University of Dundee

Carbohydrate quality and human health

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1 **Carbohydrate quality and human health: a series of systematic reviews and meta**

2 **analyses**

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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 have considered the impact of carbohydrate quality as measured by intakes of dietary fibre, whole grains or pulses, and dietary glycaemic index or glycaemic load on non-communicable disease (NCD) incidence, mortality, and risk factors to more precisely quantify the predictive potential of the markers, to determine which are most useful, and to establish an evidence base for quantitative recommendations for intakes of dietary fibre.

Methods Prospective studies published prior to April 2017 and randomised controlled trials published prior to February 2018, which reported on indicators of carbohydrate quality and NCD incidence, mortality and risk factors were systematically reviewed and meta analysed. 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. 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 135 million person years of data from prospective studies and 58 clinical trials with a total of 4,635 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, type 2 diabetes, and colorectal cancer when comparing the highest dietary fibre consumers with the lowest. Clinical trials show significantly lower body weight, systolic blood pressure and total cholesterol when comparing higher with lower intakes. Risk reduction associated with a range of critical outcomes was greatest when daily intake of dietary fibre was between 25-29 grams. Dose response curves suggested that higher intakes may confer even greater benefit with regard to protection against cardiovascular diseases, type 2 diabetes and colorectal and breast cancer. Comparable findings for wholegrain 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. Overall the certainty of evidence regarding the 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 glycaemic index. Data relating to other dietary exposures was limited.

Interpretation The complementary findings from prospective studies and clinical trials relating to the reduction in mortality, NCD incidence, and their risk factors associated with relatively high intakes of dietary fibre and whole grains as well as striking dose response evidence indicate that the relationships may be causal. Benefit to individuals and populations may be expected from implementation of dietary recommendations to increase dietary fibre intake and to replace refined grains with whole grains.

Research in Context

Evidence before this study

Carbohydrate-containing foods consisting principally of sugars, starches and dietary fibre (non starch polysaccharide) provide the major source of energy 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 and dietary guidelines typically encourage regular consumption of vegetables, cereals, pulses and whole fruit which are rich sources of these and 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 determine the extent to which the predictive potential of these indicators applies across the spectrum of non-communicable disease (NCDs) nor which are most useful in nutrition guidelines or when recommending food choices. Quantitative recommendations relating to dietary fibre have not had a strong evidence base.

Added value of this study

We have undertaken systematic reviews and meta analyses of prospective studies and clinical trials that have reported on the relationship between the most widely studied indicators of carbohydrate quality (dietary fibre, whole grains or pulses, dietary glycaemic index or glycaemic load) and mortality and incidence of a wide range of NCDs 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 magnitude and importance of the observed associations which influence the 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 related to a reduction in the risk of a wide range of NCDs and their risk factors, provide convincing evidence for nutrition recommendations to replace refined grains with whole grains and increase dietary fibre to at least 25-29g per day, with additional benefits likely to accrue with greater intakes. In the light of current evidence, dietary glycaemic index or glycaemic load may be less useful as overall measures of carbohydrate quality than dietary fibre and wholegrain content.

Introduction

Prior to the mid twentieth century carbohydrates were principally regarded as an energy source and nutrition recommendations suggested that carbohydrates should contribute the energy deficit remaining after intakes of fat and protein had been specified. From the mid 1950s there was increasing awareness of the potential of "sugar" (principally sucrose) to increase the risk of dental caries and in the 1960s Yudkin[1] popularised the view that sugar was a major contributing cause of obesity, type 2 diabetes and cardiovascular disease, an opinion shared by Cleave and Campbell who described these and other chronic conditions as saccharine diseases.[2] A substantial body of experimental, epidemiological and clinical trial data has accumulated since these early observations and based on extensive systematic reviews and meta analyses, the World Health Organization (WHO) has recently issued a strong recommendation, based on the association between free sugars and dental caries and obesity, for individuals to reduce intake to less than 10% total energy and a conditional recommendation suggesting that even greater benefit may accrue if intakes are below 5%.[3] Comparable recommendations have been made by national governments and professional organisations worldwide.

It is more than half a century since Burkitt, Trowell and Painter, based largely on epidemiological observations 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. While nutrition guidelines issued by many governments and professional organisations encourage increased consumption of vegetables, fruit and whole grains, there are fewer quantitative guidelines for sources and intakes of dietary fibre and starch. We report here on a series of systematic reviews and meta analyses on indicators of carbohydrate quality and non-communicable disease (NCD) incidence, mortality, and risk factors. The research was commissioned by WHO to inform the development of updated recommendations regarding carbohydrate intake.

Methods

We followed reporting standards for systematic reviews and meta analyses.[6] 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.

PICO tables and eligibility criteria

PICO tables (Appendix A) were agreed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG). We report here on markers of carbohydrate quality that have been measured in an appreciable number of studies and trials (dietary fibre, dietary glycaemic index or glycaemic load, and wholegrain intake) and outcomes specified in the PICO tables. For prospective studies critical outcomes included all-cause, coronary heart disease (CHD) and stroke mortality and incidence of CHD, stroke, type 2 diabetes, and colorectal cancer. Important outcomes included cardiovascular disease (CVD) incidence and mortality and incidence of adiposity-related cancers (breast, endometrial, oesophageal, and prostate). Prospective studies which included only cohorts with specified pre-existing conditions were excluded.

137   For clinical trials we have reported on adiposity, fasting glucose, fasting insulin, insulin sensitivity, HbA1c,
138   triglycerides, cholesterol, and blood pressure. We included parallel and crossover randomised clinical trials of at
139   least four weeks duration that reported on higher compared with lower intakes of the dietary markers. Eligible
140   trials could include diets with test foods provided, dietary advice, ad libitum diets or controlled feeding trials on
141   free living individuals. Weight loss trials and trials involving provision of dietary fibre supplements in the forms
142   of powders were excluded. Comparison diets were required to be matched for macronutrient composition and
143   lifestyle modifications such as exercise.

144

145   Participants of eligible trials were adults and children free from acute or chronic disease but could include those
146   with prediabetes, mild-moderate hypercholesterolemia, mild-moderate hypertension or metabolic syndrome.
147   Trials including people on medications known to effect outcomes of interest or who were pregnant or in
148   situations where regular eating habits were likely to change e.g. those suffering from eating disorders or who
149   were breast feeding were excluded.

150

151   **Literature search**
152   Prospective observational studies were initially identified from systematic reviews and meta analyses that
153   reported associations between carbohydrate intake or one of the specified measures of carbohydrate quality, and
154   one or more of the key outcome measures. These systematic reviews were found through online searches using
155   Ovid Medline, Embase, PubMed, Web of Science, and Scopus. This strategy was augmented by searches with
156   low-risk-of-bias search terms for individual prospective studies and run up to the end of April 2017 to ensure
157   identification of relevant published studies. No date or language restrictions were applied. A validation of the
158   search procedure is provided in Appendix A.

159

160   For clinical trials, highly sensitive Cochrane search strategies were used to identify trials examining the effects
161   of carbohydrate intakes on obesity, blood pressure, and cardiometabolic risk factors. OVID Medline, Embase,
162   Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews
163   (CDSR), and Food Science and Technology Abstracts (FSTA) databases were searched for trials published up
164   to February 2018. Hand searching of references of systematic reviews, prospective studies, and clinical trials
165   were completed to identify any studies that may have been missed. Search strategies are shown in Appendix A.

166

167   **Study selection**
168   Reviewers identified eligible studies by screening titles, abstracts and where appropriate full texts of articles.
169   Where there were multiple publications from the same cohort, we used data for the longest follow-up period.

170

171   **Data extraction**
172   Data were extracted using pre-tested forms.[7] For prospective studies the most adjusted values for effect size
173   were extracted, where that value did not also specifically include adjustment for other carbohydrates. For
174   clinical trials involving multiple interventions we extracted data from all relevant interventions. For crossover
175   trials involving multiple interventions we extracted data only from the most relevant intervention and either the
176   control group or the most relevant comparator intervention.

177

Risk of bias assessment

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 (NOS)[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. Where 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. Where the quantile dose range was open-ended, half the range of the adjacent quantile was used to determine the average intake. We used 30g to represent one serve of whole grains when a value for weight was not stated.[13] Non-linear dose-response was assessed using 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 RR value when necessary. Linear and spline (with 95%CI) models are shown with each data point overlaid as circles. Circle size indicates the weighting of each data point with bigger circles indicating greater influence. Absolute risk values were calculated with GRADE Pro software.[15]

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 those consuming between 15-19, 20-24, 25-29, 30-34, and 35-39 grams of fibre per day with a random effects model. When studies reported more than one quantile of data within the pre-specified intake ranges, we first combined these quantiles with a fixed effects model before including them within the pooled estimate. We did this to measure the number of critical outcomes where an improvement in relative risk 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 standard error or other relevant statistics, end of treatment values were analysed as independent samples. Subgroup analyses by fibre amount or principal starch source were conducted when there were enough studies for subgroupings including more than one trial. For example high fibre interventions (0-25, 25-30, 30-35, >35 g/day) were considered to determine whether there were threshold effects or a possible dose response.

217

218 For all analyses heterogeneity was assessed with the I^2 statistic,[16] and the Cochrane Q test.[17] Sensitivity analyses

219 were conducted when a I^2 statistic was found to be more than 50% or a p for heterogeneity of <0.10. Publication

220 bias was assessed with Egger's and Begg's tests,[18] and the trim and fill method.[19] The effect of each individual

221 study's findings was considered with an influence analysis. For prospective studies analyses excluding those

222 that scored less than six out of a possible nine with the NOS were conducted. If there was still unexplained

223 heterogeneity we considered the impact of small studies reporting less than 200 cases or less than 2000

224 participants. For clinical trials, analyses excluding trials with a high risk of bias for at least one criterion were

225 conducted to examine the influence of potential bias on outcomes. Meta regression analyses further examined

226 effects of potential explanatory factors including trial design (crossover or parallel), study or trial duration,

227 global region, differences in fibre intake achieved, source of fibre or starch and nutrition status of participants.

228 Analyses were performed using the Cochrane Collaboration software and Stata statistical software.[20,21]

229

230 We used GRADE[22] protocols, to judge the quality of the body of evidence as either high, moderate, low, or

231 very-low. More detail on this approach is provided in Appendix A. Quality of the evidence was assessed by the

232 research team and revised if required after discussion with the NUGAG Subgroup on Diet and Health.

233

234 **Role of the funding source**

235 With the exception of WHO, the funders of the study had no role in study design, data collection, data analysis,

236 data interpretation, or writing the report. The corresponding author had full access to all the data in the study

237 and had final responsibility for the decision to submit for publication.

238

239 **Results**

240 Data from 185 publications of prospective studies involving just under 135 million person years and 58 clinical

241 trials with a total of 4,635 adult participants were included in the meta analyses. A flow chart of identified

242 studies is shown in Figure 1, with details of these studies in Supplement 10. Critical outcome data for total fibre,

243 wholegrain intake, and dietary glycaemic index are summarised in Tables 1-3 and shown in full in Appendices

244 B-D for observational studies and Supplements 1 and 2 for trials. Dose response data are shown in Figures 2-4

245 and the supplementary material. Summary forest plots from clinical trial data are shown in Figure 5. Data and

246 GRADE tables relating to all other indicators and outcomes are in Supplement 1-9.

247

248 **Dietary fibre**

249 The observational data in Table 1 show that higher intakes of total dietary fibre are associated with a 15-31%

250 reduction in the risk of specified critical outcomes. For all-cause mortality and coronary heart disease incidence

251 this translates into 13 fewer deaths (95%CI 8 to 18) and 6 fewer cases of CHD (95%CI 4 to 7) per 1000

252 participants over the duration of the studies. Sensitivity analyses of the tested associations did not change the

253 direction or significance of any observed result. The quality of evidence contributing to the meta analyses of the

254 cohort studies was, with the exception of the data relating to stroke, considered to be moderate.

255

256   Figure 2 shows dose response relationships for total fibre intake and total mortality, incidence of coronary heart
257   disease, type 2 diabetes and colorectal cancer, many of which are linear with no sign of a plateau within the
258   available data. When comparing the lowest fibre intakes with pre-specified ranges the greatest benefits were
259   observed for those consuming 25-29g per day (improvement in 6 of the 7 critical outcomes), more so than those
260   consuming between 15-19g per day (improvement in 3 of the 7 critical outcomes), or 20-24g per day
261   (improvement in 4 of the 7 critical outcomes). These analyses are shown in full in Appendix B.
262

263   Mean differences between higher versus lower fibre intakes for a range of cardiometabolic risk factors are
264   shown in Table 1 and the summary forest plots in Figure 5a. Dose response or threshold effects could not be
265   determined from the clinical trial data. The quality of evidence contributing to the meta analyses of the trial data
266   relating to body weight is high and total cholesterol and systolic blood pressure moderate because of
267   unexplained heterogeneity between the trials.
268

269   Broadly similar effects were apparent in both the prospective studies and clinical trials, when examining fibre
270   from different food groups or fibre described as soluble or insoluble, though limited data were available, other
271   than for cereal fibre, the largest contributor to total dietary fibre (Supplements 1-9).
272

273   **Whole grains**
274   Cohort data showing the relationship between whole grains and the effect of increasing wholegrain intake on
275   critical outcomes are shown in Table 2. Higher intakes of whole grains were associated with a 13-33% reduction
276   in the risk. For all-cause mortality and coronary heart disease incidence this translates into 26 fewer deaths
277   (95%CI 14 to 39) and 7 fewer cases (95%CI 3 to 10) per 1000 participants over the duration of the studies.
278   Sensitivity analyses did not typically change the direction or significance of any pooled effect. The quality of
279   evidence relating to colorectal cancer incidence is moderate, whilst for other critical outcomes it is low due to
280   high heterogeneity not fully explained by sensitivity analysis. Dose response curves showing clear associations
281   with increasing wholegrain intake and all-cause mortality or risk of coronary heart disease, type 2 diabetes, and
282   colorectal cancer incidence are shown in Figure 3. Mean differences in cardiometabolic risk factors between
283   higher and lower wholegrain consumption are shown in Table 2 and summary forest plots in Figure 5b.
284   Evidence relating to body weight, cholesterol, and blood pressure is graded as moderate, downgraded due to
285   unexplained heterogeneity.
286

287   **Glycaemic index**
288   Cohort data showing the relationship between dietary glycaemic index and the effect of decreasing the dietary
289   glycaemic index on critical outcomes as demonstrated in the trials are shown in Table 3, dose responses are
290   shown in Figure 4, and summary forest plot in Figure 5c. Data relating to the cohort studies which examined the
291   effects of glycaemic load are presented in Supplement 3.
292

293   An 11% (95%CI 3% to 18%) relative risk reduction of type 2 diabetes was observed for those consuming low
294   glycaemic index diets. However sensitivity analysis due to high heterogeneity attenuated the relative risk
295   reduction to 5% (95%CI 13% less to 4% more). Stroke mortality was lower amongst those consuming lower

296 glycaemic index diets. The prospective studies generated evidence that is graded as low or very-low quality as a
297 result of high risk of bias, imprecision, and inconsistencies. Key outcome markers from the clinical trials on
298 decreasing the glycaemic index of a diet are shown in forest plots in Figure 5c. Trial data were usually of
299 moderate quality.
300
301 **Discussion**
302 Higher intakes of total dietary fibre or whole grains result in reduced incidence and mortality from several
303 NCDs. Less useful markers of carbohydrate quality are glycaemic index, glycaemic load, and sources of dietary
304 fibre where inconsistent findings or insufficient data provide low or very low quality evidence. In randomised
305 trials higher intakes of dietary fibre reduce body weight, lower blood cholesterol and systolic blood pressure.
306 These findings are supported by cohort studies that report reduced risk of coronary heart disease incidence and
307 mortality and diabetes incidence. The consistency between the trial and prospective study results together with
308 the dose response relationships are evidence that the effect on cardiometabolic diseases are likely to be causal
309 and not a consequence of confounding. In addition, prospective studies show striking reductions in and dose
310 response relationships with all-cause mortality, total cancer deaths, total cardiovascular disease, stroke
311 incidence, and colorectal, breast, and oesophageal cancer. For several of these outcomes the dose response is
312 linear. These findings together with the comparisons of clinical outcomes amongst those with different intakes
313 of dietary fibre suggest that individual adult intakes of total dietary fibre should be no less than 25 to 29 grams
314 per day with additional benefits likely to accrue with higher intakes. Population intakes in this range are
315 reported in some countries, but the majority consume less than 20 grams a day.[23] Broadly similar trends were
316 apparent in the prospective studies that examined cereal fibre, typically the largest contributor to total dietary
317 fibre. Limited data were available regarding specific sources (legume, fruit, vegetable) or subcategories
318 ('soluble', 'insoluble', or extracted) of dietary fibre.
319
320 The results for wholegrain foods reflect those for dietary fibre. Prospective studies showed a reduction in all-
321 cause mortality, coronary heart disease, cancer deaths, and incidence of type 2 diabetes. As with dietary fibre
322 the observed reductions in risk are considerable, typically around 20% with significant dose response
323 relationships. The randomised controlled trials involving an increase in the amount of whole grains showed
324 improvements in body weight and lipids. The similar protective effects of higher intakes of wholegrain foods
325 and of dietary fibre suggest that the beneficial effects of whole grains may be due to their typically high dietary
326 fibre content. The GRADE criteria categorise the evidence linking most clinical outcomes with dietary fibre as
327 moderate, and with whole grains as low quality.
328
329 Dietary starch can be divided into several categories[24] although rarely are measurements made of these
330 individual components in either prospective studies or randomised controlled trials. However the glycaemic
331 index of starch-containing foods or the overall glycaemic load of meals or diets including starchy foods provide
332 measures of starch quality and are widely reported. We have found that diets with a lower overall glycaemic
333 index appear to be associated with a reduced risk of stroke and type 2 diabetes. However the risk estimates,
334 other than for stroke mortality, are modest when compared with those for dietary fibre and following sensitivity
335 analyses were reduced and associated with confidence intervals which included 1. The findings from

336 prospective studies of glycaemic load are inconsistent. The results from trials show no consistent benefits on the
337 clinical outcomes when changing the glycaemic index of a diet.

338

339 A major strength of the present study is that it has related key markers of carbohydrate quality to total mortality
340 and mortality and incidence of the major nutrition-related non-communicable diseases and that prospective
341 studies have been considered alongside randomised controlled trials. Other reviews and meta analyses have
342 reported on a single indicator of carbohydrate quality and one or more outcomes. Our approach has enabled us
343 to use these indicators of carbohydrate quality to provide a stronger justification than had previously been
344 available for a quantitative recommendation relating to dietary fibre intake. That the evidence for the
345 associations between the quality markers and outcomes was most frequently rated as 'moderate' or 'low' rather
346 than 'high' may be regarded as a limitation. However this is an inevitable consequence of the use of GRADE
347 criteria for assessment which typically require evidence from randomised controlled trials with disease
348 endpoints in order to be rated as being of 'high'. Furthermore when using the GRADE approach downgrading
349 frequently occurs as a consequence of unexplained heterogeneity amongst the results of the different studies,
350 even when all trend in a similar direction. This may be a consequence of studies being carried out in diverse
351 populations or as a result of different methods of measuring dietary intake. With regard to the associations we
352 have reported here between dietary fibre and whole grains and a wide range of clinical outcomes, the
353 consistency of the findings, the striking dose response relationships and the substantial body of mechanistic
354 evidence all contribute to the totality of evidence and increases our confidence in the findings.

355

356 Our findings are broadly comparable with other reviews and meta analyses that have reported on the association
357 between dietary fibre and whole grains and one or more disease outcomes.[25-28] However there is less consistency
358 in our findings than in earlier reports with regard to the potential benefit of low glycaemic index or glycaemic
359 load diets. Three systematic reviews have shown a reduced incidence of type 2 diabetes associated with the
360 consumption of diets of lower glycaemic index or glycaemic load,[29-31] though the effect was modest when
361 compared with the protective effect of total dietary fibre or wholegrains. In the present study sensitivity analyses
362 due to high heterogeneity reduced risk reduction and confidence intervals included 1. A review of prospective
363 studies by Turati et al.[32] suggested a small but significant increase in colorectal cancer incidence associated with
364 high glycaemic index or glycaemic load. This finding was subject to high unexplained heterogeneity and
365 included retrospective case-control studies which may be subject to dietary recall bias. Other studies have
366 reported a lower incidence of stroke and CHD amongst those consuming low glycaemic index or glycaemic load
367 diets,[29,33-36] whilst we found a reduced risk of stroke only. We were unable to confirm an effect of low
368 glycaemic index or glycaemic load diets on haemoglobin $A1_c$ or blood cholesterol which have been reported in
369 many short and medium term trials. However we excluded trials which involved only people with diabetes or
370 marked hyperlipidaemia who were the participants in the majority of trials reporting reduction in these
371 important risk indicators. Our study does not exclude the value of these indicators of carbohydrate quality in this
372 clinical context.

373

374 Whole grains offer a useful means of increasing dietary fibre intake and reducing risk of NCDs. However fruit
375 and vegetables are also important contributors to dietary fibre intake. We did not specifically explore the

376 relationship between fruit and vegetable consumption and NCDs given the recent systematic review and meta
377 analyses by Aune et al.[37] They report risk reductions of around 10% per 200g fruit and vegetables combined for
378 CHD, stroke and total mortality and smaller but still significant reductions for total cardiovascular disease and
379 cancer. Appreciable dose response effects were apparent for most outcomes up to 800g/day. Inverse associations
380 were observed between the intake of apples, pears, citrus fruits, green leafy vegetables, cruciferous vegetables
381 and salad and cardiovascular disease and all-cause mortality. Intake of green yellow vegetables and cruciferous
382 vegetables were inversely associated with total cancer risk In addition to fibre, fruits and vegetables contain
383 many other nutrients that are potentially protective and confer some risk reduction.

384

385 The benefits of fibre reported in the present and other papers are supported by over 100 years of research into its
386 chemistry, physical properties, physiology and metabolic effects.[23,38-40] Fibre containing foods must be chewed
387 before passing through the stomach and into small bowel where they affect satiety, glucose and insulin
388 responses and lipid absorption. Whilst more recent systematic reviews have shown only small effects on
389 appetite, satiety or blood lipids[41,42] these studies have been conducted largely using defined fibre supplements
390 rather than whole foods. Whole foods that require chewing and retain much of their structure in the gut are more
391 likely to increase satiety through a variety of mechanisms leading to weight loss and to modulation of
392 carbohydrate and lipid metabolism. In the large bowel fibre is almost completely broken down by the resident
393 microflora in a series of anaerobic reactions known as fermentation.[43] The gut microbiota play a number of
394 important roles in human health including protecting against pathogens, development of the gut immune system,
395 vitamin synthesis, metabolism of xenobiotics and may be involved in complex gut-brain communication.
396 However the principal function of the microbiome is digestion of fibre and other carbohydrates that escape
397 breakdown in the small bowel and it is the availability of fibre in the diet that dominates the metabolism of the
398 gut microbiome and leads to protection from conditions such as colorectal cancer.[44,45] This coming together of
399 the epidemiological and experimental work on fibre allows conclusions to be drawn that increased fibre intakes
400 should result in improvements in population health.

401

402 While we have not considered the evidence regarding total carbohydrate intake, epidemiological evidence and
403 relatively long term clinical trials[46] suggest that a wide range of intakes is acceptable, a finding which is
404 endorsed by authoritative dietary guidelines.[47] Our study contributes to the growing body of evidence that
405 carbohydrate quality rather than quantity determines major health outcomes. Translating these findings
406 regarding dietary fibre and whole grains into dietary advice for individuals and populations should be
407 accompanied by a caveat. Dietary fibre as defined by Codex Alimentarius is naturally occurring in foods, but
408 may be extracted from foods or synthesised and added into manufactured foods. The large body of literature
409 which contributed to this and other systematic reviews and meta analyses relate principally to fibre rich foods
410 since most of the studies were undertaken before synthetic and extracted fibre were widely used. The concept of
411 wholegrain foods has also changed appreciably. Wholegrain foods are required to have a nutrient composition
412 similar to that of the original grain, without regard to the degree of processing. Many breakfast cereals and other
413 manufactured "whole grain" products are more highly processed than in the past. There is limited, but quite
414 striking evidence that increased processing of whole grains can result in a deterioration of a several biomarkers
415 of cardiometabolic disease.[48] As these are relatively recent developments there is no epidemiological evidence

416 of the consequences of these changes in the food supply on clinical outcomes and mortality. Until such evidence
417 is available it seems appropriate that dietary advice should emphasise the benefits of naturally occurring dietary
418 fibre in whole grains, vegetables and fruits that have been minimally processed.
419
420 There is a considerable body of evidence relating to the adverse consequences of high intakes of sugar
421 sweetened beverages and strong recommendations to reduce the intake of free sugars.[3] Our findings based on a
422 series of systematic reviews and meta analyses provide strong evidence for the importance of including advice
423 regarding the nature and source of other carbohydrates in dietary guidelines aimed at reducing the risk of NCDs.
424 Diets high in total dietary fibre especially from whole grains and, on the basis of another recent systematic
425 review,[36] vegetables and fruits, are associated with a significant reduction in a range of NCDs when compared
426 with lower dietary fibre and refined rather than whole grain intakes. The types of studies we have considered did
427 not identify risks associated with dietary fibre. However high intakes may be associated with deleterious effects
428 in populations with borderline iron/mineral status, amongst whom very high whole grain intakes may further
429 compromise iron status.[49] High intakes of dietary fibre and whole grains are more clearly associated with good
430 health outcomes than measures of glycaemic index or glycaemic load. Whilst glycaemic index provides a
431 measure of the glycaemic potential of the carbohydrate content of foods, some low glycaemic index foods may
432 have other attributes, which are not health promoting. Foods containing added fructose or sucrose and
433 composite foods containing both saturated fat and carbohydrate (e.g. confectionary products) may have a low
434 glycaemic index.[50] Our complementary findings from randomised controlled trials and prospective studies
435 together with the dose response effects, supported by much experimental work, are evidence that diets
436 characterised by a low content of dietary fibre contribute to the cause of a number of NCDs and that benefit will
437 accrue from implementation of quantitative recommendations regarding dietary fibre intake. Intakes in the range
438 of 25 to 29g daily are optimal whilst the dose response data show that amounts greater than 30g per day confer
439 additional benefits.
440

Contributors

442 AR was responsible for the systematic reviews and meta analyses of prospective studies, wrote the first draft of
443 the manuscript, was involved with the interpretation of results, and approved the submission of the final
444 manuscript. LTM was responsible for the systematic reviews and meta analyses of clinical trials, was involved
445 with the interpretation of results, and approved the submission of the final manuscript. JC was involved with the
446 interpretation of results, and approved the submission of the final manuscript. NW was involved with the
447 systematic reviews and meta analyses of clinical trials and approved the submission of the final manuscript. EM
448 was involved with the systematic reviews and meta analyses of prospective studies and approved the submission
449 of the final manuscript. JM was involved with the interpretation of results, had full access to all the data in the
450 study and had final responsibility for the decision to submit for publication.
451

Declarations of interest

453 We declare no competing interests
454

Acknowledgments

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570

571   **Figure 1 Flow chart indicating the process by which eligible prospective studies and randomised**

572   **controlled trials were identified**
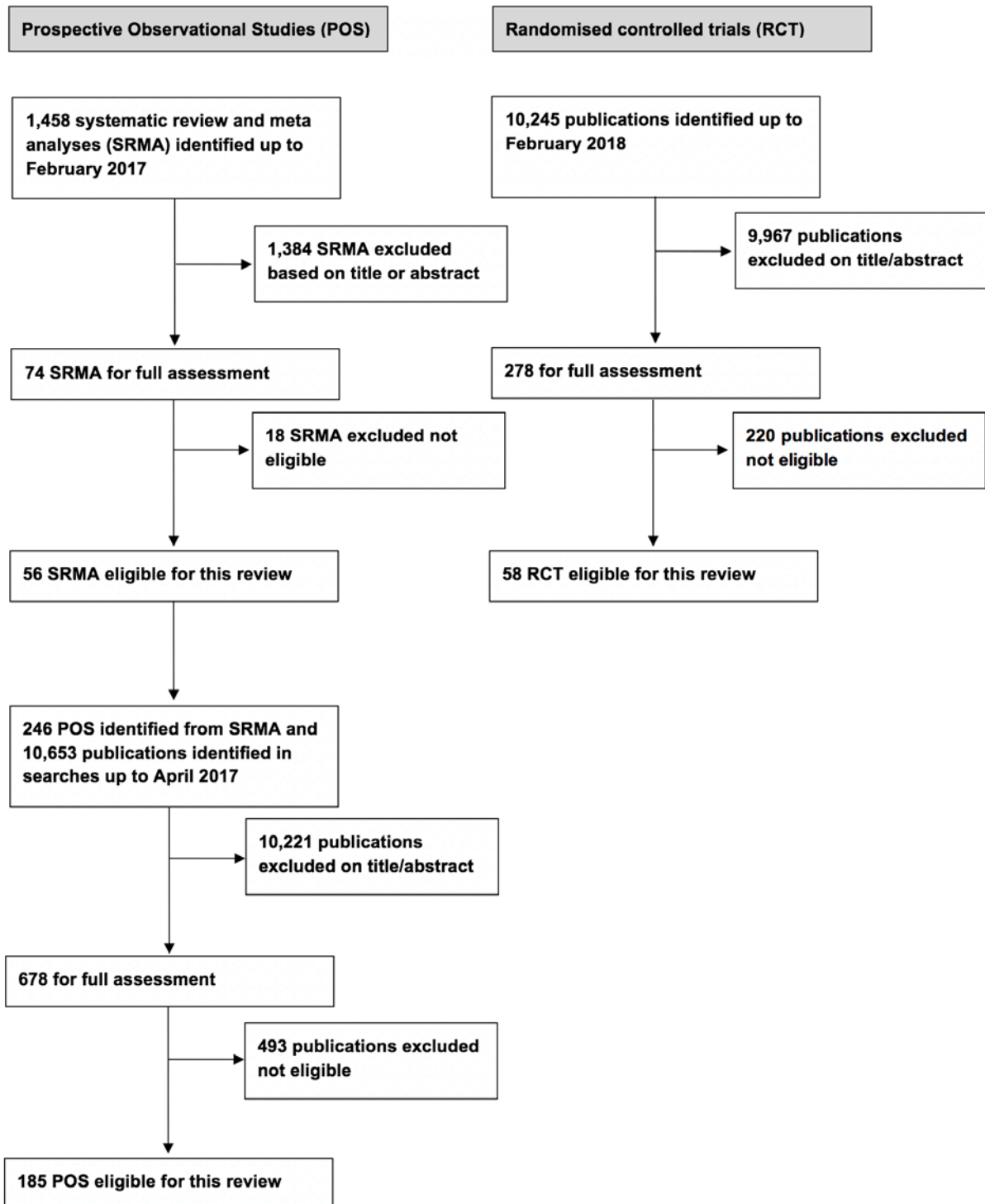
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575   **Table 1: Effects of higher compared with lower intakes of total dietary fibre on critical outcomes**

Outcome	Number of studies	Type of study	Number of cases or N in intervention	Person years or N of controls	Effect size (95%CI)	GRADE quality
All-cause mortality	10	observational	80,139	12·3 million PY	RR 0·85 (0·79 to 0·91)	Moderate
CHD mortality	10	observational	7,243	6·9 million PY	RR 0·69 (0·60 to 0·81)*	Moderate
CHD incidence	9	observational	7,155	2·7 million PY	RR 0·76 (0·69 to 0·83)	Moderate
Stroke mortality	2	observational	1,103	1·3 million PY	RR 0·80 (0·56 to 1·14)	Very low
Stroke incidence	9	observational	13,134	4·6 million PY	RR 0·78 (0·69 to 0·88)**	Low
Cancer mortality	5	observational	29,593	11·2 million PY	RR 0·87 (0·79 to 0·95)	Moderate
Type 2 diabetes incidence	17	observational	48,468	6·9 million PY	RR 0·84 (0·78 to 0·90)	Moderate
Colorectal cancer incidence	22	observational	22,920	16·9 million PY	RR 0·84 (0·78 to 0·89)	Moderate
Change in body weight (kg)	27	randomised trials	1,294	1201	MD 0·37 lower (0·63 kg lower to 0·11 kg lower)	High
Change in HbA1c (%)	6	randomised trials	191	189	SMD 0·35 lower (0·73 lower to 0·03 higher)	Low
Change in total cholesterol (mmol/L)	36	randomised trials	1,832	1,671	MD 0·15 lower** (0·22 lower to 0·07 lower)	Moderate
Change in systolic blood pressure (mm Hg)	15	randomised trials	1,064	988	MD 1·27 lower** (2·50 lower to 0·04 lower)	Moderate

576   PY person years, RR relative risk, MD mean difference, SMD standardised mean difference

577   * Egger's test for bias p = 0·0040. Trim and fill analysis did not change the direction or significance of the pooled estimate.

578   ** The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses.

579

580   Detailed justification for the GRADE quality of evidence is given in Appendix B for observational studies and Supplement 1 for trials.

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

Outcome	N of studies	Type of study	Number of cases or N in intervention	Person years or N of controls	Effect size (95%CI)	GRADE quality
All-cause mortality	9	observational	99,224	10·7 million PY	RR 0·81 (0·72 to 0·90)*	Low
CHD mortality	2	observational	1,588	2·0 million PY	RR 0·66 (0·56 to 0·77)	Low
CHD incidence	6	observational	7,697	2·8 million PY	RR 0·80 (0·70 to 0·91)*	Low
Stroke mortality	2	observational	694	2·0 million PY	RR 0·74 (0·58 to 0·94)	Low
Stroke incidence	3	observational	1,247	1·1 million PY	RR 0·86 (0·61 to 1·21)	Very low
Cancer mortality	5	observational	32,727	10·1 million PY	RR 0·84 (0·76 to 0·92)*	Low
Type 2 diabetes incidence	8	observational	14,686	3·9 million PY	RR 0·67 (0·58 to 0·78)*	Low
Colorectal cancer incidence	7	observational	8,803	6·8 million PY	RR 0·87 (0·79 to 0·96)	Moderate
Change in body weight (kg)	11	randomised trials	498	421	MD 0·62 lower (1·19 lower to 0·05 lower)	Moderate
Change in HbA1c (%)	3	randomised trials	141	141	SMD 0·54 lower (1·28 lower to 0·20 higher)	Low
Change in total cholesterol (mmol/L)	17	randomised trials	772	701	MD 0·09 lower (0·23 lower to 0·04 higher)	Moderate
Change in systolic blood pressure (mm Hg)	8	randomised trials	493	432	MD 1·01 lower (2·46 lower to 0·44 higher)	Moderate

582 PY person years, RR relative risk, MD mean difference, SMD standardised mean difference

583 * The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses.

584

585

586 Detailed justification for the GRADE quality of evidence is given in Appendix C for observational studies and Supplement 2 for trials.

587

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

Outcome	N of studies	Type of study	Number of cases or N in intervention	Person years or N of control	Effect size (95%CI)	GRADE quality
All-cause mortality	3	observational	7,698	0·6 million PY	RR 0·89 (0·70 to 1·13)*	Very low
CHD mortality	1	observational	incidence not stated	0·04 million PY	RR 1·10 (0·69 to 1·75)	Very low
CHD incidence	10	observational	8,456 + not reported in one study	2·4 million PY	RR 0·93 (0·83 to 1·04)	Low
Stroke mortality	3	observational	951	1·2 million PY	RR 0·63 (0·52 to 0·77)	Low
Stroke incidence**	5	observational	5,527	3·0 million PY	RR 0·84 (0·72 to 0·99)	Very low
Cancer mortality	1	observational	1,401	0·4 million PY	RR 1·11 (0·90 to 1·38)	Very low
Type 2 diabetes incidence**	14	observational	36,908	6·5 million PY	RR 0·89 (0·82 to 0·97)*	Very low
Colorectal cancer incidence	10	observational	11,245	8·8 million PY	RR 0·91 (0·82 to 1·01)*	Very low
Change in body weight (kg)	8	randomised trials	464	335	MD 0·29 lower (0·62 lower to 0·03 higher)	High
Change in HbA1c (%)	2	randomised trials	44	37	SMD 0·08 higher (0·35 lower to 0·52 higher)	Very low
Change in total cholesterol (mmol)	8	randomised trials	605	478	MD 0·02 lower (0·17 lower to 0·13 higher)	Moderate
Change in systolic blood pressure (mm Hg)	4	randomised trials	519	397	MD 0·17 lower (1·03 lower to 0·69 higher)	High

589   PY person years, RR relative risk, MD mean difference, SMD standardised mean difference

590   * The high heterogeneity of the pooled effect size (>50%) is unexplained by sensitivity analyses.

591   ** The pooled effect size did not maintain statistical significance during sensitivity analyses.

592   *** Only one eligible trial of children was identified in our systematic searches. Although the exposure was for diets of higher and lower GI, data from this trial has not been

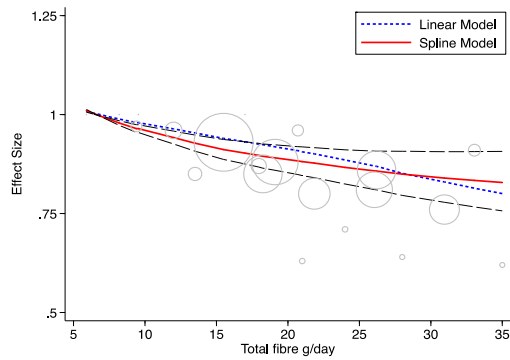593   included with that of adults shown above.

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596   Detailed justification for the GRADE quality of evidence is given in Appendix D for observational studies and Supplement 2 for trials.

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Figure 2 Dose response relationships between total dietary fibre and critical clinical outcomes based on data from prospective studies.
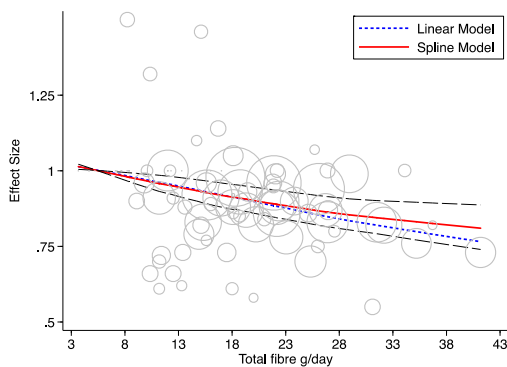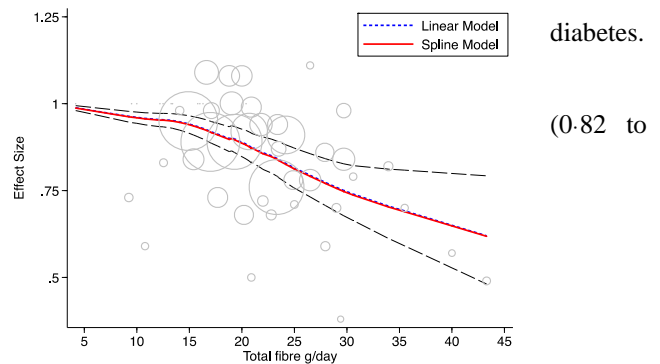

Fig 2a Total fibre and all-cause mortality. 68,183 deaths over 11·3 million person years. Assuming linearity a reduced risk ratio of 0·93 (0·90 to 0·95) was observed for every 8 grams more fibre consumed per day.
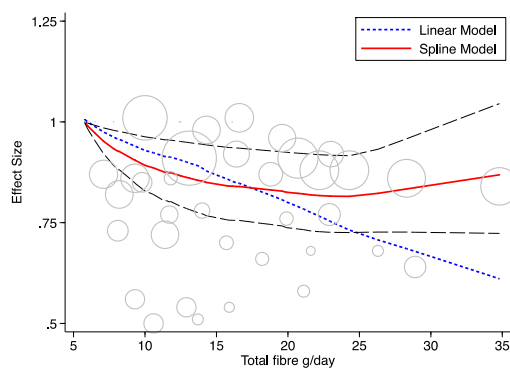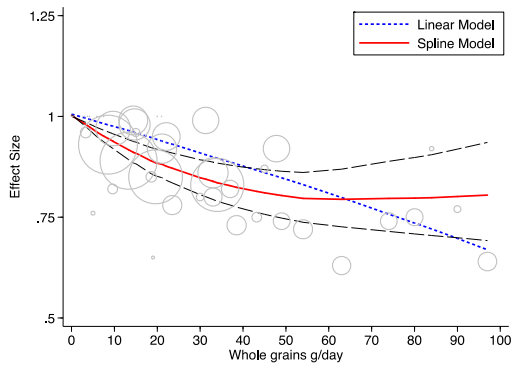

Fig 2b Total fibre and coronary heart disease incidence. 6,449 deaths over 2·5 million person years. Assuming linearity a reduced risk ratio of 0·81 (0·73 to 0·90) was observed for every 8 grams more fibre consumed per day.

Fig 2c Total fibre and incidence of type 2 22,450 cases over 3·2 million person years. Assuming linearity a reduced risk ratio of 0·85 0·89) was observed for every 8 grams more fibre consumed per day.
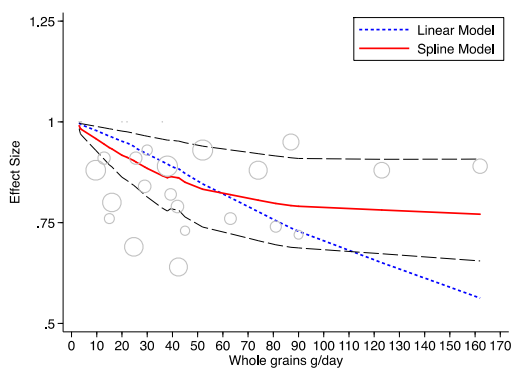

diabetes.

(0·82 to

Fig 2d Total fibre and incidence of colorectal cancer. 20,009 cases over 20·9 million person years. Assuming linearity a reduced risk ratio of 0·92 (0·89 to 0·95) was observed for every 8 grams more fibre consumed per day.

Figure 3 Dose response relationships between wholegrain intake and critical clinical outcomes based on data from prospective studies.
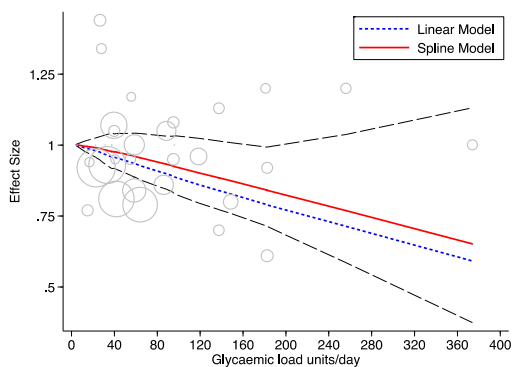

Fig 3a Wholegrain intake and all-cause mortality. 88,347 deaths over 8·2 million person years. Assuming linearity a reduced risk ratio of 0·94 (0·92 to 0·95) was observed for every 15 grams more whole grains consumed per day.

Fig 3b Wholegrain intake and incidence of coronary heart disease. 6,587 cases over 2·4 million person years. Assuming linearity a reduced risk ratio of 0·93 (0·89 to 0·98) was observed for every 15 grams more whole grains consumed per day.

Fig 3c Wholegrain intake and incidence of type 2 13,147 cases over 3·5 million person years. Assuming linearity a reduced risk ratio of 0·88 0·95) was observed for every 15 grams more grains consumed per day.

diabetes.

(0·81 to

whole

Fig 3d Wholegrain intake and incidence of colorectal cancer. 6,056 cases over 5·7 million person years. Assuming linearity a reduced risk ratio of 0·97 (0·95 to 0·99) was observed for every 15 grams more whole grains consumed per day**.**

Figure 4 Dose response relationships between dietary glycaemic index and critical clinical outcomes based on data from prospective studies.
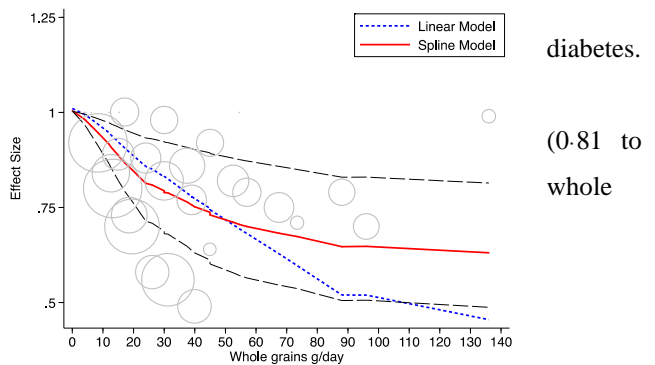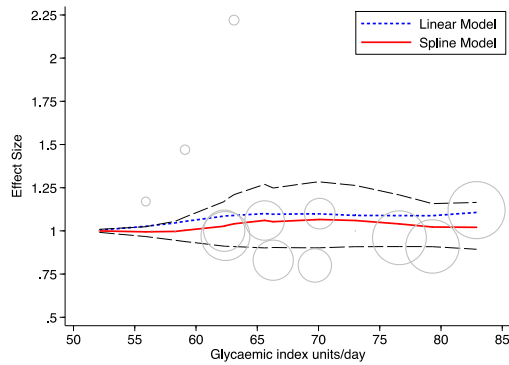

Fig 4a Glycaemic index and all-cause mortality. 7,699 deaths over 0·6 million person years. Assuming linearity a risk ratio of 1·16 (0·90 to 1·49) was observed for every 10 glycaemic index unit increase per day.

Fig 4b Glycaemic index and coronary heart incidence. 7,240 cases over 2·4 million person Assuming linearity a risk ratio of 1·09 (0·94 to was observed for every 10 glycaemic index unit per day.

disease years. 1·27) increase

Fig 4c Glycaemic index and incidence of type 2 diabetes. 31,780 cases over 4·9 million person years. Assuming linearity a risk ratio of 1·10 (1·00 to 1·20) was observed for every 10 glycaemic index unit increase per day.
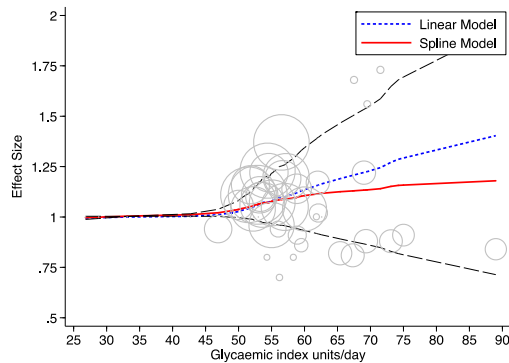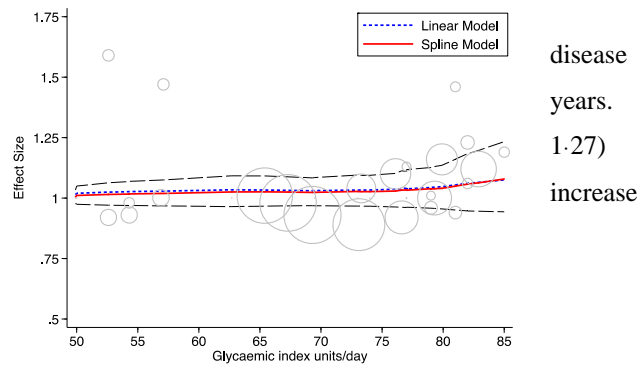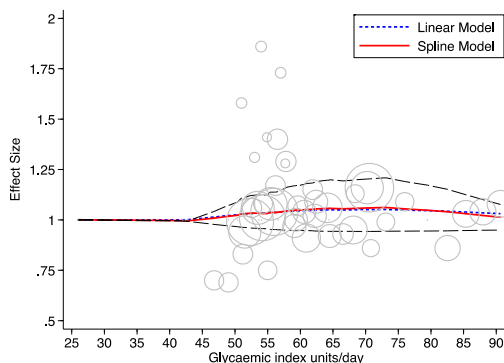

Fig 4d Glycaemic index and incidence of colorectal cancer. 10,390 cases over 6·5 million person years. Assuming linearity a risk ratio of 1·05 (1·00 to 1·10) was observed for every 10 glycaemic index unit increase per day.
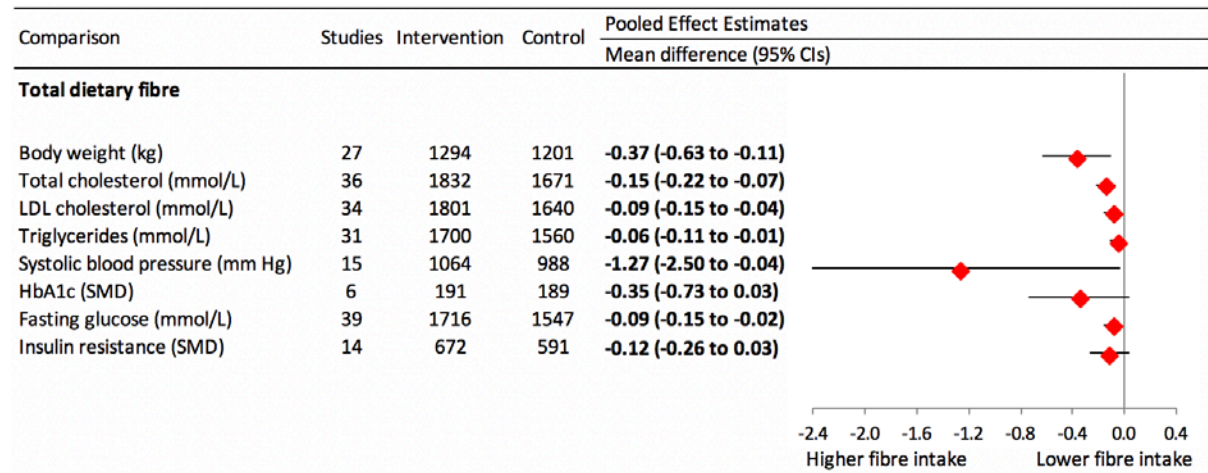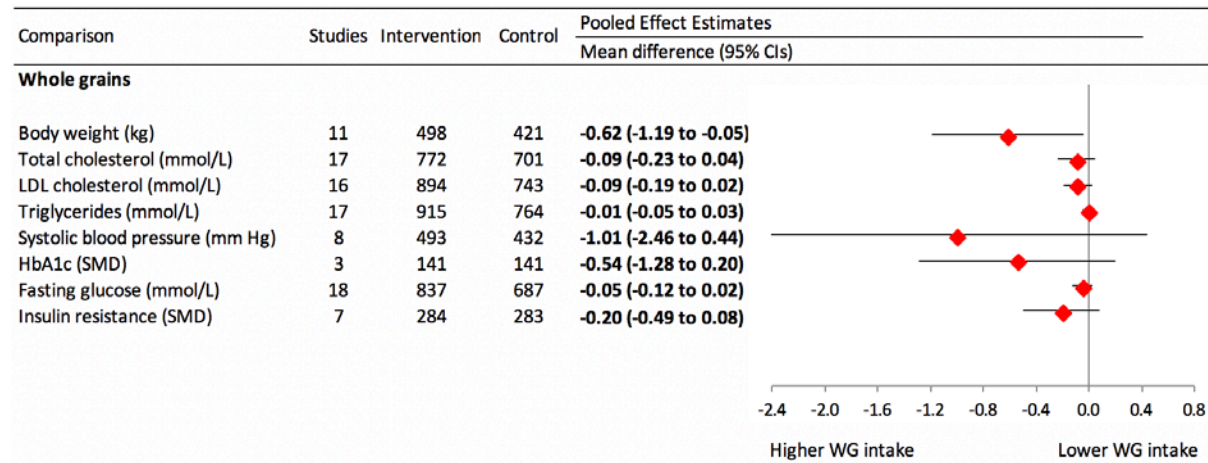
Figure 5 Summary forest plots of key outcomes from clinical trials.

Fig 5a Higher compared with lower total fibre intakes.

Comparison	Studies	Intervention	Control	Pooled Effect Estimates Mean difference (95% CIs)
Total dietary fibre				
Body weight (kg)	27	1294	1201	-0.37 (-0.63 to -0.11)
Total cholesterol (mmol/L)	36	1832	1671	-0.15 (-0.22 to -0.07)
LDL cholesterol (mmol/L)	34	1801	1640	-0.09 (-0.15 to -0.04)
Triglycerides (mmol/L)	31	1700	1560	-0.06 (-0.11 to -0.01)
Systolic blood pressure (mm Hg)	15	1064	988	-1.27 (-2.50 to -0.04)
HbA1c (SMD)	6	191	189	-0.35 (-0.73 to 0.03)
Fasting glucose (mmol/L)	39	1716	1547	-0.09 (-0.15 to -0.02)
Insulin resistance (SMD)	14	672	591	-0.12 (-0.26 to 0.03)

Figure 5b Higher compared with lower wholegrain intakes.

Comparison	Studies	Intervention	Control	Pooled Effect Estimates Mean difference (95% CIs)
Whole grains				
Body weight (kg)	11	498	421	-0.62 (-1.19 to -0.05)
Total cholesterol (mmol/L)	17	772	701	-0.09 (-0.23 to 0.04)
LDL cholesterol (mmol/L)	16	894	743	-0.09 (-0.19 to 0.02)
Triglycerides (mmol/L)	17	915	764	-0.01 (-0.05 to 0.03)
Systolic blood pressure (mm Hg)	8	493	432	-1.01 (-2.46 to 0.44)
HbA1c (SMD)	3	141	141	-0.54 (-1.28 to 0.20)
Fasting glucose (mmol/L)	18	837	687	-0.05 (-0.12 to 0.02)
Insulin resistance (SMD)	7	284	283	-0.20 (-0.49 to 0.08)

Figure 5c Comparison of diets characterised by lower compared with higher glycaemic index foods.

Comparison	Studies	Intervention	Control	Pooled Effect Estimates Mean difference (95% CIs)
Glycaemic Index				
Body weight (kg)	8	464	335	-0.29 [-0.62 to 0.03)
Total cholesterol (mmol/L)	8	605	478	-0.02 (-0.17 to 0.13)
LDL cholesterol (mmol/L)	8	605	478	0.05 (-0.13 to 0.22)
Triglycerides (mmol/L)	8	605	478	-0.02 (-0.07 to 0.03)
Systolic blood pressure (mm Hg)	4	519	397	-0.17 (-1.03 to 0.69)
HbA1c (SMD)	2	44	37	0.08 (-0.35 to 0.52)
Fasting glucose (mmol/L)	11	609	475	0 (-0.08 to 0.07)
Insulin resistance (SMD)	5	284	283	0.14 (-0.03 to 0.31)