fibrous parts of whole grains. The possible mechanisms may involve reductions in abdominal obesity (36), increases in peripheral insulin sensitivity (37), improvements in vascular endothelial function (38), and beneficial effects on the digestion and absorption of foods (39). Meanwhile, because the RRs of hypertension in association with whole-grain intake remained significant after adjustment for fiber, fiber may not be the only factor contributing to a reduced risk of hypertension; other nutritional components or their interactions also may contribute to the benefits of whole grains (27).

In contrast with the findings with respect to whole grains, previous findings on the association of refined-grain intake with BP have been highly inconsistent. In the NHS, baseline intake of selected refined-grain foods was significantly and positively associated with SBP but inversely associated with DBP during the follow-up (8). In the cohort of 4304 young adults, no significant

Table 3
Multivariate relative risks (RRs) (and 95% CIs) of hypertension according to frequencies of whole-grain intake in subgroups of women[1]

	Whole-grain intake [median (range)]					
	0.28 (0 to <0.5)	0.77 (0.5 to <1.0)	1.36 (1 to <2.0)	2.78 (2.0 to <4.0)	5.0 (≥4.0)	*P* for interaction[2]
BMI (kg/m^2)						0.65
<25 (*n*)	899	791	1249	707	124	
RR (95% CI)	1.00 (reference)	0.93 (0.84, 1.04)	0.93 (0.84, 1.02)	0.91 (0.81, 1.02)	0.72 (0.57, 0.90)	
≥25 (*n*)	1035	1061	1577	943	154	
RR (95% CI)	1.00 (reference)	0.93 (0.84, 1.02)	0.90 (0.82, 0.98)	0.91 (0.82, 1.01)	0.81 (0.67, 0.98)	
Vigorous exercise						0.93
None (*n*)	984	763	1022	575	97	
RR (95% CI)	1.00 (reference)	0.95 (0.86, 1.05)	0.92 (0.83, 1.02)	0.91 (0.81, 1.03)	0.72 (0.56, 0.93)	
Any (*n*)	1000	1123	1856	1107	191	
RR (95% CI)	1.00 (reference)	0.92 (0.84, 1.01)	0.93 (0.85, 1.01)	0.92 (0.83, 1.01)	0.79 (0.66, 0.95)	
Cigarette smoking						0.33
Never or former (*n*)	1556	1604	2585	1537	270	
RR (95% CI)	1.00 (reference)	0.95 (0.88, 1.03)	0.94 (0.87, 1.01)	0.92 (0.85, 1.01)	0.80 (0.68, 0.93)	
Current (*n*)	425	280	294	144	17	
RR (95% CI)	1.00 (reference)	0.83 (0.70, 0.98)	0.88 (0.74, 1.04)	0.89 (0.71, 1.12)	0.52 (0.30, 0.90)	
Alcohol consumption						0.19
None (*n*)	929	833	1279	808	139	
RR (95% CI)	1.00 (reference)	0.94 (0.85, 1.05)	0.95 (0.86, 1.04)	0.97 (0.87, 1.09)	0.71 (0.58, 0.88)	
Any (*n*)	1055	1054	1600	874	149	
RR (95% CI)	1.00 (reference)	0.92 (0.84, 1.02)	0.91 (0.83, 0.99)	0.87 (0.78, 0.97)	0.83 (0.68, 1.02)	

[1] Model was adjusted for the lifestyle, clinical, and dietary factors defined in Table 2 but not for the specific stratified variables.
[2] Interaction was tested by using Wald's chi-square test.

association was found between total refined-grain intake and incidence of elevated BP (9), which was consistent with our findings. Refined grains are relatively low in the beneficial nutrients because of the removal of bran and germ during the refining process. This loss of nutrient contents may explain the lack of association with the risk of hypertension.

Several potential limitations of this study deserve comment. First, dietary intake was assessed from a single measurement of SFFQ, which is subject to random error that would tend to underestimate the true association. Second, hypertension was defined according to self-reported information. Yet the validity of self-reported hypertension in health professionals was high in previous studies (40, 41). In a random sample of the WHS cohort, self-reported incident hypertension was confirmed in 48 (96%) of 50 women, and the absence of hypertension was confirmed in 45 (90%) of 50 women through the use of telephone interviews. Moreover, we performed sensitivity analyses using varied definitions of hypertension (self-reported elevated BP only, self-reported physician diagnosis or antihypertensive treatment only, or multiple indications), and the RRs were similar. Third, although the associations persisted with multivariate adjustment, in stratified analyses, and in various supplemental analyses, residual confounding cannot be completely ruled out in this observational study. Finally, our study results apply to middle-aged and older non-Hispanic white women who were generally healthy and willing to participate in a clinical trial. Studies in other populations are needed to confirm our findings.

The 2005 Dietary Guidelines from the US Department of Agriculture (USDA) recommend an intake of ≥3 whole-grain servings/d and consumption of at least one-half of the grain as whole grains (1). In our study, we found that a lower risk of hypertension began with whole-grain consumption of 1–2 and 2–4 servings/d or 43–58% of total grains as whole grains, which was consistent with the recommendations from the USDA. In addition, whole-grain consumption of >4 servings/d or consumption of ≥58% of total grains as whole grains, or both, was associated with even greater reductions in the risk of hypertension. These data offer additional support to the USDA recommendations for increasing whole-grain consumption for the prevention of hypertension. Because hypertension remains a highly prevalent disease affecting up to 50 million people in the United States (42), even a modest reduction in hypertension risk on an individual level will substantially lower the population-wide disease burden. The food industry has accelerated a change from refined-grain products to whole-grain products; nevertheless, a significant increase in whole-grain consumption is still necessary for the US diet to meet the current USDA recommendations (1).

In conclusion, our study found a modest but significant inverse association between whole-grain intake and the risk of hypertension in middle-aged and older women. In contrast, refined-grain intake was not related to the risk of hypertension. These findings support the possible benefits of increasing the amount and proportion of whole grains in the daily diet for the primary prevention of hypertension and its multiple cardiovascular complications.

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