Carbohydrate, glycemic index, glycemic load and colorectal cancer risk: a systematic review and meta-analysis of cohort studies.

Aune, D[1], Chan DSM[1], Lau, R[1], Vieira, R[1], Greenwood, DC[2], Kampman, E[3], Norat, T[1].

Affiliations

[1] Department of Epidemiology and Public Health, Imperial College, London, United Kingdom

[2] Biostatistics Unit, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, United Kingdom

[3] Division of Human Nutrition, Wageningen University and Research Centre, Wageningen, The Netherlands

Correspondence to: Dagfinn Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK.

Telephone: +44 (0) 20 7594 8478

E-mail: d.aune@imperial.ac.uk

Abstract

Background: Dietary carbohydrate, glycemic load and glycemic index are thought to influence colorectal cancer risk through hyperinsulinemia. We review and quantitatively summarize in a meta-analysis the evidence from prospective cohort studies.

Methods: We searched the PubMed database for prospective studies of carbohydrate, glycemix index and glycemic load and colorectal cancer risk, up to December 2010. Summary relative risks were estimated by use of a random effects model.

Results: We identified 14 cohort studies that could be included in the meta-analysis of carbohydrate, glycemic index and glycemic load and colorectal cancer risk. The summary RR high vs. low intake was 1.00 (95% CI: 0.87-1.14 I^2=31%) for carbohydrate, 1.07 (95% CI: 0.99-1.16, I^2=28%) for glycemic index, and 1.00 (95% CI: 0.91-1.10, I^2=39%) for glycemic load. In the dose-response analysis the summary RR was 0.97 (95% CI: 0.87-1.09, I^2=51%) per 100 grams of carbohydrate per day, 1.07 (95% CI: 0.99-1.15, I^2=39%) per 10 glycemic index units and 1.00 (95% CI: 0.94-1.06, I^2=50%) per 50 glycemic load units. Exclusion of one outlier study reduced the heterogeneity, but the results were similar.

Conclusion: This meta-analysis of cohort studies does not support an independent association between diets high in carbohydrate, glycemic index or glycemic load.

Word count abstract: 199

Key words: Carbohydrate, glycemic index, glycemic load, colorectal cancer, meta-analysis

Conflict of interest: None declared.

Introduction

Colorectal cancer is the third most common cancer worldwide with approximately 1.23 million new cases diagnosed in 2008 accounting for one in ten incident cancers (1). Ecological studies, secular trend studies and migration studies have shown that environmental factors including lifestyle are likely to be important determinants of colorectal cancer risk (2-4). However, although dietary factors are known to be important in colorectal cancer etiology, only intake of alcohol and red and processed meat are considered to be convincingly associated with colorectal cancer (5).

Several lines of evidence indicate that insulin resistance may play a role in the etiology of colorectal cancer. Some risk factors for colorectal cancer including overweight and obesity, low physical activity and type 2 diabetes are linked to insulin resistance (5-7). Epidemiological studies have reported increased colorectal cancer risk with elevated blood glucose or C-peptide (8-14). Dietary carbohydrate is the main dietary component affecting an individual's insulin secretion and glycemic response (15). Glycemic index (GI) is an index for ranking foods according to their effect on blood glucose concentrations and is defined as the area under the two hour blood glucose response curve (AUC) following intake of 50 grams carbohydrate from a particular food (16). The AUC for the test food is divided by the AUC of a reference, which is glucose or white bread, and multiplied by 100. The GI applies to foods with a reasonable carbohydrate content. Because some foods contain very little carbohydrate one would have to eat large amounts of the food to yield 50 gram carbohydrate. Glycemic load (GL) is a ranking system for the carbohydrate content of food which takes into account the portion size (GL= (GI x amount of available carbohydrate)/100) (17).

Several studies have investigated the association between diets high in carbohydrate, glycemic index or glycemic load and colorectal cancer risk, however, the results have been inconsistent (18-31). A previous meta-analysis found an elevated colorectal cancer risk with a high GI and GL among case-control studies, but not among cohort studies (32). Three large

additional cohort studies have since been published on the subject (29-31) and here we update the evidence published up to December 2010. In addition, because to our knowledge a meta-analysis of carbohydrate intake and colorectal cancer has not been published we expanded the meta-analysis to include total carbohydrate and specific types of carbohydrate (excluding fiber).

Methods

Search strategy

The Pubmed database was searched up to December 2010 for studies of carbohydrate intake, glycemic index or glycemic load and colorectal cancer risk. We followed a predefined protocol for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf) which includes details of the search terms and standard criteria for meta-analyses of observational studies (33). We also searched the reference lists of all the studies that were included in our analysis as well as those listed in the published systematic reviews and meta-analyses (32,34).

Study selection

We included prospective cohort studies, case-cohort studies and nested case-control studies which investigated the association between dietary carbohydrate, GI or GL and colorectal cancer risk. Estimates of the relative risk (hazard ratio, risk ratio) had to be available with the 95% confidence intervals in the publication and for the dose-response analysis, a quantitative measure of intake had to be provided. We identified 18 possibly relevant publications in the

search (18-31,35-38) (Figure 1). Four of these were excluded because no risk estimates were presented (35-38). Three publications were excluded from the dose-response analysis because they presented carbohydrate intake as a percentage of total energy intake, not in grams per day (19,26) or did not quantify carbohydrate intake (20).

Data extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), exposure, quantity of intake, RRs and 95% CIs and variables adjusted for in the analysis. Data were extracted into a database by one author (D. A.) and was checked for accuracy by two authors (T. N and D. A.).

Statistical methods

Random effects models were used to calculate summary RRs and 95% CIs for the highest vs. the lowest level of carbohydrate, GI, and GL intake and for the dose-response analysis (39). The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $p<0.05$ was considered statistically significant. For studies that reported results separately for men and women or proximal and distal colon, but not combined, we pooled the results using a fixed-effects model to obtain an overall combined estimate before combining with the rest of the studies.

The method described by Greenland and Longnecker (40) was used for the dose–response analysis and we computed study-specific slopes (linear trends) and 95% CIs from

the natural logs of the RRs and CIs across categories of carbohydrate and GI/GL intake. The method requires 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 are known. The distribution of cases or person-years were estimated in studies that did not report these, but reported the total number of cases/person-years, if the results were analyzed by quantiles (and could be approximated). For example, the total number of person-years was divided by 5 when data were analyzed by quintiles in order to derive the number of person-years in each quintile. The median or mean level of intake in each category of intake was assigned to the corresponding relative risk for each study. For studies that reported intakes by ranges we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended we assumed the open-ended interval length to be the same as the adjacent interval. If the intakes were reported in densities (i.e. gram per 1000 kcal) we recalculated the reported intakes to absolute intakes using the mean or median energy intake. The dose-response results in the forest plots are presented for a 10 and 50 unit increment per day for glycemic index and glycemic load, respectively and for a 100 gram per day increment for carbohydrate.

Heterogeneity between studies was assessed by the Q test and I^2 (41), the amount of total variation that is explained by between study variation. Subgroup and meta-regression analyses by sex, duration of follow-up, number of cases, geographic location and adjustment for confounding factors such as body mass index, smoking, alcohol, physical activity, intake of fruit and vegetables, energy and red and processed meat were conducted to investigate potential sources of heterogeneity. Publication bias was assessed with Egger's test (42) and with Begg's test (43) and the results were considered to indicate publication bias when $p<0.10$. We conducted sensitivity analyses excluding one study at a time to investigate whether the results were due to one large study or a study with an extreme result.

Results

We identified 14 cohort studies (18-31) that were included in the analysis of the highest vs. the lowest carbohydrate, GI and GL intake and colorectal cancer risk and 11 of these studies (21-31) were included in the dose-response analysis (Table 1, Figure 1). Eleven studies were from North-America, two from Europe and one from Asia.

Glycemic index

High vs. low analysis

Ten cohort studies (nine publications) (22-28,30,31) investigated the association between glycemic index and colorectal cancer risk and included 12382 cases among 994154 participants. The summary RR for all studies was 1.07 (95% CI: 0.99-1.16), with no significant heterogeneity, I^2=28% and $p_{heterogeneity}$=0.19 (Figure 2a).

Dose-response analysis

Ten cohort studies (nine publications) (22-28,30,31) were included in the dose-response analysis of glycemic index and colorectal cancer risk. The summary RR per 10 units per day was 1.07 (95% CI: 0.99-1.15), with little evidence of heterogeneity, I^2=39% and $p_{heterogeneity}$=0.10 (Figure 2b). The summary RR for colorectal cancer ranged from 1.04 (95% CI: 0.97-1.13) when the NIH-AARP Diet and Health Study (30) was excluded to 1.11 (95% CI: 1.05-1.17) when the Breast Cancer Detection Demonstration Project (26) was excluded.

There was no indication of publication bias with Egger's test, p=0.34 or with Begg's test, p=0.28.

Glycemic load

High vs. low analysis

Twelve cohort studies (eleven publications) (21-31) were included in the analysis of high versus glycemic load and colorectal cancer risk and included a total of 15377 cases among 1234282 participants. The summary RR was 1.00 (95% CI: 0.91-1.10), with moderate heterogeneity, I^2=39%, $p_{heterogeneity}$=0.08 (Figure 3a).

Dose-response analysis

Twelve cohort studies (eleven publications) (21-31) were included in the dose-response analysis. The summary RR per 50 units per day was 1.00 (95% CI: 0.94-1.06), with moderate heterogeneity, I^2=50%, $p_{heterogeneity}$=0.03 (Figure 3b). In a sensitivity analysis the summary RR for colorectal cancer ranged from 0.98 (95% CI: 0.92-1.03) when excluding the Health Professionals Follow-up Study (23) to 1.01 (95% CI: 0.94-1.09) when excluding the NIH-AARP Diet and Health Study (30). There was no indication of publication bias with Egger's test, p=0.12 or with Begg's test, p=0.37. The heterogeneity was largely explained by the results from the Women's Health Study (22), which seemed to be an outlier, and when excluded the results were similar, summary RR=0.99 (95% CI: 0.94-1.04), but the heterogeneity was reduced, I^2=32%, $p_{heterogeneity}$=0.15.

Carbohydrate

High vs. low analysis

Twelve cohort studies (11 publications) examined (19-26,28,29,31) total carbohydrate intake and colorectal cancer risk and included 9799 cases among 806647 participants. The summary RR was 0.93 (95% CI: 0.84-1.04) with moderate heterogeneity, I^2=40%, $p_{heterogeneity}$=0.08 (Figure 4a).

Dose-response analysis

Ten cohort studies (9 publications) (21-26,28,29,31) were included in the dose-response analysis. The summary RR per 100 g/d was 0.95 (95% CI: 0.84-1.07), with moderate heterogeneity, I^2=58%, $p_{heterogeneity}$=0.01 (Figure 4b). The summary RR ranged from 0.92 (95% CI: 0.82-1.03) when excluding the Health Professionals Follow-up Study (23) to 0.98 (95% CI: 0.87-1.09) when excluding the Breast Cancer Detection Demonstration Project (26). There was no evidence of publication bias with Egger's test, p=0.42 or with Begg's test, p=0.37.

Specific types of carbohydrate

Only four (three publications) (22-24) and five studies (four publications) (22-24,29) were included in the analyses of high versus low sucrose and fructose intake and colorectal cancer, respectively. The summary RR was 1.11 (95% CI: 0.82-1.50, I^2=79%, $p_{heterogeneity}$=0.002) for sucrose intake (Figure 5a) and 0.99 (95% CI: 0.82-1.20, I^2=63%, $p_{heterogeneity}$=0.03) for fructose intake (Figure 5b).

Subgroup, meta-regression analyses and sensitivity analyses

In meta-regression analyses only adjustment for physical activity was a significant predictor of heterogeneity in the analysis of glycemic index, $p_{heterogeneity}$=0.03. A significant positive association was found among studies that adjusted for physical activity. In addition, a significant positive association between glycemic index and colorectal cancer was observed among men, but there was no evidence of heterogeneity between genders. There were no significant predictors of heterogeneity in subgroup analyses of glycemic load or carbohydrate, although for carbohydrate, there was borderline evidence of a positive association among men, but not among women, $p_{heterogeneity}$=0.07.

In a sensitivity analysis we included one study in the dose-response analysis that reported carbohydrate intake as a percentage of energy intake, by recalculating the intake to grams using the mean energy intake among noncases (19). The summary RR was 0.94 (95% CI: 0.85-1.05, I^2=55%, $p_{heterogeneity}$=0.02).

Discussion

We found no statistically significant association between dietary carbohydrate, glycemic index or glycemic load and colorectal cancer risk in categorical and dose-response meta-analyses. In the analysis of carbohydrate and glycemic load and colorectal cancer there was significant heterogeneity, however, this was largely explained by one outlying study.

Although case-control studies have provided some evidence of a positive association (32,34), these studies may be prone to selection and recall biases which can make it difficult

to draw firm conclusions. Our results, which are based on prospective studies are not prone to recall bias, because diet is assessed before the development of disease, and in addition, selection bias is less likely to have influenced these results.

Our meta-analysis may have several limitations which must be taken into consideration. Intake of diets high in carbohydrate, GI and GL may be associated with other behaviors including physical activity, overweight and obesity, smoking and intake of alcohol and red and processed meat. The association between intake of carbohydrate, GI and GL and the confounding factors may differ between studies and populations (22,25,30,31), but nevertheless, we generally did not find evidence of significant heterogeneity between subgroups in our analyses. In stratified analyses and meta-regression analyses only one subgroup analysis showed significant heterogeneity between studies that adjusted or did not adjust for confounders. There was a significant positive association between glycemic index and colorectal cancer in studies that adjusted for physical activity, but a non-significant inverse association among studies that did not adjust for physical activity. Due to the numerous comparisons this finding may have been a chance finding. We found no statistical evidence of publication bias in this analysis, but we may have had limited power to detect such bias due to the limited number of studies.

Measurement errors in the assessment of dietary intake are known to bias effect estimates, however, none of the studies included in this meta-analysis made any corrections for measurement errors. Assessment of GI or GL may in this respect be particularly challenging, because these measures are based on their postprandial blood glucose response and are not concentration values of nutrients in the foods consumed. Most dietary questionnaires have estimated usual GI/GL values based on a limited number of food items, which may not have been specifically selected and validated for dietary GI or GL. However, when we evaluated total carbohydrate intake we found similar to the analyses of GI and GL

no significant association. In addition, the studies that have evaluated the association between glycemic index, glycemic load or carbohydrate intakes and colorectal adenomas found no evidence of an increased risk (44-51), and some even a suggestive inverse association (44,48-51). Studies using similar questionnaires have been able to detect associations between GI, GL and risk of type 2 diabetes (52) and cardiovascular disease (53), but nevertheless we cannot exclude the possibility that a more modest or weak association with colorectal cancer may have been missed due to measurement errors.

Our meta-analysis also has several strengths. Because we based our analyses on prospective studies we have effectively avoided recall and selection bias. The studies included a larger number of cases and participants than any previous meta-analysis on the topic that we are aware of, with a total of approximately 0.8-1.2 million participants and ≈8900-15000 cases. Thus, we had statistical power to detect moderate associations. Although we cannot exclude the possibility that a very weak association with a high GI may have been obscured due to measurement errors, our study, with an even larger sample size than available previously, does not provide support for the hypothesis that intake of diets high in carbohydrate, GI or GL is strongly associated with colorectal cancer risk.

In conclusion, our results do not support the hypothesis that dietary carbohydrate, GI or GL are associated with colorectal cancer risk.

Contributors

The systematic literature review team at Wageningen University conducted the search, data selection and data extraction up to June 2006. RV was responsible for developing and managing the database for the Continuous Update Project. R. Lau and D.S.M. Chan did the

updated literature search. R. Lau, D.S.M. Chan and D. Aune did the updated data extraction. D. Aune did the study selection, statistical analyses and wrote the first draft of the original manuscript. DC Greenwood was expert statistical advisor and contributed towards the statistical analyses. All authors contributed to the revision of the manuscript. E. Kampman was PI of the SLR at Wageningen University and T. Norat is the PI of the Continuous Update Project.

Role of the funding source

The sponsor of this study had no role in the decisions about the design and conduct of the study, collection, management, analysis or interpretation of the data or the preparation, review or approval of the manuscript.

Acknowledgement: We thank the systematic literature review team at the Wageningen University for their contributions to the colorectal cancer database. This work was funded by the World Cancer Research Fund (grant number 2007/SP01) as part of the Continuous Update Project. The views expressed in this review are the opinions of the authors. They may not represent the views of WCRF International/AICR and may differ from those in future updates of the evidence related to food, nutrition, physical activity and cancer risk. All authors had full access to all of the data in the study. D. Aune takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors declare that there are no conflicts of interest.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM(2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*.

2. Armstrong B, Doll R(1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* **15**: 617-31.

3. Kolonel LN(1980) Cancer patterns of four ethnic groups in Hawaii. *J Natl Cancer Inst* **65**: 1127-39.

4. Kono S(2004) Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev* **13**: 127-32.

5. World Cancer Research Fund/American Insitute for Cancer Research Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. pp. Washington DC: AICR, 2007.

6. Larsson SC, Orsini N, Wolk A(2005) Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* **97**: 1679-87.

7. Giovannucci E(2001) Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr* **131**: 3109S-20S.

8. Pisani P(2008) Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. *Arch Physiol Biochem* **114**: 63-70.

9. Ma J, Giovannucci E, Pollak M *et al.*(2004) A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst* **96**: 546-53.

10. Kaaks R, Toniolo P, Akhmedkhanov A *et al.*(2000) Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* **92**: 1592-600.

11. Wei EK, Ma J, Pollak MN *et al.*(2005) A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* **14**: 850-5.

12. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S(2007) Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. *Int J Cancer* **120**: 2007-12.

13. Jenab M, Riboli E, Cleveland RJ *et al.*(2007) Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* **121**: 368-76.

14. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM(2005) Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* **293**: 194-202.

15. Brand-Miller JC(2004) Postprandial glycemia, glycemic index, and the prevention of type 2 diabetes. *Am J Clin Nutr* **80**: 243-4.

16. Jenkins DJ, Wolever TM, Taylor RH *et al.*(1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* **34**: 362-6.

17. Atkinson FS, Foster-Powell K, Brand-Miller JC(2008) International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* **31**: 2281-3.

18. Bostick RM, Potter JD, Kushi LH *et al.*(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.

19. Chyou PH, Nomura AM, Stemmermann GN(1996) A prospective study of colon and rectal cancer among Hawaii Japanese men. *Ann Epidemiol* **6**: 276-82.

20. 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**: 276-81.

21. 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**: 914-6.

22. Higginbotham S, Zhang ZF, Lee IM *et al.*(2004) Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst* **96**: 229-33.

23. 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**: 138-47.

24. 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**: 892-6.

25. 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**: 256-61.

26. 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**: 853-63.

27. 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**: 620-9.

28. Kabat GC, Shikany JM, Beresford SA *et al.*(2008) Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control* **19**: 1291-8.

29. 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. *Am J Clin Nutr* **88**: 1074-82.

30. George SM, Mayne ST, Leitzmann MF *et al.*(2009) Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. *Am J Epidemiol* **169**: 462-72.

31. Li HL, Yang G, Shu XO *et al.*(2010) Dietary glycemic load and risk of colorectal cancer in Chinese women. *Am J Clin Nutr*.

32. Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P(2008) Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr* **87**: 1793-801.

33. Stroup DF, Berlin JA, Morton SC *et al.*(2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**: 2008-12.

34. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM(2009) Glycemic index, glycemic load, and risk of digestive tract neoplasms: a systematic review and meta-analysis. *Am J Clin Nutr* **89**: 568-76.

35. Stemmermann GN, Nomura AM, Heilbrun LK(1984) Dietary fat and the risk of colorectal cancer. *Cancer Res* **44**: 4633-7.

36. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O(1985) Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* **1**: 307-9.

37. 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.

38. Stemmermann GN, Nomura AM, Chyou PH, Yoshizawa C(1990) Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci* **35**: 1414-20.

39. DerSimonian R, Laird N(1986) Meta-analysis in clinical trials. *Control Clin Trials* **7**: 177-88.

40. Greenland S, Longnecker MP(1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* **135**: 1301-9.

41. Higgins JP, Thompson SG(2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**: 1539-58.

42. Egger M, Davey SG, Schneider M, Minder C(1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**: 629-34.

43. Begg CB, Mazumdar M(1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**: 1088-101.

44. Flood A, Peters U, Jenkins DJ *et al.*(2006) Carbohydrate, glycemic index, and glycemic load and colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr* **84**: 1184-92.

45. Oh K, Willett WC, Fuchs CS, Giovannucci EL(2004) Glycemic index, glycemic load, and carbohydrate intake in relation to risk of distal colorectal adenoma in women. *Cancer Epidemiol Biomarkers Prev* **13**: 1192-8.

46. Stemmermann GN, Heilbrun LK, Nomura AM(1988) Association of diet and other factors with adenomatous polyps of the large bowel: a prospective autopsy study. *Am J Clin Nutr* **47**: 312-7.

47. Macquart-Moulin G, Riboli E, Cornee J, Kaaks R, Berthezene P(1987) Colorectal polyps and diet: a case-control study in Marseilles. *Int J Cancer* **40**: 179-88.

48. Neugut AI, Garbowski GC, Lee WC *et al.*(1993) Dietary risk factors for the incidence and recurrence of colorectal adenomatous polyps. A case-control study. *Ann Intern Med* **118**: 91-5.

49. Lubin F, Rozen P, Arieli B *et al.*(1997) Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology. *Cancer Epidemiol Biomarkers Prev* **6**: 79-85.

50. Diergaarde B, Tiemersma EW, Braam H *et al.*(2005) Dietary factors and truncating APC mutations in sporadic colorectal adenomas. *Int J Cancer* **113**: 126-32.

51. Almendingen K, Hofstad B, Vatn MH(2004) Dietary habits and growth and recurrence of colorectal adenomas: results from a three-year endoscopic follow-up study. *Nutr Cancer* **49**: 131-8.

52. Barclay AW, Petocz P, Millan-Price J *et al.*(2008) Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. *Am J Clin Nutr* **87**: 627-37.

53. Mente A, de Koning L, Shannon HS, Anand SS(2009) A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* **169**: 659-69.

Table 1: Prospective cohort studies of intake of carbohydrate, glycemic index and glycemic load and colorectal cancer risk

Author, publication year, country	Study name	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Li et al, 2010, China	Shanghai Women's Health Study	1997-2000 – 2007, 9.1 years follow-up	73061 women, age 40-70 years: 475 CRC cases	Validated FFQ, 71 food items	Glycemic index Glycemic load Carbohydrate	225.9 vs. 159.7 units/d 76.0 vs. 64.4 units/d 302.3 vs. 242.2 g/d	0.94 (0.71-1.24) 1.09 (0.81-1.46) 0.87 (0.66-1.15)	Age, birth year, education, income, BMI, physical activity, FH – CRC, HRT, total energy intake
George et al, 2008, USA	NIH-AARP Diet and Health Study	1995-96 – 2003,	262642 men and 183535 women, age 50-71 yrs: 3031/1457 CRC cases	Validated FFQ, 124 items	Glycemic index, w Glycemic index, m Glycemic load, w Glycemic load, m	≥56.6 vs. ≤50.4 units/d ≥57.0 vs. ≤51.3 units/d ≥135.3 vs. ≤66.9 units/d ≥164.4 vs. ≤83.0 units/d	1.16 (0.98-1.37) 1.16 (1.04-1.30) 0.87 (0.64-1.18) 0.88 (0.72-1.08)	Age, race/ethnicity, education, marital status, BMI, FH – any cancer, physical activity, smoking, alcohol, total energy intake
Weijenberg et al, 2008, Netherlands	Netherlands Cohort Study	1986 – , 11.3 years follow-up	2072 men and 2053 women, age 55-69 years: 1225 CC cases 418 RC cases	Validated FFQ, 150 items	Glycemic index, m Glycemic index, w Glycemic load, m Glycemic load, w	64.5 vs. 56.6 units/d 61.9 vs. 53.7 units/d 165.4 vs. 108.7 units/d 123.6 vs. 82.5 units/d	0.81 (0.61-1.08) 1.20 (0.85-1.67) 0.83 (0.64-1.08) 1.00 (0.73-1.36)	Age, BMI, FH – CC, smoking, total energy, calcium, alcohol, education, processed meat, physical activity
Howarth et al, 2008, USA	Multiethnic Cohort Study	1993-96 - 2002, 8 yrs follow-up	191004 men and women, age 45-75 years: 2379 CRC cases	Validated FFQ, >180 food items	Glycemic load, m Glycemic load, w Carbohydrate, m Carbohydrate, w	209 vs. 96 g/d 171 vs. 82 g/d ≥331.2 vs. <243.9 g/d ≥281.1 vs. <234.5 g/d	1.15 (0.89-1.48) 0.75 (0.57-0.97) 1.09 (0.84-1.40) 0.71 (0.53-0.95)	Age, ethnicity, time since cohort entry, CR polyp, pack-years of cigarette smoking, BMI, hours of vigorous activity, NSAID use, multivitamin use, hormone replacement use, energy intake, alcohol, red meat, folate, vitamin D, calcium, dietary fiber
Kabat GC et al, 2008, USA	Women's Health Initiative	1993-98 – , 7.8 years follow-up	158800 women, age 50-79 years: 1476 CRC cases	FFQ, 122 food items	Glycemic index Glycemic load Total carbohydrate Total sugars	≥55.4 vs. <49.4 units/d ≥126.6 vs. <62.4 units/d ≥260.1 vs. <131.6 g/d ≥129.7 vs. <58.8 g/d	1.10 (0.92-1.32) 1.11 (0.82-1.49) 0.89 (0.64-1.25) 1.16 (0.91-1.49)	Age, education, cigarettes per day, BMI, height, HRT, diabetes mellitus, FH – CRC in 1st degree relative, physical activity, observational study participant, total fiber, energy, dietary calcium
Strayer L et la, 2007, USA	Breast Cancer Detection Demonstration Project	1979-81 – 1998, 8.5 yrs follow-up	45561 women, mean age 61.9 years: 490 CRC cases	Validated FFQ, 62 food items	Carbohydrate Glycemic index Glycemic load	>162 vs. <114 g/d >52.5 vs. <45 units/d >79.5 vs. <55.3	0.70 (0.50-0.97) 0.75 (0.56-1.00) 0.91 (0.70-1.20)	Age, dietary calories, NSAIDs use, fiber, smoking, menopausal hormone use, screened for colorectal cancer, BMI
McCarl M et al, 2006, USA	Iowa Women's Health Study	1986-2000, 15 years follow-up	35197 women, age 55-69 years: 957 CRC cases	FFQ, 127 food items	Glycemic index Glycemic load	>89.3 vs. <81.0 units/d >193 vs. ≤146	1.08 (0.88-1.32) 1.09 (0.88-1.35)	Age, energy intake, activity level, multivitamin use, diabetes, smoking, WHR

Larsson SC et al, 2006, Sweden	Swedish Mammography Cohort	1987-90 – 2005, 15.7 years follow-up	61433 women, age 40-76 years: 870 CRC cases	Validated FFQ, 67 food items	Glycemic index Glycemic load Carbohydrate	≥83.4 vs. <75.8 ≥200 vs. <164 units/d ≥246 vs. <211 g/d	1.00 (0.75-1.33) 1.06 (0.81-1.39) 1.10 (0.85-1.44)	Age, education, BMI, total energy intake, alcohol, cereal fiber, folate, calcium, magnesium, red meat
Michaud DS et al, 2005, USA	Health Professionals Follow-up Study	1986-2000, 14 years follow-up	47422 men, age 45-75 years: 696 CRC cases	Validated FFQ, 131 food items	Glycemic index Glycemic load Carbohydrate Sucrose Fructose	82 vs. 69 units/d 223 vs. 131 units/d 288 vs. 182 g/d 67 vs. 26 g/d 72 vs. 29 g/d	1.14 (0.88-1.48) 1.32 (0.98-1.79) 1.27 (0.93-1.72) 1.30 (0.99-1.69) 1.37 (1.05-1.78)	Age, FH – CC, prior endoscopy screening, aspirin use, height, BMI, pack-years of smoking before age 30 years, physical activity, cereal fiber, alcohol, calcium, folate, processed meat and beef, pork, lamb as main dish
Michaud DS et al, 2005, USA	Nurses' Health Study	1980-2000, 20 years follow-up	83927 women, age 34-59 years: 1113 CRC cases	Validated FFQ, 131 food items	Glycemic index Glycemic load Carbohydrate Sucrose Fructose	81 vs. 65 units/d 167 vs. 80 units/d 202 vs. 110 g/d 55 vs. 17 g/d 68 vs. 22 g/d	1.08 (0.87-1.34) 0.89 (0.71-1.11) 0.87 (0.68-1.11) 0.89 (0.72-1.11) 0.87 (0.71-1.07)	Age, FH – CC, prior endoscopy screening, aspirin use, height, BMI, pack-years of smoking before age 30 years, physical activity, cereal fiber, alcohol, calcium, folate, processed meat and beef, pork, lamb as main dish
Higginbotham S et al, 2004, USA	Women's Health Study	1993-1996 7.9 years follow-up	38451 women, age ≥45 years: 174 CRC cases	Validated FFQ, 131 food items	Glycemic index Glycemic load Carbohydrate Sucrose Fructose	57 vs. 49 units/d 143 vs. 92 units/d 267 vs. 177 g/d 51 vs. 31 g/d 56 vs. 31 g/d	1.71 (0.98-2.98) 2.85 (1.40-5.80) 2.41 (1.10-5.27) 1.51 (0.90-2.54) 2.09 (1.13-3.87)	Age, BMI, OC use, HRT, FH – CRC, smoking, alcohol use, physical activity, NSAID use, total energy intake, total fiber, total fat, folate, calcium, vitamin D
Terry PD et al, 2003, Canada	Canadian National Breast Screening Study	1980-1985 – 2000, 16.5 years follow-up	49124 women, age 40-59 years: 616 CRC cases	Validated FFQ, 86 food items	Glycemic load Total carbohydrate Total sugar	217 vs. 82.3 units/d ≥249 vs. <143 g/d ≥104 vs. <53 g/d	1.05 (0.73-1.53) 1.01 (0.68-1.51) 1.03 (0.73-1.44)	Age, energy intake, study center, treatment allocation, BMI, cigarette smoking, educational level, physical activity, OC use, HRT, parity, alcohol, red meat, folic acid
Kato et al, 1997, USA	New York University Women's Cohort Study	1985-1991 – 1994, 7.1 years follow-up	14727 women, age 34-65 years: 100 CRC cases	FFQ, 70 food items	Carbohydrate	Quartile 4 vs. 1	1.21 (0.67-2.17)	Age, total calories, place at enrollment, highest level of education
Chyou PH et al, 1996, USA	Honolulu Heart Program	1965-1995, 22 years follow-up	7940 Japanese-American men, age ≥45 years: 330 CC cases 123 RC cases	24-hour dietary recall, 54 food items	Carbohydrate, CC Carbohydrate, RC	≥54 vs. <40 % of energy ≥54 vs. <40 % of energy	1.04 (0.78-1.39) 0.43 (0.24-0.75)	Age
Bostick, 1994, USA	Iowa Women's Health Study	1986-1990, 4.8 years follow-up	35212 women, age 55-69 years: 212 CC cases	Validated FFQ, 127 food items	Total carbohydrate Sucrose Fructose	>274 vs. <152 g/d >62.5 vs. <25.8 g/d >30.6 vs. <13.4 g/d	1.30 (0.83-2.06) 1.45 (0.88-2.39) 0.93 (0.61-1.42)	Age, total egergy, height, parity, total vitamin E, vitamin A supplement

BMI=Body Mass Index, CC=colon cancer, CR=colorectal, CRC=colorectal cancer, FFQ=food frequency questionnaire, FH=Family history, HPFS=Health Professionals Follow-up Study, HRT/HT=hormone therapy, m=men, MET=metabolic equivalent task, NHS=Nurses' Health Study, RC=rectal cancer, w=women.

Table 2: Subgroup analyses of glycemic index, glycemic load, total carbohydrate and colorectal cancer, dose-response analysis

	Glycemic index					**Glycemic load**					**Total carbohydrate**				
	n	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	*n*	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	*n*	RR (95% CI)	I^2 (%)	P_h^1	P_h^2
All studies	10	1.07 (0.99-1.15)	39.0	0.10		12	1.00 (0.94-1.06)	49.9	0.03		9	0.97 (0.87-1.09)	51.2	0.04	
Duration of follow-up															
<10 yrs follow-up	5	1.08 (0.92-1.27)	65.7	0.02	0.69	6	0.99 (0.90-1.09)	54.3	0.05	0.77	4	0.99 (0.80-1.23)	59.8	0.06	0.90
≥10 yrs follow-up	5	1.06 (0.98-1.14)	0	0.73		6	1.01 (0.92-1.10)	50.6	0.07		5	0.97 (0.83-1.12)	52.7	0.08	
Sex															
Men	4	1.14 (1.04-1.24)	0	0.72	0.44	4	1.00 (0.88-1.13)	66.4	0.03	0.74	2	1.15 (0.98-1.35)	4.9	0.31	0.07
Women	8	1.05 (0.95-1.17)	48.9	0.06		11	0.98 (0.93-1.04)	24.9	0.21		8	0.92 (0.82-1.03)	40.1	0.11	
Subsite															
Colon	7	1.04 (0.95-1.13)	25.7	0.23	0.61	9	0.98 (0.91-1.05)	32.0	0.16	0.08	8	0.95 (0.86-1.06)	19.3	0.28	0.41
Rectum	7	1.09 (0.94-1.25)	0	0.92		9	1.11 (1.00-1.23)	0	0.74		7	1.03 (0.87-1.23)	0	0.59	
Proximal colon	5	1.09 (0.97-1.22)	0	0.87	0.08	6	0.88 (0.78-1.00)	32.8	0.19	0.19	5	0.77 (0.60-0.98)	47.3	0.11	0.10
Distal colon	5	0.90 (0.78-1.04)	0	0.61		6	1.01 (0.88-1.16)	26.6	0.24		5	1.17 (0.87-1.59)	50.1	0.09	
Geographic location															
Europe	2	0.95 (0.80-1.14)	0	0.96	0.53	2	0.95 (0.82-1.10)	0	0.64	0.89	1	1.21 (0.74-1.98)			0.33
America	7	1.09 (1.00-1.20)	49.0	0.07		9	1.01 (0.94-1.10)	62.5	0.006		7	0.98 (0.87-1.10)	58.4	0.03	

Asia		1	1.02 (0.81-1.29)				1	0.94 (0.77-1.15)				1	0.76 (0.49-1.16)			
Number of cases																
Cases <500		3	1.03 (0.76-1.38)	67.3	0.05	0.10	3	1.11 (0.75-1.62)	75.2	0.02	0.49	2	1.39 (0.38-5.06)	86.4	0.007	0.87
Cases 500-<1500		5	1.08 (1.00-1.16)	0	0.82		6	1.03 (0.95-1.12)	47.8	0.09		1	0.95 (0.82-1.12)			
Cases ≥1500		2	1.10 (0.90-1.35)	60.4	0.11		3	0.95 (0.90-1.00)	0	0.64		6	0.97 (0.86-1.08)	44.1	0.11	
Alcohol	Yes	6	1.10 (1.00-1.20)	33.6	0.18	0.47	8	1.00 (0.92-1.08)	61.5	0.01	0.72	6	1.05 (0.87-1.25)	59.8	0.03	0.41
	No	4	1.02 (0.89-1.18)	48.2	0.12		4	1.03 (0.94-1.12)	0	0.46		3	0.91 (0.83-1.00)	4.4	0.35	
Smoking	Yes	8	1.08 (0.99-1.18)	46.4	0.07	0.41	10	1.01 (0.94-1.08)	58.7	0.01	0.75	7	0.98 (0.87-1.10)	58.4	0.03	0.87
	No	2	0.98 (0.83-1.17)	0	0.68		2	0.96 (0.82-1.12)	0	0.76		2	0.94 (0.59-1.49)	49.0	0.16	
Body mass index, weight, WHR	Yes	10	1.07 (0.99-1.15)	39.0	0.10	NA	12	1.00 (0.94-1.06)	49.9	0.03	NA	9	0.97 (0.87-1.09)	51.2	0.04	NA
	No	0					0					0				
Physical activity	Yes	8	1.12 (1.06-1.18)	0	0.49	0.03	10	1.01 (0.94-1.08)	57.8	0.01	0.63	8	0.96 (0.86-1.08)	54.6	0.03	0.53
	No	2	0.88 (0.74-1.03)	0	0.39		2	0.94 (0.78-1.14)	0	0.50		1	1.21 (0.74-1.98)			
Red, processed meat	Yes	4	1.04 (0.95-1.14)	0	0.70	0.48	6	0.99 (0.92-1.08)	45.0	0.11	0.92	5	0.99 (0.86-1.14)	39.3	0.16	0.68
	No	6	1.09 (0.96-1.23)	57.2	0.04		6	1.01 (0.91-1.13)	60.4	0.03		4	0.96 (0.77-1.18)	66.2	0.03	
Calcium intake	Yes	6	1.06 (0.98-1.15)	0	0.48	0.98	7	1.04 (0.93-1.15)	63.2	0.01	0.40	6	1.05 (0.89-1.23)	58.2	0.04	0.19
	No	4	1.05 (0.90-1.22)	68.9	0.02		5	0.95 (0.91-1.00)	0	0.53		3	0.88 (0.80-0.97)	0	0.74	

Fruits, vegetables	Yes	0				NA	0				NA	0				NA
	No	10	1.07 (0.99-1.15)	39.0	0.10		12	1.00 (0.94-1.06)	49.9	0.03		9	0.97 (0.87-1.09)	51.2	0.04	
Folate	Yes	6	1.06 (0.95-1.18)	54.4	0.05	0.91	6	1.04 (0.92-1.17)	67.4	0.009	0.55	6	1.05 (0.87-1.25)	59.8	0.03	0.41
	No	4	1.07 (0.96-1.19)	14.6	0.32		6	0.97 (0.92-1.02)	6.7	0.37		3	0.91 (0.83-1.00)	4.4	0.35	
Energy intake	Yes	10	1.07 (0.99-1.15)	39.0	0.10	NA	12	1.00 (0.94-1.06)	49.9	0.03	NA	9	0.97 (0.87-1.09)	51.2	0.04	NA
	No	0					0					0				

n denotes the number of studies, the number of risk estimates used is lower in some analyses as one publication reported a combined estimate for two studies (ref. no 13). [1] P for heterogeneity within each subgroup, [2] P for heterogeneity between subgroups with meta-regression analysis, [3,4] subgroup analyses restricted to studies that reported results both for men and women, [5,6] subgroup analyses restricted to studies that reported results both for colon and rectum. NA: not applicable because no studies were present in one of the subgroups.

Figure 1. Flow-chart of study selection

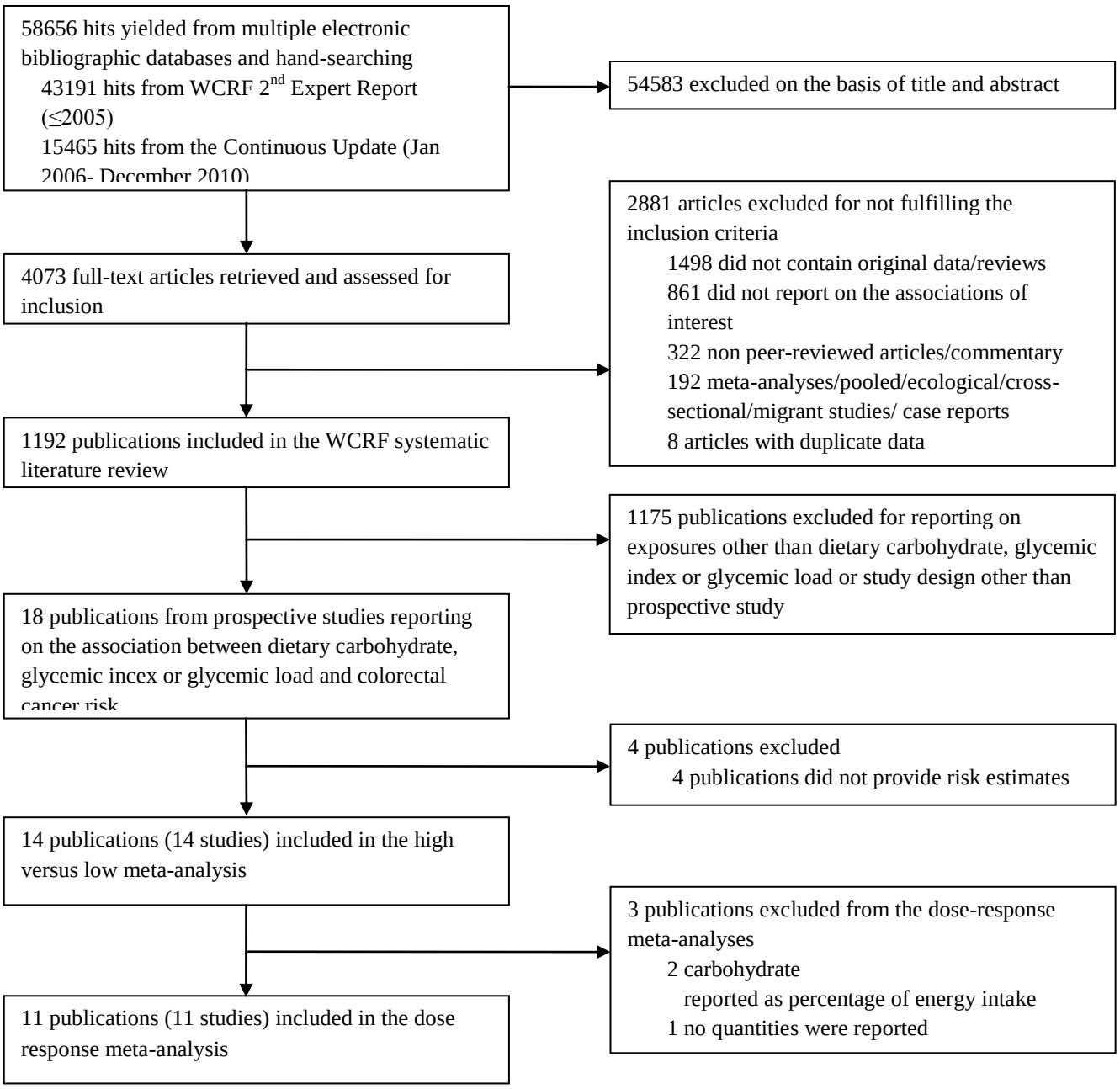


Figure 2. Glycemic index and colorectal cancer

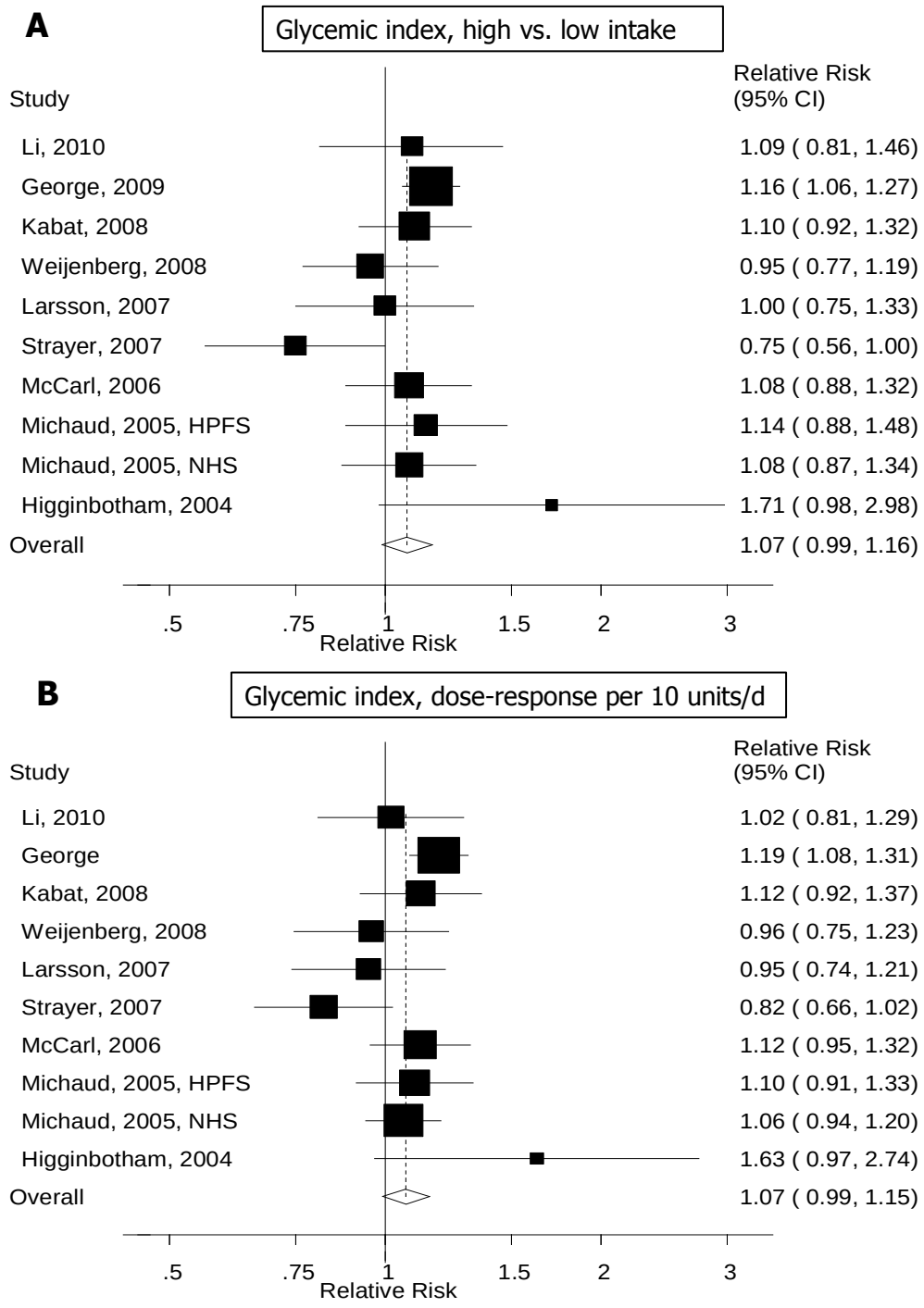


Figure 3. Glycemic load and colorectal cancer

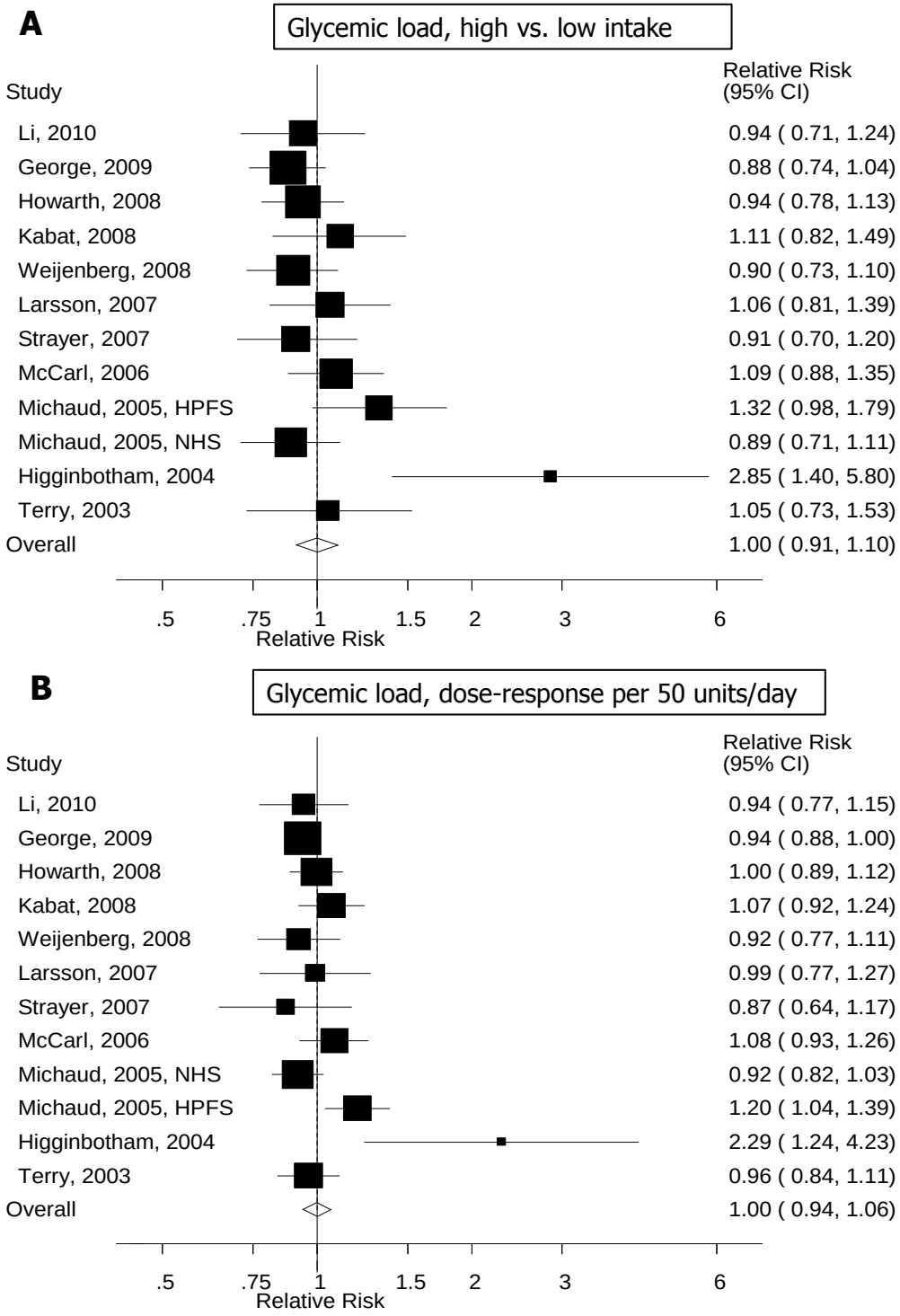


Figure 4. Total carbohydrate and colorectal cancer

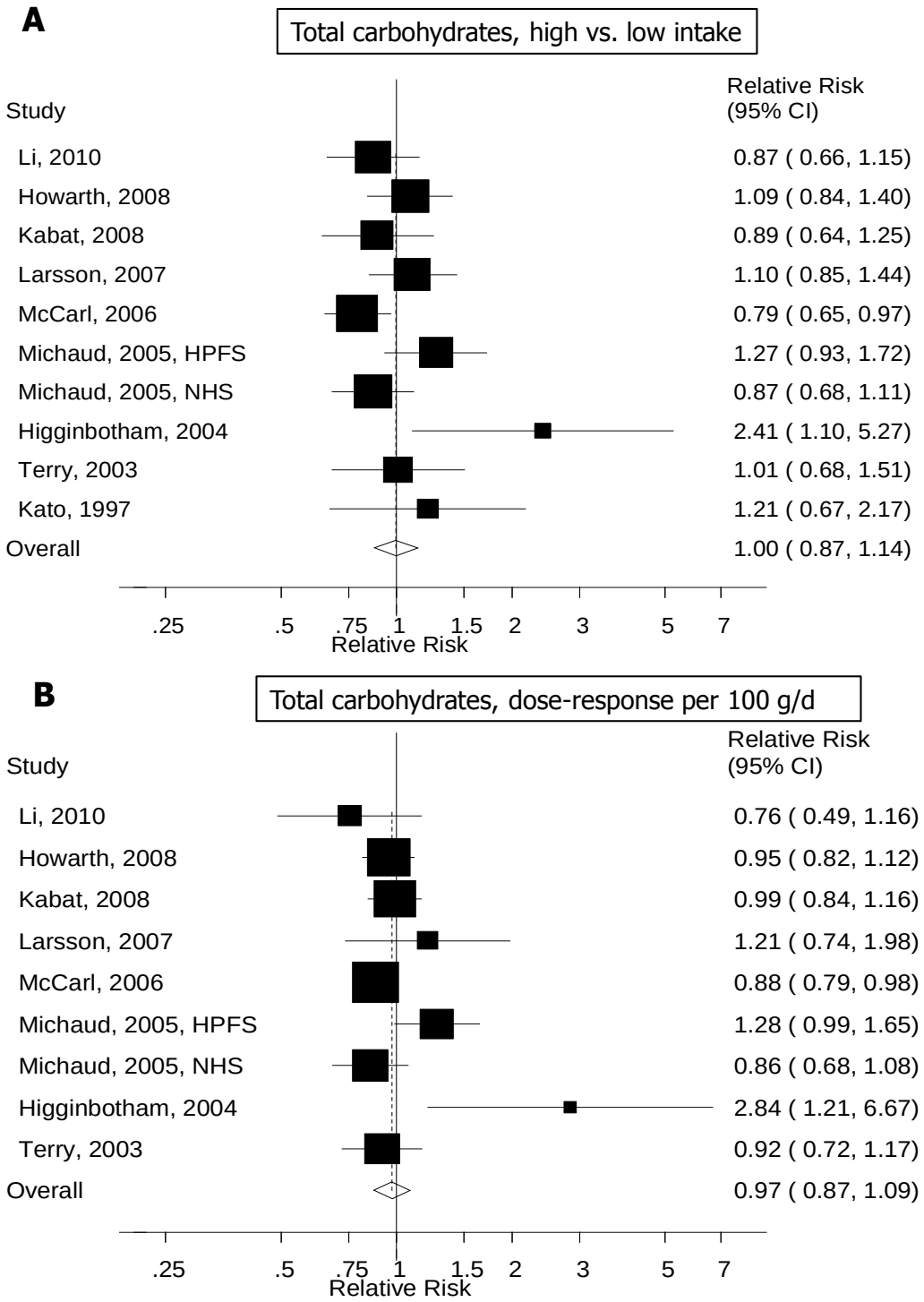
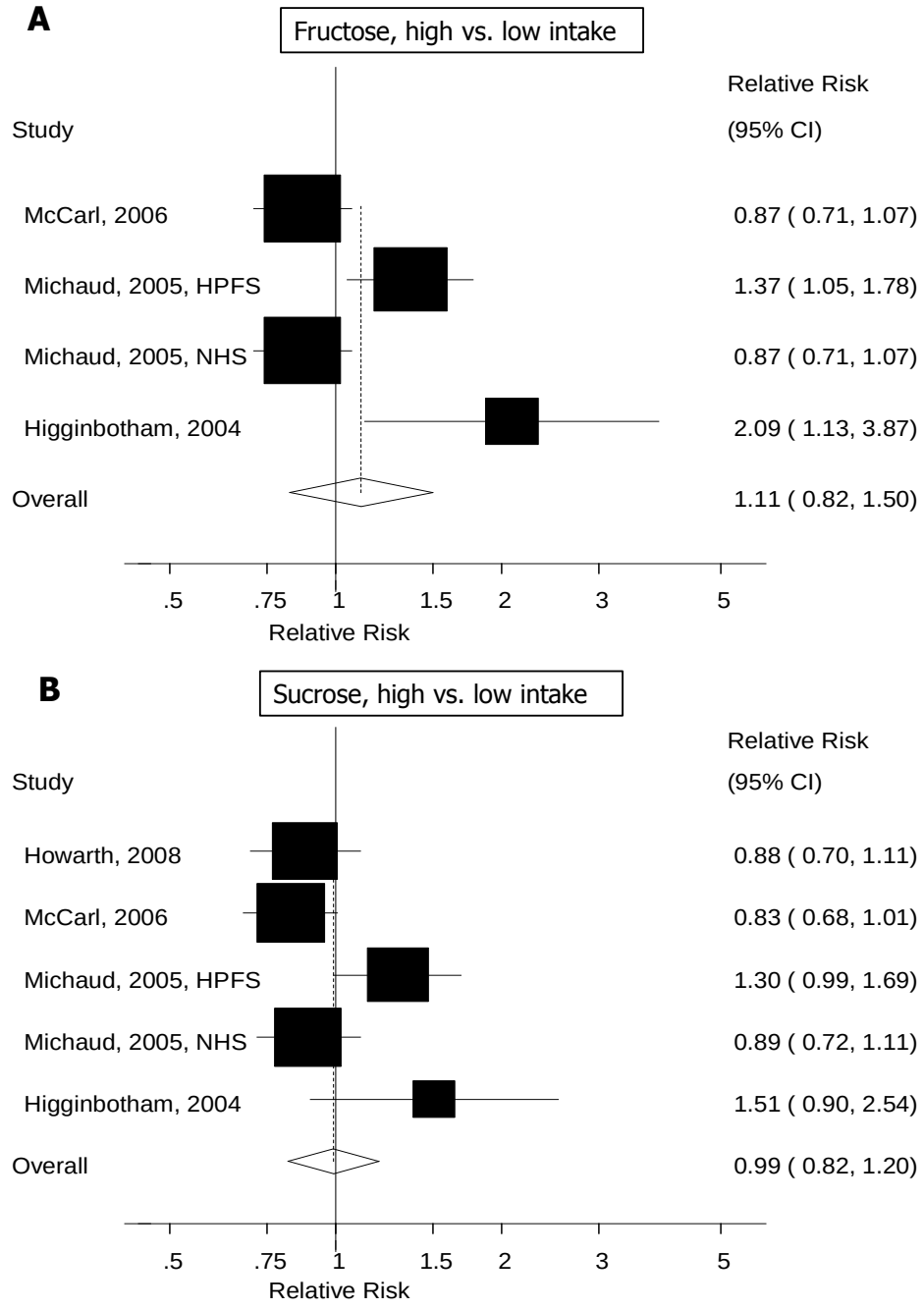
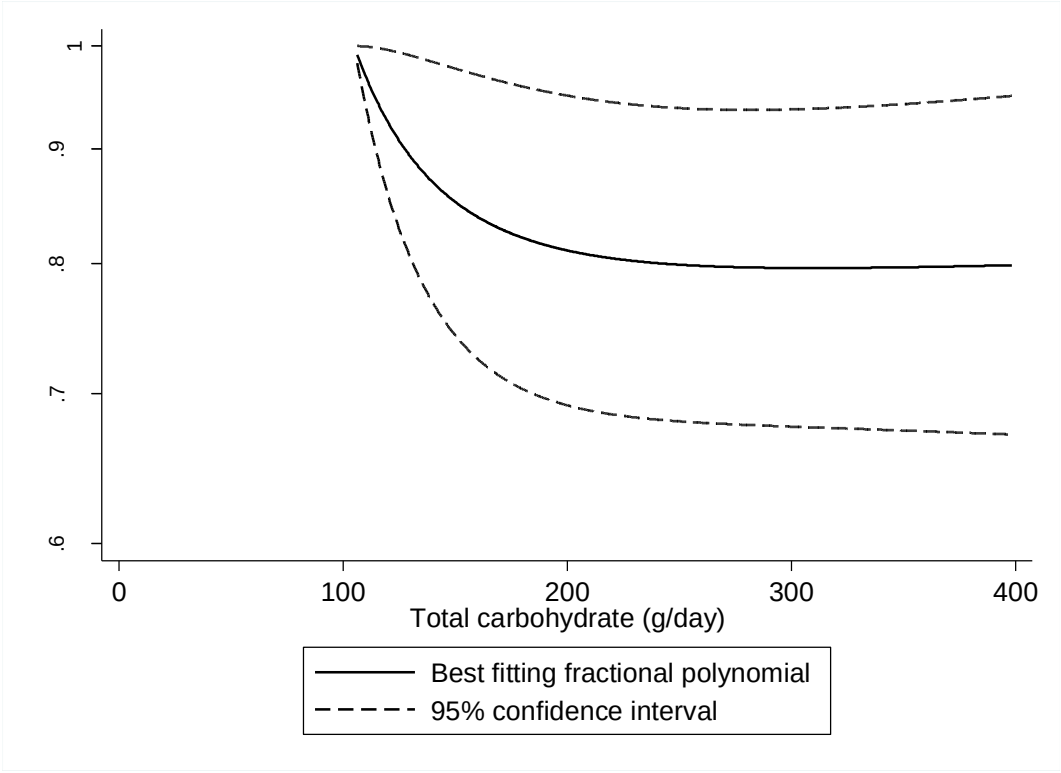


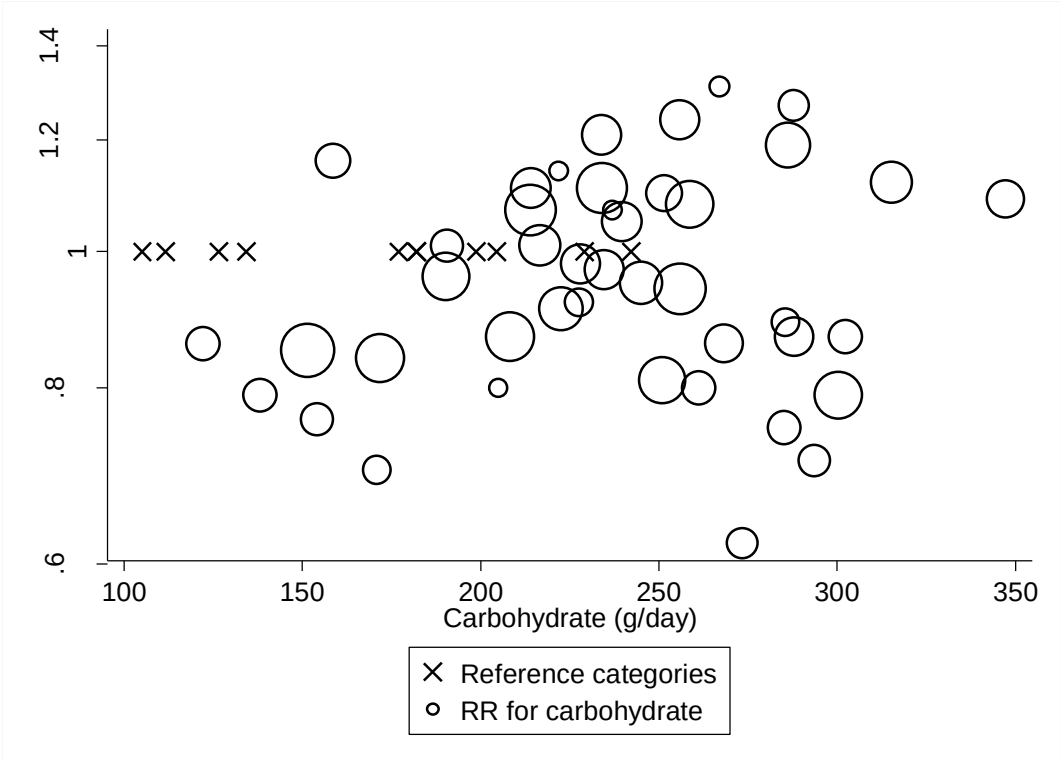
Figure 5. Fructose and sucrose intake and colorectal cancer, high versus low analysis



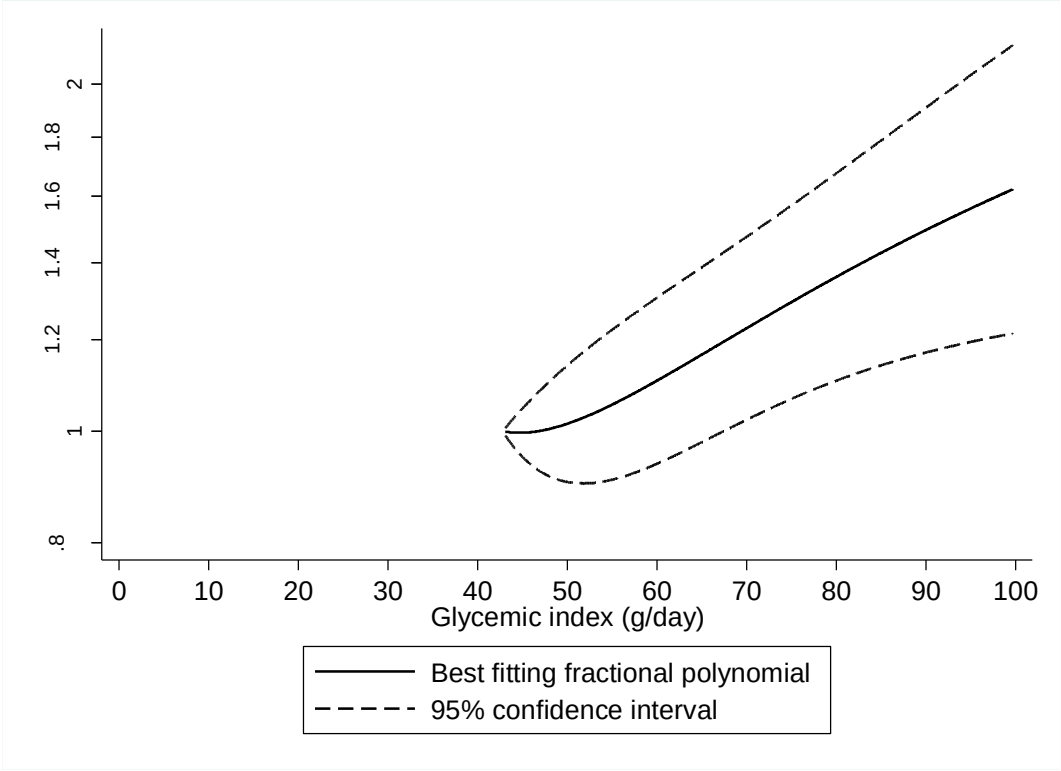
Additional material:

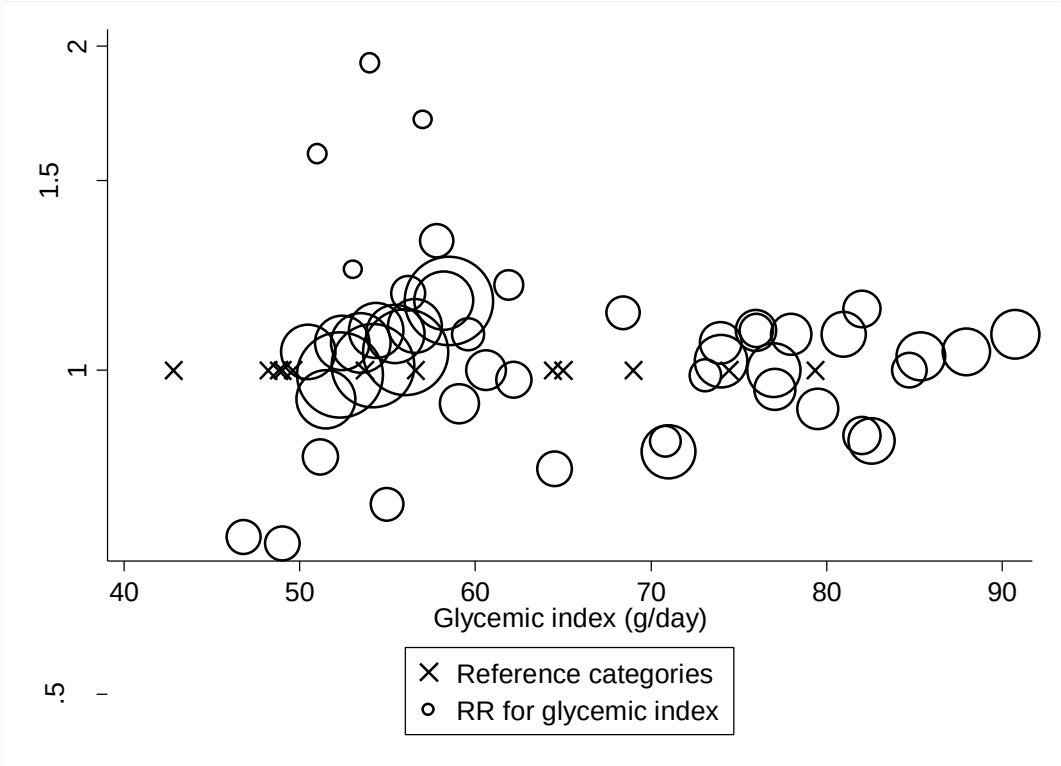
Carbohydrates

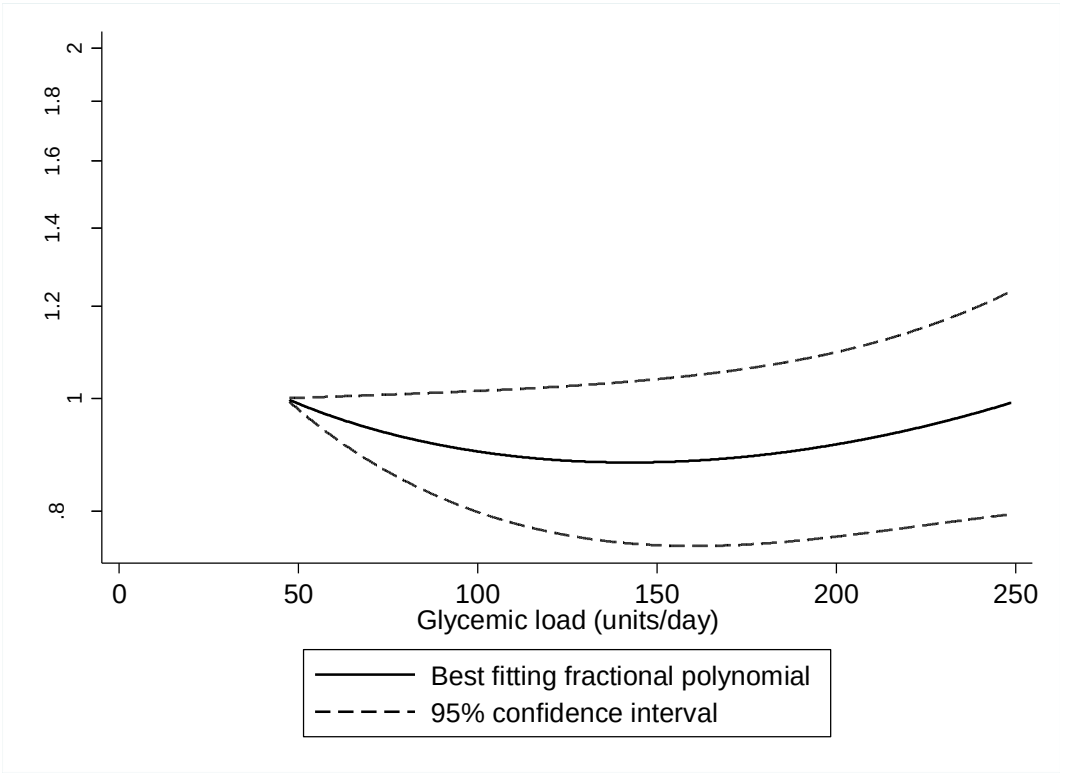




Glycemic index







Glycemic load