Published in final edited form as:
Ann Epidemiol. 2013 June ; 23(6): 321–327. doi:10.1016/j.annepidem.2013.03.010.

The Association of Whole Grain Consumption with Incident Type 2 Diabetes: The Women's Health Initiative Observational Study

Emily D Parker, PhD[1], **Simin Liu, MD, ScD**[2], **Linda Van Horn, PhD**[3], **Leslie F Tinker, PhD**[4], **James M Shikany, DrPH**[5], **Charles B Eaton, MD**[6], and **Karen L Margolis, MD**[1]

[1] HealthPartners Institute for Education and Research, HealthPartners, Bloomington, MN

[2] Department of Epidemiology, Medicine and Obstetrics and Gynecology, UCLA

[3]Department of Preventive Medicine, Northwestern University Feinburg School of Medicine, Chicago, IL

[4] Fred Hutchinson Cancer Research Center, Seattle, WA

[5] Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL

[6]Alpert Medicine School of Brown University, Center for Primary Care and Prevention, Pawtucket, RI

Abstract

PURPOSE—Whole grains may offer protection from diabetes by decreasing energy intake, preventing weight gain, and direct effects on insulin resistance. This study examined associations of whole and refined grains with incident type 2 diabetes (T2D) ascertained by self-reported medication use in a cohort of post-menopausal women.

METHODS—72,215 women free of diabetes at baseline from the Women's Health Initiative Observational Study were included. Whole grain consumption was categorized as 0, <0.5, 0.5-1.0, 1.0-<1.5, 1.5-<2.0, and ≥2.0 servings/day. Proportional hazards regression was performed to estimate hazard ratios (HR) and 95% confidence intervals adjusting for potential confounders.

RESULTS—There were 3,465 cases of incident T2D over median 7.9 years follow-up. Adjusted for age and energy intake/day, successively increasing categories of whole grain consumption were associated with statistically significant reduced risk of incident T2D (HRs= 1.00, 0.83, 0.73, 0.69, 0.61, 0.57, p for trend <0.0001). Results were attenuated after adjustment for confounders and other dietary components. Non-smokers and those who maintained their weight within 5 pounds had a greater reduced risk of T2D with higher consumption of whole grains than smokers and women who gained more weight.

CONCLUSIONS—This large, prospective study found an inverse, dose-response relationship between whole grain consumption and incident T2D in postmenopausal women.

Keywords

type 2 diabetes; whole grains; cohort studies

Corresponding author: Emily D Parker, PhD, MPH Research Investigator HealthPartners Institute for Education and Research Mail Stop 21111R 8170 33rd Ave So Bloomington, MN 55440 Office: 952-967-5247 Emily.D.Parker@healthpartners.com.

INTRODUCTION

Evidence from observational studies suggests that consumption of whole grains is associated with a reduced risk of incident type 2 diabetes (T2D).[1-5] However, the mechanism through which whole grains confer reduced risk is not fully understood. Diets high in whole grains and fiber may offer protection from diabetes through a variety of mechanisms including decreased energy intake and direct effects on insulin resistance.[6-7] Greater consumption of whole grains has been inversely associated with body weight, as well as risk of diabetes,[1-2, 8-9] coronary heart disease,[10] and stroke.[11-12]

Whole grain foods are a rich source of fiber and other nutrients. Several studies involving whole grains have found lower insulin levels or improved glucose tolerance.[5, 13-15] Fiber may act in a protective manner by slowing absorption and digestion of carbohydrates, leading to a reduced demand for insulin and lowering glucose responses.[16] Once processed, refined grains lose much of the fiber content as well as beneficial vitamins, minerals, essential fatty acids and phytochemicals that are found in whole grains. Refined grain foods tend to be energy-dense and nutrient poor and may be associated with insulin resistance, and excess weight.[17]

We examined the prospective association of whole and refined grains with the risk of incident T2D in the prospective Women's Health Initiative Observational Study, a diverse cohort of post-menopausal women. We hypothesized that greater whole grain consumption would be associated with a reduced risk of incident T2D while greater refined grain intake would be associated with an increased risk of incident T2D. Detailed dietary information and long term follow-up made possible an examination of the long term effects of whole grains on incident T2D.

MATERIALS AND METHODS

Overview of Women's Health Initiative

The Women's Health Initiative (WHI) is a cluster of four clinical trials and an observational cohort study. Details of the scientific rationale, eligibility requirements and baseline characteristics of the participants in the WHI have been published.[18-23] Briefly, the Observational Study (OS) includes women recruited directly into this study as well as those who were screened for, but did not join, the clinical trials. A total of 93,676 participants aged 50-79 were recruited between September 1994 and December 1998. Women were eligible to participate in the OS if they were post-menopausal, unlikely to change residence or die within 3 years, did not have complicating conditions such as alcoholism, drug dependency or dementia, and were not enrolled in the WHI CT, or any other clinical trial. Participants underwent initial screening visits during which personal information, medical history, family history and health-related habits were assessed using standardized questionnaires.

The key dietary assessment instrument in the WHI is a 122-item FFQ. All WHI participants completed an FFQ at screening. The WHI FFQ was designed by an ad hoc dietary assessment working group composed of WHI scientists and was based on instruments previously used in large-scale dietary intervention trials.[24-25] The FFQ nutrient database was derived from the University of Minnesota Nutrition Coding Center nutrient database (Nutrition Coordinating Center, Minneapolis, Minnesota).[26]

Exposure variables

Dietary intake was ascertained from the WHI FFQ. Intakes from the baseline and year 3 FFQ were averaged except for women (n=832) who developed T2D before the year 3 FFQ. Since the women who developed T2D before year 3 were likely to have changed their diet only the baseline FFQ was used. The FFQ includes many questions designed to characterize the type of bread, grain and cereal intake, including 2 questions that separate whole grain from refined grain bread and breakfast cereal. The methods for assigning the glycemic index (GI) and glycemic load (GL) values used in the WHI FFQ have been reported elsewhere.[27] Briefly, GI values were taken from published reports or imputed from GI values of foods with similar composition and prepared in like manner. A composite GI was computed by weighted average for FFQ line items with multiple foods. The GL was computed by multiplying the GI by grams of available carbohydrate (total carbohydrate minus total dietary fiber) by the number and frequency of servings consumed and portion size. In order to facilitate interpretation of results, we categorized whole grains by FFQ line item according to discrete servings per day with 0 servings per day being the reference category and successive categories of 0, <0.5, 0.5-1.0, 1.0-<1.5, 1.5-<2.0, and 2.0 or more servings/day. Nutrient values were energy-adjusted according to Willett.[28]

Ascertainment of Incident Diabetes

At each annual contact, participants were asked to self-report any new physician diagnosis of diabetes treated with oral hypoglycemic drugs or insulin. Diagnosis of T2D based on participant self-report was previously evaluated and deemed reliable. In a randomly selected sample of 5,884 baseline specimens from the entire WHI population, fasting glucose levels >140 mg/dL (the pre-1997 diagnostic threshold for diabetes in effect at the time most of the WHI participants were recruited) were seen in 4.7% of women without reported diabetes and 95.3% of women with reported diabetes at baseline.[29] A recent validation study in which 715 medical records were reviewed using current diabetes diagnostic criteria confirmed 92% of self-reported prevalent diabetes and 82% of self-reported incident diabetes. Evidence of diabetes was found in only 5% of women who did not report diabetes.[30]

Statistical Analysis

We included women from the WHI OS (n= 93,676) excluding those with T2D at baseline (n=5,318), implausible energy intake values (less than 500 or greater than 3,500 kcal, n=1,586), and those with missing data on whole grains consumption (n=682), energy intake (n=4,414), and other covariates (n= 9,366). The final study sample for these analyses was 72,215.

SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina) was used for all analyses. Baseline descriptive characteristics were generated as follows: for continuous variables, means and standard deviations were computed; for binary variables, percents were computed. Cox proportional hazards regression[31] was used to compute hazard ratios (HR) and 95% confidence intervals for incident T2D in relation to consumption of whole grains and refined grains. Person-years of follow-up were calculated from baseline to the self-report of diabetes, death, loss to follow-up, or end date (March 31, 2005), whichever came first. The median follow-up for diabetes analyses was 7.9 years with an interquartile range of 2.0 years. The null hypothesis that the HR for the exposure-disease association is the same at all follow-up time points was tested by modeling an interaction between whole grains and follow-up time. There was no evidence that the proportional hazards assumption was violated.

A series of models were compared to assess confounding and mediation. Model 1 was a minimally adjusted model that include age and energy intake. Model 2 further adjusted for potential confounding variables (smoking status, pack-years cigarettes, alcohol consumption, physical activity, education, income, race, and family history of diabetes). The main model, Model 3, further adjusted for BMI. In addition, we examined the potential mediating roles of other dietary components; Model 3 variables plus dairy and fruit and vegetable consumption in quintiles, and energy-adjusted nutrients (magnesium folic acid, potassium, vitamin D), and energy-adjusted dietary fiber. . Trends in HRs across categories of whole grain consumption, designated by their median values, were tested by a χ^2 statistic.

We examined effect modification by overweight status, alcohol intake, physical activity level, and smoking status in the relationship of whole grains consumption and incident T2D. In order to test the null hypothesis that there is no interaction, effect modification was examined by taking the value of the modifying variable of interest for a subject in the corresponding category of whole grain consumption and the value of 0 for all others. Additionally, we examined if there was a non-linear association by including a quadratic term for age and BMI. In a sub-analysis of women with weights taken at baseline and year 3 (n=62,149), we examined main effects and effect modification by weight gain during the first 3 years of observation.

RESULTS

Descriptive characteristics of the study population at baseline are shown in Table 1. Baseline age, BMI, waist circumference, and family history of diabetes were similar across categories of whole grain consumption. Compared to women with lower intakes of whole grains, women with higher intakes were more physically active, were less likely to be current smokers, had higher educational attainment, and were more likely to use hormone therapy. Additionally, women with higher whole grain consumption reported higher consumption of fruits and vegetables, and dairy (Table 2). We observed moderate correlations between whole grain and fiber (correlation coefficients 0.57, data not shown).

In this cohort of postmenopausal women, the incidence rate of T2D was 63/10,000 person-years. Prospective analyses are shown in Table 3. Compared with the lowest category of whole grain consumption, successively increasing categories of whole grain consumption were associated with a statistically significant reduced risk of incident T2D (HRs=1.00, 0.83, 0.73, 0.69, 0.61, 0.57, p for trend <0.0001, Model 1) after adjusting for age and energy intake/day. Results were slightly attenuated after adjustment for potential confounding variables (smoking status, pack-years cigarettes, alcohol consumption, physical activity, educational attainment, income, race and family history of diabetes) (HRs=1, 0.87, 0.80, 0.79, 0.72, 0.72, 0.63, p for trend <.0001) and more so after further adjusting for BMI (Model 3, HRs=1.00, 0.89, 0.82, 0.86, 0.82, 0.75, p for trend 0.014). We examined the role of other dietary components that might mediate the relationship of whole grain consumption with incident T2D (Table 3). The association was weakened after adjusting for dairy, fruit and vegetable intake to the main model (Model 3), and the results were similarly weakened after adjusting for quintiles of micronutrients (vitamin D, potassium, folic acid, and magnesium). After adjusting for these variables the linear trend was no longer significant, but women in the highest categories of whole grain intake still had a lower risk of diabetes. There was no longer an association of whole grains with incident T2D after including fiber in the model. In the association between refined grain intake and incident T2D, there was no linear trend (p=0.7434). The association was stronger after adjusting for potential confounders and BMI. Inclusion of vitamin D, potassium, folic acid, and magnesium further strengthened this relationship.

We found a statistically significant interaction between whole grain consumption and smoking status (p=0.029) on the risk of T2D. There was no association among women who were ever-smokers and a strong, protective association among who women who never smoked (HRs=1.00, 0.78, 0.69, 0.72, 0.72, 0.57, p for trend 0.0012) (Table 4). We did not detect effect modification by overweight status (p=0.811), alcohol intake (p=0.3444), or physical activity level (p=0.6120).

Including weight gain instead of BMI in Model 3 did not change the results (HRs=1.00, 0.85, 0.80, 0.82, 0.71 0.89, p for trend 0.0072) (Table 5). However, we detected effect modification by weight gain (p for interaction 0.0011). There was a strong, dose-response inverse association between whole grain consumption and incident T2D among women who gained fewer than 5 pounds and no association among women who gained 5 or more pounds between the baseline and year 3 follow-up.

DISCUSSION

In this large, prospective cohort study of post-menopausal women, the consumption of whole grains was inversely associated with incident T2D over a median 7.9 years of follow-up. Women who consumed greater than 2 servings of whole grains per day had a 43% reduction in risk of incident diabetes compared to women who consumed no whole grains. The lower risk of diabetes was observed even at relatively low intakes of whole grains such as 1 serving/day (HR=0.73). The association was robust and dose-related after adjusting for potential confounders but was largely attenuated by the inclusion of micronutrients in the model. These findings are consistent with other large, prospective studies[1-5]. In contrast, we did not find a dose-response association between refined grain and incident T2D.

Whole grain foods are a good source of several vitamins, minerals and fiber. They may also be a marker for a dietary pattern that protects against diabetes, as suggested by our observation that fruit and vegetable intake attenuated the inverse association between whole grain intake and incident T2D. Our results further suggest that the protective effect of whole grains may in part be related to micronutrients, including magnesium, vitamin D, folic acid, and potassium, because HRs were attenuated after including them in the model. Magnesium, which is lost in the processing of refined grains, has benefits on carbohydrate metabolism and insulin sensitivity.[32] In metabolic studies, intracellular magnesium was found to be related to insulin sensitivity.[33] Pereira et al reported an inverse dose-response relationship between whole grains and insulin resistance that was partially explained by magnesium.[17] Higher intakes of dietary magnesium have been associated with reduced risk of T2D in several prospective studies.[1, 3, 34-35] Our findings that HRs were slightly attenuated after adjusting for dietary magnesium are consistent with these studies.

Fiber in whole grains may exert a protective effect on T2D via direct intestinal effects. Fiber, in particular soluble fiber, slows the absorption of food through the digestive system and some studies have shown improved postprandial glucose response.[16] Fiber may also serve as a marker for the active phytochemicals in whole grains. [36] These phytochemicals are found in the bran and cell walls, which are lost through processing.[16] The association between whole grain consumption and incident T2D was attenuated after adjusting for energy-adjusted fiber in our study. These findings may be due to either direct effect of fiber, or a mixture of both physiologic gastrointestinal effects and delivery of phytochemicals.

It is also hypothesized that diets that are high in whole grains may prevent weight gain[37-38] which may influence diabetes risk. Indeed, we observed effect modification by weight gain whereby there was a strong, dose-response association in women who gained fewer than 5 pounds and no association among women who gained 5 or more pounds. We

looked at weight gain in a relatively short time period (between baseline and year 3) so these woman may have already been experiencing the physiologic effects of weight gain, such as altered glucose homeostasis. Furthermore, it is possible that early weight gain is a marker for continuing to gain weight after year 3 thus further increasing their risk of incident T2D over 7.9 years of follow-up.

Although both whole and refined grains contribute to glycemic load, a recent WHI study did not observe an association between glycemic load and glucose or insulin resistance in a sample of participants for whom biomarker data existed.[39] Furthermore, the literature is inconsistent; some large prospective studies have found a positive association between glycemic load and incident T2D[34-35, 40] while others have not.[1, 41] A recent meta-analysis of 9 large, prospective studies of glycemic load and chronic disease found a strong association between glycemic load and T2D independent of fiber intake.[42]

Refined grain foods lack the phytochemicals and intestinal effects of whole grains and tend to be energy-dense and nutrient-poor and are associated with higher glycemic load. Surprisingly, we did not observe an increased risk of incident T2D with increasing intakes of refined grains. Despite the higher glycemic index and poor micronutrient content of refined grains, across deciles of refined grain intake there was little variability in glycemic index (range 50.0-54.2), and energy-adjusted fiber (14.7-16.5) and magnesium (range 242.0-252.1). This may explain the absence of increased risk associated with refined grains we observed. Our findings are consistent with others in the literature.[1-4, 43]

We did not observe any protective effect of whole grains among ever-smokers, in contrast to never-smokers. The association of smoking and T2D is well-established. In a meta-analysis of over 1 million subjects, ever-smokers had higher incidence of T2D compared to never-smokers.[44] Smoking may increase diabetes risk through increased visceral fat[45-46] and insulin resistance.[47] In our study population, ever-smokers had higher BMIs and larger waist circumferences compared with never-smokers (27.1 kg/m^2 v 26.9 kg/m^2 and 84.6 v 83.2 cm, respectively). In WHI, we have observed that it takes 10 years or more following smoking cessation for diabetes risk to revert to that of a non-smoker.[48] Thus, one possibility is that the increased diabetes risk among current smokers and relatively recent quitters is masking any potential benefits of whole grain consumption.

A strength of this study is the large, diverse cohort of women with relatively long follow-up time. In addition, the baseline data allowed for the examination of numerous exposures. However, the ascertainment of T2D by self-report of medication use is an important limitation. This method finds cases later in the natural history of disease compared with glucose testing. The misclassification of some women with undiagnosed diabetes as non-diabetic would have the effect of weakening our ability to observe true associations. As well, there are limited whole grain food line items on the food frequency questionnaire. “Dark bread” is considered a whole grain but could in fact refer to bread that is high in refined grain such as pumpernickel. Also, the nature of the FFQ allows groupings of foods with different fiber and nutrient contents thereby relying upon a default code and potentially confounding actual amounts consumed. There is the possibility of misclassification of exposure status, but misclassification should be non-differential because women with existing conditions at baseline, who may have been more likely to change their diet, were excluded from the analysis. In addition, when possible, we averaged the baseline and year 3 FFQ in order to attain more stable estimates of dietary intake. Self-reported diet is subject to measurement error. While the self-reported dietary measures such as the FFQ are useful for characterizing usual diet, total intakes tend to be under-reported[49], which may bias associations toward the null. Additionally, although associations persisted with multivariate adjustment, residual confounding cannot be ruled out – this may be particularly true for

exposures such as whole grains that may reflect an overall healthier lifestyle. However, our findings remained robust in women with a BMI greater than 25 kg/m^2 and in women reporting low leisure time physical activity levels. There could be residual confounding by socioeconomic position even after adjusting for education and income. People of higher socioeconomic position tend to have better access to medical care, including preventive services, and are more likely to eat diets that are high in whole grains compared to those of lower socioeconomic position. The absence of a protective effect of whole grains among ever-smokers in our data support this assertion.

Conclusion

This large, prospective study of post-menopausal women found an inverse, dose-response relationship between whole grain consumption and incident T2D over a median of 7.9 years of follow-up. These data corroborate findings from other large studies that found strong, inverse associations between whole grain consumption and incident T2D. Furthermore, these findings provide support for hypotheses that the association between whole grains and incident T2D is modified by weight gain and smoking. The consumption of whole grains in this study population was low (mean 1.1 servings/day) and may even be slightly higher than that of the general population[50-51] therefore it is possible that even small increases in whole grain consumption could have substantial benefits at the population level.

Acknowledgments

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. A short list of WHI investigators can be found at http://www.whiscience.org/publications/WHI_investigators_shortlist.pdf

Dr. Margolis applied for a competitive grant from the General Mills Bell Institute of Health and Nutrition, entitled: Effects of whole grains, fiber, low-fat dairy products and yogurt on diabetes incidence in post-menopausal women. The funding was awarded to her institution, HealthPartners Institute for Education and Research. Neither General Mills nor The Bell Institute had any role in the design, analysis or writing of this manuscript.

The mission of the Bell Institute and its staff of doctorate-and master-level scientists and registered dietitians is to help in the development of food products and nutrition information. With backgrounds in nutrition science, public health, clinical nutrition and food science, Bell Institute experts are a valuable resource for the business teams at General Mills, as well as for health professionals around the country. Scientists in the Bell Institute contribute to research on whole grains, micronutrients and breakfast, and publish research and scientific articles in leading peer-reviewed journals. In addition, the Bell Institute also supports health professional organizations, sponsors educational efforts, and develops patient education materials and continuing education programs for health professionals.

Abbreviations

HR	hazard ratio
T2D	type 2 diabetes
WHI	Women's Health Initiative
FFQ	food frequency questionnaire
BMI	body mass index
GL	glycemic load
GI	glycemic index
OS	observational study

CT	clinical Trial
SAS	statistical analysis software

REFERENCES

1. Meyer KA, Kushi LH, Jacobs DR Jr. Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr. Apr; 2000 71(4):921–30. [PubMed: 10731498]
2. Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, et al. Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. Am J Clin Nutr. Sep; 2002 76(3):535–40. [PubMed: 12197996]
3. Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. Am J Public Health. Sep; 2000 90(9):1409–15. [PubMed: 10983198]
4. Montonen J, Knekt P, Jarvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. Am J Clin Nutr. Mar; 2003 77(3):622–9. [PubMed: 12600852]
5. McKeown NM, Meigs JB, Liu S, Wilson PW, Jacques PF. Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. Am J Clin Nutr. Aug; 2002 76(2):390–8. [PubMed: 12145012]
6. Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. Jama. Oct 27; 1999 282(16): 1539–46. [PubMed: 10546693]
7. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. J Nutr. Jul; 2012 142(7): 1304–13. [PubMed: 22649266]
8. Murtaugh MA, Jacobs DR Jr. Jacob B, Steffen LM, Marquart L. Epidemiological support for the protection of whole grains against diabetes. Proc Nutr Soc. Feb; 2003 62(1):143–9. [PubMed: 12740069]
9. Liu S. Intake of refined carbohydrates and whole grain foods in relation to risk of type 2 diabetes mellitus and coronary heart disease. J Am Coll Nutr. Aug; 2002 21(4):298–306. [PubMed: 12166526]
10. Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr. Sep; 1999 70(3):412–9. [PubMed: 10479204]
11. Liu S, Manson JE, Stampfer MJ, Rexrode KM, Hu FB, Rimm EB, et al. Whole grain consumption and risk of ischemic stroke in women: A prospective study. Jama. Sep 27; 2000 284(12):1534–40. [PubMed: 11000647]
12. Steffen LM, Jacobs DR Jr. 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. Sep; 2003 78(3):383–90. [PubMed: 12936919]
13. Jacobs DR Jr. Steffen LM. Wheat bran, whole grain, and food synergy. Diabetes Care. Sep; 2002 25(9):1652–3. [PubMed: 12196443]
14. Jacobs DR Jr. Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am J Clin Nutr. Sep 1; 2003 78(3):508S–13. 2003. [PubMed: 12936941]
15. McKeown NM, Meigs JB, Liu S, Wilson PWF, Jacques PF. Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. Am J Clin Nutr. Aug 1; 2002 76(2):390–8. 2002. [PubMed: 12145012]
16. Slavin JL, Martini MC, Jacobs DR Jr. Marquart L. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr. Sep; 1999 70(3 Suppl):459S–63S. [PubMed: 10479218]

17. Pereira MA, Jacobs DR Jr. Pins JJ, Raatz SK, Gross MD, Slavin JL, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr. May; 2002 75(5): 848–55. [PubMed: 11976158]
18. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol. Oct; 2003 13(9 Suppl):S18–77. [PubMed: 14575939]
19. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. Feb; 1998 19(1):61–109. [PubMed: 9492970]
20. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol. Oct; 2003 13(9 Suppl):S107–21. [PubMed: 14575943]
21. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. Ann Epidemiol. Oct; 2003 13(9 Suppl):S98–106. [PubMed: 14575942]
22. Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, et al. The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants. Ann Epidemiol. Oct; 2003 13(9 Suppl):S87–97. [PubMed: 14575941]
23. Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol. Oct; 2003 13(9 Suppl):S78–86. [PubMed: 14575940]
24. Henderson M, Kushi L, THompson D, Gorbach S, Clifford C, Insull W, et al. Feasibility of a randomized trial of low-fat diet for the prevention of breast cancer: dietary compliance in the Women's Health Trial Vanguard Study. Prev Med. 1990; 19:115–33. [PubMed: 2193306]
25. Kristal A, Feng Z, Coates R, Oberman A, George V. Associations of race/ethnicity, education, and dietary intervention with the validity and reliability of a food frequency questionnaire. The Women's Health Trial Feasibility Study in Minority Population. Am J Epidemiol. 1997; 146:856–69. [PubMed: 9384206]
26. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc. Oct; 1988 88(10):1268–71. [PubMed: 3171020]
27. Neuhouser ML, Tinker LF, Thomson C, Caan B, Horn LV, Snetselaar L, et al. Development of a Glycemic Index Database for Food Frequency Questionnaires Used in Epidemiologic Studies. J Nutr. Jun 1; 2006 2006 136(6):1604–9. [PubMed: 16702328]
28. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. Apr; 1997 65(4 Suppl):1220S–8S. discussion 9S-31S. [PubMed: 9094926]
29. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials. 2008; 5(3):240–7. [PubMed: 18559413]
30. Jackson JM, Defor TA, Crain AL, Kerby T, Strayer L, Lewis CE, et al. Self-reported diabetes is a valid outcome in pragmatic clinical trials and observational studies. J Clin Epidemiol. May 5.2012
31. Cox DR. Regression models and life tables (with discussion). J R Stat Soc (B). 1972; 34:187–220.
32. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. Diabetes Care. Jan; 2004 27(1):59–65. [PubMed: 14693967]
33. Paolisso G, Barbagallo M. Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium. Am J Hypertens. Mar; 1997 10(3):346–55. [PubMed: 9056694]
34. Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care. Apr; 1997 20(4):545–50. [PubMed: 9096978]
35. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. Jama. Feb 12; 1997 277(6): 472–7. [PubMed: 9020271]
36. Slavin J. Why whole grains are protective: biological mechanisms. Proc Nutr Soc. Feb; 2003 62(1):129–34. [PubMed: 12740067]

37. Liu S, Willett WC, Manson JE, Hu FB, Rosner B, Colditz G. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. Am J Clin Nutr. Nov; 2003 78(5):920–7. [PubMed: 14594777]
38. Koh-Banerjee P, Franz M, Sampson L, Liu S, Jacobs DR Jr. Spiegelman D, et al. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-y weight gain among men. Am J Clin Nutr. Nov; 2004 80(5):1237–45. [PubMed: 15531671]
39. Shikany JM, Phadke RP, Redden DT, Gower BA. Effects of low- and high-glycemic index/glycemic load diets on coronary heart disease risk factors in overweight/obese men. Metabolism. Dec; 2009 58(12):1793–801. [PubMed: 19631353]
40. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, et al. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med. Nov 26; 2007 167(21):2310–6. [PubMed: 18039989]
41. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: the ARIC study. Diabetes Care. Oct; 2002 25(10):1715–21. [PubMed: 12351467]
42. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, et al. Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. Am J Clin Nutr. Mar; 2008 87(3):627–37. [PubMed: 18326601]
43. Jacobs DR Jr. Andersen LF, Blomhoff R. Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women's Health Study. Am J Clin Nutr. Jun; 2007 85(6):1606–14. [PubMed: 17556700]
44. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. Jama. Dec 12; 2007 298(22):2654–64. [PubMed: 18073361]
45. Visser M, Launer LJ, Deurenberg P, Deeg DJ. Past and current smoking in relation to body fat distribution in older men and women. J Gerontol A Biol Sci Med Sci. Jun; 1999 54(6):M293–8. [PubMed: 10411016]
46. Barrett-Connor E, Khaw KT. Cigarette smoking and increased central adiposity. Ann Intern Med. Nov 15; 1989 111(10):783–7. [PubMed: 2817625]
47. Attvall S, Fowelin J, Lager I, Von Schenck H, Smith U. Smoking induces insulin resistance--a potential link with the insulin resistance syndrome. J Intern Med. Apr; 1993 233(4):327–32. [PubMed: 8463765]
48. Luo J, Rossouw J, Tong E, Giovino GA, Lee C, Chen C, et al. Smoking cessation, weight gain, and risk of type 2 diabetes mellitus among postmenopausal women. Arch Intern Med. Mar 12; 2012 172(5):438–40. [PubMed: 22412112]
49. Prentice RL, Shaw PA, Bingham SA, Beresford SA, Caan B, Neuhouser ML, et al. Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. Am J Epidemiol. Apr 15; 2009 169(8):977–89. [PubMed: 19258487]
50. Cleveland LE, Moshfegh AJ, Albertson AM, Goldman JD. Dietary intake of whole grains. J Am Coll Nutr. Jun; 2000 19(3 Suppl):331S–8S. [PubMed: 10875606]
51. Harnack L, Walters SA, Jacobs DR Jr. Dietary intake and food sources of whole grains among US children and adolescents: data from the 1994-1996 Continuing Survey of Food Intakes by Individuals. J Am Diet Assoc. Aug; 2003 103(8):1015–9. [PubMed: 12891150]

TABLE 1

Descriptive characteristics at baseline by whole grain consumption: the Women's Health Initiative Observational Study, 1993-1998.

	Whole grains servings per day											
	0/day n=4,349		< .5/day n=6,848		0.5-1/day n=22,778		1-1.5/day n=19,413		1.5-2/day n=10,476		2+/day n=8,351	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Age at screening	64.1	7.4	63.5	7.5	63.5	7.4	63.5	7.3	63.3	7.3	63.2	7.3
Race/ethnicity,%												
White, non-Hispanic	85.6		84.2		85.9		87.7		88.3		86.2	
Asian or Pacific Islander	2.9		4.4		3.5		2.5		1.9		1.1	
Black or African American	7.4		6.9		6.2		5.6		5.5		6.5	
Hispanic/Latino	2.6		2.7		2.7		2.6		3.3		4.4	
Other	1.6		1.8		1.7		1.7		0.5		1.7	
BMI kg/m^2	27.2	6.0	27.0	5.6	27.0	5.7	26.8	5.5	26.7	5.6	26.7	5.6
Waist, cm	84.8	13.5	84.4	13.1	84.2	13.1	83.6	12.8	83.4	12.8	83.4	13.2
Total MET hours per week	11.0	13.3	12.4	13.9	13.4	14.1	14.6	14.1	15.5	14.7	16.5	15.5
Smoking status, %												
Never smoked	45.0		48.3		48.9		51.5		52.8		52.5	
former smoker	43.5		41.8		44.3		43.8		43.2		43.9	
current smoker	11.6		9.9		6.8		4.7		3.9		3.6	
Non-drinker, %	9.3		10.1		9.5		9.9		10.2		11.6	
Alcohol, g/day	3.8	1.6	3.8	1.6	3.9	1.6	3.8	1.6	3.8	1.6	3.6	1.6
Hormone therapy use												
never	36.1		33.5		28.7		27.7		26.1		27.2	
former	22.0		21.2		21.1		20.6		20.0		20.7	
current	41.9		45.4		50.2		51.8		53.9		52.1	
Educational attainment												
high school diploma or less	26.1		23.3		20.6		18.6		16.2		15.2	
some college	37.9		38.2		38.1		35.4		34.3		33.7	
college degree or higher	36.1		38.6		41.3		46.0		49.5		51.1	
Income												
<$35,000	40.8		37.9		36.4		35.7		36.6		38.0	
35,000-75,000	39.3		39.9		41.7		42.0		42.1		41.6	

	Whole grains servings per day											
	0/day n=4,349		< .5/day n=6,848		0.5-1/day n=22,778		1-1.5/day n=19,413		1.5-2/day n=10,476		2+/day n=8,351	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
≥75,000	19.9		22.2		21.9		22.2		21.3		20.4	
Family history of diabetes, %	28.4		29.0		29.0		29.9		30.1		30.1	

TABLE 2

Dietary intakes at baseline by whole grain consumption: the Women's Health Initiative Observational Study, 1993-1998.

	Whole grains servings per day											
	0/day n=4,349		< .5/day n=6,848		0.5-1/day n=22,778		1-1.5/day n=19,413		1.5-2/day n=10,476		2+/day n=8,351	
Dietary intakes	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
Kcal/day	1145	426	1229	422	1367	440	1547	452	1720	464	1959	515
Whole Grains (median serv/day)	0.18	0.07	0.40	0.06	0.76	0.14	1.23	0.14	1.72	0.14	2.59	0.58
Refined grains (median serv/day)	1.8	1.3	2.0	1.3	2.4	1.3	2.8	1.3	3.3	1.4	4.2	1.8
Total grains (median serv/day)	2.5	1.6	2.9	1.6	3.6	1.6	4.5	1.8	5.5	2.0	7.5	2.8
Dairy (median serv/day)	1.0	0.8	1.1	0.7	1.3	0.8	1.6	0.9	1.8	0.9	2.0	1.1
Fruits (median serv/day)	1.5	1.2	1.7	1.2	1.9	1.2	2.2	1.2	2.4	1.3	2.6	1.4
Vegetables (median serv/day)	1.8	1.2	1.9	1.2	2.1	1.2	2.4	1.3	2.6	1.3	2.9	1.6
Fiber, g/day**	11.7	3.6	12.7	3.5	14.4	3.7	16.4	4.0	18.4	4.3	21.4	5.5
solube fiber, g/day**	3.4	1.0	3.6	1.0	3.9	1.0	4.3	1.1	4.7	1.2	5.4	1.4
Insoluble fiber, g/day**	8.2	2.7	9.1	2.7	10.4	2.8	12.0	3.1	13.6	3.3	16.0	4.3
total fat, g/day**	60.3	11.7	58.5	11.3	55.5	11.7	51.7	12.4	48.3	13.3	43.4	15.8
Glycemic load	67.4	34.4	73.6	31.2	84.5	32.3	98.9	33.1	112.7	33.8	133.6	40.1
glycemic index	51.7	5.5	51.7	4.4	51.8	3.8	52.1	3.5	52.2	3.3	52.7	3.3
sugar, g/day**	74.9	42.8	79.5	38.8	89.2	40.3	101.9	41.1	113.2	41.9	127.0	46.7
Folic µg/day**	264.7	75.8	278.0	75.0	296.3	75.5	316.3	79.8	333.1	83.9	350.5	97.5
Magnesium mg/day**	205.2	36.9	216.2	37.0	234.3	39.6	256.9	43.1	277.1	45.7	303.5	56.0
Potassium mg/day**	2303.3	503.1	2389.2	498.0	2510.6	518.9	2647.2	549.1	2756.8	579.2	2825.1	659.6
Vitamin D mcg/day**	4.0	2.2	4.1	2.0	4.3	2.2	4.5	2.5	4.7	2.6	4.4	2.9

** energy-adjusted

TABLE 3

Hazard Ratios and 95% confidence intervals in the association of whole, refined and total grain consumption with incident type 2 diabetes: The Women's Health Initiative Observational Study, 1993-2005.

		Whole Grains Servings per day						
		0	**<0.5**	**1.0**	**1.0-<1.5**	**1.5-2.0**	**≥2.0**	**p for trend**
Events		259	354	1081	923	476	372	
Person-years		31909	51284	172208	147281	80182	64137	
Model 1[a]	HR	1.00	0.83 (0.71, 0.98)	0.73 (0.63, 0.83)	0.69 (0.60,.0.79)	0.61 (0.53, 0.73)	0.57 (0.48, 0.67)	<.0001
Model 2[b]	HR	1.00	0.87 (0.74, 1.02)	0.80 (0.70, 0.92)	0.79 (0.68, 0.91)	0.72 (0.62, 0.85)	0.63 (0.53, 0.75)	<.0001
Model 3[c]	HR	1.00	0.89 (0.76, 1.05)	0.82 (0.72, 0.94)	0.86 (0.74, 0.99)	0.82 (0.70, 0.97)	0.75 (0.63, 0.89)	0.0139
+ Dairy, fruit, veg[d]	HR	1.00	0.91 (0.77, 1.07)	0.86 (0.75, 0.99)	0.91 (0.79, 1.05)	0.88 (0.74, 1.03)	0.79 (0.66, 0.94)	0.0659
+ Micronutrients[e]	HR	1.00	0.90 (0.76, 1.05)	0.83 (0.73, 0.96)	0.89 (0.77, 1.03)	0.87 (0.73, 1.02)	0.81 (0.67, 0.97)	0.2201
+ Fiber[f]	HR	1.00	0.90 (0.76, 1.05)	0.84 (0.73, 0.96)	0.88 (0.76, 1.03)	0.86 (0.72, 1.02)	0.78 (0.64, 0.95)	0.1026
		Refined Grains Servings per day						
		<1.0	**1.0-<2.0**	**2.0-<3.0**	**3.0-<4**	**4-<6.0**	**≥6.0**	**p for trend**
Events		176	798	947	708	628	208	
Person-years		22383	125925	166538	117401	90517	24236	
Model 1[a]	HR	1.00	0.78 (0.66, 0.92)	0.67 (0.57, 0.79)	0.68 (0.57, 0.81)	0.75 (0.62, 0.90)	0.87 (0.69, 1.10)	0.7434
Model 2[b]	HR	1.00	0.81 (0.69, 0.96)	0.71 (0.60, 0.84)	0.69 (0.58, 0.83)	0.72 (0.60, 0.87)	0.73 (0.60, 0.87)	0.0519
Model 3[c]	HR	1.00	0.83 (0.70, 0.98)	0.74 (0.63, 0.88)	0.73 (0.61, 0.87)	0.74 (0.61, 0.89)	0.76 (0.60, 0.96)	0.0849
+ Dairy, fruit, veg[d]	HR	1.00	0.84 (0.71, 0.99)	0.76 (0.64, 0.89)	0.74 (0.62, 0.88)	0.73 (0.60, 0.89)	0.73 (0.58, 0.93)	0.0292
+ Micronutrients[e]	HR	1.00	0.82 (0.70, 0.97)	0.73 (0.62, 0.86)	0.71 (0.59, 0.84)	0.71 (0.58, 0.86)	0.71 (0.58, 0.86)	0.0163
+ Fiber[f]	HR	1.00	0.83 (0.71, 0.98)	0.75 (0.63, 0.88)	0.74 (0.62, 0.88)	0.75 (0.62, 0.91)	0.77 (0.61, 0.98)	0.1383

[a]Model 1 adjusted for age at baseline and energy intake per day.

[b]Model 2 Model 1 plus confounding variables: race/ethnicity (non-Hispanic white, Asian or Pacific Islander, Black or African American, Hispanic/Latino, Other); physical activity in MET hours per week in quartiles; smoking status (current, former, never); pack years cigarettes (0, <20, 20-<40, ≥40 years); alcohol consumption (non drinker, former drinker, <1 drink/month, <1 drink/week, <7 per week,

≥7per week); hormone therapy use (current, former, never); educational attainment (high school or less, some college, college degree or higher); income (<$35,000, 35,000-<75,000, ≥75,000); family history of diabetes.

[c] Model 3 Model 2 variables plus BMI.

[d] Model 3 plus dairy, fruit, and vegetable consumption in quintiles.

[e] Model 3 plus energy adjusted folic acid, magnesium, potassium, and vitamin D.

[f] Model 3 variables plus energy adjusted fiber in quintiles.

TABLE 4

Hazard ratios and 95% confidence intervals in the association of whole grain consumption with incident type 2 diabetes stratified by smoking status: The Women's Health Initiative Observational Study, 1993-2005.

	Servings per day of whole grains						
	0	**-<0.5**	**0.5-<1.0**	**1.0-<1.5**	**1.5-2.0**	**>2.0**	**p for trend**
Smoking status							
Never- smoker							
Events	133	177	529	470	256	171	
Person years	14353	24816	84497	75949	42344	33661	
Hazard Ratio	1.00	0.78 (0.62, 0.98)	0.69 (0.57, 0.84)	0.72 (0.59, 0.88)	0.72 (0.58, 0.89)	0.57 (0.44, 0.73)	0.0012
Ever smoker							
Events	126	177	552	453	220	201	
Person years	17556	26468	87711	71332	37838	30476	
Hazard Ratio	1.00	1.01 (0.80, 1.27)	0.96 (0.79,1.17)	1.01 (0.82, 1.24)	0.92 (0.73, 1.16)	0.98 (0.77, 1.25)	0.5501

[a] Model adjusted for race/ethnicity (non-Hispanic white, Asian or Pacific Islander, Black or African American, Hispanic/Latino, Other); physical activity in MET hours per week in quartiles; BMI;alcohol consumption (non drinker, former drinker, <1 drink/month, <1 drink/week, <7 per week, ≥7per week); hormone therapy use (current, former, never); educational attainment (high school or less, some college, college degree or higher); income (<$35,000, 35,000-<75,000, ≥75,000); family history of diabetes.

[b] p for interaction 0.0291

TABLE 5

Hazard ratios and 95% confidence intervals in the association of whole grain consumption with incident type 2 diabetes stratified by weight gain : The Women's Health Initiative Observational Study, 1993-2005.

	Servings per day of whole grains						
	0	**<0.5**	**0.5-<1.0**	**1.0-<1.5**	**1.5-2.0**	**>2.0**	**p for trend**
Weight gain[a]							
Events	194	289	904	791	408	304	
Person years	26084	43562	150564	130471	71188	56493	
HR	1.00	0.85 (0.72, 1.00)	0.80 (0.67, 0.96)	0.82 (0.70, 0.96)	0.71 (0.58, 0.86)	0.89 (0.74, 1.07)	0.0072
Gained 5 or more pounds[b]							
Events	26	48	146	121	65	56	
Person years	2943	4910	18035	15085	8482	6701	
Hazard Ratio	1.00	1.07 (0.66-1.74)	0.86 (0.56-1.32)	0.91 (0.59-1.42)	0.85 (0.53-1.38)	0.86 (0.52-1.43)	0.5024
Gained <5 pounds							
Events	168	241	758	670	343	248	
Person years	23141	38653	132529	115386	62706	49793	
Hazard Ratio	1.00	0.87 (0.73-1.06)	0.81 (0.70-0.96)	0.83 (0.70-0.99)	0.77 (0.63-0.93)	0.67 (0.54-0.82)	0.0008

[a]Model adjust for race/ethnicity (non-Hispanic white, Asian or Pacific Islander, Black or African American, Hispanic/Latino, Other); physical activity in MET hours per week in quartiles; smoking status (current, former, never); pack years cigarettes (0, <20, 20-<40, ≥40 years); alcohol consumption (non drinker, former drinker, <1 drink/month, <1 drink/week, <7 per week, ≥7per week); hormone therapy use (current, former, never); educational attainment (high school or less, some college, college degree or higher); income (<$35,000, 35,000-<75,000, ≥75,000); family history of diabetes.

[b]p for interaction 0.0011