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Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis

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Abstract

Background: Lung cancer is the most common cause of cancer death. An estimated 158 040 deaths are expected to occur in 2015. Several fruits and vegetables containing carotenoids and other antioxidants have been hypothesized to decrease lung cancer risk because of their antioxidant activity. As part of the WCRF-AICR Continuous Update Project, we conducted a systematic review and meta-analysis of prospective studies to assess the dose-response relationship between fruits and vegetables and incidence and mortality of lung cancer.

Methods: We searched PubMed and several databases up to December 2014 for relevant prospective studies. We conducted meta-analyses comparing highest and lowest intakes and dose-response meta-analyses using random effects models to estimate summary relative risks (RRs) and 95% confidence intervals (CIs), and used restricted cubic splines to examine possible nonlinear associations. We combine results from the Pooling Project with the studies we identified to increase the statistical power of our analysis.

Results: When comparing the highest with the lowest intakes, the summary RR estimates were 0.86(95% CI: 0.78-0.94; n(studies)=18) for fruits and vegetables, 0.92(95% CI: 0.87-0.97; n=25) for vegetables and 0.82(95% CI: 0.76-0.89; n=29) for fruits. The association with fruit and vegetable intake was marginally significant in current smokers and inverse but not significant in former or never smokers. Significant inverse dose-response associations were observed for each 100 g/day increase: for fruit and vegetables (RR=0.96; 95% CI= 0.94-0.98, I^2 =63.9%, n=14, N(cases)=9609), vegetables (RR=0.94; 95% CI= 0.89-0.98, I^2 =47.9%, n=20, N=12 563), and fruits (RR=0.92; 95% CI= 0.89-0.95, I^2 =56.8%, n=23, N=14506). There was evidence of a non-linear relationship ($p < 0.01$) between fruit and vegetable intake

and lung cancer risk showing that no further benefit is obtained when increasing consumption above approximately 400 g per day.

Conclusions: Eliminating tobacco smoking is the best strategy to prevent lung cancer. Although residual confounding by smoking cannot be ruled out, the current evidence from prospective studies is consistent with a protective role of fruit and vegetables in lung cancer aetiology.

Key words Fruits • Vegetables •Citrus fruits • Cruciferous vegetables•Lung Cancer • Smoking • Systematic review • Meta-analysis

Key message:
Eliminating tobacco smoking is the best strategy to prevent lung cancer. This meta-analysis reinforces the importance of a diet rich in fruit and vegetable as a preventive measure against lung cancer.

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Introduction

Lung cancer is the leading cause of cancer death in males, the second leading cause of cancer death in women and the fourth most commonly diagnosed cancer worldwide (2). From 2007 to 2011, lung cancer incidence rates decreased by 3.0% per year in men and by 2.2% per year in women. In 2012, about 1.5 million people died from lung cancer (2), accounting for about one fifth of all cancer deaths. Most lung cancers are diagnosed at an advanced stage due to the relative lack of clinical symptoms during early stages. The 5-year survival of lung cancer is only 17% (2). Cigarette smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females (1, 20). Although lung cancer incidence rates in men from North America, Europe and Australia are decreasing, they have increased in Asia and Africa (1) and in women, as a reflect of changes in smoking prevalence(30). Non-smokers exposed to environmental tobacco smoke have an increased risk of lung cancer and there is also evidence that air pollution is a risk factor of lung cancer (49).
Non-smoking is the first strategy for preventing lung cancer. There is also evidence that nutritional factors may play a role in lung cancer development. In clinical trials there was an increased risk of lung cancer in smokers receiving high dose of beta-carotene supplements(12). On the other hand, several fruits and vegetables contain carotenoids and other antioxidants have been hypothesized to decrease lung cancer risk because of their antioxidant activity. In an exhaustive evaluation of the existing evidence, the expert panel of the 2007 WCRF/AICR Second Report concluded as convincing evidence that high doses of beta-carotene supplements (in smokers) increase the risk of lung cancer; fruits and foods containing carotenoids probably decrease the risk of lung cancer. The evidence suggesting a protective effect of non-starchy vegetables was limited. There was convincing evidence that

arsenic in drinking water increases the risk of lung cancer, but there was limited evidence supporting any effect of other nutritional factors investigated (1).
As part of the WCRF-AICR Continuous Update Project, we conducted a systematic review and meta-analysis of prospective studies to assess the relationship between fruits and vegetables combined, fruits only, vegetables only, cruciferous vegetables, leafy vegetables and citrus fruit and incidence and mortality of lung cancer. We specifically aimed to clarify 1) the strength and shape of the dose-response relationship by conducting linear and nonlinear dose-response analyses, 2) whether specific types of fruits and vegetables were associated with lung cancer risk, 3) and whether the association differed by geographic regions including not only studies from North America and Europe as the previous Pooling Project, but also Asian studies.

Methods

Search strategy

The search of articles published before January 2006 was conducted by several reviewers at the Johns Hopkins University during the systematic literature review for the WCRF/AICR Second Expert Report (available online http://www.wcrf.org/sites/default/files/SLR_lung.pdf). Several databases were searched up to December 2005, including Pubmed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL, AMED, National Research Register, and In Process Medline. Because all the relevant studies were identified by the PubMed search, the PubMed database was searched by the CUP team at Imperial College London for studies of fruit and vegetables and lung cancer risk published from January 2006 up to December 2014. The protocol followed for the review can be found at: http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/CUP_lung_cancer_protocol.pdf and includes the specific search criteria used. Furthermore, the reference list of the included articles and published meta-analyses and reviews identified was screened and hand searched.

Study selection

The study inclusion criteria were 1) being a randomized controlled trial or prospective study with cohort, case-cohort or nested case-control design; 2) report adjusted estimates of the relative risk (RR) (e.g. hazard ratio, risk ratio or odds ratio) and 95% confidence intervals (CIs) for the association of fruit and/or vegetables and lung cancer incidence or mortality; 3) for dose-response meta-analysis, studies should provide a quantitative measure of the intake. When the same study published more than one article on fruit and vegetables and lung cancer, we selected the newest publication with the largest number of cases.
From 29513 articles identified, 28690 articles were excluded based on the abstract and title, 800 articles did not meet the inclusion criteria and 27 articles met the inclusion criteria and were included (Flowchart of study selection – Figure 1).

Data extraction

The data extracted for each article were: first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, sex, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), type of fruit and/or vegetable, amount of intake, RRs and 95% CIs and adjustment variables. The search and data extraction of articles published up to June 2006 was conducted by several reviewers at the Johns Hopkins University during the systematic literature review for the WCRF/AICR Second Expert Report. The search and extraction from June 2006 and up to December 2014 was conducted by the CUP team at Imperial College London.

Statistical methods

We calculated summary RRs and 95% CIs for the highest compared to the lowest levels of fruits and vegetables intake using random effect models to account for anticipated heterogeneity. The natural logarithm of the relative risks was weighted by the method of Dersimonian and Laird and then pooled across studies (11). To estimate linear trends and 95% CIs from the natural logs of the RR and respective CI across categories of fruit and vegetable intake we used the method described by Greenland and Longnecker (19, 34). For this method at least three categories of intake and the number of cases and person-years or non-cases per category was required. When studies reported only the total number of cases or total person-years and the exposure was defined in quantiles, the distribution of cases or person-years was calculated dividing the total number by the number of quantiles. Whenever reported, the mean or median intake by category was assigned to the corresponding RR. The midpoint was calculated for studies that only reported a range of intake by category. When the intake range was open-ended we assumed that its width was the same as the adjacent category. For two studies that presented the exposure per given unit of energy intake, we rescaled it using the mean energy intake provided (17, 55). We expressed the dose-response by increments of 100g/day for fruits and vegetables and 50g/day for subtypes of vegetables. For studies that reported in servings, the conversion unit of 80 grams as a serving size was used, for comparison with other meta-analyses of fruit and vegetable intake and cancer risk(11). The analyses were conducted for men and women separately and for all studies combined. Where results were only presented separately for men and women in a study, these were combined for analyses on all studies using a fixed effects meta-analysis before being pooled with other studies to ensure that between-study heterogeneity was not underestimated. Between-study heterogeneity was assessed using Cochran Q test and the percentage of total variation in study estimates attributable to between-study heterogeneity (I^2). Heterogeneity was explored in stratified analysis by geographic location, lung cancer type, smoking status, outcome type and type of adjustment for smoking (smoking status only or also adjustment for smoking intensity and duration) and by visual inspection of the forest plots. Most of the studies adjusted the analysis for smoking status. Potential small-study effects, such as publication bias, were explored using Egger's test and funnel plots.

The results of a published Pooling Project of eight prospective studies (39) could not be included in the dose-response meta-analysis because cohort-specific quartiles were used in the pooled analysis. However, a meta-analysis of the highest compared to the lowest intake category including the Pooling Project and the non-overlapping studies identified in our search and a stratified analysis by smoking status was conducted. Two studies included in the Pooling Project (39) did not provide individual data to be included in our meta-analysis.

To examine possible nonlinear associations, we calculated restricted cubic splines for each study with more than three categories of exposure, using three fixed knots at 10%, 50%, and 90% through the total distribution of the reported intake, and combined them using multivariate meta-analysis. Fifteen studies presented more than three categories and could be included in the non-linear analysis (7-9, 13, 17, 18, 21, 23, 31, 33, 38, 42, 45, 46, 51).

Stata version 12 software (StataCorp, College Station, TX, USA) was used for the statistical analyses. A two-tailed $p<0.05$ was considered statistically significant.

Results

Twenty seven cohort studies were included in this analysis (3, 6-10, 13, 14, 17, 18, 21-23, 26, 28, 29, 31, 33, 35-37, 42, 45-47, 51-53, 53, 56, 57) - fourteen on fruit and vegetables, twenty two on vegetables, eleven on cruciferous vegetables, nine on leafy vegetables, twenty-seven on fruits and thirteen on citrus fruits (supplementary tables S1-S6). The total number of studies after including the non-overlapping studies from the Pooling Project was twenty-nine (40).

Fruit and vegetables

Eighteen studies with 11 941 cases were included in highest compared to the lowest meta-analyses. A significant inverse association was observed (RR: 0.86; 95% CI=0.78-0.94, I^2=37%) (figure 3a) that was more evident in current smokers (RR: 0.90 (95%CI= 0.81-1.00, I^2 =0%, 8 studies) than in never or former smokers (RR: 0.94; 0.70-1.27, I^2 =19%, and 0.95 (95%CI= 0.83-1.10, I^2 =36, 7 studies respectively) (supplementary figure S5).

Fourteen studies were included in the dose-response meta-analysis. A significant inverse association of fruit and vegetable consumption with lung cancer was observed (RR per 100 g/day: 0.96 (95% CI= 0.94-0.98, I^2 =64%, P heterogeneity (ph) <0.01) (figure 2a). Two studies excluded (52, 57) from the dose-response analyses reported non-significant associations. Two studies included in the Pooling Project (39), The New York State Cohort and the Canadian National Breast Screening Study, did not provide individual data to be included in our meta-analysis.

The observed heterogeneity persisted in analyses stratified by sex, geographic location, smoking status, and level of adjustment for smoking. No significant associations were observed in smokers and never smokers (three studies) and in the only study on former smokers. Most of the studies in the analyses adjusted by smoking status, duration and

intensity. The inverse association was observed in subgroup of studies in Europe (4 studies) but not in Asia (3 studies) and North America (7 studies) (table 1).

There was significant evidence of publication or small study bias in the dose-response meta-analysis (p for Egger's test < 0.01). Visual inspection of the funnel plot suggests that small studies showing positive or null associations may be missing (supplementary figure S1). All the studies included in the analysis on fruit and vegetables except two (38, 53) also reported on fruits and vegetables separately and lung cancer risk.

There was evidence of non-linear dose-response association (p <0.01, 11 studies). The risk decreases by 27% with increasing intakes up to approximately 400 g/day. No benefit for increasing intake is apparent above this value (figure 5a).

Vegetables

Twenty-five studies with 19 095 cases were included in the meta-analyses of the highest compared to the lowest intakes. A significant inverse association was observed (RR highest compared to lowest: 0.92; 95% CI= 0.87-0.97; I^2=0%) (figure 3b) that in stratified analysis was restricted to current smokers (RR highest compared to lowest: 0.93 (95%CI= 0.85-1.01, I^2 =0%, 10 studies). No significant association was observed in never (RR highest compared to lowest: 0.92; 95%CI= 0.73-1.16, I^2 =0%, 9 studies) and former smokers (RR highest compared to lowest: 1.01; 95%CI= 0.85-1.21, I^2 =59%, 8 studies) (supplementary figure S6).

A significant inverse association was observed in dose-response meta-analysis (RR per 100 g/day: 0.94; 95% CI= 0.89-0.98, I^2 =48%, 20 studies) (figure 2b). Four studies were excluded from the dose-response analyses; all reported non-significant associations (15, 25, 28, 52). Two studies included in the Pooling Project (39), The New York State Cohort and the Canadian National Breast Screening Study, did not provide individual data to be included in our meta-analysis.

In analysis stratified by smoking status the significant inverse association was restricted to current smokers (RR per 100g/day: 0.88 (0.71-0.99, I^2 =81%, 6 studies). No significant associations were observed in former and never smokers. A marginal significant inverse association was observed in men but not in women (table 1).

High heterogeneity was observed that persisted in stratified analyses in men, current smokers, and European studies, and in subgroups with very large number of studies. In analyses by cancer type inverse, but no significant association was observed for small cell carcinoma; only two studies were available; no association was observed in the other cancer types (four studies) (table 1).

There was significant evidence of publication or small study bias (p < 0.01). The asymmetry is driven by a small study showing an inverse association (supplementary figure S2).

There was evidence of a non-linear inverse dose-response association (p < 0.01,15 studies). The risk decreased by 18% with intakes up to approximately 300g and no further risk reduction for higher intake levels (figure 5b).

Cruciferous vegetables

Eleven studies with 11 467 cases were included in the highest compared to the lowest intake. A significant inverse association was observed (RR highest compared to lowest: 0.87, 95% CI= 0.79-0.97, I^2=43% and RR per 50g/day: 0.92, 95% CI= 0.87-0.98, I^2=33%) (figures 4a and 4b). There was evidence of a non-linear inverse dose-response association ($p < 0.01$, 9 studies) with a 19% reduced risk with intakes up to 100g/day.

Green leafy vegetables

Nine studies with 5 783 cases were included in the highest compared to the lowest intake. A significant inverse association was observed (RR highest compared to lowest: 0.85, 95% CI= 0.75-0.96, I^2=24% and RR per 50g/day: 0.89, 95% CI= 0.79-1.00, I^2=50%) (figures 4c and 4d). There was evidence of a non-linear inverse dose-response association ($p < 0.01$, 8 studies) with a 9% reduced risk with intakes up to 50g/day.

Fruits

Twenty-nine studies with 15 599 cases were included in the highest compared to the lowest intake meta-analysis. A significant inverse association was observed (RR highest compared to lowest: 0.82; 95% 0.76-0.89, I^2=32%, 29 studies) (figure 3c). The association was statistically significant in smokers (RR: 0.83; 95%CI= 0.75-0.93, I^2 =22%, 13 studies) and former smokers (RR: 0.90; 95%CI= 0.81-0.99, I^2 =0%, 9 studies); inverse, but not significant in never smokers (RR: 0.88; 95%CI= 0.68-1.15, I^2 =37%, 12 studies) (supplementary figure S7).

Twenty three studies were included in the dose-response meta-analysis. A significant inverse association was observed (RR per 100 g/day: 0.92; 95% CI= 0.89-0.95, I^2 =57%, 23 studies) (figure 2c). Five studies (15, 24, 28, 32, 52) were excluded from the dose-response analyses; all reported non-significant associations (figure 2c). Two studies included in the Pooling Project (39) did not provide individual data to be included in our meta-analysis.

In stratified analysis, similar significant inverse associations were observed in men and women. In analysis stratified by smoking status a significant inverse association was found for current smokers (RR per 100g/day: 0.90 (0.84-0.98, I^2 =63%, 8 studies), but not for former or never smokers. There was high heterogeneity across studies in current smokers (table 1).

There was significant evidence of publication or small study bias ($p < 0.01$). The funnel plot shows that the small studies identified reported stronger inverse associations than the average and there were no small studies reporting positive associations (supplementary figure S3).

There was evidence of a nonlinear dose-response relationship of lung cancer and fruit intake ($p < 0.01$, 14 studies). The inverse dose-response with 18% risk reduction is observed for increasing levels of fruit intake up to 200-300 g/day and no further risk dose-response relationship is observed above this level (figure 5c).

Citrus fruits

Fifteen studies with 12 021 cases were included in the highest compared to the lowest meta-analysis. An inverse association was observed (RR: 0.85; 95% CI= 0.78-0.93, I^2 =30%) (figure 3d).

Eleven studies (6 382 cases) were included in the dose-response meta-analysis. A significant inverse association was observed (RR per 100 g/day: 0.91; 95% CI= 0.85-0.98, I^2 =53%) (figure 2d). Three studies (14, 27, 41) were excluded from the dose-response analyses; all reported non-significant associations. One study included in the Pooling Project (39), The New York State Cohort, did not provide individual data to be included in our meta-analysis.

Inverse but not significant associations of similar magnitude were observed in men and women, in former and current smokers, but not in never smokers (RR per 100g/day: 1.27; 95% CI: 0.83-1.94, 3 studies). The same was observed in the highest compared to lowest analysis stratified by smoking (supplementary figure S8). On average, Asian studies reported stronger associations than studies from other areas. There was significant evidence of publication or small study bias ($p < 0.01$). The asymmetry is driven by small studies on the left side of the funnel plot and no small studies on the right side (supplementary figure S4).

There was evidence of non-linear dose-response relationship ($p < 0.01$, 8 studies) with 8% risk reduction in the range of citrus fruit intake up to around 70 g/day and no dose-response relationship is observed for increasing intakes above this value (figure 5d).

Discussion

This meta-analysis showed a 15-19% decreased risk of lung cancer with higher intakes of fruit and vegetables. When the analysis was stratified by smoking status the risk reduction in relation to intake of fruits and vegetables was attenuated. The dose-response association with fruits and vegetables was only significant for current smokers, but not for former or never smokers. In the meta-analyses of the highest compared to the lowest intake, a significant inverse association was also observed for fruits in former smokers. Non-linear dose-response meta-analyses suggested a threshold of risk reduction for fruit and vegetables with no further reductions in risk above 400 grams per day.

It has been suggested that the protective effect of fruit and vegetables may be due to biologically active compounds such as flavonoids which have antioxidant effects. A meta-analysis of dietary flavonoids intake and smoking related cancers showed a marginal effect on lung cancer risk (OR= 0.84, 95% CI= 0.71-1.00, I^2 =58, ph=0.02, 8 cohort and case control studies) (54). Another meta-analysis showed that an increase 20 mg/day in flavonoids intake was associated with a 10% decreased risk of developing lung cancer (RR=0.90, 95% CI=0.83–0.97, 6 cohort and 4 case control studies). After stratification by smoking status the association was only significant for smokers(48).

Dietary carotenoids were shown to be protective against lung cancer in a highest compared to lowest meta-analysis of 8 cohort studies, RR=0.79 (95% CI= 0.71-0.87, Q(7df) =3.79, p =0.80) (16). The same meta-analysis showed no effect of beta-carotene supplementation when compared to placebo, RR=1.10 (95% CI= 0.89-1.36; p=0.39, 3 intervention studies). A clinical trial of beta-carotene supplementation in smokers showed no effect in decreasing lung cancer risk (50). While high-dose supplements of single nutrients have shown no benefit in reducing lung cancer risk, such findings does not exclude the possibility that a food-based approach with fruit and vegetables, which contain many other vitamins, antioxidants and phytonutrients than just beta-carotene in more balanced doses, may have benefits in reducing lung cancer risk.

Cigarette smoking is also associated with depletion of circulating provitamin A carotenoid concentrations(4). It is known that smokers eat less fruit than never smokers (5, 43, 44) and because smoking is strongly associated with lung cancer the results found could potentially be explained by how detailed smoking was adjusted for. Therefore, we cannot exclude residual confounding because of unmeasured smoking habits. Although most of the studies adjusted for smoking dose and duration (21 studies), some studies adjusted only for smoking status and few studies have detailed information on smoking such as type of cigarettes, passive smoking, pipe and cigar smoking and time since quitting smoking.

In analyses stratified by smoking status the risk estimates were not significant in any of the analyses of never smokers, however, less than half of the studies included in each analysis provided analyses stratified by smoking status and this may have limited the statistical power in these analyses. For fruits and vegetables combined, the summary estimate was weaker among never smokers than among current and former smokers, while for fruits and vegetables separately, the summary estimates were of similar size in never smokers as in current smokers, thus it is possible that limited statistical power also may explain the null results in never smokers.

Another limitation of our study is the potential misclassification of the intake of fruit and vegetables. Study-specific quantile approach does not account for real differences in the population intake, which is a limitation of highest compared to lowest analysis. To take into account differences in fruit and vegetable intake between studies we conduct linear and nonlinear dose-response analysis. However, some between-study differences in fruit and vegetable intake may also partly be due to differences in the detail of food frequency questionnaires used which may include different types and numbers of fruit and vegetables items. In nonlinear analysis measurement error in the dietary assessment may be a reason for the curvature for higher reported intakes. The curvature can also be explained by a cohort effect where the higher intakes are only reported by one study.

Only a small number of studies reported the results stratified by lung cancer histological type therefore we could only do analysis by cancer type for fruit and vegetables separately, not for fruit and vegetables combined.

Our results were consistent among the different type of fruit and vegetables. For 50g of cruciferous and leafy vegetables and for 100g of citrus fruit there was a decrease in lung cancer risk. We could not do analysis on other specific types of fruits. We included studies from Europe, Asia and North America where fruit and vegetable eating and smoking habits differ considerably. The results were not always statistically significant because of the lower number of studies.

All studies included in the dose-response analysis had a prospective design and were at least adjusted for age, sex, and smoking status. All studies used FFQ to assess fruit and vegetables intake. One study (8) corrected for measurement error of diet using regression calibration. Similar results were observed with the calibrated intake. Repeated dietary measurements were used in the NHS and the HPFS (13). Cancer outcome was confirmed using records in cancer registries in most studies and loss of follow-up was low.

In conclusion, we observed an inverse association between fruit and vegetables consumption and lung cancer risk, for intakes up to 400g/day. Smoking is the strongest risk factor for lung cancer and we cannot exclude the possibility that these results could be due to residual confounding by smoking. Our results reinforce the evidence of previous meta-analysis which advocate for the importance of smoking cessation and consumption of fruit and vegetables as preventive measures for lung cancer. Any further studies should investigate the association between specific types of fruits and vegetables lung cancer risk and conduct analyses stratified by smoking status.

Contributors S.V. and L.A. did the updated literature search L.A. and A.R.V. did the updated data extraction. A.R.V. conducted the statistical analyses, wrote the first draft of the manuscript, and had primary responsibility for the final content. D.C.G. contributed towards the statistical analyses. All authors reviewed and contributed to the writing of the final version of the manuscript. T.N. wrote the study protocol and is the Principal Investigator of the Continuous Update Project at Imperial College London.

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Conflict of interest: The authors declare that there are no conflicts of interest.

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Table 1 Summary table of results

Figure 1 Flowchart of study selection

Figure 2 Dose-response meta-analysis of fruit and vegetables and lung cancer (2a, 2b, 2c, 2d)

Figure 3 Highest compared to lowest analysis of fruit and vegetables and lung cancer (3a, 3b, 3c, 3d)

Figure 4 Highest compared to lowest and dose-response meta-analysis of subtypes of vegetables (cruciferous and green leafy vegetables (4a, 4b, 4c, 4d)

Figure 5 Non-linear dose-response analysis (5a, 5b, 5c, 5d)

Supplementary Table 1 Table of study characteristics (S1-S6)

Supplementary figures – Funnel plots and highest compared to lowest analysis of fruit and vegetables and lung cancer stratified by smoking status (S1-S8)

Table 1 Summary table of results

Exposures	Total fruit and vegetables	Vegetables	Cruciferous Vegetables	Green Leafy Vegetables	Fruits	Citrus fruits
	Highest versus lowest analysis					
n/N	14/9609	22/ 14782	11/11467	9/5783	27/14928	13/6475
HvL RR(95%CI)	0.85(0.77-0.93) I^2=38%, ph=0.06	0.88(0.82-0.94) I^2=26%, ph=0.11	0.87(0.79-0.97) I^2=43%, ph=0.06	0.85(0.75-0.96) I^2=24%, ph=0.22	0.81(0.75-0.87) I^2=23%, ph=0.17	0.85(0.70-0.92) I^2=32%, ph=0.10
n/N	18/11941	25/19095	-	-	29/15599	15/12 021
HvL RR(95%CI) including non-overlapping studies from the Pooling Project	0.86(0.78-0.94) I^2=37%, ph=0.08	0.92(0.87-0.97) I^2=0%, ph=0.54	-	-	0.82(0.76-0.89) I^2=32%, ph=0.07	0.85(0.78-0.93) I^2=30%, ph=0.15
	Linear dose-response meta-analysis					
	Per 100g/day	Per 100g/day	Per 50g/day	Per 50g/day	Per 100g/day	Per 100g/day
n/N	14/9609	20/12563	11/11467	8/5732	23/14506	11/6382
RR (95%CI)	0.96 (0.94-0.98) I^2=64%, ph< 0.01	0.94 (0.89-0.98) I^2=48%, ph <0.01	0.92 (0.87-0.98) I^2=33%, ph =0.13	0.89 (0.79-1.00) I^2=50%,ph= 0.05	0.92 (0.89-0.95) I^2=57%, ph <0.01	0.91 (0.85-0.98) I^2=53%, ph =0.02
	Stratified highest versus lowest analysis by smoking					
Never smokers	0.94(0.70-1.27) I^2=19%, ph=0.29	0.92(0.73-1.16) I^2=0%, ph=0.55	-	-	0.88(0.68-1.15) I^2=37%, ph=0.13	1.04(0.80-1.33) I^2=0%,ph=0.91
Former smokers	0.95(0.83-1.10) I^2=36%, ph=0.19	1.01(0.85-1.21) I^2=59 %, ph=0.06	-	-	0.90(0.81-0.99) I^2=0%, ph=0.94	0.93(0.83-1.04) I^2=0%,ph=0.85
Current smokers	0.90(0.81-1.00) I^2=0%, ph=0.69	0.93(0.85-1.01) I^2=0%, ph=0.68	-	-	0.83(0.75-0.93) I^2=22%, ph=0.13	0.80(0.71-0.90) I^2=23%, ph=0.26
	Stratified linear dose-response by sex					
Men (n)	5 0.99 (0.94-1.04) I^2=57% ,ph= 0.06	9 0.94 (0.88-1.00) I^2=53% , ph=0.03	4 0.95 (0.90-1.00) I^2=0% , ph=0.97	3 0.89 (0.81-0.99) I^2=1% , ph=0.36	11 0.94 (0.89-0.99) I^2=46% , ph =0.04	4 0.83 (0.61-1.12) I^2=69% , ph =0.02
Women (n)	4 0.94 (0.87-1.01) I^2=76%, ph<0.01	6 1.01 (1.00-1.02) I^2=0%, ph=0.75	4 0.94 (0.85-1.05) I^2=57%, ph=0.07	4 0.83 (0.54-1.28) I^2=75%, ph≤0.01	22 0.95 (0.92-0.99) I^2=24%, ph =0.22	4 0.86 (0.71-1.05) I^2=70%, ph =0.02

Stratified linear dose-response by smoking					
Never smokers (n)	3 1.0(0.94-1.07) I^2=32%, ph=0.23	5 1.0 (0.91-1.10) I^2=0%, ph =0.44	-	4 0.96(0.76-1.22) I^2=0%, ph=0.94	8 1.02 (0.93-1.11) I^2=22%, ph=0.25	3 1.27 (0.83-1.94) I^2=0%, ph =0.64
Former smokers (n)	1 0.99 (0.97-1.01)	4 0.97 (0.91-1.05) I^2=25%, ph =0.26	-	3 0.63(0.41-0.95) I^2=28%, ph=0.25	4 0.97 (0.93-1.02) I^2=0%, ph =0.68	2 0.68(0.42-1.11) I^2=0%, ph =0.46
Current smokers (n)	3 0.98 (0.95-1.02) I^2=59%, ph=0.09	6 0.88 (0.71-0.99) I^2=81%, ph <0.01	-	4 0.83 (0.66-1.06) I^2=44%, ph=0.15	9 0.91 (0.85-0.98) I^2=57%, ph <0.01	3 0.74 (0.51-1.06) I^2=81%, ph <0.01
Stratified linear dose-response by adjustment for smoking						
Smoking status only(n)	2 0.74 (0.56-0.97) I^2=0%, ph =0.39	2 1.01(0.87-1.17) I^2=0%, ph=0.90	-	-	2 0.69(0.38-1.24) I^2=66%, ph =0.09	1 0.35(0.11-1.05)
Intensity and duration of smoking (n)	12 0.96 (0.94-0.99) I^2=64%, ph <0.01	18 0.93(0.88-0.98) I^2=53%, ph< 0.01	-	-	21 0.92 (0.89-0.96) I^2=57%, ph <0.01	9 0.93(0.87-0.99) I^2=42% , ph =0.09
Stratified linear dose-response by outcome						
Incidence(n)	-	16 0.94 (0.89-0.90)) I^2=56%,ph < 0.01	-	-	18 0.93 (0.89-0.97) I^2=62%, ph< 0.001	10 0.92(0.86-0.99) I^2=48%, ph =0.05
Mortality(n)	-	4 0.97 (0.85- 1.11) I^2=0%, phph =0.67	-	-	5 0.82 (0.72- 0.94) I^2=0%, ph=0.74	1 0.58(0.35-0.96)
Stratified linear dose-response by cancer type						
Small cell carcinoma (n)	-	2 0.94 (0.66-1.32) I^2=48%, ph=0.17	-	-	3 0.84 (0.62-1.15) I^2=38%, ph =0.21	-
Squamous cell carcinoma (n)	-	2 1.00(0.90-1.12) I^2=0%, ph=0.61	-	-	2 0.88 (0.70-1.11) I^2=15%, ph =0.28	-
Adenocarcinoma(n)	-	4 0.98 (0.91-1.07) I^2=0%, ph=0.84	-	-	5 0.94 (0.83-1.07) I^2=34%, ph =0.19	-

	Stratified linear dose-response by geographic location					
Asia(n)	3 0.96 (0.90- 1.03) I^2=14% , ph=0.31	5 0.98 (0.93- 1.04) I^2=0% , ph=0.97	2 0.94 (0.88- 1.00) I^2=0% , ph=0.83	3 0.90 (0.82- 0.99) I^2=0% , ph=0.76	6 0.94 (0.83- 1.06) I^2=60% , ph =0.01	3 0.66 (0.41- 1.04) I^2=37% , ph =0.21
Europe (n)	4 0.90 (0.82-0.99) I^2=84% , ph<0.01	6 0.88 (0.78-0.99) I^2=64% , ph=0.02	2 0.98 (0.85-1.12) I^2=0% , ph=0.46	2 0.97 (0.89-1.06) I^2=0% , ph=0.52	6 0.91 (0.88-0.96) I^2=20% , ph =0.28	3 0.94 (0.85-1.03) I^2=0% , ph =0.59
North America(n)	7 0.98 (0.95-1.01) I^2=40%, ph=0.25	8 0.95 (0.90-1.02) I^2=30%, ph=0.17	7 0.84 (0.72-0.98) I^2=57%, ph=0.03	3 0.76 (0.48-1.22) I^2=80%, ph=<0.01	11 0.91 (0.86-0.97) I^2=61%, ph <0.01	5 0.92 (0.84-1.01) I^2=68%, ph =0.02
$P_{non\text{-}linearity}$, n	p<0.01, 11	p<0.01, 15	p < 0.01, 9	p < 0.01, 8	p<0.01, 14	p<0.01, 8

ph p for heterogeneity
n denotes the number of studies
N the number of cases

Figure 1 Flowchart of study selection

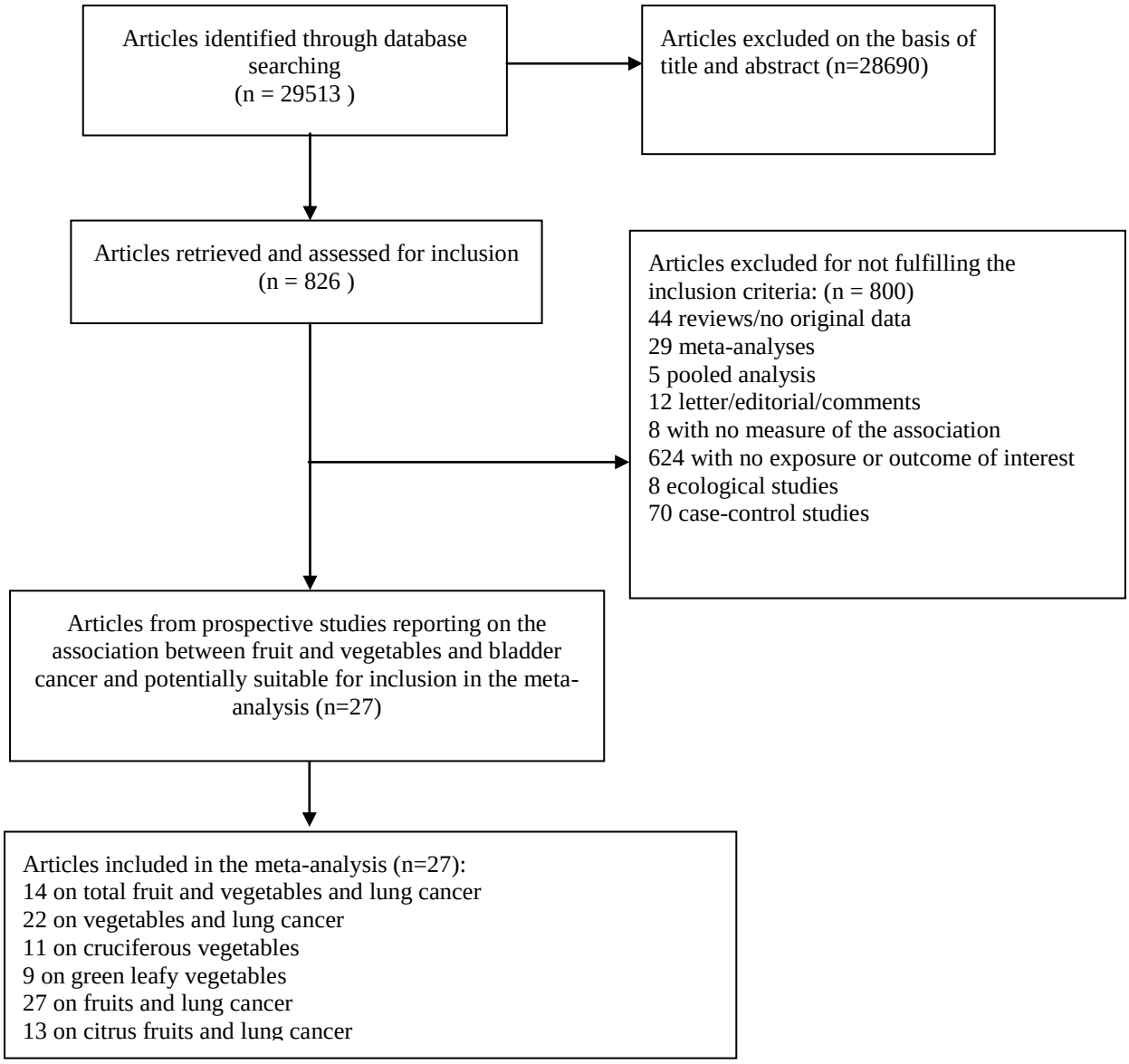
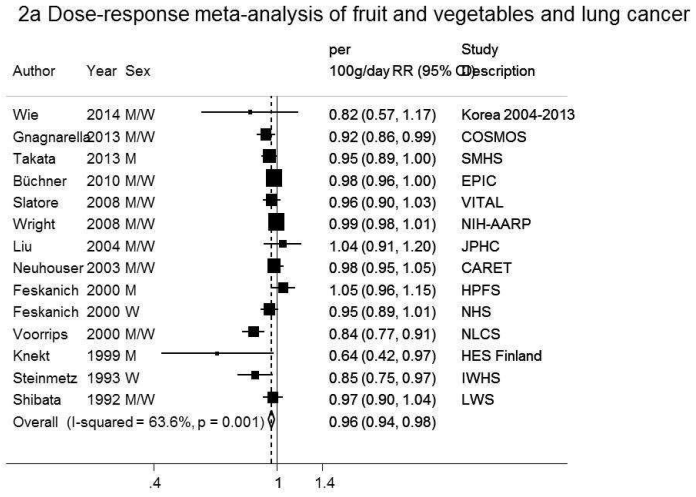
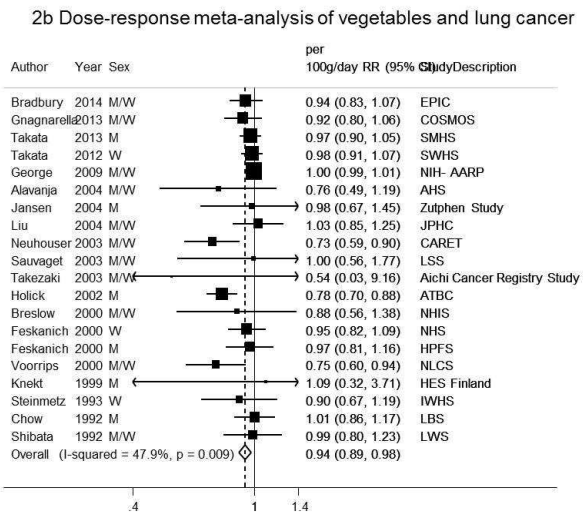
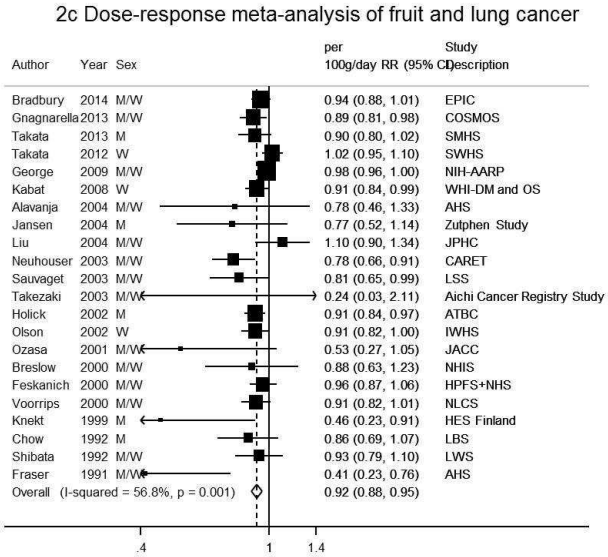
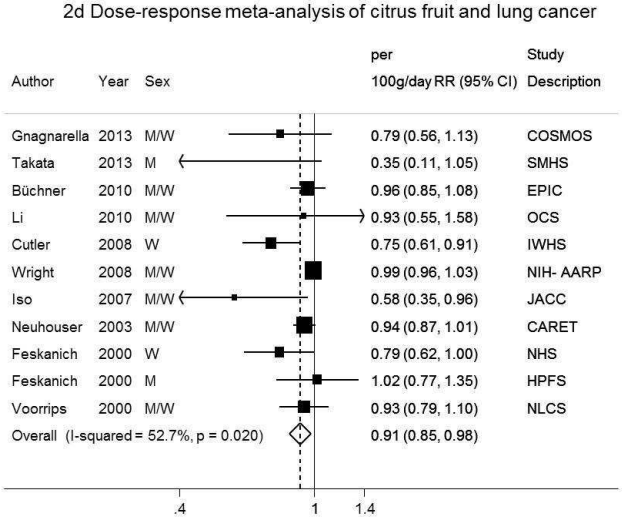


Figure 2 Dose-response meta-analysis of fruit and vegetables and lung cancer (2a, 2b, 2c, 2d)



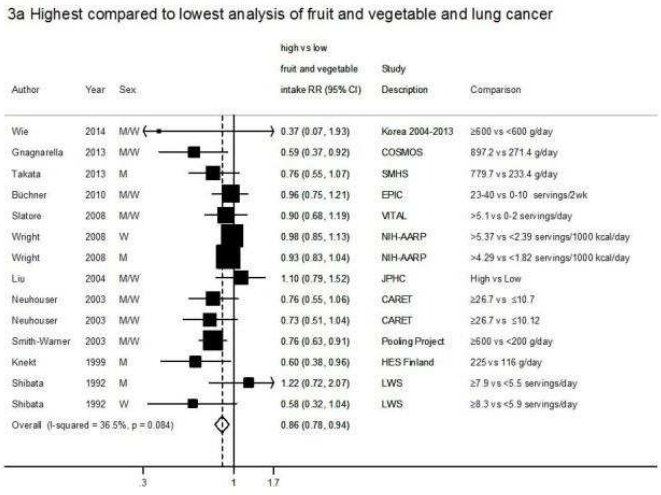


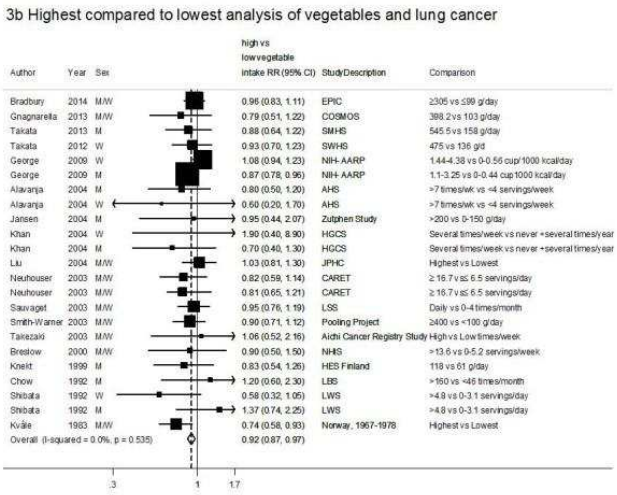


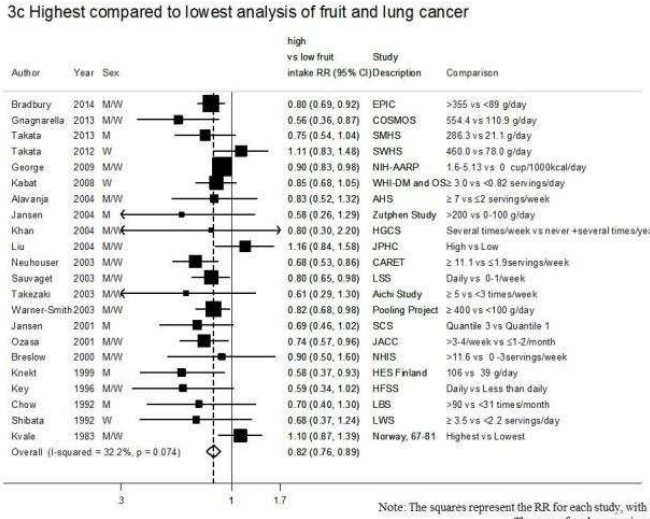


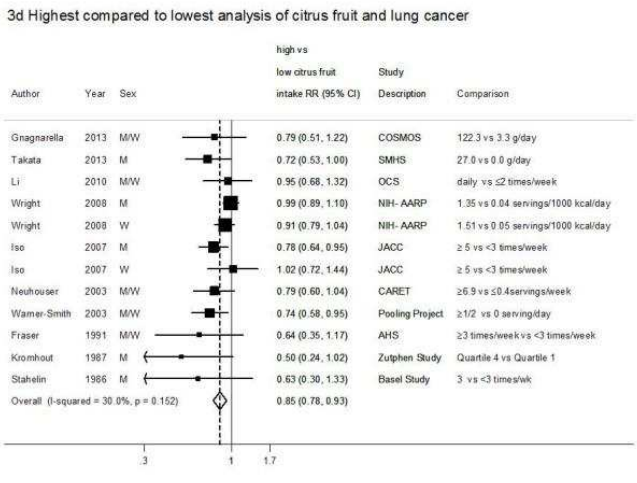
Note: The squares represent the RR for each study, with horizontal lines indicating the 95% confidence interval around this estimate.
The area of each square is proportional to its weighting in the meta-analysis.
The diamond represents the pooled estimate, with 95% confidence interval.

Figure 3 Highest compared to lowest analysis of fruit and vegetables and lung cancer (3a, 3b, 3c, 3d)





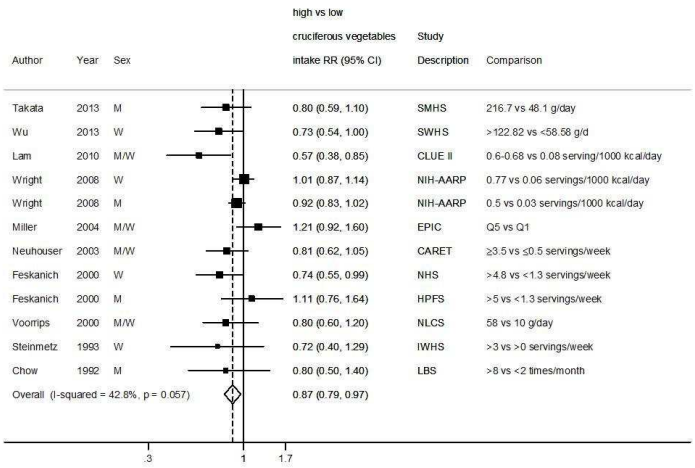




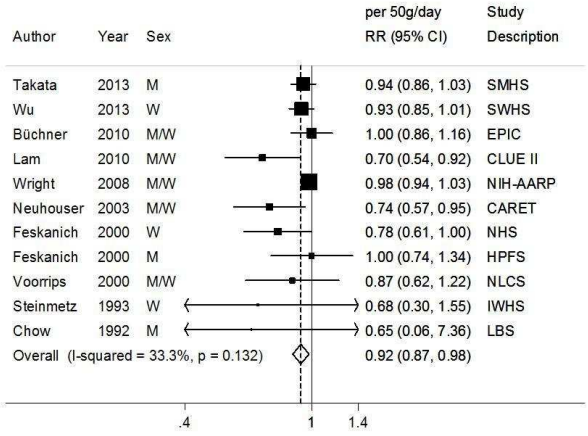
Note: The squares represent the RR for each study, with horizontal lines indicating the 95% confidence interval around this estimate.
The area of each square is proportional to its weighting in the meta-analysis.
The diamond represents the pooled estimate, with 95% confidence interval.

Figure 4 Highest compared to lowest and dose-response meta-analysis of subtypes of vegetables (4a, 4b, 4c, 4d)

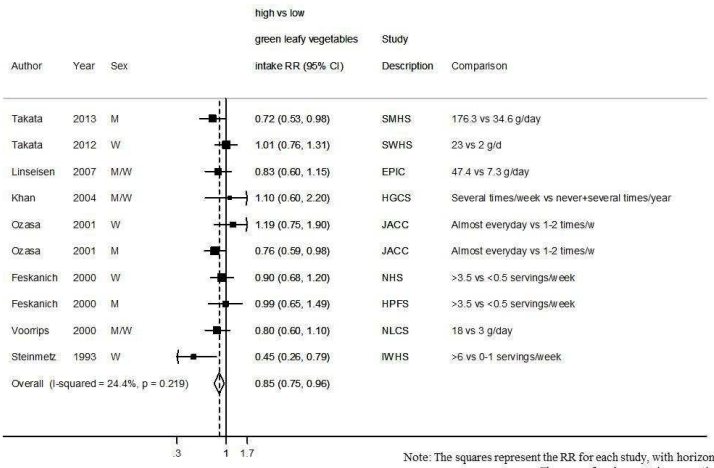
4a Highest compared to lowest analysis of cruciferous vegetables and lung cancer



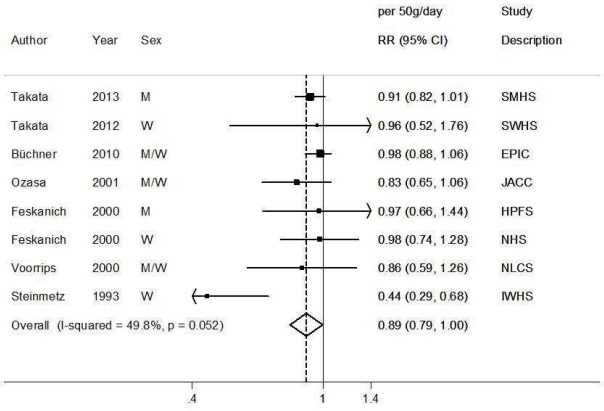
4b Dose-response meta-analysis of cruciferous vegetables and lung cancer



4c Highest compared to lowest analysis of green leafy vegetables and lung cancer

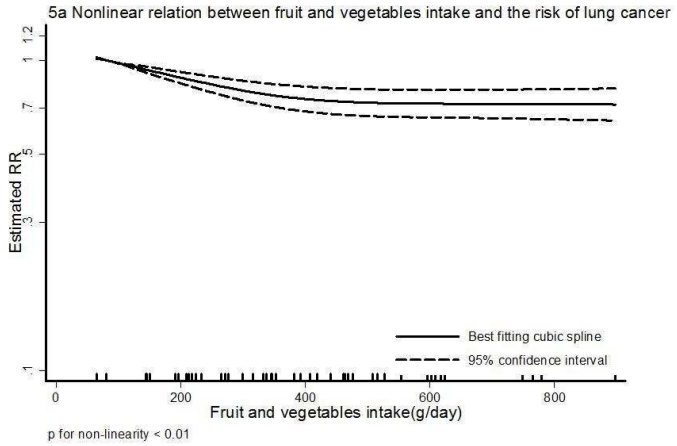


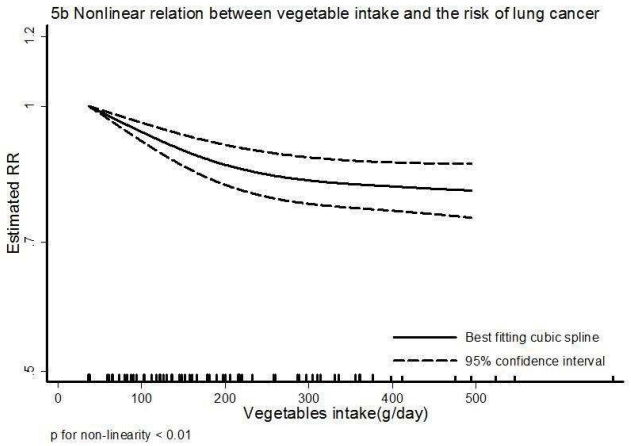
4d Dose-response meta-analysis of green leafy vegetables and lung cancer

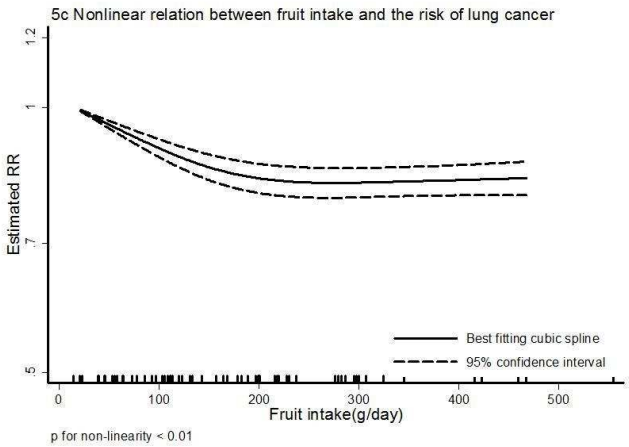


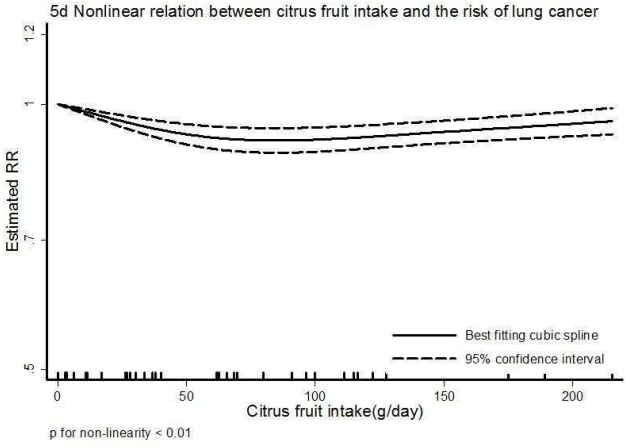
Note: The squares represent the RR for each study, with horizontal lines indicating the 95% confidence interval around this estimate.
The area of each square is proportional to its weighting in the meta-analysis.
The diamond represents the pooled estimate, with 95% confidence interval.

Figure 5 Non-linear dose-response analysis (5a, 5b, 5c, 5d)



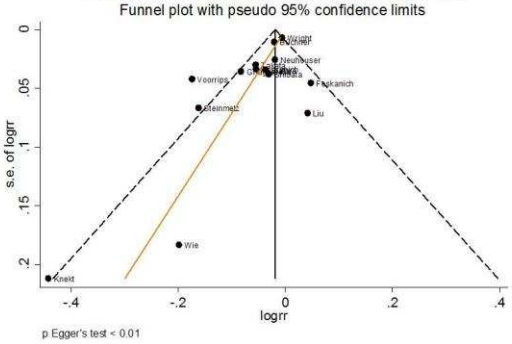




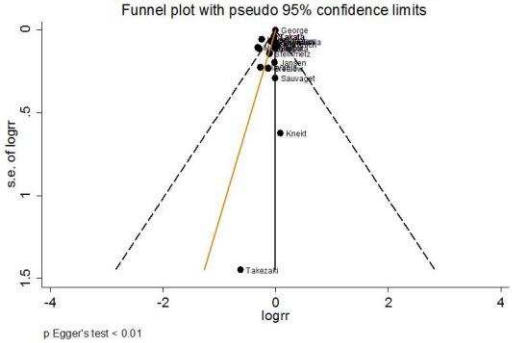


Supplementary figures (S1-S8)

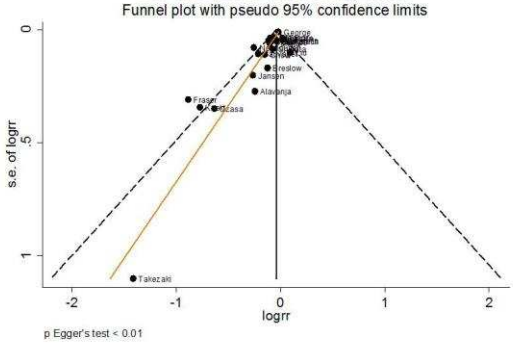
S1 Funnel plot of fruit and vegetable and lung cancer
Funnel plot with pseudo 95% confidence limits



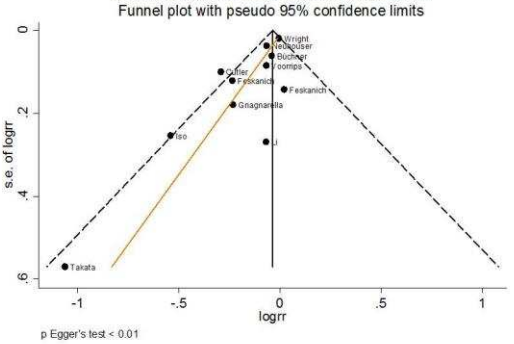
S2 Funnel plot of vegetables and lung cancer
Funnel plot with pseudo 95% confidence limits



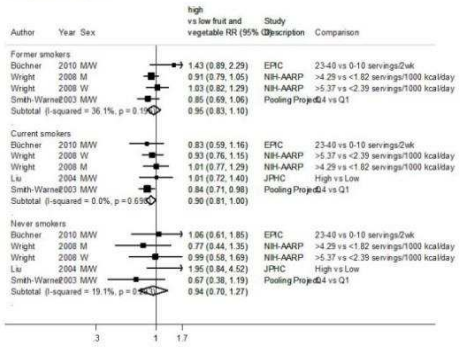
S3 Funnel plot of fruit and lung cancer
Funnel plot with pseudo 95% confidence limits



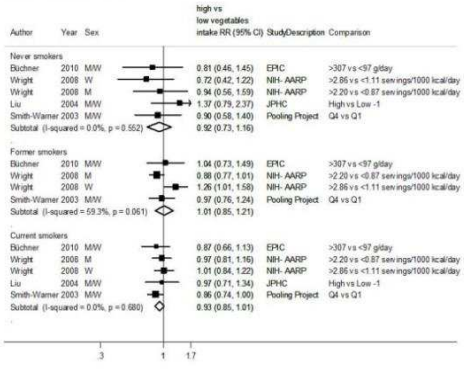
S4 Funnel plot of citrus fruit and lung cancer
Funnel plot with pseudo 95% confidence limits



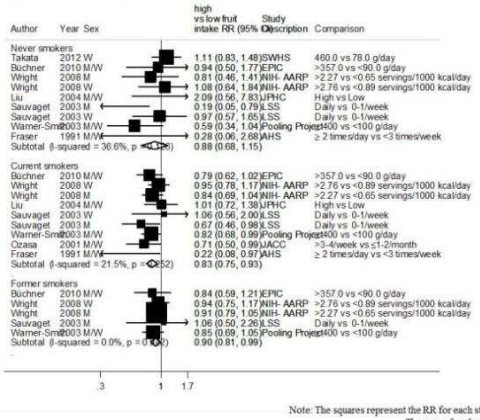
S5 Highest compared to lowest analysis of fruit and vegetables and lung cancer, stratified by smoking status



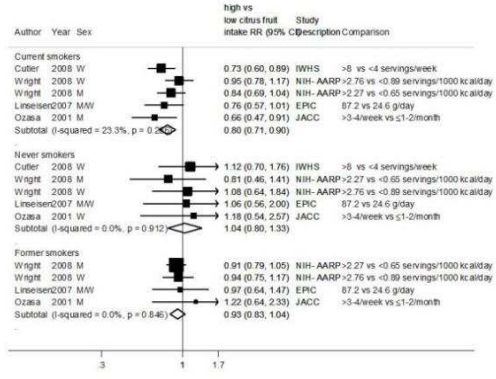
S6 Highest compared to lowest analysis of vegetables and lung cancer, stratified by smoking



S7 Highest compared to lowest analysis of fruit and lung cancer, stratified by smoking status



S8 Highest compared to lowest analysis of citrus fruit and lung cancer, stratified by smoking status



Note: The squares represent the RR for each study, with horizontal lines indicating the 95% confidence interval around this estimate.
The area of each square is proportional to its weighting in the meta-analysis.
The diamond represents the pooled estimate, with 95% confidence interval.