Consumption of whole grain reduces risk of deteriorating glucose tolerance, including progression to prediabetes[1–3]

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ABSTRACT

Background: High whole-grain intake has been reportedly associated with reduced risk of developing type 2 diabetes (T2D), which is an effect possibly subject to genetic effect modification. Confirmation in prospective studies and investigations on the impact on prediabetes is needed.

Objectives: In a prospective population-based study, we investigated whether a higher intake of whole grain protects against the development of prediabetes and T2D and tested for modulation by polymorphisms of the *TCF7L2* gene.

Design: We examined the 8–10-y incidence of prediabetes (impaired glucose tolerance, impaired fasting glucose, or the combination of both) and T2D in relation to the intake of whole grain. Baseline data were available for 3180 women and 2297 men aged 35–56 y.

Results: A higher intake of whole grain (>59.1 compared with <30.6 g/d) was associated with a 34% lower risk to deteriorate in glucose tolerance (to prediabetes or T2D; women and men combined). The association remained after adjustments for age, family history of diabetes, BMI, physical activity, smoking, education, and blood pressure (OR: 0.78; 95% CI: 0.63, 0.96). Risk reduction was significant in men (OR: 0.65; 95% CI: 0.49, 0.85) but not in women. Associations were significant for prediabetes per se (all, OR: 0.73; 95% CI: 0.56, 0.94; men, OR: 0.57; 95% CI: 0.40, 0.80). The intake of whole grain correlated inversely with insulin resistance (HOMA-IR). The impact of whole-grain intake was undetectable in men who harbored diabetogenic polymorphisms of the *TCF7L2* gene.

Conclusions: A higher intake of whole grain is associated with decreased risk of deteriorating glucose tolerance including progression from normal glucose tolerance to prediabetes by mechanisms likely tied to effects on insulin sensitivity. Effect modifications by *TCF7L2* genetic polymorphisms are supported. *Am J Clin Nutr* doi: 10.3945/ajcn.112.045583.

INTRODUCTION

The influence of diet on the development of type 2 diabetes (T2D)[4] has been intensively studied. Several studies have shown that a diet rich in fibers and, in particular, whole grain is associated with a reduced incidence of T2D (1–3). On the basis of these findings, a high-fiber and whole-grain intake has been recommended (4–6). However, whether intakes of fiber and whole grain affect the induction of prediabetic states, as defined by impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG), has not been assessed. Furthermore, although cross-sectional studies have implied that protective influences on T2D are mediated by the enhancement of insulin sensitivity (7–9), this effect needs to be documented in prospective studies.

The Stockholm Diabetes Prevention Program is a population-based prospective study (10). A previously validated (11) food-frequency questionnaire (FFQ), including dietary information that focused on fiber, was collected at baseline and follow-up, which made possible a separate assessment of the intake of whole grain. Data on glucose and insulin concentrations were available as part of an oral-glucose-tolerance test (OGTT).

The *TCF7L2* gene is a major susceptibility locus for T2D (12, 13). Conflicting results on associations between whole-grain intake and polymorphisms of *TCF7L2* have been reported (14, 15).

Our aims were to test for an association between the intake of whole grain and development of T2D and prediabetes and to compare these associations with those of cereal fiber. In addition, associations were tested with insulin resistance by using HOMA-IR and with insulin secretion by using HOMA of β cell function (HOMA-β) as well as insulin responses to OGTT. In a subgroup of the study sample who had genotyping data on *TCF7L2*, possible modifications of associations between the intake of whole grain or cereal fiber and development of T2D were tested.

SUBJECTS AND METHODS

Study design and subjects

The design of this prospective population-based cohort study has been previously described (10) (*see* Figure S1 under "Sup-

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[4] Abbreviations used: FHD, family history of diabetes; FFQ, food-frequency questionnaire; HOMA-β, homeostasis model assessment of β cell function; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; insulin-response$_{(2h-0h)}$, difference between 2- and 0-h insulin values measured during the oral-glucose-tolerance test; NGT, normal glucose tolerance; OGTT, oral-glucose-tolerance test; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes.

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plemental data" in the online issue for a flowchart of the study design). In brief, women and men aged 35–56 y and without known diabetes were enrolled for a baseline investigation between the years 1992 and 1998. By study design, the baseline sample was enriched to ~50% by subjects who had a family history of diabetes (FHD), which was defined as known diabetes in at least one first-degree relative or at least 2 second-degree relatives. Subjects without FHD had no close relative with known diabetes. A follow-up study was performed 8 (for women) to 10 (for men) years later. All subjects in the baseline sample were invited to participate, except subjects who were diagnosed with T2D at baseline or who had moved out of the Stockholm area. A health examination, including measurements of weight, height, blood pressure, and an OGTT, was performed both at baseline and follow-up. Subjects filled out a questionnaire on lifestyle factors (such as smoking, alcohol intake, physical activity, and social economic status) as well as an FFQ.

Our study included all subjects who had complete data on the FFQ as well as on potential confounders. Two partly different samples were analyzed. Our main analysis (sample 1) included all subjects who participated in the follow-up study who had either normal glucose tolerance (NGT) or prediabetes (IGT or IFG or a combination of both) at baseline (3180 women and 2297 men). Cases were subjects with deteriorated glucose tolerance at follow-up—from NGT at baseline to either prediabetes or T2D or from prediabetes to T2D (272 women and 429 men). Control subjects were all other subjects (2908 women and 1868 men) (*see* Figure S1 under "Supplemental data" in the online issue).

Because OGTT was performed also at baseline, we could separately analyze the development of prediabetes and T2D from subjects who displayed NGT at baseline. Thus the second sample (sample 2) was a subgroup of the first sample. Cases in the second sample were subjects who progressed to either prediabetes (174 women and 250 men) or T2D (57 women and 108 men), whereas control subjects were individuals who displayed NGT at both baseline and follow-up (2831 women and 1786 men) (*see* Figure S1 under "Supplemental data" in the online issue).

For analysis of the *TCF7L2* gene variants rs7903146 and rs4506565, we used genotyping data from a subgroup of the first sample (16). The subgroup comprised only men. Cases were subjects who, from NGT or prediabetes at baseline, developed T2D at follow-up (n = 178). Control subjects displayed NGT at both baseline and follow-up (n = 505).

All subjects gave informed consent to participate in the study. The study was approved by the Ethics Committee of Karolinska University Hospital. The initial recruitment date was 18 March 1992.

Calculation of intakes of whole grain and fiber from cereals

The FFQ was previously validated by a 7-d weighed dietary record in middle-aged men (11). Results from the FFQ and the 7-d weighed record corresponded well with regard to the mean daily intake of fiber and the classification of individuals into quintiles (11). It was concluded that the questionnaire assessed the total intake of fiber with good precision. Furthermore, the mean intake of total fiber in men (17.9 g/d) that was estimated in the current study corresponded well with both the FFQ-validation study (11) and the most-recent national food-data survey in Sweden (17). The 8 frequency response options were as follows: ≥4, 2–3, or 1 time/d, 4–6, 2–3, or 1 time/wk, 1–3 times/mo, and seldom or never. We used the food database (http://www7.slv.se/Naringssok/; version 2011–07-18) of the Swedish National Food Agency and a standard portion size or serving of the food items to assess the total intake of fiber in grams per day. In the current study, we assessed the intake of fiber from cereals [crisp bread, oatmeal, whole-meal bread, rye bread, muesli, wheat bread, rice, buns (sweet rolls), and pasta]. The FFQ was purposely limited to assess intakes of fiber and fat. Therefore, we could not calculate the total energy intake.

Because the food database gives data on whole-grain content, we were able to calculate the intake of whole grain. Whole-grain food is defined in Sweden as food that contains ≥50% of whole grain on a dry-matter basis (18). In these calculations, we included all food items that contained ≥50% of whole grain per serving (ie, crisp bread, whole-meal bread, oatmeal, and muesli).

From FFQ data at follow-up, we were able to evaluate whether intakes of cereal fiber and whole grain varied over time. Calculations from follow-up data were performed in the same way as for baseline data.

HOMA and insulin secretion

Homeostatic model assessment (19) was used to assess insulin resistance (HOMA-IR) according to the equation

$$[(\text{Fasting insulin} \times \text{fasting glucose}) \div 22.5] \qquad (1)$$

Insulin secretion was estimated in the basal (unstimulated) state as β cell function (HOMA-β) calculated as

$$[(\text{Fasting insulin} \times 20) \div (\text{fasting glucose} - 3.5)] \qquad (2)$$

Data also allowed us to assess the insulin response dynamically (ie, as the difference between 2- and 0-h insulin values measured during the OGTT [insulin-response$_{(2h-0h)}$].

Classification of T2D and prediabetes

An OGTT was performed at baseline and follow-up according to WHO criteria (20). Prediabetes was defined as subjects who presented with IGT or IFG or both. Subjects classified as T2D at follow-up were subjects diagnosed at the follow-up examination as well as subjects diagnosed during the period between baseline and follow-up.

Classification of established diabetes risk factors and potential confounders

FHD was dichotomized as either positive or negative. BMI (in kg/m^2) was used as a continuous variable. Physical activity was assessed on the basis of answers to the question on physical activity during leisure hours. Physical activity was categorized into 3 groups as low (sedentary), middle (moderate activity), and high (regular exercise and training) physical activity. Smoking was categorized in to 3 groups as never, former, and current smoker. Education was categorized into 3 groups as low (elementary school), middle (senior high school and technical and

vocational school), and high (university) education. Hypertension was categorized as yes in subjects who had systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or on antihypertensive treatment and as no in subjects who had blood pressure <140/90 mm Hg and no treatment of hypertension. For analysis, baseline values of all potential confounders were used.

Assays

Plasma glucose, immunoreactive insulin, and proinsulin were assayed as in Grill et al (21).

Statistical methods

Data are given as means and 95% CIs or numbers (proportions). Comparisons of continuous variables were performed by using am unpaired *t* test or 1-factor ANOVA for independent groups and a chi-square test for categorical variables. The paired *t* test was used to compare 2 dependent groups. ORs together with 95% CIs were calculated by using a multiple logistic regression analysis. Intakes of whole grain and cereal fiber were categorized into tertiles according to the distribution in all included subjects or as continuous variables reported as an increase by 30 g/d (whole grain) or 5 g/d (cereal fiber). Analyses are reported primarily for all subjects but secondarily also for men and women separately. When increasing categories of whole grain or cereal fiber were used in the logistic regression analyses, tests for linear trend were conducted by assigning median values within each tertile of whole grain or cereal fiber and used as a continuous variable. For genotype associations, both additive and dominant models were used. Multiplicative product terms were included in the logistic regression models when interactions between genotype and intake of whole grain or cereal fiber were evaluated. Differences between models with and without a product term were evaluated by using the log-likelihood ratio test. Linear regression analysis was used to evaluate associations between the intake of whole grain or cereal fiber and HOMA-IR, HOMA-β, insulin-response$_{(2h-0h)}$, or proinsulin. These variables were log transformed to improve skewness. $P < 0.05$ was considered significant. The analyses were performed with SAS Statistical Program version 9.2 (SAS Institute).

RESULTS

Progression to prediabetes and T2D

At follow-up, 701 of 5477 subjects (12.8%) had deteriorated in glucose tolerance from NGT at baseline to either prediabetes (n = 424) or T2D (n = 165) or from prediabetes at baseline to T2D (n = 112). The frequency of deterioration was higher in men (18.7%; 429 of 2297) than in women (8.6%; 272 of 3180).

Baseline characteristics

In the totality of subjects, a low intake of whole grain was more common in younger than in older subjects and in men than in women (**Table 1**). A sedentary lifestyle, current smoking, higher BMI, and lower education were more likely traits in subjects with a low intake of whole grain. Glucose tolerance, FHD, and frequency of hypertension did not differ according to the intake of whole grain. Associations were similar for the intake of cereal fiber (lowest tertile) except that no sex difference was observed (*see* Table S1 under "Supplemental data" in the online issue).

Crisp bread (made mostly from rye) dominated the intake of whole grain in both women and men (44% of the total intake in women; 50% of the total intake in men).

Association between baseline consumption of whole grain and cereal fiber and abnormal glucose tolerance at follow-up

We first analyzed subjects who had deteriorated in glucose tolerance from NGT to prediabetes or T2D or from prediabetes to T2D (sample 1). Intakes in the highest compared with lowest tertiles of both whole grain and cereal fiber were associated with decreased risk of deterioration when adjusted for age and sex (model 1; OR: 0.66; 95% CI: 0.54, 0.80) for whole grain (**Table 2**) and for cereal fiber (OR: 0.75; 95% CI: 0.62, 0.92) (*see* Table S2 under "Supplemental data" in the online issue). When additional confounders were adjusted for (model 2) the association was still significant for whole grain (OR: 0.78; 95% CI: 0.63, 0.96) but not for cereal fiber. We also performed an analysis exclusively in subjects who displayed NGT at baseline (sample 2). The intake of whole grain in the highest tertile decreased risk of developing prediabetes or T2D by 38% and after full adjustment (OR: 0.74; 95% CI: 0.59, 0.92; Table 2). The association was significant for prediabetes per se (27% decreased risk after full adjustment; $P = 0.017$; Table 2). ORs for T2D were similar to prediabetes, but significance was lost after full adjustment. Similar but weaker associations were shown for the intake of cereal fiber (*see* Table S2 under "Supplemental data" in the online issue). Associations between intakes of whole grain (Table 2) and cereal fiber (*see* Table S2 under "Supplemental data" in the online issue) and deteriorating glucose tolerance were stronger for men than women. For whole grain, risk to progress from NGT to prediabetes was decreased by 43% in men (OR: 0.57; 95% CI: 0.40, 0.80) after adjustments (corresponding data for women, OR: 1.03; 95% CI: 0.69, 1.53) (Table 2). However, a formal interaction between sex and whole-grain intake could not be documented by significance testing (P-interaction = 0.09).

Regarding whole-grain intake, we performed additional analyses to evaluate the impact of BMI and cereal fiber in both samples 1 and 2. Associations between whole-grain intake and abnormal glucose tolerance were estimated in a model including age, FHD, physical activity, smoking, education, blood pressure, and sex, if appropriate (data not shown). The addition of BMI to this model (which, thus, resulted in model 2) did not substantially change the already adjusted estimates. To evaluate the impact of cereal fiber in analyses on whole grain, cereal fiber was added to the multiadjusted model (model 2). However, the already-adjusted estimates were not substantially changed (data not shown).

To sum up, higher intake of whole grain carried decreased risk of deteriorating glucose tolerance, especially progression from NGT to prediabetes. A similar but less-strong association was seen with higher fiber intake from cereals. The associations were markedly stronger in men than in women (Table 2; *see* Table S2 under "Supplemental data" in the online issue).

TABLE 1
Baseline characteristics according to intake of whole grain (g/d)[1]

	All subjects				Cases				Control subjects			
	Whole grain (g/d)				Whole grain (g/d)				Whole grain (g/d)			
	<30.6	30.6–59.1	>59.1	*P*	<30.6	30.6–59.1	>59.1	*P*	<30.6	30.6–59.1	>59.1	*P*
n	1830	1809	1838		297	193	211		1533	1616	1627	
Age (y)	46.8 (46.6, 47.1)[2]	47.1 (46.9, 47.3)	47.6 (47.4, 47.8)	<0.001	47.8 (47.3, 48.3)	47.9 (47.2, 48.5)	49.0 (48.3, 49.5)	0.013	46.7 (46.4, 46.9)	47.0 (46.8, 47.2)	47.4 (47.2, 47.6)	<0.001
Sex				<0.001				0.004				<0.001
F	984 (53.8)	1135 (62.7)	1061 (57.7)		94 (31.7)	85 (44.0)	93 (44.1)		890 (58.1)	1050 (65.0)	968 (59.5)	
M	846 (46.2)	674 (37.3)	777 (42.3)		203 (68.3)	108 (56.0)	118 (55.9)		643 (41.9)	566 (35.0)	659 (40.5)	
Glucose tolerance at baseline				0.533				0.364				0.374
Normal	1731 (94.6)	1723 (95.2)	1752 (95.3)		254 (85.5)	164 (85.0)	171 (81.0)		1477 (96.4)	1559 (96.5)	1581 (97.2)	
Prediabetes	99 (5.4)	86 (4.8)	86 (4.7)		43 (14.5)	29 (15.0)	40 (19.0)		56 (3.7)	57 (3.6)	46 (2.8)	
Family history of diabetes				0.394				0.927				0.779
No	847 (46.3)	874 (48.3)	885 (48.2)		93 (31.3)	60 (31.1)	69 (32.7)		754 (49.2)	814 (50.4)	816 (50.2)	
Yes	983 (53.7)	935 (51.7)	953 (51.8)		204 (68.7)	133 (68.9)	142 (67.3)		779 (50.8)	802 (49.6)	811 (49.8)	
BMI				<0.001				0.874				<0.001
<25.0 kg/m^2	819 (44.8)	896 (49.5)	975 (53.0)		64 (21.6)	41 (21.2)	50 (23.7)		755 (49.3)	855 (52.9)	925 (56.9)	
25–29.9 kg/m^2	781 (42.7)	732 (40.5)	663 (36.1)		145 (48.8)	101 (52.3)	101 (47.9)		636 (41.4)	631 (39.1)	562 (34.5)	
≥30.0 kg/m^2	230 (12.6)	181 (10.0)	200 (10.9)		88 (29.6)	51 (26.4)	60 (28.4)		142 (9.3)	130 (8.0)	140 (8.6)	
Physical activity				<0.001				0.004				<0.001
Sedentary	281 (15.4)	163 (9.0)	124 (6.8)		62 (20.9)	25 (12.9)	22 (10.4)		219 (14.3)	138 (8.5)	102 (6.3)	
Moderate	1030 (56.3)	969 (53.6)	952 (51.8		170 (57.2)	110 (57.0)	121 (57.4)		860 (56.1)	859 (53.2)	831 (51.1)	
Regular exercise	519 (28.4)	677 (37.4)	762 (41.5)		65 (21.9)	58 (30.1)	68 (32.2)		454 (29.6)	619 (38.3)	694 (42.7)	
Smoking				<0.001				0.019				<0.001
Never	621 (33.9)	699 (38.6)	814 (44.3)		81 (27.3)	74 (38.3)	84 (39.8)		540 (35.2)	625 (38.7)	730 (44.9)	
Former	643 (35.2)	706 (39.0)	662 (36.0)		111 (37.4)	68 (35.2)	66 (31.3)		532 (34.7)	638 (39.5)	596 (36.6)	
Current	566 (30.9)	404 (22.3)	362 (19.7)		105 (35.4)	51 (26.4)	61 (28.9)		461 (30.1)	353 (21.8)	301 (18.5)	
Education				<0.001				0.210				0.001
Low	628 (34.3)	529 (29.2)	557 (30.3)		120 (40.4)	65 (33.7)	83 (39.3)		508 (33.1)	464 (28.7)	474 (29.1)	
Middle	726 (39.7)	694 (38.4)	692 (37.7)		123 (41.4)	86 (44.6)	76 (36.0)		603 (39.3)	608 (37.6)	616 (37.9)	
High	476 (26.0)	586 (32.4)	589 (32.0)		54 (18.2)	42 (21.8)	52 (24.7)		422 (27.5)	544 (33.7)	537 (33.0)	
Hypertension				0.477				0.948				0.765
No	1392 (76.1)	1398 (77.3)	1428 (77.7)		180 (60.6)	115 (59.6)	125 (59.2)		1212 (79.1)	1283 (79.4)	1303 (80.1)	
Yes	438 (23.9)	411 (22.7)	410 (22.3)		117 (39.4)	78 (40.4)	86 (40.8)		321 (20.9)	333 (20.6)	324 (19.9)	

[1] Values are *n* (%) unless otherwise specified. Categorization of whole grain into tertiles was performed according to the distribution in all participants (total *n* = 5477; *n* = 3180 women; *n* = 2297 men). All variables were measured or recorded at baseline. Cases were subjects who had progressed regarding glucose tolerance at follow-up from normal glucose tolerance at baseline to either prediabetes or type 2 diabetes at follow-up or from prediabetes at baseline to type 2 diabetes at follow-up. Control subjects were individuals who had not progressed regarding glucose tolerance at follow-up. *P* values are for comparisons between whole-grain groups and were derived by using the chi-square test for categorical variables and ANOVA for continuous variables.

[2] Mean; 95% CI in parentheses (all such values).

TABLE 2
ORs (95% CIs) estimated by using logistic regression analysis for the association between baseline consumption of whole grain (g/d) and abnormal glucose regulation at follow-up[1]

	Sample 1[2]				Sample 2[3]								
		Cases (progress from NGT to prediabetes or T2D or from prediabetes to T2D)				Cases							
						Progress from NGT to prediabetes			Progress from NGT to T2D			Progress from NGT to prediabetes or to T2D		
Intake of whole grain	Control subjects		OR (95% CI)	*P*	Control subjects		OR (95% CI)	*P*		OR (95% CI)	*P*		OR (95% CI)	*P*
	n	*n*			*n*	*n*			*n*			*n*		
Women and men														
Model 1														
<30.6 g/d	1533	297	1.00		1477	178	1.00		76	1.00		254	1.00	
30.6–59.1 g/d	1616	193	0.66 (0.54, 0.80)		1559	124	0.70 (0.55, 0.90)		40	0.54 (0.36, 0.80)		164	0.66 (0.53, 0.81)	
>59.1 g/d	1627	211	0.66 (0.54, 0.80)	<0.001	1581	122	0.63 (0.50, 0.81)	<0.001	49	0.59 (0.41, 0.86)	0.008	171	0.62 (0.51, 0.77)	<0.001
Continuous	4776	701	0.85 (0.78, 0.92)	<0.001	4617	424	0.83 (0.75, 0.93)	<0.001	165	0.81 (0.69, 0.96)	0.014	589	0.83 (0.76, 0.91)	<0.001
Model 2														
<30.6 g/d	1533	297	1.00		1477	178	1.00		76	1.00		254	1.00	
30.6–59.1 g/d	1616	193	0.77 (0.62, 0.95)		1559	124	0.79 (0.61, 1.02)		40	0.64 (0.43, 0.97)		164	0.76 (0.61, 0.95)	
>59.1 g/d	1627	211	0.78 (0.63, 0.96)	0.024	1581	122	0.73 (0.56, 0.94)	0.017	49	0.71 (0.48, 1.04)	0.090	171	0.74 (0.59, 0.92)	0.009
Continuous	4776	701	0.90 (0.83, 0.98)	0.018	4617	424	0.88 (0.79, 0.98)	0.015	165	0.88 (0.74, 1.04)	0.132	589	0.89 (0.81, 0.97)	0.010
Women														
Model 1														
<30.6 g/d	890	94	1.00		862	57	1.00		24	1.00		81	1.00	
30.6–59.1 g/d	1050	85	0.74 (0.55, 1.01)		1022	58	0.83 (0.57, 1.22)		16	0.54 (0.29, 1.03)		74	0.75 (0.54, 1.04)	
>59.1 g/d	968	93	0.85 (0.63, 1.15)	0.392	947	59	0.88 (0.60, 1.28)	0.572	17	0.60 (0.32, 1.12)	0.137	76	0.79 (0.57, 1.10)	0.226
Continuous	2908	272	0.92 (0.81, 1.05)	0.201	2831	174	0.90 (0.76, 1.06)	0.194	57	0.86 (0.65, 1.14)	0.285	231	0.89 (0.77, 1.02)	0.102
Model 2														
<30.6 g/d	890	94	1.00		862	57	1.00		24	1.00		81	1.00	
30.6–59.1 g/d	1050	85	0.89 (0.64, 1.23)		1022	58	0.95 (0.64, 1.41)		16	0.65 (0.33, 1.28)		74	0.87 (0.61, 1.23)	
>59.1 g/d	968	93	1.01 (0.73, 1.41)	0.851	947	59	1.03 (0.69, 1.53)	0.853	17	0.68 (0.35, 1.33)	0.284	76	0.95 (0.67, 1.35)	0.838
Continuous	2908	272	0.98 (0.85, 1.12)	0.718	2831	174	0.95 (0.81, 1.12)	0.542	57	0.90 (0.68, 1.19)	0.445	231	0.95 (0.82, 1.09)	0.445
Men														
Model 1														
<30.6 g/d	643	203	1.00		615	121	1.00		52	1.00		173	1.00	
30.6–59.1 g/d	566	108	0.61 (0.47, 0.79)		537	66	0.63 (0.46, 0.87)		24	0.53 (0.32, 0.87)		90	0.60 (0.46, 0.80)	
>59.1 g/d	659	118	0.55 (0.43, 0.71)	<0.001	634	63	0.50 (0.36, 0.69)	<0.001	32	0.59 (0.37, 0.92)	0.026	95	0.52 (0.40, 0.69)	<0.001
Continuous	1868	429	0.80 (0.72, 0.89)	<0.001	1786	250	0.79 (0.69, 0.91)	<0.001	108	0.79 (0.65, 0.97)	0.024	358	0.79 (0.71, 0.89)	<0.001
Model 2														
<30.6 g/d	643	203	1.00		615	121	1.00		52	1.00		173	1.0	
30.6–59.1 g/d	566	108	0.69 (0.53, 0.91)		537	66	0.70 (0.50, 0.98)		24	0.63 (0.38, 1.06)		90	0.68 (0.51, 0.92)	
>59.1 g/d	659	118	0.65 (0.49, 0.85)	0.002	634	63	0.57 (0.40, 0.80)	0.001	32	0.72 (0.44, 1.16)	0.183	95	0.62 (0.46, 0.82)	0.001
Continuous	1868	429	0.85 (0.76, 0.96)	0.006	1786	250	0.83 (0.72, 0.96)	0.009	108	0.87 (0.70, 1.07)	0.174	358	0.85 (0.75, 0.96)	0.007

[1] Model 1 was adjusted for age (continuous) and sex when women and men were combined. Model 2 was adjusted as for model 1 plus for family history of diabetes (yes or no), BMI (continuous), leisure-time physical activity (sedentary, moderate, or regular exercise), smoking (never, former, or current), education (low, middle, or high), blood pressure (normal blood pressure and no hypertension treatment compared with high blood pressure or hypertension treatment), and sex when women and men were combined. *P* values are for trends if whole-grain intake was a categorical variable. ORs for continuous variables of whole grain are reported per daily 30-g increased intake. NGT, normal glucose tolerance; T2D, type 2 diabetes.

[2] Sample 1 represents all subjects who participated in the follow-up study. Cases were subjects who progressed regarding glucose tolerance at follow-up from NGT at baseline to either prediabetes or T2D at follow-up or from prediabetes at baseline to T2D at follow-up. Control subjects were individuals who did not progress regarding glucose tolerance.

[3] Sample 2 represents only subjects who had NGT at baseline. Cases progressed from NGT to either prediabetes or T2D. Control subjects had NGT at both baseline and follow-up.

HOMA-IR, HOMA-β, and insulin-response$_{(2h-0h)}$

In the totality of subjects (sample 1), there was, at baseline, a negative association between HOMA-IR and the intake of whole grain, ($r = -0.06$, $P < 0.001$) when assessed by using a univariate regression model. The relation was still significant in multivariate models after adjustment for potential confounders, (r-partial correlation = -0.03, $P = 0.015$). Similar results were shown for cereal fiber in univariate analysis, but the association with HOMA-IR was lost in multivariate models. For insulin-response$_{(2h-0h)}$, there was a negative association with the intake of whole grain in the totality of subjects (r-partial correlation = -0.04, $P = 0.007$) in the multivariate analysis. The association was mainly accounted for by significant associations in all men (r-partial correlation = -0.07, $P = 0.001$). Similar negative associations were shown between the intake of cereal fibers and insulin response$_{(2h-0h)}$ (results not shown).

Subjects who progressed to either prediabetes or T2D were categorized into tertiles according to baseline values of HOMA-IR, HOMA-β, and insulin response$_{(2h-0h)}$. The majority of cases in the highest tertile of HOMA-IR were also found among those in the highest tertiles of HOMA-β and insulin response$_{(2h-0h)}$, with frequencies of 53% and 59%, respectively.

Proinsulin

Elevated concentrations of proinsulin are associated with T2D and may indicate β cell dysfunction (22); therefore, it was of interest to assess relations in the current study. Proinsulin data were restricted to men ($n = 2286$) and the baseline investigation.

Proinsulin concentrations for subjects who later deteriorated in glucose tolerance ($n = 420$) increased significantly by increasing tertiles of HOMA-β. From lowest to highest, mean (95% CI) values were 7.9 pmol/L (7.1, 8.8 pmol/L), 9.9 pmol/L (8.8, 11.2 pmol/L), and 12.8 pmol/L (11.3, 14.5 pmol/L), respectively. However, proinsulin:insulin ratios were not significantly changed with values, from lowest to highest tertiles, of 8.4% (7.6%, 9.2%), 7.7% (7.0%, 8.4%), and 7.4 (6.8%, 8.1%).

Linear regression analysis revealed a negative association between the intake of whole grain and proinsulin in all men ($r = -0.06$, $P < 0.004$). No association was shown for cereal fiber (results not shown).

Intakes of whole grain and cereal fiber at baseline compared with follow-up

We compared the intake of whole grain at baseline with that at follow-up. When intake was divided into quintiles, >70% of participants ended up in the same or adjacent quintile. Only 2% of subjects switched from the lowest to highest quintile or from the highest to lowest quintile. The mean intake of whole grain was increased from 49.0 g/d (48.2, 49.8 g/d) to 52.5 g/d (51.7, 53.4 g/d) from baseline to follow-up. This increase was primarily seen in women in whom the mean intake of whole-grain products increased from 49.5 g/d (48.5, 50.6 g/d) to 55.1 g/d (54.1, 56.2 g/d) Corresponding data for men were from 48.3 g/d (47.0, 49.6 g/d) to 49.0 g/d (47.7, 50.3 g/d). The increase was higher in women than in men ($P < 0.001$).

Also, when total cereal fiber intake at baseline was compared that with at follow-up, >70% of subjects ended up in the same or adjacent quintile of cereal fiber intake. Only 2% of subjects switched from the lowest to highest quintile or from the highest to lowest quintile. The mean intake of cereal fiber decreased from baseline from 10.4 g/d (10.2, 10.5 g/d) to 9.8 g/d (9.6, 9.9 g/d) at follow-up. The decrease was lower in women than in men ($P = 0.019$).

Associations between intakes of whole grain and cereal fiber and *TCF7L2* rs7903146 and rs4506565

With the use of a subset of men previously analyzed for polymorphisms of *TCF7L2* (16), we evaluated effect modifications according to diabetogenic risk alleles in single-nucleotide polymorphisms (SNPs) rs7903146 and rs4506565 (**Table 3**). Also in this subset of men, there was an inverse association between the baseline intake of whole grain or cereal fiber and development of T2D at follow-up. When stratified by genotype, no associations were shown in subjects who carried the T allele (ie, the risk allele for both SNPs), either in heterozygote or homozygote carriers, between the baseline intake of whole grain or cereal fiber and development of T2D after adjustment for age, BMI, physical activity, smoking, FHD, education, and blood pressure. In contrast, in nonrisk-allele carriers of genotypes CC (rs7903146) and AA (rs4506565), decreased risk of developing T2D was shown with high intakes of whole grain [ORs (95% CIs) of 0.60 (0.44, 0.82) and 0.62 (0.46, 0.84), respectively] and cereal fiber [ORs (95% CIs) of 0.69 (0.51, 0.95) and 0.71 (0.52, 0.97), respectively). With assumption of an additive model, interaction terms (genotype $\times$ intake of whole grain or cereal fiber) included in the regression model were significant for both SNPs and whole grain and cereal fiber ($P = 0.005$–0.008) (Table 3). A dominant model of inheritance was also evaluated, and similar results were obtained (Table 3).

DISCUSSION

In this prospective and population-based cohort study, we showed, for the first time to our knowledge, that high intakes of dietary whole grain and, to a lesser extent, cereal fiber reduces risk of developing prediabetes. The association was stronger in men than in women. Also we showed that associations were linked to variables that reflected insulin sensitivity. Our study also indicated effect modifications by polymorphisms of the *TCF7L2* gene for men.

Because OGTT was performed at baseline and follow-up, we were able to assess the incidence of both prediabetes and T2D. The relevance of our findings in individuals with prediabetes is highlighted by the fact that ~30–40% of individuals with prediabetes develop T2D within 8–10 y (23).

A negative association of low whole-grain intake and development of T2D in subjects having NGT at baseline was not significant after full adjustment for all confounders. This could probably be explained by the low number of individuals in the T2D group.

Our data correspond well to the meta-analysis of 6 cohort studies by de Munter et al (1) who showed that an increment of whole-grain consumption by 2-servings/d (40–60 g) decreased risk of T2D by 21%. In our study, risk of deteriorating glucose tolerance decreased by 20% per 60 g whole-grain intake/d. Risk reductions (OR) in our study were similar to those in a meta-analysis by Ye et al (3).

TABLE 3
ORs (95% CIs) estimated by using logistic regression analysis for the association between baseline consumption of whole grain or cereal fiber and T2D at follow-up in men without and with stratification for genotypes of SNPs rs7903146 and rs4506565 in the *TCF7L2* gene[1]

	Whole grain				Cereal fiber			
	Control subjects	T2D cases	OR (95% CI)	*P*	Control subjects	T2D cases	OR (95% CI)	*P*
	n	*n*			*n*	*n*		
rs7903146								
All subjects	505	178	0.79 (0.64, 0.97)		505	178	0.88 (0.71, 1.09)	
Genotype								
CC	311	86	0.60 (0.44, 0.82)		311	86	0.69 (0.51, 0.95)	
CT	165	72	1.06 (0.74, 1.53)		165	72	1.10 (0.76, 1.59)	
TT	29	20	1.51 (0.62, 3.66)	0.008[2]	29	20	1.19 (0.98, 1.44)	0.005[2]
CT+TT	194	92	1.08 (0.78, 1.51)	0.014[3]	194	92	1.24 (0.89, 1.72)	0.019[3]
rs4506565								
All subjects	503	177	0.79 (0.64, 0.98)		503	177	0.88 (0.71, 1.09)	
Genotype								
AA	297	82	0.62 (0.46, 0.84)		297	82	0.71 (0.52, 0.97)	
AT	172	75	1.05 (0.73, 1.50)		172	75	1.07 (0.74, 1.54)	
TT	34	20	1.62 (0.67, 3.91)	0.008[2]	34	20	2.59 (0.98, 6.88)	0.006[2]
AT+TT	206	95	1.09 (0.78, 1.51)	0.015[3]	206	95	1.23 (0.88, 1.70)	0.025[3]

[1] Continuous exposure variables were reported per daily 30-g increased intake of whole grain and per daily 5-g increased intake of cereal fiber. Control subjects were individuals who displayed normal glucose tolerance at both baseline and follow-up. Cases were subjects who progressed from either normal glucose tolerance or prediabetes at baseline to T2D at follow-up. Estimates were adjusted for age, family history of diabetes (yes or no), BMI (continuous), leisure-time physical activity (sedentary, moderate, or regular exercise), smoking (never, former, or current), education (low, middle, or high), blood pressure (normal blood pressure and no hypertension treatment compared with high blood pressure or hypertension treatment). SNPs, single-nucleotide polymorphisms; T2D, type 2 diabetes.

[2] *P* value for the interaction term between genotypes and intake of whole grain or cereal fiber with assumption of an additive model.

[3] *P* value for the interaction term between genotypes and intake of whole grain or cereal fiber with assumption of a dominant model.

Only one population-based prospective study outside the United States has evaluated the influence of fiber and whole grain on the development of T2D (24). A similar inverse association was shown in the Finnish study in which participants were retrieved from health care examinations, and the outcome (T2D) was assessed from medical certificates needed for reimbursement of drug costs. This association meant that individuals with T2D treated only with diet and changes in lifestyle were not identified. Furthermore, the Finnish study did not have the necessary data to adjust for FHD and physical exercise, both which were possible confounders. Also, there are differences in the genetic backgrounds of people in Finland and Sweden. In our study, all individuals with a non-Swedish background were excluded.

The positive effects of high intakes of whole grain and cereal fiber appeared stronger in men. One reason for this result may have been that our FFQ was validated in a group of middle-aged men (11) but not in women. Hence, we could not rule out the possibility that the questionnaire (which was the same for men and women) reflected somewhat less the actual intake in women than in men. Another relevant difference was the higher incidence of deteriorating glucose tolerance in men, which was in accordance with other studies (25). Also, the time to follow-up for women was somewhat shorter than for men (8 compared with 10 y). Last, women had increased their intake of whole grain at follow-up more than men did. In any case, our findings were in line with the difference by sex for risk of T2D observed in the Finnish study (24).

We showed an inverse association between the intake of whole grain or cereal fiber and insulin resistance; a high intake corresponded with low insulin resistance. This finding is in line with cross-sectional studies (8, 9, 26). It seems clear that effects on insulin sensitivity play an important part behind the protective effects. Which mechanisms underlie an effect on insulin sensitivity? From our data, we could probably exclude a secondary influence by effects on obesity because an influence on the development of BMI was small (results not shown). A separate adjustment for cereal fiber did not weaken the association between the intake of whole grain and increased glucose tolerance. Hence, the beneficial effects of whole-grain intake could not be explained by cereal fiber alone. Whole grain contains many bioactive compounds with potential beneficial effects in diabetes as well as cancer (27) and cardiovascular disease (3). Many theories on mechanisms have been presented such as effects of tocoferols, magnesium, selenium, phenolic acids, and phytosterols (27, 28). The elucidation of primary effects, which could be multiple, awaits additional studies.

Approximately 45–50% of total whole-grain intake in our study was from crisp bread, which in Sweden is mostly made from rye (29). These data also corresponded to the findings of Kyrø et al (30), whereby rye was the dominating source of whole grain in Swedes. Thus, whole-grain rye is an important component of whole-grain intake in our study. Whole-grain rye has a higher content of soluble fiber than that of whole-grain wheat (28). Certain soluble fibers may affect the viscosity of the meal and, thereby, influence blood glucose and insulin responses possibly by delayed gastric emptying (28, 31).

We showed a negative association between the intake of whole grain and proinsulin. However, the proinsulin:insulin ratios remained unchanged. Thus, our data probably reflected the increased demands on β cell secretion that were induced by insulin resistance.

Our data indicated that the protective effect of whole-grain intake on risk of developing T2D was lost in subjects who carried the *TCF7L2* rs7903146 T allele. This finding is in line with a previous report (14). It has been suggested that the diabetogenic variant of the *TCF7L2* gene decreases glucagon-like peptide-1 expression and actions (32). Because glucagon-like peptide-1 is known to slow gastric emptying, we speculate [in agreement with Fisher et al (14)] that the loss of this effect in carriers of diabetogenic risk alleles could cancel out a similar effect by dietary fibers. Our findings on *TCF7L2* were, at first glance, at odds with a meta-analysis (15), which did not find an influence of the *TCF7L2* rs4506565 genotype. However, the meta-analysis did not test for an association with T2D as in Fisher et al (14) but for an association with fasting glucose or fasting insulin measured in subjects without diabetes. Furthermore, Nettleton et al (15) used an unspecific definition of whole grain that may have influenced their results.

Our study had several strengths. The study was prospective and population based, and prediabetes and diabetes as well as insulin resistance and β cell function were assessed by using direct measurements in participants. An additional positive feature was the possibility to check for changes in the intake of whole grain and fibers between baseline and follow-up. This feature allowed us to rule out major changes with time, and we documented only a minor increase of whole grain in women compared with men. In addition, a Scandinavian population appeared especially relevant for the study of health effects of whole grain because of relatively large intakes (above all of rye) compared with those in US studies (30).

We could not calculate the total energy intake, which was a limitation of our study. Another limitation was the relatively small size of our study and, in particular, the genetic part which limited the statistical power. However, the association between *TCF7L2* genetic polymorphisms and T2D in different populations, including the Swedish one, has been replicated. In addition, our results were limited to Swedes of a certain age group; other groups may have different dietary habits and implications on glucose tolerance.

In conclusion, our study shows that a higher whole-grain intake is associated with decreased risk of deteriorating glucose tolerance, especially the progression from NGT to prediabetes. The association is primarily seen in men and likely linked to insulin resistance. Furthermore, data from this study indicate that the association is modified in men by the impact of polymorphisms of the *TCF7L2* gene.

The authors' responsibilities were as follows—AB: designed the research and had primary responsibility for the final content of the manuscript; TW, AB, and AH: conducted the research and wrote the manuscript; AH: was a statistical advisor; HFG and C-GÖ: provided essential materials to the research and contributed to the Discussion; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

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