

Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality – a systematic review and dose-response meta-analysis of prospective studies



Journal:	<i>International Journal of Epidemiology</i>
Manuscript ID	IJE-2016-01-0094.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Key Words:	Fruit and vegetables, Diet, Cardiovascular disease, Cancer, All-cause mortality, Cohort

Fruit and vegetable intake and the risk of cardiovascular
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review and dose-response meta-analysis of prospective studies

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Word count (abstract): 277

Word count (text): 7036

Abstract

Background: Questions remain about the strength and shape of the dose-response relationship between fruit and vegetable intake and risk of cardiovascular disease, cancer and mortality, and the effects of specific types of fruit and vegetables. We conducted a systematic review and meta-analysis to clarify these questions.

Methods and Results: PubMed and Embase were searched up to 29th of September 2016. Prospective studies of fruit and vegetable intake and cardiovascular disease, total cancer and all-cause mortality were included. Summary RRs were calculated using a random effects model and the mortality burden globally was estimated. Ninety five studies (142 publications) were included. For fruits and vegetables combined, the summary RR per 200 g/day was 0.92 (95% CI: 0.90-0.94, $I^2=0\%$, $n=15$) for coronary heart disease, 0.84 (95% CI: 0.76-0.92, $I^2=73\%$, $n=10$) for stroke, 0.92 (95% CI: 0.90-0.95, $I^2=31\%$, $n=13$) for cardiovascular disease, 0.97 (95% CI: 0.95-0.99, $I^2=49\%$, $n=12$) for total cancer, and 0.90 (95% CI: 0.87-0.93, $I^2=83\%$, $n=15$) for all-cause mortality. Similar associations were observed for fruits and vegetables separately. Reductions in risk were observed up to 700-800 g/day for all outcomes except cancer (600 g/day). Inverse associations were observed between apples or pears, citrus fruits, green leafy vegetables, cruciferous vegetables, and salads and cardiovascular disease and mortality, and between green yellow vegetables and cruciferous vegetables and total cancer risk. An estimated 5.6 and 7.8 million premature deaths worldwide in 2013 may be attributable to a fruit and vegetable intake below 500 and 800 grams per day, respectively.

Conclusion: Fruits and vegetable intakes were associated with reduced risk of cardiovascular disease, cancer and mortality. These results supports public health recommendations to increase fruit and vegetable intake for chronic disease prevention.

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Key words: Fruit and vegetables, diet, nutrition, cardiovascular disease, cancer, all-cause
mortality, cohort, global assessment

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Key messages

Although a high fruit and vegetable intake has been recommended for prevention of cardiovascular disease, questions remain with regard to the amounts and types of fruits and vegetables that are most strongly associated with a reduced risk of cardiovascular disease, total cancer or all-cause mortality and with regard to the burden of disease and mortality that may be attributed to a low fruit and vegetable intake.

In this meta-analysis of 95 studies (142 publications) reductions in risk of cardiovascular disease and all-cause mortality were observed up to an intake of 700-800 grams per day of fruit and vegetable intake, while for total cancer no further reductions in risk were observed above 600 grams per day.

Inverse associations were observed between intake of apples or pears, citrus fruits, green leafy vegetables, cruciferous vegetables, and salads and cardiovascular disease and mortality, and between green yellow vegetables and cruciferous vegetables and total cancer risk.

An estimated 5.6 and 7.8 million premature deaths worldwide in 2013 may be attributable to a fruit and vegetable intake below 500 and 800 grams per day, respectively.

Introduction

A high intake of fruit and vegetables is one of the cornerstones of a healthy diet and has been recommended to the general public as a way to reduce the risk of cardiovascular diseases and cancer, which are the two most common causes of premature death worldwide and which accounted collectively for 25.5 million deaths in 2013.¹ These recommendations have to a large degree been based on findings from epidemiological studies which have shown inverse associations between high fruit and vegetable intake and risk of certain cancers,² coronary heart disease,³ and stroke.⁴ However, the question of what is the *optimal* level of fruit and vegetable intake to reduce the risk of chronic diseases and premature death is still unanswered. This is reflected by the fact that recommendations for dietary intake vary globally. For example current recommendations for fruit and vegetables intake ranges from at least 400 grams per day by the World Cancer Research Fund, to 500 grams per day in Norway, to 600 grams per day in Denmark and 640-800 grams per day in the US (Table 5.2, page 60 in the report).⁵

Data regarding fruit and vegetable intake and cancer risk is less clear-cut today² than a decade or two ago.⁶ A modest association between fruit and vegetable intake or specific subtypes of fruits and vegetables and total cancer risk cannot yet be excluded,⁷ but the available studies have been inconsistent.⁷⁻²¹ Some studies reported inverse associations,^{7, 8, 11-13, 17, 21} while other studies found no clear association,^{9, 10, 14-16, 18-20} however, some of these may have had too low statistical power to detect a modest association.^{9, 10, 14} Cohort studies have been more consistent in finding an inverse association between fruit and vegetable intake and risk of coronary heart disease and stroke^{11, 22, 23} than for cancer, and this has also been shown in meta-analyses,^{3, 4} as well as in several additional studies that have been published since these meta-analyses.^{16, 19, 23-29} In addition, several,^{10, 18, 27, 30-33} but not all,³⁴⁻⁴⁰ cohort studies have found inverse associations between fruit and vegetable intake and all-cause

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mortality, but again, some of these studies may have had too low statistical power to detect an association.^{34-36, 38}

However, the question of what is an *optimal* intake of fruit and vegetables remains unclear because the shape of the dose-response relationship between fruit and vegetable intake and cardiovascular disease and total cancer incidence and mortality and all-cause mortality has not been well defined. Although a recent meta-analysis found a reduced risk of all-cause mortality and cardiovascular disease mortality, but not cancer mortality, with greater fruit and vegetable intake,⁴¹ the review missed or excluded a large number of publications on all-cause mortality^{11, 18, 30, 33-38, 42-52} and included only studies of cardiovascular disease mortality and cancer mortality, not of disease incidence. Further, at least sixteen additional cohort studies (17 publications) have since been published,^{29, 53-68} thus questions remain with regard to the strength and shape of the dose-response relationship between fruit and vegetable intake and chronic disease risk and mortality and whether fruit and vegetables also reduces the risk of incident cardiovascular disease or cancer. In addition, it is not clear whether specific types of fruits and vegetables are particularly beneficial with regard to reducing chronic disease risk and mortality, since previous reviews have not analysed fruit and vegetable subtypes.^{3, 4, 41}

We conducted a systematic review and meta-analysis of published cohort studies relating fruit and vegetable consumption to risk of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, total cancer and all-cause mortality, and we specifically aimed to clarify the strength and shape of the dose-response relationship for these associations and whether specific types of fruit and vegetables were associated with risk. At last we calculated the attributable fractions of all-cause and cause-specific mortality globally and by region under the assumption that the observed associations are causal.

Methods

Search strategy and inclusion criteria

We searched the PubMed and Embase databases from their inception (1966 and 1947, respectively) up to 19th of July 2016 and the search was later updated to 29th of September 2016. Details of the search terms used for the PubMed search are shown in Supplementary Table 1 and a similar search was conducted in Embase. Prospective studies of fruit and vegetable intake and risk of incidence or mortality from coronary heart disease (total coronary heart disease or major coronary event, nonfatal myocardial infarction (MI), MI, fatal MI, incident ischemic heart disease, fatal ischemic heart disease, acute coronary syndrome), stroke (total stroke, ischemic, hemorrhagic, intracerebral and subarachnoidal hemorrhage), total cardiovascular disease (coronary heart disease and stroke combined), total cancer and all-cause mortality were included if they reported adjusted estimates of the relative risk (RR) (including odds ratios and hazard ratios) and 95% confidence intervals (CIs) and for the dose-response analyses a quantitative measure of the intake for at least 3 categories of fruit and vegetable intake had to be available. The excluded studies are listed in Supplementary Table 2.

Data extraction

Results and study characteristics were extracted into tables and included: name of first author, publication year, country, the name of the study, follow-up period, sample size and number of cases or deaths, type of outcome, gender, age, type of fruit and vegetables, amount or frequency of intake, RRs and 95% CIs and variables adjusted for in the analysis. We followed standard criteria for reporting meta-analyses.⁶⁹ The data extraction was conducted by DA, and was checked for accuracy by LTF and NK.

Statistical methods

We calculated summary relative risks (RRs) of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, total cancer and all-cause mortality for the highest vs. the lowest level and per 200 g/d of fruits, vegetables and total fruit and vegetable intake using the random-effects model by DerSimonian and Laird⁷⁰ which takes into account both within and between study variation (heterogeneity). For specific types of fruits and vegetables we calculated summary RRs using 100 g/d as the increment. The average of the natural logarithm of the RRs was estimated and the RRs from each study were weighted by the method of DerSimonian and Laird.⁷⁰ The primary analysis of coronary heart disease, stroke, cardiovascular disease and total cancer included studies that reported both on incidence and mortality from these outcomes, but subgroup analyses were conducted separately for incidence and mortality. For studies that provided results stratified by gender, smoking status, or other subgroups, the relative risks were pooled using a fixed effects model before inclusion in the meta-analysis. One exception is a study which published separately on white³⁷ and black³⁰ subjects in two different publications and which had different durations of follow-up in the two publications and in this case both results were included without combining the subgroups. For two studies we recalculated the confidence intervals from 99% to 95%.^{43, 60}

We conducted linear dose-response analyses using the method by Greenland and Longnecker⁷¹ to calculate RRs and 95% CIs from the natural logarithm of the risk estimates across categories of intake. For each category of fruit and vegetable intake we used the mean or median if reported and the midpoint of the upper and lower bound was estimated for the remaining studies. When extreme categories were open-ended we used the width of the adjacent interval to calculate an upper or lower cut-off value. Consistent with previous meta-analyses we used 80 grams as a serving size for fruit and vegetable intake.^{72, 73} For specific fruit and vegetable types we used serving sizes as provided in a pooled analysis of cohort

studies,⁷⁴ but for some subtypes of fruits and vegetables which were not reported on in this publication we used 80 grams as a serving size as well. We contacted the authors of six studies^{16, 56, 61, 64, 75, 76} for information regarding the quantities of consumption for subtypes of fruits and vegetables or for more details of data which were only briefly described in the text and all replied and provided supplementary information.^{16, 56, 61, 64, 75, 76}

A potential nonlinear dose-response relationship between fruit and vegetable intake and cardiovascular disease, cancer and mortality risks was assessed using restricted cubic splines with 3 knots at 10%, 50%, and 90% percentiles of the distribution which was combined using multivariate meta-analysis.^{77, 78} We conducted a sensitivity analysis using fractional polynomial models for the nonlinear analysis as well,⁷⁹ and we determined the best-fitting second-order fractional polynomial regression model, which was defined as the one with the lowest deviance.

Heterogeneity between studies was evaluated using Q and I² statistics.⁸⁰ To explore potential heterogeneity we conducted subgroup analyses by study characteristics. Small study effects such as publication bias was assessed using Egger's test⁸¹ and by inspection of the funnel plots. When Egger's test indicated bias we tested whether this affected the results by excluding studies with a low number of cases or by excluding obvious outlying studies based on inspection of the funnel plots. We also conducted sensitivity analyses excluding each study at a time from each analysis to clarify if the results were robust. Study quality was assessed using the Newcastle-Ottawa scale which awards 0-9 stars based on the selection, comparability and outcome assessment.⁸² We considered studies with scores of 0-3, 4-6, and 7-9 to represent low, medium and high quality studies. Stata, version 13.0 software (StataCorp, Texas, US) was used for the analyses.

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Attributable fractions

We calculated the fraction of deaths attributable worldwide due to low fruit and vegetable intake, assuming a causal relationship, using the relative risks from the nonlinear dose-response analysis. The prevalence of low fruit and vegetable intake was calculated based on data from the World Health Survey which provided estimates of fruit and vegetable intake from 26 national population-based surveys covering 14 geographical regions.^{83, 84} We used data on mortality from the Global Burden of Disease Study 2013.¹ Because all the epidemiological studies included in this meta-analysis have been conducted in mainly adult populations we excluded the number of deaths occurring before 15 years age as well as the intake levels for subjects <15 years. The preventable proportion of deaths and cause-specific deaths attributable to a low fruit and vegetable intake was calculated using the formula proposed by Miettinen.⁸⁵ Further information about these calculations are provided in the Supplementary Methods.

Results

One hundred and forty two publications from 95 unique cohort studies were included in the analyses^{7-40, 42-68, 75, 76, 86-164} (Figure 1, Supplementary Table 3-7). Forty four studies were from Europe, 26 were from the US, 20 from Asia and 5 from Australia. One of the included publications reported results from two studies combined.⁵⁴ Throughout the text the total number of studies and publications are reported, but the number included in each high vs. low analysis and dose-response analysis may differ slightly because some studies only reported dichotomous results or results on a continuous scale. The number of studies, cases, participants and the references included in each high vs. low and dose-response analysis is provided in Table 1. The number of cases or deaths ranged between 17 742 and 43 336 for coronary heart disease, 10 560 and 46 951 for stroke, 20 329 and 81 807 for cardiovascular disease, 52 872 and 112 370 for total cancer, and 71 160 and 94 235 for all-cause mortality (Table 1). The number of participants in each analysis ranged from 226 910 to 2 123 415 (any outcome) (Table 1). Supplementary Table 3-7 shows a summary of the study characteristics of the included studies. Figure 1 shows a flow-chart of the study selection process. Figures 2-6 shows the results for the dose-response analyses and Supplementary Figures 1-31 shows the high vs. low analyses for all outcomes and the high vs. low, linear and nonlinear dose-response analyses for ischemic and hemorrhagic stroke. Results for subtypes of fruit and vegetables are shown in Table 2-6, Supplementary Tables 19-27, and Supplementary Figures 32-242.

Coronary heart disease

Seventeen studies (15 publications),^{23, 29, 31, 32, 56, 58, 64, 86, 88, 90, 91, 93, 94, 98, 132} twenty six studies (26 publications),^{9-11, 22, 23, 27, 29, 36, 55, 56, 58, 60, 62-64, 86, 88, 91, 92, 94, 95, 98-100, 104, 132} and twenty three studies (23 publications)^{9, 10, 22, 23, 27, 29, 34, 55, 56, 58, 62, 64, 86, 88, 91, 94, 95, 98, 100, 101, 103, 104, 132} were

included in the analyses of fruit and vegetables combined, fruits, and vegetables and coronary heart disease, respectively. The summary RR per 200 g/d was 0.92 (95% CI: 0.90-0.94, $I^2=0\%$) for fruits and vegetables (Figure 2a,2b, Table 1, Supplementary Figure 1), 0.90 (95% CI: 0.86-0.94, $I^2=44\%$) for fruits (Figure 2c, 2d, Table 1, Supplementary Figure 2), and 0.84 (95% CI: 0.79-0.90, $I^2=61\%$) for vegetables (Figure 2e, 2f, Table 1, Supplementary Figure 3). Although the statistical test indicated nonlinearity, $p_{\text{nonlinearity}} < 0.0001$, for fruits and vegetables, $p_{\text{nonlinearity}} < 0.0001$, the association was nearly linear from ≥ 200 grams per day with a 25% reduction in the relative risk at an intake of 800 grams per day (Figure 2b, Supplementary Table 8). Nonlinear associations were observed for fruits, $p_{\text{nonlinearity}} = 0.06$ (Figure 2d, Supplementary Table 9), and vegetables, $p_{\text{nonlinearity}} < 0.0001$ (Figure 2f, Supplementary Table 9), with most of the reductions in risk observed at the lower levels of intake, and there was a 23% reduction in relative risk up to 750 grams per day for fruits and a 30% reduction in the relative risk up to 550-600 grams per day for vegetables. Of specific types of fruit and vegetables^{9, 10, 34, 36, 56, 60, 62, 64, 89, 91, 94, 96, 97, 100, 102, 105, 106, 140-148, 163, 164} apples/pears, citrus fruits, fruit juices, green leafy vegetables, beta-carotene rich fruits and vegetables, and vitamin C-rich fruits and vegetables showed inverse associations with coronary heart disease in the high vs. low analysis and in addition tomatoes were inversely associated with coronary heart disease in the dose-response analysis (Table 2, Supplementary Table 19-20, Supplementary Figure 32-76).

Stroke

Ten studies (10 publications),^{31, 56, 58, 64, 108-110, 118, 120, 122} seventeen studies (17 publications),^{25-27, 55, 56, 58, 60, 62-64, 109, 112-114, 116, 117, 126} and fifteen studies (16 publications)^{11, 25-27, 55, 56, 58, 62, 64, 109, 112, 113, 115-117, 126} were included in the analysis of fruit and vegetables, fruits, and vegetables and total stroke risk, respectively. The summary RR per 200 g/d was 0.84 (95%

CI: 0.76-0.92, $I^2=73\%$) for fruits and vegetables (Figure 3a, 3b, Table 1, Supplementary Figure 4), 0.82 (95% CI: 0.74-0.90, $I^2=73\%$) for fruits (Figure 3c, 3d, Table 1, Supplementary Figure 5), and 0.87 (95% CI: 0.79-0.96, $I^2=63\%$) for vegetables (Figure 3e, 3f, Table 1, Supplementary Figure 6). There was evidence of a nonlinear association between fruit and vegetable, fruits, and vegetables and total stroke, $p_{\text{nonlinearity}}=0.008$ (Figure 3b, Supplementary Table 10), $p_{\text{nonlinearity}}<0.0001$ (Figure 3d, Supplementary Table 11), $p_{\text{nonlinearity}}=0.0001$ (Figure 3f, Supplementary Table 11), with stronger reductions in risk at lower levels of intake. There was a 24% reduction in the relative risk at intakes of 750 grams per day of fruits and vegetables, 21% reduction in relative risk at 300 grams per day of fruits and 26% reduction in relative risk at 500 grams per day of vegetables, and there was little evidence of further reductions in risk at higher intakes.

Seven studies (5 publications, 6 risk estimates),^{108-111, 120} eleven studies (10 publications),^{25-27, 109, 112-114, 116, 117, 126} and nine studies (8 publications)^{25-27, 109-111, 113, 116} were included in the analyses of fruits and vegetables, fruits, and vegetables and ischemic stroke, respectively. The summary RR per 200 g/d was 0.92 (95% CI: 0.87-0.97, $I^2=9\%$) for fruits and vegetables (Supplementary Figure 7, 8, 9, Supplementary Table 12, 28), 0.78 (95% CI: 0.69-0.89, $I^2=58\%$) for fruits (Supplementary Figure 10, 11, 12, Supplementary Table 12, 28) and 0.86 (95% CI: 0.76-0.97, $I^2=55\%$) for vegetables (Supplementary Figure 13, 14, 15, Supplementary Table 12, 28). Three studies (2 publications, 2 risk estimates)^{108, 109}, eight studies (7 publications, 7 risk estimates),^{19, 25-27, 63, 109, 113} and six studies (5 publications, 5 risk estimates)^{19, 25, 27, 63, 113} were included in the analyses of fruits and vegetables, fruits, and vegetables and hemorrhagic stroke, respectively. The summary RR per 200 g/d was 0.88 (95% CI: 0.78-0.99, $I^2=0\%$) for fruits and vegetables combined (Supplementary Figure 16, Supplementary Table 28), 0.66 (95% CI: 0.50-0.86, $I^2=57\%$) for fruits (Supplementary Figure

17-19, Supplementary Table 13, 28), and 0.76 (95% CI: 0.55-1.06, $I^2=42\%$) for vegetables (Supplementary Figure 20-22, Supplementary Table 13, 28).

Of specific types of fruit and vegetables^{26, 56, 60, 62, 64, 109, 112, 119, 141-144, 146, 148-150} high intakes of apples and pears, citrus fruits, fruit juice, green leafy vegetables, and pickled vegetables were inversely associated with total stroke risk, while intake of grapes was additionally inversely associated with total stroke in the dose-response analysis (Table 3, Supplementary Table 21-22, Supplementary Figure 77-109). For ischemic stroke^{26, 109-111, 121, 146, 150, 162, 164} there was evidence that intake of citrus fruits, citrus fruit juices, green leafy vegetables, and vitamin C-rich fruits and vegetables were inversely associated with risk, but none of the associations with hemorrhagic stroke were significant (Table 3, Supplementary Table 23, Supplementary Figure 110-140).

Cardiovascular disease

Seventeen studies (16 publications),^{15, 16, 18, 31, 39, 42, 53, 56, 58, 64, 75, 86-88, 98, 125} twenty four studies (23 publications)^{11, 15, 16, 19, 24, 27, 53-56, 58, 60-64, 75, 76, 88, 98, 124, 125, 127} and twenty one studies (20 publications)^{15, 16, 19, 24, 27, 53-58, 62, 64, 75, 76, 88, 98, 124, 125, 127} were included in the analysis of fruit and vegetables, fruits, and vegetables and cardiovascular disease, respectively. The summary RR was 0.92 (95% CI: 0.90-0.95, $I^2=31\%$) for fruits and vegetables (Figure 4a, 4b, Table 1, Supplementary Figure 16), 0.87 (95% CI: 0.82-0.92, $I^2=79\%$) for fruits (Figure 4c, 4d, Table 1, Supplementary Figure 17), and 0.90 (95% CI: 0.87-0.93, $I^2=12\%$) for vegetables (Figure 4e, 4f, Table 1, Supplementary Figure 18) and evidence of nonlinearity, $p_{\text{nonlinearity}}=0.005$, for fruits and vegetables (Figure 4b, Supplementary Table 14), and fruits, $p_{\text{nonlinearity}}<0.0001$, (Figure 4d, Supplementary Table 15), and for vegetables, $p_{\text{nonlinearity}}=0.04$ (Figure 4f, Supplementary Table 14), with steeper inverse associations at lower levels of intake, although for vegetables the association was approximately linear. There were 27%, 31%, and 27%

reductions in relative risk at intakes of 800 grams per day for fruits and vegetables and fruits, and 600 grams per day of vegetables, respectively.

Of specific types of fruits and vegetables^{11, 16, 19, 56, 60-62, 64, 75, 87, 123, 124, 129, 141, 142, 144, 146, 148, 151, 152, 154, 159, 164} there was evidence that high vs. low intake of apples or pears, citrus fruits, carrots, and noncruciferous vegetables were inversely associated, and tinned fruits were positively associated with cardiovascular disease risk and in the dose-response analysis there was evidence that cruciferous vegetables were inversely associated with risk, although few studies were included in these analyses (Table 4, Supplementary Table 24-25, Supplementary Figure 141-178).

Total cancer

Fourteen studies (13 publications),^{7, 8, 13, 15, 16, 18, 20, 42, 53, 56, 59, 87, 128} twenty four studies (22 publications),^{7-11, 13-17, 19-21, 53, 54, 56, 57, 59, 61, 65, 114, 128} and eighteen studies (17 publications),^{7-9, 13, 15-17, 19-21, 53, 54, 56, 57, 59, 65, 128} were included in the analysis of fruit and vegetables, fruits, and vegetables and total cancer, respectively. The summary RR was 0.97 (95% CI: 0.95-0.99, $I^2=49\%$) for fruits and vegetables combined (Figure 5a, 5b, Table 1, Supplementary Figure 19), 0.96 (95% CI: 0.94-0.99, $I^2=52\%$) for fruits (Figure 5c, 5d, Table 1, Supplementary Figure 20), and 0.96 (95% CI: 0.93-0.99, $I^2=55\%$) for vegetables (Figure 5e, 5f, Table 1, Supplementary Figure 21). There was evidence of nonlinearity for fruits and vegetables, $p_{\text{nonlinearity}}=0.02$ (Figure 5b, Supplementary Table 16), fruits, $p_{\text{nonlinearity}}=0.02$ (Figure 5d, Supplementary Table 17), and vegetables, $p_{\text{nonlinearity}}=0.03$ (Figure 5f, Supplementary Table 16), with most of the reductions in risk at lower levels of intake. There were 14%, 8%, and 12% reductions in the relative risk for intakes of 600 grams per day for fruits and vegetables, fruits, and vegetables, respectively, but there was little evidence of further reductions in risk with higher intakes.

Of specific types of fruits and vegetables^{8-12, 14-16, 19, 56, 87, 130, 143, 154-160} there was a significant inverse association between cruciferous vegetables and green-yellow vegetables and total cancer risk (Table 5, Supplementary Table 26, Supplementary Figure 179-209).

All-cause mortality

Twenty four studies (23 publications),^{18, 29, 31, 32, 39, 42-44, 47-50, 53, 56, 58, 67, 68, 75, 87, 98, 132, 134, 161} thirty five cohort studies (35 publications),^{9-11, 19, 27, 29, 30, 35-37, 40, 43, 45-47, 51, 52, 54-58, 61, 62, 66, 68, 75, 98, 131-133, 135-137, 139} and thirty two cohort studies (30 publications)^{9, 19, 27, 29, 33-35, 38, 40, 45-47, 51-58, 62, 66, 68, 75, 98, 131-133, 136, 137, 139} were included in the analysis of fruits and vegetables, fruits, and vegetables and all-cause mortality, respectively. The summary RR was 0.90 (95% CI: 0.87-0.93, $I^2=83\%$) for fruits and vegetables (Figure 6a, 6b, Table 1, Supplementary Figure 22), 0.85 (95% CI: 0.80-0.91, $I^2=90\%$) for fruits (Figure 6c, 6d, Table 1, Supplementary Figure 23), and 0.87 (95% CI: 0.82-0.92, $I^2=82\%$) for vegetables (Figure 6e, 6f, Table 1, Supplementary Figure 24). There was evidence of nonlinearity for fruits and vegetables, $p_{\text{nonlinearity}} < 0.0001$ (Figure 6b, Supplementary Table 18), fruits, $p_{\text{nonlinearity}} < 0.0001$ (Figure 6d, Supplementary Table 18), and vegetables, $p_{\text{nonlinearity}} < 0.0001$ (Figure 6f, Supplementary Table 18), respectively, with stronger reductions in risk at lower levels of intake. There were 32%, 22%, and 29% reductions in the relative risk with intakes of 800 grams per day for fruits and vegetables, and at 600 grams per day for fruits, and for vegetables separately, respectively.

Of specific types of fruits and vegetables^{9, 11, 19, 30, 34, 37, 38, 43, 44, 53, 54, 56, 61, 62, 67, 68, 75, 87, 133, 138, 143, 159} there was evidence that high vs. low intake of apples/pears, berries, citrus fruits, fruit juice, cooked vegetables, cruciferous vegetables, potatoes and salads were inversely associated with mortality and tinned fruits were positively associated with mortality, while in the dose-response analysis fruit juice, cruciferous vegetables, and salads were significantly

associated with reduced risk and tinned fruits were associated with increased risk (Table 6, Supplementary Table 27, Supplementary Figure 210-242).

Publication bias, subgroup and sensitivity analyses

There was evidence of publication bias in some of the analyses for coronary heart disease, stroke, cardiovascular disease, and mortality (Table 1-5, Supplementary Figure 243-248), however, excluding studies with <200 or <500 cases or outlying studies attenuated Egger's test in several of the analyses, but did not materially affect the strength of the associations. In the analyses of vegetables and mortality exclusion of two outlying studies explained the asymmetry in the funnel plots, but none of these exclusions materially altered the summary estimates. The results persisted in sensitivity analyses excluding one study at a time from each analysis (Supplementary Figure 249-263). We also repeated the nonlinear dose-response analyses using fractional polynomial models and in general found similar risk estimates compared to the restricted cubic spline models, although the confidence intervals were wider and there was more indication of nonlinearity (results not shown).

In subgroup analyses stratified by duration of follow-up, geographic location, number of cases, study quality and adjustment for confounding factors the findings persisted across most subgroups and there was little evidence of heterogeneity between most subgroups (Supplementary Table 28-32). The study quality was in general high as the vast majority of studies were in the group with 7-9 stars (Supplementary Table 28-32). There was suggestion of heterogeneity when studies of vegetables and coronary heart disease were stratified by adjustment for physical activity, with weaker (but still significant) associations among studies with such adjustment, $p_{\text{heterogeneity}}=0.003$, compared to studies without such adjustment. In the analysis of fruits and vegetables and cardiovascular disease there was a weaker association among studies with adjustment for BMI than among studies without such adjustment,

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$p_{\text{heterogeneity}}=0.03$, and in the analysis of vegetables and cardiovascular disease there was a stronger association among studies with mortality as the outcome compared to with incidence as the outcome, $p_{\text{heterogeneity}}=0.03$ (Supplementary Table 30). In the analysis of fruits and total cancer and mortality there was heterogeneity ($p_{\text{heterogeneity}}=0.03$ and $p_{\text{heterogeneity}}=0.02$, respectively) by adjustment for energy intake, with weaker (but still significant) associations in studies with such adjustment compared to without such adjustment (Supplementary Table 31-32). In the analysis of fruits and vegetables and mortality there was a weaker association among the studies that adjusted for red and processed meat intake, $p_{\text{heterogeneity}}<0.0001$, and in the analysis of vegetables and mortality there was a stronger association among the studies without adjustment for smoking than among studies with such adjustment, $p_{\text{heterogeneity}}=0.003$ (Supplementary Table 32).

Estimation of the fraction of deaths preventable by increasing fruit and vegetable intake

The number of premature deaths from coronary heart disease, stroke, cardiovascular disease, total cancer and all-causes attributable to a fruit and vegetable intake below 800 grams per day was 1 340 000 coronary heart disease deaths, 2 680 000 stroke deaths, 2 270 000 cardiovascular disease deaths, 660 000 cancer deaths and 7 800 000 all cause deaths (Table 7). We repeated these calculations using 500 grams per day as a reference category and arrived at 710 000 coronary heart disease deaths, 1 470 000 stroke deaths, 1 260 000 cardiovascular disease deaths, 560 000 cancer deaths, and 5 400 000 all-cause deaths (Table 7). The number of deaths for coronary heart disease and stroke was larger than for cardiovascular disease because the studies included in each analysis were not the same and showed stronger associations for stroke mortality than for coronary heart disease and cardiovascular disease mortality). The number of deaths attributable to a low fruit and

vegetable intake for each country is provided in Supplementary Table 33. In a sensitivity analysis, we only counted the cause-specific deaths (from CHD, stroke and total cancer) for Sub-Saharan Africa, and arrived at 5 240 000 and 7 630 000 premature deaths, globally for an intake of 500 and 800 g/d, respectively.

For Review Only

Discussion

There was a 8-16% reduction in the RR of coronary heart disease, 13-18% reduction in the RR of stroke, 8-13% reduction in the RR of cardiovascular disease, 3-4% reduction in the RR of total cancer, and 10-15% reduction in the RR of all-cause mortality for each 200 gram per day increment in intake of fruit, vegetables and fruit and vegetables combined. In the nonlinear models, there were 16%, 28%, 22%, 13% and 27% reductions in the RR of coronary heart disease, stroke, cardiovascular disease, total cancer and mortality, respectively, for an intake of 500 grams of fruits and vegetables per day versus 1-40 grams per day, while an intake of 800 grams/day was associated with 24%, 33%, 28%, 14%, and 31% reductions in the RR, respectively. Globally an estimated 710 000 coronary heart disease deaths, 1.47 million stroke deaths, 560 000 cancer deaths and 5.4 million premature deaths were attributable to a fruit and vegetable intake below 500 grams per day in 2013, and this increased to 1.34 million coronary heart disease deaths, 2.68 million stroke deaths, 660000 cancer deaths and 7.8 million deaths from all causes when using 800 grams per day as the optimal intake. Alternatively, using total cardiovascular disease instead of coronary heart disease and stroke mortality, an estimated 1.25 and 2.26 million cardiovascular disease deaths were attributable to a fruit and vegetable intake below 500 and 800 grams per day, respectively. There was evidence of nonlinearity in all analyses of fruits and vegetables combined, apart from one, and in most of the analyses the reduction in risk was steeper at the lower than at the higher range of fruit and vegetable intake. For fruits and vegetables combined the lowest risk was observed at an intake of 550-600 grams per day (7-7.5 servings/day) for total cancer, with little evidence of further reductions in risk with higher intakes, while for coronary heart disease, stroke, cardiovascular disease and all-cause mortality the lowest risk was observed at 700-800 grams per day (8.75-10 servings/day), which was at the high end of the range of intake across studies. Fruit and vegetable intake was

only weakly associated with overall cancer risk, particularly cancer incidence, which is consistent with the change in the assessment of the evidence for several individual cancers as well,² however, specific fruits and vegetables may be more strongly related to specific cancers. We found that several individual types of fruits and vegetables were inversely associated with coronary heart disease, stroke or cardiovascular disease (apples or pears, citrus fruits, cruciferous vegetables, green leafy vegetables, tomatoes, and beta-carotene-rich and vitamin C-rich fruit and vegetables), total cancer (cruciferous vegetables and green-yellow vegetables) and mortality (apples or pears, berries, citrus fruits, cooked vegetables, cruciferous vegetables, potatoes, and salads or green leafy vegetables). In contrast, intake of tinned fruits was associated with increased risk of cardiovascular disease and mortality. However, because of the low number of studies on fruit and vegetable subtypes, the potential for selective reporting and publication of subtypes that are significantly associated with risk, as well as confounding from other types of fruits and vegetables, further studies are needed.

Our meta-analysis is in general consistent with previous meta-analyses of fruit and vegetable intake and coronary heart disease,³ stroke,⁴ and mortality,⁴¹ but includes a much larger number of studies, more detailed dose-response, subgroup and sensitivity analyses, and results for subtypes of fruit and vegetables, and estimations of burden of disease and mortality due to a low fruit and vegetable intake as well. In comparison to the most recent meta-analysis on mortality which included less than half the studies in the present analysis, we found a stronger association between fruit and vegetable intake and all-cause mortality with reductions in risk observed up to 800 g/d, although the reduction in risk was steepest up to 400 g/d, while the previous meta-analysis found no further benefit above 5 servings per day (400 g/d).⁴¹ In addition, we found significant inverse associations with overall cancer risk, which are consistent with data for some individual cancer sites.^{2, 72, 73, 165-167} An interesting finding in the present meta-analysis is that fruit and vegetable intake was as strongly related to

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overall mortality as it was related to cardiovascular disease, but only modestly associated with cancer. One explanation may be that the studies included in each analysis do not fully overlap. In addition, it is possible that fruit and vegetable intake may be strongly associated with reduced incidence or mortality from other causes including respiratory, infectious, digestive, and inflammatory diseases,¹⁶⁸⁻¹⁷⁵, and recently in the EPIC-study inverse associations were also observed for all other causes of death for vegetables, and unknown causes of death for fruits,¹⁶⁹ however, the available evidence for all these outcomes is very limited. Finally, fruit and vegetable intake may reduce the severity of disease and progression to death. Further studies are needed to clarify the association between fruit and vegetable intake and other specific causes of death than cardiovascular disease and cancer.

Our analysis has several limitations. Combining studies from different populations increases the sample size and statistical power, but also results in heterogeneity because of differences in the characteristics of the study populations. Heterogeneity was low in the analyses of coronary heart disease, moderate to high heterogeneity for stroke, cardiovascular disease and total cancer, and high for all-cause mortality. The heterogeneity appeared to be driven by differences in the size of the association, more than variation in the presence or absence of an association as most of the studies found inverse associations. Some heterogeneity is expected as the studies varied by the age groups included, duration of follow-up, geographic location, sample sizes, detail of the dietary assessment method, and factors adjusted for in the analyses. There are also likely to be large differences in the types, amounts, and preparation methods of fruits and vegetables consumed, as well as differences in the stability of the intakes over time, and differences in the incidence of specific cancers and specific causes of death that contribute to total cancer and all-cause mortality, between populations. However, when we conducted subgroup analyses to investigate sources of the heterogeneity, we found in general little evidence of heterogeneity between most subgroups.

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3 In the few subgroup analyses where the test for heterogeneity was significant there were often
4 relatively few studies in one of the subgroups and chance can not be excluded as an
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7 explanation.
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10 Fruit and vegetable intake is often associated with other lifestyle factors such as lower
11 prevalence of smoking, less overweight and obesity, higher physical activity, and lower
12 intakes of alcohol, and red and processed meat, which could have confounded the observed
13 associations. Many studies adjusted for these and other confounding factors and we found
14 little evidence that the results varied substantially whether or not adjustment for most of these
15 confounders was done. It is possible that persons with a high fruit and vegetable intake may
16 be more likely to undergo screening, or have better access to or compliance with treatment
17 and this could lead to an improved survival and bias the results for mortality. There was little
18 heterogeneity when studies were stratified by whether incidence or mortality of
19 cardiovascular disease or total cancer was the outcome, although in a few analyses risk
20 estimates were slightly stronger for mortality, however, power may have been low to detect a
21 difference because of a moderate number of studies in each subgroup. The possibility of
22 residual confounding by imprecisely measured, unknown or unmeasured confounders cannot
23 be entirely excluded.
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40 Measurement error in the assessment of fruit and vegetable intake and changes in fruit
41 and vegetable intake during follow-up may have influenced the results, but to date only the
42 EPIC study⁷⁵ and the China Kadoorie Cohort Study⁶³ have assessed the impact of
43 measurement errors and regression dilution bias due to changes in intake during follow-up on
44 these outcomes. The HR for total mortality was 0.97 (95% CI: 0.96-0.98) per 200 gram per
45 day of fruit and vegetable intake without correction for measurement error compared with
46 0.94 (95% CI: 0.91-0.96) with correction for measurement error, and the corresponding HRs
47 for ischaemic heart disease mortality (per 80 g/d) was 0.97 (95% CI: 0.95-0.99) and 0.95
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(95% CI: 0.91-0.99),²³ respectively, in the EPIC study. In the China Kadoorie Cohort Study the HRs of cardiovascular death with one daily portion of fresh fruit intake were 0.77 (95% CI: 0.72-0.83) before and 0.63 (95% CI: 0.56-0.72) after correction for regression dilution. This suggest that both measurement error and regression dilution bias may have attenuated the observed risk estimates. We can also not entirely exclude the possibility that the weaker dose-response curve at higher compared to lower intakes partly could be due to measurement errors in the assessment of fruit and vegetable intake. Although not all studies had the same range of fruit and vegetable intake, there was a wide range of fruit and vegetable intake across most studies, thus the nonlinearity is not likely to be due to single studies with a more extreme range than others. Another limitation of the current analysis is that there were no prospective cohort data from some regions of the world including Africa, West-Asia, South and Latin-America and we cannot exclude the possibility that the associations may differ by region. However, we did not find significant heterogeneity in the association between fruits and vegetables and the outcomes considered by region for the geographic locations for which data were available (North America, Europe, Australia, and Asia). In addition, an analysis from the Latin-American countries in the INTERHEART study suggested a similar association between fruit and vegetables and coronary heart disease¹⁷⁶ as in the overall study.¹⁷⁷

Lastly, the appropriateness of the estimate of the number of deaths attributable to a fruit and vegetable intake below 500 or 800 grams per day is dependent on the validity of several assumptions that were made including that of 1) a causal relationship between fruit and vegetable intake and these outcomes, 2) lack of confounding, and 3) that the results can be generalized across populations. The observed associations appear to meet several of Bradford-Hill's criteria for causation including consistency of findings in different people and regions (by sex and geographical region), temporality, some evidence of a biological gradient, plausibility, coherence between epidemiological and laboratory findings, experimental

evidence (on intermediate risk markers), and although the strength of the association is moderate across the range of fruit and vegetable intake with a 31% reduction in the relative risk of mortality comparing an intake of 800 grams per day with no intake, weak or moderate associations should not be dismissed as non-causal.¹⁷⁸ In addition, the criteria of specificity is less important because many risk factors are causes of multiple diseases, and this is likely to be the case for fruits and vegetables. As already mentioned the association between fruit and vegetable intake and cardiovascular disease, cancer and mortality persisted in many subgroup analyses when stratified by adjustment for confounding, thus although we cannot entirely rule out the possibility that residual confounding could partly explain the associations it seems less likely that it could entirely explain the observed associations. While confounding might exaggerate the observed associations, measurement errors would tend to attenuate the observed associations. Because the distribution of causes of death differ substantially in Sub-Saharan Africa compared to other regions the results from existing cohort studies on all-cause mortality may not be generalizable to this region, however, the calculations for this region were done conservatively and we also conducted sensitivity analyses only counting the cause-specific deaths (coronary heart disease, stroke, and cancer) from Sub-Saharan Africa, but this did not substantially alter the number of deaths globally that were attributable to an inadequate fruit and vegetable intake (which was reduced from 5.4 to 5.2 million for an intake below 500 grams per day and from 7.8 to 7.6 million for an intake below 800 g/d). Nevertheless, we cannot exclude the possibility that these estimates might change when additional data from other geographic locations and on specific causes of death become available.

As a meta-analysis of published literature the analysis may have been affected by small study effects such as publication bias. There was indication of small study bias in several of the analyses, and we may therefore have slightly overestimated some of the

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associations. However, we found that exclusion of studies with a smaller number cases or deaths or exclusion of outlying studies attenuated the tests for publication bias, but in most cases did not substantially alter the summary estimates.

Fruit and vegetables contain of a myriad of nutrients and phytochemicals, including fiber, vitamin C, carotenoids, antioxidants, potassium, flavonoids and other unidentified compounds which are likely to act synergistically through several biological mechanisms to reduce risk of chronic diseases and premature mortality.¹⁷⁹ Dietary fiber and fruit and vegetable intakes have been shown to reduce cholesterol levels, blood pressure, inflammation, platelet aggregation, and to improve vascular and immune function¹⁸⁰⁻¹⁸³ and recent meta-analyses showed inverse associations between fiber intake and cardiovascular disease.^{184, 185} Antioxidants in fruit and vegetables may neutralize reactive oxygen species and reduce DNA damage,¹⁸¹ glucosinolates in cruciferous vegetables induces detoxifying enzymes,¹⁸⁶ and fruits, vegetables and fiber intake may modulate steroid hormone concentrations and hormone metabolism,¹⁸¹ and may have a beneficial effect on gut microbiota.¹⁸⁰ In addition, fruit and vegetable intake has been inversely associated with risk of developing overweight or obesity and with weight gain¹⁸⁷⁻¹⁸⁹ although data are not entirely consistent,¹⁹⁰ however, the associations observed in these analyses appear to be independent of adiposity. A high fruit and vegetable intake may also reduce chronic disease risk indirectly, by displacement of unhealthy foods high in saturated fat, transfat, glycemic load, and sodium, however, most of the associations persisted in subgroups of studies that adjusted for dietary fat or meat intake.

Strengths of this analysis include the wide search terms used, the large number of studies included from various geographic locations, and the large number of cases and deaths (up to 43000 coronary heart disease cases, 47000 stroke cases, 81000 cardiovascular disease cases, 112 000 cancer cases and >71000-93 000 deaths among up to 2.1 million participants) which provided increased statistical power to detect significant associations, the robustness of

the findings in comprehensive subgroup and sensitivity analyses, the high study quality of the included studies, and the detailed dose-response analyses which allowed us to clarify the strength and shape of the dose-response relationship between fruit and vegetable intake and these outcomes. In addition, similar associations were observed when analyses were stratified by geographic areas with different underlying patterns of diet and other confounding factors, suggesting that unknown confounders are not likely to entirely explain the associations observed. Our meta-analysis provides further support for public health recommendations, interventions, and policies to promote a high fruit and vegetable intake to reduce the risk of cardiovascular disease, cancer and premature mortality. Improving the availability and affordability of fruits and vegetables, particularly in low- and middle-income countries, might be important for increasing fruit and vegetable intake globally.¹⁹¹ Any further studies should try to further define the dose-response relationship at more extreme levels of intake and report more detailed results for subtypes of fruits and vegetables in relation to these outcomes. Further studies in other geographic locations and of other less common causes of death and incorporating biomarkers of fruit and vegetable intake are also urgently needed. This will allow us to conduct updated and more refined estimations of the mortality burden due to an inadequate fruit and vegetable intake worldwide in the future.

In conclusion, we found an inverse association between intake of fruits, vegetables, and fruit and vegetables combined and the risk of coronary heart disease, stroke, cardiovascular disease, total cancer and total mortality. In most of the analyses the reductions in risk were steeper at the lower range of intake. For total cancer the lowest risk was observed at an intake of 600 grams per day (7 servings/day), while for coronary heart disease, stroke, cardiovascular disease, and total mortality the lowest risk was observed at 700-800 grams per day (8.75-10 servings/day). Globally an estimated 1 340 000 coronary heart disease deaths,

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2 680 000 stroke deaths, 660 000 cancer deaths and 7.8 million premature deaths were attributable to a fruit and vegetable intake below 800 grams per day in 2013. Our meta-analysis provides further support for public health recommendations and interventions to increase fruit and vegetable intake for prevention of cardiovascular disease, cancer and premature mortality.

Contribution: DA had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Aune, Giovannucci, Boffetta, Tonstad. Acquisition, analysis or interpretation of data: Aune, Giovannucci, Boffetta, Keum, Fadnes, Norat, Greenwood, Tonstad. Drafting of manuscript: Aune. Critical revision of the manuscript for important intellectual content: Aune, Giovannucci, Boffetta, Keum, Fadnes, Norat, Vatten, Riboli, Greenwood, Tonstad. Statistical analysis: Aune, Greenwood. Obtained funding: Aune, Giovannucci, Boffetta, Riboli, Vatten, Tonstad. Study supervision: Tonstad.

Conflict of interest disclosures: All the authors declare no conflict of interest.

Funding: This project was funded by Olav og Gerd Meidel Raagholt's Stiftelse for Medisinsk Forskning, the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), and the Imperial College National Institute of Health Research (NIHR) Biomedical Research Centre (BRC).

Role of the Sponsors: The funding sources had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgement: We thank Max Leenders (PhD, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands) for providing supplementary data from the EPIC study, Anette Hjartåker (Professor, Department of Nutrition, University of Oslo, Oslo, Norway) and Markus Knudsen (PhD, Department of Nutrition, University of Oslo, Oslo, Norway) for providing supplementary data from the Migrant Study, Hannah Gardener (Department of Neurology, Miller School of Medicine, University of Miami, Miami, USA) for providing supplementary information from the Northern Manhattan Study, Jonathan Hodgson (Professor, School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia) for providing supplementary information from the Calcium Intake Fracture Outcome Study, and Estefania Toledo (PhD, The PREDIMED Research Network, Madrid, Spain) and Pilar Buil-Cosiales (PhD, The PREDIMED Research Network, Madrid, Spain) for providing supplementary information from the PREDIMED study.

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Table 1. Summary relative risks for high vs. low and dose-response analyses and risk of coronary heart disease, stroke, cardiovascular disease, total cancer and mortality

Coronary heart disease									
Food group	Comparison	n	Cases	Participants	RR (95% CI)	I ²	Pheterogeneity	Egger	References
Fruit and vegetables	High vs. low	16	18516	792197	0.87 (0.83-0.91)	0	0.52	0.21	23, 29, 31, 32, 56, 58, 64, 86, 88, 90, 91, 93, 94, 98
	Per 200 g/d	15	17742	775132	0.92 (0.90-0.94)	0	0.96	0.12	23, 29, 31, 32, 56, 58, 64, 86, 88, 90, 91, 94, 132
Fruit	High vs. low	25	40229	1568460	0.86 (0.82-0.91)	23.2	0.15	0.52	9-11, 22, 23, 27, 29, 36, 55, 56, 58, 60, 63, 64, 86, 88, 91, 94, 95, 98-100, 104
	Per 200 g/d	24	43336	1555553	0.90 (0.86-0.94)	43.7	0.01	0.04	9, 10, 22, 23, 27, 29, 36, 56, 58, 60, 62-64, 86, 88, 91, 92, 94, 95, 99, 104, 132
Vegetables	High vs. low	22	34754	2123415	0.87 (0.84-0.90)	1.9	0.43	0.03	9, 10, 23, 27, 29, 34, 55, 56, 58, 64, 86, 88, 91, 94, 95, 98, 100, 101, 103, 104
	Per 200 g/d	20	20853	1047071	0.84 (0.79-0.90)	60.6	<0.0001	0.001	9, 22, 23, 27, 29, 56, 58, 62, 64, 86, 88, 91, 94, 95, 100, 103, 104, 132
Stroke									
Fruit and vegetables	High vs. low	8	10560	226910	0.79 (0.71-0.88)	37.6	0.13	0.80	31, 56, 58, 64, 109, 118, 120, 122
	Per 200 g/d	10	11644	303338	0.84 (0.76-0.92)	73.3	<0.0001	0.08	31, 56, 58, 64, 108-110, 118, 120, 122
Fruit	High vs. low	17	46951	960337	0.82 (0.77-0.87)	36.3	0.07	0.60	11, 25-27, 55, 56, 58, 60, 63, 64, 109, 112-117
	Per 200 g/d	16	46203	964142	0.82 (0.74-0.90)	72.9	<0.0001	0.62	25-27, 56, 58, 60, 62-64, 109, 112-114, 116, 117, 126
Vegetables	High vs. low	13	14519	427124	0.87 (0.81-0.95)	38.2	0.08	0.82	25-27, 55, 56, 58, 64, 109, 112, 113, 115-117
	Per 200 g/d	13	14973	441670	0.87 (0.79-0.96)	63.4	0.001	0.15	25-27, 56, 58, 62, 64, 109, 112, 113, 116, 117, 126
Cardiovascular disease									
Fruit and vegetables	High vs. low	16	27842	963240	0.84 (0.79-0.90)	53.5	0.006	0.005	15, 16, 18, 31, 39, 42, 53, 56, 58, 64, 75, 86-88, 98, 125
	Per 200 g/d	13	20329	877925	0.92 (0.90-0.95)	31.3	0.13	0.05	15, 16, 18, 31, 39, 53, 56, 58, 64, 75, 86-88
Fruit	High vs. low	21	81807	1605227	0.87 (0.82-0.92)	70.9	<0.0001	0.99	11, 16, 19, 24, 27, 53-56, 58, 60, 63, 64, 75, 76, 88, 98, 124, 125, 127
	Per 200 g/d	17	72648	1492617	0.87 (0.82-0.92)	79.1	<0.0001	0.41	15, 16, 19, 24, 27, 53, 56, 58, 60-64, 75, 88, 127
Vegetables	High vs. low	18	32049	1112174	0.89 (0.85-0.94)	43.2	0.03	0.05	16, 19, 24, 27, 53-56, 58, 64, 75, 76, 88, 98, 124, 125, 127
	Per 200 g/d	14	23857	1009038	0.90 (0.87-0.93)	11.5	0.33	0.53	15, 16, 19, 24, 27, 53, 56, 58, 62, 64, 75, 88, 127

Total cancer

Food group	Comparison	n	Cases	Participants	RR (95% CI)	I ²	p _{heterogeneity}	Egger	References
Fruit and vegetables	High vs. low	13	54123	904300	0.93 (0.87-0.98)	41.2	0.06	0.97	7, 8, 13, 15, 16, 18, 20, 42, 53, 56, 59, 87, 128
	Per 200 g/d	12	52872	902065	0.97 (0.95-0.99)	48.7	0.03	0.18	7, 8, 13, 15, 16, 18, 20, 53, 56, 59, 87, 128
Fruit	High vs. low	21	105401	1569168	0.92 (0.88-0.96)	49.3	0.006	0.16	7-11, 13, 14, 16, 17, 19-21, 53, 54, 56, 57, 59, 65, 114, 128
	Per 200 g/d	20	112370	1648240	0.96 (0.94-0.99)	52.1	0.004	0.05	7-10, 13, 15-17, 19-21, 53, 56, 57, 59, 61, 65, 114, 128
Vegetables	High vs. low	17	101118	1505948	0.95 (0.90-0.99)	52.6	0.006	0.25	7-9, 13, 16, 17, 19-21, 53, 54, 56, 57, 59, 65, 128
	Per 200 g/d	17	108855	1597722	0.96 (0.93-0.99)	55.2	0.003	0.47	7-9, 13, 15-17, 19-21, 53, 56, 57, 59, 65, 128
Total mortality									
Fruit and vegetables	High vs. low	22	87574	1035556	0.82 (0.79-0.86)	62.3	<0.0001	0.001	18, 29, 31, 32, 39, 42-44, 47-50, 53, 56, 58, 67, 68, 75, 87, 98, 134, 161
	Per 200 g/d	15	71160	959083	0.90 (0.87-0.93)	82.5	<0.0001	<0.0001	18, 29, 31, 32, 39, 49, 53, 56, 58, 67, 68, 75, 87, 132, 134
Fruit	High vs. low	30	93473	>1144194	0.87 (0.84-0.90)	60.2	<0.0001	0.01	9-11, 19, 27, 29, 30, 36, 37, 43, 46, 47, 51-58, 61, 66, 68, 75, 135, 136, 139
	Per 200 g/d	27	94235	>1104255	0.85 (0.80-0.91)	89.5	<0.0001	0.10	9, 10, 19, 27, 29, 30, 35-37, 40, 43, 45, 52, 53, 56-58, 61, 62, 66, 68, 75, 131-133, 139
Vegetables	High vs. low	24	82904	1082960	0.87 (0.82-0.92)	78.6	<0.0001	0.02	9, 10, 19, 27, 29, 34, 38, 46, 47, 51-58, 66, 68, 75, 136, 137, 139
	Per 200 g/d	22	86264	1050795	0.87 (0.82-0.92)	82.3	<0.0001	0.02	9, 19, 27, 29, 33, 35, 40, 45, 52, 53, 56-58, 62, 66, 68, 75, 131-133, 139

Table 2.Fruit and vegetable subtypes and coronary heart disease risk

	High vs. low analysis					Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Apples, pears	10	0.85 (0.79-0.93)	1.9	0.42	34, 56, 60, 64, 89, 94, 142, 145, 163	8	Per 100 g/d	0.99 (0.89-1.09)	33.9	0.16	56, 60, 64, 89, 94, 142, 145
Bananas	3	0.90 (0.67-1.20)	47.2	0.15	56, 94	2	Per 100 g/d	0.81 (0.26-2.58)	69.4	0.04	56, 94
Berries	6	0.94 (0.81-1.08)	51.6	0.07	34, 56, 60, 89, 102, 163	4	Per 100 g/d	1.13 (0.90-1.43)	14.0	0.32	56, 60, 89, 102
Citrus fruits	14	0.91 (0.86-0.96)	0	0.69	9, 56, 60, 64, 89, 91, 94, 97, 142, 143, 146, 147	15	Per 100 g/d	0.95 (0.89-1.01)	19.1	0.24	9, 56, 60, 62, 64, 89, 91, 94, 97, 142, 143, 146, 147
Dried fruits	2	0.93 (0.78-1.11)	0	0.51	11, 60	1	Per 100 g/d	0.55 (0.19-1.52)			60
Fruit juices	2	0.79 (0.63-0.98)	0	0.56	60, 143	3	Per 100 g/d	0.93 (0.80-1.08)	79.6	0.007	60, 92, 143
Grapes	4	0.91 (0.76-1.10)	43.5	0.15	56, 60, 142, 145	2	Per 100 g/d	0.87 (0.56-1.37)	71.0	0.02	56, 60, 142, 145
Strawberries	2	1.17 (0.71-1.91)	76.5	0.04	142, 144	1	Per 100 g/d	4.66 (1.14-19.03)	NC	NC	144
Watermelon	2	0.87 (0.64-1.18)	0	0.36	94	2	Per 100 g/d	0.91 (0.72-1.15)	46.2	0.17	94
Allium vegetables	3	0.98 (0.79-1.20)	0	0.40	89, 94	3	Per 100 g/d	0.99 (0.34-2.86)	4.4	0.35	89, 94
Cruciferous vegetables	7	1.01 (0.90-1.13)	30.4	0.20	56, 64, 91, 94, 147	8	Per 100 g/d	0.99 (0.89-1.09)	0	0.59	56, 62, 64, 91, 94, 147
Green leafy vegetables	10	0.83 (0.75-0.91)	31.6	0.16	10, 36, 56, 64, 89, 91, 143, 147	9	Per 100 g/d	0.72 (0.64-0.82)	0.4	0.43	36, 56, 62, 64, 89, 91, 143, 147
Onions	3	0.75 (0.56-1.02)	61.9	0.07	34, 145	2	Per 100 g/d	0.60 (0.15-2.42)	76.5	0.04	145
Potatoes	5	0.92 (0.79-1.07)	64.0	0.03	100, 140, 143, 164	6	Per 100 g/d	0.99 (0.93-1.05)	48.8	0.08	92, 106, 140, 143, 164
Tomatoes	5	0.90 (0.80-1.00)	0	0.64	56, 141, 143, 145, 147	6	Per 100 g/d	0.94 (0.89-0.98)	0	0.48	56, 141, 143, 145, 147, 148
Beta-carotene rich F&V	3	0.83 (0.75-0.92)	20.4	0.29	64, 91	3	Per 100 g/d	0.77 (0.65-0.91)	27.3	0.25	64, 91
Protein rich F&V	3	0.97 (0.89-1.05)	31.2	0.23	64, 91	3	Per 100 g/d	0.80 (0.60-1.07)	9.5	0.33	64, 91
Lycopene rich F&V	3	1.01 (0.93-1.09)	0	0.39	64, 91	3	Per 100 g/d	1.00 (0.91-1.10)	0	0.77	64, 91
Vitamin C rich F&V	3	0.86 (0.78-0.95)	19.4	0.29	64, 91	3	Per 100 g/d	0.91 (0.85-0.99)	15.2	0.31	64, 91
Raw F&V	2	0.89 (0.61-1.30)	67.1	0.08	28, 96	1	Per 100 g/d	0.88 (0.77-1.01)			28

N, number of risk estimates. Some publications reported results from more than one study and for this reason the number of risk estimates and publications is not always the same.

P_h=p-value for heterogeneity

Table 3. Fruit and vegetable subtypes and risk of total stroke, ischemic stroke and hemorrhagic stroke

	Total stroke										
	High vs. low analysis					Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Apples, pears	6	0.88 (0.81-0.96)	0	0.66	56, 60, 64, 109, 142, 149	5	Per 100 g/d	0.94 (0.84-1.05)	39.7	0.16	56, 60, 64, 109, 142
Berries	5	0.98 (0.86-1.12)	51.4	0.08	26, 56, 60, 109, 150	5	Per 100 g/d	1.07 (0.79-1.45)	39.0	0.16	26, 56, 60, 109, 150
Citrus fruits	8	0.74 (0.65-0.84)	53.6	0.04	26, 56, 60, 64, 109, 112, 143, 146	9	Per 100 g/d	0.78 (0.69-0.90)	63.6	0.005	26, 56, 60, 62, 64, 109, 112, 143, 146
Citrus fruit juice	2	0.90 (0.74-1.10)	0	0.55	60, 142	2	Per 100 g/d	0.89 (0.72-1.10)	0	0.61	60, 142
Dried fruits	2	0.92 (0.74-1.15)	0	0.98	11, 60	1	Per 100 g/d	0.75 (0.32-1.81)			60
Fruit juice	2	0.67 (0.60-0.76)	0	0.98	60, 143	2	Per 100 g/d	0.72 (0.63-0.83)	0	0.69	60, 143
Grapes	2	0.72 (0.47-1.10)	35.8	0.21	56, 60	2	Per 100 g/d	0.57 (0.34-0.97)	0	0.66	56, 60
Allium vegetables	2	0.89 (0.80-1.00)	0	0.89	109, 149	1	Per 100 g/d	0.89 (0.76-1.04)			109
Cruciferous vegetables	4	0.97 (0.78-1.20)	56.8	0.07	26, 56, 64, 109	5	Per 100 g/d	1.04 (0.80-1.36)	30.6	0.22	26, 56, 62, 64, 109
Green leafy vegetables	4	0.88 (0.81-0.95)	0	0.60	56, 64, 109, 143	5	Per 100 g/d	0.73 (0.57-0.94)	35.9	0.18	56, 62, 64, 109, 143
Pickled vegetables	2	0.80 (0.73-0.88)	0	0.93	119, 143	2	Per 100 g/d	0.57 (0.43-0.74)	0	0.70	119, 143
Potatoes	4	0.94 (0.87-1.01)	0	0.43	26, 143, 164	4	Per 100 g/d	0.98 (0.94-1.02)	0	0.41	26, 143, 164
Root vegetables	2	1.01 (0.89-1.14)	0	0.38	26, 109	2	Per 100 g/d	0.96 (0.78-1.18)	0	0.54	26, 109
Tomatoes	3	0.95 (0.68-1.31)	61.0	0.08	56, 141, 143	4	Per 100 g/d	1.01 (0.96-1.06)	0	0.72	56, 141, 143, 148
	Ischemic stroke										
	High vs. low analysis					Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Berries	3	0.95 (0.75-1.21)	74.7	0.02	26, 109, 150	3	Per 100 g/d	1.02 (0.61-1.72)	70.3	0.03	26, 109, 150
Citrus fruits	7	0.78 (0.66-0.92)	66.6	0.006	26, 109-111, 121, 146, 162	7	Per 100 g/d	0.87 (0.79-0.95)	52.5	0.05	26, 109-111, 146, 162
Citrus fruit juices	2	0.65 (0.51-0.84)	0	0.47	110	2	Per 100 g/d	0.87 (0.80-0.96)	0	0.74	110
Allium vegetables	2	0.90 (0.78-1.03)	0	0.78	109, 111	2	Per 100 g/d	0.93 (0.77-1.11)	0	0.81	109, 111
Cruciferous vegetables	5	0.82 (0.66-1.01)	66.5	0.02	26, 109-111	5	Per 100 g/d	0.66 (0.41-1.07)	71.7	0.007	26, 109-111
Green leafy vegetables	4	0.88 (0.78-0.99)	0	0.45	109-111	4	Per 100 g/d	0.74 (0.62-0.89)	0	0.78	109-111
Potatoes	5	0.97 (0.87-1.08)	3.5	0.39	26, 110, 164	5	Per 100 g/d	1.00 (0.95-1.05)	0	0.60	26, 110, 164
Root vegetables	3	0.93 (0.73-1.18)	57.3	0.10	26, 109, 111	3	Per 100 g/d	0.91 (0.64-1.30)	58.9	0.09	26, 109, 111

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Vitamin C-rich F&V	2	0.80 (0.69-0.92)	0	0.88	¹¹⁰	2	Per 100 g/d	0.92 (0.86-0.98)	0	0.71	¹¹⁰
	Hemorrhagic stroke										
	High vs. low analysis					Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Berries	3	1.15 (0.89-1.49)	0	0.60	^{26, 109, 150}	3	Per 100 g/d	1.66 (0.91-3.03)	0	0.66	^{26, 109, 150}
Citrus fruits	3	0.74 (0.55-1.01)	28.2	0.25	^{26, 109, 146}	3	Per 100 g/d	0.79 (0.59-1.06)	32.2	0.23	^{26, 109, 146}
Cruciferous vegetables	2	0.83 (0.33-2.12)	84.1	0.01	^{26, 109}	2	Per 100 g/d	0.27 (0.01-12.54)	77.0	0.04	^{26, 109}
Potatoes	3	1.06 (0.83-1.36)	0	0.90	^{26, 164}	3	Per 100 g/d	1.03 (0.91-1.16)	0	0.77	^{26, 164}
Root vegetables	2	1.05 (0.76-1.44)	0	0.92	^{26, 109}	2	Per 100 g/d	1.16 (0.66-2.02)	0	0.85	^{26, 109}

P_h=p-value for heterogeneity

Table 4. Fruit and vegetable subtypes and cardiovascular disease risk

	High vs. low analysis					Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Apples, pears	7	0.86 (0.80-0.93)	0	0.74	56, 60, 61, 64, 129, 142, 152	7	Per 100 g/d	0.92 (0.82-1.03)	46.9	0.08	56, 60, 61, 64, 129, 142, 152
Berries	2	1.02 (0.94-1.11)	0	0.44	56, 60	2	Per 100 g/d	1.13 (0.88-1.46)	0	0.68	56, 60
Citrus fruits	6	0.78 (0.66-0.92)	72.3	0.003	16, 56, 60, 64, 124, 146	8	Per 100 g/d	0.92 (0.84-1.00)	65.8	0.005	15, 16, 56, 60-62, 64, 146
Citrus fruit juice	2	0.88 (0.53-1.46)	48.3	0.16	60, 124	2	Per 100 g/d	0.98 (0.95-1.02)	6.9	0.30	15, 60
Dried fruits	3	0.94 (0.83-1.06)	0	0.80	11, 60, 151	1	Per 100 g/d	0.66 (0.33-1.26)			60
Fruit juice	1	0.67 (0.41-1.10)			60	2	Per 100 g/d	0.99 (0.93-1.06)	0	0.58	60, 154
Grapes	3	0.86 (0.70-1.05)	62.3	0.07	56, 60, 142	3	Per 100 g/d	0.83 (0.48-1.45)	66.7	0.05	56, 60, 142
Strawberries	3	1.02 (0.79-1.32)	57.2	0.10	142, 144, 151	1	Per 100 g/d	1.06 (0.95-1.17)	NC	NC	144
Pinned fruits	3	1.23 (1.06-1.43)	0	0.51	159	4	Per 100 g/d	1.30 (0.81-2.08)	66.0	0.03	154, 159
Broccoli	3	0.87 (0.67-1.13)	25.0	0.26	142, 144, 151	2	Per 100 g/d	0.75 (0.49-1.14)	0	0.57	142, 144
Carrots	2	0.81 (0.70-0.93)	0	0.73	56, 123	1	Per 100 g/d	0.97 (0.72-1.30)			56
Cruciferous vegetables	8	0.88 (0.73-1.05)	77.5	<0.0001	16, 19, 56, 64, 87, 124, 151	9	Per 100 g/d	0.89 (0.77-1.02)	65.1	0.003	15, 16, 19, 56, 62, 64, 87, 154
Green leafy vegetables	5	0.84 (0.71-0.99)	74.0	0.004	16, 56, 64, 124, 151	5	Per 100 g/d	0.83 (0.65-1.08)	66.7	0.02	15, 16, 56, 64
Noncruciferous vegetables	2	0.76 (0.59-0.97)	50.1	0.16	19	2	Per 100 g/d	0.91 (0.82-1.01)	74.5	0.05	19
Potatoes	3	1.01 (0.91-1.13)	60.0	0.08	124, 164	4	Per 100 g/d	1.01 (0.97-1.04)	13.4	0.33	15, 154, 164
Raw vegetables	2	0.83 (0.66-1.05)	88.0	0.004	11, 75	1	Per 100 g/d	0.86 (0.81-0.90)	NC	NC	75
Tomatoes	4	0.94 (0.86-1.02)	0.4	0.39	56, 141, 142, 151	4	Per 100 g/d	0.92 (0.80-1.07)	52.6	0.10	56, 141, 142, 148
Beta-carotene rich F&V	2	0.96 (0.89-1.03)	0	0.77	64, 124	2	Per 100 g/d	0.94 (0.89-0.99)	0	0.55	64, 124
Vitamin C rich F&V	1	0.91 (0.44-1.90)			64	2	Per 100 g/d	0.95 (0.92-0.98)	0	0.88	15, 64

P_h=p-value for heterogeneity

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Table 5. Fruit and vegetable subtypes and total cancer risk

High vs. low analysis						Dose-response analysis					
Fruit, vegetable subtype	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Citrus fruits	5	0.97 (0.90-1.04)	61.0	0.04	9, 16, 143, 155, 156	6	Per 100 g/d	0.99 (0.95-1.04)	70.3	0.005	15, 16, 143, 156
Dried fruits	2	0.89 (0.61-1.30)	32.7	0.22	11, 153	0	Per 100 g/d				
Canned fruits	3	0.90 (0.77-1.05)	0	0.99	159	4	Per 100 g/d	0.82 (0.66-1.01)	0	0.96	154, 159
Fruit juice	1	0.99 (0.92-1.07)			143	2	Per 100 g/d	0.99 (0.95-1.02)	0	0.84	143, 154
Broccoli	2	1.03 (0.87-1.22)	0	0.46	130, 153	1	Per 100 g/d	1.22 (0.86-1.72)			130
Cruciferous vegetables	5	0.84 (0.72-0.97)	65.5	0.02	16, 19, 56, 87	6	Per 100 g/d	0.91 (0.82-1.02)	67.7	0.008	15, 16, 19, 56, 87, 154
Green vegetables	3	0.96 (0.90-1.02)	0	0.43	8, 10, 143	2	Per 100 g/d	0.91 (0.80-1.03)	0	0.74	8, 143
Green yellow vegetables	5	0.88 (0.77-1.00)	17.1	0.31	9, 12, 14, 153, 157	4	Per 100 g/d	0.89 (0.83-0.96)	8.0	0.35	9, 12, 153, 157
Mushrooms	1	1.07 (0.99-1.16)			143	2	Per 100 g/d	1.20 (1.01-1.44)	0	0.80	143, 154
Noncruciferous vegetables	2	1.05 (0.90-1.23)	16.8	0.27	19	2	Per 100 g/d	1.01 (0.97-1.06)	0	0.41	19
Onions	2	0.91 (0.81-1.02)	0	0.34	105, 130	2	Per 100 g/d	0.75 (0.54-1.04)	0	0.52	105, 130
Pickled vegetables	2	0.96 (0.90-1.02)	0	0.99	14, 143	1	Per 100 g/d	0.92 (0.78-1.10)			143
Potatoes	2	1.02 (0.86-1.22)	31.0	0.23	14, 143	3	Per 100 g/d	0.99 (0.95-1.02)	0	0.77	15, 143, 154
Salads	4	0.98 (0.89-1.07)	0	0.88	11, 54, 56, 153	1	Per 100 g/d	0.88 (0.49-1.59)			56
Potatoes	3	0.86 (0.67-1.10)	70.1	0.04	56, 143, 153	2	Per 100 g/d	0.94 (0.83-1.07)	0	0.84	56, 143
Yellow vegetables	3	0.97 (0.92-1.03)	0	0.51	8, 16, 143	3	Per 100 g/d	0.97 (0.89-1.06)	0	0.47	8, 16, 143
Juice	1	0.98 (0.81-1.19)			160	2	Per 100 g/d	1.00 (0.94-1.07)	0	0.54	158, 160

P_h=p-value for heterogeneity

Table 6. Fruit and vegetable subtypes and total mortality risk

Fruit, vegetable subtype	High vs. low analysis					Dose-response analysis					
	N	RR (95% CI)	I ²	p _h	References	N	Increment	RR (95% CI)	I ²	p _h	References
Apples, pears	5	0.80 (0.70-0.91)	84.9	<0.0001	34, 56, 61, 75, 138	3	Per 100 g/d	0.80 (0.64-1.01)	95.3	<0.0001	56, 61, 75
Bananas	2	0.91 (0.80-1.03)	18.8	0.27	56, 61	2	Per 100 g/d	0.95 (0.80-1.14)	70.5	0.07	56, 61
Berries	3	0.92 (0.88-0.97)	8.0	0.34	34, 56, 75	2	Per 100 g/d	0.85 (0.70-1.03)	0	0.61	56, 75
Citrus fruits	6	0.90 (0.86-0.94)	12.3	0.34	9, 38, 56, 61, 75, 143	7	Per 100 g/d	0.94 (0.88-1.00)	49.9	0.06	9, 38, 56, 61, 62, 75, 143
Fruit juice	1	0.87 (0.83-0.91)			143	2	Per 100 g/d	0.88 (0.84-0.92)	0	0.71	53, 143
Tinned fruits	3	1.13 (1.04-1.23)	0	0.72	159	4	Per 100 g/d	1.14 (1.07-1.21)	0	0.71	53, 159
Cruciferous vegetables	6	0.88 (0.80-0.97)	78.9	<0.0001	19, 56, 75, 87, 138	6	Per 100 g/d	0.90 (0.85-0.95)	35.2	0.17	19, 56, 62, 75, 87
Mushrooms	2	0.93 (0.84-1.01)	79.3	0.03	75, 143	2	Per 100 g/d	0.74 (0.46-1.20)	77.7	0.03	75, 143
Noncruciferous vegetables	2	0.85 (0.67-1.07)	82.7	0.02	19	2	Per 100 g/d	0.95 (0.89-1.02)	83.1	0.02	19
Onions, allium vegetables	3	0.85 (0.69-1.06)	84.0	0.002	34, 75, 105	2	Per 100 g/d	0.76 (0.40-1.46)	50.3	0.16	75, 105
Potatoes	4	0.78 (0.74-0.83)	2.8	0.38	43, 44, 67, 75	4	Per 100 g/d	0.91 (0.81-1.03)	59.0	0.06	43, 67, 75, 133
Root vegetables	2	0.93 (0.77-1.13)	89.2	0.002	75, 138	1	Per 100 g/d	0.76 (0.66-0.88)			75
Green leafy vegetables, salads	7	0.92 (0.86-0.97)	39.5	0.13	11, 30, 37, 43, 54, 56, 75	7	Per 100 g/d	0.78 (0.71-0.86)	11.1	0.34	11, 30, 43, 53, 56, 62, 75
Cooked vegetables	5	0.87 (0.80-0.94)	66.4	0.02	30, 38, 43, 68, 75	4	Per 100 g/d	0.89 (0.80-0.99)	94.0	<0.0001	30, 38, 43, 68, 75
Raw vegetables	2	0.88 (0.79-0.98)	74.4	0.05	68, 75	2	Per 100 g/d	0.91 (0.80-1.02)	90.8	0.001	68, 75

P_h=p-value for heterogeneity

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Table 7. Attributable fractions and number of deaths due to coronary heart disease, stroke, cardiovascular disease, cancer and all-cause mortality by region attributable to a fruit and vegetable intake below 500 grams per day or 800 grams per day, reporting on coronary heart disease, stroke, cardiovascular disease, and cancer mortality only (excluding studies on incidence).

Region	Coronary heart disease				Stroke				Cardiovascular disease				Total cancer				All-cause mortality			
	500 g/d		800 g/d		500 g/d		800 g/d		500 g/d		800 g/d		500 g/d		800 g/d		500 g/d		800 g/d	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
America A	9.1	55739	16.9	103482	23.2	44723	41.2	79448	8.8	70703	15.1	124284	7.3	53914	8.5	62586	11.9	360444	16.9	510322
America B	12.5	54117	20.7	89771	31.1	90528	49.7	144756	11.7	85227	18.8	135863	10.1	51598	11.4	58345	16.9	487772	22.0	637414
America D	8.5	4176	16.5	8081	21.6	7190	39.9	13247	8.3	6833	14.6	12436	7.4	4433	8.1	5196	11.0	43683	16.1	63877
Europe A	4.5	37864	10.2	85867	11.4	49792	24.2	105828	4.6	58739	8.9	121756	3.6	43103	4.4	52348	5.6	240217	9.2	397116
Europe B	8.4	35195	15.6	65281	21.6	66257	38.3	117708	8.1	58946	14.0	103551	6.8	23213	7.9	26921	11.1	193826	15.7	273948
Europe C	12.3	149042	21.5	260970	30.9	171813	51.9	288916	11.7	206530	19.3	345109	9.9	47412	11.3	54399	16.2	492439	22.0	669572
South-East Asia B	12.2	33451	21.9	60025	30.6	111368	52.6	191272	11.7	74412	19.5	126895	9.8	24715	11.4	28590	15.9	324696	22.0	450661
South-East Asia D	11.4	158497	20.9	291326	28.5	288454	50.1	506323	10.9	263073	18.6	457867	9.2	86619	10.7	100739	14.7	1537085	20.8	2171656
Eastern Mediterranean B	7.8	9949	15.5	19680	19.9	14075	37.4	26446	7.7	15197	13.7	28171	6.3	5005	7.5	5899	10.1	57236	15.0	85085
Eastern Mediterranean D	6.8	26452	13.9	54293	21.6	51646	33.4	100319	6.7	46384	12.3	88655	5.5	14127	6.5	16785	8.6	194416	13.2	297235
Africa D	7.0	8532	14.2	17381	24.2	46683	34.2	65992	6.9	21762	12.6	41334	7.4	11432	6.7	10283	8.9	122406	13.5	152326
Africa E	10.3	14537	19.5	27664	25.7	57088	46.6	103399	10.0	36223	17.3	64917	8.3	17767	9.7	20827	13.1	175970	19.0	253150
Western Pacific A	5.9	10780	12.3	22575	15.0	30799	29.6	60958	5.9	22802	10.9	44328	4.7	22851	5.7	27257	7.5	116071	11.6	180053
Western Pacific B	7.9	112025	16.9	238931	19.6	437848	39.3	877746	8.0	291165	14.9	571986	6.4	155867	7.7	187748	9.8	1035701	15.5	1648878
Globally		710356		1345327		1468264		2682358		1257996		2267152		562056		657923		5381962		7791293

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Figure 1. Flow-chart of study selection

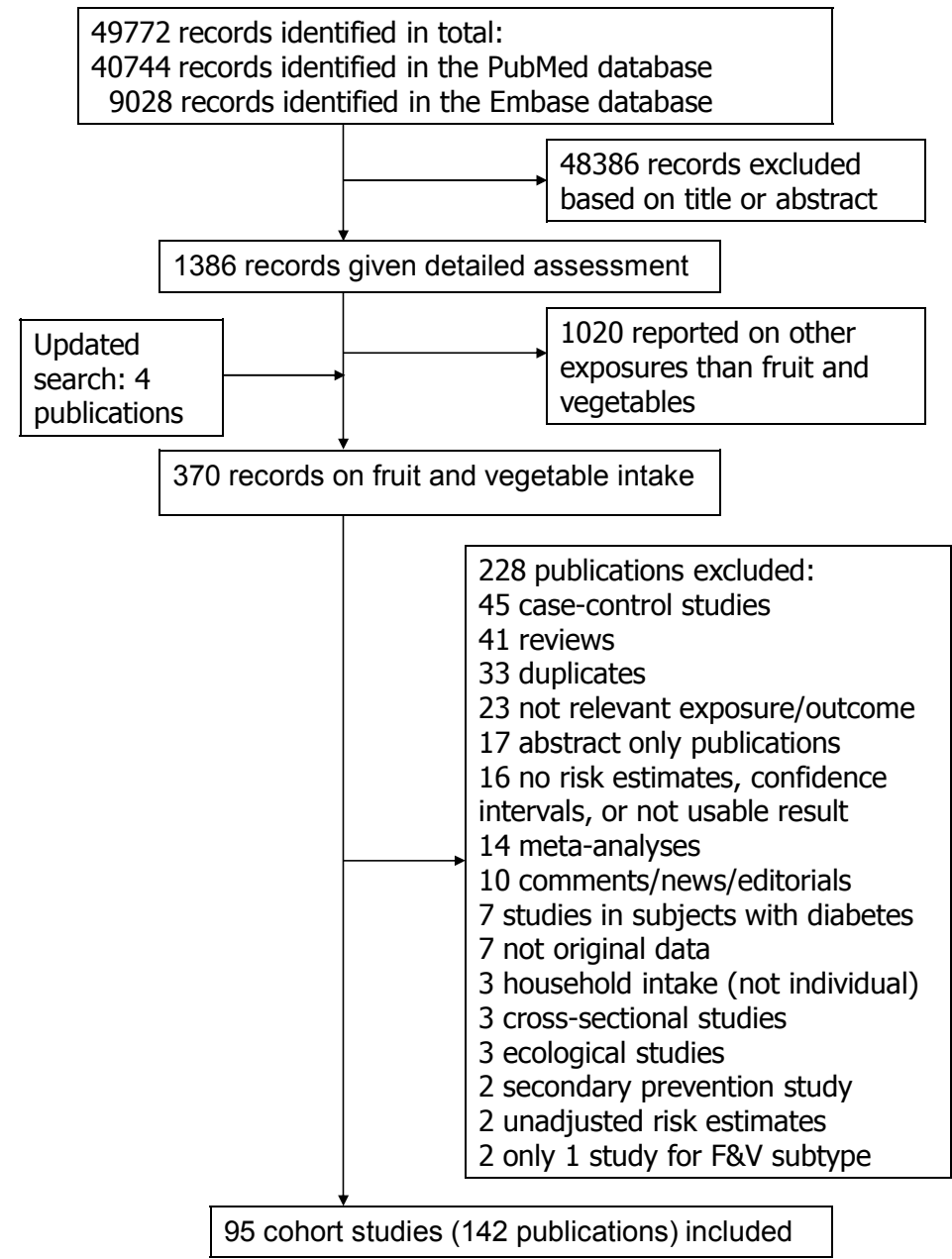


Figure 2. Fruits, vegetables and coronary heart disease, linear and nonlinear dose-response

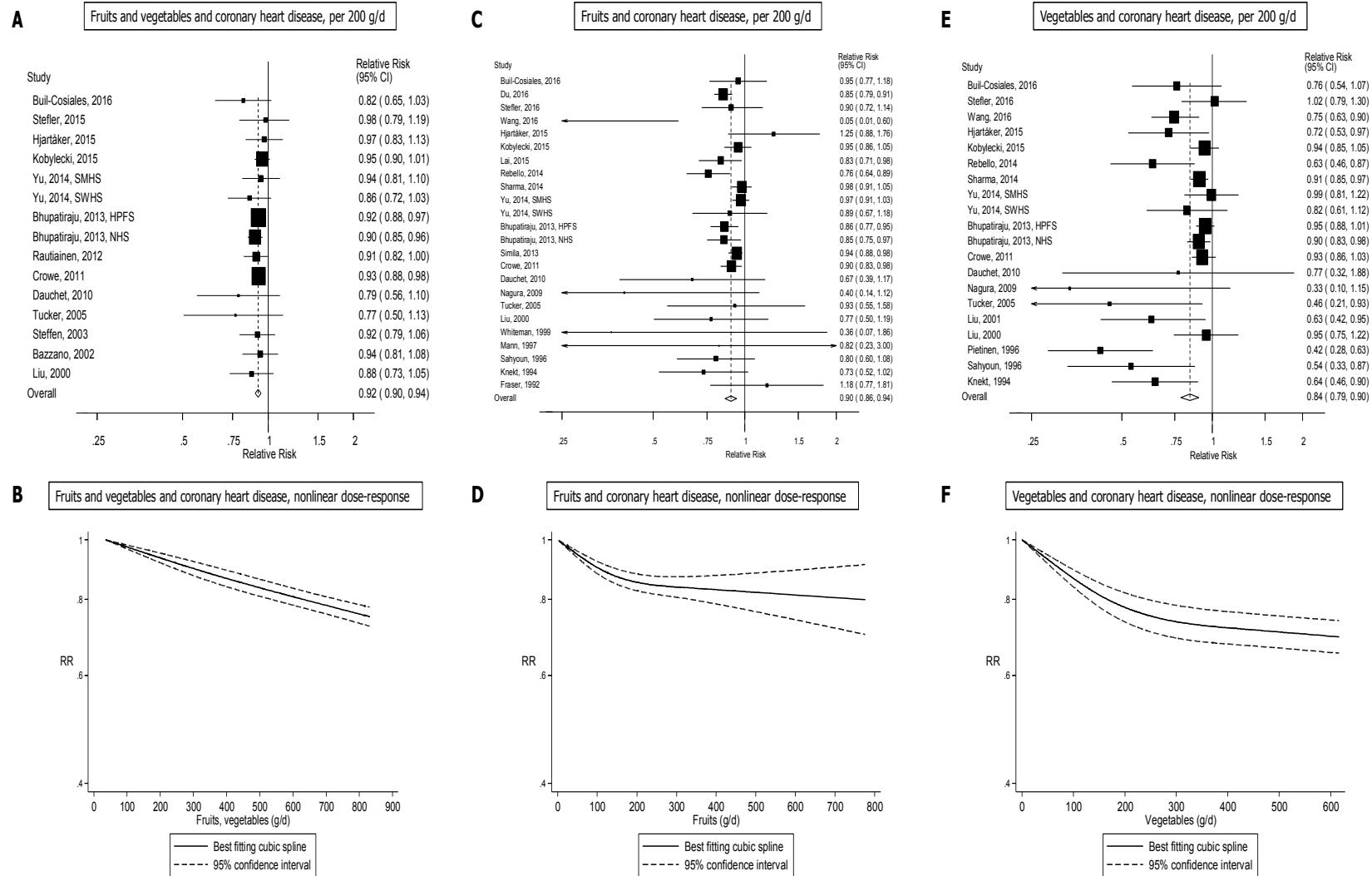


Figure 3. Fruits and vegetables and stroke, linear and nonlinear dose-response

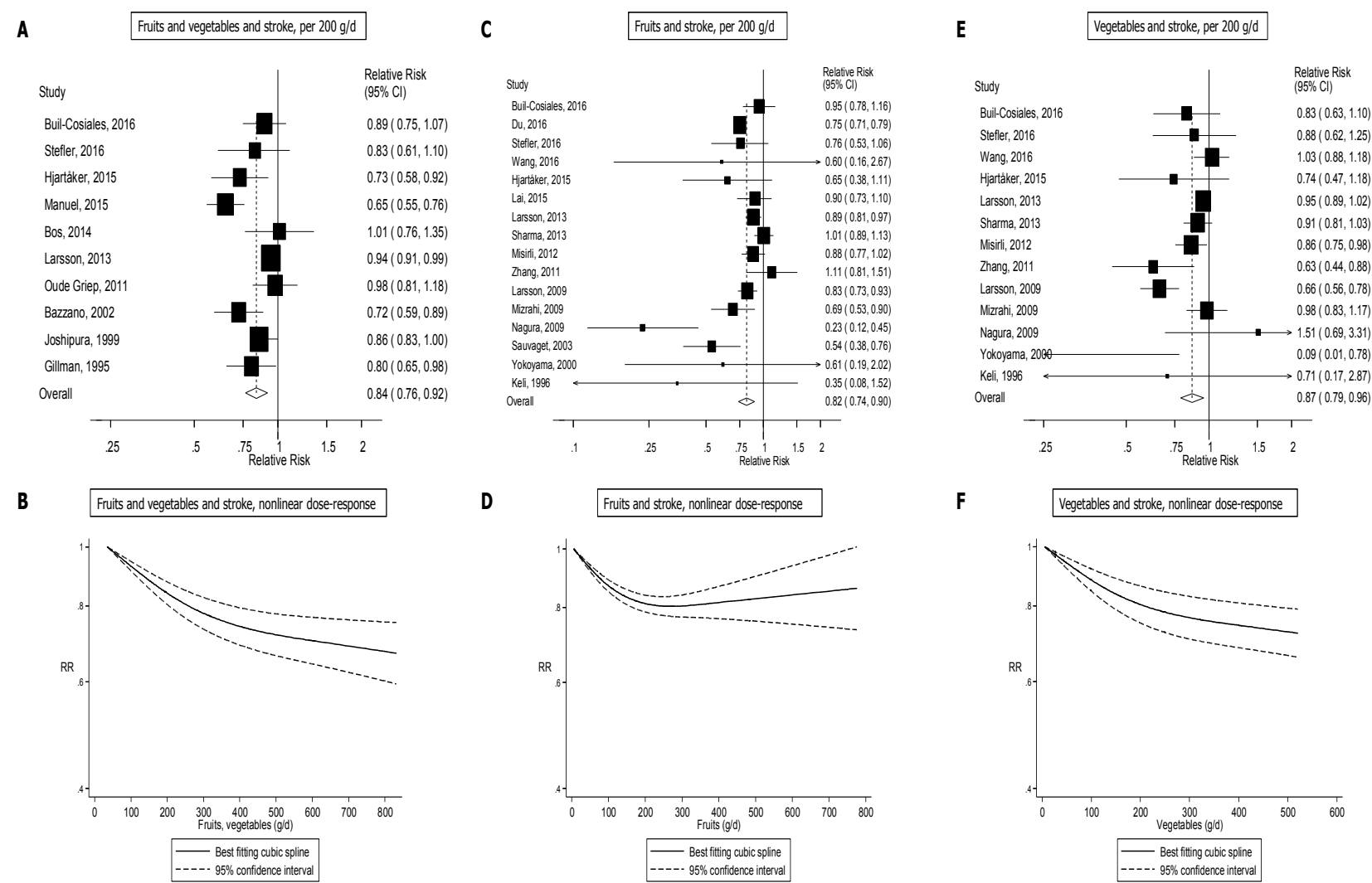


Figure 4. Fruits and vegetables and cardiovascular disease, linear and nonlinear dose-response

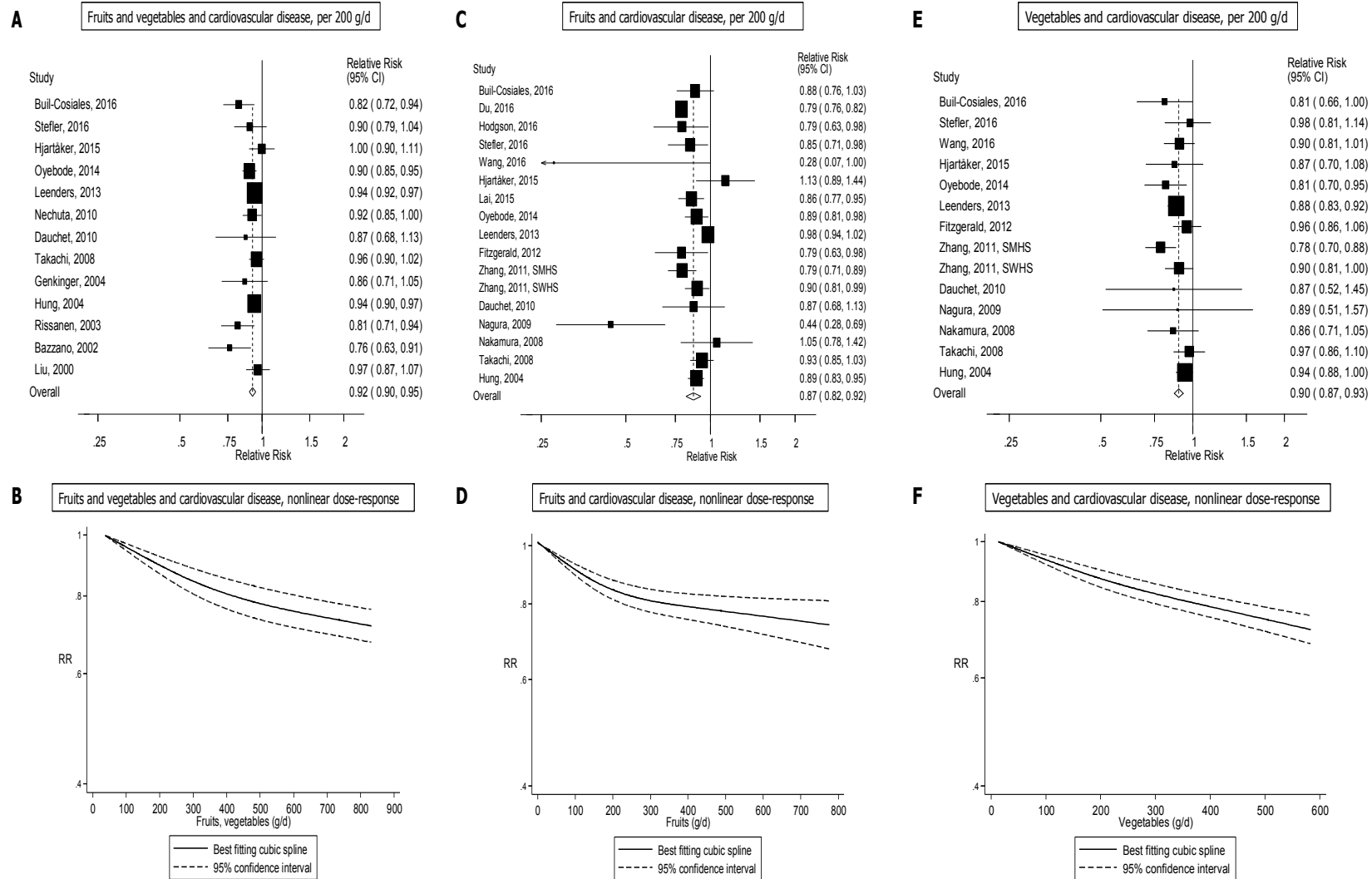


Figure 5. Fruits and vegetables and total cancer, linear and nonlinear dose-response

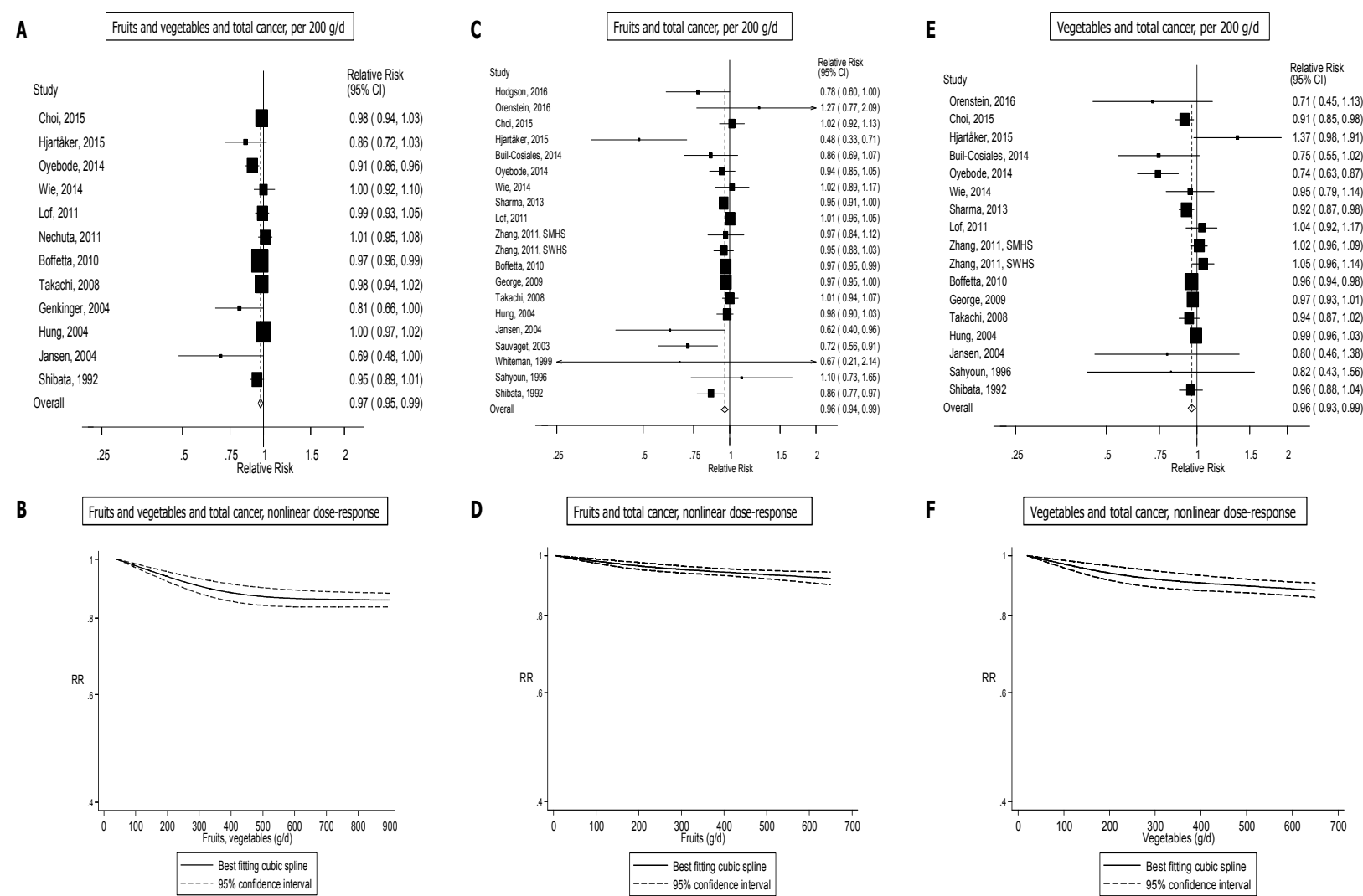


Figure 6. Fruits, vegetables and total mortality, linear and nonlinear dose-response

