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Whole grain, cereal fiber, bran, and germ intake and the risks of all-cause and CVD-specific mortality among women with type 2 diabetes

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Abstract

Background—Although whole grain consumption has been associated with a lower risk of cardiovascular diseases (CVD) and mortality in the general population, the association of whole grain with mortality in diabetic patients remain to be determined. This study investigated whole grain and its components cereal fiber, bran and germ in relation to all-cause and CVD-specific mortality in patients with type 2 diabetes.

Methods and Results—We followed 7,822 US women with type 2 diabetes in the Nurses' Health Study (NHS). Dietary intakes and potential confounders were assessed with regularly administered questionnaires. We documented 852 all-cause deaths and 295 CVD-deaths during up to 26 years of follow-up. After adjustment for age, the highest versus the lowest fifth of intakes of whole grain, cereal fiber, bran, and germ were associated with 16–31% lower all-cause mortality. After further adjustment for lifestyle and dietary risk factors, only the association for bran intake remained significant (*P* for trend = 0.01). The multivariate relative risks (RRs) across the fifths of bran intake were 1.0 (reference), 0.94 (0.75–1.18), 0.80 (0.64–1.01), 0.82 (0.65–1.04), and 0.72 (0.56–0.92). Similarly, bran intake was inversely associated with CVD-specific mortality (*P* for trend = 0.04). The RRs across the fifths of bran intake were 1.0 (reference), 0.95 (0.66–1.38), 0.80 (0.55–1.16), 0.76 (0.51–1.14), and 0.65 (0.43–0.99). Similar results were observed for added bran alone.

Conclusions—Whole grain and bran intakes were associated with reduced all-cause and CVD-specific mortality in women with diabetes. These findings suggest a potential benefit of whole grain intake in reducing mortality and cardiovascular risk in diabetic patients.

Keywords

Cardiovascular diseases; mortality; diabetes mellitus; whole grain; bran

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Disclosures

None.

Several epidemiologic studies have suggested that whole grain intake may reduce the risk of type 2 diabetes[1], cardiovascular disease (CVD)[2] and mortality [3,4]. Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other un-measured constituents[5], which may have favorable effects on health by lowering serum lipids[6] and blood pressure[7], improving glucose and insulin metabolism[8], endothelial function, and alleviating oxidative stress[9] and inflammation[10].

Patients with type 2 diabetes have 2–3 fold higher risk of cardiovascular disease (CVD) and premature mortality than the general population[11]. A randomized crossover trial indicated that high-fiber diet can improve glycemic control, lower hyperinsulinemia, and improve blood lipid concentrations in diabetic patients[12]. In addition, results from our previous study among diabetic participants suggested that high intakes of whole grain and components such as cereal fiber and bran might protect against systemic inflammation and endothelial dysfunction [13]. We therefore hypothesized that whole grain consumption might lower mortality especially cardiovascular mortality in diabetic patients.

To test this hypothesis, we prospectively examined the association between long-term intakes of whole grain, the grain subcomponents cereal fiber, bran, and germ, and the risks of all-cause and CVD-specific mortality among diabetic women from the Nurses' Health Study (NHS).

Methods

Study population

The NHS cohort began in 1976 with the recruitment of 121,700 female registered nurses (aged 30–55 years old) residing in 11 large US states. The medical history, lifestyle information and disease diagnosis were updated every 2 years by using a validated questionnaire[14]. The current study included 7,822 women with type 2 diabetes diagnosed between 1976 and 2006. Women with diabetes diagnosed before the age of 30 years, or with a history of CVD (including stroke, myocardial infarction [MI], angina, and/or coronary revascularization) or cancer reported on the 1980 questionnaire (when diet was first assessed) or before, were excluded. The present study was approved by the institutional review board at Brigham and Women's Hospital and returning the questionnaires was supposed to imply informed consent.

Confirmation of diabetes mellitus

Incident cases of type 2 diabetes were defined as self-reported diabetes confirmed by a validated supplementary questionnaire regarding symptoms, diagnostics tests, and hypoglycemic therapy. We used National Diabetes Data Group criteria [15] to diagnose diabetes before the release of the American Diabetes Association (ADA) criteria in 1997. The ADA diagnostic criteria was adopted to diagnose of diabetes cases during the 1998 and 2006 cycles[16]. Our validation study revealed that 98% of the self-reported type 2 diabetes cases were confirmed by medical records review [17]. The diagnostic criteria that we used have been reported in detail elsewhere [18].

Death ascertainment

The end points in this study included all-cause and CVD-specific mortality. The ascertainment of death has been documented in previous study[19]. Briefly, deaths were reported by next of kin or the postal system or identified through the National Death Index. We previously estimated that follow-up for deaths was more than 98% complete[20]. We obtained death certificate copies and medical records, and determined causes of death according to the International Classification of Diseases, Ninth Revision.

Assessment of whole grain, cereal fiber, bran, and germ consumption

Semi-quantitative food-frequency questionnaires were sent to the NHS participants in 1980, 1984, 1986, 1990, 1994, 1998 and 2002. On each questionnaire, participants were asked to report how often on average they had consumed of foods and beverages with a specified used unit or portion size during the previous year. Whole grain were defined and calculated as previously described[21]. Briefly, the portions were converted to grams per serving, and intake of whole grains was calculated by multiplying the consumption frequency of each unit of food by the whole grain content in grams. Intake of whole grain (in grams per day) was estimated based on the dry weight of whole grain ingredients of all grain foods (including rice, pasta, bread, and breakfast cereals). Whole grain intake from the breakfast cereals was calculated from more than 250 brand name cereals according to the information from product labels or provided by breakfast cereal manufacturers. Total intake of bran and germ (in grams per day) in this study included added and naturally occurring forms from whole grain and was calculated in a similar manner. We used the residual method to energy-adjust the intakes of whole-grain and fiber[22].

Statistical analysis

We calculated cumulative averages of food and nutrient intakes from the repeated questionnaires. Non-dietary covariates were updated at each biennial follow-up cycle. Person-time was calculated for each participant from the return of the questionnaire on which type 2 diabetes was first diagnosed to the occurrence of death or the end of the study period (1 June 2006). Cox proportional hazards regression was used to examine the associations between the dietary factors and all-cause and CVD-specific mortality. Multivariable models were first adjusted for age, smoking status, BMI, alcohol intake, physical activity, parental history of MI, menopausal status and use of hormone therapy, and duration of diabetes. We further adjusted for cumulative averages of dietary factors including total energy, intakes of polyunsaturated fat, saturated fat, *trans* fat, magnesium, and folate. The median value of each category of dietary factors consumption was used as a continuous variable to test for linear trends. To represent the long-term intake of dietary factors and to reduce measurement error, we conducted analyses using updating dietary data by taking the average of all available dietary questionnaires[23]. To minimize residual confounding, we performed additional analyses of the association of these specific dietary factors with all-cause mortality stratified by BMI, smoking, alcohol intake and physical activity. The SAS statistical package was used for all analyses (SAS, Version 9.0 for UNIX; SAS Institute, Cary, NC). All *P* values are two sided.

Results

Baseline characteristics

Compared with the lowest fifth of whole grain intake, women in the higher fifth had a lower BMI and were less likely to smoke, but more likely to be engaged in physical activity, to use postmenopausal hormones, and to have hypercholesterolemia and hypertension. Women with higher intakes of whole grain also had higher intakes of folate, multivitamin supplements, and vitamin E supplements, and lower intakes of alcohol, saturated fat, polyunsaturated fat, and *trans* fat (Table 1). The baseline characteristics across the fifths of cereal fiber, germ, and bran were similar to those for whole grains (data not shown). Correlations with whole grain intake were 0.69 for cereal fiber, 0.78 for bran, and 0.61 for germ.

Intakes of whole grain, cereal fiber, bran, and germ in relation to all-cause mortality

During up to 26 years of follow up (70,102 person-years), we confirmed 852 deaths (295 deaths from CVD, including 195 deaths from coronary heart disease [CHD] and 100 from stroke). In an age-adjusted analysis, we observed an inverse association between whole grain intake and

all-cause mortality (*P* for trend = 0.004; Table 2). Compared with the lowest fifth of whole grain intake, the relative risk (RR) for all-cause mortality was 0.80 (95% CI: 0.64–1.00) in the highest fifth. Further adjustment for lifestyle and dietary covariates attenuated the association to borderline significance. The multivariable RRs across the fifths of whole grain intakes were 1.0 (reference), 1.24 (0.99–1.54), 0.82 (0.65–1.04), 0.89 (0.70–1.13), and 0.89 (0.69–1.14). Per 20-g/d increment in whole grain intake corresponded to 13% reduction (95% CI: 2–23%) in all-cause mortality after adjustment for age.

We then examined the associations between the components of whole grain (cereal fiber, bran, and germ) and all-cause mortality. All three components were significantly, inversely associated with risk, after adjustment for age. The association between bran intake and all-cause mortality remained significant after adjustment for lifestyle factors and other covariates (RR: 0.75, 95% CI: 0.60–0.95 for the highest versus the lowest fifth; *P* for trend = 0.01). Further adjustment for dietary factors did not materially change the association. The RRs across the fifths of bran intakes were 1.0 (reference), 0.94 (0.75–1.18), 0.80 (0.64–1.01), 0.82 (0.65–1.04), and 0.72 (0.56–0.92; *P* for trend = 0.01). Per 1-g/d increment in bran intake corresponded to a 2% (95% CI: 1–4%) reduction in all-cause mortality after adjustment for age. Significant associations were found for cereal fiber after adjustment for lifestyle and other covariates. The RRs across the fifths of cereal fiber intakes were 1.0 (reference), 1.03 (0.82–1.29), 0.99 (0.78–1.25), 0.88 (0.70–1.12), and 0.81 (0.64–1.03) (*P* for trend = 0.02). Further adjustment for dietary factors weakened the association (*P* for trend = 0.10). Per 1-g/d increment in cereal fiber intake corresponded to 8% (95% CI: 4–11%) reduction in all-cause mortality after adjustment for age. The association between germ intake and total-mortality was not significant in the multivariate models. The RRs across the fifths of germ intakes were 1.0 (reference), 1.12 (0.91–1.40), 0.89 (0.72–1.11), 0.89 (0.71–1.13), and 0.99 (0.78–1.26) (*P* for trend = 0.69; Table 2). We found similar inverse associations between these dietary factors with all-cause mortality stratified by BMI (< 30 vs. ≥ 30 kg/m^2), smoking (never vs. past and current smoking), alcohol intake (nondrinkers vs. drinkers) and physical activity (used median as the cut point; <11.8 vs. $\geq$ 11.8 MET h/week) (data not shown).

Intakes of whole grain, cereal fiber, bran, and germ and CVD-specific mortality

We further examined the associations between intakes of whole grain and subcomponents with CVD-specific mortality. In age-adjusted models, intakes of whole grain, cereal fiber, and bran were inversely associated with CVD-specific mortality. Further adjustment for lifestyle and dietary variables attenuated the associations for whole grain (The multivariable RRs and 95% CI across the fifths of whole grain intakes were 1.0 [reference], 1.06 [0.74–1.52], 0.66 [0.44–0.97], 0.77 [0.52–1.14], and 0.70 [0.46–1.06; *P* for trend = 0.07]) and cereal fiber (The multivariable RRs and 95% CI across the fifths of cereal fiber intakes were 1.0 [reference], 1.20 [0.81–1.76], 1.12 [0.75–1.69], 1.09 [0.71–1.67], and 0.89 [0.57–1.41; *P* for trend = 0.41]). However, the association between bran intake and CVD-specific mortality remained significant in the fully-adjusted model. The highest fifth of bran intake were associated with 35% lower risk of CVD-specific mortality as compared with the lowest fifth (RR: 0.65, 95% CI: 0.43–0.99; *P* for trend = 0.04) (Table 3). Germ intake was not substantially associated with CVD-specific mortality. The RRs across the fifths of germ intakes were 1.0 (reference), 0.96 (0.68–1.37), 0.71 (0.49–1.02), 0.61 (0.41–0.91), and 0.85 (0.58–1.25) in the fully-adjusted model (*P* for trend = 0.37).

In order to assess whether added bran has similar benefits as total bran, we further examined the association of added bran intakes with all-cause and CVD-specific mortality. A large proportion (26,705 person-years) of the study population did not eat products with added bran. We defined these participants with “no intake” as the reference group, and created four additional categories for those who did consume added bran. Compared with non-consumers

of added bran, the inverse association for added bran and all-cause mortality was similar with that observed for total bran intake after adjusting for age. Further adjustment for lifestyle and dietary factors did not attenuate the inverse association when the subjects with the highest intake of added bran was compared with nonuser (RR: 0.45, 95% CI: 0.36–0.57; *P* for trend < 0.001). Similar results were observed for CVD-specific mortality (RR: 0.36, 95% CI: 0.24–0.54; *P* for trend < 0.001; data not shown). We did not find associations of added germ intake and all-cause or CVD-specific mortality.

Discussion

In this prospective study of 7,822 women with type 2 diabetes, we observed that intakes of whole grain, cereal fiber and bran were inversely associated with all-cause and CVD-specific mortality during 26-y follow-up. The association for bran intake was independent of other lifestyle and dietary factors. We did not find an association of germ intake with all-cause or CVD-specific mortality.

Several mechanisms have been suggested to be underlying the protective effects of whole grain and it's components on health, including reduction in serum lipids[6] and blood pressure[7], improvement of glucose and insulin metabolism[8] and endothelial function, and alleviation of oxidative stress[9] and inflammation[10]. Whole grain is composed of three parts: bran, germ, and endosperm. The bran and germ contain many nutrients and phytochemicals and have various potential beneficial health effects [24]. In line with our observation in participants without diabetes in the NHS cohort, bran intake was more strongly associated with reduced CHD risk than germ intake[25]. Bran is the major source of cereal fiber and contains important bioactive constituents[26]. Jacobs et al. found that fiber from whole grain products, but not fiber from refined grain products was inversely associated with mortality, suggesting that the botanically linked fiber and phytochemicals in bran may confer additional health benefits beyond the effect of fiber alone[3]. Although germ also contains micronutrients and phytochemicals, our previous study in men only found inverse associations of whole grain and bran, but not germ, with CHD[27], consistent with our results.

Our findings are also consistent with findings from clinic trials that whole grain and bran consumption may improve the metabolic profiles in diabetic patients. In a randomized controlled trial conducted in hyperinsulinemic adults, consumptions of whole grains for six weeks improved insulin sensitivity when compared with refined grains[28]. Another clinical trial found that consumption of whole grain and legume powder can reduce fasting glucose levels in diabetic patient with coronary artery disease when compared with those consumption of refined rice[29]. Results of intervention studies of wheat bran are inconsistent. Two studies found there were beneficial effects on glucose tolerance in individuals with or without glucose intolerance[30,31], another study including 23 diabetic patients who completed two 3-month phases diet intervention did not find favorable effects of wheat bran on glycemic control[32]. Nevertheless, oat bran can improve glycemic and insulinemic responses and beneficially influence plasma lipid levels in diabetic patients [33]. In the present study, although we did not analyze different sources of bran, both total and added bran intakes were inversely associated with all-cause or CVD-specific mortality in diabetic patients. However, additional investigations relating difference sources of bran to beneficial effects on diabetic patients are warranted in future studies.

Several cohort studies found that the whole grain components magnesium and folate were inversely associated with risk of all-cause mortality and CVD-specific mortality[34,35]. However, in our study, magnesium and folate did not fully explain the inverse associations between whole grain and subcomponents and mortality, suggesting other components of whole grain may play important roles.

Our study had several strengths. First, we analyzed data collected in a prospective cohort study. This minimizes recall bias and reverse causation. Second, we used cumulative average intakes of multiple repeated measurements of dietary intakes from updated dietary questionnaires reflecting the long-term dietary intakes, and therefore reduced the measurement error[23]. There are several potential limitations that also need to be considered. Higher intake of whole grain is part of a cluster of healthier dietary and lifestyle habits (eg, less smoking, more physical activity, and lower BMI). Although we adjusted for the lifestyle and dietary factors known to be associated with CVD and mortality, the potential of uncontrolled and unmeasured confounders might still remain. The observed associations may be confounded by the correlation between whole grain intakes and other greater health conscious behaviors and better glycemic control through unknown means. In addition, although we used cumulative average intakes of multiple repeated measurements reflecting the long-term diet, the measurement error of dietary intake assessment is unavoidable. Despite a relatively large sample size, our study was still underpowered to detect modest associations. For the all-cause mortality, we had 80% power to detect the association with RR ≤ 0.72 (or RR ≥ 1.38; $\alpha = 0.05$); for CVD-specific mortality, we could detect RR ≤ 0.59 (or RR ≥ 1.69) with 80% power and $\alpha = 0.05$. Thus, the nonsignificant associations with whole grains and cereal fiber may be due to limited power of our study. Finally, because the present study was conducted in white women, the associations need to be examined in men and other ethnic groups.

In summary, we found that intakes of whole grain especially its subcomponent bran were inversely associated with all-cause and CVD-specific mortality among women with type 2 diabetes. Our findings suggest that low whole grain intake may be considered an important modifiable risk factor for decreasing mortality and cardiovascular risk in diabetic patients.

CLINICAL PERSPECTIVE

Although whole grain consumption has been associated with a lower risk of cardiovascular disease incidence and mortality in the general population, little is known about the effect of whole grain and its components on cardiovascular risk and mortality in diabetic patients. In this prospective study, we followed 7,822 US women with type 2 diabetes for up to 26 years to investigate intakes of whole grain and its components cereal fiber, bran and germ in relation to all-cause and CVD-specific mortality. Our results indicated that intakes of whole grain especially its subcomponent bran were inversely associated with all-cause and CVD-specific mortality among women with type 2 diabetes. Low whole grain intake may be considered an important modifiable risk factor for decreasing mortality and cardiovascular risk in persons with diabetes.

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References

1. Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. American journal of public health 2000;90:1409–1415. [PubMed: 10983198]

2. Liu S, Manson JE, Stampfer MJ, Rexrode KM, Hu FB, Rimm EB, Willett WC. Whole grain consumption and risk of ischemic stroke in women: A prospective study. Jama 2000;284:1534–1540. [PubMed: 11000647]

3. Jacobs DR, Pereira MA, Meyer KA, Kushi LH. Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study. Journal of the American College of Nutrition 2000;19:326S–330S. [PubMed: 10875605]

4. Jacobs DR Jr, 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. American journal of public health 1999;89:322–329. [PubMed: 10076480]

5. Anderson JW, Hanna TJ. Whole grains and protection against coronary heart disease: what are the active components and mechanisms? The American journal of clinical nutrition 1999;70:307–308. [PubMed: 10479191]

6. Jenkins DJ, Kendall CW, Axelsen M, Augustin LS, Vuksan V. Viscous and nonviscous fibres, nonabsorbable and low glycaemic index carbohydrates, blood lipids and coronary heart disease. Current opinion in lipidology 2000;11:49–56. [PubMed: 10750694]

7. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England journal of medicine 1997;336:1117–1124. [PubMed: 9099655]

8. Juntunen KS, Laaksonen DE, Poutanen KS, Niskanen LK, Mykkanen HM. High-fiber rye bread and insulin secretion and sensitivity in healthy postmenopausal women. The American journal of clinical nutrition 2003;77:385–391. [PubMed: 12540398]

9. Slavin J. Why whole grains are protective: biological mechanisms. The Proceedings of the Nutrition Society 2003;62:129–134. [PubMed: 12740067]

10. Qi L, Hu FB. Dietary glycemic load, whole grains, and systemic inflammation in diabetes: the epidemiological evidence. Current opinion in lipidology 2007;18:3–8. [PubMed: 17218824]

11. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Archives of internal medicine 2004;164:1422–1426. [PubMed: 15249351]

12. Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. The New England journal of medicine 2000;342:1392–1398. [PubMed: 10805824]

13. Qi L, van Dam RM, Liu S, Franz M, Mantzoros C, Hu FB. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. Diabetes care 2006;29:207–211. [PubMed: 16443861]

14. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62. [PubMed: 9065374]

15. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057. [PubMed: 510803]

16. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes care 1997;20:1183–1197. [PubMed: 9203460]

17. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–778. [PubMed: 1681160]

18. Qi L, van Dam RM, Rexrode K, Hu FB. Heme iron from diet as a risk factor for coronary heart disease in women with type 2 diabetes. Diabetes care 2007;30:101–106. [PubMed: 17192341]

19. Zhang WL, Lopez-Garcia E, Li TY, Hu FB, van Dam RM. Coffee consumption and risk of cardiovascular events and all-cause mortality among women with type 2 diabetes. Diabetologia 2009;52:810–817. [PubMed: 19266179]

20. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. American journal of epidemiology 1984;119:837–839. [PubMed: 6720679]

21. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. PLoS medicine 2007;4:e261. [PubMed: 17760498]
22. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. The American journal of clinical nutrition 1997;65:1220S–1228S. discussion 1229S–1231S. [PubMed: 9094926]
23. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. American journal of epidemiology 1999;149:531–540. [PubMed: 10084242]
24. Slavin J, Jacobs D, Marquart L. Whole-grain consumption and chronic disease: protective mechanisms. Nutrition and cancer 1997;27:14–21. [PubMed: 8970176]
25. Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. The American journal of clinical nutrition 1999;70:412–419. [PubMed: 10479204]
26. Anderson JW. Whole grains and coronary heart disease: the whole kernel of truth. The American journal of clinical nutrition 2004;80:1459–1460. [PubMed: 15585755]
27. Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Gronbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. The American journal of clinical nutrition 2004;80:1492–1499. [PubMed: 15585760]
28. Pereira MA, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL, Seaquist ER. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. The American journal of clinical nutrition 2002;75:848–855. [PubMed: 11976158]
29. 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. Arteriosclerosis, thrombosis, and vascular biology 2001;21:2065–2071.
30. Bosello O, Ostuzzi R, Armellini F, Micciolo R, Scuro LA. Glucose tolerance and blood lipids in bran-fed patients with impaired glucose tolerance. Diabetes care 1980;3:46–49. [PubMed: 6250774]
31. Brodribb AJ, Humphreys DM. Diverticular disease: three studies. Part III - Metabolic effect of bran in patients with diverticular disease. British medical journal 1976;1:428–430. [PubMed: 1252775]
32. Jenkins DJ, Kendall CW, Augustin LS, Martini MC, Axelsen M, Faulkner D, Vidgen E, Parker T, Lau H, Connelly PW, Teitel J, Singer W, Vandenbroucke AC, Leiter LA, Josse RG. Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in type 2 diabetes. Diabetes care 2002;25:1522–1528. [PubMed: 12196421]
33. Pick ME, Hawrysh ZJ, Gee MI, Toth E, Garg ML, Hardin RT. Oat bran concentrate bread products improve long-term control of diabetes: a pilot study. Journal of the American Dietetic Association 1996;96:1254–1261. [PubMed: 8948386]
34. Haglin L, Tornkvist B, Backman L. Prediction of all-cause mortality in a patient population with hypertension and type 2 DM by using traditional risk factors and serum-phosphate,-calcium and-magnesium. Acta diabetologica 2007;44:138–143. [PubMed: 17721752]
35. Loria CM, Ingram DD, Feldman JJ, Wright JD, Madans JH. Serum folate and cardiovascular disease mortality among US men and women. Archives of internal medicine 2000;160:3258–3262. [PubMed: 11088087]

Table 1

Baseline characteristics according to quintiles of whole grain intake among women with type 2 diabetes (n = 7,822)*

	Whole-grain intake (g/day)					
Variables	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***P* trend**
Age (years)	46	47	46	47	49	
Risk factors						
BMI (kg/m^2)	30.3	30.2	30.2	29.8	28.5	< 0.01
Current smokers (%)	21.3	16.9	11.6	9.0	10.6	< 0.01
History of hypertension (%)	41.5	41.9	49.1	50.0	46.0	< 0.01
History of hypercholesterolemia (%)	34.2	31.7	42.9	45.3	45.1	< 0.01
Parental history of MI (%)	22.6	21.2	23.6	21.4	24.1	0.23
Postmenopausal hormone use (%)	14.1	14.4	22.9	22.5	24.7	< 0.01
Aspirin use (%)	14.9	15.5	15.4	18.2	18.4	0.015
Physical activity (h/week)	1.95	2.17	2.39	2.50	2.74	< 0.01
Alcohol(g/day)	5.5	3.8	3.5	3.1	2.8	< 0.01
Dietary daily intake						
Saturated fat (% energy)	14.3	14.2	13.7	13.2	12.4	< 0.01
Polyunsaturated fat (% energy)	5.8	5.7	5.8	5.7	5.5	< 0.01
Trans fat (% energy)	2.1	2.1	2.0	1.9	1.8	< 0.01
Folate (ug/day)	341.3	364.0	386.6	408.8	440.8	< 0.01
Glycemic load	100.0	100.8	101.9	103.3	99.2	0.61
Supplements						
Multivitamins (%)	34.1	35.2	39.5	46.0	50.0	< 0.01
Vitamin E (%)	19.5	19.3	25.9	32.1	35.5	< 0.01

*Values are means, unless otherwise indicated. MI, myocardial infarction.

Table 2

Relative risk (95% confidence interval) of all-cause mortality in women with diabetes according to the cumulative average intakes of whole grain, cereal fiber, bran, and germ (g/day) (1980–2006)*

	RR (95% CI) according to intakes					
Variables	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***P* trend**
Whole-grain intake	4.8 (< 7.8)	10.5 (7.8–12.1)	14.4(12.2–17.4)	20.6 (17.5–25.4)	32.6 (25.5–146.0)	
Number of cases	154	191	154	175	178	
Person-years	13994	14163	13947	13945	14053	
Age- adjusted	1.00	1.18(0.95–1.45)	0.81(0.65–1.02)	0.83(0.67–1.04)	0.80(0.64–1.00)	0.004
Multivariate model 1†	1.00	1.24(1.00–1.54)	0.84(0.67–1.06)	0.91(0.73–1.14)	0.89(0.71–1.11)	0.06
Multivariate model 2‡	1.00	1.24(0.99–1.54)	0.82(0.65–1.04)	0.89(0.70–1.13)	0.89(0.69–1.14)	0.11
Cereal fiber intake	1.9 (< 2.57)	2.99 (2.57–3.40)	3.80(3.41–4.22)	4.70 (4.23–5.30)	6.29 (5.31–22.50)	
Number of cases	147	176	177	176	176	
Person-years	13956	13949	14079	14084	14035	
Age- adjusted	1.00	0.94(0.75–1.18)	0.86(0.68–1.07)	0.77(0.61–0.97)	0.69(0.54–0.87)	0.0003
Multivariate model 1†	1.00	1.03(0.82–1.29)	0.99(0.78–1.25)	0.88(0.70–1.12)	0.81(0.64–1.03)	0.02
Multivariate model 2‡	1.00	1.08(0.85–1.36)	1.06(0.83–1.35)	0.95(0.74–1.23)	0.86(0.66–1.12)	0.10
Bran intake	0.8 (< 1.40)	1.88 (1.40–2.50)	3.22(2.51–4.04)	5.16 (4.05–6.85)	9.73 (6.86–68.4)	
Number of cases	164	160	177	174	177	
Person-years	14116	14045	14209	13687	14044	
Age- adjusted	1.00	0.90(0.72–1.12)	0.81(0.65–1.00)	0.75(0.60–0.94)	0.69(0.55–0.86)	0.001
Multivariate model 1†	1.00	0.95(0.76–1.18)	0.85(0.68–1.05)	0.86(0.68–1.07)	0.75(0.60–0.95)	0.01
Multivariate model 2‡	1.00	0.94(0.75–1.18)	0.80(0.64–1.01)	0.82(0.65–1.04)	0.72(0.56–0.92)	0.01
Germ intake	0.2 (< 0.33)	0.46 (0.33–0.51)	0.61(0.52–0.74)	0.9 (0.75–1.10)	1.51 (1.11–18.3)	
Number of cases	166	178	175	160	173	
Person-years	14218	14014	13914	13969	13987	
Age- adjusted	1.00	1.10(0.89–1.35)	0.90(0.72–1.11)	0.80(0.64–0.99)	0.84(0.68–1.05)	0.03
Multivariate model 1†	1.00	1.13(0.91–1.40)	0.92(0.74–1.14)	0.89(0.71–1.12)	0.95(0.76–1.18)	0.35
Multivariate model 2‡	1.00	1.12(0.91–1.40)	0.89(0.72–1.11)	0.89(0.71–1.13)	0.99(0.78–1.26)	0.69

* For the intake level at each quintile, values were expressed as median (range).

[†]Adjusted for age (5-year categories), smoking status (never, past and current 1–14, 15–24 or ≥ 25 cigarettes/day), BMI (<23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9 or ≥ 30.0 kg/m^2), alcohol intake (0, 0.1–4.9, 5–14 or ≥ 15 g/day), physical activity (<1, 1–1.9, 2–3.9, 4–6.9 or ≥ 7 h/week), parental history of MI, menopausal status and use of hormone therapy, and duration of diabetes (<5, 5–10, 11–15 or ≥ 15 years).

[‡]Adjusted for covariates in model 1 plus total energy, intakes of polyunsaturated, saturated and *trans* fat, magnesium, and folate (all in quintiles). RR, relative risk; CI, confidence interval.

Table 3

Relative risk (95% confidence interval) of CVD-specific mortality in women with diabetes according to the cumulative average intakes of whole grain, cereal fiber, bran, and germ (1980–2006)

	RR (95% CI) according to intakes					
Variables	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***P* trend**
Whole-grain intake						
Number of cases	62	65	52	59	57	
Age- adjusted	1.00	1.03(0.73–1.46)	0.70(0.48–1.02)	0.78(0.55–1.13)	0.71(0.49–1.03)	0.04
Multivariate model 1*	1.00	1.10(0.78–1.57)	0.73(0.50–1.07)	0.88(0.61–1.27)	0.81(0.56–1.19)	0.21
Multivariate model 2†	1.00	1.06(0.74–1.52)	0.66(0.44–0.97)	0.77(0.52–1.14)	0.70(0.46–1.06)	0.07
Cereal fiber intake						
Number of cases	53	65	61	62	54	
Age- adjusted	1.00	0.99(0.68–1.43)	0.88(0.60–1.29)	0.84(0.57–1.24)	0.69(0.46–1.02)	0.03
Multivariate model 1*	1.00	1.08(0.74–1.57)	1.04(0.70–1.54)	1.00(0.68–1.49)	0.85(0.56–1.29)	0.31
Multivariate model 2†	1.00	1.20(0.81–1.76)	1.12(0.75–1.69)	1.09(0.71–1.67)	0.89(0.57–1.41)	0.41
Bran intake						
Number of cases	61	57	65	55	57	
Age- adjusted	1.00	0.90(0.62–1.29)	0.83(0.58–1.19)	0.73(0.50–1.06)	0.69(0.47–1.00)	0.04
Multivariate model 1*	1.00	0.98(0.68–1.42)	0.88(0.62–1.27)	0.86(0.58–1.25)	0.78(0.53–1.15)	0.18
Multivariate model 2†	1.00	0.95(0.66–1.38)	0.80(0.55–1.16)	0.76(0.51–1.14)	0.65(0.43–0.99)	0.04
Germ intake						
Number of cases	69	62	59	44	61	
Age- adjusted	1.00	0.96(0.68–1.35)	0.76(0.54–1.08)	0.59(0.41–0.87)	0.80(0.56–1.13)	0.13
Multivariate model 1*	1.00	0.98(0.69–1.39)	0.77(0.54–1.11)	0.66(0.45–0.97)	0.91(0.64–1.31)	0.50
Multivariate model 2†	1.00	0.96(0.68–1.37)	0.71(0.49–1.02)	0.61(0.41–0.91)	0.85(0.58–1.25)	0.37

* *and* † Adjustment for covariates as described in the footnotes to Table 2. RR, relative risk; CI, confidence interval.