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

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4

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24

25 **Summary**

26 **Background** Previous systematic reviews and meta analyses explaining the relationship between carbohydrate
27 quality and health have usually examined a single marker and a limited number of clinical outcomes. We have
28 considered the impact of carbohydrate quality as measured by intakes of dietary fibre, whole grains or pulses,
29 and dietary glycaemic index or glycaemic load on non-communicable disease (NCD) incidence, mortality, and
30 risk factors to more precisely quantify the predictive potential of the markers, to determine which are most
31 useful, and to establish an evidence base for quantitative recommendations for intakes of dietary fibre.

32
33 **Methods** Prospective studies published prior to April 2017 and randomised controlled trials published prior to
34 February 2018, which reported on indicators of carbohydrate quality and NCD incidence, mortality and risk
35 factors were systematically reviewed and meta analysed. Studies were identified by searches in PubMed, Ovid
36 Medline, Embase, and the Cochrane Central Register of Controlled Trials and by hand searching of previous
37 publications. Searches, data extraction, and bias assessment were duplicated independently. Robustness of
38 pooled estimates from random effects models was considered with sensitivity analyses, meta regression, dose
39 response testing, and subgroup analyses. The GRADE approach was used to assess quality of evidence.

40
41 **Findings** 135 million person years of data from prospective studies and 58 clinical trials with a total of 4,635
42 adult participants were included in the analyses. Observational data suggest a 15-30% decrease in all-cause and
43 cardiovascular related mortality, and incidence of coronary heart disease, stroke, type 2 diabetes, and colorectal
44 cancer when comparing the highest dietary fibre consumers with the lowest. Clinical trials show significantly
45 lower body weight, systolic blood pressure and total cholesterol when comparing higher with lower intakes.
46 Risk reduction associated with a range of critical outcomes was greatest when daily intake of dietary fibre was
47 between 25-29 grams. Dose response curves suggested that higher intakes may confer even greater benefit with
48 regard to protection against cardiovascular diseases, type 2 diabetes and colorectal and breast cancer.
49 Comparable findings for wholegrain intake were observed. Smaller or no risk reductions were found with the
50 observational data when comparing the effects of diets characterised by low rather than higher glycaemic index
51 or load. Overall the certainty of evidence regarding the relationships between carbohydrate quality and critical
52 outcomes was graded as moderate for dietary fibre, low to moderate for whole grains, and low to very-low for
53 glycaemic index. Data relating to other dietary exposures was limited.

54
55 **Interpretation** The complementary findings from prospective studies and clinical trials relating to the reduction
56 in mortality, NCD incidence, and their risk factors associated with relatively high intakes of dietary fibre and
57 whole grains as well as striking dose response evidence indicate that the relationships may be causal. Benefit to
58 individuals and populations may be expected from implementation of dietary recommendations to increase
59 dietary fibre intake and to replace refined grains with whole grains.

60
61 **Funding** This research was supported by funding from: the Health Research Council of New Zealand; World
62 Health Organization; Riddet Centre of Research Excellence; Healthier Lives National Science Challenge;
63 Department of Medicine, University of Otago; and the Otago Southland Diabetes Research Trust.

64 **Research in Context**

65 **Evidence before this study**

66 Carbohydrate-containing foods consisting principally of sugars, starches and dietary fibre (non starch
67 polysaccharide) provide the major source of energy worldwide. The role of free sugars as a determinant of
68 adverse health outcomes has been clarified and clear guidelines relating to their restriction issued. Dietary fibre
69 and some starches are associated with health benefits and dietary guidelines typically encourage regular
70 consumption of vegetables, cereals, pulses and whole fruit which are rich sources of these and other health
71 promoting nutrients. However, previous systematic reviews and meta analyses examining the relationship
72 between starches and dietary fibre, and health outcomes have usually examined a single indicator of
73 carbohydrate quality and a limited number of disease outcomes. Thus it has not been possible to determine the
74 extent to which the predictive potential of these indicators applies across the spectrum of non-communicable
75 disease (NCDs) nor which are most useful in nutrition guidelines or when recommending food choices.
76 Quantitative recommendations relating to dietary fibre have not had a strong evidence base.

77

78 **Added value of this study**

79 We have undertaken systematic reviews and meta analyses of prospective studies and clinical trials that have
80 reported on the relationship between the most widely studied indicators of carbohydrate quality (dietary fibre,
81 whole grains or pulses, dietary glycaemic index or glycaemic load) and mortality and incidence of a wide range
82 of NCDs and their risk factors. Parallel consideration of prospective studies and clinical trials has enabled an
83 exploration of the extent to which changes in cardiometabolic risk factors associated with altering intake of
84 dietary carbohydrate align with the effect of carbohydrate quality on disease risk observed in the prospective
85 studies. Dose response curves were generated and the benefits from different amounts of total dietary fibre were
86 calculated. The approach recommended by the GRADE Working Group has been used to assess the quality of
87 evidence and the magnitude and importance of the observed associations which influence the confidence in
88 nutrition recommendations.

89

90 **Implications of all the available evidence**

91 The complementary findings from prospective studies and clinical trials, which show that higher intakes of
92 dietary fibre or whole grains are related to a reduction in the risk of a wide range of NCDs and their risk factors,
93 provide convincing evidence for nutrition recommendations to replace refined grains with whole grains and
94 increase dietary fibre to at least 25-29g per day, with additional benefits likely to accrue with greater intakes. In
95 the light of current evidence, dietary glycaemic index or glycaemic load may be less useful as overall measures
96 of carbohydrate quality than dietary fibre and wholegrain content.

97 **Introduction**

98 Prior to the mid twentieth century carbohydrates were principally regarded as an energy source and nutrition
99 recommendations suggested that carbohydrates should contribute the energy deficit remaining after intakes of
100 fat and protein had been specified. From the mid 1950s there was increasing awareness of the potential of
101 “sugar” (principally sucrose) to increase the risk of dental caries and in the 1960s Yudkin¹ popularised the view
102 that sugar was a major contributing cause of obesity, type 2 diabetes and cardiovascular disease, an opinion
103 shared by Cleave and Campbell who described these and other chronic conditions as saccharine diseases.² A
104 substantial body of experimental, epidemiological and clinical trial data has accumulated since these early
105 observations and based on extensive systematic reviews and meta analyses, the World Health Organization
106 (WHO) has recently issued a strong recommendation, based on the association between free sugars and dental
107 caries and obesity, for individuals to reduce intake to less than 10% total energy and a conditional
108 recommendation suggesting that even greater benefit may accrue if intakes are below 5%.³ Comparable
109 recommendations have been made by national governments and professional organisations worldwide.

110

111 It is more than half a century since Burkitt, Trowell and Painter, based largely on epidemiological observations
112 in Africa, suggested that processing of cereal based foods (grains) with removal of what came to be called
113 dietary fibre, rather than excessive intakes of sugar, were key determinants of both cardiometabolic and large
114 bowel diseases.^{4,5} Nevertheless, until relatively recently rather less attention has been given to starches and
115 dietary fibre, the other major components of dietary carbohydrate. While nutrition guidelines issued by many
116 governments and professional organisations encourage increased consumption of vegetables, fruit and whole
117 grains, there are fewer quantitative guidelines for sources and intakes of dietary fibre and starch. We report here
118 on a series of systematic reviews and meta analyses on indicators of carbohydrate quality and non-
119 communicable disease (NCD) incidence, mortality, and risk factors. The research was commissioned by WHO
120 to inform the development of updated recommendations regarding carbohydrate intake.

121

122 **Methods**

123 We followed reporting standards for systematic reviews and meta analyses.⁶ Literature searches, identification
124 of eligible studies, data extraction and bias assessment were undertaken independently by at least two
125 researchers, with discrepancies resolved with an additional reviewer.

126

127 **PICO tables and eligibility criteria**

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

136

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

178 **Risk of bias assessment**

179 We used the ROBIS assessment tool⁸ to assess systematic reviews and meta analyses for quality and risk of
180 bias, and the Newcastle Ottawa Scale (NOS)⁹ to assess risk of bias of each prospective study. For clinical trials
181 we used Cochrane criteria.¹⁰

182

183 **Data analysis**

184 For prospective studies we pooled the reported odds ratios or risk ratios with the DerSimonian and Laird
185 random effects model¹¹ in a high quantile versus low quantile analysis. When individual studies reported results
186 separately by sex, we first combined these effect size estimates with a fixed effects model before including them
187 within the pooled estimate. When eligible studies were based on and reported combined results from multiple
188 cohort studies we extracted results for each cohort to include in the meta-analysis. Prospective studies reporting
189 incidence or mortality were analysed separately. Where data were reported in a suitable format, we considered
190 dose response relationships with the Greenland and Longnecker method¹² assuming linearity with a two-stage
191 dose response random-effects analysis. The average or mid-point of each defined quantile was used for the dose
192 amount. Where the quantile dose range was open-ended, half the range of the adjacent quantile was used to
193 determine the average intake. We used 30g to represent one serve of whole grains when a value for weight was
194 not stated.¹³ Non-linear dose-response was assessed using restricted cubic splines with three knots at 10%, 50%,
195 and 90% of distribution combined with multivariate meta analyses.¹⁴ We imputed the number of cases per
196 quantile from the RR value when necessary. Linear and spline (with 95%CI) models are shown with each data
197 point overlaid as circles. Circle size indicates the weighting of each data point with bigger circles indicating
198 greater influence. Absolute risk values were calculated with GRADE Pro software.¹⁵

199

200 To help establish optimal intakes of dietary fibre we considered the dose-response curves for total dietary fibre
201 intake and critical health outcomes. We also compared the lowest consumers of dietary fibre with those
202 consuming between 15-19, 20-24, 25-29, 30-34, and 35-39 grams of fibre per day with a random effects model.
203 When studies reported more than one quantile of data within the pre-specified intake ranges, we first combined
204 these quantiles with a fixed effects model before including them within the pooled estimate. We did this to
205 measure the number of critical outcomes where an improvement in relative risk was observed in the higher
206 intake categories.

207

208 For clinical trials high-versus-low analyses were undertaken with generic inverse models and random-effects.
209 For outcomes that could be measured by different units, reported effects were presented as standardised mean
210 differences. For studies reporting multiple follow-ups over time, the most recent, appropriately reported
211 published data were used in the meta analyses. When crossover (paired data) studies did not report the mean
212 difference between treatments and its standard error or other relevant statistics, end of treatment values were
213 analysed as independent samples. Subgroup analyses by fibre amount or principal starch source were conducted
214 when there were enough studies for subgroupings including more than one trial. For example high fibre
215 interventions (0-25, 25-30, 30-35, >35 g/day) were considered to determine whether there were threshold effects
216 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 GRADE²² 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 categories²⁴ 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 trials⁴⁶ 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

441 **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

452 **Declarations of interest**

453 We declare no competing interests

454

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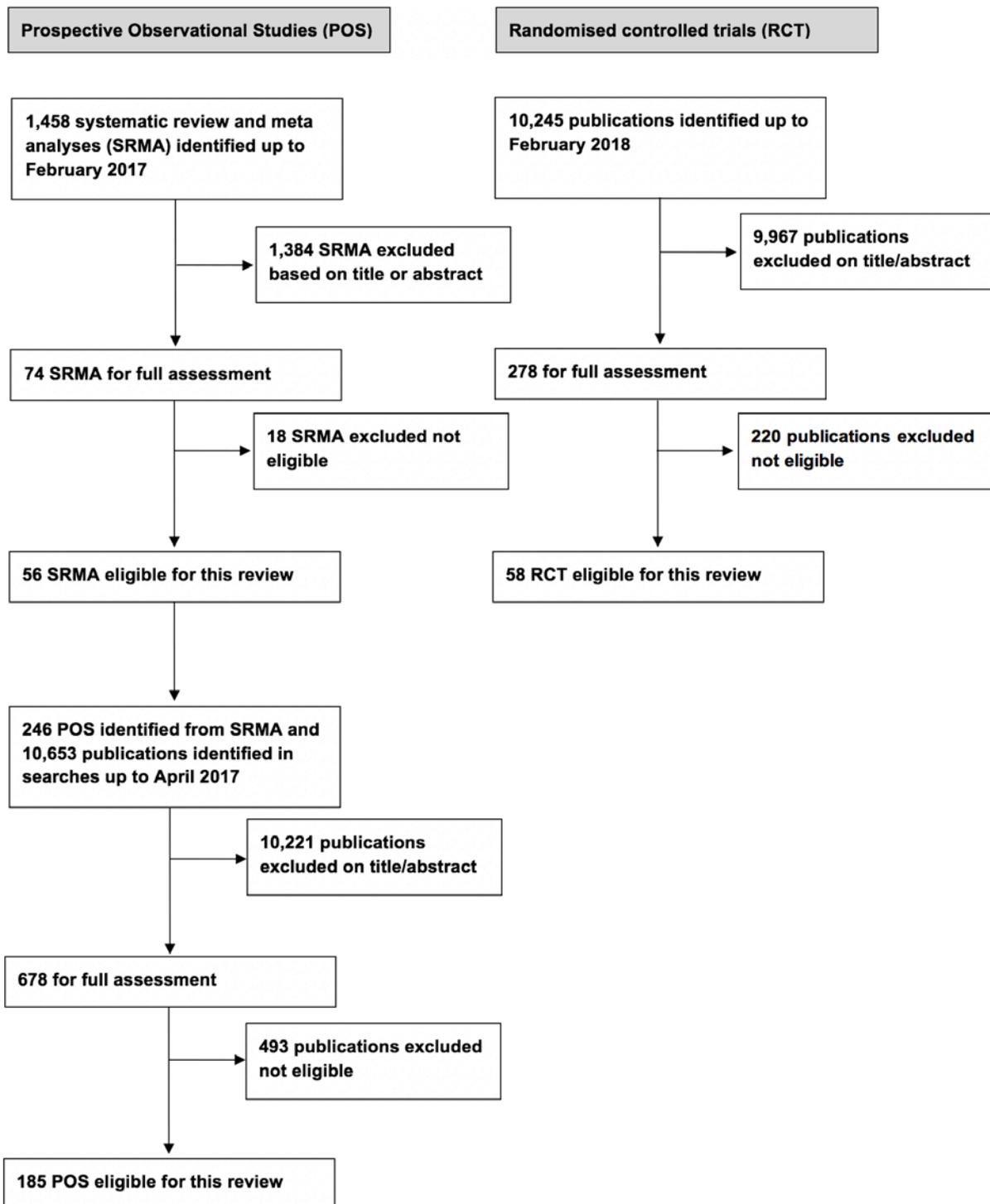
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- 570

571 **Figure 1** Flow chart indicating the process by which eligible prospective studies and randomised
 572 controlled trials were identified



573
 574

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.

594

595

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

597

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

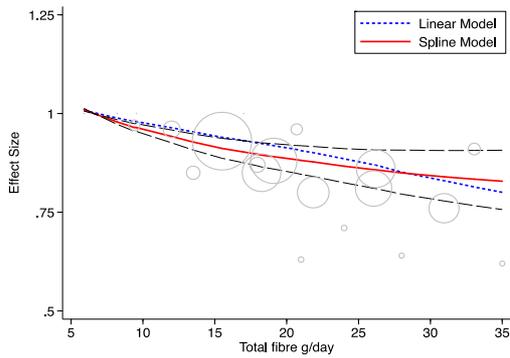


Fig 2a Total fibre and all-cause mortality. 68,183 deaths over 11.3 million person years. Assuming linearity a reduced risk ratio of 0.93 (0.90 to 0.95) was observed for every 8 grams more fibre consumed per day.

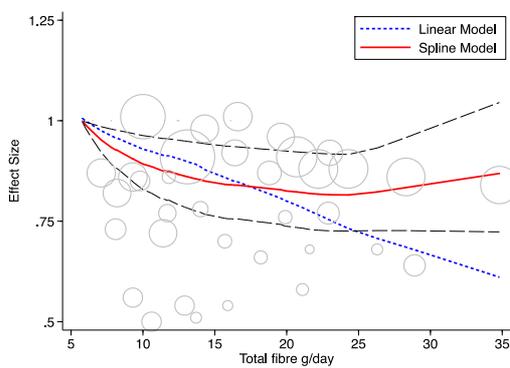


Fig 2b Total fibre and coronary heart disease incidence. 6,449 deaths over 2.5 million person years. Assuming linearity a reduced risk ratio of 0.81 (0.73 to 0.90) was observed for every 8 grams more fibre consumed per day.

Fig 2c Total fibre and incidence of type 2 diabetes. 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.

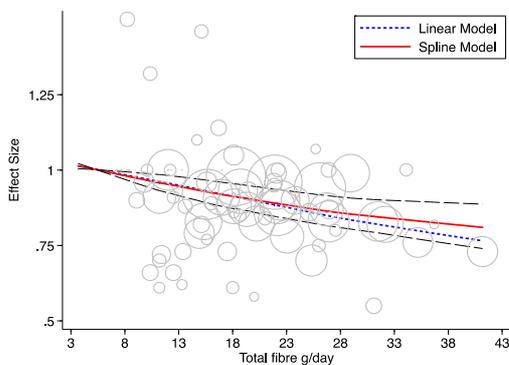
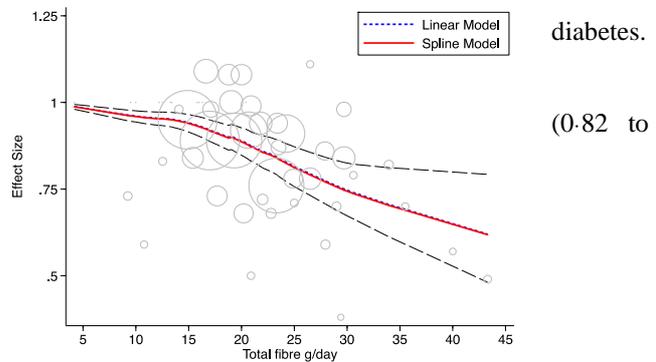


Fig 2d Total fibre and incidence of colorectal cancer. 20,009 cases over 20.9 million person years. Assuming linearity a reduced risk ratio of 0.92 (0.89 to 0.95) was observed for every 8 grams more fibre consumed per day.

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

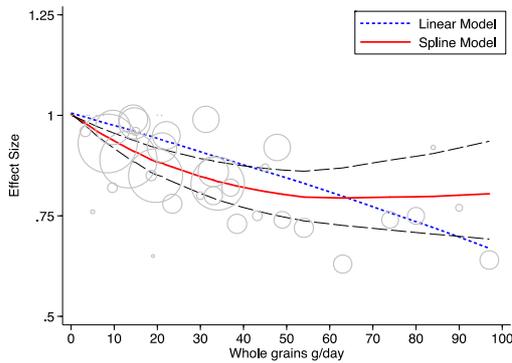


Fig 3a Wholegrain intake and all-cause mortality. 88,347 deaths over 8.2 million person years. Assuming linearity a reduced risk ratio of 0.94 (0.92 to 0.95) was observed for every 15 grams more whole grains consumed per day.

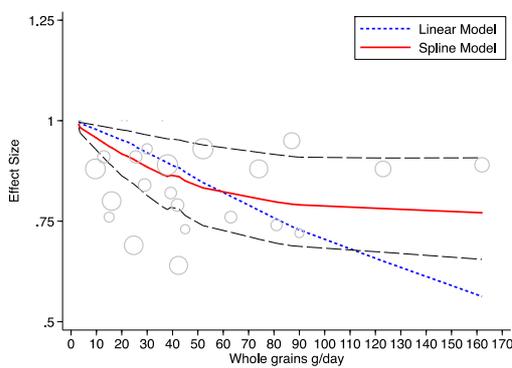


Fig 3b Wholegrain intake and incidence of coronary heart disease. 6,587 cases over 2.4 million person years. Assuming linearity a reduced risk ratio of 0.93 (0.89 to 0.98) was observed for every 15 grams more whole grains consumed per day.

Fig 3c Wholegrain intake and incidence of type 2 diabetes. 13,147 cases over 3.5 million person years. Assuming linearity a reduced risk ratio of 0.88 (0.81 to 0.95) was observed for every 15 grams more whole grains consumed per day.

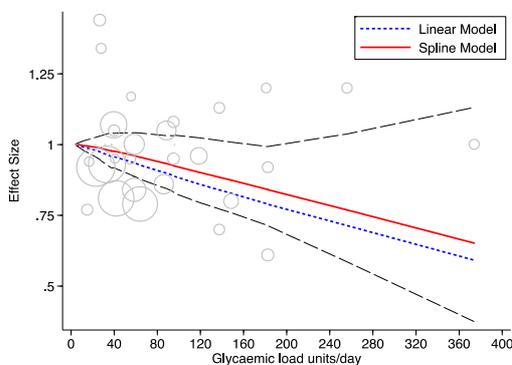
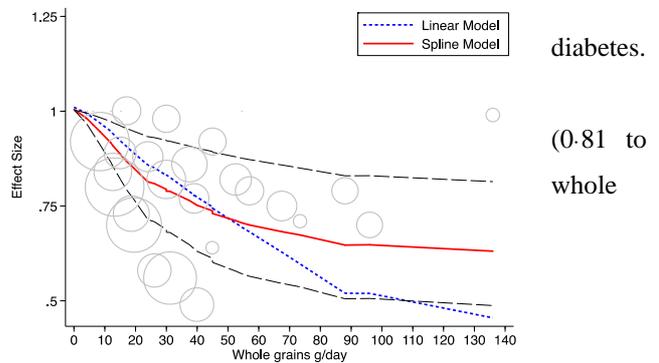


Fig 3d Wholegrain intake and incidence of colorectal cancer. 6,056 cases over 5.7 million person years. Assuming linearity a reduced risk ratio of 0.97 (0.95 to 0.99) was observed for every 15 grams more whole grains consumed per day.

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

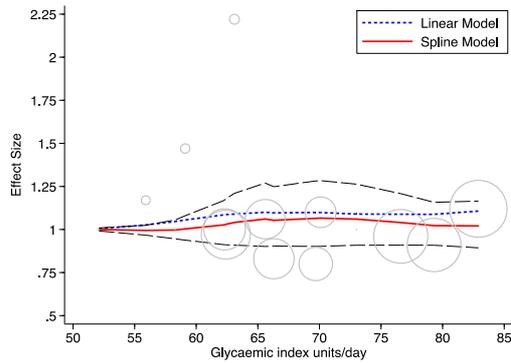


Fig 4a Glycaemic index and all-cause mortality. 7,699 deaths over 0.6 million person years. Assuming linearity a risk ratio of 1.16 (0.90 to 1.49) was observed for every 10 glycaemic index unit increase per day.

Fig 4b Glycaemic index and coronary heart incidence. 7,240 cases over 2.4 million person years. Assuming linearity a risk ratio of 1.09 (0.94 to 1.27) was observed for every 10 glycaemic index unit increase per day.

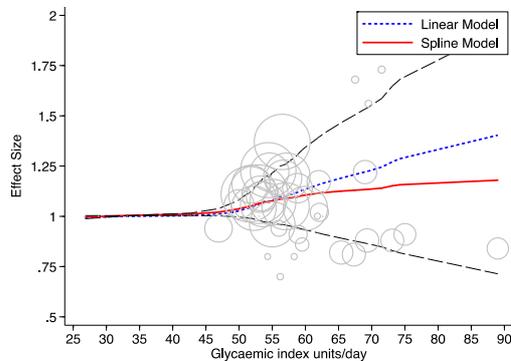
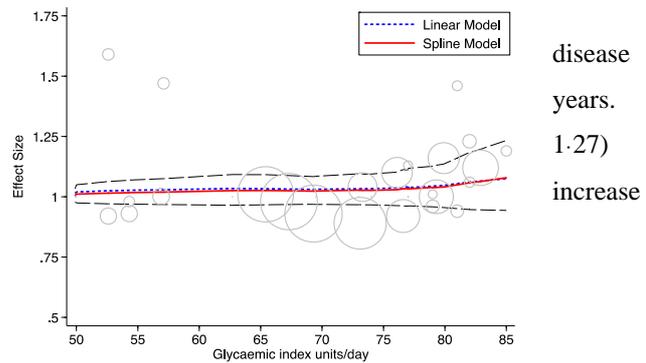


Fig 4c Glycaemic index and incidence of type 2 diabetes. 31,780 cases over 4.9 million person years. Assuming linearity a risk ratio of 1.10 (1.00 to 1.20) was observed for every 10 glycaemic index unit increase per day.

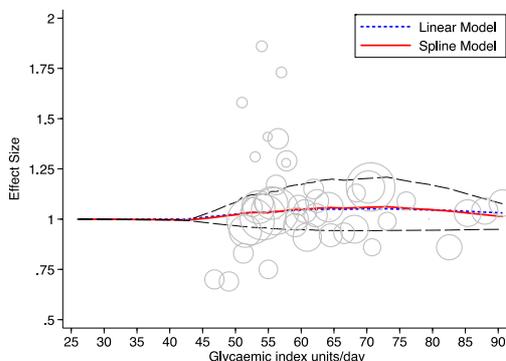


Fig 4d Glycaemic index and incidence of colorectal cancer. 10,390 cases over 6.5 million person years. Assuming linearity a risk ratio of 1.05 (1.00 to 1.10) was observed for every 10 glycaemic index unit increase per day.

Figure 5 Summary forest plots of key outcomes from clinical trials.

Fig 5a Higher compared with lower total fibre intakes.

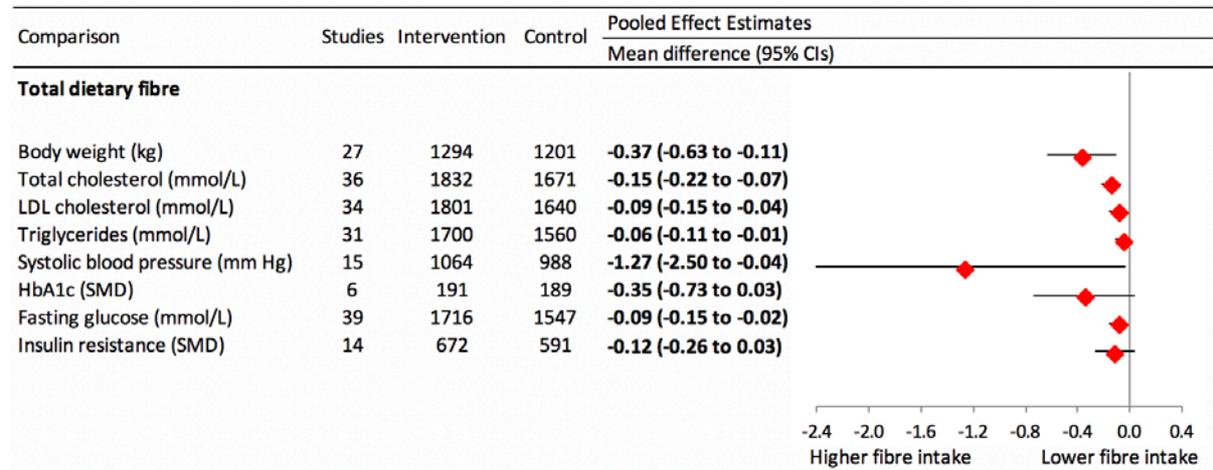


Figure 5b Higher compared with lower wholegrain intakes.

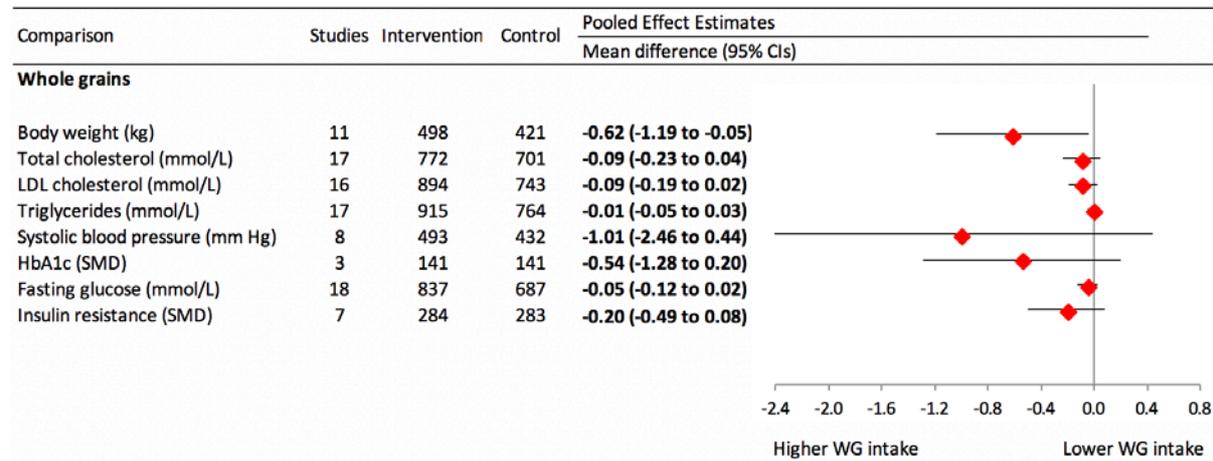


Figure 5c Comparison of diets characterised by lower compared with higher glycaemic index foods.

