Whole grain foods for the prevention of type 2 diabetes mellitus

Marion G. Priebe
Jaap J. van Binsbergen
Rien de Vos
Roel J. Vonk

Adapted from: Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD006061. DOI: 10.1002/14651858.CD006061
Abstract

Background
Diet as one aspect of lifestyle is thought to be one of the modifiable risk factors for the development of type 2 diabetes mellitus (T2DM). Information is needed as to which components of the diet could be protective for this disease.

Objectives
To assess the effect of whole-grain foods for the prevention of T2DM.

Search strategy
We searched CENTRAL, MEDLINE, EMBASE, CINAHL and AMED.

Selection criteria
We selected cohort studies with a minimum duration of five years that assessed the association between intake of whole-grain foods or cereal fiber and incidence of T2DM. Randomised controlled trials lasting at least six weeks were selected that assessed the effect of a diet rich in whole-grain foods compared to a diet rich in refined grain foods on T2DM and its major risk factors.

Data collection & analysis
Two reviewers independently selected the studies, assessed study quality and extracted data. Data of studies were not pooled because of methodological diversity.

Main results
One randomised controlled trial and 11 prospective cohort studies were identified. The randomised controlled trial, which was of low methodological quality, reported the change in insulin sensitivity in 12 obese hyperinsulinaemic subjects after six week long interventions. Intake of whole grain foods resulted in a slight improvement of insulin sensitivity and no adverse effects. Patient satisfaction, health related quality of life, total mortality and morbidity was not reported.

Four of the 11 cohort studies measured cereal fiber intake, three studies whole grain intake and two studies both. Two studies measured the change in whole grain food intake and one of them also change in cereal fiber intake. The incidence of T2DM was assessed in nine studies and changes in weight gain in two studies. The
prospective studies consistently showed a reduced risk for high intake of whole grain foods (27–30 %) or cereal fiber (28–37 %) on the development of T2DM.

**Reviewers’ conclusions**

The evidence from only prospective cohort trials is considered to be too weak to be able to draw a definite conclusion about the preventive effect of whole grain foods on the development of T2DM. Properly designed long-term randomised controlled trials are needed. To facilitate this, further mechanistic research should focus on finding a set of relevant intermediate endpoints for T2DM and on identifying genetic subgroups of the population at risk that are most susceptible to dietary intervention.

**Background**

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (i.e. elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under ‘Additional information’ in the information on the Metabolic and Endocrine Disorders Group on The Cochrane Library (see ‘About the Cochrane Collaboration’, ‘Collaborative review groups’). For an explanation of methodological terms, see the main Glossary on The Cochrane Library.”

**Type 2 diabetes**

Type 2 diabetes is the most prevalent form of diabetes worldwide and develops as a consequence of two defects. In an early stage target tissues are unable to respond to normal circulating concentrations of insulin (insulin resistance). As a consequence the output of insulin from the pancreatic beta-cells is increased (hyperinsulinaemia) to maintain normal blood glucose levels. In a later stage insulin secretion may decline as a result of beta-cell dysfunction. This leads to impaired glucose tolerance and/or impaired fasting glycaemia (glucose values above the normal range but below those defined as diagnostic of diabetes) which is associated with an increased risk of type 2 diabetes (Unwin 2002, WHO 1999). Excessive weight gain and central obesity are other well established risk factors for the development of type 2 diabetes (FAO/WHO 2003). The incidence of obesity and
type 2 diabetes are increasing rapidly worldwide and pose enormous economic as well as social costs to societies, urging for preventive measures. Although genetic elements are involved in the pathogenesis of type 2 diabetes, the rapid changes in incidence rates suggest a particularly important role for environmental factors. Besides physical activity, diet is thought to play a key role as a modifiable risk factor. Characteristics of a diet favouring the development of obesity and type 2 diabetes are currently defined as high in saturated fat and energy-dense foods as well as low in fruit and vegetables (FAO/WHO 2003). The contribution of the type of starchy food – an important component of the diet worldwide – however, has not been established well. Starchy foods are derived mainly from cereal grains which undergo a refining process or will be used entirely (whole grain foods).

**Whole grain foods**

Food products derived from cereals as wheat, rice, corn, rye, oat, and barley constitute a major part of the daily diet in many countries (FAO 1998). In refined-grain products, the bran and germ of the grain which contain the major amount of micronutrients, phytochemicals and dietary fibre (non-digestible carbohydrates and lignin), have been removed and only the starchy endosperm (ca. 80 % of the whole grain) is used. Whole grain foods contain either intact, flaked or broken grain kernels, coarsely ground kernels or flour that is made from whole grains (whole-meal flour). In epidemiological studies foods commonly are classified as whole grain as they contain more than 25 % by weight whole-grain or bran (Jacobs 1998). The Food and Drug Administration (FDA 2005) has approved a health claim for whole-grain foods with a whole-grain content of more than 51 % by weight per reference amount customarily consumed and more recently has announced in a FDA guidance document (draft guidelines) that it “considers ‘whole grain’ to include cereal grains that consist of the intact, ground, cracked or flaked fruit of the grains whose principal components – the starchy endosperm, germ and bran – are present in the same relative proportions as they exist in the intact grain” (FDA 2006).

Changes in food patterns such as a decrease of consumption of whole grain foods which occurred simultaneously with the increase of prevalence of chronic disease over the last decades have lead to the hypothesis that constituting whole grain food by highly refined grain foods is linked to the development of type 2 diabetes and other chronic disease (Burkitt 1975, Trowell 1975). There are several hypotheses as to how whole grain foods might prevent type 2 diabetes. Beneficial effects on weight gain, for example, could be explained by the larger volume and
relatively low energy density of whole grain food which is due to the presence of cereal fibre. This promotes satiation and satiety thus leading to decreased energy intake (Koh-Banerjee 2003). Consumption of whole grain foods containing intact, broken or coarsely ground kernels or viscous soluble fibre results in a lower postprandial plasma glucose and insulin response as compared to refined grain foods (Slavin 2003). In view of the proposed aggravating effects of high postprandial glucose and insulin concentrations on insulin sensitivity and beta-cell failure, their suppression is considered to be beneficial (Ludwig 2002; Willett 2002). Also, the high content of antioxidants such as vitamin E, phytic acid and selenium might be advantageous (Slavin 2003) since there is emerging evidence that the pathogenesis of diabetes is associated with increased oxidative stress (Dandona 2004, Robertson 2004; Sjöholm 2005).

From observational studies there is evidence for a protective effect of whole-grain foods with regard to the development of type 2 diabetes (Fung 2002; McKeown 2002, Meyer 2000; Montonen 2003). More recently, higher intake of whole grains was also associated with decreases in insulin resistance – a risk factor related to the development of type 2 diabetes (Liese 2003; McKeown 2004; Steffen 2003).

However, the protective effect of whole-grain foods on the development of type 2 diabetes would ideally be evaluated by randomised control trials because of their optimal control of confounding factors. To be able to observe differences in incidence of type 2 diabetes the duration of the dietary intervention would need to be very long. Alternatively persons with at least one major risk factor for type 2 diabetes could be chosen. Amelioration of the risk factor could then be used as an indication of decreased risk of development of type 2 diabetes. Still, it is likely that compliance with the whole-grain diet decreases with time, especially in persons who regard the diet as less palatable or might experience adverse effects of the intervention. The relatively high content of cereal fibre and resistant starch in the whole-grain diet might cause increased bloating and/or flatulence in sensitive persons. Due to these limitations with regard to trial duration and compliance randomised controlled trials assessing the effect of whole-grain foods on the development of type 2 diabetes are likely to be scarce.

Some reviews have been published addressing the relation between whole grain foods and the incidence of type 2 diabetes (Liu 2002; Murtaugh 2003). However, they were not systematically performed with respect to literature search and did not include quality assessment. Summarizing and evaluating the available evidence -derived from prospective cohort studies and intervention trials – concerning
the possible protective effect of whole grain foods could aid in identifying further research need and assist in defining recommendations with regard to the intake of starchy foods for the prevention of the development of type 2 diabetes.

**Objectives**

To assess the effect of whole-grain foods for the prevention of T2DM.

**Criteria for considering studies for this review**

**Types of studies**
Randomised controlled trials, controlled clinical trials and cohort studies were considered.

**Types of participants**

*Randomised controlled trials or controlled clinical trials*

*Inclusion criteria*
Healthy persons and persons with at least one major risk factor for type 2 diabetes were included. Major risk factors are overweight, abdominal obesity, impaired glucose tolerance and insulin resistance. We excluded children and adolescents less than 18 years because of the well known differences in eating patterns.

*Cohort studies*

*Inclusion criteria*
Free living persons (older than 18 years of age) without previously diagnosed diabetes mellitus.

*Diagnostic criteria*
Type 2 diabetes and impaired glucose tolerance: the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (ADA 1997; ADA 1999; NDDG 1979; Unwin 2002; WHO 1980; WHO 1985; WHO 1999).
Overweight
Body mass index greater than 25 (body mass in kg / height in (m²)) (FAO/WHO 2003).

Abdominal obesity
Waist circumference equal to or more than 102 cm in men and equal to or more than 88 cm in women (FAO/WHO 2003).

Insulin resistance
Cut-off values for defining insulin resistance vary since different methods are used for assessment of insulin resistance (Monzillo 2003). Under hyperinsulinaemic, euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation is defined as insulin resistance according to the WHO (WHO 1999).

Types of interventions

Randomised controlled trials or controlled clinical trials
Trials were included which compared diets rich in whole-grain foods (foods that contain more than 51 % of whole grain) with diets rich in refined-grain foods. Both diets should have similar overall sugar, starch, fat and protein content.

Cohort studies
Studies had to assess the intake of whole-grain foods (foods that contain more than 25 % of whole grain) or cereal fiber (as marker for whole grain food intake).

Types of outcome measures

Randomised controlled trials or controlled clinical trials

Primary outcome measures
Ideally incidence of type 2 diabetes is the main outcome. However, it was anticipated that there are hardly any randomised controlled trials or controlled clinical trials assessing the incidence of type 2 diabetes because of the long intervention duration needed.
Therefore, also trials assessing the changes in major risk factors for type 2 diabetes, including impaired glucose tolerance, insulin resistance and overweight were considered.

**Secondary outcome measures**
- adverse effects (bloating, flatulence);
- patient satisfaction;
- health-related quality of life;
- total mortality;
- morbidity;
- costs.

**Confounders**
- compliance.

**Timing of outcome assessment**
Trials should have a minimum of 6 weeks of intervention period.

**Cohort studies**

**Primary outcome measures**
- Incidence of type 2 diabetes mellitus.

**Secondary outcome measures**
- Incidence of major risk factors for type 2 diabetes, including impaired glucose tolerance, insulin resistance, overweight.

**Confounders**
- age;
- physical activity;
- family history of diabetes;
- body mass index.

**Timing of outcome assessment**
Prospective studies need to be of a minimum duration of 5 years.
Search strategy for identification of studies

Electronic searches
The following electronic data bases were searched:
- Cochrane Central Register of Controlled Trials, (The Cochrane Library issue 2, 2006)
- MEDLINE (1966 – May 2006);
- EMBASE (1989 – May 2006);
- CINAHL (1982 – May 2006);

Also the database of ongoing trials: Current Controlled Trials (www.controlled-trials.com) was searched (May 2006).

The Science Citation Index was searched (October 2006) to identify relevant studies that have cited the primarily retrieved studies.

No language restriction was applied for searching and study inclusion.

The following MEDLINE search strategy was adapted for the other electronic databases searched.

MEDLINE (1966 to May 2006)
1  wholemeal$.tw.
2  whole meals$.tw.
3  wholegrain$.tw.
4  whole grain$.tw
5  exp CEREALS
6  cereal$.tw.
7  grains$.tw.
8  exp Dietary Fiber/
9  dietary fiber$.tw.
10  dietary fibre$.tw.
11  exp Dietary Carbohydrates/
12  exp Glycemic index/
13  dietary carbohydrate$.tw.
14  (glyc?emic ind$ or GI).tw.
15  or/1-14
16  exp Insulin Resistance/
17 impaired glucose toleranc$.tw.
18 glucose intoleranc$.tw.
19 insulin resistanc$.tw.
20 exp Obesity/
21 pluri?metabolic syndrom$.tw.
22 exp Diabetes Mellitus, type 2
23 exp Metabolic Syndrome X/
24 or /16-23
25 15 and 24

**Hand searches**
The reference lists of all included studies and of review articles were screened in order to identify possible studies of interest. The hand search of specialised journals was not done because the sensitivity of the electronic data base search improved by omitting study design limitations and all relevant journals were included in the electronic data bases.

**Additional searches**
Authors of relevant identified studies and other experts (authors of reviews) have been contacted in order to obtain additional references, unpublished trials or ongoing trials.

**Methods of the review**

**Trials selection**
The title and abstract of each record of the search was assessed by two reviewers (MGP, JJVB) independently. Studies were rejected if the article definitely did not meet the review’s inclusion criteria; otherwise the full text of the study was obtained. Interrater agreement for study selection was measured using the kappa statistic (Cohen 1960). Differences between reviewers’ results were resolved by discussion.

Duplicate publications were aimed to be identified by comparing publications of the same authors with respect to study populations, location, date and follow-up time of the study.
Quality assessment

**Randomised controlled trials or controlled clinical trials**
The quality of reporting of each trial was assessed based largely on the quality criteria specified by Schulz and by Jadad (Jadad 1996; Schulz 1995). In particular, the following factors were studied:

1. Minimisation of selection bias – a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
2. Minimisation of performance bias – were the participants and people administering the treatment blind to the intervention?
3. Minimisation of attrition bias – a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
4. Minimisation of detection bias – were outcome assessors blind to the intervention?

Ad 2) As the treatment is a dietary intervention in which blinding participants and people administering the food is not possible, these criteria were not rated.

Based on these criteria, studies were broadly subdivided into the following three categories (Alderson 2004):

A  All quality criteria met: low risk of bias.
B  One or more of the quality criteria only partly met: moderate risk of bias.
C  One or more criteria not met: high risk of bias.

This classification was intended to be used as the basis of a sensitivity analysis.

**Cohort studies**
The quality of cohort studies was assessed using the following criteria (derived from Form III for the assessment of a cohort study, version February 2003, www.cochrane.nl):

- Number of appropriate confounders investigated and adjusted for;
- Same method of measurement of outcome in exposed and unexposed group;
- Quality of method used to assess outcome measures: self report without validation, self report with validation, direct measurement/medical records;
• Quality of method used to assess whole-grain intake: food frequency questionnaire without validation, food frequency questionnaire with validation; single measurement, repeated measurement;
• Duration and completeness of follow-up.

Quality of studies was examined by two reviewers independently. Differences in results were resolved by discussion and if necessary a third reviewer was consulted.

Data extraction
From original reports of the studies data were extracted by the two reviewers independently. Differences in results were resolved by discussion and if necessary a third reviewer was consulted.

From (randomised) controlled trials the following data were extracted:
1 General information: published/unpublished, title, authors, source, country, year of publication, funding, duplicate publication;
2 Trial characteristics: design, duration, randomizations, concealment of allocation, blinding, checking of blinding;
3 Intervention: length of intervention, dietary advice/diet provided, comparison interventions,
4 Participants: population, exclusion criteria, number (total, per compared groups), age, gender, health condition, diagnostic criteria used to define health condition, similarity groups at baseline, medication used, assessment of compliance, withdrawals/losses to follow-up, confounders: body mass index, physical activity, family history of diabetes;
5 Outcomes: outcomes specified above, main outcomes assessed in the study;
6 Results: for outcomes and times of assessment (including a measure of variation), intention-to-treat analyses.

The following data were extracted from cohort studies (adapted data extraction form of the Cochrane Non-Randomised Studies Methods Group).
1 General information: published/unpublished, title, authors, source, country, year of publication, duplicate publication;
2 Study characteristics: design, dates of enrolment, follow-up;
3 Exposure: type, type of measurement, validation of measurement, time-points measurements;
4 Outcome: type, criteria used, type of measurement, validation of measurement;
Participants: number identified, number excluded, number lost to follow-up, characteristics;

Results: total number cases, cases in group with lowest and highest intake, results of outcome, confounders adjusted for.

Data analyses
Data were intended to be summarized statistically if they were sufficiently similar, and of sufficient quality.

For continuous outcomes, weighted mean differences were to be used to analyse the size of the effects of the interventions. The effect sizes for dichotomous data were to be expressed in terms of relative risks, odds ratio’s or hazard ratio’s.

In RCTs intention-to-treat analysis were to be used when the information is provided.

All data were to be initially analysed with a fixed effect model. Heterogeneity between trial results were to be tested by using a standard chi-squared test. To quantify inconsistency the I squared statistic was to be used (Higgins 2002) which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50 % was to be considered substantial heterogeneity. Possible causes of heterogeneity were to be explored by conducting subgroup and sensitivity analyses. If significant heterogeneity is found, it is unreasonable to assume that there is one ‘true’ effect underlying the data, that is constant across different populations and therefore a random effects model was to be used.

Subgroup analyses
When the amount of data permits, subgroup analyses were to be conducted according to age, sex, duration of intervention, types of whole grain foods and amounts of whole grain foods consumed, since variations may be due to characteristics of dietary intervention.

Sensitivity analyses
It was intended to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

1. Repeating the analysis excluding unpublished studies (if there were any).
2. Repeating the analysis taking account of study quality, as specified above.
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
4 Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

5 Repeating the analysis excluding studies about which no primary consensus was reached.

The robustness of the results was also to be tested by repeating the analysis using different measures of effect size (risk difference, odds ratio etc.) and different statistic models (fixed and random effects models).

Assessment of publication bias
Publication bias was to be assessed by preparation of a ‘funnel plot’ and examined statistically for signs of asymmetry (Egger 1997).

Description of studies

Trials identified
With the medline search 3395 possibly eligible studies were found. With the search in Embase 1560 additional studies were identified. The search in CINAHL added another 586 studies, the search in AMED four and the search in CENTRAL 259 more studies (total 5804 possibly eligible studies). With the initial screening of the 5804 possibly eligible studies 23 studies were identified and the full text of these studies was obtained. After detailed examination 11 studies were excluded.

No further study was found searching the database of ongoing trials: Current Controlled Trials (www.controlled-trials.com) and scanning the reference lists of all so far included studies and of review articles.

By searching the Science Citation Index to identify relevant studies that have cited the primarily retrieved studies one further study was found (van Dam 2006).

(Figure 1)

Authors of the identified relevant studies and other experts (authors of reviews) were contacted in order to obtain additional references, unpublished trials, or ongoing trials. No additional study has been retrieved by this means. The possibility that certain publications were duplicates has been examined by comparing publications of the same authors with respect to study populations, location, date and follow-up time of the study. No duplicate publications were identified.
Interrater agreement
The interrater agreement for study selection was measured using the kappa statistic (Cohen 1960) and was 0.57 which indicates moderate agreement. Differences between reviewers’ results were resolved by discussion.

Missing data
Two authors were contacted to retrieve additional information.

Excluded studies
11 studies were excluded. The main reason of exclusion was that the diet administered during the intervention did not fulfill the inclusion criteria (for details see Table 1).
Table 1 Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker 1998</td>
<td>Only intake of total dietary fiber and not of cereal fiber was measured.</td>
</tr>
<tr>
<td>Feskens 1991</td>
<td>Only carbohydrate intake was measured and not whole-grain intake.</td>
</tr>
<tr>
<td>Hodge 1996</td>
<td>Only intake of total dietary fiber and not of cereal fiber was measured.</td>
</tr>
<tr>
<td>Juntunen 2003</td>
<td>The test meals did not fulfill our inclusion criteria.</td>
</tr>
<tr>
<td>Liese 2003</td>
<td>This was a cross-sectional study.</td>
</tr>
<tr>
<td>Marshall 1993</td>
<td>Only intake of total dietary fiber and not of cereal fiber was measured.</td>
</tr>
<tr>
<td>Sloth 2004</td>
<td>Dietary interventions consisted of whole-grain foods.</td>
</tr>
<tr>
<td>Vinceti 1994</td>
<td>Intake of whole-grain or cereal fiber was not measured.</td>
</tr>
<tr>
<td>Weickert 2006</td>
<td>The test meals did not fulfill our inclusion criteria.</td>
</tr>
<tr>
<td>Wolever 2002</td>
<td>The dietary intervention did not fulfill our inclusion criteria.</td>
</tr>
<tr>
<td>Wolever 2003</td>
<td>The dietary intervention did not fulfill our inclusion criteria.</td>
</tr>
</tbody>
</table>

Included studies
In total 12 studies were identified that met all the inclusion criteria. One study was a randomised controlled trial and 11 were cohort studies. Details of the randomised controlled trial are listed in Table 2 and details of the prospective cohort studies are shown in Table 3. The following gives a brief overview:

Randomised controlled trial

Design and duration
The trial of Pereira et al (Pereira 2002) had a cross-over design with two six-week feeding periods and a wash-out period of six to nine weeks.

Participants
12 overweight or obese (BMI 27–36 kg/m²) hyperinsulinaemic adults aged 25–56 (six women, six men) took part in the trial.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pereira 2002</td>
<td>Cross-over nonblinded RCT; 2 feeding periods of 6 weeks, wash-out period of 6–9 weeks; randomisation done but method unclear</td>
<td>6 men, 6 women; age: 21–65 y exclusion criteria: • Body Mass Index &lt; 26 or &gt; 36 • Body weight fluctuation over the past 6 mo of &gt; 10 % • Smoking cigarettes • Consuming &gt; 2 alcoholic beverages/d • Having diabetes, cancer, cardiovascular disease and other chronic clinical conditions • Taking medications that would affect glucose, insulin, lipids or blood pressure • Engaging in a high level of physical activity • Following a special diet • Allergic to any foods • Planning to change dietary habits, increase physical activity, change body weight, move out of town or take a lengthy vacation during the time of the study • Fasting blood glucose &gt; 6.0 mmol/L • Fasting insulin &lt; 90 pmol/L</td>
<td>Refined grain foods versus whole grain foods at breakfast, lunch and dinner; food provided</td>
<td>Body weight, satiety, self-reported physical activity, fasting insulin, postprandial insulin, insulin resistance, insulin sensitivity, side effects</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
### Table 3 Characteristics cohort studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study location</th>
<th>Base-line cohort</th>
<th>Years of follow-up</th>
<th>Age range at base line</th>
<th>Dietary assessment, correlation coefficient</th>
<th>No of cases</th>
<th>Median intake lowest quintile (<em>quartile</em>)</th>
<th>Median intake highest quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nurses’ Health Study (Salmeron 1997)</strong></td>
<td>United States</td>
<td>65 173 women</td>
<td>1986–1992</td>
<td>40–56 y</td>
<td>134-item FFQ validated</td>
<td>915</td>
<td>Cereal fiber: 2 g/d</td>
<td>Cereal fiber: 7.5 g/d</td>
</tr>
<tr>
<td><strong>Health Professional Follow-up study (Salmeron 1997)</strong></td>
<td>United States</td>
<td>42 759 men</td>
<td>1986–1992</td>
<td>40–75 y</td>
<td>131-item FFQ</td>
<td>523</td>
<td>Cereal fiber: 2.5 g/d</td>
<td>Cereal fiber: 10.2 g/d</td>
</tr>
<tr>
<td><strong>Nurses’ Health Study (Liu 2000)</strong></td>
<td>United States</td>
<td>75 521 women</td>
<td>1984–1994</td>
<td>38–63 y</td>
<td>126-item FFQ validated: 0.77 dark bread Repeated ’86, ’90</td>
<td>1879</td>
<td>Whole grain: 0.13 servings/day</td>
<td>Whole grain: 2.7 servings/day</td>
</tr>
<tr>
<td><strong>Iowa Womens’ Health Study (Meyer 2000)</strong></td>
<td>United States</td>
<td>35 988 women</td>
<td>1986–1992</td>
<td>55–69 y</td>
<td>127-item FFQ validated: 0.45 carbohydrates 0.24 crude fiber</td>
<td>1141</td>
<td>Cereal fiber: 2.66 g/d Whole grain: 1 serving/week</td>
<td>Cereal fiber: 9.43 g/d Whole grain: 20.5 servings/week</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Period</td>
<td>Age</td>
<td>Outcomes</td>
<td>Whole Grain Intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Professional Follow-up study</td>
<td>United States</td>
<td>42,898 men</td>
<td>1986–1998</td>
<td>40–75 y</td>
<td>131-item FFQ validated: 0.77 dark breads repeated ‘90, ‘94, ‘98</td>
<td>0.4 servings/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fung 2002)</td>
<td></td>
<td></td>
<td>12 years</td>
<td></td>
<td></td>
<td>3.2 servings/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finnish Mobile Clinic Health Examination</td>
<td>Finland</td>
<td>4,316: 2,286 men, 2,030 women</td>
<td>1966–1972</td>
<td>40–69 y</td>
<td>dietary history interview with 100-item FFQ validated: short term 0.62, long term 0.39 total grain</td>
<td>0.47 – 12.0 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survey (Montonen 2003)</td>
<td></td>
<td></td>
<td>6 years</td>
<td></td>
<td></td>
<td>0–109 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stevens 2002)</td>
<td></td>
<td></td>
<td>8 years</td>
<td></td>
<td></td>
<td>8.1 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Atherosclerosis Risk in Communities</td>
<td>United States</td>
<td>12,251: 9,529 white, 2,722 African-American</td>
<td>1987–1998</td>
<td>45–65 y</td>
<td>Diabetes no distinction type 1 and 2 serum glucose measured</td>
<td>1.75 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>study (ARIC)</td>
<td></td>
<td></td>
<td>9 years</td>
<td></td>
<td></td>
<td>6.75 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Stevens 2002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.75 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurses’ Health Study (Liu 2003)</td>
<td>United States</td>
<td>74,091 women</td>
<td>1984–1996</td>
<td>38–63 y</td>
<td>Obesity, body weight change, self-report validated: correlation 0.96</td>
<td>0.59 serving/1000 kcal/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Liu 2003)</td>
<td></td>
<td></td>
<td>12 years</td>
<td></td>
<td></td>
<td>0.90 serving/1000 kcal/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3 Characteristics cohort studies (continued)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study location</th>
<th>Base-line cohort</th>
<th>Years of follow-up</th>
<th>Age range at base line</th>
<th>Dietary assessment, correlation coefficient</th>
<th>No of cases</th>
<th>Median intake lowest quintile (<em>quartile</em>)</th>
<th>Median intake highest quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Professional Follow-up study (Koh-Banerjee 2004)</td>
<td>United States</td>
<td>27 082 men</td>
<td>1986–1994</td>
<td>40–75 y</td>
<td>Body weight change self-report validated: correlation 0.97</td>
<td></td>
<td>Change in whole grain intake, def. Jacobs et al – 11.0 g/d</td>
<td>Change in whole grain intake, def. Jacobs et al 27 g/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 years</td>
<td></td>
<td></td>
<td></td>
<td>Change in whole grain intake, def. FDA – 17.8 g/d</td>
<td>Change in whole grain intake, def. FDA 15.6 g/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change in cereal fiber intake – 2.2 g/d</td>
<td>Change in cereal fiber intake 5.1 g/d</td>
</tr>
<tr>
<td>Black Women’s Health Study (Davies, 2006)</td>
<td>United States</td>
<td>41 186 African-American women</td>
<td>1995–2003</td>
<td>21–69 y</td>
<td>T2 DM Self-report validated: 95 % confirmed</td>
<td>1964</td>
<td>Whole grains: 0.03 servings/day</td>
<td>Whole grains: 1.29 servings/day</td>
</tr>
</tbody>
</table>

* data retrieved from the author
Interventions
One diet contained products of refined grains, thus products with no bran or germ and little fiber. In the other diet the refined grain products where substituted by whole grain products. All food of the two different diets was prepared at the metabolic kitchen of the Research Center where the study was conducted. The participants stayed there during the 2 feeding periods and were asked to consume all of the food provided to them and to consume no other food, except energy-free beverages.

Outcome measures
Fasting insulin concentrations, insulin resistance (homeostasis method) and insulin sensitivity (euglycaemic hyperinsulinaemic clamp test) were determined.

Cohort studies

Design and duration
All 11 studies were prospective cohort studies. Four had a follow-up duration of six years (Meyer 2000; Montonen 2003; Salmeron 1997a; Salmeron 1997b), three lasted eight years (Koh-Banerjee 2004; Schulze 2004; van Dam 2006), one nine years (Stevens 2002), one 10 years (Liu 2000) and two 12 years (Fung 2002; Liu 2003). In all but one studies the results were reported in risks across quintiles of whole-grain or cereal fiber intake. Montonen et al. (Montonen 2003) assessed the risk across quartiles.

Participants
All participants were without previous diagnosis of diabetes. In six studies participants were only women (Liu 2000; Liu 2003; Meyer 2000; Salmeron 1997a; Schulze 2004; van Dam 2006). In three studies only men participated (Fung 2002; Koh-Banerjee 2004; Salmeron 1997b), in the other two studies participants were men and women. Age at base line of inclusion was 21–75 years, and the age range of the cohorts varied from 14 to 47 years. One study compared the risk of whites with that of African-American (Stevens 2002). In one study participants were only African-American women (van Dam 2006). In the other studies ethnicity was not mentioned. All studies were conducted in the United States, with the exception of one, which was located in Finland (Montonen 2003). In seven (Liu 2000; Liu 2003; Fung 2002; Koh-Banerjee 2004; Salmeron 1997a; Salmeron 1997b; Schulze 2004) of the eleven studies participants were health professionals.


Exposure
Four studies assessed cereal fiber intake (Salmeron 1997a; Salmeron 1997b; Schulze 2004; Stevens 2002), three studies whole grain intake (Fung 2002; Liu 2003; van Dam 2006) and two studies both whole grain and cereal fiber intake (Meyer 2000; Montonen 2003). Two studies measured the change in whole grain intake (Koh-Banerjee 2004; Liu 2003) and one of them also the change in cereal fiber intake (Koh-Banerjee 2004).

Whole grain food was in most studies defined (Fung 2002; Liu 2000; Liu 2003; Meyer 2000) according to Jacobs et al (Jacobs 1998) and Liu et al (Liu 1999) and included dark bread, popcorn, cooked oatmeal, wheat germ, brown rice, bran and other grains (e.g. bulgar, kasha, couscous). Whole-grain breakfast cereals were classified as whole grain as they contained more than 25 % whole grain or bran. Montonen et al (Montonen 2003) modified this classification and did not include wheat germ and bran. Reported amounts of food were converted to grams per day in their study. Koh-Banerjee et al (Koh-Banerjee 2004) used in addition to the previous described classification the definition issued by the FDA for products eligible for a whole-grain health claim: foods that contain more than 51 % of whole grain (all portions of the kernel) per reference amount customarily consumed (FDA 2005). Van Dam et al (van Dam 2006) assessed the intake of whole grains in form of “dark breads, such as wheat, rye, pumpernickel” and “high fiber, bran or granola cereals, shredded wheat”.

Outcome measures
Nine studies measured the incidence of type 2 diabetes (Fung 2002; Liu 2000; Meyer 2000; Montonen 2003; Salmeron 1997a; Salmeron 1997b; Schulze 2004; Stevens 2002; van Dam 2006) and two studies changes in weight gain (Koh-Banerjee 2004; Liu 2003). One study reported the incidence of obesity (BMI more than 30 kg/m²) and severe weight gain (more than 25 kg) (Liu 2003). The effect sizes for dichotomous data were expressed in terms of relative risks (RR) in most studies, odds ratio’s (OR) in one study (Liu 2003) or hazard ratio’s (HR) (Stevens 2002; van Dam 2006) in two studies. RRS and HRS reported are comparisons between the upper category of intake (highest quartile/quintile) and the lowest category (lowest quartile/quintile). The methods used to determine RRS and HRS are listed in the able “Quality assessment cohort studies” as well as the initial and adjusted effect sizes. In the publications no information of goodness of fit of the statistical models are given. In all but two studies outcome was assessed with a biennial questionnaire which was mailed to all participants. Stevens et al
(Stevens 2002) assessed incidence of diabetes every three years and Montonen et al (Montonen 2003) gained information about new type 2 diabetes cases needing drug therapy via a central register of all patients receiving drug reimbursement. None of the studies reported insulin sensitivity or glucose intolerance.

Original purpose
The original purpose of most studies was to investigate how diet and other lifestyle factors influence the development of various diseases. The primary aim of the Black women’s Health study (van Dam 2006) was to identify risk factors for diseases with high prevalence in black women. The ARIC study (Stevens 2002) was designed to investigate the etiology of atherosclerosis and variation in cardiovascular risk factors, medical care and disease by race, gender, location and date.

Methodological quality of included studies

Randomised controlled trials
The included trial (Pereira 2002) was a six-week intervention study in 12 persons with a crossover design and a wash-out period of six to nine weeks.

Minimisation of selection bias
In the publication the trial was described as randomised but no information about the randomisation procedure was given. Also, no attempt to allocation concealment was described.

Minimisation of attrition bias
Data of 3 persons (25 %) could not be used for the outcome insulin sensitivity. One person became ill during the wash-out period and did not complete the study. In two persons the clamp tests were not completed due to technical difficulties.

Minimisation of detection bias
According to the protocol blinding of participants and people administering the food was not rated as this concerns a dietary intervention in which blinding is not possible. Blinding of the outcome assessor was not reported in the publication. Based on these quality criteria there is a high risk of bias in this trial (category C).
Cohort studies

Number of appropriate confounders investigated and adjusted for
The number of confounders that were used to correct the results varied considerably between the studies included (Table 4). 36% of the studies did not adjust for confounders that should have been minimally considered namely BMI, physical activity and family history of diabetes. Three studies (Meyer 2000; Montonen 2003; Stevens 2002) did not correct for family history of diabetes and one study did not account for physical activity (Montonen 2003). Confounders were assessed with a self-administered questionnaire. Five studies (Meyer 2000; Montonen 2003; Salmeron 1997a; Salmeron 1997b; van Dam 2006) did not repeat the assessment done at baseline, three studies (Fung 2002; Koh-Banerjee 2004; Schulze 2004) repeated the assessment every two years and one study (Liu 2003) once after two years and twice after four years. From two publications (Liu 2000; Stevens 2002) it became not clear whether assessment of confounders was repeated.

Same method of measurement of outcome in exposed and unexposed group
In all studies in all participants the same method of outcome measurement was used regardless of the level of whole grain or cereal fiber intake.

Quality of method used to assess outcome measures: self report without validation, self report with validation, direct measurement/medical records
In nine studies the outcome was self-reported. In one study it was directly measured (serum glucose concentrations) (Stevens 2002) and in one study (Montonen 2003) a central register of patients receiving drug reimbursement was used. All studies using self-reported diagnosis of type 2 diabetes validated the outcome in subgroups by comparing it with medical records. Studies with weight gain as outcome measure validated the self-reported weight in subgroups by measuring weight directly (Koh-Banerjee 2004; Liu 2003). The validation studies showed over all a high agreement between self report and control assessment (Table 4). The number of participants in the validation studies lay between 59 and 184. No information was given on what ground the subgroup size was chosen.
Quality of method used to assess whole-grain intake
Dietary intake over the previous year was assessed with mailed semi-quantitative food frequency questionnaires (FFQ) in nine studies, in one study (Stevens 2002) it was interviewer administered and in one study (Montonen 2003) a dietary history interview was taken. The FFQ mostly assessed the intake of 100–134 items; two studies assessed intake of less than 100 items (68 items (van Dam 2006); 66 items (Stevens 2002)). Dietary assessment was repeated one to three times in five studies (Fung 2002; Koh-Banerjee 2004; Liu 2000; Liu 2003; Schulze 2004), the other studies did not repeat the assessment. In all studies results of the dietary assessment were validated against results of detailed diet records in subgroups. In two studies (Schulze 2004; Stevens 2002) a FFQ was used that was not validated in a subgroup of the same population. Examples of relevant correlation coefficients are listed in (Table 4) and showed variable agreement. The number of participants in the validation studies lay between 44 and 1844. No information was given on what ground the subgroup size was chosen.

Duration and completeness of follow-up
The duration of the studies ranged between six and 12 years and was considered to be long enough. Loss to follow-up (from sample to study population) was only described in one study. Stevens et al (Stevens 2002) reported an initial response rate of 67 % in whites and of 42 % in African-American. Four studies reported response rates to the repeated assessments of outcome. More than 80 % responded to biennial questionnaires send to the study population in the study of van Dam et al (van Dam 2006) and 94 % in that of Fung et al. (Fung 2002). The response rate to the questionnaires in the study of Meyer et al (Meyer 2000) declined during the study period (91 %, 86 %, 79 %). Stevens et al (Stevens 2002) reported that a total of approximately 80 % of the study population that remained alive at the end of the study period was examined at all four visits.

Interrater agreement
The interrater agreement for study quality was measured using the kappa statistic (Cohen 1960) and was 0.88. Differences between reviewers’ results were resolved by discussion.
## Table 4 Quality assessment cohort studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Dietary assessment repeated</th>
<th>Dietary assessment validated</th>
<th>Validation correlation coefficient</th>
<th>Method outcome assessment</th>
<th>Validation outcome assessment</th>
<th>RRs/HRs (95% CI) corrected for all confounders</th>
<th>RR/HRs (95% CI) initial analyses</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses’ Health Study (Salmeron 1997)</td>
<td>No</td>
<td>Yes</td>
<td>n = 173 white bread: 0.71</td>
<td>Self-report</td>
<td>n = 62 % confirmed by medical record</td>
<td>0.72 (0.58 to 0.90) RR, RRs simultaneously adjusted for other variables by logistic regression analysis</td>
<td>N.A.</td>
<td>Age, BMI, alcohol intake, smoking status, physical activity, family history of diabetes Assessed at beginning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dark bread: 0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>With detailed dietary records</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fiber: 0.78</td>
<td>Self-report</td>
<td>As Salmeron 1997</td>
<td>0.70 (0.51 to 0.96) RRs as odds ratios using logistic regression analysis</td>
<td>N.A.</td>
<td>Age, BMI, alcohol intake, smoking status, physical activity, family history of diabetes Assessed at beginning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carbohydrates: 0.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Professional Follow-up study (Salmeron 1997)</td>
<td>Repeated 1986, 1990</td>
<td>Yes</td>
<td>As Salmeron 1997</td>
<td>Self-report</td>
<td>As Salmeron 1997</td>
<td>0.73 (0.63 to 0.85) RR, pooled logistic regression multivariate models to adjust for confounders</td>
<td>0.62 (0.53 to 0.71) age, energy-adjusted</td>
<td>Age, BMI, physical activity, cigarette smoking, alcohol intake, family history of diabetes in first-degree relatives, use of multivitamins or vitamin E supplements, total energy intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Description</td>
<td>Repeated</td>
<td>Yes</td>
<td>n =</td>
<td>Self-report</td>
<td>n =</td>
<td>RR</td>
<td>RR Proportional Hazards Regression</td>
<td>RR Pooled Logistic Regression</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>----------</td>
<td>-----</td>
<td>-----</td>
<td>-------------</td>
<td>-----</td>
<td>----</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Iowa Women's Health Study (Meyer 2000)</td>
<td></td>
<td>Yes</td>
<td>44</td>
<td>Self-report</td>
<td>44</td>
<td></td>
<td>Cereal fiber: 0.64 (0.53 to 0.79)</td>
<td>pos: 64 % by physicians</td>
</tr>
<tr>
<td>Health Professional Follow-up Study (Fung 2002)</td>
<td>Repeated</td>
<td>Yes</td>
<td>59</td>
<td>Self-report</td>
<td>59</td>
<td>0.72 (0.57 to 0.85) RR pooled logistic regression</td>
<td>0.57 (0.48 to 0.69) age-adjusted</td>
<td>Age, BMI, physical activity, energy intake, missing food frequency questionnaire, smoking, family history of diabetes, alcohol intake, fruit intake, vegetable intake</td>
</tr>
<tr>
<td>Finnish Mobile Clinic Health Examination Survey (Montonen 2003)</td>
<td></td>
<td>Yes</td>
<td>93</td>
<td>Medical certificate needed for reimbursement of drug costs</td>
<td>93</td>
<td>Cereal fiber: 0.37 (0.16 to 0.82)</td>
<td>Cereal fiber: 0.36 (0.18 to 0.70)</td>
<td>Age, sex, geographic area, smoking, BMI intakes of energy, fruit, berries, vegetables, saturated fat, vitamins E and C, beta-carotene, vitamin B 6, folic acid, flavonoids, magnesium</td>
</tr>
<tr>
<td></td>
<td>Repeated</td>
<td></td>
<td>1844</td>
<td>Self-report</td>
<td>1844</td>
<td></td>
<td>Cereal fiber: 0.67 (0.32 to 1.38) RR with Cox's life table regression model for confounders</td>
<td>0.64 (0.36 to 1.15) adjusted for age, sex, geographic area, energy intake</td>
</tr>
</tbody>
</table>

**Whole Grain Foods and Type 2 Diabetes (T2DM)**
Table 4 Quality assessment cohort studies (continued)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Dietary assessment repeated</th>
<th>Dietary assessment validated</th>
<th>Validation correlation coefficient</th>
<th>Method outcome assessment</th>
<th>Validation outcome assessment</th>
<th>RR/HRs (95% CI) corrected for all confounders methods used</th>
<th>RR/HRs (95% CI) initial analyses</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses’ Health Study (Schulze 2004)</td>
<td>Repeated 1995</td>
<td>Not in same population</td>
<td>As Liu 2000, Salmeron 1997</td>
<td>Self-report not in same population</td>
<td>As Liu 2000, Salmeron 1997</td>
<td>Cereal fiber: 0.63 (0.47 to 0.85) RR with Cox’s proportional hazards analysis; multivariate models for confounders</td>
<td>Cereal fiber: 0.32 (0.25 to 0.41) age-adjusted</td>
<td>Age, BMI, energy intake, alcohol, smoking, physical activity, family history of diabetes, history of high blood pressure/high blood cholesterol, postmenopausal hormone use, oral contraceptive used, glycemic load, magnesium, caffeine</td>
</tr>
<tr>
<td>The Atherosclerosis Risk in Communities study (ARIC) (Stevens 2002)</td>
<td>No</td>
<td>Not in same population</td>
<td>Direct measurement fasting glucose, no distinction type 1 and 2 diabetes mellitus</td>
<td></td>
<td></td>
<td>Cereal fiber: Whites 0.75 (0.60 to 0.92) African Americans 0.86 (0.65 to 1.15) Total population 0.79 (0.66 to 0.93) Cox’s proportional hazards analysis; multivariate models for confounders</td>
<td></td>
<td>Age, BMI, energy intake, sex, smoking, education, physical activity, field center, race</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Data Collection</td>
<td>Sample Size</td>
<td>Analysis Method</td>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurses’ Health Study (Liu 2003)</td>
<td>Repeated 1986, 1990, 1994</td>
<td>Yes Self-report</td>
<td>n = 184</td>
<td>Mean change in BMI and in weight; Odds ratio for each quintile of changes in grain intake</td>
<td>Age; changes in exercise; change in smoking status; change in hormone replacement therapy status; changes in intakes of alcohol, caffeine, and total energy; changes in intakes of saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, and protein; and BMI at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Professional Follow-up study (Koh-Banerjee 2004)</td>
<td>Repeated 1990, 1994</td>
<td>Yes Self-report</td>
<td>n = 127</td>
<td>Multivariate linear regression</td>
<td>Age, respective baseline exposure, smoking, baseline weight, baseline values and changes in refined grains, calories, total physical activity, alcohol, protein, trans, saturated, monounsaturated and polyunsaturated fats</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4 Quality assessment cohort studies (continued)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Dietary assessment repeated</th>
<th>Dietary assessment validated</th>
<th>Validation correlation coefficient</th>
<th>Method outcome assessment</th>
<th>Validation outcome assessment</th>
<th>RR/HRs (95 % CI) corrected for all confounders methods used</th>
<th>RR/HRs (95 % CI) initial analyses</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Women’s Health Study (Dam v., 2006)</td>
<td>No</td>
<td>Yes</td>
<td>n = 408 fiber 0.57</td>
<td>Self-report</td>
<td>n = 141</td>
<td>Whole grain: 0.69 (0.60 to 0.79)</td>
<td>Whole grain: 0.52 (0.46 to 0.60)</td>
<td>Age, total energy intake, BMI, smoking status, strenuous physical activity, alcohol consumption, parental history of diabetes, education level, coffee consumption, sugar-sweetened soft drink consumption, quintiles of processed meat and other red meat consumption</td>
</tr>
</tbody>
</table>
Results

Randomised controlled trials

*Primary outcome measures*

Results of insulin sensitivity of both intervention periods were retrieved from the author (Pereira 2002) as only the mean difference was given in the publication. Insulin sensitivity (M value) was measured with the euglycemic hyperinsulinemic clamp test and was significantly higher after the feeding period with whole grain $(0.396 \times 10^{-4} \pm 0.131 \times 10^{-4} \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per pmol/L})$ than after that with refined grain $(0.323 \times 10^{-4} \pm 0.043 \times 10^{-4} \text{ mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per pmol/L})$ (mean difference: $0.07 \times 10^{-4} \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per pmol/L}; 95 \% \text{ CI: } 0.003 \times 10^{-4}, 0.144 \times 10^{-4}; P < 0.05$). To assess violation of the crossover design assumption period X treatment interaction was assessed in the statistical models and not found to be significant.

*Secondary outcome measures*

*Adverse effects*

Gastrointestinal symptoms recorded (heartburn, indigestion, diarrhoea, loose stools) were not significantly different between diets. Frequency of bowel movements significantly increased with the whole-grain diet $(1.8 \pm 0.17 \text{ vs. } 1.4 \pm 0.17 \text{ movements/d}; P < 0.001)$.

*Patient satisfaction*

Patient satisfaction was not included as an outcome.

*Health-related quality of life*

Health-related quality of life was not included as an outcome.

*Total mortality*

Total mortality was not included as an outcome.

*Morbidity*

Morbidity was not included as an outcome.
Costs
Costs were not included as a outcome.

Confounders
Compliance was controlled by comparing the energy content of supplied food not eaten and food that was extra eaten (not supplied).

The energy content of food not eaten during the intervention periods did not differ significantly between the whole-grain (159 ± 75 kJ/d) and the refined-grain (222 ± 126 kJ/d) diets. Also, the energy content of extra food intake was not different (46 ± 25 kJ/d whole-grain diet; 63 ± 33 kJ/d refined-grain diet).

Cohort studies
Data of studies were not pooled because of methodological diversity (measures of effect size, statistical analyses used, number of collected confounders).

Whole grain intake and incidence of type 2 diabetes
Intake of whole grain was inversely associated with risk of type 2 diabetes in all five studies (Figure 02) which, however, was not statistically significant in one study (Montonen 2003). The discrepancy of this results with that of the other studies could be caused by the relatively low number of participants (4316) in this study compared to mostly far more than 10 000 participants in the other studies and which is also reflected in the width of the confidential interval (0.67 (95 %CI 0.32 to 1.38)).

The relative risks (RR) varied between 0.67 (95 %CI 0.32 to 1.38) and 0.79 (95% CI 0.65 to 0.96). After exclusion of studies that did not correct for family history of diabetes (Meyer 2000; Montonen 2003) and physical activity (Montonen 2003), the observed effect was very similar in the rest of the studies (RR of 0.70, 0.73 and 0.73, Figure 2).
Cereal fiber intake and incidence of type 2 diabetes

Intake of cereal fiber was inversely associated with type 2 diabetes in all six studies (Figure 3). The RR varied between 0.37 (95% CI 0.20 to 0.77) and 0.79 (95% CI 0.67 to 0.93). Exclusion of studies that did not correct for family history of diabetes (Meyer 2000; Montonen 2003; Stevens 2002) and physical activity (Montonen 2003) narrowed the range of the effect; the RR lay between 0.63 and 0.72.

Stevens et al (Stevens 2002) also compared the hazard ratios of diabetes in two subpopulations: cereal fiber intake was inversely associated with risk of diabetes in whites and African-American (0.86 (95% CI 0.65 to 1.15)) but statistically different only in whites (0.75 (95% CI 0.60 to 0.92)).

Figure 3 Cereal fiber intake and incidence of type 2 diabetes

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>log[RR] (SE)</th>
<th>RR (random)</th>
<th>Weight %</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2000</td>
<td>-0.3147 (0.0776)</td>
<td>30.61</td>
<td>0.73 (0.63, 0.85)</td>
<td></td>
</tr>
<tr>
<td>Meyer 2000</td>
<td>-0.2357 (0.0994)</td>
<td>18.66</td>
<td>0.79 (0.65, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Fung 2002</td>
<td>-0.3567 (0.0991)</td>
<td>18.77</td>
<td>0.70 (0.58, 0.85)</td>
<td></td>
</tr>
<tr>
<td>Montonen 2003</td>
<td>-0.4005 (0.3687)</td>
<td>1.36</td>
<td>0.67 (0.33, 1.38)</td>
<td></td>
</tr>
<tr>
<td>van Dam 2006</td>
<td>-0.3147 (0.0776)</td>
<td>30.61</td>
<td>0.73 (0.63, 0.85)</td>
<td></td>
</tr>
</tbody>
</table>
**Change in whole grain intake and change in weight gain**

The results of the studies investigating the association between change in whole grain or cereal fiber intake and change in weight gain are shown in Table 5. Over a time period of eight years weight gain was reduced by 0.5 or 0.3 kg in the groups that increased whole grain intake the most (dependent on the definition of whole grain) in one study in men (Koh-Banerjee 2004) and by 0.4 kg over a period of 12 years in another study in women (Liu 2003). Similar results were observed when change in cereal fiber intake was considered (0.4 kg less weight gain in eight years) (Koh-Banerjee 2004). The odds of developing obesity (0.81 (95 %CI 0.73 to 0.91))

**Table 5 Results of studies assessing change and gain in weight**

<table>
<thead>
<tr>
<th>Study</th>
<th>Median change in whole grain intake (g/d)</th>
<th>Lowest quintile</th>
<th>Highest quintile</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh-Banerjee 2003</td>
<td>Jacobs et al definition</td>
<td>-11.0</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in weight (kg) (mean ± SE)</td>
<td>1.25 ± 0.22</td>
<td>0.73 ± 0.22</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Median change in whole grain intake (g/d)</td>
<td>-17.8</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA definition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in weight (kg) (mean ± SE)</td>
<td>0.96 ± 0.22</td>
<td>0.69 ± 0.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Liu 2004</td>
<td>Median change in cereal fiber intake (g/d)</td>
<td>-2.2</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in weight (kg) (mean ± SE)</td>
<td>1.10 ± 0.20</td>
<td>0.76 ± 0.20</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Median change in whole grain intake (serving/1000 kcal/day)</td>
<td>-0.59</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in weight (kg) (mean ± SE)</td>
<td>4.51 ± 0.10</td>
<td>4.12 ± 0.09</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Odds ratio for BMI ≥ 30 (95 % CI) (n = 6400)</td>
<td>1</td>
<td>0.81 (0.73, 0.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Odds ratio for weight gain ≥ 25 kg (95 % CI) (n = 657)</td>
<td>1</td>
<td>0.77 (0.59, 1.01)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
or having a major weight gain (0.77 (95% CI 0.59 to 1.01)) tended to be lower with increased intake of whole grain foods, as reported in the study of Liu et al (Liu 2003).

Assessment of publication bias
Publication bias was not assessed as it was considered to be not useful due to the low number of studies (Lau 2006).

Discussion

Summary
This review identified 12 studies examining the relation between whole grain intake and the development of type 2 diabetes. Only one study was a randomised controlled trial, the other 11 prospective cohort studies. The RCT had a crossover design and showed slight improvement of insulin sensitivity in obese hyperinsulinaemic subjects after the whole grain intervention of six weeks. However, the risk of bias in this study is considered to be high since allocation concealment was not stated and the randomisation procedure was not described. The trial was of short duration (minimum time period needed for inclusion) with a small sample size. Whether the small elevation of the insulin sensitivity has any clinical relevance is doubtful. However, from theoretical perspective it could add to the delay of the onset of type 2 diabetes.

The results of the cohort studies were homogenous. None of the studies showed the opposite effect; in one study the effect was not significant. Significantly decreased risk of development of type 2 diabetes was associated in four cohort studies with high whole grain intake (range: 21–30 %) and in six studies with high cereal fiber intake, (range: 21–63 %) which can be considered to be a marker of whole grain consumption. Two studies investigated the effect of whole grain consumption on overweight, an important risk factor for type 2 diabetes. Increased whole grain consumption was associated with only a very slight reduction (0.3–0.5 kg) in weight gain and a reduced risk of becoming obese during the follow-up period. The slight reductions in weight gain can not be regarded as clinical relevant considering the long time periods (eight and 12 years) in which they were observed.

The methodological quality varied between studies mainly with regard to the food intake assessment and the numbers of confounders considered. Food intake was in most studies assessed with food frequency questionnaires. One limitation of this approach is the small number of food items listed (66–134 items) which
restricts extensive assessment of the food products of interest. None of the food frequency questionnaires was designed especially for assessment of whole grain foods. Measurement error of food intake due to interindividual variation during the course of the years can be reduced by repeated collection of dietary information. Only five studies repeated the measurement to obtain a better reflection of the long-term intake. Measurement errors in dietary intake may thus have limited the ability to obtain accurate risk estimates. Residual confounding is a problem in prospective cohort studies. As observed in these studies, higher intake of whole grain food tends to be associated with healthier lifestyle and incomplete adjustment for lifestyle factors may result in an overestimation of the effect.

Limitations of the review
The main limitation of this review is that evidence of a possible protective effect of a diet rich in whole grain foods on the development of type 2 diabetes is retrieved only from prospective cohort studies of which some were of limited quality. As prospective cohort studies are more prone to bias and confounding than randomised controlled trials results have to be interpreted with caution.

Generalisability and applicability of results
All but one study were conducted in the United States. Most American studies were done in health care workers but the results of three different populations (Iowa women Health study (Meyer 2000), Atherosclerosis Risk in Communities study (Stevens 2002) and U.S. black women study (van Dam 2006)) were comparable as were those of the study conducted in Finland (Montonen 2003). As the majority of studies was conducted in only one part of the world generalisability of results is uncertain.

Reviewers’ conclusions

Implications for practice
The evidence from the prospective cohort trials is considered to be too weak to be able to draw a definite conclusion about the preventive effect of whole grain foods on the development of type 2 diabetes.
Implications for research
Properly designed long-term randomised controlled trials are needed to establish whether whole grain foods are protective for the development of type 2 diabetes. To facilitate this, further mechanistic research should focus on finding a set of relevant intermediate endpoints for type 2 diabetes and on identifying genetic subgroups of the population at risk that are most susceptible to dietary intervention.

Acknowledgements

We thank prof. Mark Pereira and prof. June Stevens for providing additional data on their studies. We are grateful to prof. Ronald Stolk for advice on the final review.

This paper has been written with financial support from the Commission of the European Communities, specific RTD programme “Quality of Life and Management of Living Resources”, QLK 1-2001-00431 “Stable isotope applications to monitor starch digestion and fermentation for the development of functional foods” (www.eurostarch.org). It does not necessarily reflect its views and in no way anticipates the Commission’s future policy in this area.

References

Appendix 1


