Whole grain foods for the prevention of type 2 diabetes mellitus
Priebe, Marion; van Binsbergen, J. J.; de Vos, R.; Vonk, R. J.

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD006061.pub2

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
https://doi.org/10.1002/14651858.CD006061.pub2
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>4</td>
</tr>
<tr>
<td>RESULTS</td>
<td>7</td>
</tr>
<tr>
<td>Figure 1</td>
<td>8</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>12</td>
</tr>
<tr>
<td>AUTHORS' CONCLUSIONS</td>
<td>13</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>13</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>13</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>16</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>18</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 incidence of type 2 diabetes, Outcome 1 Low versus high intake of whole grain</td>
<td>18</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 incidence of type 2 diabetes, Outcome 2 Low versus high intake of cereal fiber.</td>
<td>19</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>19</td>
</tr>
<tr>
<td>WHAT'S NEW</td>
<td>30</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>30</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>31</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>31</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>31</td>
</tr>
</tbody>
</table>

Whole grain foods for the prevention of type 2 diabetes mellitus (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Whole grain foods for the prevention of type 2 diabetes mellitus

Marion Priebe¹, Jaap van Binsbergen², Rien de Vos³, Roel J Vonk¹

¹Department of Medical Biomics, Laboratory Nutrition and Metabolism, University Medical Centre Groningen (UMCG), Groningen, Netherlands. ²Department of General Practice, University Medical Centre, Nijmegen, Netherlands. ³Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

Contact address: Marion Priebe, Department of Medical Biomics, Laboratory Nutrition and Metabolism, University Medical Centre Groningen (UMCG), Antonius Deusinglaan 1, Building 3215 4th floor, Groningen, 9713 AV, Netherlands. M.G.Priebe@med.umcg.nl

Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.


A B S T R A C T

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 effects of whole-grain foods for the prevention of T2DM.

Search methods
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 fibre 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 and analysis
Two authors 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 eleven prospective cohort studies were identified. The randomised controlled trial, which was of low methodological quality, reported the change in insulin sensitivity in 12 obese hyperinsulinemic participants 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 eleven cohort studies measured cereal fibre 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 fibre 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% to 30%) or cereal fibre (28% to 37%) on the development of T2DM.
Authors’ 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.

Plain language summary

Whole grain foods for the prevention of type 2 diabetes mellitus

Food products derived from cereal grains as wheat, rice, corn, rye, oat, and barley constitute a major part of the daily diet in many countries. In refined-grain products, the bran and germ of the grain, which contain the major amount of nutrients and dietary fibre, have been removed and only the starchy inner part of the grain (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 this review the effect of whole grain foods and cereal fibre (as a marker of whole-grain food intake) on the prevention of type 2 diabetes mellitus (T2DM) was assessed using all available prospective cohort studies and randomised controlled trials. Only one randomised controlled trial was found which was of low methodological quality. This study investigated in 12 overweight persons during six weeks the effect of the consumption of refined grain foods versus that of whole grain foods on insulin sensitivity (risk factor for the development of T2DM). Intake of whole grain foods resulted in a slight improvement of insulin sensitivity, increased bowel movements and no adverse effects. No information was given about patient satisfaction, health related quality of life, total mortality and morbidity. In addition eleven prospective cohort studies were found. One study was conducted in Finland and the rest in the United States of America of which seven were done in health care workers. Some of the studies were of limited quality. They consistently showed that a high intake of whole grain foods or cereal fibre is associated with a lower risk of the development of T2DM. However, evidence for a protective effect coming from prospective cohort studies only has to be considered as weak as with this design no cause and effect relationship can be established. Well-designed randomised controlled trials are needed to be able to draw definite conclusions about the preventive effects of whole grain consumption on development of T2DM.

Description of the condition

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 (hyperinsulinemia) 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, impaired fasting glycaemia (glucose values above the normal range but below those defined as diagnostic of diabetes) or both which are 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 impor-
tant 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).

How the intervention might work

Food products derived from cereals as wheat, rice, corn, rye, oat, 
and barley constitute a major part of the daily diet in many coun-
tries (FAO 1998). In refined-grain products, the bran and germ of 
the grain which contain the major amount of micronutrients, phyto-
chemicals 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 ei-
ther intact, flaked or broken grain kernels, coarsely ground ker-
nels 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 com-
ponents -- 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 foods by highly refined 
grain foods is linked to the development of type 2 diabetes and 
other chronic diseases (Burkiit 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 foods 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; Sjoholm 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 asso-
ciated 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 de-
velopment of type 2 diabetes would ideally be evaluated by ran-
domised control trials because of their optimal control of con-
 founding 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 factors 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 compli-
ance 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, flatulence or both in sensitive persons. Due to 
these limitations with regard to trial duration and compliance ran-
domised controlled trials assessing the effect of whole-grain foods 
 on the development of type 2 diabetes are likely to be scarce.

Why it is important to do this review

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 ev-
idence -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 effects of whole-grain foods for the prevention of type 
2 diabetes mellitus.
METHODS

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.

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 (m^2)) (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 hyperinsulinemic, euglycemic conditions, glucose uptake below lowest quartile for background population under investigation is defined as insulin resistance according to the WHO (WHO 1999).

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 (m^2)) (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 hyperinsulinemic, euglycemic 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 fibre (as marker for whole grain food intake).
Types of outcome measures

Primary outcomes

Randomised controlled trials or controlled clinical trials
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.

Cohort studies
- Incidence of type 2 diabetes mellitus.

Secondary outcomes

Randomised controlled trials or controlled clinical trials
- adverse effects (for example bloating, flatulence);
- patient satisfaction;
- health-related quality of life;
- total mortality;
- morbidity;
- costs.

Search methods for identification of studies

Electronic searches
The following electronic data bases were searched:
- The Cochrane Library (issue 2, 2006);
- MEDLINE (until May 2006);
- EMBASE (until May 2006);
- CINAHL (until May 2006);
- AMED (until May 2006).

The database of ongoing trials, 'Current Controlled Trials' (www.controlled-trials.com - until May 2006) and the 'Science Citation Index' was searched (until October 2006), the latter to identify relevant studies that cited the primarily retrieved studies. No language restriction was applied for searching and study inclusion.

The described search strategy (see for a detailed search strategy under Appendix 1) was used for MEDLINE. For use with the other databases this strategy was slightly adapted.

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

Handsearches
The reference lists of all included studies and of review articles were screened in order to identify possible studies of interest. The handsearch 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.

Data collection and analysis

Selection of studies
The title and abstract of each record of the search was independently assessed by two authors (MGP, JvB). 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.
Differences between authors’ 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.

Data extraction and management

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

From (randomised) controlled trials the following data were extracted:

- general information: published/unpublished, title, authors, source, country, year of publication, funding, duplicate publication;
- trial characteristics: design, duration, randomizations, concealment of allocation, blinding, checking of blinding;
- intervention: length of intervention, dietary advice/diet provided, comparison interventions;
- 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;
- outcomes: outcomes specified above, main outcomes assessed in the study;
- 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).

- general information: published/unpublished, title, authors, source, country, year of publication, duplicate publication;
- study characteristics: design, dates of enrolment, follow-up;
- exposure: type, type of measurement, validation of measurement, time-points measurements;
- 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.

Assessment of risk of bias in included studies

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 drop-outs completely described? was analysis by intention-to-treat?
4. Minimisation of detection bias - were outcome assessors blind to the intervention?

Ad 2) As the treatment was 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 (Higgins 2005):

- 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 independently examined by two authors. Differences in results were resolved by discussion and if necessary a third author was consulted.

Assessment of reporting biases

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

Data synthesis

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 ratios or hazard ratios. In RCTs intention-to-treat analysis was planned to be used when the information was 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 2003) 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 analysis and investigation of heterogeneity

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 analysis

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

- repeating the analysis excluding unpublished studies (if there were any).
- repeating the analysis taking account of study quality, as specified above.
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.
- 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 statistical models (fixed and random-effects models).

RESULTS

Description of studies

Results of the search

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 The Cochrane Library 259 more studies (total 5804 possibly eligible studies). With the initial screening of the 5804 possibly eligible studies 22 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). For an overview of study selection please see Figure 1 showing details of the amended QUOROM (quality of reporting of meta-analyses) statement.
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 was retrieved by this means. The possibility that certain publications were duplicates was 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 authors’ results were resolved by discussion.

**Missing data**

Two authors were contacted to retrieve additional information.

**Included studies**

In total 12 studies were identified that met all the inclusion criteria. One study was a randomised controlled trial and eleven were cohort studies. Details of the randomised controlled trial are listed in Appendix 2 and details of the prospective cohort studies are shown in Appendix 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 washout period of six to nine weeks.

**Participants**

Twelve overweight or obese (BMI 27 to 36 kg/m²) hyperinsulinemic adults aged 25 to 56 years (six women, six men) took part in the trial.
Interventions

One diet contained products of refined grains, thus products with no bran or germ and little fibre. 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 centre where the study was conducted. The participants stayed there during the two 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 (euglycemic hyperinsulinemic 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 fibre 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 to 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-Americans (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 fibre 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 fibre 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 fibre intake (Koh-Banerjee 2004).

Whole grain food was defined in most studies (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 fibre, 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/m$^2$) 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 ratios (OR) in one study (Liu 2003) or hazard ratios (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 (see under Appendix 4. Qality assessment of cohort studies” as well as the initial and adjusted effect sizes. In the publications no information of goodness of fit of the statistical models were 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 aetiology of atherosclerosis and variation in cardiovascular risk factors, medical care and disease by race, gender, location and date.

**Excluded studies**

Eleven studies were excluded. The main reason of exclusion was that the diet administered during the intervention did not fulfil the inclusion criteria (for details see under Characteristics of excluded studies).

**Risk of bias in included studies**

**Randomised controlled trials**

The included trial (Pereira 2002) was a six-week intervention study in 12 persons with a cross-over design and a washout 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 three 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 (see under Appendix 4). Thirty six percent 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 fibre 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 an 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 (see Appendix 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 to 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)
an FFQ was used that was not validated in a subgroup of the same
population. Examples of relevant correlation coefficients are listed
in Appendix 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 lay between six and twelve 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 sent 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
authors’ results were resolved by discussion.

Effects of interventions

Randomised controlled trial

**Primary outcome measures**

Results of insulin sensitivity measurements 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 \((0.323 \times 10^{-4} \pm 0.043 \times 10^{-4} \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per pmol/L})\) (mean difference: \(0.07 \times 10^{-4} \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ per pmol/L}, 95\%\ CI 0.003 \times 10^{-4} \text{ to } 0.144 \times 10^{-4}; P < 0.05\)). To examine violation of the cross-over design assumption, the period by treatment interaction was
assessed in statistical models and not found to be significant. In
all the final models the main effect of period was included.

**Secondary outcome measures**

**Adverse effects**

Gastrointestinal symptoms recorded (heartburn, indigestion, di-
arrhoea, loose stools) were not significantly different between di-
ets. Frequency of bowel movements significantly increased with
the whole-grain diet \((2 \pm 0.2 \text{ versus } 1 \pm 0.2 \text{ movements/d}; P <
0.001)\).

**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 an outcome.

**Confounders**

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

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

**Cohort studies**

Data of studies were not pooled because of methodological diver-
sity (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 (comparison 01.01) which, however, was not statistically significant in one study (Montonen 2003). The discrepancy of this result with that of the other studies could be caused by the relatively low number of participants (4,316) in this study compared to mostly far more than 10,000 participants in the other studies, which is also reflected by the width of the confidential interval (0.67, 95% confidence interval (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; Stevens 2002) 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).

**Cereal fibre intake and incidence of type 2 diabetes**

Intake of cereal fibre was inversely associated with type 2 diabetes in all six studies (comparison 01.02). 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 fibre intake was inversely associated with risk of diabetes in whites and African-Americans (0.86,95% CI 0.65 to 1.15) but statistically different only in whites (0.75, 95% CI 0.60 to 0.92).

**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 fibre intake and change in weight gain are shown in Appendix 5. Over a time period of eight years weight gain was reduced by 0.5 kg 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 fibre 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) 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 of main results**

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 cross-over design and showed slight improvement of insulin sensitivity in obese hyperinsulinaemic participants 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 a 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% to 30%) and in six studies with high cereal fibre intake, (range: 21% to 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 to 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 twelve 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 to 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 inter-individual 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 of lifestyle factors may result in an overestimation of the effect.
Potential biases in the review process

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.

AUTHORS’ 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 draft of the 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

References to studies included in this review

Fung 2002 [published data only]

Koh-Banerjee 2004 [published data only]

Liu 2000 [published data only]

Liu 2003 [published data only]

Meyer 2000 [published data only]

Montonen 2003 [published data only]

Pereira 2002 [published data only]

Salmeron 1997a [published data only]
Whole grain foods for the prevention of type 2 diabetes mellitus (Review)

References to studies excluded from this review

Bakker 1998 [published data only]

Feskens 1991 [published data only]

Hodge 1996 [published data only]

Wolever 2002 [published data only]

Wolever 2003 [published data only]

Additional references

ADA 1997

ADA 1999

Burkitt 1975

Cohen 1960

Dandona 2004

Egger 1997

FAO 1998
Whole grain foods for the prevention of type 2 diabetes mellitus (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.


**FAO/WHO 2003**

**FDA 2005**

**FDA 2006**

**Fung 2002**

**Higgins 2003**

**Higgins 2005**

**Jacobs 1998**

**Jadad 1996**

**Koh-Banerjee 2003**

**Lau 2006**

**Liu 1999**

**Liu 2002**

**Liu 2003**

**Ludwig 2002**

**McKown 2002**

**McKown 2004**

**Meyer 2000**

**Montonen 2003**

**Monzillo 2003**

**Murtaugh 2003**

**NDDG 1979**

**Robertson 2004**
Schulz 1995

Sjoholm 2005

Slavin 2003

Steffen 2003

Trowell 1975

Unwin 2002

WHO 1980

WHO 1985

WHO 1999

Willett 2002

* Indicates the major publication for the study
### CHARACTERISTICS OF STUDIES

**Characteristics of excluded studies  [ordered by study ID]**

<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>Both 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>
### DATA AND ANALYSES

**Comparison 1. incidence of type 2 diabetes**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Low versus high intake of whole grain</td>
<td>5</td>
<td>RR or HR (Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
<tr>
<td>2 Low versus high intake of cereal fiber</td>
<td>6</td>
<td>RR or HR (Random, 95% CI)</td>
<td>Totals not selected</td>
<td></td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 incidence of type 2 diabetes, Outcome 1 Low versus high intake of whole grain.**

Review: Whole grain foods for the prevention of type 2 diabetes mellitus

Comparison: 1 incidence of type 2 diabetes

Outcome: 1 Low versus high intake of whole grain

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [RR or HR] (SE)</th>
<th>RR or HR (IV, Random, 95% CI)</th>
<th>RR or HR (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2000</td>
<td>-0.3147 (0.0776)</td>
<td>0.73 [0.63, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Meyer 2000</td>
<td>-0.2357 (0.0994)</td>
<td>0.79 [0.65, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Fung 2002</td>
<td>-0.3567 (0.0991)</td>
<td>0.70 [0.58, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Montonen 2003</td>
<td>-0.4005 (0.3687)</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>0.73 [0.63, 0.85]</td>
<td></td>
</tr>
</tbody>
</table>

Favours high intake  
Favours low intake
# Analysis 1.2. Comparison 1 incidence of type 2 diabetes, Outcome 2 Low versus high intake of cereal fiber.

**Review:** Whole grain foods for the prevention of type 2 diabetes mellitus

**Comparison:** 1 incidence of type 2 diabetes

**Outcome:** 2 Low versus high intake of cereal fiber

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [RR or HR] (SE)</th>
<th>RR or HR IV/Random 95% CI</th>
<th>RR or HR IV/Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeron 1997a</td>
<td>-0.3285 (0.1138)</td>
<td>0.72 [0.58, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Salmeron 1997b</td>
<td>-0.3567 (0.1611)</td>
<td>0.70 [0.51, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Meyer 2000</td>
<td>-0.4463 (0.1074)</td>
<td>0.64 [0.52, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Stevens 2002</td>
<td>-0.2357 (0.0832)</td>
<td>0.79 [0.67, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Montonen 2003</td>
<td>-0.9934 (0.406)</td>
<td>0.37 [0.17, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Schulze 2004</td>
<td>-0.462 (0.1528)</td>
<td>0.63 [0.47, 0.85]</td>
<td></td>
</tr>
</tbody>
</table>

Favours high intake 0.2 0.5 1 2 5
Favours low intake

## APPENDICES

### Appendix 1. Search strategy

**Search terms**

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

1. wholemeal$.tw.
2. whole meal$.tw.
3. wholegrain$.tw.
4. whole grain$.tw.
5. exp CEREALS/
6. cereal$.tw.
7. grain$.tw.
8. exp Dietary fibre/
9. dietary fibre$.tw.
10. dietary fibre$.tw.
11. exp Dietary Carbohydrates/
12. exp Glycemic index/
13. dietary carbohydrate$.tw.
14. (glycemic ind$ 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/
22. exp Diabetes Mellitus, Type 2
23. exp Metabolic Syndrome X/
24. or /16-23
25. 15 and 24

Appendix 2. Characteristics: randomized controlled trial

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Allocation conc.</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 &gt; 26 and &lt; 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</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>
- 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 > 6.0 mmol/L
- Fasting insulin < 90 pmol/L

### Appendix 3. Characteristics: cohort studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Allocation conc.</th>
<th>Outcome</th>
<th>No. cases</th>
<th>Med. intake low qu.</th>
<th>Med. intake high qu.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pereira 2002</td>
<td>Cross-over non-blinded RCT; 2 feeding periods of 6 weeks, wash-out period of 6 - 9 weeks; randomisation done but method</td>
<td>6 men, 6 women; age: 21 - 65 y</td>
<td>Exclusion criteria: - Body Mass Index &gt; 26 and &lt; 36 - Body weight fluctuation over</td>
<td>Refined grain foods versus whole grain foods at breakfast, lunch and dinner; food provided</td>
<td>Unclear</td>
<td>T2 DM</td>
<td>915</td>
<td>Cereal fibre: 2 g/d</td>
<td>Cereal fibre: 8 g/d</td>
</tr>
</tbody>
</table>
### Continued

<table>
<thead>
<tr>
<th></th>
<th>the past 6 mo of &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Smoking cigarettes</td>
</tr>
<tr>
<td></td>
<td>- Consuming &gt; 2 alcoholic beverages/d</td>
</tr>
<tr>
<td></td>
<td>- Having diabetes, cancer, cardiovascular disease and other chronic clinical conditions</td>
</tr>
<tr>
<td></td>
<td>- Taking medications that would affect glucose, insulin, lipids or blood pressure</td>
</tr>
<tr>
<td></td>
<td>- Engaging in a high level of physical activity</td>
</tr>
<tr>
<td></td>
<td>- Following a special diet</td>
</tr>
<tr>
<td></td>
<td>- Allergic to any foods</td>
</tr>
<tr>
<td></td>
<td>- Planning to change dietary habits, increase physical activity, change insulin sensitivity, side effects</td>
</tr>
</tbody>
</table>

**Whole grain foods for the prevention of type 2 diabetes mellitus (Review)**

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Body weight, move out of town or take a lengthy vacation during the time of the study
- Fasting blood glucose > 6.0 mmol/L
- Fasting insulin < 90 pmol/L

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number</th>
<th>Follow-up</th>
<th>Age</th>
<th>FFQ Description</th>
<th>T2 DM</th>
<th>Cereal fibre: d</th>
<th>Whole grain: servings/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer 2000</td>
<td>United States</td>
<td>35 988 women</td>
<td>1986 - 1992 6 years</td>
<td>55 - 69 y</td>
<td>127-item FFQ</td>
<td>T2 DM</td>
<td>1141</td>
<td>Whole grain: 0 servings/day</td>
</tr>
<tr>
<td>Fung 2002</td>
<td>United States</td>
<td>42 898 men</td>
<td>1986 - 1998 12 years</td>
<td>40 - 75 y</td>
<td>131-item FFQ</td>
<td>T2 DM</td>
<td>1197</td>
<td>Whole grain: 1 serving/week</td>
</tr>
<tr>
<td>Montonen 2003</td>
<td>Finland</td>
<td>4 316: 2 286 men 2 030 women</td>
<td>1966 - 1972 6 years</td>
<td>40 - 69 y</td>
<td>dietary history interview with 100-item FFQ</td>
<td>T2 DM</td>
<td>156</td>
<td>Whole grain: 0 - 109 g/d</td>
</tr>
</tbody>
</table>

Footnotes conc: concealment
<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gender</th>
<th>Number of Participants</th>
<th>Years</th>
<th>FFQ Type</th>
<th>T2 DM</th>
<th>Cereal fibre:</th>
<th>Cereal fibre:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulze 2004</td>
<td>United States</td>
<td>91 women</td>
<td>249</td>
<td>1991-1999 8 years</td>
<td>24-44 y</td>
<td>133-item FFQ</td>
<td>741</td>
<td>3 g/d</td>
</tr>
<tr>
<td>Stevens 2002</td>
<td>United States</td>
<td>12 whites</td>
<td>251 9</td>
<td>1987-1998 11 years</td>
<td>45-65 y</td>
<td>66-item FFQ interviewer administered</td>
<td>1447</td>
<td>2 g/d</td>
</tr>
<tr>
<td>Liu 2003</td>
<td>United States</td>
<td>74 women</td>
<td>091</td>
<td>1984-1996 12 years</td>
<td>38-63 y</td>
<td>126-item FFQ</td>
<td></td>
<td>Obesity, body weight change</td>
</tr>
<tr>
<td>Koh-Banerjee 2004</td>
<td>United States</td>
<td>27 men</td>
<td>082</td>
<td>1986-1994 8 years</td>
<td>40-75 y</td>
<td>131-item FFQ</td>
<td></td>
<td>Body weight change</td>
</tr>
<tr>
<td>van Dam 2006</td>
<td>United States</td>
<td>41 African-American women</td>
<td>186</td>
<td>1995-2003 8 years</td>
<td>21-69 y</td>
<td>68-item FFQ</td>
<td>1964</td>
<td>Whole grains: 0 servings/day</td>
</tr>
</tbody>
</table>
**Appendix 4. Quality assessment: of cohort studies**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Diet. ass. repeated</th>
<th>Diet. ass. validated</th>
<th>Validation corr. co.</th>
<th>Method outcome ass.</th>
<th>Validation outcome</th>
<th>Crude RR/HR, method</th>
<th>Adjusted RR/HR</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeron 1997a</td>
<td>no</td>
<td>yes</td>
<td>n = 173</td>
<td>white bread: 0.71 dark bread: 0.77</td>
<td>self-report</td>
<td>n = 62 confirmed by medical record</td>
<td>not reported</td>
<td>Cereal fibre: 0.72 (95% CI 0.58 to 0.90) age, BMI, alcohol intake, smoking status, physical activity, family history of diabetes</td>
</tr>
<tr>
<td>Salmeron 1997b</td>
<td>no</td>
<td>yes</td>
<td>n = 127</td>
<td>fibre: 0.78 carbohydrates: 0.81</td>
<td>self-report</td>
<td>as Salmeron 1997a</td>
<td>not reported</td>
<td>Cereal fibre: 0.70 (95% CI 0.51 to 0.96) age, BMI, alcohol intake, smoking status, physical activity, family history of diabetes</td>
</tr>
<tr>
<td>Liu 2000</td>
<td>repeated 1986, 1990</td>
<td>yes</td>
<td>as Salmeron 1997a</td>
<td>self-report</td>
<td>as Salmeron 1997a</td>
<td>Whole grain: 0.62 (95% CI 0.53 to 0.71) age, energy adjusted pooled logistic regression</td>
<td>Whole grain: 0.73 (95% CI 0.63 to 0.85) age, BMI, physical activity, cigarette smoking, alcohol intake, family history of diabetes in first-</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes**
- FFQ: food frequency questionnaire
- T2 DM: type 2 diabetes mellitus
- med: median
- low: lowest
- high: highest
- qu: quartile/quintile

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Randomization</th>
<th>Number</th>
<th>Setting</th>
<th>Method of assessing grain intake</th>
<th>Method of assessing fibre</th>
<th>Adjusted for variables</th>
<th>Results of fibre intake</th>
<th>Results of whole grain intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer 2000</td>
<td>no</td>
<td>yes</td>
<td>n = 44</td>
<td>self-report</td>
<td>n = 41 (100%) pos: 64% by physicians</td>
<td>not reported proportional hazard regression</td>
<td>age, total energy intake, BMI, waist-to-hip ratio, education, pack-years of smoking, alcohol intake, physical activity</td>
<td>Cereal fibre: 0.64 (95% CI 0.53 to 0.79) Whole grain: 0.79 (95% CI 0.65 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>Fung 2002</td>
<td>repeated 1990, 1994, 1998</td>
<td>yes</td>
<td>as Salmeron 1997b self-report</td>
<td>n = 59 (97% confirmed) Whole grain: 0.57 (95% CI 0.48 to 0.69) age adjusted, pooled logistic regression</td>
<td>Whole grain: 0.72 (95% CI 0.57 to 0.85)</td>
<td>age, BMI, physical activity, energy intake, missing food frequency questionnaire, smoking, family history of diabetes, alcohol intake, fruit intake, vegetable intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montonen 2003</td>
<td>no</td>
<td>yes</td>
<td>4-8 mo, n = 93 total grain: 0.62, 4-7 y, n = 1844 total grain: 0.39 medical certificate needed for reimbursement of drug costs</td>
<td>not reported Cox's life table regression model</td>
<td>Cereal fibre: 0.37 (95% CI 0.16 to 0.82) Whole grain: 0.67 (95% CI 0.32 to 1.38)</td>
<td>age, sex, geographic area, smoking, BMI, intakes of energy, fruit, berries, vegetables, saturated fat, vitamins E and C, beta-carotene, vi-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study, Year</td>
<td>Design</td>
<td>Population</td>
<td>Methodology</td>
<td>Measures of Association</td>
<td>Covariates</td>
<td>Study Quality</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>
<td></td>
</tr>
<tr>
<td>Schulze 2004</td>
<td>repeated 1995</td>
<td>not in same population</td>
<td>self-report not in same population</td>
<td>Cereal fibre: 0.32 (95% CI 0.25 to 0.41)</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 use, glycemic load, magnesium, caffeine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens 2002</td>
<td>no</td>
<td>not in same population</td>
<td>direct measurement of fasting glucose, no distinction type 1 and 2 diabetes mellitus</td>
<td>Cereal fibre: Whites: 0.75 (95% CI 0.60 to 0.92) African Americans: 0.86 (95% CI 0.65 to 1.15) Total population: 0.79 (95% CI 0.66 to 0.93)</td>
<td>age, BMI, energy intake, sex, smoking, education, physical activity, field center, race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2003</td>
<td>repeated 1986, 1990, 1994</td>
<td>yes</td>
<td>self-report</td>
<td>n = 184 correlation 0.96 self-report</td>
<td>not applicable for results</td>
<td>age, changes in exercise, change in smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koh-Banerjee 2004</td>
<td>repeated 1990, 1994</td>
<td>yes</td>
<td>n = 127 refined-grain foods: 0.30 cold breakfast cereals: 0.86</td>
<td>self-report:</td>
<td>n = 123 correlation 0.97 self-reported with measured</td>
<td>see 'Additional tables' Table 04</td>
<td>BMI at baseline, 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, BMI at baseline</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>
<td></td>
</tr>
<tr>
<td>van Dam 2006</td>
<td>no</td>
<td>yes</td>
<td>n = 408 fibre 0.57</td>
<td>self-report</td>
<td>n = 141 95% confirmed by physicians Whole grain: 0.52 (95% CI 0.46 to 0.60) age-</td>
<td>Whole grain: 0.69 (95% CI 0.60 to 0.79)</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>
</tr>
</tbody>
</table>
adjusted Cox’s proportional hazard regression models

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, low-fat dairy consumption

Footnotes: diet: dietary assessment corr: correlation co: coefficient

Appendix 5. Results of studies assessing change and gain in weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Measurement</th>
<th>Lowest quintile</th>
<th>Highest quintile</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh-Banerjee 2003</td>
<td>Median change in whole grain intake (g/d)</td>
<td>- 11</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jacobs 1998 definition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in weight (kg) (mean +/- SE)</td>
<td>1.3 +/- 0.2</td>
<td>0.7 +/- 0.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Koh-Banerjee 2003</td>
<td>Median change in whole grain intake (g/d)</td>
<td>- 18</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA definition</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Continued

<table>
<thead>
<tr>
<th>Change in weight (kg) (mean +/- SE)</th>
<th>1.0 +/- 0.2</th>
<th>0.7 +/- 0.2</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh-Banerjee 2003</td>
<td>Median change in cereal fibre intake (g/d)</td>
<td>- 2</td>
<td>5</td>
</tr>
<tr>
<td>Change in weight (kg) (mean +/- SE)</td>
<td>1.1 +/- 0.2</td>
<td>0.8 +/- 0.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>Liu 2004</td>
<td>Median change in whole grain intake (serving/day)</td>
<td>- 1</td>
<td>1</td>
</tr>
<tr>
<td>Change in weight (kg) (mean SE)</td>
<td>4.5 +/- 0.1</td>
<td>4.1 +/- 0.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Liu 2004</td>
<td>Odds ratio for BMI &gt; 29.9 (n = 6 400)</td>
<td>1</td>
<td>0.81 (95% CI 0.73 to 0.91)</td>
</tr>
<tr>
<td>Liu 2004</td>
<td>Odds ratio for weight gain &gt; 24.9 kg (n = 657)</td>
<td>1</td>
<td>0.77 (95% CI 0.59 to 1.01)</td>
</tr>
</tbody>
</table>

**WHAT’S NEW**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 November 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>
CONTRIBUTIONS OF AUTHORS

MARION G PRIEBE: drafting protocol/review, searching and selection of studies, data extraction, quality assessment, data analysis and presentation

JAAP J VAN BINSBERGEN: contribution nutritional knowledge, co-drafting protocol, searching and selection of studies, data extraction, quality assessment, data presentation, co-drafting review

RIEN DE VOS: assistance with statistics and data analysis

ROEL J VONK: securing funding for review, co-drafting review, providing general advice on the review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• Commission of the European Communities, Brussels, Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

*Edible Grain [adverse effects]; Diabetes Mellitus, Type 2 [*prevention & control]; Dietary Fiber [administration & dosage]; Insulin Resistance

MeSH check words

Humans