

## Epidemiological support for the protection of whole grains against diabetes

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The epidemic of type 2 diabetes among children, adolescents and adults is increasing along with the increasing prevalence of overweight and obesity. Overweight is the most powerful modifiable risk factor for type 2 diabetes. Intake of wholegrain foods may reduce diabetes risk. Three prospective studies in 160 000 men and women examined the relationship of whole-grain or cereal-fibre intake with the risk of type 2 diabetes. Each study used a mailed Willett food-frequency questionnaire and similar methods of quantifying wholegrain foods and cereal fibre. The self-reported incident diabetes outcome was more reliably determined in the two studies of health-care professionals than in the study of Iowa women. Risk for incident type 2 diabetes was 21–27 % lower for those in the highest quintile of whole-grain intake, and 30–36 % lower in the highest quintile of cereal-fibre intake, each compared with the lowest quintile. Risk reduction persisted after adjustment for the healthier lifestyle found among habitual whole-grain consumers. Observations in non-diabetic individuals support an inverse relationship between whole-grain consumption and fasting insulin levels. In feeding studies in non-diabetic individuals insulin resistance was reduced using whole grains or diets rich in whole grains. Glucose control improved with diets rich in whole grains in feeding studies of subjects with type 2 diabetes. There is accumulating evidence to support the hypothesis that whole-grain consumption is associated with a reduced risk of incident type 2 diabetes; it may also improve glucose control in diabetic individuals.

### Diabetes mellitus: Diet: Whole grains: Fibre

Although several risk factors for the development of type 2 diabetes among children, adolescents and adults (Rosenbloom, 2002) are well recognized, there is a growing epidemic of type 2 diabetes. Several of the risk factors for type 2 diabetes are non-modifiable, including family history, age and ethnicity, while other factors are modifiable, including obesity (Rosenbloom, 2002), central adiposity (Franz *et al.* 2002), and a sedentary lifestyle (Engelgau *et al.* 2000). The results of three randomized clinical trials showed that changes in these modifiable risk factors could alter the incidence rate of type 2 diabetes (Pan *et al.* 1997; Hu *et al.* 2001; Tuomilehto *et al.* 2001; Knowler *et al.* 2002). In the USA a lifestyle intervention of increasing physical activity and a low-energy low-fat diet, without specific mention of an increase in fibre or whole-grain intake, reduced the risk of diabetes by 58 %; use of the

medication metformin was associated with a 31 % reduction in risk. In China a diet that focused on increasing the consumption of vegetables and reducing the intake of alcohol and simple sugars reduced the risk of type 2 diabetes in individuals with impaired glucose tolerance by 31 % after adjustment for baseline glucose and BMI (Pan *et al.* 1997). A lifestyle intervention aimed at increasing physical activity and fibre intake and decreasing body weight and total and saturated fat intake was associated with a 58 % reduction in the risk of type 2 diabetes in Finland (Tuomilehto *et al.* 2001). In these studies, it is not clear what proportion of the decrease in risk is attributable to specific dietary changes and what proportion is attributable to weight loss; however, they demonstrate the point that lifestyle modification, including diet modification, may be a strong mediator of the development of type 2 diabetes.

**Abbreviation:** RR, relative risk.

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**Table 1.** Composition of whole and refined wheat and loss of selected nutrients with refining of wheat (adapted from Thompson, 1992)

Component	Whole wheat	Refined wheat	Lost in refining (%)
Insoluble dietary fibre (g/kg)	115	19	83
Protein (g/kg)	140	140	0
Fat (g/kg)	27	14	48
Starch and sugar (g/kg)	700	830	-19
Zn ( $\mu\text{g/g}$ )	29	8	72
Fe ( $\mu\text{g/g}$ )	35	13	63
Se ( $\mu\text{g/g}$ )	0.06	0.02	67
Mg (mg/g)	1.38	0.22	84
Vitamin B <sub>6</sub> (mg/g)	7.5	1.4	81
Folic acid (mg/g)	0.57	0.11	81
Ferulic acid (mg/g)	0.5	0.04	92
$\beta$ -Tocotrienol ( $\mu\text{g/g}$ )	32.8	5.7	83

A larger role for whole-grain intake in prevention of type 2 diabetes should be considered. A differential effect of whole grain and refined grain is supported by the lower nutrient density of refined wheat compared with whole wheat (Table 1; Thompson, 1992). The macronutrient content of grains is less affected by refining than is the content of vitamins, minerals and phytochemicals. Although fortification of flour and cereal grains has been successful in replacing the B vitamins and preventing vitamin deficiencies, other nutrients lost in refining have not been replaced. Thus, refined wheat and other refined grain products remain relatively nutrient-poor when compared with wholegrain products. Thus, the altered nutrient profile of diets that contain considerable refined grain may enhance risk of type 2 diabetes; switching to whole grains would be expected to reduce risk.

The present review focuses on prospective studies examining whole-grain or cereal-fibre consumption on the incidence of diabetes (Salmeron *et al.* 1997a,b; Liu *et al.* 2000a; Meyer *et al.* 2000). Further evidence from observational studies that measured factors related to development of diabetes (glucose and insulin measures) and clinical trials with high-fibre or whole-grain-rich diets in individuals with and without type 2 diabetes is cited, in order to examine changes in risk factors for diabetes with an increase in cereal-fibre or whole-grain intake.

### Prospective studies

The methodology used in the Iowa Women's Health Study (Meyer *et al.* 2000, 2001), the Nurse's Health Study (Liu *et al.* 2000a; Salmeron *et al.* 2001) and The Health Professionals Study (Salmeron *et al.* 1997b) were grossly similar, although the design used in the Harvard studies (Liu *et al.* 2000a; Salmeron *et al.* 1997b, 2001) had some advantages over that used in the Iowa study (Meyer *et al.* 2000, 2001). Detailed questionnaires of diet (food-frequency-style questionnaire with varying numbers of questions used in each), lifestyle factors and health outcomes were mailed to participants at defined intervals. Prevalent cases of type 2 diabetes existing at baseline were

excluded from these analyses. The associations of diet and lifestyle factors with incident self-reported diabetes were studied. Case ascertainment in the female nurses and male health professionals has been shown to agree almost perfectly with medical records (Colditz *et al.* 1990), but agreement was found in only 64 % of the lay Iowa women (Meyer *et al.* 2000).

These studies used identical methods to classify breakfast cereals and other grain products as whole or refined grain and formed whole- and refined-grain food groups. The amount of cereal fibre is much greater in whole-grain and bran products than it is in refined grain. Thus, it is probable that the cereal-fibre intake is closely reflective of the whole-grain intake. Studies that focus on whole grain or on cereal fibre as the exposure measurements are, therefore, often measuring approximately the same entity.

Dietary assessment methods are associated with measurement error inherent in all dietary measures because individual diets vary greatly from day-to-day, in addition to special problems in the definition of wholegrain foods. Participants were asked how much dark bread they ate; dark breads are often, but not always, made from whole grain. One major strength of the Harvard studies was the updated estimate of dietary intake as the study progressed (Salmeron *et al.* 1997a,b; Liu *et al.* 2000a,b). The food frequency questionnaire was self-administered only once in the Iowa study (Meyer *et al.* 2000). Generally the imprecision in the dietary methods results in an underestimation of diet-disease relationships. However, the large sample size of these cohorts may provide adequate power to detect a true association between the relationship of whole-grain intake and risk of diabetes incidence.

The Iowa Women's Health Study randomly sampled nearly 100 000 post-menopausal women aged 55–69 who had a valid Iowa driver's license. In 6 years of follow-up of 35 988 women who had complete and reliable dietary intake reports and did not have diabetes when they first participated in the study (1986), 1141 women reported that they had been diagnosed with diabetes or were being treated with insulin or pills for diabetes (Meyer *et al.* 2001). Women who consumed the most whole grains (>17.5 servings/week) had a 21 % lower risk of diabetes compared with those with the lowest intakes of whole grains (<three servings/week) even after adjusting for lifestyle factors, i.e. physical activity, BMI, waist:hip (measured by a spouse or friend using a paper tape measure enclosed with the mailed questionnaire; Kushi *et al.* 1988), smoking, alcohol intake, and education. In this study, there was also a negative relationship of total insoluble fibre (relative risk (RR) 0.75 (95 % CI 0.61, 0.91)), fibre from cereals (RR 0.64 (95 % CI 0.7, 1.08)) and total grain intake (RR 0.68 (CI 0.54, 0.87)) to diabetes, but no significant reduction in the risk of diabetes with intake of refined grains (RR 0.87 (95 % CI 0.7, 1.08)), glycaemic index (RR 5th quintile compared with first quintile 0.89 (95 % CI 0.73, 1.10)), or glycaemic load (RR 0.95 (95 % CI 0.78, 1.16)). The relationship of whole grain to diabetes was attenuated after simultaneous adjustment for cereal fibre (RR 5th quintile compared with first quintile 0.93 (95 % CI 0.75, 1.16)) or cereal fibre and Mg simultaneously (RR 5th quintile compared with first quintile 0.82 (95 % CI 0.78, 1.21)), raising the possibility

that the cereal fibre and Mg are the operable components of whole grain responsible for association to type 2 diabetes. However, because fibre is mostly contained in the nutrient-rich bran of the whole grain and because of the high correlation among the nutrient components of whole grain, it is difficult to tell whether it was the cereal fibre or Mg *per se* that was responsible for the relationship or whether fibre and Mg were markers of phytochemicals in the whole grain generally, or were merely more reliable measures than other components that were investigated.

Understanding the relationship of whole-grain consumption to risk for disease is complex when one considers other differences between those who frequently consume whole grains and those who do so less frequently. For example, the Iowa women with the highest intakes of whole grain were more likely to engage in vigorous physical activity, be a high-school graduate, be a non-smoker, and have a lower waist:hip (Meyer *et al.* 2001). In addition, women with the highest intakes of whole grain had a lower BMI (0.3 kg/m<sup>2</sup> equivalent to approximately 1 kg) (Jacobs *et al.* 1998). Although the estimate of the association of whole-grain intake was adjusted for these lifestyle factors and BMI, the possibility of residual confounding remains; we cannot completely rule out the possibility that the consumption of whole grains is merely a marker for an overall healthier lifestyle. This is an issue for all of the prospective studies being reviewed in the present review (Salmeron *et al.* 1997a,b; Liu *et al.* 2000a,b; Meyer *et al.* 2000).

The Nurses' Health Study enrolled 121 700 female registered nurses who returned a mailed questionnaire about known and suspected risk factors for cardiovascular disease and cancer in 1976 (Willett *et al.* 1985). Several papers investigating the relationship of cereal fibre or whole grain to incident diabetes have been published from this study using different baseline and follow-up examinations (Colditz *et al.* 1992; Salmeron *et al.* 1997b; Liu *et al.* 2000a,b). The first report, based on a sixty-one-item food frequency questionnaire and 702 cases of type 2 diabetes in 6 years of follow-up of 84 360 women, did not find a significant relationship between total carbohydrate, sucrose or total dietary fibre and risk of diabetes although vegetable fat, K, Mg and Ca were inversely related to the risk of type 2 diabetes (Colditz *et al.* 1992). Neither whole grain nor cereal fibre was explicitly studied. Several subsequent reports from these studies did detect a reduction in risk of diabetes with greater whole-grain or cereal-fibre intake.

An inverse relationship of whole grain or cereal fibre to risk of type 2 diabetes was reported from the Nurses' Health Study using the 1984 (Liu *et al.* 1999) or 1986 (Salmeron *et al.* 1997b) examinations as the baseline and food frequency questionnaires with a greater number of items than was available in the first report from the Nurses' study (Colditz *et al.* 1992). The risk of diabetes among 75 521 women during 10 years of follow-up (1879 cases) was reduced by 27 % (95 % CI 0.63, 0.85) among those women who consumed the most wholegrain foods (1.8–15.9 servings/d) compared with those with the lowest intake of whole grains (0–0.26 servings/d) after adjustment for BMI and lifestyle factors (Liu *et al.* 1999). Greater consumption of dark bread, wholegrain breakfast cereal and bran were also associated with a significant reduction in the risk of

diabetes of a magnitude of 23–46 %. The relationship of whole grain to diabetes was similar among those who were obese (BMI > 25) and was not modified by adjustment for saturated fat.

In a separate report using data from 1986–1992 (65 173 women and 915 incident cases of diabetes) the relationship between dietary fibre and incident diabetes was very similar to the relationship of whole grain and type 2 diabetes (Salmeron *et al.* 1997b). Women in the highest quintile of dietary fibre intake (median intake 24.1 g/d) had a 28 % (95 % CI 0.62, 0.98) lower risk of diabetes than those in the lowest quintile (median intake 14.7 g/d). The difference was similar in magnitude for cereal fibre (RR 5th quintile compared with first quintile 0.72 (95 % CI 0.58, 0.9)). There was not a significant reduction in the risk of diabetes in the highest quintile of fruit-fibre intake compared with the lowest (RR 0.87 (95 % CI 0.70, 1.08)) and there was a non-significant increase in the RR of diabetes in the highest quintile of vegetable fibre compared with the lowest quintile (RR 1.17 (95 % CI 0.93, 1.45)). These results suggest that it was the cereal fibre that was responsible for this relationship.

In the Health Professionals Follow-up Study, 51 529 white (5 % non-white) male dentists, veterinarians, pharmacists, optometrists, osteopaths and podiatrists aged 40–75 in 1986 returned a mailed questionnaire on diet (131-item food frequency questionnaire), medical history and medications (Salmeron *et al.* 1997a). While 42 759 men were without diabetes, cancer, and heart disease and had reliably reported dietary intake at baseline, 523 men developed diabetes during 6 years of follow-up. There was not a significant reduction in the risk of diabetes with an increase in total dietary fibre. However, the risk of type 2 diabetes was decreased by 30 % (RR 0.70 (95 % CI 0.51, 0.96)) in the highest quintile of cereal-fibre intake (median 10.2 g/d) compared with the lowest quintile (median intake 1.14 g/d) after adjustment for a modicum of lifestyle factors, BMI and family history of diabetes. No significant relationship of fruit or vegetable fibre to risk of diabetes was detected. These results are similar to the results of the Nurses' Health Study (Salmeron *et al.* 1997b) in the magnitude of the reduction in risk of diabetes that is associated with cereal fibre.

The relationship between fibre and type 2 diabetes was also examined in the San Luis Valley Diabetes Study (Marshall *et al.* 1993). Dietary intake was ascertained retrospectively among 242 individuals with known diabetes and 460 individuals without a prior diagnosis of diabetes among 20- to 74-year-olds in southern Colorado from 1984–1986. Odds ratios were adjusted for age, sex, ethnicity, BMI, and energy and carbohydrate intake. Reported fibre intake was higher among those who had diabetes than those without; a decrease in fibre of 10 g/d was associated with a 25 % lower prevalence of diabetes (95 % CI 0.59, 0.96). However, when the analyses were limited to those eighty-five cases having been diagnosed within the past 5 years, the relationship was no longer significant (RR 0.94 (95 % CI 0.62, 1.43)). Prospective analyses using the same cohort found an inverse association between current fibre intake and fasting insulin and a non-significant increase in the risk of type 2 diabetes (RR 1.04 (95 % CI 0.59, 1.84)) for a 10 g decrease in fibre

**Table 2.** Prospective studies with incident type 2 diabetes as the outcome

Reference	Sample size and general description	Primary outcomes	Change in risk of type 2 diabetes from the highest to the lowest quintile
Meyer <i>et al.</i> (2000)	Post-menopausal women from Iowa Women's Health Study (n 35 988)	Total grain, refined grain, whole grain, cereal fibre	Whole grain: 21 % reduction Total grain: 21 % reduction Refined grain: non-significant 13 % reduction Total dietary fibre: 22 % reduction Cereal fibre: 36 % reduction
Liu <i>et al.</i> (2000a)	38–63-year-old women from Nurses' Health Study (n 75 521)	Total grain, whole grain, refined grain	Total grain intake: 25 % reduction Whole-grain intake: 27 % reduction Refined-grain intake: non-significant 11 % increase
Salmeron <i>et al.</i> (1997b)	40–65-year-old women from Nurses' Health Study (n 65 173)	Total dietary fibre, cereal fibre	Total dietary fibre: 22 % reduction Fruit fibre: non-significant 13 % reduction Vegetable fibre: non-significant 17 % increase High glycaemic load and low cereal fibre intake: reduced risk 2.5 (95 % CI 1.14, 5.51)
Salmeron <i>et al.</i> (1997a)	40–75-year-old men from Health Professionals follow-up study (n 42 759)	Glycaemic index, total dietary fibre, cereal fibre	Total dietary fibre: non-significant 2 % reduction Cereal fibre: 30 % reduction Fruit fibre: No relationship (odds ratio 1.01) Vegetable fibre: 12 % non-significant increase

intake/d. The authors interpreted their data as not supporting a role for increasing fibre intake in reducing the occurrence of type 2 diabetes. The retrospective design is problematic and subject to recall bias or reverse causality (diabetics starting to eat more whole grain or dietary fibre because of their diagnosis). The results of the prospective analysis are based on far fewer cases of type 2 diabetes (<eighty-five cases) and were not significant. Furthermore, fasting insulin, a factor presumed to be on the causal pathway to diabetes, was decreased with greater fibre intake (10 g/d decrease in fibre associated with a 4.3 % lower fasting insulin) independent of energy and carbohydrate intake. Therefore, it is plausible that the study design, sample size, or chance is responsible for the negative findings.

These prospective studies provide fairly consistent evidence in support of the role of whole grains and/or cereal fibre in reducing the risk of diabetes using a similar food frequency questionnaire. The reduction in risk of type 2 diabetes related to the highest *v.* the lowest intakes of whole grain or cereal fibre is reportedly 20–30 %, consistently in men and women (Table 2).

Epidemiological evidence is best interpreted in the context of the full body of evidence. Therefore, a review of studies of intermediate effects of whole-grain consumption and clinical trials of whole grain or fibre is desirable to support or refute the relationship of whole grains to the development of diabetes.

### Intermediate effects

Several studies have addressed the relationship of whole-grain consumption to glucose and insulin levels (Pereira *et al.* 1998; McKeown *et al.* 2002). The first investigated the relationship of whole-grain consumption to fasting insulin and glucose in a cohort of 3627 black and white young Americans aged 18–30 at the first examination (Pereira *et al.* 1998). Dietary intake was estimated using an interviewer-administered dietary history at years 0 and 7 of follow-up. Physical measures and insulin were taken at the

year 10 follow-up examination. Whole-grain consumption at years 0 and 7 was inverse and graded in association to fasting insulin levels at year 10 of follow-up after adjustment for race, sex, field centre, education, smoking status, energy intake, alcohol consumption, and physical activity. The relationship was stronger at year 7 than year 0 and not present in black men or women at year 0 or in black women at year 7. Wholegrain cereal, brown and wild rice and other whole grains were negatively associated with fasting insulin after adjustment for race, sex, field centre, education, smoking status, energy intake, alcohol consumption, and physical activity. BMI was 0.6 units lower (2–3 kg) among those who consumed nine or more servings of whole grain/d when compared with those consuming 0–2 servings of wholegrain foods/d. After adjustment for BMI, Mg, or fibre at year 0 the relationship of whole grain to fasting insulin was no longer significant, suggesting that these factors may be explanatory of the relationship of whole grain and insulin. At year 7, the relationship of whole grain to fasting insulin remained after separate adjustment for BMI, Mg, or fibre, but was explained by adjustment for these three factors simultaneously. These data support a dose–response relationship between whole-grain intake and fasting insulin.

The relationship of whole grain to fasting insulin to metabolic risk factors for type 2 diabetes, including glucose and insulin, was examined using the Framingham Offspring Study, a community-based study of cardiovascular disease (McKeown *et al.* 2002). Dietary intake was determined using a mailed 126-item semi-quantitative food frequency questionnaire. Medical history and physical measures including a 2 h oral glucose tolerance test were available for the 5th examination of this study. Whole-grain consumption in the highest quintile (13–64 servings/week) was associated with a significant decrease in fasting insulin when compared with those with the lowest whole-grain consumption (0–1.5 servings/week) after adjustment for age, sex, energy intake, treatment for hypertension, smoking, alcohol intake, multi-vitamin use, oestrogen use and physical activity ( $P = 0.01$ ).

The relationship between whole-grain intake and fasting insulin remained significant after further adjustment for BMI, polyunsaturated fatty acid, meat, fish, fruit, and vegetable intake ( $P = 0.03$ ), but was no longer significant after additional adjustment for Mg ( $P = 0.30$ ), total fibre ( $P = 0.16$ ) or insoluble fibre. Weight was 1–2 kg higher among those with the lowest intake of whole grain when compared with those in the upper 20 % of whole-grain intake. In addition, the relationship between whole grain and fasting insulin was stronger among those who had BMI of 30 or greater ( $P$  for interaction of BMI and whole grain = 0.02). The relationship between whole grain and fasting glucose and 2 h insulin was attenuated after adjustment for BMI and no relationship was observed between whole-grain intake and either glycosylated haemoglobin or 2 h post-challenge glucose. These results (McKeown *et al.* 2002) agree with Coronary Artery Risk Development in Young Adults (CARDIA) data (Pereira *et al.* 1998) and the San Luis Valley Diabetes Study data (Marshall *et al.* 1993) in supporting the hypothesis that whole grains are related to insulin levels.

These epidemiological studies provide essential information from large numbers of individuals but offer a relatively crude measure of whole-grain or fibre intake and may underestimate the risk of diabetes. Methodological difficulty in measuring whole-grain consumption abounds. Fortunately, most studies examining whole-grain intake have used similar methodology to quantify whole grains. The food frequency questionnaire ranks individuals according to intake, but is not an ideal tool to assess the amount of dietary fibre or whole grain needed to produce reduction in the risk for type 2 diabetes. The definition of whole grain is not standard, although the same definition was used for the studies reviewed here (whole grain is defined as  $\geq 25$  % whole grain or bran by weight; Jacobs *et al.* 1998). In most of the studies with diabetes as an endpoint, diabetes was self-reported. Follow-up questionnaires and validity studies suggest the method is reliable, but some misclassification is expected. The food frequency questionnaires used to estimate cereal fibre do not differentiate between fibre that comes from whole grains and fibre that comes from bran products. The true risk of diabetes may be attenuated by these limitations in diabetes and dietary intake estimates. Therefore, studies that control food intake and measure insulin sensitivity using the gold standard measure, the hyperinsulinaemic–euglycaemic clamp are useful to support the epidemiological evidence and provide some indication about whether change in insulin sensitivity is the mechanism responsible for the reduction in risk identified by the epidemiological studies.

#### Clinical trials in individuals without type 2 diabetes

Two clinical trials were identified that address the relationship of fibre or whole grain to insulin sensitivity (Fukagawa *et al.* 1990; Pereira *et al.* 2002). The extra-alimentary effect, including insulin sensitivity, of high-carbohydrate (68 % carbohydrate) high-fibre (33 g/d) diets was examined in twelve healthy adults (six young, six old) (Fukagawa *et al.* 1990). No sucrose was added to the

whole food high-carbohydrate high-fibre diet. Of the fibre, 40 % was from grains and cereals, 51 % from vegetables and 9 % from fruits. Fasting glucose was decreased by 5 % and fasting insulin by 24 % after 21–28 d of the high-carbohydrate high-fibre diet. Insulin-stimulated glucose uptake (insulin sensitivity) increased by 26 % after the high-carbohydrate high-fibre diet. No change was detected in hepatic glucose output (measured by using stable isotopes during the hyperinsulinaemic–euglycaemic clamp) after the high-carbohydrate high-fibre diet. This study suggests that the effect of the high-carbohydrate high-fibre diet is a change in insulin sensitivity rather than a change in hepatic glucose output. However, the control diet had approximately 43 % carbohydrate and 7 g fibre/d, whereas the high-carbohydrate diet had 68 % carbohydrate and 33 g fibre/d; therefore, it is not possible to separate the effects of change in the macronutrients in the diet from the increase in fibre.

The effect of substitution of whole grain for refined grain on insulin sensitivity was studied in a randomized cross-over feeding study of eleven overweight (BMI 26–36) generally healthy hyperinsulinaemic adults (Pereira *et al.* 2002). Participants were fed energy-equivalent diets with either refined or whole grains for 6 weeks, with 6 weeks of washout between the two diets. Fasting insulin was significantly lower (–9.6 %) after 6 weeks on the whole-grain diet than on the refined-grain diet. As expected, no significant difference was found in fasting glucose in these normal glucose-tolerant participants. Insulin sensitivity was greater after the whole-grain diet whether it was estimated using the Homeostasis Model Assessment (HOMA) calculation (fasting glucose (mmol/l)  $\times$  fasting insulin ( $\mu$ mol/l)/22.5;  $P < 0.01$ ) or measured directly using the hyperinsulinaemic–euglycaemic clamp method ( $P < 0.05$ ). This pilot study supports the hypothesis that a change in insulin sensitivity may be responsible for the change in insulin levels and risk of type 2 diabetes reported in epidemiological studies. The reduction in fasting insulin from substituting whole grains for refined grains was about half that of the high-carbohydrate high-fibre diet and is consistent with the results of the high-fibre high-carbohydrate-diet study. It is difficult to know whether the inclusion of elderly participants in the high-carbohydrate high-fibre-diet study or the small sample sizes or the diets were responsible for the difference in magnitude of the effect.

#### Clinical trials and intervention in individuals with type 2 diabetes

Increasing dietary fibre in the diets of individuals with type 2 diabetes in order to improve glycaemic control was the topic of a randomized crossover study of thirteen participants (Chandalia *et al.* 2000). Each diet was fed for 6 weeks with a 1-week washout between diets. The high-fibre diet provided 50 g fibre and the American Diabetes Association Diet contained 24 g fibre in an energy-equivalent diet with 55 % carbohydrate, 15 % protein and 30 % fat. Wholegrain breads and cereals, bran products, fruits and vegetables contributed to the increase in fibre. Mean preprandial plasma glucose was 8.9 % lower (130 mg/l or 0.7 mmol/l) and mean 24 h glucose and insulin

(areas under the curve) were 10 and 12 % lower, respectively, after the high-fibre diet than after the American Diabetes Association diet.

A slightly different approach was taken in a study which aimed to replace white rice with whole grains and other plant products to reduce the risk of coronary artery disease (Jang *et al.* 2001). Breakfast was replaced by 70 g of whole-grain and legume powder (66 % whole grains, 22 % legumes, 5.6 % seeds, 5.6 % vegetables) in seventy-six men with coronary artery disease. Fasting glucose levels decreased significantly (22 %;  $P < 0.0001$ ) in the fifty-five participants without diabetes and in the twenty-one (27 %;  $P < 0.03$ ) with newly diagnosed type 2 diabetes. Among those without diabetes, the area under the glucose ( $P < 0.0001$ ) and insulin ( $P < 0.03$ ) curves during a 75 g oral glucose tolerance test were significantly lower among those who received the whole-grain and legume powder meal replacement.  $\beta$ -Cell function estimates were significantly improved and insulin resistance was significantly reduced using the HOMA estimates. Among those with diabetes only the area under the glucose curve was significantly improved after receiving the whole-grain and legume powder meal replacement ( $P < 0.02$ ). Area under the insulin curve, and the HOMA estimates of  $\beta$ -cell function and insulin resistance changed in the expected direction in those with type 2 diabetes non-significantly, but power was limited by the small number of subjects ( $n$  9 on control diet;  $n$  12 receiving the whole-grain and legume powder meal replacement).

These clinical data are provocative in two important ways. First, the interventions with a whole-grain and legume powder meal replacement or increase in dietary fibre were met with significant benefits in glucose control and insulin metabolism. Second, the effect of whole grain or increase in fibre seems to extend to secondary prevention through an improvement in glucose and insulin metabolism in individuals with type 2 diabetes.

### Mechanisms

A complete review of the mechanisms through which whole-grain consumption may reduce the risk of diabetes and other diseases is available elsewhere (Slavin *et al.* 1997; Slavin, 2003). Briefly, there are a number of possible mechanisms through which whole grain might influence the risk of diabetes. The possibility that the effects are through modification of body weight or BMI remain, although adjustment for body weight did not explain the effects of cereal fibre or whole grain on risk of diabetes or metabolic intermediates, and body weight was controlled in the clinical studies. The possibility that whole-grain and/or cereal-fibre intake is actually a marker of an overall healthy lifestyle cannot be ruled out, although the results of the intermediate outcome and clinical studies reviewed (Fukagawa *et al.* 1990; Pereira *et al.* 1998, 2002; McKeown *et al.* 2002) support an effect of whole grain or fibre. The effects of whole grain may be a synergistic effect of several components such as phytochemicals, vitamin E content, and Mg or other food components (Slavin *et al.* 1997).

### Conclusion

Evidence is accumulating in support of the hypothesis that whole-grain consumption may reduce the risk of development of type 2 diabetes. The evidence from prospective studies consistently (Salmeron *et al.* 1997*a,b*; Liu *et al.* 2000*a*; Meyer *et al.* 2000), but not unanimously (Colditz *et al.* 1992; Marshall *et al.* 1993), supports a 20–30 % reduction in risk of type 2 diabetes associated with higher intakes of whole grain or cereal fibre. These data support the statement of the American Diabetes Association (Franz *et al.* 2002) that there is some evidence to support the role of whole grain or dietary fibre in reducing the risk of type 2 diabetes. The data reviewed here suggest that cereal fibre contributes far more to the reduction in risk of diabetes than fibre from fruits and vegetables (Salmeron *et al.* 2001; McKeown *et al.* 2002). Fasting insulin and body weight may be important intermediaries between whole grain and development of diabetes. Preliminary clinical studies support the hypotheses generated by the prospective studies; that insulin resistance may be reduced with whole-grain consumption. Future study is needed to address the specific amounts of whole grain needed to reduce risk of type 2 diabetes and to further elucidate the mechanisms responsible for the effect and the components of whole grain that are responsible for the effects.

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