Carbohydrate quality and human health: a series of systematic reviews and meta-analyses

Andrew Reynolds, Jim Mann, John Cummings, Nicola Winter, Evelyn Mete, Lisa Te Morenga

Summary

Background Previous systematic reviews and meta-analyses explaining the relationship between carbohydrate quality and health have usually examined a single marker and a limited number of clinical outcomes. We aimed to more precisely quantify the predictive potential of several markers, to determine which markers are most useful, and to establish an evidence base for quantitative recommendations for intakes of dietary fibre.

Methods We did a series of systematic reviews and meta-analyses of prospective studies published from database inception to April 30, 2017, and randomised controlled trials published from database inception to Feb 28, 2018, which reported on indicators of carbohydrate quality and non-communicable disease incidence, mortality, and risk factors. Studies were identified by searches in PubMed, Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, and by hand searching of previous publications. We excluded prospective studies and trials reporting on participants with a chronic disease, and weight loss trials or trials involving supplements. Searches, data extraction, and bias assessment were duplicated independently. Robustness of pooled estimates from random-effects models was considered with sensitivity analyses, meta-regression, dose-response testing, and subgroup analyses. The GRADE approach was used to assess quality of evidence.

Findings Just under 135 million person-years of data from 185 prospective studies and 58 clinical trials with 4635 adult participants were included in the analyses. Observational data suggest a 15–30% decrease in all-cause and cardiovascular related mortality, and incidence of coronary heart disease, stroke incidence and mortality, type 2 diabetes, and colorectal cancer when comparing the highest dietary fibre consumers with the lowest consumers Clinical trials show significantly lower bodyweight, systolic blood pressure, and total cholesterol when comparing higher with lower intakes of dietary fibre. Risk reduction associated with a range of critical outcomes was greatest when daily intake of dietary fibre was between 25 g and 29 g. Dose-response curves suggested that higher intakes of dietary fibre could confer even greater benefit to protect against cardiovascular diseases, type 2 diabetes, and colorectal and breast cancer. Similar findings for whole grain intake were observed. Smaller or no risk reductions were found with the observational data when comparing the effects of diets characterised by low rather than higher glycaemic index or load. The certainty of evidence for relationships between carbohydrate quality and critical outcomes was graded as moderate for dietary fibre, low to moderate for whole grains, and low to very low for dietary glycaemic index and glycaemic load. Data relating to other dietary exposures are scarce.

Interpretation Findings from prospective studies and clinical trials associated with relatively high intakes of dietary fibre and whole grains were complementary, and striking dose-response evidence indicates that the relationships to several non-communicable diseases could be causal. Implementation of recommendations to increase dietary fibre intake and to replace refined grains with whole grains is expected to benefit human health. A major strength of the study was the ability to examine key indicators of carbohydrate quality in relation to a range of non-communicable disease outcomes from cohort studies and randomised trials in a single study. Our findings are limited to risk reduction in the population at large rather than those with chronic disease.

Funding Health Research Council of New Zealand, WHO, Riddet Centre of Research Excellence, Healthier Lives National Science Challenge, University of Otago, and the Otago Southland Diabetes Research Trust.

Published **Online** January 10, 2019 http://dx.doi.org/10.1016/S0140-6736(18)31809-9

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(18)32468-1

Department of Medicine (A Reynolds PhD, Prof J Mann DM), **Department of Human Nutrition** (A Reynolds, Prof J Mann, N Winter MDiet, E Mete MDiet, L Te Morenga PhD), **and Edgar National Centre for Diabetes and Obesity Research** (A Reynolds , Prof J Mann, L Te Morenga), **University of Otago, Dunedin, Otago, New Zealand; Department of Medicine, Riddet Centre of Research Excellence, New Zealand** (Prof J Mann, L Te Morenga); **School of Medicine, University of Dundee, Dundee, Scotland** (Prof J Cummings MD); **and Healthier Lives National Science Challenge, New Zealand** (Prof J Mann)

Correspondence to:
Prof Jim Mann, Department of Medicine, University of Otago, Dunedin, Otago 9016, New Zealand
jim.mann@otago.ac.nz

Introduction

Before the mid-20th century, carbohydrates were principally regarded as an energy source, and nutrition recommendations suggested that carbohydrates should contribute to the energy deficit remaining after taking into account recommended intakes of fat and protein. From the mid-1950s, awareness increased of the potential of sugar (principally sucrose) to increase the risk of dental caries, and in the 1960s the view that sugar was a major cause of obesity, type 2 diabetes, and cardiovascular disease was promoted.[1,2] A substantial body of experimental, epidemiological, and clinical trial data have accumulated since these early observations. On the basis of extensive systematic reviews and meta-analyses, in 2015, WHO issued a recommendation, that individuals reduce intake to less than 10% of total energy. They also

Research in context

Evidence before this study

Foods containing carbohydrate consisting principally of sugars, starches, and dietary fibre (non-starch polysaccharide) provide the main source of dietary energy for people worldwide. The role of free sugars as a determinant of adverse health outcomes has been clarified, and clear guidelines relating to their restriction issued. Dietary fibre and some starches are associated with health benefits. Dietary guidelines typically encourage regular consumption of vegetables, cereals, pulses, and whole fruit, which are rich sources of dietary fibre and some starches, as well as other health promoting nutrients. However, previous systematic reviews and meta-analyses examining the relationship between starches and dietary fibre and health outcomes have usually examined a single indicator of carbohydrate quality and a limited number of disease outcomes. Thus, it has not been possible to establish the extent to which the predictive potential of these indicators applies across the spectrum of non-communicable disease, nor which are most useful in nutrition guidelines or when recommending food choices. Quantitative recommendations relating to dietary fibre do not have a strong evidence base. We searched PubMed, Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for prospective studies published from database inception to April 30, 2017, and randomised controlled trials published from database inception to Feb 28, 2018, and by hand searching of previous publications. Prospective studies and trials reporting on participants with a chronic disease, and weight loss trials or trials involving supplements were excluded. Robustness of pooled estimates from random-effects models was considered with sensitivity analyses, meta-regression, dose-response testing, and subgroup analyses.

Added value of this study

We did a systematic review and meta-analyses of prospective studies and clinical trials reporting on the relationship between the most widely studied indicators of carbohydrate quality (ie, dietary fibre, whole grains or pulses, dietary glycaemic index, or glycaemic load) and mortality and incidence of a wide range of non-communicable diseases and their risk factors. Parallel consideration of prospective studies and clinical trials has enabled an exploration of the extent to which changes in cardiometabolic risk factors associated with altering intake of dietary carbohydrate align with the effect of carbohydrate quality on disease risk observed in the prospective studies. Dose-response curves were generated and the benefits from different amounts of total dietary fibre were calculated. The approach recommended by the GRADE Working Group has been used to assess the quality of evidence and the importance of the observed associations that influence confidence in nutrition recommendations.

Implications of all the available evidence

The complementary findings from prospective studies and clinical trials, which show that higher intakes of dietary fibre or whole grains are associated with a reduction in the risk of mortality and incidence of a wide range of non-communicable diseases and their risk factors, provide convincing evidence for nutrition recommendations to replace refined grains with whole grains and increase dietary fibre to at least 25–29 g per day, with additional benefits likely to accrue with greater intakes. Considering current evidence, dietary glycaemic index or glycaemic load might be less useful as overall measures of carbohydrate quality than dietary fibre and whole grain content.

issued a conditional recommendation suggesting that even greater benefit could accrue if intakes of sugar are less than 5% of total energy.[3] Similar recommendations have been made by national governments and professional organisations worldwide.

It is more than half a century since epidemiological observations, largely in Africa, suggested that processing of cereal-based foods (grains) with removal of what came to be called dietary fibre, rather than excessive intakes of sugar, were key determinants of both cardiometabolic and large bowel diseases.[4,5] Nevertheless, until relatively recently, rather less attention has been given to starches and dietary fibre, the other major components of dietary carbohydrate. Although nutrition guidelines issued by many governments and professional organisations encourage increased consumption of vegetables, fruit, and whole grains, fewer quantitative guidelines for sources and intakes of dietary fibre and starch are available. We report here on indicators of carbohydrate quality and non-communicable disease (NCD) incidence, mortality, and risk factors. This study is essential at this time of increased interest in the area of nutrition and NCDs, and growing knowledge of the impact of carbohydrate intake on public health. The research was commissioned by WHO to inform the development of updated recommendations regarding carbohydrate intake.

See Online for appendix

Methods

Search strategy and selection criteria

We did a series of systematic reviews and meta-analyses following recognised reporting guidelines.[6] Population, Intervention, Comparison, Outcome (PICO) tables (appendix p 2) were agreed by the WHO Nutrition Guidance Expert Advisory Group. We report here on markers of carbohydrate quality that have been measured in an appreciable number of studies and trials (ie, dietary fibre, dietary glycaemic index or glycaemic load, and whole grain intake) and outcomes specified in the PICO tables. For prospective studies, critical outcomes comprised all-cause mortality, coronary heart disease mortality, and stroke mortality; and incidence of coronary heart disease, stroke, type 2 diabetes, and colorectal cancer. Important outcomes comprised cardiovascular disease incidence and mortality, and incidence of adiposity-related

cancers (ie, breast, endometrial, oesophageal, and prostate cancer). Prospective studies including only cohorts with specified pre-existing conditions were excluded.

For clinical trials, we have reported on adiposity, fasting glucose, fasting insulin, insulin sensitivity, glycated haemoglobin A_{1c}, triglycerides, cholesterol, and blood pressure. We included parallel and crossover randomised clinical trials of at least 4 week's duration that reported on higher intakes compared with lower intakes of the dietary components. Eligible trials could include those investigating diets with test foods provided, dietary advice, ad libitum diets, or controlled feeding trials on free living individuals. Weight loss trials and trials involving provision of dietary fibre supplements in powder form were excluded. Comparison diets were required to be matched for macronutrient composition and lifestyle modifications, such as exercise.

Participants of eligible trials were adults and children without acute or chronic disease, but could include individuals with prediabetes, mild to moderate hypercholesterolaemia, mild to moderate hypertension, or metabolic syndrome. Trials including people on medications known to effect the outcomes we were assessing, or who were pregnant or in situations in which regular eating habits were likely to change (eg, individuals with eating disorders or who were breastfeeding) were excluded.

Prospective observational studies were initially identified from systematic reviews and meta-analyses that reported associations between carbohydrate intake or one of the specified measures of carbohydrate quality, and one or more of the key outcome measures. These systematic reviews were found through online searches with Ovid MEDLINE, Embase, PubMed, Web of Science, and Scopus. This strategy was augmented by searches with low risk of bias terms for individual prospective studies and run to the end of April 30, 2017, to ensure identification of relevant published studies. No language restrictions were applied and foreign language articles were translated. A validation of the search procedure is provided in the appendix (p 4).

For clinical trials, highly sensitive Cochrane search strategies were used to identify trials examining the effects of carbohydrate intakes on obesity, blood pressure, and cardiometabolic risk factors. Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Food Science and Technology Abstracts databases were searched for trials published from database inception to Feb 28, 2018, with no language restrictions. Hand searching of references of systematic reviews, prospective studies, and clinical trials were completed to identify any studies that could have been missed. Search strategies are shown in the appendix (p 4). Reviewers identified eligible studies by screening titles, abstracts, and when appropriate, full texts of articles. If there were multiple publications from the same cohort, we used data for the longest follow-up period. Study authors were contacted, but non-peer reviewed sources were not considered. Literature searches, identification of eligible studies, data extraction, and bias assessment were undertaken independently by at least two researchers, with discrepancies resolved with an additional reviewer.

Data were extracted by use of pre-tested forms.[7] For prospective studies, the most adjusted values for effect size were extracted, in which that value did not also specifically include adjustment for other carbohydrates. For clinical trials involving multiple interventions, we extracted data from all relevant interventions. For crossover trials with multiple interventions, we extracted data only from the most relevant intervention and either the control group or the most relevant comparator intervention.

We used the ROBIS assessment tool[8] to assess systematic reviews and meta-analyses for quality and risk of bias, and the Newcastle–Ottawa Scale[9] to assess risk of bias of each prospective study. For clinical trials, we used Cochrane criteria.[10]

Data analysis

For prospective studies, we pooled the reported odds ratios or risk ratios with the DerSimonian and Laird random-effects model[11] in a high quantile versus low quantile analysis. When individual studies reported results separately by sex, we first combined these effect size estimates with a fixed effects model before including them within the pooled estimate. When eligible studies were based on and reported combined results from multiple cohort studies, we extracted results for each cohort to include in the meta-analysis. Prospective studies reporting incidence or mortality were analysed separately. When data were reported in a suitable format, we considered dose-response relationships with the Greenland and Longnecker method,[12] assuming linearity with a two-stage, dose-response, random effects analysis. The average or mid-point of each defined quantile was used for the dose amount. If the quantile dose range was open ended, half the range of the adjacent quantile was used to establish the average intake. We used 30 g to represent one serving of whole grains when a value for weight was not stated.[13] Non-linear dose-response was assessed by restricted cubic splines with three knots at 10%, 50%, and 90% of distribution combined with multivariate meta-analyses.[14] We imputed the number of cases per quantile from the relative risk (RR) value when necessary. Linear and spline (with 95% CI) models are shown in figures 1–3 with each datapoint overlaid as circles. Circle size indicates the weighting of each datapoint with bigger circles indicating greater influence. Absolute risk values were calculated with GRADEpro GDT software. Duplicate data were not used.

To help establish optimal intakes of dietary fibre, we considered the dose-response curves for total dietary fibre intake and critical health outcomes. We also compared the lowest consumers of dietary fibre with individuals consuming between 15–19 g, 20–24 g, 25–29 g, 30–34 g, and 35–39 g of fibre per day with a

	Number of studies	Number of cases or number in intervention	Person-years or number of controls	Effect size (95% CI)	GRADE quality
Observational studies					
All-cause mortality	10	80 139	12·3 million person-years	RR 0·85 (0·79–0·91)	Moderate
Coronary heart disease mortality	10	7243	6·9 million person-years	RR 0·69 (0·60–0·81)*	Moderate
Coronary heart disease incidence	9	7155	2·7 million person-years	RR 0·76 (0·69–0·83)	Moderate
Stroke mortality	2	1103	1·3 million person-years	RR 0·80 (0·56–1·14)	Very low
Stroke incidence	9	13 134	4·6 million person-years	RR 0·78 (0·69–0·88)†	Low
Type 2 diabetes incidence	17	48 468	6·9 million person-years	RR 0·84 (0·78–0·90)	Moderate
Colorectal cancer incidence	22	22 920	16·9 million person-years	RR 0·84 (0·78–0·89)	Moderate
Cancer mortality	5	29 593	11·2 million person-years	RR 0·87 (0·79–0·95)	Moderate
Randomised trials					
Change in bodyweight (kg)	27	1294	1201	MD −0·37 (−0·63 to −0·11)	High
Change in glycated haemoglobin A_{1c} (%)	6	191	189	SMD −0·35 (−0·73 to 0·03)	Low
Change in total cholesterol (mmol/L)	36	1832	1671	MD −0·15† (−0·22 to −0·07)	Moderate
Change in systolic blood pressure (mm Hg)	15	1064	988	MD −1·27† (−2·50 to −0·04)	Moderate

RR=relative risk. MD=mean difference. SMD=standardised mean difference. *Egger's test for bias (p=0·0040). Trim and fill analysis did not change the direction or significance of the pooled estimate. †The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses.

Table 1: **Effects of higher compared with lower intakes of total dietary fibre on critical outcomes**

random-effects model. When studies reported more than one quantile of data within the prespecified intake ranges, we first combined these quantiles with a fixed effects model before including them within the pooled estimate. We combined the quantiles to measure the number of critical outcomes when an improvement in RR was observed in the higher intake categories.

For clinical trials, high versus low analyses were undertaken with generic inverse models and random effects. For outcomes that could be measured by different units, reported effects were presented as standardised mean differences. For studies reporting multiple follow-ups over time, the most recent, appropriately reported published data were used in the meta-analyses. When crossover (paired data) studies did not report the mean difference between treatments and its SE or other relevant statistics, end of treatment values were analysed as independent samples. Subgroup analyses by fibre amount or principal starch source were done when there were enough studies for subgroupings including more than one trial. For example, high fibre interventions (0–25 g, 25–30 g, 30–35 g, >35 g per day) were considered to determine whether there were threshold effects or a possible dose-response.

For all analyses, heterogeneity was assessed with the I^2 statistic,[15] and Cochran's Q test.[16] Sensitivity analyses were done when an I^2 statistic was more than 50% or a p value for heterogeneity was less than 0·10. Publication bias was assessed with Egger's and Begg's tests,[17] and the trim and fill method.[18] The effect of each individual study's findings was considered with an influence analysis. For prospective studies, analyses excluding those that scored less than six out of a possible nine with the Newcastle–Ottawa Scale were done. If there was still unexplained heterogeneity, we considered the effect of small studies reporting less than 200 cases or less than 2000 participants. For clinical trials, analyses excluding trials with a high risk of bias for at least one criterion were done to examine the influence of potential bias on outcomes. Meta-regression analyses further examined effects of potential explanatory factors including trial design (ie, crossover or parallel), study or trial duration, global region, differences in fibre intake, source of fibre or starch, and nutrition status of participants. Analyses were done with RevMan (version 5) and Stata statistical software (version 15).

We used GRADE[19] protocols to judge the quality of the body of evidence as either high, moderate, low, or very low. More detail on this approach is provided in appendix (p 24–34). Quality of the evidence was assessed by the research team and revised if required after discussion with the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health.

Role of the funding source

With the exception of WHO, the funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The research was commissioned by WHO to inform the development of updated recommendations regarding carbohydrate intake. The WHO Nutrition Guidance Expert Advisory Group specified the PICO criteria (including exposure and outcome measures) and confirmed or modified the quality judgments but had no other involvement in the conduct or interpretation of the research. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Number of studies	Number of cases or number in intervention	Person-years or number of controls	Effect size (95% CI)	GRADE quality
Observational studies					
All-cause mortality	9	99 224	10·7 million person-years	RR 0·81 (0·72–0·90)*	Low
Coronary heart disease mortality	2	1588	2·0 million person-years	RR 0·66 (0·56–0·77)	Low
Coronary heart disease incidence	6	7697	2·8 million person-years	RR 0·80 (0·70–0·91)*	Low
Stroke mortality	2	694	2·0 million person-years	RR 0·74 (0·58–0·94)	Low
Stroke incidence	3	1247	1·1 million person-years	RR 0·86 (0·61–1·21)	Very low
Type 2 diabetes incidence	8	14 686	3·9 million person-years	RR 0·67 (0·58–0·78)*	Low
Colorectal cancer incidence	7	8803	6·8 million person-years	RR 0·87 (0·79–0·96)	Moderate
Cancer mortality	5	32 727	10·1 million person-years	RR 0·84 (0·76–0·92)*	Low
Randomised trials					
Change in bodyweight (kg)	11	498	421	MD −0·62 (−1·19 to −0·05)	Moderate
Change in glycated haemoglobin A_{1c} (%)	3	141	141	SMD −0·54 (−1·28 to 0·20)	Low
Change in total cholesterol (mmol/L)	17	772	701	MD −0·09 (−0·23 to 0·04)	Moderate
Change in systolic blood pressure (mm Hg)	8	493	432	MD −1·01 (−2·46 to 0·44)	Moderate

Detailed justification for the GRADE quality of evidence is given in the appendix pp 35–50 for observational studies and appendix pp 105–136 for trials. RR=relative risk. MD=mean difference. SMD=standardised mean difference. *The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses.

Table 2: **Effects of higher compared with lower intakes of whole grains on critical outcomes**

	Number of studies	Number of cases or number in intervention	Person-years or number of controls	Effect size (95% CI)	GRADE quality
Observational studies					
All-cause mortality	3	7698	0·6 million person-years	RR 0·89 (0·70–1·13)*	Very low
Coronary heart disease mortality	1	Incidence not stated	0·04 million person-years	RR 1·10 (0·69–1·75)	Very low
Coronary heart disease incidence	10	8456; not reported in one study	2·4 million person-years	RR 0·93 (0·83–1·04)	Low
Stroke mortality	3	951	1·2 million person-years	RR 0·63 (0·52–0·77)	Low
Stroke incidence†	5	5527	3·0 million person-years	RR 0·84 (0·72–0·99)	Very low
Type 2 diabetes incidence†	14	36 908	6·5 million person-years	RR 0·89 (0·82–0·97)*	Very low
Colorectal cancer incidence	10	11 245	8·8 million person-years	RR 0·91 (0·82–1·01)*	Very low
Cancer mortality	1	1401	0·4 million person-years	RR 1·11 (0·90–1·38)	Very low
Randomised trials					
Change in bodyweight (kg)	8	464	335	MD −0·29 (−0·62 to 0·03)	High
Change in glycated haemoglobin A_{1c} (%)	2	44	37	SMD 0·08 (−0·35 to 0·52)	Very low
Change in total cholesterol (mmol)	8	605	478	MD −0·02 (−0·17 to 0·13)	Moderate
Change in systolic blood pressure (mm Hg)	4	519	397	MD −0·17 (−1·03 to 0·69)	High

Detailed justification for the GRADE quality of evidence is given in appendix D for observational studies and supplement 2 for trials. Only one eligible trial of children was identified in our systematic searches. Although the exposure was for diets of higher and lower glycaemic index, data from this trial have not been included with that of adults shown above. RR=relative risk. MD=mean difference. SMD=standardised mean difference. *The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses. †The pooled effect size did not maintain statistical significance during sensitivity analyses.

Table 3: **Effects of diets characterised by lower compared with higher glycaemic index on critical outcomes**

Results

22 356 titles were assessed for eligibility and 22 057 were ineligible. Data from 185 publications of prospective studies involving just under 135 million person-years and 58 clinical trials with 4635 adult participants were included in the meta-analyses. Only one eligible trial of children was identified in our systematic searches. Data from this trial have not been included with those of adults. The study selection is shown in the appendix p 245, with details of these studies in the appendix pp 246–316. Critical outcome data for total fibre, whole grain intake, and dietary glycaemic index are summarised in tables 1–3 and shown in full in the appendix pp 6–66 for observational studies, and appendix pp 67–136 for trials. Dose-response data are shown in figures 1–3 and the appendix. Summary forest plots from clinical trial data are shown in figure 4. Data and GRADE tables relating to all other indicators and outcomes are in the appendix.

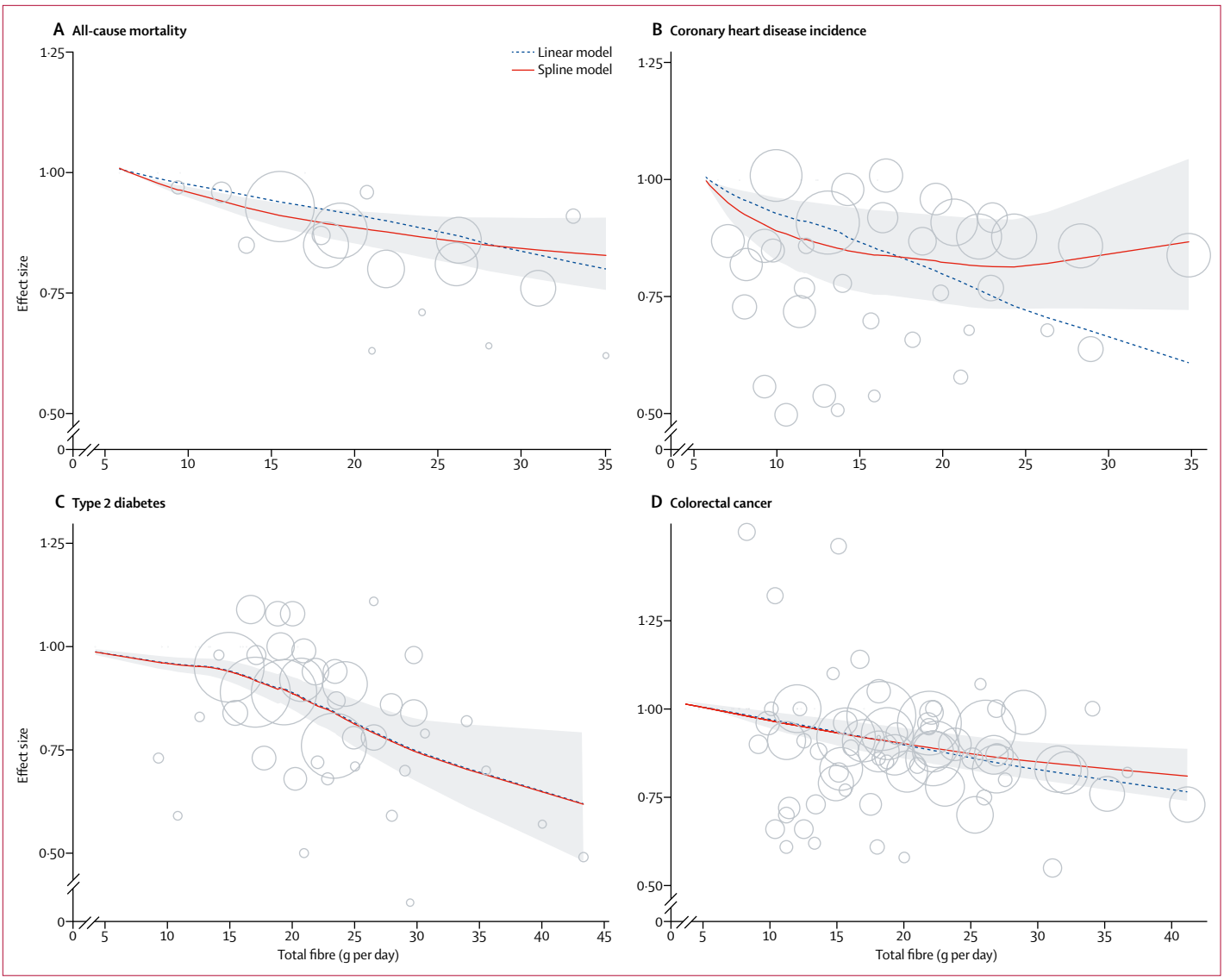

Figure 1: **Dose-response relationships between total dietary fibre and critical clinical outcomes based on data from prospective studies**
(A) Total fibre and all-cause mortality. 68 183 deaths over 11·3 million person-years. Assuming linearity a risk ratio of 0·93 (95% CI 0·90–0·95) was observed for every 8 g more fibre consumed per day. (B) Total fibre and incidence of coronary heart disease. 6449 deaths over 2·5 million person-years. Assuming linearity a risk ratio of 0·81 (0·73–0·90) was observed for every 8 g more fibre consumed per day.(C) Total fibre and incidence of type 2 diabetes. 22 450 cases over 3·2 million person-years. Assuming linearity a risk ratio of 0·85 (0·82–0·89) was observed for every 8 g more fibre consumed per day. (D) Total fibre and incidence of colorectal cancer. 20 009 cases over 20·9 million person-years. Assuming linearity a risk ratio of 0·92 (0·89–0·95) was observed for every 8 g more fibre consumed per day.

The observational data in table 1 show that higher intakes of total dietary fibre are associated with a 15–31% reduction in the risk of specified critical outcomes. For all-cause mortality and coronary heart disease incidence, this reduction translates into 13 fewer deaths (95% CI eight to 18) and six fewer cases of coronary heart disease (four to seven) per 1000 participants over the duration of the studies. Sensitivity analyses of the tested associations did not change the direction or significance of any observed result. The quality of evidence contributing to the meta-analyses of the cohort studies was, with the exception of the data relating to stroke in which GRADE quality was low, considered to be moderate.

Figure 1 shows dose-response relationships for total fibre intake and total mortality, incidence of coronary heart disease, type 2 diabetes, and colorectal cancer, many of which are linear with no sign of a plateau within the available data. When comparing the lowest fibre intakes with prespecified ranges, the greatest benefits were observed for individuals consuming 25–29 g per day (improvement in six of the seven critical outcomes), more so than individuals consuming 15–19 g per day (improvement in three of the seven critical outcomes), or 20–24 g per day (improvement in four of the seven critical outcomes). These analyses are shown in full in the appendix.

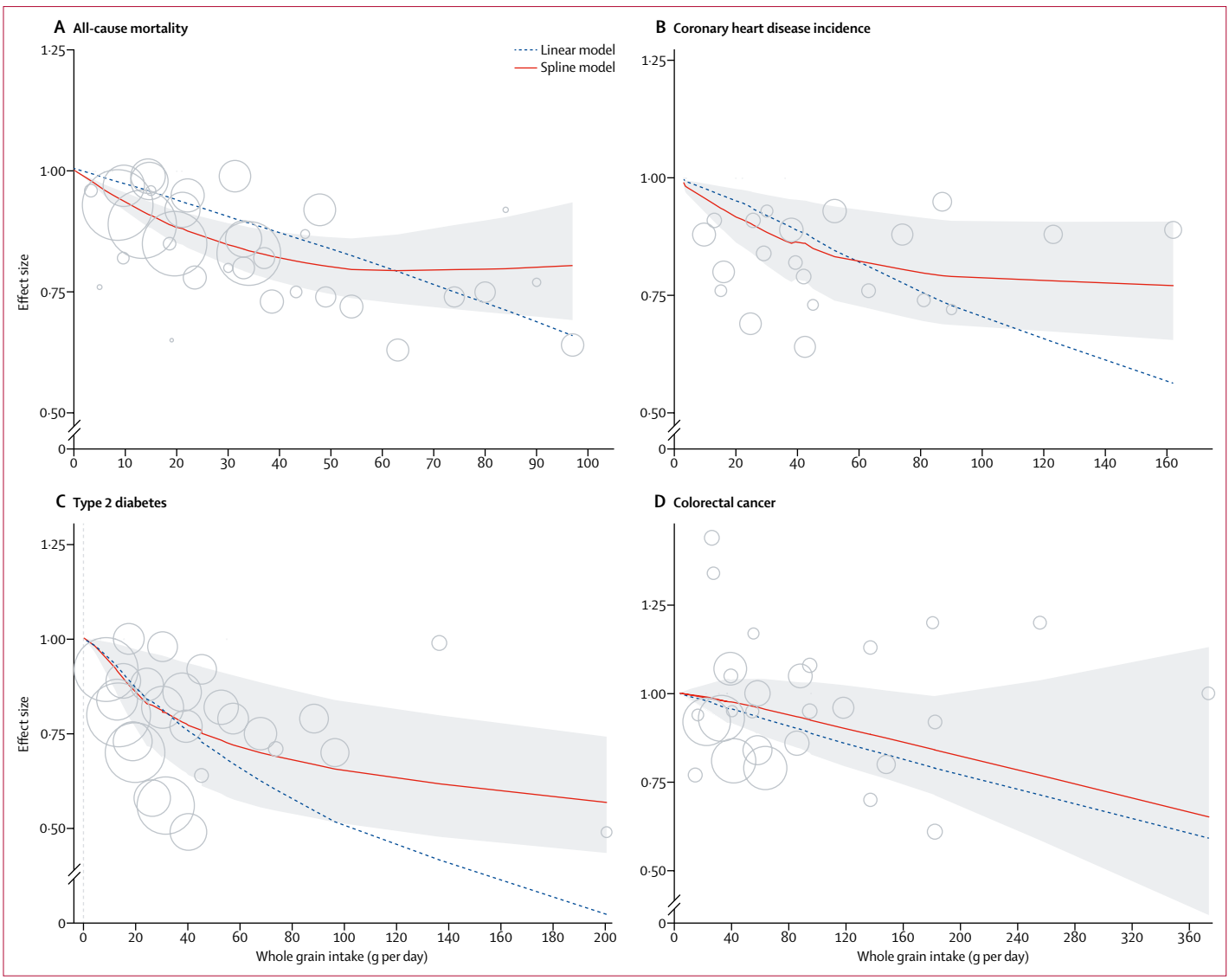

Figure 2: **Dose-response relationships between whole grain intake and critical clinical outcomes based on data from prospective studies**
(A) Whole grain intake and all-cause mortality. 88 347 deaths over 8·2 million person-years. Assuming linearity a risk ratio of 0·94 (95% CI 0·92–0·95) was observed for every 15 g more whole grains consumed per day. (B) Whole grain intake and incidence of coronary heart disease. 6587 cases over 2·4 million person-years. Assuming linearity a risk ratio of 0·93 (0·89–0·98) was observed for every 15 g more whole grains consumed per day. (C) Whole grain intake and incidence of type 2 diabetes. 13 147 cases over 3·5 million person-years. Assuming linearity a risk ratio of 0·88 (0·81–0·95) was observed for every 15 g more whole grains consumed per day. (D) Whole grain intake and incidence of colorectal cancer. 6056 cases over 5·7 million person-years. Assuming linearity a risk ratio of 0·97 (0·95–0·99) was observed for every 15 g more whole grains consumed per day.

Mean differences between higher versus lower fibre intakes for a range of cardiometabolic risk factors are shown in table 1 and the summary forest plots in figure 4A. Dose-response or threshold effects could not be established from the clinical trial data. The quality of evidence contributing to the meta-analyses of the trial data relating to bodyweight is high, and total cholesterol and systolic blood pressure moderate because of unexplained heterogeneity between the trials.

Broadly similar effects were apparent in both the prospective studies and clinical trials, when examining fibre from different food groups or fibre described as soluble or insoluble. However, limited data were available, other than for cereal fibre, the largest contributor to total dietary fibre (appendix).

Cohort data showing the relation between levels of whole grain intake on critical outcomes are shown in table 2. Higher intakes of whole grains were associated with a 13–33% reduction in the risk for all critical outcomes. For all-cause mortality and coronary heart disease incidence, this reduction translates into 26 fewer deaths (95% CI 14–39) and seven fewer cases (3–10) per 1000 participants over the duration of the studies. Sensitivity analyses did not typically change the direction or significance of any

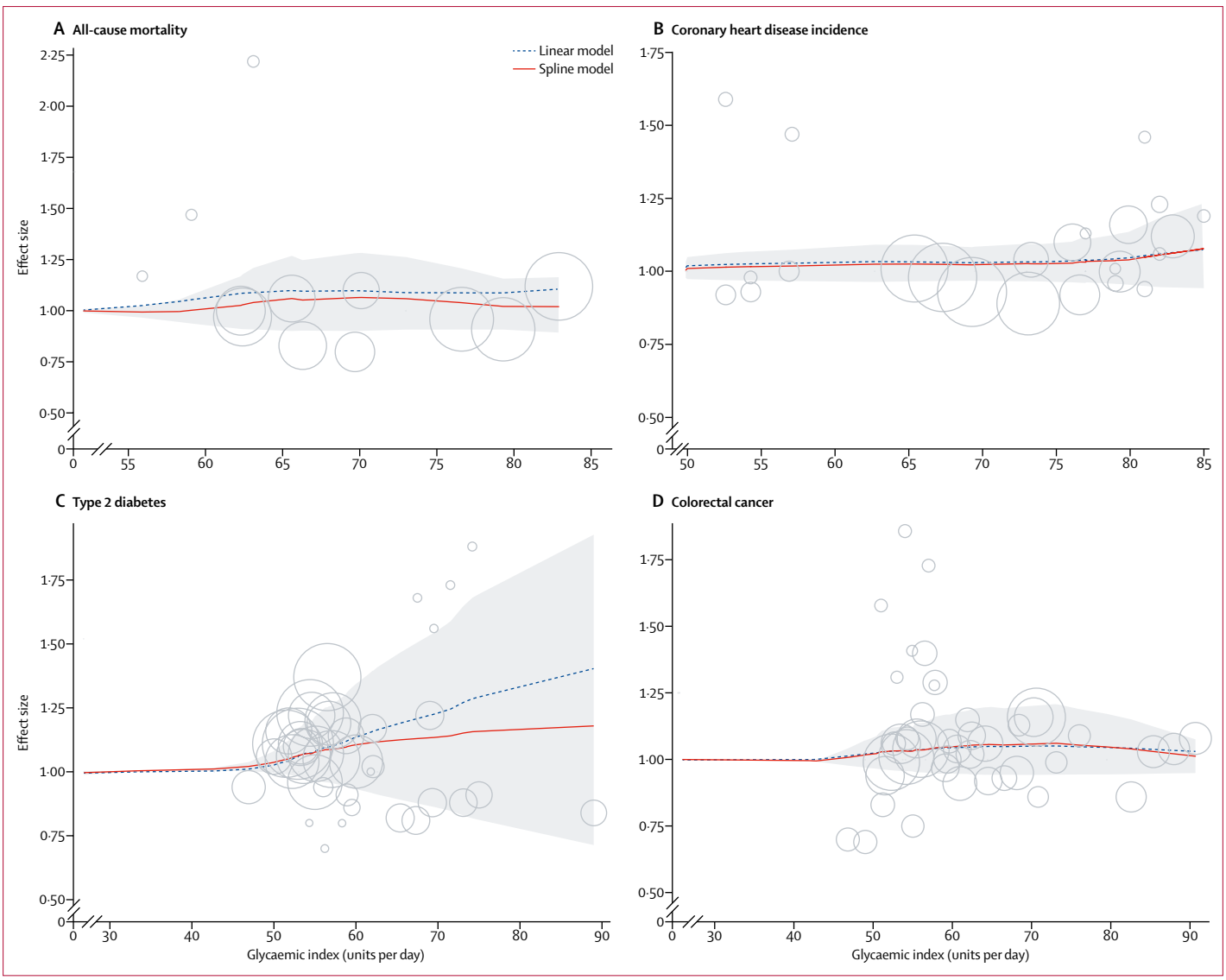

Figure 3: **Dose-response relationships between dietary glycaemic index and critical clinical outcomes based on data from prospective studies**
(A) Glycaemic index and all-cause mortality. 7699 deaths over 0·6 million person-years. Assuming linearity a risk ratio of 1·16 (0·90–1·49) was observed for every 10 glycaemic index unit increase per day. (B) Glycaemic index and incidence of coronary heart disease. 7240 cases over 2·4 million person-years. Assuming linearity a risk ratio of 1·09 (0·94–1·27) was observed for every 10 glycaemic index unit increase per day. (C) Glycaemic index and incidence of type 2 diabetes. 31780 cases over 4·9 million person-years. Assuming linearity a risk ratio of 1·10 (1·00–1·20) was observed for every 10 glycaemic index unit increase per day. (D) Glycaemic index and incidence of colorectal cancer. 10390 cases over 6·5 million person-years. Assuming linearity a risk ratio of 1·05 (1·00–1·10) was observed for every 10 glycaemic index unit increase per day.

pooled effect (appendix). The quality of evidence relating to colorectal cancer incidence is moderate, whereas for other critical outcomes it is low because of high heterogeneity not fully explained by sensitivity analysis. Dose-response curves showing clear associations with increasing whole grain intake and clinical outcomes are shown in figure 2. Mean differences in cardiometabolic risk factors between higher and lower whole grain consumption are shown in table 2 and summary forest plots in figure 4B. Evidence relating to bodyweight, cholesterol, and blood pressure is downgraded to moderate because of unexplained heterogeneity.

Cohort and trial data showing the relation between dietary glycaemic index and critical outcomes are shown in table 3, dose-responses are shown in figure 3, and the summary forest plot in figure 4C. Data relating to the cohort studies that examined the effects of glycaemic load are shown in the appendix (pp 137–153).

An 11% (95% CI 3–18) RR reduction of type 2 diabetes incidence was observed for individuals consuming low glycaemic index diets. However, sensitivity analysis due to high heterogeneity attenuated the RR reduction to 5% (95% CI –13 to 4). Stroke mortality was lower among individuals consuming lower glycaemic index diets.

The prospective studies generated evidence that is graded as low or very low quality as a result of high risk of bias, imprecision, and inconsistencies. Key outcome markers from the clinical trials on lowering the glycaemic index of a diet are shown in forest plots in figure 4C. Trial data varied but were usually of moderate quality (table 3).

Discussion

Higher intakes of total dietary fibre or whole grains are associated with reduced incidence and mortality from several NCDs. Less useful markers of carbohydrate quality are glycaemic index, glycaemic load, and sources of dietary fibre, in which inconsistent findings or insufficient data provide evidence of low quality or very low quality. In randomised trials, higher intakes of dietary fibre reduced bodyweight and lowered blood cholesterol and systolic blood pressure. These findings are supported by cohort studies, which report reduced risk of coronary heart disease incidence and mortality and incidence of diabetes. The consistency between the trial and prospective study results, together with the dose-response relationships, provide support that the effect on cardiometabolic diseases is likely to be causal and not a consequence of confounding variables. Additionally, prospective studies show striking reductions in, and dose-response relationships with, all-cause mortality, total cancer deaths, total cardiovascular disease deaths and incidence, stroke incidence, and incidence of colorectal, breast, and oesophageal cancer. For several of these outcomes, the dose-response is linear. These findings, together with the comparisons of clinical outcomes among individuals with different intakes of dietary fibre, suggest that individual adult intakes of total dietary fibre should be no less than 25–29 g per day with additional benefits likely to accrue with higher intakes. Population intakes in this range are reported in some countries, but the majority of individuals globally consume less than 20 g per day.[20] Broadly similar trends were apparent in the prospective studies that examined cereal fibre, typically the largest contributor to total dietary fibre. Limited data were available regarding specific sources (eg, legumes, fruits, or vegetables) or subcategories (eg, soluble, insoluble, or extracted) of dietary fibre.

The results for whole grain foods are similar to those for dietary fibre. Prospective studies showed a reduction in all-cause mortality, coronary heart disease, cancer deaths, incidence of type 2 diabetes, and stroke mortality. As with dietary fibre, the observed reductions in risk are considerable, typically around 20% with significant dose-response relationships. The randomised controlled trials involving an increase in the intake of whole grains showed reduction in bodyweight and cholesterol. The similar protective effects of higher intakes of whole grain foods and of dietary fibre suggest that the beneficial effects of whole grains could be because of their high dietary fibre content. The GRADE criteria categorise the evidence linking most clinical outcomes with dietary fibre as moderate, and with whole grains as low quality. This could reflect the high fibre content of whole grains.

Dietary starch can be divided into several categories,[21] although rarely are measurements made of these individual components. However, the glycaemic index of foods containing starch or the overall glycaemic load of meals or diets including starchy foods, provide measures of starch quality and are widely reported. We found that

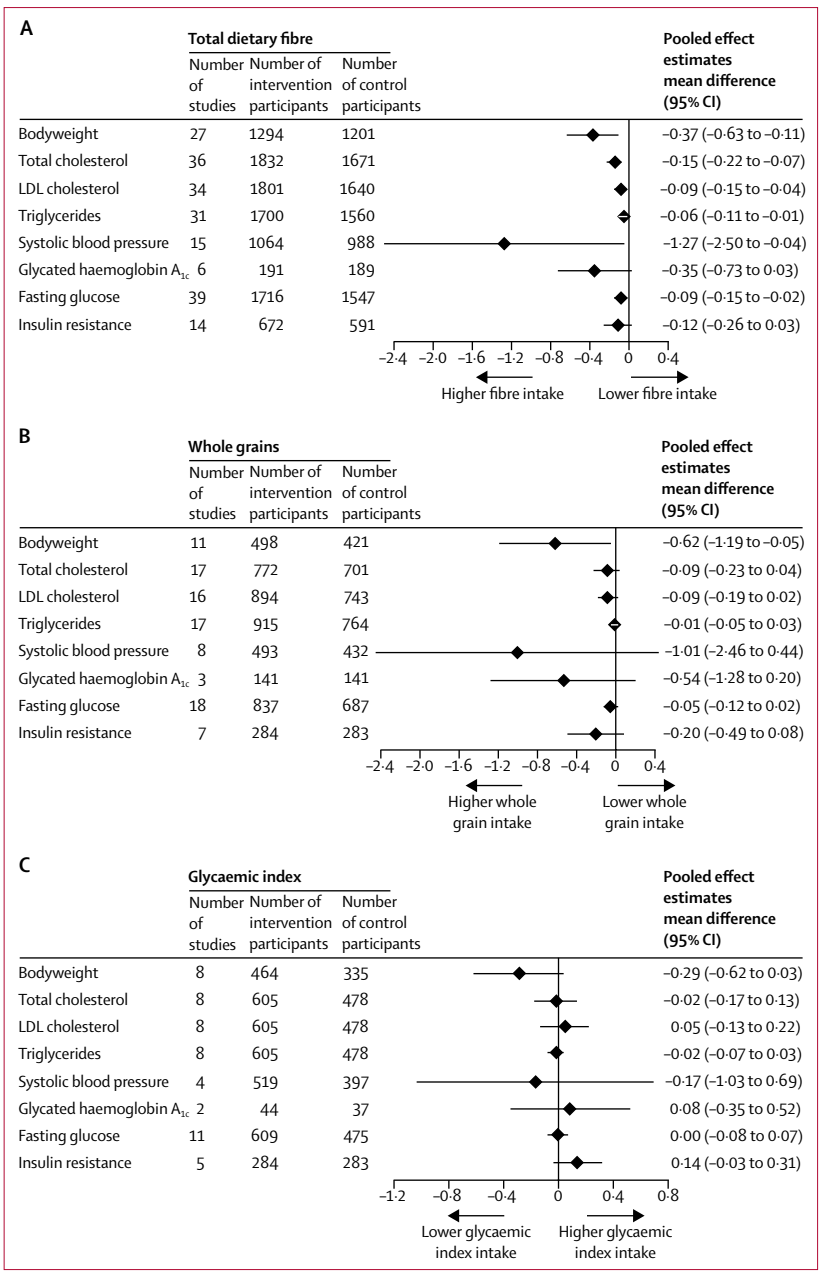

Figure 4: **Summary forest plots of key outcomes from clinical trials**
(A) Higher compared with lower total fibre intakes. (B) Higher compared with lower whole grain intakes. (C) Comparison of diets characterised by lower compared with higher glycaemic index foods.

diets with a lower overall glycaemic index appear to be associated with a reduced risk of stroke and type 2 diabetes incidence. However, the risk estimates, other than for stroke mortality, are modest when compared with those for dietary fibre, and following sensitivity analyses were reduced and associated with CIs that included 1·00. The findings from prospective studies of glycaemic load are inconsistent. The results from trials show no consistent benefits on clinical outcomes when changing the glycaemic index of a diet.

A major strength of the present study is that it has related key markers of carbohydrate quality to total mortality, and mortality and incidence of the major nutrition-related NCDs. Additionally, prospective studies have been considered alongside randomised controlled trials. Other reviews and meta-analyses have reported on a single indicator of carbohydrate quality and one or more outcomes. Our approach has enabled us to use these indicators of carbohydrate quality to provide a stronger justification than had previously been available for quantitative recommendations of dietary fibre intake. The evidence for the associations between the quality markers and outcomes was most frequently rated as moderate or low, rather than high, which could be regarded as a limitation. However, this limitation is an inevitable consequence of the use of GRADE criteria for assessment, which typically require data to be from randomised controlled trials with disease endpoints to be rated as high. Furthermore, with the GRADE approach, downgrading frequently occurs because of unexplained heterogeneity in the results of the different studies, even when all results follow similar trends. This heterogeneity might be a consequence of studies being done in diverse populations or as a result of different methods of measuring dietary intake. Regarding the associations reported here between dietary fibre and whole grains and a wide range of clinical outcomes, the consistency of the findings, the striking dose-response relationships, and the substantial body of mechanistic evidence all contribute to the total body of evidence and increases our confidence in the findings.

Our findings are broadly similar to other reviews and meta-analyses that have reported on the association between dietary fibre and whole grains and one or more disease outcomes.[22–25] However, there is less consistency in our findings than in earlier reports regarding the potential benefit of low glycaemic index or glycaemic load diets. Three systematic reviews have shown a reduced incidence of type 2 diabetes associated with the consumption of diets of lower glycaemic index or glycaemic load,[26–28] although the effect was modest when compared with the protective effect of total dietary fibre or whole grains. In the present study, sensitivity analyses due to high heterogeneity showed a reduced risk reduction and CIs included 1·00. A review of prospective studies by Turati and colleagues[29] suggested a small but significant increase in colorectal cancer incidence associated with diets with high glycaemic index or glycaemic load. This finding was subject to high unexplained heterogeneity and included retrospective case-control studies, which could be subject to dietary recall bias. Other studies have reported a lower incidence of stroke and coronary heart disease among individuals consuming low glycaemic index or glycaemic load diets,[26,30–33] whereas we found a reduced risk of stroke only. We were unable to provide support for an effect of low glycaemic index or glycaemic load diets on haemoglobin A_{1c} or blood cholesterol, which have been reported in many short-term (typically 4–6 weeks) and medium-term (typically 8–10 weeks) trials. However, we excluded trials that involved only people with diabetes or marked hyperlipidaemia who were the participants in the majority of trials reporting reduction in these important risk indicators. Our study does not exclude the value of these indicators of carbohydrate quality in this clinical context.

Consumption of whole grains offer a useful means of increasing dietary fibre intake and reducing risk of NCDs. However, fruit and vegetables are also important contributors to dietary fibre intake. We did not specifically explore the relationship between fruit and vegetable consumption and NCDs given the 2017 systematic review and meta-analyses by Aune and colleagues.[34] They reported risk reductions of around 10% per 200 g fruit and vegetables combined for coronary heart disease, stroke, and total mortality; and smaller, but still significant, reductions for total cardiovascular disease and cancer. Appreciable dose-response effects were apparent for most outcomes up to 800 g per day. Inverse associations were observed between the intake of apples, pears, citrus fruits, green leafy vegetables, cruciferous vegetables, and salad, and cardiovascular disease and all-cause mortality. Intake of green or yellow vegetables and cruciferous vegetables were inversely associated with total cancer risk. In addition to fibre, fruits and vegetables contain many other nutrients that are potentially protective and confer some risk reduction.

The benefits of fibre are supported by over 100 years of research into its chemistry, physical properties, physiology, and metabolic effects.[20,35–37] Fibre containing foods should be chewed before passing through the stomach and into small bowel where they affect satiety, glucose and insulin responses, and lipid absorption. Although more recent systematic reviews have shown only small effects on appetite, satiety, or blood lipids,[38,39] these studies have been done largely with defined fibre supplements rather than whole foods. Whole foods that require chewing and retain much of their structure in the gut are more likely to increase satiety through various mechanisms, leading to weight loss and modulation of carbohydrate and lipid metabolism. In the large bowel, fibre is almost completely broken down by the resident microflora in a series of anaerobic reactions known as fermentation.[40] The gut microbiota play many important

roles in human health, including protecting against pathogens, development of the gut immune system, vitamin synthesis, metabolism of xenobiotics, and might be involved in complex gut-brain communication. However, the principal function of the microbiome is digestion of fibre and other carbohydrates that escape breakdown in the small bowel, and it is the availability of fibre in the diet that dominates the metabolism of the gut microbiome and leads to protection from conditions such as colorectal cancer.[41,42] This coming together of the epidemiological and experimental work on fibre allows conclusions to be drawn that increased fibre intakes should result in improvements in population health.

Although we have not considered the evidence regarding total carbohydrate intake, epidemiological evidence and long-term clinical trials[43] suggest that a wide range of intakes is acceptable, a finding that is endorsed by authoritative dietary guidelines.[44] Our study contributes to the growing body of evidence that carbohydrate quality rather than quantity determines major health outcomes. Translating these findings regarding dietary fibre and whole grains into dietary advice for individuals and populations should be accompanied by a caveat. Dietary fibre as defined by *Codex Alimentarius* is naturally occurring in foods, but can be extracted from foods or synthesised and added into manufactured foods. The large body of literature that contributed to this Article and other systematic reviews and meta-analyses relate principally to fibre-rich foods as most of the studies were undertaken before synthetic and extracted fibre were widely used. The concept of whole grain foods has also changed appreciably. Whole grain foods are required to have a nutrient composition similar to that of the original grain, without regard to the degree of processing. Many breakfast cereals and other manufactured so-called whole grain products are more highly processed than they were in the past. Scarce, but quite striking evidence exists that consumption of whole grains that have undergone increased processing can result in a deterioration of several biomarkers of cardiometabolic disease.[45] As these are relatively recent developments, no epidemiological evidence exists of the consequences of such changes in the food supply on clinical outcomes and mortality. Until evidence is available, it seems appropriate that dietary advice should emphasise the benefits of naturally occurring dietary fibre in whole grains, vegetables, and fruits that have been minimally processed.

Substantial evidence has provided support for the adverse consequences of high intakes of sugar-sweetened beverages and reducing the intake of free sugars is highly recommended.[3] Our findings, based on a series of systematic reviews and meta-analyses, provide convincing evidence for the importance of including advice regarding the nature and source of other carbohydrates in dietary guidelines aimed at reducing the risk of NCDs. The types of studies we have considered did not identify risks associated with dietary fibre. However, high intakes might be associated with deleterious effects in populations with borderline iron or mineral status, among whom very high whole grain intakes could further compromise iron status.[46] High intakes of dietary fibre and whole grains are more clearly associated with good health outcomes than measures of glycaemic index or glycaemic load. Although glycaemic index provides a measure of the glycaemic potential of the carbohydrate content of foods, some low glycaemic index foods might have other attributes that are not health promoting. Foods containing added fructose or sucrose and composite foods containing both saturated fat and carbohydrate (eg, confectionary products) can have a low glycaemic index.[47] Our complementary findings from randomised controlled trials and prospective studies, together with the dose-response effects supported by much experimental work, show that diets characterised by a low content of dietary fibre contribute to various NCDs and that implementation of quantitative recommendations for dietary fibre intake will be beneficial. Intakes in the range of 25–29 g daily are adequate, while the dose-response data suggest that amounts greater than 30 g per day confer additional benefits. Given that most people worldwide currently consume less than 20 g of dietary fibre per day, reinforcement of relevant nutrition policy will be required to achieve the potential reduction in NCDs.

Contributors

AR was responsible for the systematic review and meta-analyses of prospective studies, wrote the manuscript, and was involved with the interpretation of results. LTM was responsible for the systematic reviews and meta-analysis of clinical trials, and was involved with the interpretation of results. JC was involved with the interpretation of results. NW was involved with the systematic reviews and meta-analyses of clinical trials. EM was involved with the systematic review and meta-analyses of prospective studies. JM wrote the manuscript, was involved with he interpretation of results, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. All authors approved the submission of the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This Article was supported by funding from the Health Research Council of New Zealand; WHO; Riddet Centre of Research Excellence; Healthier Lives National Science Challenge; Department of Medicine, University of Otago, New Zealand; and the Otago Southland Diabetes Research Trust.

References

1 Yudkin J. Pure, white and deadly: the problem of sugar. London: Davis-Poynter Ltd, 1972.
2 Cleave T, Campbell G, Painter N. Diabetes, coronary thrombosis and saccharine disease. Bristol: John Wright & Sons, Ltd, 1966.
3 WHO. Guideline: sugars intake for adults and children. Geneva: World Health Organization, 2015. http://apps.who.int/iris/bitstream/handle/10665/149782/9789241549028_eng.pdf?sequence=1 (accessed May 1, 2018).
4 Cummings JH, Engineer A. Denis Burkitt and the origins of the dietary fibre hypothesis. *Nutr Res Rev* 2017; **31:** 1–15.
5 Trowell H, Burkitt D. Concluding considerations. In: Refined carbohydrate foods and disease. London: Elsevier, 1975: 333–45.

6 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.

7 Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 2013; **346:** e7492.

8 Whiting P, Savović J, Higgins JP, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016; **69:** 225–34.

9 Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed May 18, 2017).

10 Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.

11 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

12 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; **135:** 1301–09.

13 Aune D, Chan DS, Lau R, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011; **343:** d6617.

14 Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006; **6:** 40.

15 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557.

16 Cochrane Working Group. The combination of estimates from different experiments. *Biometrics* 1954; **10:** 101–29.

17 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315:** 629–34.

18 Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56:** 455–63.

19 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924.

20 Stephen AM, Champ MM, Cloran SJ, et al. Dietary fibre in Europe: current state of knowledge on definitions, sources, recommendations, intakes and relationships to health. *Nutr Res Rev* 2017; **30:** 149–90.

21 Englyst HN, Kingman S, Cummings JH. Classification and measurement of nutritionally important starch fractions. *Eur J Clin Nutr* 1992; **46:** S33–50.

22 Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016; **353:** i2716.

23 Aune D, Chan DS, Lau R, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011; **343:** d6617.

24 Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr* 2012; **142:** 1304–13.

25 Liu L, Wang S, Liu J. Fiber consumption and all-cause, cardiovascular, and cancer mortalities: a systematic review and meta-analysis of cohort studies. *Mol Nutr Food Res* 2015; **59:** 139–46.

26 Barclay AW, Petocz P, McMillan-Price J, et al. Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies. *Am J Clin Nutr* 2008; **87:** 627–37.

27 Dong JY, Zhang L, Zhang YH, Qin LQ. Dietary glycaemic index and glycaemic load in relation to the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Br J Nutr* 2011; **106:** 1649–54.

28 Bhupathiraju SN, Tobias DK, Malik VS, et al. Glycemic index, glycemic load, and risk of type 2 diabetes: results from 3 large US cohorts and an updated meta-analysis. *Am J Clin Nutr* 2014; **100:** 218–32.

29 Turati F, Galeone C, Gandini S, et al. High glycemic index and glycemic load are associated with moderately increased cancer risk. *Mol Nutr Food Res* 2015; **59:** 1384–94.

30 Cai X, Wang C, Wang S, et al. Carbohydrate intake, glycemic index, glycemic load, and stroke: a meta-analysis of prospective cohort studies. *Asia Pac J Public Health* 2015; **27:** 486–96.

31 Fan J, Song Y, Wang Y, Hui R, Zhang W. Dietary glycemic index, glycemic load, and risk of coronary heart disease, stroke, and stroke mortality: a systematic review with meta-analysis. *PLoS One* 2012; **7:** e52182.

32 Mirrahimi A, de Souza RJ, Chiavaroli L, et al. Associations of glycemic index and load with coronary heart disease events: a systematic review and meta-analysis of prospective cohorts. *J Am Heart Assoc* 2012; **1:** e000752.

33 Rossi M, Turati F, Lagiou P, Trichopoulos D, La Vecchia C, Trichopoulou A. Relation of dietary glycemic load with ischemic and hemorrhagic stroke: a cohort study in Greece and a meta-analysis. *Eur J Nutr* 2015; **54:** 215–22.

34 Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* 2017; **46:** 1029–56.

35 McCance R, Lawrence R. The carbohydrate content of foods. Medical Research Council Special Report Series No 135. London: HMS Office, 1929.

36 Cummings JH. Dietary fibre. *Gut* 1973; **14:** 69.

37 Spiller GA. CRC handbook of dietary fiber in human nutrition. UK: Taylor & Francis, 2001.

38 Clark MJ, Slavin JL. The effect of fiber on satiety and food intake: a systematic review. *J Am Coll Nutr* 2013; **32:** 200–11.

39 Wanders AJ, van den Borne JJ, de Graaf C, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev* 2011; **12:** 724–39.

40 Stephen AM, Cummings JH. Mechanism of action of dietary fibre in the human colon. *Nature* 1980; **284:** 283.

41 Elia M, Cummings JH. Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. *Eur J Clin Nutr* 2007; **61** (suppl 1): S40.

42 Shanahan F, van Sinderen D, O'toole PW, Stanton C. Feeding the microbiota: transducer of nutrient signals for the host. *Gut* 2017; **66:** 1709–17.

43 Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat *vs* low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA* 2018; **319:** 667–79.

44 European Food Safety Authority (EFSA). Dietary reference values for nutrients: Summary report. 2017. https://www.efsa.europa.eu/en/supporting/pub/e15121 (accessed Jan 21, 2018).

45 Järvi AE, Karlström BE, Granfeldt YE, Björck IE, Asp NG, Vessby B. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* 1999; **22:** 10–18.

46 Hunt JR. Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. *Am J Clin Nutr* 2003; **78:** 633S–39.

47 Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 2008; **31:** 2281–83.