Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies.

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Abstract

Background: The association between fruit and vegetable intakes and colorectal cancer risk has been investigated in a large number of studies, but with inconsistent results. As part of the Continuous Update Project of the World Cancer Research Fund we conducted an updated systematic review and meta-analysis of fruit and vegetable intakes and colorectal cancer risk.

Methods: We searched the PubMed database for prospective cohort and nested case-control studies of fruit and vegetable intakes and risk of colorectal cancer, up to May 2010. Summary relative risks were estimated by use of a random effects model.

Results: We identified 19 cohort studies that could be included in the meta-analysis of fruit and vegetables and colorectal cancer risk. The summary RR for high vs. low intake was 0.92 (95% CI: 0.86-0.99) for intake of fruit and vegetables combined, 0.90 (95% CI: 0.83-0.98) for intake of fruit and 0.91 (95% CI: 0.86-0.96) for vegetables. The inverse associations were restricted to colon cancer. In the linear dose-response analysis the summary RR was 0.99 (95% CI: 0.98-1.00) per 100 grams per day of total fruit and vegetable intake, 0.98 (95% CI: 0.94-1.01) for fruit and 0.98 (95% CI: 0.97-0.99) for vegetables. However, there was evidence of a non-linear association and the greatest reduction in risk was observed when increasing intake from very

low levels of intake. There was generally little evidence of heterogeneity in the analyses and there was no evidence of small-study bias.

Conclusion: This meta-analysis suggests that there is a weak, but statistically significant non-linear inverse association between fruit and vegetable intake and colorectal cancer risk. Further cohort studies incorporating biomarkers of fruit and vegetable intake, are warranted to clarify associations between specific types of fruit and vegetables and colorectal cancer, the impact of measurement errors on the results and whether similar associations are found in non-Caucasian populations.

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Introduction

Intake of fruit and vegetables has been hypothesized to protect against a number of cancers, including colorectal cancer (1). Experimental animal studies and human feeding studies have provided biologically plausible mechanisms by which fruit and vegetables could reduce colorectal cancer risk (2;3), but epidemiological studies have provided inconsistent results. The first large report from the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) from 1997 concluded that there was convincing evidence that vegetable intake, but not fruit intake, protects against colorectal cancer, based on a narrative review of the results from 22 case-control studies and four cohort studies (4). In contrast, most (5-25), but not all (26;27) prospective cohort studies published in the ten following years found no statistically significant associations between fruit and/or vegetable intakes and colorectal cancer risk. In line with this, several reviews and meta-analyses and a pooled analysis did not find statistically significant inverse associations between fruit and vegetable intakes and colorectal cancer risk in cohort studies (28-31). Although case-control studies continue to show strong evidence of an inverse association (28;29), these studies are more liable to recall and selection biases which can hamper the interpretation of their results.

Also, the 2nd report from the WCRF/AICR published in 2007, “Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective” stated that there was limited suggestive evidence for a reduction in risk with intakes of fruits and non-starchy vegetables, based on quantitative systematic reviews and meta-analyses of the available data from cohort studies, thus a downgrading of the evidence compared with the previous report (5). Results from a number of additional

large prospective cohort studies have been published since the 2nd WCRF/AICR report (32-37). Therefore, we update the evidence with these prospective studies published up to May, 2010.

Methods

Search strategy

We updated the systematic literature review published in 2007 (5) and searched the PubMed database up to May 2010 for cohort studies of fruit and vegetable intake and colorectal cancer risk. We followed a prespecified protocol, which includes details of the search terms used, for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf) (38). We also searched the reference lists of all the studies that were included in the analysis and the reference lists of the published systematic reviews and meta-analyses.

Study selection

To be included, the study had to have a prospective cohort, case-cohort or nested case-control design and to investigate the association between the intake of fruit, vegetables or fruits and vegetables combined and colorectal cancer risk. We did not include studies of colorectal cancer mortality because dietary changes after colorectal cancer diagnosis may influence survival. Estimates of the relative risk (RR) (such as hazard ratio or 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 and the total number of cases and person-years had to be available in the publication. When multiple publications from the same study were

available we used the publication which presented the results with enough detail to be incorporated into dose-response analyses or the publication with the largest number of cases. Six studies on colorectal cancer mortality were excluded (8;19-21;39;40), three studies which did not provide risk estimates were excluded (9;12;16), seven duplicate publications were excluded (7;41-46) and for the dose-response analyses two publications were excluded because no quantities were provided (6;25) and two others because only the highest vs. the lowest level of intake was reported (34;47) (Figure 1).

Data extraction

We extracted the following data 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 (by type of outcome), quantity of intake, RRs and 95% CIs for the highest vs. the lowest fruit and vegetable intake and variables adjusted for in the analysis. The search and data extraction of articles published up to June 2006 was conducted by several reviewers at Wageningen University during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Colon_and_Rectum_SLR.pdf). The search from June 2006 and up to May 2010 was conducted by two of the authors (D. S. M. C. and R. L). Data was extracted into a database by three authors (D. S. M. C., R.L. and D. A.) and was checked for accuracy by another author (T. N).

Statistical methods

We used random effects models to calculate summary RRs and 95% CIs for the highest vs. the lowest level of fruit and vegetable intake and for the dose-response analysis (48). 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, but not combined, we combined the results using a fixed-effects model to obtain an overall estimate for both genders. For studies that reported separately on colon and rectal cancer, but not for colorectal cancer, we used the method developed by Hamling et al. to combine the results (49). For two studies (reported in one paper) (14) that did not provide the information which was needed to use the Hamling method we used a fixed effects model to pool the results for colon and rectal cancer.

We used the method described by Greenland and Longnecker (50) for the dose–response analysis and computed study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across categories of fruit and vegetable 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. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases/person-years, if the results were analysed by quantiles (and could be approximated). If this information was missing and the results were reported by functional categories, we used variance weighted least squares regression to estimate the slopes. We examined a potential non-linear dose-response relationship between fruit and vegetable intakes and colorectal cancer by using fractional

polynomial models (51). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the non-linear and linear models to test for nonlinearity (52). The median or mean level of fruit and vegetable intake in each category of intake was assigned to the corresponding relative risk for each study when provided in the paper. For studies that reported fruit and vegetable intake by ranges of intake we estimated the mean intake in each category by calculating the average of the lower and upper bound. When the highest category was open-ended we assumed the open-ended interval length to be the same as the adjacent interval. When the lowest category was open-ended we set the lower boundary to zero. If the intakes were reported in densities (i.e. gram per 1000 kcal or gram per 1000 kJ) (15;32;33;35) we recalculated the reported intakes to absolute intakes using the mean or median energy intake. In studies that reported the intakes by frequency we used 80 grams as a serving size for recalculation of the intakes to a common scale (grams per day) (28). The dose-response results in the forest plots are presented for a 100 gram per day increment.

Heterogeneity between studies was assessed using Q and I^2 statistics (53). I^2 is the amount of total variation that is explained by between study variation. I^2 values of approximately 25%, 50% and 75% are considered to indicate low, moderate and high heterogeneity, respectively.

Subgroup and meta-regression analyses by sex, cancer subsite, duration of follow-up, number of cases, geographic location and adjustment for confounding factors such as body mass index, smoking, alcohol, physical activity, intakes of dairy products/calcium, energy and red and processed meat were conducted to investigate potential sources of heterogeneity. Small-study bias, such as publication

bias, was assessed using a funnel plot and Egger's test (54) and with results considered to indicate potential small-study bias when $p<0.10$. We conducted sensitivity analyses excluding one study at a time to ensure that the results were not simply due to one large study or a study with an extreme result and overall summary estimates from these sensitivity analyses are presented excluding the studies with the largest negative and positive effect on the summary estimate. In addition, we conducted sensitivity analyses to assess the potential influence on the results of the studies which were excluded from the dose-response analyses (due to insufficient data for inclusion in the dose-response analysis), by also excluding these studies from the high versus low analysis and comparing the summary RRs with those from all studies combined.

Stata version 10.1 software (StataCorp, College Station, TX, USA) was used for the statistical analyses.

Role of the funding source

The sponsor of this study had no role in the decisions about the study design, collection, analysis or interpretation of the results, the writing of the report or in the decision to submit the paper for publication.

Results

We identified 19 cohort studies (22 publications) (6;10;11;13-15;18;22-27;32-37;47;55;56) that were included in the analysis of the highest vs. the lowest fruit and/or vegetable intake and colorectal cancer incidence and 15 of these studies (18 publications) (10;11;13-15;18;22-24;26;27;32;33;35-37;55;56) were included in the

dose-response analysis (Table 1, Figure1). Five of the studies were from Europe, ten from America and four from Asia.

Total fruit and vegetables

High vs. low analysis

Eleven cohort studies (ten publications) (13;14;23;24;26;27;32;33;36;37) investigated the association between total fruit and vegetable intakes and colorectal cancer incidence and included 11853 cases among 1523860 participants. For colorectal cancer, the summary RR for all studies was 0.92 (95% CI: 0.85-0.99), with little evidence of heterogeneity, I^2=22% and $p_{heterogeneity}$=0.24 (Figure 2a). However, when stratified by cancer site the inverse association was limited to colon cancer and there was no association with rectal cancer (Table 2, Figure 2a).(13;14;18;24;26;32;33;36;37;55;56)(10;13;14;24;26;32;33;36;37)

Dose-response analysis

Eleven cohort studies (ten publications) (13;14;23;24;26;27;32;33;36;37) were included in the dose-response analysis of total fruit and vegetable intakes and colorectal cancer incidence. The summary RR per 100 grams per day (g/d) was 0.99 (95% CI: 0.98-1.00), with little evidence of heterogeneity, I^2=38% and $p_{heterogeneity}$=0.10 (Figure 2b). The summary RR was 0.99 (95% CI: 0.97-1.00, n=11) for colon cancer (13;14;18;24;26;32;33;36;37;55;56), with little evidence of heterogeneity, I^2=25% and $p_{heterogeneity}$=0.21 and 0.99 (95% CI: 0.97-1.01, n=10) for rectal cancer (10;13;14;24;26;32;33;36;37) with little evidence of heterogeneity, I^2=0% and $p_{heterogeneity}$=0.63 (Table 2, Figure 2b). The summary RR for colorectal

cancer ranged from 0.99 (95% CI: 0.98-0.99) when the Shanghai Women's Health Study (37) was excluded to 0.99 (95% CI: 0.98-1.01) when the EPIC-study (36) was excluded. There was no indication of publication bias with Egger's test, p=0.52, p=0.15 and p=0.80 for colorectal, colon and rectal cancer, respectively. Because of differences in the intake in the reference category among the studies we could not fit an interpretable non-linear model of fruit and vegetables and colorectal cancer.

Fruits

High vs. low analysis

Fourteen cohort studies (6;11;13;15;22-27;33-36) were included in the analysis of high versus low fruit intake and colorectal cancer incidence and included a total of 14876 cases among 1558147 participants. The summary RR was 0.90 (95% CI: 0.83-0.98), with moderate heterogeneity, I^2=42%, $p_{heterogeneity}$=0.05 (Figure 3a). However, when stratified by cancer site the inverse association was again limited to colon cancer and the association with rectal cancer was not significant (Table 2, Figure 3a).(13;18;24-26;32;33;36;47;55;56)(13;24-26;32;33;36)

Dose-response analysis

Thirteen cohort studies (12 publications) (11;13-15;22-24;26;27;33;35;36) were included in the dose-response analysis. The summary RR per 100 g/d was 0.98 (95% CI: 0.94-1.01), with moderate heterogeneity, I^2=64%, $p_{heterogeneity}$=0.001 (Figure 3b). In meta-regression analyses none of the study characteristics investigated were found to be significant predictors of the heterogeneity (e.g. geographic location, number of cases, sample size, duration of follow-up, adjustment for confounders). A suggestion of a weaker effect in studies with adjustment for

physical activity and BMI was found, but was not statistically significant (p=0.07 for both, results not shown). The summary RR was 0.98 (95% CI: 0.96-1.01, n=11) for colon cancer (13;14;18;24;26;32;33;36;55;56) (I^2=38%, $p_{heterogeneity}$=0.10) and 0.99 (95% CI: 0.95-1.03, n=8) for rectal cancer (13;14;24;26;32;33;36) (I^2=54%, $p_{heterogeneity}$=0.04), respectively (Table 2, Figure 3b). In a sensitivity analysis the summary RR for colorectal cancer ranged from 0.96 (95% CI: 0.94-0.99) when excluding the Health Professionals Follow-up Study (14) to 0.98 (95% CI: 0.95-1.01) when excluding the Swedish Mammography Study (26). There was no indication of publication bias with Egger's test, p=0.79, p=0.79 and p=0.46 for colorectal, colon and rectal cancer, respectively. There was evidence of a non-linear association between fruit intake and colorectal cancer risk, p for non-linearity <0.001, with the greatest reduction in risk when increasing intake from very low levels. Higher intakes was associated with a more modest decrease in the risk (Figure 5a).

Vegetables

High vs. low analysis

Sixteen cohort studies (15 publications) (6;11;13-15;22-27;33-36) were included in the analysis of high versus low vegetable intake and colorectal cancer and included 16057 cases among 1694236 participants. The summary RR was 0.91 (95% CI: 0.86-0.96) and there was no indication of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.54 (Figure 4a). As observed for fruit and vegetables combined and fruit, the inverse association with vegetable intake was limited to colon cancer (Table 2, Figure 4a).(13;14;18;24-26;32;33;36;55;56)(13;14;24-26;32;33;36)

Dose-response analysis

Twelve cohort studies (11;13-15;23;24;26;27;33;35;36) were included in the dose-response analysis. The summary RR per 100 g/d was 0.98 (95% CI: 0.97-0.99), with no indication of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.69 (Figure 4b). The summary RR was 0.96 (95% CI: 0.94-0.98, n=11) for colon cancer (13;14;18;24;26;32;33;36;55;56) (I^2=0%, $p_{heterogeneity}$=0.65) and 1.00 (95% CI: 0.96-1.03, n=8) for rectal cancer (13;14;24;26;32;33;36) (I^2=0%, $p_{heterogeneity}$=0.88, Table 2, Figure 4b). The summary RR for colorectal cancer ranged from 0.98 (95% CI: 0.96-0.99) when excluding the Iowa Women's Health Study (27) to 0.99 (95% CI: 0.97-1.01) when excluding the NIH-AARP Diet and Health study (35). There was no indication of publication bias with Egger's test, p=0.14, p=0.43 and p=0.67 for colorectal, colon and rectal cancer, respectively. There was evidence for a non-linear association between vegetable intake and colorectal cancer risk, p for non-linearity = 0.001, with the greatest reduction for an intake up to 200 grams per day, but little evidence of a further reduction with higher intakes (Figure 5b).

Subgroup and sensitivity analyses

In stratified analyses, the association between high versus low fruit and vegetable intake and colorectal cancer was inverse in all strata, although not always statistically significant, but when stratified by gender the results were statistically significant among men, but not in women. For fruits and vegetables separately all strata showed inverse associations, but the results were significant among women and not in men (Table 2). In meta-regression analyses only geographic location was found to modify the association between high versus low fruit and vegetable intake and colorectal cancer, with a significant inverse association among European studies, but not among American or Asian studies. Similar results were found for

total fruit but the test for heterogeneity was not significant, p=0.31. For vegetables studies with ≥1500 cases showed some tendency of a stronger inverse association than studies with <500 cases, p for heterogeneity=0.09 (Table 2).

Further, to assess whether the studies excluded from the dose-response analysis might have biased the dose-response results we repeated the high versus low analyses restricted to the studies included in the dose-response analyses. The summary RRs for fruit and for vegetables and colorectal cancer risk were 0.89 (95% CI: 0.81-0.98) and 0.90 (95% CI: 0.85-0.95), respectively, almost identical to the results including all studies.

It has been hypothesized that only very low intakes of fruit and vegetables increases risk. Therefore we conducted additional analyses among the four studies that reported results for very low vs. moderate to high intake by dividing the lowest intake category into several subcategories (very low intakes were generally <2 servings/day for fruit and vegetables, <0.5 serving/day for fruits and <1 serving/day for vegetables) and merging the intakes in e.g. quintile 2-5 which was then used as a reference category. The summary RR was 1.32 (95% CI: 1.13-1.54, I^2=69%, $p_{heterogeneity}$=0.07) for the two studies that reported very low vs. moderate to high intakes of fruit and vegetables (26;32), 1.14 (95% C: 0.83-1.58, I^2=72%, $p_{heterogeneity}$=0.01) for the four studies of very low vs. moderate to high fruit intake (14;18;32) and 1.18 (95% CI: 1.02-1.37, I^2=0%, $p_{heterogeneity}$=0.47) for the four studies of very low vs. moderate to high vegetable intake (14;18;32).

Discussion

In this meta-analysis intakes of fruit, vegetables and fruit and vegetables combined was associated with a small, but statistically significant reduction in the risk of colorectal cancer incidence in the high vs. low comparison. In the linear dose-response analysis a significant inverse association was observed only for vegetables, but there was some evidence of a non-linear association inverse association for fruits and vegetables with the greatest reduction in risk at the lower range of intake.

The hypothesis that fruit and vegetable intake protects against colorectal cancer has received much interest both among medical professionals and the general population. *In vitro*, experimental animal studies and human feeding studies have provided biologic plausibility for the hypothesis (2;3), but epidemiological studies have been inconsistent. Although the first report from the WCRF/AICR concluded that there was convincing evidence that intakes of vegetables, but not fruit, protects against colorectal cancer, most of that evidence was based on case-control studies (4). These results has generally not been supported by the results from subsequent cohort studies (6;11;13;14;18;23-25), several reviews and meta-analyses (28-31). Case-control studies may have been affected by recall and selection biases, In the 2nd report "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective" from the WCRF/AICR published in 2007 it was stated that there was limited suggestive evidence that fruit and non-starchy vegetables protect against colorectal cancer, thus a downgrading of the evidence since the 1st report (5). Our linear dose-response analyses are consistent with the results from the WCRF/AICR report, with the exception of vegetables, for which some recent large cohort studies (33-36) may have contributed to the statistically significant inverse association we found (33-36). However, when non-

linear dose-response models were used for the analyses we found evidence for a non-linear association and the greatest benefit was seen when increasing intakes from low levels. The lack of significance of the result in the linear dose-response model is likely because the linear model doesn't fit with the data, thus examining the shape of the dose-response curve might be important to clarify associations between diet and cancer risk.

The possible limitations of our meta-analysis must be taken into consideration. It is possible that the observed inverse association between fruit and vegetable intake and colorectal cancer risk could be due to unmeasured or residual confounding. Higher intake of fruit and vegetables is oftentimes associated with other healthy behaviours including higher levels of physical activity, lower prevalence of smoking and overweight/obesity and lower intakes of alcohol and red and processed meat. However, most of the studies included in this meta-analysis adjusted for known confounding factors such as age, BMI, smoking, alcohol, red and processed meat and energy intake. Also, the results were generally similar in the subgroup analyses when we stratified the studies according to whether they adjusted for confounding factors, although in some of these subgroups there were few studies which resulted in wider confidence intervals. Meta-regression analyses did not show significant heterogeneity in the results between studies that adjusted or did not adjust for these confounding factors. Nevertheless, because we found an association between very low levels of fruit and vegetables and increased colorectal cancer risk and because those with a very low intake of fruit and vegetables may have very different lifestyles compared with the general population we cannot exclude the possibility of residual confounding. We did not find strong evidence of heterogeneity when studies were stratified by duration of follow-up, gender, subsite within colon or

by number of cases. There was some evidence that geographic location modified the association between fruit and vegetables combined and colorectal cancer risk, with the strongest inverse association among European studies and no significant association among American and Asian studies and similar results were found for fruit, while for vegetables a significant association was found among American studies, although the test for interaction was not significant for fruit and vegetables separately. Although we cannot exclude the possibility that either chance or genetic factors could explain this finding it is possible that these results could be due to differences in the absolute intakes or differences in the intakes in the referent category. Because we found evidence of a non-linear association between fruit and vegetables and colorectal cancer risk with the strongest reduction at low levels of intake it is possible that some studies may have missed an effect because the intake in the referent category already may have been sufficient to reduce risk. For example the mean intake of fruits and vegetables in the reference category was 155, 200 and 217 g/d for the European, American and Asian studies, respectively. For fruits and vegetables separately the respective figures were 37, 51 and 48 g/d and 58, 103 and 123 g/d, respectively. Another possibility is that the studies differ by the types of fruits and vegetables consumed, which also may vary geographically, but further cohort studies of specific types of fruits and vegetables and colorectal cancer risk are needed.

Measurement errors in the assessment of dietary intake are known to bias effect estimates, however, since we included only prospective cohort studies in this meta-analysis the measurement errors would most likely be non-differential and would result in bias toward the null. Thus, we cannot exclude the possibility that measurement errors might have resulted in attenuated associations and that such

attenuation may partly explain why the associations we observed are weak. Dietary changes after baseline may also attenuate associations between dietary intake and cancer risk, however, only two of the included studies used repeated assessments of diet and the results were not materially different when using only the baseline questionnaire for the analyses (14). Almost all the studies included in our meta-analysis used validated food-frequency questionnaires, but only one of the studies corrected the results for measurement error (36). The results did not differ substantially before and after measurement error correction (RR=0.98, 95% CI: 0.97-1.00 vs. 0.97, 95% CI: 0.93-1.01 per 100 grams per day of fruit and vegetable intake, respectively), but the increment for which the observed and calibrated results were presented was also small. Any further studies might benefit from incorporating biomarkers of fruit and vegetable intakes in the analyses (57).

Misclassification of the exposure may also be present because fruit and vegetable intakes have been modeled in different ways in various studies using tertiles, quartiles, quintiles or absolute cut-off points to categorize intakes depending on the study size and the variation in intakes. Analyses of high versus low intakes are therefore limited by the fact that true differences in the level and range of intake between studies are not taken into account in the analyses and this may contribute to heterogeneity in the results. Thus, to take into account real differences in intake between studies we also conducted linear and non-linear dose-response analyses, with the results from the non-linear dose-response being most consistent with the high versus low analysis. Misclassification of intakes may, however, also occur because of differences between studies in the detail of the assessment of fruit and vegetable intakes because of questionnaire differences. Also, the data required for dose-response analyses are not always presented in the articles, thus some studies

are usually excluded from these analyses and this could potentially influence the dose-response results (58). However, when we repeated the high versus low analyses with the same studies that were included in the dose-response analysis the results were similar to the original analyses, thus the few studies excluded from the dose-response analyses are not likely to have altered the dose-response results materially.

Although we found no statistical evidence of publication bias in this analysis, some degree of publication bias may still exist since there are several ongoing cohort studies which have not yet published their results on fruit and vegetable intake and colorectal cancer risk.

Several potential mechanisms may explain an inverse association between fruit and vegetables and colorectal cancer risk. Fruit and vegetables are good sources of fiber which may prevent colorectal cancer by increasing stool bulk, decreasing transit time in the colon and dilute potential carcinogens (5). We found an inverse association between fruit and vegetable intake and colon cancer, but little evidence of an inverse association with rectal cancer. Apart from the possibility that fewer studies conducted analyses of rectal cancer which may have limited our statistical power to detect an association, is the possibility of a real difference in the effects of fruit and vegetables on risk of colon and rectal cancer. Such a difference has also been observed for physical activity, with an established inverse association for colon cancer, but currently little evidence for an association with rectal cancer (5;59). Both physical activity and high fiber intake may decrease the transit time in the colon without altering the storage time in the rectum and may account for the differences in the results for the two sites, but we cannot exclude the possibility that other mechanisms may explain these observations. Fruit and vegetables are also good sources of

folate, which has been associated with decreased risk of colorectal cancer in a number of studies, but not all studies (5). Folate plays an important role in DNA methylation and is necessary for synthesis of thymine. Folate deficiency can lead to misincorporation of uracil instead of thymine into DNA (60) and increase the number of chromosomal breaks (61). In addition, fruit and vegetables are good sources of various antioxidants, vitamins, minerals and other bioactive compounds, including flavonoids, carotenoids, glucosinolates, indoles, isothiocyanates and selenium which may prevent cancer by inducing the activity of detoxifying enzymes, reducing oxidative stress and inflammation (2). High intake of fruit and vegetables may also decrease the risk of overweight/obesity (62-66) which is an established risk factor for colorectal cancer, but to our knowledge no study has assessed whether overweight/obesity might be a mediating factor.

Our meta-analysis also has several strengths. Because we based our analyses on prospective studies we have minimised the possibility that our findings may be due to 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 1.5-1.7 million participants and 11800-16000 cases. Thus, we had statistical power to detect moderate and weak associations. It is likely that the weak inverse associations found in this meta-analysis are too weak to be detected in most individual cohort studies and only possible to detect in meta-analyses or pooled analyses of numerous large cohort studies. Our results are comparable with the results of a pooled analysis of 14 cohort studies which found a 6-13% reduction in colon cancer risk for high versus low intake of fruit and vegetables (30). Also consistent with that analysis is our finding that there seems to be a relatively low threshold level above which there is little further benefit of

increasing fruit and vegetable intake in terms of colorectal cancer risk. Thus, from a public health perspective targeting persons with a very low fruit and vegetable intake may be most effective for colorectal cancer prevention even though the overall impact on colorectal cancer risk may be moderate or limited because of the small size of the association. However, public health recommendations for a high fruit and vegetable intake are justified because of the greater reductions in risk of coronary heart disease (67), stroke (68) and other cancers (69) associated with higher levels of fruit and vegetable intake.

In conclusion, our results suggest that there is a weak and non-linear inverse association between intake of fruit and vegetables and colorectal cancer risk, with the greatest reduction in risk when increasing intake from very low levels. Further prospective studies, preferably incorporating biomarkers of fruit and vegetable intake, are needed to assess whether there is an increased risk in very low consumers of fruit and vegetables and for an assessment of the impact of measurement errors on the results. In addition, studies among non-Caucasian populations are needed to clarify whether the apparent differences in results by geographical regions is explained by specific types or amounts of fruits and vegetables.

Contributors

The systematic literature review team at Wageningen University conducted the search, dataselection and dataextraction up to June 2006. 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. 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.

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Table 1: Prospective cohort studies of fruits, vegetable intake and colorectal cancer incidence

Author, publication year, country/ region	Study name	Follow-up period	Study size, gender, age, number of cases	Dietary assessment	Exposure	Quantity	RR (95% CI)	Adjustment for confounders
Lee et al., 2009, China	Shanghai Women's Health Study	1997-2000 – 2007, 7.4 years follow-up	73224 women, age 40-70 years: 394 CRC cases 236 CC cases 158 RC cases	Validated FFQ, 77 food items	Fruit, vegetables, CRC Fruit, vegetables, CC Fruit, vegetables, RC	≥663 vs. <325 g/d ≥663 vs. <325 g/d ≥663 vs. <325 g/d	1.2 (0.9-1.6) 1.3 (0.8-1.9) 1.0 (0.6-1.7)	Age
Van Duijnhoven et al., 2009, Europe	European Prospective Investigation into Cancer and Nutrition	1992-2000 – 2006, 8.8 years follow-up	452755 men and women, age 35-70 years: 2819 CRC cases 1828 CC cases 783 PCC cases 790 DCC cases 255 overlapping, unspecified	Validated FFQ, diet history and/or 14-day record	Fruit, vegetables, CRC Fruit, vegetables, CC Fruit, vegetables, RC Vegetables, CRC Vegetables, CC Vegetables, RC	>603.6 vs. <221.1 g/d Per 100 g/d, observed >603.6 vs. <221.1 g/d Per 100 g/d, observed >603.6 vs. <221.1 g/d Per 100 g/d, observed >284.47 vs. <95.1 g/d Per 100 g/d, observed >284.47 vs. <95.1 g/d Per 100 g/d, observed >284.47 vs. <95.1 g/d Per 100 g/d, observed	0.86 (0.75-1.00) 0.98 (0.97-1.00) 0.76 (0.63-0.91) 0.97 (0.95-1.00) 1.09 (0.85-1.40) 1.00 (0.97-1.04) 0.92 (0.79-1.06) 0.99 (0.95-1.03) 0.85 (0.71-1.02) 0.97 (0.93-1.02) 1.04 (0.81-1.33) 1.02 (0.96-1.09)	Age, sex, center, energy from fat, energy from nonfat, weight, height, physical activity, smoking status, alcohol consumption, red and processed meat consumption, fish consumption, dietary fiber from cereal sources

			CC cases 991 RC cases		Fruits, CRC Fruits, CC Fruits, RC	>342.7 vs. <92.8 g/d Per 100 g/d, observed >342.7 vs. <92.8 g/d Per 100 g/d, observed >342.7 vs. <92.8 g/d Per 100 g/d, observed	0.88 (0.76-1.01) 0.98 (0.96-1.01) 0.84 (0.71-1.00) 0.97 (0.94-1.01) 0.96 (0.76-1.21) 0.99 (0.95-1.04)	
George et al, 2009, USA	NIH-AARP Diet and Health Study	1995-96 – 2003, 8 years	288109 men: 3421 CRC cases 195229 women: 1618 CRC cases Age 50-71 yrs	Validated FFQ, 124 food items	Fruit, w Vegetables Fruit, m Vegetables	1.90-5.58 vs. 0-0.60 cup equivalents/1000 kcal/d 1.43-4.38 vs. 0-0.56 cup equivalents/1000 kcal/d 1.59-5.13 vs. 0-0.44 cup equivalents/1000 kcal/d 1.10-3.25 vs. 0.06-0.44 cup equivalents/1000 kcal/d	0.93 (0.79-1.09) 0.87 (0.74-1.02) 0.94 (0.84-1.05) 0.84 (0.75-0.93)	Age, smoking, energy intake, BMI, alcohol, physical activity, education, race, marital status, FH – cancer, menopausal HT, mutual adjustment between fruit and vegetables
Nomura et al, 2008, USA	Multiethnic Cohort Study	1993-96 – 2001, 7.3 yrs of follow-up	85903 men and 105108 women, age 40-75 years: 1138/972 CRC cases (m/w) 734/617 CC cases 276/179 RC cases	Validated FFQ, 180 food items	Fruit, vegetables, m Vegetables Fruit Fruit, vegetables, w Vegetables Fruit	483.2 vs. 134.7 g/1000 kcal/d 236.2 vs. 71.9 g/1000 kcal/d 295.9 vs. 30.1 g/1000 kcal/d 608.1 vs. 176.3 g/1000 kcal/d 286.5 vs. 85.5 g/1000 kcal/d 381.5 vs. 47.3 g/1000 kcal/d	0.74 (0.59-0.93) 0.85 (0.69-1.05) 0.80 (0.64-0.99) 1.04 (0.81-1.33) 0.94 (0.75-1.17) 0.83 (0.65-1.06)	Age, ethnicity, time since cohort entry, FH – CRC, CR polyp, pack-years of cigarette smoking, BMI, vigorous activity, aspirin use, multivitamin use, HRT, log energy intake, alcohol, red meat, folate, vitamin D, calcium

Butler et al, 2008, Singapore	Singapore Chinese Health Study	1993-98 – 2005, 9.8 years follow-up	61321 men and women, age 45-74 years: 961 CRC cases	Validated FFQ, 165 food items	Vegetables Fruits	Quartile 4 vs. 1 Quartile 4 vs. 1	0.98 (0.79-1.21) 0.89 (0.72-1.09)	Age, sex, dialect group, interview year, diabetes at baseline, smoking history, BMI, alcohol, education, physical activity, 1st degree relative with CRC, total daily energy intake
Park et al. 2007, USA	NIH-AARP Diet and Health Study	1995-96 – 2000, 4.3 years follow-up, 2121664 person-years	488043 men and women: 2972 CRC cases Age 50-71 years	Validated FFQ, 124 food items	Fruit, vegetables, m Fruit, vegetables, w	5.2 vs. 1.4 serv./1000 kcal/d 6.5 vs. 1.8 serv./1000 kcal/d	0.91 (0.76-1.05) 1.08 (0.86-1.35)	Age, education, physical activity, smoking, alcohol consumption, red meat, dietary calcium, total energy
McCarl et al., 2006, USA	Iowa Women's Health Study	1986-2000, 15 years follow-up	35197 women, age 55-69 years: 954 CRC cases	Validated FFQ, 127 food items	Fruit, vegetables Fruits Vegetables	≥58.01 vs. ≤27.4 serv./wk ≥25.5 vs. ≤9.8 serv./wk ≥34.5 vs. ≤14.5 serv./wk	0.90 (0.73-1.10) 0.79 (0.65-0.97) 0.89 (0.73-1.08)	Age
Tsubono et al, 2005, Japan	Japan Public Health Center-based Cohort study 1 & 2	Cohort 1/2: 1990-1999/ 1993-1999, total 694074 person-years follow-up	88658 men and women, age 40-59 and age 40-69 years: 705 CRC cases	Cohort 1/2: validated FFQ 44/52 items	Fruit, CRC, all Vegetables Fruit, CC Vegetables Fruit, RC Vegetables	Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1	0.92 (0.70-1.19) 1.00 (0.79-1.27) 0.92 (0.66–1.28) 1.08 (0.80–1.45) 0.91 (0.59–1.40) 0.87 (0.58–1.31)	Age, sex, Public Health Centre area, BMI, frequency of sports, smoking, alcohol, vitamin supplement use, quartiles of energy, cereals, meats and fish

					Fruit, CRC, m Vegetables Fruit, CC Vegetables Fruit, RC Vegetables Fruit, CRC, w Vegetables Fruit, CC Vegetables Fruit, RC Vegetables	Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1 Quartile 4 vs. 1	1.06 (0.70–1.61) 1.18 (0.88–1.59) 1.02 (0.61–1.70) 1.24 (0.86–1.79) 1.19 (0.59–2.36) 1.06 (0.63–1.78) 0.93 (0.61–1.42) 0.88 (0.57–1.35) 0.87 (0.49–1.52) 1.01 (0.58–1.76) 0.84 (0.43–1.65) 0.71 (0.36–1.38)	
Lin et al, 2005, USA	Women's Health Study	1993-2003, 10 years follow up	36976 women, age ≥45 years: 223 CRC cases	Validated FFQ, 131 food items	Fruit, vegetables Fruit Vegetables	10.0 vs. 2.6 serv./d (median) 3.8 vs. 0.6 6.8 vs. 1.5	0.96 (0.58-1.62) 0.79 (0.48-1.30) 0.89 (0.56-1.41)	Age, randomized treatment assignment, BMI, FH – CRC in a 1st degree relative, history of colon polyps, physical activity, smoking status, baseline aspirin use, red meat intake, alcohol, total energy intake, menopausal status, postmenopausal HRT use
Sato et al., 2005, Japan	Miyagi Cohort Study	1990-1997, 7 years follow up	47605 men and women, age 40-64 years:	Validated FFQ, 40 items	Fruit, vegetables, CC Vegetables Fruit	≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d	1.13 (0.73–1.75) 1.24 (0.79–1.95) 1.45 (0.85–2.47)	Age, sex, smoking status, alcohol, BMI, education, FH – cancer, walking time, meat consumption,

			165 CC cases 110 RC cases		Fruit, vegetables, CC, men Vegetables Fruit Fruit, vegetables, CC, women Vegetables Fruit Fruit, vegetables, RC Vegetables Fruit Fruit, vegetables, RC, men Vegetables Fruit Fruit, vegetables, RC, women Vegetables Fruit	≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d ≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d ≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d ≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d ≥698 vs. ≤543 g/d ≥313 vs. ≤245 g/d ≥242 vs. ≤95 g/d	0.92 (0.54-1.59) 1.00 (0.56-1.77) 1.75 (0.89-3.44) 1.55 (0.72-3.32) 1.65 (0.78-3.49) 0.99 (0.23-4.25) 1.12 (0.67–1.89) 1.14 (0.67–1.93) 1.41 (0.73–2.73) 1.10 (0.55-2.17) 1.32 (0.67-2.60) 0.28 (0.04-2.09) 1.26 (0.56-2.86) 0.99 (0.42-2.32) 1.53 (0.68-3.45) no cases in ref. categ.	energy
Sanjoaquin et al, 2004, England	Oxford Vegetarian Study	1980-1984 – 1999, 17 years follow-up	10998 men and women, age 16-89 years: 95 CRC cases	FFQ (validated for fibre intake)	Fresh or dried fruit Vegetables	≥10 vs. <5/wk Tertile 3 vs. 1	0.60 (0.35-1.02) 0.86 (0.54-1.38)	Age, sex, alcohol, smoking
McCullough et al., 2003, USA	Cancer Prevention Study 2	1992-1993 – 1997, 4.5 years	62609 men and 70554 women, age	Validated FFQ, 68 food	Fruit, m Vegetables	≥6.2 vs. 1.2 serv./d ≥3.3 vs. 1.3 serv./d	1.11 (0.76-1.62) 0.69 (0.47-1.03)	Age, exercise METs, aspirin, smoking, FH – CRC, BMI, education,

	Nutrition Cohort	follow-up	50-74 years: 298/210 CC cases (m/w)	items	Fruit, vegetables Fruit, w Vegetables Fruit, vegetables	H vs l 5 ≥6.0 vs. 1.2 serv./d ≥3.3 vs. 1.3 serv./d H vs l 5	1.23 (0.83-1.83) 0.74 (0.47-1.16) 0.91 (0.56-1.48) 0.70 (0.43-1.15)	energy, multivitamin use, total calcium, red meat intake and HRT use (women)
Flood et al, 2002, USA	Breast Cancer Detection & Demonstration Project	1987-1989 – 1998, 8.7 years follow-up, 386142 person-years	45490 women, median age 61.8 years: 485 CRC cases	Validated FFQ, 62 items	Fruits Vegetables	0.50 vs. 0.05 serv./1000 kJ/d 0.98 vs. 0.25 serv./1000 kJ/d	1.15 (0.86-1.53) 0.95 (0.71-1.26)	Age, multivitamin use, BMI, height, NSAIDS, smoking status, education level, physical activity, grains, red meat, calcium, vitamin D, alcohol, nutrient density (total calories), mutual adjustment between fruits and vegetables
Terry et al, 2001, Sweden	Swedish Mammography Screening Cohort Study	1987-1990 / 1998, 9.6 years follow-up	61463:460 CRC women 291 CC cases 159 RC cases 10 combined	Validated FFQ, 67 items	Fruit, vegetables, CRC Vegetables Fruits Fruit, vegetables, CC Vegetables Fruits Fruit, vegetables, PCC Vegetables Fruits Fruit, vegetables, DCC Vegetables Fruits	>5.0 vs. <2.5 serv./d >2.0 vs. <1.0 serv./d >2.0 vs. <1.0 serv./d >5.0 vs. <2.5 serv./d >2.0 vs. <1.0 serv./d >2.0 vs. <1.0 serv./d >5.0 vs. <2.5 serv./d >2.0 vs. <1.0 serv./d >2.0 vs. <1.0 serv./d >5.0 vs. <2.5 serv./d >2.0 vs. <1.0 serv./d >2.0 vs. <1.0 serv./d	0.73 (0.56-0.96) 0.84 (0.65-1.09) 0.68 (0.52-0.89) 0.81 (0.59-1.13) 0.90 (0.66-1.24) 0.76 (0.55-1.06) 0.91 (0.55-1.51) 0.72 (0.44-1.20) 0.97 (0.57-1.64) 0.87 (0.49-1.54) 1.13 (0.66-1.94) 0.91 (0.53-1.55)	Age, red meat, dairy products, total calories

					Fruit, vegetables, RC Vegetables Fruits	>5.0 vs. <2.5 serv./d >2.0 vs. <1.0 serv./d >2.0 vs. <1.0 serv./d	0.60 (0.38-0.96) 0.71 (0.45-1.12) 0.54 (0.33-0.89)	
Michels et al, 2000, USA	Health Professionals Follow-up Study & Nurses' Health Study	NHS: 1980-1996, 1327029 person-years HPFS: 1986-1996, 416616 person-years Total: 1743645 person-years	88764 women: 569 CC cases 155 RC cases 47325 men: 368 CC cases 244 RC cases Total: 937 CC cases 244 RC cases	Validated FFQ, 61-87 food items	Fruit, vegetables, all, CC Fruit, vegetables, HPFS Fruit, vegetables, NHS Fruit, all Fruit, HPFS Fruit, NHS Vegetables, all Vegetables, HPFS Vegetables, NHS Fruit, vegetables, all, RC 	≥6 vs. ≤2 serv./d 1 serv./d increase ≥6 vs. ≤2 serv./d 1 serv./d increase ≥6 vs. ≤2 serv./d 1 serv./d increase ≥5 vs. ≤1 serv./d 1 serv./d increase ≥5 vs. ≤1 serv./d 1 serv./d increase ≥5 vs. ≤1 serv./d 1 serv./d increase ≥5 vs. ≤1 serv./d 1 serv./d increase ≥5 vs. ≤1 serv./d 1 serv./d increase ≥6 vs. ≤2 serv./d 1 serv./d increase	1.08 (0.84-1.38) 1.02 (0.98-1.05) 1.28 1.05 (0.99-1.11) 0.96 1.00 (0.96-1.04) NE NE 1.35 1.08 (1.00-1.16) 0.80 0.96 (0.89-1.03) 1.00 (0.72-1.38) 1.03 (0.97-1.09) 1.24 1.01 (0.90-1.14) 0.96 1.03 (0.97-1.10) 0.99 (0.62-1.56) 1.02 (0.95-1.09)	Women (NHS): Age, FH – CRC, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol, physical activity, menopausal status, postmenopausal HRT use, aspirin, vitamin supplement use, total calories, red meat Men (HPFS): Age, FH – CRC, sigmoidoscopy, height, BMI, pack-years of smoking, alcohol, physical activity, aspirin, vitamin supplement use, total calories, red meat

					Fruit, vegetables, HPFS	≥6 vs. ≤2 serv./d	1.20	
						1 serv./d increase	1.06 (0.95-1.18)	
					Fruit, vegetables, NHS	≥6 vs. ≤2 serv./d	0.88	
						1 serv./d increase	1.00 (0.92-1.09)	
					Fruit, all	≥5 vs. ≤1 serv./d	NE	
						1 serv./d increase	1.02 (0.92-1.13)	
					Fruit, HPFS	≥5 vs. ≤1 serv./d	2.04	
						1 serv./d increase	1.09 (0.94-1.26)	
					Fruit, NHS	≥5 vs. ≤1 serv./d	0.66	
						1 serv./d increase	0.96 (0.83-1.11)	
					Vegetables, all	≥5 vs. ≤1 serv./d	0.97 (0.58-1.64)	
						1 serv./d increase	1.05 (0.89-1.23)	
					Vegetables, HPFS	≥5 vs. ≤1 serv./d	1.50	
						1 serv./d increase	1.12 (0.89-1.40)	
					Vegetables, NHS	≥5 vs. ≤1 serv./d	0.72	
						1 serv./d increase	0.98 (0.78-1.23)	
Voorrips et al, 2000, Netherlands	Netherlands Cohort Study	1986-1992, 6.3 years follow-up	Total fruit & vegetables, vegetables: 62753 women, age 55-69 years subcohort	Validated FFQ, 150 food items	Fruit, vegetables, CC, m	519 vs. 177 g/d (median)	0.95 (0.64-1.41)	Age, FH – CRC, alcohol intake
					Vegetables	285 vs. 100 g/d	0.85 (0.57-1.27)	
					Fruits	286 vs. 34 g/d	1.33 (0.90-1.97)	
					Fruit, vegetables, CC, w	578 vs. 208 g/d	0.66 (0.44-1.01)	
					Vegetables	293 vs. 107 g/d	0.83 (0.54-1.26)	
					Fruits	343 vs. 65 g/d	0.73 (0.48-1.11)	
					Fruit, vegetables, RC, m	519 vs. 177 g/d	0.88 (0.56-1.37)	

			1497: 465 CRC 266 CC 199 RC 58279 men, age 55-69 years: Subcohort: 1456: 427 CRC 312 CC 115 RC Total fruits: Subcohort 1525 m: 332 CC 217 RC 1497 w: 288 CC 127 RC		Vegetables Fruits Fruit, vegetables, RC, w Vegetables Fruits Fruit, vegetables, PCC, m Vegetables Fruits Fruit, vegetables, DCC, m Vegetables Fruits Fruit, vegetables, PCC, w Vegetables Fruits Fruit, vegetables, DCC, w Vegetables Fruits	285 vs. 100 g/d 286 vs. 34 g/d 578 vs. 208 g/d 293 vs. 107 g/d 343 vs. 65 g/d 519 vs. 177 g/d 285 vs. 100 g/d 286 vs. 34 g/d 519 vs. 177 g/d 285 vs. 100 g/d 286 vs. 34 g/d 578 vs. 208 g/d 293 vs. 107 g/d 343 vs. 65 g/d 578 vs. 208 g/d 293 vs. 107 g/d 343 vs. 65 g/d	0.88 (0.55-1.41) 0.85 (0.55-1.32) 1.17 (0.63-2.17) 1.78 (0.94-3.38) 0.67 (0.34-1.33) 0.89 (0.51-1.56) 1.03 (0.59-1.81) 1.20 (0.71-2.05) 1.04 (0.62-1.75) 0.76 (0.27-1.30) 1.49 (0.88-2.54) 0.89 (0.52-1.51) 0.99 (0.57-1.72) 0.81 (0.47-1.39) 0.44 (0.32-0.82) 0.64 (0.36-1.17) 0.59 (0.30-1.13)	
Pietinen, 1999, Finland	ATBC Cancer Prevention Study	1987-1995, 8 years follow-up	27111 male smokers, age 55-69 years: 185 CRC cases	Validated FFQ, 276 food items	Vegetables Fruit	191 vs. 44 g/d (median) 216 vs. 30 g/d	1.2 (0.8-1.9) 1.1 (0.8-1.7)	Age, supplement group, tobacco years, BMI, alcohol, education, physical activity at work, calcium, energy

Zheng et al, 1998, USA	Iowa Women's Health Study	1986-1994, 9 years follow-up	34702 women, age 55-69 years: 144 RC cases	Validated FFQ, 127 food items	Fruit, vegetables	≥48.6 vs. <33.5 serv./wk	0.97 (0.62-1.51)	Age
Kato, 1997, USA	New York University Women's Cohort Study	1985-1991 – 1994, 7.1 years follow-up, 105044 person-years	14727 women, age 34-65 years: 100 CRC cases	FFQ, 70 food items	Fruits Vegetables	Quartile 4 vs. 1 Quartile 4 vs. 1	1.49 (0.82-2.70) 1.63 (0.92-2.89)	Age, total calories, place at enrollment, highest level of education
Steinmetz et al., 1994, USA	Iowa Women's Health Study	1986-1990, 5 years follow-up, 167447 person-years	35216 women, age 55-69 years: 212 CC cases	Validated FFQ, 127 food items	Fruit, vegetables Vegetables Fruit Fruit, vegetables, PCC Vegetables Fruit Fruit, vegetables, DCC Vegetables Fruit	≥47.1 vs. <24.6 serv./wk ≥30.5 vs. <15.1 serv./wk ≥17.5 vs. <7.5 serv./wk ≥47.1 vs. <24.6 serv./wk ≥30.5 vs. <15.1 serv./wk ≥17.5 vs. <7.5 serv./wk ≥47.1 vs. <24.6 serv./wk ≥30.5 vs. <15.1 serv./wk ≥17.5 vs. <7.5 serv./wk	0.89 (0.57-1.40) 0.73 (0.47-1.13) 0.86 (0.58-1.29) 0.78 (0.37-1.66) 0.90 (0.44-1.82) 0.80 (0.40-1.59) 0.91 (0.50-1.64) 0.62 (0.35-1.09) 0.97 (0.58-1.61)	Age, smoking status, alcohol intake, total energy
Shibata et al., 1992, USA	Leisure World Cohort Study	**1981-1985 – 1989, 70159 person-years follow-up**	**11,580: 97/105 cases (m/w)** **Age 65-82 years (mean 74.9/73.8 years m/w)**	**FFQ, 59 food items**	**Fruit, vegetables, m** **Vegetables** **Fruit** **Fruit, vegetables, w**	9.66 vs. 4.14 serv./d (median) 5.70 vs. 2.16 serv./d 4.38 vs. 1.45 serv./d 10.06 vs. 4.54 serv./d 5.98 vs. 2.34 serv./d	**1.50 (0.91-2.46)** **1.39 (0.84-2.30)** **1.12 (0.69-1.81)** **0.63 (0.40-1.00)**	Age, smoking

					Vegetables **Fruit**	4.58 vs. 1.66 serv./d	**0.72 (0.45-1.16)** **0.50 (0.31-0.80)**	

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

Table 2: Subgroup analyses of fruit and vegetable intakes and colorectal cancer, high versus low intake

	Total fruit and vegetables					**Fruits**					**Vegetables**				
	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	11	0.92 (0.86-0.99)	21.9	0.24		14	0.90 (0.83-0.98)	41.6	0.05		15	0.91 (0.86-0.96)	0	0.53	
Duration of follow-up															
<10 yrs follow-up	7	0.91 (0.83-1.00)	38.5	0.14	0.52	11	0.93 (0.85-1.01)	43.9	0.06	0.16	11	0.92 (0.86-0.99)	17.1	0.28	0.97

≥10 yrs follow-up	4	0.97 (0.84-1.12)	0	0.57		3	0.77 (0.64-0.91)	0	0.64		4	0.92 (0.80-1.06)	0	0.85	
Sex															
Men	5	0.87 (0.79-0.97)	0	0.63	0.42	7	0.94 (0.87-1.02)	1.0	0.42	0.26	7	0.91 (0.83-1.01)	21.9	0.26	0.75
Women	9	0.94 (0.83-1.06)	38.1	0.11		11	0.87 (0.79-0.97)	32.3	0.14		11	0.91 (0.84-0.98)	0	0.64	
Men [3]	5	0.88 (0.80-0.97)	0	0.58	0.39	6	0.88 (0.80-0.98)	0	0.60	0.42	6	0.89 (0.82-0.98)	0	0.59	0.71
Women [4]	5	0.96 (0.82-1.13)	43.2	0.13		6	0.93 (0.85-1.02)	6.8	0.37		6	0.90 (0.83-0.99)	0	0.64	
Subsite															
Colon	12	0.91 (0.84-0.99)	12.9	0.32	0.41	11	0.89 (0.81-0.98)	32.9	0.14	0.72	11	0.87 (0.81-0.94)	0	0.70	0.26
Rectum	10	0.97 (0.86-1.09)	0	0.65		7	0.91 (0.76-1.09)	45.2	0.09		8	0.94 (0.85-1.04)	0	0.59	
Colon [5]	7	0.89 (0.79-0.99)	33.9	0.17	0.35	7	0.92 (0.82-1.04)	47.6	0.08	0.99	8	0.88 (0.81-0.95)	0	0.60	0.33
Rectum [6]	7	0.97 (0.85-1.10)	0	0.42		7	0.91 (0.76-1.09)	45.2	0.09		8	0.94 (0.85-1.04)	0	0.59	
Proximal colon	5	0.89 (0.77-1.02)	0	0.80	0.43	5	0.96 (0.84-1.09)	0	0.89	0.99	6	0.89 (0.78-1.01)	0	0.65	0.97
Distal colon	5	0.80 (0.68-0.94)	10	0.35		5	0.96 (0.85-1.09)	0	0.62		6	0.89 (0.79-1.01)	0	0.58	
Geographic location															
Europe	3	0.84 (0.75-	0	0.55	0.03	5	0.85 (0.73-0.99)	40.9	0.15	0.31	5	0.92 (0.83-1.02)	0	0.73	0.43

			0.93)													
America		6	0.94 (0.86-1.02)	0	0.64		6	0.91 (0.80-1.03)	48.6	0.08		7	0.89 (0.83-0.96)	7.2	0.37	
Asia		2	1.17 (0.94-1.45)	0	0.79		3	1.00 (0.79-1.28)	50.6	0.13		3	1.02 (0.89-1.18)	0	0.60	
Number of cases																
Cases <500		5	0.95 (0.78-1.15)	49.6	0.09	0.63	8	0.96 (0.78-1.18)	60.2	0.01	0.55	8	0.98 (0.87-1.10)	3.0	0.41	0.09
Cases 500-<1500		3	0.97 (0.83-1.14)	12.0	0.29		3	0.85 (0.75-0.97)	0	0.61		4	0.96 (0.86-1.08)	0	0.81	
Cases ≥1500		3	0.90 (0.83-0.98)	0	0.43		3	0.89 (0.82-0.97)	18.2	0.29		3	0.87 (0.82-0.93)	0	0.64	
Adjustment for confounders																
Alcohol	Yes	8	0.92 (0.86-0.99)	0	0.50	0.89	11	0.92 (0.85-0.99)	24.7	0.21	0.17	12	0.91 (0.86-0.96)	0	0.67	0.93
	No	3	0.92 (0.71-1.19)	67.4	0.05		3	0.83 (0.62-1.12)	63.9	0.06		3	0.95 (0.74-1.23)	54.6	0.11	
Smoking	Yes	7	0.93 (0.86-1.00)	0	0.42	0.65	10	0.92 (0.84-1.01)	32.2	0.15	0.31	11	0.91 (0.86-0.96)	0	0.59	0.97
	No	4	0.90 (0.75-1.07)	52.5	0.10		4	0.85 (0.69-1.04)	56.4	0.08		4	0.93 (0.79-1.09)	32.7	0.22	
Body mass index, weight, WHR	Yes	6	0.92 (0.83-1.02)	12.2	0.34	0.94	9	0.93 (0.85-1.01)	26.1	0.21	0.19	10	0.91 (0.86-0.96)	0	0.50	0.96
	No	5	0.92 (0.81-1.04)	42.2	0.14		5	0.82 (0.67-0.99)	51.2	0.09		5	0.92 (0.80-1.05)	11.7	0.34	
Physical activity	Yes	7	0.93 (0.86-1.00)	0	0.42	0.65	9	0.93 (0.85-1.01)	26.1	0.21	0.19	10	0.91 (0.86-0.96)	0	0.50	0.96

	No	4	0.90 (0.75-1.07)	52.5	0.10		5	0.82 (0.67-0.99)	51.2	0.09		5	0.92 (0.80-1.05)	11.7	0.34	
Red, processed meat	Yes	8	0.91 (0.84-1.00)	23.3	0.25	0.73	7	0.90 (0.78-1.04)	55.3	0.04	0.82	8	0.93 (0.86-1.01)	0	0.79	0.41
	No	3	0.95 (0.80-1.14)	43.6	0.17		7	0.91 (0.82-1.01)	27.8	0.22		7	0.92 (0.83-1.02)	26.8	0.22	
Dairy products, calcium intake	Yes	3	0.88 (0.76-1.00)	44.9	0.16	0.36	4	0.89 (0.71-1.12)	66.6	0.03	0.66	4	0.91 (0.81-1.02)	0	0.55	0.85
	No	8	0.95 (0.86-1.05)	18.4	0.29		10	0.91 (0.83-0.99)	27.9	0.19		11	0.92 (0.86-0.98)	7.1	0.38	
Energy intake	Yes	8	0.91 (0.84-1.00)	23.3	0.25	0.73	11	0.92 (0.84-1.02)	44.9	0.05	0.35	12	0.93 (0.87-0.99)	13.3	0.31	0.84
	No	3	0.95 (0.80-1.14)	43.6	0.17		3	0.82 (0.70-0.97)	19.4	0.29		3	0.91 (0.79-1.04)	0	0.91	

n denotes the number of risk estimates, the number of studies used is higher 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 for both colon and rectum.

Figure 1. Flow-chart of study selection

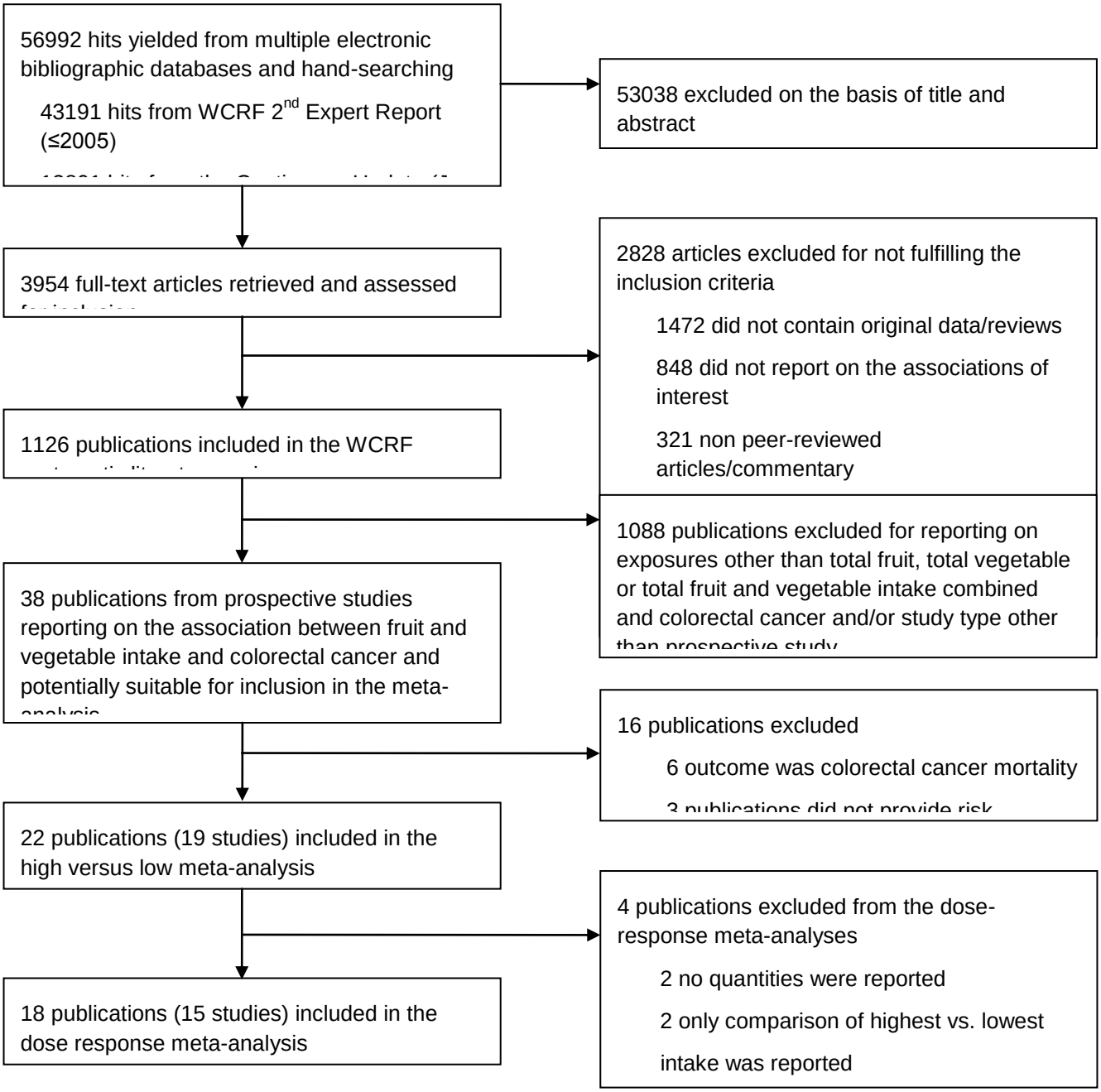

Figure 2. Fruits, vegetables and colorectal cancer

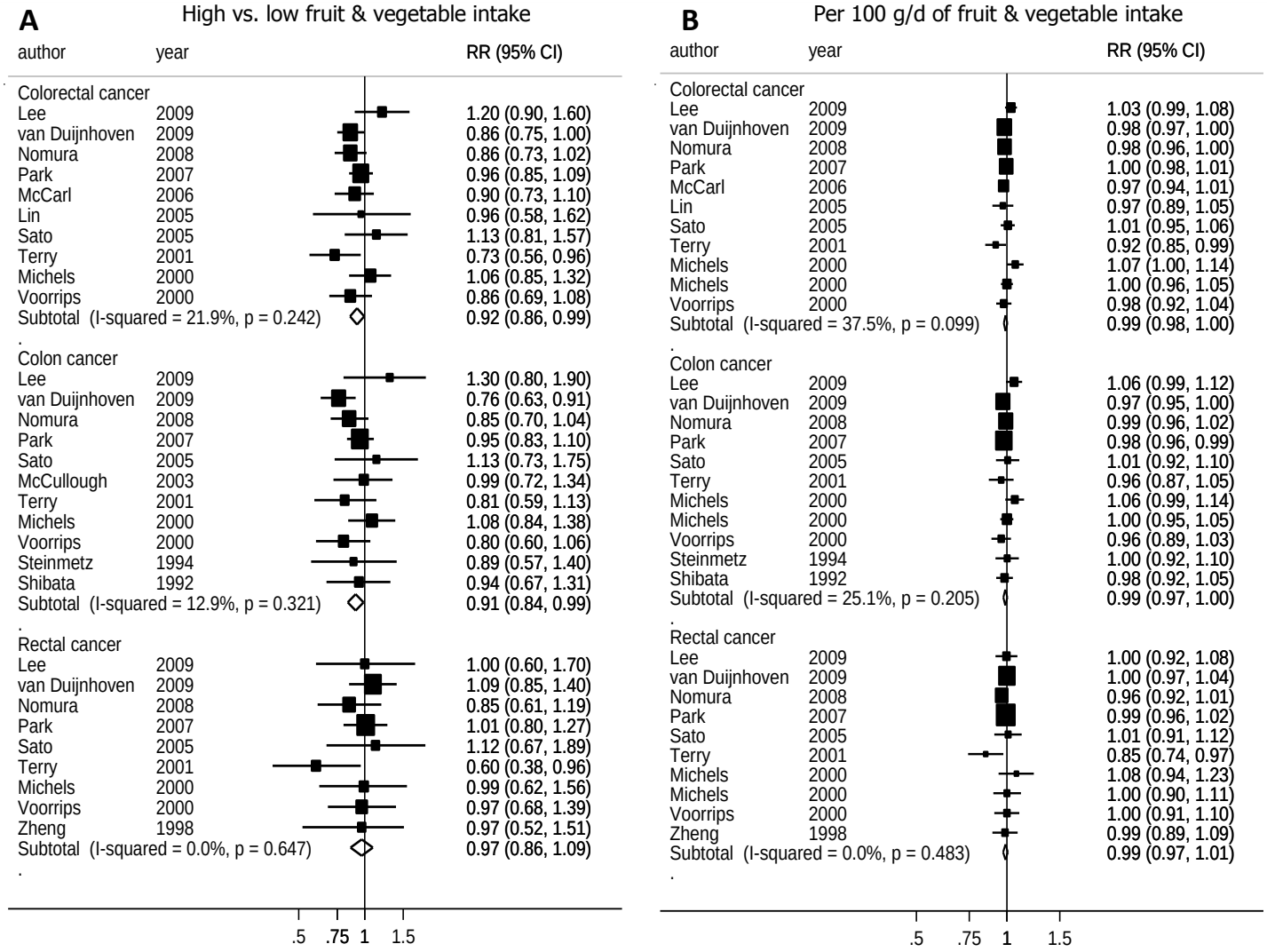

Figure 3. Fruits and colorectal cancer

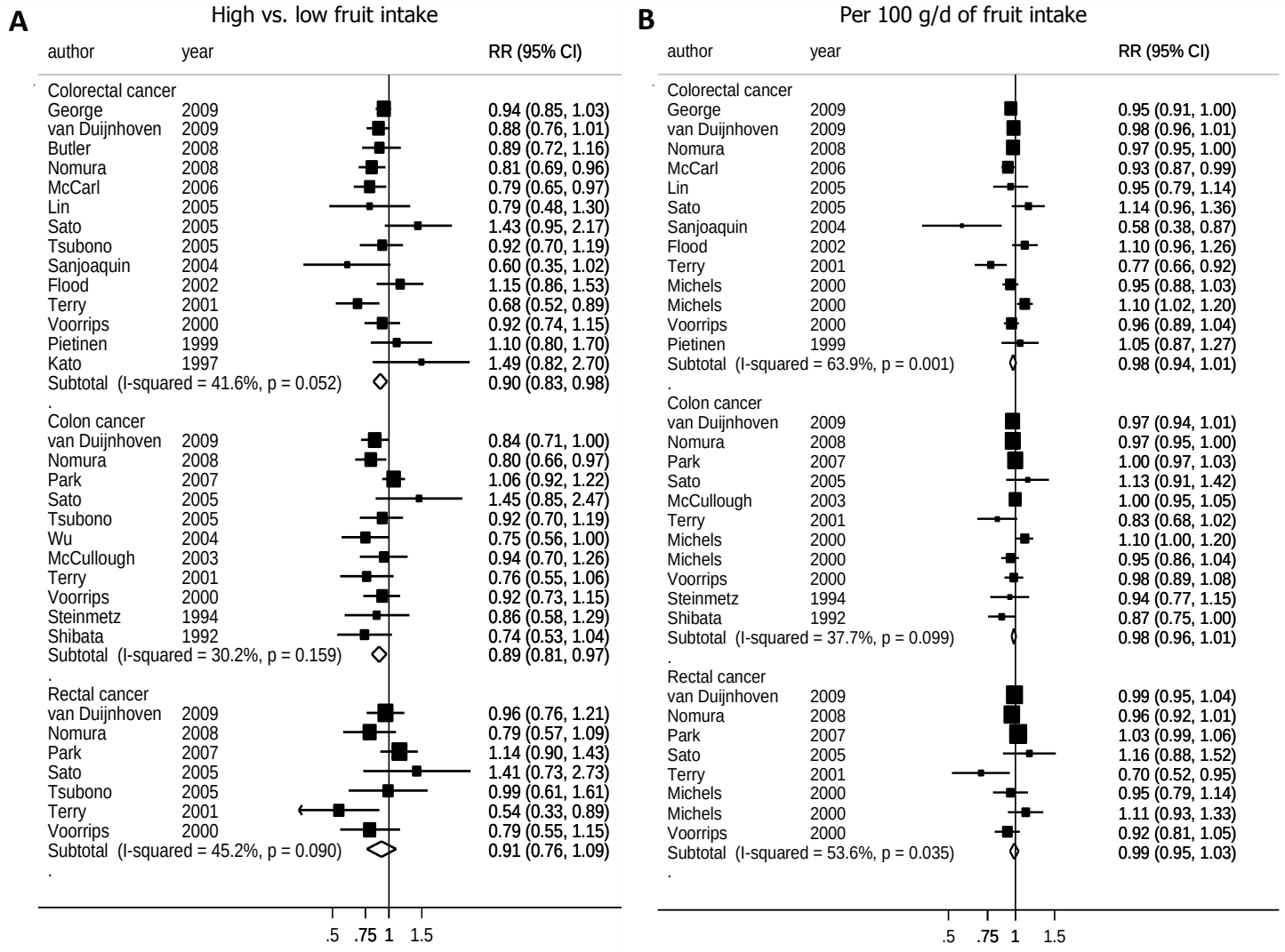
A
High vs. low fruit intake
author
year
RR (95% CI)
Colorectal cancer
George 2009 0.94 (0.85, 1.03)
van Duijnhoven 2009 0.88 (0.76, 1.01)
Butler 2008 0.89 (0.72, 1.16)
Nomura 2008 0.81 (0.69, 0.96)
McCarl 2006 0.79 (0.65, 0.97)
Lin 2005 0.79 (0.48, 1.30)
Sato 2005 1.43 (0.95, 2.17)
Tsubono 2005 0.92 (0.70, 1.19)
Sanjoaquin 2004 0.60 (0.35, 1.02)
Flood 2002 1.15 (0.86, 1.53)
Terry 2001 0.68 (0.52, 0.89)
Voorrips 2000 0.92 (0.74, 1.15)
Pietinen 1999 1.10 (0.80, 1.70)
Kato 1997 1.49 (0.82, 2.70)
Subtotal (I-squared = 41.6%, p = 0.052) 0.90 (0.83, 0.98)
Colon cancer
van Duijnhoven 2009 0.84 (0.71, 1.00)
Nomura 2008 0.80 (0.66, 0.97)
Park 2007 1.06 (0.92, 1.22)
Sato 2005 1.45 (0.85, 2.47)
Tsubono 2005 0.92 (0.70, 1.19)
Wu 2004 0.75 (0.56, 1.00)
McCullough 2003 0.94 (0.70, 1.26)
Terry 2001 0.76 (0.55, 1.06)
Voorrips 2000 0.92 (0.73, 1.15)
Steinmetz 1994 0.86 (0.58, 1.29)
Shibata 1992 0.74 (0.53, 1.04)
Subtotal (I-squared = 30.2%, p = 0.159) 0.89 (0.81, 0.97)
Rectal cancer
van Duijnhoven 2009 0.96 (0.76, 1.21)
Nomura 2008 0.79 (0.57, 1.09)
Park 2007 1.14 (0.90, 1.43)
Sato 2005 1.41 (0.73, 2.73)
Tsubono 2005 0.99 (0.61, 1.61)
Terry 2001 0.54 (0.33, 0.89)
Voorrips 2000 0.79 (0.55, 1.15)
Subtotal (I-squared = 45.2%, p = 0.090) 0.91 (0.76, 1.09)
.5 .75 1 1.5
B
Per 100 g/d of fruit intake
author
year
RR (95% CI)
Colorectal cancer
George 2009 0.95 (0.91, 1.00)
van Duijnhoven 2009 0.98 (0.96, 1.01)
Nomura 2008 0.97 (0.95, 1.00)
McCarl 2006 0.93 (0.87, 0.99)
Lin 2005 0.95 (0.79, 1.14)
Sato 2005 1.14 (0.96, 1.36)
Sanjoaquin 2004 0.58 (0.38, 0.87)
Flood 2002 1.10 (0.96, 1.26)
Terry 2001 0.77 (0.66, 0.92)
Michels 2000 0.95 (0.88, 1.03)
Michels 2000 1.10 (1.02, 1.20)
Voorrips 2000 0.96 (0.89, 1.04)
Pietinen 1999 1.05 (0.87, 1.27)
Subtotal (I-squared = 63.9%, p = 0.001) 0.98 (0.94, 1.01)
Colon cancer
van Duijnhoven 2009 0.97 (0.94, 1.01)
Nomura 2008 0.97 (0.95, 1.00)
Park 2007 1.00 (0.97, 1.03)
Sato 2005 1.13 (0.91, 1.42)
McCullough 2003 1.00 (0.95, 1.05)
Terry 2001 0.83 (0.68, 1.02)
Michels 2000 1.10 (1.00, 1.20)
Michels 2000 0.95 (0.86, 1.04)
Voorrips 2000 0.98 (0.89, 1.08)
Steinmetz 1994 0.94 (0.77, 1.15)
Shibata 1992 0.87 (0.75, 1.00)
Subtotal (I-squared = 37.7%, p = 0.099) 0.98 (0.96, 1.01)
Rectal cancer
van Duijnhoven 2009 0.99 (0.95, 1.04)
Nomura 2008 0.96 (0.92, 1.01)
Park 2007 1.03 (0.99, 1.06)
Sato 2005 1.16 (0.88, 1.52)
Terry 2001 0.70 (0.52, 0.95)
Michels 2000 0.95 (0.79, 1.14)
Michels 2000 1.11 (0.93, 1.33)
Voorrips 2000 0.92 (0.81, 1.05)
Subtotal (I-squared = 53.6%, p = 0.035) 0.99 (0.95, 1.03)
.5 .75 1 1.5

Figure 4. Vegetables and colorectal cancer

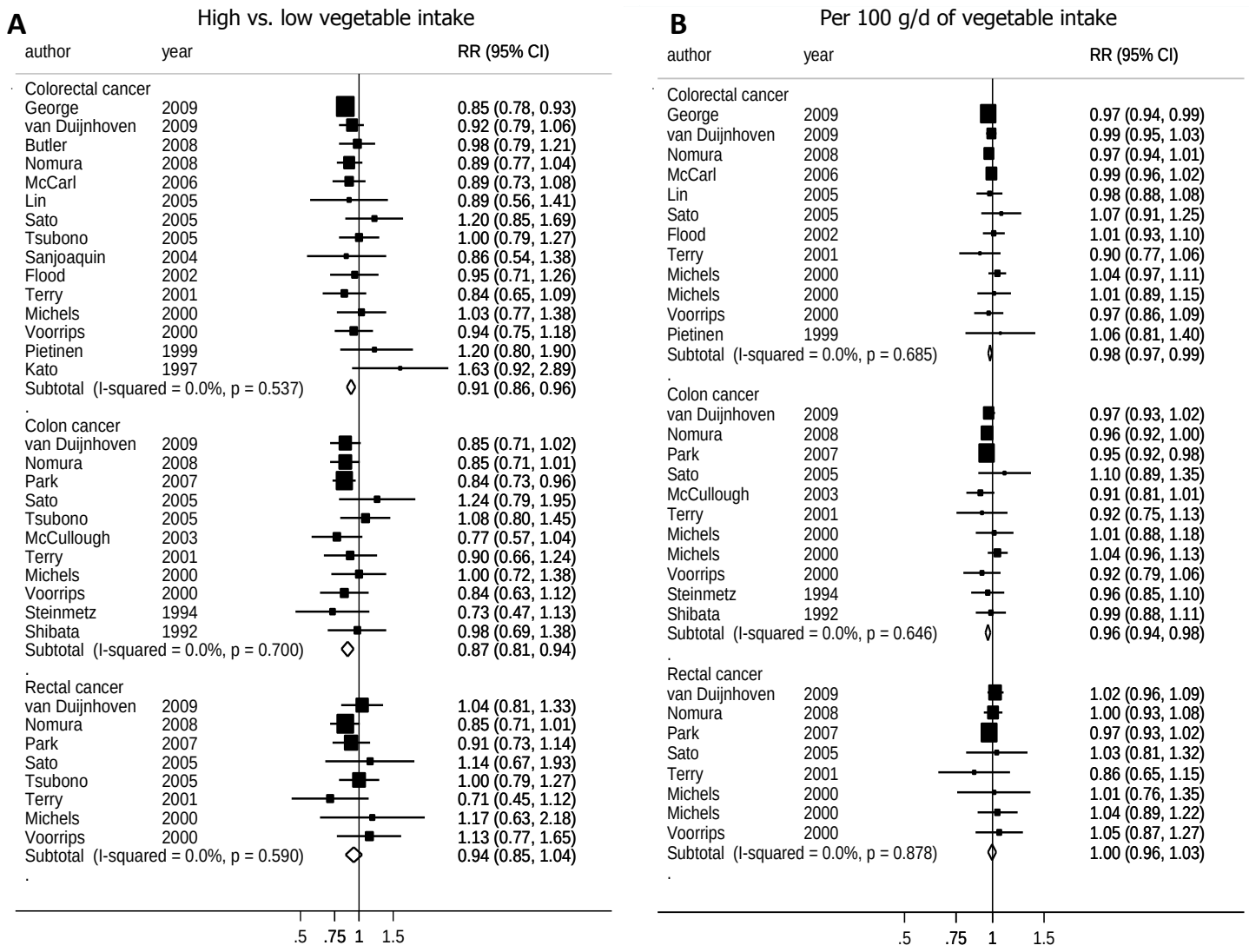
A
High vs. low vegetable intake
author
year
RR (95% CI)
Colorectal cancer
George 2009 0.85 (0.78, 0.93)
van Duijnhoven 2009 0.92 (0.79, 1.06)
Butler 2008 0.98 (0.79, 1.21)
Nomura 2008 0.89 (0.77, 1.04)
McCarl 2006 0.89 (0.73, 1.08)
Lin 2005 0.89 (0.56, 1.41)
Sato 2005 1.20 (0.85, 1.69)
Tsubono 2005 1.00 (0.79, 1.27)
Sanjoaquin 2004 0.86 (0.54, 1.38)
Flood 2002 0.95 (0.71, 1.26)
Terry 2001 0.84 (0.65, 1.09)
Michels 2000 1.03 (0.77, 1.38)
Voorrips 2000 0.94 (0.75, 1.18)
Pietinen 1999 1.20 (0.80, 1.90)
Kato 1997 1.63 (0.92, 2.89)
Subtotal (I-squared = 0.0%, p = 0.537) 0.91 (0.86, 0.96)
Colon cancer
van Duijnhoven 2009 0.85 (0.71, 1.02)
Nomura 2008 0.85 (0.71, 1.01)
Park 2007 0.84 (0.73, 0.96)
Sato 2005 1.24 (0.79, 1.95)
Tsubono 2005 1.08 (0.80, 1.45)
McCullough 2003 0.77 (0.57, 1.04)
Terry 2001 0.90 (0.66, 1.24)
Michels 2000 1.00 (0.72, 1.38)
Voorrips 2000 0.84 (0.63, 1.12)
Steinmetz 1994 0.73 (0.47, 1.13)
Shibata 1992 0.98 (0.69, 1.38)
Subtotal (I-squared = 0.0%, p = 0.700) 0.87 (0.81, 0.94)
Rectal cancer
van Duijnhoven 2009 1.04 (0.81, 1.33)
Nomura 2008 0.85 (0.71, 1.01)
Park 2007 0.91 (0.73, 1.14)
Sato 2005 1.14 (0.67, 1.93)
Tsubono 2005 1.00 (0.79, 1.27)
Terry 2001 0.71 (0.45, 1.12)
Michels 2000 1.17 (0.63, 2.18)
Voorrips 2000 1.13 (0.77, 1.65)
Subtotal (I-squared = 0.0%, p = 0.590) 0.94 (0.85, 1.04)
.5
.75
1
1.5
B
Per 100 g/d of vegetable intake
author
year
RR (95% CI)
Colorectal cancer
George 2009 0.97 (0.94, 0.99)
van Duijnhoven 2009 0.99 (0.95, 1.03)
Nomura 2008 0.97 (0.94, 1.01)
McCarl 2006 0.99 (0.96, 1.02)
Lin 2005 0.98 (0.88, 1.08)
Sato 2005 1.07 (0.91, 1.25)
Flood 2002 1.01 (0.93, 1.10)
Terry 2001 0.90 (0.77, 1.06)
Michels 2000 1.04 (0.97, 1.11)
Michels 2000 1.01 (0.89, 1.15)
Voorrips 2000 0.97 (0.86, 1.09)
Pietinen 1999 1.06 (0.81, 1.40)
Subtotal (I-squared = 0.0%, p = 0.685) 0.98 (0.97, 0.99)
Colon cancer
van Duijnhoven 2009 0.97 (0.93, 1.02)
Nomura 2008 0.96 (0.92, 1.00)
Park 2007 0.95 (0.92, 0.98)
Sato 2005 1.10 (0.89, 1.35)
McCullough 2003 0.91 (0.81, 1.01)
Terry 2001 0.92 (0.75, 1.13)
Michels 2000 1.01 (0.88, 1.18)
Michels 2000 1.04 (0.96, 1.13)
Voorrips 2000 0.92 (0.79, 1.06)
Steinmetz 1994 0.96 (0.85, 1.10)
Shibata 1992 0.99 (0.88, 1.11)
Subtotal (I-squared = 0.0%, p = 0.646) 0.96 (0.94, 0.98)
Rectal cancer
van Duijnhoven 2009 1.02 (0.96, 1.09)
Nomura 2008 1.00 (0.93, 1.08)
Park 2007 0.97 (0.93, 1.02)
Sato 2005 1.03 (0.81, 1.32)
Terry 2001 0.86 (0.65, 1.15)
Michels 2000 1.01 (0.76, 1.35)
Michels 2000 1.04 (0.89, 1.22)
Voorrips 2000 1.05 (0.87, 1.27)
Subtotal (I-squared = 0.0%, p = 0.878) 1.00 (0.96, 1.03)
.5
.75
1
1.5

Figure 5. Fruits and vegetables and colorectal cancer