Whole-grain and body weight changes in apparently healthy adults:

A systematic review and meta-analysis of controlled trials

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SYNOPSIS

BACKGROUND: Observational studies have found that whole-grain intake is related to CVD and to some extent diabetes and metabolic syndrome. One explanatory mechanism is that whole-grain intake reduces weight gain or induces weight loss. To combine all evidence, a systematic review and meta-analysis of controlled trials will be performed.

PURPOSE: To evaluate the evidence for a role of whole-grain and whole-grain foods compared to non-whole-grain or refined grain foods in body weight and body composition in apparently healthy adults.

DATA SOURCES: Selected bibliographic databases will be systematically searched; also reference lists from the retrieved trials and main reviews will be searched by hand to find additional studies.

STUDY SELECTION: Controlled trials performed in humans will be eligible if the effect of whole-grain consumption can be extracted between the intervention and control group. Change in body weight or body composition should be an outcome measure (major or minor).

DATA EXTRACTION: Weighted mean differences will be calculated using RevMan and SAS Software, and meta-regression analysis will be performed using duration of intervention (weeks) and dose of whole grain (g/d).

PERSPECTIVES: This systematic review and meta-analysis will provide an overview on the impact of whole-grain consumption on changes in body weight based on the current evidence.

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BACKGROUND

Overweight and obesity have become one of the biggest public health problems in Western society nowadays. Because obesity leads to serious health problems like diabetes mellitus type 2, cardiovascular diseases, metabolic syndrome and some types of cancer (1), reducing and preventing obesity is an urgent public health aim.

Whole-grain has become a hot topic in recent years (2). This is indicated by the number of papers published on whole-grain has increased markedly (76 hits in PubMed ‘on wholegrain’/’whole grain’ in 1990-1999 to 248 hits in 2000-2009). Many observational studies link high intakes of whole-grain foods with reduced risk of cardiovascular disease (3-7), incidence of type 2 diabetes (5;8-11) and mortality (7;12), whereas the link to risk for developing different types of cancers is less consistent (13). Observational studies also show that a high intake of whole-grain foods has been associated with a smaller weight gain per energy intake (7;14-17). When body weight is reduced in overweight subjects, insulin sensitivity, blood pressure, lipid metabolism and inflammation will be improved, with an overall beneficial effect on the cardiovascular risk profile (18). The role of whole-grain in health and disease has therefore become clearer, but the overall effect on changes in body weight is not known yet.

The main whole-grains consumed worldwide are wheat, rice, and maize, followed by oats, rye, barley, triticale, millet, and sorghum (19). Whole-grain cereals are a rich source of fiber and bioactive compounds.

According to the Danish guidelines the definition for whole-grain used in this review is as follows: "Whole grain shall consist of the intact, ground, cracked or flaked kernel after the removal of inedible parts such as the hull and husk. The principal anatomical components - the starchy endosperm, germ and bran - are present in the same
relative proportions as they exist in the intact kernel. Small losses of components - i.e. less than 2% of the grain/10% of the bran - that occur through processing methods consistent with safety and quality are allowed.” Foods containing other ingredients than whole-grain should contain ≥51% whole-grain in dry matter to be a whole-grain food (20).

Proposed mechanisms of action

Whole-grain consumption can affect body weight in several ways. Fardet (2011) suggested a number of potential mechanisms of whole-grain on weight loss. Firstly, bioactive compounds in whole-grain such as dietary fiber, fructans, resistant starch, zinc, calcium, tocotrienols, phenolic acids, flavonoids, choline, and p-aminobenzoic acid may be involved in weight change, by increasing satiation, decreasing energy intake, decreasing glycemia, regulating fat metabolism in adipocytes, increasing fatty acid oxidation and decreasing adipose tissues (19). Secondly, whole-grain can affect the mechanical part on the digestive tract by increasing transit time in the gastrointestinal tract and fecal bulking (by e.g. particle size and food structure). Finally, whole-grain intake can induce a change in the content of microbiota, the composition of microbiota, and the products of fermentation (21), which has also been suggested to be involved in body weight regulation.

Why is this review important?

There are indications from observational studies that whole-grain may positively affect body weight management, but until now no systematic review and meta-analysis have been carried out to quantify the effect of whole-grain on body weight. Therefore, we will
carry out a systematic review and meta-analysis, to quantify the evidence whether whole-grain intake is useful in maintaining a healthy body weight in apparently healthy adults.

**Objectives**

The objective is to evaluate the evidence for a role of whole-grain and whole-grain foods in terms of a healthier body weight and body composition compared to non-whole-grain or refined grain foods in apparently healthy adults. Furthermore, we will also explore whether the effect of whole-grain on body weight depends on whole-grain type, dose of whole-grain, background diet (calorie-restricted or not), and which control is used (refined grain versus nothing).
METHODS

Protocol and registration

A systematic literature search followed by study selection, according to defined eligibility criteria, data mining, and statistical analysis will be performed based on this predefined protocol which is designed according to the Cochrane Collaboration guidelines (http://www.cochrane-handbook.org/). The further reporting will follow the recommendations from the PRISMA statement (22).

Eligibility criteria

Controlled trials, both parallel and crossover interventions, will be considered eligible if they (i) Enrolled apparently healthy adults - i.e. males and females >18 and <65 years of age, normal, overweight or obese, and not diagnosed with diabetes mellitus, cardiovascular diseases, or on statin treatment; (ii) Examined the effect of whole-grain foods or diets high in whole-grain foods compared to the same background diet or diets not containing whole-grain, whether they are calorie-restricted or not and (iii) Reported changes in body weight (kg). Multiple-component interventions or interventions which incorporated factors other than whole-grain foods or diets, unless the effect of whole-grain foods or diets can be separated from the other factors, will be excluded. Also, studies on foods which were based only on individual components (e.g. bran, germ, or other components) of the grain will be excluded. Studies that examined the effects of high fiber, dietary fiber or cereal fiber, but where the specific effect of whole-grain foods or diets could not be distinguished, will also be excluded. There will be no limit on the duration of the studies considered to be eligible. Blinding is very difficult in a trial about whole-grain. Therefore this will not be an exclusion criterion in our review.
**Information sources**

The preliminary literature search for potentially eligible studies will be conducted by KP & MK and supervised by an experienced research librarian (EMB). The following bibliographic databases will be searched: MEDLINE (via PubMed, from 1953 until recent), Embase (via Ovid, from 1980 until recent), AGRICOLA (via Ovid, from 1970 until recent), AGRIS (via Ovid, from 1975 until recent), CAB Abstracts (via Ovid, from 1910 until recent), Food Science and Technology Abstracts (FSTA) (via Ovid, from 1969 until recent), Web of Science (from 1900 until recent), and Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane library).

**Search**

The searches will be limited to human studies, but there will be no limits on language or publication type.

We will search for the following words: (whole grain* OR wholegrain* OR wholemeal OR whole meal OR wholewheat OR whole wheat OR brown rice) AND (wheat* OR rice OR barley OR maize OR corn OR rye OR oat* OR millet* OR sorghum OR tef* OR triticale OR canary seed OR Job’s tears OR fonio OR wild rice OR amaranth OR buckwheat OR quinoa OR spelt OR emmer OR faro OR einkorn OR kamut OR durum* OR bread OR cereals OR flour) AND (body weight OR weight gain OR weight loss OR body weight change* OR body mass index OR BMI OR waist circumference OR body fat OR fat percentage OR fat mass OR body fat distribution OR body weights and measures OR abdominal fat) AND controlled.
In addition, the reference lists of included studies and reviews on this topic will be searched in order to find other potentially eligible studies. Known experts in the field will also be contacted and asked whether they know about further studies concerning this topic.

**Study selection**

To determine the studies to be assessed further, two authors (KP & MK) will independently scan titles and abstracts of every record retrieved. Then all potentially relevant articles will be investigated as full text by the same two authors. Where differences of opinion exist, these will be resolved by a third party (IT).

**Data collection process**

For studies that fulfill the inclusion criteria, two investigators (KP & MK) will independently abstract relevant population and intervention characteristics, using standard data extraction templates, including (i) General information, i.e. title, authors, year of publication, abstract / full paper; (ii) Trial characteristics – i.e. design, duration (weeks), randomization (and method), allocation concealment (and method); (iii) Intervention – i.e. dietary information/foods provided, types and amounts of whole-grains (g/day), length of intervention, comparison intervention, background diet calorie-restricted or not; (iv) Participants, i.e. total number and number in comparison groups, gender, average age, sampling (random/convenience), withdrawals and losses to follow up, assessment of compliance and (v) Outcomes, i.e. body weight (kg), body fat (% or kg), waist circumference (cm), total cholesterol (mmol/L), and adverse events. Any relevant missing
information on a trial will be sought from the original author(s) of the study, if required. Two investigators (KP & MK) will be responsible for the data mining.

**Data items**

Besides the major outcome, body weight change (kg), three minor outcome measures will be investigated which are body fat (%), waist circumference (cm), and total cholesterol (mmol/L).

**Risk of bias in individual studies**

In order to assess risk of bias, using the Cochrane Collaboration’s tool (23), two authors (KP & MK) will independently assess whether each of the following domains would be considered adequate, i.e. presumably with a low risk of bias (i) ‘Adequate sequence generation’; (ii) ‘Allocation concealment’; (iii) ‘Blinding of participants and personnel’; (iv) ‘Incomplete outcome data addressed’; (v) ‘Free of selective reporting’ and (vi) ‘Free of other biases’. Each of these key components of methodological quality will be assessed on a Yes/No/Unclear basis.

**Summary measures**

We will calculate the weighted mean difference for the difference in means for all the continuous outcomes extracted. For crossover trials lacking data on standard errors (SEs) for paired differences (SEΔ), the pooled SE will be estimated assuming a correlation at a conservative level of 0 between intervention and control periods (r = .0) in crossover trials.
Synthesis of results

To combine the individual study results, we will perform a meta-analysis using Review Manager and SAS software (PROC MIXED version 9.1.3; SAS Institute Inc., Cary, NC, USA), applying a restricted maximum likelihood [REML] method to estimate the between-study variance (i.e. $T^2$) and the combined efficacy. We will examine heterogeneity between trials with a standard Q-test statistic (24), and will present the $I^2$ value (25), which can be interpreted as the amount of inconsistency in the reported results between the individual studies (26). When heterogeneity is found, we will try to find potential reasons behind it by examining individual study and subgroup characteristics.

We will perform a number of predefined stratified analyses, stratifying the available trials according to (i) Different types of individual whole-grains, i.e. if applicable wheat, barley, oat, rice, rye, corn, millet, sorghum or mixed grains; (ii) The energy content of the background diets, i.e. calorie-restricted or not, and (iii) The different control diets, i.e. with or without refined grain. REML-based (i.e. random-effects) meta-regression analysis (27) will be applied in order to answer the specific question raised by the secondary hypothesis – whether the amount of whole-grain could predict the quantitative changes in body weight.

We will perform sensitivity analysis, meta-regression stratified analysis by duration of trial (weeks), and dose of whole-grain (grams/d), according to the risk of bias and Table 1 in general.

Acknowledgements and declarations of interest

None to declare.
REFERENCES


7. Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. The American journal of clinical nutrition 2006;83.


17. van de Vijver LPL, van den Bosch LMC, van den Brandt PA, Goldbohm RA. Whole-grain consumption, dietary fibre intake and body mass index in the Netherlands cohort study. European journal of clinical nutrition 2007;63.


