Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study[1–4]

Nicola M McKeown, James B Meigs, Simin Liu, Peter WF Wilson, and Paul F Jacques

ABSTRACT

Background: The influence of whole grains on cardiovascular disease risk may be mediated through multiple pathways, eg, a reduction in blood lipids and blood pressure, an enhancement of insulin sensitivity, and an improvement in blood glucose control.

Objective: The objective was to examine the association between diets rich in whole- or refined-grain foods and several metabolic markers of disease risk in the Framingham Offspring Study cohort.

Design: Whole-grain intake and metabolic risk markers were assessed in a cross-sectional study of 2941 subjects.

Results: After adjustment for potential confounding factors, whole-grain intake was inversely associated with body mass index ($\bar{x}$: 26.9 in the lowest and 26.4 in the highest quintile of intake; *P* for trend = 0.06), waist-to-hip ratio (0.92 and 0.91, respectively; *P* for trend = 0.005), total cholesterol (5.20 and 5.09 mmol/L, respectively; *P* for trend = 0.06*)*, LDL cholesterol (3.16 and 3.04 mmol/L, respectively; *P* for trend = 0.02), and fasting insulin (205 and 199 pmol/L, respectively; *P* for trend = 0.03). There were no significant trends in metabolic risk factor concentrations across quintile categories of refined-grain intake. The inverse association between whole-grain intake and fasting insulin was most striking among overweight participants. The association between whole-grain intake and fasting insulin was attenuated after adjustment for dietary fiber and magnesium.

Conclusion: Increased intakes of whole grains may reduce disease risk by means of favorable effects on metabolic risk factors. *Am J Clin Nutr* 2002;76:390–8.

KEY WORDS Whole grains, refined grains, risk factors, survey, Framingham Offspring Study, food-frequency questionnaire, type 2 diabetes, cardiovascular disease

INTRODUCTION

There is substantial interest in the role of nutrients in chronic disease (1, 2) but comparatively little emphasis on the specific contributions of food groups, particularly whole-grain foods. Although current dietary guidelines (3) recommend the consumption of several daily servings of whole-grain foods, in the United States most grain products consumed are refined, and the average consumption of whole grains is only one serving per day (4). Refined-grain foods contain lower amounts of vitamin E, fiber, and magnesium than do whole-grain foods, but the enrichment of refined flour with thiamine, riboflavin, niacin, and iron and the recent fortification with folic acid have improved the nutritional value of refined grains (5, 6). However, in contrast with whole grains, there appears to be no evidence of a protective association between refined-grain intake and risk of heart disease (7) or type 2 diabetes (8, 9).

Several epidemiologic studies found that diets rich in whole grains may protect against cardiovascular disease (7, 10, 11), stroke (12), type 2 diabetes (8, 9), and certain cancers (13, 14). The protective effects of whole grains may depend on the presence or interaction of several biologically active constituents, including dietary fiber, vitamin E, magnesium, folate, and other nutrients and nonnutrients (15). Dietary fiber has been shown to decrease glucose, insulin, and serum lipid concentrations in both diabetic and nondiabetic persons (16, 17). Magnesium, a rich constituent of the grain germ, is associated with low insulin concentrations (18, 19) and a low incidence of type 2 diabetes (8, 20, 21). In epidemiologic studies, vitamin E, folate, and fiber have independently been associated with a reduced risk of coronary heart disease (1, 2, 22). However, diets rich in whole-grain foods have

[1] From the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston (NMM and PFJ); the General Medicine Division and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston (JBM); the Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (SL); and The Boston University School of Public Health, Department of Epidemiology and Biostatistics, and the National Heart, Lung, and Blood Institute's Framingham Heart Study (PWFW).

[2] Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the US Department of Agriculture.

[3] Supported by a clinical research grant from the American Diabetes Association and a Junior Faculty Development Award from SmithKline Beecham and based on work supported in part by the US Department of Agriculture (agreement no. 58-1950-9-001); the National Institutes of Health, National Heart, Lung, and Blood Institute's Framingham Heart Study (contract N01-HC-38038); and an NIH postdoctoral training grant in Human Nutrition and Metabolism (T32 DK 07651).

[4] Reprints not available. Address correspondence to PF Jacques, Epidemiology Program, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, 711 Washington Street, Tufts University, Boston, MA 02111. E-mail: paul@hnrc.tufts.edu.

Received April 13, 2001.

Accepted for publication July 19, 2001.

been associated with a reduction in the risk of coronary heart disease and type 2 diabetes, independent of the effects of select nutrients found in whole grains (7, 9, 10).

The influence of whole grains on cardiovascular disease risk may be mediated through multiple pathways, eg, a reduction in blood lipids (23, 24) and blood pressure (25, 26), an enhancement of insulin sensitivity, and an improvement in blood glucose control (27). To explore mechanisms whereby diets enriched in whole-grain foods may protect against cardiovascular disease and type 2 diabetes, we examined the association between whole-grain and refined-grain intakes on several metabolic markers of disease risk in the Framingham Offspring Study.

SUBJECTS AND METHODS

Subjects

The Framingham Offspring Study is a longitudinal, community-based study of cardiovascular disease among the offspring of the original participants of the Framingham Heart Study cohort and their spouses (28). In 1971, 5135 participants were enrolled in the study (29); since then, the cohort has been examined every 3–4 y. Between 1991 and 1995, during the fifth examination cycle of the Framingham Offspring Study, 3799 participants underwent a standardized medical history and physical examination. Valid data from food-frequency questionnaires (FFQs) were available for 3418 participants. Participants were excluded from these analyses if they had a diagnosis of diabetes based on the use of insulin or oral hypoglycemic medication ($n = 126$) or if they were taking cholesterol-lowering medication ($n = 214$). Participants with missing covariate information were also excluded, which reduced the final sample to 2941 (1338 men and 1603 women). The final sample was younger ($\bar{x}$ age: 54 y compared with 59 y; $P < 0.001$) and had a lower mean body mass index [BMI; in kg (wt)/m^2 (ht): 27.0 compared with 28.2; $P < 0.001$] than did those who were excluded from the analyses. There was no significant difference in reported energy intakes between the participants and those excluded from the analyses. The Institutional Review Board for Human Research at Boston University and the Human Investigation Research Committee at New England Medical Center approved the protocol.

Assessment of dietary intake

Usual dietary intake during the previous year was assessed during the fifth examination cycle with the use of a semiquantitative, 126-item FFQ (30). The questionnaires were mailed to the participants before the examination, and the participants were asked to bring the completed FFQ with them to their appointment. The FFQ consisted of a list of foods with a standard serving size and a selection of 9 frequency categories ranging from never or < 1 serving/mo to > 6 servings/d. Participants were asked to report their frequency of consumption of each food item during the previous year. Separate questions about the use of vitamin and mineral supplements and the type of breakfast cereal most commonly consumed were also included in the FFQ. Nutrient intakes were calculated by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient content of the specified portion. Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes were < 2.51 MJ/d (600 kcal/d) or > 16.74 MJ/d (4000 kcal/d) for women and > 17.57 MJ/d (4200 kcal/d) for men or if ≥ 12 food items were left blank. The relative validity of the FFQ for both nutrients and foods was examined previously in several populations (30–32).

Breakfast cereal intake was subdivided into whole and refined grain based on the content of whole grain or bran of the cereal, as reported by Jacobs et al (7) and others (10). A breakfast cereal was considered whole grain if it contained ≥ 25% whole grain or bran by weight. Other whole-grain foods included dark bread, popcorn, cooked oatmeal, wheat germ, brown rice, and other grains (eg, bulgur, kasha, and couscous). Refined-grain foods included cold breakfast cereals (< 25% whole grain or bran), muffins, cakes, cookies, white bread and rolls, white rice, pancakes, waffles, pasta, and pizza. In the absence of information on brand names, breakfast cereals were classified as refined grain. Crackers could not be distinguished as whole- or refined-grain products and thus were classified as unspecified grains and were not included in the analyses.

Outcome measurements

Height, weight, waist, and hip circumferences were measured while the subjects were standing. BMI was calculated, and obesity was defined as a BMI ≥ 30 (33, 34). Fasting blood samples were drawn after the subjects had fasted overnight for the measurement of glucose, insulin, and lipid concentrations. Fasting insulin concentrations were measured in plasma as total immunoreactive insulin. Among patients without diagnosed diabetes, a 75-g oral-glucose-tolerance test was administered according to World Health Organization standards (35), and 2-h postchallenge glucose and insulin concentrations were measured. Previously undiagnosed diabetes was defined as a fasting plasma glucose concentration of ≥ 7.0 mmol/L or a 2-h postchallenge glucose concentration of ≥ 11.1 mmol/L (36). Glycated hemoglobin (Hb A_{1c}) was measured as a marker of long-term glucose homeostasis (37). Serum lipid profiles included enzymatic measurement of total cholesterol and triacylglycerol concentrations (38) and the measurement of the HDL-cholesterol fraction after precipitation of LDL and VLDL cholesterol with dextran sulfate–magnesium (39). LDL-cholesterol concentrations were calculated with the use of the Friedewald equation (40) for individuals with triacylglycerol concentrations < 4.5 mmol/L (400 mg/dL). Blood pressure was measured twice after the participants sat for ≥ 5 min. Subjects were classified as hypertensive if both of the 2 measurements for diastolic or systolic blood pressure were > 90 mm Hg or > 140 mm Hg, respectively, or if use of antihypertensive medication was reported (41). Additional covariate information included age, smoking dose (0, 1–15, 16–25, or > 25 cigarettes/d), alcohol intake (g/d), current multivitamin use (yes or no), physical activity score (42), and current use of estrogen replacement therapy in postmenopausal women.

Statistical methods

SAS statistical software (release 8.0; SAS Institute, Cary, NC) was used for all statistical analyses. Dependent variables were waist-to-hip ratio (WHR), systolic and diastolic blood pressure, LDL cholesterol, and the natural logarithms of BMI, total cholesterol, HDL cholesterol, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, and triacylglycerols. To express transformed variables in their natural scale, geometric means were computed by exponentiation of adjusted least-squares means. In separate models, first-order interactions between sex and whole- and

refined-grain intakes were entered to determine whether associations were similar between men and women. There were no significant ($P < 0.05$) interactions by sex on the association of whole grain and metabolic risk factors.

We determined age- and sex-adjusted and energy-adjusted geometric means for lifestyle and dietary characteristics across increasing quintiles of whole- and refined-grain intakes by using SAS PROC GLM. We assessed the statistical significance (defined as a two-tailed P value < 0.05) of trends across categories of grain consumption with linear (for continuous outcome variables) or logistic (for dichotomous outcome variables) regression models by using grain consumption (in servings/wk) as an ordinal variable with the median grain intake value in each category assigned as a score.

Multivariable models included sex, age (y), energy intake (kcal/d), multivitamin supplementation use (yes or no), alcohol intake (g/d), use of blood pressure medication (yes or no), current cigarette smoking (categorical), physical activity score (continuous), and current estrogen replacement therapy (yes or no) among women. Multivariate models were also used to evaluate the potential role of BMI as a mediator or confounder in the association between whole-grain intake and these metabolic risk factors. For dependent variables in which a positive association with whole-grain intake was observed, we further examined the possibility that dietary patterns associated with diets high in whole grains would explain these associations by adjusting for the percentage of polyunsaturated fatty acids and intakes of meat, fish, fruit, and vegetables. We also considered constituents found in whole grains that may be potential mediating nutrients. For these analyses, we further adjusted for intakes of dietary fiber, vitamin E, folate, magnesium, and vitamin B-6. We examined whether there was a significant interaction between BMI and whole grains on insulin concentrations. Insulin curves over BMI were smoothed by using the locally weighted regression scatter plot smoothing procedure (43). All correlation coefficients reported were calculated as Spearman rank-order correlation coefficients.

RESULTS

The reported mean weekly intakes of whole-grain foods were 8.3 and 8.8 servings/wk in men and women, respectively (**Table 1**). The reported median intake was lower, 6.0 and 6.5 servings/wk in men and women, respectively. The food items on the FFQ that contributed most to whole-grain intakes were dark bread, cold cereals, and popcorn. Both men and women reported higher intakes of refined grain than of whole grain: 22.0 and 18.5 servings/wk in men and women, respectively. Of the 2086 subjects who reported eating breakfast cereals, 63% ($n = 1313$) reported eating breakfast cereals that contained ≥ 50% whole grain or bran by weight, whereas 4% ($n = 74$) reported eating cereals that contained between 25% and 50% whole grain. A total of 33% ($n = 699$) reported eating refined-grain cereals, which included those cereals that contained a small amount of whole grain (1–24%).

The age-, sex-, and energy-adjusted descriptive characteristics of the study population across quintile categories of whole-grain intake are shown in **Table 2**. The median intake of whole-grain foods ranged from 0.9 to 20.5 serving/wk, from the lowest to the highest quintile category of whole-grain intake. Compared with participants in the lower category, those in the upper category of whole-grain intake tended to be older, tended to have a lower BMI and WHR (the latter even after adjustment for BMI), were less likely to smoke (if they did smoke, they smoked fewer cigarettes on average), were more likely to take multivitamin supplements, and were more likely to take estrogen replacement therapy (women only). A higher intake of whole grains was associated with a healthier diet, with those in the upper category also consuming less saturated fatty acids, alcohol, and meat and more

TABLE 1
Distribution of grain foods for men and women in the Framingham Offspring Study

Grain type	Men ($n = 1338$)		Women ($n = 1603$)	
	$\bar{x} \pm$ SD	Median (interquartile range)	$\bar{x} \pm$ SD	Median (interquartile range)
	servings/wk		*servings/wk*	
Whole grains				
Dark bread	4.3 ± 6.6[1]	1.0 (0.5–5.5)	4.1 ± 5.9	3.0 (0.5–5.5)
Whole-grain breakfast cereals[2]	1.7 ± 2.7	0 (0–3.0)	1.5 ± 2.7	0 (0–3.0)
Cooked oatmeal	0.5 ± 1.6	0 (0–0.5)	0.6 ± 1.3	0 (0–0.5)
Popcorn	1.1 ± 2.5	0.5 (0–1.0)	1.6 ± 3.6	0.47 (0–1.0)
Other grains[3]	0.7 ± 2.1	0 (0–0.5)	0.9 ± 2.7	0 (0–1.0)
Total	8.3 ± 8.8	6.0 (2.0–10.5)	8.8 ± 8.7	6.5 (3.0–11.0)
Refined grains				
White bread	6.3 ± 8.1	3.0 (0.5–7.0)	4.8 ± 6.6	3.0 (0.5–5.5)
Refined-grain breakfast cereals[2]	1.0 ± 2.7	0 (0–0.5)	0.9 ± 2.2	0 (0–0.47)
English muffins or bagels	1.8 ± 2.4	1.8 (0.5–3.0)	2.0 ± 2.4	1.0 (0.5–3.0)
Muffins or biscuits	1.1 ± 1.7	0.5 (0–1.0)	1.0 ± 2.4	0.45 (0–1.0)
Pasta	1.8 ± 1.4	1.0 (1.0–3.0)	1.9 ± 1.6	1.0 (1.0–3.0)
Sweets[4]	7.9 ± 9.1	5.0 (2.0–10.0)	6.0 ± 6.9	4.0 (2.0–7.5)
Other grains[5]	2.2 ± 1.7	1.5 (1.0–3.0)	1.9 ± 1.7	1.5 (1.0–2.5)
Total	22.0 ± 14.8	18 (11.5–29.0)	18.5 ± 11.7	15.0 (10.5–24.0)
Unspecified grains				
Crackers	2.9 ± 6.5	1.0 (0.5–3.0)	3.7 ± 7.7	1.0 (0.5–3.0)

[1] $\bar{x} \pm$ SD.
[2] Breakfast cereals with ≥ 25% whole-grain or bran content by weight were classified as whole grain, otherwise they were refined grain.
[3] Includes brown rice, bran, wheat germ, and other grains (eg, bulgur, kasha, and couscous).
[4] Includes cookies, brownies, doughnuts, cakes, sweet rolls, and pies.
[5] Includes white rice, pancakes, waffles, and pizza.

TABLE 2
Characteristics of the Framingham Offspring Study participants by quintiles of whole-grain intake[1]

	Whole-grain quintile categories					
	1 (n = 566)	2 (n = 595)	3 (n = 591)	4 (n = 593)	5 (n = 596)	P for trend
Whole-grain intake (servings/wk)						
Median	0.90	3.5	6.4	9.5	20.5	—
Range	0–1.5	1.9–4.4	4.5–7.5	7.9–12.9	13.0–64.0	—
Women (%)	48	52	59	58	55	0.06
Age (y)	54.4	53.2	52.9	53.9	55.6	<0.001
BMI (kg/m^2)	27.0	26.9	27.3	26.7	26.6	0.04
Waist-to-hip ratio	0.91	0.90	0.91	0.89	0.88	<0.001[2]
Waist circumference (in)	36.7	36.4	36.9	36.1	35.9	0.004
Lifestyle factors						
Current smoker						
(%)	30	25	18	13	11	<0.001
(cigarettes/d)	7	6	4	3	2	<0.001
Alcohol (% never drank)	29	26	27	21	26	0.39
Multivitamin use (%)	26	26	30	30	34	<0.001
Current estrogen use (%)[3]	15	14	15	19	21	0.01
Hypertension (%)	20	18	22	17	19	0.33
Undiagnosed diabetes (%)[4]	4	3	5	2	5	0.63
Physical activity score	35.0	35.2	34.8	34.6	34.9	0.50
Nutrients (daily intakes)						
Total energy (kJ)	6433.2	6904.7	7132.4	7708.9	8821.5	<0.001
Carbohydrate (% of total energy)	46.0	46.3	47.3	49.0	50.1	<0.001
PUFA (% of total energy)	5.7	5.8	5.8	5.8	6.1	<0.001
MUFA (% of total energy)	11.8	11.8	11.4	10.8	10.5	<0.001
SFA (% of total energy)	11.4	11.3	10.7	10.1	9.6	<0.001
Protein (% of total energy)	16.0	16.4	17.1	17.2	17.4	<0.001
Cholesterol (mg)	208.4	216.6	217.2	202.8	189.9	<0.001
Dietary fiber (g)	13.8	15.0	17.3	19.0	21.2	<0.001
Alcohol (g)	5.5	5.6	5.4	5.3	4.5	<0.001
Vitamin E without supplements (mg)	4.9	5.4	5.8	6.3	6.5	<0.001
Folate without supplements (μg)	239.7	248.9	285.3	316.7	325.4	<0.001
Magnesium (mg)	224.1	255.9	282.6	307.0	334.9	<0.001
Foods (servings/wk)						
Fruit[5]	6.8	7.2	8.6	9.9	10.9	<0.001
Vegetables[6]	17.1	18.2	20.3	21.7	23.2	<0.001
Meat[7]	6.2	6.0	5.8	5.1	4.2	<0.001
Fish[8]	1.8	2.1	2.3	2.5	2.6	<0.001
Refined grains	23.7	21.9	20.7	18.2	16.2	<0.001

[1] All lifestyle characteristics were adjusted for age and sex. Reported nutrient and food intakes were adjusted for age, sex, and total energy intake. Values are means unless indicated otherwise. PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.
[2] Remained significant after adjustment for BMI ($P < 0.001$).
[3] In women only.
[4] On the basis of plasma fasting glucose concentrations ≥ 7.0 mmol/L or 2-h glucose concentrations ≥ 11.1 mmol/L.
[5] Includes raisins, prunes, bananas, cantaloupe, watermelon, apples, pears, oranges, grapefruit, strawberries, blueberries, and peaches.
[6] Includes tomatoes, string beans, broccoli, cabbage, coleslaw, cauliflower, Brussels sprouts, raw carrots, cooked carrots, corn, peas, lima beans, mixed vegetables, beans, lentils, squash, yams (sweet potatoes), spinach, kale, lettuce, celery, beets, alfalfa sprouts, and potatoes.
[7] Includes bacon, hot dogs, processed meats, liver, hamburger, meat as a main dish, and meat in a sandwich or casserole.
[8] Includes tuna, dark fish, other fish, shellfish, and shrimp.

dietary fiber, polyunsaturated fatty acids, fruit, and vegetables. Favorable trends in lifestyle and dietary factors across quintile categories of whole-grain intake were significant for most factors. The intake of whole grains was positively associated with total intakes of dietary fiber ($r = 0.54$), magnesium ($r = 0.51$), folate ($r = 0.45$), vitamin E ($r = 0.40$), and vitamin B-6 ($r = 0.45$), which are important constituents of whole grains.

The median intake of refined-grain foods ranged from 6.9 to 38.9 servings/wk across quintile categories (**Table 3**). Associations between lifestyle and dietary factors were opposite to associations observed for whole grains for multivitamin and current estrogen use; percentage intakes of monounsaturated and saturated fatty acids; and intakes of protein, folate, magnesium, fruit, vegetables, and fish.

Multivariate-adjusted mean concentrations of metabolic risk factors across quintile categories of whole grain are shown in **Table 4**. After adjustment for potential confounding variables and dietary factors associated with diets high in whole grains, whole-grain intake was significantly inversely associated with WHR (mean difference: 0.1; P for trend < 0.005), LDL cholesterol (mean difference: 0.12 mmol/L; P for trend = 0.02), and fasting insulin (mean difference: 6 pmol/L; P for trend = 0.03). Marginally significant inverse associations remained between

TABLE 3
Characteristics of the Framingham Offspring Study participants by quintiles of refined-grain intake[1]

	Refined-grain quintile categories					
	1 (n = 586)	2 (n = 599)	3 (n = 580)	4 (n = 590)	5 (n = 586)	P for trend
Refined-grain intake (servings/wk)						
Median	6.9	11.8	16.7	23.6	38.9	—
Range	0–9.6	9.7–13.9	14.0–19.7	19.8–29.3	29.4–92.5	—
Women (%)	61	58	57	52	46	<0.001
Age (y)	54.6	54.3	53.0	54.1	54.2	0.78
BMI (kg/m^2)	26.9	26.8	26.9	27.0	26.8	0.79
Waist-to-hip ratio	0.90	0.90	0.90	0.90	0.90	0.55
Waist circumference (in)	36.4	36.2	36.5	36.5	36.5	0.42
Lifestyle factors						
Current smoker						
(%)	24	20	17	18	18	0.12
(cigarettes/d)	5	4	4	4	4	0.05
Alcohol (% never drank)	22	26	24	25	33	<0.001
Multivitamin use (%)	32	31	31	25	27	<0.001
Current estrogen use (%)[2]	20	17	15	17	13	0.04
Hypertension (%)	22	16	19	18	20	0.59
Undiagnosed diabetes (%)[3]	3	3	4	4	4	0.66
Physical activity score	34.3	34.5	34.6	34.4	34.4	0.93
Nutrients (daily intakes)						
Total energy (kJ)	7067.0	7336.7	7484.4	7466.7	7244.8	<0.001
Carbohydrate (% of total energy)	48.7	50.8	51.2	51.4	52.7	<0.001
PUFA (% of total energy)	5.6	5.7	5.8	6.0	6.2	<0.001
MUFA (% of total energy)	10.6	11.1	11.1	11.5	12.0	<0.001
SFA (% of total energy)	10.5	10.7	10.5	10.6	10.8	<0.001
Protein (% of total energy)	17.5	17.4	16.9	16.5	15.9	<0.001
Cholesterol (mg)	205	212	215	212	189	<0.001
Dietary fiber (g)	16.1	17.9	17.6	17.4	16.3	0.12
Alcohol (g)	8.3	5.6	5.6	4.9	3.1	<0.001
Vitamin E without supplements (mg)	5.4	6.0	6.0	5.9	5.5	0.43
Folate without supplements (μg)	279.2	293.8	293.2	281.0	260.0	<0.001
Magnesium (mg)	303.5	300.2	288.5	275.2	251.0	<0.001
Foods (servings/wk)						
Fruit[4]	9.6	10.1	9.0	8.3	6.6	<0.001
Vegetables[5]	22.3	22.0	21.0	19.3	15.9	<0.001
Meat[6]	5.6	5.6	5.4	5.5	5.2	0.19
Fish[7]	2.4	2.5	2.4	2.2	1.8	<0.001
Whole grains	11	10	9	8	5	<0.001

[1] All lifestyle characteristics were adjusted for age and sex. Reported nutrient and food intakes were adjusted for age, sex, and total energy intake. Values are means unless indicated otherwise. PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.
[2] In women only.
[3] On the basis of plasma fasting glucose concentrations ≥ 7.0 mmol/L or 2-h glucose concentrations ≥ 11.1 mmol/L.
[4] Includes raisins, prunes, bananas, cantaloupe, watermelon, apples, pears, oranges, grapefruit, strawberries, blueberries, and peaches.
[5] Includes tomatoes, string beans, broccoli, cabbage, coleslaw, cauliflower, Brussels sprouts, raw carrots, cooked carrots, corn, peas, lima beans, mixed vegetables, beans, lentils, squash, yams (sweeet potatoes), spinach, kale, lettuce, celery, beets, alfalfa sprouts, and potatoes.
[6] Includes bacon, hot dogs, processed meats, liver, hamburger, meat as a main dish, and meat in sandwich or casserole.
[7] Includes tuna, dark fish, other fish, shellfish, and shrimp.

whole-grain intake and BMI (mean difference: 0.5; P for trend = 0.06) and HDL-cholesterol (mean difference: 0.3 mmol/L; P for trend = 0.16), total cholesterol (mean difference: 0.11 mmol/L; P for trend = 0.06), and triacylglycerol concentrations (mean difference: 0.11 mmol/L; P for trend = 0.07) after adjustment for covariates. The inverse associations between whole-grain intake, systolic blood pressure, diastolic blood pressure, fasting glucose, and 2-h insulin were attenuated after BMI was controlled for (model 2). There was no association between whole-grain intake and Hb A_{1c} or 2-h postchallenge glucose concentrations.

To better understand the association between whole-grain intakes and risk factors related to nutrients found in whole grains, we individually adjusted metabolic risk factors that were significant in model 3 for potential mediating nutrients, including fiber, folate, magnesium, vitamin E, and vitamin B-6 (data not shown). The association between whole-grain intake and both WHR and LDL cholesterol was not attenuated after adjustment for these nutrients and the covariates in model 2. The association between whole-grain intake and fasting insulin (207 and 198 pmol/L for the highest compared with the lowest quintile category, respectively; P = 0.002) was attenuated after adjustment for intake of magnesium (206 and 202 pmol/L, respectively; P = 0.30) or dietary fiber (205 and 201 pmol/L, respectively; P = 0.16). When fiber was separated into soluble and insoluble fiber, the inverse association between fasting insulin and whole-grain intake was

TABLE 4
Metabolic risk factors by quintile of whole-grain intake[1]

	Whole-grain quintile categories					
	1 (n = 566)	2 (n = 595)	3 (n = 591)	4 (n = 593)	5 (n = 596)	P for trend
BMI						
Model 1 (n = 2941)	27.0	26.8	27.1	26.4	26.3	0.003
Model 3 (n = 2941)	26.9	26.6	27.0	26.5	26.4	0.06
Waist-to-hip ratio						
Model 1 (n = 2941)	0.92	0.91	0.92	0.91	0.90	<0.001
Model 2 (n = 2941)	0.92	0.91	0.92	0.91	0.90	<0.001
Model 3 (n = 2941)	0.92	0.92	0.92	0.91	0.91	0.005
Systolic blood pressure (mm HG)[2]						
Model 1 (n = 2480)	124.5	123.0	123.4	122.0	122.2	0.07
Model 2 (n = 2480)	124.4	123.2	123.3	122.5	123.1	0.38
Diastolic blood pressure (mm HG)[2]						
Model 1 (n = 2480)	74.5	74.1	74.5	74.1	73.1	0.02
Model 2 (n = 2480)	75.6	74.4	74.6	74.7	73.8	0.19
Total cholesterol (mmol/L)						
Model 1 (n = 2941)[3]	5.21	5.14	5.25	5.18	5.08	0.02
Model 2 (n = 2941)[3]	5.20	5.15	5.24	5.19	5.09	0.03
Model 3 (n = 2941)[3]	5.20	5.14	5.24	5.18	5.09	0.06
HDL cholesterol (mmol/L)						
Model 1 (n = 2941)[3]	1.19	1.21	1.20	1.18	1.24	0.02
Model 2 (n = 2941)[3]	1.20	1.20	1.21	1.19	1.23	0.05
Model 3 (n = 2941)[3]	1.20	1.21	1.21	1.18	1.23	0.16
LDL cholesterol (mmol/L)						
Model 1 (n = 2879)[3]	3.17	3.14	3.22	3.17	3.04	0.006
Model 2 (n = 2879)[3]	3.17	3.14	3.21	3.17	3.04	0.008
Model 3 (n = 2879)[3]	3.16	3.13	3.21	3.16	3.04	0.02
Triacylglycerol (mmol/L)						
Model 1 (n = 2941)[3]	1.70	1.60	1.61	1.66	1.56	0.02
Model 2 (n = 2941)[3]	1.69	1.61	1.64	1.68	1.58	0.07
Fasting glucose (mmol/L)						
Model 1 (n = 2748)	5.32	5.24	5.30	5.23	5.22	0.05
Model 2 (n = 2748)	5.30	5.24	5.29	5.24	5.24	0.24
2-h Glucose (mmol/L)						
Model 1 (n = 2748)	5.88	5.74	5.94	5.63	5.78	0.36
Model 2 (n = 2748)	5.84	5.75	5.91	5.65	5.82	0.87
Fasting insulin (pmol/L)[4]						
Model 1 (n = 2747)	210	209	204	197	195	0.001
Model 2 (n = 2747)	207	209	201	198	198	0.002
Model 3 (n = 2747)	205	207	200	198	199	0.03
2-h Insulin (pmol/L)						
Model 1 (n = 2747)	605	596	588	555	561	0.02
Model 2 (n = 2747)	592	595	575	557	568	0.16
Glycated hemoglobin (%)						
Model 1 (n = 2099)	5.27	5.31	5.23	5.27	5.24	0.99
Model 2 (n = 2099)	5.26	5.29	5.22	5.28	5.24	0.63

[1] Model 1: adjusted for age, sex, energy intake, treatment of hypertension, smoking, alcohol intake, multivitamin use, estrogen use, and physical activity; model 2: model 1 with additional adjustment for BMI; model 3: model 2 with additional adjustment for percentage of polyunsaturated fatty acids and intakes of meat, fish, fruit, and vegetables.
[2] Excluded those taking blood pressure medication.
[3] Also adjusted for the percentage of saturated fatty acids.
[4] Converted from μU/mL to pmol/L by multiplyig by 7.175.

attenuated after insoluble, rather than soluble fiber, was included in the model.

Because insulin concentrations may mediate the association between whole-grain intake and total or regional adiposity, we further adjusted estimates of these characteristics for concentrations of fasting insulin. Adjustment for fasting insulin concentrations attenuated the association between BMI and whole-grain intake (BMI: 26.9 in lowest quintile category and 26.6 in the highest quintile category; P for trend = 0.38), but did not change the association between whole-grain intake and WHR. Fasting insulin did not attenuate the association between whole-grain intake and total or LDL cholesterol (data not shown). To further explore the association between BMI and insulin, an interaction term for BMI by whole-grain intake was included in the model 2. Because this interaction was significant (P = 0.02) for insulin concentrations, the relation between whole-grain intake and insulin was stratified by BMI, as shown in **Figure 1**. This inverse association between whole-grain intake and fasting insulin was much stronger for those

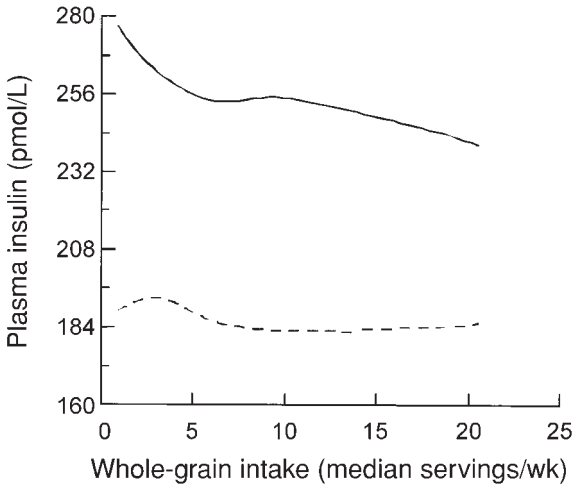

FIGURE 1. Association between whole-grain intake and fasting plasma insulin concentrations by BMI: BMI < 30 (- - - -; n = 2123) and BMI ≥ 30 (——; *n* = 624). Values were adjusted for age, sex, energy intake, treatment of hypertension, smoking, alcohol intake, multivitamin use, current estrogen replacement therapy, physical activity, and BMI. *P* for trend = 0.10 for BMI < 30 and 0.003 for BMI ≥ 30; *P* = 0.02 for the interaction between BMI and whole-grain intake.

with a higher BMI (≥30; *P* for trend = 0.003) than for those with a lower BMI (<30; *P* for trend = 0.10).

We also examined the relation between mean concentrations of these metabolic risk factors and intakes of refined grains (data not shown). In contrast with whole-grain intakes, there were no significant trends across quintile categories of refined-grain intake for these risk factors, except for Hb A_{1c}. After adjustment for potential confounders, mean Hb A_{1c} (%) values in the lowest to highest intake categories of refined grains were 5.4, 5.4, 5.3, 5.4, and 5.3 (*P* for trend = 0.05).

DISCUSSION

In the current study, we examined associations between diets rich in whole-grain or refined-grain foods in relation to several metabolic risk factors for cardiovascular disease or type 2 diabetes. We found favorable associations between whole-grain intake and WHR and total cholesterol, LDL-cholesterol, and fasting insulin concentrations. In contrast, refined-grain intake was not related to concentrations of these metabolic risk factors.

Although the risk of both cardiovascular disease and type 2 diabetes is mediated in part by tissue sensitivity to the effects of insulin (44), relatively few epidemiologic studies have examined the association of whole-grain intake and insulin sensitivity (45). In the current study, fasting insulin concentrations were lower in those with a higher intake of whole-grain foods, after control for BMI and other potential confounders. The association between whole-grain intake and insulin was most striking among obese subjects, such that the highest fasting insulin concentrations were among those subjects with higher BMIs and lower intakes of whole grains. Other studies have shown that insulin resistance is higher among obese persons (46). A recent crossover study involving 11 overweight hyperinsulinemic subjects found that insulin sensitivity, as measured by the euglycemic hyperinsulinemic clamp, improved more after 6 wk of a whole-grain diet than after a refined-grain diet, independent of body weight (47). Other studies found that diets rich in whole-grains foods are associated with lower insulin concentrations (45, 48).

However, consistent with other findings (45), we found that the association between whole-grain intake and fasting insulin concentrations was attenuated after adjustment for dietary fiber and magnesium. This suggests that the apparent insulin-sensitizing effect of whole grains might be partially mediated by the effect of these nutrients.

Improved insulin sensitivity with elevated fiber intake may be one mechanism whereby diets rich in whole-grain foods may protect against the development of type 2 diabetes. Fiber has been shown to improve the glycemic response and circulating insulin concentrations both in healthy subjects and in those with type 2 diabetes (17, 49–51). Fiber intake is not only inversely associated with fasting insulin (52), but insoluble and cereal fiber intakes significantly reduce the risk of type 2 diabetes (8, 20, 21). The improved insulin sensitivity with high-fiber diets may occur because the gel-forming properties of soluble fibers delays the rate of carbohydrate absorption (53). However, in the current study, it appears that insoluble cereal fiber rather than soluble fiber was the predominant fiber having a favorable effect on fasting insulin. Magnesium is another component in whole grains that may improve insulin sensitivity. Intracellular magnesium has also been linked to insulin sensitivity in metabolic studies (54, 55), and clinical studies have shown that supplementation with magnesium improves insulin sensitivity (56, 57). Furthermore, an inverse association between dietary and serum magnesium and incidence of type 2 diabetes is supported by some epidemiologic data (8, 20, 58).

It is possible that the protective mechanism of whole grains can be attributed to yet additional components in whole grains. Liu et al (9) found that although fiber and magnesium intakes attenuate the association between whole-grain intake and the risk of type 2 diabetes, this observation was not entirely explained by either component. Hence, in addition to the previously discussed roles of nutrients, a low glycemic index and a greater particle size of most whole-grain products compared with refined-grain products (59) may have a beneficial effect on risk factors for cardiovascular disease (60).

Evidence from epidemiologic studies also suggests that refined-grain intake is not associated with fasting insulin concentrations (45) or an increased incidence of type 2 diabetes (8). On the other hand, a high intake of refined grain relative to whole grain has been related to an increased risk of type 2 diabetes (9). In the current study, refined-grain intake appeared to be unrelated to concentrations of fasting insulin; however, there was an unexplained weak inverse association with refined-grain intake on concentrations of Hb A_{1c}.

Consistent with the results of earlier epidemiologic studies (7, 45), we found that whole-grain but not refined-grain intake was inversely association with body weight and fat distribution. The inherent high-fiber content of most whole-grain foods may prevent weight gain or promote weight loss (52, 61, 62). Metabolic studies suggest that high-fiber diets help control appetite by providing a longer feeling of satiety (63, 64). After adjustment for other factors associated with diets rich in whole grains, such as fruit and vegetable consumption, the inverse association between whole-grain intake and BMI was only marginally significant, perhaps suggesting that the association with BMI may have been attributable in part to an overall healthier lifestyle. However, the

association between whole-grain intake and BMI was substantially attenuated after adjustment for insulin, which may suggest that insulin is a potential mediator in the causal pathway.

It is well documented that a reduction in total and LDL cholesterol and an increase in HDL cholesterol is associated with a decrease in the risk of future coronary events (65–68). Randomized clinical trials (24) and metabolic studies (23) have shown that oats and oat bran reduce total blood cholesterol. Moreover, rye bread, which is considered a whole-grain food, has been shown to reduce total cholesterol concentrations in moderately hypercholesterolemic men, whereas refined wheat bread had no favorable effect on cholesterol concentrations (69). In the current study, total cholesterol and LDL concentrations were lower in the highest quintile category of whole-grain intake. Although the association between total cholesterol and whole-grain intake was largely attributed to dietary fiber and other dietary factors associated with a healthier lifestyle, whole-grain intake remained inversely association with LDL cholesterol, independent of both dietary fiber and saturated fat intakes.

Methodologic issues in our study may have accounted for the presence or absence of associations between grain intake and intermediate metabolic markers. Because of the fixed food categories associated with the FFQ, it is difficult to separate whole- and refined-grain foods accurately from some foods. For example, dark breads such as pumpernickel or wheat bread may include breads made with refined-grain flour. Yet, despite this potential measurement error in exposure, which would tend to attenuate associations, we found significant associations between whole-grain intake and concentrations of several biomarkers of disease risk. Additionally, diets rich in whole-grain foods appear to reflect an overall healthier lifestyle that may not have been accurately captured and controlled in our analysis, resulting in residual confounding. Nevertheless, our data suggest that whole-grain diets are associated with favorable effects on several metabolic risk factors. Thus, an improvement in the global metabolic milieu may be one mechanism whereby whole-grain intake may reduce the risk of type 2 diabetes and cardiovascular disease.

REFERENCES

1. Rimm EB, Willett WC, Hu FB, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. JAMA 1998;279:359–64.
2. Wolk A, Manson JE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. JAMA 1999;281:1998–2004.
3. US Department of Agriculture. Nutrition and your health: dietary guidelines for Americans. Washington, DC: US Government Printing Office, 2000.
4. Cleveland LE, Moshfegh AJ, Albertson AM, Goldman JD. Dietary intake of whole grains. J Am Coll Nutr 2000;19:331S–8S.
5. Slavin JL, Jacobs D, Marquart L. Grain processing and nutrition. Crit Rev Food Sci Nutr 2000;40:309–26.
6. FDA. Food standards: amendment of the standards of identity for enriched grain products to require addition of folic acid. Final rule. Fed Regist 1996;61:8781–97.
7. Jacobs DR Jr, 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.
8. 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 2000;71:921–30.
9. Liu S, Manson JE, Stampfer MJ, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. Am J Public Health 2000;90:1409–15.
10. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999;70:412–9.
11. 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. Am J Public Health 1999;89:322–9.
12. 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.
13. Jacobs DR Jr, Marquart L, Slavin J, Kushi LH. Whole-grain intake and cancer: an expanded review and meta-analysis. Nutr Cancer 1998;30:85–96.
14. Levi F, Pasche C, Lucchini F, Chatenoud L, Jacobs DR Jr, La Vecchia C. Refined and whole grain cereals and the risk of oral, oesophageal and laryngeal cancer. Eur J Clin Nutr 2000;54:487–9.
15. Slavin JL, Martini MC, Jacobs DR Jr, Marquart L. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr 1999; 70(suppl):459S–63S.
16. Anderson JW, Hanna TJ. Impact of nondigestible carbohydrates on serum lipoproteins and risk for cardiovascular disease. J Nutr 1999; 129(suppl):1457S–66S.
17. 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. N Engl J Med 2000;342:1392–8.
18. Manolio TA, Savage PJ, Burke GL, et al. Correlates of fasting insulin levels in young adults: the CARDIA study. J Clin Epidemiol 1991; 44:571–8.
19. Ma J, Folsom AR, Melnick SL, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol 1995; 48:927–40.
20. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545–50.
21. 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 1997;277:472–7.
22. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 1993;328:1444–9.
23. Ripsin CM, Keenan JM, Jacobs DR Jr, et al. Oat products and lipid lowering. A meta-analysis. JAMA 1992;267:3317–25.
24. Johnston L, Reynolds HR, Patz M, Hunninghake DB, Schultz K, Westereng B. Cholesterol-lowering benefits of a whole grain oat ready-to-eat cereal. Nutr Clin Care 1998;1:6–12.
25. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336:1117–24.
26. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001;344:3–10.
27. Jenkins DJ, Axelsen M, Kendall CW, Augustin LS, Vuksan V, Smith U. Dietary fibre, lente carbohydrates and the insulin-resistant diseases. Br J Nutr 2000;83(suppl):S157–63.
28. Dawber T, Meadors G, Moore FJ. Epidemiological approaches to heart disease: The Framingham Study. Am J Public Health 1951;41: 279–86.
29. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med 1975;4:518–25.
30. 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, 1127–36.
31. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
32. 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.
33. Kuczmarski RJ, Carroll MD, Flegal KM, Troiano RP. Varying body mass index cutoff points to describe overweight prevalence among U.S. adults: NHANES III (1988 to 1994). Obes Res 1997;5:542–8.
34. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. Obes Res 1998;6:51S–209S
35. WHO Expert Committee on Diabetes Mellitus. Second report. World Health Organ Tech Rep Ser 1980;646.
36. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–97.
37. Koenig RJ, Cerami A. Hemoglobin A_{1c} and diabetes mellitus. Annu Rev Med 1980;31:29–34.
38. McNamara JR, Schaefer EJ. Automated enzymatic standardized lipid analyses for plasma and lipoprotein fractions. Clin Chim Acta 1987; 166:1–8.
39. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-$Mg2^{+}$ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem 1982;28:1379–88.
40. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
41. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154–83.
42. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. Arch Intern Med 1979;139:857–61.
43. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979;74:829–36.
44. Haffner SM, Miettinen H. Insulin resistance implications for type II diabetes mellitus and coronary heart disease. Am J Med 1997;103: 152–62.
45. Pereira MA, Jacobs DR, Slattery ML, et al. The association of whole grain intake and fasting insulin in a biracial cohort of young adults: The CARDIA Study. CVD Prev 1998;1:231–42.
46. Folsom AR, Jacobs DR Jr, Wagenknecht LE, et al. Increase in fasting insulin and glucose over seven years with increasing weight and inactivity of young adults. The CARDIA Study. Coronary Artery Risk Development in Young Adults. Am J Epidemiol 1996;144:235–46.
47. Pereira MA, Jacobs DR Jr, Pins JJ, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr J 2002;75:848–55.
48. Fung TT, Rimm EB, Spiegelman D, et al. Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001;73:61–7.
49. Anderson JW, Zeigler JA, Deakins DA, et al. Metabolic effects of high-carbohydrate, high-fiber diets for insulin-dependent diabetic individuals. Am J Clin Nutr 1991;54:936–43.
50. Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr 1990; 52:524–8.
51. Hallfrisch J, Scholfield DJ, Behall KM. Diets containing soluble oat extracts improve glucose and insulin responses of moderately hypercholesterolemic men and women. Am J Clin Nutr 1995;61: 379–84.
52. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. JAMA 1999;282:1539–46.
53. Anderson JW, Smith BM, Gustafson NJ. Health benefits and practical aspects of high-fiber diets. Am J Clin Nutr 1994;59(suppl): 1242S–7S.
54. Resnick LM, Barbagallo M, Gupta RK, Laragh JH. Ionic basis of hypertension in diabetes mellitus. Role of hyperglycemia. Am J Hypertens 1993;6:413–7.
55. Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. Diabetologia 1990;33:511–4.
56. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. Diabetes Care 1989; 12:265–9.
57. Paolisso G, Sgambato S, Gambardella A, et al. Daily magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr 1992;55:1161–7.
58. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med 1999;159:2151–9.
59. Foster-Powell K, Miller JB. International tables of glycemic index. Am J Clin Nutr 1995;62(suppl):871S–90S.
60. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455–61.
61. Rolls BJ. Carbohydrates, fats, and satiety. Am J Clin Nutr 1995; 61(suppl):960S–7S.
62. Levine AS, Billington CJ. Dietary fiber: does it affect food intake and body weight ? In: Fernstrom JD, Miller GD, eds. Appetite and body weight regulation; sugar, fat and macronutrient substitutes. Boca Raton, FL: CRC Press Inc, 1994:191–200.
63. Porikos K, Hagamen S. Is fiber satiating? Effects of a high fiber preload on subsequent food intake of normal-weight and obese young men. Appetite 1986;7:153–62.
64. Blundell JE, Burley VJ. Satiation, satiety and the action of fibre on food intake. Int J Obes 1987;11:9–25.
65. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351–64.
66. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365–74.
67. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8–15.
68. Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis 1996;124(suppl):S1–9.
69. Leinonen KS, Poutanen KS, Mykkanen HM. Rye bread decreases serum total and LDL cholesterol in men with moderately elevated serum cholesterol. J Nutr 2000;130:164–70.

The American Journal of Clinical Nutrition