Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women's Health Study[1–4]

David R Jacobs Jr, Lene Frost Andersen, and Rune Blomhoff

ABSTRACT

Background: It has recently been shown that oxidative stress, infection, and inflammation are predominant pathophysiologic factors for several major diseases.

Objective: We investigated the association of whole-grain intake with death attributed to noncardiovascular, noncancer inflammatory diseases.

Design: Postmenopausal women (n = 41 836) aged 55–69 y at baseline in 1986 were followed for 17 y. After exclusions for cardiovascular disease, cancer, diabetes, colitis, and liver cirrhosis at baseline, 27 312 participants remained, of whom 5552 died during the 17 y. A proportional hazards regression model was adjusted for age, smoking, adiposity, education, physical activity, and other dietary factors.

Results: Inflammation-related death was inversely associated with whole-grain intake. Compared with the hazard ratios in women who rarely or never ate whole-grain foods, the hazard ratio was 0.69 (95% CI: 0.57, 0.83) for those who consumed 4–7 servings/wk, 0.79 (0.66, 0.95) for 7.5–10.5 servings/wk, 0.64 (0.53, 0.79) for 11–18.5 servings/wk, and 0.66 (0.54, 0.81) for ≥19 servings/wk (P for trend = 0.01). Previously reported inverse associations of whole-grain intake with total and coronary heart disease mortality persisted after 17 y of follow-up.

Conclusions: The reduction in inflammatory mortality associated with habitual whole-grain intake was larger than that previously reported for coronary heart disease and diabetes. Because a variety of phytochemicals are found in whole grains that may directly or indirectly inhibit oxidative stress, and because oxidative stress is an inevitable consequence of inflammation, we suggest that oxidative stress reduction by constituents of whole grain is a likely mechanism for the protective effect. *Am J Clin Nutr* 2007;85:1606–14.

KEY WORDS Whole-grain foods, carbohydrate, fiber, inflammation

INTRODUCTION

Habitual whole-grain food consumption has consistently been associated with a reduced risk of both coronary heart disease (CHD) and type 2 diabetes (1), and several studies also suggest that whole-grain intake reduces the risk of other diseases (2, 3). Refined grains, in contrast, do not appear to offer protection and may instead increase the risk of chronic diseases (4). The *Dietary Guidelines for Americans* therefore recommends an intake of 3 servings of whole-grain products/d (5). In the United States, the mean intake of whole grains is <1 serving/d, and that of refined grains is 5 servings/d (6).

It was previously reported that whole-grain intake in postmenopausal women in Iowa is associated with a reduction in total mortality of ≈15%, with reductions clearest in mortality attributed to cardiovascular diseases and suggestive in noncardiovascular, noncancer mortality, including that due to nonmalignant respiratory diseases (7) and diabetes (8). There has been little investigation of what other diseases contribute to the reduction in mortality reduction associated with whole-grain consumption.

Likely candidates for such other diseases are inflammatory diseases. Although inflammation of short duration may help restore disrupted tissue structure and function, prolonged inflammation can contribute to pathogenesis. Inflammation has recently been suggested to be a common underlying mechanism of a variety of different diseases, including diseases of infectious origin, diabetes, and rheumatoid arthritis (9, 10). Numerous examples support this suggestion. Other pathologic mechanisms are clearly active in these diseases, but inflammation seems to contribute significantly to the severity of these diseases. Furthermore, inflammation promotes the production of reactive oxygen (ROS) and reactive nitrogen species (RNS) to ward off foreign invaders, which ultimately leads to oxidative stress (11, 12). Thus, chronic or prolonged inflammatory reactions inevitably lead to oxidative stress, and antioxidant therapy (ROS or RNS decomposition catalysts or selective antioxidant enzyme mimics) has been shown to prevent in vivo tissue injury during inflammation (13–15). Several epidemiologic studies have identified whole grains as part of a food pattern that is inversely related

[1] From the Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway (DRJ, LFA, and RB); the Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN (DRJ).

[2] The contents of this manuscript are solely the responsibilities of the authors and do not necessarily represent the official view of the funding bodies.

[3] RB was supported by grants from the Norwegian Research Council, The Johan Throne Holst Nutrition Research Foundation, and The Norwegian Cancer Society. DRJ was supported by the Norwegian Research Council and by a grant (RO1 CA39742) from the National Cancer Institute.

[4] Address reprint requests to DR Jacobs Jr, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55454-1015. E-mail: jacobs@epi.umn.edu.

Received October 25, 2006.

Accepted for publication January 12, 2007.

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008

to inflammatory markers, whereas refined grains are positively associated with these markers (16–19). One short-term clinical study of whole-grain intake showed reductions in oxidative stress and related inflammatory factors (20).

Thus, it is reasonable to hypothesize that intake of whole grains may not only reduce the risk of cardiovascular disease and cancer, which clearly are related to inflammation (9, 21, 22), but may also reduce the risk of other diseases for which inflammation or oxidative stress is a predominant pathophysiologic factor. We have studied this hypothesis in postmenopausal women in Iowa aged 55–69 y after they were recruited in 1986. For this purpose, we formed a composite of causes of death selected a priori for which inflammation has been documented as a significant pathologic factor. Because whole-grain intake may reduce plasma biomarkers of inflammation, we investigated whether intake of whole or refined grains was associated with death attributed to this novel categorization of inflammatory diseases.

SUBJECTS AND METHODS

The Iowa Women's Health Study (IWHS) cohort comprises 41 836 women aged 55–69 y recruited via a baseline questionnaire mailed in 1986 and followed through 31 December 2001. A previous report explained how self-reported baseline risk factors were assessed and defined (23). Baseline histories of physician-diagnosed cancer (other than skin cancer), heart disease, or angina were obtained. In the present study we excluded women who were not postmenopausal ($n = 569$) and those with self-reported baseline heart disease ($n = 3459$), nonskin cancer ($n = 3497$), diabetes ($n = 2386$), chronic colitis ($n = 2357$), or liver cirrhosis ($n = 313$) and those who reported <600 or >5000 kcal/d or left >30 items on the diet questionnaire blank ($n = 3096$). Data were missing for waist-hip ratio for 134 women, estrogen use for 147 women, physical activity status for 579 women, and smoking status for 510 women. Some exclusions overlapped; the models used included 27 312 women. The study was approved by the Institutional Review Board of the University of Minnesota.

Dietary intake at baseline was assessed by using a 127-item food-frequency questionnaire (24). As previously described (25), servings per week of several whole-grain foods were computed. Whole-grain foods included the following verbatim items: dark bread, cold breakfast cereal, brown rice, popcorn, wheat germ, bran, cooked oatmeal, and other grains (eg, bulgar, kasha, and couscous). The participants were asked to name the single breakfast cereal usually eaten, which was then evaluated for whole-grain and bran contents. Breakfast cereals were considered to be whole grain if the product contained ≥25% whole grain or bran by weight. Bran cereals were included in the whole-grain category because findings were similar for bran cereals and nonbran, whole-grain cereals. The reliability and validity of the questionnaire were evaluated in 2 studies (26, 27). Correlations with 28 d of food records were 0.75 for cold breakfast cereals and 0.66 for dark bread (28).

Deaths were identified by annual linkage of cohort identifiers to Iowa state-wide death records through 31 December 2003. Deaths for subjects who had emigrated from Iowa were identified through the National Death Index. Cause of death was that assigned as the single underlying cause by State Health Department. We considered noncardiovascular, noncancer inflammatory diseases to be those that had an inflammatory, oxidative stress, or infectious component as the predominant pathophysiology. However, there is no simple rule for categorizing thousands of International Classification of Disease (ICD) codes. Therefore, we examined each ICD code that occurred in our sample, and those that we classified as having a predominantly inflammatory cause are listed below according to the major ICD grouping (ICD9 codes begin with a number; ICD10 codes begin with a letter):

1) infectious diseases: **11.6, 28.9, 31.0, 38.0, 38.1, 38.4, 38.9, 42.9, 46.1, 54.3, 54.7, 70.3, 70.5, 75.0, 78.5, 117.5, 117.9,** 135.0, 136.3, **137.0, A04.4, A04.7, A08.4, A31.9,** A40.3, A41.2, A41.4, **A41.9, A49.0, A81.0,** A92.3, B16.9, **B18.2,** B37.8, **B44.1, B49,** B94.2, **B94.8,** and B99 ($n = 59$);

2) endocrine, nutritional, and metabolic diseases: 250.0, 250.1, 250.3, 250.6, 277.3, 279.3, E10.2, E10.5, E10.7, E10.9, E11.2, E11.5, E11.9, E14.1, E14.2, E14.4, E14.5, E14.6, E14.7, E14.9, E85.3, E85.4, and E85.9 ($n = 60$);

3) nervous system disorders: **322.9, 323.9**, 331.0, 332.0, 335.2, 340.0, 341.9, 348.3, 355.9, 357.0, **G03.9,** G04.9, G12.2, G20, G30.1, G30.9, G31.9, and G35 ($n = 241$);

4) respiratory system diseases: 466.0, **473.9, 480.9, 481.0, 482.0, 482.1, 482.3, 482.4, 482.8, 485.0, 486.0, 487.1**, 491.2, 491.8, 491.9, 492.0, 493.1, 493.9, 494.0, 496.0, 507.0, 515.0, **J11.0, J11.1,** J12.9, J15.1, **J15.2,** J15.4, **J15.9, J18.0, J18.1, J18.9**, J20.9, **J22**, J40, J42, J43.9, J44.0, J44.1, J44.8, J44.9, J45.9, J46, J47, J69.0, J80, J84.1, and J98.4 ($n = 569$; 151 pneumonia and 418 respiratory diseases that were not infections);

5) digestive system diseases: 303.0, 530.1, **531.4, 531.5, 531.9**, **540.0**, 541.0, **555.9**, 556.0, 558.0, 562.1, **566.0**, **567.2**, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6, 573.3, 574.1, K25.4, K25.5, K25.9, K50.9, K52.9, **K65.9**, K73.2, K74.6, K75.0, K81.0, K81.9, and K85 ($n = 60$);

6) skin diseases: **682.6**, 707.0, **L02.9,** L08.9, and L40.5 ($n = 4$);

7) musculoskeletal and connective tissue disorders: 710.0, 710.1, 710.4, 714.0, 715.3, 725.0, 729.4, M00.9, M05.1, M06.9, M19.9, M30.0, M30.1, M31.3, M34.1, M34.8, M34.9, M46.2, M47.8, and M86.9 ($n = 42$); and

8) genitourinary diseases: 580.8, 583.8, 585.0, 586.0, **614.4**, N11.9, N12, N180, N189, N19, N258, N321, and N390 ($n = 37$). The boldface ICD codes are separately classified as infectious diseases, regardless of ICD major grouping ($n = 233$); the nonboldface codes are the remaining noncardiovascular, noncancer inflammatory diseases ($n = 839$). Note that we previously defined this mortality variable on the basis of 15 y of follow-up (28); after 2 y of additional follow-up in the present study, we identified several more ICD codes that belong to the inflammatory category. Noncancer, noncardiovascular causes of death that were not included in the inflammatory category included injury, acute organ failure, psychoses, substance abuse, and some metabolic disorders.

Statistical analyses were performed with SAS software (version 8.2; SAS Institute, Inc, Cary, NC). Whole-grain consumption was categorized in approximate quintiles. Cox proportional hazards regression analysis was used to assess the association between whole-grain food consumption and death, presented as estimates of hazard ratios and their 95% CIs. In the models below, the interaction of whole-grain food intake (continuous

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008

TABLE 1
Subject characteristics according to quintile (Q) of whole grain food intake in 27 312 women free of cancer (other than skin), heart disease, diabetes, colitis, and liver cirrhosis at baseline in the Iowa Women's Health Study, 1986

	Whole-grain food intake (servings/wk)					
	Q1 (0–3.5) (n = 5142)	Q2 (4–7) (n = 5345)	Q3 (7.5–10.5) (n = 5757)	Q4 (11–18.5) (n = 5761)	Q5 (≥19) (n = 5307)	P^1
Age (y)	61.1 ± 4.2[2]	61.1 ± 4.2	61 ± 4.1	61.6 ± 4.2	61.6 ± 4.2	< .0001
BMI (kg/m^2)	27.0 ± 5.2	26.9 ± 4.9	26.8 ± 4.8	26.5 ± 4.7	26.5 ± 4.8	< .0001
Waist-hip ratio	0.84 ± 0.09	0.83 ± 0.08	0.83 ± 0.08	0.83 ± 0.08	0.83 ± 0.08	< .0001
Alcohol intake (g/d)	5.2 ± 11.6	4.2 ± 9.2	3.8 ± 8.5	3.4 ± 7.7	3.3 ± 7.7	< .0001
Energy intake (kcal/d)	1613 ± 602	1678 ± 575	1759 ± 558	1883 ± 578	2069 ± 613	< .0001
Whole grain (servings/wk)	1.8 ± 1.1	5.6 ± 1.1	8.8 ± 1.0	14.5 ± 2.5	25.6 ± 7.2	< .0001
Refined grain (servings/wk)	17.1 ± 12.8	15.0 ± 11.3	14.1 ± 10.2	13.5 ± 10.4	13.3 ± 10.8	< .0001
Red meat (servings/wk)	5.9 ± 4.2	5.8 ± 3.8	5.8 ± 3.8	6.0 ± 3.9	6.0 ± 4.1	0.003
Seafood (servings/wk)	1.3 ± 1.5	1.5 ± 1.7	1.7 ± 2.0	1.8 ± 2.2	2.1 ± 2.5	< .0001
Total fruit and vegetable (servings/wk)	35.2 ± 18.4	40.4 ± 19.2	44.0 ± 20.1	47.7 ± 21.5	51.1 ± 24.3	< .0001
User of multivitamin supplement (%)	25.7	30.4	33.9	36.3	37.0	< .0001
Smoking status (%)						
Never smoker	57.2	64.6	69.3	71.2	68.9	< .0001
Past smoker, <15 cigarettes/wk	7.5	9.4	9.3	10.1	10.7	< .0001
Past smoker, ≥15 cigarettes/wk	10.2	9.6	8.9	8.1	9.1	0.03
Current smoker, <15 cigarettes/wk	6.8	4.5	4.1	3.7	4.0	< .0001
Current smoker, ≥15 cigarettes/wk	18.4	12.6	8.4	6.9	7.0	< .0001
Physical activity						
Low (%)	58.7	48.7	45.7	40.5	40.3	< .0001
Moderate (%)	23.5	27.7	29.4	29.2	29.6	< .0001
High (%)	17.8	23.6	24.9	30.3	30.1	< .0001
Education (%)						
Less than high school (%)	21.9	18.4	15.5	13.9	14.9	< .0001
High school (%)	45.2	43.9	42.5	40.5	39.5	< .0001
More than high school (%)	32.9	37.7	42.0	45.6	45.6	< .0001
Estrogen use						
Never used (%)	67.1	63.7	62.1	61.9	58.6	< .0001
Past user (%)	24.2	25.5	26.7	26.4	28.5	< .0001
Current user (%)	8.7	10.8	11.2	11.7	12.9	< .0001
Arthritis at baseline (%)[3]	49.2	48.4	49.7	49.8	50.1	0.43

[1] F statistic with 4, 27 307 df derived from ANOVA with each row variable as the dependent variable and the whole-grain categories as the independent variable.
[2] $\bar{x}$ ± SD (all such values).
[3] The type of arthritis was not asked about.

variable) with time in study was nonsignificant; therefore, the proportionality assumption was deemed acceptable. The minimally adjusted model included only age (y) and energy intake (continuous; kcal) as covariates. The multivariable-adjusted model also included smoking (5 categories: never; current smokers, <15 cigarettes/wk; current smokers, ≥15 cigarettes/wk; past smokers, <15 cigarettes/wk; past smokers, ≥15 cigarettes/wk), intake of alcohol (continuous, as a quadratic function; g/d), body mass index (BMI), waist-hip ratio, education (less than high school, high school, more than high school), physical activity (low, moderate, high), use of estrogen (never used, current use, past use), use of multivitamin supplements (yes, no or don't know), and intakes of coffee (continuous; servings/d), refined grain (continuous; servings/d), red meat (continuous; servings/d), fish and seafood (continuous; servings/d), and total fruit and vegetables (continuous; servings/d). We performed a test for trend by treating whole-grain food intake as a continuous variable. The a priori focus of this work was the composite variable noncardiovascular, noncancer inflammatory disease mortality. The primary contrast being the remaining noncardiovascular, noncancer deaths. In response to the blind reviewers, we explored the association of whole-grain intake with the subcategories of diseases provided above, with 2 separate subgroupings: major ICD categories and infectious versus noninfectious inflammatory conditions.

RESULTS

The mean (±SD) consumption of whole- and refined-grain foods in the IWHS was 11.3 ± 8.9 and 14.5 ± 11.2 servings/d, respectively. As previously described, whole-grain intake (25) was generally associated with a healthier lifestyle, including increased physical activity, reduced smoking, and a choice of other foods generally thought to be healthy (**Table 1**). Women who habitually consumed whole-grain food were generally somewhat thinner than those who rarely consumed whole-grain food. Only a general question was asked about arthritis, an important noncardiovascular, noncancer inflammatory condition.

The American Journal of Clinical Nutrition
Downloaded from www.ajcn.org by on December 8, 2008

TABLE 2
Hazard ratios (and 95% CIs) for total and cause-specific mortality according to quintile (Q) of total intake of whole-grain food in 27 312 women in the Iowa Women's Health Study, 1986–2003

	Whole-grain food intake (servings/wk)					*P* for trend
	Q1 (0–3.5)	Q2 (4–7)	Q3 (7.5–10.5)	Q4 (11–18.5)	Q5 (≥19)	
Total death						
No. of cases	1288	1089	1149	1041	985	—
Person-years	83 923	88 977	96 235	96 790	89 016	—
Minimal adjustment[1]	1	0.78 (0.72, 0.85)	0.73 (0.67, 0.79)	0.63 (0.58, 0.69)	0.64 (0.59, 0.70)	< 0.0001
Multivariate adjustment[2]	1	0.88 (0.81, 0.96)	0.88 (0.81, 0.96)	0.80 (0.73, 0.87)	0.79 (0.72, 0.87)	< 0.0001
CVD death						
No. of cases	432	404	375	376	313	—
Minimal adjustment[1]	1	0.87 (0.76, 0.99)	0.70 (0.61, 0.81)	0.68 (0.59, 0.78)	0.61 (0.53, 0.71)	< 0.0001
Multivariate adjustment[2]	1	0.96 (0.84, 1.10)	0.83 (0.72, 0.96)	0.83 (0.71, 0.96)	0.73 (0.62, 0.86)	0.0001
CHD death						
No. of cases	233	229	209	193	170	—
Minimal adjustment[1]	1	0.91 (0.76, 1.09)	0.73 (0.60, 0.88)	0.64 (0.53, 0.78)	0.61 (0.50, 0.75)	< 0.0001
Multivariate adjustment[2]	1	1.01 (0.84, 1.22)	0.85 (0.70, 1.04)	0.79 (0.64, 0.97)	0.72 (0.57, 0.90)	0.002
Death from stroke						
No. of cases	89	80	81	86	78	—
Minimal adjustment[1]	1	0.83 (0.61, 1.12)	0.73 (0.54, 0.99)	0.74 (0.55, 1.00)	0.73 (0.53, 1.00)	0.11
Multivariate adjustment[2]	1	0.91 (0.67, 1.24)	0.84 (0.61, 1.15)	0.88 (0.64, 1.22)	0.85 (0.60, 1.21)	0.52
Death from intracranial hemorrhagic stroke						
No. of cases	17	23	27	21	25	—
Minimal adjustment[1]	1	1.25 (0.67, 2.34)	1.29 (0.70, 2.36)	0.96 (0.50, 1.83)	1.24 (0.66, 2.34)	0.91
Multivariate adjustment[2]	1	1.28 (0.68, 2.42)	1.33 (0.71, 2.49)	1.01 (0.51, 1.99)	1.28 (0.64, 2.56)	0.93
Death from nonhemorrhagic stroke						
No. of cases	59	45	45	53	49	—
Minimal adjustment[1]	1	0.71 (0.48, 1.04)	0.61 (0.42, 0.90)	0.69 (0.47, 1.00)	0.70 (0.47, 1.03)	0.22
Multivariate adjustment[2]	1	0.79 (0.53, 1.18)	0.74 (0.49, 1.11)	0.87 (0.58, 1.31)	0.88 (0.57, 1.36)	0.94
Cancer death						
No. of cases	480	393	448	387	391	—
Minimal adjustment[1]	1	0.76 (0.67, 0.87)	0.78 (0.69, 0.89)	0.66 (0.58, 0.76)	0.72 (0.63, 0.82)	< 0.0001
Multivariate adjustment[2]	1	0.86 (0.75, 0.99)	0.95 (0.83, 1.09)	0.83 (0.72, 0.96)	0.89 (0.77, 1.04)	0.20
Death attributed to noncardiovascular, noncancer, inflammatory diseases						
No. of cases	291	188	223	183	187	—
Minimal adjustment[1]	1	0.59 (0.49, 0.71)	0.60 (0.51, 0.72)	0.47 (0.39, 0.56)	0.49 (0.41, 0.60)	< 0.0001
Multivariate adjustment[2]	1	0.69 (0.57, 0.83)	0.79 (0.66, 0.95)	0.64 (0.53, 0.79)	0.66 (0.54, 0.81)	0.008
Death attributed to noncardiovascular, noncancer, noninflammatory diseases						
No. of cases	85	105	103	95	94	—
Minimal adjustment[1]	1	1.13 (0.85, 1.51)	0.97 (0.73, 1.29)	0.85 (0.63, 1.14)	0.88 (0.65, 1.19)	0.16
Multivariate adjustment[2]	1	1.25 (0.94, 1.67)	1.12 (0.83, 1.51)	1.02 (0.74, 1.39)	1.02 (0.74, 1.42)	0.64

[1] Adjusted for age and energy intake.
[2] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol^2, ie, linear and quadratic terms of alcohol as a continuous variable), refined grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

Almost 50% of the women responded affirmatively to this question at baseline, with no gradient across whole-grain intake category. Of the 27 312 participants, 5552 had died after 17 y of follow-up; the death of 1071 of these participants was attributed to inflammatory causes.

Noncardiovascular, noncancer inflammatory death showed an inverse association with total whole-grain intake (**Table 2**). Compared with the women who rarely or never ate whole-grain foods, the hazard ratio was 0.69 for those who consumed 4–7 servings of whole grain/wk, 0.79 for 7.5–10.5 servings/wk, 0.64 for 11–18.5 servings/wk, and 0.66 for ≥19 servings/wk. These mortality rates followed corresponding patterns for dark bread, whole-grain breakfast cereal, and other whole-grain foods; the pattern was weakest for whole-grain breakfast cereals (**Table 3, Table 4**, and **Table 5**). As previously reported (7) after a shorter follow-up duration, inverse associations were observed for total and CHD mortality. Exclusion of the first 5 y of death did not substantially alter any of the findings.

The relation of whole-grain intake to subsets of the noncardiovascular, noncancer inflammatory death variable is reported in **Table 6**. Most associations were inverse, although digestive, endocrine, nutritional, and metabolic (including primarily diabetes), musculoskeletal, and genitorenal disorders were each based on small numbers of cases. The strongest and statistically

The American Journal of Clinical Nutrition
Downloaded from www.ajcn.org by on December 8, 2008

TABLE 3
Hazard ratios (and 95% CIs) for death attributed to noncardiovascular, noncancer, inflammatory diseases according to total intake of dark bread in 27 312 women in the Iowa Women's Health Study, 1986–2003

	Dark bread intake (servings/wk)					*P* for trend
	0–0.5	1–3	5.5	7	17.5–42	
No. of cases	315	257	108	185	207	—
Person-years	92 405	129 887	54 348	86 624	91 676	—
Minimal adjustment[1]	1	0.57 (0.48, 0.67)	0.55 (0.44, 0.69)	0.57 (0.48, 0.69)	0.59 (0.49, 0.71)	0.0006
Multivariate adjustment[2]	1	0.70 (0.59, 0.83)	0.72 (0.57, 0.90)	0.76 (0.63, 0.92)	0.75 (0.62, 0.91)	0.13

[1] Adjusted for age and energy intake.
[2] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol^2, ie, linear and quadratic terms of alcohol as a continuous variable), refined grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

most robust associations were for respiratory system disorders, especially noninfectious ones. Mortality attributed to nervous system disorders showed little relation to whole-grain intake.

The association of whole-grain food intake with noncardiovascular, noncancer inflammatory death did not vary by obesity status (normal weight, overweight, obese; *P* interaction = 0.76).

We conducted the same type of analysis for refined-grain intake. Of the several causes of death, noncardiovascular, noncancer inflammatory death was related, but only suggestively after multivariate adjustment, to refined-grain intake (**Table 7**). Compared with the women with intakes in the lowest quintile, the hazard ratios in the adjusted model were 0.98, 0.95, 1.12, and 1.21 (*P* for trend = 0.04) for women with intakes in quintiles 2, 3, 4, and 5, respectively.

DISCUSSION

We prospectively studied the relation of whole-grain food intake with death attributed to oxidative stress, inflammatory, and infectious processes as a predominant pathophysiologic cause. Inflammatory disease as an underlying cause includes most infectious and various chronic degenerative diseases, such

TABLE 4
Hazard ratios (and 95% CIs) for death attributed to noncardiovascular, noncancer, inflammatory diseases according to total intake of whole-grain breakfast cereals in 27 312 women in the Iowa Women's Health Study, 1986–2003

	Whole-grain breakfast cereal intake (servings/wk)				*P* for trend
	0	0.5–1	3	5.5–7	
No. of cases	514	189	169	196	—
Person-years	193 639	91 914	84 326	84 311	—
Minimal adjustment[1]	1	0.77 (0.65, 0.91)	0.70 (0.58, 0.83)	0.78 (0.66, 0.92)	0.004
Multivariate adjustment[2]	1	0.85 (0.72, 1.01)	0.87 (0.73, 1.04)	0.94 (0.79, 1.12)	0.62

[1] Adjusted for age and energy intake.
[2] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol^2, ie, linear and quadratic terms of alcohol as a continuous variable), refined grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

TABLE 5
Hazard ratios (and 95% CIs) for death attributed to noncardiovascular, noncancer, inflammatory diseases according to total intake of other whole-grain foods in 27 312 women in the Iowa Women's Health Study, 1986–2003

	Other whole-grain food intake (servings/wk)[1]					*P* for trend
	0–2.5	3–5.5	6–8	8.5–17.5	18–101.5	
No. of cases	299	198	209	172	194	—
Person-years	85 737	89 173	91 597	94 399	94 033	—
Minimal adjustment[2]	1	0.64 (0.53, 0.76)	0.62 (0.52, 0.74)	0.46 (0.38, 0.55)	0.51 (0.42, 0.61)	< .0001
Multivariate adjustment[3]	1	0.75 (0.62, 0.90)	0.76 (0.64, 0.92)	0.62 (0.50, 0.75)	0.66 (0.54, 0.80)	0.009

[1] Refers to whole-grain foods other than dark breada and breakfast cereals (eg, bulgar, kasha, and couscous).
[2] Adjusted for age and energy intake.
[3] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol^2, ie, linear and quadratic terms of alcohol as a continuous variable), refined grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008

TABLE 6
Hazard ratios for subsets of noncardiovascular, noncancer, inflammatory disease mortality according to quintile (Q) of total intake of whole-grain food in 27 312 women in the Iowa Women's Health Study, 1986–2003[1]

	Whole-grain food intake (servings/wk)					*P* for trend
	Q1 (0–3.5)	Q2 (4–7)	Q3 (7.5–10.5)	Q4 (11–18.5)	Q5 (≥19)	
Cause of death within inflammatory causes—subsets by main categories in the ICD						
1. Respiratory system diseases						
No. of cases	184	102	100	88	95	—
Person-years	83 923	88 977	96 235	96 790	89 016	—
Minimal adjustment[2]	1	0.50 (0.40, 0.64)	0.43 (0.33, 0.54)	0.35 (0.27, 0.45)	0.38 (0.30, 0.49)	< .0001
Multivariate adjustment[3]	1	0.65 (0.51, 0.83)	0.65 (0.50, 0.84)	0.58 (0.44, 0.76)	0.60 (0.46, 0.80)	0.006
1a. Pneumonia						
No. of cases	44	22	23	33	29	—
Minimal adjustment[2]	1	0.46 (0.27, 0.76)	0.41 (0.25, 0.68)	0.55 (0.35, 0.86)	0.51 (0.31, 0.83)	0.11
Multivariate adjustment[3]	1	0.54 (0.32, 0.90)	0.52 (0.31, 0.87)	0.74 (0.45, 1.21)	0.67 (0.39, 1.14)	0.62
1b. Noninfectious respiratory diseases						
No. of cases	140	80	77	55	66	—
Minimal adjustment[2]	1	0.52 (0.39, 0.68)	0.43 (0.33, 0.57)	0.29 (0.21, 0.39)	0.35 (0.26, 0.47)	< 0.0001
Multivariate adjustment[3]	1	0.69 (0.52, 0.91)	0.71 (0.53, 0.95)	0.51 (0.37, 0.71)	0.59 (0.42, 0.81)	0.004
2. Nervous system disorders						
No. of cases	40	38	69	47	47	
Minimal adjustment[2]	1	0.86 (0.55, 1.34)	1.35 (0.91, 2.00)	0.86 (0.56, 1.32)	0.91 (0.59, 1.40)	0.71
Multivariate adjustment[3]	1	0.84 (0.53, 1.32)	1.33 (0.88, 1.99)	0.83 (0.53, 1.31)	0.89 (0.55, 1.42)	0.18
3. Nonrespiratory, nonnervous system disorders						
No. of cases	67	48	54	48	45	—
Minimal adjustment[2]	1	0.66 (0.46, 0.95)	0.65 (0.45, 0.93)	0.55 (0.38, 0.81)	0.55 (0.37, 0.82)	0.04
Multivariate adjustment[3]	1	0.75 (0.52, 1.09)	0.79 (0.54, 1.15)	0.71 (0.48, 1.06)	0.70 (0.46, 1.08)	0.44
3a. Infection (per major ICD subcategory)						
No. of cases	13	11	12	14	9	—
Minimal adjustment[2]	1	0.77 (0.34, 1.71)	0.71 (0.33, 1.57)	0.76 (0.36, 1.64)	0.49 (0.20, 1.16)	0.42
Multivariate adjustment[3]	1	0.89 (0.39, 2.02)	0.92 (0.41, 2.09)	1.03 (0.46, 2.33)	0.68 (0.26, 1.75)	0.99
3b. Digestive disorders						
No. of cases	16	17	12	7	8	—
Minimal adjustment[2]	1	1.01 (0.51, 2.00)	0.64 (0.30, 1.37)	0.38 (0.15, 0.92)	0.48 (0.20, 1.17)	0.04
Multivariate adjustment[3]	1	1.27 (0.63, 2.55)	0.89 (0.40, 1.97)	0.56 (0.22, 1.45)	0.76 (0.29, 1.99)	0.31
3c. Endocrine, nutritional, and metabolic disorders						
No. of cases	19	8	13	9	11	—
Minimal adjustment[2]	1	0.38 (0.17, 0.88)	0.55 (0.27, 1.11)	0.36 (0.16, 0.80)	0.46 (0.21, 0.99)	0.06
Multivariate adjustment[3]	1	0.44 (0.19, 1.02)	0.65 (0.31, 1.37)	0.46 (0.20, 1.08)	0.55 (0.24, 1.28)	0.17
3d. Musculoskeletal disorders						
No. of cases	12	5	7	7	11	—
Minimal adjustment[2]	1	0.38 (0.14, 1.09)	0.47 (0.19, 1.20)	0.45 (0.18, 1.15)	0.74 (0.32, 1.74)	0.37
Multivariate adjustment[3]	1	0.44 (0.15, 1.27)	0.59 (0.22, 1.56)	0.58 (0.22, 1.59)	1.02 (0.39, 2.64)	0.1
3e. Genitorenal diseases						
No. of cases	7	6	10	9	5	—
Minimal adjustment[2]	1	0.80 (0.27, 2.38)	1.18 (0.45, 3.13)	1.04 (0.38, 2.84)	0.66 (0.20, 2.16)	0.51
Multivariate adjustment[3]	1	0.75 (0.25, 2.27)	1.08 (0.40, 2.94)	0.93 (0.32, 2.70)	0.55 (0.15, 1.98)	0.35
Cause of death within inflammatory causes—subsets by infection within any main category in the ICD versus all others						
A. Infections within any ICD subcategory						
No. of cases	63	38	39	55	39	—
Minimal adjustment[2]	1	0.55 (0.37, 0.82)	0.48 (0.32, 0.72)	0.63 (0.44, 0.91)	0.47 (0.31, 0.70)	0.02
Multivariate adjustment[3]	1	0.64 (0.42, 0.96)	0.60 (0.40, 0.91)	0.83 (0.56, 1.22)	0.60 (0.38, 0.95)	0.31
B. Noncardiovascular, noncancer inflammatory diseases other than infections						
No. of cases	228	150	184	128	148	—
Minimal adjustment[2]	1	0.60 (0.49, 0.74)	0.64 (0.53, 0.78)	0.42 (0.34, 0.52)	0.50 (0.40, 0.62)	< 0.0001
Multivariate adjustment[3]	1	0.71 (0.57, 0.87)	0.85 (0.69, 1.04)	0.59 (0.47, 0.74)	0.68 (0.54, 0.86)	0.01

[1] ICD, International Classification of Disease.
[2] Adjusted for age and energy intake.
[3] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol^2, ie, linear and quadratic terms of alcohol as a continuous variable), refined grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008

TABLE 7
Hazard ratios (and 95% CIs) for total and cause-specific mortality according to quintile (Q) of total intake of refined-grain foods in 27 312 women in the Iowa Women's Health Study 1986–2003[1]

	Refined-grain food intake (servings/wk)					*P* for trend
	Q1 (0–5.75)	Q2 (6–9.5)	Q3 (9.6–13.5)	Q4 (14–22)	Q5 (≥22.5)	
Total death						
No. of cases	1092	1125	984	1121	1230	—
Person-years	90 170	96 715	84 427	95 016	88 611	—
Minimal adjustment[2]	1	0.95 (0.87, 1.03)	0.94 (0.86, 1.03)	0.95 (0.87, 1.04)	1.14 (1.03, 1.25)	< 0.0001
Multivariate adjustment[3]	1	0.98 (0.90, 1.06)	0.95 (0.87, 1.04)	0.92 (0.84, 1.01)	1.01 (0.91, 1.12)	0.96
CVD death						
No. of cases	405	403	343	340	409	—
Minimal adjustment[2]	1	0.92 (0.80, 1.06)	0.89 (0.77, 1.03)	0.79 (0.68, 0.92)	1.06 (0.91, 1.24)	0.26
Multivariate adjustment[3]	1	0.94 (0.82, 1.08)	0.89 (0.76, 1.03)	0.75 (0.64, 0.88)	0.94 (0.78, 1.12)	0.33
CHD death						
No. of cases	216	219	187	195	217	—
Minimal adjustment[2]	1	0.93 (0.77, 1.13)	0.90 (0.74, 1.10)	0.84 (0.68, 1.03)	1.02 (0.82, 1.27)	0.63
Multivariate adjustment[3]	1	0.96 (0.79, 1.16)	0.90 (0.74, 1.11)	0.80 (0.64, 0.99)	0.89 (0.70, 1.14)	0.22
Death from stroke						
No. of cases	80	95	78	69	92	—
Minimal adjustment[2]	1	1.09 (0.81, 1.48)	1.02 (0.74, 1.40)	0.81 (0.58, 1.13)	1.20 (0.85, 1.70)	0.66
Multivariate adjustment[3]	1	1.15 (0.85, 1.56)	1.09 (0.78, 1.51)	0.86 (0.60, 1.22)	1.30 (0.88, 1.91)	0.24
Death from intracranial hemorrhagic stroke						
No. of cases	28	24	20	16	25	—
Minimal adjustment[2]	1	0.77 (0.44, 1.33)	0.71 (0.40, 1.28)	0.50 (0.26, 0.95)	0.82 (0.44, 1.54)	0.48
Multivariate adjustment[3]	1	0.84 (0.48, 1.47)	0.82 (0.45, 1.50)	0.61 (0.31, 1.20)	1.10 (0.54, 2.23)	0.87
Death from nonhemorrhagic stroke						
No. of cases	47	59	50	43	52	—
Minimal adjustment[2]	1	1.16 (0.79, 1.70)	1.11 (0.74, 1.67)	0.86 (0.56, 1.33)	1.17 (0.75, 1.84)	0.73
Multivariate adjustment[3]	1	1.22 (0.82, 1.80)	1.16 (0.76, 1.76)	0.87 (0.55, 1.38)	1.19 (0.72, 1.97)	0.40
Cancer death						
No. of cases	416	437	370	443	433	—
Minimal adjustment[2]	1	0.97 (0.85, 1.11)	0.94 (0.82, 1.09)	1.00 (0.87, 1.15)	1.05 (0.90, 1.23)	0.35
Multivariate adjustment[3]	1	1.00 (0.88, 1.15)	0.96 (0.83, 1.11)	0.98 (0.85, 1.14)	0.98 (0.82, 1.16)	0.49
Death attributed to noncardiovascular, noncancer, inflammatory diseases						
No. of cases	187	191	173	241	279	—
Minimal adjustment[2]	1	0.93 (0.76, 1.14)	0.95 (0.77, 1.17)	1.17 (0.96, 1.43)	1.46 (1.18, 1.81)	< 0.0001
Multivariate adjustment[3]	1	0.98 (0.80, 1.20)	0.95 (0.77, 1.18)	1.12 (0.91, 1.4)	1.21 (0.96, 1.53)	0.04
Death attributed to noncardiovascular, noncancer, noninflammatory diseases						
No. of cases	84	94	98	97	109	—
Minimal adjustment[2]	1	1.00 (0.75, 1.35)	1.16 (0.86, 1.57)	1.00 (0.73, 1.35)	1.16 (0.84, 1.61)	0.54
Multivariate adjustment[3]	1	1.05 (0.78, 1.41)	1.19 (0.88, 1.61)	1.00 (0.73, 1.38)	1.10 (0.76, 1.57)	0.07

[1] CVD, cardiovascular disease; CHD, coronary heart disease.
[2] Adjusted for age and energy intake.
[3] Additionally adjusted for BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, (alcohol, alcohol ^{2}, ie, linear and quadratic terms of alcohol as a continuous variable), whole grain, coffee (regular and decaffeinated), red meat, fish and seafood, and total fruit and vegetables.

as rheumatoid arthritis, gout, chronic obstructive pulmonary disease, emphysema, asthma, ischemia-reperfusion, ulcerative colitis, Crohn disease, type 1 and 2 diabetes, and several types of neurodegenerative diseases. A common feature in all of these infections and chronic degenerative diseases is that tissue degradation and repair, and hence inflammation, are causally linked to the progression of the diseases. In the present study, we excluded cardiovascular diseases and cancer from the inflammation categorization because other mechanisms (eg, deposition of atherosclerotic plaque, DNA changes) are likely to be at least as important causes of mortality in several of these diseases.

We found a reduction in risk of death attributed to inflammatory disease of >35% for those who reported the highest intake of whole grain. This risk reduction was numerically somewhat larger than the 28% reduction in risk for CHD death. It was also a greater reduction than the 20% risk reduction found for risk of incident diabetes in this study (8). Therefore, it may be that there is a specific effect of whole-grain intake on the reduction of chronic inflammatory processes that is also involved in the reduction in risk of CHD death and incident diabetes. In contrast, there was little relation between refined-grain intake and any cause of death, and its relation with inflammatory death was

The American Journal of Clinical Nutrition
Downloaded from www.ajcn.org by on December 8, 2008

positive, but barely statistically significant. These modest associations are consistent with the findings for refined grain reported after 9 y of follow-up in the IWHS (7).

The results of one short-term study in which whole grain was provided as a supplement support this idea (20). A powder consisting of whole grains (mostly brown rice and barley) and legumes was provided in a drink for 16 wk to male patients ($n = 76$) with coronary artery disease. The control group maintained their usual diet. Fasting serum glucose concentrations, 2 measures of lipid peroxidation (serum malondialdehyde and urinary 8-epiprostaglandin F_2), and homocysteine concentrations decreased significantly and serum retinol, α-carotene, and α-tocopherol significantly increased after 16 wk in the whole-grain and legume-drink group compared with the control group. Epidemiologic studies also identify whole-grain foods as inversely related to inflammatory markers (16–19).

Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other phytochemicals that are removed during the refining process (29–33). Interestingly, many of these compounds can support the antioxidant defense and thereby reduce the damaging effects of chronic inflammation via several mechanisms, including cell cycle control, protein chaperoning and repair, DNA and chromatin stabilization and repair, removal of reactive molecular species, and induction of antioxidant defense and detoxification mechanisms (33, 34). Many of these compounds are redox-active secondary plant metabolites (ie, redox-active antioxidants or reductants) (32, 33, 35, 36) that are produced by plants in response to oxidative and other types of stress and activate defense-related genes in plant cells. It has been suggested that these molecules also can mount an antioxidant defense in animal cells (after intake by the animal) by inducing gene expression of similar genes for antioxidant and detoxification enzymes (33, 37, 38). Therefore, we think it is plausible that whole-grain intake may reduce the risk of inflammatory conditions, possibly through support of antioxidant defense mechanisms.

We previously analyzed the total content of redox active molecules (ie, antioxidant capacity) in several thousand foods (32, 33, 35, 36) and were surprised to learn, after analyzing 1113 food samples obtained from the US Department of Agriculture National Food and Nutrient Analysis Program, that coffee and several whole-grain products were at the top of the ranked list. Furthermore, we recently studied the association between coffee consumption, the main antioxidant contributor in the diet, and risk of death attributed to inflammatory diseases in the IWHS using the same type of inflammatory categorization that we used in the present study (28). In the fully adjusted model, the hazard ratio of death attributed to inflammatory diseases was 0.72 for consumption of 1–3 cups (237–711 mL)/d, 0.67 for 4–5 cups (948–1185 mL)/d, and 0.68 for ≥6 cups (1422 mL)/d. We suggest that whole grains and coffee, both of which are rich in phytochemicals and other molecules that support the antioxidant defense, reduce the risk of cardiovascular disease and other inflammatory diseases in postmenopausal women via similar mechanisms. For example, dietary intake of both whole grains and coffee are positively associated with plasma enterolactone concentrations (39–41). Enterolactone, which is produced by the intestinal microflora from lignan precursors found in foods such as whole grains and coffee, is a phytoestrogen with antioxidant properties that has been linked to a reduced risk of inflammation-related diseases (42–44).

Caution is in order when interpreting our present findings. Although the formation of the inflammatory death endpoint is novel, most existing prospective studies assemble little information about the set of diseases that we included here. Use of the underlying cause of death as the indicator or inflammatory processes is likely to underestimate the number of women who suffer from the diseases; violent death, cancer, and cardiovascular diseases are preferentially coded as underlying cause if they coexist with one of the less common diseases studied here. It has long been thought that fiber is related to inflammatory diseases (45), and recent observations tend to support this view (46, 47). However, these studies have not focused specifically on whole grains or even cereal fiber. Residual confounding is a possibility, particularly because the correlates of the inflammatory death endpoint are not well known; however, we identified several other powerful predictors of this endpoint and adjusted for those variables. Reverse causality remains a possibility because there are inflammatory conditions that we did not ask about at baseline; however, we did exclude those with many of the most prevalent historical inflammatory conditions.

In conclusion, our results are consistent with a protective effect of whole-grain food intake on death attributed to pathology of inflammatory, oxidative stress, and infectious origin. These findings may lead to additional areas of research that will help to elucidate the reduced chronic disease risk associated with whole-grain food intake.

The authors' responsibilities were as follows—DRJ and RB: had original idea and obtained funding; LFA and DRJ: had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; all authors: contributed to the analysis and interpretation of data and critically revised and approved the manuscript for important intellectual content. None of the authors had a conflict of interest.

REFERENCES

1. Jacobs DR, Gallaher DD. Whole grain intake and cardiovascular disease: a review. Curr Atheroscler Rep 2004;6:415–23.
2. Liu S, Manson JE, Stampfer MJ, et al. Whole grain consumption and risk of ischemic stroke in women: a prospective study. JAMA 2000;284:1534–40.
3. Jacobs DR, Marquart L, Slavin J, Kushi LH. Whole-grain intake and cancer: an expanded review and meta-analysis. Nutr Cancer 1998;30:85–96.
4. Steffen LM, Jacobs DR, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2003;78:383–90.
5. US Department of Health and Human Services and US Department of Agriculture. Dietary guidelines for Americans, 2005. Internet: http://www.healthierus.gov/dietaryguidelines (accessed 12 October 2006).
6. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care 2004;27:538–46.
7. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. Am J Public Health 1999;89:322–9.
8. Meyer KA, Kushi LH, Jacobs DR, et al. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 2000;71:921–330.
9. Nathan C. Points of control in inflammation. Nature 2002;420:846–52.

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008

10. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease—a double-edged sword. Neuron 2002;35:419–32.
11. Quinn MT, Gauss KA. Structure and regulation of the neutrophil respiratory burst oxidase: comparison with nonphagocyte oxidases. J Leukoc Biol 2004;76:760–81.
12. Bogdan C, Rollinghoff M, Diefenbach A. Reactive oxygen and reactive nitrogen intermediates in innate and specific immunity. Curr Opin Immunol 2000;12:64–76.
13. Antonicelli F, Brown D, Parmentier M, et al. Regulation of LPS-mediated inflammation in vivo and in vitro by the thiol antioxidant Nacystelyn. Am J Physiol Lung Cell Mol Physiol 2004;286:L1319–27.
14. Cuzzocrea S, Riley DP, Caputi AP, Salvemini D. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. Pharmacol Rev 2001;53:135–59.
15. Cuzzocrea S, Thiemermann C, Salvemini D. Potential therapeutic effect of antioxidant therapy in shock and inflammation. Curr Med Chem 2004;11:1147–62.
16. Schulze MB, Hoffmann K, Manson JE, et al. Dietary pattern, inflammation, and incidence of type 2 diabetes in women. Am J Clin Nutr 2005;82:675–84.
17. Ford ES, Mokdad AH, Liu S. Healthy Eating Index and C-reactive protein concentration: findings from the National Health and Nutrition Examination Survey III, 1988–1994. Eur J Clin Nutr 2005;59:278–83.
18. Lopez-Garcia E, Schulze MB, Fung TT, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2004;80:1029–35.
19. Hoffmann K, Zyriax BC, Boeing H, Windler E. A dietary pattern derived to explain biomarker variation is strongly associated with the risk of coronary artery disease. Am J Clin Nutr 2004;80:633–40.
20. Jang Y, Lee JH, Kim OY, Park HY, Lee SY. Consumption of whole grain and legume powder reduces insulin demand, lipid peroxidation, and plasma homocysteine concentrations in patients with coronary artery disease: randomized controlled clinical trial. Arterioscler Thromb Vasc Biol 2001;21:2065–71.
21. Moss SF, Blaser MJ. Mechanisms of disease: inflammation and the origins of cancer. Nat Clin Pract Oncol 2005;2:90–7.
22. Libby P. Inflammation in atherosclerosis. Nature 2002;420:868–74.
23. Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160:2117–28.
24. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
25. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. Am J Clin Nutr 1998;68:248–57.
26. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200.
27. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
28. Andersen LF, Jacobs DR, Carlsen MH, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. Am J Clin Nutr 2006;83:1039–46.
29. Adom KK, Liu RH. Antioxidant activity of grains. J Agric Food Chem 2002;50:6182–7.
30. Adom KK, Sorrells ME, Liu RH. Phytochemicals and antioxidant activity of milled fractions of different wheat varieties. J Agric Food Chem 2005;53:2297–306.
31. Miller HE, Rigelhof F, Marquart L, Prakash A, Kanter M. Antioxidant content of whole grain breakfast cereals, fruits and vegetables. J Am Coll Nutr 2000;19(suppl):312S–9S.
32. Halvorsen BL, Holte K, Myhrstad MC, et al. A systematic screening of total antioxidants in dietary plants. J Nutr 2002;132:461–71.
33. Blomhoff R. Dietary antioxidants and cardiovascular disease. Curr Opin Lipidol 2005;16:47–54.
34. Gutteridge JM, Halliwell B. Free radicals and antioxidants in the year 2000. A historical look to the future. Ann N Y Acad Sci 2000;899:136–47.
35. Dragland S, Senoo H, Wake K, Holte K, Blomhoff R. Several culinary and medicinal herbs are important sources of dietary antioxidants. J Nutr 2003;133:1286–90.
36. Halvorsen BL, Carlsen MH, Phillips KM, et al. Content of redox-active compounds (ie, antioxidants) in foods consumed in the United States. Am J Clin Nutr 2006;84:95–135.
37. Moskaug JO, Carlsen H, Myhrstad MC, Blomhoff R. Polyphenols and glutathione synthesis regulation. Am J Clin Nutr 2005;81(suppl):277S–83S.
38. Lamming DW, Wood JG, Sinclair DA. Small molecules that regulate lifespan: evidence for xenohormesis. Mol Microbiol 2004;53:1003–9.
39. Jacobs DR Jr, Pereira MA, Stumpf K, Pins JJ, Adlercreutz H. Whole grain food intake elevates serum enterolactone. Br J Nutr 2002;88:111–6.
40. Horner NK, Kristal AR, Prunty J, Skor HE, Potter JD, Lampe JW. Dietary determinants of plasma enterolactone. Cancer Epidemiol Biomarkers Prev 2002;11:121–6.
41. Johnsen NF, Hausner H, Olsen A, et al. Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J Nutr 2004;134:2691–7.
42. Vanharanta M, Voutilainen S, Lakka TA, van der Lee M, Adlercreutz H, Salonen JT. Risk of acute coronary events according to serum concentrations of enterolactone: a prospective population-based case-control study. Lancet 1999 Dec;354(9196):2112-15.
43. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. Lancet 1997;350:990–4.
44. Davies MJ, Bowey EA, Adlercreutz H, Rowland IR, Rumsby PC. Effects of soy or rye supplementation of high-fat diets on colon tumour development in azoxymethane-treated rats. Carcinogenesis 1999;20:927–31.
45. Burkitt DP, Walker AR, Painter NS. Dietary fiber and disease. JAMA 1974;229:1068–74.
46. Aldoori WH, Giovannucci EL, Stampfer MJ, Rimm EB, Wing AL, Willett WC. Prospective study of diet and the risk of duodenal ulcer in men. Am J Epidemiol 1997;145:42–50.
47. Aldoori WH, Giovannucci EL, Rockett HR, Sampson L, Rimm EB, Willett WC. A prospective study of dietary fiber types and symptomatic diverticular disease in men. J Nutr 1998;128:714–9.

The American Journal of Clinical Nutrition

Downloaded from www.ajcn.org by on December 8, 2008