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Whole Grain Consumption and Risk of Ischemic Stroke: Results from Two Prospective Cohort Studies

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Abstract

Background and Purpose—Higher intake of whole grains may exert cardiometabolic benefits, although findings regarding stroke risk are inconclusive. The potentially differential effects of individual whole grain foods on ischemic stroke have not been examined.

Methods—We analyzed whole grain consumption in relation to ischemic stroke among 71,750 women from the Nurses' Health Study and 42,823 men from the Health Professionals Follow-up Study who were free of cardiovascular disease, diabetes, and cancer at baseline (1984 and 1986, respectively) through 2010 using a Cox proportional hazards model. Validated semi-quantitative food frequency questionnaires were used to assess consumption of whole grain intake, including whole grain cold breakfast cereal, dark bread, oatmeal, brown rice, popcorn, bran, and germ. Self-reported incident cases of ischemic stroke were confirmed through medical record review.

Results—During 2,820,128 person-years of follow-up in the two cohorts, 2,458 cases of ischemic stroke were identified and confirmed. Intake of total whole grains was not associated with risk of ischemic stroke after adjustment for covariates: the pooled hazard ratio (HR) (95% confidence interval [CI]) comparing extreme intake levels was 1.04 (0.91–1.19). However, intake of whole grain cold breakfast cereal and total bran was inversely associated with ischemic stroke after multivariate adjustment: the pooled HRs (95% CIs) were 0.88 (0.80–0.96; P_{trend} = 0.008) and

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DISCLOSURES

None.

0.89 (0.79–1.00; P_{trend} = 0.004), respectively. Other whole grain foods were not associated with a lower risk of ischemic stroke.

Conclusions—Although overall consumption of whole grains was not associated with lower risk of ischemic stroke, greater consumption of whole grain cold breakfast cereal and bran was significantly associated with a lower risk of ischemic stroke. More studies are needed to replicate these associations between individual whole grain foods and risk of ischemic stroke, among other populations.

Keywords

whole grain; individual whole grain foods; ischemic stroke; prospective cohort study; meta-analysis; stroke; cohort studies

Subject terms

Diet and Nutrition; Ischemic Stroke

INTRODUCTION

A high intake of whole grains has been widely recommended in numerous dietary guidelines around the world for improving human health[1, 2]. Previous prospective studies have provided consistent evidence suggesting that higher intake of whole grains is associated with a lower risk of cardiometabolic conditions[3], including type 2 diabetes[4] and coronary heart disease (CHD)[5]. In contrast, epidemiological findings on whole grains and risk of stroke are inconclusive[5–7]. A recent meta-analysis reported a non-significant inverse association with stroke risk when comparing the highest versus lowest intake levels of whole grains[5].

Emerging data indicate that individual whole grain foods may potentially have heterogeneous effects because of the different compositions of cereal fiber, starch, micronutrients, and other phytochemicals[8]. Additionally, glycemic index values may also differ among individual whole grain foods[9]. One study conducted in a Scandinavian cohort reported that higher intake of breakfast cereal was associated with a lower risk of CHD, whereas whole grain bread was not[10]. Another prospective study conducted in Denmark showed that oatmeal intake was significantly associated with lower risk of myocardial infarction in men, whereas no significant association was found for whole grain bread intake[11]. In contrast, the potentially differential effects of individual whole grain foods/ingredients on ischemic stroke have not been examined.

To fill this knowledge gap, in the current analysis we aimed to examine whether individual whole grain foods/ingredients are differentially associated with risk of ischemic stroke in men and women participating in the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS).

METHODS

Data sharing is fully appreciated and supported by NHS and HPFS investigators. Individuals who are interested in data, analytic methods, or study materials can look at study websites

www.nurseshealthstudy.org and content.sph.harvard.edu for information on how to request such access.

Study Populations

The NHS was a prospective cohort study initiated in 1976, and 121,701 female registered nurses, aged 30–55 years, were enrolled from 11 large U.S. states[12]. The HPFS was established in 1986 and was consisted of 51,529 male health professionals from 50 states who were aged 40–75 years[13].

For this investigation, we excluded participants who reported a diagnosis of cancer, cardiovascular disease (CVD), and diabetes at baseline (1984 for NHS, 1986 for HPFS); participants who had incomplete information of whole grain consumption at baseline; or those who reported implausible total energy intake levels (<500 or >3500 kcal/day for NHS, and <800 or >4200 kcal/day for HPFS). After exclusion, a total of 71,750 women from NHS and 42,823 men from HPFS were eligible in the current analysis.

The study protocol has been approved by the Institutional Review Board of Brigham and Women's Hospital and Human Subjects Committee Review Board of Harvard T.H. Chan School of Public Health, Boston, Massachusetts, U.S. The completion of the self-administered questionnaire was considered to imply informed consent of the participants.

Assessment of Diet and Covariates

Semi-quantitative food frequency questionnaires (sFFQs) were used to collect usual intake of whole grains and other dietary information since baseline and every four years thereafter. The description, validity, and reproducibility of the sFFQs have been described in detail elsewhere[14, 15]. Briefly, we asked the participants how often, on average, they consumed each food of a prespecified portion size during the previous year with nine response options from never or less than once per month to 6+/day. The type and brand of breakfast cereal were also assessed in the sFFQs. Starting in 2002, we further inquired the intake of regular popcorn and light/fat-free popcorn separately in the sFFQ.

Total whole grain consumption (gram/day) was derived from intake of dark bread, whole grain cold breakfast cereal, brown rice, popcorn, cooked oatmeal, wheat germ, bran, and other grains (e.g., bulgur, kasha, couscous) according to the dry weight of whole grain ingredients in each food. Total bran and total germ intake (gram/day) were the sum of bran and germ intake directly from whole grain foods and those added during industrial processing or during cooking by participants. Individual whole grain foods (serving/day), including dark bread, whole grain cold breakfast cereal, brown rice, popcorn, oatmeal, were estimated by multiplying the reported intake frequency of each food by the pre-specified serving size.

In both cohorts, a multitude of demographic, lifestyle characteristics, medical history, disease diagnosis and other factors were assessed using questionnaires (Supplemental Methods). We applied various strategies to alleviate the impact of random and systematic measurement errors of diet assessments on associations of interest (Supplemental Methods).

Ascertainment of Ischemic Stroke

Self-reported incident cases of stroke on follow-up questionnaires were confirmed through medical record review. Study physicians blinded to the exposure status reviewed medical records and confirmed or refuted self-reported stroke cases. Ischemic strokes were confirmed according to the criteria of National Survey of Stroke which require evidence of a constellation of neurological deficits of sudden or rapid onset lasting for greater than 24 hours or until death due to thrombotic or embolic occlusion of a cerebral artery with imaging data from computerized tomography or magnetic resonance imaging[16].

Nonfatal ischemic strokes, for which the confirmatory information was obtained by telephone interview or letter correspondence only and the medical records were inadequate or unavailable, were considered as probable. Fatal events were identified by reports from next of kin or postal authorities, or by systematic searching the National Death Index (NDI). Fatal ischemic stroke was confirmed by reviewing death certificates, hospital records, or autopsy records. Our analysis included both confirmed and probable cases of nonfatal and fatal ischemic stroke. The exclusion of probable ischemic strokes did not materially alter the results.

Statistical Analysis

For each participant, we calculated person-years of follow-up from the return date of the baseline dietary questionnaire to the date of first diagnosis of ischemic stroke, death, or the end of follow-up (2010), whichever came first. Time-dependent Cox proportional hazards regressions, including age in years as the time scale and stratified by calendar time in 2-year intervals, were used to investigate the associations between consumption of total whole grain, total bran, total germ, and individual whole grain foods and risk of ischemic stroke. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated comparing the risk among participants in higher intake levels with that in the lowest intake levels. In multivariable-adjusted models, we adjusted for various potential confounding factors, including age, ethnicity, body mass index (BMI), smoking status, alcohol intake, physical activity, multivitamin use, family history of myocardial infarction (MI), cancer, or diabetes, hypertension and high cholesterol at baseline, total energy intake, and the modified alternative healthy eating index (aHEI) score. For women, we also adjusted for menopausal status and postmenopausal hormone use. We mutually adjusted for total bran and total germ when evaluating their associations with ischemic stroke risk. Tests for trend were conducted by modeling the median value of each category as a continuous variable in the regression model. The proportional hazards assumptions were tested using likelihood ratio tests comparing models with and without interaction terms between consumption of whole grains and follow-up duration, and we observed no violation of the assumptions ($P > 0.05$ for all tests). All analyses were conducted in each cohort separately to better control for confounding, and results were then pooled to obtain overall estimates using an inverse variance-weighted fixed-effects meta-analysis. In our secondary analysis, we evaluated regular popcorn and light/fat-free popcorn separately to investigate whether they are equally associated with ischemic stroke risk using the last eight years of follow-up data as this information was not available until 2002 in the sFFQs.

All statistical analyses were conducted by SAS statistical package, version 9.4 (SAS Institute Inc.). All *P* values presented were two-sided, and statistical significance was defined as $p<0.05$.

RESULTS

The participants' baseline characteristics by quintiles of total whole grain intake are shown in Supplemental Table I. During 26 years (1,838,846 person-years) of follow-up in NHS and 24 years (981,282 person-years) of follow-up in HPFS, 2,458 cases of ischemic stroke (1,550 in NHS and 908 in HPFS) were identified and confirmed. Higher intake of total whole grains was associated with a lower risk of ischemic stroke in age-adjusted models (Supplemental Table II), although further adjustment for demographic, lifestyle factors, as well as modified aHEI score attenuated the association to the null (Table 1).

Table 2 and Supplemental Table III show associations between five main individual whole grain foods and risk of ischemic stroke. Intake of whole grain cold breakfast cereal was inversely associated with ischemic stroke risk after multivariate adjustments: the pooled HR (95% CI) was 0.88 (0.80–0.96, $P_{trend} = 0.008$) comparing extreme intake levels. In contrast, popcorn consumption was associated with a higher risk of developing ischemic stroke: comparing >1 serving/week with <1 serving/month, there was a 15% (HR: 1.15, 95% CI: 1.03–1.28, $P_{trend} = 0.01$) higher risk of ischemic stroke (Table 2). In addition, when we further mutually adjusted for individual whole grain foods, the associations largely persisted with wider confidence intervals, probably because of the collinearity between individual whole grain foods (data not shown). Other whole grain foods were not associated with ischemic stroke risk.

We subsequently evaluated regular popcorn and light/fat-free popcorn separately, and observed a stronger association for regular popcorn intake, but not for light popcorn intake (Supplemental Table IV). After multivariate adjustment for covariates, the pooled HRs (95% CIs) were 1.36 (1.03–1.80; $P_{trend} = 0.01$) for intake of regular popcorn and 1.11 (0.85–1.45; $P_{trend} = 0.40$) for intake of light/fat-free popcorn, respectively. After further adjustment for key components of western diet pattern, including butter, high fat dairy, refined grain, *trans* fat, and saturated fat, the pooled HR (95% CI) for regular popcorn intake changed little: the pooled HR (95% CI) was 1.34 (1.01–1.77; $P_{trend} = 0.02$).

We further estimated the associations between intake of total bran and total germ, two key ingredients of whole grains, and risk of ischemic stroke (Table 3 and Supplemental Table V). Total bran consumption was significantly associated with a lower risk of ischemic stroke. The pooled multivariable-adjusted HR (95% CI) comparing extreme tertiles of total bran intake was 0.89 (0.79–1.00; $P_{trend} = 0.004$) (Table 3). We did not find any associations between total germ intake and risk of ischemic stroke.

DISCUSSION

In these two well-characterized large ongoing prospective cohort studies of U.S. male health professionals and female nurses, we observed that greater consumption of whole grain cold breakfast cereal and total bran were significantly associated with a lower risk of ischemic

stroke, whereas a higher intake of regular popcorn was linked to an elevated risk of developing ischemic stroke. We did not find an association for the consumption of total whole grains in relation to the risk of ischemic stroke after adjustment for covariates.

Our findings are largely concordant with evidence from meta-analyses that overall suggested a null association between whole grain intake and stroke risk[5, 17]. For example, a recent meta-analysis summarized data from three cohort studies, and the results showed that whole grain intake was non-significantly associated with stroke risk: the pooled relative risk (95% CI) comparing high versus low whole grain intake levels was 0.86 (0.60–1.20; P=0.06)[5]. Of note, in an early analysis in the NHS (1984–1996), an inverse association was observed between whole grain intake and ischemic stroke, even after further adjustment for established CVD risk factors[18]. The reasons for these inconsistent findings between the current and previous analyses are not entirely clear, although changes of individual whole grain foods intake might play a role. For instance, in the NHS, cold breakfast cereal made up 33%–40% of total whole grain between 1984–1994, whereas less than 28% of total whole grain was from cold breakfast cereal between 1998–2010. Likewise, brown rice made up 11%–13% of total whole grain between 1984–1994, whereas only 7% or so of total whole grain was from brown rice between 1998–2010 (Supplemental Figure I). Indeed, our current analysis illustrated the possibility that individual whole grain foods may have different associations with the risk of developing ischemic stroke.

Our rationale for examination of individual whole grain foods was based on the differences among whole grain foods regarding their nutritional profiles and glycemic properties[8, 9, 19]. For example, whole grain rye contains as much as 20% dietary fiber on a dry matter basis, whereas whole grain oats contain only 10%[20]. The content of magnesium, an essential mineral in our diet, is the highest in oat bran (>300mg/100g), but much lower in brown rice (39mg/100g)[21]. In addition, the glycemic index (GI) of individual whole grain foods can also be quite different. For instance, the average GI is 42 for whole grain cold breakfast cereals, 55 for oatmeal and brown rice, and 72 for popcorn[22]. These ingredients or properties are known to be able to modulate stroke risk in previous studies[19, 23].

Whole grain foods are known to benefit cardiometabolic health by lowering blood pressure, participating in antioxidant defense, and improving lipid levels, glucose and insulin metabolism[24]. These mechanisms may at least partially explain the beneficial associations for bran, which is the primary component of whole grains that contains dietary fiber, folate, vitamins, minerals, phytochemicals, and other bioactive components (such as lignans and ferulic acid)[25]. However, the inverse association observed for whole grain cold breakfast cereal, which can consist various types of grains, was unlikely primarily explained by these mechanisms. Breakfast cereals are a significant source of fortified folic acid in the U.S. diet and its consumption significantly contributed to higher circulating levels of folate and lower levels of homocysteine in the U.S. populations[26]. Clinical trials have demonstrated modest, beneficial effects of homocysteine-lowering therapy through folic acid and vitamin B supplementation in the primary prevention of stroke[27]. In addition, whole grain cold breakfast cereals are typically consumed in the morning. Skipping breakfast may lead to the development of dyslipidemia and insulin resistance[28] and was linked to the risk of developing multiple cardiometabolic conditions[29]. Randomized cross-over trials showed that

whole grains, especially whole grain flakes, when consumed in the morning resulted in increased satiety and improved postprandial glucose response[30].

An interesting finding of our study is that regular popcorn intake was associated with an increased risk of developing ischemic stroke after further adjustment for key components of western dietary pattern. This positive association was primarily driven by the intake of regular popcorn, but not for light/fat-free popcorn intake, suggesting that it is other ingredients rather than corn grains themselves that increase ischemic stroke risk. Although such an observation may simply reflect an overall unhealthy diet and lifestyle, ingredients added to regular popcorn during food processing, such as *trans* fat, butter, and sodium could also potentially explain at least partially this positive association.[31, 32]. Although use of *trans* fat has been largely phased out in the U.S. food supply[33], the *trans* fat content of popcorn has remained substantial and stable over time, in comparison with other foods that formerly contained significant amounts of *trans* fat[32]. The harmful effects of butter and sodium on cardiometabolic health and blood pressure have been well-established[34, 35]. Moreover, microwave popcorn bags contain anthropogenic chemicals called perfluoroalkyl substances (PFASs)[36], which are endocrine disruptors[37] and may contribute to the etiology of cardiometabolic conditions[38]. Overall, the findings regarding popcorn imply that unhealthy ingredients added or transferred to whole grain foods may likely offset the health benefits of whole grain foods.

There are several limitations of the current study. First, measurement errors in whole grain intake and other dietary factors are inevitable. However, the sFFQs used in our cohorts have been validated against diet records with reasonable reproducibility and validity[14, 15]. Moreover, we repeatedly assessed diet and various confounders, and applied cumulative averages of diet to minimize the impact of measurement errors. With the prospective study design, the measurement errors are more likely to be random in our study and therefore the true associations are more likely to be attenuated toward the null. Second, the participants included in our study were predominantly middle-aged and older health professionals and nurses primarily with European ancestry, limiting the generalizability of our findings to populations of other demographic or ethnic groups. However, the homogeneity of educational and socioeconomic status helps to minimize potential residual confounding. Third, in this observational study, we cannot exclude the possibility of unmeasured or residual confounding, especially for the positive association of regular popcorn intake. In addition, the role of chance finding cannot be excluded, either, although the consistent findings between the two cohorts made such a possibility small.

SUMMARY

Our results indicate that individual whole grain foods and ingredients may likely have different effects on ischemic stroke incidence. Greater consumption of whole grain cold breakfast cereal and bran was significantly associated with a lower risk of ischemic stroke, whereas a higher intake of regular popcorn was linked to an elevated risk of developing ischemic stroke among U.S. men and women. More studies are needed to replicate these associations between individual whole grain foods and risk of ischemic stroke, among other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Hazard Ratio (95% CI) of Ischemic Stroke according to Quintiles of Whole Grain Intake among participants in NHS and HPFS.

	Quintiles of Whole Grain Intake					P_{trend}
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	
NHS						
Median	4.43	10.10	15.15	21.46	33.23	
No. of cases/ Person-years	328/365029	262/367305	310/368956	282/368999	368/368557	
Multivariable model *	1.00	0.83(0.70,0.98)	0.98(0.84,1.15)	0.86(0.72,1.01)	1.03(0.88,1.21)	0.35
HPFS						
Median	5.92	14.47	22.35	31.50	47.90	
No. of cases/ Person-years	188/194616	223/196243	167/196459	147/197139	183/196825	
Multivariable model *	1.00	1.27(1.04,1.55)	0.95(0.77,1.18)	0.83(0.66,1.03)	1.06(0.85,1.32)	0.37
Pooled †						
Multivariable model *	1.00	0.99(0.87, 1.12)	0.97(0.86, 1.10)	0.84(0.74, 0.97)	1.04(0.91, 1.19)	0.97

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

* Multivariable model was adjusted for age (years), BMI (<18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, or ≥35.0 kg/m^2), smoking status (never, past, current [1–14,15–24, or ≥25 cigarettes/day]), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day for women and 0, 0.1–4.9, 5.0–29.9 or ≥30.0 g/day for men), physical activity (quintiles), family history of diabetes, cancer and heart disease(yes or no), multivitamin use(yes or no), hypertension, high cholesterol at baseline (yes or no), total energy intake (kcal/day) and modified alternative health eating index score, which did not include whole grains, as a summary measure of diet quality. For women, menopausal status and postmenopausal hormone use were further adjusted for.

† Pooled hazard ratios were calculated using a fixed-effects meta-analysis.

Table 2

Hazard Ratio (95% CI) of Ischemic Stroke by Individual Whole Grain Foods Intake among participants in NHS and HPFS.

	HRs for categorical intake variables			HR for continuous intake variables	P_{trend}
	< 1 serving/month	1 serving/month-1serving/week	> 1 serving/week	1 serving/day	
Whole grain cold breakfast cereal					
NHS					
No. of cases/ Person-years	386/423700	224/263805	940/1151403		
Multivariable model *	1.00	0.94(0.80,1.11)	0.90(0.79,1.01)	0.95(0.82,1.10)	0.09
HPFS					
No. of cases/ Person-years	275/262406	122/134968	511/583908		
Multivariable model *	1.00	0.92(0.74,1.14)	0.85(0.73,0.99)	0.86(0.72,1.04)	0.04
Pooled †					
Multivariable model *	1.00	0.93(0.82, 1.06)	0.88(0.80, 0.96)	0.92(0.82,1.03)	0.008
Oatmeal					
NHS					
No. of cases/ Person-years	543/674537	603/798228	404/366143		
Multivariable model *	1.00	1.10(0.97,1.24)	1.10(0.96,1.26)	1.05(0.80,1.37)	0.30
HPFS					
No. of cases/ Person-years	424/458739	246/274888	238/247655		
Multivariable model *	1.00	0.95(0.81,1.11)	0.90(0.76,1.06)	0.93(0.67,1.28)	0.22
Pooled †					
Multivariable model *	1.00	1.04(0.95, 1.15)	1.01(0.91, 1.13)	1.00(0.81,1.23)	0.96
Dark Bread					
NHS					
No. of cases/ Person-years	103/130512	176/236539	1271/1471857		
Multivariable model *	1.00	1.07(0.84,1.37)	1.07(0.87,1.32)	1.01(0.97,1.05)	0.65
HPFS					
No. of cases/ Person-years	130/124924	122/153822	656/702536		
Multivariable model *	1.00	0.83(0.65,1.07)	0.90(0.74,1.10)	0.99(0.90,1.09)	0.81

	HRs for categorical intake variables			HR for continuous intake variables	P_{trend}
	< 1 serving/month	1 serving/month-1serving/week	> 1 serving/week	1 serving/day	
Pooled†					
Multivariable model*	1.00	0.95(0.79, 1.13)	0.98(0.85, 1.13)	1.01(0.97,1.05)	0.86
Brown Rice					
NHS					
No. of cases/ Person-years	1029/1248570	399/474292	122/116045		
Multivariable model*	1.00	1.02(0.91,1.15)	1.18(0.96,1.44)	1.00(0.93,1.06)	0.12
HPFS					
No. of cases/ Person-years	438/444974	352/387185	118/149123		
Multivariable model*	1.00	1.08(0.94,1.25)	1.13(0.91,1.39)	1.32(0.75,2.31)	0.23
Pooled†					
Multivariable model*	1.00	1.05(0.96, 1.15)	1.15(0.99, 1.33)	1.00(0.93,1.07)	0.05
Popcorn					
NHS					
No. of cases/ Person-years	473/478234	719/963695	358/396979		
Multivariable model*	1.00	1.16(1.03,1.31)	1.23(1.07,1.42)	1.00(0.98,1.03)	0.01
HPFS					
No. of cases/ Person-years	318/279858	316/376635	274/324789		
Multivariable model*	1.00	0.92(0.78,1.08)	1.04(0.88,1.23)	1.01(0.80,1.28)	0.37
Pooled†					
Multivariable model*	1.00	1.07(0.97, 1.18)	1.15(1.03, 1.28)	1.00(0.98,1.03)	0.01

Abbreviations: CI, confidence interval; HR, Hazard Ratio; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

*Multivariable model was adjusted for the same covariates listed in the footnote of table 1.

†Pooled hazard ratios were calculated using a fixed-effects meta-analysis.

Table 3

Hazard Ratio (95% CI) of Ischemic Stroke by Individual Whole Grain Ingredients Intake among participants in NHS and HPFS.

	Individual Whole Grain Ingredients			P_{trend}
	T1	T2	T3	
Total Bran‡				
NHS				
Median	1.10	3.64	8.50	
No. of cases/ Person-years	489/610232	516/615654	545/613022	
Multivariable model *	1.00	1.07(0.93,1.22)	1.00(0.86,1.16)	0.62
HPFS				
Median	1.30	4.85	11.91	
No. of cases/ Person-years	334/325482	298/328270	276/327530	
Multivariable model *	1.00	0.89(0.74,1.06)	0.73(0.60,0.88)	<0.001
Pooled †				
Multivariable model *	1.00	1.00(0.89, 1.11)	0.89(0.79, 1.00)	0.004
Total Germ‡				
NHS				
Median	0.26	0.63	1.26	
No. of cases/Person-years	549/603767	480/611376	521/623764	
Multivariable model *	1.00	0.94(0.82,1.08)	1.02(0.88,1.18)	0.49
HPFS				
Median	0.34	0.90	1.80	
No. of cases/Person-years	355/333085	272/321337	281/326860	
Multivariable model *	1.00	0.97(0.81,1.15)	1.12(0.92,1.35)	0.20
Pooled †				
Multivariable model *	1.00	0.95(0.85, 1.06)	1.06(0.94, 1.18)	0.16

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

* Multivariable model was adjusted for the same covariates listed in the footnote of table 1.

† Pooled hazard ratios were calculated using a fixed-effects meta-analysis.

‡ Total bran and total germ were mutually adjusted in all models.