sacn

Scientific Advisory Committee on Nutrition

Systematic review of evidence:

Carbohydrates and Colo-rectal Health

Contents

Carbohydrate and Colo-rectal Health

Term of reference

1. The colo-rectal health review is to consider the evidence for a role of dietary carbohydrate in colo-rectal health in adults and in infancy and childhood.

Colo-rectal health endpoints

- Normal colo-rectal function as defined by faecal weight, total intestinal transit time and faecal microflora and short chain fatty acid content
- Prevention of impaired colo-rectal function, including constipation, diarrhoea, irritable bowel syndrome and diverticular disease
- Colo-rectal cancer

Dietary exposures

- Carbohydrate e.g. total carbohydrate, sugars (fructose, sucrose, lactose, glucose, lactose, galactose, maltose) disaccharides, monosaccharides, starch, resistant starch, oligosaccharides and inulin, non-milk extrinsic sugars, added sugars, soluble fibres (including guar gum, psyllium, beta glucans), non starch polysaccharides, dietary fibre (including cereal, fruit and vegetable), polyols (e.g. xylitol, mannitol and sorbitol).
- Dietary sources e.g. cereal, fruit, vegetables (including legumes), wholegrain (wheat, oats, rice, rye), sweets, confectionary, chewing gum, cakes and biscuits, carbohydrate/sugar containing drinks, jams and spreads, honey, milled flour, high fructose corn syrup, fruit juice, smoothies and yogurt.

Carbohydrate classification

2. The primary classification of dietary carbohydrate, as with other macronutrients, is based on chemistry, i.e. the character of individual monomers, degree of polymerization (DP) and type of linkage (alpha or beta), as recommended at the Food and Agriculture Organization/World Health Organization Expert Consultation in 1997 (FAO/WHO, 1997). This divides carbohydrates into three main groups, sugars (DP 1–2), oligosaccharides (short-chain carbohydrates) (DP 3–9) and polysaccharides (DP ≥10).

3. In 2006, an FAO/WHO update on some of the key issues relating to carbohydrates in human nutrition endorsed the primary classification recommended by the 1997 Expert Consultation, but acknowledged that a chemical classification, although providing a practical basis for measurement and labelling, did not allow a simple translation into nutritional effects (Mann *et al.*, 2007). Each class of carbohydrate has overlapping physiological properties and effects on health.

4. This dichotomy has led to the use of a number of terms to describe carbohydrate in foods, such as intrinsic and extrinsic sugars, non-digestible carbohydrate or oligosaccharide, resistant starch, non-starch polysaccharide (NSP), dietary fibre,

available and unavailable carbohydrate, complex carbohydrate, glycaemic index and whole grain (Cummings & Stephen, 2007).

5. The principal carbohydrates that reach the human large bowel are NSP, resistant starch, non-α-glucan oligosaccharides and polysaccharides (non-digestible oligosaccharides and inulin), and some polyols and modified starches (Elia & Cummings, 2007); these have been collectively termed 'non-digestible carbohydrate' throughout this report. Carbohydrates that are digested in the small intestine and do not normally reach the large bowel have been termed 'digestible carbohydrate' throughout this report. Modified starches, which also qualify as resistant starch (Topping *et al.*, 2003) and polyols are usually added by the food industry, for their functional and sweetening properties, respectively. Virtually all carbohydrates that reach the large bowel are at least partially fermentable by the commensal bacteria in the colon.

6. In 2008, the SACN reviewed the available scientific evidence for components under consideration for inclusion in the Codex definition of dietary fibre for nutrition labelling purposes (Scientific Advisory Committee on Nutrition, 2008). These components included total fibre, NSP, fibre components from cereal, fibre components from fruit and vegetables, starch, resistant starch, polydextrose, oligosaccharides (including fructo-oligosaccharides, galacto-oligosaccharides and inulin), lignin, soluble fibres (including pectin and guar gum). The SACN considered that a material can be considered as dietary fibre if it is resistant to digestion and absorption in the small intestine and has a demonstrable physiological effect potentially associated with health benefits in the body, such as increasing stool bulk, decreasing intestinal transit time or decreasing postprandial glycaemia. Based on the available evidence the SACN concluded that there was sufficient evidence for an association between those compounds identified as NSP and colonic function (including stool weight/mass and transit time), and between those compounds identified as soluble fibre (from oats, psyllium, pectin and guar gum) and lowering of total cholesterol and low density lipoprotein cholesterol.

7. In 2008, the 30th Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses agreed a definition of dietary fibre (Cummings *et al.*, 2009). Dietary fibre was defined as carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by endogenous enzymes in small intestine of human beings and belong to following categories: edible carbohydrate polymers naturally occurring in food as consumed; carbohydrate polymers, which have been obtained from raw material in food by physical, enzymatic, or chemical means and which have been shown to have physiological effect of benefit to health by generally accepted scientific evidence to competent authorities; and synthetic carbohydrate polymers, which have been shown to have physiological effect of benefit to health by generally accepted scientific evidence to competent authorities

8. In 2010, the European Food Saftey Authority established a dietary reference value for dietary fibre (EFSA Panel on Dietetic Products, 2010). Their opinion stated that: 'dietary fibre is defined as non-digestible carbohydrates plus lignin, including non-starch polysaccharides – cellulose, hemicelluloses, pectins, hydrocolloids (i.e., gums, mucilages, ß-glucans), resistant oligosaccharides – fructo-oligosaccharides, galacto-oligosaccharides, other resistant oligosaccharides, resistant starch – consisting of

physically enclosed starch, some types of raw starch granules, retrograded amylose, chemically and/or physically modified starches, and lignin associated with the dietary fibre polysaccharides.

9. Although psyllium husk is a source of soluble fibre (mucilage polysaccharides) it is unlike anything that occurs in the diet, and is essentially a pharmaceutical preparation. Psyllium and ispaghula are both processed materials derived from husks of *Plantago ovata* and have been used in several of the trials described below. The major types of soluble fibre derived from food are pectin or oat beta glucan, but trials with psyllium are not indicative of the possible efficacy of these types of soluble fibre. The peculiar property of psyllium, which may make it particularly effective as a laxative, is the presence of a poorly fermentable arabinoxylan fraction that stays intact all the way through the colon (Marlett *et al.*, 2000).

Dietary fibre analysis

10. The proximate analysis of food and feed developed in the 19th century gave rise to the development of the crude fibre method using a successive acid and alkaline digestion to isolate this indigestible fraction (Asp, 1995; McCleary, 2003).

11. In the 1920s, the differentiation between 'available' and 'unavailable' carbohydrates was introduced (McCance & Lawrence, 1929). The main objective was to differentiate those carbohydrates that affected the blood glucose levels, i.e. those 'available' for digestion and absorption in the small intestine. Methods were subsequently developed for analysing reducing sugars, sucrose and starch in foods as a measure of the available carbohydrates (Widdowson & McCance, 1935). Unavailable carbohydrates were determined as the insoluble residue, corrected for protein and ash. A further methodological development simulated digestion by incubating a food sample with the enzymes pepsin and pancreatin (Williams & Olmsted, 1935).

12. More recent developments in dietary fibre methodology have adopted two general approaches: enzymic–gravimetric methods and enzymic–chemical methods. The work by Williams and Olmsted (1935) formed the basis for the acid detergent and neutral detergent fibre methods in the 1960s (Van Soest, 1963; Van Soest & Wine, 1967), which were subsequently developed into the enzymatic gravimetric methods of dietary fibre analysis (Hellendoorn *et al.*, 1975). In the gravimetric methods the non-fibre components are removed and the residue is weighed. This residue can be analyzed for monomeric composition or starch residues and also for protein and ash. A gas-liquid chromatography (GLC) method for the characterisation of gravimetrically determined soluble and insoluble dietary fibre residues was subsequently developed (Schweizer & Wursch, 1979).

13. The first American Association of Official Analytical Chemists (AOAC) enzymatic gravimetric methods were developed (Prosky *et al.*, 1985; Prosky *et al.*, 1988; Prosky *et al.*, 1994) using alcohol precipitation to recover soluble fibre components. These

methods measure ‘total dietary fibre’ or soluble and insoluble components separately, with appropriate correction for protein and ash in the fibre residue.

14. The enzymic–chemical methods use more or less specific determination of monomeric constituents, with subsequent summing up for a total fibre determination. As in the gravimetric methods, soluble and insoluble components can be determined separately. Southgate (Southgate, 1969b; Southgate, 1969a) developed a procedure following the principles of Widdowson & McCance (1935), so that a complete carbohydrate analysis of sugars, starches, non-cellulose polysaccharides, cellulose and lignin could be carried out sequentially on the same sample. Subsequently, the determination and characterisation of soluble and insoluble fractions of dietary fibre by gas-liquid chromatography (GLC) was developed (Theander *et al.*, 1990) and Englyst also developed a GLC-based method as an extension of the method of Southgate (Southgate *et al.*, 1978; Englyst *et al.*, 1982; Englyst & Cummings, 1988). The solubility of polysaccharides, however, is method-dependent and is determined by temperature, time, and pH (Monro, 1991). Over the years the Englyst method has undergone many changes with the use of high-performance liquid chromatography or GLC for neutral sugar components, and a colorimetric assay for uronic acids (Englyst *et al.*, 1994; Quigley & Englyst, 1994).

15. The Englyst method quantifies all constituent NSP and the AOAC International method quantifies ‘total dietary fibre’ defined as NSP, some resistant starch (retrograded resistant starch, see next section), some non-digestible oligosaccharides (high molecular weight fraction of fructo-oligosaccharides) and all lignin. Recent developments of the AOAC methodology have been to include all non-digestible oligosaccharides and all resistant starch in the ‘total dietary fibre’ definition (McCleary, 2007; Nishibata *et al.*, 2009).

16. Table 1 outlines data on the fibre content per 100g of a selection of foods, as measured by the Englyst (NSP) and AOAC methods. The data presented are for composite samples of foods. The NSP contents of foods tend to be lower than for dietary fibre analysed by the AOAC method (Kontraszti et al., 1999). The difference is not consistent, however, since NSP values are very similar for some foods, such as some fruit and vegetables and some wholegrain cereals and breads, but about a third lower for many other products, particularly baked goods and mixed dishes. Hence intakes of AOAC fibre should be higher than for NSP, although in one study total fibre intakes calculated from the AOAC method were not appreciably different from those determined using the Southgate or Englyst methods (Aldoori et al., 1998). Also, dietary fibre estimates for the US NHANES in 2001/02 are not that different from NDNS (about 15-20% higher), with average intake for adult men aged 19 years and over of 18.0 g/day and for women 14.3 g/day. The 95th percentile intake was 31.0 g/day for men and 24.6 g/day for women.

Table 1. Data on the dietary fibre content of selected foods as determined by Englyst or AOAC methods

Food	Englyst Fibre (NSP) (g/100g)	AOAC Fibre (g/100g)
Data taken from the Food Standards Agency's Nutrient Analysis Survey of Selected Foods Containing Trans Fats, (2009)[1]†.		
Garlic and herb bread	0.8g	2.7 g
Beef pie, purchased, individual, flaky pastry	1.3g	2.1g
Cheese and tomato pizza, retail, all bases, not stuffed crust	1.7g	2.9g
Cod in breadcrumbs, grilled/oven baked	1.7g	1.9g
Potato chips, oven ready, baked (not battered)	2.7g	3.5g
Data taken from the Food Standards Agency's Nutrient Analysis Survey of Biscuits, Buns, Cakes and Pastries, (2008)[1]†.		
Carrot cake, iced	1.1g	1.9g
Small fruit pies	1.6g	4.3g
Plain scones	2.3g	2.2g
Data taken from the Food Standards Agency's Nutrient Survey of Flour and Grains, (2004)[1].		
Basmati rice, cooked	0.6g	0.6g
Brown wholegrain rice, cooked	0.9g	1.5g
Cous cous (plain), cooked	1.9g	2.2g
Semolina	2.4g	2.9g
Soft plain white flour	3.4g	4.0g
Wheatgerm	11.6g	13.9g
Rye flour	11.8g	14.1g
Bran, wheat	33.0g	41.3g
Data taken from the Food Standards Agency's Nutrient Survey of Pasta and Pasta Sauces, (2004)[1].		
Fresh white egg tagliatelle, cooked	0.9g	2.0g
Dried white spaghetti, cooked	1.5g	1.7g
Canned Ravioli in tomato sauce	1.6g	1.1g
Data taken from the Food Standards Agency's Nutrient Survey of Breakfast Cereals, (2004)[1].		
Cornflakes	1.8g	2.6g
Porridge oats, cooked	6.5g	7.6g
Muesli, Swiss style e.g. Original Alpen ®		
Wheat Biscuits e.g. Weetabix ®	6.7g	8.8g
	7.3g	9.7g
Data taken from the Food Standards Agency's Nutrient Analysis Catch Up Project, (2003)[2].		
Sushi, vegetable	1.2g	1.6g
Quiche, meat	1.3g	1.8g
Vegetable curry, no rice (ready meal), cooked	1.5g	1.8g
Data taken from the Ministry of Agriculture Fisheries and Food's Nutrient Analysis of Bread and Morning Goods, (1999)[3].		
White bread, standard, sliced, large	1.9g	2.5g
Brown bread, sliced, large	3.5g	5.0g
Data taken from the Ministry of Agriculture Fisheries and Food's Nutrient Analysis of Ethnic Takeaway Foods, (1997)[4].		
Stir-fry vegetables	1.8g	2.1g

[1] AOAC Official Method 985.29; [2] Analysis by Direct Laboratories. In house method Q/026 – UKAS accredited. [3] AOAC Official Method 991.43: [4] Method reference AM/c/309/2.
†Analytical data has yet to be published and in some cases is provisional. Data should therefore not be circulated wider or quoted in publications.

Carbohydrate intake in the UK

17. The National Diet and Nutrition Survey, 2000/2001 (Henderson *et al.*, 2003), provides total carbohydrate, sugars (non-milk extrinsic sugars and intrinsic and milk sugars) and non-starch polysaccharide intakes for UK adults aged 19-64 years (see Table 2).

Table 2. National Diet and Nutrition Survey, 2000/1, carbohydrate intake for adults

	Total carbohydrate (g/d)	Non–milk extrinsic sugars (g/d)	Intrinsic and milk sugars (g/d)	NSP (g/d)
Male	275* (135-452)	79 (14-188)	39 (11-89)	15.2 (6.2-28.9)
Female	203 (90-317)	51 (5-129)	37 (11-77)	12.6 (5.0-24.2)

*data given as mean (lower and upper 2.5 percentile)

18. The major contributor to total carbohydrate intake was cereals and cereal products, with bread providing the largest component. Information on sugars is given as intakes of non-milk extrinsic sugars and intrinsic and milk sugars. The main food sources of non-milk extrinsic sugars for both men and women were drinks and sugars, preserves and confectionery, while the major food sources of intrinsic and milk sugars were fruit and nuts and milk and milk products. The three main food sources of non-starch polysaccharides, accounting for about three-quarters of intake, were cereals and cereal products, vegetables (excluding potatoes) and potatoes and savoury snacks. Within the cereals and cereal products group, whole grain & high fibre breakfast cereals provided 11% of the intake and white bread provided a further 9%.

19. Information on resistant starch, polyol or non-digestible oligosaccharide and inulin intakes in the UK is not available from NDNS or the Total Diet Study. National statistics for consumption of starchy foods have been used, however, to estimate the habitual intake of resistant starch in Europe as 4.1 g/day (no variance data given) with variation in mean intakes from 3.2 to 5.7 between different European countries (Asp et al., 1996). The calculations were based on literature data using the Englyst method (Englyst *et al.*, 1992) or separate analyses of foods with the Englyst method or the modified Berry method (Champ *et al.*, 2003). Resistant starch intake in Sweden was estimated to be 3.2g/day (no variance data given) (Liljeberg Elmstahl, 2002), based on consumption data from the 1997-1998 national survey and calculated from the individual foods analysed using a modified Berry method (Akerberg *et al.*, 1998). In the UK, mean resistant starch intake has been estimated at about 2.8g/day (no variance data given), derived from published food and food ingredient values for resistant starch in conjunction with the average weekly consumption of these foods (and foods prepared from the food ingredients) by the general UK population (Annual Report of the Food Survey Committee, 1985) (Tomlin & Read, 1990).

20. Using national food consumption data from surveys conducted during the 1980s and determination of food resistant starch content by a modified Berry method (Berry, 1986; Champ *et al.*, 2003), Italian intakes of resistant starch were estimated at 8.5 g/day (no variance data given), with regional differences (from 7.2 g/day in the north-west to 9.2 g/day in the south) (Brighenti *et al.*, 1998). In Australia, intakes of

resistant starch were estimated to be between 3.4 and 9.4g/day using the 1995 National Nutrition Survey and published values of food resistant starch content. The calculations were based on literature data obtained using the Englyst method (Roberts *et al.*, 2004). In the USA, resistant starch mean intake has been estimated to be approximately 4.9 g/day (range 2.8 to 7.9 g/day) based on the 1999-2002 National Health and Nutrition Examination Surveys and literature data of food resistant starch concentrations using the modified Berry method (Murphy *et al.*, 2008).

21. Based on the analytical determined inulin and oligofructose content of specific foods (cereals, fruits and vegetables) and consumption data from the USA and Europe, it has been estimated that the intake of inulin-type fructans ranges between 1 and 10 g/day (van Loo *et al.*, 1995). It was concluded that the main source of inulin-type fructans in a typical Western diet were wheat and onions.

Carbohydrate and colo-rectal function literature searches

22. Relevant publications were identified by searching Medline, Embase and CINAHL. The search was conducted up to November 2010. The articles listed on Embase and CINAHL date back to 1980, while those on PubMed date back to 1952. Searches were performed for normal colo-rectal function, constipation, diarrhoea, diverticular disease, irritable bowel syndrome (IBS), well-being and calcium and magnesium absorption in relation to the carbohydrate exposure**.**

23. A filter was used to limit searches to human controlled studies. Only articles reported in English were included in the review, although the search was not restricted on language. In Medline many articles have no available abstract for studies before 1980, so the filter would fail to identify relevant articles before this time. For Medline searches between 1952 and 1980, the human controlled studies filter was not used. A manual search of references cited by the articles identified as relevant, and of review articles was also performed.

24. For carbohydrate and colo-rectal cancer, the World Cancer Research Fund kindly provided details of the articles identified in their systematic review, including searches performed up to and including 2009. Searches were performed for colo-rectal cancer in relation to the carbohydrate exposure for articles published after 2009 (see Appendix 1).

25. All references identified in the searches were downloaded to the bibliographic software Endnote. The title and/or abstract of all references identified in the searches were screened for relevancy by a single assessor, based on exposure/endpoint and inclusion/exclusion criteria. All articles that were identified as potentially relevant were grouped together based on their study design, exposure and endpoint. A 10% sample of the references identified as not relevant at the title and abstract stage was checked by an independent assessor.

26. Full text copies of the potentially relevant articles were obtained and considered by a single assessor to determine whether they were eligible for inclusion in the review.

Any references identified as not relevant at the full text stage was checked by an independent assessor. The reasons for excluding any articles at the full text stage were stated. Any articles for which the initial reviewer was uncertain as to inclusion were sent to Working Group Members for consideration/agreement. The articles identified as eligible were discussed in detail in the relevant report sections. Details of the searches are given in Appendix 1 and details of the articles excluded at the full text stage are given in Appendix 2.

Study quality assessment

27. A consideration of trial quality has been given in the associated commentary of the colo-rectal health section, based on the data extracted. Data have been extracted from each publication on study design and location, sample size, number of endpoint cases and case definitions, population demographics, exclusion criteria, methods of dietary ascertainment and assessment, dietary intakes, adjustments for confounders (e.g. information on BMI, physical activity, alcohol, smoking and other potential confounders), statistical analyses used and results. The methods used to define carbohydrate components have been recorded and considered. For trials, data were extracted on whether a trial was described as randomised and level of blinding, the methods for generation of the allocation schedule and blinding, duration of intervention and whether there was a description of dropouts during the trial (Jadad *et al.*, 1996).

28. The criteria for judging risk of bias were based on the Cochrane Handbook. If insufficient information was reported, a judgement of 'unclear' (uncertain risk of bias) was given. A consideration of trial quality was given in the associated commentary of the colo-rectal health section, based on the data extracted. No scale for assessing study quality or risk of bias was employed. Sequence generation refers to the description of the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. The allocation concealment refers to the description of the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. The blinding of participants, personnel and outcome assessors refers to assessments of each main outcome (or class of outcomes) and describe the measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Incomplete outcome data refers to whether assessments were made for each main outcome (or class of outcomes) and the completeness and reporting of outcome data for each main outcome, including attrition and exclusions from the analysis.

Inclusion criteria

Normal colo-rectal function

29. Controlled human studies or trials investigating an effect of carbohydrate intake on

bowel habit, fermentation products, calcium and magnesium absorption, and gut microflora were considered.

30. Randomised controlled trials were included. Non-randomised controlled studies were included if they employed a parallel design, or cross-over design with a Latin-square allocation to control and intervention periods. Cohort before-and-after studies, where subjects were assessed at base-line and again after the intervention, were not included in the data synthesis, but have been used to inform some of the background sections.

31. Only trials with objective measures were considered, with subjects defined as healthy and free of gastrointestinal disorders. Faecel weight trials must have collected all faeces for a minimum of three consecutive days. For trials investigating calcium and magnesium absorption only stable isotope absorption studies that directly assessed the fractional absorption of calcium or magnesium were included.

Prevention of impaired colorectal function

32. Only randomised controlled trials of well-being, constipation, diarrhoea, diverticular disease and irritable bowel syndrome were included. Only trials in patients free of gastrointestinal disease associated with demonstrable change in a bodily organ or tissue were included. For constipation clinical improvement was the key outcome of interest, and the criteria used to define the condition recorded. For constipation, objective measures of function were only considered in trials where laxative use had been prohibited during the trial. For diarrhoea, diverticular disease and irritable bowel syndrome, only prevention trials were considered.

Colo-rectal cancer

33. For carbohydrate and colo-rectal cancer, prospective cohort studies and randomised controlled trials were included. Case-control studies were not included, as they are more prone to bias, and there were sufficient prospective cohort studies available on which to base conclusions. Studies investigating colo-rectal cancer endpoints were included and, for randomised controlled trials only, risk of colo-rectal adenoma was also included.

34. For prospective cohort studies, the minimum information necessary to estimate the relative risk (RR) associated with the endpoint and a corresponding measure of uncertainty (i.e., 95% confidence interval, standard error (SE), variance, or P value of the significance of the estimate) was required for inclusion. In the case of multiple reports on the same population or subpopulation, estimates from the most recent or most informative report were considered. For some exposures and endpoints, it was necessary to decide whether to use the results from pooled analyses or whether to use the results from separate reports from the individual studies. Decisions on the best approach to take have been made on a case-by-case basis.

35. When multiple risk ratios were presented in the original articles, the risk ratio and 95% CI that were adjusted for the most extensive confounding variables available were included. Only prospective cohort studies that adjusted for alcohol intake, smoking, physical activity, age and overweight/obesity were included.

Exclusion criteria

36. Trials investigating enteral feeds or ileostomy subjects were excluded, as were trials involving surgery. Trials in subjects with lactose intolerance have been excluded. Trials in preterm infants were excluded. Trials investigating the *in vitro* fermentation of carbohydrate by colonic microbes were excluded. Trials were excluded if the dietary intervention was in conjunction with drug therapy, with the exception of trials investigating constipation, where the effect of carbohydrate on reducing laxative therapy was considered. Trials in severely malnourished subjects were excluded.

37. The clinical outcome 'inflammatory bowel disease' (ulcerative colitis and Crohn's disease) was not considered. Treatment trials of diarrhoea, diverticular disease and irritable bowel syndrome were not considered.

38. Single meal or single challenge studies were excluded. Trials of carbohydrate intolerance and mal-absorption were excluded, but have been used to inform some of the background sections. Trials investigating the effect of synthetic non-absorbable sugars, e.g. lactulose, tagatose, difructose anhydride, or synthetic oligosaccharides, e.g. lactosucrose, were excluded. Mixed interventions employing non-carbohydrate components e.g. non-digestible oligosaccharide with probiotics, were excluded. Ecological and prevalence studies were excluded. Abstracts and articles in non-peer reviewed journals were excluded.

Data analysis

39. A forest plot has been used to present/summarise the results of a number of studies/trials when sufficient studies were available to permit a meta-analysis to be performed. A meta-analysis was conducted when three or more cohorts/trials, with sufficient information, were available and when the I^2 statistic was not greater than 75% (Higgins *et al.*, 2003). All meta-analyses were performed using MIX 2.0 Pro. For cross-over trials with multiple intervention groups, all relevant experimental intervention groups were combined into a single group in order to create a single pair-wise comparison, as recommended by the Cochrane Handbook for systematic reviews of interventions. When results were only reported separately for men and women in the same cohort these have been combined using the fixed-effects model. Where reported, and when sufficient studies were available, differences in response have been assessed, e.g. due to sex, age, ethnicity etc. For studies/trials meta-analyses have been performed using random-effect analyses. Forest plots have been given for random-effect analyses.

40. The extent of heterogeneity was investigated by using the chi-square test and I^2 statistic (Higgins *et al.*, 2003). When heterogeneity was significant, as assessed by the I^2 statistic, this was investigated using stratified forest plots or meta regression when there were 10 or more cohorts/trials in the meta analysis and at least 3 cohorts/trials in each stratum. Study estimates have been plotted against their corresponding standard errors to produce funnel plots (providing there were sufficient

studies/trials), which were checked for asymmetry to investigate publication bias in each meta-analysis. Egger's linear regression test was used to test for the presence of potential publication bias. The accuracy of this test is, however, limited as the power of the Egger method to detect bias is low with a small number of studies.

41. Meta-analyses of prospective cohort studies have been performed using the highest quantile vs. lowest quantile approach, and when studies provided the necessary dietary exposure data and risk assessment data, a representative per unit meta-analysis was also performed. The dose-response or per unit approach was performed using the method of Greenland and Longnecker (Greenland & Longnecker, 1992) to compute study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of dietary intake. Stata software was used to derive the study-specific linear dose-response trend slopes. The method required that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories were known. The estimation of the distribution of cases and person-years in studies that did not report these, but reported the total number of cases/person-years, was divided by the number of quantiles in order to estimate the number of person-years in each quantile. The median or mean level of carbohydrate intake in each category of intake was assigned to the corresponding RR for each study. For studies that reported dietary intake by ranges, the midpoint in each category was estimated by calculating the average of the lower and upper bound. When the highest or the lowest category was open-ended, it was assumed that the open-ended interval length had the same length as the adjacent interval. If the intakes were reported in densities (i.e. g per 1000 kcal), the reported intakes were recalculated to absolute intakes using the mean or median energy intake reported in the publication. .

Carbohydrate and normal colo-rectal function

Colo-rectal function parameters and health

42. The main parameters considered in relation to colo-rectal function are faecal weight, intestinal transit time, faecal short chain fatty acid and microflora content. The magnitude of response of these parameters to a carbohydrate intervention may be affected by the base-line values, e.g. in relation to transit times (see Figure 2 and paragraph 111, page 44). Overall, there is a paucity of human data pertaining to the relationship between these parameters and diseases, e.g. colo-rectal cancer. All of these parameters show marked individual variability and are indirect indices that may not accurately reflect the processes occurring in the lumen of the colon. What is observed in the faecal output provides only a small snapshot of the metabolic activity occurring in the ascending colon and, therefore, limits what can be concluded from these measures.

Faecal weight and transit time

43. Carbohydrate that is not digested in the small intestine enters the large bowel where it stimulates anaerobic fermentation, leading to an increase in microbial cell mass. Most of the carbohydrate that reaches the colon is metabolised. For example, in one study of healthy subjects fed dietary fibre in mixed diets 70-80% was broken down during passage through the gut (Southgate & Durnin, 1970). The cellulosic fraction tends to be broken down less than the non-cellulosic polysaccharides, and dietary fibre from cereals is less broken down in the colon than that from fruit and vegetables. In one study cabbage fibre was 90% broken down, whereas wheat fibre was 40% broken down (Stephen & Cummings, 1980a). Another study reported degradation of purified cellulose in the gastrointestinal tract to be about 40% (Kelleher *et al.*, 1984). In quantitative terms, plant cell wall polysaccharides (celluloses and non-cellulosic polysaccharides such as arabinogalactans, xylans, pectins, gums and mucilages) are generally the principal fermentation substrates in the large bowel (Cummings & Englyst, 1987). The stimulation of bacterial growth, together with the water-binding to residual unfermented carbohydrate, leads to an increase in faecal weight, dilution of colonic contents, and may also reduce transit time through the colon; in healthy subjects consuming 22 g/day of dietary fibre, bacterial mass was shown to account for over 50% of faecal solids (Stephen & Cummings, 1980b) and wheat bran has been shown to increase the faecal concentration of sugars and mass of plant material more than oat bran, but oat bran increased faecal bacterial mass more (Chen *et al.*, 1998).

44. Transit time, the time it takes a substance to pass through the gut, can be measured using a number of techniques, in the majority of which an oral dose of inert marker is given with food and its appearance noted (Cummings, 2001a). The values for transit time obtained are very dependent on the method used. Coloured dyes give relatively short transit times since it is difficult to detect other than the 'first appearance' of marker in the faeces. Methods which measure mean transit time may be more accurate, while the radio-opaque pellet technique (Hinton *et al.*, 1969) gives values which are about twenty percent greater than the mean transit methods.

45. It has been hypothesised that low faecal weight and slow bowel transit time may increase bowel cancer risk, by increasing concentrations of carcinogens (dietary or gut metabolite or microflora-generated) in the faeces and increasing their contact with the gut wall, but relatively few published data defining bowel habits and disease risk exist (Lewis & Heaton, 1999).

46. Several ecologic studies of faecal weights and transit times in populations with markedly different cancer incidence have observed faecal weights, but not transit times, to be inversely related to colo-rectal cancer incidence, with larger faecal weights being reported in the low-risk populations (Glober *et al.*, 1977; Maclennan & Jensen, 1977; MacLennan *et al.*, 1978; Reddy *et al.*, 1978; Cummings *et al.*, 1982), although one study observed no relationship (Jensen *et al.*, 1982).

47. A study compiling data from 20 populations in 12 countries reported average faecal weights to vary from 72 to 470 g/day and to be inversely related to colon cancer risk. The faecal weights in many developed populations were relatively low (80-120 g/day) and this was associated with increased colon cancer risk (Cummings *et al.*, 1992).

48. Data from several case-control studies suggest an increased risk for colo-rectal cancer with constipation (Sonnenberg & Muller, 1993; Jacobs & White, 1998; Roberts *et al.*, 2003), but not all (Kune *et al.*, 1988; Chan *et al.*, 2007b). Constipation, however, is not defined by faecal weight, and infrequent bowel motion is only one of the criteria (see constipation section in clinical aspects section). Several prospective cohort studies have investigated the association between bowel frequency and subsequent colo-rectal cancer risk. While one study reported an increased risk in subjects with a bowel movement frequency of less than once per day (Watanabe *et al.*, 2004), another three studies reported no association between bowel frequency and colo-rectal cancer risk (Dukas *et al.*, 2000; Otani *et al.*, 2006a; Park *et al.*, 2009). One study did observe loose stools compared with soft stools to be associated with an increased risk (Park *et al.*, 2009).

Faecal microflora and short chain fatty acid content

49. Commensal microflora consists of those micro-organisms present on body surfaces covered by epithelial cells and exposed to the external environment (gastrointestinal and respiratory tract, vagina, skin, etc.). The most abundant microflora is present in the distal parts of the gut; the majority of the intestinal bacteria are Gram-negative anaerobes. Numerically predominant organisms in the microflora belong to two eubacterial divisions, the *Cytophaga-Flavobacterium-Bacteroides* and the *Firmicutes*. The prevalence and diversity of bacteria in different areas of the gastrointestinal tract are influenced by the different conditions at these sites and thus the microflora of the stomach and jejunum vary with that of the large intestine. Host genotype, age and diet have also been shown to affect microbial diversity in the gastrointestinal tract (Kolida & Gibson, 2007).

50. The colon is the most heavily populated area of the gastrointestinal tract, with microorganisms (primarily bacteria, but also fungi and protozoa) typically in the region of 10^{12}/g of contents. The environment with a slow transit time, ready availability of nutrients and a suitable pH is favourable for bacterial growth. It has been estimated that at least 500 different microbial species may exist, although on a

quantitative basis about 10–20 genera appear to predominate, e.g. *Bacteroides, Lactobacillus, Clostridium, Fusobacterium, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Escherichia,* and *Veillonella* (Kolida & Gibson, 2007).

51. The main bacterial fermentation products, the short chain fatty acids acetate, proprionate and butyrate, can be nutrients as well as growth signals for the intestinal epithelium. Various bioactive molecules such as carcinogenic xenobiotics, dietary phytoestrogens, and primary bile acids can be metabolised by commensal bacteria. The microflora facilitates the excretion of various toxic substances and the exclusion of pathogenic microorganisms from the human host and appear to modulate immune function through Peyer's patches and other gut-associated lymphoid tissue (Mai & Morris, 2004).

52. The intraluminal microflora affects the development of the intestinal immune system, supplies key nutrients, and modulates energy metabolism (Backhed *et al.*, 2005). It is thought that the human neonatal gut is immature at birth, and that breast milk contains functional nutrients that help provide the microenvironment for gut protection and maturation (Walker, 2010). The critical stages of gut colonisation are after birth, and during weaning, and vary depending on whether or not the infant is breastfed: lactic acid bacteria dominate (*bifidobacteria* and *lactobacilli*) the flora of the breast-fed infant, while the formula-fed infant has a more diverse flora and contain more *bacteroides*, *clostridia* and *Enterobacteriaceae* (Edwards & Parrett, 2002; Hopkins *et al.*, 2005). The preponderance of *bifidobacteria* and *lactobacilli* in breast-fed babies may relate, to some extent, to the presence of non-digestible oligosaccharides in breast milk. In infants, *Bifidobacterium longum* subspecies *infantis* efficiently consumes several small mass human milk non-digestible oligosaccharides; in contrast, adult-associated *bifidobacteria*, e.g. *Bifidobacterium longum* subspecies *Longum*, does not, but does ferment plant non-digestible oligosaccharides (Sela & Mills, 2010). The intestinal microflora changes rapidly during the first year of life, with the flora of the formula-fed infant developing more quickly than that of the breast-fed infant, and is characterized by a reduction in *Lactobacillus* and *Bifidobacterium* species. In adults, each person's unique population of faecal microflora is fairly stable over time, but fluctuations occur in response to environmental and developmental factors and in disease (Backhed *et al.*, 2005; Eckburg *et al.*, 2005).

53. The use of animals bred under germ-free conditions provides much of the information about the effect of the microbial community of the gut on host physiology and pathology. This evidence suggests that microflora have important and specific metabolic, trophic, and protective functions (Guarner & Malagelada, 2003). These include the fermentation of non-digestible dietary residue and endogenous mucus resulting in salvage of energy as short-chain fatty acids, production of vitamin K and absorption of ions; the control of epithelial cell proliferation and differentiation; development and homoeostasis of the immune system and protection against pathogens (the barrier effect).

54. The faecal flora can be analyzed by microbiological culture techniques, but this is limited in scope, as a majority of the bacterial species present in faeces are not

culturable using standard microbiologic techniques (Mai & Morris, 2004). Molecular tools based on 16S rDNA sequence similarities have helped to overcome these limitations in conventional microbiological plating methods for studying the faecal microflora composition.

55. Being exclusively breastfed is associated with reduced risk for atopic dermatitis (Gdalevich *et al.*, 2001a) and asthma (Gdalevich *et al.*, 2001b; Ip *et al.*, 2009) and differences in the neonatal gut microflora have been shown to precede the development of atopic disease. Several studies have reported differences in the early intestinal microflora between infants developing and those not developing allergic disease, with more prominent colonization by *Bifidobacterium* species but less by Clostridium species in the latter group. (Björkstén *et al.*, 2001; Kalliomaki *et al.*, 2001; Sepp *et al.*, 2005) Another study, however, saw no association with *bifidobacteria*, but reported that colonization by *Clostridium difficile* at 1 month of age was associated with later allergy development (Penders *et al.*, 2007b). Several case-control studies also lend some support to atopic diseases being linked to differences in infant intestinal microflora composition (Kirjavainen *et al.*, 2002; Watanabe *et al.*, 2003; Mah *et al.*, 2006; Penders *et al.*, 2006; Gore *et al.*, 2008). Although most studies indicated an association between the gut microflora composition and atopic sensitization or symptoms, no specific harmful or protective microbes have been firmly identified yet (Penders *et al.*, 2007a). One study does suggest, however, that colonisation of one-month old infants with specific *Lactobacillus* species, *L. paracasei*, is associated with a reduced risk of developing allergic disorders at two years of age (Penders *et al.*, 2010).

56. Faecal microflora have been implicated in the development of inflammatory bowel disease with decreased biodiversity of commensal bacteria, most notably the phyla *Bacteroidetes* and *Firmicutes*, including *Faecalibacterium prausnitzii*, and increased *E. coli* concentrations (Frank *et al.*, 2007; Packey & Sartor, 2009; Sokol *et al.*, 2009; Schwiertz *et al.*, 2010). Differences in faecal and mucosa-associated microflora have been observed in irritable bowel syndrome patients as compared with controls (Balsari *et al.*, 1982; Malinen *et al.*, 2005; Matto *et al.*, 2005; Kassinen *et al.*, 2007; Krogius-Kurikka *et al.*, 2009; Parkes *et al.*, 2010; Salonen *et al.*, 2010). Differences in the microflora have also been linked with obesity (Ley *et al.*, 2006; Kalliomäki *et al.*, 2008; Turnbaugh *et al.*, 2009). It is still unclear, however, whether these differences in the the microflora are causes or effects of these disease states.

57. There is some evidence that the administration of *Bifidobacteria* and some L*actobacillus* species may alleviate some of the symptoms of irritable bowel syndrome (Hoveyda *et al.*, 2009) and possibly shorten the duration of various forms of diarrhoea (Sazawal *et al.*, 2006; Szajewska *et al.*, 2006; McFarland, 2007), but available evidence is inconsistent for inflammatory bowel disease (Rahimi *et al.*, 2008). There is some evidence for the pre- and postnatal administration of *Bifidobacteria* and some *Lactobacillus* species in the prevention of paediatric atopic dermatitis (Kristin *et al.*, 2008; Lee *et al.*, 2008), but, overall, available evidence is inconclusive (Osborn & Sinn, 2007; Boyle *et al.*, 2009; van der Aa *et al.*, 2010).

58. It has been hypothesised that intestinal bacteria may play a role in the initiation of colo-rectal cancer through the production of carcinogens, co-carcinogens or pro-carcinogens and induction of chronic mucosal inflammation (Hope *et al.*, 2005).

Most ecological studies, but not all (Keathley & Needham, 1982; Schwan *et al.*, 1982), have observed differences in the faecal flora and bacterial enzyme activity in populations with markedly different cancer incidence (Aries *et al.*, 1969; Hill *et al.*, 1971; Drasar & Hill, 1972; Peach *et al.*, 1974; Crowther *et al.*, 1976; Koornhof *et al.*, 1979; Benno *et al.*, 1991; Moore & Moore, 1995). Overall, these generally show lower faecal *Bacteroides* and *Bifidobacteria* in low risk populations and fewer *Enterococci* and *Enterobacteria* and *Lactobacillus* in high risk populations; the results from case-control studies, however, do not support these observations (Finegold *et al.*, 1975; Vargo *et al.*, 1980; Kanazawa *et al.*, 1996). Differences in mucosal adherent bacteria composition between subjects with and without colo-rectal adenomas or cancer have been observed in several case-control studies (Edmiston *et al.*, 1982; Scanlan *et al.*, 2008; Shen *et al.*, 2010).

59. The rate and amount of short chain fatty acid (SCFA) production depends on the species and amounts of microflora present in the colon, the substrate source and gut transit time (Lewis & Heaton, 1997a). SCFAs are readily absorbed and butyrate is the major energy source for colonocytes, being converted to ketone bodies or carbon dioxide. The remainder is removed by the liver. Proprionate is largely taken up by the liver and is converted to glucose. Acetate enters the peripheral circulation to be metabolized by peripheral tissues, especially fat and muscle (Hamer *et al.*, 2008). It has been estimated that SCFA contribute approximately 10% of energy requirements for humans, but the amount of non-digestible carbohydrate in the diet undoubtedly affects the amount produced (Bergman, 1990). *In vitro* and animal studies suggest that butyrate has diverse and apparently paradoxical effects on cellular proliferation, apoptosis and differentiation that may be either pro-neoplastic or anti-neoplastic, depending upon factors such as the level of exposure, availability of other metabolic substrate and the intracellular milieu (Sengupta *et al.*, 2006).

60. Faecal SCFA content has been investigated in relation to inflammatory bowel disease, but results are inconclusive with increased (Roediger *et al.*, 1982; Roediger, 1990), as well as decreased (Vernia *et al.*, 1988; Takaishi *et al.*, 2008), concentrations of butyrate being reported in patients relative to controls.

61. In relation to colo-rectal cancer, data from case-control studies, in patients with colon adenomas or cancer, are inconclusive. One study observed an association of high acetate and low butyrate ratios to total SCFA with adenomatous polyps and colon cancer (Weaver *et al.*, 1988), and another reported lower faecal butyrate concentrations in patients with polyps (Kashtan *et al.*, 1992a). Others have observed no differences in faecal SCFA concentrations between controls and patients with colonic adenomas or colonic cancer (Clausen *et al.*, 1991) or in subjects with familial adenomatous polyposis (Bradburn *et al.*, 1993). One ecological study observed faecal total SCFA and butyrate concentrations to be higher in populations with a lower cancer incidence relative to populations with higher colo-rectal cancer incidence (O'Keefe *et al.*, 2009).

62. The reduction in pH associated with the production of SCFAs has been proposed as a protective factor, as ecological studies have observed a higher faecal pH in populations at high risk for colo-rectal cancer (Malhotra, 1982; Walker *et al.*, 1986; Levy *et al.*, 1994; Segal *et al.*, 1995). Case-control studies where colonic mucosal

and faecal pH were determined, however, have failed to confirm these findings (Pye *et al.*, 1990; Bradburn *et al.*, 1993; Hove *et al.*, 1993; McDougall *et al.*, 1993; Little *et al.*, 2002).

Digestible carbohydrate and colo-rectal function

The effect of digestible carbohydrate on faecal output

Background

63. The administration of 25-50g fructose, as a free monosaccharide, has been shown to result in colonic carbohydrate fermentation, as assessed by postprandial hydrogen breath test (Ravich *et al.*, 1983; Truswell *et al.*, 1988; Hoekstra *et al.*, 1996; Beyer *et al.*, 2005; Skoog *et al.*, 2008). Fructose given as sucrose or in equimolar combinations with glucose was well absorbed, and only fructose in excess of glucose undergoes colonic fermentation (Rumessen, 1992; Skoog & Bharucha, 2004). Honey contains fructose in excess of glucose and one study showed administration of 50-100g honey resulted in carbohydrate colonic fermentation, due to its fructose content (Ladas *et al.*, 1995).

64. In lactose-tolerant adults a single dose of lactose (45g/day) has been shown not to affect small bowel (oro-cecal) transit time (He *et al.*, 2006) or total intestinal transit time (Ewe *et al.*, 1995).

65. One cohort before-and-after study, that reported no difference between diets high (165 g/day) and low (60g/day) in sugars on faecal weight (Kruis *et al.*, 1991), observed increased colonic fermentation on the high sugar diet, as determined by breath hydrogen tests, while total intestinal transit time was significantly prolonged, despite a shortened small bowel transit time. Another cohort before-and-after study in three subjects, observed a diet high in sugars to increase faecal wet weight (Williams & Olmsted, 1936).

Trial design

66. One trial was identified as eligible and compared diets high and low in sugars (reported only as 'simple sugars') on bowel function (Yadrick *et al.*, 1992) (see Appendix 2 for studies excluded). The trial design details have been summarised in Table 3. The trial had a cross-over design with a three-day wash-out period between interventions on a basal diet. The trial was conducted in adults and all food was provided. The trial compared a low sugars high starch (90% carbohydrate intake) diet, with a high sugars (70% carbohydrate intake) low starch diet. While food composition data for sample menus were provided, the actual intakes were not reported. Changes in faecal weight and total intestinal transit times in response to the intervention were measured. The funding source was not reported.

Risk of Bias

67. A summary of the risk of bias assessment has been given in Table 4. The trial was randomised, but there is no indication of how this was achieved. The trial was open, which may reflect the nature of the intervention, but there was no mention of whether assessors were blind. There were no drop-outs.

Results

68. The findings from the trial have been summarised in Table 5. No effect on faecal weight was observed between a low sugar, high refined starch (90% carbohydrate intake) diet and a high sugar (70% carbohydrate intake), low refined starch diet. No significant difference in total intestinal transit time was observed, although mean values were lower in the low sugar group. The authors note that the dietary fibre content of the low sugar diet was higher than that of the high sugar diet. Overall, available evidence is insufficient to draw conclusions, but one trial suggests that diets differing in their sugar and starch content are unlikely to affect bowel function.

Table 3. Digestible carbohydrate and faecal output trial design

Study	Date	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Total control intake (g/d)	Additional intervention dose (g/d)	Dietary fibre method	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Yadrick	1992	XO – 3d washout	USA	Adults; 9M	Controlled – low dietary fibre	Low sugar ; high refined starch 90% carbohydrate intake	High sugar 70% carbohydrate intake; low refined starch	NR	NR	1	9	1 wk	7	9	NR

XO, , cross-over; NR, not reported; d, day; y, year; wk ,week; M, male; F, female.

Table 4. Digestible carbohydrate and faecal output risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Yadrick	1992	Yes	NR	NR	Open	No missing outcome data	0

YES – low risk of bias; No – high risk of bias; Unclear – uncertain risk of bias; NR, not reported.

Table 5. Digestible carbohydrate and faecal output results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Yadrick, 1992	High sugar 70% carbohydrate intake; low refined starch	NR	1 wk	95±34	89±29	NR	NR	1.03	0.94	NR	NR	45±27	65±30	1	No difference between a diet high in simple sugars and one low in simple sugars on faecal weight or total intestinal transit time

Intestinal transit time method: 1 (Hinton *et al.*, 1969)

The effect of digestible carbohydrate on magnesium and calcium absorption

Background

69. Cohort before-and-after, single meal and metabolic balance studies have not been included in the detailed review, but an overview of their findings is given as background.

70. Results of studies in lactose-tolerant adults examining an effect of lactose, or its constituent sugars, on calcium or magnesium absorption were inconsistent. Several uncontrolled balance studies, but not all (Greenwald *et al.*, 1963), have suggested that the disaccharide lactose might increase intestinal calcium absorption (Condon *et al.*, 1970; Pansu & Chapuy, 1970). In single meal studies co-administration of lactose has been observed to increase calcium fractional absorption, relative to no lactose being administered (Kocian *et al.*, 1973; Cochet *et al.*, 1983; Schuette *et al.*, 1991).

71. Several single meal studies have compared cow's milk with and without lactose on fractional calcium absorption. One study reported no difference between lactose-containing and lactose-free milk (containing glucose) (Tremaine *et al.*, 1986), another observed the milk containing lactose, but not its constituent monosaccharides (glucose and galactose), to enhance fractional calcium absorption (Schuette et al., 1991), while another observed a decrease in fractional calcium absorption after administration of lactose-containing compared with lactose-free milk (containing glucose), in seven out of eight subjects, although this result was not statistically significant due to an increased absorption in one subject (Griessen *et al.*, 1989a). A crossover study comparing lactose-hydrolysed or un-hydrolysed milk consumed for one week, reported no effect of lactose on calcium or magnesium absorption as determined by the urinary excretion of magnesium or calcium (Brink *et al.*, 1993).

72. Several single meal studies have shown the constituents of lactose, glucose and galactose, to increase fractional calcium absorption relative to no sugar administration (Kelly *et al.*, 1984; Wood *et al.*, 1987; Knowles *et al.*, 1988; Griessen *et al.*, 1989c). One study observed no difference between lactose, glucose and galactose on calcium fractional absorption (Zittermann *et al.*, 2000).

73. Several balance studies, which measured the input and output of a nutrient, rather than actual absorption, have examined the effects of lactose on calcium balance in term infants, but their results have been inconclusive and the studies have been of small sample sizes. Several studies do suggest that calcium absorption from lactose-free or lactose-reduced formulas is lower (Kobayashi *et al.*, 1975; Ziegler & Fomon, 1983; Moya *et al.*, 1992), but one larger study did not observe any effect (Moya *et al.*, 1999).

74. Several balance studies in adults have examined an effect of fructose on calcium and magnesium balance. Two studies have observed fructose, relative to starch, to enhance magnesium balance (Holbrook *et al.*, 1989; Milne & Nielsen, 2000), while one of which observed fructose to enhance calcium balance (Holbrook *et al.*, 1989) and the other did not (Milne & Nielsen, 2000). Relative to sucrose, high fructose corn syrup (which also contains roughly equal amounts of fructose and glucose) had no

effect on magnesium or calcium balance (Ivaturi & Kies, 1992). A single meal study observed that the addition of rice cereal to infant formula did not affect the fractional absorption of calcium in infants (Garg *et al.*, 1990).

75. In one single meal study, calcium fractional absorption was observed to increase when co-administered with apple juice relative to orange juice (Andon *et al.*, 1996) The effect was attributed to the differences in the sugar and polyol content of the juices.

Trial design

76. Two trials were included (Garg *et al.*, 1990; Abrams *et al.*, 2002). The trial design details have been summarised in Table 6. Both trials employed a cross-over design with no washout period. One trial was conducted in adults; the other was conducted in infants. One trial, conducted in controlled conditions, compared the effect of a high carbohydrate diet (60% total energy intake either high in sugars or starch) to a low carbohydrate/high fat diet on fractional calcium absorption (Garg *et al.*, 1990). The carbohydrate content of the diets was reported as being either 'simple' or 'complex'. The other trial, conducted in *ad libitum* conditions, compared lactose-free formula (replaced with maltodextrin) with lactose-containing formula on fractional calcium absorption (Abrams *et al.*, 2002). The trial in adults assessed fractional absorption using a single isotope technique, while the trial in infants used a dual-isotope technique. The duration of interventions for both trials was two weeks. The initial sample size was 8 for the trial in adults and 22 for the trial in infants.

Risk of Bias

77. A summary of the risk of bias assessment has been given in Table 7. Both trials reported being randomised, but only in the infant trials were participants, personnel and assessors blind to the intervention. The trial in adults was open, reflecting the nature of the intervention. The trial in infants reported on drop-out rates and gave some description of the causes, but it was unclear from the trial in adults why three subjects dropped out. In the trial in infants it seemed unlikely missing outcome data were related to the intervention, with similar reasons for missing data across groups.

78. Overall, the quality of study design was good, more so for the trial in infants, and the risk of bias generally low, although only one trial reported on the method of randomisation and neither reported on how intervention allocation was concealed.

Results

79. The results have been summarised in Table 8. In adults, there was no difference in the fractional absorption of calcium between those subjects receiving a high carbohydrate diet (60% of total energy intake either high in sugars or starch) or a low carbohydrate/high fat diet (35% total energy as carbohydrate) (Garg *et al.*, 1990). This reported no effect of varying the carbohydrate content of the diet between 35% and 60% of total energy intake on calcium absorption. The high starch carbohydrate diet contained 12.5% total energy as sugars and 47.5% as starch; the high simple carbohydrate diet contained 37.5% total energy as sugars and 22.5% as starch.

80. In infants, lactose supplementation of breast-milk substitute was observed to increase the fractional absorption of calcium, relative to lactose-free formula (Abrams *et al.*, 2002). The fractional calcium absorption from both infant formulas in the trial was within 5% of the value for human milk. The fractional calcium absorption observed in 5- to 7-month-old infants from human milk was 61% ± SD 23 (Abrams *et al.*, 1997). Human milk has a much lower calcium content (250mg/L) than the formulas (460mg/L), so absorption of calcium from a lactose-free infant formula would be adequate to meet the calcium needs of full-term infants at calcium concentrations similar to those found in routine lactose-containing infant formulas.

81. The funding sources for both trials were reported, one being Governmental (Garg *et al.*, 1990), while the other was Governmental and Comercial (Abrams *et al.*, 2002).

Table 6. Calcium absorption trial description

Study	Date	Study design	Isotope absorption method	Oral isotope carrier	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Dose (g/d)	Sample size at start	Duration	Funding Source
Adults													
Garg	1990	XO - no washout	^{47}Ca	water	USA	Adults aged 21-33y; 8M	Controlled	high fat diet, 35% total En CHO	complex or simple CHO	60 % En	8	2 wk	National Institutes of Health, USA
Infants													
Abrams	2002	XO - no washout	^{44}Ca, ^{46}Ca	formula	USA	infants aged 8–12 wk at enrolment; 16M, 2F	*ad libitum*	lactose-free formula with maltodextrin	formula with lactose	2.4g/dl	22	2 wk	USA Department of Agriculture and Nestlé USA, Inc

En, energy; CHO, carbohydrate; M, male; F, female

Table 7. Risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Adults							
Garg	1990	Yes	NR	NR	Open	NR	25
Infants							
Abrams	2002	Yes	Randomised lottery	NR	Participants, personnel and assessors blind	Missing outcome data unlikely to be related to outcome	18

NR, not reported.

Table 8. Results of Calcium absorption trials

Study	Date	Intervention	Dose (g/d)	Duration	Mineral absorption determined	Control % Ca absorbed ± SD	Intervention % Ca absorbed ± SD	Results
Adults								
Garg	1990	Complex CHO	60% En	2 wk	Ca	41±9	40.0±21.0	No effect on % Ca absorption of either high complex or high simple CHO diets relative to a low carbohydrate/high fat diet
		Simple CHO	60% En				39.0±9.0	
Infants								
Abrams	2002	Lactose	2.4g/dl	2 wk	Ca	56.2±15.3	66.5±11.9	Increased percentage and total absorption of calcium with lactose containing formula relative to lactose-free formula

En, energy; CHO, carbohydrate

Non-digestible carbohydrate and and colo-rectal function

82. This section has been divided into the following sub-sections: dietary fibre and faecal output; resistant starch and faecal output; non-digestible oligosaccharide and inulin, polyols and polydextrose and faecal output; and the effects of non-digestible carbohydrates on faecal bacteria, short chain fatty acid content and pH.

83. Where sufficient data were available faecal wet weight data have been synthesised. It was not possible to synthesise data on faecal short chain fatty acid concentrations due to the different ways in which these data were expressed, e.g. mmol/L; µmol/g or mmol/g faeces wet or dry weight or % change. It was also not possible to synthesise data on the bacterial content of faeces due to the different methods employed and the different ways in which data were expressed.

Background

84. There is a large body of work investigating the effect of dietary fibre on faecal bulking and intestinal transit time. While it appears that all sources of dietary fibre can increase faecal output, not all fibres are equal in this respect (Cummings, 2001b).

85. Many before-and-after studies in human cohorts have shown wheat bran (10-40g/day), cooked and raw, or cellulose to increase faecal weight (Cowgill & Anderson, 1932; Williams *et al.*, 1936; Marks, 1949; Hamilton *et al.*, 1972; Eastwood *et al.*, 1973; Findlay *et al.*, 1974; Jenkins *et al.*, 1975; Payler *et al.*, 1975; Cummings *et al.*, 1976a; Cummings *et al.*, 1976b; Fuchs *et al.*, 1976; Wyman *et al.*, 1976; Ismail-Beigi *et al.*, 1977; Kay & Truswell, 1977; Floch & Fuchs, 1978; Mathur *et al.*, 1978; Cummings *et al.*, 1979a; Cummings *et al.*, 1979b; Munoz *et al.*, 1979; Huijbregts *et al.*, 1980; Slavin & Marlett, 1980b; Tucker *et al.*, 1981; Marlett *et al.*, 1986; Balasubramanian *et al.*, 1987; Hamilton *et al.*, 1988; Villaume *et al.*, 1988; Melcher *et al.*, 1991a; Davidsson *et al.*, 1996; Lewis & Heaton, 1997a; Switzer *et al.*, 1997; Chen *et al.*, 1998; Pittaway *et al.*, 2007). One study also showed the effect of wheat bran on increasing faecal weight not to be affected by water intake of 600ml/day (Ziegenhagen *et al.*, 1991).

86. A dose-response relationship between dietary intake (5-30g/day) of wheat bran and faecal weight increase has been shown, with higher doses also reducing intestinal transit time (Spiller *et al.*, 1986; Jenkins *et al.*, 1987). Overall, the effect of wheat bran on transit times was less consistent between studies.

87. The particle size of wheat bran may affect its faecal bulking properties, with larger particles sizes, e.g. course ground bran compared with fine ground bran, producing greater effects on faecal weight and transit times (Brodribb & Groves, 1978; Heller *et al.*, 1980; Van Dokkum *et al.*, 1983). Equally, a comparison of intact and ground cereals and legumes observed intact seeds to increase faecal output more than ground seeds (Hovey *et al.*, 2003). A comparison of wheat bran and plastic particles reported both to have similar effects on faecal output, but only bran increased faecal water content (Lewis & Heaton, 1997b).

88. Several studies show replacing white bread with wholemeal bread in the diet results in

an increase in faecal output (McCance & Widdowson, 1942a; Andersson *et al.*, 1983; Van Dokkum *et al.*, 1983; Wrick *et al.*, 1983; Eastwood *et al.*, 1986; Srikumar, 2000)

89. Studies investigating the effect of other whole cereal fibres on faecal output have mostly shown an increase in response to barley fibre (Lupton *et al.*, 1993; Kanauchi *et al.*, 1998a; Kanauchi *et al.*, 1998b) corn fibre (Fleming *et al.*, 1983; Fleming & Rodriguez, 1983; Sugawara *et al.*, 1991) oat fibre (Calloway & Kretsch, 1978; Kretsch *et al.*, 1979; Judd & Truswell, 1981; Anderson *et al.*, 1984; Chen *et al.*, 1998; Schaarmann *et al.*, 1999), flax fibre (Dahl *et al.*, 2005a), sorghum fibre (Cornu & Delpeuch, 1981; Fedail *et al.*, 1984) and rice fibre (Miyoshi *et al.*, 1986; Miyoshi *et al.*, 1987). A comparison of sugar beet fibre with wheat bran reported both as effective in increasing faecal weights (Lampe *et al.*, 1993b).

90. Diets rich in fruit and vegetable and/or cereal fibre have been shown to increase faecal output (Antonis & Bersohn, 1962; Beyer & Flynn, 1978; Kelsay *et al.*, 1978; Kaneko *et al.*, 1986; Reddy *et al.*, 1988; Saito *et al.*, 1991; Nagengast *et al.*, 1993; Gelissen *et al.*, 1994; Rao *et al.*, 1994; Haack *et al.*, 1998a; Jenkins *et al.*, 2001), although effects on intestinal transit time were less consistent.

91. Differential effects of individual fibres from fruit and vegetables on faecal output have also been shown (Drasar & Jenkins, 1976; Raymond *et al.*, 1977; Cummings *et al.*, 1978; Stephen & Cummings, 1980a; Wrick *et al.*, 1983), but dietary fibre extracted from pea hulls and carrots had no effect on colonic motility in one study (Guedon *et al.*, 1996).

92. Increased consumption of carrots (Robertson *et al.*, 1979) and sun-dried raisins (Spiller *et al.*, 2003a; Spiller *et al.*, 2003b) has been observed to increase faecal output. In some studies increased legume intake was observed to increase faecal output (Leeds *et al.*, 1982; Fleming *et al.*, 1985), but in others it did not (Anderson *et al.*, 1984; Kurpad *et al.*, 1988), while soybean fibre was observed to increase faecal output (Schweizer *et al.*, 1983; Tsai *et al.*, 1983). Starch-rich foods have also been shown to increase faecal output (Flynn *et al.*, 1977; Shetty & Kurpad, 1986).

93. Several studies show faecal output to be increased by psyllium (Gray & Tainter, 1941; Prynne & Southgate, 1979; Abraham & Mehta, 1988; Stevens *et al.*, 1988; Tomlin & Read, 1988c; Tomlin & Read, 1988a; Miettinen & Tarpila, 1989; Marlett *et al.*, 2000; Dahl *et al.*, 2005a). In one study, bran had a greater effect on transit time than psyllium, but psyllium had a greater effect on the amount of water found in the faeces and faecal weight (Stevens *et al.*, 1988).

94. Pectin has also been shown to have a small effect on faecal bulking in some studies (Durrington *et al.*, 1976; Miettinen & Tarpila, 1977; Cummings *et al.*, 1979c; Ross & Leklem, 1981; Vargo *et al.*, 1985).

95. Various isolated and chemically modified fibre fractions and related synthetic materials added to manufactured foods have also been investigated in relation to faecal bulking. These generally suggest a faecal bulking effect of polydextrose (Tomlin & Read, 1988a; Achour *et al.*, 1994), agar agar (Williams *et al.*, 1936), xanthan gum (Eastwood *et al.*, 1987; Tomlin & Read, 1988c; Daly *et al.*, 1993), gellan gum (Anderson *et al.*, 1988), gum tragacanth (Eastwood *et al.*, 1984), locust

bean gum (Behall *et al.*, 1987), acacia gum (Cherbut *et al.*, 2003), sodium alginate (Anderson *et al.*, 1991), glucomannan (Gallaher *et al.*, 2002; Liu *et al.*, 2005; Chen *et al.*, 2006) , methyl cellulose (Tainter, 1943; Berberian *et al.*, 1952; Eastwood *et al.*, 1990) and carboxymethylcellulose (Behall *et al.*, 1987). Results were conflicting for karaya gum (Eastwood *et al.*, 1983; Behall *et al.*, 1987). In one study gum arabic had no effect (Ross *et al.*, 1983), while two other studies reported no effect of guar gum on faecal output (Penagini *et al.*, 1986; Tomlin & Read, 1988c). At higher doses, however, guar gum was observed to increase faecal output (Miettinen & Tarpila, 1989; Takahashi *et al.*, 1993).

96. The results from these studies have been synthesised based on the mean increase in faecal weight per gram fibre fed (Cummings, 2001b; Elia & Cummings, 2007). The results from this have been given in Table 9. Overall, pectin appears to have the least effect, while fruit and vegetables and wheat bran are most effective.

Table 9 The weighted mean increase in faecal wet weight per gram dietary fibre fed (Elia & Cummings, 2007)

Fibre type or source	Mean increase (g/g dietary fibre fed)	Range (g//g dietary fibre fed)
Wheat bran – raw	7.2	3-14.4
Fruit and vegetables	6.0	1.4-19.6
Wheat bran – cooked	4.4	2-12.3
Psyllium	4.0	0.9-6.6
Oats	3.4	1-5.5
Other gums and mucilages	3.1	0.3-10.2
Corn	2.9	2.8-3.0
Legumes	1.5	0.3-3.1
Pectin	1.3	0-3.6

97. Other studies have investigated carbohydrates other than dietary fibre. Three studies report resistant starch to increase faecal output (van Munster *et al.*, 1994; Hylla *et al.*, 1998; Maki *et al.*, 2009), while studies using non-digestible oligosaccharide and inulin interventions generally show little effect on faecal output (Bouhnik *et al.*, 1997; Brighenti *et al.*, 1999).

98. Carbohydrate, when fermented in the colon to short chain fatty acids (SCFA), affects the growth and metabolic activities of the microflora. An increase in faecal concentration of SCFA has been shown in response to supplementation with some non-digestible carbohydrates, e.g. wheat pentosan, more than inulin (Grasten *et al.*, 2003) and with oat β-glucans (Nilsson *et al.*, 2008); as has a reduction in faecal pH (Kashtan *et al.*, 1990; Melcher *et al.*, 1991a). Dietary fibre appears to stimulate microbial growth non-specifically (Drasar *et al.*, 1976; Fuchs *et al.*, 1976; Floch & Fuchs, 1978; Vargo *et al.*, 1985; Sugawara *et al.*, 1991; Rao *et al.*, 1994; Chen *et al.*, 2006), although in a comparison trial, whole-grain cereals, but not wheat bran, selectively increased faecal *Bifidobacteria* concentration (Costabile *et al.*, 2008), and brown rice, relative to polished rice, was also observed to increase faecal *Bifidobacteria* concentration (Benno *et al.*, 1989). Non-digestible oligosaccharide and inulin tend to increase *Bifidobacteria* species selectively and reduce faecal pH (Ito *et al.*, 1993a; Gibson *et al.*, 1995b; Buddington *et al.*, 1996; Bouhnik *et al.*, 1997;

Teuri *et al.*, 1998; Brighenti *et al.*, 1999; Kruse *et al.*, 1999; Menne *et al.*, 2000; Rao, 2001; Guigoz *et al.*, 2002; Harmsen *et al.*, 2002; Euler *et al.*, 2005; Dinoto *et al.*, 2006; Bouhnik *et al.*, 2007a; Chung *et al.*, 2007; Myung *et al.*, 2007), and this appears to be most marked in those volunteers with low starting levels of *Bifidobacteria* species (Tuohy *et al.*, 2001a; Kolida *et al.*, 2007; de Preter *et al.*, 2008).

99. In one study arabinogalactan was shown to increase total faecal anaerobes and increase *Lactobacillus* species (Robinson *et al.*, 2001). Xylitol supplementation shifted faecal microbial populations from Gram-negative to Gram-positive bacteria in one study (Salminen *et al.*, 1985) and gum arabic and acacia gum have been reported to selectively increase *Bifidobacterium* species (Wyatt *et al.*, 1986; Cherbut *et al.*, 2003).

The effect of dietary fibre on faecal output

Trial design

100. Forty one articles were identified as eligible (see Appendix 2 for studies excluded) (Macrae *et al.*, 1942; Connell & Smith, 1974; Jenkins *et al.*, 1975; Walters *et al.*, 1975; Cummings *et al.*, 1976a; Southgate *et al.*, 1976; Wyman *et al.*, 1976; Beyer & Flynn, 1978; Kelsay *et al.*, 1978; Spiller *et al.*, 1979; Stasse-Wolthuis *et al.*, 1979; Spiller *et al.*, 1980; Stasse-Wolthuis *et al.*, 1980; Andersson *et al.*, 1983; Hillman *et al.*, 1983; Tsai *et al.*, 1983; Spiller *et al.*, 1986; Behall *et al.*, 1987; Stevens *et al.*, 1988; Tomlin & Read, 1988b; Kesaniemi *et al.*, 1990; Effertz *et al.*, 1991; Lampe *et al.*, 1992; Fredstrom *et al.*, 1994; Marteau *et al.*, 1994; Wisker *et al.*, 1994a; Wisker *et al.*, 1994b; Stephen *et al.*, 1995; Cummings *et al.*, 1996; Cherbut *et al.*, 1997; Jenkins *et al.*, 1998; Jenkins *et al.*, 1999a; Vuksan *et al.*, 1999; Grasten *et al.*, 2000; Jenkins *et al.*, 2000; McRorie *et al.*, 2000; McIntosh *et al.*, 2003; Muir *et al.*, 2004; Johnson *et al.*, 2006; Bird *et al.*, 2008; Vuksan *et al.*, 2008), of which two report different aspects of the same intervention: (Jenkins *et al.*, 1975; Cummings *et al.*, 1976a) and (Lampe *et al.*, 1992; Fredstrom *et al.*, 1994). Two trials have also been included in study design description that only examine the effects of dietary fibre on faecal SCFA content and their results have been considered in the section on the effects of non-digestible carbohydrates on faecal pH and short chain fatty acid content (Noakes *et al.*, 1996; Carabin *et al.*, 2009). The papers have not been sub-divided into classes of dietary fibre, as many of the trials investigated the effects of different classes of dietary fibres, but for data synthesis the different classes have been considered separately.

101. The trial design details have been summarised in Table 10. Thirty eight trials employed a cross-over design, of which 19 did not have a washout period. The other five trials used a parallel design. All the trials were in adults, mostly younger adults. The basal diet was either a controlled diet, where all food was provided and energy intakes were controlled, or an *ad libitum* diet, which usually involved a low dietary fibre intake.

102. The methods used to measure dietary fibre varied from crude fibre in the early studies to the Southgate and Van Soest methods, through to the Englyst method for NSP and the AOAC method for total dietary fibre, which includes a significant quantity of

resistant starch (for details see the ‘dietary fibre analysis’ section on page 7).

103. The duration of intervention periods ranged from one week to 12 weeks and the sample sizes ranged from five to 46. The funding sources for all trials, where reported, were either Governmental or Commercial or both; 33% of trials did not report funding sources.

Table 10. Dietary fibre and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Total control intake (g/d)	Additional intervention dose (g/d)	Dietary fibre method	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Macrae, 1942	XO - 1 wk washout	England	Adults; 6M	Semi-controlled - mainly bread	White bread (530-630g)	Medium ground wholemeal bread	NR	10.8 CF	1	6	1 wk	7	6	NR
						Fine ground wholemeal bread		11.1 CF	1	6				
Connell, 1974	XO - no washout	USA	Adults aged 25-45y	Ad libitum	Cornflakes (1oz)	Wheat bran (bran buds 1 oz)	NR	8 to 10 DF	3	10	4 wk	7	8	NR
Jenkins, 1975	XO - no washout	England	Adults aged 21-25y; 6M	Controlled § fluid intake constant	No treatment	Wheat bran	17.0	28.0 DF	2	6	3 wk	7	6	British Nutrition Foundation
Walters, 1975	XO - no washout	England	Adults aged 25-72y; 19F	Ad libitum	Low-fibre biscuit	Bagasse 10.5g (sugar cane fibre)	NR	nearly 9 DF	2	19	12 wk	7	9	Cancer Research Campaign, Beecham Pharmaceutical, Medical Reseacrh Council
Southgate, 1976	XO - no washout	England	Adults aged 65-69y; 3M, 2F	Controlled low fibre	Low-fibre biscuit	Wheat bran (38g)	14.0	13.8 DF	2	5	1 wk	7	5	NR
Wyman, 1976	XO - 1 wk washout	USA	One child (aged 11) and Adults aged 25-41; 10M	Ad libitum low-fibre diet	Ad libitum low-fibre diet	Raw wheat bran (12g)	NR	NR	1	10	2 wk	5	10	NR
						Raw wheat bran (20g)		NR						
						Cooked wheat bran (13.2g)		NR	1					
						Cooked wheat bran (22g)		NR	1					
Beyer, 1978	XO - no washout	USA	Adults aged 21-29y; 6M	Controlled	Controlled low fibre	High fibre diet		7.6 CF	1	5	5 d	5	6	Doyle Pharmaceurical Company, USA
Kelsay, 1978	XO - no washout	USA	Adults aged37-58y; 12M	Controlled for energy intake - no whole grain cereals or nuts	Low-fibre diet contained fruit and vegetable juices	High fibre diet containing fruits and vegetables	NR	16.4 DF	3	12	26 d	7	12	NR
Spiller, 1979	P	USA	Adults aged 25-65y with slow transit times	Ad libitum low-fibre diet	Placebo	Psyllium	NR	10.0 DF	NR	40	3 wk	7	24	NR
				Ad libitum low-fibre diet	Placebo	Cellulose/pectin (70:30)		20.0 DF	NR	40	4 wk	7	30	
Stasse-Wolthuis, 1979	XO - no washout	Holland	Adults aged 20-27y; 23M 23F	Controlled for energy intake	Low-fibre diet	High fibre diet containing cereals and fruits and vegetables	12 .0	33.0 DF	2	46	3 wk	4	46	The Netherlands Heart Foundation
Spiller, 1980	P	USA	Adults aged 23-60y; 42M, with slow transit times	Ad libitum low-fibre diet	Placebo	Cellulose	NR	14.0 DF	NR	27	24 d	7	27	NR
				Ad libitum low-fibre diet		Pectin		6.0 DF	NR	26	24 d	7	26	
Stasse-Wolthuis, 1980	P	Holland	Adults aged 18-28y; 40M, 22F	Controlled low fibre	Placebo	High fibre diet containing fruits and vegetables	14.9	11.6 DF	4	31	5 wk	7	61	The Netherlands Heart Foundation
						Pectin		4.9 DF	4	31	5 wk	7		
						Wheat bran course		10.1 DF	4	32	5 wk	7		

Key for dietary fibre method: 1 crude fibre; 2 Southgate; 3 Van Soest and modifications;4 McCance, Widdowson & Shackleton; 5 Englyst; 6 Prosky 1985/1988 total dietary fibre, AOAC.
P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; M, male; F, female. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre

Dietary fibre and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Total control intake (g/d)	Additional intervention dose (g/d)	Dietary fibre method	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Hillman, 1983	XO - no washout	New Zealand	Adults aged 21-43; 8M, 22F	Ad libitum	No treatment	Cellulose	NR	15.0 DF	2	10	4 wk	2	10	Medical Research Council of New Zealand
						Pectin		15.0 DF	2	10	4 wk	2	10	
Andersson, 1983	XO - no washout	England	Adults aged 25-55y; 5M, 1F	Controlled	White bread (200g)	Brown bread (200g)	16.1	23.7 DF	2	6	24 d	6	6	Swedish National Board for Technical Developments, Marabou Company and MEDA, Sweden
						Wholemeal bread (200g)		31.5 DF	2	6	24 d			
Tsai, 1983	XO - 2 wk washout	USA	Adults aged 20-30y; 14M	Controlled	No treatment	Soy polysaccharide (25g)	NR	17.0 DF		14	17 d	4	14	Ralston Purina Company
Spiller, 1986	XO - no washout	USA	Adults aged 18-32y; 36F	Ad libitum low-fibre diet	White bread	Wheat bran (13.2g)	15.0	5.8 TDF	6	36	13d	5	35	NR
						Wheat bran (39.6g)		17.4 TDF						
						Wheat bran (66g)		29.0 TDF						
Behall, 1987	XO - no washout	USA	Adults aged 23-62y; 11M	Controlled low fibre	No treatment	Locust bean gum (7.5 g fibre/1000 kcal)	NR	23.7 DF	3	11	4 wk	8	11	NR
						Karaya gum		24.1 DF						
						Carboxymethylcellulose		23.5 DF						
						Cellulose		23.2 DF						
Tomlin, 1988	XO - no washout	England	Adults aged 23-30y; 8M	Ad libitum low-fibre diet	No treatment	Rice bran (75g)	NR	15.0 DF	5	8	10d	7	8	NR
						Wheat bran (37.5g)		17.1 DF						
Stevens, 1988	XO - no washout	USA	Adults aged 22-38y; 12F	Semi - controlled	Control cracker	Wheat bran	21	19.0 TDF	3 and 6	12	2 wk	7	12	C.D' SearleC ompany USA
						Psyllium		19.0 TDF						
						Wheat bran and psyllium		19.0 TDF						
Kesaniemi, 1990	XO - no washout	Finland	Adults aged 34-50y; 34M*	Ad libitum	Low fibre diet	High fruit, vegetable and cereal fibre diet	11.6	14.6 DF	2	34	8 wk	3	34	Juho Vainio Foundation, the Sigrid Juselius Foundation, Medical Council ofthe Academy of Finland, Finnish Life Insurance Companies
Effertz, 1991	P	USA	Overweight adults (BMI = 20) mean age 36y; 1M, 29F	Ad libitum	Control cracker	Soy polysaccharide	NR	19.6 TDF	6	40	14 wk	6	17	NR
Tinker, 1991	XO - no washout	USA	Adults with mild hypercholesterolemia aged 29-79y; 41M	Ad libitum	Grape juice	Prunes (100g/d)	NR	6.0 TDF	6	41	4 wk	3	41	California Prune Board and National Institutes of Health, USA

Key for dietary fibre method: 1 crude fibre; 2 Southgate; 3 Van Soest and modifications;4 McCance, Widdowson & Shackleton; 5 Englyst; 6 Prosky 1985/1988 total dietary fibre, AOAC.
P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; M, male; F, female. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre

Dietary fibre and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Total control intake (g/d)	Additional intervention dose (g/d)	Dietary fibre method	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Lampe, 1992	XO - 10 d washout	USA	Adults aged 19-50y; 18M, 16F	Controlled fibre-free formula	Bread w/o added fibre	Wheat bran (10g)	2.1	8.9 TDF	6	46	3 wk	7	34	National Cancer Institute. USA
						Wheat bran (30g)		27.8 TDF						
						Mixed vegetable fibres (pea, soy and citrus pectin) (10g)		12.2 TDF						
						Mixed vegetable fibres (30g)		34.4 TDF						
Marteau, 1994	XO - 3 wk washout	France	Adults aged 21-35y; 5M, 2F	Controlled low-fibre	Placebo	Psyllium (18g)	NR	NR	NR;	7	15 d	6	7	Corps des Medecins des H6pitaux de Paris, France
Wisker, 1994	XO - 4 wk washout	Germany	Adults aged 22-31y; 10F	Controlled	Low-fibre bread	Citrus fibre concentrate (35g/d) added to bread	NR	24.0 TDF	6	10	4 wk	7	10	NR
Wisker, 1994	XO - 3 wk washout	Germany	Adults aged 22-29y; 12F	Controlled low-fibre	Sugar jelly	Carrots raw frozen (575g/d)	NR	15.0 TDF	6	12	3 wk	7	12	NR
						Carrots blanched frozen (508g/d)		15.0 TDF						
						Carrots canned (688g/d)		15.0 TDF						
Stephen, 1995	XO - no washout	Canada	Adults aged 19-38y; 9M	Controlled low-fibre	Bread, cakes, and soups w/o intervention	Lentils (130g dry/d) incorporated into bread, cakes, and soups	NR	11.8 NSP	5	10	3 wk	7	9	Agriculture Development Fund, Canada
Cummings, 1996	XO - no washout	England	Adults aged 22-43y	Controlled	Digestible starch - slow and rapid (also a starch-free group)	Wheat bran	16.0	15.0 NSP	5;	12	15d	5	12	Ministry of Agriculture, Fisheries and Food, UK
Noakes, 1996	XO – no washout	Australia	Adults aged 44-64y; 13M, 10F	Ad libitum	Low-amylose diet (maize cornstarch and wheat flour	high amylose diet or a diet high in oat bran,	11-13 TDF	28-37; 24-29 TDF	6	29	4 wk	1*	23	NR
Cherbut, 1997	XO - 3 wk washout	France	Adults aged 24-48y; 8M, 10F	Controlled low-fibre	sucrose	Maize fibre	NR	15.0 DF	NR	9	3 wk	7	18	Roqquette Frères, France
						Potato fibre		15.0 DF		9				
Jenkins, 1998	XO - 2 wk washout	Canada	Adults aged 22-53y; 12M. 12F	Ad libitum	Low-fibre control	Wheat bran	22	23 TDF	6	24	2 wk	4	24	Natural Sciences and Engineering Research Canada, Nacan Products Ltd., Canada
Jenkins, 1999	XO - 2 wk washout	Canada	Adults aged 35-72y; 15M, 8F	Controlled	Low-fibre control bread	Wheat bran fine particle size	NR	19-20 TDF	6	23	4 wk	3	23	Natural Sciences and Engineering Research Council of Canada The Kellogg Company, Canada
						Wheat bran medium particle size		19-20 TDF						
	XO - 2 wk washout		Adults aged 17-57y; 12M, 12F	Ad libitum	Low-fibre control cereal	Wheat bran medium particle size		19.0 TDF	6	24	2 wk	4	24	
						Wheat bran course particle size		19.0 TDF						

Key for dietary fibre method: 1 crude fibre; 2 Southgate; 3 Van Soest and modifications;4 McCance, Widdowson & Shackleton; 5 Englyst; 6 Prosky 1985/1988 total dietary fibre, AOAC.
P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; M, male; F, female. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre; * only effects on faecal SCFA content extracted.

Dietary fibre and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Total control intake (g/d)	Additional intervention dose (g/d)	Dietary fibre method	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Vuksan, 1999	XO - 2 wk washout	Canada	Adults aged 21-60y; 12M, 12F	Ad libitum	Low-fibre control cereal	Wheat fibre from amylolytic digestion	16.3	17 TDF	6	24	2 wk	4	24	Natural Sciences and Research Council of Canada, and Mohawk Canada Ltd.
						Wheat bran		17 TDF						
Gråsten, 2000	XO - 4 wk washout	Finland	Adults aged 28-51y; 8M, 9F	Ad libitum low-fibre diet	White wheat bread men	Whole grain rye bread men	15.2	24.2 DF	NR	17	4 wk	5	17	Fazer Bakeries Ltd, Vaasan & Vaasan Ltd and the Technology Development Center of Finland.
					White wheat bread women	Wholegrain rye bread women	12.7	17.4 DF						
McRorie , 2000	P	USA	Adults aged 18-82y; 26M, 24F	Ad libitum - meals provided in metabolic ward	Potato chips	Wheat bran (20g)	NR	NR	NR	12	6 d	6	12	The Proctcr& Gamble Company
						Wheat bran (40g)				12				
Jenkins, 2000	XO - 2 wk washout	Canada	Adults aged 22-57y; 13M, 12F	Ad libitum	Low-fibre control cereal	Cocoa bran	17.0	25 TDF	6	25	2 wk	4	25	Natural Scienccs and Research Council ol' Cannada; Loblaw Brands Ltcl
McIntosh, 2003	XO - no washout	Australia	Adults aged 40-65y; 31M	Ad libitum	Ad libitum low fibre	High-fibre wheat diet	19.0	13.0 TDF	6	31	4 wk	3	28	George Weston Foods Ltd and the Australian Government
						High-fibre rye diet		13.0 TDF						
Muir, 2004	XO - 1 wk washout	Australia	Adults aged 22-67y; 11M, 9F **	Ad libitum low-fibre and RS	Low fibre and RS foods	Wheat bran	22.5	7.2 TDF;	6	20	3 wk	5	20	National Health and Medical Research Council of Australia and Meat and Livestock Australia
Johnson, 2006	XO - 4 wk washout	Australia	Adults aged 24-64y; 38M	Semi-controlled excluding legumes	Low-fibre control w/o intervention	Legume fibre (lupin kernel)	23.2	22.2 DF	NR -	44	4 wk	3	38	Grains Research and Development Corporation, the Australian Research Council
Bird, 2008	XO - no washout	Australia	Adults aged 31-66y; 11M, 13F	Ad libitum low-fibre	Refined cereals	Wholemeal wheat	21·4	11.0 TDF	6	24	4 wk	2	18	CSIRO and ACVL Ltd.
						Barley novel hull-less (Himalaya 292)		23.2 TDF						
Vuksan, 2008	XO - 1 wk washout	Canada	Adults aged 19-59y; 12M, 11F	10 d ad libitum followed by 11 d controlled	Low-fibre control cereal	Wheat bran	12.2	26.6 TDF	6	25	3 wk	7	23	Kellogg Company
						Wheat and corn bran		25.3 TDF						
						Wheat bran and psyllium		27.6 TDF						
						Wheat and corn bran and fibre preparation (70% glucomannan and 30% xanthan)		26.1 TDF						
Carabin, 2009	P	Canada	Adults aged 18-55y; 25M, 29 F	Ad libitum	Skim milk powder	Konjac powder, sodium alginate, and xanthan gum	NR	10 TDF	6	54	3 wk	1***	54	InovoBiologic, Inc., Canada.

§ eating only food prepared in a metabolic kitchen controlled for energy intake; * Three subjects had mild hypertension and they received small doses of diuretics or beta-blockers. Three subjects had gallstones, one had a history of myocardial infarction, and one had maturity-onset diabetes mellitus treated with sulphonylurea. ** Eighteen subjects had a close family history of colorectal cancer (first degree relative), and 2 subjects had previously had colonic adenomas removed. One male subject had well-controlled type 2 diabetes.

Key for dietary fibre method: 1 crude fibre; 2 Southgate; 3 Van Soest and modifications;4 McCance, Widdowson & Shackleton; 5 Englyst; 6 Prosky 1985/1988 total dietary fibre, AOAC.

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; M, male; F, female. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre; *** only effects on faecal SCFA content extracted.

Risk of bias

104. A summary of the risk of bias assessment has been given in Table 11.

105. Eleven trials were not randomised and only one of the randomised trials reported the method of sequence generation. Most of the trials were open with only five being blind to both participants and personnel and one blind to participants only. This reflected the nature of most of the interventions.

106. The dropout percentages were generally low with thirty one trials reporting no missing outcome data. Drop-out rates ranged up to 26%, with four trials having 20% or more. In those that reported drop-outs, either missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups, or missing outcome data were unlikely to be related to the intervention.

Table 11. Dietary fibre and faecal output trial risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Macrae	1942	Yes	NR	NR	Open	No missing outcome data	0
Connell	1974	No	-	-	Open	Missing outcome data similar in numbers across intervention groups	20
Jenkins	1975	No	-	-	Open	No missing outcome data	0
Walters	1975	No	-	-	Open	No missing outcome data	0
Southgate	1976	No	-	-	Open	No missing outcome data	0
Wyman	1976	Yes	NR	NR	Open	No missing outcome data	0
Beyer	1978	No	-	-	Open	No missing outcome data	0
Kelsay	1978	No	-	-	Open	No missing outcome data	0
Spiller	1979	No	-	-	Participants and personnel blind	No missing outcome data	0
Stasse- Wolthuis	1979	No	-	-	Open	No missing outcome data	0
Spiller	1980	No	-	-	Open	Missing outcome data unlikely to be related to outcome	4
Stasse- Wolthuis	1980	No	-	-	Open	No missing outcome data	0
Hillman	1983	Yes	NR	NR	Open	No missing outcome data	0
Andersson	1983	Yes	NR	NR	Open	No missing outcome data	0
Tsai	1983	Yes	NR	NR	Open	No missing outcome data	0
Spiller	1986	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	3
Behall	1987	Yes	NR	NR	Open	No missing outcome data	0
Tomlin	1988	Yes	NR	NR	Open	No missing outcome data	0
Stevens	1988	No	-	-	Open	No missing outcome data	0
Kesaniemi	1990	Yes	NR	NR	Open	No missing outcome data	0
Effertz	1991	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	25
Tinker	1991	Yes	NR	NR	Open	No missing outcome data	0
Lampe	1992	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	26
Marteau	1994	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Wisker	1994	Yes	NR	NR	Open	No missing outcome data	0
Wisker	1994	Yes	NR	NR	Open	No missing outcome data	0
Stephen	1995	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	10

NR, not reported.

Dietary fibre and faecal output trial risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Cummings	1996	Yes	NR	NR	Open	No missing outcome data	0
Noakes	1996	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	20
Cherbut	1997	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Jenkins	1998	Yes	NR	NR	Open	No missing outcome data	0
Jenkins	1999	Yes	NR	NR	Open	No missing outcome data	0
Vuksan	1999	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	13
Gråsten	2000	Yes	NR	NR	Open	No missing outcome data	0
McRorie	2000	Yes	NR	NR	Open	No missing outcome data	0
Jenkins	2000	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
McIntosh	2003	Yes	Randomly generated numbers	NR	Open	Missing outcome data unlikely to be related to outcome	10
Muir	2004	Yes	NR	NR	Open	No missing outcome data	0
Johnson	2006	Yes	NR	NR	Participants blind only	Missing outcome data unlikely to be related to outcome	14
Bird	2008	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	25
Vuksan	2008	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	8
Carabin	2009	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0

NR, not reported.

Results

107. The findings from all trials have been summarised in Table 18. Outcome data, expressed as mean with standard deviation (where extractable), have been given for faecal wet and dry weights, bowel frequency, faecal moisture content and total intestinal transit time.

108. Most of the trials reported on the effect of wheat fibre on faecal output. Eighteen of these articles had sufficient variance data to be synthesised on the basis of faecal wet weight data (Connell & Smith, 1974; Jenkins *et al.*, 1975; Southgate *et al.*, 1976; Wyman *et al.*, 1976; Stasse-Wolthuis *et al.*, 1980; Andersson *et al.*, 1983; Spiller *et al.*, 1986; Stevens *et al.*, 1988; Tomlin & Read, 1988b; Cummings *et al.*, 1996; Jenkins *et al.*, 1998; Jenkins *et al.*, 1999a; Vuksan *et al.*, 1999; McRorie *et al.*, 2000; McIntosh *et al.*, 2003; Muir *et al.*, 2004; Bird *et al.*, 2008; Vuksan *et al.*, 2008). There were insufficient trials on other dietary fibre classes to warrant data synthesis and these have been discussed below and mean difference values for wet faecal weight data tabulated. Four trials were excluded from the analysis as additional doses of dietary fibre were less than 10g/day or more than 25g/day (Connell & Smith, 1974; Jenkins *et al.*, 1975; Wyman *et al.*, 1976; Muir *et al.*, 2004). For cross-over trials with multiple intervention groups, all relevant experimental intervention groups were combined into a single group in order to create a single pair-wise comparison, as recommended by the Cochrane Handbook for systematic reviews of interventions.

109. Fifteen trials reported on wheat fibre (dose range included 10-25g/day; mean approximately 17g/day if NSP, DF and TDF values were used together) in relation to faecal wet weight, providing 15 mean difference measures with a total of 591 data points (see Figure 1). The results of the meta-analysis have been summarised in Table 28. There was no significant evidence of heterogeneity between trials (see Table 12). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

110. The effects on faecal weight were highly significant ($p<0.001$), with a mean difference of 68g/day (95% CI: 59-77). There was a large degree of variation around the point estimates for change in faecal weight in many trials, as can be seen from the 95% confidence intervals (see Figure 1). Overall, the effect of wheat fibre on faecal wet weights broadly equated to a 4g increase in faecal wet weight per 1g wheat fibre, if NSP, DF and TDF dose values were used together.

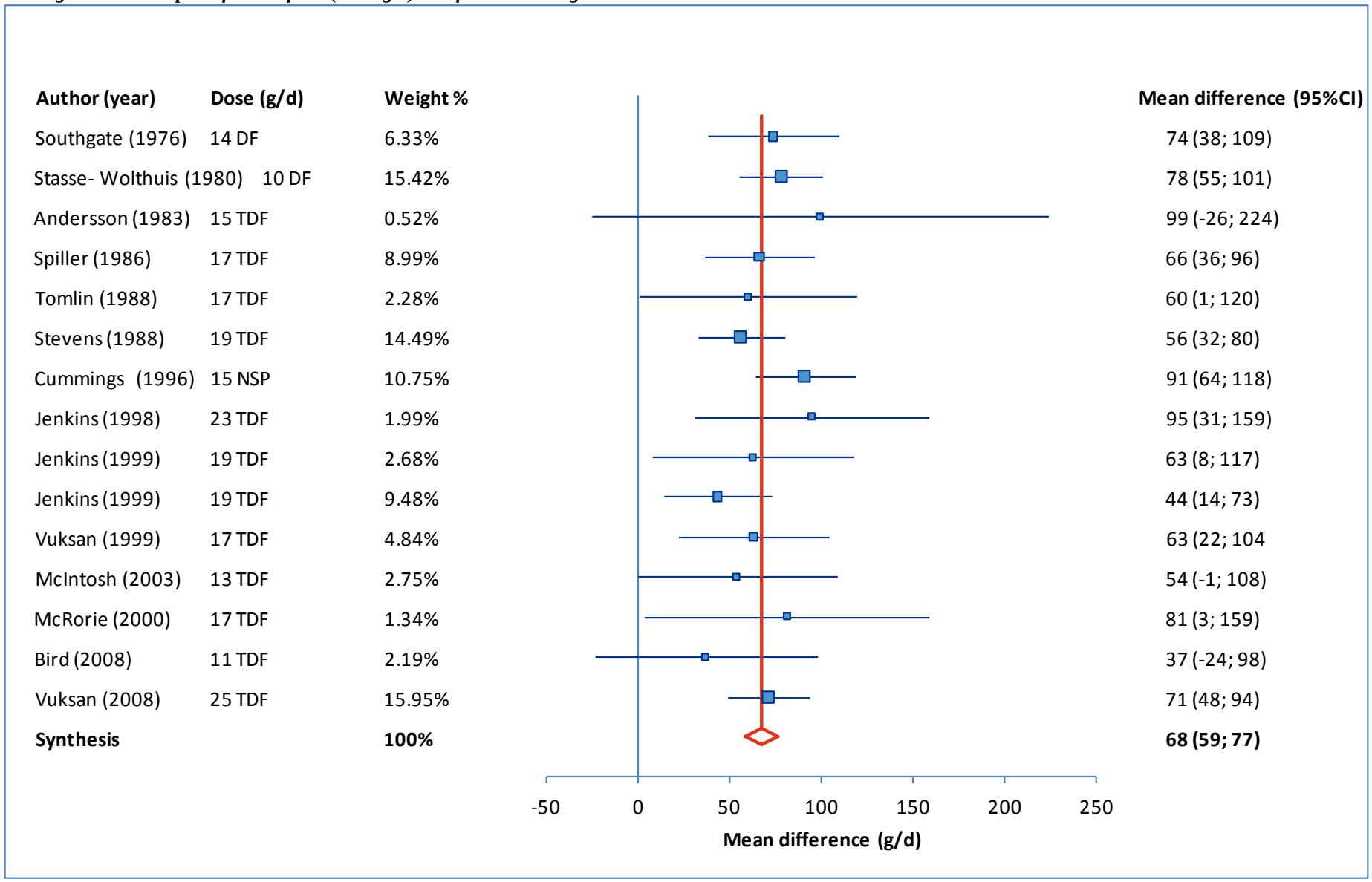
Table 12. Results of meta-analysis for all wheat fibre (dose range included 10-25g/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	15	68 (59-77)	14.78(p<0.001)

[1] I^2 = 0.00% (95% CI 0.00-53.61%); p for test of heterogeneity = 0.780

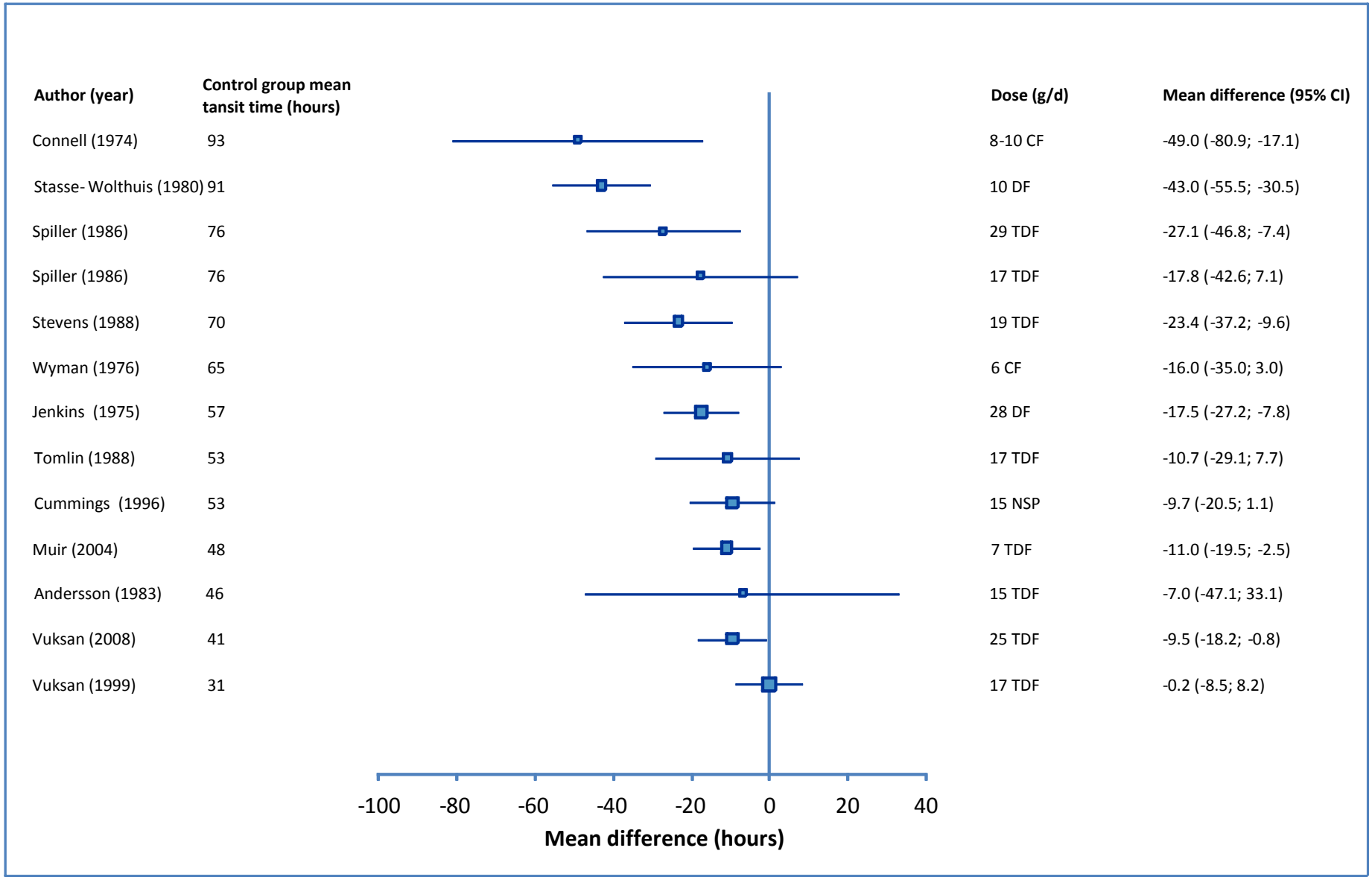
[2] No. of RR estimates included in pooled analysis.

Figure 1. Forest plot of wheat fibre (10-25g/d) and faecal wet weight



DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre.

Figure 2. Forest plot of the effect of wheat fibre on total intestinal transit time in relation to control transit time



CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre.

111. Most of the wheat fibre trials reported an increase in faecal wet and dry weight and, less consistently, a decrease in total intestinal transit time. When the effect of wheat fibre on total intestinal transit time was plotted in order of decreasing control transit times (see Figure 2), the reduction in transit times in response to wheat fibre was most marked in those subjects with initially high values. This has also been observed in trials conducted in patients with constipation (see page 140). A dose-response effect of wheat fibre on total intestinal transit times was observed in one trial (Spiller *et al.*, 1986) and, generally, transit times were reduced at higher doses of wheat fibre supplementation (see Table 18). The different methods used to measure transit time make direct comparison between studies difficult, but overall it appears that the effect size on transit time was dependent on initial time in the study population and, to a lesser extent, the dose of dietary fibre. When the effect of wheat fibre on faecal wet weight was plotted in order of decreasing control faecal wet weights (data not shown), there was no appreciable difference in response to wheat fibre between subjects populations with initially high or low faecal wet weights.

112. A dose-response effect of wheat fibre on faecal weight was observed in two trials (Spiller *et al.*, 1986; Lampe *et al.*, 1992), while one trial reported no difference between 20g/day and 40g/day wheat bran on increasing faecal weight (McRorie *et al.*, 2000). Several trials showed consumption of whole grain wheat bread increased faecal wet and dry weights relative to white bread (Macrae *et al.*, 1942; Andersson *et al.*, 1983; Grasten *et al.*, 2000).

113. Two trials, one where intakes were *ad libitum* and the other controlled, reported no effect of wheat bran particle size on faecal weight or faecal water content (Jenkins *et al.*, 1999a). One other trial observed medium ground wholemeal bread to produce significantly bulkier stools than fine ground wholemeal bread (Macrae *et al.*, 1942). Raw bran, but not cooked bran, significantly increased faecal dry weight and decreased transit time in one trial (Wyman *et al.*, 1976).

114. Five trials reported that high fibre diet containing cereals, fruits and vegetables were effective in increasing faecal wet and dry weights and decreasing transit times (see Table 13) (Beyer & Flynn, 1978; Kelsay *et al.*, 1978; Stasse-Wolthuis *et al.*, 1979; Stasse-Wolthuis *et al.*, 1980; Kesaniemi *et al.*, 1990). Overall, a high fibre diet containing cereals, fruits and vegetables had very significant effects on faecal weight and the observed effect sizes were similar to those observed for wheat fibre alone; also, total intestinal transit time reductions were observed in relation to transit times of between 40-55 hours in the control group.

115. Five trials reported that cereal fibres other than wheat were effective in increasing faecal wet weights (see Table 14). A novel barley (containing more resistant starch and NSP than normal barley) increased faecal wet weight to a similar extent as wholemeal wheat (Bird *et al.*, 2008). Both rye and wheat high-fibre diets were shown to increase faecal wet weight equally (McIntosh *et al.*, 2003), while another trial also reported that whole grain rye bread increased faecal weights and decreased transit time (Grasten *et al.*, 2000). In one trial maize fibre increased faecal wet and dry weight and reduced transit time (Cherbut *et al.*, 1997). Rice bran was also observed to increase faecal weight and decrease total intestinal transit times (Tomlin & Read, 1988b). Very significant effects on faecal weight were observed with effect sizes similar to those observed for wheat fibre alone; also, total intestinal transit time

reductions were observed in relation to transits times of between 40-55 hours in the control group. Overall, cereal fibres other than wheat had very significant effects on faecal weight and observed effect sizes were similar to those observed for wheat fibre alone; also, reductions in total intestinal transit time were observed in relation to transits times of between 40-60 hours in the control group.

116. The faecal wet weight and total intestinal transit time mean difference values for fruit and vegetable fibres have been given in Table 15. A comparison between a vegetable fibre mixture (pea fibre, soy polysaccharide and pectin) and wheat bran reported wheat bran at equivalent doses to be more effective in increasing faecal weight and reducing transit time than vegetable fibre (Lampe *et al.*, 1992). Only 30g/day, but not 10g/day, vegetable fibre mixture resulted in greater faecal weights with no significant effect on transit time observed. Legume fibre increased faecal wet weight, moisture content and bowel frequency and decreased transit time (Johnson *et al.*, 2006). Other trials reported lentils (dry 130g/day) increased faecal weight (Stephen *et al.*, 1995), and carrot consumption (500-600g/day) also increased faecal wet and dry weight and moisture content (Wisker *et al.*, 1994b). Potato fibre increased faecal wet and dry weight, but did not affect transit time (Cherbut *et al.*, 1997). Soy polysaccharide increased faecal weight without affecting transit time, in two trials (Tsai *et al.*, 1983; Effertz *et al.*, 1991). Other trials reported that sugar cane fibre (Walters *et al.*, 1975) and cocoa bran (Jenkins *et al.*, 2000) increased faecal weights; no significant effect of sugar cane fibre was observed on transit by radio-opaque pellet method, but an effect was observed for carmine dye method (Walters *et al.*, 1975). One trial reported that prunes (providing 6g dietary fibre/day) increased faecal wet weight and dry weight, but had no effect on percent water (Tinker *et al.*, 1991), while three other trials reported that higher amounts of fruit and vegetable fibres increased faecal wet and dry weight and, less consistently, increased the faecal moisture content (Wisker *et al.*, 1994a; Cherbut *et al.*, 1997; Johnson *et al.*, 2006).

117. Three trials examined the effect of pectin on faecal output (see Table 16) (Spiller *et al.*, 1980; Stasse-Wolthuis *et al.*, 1980; Hillman *et al.*, 1983), but these reported no effect on faecal weight or intestinal transit time. Cellulose and carboxy-methylcellulose increased both wet and dry faecal weights and decreased transit times to a similar extent as wheat fibre (Spiller *et al.*, 1980; Hillman *et al.*, 1983; Behall *et al.*, 1987).

118. Two trials reported that psyllium increased faecal wet and dry weights, percentage water and bowel frequency, without significantly affecting transit times (see Table 17) (Stevens *et al.*, 1988; Marteau *et al.*, 1994). Two trials investigated wheat bran and psyllium together, one reported increased faecal weight over wheat bran alone (Vuksan *et al.*, 2008), while the other did not (Stevens *et al.*, 1988). In one trial psyllium and a cellulose/pectin mixture equally increased faecal wet weight, but only cellulose/pectin decreased transit time (Spiller *et al.*, 1979). In another trial the food additives locust bean gum and karaya gum increased faecal wet and dry weight, without effect on transit time (Behall *et al.*, 1987).

Table 13. Faecal wet weight and transit time mean difference values for high fibre diets including cereal, fruit and vegetable fibres

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Transit time mean difference (hours, 95% CI)	Control mean transit time (hours±sd)
Beyer, 1978	High fibre diet	7.6 CF	105 (71 to 139)	-36 (-42 to -30)	47±7
Kelsay, 1978	High fibre diet containing fruits and vegetables	16.4 DF	120 (95 to 145)	-14 (-25 to – 3)	52±14
Stasse-Wolthuis, 1979	High fibre diet containing cereals and fruits and vegetables	33 DF	155 (89 to 141)	-18 (-24 to -12)	55±17
Kesaniemi, 1990	High fruit, vegetable and cereal fibre diet	14.6 DF	53 (28 to 78)		
Vuksan, 2008	Wheat and corn bran and viscous fibre preparation	26.1 TDF	69 (39 to 99)	-12 (-21 to -3)	41±19

* as reported; CF, crude fibre; DF, dietary fibre; TDF, total dietary fibre.

Table 14. Faecal wet weight and transit time mean difference values for cereals other than wheat

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Transit time mean difference (hours, 95% CI)	Control mean transit time (hours±sd)
Tomlin, 1988	Rice bran	15.0 DF	134 (75 to 194)	-10 (-30 to 10)	53±23
Cherbut, 1997	Maize fibre	15.0 DF	36 (18 to 54)	-28 (-51 to -5)	61±29
Gråsten, 2000	Whole grain rye bread men	24.2 DF	137 (60 to 214)	-8.5 (-22 to 5)	39±16
Gråsten, 2000	Wholegrain rye bread women	17.4 DF	52 (-4 to 108)	-11 (-28 to 5)	56±22
McIntosh, 2003	High-fibre rye cereal and bread diet	13.0 TDF	75 (28 to 122)		
Bird, 2008	Novel barley	23.2 TDF	50 (-7 to 107)		

* as reported; CF, crude fibre; DF, dietary fibre; TDF, total dietary fibre.

Table 15. Faecal wet weight and transit time mean difference values for fruit and vegetable fibres

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Transit time mean difference (hours, 95% CI)	Control mean transit time (hours±sd)
Stasse-Wolthuis, 1980	High fruit and vegetable diet	11.6 DF	49 (21 to 77)	-38 (-30 to -16)	91±39
Tinker, 1991	Prunes (100g/d)	6.0 TDF	38 (2 to 74)		
Lampe, 1992	Mixed vegetable fibres ***	12.2 TDF	12**		
	Mixed vegetable fibres	34.4 TDF	45**		
Wisker, 1994	Citrus fibre (35g/d)	24.0 TDF	36 (-6 to 78)		
Wisker, 1994	Carrots (575g/d)	15.0 TDF	56**		
Stephen, 1995	Lentils (130g dry/d)	11.8 NSP	59 (17 to 100)	-2.8 (-17 to 11)	46±18
Cherbut, 1997	Potato fibre	15.0 DF	36 (10 to 62)	-6 (-24 to 11)	62±19
Johnson, 2006	Legume fibre (lupin kernel)	22.2 TDF	36 (1 to 71)	-7 (-14 to -1)	44±17
Tsai, 1983	Soy polysaccharide (25g)	17.0	36 (-1 to 74)	3 (-5 to 11)	26±10 #
Effertz, 1991	Soy polysaccharide	19.6 TDF	11 (-14 to 36)	-12 (-27 to 3.6)	58±9
Walters, 1975	Bagasse 10.5g (sugar cane fibre)	9.0 DF	51 (35 to 68)	-10 (-23 to 4)	47±27
Jenkins, 2000	Cocoa bran	25.0 TDF	56 (19 to 93)		

* as reported; **, no variance data reported; ***pea, soy and citrus pectin; # as measured by 'first appearance' coloured dye method; DF, dietary fibre; TDF, total dietary fibre; NSP, non-starch polysaccharide

Table 16. Faecal wet weight and transit time mean difference values for purified dietary fibres.

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Transit time mean difference (hours, 95% CI)	Control mean transit time (hours±sd)
Spiller, 1980	Pectin	6.0	1 (-20 to 21)	4.8 (-38 to 47)	115±58
Stasse-Wolthuis, 1980	Pectin	4.9	11 (-12 to 34)	-28 (-54 to -2)	91±39
Hillman, 1983	Pectin	15.0	-16 (-81 to 48)	6.3 (-10 to 23)	51±24
Spiller, 1980	Cellulose	14.0	44 (19 to 69)	-53 (-86 to -20)	115±58
Hillman, 1983	Cellulose	15.0	75 (5 to 145)	-15 (-29 to 0)	55±20
Behall, 1987	Cellulose	23.2	47 (9 to 86)	-3 (-12 to 7)	27±14 #
Behall, 1987	Carboxymethyl-cellulose	23.5	167 (102 to 233)	-3 (-12 to 7)	27±14 #

* as reported; # as measured by 'first appearance' coloured dye method; DF, dietary fibre; TDF, total dietary fibre; NR, not reported.

Table 17. Faecal wet weight and transit time mean difference values for psyllium and food additives

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Transit time mean difference (hours, 95% CI)	Control mean transit time (hours±sd)
Spiller, 1979	Psyllium	10.0 DF	39**		
Stevens, 1988	Psyllium	19.0 TDF	84 (57 to 111)	-11 (-25 to 3)	70±22
Marteau, 1994	Psyllium 18g/d	NR	109 (76 to 142)	-11 (-31 to 9)	53±21
Stevens, 1988	Wheat bran and psyllium	19.0 DF	64 (42 to 86)	-15 (-30 to -1)	70±22
Vuksan, 2008	Wheat bran and psyllium	27.6 DF	119 (80 to 158)	-10 (-21 to 1)	41±19
Behall, 1987	Locust bean gum	23.7 DF	52 (12 to 92)	3 (-8 to 13)	27±14 #
Behall, 1987	Karaya gum	24.1 DF	61 (17 to 105)	1 (-12 to 12)	27±14 #

* as reported; **, no variance data reported; DF, dietary fibre; TDF, total dietary fibre.

Table 18. Dietary fibre and faecal output trial results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Macrae, 1942	Medium ground wholemeal bread	10.8 CF	1 wk	62±20	283±36	18±3	69±6								Medium ground wholemeal bread produced significantly bulkier stools than fine ground wholemeal flour bread - both increased faecal weight compared with control
	Fine ground wholemeal bread	11.1 CF		62±20	232±25	18±3	69±7								
Connell, 1974	Wheat bran (bran buds 1 oz)	8 to 10 DF	4 wk	123±27	240±82							93±45	44±10	1	Wheat bran increased faecal weight and decreased intestinal transit time
Jenkins, 1975	Wheat bran	28.0 DF	3 wk	79±7	228±30	21±2	45±6			73.0	80.0	58±8	40±9	2	Wheat bran increased faecal weight and decreased intestinal transit time.
Walters, 1975	Bagasse 10.5g (sugar cane fibre)	nearly 9 DF	12 wk	88±19	140±31	22±5	33±5					47±27	37±12	1 (80% in stool)	Bagasse increased wet and dry faecal weight, but no significant effect on transit by radio-opaque pellet method, but effect observed for carmine dye method
Southgate, 1976	Wheat bran (38g)	13.8 DF	1 wk	93±23	166±34	23±3	38±19			75.0	77.0				Wheat bran increased faecal weight and water excretion
Wyman, 1976	Raw wheat bran (20g)	5.9 CF	2 wk	131±53	159±41	30±9	38±10	1.0±0.3	1.1±0.3	75.0±4.4	75.9±3.5	65±25	48±22	1 (80% in stool)	No effect of wheat bran on wet faecal weight or water content, but raw bran, not cooked bran, increased dry weight and decreased transit time
	Cooked wheat bran (13.2g)	3.6 CF		131±53	139±27	30±9	37±10	1.0±0.3	1.1±0.4	75.0±4.4	73.0±6.3	65±25	58±19		
	Cooked wheat bran (22g)	5.8 CF		131±53	164±63	30±9	35±10	1.0±0.3	1.1±2.3	75.04.4	77.0±4.1	65±25	50±28		
Beyer, 1978	High fibre diet	7.6 CF	5 d	51±12	157±37	NR	NR	NR	NR	NR	NR	47±7	11±2		High-fibre diet increased faecal wet weight relative to a low-fibre diet; transit time only measured in half the subjects but was observed to decrease with increased fibre intake
Kelsay, 1978	High fibre diet containing fruits and vegetables	16.4 DF	26 d	89±32	209±31	23±7	52±9			73.0±3.1	74.6±3.1	52±14	38±14	3	Fruit and vegetable fibre -rich diet increased wet and dry faecal weight, faecal water excretion, but not percentage water, and decreased transit time.
Spiller, 1979	Psyllium	10.0 DF	3 wk	62	101							NE	NE	1 (80% in stool)	Psyllium and cellulose/pectin equally increased faecal wet weight and faecal
	Cellulose/pectin (70:30)	20.0 DF			104							NE	NE	1 (80% in stool)	water excretion, but only cellulose/pectin decreased transit time relative to placebo
Stasse-Wolthuis, 1979	High fibre diet containing cereals and fruits and vegetables	33.0 DF	3 wk	69±50	184±75	18±10	25±6	0.7±0.5	1.4±0.6			55±17	37±12	2	High-fibre diet increased faecal wet and dry weight, bowel frequency and decreased transit time
Spiller, 1980	Cellulose	14.0 DF	24 d	54±26	97±39							115±58	62±24	1 (80% in stool)	Cellulose, but not pectin, increased faecal wet weight and decreased transit time. .
	Pectin	6.0 DF			54±27							115±58	120±53	1 (80% in stool)	

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day; y, year; wk ,week; LSM, least squared means; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. BM, bowel motion. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre. NE, not extractable.

Dietary fibre and faecal output trial results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Stasse-Wolthuis, 1980	High fibre diet containing fruits and vegetables	11.6 DF	5 wk	88±35	137±44	24±4	23±4	0.8±0.4	1.0±0.3			91±39	53±22	2	High fibre diet and more so bran, but not pectin, increased faecal weight. Bran and the high fibre diet decreased transit time, but the control group had a significant increase from baseline.
	Pectin	4.9 DF			99±29	24±4	24±2	0.8±0.4	0.9±0.4			91±39	63±35	2	
	Wheat bran course	10.1 DF			166±31	24±4	22±4	0.8±0.4	1.0±0.3			91±39	48±19	2	
Hillman, 1983	Cellulose	15.0 DF	4 wk	133±63	208±94							55±20	40±13	2	Cellulose, but not pectin, decreased transit time and PH and increased faecal weight
	Pectin	15.0 DF			119±80							51±24	57±14	2	
Andersson, 1983	Brown bread (200g)	7.6 DF	24 d	137±93	175±122	29±12	37±14					46±41	41±33	2	The addition of wheat bran to bread increased faecal wet and dry weight in a dose-repose manner, but no significant effect on transit times
	Wholemeal bread (200g)	15.4 DF			236±125	29±12	48±16					46±41	39±29	2	
Tsai, 1983	Soy polysaccharide (25g)	17.0 DF	17 d	140±41	177±58	34±10	39±14			76.0	78.0	26±10	29±11	3	Soy polysaccharide increases wet faecal weight, but not dry weight or transit time
Spiller, 1986	Wheat bran (13.2g)	5.8 TDF	13d	73±26	95±41	20±6	25±9			72.5±3.1	72.5±4.8	76±30	58±24	1 (80% in stool)	Wheat bran, in a dose-dependent manor, increased faecal wet and dry weight and decreased transit time
	Wheat bran (39.6g)	17.4 TDF			140±49	20±6	34±11				74.9±3.9		59±36		
	Wheat bran (66g)	29.0 TDF			212±70	20±6	49±14				76.3±4.0		49±21		
Behall, 1987	Locust bean gum (7.5 g fibre/1000 kcal)	23.7 DF	4 wk	100±43	152±53	25±5	35±11	0.9±0.4	1.1±0.4			27±14	30±11	3	Carboxymethylcellulose increased faecal wet weight and bowel frequency. Carboxy methylcellulose, cellulose and, less so, karaya gum and locust bean gum increased faecal wet weight. No effect on transit times were observed.
	Karaya gum	24.1 DF		100±43	161±61	25±5	35±9	0.9±0.4	1.0±0.4				27±16		
	Carboxy-methylcellulose	23.5 DF			267±102		54±16		1.5±0.4				24±8		
	Cellulose	23.2 DF			147±50		46±9		1.1±0.4				24±8		
Tomlin, 1988	Rice bran (75g)	15.0 DF	10d	163±57	297±65			1.1±0.4	1.7±0.6			53±23	43±16	2	Rice bran more so than wheat bran increased faecal weight and frequency. Both equally decreased transit time
	Wheat bran (37.5g)	17.1 DF			223±65				1.3±0.3				42±12		

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day; y, year; wk ,week; LSM, least squared means; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. BM, bowel motion. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre.

Dietary fibre and faecal output trial results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Stevens, 1988	Wheat bran	19.0 TDF	2 wk	79±28	135±31	20±4	34±7	0.9±0.4	1.4±0.4	75.0±6.9	75.0±3.5	70±22	47±11	Plastic pellets	Wheat bran, psyllium alone and in combination increased faecal wet and dry weight, psyllium more so, increased bowel frequency and decreased transit time, bran more so. Only psyllium increased the percentage of faecal moisture. Four transit time methods were used: Cr-mordant, Co-EDTA, terbiumoxide and plastic pellets (data given). The results from each were not significantly different.
	Psyllium	19.0 TDF		79±28	163±38		33±4		1.4±0.4	75.0±6.9	81.0±3.5		60±12		
	Wheat bran and psyllium	19.0 TDF			143±28		34±4		1.4±0.4	75.0±6.9	76.0±3.5		55±14		
Kesaniemi, 1990	High fruit, vegetable and cereal fibre diet	14.6 DF	8 wk	144±47	197±58	33±8	43±10								High mixed-fibre diet increased faecal wet and dry weights.
Effertz, 1991	Soy polysaccharide	19.6 TDF	14 wk	221±20	232±33	81±7	68±12	1.4	1.2	63.3±4.7	70.1±6.3	58±9	47±23	2	Soy fibre had no effect on faecal wet weight, frequency or transit time, but an decrease in faecal dry weight was observed
Tinker, 1991	Prunes (100g/d)	6.0 TDF	4 wk	171±73	209±94	40±17	47±19			76.0±4.5	77.0±7.0			2	Prunes had no effect on faecal wet weight, dry weight or percent water
Lampe , 1992	Wheat bran (10g)	8.9 TDF	3 wk	64	94	18	26			71.3	71.2	81	54		Wheat bran and, less so, vegetable fibre increased faecal wet and dry weight and decreased transit time.
	Wheat bran (30g)	27.8 TDF			170	18	43			71.3	74.7	81	44		
	Mixed vegetable fibres (pea, soy and citrus pectin) (10g)	12.2 TDF			76	18	23			71.3	68.5	81	68		
	Mixed vegetable fibres (pea, soy and citrus pectin) (30g)	34.4 TDF			109	18	35			71.3	68.0	81	65		
Marteau, 1994	Psyllium (18g)	NR	15 d	122±29	231±34	38±16	51±11	1.0±0.3	1.2±0.3	69.0±2.6	77.0±7.9	53±21	42±16	2	Psyllium increased faecal wet and dry weights, percentage water and bowel frequency, but no significant effect on transit times
Wisker, 1994	Citrus fibre concentrate (35g/d) added to bread	24.0 TDF	4 wk	106±42	142±54	26±6	32±6			74.4±3.3	76.3±4.5				Citrus fruit fibre increased faecal wet and dry weight and increased faecal moisture content.
Wisker, 1994	Carrots raw frozen (575g/d)	15.0 TDF	3 wk	93	149	21	28			74.7	79.3				Carrot consumption increased faecal wet and dry weight and increased faecal moisture content. An influence of processing of carrots could only be observed in the case of stool water which was higher during the consumption of raw frozen and blanched frozen carrots compared with canned carrots.
	Carrots blanched frozen (508g/d)	15.0 TDF		93	151	21	28			74.7	79.1				
	Carrots canned (688g/d)	15.0 TDF		93	129	21	27			74.7	76.9				

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day; y, year; wk ,week; LSM, least squared means; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. BM, bowel motion. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre.

Dietary fibre and faecal output trial results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Stephen, 1995	Lentils (130g dry/d) incorporated into bread, cakes, and soups	11.8 NSP	3 wk	131±35	189±52	30±5	43±8			76.0±3.9	76.1±3.9	46±18	43±12	2	Lentils increased faecal wet and dry weight, but had no effect on faecal moisture content or transit time
Cummings , 1996	Wheat bran	15.0 NSP	15d	110±34	201±34	26±7	44±7	0.7±0.3	0.9±0.3	74.7±2.5	77.5±2.5	53±14	43±14		Wheat bran increased wet and dry faecal weight.
Cherbut, 1997	Maize fibre	15.0 DF	3 wk	73±22	108±16	19±6	32±5	0.9±0.1	1.0±0.2	72.8±3.3	70.8±2.1	61±29	33±21	2	Potato and maize fibre increased faecal wet and dry weight, but only maize fibre
	Potato fibre	15.0 DF		79±29	116±27	19±7	28±7	0.9±0.2	1.1±0.4	76.0±4.2	74.8±3.9	62±19	55±19		reduced transit time. Faecal water excretion increased, but there was no difference in faecal moisture content.
Jenkins, 1998	Wheat bran	23 TDF	2 wk	163±113	258±113										Wheat bran increased wet and dry faecal weight.
Jenkins, 1999	Wheat bran fine particle size	19-20 TDF	4 wk	211±110	268±110			1.3±0.5	1.4±0.5	78.0±4.8	79.0±4.8				In both the controlled and the ad lib trials, wheat bran increased faecal wet weights
	Wheat bran medium particle size	19-20 TDF			279±110				1.5±0.5		78.0±4.8				with no effect of particle size.
	Wheat bran medium particle size	19.0 TDF	2 wk	141±59	187±69			1.1 to 1.2		76.0±4.9	77.0±4.9				
	Wheat bran course particle size	19.0 TDF			182±54						77.0±4.9				
Vuksan, 1999	Wheat fibre from amylolytic digestion	17 TDF	2 wk	166±78	240±93	32±12	46±14			79.3±4.4	80.3±2.5	31±15	29±10	1 (80% in stool) and 2	Wheat bran and modified wheat fibre increased faecal wet and dry weight equally, but no effect on transit time or faecal
	Wheat bran	17 TDF			217±93		42±16				80.2±2.9		32±14		moisture content
Gråsten, 2000	Whole grain rye bread men	24.2 DF	4 wk	198±62	335±92			0.9±0.4	1.2±0.4	82.6±4.2	82.8±2.8	39±16	31±12	radio-opaque rings	Whole-meal rye bread significantly increased faecal weight and bowel frequency and decreased mean intestinal
	Wholegrain rye bread women	17.4 DF		151±63	203±58			1.4±0.6	1.6±0.6	81.0±3.4	81.3±3.4	56±22	45±13		transit time
McRorie, 2000	Wheat bran (20g)	8.6 TDF*	6 d	150±101	246±121			2.2±1.4	2.6±1.4	81.2±2.8	83.9±2.8				Both doses of wheat bran equally increased faecal weight, but had no effect on bowel
	Wheat bran (40g)	17.2 TDF*			231±94				2.4±1.4		83.4±2.4				frequency, faecal moisture content or measured faecal viscosity
Jenkins, 2000	Cocoa bran	25 TDF	2 wk	135±50	191±80			1.0±0.3	1.3±0.4						Cocoa bran increased faecal weight and bowel frequency to a similar extent to that observed with wheat bran in previous trials

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day; y, year; wk ,week; LSM, least squared means; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. BM, bowel motion. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre. * estimated from Kellogs bran buds nutrional information

Dietary fibre and faecal output trial results

Study	Intervention	Dose (g/d)	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
McIntosh, 2003	High-fibre wheat diet	13.0 TDF	4 wk	203±95	257±111										Both rye and wheat high-fibre diets increased faecal wet weight.
	High-fibre rye diet	13.0 TDF			278±85										
Muir, 2004	Wheat bran	7.2 TDF;	3 wk	131±64	161±67	34±13	41±15	1.2±0.5	1.3±0.6			48±16	37±11	radio-opaque rings.	Wheat bran with and without RS increased faecal wet and dry weights, decreased transit time.
Johnson, 2006	legume fibre (lupin kernel)	22.2 DF	4 wk	172±68	208±86			1.3±0.6	1.5±0.6	72.1±5.4	73.7±5.4	44±17	37±12	radio-opaque rings -	Legume fibre increased faecal wet weight, moisture content and bowel frequency, while decreasing transit time.
Bird, 2008	Wholemeal wheat	11.0 TDF	4 wk	150±81	187±104			1.0±0.4	1.1±0.4	73.8±3.3	76.8±3.3				The novel hull-less barley (containing more RS and NSP than normal barley) and whole wheat increased faecal wet weight. There was no effect on bowel frequency.
	Barley, novel hull-less (Himalaya 292)	23.2 TDF			200±93				1.1±0.4		77.3±6.4				
Vuksan, 2008	Wheat bran	26.6 TDF	3 wk	128±38	199±56	28±8	44±12	1.0±0.3	1.2±0.4	77.4±3.8	77.8±2.1	41±19	29±10	3 (80% in stool)	All study cereals increased faecal wet weights, but the wheat bran psyllium mixture increased weight the most. All cereals increased faecal dry weights, bowel frequency and faecal moisture content. Transit time was reduced, when analysed non-parametrically, in all cereal groups except in those receiving the wheat bran psyllium mixture.
	Wheat and corn bran	25.3 TDF			199±57		49±15		1.2±0.4		75.6±2.4		34±17		
	Wheat bran and psyllium	27.6 TDF			247±87		50±14		1.3±0.5		79.1±2.2		31±18		
	Wheat and corn bran and fibre preparation (70% glucomannan and 30% xanthan)	26.1 TDF			197±63		43±13		1.2±0.4		77.6±3.4		29±10		

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day; y, year; wk ,week; LSM, least squared means; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. BM, bowel motion. CF, crude fibre; DF, dietary fibre; NSP, non-starch polysaccharide; TDF, total dietary fibre.

The effect of resistant starch on faecal output

119. Resistant starch (RS) is the sum of starch and products of starch digestion that are not absorbed in the small intestine (Englyst *et al.*, 1992; Goni *et al.*, 1996; Champ *et al.*, 2003). While all unmodified starch, if solubilised, can be hydrolysed by pancreatic α-amylase, the rate and extent to which starch is broken down is altered by a number of physical and chemical properties. This has led to the classification of RS into four types (Englyst *et al.*, 1992):
    - Physically inaccessible starch (RS_1), such as whole, and partly milled grains, seeds, and legumes;
    - Resistant starch granules (RS_2), such as raw potato, banana, and high amylose corn;
    - Retrograded amylose (RS_3), such as cooked, cooled potato, bread, and cornflakes; and
    - Chemically modified starch (RS_4), which is commercially manufactured.

Trial design

120. Nine articles were identified as eligible (see Appendix 2 for studies excluded) (Tomlin & Read, 1990; Phillips *et al.*, 1995; Cummings *et al.*, 1996; Silvester *et al.*, 1997; Heijnen *et al.*, 1998; Jenkins *et al.*, 1998; Behall *et al.*, 2002; Muir *et al.*, 2004; Vermorel *et al.*, 2004), of which three also reported a comparison with wheat bran (Cummings *et al.*, 1996; Jenkins *et al.*, 1998; Muir *et al.*, 2004). The trial design details have been summarised in Table 19.

121. All trials employed a cross-over design and three had no washout period. Most trials used the Englyst method for the determination of resistant starch (Englyst *et al.*, 1992), but one trial (Jenkins *et al.*, 1998) used another method (Goni *et al.*, 1996) and another two (Phillips *et al.*, 1995; Muir *et al.*, 2004) used an *in vitro* assay developed in their laboratory (Muir & O'Dea, 1993), while one used an AOAC dietary fibre method with and without pre-treatment with dimethyl sulfoxide (Prosky *et al.*, 1994).

122. The duration of interventions was between one week and fourteen. Two of the trials had controlled diets, whereas the rest had *ad libitum* diets, generally low in resistant starch and fibre. The funding sources for all trials, where reported, were Governmental, Commercial or both; only one trial did not report funding sources.

Table 19. Resistant starch and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Control dose (g/d)	Additional intervention dose (g/d)	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
Tomlin, 1990	XO - 1 wk washout	England	Adults; 8M	Ad libitum	Rice krispies	Cornflakes RS3	0.86 RS	10.33 RS	8	1 wk	5	8	NR
Phillips, 1995	XO - no washout	Australia	Adults aged 22-54y; 5M, 6F	Ad libitum low-fibre and resistant starch	Low resistant starch supplemented foods	Mixed RS1, 2 & 3	mean 5.3 (3-8) RS	mean 38.6 (26-50) RS	11	3 wk	7	11	National Health and Medical Research Council of Australia, Australian Research Council
Cummings, 1996	XO - no washout	England	Adults aged 22-43y	Controlled	Digestible starch - slow and rapid			26.8 RS	12	15d	5	12	Ministry of Agriculture, Fisheries and Food, UK
						Banana RS2		30 RS					
						Wheat RS3		17.4 RS					
						Corn RS3		19 RS					
Silvester, 1997	XO - 2 d washout	England	Adults aged 29-48y; 8M	Controlled high meat	No intervention	Potato and corn RS3		40 RS	8	19 d	5	8	Medical Rcsearch Council, UK
Heijnen, 1998	XO - 1 wk washout	Holland	Adults mean age 23; 24M	Ad libitum low-RS	Glucose	Corn RS2		30 RS	24	1 wk	2	22	Unilever Research Laboratorium, The Netherlands
						Corn RS3		30 RS					
Jenkins, 1998	XO - 2 wk washout	Canada	Adults aged 22-53y; 12M. 12F	Ad libitum	Low-fibre control	Corn RS2	2.3 RS	21.5 RS	24	2 wk	4	24	NSERC Canada, and Nacan Products Ltd., Canada
						Corn RS3		27.9 RS					
Behall, 2002	XO - no washout	USA	10 control and 14 hyperinsulinemic men aged 28-58y	10 wk ad libitum followed by 4 wk controlled	Cornstarch	Corn RS2	3 RS	29.4 RS	29	14 wk	5	20	Agricultural Research Service, USA
Muir, 2004	XO - 1 wk washout	Australia	Adults aged 22-67y; 11M, 9F **	Ad libitum low-fibre and RS	Wheat bran	Wheat bran and RS2	29.7 DF; 1.8 RS	29.5 DF; 21.6 RS	20	3 wk	10	10	National Health and Medical Research Council of Australia and Meat and Livestock Australia
Vermorel, 2004	XO - 4wk washout	France	Adults mean age 23y; 10M	Controlled	Dextrose	Corn RS4		99.8 RS	10	13 d	7	11	Roquette Frères company, France
Stewart, 2010	XO – 3 wk washout	USA	Adults, mean age 32y; 12M	Ad libitum	Maltodextrin	Corn RS3	0 TDF	12 TDF	10	2 wk	4	10	National Institutes of Health, USA; Tate and Lyle Inc. USA
						Corn dextrin RS4		12 TDF					
						Tapioca dextrin RS4		12 TDF					
						Corn RS4		12 TDF					

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week, DF, dietary fibre; RS, resistant starch; M, male; F, female.

Risk of bias

123. A summary of the risk of bias assessment has been given in Table 20. All the trials reported being randomised, except the two most recent, which used Latin square allocations. None of the trials reported on how randomisation was achieved or how allocation was concealed. All trials were open, apart from two where only the participants were blind. Only one trial, with the longest duration, reported any missing outcome data, which was 17%.

Table 20. Resistant starch and faecal output trial risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Tomlin	1990	Yes	NR	NR	Open	No missing outcome data	0
Phillips	1995	Yes	NR	NR	Open	No missing outcome data	0
Cummings	1996	Yes	NR	NR	Open	No missing outcome data	0
Silvester	1997	Yes	NR	NR	Open	No missing outcome data	0
Heijnen	1998	Yes	NR	NR	Participants blind only	No missing outcome data	0
Jenkins	1998	Yes	NR	NR	Open	No missing outcome data	0
Behall	2002	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	17
Muir	2004	Yes	NR	NR	Open	No missing outcome data	0
Vermorel	2004	No	-	-	NR	No missing outcome data	0
Stewart	2010	No	-	-	Participants blind only	No missing outcome data	0

NR, not reported.

Results

124. The findings from all trials have been summarised in Table 24. Outcome data, expressed as mean with standard deviation (where extractable), have been given for faecal wet weight, moisture content and intestinal transit time.

125. In the two trials where resistant starch was directly compared with wheat bran, wheat bran had more of an effect on faecal weight than resistant starch at an equivalent dose (Cummings *et al.*, 1996; Jenkins *et al.*, 1998). In another trial resistant starch in conjunction with wheat bran was reported to have an additive effect on faecal weight relative to wheat bran alone, and compared with control; also, while wheat bran reduced transit time compared with control the addition of resistant starch had no further effect (Muir *et al.*, 2004). Overall, resistant starch appeared to have little effect on transit time or faecal moisture content, but increased faecal weight.

126. Seven of the trials had sufficient data to allow synthesis of faecal wet weight data (see Figure 3). For one trial, where 100g/day of chemically modified starch (RS_4) increased faecal weight, the data could not be included as they were given as least square means (i.e. in an analysis of covariance model, they were the group means after having controlled for a covariate) (Vermorel *et al.*, 2004), while another gave no variance data, but observed no effect on faecal weight of 9.5g/day RS_3 (retrograded amylose) (Tomlin & Read, 1990). Another trial reported no effect of 12g/day RS_3 on faecal wet weight (Stewart *et al.*, 2010). The doses of resistant starch employed in the trials that have been included in the syntheses ranged from 17-37g/day (mean 27g/day) (see Table 24). Two trials reported on RS_4 in relation to faecal wet weight; one reported 100g/day modified starch to increase faecal weight (Vermorel *et al.*, 2004), while the other observed no effect on faecal weight of 12g/day of three different corn and tapioca modified starches (Stewart *et al.*, 2010). For cross-over trials with multiple intervention groups, all relevant experimental intervention groups were combined into a single group in order to create a single pair-wise comparison, as recommended by the Cochrane Handbook for systematic reviews of interventions.

127. Six trials reported on RS_2 (resistant starch granules) in relation to faecal wet weight (dose range included 21.5-37g/day; mean 28.3g/day), providing six mean difference measures with a total of 226 data points (see Figure 3). The results of the meta-analysis have been summarised in Table 21. There was no significant evidence of heterogeneity between trials (see Table 21). For all analyses, tests for publication bias (Egger's linear regression test) were not significant.

128. Three trials reported on faecal wet weight in relation to the RS_3 dose range 17.4-32g/day; mean 24.1g/day, providing three mean difference measures with a total of 122 data points (see Figure 4). The results of the meta-analysis have been summarised in Table 22. There was no significant evidence of heterogeneity between trials (see Table 21). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

129. Seven trials reported on all types of RS in relation to faecal wet weight, providing seven mean difference measures from a total of 312 data points (see Figure 5). The results of the meta-analysis have been summarised in Table 22. There was no

significant evidence of heterogeneity between trials (see Table 23). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

130. All meta-analyses gave similar results. The mean difference in faecal weight was highly significant ($p<0.001$) at about 40g/day. There appeared to be no difference in the faecal bulking capacity of the different types of resistant starch (1,2 and 3), which broadly equated to a 1-2g increase in faecal wet weight per 1g resistant starch (see Table 21 and Table 22).

131. It appeared that doses of RS greater than 12g/d were required to produce an effect on faecal wet weight (Tomlin & Read, 1990), with doses ranging from 17-37g/day (mean for all trials 27g/d) having been shown to significantly increase faecal output.

Table 21. Results of meta-analysis for RS2 and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	6	38 (23-53)	4.87 (p<0.001)

[1] I^2 = 0.00% (95% CI 0.00-74.62); p for test of heterogeneity = 0.947
[2] No. of RR estimates included in pooled analysis.

Table 22. Results of meta-analysis for RS3 and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	3	46 (23-68)	3.99 (p<0.001)

[1] I^2 = 0.00% (95% CI 0.00-89.60); p for test of heterogeneity = 0.558
[2] No. of RR estimates included in pooled analysis.

Table 23. Results of meta-analysis for all RS types and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	7	40 (26-54)	5.55 (p<0.001)

[1] I^2 = 0.00% (95% CI 0.00-70.81); p for test of heterogeneity = 0.905
[2] No. of RR estimates included in pooled analysis.

Table 24. Resistant starch and faecal output trial results

Study	Date	Dose (g/d)	RS type #	Duration	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Tomlin	1990	9.5 *	3		196	178	NR	NR			40	43	1 (80% in stool)	No effect on faecal wet weight, frequency or transit time of increasing RS intake by 9.5g
Phillips	1995	33.3±9.9 **	1, 2 & 3	3 wk	138±73	197±123	38±7	54±23						The high RS diet increased faecal wet and dry weight
Cummings	1996	26.8 *	2	15d	110±34	151±36	26±7	35±7	75±2	76±3	53±14	63±15	2	All RS diets and, more so, bran increased wet and dry faecal weight. RS granules (RS2) tended to increase transit time. No difference in faecal wet increase was observed between the different RS2 sources (potato and banana resistant starch granules) and the different RS3 sources (wheat and maize retrograded starch)
		30.0 *	2			161±37		37±7	75±2	76±3	53±14	66±14		
		17.4 *	3			153±36		36±7	75±2	76±3	53±14	50±14		
		19.0 *	3			161±37		35±7	75±2	77±3	53±14	50±14		
Silvester	1997	37.0 *	2	19 d	118±31	153±31	33±10	39±7	71±8	74±6	74±42	67±23	2	RS increased faecal wet weight, but had no effect on intestinal transit time
Heijnen	1998	32 ± 2.9 *	2	1 wk	232±88	277±96	55±14	66±24	75±4	76±3				Both resistant starch supplements increased faecal wet weight in a similar fashion, but had no effect on dry weight or moisture content.
		32 ± 2.5 *	3			301±139		66±19	75±4	77±4				
Jenkins	1998	21.5 ***	2	2 wk	163±108	187±118	NR	NR						All RS diets and, more so, bran increased wet and dry faecal weight.
		27.9 ***	3			182±113		NR						
Behall	2002	29.4 ****	2	14 wk	246±71	269±71	43±15	37±15			34±13	42±14	3	RS had no effect on faecal wet or dry weight but increased transit time
Muir	2004	21.6 ***	2	3 wk	161±67	204±84	41±15	49±18			37±11	38±13	2	RS increased faecal wet and dry weights with no effect on transit time.
Vermorel	2004	99.8	4	13 d	93	131	23	37	77	63				RS increased faecal wet and dry weight and decrease moisture content, but no effect on bowel frequency. At doses above 50g/d increased flatulence was observed. Data analysed as least square means
Stewart	2010	12*****	3	2 wk	143±18	147±19	NR	NR						RS had no effect on faecal wet weight
		12	4			153±26		NR						
		12	4			149±25		NR						
		12	4			136±20		NR						

C, control; I, intervention; wk, week; d, day; h, hour; GLC, gas-liquid chromatography; HPLC, high-performance liquid chromatography; SCFA, short chain fatty acid; RS, resistant starch. I, intervention; C, control. # RS classification into four ty pes (Englyst *et al.*, 1992)

* measured by in vitro assay (Englyst *et al.*, 1992); ** measured by in vitro assay (Muir & O'Dea, 1993); *** measured by in vitro assay (Goni *et al.*, 1996); **** measured by in vitro assay with and without pretreatment with dimethyl sulfoxide (Prosky *et al.*, 1994); ***** measured by in vitro assay (Fu *et al.*, 2008)

Figure 3. Forest plot of resistant starch type 2 and faecal wet weight

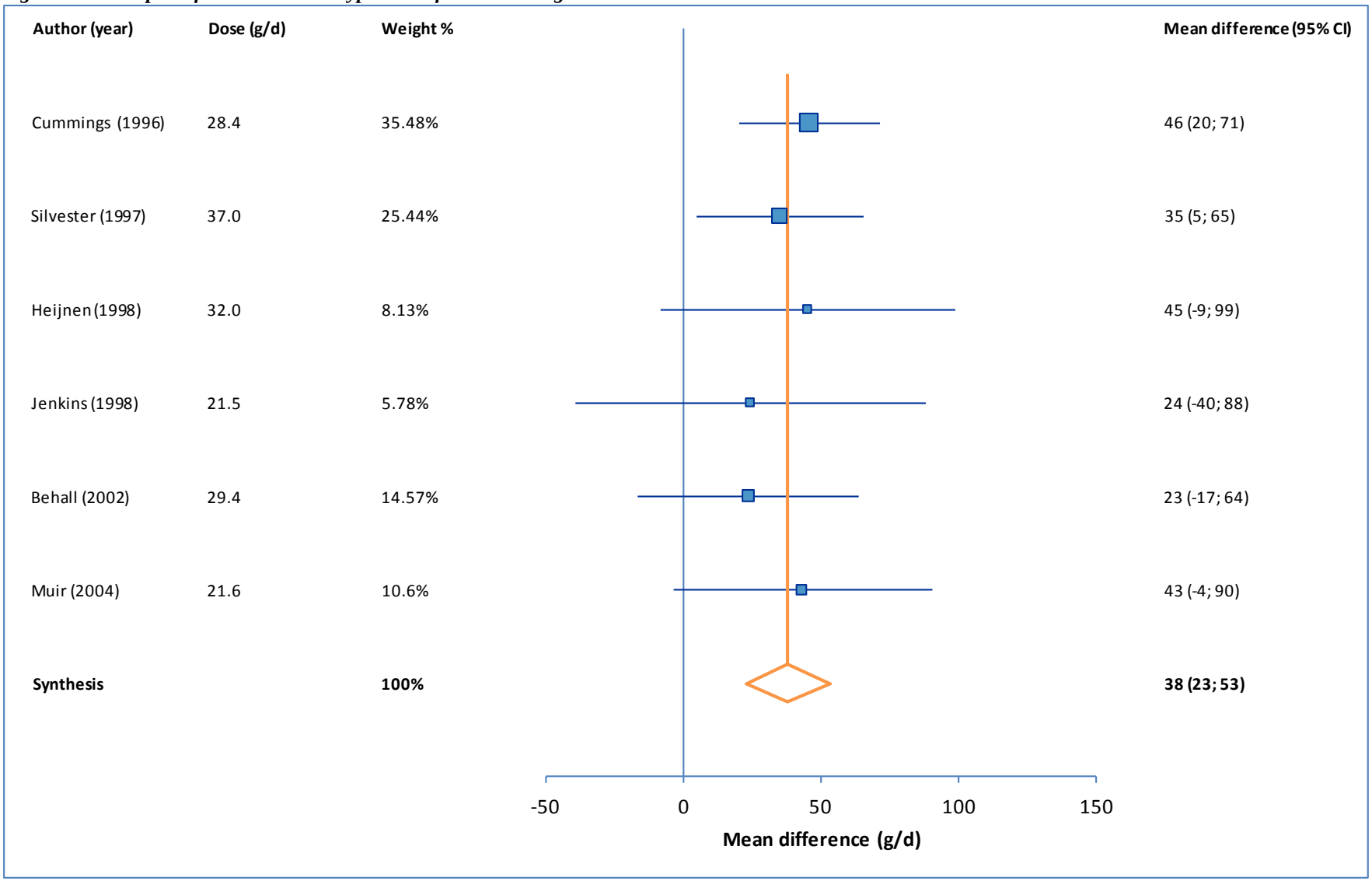


Figure 4. Forest plot of resistant starch type 3 and faecal wet weight

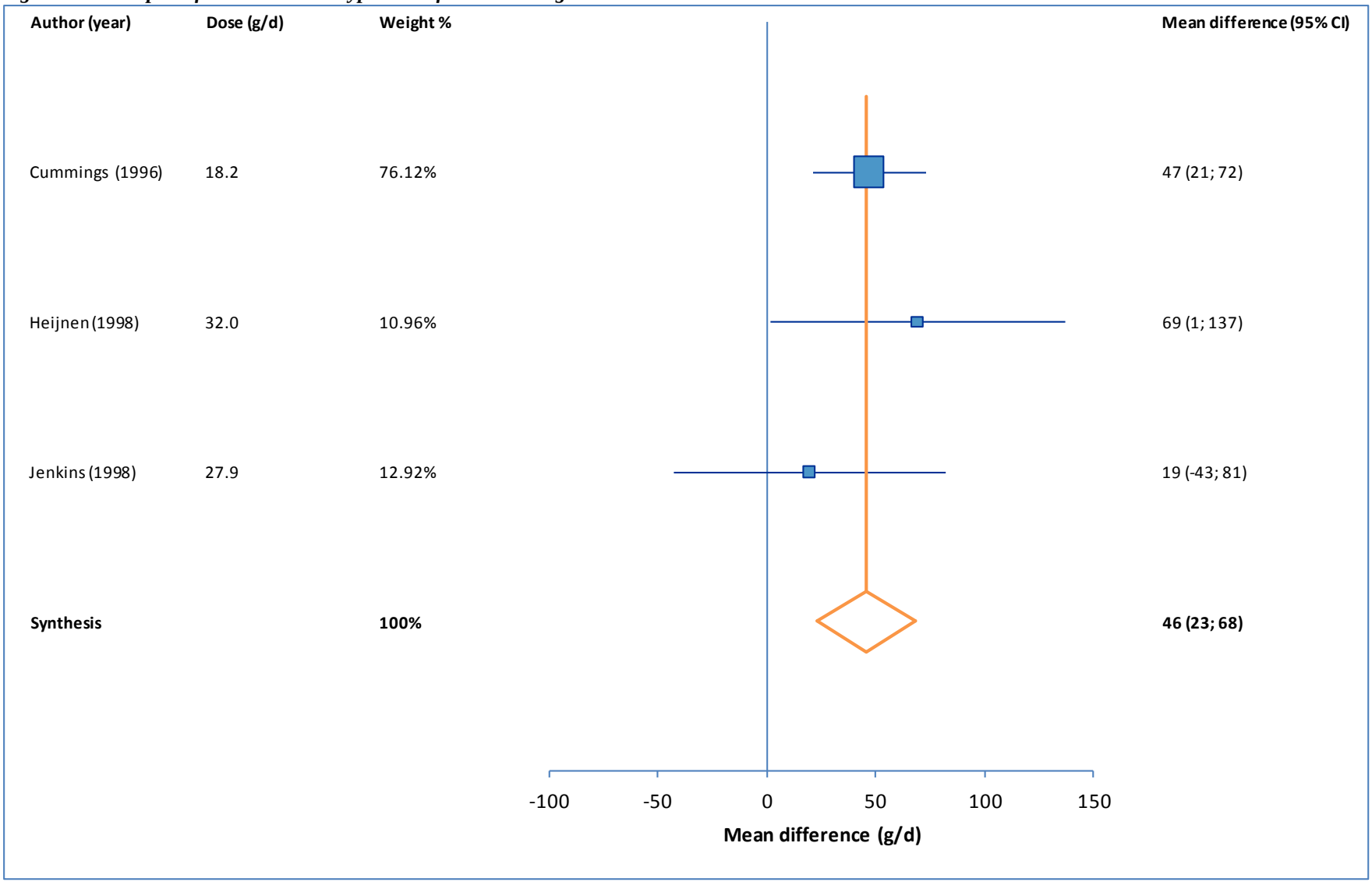
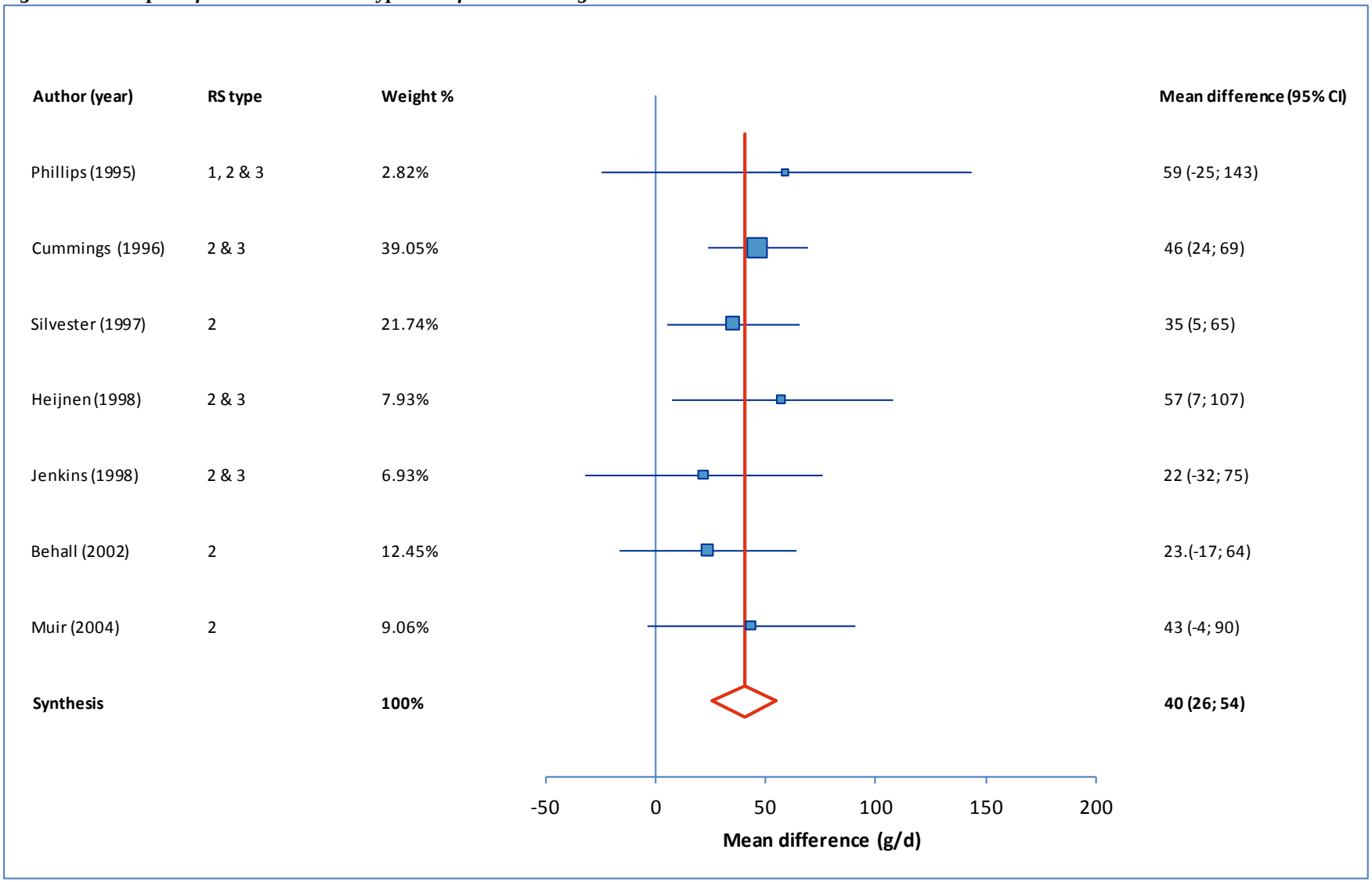


Figure 5. Forest plot of all resistant starch types and faecal wet weight



The effect of non-digestible oligosaccharide, inulin, polyols and polydextrose on faecal output

132. Sixteen articles were identified as eligible, of which one was identified from article citation lists (Ito *et al.*, 1990) (see Appendix 2 for studies excluded). Nine involved interventions with non-digestible oligosaccharides and inulin (Ito *et al.*, 1990; Bouhnik *et al.*, 1996; Alles *et al.*, 1999; van Dokkum *et al.*, 1999; Causey *et al.*, 2000; Den Hond *et al.*, 2000; Tahiri *et al.*, 2001; Swanson *et al.*, 2002; Scholtens *et al.*, 2006b); Five involved interventions with a polyol (Van Es *et al.*, 1986; Ballongue *et al.*, 1997; Sinaud *et al.*, 2002; Gostner *et al.*, 2005; Gostner *et al.*, 2006), of which two reported different aspects of the same trial (Gostner *et al.*, 2005; Gostner *et al.*, 2006); and two involved interventions with polydextrose (Jie *et al.*, 2000; Hengst *et al.*, 2008). One trial was also identified that reported no effect of 10g/day arabinoxylan-oligosaccharides on faecal weight, but as no data were reported it could not be included (Cloetens *et al.*, 2010).

133. The trial design details have been summarised in Table 25. Nine trials employed a cross-over design, of which four have no washout, and six trials employed a parallel design. All the trials were conducted in adults.

134. One trial had a faecal collection period of one day (Hengst *et al.*, 2008). The faecal weight data from this trial have not been used, but the intestine transit time was recorded. One trial only reported on bowel frequency (Swanson *et al.*, 2002).

135. The duration of interventions ranged from one to four weeks and initial sample sizes ranged from six to one hundred and twenty subjects. The funding sources for all trials, where reported, were Commercial, Governmental or both; 53% of trials did not report funding sources.

Table 25 Non-digestible oligosaccharide and inulin, polyols and polydextrose and faecal output trial design

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Additional intervention dose (g/d)	Sample size at start	Duration	Faecal collection period (d)	Number collecting faeces	Funding Source
NDO and inulin												
Ito, 1990	XO - 1 wk washout	Japan	Adults aged 26-48y; 12M	Ad libitum excluding probiotics and NDO	placebo	GOS	2.5, 5 or 10	12	1 wk	3	12	NR
Bouhnik, 1996	P	France	Adults aged 22-39y; 10M, 10F	Ad libitum low fibre and low NDO	sucrose	FOS	12.5	20	12 d	3	20	NR
Alles, 1999	P	Holland	Adults mean age 39y; 22M, 18F	Controlled - low fibre	glucose and lactose	GOS	8.5 or 14.4	41	3 wk	21	40	Netherlands Ministry of Agriculture, Nutreco, Netherlands; ORAFTI, Belgium
van Dokkum, 1999	XO - no washout	Holland	Adults mean age 23y; 12M	Controlled excluded probiotics and NDO	sucrose	Chicory inulin, FOS or GOS	15	12	3 wk	2	12	NR
Causey, 2000	XO - no washout	USA	Adults aged27-49y; 12 M hypercholesterolemic	Controlled	sucrose	Chicory inulin	20	12	3 wk	6	12	National Center for Research Resourceas, USA Sugarland USA
Den Hond, 2000	XO - 1 wk washout	Belgium	Adults aged 20-49y; 1M, 5F with BM<1/d>3/d	Ad libitum excluded probiotics and NDO	sucrose	Chicory inulin	15.0	6	1 wk	5	6	ORAFTI, Belgium
Tahiri, 2001	XO - 3 wk washout	France	Adults aged 54-70; 11F postmenopausal	Ad libitum excluding NDO for first 23 d, than controlled low fibre (12g DF/d) for last 10-12 d	sucrose	FOS	10	14	35 d	3	11	French Miristry of National Education and Scientific Research and Technology
Swanson, 2002	P	USA	Adults mean age 25y; 13M, 18F	Ad libitum excluding probiotics and NDO	sucrose	FOS	3	34	4 wk			NR
Scholtens 2006	XO - 2 wk washout	Holland	Adults aged 18-35y; 6M, 6F	Ad libitum excluding probiotics and NDO	maltodextrin	FOS	25-30	12	2 wk	3	11	NR
Polyol												
Van Esm 1986	XO - 1 wk washout	Holland	Adults aged 19-26y; 4M, 4F	Controlled	sucrose	Lactitol	50	8	8d	4	8	NR
Ballongue, 1997	P	Switzerland	Adults aged 24-31y	Ad libitum	Glucose-lactose 50:50	Lactitol	20	12	4 wk			NR
Sinaud, 2002	XO - no washout	France	Adults, mean age 20.5y; 9M	Controlled low fibre	dextrose	Maltitol or maltitol hydrogenated polysaccharide fraction	100	9	2 wk	10	9	Roquette Frères, France
Gostner, 2005	XO - no washout	Germany	Adults aged 21-54; 12M, 7F	Controlled low -fibre	sucrose	Polyol isomalt	30	20	3 wk	5	19	NR
Polydextrose												
Jie, 2000	P	China	Adults mean age ~30y ; 66M 54F	Controlled	placebo	Polydextrose	4, 8 or 12	120	4 wk	3		Danisco Cultor, USA
Hengst, 2008	P	Germany	Adults aged 19-66y; 8M, 37F	Ad libitum	yoghurt w/o intervention	Polydextrose	8	45	3 wk	1	45	Zott GmbH & co, Germany

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week, M, male; F, female; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; NDO, non-digestible oligosaccharide.

Risk of bias

136. A summary of the risk of bias assessment has been given in Table 26. Four of the trials were non-randomised and only two of the randomised trials reported the method of sequence generation. For the non-digestible oligosaccharide and inulin trials most were blind, although two trials stated the use of placebo, but did not report on blinding. Two of the polyol trials were open, as well as non-randomised.

137. The dropout percentages were generally low with only four trials reporting missing outcome data. Drop-out rates ranged from 2 to 21%. In those that reported drop-outs it seemed unlikely that missing outcome data were related to the intervention.

Table 26. Non-digestible oligosaccharide and inulin, polyols and polydextrose and faecal output trials risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
NDO and inulin							
Ito	1990	No	-	-	Participants blind only	No missing outcome data	0
Bouhnik	1996	Yes	NR	NR	NR	No missing outcome data	0
Alles	1999	No	-	-	NR	Missing outcome data unlikely to be related to outcome	2
van Dokkum	1999	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Causey	2000	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Den Hond	2000	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Tahiri	2001	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	21
Swanson	2002	Yes	Computer generated	Sealed envelopes	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	13
Scholtens	2006	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	8
Polyol							
Van Es	1986	No	-	-	Open	No missing outcome data	0
Ballongue	1997	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Sinaud	2002	No	-	-	Open	No missing outcome data	0
Gostner	2005 & 2006	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	5
Polydextrose							
Jie	2000	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Hengst	2008	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0

NR, not reported; NDO, non-digestible oligosaccharide.

Results

138. The findings from the non-digestible oligosaccharide and inulin intervention trials have been summarised in Table 33 and the polyol and polydextrose trials have been summarised in Table 34. Outcome data, expressed as mean with standard deviation (where extractable), have been given for faecal wet weights, bowel frequency, faecal moisture content and intestinal transit time. The faecal wet weight mean difference values for the polyol and polydextrose trials have been summarised in Table 27.

139. The results from polyol intervention trials were mixed, but most trials reported an increase in faecal weight (see Table 27), which was in the order of a 0.5-1g increase in faecal wet weight per 1g polyol. One of the trials also reported total intestinal transit time in response to a polyol supplementation, but observed no effect (Gostner *et al.*, 2005) (see Table 34).

140. One trial reported faecal weight change in response to polydextrose, showing a dose-response effect on wet and dry weights and bowel frequency (Jie *et al.*, 2000), which was in the order of a 2-3g increase in faecal wet weight per 1g polydextrose. Another trial, which measured total intestinal transit time (faecal weights were determined from a one-day collection, so the data were not used) observed no effect of 8g/d polydextrose (Hengst *et al.*, 2008) (see Table 34).

Table 27. Faecal wet weight mean difference values for polyols and polydextrose

Study	Intervention	Dose * (g/d)	Faecal wet wt mean difference g/d (95% CI)	Control faecal wet wt (g/d±sd)
Van Es, 1986	lactitol	50	54 (20 to 87)	144±38
Sinaud, 2002	maltitol	100	48 (11 to 85)	105±29
	maltitol hydrogenated polysaccharide fraction	100	61 (27 to 95)	
Gostner, 2005	polyol isomalt	30	12 (-13 to 36)	99±38
Jie, 2000	polydextrose	4	9 (1 to 17)	106±15
	polydextrose	8	22 (11 to 33)	
	polydextrose	12	36 (27 to 45)	

* as reported.

141. For non-digestible oligosaccharide and inulin, the individual trials reported little effect on faecal output (see Table 33). Two trials reported increased bowel frequency in response to non-digestible oligosaccharide or inulin supplementation, but two others reported no effect. The degree of polymerisation of the saccharide units in non-digestible oligosaccharides and inulin has been included in Table 33.

142. The data for changes in faecal wet weight in response to non-digestible oligosaccharide and inulin supplementation were synthesised, and analyzed as continuous data. Faecal weight data from trials involving interventions with non-digestible oligosaccharide and inulin doses less than 10g/day were excluded, as these were the lower ranges of dose-response trials and showed no evidence for an effect on faecal wet weight (see Table 33). For cross-over trials with multiple intervention groups, all relevant experimental intervention groups were combined into a single group in order to create a single pair-wise comparison, as recommended by the Cochrane Handbook for systematic reviews of interventions. Eight trials reported on non-digestible oligosaccharide and inulin (dose range included 10-30g/day; mean 15.4g/day) in relation to faecal wet weight, providing eight mean difference measures with a total of 199 data points (see Figure 6). The results of the meta-analysis have been summarised in Table 28. There was no significant evidence of heterogeneity between trials (see Table 28). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

143. The trial with the largest effect size on faecal weight employed a dose of 25-30g/day non-digestible oligosaccharide (Scholtens *et al.*, 2006b). Faecal wet weight data were synthesised by excluding responses to non-digestible oligosaccharide and inulin doses of more than 20g/day. Seven trials reported on non-digestible oligosaccharide and inulin (dose range included 10-20g/day; mean 14.1g/day) in relation to faecal wet weight, providing seven mean difference measures with a total of 177 data points (see Figure 7). The results of the meta-analysis have been summarised in Table 29. There was no significant evidence of heterogeneity between trials (see Table 29). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

144. Six trials reported on fructo-oligosaccharide or inulin, (which contains fructo-oligo- and fructo-poly-saccharides; see degree of polymerisation in Table 33), in the dose range 10-30g/day (mean 16.4g/day) in relation to faecal wet weight, providing six mean difference measures with a total of 136 data points (see Figure 8). The results of the meta-analysis have been summarised in Table 30. There was no significant evidence of heterogeneity between trials (see Table 30). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

145. Five trials reported on fructo-oligosaccharide or inulin in the dose range 10-20g/day (mean 14.6g/day) in relation to faecal wet weight, providing five mean difference measures with a total of 114 data points (see Figure 9). The results of the meta-analysis have been summarised in Table 31. There was no significant evidence of heterogeneity between trials (see Table 31). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

146. Three trials reported on galacto-oligosaccharide in the dose range 10-15g/day (mean 13g/day) in relation to faecal wet weight, providing three mean difference measures with a total of 75 data points (see Figure 10). The results of the meta-analysis have been summarised in Table 32. There was no significant evidence of heterogeneity between trials (see Table 32). For all analyses tests for publication bias (Egger's linear regression test) were not significant.

Table 28. Results of meta-analysis for all non-digestible oligosaccharide and inulin (dose range included

10-30g/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	8	20 (6-35)	2.74(p=0.006)

[1] I^2 = 0.00% (95% CI 0.00-67.58%); p for test of heterogeneity = 0.804
[2] No. of RR estimates included in pooled analysis.

Table 29. Results of meta-analysis for all non-digestible oligosaccharide and inulin (dose range included 10-20g/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	7	18 (3-33)	2.32(p=0.020)

[1] I^2 = 0.00% (95% CI 0.00-70.81%); p for test of heterogeneity = 0.877
[2] No. of RR estimates included in pooled analysis.

Table 30. Results of meta-analysis for fructo-oligosaccharide (dose range 10-30g/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	6	23 (7-40)	2.75 (p=0.006)

[1] I^2 = 0.00% (95% CI 0.00-74.62%); p for test of heterogeneity = 0.648
[2] No. of RR estimates included in pooled analysis.

Table 31. Results of meta-analysis for fructo-oligosaccharide (dose range 10-20g/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	5	20 (3-38)	2.28 (p=0.023)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.699
[2] No. of RR estimates included in pooled analysis.

Table 32. Results of meta-analysis for all galacto- oligosaccharide (dose range included 10-15/day) and faecal wet weight

Model	Pooled mean difference estimate[1]		
	No.[2]	MD g/d (95%CI)	Z (p-value)
Random effect	3	13 (-11-37)	1.05(p=0.292)

[1] I^2 = 0.00% (95% CI 0.00-89.60%); p for test of heterogeneity = 0.845
[2] No. of RR estimates included in pooled analysis.

147. All meta-analyses gave similar results. The mean difference in faecal weight was significant for all non-digestible oligosaccharide and inulin in the dose range 10-30g/day (see Table 28) and 10-20g/day (see Table 29). A separate analysis for fructo-oligosaccharide and inulin showed a significant increase in faecal wet in the dose range 10-30g/day (see Table 30) and for 10-20g/day (see Table 31). Only three trials determined the faecal weight response to galacto-oligosaccharide, with a dose range of 10-15g/day, but the mean difference was not significant. There was no evidence that the degree of polymerisation affected the capacity of non-digestible oligosaccharides and inulin in this regard. Overall, there appeared to be no difference in the faecal bulking capacity of the different types of non-digestible oligosaccharide investigated (galacto-oligosaccharide and fructo-oligosaccharide) or inulin, which broadly equated to a 1-1.5g increase in faecal wet weight per 1g non-digestible

oligosaccharide or inulin. It appeared that doses of non-digestible oligosaccharide and inulin of 10g/day or more were required to produce an effect on faecal wet weight (see Table 33).

Table 33. Non-digestible oligosaccharide and inulin and faecal output trial results

Study	Date	Duration	NDO	DP	Dose (g/d)	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
NDO and inulin																	
Ito	1990	1 wk	GOS	2-6	2.5	151±63	134.4±49	NR	NR								No effect on faecal weight
					5	151±63	151±77		NR								
					10	151±63	162±71		NR								
Bouhnik	1996	12 d	FOS	2-4	12.5	121±60.	134±69	NR	NR								No effect on faecal weight
Alles	1999	3 wk	GOS	2-6	8.5	139±50	127±50		NR	1.1±0.3	0.9±0.1	75.4±4.7	74.0±4.69				No effect on faecal wet or dry weights or bowel frequency
					14.4	139±50	142±67		NR		1.1±0.5		74.3±5.61				
van Dokkum	1999	3 wk	Chicory inulin	2-60	15	129±42	155±76	43±14	44±18			66.8±4.3	70.4±6.2	55.1±18.9	52.5±14.3	1 (80% in stool) and 2	No effect on faecal weights and transit time
			FOS	2-8	15	129±42	108±45		33±13				69.2±4.1		45.3±14.3		
			GOS	2-6	15	129±42	148±42		34±16				71.0±7.9		50.4±20.0		
Causey	2000	3 wk	Chicory inulin	2-60	20	150±54	164±56	NR	NR					32.5±25.3	30.5±16.1	1 (80% in stool)	No effect on faecal weight and transit time.
Den Hond	2000	1 wk	Chicory inulin	11-60	15	91±26	113±53	24±4	28±7	0.6±0.1	0.9±0.3			84.0±2.4	78.0±17.1	3	No effect on faecal weight and transit time, but bowel frequency increased
Tahiri	2001	35 d	FOS	2-4	10.0	83±28	119.±39	19±4	24±5								Increased faecal wet and dry weight
Swanson	2002	4 wk	FOS	NR	3	NR	NR	NR	NR	1.28	1.41						No effect on bowel frequency
Scholtens	2006	2 wk	FOS	2-7	25-30	174±64	225±64.	47±14	52±14	1.2±0.2	1.5±0.2	73.8±3.3	76.1±3.3				Increased bowel frequency and a tendency to increase faecal wet weight

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day wk, week. I, intervention; C, control. BM, bowel motion. FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; NDO, non-digestible oligosaccharide. NR, not reported; DP, degree of polymerisation.

Table 34. Polyols and polydextrose and faecal output trial results

Study	Date	Duration	Intervention	Dose (g/d)	Faecal wet weight C (g/d)	Faecal wet weight I (g/d)	Faecal dry weight C (g/d)	Faecal dry weight I (g/d)	BM/d C	BM/d I	Moisture C (%)	Moisture I (%)	Transit time C (h)	Transit time I (h)	Transit time method	Results
Polyol																
Van Es	1986	8d	lactitol	50	144±38	198±30	NR	NR			75.3±3.6	78.7±2.7				Increased faecal moisture content and tendency to increase faecal weight
Ballongue	1997	4 wk	lactitol	20	NR	NR	NR	NR			78.8±1.6	88.9±1.7				Increased faecal moisture content.
Sinaud	2002	2 wk	maltitol	100	105±29	153±49	25±7	39±13	1.0±0.3	1.1±0.4	76.0±4.6	73.5±6.4				Both increased faecal wet and dry weights without effect on bowel frequency or faecal moisture content
			maltitol hydrogenated polysaccharide fraction	100		166±44		42±12		1.02±0.2		74.6±3.3				
Gostner	2005	3 wk	polyol isomalt	30	99±38	110±39	28±8	24±8	1.1±0.4	1.3±0.4	74.4±5.2	74.1±5.2	54.5±27.0	52.0±19.6	3	No effect on faecal wet and dry weights, transit time or faecal moisture content, although bowel frequency increased.
Polydextrose																
Jie	2000	4 wk	polydextrose	4	106±15	115±17	32±8	34±7	1.1±0.2	1.47±0.3						Faecal weight (wet and dry) and bowel frequency increased in dose-response manner
			polydextrose	8		128±27		32±7		1.74±0.4						
			polydextrose	12		142±18		30±9		1.89±0.3						
Hengst	2008	3 wk	polydextrose	8	*	*	*	*					37.7±14.9	37.2±24.2	3	No effect on transit time

Intestinal transit time methods: 1 (Hinton *et al.*, 1969); 2: (Cummings *et al.*, 1976b); 3: Coloured dyes – 'first appearance' method; h, hour; d, day wk, week. I, intervention; C, control. BM, bowel motion. FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide. Faecal collection period only one day, so data not included.

Figure 6. Forest plot of non-digestible oligosaccharide and inulin (10-30g/d) and faecal wet weight

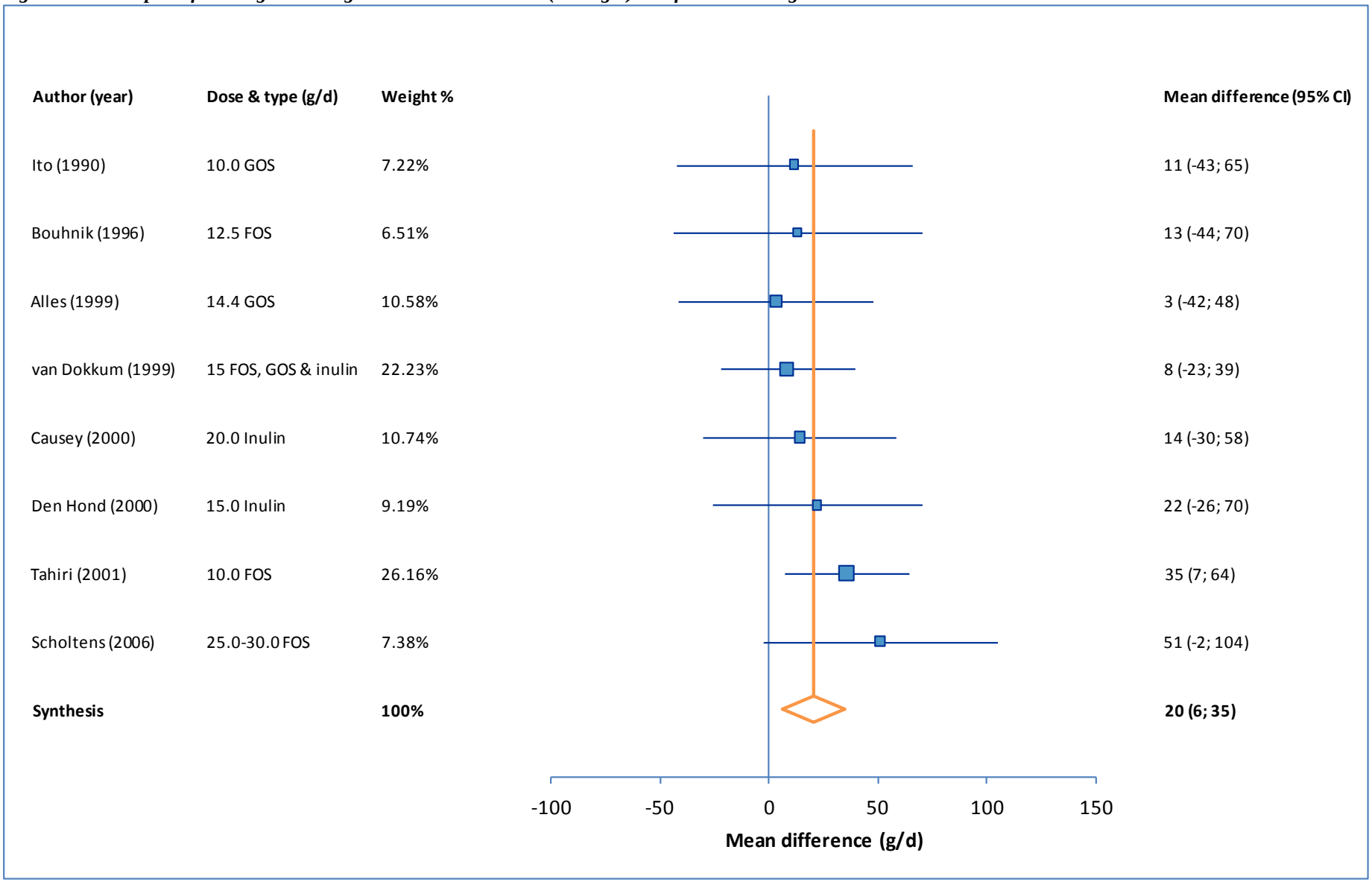


Figure 7. Forest plot of non-digestible oligosaccharide and inulin (10-20g/d) and faecal wet weight

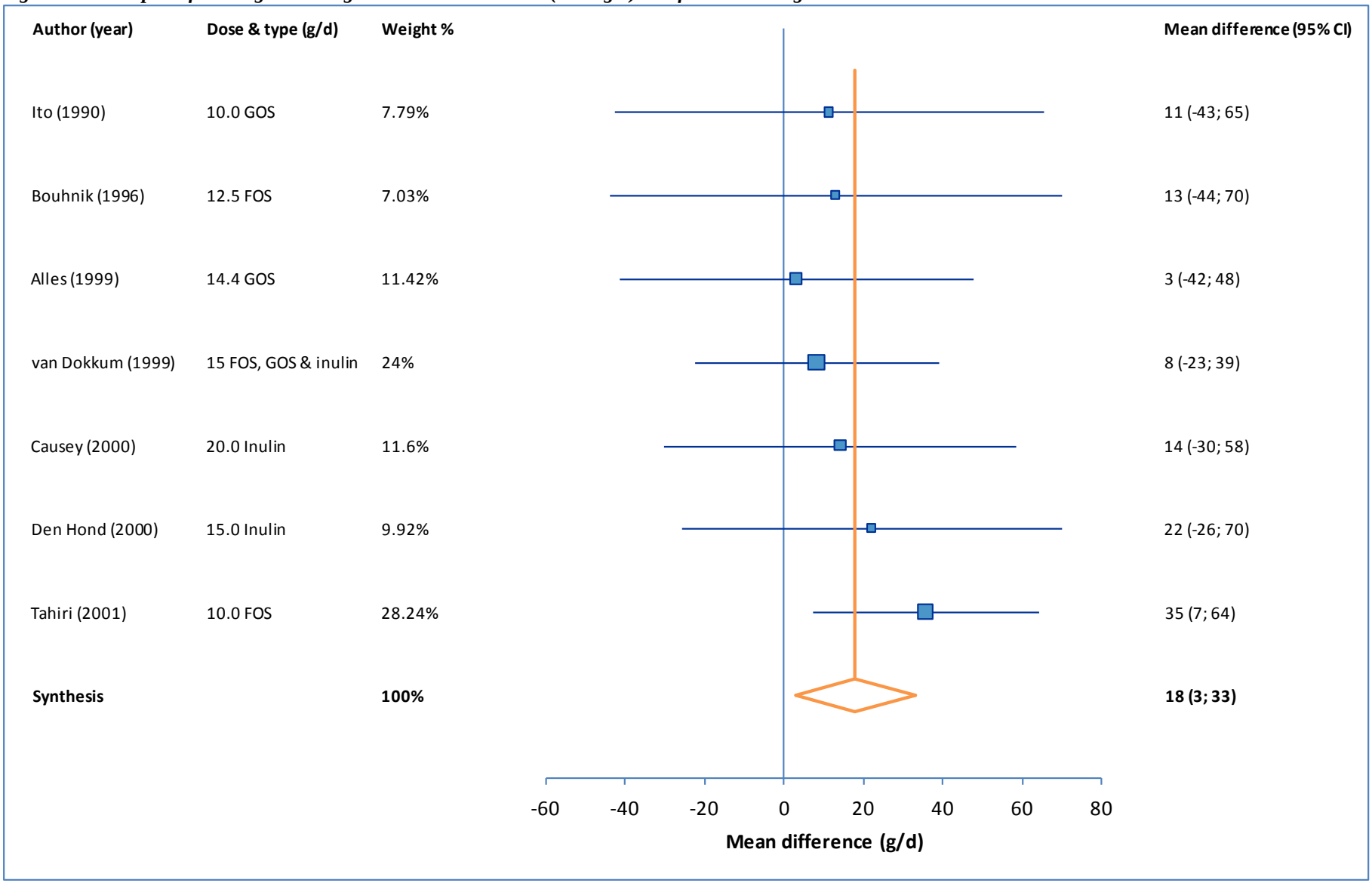


Figure 8. Forest plot of fructo-oligosaccharide (10-30g/d) and faecal wet weight

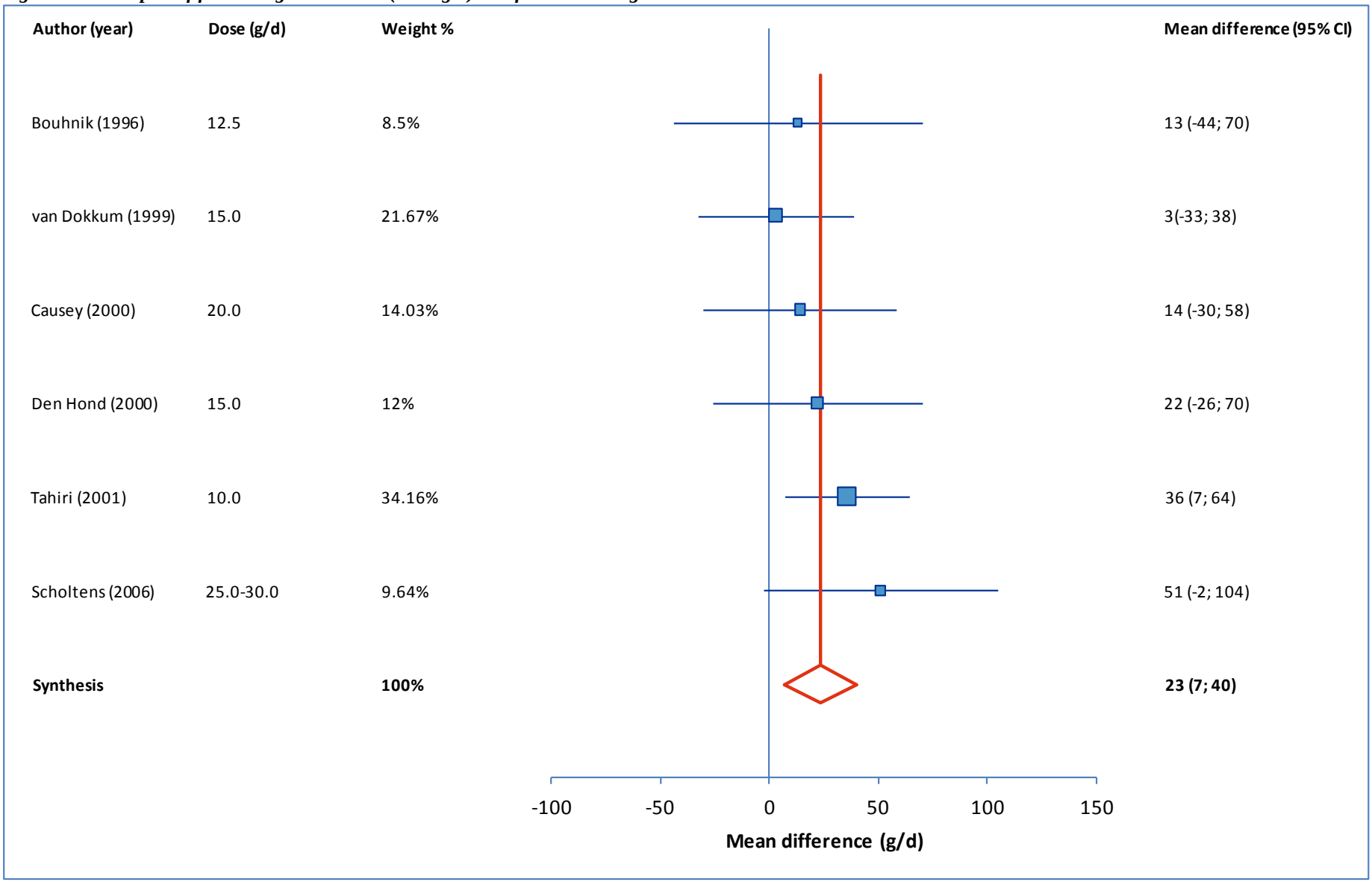


Figure 9. Forest plot of fructo-oligosaccharide (10-20g/d) and faecal wet weight

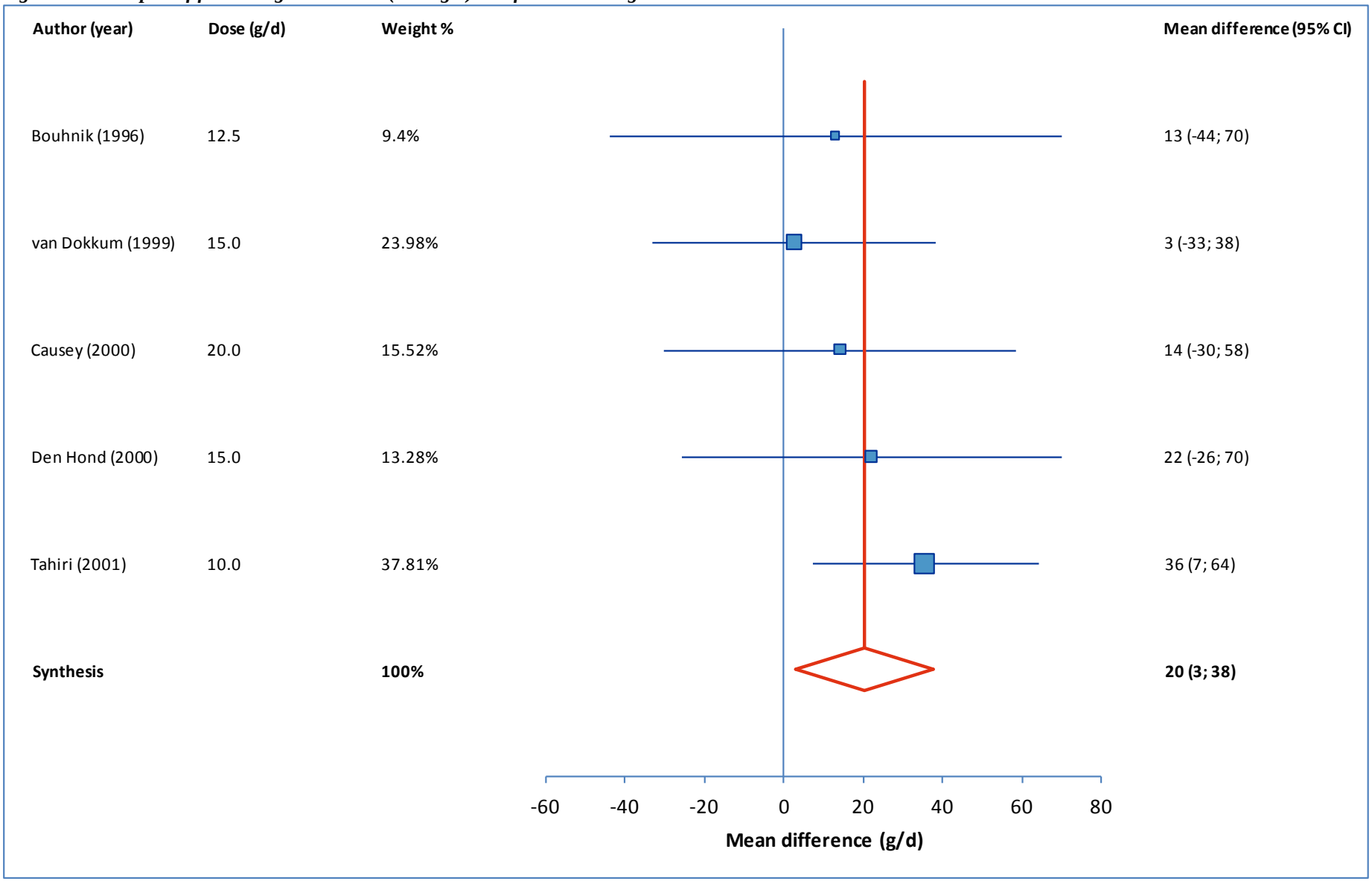
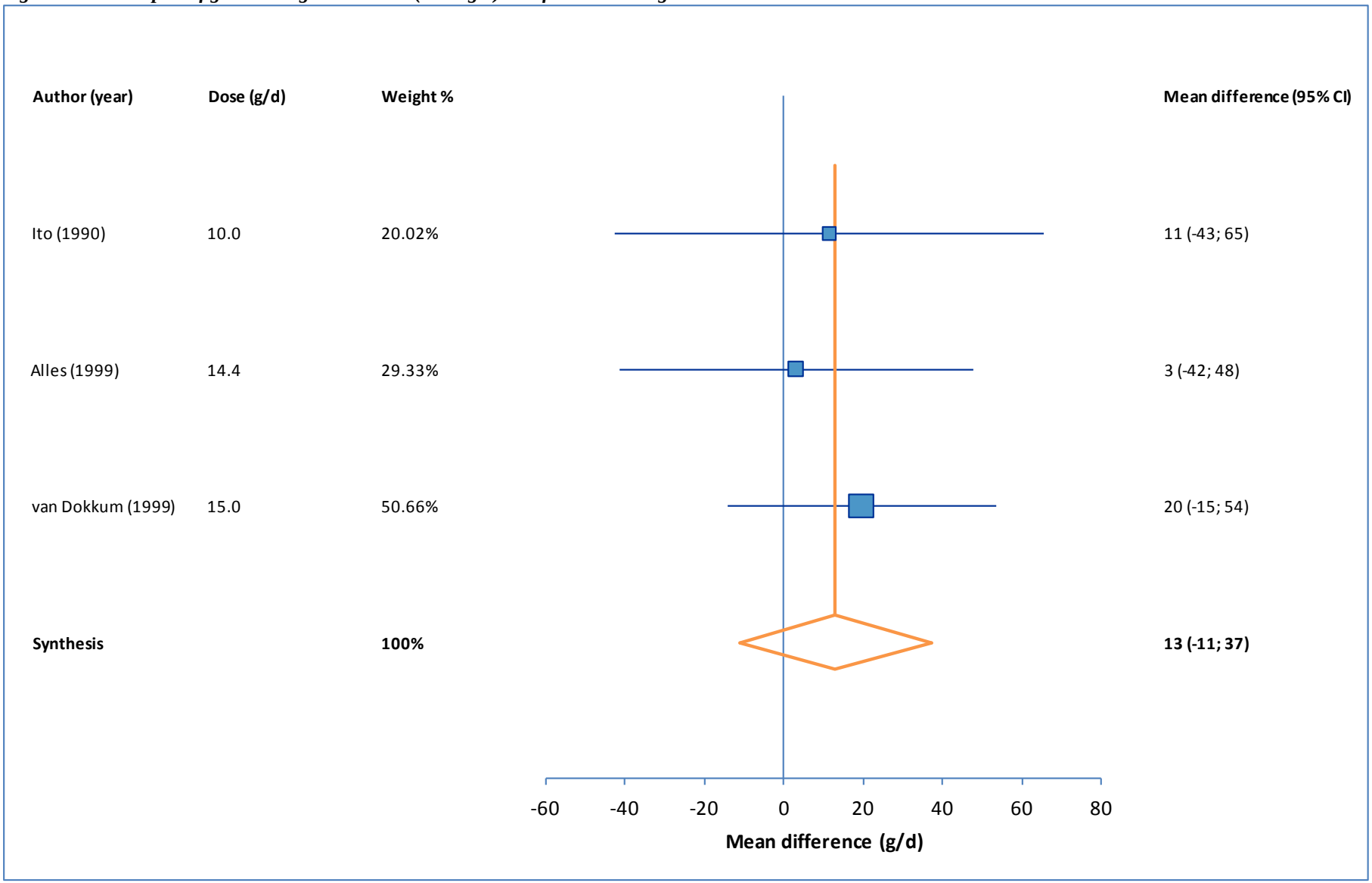


Figure 10. Forest plot of galacto-oligosaccharide (10-15g/d) and faecal wet weight



The effect of non-digestible carbohydrates on faecal bacteria in adults

148. Trials in adults have been considered in this section, while the following section considered trials in infants.

149. In adults, thirty two articles were identified as eligible (see Appendix 2 for studies excluded). There were nineteen articles reporting a non-digestible oligosaccharide or inulin intervention (Ito *et al.*, 1990; Bouhnik *et al.*, 1996; Alles *et al.*, 1999; Bouhnik *et al.*, 1999; Tuohy *et al.*, 2001b; Gopal *et al.*, 2003; Bouhnik *et al.*, 2004; Tannock *et al.*, 2004; Bouhnik *et al.*, 2006; Bouhnik *et al.*, 2007a; Fuller *et al.*, 2007; Kleessen *et al.*, 2007; Calame *et al.*, 2008; Depeint *et al.*, 2008; Vulevic *et al.*, 2008; Cloetens *et al.*, 2010; Costabile *et al.*, 2010; Ramnani *et al.*, 2010; Walton *et al.*, 2010). There were eight articles reporting on dietary fibre or modified starch interventions (Jenkins *et al.*, 1999b; Martensson *et al.*, 2005; Pasman *et al.*, 2006; Smith *et al.*, 2006; Grasten *et al.*, 2007; Calame *et al.*, 2008; Fastinger *et al.*, 2008; Carvalho-Wells *et al.*, 2010). Three articles reported on polyols (Ballongue *et al.*, 1997; Gostner *et al.*, 2006; Finney *et al.*, 2007) and two on polydextrose (Jie *et al.*, 2000; Hengst *et al.*, 2008). One trial reported on polyols, polydextrose and resistant starch type 4(Beards *et al.*, 2010).

150. The trial design details have been summarised in Table 35. Fourteen trials employed a cross-over design, of which three had no washout period. Eighteen trials employed a parallel design.

151. The duration of interventions ranged from one to ten weeks and initial sample sizes ranged from 12-120 subjects. The funding sources for all trials, where reported, were either Governmental or Commercial or both; 13% of trials did not report funding sources.

Table 35 Non-digestible carbohydrates and faecal bacteria trial design -adults

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Intervention dose (g/d)	Sample size at start	Duration	Funding source
NDO and inulin										
Ito, 1990	XO - 1 wk washout	Japan	Adults aged 26-48y; 12M	Ad libitum excluding lactose, milk, fermentation products	placebo	GOS	2.5, 5 or 10	12	1 wk	Study location: Yakult Central Institute for Microbiological Research (Tokyo, Japan)
Bouhnik, 1996	P	France	Adults aged 22-39y; 10M, 10F	Ad libitum low fibre and low NDO	sucrose	FOS	12.5	20	12 d	NR
Alles, 1999	P	Holland	Adults mean age 39y; 22M, 18F	Controlled - low fibre	glucose and lactose	GOS	8.5 or 14.4	41	3 wk	Netherlands Ministry of Agriculture, Dutch Dairy Foundation; Nutreco, Netherlands; AVEBE, Netherlands; ORAFTI, Belgium
Bouhnik, 1999	P	France	Adults aged 18-47y; 18M, 22F	Ad libitum excluding probiotics and NDO	sucrose	FOS	2.5, 5, 10 or 20	40	1 wk	NR
Tuohy, 2001	XO - no washout	England	Adults aged 18-50y; 14M, 17F	Ad libitum excluding probiotics and NDO	biscuit w/o intervention	FOS; partially hydrolysed guar gum	6.6 FOS and 3.4 PHGG	31	3 wk	Novartis, Switzerland
Gopal, 2003	P	New Zealand	Adults aged 20-60y; 18M, 12F	Ad libitum excluding probiotics	milk powder	GOS	2.4	30	4 wk	NR
Bouhnik, 2004	P	France	Adults aged 18-54y;	Ad libitum excluding probiotics and NDO	sucrose, maltodextrin	FOS, Soybean OS, GOS, RS retrograded, long-chain chicory inulin or isomalto OS	10	56	1 wk	Health & Nutrition Group, Belgium
Tannock, 2004	XO - 2 wk washout	New Zealand	Adults; 7M, 8F	Ad libitum	biscuit w/o intervention	GOS or FOS	2.5	15	3 wk	Fonterra, New Zealand
Bouhnik, 2006	P	France	Adults, mean age 29y; 18M, 22F	Ad libitum excluding probiotics and NDO	sucrose, maltodextrin	FOS	2.5, 5, 7.5 or 10	40	1 wk	Health & Nutrition Group, Belgium
Bouhnik, 2007	P	France	Adults aged 20-58y	Ad libitum excluding probiotics and NDO	maltodextrin/sucrose	Chicory inulin	5	39	4 wk	Cosucra, Belgium
Fuller, 2007	XO - no washout	Scotland	Adults aged 25-51y; 3M, 9F	Ad libitum excluding supplements	no intervention	Chicory inulin	10	12	16 d	Food Standards Agency, UK
Kleessen, 2007	P	Germany	Adults mean age 22.4y; 10M, 35F	Ad libitum excluding probiotics and NDO	snack bar w/o intervention	Chicory inulin or Jerusalem artichoke inulin	7.5 first wk then 15	45	3 wk	BMBF InnoRegio BioMeT, Germany
Calame, 2008	P	Holland	Adults, mean age 31y	Ad libitum	water	Chicory inulin	10	16 - 18	4 wk	Kerry Ingredients, UK
Depeint, 2008	XO - 1 wk washout	England	Adults mean age 36.4y; 12M, 18F	Ad libitum excluding probiotics and NDO	sucrose	V-GOS or B-GOS	V-GOS 7g; B-GOS 3.6 or 7g	30	1 wk	Clasado Inc, UK
Vulevic, 2008	XO - 4wk washout	England	Adults aged 64-79y; 16M, 28F	Ad libitum excluding probiotics and NDO	maltodextrin	B-GOS	5.5	44	10 wk	Clasado Inc, UK
Cloetens, 2010	XO - 4wk washout	Belgium	Adults mean age 24y; 6M,14F	Ad libitum excluding probiotics and NDO	maltodextrin	Arabinoxylan-OS	10	20	3 wk	Research Foundation Flanders, Belgium; Katholieke Universiteit Leuven, Belgium;
Costabile, 2010	XO - 3wk washout	England	Adults aged 20-42y; 14M, 18F	Ad libitum excluding probiotics and NDO	maltodextrin	Very long chain globe artichoke inulin	10	32	3 wk	Bayer BioScience, Germany
Ramnani, 2010	P	England	Adults aged 18-50y; 33M, 33F	Ad libitum excluding probiotics and NDO	drink w/o intervention	Jerusalem artichoke inulin	5	66	3 wk	Unilever, The Netherlands
Walton, 2010	XO - 2wk washout	England	Adults aged 18-39y; 13M,20F	Ad libitum excluding probiotics and NDO	coffee w/o intervention	Manno-OS	3 or 5	33	3 wk	Kraft foods, USA

* V-GOS, galacto-oligosaccharides in beta1-4 and beta1-6 linkages; B-GOS, galacto-oligosaccharides mainly in beta1-3 as well as beta1-4 and beta1-6 linkages; FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; OS, oligosaccharide; NDO, non-digestible oligosaccharide; PHGG, partially hydrolysed guar gum. M, male; F, female; d, day; y, year; wk ,week; TDF, total dietary fibre; DF, dietary fibre; RS, resistant starch.

Non-digestible carbohydrates and faecal bacteria trial design -adults

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Intervention dose (g/d)	Sample size at start	Duration	Funding Source
Dietary fibres and RS										
Jenkins, 1999	XO - 2 wk washout	Canada	Adults aged 22-53y; 12M. 12F	Ad libitum	low-fibre control	Wheat bran,	31 TDF - 1.5 RS	24	2 wk	Univeristy-Industry Program of National Sciences Research Council, Canada; Nacan Products, Canada
						RS2 or RS3	30 TDF; 21.5 or 27.9 RS			
Martensson, 2005	P	Sweden	Adults aged 23-71 with mild hypercholesterolaemia; 24M, 32F	Ad libitum excluding probiotic	fermented dairy-based product (600ml)	Fermented oat-based product (600ml)	3 beta glucan; 7.2 DF	62	5 wk	Swedish Farmers Cooperation; Swedish Scientific Research Council; Ceba Foods, Sweden
						Fermented oat based product with microbial beta glucans (600ml)	3.6 beta glucan; 8.4 DF			
Pasman, 2006	P	Holland	Adults aged 20-45y; 48M	Ad libitum excluding probiotics and NDO	maltodextrin	Wheat dextrin RS4	30 or 45 RS	48	4 wk	TNO, The Netherlands; Roquette Frères, France
Smith, 2006	XO - 4 wk washout	Australia	Adults aged 25-64y; 18M	Semi-controlled excluding legumes and fermented products	low-fibre control w/o intervention	legume fibre (lupin kernel)	45.4 TDF	18	4 wk	Grains R & D Corportion, Ausralia; Australian Research Council; Department of Agriculture, Western Australia, Deakin University
Gråsten, 2007	XO - 8 wk washout	Finland	Adults aged 46-68y; 39F	Ad libitum low-fibre diet excluding probiotics	White wheat bread	Whole grain rye bread with incr. fibre content	31.5 TDF	43	8 wk	Technology Development Center, Finland
Calame, 2008	P	Holland	Adults mean age 31y	Ad libitum excluding probiotics and NDO	water	Partially hydrolysed guar gum	5, 10, 20 or 40	51	4wk	Kerry Ingredients, Ireland
						Chicory inulin	10			
Fastinger, 2008	P	USA	Adults mean age 27y; 20M, 19F	Ad libitum low-fibre diet excluding probiotics and NDO	maltodextrin	Corn RS4	7.5, or 15 RS	39	3 wk	Matsutani Chemical Industry Co, Japan
Carvalho-Wells, 2010	XO – 3 wk washout	England	Adults aged 21-51y: 11M, 21F	Ad libitum excluding probiotics, NDO and wholegrain cereals	Refined-grain breakfast cereal	Whole-grain corn breakfast cereal	14.2 TDF	33	3 wk	Cereals Partners Worldwide, UK
Polyol										
Ballongue, 1997	P	Switzerland	Adults aged 24-31y	Ad libitum	glucose/lactose 50:50	Lactitol	20	24	4 wk	NR
Gostner, 2006	XO – 4 wk washout	Germany	Adults aged 21-54; 12M, 7F	Controlled low -fibre	sucrose	Polyol isomalt	30.0	20	3 wk	Suedzucker AG, Germany
Finney, 2007	P	England	Adults aged 18-24y; 39M, 26F	Ad libitum low polyol, excluding probiotics and NDO	sucrose	Lactitol	5 or 10	75	1 wk	Purac Biochem, The Netherlands
Polydextrose										
Jie, 2000	P	China	Adults mean age ~30y ; 66M 54F	Controlled	placebo	polydextrose	4, 8 or 12	120	4 wk	Danisco Cultor, USA
Hengst, 2008	P	Germany	Adults aged 19-66y; 8M, 37F	Ad libitum excluding probiotics and NDO	yoghurt w/o intervention	Polydextrose	8	56	3 wk	Zott GmbH & co, Germany
Mixture										
Beards, 2010	P	England	Adults mean age ~33y ; 13M, 27F	Ad libitum	sucrose	Maltitol	22.8 – 45.6	40	6 wk	Cadbury's, UK
						Maltitol and polydextrose	22.8 – 45.6			
						Maltitol and RS4 - wheat dextrin	22.8 – 45.6			

M, male; F, female; d, day; y, year; wk ,week; TDF, total dietary fibre; DF, dietary fibre; RS, resistant starch.

Risk of bias

152. A summary of the risk of bias assessment has been given in Table 36. Three of the trials did not report whether they were randomised. Only one randomised trial (Calame *et al.*, 2008) reported the method of sequence generation. No trial gave any indication of how allocation was concealed. Twenty three of the trials reported participants and personnel to be blind, one reported participants blind only, three were open, and eight unclear as to the nature of blinding if any.

153. The dropout percentages were generally low with eigthteen trials reporting no missing outcome data. Of the fifteen trials reporting missing outcome data, drop-out rates ranged from 2 to 20%. In those that reported drop-outs it either seemed unlikely missing outcome data were related to the intervention or missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Table 36. Non-digestible carbohydrates and faecal bacteria trial risk of bias assessment -adults

Study	Time	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Ito	1990	NR		-	Participants blind only	No missing outcome data	0
Bouhnik	1996	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Alles	1999	NR	-	-	NR	Missing outcome data unlikely to be related to outcome	2
Bouhnik	1999	Yes	NR	NR	NR	No missing outcome data	0
Tuohy	2001	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Gopal	2003	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	3
Bouhnik	2004	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Tannock	2004	NR	-	-	Participants and personnel blind	No missing outcome data	0
Bouhnik	2006	Yes	NR	NR	NR	No missing outcome data	0
Bouhnik	2007	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Fuller	2007	Yes	No	No	Open	Missing outcome data unlikely to be related to outcome	8
Kleessen	2007	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Calame	2008	Yes	Yes	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	6
Depeint	2008	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Vulevic	2008	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	7
Cloetens	2010	Yes	NR	NR	NR	no missing outcome data	0
Costabile	2010	Yes	NR	NR	participants and personnel blind	Missing outcome data unlikely to be related to outcome	3
Ramnani	2010	Yes	NR	NR	participants and personnel blind	no missing outcome data	0
Walton	2010	Yes	NR	NR	participants and personnel blind	Missing outcome data unlikely to be related to outcome	6
Jenkins	1999	Yes	NR	NR	Open	No missing outcome data	0
Martensson	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	10
Pasman	2006	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	10
Smith	2006	Yes	NR	NR	Participants blind only	No missing outcome data	0
Gråsten	2007	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	9
Calame	2008	Yes	Yes	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	6
Fastinger	2008	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	3
Carvalho-Wells	2010	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	3

NR, not reported.

Non-digestible carbohydrates and faecal bacteria trial risk of bias assessment -adults

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Ballongue	1997	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Gostner	2006	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	5
Finney	2007	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Jie	2000	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Hengst	2008	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	20
Beards	2010	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0

NR, not reported.

Results

154. The findings from all trials have been summarised in Table 37 and Table 38. The most consistent finding with regard to non-digestible oligosaccharide and inulin interventions was an increase in faecal content of *Bifidobacterium* spp. Several of the trials, however, observed no effect or only a change from baseline,but not relative to control. Two trials reported that volunteers with the lowest initial *Bifidobacterium* spp population levels produced the largest increase in response to non-digestible oligosaccharide and *visa versa* (Tuohy *et al.*, 2001b; Bouhnik *et al.*, 2004). The duration of non-digestible oligosaccharide or inulin supplementation affected the observed increase in faecal content of *Bifidobacterium* spp in two trials, which progressively increased over 3 weeks (Kleessen *et al.*, 2007) and ten weeks (Vulevic *et al.*, 2008). Although, in trials of a duration of one week to 16 days (Ito *et al.*, 1990; Bouhnik *et al.*, 1999; Bouhnik *et al.*, 2004; Bouhnik *et al.*, 2006; Fuller *et al.*, 2007; Depeint *et al.*, 2008), all, except one (Bouhnik *et al.*, 2006), reported that non-digestible oligosaccharide supplementation increased faecal *Bifidobacterium* spp content.

155. The degree of polymerisation of the saccharide units in the non-digestible oligosaccharides and inulin has been included in Table 37. Six trials investigated the effect of fructo-oligosaccharide on faecal bacteria content. At doses of 10g/day or more fructo-oligosaccharide generally increased faecal *Bifidobacterium* spp. content relative to control. Seven trials investigated the effect of galacto-oligosaccharide on faecal bacteria content. At doses of 10g/day or more galacto-oligosaccharide generally increased faecal *Bifidobacterium* spp. content relative to control.

156. Eight trials investigated the effect of inulin (various sources), on faecal bacteria content. At doses of 5-10g/day or more inulin generally increased faecal *Bifidobacterium* spp. content relative to control; however, the results were more mixed than for fructo-oligosaccharide and galacto-oligosaccharide, with three trials reporting no effect of chicory inulin at doses of 5-10g/day, one of which used long chain chicory inulin containing no oligosaccharides (Bouhnik *et al.*, 2004). Two other trials reported that chicory inulin at doses of 5-10g/day increased faecal *Bifidobacterium* spp. content relative to control, one of which reported inulin derived from Jerusalem artichoke and chicory to be equivalent in this regard (Kleessen *et al.*, 2007). Another trial reported that very long chain inulin derived from globe artichoke was effective in increasing faecal *Bifidobacterium* spp. content relative to control (Costabile *et al.*, 2010). It was unclear if the degree of polymerisation affected the capacity of non-digestible oligosaccharides and inulin to increase faecal *Bifidobacterium* spp. content.

157. For the dietary fibre and resistant starch intervention trials (see Table 38), there

appeared to be little overall impact on faecal bacteria content, although total excretion would be expected to increase with increased faecal output. Three trials reported effects on faecal bacteria content however. Legume fibre and partially hydrolysed guar gum were reported to increase the faecal content of *Bifidobacterium* spp. in two trials (Smith *et al.*, 2006; Calame *et al.*, 2008), while whole grain corn breakfast cereal consumption also increased the faecal content of *Bifidobacterium* spp (Carvalho-Wells *et al.*, 2010).

158. The polyol intervention trials generally reported increased faecal *Bifidobacterium* spp, in response to supplementation and two reported a corresponding reduction in faecal *Bacteriode* concentration.

159. One trial reported increased faecal *Bifidobacterium* spp. and reduced faecal *Bacteriodes* in response to supplementation with polydextrose (Jie *et al.*, 2000); however, another trial reported no effect of polydextrose on the faecal content of *Lactobacillus acidophilus*, *Bifidobacterium lactis* and *Eubacterium* spp (Hengst *et al.*, 2008).

160. One trial supplemented subjects with increasing doses (22.8-45.6 g/day) over six weeks of either the polyol maltitol, maltitol and polydextrose or maltitol and RS4 (a modified dextrin) (Beards *et al.*, 2010). The data, however, were not analysed in comparison to the control group values, but as an increase from baseline values. There appeared to be no evidence of an effect on faecal bacteria content in comparison to control.

Table 37. Non-digestible oligosaccharide and inulin and faecal bacteria trial results -adults

Study	Time	Intervention	Degree of polymerisation	Dose (g/d)	Flora unit of measure	Bif C	Bif. I	Microbiological method	Bacteria investigated	Results
Ito, 1990	1 wk	GOS	2-6	2.5	log 10 cells /g faeces wet wt	9.8±0.2	9.8±0.2	cultured on selective media	Total bacteria, Bif, Bact, Entero, Lact, Enterococci	The highest dose of GOS increased faecal Bif content, with a linear correlation (r=0.42) at all doses. There was also an increase in faecal Lact content with GOS administration. There was no effect on the other faecal bacteria investigated
				5			9.9±0.3			
				10			10.1±0.3			
Bouhnik, 1996	12 d	FOS	2-4	12.5	log 10 cfu/g faeces wet wt	8.4±1.3	9.1±0.9	cultured on selective media	Total anaerobes, Bif	FOS increased faecal Bif counts, but had no effect on total anaerobes
Alles, 1999	3 wk	GOS	2-6	8.5	log 10 cfu/g faeces wet wt	9.8±0.4	9.7±0.4	cultured on selective media	Total anaerobe and aerobe, Bif, Lact, E. coli, Clost	There was no effect of GOS on any of the faecal bacteria investigated.The number of Bif increased from baseline after both placebo and trans-galacto-oligosaccharides ingestion
				14.4			9.6±0.4			
Bouhnik, 1999	1 wk	FOS	2-4	2.5	log 10 cfu/g faeces wet wt	8.3±3.0	8.2±3.0	cultured on selective media	Total anaerobe, Bif	FOS increased faecal Bif content at 10 and 20g/d relative to control. There was a correlation between the dose of ingested FOS and the faecal Bif counts (r = 0.53). No effect on faecal total anaerobe content
				5			9.1±1.2			
				10			9.5±0.9			
				20			9.5±1.7			
Tuohy, 2001	3 wk	FOS; partially hydrolysed guar gum	NR	6.6 g FOS/d and 3.4gPHGG /	log 10 cells/g faeces wet wt	9.2±0.5	9.6±0.3	FISH employing 16S rRNA-targeted probes	Total, Bact, Bif, Clost, Lact.	FOS and partially hydrolyzed guar gum increased Bif faecal content and had no effect on other bacterial populations investigated. Those volunteers showing the lowest initial Bif population levels gave the largest increase on ingestion of the experimental biscuits and visa versa.
Gopal, 2003	4 wk	GOS	2-3 (4 traces)	2.4	log 10 /g faeces wet wt	8.7±0.2	9.4±0.2	cultured on selective media	Bif, Lact, Entero,Sstreptococci, Clost, Bact, total anaerobe	GOS increased the faecal Bif and Lact without effect on the other bacteria investigated
Bouhnik, 2004	1 wk	FOS	2-4	10	log 10 cfu/g faeces wet wt	7.9±1.7	9.7±0.6	cultured on selective media	Total anaerobe, Bif, Lact, Bact, Entero	FOS, GOS and soybean OS increased faecal Bif content, but inulin and isomalto OS showed no effect. There was no effect on faecal count of total anaerobes, Lact, Bact or Entero. In a follow-up dose-response study, using those carbohydrates shown to increase Bif, there was no difference in faecal Bif content in response to doses 2.5, 5, 7.5 or 10g/d over one week. A low baseline Bif count was significantly associated with the Bif response to treatment
		Soybean OS	NR	10			9.8±1.2			
		GOS	NR	10			10.1±0.3			
		Chicory inulin	NR	10			7.7±2.1			
		Isomalto OS	NR	10			8.7±1.2			
Tannock, 2004	3 wk	GOS or FOS	NR	2.5	NR	NR	NR	cultured on selective media, DGGE and FISH	Bif, Lact, Entero by culture; Bif by DGGE; B. adolescentis and Colinsella aerofaciens by FISH	No effect of non-digestible oligosaccharide on bacterial species examined
Bouhnik, 2006	1 wk	FOS	2-4	2.5	log 10 cfu/g faeces wet wt	9.6±0.6	9.4±2.0	cultured on selective media	Total anaerobes, Bif, Bact, Entero, Lact,	No effect of FOS on faecal bacteria content investigated as compared with control, although change from baseline data showed an increase in Bif content in response to all doses of FOS.
				5			10.7±0.6			
				7.5			9.9±1.0			
				10			10.2±1.7			

I, intervention; C, control; Cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values; NR, not reported.

Non-digestible oligosaccharide and inulin and faecal bacteria trial results adults

Study	Duration	Intervention	Degree of polymerisation	Dose (g/d)	Flora unit of measure	Bif C	Bif. I	Microbiological method	Bacteria investigated	Results
Bouhnik, 2007	4 wk	Chicory inulin	2-60	5	log 10 cfu/g faeces wet wt	8.6±1.3	9.0±0.4	Cultured on selective media	Total anaerobes, Bif, Bact, Entero, Lact,	No effect of inulin on faecal bacteria content investigated as compared with control; increase in Bif from baseline for intervention only, while total anaerobes and Bact increased from baseline in both placebo and intervention groups. Lact decreased in the placebo group.
Fuller, 2007	16 d	Chicory inulin	2-60	10	% Bif 16S rRNA genes	4.2	1.1	Quantitative real-time PCR	Bif	Inulin increased the faecal content of Bif.
Kleessen, 2007	3 wk	Chicory inulin	24% < 5; 46% 5–12; 30% > 12	7.5 - 15	log 10 cfu/g faeces wet wt	8.6±0.5	9.6±0.4	Cultured on selective media, FISH with species- and group-specific oligonucleotide probes	Total bacteria, Atopobium group, Bacteroides and Prevotella, Bif, Clostridium histolyticum group & C. lituseburense group, C. coccoides/Eubacterium rectale cluster, Faecalibacterium prausnitzii, Lactobacillus, Enterococcus group, Enterobacteriaceae and C. perfringens	Both inulins increased faecal content of Bif, which became more so during the 3 weeks of the trial. In 3rd week, bacteriodes/prevotella. were decreased. Clostridium coccoides/Eubacterium rectale cluster were decreased compared to baseline. There was no effect on the other bacteria investigated.
		Jerusalem artichoke inulin	40% < 5; 49% 5–12; 11% > 12	7.5 - 15			9.7±0.5			
Calame, 2008	4 wk	Chicory inulin	mean 9	10	log 10 cells/g faeces wet wt	8.5±1.2	8.7±1.1	Quantitative real-time PCR	Bif, Bact, Lact, enterocicci, C. difficile	Inulin had no effect on any of the faecal bacteria investigated relative to control
Depeint, 2008	1 wk	V-GOS	NR	7	Bacterial proportions of microflora	5.0±1.5	6.0±1.1	FISH employing gp-sepcific 16S rRNA-targeted probes	Total bacteria, Bif, Clostridium perfringens–histolyticum subgroup, Bacteroides-Prevotella, Lactobacillus-Enterococcus spp	Both GOS increased faecal Bif content relative to control, but had no effect on the other bacteria investigated. B-GOS appeared to increase faecal Bif more than V-GOS.
		B-GOS	2-5	3.6 7		4.0±1.8	5.4±1.1 6.7±1.2			
Vulevic, 2008	10 wk	B-GOS	2-5	5.5	log 10 cells/g faeces wet wt	9.3±0.3	10.0±0.4	FISH employing gp-sepcific 16S rRNA-targeted probes	Total bacteria, Bif, Bact, Lactobacillus-Enterococcus spp., the Clostridium coccoides–Eubacterium rectale group, the Clostridium histolyticum group, E. coli, and Desulfovibrio spp.	GOS increased the faecal content of Bif spp., Lactobacillus-Enterococcus spp., Clostridium coccoides–Eubacterium rectale and dcreased the faecal content of Bacteroides spp., Clostridium histolyticum group, Escherichia coli and Desulfovibrio spp. compared with placebo.
Cloetens, 2010	3 wk	Arabinoxylan -OS	mean 6	10	log 10 cells/g faeces dry wt	8.2*	8.2*	Quantitative real-time PCR	Total bacteria, Bif, Bact, Lactobacilli, Roseburia–Eubacterium rectale group, Enterobacteria	Arabinoxylan-OS had no effect on the faecal bacteria investigated relative to control.
Costabile, 2010	3 wk	Globe artichoke inulin	mean >55	10	log 10 cells/g faeces wet wt	9.2±0.3	9.7±0.2	FISH employing gp-sepcific 16S rRNA-targeted probes	Total bacteria, Bif, Bact, Lactobacilli-enterococcus, Atopobium, E. coli, Eubacterium rectal-Clostridium coccoides, E. rectal-Roseburia, Ruminococcus, C. lituseburense, C. histolyticum, Clostridium cluster I, II, XVI	Inulin increased Bif, Lactobacilli-enterococcus and Atopobium and decreased Bacteroides-Prevotella faecal content relative to control.
Ramnani, 2010	3 wk	Jerusalem artichoke inulin	NR	5	log 10 cells/g faeces wet wt	9.3±0.4	10.0±0.2	FISH employing gp-sepcific 16S rRNA-targeted probes	Total bacteria, Bif, Bact, Lactobacilli-enterococcus, Clostridium histolyticum, Eubacterium rectal-Clostridium coccoides Atopobium, Faecalibacterium prausnitzii, Propionibacterium	Inulin in both fruit and vegetable preparations increased faecal Bif and Lact content relative to control.
				5			9.8±0.2			
Walton, 2010	3 wk	Manno-OS	NR	3 or 5	log 10 cells/g faeces wet wt	NR	NR	FISH employing gp-sepcific 16S rRNA-targeted probes	Total bacteria, Bif, Bact, Lactobacilli-enterococcus, Clostridium histolyticum, Eubacterium rectal Atopobium, E.coli	Coffee-derived manno-OS at 3g/day, but not 5g/day, increased faecal Bif content relative to control

I, intervention; C, control; Cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values. NR, not reported. V-GOS, galacto-oligosaccharides in beta1-4 and beta1-6 linkages; B-GOS, galacto-oligosaccharides mainly in beta1-3 as well as beta1-4 and beta1-6 linkages

Table 38. Dietary fibres, resistant starch, polyols and polydextrose and faecal bacteria trial results -adults

Study	Date	Intervention	Intervention dose (g/d)	Flora unit of measure	Bif C	Bif. I	Microbiological method	Bacteria investigated	Results
Dietary fibres and RS									
Jenkins, 1999	2 wk	Wheat bran	31 TDF	log 10 cfu/g faeces wet wt	9.0±1.1	9.0±1.5	cultured on selective media	Total anaerobes and aerobes, Bif, Bact, Fusobacteria	Neither wheat bran nor RS affected the faecal content of bacteria counted
		RS2	21.5			8.3±1.5			
		RS3	27.9			8.6±±2.2			
Bouhnik, 2004	1 wk	RS3	10	log 10 cfu/g faeces wet wt	7.9±1.7	9.4±1.4	cultured on selective media	Total anaerobe, Bif	A non-signifcant trend for RS to increase Bif. No effect on total anaerobe counts.
Martensson, 2005	5 wk	Oat beta-glucans	3	log 10 cells/g faeces wet wt	9.1 *	9.2*	FISH	Total bacteria, Bif	Increased faecal Bif content in response to fermented oat based product with microbial beta glucans, but not with oat beta glucans alone. No effect on total faecal bacteria content
		Oat and microbial beta glucans	3.6			9.4*			
Pasman, 2006	4 wk	Wheat dextrin RS4	30 or 45	log 10 cfu/g faeces wet wt	NR	NR	cultured on selective media	Total anaerobes, Bif, Bact, Lact, Entero, Clost, Enterococci	No effect of modified starch relative to control on faecal bacteria investigated
Smith, 2006	4 wk	legume fibre (lupin kernel)	45.4 TDF	log 10 cells/g faeces dry wt	8.9±0.6	9.2 ±1.5	FISH employing gp-sepcific 16S rRNA-targeted probes	Total, Bif, Bact, prevotella, Clostridium coccoidess-Eubacterium reactale gp, E coli, Clostridium lituseburense and histolyticum gps, Lactobacillus-Enterococci, C. ramosum, spiroforme and cocleatum	Legume fibre increased faecal content of Bif and decreased the Clostridia group (C. Ramosum, C. spiroforme & C. cocleatum). There was a trend (p=0.053) for Bacteriodes-Prevotella gp bacteria content to decrease. There was no effect on other bacteria populations investigated.
Gråsten, 2007	8 wk	Whole grain rye bread	31.5 TDF	log 10 cfu/g faeces wet wt	8.0±1.4	8.2±0.9	Cultured on selective media	Total anaerobes and aerobes, Bif, Lact, Entero	No effect of wholegrain rye bread on faecal bacterial
Calame, 2008	4 wk	Partially hydrolysed guar gum	5	log 10 cells/g faeces wet wt	8.5±1.2	7.8±0.9	Quantitative real-time PCR	Bif, Bact, Lact, enterocicci, C. difficile	Guar gum doses of 10g or more tended to increase Bif to a similar extent compared with control, but data analysed as base-line comparisons. In comparison to control, there was no effect of guar gum reported for any of the faecal bacteria investigated.
			10			9.1±1.2			
			20			8.9±1.1			
			40			9.1±1.4			
Fastinger, 2008	3 wk	Corn RS4	7.5 RS	log 10 cfu/g faeces dry wt	9.6	9.6	Quantitative real-time PCR +	Bif, Lact, Clostridium perfringens	No effect of modified starch on investigated faecal bacteria.
		Corn RS4	15 RS			10.0			
Carvahlo-Wells, 2010	3 wk	Wholegrain corn	14.2 TDF	log 10 cells/g faeces wet wt	9.6±0.3	9.8±0.3	FISH employing gp-sepcific 16S rRNA-targeted probes	Total, Bif, Lact, enterocicci Bact, Clostridia, Eubacterium reactale gp, Atopobium	Wholegrain corn breaskfat cereal consumption increased faecal Bif content. No effect on other faecal bacteria.

RS, resistant starch; I, intervention; C, control; Cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values.

Dietary fibres, resistant starch, polyols and polydextrose and faecal bacteria trial results -adults

Study	Time	Intervention	Dose (g/d)	Flora unit of measure	Bif C	Bif. I	Microbiol method	Bacteria investigated	Results
Polyol									
Ballongue, 1997	4 wk	Lactitol	20	log units	8.4±0.2	8.9±0.3	cultured on selective media	Bif, Bact, Clost, Lact, Coliforms, Eubacterium, Streptococcus	Lactitol increased faecal Bif ,Lact and Streptococcus bacterial counts and decreased putrifactive (bacteriode, clostridium, coliform and eubacterium) bacterial counts.
Gostner, 2006	3 wk	Polyol isomalt	30	counts x 10^9/g faeces wet wt	9.3±3.7	12.0±6.5	cultured on selective media, FISH with species- and group-specific oligonucleotide probes	Total microflora, Atopobium group, Bacteroides and Prevotella, Bif, Clostridium histolyticum,group, Clostridium lituseburense group, Eubacterium cylindroides cluster, Eubacterium rectale cluster, Faecalibacterium prausnitzii, Proteobacteria g-group, Lactobacillus/Enterococcus group, E. coli, Gram positive bacteria, Actinobacteria and Roseburia intestinalis	Isomalt increased faecal Bif content, as assessed by both methods, and decreased Bacteriodes, Prevotella and Roseburia intestinalis, by FISH method. There was no effect on the other faecal bacteria investigated
Finney, 2007	1 wk	Lactitol	5 or 10	log 10 cfu/g faeces wet wt	NR	10.06	cultured on selective media	Lact, Bif, Entero, total anaerobes & aerobes	No effect of lactitol on faecal bacterial content compared with control, although an increase in Bif from baseline was observed with the 10g dose.
Polydextrose									
Jie, 2000	4 wk	Polydextrose	4	counts x 10^9/g faeces wet wt	0.5±0.2	1.5±0.4	cultured on selective media	Bacteroides fragilis, B. vulgatus, B. intermedius, Bif, Lact	There were substantial changes in faecal anaerobes after polydextrose intake. Bacteroides species (B. fragilis, B. vulgatus, and B. intermedius) decreased, whereas Lact and Bif species increased.
		Polydextrose	8			3.1±1.1			
		Polydextrose	12			5.3±1.7			
Hengst, 2009	3 wk	Polydextrose	8	NR	NR	NR	FISH with species- and group-specific oligonucleotide probes	Lactobacillus acidophilus, Bifidobacterium lactis, Eubacterium	No effect on faecal bacteria content
Mixture									
Beards, 2010	6 wk	Maltitol	22.8-45.6	log 10 cells/g faeces wet wt	9.1**	9.4	FISH with species- and group-specific oligonucleotide probes	Total Bif, Bact, Clost, Lact, Eubacteria. Atopobium, Fusobacterium prausnitzi, Ruminococcus flavefaciens/bromii	No effect on faecal bacteria content. The data were not analysed in comparison to control group, but as an increase from baseline values. No evidence of an effect on faecal bacteria content in comparison to control.
		Maltitol and polydextrose	22.8-45.6			9.3			
		Maltitol and wheat dextrin RS4	22.8-45.6			9.2			

I, intervention; C, control; Cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values; ** variance data reported as pooled sem only.

The effect of non-digestible carbohydrates on faecal bacteria in infants

161. Human milk contains a complex mixture of more than 100 different oligosaccharides in small amounts, which among other functions may also serve as substrates for colonic fermentation (Kunz *et al.*, 1999). Small-chain oligosaccharides, evident in abundance in the early stage of lactation, are selectively fermented by specific stains of *Bifidobacterium longum biovar, infantis* (Niñonuevo & Lebrilla, 2009). Oligofructose is not found in human milk and oligogalactose is found only in trace amounts. Breast fed infants typically show a Bifidus-dominated gut flora. In infants, the promotion of a Bifidus-dominated flora is considered to have beneficial effects, such as some protection against enteric infections. Breast-fed infants generally harbour a more diverse range of *Bifidobacterium* species than breast milk substitute-fed infants (Klaassens *et al.*, 2009; Roger *et al.*, 2010) and large inter-individual variation has been observed in the infant faecal microflora and its development (Roger & McCartney, 2010). Supplementation of breast milk substitutes and follow-on formulae with non-digestible oligosaccharides, such as galacto-oligosaccharide and fructo-oligosaccharide, or inulin, has been investigated as a means of changing infant gut microflora to become more similar to the *Bifidus*-dominated breastfed infant.

162. Eighteen articles were identified as eligible and all used a non-digestible oligosaccharide or inulin intervention (see Appendix 2 for studies excluded). Seventeen supplemented infants and young children (Moro *et al.*, 2002; Ben *et al.*, 2004; Bakker-Zierikzee *et al.*, 2005; Fanaro *et al.*, 2005; Brunser *et al.*, 2006; Scholtens *et al.*, 2006a; Alliet *et al.*, 2007; Kim *et al.*, 2007; Waligora-Dupriet *et al.*, 2007; Ben *et al.*, 2008; Costalos *et al.*, 2008; Magne *et al.*, 2008; Fanaro *et al.*, 2009; Nakamura *et al.*, 2009), some of which reported on different aspects of the same trial: (Knol *et al.*, 2005; Haarman & Knol, 2006) and (Alliet *et al.*, 2007; Scholtens *et al.*, 2008). One trial supplemented pregnant women and subsequently examined both mother and neonate faecal bacteria (Shadid *et al.*, 2007). The trial design details have been summarised in Table 39. Only one trial employed a cross-over design, with no washout period. All the other trials employed a parallel design.

163. The age of the infants at trial enrolment varied from three days to several months. There were seven trials in infants aged less than one month at enrolment (Moro *et al.*, 2002; Ben *et al.*, 2004; Bakker-Zierikzee *et al.*, 2005; Fanaro *et al.*, 2005; Ben *et al.*, 2008; Costalos *et al.*, 2008; Scholtens *et al.*, 2008), and of the other trials four were in infants aged several months at enrolment (Brunser *et al.*, 2006; Scholtens *et al.*, 2006b; Waligora-Dupriet *et al.*, 2007; Fanaro *et al.*, 2009). Several of the trials also included breast-fed infant comparison groups (Ben *et al.*, 2004; Bakker-Zierikzee *et al.*, 2005; Knol *et al.*, 2005; Brunser *et al.*, 2006; Ben *et al.*, 2008; Scholtens *et al.*, 2008). The mothers of the enrolled infants in these trials could not, or chose not, to breast feed or had ceased breast feeding after a week or more.

164. The duration of interventions ranged from three weeks to six months and initial sample sizes ranged from 14-176 subjects. 1. The funding sources, where reported, were Commercial; 25% of trials did not report funding sources.

Table 39. Non-digestible oligosaccharide and inulin and faecal bacteria trial design - infants and pregnant mothers

Study	Study design	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Intervention dose (g/d)	Sample size at start	Duration	Funding source
Infants										
Moro, 2002	P	Italy	Infants mean age at study entry 6-7d; 46M, 46F	Formula	maltodextrins	GOS/FOS mixture	4g/L 8g/L	92	4 wk	NR
Ben, 2004	P	China	Infants initially breast fed	Formula	formula w/o intervention	GOS	2.4g/L	121	6 mth	Friesland Nutrition Institute, Netherlands; Edward Keller Co. Ltd. China
Bakker-Zierikzee, 2005	P	Holland	Infants age at enrolment 3 d; 19M, 19F	Formula	formula w/o intervention	GOS/FOS mixture in a 9:1 ratio	6g/L	38	16 wk	NR
Fanaro, 2005	P	Italy	Infants mean age at study entry 3d	Formula	maltodextrins	acidic oligosaccharides derived from citrus pectin by enzymatic hydrolysis; neutral oligosaccharides (FOS + GOS, 6g/L) + acidic oligosaccharides (2g/L)	2 g/L 8 g/L	51	6 wk	Numico, Germany
Knol, 2005	P	Germany	Infants mean age at enrolment 7.7 wk	Formula	Formula w/o intervention	GOS/FOS mixture in a 9:1 ratio	8g/L	68	6 wk	Numico, Germany
Brunser, 2006	P	Chile	Infants aged 3.5 mth	Formula	Formula w/o intervention	FOS	2g/L	58	7 wk	NR
Scholtens, 2006	P	Holland	Infants aged 4-6 mth	Weaning foods	maltodextrins	GOS/FOS mixture in a 9:1 ratio	2.5-4	35	6 wk	Numico, Germany
Kim, 2007	XO - no washout	Korea	Infants previously bottle fed - mean age 12.6 wk; 10M, 4F	Formula (contained 0.5g each, raffinose, GOS, FOS per 100g dry wght)	Formula w/o intervention	Chicory inulin	1.5	14	3 wk	Sensus, Netherlands
Waligora-Dupriet, 2007	P	France	Infants and young children aged 7-19 mth at day -nurseries	Ad libitum	maltodextrins	FOS	2	35	3 wk	ORAFTI, Belgium
Ben, 2008	P	China	Infants aged up to 4 weeks; initialy breast-fed; 44M, 38F	Formula	formula w/o intervention	GOS	2.4g/L	82	3 mth	NR
Magne, 2008	P	Algeria	Infants previously breast fed aged 1 wk - 3 mth	Formula	formula w/o intervention	GOS/FOS 9:1 ratio GOS/FOS/pectin-derived acidic oligosaccharides 9:1:3 ratio	6 g/L 8 g/L	72	2 mth	Numico, The Netherlands
Costalos, 2008	P	Greece	Infants mean age at study entry 5d	Formula	formula w/o intervention	GOS/FOS 9:1 ratio	4g/L	64	6 wk	Numico, The Netherlands
Scholtens, 2008	P	Belgium	Infants enrolled after birth or after initial breast-feeding	Formula	formula w/o intervention	GOS/FOS 9:1 ratio	6g/L	176	26 wk	Numico, The Netherlands
Fanaro, 2009	P	Italy & Spain	Infants aged 4-6 mth; 75M, 84F	Follow-on formula, excluding NDO and probiotcs	maltodextrins	GOS	5g/L	159	18 wk	Humana GmbH, Germany.
Nakamura , 2009	P	USA	Infants aged 13-92d at enrolment	Formula	formula w/o intervention	GOS/polydextrose in 1:1 ratio	4g/L	52	4 wk	Mead Johnson & Company, USA
Pregnancy										
Shadid, 2007	P	Germany	Pregnant women aged 18–45 y enrolled at week 25 of gestation	Ad libitum excluding probiotics and NDO	maltodextrins	GOS/FOS 9:1 ratio	9g	48	15 wk	Numico, Germany; Child Health Foundation;Bristol-Myers Squibb Foundation

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; mth, month; wk ,week; M, male; F, female; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; NDO, non-digestible oligosaccharide.
* V-GOS, galacto-oligosaccharides in beta1-4 and beta1-6 linkages; B-GOS, galacto-oligosaccharides mainly in beta1-3 as well as beta1-4 and beta1-6 linkages

Risk of bias

165. A summary of the risk of bias assessment has been given in Table 40. All of the trials reported being randomised; three described the method of randomisation, while two gave some indication of the allocation concealment process. Three trials did not report whether blinding of participants or personnel had occurred (Ben *et al.*, 2004; Kim *et al.*, 2007; Ben *et al.*, 2008).

166. Three trials did not report missing outcome data. Of the eleven trials reporting missing outcome data, drop-out rates ranged from 2 to 43%. In those that reported drop-outs it either seemed unlikely that missing outcome data were related to the intervention or missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups.

Table 40. Non-digestible oligosaccharide and inulin and faecal bacteria trial risk of bias assessment - infants and pregnant mothers

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Infants							
Moro	2002	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	2
Ben	2004	Yes	NR	NR	NR	NR	NR
Bakker-Zierikzee	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	21
Fanaro	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	10
Knol	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	22
Brunser	2006	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	28%
Scholtens	2006	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	43
Kim	2007	Yes	NR	NR	NR	NR	NR
Waligora-Dupriet	2007	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	43
Ben	2008	Yes	NR	NR	NR	NR	NR
Magne	2008	Yes	NR	Sealed envelope	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	6
Costalos	2008	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	13
Scholtens	2008	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	11
Fanaro	2009	Yes	Computer generated	Sealed envelope	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	28
Nakamura	2009	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	15
Pregnancy							
Shadid	2007	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	31

NR, not reported.

Results

167. The findings from all trials have been summarised in Table 41. Outcome data, expressed as mean with standard deviation (where extractable) unless otherwise indicated, have been given for faecal *Bifidobacterium* spp concentration or relative proportion. It was also not possible to synthesise data on the bacterial content of faeces due to the different methodologies employed and the different ways in which data were expressed. No trials reported the degree of polymerisation of the saccharide units in non-digestible oligosaccharides and inulin.

168. In those trials in younger infants, aged less than 3 months, three reported no effect on the faecal content of *Bifidobacterium* spp (Bakker-Zierikzee *et al.*, 2005; Costalos *et al.*, 2008; Nakamura *et al.*, 2009), while eight reported non-digestible oligosaccharide or inulin interventions to increase the faecal content or proportion of *Bifidobacterium* spp (Moro *et al.*, 2002; Ben *et al.*, 2004; Fanaro *et al.*, 2005; Knoll et al., 2008; Kim *et al.*, 2007; Ben *et al.*, 2008; Scholtens *et al.*, 2008; Magne *et al.*, 2008). Where comparisons with breastfed infants were made, faecal *Bifidobacterium* spp counts were similar to supplemented infants.

169. In older infants, aged more than 3 months, two trials reported no effect on the faecal content of *Bifidobacterium* spp (Brunser *et al.*, 2006; Scholtens *et al.*, 2006b), one a trend towards increased faecal concentrations (Waligora-Dupriet *et al.*, 2007), while one reported an increase in concentration (Fanaro *et al.*, 2009).

170. Overall, the trials in younger infants tended to report that non-digestible oligosaccharide or inulin interventions increased the faecal content of *Bifidobacterium* spp. In several of the trials, however, no effect, or only a change from baseline and not relative to control, was observed. Many of the trials also observed a reported softening of faeces.

171. In the one trial where pregnant women were supplemented with non-digestible oligosaccharide, there was an increase in maternal faecal *Bifidobacterium* spp. content, but no effect on neonate faecal bacteria content (Shadid *et al.*, 2007).

172. At this time there is little conclusive evidence on the relationship between a bifidobacteria-dominated flora and relevant outcomes on health and well-being in later life. It has been suggested that it will be important to gain a greater understanding of the gut bacterial colonisation process before attempting to change the flora of infant populations in general (Edwards & Parrett, 2002).

Table 41. Non-digestible oligosaccharide and inulin and faecal bacteria trial results - infants and pregnant mothers

Study	Intervention	Dose	Duration	Flora unit of measure	Bif C	Bif. I	Microbiological method	Bacteria investigated	Results
Infants									
Moro, 2002	GOS/FOS mixture	4g/L	4 wk	log 10 cfu/g faeces wet wt	7.2*	9.3*	Cultured on selective media	Bif, Lact, Bact, Clost, E. coli, Entero, Citrobacter, Proteus, Klebsiella, Candida	Dose-response increase in Bif content, while Lact content was increased equally by both NDO doses. No effect on the faecal content of the other bacteria investigated. Faeces were observed to be softer in infants fed NDO.
		8g/L				9.7*			
Ben, 2004	GOS	2.4g/L	6 mth	log 10 cfu/g faeces wet wt	6.0±0.9	7.9±1.3	Cultured on selective media	Bif, Lact, E. coli	GOS formula and human milk increased faecal Bif and Lact. No effect on faecal E. coli content.
	Human milk					7.5±1.4			
Bakker-Zierikzee, 2005	GOS/FOS mixture in a 9:1 ratio	6g/L	16 wk	% Bif. from total number of bacterial cells /g faeces wet wt	51.8	59.2	FISH	Bif spp.	No difference between human milk, GOS formula or standard formula on faecal Bif content.
	Human milk					~48			
Fanaro, 2005	acidic citrus pectin OS	2 g/L	6 wk	log 10 cfu/g faeces wet wt	8.7±0.5	8.6±0.9	Cultured on selective media	Bif, Lact, Bact, Clost, E coli, entero, citrobacter, proteus, klebsiella, candida	Acidic oligosaccharides alone had no effect on bacterial content. In conjunction with FOS and GOS increased faecal Bif and Lact, but had no effect on the other bacteria investigated. Both interventions, FOS/GOS more so, resulted in softer faeces.
	FOS/GOS and acidic citrus pectin OS	8 g/L				9.6±0.9			
Knol, 2005	GOS/FOS mixture in a 9:1 ratio	8g/L	6 wk	% Bif. from total number of bacterial cells /g faeces wet wt	49.5	59.6	FISH	Bif	NDO had no significant effect on the numbers of Bif, but increased the percentage of Bif to a similar extent as that seen in breast-fed infants. No effect on faecal consistency was observed.
	Human milk					67.7			
Brunser, 2006	FOS	2g/L	7 wk	log 10 cfu/g faeces wet wt	9.6±2.3	9.4±1.9	Cultured on selective media and FISH	Bif, Lact, Clost, Enterobacteria, Enterococci	NDO had no effect on faecal bacteria investigated, but in breast-fed infants faecal Lact content was higher and enterobacteria lower than control.
	Human milk					9.5±2.4			
Scholtens, 2006	GOS/FOS mixture in a 9:1 ratio	2.5-4g/d	6 wk	cells x 10^9/g faeces wet wt	7.5	10.6	FISH	Bif	NDO had no significant effect on the numbers of Bif relative to control, but increased the percentage and number of Bif from baseline. No effect on faecal consistency.
Kim, 2007	Chicory inulin	1.5g/d	3 wk	log 10 cfu/g faeces wet wt	9.2±0.7	9.9±0.5	Cultured on selective media	Bif, Bact, Lact, total anaerobes	Inulin increased faecal Bif and Lact, but no effect on other bacteria investigated. Faecal consistency tended (p=0.058) to be softer in the inulin group.
Waligora-Dupriet, 2007	FOS	2g/d	3 wk	log 10 cfu/g faeces wet wt	9.0±0.7	9.5±0.8	Cultured on selective media	Bif, Bact, Clost, Entero, enterococci	NDO tended to increase faecal Bif content (p=0.095), but had no effect on the other faecal bacteria investigated. No effect on faecal consistency or well-being was observed
Ben, 2008	GOS	2.4g/L	3 mth	log 10 cfu/g faeces wet wt	8.2±1.0	9.0±1.2	Cultured on selective media	Bif, Lact, E. coli	GOS increased faecal Bif, Lact compared with control resulting in concentrations similar to those observed in breast fed infants. No effect on faecal E coli content.
	Human milk					9.3±0.9			

I, intervention; C, control; Cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; OS, oligosaccharide; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values; NDO, non-digestable oligosacharides.

Non-digestible oligosaccharide and inulin and faecal bacteria trial results - infants and pregnant mothers

Study	Intervention	Dose	Duration	Flora unit of measure	Bif C	Bif. I	Microbiological method	Bacteria investigated	Results
Magne, 2008	GOS/FOS 9:1 ratio	6g/L	2 mth	% Bif. from total number of bacterial cells /g of wet wt	~19	~30	FISH	Bif, Bact, Entero, Clostridium coccoidess gp	Compared to control, both NDO groups increased the proportion of faecal Bif, GOS/FOS/acidic citrus pectin OS, more so than GOS/FOS. Both NDO groups decreased the proportion of faecal Bact and Clost compared with control. No effect on faecal consistency.
	GOS/FOS 9:1 ratio and acidic citrus pectin OS	8g/L				~45			
Costalos, 2008	GOS/FOS 9:1 ratio	4g/L	6 wk	% Bif. from total number of bacterial cells /g of wet wt	14.9*	39.7*	FISH	Bif, Clost, E coli	NDO had no significant effect on the faecal content of bacteria investigated. Large inter-individual variation was observed. NDO supplementation resulted in softer faeces
Scholtens, 2008	GOS/FOS 9:1 ratio	6g/L	26 wk	% Bif. from total number of bacterial cells /g of wet wt	47.2*	59.8*	FISH	Bif, Clostridium histolyticum/Clostridium lituseburense group, Escherichia coli	Relative to control, NDO increased the faecal content of Bif and decreased Clostridium spp content to a similar extent as observed in breast fed infants. No effect was observe on faecal E coli content A subgroup analysis of exclusively formula-fed infants showed no difference to the results obtained from the whole group.
	Human milk					63.9*			
Fanaro, 2009	GOS	5g/L	18 wk	log 10 cfu/g faeces wet wt	9.4*	9.9*	Cultured on selective media	Bif, Bact, Lact, Clost, Entero, E coli	GOS increased the faecal content of Bif, but had no effect on the faecal content of the other faecal bacteria investigated. GOS supplementation produced softer faeces, but had no effect on bowel frequency
Nakamura, 2009	GOS/PDX in 1:1 ratio	4g/L	4 wk	% Bif. from total number of bacterial cells /g of wet wt	NR	NR	Cultured on selective media, FISH and DGGE	Bif, Bact, Entero, Clostridium clusters,	NDO had no effect on the faecal content of bacteria investigated. In a breast fed control group faecal consistency was observed to be softer than formula fed groups.
Pregnancy									
Shadid, 2007	GOS/FOS 9:1 ratio	9g/d	15 wk	% Bif. from total number of bacterial cells /g of wet wt	~11*	~15*	Quantitative real-time PCR and FISH	Bif, Lact	NDO increased the percentage of maternal faecal Bif, but had no effect on total bacterial counts or percentages of lactobacilli. The total numbers of bacteria and the percentages of neonatal faecal Bif and lactobacilli on days 5, 20, and 182 after birth, did not differ, although the percentage of faecal Bif spp. and lactobacilli spp. changed over time in both groups

I, intervention; C, control; cfu, colony forming unit; wt, weight, wk, week, d, day; NR, not reported; PDX, polydextrose; OS, oligosaccharide; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; FISH, fluorescence in situ hybridization; DGGE, denaturing gradient gel electrophoresis; Bif, *Bifidobacterium* spp.; Lact, *Lactobacillus* spp.; Bact, *Bacteroides* spp.; Clost, *Clostridium* spp. Entero, *Enterobacteriaceae* spp; E. coli, *Escherichia coli*; * median values; NDO, non-digestable oligosacharides.

The effect of non-digestible carbohydrates on faecal pH and short chain fatty acid content

173. Many of the trials considered in detail in the previous sections also investigated whether non-digestible carbohydrates affect faecal pH and short chain fatty acid (SCFA) content. The results from these trials have been compilied in this section.

174. The findings from all relevant trials have been summarised in the tables below. Outcome data, expressed as mean with standard deviation (where extractable), unless otherwise indicated, have been given for faecal pH and SCFA concentration or relative proportions. It was not possible to synthesise data on faecal SCFA concentration, due to the different ways in which the data were expressed, e.g. mmol/L; µmol/g or mmol/g faeces wet or dry weight or % change.

175. The results from trials investigating an effect on faecal pH and SCFA of non-digestible carbohydrates have been compiled for dietary fibres (see Table 42), polyols and polydextrose (see Table 43), resistant starches (see Table 44) and non-digestible oligosaccharides and inulin in adults (Table 45) and in infants (see Table 46).

Dietary fibre

176. Sixteen trials reported on the effect of dietary fibre interventions on faecal pH and/or SCFA content (see Table 42) (Jenkins *et al.*, 1975; Spiller *et al.*, 1980; Hillman *et al.*, 1983; Lampe *et al.*, 1992; Cummings *et al.*, 1996; Noakes *et al.*, 1996; Jenkins *et al.*, 1998; Jenkins *et al.*, 1999a; Grasten *et al.*, 2000; McIntosh *et al.*, 2003; Muir *et al.*, 2004; Johnson *et al.*, 2006; Grasten *et al.*, 2007; Bird *et al.*, 2008; Carabin *et al.*, 2009; Carvalho-Wells et al., 2010). While wheat bran, at sufficient doses, increased faecal weight and the total daily faecal SCFA excretion in some trials (Jenkins *et al.*, 1975; Cummings *et al.*, 1996; Jenkins *et al.*, 1998; Jenkins *et al.*, 1999a), no effect on faecal SCFA concentration was observed in other trials (McIntosh *et al.*, 2003; Muir *et al.*, 2004; Bird *et al.*, 2008). One trial observed wheat bran to increase total SCFA and butyrate concentrations compared with a low- fibre bread control (Lampe *et al.*, 1992), while another observed only finely ground wheat bran to increase faecal butyrate concentrations (Jenkins *et al.*, 1999a).

177. Several trials were designed to investigate the effect of rye bran on faecal pH and

SCFA content. One reported that a rye diet reduced faecal pH and increased faecal butyrate concentration (McIntosh *et al.*, 2003); in another trial increased butyrate concentration was only observed in men (Grasten *et al.*, 2000), while a later trial, by the same authors, observed no effect of whole grain rye bread on faecal SCFA concentration (Grasten *et al.*, 2007). One trial reported that a novel barley (lacking activity of a key enzyme of starch synthesis giving a grain containing less total starch, more amylose and higher total dietary fibre) reduced faecal pH and increased butyrate concentration (Bird *et al.*, 2008). Wholegrain corn breakfast cereal consumption was observed to have no effect on faecal SCFA content relative to a refined corn breaskfast cereal, despite increasing faecal *Bifidobacterium* spp. content (Carvalho-Wells *et al.*, 2010). Oat fibre was also observed to have no effect on faecal SCFA content in one trial (Noakes *et al.*, 1996) and another observed a mixture of food additives (Konjac powder, sodium alginate, and xanthan gum) to have no effect on faecal SCFA content (Carabin *et al.*, 2009).

178. A vegetable fibre (mixture of pea fibre, soy polysaccharide, and pectin, added at levels of 62, 33, and 5%) was observed to increase total SCFA concentration compared with a low- fibre bread control (Lampe *et al.*, 1992), and a legume fibre was also observed to increase faecal total SCFA, acetate and butyrate concentration (Johnson *et al.*, 2006)

179. In a trial where faecal pH was determined, cellulose, but not pectin, reduced faecal pH (Hillman *et al.*, 1983). A mixture of vegetable fibres, and to a greater extent wheat bran, were observed to reduce pH (Lampe *et al.*, 1992). Legume fibre was observed to reduce faecal pH (Johnson *et al.*, 2006). In one trial a high fibre wheat diet and a high fibre rye diet were both observed to reduce faecal pH (McIntosh *et al.*, 2003), but in another trial only a diet containing a novel barley, but not wheat bran, reduced faecal pH (Bird *et al.*, 2008). Oat fibre was observed in one trial to reduce faecal pH (Noakes *et al.*, 1996).

Polyols and polydextrose

180. Three trials reported on the effect of polyols (Ballongue *et al.*, 1997; Gostner *et al.*, 2006; Finney *et al.*, 2007) and two on the effect of polydextrose interventions (Jie *et al.*, 2000; Hengst *et al.*, 2008) on faecal pH and SCFA content (see Table 43). While lactitol was observed to decrease faecal pH in two trials (Ballongue *et al.*, 1997; Finney *et al.*, 2007), the effect only became apparent at a dose of 10g/day, and while one observed a lowering of faecal propionate and an increase in acetate concentration, the other appeared to show an increase in faecal propionate concentration. In one trial, no effect of the polyol isomalt on faecal pH or SCFA content was observed (Gostner *et al.*, 2006).

181. Faecal pH decreased with increasing polydextrose intake in a dose-response trial (Jie *et al.*, 2000), which corresponded to an increase in faecal butyrate and acetate concentration. In another trial no effect of polydextrose on faecal pH or SCFA content was observed (Hengst *et al.*, 2008)

182.

183. One trial supplemented subjects with increasing doses (22.8-45.6 g/day) over six weeks of either the polyol maltitol, maltitol and polydextrose or maltitol and RS_4 (a

modified dextrin) and measured faecal SCFA content (Beards *et al.*, 2010). The data, however, were not analysed in comparison with the control group values, but as an increase from baseline values, so it was not possible to draw conclusions.

Resistant starch

184. Ten trials reported on the effect of resistant starches on faecal pH or SCFA content (see Table 44) (Phillips *et al.*, 1995; Cummings *et al.*, 1996; Noakes *et al.*, 1996; Silvester *et al.*, 1997; Heijnen *et al.*, 1998; Jenkins *et al.*, 1998; Muir *et al.*, 2004; Pasman *et al.*, 2006; Fastinger *et al.*, 2008; Stewart *et al.*, 2010). Three trials investigated the effect of modified starches (RS_4). None of the three trials reported an effect on faecal pH. While one of the trials reported all faecal SCFA concentrations, except butyrate, to be lowered by the RS_4 intervention (Fastinger *et al.*, 2008), the other two reported no effect (Pasman *et al.*, 2006; Stewart *et al.*, 2010).

185. Five trials reported that retrograded, granular and high amylose resistant starches (RS_1, RS_2 and RS_3) increased faecal butyrate concentration or proportion (Phillips *et al.*, 1995; Cummings *et al.*, 1996; Noakes *et al.*, 1996; Jenkins *et al.*, 1998; Muir *et al.*, 2004), but two other trials, conducting interventions with 30g/day (Heijnen *et al.*, 1998) and 12g/day (Stewart *et al.*, 2010), reported no effect. Four trials reported a reduction in faecal pH in response to resistant starch administration (Phillips *et al.*, 1995; Noakes *et al.*, 1996; Silvester *et al.*, 1997; Muir *et al.*, 2004), while two reported no effect (Heijnen *et al.*, 1998; Stewart *et al.*, 2010).

186. Overall, resistant starch (RS_1, RS_2 and RS_3) at doses of 20-40g/day generally lowered faecal pH and increased either the concentration or proportion of faecal butyrate.

Non-digestible oligosaccharide and inulin

187. Fifteen trials reported on the effect of non-digestible oligosaccharide or inulin on faecal pH or SCFA content in adults (see Table 45) (Bouhnik *et al.*, 1996; Alles *et al.*,

1999; Bouhnik *et al.*, 1999; van Dokkum *et al.*, 1999; Causey *et al.*, 2000; Tahiri *et al.*, 2001; Tuohy *et al.*, 2001b; Swanson *et al.*, 2002; Bouhnik *et al.*, 2004; Bouhnik *et al.*, 2006; Scholtens *et al.*, 2006b; Bouhnik *et al.*, 2007b; Kleessen *et al.*, 2007; Ramnani *et al.*, 2010; Walton *et al.*, 2010). The degree of polymerisation of the saccharide units in the non-digestible oligosaccharides and inulin has been included in Table 45. Of the nine trials that determined faecal SCFA content none reported an effect on total SCFA concentration, but three reported an increase in the concentration or proportion of faecal acetate in response to 15g/day chicory inulin or galacto-oligosaccharide, but not fructo-oligosaccharide (van Dokkum *et al.*, 1999), 20g/day chicory inulin (Causey *et al.*, 2000) and 25-30g/day fructo-oligosaccharide (Scholtens *et al.*, 2006b); while four observed no effect of non-digestible oligosaccharide (3-14.4g/day) or inulin (5-15g/day) on individual faecal SCFA content (Alles *et al.*, 1999; Swanson *et al.*, 2002; Ramnani *et al.*, 2010; Walton *et al.*, 2010). An effect on the concentration or proportion of faecal acetate was observed only in those trials employing relatively high doses of non-digestible oligosaccharides or inulin. There was no evidence that the degree of polymerisation affected the capacity of non-digestible oligosaccharides and inulin in this regard. None of the trials reported a significant effect of non-digestible oligosaccharide or inulin on faecal pH.

188. Nine trials reported on the effect of non-digestible oligosaccharide or inulin on faecal pH or SCFA content in infants (see Table 46) (Moro *et al.*, 2002; Ben *et al.*, 2004; Bakker-Zierikzee *et al.*, 2005; Fanaro *et al.*, 2005; Knol *et al.*, 2005; Scholtens *et al.*, 2006a; Kim *et al.*, 2007; Ben *et al.*, 2008; Scholtens *et al.*, 2008). No trials reported the degree of polymerisation of the saccharide units in non-digestible oligosaccharides and inulin. In those trials that determined faecal SCFA content, three trials reported an increase in the faecal concentration or proportion of faecal acetate (Ben *et al.*, 2004; Knol *et al.*, 2005; Ben *et al.*, 2008), but one, in older infants, reported no significant effect. In those trials where a comparison with breast-fed infants was reported the interventions produce similar effects on faecal acetate content to those observed in the breast-fed infants (Ben *et al.*, 2004; Bakker-Zierikzee *et al.*, 2005; Knol *et al.*, 2005; Ben *et al.*, 2008). All trials, except two (Scholtens *et al.*, 2006a; Kim *et al* 2007), reported that the administration of non-digestible oligosaccharide or inulin lowered faecal pH.

Table 42. Dietary fibre and faecal pH and SCFA concentrations

Study	Intervention	Time	Additional DF dose(g/d) in I	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Jenkins, 1975[$]	Wheat bran	3 wk	28			GLC	Faecal output g/day	~1.75	~2.75	NR	NR	NR	NR	NR	NR	No change in faecal SCFA concentrations, but increased daily total excretion
Spiller, 1980	Cellulose	24 d	14			GLC	Faecal output g/ 7 days	2.4±1.4	4.3 ±3.4	0.4±0.2	0.7±0.8	0.5±0.3	0.9±0.7	1.2±0.7	2.1±1.6	Total daily SCFA excreted increased more in cellulose group (14g/d) than in pectin group (6g/d).
	Pectin		6						3.3±3.7		0.6±0.7		0.6±0.7		1.7±1.9	
Hillman, 1983	Cellulose	4 wk	15	6.4±0.3	6.1±0.4											Cellulose, but not pectin, reduced faecal pH
	Pectin		15	6.5±0.6	6.5±0.4											
Lampe, 1992[#]	Wheat bran	3 wk	8.9	7.9 ±0.04	7.5 ±0.04	GLC	Total SCFA mmol/L and	58.2 *	99.3	9.3	13.6	23.1	21.8	54.9	54.9	Total SCFA concentrations were lower and pH higher on a low- fibre bread
	Wheat bran		27.8		7.2 ±0.04		molar % for individual		75.5		16.2		22.4		52.2	control than the treatment breads.
	Vegetable fibres ***		12.2		7.7 ±0.04		SCFA		74.5		10.4		21.6		57.6	Butyrate concentrations were higher with wheat bran than vegetable fibre treatments.
	Vegetable fibres***		34.4		7.5 ±0.04				90.0		11.7		21.6		60.0	
Cummings, 1996	Wheat bran	15d	15.0			GLC	mmol/kg faeces wet wt	98.9±23.1	77.1±21.9	15.0±3.2	15.8±3.0	18.8±4.4	18.4±4.2	55.8±5.1	57.1±4.8	Total faecal SCFA concentration was lower in the wheat bran group, although daily excretion of all SCFA increased overall. No effect on individual SCFAs.
Noakes, 1996	Oat bran	4 wk	14-21	6.4±0.6	6.2±0.5	GLC	mmol/L faecal water			20.1±6.2	23.5±12.9	20.8±3.9	22.0±5.5	59.7±11.7	55.6±5.5	Oat bran reduced faecal pH, but had no effect on faecal SCFA content.
Jenkins, 1998	Wheat bran	2 wk	23			HPLC	mmol/L	102.8±34.8	107.9±27.4	19.2±11.8	21.3±9.3	14.2±5.9	14.3±5.9	60.7±22.5	64.2±19.1	No effect on faecal SCFA concentrations.Because of increased fecal weight, the daily output of total and individual SCFAs was increased in the wheat bran group.
Jenkins, 1999	Wheat bran fine particle size	4 wk	19-20			HPLC	mmol/L	115.0±32.5	125.1±34.4	16.3±7.3	20.1±9.2	14.7±6.0	15.5±6.0	57.0±21.5	63.8±21.1	Only butyrate concentrations in the fine ground wheat bran group increased relative to control. (and medium ground group). Both interventions increased daily excretion of total SCFA.
	Wheat bran medium particle size		19-20						111.8±25.7		16.3±6.4		13.3±4.6		54.3±16.5	
Gråsten, 2000	Rye bread men	4 wk	24.2			GLC	mmol/kg faeces wet wt	45.0±4.4	48.2±3.8	7.5±0.7	10.2±1.1	7.2±0.9	7.0±0.1	29.4±3.2	32.0±2.7	No effect on faecal SCFA concentrations overall, but in men rye bread raised butyrate concentration only.
	Rye bread women		17.4					39.3±4.4	43.6±2.2	6.1±0.7	7.4±0.6	5.8±0.7	5.8±0.4	26.3±3.1	27.0±1.2	
McIntosh. 2003	High-fibre wheat diet	4 wk	13	7.0±0.4	6.8±0.4	GLC	µmol/g faeces wet wt	102.0±30.2	104.0±27.5	20.4±9.0	22.6±7.9	18.9±7.9	16.6±4.8	62.9±17.5	65.1±18.0	Both fibre diets reduced faecal pH. Compared with control, faecal propionate concentration was lower with the wheat diet and faecal butyrate higher with the rye diet.
	High-fibre rye diet		13		6.8±0.3				112.0±38.6		27.8±11.6		18.7±5.8		68.5±20.1	
Muir, 2004	Wheat bran	3 wk	7.2	6.4±0.2	6.5±0.2	GLC	mmol/L	96.0**	92.0	15.1	16.0	14.1	13.2	59.0	54.4	Wheat bran had no effect on single or total SCFA concentrations or on faecal pH.
Johnson, 2006	legume fibre	4 wk	22.2	6.6±0.5	6.3±0.4	GLC	µmol/g faeces wet wt	108.6±33.3	128.7±33.9	18.7±8.6	21.6±7.4	17.6±6.8	21.2±11.7	64.7±21.0	78.9±21.6	Legume fibre increased faecal total SCFA, acetate and butyrate concentrations, and decreased faecal pH

I, intervention group; C, control group; NR, not reported; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight. * Values least squared means; ** Median values; Vegetable fibre from pea, soy and citrus pectin; [$] SCFA data from Cummings et al., 1976a; [#] SCFA datra from Fredstrom et al., 1994

Dietary fibre and faecal pH and SCFA concentrations

Study	Intervention	Time	Additional DF dose (g/d) in I	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Gråsten, 2007	Whole grain rye bread	8 wk	31.5			GLC	µmol/g faeces wet wt mmol/L	NR	NR	8.1±3.7	12.1±4.6	6.1±1.8	6.2±2.4	34.0±11.8	34.8±10.4	No effect of wholegrain rye bread SCFA concentrations.
Bird, 2008	Wholemeal wheat	4 wk	11.0	7.2±0.6	7.2±0.7	GLC		111.6±44.9	111.1±43.7	20.9±12.8	23.4±12.4	15.1±4.9	15.0±5.4	69.4±30.5	67.7±28.9	Only the novel barley reduced faecal pH and increased faecal butyrate concentrations. No other faecal SCFA concentrations were affected.
	Barley, novel hull-less		23.2		7.0±0.7				133.0±47.8		29.7±14.4		17.3±7.4		79.5±28.9	
Carabin, 2009	Konjac powder, sodium alginate, and xanthan gum	3 wk	10			NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No effect on faecal SCFA content observed – data not reported
Carvalho-Wells, 2010	Whole-grain corn breakfast cereal	3 wk	14.2			HPLC	NR	NR	NR	NR	NR	NR	NR	NR	NR	No effect on faecal SCFA content observed – data not reported

I, intervention group; C, control group; NR, not reported; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight. * Values least squared means; ** Median values

Table 43. Polyols, polydextrose and faecal pH and SCFA content

Study	Intervention	Time	Dose (g/d)	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Ballongue, 1997	lactitol	4 wk	20	6.9±0.2	6.3±0.3	HPLC	mmol/L			5.4±0.3	5.1±0.4	13.0±0.6	11.8±0.8	54.8±2.1	60.6±3.2	Lactitol decreased faecal pH, increased faecal acetate content, while lowering faecal propionate content.
Gostner, 2006	polyol isomalt	3 wk	30	6.6±0.4	6.7±0.4	GLC	mg/g faeces wet wt	7.8.0±1.6	7.7±1.6							There was no effect on faecal pH or SCFA content
Finney, 2007	lactitol	1 wk	5	6.7	6.8	GLC	µmol/g faeces wet wt			~10	~11	~10	~15	~9	~9	Faecal pH decreased at the 10g dose only. Faecal SCFA content data were only considered as a change from baseline and graphically, so it is not possible to determine the effect of the intervention..
			10		6.5						~15		~17			
Jie, 2000	polydextrose	4 wk	4	7.0±0.2	6.9±0.2	GLC	mg/g faeces wet wt			0.94±0.23	1.10±0.17	1.50±0.24	1.52±0.22	4.12±0.19	4.18±0.26	Faecal pH decreased in all interventions and faecal butyrate and acetate concentration increased in 8 & 12 g/d groups
	polydextrose		8		6.7±0.2						1.31±0.24		1.55±0.36		4.70±0.33	
	polydextrose		12		6.4±0.3						1.41±0.34		1.48±0.35		5.12±0.31	
Hengst, 2008	polydextrose	3 wk	8	6.6±0.4	6.5±0.4	GLC	µmol/g faeces wet wt			NR	1.6	NR	~10	NR	~38	No effect of polydextrose on faecal SCFA or pH.
Beards, 2010	Maltitol	6 wk	22.8-45.6	NR	NR	GLC	mmol/L			6.9 ***	13.5	5.8	11.3	17.5	23.3	Data not analysed in comparison to control group, but as an increase from baseline values. Faecal SCFA contcentrations appear to increase in response to all interventions compared with control values, but this was not statistically analysed.
	Maltitol and polydextrose		22.8-45.6								18.7		14.1		28.4	
	Maltitol and RS4		22.8-45.6								12.8		11.5		26.3	

I, intervention group; C, control group; NR, not reported; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight.
* Values least squared means; ** Median values; *** variance data reported as pooled sem only.

Table 44. Resistant starch and faecal pH and SCFA content

Study & duration	Intervention	Time	Dose (g/d)	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Phillips, 1995	Mixed RS1, 2 & 3	3 wk	33.3	6.9±0.3	6.3±0.3	GLC	mmol/L	128±43	154±45	19.0±8.6	26.2±20.6	20.5±7.3	18.0±6.0	79.0±28.2	99.5±31.5	The high RS diet lowered faecal pH and increased faecal concentrations of butyrate and acetate. The total daily excretion of SCFA was increased by RS.
Cummings, 1996	Potato RS2	15d	26.4			GLC	mmol/kg faeces wet wt	98.9±23.1	99.7±21.7	15.0±3.2	18.4±2.9	18.8±4.4	16.0±4.2	55.8±5.1	55.6±4.8	No effect on faecal total SCFA. Potato-RS2 increased faecal butyrate concentration. Potato- and banana-RS2 decreased faecal propionate concentration. Molar ratios of proprionate to total SCFA were lower for RS2 The molar ratio for butyrate was higher for potatoe RS2.
	Banana RS2		29.6						97.5±21.7		16.7±2.9		15.0±4.2		59.4±4.8	
	Wheat RS3		17.1						83.4±21.7		15.2±2.9		20.8±4.0		52.1±4.7	
	Corn RS3		18.7						85.7±21.7		17.0±3.0		17.5±4.2		51.6±4.8	
Heijnen, 1998	Corn RS2	1 wk	30	6.7±0.5	6.6±0.5	GLC	Total SCFA: mmol/kg faeces wet wt; Single SCFA: % of total SCFA	106.5±29.1	115.6±31.6	16.5±2.3	17.7+5.5	16.2±3.3	15.1±2.7	59.4±4.2	59.8±6.4	No effect on pH or SCFA content or daily total SCFA excretion in faeces.
	Corn RS3		27.6		6.5±1.0				109.0±33.9		17.6±3.7		15.4±6.0		59.5±7.8	
Jenkins, 1998	Corn RS2 or RS3	2 wk	19.2 or 25.6			HPLC	mmol/L	102.8±34.8	108.1±31.8	19.2±11.8	22.7±8.3	14.2±5.9	13.0±5.9	60.7±22.5	63.6±21.6	Both, RS2 and RS3 increased butyrate concentrations. No effect on other faecal SCFA concentrations. RS increased the butyrate to total SCFA ratio and total daily SCFA exrection (for pooled RS2 & RS3 data).
Noakes, 1996	Corn RS2	4 wk	11-18	6.4±0.6	6.2±0.4	GLC	mmol/L faecal water			20.1±6.2	31.1±11.7	20.8±3.9	23.2±3.8	59.7±11.7	64.9±9.9	RS reduced faecal pH and increased butyrate concentration.
Silvester, 1997	Potato RS3	19 d	37	7.2±0.3	6.6±0.3											RS reduced faecal pH
Muir, 2004	Corn RS2	3 wk	19.8	6.5±0.2	6.3±0.4	GLC	mmol/L	92.0 **	117.0	16.0	27.1	13.2	11.7	54.4	67.6	RS lowered faecal pH and increased faecal total SCFA, acetate and butyrate concentrations. RS increased total daily faecal SCFA excretion.
Pasman, 2006	Wheat dextrin RS4	4 wk	30	6.5±0.3	6.1±0.4	GLC	mmol/L	128.1±30.9	131.3±32.2	NR	NR	NR	NR	NR	NR	No effect of RS4 on faecal SCFA concentrations or pH
	Wheat dextrin RS4		45		6.1±0.6				134.0±30.4							
Fastinger, 2008	Corn RS4	3 wk	7.5	7.0	7.3	GLC	mmol/g faeces dry wt	716.2 **	560.2	106.4	86.8	136.1	99.2	473.7	374.2	RS4 lowered all faecal SCFA concentrations, except butyrate. No effect on faecal pH.
			15		6.7				590.7		99.1		97.3		394.4	
Stewart, 2010	Corn RS3	2 wk	12	6.3±0.1	6.4±0.1	GLC	Total SCFA: mmol/kg faeces wet wt; Single SCFA: % of total SCFA	144±31	137±40	32.0±5.8	33.3±6.3	25.1±3.6	23.1±3.6	42.8±4.0	43.6±4.9	Corn RS3 decreased propionate ratio. No other effects on faecal SCFA ratios or faecal pH.
	Corn dextrin RS4		12		6.3±0.1				156±40		32.8±6.3		26.3±4.0		40.9±4.5	
	Tapioca dextrin RS4		12		6.1±0.1				160±58		31.1±6.3		25.0±4.0		43.8±4.0	
	Corn RS4		12		6.4±0.1				162±54		31.4±3.6		25.7±4.5		42.9±4.0	

RS, resistant starch; I, intervention group; C, control group; NR, not reported; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight.
* Values least squared means; ** Median values

Table 45. Non-digestible oligosaccharide and inulin and faecal pH and SCFA content in adults

Study	Intervention	DP	Dose (g/d)	Time	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Bouhnik, 1996	FOS	2-4	12.5	12 d	7.0±0.3	6.8±0.6											No effect on faecal pH
Alles, 1999	GOS	2-6	8.5	3 wk	6.7±0.4	6.7±0.4	GLC	mmol/L	110.5±30.4	112.5±27.4	10.5±4.7	12.1±4.2	22.6±7.3	20.6±5.5	70.4±19.6	69.9±18.7	No effect on faecal pH or SCFA concentration or daily faecal total SCFA excretion.
			14.4			6.7±0.4				116.5±30.1		11.9±5.2		23.0±10.4		71.6±16.6	
Bouhnik, 1999	FOS	2-4	2.5	1 wk	7.0±2.2	6.4±1.5											No effect on faecal pH
			5			6.5±1.5											
			10			6.8±1.2											
			20			6.4±1.6											
Van Dokkum, 1999	Chicory inulin	2-60	15	3 wk	6.8±0.2	6.7±0.5	HPLC	mg/ 100g faeces dry wt			313±177	401±179	671±297	795±300	854±541	1181±355	No effect on faecal pH. Faecal acetate concentration, but not any other SCFA, were higher in the inulin and GOS groups
	FOS	2-8	15			6.9±0.2						318±105		707±297		1058±444	
	GOS	2-6	15			6.7±0.5						369±199		679±293		1246±698	
Causey, 2000	Chicory inulin	2-60	20	3 wk			GLC	mmol/L/g faeces wet wt	5.93±4.32	9.42±12.96	0.91±0.67	1.96±3.29	1.06±0.85	1.38±1.61	3.38±2.66	5.84±7.91	Inulin increased faecal acetate concentrations, but had no significant effect on other SCFA concentrations.
Tahiri, 2001	FOS	2-4	10	5 wk	7.5±0.7	7.4±0.5											No effect on faecal pH
Tuohy, 2001	FOS; partially hydrolysed guar gum	NR	6.6 3.4	3 wk	7.1	7.1											No effect on faecal pH
Swanson, 2002	FOS	NR	3	4 wk	6.7	6.8	GLC	µmol/g faeces dry wt	433.8	285.2	62.9	40.1	70.1	40.1	300.9	205.0	No significant effect on faecal pH or SCFA concentration.
Bouhnik, 2004	FOS, Soybean OS, GOS, chicory inulin, isomalto OS	NR	10	1 wk	NR	NR											No effect of any NDO or inulin on faecal pH
Scholtens, 2006	FOS	2-7	25-30	2 wk	6.6±0.5	6.1±0.6	GLC	Total SCFA: mmol/kg faeces wet wt; Single SCFA: % of total SCFA	97.3±22.2	90.6±24.5	20.5±4.0	13.0±4.6	17.5±4.3	14.9±4.6	62.0±6.6	72.0±7.3	The proportion of acetate was higher and the proportion of butyrate lower in the FOS group. No effect on faecal pH.
Bouhnik, 2006	FOS	2-4	2.5	1 wk	6.9±0.3	6.8±0.4											No effect on faecal pH.
			5			6.5±0.3											
			7.5			6.8±0.4											
			10			7.2±0.7											
Bouhnik, 2007	Chicory inulin	2-60	5	4 wk	6.5±0.4	6.4±0.4											No effect on faecal pH.

DP, degree of polymerisation; I, intervention group; C, control group; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; OS, oligosaccharide; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight. * Values least squared means; ** Median values

Non-digestible oligosaccharide and inulin and faecal pH and SCFA content in adults

Study	Intervention	DP	Dose (g/d)	Time	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Kleessen, 2007	Chicory inulin	24% < 5; 46% 5–12; 30% > 12	7.5-15	3 wk			GLC	µmol/g faeces wet wt	138.8±39.4	142.4±43.7	NR	NR	NR	NR	NR	NR	No effect on faecal SCFA concentration
	Jerusalem artichoke inulin	40% < 5; 49% 5–12; 11% > 12	7.5-15							135.2±50.7							
Ramnani, 2010	Jerusalem artichoke inulin	NR	5	3 wk			GLC	% of total SCFA concentration			4.8±8.5	3.2±5.2	14.0±21.2	6.4±8.4	81.1±22.5	89.8±10.9	No effect on faecal SCFA concentration
			5									2.0±4.4		6.4±7.7		91.6±8.9	
Walton, 2010	Manno-OS	NR	3	3 wk	6.45	6.51	GLC	mmol/kg			~9	~9	~11	~11	~30	~32	No effect on faecal SCFA concentration or pH.
			5			6.23						~9		~11		~33	

DP, degree of polymerisation; I, intervention group; C, control group; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; OS, oligosaccharide; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight.
* Values least squared means; ** Median values

Table 46. Non-digestible oligosaccharide and inulin and faecal pH and SCFA content in infants

Study	Intervention	Dose (g/d)	Time	Faecal pH C	Faecal pH I	SCFA method	SCFA unit of measure	Total SCFA C	Total SCFA I	Butyrate C	Butyrate I	Propionate C	Propionate I	Acetate C	Acetate I	Results
Moro, 2002	GOS/FOS mixture	4g/L	4 wk	6.1±0.7	5.4±0.5											No significant effect on faecal pH . NDO reduced faecal pH in dose-dependent manner.
		8g/L			5.2±0.4											
Ben, 2004	GOS	2.4g/L	6 mth	5.8±0.5	5.2±0.3	GLC	µmol/L/g faeces wet wt							12.3±4.6	22.2±4.7	GOS and human milk increased faecal acetate and decreased pH at 3 and 6 months
	Human milk				5.4±0.3										19.7±5.6	
Bakker-Zierikzee, 2005	GOS/FOS mixture in a 9:1 ratio	6g/L	16 wk	6.6±0.9	5.6±0.9	GLC	Total SCFA: mmol/kg faeces wet wt; Single SCFA: % of total SCFA	68.6±48.5	67.7±43.8	5.6±3.1	2.1±1.5	19.6±9.4	14.3±18.3	69.9±13.5	82.2±19.8	No effect on total SCFA concentration, GOS/FOS and human milk decreased the proportion of butyrate, and lowered faecal pH
	Human milk				5.7±0.9				59.2±28.4		1.6±1.6		6.4±8.7		89.7±11.1	
Fanaro, 2005	acidic citrus pectin OS	2 g/L	6 wk	6.3±0.7	6.1±0.9											Only pH change from baseline was assessed. GOS/FOS plus acidic OS lowered pH more than acidic OS alone
	FOS/GOS and acidic citrus pectin OS	8 g/L			5.2±0.4											
Knol, 2005	GOS/FOS mixture in 9:1 ratio	8 g/L	6 wk	6.3	5.7	GLC	% of total SCFA			4.0	2.4	17.8	12.0	77.2	85.2	NDO, to a lesser extent than human milk, increased the proportion of faecal acetate and decreased the proportion of propionate. NDO reduced faecal pH
	Human milk				5.8						1.9		6.9		89.9	
Scholtens, 2006	GOS/FOS mixture in a 9:1 ratio	2.5-4g/d	6 wk	6.5±0.8	6.3±1.2	GLC	Total SCFA: mmol/kg faeces wet wt; Single SCFA: % of total SCFA	28.6 **	27.9**	4.5	3.0	22.8	25.5	61.0	72.2	NDO had no significant effect on faecal SCFA or pH
Kim, 2007	Chicory inulin	1.5g/d	3 wk	6.5±0.5	6.3±0.3											No significant effect on faecal pH
Ben, 2008	GOS	2.4g/L	3 mth	5.6±0.5	5.2±0.3	GLC	mmol/g faeces wet wt							19.4±5.4	25.9±6.8	GOS and human milk increased faecal acetate concentration and decreased pH
	Human milk				5.3±0.2										23.8±5.7	
Scholtens, 2008	GOS/FOS 9:1 ratio	6g/L	26 wk	6.5	6.2											NDO decreased faecal pH.

I, intervention group; C, control group; NR, not reported; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; SCFA, short chain fatty acid; GLC, gas chromatography; HPLC, high-performance liquid chromatography; wk, week; d, day; wt, weight.
* Values least squared means; ** Median values

The effect of non-digestible carbohydrate on magnesium and calcium absorption

Background

189. Most calcium absorption occurs in the small intestine, but about 5% has been shown to occur in the colon (Barger-Lux *et al.*, 1989). Experimental work shows that short-chain fatty acids may stimulate calcium (Trinidad *et al.*, 1993; Trinidad *et al.*, 1996; Trinidad *et al.*, 1997) and magnesium absorption in the colon (Coudray *et al.*, 2003b), suggesting that increased colonic fermentation of carbohydrate may stimulate mineral absorption.

Balance studies

190. Balance studies have been used to measure the input and output of a nutrient, rather than actual absorption, and when input and output were equal, it has been assumed that the body was saturated. It has been known since the 1940s that subjects fed a high proportion of whole wheat products go into negative mineral balance, and this was ascribed to the phytic acid content of whole wheat (McCance & Widdowson, 1942b; McCance & Widdowson, 1942a; Widdowson & McCance, 1942). Phytic acid forms complexes with divalent cations, creating insoluble compounds in the intestine that are unavailable for absorption. An inhibitory effect of phytates on the absorption of iron (Hallberg *et al.*, 1989), zinc (Fredlund *et al.*, 2006), calcium (Heaney *et al.*, 1991) and magnesium (Bohn *et al.*, 2004b) has been demonstrated in single meal isotope studies. The oxalic acid content of food may also affect mineral balance, which also through the formation of complexes with divalent cations, may affect mineral balance (Bohn *et al.*, 2004a).

191. Dietary fibre may have mineral-binding capacities, which may alter mineral bioavailability. *In vitro*, dietary fibre binds calcium ions in direct proportion to its uronic acid content (James *et al.*, 1978). Microbial digestion in the colon of uronic acids, to which calcium is mainly bound, could make the ions available for colonic absorption.

192. Fifteen studies were identified that examined the effect of refined dietary fibres on calcium or magnesium balance (McCance & Widdowson, 1942a; Ismail-Beigi *et al.*, 1977; Cummings *et al.*, 1979b; Cummings *et al.*, 1979c; Drews *et al.*, 1979; Slavin & Marlett, 1980b; Stasse-Wolthuis *et al.*, 1980; Godara *et al.*, 1981; Behall *et al.*, 1987; Behall *et al.*, 1989; Behall, 1990; Wisker *et al.*, 1991; Kawatra *et al.*, 1993; Coudray *et al.*, 1997; Behall *et al.*, 2002). While some earlier studies suggested that cereal fibres may produce a negative mineral balance, overall, it appeared that the plant cell-wall polysaccharides of cereal brans, in amounts customarily eaten, were unlikely to exert a significant effect on mineral absorption in man, independently of the effect of any phytate present (Andersson *et al.*, 1983). Studies that have investigated the effect of soluble fibres, e.g. pectin and guar gum, have generally observed no effect on mineral balance (Cummings *et al.*, 1979c; Drews *et al.*, 1979; Stasse-Wolthuis *et al.*, 1980; Behall *et al.*, 1987; Behall *et al.*, 1989).

193. Twelve studies were identified that examined the effect of fibre-rich foods on calcium

or magnesium balance (Reinhold *et al.*, 1976; Stasse-Wolthuis *et al.*, 1980; Kelsay *et al.*, 1981; Van Dokkum *et al.*, 1982; Andersson *et al.*, 1983; Kelsay & Prather, 1983; Kelsay *et al.*, 1988; Spencer *et al.*, 1991; Dahl *et al.*, 1995; Knudsen *et al.*, 1996; Haack *et al.*, 1998b; Shah *et al.*, 2009). Overall, these studies demonstrated little or no effect on mineral balance.

194. Several studies have suggested that certain non-digestible carbohydrates may increase calcium or magnesium balance. The carbohydrates used included a novel resistant starch (Vermorel *et al.*, 2004), 100g/day polyol (Coudray *et al.*, 2003a), but not 30g/day (Gostner *et al.*, 2005), karaya gum (Behall *et al.*, 1987) and inulin or sugar beet fibre (Coudray *et al.*, 1997).

195. Overall, the balance studies suggested the effects of non-digestible carbohydrate on mineral balance depended largely on the nature of the fibres (soluble/insoluble, the degree to which they are fermented in the colon), on the amount ingested, especially on the presence of associated components in the diet such as phytates and on the homeostasis of concerned minerals (Coudray *et al.*, 2003b).

196. Balance studies, however, do not measure true fractional mineral absorption (Griffin & Abrams, 2005). This is determined by mineral isotope studies, especially dual isotope studies where two different isotopes are administered – one orally and one intravenously – and absorption is measured from the relative recovery of the oral and intravenous isotopes in a urine sample (Griffin & Abrams, 2005). If the urine collection is prolonged then the dual isotope tracer method may also capture any colonic component of calcium absorption. The use of methods such as the 5 hour specific activity or urine excretion methods carried out a few hours after administration of the test meal would be inadequate for this purpose.

Trial design

197. Ten articles were identified as eligible (see Appendix 2 for studies excluded). All examined the effect of non-digestible oligosaccharide and inulin on calcium or magnesium absorption (Van den Heuvel *et al.*, 1998; van den Heuvel *et al.*, 1999; van den Heuvel *et al.*, 2000; Tahiri *et al.*, 2001; Griffin *et al.*, 2002; Griffin *et al.*, 2003; Tahiri *et al.*, 2003; Abrams *et al.*, 2005; Holloway *et al.*, 2007; van den Heuvel *et al.*, 2009)

198. The trial design details have been summarised in Table 47. One trial employed a parallel design and the other nine employed cross-over designs, of which only one had no washout period.

199. Five trials were in adults (Van den Heuvel *et al.*, 1998; van den Heuvel *et al.*, 2000; Tahiri *et al.*, 2001; Tahiri *et al.*, 2003; Holloway *et al.*, 2007), four of which were in postmenopausal women, and five were in children and adolescents (van den Heuvel *et al.*, 1999; Griffin *et al.*, 2002; Griffin *et al.*, 2003; Abrams *et al.*, 2005; van den Heuvel *et al.*, 2009). All trials employed a non-digestible oligosaccharide or inulin intervention.

200. Eight of the trials assessed fractional absorption using dual-isotope techniques, while two used a single isotope technique (Tahiri *et al.*, 2001; Tahiri *et al.*, 2003). One trial

measured Mg absorption only (Tahiri *et al.*, 2001), seven measured calcium absorption only (Van den Heuvel *et al.,* 1998; van den Heuvel *et al.*, 1999; van den Heuvel *et al.,* 2000; Griffin *et al.*, 2002; Griffin *et al.*, 2003; Tahiri *et al.*, 2003; Abrams *et al.*, 2005) and two trials measured both magnesium and calcium absorption (Holloway *et al.,* 2007; van den Heuvel *et al.*, 2009). The majority of trials used orange juice, usually calcium-fortified, as the carrier for the oral isotope, although two used water (Tahiri *et al.*, 2001; Tahiri *et al.*, 2003) and one used a yoghurt drink (van den Heuvel *et al.*, 2000).

201. The duration of most interventions was three or four weeks, but ranged from 2 trials at nine days to one at 12 months. The initial sample sizes were generally smaller in the adult trials e.g. 12-15 subjects, while three of the trials in children had about 30, 50 and 55 subjects in each group.

202. Only one trial, which employed a controlled-diet, reported baseline dietary fibre intakes (Van den Heuvel *et al.,* 1998). Most trials employed either 3 or 4 day food records or weighed intakes to determine whether subjects maintained their habitual diet and a constant calcium intake.

203. The funding sources for all trials were either Governmental or Commercial or both; all trials reported funding sources.

Table 47. Calcium and magnesium absorption trial description

Study	Study design	Isotope absorption method	Oral isotope carrier	Country	Subject characteristics	Basal diet	Control intervention	Intervention	Dose (g/d)	Sample size at start	Duration	Funding source
Adults												
Van den Heuvel, 1998	XO - no washout	^{44}Ca, ^{48}Ca	orange juice	Holland	Adults aged 20-30y; 12M	Controlled	no added NDO	Chicory inulin, FOS or GOS	15	12	3 wk	European Union; ORAFTI, Belgium.
Van den Heuvel, 2000	XO - 19 d washout	^{44}Ca, ^{48}Ca	yogurt drink	Holland	Adults aged 55-65y; 12F postmenopausal	Ad libitum excluding NDO and probiotics	sucrose	GOS	20	12	9 d	Borculo Domo Ingredients, The Netherlands
Tahiri, 2001	XO - 3 wk washout	^{25}Mg	water	France	Adults aged 54-70; 11F postmenopausal	Ad libitum excluding NDO for first 23 d, than controlled low fibre (12g DF/d) for last 10-12 d	sucrose	FOS	10	14	5 wk	French Ministry of National Education and Scientific Research and Technology
Tahiri, 2003	XO - 3 wk washout	^{44}Ca	water	France	Adultsaged 50-70 (mean 60); 12F postmenopausal	Ad libitum excluding NDO for first 23 d, than controlled low fibre (12g DF/d) for last 10-12 d	sucrose	FOS	10	14	5 wk	French Ministry of National Education and Scientific Research and Technology
Holloway, 2007	XO - 6 wk washout	^{42}Ca, ^{46}Ca; ^{25}Mg, ^{26}Mg	orange juice	USA	Adults mean age 72y; 15F postmenopausal	Ad libitum with constant Ca intake	maltodextrin	Chicory inulin, FOS 1:1 ratio	10	15	6 wk	ORAFTI, Belgium
Children												
Van den Heuvel, 1999	XO - 19 d washout	^{44}Ca, ^{48}Ca	orange juice	Holland	Children aged 14-16y; 12M	Ad libitum low fibre excluding NDO and probiotics	sucrose	FOS	15	12	9 d	European Union; ORAFTI, Belgium
Griffin, 2002	XO - 2 wk washout	^{42}Ca, ^{46}Ca	orange juice	USA	Children aged 11-14y; 30F	Ad libitum with 1.2g/d Ca intake	sucrose	FOS	8	30	3 wk	Department of Agriculture, USA ORAFTI, Belgium
Griffin, 2003	XO - 2 wk washout	^{42}Ca, ^{46}Ca	orange juice	USA	Children aged 10-15y; 55F	Ad libitum with 1.2g/d Ca intake	sucrose	Chicory inulin, FOS 1:1 ratio	8	55	3 wk	Department of Agriculture, USA ORAFTI, Belgium
Abrams, 2005	P	^{42}Ca, ^{46}Ca	orange juice.	USA	Children aged 9-13y; 50M, 50F	Ad libitum with constant Ca intake	maltodextrin	Chicory inulin, FOS 1:1 ratio	8	100	12 months	National Institutes of Health, USA
Van den Heuvel, 2009	XO - 12 d washout	^{44}Ca, ^{48}Ca; ^{25}Mg, ^{26}Mg	orange juice	Holland	Children with Ca intakes less than 1.1g/d, aged 12-14y; 14F	Ad libitum excluding probiotics and NDO	maltodextrin	FOS	5-10	14	36 d	Cerestar, Belgium

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week, M, male; F, female; FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; NDO, non-digestible oligosaccharide.

Risk of Bias

204. A summary of the risk of bias assessment has been given in Table 48. All trials reported being randomised, with blinding of participants and personnel to the intervention. All trials reported on drop-out rates and gave some description of the causes. The dropout percentages varied from none to 21%. Where dropouts were reported, it either seems unlikely that missing outcome data were related to the intervention, or the missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups.

205. Overall, the quality of study design was good and the risk of bias generally low, although no trials reported on the method of randomisation or how intervention allocation was concealed.

Table 48. Risk of bias assessment

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Adults							
Van den Heuvel	1998	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Van den Heuvel	2000	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	8
Tahiri	2001	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	21
Tahiri	2003	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	14
Holloway	2007	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	7
Children							
Van den Heuvel	1999	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Griffin	2002	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Griffin	2003	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	2
Abrams	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	8
Van den Heuvel	2009	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	14

NR, not reported.

Results

206. The results from all trials have been summarised in Table 49. Outcome data, expressed as mean with standard deviation, have been given for the percentage calcium absorbed; however, these appear insufficiently comparable for quantitative synthesis. The degree of polymerisation of the saccharide units in non-digestible oligosaccharides and inulin has been included in Table 49.

207. In adults, one of the trials reported that 20g/day galacto-oligosaccharide increased the percentage of calcium absorbed. , One trial reported a significant greater *change from baseline* in the intervention group than in the control group, in response to a 10g/day inulin-derived 1:1 mixture of fructo-oligosaccharide and fructo-polysaccharide. The other two trials reported no effect, in response to supplementation with non-digestible oligosaccharide or inulin (10-15g/day). In children, two trials reported an increase in percentage calcium absorption in response to an 8g/day inulin- derived 1:1 mixture of fructo-oligosaccharide and fructo-polysaccharide. One trial did report that 15g/day fructo-oligosaccharide increased percentage calcium absorption in children, while another reported that 5 to 10g/day fructo-oligosaccharide had no effect.

208. One of the trials reported no effect of 15g/day of two different non-digestible oligosaccharides (fructo-oligosaccharide or galacto-oligosaccharide) or high-molecular-weight inulin, in twelve men, using the dual isotope calcium tracer technique (Van den Heuvel *et al.*, 1998). It was speculated that the 24 hour collection period used may have been inadequate to capture any effect of the oligosaccharides on colonic calcium absorption. Subsequent trials by the same authors included a 36-48 hour urine collection, and while two trials reported that 20g/day galacto-oligosaccharide and 15g/day fructo-oligosaccharide increased percentage calcium absorption (van den Heuvel *et al.*, 1999; van den Heuvel *et al.*, 2000), another reported that 5 to 10g/day fructo-oligosaccharide had no effect (van den Heuvel *et al.*, 2009). The other trials collected 48 hour urine samples. Two other trials reported that 8 or 10g/day fructo-oligosaccharide did not affect the percentage of calcium absorbed (Griffin *et al.*, 2002; Tahiri *et al.*, 2003). In trials that employed 36-48 hour urine collections, non-digestible oligosaccharides alone only increased the percentage of calcium absorbed at doses of 15g/day or more. When fructo-oligosaccharide and fructo-polysaccharide were administered together, lower doses (8-10g/day) were generally effective in increasing the percentage of calcium absorbed. The degree of polymerisation, therefore, may be factor, but further trials are required to elucidate this aspect.

209. Two trials measured magnesium absorption in response to supplementation with 10g/day fructo-oligosaccharide alone (Tahiri *et al.*, 2001; van den Heuvel *et al.*, 2009) and one trial in response to a 10g/day inulin-derived 1:1 mixture of fructo-oligosaccharide and fructo-polysaccharide (Holloway *et al.*, 2007). Two trials reported an increase in the percentage magnesium absorbed in response to fructo-oligosaccharide alone, while the trial measuring the response to the fructo-oligosaccharide and fructo-polysaccharide mixture reported a significant greater change from baseline in the intervention group than in the control group.

210. A study of eight adults, previously shown to increase their calcium absorption from

baseline values in response to eight weeks supplementation with 8g/d inulin-type fructans, reported that the increased absorption was mainly due (about 70% of the increase) to increased absorption occurring seven hours after oral dosing (Abrams *et al.*, 2007). This provided some support for the concept that an increase in fractional absorption of calcium could be due to increased colonic absorption stimulated by the fermentation of carbohydrate.

Table 49. Results of magnesium and calcium absorption trials

Study	Date	Intervention	Degree of polymerisation	Dose (g/d)	Duration	Mineral absorption determined	Control % calcium absorbed ± SD	Intervention % calcium absorbed ± SD	Results
Adults									
Van den Heuvel	1998	Chicory inulin	2-60	15	3 wk	Ca	28.1±14.9	25.8±8.0	NDO and inulin had no effect on % Ca absorption
		FOS	2-8	15				26.3±6.6	
		GOS	2-6	15				26.3±9.0	
Van den Heuvel	2000	GOS	2-8	20	9 d	Ca	20.6±7.0	23.9±6.9	NDO increased % Ca absorption (p=0.04 with one-sided test)
Tahiri	2001	FOS	2-4	10	5 wk	Mg	30.2±5.0	33.9±7.2	NDO increased the % Mg absorption
Tahiri	2003	FOS	2-4	10	5 wk	Ca	35.6±9.4	36.6±8.5	NDO had no effect on % Ca absorption
Holloway	2007	Chicory inulin, FOS 1:1 ratio*	2-65	10	6 wk	Ca, Mg	20.8±9.0	27.3±15.7	It was not reported if there was a significant difference between interventional and control and the end of the intervention. *The change* in Ca and MG absorption from baseline was sign. greater in the intervention than the control group.
Children									
Van den Heuvel	1999	FOS	2-8	15	9 d	Ca	47.8±16.4	60.1±17.2	NDO increased % Ca absorption (p<0.05, one sided)
Griffin	2002	FOS	2-8	8	3 wk	Ca	31.8±9.3	31.8±10.0	NDO had no effect on % Ca absorption
Griffin	2003	Chicory inulin, FOS 1:1 ratio*	2-65	8	3 wk	Ca	33.1±9.2	36.1±9.8	NDO/inulin increased % Ca absorption
Abrams	2005	Chicory inulin, FOS 1:1 ratio *	2-65	8	12 months	Ca	31.7±15.6	37.7±14.2	NDO/inulin increased % Ca absorption at 12 months, as well as 8 weeks after intervention start
Van den Heuvel	2009	FOS	2-4	5 to 10	36 d	Ca, Mg	45.5±17.0	44.8±16.8	NDO increased fractional absorption of Mg, but not Ca, after 36 days of supplementation. After 8 days of supplementation NDO had no effect.

d, day; y, year; wk ,week, FOS fructo-oligosaccharide; GOS, galacto-oligosaccharide; NDO, non-digestible oligosaccharide. * The FOS, inulin mix is a 1:1 mixture of fructo-oligosaccharide with a degree of polymerisation of 3–8 (mean 4), produced by means of a partial enzymatic hydrolysis of chicory inulin, and long-chain chicory inulin with a degree of polymerisation of 10–65 (mean 25).

Summary

The effect of carbohydrate on faecal weight and transit time

211. Available evidence was insufficient to conclude whether digestible carbohydrate had an effect on bowel habit, although one trial suggested starch and sugar were unlikely to affect faecal weight and total intestinal transit time. Available evidence showed a large faecal bulking capacity of wheat fibre, other cereal fibres, diets high in cereal and fruit and vegetable fibre, and fruit and vegetable fibres alone. Purified dietary fibres, such as cellulose and psyllium, but not pectin, were also shown to have a similar effect. Although inter-individual variation in response measures was large the effect on faecal wet weights broadly equated to a 4g increase in faecal wet weight per 1g dietary fibre.

212. Dietary fibres have been observed to reduce total intestinal transit time, but the effect size appears dependent on the basal transit times in the population studied, such that a reduction in transit times in response to dietary fibre was most marked in those subjects with initially high values and was least marked, if significant, in those subjects with initially low values.

213. Available evidence showed resistant starch to have a faecal bulking capacity, but not to affect transit times. It appeared that doses of resistant starch greater than 12g/d were required to produce an effect on faecal wet weight – the lowest dose shown to increase faecal weight was 17g/day. Evidence showed there were no differences in the faecal bulking capacities of the different types of resistant starch (1, 2 and 3), which broadly equated to a 1-2g increase in faecal wet weight per 1g resistant starch.

214. The results from polyol intervention trials generally reported an increase in faecal weight, which was in the order of a 0.5-1g increase in faecal wet weight per 1g polyol, but these involved high doses of polyol. Only one trial reported faecal weight data in response to polydextrose, showing a faecal bulking capacity in the order of a 2-3g increase in faecal wet weight per 1g polydextrose.

215. At daily doses of 10g or more, non-digestible oligosaccharides or inulin have been shown to have a faecal bulking capacity. There appeared to be no differences in the faecal bulking capacities of the different types of non-digestible oligosaccharide (fructo-oligosaccharide or galacto-oligosaccharide) or inulin investigated, which broadly equated to a 1-1.5g increase in faecal wet weight per 1g non-digestible oligosaccharide or inulin.

216. The National Diet and Nutrition Survey, 2000/2001 (Henderson *et al.*, 2003),

observed the lower and upper 2.5 percentile intakes of non-starch polysaccharide intakes in UK adults aged 19-64 years to be five and 24/day for women and six and 29g/day for men. An intake increase of 10g/day of non-starch polysaccharide is within this range and capable of increasing faecal weight. Information on resistant starch, polyol or non-digestible oligosaccharide and inulin intakes in the UK is not available from National Diet and Nutrition Survey or the Total Diet Study, but national surveys from other European countries suggest intakes to be less than 10g/day. It is unlikely that an increase in resistant starch, polyol or non-digestible oligosaccharide and inulin intakes within the range of current intakes would be sufficient to have an observable effect on faecal weight.

The effect of carbohydrate on faecal microflora and short chain fatty acid content

217. For the dietary fibres and resistant starches investigated there appeared to be little impact on faecal bacteria content, although total excretion would increase with increased faecal output. The non-digestible oligosaccharide and inulin interventions of 10g/day or more tended to selectively increase faecal content of *Bifidobacterium* spp. in adults, and there was limited evidence to suggest that polydextrose and polyol may also selectively increase the faecal content of *Bifidobacterium* spp. In infants, supplementation of breast milk substitutes and follow-on formulae with non-digestible oligosaccharide or inulin has been investigated as a means of changing infant gut microflora to become more *Bifidus* dominated, as observed in breastfed infants. Trials in infants aged less than 3 months tended to report that non-digestible oligosaccharide or inulin interventions increased the faecal content of *Bifidobacterium* spp., but trials in older infants were less consistent.

218. Overall, available evidence suggested dietary fibres have little impact on faecal short chain fatty acid content or pH, although total excretion would increase with increased faecal output. Results from polyol trials were inconclusive. An increase in faecal butyrate concentration was observed after supplementation with polydextrose, in one trial.

219. Resistant starch at doses of 20-40g/day appeared to lower faecal pH and increase faecal concentration or proportion of butyrate, but not at lower doses.

220. There was little evidence to suggest non-digestible oligosaccharide or inulin supplementation affected faecal pH or short chain fatty acid content in adults, although daily doses of 15g/day or more were observed to increase the faecal concentration or proportion of acetate. In infants supplementation of breast milk substitutes and follow-on formulae with non-digestible oligosaccharide or inulin has been investigated as a means to change infant faecal pH and short chain fatty acid content to be more similar to breastfed infants. In younger infants the faecal concentration or proportion of acetate was observed to increase in response to non-digestible oligosaccharide, to levels similar to those observed in the breast-fed infants. In older infants, non-digestible oligosaccharide supplementation was observed to lower faecal pH.

221. At this time, however, there is little conclusive evidence on the relationship between a *bifidobacteria*-dominated microflora, or an increased faecal butyrate concentration,

and relevant outcomes on health and well-being in later life.

The effect of carbohydrate on calcium and magnesium absorption

222. There was only limited evidence examining an effect of digestible carbohydrate on calcium and magnesium absorption. One trial in adults reported no difference in the fractional absorption of calcium between those subjects receiving a high carbohydrate diet or a low carbohydrate/high fat diet; while one trial in infants reported that lactose supplementation of breast-milk substitute increased the fractional absorption of calcium, relative to lactose-free formula.

223. Several trials investigated the effect of non-digestible oligosaccharide or inulin on calcium and magnesium absorption. Non-digestible oligosaccharide at doses of 15g/day or more tended to increase the percentage calcium absorbed, but when fructo-oligosaccharide and fructo-polysaccharide were administered together, lower doses (8-10g/day) were generally effective in increasing the percentage of calcium absorbed. More limited evidence suggested non-digestible oligosaccharides at doses of 10g/day were effective in increasing percentage magnesium absorption. There was a lack of evidence from trials investigating any possible effects of other carbohydrates on calcium and magnesium absorption.

Prevention of impaired colo-rectal function

Chronic constipation

224. Chronic constipation may be secondary to systemic metabolic disorders (e.g. hypothyroidism, diabetes mellitus, hypo-/hypercalcemia), neurogenic disorders (e.g. autonomic neuropathy, chronic intestinal pseudo-obstruction, Parkinson's disease, spinal cord injury), various medications (e.g. anticholinergics, antihypertensives, opiates), or structural abnormalities (e.g. mechanical obstruction). In the majority of patients of all ages, however, no obvious morphologic or biochemical abnormalities can be identified and these patients are considered to have functional constipation (Thompson *et al.*, 1999). The term 'functional' is used to describe symptoms or problems where no underlying pathophysiological cause can be determined, although factors such as poor dietary intake, intercurrent illness and underlying serious disorders are risk factors. Only trials in patients free of gastrointestinal disease associated with demonstrable change in a bodily organ or tissue have been included in the report, but inclusion has not been restricted on the basis of the constipation criteria used.

225. There is no single definition of constipation and patients' criteria for constipation often differ from their physicians' (Spiller & Thompson, 2010). Most patients define constipation by one or more symptoms: hard stools, infrequent stools (typically fewer than three per week), the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent on the toilet or in unsuccessful defecation. Constipation is more prevalent in women than in men, in non-whites than in white persons, in children than in adults, and in older than in younger adults (Lembo & Camilleri, 2003).

226. Constipation was traditionally defined as less than three bowel movements per week (Connell *et al.*, 1965), but many who fit this definition do not consider themselves constipated, while many who do consider themselves constipated also do not fit this definition. Subsequent evidence has suggested effort to defecate and stool consistency, or form, to be more important (Spiller & Thompson, 2010). Stool consistency or form (assessed using the Bristol Stool Form Scale), but not bowel frequency, has been shown to correlate with total intestinal transit time in irritable bowel patients (O'Donnell *et al.*, 1990; Heaton & O'Donnell, 1994) and chronically constipated patients (Saad *et al.*, 2010); in healthy subjects, however, results are less clear (Degen & Phillips, 1996; Lewis & Heaton, 1997c; Saad *et al.*, 2010). While hard stools correlate well with slow transit, and loose stools with fast transit through the colon, difficulty with defecation and stool frequency do not, as they are determined by factors other than colon transit (Spiller & Thompson, 2010).

Functional constipation

227. Since 1990, successive Rome working parties have developed a consensus definition of functional constipation, as defined by symptom-based diagnostic criteria. The most recent Rome criteria (Rome III) (Drossman, 2006) are applied to patients who do not take laxatives and report at least two of the following in any 12-week period during the previous 12 months:

- Fewer than three bowel movements per week
- Hard stool in more than 25% of bowel movements
- A sense of incomplete evacuation in more than 25% of bowel movements
- Excessive straining in more than 25% of bowel movements
- A need for digital manipulation to facilitate evacuation

228. Functional constipation is also defined as constipation-predominant irritable bowel syndrome (Longstreth *et al.*, 2006), for which abdominal pain is associated with a disturbed bowel habit.

Background

229. The settings for most of the cohort before-and-after and non-randomised studies assessing laxative use as an outcome measure were geriatric wards and nursing homes. The incorporation into the diet of wheat bran (Clark & Scott, 1976; McCallum *et al.*, 1978; Battle & Hanna, 1980; Sandman *et al.*, 1983; Valle-Jones, 1985; Rodrigues-Fisher *et al.*, 1993), prunes (Ferrer & Boyd, 1955) and oatmeal (Hull *et al.*, 1980; Hope & Down, 1986; Gibson *et al.*, 1995a; Selig & Boyle, 2003; Gostner *et al.*, 2005; Sturtzel & Elmadfa, 2008) or supplementation with a fibre concentrate (Khaja *et al.*, 2005), germinated barley (Kanauchi *et al.*, 1998b), guar gum (Patrick *et al.*, 1998), inulin (Kleessen *et al.*, 1997), sorbitol (Lederle *et al.*, 1990), partially defatted flaxseed (Tarpila *et al.*, 2004) or cellulose (Marks, 1949; Assisi *et al.*, 2000) were reported to reduce laxative use and/or improve symptoms. Most studies (Block, 1947; Perkin, 1977; Borgia *et al.*, 1983; Pers & Pers, 1983; Bass *et al.*, 1988; Chokhavatia *et al.*, 1988; Rouse *et al.*, 1991; Kinnunen *et al.*, 1993; Passmore *et al.*, 1993a; Passmore *et al.*, 1993b; Dettmar & Sykes, 1998), but not all (Tarpila *et al.*, 2004; Quah *et al.*, 2006), also reported psyllium supplementation to improve symptoms. A comparison trial reported that a high-fibre diet improved symptoms and reduced laxative use, which was more effective when water consumption was also increased (Anti *et al.*, 1998). One cohort before-and-after study reported xylo-oligosaccharide supplementation to improve constipation symptoms in pregnant women (Tateyama *et al.*, 2005) and, in children, the supplementation with mixed non-digestible carbohydrates (galacto-oligosaccharide, inulin, soy fibre and resistant starch) or bran and a high fibre diet was reported to improve constipation symptoms (Olness & Tobin, 1982; Kokke *et al.*, 2008).

230. Other cohort before-and-after studies measured faecal weight and total intestinal transit time in response to carbohydrate interventions. These studies reported an increase in faecal weight and/or a decrease in transit time from baseline when patients

were supplemented with wheat bran (Cowgill & Sullivan, 1933; Payler *et al.*, 1975; Graham *et al.*, 1982; Marcus & Heaton, 1986), corn bran (Graham *et al.*, 1982), methylcellulose (Hamilton *et al.*, 1988), psyllium (Srivastava *et al.*, 1976; Marlett *et al.*, 1987; McRorie *et al.*, 1998), fructo-oligosaccharide (Chen *et al.*, 2000), isomalto-oligosaccharide (Chen *et al.*, 2001), glucomannan (Marzio *et al.*, 1989; Chen *et al.*, 2008), lactitol (Ravelli *et al.*, 1995) and kiwifruit (Chan *et al.*, 2007a). One of the comparison trials in older patients reported wheat bran to be more effective than psyllium in decreasing total intestinal transit time (Andersson *et al.*, 1979). In two studies no effect of cellulose (Danjo *et al.*, 2008) or partially hydrolyzed guar gum (Takahashi *et al.*, 1994) was observed on faecal weight. In one study, only patients without pathological findings, such as rectocele or internal prolapse, showed reduced total intestinal transit times in response to psyllium, and slow transit and disordered defecation at baseline were associated with a poor response to psyllium (Voderholzer *et al.*, 1997). Of the patients with no evidence of pelvic floor dysfunction or slow-transit constipation, 85% improved, but 80% of those with slow-transit constipation and 63% of those with pelvic floor dysfunction did not improve with the use of psyllium.

231. Overall, these studies suggest that in some patients different non-digestible carbohydrates may relieve symptoms, reduce laxative use, decrease transit time, and increase faecal weight in constipated patients. Cohort before-and-after studies are non-randomised studies that lack an appropriate control and have not, therefore, been included in the synthesis below, but have been mentioned as they form the background to the trials included.

Trial design

232. Twenty four articles were identified as eligible, of which one was identified from article citation lists (Brown & Everett, 1990) (see Appendix 2 for studies excluded). Ten trials investigated cereal fibre and constipation (Sculati & Giampiccoli, 1984; Anderson & Whichelow, 1985; Finlay, 1988; Brown & Everett, 1990; Mantle, 1992; Badiali *et al.*, 1995; Howard et *al.*, 2000; Rees *et al.*, 2005; Hongisto *et al.*, 2006; Holma *et al.*, 2010); four investigated psyllium and constipation (Fenn *et al.*, 1986; Ashraf *et al.*, 1995; Cheskin *et al.*, 1995; Ashraf *et al.*, 1997); one investigated psyllium and wheat bran and constipation (Corinaldesi *et al.*, 1982); two investigated glucomannan and constipation (Staiano *et al.*, 2000; Loening-Baucke *et al.*, 2004); one investigated polyol and constipation (Vanderdonckt *et al.*, 1990); three investigated mixed dietary fibres and constipation (Rajala *et al.*, 1988; Odes & Madar, 1991; Sairanen *et al.*, 2007); one investigated cocoa husk and constipation (Castillejo *et al.*, 2006); and two investigated non-digestible oligosaccharides and constipation (Teuri & Korpela, 1998; Surakka *et al.*, 2009).

233. Trials in adults have been divided into hospitalised or institutionalised patients (see Table 50), who tended to be older adults, and outpatients with constipation or patients with self-reported constipation (see Table 51), who tended to be younger and without co-morbidities. Trials in pregnancy and children have been summarised in Table 52.

Many of the trials in hospitalised or institutionalised patients aimed to reduce laxative use and/or affect symptoms, while many of the trials in outpatients with constipation, or patients with self-reported constipation, did not allow laxative use during the study period or discontinued regular laxative use, but allowed laxatives if symptoms require medication. Several trials did not report laxative use.

234. Twenty trials were in adults (Corinaldesi *et al.*, 1982; Sculati & Giampiccoli, 1984; Fenn *et al.*, 1986; Finlay, 1988; Rajala *et al.*, 1988; Brown & Everett, 1990; Vanderdonckt *et al.*, 1990; Odes & Madar, 1991; Mantle, 1992; Ashraf *et al.*, 1995; Badiali *et al.*, 1995; Cheskin *et al.*, 1995; Ashraf *et al.*, 1997; Teuri & Korpela, 1998; Howard *et al.*, 2000; Rees *et al.*, 2005; Hongisto *et al.*, 2006; Sairanen *et al.*, 2007; Surakka *et al.*, 2009; Holma *et al.*, 2010) and these have been grouped into the different carbohydrate interventions. Three trials were in children (Staiano *et al.*, 2000; Loening-Baucke *et al.*, 2004; Castillejo *et al.*, 2006) and one was in pregnant women (Anderson & Whichelow, 1985). Sixteen trials employed a parallel design while eight employed a cross-over design, of which three had a washout period. There was a higher proportion of women in most trials.

235. Three trials assessed water intake, finding no difference between intervention groups (Teuri & Korpela, 1998; Sairanen *et al.*, 2007; Holma *et al.*, 2010). Other trials either provided water with the supplement or tried to ensure a minimum intake; thirteen trials did not report on water intakes. The efficacy of increasing water intake in the management of constipation, however, has been questioned, as it was shown to have no effect in one trial in children (Young *et al.*, 1998).

236. The criteria for chronic constipation varied considerably between trials, from either no criteria or healthy subjects self-reporting constipation, to laxative use or Rome criteria. Only two trials used the Rome criteria to define constipation (Rees *et al.*, 2005; Castillejo *et al.*, 2006). The duration of constipation was reported in only ten trials; most gave no details. The type of constipation was described in only four trials in adults as functional (Fenn *et al.*, 1986; Vanderdonckt *et al.*, 1990; Rees *et al.*, 2005; Hongisto *et al.*, 2006). Two trials in children described constipation as functional (Loening-Baucke *et al.*, 2004; Castillejo *et al.*, 2006), one of which included children with, or without, encopresis (the involuntary loss of formed, semi-formed, or liquid stool into the child's underwear in the presence of functional constipation in a child 4 years of age or more) (Loening-Baucke *et al.*, 2004).

237. Only two trials screened patients for inclusion on the basis of low bowel motion frequency (Ashraf *et al.*, 1995; Ashraf *et al.*, 1997). One trial demonstrated constipated patients to have slower total intestinal transit times than normal subjects at baseline. Patients had a mean total intestinal transit time of 155.6 hours, whereas in normal subjects it was 40.3 hours (Corinaldesi *et al.*, 1982). One trial screened patients for inclusion on the basis of a prolonged total intestinal transit time: mean basal transit time was 177 hours (Badiali *et al.*, 1995)

238. Most trials reported clinical outcomes, but several also/or reported physiological outcomes, e.g. transit times, faecal weight. Most of the trials in outpatients with constipation or adult patients with self-reported constipation investigated physiological measures, mainly transit times, but also faecal weight (see Table 51). Most of these trials reported that laxatives were prohibited during the trial, but in

three trials laxative use was not reported (Sculati & Giampiccoli, 1984; Cheskin *et al.*, 1995; Hongisto *et al.*, 2006), also in two trial laxatives were allowed if required (Sairanen *et al.*, 2007; Surakka *et al.*, 2009). Two trials in children reported physiological measures: one in neurologically impaired children allowed laxative use when required (Staiano *et al.*, 2000), while the other prohibited laxative use during the trial (Castillejo *et al.*, 2006).

239. Six trials in adults (Anderson & Whichelow, 1985; Brown & Everett, 1990; Rees *et al.*, 2005; Hongisto *et al.*, 2006; Sairanen *et al.*, 2007) reported baseline dietary fibre intakes (range 10-21g/day) and two in children reported a range of 5-13g/day (Staiano *et al.*, 2000; Castillejo *et al.*, 2006). Many trials did not report the dietary fibre content of the intervention and only two trials reported the method used to determine dietary fibre content (Rees *et al.*, 2005; Castillejo *et al.*, 2006).

240. The duration of interventions ranged from 2to 13 weeks: eight trials had a duration of less than four weeks, and 19 trials had a duration of 4 weeks or more. The initial sample sizes ranged from seven to 201 patients. None of the trials in hospitalised or institutionalised adult patients with constipation reported their funding source. The funding sources for all other trials, where reported, were either Governmental or Commercial or both; 50% of trials did not report funding sources.

Table 50. Trials in hospitalised or institutionalised adult patients with constipation

Study	Study design	Country	Constipation criteria	Water intake	Laxative use	Subject characteristics	Clinical outcomes assessed	Control intervention	Intervention	Daily dose (g/d)	Sample size at start	Duration	Funding source
Cereal fibre													
Finlay, 1988	P	England	laxative use; manual evacuations	attempted to ensure adequate fluid intake	Discontinued unless required	Hospital geriatric ward patients, mean age 80y; 12 women (100%)	Bowel frequency and laxative use	no treatment	Wheat bran	1.5 gross	12	6 wk	NR
Brown, 1990	P	Canada	laxative use;	Instructed to have an intake of at least 1500ml/d	as required	Nursing home patients, mean age 83y, 32 women (78%)	Bowel frequency and laxative use	no treatment	Wheat bran	2 g/d	41	12 wk	NR
Mantle, 1992	P	Canada	laxative use;	NR	as required	Nursing home patients	Bowel frequency, stool consistency and laxative use	no treatment	Wheat bran	1-3 tablespoons (1.5g/d crude fibre)	50	13 wk	NR
Howard, 2000	P	USA	BM<3/wk and laxative use	average fluid intake of at least 1500ml/d	as required	Intermediate care unit patients aged 61-80y (mean 73y); 0 women	Bowel frequency and laxative use	no treatment	Wheat bran	4-6 tablespoons	12	6 wk	NR
Mixed carbohydrates													
Rajala, 1988	P	Finland	laxative use and BM<1/d	NR	as required	Hospital surgery and internal medicine patients. Study completers aged 58-88y; 22 women (66%)	Bowel frequency, symptoms and laxative use	placebo	lactitol, wheat bran and guar gum	lactitol ~6g; bran ~0.6g; gum ~1.1g.	51	2 wk	NR
Polyol													
Vanderdonckt, 1990	XO - 4 wk washout	Belgium	when not taking laxative, BM<3/wk and generally hard stools	lactitol dissolved in 250ml water	Discontinued unless required	Hospital patients. Study completers aged 63-101y (mean 84y); 28 women (67%)	Bowel frequency, symptoms and laxative use	placebo (dextronse)	Lactitol	10-30	46	4 wk	NR
Non-digestible oligosaccharide													
Teuri, 1998	XO - no washout	Finland	BM<3/wk, laxative use or hard stools	Mean 1.28 – 1.36 l/d	Discontinued unless required	Nursing home patients, aged 69-87y (mean 80y); 14 women (100%)	Bowel frequency, stool consistency and symptoms	placebo	GOS	9	15	2 wk	NR

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; SCFA, short chain fatty acid; NDO, non-digestible oligosaccharide; GOS, galacto-oligosaccharide; DF, dietary fibre; BM, bowel movement

Table 51. Trials in adult outpatients with constipation or patients with self-reported constipation

Study	Study design	Country	Constipation criteria	Water intake	Laxative use	Subject characteristics	Outcomes assessed	Control intervention	Intervention	Daily dose (g/d)	Sample size at start	Duration	Funding source
Cereal fibre													
Corinaldesi, 1982	XO - no washout	Italy	BM<3/wk	NR	No laxatives allowed	Outpatients, mean age 36y; 11 women (91%)	Total intestinal transit time	placebo	Wheat bran	20g gross	12	3 wk	NR
Sculati, 1984	P	Italy	NR	instructed to have 800ml/d	NR	Outpatients, aged 21-73y; 33 women (82%)	BM, stool consistency and painful defecation	no treatment	Wheat fibre preparation	7 gross (5.6 DF)	40	30 d	NR
Badiali, 1995	XO - no washout	Italy	BM<3/wk, incomplete evacuation, hard stools or straining with prolonged transit times	instructed to have 1500ml water/d	No laxatives allowed	Outpatients, aged 20-65y (mean 37y); 26 women (90%)	BM and symptoms, total intestinal transit time, faecal weight	placebo	Wheat bran	20 gross (12.5 DF)	29	4 wk	NR
Rees, 2005	P	England	Rome I criteria	NR	No laxatives allowed	Outpatients with constipation predominant IBS aged 20-69y; 24 (86%) women	BM, and symptoms, total intestinal transit time, faecal weight	placebo	Wheat bran	10-20 gross (3.6-7.3 DF)	28	8 - 12 wk	NR
Hongisto, 2006	P	Finland	self-reported reduced BM and straining at defecation	NR	NR	Subjects aged 18-57y (mean 42y); 29 women (100%)	BM, stool consistency, abdominal pain and straining, total intestinal transit time	low-fibre bread (6.6g fibre/d)	Rye bread	30 DF	29	3 wk	NR
Holma, 2010	P	Finland	self-reported constipation, BM<5/wk	Recorded	No laxatives allowed	Subjects aged 24–78 y ; ~18 women (~90%)	BM, stool consistency, abdominal pain and straining, total intestinal transit time, faecal weight, pH and SCFA	low-fibre bread (8.6g fibre/d)	Rye bread	30 DF	20	3 wk	Finnish National Technology Agency, Valio Ltd, Fazer Bakeries Ltd.
Psyllium													
Corinaldesi, 1982	XO - no washout	Italy	BM<3/wk	NR	No laxatives allowed	Outpatients, mean age 36y; 11 women (91%)	Total intestinal transit time	placebo	Psyllium	14g gross	12	3 wk	NR
Fenn, 1986	P	England	NR	NR	No laxatives allowed	Outpatients, aged 17-70y (median 49y); 151 women (75%)	BM, stool consistency, abdominal pain and straining	placebo	Psyllium	3 sachets (10.8 DF)	201	2 wk	NR
Ashraf, 1995	P	USA	BM<3/wk - confirmed by stool diary at baseline	NR	No laxatives allowed	Outpatients, aged 40-75y (mean 51y); 14 women (64%)	Bowel frequency, consistency, pain and straining, c olon transit time, faecal weight	placebo	Psyllium	10 gross	22	8 wk	Procter & Gamble Co. USA
Cheskin, 1995	XO - no washout	USA	BM<3/wk, incomplete evacuation, hard stools plus excessive straining	placebo or fibre taken with 1000ml water/d	NR	Outpatients, aged 66-87y, 5 women (50%)	BM and stool consistency, total intestinal transit time, faecal weight, colonic motility	placebo	Psyllium	24 gross	10	4 wk	The John Hartford Foundation :and Konsyl Pharmaceuticals
Ashraf, 1997	P	USA	BM<3/wk - confirmed by stool diary at baseline	placebo or fibre taken with 500ml water/d	No laxatives allowed	Patients with Parkinson's disease, aged 54-80y (mean 66y); 3 women (43%)	Bowel frequency, stool consistency, straining, pain, colon transit time, faecal weight	placebo	Psyllium	10.2 gross	7	8 wk	Procter & Gamble Co. USA

Trials in adult outpatients with constipation or patients with self-reported constipation

Study	Study design	Country	Constipation criteria	Water intake	Laxative use	Subject characteristics	Outcomes assessed	Control intervention	Intervention	Daily dose (g/d)	Sample size at start	Duration	Funding source
Mixed carbohydrate													
Odes, 1991	P	Israel	constipation (BM<3/wk) requiring laxative use for at least 2 years.	NR	As required	Outpatients with constipation or constipation predominant-IBS, aged 19-76y; 22 women (69%)	BM, consistency, symptoms and laxative use	placebo	Celandin-aloevera-psyllium (ratio 6:3:1)	0.5-1.5 (0.2-0.7 DF)	35	4 wk	Ronen Nature Industries Ltd, Israel
Sairanen, 2007	XO - 2 wk washout	Finland	self-reported; BM<5/wk or straining at defecation	Recorded	Discontinued unless required (BM<1/2d)	Subjects aged 61-92y (mean 76y); 32 women (74%)	BM, stool consistency, abdominal pain and straining	placebo yoghurt	GOS (12g/d), prune (12g/d) and linseed (6g/d)	NR	43	3 wk	Valio Ltd, R& D
Non-digestible oligosaccharide													
Surakka, 2009	XO - 2 wk washout	Finland	BM<5/wk and/or difficulties in defecation	NR	Discontinued unless required	Subjects aged 60-80y (mean 68y); 31 women (76%)	BM, stool consistency, abdominal pain and straining, total intestinal transit time,	placebo yoghurt	GOS	10	42	3 wk	Finnish National Technology Agency and Valio Ltd

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; SCFA, short chain fatty acid; NDO, non-digestible oligosaccharide; GOS, galacto-oligosaccharide; DF, dietary fibre; BM, bowel motions

Table 52. Trials in pregnant women and children with constipation

Study	Study design	Country	Constipation criteria	Water intake	Laxative use	Subject characteristics	Outcomes assessed	Control intervention	Intervention	Daily dose (g/d)	Sample size at start	Duration	Funding source
Pregnancy													
Anderson, 1985	P	England	Changed frequency and consistency of bowel function for at least 1 week.	NR	none	Pregnant women in third trimester attending antinatal clinics; mean age 28y	Bowel frequency, stool consistency and painful defecation	no treatment	Corn bran	20 gross (8.3 DF)	40	2 wk	NAPP Laboratories
									Wheat bran	23 gross (9.4 DF)		2 wk	
Children													
Staiano, 2000	P	Italy	Caretaker report constipation of at least 12 months duration	~500ml/d (100ml water 500mg fibre or placebo)	as required	Neurologically impaired children, mean age 5.7y	Bowel frequency, stool consistency, abdominal pain and laxative use, total intestinal transit time, faecal weight	placebo	Glucomannan	200mg/kg body wt	20	12 wk	NR
Loening-Baucke, 2004	XO - no washout	USA and Italy	Delay or difficulty in defecation for ≥ 6 months	50ml/500mg fibre or placebo	as required	Outpatients aged 4-12y (mean 7y); 15 girls (48%)	Bowel frequency, stool consistency, abdominal pain and laxative use	placebo	Glucomannan	100mg/kg body wt (max. 5g/d)	46	4 wk	DicoFarm, Italy
Castillejo, 2006	P	Spain	Rome II criteria	placebo or fibre taken with 400ml milk/d	No laxatives allowed	Outpatients aged 3-10 (mean 6y); 34 girls (61%)	Bowel frequency, stool consistency and abdominal pain, colon transit time	placebo	Cocoa husk and beta fructosans (4:1 ratio)	5.5 (for 3-6y) or 11 (for 7-10y)	56	4 wk	Madaus SA, Instituto de Salud Carlos III, Spain

P, parallel; XO, cross-over; NR, not reported; d, day; y, year; wk ,week; SCFA, short chain fatty acid; NDO, non-digestible oligosaccharide; GOS, galacto-oligosaccharide; DF, dietary fibre

Risk of bias

241. A summary of the risk of bias assessment has been given for trials in adults in hospitalised or institutionalised patients (see Table 53), those in outpatients with constipation or patients with self-reported constipation (see Table 55), and trials in pregnancy and children (see Table 54). Only two trials reported on how randomisation was achieved and only one clearly reported how allocation was concealed (Castillejo *et al.*, 2006).

242. Ten trials were open and all used either wheat bran or psyllium interventions. Difficulty in blinding participants and personnel to bran interventions has been noted (Anderson & Whichelow, 1985). There were twelve trials reporting blinding of participants and personnel. Most trials reported on drop-out rates and gave some description of the causes, but one trial did not ,and repored only on patients who completed the trial (Mantle, 1992). The dropout percentages varied from none to 35%. Ninetrials reported that they had no drop-outs. In trials that did report drop-outs, either it seemed unlikely that missing outcome data were related to the intervention, or missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups.

243. Overall, the quality of study design was variable, with the highest proportion of trials at highest risk of bias being in hospitalised or institutionalised patients; particularly for cereal fibre interventions (see Table 53). The trials in children had the best study design and lowest risk of bias.

Table 53. Risk of bias assessment of trials in hospitalised or institutionalised adult patients with constipation

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Cereal fibre							
Finlay	1988	Yes	NR	NR	Open	No missing outcome data	0
Brown	1990	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	7
Mantle	1992	Yes	NR	NR	Open	Unclear – not discussed	26
Howard	2000	Yes	NR	NR	Open	No missing outcome data	0
Mixed carbohydrates							
Rajala	1988	Yes	NR	NR	Participants and personnel blind	Missing outcome data similar in numbers across intervention groups	35
Polyol							
Vanderdonckt	1990	Yes	Consecutive patients	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	9
Non-digestible oligosaccharide							
Teuri	1998	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	7

NR, not reported; BM, bowel motion

Table 54. Risk of bias assessment of trials in pregnant women and children with constipation

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Pregnancy							
Anderson	1985	Yes	NR	NR	Open	No missing outcome data	0
Children							
Staiano	2000	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	5
Loening-Baucke	2004	Yes	NR	Envelope	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	33
Castillejo	2006	Yes	Computer generated	Sealed envelope	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	14

NR, not reported; BM, bowel motion

Table 55. Risk of bias assessment of trials in adult outpatients with constipation or patients with self-reported constipation

Study	Date	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Cereal fibre							
Corinaldesi	1982	Yes	NR	NR	Open	No missing outcome data	0
Sculati	1984	Yes	NR	NR	Open	One patient dropped out from intervention group due to flatulence	3
Badiali	1995	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	17
Rees	2005	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	21
Hongisto	2008	Yes	NR	NR	Open	No missing outcome data	0
Holma	2010	Yes	NR	NR	Open	Missing outcome data unlikely to be related to outcome	4
Psyllium							
Corinaldesi	1982	Yes	NR	NR	Open	No missing outcome data	0
Fenn	1986	Yes	NR	NR	Participants blind only	Missing outcome data balanced in numbers across intervention groups	9
Ashraf	1995	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Cheskin	1995	Yes	NR	NR	Participants blind only	Missing outcome data unlikely to be related to outcome	30
Ashraf	1997	Yes	NR	NR	Participants blind only	No missing outcome data	0
Mixed carbohydrates							
Odes	1991	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	9
Sairanen	2007	Yes	NR	NR	Participants and personnel blind	No missing outcome data	0
Non-digestible oligosaccharide							
Surakka	2009	Yes	NR	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	2

NR, not reported; BM, bowel motion

Results

244. Data on subjective measures of bowel habit were insufficiently comparable for quantitative synthesis, but findings have been summarised in Table 56 to Table 58. Data on objective measures of bowel habit, bowel motions and faecal weight, were also insufficiently comparable for quantitative synthesis, but these have been summarised in Table 59. Trials generally reported average values, but not the necessary variance data (i.e. standard deviations) to enable synthesis of the data. The mean values for bowel motion frequency, faecal weight and transit time have been tabulated.

Clinical outcomes

Hospitalised or institutionalised patients

245. The results from trials in hospitalised or institutionalised patients have been summarised in Table 56. All trials allowed laxative use during the intervention period. Laxative use was the main criterion for constipation in these trials and reduction in laxative use was the main outcome measure.

246. Cereal fibre was effective in reducing laxative use in two trials (Brown & Everett, 1990; Howard *et al.*, 2000) and there was a tendency to reduce laxative use in the other two (Finlay, 1988; Mantle, 1992). In other trials of institutionalised patients, laxative use was reduced by lactitol (10-20g/d) (Vanderdonckt *et al.*, 1990), but was unaffected by non-digestible oligosaccharide supplementation (9g/d) (Teuri & Korpela, 1998) or a combination of lactitol, wheat bran and guar gum, although the dose was not reported (Rajala *et al.*, 1988).

247. Differences in bowel frequency between intervention groups were less consistent in trials of institutionalised patients. None of the trials recruited patients on the basis of low bowel motion frequency. Only one of the four trials supplementing with cereal fibre alone observed an increase bowel frequency (Brown & Everett, 1990) while another reported a higher proportion of patients with 2-7 bowel motions a week of soft or firm consistency in response to wheat bran (Mantle, 1992). Lactitol alone (Vanderdonckt *et al.*, 1990), and in conjunction with wheat bran and guar gum (Rajala *et al.*, 1988) was effective at increasing bowel frequency, as was non-digestible oligosaccharide supplementation (Teuri & Korpela, 1998).

248. Overall, these results suggested that cereal fibre and lactitol reduced total laxative use in an institutionalised or hospital setting; however, as noted in the risk of bias assessment the highest proportion of trials at highest risk of bias were conducted in hospitalised or institutionalised patients. Available evidence consisted of a small number of low quality trials. High quality trials are required to determine an effect on reducing laxative use before conclusions can be drawn.

Outpatients with constipation or patients with self-reported constipation

249. The results from trials in outpatients with constipation or adults with self-reported constipation have been summarised in Table 57. A reduced bowel frequency was the main criterion for constipation in these trials and bowel motion frequency and stool consistency or symptoms were the main outcome measures. The constipation criteria used for these trials varied considerably, from either no reported criteria, or healthy subjects self-reporting constipation, to Rome criteria; equally, the setting for these trials varied between gastroenterology outpatient clinics to self-medicated subjects. All trials in outpatients with constipation or adults with self-reported constipation reported on bowel frequency, but only two trials screened patients for inclusion on the basis of low bowel motion frequency (Ashraf *et al.*, 1995; Ashraf *et al.*, 1997).

250. Most trials in adults did not allow laxative use during the intervention, while three trials did not report on whether laxative use was allowed (Sculati & Giampiccoli, 1984; Cheskin *et al.*, 1995; Hongisto *et al.*, 2006). Three trials reported allowing laxative use during the intervention (Odes & Madar, 1991; Sairanen *et al.*, 2007; Surakka *et al.*, 2009), of which, one reported on any sparing of laxative use during the trial: it reported a yoghurt containing non-digestible oligosaccharide (12g/day), prunes (12g/day) and linseed (6g/day) to have no effect (Sairanen *et al.*, 2007)., Another trial observed that, compared to baseline use, a combination of celandin-aloevera-psyllium (0.2-0.7g dietary fibre/day) reduced laxative use in patients with constipation or constipation-predominant-irritable bowel syndrome (Odes & Madar, 1991).

251. Four trials investigated the effect of a psyllium intervention (Fenn *et al.*, 1986; Ashraf *et al.*, 1995; Cheskin *et al.*, 1995; Ashraf *et al.*, 1997). Two reported increased bowel motion frequency in response to supplementation, while in another trial there was a tendency for bowel frequency to be increased with psyllium. Stool consistency and abdominal pain were reported to be improved in one larger trials (Fenn *et al.*, 1986), but not the other trials (Ashraf *et al.*, 1995, Cheskin *et al.*, 1995; Ashraf *et al.*, 1997). In one of these trials, patients also had Parkinson's disease (Ashraf *et al.*, 1997), while the other trials were all in outpatients.

252. Of the two mixed carbohydrate interventions, non-digestible oligosaccharide, prunes and linseed (Sairanen *et al.*, 2007), and celandin-aloevera-psyllium (Odes & Madar, 1991) only the former reported an increase in bowel frequency; while there was a tendency for bowel frequency to be higher with non-digestible oligosaccharide alone (Surakka *et al.*, 2009). Less strain at defecation was reported in response to non-digestible oligosaccharide, either alone (Surakka *et al.*, 2009) or with prunes and linseed (Sairanen *et al.*, 2007). Also with prunes and linseed, a trend towards improvement stool consistency was observed. The subjects in both the trials conducting a non-digestible oligosaccharide intervention had milder constipation than those in the trial conducting the celandin-aloevera-psyllium intervention.

253. Cereal fibre was used as an intervention in five trials (Sculati & Giampiccoli, 1984; Badiali *et al.*, 1995; Rees *et al.*, 2005; Hongisto *et al.*, 2006; Holma *et al.*, 2010). Two trials in adults with self-reported constipation reported that rye bread increased bowel frequency, improved stool consistency and resulted in less strain at defecation relative to low-fibre bread (Hongisto *et al.*, 2006; Holma *et al.*, 2010); one trial in dietetic clinic outpatients with constipation observed that wheat fibre preparation increased bowel frequency and improved stool consistency, even though it is unclear if this was

in relation to baseline or the control group (Sculati & Giampiccoli, 1984).Two other trials focused on inpatients with constipation from gastroenterology outpatient clinics observed no effect of wheat bran on bowel frequency, strain at defecation or other symptoms (Badiali *et al.*, 1995; Rees *et al.*, 2005).

254. Two trials were conducted in patients with constipation-predominant IBS. While one observed no effect of wheat bran (10-20g/day for 12 weeks) on bowel frequency or symptoms (Rees *et al.*, 2005), the other reported outcomes in relation to baseline only (Odes & Madar, 1991).

255. The results from trials in pregnant women and children with constipation have been summarised in Table 58. Two of the trials, both in children, allowed laxative use (Staiano *et al.*, 2000; Loening-Baucke *et al.*, 2004). Both trials investigated the effect of glucomannan on constipation. One, reported results in relation to baseline only (Staiano *et al.*, 2000); the other reported glucomannan to reduce the proportion of children with abdominal pain and with less than three bowel motions a week, but had no effect on overall bowel frequency, laxative use or stool consistency compared with placebo (Loening-Baucke *et al.*, 2004). One other trial in children with constipation, as defined by the Rome II criteria, showed cocoa husk (4g/day) and beta fructosans (1g/day) to increase the number of children with improved stool consistency, but the intervention had no effect on bowel frequency (Castillejo *et al.*, 2006).

256. Only one trial investigated an effect of non-digestible carbohydrates on constipation in pregnancy (Anderson & Whichelow, 1985), but it reported results relative to baseline only. This trial, conducted in pregnant women in their third trimester, observed wheat bran supplementation to increase bowel motion frequency, while there was a tendency for corn fibre supplementation to do so also. No significant effects on stool consistency and abdominal pain were observed, but there was a tendency towards improvement by the fibre intervention. These subjects were defined as constipated on the basis of changed frequency and consistency of bowel function.

Table 56. Trials in hospitalised or institutionalised adults with constipation - clinical outcomes

Study	Duration	Bowel motion control (/wk)	Bowel motion intervention (/wk)	Bowel motion increase[#]	Overall symptom improvement[#]	Laxative use sparing[#]	Improved stool consistency[#]	Less abdominal pain[#]	Less strain at defecation[#]	Results
Cereal fibre										
Finlay, 1988	6 wk	NR	NR	N	N	N	NR	NR	NR	No difference between wheat bran and control on bowel motions or laxative use, although laxative use tended to be lower in the bran group
Brown, 1990	12 wk	4.1	8.0	Y	NR	Y	NR	NR	NR	Wheat bran reduced the frequenzy of laxative use and increased bowel motion frequency relative to untreated controls
Mantle, 1992	13 wk	NR	NR	Y	NR	N	N	NR	NR	No difference between wheat bran and control on laxative use, although both groups showed a decrease, the bran group showed a larger decrease.. The bran group had a higher proportion of patients with 2-7 bowel motions/wk of soft or firm consistency than the control group
Howard, 2000	6 wk	2.67	2.28	N	NR	NR	NR	NR	NR	Bran had no effect on bowel motion frequency, but replaced laxative use and reduced total bowel medication relative to untreated controls
Mixed carbohydrates										
Rajala, 1988	2 wk	4.3	5.9	Y	N	N	NR	NR	NR	The lactitol, wheat bran and guar gum yoghurt increased bowel motion frequency with no effect on laxative use. There was a non-signicant change in patient reported relieve from constipation, from 25% in the control group to 50% in intervention group.
Polyol										
Vanderdonckt, 1990	4 wk	~3.5	~6.3	Y	NR	Y	Y	NR	NR	Lactitol increased bowel motion frequency, improved stool consistency and reduced laxative use compared with placebo
Non-digestible oligosaccharide										
Teuri, 1998	2 wk	5.9	7.1	Y	N	N	N	N	(p=0.07)	Galactooligosaccharide increased bowel motion frequency, but had no effect on symptoms or laxative use, compared with placebo. There was a tendency for GOS to reduce strain at defecation. (p=0.07).

Y, yes; N, no; NR, comparison to control group not reported; wk, week; d, day; NDO, non-digestible oligosaccharide. [#] A number of differing outcome measures were reported in the various studies. Refer to 'Results' column for further detail. Comparisons to baseline have not been recorded in this column.

Table 57. Trials in adult outpatients with constipation or adults with self-reported constipation- clinical outcomes

Study	Duration	Bowel motion control (/wk)	Bowel motion intervention (/wk)	Bowel motion increase[#]	Overall symptom improvement[#]	Laxative use sparing[#]	Improved stool consistency[#]	Less abdominal pain[#]	Less strain at defecation[#]	Results
Cereal fibre										
Sculati, 1984	30 d	NR	NR	(NR/Y)	NR	NR	(NR/Y)	NR	NR	While a significant decrease was reported in the number of patients with constipation (1 defecation every 3 or more days) and those with hard or semi-hard feces, it is unclear if this significant decrease was in relation to baseline or the control group.
Badiali, 1995	4 wk	5.1	6.4	N	N	*	NR	N	N	Both bran and placebo equally increased bowel frequency from baseline, with no difference between groups. All patients were instructed to have daily dietary intake of 15g fibre after baseline period, which may explain the placebo response. A carry over effect into the placebo period on bowel frequency and transit time was observed for bran.
Rees, 2005	8 - 12 wk	7.0	8.4	N	N	*	N	N	N	No difference between bran and placebo on bowel frequency. Bran and placebo equally improved overall symptoms.
Hongisto, 2006	3 wk	6.3	9.7	Y	N (symptoms worsened; p<0.001)	NR	Y	NR	Y	Rye bread improved stool consistency and strain at defecation, and increased bowel frequency relative to low-fibre bread Rye bread increased gastrointestinal symptom score (abdominal pain + flatulence + bloating + hard or loose stools) through 3-week intervention and especialy during initial intervention week.
Holma, 2010	3 wk	5.5	6.2	Y	NR	*	Y	N	Y	Rye increased bowel motion frequency and more frequently softened stool consistency and eased defecation, relative to low-fibre bread.
Psyllium										
Fenn, 1986	2 wk	median 9	median 14	Y	Y	*	Y	Y	Y	Psyllium increased bowel motion frequency, and improved stool consistency compared with placebo. Comparing baseline to study end, abdominal pain and straining was reduced in significantly more subjects in the psyllium than in the placebo group. Invesitgators rated treatment to be effective in significantly more subjects in the psyllium group, than control group. In the psyllium group, significantly more subjects rated their constipation to be better, than in the control group.
Ashraf, 1995	8 wk	3.1	3.8	NR	NR	*	NR	NR	NR	Compared to baseline, psyllium increased bowel motion frequency, reduced abdominal pain and improved stool consistency.
Cheskin, 1995	4 wk	5.6	9.1	P<0.1	NR	NR	N	NR	NR	No difference between psyllium and control on stool consistency, but there was a tendency for bowel frequency to be higher on psyllium (p<0.1).
Ashraf, 1997	8 wk	3.4	5.7	Y	NR	*	N	N	N	Psyllium increased bowel motions compared with placebo. No effect on symptoms.
Mixed carbohydrates										
Odes, 1991	4 wk	4.3	7.9	NR	NR	NR	NR	NR	NR	Compared to baseline, celandin-aloevera-psyllium increased bowel motions, improved stool consistency and reduced laxative use, but- no effect on abdominal pain was observed. No comparison of intervention group and control group was made.
Sairanen, 2007	3 wk	7.1	8	Y	N	N	(p<0.06)	Y	Y	The galactooligosaccharide, prune and linseed yoghurt increased bowel frequency, reduced abdominal pain and improved ease of defecation relative to placebo yoghurt and there was a tendency for the enriched yoghurt to improve stool consistency (p<0.06). No effect on laxative use.
Non-digestible oligosaccharide										
Surakka, 2009	3 wk	5.9	6.4	(p=0.08)	NR	NR	NR	N	Y	Galactooligosaccharide improved ease of defecation.releative to placebo. There was also a tendency for increased bowel motion frequency (p=0.08). There was no effect on abdominal pain. The study's between-group comparisons, were based on each group's change from baseline to study end.

Y, yes; N, no; NR, not reported; wk, week; d, day; NDO, non-digestible oligosaccharide; * no laxatives allowed. [#] A number of differing outcome measures were reported in the various studies. Refer to 'Results' column for further detail. Comparisons to baseline have not been recorded in this column.

Table 58. Trials in pregnant women and children with constipation - clinical outcomes

Study	Duration	Bowel motion control (/wk)	Bowel motion intervention (/wk)	Bowel motion increase [#]	Overall symptom improvement[#]	Laxative use sparing[#]	Improved stool consistency[#]	Less abdominal pain[#]	Less strain at defecation[#]	Results
Pregnancy										
Anderson, 1985	2 wk	NE	NE	NR	NR	*	NR	NR	NR	Results were reported relative to baseline only. Compared to baseline, wheat bran significantly increased bowel motions and there was a tendency for corn bran to do so also. No significant effect observed on stool consistency,abdominal pain or straining, but there was a tendency for these to be improved by fibre intervention, compared to baseline (no p-values reported).
Children										
Staiano, 2000	12 wk	2.0	3.8	NR	NR	NR	NR	NR	NR	Results were reported relative to baseline only. Relative to baseline, glucomannan increased bowel frequency, improved stool consistency and reduced pain at defecation and laxative use. . No significant changes were observed within the placebo group
Loening-Baucke, 2004	4 wk	3.8	4.5	N	Y	N	N	Y	NR	Glucomannan reduced the proportion of children with <3 BM/wk and the proportion with abdominal pain. Physicians and parents rated children's symptoms and both found a higher proportion of children with improved symptoms in the glucomanan group. ,No difference was observed for overall bowel frequency, laxative use and stool consistency compared with placebo.
Castillejo, 2006	4 wk	5.1	6.2	N	NR	*	Y	N	NR	Coca husk increased the number of children with improved stool consistency, but had no effect on bowel motion frequency, relative to placeboBowel motion frequency and the number of children with hard stool consistency improved from baseline in both, the placebo and cocoa husk group.

Y, yes; N, no; NE, data not extractable; wk, week; d, day; NDO, non-digestible oligosaccharide; * no laxatives allowed. [#] A number of differing outcome measures were reported in the various studies. Refer to 'Results' column for further detail. Comparisons to baseline have not been recorded in this column.

Table 59. Constipation trials - physiological outcomes

Study	Dose (g/d)	Faecal collection period (d)	Number collecting faeces	Faecal wet weight control (g/d)	Faecal wet weight intervention (g/d)	Transit time control (h)	Transit time intervention (h)	Transit time method	Results
Adults									
Cereal fibre									
Corinaldesi, 1982	20	NR	NR	NR	NR	102.5	66.5	modified 2 with $^{51}CrCl_3$	Bran decreased transit times compared with placebo.
Badiali, 1995	20	10	17	108	131	134	98	1	Bran reduced transit time relative to placebo. Both, bran and placebo, equally increased bowel frequency and faecal weight from baseline, with no difference between groups. All patients were instructed to have daily dietary intake of 15g fibre after baseline period, which may explain the placebo response.
Rees, 2005	10-20	7	22	125	123	52	63	3	Faecal weight increased from baseline in the bran group, but there were no significant differences with placebo group. There was also no significant difference between groups for transit time
Hongisto, 2008	23 DF	5	29	NR	NR	86	71	3	There was a tendency for rye bread to decrease transit time
Holma, 2010	21 DF	5	19	145	159	66	43	3	Rye bread decreased transit time
Psyllium									
Corinaldesi, 1982	14	NR	NR	NR	NR	102.5	73.1	modified 2 with $^{51}CrCl_3$	Psyllium decreased transit times compared with placebo.
Ashraf, 1995	10	7	22	103	95	~52 *	54.2 *	4	No effect on colon transit time.Psyllium increased faecal weight compared with baseline
Cheskin, 1995	24	NR	NR	173	175	53.9	30	1 & 4	Psyllium reduced total intestinal transit time, speeding transit in the colon, but not in the rectosigmoid. No difference between psyllium and control on faecal weight, colonic motility or pelvic floor dyssynergia
Ashraf, 1997	10	7	7	117	188	63*	56*	4	Psyllium increased faecal weight compared to control, but had no effect on colon transit time.
Children									
Castillejo , 2006	2.8 - 5.6 Cocoa husk and beta fructosans	NR	NR	NR	NR	61.5 *	43.6 *	4	There was a tendency for cocoa husk to reduce colon transit time as compared with placebo. In a subgroup analysis of children with slow basal colon transit time (>50th percentile; n=12), cocoa husk reduced total and right colon transit time. Coca husk improved stool consistency, but had no effect on bowel frequency, relative to placebo, although both bowel frequency and stool consistency improved from baseline in placebo and cocoa husk.

*, Colon transit time. For transit measures: 1, (Hinton *et al.*, 1969); 2, (Kirwan & Smith, 1974); 3, (Cummings *et al.*, 1976b); and 4, (Metcalf *et al.*, 1987). DF, dietary fibre; NDO, non-digestible oligosaccharide; min, minutes

Physiological outcomes

257. Trials investigating physiological outcomes that report laxative use by trial participants have been excluded. Three trials provided no information on patient laxative use during the intervention, but these have been included (Sculati & Giampiccoli, 1984; Cheskin *et al.*, 1995; Hongisto *et al.*, 2006). All trials were conducted in outpatients with constipation or patients with self-reported constipation. All trials were in adults, except one that was conducted in children (Castillejo *et al.*, 2006), which reported on colon transit time in relation to cocoa husk and beta fructosan supplementation.

258. One trial reported constipated patients to have slower total intestinal transit times than normal subjects at baseline: patients had a mean total intestinal transit time of 155.6 hours, which in normal subjects was 40.3 hours (Corinaldesi *et al.*, 1982). One trial screened patients for inclusion on the basis of a prolonged total intestinal transit time: mean basal transit time was 177 hours (Badiali *et al.*, 1995). The results from trials in healthy subjects showed large inter-individual variation in total intestinal transit times (see Table 18) (mean times ranged from 40-100 hours), although this may have reflected the different methodologies used to some extent.

259. All the five trials conducting cereal fibre interventions measured total intestinal transit time (Corinaldesi *et al.*, 1982; Badiali *et al.*, 1995; Rees *et al.*, 2005; Hongisto *et al.*, 2006; Holma *et al.*, 2010), with control mean values ranging from 134 to 52 hours. In all trials mean bowel motion frequency was more than five times weekly, although one trial did not report bowel frequency (Corinaldesi *et al.*, 1982) (see Table 57). In three of the trials patients were supplemented with wheat bran fibre, and in two of these it was observed that 20g/day bran decreased total intestinal transit time relative to mean control times of over 100 hours. In the other trial, in which patients had constipation-predominant irritable bowel syndrome, there was a tendency for 10-20g/day bran to increase total intestinal transit time from 50 to 63 hours. Two trials, by the same authors, reported the outcome of an intervention with rye bread (providing an additional 20g/day dietary fibre) and observed a tendency for a decrease (Hongisto *et al.*, 2006; Holma *et al.*, 2010), in total intestinal transit time. Only three trials that conducted a cereal fibre intervention measured wet faecal weight. None of the trials found a significant difference in faecal weight between groups (Holma *et al.*, 2010; Rees *et al.*, 2005; Badiali *et al.*, 1995). In one trial faecal weight was observed to increase from baseline in the bran group, but there were no differences with placebo group at trial completion, as baseline weights for the two groups were different (Rees *et al.*, 2005). Another trial (Badiali *et al.*, 1995) reported no effect on faecal weight, but this may have been due to all patients being instructed to have daily dietary intake of 15g dietary fibre after the baseline period, resulting in both bran and placebo equally increasing bowel frequency and faecal weight from baseline.

260. One trial compared wheat bran (20g/d) and psyllium (14g/d) to placebo and reported that wheat bran and psyllium produced equivalent decreases in total intestinal transit time, with a control mean total intestinal transit time of 102.5 hours (Corinaldesi *et al.*, 1982). Two other trials employing psyllium supplementation measured colon transit time (Ashraf *et al.*, 1995; Ashraf *et al.*, 1997), but observed no effect with 10g/day. One other trial reported the effect of 24g/day psyllium on both total

intestinal transit time and colon transit time (Cheskin *et al.*, 1995): total intestine transit time was reduced by supplementation, with a control mean transit time of 53.9 hours; transit through the colon was observed to be reduced.

261. A trial in children observed a tendency for cocoa husk to reduce colon transit time as compared with placebo (Castillejo *et al.*, 2006). In a subgroup analysis of children with slow basal colon transit time (less than 50th percentile; n=12), cocoa husk was observed to reduce total and right colon transit time.

Summary

262. There was a paucity of high quality trials investigating an effect of non-digestible carbohydrate on bowel habit and symptoms in constipated subjects, and most available evidence consisted of trials of generally low quality. The difficulty of doing such trials, both in terms of design and of funding, should be noted. If correctly designed, such trials could go a considerable way to providing a robust evidence base. Any conclusions based on available evidence, however, were limited.

263. In outpatients with constipation or patients with self-reported constipation most of the cereal fibre intervention trials (12-20g dietary fibre/day) reported an improvement in stool consistency and a reduction in total intestinal transit times, but evidence was less consistent for of an effect on bowel frequency or faecal weight. An improvement in ease of defecation was only reported in the two trials in patients with mild constipation, and not in trials in outpatients with more severe constipation.

264. In hospital outpatients with constipation, higher doses of psyllium (14-20g/day) were observed to decrease total intestinal transit time and most trials reported an increase in bowel frequency; there was inconsistent evidence of an effect on stool consistency and faecal weight. There was some evidence for an improvement in abdominal pain and ease of defecation, with psyllium supplementation.

265. In outpatients with constipation or patients with self-reported constipation, a mixed carbohydrate intervention increased bowel frequency, in one of two trials. An improvement in ease of defecation was only reported in the two trials in patients with mild constipation in response to a non-digestible oligosaccharide intervention, either alone or in combination with prunes and linseed.

266. A small number of trials in children with constipation provided inconsistent evidence for an effect of non-digestible carbohydrate on bowel frequency or other symptoms.

267. Overall, in outpatients with constipation or patients with self-reported constipation it appears that total intestinal transit time and, to some extent stool consistency, may be improved by supplementation with non-digestible carbohydrate, especially in patients with slow transit times. In outpatients with more severe constipation there was little evidence of an effect on ease of defecation; however, in patients with self-reported milder constipation there was some evidence that non-digestible carbohydrate may improve ease of defecation. Psyllium, in particular, increased bowel frequency, but for other non-digestible carbohydrates the evidence was less consistent.

268. In institutionalised patients, or hospital ward patients, with constipation, the available

evidence suggested that supplementation with cereal fibre and lactitol reduced total laxative use; however, as noted in the risk of bias assessment the highest proportion of trials at highest risk of bias were those conducted in hospitalised or institutionalised settings.

269. It may be that certain subgroups of patients with constipation were more, or less, likely to respond to non-digestible carbohydrate interventions. Available evidence consisted of a small number of variable quality trials, where the diagnostic criteria for constipation varied considerably. High quality trials are required to determine an effect of non-digestible carbohydrate on constipation symptoms, laxative use and physiological measures, before firm conclusions can be drawn. Studies are also required to determine whether dietary carbohydrate affects the risk of developing constipation. In general, however, non-digestible carbohydrate is likely to be beneficial in most patients of all ages with constipation as part of the overall treatment strategy.

Diarrhoea

270. Diarrhoea results from the small intestine being unable to complete absorption of electrolytes and water from luminal contents, or as a consequence of inflammatory change in the colon. This can happen when a non-absorbable, osmotically active substance is ingested or an absorbable osmotically active substance is malabsorbed (osmotic diarrhoea) or when electrolyte absorption is impaired (secretory diarrhoea). Most cases of acute and chronic diarrhoea are due to the latter mechanism. In children most cases are due to osmotic diarrhoea, e.g. rotavirus or transisent malabsorption. Secretory diarrhoea can result from bacterial toxins, reduced absorptive surface area caused by disease or resection, luminal secretagogues (such as bile acids or laxatives), circulating secretagogues (such as various hormones, drugs, and poisons), and medical problems that compromise regulation of intestinal function (Schiller, 1999).

271. Diarrhoea that is caused by pathogens can be classified as non-inflammatory or inflammatory diarrhoea. The non-inflammatory diarrhoeas are caused by enterotoxin-producing organisms such as *Vibrio cholerae* and enterotoxigenic *Escherichia coli*, or by viruses that adhere to the mucosa and disrupt the absorptive and/or secretory processes of the enterocyte without causing acute inflammation or mucosal destruction. Inflammatory diarrhoea is caused by two groups of organisms: cytotoxin-producing, non-invasive bacteria (e.g. enteroaggregative *Escherichia coli*, enterohemorrhagic *Escherichia coli* and *Clostridium difficile*), or by invasive organisms (e.g. *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Entamoeba histolytica*). The cytotoxin-producing organisms adhere to the mucosa, activate cytokines and stimulate the intestinal mucosa to release inflammatory mediators. Invasive organisms, which can also produce cytotoxins, invade the intestinal mucosa to induce an acute inflammatory reaction, involving the activation of cytokines and inflammatory mediators (Navaneethan & Giannella, 2008).

272. The loss of fluids through diarrhoea can cause dehydration and electrolyte imbalances. Oral rehydration therapy is the administration of fluid by mouth to prevent or correct dehydration and electrolyte imbalance that is a consequence of diarrhoea; this refers to a specific solution which contains electrolytes and glucose.

Diarrhoea criteria

273. Diarrhoea may be defined in terms of stool frequency, consistency, volume or weight. Patients' conceptions of diarrhoea often focus around stool consistency (Wenzl *et al.*, 1995). Acute diarrhoea is defined as an abnormally frequent discharge of semi-solid or fluid faecal matter from the bowel, lasting less than 14 days. Causative agents are bacteria (e.g. *Escherichia coli*, *Campylobacter*, *Shigella* species, *Vibrio cholerae* and *Salmonella*), viruses and parasites. In developing countries, enteric bacteria and parasites are more prevalent than viruses. In developed countries, viruses (e.g. rotavirus, human caliciviruses and adenovirus) are the predominant cause of acute diarrhoea. Parasitic agents (e.g. *Giardia* intestinalis, *Cryptosporidium parvum*, *Entamoeba histolytica*, and *Cyclospora cayetanensis*) can be a cause of acute diarrhoeal illness in children in developing countries. In the developed world this cause is uncommon and usually restricted to travellers (World Gastroenterology

Organisation, 2008).

274. Acute diarrhoea, associated with contaminated food or water, that occurs during or shortly after travel is known as traveller's diarrhoea. Watery stools and abdominal pain and cramps are experienced in 80% of cases of traveller's diarrhoea (World Health Organization, 2009).

275. Acute diarrhoea can be a consequence of treatment with antibiotics – antibiotic-associated diarrhoea. Antibiotics can cause diarrhoea via several mechanisms: disruption of the bowel microflora (the most common cause); as a direct effect of the antibiotic (independent of its antimicrobial effect), e.g. erythromycin can increase the rate of gastric emptying by acting as a motilin receptor agonist; overgrowth of *Clostridium difficile* due to loss of bowel flora (less common); and as an allergic response to the antibiotic (rare).

276. Chronic diarrhoea has been defined as the abnormal passage of three or more loose or liquid stools per day for more than four weeks and/or a daily stool weight greater than 200 g/day (in older children and adults). It can be caused by a bacterial or viral infection, laxatives, dietary factors (e.g. excessive intake of coffee or alcohol), or a long-term condition, e.g. colonic neoplasia/inflammation, small bowel inflammation, inflammatory bowel disease, small bowel malabsorption (such as Coeliac disease), ulcerative colitis, maldigestion due to pancreatic insufficiency; or motility disorder (Thomas *et al.*, 2003).

277. Insufficient absorption of osmotically active substances in the gut can cause diarrhoea, e.g. lactose or fructose intolerance. Lactulose and polyols, when ingested in sufficient amounts, cause diarrhoea induced by the hyperosmotic retention of fluid in the intestine (Livesey, 2001).

Background

278. Chronic non-specific diarrhoea of infancy, toddler's diarrhoea, is seen in children, between about one and four years who were otherwise healthy (Kneepkens & Hoekstra, 1996). This may be due to a high intake of fruit juices and cordials, which are rich in fructose and, in addition, contain sorbitol, e.g. pear juice, 2%; apple juice, 0.5%. Withdrawal of fruit juice from the diet cures the chronic non-specific diarrhoea (Hyams & Leichtner, 1985; Kneepkens *et al.*, 1989).

279. In infants and children with and without chronic non-specific diarrhoea a serving of apple or pear juice (about 150-250 ml) has been shown to result in colonic fermentation of carbohydrate, as assessed by breath hydrogen responses (Kneepkens *et al.*, 1989; Smith *et al.*, 1995; Nobigrot *et al.*, 1997), which may lead to recurrence of diarrhoea (Lebenthal-Bendor *et al.*, 2001; Ribeiro *et al.*, 2001) This has been shown to be due to the fructose and sorbitol content of the juices (Kneepkens *et al.*, 1989; Nobigrot *et al.*, 1997) and the efficiency of carbohydrate absorption of one age-specific serving of juice increases with advancing age of children. Decreased carbohydrate absorption occurs more often after ingestion of juices that contain more sorbitol and higher concentrations of fructose over glucose than after ingestion of juices which lack sorbitol and contain equal amounts of fructose and glucose (Nobigrot *et al.*, 1997). In healthy infants aged 5 to 9 months, a dose of 10

mL/kg/day pear juice for 2 weeks was shown to be well absorbed (Lifschitz, 2000).

280. A cross-over trial in children formerly diagnosed as having chronic non-specific diarrhoea reported that consumption of 'clear' apple juice caused more carbohydrate malabsorption than 'cloudy' apple juice and only 'clear' apple juice was shown to influence stool frequency and consistency compared with the basal period (Hoekstra *et al.*, 1995). The two juices differ in their fibre and non-absorbable monosaccharide and oligosaccharide contents.

281. In a trial of children with acute diarrhoea, fed twice-daily 30 ml/kg/day apple or grape juice or water, reported that the intake of juices with different fructose/glucose ratios and osmolarities resulted in more faecal losses and more prolonged diarrhoea as compared with water feedings, but the patients given juice ingested more calories and gained more weight, particularly among those being fed the juice with equimolar concentrations of fructose and glucose (Valois *et al.*, 2005).

Trial design

282. Five trials were identified as eligible (Cummings *et al.*, 2001; Duggan *et al.*, 2003; Lewis *et al.*, 2005a; Lewis *et al.*, 2005b; Drakoularakou *et al.*, 2010) (see Appendix 2 for studies excluded). One trial was conducted in infants in a developing country (Duggan *et al.*, 2003). Four trials were conducted in adults in developed countries (Cummings *et al.*, 2001; Lewis *et al.*, 2005a; Lewis *et al.*, 2005b; Drakoularakou *et al.*, 2010).

283. The trial design details have been summarised in Table 60. The trials have been grouped on the basis of whether the study population is in the developing or developed countries. All trials employed a parallel design.

284. All carbohydrate interventions were non-digestible oligosaccharide: fructo-oligosaccharide or galacto-oligosaccharide.

285. Diarrhoea was commonly defined as 3 or more liquid stools during previous 24 hours. One prevention trial was conducted in a developing world population with the main outcome measure being the incidence and prevalence of diarrhoea over a duration of six months (Duggan *et al.*, 2003).

286. Two trials investigated prevention of acute traveller's diarrhoea (Cummings *et al.*, 2001; Drakoularakou *et al.*, 2010), one recurrence of acute *Clostridium difficile* toxin positive diarrhoea (Lewis *et al.*, 2005a) and one investigated the prevalence of antibiotic-associated diarrhoea (Lewis *et al.*, 2005b).

287. None of the trials reported baseline dietary fibre intakes. The duration of interventions ranged from three weeks to six months. The initial sample sizes ranged from 142 to 450 subjects. The funding sources for all trials, where reported, were either Governmental or Commercial; 20% of trials did not report funding sources.

Table 60. Diarrhoea trial description

Study	Date	Study design	Country	Type of diarrhoea	Diarrhoea criteria	Subject characteristics	Clinical outcomes assessed	Physiological outcomes assessed	Control intervention	Intervention	Dose (g/d)	Sample size at start	Duration (d)	Funding source
Developing countries														
Duggan	2003	P	Peru	acute and chronic	3 or more liquid stools during 24 h	Infants aged 6-12 mth; 137M, 145F	Prevalence of diarrhoea and severe diarrhoea [5] and incidence of chronic diarrhoea	none	cereal w/o intervention	FOS	(0.55 g/15 g cereal)	282	6 mth	Gerber Products Company, USA
Developed countries														
Cummings	2001	P	Scotland	acute - traveller's	NR	Adults mean age 50y; 131M,113F	Prevalence of diarrhoea - bowel habit and symptoms	Well-being	placebo	FOS	10	363	4 wk	Lambert Healthcare
Lewis	2005a	P	England and Wales	acute - C. difficile toxin positive	3 or more liquid stools during previous 24 h	Adults, mean age 75y; 59M, 83F	Recurrence of diarrhoea[7] after cessation, bowel habit and symptoms	Faecal microflora (bacterial counts)	placebo	FOS	12	142	30	NR
Lewis	2005 b	P	England and Wales	antibiotic-associated - C. difficile toxin positive	3 or more liquid stools during previous 24 h	Adults mean age 77y; 213M, 222F	Prevalence of diarrhoea - bowel habit and symptoms	Faecal microflora (bacterial counts)	placebo	FOS	12	450	14	Welsh Office Research and Development Fund
Drakoularakou	2010	P	England	acute - traveller's	3 or more liquid stools /day	Adults mean age 38y; 91M, 68F	Prevalence of diarrhoea - bowel habit and symptoms	Quality of life	placebo	GOS	2.6	201	at least 3 wk	Clasado Ltd

P, parallel; XO, cross-over; NR, not reported; d, day; wk ,week; mth, month; y, year; M, male; F, female; w/o, without. [1]as defined by the number of hours post-admission until excretion of the last liquid or semiliquid stool not followed by another abnormal stool within 24 hours; [2] duration in hours from the time of randomisation to the last watery or loose stool; [3] defined as the period from the start of oral hydration until the first mushy or formed stool; [4] as defined by the number of hours from the first feeding until the last liquid or semiliquid stool was passed and no other liquid or semiliquid stool was seen for 24 hour; [5] as defined by > 5 loose or watery stools in 24 h plus ≥ 1 incident of vomiting, fever, office visit for evaluation, or dehydration; [6] defined as the passage of stool of normal consistency over a period of at least 48 hours. Duration of diarrhoea was calculated as the duration in hours from the time of randomisation to the last watery or loose stool within seven days; [7] defined as time from onset of oral rehydration therapy until the last unformed stool; [8] as defined by the number of hours time from administration of ORS to first formed stool; [9] time from administration of ORS to the passage of two formed stools or no stool for 12 hours; NDC, non-digestible carbohydrates; * soy polysaccharide 25%, alfa-cellulose 9%, gum arabic 19%, fructo-oligosaccharides 18.5 %, inulin 21.5% and resistant starch 7%

Risk of bias

288. A summary of the risk of bias assessment has been given in Table 61. All trials reported being randomised. Three reported how this was done, but only one clearly reported how allocation was concealed. All trials were blinded to both participants and personnel.

289. All trials reported on drop-out rates and gave some description of the causes. The dropout percentages varied from three to 33%. It seemed unlikely that missing outcome data were related to the intervention and missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups

Table 61. Diarrhoea trials risk of bias

Study	Randomisation	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Dropouts (%)
Developing countries						
Duggan, 2003	Yes	NR	Sealed envelope	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	11
Developed countries						
Cummings, 2001	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	33
Lewis, 2005a	Yes	Consecutive patients	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome	6
Lewis, 2005b	Yes	Computer generated	NR	Participants and personnel blind	Missing outcome data unlikely to be related to outcome and analysed on ITT	3
Drakoularakou, 2010	Yes	NR	NR	Participants and personnel blind	Missing outcome data balanced in numbers across intervention groups	21

NR, not reported; ITT, intention to treat.

Results

290. Data on quantitative aspects of diarrhoea, e.g. duration of diarrhoea and faecal weight, were not sufficiently comparable for quantitative synthesis, but findings have been summarised in Table 62. Trials generally reported average or median values, but not the necessary variance data to enable synthesis of the data.

291. All diarrhoea prevention trials conducted interventions with non-digestible oligosaccharide (see Table 62). One trial was conducted in a developing country population and examined an effect of non-digestible oligosaccharide on the prevalence of acute and chronic diarrhoea in infants in a community with a high burden of gastrointestinal and other infections over a 6 month period. No difference in the prevalence of diarrhoea or its severity was observed between infants receiving cereal supplemented with fructo-oligosaccharide and those receiving non-supplemented cereal (Duggan *et al.*, 2003).

Table 62. Results of diarrhoea prevention trials

Study	Intervention	Trial duration	Control percentage developing diarrhoea	Intervention percentage developing diarrhoea	Results
Developing countries					
Duggan, 2003	FOS	6 mth	NR	NR	FOS had no effect on the prevalence of diarrhoea or its severity; Mean days with diarrhoea was 9.8 ±11.0 in the FOS group and 10.3± 9.6 in the control group
Developed countries					
Cummings, 2001	FOS	4 wk	19.5	11.2	There was a tendency for the FOS group to report less incidence of diarrhoea relative to the placebo (p=0.08). FOS had no effect on bowel habit, except an increase in flatulence, but did improve reported well-being.
Lewis, 2005a	FOS	30d	34.3	8.3	21% of patients treated for *C. difficile*-associated diarrhoea developed further diarrhoea. Patients taking FOS were less likely to develop further diarrhoea than those taking placebo (6 in FOS group compared with 24 in placebo group. FOS also increased faecal *Bifidobacteria* concentrations. No effect on bowel frequency or abdominal symptoms was observed.
Lewis, 2005b	FOS	14d	9.5	8.8	Of 435 patients prescribed a broad-spectrum antibiotic 40 (9%) developed C. difficile toxin-positive diarrhoea, but the incidence was unaffected by FOS supplementation. FOS increased faecal *Bifidobacteria* concentrations.
Drakoularakou, 2010	GOS	3 wk or more	38.5	23.5	The GOS group reported lower incidence and duration of diarrhoea relative to the placebo. For those subjects in the GOS group that experience diarrhoea, the duration of abdominal pain was lower, and the quality of life higher, than in the placebo group. The GOS group had fewer bowel motions than the placebo group, but other bowel habits and quality of life were not different between groups.

FOS ,fructo- oligosaccharide; GOS, galacto-oligosaccharide; mth, month; wk, week; d, day.

292. The four trials in developed county populations were all in adults. Two investigated the effect of non-digestible oligosaccharide on the prevalence of traveller's diarrhoea: one using fructo-oligosaccharide (Cummings *et al.*, 2001) and the other using galacto-oligosaccharide (Drakoularakou *et al.*, 2010). In the trial conducting the fructo-oligosaccharide intervention, subjects received either intervention or placebo for two weeks prior to and during two weeks holiday in a high risk destination for diarrhoea. There was a tendency for the oligosaccharide group to report less incidence of diarrhoea relative to the placebo. There was no effect on bowel habit, except an increase in flatulence, but subjects reported improved well-being in the intervention group compared with placebo (Cummings *et al.*, 2001). In the trial conducting the galacto-oligosaccharide intervention, subjects received either intervention or placebo for one week prior to and during at least two weeks holiday in a high risk destination

for diarrhoea (Drakoularakou *et al.*, 2010). There was a lower incidence and duration of diarrhoea, as well as lower bowel motion frequency, in those subjects who received non-digestible oligosaccharide relative to the placebo. In this trial overall quality of life, as determined by a scoring system, was not different between groups, but in those subjects developing diarrhoea, quality of life was higher and the duration of abdominal pain lower in those receiving non-digestible oligosaccharide relative to the placebo.

293. One trial investigating recurrence of *C. difficile*-associated diarrhoea reported that patients receiving non-digestible oligosaccharide were less likely to develop further diarrhoea than those taking placebo (Lewis *et al.*, 2005a). Fructo-oligosaccharide supplementation also increased faecal *Bifidobacterium* spp. concentration, but had no effect on bowel frequency or abdominal symptoms. In another trial by the same authors (Lewis *et al.*, 2005b), however, in 435 patients prescribed a broad-spectrum antibiotic, where 40 (9%) developed *C. difficile* toxin-positive diarrhoea, the incidence was unaffected by fructo-oligosaccharide supplementation, although fructo-oligosaccharide increased faecal *Bifidobacterium* spp concentrations relative to placebo.

Summary

294. All diarrhoea prevention trials supplemented subjects with non-digestible oligosaccharides. There was little evidence for an effect on acute and chronic diarrhoea in infants in developing country populations or antibiotic-associated diarrhoea in adults from developed country populations. Two trials investigated an effect on the incidence of traveller's diarrhoea suggesting a possible protective effect, but further trials are required to confirm this.

Irritable bowel syndrome

295. No prevention trials were identified as eligible (see Appendix 2 for excluded articles)

Diverticular disease

296. No prevention trials were identified as eligible (see Appendix 2 for excluded articles)

Well-being

297. Four trials were identified as eligible; all were considered in detail in other report sections (see Appendix 2 for excluded articles).

298. One trial, (Waligora-Dupriet *et al.*, 2007) observed no effect of fructo-oligosaccharide supplementation of healthy children on parent- or care-giver-reported child well-being.

299. Within the clinical outcomes considered above, three trials reported on patient well-being. These trials were reported in detail in the previous sections. One trial investigating the effect of fructo-oligosaccharide on prevalence of traveller's diarrhoea reported subject-reported well-being to be higher in the intervention group relative to placebo (Cummings *et al.*, 2001). Two trials in patients with irritable bowel syndrome reported well-being to be improved in response to psyllium supplementation relative to control (Prior & Whorwell, 1987; Jalihal & Kurian, 1990).

Carbohydrate and colo-rectal cancer

300. This section considers evidence from prospective cohort studies investigating risk of colo-rectal cancer and randomised controlled trials investigating risk of colo-rectal adenoma in relation to carbohydrate interventions.

Prospective cohort studies

Dietary fibre intake and risk of colo-rectal cancer

301. Several studies have shown that multivariate adjustment attenuated observed inverse associations between dietary fibre and colo-rectal cancer incidence observed with age-adjusted and limited covariate adjusted models (Bingham *et al.*, 2005; Michels *et al.*, 2005; Park *et al.*, 2005; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007). This suggested confounding by other dietary and lifestyle factors of the relationship between dietary fibre intake and colo-rectal cancer. To address this, inclusion was limited to those prospective cohort studies that adjusted for, or investigated the effect of, the major risk factors for colo-rectal cancer: age, alcohol intake, smoking, physical activity and overweight/obesity.

302. Fourteen studies were identified as eligible (Pietinen *et al.*, 1999; Mai *et al.*, 2003; McCullough *et al.*, 2003; Bingham *et al.*, 2005; Larsson *et al.*, 2005; Lin *et al.*, 2005; Michels *et al.*, 2005; Park *et al.*, 2005; Otani *et al.*, 2006b; Shin *et al.*, 2006; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007; Wakai *et al.*, 2007; Butler *et al.*, 2008) (see Appendix 2 for studies excluded).

303. Several of the studies included did not adjust for all the identified confounders (alcohol intake, smoking, physical activity, age and overweight/obesity) in their multivariant analyses (see Table 64); however, these studies did investigate the influence of any missing identified confounder on effect estimates and reported them not to change the estimates produced (Mai *et al.*, 2003; McCullough *et al.*, 2003; Larsson *et al.*, 2005; Shin *et al.*, 2006; Schatzkin *et al.*, 2007).

304. A pooled analysis of 13 prospective cohort studies (Park *et al.*, 2005) included the following cohorts: the New York University Women's Health Study (Kato *et al.*, 1997); the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Pietinen *et al.*, 1999); Swedish mammography screening cohort study (Terry *et al.*, 2001; Larsson *et al.*, 2005); Breast Cancer Detection Demonstration Project follow-up cohort (Mai *et al.*, 2003) Cancer Prevention Study II Nutrition Cohort (McCullough *et al.*, 2003); the Women's Health Study (Lin *et al.*, 2005) the Nurses' Health Study and the Health Professionals Follow-Up Study (Michels *et al.*, 2005); the Iowa Women's Health Study (McCarl *et al.*, 2006). Four other cohorts were included in this analysis that had not previously reported the minimum information necessary to estimate the relative risk associated with the endpoint and a corresponding measure of uncertainty (van den Brandt *et al.*, 1990; Bandera *et al.*, 1997; Sieri *et al.*, 2002; Terry *et al.*, 2002). The pooled analysis adjusted for alcohol intake, smoking, physical activity, age and overweight/obesity and included several studies that when originally published had not included all these confounders and were, therefore, ineligible for inclusion here (Kato *et al.*, 1997; Terry *et al.*, 2001; McCarl *et al.*, 2006).

Study design

305. The study design details have been summarised in Table 63. Seven of the studies were conducted in the North America, three in Europe and four in Asia. The pooled analysis includes cohorts from North America and Europe. All studies had a propective cohort design. The two largest individual cohorts each contained about half a million subjects (Bingham *et al.*, 2005; Schatzkin *et al.*, 2007). The average length of follow-up ranged from 6 to 16 years. The pooled analysis (Park *et al.*, 2005), which included 725,628 subjects and over 8,000 cases has been included in specific analyses (see results section below).

306. With the exception of the Larsson *et al*. (2005) study, all studies reported on dietary fibre intake and colo-rectal cancer and/or colon cancer risk. Two studies reported on soluble and insoluble fibre intake in relation to colo-rectal cancer risk (Pietinen *et al.*, 1999; Wakai *et al.*, 2007). Seven studies reported on cereal fibre intake in relation to colo-rectal cancer risk (Mai *et al.*, 2003; Bingham *et al.*, 2005; Larsson *et al.*, 2005; Lin *et al.*, 2005; Michels *et al.*, 2005; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007). Eight studies reported on both vegetable and fruit fibre intake in relation to colo-rectal cancer risk (Terry *et al.*, 2001; Mai *et al.*, 2003; Bingham *et al.*, 2005; Lin *et al.*, 2005; Michels *et al.*, 2005; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007; Wakai *et al.*, 2007). Six studies reported on legume fibre intake in relation to colo-rectal cancer risk (Mai *et* al., 2003; Bingham *et al.*, 2005; Lin *et al.*, 2005; Michels *et al.*, 2005; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007; Wakai *et al.*, 2007). Four studies reported on wholegrain cereal intake in relation to colo-rectal cancer incidence (Pietinen *et al.*, 1999; McCullough *et al.*, 2003; Larsson *et al.*, 2005; Schatzkin *et al.*, 2007). The pooled analysis reported on dietary fibre, cereal fibre, vegetable fibre and fruit fibre (Park *et al.*, 2005).

307. The funding sources for all studies, where reported, were Governmental; one study did not report funding sources.

308. The results for studies investigating constituent dietary fibres (cereal, vegetable, fruit and legume fibre), and wholegrain cereal, intake in relation to colo-rectal cancer incidence have been presented in Appendix 3.

Table 63. Cohort studies of dietary fibre intake and risk of colo-rectal cancer

Cohort	Author	Year	Country	Sex	Age (y)	CRC cases	CC cases	RC cases	Cohort size	Mean follow-up duration (y)	Dietary assessment method	Dietary fibre components investigated	Funding source
Individual cohorts													
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Pietinen	1999	Finland	Men	50-69	185	NR	NR	27111	8	Dietary history questionnaire	Dietary fibre, Insoluble fibre, Soluble fibre, Wholegrain	National Cancer Institute, USA
Breast Cancer Detection Demonstration Project follow-up cohort	Mai	2003	USA	Women	mean 62	487	NR	NR	45491	8.5	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	Medical Research Council, USA
Cancer Prevention Study II Nutrition Cohort	McCullough	2003	USA	Mixed	50-74	NR	508	NR	133163	5	FFQ	Dietary fibre, Wholegrain	NR
European Prospective Investigation into Cancer and Nutrition	Bingham	2005	Europe	Mixed	25-70	1721	1178	648	519978	6.2	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	European Commission and National funding agencies
Women's Health Study	Lin	2005	USA	Women	mean 45	223	172	46	36976	10	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	National Cancer Institute; Nalional Heart, Lung, and Blood Institute, USA
Swedish Mammography Cohort	Larsson	2005	Sweden	Women	40-76	805	547	252	61433	14.8	FFQ	Cereal fibre, Wholegrain	Swedish Cancer Foundation; the Swedish Research Council
Nurses' Health Study and Health Professionals Follow-Up Study	Michels	2005	USA	Mixed	30-75	1596	1202	310	124226	14-16	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	National Institutes of Health, USA
Japan Public Health Center-Based Prospective Study	Otani	2006	Japan	Mixed	mean 57 (40-69)	522	367	155	86412	10	FFQ *	Dietary fibre	Ministry of Health, Labor and Welfare of Japan
Shanghai Women's Health Study	Shin	2006	China	Women	40-70	283	165	118	73314	5.74	FFQ	Dietary fibre	National Institutes of Health, USA
Hawaii-Los Angeles Multiethnic Cohort Study	Nomura	2007	USA	Mixed	45-75	2110	1571	515	191011	7.3	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	National Cancer Institute, USA
National Institutes of Health-AARP Diet and Health Study	Schatzkin	2007	USA	Mixed	50-71	2974	2140	852	489611	5	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre, Wholegrain	National Cancer Institute, USA
Japan Collaborative Cohort Study	Wakai	2007	Japan	Mixed	40-79	443	291	142	43115	7.6	FFQ	Dietary fibre, Insoluble fibre, Soluble fibre, Vegetable fibre, Fruit fibre	Ministry of Health, Labor and Welfare of Japan
Singapore Chinese Health study	Butler	2008	Singapore	Mixed	45-74	961	591	370	61321	9.8	FFQ	Dietary fibre	National Cancer Institute, USA
Pooled analysis													
13 cohorts	Park	2004	North America, Europe	Mixed	NR	8081	5726	2188	725628	6-20	FFQ	Dietary fibre, Cereal fibre, Vegetable fibre, Fruit fibre	National Institutes of Health, USA

* Dietary fibre intake, assessed by 5-yr follow-up survey was reported to be more precise than the baseline survey, so HR were used based on the 5 year follow-up survey; NR, not reported; CRC colo-rectal cancer; CC, colon cancer; RC, rectal cancer.

Table 64. Adjusted confounders for studies investigating dietary fibre and constituent fibres

Study	Age	Sex ~	BMI	Energy	Smoking	Family	Education	Alcohol	PA	NSAIDs	Meat	Folate	Calcium	Multivitamin use	HRT use
Individual cohorts															
Pietinen, 1999	Y		Y	Y	Y		Y	Y	Y				Y		
Mai, 2003 ****	Y		Y	Y	Y		Y	Y		Y	Y		Y *		
McCullough, 2003	Y		Y	Y	Y	Y	Y		Y		Y		Y		Y
Michels, 2005	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y
Lin, 2005	Y		Y	Y	Y	Y		Y	Y	Y	Y	Y			Y
Larsson, 2005	Y		Y	Y			Y				Y		Y		
Bingham, 2005	Y	Y	Y ***	Y	Y		Y	Y	Y		Y	Y			
Otani, 2006	Y		Y	Y	Y			Y	Y		Y	Y	Y		
Shin, 2006	Y			Y	Y	Y	Y	Y	Y					Y	
Nomura, 2007	Y		Y	Y	Y	Y		Y	Y	Y	Y	Y	Y *	Y	Y
Schatzkin, 2007	Y	Y		Y	Y				Y		Y	Y	Y		Y
Wakai, 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y *		
Butler, 2008	Y *****	Y	Y	Y	Y	Y	Y	Y	Y						
Pooled analysis															
Park, 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y

*and vitamin D; **only for RC; *** height and weight not BMI; **** adjusted for dietary fibre only, constituent fibre RR were unadjusted; *****and diabetes; PA, physical activity; Family, family history of colo-rectal cancer; NSAIDs, non-steroidal anti-inflammatory drugs, HRT, hormone replacement therapy

~ this was not applicable in studies where the cohort was of a single sex

Results

309. Adjusted confounders for studies investigating dietary fibre have been summarised in Table 64.

310. For each exposure and endpoint a meta-analysis of cohort studies was performed. One of the studies was excluded for constituent fibre analyses as the risk ratios reported for these were unadjusted (Mai *et al.*, 2003). A further meta-analysis was performed that included the pooled analysis (Park *et al.*, 2005) and additional studies not included in the pooled analysis. This is presented for those endpoints and exposures reported in the pooled analysis.

311. The findings from all cohort studies have been summarised in Table 65. Outcome data, expressed as adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colon or rectal cancer risk, where reported. Most of the studies reported no significant association between dietary fibre intakes and the incidence of colo-rectal cancer. Only a few studies reported the method used to determine dietary fibre, but among those that did the American Association of Official Analytical Chemists (AOAC) total dietary fibre method was the most frequently used, while two studies reported using the Englyst non-starch polysaccharide method. One study compared the two different dietary fibre methodologies in relation to colo-rectal cancer incidence (Michels *et al.*, 2005). This reported that the Englyst and AOAC methods for fibre intake determination produced similar risk estimates for highest quintile compared with the lowest quintile of intake: for Englyst, HR 1.04 (95% CI 0.75-1.44) for women and 0.96 (0.69-1.34) for men compared with AOAC HR 0.98 (0.70-1.37) for women and 0.91 (0.65-1.28). The Pearson correlation coefficient between AOAC and Englyst fibre was 0.99 in the cohorts. The quintile ranges for lowest and highest were <8.0 to >14.0 g/1000kcal/day using the AOAC method and <6.0 to >10.5 g/1000kcal/day using the Englyst method, showing the lower value obtained using the Englyst method.

312. The range of dietary fibre intakes reported within studies may be another factor that has contributed to different findings among studies. If the range of intake of a nutrient was very narrow, a null association is more likely observed. The EPIC Study, which reported an inverse association of dietary fibre with colo-rectal cancer (Bingham *et al.*, 2005), involved subjects with a wide range of intakes. Other studies, involving subjects with a narrower range of intakes tended to find no association, e.g. (Terry *et al.*, 2001; Mai *et al.*, 2003; Lin *et al.*, 2005; Michels *et al.*, 2005; Otani *et al.*, 2006b). This explanation appeared to be contradicted by the results from the Pooling Project (Park *et al.*, 2005), which reported no association between high fibre intakes and colorectal cancer, even though the median intakes for the first and fifth quintiles of intake (9–20 and 23–41 g/d for men across studies; 8–17 and 20–35 g/d for women across studies) were comparable with those in the EPIC study. The fibre intakes given in Table 65 for the Pooling Project are for the across-study cut-points whereas the RRs are for the study-specific quintiles. For the across-study cut-points, the MV RR in the top fibre category could be estimated as 0.85. The Pooling Project also reported that cereals were a major contributor to dietary fibre intake in the European

studies, whereas fruits and vegetables were the main sources in the North American studies. The pooled multivariate RR for the highest quintile vs the lowest were similar for European and North American studies: 0.99 (95% CI, 0.80-1.23) for the European studies and 0.92 (95% CI, 0.83-1.02) for the North American studies.

313. The meta-analyses for dietary fibre and colo-rectal cancer risk and colon or rectal cancer risk were presented below, while the data syntheses for dietary fibre constituents and colo-rectal cancer risk have been presented in Appendix 3.

Table 65. Adjusted relative risk ratios for the highest compared with the lowest quantile of dietary fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	DF technique	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Individual cohorts											
Pietinen, 1999	Men	CRC	NSP	Q1 16.0g/d vs Q4 34.1g/d ***	1.0 (0.6-1.5)			0.79			No association observed
Mai, 2003	Women	CRC	NR	Q1 <6.3g/1000kcal vs Q5 >12g/1000 kcal **	0.94 (0.7-1.26)						No association observed
McCullough, 2003	Women	CC	NR	Q1 <8.0g/d vs Q5 14.4+g/d **		0.86 (0.52-1.42)			0.71		No association observed
	Men			Q1 <9.3g/d vs Q5 16.6+g/d		0.92 (0.64-1.32)			0.95		
Bingham, 2005	Mixed	CC, RC, CRC	NSP	Men Q1 18.2g/d vs Q5 30.1g/d; Women Q1 15.5g/d vs Q5 24.3g/d ****	0.79 (0.63-0.99)	0.77 (0.58-1.02)	0.81 (0.55-1.21)	0.01	0.01	0.5	Inverse association observed with CRC and CC risk, especially left-sided CC, but not RC.
Lin, 2005	Women	CRC	AOAC	Q1 12g/d vs Q5 26g/d ***	0.75 (0.47-1.18)			0.11			No association observed
Michels, 2005	Women	CC, RC, CRC	AOAC	Q1 < 8.0g/1000kcal/d vs Q5 14.0g/1000kcal/d **	0.98 (0.70-1.37)	0.95 (0.65-1.39)	1.10 (0.52-2.29)	0.7	0.63	0.91	No association observed
	Men		AOAC	Q1 < 8.0g/1000kcal/d vs Q5 14.0g/1000kcal/d **	0.91 (0.65-1.28)	0.85 (0.56-1.30)	1.34 (0.62-2.89)	0.86	0.76	0.58	
Otani, 2006	Women	CC, RC, CRC	AOAC	Q1 6.4g/d vs Q5 18.7g/d ****	0.58 (0.31-1.1)	0.48 (0.23-1.0	1.0 (0.32-3.3)	0.21	0.12	0.82	No association observed overall, although the risk for only the lowest quintile was significantly higher, compared with the second to the fifth quintiles
	Men			Q1 8.3 g/d vs Q5 20.0g/d	0.85 (0.53-1.4)	0.80 (0.45-1.4)	0.95 (0.40-2.3)	0.48	0.39	0.99	
Shin, 2006	Women	CC, RC, CRC	NR	Q1 <7.4g/d vs Q5 >13.45g/d **	1.1 (0.6-1.8)	1.2 (0.6-2.4)	0.9 (0.4-2.1)	0.48	0.84	0.34	No association observed
Nomura, 2007	Women	CC, RC, CRC	AOAC	Q1 7.5g/1000kcal/d vs Q5 18.6g/1000kcal/d ***	0.88 (0.67-1.14)	0.92 (0.68-1.25)	0.82 (0.48-1.43)	0.25	0.361	0.639	Inverse association observed in men for CRC and subsite cancer risk, but in women no association was observed after adjustment for HRT and other factors
	Men			Q1 6.1g/1000kcal/d vs Q5 16.5g/1000kcal/d	0.62 (0.48-0.79)	0.64 (0.48-0.86)	0.52 (0.32-0.84)	0.002	0.031	0.004	
Schatzkin, 2007	Mixed	CC, RC, CRC	AOAC	Q1 6.6g/1000kcal/d vs Q5 15.9g/1000kcal/d ***	0.99 (0.85-1.15)	0.96 (0.80-1.15)	1.13 (0.84-1.51)	0.96	0.77	0.39	No association observed
Wakai, 2007	Mixed	CC, RC, CRC	AOAC	Q1 vs Q4 *	0.73 (0.51-1.03)	0.58 (0.38-0.88)	1.10 (0.59-2.07)	0.028	0.002	0.67	Inverse association observed for CRC and CC
Butler, 2008	Mixed	CRC	NR	Q1 vs Q4 *	0.98 (0.81 – 1.19)			0.78			No association observed
Pooled analysis											
Park 2005	Mixed	CC, RC, CRC	NR	Q1 vs Q5 *	0.94 (0.86-1.03)	1.00 (0.90-1.11)	0.85 (0.72-1.01)	0.75	0.40	0.18	No association observed

PCC, proximal colon cancer; DCC, distal colon cancer ;NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer; NSP, non-starch polysaccharide; AOAC, American Association of Official Analytical Chemists
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and dietary fibre intake

314. Eleven studies reported on colo-rectal cancer in relation to dietary fibre intake, providing twelve risk estimates (see Figure 11). All eleven studies provided sufficient data for a highest quantile compared with lowest quantile meta-analysis to be performed and ten studies provided sufficient data for a per unit meta-analyses to be performed: one study did not provide information on the quantile intake values (Butler *et al.*, 2008). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 66 and Figure 11. The results of the per unit meta-analyses (10 g/day) for colo-rectal cancer incidence and dietary fibre intake have been summarised in Table 68 and Figure 13. Incorporation of the Pooling Project and and studies not included in the pooled analysis left eight studies providing nine risk estimates (see Figure 12). The results from the highest quantile compared with lowest quantile meta-analysis incorporating the Pooling Project have been summarised in Table 67.

315. There was no significant evidence of heterogeneity between studies, although for the highest quantile compared with lowest quantile analysis including the Pooling Project, and the per unit analysis, heterogeneity were high (see Table 67). For all analyses tests for publication bias (Egger's linear regression test) were not significant. Both the highest quantile compared with lowest quantile meta-analyses gave similar results: for the highest compared with the lowest quantile of dietary fibre intake a significant reduction in the incidence of colo-rectal cancer was observed with a point estimate of a 12% reduction. The per unit meta-analysis also indicated a significant reduction in the incidence of colo-rectal cancer with a 10g/day increase in dietary fibre associated with a point estimate of a 13% reduction.

Table 66. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	12	0.88 (0.81-0.95)	-3.08 (p=0.002)

[1] I^2 = 11.03% (95% CI 0.00-62.91); p for test of heterogeneity = 0.337
[2] No. of RR estimates included in pooled analysis.

Table 67. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary fibre intake including pooled analysis and excluding cohorts contained within

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	0.88 (0.80-0.97)	-2.61 (p=0.009)

[1] I^2 = 43.63% (95% CI 0.00-75.06%); p for test of heterogeneity = 0.111
[2] No. of RR estimates included in pooled analysis.

Table 68. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	11	0.87 (0.80-0.96)	-2.93 (p=0.004)

[1] I^2 = 53.37% (95% CI 8.14-76.53%); p for test of heterogeneity = 0.018
[2] No. of RR estimates included in pooled analysis.

316. Sex-specific meta-analyses were performed for dietary fibre intake and incidence of colo-rectal cancer. For the highest quantile compared with lowest quantile meta-analysis there were eight risk estimates for women and six for men (see Table 69 and Table 71). For the per unit meta-analyses there were seven risk estimates for women and five for men (see Table 70and Table 72). One study could not be used in sex-specific per unit analyses, as the mean energy intake by sex was not provided, so it was not possible to convert units from per 1000kcal/day to /day (Schatzkin *et al.*, 2007).

317. There was no significant evidence of heterogeneity between studies, although in men heterogeneity was high for both analyses. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

318. There were no differences in the incidence of colo-rectal cancer for the highest compared with the lowest quantile analyses (see Table 69 and Table 71), but the per unit analyses indicated a significant reduction in the incidence of colo-rectal cancer with a 10g/day increase in dietary fibre in men, but not women (see Table 70 and Table 72).

Table 69. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary fibre intake in women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	0.93 (0.81-1.05)	-1.21(p=0.226)

[1] I^2 = 0.00% (95% CI 0.00-67.58%); p for test of heterogeneity = 0.559
[2] No. of RR estimates included in pooled analysis.

Table 70. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and dietary fibre intake women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.92 (0.84-1.01)	-1.83 (p=0.067)

[1] I^2 = 0.00% (95% CI 0.00-70.81%); p for test of heterogeneity = 0.824
[2] No. of RR estimates included in pooled analysis.

Table 71. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary fibre intake in men only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	6	0.84 (0.68-1.05)	-1.53 (p=0.127)

[1] I^2 = 60.70% (95% CI .3.79-83.95%); p for test of heterogeneity = 0.026

[2] No. of RR estimates included in pooled analysis.

Table 72. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and dietary fibre intake men only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.88 (0.78-0.99)	-2.12 (p=0.034)

[1] I^2 = 34.46% (95% CI 0.00-75.32%); p for test of heterogeneity = 0.192

[2] No. of RR estimates included in pooled analysis.

Figure 11. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and colo-rectal cancer risk

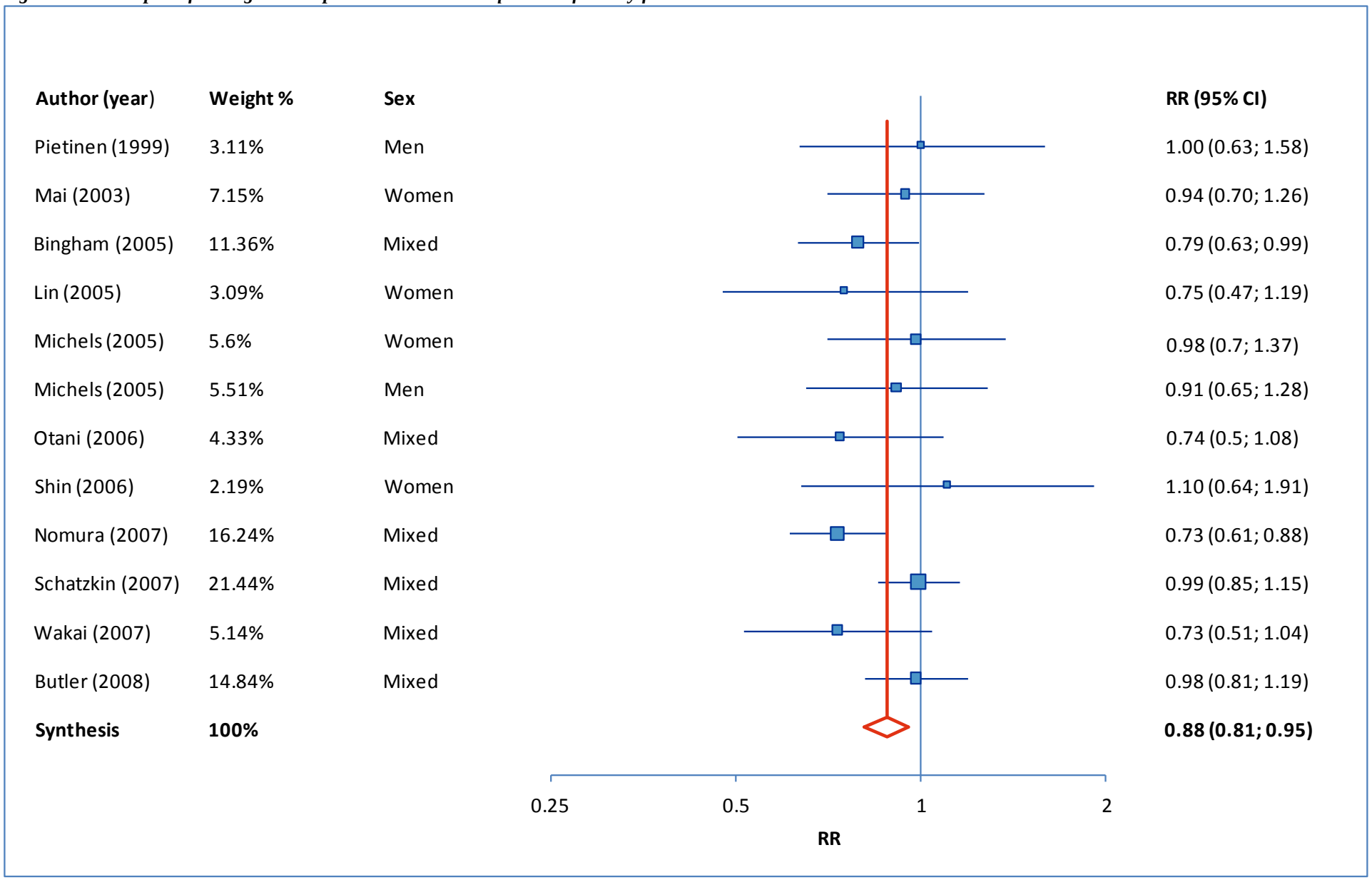


Figure 12. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and colo-rectal cancer risk, including pooled analysis and studies not included in the pooled analysis

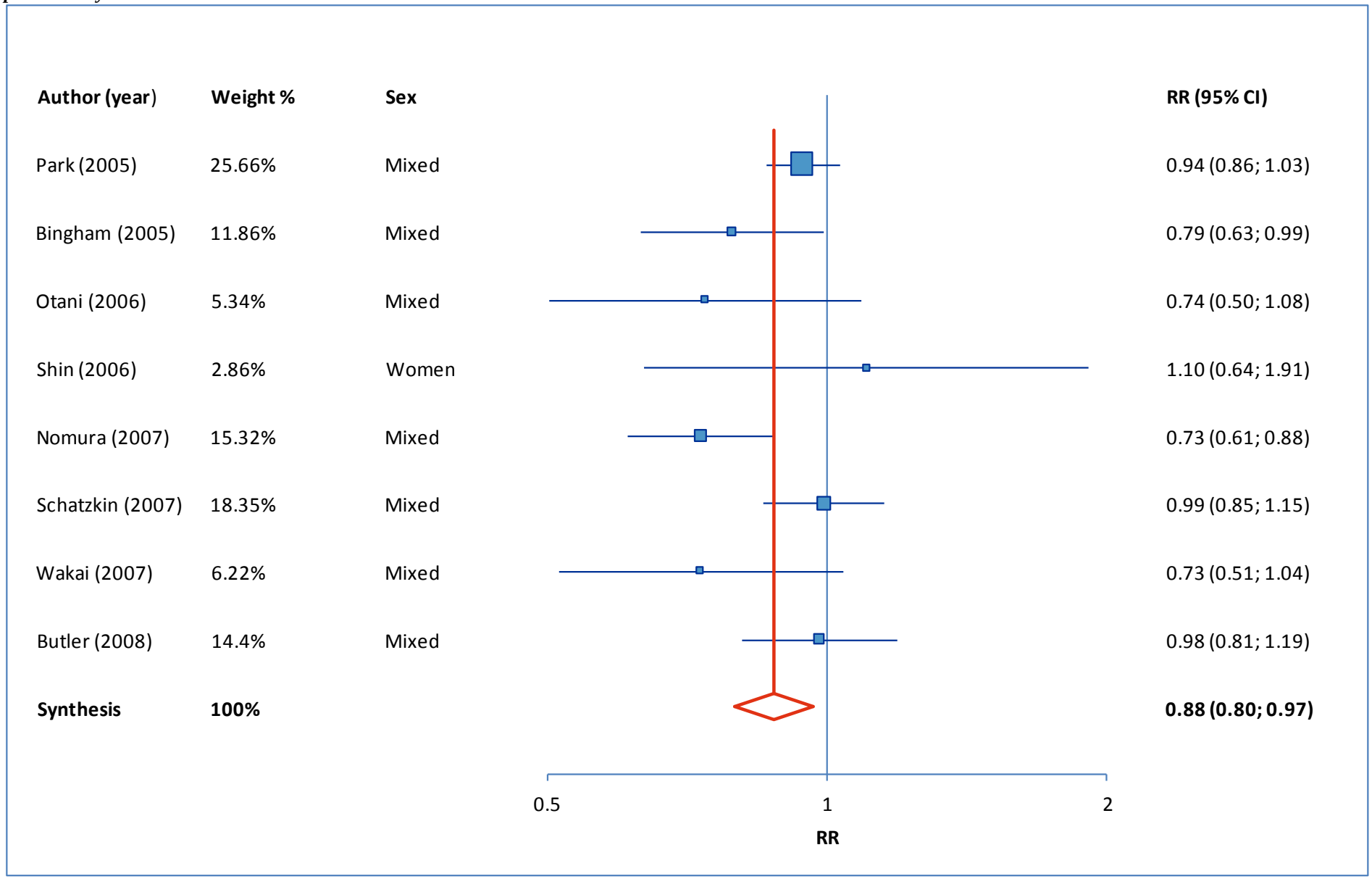
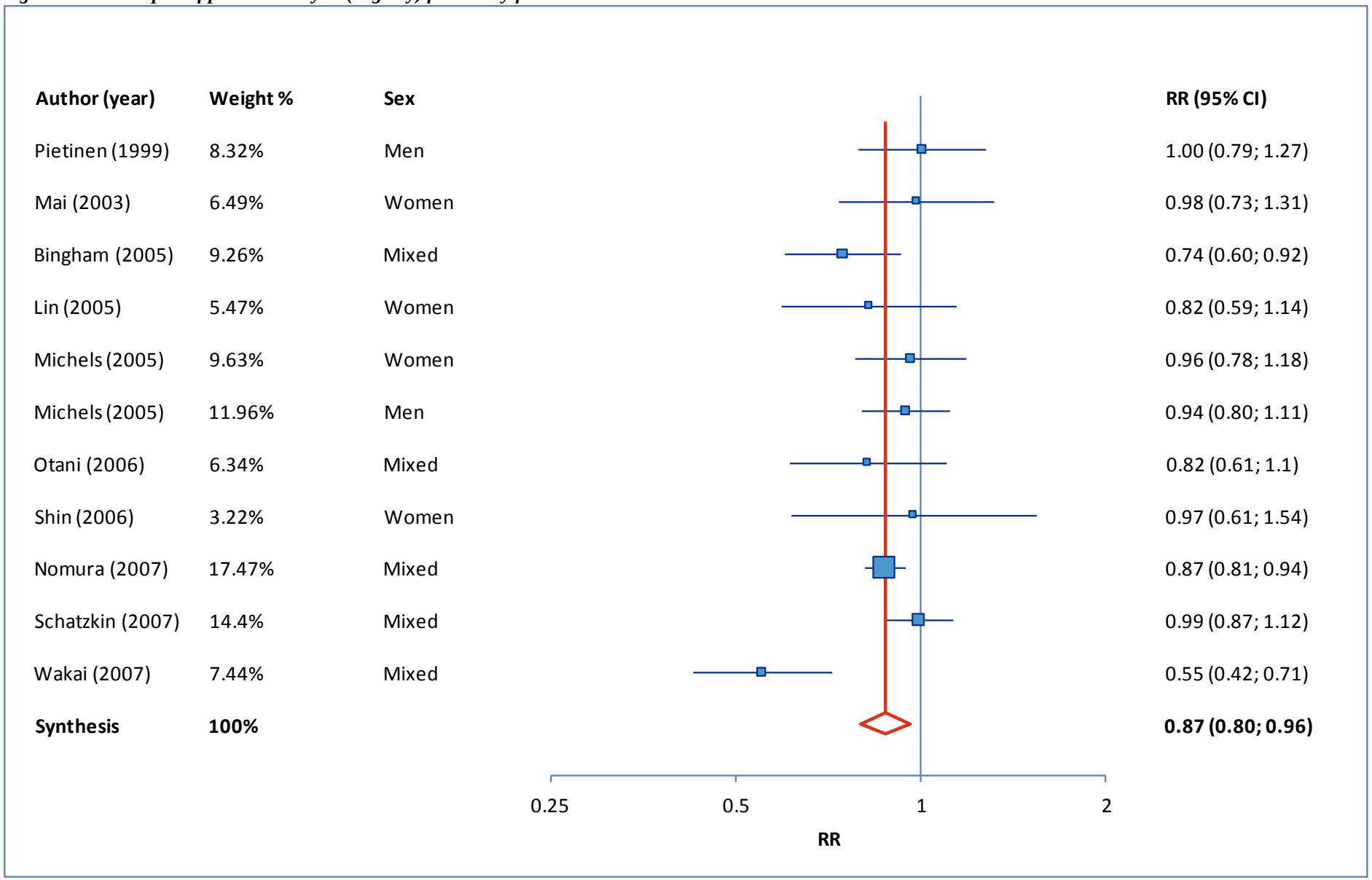


Figure 13. Forest plot of per unit analysis (10g/day) for dietary fibre intake and colo-rectal cancer risk



Colon cancer incidence and dietary fibre intake

319. Eight studies reported on colon cancer in relation to dietary fibre intake. All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. The eight studies included provided nine risk estimates (see Figure 14). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 73 and Figure 14. The results of the per unit meta-analysis (10 g/day) have been summarised in Table 75 and Figure 16. Incorporation of the Pooling Project and studies not included in the pooled analysis, left seven studies, providing seven risk estimates (Figure 15). The results from the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 74.

320. Heterogeneity was high for the analysis including the Pooling Project heterogeneity (see Table 74) and the per unit analysis (see Table 75). The number of estimates was too small to substantiate an explanation for the heterogeneity. For all analyses tests for publication bias (Egger's linear regression test) were not significant, although the p value Egger's regression test for zero intercept was almost significant (p=0.054), despite the analysis including more studies as part of the Pooling project than included in the other analyses.

321. Both highest quantile compared with lowest quantile meta-analyses indicated a significant reduction in the incidence of colon cancer by a point estimate of 16-17%. The per unit meta-analysis also indicated a significant reduction in the incidence of colon cancer with a 10g/day increase in dietary fibre, with a point estimate of a 12% reduction.

Table 73. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	9	0.83 (0.75-0.93)	-3.27 (p=0.001)

[1] I^2 = 11.05% (95% CI 0.00-68.69%); p for test of heterogeneity = 0.343
[2] No. of RR estimates included in pooled analysis.

Table 74. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and dietary fibre intake including the pooled analysis and excluding cohorts contained within

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.84 (0.73-0.98)	-2.42 (p=0.025)

[1] I^2 = 58.66% (95% CI 4.64-82.08%); p for test of heterogeneity = 0.024
[2] No. of RR estimates included in pooled analysis.

Table 75. Results of per unit (10g/day) meta-analysis for colon cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	9	0.88 (0.79-0.97)	-2.46 (p=0.014)

[1] I^2 = 50.37% (95% CI 0.00-76.81%); p for test of heterogeneity = 0.041
[2] No. of RR estimates included in pooled analysis.

Figure 14. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and colon cancer risk

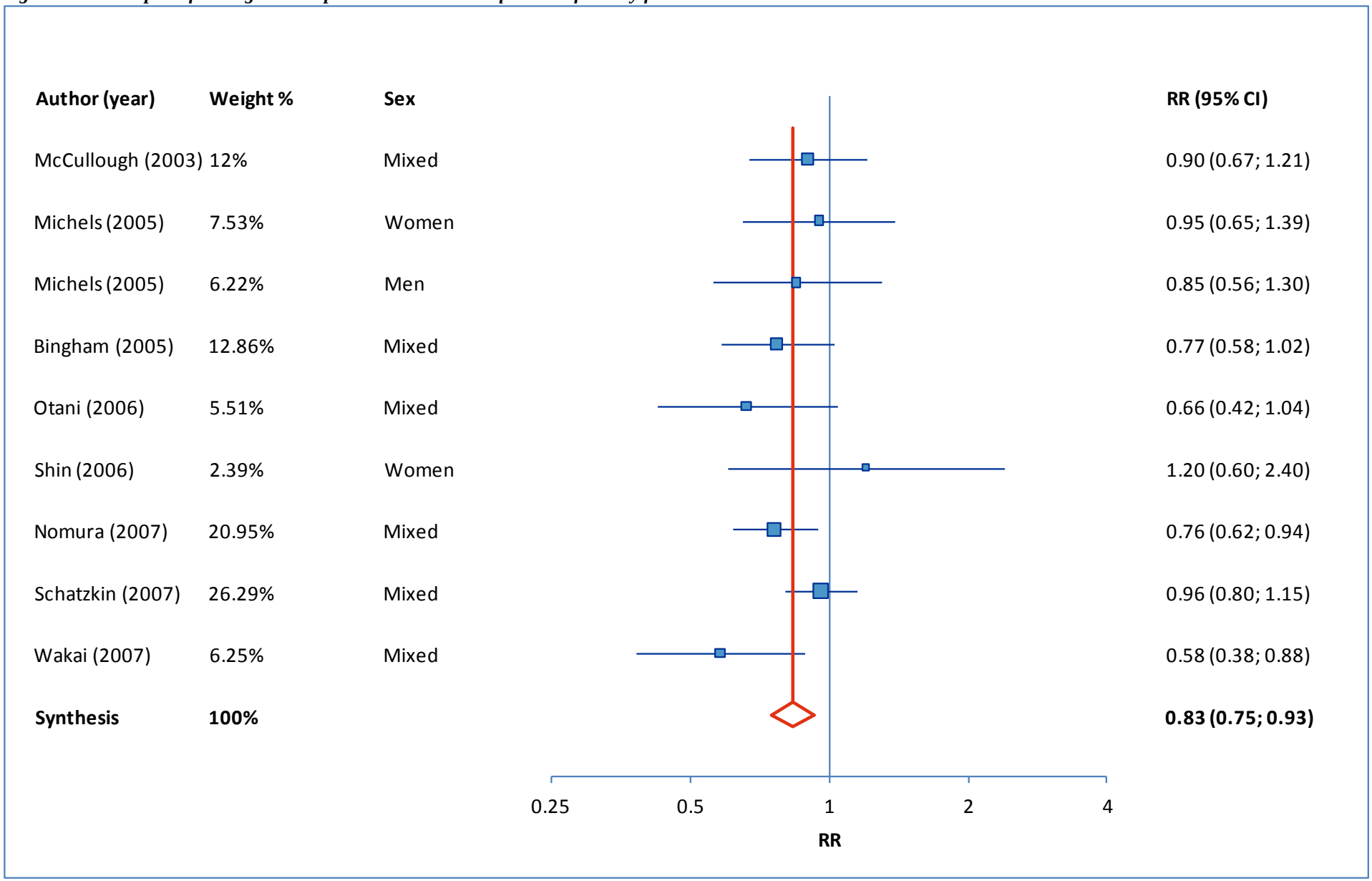


Figure 15. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and colon cancer risk including the pooled analysis and studies not included in the pooled analysis

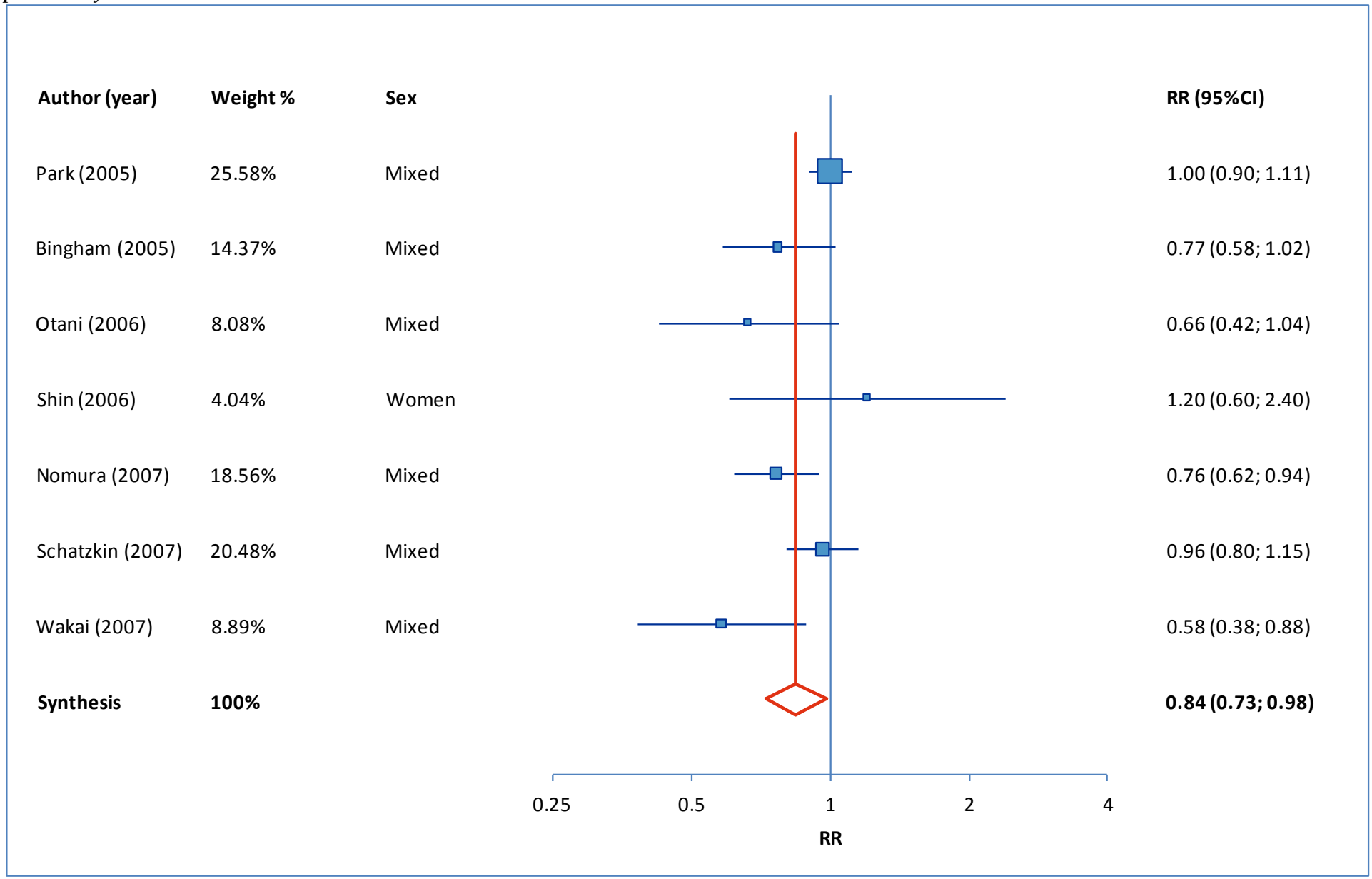
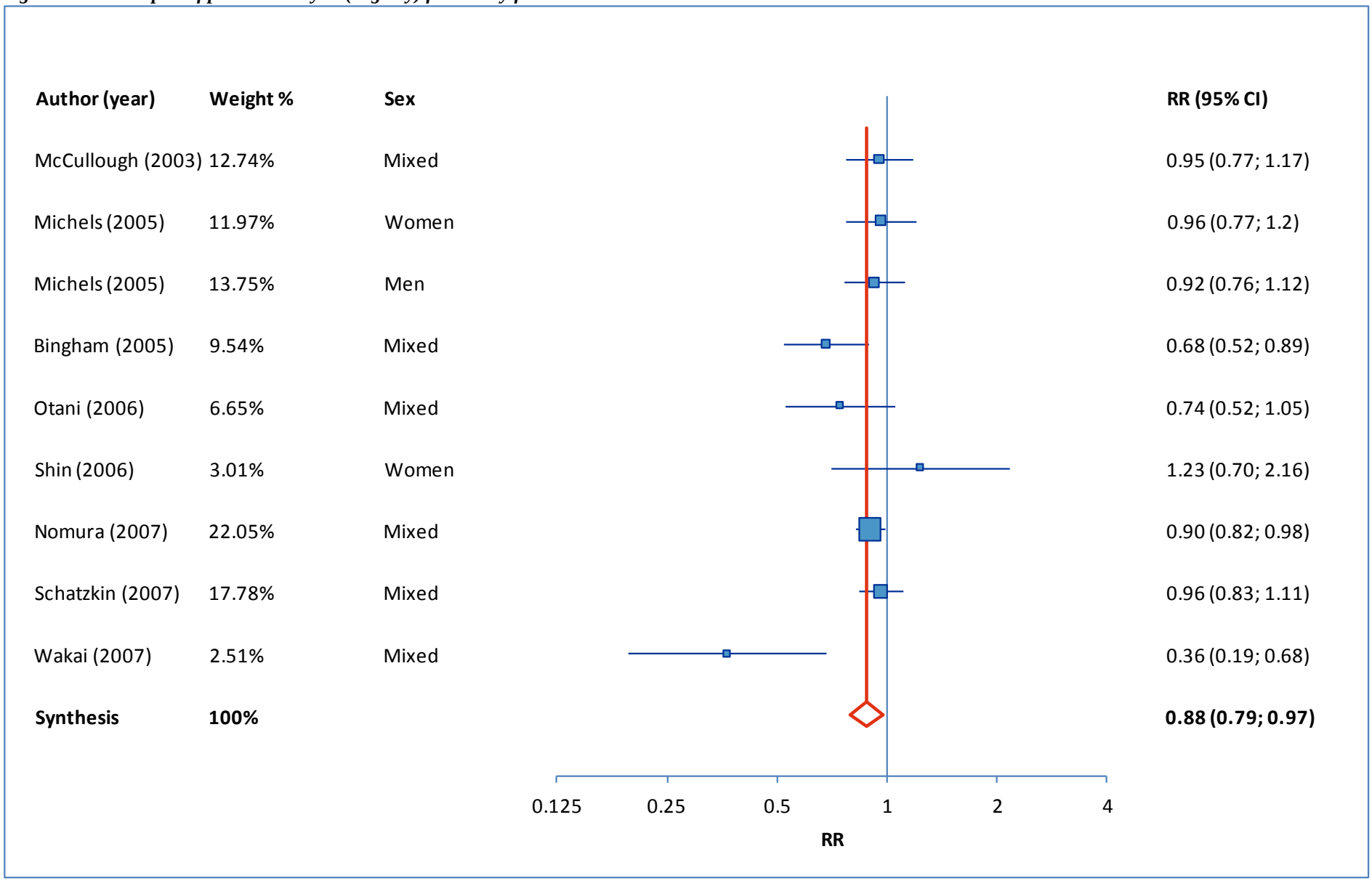


Figure 16. Forest plot of per unit analysis (10g/day) for dietary fibre intake and colon cancer risk



Rectal cancer incidence and dietary fibre intake

322. Seven studies reported on rectal cancer in relation to dietary fibre intake providing eight risk estimates (see Figure 17). All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 76 and Figure 17. The results of the per unit meta-analyses (10 g/day) for rectal cancer incidence and dietary fibre intake have been summarised in Table 78 and Figure 19. Incorporation of the Pooling Project and and studies not included in the pooled analysis left seven studies providing seven risk estimates (see Figure 18). The results from the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 77.

323. There was no significant evidence of heterogeneity between studies. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

324. All meta-analyses indicated no significant association between dietary fibre intake and the incidence of rectal cancer.

Table 76. Results of highest quantile compared with lowest quantile meta-analysis for rectal cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	0.93 (0.77-1.11)	-0.823 (p=0.416)

[1] I^2 = 10.24% (95% CI 0.00-70.90%); p for test of heterogeneity = 0.351
[2] No. of RR estimates included in pooled analysis.

Table 77. Results of highest quantile compared with lowest quantile meta-analysis for rectal cancer incidence and dietary fibre intake including the pooled analysis and excluding cohorts contained within

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.88 (0.76-1.01)	-2.20 (p=0.067)

[1] I^2 = 11.72% (95% CI 0.00-74.23); p for test of heterogeneity = 0.340
[2] No. of RR estimates included in pooled analysis.

Table 78. Results of per unit (10g/day) meta-analysis for rectal cancer incidence and dietary fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	0.89 (0.79-1.01)	-1.75 (p=0.079)

[1] I^2 = 11.97% (95% CI 0.00-71.46%); p for test of heterogeneity = 0.337
[2] No. of RR estimates included in pooled analysis.

Figure 17. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and rectal cancer risk

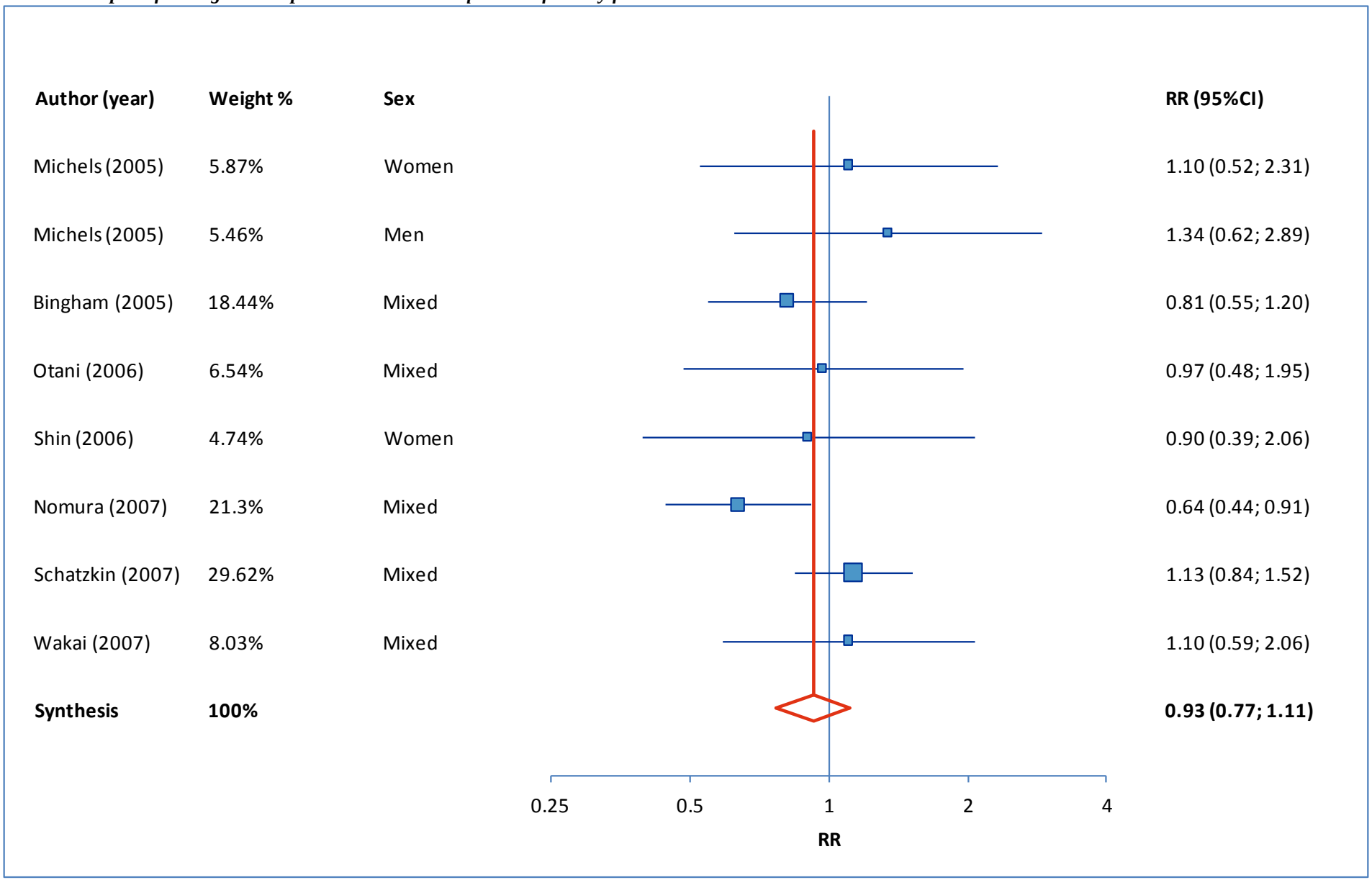


Figure 18. Forest plot of the highest compared with the lowest quantile of dietary fibre intake and rectal cancer risk including the pooled analysis and studies not included in the pooled analysis

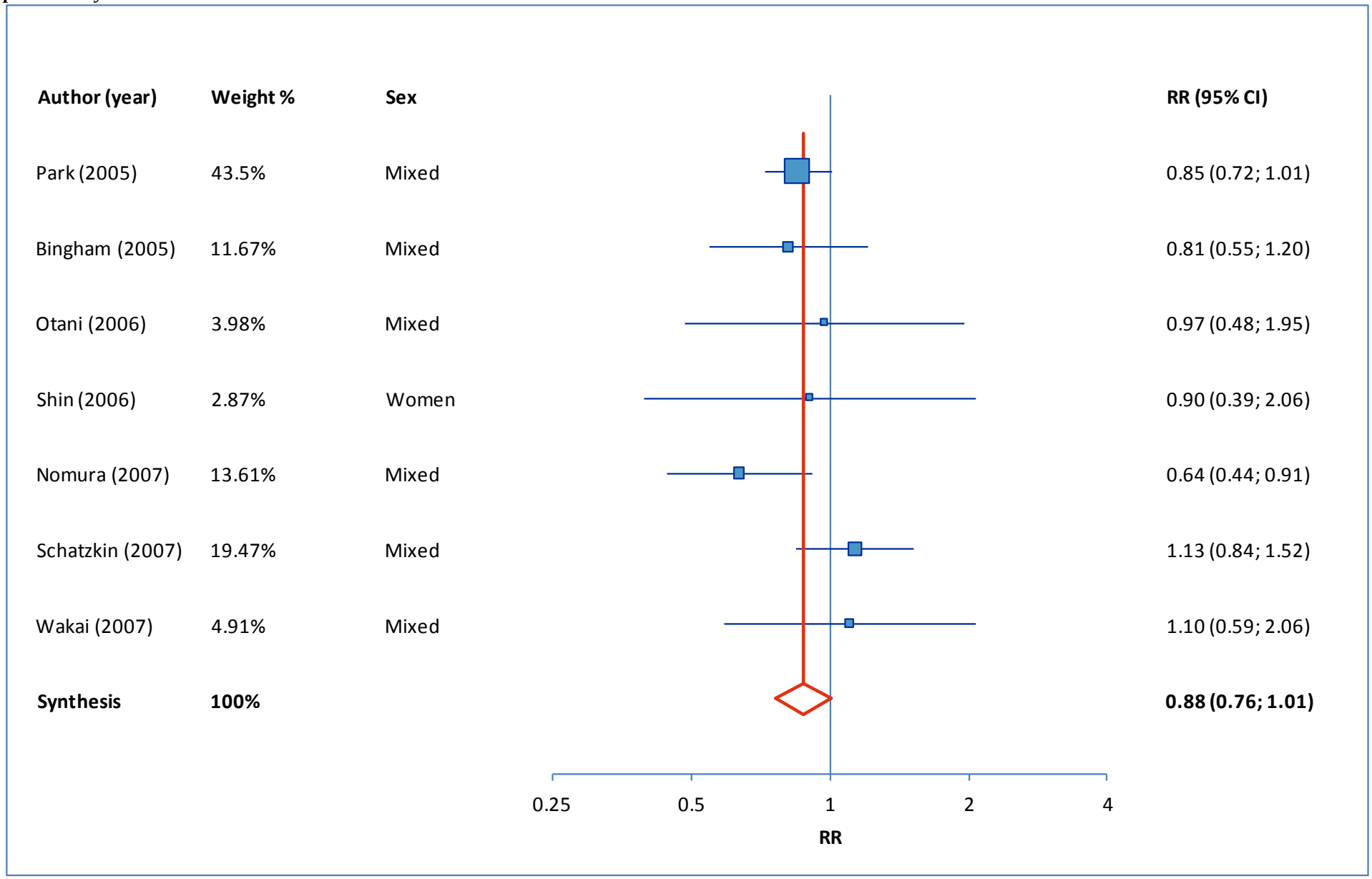
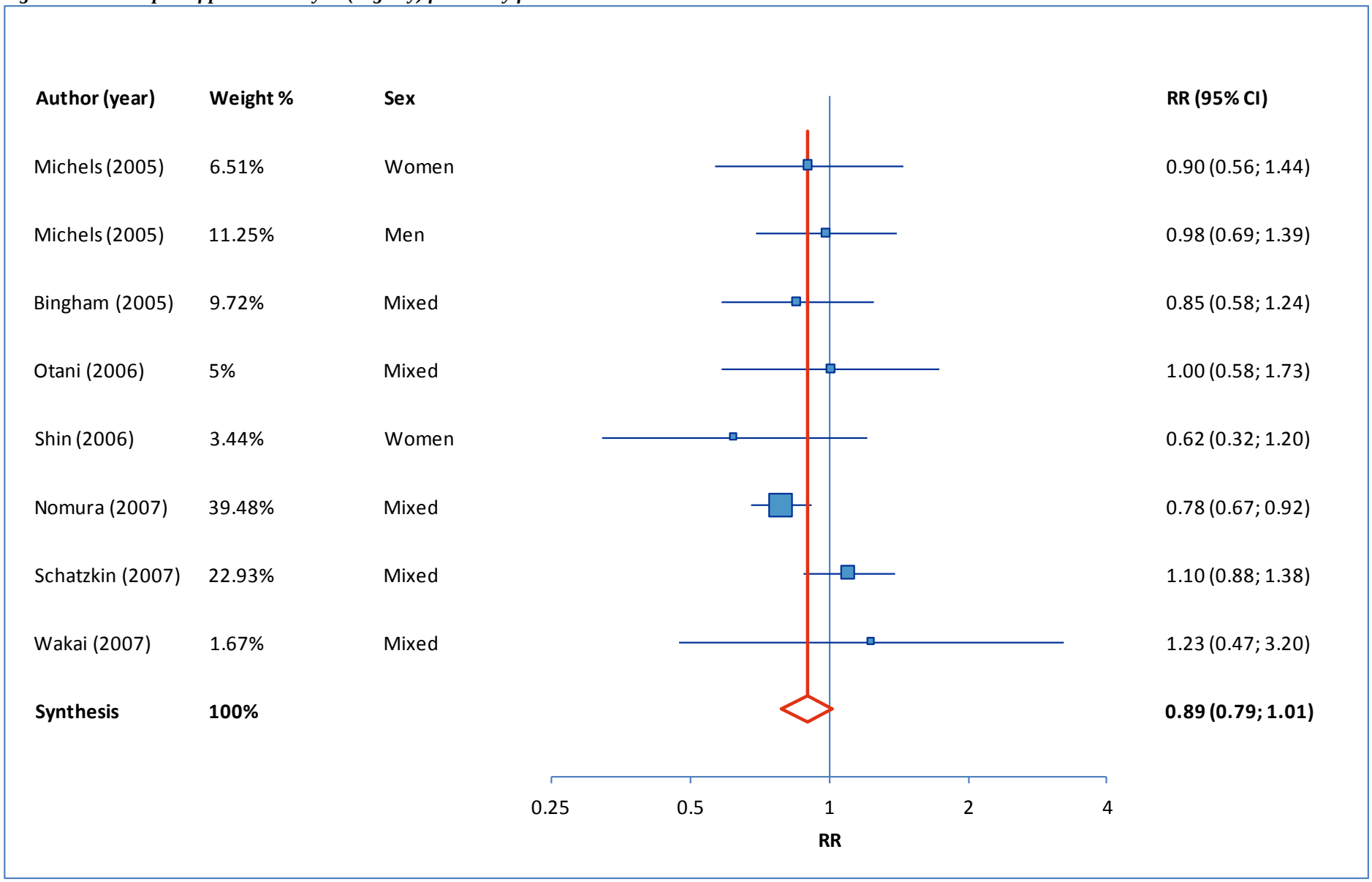


Figure 19. Forest plot of per unit analysis (10g/day) for dietary fibre intake and rectal cancer risk



Summary

325. Synthesis of available evidence from cohort studies showed that for the highest compared with the lowest quantile of dietary fibre intake a reduction in the incidence of colo-rectal cancer was observed with a point estimate of a 12% reduction: RR 0.88 (95% CI 0.81-0.95). A similar reduction in the incidence of colo-rectal cancer was also observed with a 10g/day increase in dietary fibre intake: RR 0.87 (95% CI 0.80-0.96). For the highest compared with the lowest quantile of dietary fibre intake a 17% reduction in the incidence of colon cancer was observed: RR 0.83 (95% CI 0.75-0.93). The per unit meta-analysis indicated a 12%: reduction in the incidence of colon cancer with a 10g/day increase in dietary fibre: RR 0.88 (95% CI 0.79-0.97). There was no significant evidence to suggest an association with the incidence of rectal cancer and dietary fibre intake.

326. The dietary assessment in cohort studies investigating dietary fibre intake in relation to colo-rectal cancer incidence has been based on data obtained mostly from food-frequency questionnaires (see Table 63). It is possible that measurement error inherent within this approach could be a factor that has contributed to the lack of convincing evidence for an inverse association between dietary fibre intake and colo-rectal cancer risk in many studies. If the observed association is due to a true biological effect, then the impact of measurement error is to dilute the association (which is likely to underestimate the relative risk) and the true magnitude of the association is probably substantially greater. In a nested case-control study of seven prospective UK cohorts (including the UK EPIC cohorts) (Dahm *et al.*, 2010), data from 579 colorectal cancer case patients and 1996 matched control subjects showed an inverse association between intakes of dietary fibre (non-starch polysaccharide), as estimated from four- to seven-day food records, and the risk of colo-rectal cancer, particularly the risk of colon cancer. This inverse association, however, was weaker and not statistically significant when dietary fibre consumption, in the same case and control subjects, was estimated using food-frequency questionnaires.

Total carbohydrate, starch or sugar intake, dietary glycaemic index or load and risk of colo-rectal cancer

327. Twelve studies were identified as eligible (Kearney *et al.*, 1996; Terry *et al.*, 2003; Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; McCarl *et al.*, 2006; Larsson *et al.*, 2007; Strayer *et al.*, 2007; Butler *et al.*, 2008; Howarth *et al.*, 2008; Weijenberg *et al.*, 2008; George *et al.*, 2009; Zhang *et al.*, 2010) (see Appendix 2 for studies excluded).

328. Several of the studies included did not adjust for all the required confounders (alcohol intake, smoking, physical activity and overweight/obesity) in their multivariant analyses (see Table 80); however, these studies did investigate the influence of any missing necessary confounder on effect estimates and reported them not to change the estimates produced (McCarl *et al.*, 2006) (Larsson *et al.*, 2007; Strayer *et al.*, 2007).

329. One of the studies reported a pooled analysis of 13 prospective cohort studies (Zhang *et al.*, 2010). The cohorts included were the same as those in the pooled analysis of dietary fibre and colo-rectal cancer risk (Park *et al.*, 2005).

Study design

330. The study design details have been summarised in Table 79. Eight studies were conducted in North America, two in Europe and one in Asia. The majority of subjects were women. All studies were cohort studies. The individual cohort sizes ranged from 8,006 to 566,402. The average length of follow-up ranged from 6 to 20 years. The pooled analysis included data from 731,441 subjects.

331. Seven studies reported on carbohydrate intake in relation to colo-rectal cancer risk (Terry *et al.*, 2003; Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; McCarl *et al.*, 2006; Larsson *et al.*, 2007; Strayer *et al.*, 2007; Howarth *et al.*, 2008). Six studies reported on sugar intake in relation to colo-rectal cancer risk (Kearney *et al.*, 1996; Terry *et al.*, 2003; Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; McCarl *et al.*, 2006; Howarth *et al.*, 2008). Three studies reported on starch intake in relation to colo-rectal cancer risk (Higginbotham *et al.*, 2004; McCarl *et al.*, 2006; Butler *et al.*, 2008). Nine studies reported on dietary glycaemic index or load in relation to colo-rectal cancer risk (Terry *et al.*, 2003; Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; McCarl *et al.*, 2006; Larsson *et al.*, 2007; Strayer *et al.*, 2007; Howarth *et al.*, 2008; Weijenberg *et al.*, 2008; George *et al.*, 2009). A pooled analysis reported on sugar-sweetened carbonated soft drink consumption in relation to colon cancer risk (Zhang *et al.*, 2010).

332. The funding sources for all studies, where reported, were Governmental; one study did not report funding sources.

Table 79. Cohort studies of total carbohydrate, starch or sugar intake, dietary glycaemic index or load and risk of colo-rectal cancer

Cohort	Author	Year	Counrty	Sex	Age (y)	CRC cases	CC cases	RC cases	Cohort size	Mean follow-up duration	Dietary assessment method	Carbohydrate components investigated	Funding source
Individual cohorts													
Health professionals follow-up study	Kearney	1996	USA	Men	40-75	NR	203	NR	47935	6	FFQ	Lactose	National Institutes of Health, USA; American Cancer Society
Canadian National Breast Screening Study	Terry	2003	Canada	Women	40-59	616	436	180	49124	16.5y	FFQ	Total carbohydrate, total sugars, GL	National Cancer Institute of Canada
Women's Health Study	Higginbotham	2004	USA	Women	mean 54	174	148	26	38451	7.9y	FFQ	Total carbohydrate, starch, fructose, sucrose, GI, GL	National Institutes of Health, USA
Nurses' Health Study Cohort and Health Professionals' Follow-up Study	Michaud	2005	USA.	Mixed	30-55	1809	1431	378	131349	up to 20y	FFQ	Total carbohydrate, fructose, sucrose, GI, GL	National Institutes of Health, USA
Iowa Women's Health Study	McCarl	2006	USA	Women	mean 62 (55-69)	954	757	209	35197	15y	FFQ	GI, GL **	National Cancer Institute, USA
Swedish Mammography Cohort	Larsson	2007	Sweden	Women	40-76	870	594	283	61433	15.7y	FFQ	Total carbohydrate, GI, GL	Swedish Cancer Society; Swedish Research Council
Breast Cancer Detection Demonstration Project follow-up cohort	Strayer	2007	USA	Women	62	490	NR	NR	45561	8.5y	FFQ	Energy intake from carbohydrate, GI, GL	NR
Singapore Chinese Health study	Butler	2008	Singapore	Mixed	45-74	961	591	370	61321	9.8y	FFQ	Starch	National Cancer Institute, USA
Hawaii-Los Angeles Multiethnic Cohort Study	Howarth	2008	USA	Mixed	45-75	2379	1782	578	191004	8.2y	FFQ	Total carbohydrate, sucrose, GL	National Cancer Institute, USA
Netherlands Cohort Study	Weijenberg	2008	The Netherlands	Mixed	NR	1811	1225	418	120852	11.3y	FFQ	GI, GL	NR
National Institutes of Health–AARP Diet and Health Study	George	2009	USA	Mixed	50-71	4498	NR	NR	566402	up to 8y	FFQ	GI, GL	National Cancer Institute, USA
Pooled analysis													
13 cohorts	Zhang,	2010	North America, Europe	Mixed	NR	NR	5604	NR	731441	6-20y	FFQ	Sugar-sweetened carbonated soft drinks	National Institutes of Health, USA

NR, not reported, y, year; d, day; FFQ, food frequency questionnaire; *about 10% of population had diabetes at baseline; ** other carbohydrate exposures not adjusted for necessary confounders, so not included; CRC colo-rectal cancer; CC, colon cancer; RC, rectal cancer; GI, glycaemic index; GL, glycaemic load.

Table 80. Adjusted confounders for studies investigating carbohydrate, starch, sugar, glycaemic index or load

Study	Age	Sex **	BMI	Energy	Smoking	Family	Education	Alcohol	PA	NSAIDs	Fibre	Meat	Folate	Calcium	Multivitamin use	HRT use
Individual cohorts																
Kearney, 1996	Y		Y		Y	Y		Y	Y		Y	Y				
Terry, 2003	Y		Y	Y	Y		Y	Y	Y			Y	Y			Y
Higginbotham, 2004	Y		Y	Y	Y	Y		Y	Y	Y	Y	Y	y	Y		Y
Michaud, 2005	Y		Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y		
McCarl, 2006	Y		Y	Y	Y				Y							
Larsson, 2007	Y		Y	Y	Y		Y	Y			Y	Y	Y	Y and magnesium		
Strayer, 2007	Y		Y	Y	Y					Y	Y					Y
Butler, 2008	Y *	Y	Y	Y	Y	Y	Y	Y	Y							
Howarth, 2008	Y		Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y		Y
Weijenberg *et al*., 2008	Y		Y	Y	Y	Y	Y	Y	Y	Y		Y		Y		
George *et al*., 2009	Y		Y	Y	Y	Y	Y	Y	Y							Y
Pooled analysis																
Zhang, 2010	Y		Y	Y	Y	Y	Y	Y	Y	Y		Y	Y		Y	Y

* and diabetes; ** this was not applicable in studies where the cohort was of a single sex; PA, physical activity; Family, family history of colo-rectal cancer; NSAIDs, non-steroidal anti-inflammatory drugs; HRT, hormone replacement therapy

Results

333. Adjusted confounders for studies investigating carbohydrate, starch, sugar, glycaemic index or load have been summarised in Table 80. Insufficient studies were available to perform meta-analyses for starch or sugar intake. Meta-analyses were performed for studies investigating dietary glycaemic index or load and risk of colo-rectal cancer and subsite cancers.

Colo-rectal cancer incidence and carbohydrate intake

334. The findings from all cohort studies have been summarised in Table 83. All studies provided sufficienty data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. Adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colo-rectal cancer subsite risk, where reported.

335. Six studies reported on colo-rectal cancer in relation to carbohydrate intake on a gram per day basis, providing seven risk estimates (see Figure 20 and Figure 21). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 81. The results of the per unit meta-analysis have been summarised in Table 82.

336. Heterogeneity was high, but not significant. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

337. There were no differences between the highest compared with the lowest quantile, or the per unit analysis, of dietary carbohydrate intake in relation to the incidence of colo-rectal cancer.

Table 81. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.00 (0.83-1.19)	-0.04 (p=0.964)

[1] I^2 = 57.23% (95% CI 0.87-81.55%); p for test of heterogeneity = 0.029
[2] No. of RR estimates included in pooled analysis.

Table 82. Results of per unit (100g/day) meta-analysis for colo-rectal cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.00 (0.82-1.21)	-0.01 (p=0.989)

[1] I^2 = 66.83% (95% CI 26.07-85.12%); p for test of heterogeneity = 0.006
[2] No. of RR estimates included in pooled analysis.

Table 83. Adjusted relative risk ratios for the highest compared with the lowest quantile of carbohydrate intake and colo-rectal cancer risk

Study	Sex	Measure	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Terry, 2003	Women	g/d	CRC, CC, RC	Q1 <143g/d vs Q5 > 249/d **	1.01 (0.68-1.51)	1.04 (0.63-1.72)	0.98 (0.49-1.97)	0.66	0.8	0.85	No association observed
Higginbotham, 2004	Women	g/d	CRC	Q1 vs Q5 *	2.41 (1.10-5.27)			0.02			Positive association observed
Michaud, 2005	Women	g/d	CRC, CC, RC	Q1 110g/d vs Q5 202g/d ***	0.87 (0.68-1.11)	0.86 (0.65-1.13)	0.91 (0.53-1.55)	0.15	0.14	0.78	No association observed
	Men	g/d	CRC, CC, RC	Q1 182g/d vs Q5 288g/d	1.27 (0.93-1.72)	1.21 (0.85-1.71)	1.45 (0.73-2.38)	0.11	0.2	0.34	
Larsson, 2007	Women	g/d	CRC, CC, RC	Q1 <211g/d vs Q5 >245g/d **	1.10 (0.85-1.44)	1.14 (0.83-1.57)	0.94 (0.59-1.50)	0.45	0.64	0.78	No association observed
Strayer, 2007	Women	g/d	CRC	Q1 <114g/d vs Q5 >162 **	0.70 (0.50-0.97)			0.08			Inverse association observed
Howarth, 2008	Women	g/d	CRC, CC, RC	Q1 <210.7g/d vs Q5 >281.0g/d **	0.71 (0.53-0.95)	0.69 (0.50-0.96)	0.78 (0.42-1.44)	0.025	0.038	0.337	Inverse association observed in women, but not men.
	Men	g/d	CRC, CC, RC	Q1 <243.9g/d vs Q5 >331.1	1.09 (0.84-1.40)	1.10 (0.81-1.49)	0.98 (0.60-1.59)	0.603	0.452	0.642	

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Figure 20. Forest plot of the highest compared with the lowest quantile of carbohydrate intake and colo-rectal cancer risk

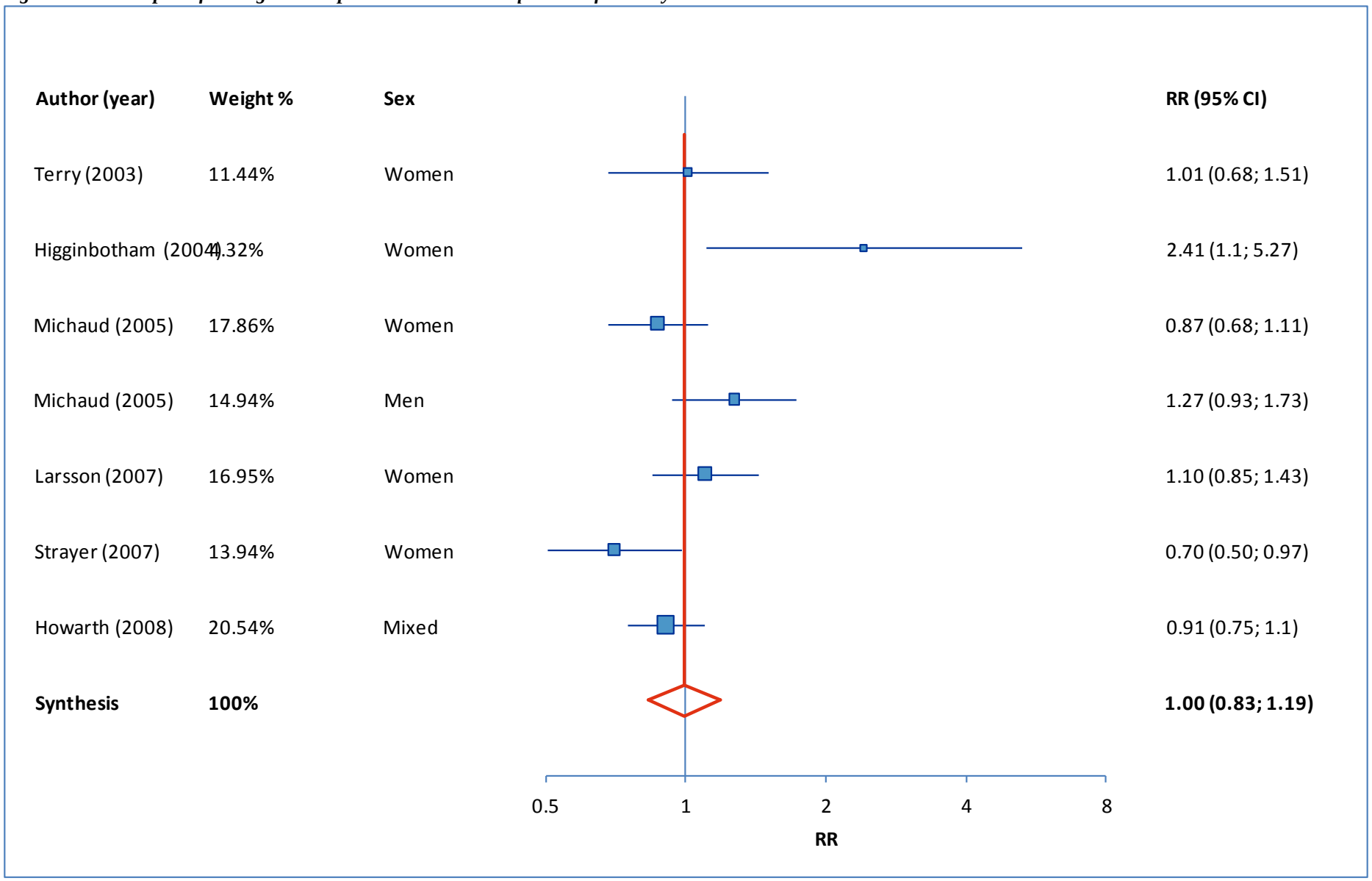
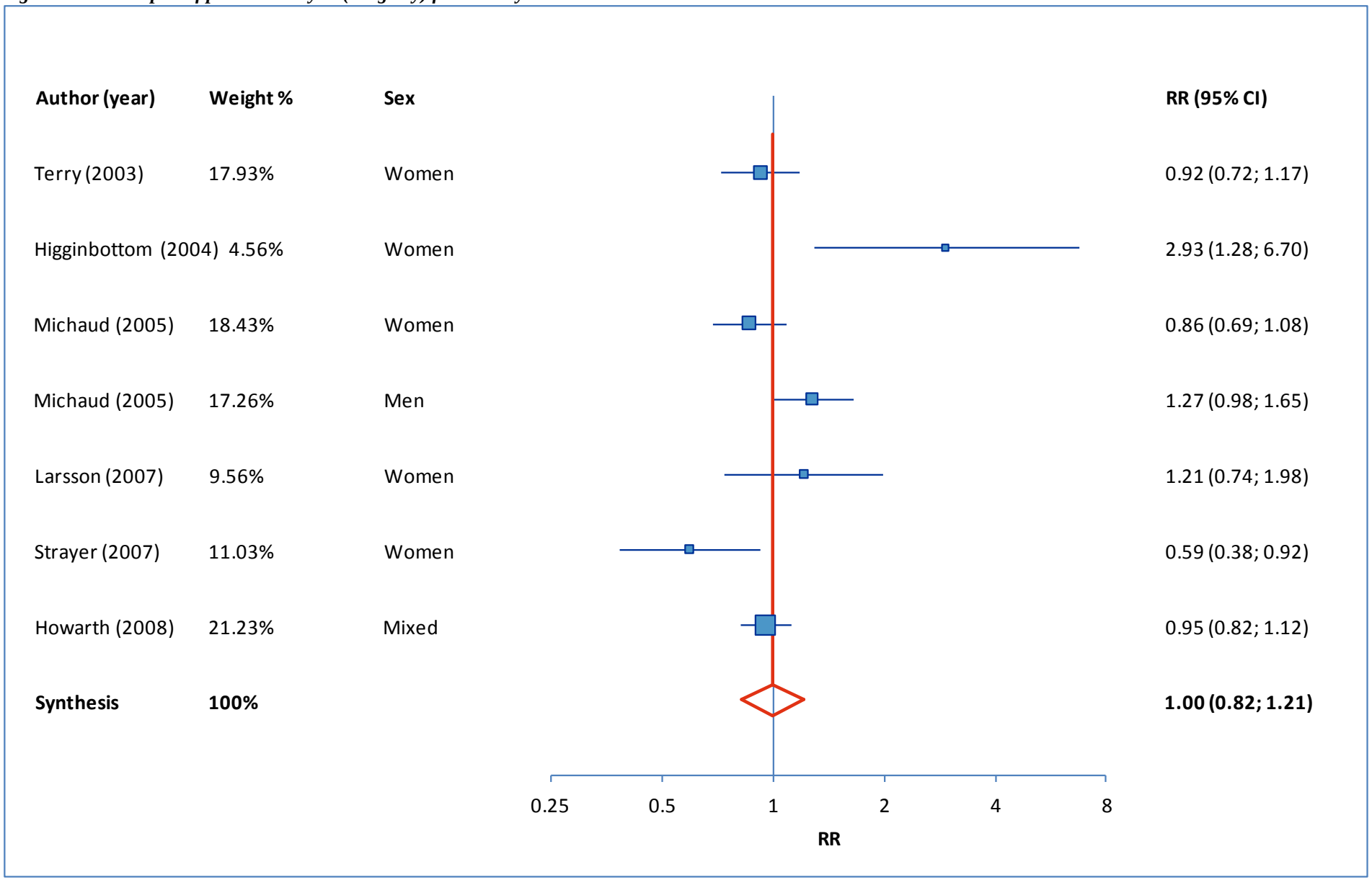


Figure 21. Forest plot of per unit analysis (100g/day) for carbohydrate intake and colo-rectal cancer risk



Colon and rectal cancer incidence and carbohydrate intake

338. Four studies reported on colon cancer incidence in relation to dietary carbohydrate intake. The four studies included provided five risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 84. The results of the per unit meta-analysis have been summarised in Table 85. Four studies reported on rectal cancer incidence in relation to dietary carbohydrate intake (see Table 83). The four studies included provided five risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 86. The results of the per unit meta-analysis have been summarised in Table 87.

339. Heterogeneity was not significant for either the colon cancer analyses or the rectal cancer analyses. Tests for publication bias (Egger's linear regression test) were not significant. There were no differences between the highest compared with the lowest quantile or the per unit analyses of dietary carbohydrate intake in relation to the incidence of colon or rectal.

Table 84. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.97 (0.85-1.11)	-0.38 (p=0.706)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.410
[2] No. of RR estimates included in pooled analysis.

Table 85. Results of per unit (100g/day) meta-analysis for colon cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.98 (0.85-1.12)	-0.31 (p=0.754)

[1] I^2 = 19.84% (95% CI 0.00-83.33%); p for test of heterogeneity = 0.288
[2] No. of RR estimates included in pooled analysis.

Table 86. Results of highest quantile compared with lowest quantile meta-analysis for rectal cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.98 (0.79-1.23)	-0.14 (p=0.884)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.737
[2] No. of RR estimates included in pooled analysis.

Table 87. Results of per unit (100g/day) meta-analysis for rectal cancer incidence and carbohydrate intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.98 (0.81-1.20)	-0.72 (p=0.863)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.665
[2] No. of RR estimates included in pooled analysis.

Colo-rectal cancer incidence and sugar intake

340. The findings from all cohort studies have been summarised in Table 88. Adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colon or rectal cancer risk, where reported. There were insufficient studies to perform a meta-analysis for any of the sugar groups and for sucrose one study only reported data for women, where an inverse association was observed, but not for men, where no association was observed (Howarth *et al.*, 2008).

341. One study reported on lactose intake in relation to colo-rectal cancer incidence (Kearney *et al.*, 1996). This reported no difference in colo-rectal cancer incidence between the highest compared with the lowest quantile of dietary lactose intake: multivariate adjusted RR = 0.84 (95% CI: 0.54- 1.29; p trend=0.74).

342. Two studies reported on dietary fructose intake in relation to colo-rectal cancer incidence (Higginbotham *et al.*, 2004; Michaud *et al.*, 2005). One study in women (Higginbotham *et al.*, 2004) reported an increased incidence of colo-rectal cancer in the highest compared with the lowest quantile of fructose intake (multivariate adjusted RR= 2.09 ;95% CI 1.13-3.87), but the other study reported no difference in the incidence of colo-rectal cancer in women (reporting an adjusted RR=0.87; 95% CI 0.71-1.07). Fructose intake in men, however, was observed to be associated with increased colo-rectal cancer incidence, with an increased incidence in the highest compared with the lowest quantile of intake; multivariate adjusted RR=1.37 (95% CI: 1.05-1.78) (Michaud *et al.*, 2005).

343. Three studies reported on sucrose intake in relation to colo-rectal cancer incidence (Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; Howarth *et al.*, 2008). The findings mirror the associations observed for fructose intake. One study in women (Higginbotham *et al.*, 2004) reported an higher incidence of colo-rectal cancer in the highest compared with the lowest quantile of sucrose intake (multivariate adjusted RR= 1.51 (95% CI 0.90-2.54), while another reported a lower incidence of colo-rectal cancer in the highest compared with the lowest quantile of sucrose intake (multivariate adjusted RR= 0.71 (95% CI 0.53-0.95) (Howarth *et al.*, 2008). The other study reported no difference in the incidence of colo-rectal cancer in women in relation to sugar intake (Michaud *et al.*, 2005). Two reported on sucrose intake in men in relation to colo-rectal cancer incidence (Michaud *et al.*, 2005; Howarth *et al.*, 2008). One study reported an increased incidence in the highest compared with the lowest quantile of intake; multivariate adjusted RR=1.30 (95% CI: 0.99-1.69) (Michaud *et al.*, 2005). The other study reported no difference in incidence in the highest compared with the lowest quantile of intake (data not reported) (Howarth *et al.*, 2008).

344. One study reported on total sugar intake in relation to colo-rectal cancer incidence, but did not observe an association (Terry *et al.*, 2003). A pooled analysis of 13 cohorts studies observed no association between sugar-sweetened carbonated soft drink consumption and colon cancer risk, as compared with non-consumers (Zhang *et al.*, 2010); for men and women combined the adjusted risk ratio comparing consumption of 550g/day to non-consumers was 0.94 (95% CI 0.66-1.32; P_{trend} = 0.91). In summary, there was contradictory and inconsistent evidence for an association between dietary sugar intake and colo-rectal cancer incidence.

Table 88. Adjusted relative risk ratios for the highest compared with the lowest quantile of sugar intake and colo-rectal cancer risk

Study	Sex	Sugar investigated	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Individual cohorts											
Kearney, 1996	Men	Lactose	CC	Q1 vs. Q5 *		0.84 (0.54-1.29)		0.74			No association observed
Higginbotham, 2004	Women	Fructose	CRC	Q1 vs Q5 *	2.09 (1.13-3.87)			0.08			Positive association observed
Michaud, 2005	Women	Fructose	CRC, CC, RC	Q1 22g/d vs Q5 68g/d ***	0.87 (0.71-1.07)	0.86 (0.68-1.09)	0.92 (0.59-1.44)	0.2	0.15	0.47	Positive association observed for men, but not women
	Men	Fructose	CRC, CC, RC	Q1 29g/d vs Q5 72 g/d ***	1.37 (1.05-1.78)	1.38 (1.03-1.86)	1.31 (0.72-2.38)	0.008	0.02	0.33	
Higginbotham, 2004	Women	Sucrose	CRC	Q1 vs Q5 *	1.51 (0.90-2.54)			0.06			Positive association observed
Michaud, 2005	Women	Sucrose	CRC, CC, RC	Q1 17g/d vs Q5 55g/d ***	0.89 (0.72-1.11)	0.99 (0.78-1.26)	0.62 (0.39-0.99)	0.1	0.49	0.17	Positive association observed for men, but not women
	Men	Sucrose	CRC, CC, RC	Q1 26g/d vs Q5 67g/d ***	1.30 (0.99-1.69)	1.25 (0.93-1.68)	1.47 (0.81-2.66)	0.03	0.13	0.11	
Howarth, 2008	Women	Sucrose	CRC, CC	Q1 vs Q5 *	0.88 (0.70-1.11)	0.85 (0.66-1.11)		0.158	0.155		No associations observed for men women
	Men	Sucrose	CRC, CC	Q1 vs Q5 *	NR	NR					
Terry, 2003	Women	Total sugars	CRC, CC, RC	Q1 <53g/d vs Q5 >103g/d **	1.03 (0.73-1.44)	1.10 (0.72-1.66)	0.90 (0.49-1.66)	0.71	0.52	0.87	No association observed
Pooled analysis											
Zhang, 2010	Women	Sugar-sweetened carbonated soft drinks	CC	Q1 non-drinkers vs Q4 >550g/d		1.08 (0.67-1.73			0.89		No association observed
	Men	Sugar-sweetened carbonated soft drinks				0.77 (0.46-1.29)			0.74		

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer; PCC, proximal colon cancer; DCC, distal colon cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and starch intake

345. The findings from all cohort studies have been summarised in Table 89. Adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colon or rectal cancer risk, where reported. There were insufficient studies to perform a meta-analysis for starch intake and colo-rectal cancer incidence.

346. Two studies reported on starch intake in relation to colo-rectal cancer incidence (Higginbotham *et al.*, 2004; Butler *et al.*, 2008). One study observed no difference in the incidence of colo-rectal cancer in the highest compared with the lowest quantile of starch (Butler *et al.*, 2008). One study in women (Higginbotham *et al.*, 2004) reported a higher incidence of colo-rectal cancer in the highest compared with the lowest quantile of starch intake (multivariate adjusted RR= 2.60 (95% CI 1.22-5.54). In summary, there was contradictory and inconsistent evidence for an association between dietary starch intake and colo-rectal cancer incidence and there were insufficient studies to enable a meaningful interpretation.

Table 89. Adjusted relative risk ratios for the highest compared with the lowest quantile of starch intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CRC P for trend	Reported association
Higginbotham, 2004	Women	CRC	Q1 vs Q5 *	2.60 (1.22-5.54)	0.02	Positive association observed
Butler, 2008	Mixed	CRC	Q1 vs Q5 *	1.09 (0.90 – 1.31)	0.56	No association observed

; NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer
* no quantile exposure data reported;

Colo-rectal cancer incidence and dietary glycaemic index or load

347. The glycaemic index is defined methodologically as the incremental area under the curve for the blood glucose response after consumption of a food relative to that produced by a reference food (usually glucose or white bread) given in an equivalent digestible carbohydrate amount (50 or 25 g) (Jenkins *et al.*, 1981). The concept of glycaemic load was introduced as an indicator of a glucose response or insulin demand induced by the total carbohydrate intake, and quantifies the overall glycaemic effect of a portion of food (Salmerón *et al.*, 1997a; Salmerón *et al.*, 1997b). The glycaemic load of a typical serving of food is the product of the amount of digestible carbohydrate in that serving and the glycaemic index of the food. A higher glycaemic load reflects either greater carbohydrate consumption, intake of foods with a higher glycaemic index, or both.

348. The glycaemic load for a food item is calculated by multiplying the food's glycemic index by the number of carbohydrate grams in a serving and the total dietary glycaemic load is the sum of the glycaemic load for the total servings of all carbohydrate-containing foods consumed per day, on average. The overall glycaemic index reflects the average quality of carbohydrates consumed, whereas the total dietary glycaemic load reflects both the average quantity and quality of carbohydrates.

349. The glycaemic index values used in the cohort studies were obtained from tables compiling published and unpublished results from human studies of glycaemic response to different foods using standardised methodology, with either glucose or white bread as the reference food (Foster-Powell & Miller, 1995; Foster-Powell *et al.*, 2002; Brand-Miller *et al.*, 2003; Atkinson *et al.*, 2008).

350. Median glycaemic index intakes varied from 49 to 80 and median daily glycaemic load ranged from 67 to 210; however, the choice of reference food influenced the reported glycaemic index and glycaemic load values. Glycaemic index values obtained using glucose as the reference food were approximately 0.7 of the glycaemic index values obtained using white bread as the reference food (Foster-Powell *et al.*, 2002). The intake values, therefore, were not directly comparable and several studies did not report the reference food used.

351. All studies investigated glycaemic load in relation to colo-rectal cancer risk, but two did not report on glycaemic index in relation to colo-rectal cancer risk (Terry *et al.*, 2003; Howarth *et al.*, 2008). Two studies only reported on overall colo-rectal cancer risk (Strayer *et al.*, 2007; George *et al.*, 2009), while the others also reported colon and rectal risk separately. Three studies reported proximal and distal cancer risk in relation to glycaemic load or glycaemic index intake (Terry *et al.*, 2003; Michaud *et al.*, 2005; Weijenberg *et al.*, 2008).

352. The findings from all cohort studies have been summarised in Table 98. Adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colon or rectal cancer risk, where reported.

353. Three studies reported some positive associations between glycaemic load or glycaemic index and colo-rectal cancer risk (Higginbotham *et al.*, 2004; Michaud *et*

al., 2005; George *et al.*, 2009), two reported some negative associations between glycaemic load or glycaemic index and colo-rectal cancer risk (Strayer *et al.*, 2007; Howarth *et al.*, 2008), while the remainder reported no associations (Terry *et al.*, 2003; McCarl *et al.*, 2006; Larsson *et al.*, 2007; Weijenberg *et al.*, 2008).

354. All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. Nine studies reported on colo-rectal cancer in relation to dietary glycaemic index or load, providing eight risk estimates for glycaemic index (see Figure 22 and Figure 24) and ten risk estimates for dietary glycaemic load (see Figure 23 and Figure 25). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 90 and Table 92 for dietary glycaemic index and load, respectively. The results of the per unit meta-analyses (10 glycaemic index units/day or 50 glycaemic load units /day) for colo-rectal cancer incidence and dietary glycaemic index or load have been summarised in Table 91 and Table 93, respectively. Meta-analyses were performed for women only, for glycaemic index there were seven risk estimates (see Table 94, and Table 95) and for glycaemic load there were nine risk estimates (see Table 96, and Table 97,) and incidence of colo-rectal cancer.

355. Heterogeneity was high in all analyses, especially for glycaemic load, largely due to the positive associations observed in the study by Higginbottom *et al*. (2004). Tests for publication bias (Egger's linear regression test) were not significant for analyses of glycaemic index, but for the highest quantile compared with lowest quantile analyses of glycaemic load, tests were significant (p=0.012 for all subjects; p=0.052 for women only). The number of estimates was too small to substantiate an explanation for the heterogeneity or publication bias.

Table 90. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	1.06(0.95-1.18)	1.05 (p=0.292)

[1] I^2 = 44.62% (95% CI 0.00-75.47%); p for test of heterogeneity = 0.081
[2] No. of RR estimates included in pooled analysis.

Table 91. Results of per unit (10 glycaemic index units/day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	8	1.06(0.97-1.17)	1.25 (p=0.210)

[1] I^2 = 51.99% (95% CI 0.00-78.46%); p for test of heterogeneity = 0.042
[2] No. of RR estimates included in pooled analysis.

Table 92. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	10	1.00 (0.90-1.12)	0.01 (p=0.996)

[1] I^2 = 48.43 (95% CI 0.00-75.08%); p for test of heterogeneity = 0.042
[2] No. of RR estimates included in pooled analysis.

Table 93. Results of per unit (50 glycaemic load units /day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	10	1.00 (0.93-1.07)	-0.05 (p=0.957)

[1] I^2 = 56.05% (95% CI 10.81-78.35%); p for test of heterogeneity = 0.015
[2] No. of RR estimates included in pooled analysis.

Table 94. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary glycaemic index for women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.07 (0.94-1.22)	1.07 (p=0.257)

[1] I^2 = 40.29% (95% CI 0.00-74.90%); p for test of heterogeneity = 0.123
[2] No. of RR estimates included in pooled analysis.

Table 95. Results of per unit (10 glycaemic index units /day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic index women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.07 (0.95-1.19)	-1.14 (p=0.254)

[1] I^2 = 48.80% (95% CI 0.00-78.35%); p for test of heterogeneity = 0.069
[2] No. of RR estimates included in pooled analysis.

Table 96. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and dietary glycaemic load for women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	9	0.98 (0.85-1.12)	-0.32 (p=0.747)

[1] I^2 = 48.25% (95% CI 0.00-75.92%); p for test of heterogeneity = 0.051
[2] No. of RR estimates included in pooled analysis.

Table 97. Results of per unit (50 glycaemic load units /day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic load women only

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	9	0.96 (0.88-1.04)	-0.94 (p=0.347)

[1] I^2 = 45.08% (95% CI 0.00-74.58%); p for test of heterogeneity = 0.068
[2] No. of RR estimates included in pooled analysis.

356. All meta-analyses gave similar results: for either the highest compared with the lowest quantile analysis or the per unit analysis for dietary glycaemic index or glycaemic load, and there was no difference in the incidence of colo-rectal cancer, whether in all subjects or in women only.

357. Several studies indicated that they had performed subgroup analyses based on strata of BMI categories. One study observed positive associations between glycaemic index and glycaemic load intake and colo-rectal cancer risk among participants with an above-normal BMI (McCarl *et al.*, 2006), while another reported associations to be slightly stronger among men with elevated BMI, but not women (Michaud *et al.*,

2005). Other studies, however, observed no associations in any BMI strata (Larsson *et al.*, 2007; Weijenberg *et al.*, 2008) and one study detected an inverse association between glycaemic index or glycaemic load intake and colorectal cancer risk among sedentary overweight individuals (Strayer *et al.*, 2007).

Table 98. Adjusted relative risk ratios for the highest compared with the lowest quintile of glycaemic index and glycaemic load intake and colo-rectal cancer risk

Study	Sex	GI reference table	GI value reference food	Glycaemic index							Glycaemic load							Reported association
				GI/d comparison	CRC RR≠	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	GL g/d comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	
Terry *et al*., 2003	Women	Foster-Powell, 2002	NR								Q1 82 vs Q5 217	1.05 (0.73-1.53)	0.95 (0.61-1.50)	1.34 (0.70-2.58)	0.94	0.49	0.31	No association observed
Higginbottom *et al*., 2004	Women	Foster-Powell, 1995 §	glucose	Q1 49 vs Q5 57 ****	1.71 (0.98-2.98)			0.05			Q1 92 vs Q5 143	2.85 (1.40-5.80)			0.004			Positive association observed for GI and GL
Michaud *et al*., 2005	Women	Foster-Powell, 1995	white bread	Q1 65 vs Q5 81 ***	1.08 (0.87-1.34)	1.06 (0.83-1.36)	1.14 (0.73-1.78)	0.27	0.29	0.70	Q1 80 vs Q5 167	0.89 (0.71-1.11)	0.89 (0.69-1.15)	0.87 (0.52-1.44)	0.15	0.11	0.95	Positive association observed for GI in men, but not for GL and not in women
	Men			Q1 69 vs Q5 82 ***	1.14 (0.88-1.48)	1.13 (0.84-1.51)	1.21 (0.68-2.15)	0.33	0.40	0.65	Q1 131 vs Q5 223	1.32 (0.98-1.79)	1.25 (0.88-1.25)	1.61 (0.82-3.17)	0.04	0.11	0.17	
McCarl *et al*., 2006	Women	Foster-Powell, 2002	NR	Q1 <81 vs Q5 >89 **	1.08 (0.88-1.32)	1.10 (0.88-1.37),	0.82 (0.49-1.40)	0.15			Q1 <146 vs Q5 >193	1.09 (0.88-1.35)	1.10 (0.86-1.40),	1.02 (0.64-1.63),	0.33			No overall association observed, but among obese women (BMI 30 kg/m^2 or more) a positive association observed for GI, but not GL
Larsson *et al*., 2007	Women	Foster-Powell, 2002	white bread	Q1 <76 vs Q5 >83 **	1.00 (0.75-1.33)	0.84 (0.60-1.18)	1.32 (0.80-2.17)	0.55	0.21	0.62	Q1 <164 vs Q5 >200	1.06 (0.81-1.39)	0.97 (0.70-1.32)	1.2 (0.74-1.95)	0.78	0.66	0.45	No association observed
Strayer *et al*., 2007	Women	Foster-Powell, 2002	glucose	Q1 <45 vs Q5 >52 **	0.75 (0.56-1.00)			0.03			Q1 <55 vs Q5 >80	0.91 (0.70-1.20)			0.32			Inverse association observed for GI, but not GL
Howarth *et al*., 2008	Women	Foster-Powell, 2002;	glucose								Q1 <133.9 vs Q5 ≥156.9	0.75 (0.57-0.97)	0.77 (0.57-1.04)	0.70 (0.39-1.25)	0.02	0.04	0.30	Inverse association observed for GI in women, but not for GL or in men
	Men	Brand-Miller et al, 2003									Q1 <130.5 vs Q5 ≥188.5	1.15 (0.89-1.48)	1.22 (0.90-1.65)	0.97 (0.60-1.56)	0.19	0.08	0.69	
Weijenberg *et al*., 2008	Women	Foster-Powell, 2002	glucose	Q1 53 vs Q5 61 ***	1.20 (0.85-1.67)	1.34 (0.91-1.96)	1.01 (0.52-1.98)	0.53	0.22	0.81	Q1 82 vs Q5 123	1.00 (0.73-1.36)	1.13 (0.79-1.60)	0.79 (0.43-1.43)	0.81	0.32	0.44	No association observed with CRC, but for CC an inverse association observed with GI in men, while in women there was a trend towards a positive association
	Men			Q1 56 vs Q5 64 ***	0.81 (0.61-1.08)	0.64 (0.46-0.89)	1.38 (0.92-2.08)	0.27	0.01	0.08	Q1 108 vs Q5 165	0.83 (0.64-1.08)	0.72 (0.51-1.00)	1.01 (0.68-1.51)	0.37	0.10	0.37	
George *et al*., 2009	Women	Foster-Powell, 2002	glucose	Q1 48.8 vs Q5 58.2 ***	1.16 (0.98-1.37)			0.026			Q1 54.1 vs Q5 163.9	0.87 (0.64-1.18)			0.416			Positive association observed for GI, but no association observed with GL
	Men			Q1 49.6 vs Q5 58.5 ***	1.16 (1.04-1.30)			0.007			Q1 68 vs Q5 197.2	0.88 (0.72-1.08)			0.346			

≠ Risk ratio or Hazards ratio (95% confidence interval); § and the Nutrition Center of the University of Toronto values; PCC, proximal colon cancer; DCC, distal colon cancer; NR, not reported, y, year; d, day; FFQ, food frequency questionnaire; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer. GI values obtained from published tables (Foster-Powell & Miller, 1995; Foster-Powell *et al.*, 2002; Brand-Miller *et al.*, 2003).
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Figure 22. Forest plot of the highest compared with the lowest quantile of glycaemic index and colorectal cancer risk

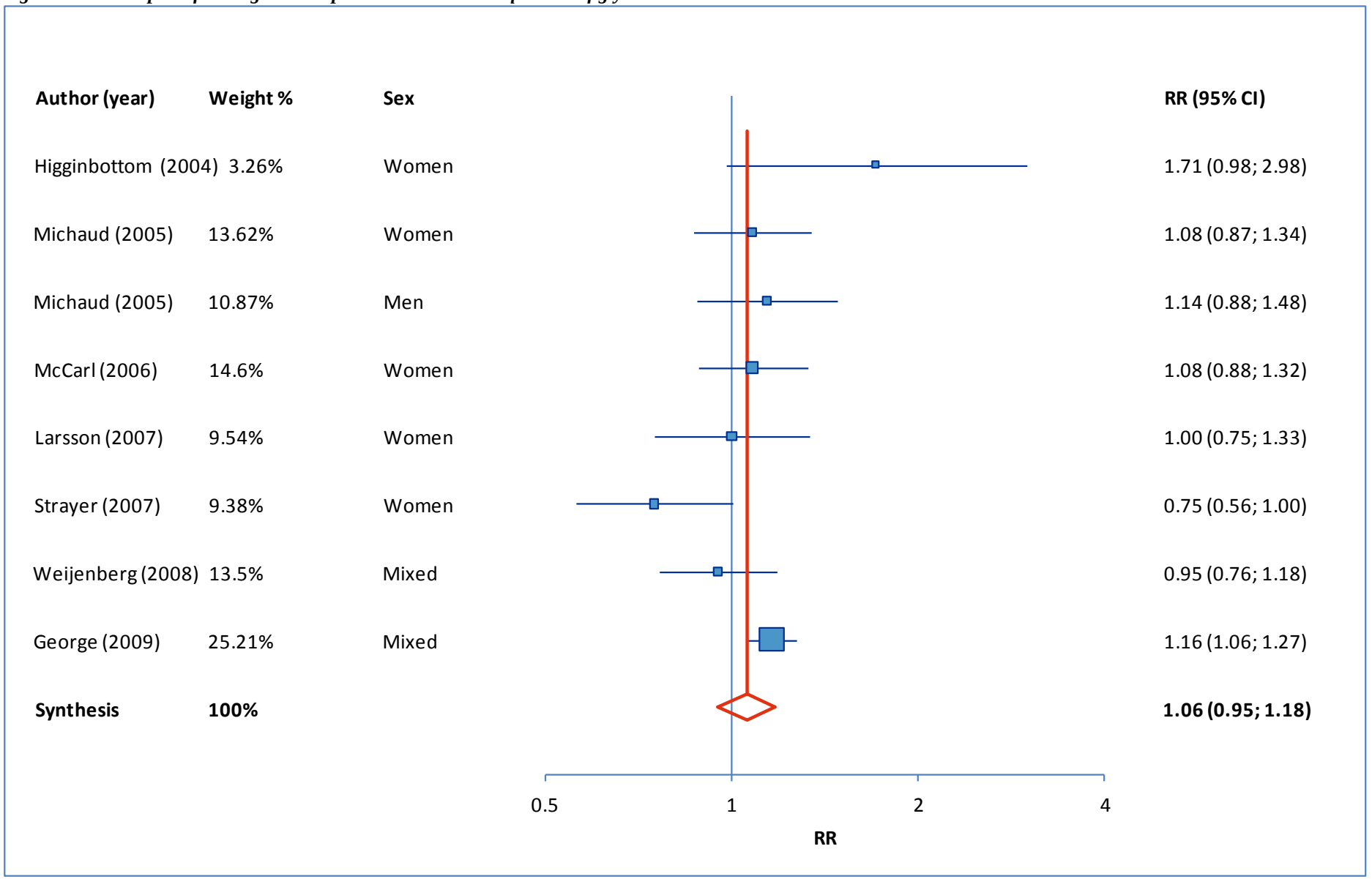


Figure 23. Forest plot of the highest compared with the lowest quantile of glycaemic load and colorectal cancer risk

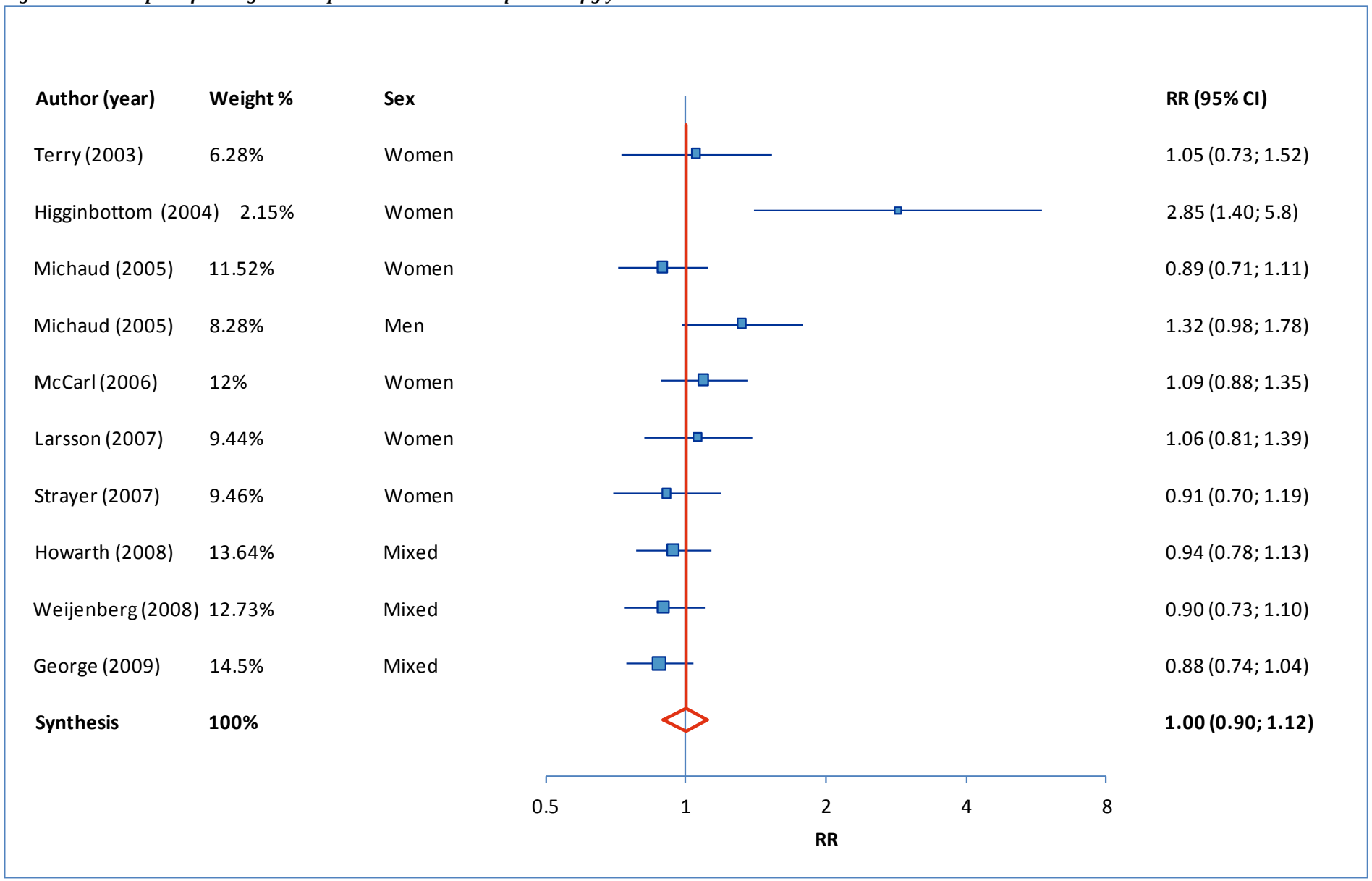


Figure 24. Forest plot of per unit (10 glycaemic index units/day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic index

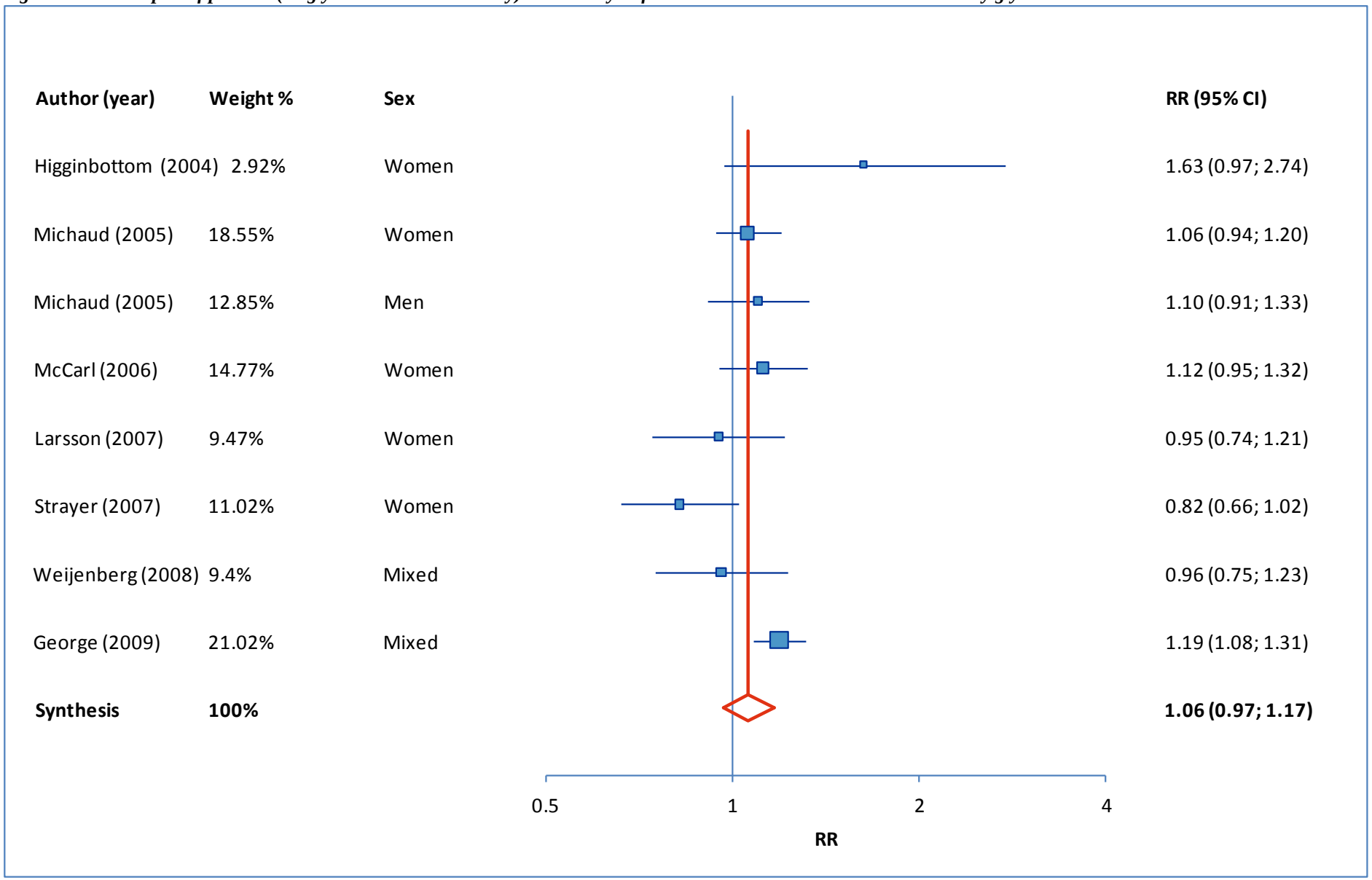
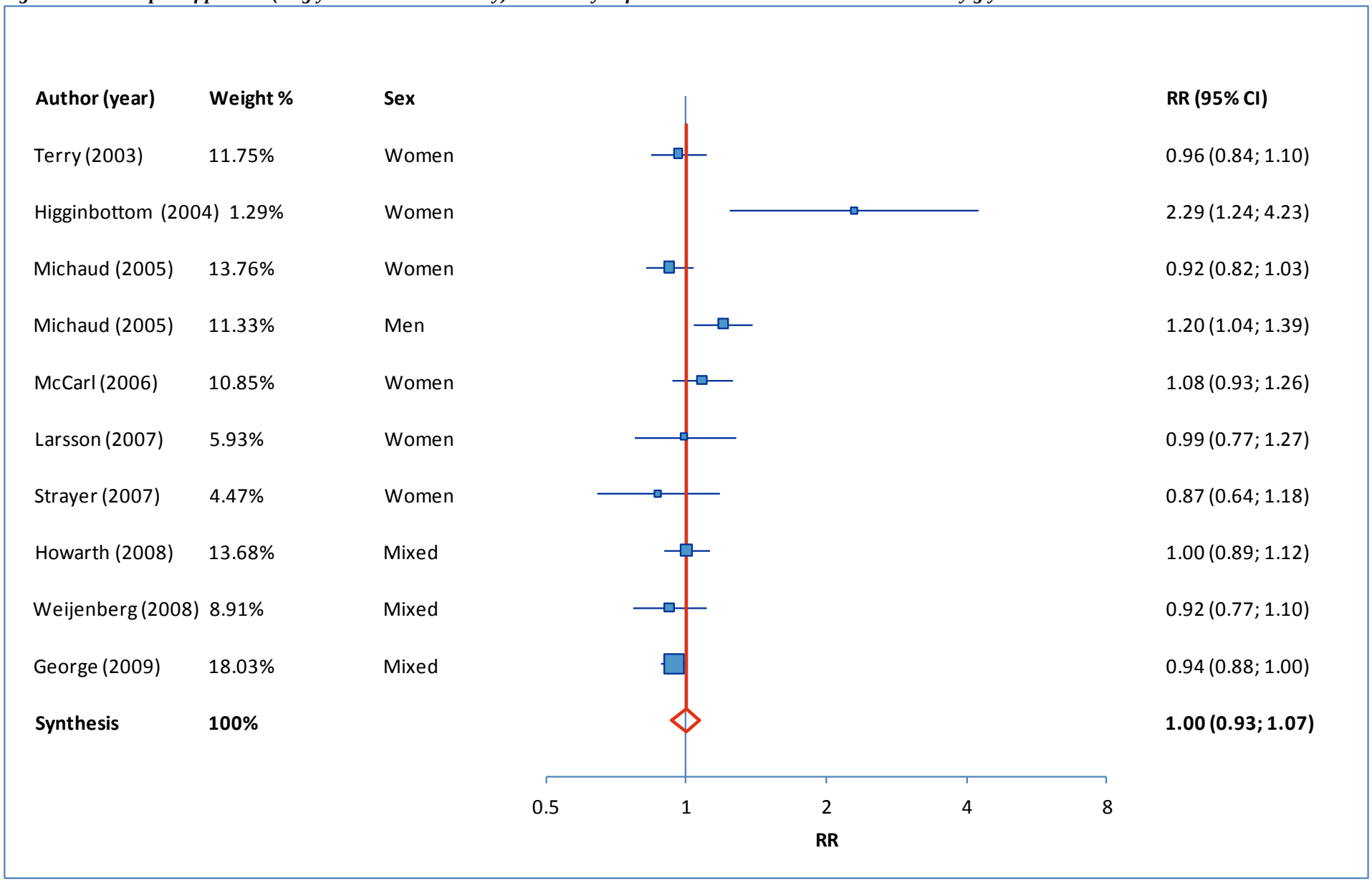


Figure 25. Forest plot of per unit (50 glycaemic load units /day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic load



358. Four studies reported on colon cancer incidence in relation to dietary glycaemic index (see Table 98). The four studies included provided five risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 99. The results of the per unit meta-analysis have been summarised in Table 100.

359. Six studies reported on colon cancer incidence in relation to dietary glycaemic load (see Table 98). The six studies included provided seven risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 101. The results of the per unit meta-analysis have been summarised in Table 102.

360. Four studies reported on rectal cancer incidence in relation to dietary glycaemic index (see Table 98). The four studies included provided five risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 103. The results of the per unit meta-analysis have been summarised in Table 104.

361. Six studies reported on rectal cancer incidence in relation to dietary glycaemic load (see Table 98). The six studies included provided seven risk estimates. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 105. The results of the per unit meta-analysis have been summarised in Table 106.

362. Heterogeneity was not significant for either the colon or rectal cancer analyses. Tests for publication bias (Egger's linear regression test) were not significant. Overall, there were no significant differences observed for the highest compared with the lowest quantile analyses or the per unit analyses of dietary glycaemic index or glycaemic load intake in relation to the incidence of colon or rectal.

Table 99. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	1.01 (0.90-1.13)	0.16 (p=0.875)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.454
[2] No. of RR estimates included in pooled analysis.

Table 100. Results of per unit (10 glycaemic index units /day) meta-analysis for colon cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	1.04 (0.93-1.15)	0.67 (p=0.505)

[1] I^2 = 23.49% (95% CI 0.00-84.09%); p for test of heterogeneity = 0.265
[2] No. of RR estimates included in pooled analysis.

Table 101. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.02 (0.91-1.14)	0.37 (p=0.712)

[1] I^2 = 26.19% (95% CI 0.00-67.87%); p for test of heterogeneity = 0.229
[2] No. of RR estimates included in pooled analysis.

Table 102. Results of per unit (50 glycaemic load units /day) meta-analysis for colo-rectal cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.98 (0.90-1.07)	-0.36 (p=0.717)

[1] I^2 = 44.35% (95% CI 0.00-76.58%); p for test of heterogeneity = 0.095
[2] No. of RR estimates included in pooled analysis.

Table 103. Results of highest quantile compared with lowest quantile meta-analysis for rectal cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	1.16 (0.95-1.42)	1.45 (p=0.148)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.695
[2] No. of RR estimates included in pooled analysis.

Table 104. Results of per unit (10 glycaemic index units /day) meta-analysis for rectal cancer incidence and dietary glycaemic index

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	1.07 (0.91-1.25)	-0.77 (p=0.441)

[1] I^2 = 0.00% (95% CI 0.00-79.20%); p for test of heterogeneity = 0.787
[2] No. of RR estimates included in pooled analysis.

Table 105. Results of highest quantile compared with lowest quantile meta-analysis for rectal cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.01 (0.85-1.201)	0.10 (p=0.923)

[1] I^2 = 0.00% (95% CI 0.00-70.81%); p for test of heterogeneity = 0.624
[2] No. of RR estimates included in pooled analysis.

Table 106. Results of per unit (50 glycaemic load units /day) meta-analysis for rectal cancer incidence and dietary glycaemic load

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	1.06 (0.95-1.19)	1.12 (p=0.265)

[1] I^2 = 0.00% (95% CI 0.00-70.81%); p for test of heterogeneity = 0.815
[2] No. of RR estimates included in pooled analysis.

Summary

363. There was no difference in the incidence of colo-rectal cancer in relation to total carbohydrate intake, dietary glycaemic index or load. For sugar and starch intake in relation to colo-rectal cancer risk, the evidence was contradictory and inconsistent, suggesting no association between dietary starch or sugar intake and risk of colo-rectal cancer.

364. Many studies reported on several carbohydrate components in relation to incidence of colo-rectal cancer. In general, any association or lack of association observed with colo-rectal cancer risk was usually mirrored in the other components studied, i.e. glycaemic index or load, sugar intake and total carbohydrate intake. For example, studies finding positive associations between glycaemic index or load and colo-rectal cancer risk usually observed positive associations with either sugar intake or total carbohydrate intake and colo-rectal cancer risk (Higginbotham *et al.*, 2004; Michaud *et al.*, 2005); studies finding negative associations with glycaemic index or load and colo-rectal cancer risk usually observed negative associations with either sugar intake or total carbohydrate intake and colo-rectal cancer risk (Strayer *et al.*, 2007; Howarth *et al.*, 2008); and studies finding no association usually observed no associations with either sugar intake or total carbohydrate intake and colo-rectal cancer risk (Terry *et al.*, 2003; Weijenberg *et al.*, 2008).

Randomised controlled trials investigating risk of colo-rectal adenoma in relation to carbohydrate interventions

365. Seven randomised controlled trials were identified in which an effect of carbohydrate, either alone or as part of a mixed intervention, on risk of colo-rectal adenoma was investigated (McKeown-Eyssen *et al.*, 1994; MacLennan *et al.*, 1995; Alberts *et al.*, 2000; Bonithon-Kopp *et al.*, 2000; Schatzkin *et al.*, 2000; Ishikawa *et al.*, 2005; Burn *et al.*, 2008). A further five articles were identified that described additional analyses of these trials (Maclennan *et al.*, 1999; Jacobs *et al.*, 2002; Jacobs *et al.*, 2006; Lanza *et al.*, 2007; Sansbury *et al.*, 2009).

Trial design

366. A summary of trial design has been given in Table 107. Two of the seven trials solely used a carbohydrate intervention: one used psyllium (Bonithon-Kopp *et al.*, 2000) and the other wheat bran (Alberts *et al.*, 2000). Of the other five trials, two used mixed interventions (McKeown-Eyssen *et al.*, 1994; Schatzkin *et al.*, 2000), while the three others used a factorial design including a non-carbohydrate intervention (MacLennan *et al.*, 1995; Ishikawa *et al.*, 2005; Burn *et al.*, 2008). The two mixed intervention trials examined the effect of a diet low in fat and high in dietary fibre (McKeown-Eyssen *et al.*, 1994; Schatzkin *et al.*, 2000). Six of the trials used a dietary fibre intervention, while one used resistant starch (Burn *et al.*, 2008).

367. Six of the trials were conducted in patients who had received polypectomy of adenomas, but one was in patients with a genetic defect that confers a predisposition to colo-rectal cancer: hereditary nonpolyposis colon cancer (Lynch syndrome) (Burn *et al.*, 2008) which results from an autosomal dominant mismatch-repair mutation. Hereditary nonpolyposis colorectal cancer (Lynch Syndrome) accounts for between 3-5% of the incidence of colo-rectal cancer, while familial adenomatous polyposis is thought to contribute less than 1% of the incidence; most cases of colo-rectal cancer (about 85%) were considered sporadic (Half *et al.*, 2009).

368. The duration of trials varied from two to four years and sample size varied from 165 (McKeown-Eyssen *et al.*, 1994) to 1905 for the Polyp Prevention Trial (Schatzkin *et al.*, 2000). All trials were in mixed sex populations.

369. Two trials were multicentre trials (Bonithon-Kopp *et al.*, 2000; Burn *et al.*, 2008). All trials assessed dietary intakes, with most using three- or four-day food records. Only one reported the method used to determine dietary fibre intakes (McKeown-Eyssen *et al.*, 1994), while one reported the method used to determine resistant starch intakes (Burn *et al.*, 2008).

370. The funding sources for all trials were Governmental, while two trials also incuded some Commercial sources; all trials reported funding sources.

Table 107. Trial design

Author	Trial design	Cohort	Country	Age (y)	Patient characteristics prior to randomization	Duration (y)	Cohort size	Dietary assessment method	Intervention	Control intervention	Funding source
McKeown-Eyssen, 1994	Parallel	Toronto polyp prevention trial	Canada	mean 58	Patients who received polypectomy for at least one adenoma	2	165	4-d food records	Diet low in fat (less than 25% of energy) and high in fibre (30-35 g/d; including wheat bran snack product)	Normal diet with low fibre snack product	Ludwig Institute for Cancer Research, Canada
MacLennan, 1995	Factorial	Australian Polyp Prevention Trial	Australia	Mean 56 (30-74)	Patients who received polypectomy for at least one adenoma	2 and 4	390 at 2yrs; 306 at 4yrs	FFQ and 4-d food record	25g/d raw wheat bran (11g/d dietary fibre) with or without a low fat diet or beta carotene (20mg/d)	Normal diet or low fat diet with or without beta carotene (20mg/d)	Australian National Health and Medical Research Council, regional Cancer Funds, Meat Research Corporation and Kellogg Company Ltd.
Alberts, 2000	Parallel	Wheat Bran Fiber Trial	USA	40-80	Patients who received polypectomy for at least one adenoma of 3mm diameter or more	3	1303	FFQ	Wheat bran fibre supplement (13.5 g/d dietary fibre)	Low-fibre supplement (2g/d)	National Cancer Institute, USA, Kellogg Company Ltd
Bonithon-Kopp, 2000	Parallel	European Cancer Prevention Organisation Intervention Study	Belgium, Denmark, France, Germany, Ireland, Israel, Italy, Portugal, Spain, UK	mean 59 (35-75)	Patients who received polypectomy for at least 2 adenomas or 1 adenoma of 5mm diameter or more	3	376	Diet history questionnaire	3.5g /d psyllium - one sachet	Placebo	Europe Against Cancer Programme and National funding agencies
Schatzkin, 2000	Parallel	Polyp Prevention Trial	USA	mean 61 (≥35)	Patients who received polypectomy for at least one adenoma	median 3	1905	4-d food records, followed by FFQ	Diet low in fat (24% total energy) and high in fibre (17.4 g of dietary fiber per 1000 kcal), fruits, and vegetables (3.4 servings per 1000 kcal)	Normal diet: dietary fibre (10.0g/1000 kcal) ; fruits, and vegetables (2.2 servings per 1000 kcal); fat (34% energy)	National Cancer Institute, USA
Ishikawa, 2005	Factorial	Osaka polyp prevention trial	Japan	mean 55 (40-65)	Patients who received polypectomy for at least 2 colorectal tumours (adenomas and or early cancers)	4 (split into two 2 year periods: 0-2 years; and 2- 4 years)	284	3-d food record	7.5g/d wheat bran with or without *Lactobacillus casei* preparation	No treatment or *Lactobacillus casei* preparation	Ministry of Health, Labor and Welfare, Japan
Burn, 2008	Factorial	Colorectal Adenoma/ Carcinoma Prevention Programme 2	Americas, southern Europe (the Iberian Peninsula and Italy), northern Europe, South Africa, the UK, Australia and Hong Kong	mean 44 (25-78)	Lynch syndrome patients	mean 29 months (range, 7 to 74 months)	727	4-d diet record in subgroup of 100 UK participants only	13.2g/d resistant starch – granular and non-granular, with or without aspirin	Placebo with or without aspirin	Bayer; UK Medical Research Council; Cancer Research UK; European Union; Cancer Council Victoria (Australia); Technology and Human Resources for Industry Programme – South Africa; Finnish Cancer Foundation.

NR, not reported; y, year; d, day

Risk of bias

371. A summary of the risk of bias assessment has been given in Table 108.

Table 108. Risk of bias assessment

Study	Randomisation	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Dropouts (%)
McKeown-Eyssen, 1994	Yes	NR	NR	Open	Analysed on intention to treat basis	17.9
MacLennan, 1995	Yes	Computer generated	NR	Open to patients, but personnel and assessors blind	Analysed on intention to treat basis	5.1
Alberts, 2000	Yes	NR	NR	Participants personnel and assessors blind	Analysed on intention to treat basis	8.8
Bonithon-Kopp, 2000	Yes	NR	NR	Participants personnel and assessors blind	Analysed on intention to treat basis	15.9
Schatzkin, 2000	Yes	Computer generated	NR	Open to patients and personnel, but assessors blind	Analysed on intention to treat basis	8.4
Ishikawa, 2005	Yes	NR	NR	Open to patients and personnel. Only histological analysts blind.	Analysed on intention to treat basis	5.0
Burn, 2008	Yes	Computer generated	NR	Participants personnel and assessors blind	Analysed on intention to treat basis	21.0

NR, not reported

372. All trials reported being randomised. Allocation concealment was not reported in any of the trials. The drop-out rate ranged from 4.5-21%, but missing outcome data were generally balanced in numbers across intervention groups, with similar reasons for missing data across groups. All trials conducted data analysis on the basis of intention-to-treat.

373. One trial was open and not blind (McKeown-Eyssen *et al.*, 1994), while three were open to patients, but the clinical assessors were blind (MacLennan *et al.*, 1995; Schatzkin *et al.*, 2000; Ishikawa *et al.*, 2005). These trials involved wheat bran interventions and dietary modifications such as reducing fat intake or increasing fruit and vegetable intakes. In the other trials participants, personnel and assessors were blind. Overall the risk of bias appeared low for these trials.

Results

374. The trial findings have been summarised in Table 109. Data were given for the number of participants with and without adenomas at trial completion, and the reported risk assessment. The different nature of the interventions means the trials were insufficiently comparable to allow a quantitative synthesis of the results.

Table 109. Trial results

Study	Control adenoma cases/subject number (%)	Intervention adenoma cases/subject number (%)	Risk for the presence of at least one adenoma (95% CI)	Adjustments	Results
McKeown-Eyssen, 1994	16/87 (18.4%)	17/78 (21.8%)	incidence ratio = 1.2 (0.6-2.2)	unadjusted	No effect on recurrence observed, but sex specific analyses showed LFHF men RR=1.6 (0.7-3.6), while for women RR=0.7 (0.3-2.0)
MacLennan, 1995	41/197 (20.8) *	45/193 (23.3)	OR = 1.5 (0.9-2.4)	number of adenomas at entry colonoscopy, number of adenomas prior to study entry and history of colon cancer in first degree relatives	No effect on recurrence observed, but recurrence of large adenomas ≥10mm tended to be lower in the bran group, which became significant when in conjunction with a low fat diet
	46/156 (29.5) **	49/150 (32.7)	OR = 1.5 (0.9-2.5)		
Alberts, 2000	299/584 (51.2)	338/719 (47.0)	OR = 0.88 (0.70-1.11)	randomization scheme	No effect on recurrence observed. RR of recurrence according to the number of adenomas was 0.99 (0.71 to 1.36)
Bonithon-Kopp, 2000	36/178 (20.2)	58/198(29.3)	OR = 1.67 (1.01-2.76)	age, sex, adenoma history, and number and location of adenomas	The risk of recurrence was increased in patients receiving the fibre treatment
Schatzkin, 2000	374/947 (39.5)	380/958 (39.7)	RR = 1.00 (0.90-1.12)	Unadjusted (adjustments showed no effect)	No effect on recurrence observed
Ishikawa, 2005	0-2 years: 106/189 (56.1) 2-4 years: 93/189(49.2)	0-2 years: 119/191 (62.3) 2-4 years: 106/191 (55.5)	0-2 years: OR = 1.31 (0.87-1.98) 2-4 years: OR = 1.31 (0.87-1.97)	age, sex and Lactobacillus group.	No effect on recurrence observed. Higher number of adenomas ≥3mm (but not ≥4mm or ≥10mm) were seen in the wheat bran group for 2 to 4 year period (OR=1.57 (1.04-2.37), but not for baseline to 2 year period (OR=1.14(0.76-1.72).
Burn, 2008	68/369 (18.4)	67/358 (18.7)	OR = 1.0 (0.7-1.4).	unadjusted	No effect on occurrence observed

OR, odds ratio; RR, risk ratio; NR, not reported; * 2 year follow-up; ** 4 year follow-up

375. Two trials examined the effect of a diet low in fat and high in dietary fibre (LFHF) on adenoma recurrence (McKeown-Eyssen *et al.*, 1994; Schatzkin *et al.*, 2000). In the smaller of these trials (McKeown-Eyssen *et al.*, 1994), 21.8% of the 78 subjects assigned to the LFHF group had at least one pathologically confirmed neoplastic polyp, while the percentage was 18.4% among the 87 persons assigned to the normal diet group; the corresponding incidence rate showed no difference: 1.2 (95% CI: 0.6-2.2). Patterns of recurrence were different for men and women. In men, the cumulative incidence of neoplastic polyps indicated a trend towards a higher recurrence in those assigned to the LFHF group: 1.6 (95% CI 0.7-3.6). In women, however, the RR indicated a trend towards a lower recurrence: 0.7 (95% CI: 0.3-2.0).

376. The effect of a comprehensive dietary intervention – counselling of patients and assignment to a diet low in fat and high in dietary fibre, fruits, and vegetables – on the recurrence of large-bowel adenomas was investigated in the Polyp Prevention Trial (Schatzkin *et al.*, 2000). At least one recurrent adenoma was reported in 39.7% of the 958 subjects in the intervention group and 39.5% of the 947 subjects in the control group; the unadjusted risk ratio showed no difference between groups: 1.00 (95% CI: 0.90-1.12; p=0.98). Among men, the recurrence rate tended to be lower in the intervention group than in the control group; risk ratio =0.89 (95% CI: 0.79-1.02).

Among women, the rate of recurrence tended to be higher in the intervention group than in the control group (risk ratio =1.30 [95% CI: 1.04-1.63]). No significant differences between groups were reported for proximal adenomas (RR=1.16; 95% CI: 0.97-1.39), large adenomas (>1 cm) (RR=0.88; 95% CI: 0.60-1.28), or advanced adenomas (RR= 0.90; 95% CI: 0.64-1.26).

377. Three trials have investigated the effect of wheat bran supplement on adenoma recurrence (MacLennan *et al.*, 1995; Alberts *et al.*, 2000; Ishikawa *et al.*, 2005). The largest of these, the Wheat Bran Fiber Trial (Alberts *et al.*, 2000), reported no association between wheat-bran fibre supplementation and recurrence of colorectal adenomas. The odds ratio for the presence of at least one recurrent adenoma in the high-fibre group (13.5 g/day) as compared with the low-fibre group (2 g/day), adjusted for randomisation scheme, was 1.04 (95% CI 0.79-1.38) for a follow-up period starting after colonoscopy at 1 year. For a follow-up period starting after randomisation, the adjusted OR was 0.88 (0.70-1.11). The relative risk of recurrent adenomas in the high-fibre group as compared with the low-fibre group was 1.08 (0.71-1.64) for a follow-up period starting after colonoscopy at 1 year. For a follow-up period starting after randomisation, the adjusted RR was 0.99 (0.71-1.36).

378. Three further studies analysed data from the Polyp Prevention trial (Schatzkin, et al., 2000). A subsequent analysis of the Polyp Prevention Trial examined the risk of adenoma recurrence among participants who reported that they met or exceeded each of the three dietary goals at all four annual visits (210 of the 948 intervention participants) (Jacobs *et al.*, 2002). Multivariate logistic regression models were used to estimate the association between dietary adherence and adenoma recurrence. Adjustments were made for educational level; smoking status; waist-to-hip ratio; fat intake at baseline; intake of fibre, fruit and vegetables, and red and processed meats; ratio of red meat to chicken and fish; intake of legumes and cruciferous vegetables; calcium supplement use; intake of folate, total carotenoids, bran cereals, and supplemental vitamin E and time of colonoscopy. A reduced risk for adenoma recurrence among participants who most adhered to the three dietary goals was observed compared with the control group (n=947) (odds ratio = 0.65, 95% CI 0.47-0.92). These findings suggested that high compliance with a low-fat, high-fibre diet may be associated with a reduced risk of adenoma recurrence.

379. A continued follow-up study of a sub-cohort of the Polyp Prevention Trial was conducted for an additional four years (total eight years) (Lanza *et al.*, 2007). Of the 1,905 Polyp Prevention Trial participants, confirmed colonoscopy reports were obtained on 801 participants (396 control; 405 intervention). During the follow-up period, the intervention group participants had increased their fat intake and decreased their intakes of dietary fibre, fruits, and vegetables, but intake for each of the three dietary goals was different from the baseline diet and from that in the controls. No effect of a low-fat, high-fiber, high-fruit- and -vegetable eating pattern on adenoma recurrence was observed. The relative risks of recurrent adenoma in the intervention group compared with the control group was 0.98 (95% CI 0.88-1.09) and the relative risk for recurrence of an advanced adenoma (1.06; 95% CI 0.81-1.39) or multiple adenomas (0.92; 95% CI 0.77-1.10) were not different between intervention and control groups.

380. A further sub-cohort analysis of the Polyp Prevention Trial assessed the adenoma risk

of participants who completed all four annual food frequency questionnaires and met a total of 9 to12 food frequency questionnaire goals over the trial period (Sansbury *et al.*, 2009). These participants, defined as 'super compliers' (n = 210 out of 821 in the intervention group who finished the trial), had a reduced risk of adenoma recurrence (OR = 0.68; 95%CI 047, 0.98) as compared with the trial control group (n=947), in a multivariate model. There was also nearly a 50% lower odds of multiple adenoma recurrence (OR =0.51; 95%CI 030, 0.89) and advanced adenoma recurrence (OR = 0.44; 95%CI 018, 1.05) among the super compliers compared with controls, in a multivariate model. These results suggested that consistent adherence to a low-fat, high-fibre, and high fruit and vegetable diet may have had some benefit in attempting to prevent recurrence of colorectal adenomas.

381. A pooled analysis of the Wheat Bran Fiber Trial (Alberts *et al.*, 2000) and the Polyp Prevention Trial (Schatzkin *et al.*, 2000) included data from 3209 participants. Analysis using logistic regression models was used to examine the effect of a dietary intervention on colorectal adenoma recurrence as a whole, and by sex (Jacobs *et al.*, 2006). The adjusted odds ratio for adenoma recurrence for those in the intervention group of either the Wheat Bran Fiber Trial or the Polyp Prevention Trial was not significant: 0.91 (95% CI: 0.78, 1.06). For men, the intervention was associated with reduced odds of recurrence with an odds ratio of 0.81 (95% CI: 0.67, 0.98); for women, no significant association was observed. Adjustments were made for age, BMI, sex (for total population only), family history of colorectal cancer, dietary calcium, alcohol intake, study, history of previous polyps, number of colonoscopies, number of adenomas at baseline, largest adenoma at baseline, and location of adenomas at baseline.

382. Two factorial trials reporting on the effect of a wheat bran supplement (MacLennan *et al.*, 1995; Ishikawa *et al.*, 2005) observed no effect on the recurrence of colorectal adenomas. In one trial (Ishikawa *et al.*, 2005), although no difference between groups on adenoma recurrence was observed (adjusted OR = 1.31; 0.87-1.98), a higher number of adenomas larger than 3mm were observed in the wheat bran group compared with the control group (adjusted OR=1.57; 1.04-2.37); however, no difference between groups was observed for risk of adenomas larger than 4mm or 10mm.

383. In the other trial (MacLennan *et al.*, 1995), complete outcome data were collected from 390 subjects at 24 months and, in a follow-up trial, from 306 subjects at 48 months. After 24 months of follow-up the adjusted OR for recurrence of adenomas of any size was 1.5 (95% CI: 0.9-2.4). For adenoma larger than 10mm the adjusted OR was 0.8 (95% CI: 0.3-2.2) and for adenomas with moderate or severe dysplasia the adjusted OR was 0.6 (95% CI: 0.2-1.6). After 48 months of follow-up, these adjusted ORs were 1.5 (95% CI: 0.9-2.5), 0.8 (95% CI: 0.3-2.5), and 0.7 (95% CI: 0.2-2.0), respectively. In a subsequent analysis examining sex-specific risk (Maclennan *et al.*, 1999) men tended to have an increased risk for adenoma recurrence with bran supplementation, but none of the analyses for women or men at 2 year or 4 year follow-ups were significant. When analyses were performed in relation to the degree of subject compliance to the intervention, no difference was observed.

384. One parallel trial investigated the effect of psyllium (3.5g/d) on the recurrence of colorectal adenomas (Bonithon-Kopp *et al.*, 2000). An adverse effect on adenoma

recurrence was observed: 29.3% of the 198 patients assigned to the psyllium group had at least one pathologically confirmed neoplastic polyp while the percentage was 20.2% among the 178 patients assigned to the control group (OR=1.67; 95% CI: 1.01-2.76). There was no significant interaction between the treatment effects and sex, history of adenomas, or characteristics of adenomas at inclusion. The adverse effect of fibre treatment was stronger in patients with a baseline dietary calcium intake above the median (OR=2.81; 95% CI: 1.33-5.92) than in patients with dietary calcium intake below the median (OR=1.04; 95% CI: 0.49-2.18); p for interaction =0.028). Baseline dietary fibre and dietary fat intake did not modify the effect of supplemental fibre. Among patients who completed dietary assessment at both, initial and final examination, the adjusted OR for adenoma recurrence was 2.24 (95% CI: 1.24, 4.03). Further adjustments for three-year changes in dietary intake of total calories, calcium, and fibre did not change the effects of fibre treatment on adenoma recurrence (OR=2.27; 95% CI: 1.25-4.11). The adjusted OR for adenomas with a diameter of 0.5 mm or larger was 1.86 (95% CI: 0.99-3.50). The adjusted OR for recurrence on the left colo-rectum was 1.70 (95% CI: 0.95-3.00) and the OR for the right colo-rectum was 1.39 (95% CI: 0.72-2.68).

385. One factorial trial examined the effect of resistant starch (mean intake 13.2g/day) on adenoma recurrence among adults with the Lynch syndrome (Burn et al., 2008). No effect was observed: 18.7% of the 358 patients assigned to the resistant starch group had at least one pathologically confirmed neoplastic polyp while the percentage was 18.4%. among the 369 patients assigned to the control group (OR= 1.0; 95% CI: 0.7-1.4). It has been suggested that resistant-starch consumption in the trial was insufficient to affect the colonic production of short-chain fatty acids, and hence risk of neoplasia (Topping *et al.*, 2009). In response, the authors stated that the 30 g/day of resistant starch (Novelose) used in the trial may have delivered more than 13.2 g of resistant starch, which in addition to the estimate of 4.1 g/day in the typical European diet, gave an estimated total of 17.3 g/day on average. The dose used was thought to be as much as participants were able to add to their diet for up to four years, and the slightly higher number of withdrawals in the resistant starch group was attributable to symptoms of bloating, suggesting the dose produced physiological effects (Bishop *et al.*, 2009).

Summary

386. Overall, trials investigating an effect of dietary fibre supplementation on the recurrence of colorectal adenomas have not demonstrated any effect. One trial, however, using a single sachet of psyllium per day (3.5g/day) demonstrated an adverse effect on adenoma recurrence (Bonithon-Kopp *et al.*, 2000). A potential reason for the observed lack of effect in most dietary intervention trials may be low complicance with the intervention among participants (Sansbury *et al.*, 2009). The design of these trials, also, may limit their interpretation, e.g. adenoma recurrence may not be an appropriate end point to investigate an effect of dietary factors on colo-rectal cancer risk.

387. Most of the adenoma recurrence trials have lasted three to four years, whereas colo-rectal carcinogenesis in humans has been estimated to take 10 to 40 years (Kinzler & Vogelstein, 1996). A dietary intervention could affect different stages of adenoma progression to cancer: (a) initial appearance, (b) growth, or (c) transformation into

carcinoma. If diet affects early events in the neoplastic process, such as the initial growth of an adenoma, intervention effects might not emerge during the short duration of the trial. A large body of evidence suggests that adenomatous polyps are the precursor for most colorectal cancers (Kinzler & Vogelstein, 1996), but the adenoma is not a reliable surrogate, as only a small proportion of adenomas progress to invasive cancer (Schatzkin & Gail, 2002). Another shortcoming of adenoma recurrence trials is that the majority of recurrent adenomas are small (<1 cm), tubular adenomas with low-grade dysplasia that are thought to have less potential of proceeding to cancer compared with advanced adenomas.

References

Abell GC, Cooke CM, Bennett CN, Conlon MA & McOrist AL (2008) Phylotypes related to Ruminococcus bromii are abundant in the large bowel of humans and increase in response to a diet high in resistant starch. *FEMS Microbiology Ecology* **66**, 505-515.

Abraham ZD & Mehta T (1988) Three-week psyllium-husk supplementation: effect on plasma cholesterol concentrations, fecal steroid excretion, and carbohydrate absorption in men. *American Journal of Clinical Nutrition* **47**, 67-74.

Abrams SA, Griffin IJ & Davila PM (2002) Calcium and zinc absorption from lactose-containing and lactose-free infant formulas. *American Journal of Clinical Nutrition* **76**, 442-446.

Abrams SA, Griffin IJ, Hawthorne KM, Liang L, Gunn SK, Darlington G & Ellis KJ (2005) A combination of prebiotic short- and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. *Am J Clin Nutr* **82**, 471-476.

Abrams SA, Hawthorne KM, Aliu O, Hicks PD, Chen Z & Griffin IJ (2007) An inulin-type fructan enhances calcium absorption primarily via an effect on colonic absorption in humans. *Journal of Nutrition* **137**, 2208-2212.

Abrams SA, Wen J & Stuff JE (1997) Absorption of calcium, zinc, and iron from breast milk by five- to seven-month-old infants. *Pediatr Res* **41**, 384-390.

Achour L, Flourie B, Briet F, Pellier P, Marteau P & Rambaud JC (1994) Gastrointestinal effects and energy value of polydextrose in healthy nonobese men. *American Journal of Clinical Nutrition* **59**, 1362-1368.

Akerberg AK, Liljeberg HG, Granfeldt YE, Drews AW & Bjorck IM (1998) An in vitro method, based on chewing, to predict resistant starch content in foods allows parallel determination of potentially available starch and dietary fiber. *Journal of Nutrition* **128**, 651-660.

Alam NH, Islam S, Sattar S, Monira S & Desjeux JF (2009) Safety of rapid intravenous rehydration and comparative efficacy of 3 oral rehydration solutions in the treatment of severely malnourished children with dehydrating cholera. *Journal of Pediatric Gastroenterology & Nutrition* **48**, 318-327.

Alam NH, Meier R, Sarker SA, Bardhan PK, Schneider H & Gyr N (2005) Partially hydrolysed guar gum supplemented comminuted chicken diet in persistent diarrhoea: a randomised controlled trial. *Archives of Disease in Childhood* **90**, 195-199.

Alam NH, Meier R, Schneider H, Sarker SA, Bardhan PK, Mahalanabis D, Fuchs GJ & Gyr N (2000) Partially hydrolyzed guar gum-supplemented oral rehydration solution in the treatment of acute diarrhea in children. *Journal of Pediatric Gastroenterology and Nutrition* **31**, 503-507.

Alarcon P, Montoya R, Rivera J, Perez F, Peerson JM & Brown KH (1992) Effect of inclusion of beans in a mixed diet for the treatment of Peruvian children with acute watery diarrhea. *Pediatrics* **90**, 58-65.

Alberts DS, Martinez ME, Roe DJ, Guillen-Rodriguez JM, Marshall JR, van Leeuwen JB, Reid ME, Ritenbaugh C, Vargas PA, Bhattacharyya AB, Earnest DL, Sampliner RE, Parish D, Koonce K, Fales L & The Phoenix Colon Cancer Prevention Physicians N (2000) Lack of Effect of a High-Fiber Cereal Supplement on the Recurrence of Colorectal Adenomas. *N Engl J Med* **342**, 1156-1162.

Aldoori WH, Giovannucci EL, Rockett HRH, Sampson L, Rimm EB, Willett & C. W (1998) A Prospective Study of Dietary Fiber Types and Symptomatic Diverticular Disease in Men. *Journal of Nutrition* **128**, 714-719.

Aller R, De Luis DA, Izaola O, La Calle F, Del Olmo L, Fernandez L, Arranz T & Gonzalez Hernandez JM (2004) Effects of a high-fiber diet on symptoms of irritable bowel syndrome: A randomized clinical trial. *Nutrition* **20**, 735-737.

Alles MS, Hartemink R, Meyboom S, Harryvan JL, Van Laere KM, Nagengast FM & Hautvast JG (1999) Effect of transgalactooligosaccharides on the composition of the human intestinal microflora and on putative risk markers for colon cancer. *American Journal of Clinical Nutrition* **69**, 980-991.

Alliet P, Scholtens P, Raes M, Hensen K, Jongen H, Rummens JL, Boehm G & Vandenplas Y (2007) Effect of prebiotic galacto-oligosaccharide, long-chain fructo-oligosaccharide infant formula on serum cholesterol and triacylglycerol levels. *Nutrition* **23**, 719-723.

Anderson AS & Whichelow MJ (1985) Constipation during pregnancy: dietary fibre intake and the effect of fibre supplementation. *Human Nutrition - Applied Nutrition* **39**, 202-207.

Anderson DM, Brydon WG & Eastwood MA (1988) The dietary effects of gellan gum in humans. *Food Additives & Contaminants* **5**, 237-249.

Anderson DM, Brydon WG, Eastwood MA & Sedgwick DM (1991) Dietary effects of sodium alginate in humans. *Food Additives & Contaminants* **8**, 237-248.

Anderson JW, Story L & Sieling B (1984) Hypocholesterolemic effects of oat-bran or bean intake for hypercholesterolemic men. *American Journal of Clinical Nutrition* **40**, 1146-1155.

Andersson H, Bosaeus I, Falkheden T & Melkersson M (1979) Transit time in constipated geriatric patients during treatment with a bulk laxative and bran: a comparison. *Scandinavian Journal of Gastroenterology* **14**, 821-826.

Andersson H, Navert B, Bingham SA, Englyst HN & Cummings JH (1983) The effects of breads containing similar amounts of phytate but different amounts of wheat bran on calcium, zinc and iron balance in man. *British Journal of Nutrition* **50**, 503-510.

Andon MB, Peacock M, Kanerva RL & De Castro JAS (1996) Calcium absorption from apple and orange juice fortified with calcium citrate malate (CCM). *Journal of the American College of Nutrition* **15**, 313-316.

Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R, Lamazza A, Pretaroli AR, Pace V, Leo P, Castelli A & Gasbarrini G (1998) Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. *Hepato-Gastroenterology* **45**, 727-732.

Antonis A & Bersohn I (1962) The Influence of Diet on Fecal Lipids in South African White and Bantu Prisoners. *American Journal of Clinical Nutrition* **11**, 142-155.

Arffman S, Andersen JR & Hegnhoj J (1985) The effect of coarse wheat bran in the irritable bowel syndrome. A double-blind cross-over study. *Scandinavian Journal of Gastroenterology* **20**, 295-298.

Aries V, Crowther JS, Drasar BS, Hill MJ & Williams RE (1969) Bacteria and the aetiology of cancer of the large bowel. *Gut* **10**, 334-335.

Arthurs Y & Fielding JF (1983) Double blind trial of ispaghula/poloxamer in the Irritable Bowel Syndrome. *Irish Medical Journal* **76**.

Ashraf W, Park F, Lof J & Quigley EM (1995) Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. *Alimentary Pharmacology and Therapeutics* **9**, 639-647.

Ashraf W, Pfeiffer RF, Park F, Lof J & Quigley EM (1997) Constipation in Parkinson's disease: objective assessment and response to psyllium. *Movement Disorders* **12**, 946-951.

Asp N (1995) Classification and methodology of food carbohydrates as related to nutritional

effects. *American Journal of Clinical Nutrition* **61**, 930S-937.
Asp NG, van Amelsvoort JM & Hautvast JG (1996) Nutritional implications of resistant starch. *Nutr Res Rev* **9**, 1-31.
Assisi RF, Arcidiacono R, Camarri E, Claar GM, Frosini G, Moschetta R, Pellizzeri F, Quondamcarlo C, Reboa G & Siani A (2000) Efficacy of microcristalline cellulose in the treatment of idiopathic chronic constipation. *Gastroenterology International* **13**, 167-171.
Astrup A, Vrist E & Quaade F (1990) Dietary fibre added to very low calorie diet reduces hunger and alleviates constipation. *International Journal of Obesity* **14**, 105-112.
Atkinson FS, Foster-Powell K & Brand-Miller JC (2008) International Tables of Glycemic Index and Glycemic Load Values: 2008. *Diabetes Care* **31**, 2281-2283.
Austin GL, Dalton CB, Hu Y, Morris CB, Hankins J, Weinland SR, Westman EC, Yancy Jr WS & Drossman DA (2009) A Very Low-Carbohydrate Diet Improves Symptoms and Quality of Life in Diarrhea-Predominant Irritable Bowel Syndrome. *Clinical Gastroenterology and Hepatology* **7**, 706-708.e701.
Backhed F, Ley RE, Sonnenburg JL, Peterson DA & Gordon JI (2005) Host-Bacterial Mutualism in the Human Intestine. *Science* **307**, 1915-1920.
Badiali D, Corazziari E, Habib FI, Tomei E, Bausano G, Magrini P, Anzini F & Torsoli A (1995) Effect of wheat bran in treatment of chronic nonorganic constipation. A double-blind controlled trial. *Digestive Diseases and Sciences* **40**, 349-356.
Baird IM, Walters RL, Davies PS, Hill MJ, Drasar BS & Southgate DA (1977) The effects of two dietary fiber supplements on gastrointestinal transit, stool weight and frequency, and bacterial flora, and fecal bile acids in normal subjects. *Metabolism: Clinical and Experimental* **26**, 117-128.
Bakker-Zierikzee AM, Alles MS, Knol J, Kok FJ, Tolboom JJ & Bindels JG (2005) Effects of infant formula containing a mixture of galacto- and fructo-oligosaccharides or viable Bifidobacterium animalis on the intestinal microflora during the first 4 months of life. *British Journal of Nutrition* **94**, 783-790.
Balasubramanian R, Johnson EJ & Marlett JA (1987) Effect of wheat bran on bowel function and fecal calcium in older adults. *Journal of the American College of Nutrition* **6**, 199-208.
Ballongue J, Schumann C & Quignon P (1997) Effects of lactulose and lactitol on colonic microflora and enzymatic activity. *Scandinavian Journal of Gastroenterology, Supplement* **32**, 41-44.
Balsari A, Ceccarelli A, Dubini F, Fesce E & Poli G (1982) The fecal microbial population in the irritable bowel syndrome. *Microbiologica* **5**, 185-194.
Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, Baptiste M & Graham S (1997) Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). *Cancer Causes Control* **8**, 828-840.
Bang MH, Chio OS & Kim WK (2007) Soyoligosaccharide increases fecal bifidobacteria counts, short-chain fatty acids, and fecal lipid concentrations in young Korean women. *Journal of Medicinal Food* **10**, 366-370.
Barger-Lux MJ, Heaney RP & Recker RR (1989) Time course of calcium absorption in humans: evidence for a colonic component. *Calcif Tissue Int* **44**, 308-311.
Bass P, Clark C & DoPico GA (1988) Comparison of the laxative efficacy and patient preference of calcium polycarbophil tablets and psyllium suspension. *Current Therapeutic Research - Clinical and Experimental* **43**, 770-774.
Battle EH & Hanna CE (1980) Evaluation of a dietary regimen for chronic constipation. Report of a pilot study. *Journal of Gerontological Nursing* **6**, 527-532.
Beards E, Tuohy K & Gibson G (2010) A human volunteer study to assess the impact of

confectionery sweeteners on the gut microbiota composition. *British Journal of Nutrition* **104**, 701-708.
Behall KM (1990) Effect of soluble fibers on plasma lipids, glucose tolerance and mineral balance. *Advances in Experimental Medicine & Biology* **270**, 7-16.
Behall KM & Howe JC (1996) Resistant starch as energy. *Journal of the American College of Nutrition* **15**, 248-254.
Behall KM, Howe JC & Anderson RA (2002) Apparent mineral retention is similar in control and hyperinsulinemic men after consumption of high amylose cornstarch. *Journal of Nutrition* **132**, 1886-1891.
Behall KM, Scholfield DJ & Lee K (1987) Mineral balance in adult men: Effect of four refined fibers. *American Journal of Clinical Nutrition* **46**, 307-314.
Behall KM, Scholfield DJ, McIvor ME, Van Duyn MS, Leo TA, Michnowski JE, Cummings CC & Mendeloff AI (1989) Effect of guar gum on mineral balances in NIDDM adults. *Diabetes Care* **12**, 357-364.
Bell EW, Emken EA, Klevay LM & Sandstead HH (1981) Effects of dietary fiber from wheat, corn, and soy hull bran on excretion of fecal bile acids in humans. *American Journal of Clinical Nutrition* **34**, 1071-1076.
Ben XM, Li J, Feng ZT, Shi SY, Lu YD, Chen R & Zhou XY (2008) Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal Bifidobacteria and Lactobacilli. *World Journal of Gastroenterology* **14**, 6564-6568.
Ben XM, Zhou XY, Zhao WH, Yu WL, Pan W, Zhang WL, Wu SM, Van Beusekom CM & Schaafsma A (2004) Supplementation of milk formula with galacto-oligosaccharides improves intestinal micro-flora and fermentation in term infants. *Chinese Medical Journal* **117**, 927-931.
Benno Y, Endo K, Miyoshi H, Okuda T, Koishi H & Mitsuoka T (1989) Effect of rice fiber on human fecal microflora. *Microbiology and Immunology* **33**, 435-440.
Benno Y, Mitsuoka T & Kanazawa K (1991) Human faecal flora in health and colon cancer. *Acta Chirurgica Scandinavica, Supplement* **157**, 15-23.
Benus RF, van der Werf TS, Welling GW, Judd PA, Taylor MA, Harmsen HJ & Whelan K (2010) Association between Faecalibacterium prausnitzii and dietary fibre in colonic fermentation in healthy human subjects. *British Journal of Nutrition* **104**, 693-700.
Berberian DA, Pauly RJ & Tainter ML (1952) Comparison of a plain methyl cellulose with a compound bulk laxitive. *Gastroenterology* **20**, 143.
Bergman EN (1990) Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiological Reviews* **70**, 567-590.
Berry CS (1986) Resistant starch: Formation and measurement of starch that survives exhaustive digestion with amylolytic enzymes during the determination of dietary fibre. *Journal of Cereal Science* **4**, 301-314.
Beyer PL, Caviar EM & McCallum RW (2005) Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults. *Journal of the American Dietetic Association* **105**, 1559-1566.
Beyer PL & Flynn MA (1978) Effects of high- and low-fiber diets on human feces. *Journal of the American Dietetic Association* **72**, 271-277.
Bijkerk CJ, de Wit NJ, Muris JWM, Whorwell PJ, Knottnerus JA & Hoes AW (2009) Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. *BMJ* **339**, b3154-.
Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, Clavel-Chapelon F, Kesse E, Nieters A, Boeing H, Tjonneland A, Overvad K, Martinez C, Dorronsoro M, Gonzalez CA, Key TJ, Trichopoulou A, Naska A, Vineis P, Tumino R, Krogh V, Bueno-de-Mesquita HB, Peeters PH, Berglund G, Hallmans G, Lund E, Skeie G,

Kaaks R & Riboli E (2003) Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* **361**, 1496-1501.

Bingham SA, Norat T, Moskal A, Ferrari P, Slimani N, Clavel-Chapelon F, Kesse E, Nieters A, Boeing H, Tjonneland A, Overvad K, Martinez C, Dorronsoro M, Gonzalez CA, Ardanaz E, Navarro C, Quiros JR, Key TJ, Day NE, Trichopoulou A, Naska A, Krogh V, Tumino R, Palli D, Panico S, Vineis P, Bueno-de-Mesquita HB, Ocke MC, Peeters PHM, Berglund G, Hallmans G, Lund E, Skeie G, Kaaks R & Riboli E (2005) Is the Association with Fiber from Foods in Colorectal Cancer Confounded by Folate Intake? *Cancer Epidemiology Biomarkers Prevention* **14**, 1552-1556.

Bird AR, Vuaran MS, King RA, Noakes M, Keogh J, Morell MK & Topping DL (2008) Wholegrain foods made from a novel high-amylose barley variety (Himalaya 292) improve indices of bowel health in human subjects. *British Journal of Nutrition* **99**, 1032-1040.

Bishop DT, Burn J & Mathers JC (2009) Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome. *N Engl J Med* **360**, 1461-1463.

Björkstén B, Sepp E, Julge K, Voor T & Mikelsaar M (2001) Allergy development and the intestinal microflora during the first year of life. *The Journal of allergy and clinical immunology* **108**, 516-520.

Block LH (1947) Management of constipation with a refined psyllium combined with polydextrose. *American Journal of Digestive Diseases* **14**, 64.

Bohn T, Davidsson L, Walczyk T & Hurrell RF (2004a) Fractional magnesium absorption is significantly lower in human subjects from a meal served with an oxalate-rich vegetable, spinach, as compared with a meal served with kale, vegetable with a low oxalate content. *British Journal of Nutrition* **91**, 601-606.

Bohn T, Davidsson L, Walczyk T & Hurrell RF (2004b) Phytic acid added to white-wheat bread inhibits fractional apparent magnesium absorption in humans. *American Journal of Clinical Nutrition* **79**, 418-423.

Bond JH, Currier BE, Buchwald H & Levitt MD (1980) Colonic conservation of malabsorbed carbohydrate. *Gastroenterology* **78**, 444-447.

Bond JH & Levitt MD (1978) Effect of dietary fiber on intestinal gas production and small bowel transit time in man. *American Journal of Clinical Nutrition* **31**, S169-S174.

Bongers ME, de Lorijn F, Reitsma JB, Groeneweg M, Taminiau JA & Benninga MA (2007) The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. *Nutrition Journal* **6**.

Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U & Faivre J (2000) Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* **356**, 1300-1306.

Borgia M, Sepe N, Brancato V, Costa G, Simone P, Borgia R & Lugli R (1983) Treatment of chronic constipation by a bulk-forming laxative (Fibrolax). *Journal of International Medical Research* **11**, 124-127.

Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, Gapstur SM & Folsom AR (1994) Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* **5**, 38-52.

Bouhnik Y, Achour L, Paineau D, Riottot M, Attar A & Bornet F (2007a) Four-week short chain fructo-oligosaccharides ingestion leads to increasing fecal bifidobacteria and cholesterol excretion in healthy elderly volunteers. *Nutrition Journal* **6**, 1-7.

Bouhnik Y, Flourie B, D'Agay-Abensour L, Pochart P, Gramet G, Durand M & Rambaud JC (1997) Administration of transgalacto-oligosaccharides increases fecal bifidobacteria

and modifies colonic fermentation metabolism in healthy humans. *Journal of Nutrition* **127**, 444-448.
Bouhnik Y, Flourie B, Riottot M, Bisetti N, Gailing MF, Guibert A, Bornet F & Rambaud JC (1996) Effects of fructo-oligosaccharides ingestion on fecal bifidobacteria and selected metabolic indexes of colon carcinogenesis in healthy humans. *Nutrition and Cancer* **26**, 21-29.
Bouhnik Y, Raskine L, Champion K, Andrieux C, Penven S, Jacobs H & Simoneau G (2007b) Prolonged administration of low-dose inulin stimulates the growth of bifidobacteria in humans. *Nutrition Research* **27**, 187-193.
Bouhnik Y, Raskine L, Simoneau G, Paineau D & Bornet F (2006) The capacity of short-chain fructo-oligosaccharides to stimulate faecal bifidobacteria: a dose-response relationship study in healthy humans. *Nutrition Journal* **5**, 1-6.
Bouhnik Y, Raskine L, Simoneau G, Vicaut E, Neut C, Flourie B, Brouns F & Bornet FR (2004) The capacity of nondigestible carbohydrates to stimulate fecal bifidobacteria in healthy humans: a double-blind, randomized, placebo-controlled, parallel-group, dose-response relation study. *American Journal of Clinical Nutrition* **80**, 1658-1664.
Bouhnik Y, Vahedi K, Achour L, Attar A, Salfati J, Pochart P, Marteau P, Flourie B, Bornet F & Rambaud JC (1999) Short-chain fructo-oligosaccharide administration dose-dependently increases fecal bifidobacteria in healthy humans. *Journal of Nutrition* **129**, 113-116.
Boutron-Ruault MC, Marteau P, Lavergne-Slove A, Myara A, Gerhardt MF, Franchisseur C & Bornet F (2005) Effects of a 3-mo consumption of short-chain fructo-oligosaccharides on parameters of colorectal carcinogenesis in patients with or without small or large colorectal adenomas. *Nutrition and Cancer* **53**, 160-168.
Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF & Tang ML-K (2009) Probiotics for the treatment of eczema: a systematic review. *Clinical & Experimental Allergy* **39**, 1117-1127.
Bradburn DM, Mathers JC, Gunn A, Burn J, Chapman PD & Johnston ID (1993) Colonic fermentation of complex carbohydrates in patients with familial adenomatous polyposis. *Gut* **34**, 630-636.
Brand-Miller J, Burani J, Foster-Powell K & Holt S (2003) *The new glucose revolution: complete guide to glycemic index values*. New York, NY: Marlowe and Company.
Brighenti F, Casiraghi MC & Baggio C (1998) Resistant starch in the Italian diet. *British Journal of Nutrition* **80**, 333-341.
Brighenti F, Casiraghi MC, Canzi E & Ferrari A (1999) Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers. *European Journal of Clinical Nutrition* **53**, 726-733.
Brink EJ, van Beresteijn EC, Dekker PR & Beynen AC (1993) Urinary excretion of magnesium and calcium as an index of absorption is not affected by lactose intake in healthy adults. *British Journal of Nutrition* **69**, 863-870.
Brinkworth GD, Noakes M, Clifton PM & Bird AR (2009) Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *British Journal of Nutrition* **101**, 1493-1502.
Brodribb AJ (1977) Treatment of symptomatic diverticular disease with a high-fibre diet. *Lancet* **1**, 664-666.
Brodribb AJ & Groves C (1978) Effect of bran particle size on stool weight. *Gut* **19**, 60-63.
Brodribb AJ & Humphreys DM (1976a) Diverticular disease: three studies. Part III - Metabolic effect of bran in patients with diverticular disease. *British Medical Journal* **1**, 428-430.

Brodribb AJ & Humphreys DM (1976b) Diverticular disease: threee studies. Part II - Treatment with bran. *British Medical Journal* **1**, 425-428.
Brown KH, Perez F, Peerson JM, Fadel J, Brunsgaard G, Ostrom KM & MacLean Jr WC (1993) Effect of dietary fiber (soy polysaccharide) on the severity, duration, and nutritional outcome of acute, watery diarrhea in children. *Pediatrics* **92**, 241-247.
Brown MK & Everett I (1990) Gentler bowel fitness with fiber. *Geriatr Nurs* **11**, 26-27.
Bruce B, Spiller GA, Klevay LM & Gallagher SK (2000) A diet high in whole and unrefined foods favorably alters lipids, antioxidant defenses, and colon function. *Journal of the American College of Nutrition* **19**, 61-67.
Brunser O, Figueroa G, Gotteland M, Haschke-Becher E, Magliola C, Rochat F, Cruchet S, Palframan R, Gibson G, Chauffard F & Haschke F (2006) Effects of probiotic or prebiotic supplemented milk formulas on fecal microbiota composition of infants. *Asia Pacific Journal of Clinical Nutrition* **15**, 368-376.
Buddington RK, Williams CH, Chen SC & Witherly SA (1996) Dietary supplement of neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects. *American Journal of Clinical Nutrition* **63**, 709-716.
Burkitt DP, Walker AR & Painter NS (1972) Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet* **2**, 1408-1412.
Burks AW, Vanderhoof JA, Mehra S, Ostrom KM & Baggs G (2001) Randomized clinical trial of soy formula with and without added fiber in antibiotic-induced diarrhea. *Journal of Pediatrics* **139**, 578-582.
Burn J, Bishop DT, Mecklin J, Macrae F, Möslein G, Olschwang S, Bisgaard M, Ramesar R, Eccles D, Maher ER, Bertario L, Jarvinen HJ, Lindblom A, Evans DG, Lubinski J, Morrison PJ, Ho JWC, Vasen HFA, Side L, Thomas HJW, Scott RJ, Dunlop M, Barker G, Elliott F, Jass JR, Fodde R, Lynch HT & Mathers JC (2008) Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *New England Journal of Medicine* **359**, 2567-2579.
Butler LM, Wang R, Koh WP & Yu MC (2008) Prospective study of dietary patterns and colorectal cancer among Singapore Chinese. *Br J Cancer* **99**, 1511-1516.
Calame W, Weseler AR, Viebke C, Flynn C & Siemensma AD (2008) Gum arabic establishes prebiotic functionality in healthy human volunteers in a dose-dependent manner. *British Journal of Nutrition* **100**, 1269-1275.
Calloway DH & Kretsch MJ (1978) Protein and energy utilization in men given a rural Guatemalan diet and egg formulas with and without added oat bran. *American Journal of Clinical Nutrition* **31**, 1118-1126.
Cann PA, Read NW & Holdsworth CD (1984) What is the benefit of coarse wheat bran in patients with irritable bowel syndrome? *Gut* **25**, 168-173.
Capra SM & Hannan-Jones M (1993) A controlled dietary trial for improving bowel function in a group of training centre residents with severe or profound intellectual disability. *Australia and New Zealand Journal of Developmental Disabilities* **18**, 111-121.
Carabin IG, Lyon MR, Wood S, Pelletier X, Donazzolo Y & Burdock GA (2009) Supplementation of the diet with the functional fiber PolyGlycoplex is well tolerated by healthy subjects in a clinical trial. *Nutrition Journal* **8**, 1-11.
Carvalho-Wells AL, Helmolz K, Nodet C, Molzer C, Leonard C, McKevith B, Thielecke F, Jackson KG & Tuohy KM (2010) Determination of the in vivo prebiotic potential of a maize-based whole grain breakfast cereal: a human feeding study. *British Journal of Nutrition* **104**, 1353-1356.
Castillejo G, Bullo M, Anguera A, Escribano J & Salas-Salvado J (2006) A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated pediatric patients.

Pediatrics **118**, e641-648.
Causey JL, Feirtag JM, Gallaher DD, Tungland BC & Slavin JL (2000) Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. *Nutrition Research* **20**, 191-201.
Champ M, Langkilde AM, Brouns F, Kettlitz B & Bail-Collet YL (2003) Advances in dietary fibre characterisation. 2. Consumption, chemistry, physiology and measurement of resistant starch; implications for health and food labelling. *Nutr Res Rev* **16**, 143-161.
Chan AO, Leung G, Tong T & Wong NY (2007a) Increasing dietary fiber intake in terms of kiwifruit improves constipation in Chinese patients. *World Journal of Gastroenterology* **13**, 4771-4775.
Chan AOO, Hui WM, Leung G, Tong T, Hung IFN, Chan P, Hsu A, But D, Wong BCY, Lam SK & Lam KF (2007b) Patients with functional constipation do not have increased prevalence of colorectal cancer precursors. *Gut* **56**, 451-452.
Chapman ND, Grillage MG, Mazumder R & Atkinson SN (1990) A comparison of mebeverine with high-fibre dietary advice and mebeverine plus ispaghula in the treatment of irritable bowel syndrome: an open, prospectively randomised, parallel group study. *British Journal of Clinical Practice* **44**, 461-466.
Cheatham RA, Roberts SB, Das SK, Gilhooly CH, Golden JK, Hyatt R, Lerner D, Saltzman E & Lieberman HR (2009) Long-term effects of provided low and high glycemic load low energy diets on mood and cognition. *Physiology & Behavior* **98**, 374-379.
Chen HL, Cheng HC, Liu YJ, Liu SY & Wu WT (2006) Konjac acts as a natural laxative by increasing stool bulk and improving colonic ecology in healthy adults. *Nutrition* **22**, 1112-1119.
Chen HL, Cheng HC, Wu WT, Liu YJ & Liu SY (2008) Supplementation of konjac glucomannan into a low-fiber Chinese diet promoted bowel movement and improved colonic ecology in constipated adults: a placebo-controlled, diet-controlled trial. *Journal of the American College of Nutrition* **27**, 102-108.
Chen HL, Haack VS, Janecky CW, Vollendorf NW & Marlett JA (1998) Mechanisms by which wheat bran and oat bran increase stool weight in humans. *American Journal of Clinical Nutrition* **68**, 711-719.
Chen HL, Lu YH, Lin JJ & Ko LY (2000) Effects of fructooligosaccharide on bowel function and indicators of nutritional status in constipated elderly men. *Nutrition Research* **20**, 1725-1733.
Chen HL, Lu YH, Lin JJ & Ko LY (2001) Effects of isomalto-oligosaccharides on bowel functions and indicators of nutritional status in constipated elderly men. *Journal of the American College of Nutrition* **20**, 44-49.
Cherbut C, Aube AC, Mekki N, Dubois C, Lairon D & Barry JL (1997) Digestive and metabolic effects of potato and maize fibres in human subjects. *British Journal of Nutrition* **77**, 33-46.
Cherbut C, Michel C, Raison V, Kravtchenko T & Severine M (2003) Acacia gum is a bifidogenic dietary fibre with high digestive tolerance in healthy humans. *Microbial Ecology in Health and Disease* **15**, 43-50.
Cheskin LJ, Kamal N, Crowell MD, Schuster MM & Whitehead WE (1995) Mechanisms of constipation in older persons and effects of fiber compared with placebo. *Journal of the American Geriatrics Society* **43**, 666-669.
Chokhavatia S, Phipps T & Anuras S (1988) Comparative laxation of calcium polycarbophil with psyllium mucilloid in an ambulatory geriatric population. *Current Therapeutic Research - Clinical and Experimental* **44**, 1013-1019.
Chung YC, Hsu CK, Ko CY & Chan YC (2007) Dietary intake of xylooligosaccharides improves the intestinal microbiota, fecal moisture, and pH value in the elderly.

Nutrition Research **27**, 756-761.
Chyou PH, Nomura AM & Stemmermann GN (1996) A prospective study of colon and rectal cancer among Hawaii Japanese men. *Ann Epidemiol* **6**, 276-282.
Clark AN & Scott JF (1976) Wheat bran in dyschezia in the aged. *Age and Ageing* **5**, 149-154.
Clausen MR, Bonnen H & Mortensen PB (1991) Colonic fermentation of dietary fibre to short chain fatty acids in patients with adenomatous polyps and colonic cancer. *Gut* **32**, 923-928.
Cleave TL (1973) Effects of dietary fibre on intestinal transit. *Lancet* **1**, 1443.
Cloetens L, Broekaert WF, Delaedt Y, Ollevier F, Courtin CM, Delcour JA, Rutgeerts P & Verbeke K (2010) Tolerance of arabinoxylan-oligosaccharides and their prebiotic activity in healthy subjects: a randomised, placebo-controlled cross-over study. *British Journal of Nutrition* **103**, 703-713.
Cochet B, Jung A & Griessen M (1983) Effects of lactose on intestinal calcium absorption in normal and lactase-deficient subjects. *Gastroenterology* **84**, 935-940.
Colbert LH, Hartman TJ, Malila N, Limburg PJ, Pietinen P, Virtamo J, Taylor PR & Albanes D (2001) Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers. *Cancer Epidemiol Biomarkers Prev* **10**, 265-268.
Condon JR, Nassim JR, Millard FJ, Hilbe A & Stainthorpe EM (1970) Calcium and phosphorus metabolism in relation to lactose tolerance. *Lancet* **1**, 1027-1029.
Connell AM, Hilton C, Irvine G, Lennard-Jones JE & Misiewicz JJ (1965) Variation of bowel habit in two population samples. *British Medical Journal* **2**, 1095-1099.
Connell AM & Smith CL (1974) The effect of dietary fibre on transit time. In *Proc 4th Int Symp GI Motility*. Vancouver, Canada: Mitchell Press.
Cook IJ, Irvine EJ, Campbell D, Shannon S, Reddy SN & Collins SM (1990) Effect of dietary fiber on symptoms and rectosigmoid motility in patients with irritable bowel syndrome. A controlled, crossover study. *Gastroenterology* **98**, 66-72.
Corinaldesi R, Stanghellini V & Bocci G (1982) Dietary fibers and intestinal transit times. *Current Therapeutic Research - Clinical and Experimental* **31**, 173-180.
Cornu A & Delpeuch F (1981) Effect of fiber in sorghum on nitrogen digestibility. *American Journal of Clinical Nutrition* **34**, 2454-2459.
Costabile A, Klinder A, Fava F, Napolitano A, Fogliano V, Leonard C, Gibson GR & Tuohy KM (2008) Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study. *British Journal of Nutrition* **99**, 110-120.
Costabile A, Kolida S, Klinder A, Gietl E, Bauerlein M, Frohberg C, Landschutze V & Gibson GR (2010) A double-blind, placebo-controlled, cross-over study to establish the bifidogenic effect of a very-long-chain inulin extracted from globe artichoke (Cynara scolymus) in healthy human subjects. *British Journal of Nutrition* **104**, 1007-1017.
Costalos C, Kapiki A, Apostolou M & Papathoma E (2008) The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. *Early Human Development* **84**, 45-49.
Coudray C, Bellanger J, Castiglia-Delavaud C, Remesy C, Vermorel M & Rayssignuier Y (1997) Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. *European Journal of Clinical Nutrition* **51**, 375-380.
Coudray C, Bellanger J, Vermorel M, Sinaud S, Wils D, Feillet-Coudray C, Brandolini M, Bouteloup-Demange C & Rayssiguier Y (2003a) Two polyol, low digestible carbohydrates improve the apparent absorption of magnesium but not of calcium in

healthy young men. *Journal of Nutrition* **133**, 90-93.
Coudray C, Demigne C & Rayssiguier Y (2003b) Effects of dietary fibers on magnesium absorption in animals and humans. *Journal of Nutrition* **133**, 1-4.
Cowgill GR & Anderson WE (1932) Laxative effects of wheat bran and "washed bran" in healthy men: a comparative study. *J Am Med Assoc* **98**, 1866-1875.
Cowgill GR & Sullivan AJ (1933) Further studies on the use of wheat bran as a laxative: observations on patients. *J Am Med Assoc* **100**, 795-802.
Crowther JS, Drasar BS, Hill MJ, Maclennan R, Magnin D, Peach S & Teoh-chan CH (1976) Faecal steroids and bacteria and large bowel cancer in Hong Kong by socio-economic groups. *Br J Cancer* **34**, 191-198.
Cummings JH (2001a) The effect of dietary fiber on fecal weight and composition. In *CRC Handbook of Dietary Fiber in Human Nutrition*, pp. 183-252 [GA Spiller, editor]. Tampa, Florida: CRC Press LLC.
Cummings JH (2001b) The effect of dietary fiber on fecal weight and composition. In *CRC Handbook of Dietary Fiber in Human Nutrition*, pp. 183-252 [GA Spiller, editor]. Tampa, Florida: CRC Press LLC.
Cummings JH, Beatty ER, Kingman SM, Bingham SA & Englyst HN (1996) Digestion and physiological properties of resistant starch in the human large bowel. *British Journal of Nutrition* **75**, 733-747.
Cummings JH, Bingham SA, Heaton KW & Eastwood MA (1992) Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). *Gastroenterology* **103**, 1783-1789.
Cummings JH, Branch W, Jenkins DJ, Southgate DA, Houston H & James WP (1978) Colonic response to dietary fibre from carrot, cabbage, apple, bran. *Lancet* **1**, 5-9.
Cummings JH, Branch WJ, Bjerrum L, Paerregaard A, Helms P & Burton R (1982) Colon cancer and large bowel function in Denmark and Finland. *Nutr Cancer* **4**, 61-66.
Cummings JH, Christie S & Cole TJ (2001) A study of fructo oligosaccharides in the prevention of travellers' diarrhoea. *Alimentary Pharmacology and Therapeutics* **15**, 1139-1145.
Cummings JH & Englyst HN (1987) Fermentation in the human large intestine and the available substrates. *Am J Clin Nutr* **45**, 1243-1255.
Cummings JH, Hill MJ, Bone ES, Branch WJ & Jenkins DJ (1979a) The effect of meat protein and dietary fiber on colonic function and metabolism. II. Bacterial metabolites in feces and urine. *American Journal of Clinical Nutrition* **32**, 2094-2101.
Cummings JH, Hill MJ, Jenkins DJ, Pearson JR & Wiggins HS (1976a) Changes in fecal composition and colonic function due to cereal fiber. *American Journal of Clinical Nutrition* **29**, 1468-1473.
Cummings JH, Hill MJ, Jivraj T, Houston H, Branch WJ & Jenkins DJ (1979b) The effect of meat protein and dietary fiber on colonic function and metabolism. I. Changes in bowel habit, bile acid excretion, and calcium absorption. *American Journal of Clinical Nutrition* **32**, 2086-2093.
Cummings JH, Jenkins DJ & Wiggins HS (1976b) Measurement of the mean transit time of dietary residue through the human gut. *Gut* **17**, 210-218.
Cummings JH, Mann JI, Nishida C & Vorster HH (2009) Dietary fibre: an agreed definition. *Lancet* **373**, 365-366.
Cummings JH, Southgate DA, Branch WJ, Wiggins HS, Houston H, Jenkins DJ, Jivraj T & Hill MJ (1979c) The digestion of pectin in the human gut and its effect on calcium absorption and large bowel function. *British Journal of Nutrition* **41**, 477-485.
Cummings JH & Stephen AM (2007) Carbohydrate terminology and classification. *Eur J Clin Nutr* **61**, S5-S18.

D'Inca R, Pomerri F, Vettorato MG, Dal Pont E, Di Leo V, Ferronato A, Medici V & Sturniolo GC (2007) Interaction between rifaximin and dietary fibre in patients with diverticular disease. *Alimentary Pharmacology and Therapeutics* **25**, 771-779.

Dahl WJ, Lockert EA, Cammer AL & Whiting SJ (2005a) Effects of flax fiber on laxation and glycemic response in healthy volunteers. *Journal of Medicinal Food* **8**, 508-511.

Dahl WJ, Whiting SJ, Isaac TM, Weeks SJ & Arnold CJ (2005b) Effects of thickened beverages fortified with inulin on beverage acceptance, gastrointestinal function, and bone resorption in institutionalized adults. *Nutrition* **21**, 308-311.

Dahl WJ, Whiting SJ & Stephen AM (1995) Dietary lentils and calcium balance in adult men. *Nutrition Research* **15**, 1587-1598.

Dahm CC, Keogh RH, Spencer EA, Greenwood DC, Key TJ, Fentiman IS, Shipley MJ, Brunner EJ, Cade JE, Burley VJ, Mishra G, Stephen AM, Kuh D, White IR, Luben R, Lentjes MAH, Khaw KT & Rodwell SA (2010) Dietary Fiber and Colorectal Cancer Risk: A Nested Case-Control Study Using Food Diaries. *J. Natl. Cancer Inst.* **102**, 614-626.

Daly J, Tomlin J & Read NW (1993) The effect of feeding xanthan gum on colonic function in man: Correlation with in vitro determinants of bacterial breakdown. *British Journal of Nutrition* **69**, 897-902.

Danjo K, Sakamoto J, Iwane S, Tamura K, Nakaji S, Fukuda S, Murakami H, Shimoyama T, Takahashi I & Umeda T (2008) Effects of cellulose supplementation on fecal consistency and fecal weight. *Digestive Diseases and Sciences* **53**, 712-718.

Davidsson L, Mackenzie J, Kastenmayer P, Rose A, Golden BE, Aggett PJ & Hurrell RF (1996) Dietary fiber in weaning cereals: a study of the effect on stool characteristics and absorption of energy, nitrogen, and minerals in healthy infants. *Journal of Pediatric Gastroenterology and Nutrition* **22**, 167-179.

Davies GJ, Dettmar PW & Hoare RC (1998) The influence of ispaghula husk on bowel habit. *Journal of the Royal Society for the Promotion of Health* **118**, 267-271.

De Preter V, Geboes K, Verbrugghe K, De Vuyst L, Vanhoutte T, Huys G, Swings J, Pot B & Verbeke K (2004) The in vivo use of the stable isotope-labelled biomarkers lactose-[15N]ureide and [2H4]tyrosine to assess the effects of pro- and prebiotics on the intestinal flora of healthy human volunteers. *British Journal of Nutrition* **92**, 439-446.

de Preter V, Vanhoutte T, Huys G, Swings J, Rutgeerts P & Verbeke K (2008) Baseline microbiota activity and initial bifidobacteria counts influence responses to prebiotic dosing in healthy subjects. *Alimentary Pharmacology and Therapeutics* **27**, 504-513.

De Vries JJ, Collin T, Bijleveld CMA, Kleibeuker JH & Vonk RJ (1988) The use of complex carbohydrates in barley groats for determination of the mouth-to-caecum transit time. *Scandinavian Journal of Gastroenterology* **23**, 905-912.

DeCosse JJ, Miller HH & Lesser ML (1989) Effect of Wheat Fiber and Vitamins C and E on Rectal Polyps in Patients With Familial Adenomatous Polyposis. *J. Natl. Cancer Inst.* **81**, 1290-1297.

Degen LP & Phillips SF (1996) How well does stool form reflect colonic transit? *Gut* **39**, 109-113.

Den Hond E, Geypens B & Ghoos Y (2000) Effect of high performance chicory inulin on constipation. *Nutrition Research* **20**, 731-736.

Depeint F, Tzortzis G, Vulevic J, I'Anson K & Gibson GR (2008) Prebiotic evaluation of a novel galactooligosaccharide mixture produced by the enzymatic activity of Bifidobacterium bifidum NCIMB 41171, in healthy humans: a randomized, double-blind, crossover, placebo-controlled intervention study. *American Journal of Clinical Nutrition* **87**, 785-791.

Dettmar PW & Sykes J (1998) A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Current Medical Research and Opinion* **14**, 227-233.
Dinoto A, Marques TM, Sakamoto K, Fukiya S, Watanabe J, Ito S & Yokota A (2006) Population dynamics of Bifidobacterium species in human feces during raffinose administration monitored by fluorescence in situ hybridization-flow cytometry. *Applied and Environmental Microbiology* **72**, 7739-7747.
Drakoularakou A, Tzortzis G, Rastall RA & Gibson GR (2010) A double-blind, placebo-controlled, randomized human study assessing the capacity of a novel galacto-oligosaccharide mixture in reducing travellers' diarrhoea. *European Journal of Clinical Nutrition* **64**, 146-152.
Drasar BS & Hill MJ (1972) Intestinal bacteria and cancer. *Am J Clin Nutr* **25**, 1399-1404.
Drasar BS & Jenkins DJ (1976) Bacteria, diet, and large bowel cancer. *American Journal of Clinical Nutrition* **29**, 1410-1416.
Drasar BS, Jenkins DJ & Cummings JH (1976) The influence of a diet rich in wheat fibre on the human faecal flora. *Journal of Medical Microbiology* **9**, 423-431.
Drews LM, Kies C & Fox HM (1979) Effect of dietary fiber on copper, zinc, and magnesium utilization by adolescent boys. *American Journal of Clinical Nutrition* **32**, 1893-1897.
Drossman DA (2006) The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology* **130**, 1377-1390.
Duggan C, Penny ME, Hibberd P, Gil A, Huapaya A, Cooper A, Coletta F, Emenhiser C & Kleinman RE (2003) Oligofructose-supplemented infant cereal: 2 randomized, blinded, community-based trials in Peruvian infants. *American Journal of Clinical Nutrition* **77**, 937-942.
Dukas L, Willett WC, Colditz GA, Fuchs CS, Rosner B & Giovannucci EL (2000) Prospective Study of Bowel Movement, Laxative Use, and Risk of Colorectal Cancer among Women. *Am. J. Epidemiol.* **151**, 958-964.
Duro D, Rising R, Cedillo M & Lifshitz F (2002) Association between infantile colic and carbohydrate malabsorption from fruit juices in infancy. *Pediatrics* **109**, 797-805.
Durrington PN, Manning AP, Bolton CH & Hartog M (1976) Effect of pectin on serum lipids and lipoproteins, whole-gut transit-time, and stool weight. *Lancet* **2**, 394-396.
Eastwood MA, Brydon WG & Anderson DM (1983) The effects of dietary gum karaya (Sterculia) in man. *Toxicology Letters* **17**, 159-166.
Eastwood MA, Brydon WG & Anderson DM (1984) The effects of dietary gum tragacanth in man. *Toxicology Letters* **21**, 73-81.
Eastwood MA, Brydon WG & Anderson DM (1987) The dietary effects of xanthan gum in man. *Food Additives & Contaminants* **4**, 17-26.
Eastwood MA, Brydon WG & Anderson DM (1990) The effects of dietary methylcellulose in man. *Food Additives & Contaminants* **7**, 9-19.
Eastwood MA, Elton RA & Smith JH (1986) Long-term effect of wholemeal bread on stool weight, transit time, fecal bile acids, fats, and neutral sterols. *American Journal of Clinical Nutrition* **43**, 343-349.
Eastwood MA, Kirkpatrick JR, Mitchell WD, Bone A & Hamilton T (1973) Effects of dietary supplements of wheat bran and cellulose on faeces and bowel function. *British Medical Journal* **4**, 392-394.
Eastwood MA, Smith AN, Brydon WG & Pritchard J (1978) Comparison of bran, ispaghula, and lactulose on colon function in diverticular disease. *Gut* **19**, 1144-1147.
Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE & Relman DA (2005) Diversity of the Human Intestinal Microbial Flora. *Science* **308**, 1635-1638.

Edmiston CE, Jr., Avant GR & Wilson FA (1982) Anaerobic bacterial populations on normal and diseased human biopsy tissue obtained at colonoscopy. *Appl Environ Microbiol* **43**, 1173-1181.
Edwards CA & Parrett AM (2002) Intestinal flora during the first months of life: new perspectives. *Br J Nutr* **88 Suppl 1**, S11-18.
Effertz ME, Denman P & Slavin JL (1991) The effect of soy polysaccharide on body weight, serum lipids, blood glucose, and fecal parameters in moderately obese adults. *Nutrition Research* **11**, 849-859.
EFSA Panel on Dietetic Products NaA (2010) Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre. *EFSA Journal* **8**, 1462
Egeberg R, Olsen A, Loft S, Christensen J, Johnsen NF, Overvad K, Tj, x00F & nneland A (2010) Intake of wholegrain products and risk of colorectal cancers in the Diet, Cancer and Health cohort study. *British Journal of Cancer* **103**, 730-734.
Eherer AJ, Santa Ana CA, Porter J & Fordtran JS (1993) Effect of psyllium, calcium polycarbophil, and wheat bran on secretory diarrhea induced by phenolphthalein. *Gastroenterology* **104**, 1007-1012.
Elia M & Cummings JH (2007) Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. *Eur J Clin Nutr* **61**, S40-S74.
Englyst H, Wiggins HS & Cummings JH (1982) Determination of the non-starch polysaccharides in plant foods by gas-liquid chromatography of constituent sugars as alditol acetates. *Analyst* **107**, 307-318.
Englyst HN & Cummings JH (1988) Improved method for measurement of dietary fiber as non-starch polysaccharides in plant foods. *Journal - Association of Official Analytical Chemists* **71**, 808-814.
Englyst HN, Kingman SM & Cummings JH (1992) Classification and measurement of nutritionally important starch fractions. *European Journal of Clinical Nutrition* **46 Suppl 2**, S33-50.
Englyst HN, Quigley ME & Hudson GJ (1994) Determination of dietary fibre as non-starch polysaccharides with gas-liquid chromatographic, high-performance liquid chromatographic or spectrophotometric measurement of constituent sugars. *Analyst* **119**, 1497-1509.
Euler AR, Mitchell DK, Kline R & Pickering LK (2005) Prebiotic effect of fructo-oligosaccharide supplemented term infant formula at two concentrations compared with unsupplemented formula and human milk. *Journal of Pediatric Gastroenterology and Nutrition* **40**, 157-164.
Ewe K, Ueberschaer B, Press AG, Kurreck C & Klump M (1995) Effect of lactose, lactulose and bisacodyl on gastrointestinal transit studied by metal detector. *Alimentary Pharmacology and Therapeutics* **9**, 69-73.
Ewerth S, Ahlberg J & Holmstrom B (1980) Influence on symptoms and transit-time of Vi-Siblin in diverticular disease. *Acta Chirurgica Scandinavica* **146**, 49-50.
Fanaro S, Jelinek J, Stahl B, Boehm G, Kock R & Vigi V (2005) Acidic oligosaccharides from pectin hydrolysate as new component for infant formulae: effect on intestinal flora, stool characteristics, and pH. *Journal of Pediatric Gastroenterology and Nutrition* **41**, 186-190.
Fanaro S, Marten B, Bagna R, Vigi V, Fabris C, Pena-Quintana L, Arguelles F, Scholz-Ahrens KE, Sawatzki G, Zelenka R, Schrezenmeir J, de Vrese M & Bertino E (2009) Galacto-oligosaccharides are bifidogenic and safe at weaning: a double-blind randomized multicenter study. *Journal of Pediatric Gastroenterology and Nutrition* **48**, 82-88.
FAO/WHO (1997) Carbohydrates in human nutrition. In *Food and Nutrition Paper*. Rome:

FAO.
Fastinger ND, Karr-Lilienthal LK, Spears JK, Swanson KS, Zinn KE, Nava GM, Ohkuma K, Kanahori S, Gordon DT & Fahey GC, Jr. (2008) A novel resistant maltodextrin alters gastrointestinal tolerance factors, fecal characteristics, and fecal microbiota in healthy adult humans. *Journal of the American College of Nutrition* **27**, 356-366.
Fedail SS, Badi SE & Musa AR (1984) The effects of sorghum and wheat bran on the colonic functions of healthy Sudanese subjects. *American Journal of Clinical Nutrition* **40**, 776-779.
Fenn GC, Wilkinson PD, Lee CE & Akbar FA (1986) A general practice study of the efficacy of Regulan in functional constipation. *British Journal of Clinical Practice* **40**, 192-197.
Ferrer FP & Boyd LJ (1955) Effect of yogurt with prune whip on constipation. *American Journal of Digestive Diseases* **22**, 272-273.
Findlay JM, Smith AN, Mitchell WD, Anderson AJ & Eastwood MA (1974) Effects of unprocessed bran on colon function in normal subjects and in diverticular disease. *Lancet* **1**, 146-149.
Finegold SM, Flora DJ, Attebery HR & Sutter VL (1975) Fecal bacteriology of colonic polyp patients and control patients. *Cancer Res* **35**, 3407-3417.
Finlay M (1988) The use of dietary fibre in a long-stay geriatric ward. *Journal of Nutrition for the Elderly* **8**, 19-30.
Finley JW, Burrell JB & Reeves PG (2007) Pinto bean consumption changes SCFA profiles in fecal fermentations, bacterial populations of the lower bowel, and lipid profiles in blood of humans. *Journal of Nutrition* **137**, 2391-2398.
Finney M, Smullen J, Foster HA, Brokx S & Storey DM (2007) Effects of low doses of lactitol on faecal microflora, pH, short chain fatty acids and gastrointestinal symptomology. *European Journal of Nutrition* **46**, 307-314.
Fleming SE, Marthinsen D & Kuhnlein H (1983) Colonic function and fermentation in men consuming high fiber diets. *Journal of Nutrition* **113**, 2535-2544.
Fleming SE, O'Donnell AU & Perman JA (1985) Influence of frequent and long-term bean consumption on colonic function and fermentation. *American Journal of Clinical Nutrition* **41**, 909-918.
Fleming SE & Rodriguez MA (1983) Influence of dietary fiber on fecal excretion of volatile fatty acids by human adults. *Journal of Nutrition* **113**, 1613-1625.
Floch MH & Fuchs HM (1978) Modification of stool content by increased bran intake. *American Journal of Clinical Nutrition* **31**, S185-S189.
Flynn JF, SF OB & Burkitt DP (1977) The potato as a source of fibre in the diet. *Irish Journal of Medical Science* **146**, 285-288.
Foster-Powell K, Holt SH & Brand-Miller JC (2002) International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* **76**, 5-56.
Foster-Powell K & Miller JB (1995) International tables of glycemic index. *Am J Clin Nutr* **62**, 871S-890S.
Fowlie S, Eastwood MA & Prescott R (1992) Irritable bowel syndrome: assessment of psychological disturbance and its influence on the response to fibre supplementation. *Journal of Psychosomatic Research* **36**, 175-180.
Francis RM, Peacock M, Barkworth SA & Marshall DH (1986) A comparison of the effect of sorbitol and glucose on calcium absorption in postmenopausal women. *American Journal of Clinical Nutrition* **43**, 72-76.
Frank DN, St. Amand AL, Feldman RA, Boedeker EC, Harpaz N & Pace NR (2007) Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of*

Sciences **104**, 13780-13785.
Fredlund K, Isaksson M, Rossander-Hulthen L, Almgren A & Sandberg AS (2006) Absorption of zinc and retention of calcium: dose-dependent inhibition by phytate. *Journal of Trace Elements in Medicine & Biology* **20**, 49-57.
Fredstrom SB, Lampe JW, Jung HJ & Slavin JL (1994) Apparent fiber digestibility and fecal short-chain fatty acid concentrations with ingestion of two types of dietary fiber. *Jpen: Journal of Parenteral & Enteral Nutrition* **18**, 14-19.
Fritz M, Siebert G & Kasper H (1985) Dose dependence of breath hydrogen and methane in healthy volunteers after ingestion of a commercial disaccharide mixture, Palatinit. *British Journal of Nutrition* **54**, 389-400.
Fu B, Wang J, Roturier JM, Tang Z, Li H & Wei G (2008) Determination of total dietary fiber in selected foods containing resistant maltodextrin by a simplified enzymatic-gravimetric method and liquid chromatography: interlaboratory study in China. *Journal of AOAC International* **91**, 614-621.
Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE & Willett WC (1999) Dietary fiber and the risk of colorectal cancer and adenoma in women. *N.Engl.J.Med.* **340**, 169-176.
Fuchs HM, Dorfman S & Floch MH (1976) The effect of dietary fiber supplementation in man. II. Alteration in fecal physiology and bacterial flora. *American Journal of Clinical Nutrition* **29**, 1443-1447.
Fuller Z, Louis P, Mihajlovski A, Rungapamestry V, Ratcliffe B & Duncan AJ (2007) Influence of cabbage processing methods and prebiotic manipulation of colonic microflora on glucosinolate breakdown in man. *British Journal of Nutrition* **98**, 364-372.
Gaard M, Tretli S & Loken EB (1996) Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev* **5**, 445-454.
Gallaher DD, Gallaher CM, Mahrt GJ, Carr TP, Hollingshead CH, Hesslink R, Jr. & Wise J (2002) A glucomannan and chitosan fiber supplement decreases plasma cholesterol and increases cholesterol excretion in overweight normocholesterolemic humans. *Journal of the American College of Nutrition* **21**, 428-433.
Garg A, Bonanome A, Grundy SM, Unger RH, Breslau NA & Pak CY (1990) Effects of dietary carbohydrates on metabolism of calcium and other minerals in normal subjects and patients with noninsulin-dependent diabetes mellitus. *Journal of Clinical Endocrinology & Metabolism* **70**, 1007-1013.
Gdalevich M, Mimouni D, David M & Mimouni M (2001a) Breast-feeding and the onset of atopic dermatitis in childhood: A systematic review and meta-analysis of prospective studies. *Journal of the American Academy of Dermatology* **45**, 520-527.
Gdalevich M, Mimouni D & Mimouni M (2001b) Breast-feeding and the risk of bronchial asthma in childhood: A systematic review with meta-analysis of prospective studies. *The Journal of pediatrics* **139**, 261-266.
Gelissen IC, Allgood GS & Eastwood MA (1994) Reproducibility of the breath hydrogen measurement after a low and high fibre meal. *European Journal of Clinical Nutrition* **48**, 266-272.
George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, Hollenbeck A & Subar AF (2009) Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. *Am J Epidemiol* **169**, 462-472.
Gibson CJ, Opalka PC, Moore CA, Brady RS & Mion LC (1995a) Effectiveness of bran supplement on the bowel management of elderly rehabilitation patients. *Journal of Gerontological Nursing* **21**, 21-30.
Gibson GR, Beatty ER, Wang X & Cummings JH (1995b) Selective stimulation of

bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* **108**, 975-982.
Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A & Willett WC (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* **54**, 2390-2397.
Glober GA, Kamiyama S, Nomura A, Shimada A & Abba BC (1977) Bowel transit-time and stool weight in populations with different colon-cancer risks. *Lancet* **2**, 110-111.
Glynn SA, Albanes D, Pietinen P, Brown CC, Rautalahti M, Tangrea JA, Gunter EW, Barrett MJ, Virtamo J & Taylor PR (1996) Colorectal cancer and folate status: a nested case-control study among male smokers. *Cancer Epidemiol Biomarkers Prev* **5**, 487-494.
Godara R, Kaur AP & Bhat CM (1981) Effect of cellulose incorporation in a low fiber diet on fecal excretion and serum levels of calcium, phosphorus, and iron in adolescent girls. *American Journal of Clinical Nutrition* **34**, 1083-1086.
Goetze O, Fruehauf H, Pohl D, Giarre M, Rochat F, Ornstein K, Menne D, Fried M & Thumshirn M (2008) Effect of a prebiotic mixture on intestinal comfort and general wellbeing in health. *British Journal of Nutrition* **100**, 1077-1085.
Golechha AC, Chadda VS, Chadda S, Sharma SK & Mishra SN (1982) Role of ispaghula husk in the management of irritable bowel syndrome (a randomized double-blind crossover study). *Journal of the Association of Physicians of India* **30**, 353-355.
Goni I, Garcia-Diz L, Manas E & Saura-Calixto F (1996) Analysis of resistant starch: A method for foods and food products. *Food Chemistry* **56**, 445-449.
Gonlachanvit S, Coleski R, Owyang C & Hasler W (2004) Inhibitory actions of a high fibre diet on intestinal gas transit in healthy volunteers. *Gut* **53**, 1577-1582.
Gopal PK, Prasad J & Gill HS (2003) Effects of the consumption of Bifidobacterium lactis HN019 (DR10[trademark]) and galacto-oligosaccharides on the microflora of the gastrointestinal tract in human subjects. *Nutrition Research* **23**, 1313-1328.
Gore C, Munro K, Lay C, Bibiloni R, Morris J, Woodcock A, Custovic A & Tannock GW (2008) Bifidobacterium pseudocatenulatum is associated with atopic eczema: A nested case-control study investigating the fecal microbiota of infants. *The Journal of allergy and clinical immunology* **121**, 135-140.
Gostner A, Blaut M, Schaffer V, Kozianowski G, Theis S, Klingeberg M, Dombrowski Y, Martin D, Ehrhardt S, Taras D, Schwiertz A, Kleessen B, Luhrs H, Schauber J, Dorbath D, Menzel T & Scheppach W (2006) Effect of isomalt consumption on faecal microflora and colonic metabolism in healthy volunteers. *British Journal of Nutrition* **95**, 40-50.
Gostner A, Schaffer V, Theis S, Menzel T, Luhrs H, Melcher R, Schauber J, Kudlich T, Dusel G, Dorbath D, Kozianowski G & Scheppach W (2005) Effects of isomalt consumption on gastrointestinal and metabolic parameters in healthy volunteers. *British Journal of Nutrition* **94**, 575-581.
Gotestam KG (1977) A double-blind comparison of two bulk laxatives on geriatric patients. *Scandinavian Journal of Social Medicine. Supplementum* **14**, 141-145.
Graham DY, Moser SE & Estes MK (1982) The effect of bran on bowel function in constipation. *American Journal of Gastroenterology* **77**, 599-603.
Grasten S, Liukkonen KH, Chrevatidis A, El-Nezami H, Poutanen K & Mykkanen H (2003) Effects of wheat pentosan and inulin on the metabolic activity of fecal microbiota and on bowel function in healthy humans. *Nutrition Research* **23**, 1503-1514.
Grasten SM, Juntunen KS, Matto J, Mykkanen OT, El-Nezami H, Adlercreutz H, Poutanen KS & Mykkanen HM (2007) High-fiber rye bread improves bowel function in postmenopausal women but does not cause other putatively positive changes in the metabolic activity of intestinal microbiota. *Nutrition Research* **27**, 454-461.

Grasten SM, Juntunen KS, Poutanen KS, Gylling HK, Miettinen TA & Mykkanen HM (2000) Rye bread improves bowel function and decreases the concentrations of some compounds that are putative colon cancer risk markers in middle-aged women and men. *Journal of Nutrition* **130**, 2215-2221.

Gray H & Tainter ML (1941) Colloid laxitives available for clinical use. *American Journal of Digestive Diseases* **8**, 130.

Greenland S & Longnecker MP (1992) Methods for Trend Estimation from Summarized Dose-Response Data, with Applications to Meta-Analysis. *American Journal of Epidemiology* **135**, 1301-1309.

Greenwald E, Samachson J & Spencer H (1963) Effect of lactose on calcium metabolism in man. *J Nutr* **79**, 531-538.

Griessen M, Cochet B, Infante F, Jung A, Bartholdi P, Donath A, Loizeau E & Courvoisier B (1989a) Calcium absorption from milk in lactase-deficient subjects. *American Journal of Clinical Nutrition* **49**, 377-384.

Griessen M, Speich PV, Infante F, Bartholdi P, Cochet B, Donath A, Courvoisier B & Bonjour -Ph J (1989b) Effect of absorbable and nonabsorbable sugars on intestinal calcium absorption in humans. *Gastroenterology* **96**, 769-775.

Griessen M, Speich PV, Infante F, Bartholdi P, Cochet B, Donath A, Courvoisier B & Bonjour JP (1989c) Effect of absorbable and nonabsorbable sugars on intestinal calcium absorption in humans. *Gastroenterology* **96**, 769-775.

Griffin IJ & Abrams SA (2005) Methodological considerations in measuring human calcium absorption: Relevance to study the effects of inulin-type fructans. *British Journal of Nutrition* **93**, S105-S110.

Griffin IJ, Davila PM & Abrams SA (2002) Non-digestible oligosaccharides and calcium absorption in girls with adequate calcium intakes. *British Journal of Nutrition* **87**, S187-S191.

Griffin IJ, Hicks PMD, Heaney RP & Abrams SA (2003) Enriched chicory inulin increases calcium absorption mainly in girls with lower calcium absorption. *Nutrition Research* **23**, 901-909.

Guarner F & Malagelada JR (2003) Gut flora in health and disease. *Lancet* **361**, 512-519.

Guedon C, Ducrotte P, Antoine JM, Denis P, Colin R & Lerebours E (1996) Does chronic supplementation of the diet with dietary fibre extracted from pea or carrot affect colonic motility in man? *British Journal of Nutrition* **76**, 51-61.

Guigoz Y, Rochat F, Perruisseau-Carrier G, Rochat I & Schiffrin EJ (2002) Effects of oligosaccharide on the faecal flora and non-specific immune system in elderly people. *Nutrition Research* **22**, 13-25.

Gulliford MC, Pover GG, Bicknell EJ & Scarpello JHB (1988) Guar delays intestinal calcium absorption in man. *European Journal of Clinical Nutrition* **42**, 451-454.

Haack VS, Chesters JG, Vollendorf NW, Story JA & Marlett JA (1998a) Increasing amounts of dietary fiber provided by foods normalizes physiologic response of the large bowel without altering calcium balance or fecal steroid excretion. *American Journal of Clinical Nutrition* **68**, 615-622.

Haack VS, Chesters JG, Vollendorf NW, Story JA & Marlett JA (1998b) Increasing amounts of dietary fiber provided by foods normalizes physiologic response of the large bowel without altering calcium balance or fecal steroid excretion. *American Journal of Clinical Nutrition* **68**, 615-622.

Haarman M & Knol J (2006) Quantitative Real-Time PCR Analysis of Fecal Lactobacillus Species in Infants Receiving a Prebiotic Infant Formula. *Applied and Environmental Microbiology* **72**, 2359-2365.

Half E, Bercovich D & Rozen P (2009) Familial adenomatous polyposis. *Orphanet Journal*

of Rare Diseases **4**, 22.
Hallberg L, Brune M & Rossander L (1989) Iron absorption in man: ascorbic acid and dose-dependent inhibition by phytate. *American Journal of Clinical Nutrition* **49**, 140-144.
Hamaker BR, Rivera K, Morales E & Graham GG (1991) Effect of dietary fiber and starch on fecal composition in preschool children consuming maize, amaranth, or cassava flours. *Journal of Pediatric Gastroenterology and Nutrition* **13**, 59-66.
Hamberg O, Rumessen JJ & Gudmand-Hoyer E (1989) Inhibition of starch absorption by dietary fibre. A comparative study of wheat bran, sugar-beet fibre, and pea fibre. *Scandinavian Journal of Gastroenterology* **24**, 103-109.
Hamer HM, Jonkers D, Venema K, VanHoutvin S, Troost FJ & Brummer R-J (2008) Review article: the role of butyrate on colonic function. *Alimentary Pharmacology & Therapeutics* **27**, 104-119.
Hamilton JW, Wagner J, Burdick BB & Bass P (1988) Clinical evaluation of methylcellulose as a bulk laxative. *Digestive Diseases and Sciences* **33**, 993-998.
Hamilton T, Kirkpatrick JR, Mitchell D & Eastwood MA (1972) The effects of dietary supplements of wheat bran and cellulose upon bowel function. *British Journal of Surgery* **59**.
Harmsen HJM, Raangs GC, Franks AH, Wildeboer-Veloo ACM & Welling GW (2002) The effect of the prebiotic inulin and the probiotic Bifidobacterium longum on the fecal microflora of healthy volunteers measured by FISH and DGGE. *Microbial Ecology in Health and Disease* **14**, 211-219.
Harvey RF, Pomare EW & Heaton KW (1973) Effects of increased dietary fibre on intestinal transit. *Lancet* **1**, 1278-1280.
He T, Priebe MG, Welling GW & Vonk RJ (2006) Effect of lactose on oro-cecal transit in lactose digesters and maldigesters. *European Journal of Clinical Investigation* **36**, 737-742.
Heaney RP & Weaver CM (1995) Effect of psyllium on absorption of co-ingested calcium. *Journal of the American Geriatrics Society* **43**, 261-263.
Heaney RP, Weaver CM & Fitzsimmons ML (1991) Soybean phytate content: effect on calcium absorption. *American Journal of Clinical Nutrition* **53**, 745-747.
Heaton KW & O'Donnell LJD (1994) An Office Guide to Whole-Gut Transit Time: Patients' Recollection of their Stool Form. *Journal of Clinical Gastroenterology* **19**, 28-30.
Heijnen MLA, Van Amelsvoort JMM, Deurenberg P & Beynen AC (1998) Limited effect of consumption of uncooked (RS₂) or retrograded (RS₃) resistant starch on putative risk factors for colon cancer in healthy men. *American Journal of Clinical Nutrition* **67**, 322-331.
Heilbrun LK, Nomura A, Hankin JH & Stemmermann GN (1989) Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* **44**, 1-6.
Hellendoorn EW, Noordhoff MG & Slagman J (1975) Enzymatic determination of the indigestible residue (dietary fibre) content of human food. *Journal of the Science of Food and Agriculture* **26**, 1461-1468.
Heller SN, Hackler LR, Rivers JM, Van Soest PJ, Roe DA, Lewis BA & Robertson J (1980) Dietary fiber: the effect of particle size of wheat bran on colonic function in young adult men. *American Journal of Clinical Nutrition* **33**, 1734-1744.
Henderson L, Gregory J, Irving K & Swan G (2003) The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 2: Energy, protein, carbohydrate, fat and alcohol intake. London: TSO.
Hengst C, Ptok S, Roessler A, Fechner A & Jahreis G (2008) Effects of polydextrose supplementation on different faecal parameters in healthy volunteers. *International Journal of Food Sciences and Nutrition*, 1-10.

Higginbotham S, Zhang ZF, Lee IM, Cook NR, Giovannucci E, Buring JE & Liu S (2004) Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst* **96**, 229-233.
Higgins JPT, Thompson SG, Deeks JJ & Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560.
Hill MJ, Drasar BS, Hawksworth G, Aries V, Crowther JS & Williams RE (1971) Bacteria and aetiology of cancer of large bowel. *Lancet* **1**, 95-100.
Hillman L, Peters S, Fisher A & Pomare EW (1983) Differing effects of pectin, cellulose and lignin on stool pH, transit time and weight. *British Journal of Nutrition* **50**, 189-195.
Hinton JM, Lennard-Jones JE & Young AC (1969) A new method for studying gut transit times using radioopaque markers. *Gut* **10**, 842-847.
Hodgson WJ (1977) The placebo effect. Is it important in diverticular disease? *Am J Gastroenterol* **67**, 157-162.
Hoekstra JH, Szajewska H, Zikri MA, Micetic-Turk D, Weizman Z, Papadopoulou A, Guarino A, Dias JA & Oostvogels B (2004) Oral rehydration solution containing a mixture of non-digestible carbohydrates in the treatment of acute diarrhea: a multicenter randomized placebo controlled study on behalf of the ESPGHAN working group on intestinal infections. *Journal of Pediatric Gastroenterology and Nutrition* **39**, 239-245.
Hoekstra JH, van den Aker JH, Ghoos YF, Hartemink R & Kneepkens CM (1995) Fluid intake and industrial processing in apple juice induced chronic non-specific diarrhoea. *Archives of Disease in Childhood* **73**, 126-130.
Hoekstra JH, van den Aker JH, Kneepkens CM, Stellaard F, Geypens B & Ghoos YF (1996) Evaluation of 13CO2 breath tests for the detection of fructose malabsorption. *Journal of Laboratory and Clinical Medicine* **127**, 303-309.
Holbrook JT, Smith JC, Jr. & Reiser S (1989) Dietary fructose or starch: effects on copper, zinc, iron, manganese, calcium, and magnesium balances in humans. *American Journal of Clinical Nutrition* **49**, 1290-1294.
Holloway L, Moynihan S, Abrams SA, Kent K, Hsu AR & Friedlander AL (2007) Effects of oligofructose-enriched inulin on intestinal absorption of calcium and magnesium and bone turnover markers in postmenopausal women. *British Journal of Nutrition* **97**, 365-372.
Holma R, Hongisto SM, Saxelin M & Korpela R (2010) Constipation is relieved more by rye bread than wheat bread or laxatives without increased adverse gastrointestinal effects. *Journal of Nutrition* **140**, 534-541.
Hongisto SM, Paajanen L, Saxelin M & Korpela R (2006) A combination of fibre-rich rye bread and yoghurt containing Lactobacillus GG improves bowel function in women with self-reported constipation. *European Journal of Clinical Nutrition* **60**, 319-324.
Hope AK & Down EC (1986) Dietary fibre and fluid in the control of constipation in a nursing home population. *Medical Journal of Australia* **144**, 306-307.
Hope ME, Hold GL, Kain R & El-Omar EM (2005) Sporadic colorectal cancer - role of the commensal microbiota. *FEMS Microbiology Letters* **244**, 1-7.
Hopkins MJ, Macfarlane GT, Furrie E, Fite A & Macfarlane S (2005) Characterisation of intestinal bacteria in infant stools using real-time PCR and northern hybridisation analyses. *FEMS Microbiol Ecol* **54**, 77-85.
Hove H, Rye Clausen M & Brobech Mortensen P (1993) Lactate and pH in faeces from patients with colonic adenomas or cancer. *Gut* **34**, 625-629.
Hovey AL, Jones GP, Devereux HM & Walker KZ (2003) Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pacific Journal of Clinical Nutrition* **12**, 477-482.

Hoveyda N, Heneghan C, Mahtani K, Perera R, Roberts N & Glasziou P (2009) A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterology* **9**, 15.
Howard LV, West D & Ossip-Klein DJ (2000) Chronic constipation management for institutionalized older adults [corrected] [published erratum appears in GERIATR NURS 2000 May-Jun; 21(3): 119]. *Geriatric Nursing* **21**, 78-84.
Howarth NC, Murphy SP, Wilkens LR, Henderson BE & Kolonel LN (2008) The association of glycemic load and carbohydrate intake with colorectal cancer risk in the Multiethnic Cohort Study. *American Journal of Clinical Nutrition* **88**, 1074-1083.
Huijbregts AW, Van Berge-Henegouwen GP, Hectors MP, Van Schaik A & Van der Werf SD (1980) Effects of a standardized wheat bran preparation on biliary lipid composition and bile acid metabolism in young healthy males. *European Journal of Clinical Investigation* **10**, 451-458.
Hull C, Greco RS & Brooks DL (1980) Alleviation of constipation in the elderly by dietary fiber supplementation. *Journal of the American Geriatrics Society* **28**, 410-414.
Hunter JO, Tuffnell Q & Lee AJ (1999) Controlled trial of oligofructose in the management of irritable bowel syndrome. *Journal of Nutrition* **129**, 1451S-1453S.
Hyams JS & Leichtner AM (1985) Apple juice. An unappreciated cause of chronic diarrhea. *American Journal of Diseases of Children* **139**, 503-505.
Hyland JM & Taylor I (1980) Does a high fibre diet prevent the complications of diverticular disease? *British Journal of Surgery* **67**, 77-79.
Hylla S, Gostner A, Dusel G, Anger H, Bartram HP, Christl SU, Kasper H & Scheppach W (1998) Effects of resistant starch on the colon in healthy volunteers: possible implications for cancer prevention. *American Journal of Clinical Nutrition* **67**, 136-142.
Ip S, Chung M, Raman G, Trikalinos TA & Lau J (2009) A Summary of the Agency for Healthcare Research and Quality's Evidence Report on Breastfeeding in Developed Countries. *Breastfeeding Medicine* **4**, S-17-S-30.
Ishikawa H, Akedo I, Otani T, Suzuki T, Nakamura T, Takeyama I, Ishiguro S, Miyaoka E, Sobue T & Kakizoe T (2005) Randomized trial of dietary fiber and Lactobacillus casei administration for prevention of colorectal tumors. *Int J Cancer* **116**, 762-767.
Ismail-Beigi F, Reinhold JG, Faraji B & Abadi P (1977) Effects of cellulose added to diets of low and high fiber content upon the metabolism of calcium, magnesium, zinc and phosphorus by man. *Journal of Nutrition* **107**, 510-518.
Ito M, Deguchi Y, Matsumoto K, Kimura M, Onodera N & Yajima T (1993a) Influence of galactooligosaccharides on the human fecal microflora. *Journal of Nutritional Science and Vitaminology* **39**, 635-640.
Ito M, Deguchi Y, Miyamori A, Matsumoto K, Kikuchi H, Kobayashi Y, Yajima T & Kan T (1990) Effects of Administration of Galactooligosaccharides on the Human Faecal Microflora, Stool Weight and Abdominal Sensation. *Microbial Ecology in Health and Disease* **3**, 285 - 292.
Ito M, Kimura M, Deguchi Y, Miyamori-Watabe A, Yajima T & Kan T (1993b) Effects of transgalactosylated disaccharides on the human intestinal microflora and their metabolism. *Journal of Nutritional Science & Vitaminology* **39**, 279-288.
Ivaturi R & Kies C (1992) Mineral balances in humans as affected by fructose, high fructose corn syrup and sucrose. *Plant Foods for Human Nutrition* **42**, 143-151.
Jacobs EJ & White E (1998) Constipation, laxative use, and colon cancer among middle-aged adults. *Epidemiology* **9**, 385-391.
Jacobs ET, Giuliano AR, Roe DJ, Guillen-Rodriguez JM, Hess LM, Alberts DS & Martinez ME (2002) Intake of supplemental and total fiber and risk of colorectal adenoma

recurrence in the wheat bran fiber trial. *Cancer Epidemiol Biomarkers Prev* **11**, 906-914.
Jacobs ET, Lanza E, Alberts DS, Hsu C-H, Jiang R, Schatzkin A, Thompson PA & Martinez ME (2006) Fiber, sex, and colorectal adenoma: results of a pooled analysis. *Am J Clin Nutr* **83**, 343-349.
Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ & McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* **17**, 1-12.
Jalihal A & Kurian G (1990) Ispaghula therapy in irritable bowel syndrome: improvement in overall well-being is related to reduction in bowel dissatisfaction. *Journal of Gastroenterology and Hepatology* **5**, 507-513.
James WP, Branch WJ & Southgate DA (1978) Calcium binding by dietary fibre. *Lancet* **1**, 638-639.
Jarvinen R, Knekt P, Hakulinen T & Aromaa A (2001) Prospective study on milk products, calcium and cancers of the colon and rectum. *Eur J Clin Nutr* **55**, 1000-1007.
Jenkins D, Wolever T, Taylor R, Barker H, Fielden H, Baldwin J, Bowling A, Newman H, Jenkins A & Goff D (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* **34**, 362-366.
Jenkins DJ, Hill MS & Cummings JH (1975) Effect of wheat fiber on blood lipids, fecal steroid excretion and serum iron. *American Journal of Clinical Nutrition* **28**, 1408-1411.
Jenkins DJ, Kendall CW, Popovich DG, Vidgen E, Mehling CC, Vuksan V, Ransom TP, Rao AV, Rosenberg-Zand R, Tariq N, Corey P, Jones PJ, Raeini M, Story JA, Furumoto EJ, Illingworth DR, Pappu AS & Connelly PW (2001) Effect of a very-high-fiber vegetable, fruit, and nut diet on serum lipids and colonic function. *Metabolism: Clinical and Experimental* **50**, 494-503.
Jenkins DJ, Kendall CW, Vuksan V, Augustin LS, Li YM, Lee B, Mehling CC, Parker T, Faulkner D, Seyler H, Vidgen E & Fulgoni V (1999a) The effect of wheat bran particle size on laxation and colonic fermentation. *Journal of the American College of Nutrition* **18**, 339-345.
Jenkins DJ, Kendall CW, Vuksan V, Vidgen E, Wong E, Augustin LS & Fulgoni V, 3rd (2000) Effect of cocoa bran on low-density lipoprotein oxidation and fecal bulking. *Archives of Internal Medicine* **160**, 2374-2379.
Jenkins DJ, Peterson RD, Thorne MJ & Ferguson PW (1987) Wheat fiber and laxation: dose response and equilibration time. *American Journal of Gastroenterology* **82**, 1259-1263.
Jenkins DJ, Reynolds D, Leeds AR, Waller AL & Cummings JH (1979) Hypocholesterolemic action of dietary fiber unrelated to fecal bulking effect. *American Journal of Clinical Nutrition* **32**, 2430-2435.
Jenkins DJ, Vuksan V, Kendall CW, Wursch P, Jeffcoat R, Waring S, Mehling CC, Vidgen E, Augustin LS & Wong E (1998) Physiological effects of resistant starches on fecal bulk, short chain fatty acids, blood lipids and glycemic index. *Journal of the American College of Nutrition* **17**, 609-616.
Jenkins DJ, Vuksan V, Rao AV, Vidgen E, Kendall CW, Tariq N, Wursch P, Koellreutter B, Shiwnarain N & Jeffcoat R (1999b) Colonic bacterial activity and serum lipid risk factors for cardiovascular disease. *Metabolism: Clinical and Experimental* **48**, 264-268.
Jensen OM, MacLennan R & Wahrendorf J (1982) Diet, bowel function, fecal characteristics, and large bowel cancer in Denmark and Finland. *Nutr Cancer* **4**, 5-19.
Jie Z, Bang-yao L, Ming-jie X, Hai-wei L, Zu-kang Z, Ting-song W & Craig SAS (2000)

Studies on the effects of polydextrose intake on physiologic funtions in Chinese people. *American Journal of Clinical Nutrition* **72**, 1503-1509.
Johnson SK, Chua V, Hall RS & Baxter AL (2006) Lupin kernel fibre foods improve bowel function and beneficially modify some putative faecal risk factors for colon cancer in men. *British Journal of Nutrition* **95**, 372-378.
Judd PA & Truswell AS (1981) The effect of rolled oats on blood lipids and fecal steroid excretion in man. *American Journal of Clinical Nutrition* **34**, 2061-2067.
Kabat GC, Shikany JM, Beresford SA, Caan B, Neuhouser ML, Tinker LF & Rohan TE (2008) Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control* **19**, 1291-1298.
Kacmaz Z & Kasici M (2007) Effectiveness of bran supplement in older orthopaedic patients with constipation. *Journal of Clinical Nursing* **16**, 928-936.
Kalliomäki M, Carmen Collado M, Salminen S & Isolauri E (2008) Early differences in fecal microbiota composition in children may predict overweight. *The American Journal of Clinical Nutrition* **87**, 534-538.
Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S & Isolauri E (2001) Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* **107**, 129-134.
Kanauchi O, Fujiyama Y, Mitsuyama K, Araki Y, Ishii T, Nakamura T, Hitomi Y, Agata K, Saiki T, Andoh A, Toyonaga A & Bamba T (1999) Increased growth of Bifidobacterium and Eubacterium by germinated barley foodstuff, accompanied by enhanced butyrate production in healthy volunteers. *International Journal of Molecular Medicine* **3**, 175-179.
Kanauchi O, Mitsuyama K, Saiki T, Fushikia T & Iwanaga T (1998a) Germinated barley foodstuff increases fecal volume and butyrate production in humans. *International Journal of Molecular Medicine* **1**, 937-941.
Kanauchi O, Mitsuyama K, Saiki T, Nakamura T, Hitomi Y, Bamba T, Araki Y & Fujiyama Y (1998b) Germinated barley foodstuff increases fecal volume and butyrate production at relatively low doses and relieves constipation in humans. *International Journal of Molecular Medicine* **2**, 445-450.
Kanazawa K, Konishi F, Mitsuoka T, Terada A, Itoh K, Narushima S, Kumemura M & Kimura H (1996) Factors influencing the development of sigmoid colon cancer. Bacteriologic and biochemical studies. *Cancer* **77**, 1701-1706.
Kaneko K, Nishida K, Yatsuda J, Osa S & Koike G (1986) Effect of fiber on protein, fat and calcium digestibilities and fecal cholesterol excretion. *Journal of Nutritional Science and Vitaminology* **32**, 317-325.
Kashtan H, Stern H, Jenkins D, Jenkins A, Thompson L, Hay K, Marcon N, Minkin S & Bruce W (1992a) Colonic fermentation and markers of colorectal-cancer risk. *Am J Clin Nutr* **55**, 723-728.
Kashtan H, Stern HS, Jenkins DJ, Jenkins AL, Thompson LU, Hay K, Marcon N, Minkin S & Bruce WR (1992b) Colonic fermentation and markers of colorectal-cancer risk. *American Journal of Clinical Nutrition* **55**, 723-728.
Kashtan H, Stern HS, Jenkins DJA, Gregoire R, Hay K, Jenkins AL, Minkin S & Bruce WR (1990) Manipulation of fecal pH by dietary means. *Preventive Medicine* **19**, 607-613.
Kassinen A, Krogius-Kurikka L, Makivuokko H, Rinttila T, Paulin L, Corander J, Malinen E, Apajalahti J & Palva A (2007) The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology* **133**, 24-33.
Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE & Riboli E (1997) Prospective

study of diet and female colorectal cancer: the New York University Women's Health Study. *Nutr Cancer* **28**, 276-281.
Kawatra A, Bhat CM & Arora A (1993) Effect of isabgol husk supplementation in a low-fibre diet on serum levels and calcium, phosphorus and iron balance in adolescent girls. *European Journal of Clinical Nutrition* **47**, 297-300.
Kay RM & Truswell AS (1977) The effect of wheat fibre on plasma lipids and faecal steroid excretion in man. *British Journal of Nutrition* **37**, 227-235.
Kearney J, Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing A, Kampman E & Willett WC (1996) Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol* **143**, 907-917.
Keathley JD & Needham CA (1982) Analysis of the Fecal Microflora and Its Enzymatic Activity in Individuals Genetically Predisposed to Colon Cancer. *Cancer Res* **42**, 4284-4288.
Kelleher J, Walters MP & Srinivasan TR (1984) Degradation of cellulose within the gastrointestinal tract in man. *Gut* **25**, 811-815.
Kelly SE, Chawla-Singh K & Sellin JH (1984) Effect of meal composition on calcium absorption: Enhancing effect of carbohydrate polymers. *Gastroenterology* **87**, 596-600.
Kelsay JL, Behall KM & Prather ES (1978) Effect of fiber from fruits and vegetables on metabolic responses of human subjects I. Bowel transit time, number of defecations, fecal weight, urinary excretions of energy and nitrogen and apparent digestibilities of energy, nitrogen, and fat. *American Journal of Clinical Nutrition* **31**, 1149-1153.
Kelsay JL, Clark WM, Herbst BJ & Prather ES (1981) Nutrient utilization by human subjects consuming fruits and vegetables as sources of fiber. *J Agric Food Chem* **29**, 461-465.
Kelsay JL & Prather ES (1983) Mineral balances of human subjects consuming spinach in a low-fiber diet and in a diet containing fruits and vegetables. *American Journal of Clinical Nutrition* **38**, 12-19.
Kelsay JL, Prather ES, Clark WM & Canary JJ (1988) Mineral balances of men fed a diet containing fiber in fruits and vegetables and oxalic acid in spinach for six weeks. *Journal of Nutrition* **118**, 1197-1204.
Kesaniemi YA, Tarpila S & Miettinen TA (1990) Low vs high dietary fiber and serum, biliary, and fecal lipids in middle-aged men. *American Journal of Clinical Nutrition* **51**, 1007-1012.
Khaja M, Thakur CS, Bharathan T, Baccash E & Goldenberg G (2005) 'Fiber 7' supplement as an alternative to laxatives in a nursing home. *Gerodontology* **22**, 106-108.
Kim SH, Lee da H & Meyer D (2007) Supplementation of baby formula with native inulin has a prebiotic effect in formula-fed babies. *Asia Pacific Journal of Clinical Nutrition* **16**, 172-177.
Kinnunen O, Winblad I, Koistinen P & Salokannel J (1993) Safety and efficacy of a bulk laxative containing senna versus lactulose in the treatment of chronic constipation in geriatric patients. *Pharmacology* **47 Suppl 1**, 253-255.
Kinzler KW & Vogelstein B (1996) Lessons from hereditary colorectal cancer. *Cell* **87**, 159-170.
Kirby RW, Anderson JW & Sieling B (1981) Oat-bran intake selectively lowers serum low-density lipoprotein cholesterol concentrations of hypercholesterolemic men. *American Journal of Clinical Nutrition* **34**, 824-829.
Kirjavainen PV, Arvola T, Salminen SJ & Isolauri E (2002) Aberrant composition of gut microbiota of allergic infants: a target of bifidobacterial therapy at weaning? *Gut* **51**, 51-55.
Kirwan WO & Smith AN (1974) Gastrointestinal transit estimated by an isotope capsule.

Scandinavian Journal of Gastroenterology **9**, 763-766.
Kitler ME, Luginbuhl M, Lang O, Wuhl F, Wyss A & Lebek G (1992) Lactitol and lactulose. An in vivo and in vitro comparison of their effects on the human intestinal flora. *Drug Investigation* **4**, 73-82.
Klaassens ES, Boesten RJ, Haarman M, Knol J, Schuren FH, Vaughan EE & de Vos WM (2009) Mixed-species genomic microarray analysis of fecal samples reveals differential transcriptional responses of bifidobacteria in breast- and formula-fed infants. *Applied & Environmental Microbiology* **75**, 2668-2676.
Kleessen B, Schwarz S, Boehm A, Fuhrmann H, Richter A, Henle T & Krueger M (2007) Jerusalem artichoke and chicory inulin in bakery products affect faecal microbiota of healthy volunteers. *British Journal of Nutrition* **98**, 540-549.
Kleessen B, Sykura B, Zunft H & Blaut M (1997) Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons. *American Journal of Clinical Nutrition* **65**, 1397-1403.
Kneepkens CM & Hoekstra JH (1996) Chronic nonspecific diarrhea of childhood: pathophysiology and management. *Pediatric Clinics of North America* **43**, 375-390.
Kneepkens CM, Jakobs C & Douwes AC (1989) Apple juice, fructose, and chronic nonspecific diarrhoea. *European Journal of Pediatrics* **148**, 571-573.
Knol J, Scholtens P, Kafka C, Steenbakkers J, Gro S, Helm K, Klarczyk M, Schopfer H, Bockler HM & Wells J (2005) Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: more like breast-fed infants. *Journal of Pediatric Gastroenterology and Nutrition* **40**, 36-42.
Knowles JB, Wood RJ & Rosenberg IH (1988) Response of fractional calcium absorption in women to various coadministered oral glucose doses. *American Journal of Clinical Nutrition* **48**, 1471-1474.
Knudsen E, Sandstrom B & Solgaard P (1996) Zinc, copper and magnesium absorption from a fibre-rich diet. *Journal of Trace Elements in Medicine & Biology* **10**, 68-76.
Kobayashi A, Kawai S, Obe Y & Nagashima Y (1975) Effects of dietary lactose and lactase preparation on the intestinal absorption of calcium and magnesium in normal infants. *American Journal of Clinical Nutrition* **28**, 681-683.
Kochen MM, Wegscheider K & Abholz HH (1985) Prophylaxis of constipation by wheat bran: a randomized study in hospitalized patients. *Digestion* **31**, 220-224.
Kocian J, Skala I & Bakos K (1973) Calcium absorption from milk and lactose-free milk in healthy subjects and patients with lactose intolerance. *Digestion* **9**, 317-324.
Koh WP, Yuan JM, van den Berg D, Lee HP & Yu MC (2004) Interaction between cyclooxygenase-2 gene polymorphism and dietary n-6 polyunsaturated fatty acids on colon cancer risk: the Singapore Chinese Health Study. *Br J Cancer* **90**, 1760-1764.
Kokke FT, Scholtens PA, Alles MS, Decates TS, Fiselier TJ, Tolboom JJ, Kimpen JL & Benninga MA (2008) A dietary fiber mixture versus lactulose in the treatment of childhood constipation: a double-blind randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition* **47**, 592-597.
Kolida S & Gibson GR (2007) Prebiotic Capacity of Inulin-Type Fructans. *J. Nutr.* **137**, 2503S-2506.
Kolida S, Meyer D & Gibson GR (2007) A double-blind placebo-controlled study to establish the bifidogenic dose of inulin in healthy humans. *European Journal of Clinical Nutrition* **61**, 1189-1195.
Kontraszti M, Hudson GJ & Englyst HN (1999) Dietary fibre in Hungarian foods measured by the Englyst NSP procedure and the AOAC Prosky procedure: a comparison study. *Food Chemistry* **64**, 445-450.
Koornhof HJ, Richardson NJ, Wall DM & Moore WE (1979) Fecal bacteria in South African

rural blacks and other population groups. *Isr J Med Sci* **15**, 335-340.
Korpela JT, Korpela R & Adlercreutz H (1992) Fecal bile acid metabolic pattern after administration of different types of bread. *Gastroenterology* **103**, 1246-1253.
Kretsch MJ, Crawford L & Calloway DH (1979) Some aspects of bile acid and urobilinogen excretion and fecal elimination in men given a rural Guatemalan diet and egg formulas with and without added oat bran. *American Journal of Clinical Nutrition* **32**, 1492-1496.
Kristin W, Peter NB, Thorsten VS, Edwin M, Penny F, Gerald WT, Gordon P & Julian C (2008) A differential effect of 2 probiotics in the prevention of eczema and atopy: A double-blind, randomized, placebo-controlled trial. *The Journal of allergy and clinical immunology* **122**, 788-794.
Krogius-Kurikka L, Lyra A, Malinen E, Aarnikunnas J, Tuimala J, Paulin L, Makivuokko H, Kajander K & Palva A (2009) Microbial community analysis reveals high level phylogenetic alterations in the overall gastrointestinal microbiota of diarrhoea-predominant irritable bowel syndrome sufferers. *BMC Gastroenterology* **9**.
Kruis W, Forstmaier G, Scheurlen C & Stellaard F (1991) Effect of diets low and high in refined sugars on gut transit, bile acid metabolism, and bacterial fermentation. *Gut* **32**, 367-371.
Kruis W, Weinzierl M, Schussler P & Holl J (1986) Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with the irritable bowel syndrome. *Digestion* **34**, 196-201.
Kruse HP, Kleessen B & Blaut M (1999) Effects of inulin on faecal bifidobacteria in human subjects. *British Journal of Nutrition* **82**, 375-382.
Kumar A, Kumar N & Vij JC (1987) Optimum dosage of ispaghula husk in patients with irritable bowel syndrome: Correlation of symptom relief with whole gut transit time and stool weight. *Gut* **28**, 150-155.
Kune GA, Kune S, Field B & Watson LF (1988) The role of chronic constipation, diarrhea, and laxative use in the etiology of large-bowel cancer. Data from the Melbourne Colorectal Cancer Study. *Dis Colon Rectum* **31**, 507-512.
Kunz C, Rodriguez-Palmero M, Koletzko B & Jensen R (1999) Nutritional and biochemical properties of human milk, Part I: General aspects, proteins, and carbohydrates. *Clin Perinatol* **26**, 307-333.
Kurpad AV, Holmes J & Shetty PS (1988) Effect of fibre supplementation and activated charcoal on faecal parameters and transits in the tropics. *Indian Journal of Gastroenterology* **7**, 199-201.
Ladas SD, Haritos DN & Raptis SA (1995) Honey may have a laxative effect on normal subjects because of incomplete fructose absorption. *American Journal of Clinical Nutrition* **62**, 1212-1215.
Lampe JW, Fredstrom SB, Slavin JL & Potter JD (1993a) Sex differences in colonic function: a randomised trial. *Gut* **34**, 531-536.
Lampe JW, Slavin JL, Melcher EA & Potter JD (1992) Effects of cereal and vegetable fiber feeding on potential risk factors for colon cancer. *Cancer Epidemiology, Biomarkers & Prevention* **1**, 207-211.
Lampe JW, Wetsch RF, Thompson WO & Slavin JL (1993b) Gastrointestinal effects of sugarbeet fiber and wheat bran in healthy men. *European Journal of Clinical Nutrition* **47**, 543-548.
Langlands SJ, Hopkins MJ, Coleman N & Cummings JH (2004) Prebiotic carbohydrates modify the mucosa associated microflora of the human large bowel. *Gut* **53**, 1610-1616.
Lanza E, Yu B, Murphy G, Albert PS, Caan B, Marshall JR, Lance P, Paskett ED, Weissfeld

J, Slattery M, Burt R, Iber F, Shike M, Kikendall JW, Brewer BK & Schatzkin A (2007) The Polyp Prevention Trial–Continued Follow-up Study: No Effect of a Low-Fat, High-Fiber, High-Fruit, and -Vegetable Diet on Adenoma Recurrence Eight Years after Randomization. *Cancer Epidemiology Biomarkers & Prevention* **16**, 1745-1752.

Larsson SC, Giovannucci E, Bergkvist L & Wolk A (2005) Whole grain consumption and risk of colorectal cancer: a population-based cohort of 60,000 women. *Br J Cancer* **92**, 1803-1807.

Larsson SC, Giovannucci E & Wolk A (2007) Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol* **165**, 256-261.

Leahy AL, Ellis RM, Quill DS & Peel AL (1985) High fibre diet in symptomatic diverticular disease of the colon. *Annals of the Royal College of Surgeons of England* **67**, 173-174.

Lebenthal-Bendor Y, Theuer RC, Lebenthal A, Tabi I & Lebenthal E (2001) Malabsorption of modified food starch (acetylated distarch phosphate) in normal infants and in 8-24-month-old toddlers with non-specific diarrhea, as influenced by sorbitol and fructose. *Acta Paediatrica* **90**, 1368-1372.

Lederle FA, Busch DL, Mattox KM, West MJ & Aske DM (1990) Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. *American Journal of Medicine* **89**, 597-601.

Lee J, Seto D & Bielory L (2008) Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *The Journal of allergy and clinical immunology* **121**, 116-121.e111.

Leeds A, Khumalo TD, Ndaba G & Lincoln D (1982) Haricot beans, transit time and stool weight. *J Plant Foods* **4**, 33.

Lembcke B, Ebert R & Ptok M (1984) Role of gastrointestinal transit in the delay of absorption by viscous fibre (guar). *Hepato-Gastroenterology* **31**, 183-186.

Lembo A & Camilleri M (2003) Chronic Constipation. *New England Journal of Medicine* **349**, 1360-1368.

Levitt MD, Hirsh P, Fetzer CA, Sheahan M & Levine AS (1987) H2 excretion after ingestion of complex carbohydrates. *Gastroenterology* **92**, 383-389.

Levy RD, Segal I, Hassan H & Saadia R (1994) Stool weight and faecal pH in two South African populations with a dissimilar colon cancer risk. *S Afr J Surg* **32**, 127-128; discussion 128-129.

Lewis S, Burmeister S & Brazier J (2005a) Effect of the prebiotic oligofructose on relapse of Clostridium difficile-associated diarrhea: a randomized, controlled study. *Clinical Gastroenterology & Hepatology* **3**, 442-448.

Lewis S, Burmeister S, Cohen S, Brazier J & Awasthi A (2005b) Failure of dietary oligofructose to prevent antibiotic-associated diarrhoea. *Alimentary Pharmacology and Therapeutics* **21**, 469-477.

Lewis SJ & Heaton KW (1997a) Increasing butyrate concentration in the distal colon by accelerating intestinal transit. *Gut* **41**, 245-251.

Lewis SJ & Heaton KW (1997b) The intestinal effects of bran-like plastic particles: is the concept of 'roughage' valid after all? *European Journal of Gastroenterology and Hepatology* **9**, 553-557.

Lewis SJ & Heaton KW (1997c) Stool Form Scale as a Useful Guide to Intestinal Transit Time. *Scandinavian Journal of Gastroenterology* **32**, 920-924.

Lewis SJ & Heaton KW (1999) The metabolic consequences of slow colonic transit. *Am J Gastroenterol* **94**, 2010-2016.

Ley RE, Turnbaugh PJ, Klein S & Gordon JI (2006) Microbial ecology: Human gut microbes associated with obesity. *Nature* **444**, 1022-1023.
Li J, Kaneko T, Qin LQ, Wang J & Wang Y (2003) Effects of barley intake on glucose tolerance, lipid metabolism, and bowel function in women. *Nutrition* **19**, 926-929.
Lifschitz CH (2000) Carbohydrate absorption from fruit juices in infants. *Pediatrics* **105**.
Liljeberg Elmstahl H (2002) Resistant starch content in a selection of starchy foods on the Swedish market. *European Journal of Clinical Nutrition* **56**, 500-505.
Lin J, Zhang SM, Cook NR, Lee IM & Buring JE (2004) Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Epidemiol* **160**, 1011-1022.
Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, Lee IM & Buring JE (2005) Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). *Cancer Causes Control* **16**, 225-233.
Little J, Owen RW, Fernandez F, Hawtin PG, Hill MJ, Logan RF, Thompson MH & Hardcastle JD (2002) Asymptomatic colorectal neoplasia and fecal characteristics: a case-control study of subjects participating in the nottingham fecal occult blood screening trial. *Diseases of the Colon & Rectum* **45**, 1233-1241.
Liu YJ, Cheng HC, Wang JH & Chen HL (2005) Effects of konjac glucomannan on the defecation characteristics and nutritional status in healthy adults. *Nutritional Sciences Journal* **30**, 127-134.
Livesey G (2001) Tolerance of low-digestible carbohydrates: a general view. *British Journal of Nutrition* **85 Suppl 1**, S7-16.
Loeb H, Vandenplas Y, Wursch P & Guesry P (1989) Tannin-rich carob pod for the treatment of acute-onset diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* **8**, 480-485.
Loening-Baucke V, Miele E & Staiano A (2004) Fiber (glucomannan) is beneficial in the treatment of childhood constipation. *Pediatrics* **113**, e259-264.
Longstreth GF, Fox DD & Youkeles L (1981) Psyllium therapy in the irritable bowel syndrome. A double-blind trial. *Annals of Internal Medicine* **95**, 53-56.
Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F & Spiller RC (2006) Functional Bowel Disorders. *Gastroenterology* **130**, 1480-1491.
Lopez-Huertas E, Teucher B, Boza JJ, Martinez-Ferez A, Majsak-Newman G, Baro L, Carrero JJ, Gonzalez-Santiago M, Fonolla J & Fairweather-Tait S (2006) Absorption of calcium from milks enriched with fructo-oligosaccharides, caseinophosphopeptides, tricalcium phosphate, and milk solids. *Am J Clin Nutr* **83**, 310-316.
Lucey MR, Clark ML, Lowndes J & Dawson AM (1987) Is bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study. *Gut* **28**, 221-225.
Lupton JR, Morin JL & Robinson MC (1993) Barley bran flour accelerates gastrointestinal transit time. *Journal of the American Dietetic Association* **93**, 881-885.
Maclennan R & Jensen OM (1977) Dietary fibre, transit-time, faecal bacteria, steroids, and colon cancer in two Scandinavian populations. Report from the International Agency for Research on Cancer Intestinal Microecology Group. *Lancet* **2**, 207-211.
MacLennan R, Jensen OM, Mosbech J & Vuori H (1978) Diet, transit time, stool weight, and colon cancer in two Scandinavian populations. *Am J Clin Nutr* **31**, S239-S242.
MacLennan R, Macrae F, Bain C, Battistutta D, Chapuis P, Gratten H, Lambert J, Newland RC, Ngu M, Russell A, Ward M, Wahlqvist ML & the Australian Polyp Prevention P (1995) Randomized Trial of Intake of Fat, Fiber, and Beta Carotene to Prevent Colorectal Adenomas. *J. Natl. Cancer Inst.* **87**, 1760-1766.
Maclennan R, Macrae F, Bain C & Newland RC (1999) Effect of fat, fibre, and beta carotene

intake on colorectal adeniomas: Further analysis of a randomized controlled dietary intervention trial after colonscopic polypectomy. *Asia Pac J Clin Nutr* **8(Suppl)**, S54-58.
Macrae TF, Hutchinson JC, Irwin JO, BaconJ.S. & McDougall EI (1942) Comparative digestibility of wholemeal and white breads and the effect of the degree of fineness and grinding on the former. *J Hyg Camb* **42**, 423-435.
Madeo M, Whitlock M & Martin CR (1999) A randomized controlled trial comparing Lactobacillus combined with Bifidobacterium bifidum against fructo-oligosaccharides in reducing the incidence of antibiotic-associated diarrhoea: a preliminary investigation. *Clinical Effectiveness in Nursing* **3**, 83-88.
Madsen JL, Linnet J & Rumessen JJ (2006) Effect of nonabsorbed amounts of a fructose-sorbitol mixture on small intestinal transit in healthy volunteers. *Digestive Diseases and Sciences* **51**, 147-153.
Magne F, Hachelaf W, Suau A, Boudraa G, Bouziane-Nedjadi K, Rigottier-Gois L, Touhami M, Desjeux JF & Pochart P (2008) Effects on faecal microbiota of dietary and acidic oligosaccharides in children during partial formula feeding. *Journal of Pediatric Gastroenterology and Nutrition* **46**, 580-588.
Mah KW, Bjorksten B, Lee BW, van Bever HP, Shek LP, Tan TN, Lee YK & Chua KY (2006) Distinct pattern of commensal gut microbiota in toddlers with eczema. *Int Arch Allergy Immunol* **140**, 157-163.
Mai V, Flood A, Peters U, Lacey JV, Jr., Schairer C & Schatzkin A (2003) Dietary fibre and risk of colorectal cancer in the Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort. *Int J Epidemiol* **32**, 234-239.
Mai V & Morris JG, Jr. (2004) Colonic Bacterial Flora: Changing Understandings in the Molecular Age. *J. Nutr.* **134**, 459-464.
Maki KC, Sanders LM, Reeves MS, Kaden VN, Rains TM & Cartwright Y (2009) Beneficial effects of resistant starch on laxation in healthy adults. *International Journal of Food Sciences and Nutrition* **60 Suppl 4**, 296-305.
Malhotra S (1982) Faecal urobilinogen levels and pH of stools in population groups with different incidence of cancer of the colon, and their possible role in its aetiology. *J R Soc Med* **75**, 709-714.
Malinen E, Rinttila T, Kajander K, Matto J, Kassinen A, Krogius L, Saarela M, Korpela R & Palva A (2005) Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. *American Journal of Gastroenterology* **100**, 373-382.
Mann J, Cummings JH, Englyst HN, Key T, Liu S, Riccardi G, Summerbell C, Uauy R, van Dam RM, Venn B, Vorster HH & Wiseman M (2007) FAO/WHO Scientific Update on carbohydrates in human nutrition: conclusions. *Eur J Clin Nutr* **61**, S132-S137.
Manning AP, Heaton KW & Harvey RF (1977) Wheat fibre and irritable bowel syndrome. A controlled trial. *Lancet* **2**, 417-418.
Mantle J (1992) Research and serendipitous secondary findings. *Canadian Nurse* **88**, 15-18.
Marcus SN & Heaton KW (1986) Effects of a new, concentrated wheat fibre preparation on intestinal transit, deoxycholic acid metabolism and the composition of bile. *Gut* **27**, 893-900.
Marks MM (1949) Cellulose esters in the treatment of constipation. *American Journal of Digestive Diseases* **16**, 215.
Marlett JA, Balasubramanian R, Johnson EJ & Draper NR (1986) Determining compliance with a dietary fiber supplement. *Journal of the National Cancer Institute* **76**, 1065-1070.
Marlett JA, Kajs TM & Fischer MH (2000) An unfermented gel component of psyllium seed

husk promotes laxation as a lubricant in humans. *American Journal of Clinical Nutrition* **72**, 784-789.
Marlett JA, Li BU, Patrow CJ & Bass P (1987) Comparative laxation of psyllium with and without senna in an ambulatory constipated population. *American Journal of Gastroenterology* **82**, 333-337.
Marteau P, Flourie B, Cherbut C, Correze JL, Pellier P, Seylaz J & Rambaud JC (1994) Digestibility and bulking effect of ispaghula husks in healthy humans. *Gut* **35**, 1747-1752.
Martensson O, Biorklund M, Lambo AM, Duenas-Chasco M, Irastorza A, Holst O, Norin E, Welling G, Oste R & Onning G (2005) Fermented, ropy, oat-based products reduce cholesterol levels and stimulate the bifidobacteria flora in humans. *Nutrition Research* **25**, 429-442.
Marzio L, Del Bianco R, Donne MD, Pieramico O & Cuccurullo F (1989) Mouth-to-cecum transit time in patients affected by chronic constipation: effect of glucomannan. *American Journal of Gastroenterology* **84**, 888-891.
Mathur MS, Ram H & Chadda VS (1978) Effect of bran on intestinal transit time in normal Indians and in intestinal amoebiasis. *American Journal of Proctology, Gastroenterology and Colon and Rectal Surgery* **29**, 30-32, 34.
Matto J, Maunuksela L, Kajander K, Palva A, Korpela R, Kassinen A & Saarela M (2005) Composition and temporal stability of gastrointestinal microbiota in irritable bowel syndrome--a longitudinal study in IBS and control subjects. *FEMS Immunology and Medical Microbiology* **43**, 213-222.
McCallum G, Ballinger BR & Presly AS (1978) A trial of bran and bran biscuits for constipation in mentally handicapped and psychogeriatric patients. *Journal of Human Nutrition* **32**, 369-372.
McCance RA & Lawrence RD (1929) The carbohydrate content of foods. Medical research council special report series no. 135. London.
McCance RA & Widdowson EM (1942a) Mineral metabolism of healthy adults on white and brown bread dietaries. *The Journal of Physiology* **101**, 44-85.
McCance RA & Widdowson EM (1942b) Mineral metabolism on dephytinized bread. *The Journal of Physiology* **101**, 304-313.
McCarl M, Harnack L, Limburg PJ, Anderson KE & Folsom AR (2006) Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev* **15**, 892-896.
McCleary BV (2003) Dietary fibre analysis. *Proceedings of the Nutrition Society* **62**, 3-9.
McCleary BV (2007) An integrated procedure for the measurement of total dietary fibre (including resistant starch), non-digestible oligosaccharides and available carbohydrates. *Anal Bioanal Chem* **389**, 291-308.
McCullough ML, Robertson AS, Chao A, Jacobs EJ, Stampfer MJ, Jacobs DR, Diver WR, Calle EE & Thun MJ (2003) A prospective study of whole grains, fruits, vegetables and colon cancer risk. *Cancer Causes Control* **14**, 959-970.
McDougall CJ, Wong R, Scudera P, Lesser M & DeCosse JJ (1993) Colonic mucosal pH in humans. *Dig Dis Sci* **38**, 542-545.
McFarland LV (2007) Meta-analysis of probiotics for the prevention of traveler's diarrhea. *Travel Med Infect Dis* **5**, 97-105.
McIntosh GH, Noakes M, Royle PJ & Foster PR (2003) Whole-grain rye and wheat foods and markers of bowel health in overweight middle-aged men. *American Journal of Clinical Nutrition* **77**, 967-974.
McKeown-Eyssen GE, Bright-See E, Bruce WR, Jazmaji V, Cohen LB, Pappas SC & Saibil FG (1994) A randomized trial of a low fat high fibre diet in the recurrence of

colorectal polyps. Toronto Polyp Prevention Group. *J Clin Epidemiol* **47**, 525-536.
McNamara EA, Levine A, Levitt M & Slavin JL (1985) Hydrogen and methane production by human subjects consuming various diets with and without dietary fiber. *Nutrition Research* **5**, 1199-1207.
McRorie J, Kesler J, Bishop L, Filloon T, Allgood G, Sutton M, Hunt T, Laurent A & Rudolph C (2000) Effects of wheat bran and Olestra on objective measures of stool and subjective reports of GI symptoms. *American Journal of Gastroenterology* **95**, 1244-1252.
McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB & Robinson M (1998) Psyllium is superior to docusate sodium for treatment of chronic constipation. *Alimentary Pharmacology and Therapeutics* **12**, 491-497.
Melcher EA, Levitt MD & Slavin JL (1991a) Methane production and bowel function parameters in healthy subjects on low- and high-fiber diets. *Nutrition and Cancer* **16**, 85-92.
Melcher EA, Levitt MD & Slavin JL (1991b) Reports. Methane production and bowel function parameters in healthy subjects on low- and high-fiber diets. *Nutrition and Cancer* **16**, 85-92.
Menne E, Guggenbuhl N & Roberfroid M (2000) Fn-type chicory inulin hydrolysate has a prebiotic effect in humans. *Journal of Nutrition* **130**, 1197-1199.
Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW & Wolff BG (1987) Simplified assessment of segmental colonic transit. *Gastroenterology* **92**, 40-47.
Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA & Giovannucci E (2005) Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev* **14**, 138-147.
Michels KB, Fuchs CS, Giovannucci E, Colditz GA, Hunter DJ, Stampfer MJ & Willett WC (2005) Fiber Intake and Incidence of Colorectal Cancer among 76,947 Women and 47,279 Men. *Cancer Epidemiology Biomarkers Prevention* **14**, 842-849.
Miettinen TA & Tarpila S (1977) Effect of pectin on serum cholesterol, fecal bile acids and biliary lipids in normolipidemic and hyperlipidemic individuals. *Clinica Chimica Acta* **79**, 471-477.
Miettinen TA & Tarpila S (1989) Serum lipids and cholesterol metabolism during guar gum, plantago ovata and high fibre treatments. *Clinica Chimica Acta* **183**, 253-262.
Miles CW, Kelsay JL & Wong NP (1988) Effect of dietary fiber on the metabolizable energy of human diets. *Journal of Nutrition* **118**, 1075-1081.
Milne DB & Nielsen FH (2000) The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *Journal of the American College of Nutrition* **19**, 31-37.
Minamida K, Sujaya IN, Tamura A, Shigematsu N, Sone T, Yokota A, Asano K, Benno Y & Tomita F (2004) The effects of Di-D-fructofuranose-1,2':2,3'-dianhydride (DFA III) administration on human intestinal microbiota. *Journal of Bioscience and Bioengineering* **98**, 244-250.
Mitsou EK, Turunen K, Anapliotis P, Zisi D, Spiliotis V & Kyriacou A (2009) Impact of a jelly containing short-chain fructo-oligosaccharides and Sideritis euboea extract on human faecal microbiota. *International Journal of Food Microbiology* **135**, 112-117.
Mitsui T, Shimaoka K, Kanao Y & Kondo T (2001) Colonic fermentation after ingestion of fructose-containing sports drink. *Journal of Sports Medicine and Physical Fi ness* **41**, 121-123.
Miyoshi H, Okuda T, Oi Y & Koishi H (1986) Effects of rice fiber on fecal weight, apparent digestibility of energy, nitrogen and fat, and degradation of neutral detergent fiber in young men. *Journal of Nutritional Science and Vitaminology* **32**, 581-589.

Miyoshi H, Okuda T, Okuda K & Koishi H (1987) Effects of brown rice on apparent digestibility and balance of nutrients in young men on low protein diets. *Journal of Nutritional Science and Vitaminology* **33**, 207-218.
Monro JA (1991) Dietary fiber pectic substances: source of discrepancy between methods of fiber analysis. *J Food Comp Anal* **4**, 88-99.
Moore N, Chao C, Yang LP, Storm H, Oliva-Hemker M & Saavedra JM (2003) Effects of fructo-oligosaccharide-supplemented infant cereal: a double-blind, randomized trial. *British Journal of Nutrition* **90**, 581-587.
Moore W & Moore L (1995) Intestinal floras of populations that have a high risk of colon cancer. *Appl. Environ. Microbiol.* **61**, 3202-3207.
Moro G, Minoli I, Mosca M, Fanaro S, Jelinek J, Stahl B & Boehm G (2002) Dosage-related bifidogenic effects of galacto- and fructooligosaccharides in formula-fed term infants. *Journal of Pediatric Gastroenterology and Nutrition* **34**, 291-295.
Moro GE, Mosca F, Miniello V, Fanaro S, Jelinek J, Stahl B & Boehm G (2003) Effects of a new mixture of prebiotics on faecal flora and stools in term infants. *Acta Paediatrica Supplement* **91**, 77-79.
Moro GE, Stahl B, Fanaro S, Jelinek J, Boehm G & Coppa GV (2005) Dietary prebiotic oligosaccharides are detectable in the faeces of formula-fed infants. *Acta Paediatrica Supplement* **94**, 27-30.
Mortensen PB, Andersen JR, Arffmann S & Krag E (1987) Short-chain fatty acids and the irritable bowel syndrome: the effect of wheat bran. *Scandinavian Journal of Gastroenterology* **22**, 185-192.
Moukarzel AA, Lesicka H & Ament ME (2002) Irritable bowel syndrome and nonspecific diarrhea in infancy and childhood--relationship with juice carbohydrate malabsorption. *Clinical Pediatrics* **41**, 145-150.
Moya M, Cortes E, Ballester MI, Vento M & Juste M (1992) Short-term polycose substitution for lactose reduces calcium absorption in healthy term babies. *Journal of Pediatric Gastroenterology & Nutrition* **14**, 57-61.
Moya M, Lifschitz C, Ameen V & Euler AR (1999) A metabolic balance study in term infants fed lactose-containing or lactose-free formula. *Acta Paediatrica* **88**, 1211-1215.
Mrazek J, Koppova I, Kopecny J, Simunek J & Fliegerova K (2010) PCR-DGGE-based study of fecal microbial stability during the long-term chitosan supplementation of humans. *Folia Microbiologica* **55**, 352-358.
Muir JG & O'Dea K (1993) Validation of an in vitro assay for predicting the amount of starch that escapes digestion in the small intestine of humans. *American Journal of Clinical Nutrition* **57**, 540-546.
Muir JG, Walker KZ, Kaimakamis MA, Cameron MA, Govers MJ, Lu ZX, Young GP & O'Dea K (1998) Modulation of fecal markers relevant to colon cancer risk: a high-starch Chinese diet did not generate expected beneficial changes relative to a Western-type diet. *American Journal of Clinical Nutrition* **68**, 372-379.
Muir JG, Yeow EG, Keogh J, Pizzey C, Bird AR, Sharpe K, O'Dea K & Macrae FA (2004) Combining wheat bran with resistant starch has more beneficial effects on fecal indexes than does wheat bran alone. *American Journal of Clinical Nutrition* **79**, 1020-1028.
Munoz JM, Sandstead HH, Jacob RA, Logan GM, Jr., Reck SJ, Klevay LM, Dintzis FR, Inglett GE & Shuey WC (1979) Effects of some cereal brans and textured vegetable protein on plasma lipids. *American Journal of Clinical Nutrition* **32**, 580-592.
Murphy MM, Douglass JS & Birkett A (2008) Resistant Starch Intakes in the United States. *Journal of the American Dietetic Association* **108**, 67-78.

Myung HB, Ok SC & Woo KK (2007) Soyoligosaccharide increases fecal bifidobacteria counts, short-chain fatty acids, and fecal lipid concentrations in young Korean women. *Journal of Medicinal Food* **10**, 366-370.

Nagengast FM, van den Ban G, Ploemen JP, Leenen R, Zock PL, Katan MB, Hectors MP, de Haan AF & van Tongeren JH (1993) The effect of a natural high-fibre diet on faecal and biliary bile acids, faecal pH and whole-gut transit time in man. A controlled study. *European Journal of Clinical Nutrition* **47**, 631-639.

Nakamura N, Gaskins HR, Collier CT, Nava GM, Rai D, Petschow B, Russell WM, Harris C, Mackie RI, Wampler JL & Walker DC (2009) Molecular ecological analysis of fecal bacterial populations from term infants fed formula supplemented with selected blends of prebiotics. *Applied and Environmental Microbiology* **75**, 1121-1128.

Nakamura S, Hongo R, Moji K & Oku T (2007) Suppressive effect of partially hydrolyzed guar gum on transitory diarrhea induced by ingestion of maltitol and lactitol in healthy humans. *European Journal of Clinical Nutrition* **61**, 1086-1093.

Navaneethan U & Giannella RA (2008) Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol* **5**, 637-647.

Nigam P, Kapoor KK, Rastog CK, Kumar A & Gupta AK (1984) Different therapeutic regimens in irritable bowel syndrome. *Journal of the Association of Physicians of India* **32**, 1041-1044.

Nilsson U, Johansson M, Nilsson A, Bjorck I & Nyman M (2008) Dietary supplementation with beta-glucan enriched oat bran increases faecal concentration of carboxylic acids in healthy subjects. *European Journal of Clinical Nutrition* **62**, 978-984.

Niñonuevo MR & Lebrilla CB (2009) Mass spectrometric methods for analysis of oligosaccharides in human milk. *Nutrition Reviews* **67**, S216-S226.

Nishibata T, Tashiro K, Kanahori S, Hashizume C, Kitagawa M, Okuma K & Gordon DT (2009) Comprehensive Measurement of Total Nondigestible Carbohydrates in Foods by Enzymatic−Gravimetric Method and Liquid Chromatography. *Journal of Agricultural and Food Chemistry* **57**, 7659-7665.

Noakes M, Clifton PM, Nestel PJ, Le Leu R & McIntosh G (1996) Effect of high-amylose starch and oat bran on metabolic variables and bowel function in subjects with hypertriglyceridemia. *American Journal of Clinical Nutrition* **64**, 944-951.

Nobigrot T, Chasalow FI & Lifshitz F (1997) Carbohydrate absorption from one serving of fruit juice in young children: age and carbohydrate composition effects. *Journal of the American College of Nutrition* **16**, 152-158.

Nomura AM, Hankin JH, Henderson BE, Wilkens LR, Murphy SP, Pike MC, Marchand LL, Stram DO, Monroe KR & Kolonel LN (2007) Dietary fiber and colorectal cancer risk: the multiethnic cohort study. *Cancer Causes Control* **18**, 753-764.

Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjonneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, Gonzalez C, Navarro C, Quiros JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hemon B, Saracci R, Kaaks R & Riboli E (2005) Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* **97**, 906-916.

O'Donnell LJ, Virjee J & Heaton KW (1990) Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *British Medical Journal* **300**, 439-440.

O'Keefe SJ, Ou J, Aufreiter S, O'Connor D, Sharma S, Sepulveda J, Fukuwatari T, Shibata K & Mawhinney T (2009) Products of the colonic microbiota mediate the effects of diet

on colon cancer risk. *Journal of Nutrition* **139**, 2044-2048.
Odes HS, Lazovski H, Stern I & Madar Z (1993) Double-blind trial of a high dietary fiber, mixed grain cereal in patients with chronic constipation and hyperlipidemia. *Nutrition Research* **13**, 979-985.
Odes HS & Madar Z (1991) A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation. *Digestion* **49**, 65-71.
Ohkusa T, Ozaki Y, Sato C, Mikuni K & Ikeda H (1995) Long-term ingestion of lactosucrose increases Bifidobacterium sp. in human fecal flora. *Digestion* **56**, 415-420.
Oku T, Hongo R & Nakamura S (2008) Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in healthy female subjects. *Journal of Nutritional Science and Vitaminology* **54**, 309-314.
Olesen M & Gudmand-Hoyer E (2000) Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome. *American Journal of Clinical Nutrition* **72**, 1570-1575.
Olness K & Tobin J, Sr. (1982) Chronic constipation in children: can it be managed by diet alone? *Postgraduate Medicine* **72**, 149-154.
Ornstein MH, Littlewood ER, Baird IM, Fowler J, North WR & Cox AG (1981) Are fibre supplements really necessary in diverticular disease of the colon? A controlled clinical trial. *British Medical Journal Clinical Research Ed.* **282**, 1353-1356.
Osborn DA & Sinn JK (2007) Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev*, CD006475.
Otani T, Iwasaki M, Inoue M, Sasazuki S, Tsugane S & For The Japan Public Health Center-Based Prospective Study G (2006a) Bowel movement, state of stool, and subsequent risk for colorectal cancer: the Japan public health center-based prospective study. *Annals of Epidemiology* **16**, 888-894.
Otani T, Iwasaki M, Ishihara J, Sasazuki S, Inoue M & Tsugane S (2006b) Dietary fiber intake and subsequent risk of colorectal cancer: the Japan Public Health Center-based prospective study. *Int J Cancer* **119**, 1475-1480.
Packey CD & Sartor RB (2009) Commensal bacteria, traditional and opportunistic pathogens, dysbiosis and bacterial killing in inflammatory bowel diseases. *Current Opinion in Infectious Diseases June* **22**, 292-301.
Paineau D, Payen F, Panserieu S, Coulombier G, Sobaszek A, Lartigau I, Brabet M, Galmiche JP, Tripodi D, Sacher-Huvelin S, Chapalain V, Zourabichvili O, Respondek F, Wagner A & Bornet FR (2008) The effects of regular consumption of short-chain fructo-oligosaccharides on digestive comfort of subjects with minor functional bowel disorders. *British Journal of Nutrition* **99**, 311-318.
Painter NS (1974) The high fibre diet in the treatment of diverticular disease of the colon. *Postgraduate Medical Journal* **50**, 629-635.
Painter NS, Almeida AZ & Colebourne KW (1972) Unprocessed bran in treatment of diverticular disease of the colon. *British Medical Journal* **2**, 137-140.
Pansu D & Chapuy MC (1970) Calcium absorption enhanced by lactose and xylose. *Calcified Tissue Research*, Suppl:155-156.
Parisi G, Bottona E, Carrara M, Cardin F, Faedo A, Goldin D, Marino M, Pantalena M, Tafner G, Verdianelli G, Zilli M & Leandro G (2005) Treatment effects of partially hydrolyzed guar gum on symptoms and quality of life of patients with irritable bowel syndrome. A multicenter randomized open trial. *Digestive Diseases and Sciences* **50**, 1107-1112.
Parisi GC, Zilli M, Miani MP, Carrara M, Bottona E, Verdianelli G, Battaglia G, Desideri S, Faedo A, Marzolino C, Tonon A, Ermani M & Leandro G (2002) High-fiber diet supplementation in patients with irritable bowel syndrome (IBS): a multicenter,

randomized, open trial comparison between wheat bran diet and partially hydrolyzed guar gum (PHGG). *Digestive Diseases and Sciences* **47**, 1697-1704.
Park E & Jhon D (2009) Effects of bamboo shoot consumption on lipid profiles and bowel function in healthy young women. *Nutrition* **25**, 723-729.
Park JY, Mitrou PN, Luben R, Khaw KT & Bingham SA (2009) Is bowel habit linked to colorectal cancer? - Results from the EPIC-Norfolk study. *European Journal of Cancer* **45**, 139-145.
Park Y, Hunter DJ, Spiegelman D, Bergkvist L, Berrino F, van den Brandt PA, Buring JE, Colditz GA, Freudenheim JL, Fuchs CS, Giovannucci E, Goldbohm RA, Graham S, Harnack L, Hartman AM, Jacobs DR, Jr., Kato I, Krogh V, Leitzmann MF, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zhang SM & Smith-Warner SA (2005) Dietary Fiber Intake and Risk of Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies. *JAMA* **294**, 2849-2857.
Parkes GC, Sanderson JD & Whelan K (2010) Treating irritable bowel syndrome with probiotics: the evidence. *Proceedings of the Nutrition Society* **69**, 187-194.
Parsons DS (1973) Dietary fibre, stool output, and transit-time. *Lancet* **1**.
Pasman W, Wils D, Saniez MH & Kardinaal A (2006) Long-term gastrointestinal tolerance of NUTRIOSEFB in healthy men. *European Journal of Clinical Nutrition* **60**, 1024-1034.
Passmore AP, Davies KW, Flanagan PG, Stoker C & Scott MG (1993a) A comparison of Agiolax and lactulose in elderly patients with chronic constipation. *Pharmacology* **47**, 249-252.
Passmore AP, Wilson-Davies K, Stoker C & Scott ME (1993b) Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination. *BMJ* **307**, 769-771.
Patrick PG, Gohman SM, Marx SC, DeLegge MH & Greenberg NA (1998) Effect of supplements of partially hydrolyzed guar gum on the occurrence of constipation and use of laxative agents. *Journal of the American Dietetic Association* **98**, 912-914.
Payler DK, Pomare EW, Heaton KW & Harvey RF (1975) The effect of wheat bran on intestinal transit. *Gut* **16**, 209-213.
Peach S, Fernandez F, Johnson K & Drasar BS (1974) The non-sporing anaerobic bacteria in human faeces. *J Med Microbiol* **7**, 213-221.
Penagini R, Velio P & Vigorelli R (1986) The effect of dietary guar on serum cholesterol, intestinal transit, and fecal output in man. *American Journal of Gastroenterology* **81**, 123-125.
Penders J, Stobberingh EE, Thijs C, Adams H, Vink C, Ree Rv & Brandt PAvd (2006) Molecular fingerprinting of the intestinal microbiota of infants in whom atopic eczema was or was not developing. *Clinical & Experimental Allergy* **36**, 1602-1608.
Penders J, Stobberingh EE, van den Brandt PA & Thijs C (2007a) The role of the intestinal microbiota in the development of atopic disorders. *Allergy* **62**, 1223-1236.
Penders J, Thijs C, Mommers M, Stobberingh EE, Dompeling E, Reijmerink NE, van den Brandt PA, Kerkhof M, Koppelman GH & Postma DS (2010) Intestinal lactobacilli and the DC-SIGN gene for their recognition by dendritic cells play a role in the aetiology of allergic manifestations. *Microbiology* **156**, 3298-3305.
Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F, Adams H, van Ree R & Stobberingh EE (2007b) Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut* **56**, 661-667.
Perkin JM (1977) Constipation in childhood: a controlled comparison between lactulose and standardized senna. *Current Medical Research and Opinion* **4**, 540-543.

Pers M & Pers B (1983) A crossover comparative study with two bulk laxatives. *Journal of International Medical Research* **11**, 51-53.
Phillips J, Muir JG, Birkett A, Lu ZX, Jones GP, O'Dea K & Young GP (1995) Effect of resistant starch on fecal bulk and fermentation-dependent events in humans. *American Journal of Clinical Nutrition* **62**, 121-130.
Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D & Virtamo J (1999) Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **10**, 387-396.
Pittaway JK, Ahuja KD, Robertson IK & Ball MJ (2007) Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *Journal of the American College of Nutrition* **26**, 334-340.
Portnoy BL, DuPont HL, Pruitt D, Abdo JA & Rodriguez JT (1976) Antidiarrheal agents in the treatment of acute diarrhea in children. *JAMA* **236**, 844-846.
Prior A & Whorwell PJ (1987) Double blind study of ispaghula in irritable bowel syndrome. *Gut* **28**, 1510-1513.
Prosky L, Asp NG, Furda I, DeVries JW, Schweizer TF & Harland BF (1985) Determination of total dietary fiber in foods and food products: collaborative study. *Journal - Association of Official Analytical Chemists* **68**, 677-679.
Prosky L, Asp NG, Schweizer TF, DeVries JW & Furda I (1988) Determination of insoluble, soluble, and total dietary fiber in foods and food products: interlaboratory study. *Journal - Association of Official Analytical Chemists* **71**, 1017-1023.
Prosky L, Asp NG, Schweizer TF, DeVries JW, Furda I & Lee SC (1994) Determination of soluble dietary fiber in foods and food products: collaborative study. *Journal of AOAC International* **77**, 690-694.
Prynne CJ & Southgate DA (1979) The effects of a supplement of dietary fibre on faecal excretion by human subjects. *British Journal of Nutrition* **41**, 495-503.
Pye G, Evans DF, Ledingham S & Hardcastle JD (1990) Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma. *Gut* **31**, 1355-1357.
Quah HM, Ooi BS, Seow-Choen F, Sng KK & Ho KS (2006) Prospective randomized crossover trial comparing fibre with lactulose in the treatment of idiopathic chronic constipation. *Techniques in Coloproctology* **10**, 111-114.
Quigley ME & Englyst HN (1994) Determination of the uronic acid constituents of non-starch polysaccharides by high-performance liquid chromatography with pulsed amperometric detection. *Analyst* **119**, 1511-1518.
Qvitzau S, Matzen P & Madsen P (1988) Treatment of chronic diarrhoea: loperamide versus ispaghula husk and calcium. *Scandinavian Journal of Gastroenterology* **23**, 1237-1240.
Rabbani GH, Teka T, Zaman B, Majid N, Khatun M & Fuchs GJ (2001) Clinical studies in persistent diarrhea: dietary management with green banana or pectin in Bangladeshi children. *Gastroenterology* **121**, 554-560.
Raghupathy P, Ramakrishna BS, Oommen SP, Ahmed MS, Priyaa G, Dziura J, Young GP & Binder HJ (2006) Amylase-resistant starch as adjunct to oral rehydration therapy in children with diarrhea. *Journal of Pediatric Gastroenterology and Nutrition* **42**, 362-368.
Rahimi R, Nikfar S, Rahimi F, Elahi B, Derakhshani S, Vafaie M & Abdollahi M (2008) A Meta-Analysis on the Efficacy of Probiotics for Maintenance of Remission and Prevention of Clinical and Endoscopic Relapse in Crohn's Disease. *Digestive Diseases and Sciences* **53**, 2524-2531.
Rajala SA, Salminen SJ, Seppanen JH & Vapaatalo H (1988) Treatment of chronic constipation with lactitol sweetened yoghurt supplemented with guar gum and wheat

bran in elderly hospital in-patients. *Comprehensive Gerontology. Section A, Clinical and Laboratory Sciences* **2**, 83-86.
Ramakrishna BS, Subramanian V, Mohan V, Sebastian BK, Young GP, Farthing MJ & Binder HJ (2008) A randomized controlled trial of glucose versus amylase resistant starch hypo-osmolar oral rehydration solution for adult acute dehydrating diarrhea. *PLoS ONE [Electronic Resource]* **3**.
Ramakrishna BS, Venkataraman S, Srinivasan P, Dash P, Young GP & Binder HJ (2000) Amylase-resistant starch plus oral rehydration solution for cholera. *New England Journal of Medicine* **342**, 308-313.
Ramirez-Farias C, Slezak K, Fuller Z, Duncan A, Holtrop G & Louis P (2009) Effect of inulin on the human gut microbiota: stimulation of Bifidobacterium adolescentis and Faecalibacterium prausnitzii. *British Journal of Nutrition* **101**, 541-551.
Ramnani P, Gaudier E, Bingham M, van Bruggen P, Tuohy KM & Gibson GR (2010) Prebiotic effect of fruit and vegetable shots containing Jerusalem artichoke inulin: a human intervention study. *British Journal of Nutrition* **104**, 233-240.
Rao AV, Shiwnarain N, Koo M & Jenkins DJA (1994) Effect of fiber-rich foods on the composition of intestinal microflora. *Nutrition Research* **14**, 523-535.
Rao VA (2001) The prebiotic properties of oligofructose at low intake levels. *Nutrition Research* **21**, 843-848.
Ravelli GP, Whyte A, Spencer R, Hotten P, Harbron C & Keenan R (1995) The effect of lactitol intake upon stool parameters and the faecal bacterial flora in chronically constipated women. *Acta Therapeutica* **21**, 243-255.
Ravich WJ, Bayless TM & Thomas M (1983) Fructose: incomplete intestinal absorption in humans. *Gastroenterology* **84**, 26-29.
Raymond TL, Connor WE, Lin DS, Warner S, Fry MM & Connor SL (1977) The interaction of dietary fibers and cholesterol upon the plasma lipids and lipoproteins, sterol balance, and bowel function in human subjects. *Journal of Clinical Investigation* **60**, 1429-1437.
Reddy BS, Engle A, Simi B, O'Brien LT, Barnard RJ, Pritikin N & Wynder EL (1988) Effect of low-fat, high-carbohydrate, high-fiber diet on fecal bile acids and neutral sterols. *Preventive Medicine* **17**, 432-439.
Reddy BS, Hedges AR, Laakso K & Wynder EL (1978) Metabolic epidemiology of large bowel cancer: fecal bulk and constituents of high-risk North American and low-risk Finnish population. *Cancer* **42**, 2832-2838.
Rees G, Davies J, Thompson R, Parker M & Liepins P (2005) Randomised-controlled trial of a fibre supplement on the symptoms of irritable bowel syndrome. *Journal of the Royal Society of Health* **125**, 30-34.
Reinhold JG, Faradji B, Abadi P & Ismail-Beigi F (1976) Decreased absorption of calcium, magnesium, zinc and phosphorus by humans due to increased fiber and phosphorus consumption as wheat bread. *Journal of Nutrition* **106**, 493-503.
Ribeiro H, Jr., Ribeiro TC, Valois S, Mattos A & Lifshitz F (2001) Incomplete carbohydrate absorption from fruit juice consumption after acute diarrhea. *Journal of Pediatrics* **139**, 325-327.
Rigaud D, Ryttig KR, Leeds AR, Bard D & Apfelbaum M (1987) Effects of a moderate dietary fibre supplement on hunger rating, energy input and faecal energy output in young, healthy volunteers. A randomized, double-blind, cross-over trial. *International Journal of Obesity* **11 Suppl 1**, 73-78.
Ritchie JA & Truelove SC (1979) Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *British Medical Journal* **1**, 376-378.
Ritchie JA & Truelove SC (1980) Comparison of various treatments for irritable bowel

syndrome. *British Medical Journal* **281**, 1317-1319.
Roberts J, Jones GP, Rutishauser IHE, Birkett A & Gibbons C (2004) Resistant starch in the Australian diet. *Nutr Diet* **61**, 98-104.
Roberts MC, Millikan RC, Galanko JA, Martin C & Sandler RS (2003) Constipation, laxative use, and colon cancer in a North Carolina population. *Am J Gastroenterol* **98**, 857-864.
Robertson J, Brydon WG, Tadesse K, Wenham P, Walls A & Eastwood MA (1979) The effect of raw carrot on serum lipids and colon function. *American Journal of Clinical Nutrition* **32**, 1889-1892.
Robinson RR, Feirtag J & Slavin JL (2001) Effects of dietary arabinogalactan on gastrointestinal and blood parameters in healthy human subjects. *Journal of the American College of Nutrition* **20**, 279-285.
Rodrigues-Fisher L, Bourguignon C & Good BV (1993) Dietary fiber nursing intervention: prevention of constipation in older adults. *Clinical Nursing Research* **2**, 464-477.
Roediger WE (1990) The starved colon--diminished mucosal nutrition, diminished absorption, and colitis. *Dis Colon Rectum* **33**, 858-862.
Roediger WE, Heyworth M, Willoughby P, Piris J, Moore A & Truelove SC (1982) Luminal ions and short chain fatty acids as markers of functional activity of the mucosa in ulcerative colitis. *J Clin Pathol* **35**, 323-326.
Roger LC, Costabile A, Holland DT, Hoyles L & McCartney AL (2010) Examination of faecal Bifidobacterium populations in breast- and formula-fed infants during the first 18 months of life. *Microbiology* **156**, 3329-3341.
Roger LC & McCartney AL (2010) Longitudinal investigation of the faecal microbiota of healthy full-term infants using fluorescence in situ hybridization and denaturing gradient gel electrophoresis. *Microbiology* **156**, 3317-3328.
Ross AH, Eastwood MA, Brydon WG, Anderson JR & Anderson DM (1983) A study of the effects of dietary gum arabic in humans. *American Journal of Clinical Nutrition* **37**, 368-375.
Ross JK & Leklem JE (1981) The effect of dietary citrus pectin on the excretion of human fecal neutral and acid steroids and the activity of 7alpha-dehydroxylase and beta-glucuronidase. *American Journal of Clinical Nutrition* **34**, 2068-2077.
Rouse M, Chapman N, Mahapatra M, Grillage M, Atkinson SN & Prescott P (1991) An open, randomised, parallel group study of lactulose versus ispaghula in the treatment of chronic constipation in adults. *British Journal of Clinical Practice* **45**, 28-30.
Rumessen JJ (1992) Fructose and related food carbohydrates. Sources, intake, absorption, and clinical implications. *Scandinavian Journal of Gastroenterology* **27**, 819-828.
Rumessen JJ, Bode S, Hamberg O & Gudmand-Hoyer E (1990) Fructans of Jerusalem artichokes: Intestinal transport, absorption, fermentation, and influence on blood glucose, insulin, and C-peptide responses in healthy subjects. *American Journal of Clinical Nutrition* **52**, 675-681.
Saad RJ, Rao SS, Koch KL, Kuo B, Parkman HP, McCallum RW, Sitrin MD, Wilding GE, Semler JR & Chey WD (2010) Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. *American Journal of Gastroenterology* **105**, 403-411.
Sairanen U, Piirainen L, Nevala R & Korpela R (2007) Yoghurt containing galacto-oligosaccharides, prunes and linseed reduces the severity of mild constipation in elderly subjects. *European Journal of Clinical Nutrition* **61**, 1423-1428.
Saito T, Hayakawa T, Nakamura K, Takita T, Suzuki K & Innami S (1991) Fecal output, gastrointestinal transit time, frequency of evacuation and apparent excretion rate of dietary fiber in young men given diets containing different levels of dietary fiber.

Journal of Nutritional Science and Vitaminology **37**, 493-508.
Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL & Willett WC (1997a) Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* **20**, 545-550.
Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL & Willett WC (1997b) Dietary Fiber, Glycemic Load, and Risk of Non--insulin-dependent Diabetes Mellitus in Women. *JAMA* **277**, 472-477.
Salminen S, Salminen E, Koivistoinen P, Bridges J & Marks V (1985) Gut microflora interactions with xylitol in the mouse, rat and man. *Food and Chemical Toxicology* **23**, 985-990.
Salonen A, de Vos WM & Palva A (2010) Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. *Microbiology* **156**, 3205-3215.
Sandman PO, Adolfsson R, Hallmans G, Nygren C, Nystrom L & Winblad B (1983) Treatment of constipation with high-bran bread in long-term care of severely demented elderly patients. *Journal of the American Geriatrics Society* **31**, 289-293.
Sanjoaquin MA, Appleby PN, Thorogood M, Mann JI & Key TJ (2004) Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10998 vegetarians and non-vegetarians in the United Kingdom. *Br J Cancer* **90**, 118-121.
Sansbury LB, Wanke K, Albert PS, Kahle L, Schatzkin A & Lanza E (2009) The effect of strict adherence to a high-fiber, high-fruit and -vegetable, and low-fat eating pattern on adenoma recurrence. *Am J Epidemiol* **170**, 576-584.
Savino F, Cresi F, Maccario S, Cavallo F, Dalmasso P, Fanaro S, Oggero R, Vigi V & Silvestro L (2003) "Minor" feeding problems during the first months of life: effect of a partially hydrolysed milk formula containing fructo- and galacto-oligosaccharides. *Acta Paediatrica Supplement* **91**, 86-90.
Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S & Black RE (2006) Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis* **6**, 374-382.
Scanlan PD, Shanahan F, Clune Y, Collins JK, O'Sullivan GC, O'Riordan M, Holmes E, Wang Y & Marchesi JR (2008) Culture-independent analysis of the gut microbiota in colorectal cancer and polyposis. *Environmental Microbiology* **10**, 789-798.
Schaarmann G, Schneider J, Zorn A, Schubert K, Flachowsky G & Jahreis G (1999) Influence of soluble dietary fibre on the faecal excretion of tocopherol and blood lipids in women. *Nutrition Research* **19**, 689-695.
Schatzkin A & Gail M (2002) The promise and peril of surrogate end points in cancer research. *Nat Rev Cancer* **2**, 19-27.
Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J, Freedman L, Marshall J, Schoen RE, Slattery M & The Polyp Prevention Trial Study G (2000) Lack of Effect of a Low-Fat, High-Fiber Diet on the Recurrence of Colorectal Adenomas. *N Engl J Med* **342**, 1149-1155.
Schatzkin A, Mouw T, Park Y, Subar AF, Kipnis V, Hollenbeck A, Leitzmann MF & Thompson FE (2007) Dietary fiber and whole-grain consumption in relation to colorectal cancer in the NIH-AARP Diet and Health Study. *American Journal of Clinical Nutrition* **85**, 1353-1360.
Schiller LR (1999) Secretory diarrhea. *Curr Gastroenterol Rep* **1**, 389-397.
Schmelzer M (1990) Effectiveness of wheat bran in preventing constipation of hospitalized orthopaedic surgery patients. *Orthopaedic Nursing* **9**, 55-59.
Schmelzle H, Wirth S, Skopnik H, Radke M, Knol J, Bockler HM, Bronstrup A, Wells J & Fusch C (2003) Randomized double-blind study of the nutritional efficacy and bifidogenicity of a new infant formula containing partially hydrolyzed protein, a high

beta-palmitic acid level, and nondigestible oligosaccharides. *Journal of Pediatric Gastroenterology and Nutrition* **36**, 343-351.
Scholtens PA, Alles MS, Bindels JG, van der Linde EG, Tolboom JJ & Knol J (2006a) Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *Journal of Pediatric Gastroenterology and Nutrition* **42**, 553-559.
Scholtens PA, Alles MS, Willemsen LE, van den Braak C, Bindels JG, Boehm G & Govers MJ (2006b) Dietary fructo-oligosaccharides in healthy adults do not negatively affect faecal cytotoxicity: a randomised, double-blind, placebo-controlled crossover trial. *British Journal of Nutrition* **95**, 1143-1149.
Scholtens PA, Alliet P, Raes M, Alles MS, Kroes H, Boehm G, Knippels LM, Knol J & Vandenplas Y (2008) Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. *Journal of Nutrition* **138**, 1141-1147.
Schuette SA, Knowles JB & Ford HE (1989) Effect of lactose or its component sugars on jejunal calcium absorption in adult man. *American Journal of Clinical Nutrition* **50**, 1084-1087.
Schuette SA, Yasillo NJ & Thompson CM (1991) The effect of carbohydrates in milk on the absorption of calcium by postmenopausal women. *Journal of the American College of Nutrition* **10**, 132-139.
Schwan A, Ryden AC & Laurell G (1982) Fecal bacterial flora of four nordic population groups with diverse incidence of large bowel cancer. *Nutr Cancer* **4**, 74-79.
Schweizer TF, Bekhechi AR & Koellreutter B (1983) Metabolic effects of dietary fiber from dehulled soybeans in humans. *American Journal of Clinical Nutrition* **38**, 1-11.
Schweizer TF & Wursch P (1979) Analysis of dietary fibre. *Journal of the Science of Food and Agriculture* **30**, 613-619.
Schwiertz A, Jacobi M, Frick JS, Richter M, Rusch K, x00F & hler H (2010) Microbiota in pediatric inflammatory bowel disease. *Journal of Pediatrics* **157**, 240-244.e241.
Scientific Advisory Committee on Nutrition (2008) Draft SACN position statement on dietary fibre & health and the dietary fibre definition - August 2008.
Sculati O & Giampiccoli G (1984) Clinical trial of a new preparation with a high concentration of dietary fiber (fibraform). *Current Therapeutic Research - Clinical and Experimental* **36**, 261-266.
Segal I, Hassan H, Walker AR, Becker P & Braganza J (1995) Fecal short chain fatty acids in South African urban Africans and whites. *Dis Colon Rectum* **38**, 732-734.
Sela DA & Mills DA (2010) Nursing our microbiota: molecular linkages between bifidobacteria and milk oligosaccharides. *Trends in Microbiology* **18**, 298-307.
Selig H & Boyle J (2003) Initiating a bowel care and maintenance program: the economic and bowel-care benefits of a fibre-rich, flaxflour-based diet. *Canadian Nursing Home* **14**, 26-30.
Sellers TA, Bazyk AE, Bostick RM, Kushi LH, Olson JE, Anderson KE, Lazovich D & Folsom AR (1998) Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). *Cancer Causes Control* **9**, 357-367.
Sengupta S, Muir JG & Gibson PR (2006) Does butyrate protect from colorectal cancer? *Journal of Gastroenterology and Hepatology* **21**, 209-218.
Sepp E, Julge K, Mikelsaar M & Bjorksten B (2005) Intestinal microbiota and immunoglobulin E responses in 5-year-old Estonian children. *Clin Exp Allergy* **35**, 1141-1146.
Seppanen S, Niittynen L, Poussa T & Korpela R (2008) Removing lactose from milk does

not delay bowel function or harden stool consistency in lactose-tolerant women. *European Journal of Clinical Nutrition* **62**, 727-732.
Shadid R, Haarman M, Knol J, Theis W, Beermann C, Rjosk-Dendorfer D, Schendel DJ, Koletzko BV & Krauss-Etschmann S (2007) Effects of galactooligosaccharide and long-chain fructooligosaccharide supplementation during pregnancy on maternal and neonatal microbiota and immunity - A randomized, double-blind, placebo-controlled study. *American Journal of Clinical Nutrition* **86**, 1426-1437.
Shah M, Chandalia M, Adams-Huet B, Brinkley LJ, Sakhaee K, Grundy SM & Garg A (2009) Effect of a high-fiber diet compared with a moderate-fiber diet on calcium and other mineral balances in subjects with type 2 diabetes. *Diabetes Care* **32**, 990-995.
Shen XJ, Rawls JF, Randall T, Burcal L, Mpande CN, Jenkins N, Jovov B, Abdo Z, Sandler RS & Keku TO (2010) Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. *Gut Microbes* **1**, 138-147.
Shetty PS & Kurpad AV (1986) Increasing starch intake in the human diet increases fecal bulking. *American Journal of Clinical Nutrition* **43**, 210-212.
Shin A, Li H, Shu XO, Yang G, Gao YT & Zheng W (2006) Dietary intake of calcium, fiber and other micronutrients in relation to colorectal cancer risk: Results from the Shanghai Women's Health Study. *Int J Cancer* **119**, 2938-2942.
Shinohara K, Ohashi Y, Kawasumi K, Terada A & Fujisawa T (2010) Effect of apple intake on fecal microbiota and metabolites in humans. *Anaerobe* **16**, 510-515.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P & Berrino F (2002) Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer* **42**, 10-17.
Silk DBA, Davis A, Vulevic J, Tzortzis G & Gibson GR (2009) Clinical trial: The effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics* **29**, 508-518.
Silvester KR, Bingham SA, Pollock JR, Cummings JH & O'Neill IK (1997) Effect of meat and resistant starch on fecal excretion of apparent N-nitroso compounds and ammonia from the human large bowel. *Nutrition and Cancer* **29**, 13-23.
Simons CC, Leurs LJ, Weijenberg MP, Schouten LJ, Goldbohm RA & van den Brandt PA (2010) Fluid intake and colorectal cancer risk in the Netherlands Cohort Study. *Nutrition & Cancer* **62**, 307-321.
Sinaud S, Montaurier C, Wils D, Vernet J, Brandolini M, Bouteloup-Demange C & Vermorel M (2002) Net energy value of two low-digestible carbohydrates, LycasinHBC and the hydrogenated polysaccharide fraction of LycasinHBC in healthy human subjects and their impact on nutrient digestive utilization. *British Journal of Nutrition* **87**, 131-139.
Skoog SM & Bharucha AE (2004) Dietary fructose and gastrointestinal symptoms: A review. *American Journal of Gastroenterology* **99**, 2046-2050.
Skoog SM, Bharucha AE & Zinsmeister AR (2008) Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterology and Motility* **20**, 505-511.
Slavin JL, Brauer PM & Marlett JA (1981a) Neutral detergent fiber, hemicellulose and cellulose digestibility in human subjects. *Journal of Nutrition* **111**, 287-297.
Slavin JL & Marlett JA (1980a) Effect of refined cellulose on apparent energy, fat and nitrogen digestibilities. *Journal of Nutrition* **110**, 2020-2026.
Slavin JL & Marlett JA (1980b) Influence of refined cellulose on human bowel function and calcium and magnesium balance. *American Journal of Clinical Nutrition* **33**, 1932-1939.
Slavin JL, Melcher EA, Sundeen M & Schwartz S (1991) Effects of high-fiber diet on fecal blood content (HemoQuant assay) in healthy subjects. *Digestive Diseases and*

Sciences **36**, 929-932.
Slavin JL, Nelson NL, McNamara EA & Cashmere K (1985) Bowel function of healthy men consuming liquid diets with and without dietary fiber. *Jpen: Journal of Parenteral & Enteral Nutrition* **9**, 317-321.
Slavin JL, Sempos CT, Brauer PM & Marlett JA (1981b) Limits of predicting gastrointestinal transit time from other measures of bowel function. *American Journal of Clinical Nutrition* **34**, 2111-2116.
Smith A, Bazzoni C, Beale J, Elliott-Smith J & Tiley M (2001) High fibre breakfast cereals reduce fatigue. *Appetite* **37**, 249-250.
Smith AN, Drummond E & Eastwood MA (1981) The effect of coarse and fine Canadian Red Spring Wheat and French Soft Wheat bran on colonic motility in patients with diverticular disease. *Am J Clin Nutr* **34**, 2460-2463.
Smith AP (2010) An investigation of the effects of breakfast cereals on alertness, cognitive function and other aspects of the reported well-being of children. *Nutritional Neuroscience* **13**, 230-236.
Smith MM, Davis M, Chasalow FI & Lifshitz F (1995) Carbohydrate absorption from fruit juice in young children. *Pediatrics* **95**, 340-344.
Smith RG, Rowe MJ, Smith AN, Eastwood MA, Drummond E & Brydon WG (1980) A study of bulking agents in elderly patients. *Age and Ageing* **9**, 267-271.
Smith SC, Choy R, Johnson SK, Hall RS, Wildeboer-Veloo AC & Welling GW (2006) Lupin kernel fiber consumption modifies fecal microbiota in healthy men as determined by rRNA gene fluorescent in situ hybridization. *European Journal of Nutrition* **45**, 335-341.
Smits BJ, Whitehead AM & Prescott P (1990) Lactulose in the treatment of symptomatic diverticular disease: a comparative study with high-fibre diet. *British Journal of Clinical Practice* **44**, 314-318.
Snook J & Shepherd HA (1994) Bran supplementation in the treatment of irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics* **8**, 511-514.
Snustad D, Lee V, Abraham I, Alexander C, Bella D & Cumming C (1991) Dietary fiber in hospitalized geriatric patients: too soft a solution for too hard a problem? *Journal of Nutrition for the Elderly* **10**, 49-63.
Sokol H, Seksik P, Furet JP, Firmesse O, Nion-Larmurier I, Beaugerie L, Cosnes J, Corthier G, Marteau P, Dor & x00E (2009) Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflammatory Bowel Diseases* **15**, 1183-1189.
Soltoft J, Krag B, Gudmand-Hoyer E, Kristensen E & Wulff HR (1976) A double-blind trial of the effect of wheat bran on symptoms of irritable bowel syndrome. *Lancet* **1**, 270-272.
Sonnenberg A & Muller AD (1993) Constipation and cathartics as risk factors of colorectal cancer: a meta-analysis. *Pharmacology* **47 Suppl 1**, 224-233.
Southgate DA (1969a) Determination of carbohydrates in foods. I. Available carbohydrate. *Journal of the Science of Food and Agriculture* **20**, 326-330.
Southgate DA (1969b) Determination of carbohydrates in foods. II. Unavailable carbohydrates. *Journal of the Science of Food and Agriculture* **20**, 331-335.
Southgate DA, Branch WJ, Hill MJ, Drasar BS, Walters RL, Davies PS & Baird IM (1976) Metabolic responses to dietary supplements of bran. *Metabolism: Clinical and Experimental* **25**, 1129-1135.
Southgate DA & Durnin JV (1970) Calorie conversion factors. An experimental reassessment of the factors used in the calculation of the energy value of human diets. *British Journal of Nutrition* **24**, 517-535.
Southgate DA, Hudson GJ & Englyst H (1978) The analysis of dietary fibre--the choices for

the analyst. *Journal of the Science of Food and Agriculture* **29**, 979-988.
Spencer H, Norris C, Derler J & Osis D (1991) Effect of oat bran muffins on calcium absorption and calcium, phosphorus, magnesium and zinc balance in men. *Journal of Nutrition* **121**, 1976-1983.
Spiller GA, Chernoff MC & Hill RA (1980) Effect of purified cellulose, pectin, and a low-residue diet on fecal volatile fatty acids, transit time, and fecal weight in humans. *American Journal of Clinical Nutrition* **33**, 754-759.
Spiller GA, Shipley EA, Chernoff MC & Cooper WC (1979) Bulk laxative efficacy of a psyllium seed hydrocolloid and of a mixture of cellulose and pectin. *Journal of Clinical Pharmacology* **19**, 313-320.
Spiller GA, Story JA, Furumoto EJ, Chezem JC & Spiller M (2003a) Effect of tartaric acid and dietary fibre from sun-dried raisins on colonic function and on bile acid and volatile fatty acid excretion in healthy adults. *British Journal of Nutrition* **90**, 803-807.
Spiller GA, Story JA, Lodics TA, Pollack M, Monyan S, Butterfield G & Spiller M (2003b) Effect of sun-dried raisins on bile acid excretion, intestinal transit time, and fecal weight: a dose-response study. *Journal of Medicinal Food* **6**, 87-91.
Spiller GA, Story JA, Wong LG, Nunes JD, Alton M, Petro MS, Furumoto EJ, Whittam JH & Scala J (1986) Effect of Increasing Levels of Hard Wheat Fiber on Fecal Weight, Minerals and Steroids and Gastrointestinal Transit Time in Healthy Young Women. *Journal of Nutrition* **116**, 778-785.
Spiller RC & Thompson WG (2010) Bowel Disorders. *American Journal of Gastroenterology* **105**, 775-785.
Srikumar TS (2000) Effects of consumption of white bread and brown bread on the concentrations of fecal bile acids and neutral steroids and on fecal enzyme activities. *Nutrition Research* **20**, 327-333.
Srivastava GS, Smith AN & Painter NS (1976) Sterculia bulk-forming agent with smooth-muscle relaxant versus bran in diverticular disease. *British Medical Journal* **1**, 315-318.
Staiano A, Simeone D, Del Giudice E, Miele E, Tozzi A & Toraldo C (2000) Effect of the dietary fiber glucomannan on chronic constipation in neurologically impaired children. *Journal of Pediatrics* **136**, 41-45.
Staniforth DH, Baird IM, Fowler J & Lister RE (1991) The effects of dietary fibre on upper and lower gastro-intestinal transit times and faecal bulking. *Journal of International Medical Research* **19**, 228-233.
Stasse-Wolthuis M, Albers HF, van Jeveren JG, Wil de Jong J, Hautvast JG, Hermus RJ, Katan MB, Brydon WG & Eastwood MA (1980) Influence of dietary fiber from vegetables and fruits, bran or citrus pectin on serum lipids, fecal lipids, and colonic function. *American Journal of Clinical Nutrition* **33**, 1745-1756.
Stasse-Wolthuis M, Hautvast JG, Hermus RJ, Katan MB, Bausch JE, Rietberg-Brussaard JH, Velema JP, Zondervan JH, Eastwood MA & Brydon WG (1979) The effect of a natural high-fiber diet on serum lipids, fecal lipids, and colonic function. *American Journal of Clinical Nutrition* **32**, 1881-1888.
Steinmetz KA, Kushi LH, Bostick RM, Folsom AR & Potter JD (1994) Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* **139**, 1-15.
Stemmermann GN, Nomura AM, Chyou PH & Yoshizawa C (1990) Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci* **35**, 1414-1420.
Stemmermann GN, Nomura AM & Heilbrun LK (1984) Dietary fat and the risk of colorectal cancer. *Cancer Res* **44**, 4633-4637.
Stephen AM & Cummings JH (1979) Water-holding by dietary fibre in vitro and its

relationship to faecal output in man. *Gut* **20**, 722-729.
Stephen AM & Cummings JH (1980a) Mechanism of action of dietary fibre in the human colon. *Nature* **284**, 283-284.
Stephen AM & Cummings JH (1980b) The microbial contribution to human faecal mass. *Journal of Medical Microbiology* **13**, 45-56.
Stephen AM, Dahl WJ, Sieber GM, van Blaricom JA & Morgan DR (1995) Effect of green lentils on colonic function, nitrogen balance, and serum lipids in healthy human subjects. *American Journal of Clinical Nutrition* **62**, 1261-1267.
Stern FH (1966) Constipation--an omnipresent symptom: effect of a preparation containing prune concentrate and cascarin. *Journal of the American Geriatrics Society* **14**, 1153-1155.
Stevens J, VanSoest PJ, Robertson JB & Levitsky DA (1988) Comparison of the effect of psyllium and wheat bran on gastrointestinal transit time and stool characteristics. *Journal of the American Dietetic Association* **88**, 323-326.
Stewart ML, Nikhanj SD, Timm DA, Thomas W & Slavin JL (2010) Evaluation of the effect of four fibers on laxation, gastrointestinal tolerance and serum markers in healthy humans. *Annals of Nutrition and Metabolism* **56**, 91-98.
Storey D, Lee A, Bornet F & Brouns F (2007) Gastrointestinal responses following acute and medium term intake of retrograded resistant maltodextrins, classified as type 3 resistant starch. *European Journal of Clinical Nutrition* **61**, 1262-1270.
Strayer L, Jacobs DR, Jr., Schairer C, Schatzkin A & Flood A (2007) Dietary carbohydrate, glycemic index, and glycemic load and the risk of colorectal cancer in the BCDDP cohort. *Cancer Causes Control* **18**, 853-863.
Stumm RE, Thomas MS, Coombes J, Greenhill J & Hay J (2001) Managing constipation in elderly orthopaedic patients using either pear juice or a high fibre supplement. *Australian Journal of Nutrition & Dietetics* **58**, 181-186.
Sturtzel B, Dietrich A, Wagner KH, Gisinger C & Elmadfa I (2010) The status of vitamins B6, B12, folate, and of homocysteine in geriatric home residents receiving laxatives or dietary fiber. *Journal of Nutrition, Health & Aging* **14**, 219-223.
Sturtzel B & Elmadfa I (2008) Intervention with dietary fiber to treat constipation and reduce laxative use in residents of nursing homes. *Annals of Nutrition and Metabolism* **52 Suppl 1**, 54-56.
Sugawara M, Sato Y, Yokoyama S & Mitsuoka T (1991) Effect of corn fiber residue supplementation on fecal properties, flora, ammonia, and bacterial enzyme activities in healthy humans. *Journal of Nutritional Science and Vitaminology* **37**, 109-116.
Surakka A, Kajander K, Rajilic-Stojanovic M, Karjalainen H, Hatakka K, Vapaatalo H, Zoetendal EG, De Vos WM, Korpela R & Tynkkynen S (2009) Yoghurt containing galactooligosaccharides facilitates defecation among elderly subjects and selectively increases the number of Bifidobacteria. *International Journal of Probiotics and Prebiotics* **4**, 65-74.
Swanson KS, Grieshop CM, Flickinger EA, Bauer LL, Wolf BW, Chow J, Garleb KA, Williams JA & Fahey Jr GC (2002) Fructooligosaccharides and Lactobacillus acidophilus modify bowel function and protein catabolites excreted by healthy humans. *Journal of Nutrition* **132**, 3042-3050.
Switzer BR, Stark AH, Atwood JR, Ritenbaugh C, Travis RG & Wu HM (1997) Development of a urinary riboflavin adherence marker for a wheat bran fiber community intervention trial. *Cancer Epidemiology, Biomarkers & Prevention* **6**, 439-442.
Szajewska H, Ruszczyński M & Radzikowski A (2006) Probiotics in the prevention of antibiotic-associated diarrhea in children: A meta-analysis of randomized controlled

trials. *The Journal of pediatrics* **149**, 367-372.e361.
Tahiri M, Tressol JC, Arnaud J, Bornet F, Bouteloup-Demange C, Feillet-Coudray C, Ducros V, Pepin D, Brouns F, Rayssiguier AM & Coudray C (2001) Five-week intake of short-chain fructo-oligosaccharides increases intestinal absorption and status of magnesium in postmenopausal women. *Journal of Bone and Mineral Research* **16**, 2152-2160.
Tahiri M, Tressol JC, Arnaud J, Bornet FRJ, Bouteloup-Demange C, Feillet-Coudray C, Brandolini M, Ducros V, Pepin D, Brouns F, Roussel AM, Rayssiguier Y & Coudray C (2003) Effect of short-chain fructooligosaccharides on intestinal calcium absorption and calcium status in postmenopausal women: A stable-isotope study. *American Journal of Clinical Nutrition* **77**, 449-457.
Tainter ML (1943) Methyl cellulose as a colloid laxitive. *Proceedings of the Society for Experimental Biology and Medicine* **54**, 77.
Takahashi H, Sung Ik Y, Hayashi C, Kim M, Yamanaka J & Yamamoto T (1993) Effect of partially hydrolyzed guar gum on fecal output in human volunteers. *Nutrition Research* **13**, 649-657.
Takahashi H, Wako N, Okubo T, Ishihara N, Yamanaka J & Yamamoto T (1994) Influence of partially hydrolyzed guar gum on constipation in women. *Journal of Nutritional Science and Vitaminology* **40**, 251-259.
Takaishi H, Matsuki T, Nakazawa A, Takada T, Kado S, Asahara T, Kamada N, Sakuraba A, Yajima T, Higuchi H, Inoue N, Ogata H, Iwao Y, Nomoto K, Tanaka R & Hibi T (2008) Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. *Int J Med Microbiol* **298**, 463-472.
Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, Virtamo J & Albanes D (1997) Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* **8**, 615-625.
Tannock GW, Munro K, Bibiloni R, Simon MA, Hargreaves P, Gopal P, Harmsen H & Welling G (2004) Impact of consumption of oligosaccharide-containing biscuits on the fecal microbiota of humans. *Applied and Environmental Microbiology* **70**, 2129-2136.
Tarpila S, Miettinen TA & Metsaranta L (1978) Effects of bran on serum cholesterol, faecal mass, fat, bile acids and neutral sterols, and biliary lipids in patients with diverticular disease of the colon. *Gut* **19**, 137-145.
Tarpila S, Tarpila A, Grohn P, Silvennoinen T & Lindberg L (2004) Efficacy of ground flaxseed on constipation in patients with irritable bowel syndrome. *Current Topics in Nutraceutical Research* **2**, 119-125.
Tateyama I, Hashii K, Johno I, Iino T, Hirai K, Suwa Y & Kiso Y (2005) Effect of xylooligosaccharide intake on severe constipation in pregnant women. *Journal of Nutritional Science and Vitaminology* **51**, 445-448.
Taylor I & Duthie HL (1976) Bran tablets and diverticular disease. *British Medical Journal* **1**, 988-990.
Terry P, Giovannucci E, Michels KB, Bergkvist L, Hansen H, Holmberg L & Wolk A (2001) Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* **93**, 525-533.
Terry P, Jain M, Miller AB, Howe GR & Rohan TE (2002) Dietary intake of folic acid and colorectal cancer risk in a cohort of women. *Int J Cancer* **97**, 864-867.
Terry PD, Jain M, Miller AB, Howe GR & Rohan TE (2003) Glycemic load, carbohydrate intake, and risk of colorectal cancer in women: a prospective cohort study. *J Natl Cancer Inst* **95**, 914-916.
Teuri U & Korpela R (1998) Galacto-oligosaccharides relieve constipation in elderly people.

Annals of Nutrition and Metabolism **42**, 319-327.
Teuri U, Korpela R, Saxelin M, Montonen L & Salminen S (1998) Increased fecal frequency and gastrointestinal symptoms following ingestion of galacto-oligosaccharide-containing yogurt. *Journal of Nutritional Science and Vitaminology* **44**, 465-471.
Theander O, Aman P, Westerlund E & Graham H (1990) The Uppsala method for rapid analysis of total dietary fiber. *Advances in Experimental Medicine and Biology* **270**, 273-281.
Thomas PD, Forbes A, Green J, Howdle P, Long R, Playford R, Sheridan M, Stevens R, Valori R, Walters J, Addison GM, Hill P & Brydon G (2003) Guidelines for the investigation of chronic diarrhoea, 2nd edition. *Gut* **52 Suppl 5**, v1-15.
Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ & Muller-Lissner SA (1999) Functional bowel disorders and functional abdominal pain. *Gut* **45**, ii43-47.
Tinker LF, Schneeman BO, Davis PA, Gallaher DD & Waggoner CR (1991) Consumption of prunes as a source of dietary fiber in men with mild hypercholesterolemia. *American Journal of Clinical Nutrition* **53**, 1259-1265.
Tomlin J & Read NW (1988a) A comparative study of the effects on colon function caused by feeding ispaghula husk and polydextrose. *Alimentary Pharmacology and Therapeutics* **2**, 513-519.
Tomlin J & Read NW (1988b) Comparison of the effects on colonic function caused by feeding rice bran and wheat bran. *European Journal of Clinical Nutrition* **42**, 857-861.
Tomlin J & Read NW (1988c) The relation between bacterial degradation of viscous polysaccharides and stool output in human beings. *British Journal of Nutrition* **60**, 467-475.
Tomlin J & Read NW (1990) The effect of resistant starch on colon function in humans. *British Journal of Nutrition* **64**, 589-595.
Tomlin J & Read NW (1992) A comparison of the effect of 9.5 gram/day resistant starch and lactulose on colon function. *European Journal of Clinical Nutrition* **46 Suppl 2**, S139-140.
Topping DL, Bird AR & Young GP (2009) Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome... N Engl J Med. 2008 Dec 11;359(24):2567-78. *New England Journal of Medicine* **360**, 1462-NaN.
Topping DL, Fukushima M & Bird AR (2003) Resistant starch as a prebiotic and synbiotic: state of the art. *Proc Nutr Soc* **62**, 171-176.
Tremaine WJ, Newcomer AD, Riggs BL & McGill DB (1986) Calcium absorption from milk in lactase-deficient and lactase-sufficient adults. *Digestive Diseases & Sciences* **31**, 376-378.
Trinidad TP, Wolever TM & Thompson LU (1996) Effect of acetate and propionate on calcium absorption from the rectum and distal colon of humans. *Am J Clin Nutr* **63**, 574-578.
Trinidad TP, Wolever TMS & Thompson LU (1993) Interactive effects of calcium and short chain fatty acids on absorption in the distal colon of man. *Nutrition Research* **13**, 417-425.
Trinidad TP, Wolever TMS & Thompson LU (1997) Effect of short chain fatty acids on calcium absorption in humans. *Advances in Experimental Medicine and Biology* **427**, 183-189.
Truswell AS, Seach JM & Thorburn AW (1988) Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of glucose. *American Journal of Clinical Nutrition* **48**, 1424-1430.
Tsai AC, Mott EL, Owen GM, Bennick MR, Lo GS & Steinke FH (1983) Effects of soy

polysaccharide on gastrointestinal functions, nutrient balance, steroid excretions, glucose tolerance, serum lipids, and other parameters in humans. *American Journal of Clinical Nutrition* **38**, 504-511.

Tucker DM, Sandstead HH, Logan GM, Jr., Klevay LM, Mahalko J, Johnson LK, Inman L & Inglett GE (1981) Dietary fiber and personality factors as determinants of stool output. *Gastroenterology* **81**, 879-883.

Tuohy KM, Finlay RK, Wynne AG & Gibson GR (2001a) A human volunteer study on the prebiotic effects of HP-inulin - Faecal bacteria enumerated using fluorescent In situ hybridisation (FISH). *Anaerobe* **7**, 113-118.

Tuohy KM, Kolida S, Lustenberger AM & Gibson GR (2001b) The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccharides - A human volunteer study. *British Journal of Nutrition* **86**, 341-348.

Turconi G, Bazzano R, Caramella R & Lanzola E (1995) The effects of high-fibre cereal-based breakfast meals on daily dietary intakes and bowel function. *European Journal of Clinical Nutrition* **49 Suppl 3**, S312-316.

Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R & Gordon JI (2009) A core gut microbiome in obese and lean twins. *Nature* **457**, 480-484.

Ullrich IH, Lai HY & Vona L (1981) Alterations of fecal steroid composition induced by changes in dietary fiber consumption. *American Journal of Clinical Nutrition* **34**, 2054-2060.

Valle-Jones JC (1985) An open study of oat bran meal biscuits ('Lejfibre') in the treatment of constipation in the elderly. *Current Medical Research and Opinion* **9**, 716-720.

Valois S, Costa-Ribeiro H, Jr., Mattos A, Ribeiro TC, Mendes CM & Lifshitz F (2005) Controlled, double-blind, randomized clinical trial to evaluate the impact of fruit juice consumption on the evolution of infants with acute diarrhea. *Nutrition Journal* **4**.

van den Brandt PA, Goldbohm RA, van 't Veer P, Volovics A, Hermus RJ & Sturmans F (1990) A large-scale prospective cohort study on diet and cancer in The Netherlands. *J Clin Epidemiol* **43**, 285-295.

van den Heuvel EG, Muijs T, Brouns F & Hendriks HF (2009) Short-chain fructo-oligosaccharides improve magnesium absorption in adolescent girls with a low calcium intake. *Nutrition Research* **29**, 229-237.

van den Heuvel EGHM, Muys T, van Dokkum W & Schaafsma G (1999) Oligofructose stimulates calcium absorption in adolescents. *Am J Clin Nutr* **69**, 544-548.

Van den Heuvel EGHM, Schaafsma G, Muys T & Van Dokkum W (1998) Nondigestible oligosaccharides do not interfere with calcium and nonheme-iron absorption in young, healthy men. *American Journal of Clinical Nutrition* **67**, 445-451.

van den Heuvel EGHM, Schoterman MHC & Muijs T (2000) Transgalactooligosaccharides Stimulate Calcium Absorption in Postmenopausal Women. *J. Nutr.* **130**, 2938-2942.

van der Aa LB, Heymans HS, van Aalderen WM & Sprikkelman AB (2010) Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. *Pediatric Allergy & Immunology* **21**, e355-367.

Van Dokkum W, Pikaar NA & Thissen JT (1983) Physiological effects of fibre-rich types of bread. 2. Dietary fibre from bread: digestibility by the intestinal microflora and water-holding capacity in the colon of human subjects. *British Journal of Nutrition* **50**, 61-74.

Van Dokkum W, Wesstra A & Schippers FA (1982) Physiological effects of fibre-rich types of bread. 1. The effect of dietary fibre from bread on the mineral balance of young men. *British Journal of Nutrition* **47**, 451-460.

van Dokkum W, Wezendonk B, Srikumar TS & van den Heuvel EG (1999) Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. *European Journal of Clinical Nutrition* **53**, 1-7.

Van Es AJ, De Groot L & Vogt JE (1986) Energy balances of eight volunteers fed on diets supplemented with either lactitol or saccharose. *British Journal of Nutrition* **56**, 545-554.

van Loo J, Coussement P, de Leenheer L, Hoebregs H & Smits G (1995) On the presence of inulin and oligofructose as natural ingredients in the western diet. *Crit Rev Food Sci Nutr* **35**, 525-552.

van Munster IP, Tangerman A & Nagengast FM (1994) Effect of resistant starch on colonic fermentation, bile acid metabolism, and mucosal proliferation. *Digestive Diseases and Sciences* **39**, 834-842.

Van Soest PJ (1963) Use of detergents in the analysis of fibrous feeds. I. Preparation of fiber residues of low nitrogen content. *J Assoc Off Agric Chemists* **46**, 825-829.

Van Soest PJ & Wine RH (1967) Use of detergent in the analysis of fibrous feeds. IV. Determination of plant cell wall constituents. . *Journal - Association of Official Analytical Chemists* **50**, 50-55.

Vanderdonckt J, Coulon J, Denys W & Ravelli GP (1990) Study of the laxative effect of lactitol (importal(R)) in an elderly institutionalized, but not bedridden, population suffering from chronic constipation. *Journal of Clinical and Experimental Gerontology* **12**, 171-189.

Vanderhoof JA, Murray ND, Paule CL & Ostrom KM (1997) Use of soy fiber in acute diarrhea in infants and toddlers. *Clinical Pediatrics* **36**, 135-139.

Vargo D, Doyle R & Floch MH (1985) Colonic bacterial flora and serum cholesterol: alterations induced by dietary citrus pectin. *American Journal of Gastroenterology* **80**, 361-364.

Vargo D, Moskovitz M & Floch MH (1980) Faecal bacterial flora in cancer of the colon. *Gut* **21**, 701-705.

Vermorel M, Coudray C, Wils D, Sinaud S, Tressol JC, Montaurier C, Vernet J, Brandolini M, Bouteloup-Demange C & Rayssiguier Y (2004) Energy value of a low-digestible carbohydrate, NUTRIOSE FB, and its impact on magnesium, calcium and zinc apparent absorption and retention in healthy young men. *European Journal of Nutrition* **43**, 344-352.

Vernia P, Gnaedinger A, Hauck W & Breuer RI (1988) Organic anions and the diarrhea of inflammatory bowel disease. *Dig Dis Sci* **33**, 1353-1358.

Villagrasa M, Boix J, Humbert P & Quer JC (1991) Aleatory clinical study comparing otilonium bromide with a fiber-rich diet in the treatment of irritable bowel syndrome. *Italian Journal of Gastroenterology* **23**, 67-70.

Villaume C, Bam HW & Mejean L (1988) Physico-chemical properties of wheat bran and long term physiological effects in healthy man. *Diabete Metab* **14**, 664-666.

Voderholzer WA, Schatke W, Muhldorfer BE, Klauser AG, Birkner B & Muller-Lissner SA (1997) Clinical response to dietary fiber treatment of chronic constipation. *American Journal of Gastroenterology* **92**, 95-98.

Vuksan V, Jenkins AL, Jenkins DJ, Rogovik AL, Sievenpiper JL & Jovanovski E (2008) Using cereal to increase dietary fiber intake to the recommended level and the effect of fiber on bowel function in healthy persons consuming North American diets. *American Journal of Clinical Nutrition* **88**, 1256-1262.

Vuksan V, Jenkins DJ, Vidgen E, Ransom TP, Ng MK, Culhane CT & O'Connor D (1999) A novel source of wheat fiber and protein: effects on fecal bulk and serum lipids.

American Journal of Clinical Nutrition **69**, 226-230.
Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G & Gibson GR (2008) Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *American Journal of Clinical Nutrition* **88**, 1438-1446.
Wakai K, Date C, Fukui M, Tamakoshi K, Watanabe Y, Hayakawa N, Kojima M, Kawado M, Suzuki K, Hashimoto S, Tokudome S, Ozasa K, Suzuki S, Toyoshima H, Ito Y, Tamakoshi A & for the JSG (2007) Dietary Fiber and Risk of Colorectal Cancer in the Japan Collaborative Cohort Study. *Cancer Epidemiology Biomarkers Prevention* **16**, 668-675.
Waligora-Dupriet AJ, Campeotto F, Nicolis I, Bonet A, Soulaines P, Dupont C & Butel MJ (2007) Effect of oligofructose supplementation on gut microflora and well-being in young children attending a day care centre. *International Journal of Food Microbiology* **113**, 108-113.
Walker A (2010) Breast Milk as the Gold Standard for Protective Nutrients. *Journal of Pediatrics* **156**, S3-S7.
Walker AR, Walker BF & Walker AJ (1986) Faecal pH, dietary fibre intake, and proneness to colon cancer in four South African populations. *Br J Cancer* **53**, 489-495.
Walters RL, Baird IM, Davies PS, Hill MJ, Drasar BS, Southgate DA, Green J & Morgan B (1975) Effects of two types of dietary fibre on faecal steroid and lipid excretion. *British Medical Journal* **2**, 536-538.
Walton GE, Rastall RA, Martini MC, Williams CE, Jeffries RL & Gibson GR (2010) A double-blind, placebo controlled human study investigating the effects of coffee derived manno-oligosaccharides on the faecal microbiota of a healthy adult population. *International Journal of Probiotics and Prebiotics* **5**, 75-83.
Washington N, Harris M, Mussellwhite A & Spiller RC (1998) Moderation of lactulose-induced diarrhea by psyllium: effects on motility and fermentation. *American Journal of Clinical Nutrition* **67**, 317-321.
Watanabe S, Narisawa Y, Arase S, Hiroshi O, Takeshi I, Yoshito T & Megumi K (2003) Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. *The Journal of allergy and clinical immunology* **111**, 587-591.
Watanabe T, Nakaya N, Kurashima K, Kuriyama S, Tsubono Y & Tsuji I (2004) Constipation, laxative use and risk of colorectal cancer: The Miyagi Cohort Study. *Eur J Cancer* **40**, 2109-2115.
Weaver GA, Krause JA, Miller TL & Wolin MJ (1988) Short chain fatty acid distributions of enema samples from a sigmoidoscopy population: an association of high acetate and low butyrate ratios with adenomatous polyps and colon cancer. *Gut* **29**, 1539-1543.
Weijenberg MP, Mullie PF, Brants HA, Heinen MM, Goldbohm RA & van den Brandt PA (2008) Dietary glycemic load, glycemic index and colorectal cancer risk: results from the Netherlands Cohort Study. *Int J Cancer* **122**, 620-629.
Wenzl HH, Fine KD, Schiller LR & Fordtran JS (1995) Determinants of decreased fecal consistency in patients with diarrhea. *Gastroenterology* **108**, 1729-1738.
Whelan K, Judd PA, Preedy VR, Simmering R, Jann A & Taylor MA (2005) Fructooligosaccharides and fiber partially prevent the alterations in fecal microbiota and short-chain fatty acid concentrations caused by standard enteral formula in healthy humans. *Journal of Nutrition* **135**, 1896-1902.
Widdowson EM & McCance RA (1935) The available carbohydrate of fruits: Determination of glucose, fructose, sucrose and starch. *Biochemical Journal* **29**, 151-156.
Widdowson EM & McCance RA (1942) Iron exchanges of adults on white and brown breas diets. *The Lancet* **239**, 588-591.

Willett WC, Stampfer MJ, Colditz GA, Rosner BA & Speizer FE (1990) Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* **323**, 1664-1672.
Williams RD & Olmsted WH (1935) A biochemical method for determining indigestible residue (crude fiber) in feces: lignin, cellulose, and non-water soluble hemicelluloses. *Journal of Biological Chemistry* **108**, 653-666.
Williams RD & Olmsted WH (1936) The manner in which food controls the bulk of feces *Annals of Internal Medicine* **10**, 717-727.
Williams RD, Olmsted WH, Hamann CH, Fiorito JA & Duckles D (1936) The Effect of Cellulose, Hemicellulose and Lignin on the Weight of the Stool: A Contribution to the Study of Laxation in Man: Two Figures. *Journal of Nutrition* **11**, 433-449.
Wisker E, Daniel M & Feldheim W (1994a) Effects of a fiber concentrate from citrus fruits in humans. *Nutrition Research* **14**, 361-372.
Wisker E, Daniel M, Rave G & Feldheim W (1998) Fermentation of non-starch polysaccharides in mixed diets and single fibre sources: comparative studies in human subjects and in vitro. *British Journal of Nutrition* **80**, 253-261.
Wisker E, Nagel R, Tanudjaja TK & Feldheim W (1991) Calcium, magnesium, zinc, and iron balances in young women: effects of a low-phytate barley-fiber concentrate. *American Journal of Clinical Nutrition* **54**, 553-559.
Wisker E, Schweizer TF, Daniel M & Feldheim W (1994b) Fibre-mediated physiological effects of raw and processed carrots in humans. *British Journal of Nutrition* **72**, 579-599.
Wisten A & Messner T (2005) Fruit and fibre (Pajala porridge) in the prevention of constipation. *Scandinavian Journal of Caring Sciences* **19**, 71-76.
Wong HL, Seow A, Arakawa K, Lee HP, Yu MC & Ingles SA (2003) Vitamin D receptor start codon polymorphism and colorectal cancer risk: effect modification by dietary calcium and fat in Singapore Chinese. *Carcinogenesis* **24**, 1091-1095.
Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, Holmes C & Jenkins DJ (2010) The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. *Metabolism: Clinical & Experimental* **59**, 1331-1340.
Wood RJ, Gerhardt A & Rosenberg IH (1987) Effects of glucose and glucose polymers on calcium absorption in healthy subjects. *Am J Clin Nutr* **46**, 699-701.
World Gastroenterology Organisation (2008) Acute diarrhea. In *World Gastroenterology Organisation Practice Guidelines*: World Gastroenterology Organisation.
World Health Organization (2009) International travel and health: situation as on 1 January 2009: World Health Organization.
Wrick KL, Robertson JB, Van Soest PJ, Lewis BA, Rivers JM, Roe DA & Hackler LR (1983) The influence of dietary fiber source on human intestinal transit and stool output. *Journal of Nutrition* **113**, 1464-1479.
Wu AH, Paganini-Hill A, Ross RK & Henderson BE (1987) Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. *Br J Cancer* **55**, 687-694.
Wyatt GM, Bayliss CE & Holcroft JD (1986) A change in human faecal flora in response to inclusion of gum arabic in the diet. *British Journal of Nutrition* **55**, 261-266.
Wyman JB, Heaton KW, Manning AP & Wicks AC (1976) The effect on intestinal transit and the feces of raw and cooked bran in different doses. *American Journal of Clinical Nutrition* **29**, 1474-1479.
Yadrick MM, Halling JF, Beyer PL & Rhodes JB (1992) Comparison of the effects of diets high and low in simple sugars on bowel function in healthy, lactose-tolerant men. *Journal of the American Dietetic Association* **92**, 1121-1123.

Young RJ, Beerman LE & Vanderhoof JA (1998) Increasing oral fluids in chronic constipation in children. *Gastroenterology Nursing* **21**, 156-161.

Zhang X, Albanes D, Beeson WL, van den Brandt PA, Buring JE, Flood A, Freudenheim JL, Giovannucci EL, Goldbohm RA, Jaceldo-Siegl K, Jacobs EJ, Krogh V, Larsson SC, Marshall JR, McCullough ML, Miller AB, Robien K, Rohan TE, Schatzkin A, Sieri S, Spiegelman D, Virtamo J, Wolk A, Willett WC, Zhang SM & Smith-Warner SA (2010) Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. *Journal of the National Cancer Institute* **102**, 771-783.

Ziegenhagen DJ, Tewinkel G, Kruis W & Herrmann F (1991) Adding more fluid to wheat bran has no significant effects on intestinal functions of healthy subjects. *Journal of Clinical Gastroenterology* **13**, 525-530.

Ziegler E, Vanderhoof JA, Petschow B, Mitmesser SH, Stolz SI, Harris CL & Berseth CL (2007) Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *Journal of Pediatric Gastroenterology and Nutrition* **44**, 359-364.

Ziegler EE & Fomon SJ (1983) Lactose enhances mineral absorption in infancy. *Journal of Pediatric Gastroenterology & Nutrition* **2**, 288-294.

Zittermann A, Bock P, Drummer C, Scheld K, Heer M & Stehle P (2000) Lactose does not enhance calcium bioavailability in lactose-tolerant, healthy adults. *American Journal of Clinical Nutrition* **71**, 931-936.

Appendix 1. Search terms

Carbohydrate exposure search terms

General **carbohydrate** terms: exploded Emtree terms “CARBOHYDRATE DIET” OR “CARBOHYDRATE INTAKE” OR “STARCH” OR “Polysaccharides” OR “oligosaccharides” OR “pasta” OR exploded MeSH terms “DIETARY CARBOHYDRATES” OR “STARCH” OR” Polysaccharide” OR “oligosaccharides” OR CINAHL exploded “DIETARY CARBOHYDRATES” OR “Polysaccharide” OR “oligosaccharides” OR free-text terms “carbohydrate*” OR “starch*” OR “polysaccharide*” oligosaccharide* OR "refined grain" OR . ("cake*" OR "biscuit*" OR "cookie*" OR "confectionery") AND ("diet" OR "intake")

Sugars terms: exploded Emtree terms “SUGAR INTAKE” OR “SUCROSE” OR “FRUCTOSE” OR “LACTOSE” OR “GALACTOSE” OR “Maltose” OR “Isomaltose” OR “carbonated beverages” OR exploded MeSH terms “DIETARY SUCROSE” OR “FRUCTOSE” OR “LACTOSE” OR “GALACTOSE” OR “candy” OR “carbonated beverages” OR “Isomaltose” OR “Maltose” OR CINAHL thesaurus terms “DIETARY SUCROSE” OR “FRUCTOSE” OR “LACTOSE” OR “candy” OR “carbonated beverages” OR free-text terms “sugar*” OR “sucrose” OR “fructose” OR “lactose” OR “galactose” OR “maltose” OR “disaccharide*” OR “monosaccharide*” OR (“soda” OR “carbonated” OR “sweet*” OR “sugar*”) AND (drink* OR beverage*) OR “soft drink”.

Polyol terms: exploded Emtree terms “Polyol” OR “SUGAR ALCOHOL” OR “SORBITOL” OR “XYLITOL” OR exploded MeSH terms “SUGAR ALCOHOLS” OR “SORBITOL” OR “XYLITOL” OR free-text terms “polyol*” OR “sorbitol” OR “maltitol” OR “isomalt” OR “ xylitol” OR “erythritol” OR “lactitol” OR “mannitol” OR “polyglycitol” OR CINAHL thesaurus terms “SORBITOL” OR “XYLITOL”OR exploded “SUGAR ALCOHOLS”

Non-digestible oligosaccharide terms: exploded Emtree terms “PREBIOTIC AGENT” OR “FRUCTAN” OR “INULIN” OR “FRUCTOSE OLIGOSACCHARIDE” OR “GALACTOSE OLIGOSACCHARIDE” OR “RAFFINOSE” OR mannans/ OR exploded MeSH terms “FRUCTANS” OR “INULIN” OR “RAFFINOSE” OR mannans/ OR CINAHL thesaurus terms “PREBIOTICS” OR free-text terms “prebiotic*” OR “inulin” OR “fructan*” OR “raffinose” OR "polydextrose" OR ((“galacto*” OR “fructo*” OR “non-digestible” OR “nondigestible” OR “low-digestible” OR “indigestible”) AND (“oligosaccharide*”))

NSP/dietary fibre terms: Exploded Emtree terms “DIETARY FIBER” OR “ISPAGULA” OR “BETA GLUCAN” OR “STERCULIA” OR “KARAYA GUM” OR “BULKING AGENT” OR “BRAN” OR “WHEAT BRAN” OR “GUAR GUM” OR “ARABINOXYLAN” OR “PECTIN” OR “HEMICELLULOSE” OR “Alginic acid” OR “carageenan” OR “cellulose” OR “methylcellulose” OR “lignin” OR “carboxymethylcellulose” OR “plant gum” OR “gum Arabic” OR “gum tragacanth” OR “cereal” OR “legume” OR “bread” OR exploded MeSH terms “DIETARY FIBER” OR “PSYLLIUM” OR “BETA-GLUCANS” OR “STERCULIA” OR “KARAYA GUM” OR “PECTINS” OR “Alginates” OR “carageenan” OR “cellulose” OR “methylcellulose” OR “lignin” OR “carboxymethylcellulose” OR “plant gums” OR “gum Arabic” OR

“tragacanth” OR “cereals” OR “fabaceae” OR “bread” OR CINAHL thesaurus terms “DIETARY FIBER” OR “PSYLLIUM” OR “alginates” OR “cellulose” OR “cereals” OR “bread” OR “legumes OR free-text terms “whole grain*” OR “wholegrain*” OR “whole meal” OR “wholemeal” OR “complex carbohydrate*” OR “unavailable carbohydrate*” OR “resistant starch*” OR “amylose” OR “psyllium” OR “sterculia” OR “karaya gum” OR “bulking agent” OR “husk” OR “bran” OR “ispaghula” OR “roughage*” OR “raw starch” OR “cellulose” OR “hemicellulose” OR “pectin” OR “arabinoxylan*” OR “plant gum*” OR “guar gum” OR “beta-glucan*” OR ((“non-starch” OR “nonstarch” OR “low-digestible” OR “non-digestible ” OR “nondigestible” OR “indigestible”) AND (“polysaccharide*” OR “carbohydrate*”)) OR (("fibre*" OR "fiber*") AND (“dietary” OR “plant” OR “high” OR “crude” OR “insoluble” OR “soluble”)) OR “wheat” OR “rice” OR "cereal*" OR “oat*” OR “porridge” OR “rye*” OR “barley” OR “grain*” OR “bread*” OR (“whole” AND “grain*”) OR “vegetable*” OR “fruit*” OR “bean*” OR “prune*” OR “legume*” OR “potato” OR “maise” OR “alginate” OR “xanthan” OR “carageenan” OR “methylcellulose” OR “hydroxymethylcellulose” OR (("acacia" OR "arabic" OR "bean") AND “gum”)

Glycaemic index and load: exploded Emtree terms “GLYCEMIC INDEX” OR “GLYCEMIC LOAD” OR “GLUCOSE BLOOD LEVEL” OR exploded MeSH terms “GLYCEMIC INDEX” OR “BLOOD GLUCOSE” OR CINAHL thesaurus terms “GLYCEMIC INDEX” OR “BLOOD GLUCOSE” OR ((index OR load) adj3 glycaemic) OR ((index or load) adj3 glycemic) OR ((sugar* OR glucose) adj3 blood)

Normal colo-rectal function, well-being, constipation, diverticular disease, diarrhoea and irritable bowel syndrome terms

Exploded Emtree terms “DIARRHEA” OR “DEFECATION” OR “CONSTIPATION” OR “FECES” OR “DEFECATION HABIT” OR “INTESTINE TRANSIT TIME” OR“LACTOBACILLUS” OR “BIFIDOBACTERIUM” OR “INTESTINE FLORA” OR “COLON FLORA” OR “SHORT CHAIN FATTY ACID” OR “DYSPEPSIA” OR “ABDOMINAL PAIN” OR “MOOD” OR “INTESTINE FUNCTION” OR “WELLBEING” OR “BLOATING” OR “IRRITABLE COLON” OR "Diverticulum"

Or exploded MeSH terms “DIARRHEA” OR “DEFECATION” OR “CONSTIPATION” OR “FECES” “LACTOBACILLUS” OR “BIFIDOBACTERIUM” OR “FATTY ACIDS, VOLATILE” OR “DYSPEPSIA” OR “ABDOMINAL PAIN” OR “AFFECT” OR “NAUSEA” OR “IRRITABLE BOWEL SYNDROME”, "Diverticulum" OR “COLONIC DISEASES, FUNCTIONAL”

Or CINAHL thesaurus terms “DIARRHEA” OR “DEFECATION” OR “CONSTIPATION” OR “FECES” OR “BIFIDOBACTERIUM” OR “FATTY ACIDS, VOLATILE” OR exploded “LACTOBACILLUS” OR “DYSPEPSIA” OR “AFFECT” OR “NAUSEA” OR exploded “ABDOMINAL PAIN” OR "Diverticulum" OR “IRRITABLE BOWEL SYNDROME”

And the free-text terms “stool” OR “diarrhoea” OR "diarrhea" OR "feces" OR "faeces" OR "faecal" OR "fecal" OR "constipation" OR "laxation" OR "dyschezia"

OR "defecation" OR “bifidobacteri*” OR “lactobacill*” OR “acetate*” OR “propionate*” OR “butyrate*” OR “short chain fatty acid*” OR“abdominal pain” OR “stomach pain” OR “bloating” OR “bloatedness” OR “indigestion” OR “dyspepsia” OR “nausea” OR “mood” OR “well-being” OR “wellbeing” OR “irritable bowel syndrome” OR “IBS” OR “spastic colon” OR “irritable colon” OR ((“colon*” OR “bowel” OR “intestin*” OR “gut”) AND (“transit" OR “habit” OR “function” OR "dysfunction" OR "microbe*" OR "bacteria" OR "microbiota" OR "microflora" OR "fermentation" OR “inertia”)) OR "diverticulum" OR "diverticulosis" OR ("diverticular" AND "disease")

Human controlled study filter terms

388. For the retrieval of controlled human studies search terms were adapted from a randomized controlled trial filter described in the Cochrane Handbook and the International Epidemiological Association.

For Medline, exploded MeSH terms: “randomized controlled trial” OR “controlled clinical trial” OR “clinical trial” OR “random allocation” OR “double-blind method” OR “single-blind method” OR “placebos” OR “cross-over studies” OR “multicenter study” unexploded MeSH term: “research design” OR EMTREE terms: “crossover-procedure” OR “double-blind procedure” OR “single-blind procedure” OR “randomized controlled trial” OR “multicenter study” OR “randomization” OR CINAHL thesaurus terms : exploded “clinical trials” OR “random assignment” OR “double-blind studies” OR “single-blind studies” OR “placebos” OR “crossover design” OR “multicenter studies”

And the free-text terms: “trial” OR ((“singl*” OR “doubl*” OR “trebl*” OR “tripl*”) AND (“mask*” OR “blind*”)) OR “placebo*” OR “random*” OR “control*” OR “volunteer*” OR “subject*” OR “factorial*” OR “crossover*” OR “cross over*” OR “cross-over*” OR “assign*” OR “allocate*”

Ca and Mg absorption outcome terms

Exploded Emtree terms: (INTESTINE ABSORPTION AND “CALCIUM INTAKE”) OR Exploded MeSH terms (INTESTINAL ABSORPTION AND CALCIUM, DIETARY) OR Cinahl thesaurus terms (INTESTINAL ABSORPTION AND “CALCIUM, DIETARY”) OR free text terms ((“calcium” OR “magnesium” OR “Ca” OR “Mg” OR “mineral*” OR “trace element*”) AND (“absorption” OR “balance”))

AND all carbohydrate terms

Colo-rectal cancer/adenoma outcome terms

#1 exploded Emtree terms “COLORECTAL CANCER” OR “COLORECTAL TUMOR” OR “INTESTINE POLYP” OR “COLON POLYP” OR exploded MeSH term “COLORECTAL NEOPLASMS” OR “INTESTINAL POLYPS” OR “COLONIC POLYPS” OR exploded CINAHL thesaurus terms COLORECTAL

NEOPLASMS” OR “ADENOMATOUS POLYPS” OR exploded “INTESTINAL POLYPS” OR “COLONIC POLYPS”
#2 "malign*" OR "neoplasm*" OR "carcinoma*" OR "cancer*" OR "tumor*" OR "tumour*" OR "polyp*" OR "adenoma*" OR "adenocarcinoma"
#3 "colon*" OR "rectum" OR "rectal" OR "colorectum" OR "colorectal" OR "bowel" OR "large intestine" OR "gut"
#4 #1 OR (#2 AND #3)

Appendix 2. Articles excluded at full-text stage

Digestible carbohydrate and colo-rectal function

389. The initial search identified 15 articles, which were assessed as full-text articles for eligibility. Of these 14 were excluded for the following reasons:

- No objective measure: (Seppanen *et al.*, 2008).
- Single challenge studies or cohort before-and-after studies, but were briefly discussed in the background section (Williams & Olmsted, 1936; Bond *et al.*, 1980; Ravich *et al.*, 1983; Truswell *et al.*, 1988; Kruis *et al.*, 1991; Ewe *et al.*, 1995; Ladas *et al.*, 1995; Hoekstra *et al.*, 1996; Mitsui *et al.*, 2001; Beyer *et al.*, 2005; He *et al.*, 2006; Madsen *et al.*, 2006; Skoog *et al.*, 2008)

Non-digestible carbohydrate and and colo-rectal function

390. The initial search identified 329 articles, which were assessed as full-text articles for eligibility. Of these 220 were excluded for the following reasons:

- Reviews or letters with no relevant data: (Burkitt *et al.*, 1972; Cleave, 1973)
- Not healthy subjects: (Harvey *et al.*, 1973; Kirby *et al.*, 1981; Hamaker *et al.*, 1991; Kashtan *et al.*, 1992b; Savino *et al.*, 2003; Langlands *et al.*, 2004; Boutron-Ruault *et al.*, 2005; Dahl *et al.*, 2005b)
- Data reported in previous article: (Baird *et al.*, 1977; Jenkins *et al.*, 1979; Stephen & Cummings, 1979; Slavin & Marlett, 1980a; Bell *et al.*, 1981; Slavin *et al.*, 1981b; Slavin *et al.*, 1991; Tomlin & Read, 1992; Lampe *et al.*, 1993a; Kanauchi *et al.*, 1999; Moro *et al.*, 2003; Abell *et al.*, 2008)
- No relevant data reported: (Parsons, 1973; Slavin *et al.*, 1981a; Ullrich *et al.*, 1981; Van Dokkum *et al.*, 1982; Rigaud *et al.*, 1987; Miles *et al.*, 1988; Kitler *et al.*, 1992; Korpela *et al.*, 1992; Behall & Howe, 1996; Wisker *et al.*, 1998; De Preter *et al.*, 2004; Gonlachanvit *et al.*, 2004; Moro *et al.*, 2005; Finley *et al.*, 2007)
- Enteral feed intervention: (Slavin *et al.*, 1985; Whelan *et al.*, 2005; Benus *et al.*, 2010)
- Single meal study: (Bond & Levitt, 1978; Kelleher *et al.*, 1984; Lembcke *et al.*, 1984; Fritz *et al.*, 1985; McNamara *et al.*, 1985; Salminen *et al.*, 1985; Levitt *et al.*, 1987; De Vries *et al.*, 1988; Hamberg *et al.*, 1989; Rumessen *et al.*, 1990)
- No objective bowel function measures: (Turconi *et al.*, 1995; Davies *et al.*, 1998; Bruce *et al.*, 2000; Li *et al.*, 2003; Moore *et al.*, 2003; Storey *et al.*, 2007; Ziegler *et al.*, 2007; Park & Jhon, 2009)
- Mixed intervention, e.g. energy restriction and dietary fibre: (Astrup *et al.*, 1990; Staniforth *et al.*, 1991; Muir *et al.*, 1998; Brinkworth *et al.*, 2009; Cheatham *et al.*, 2009; Mitsou *et al.*, 2009; Wong *et al.*, 2010) or formula with hydrolyzed whey protein (Schmelzle *et al.*, 2003)
- Cohort before-and-after studies and comparison studies with no control, but were

briefly discussed in the background section: (Cowgill & Anderson, 1932; Williams *et al.*, 1936; Gray & Tainter, 1941; McCance & Widdowson, 1942a; Tainter, 1943; Marks, 1949; Berberian *et al.*, 1952; Antonis & Bersohn, 1962; Hamilton *et al.*, 1972; Eastwood *et al.*, 1973; Findlay *et al.*, 1974; Jenkins *et al.*, 1975; Payler *et al.*, 1975; Cummings *et al.*, 1976a; Cummings *et al.*, 1976b; Drasar & Jenkins, 1976; Durrington *et al.*, 1976; Fuchs *et al.*, 1976; Wyman *et al.*, 1976; Flynn *et al.*, 1977; Ismail-Beigi *et al.*, 1977; Kay & Truswell, 1977; Miettinen & Tarpila, 1977; Raymond *et al.*, 1977; Beyer & Flynn, 1978; Brodribb & Groves, 1978; Calloway & Kretsch, 1978; Cummings *et al.*, 1978; Floch & Fuchs, 1978; Kelsay *et al.*, 1978; Mathur *et al.*, 1978; Cummings *et al.*, 1979a; Cummings *et al.*, 1979b; Cummings *et al.*, 1979c; Kretsch *et al.*, 1979; Munoz *et al.*, 1979; Prynne & Southgate, 1979; Robertson *et al.*, 1979; Heller *et al.*, 1980; Huijbregts *et al.*, 1980; Slavin & Marlett, 1980b; Stephen & Cummings, 1980a; Cornu & Delpeuch, 1981; Judd & Truswell, 1981; Ross & Leklem, 1981; Tucker *et al.*, 1981; Leeds *et al.*, 1982; Andersson *et al.*, 1983; Eastwood *et al.*, 1983; Fleming *et al.*, 1983; Fleming & Rodriguez, 1983; Ross *et al.*, 1983; Schweizer *et al.*, 1983; Tsai *et al.*, 1983; Van Dokkum *et al.*, 1983; Wrick *et al.*, 1983; Anderson *et al.*, 1984; Eastwood *et al.*, 1984; Fedail *et al.*, 1984; Fleming *et al.*, 1985; Vargo *et al.*, 1985; Eastwood *et al.*, 1986; Kaneko *et al.*, 1986; Marlett *et al.*, 1986; Miyoshi *et al.*, 1986; Penagini *et al.*, 1986; Shetty & Kurpad, 1986; Spiller *et al.*, 1986; Wyatt *et al.*, 1986; Balasubramanian *et al.*, 1987; Behall *et al.*, 1987; Eastwood *et al.*, 1987; Jenkins *et al.*, 1987; Miyoshi *et al.*, 1987; Abraham & Mehta, 1988; Anderson *et al.*, 1988; Hamilton *et al.*, 1988; Kurpad *et al.*, 1988; Reddy *et al.*, 1988; Stevens *et al.*, 1988; Tomlin & Read, 1988a; Tomlin & Read, 1988c; Villaume *et al.*, 1988; Benno *et al.*, 1989; Miettinen & Tarpila, 1989; Eastwood *et al.*, 1990; Kashtan *et al.*, 1990; Anderson *et al.*, 1991; Melcher *et al.*, 1991a; Melcher *et al.*, 1991b; Saito *et al.*, 1991; Sugawara *et al.*, 1991; Ziegenhagen *et al.*, 1991; Daly *et al.*, 1993; Ito *et al.*, 1993a; Ito *et al.*, 1993b; Lampe *et al.*, 1993b; Lupton *et al.*, 1993; Nagengast *et al.*, 1993; Takahashi *et al.*, 1993; Achour *et al.*, 1994; Gelissen *et al.*, 1994; Rao *et al.*, 1994; van Munster *et al.*, 1994; Gibson *et al.*, 1995b; Ohkusa *et al.*, 1995; Buddington *et al.*, 1996; Davidsson *et al.*, 1996; Guedon *et al.*, 1996; Bouhnik *et al.*, 1997; Lewis & Heaton, 1997a; Lewis & Heaton, 1997b; Switzer *et al.*, 1997; Chen *et al.*, 1998; Haack *et al.*, 1998a; Hylla *et al.*, 1998; Kanauchi *et al.*, 1998a; Kanauchi *et al.*, 1998b; Teuri *et al.*, 1998; Brighenti *et al.*, 1999; Kruse *et al.*, 1999; Schaarmann *et al.*, 1999; Marlett *et al.*, 2000; Menne *et al.*, 2000; Srikumar, 2000; Jenkins *et al.*, 2001; Rao, 2001; Robinson *et al.*, 2001; Tuohy *et al.*, 2001a; Gallaher *et al.*, 2002; Guigoz *et al.*, 2002; Harmsen *et al.*, 2002; Cherbut *et al.*, 2003; Grasten *et al.*, 2003; Hovey *et al.*, 2003; Spiller *et al.*, 2003a; Spiller *et al.*, 2003b; Minamida *et al.*, 2004; Dahl *et al.*, 2005a; Euler *et al.*, 2005; Liu *et al.*, 2005; Chen *et al.*, 2006; Dinoto *et al.*, 2006; Bang *et al.*, 2007; Bouhnik *et al.*, 2007a; Chung *et al.*, 2007; Kolida *et al.*, 2007; Myung *et al.*, 2007; Pittaway *et al.*, 2007; Costabile *et al.*, 2008; de Preter *et al.*, 2008; Nilsson *et al.*, 2008; Maki *et al.*, 2009; Mrazek *et al.*, 2010; Shinohara *et al.*, 2010)

Digestible carbohydrate carbohydrate and magnesium and calcium absorption

391. The initial search identified 26 articles, which were assessed as full-text articles for

eligibility. Of these 24 were excluded for the following reasons:

- Mineral balance studies, which were briefly discussed in the background section (Greenwald *et al.*, 1963; Condon *et al.*, 1970; Pansu & Chapuy, 1970; Kobayashi *et al.*, 1975; Ziegler & Fomon, 1983; Holbrook *et al.*, 1989; Ivaturi & Kies, 1992; Moya *et al.*, 1992; Brink *et al.*, 1993; Moya *et al.*, 1999; Milne & Nielsen, 2000)
- Single meal or challenge studies, which were briefly discussed in the background section (Kocian *et al.*, 1973; Cochet *et al.*, 1983; Kelly *et al.*, 1984; Tremaine *et al.*, 1986; Wood *et al.*, 1987; Knowles *et al.*, 1988; Griessen *et al.*, 1989a; Griessen *et al.*, 1989c; Schuette *et al.*, 1989; Garg *et al.*, 1990; Schuette *et al.*, 1991; Andon *et al.*, 1996; Zittermann *et al.*, 2000).

Non-digestible carbohydrate carbohydrate and magnesium and calcium absorption

392. The initial search identified 48 articles, which were assessed as full-text articles for eligibility. Of these 38 were excluded for the following reasons:

393.

- Mineral balance studies, which were briefly discussed in the background section: (McCance & Widdowson, 1942a; Reinhold *et al.*, 1976; Ismail-Beigi *et al.*, 1977; Cummings *et al.*, 1979b; Cummings *et al.*, 1979c; Drews *et al.*, 1979; Slavin & Marlett, 1980b; Stasse-Wolthuis *et al.*, 1980; Godara *et al.*, 1981; Kelsay *et al.*, 1981; Van Dokkum *et al.*, 1982; Andersson *et al.*, 1983; Kelsay & Prather, 1983; Behall *et al.*, 1987; Kelsay *et al.*, 1988; Behall *et al.*, 1989; Behall, 1990; Spencer *et al.*, 1991; Wisker *et al.*, 1991; Kawatra *et al.*, 1993; Dahl *et al.*, 1995; Knudsen *et al.*, 1996; Coudray *et al.*, 1997; Haack *et al.*, 1998b; Behall *et al.*, 2002; Coudray *et al.*, 2003a; Vermorel *et al.*, 2004; Gostner *et al.*, 2005; Shah *et al.*, 2009)
- Single meal studies (Francis *et al.*, 1986; Gulliford *et al.*, 1988; Griessen *et al.*, 1989b; Heaney & Weaver, 1995; Davidsson *et al.*, 1996; Lopez-Huertas *et al.*, 2006)
- One cohort before-and-after study that observed oat bran to have no effect on the absorption of calcium, as determined with ^{47}Ca (Spencer *et al.*, 1991)

Chronic constipation

394. The initial search identified 94 articles, which were assessed as full-text articles were for eligibility. Of these 70 articles were excluded for the following reasons:

- Dietary intervention in conjunction with other therapy (Stern, 1966; Capra & Hannan-Jones, 1993)
- Mixed patients groups - not all patients described as constipated (Gotestam, 1977; Kochen *et al.*, 1985; Schmelzer, 1990; Snustad *et al.*, 1991; Fowlie *et al.*, 1992; Den Hond *et al.*, 2000; Wisten & Messner, 2005; Kacmaz & Kasici, 2007)
- Lack of appropriate control (Odes *et al.*, 1993) – (XO design where 9 of 10 subjects randomised to receive placebo in first phase dropped out due to lack of effect – analysis based on 7 from treatment-first group and one from placebo-first

group)
- Trial involved surgery (Stumm *et al.*, 2001)
- Mixed intervention with non-carbohydrate constituents that could affect bowel habit (Bongers *et al.*, 2007)
- Report physiological outcomes only, but did not exclude laxative use (Smith *et al.*, 1980)
- Study group allocation not randomised, which were briefly discussed in the background section (Battle & Hanna, 1980; Marzio *et al.*, 1989; Sturtzel & Elmadfa, 2008; Sturtzel *et al.*, 2010)
- No control group – cohort before-and-after studies, which were briefly discussed in the background section (Cowgill & Sullivan, 1933; Block, 1947; Marks, 1949; Ferrer & Boyd, 1955; Payler *et al.*, 1975; Clark & Scott, 1976; Srivastava *et al.*, 1976; Perkin, 1977; McCallum *et al.*, 1978; Hull *et al.*, 1980; Graham *et al.*, 1982; Olness & Tobin, 1982; Borgia *et al.*, 1983; Pers & Pers, 1983; Sandman *et al.*, 1983; Valle-Jones, 1985; Hope & Down, 1986; Marcus & Heaton, 1986; Marlett *et al.*, 1987; Bass *et al.*, 1988; Chokhavatia *et al.*, 1988; Hamilton *et al.*, 1988; Lederle *et al.*, 1990; Rouse *et al.*, 1991; Kinnunen *et al.*, 1993; Passmore *et al.*, 1993a; Passmore *et al.*, 1993b; Rodrigues-Fisher *et al.*, 1993; Gibson *et al.*, 1995a; Ravelli *et al.*, 1995; Kleessen *et al.*, 1997; Anti *et al.*, 1998; Dettmar & Sykes, 1998; Kanauchi *et al.*, 1998b; McRorie *et al.*, 1998; Patrick *et al.*, 1998; Assisi *et al.*, 2000; Chen *et al.*, 2000; Chen *et al.*, 2001; Selig & Boyle, 2003; Tarpila *et al.*, 2004; Gostner *et al.*, 2005; Khaja *et al.*, 2005; Tateyama *et al.*, 2005; Quah *et al.*, 2006; Chan *et al.*, 2007a; Chen *et al.*, 2008; Danjo *et al.*, 2008; Kokke *et al.*, 2008)
- Comparison trial with no control group, which were briefly discussed in the background section (Andersson *et al.*, 1979; Takahashi *et al.*, 1994; Voderholzer *et al.*, 1997)

Diarrhoea

395. The initial search identified 37 articles, which were assessed as full-text articles for eligibility. Of these 18 articles were excluded for the following reasons:

- Treatment trials, not prevention trials (Portnoy *et al.*, 1976; Alarcon *et al.*, 1992; Brown *et al.*, 1993; Eherer *et al.*, 1993; Vanderhoof *et al.*, 1997; Washington *et al.*, 1998; Alam *et al.*, 2000; Ramakrishna *et al.*, 2000; Burks *et al.*, 2001; Rabbani *et al.*, 2001; Duggan *et al.*, 2003; Hoekstra *et al.*, 2004; Alam *et al.*, 2005; Raghupathy *et al.*, 2006; Ramakrishna *et al.*, 2008)
- Mixed intervention (Loeb *et al.*, 1989)
- No control group – a comparison study of calcium and psyllium (Qvitzau *et al.*, 1988) and two time series studies (Nakamura *et al.*, 2007; Oku *et al.*, 2008)
- One trial investigated the effect of fructo-oligosaccharide supplementation on the incidence of antibiotic-associated diarrhoea in hospital patients, but the incidence rate was too low for the results to be meaningful, i.e. 0/18 in the fructo-oligosaccharide group and 2/18 in the placebo group. (Madeo *et al.*, 1999)
- Severely malnourished infants (Alam *et al.*, 2009)
- Trial reported in previously identified paper (Lewis *et al.*, 2005b)
- Not a trial - case reports (Hyams & Leichtner, 1985)

- Single meal studies (mainly postprandial breath hydrogen test) (Kneepkens *et al.*, 1989; Hoekstra *et al.*, 1995; Smith *et al.*, 1995; Nobigrot *et al.*, 1997; Lifschitz, 2000; Lebenthal-Bendor *et al.*, 2001; Ribeiro *et al.*, 2001; Duro *et al.*, 2002; Moukarzel *et al.*, 2002)
- Mal-absorption trial (Valois *et al.*, 2005)

Irritable bowel syndrome

396. Initial search identified 31 articles, which were assessed as full-text articles for eligibility. Of these 15 articles were excluded for the following reasons:

- Treatment trials, not prevention trials(Manning *et al.*, 1977; Ritchie & Truelove, 1979; Longstreth *et al.*, 1981; Golechha *et al.*, 1982; Nigam *et al.*, 1984; Kruis *et al.*, 1986; Prior & Whorwell, 1987; Cook *et al.*, 1990; Jalihal & Kurian, 1990; Fowlie *et al.*, 1992; Snook & Shepherd, 1994; Hunter *et al.*, 1999; Olesen & Gudmand-Hoyer, 2000; Rees *et al.*, 2005; Bijkerk *et al.*, 2009; Silk *et al.*, 2009)
- Intervention group not compared with control group (no placebo arm) (Kumar *et al.*, 1987; Chapman *et al.*, 1990; Villagrasa *et al.*, 1991; Parisi *et al.*, 2002; Aller *et al.*, 2004; Tarpila *et al.*, 2004; Parisi *et al.*, 2005; Austin *et al.*, 2009)
- Dietary intervention in conjunction with drug therapy (Soltoft *et al.*, 1976; Ritchie & Truelove, 1980; Arthurs & Fielding, 1983; Cann *et al.*, 1984; Arffman *et al.*, 1985; Lucey *et al.*, 1987)
- Results reported in previous article (Mortensen *et al.*, 1987)

Diverticular disease

397. The initial search identified 18 articles, which were assessed as full-text articles for eligibility Of these 14 have been excluded for the following reasons:

- Treatment trials, not prevention trials (Brodribb, 1977; Hodgson, 1977; Ewerth *et al.*, 1980; Ornstein *et al.*, 1981)
- No control group - cohort before-and-after studies: (Painter *et al.*, 1972; Findlay *et al.*, 1974; Painter, 1974; Brodribb & Humphreys, 1976a; Brodribb & Humphreys, 1976b; Srivastava *et al.*, 1976; Taylor & Duthie, 1976; Eastwood *et al.*, 1978; Smith *et al.*, 1981); comparison study with no control group (Smits *et al.*, 1990; D'Inca *et al.*, 2007)
- Retrospective reviews of patients advised to increase their fibre intake after hospital admission and not trials (Hyland & Taylor, 1980; Leahy *et al.*, 1985)
- No clinical assessment (Tarpila *et al.*, 1978)

Well-being

398. The initial search identified 8 articles, which were assessed as full-text articles for eligibility. Of these 4 have been excluded for the following reasons:

- Not in healthy subjects or in patients with clinical outcomes considered – subjects

with minor functional bowel disorders (Paineau *et al.*, 2008)
- Not an intervention study (Smith *et al.*, 2001)
- No control group (Goetze *et al.*, 2008).
- Breakfast cereal consumption in comparison to no breakfast consumption on well-being, not carbohydrate intake *per se* (Smith, 2010)

Colo-rectal cancer

399. Forty eight relevant articles were identified from the WCRF dataset and report, which included searches upto 2009 (Stemmermann *et al.*, 1984; Wu *et al.*, 1987; Heilbrun *et al.*, 1989; Stemmermann *et al.*, 1990; Willett *et al.*, 1990; Bostick *et al.*, 1994; Giovannucci *et al.*, 1994; Steinmetz *et al.*, 1994; Chyou *et al.*, 1996; Gaard *et al.*, 1996; Glynn *et al.*, 1996; Kearney *et al.*, 1996; Kato *et al.*, 1997; Tangrea *et al.*, 1997; Sellers *et al.*, 1998; Fuchs *et al.*, 1999; Pietinen *et al.*, 1999; Colbert *et al.*, 2001; Jarvinen *et al.*, 2001; Terry *et al.*, 2001; Bingham *et al.*, 2003; Mai *et al.*, 2003; McCullough *et al.*, 2003; Terry *et al.*, 2003; Wong *et al.*, 2003; Higginbotham *et al.*, 2004; Koh *et al.*, 2004; Lin *et al.*, 2004; Sanjoaquin *et al.*, 2004; Bingham *et al.*, 2005; Larsson *et al.*, 2005; Michaud *et al.*, 2005; Michels *et al.*, 2005; Norat *et al.*, 2005; Park *et al.*, 2005; McCarl *et al.*, 2006; Otani *et al.*, 2006b; Shin *et al.*, 2006; Larsson *et al.*, 2007; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007; Strayer *et al.*, 2007; Wakai *et al.*, 2007; Butler *et al.*, 2008; Howarth *et al.*, 2008; Kabat *et al.*, 2008; Weijenberg *et al.*, 2008; George *et al.*, 2009).

400. Several of these articles report on the same population or subpopulation. A number of studies reported on the Nurses' Health Study Cohort (Willett *et al.*, 1990; Fuchs *et al.*, 1999) and the Health Professionals' Follow-up Study (Giovannucci *et al.*, 1994; Kearney *et al.*, 1996), while two studies reported on different exposures for both cohorts (Michaud *et al.*, 2005; Michels *et al.*, 2005). The two more recent reports (Michaud *et al.*, 2005; Michels *et al.*, 2005) were included, along with an earlier study that reported on lactose, which is not included in the more recent studies (Kearney *et al.*, 1996). Two studies reported on the Women's Health Study (Higginbotham *et al.*, 2004; Lin *et al.*, 2005), only the most recent was included for dietary fibre (Lin *et al.*, 2005) , while the earlier study was included in the glycaemic index analysis.

401. Three studies (Wong *et al.*, 2003; Koh *et al.*, 2004; Butler *et al.*, 2008) reported on the Singapore Chinese Health study, so only the most recent report was included (Butler *et al.*, 2008). Four studies (Glynn *et al.*, 1996; Tangrea *et al.*, 1997; Pietinen *et al.*, 1999; Colbert *et al.*, 2001) reported on the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. The most recent report of these four publications (Colbert *et al.*, 2001) did not provide enough information to be included in the meta-analysis, so the second-most recent report was included (Pietinen *et al.*, 1999).

402. Three studies (Bingham *et al.*, 2003; Bingham *et al.*, 2005; Norat *et al.*, 2005) reported on the European Prospective Investigation into Cancer and Nutrition study, the most recent study was included (Bingham *et al.*, 2005). Four studies (Bostick *et al.*, 1994; Steinmetz *et al.*, 1994; Sellers *et al.*, 1998; McCarl *et al.*, 2006) report on the Iowa Women's Health study, of which the most recent report included all exposures previously covered (in the WCRF dataset not the published in paper) (McCarl *et al.*, 2006).

403. Three articles reported on same exposure, energy intake from carbohydrate, from the Honolulu Heart Program study (Stemmermann *et al.*, 1984; Stemmermann *et al.*, 1990; Chyou *et al.*, 1996). The most recent of these reports (Chyou *et al.*, 1996) was included.

Dietary fibre intake and risk of colo-rectal cancer – prospective cohort studies

404. Twenty three studies were initially included for consideration (Wu *et al.*, 1987; Heilbrun *et al.*, 1989; Gaard *et al.*, 1996; Kato *et al.*, 1997; Pietinen *et al.*, 1999; Terry *et al.*, 2001; Mai *et al.*, 2003; McCullough *et al.*, 2003; Higginbotham *et al.*, 2004; Sanjoaquin *et al.*, 2004; Bingham *et al.*, 2005; Larsson *et al.*, 2005; Lin *et al.*, 2005; Michels *et al.*, 2005; Park *et al.*, 2005; McCarl *et al.*, 2006; Otani *et al.*, 2006b; Shin *et al.*, 2006; Nomura *et al.*, 2007; Schatzkin *et al.*, 2007; Wakai *et al.*, 2007; Butler *et al.*, 2008; Kabat *et al.*, 2008). Eight studies were subsequently excluded, as they did not adjust for or investigate all the necessary confounders, alcohol intake, smoking, physical activity, age and overweight/obesity:

- (Wu *et al.*, 1987; Heilbrun *et al.*, 1989; Gaard *et al.*, 1996; Kato *et al.*, 1997; Terry *et al.*, 2001; Sanjoaquin *et al.*, 2004; McCarl *et al.*, 2006; Kabat *et al.*, 2008)

405. One study adjusted for all the necessary confounders in relation to wholegrain cereal intake and colo-rectal cancer incidence (Larsson *et al.*, 2005), but did not do so for an analysis of cereal fibre and colon cancer incidence. Only the wholegrain cereal intake and colo-rectal cancer incidence aspects was included.

406. A literature search of articles published from 2009 until November 2010 identified 4 further articles, which were assessed as full-text articles for eligibility. Of these 3 have been excluded for the following reasons:

- No relevant data (Simons *et al.*, 2010)
- A prospective nested case-control study within seven UK cohort studies, but two of the cohorts were included in the EPIC study, which was more comprehensive (Dahm *et al.*, 2010)
- Report on wholegrain food intake only, but does not adjust for smoking in multivariate analysis (Egeberg *et al.*, 2010)

Total carbohydrate, starch or sugar intake, dietary glycaemic index or load and risk of colo-rectal cancer – prospective cohort studies

407. Fifteen studies were initially included for consideration (Chyou *et al.*, 1996; Kearney *et al.*, 1996; Kato *et al.*, 1997; Jarvinen *et al.*, 2001; Terry *et al.*, 2003; Higginbotham *et al.*, 2004; Michaud *et al.*, 2005; McCarl *et al.*, 2006; Larsson *et al.*, 2007; Strayer *et al.*, 2007; Butler *et al.*, 2008; Howarth *et al.*, 2008; Kabat *et al.*, 2008; Weijenberg *et al.*, 2008; George *et al.*, 2009). Four studies were subsequently excluded, as they did not adjust for or investigate all the necessary confounders, alcohol intake, smoking, physical activity, age and overweight/obesity:

- (Chyou *et al.*, 1996; Kato *et al.*, 1997; Jarvinen *et al.*, 2001; Kabat *et al.*, 2008)

408. A literature search of articles published from 2009 until November 2010 identified one further article for inclusion (Zhang *et al.*, 2010).

Randomised controlled trials of carbohydrate and adenoma risk

409. Eight trials were identified from the WCRF dataset and report, which included searches upto 2009, that investigated an effect of carbohydrate, either alone or as part of a mixed intervention, on risk of colo-rectal adenoma (DeCosse *et al.*, 1989; McKeown-Eyssen *et al.*, 1994; MacLennan *et al.*, 1995; Alberts *et al.*, 2000; Bonithon-Kopp *et al.*, 2000; Schatzkin *et al.*, 2000; Ishikawa *et al.*, 2005; Burn *et al.*, 2008). A further five articles were identified that conducted additional analyses of these trials (Maclennan *et al.*, 1999; Jacobs *et al.*, 2002; Jacobs *et al.*, 2006; Lanza *et al.*, 2007; Sansbury *et al.*, 2009). Of these one article was excluded:

- No results were reported (DeCosse *et al.*, 1989).

410. A literature search of articles published from 2009 until November 2010 identified no further articles for inclusion.

Appendix 3. Constituent dietary fibre intake, wholegrain cereal intake and colo-rectal cancer risk

Colo-rectal cancer incidence and cereal fibre intake

411. Six studies reported on colo-rectal cancer in relation to cereal fibre intake providing six risk estimates (see Table 113). All six studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. One study reported colon and rectal cancer incidence separately and could not be included (Larsson et al., 2005), finding an inverse association between cereal fibre intake and colon, but not rectal, cancer incidence. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 110 and Figure 26. The results of the per unit meta-analysis (10 g/day) have been summarised in Table 112 and Figure 28. Incorporation of the Pooling Project and studies not included in the pooled analysis left four studies providing four risk estimates (Figure 27). The results from the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 111.

412. There was no significant evidence of heterogeneity between studies. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

413. The highest quantile compared with lowest quantile meta-analysis (Table 110) observed a reduction in the incidence of colo-rectal cancer between the highest compared with the lowest quantile of cereal fibre intake, by a point estimate of 11%. The per unit meta-analysis also observed a significant reduction in the incidence of colo-rectal cancer with a 10g/day increase in cereal fibre, by a point estimate of 12%. For the analysis including the Pooling Project, however, the incidence of colo-rectal cancer between the highest compared with the lowest quantile of cereal fibre intake was not significantly different (see Table 111).

Table 110. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and cereal fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	6	0.89 (0.82-0.96)	-3.03 (p=0.002)

[1] I^2 = 0.00% (95% CI 0.00-74.62%); p for test of heterogeneity = 0.914

[2] No. of RR estimates included in pooled analysis.

Table 111. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and cereal fibre intake including the pooled analysis and studies not included in the pooled analysis

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	4	0.94 (0.87-1.02)	-1.55 (p=0.121)

[1] I^2 = 30.74% (95% CI 0.00-89.39%); p for test of heterogeneity = 0.228

[2] No. of RR estimates included in pooled analysis.

Table 112. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and cereal fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	6	0.88 (0.81-0.96)	-2.80 (p=0.005)

[1] I^2 = 0.00% (95% CI 0.00-74.62%); p for test of heterogeneity = 0.659

[2] No. of RR estimates included in pooled analysis.

Table 113. Adjusted relative risk ratios for the highest compared with the lowest quantile of cereal fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Individual cohorts										
Michels, 2005	Women	CRC	Q1 2.3g/1000kcal vs Q5 8.0g/1000kcal ****	0.89 (0.71-1.12)			0.63			No association observed
	Men	CRC	Q1 2.8g/1000kcal vs Q5 11.45g/1000kcal ****	0.79 (0.60-1.05)			0.19			
Lin, 2005	Women	CRC	Q1 3.1g/d vs Q5 6.1g/d ***	0.97 (0.66-1.42)			0.69			No association observed
Larsson, 2005	Women	CC, RC	Q1 <7.4g/d vs Q5 >13.6g/d **		0.77 (0.57-1.03)	0.99 (0.64-1.53)		0.03	NR	Inverse association observed for CC, but not RC
Bingham, 2005	Mixed	CRC	Men Q1 6.6g/d vs Q5 13.1g/d; Women Q1 4.9g/d vs Q5 9.2g/d ****	0.93 (0.76-1.15)			0.44			No association observed
Nomura, 2007	Women	CRC	Q1 2.4g/1000kcal/d vs Q5 14.0g/1000kcal/d ***	1.00 (0.78-1.27)			0.68			No association observed
	Men	CRC	Q1 2.8g/1000kcal/d vs Q5 15.6g/1000kcal/d ***	0.86 (0.69-1.07)			0.479			
Schatzkin, 2007	Mixed	CRC	Q1 6.6g/1000kcal/d vs Q5 15.9g/1000kcal/d ***	0.86 (0.76-0.98)			0.01			Inverse association observed
Pooled analysis										
Park, 2005	Mixed	CRC	Q1 vs Q5 *	1.00 (0.93-1.08)						No association observed

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Figure 26. Forest plot of the highest compared with the lowest quantile of cereal fibre intake and colo-rectal cancer risk

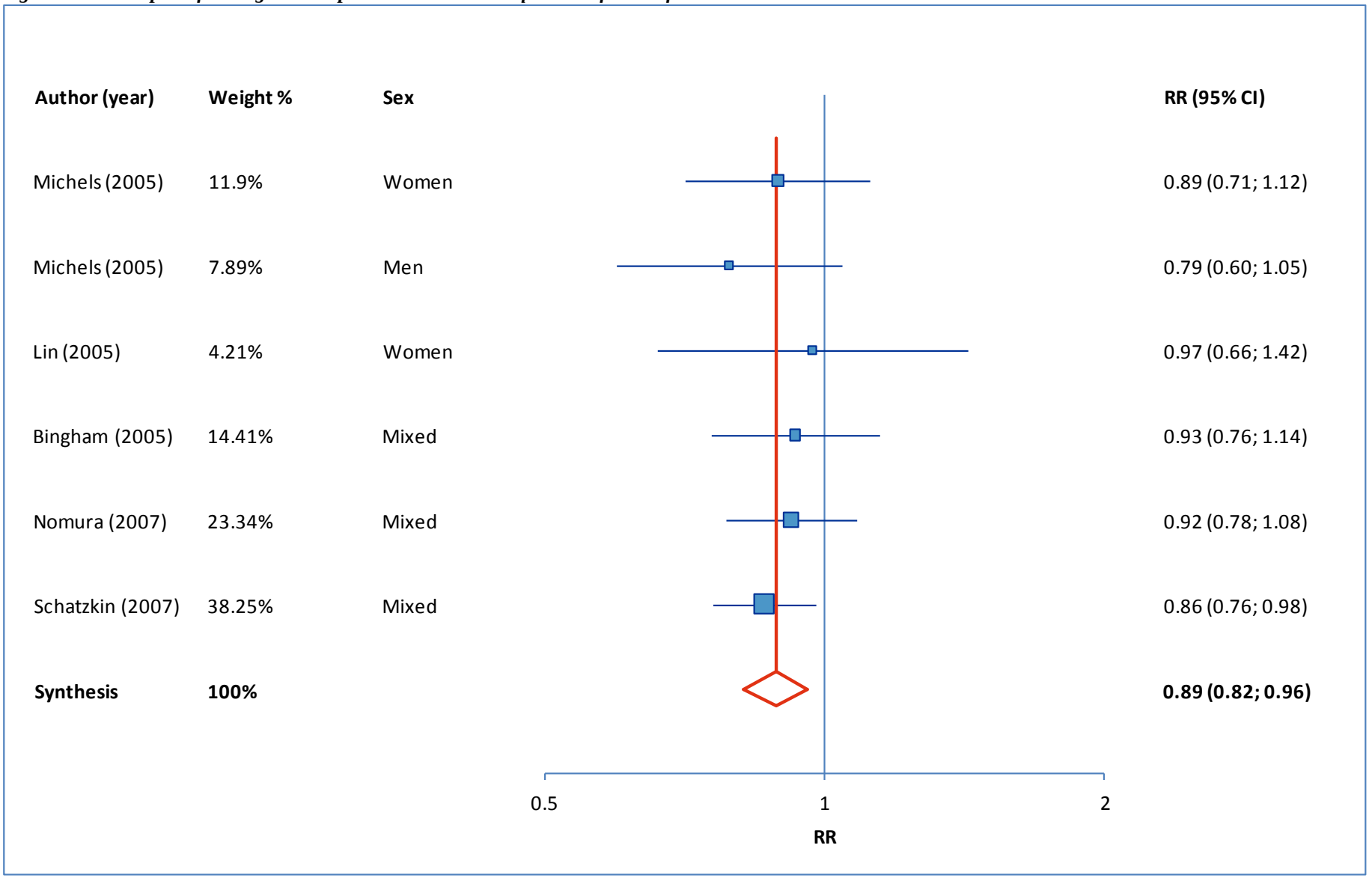


Figure 27. Forest plot of the highest compared with the lowest quantile of cereal fibre intake and colo-rectal cancer risk including the pooled analysis and studies not included in the pooled analysis

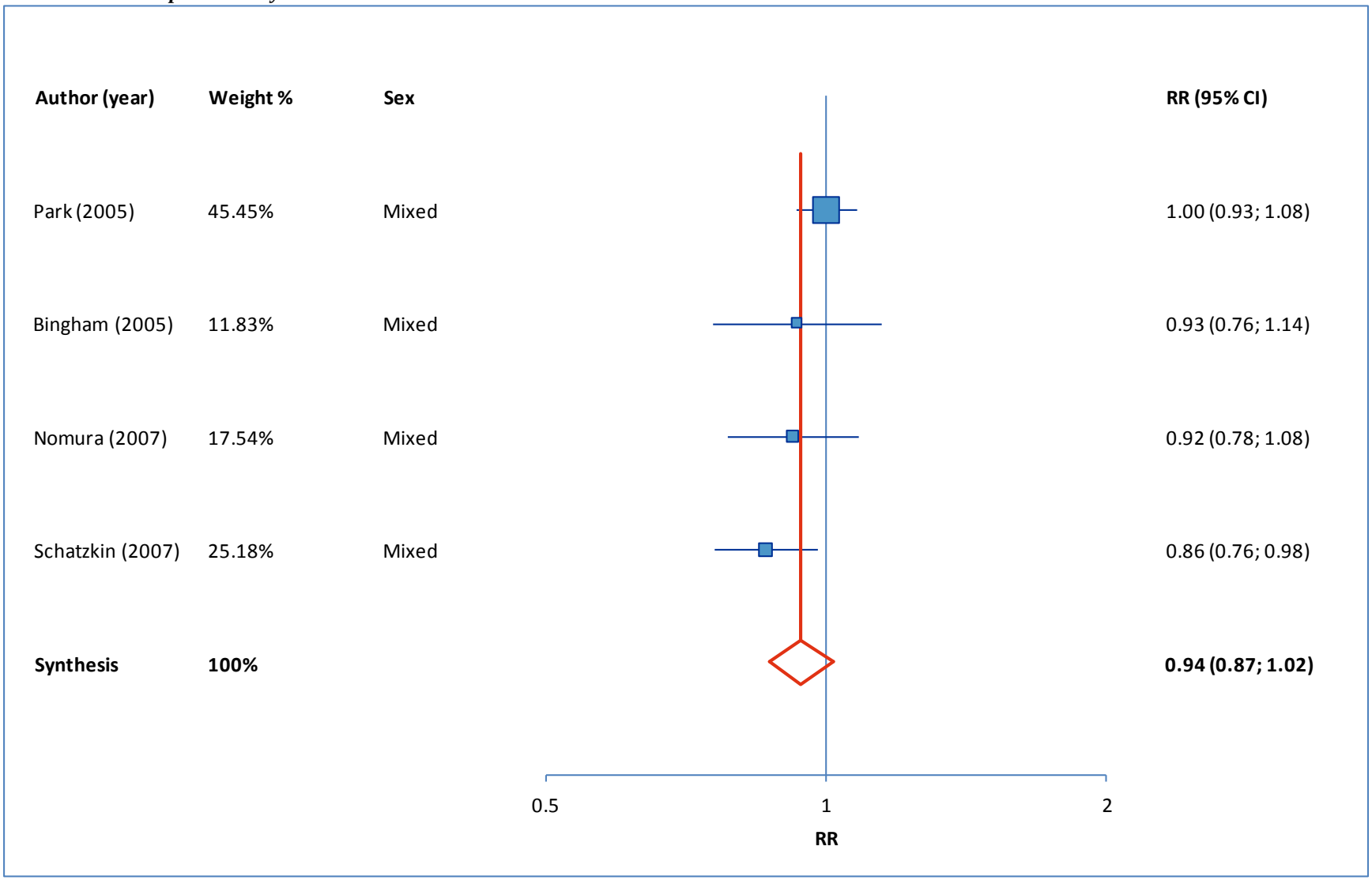


Figure 28. Forest plot of per unit analysis (10g/day) for cereal fibre intake and colo-rectal cancer risk

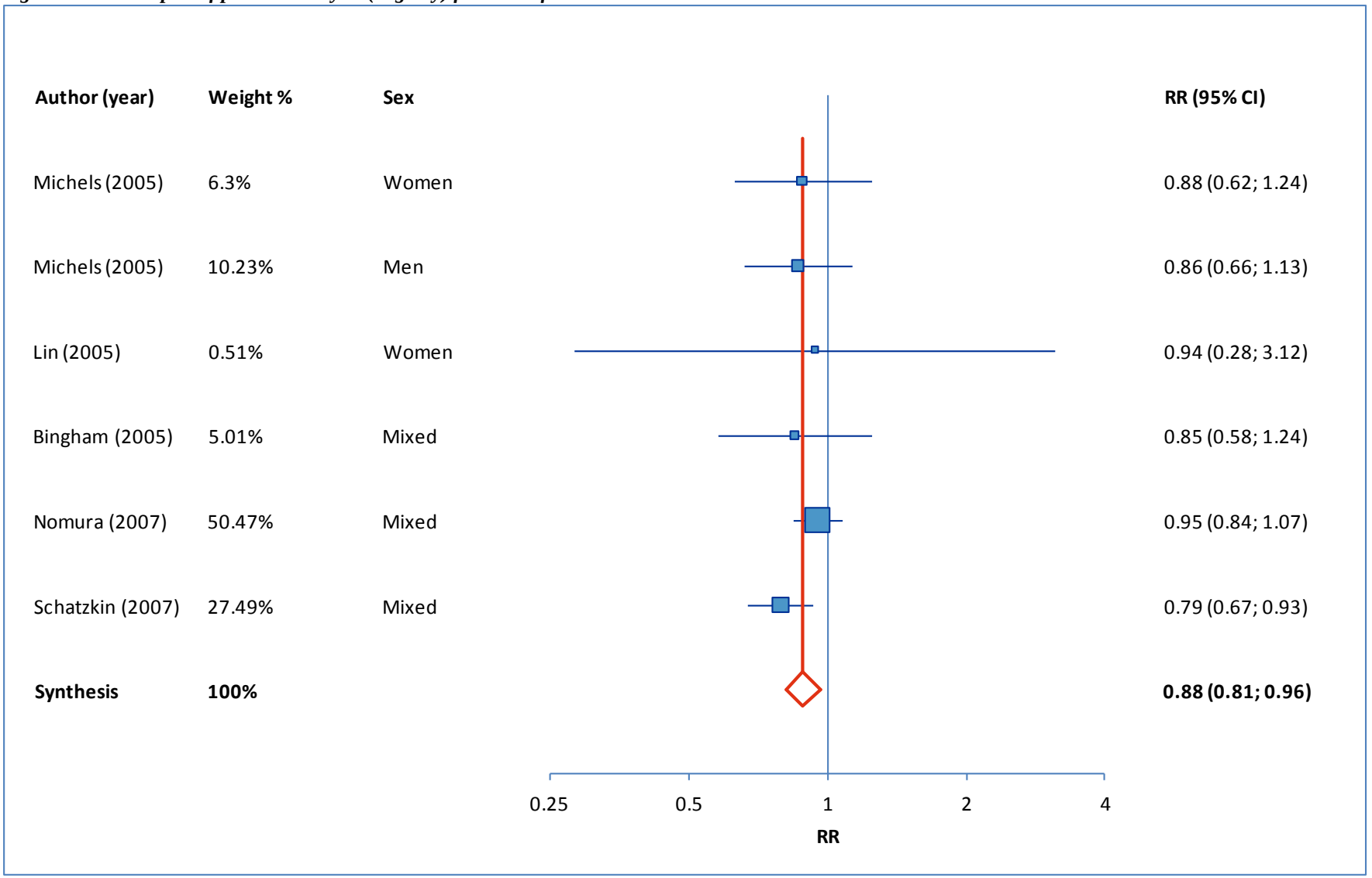


Table 114. Adjusted relative risk ratios for the highest compared with the lowest quantile of vegetable fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Individual cohorts										
Michels, 2005	Women	CRC	Q1 3.6g/1000kcal vs Q5 10.0g/1000kcal ****	1.20 (0.94-1.56)			0.11			No association observed
	Men	CRC	Q1 3.6g/1000kcal vs Q5 12.2g/1000kcal ****	1.09 (0.83-1.42)			0.57			
Lin, 2005	Women	CRC	Q1 5.9g/d vs Q5 8.0g/d ***	1.00 (0.65-1.56)			0.66			No association observed
Bingham, 2005	Mixed	CRC	Men Q1 2.7g/d vs Q5 5.3g/d; Women Q1 2.8g/d vs Q5 5.4g/d ****	0.94 (0.76-1.16)			0.52			No association observed
Nomura, 2007	Women	CRC	Q1 3.0g/1000kcal/d vs Q5 17.2g/1000kcal/d ***	0.95 (0.75-1.20)			0.77			Inverse association in men, but not women
	Men	CRC	Q1 3.0g/1000kcal/d vs Q5 18.4g/1000kcal/d ***	0.78 (0.62-0.97)			0.05			
Schatzkin, 2007	Mixed	CRC	Q1 6.6g/1000kcal/d vs Q5 15.9g/1000kcal/d ***	1.01 (0.89-1.15)			0.70			No association observed
Wakai, 2007	Mixed	CRC, CC, RC	Energy adjusted: Q1 2.0g/d vs Q4 5.1g/d ****	0.89 (0.65-1.24)	0.74 (0.50-1.11)	1.68 (0.91-3.11)	0.65	0.17	0.06	No association observed
Pooled analysis										
Park, 2005	Mixed	CRC	Q1 vs Q5 *	1.02 (0.94-1.11)			0.58			No association observed

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and vegetable fibre intake

414. Six studies reported on colo-rectal cancer in relation to vegetable fibre intake providing seven risk estimates. All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. One study reported on colo-rectal cancer in relation to cruciferous vegetable fibre intake finding no association (Lin *et al.*, 2005): RR 0.74 (0.47-1.17); P for trend 0.40. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 115 and Figure 29. The results of the per unit meta-analysis (10 g/day) have been summarised in Table 117 and Figure 31. Incorporation of the Pooling Project and studies not included in the pooled analysis left five studies providing five risk estimates (see Figure 30). The results from a highest quantile compared with lowest quantile meta-analysis have been summarised in Table 116.

415. There was no significant evidence of heterogeneity between studies. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

416. Both highest quantile compared with lowest quantile meta-analyses and the per unit meta-analysis observed no association between the incidence of colo-rectal cancer and dietary vegetable fibre intake.

Table 115. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and vegetable fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.98 (0.90-1.06)	-0.518 (p=0.605)

[1] I^2 = 4.11% (95% CI 0.00-72.01%); p for test of heterogeneity = 0.395
[2] No. of RR estimates included in pooled analysis.

Table 116. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and vegetable fibre intake including the pooled analysis and studies not included in the pooled analysis

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.98 (0.92-1.04)	-0.580 (p=0.562)

[1] I^2 = 1.76% (95% CI 0.00-79.57%); p for test of heterogeneity = 0.396
[2] No. of RR estimates included in pooled analysis.

Table 117 Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and vegetable fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.98 (0.91-1.06)	-0.53 (p=0.592)

[1] I^2 = 0.00% (95% CI 0.00-70.81%); p for test of heterogeneity = 0.633
[2] No. of RR estimates included in pooled analysis.

Figure 29. Forest plot of the highest compared with the lowest quantile of vegetable fibre intake and colo-rectal cancer risk

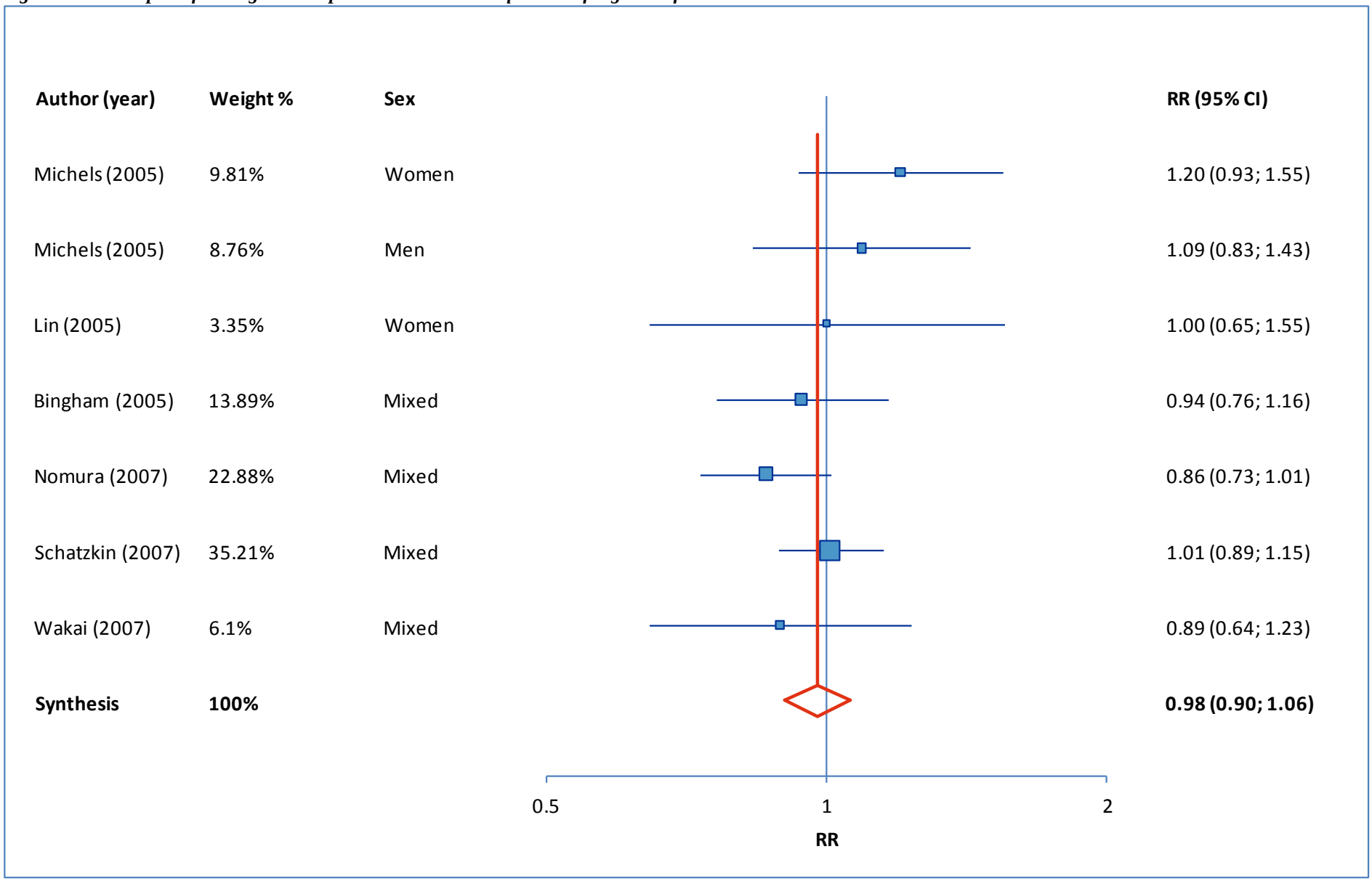


Figure 30. Forest plot of the highest compared with the lowest quantile of vegetable fibre intake and colo-rectal cancer risk including the pooled analysis and studies not included in the pooled analysis

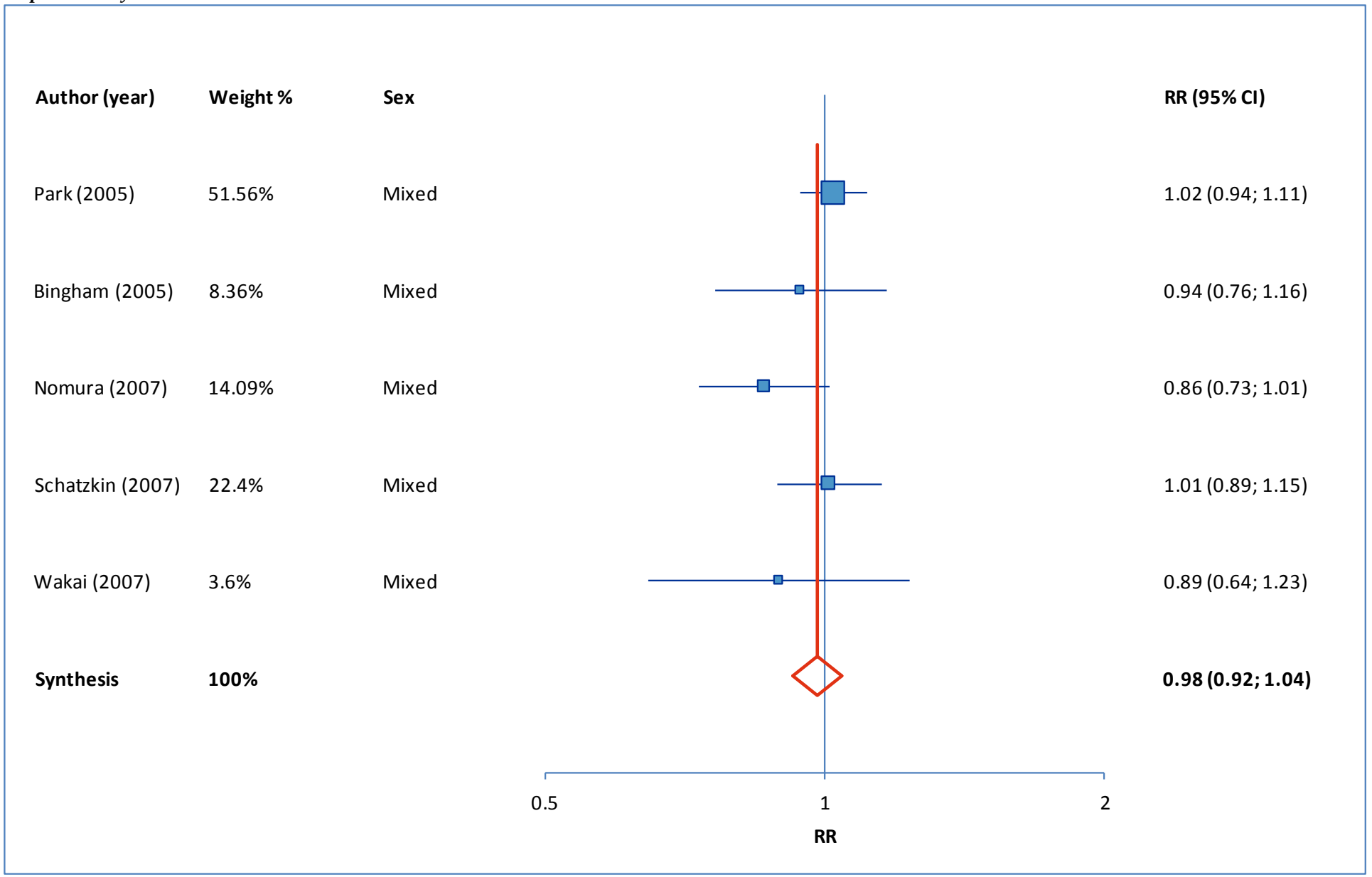


Figure 31. Forest plot of per unit analysis (10g/day) for vegetable fibre intake and colo-rectal cancer risk

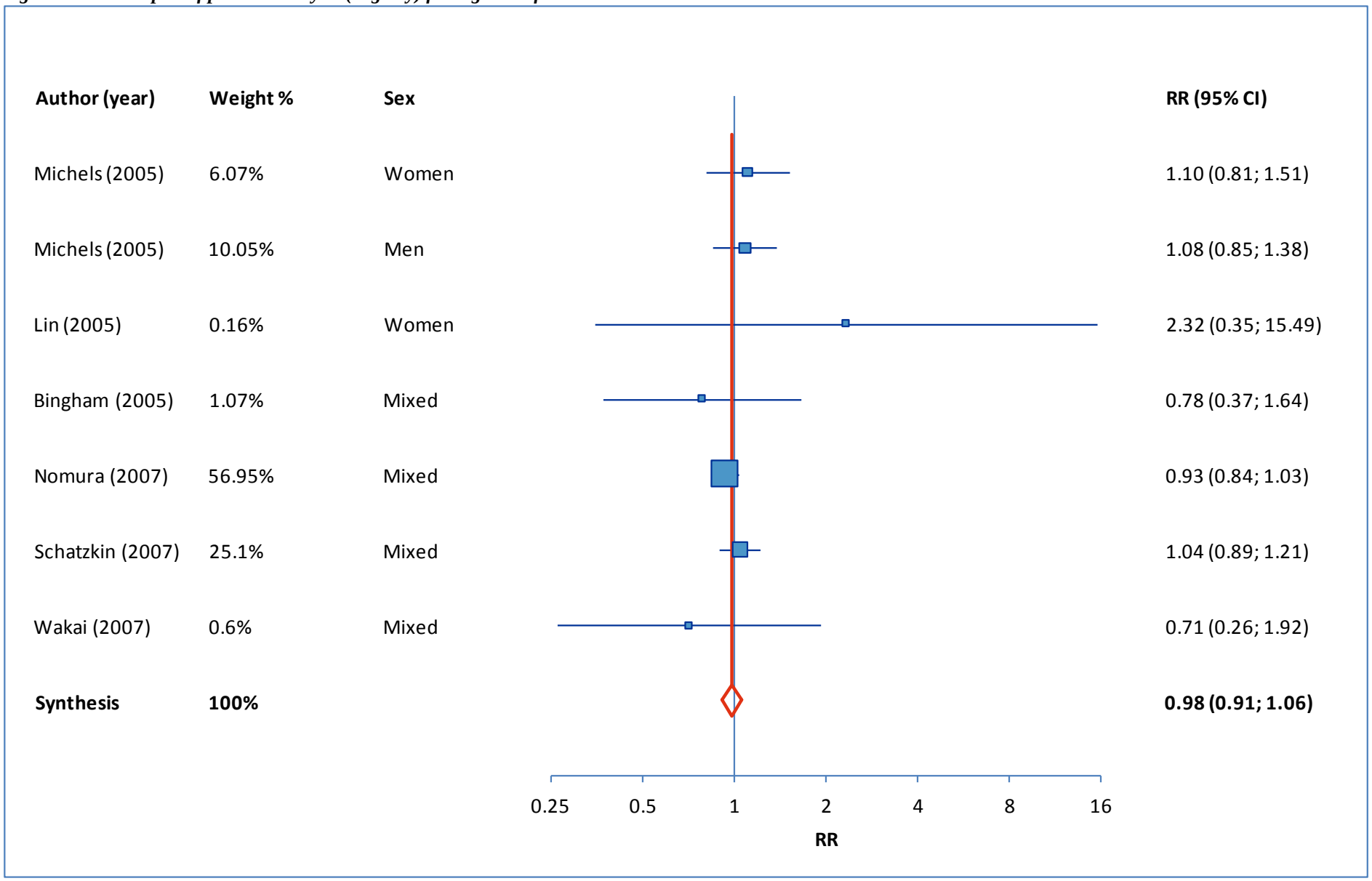


Table 118. Adjusted relative risk ratios for the highest compared with the lowest quantile of fruit fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Individual cohorts										
Michels, 2005	Women	CRC	Q1 1.4g/1000kcal vs Q5 7.3g/1000 kcal ****	0.88 (0.68-1.13)			0.20			No association observed
	Men	CRC	Q1 1.4g/1000kcal vs Q5 9.3g/1000kcal ****	0.92 (0.68-1.23)			0.62			
Lin, 2005	Women	CRC	Q1 2.5g/d vs Q5 6.0g/d ***	1.00 (0.67-1.49)			0.65			No association observed
Bingham, 2005	Mixed	CRC	Men Q1 2.7g/d vs Q5 5.3g/d; Women Q1 2.8g/d vs Q5 5.4g/d ****	0.81 (0.68-0.97)			0.42			No association observed
Nomura, 2007	Women	CRC	Q1 1.2g/1000kcal/d vs Q5 14.0g/1000kcal/d ***	0.82 (0.64-1.05)			0.48			Inverse association in men, but not women
	Men	CRC	Q1 0.9g/1000kcal/d vs Q5 12.6g/1000kcal/d ***	0.78 (0.63-0.97)			0.08			
Schatzkin, 2007	Mixed	CRC	Q1 6.6g/1000kcal/d vs Q5 15.9g/1000kcal/d ***	1.08 (0.95-1.23)			0.14			No association observed
Wakai, 2007	Mixed	CRC, CC, RC	Energy adjusted: Q1 0.4g/d vs Q4 2.2g/d ****	1.06 (0.78-1.43)	1.06 (0.73-1.54)	0.92 (0.55-1.54)	0.55	0.83	0.84	No association observed
Pooled analysis										
Park, 2005	Mixed	CRC	Q1 vs Q5 *	0.96 (0.89-1.04)			0.30			No association observed

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and fruit fibre intake

417. Six studies reported on colo-rectal cancer in relation to fruit fibre intake providing seven risk estimates (see Table 118 and Figure 32). All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. One study also determined risk of colon and rectal cancer separately, but observed no association (Wakai et al., 2007). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 119 and Figure 32. The results of the per unit meta-analysis (10 g/day) have been summarised in Table 121 and Figure 34. Incorporation of the Pooling Project and and studies not included in the pooled analysis, left five studies providing five risk estimates (see Figure 33). The results from a highest quantile compared with lowest quantile meta-analysis have been summarised in Table 120.

418. There was no significant evidence of heterogeneity between studies. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

419. Both highest quantile compared with lowest quantile meta-analyses and the per unit meta-analysis observed no association between the incidence of colo-rectal cancer and dietary fruit fibre intake.

Table 119. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and fruit fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.92 (0.82-1.03)	-1.41 (p=0.160)

[1] I^2 = 49.26% (95% CI 0.00-78.53%); p for test of heterogeneity = 0.066
[2] No. of RR estimates included in pooled analysis.

Table 120. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and fruit fibre intake including including the pooled analysis and studies not included in the pooled analysis

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.93 (0.83-1.04)	-1.22 (p=0.223)

[1] I^2 = 66.02% (95% CI 11.36-86.97%); p for test of heterogeneity = 0.019
[2] No. of RR estimates included in pooled analysis.

Table 121. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and fruit fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	7	0.91 (0.78-1.05)	-1.26 (p=0.206)

[1] I^2 = 42.35% (95% CI 0.00-75.76%); p for test of heterogeneity = 0.108
[2] No. of RR estimates included in pooled analysis.

Figure 32. Forest plot of the highest compared with the lowest quantile of fruit fibre intake and colo-rectal cancer risk

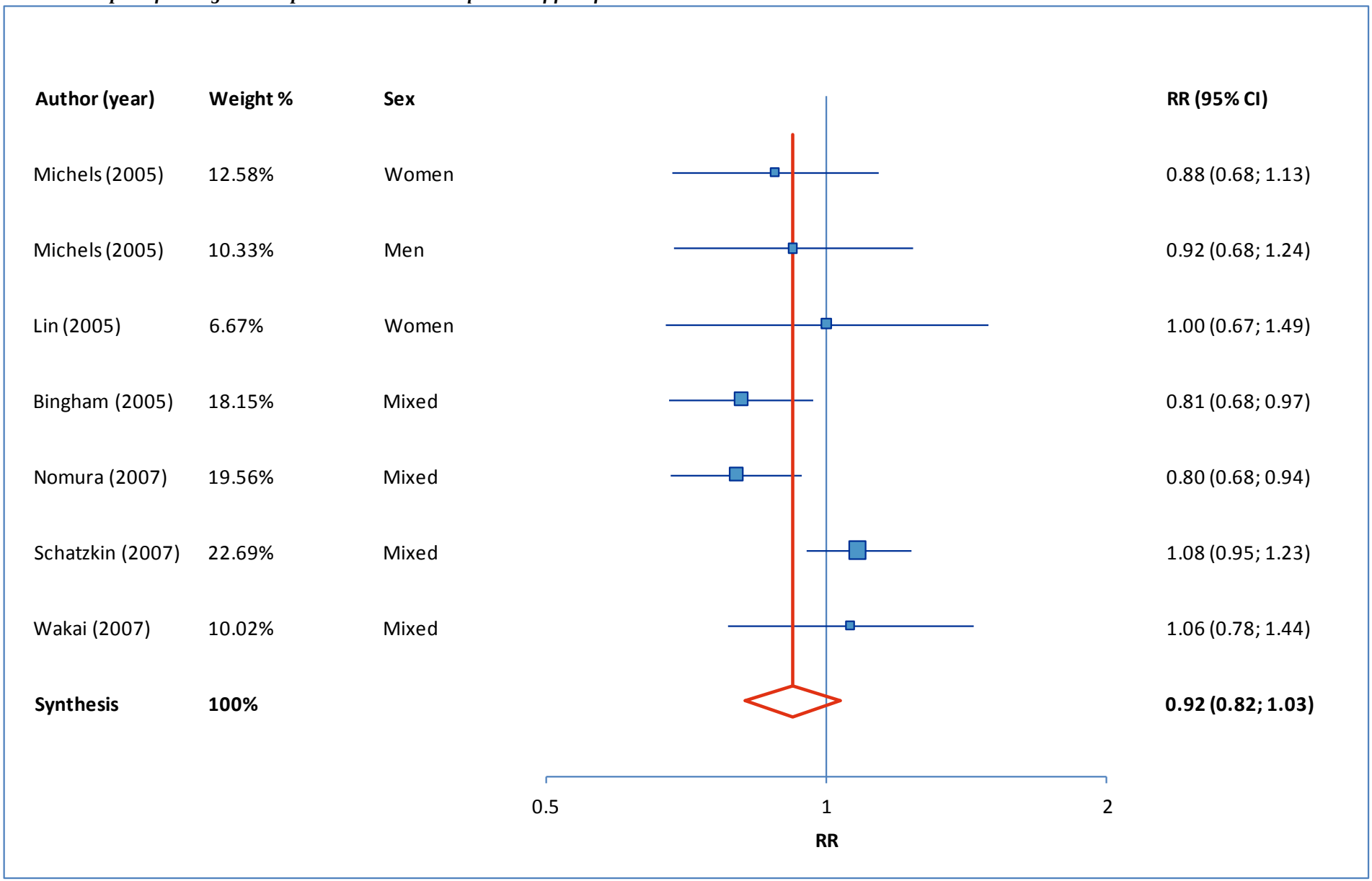


Figure 33. Forest plot of the highest compared with the lowest quantile of fruit fibre intake and colo-rectal cancer risk including the pooled analysis and studies not included in the pooled analysis

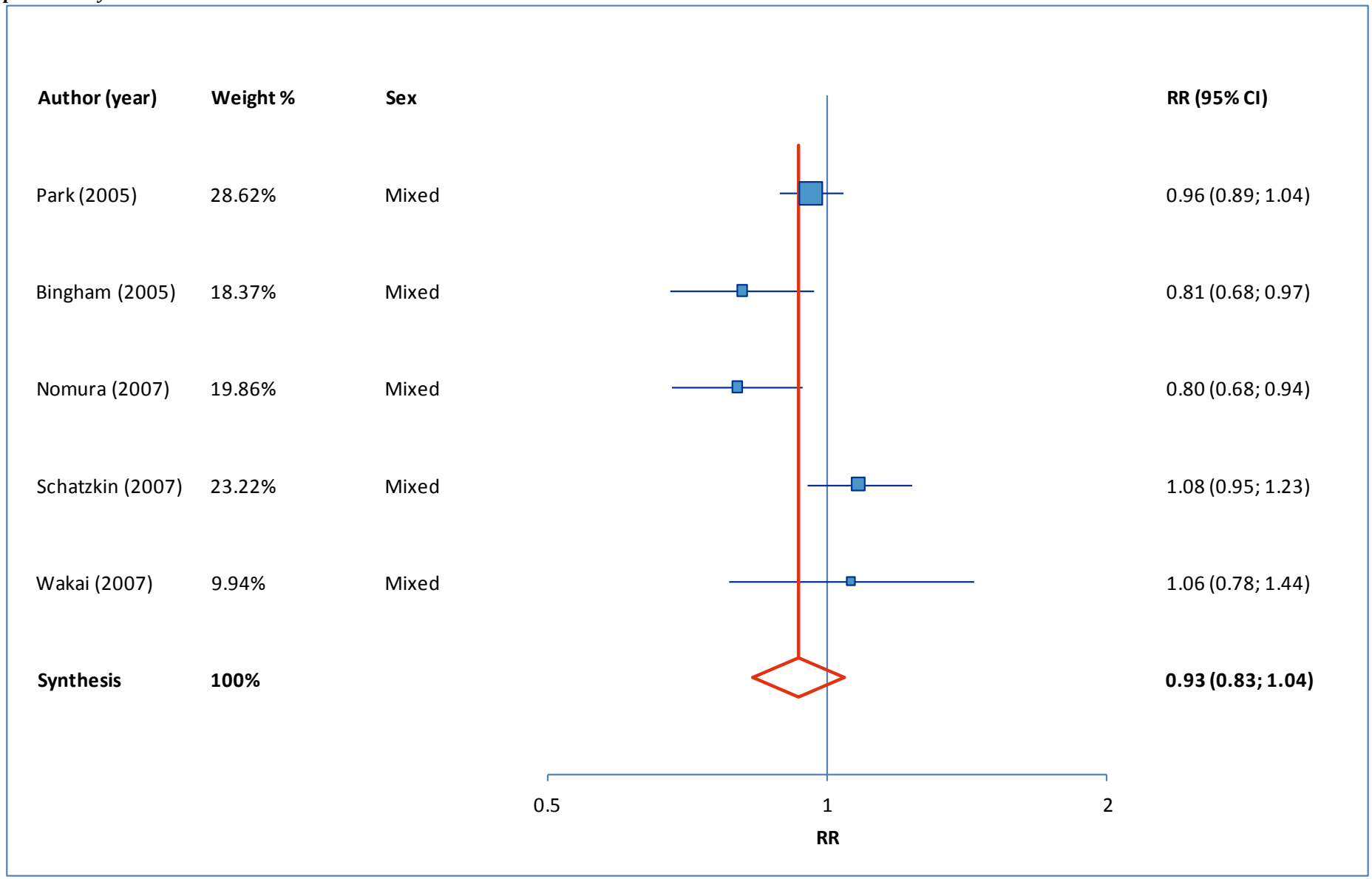


Figure 34. Forest plot of per unit analysis (10g/day) for fruit fibre intake and colo-rectal cancer risk

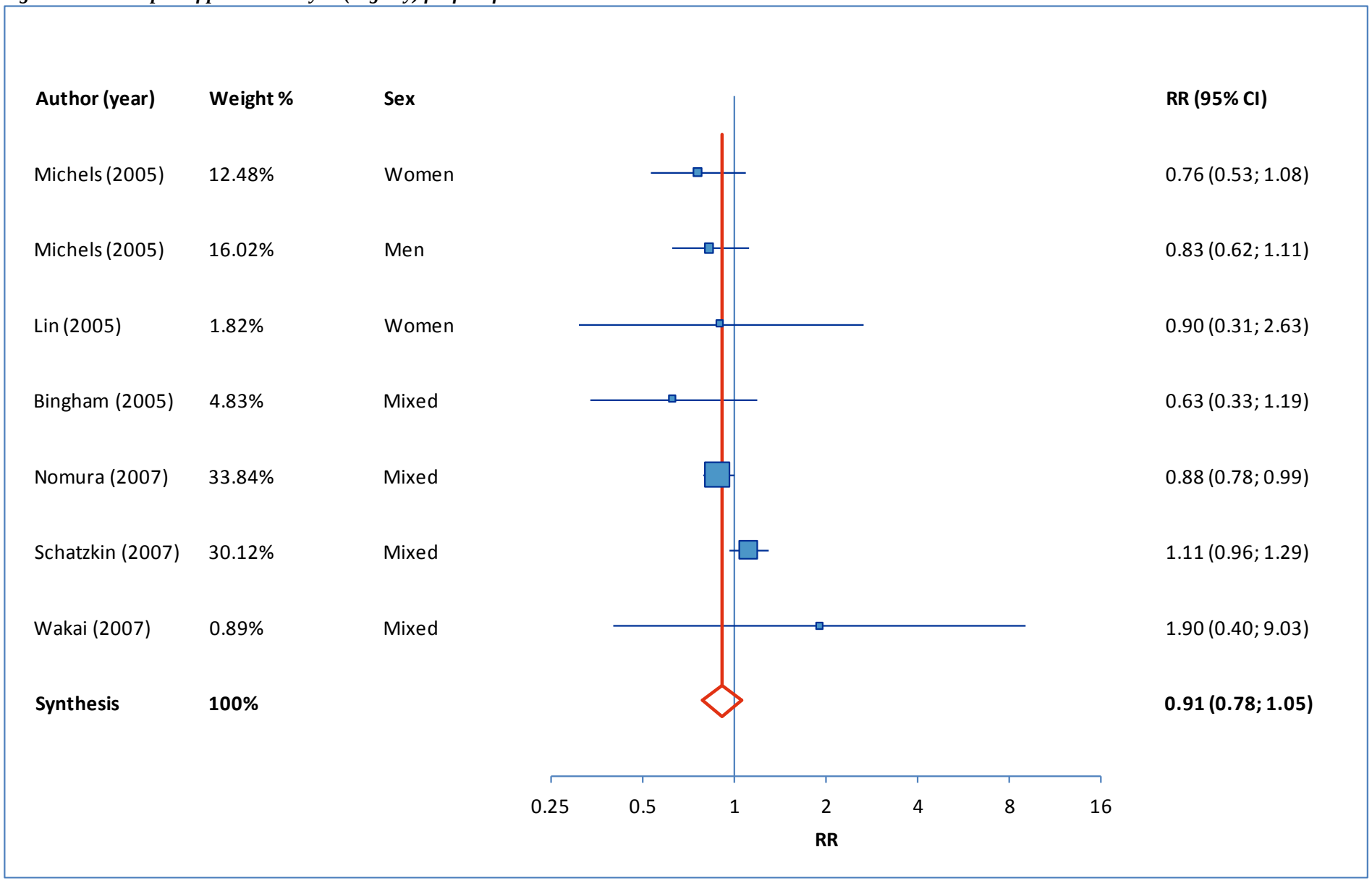


Table 122. Adjusted relative risk ratios for the highest compared with the lowest quantile of legume fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Lin, 2005	Women	CRC	Q1 0.4g/d vs Q5 1.8g/d ***	0.60 (0.40-0.91)			0.02			Inverse association observed
Bingham, 2005	Mixed	CRC	Men Q1 0g/d vs Q5 1.9g/d; Women Q1 0g/d vs Q5 1.0g/d ****	0.98 (0.82-1.17)			0.86			No association observed
Nomura, 2007	Women	CRC	Q1 0.2g/1000kcal/d vs Q5 5.8g/1000kcal/d ***	1.16 (0.90-1.49)			0.32			No association observed
	Men	CRC	Q1 0.3g/1000kcal/d vs Q5 7.6g/1000kcal/d ***	0.87 (0.68-1.10)			0.192			No association observed
Schatzkin, 2007	Mixed	CRC	Q1 0.2g/1000kcal/d vs Q5 2.3g/1000kcal/d ***	0.93 (0.83-1.04)			0.25			No association observed
Wakai, 2007	Mixed	CRC, CC, RC	energy adjusted: Q1 0.2g/d vs Q4 1.4g/d ****	0.74 (0.55-0.99)	0.67 (0.47-0.95)	0.81 (0.48-1.37)	0.055	0.037	0.42	Inverse association observed for CRC and CC

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and legume fibre intake

420. Five studies reported on colo-rectal cancer in relation to legume fibre intake providing five risk estimates. All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. One study also determined risk of colon and rectal cancer in relation to legume fibre separately, observing an inverse association with colon cancer, but not rectal cancer (Wakai *et al.*, 2007). The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 123 and Figure 35. The results of the per unit meta-analysis (10 g/day) have been summarised in Table 124 and Figure 36.

421. Evidence of heterogeneity was high. The number of estimates was too small to substantiate an explanation for the heterogeneity. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

422. Both the highest quantile compared with lowest quantile meta-analysis and the per unit meta-analysis observed no association between the incidence of colo-rectal cancer and dietary legume fibre intake.

Table 123. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and legume fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.90 (0.80-1.02)	-1.67 (p=0.095)

[1] I^2 = 47.77 (95% CI 0.00-80.86%); p for test of heterogeneity = 0.105
[2] No. of RR estimates included in pooled analysis.

Table 124. Results of per unit (10g/day) meta-analysis for colo-rectal cancer incidence and legume fibre intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	5	0.79 (0.52-1.20)	-1.10 (p=0.275)

[1] I^2 = 60.33% (95% CI 0.00-85.14%); p for test of heterogeneity = 0.039
[2] No. of RR estimates included in pooled analysis.

Figure 35. Forest plot of the highest compared with the lowest quantile of legume fibre intake and colo-rectal cancer risk

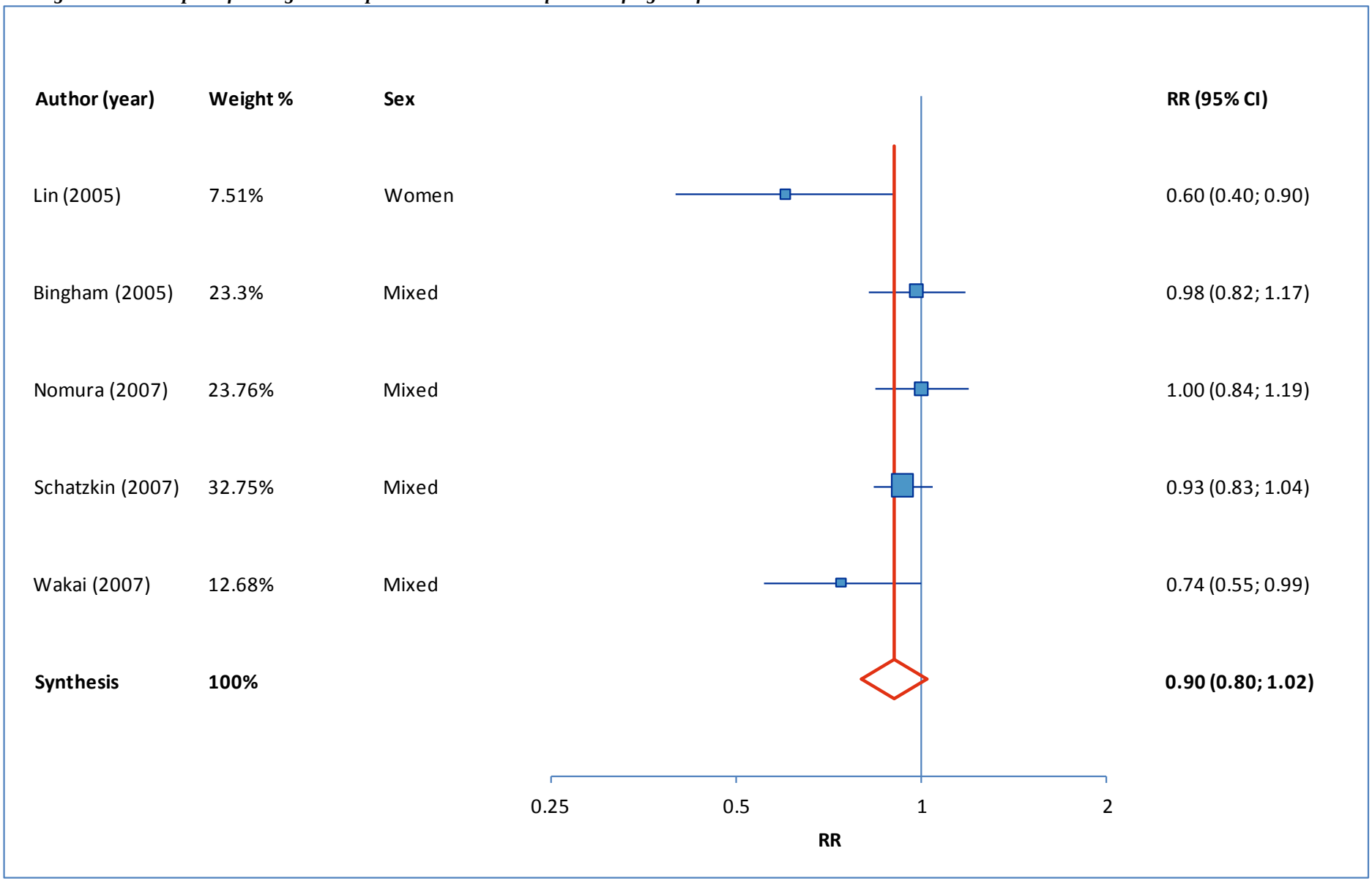


Figure 36. Forest plot of per unit analysis (10g/day) for legume fibre intake and colo-rectal cancer risk

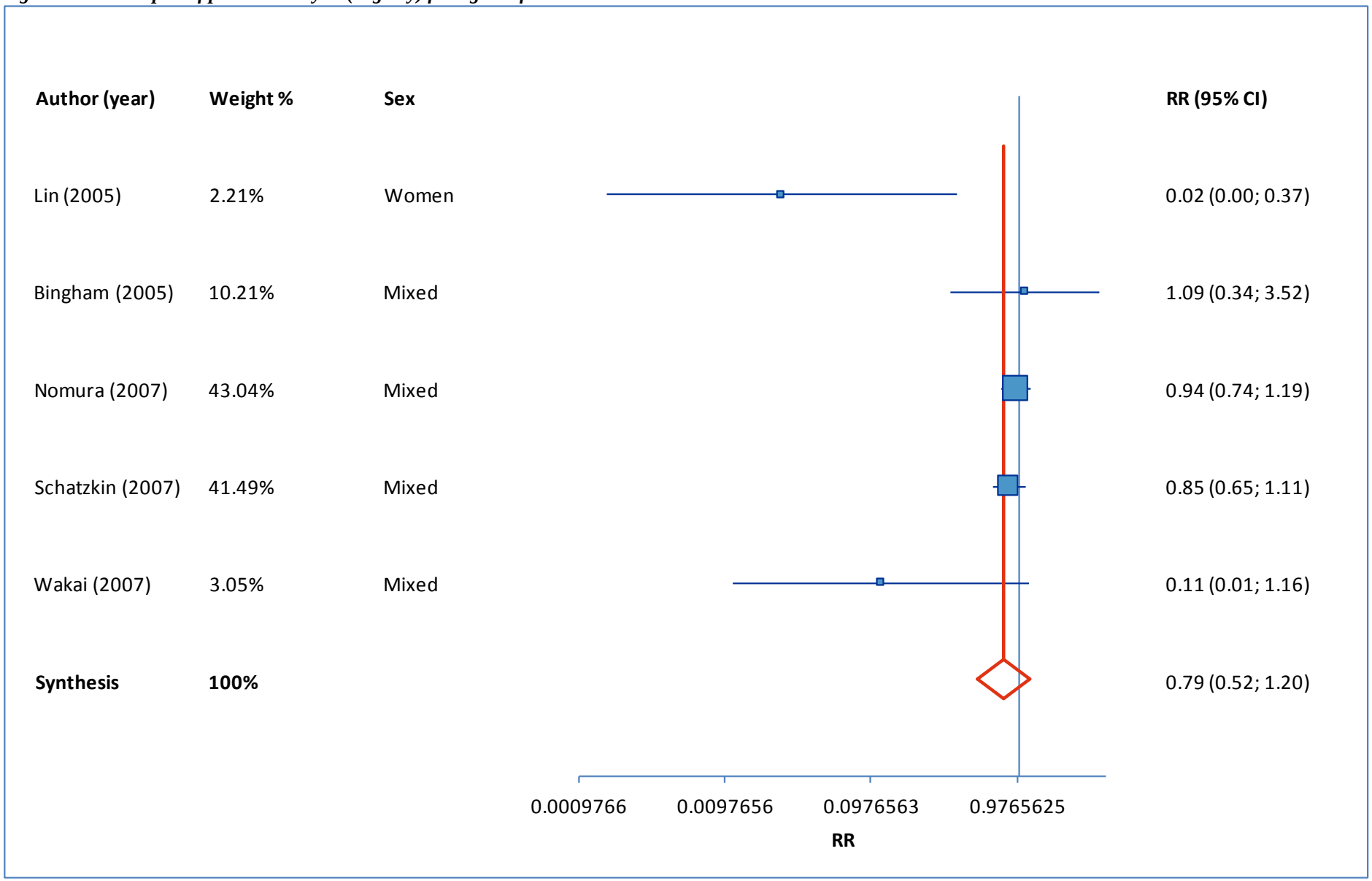


Table 125. Adjusted relative risk ratios for the highest compared with the lowest quantile of soluble fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Pietinen, 1999	Men	CRC	Q1 3.7g/d vs Q4 7.3g/d ***	1.1 (0.7-1.6)			0.91			No association observed
Wakai, 2007	Mixed	CRC, CC, RC	Energy adjusted: Q1 1.2g/d vs Q4 2.6g/d ****	0.67 (0.47-0.95)	0.55 (0.36-0.84)	0.94 (0.49-1.78)	0.022	0.002	0.64	Inverse association observed

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Table 126. Adjusted relative risk ratios for the highest compared with the lowest quantile of insoluble fibre intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Pietinen, 1999	Men	CRC	Q1 12.2g/d vs Q4 27.1g/d ***	1.0 (0.6-1.5)			0.73			No association observed
Wakai, 2007	Mixed	CRC, CC, RC	Energy adjusted: Q1 5.3g/d vs Q4 9.6g/d ****	0.77 (0.55-1.08)	0.63 (0.42-0.96)	1.08 (0.58-2.02)	0.041	0.004	0.66	Inverse association observed

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer
* no quantile exposure data reported; ** quantile exposure data reported as ranges; *** quantile exposure data reported as median values; **** quantile exposure data reported as mean values

Colo-rectal cancer incidence and soluble and insoluble fibre intake

423. Three studies reported on colo-rectal cancer in relation to soluble and insoluble fibre intake (see Table 125 and Table 126). The results from each study reflected their findings with dietary fibre overall. Adjusted relative risk with 95% confidence intervals, were given for colo-rectal cancer risk and colon or rectal cancer risk, where reported. There were insufficient studies to perform a meta-analysis for soluble or insoluble fibre intake and colo-rectal cancer incidence.

424. The one study reporting inverse associations with colo-rectal cancer incidence and dietary fibre also observed inverse associations with soluble and insoluble fibre (Wakai *et al.*, 2007), and the study observing no association with soluble and insoluble fibre also observed no association with dietary fibre (Pietinen *et al.*, 1999) (see Table 65). One study determined risk of colon and rectal cancer in relation to insoluble and soluble fibre separately, observing an inverse association with colon cancer, but not rectal cancer (Wakai *et al.*, 2007).

Colo-rectal cancer incidence and wholegrain cereal intake

425. Three studies reported on colo-rectal cancer in relation to wholegrain cereal intake providing three risk estimates (see Table 131). All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 127 and Figure 37. The results of the per unit meta-analysis (three servings/day) have been summarised in Table 129 and Figure 38.

426. One study only determined risk of only colon cancer in relation to wholegrain cereal (McCullough *et al.*, 2003). Overall, three studies reported on colon cancer in relation to wholegrain cereal intake providing three risk estimates (see Table 131). All studies provided sufficient data for both highest quantile compared with lowest quantile and per unit meta-analyses to be performed. The results of the highest quantile compared with lowest quantile meta-analysis have been summarised in Table 128 and Figure 39. The results of the per unit meta-analysis (three servings/day) have been summarised in Table 130 and Figure 40.

427. There was no significant evidence of heterogeneity between studies, except for the per unit analysis in relation to colo-rectal incidence. The number of estimates was too small to substantiate an explanation for the heterogeneity. For all analyses tests for publication bias (Egger's linear regression test) were not significant.

428. Both highest quantile compared with lowest quantile meta-analyses observed a significant reduction in the incidence of colo-rectal and colon cancer. The per unit meta-analysis also observed a significant reduction in the incidence of colon cancer with three servings/day increase in wholegrain cereal, but the association with colo-rectal cancer was not significant.

429. The findings observed in each study tended to reflect those observed for ceral fibre. One study that observed an inverse association between wholegrain cereal intake and colo-rectal cancer incidence, observed no association with dietary fibre, but did observe inverse associations with cereal fibre intake and colo-rectal cancer incidence (Schatzkin *et al.*, 2007). Another also observed an inverse association between wholegrain cereal intake and colon cancer incidence also observed an inverse association between cereal fibre intake and colon cancer incidence (Larsson *et al.*, 2005). The two studies that observed no association between wholegrain cereal intake and colo-rectal cancer (Pietinen *et al.*, 1999) or colon cancer (McCullough *et al.*, 2003) did not investigate cereal fibre in relation to colo-rectal cancer, but they did observe no association between dietary fibre intake and colo-rectal cancer or colon cancer, respectively.

430. Two studies reported on rectal cancer in relation to wholegrain cereal intake (see Table 131). One observed no association (Larsson *et al.*, 2005), while the other reported an inverse association (Schatzkin *et al.*, 2007).

Table 127. Results of highest quantile compared with lowest quantile meta-analysis for colo-rectal cancer incidence and wholegrain cereal intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	3	0.80 (0.72-0.89)	-4.08 (p<0.0001)

[1] I^2 = 0.00% (95% CI 0.00-89. 60%); p for test of heterogeneity = 0.530

[2] No. of RR estimates included in pooled analysis.

Table 128. Results of highest quantile compared with lowest quantile meta-analysis for colon cancer incidence and wholegrain cereal intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	3	0.83 (0.71-0.97)	-2.30 (p=0.021)

[1] I^2 = 14.47% (95% CI 0.00-91.10%); p for test of heterogeneity = 0.311

[2] No. of RR estimates included in pooled analysis.

Table 129. Results of per unit (three servings/day) meta-analysis for colo-rectal cancer incidence and wholegrain cereal intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	3	0.85 (0.70-1.02)	-1.77 (p=0.077)

[1] I^2 = 73.87% (95% CI 12.71-92.18%); p for test of heterogeneity = 0.022

[2] No. of RR estimates included in pooled analysis.

Table 130. Results of per unit (three servings/day) meta-analysis for colon cancer incidence and wholegrain cereal intake

Model	Pooled RR estimate[1]		
	No.[2]	RR (95%CI)	Z (p-value)
Random effect	3	0.84 (0.73-0.97)	-2.43 (p=0.015)

[1] I^2 = 0.00% (95% CI 0.00-89.60%); p for test of heterogeneity = 0.383

[2] No. of RR estimates included in pooled analysis.

Table 131. Adjusted relative risk ratios for the highest compared with the lowest quantile of wholegrain cereal intake and colo-rectal cancer risk

Study	Sex	Outcome	Comparison	Difference between midpoint exposures in the highest and lowest quantiles	CRC RR	CC RR	RC RR	CRC P for trend	CC P for trend	RC P for trend	Reported association
Pietinen, 1999	Men	CRC	Q1 96g/d vs Q4 374g/d ***	4.6 servings/day (60g = one serving))	1.00 (0.70-1.60)			0.99			No association observed
McCullough, 2003	Mixed	CC	Q1 <2 servings/wk vs Q5 >11 servings/wk **	2.1 servings/day		0.95 (0.64-1.42)			0.78		No association observed
Larsson, 2005	Women	CRC, CC, RC	Q1 <1.5 servings/d vs Q5 >4.5 servings/d **	3.9 servings/day	0.76[$] (0.56-1.03)	0.65[$] (0.45-0.94)	1.07[$] (0.62-1.82)	0.10	0.04	0.99	Inverse association observed for CRC and CC, but not RC
Schatzkin, 2007	Mixed	CRC, CC, RC	Q1 0.2g/1000kcal/d vs Q5 1.3g/1000kcal/d ***		0.79 (0.70-0.89)	0.86 (0.75-0.99)	0.64 (0.51-0.81)	<0.001	0.03	<0.001	Inverse association observed for CRC, CC and moreso RC

NR, not reported, y, year; d, day; Q, quantile; CRC, colo-rectal cancer; CC colon cancer; RC rectal cancer;[$] e xcluding cases with follow-up < 2 years

** quantile exposure data reported as ranges; *** quantile exposure data reported as median values

Figure 37. Forest plot of the highest compared with the lowest quantile of wholegrain cereal intake and colo-rectal cancer risk

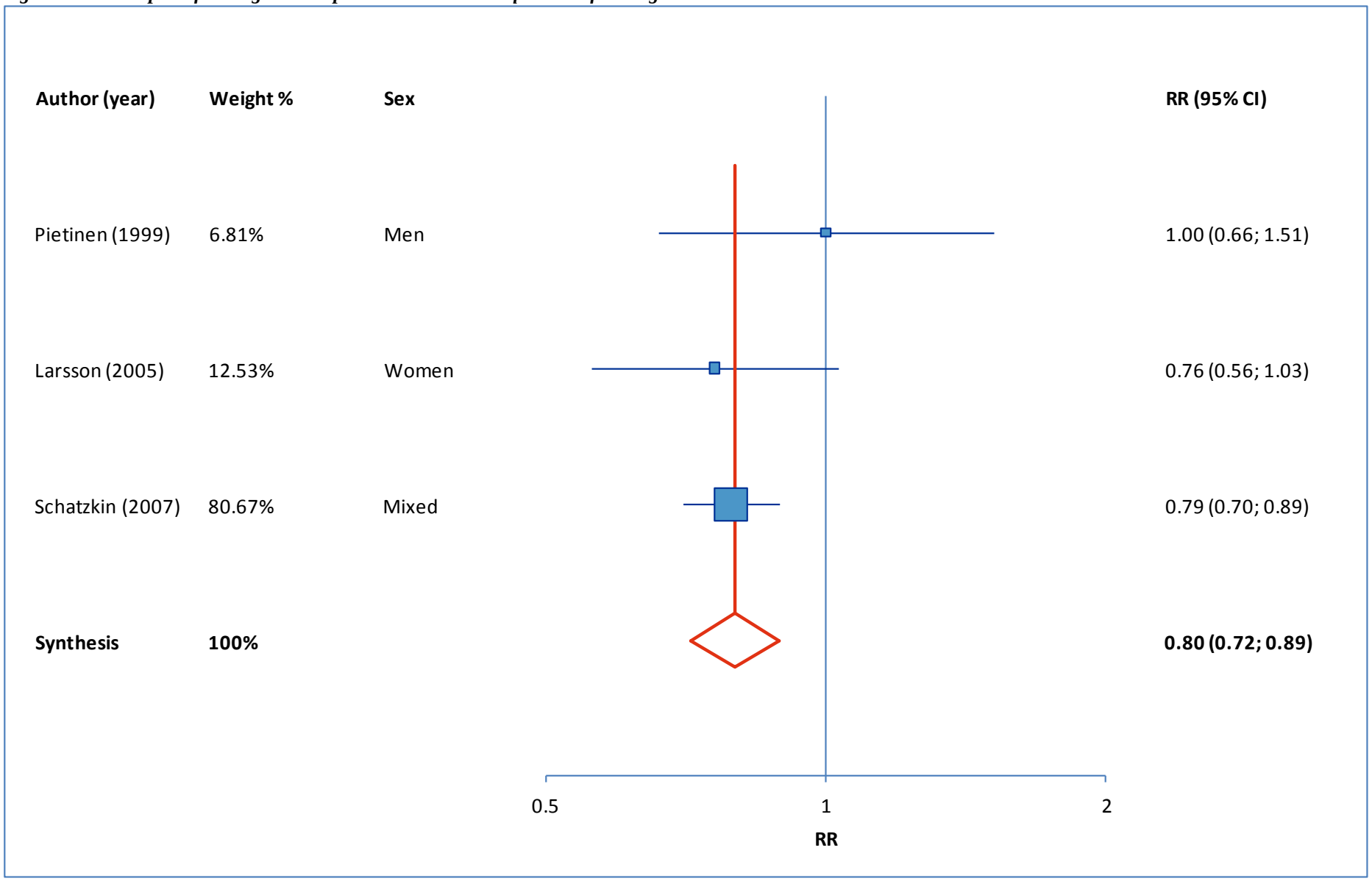


Figure 38. Forest plot of per unit analysis (three servings/day) for wholegrain cereal intake and colo-rectal cancer risk

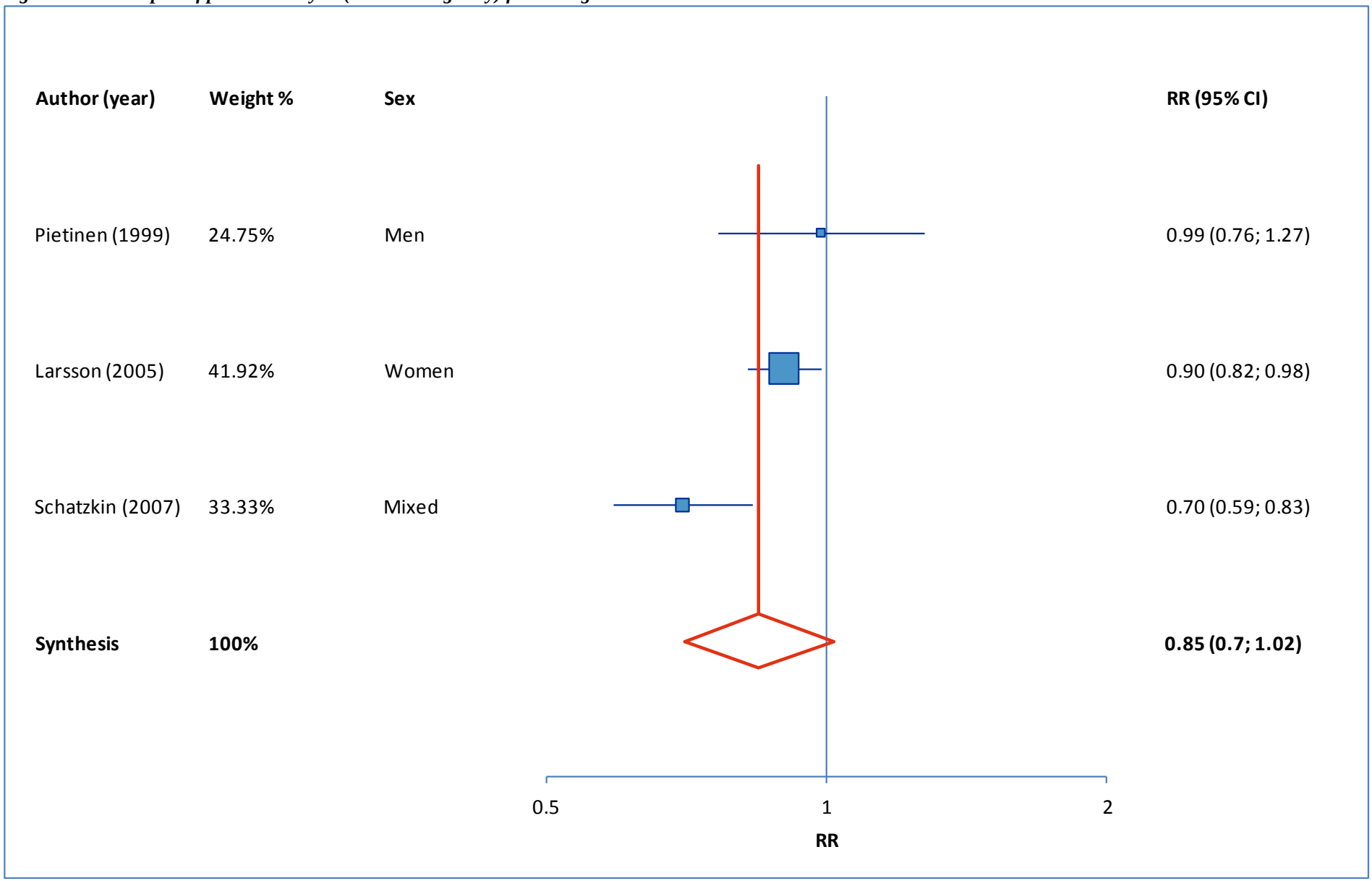


Figure 39. Forest plot of the highest compared with the lowest quantile of wholegrain cereal intake and colon cancer risk

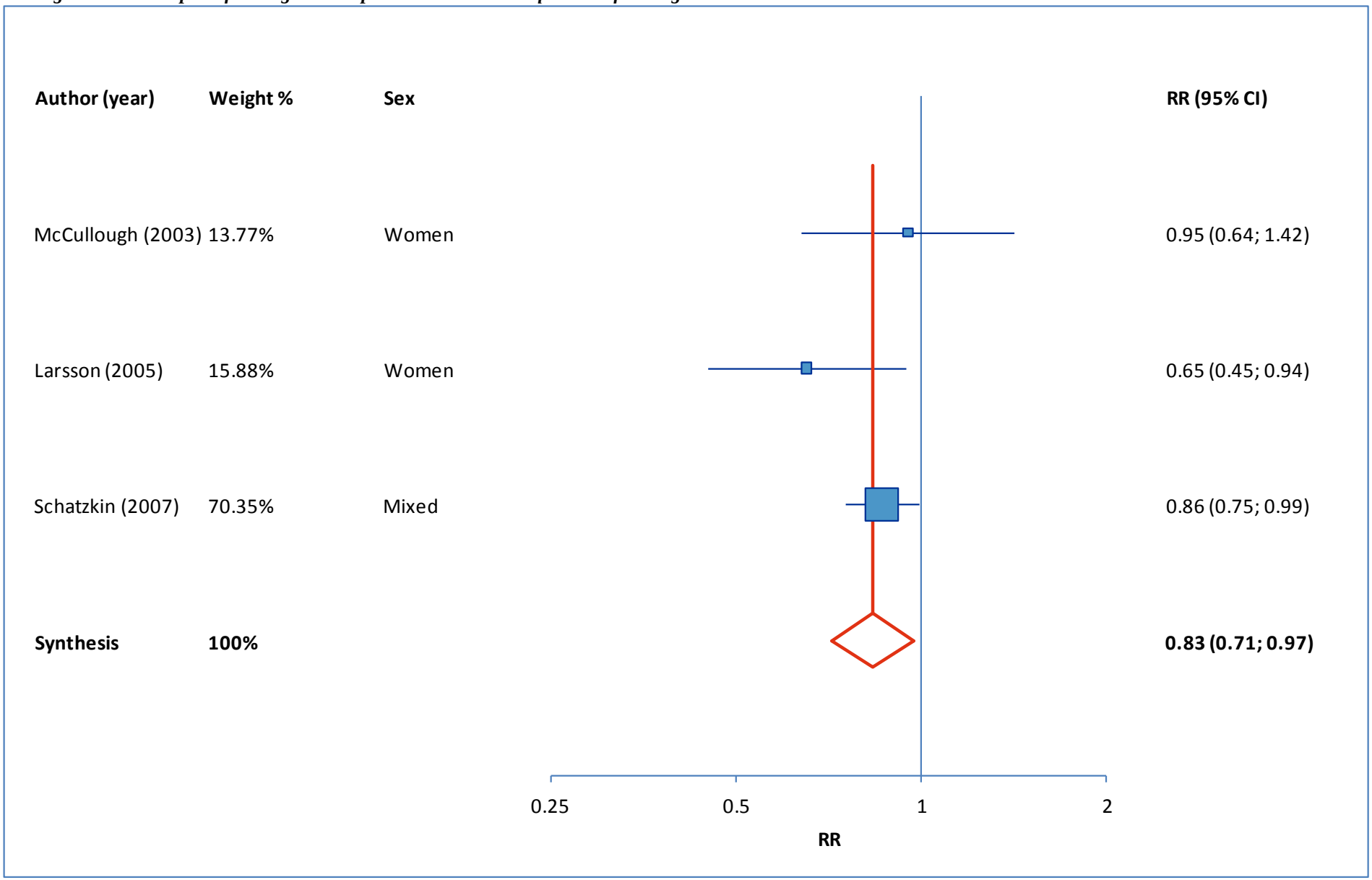
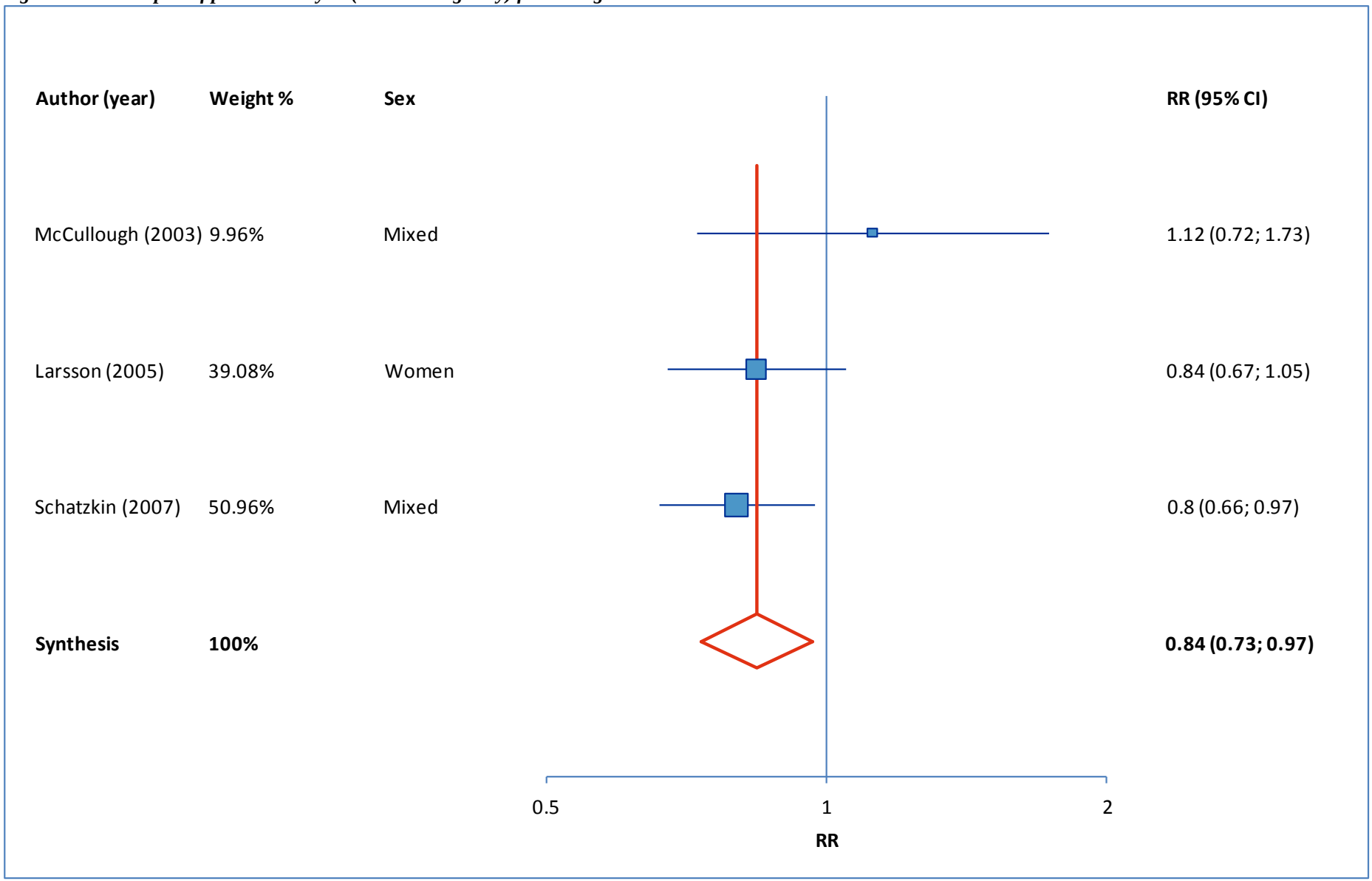


Figure 40. Forest plot of per unit analysis (three servings/day) for wholegrain cereal intake and colon cancer risk



Summary

431. While some evidence suggested cereal fibre intake may be inversely associated with colo-rectal cancer incidence, available evidence for vegetable fibre showed no association. For fruit and legume fibre there was no significant difference, but colo-rectal cancer incidence tended to be lower for the highest compared with the lowest quantile of intake. Insufficient studies have examined insoluble and soluble fibre in relation to colo-rectal cancer incidence to enable a meaningful interpretation. A limited number of studies suggested that wholegrain cereal intake may be inversely associated with colo-rectal cancer incidence and this tended to reflect associations observed for cereal fibre.