Miscellaneous

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

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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 associations.

Methods: PubMed and Embase were searched up to 29 September 2016. Prospective studies of fruit and vegetable intake and cardiovascular disease, total cancer and all-cause mortality were included. Summary relative risks (RRs) were calculated using a random effects model, and the mortality burden globally was estimated; 95 studies (142 publications) were included.

Results: For fruits and vegetables combined, the summary RR per 200 g/day was 0.92 [95% confidence interval (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 800 g/day for all outcomes except cancer (600 g/day). Inverse associations were observed between the intake

of apples and pears, citrus fruits, green leafy vegetables, cruciferous vegetables, and salads and cardiovascular disease and all-cause mortality, and between the intake of 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 g/day, respectively, if the observed associations are causal.

Conclusions: Fruit and vegetable intakes were associated with reduced risk of cardiovascular disease, cancer and all-cause mortality. These results support public health recommendations to increase fruit and vegetable intake for the prevention of cardiovascular disease, cancer, and premature mortality.

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 and some cancers, 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 800 g/day of fruit and vegetables combined, whereas for total cancer no further reductions in risk were observed above 600 g/day.
- Inverse associations were observed between intake of apples/pears, citrus fruits, green leafy vegetables/salads and cruciferous vegetables 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 g/day, respectively, if the observed associations are causal.

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 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 vegetable intake range from at least 400 g/day by the World Cancer Research Fund, the WHO, and in England, to 500 g/day in Sweden, to 600 g/day in Denmark, 650–750 g/day in Norway, and 640–800 g/day in the USA (Table 5.2, page 60 in the report).[5]

Data regarding fruit and vegetable intake and cancer risk are less clear-cut today[2] 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] whereas other studies found no clear association;[9,10,14–16,18–20] however, some of these may have had statistical power too low 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 mortality but again, some of these studies may have had statistical power too low 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 incidence or mortality from cardiovascular disease and total cancer as well as the association with 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 16 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 reduce 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 prospective studies relating fruit and vegetable consumption to risk of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, and total cancer, and to 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. 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 19 July 2016, and the search was later updated to 29 September 2016. Details of the search terms used for the PubMed search are shown in Supplementary Table 1 (available at *IJE* online) 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), any MI, fatal MI, incident ischaemic heart disease, fatal ischaemic heart disease, acute coronary syndrome), stroke (total stroke, ischaemic, haemorrhagic, intracerebral and subarachnoidal haemorrhage),

total cardiovascular disease (coronary heart disease and stroke combined), and 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 three categories of fruit and vegetable intake had to be available. The excluded studies are listed in Supplementary Table 2, available at *IJE* online.

Data extraction

Results and study characteristics were extracted into tables and included: name of first author, publication year, country or region, 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 D.A., and was checked for accuracy by L.T.F. and N.K.

Statistical methods

We calculated summary relative risks (RRs) of incidence or mortality from coronary heart disease, stroke, total cardiovascular disease, and total cancer, and of all-cause mortality for the highest vs the lowest level and per 200 g/day of fruits, vegetables and total fruit and vegetable intake using the random-effects model by DerSimonian and Laird[70] 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/day as the increment. The average of the natural logarithm of the RRs was estimated and the RR from each study was 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 on both 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, but not overall, 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 White[37] and Black[30] 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 Longnecker[71] 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 g 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 g 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 three 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 I^2 statistics.[80] To explore potential heterogeneity we conducted subgroup analyses by study characteristics. Small-study effects such as publication bias were assessed using Egger's test[81] 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, respectively. Stata version 13.0 software (StataCorp, TX, USA) was used for the analyses.

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 is provided in the Supplementary Methods, available at *IJE* online.

Results

A total of 142 publications from 95 unique cohort studies were included in the analyses[7–40,42–68,75,76,86–164] (Figure 1; Supplementary Tables 3–7, available at *IJE* online); 44
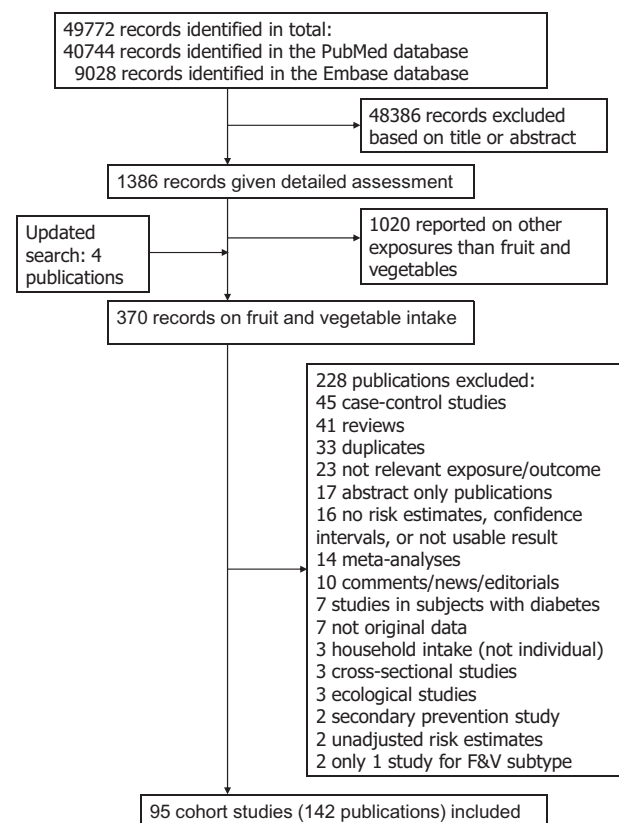

Figure 1. Flow-chart of study selection.

studies were from Europe, 26 were from the USA, 20 from Asia and five from Australia. Five publications reported results from two studies that were combined.[15,54,124,134,140] 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 for the studies included in each high vs low and dose-response analysis are 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 Tables 3–7 show a summary of the study characteristics of the included studies. Figure 1 shows a flowchart of the study selection process. Figures 2–6 show the results for the dose-response analyses, and Supplementary Figures 1–31 (available at *IJE* online) shows the high vs low analyses for all outcomes and the high vs low, linear and nonlinear dose-response analyses for ischaemic and haemorrhagic stroke. Supplementary Tables 8-18 shows the results from the nonlinear dose-response analyses for all outcomes. Results for subtypes of fruit and vegetables are shown in Tables 2–6 (also see 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] 26 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 23 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 alone and vegetables alone and coronary heart disease, respectively. The summary RR per 200 g/day was 0.92 (95% CI: 0.90–0.94, $I^2 = 0\%$) for fruits and vegetables (Figure 2a, b, Table 1; Supplementary Figure 1), 0.90 (95% CI: 0.86–0.94, $I^2 = 44\%$) for fruits (Figure 2c, d, 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). There was no evidence of a nonlinear association for fruits and vegetables, $P_{nonlinearity} = 0.30$, and there was a 24% reduction in the relative risk at an intake of 800 g/day (Figure 2b; Supplementary Table 8). Nonlinear associations were observed for fruits, $P_{nonlinearity} < 0.0001$ (Figure 2d, Supplementary Table 9), and vegetables,

$P_{nonlinearity} < 0.0001$ (Figure 2f, Supplementary Table 9), with most of the reductions in risk observed at the lower levels of intake, and there was a 21% reduction in relative risk up to 750–800 g/day for fruits and a 30% reduction in the relative risk up to 550–600 g/day for vegetables.

Of specific types of fruit and vegetables[9,10,11,28,34,36,56,60,62,64,89,91,92,94,96,97,100,102,105,106,140–148,163,164] 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 Tables 19–20, Supplementary Figures 32–76).

Stroke

Ten studies (10 publications),[31,56,58,64,108–110,118,120,122] 19 studies (19 publications),[11,25–27,55,56,58,60,62–64,109,112–117,126] and 14 studies (15 publications) [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/day was 0.84 (95% CI: 0.76–0.92, $I^2 = 73\%$) for fruits and vegetables (Figure 3a, b, Table 1; Supplementary Figure 4), 0.82 (95% CI: 0.74–0.90, $I^2 = 73\%$) for fruits (Figure 3c, d, Table 1; Supplementary Figure 5), and 0.87 (95% CI: 0.79–0.96, $I^2 = 63\%$) for vegetables (Figure 3e, f, Table 1; Supplementary Figure 6). There was evidence of a nonlinear association between fruit and vegetables, fruits, and vegetables, and total stroke, $P_{nonlinearity} < 0.0001$ (Figure 3b; Supplementary Table 10), $P_{nonlinearity} < 0.0001$ (Figure 3d; Supplementary Table 11), $P_{nonlinearity} < 0.0001$ (Figure 3f; Supplementary Table 11), with stronger reductions in risk at lower levels of intake. There was a 33% reduction in the relative risk at intakes of 800 g/day of fruits and vegetables, 20% reduction in the relative risk at 200–350 g/day of fruits and 28% reduction in the relative risk at 500 g/day of vegetables, and there was little evidence of further reductions in risk at higher intakes.

Eight studies (seven publications),[25,32,108–111,120] 11 studies (10 publications),[25–27,109,112–114,116,117,126] and nine studies (eight publications)[25–27,109–111,113,116] were included in the analyses of fruits and vegetables combined, fruits, and vegetables, and ischaemic stroke, respectively. The summary RR per 200 g/day was 0.92 (95% CI: 0.87–0.97, $I^2 = 9\%$) for fruits and vegetables (Supplementary Figures 7–9, Supplementary Tables 12, 29, available at *IJE* online), 0.78 (95% CI: 0.69–0.89, $I^2 = 58\%$) for fruits (Supplementary Figures 10–12, Supplementary Tables 12, 29) and 0.86 (95% CI: 0.76–0.97, $I^2 = 55\%$) for vegetables (Supplementary Figures 13–15, Supplementary Tables 12,

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

Food group	Comparison	n	Cases	Participants	RR (95% CI)	I^2	$P_{heterogeneity}$	Egger	References
Coronary heart disease									
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	11,16,19,24,27,33–56,58,60,63,64,75,76,88,98,124,125,127
	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									
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
All-cause 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	9–11,19,27,29,30,36,37,43,46,47,51–58,61,66,68,75,98,135–137,139
	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	9,19,27,29,34,38,46,47,51–58,66,68,75,98,136,137,139
	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

A | Fruits and vegetables and coronary heart disease, per 200 g/d

Study		Relative Risk (95% CI)
Buli-Cosiales, 2016		0.82 (0.65, 1.03)
Stefler, 2015		0.98 (0.79, 1.19)
Hjartåker, 2015		0.97 (0.83, 1.13)
Kobylecki, 2015		0.95 (0.90, 1.01)
Yu, 2014, SMHS		0.94 (0.81, 1.10)
Yu, 2014, SWHS		0.86 (0.72, 1.03)
Bhupatiraju, 2013, HPFS		0.92 (0.88, 0.97)
Bhupatiraju, 2013, NHS		0.90 (0.85, 0.96)
Rautiainen, 2012		0.91 (0.82, 1.00)
Crowe, 2011		0.93 (0.88, 0.98)
Dauchet, 2010		0.79 (0.56, 1.10)
Tucker, 2005		0.77 (0.50, 1.13)
Steffen, 2003		0.92 (0.79, 1.06)
Bazzano, 2002		0.94 (0.81, 1.08)
Liu, 2000		0.88 (0.73, 1.05)
Overall		0.92 (0.90, 0.94)

C | Fruits and coronary heart disease, per 200 g/d

Study		Relative Risk (95% CI)
Buli-Cosiales, 2016		0.95 (0.77, 1.18)
Du, 2016		0.85 (0.79, 0.91)
Stefler, 2016		0.90 (0.72, 1.14)
Wang, 2016		0.05 (0.01, 0.60)
Hjartåker, 2015		1.25 (0.88, 1.76)
Kobylecki, 2015		0.95 (0.86, 1.05)
Lai, 2015		0.83 (0.71, 0.98)
Rebello, 2014		0.76 (0.64, 0.89)
Sharma, 2014		0.98 (0.91, 1.05)
Yu, 2014, SMHS		0.97 (0.91, 1.03)
Yu, 2014, SWHS		0.89 (0.67, 1.18)
Bhupatiraju, 2013, HPFS		0.86 (0.77, 0.95)
Bhupatiraju, 2013, NHS		0.85 (0.75, 0.97)
Similä, 2013		0.94 (0.88, 0.98)
Crowe, 2011		0.90 (0.83, 0.98)
Dauchet, 2010		0.67 (0.39, 1.17)
Nagura, 2009		0.40 (0.14, 1.12)
Tucker, 2005		0.93 (0.55, 1.58)
Liu, 2000		0.77 (0.50, 1.19)
Whiteman, 1999		0.82 (0.23, 3.00)
Mann, 1997		0.80 (0.60, 1.08)
Sahyoun, 1996		0.73 (0.52, 1.02)
Knekt, 1994		1.18 (0.77, 1.81)
Fraser, 1992		
Overall		0.90 (0.86, 0.94)

E | Vegetables and coronary heart disease, per 200 g/d

Study		Relative Risk (95% CI)
Buli-Cosiales, 2016		0.76 (0.54, 1.07)
Stefler, 2016		1.02 (0.79, 1.30)
Wang, 2016		0.75 (0.63, 0.90)
Hjartåker, 2015		0.72 (0.53, 0.97)
Kobylecki, 2015		0.94 (0.85, 1.05)
Rebello, 2014		0.63 (0.46, 0.87)
Sharma, 2014		0.91 (0.85, 0.97)
Yu, 2014, SMHS		0.99 (0.81, 1.22)
Yu, 2014, SWHS		0.82 (0.61, 1.12)
Bhupatiraju, 2013, HPFS		0.95 (0.88, 1.01)
Bhupatiraju, 2013, NHS		0.90 (0.83, 0.98)
Crowe, 2011		0.93 (0.86, 1.03)
Dauchet, 2010		0.77 (0.32, 1.88)
Nagura, 2009		0.33 (0.10, 1.15)
Tucker, 2005		0.46 (0.21, 0.93)
Liu, 2001		0.63 (0.42, 0.95)
Liu, 2000		0.95 (0.75, 1.22)
Pietinen, 1996		0.42 (0.28, 0.63)
Sahyoun, 1996		0.54 (0.33, 0.87)
Knekt, 1994		0.64 (0.46, 0.90)
Overall		0.84 (0.79, 0.90)

B | Fruits and vegetables and coronary heart disease, nonlinear dose-response

D | Fruits and coronary heart disease, nonlinear dose-response

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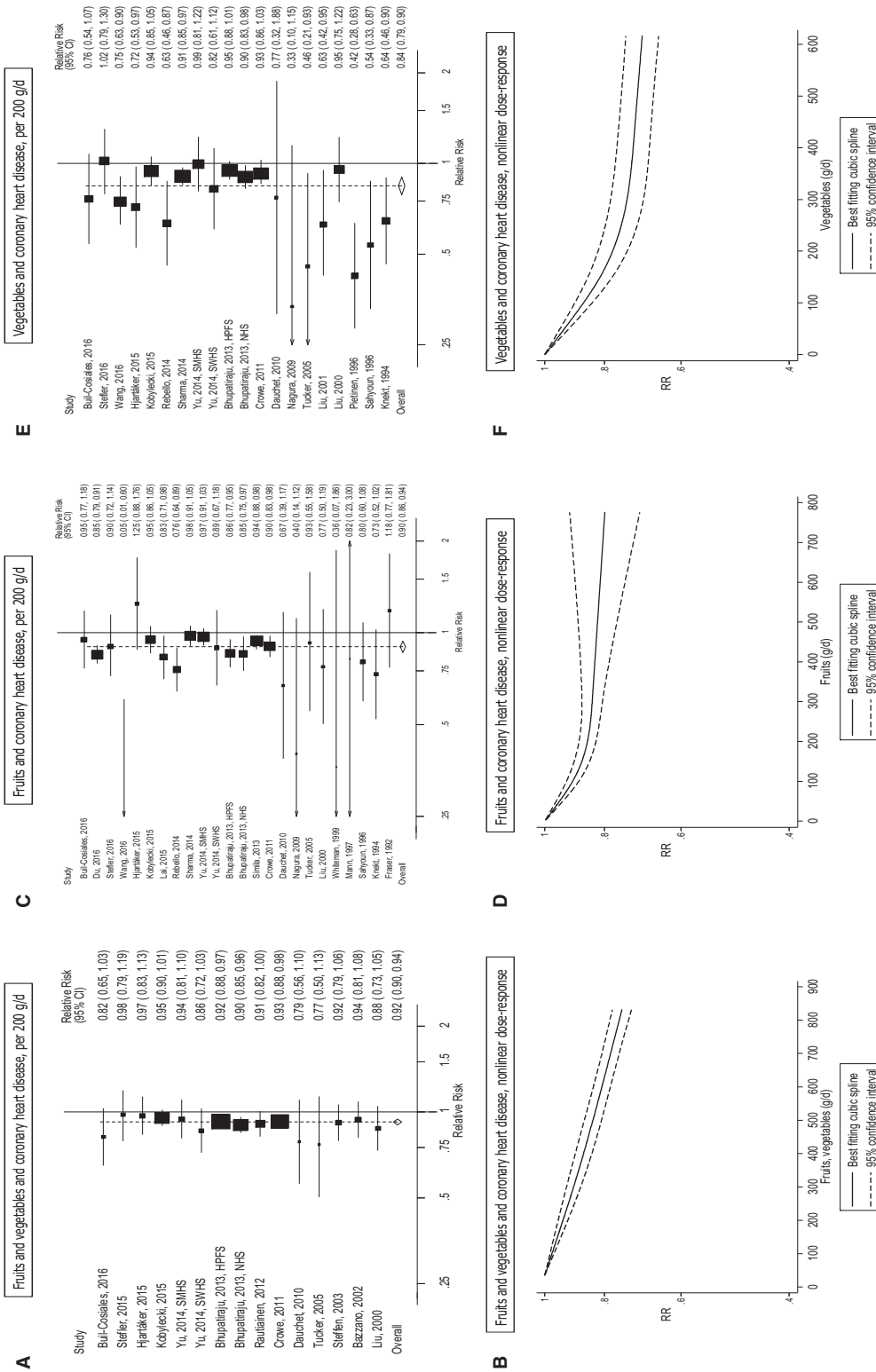
Figure 2. Fruits, vegetables and coronary heart disease, linear and nonlinear dose-response.

Table 2. Fruit and vegetable subtypes and coronary heart disease

Fruit, vegetable subtype	High vs low analysis					Dose-response analysis					
	n	RR (95% CI)	I²	P_h	References	n	Increment	RR (95% CI)	I²	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	3	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	4	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)	–	–	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	34,105,145	2	Per 100 g/d	0.60 (0.15–2.42)	76.5	0.04	105,145
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
Lutein 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

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.

F&V, fruit and vegetables.
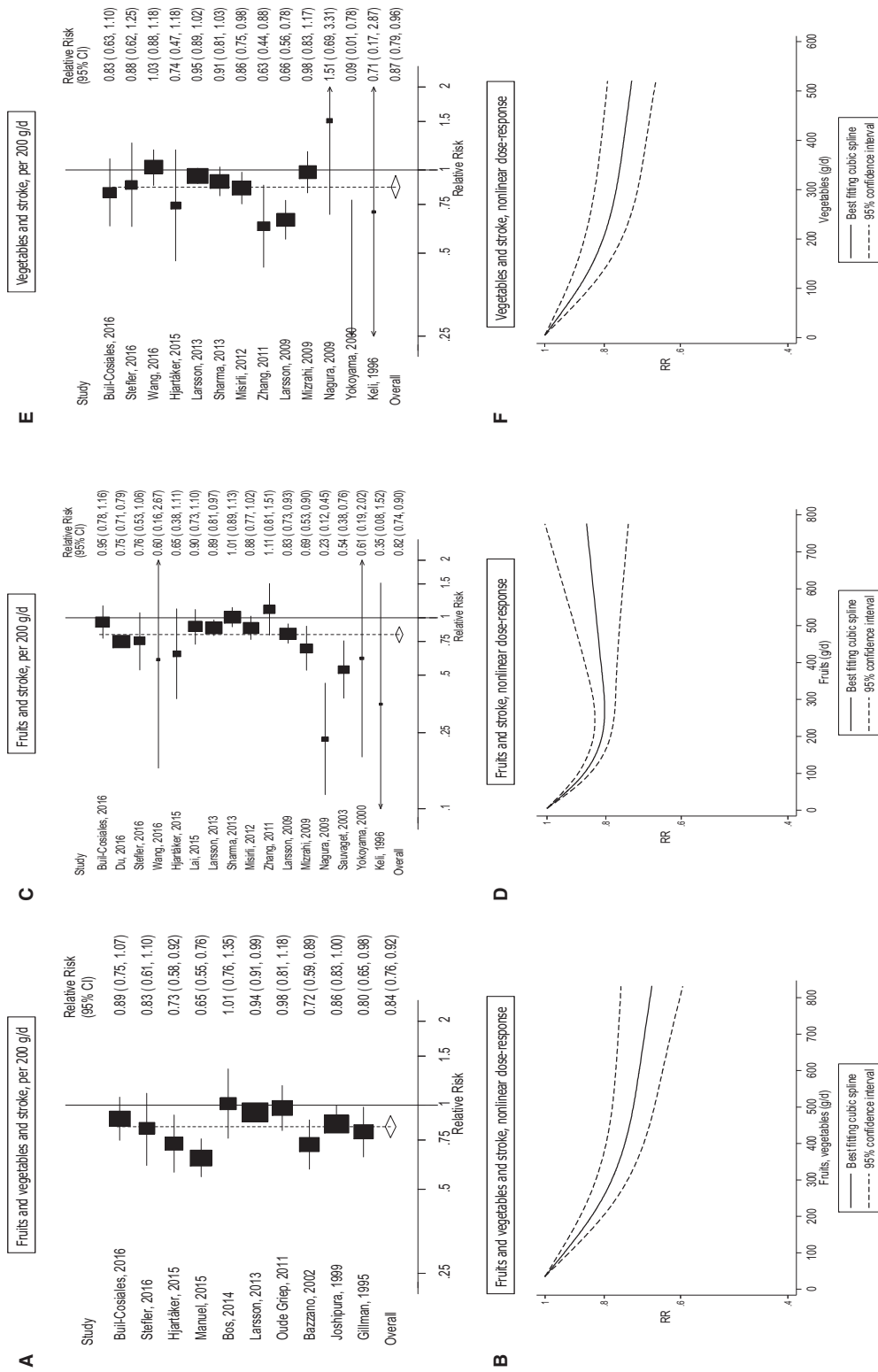
P_h = P-value for heterogeneity.

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

29). Three studies (two publications, two risk estimates)[108,109], eight studies (seven publications, seven risk estimates)[19,25–27,63,109,113] and six studies (five publications, five risk estimates)[19,25,27,63,113] were included in the analyses of fruits and vegetables combined, fruits, and vegetables, and haemorrhagic stroke, respectively. The summary RR per 200 g/day was 0.88 (95% CI: 0.78–0.99, $I^2 = 0\%$) for fruits and vegetables combined (Supplementary Figure 16, Supplementary Table 29), 0.66 (95% CI: 0.50–0.86, $I^2 = 57\%$) for fruits (Supplementary Figures 17–19, Supplementary Tables 13, 29), and 0.76 (95% CI: 0.55–1.06, $I^2 = 42\%$) for vegetables (Supplementary Figures 20–22, Supplementary Tables 13, 29).

Of specific types of fruit and vegetables,[11,26,56,60,62,64,109,112,119,141–144,146,148–150,164] high intakes of apples/pears, citrus fruits, fruit juice, green leafy vegetables and pickled vegetables were inversely associated with total stroke risk, whereas intake of grapes was also inversely associated with total stroke in the dose-response analysis (Table 3, Supplementary Tables 21–22, Supplementary Figures 77–109). For ischaemic 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 haemorrhagic stroke[26,109,146,150,164] were significant (Table 3; Supplementary Table 23, Supplementary Figures 110–140).

Cardiovascular disease

Seventeen studies (16 publications),[15,16,18,31,39,42,53,56,58,64,75,86–88,98,125] 25 studies (23 publications)[11,15,16,19,24,27,53–56,58,60–64,75,76,88,98,124,125,127] and 22 studies (19 publications)[15,16,19,24,27,53–56,58,62,64,75,76,88,98,124,125,127] 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, b, Table 1; Supplementary Figure 23), 0.87 (95% CI: 0.82–0.92, $I^2 = 79\%$) for fruits (Figure 4c, d, Table 1; Supplementary Figure 24), and 0.90 (95% CI: 0.87–0.93, $I^2 = 12\%$) for vegetables (Figure 4e, 4f, Table 1, Supplementary Figure 25). There was evidence of nonlinearity, $P_{nonlinearity} < 0.0001$, for fruits and vegetables (Figure 4b; Supplementary Table 14), and fruits, $P_{nonlinearity} < 0.0001$, (Figure 4d; Supplementary Table 15), and for vegetables, $P_{nonlinearity} = 0.04$ (Figure 4f; Supplementary Table 15), with steeper inverse associations at lower levels of intake, although for vegetables the association was approximately linear. There were 28%, 27% and 28% reductions in relative risk at intakes of 800 g/day for fruits

and vegetables and fruits, and 600 g/day of vegetables, respectively.

Of specific types of fruits and vegetables[11,15,16,19,56,60–62,64,75,87,123,124,129,141,142,144,146,148,151,152,154,159,164] there was evidence that high vs low intake of apples/pears, citrus fruits, carrots and noncruciferous vegetables were inversely associated, and tinned fruits were positively associated with cardiovascular disease risk, and in the nonlinear dose-response analysis there was evidence that cruciferous vegetables, green leafy vegetables, and tomatoes were inversely associated with risk, although few studies were included in these analyses (Table 4; Supplementary Tables 24 and 25, Supplementary Figures 141–178).

Total cancer

Fourteen studies (13 publications),[7,8,13,15,16,18,20,42,53,56,59,87,128] 25 studies (22 publications),[7–11,13–17,19–21,53,54,56,57,59,61,65,114,128] and 19 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, b, Table 1; Supplementary Figure 26), 0.96 (95% CI: 0.94–0.99, $I^2 = 52\%$) for fruits (Figure 5c, d, Table 1; Supplementary Figure 27) and 0.96 (95% CI: 0.93–0.99, $I^2 = 55\%$) for vegetables (Figure 5e, f, Table 1; Supplementary Figure 28). There was evidence of nonlinearity for fruits and vegetables, $P_{nonlinearity} = 0.02$ (Figure 5b; Supplementary Table 16), fruits, $P_{nonlinearity} = 0.02$ (Figure 5d; Supplementary Table 17), and vegetables, $P_{nonlinearity} = 0.03$ (Figure 5f; Supplementary Table 17), 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 550–600 g/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[8–12,14–16,19,54,56,87,105,130,143,153–160] there were significant inverse associations between cruciferous vegetables and green-yellow vegetables and total cancer risk (Table 5; Supplementary Table 26, Supplementary Figures 179–209).

All-cause mortality

In all, 24 studies (23 publications),[18,29,31,32,39,42–44,47–50,53,56,58,67,68,75,87,98,132,134,161] 37 studies (36 publications),[9–11,19,27,29,30,35–37,40,43,45–47,51–58,61,62,66,68,75,98,131–133,135–137,139] and 33 studies (31 publications)[9,19,27,29,33–

Table 3. Fruit and vegetable subtypes and total stroke, ischaemic stroke and haemorrhagic stroke

| Fruit, vegetable subtype | High vs low analysis | | | | | Dose-response analysis | | | | | |
	n	RR (95% CI)	I²	P_h	References	n	Increment	RR (95% CI)	I²	P_h	References
Total stroke											
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
Ischaemic stroke											
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)	3.5	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)	0	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
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
Haemorrhagic stroke											
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

F&V, fruit and vegetables.

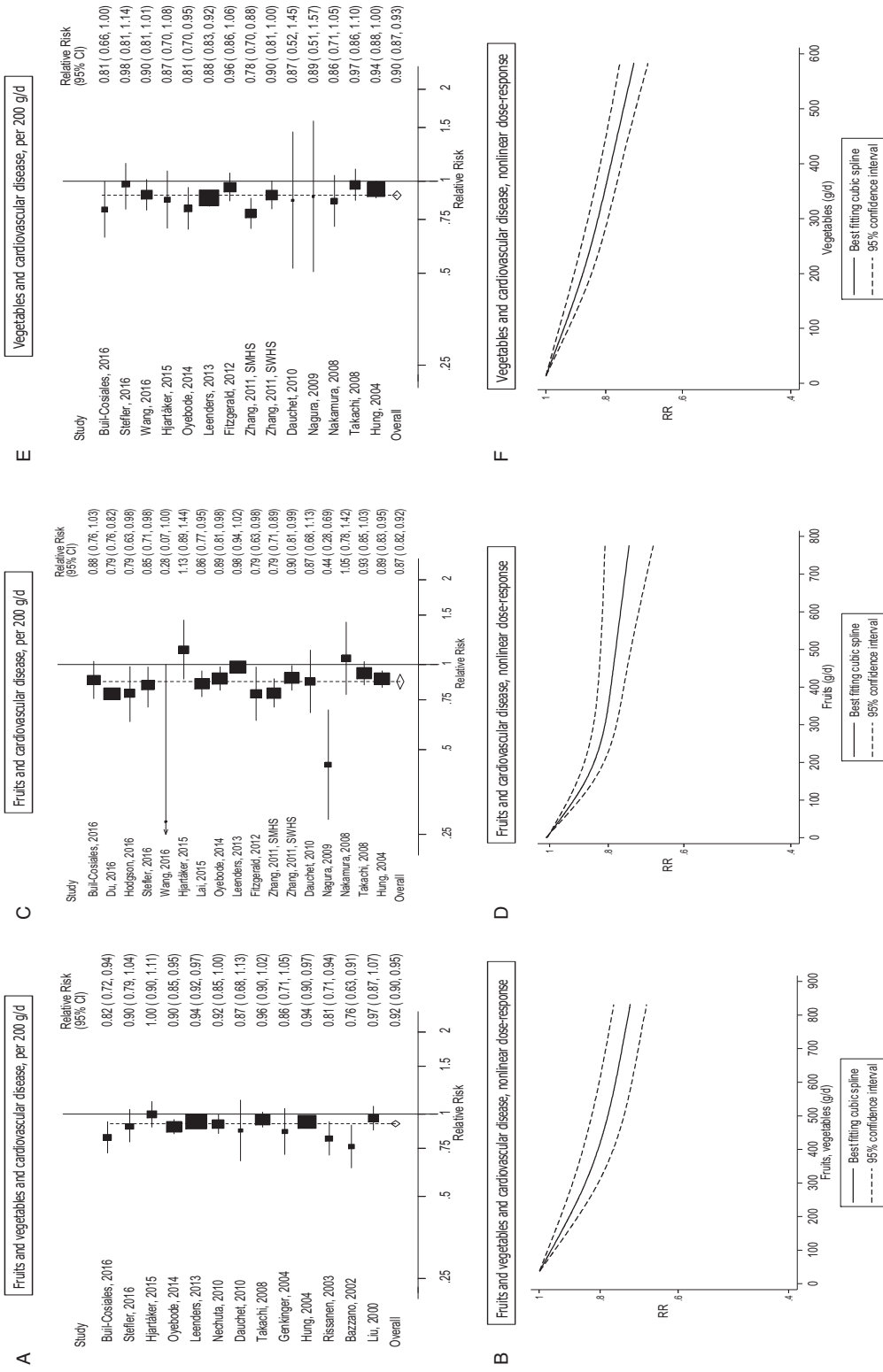P_h = P-value for heterogeneity.

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

Table 4. Fruit and vegetable subtypes and cardiovascular disease

Fruit, vegetable subtype	High vs low analysis					Dose-response analysis					
	n	RR (95% CI)	I²	Pₕ	References	n	Increment	RR (95% CI)	I²	Pₕ	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)	-	-	144
Tinned 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)	-	-	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

F&V, fruit and vegetables.
Pₕ = P-value for heterogeneity.

A Fruits and vegetables and total cancer, per 200 g/d

Study		Relative Risk (95% CI)
Choi, 2015		0.98 (0.94, 1.03)
Hjartåker, 2015		0.86 (0.72, 1.03)
Oyebode, 2014		0.91 (0.86, 0.96)
Wie, 2014		1.00 (0.92, 1.10)
Lof, 2011		0.99 (0.93, 1.05)
Boffetta, 2010		0.97 (0.96, 0.99)
Nechuta, 2010		1.01 (0.95, 1.08)
Takachi, 2008		0.98 (0.94, 1.02)
Genkinger, 2004		0.81 (0.66, 1.00)
Hung, 2004		1.00 (0.97, 1.02)
Jansen, 2004		0.69 (0.48, 1.00)
Shibata, 1992		0.95 (0.89, 1.01)
Overall		0.97 (0.95, 0.99)

B Fruits and vegetables and total cancer, nonlinear dose-response

C Fruits and total cancer, per 200 g/d

Study		Relative Risk (95% CI)
Hodgson, 2016		0.78 (0.60, 1.00)
Orenstein, 2016		1.27 (0.77, 2.09)
Choi, 2015		1.02 (0.92, 1.13)
Hjartåker, 2015		0.48 (0.33, 0.71)
Bull-Cosiales, 2014		0.86 (0.69, 1.07)
Oyebode, 2014		0.94 (0.85, 1.05)
Wie, 2014		1.02 (0.89, 1.17)
Sharma, 2013		0.95 (0.91, 1.00)
Lof, 2011		1.01 (0.96, 1.05)
Zhang, 2011, SMHS		0.97 (0.84, 1.12)
Zhang, 2011, SWHS		0.95 (0.88, 1.03)
Boffetta, 2010		0.97 (0.95, 0.99)
George, 2009		1.01 (0.94, 1.07)
Takachi, 2008		0.98 (0.90, 1.03)
Hung, 2004		0.62 (0.40, 0.96)
Jansen, 2004		0.72 (0.56, 0.91)
Sauvaget, 2003		0.67 (0.21, 2.14)
Whiteman, 1999		1.10 (0.73, 1.65)
Sahyoun, 1996		0.86 (0.77, 0.97)
Shibata, 1992		0.96 (0.94, 0.99)
Overall		

D Fruits and total cancer, nonlinear dose-response

E Vegetables and total cancer, per 200 g/d

Study		Relative Risk (95% CI)
Orenstein, 2016		0.71 (0.45, 1.13)
Choi, 2015		0.91 (0.85, 0.98)
Hjartåker, 2015		1.37 (0.98, 1.91)
Bull-Cosiales, 2014		0.75 (0.55, 1.02)
Oyebode, 2014		0.74 (0.63, 0.87)
Wie, 2014		0.95 (0.79, 1.14)
Sharma, 2013		0.92 (0.87, 0.98)
Lof, 2011		1.04 (0.92, 1.17)
Zhang, 2011, SMHS		1.02 (0.96, 1.09)
Zhang, 2011, SWHS		1.05 (0.96, 1.14)
Boffetta, 2010		0.96 (0.94, 0.98)
George, 2009		0.97 (0.93, 1.01)
Takachi, 2008		0.94 (0.87, 1.02)
Hung, 2004		0.99 (0.96, 1.03)
Jansen, 2004		0.80 (0.46, 1.38)
Sahyoun, 1996		0.82 (0.43, 1.56)
Shibata, 1992		0.96 (0.88, 1.04)
Overall		0.96 (0.93, 0.99)

F Vegetables and total cancer, nonlinear dose-response

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

Table 5. Fruit and vegetable subtypes and total cancer

Fruit, vegetable subtype	n	High vs low analysis				n	Dose-response analysis				
		RR (95% CI)	I²	P_h	References		Increment	RR (95% CI)	I²	P_h	References
Citrus fruits	5	0.97 (0.90–1.04)	61.0	0.04	9,16,143,155,156	6	Per 100g/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 100g/d	–	–	–	–
Tinned fruits	3	0.90 (0.77–1.05)	0	0.99	159	4	Per 100g/d	0.82 (0.66–1.01)	0	0.96	154,159
Fruit juice	1	0.99 (0.92–1.07)	–	–	143	2	Per 100g/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 100g/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 100g/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 100g/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 100g/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 100g/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 100g/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 100g/d	0.75 (0.54–1.04)	0	0.52	105,130
Pickled vegetbles	2	0.96 (0.90–1.02)	0	0.99	14,143	1	Per 100g/d	0.92 (0.78–1.10)	–	–	143
Potatoes	2	1.02 (0.86–1.22)	31.0	0.23	14,143	3	Per 100g/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 100g/d	0.88 (0.49–1.59)	–	–	56
Tomatoes	3	0.86 (0.67–1.10)	70.1	0.04	56,143,153	2	Per 100g/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 100g/d	0.97 (0.89–1.06)	0	0.47	8,16,143
Juice	1	0.98 (0.81–1.19)	–	–	160	2	Per 100g/d	1.00 (0.94–1.07)	0	0.54	158,160

P_h = P-value for heterogeneity.

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, b, Table 1; Supplementary Figure 29), 0.85 (95% CI: 0.80–0.91, $I^2 = 90\%$) for fruits (Figure 6c, d, Table 1; Supplementary Figure 30), and 0.87 (95% CI: 0.82–0.92, $I^2 = 82\%$) for vegetables (Figure 6e, f, Table 1; Supplementary Figure 31). 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 31%, 19% and 25% reductions in the relative risk with intakes of 800 g/day for fruits and vegetables combined, and at 600 g/day for fruits, and for vegetables, respectively.

Of specific types of fruits and vegetables,[9,11,19,30,34,37,38,43,44,53,54,56,61,62,67,68,75,87,105,133,138,143,159] there was evidence that high vs low intake of apples/pears, berries, citrus fruits, fruit juice, cooked vegetables, cruciferous vegetables, potatoes and green leafy vegetables/salads were inversely associated with all-cause mortality and tinned fruits were positively associated with all-cause mortality; whereas in the dose-response analysis fruit juice, cruciferous vegetables and green leafy vegetables/salads were significantly associated with reduced risk and tinned fruits were associated with increased risk (Table 6; Supplementary Table 27, Supplementary Figures 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 all-cause mortality (Table 1; Supplementary Figures 243–248, available at *IJE* online). However, excluding studies with < 150 or < 200 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 all-cause 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 Figures 249–263, available at *IJE* online). We also repeated the nonlinear dose-response analyses using fractional polynomial models and in general found
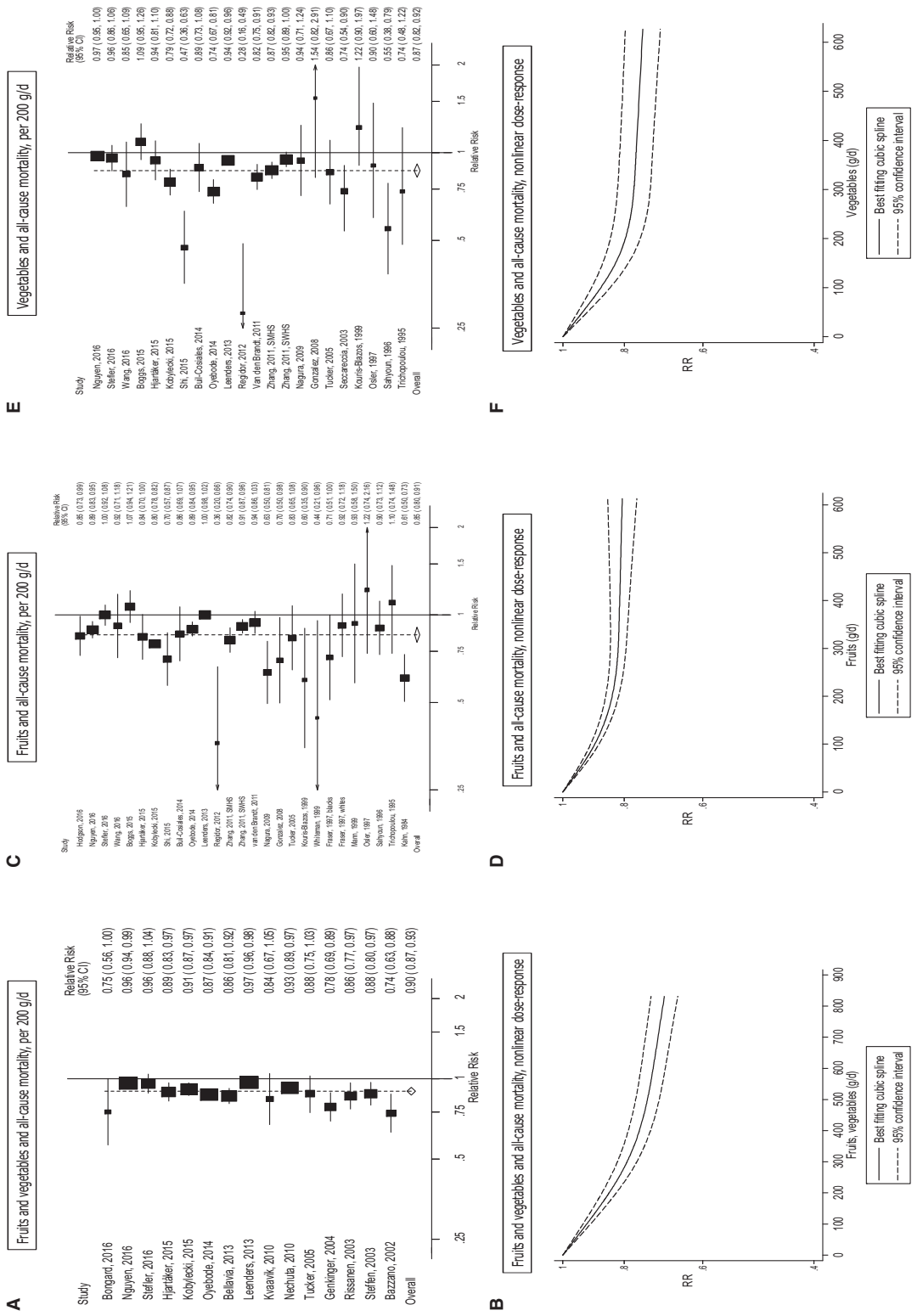
Figure 6. Fruits, vegetables and all-cause mortality, linear and nonlinear dose-response.

Table 6. Fruit and vegetable subtypes and all-cause mortality

Fruit, vegetable subtype	High vs low analysis					Dose-response analysis					
	n	RR (95% CI)	I²	P_h	References	n	Increment	RR (95% CI)	I²	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.

similar risk estimates compared with 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, outcome type (incidence vs mortality), outcome subtype (MI vs. total CHD, or ischemic vs hemorrhagic), sex, geographical 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 Tables 28–32, available at *IJE* online). The study quality was in general high as the vast majority of studies were in the group with 7–9 stars (Supplementary Tables 28–32). The mean (median) study quality scores of the studies included in the dose-response analysis were 8.0 (8.0), 7.5 (8.0), 7.7 (8.0) for fruits and vegetables, fruits, and vegetables and coronary heart disease, respectively. The respective means (medians) were 7.9 (8.0), 7.7 (8.0), and 7.7 (8.0) for stroke, 7.8 (8.0), 7.7 (8.0), 7.8 (8.0) for cardiovascular disease, 7.9 (8.0), 8.0 (8.0), and 8.1 (8.0) for total cancer, and 7.7 (8.0), 7.1 (7.0), and 7.5 (8.0) for all-cause mortality. 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, $P_{heterogeneity} = 0.003$, 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 body mass index (BMI) than among studies without such adustment, $P_{heterogeneity} = 0.03$, and in the analysis of vegetables and cardiovascular disease there was a stronger association among studies with mortality as the outcome compared with studies with incidence as the outcome, $P_{heterogeneity} = 0.03$ (Supplementary Table 30). In the analysis of fruits and total cancer and all-cause mortality there was heterogeneity ($P_{heterogeneity} = 0.03$ and $P_{heterogeneity} = 0.02$, respectively) by adjustment for energy intake, with weaker (but still significant) associations in studies with such adjustment compared to studies without such adjustment (Supplementary Tables 31, 32). In the analysis of fruits and vegetables and all-cause mortality there was a weaker association among the studies that adjusted for red and processed meat intake compared to studies with such adjustment, $P_{heterogeneity} < 0.0001$, and in the analysis of vegetables and all-cause mortality there was a stronger association among the studies without adjustment for smoking than among studies with such adjustment, $P_{heterogeneity} = 0.003$ (Supplementary Table 32).

Table 7. Attributable fractions and numbers of deaths from coronary heart disease, stroke, cardiovascular disease, cancer and all-causes by region due to a fruit and vegetable intake below 500 g/day or 800 g/day (based on studies reporting on coronary heart disease, stroke, cardiovascular disease and cancer mortality only and 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	9.3	710356	17.7	1345327	22.9	1468264	41.8	2682358	7.7	1257996	13.8	2267152	6.9	562056	8.1	657923	11.3	5381962	16.3	7791293

A list of the country-specific attributable fractions and numbers of deaths attributable to a low fruit and vegetable intake is found in Supplementary Table 33

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

Under the assumption that the observed associations are causal we estimated that the number of premature deaths attributable to a fruit and vegetable intake below 800 g/day in 2013 was 1 340 000 for coronary heart disease, 2 680 000 for stroke, 2 270 000 for cardiovascular disease, 660 000 for cancer and 7 800 000 for all-cause mortality (Table 7). We repeated these calculations using 500 g/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 combined number of deaths potentially preventable from coronary heart disease and stroke was larger than for cardiovascular disease probably because the studies included in each analysis were not the same and because there was a stronger association 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 coronary heart disease, 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/day, respectively.

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 g/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 all-cause mortality, respectively, for an intake of 500 g of fruits and vegetables per day vs 0–40 g/day, whereas an intake of 800 g/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 g/day in 2013, and this increased to 1.34 million coronary heart disease deaths, 2.68 million stroke deaths, 660 000 cancer deaths and 7.8 million deaths from all causes when using 800 g/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 g/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 g/day (7–7.5 servings/day) for total cancer, with little evidence of further reductions in risk with higher intakes, whereas for coronary heart disease, stroke, cardiovascular disease and all-cause mortality the lowest risk was observed at 800 g/day (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/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 all-cause mortality (apples/pears, berries, citrus fruits, cooked vegetables, cruciferous vegetables, potatoes, and green leafy vegetables/salads). In contrast, intake of tinned fruits was associated with increased risk of cardiovascular disease and all-cause 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, results for subtypes of fruit and vegetables and estimations of the burden of mortality due to a low fruit and vegetable intake as well. In comparison with the most recent meta-analysis on mortality which included less than half the studies in the present analysis, we found a slightly stronger association between fruit and vegetable intake and all-cause mortality with reductions in risk observed up to 800 g/day (or ten servings per day), although

the reduction in risk was steepest up to 400 g/day, whereas the previous meta-analysis found no further benefit above five servings per day (400 g/day).[41] In addition, we found significant inverse associations with overall cancer risk, which is consistent with data for some individual cancer sites,[2,72,73,165–167] but in contrast to the previous meta-analysis which may have had limited power to detect a weak association.[41] An interesting finding in the present meta-analysis is that fruit and vegetable intake was as strongly related to 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 specific causes of death other than cardiovascular disease and cancer.

Fruit and vegetables contain of a myriad of nutrients and phytochemicals, including fibre, 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.[176] Dietary fibre and fruit and vegetable intakes have been shown to reduce cholesterol levels, blood pressure, inflammation and platelet aggregation, and to improve vascular and immune function,[177–180] and recent meta-analyses showed inverse associations between fibre intake and cardiovascular disease.[181,182] Antioxidants in fruit and vegetables may neutralize reactive oxygen species and reduce DNA damage,[178] glucosinolates in cruciferous vegetables induce detoxifying enzymes[183] and intake of fruits, vegetables and fibre may modulate steroid hormone concentrations and hormone metabolism[178] and may have a beneficial effect on gut microbiota.[177] In addition, fruit and vegetable intake has been inversely associated with risk of developing overweight or obesity and with weight gain[184–186] although data are not entirely consistent;[187] 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, glycaemic load and sodium; however, most of the associations persisted in subgroups of studies that adjusted for dietary fat or meat intake.

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 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 by 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, geographical location, sample sizes, detail of the dietary assessment method, and factors adjusted for in the analyses. There are also likely to be large differences between populations 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. However, when we conducted subgroup analyses to investigate sources of the heterogeneity, we found in general little evidence of heterogeneity between most subgroups. In the few subgroup analyses where the test for heterogeneity was significant there were often relatively few studies in one of the subgroups, and chance can not be excluded as an explanation.

Fruit and vegetable intake is often associated with other lifestyle factors such as lower prevalence of smoking, less overweight and obesity, higher physical activity and lower intakes of alcohol and red and processed meat, which could have confounded the observed associations. Many studies adjusted for these and other confounding factors, and we found little evidence that the results varied substantially whether or not adjustment for most of these confounders was done. It is possible that persons with a high fruit and vegetable intake may be more likely to undergo screening or have better access to or compliance with treatment, and this could lead to an improved survival and bias the results for mortality. There was little heterogeneity when studies were stratified by whether the outcome was incidence or mortality of cardiovascular disease or total cancer, although in a few analyses risk estimates were slightly stronger for mortality; however, power may have been low to detect a difference because of a moderate number of studies in each subgroup. The possibility of residual confounding by imprecisely measured, unknown or unmeasured confounders cannot be entirely excluded.

Measurement error in the assessment of fruit and vegetable intake and changes in fruit and vegetable intake during follow-up may have influenced the results, but to date only the EPIC study[23,75] and the China Kadoorie Cohort Study[63] have assessed the impact of measurement errors and

regression dilution bias due to changes in intake during follow-up on these outcomes. The HR for all-cause mortality was 0.97 (95% CI: 0.96–0.98) per 200 g/day of fruit and vegetable intake without correction for measurement error compared with 0.94 (95% CI: 0.91–0.96) with correction for measurement error,[75] and the corresponding HRs for ischaemic heart disease mortality (per 80 g/day) were 0.97 (95% CI: 0.95–0.99) and 0.95 (95% CI: 0.91–0.99),[23] respectively, in the EPIC study. In the China Kadoorie Cohort Study the HR of cardiovascular death with one daily portion of fresh fruit intake was 0.77 (95% CI: 0.72–0.83) before and 0.63 (95% CI: 0.56–0.72) after correction for regression dilution. This suggests 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 with lower intakes could partly 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 and 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 or ethnicity. However, we did not find significant heterogeneity in the association between fruits and vegetables and the outcomes considered by region for the geographical locations for which data were available (North America, Europe, Australia and Asia). Two studies on fruit and vegetable intake and all-cause mortality in African Americans showed mixed results, with one reporting an inverse association,[30] and a second study reporting no clear association.[139] An analysis from the Latin American countries in the INTERHEART study suggested a similar association between fruit and vegetable intake and coronary heart disease[188] as in the overall study.[189]

Last, the appropriateness of the estimates of the number of deaths attributable to a fruit and vegetable intake below 500 or 800 g/day is dependent on the validity of several assumptions that were made including that of: (i) a causal relationship between fruit and vegetable intake and these outcomes; (ii) lack of confounding; and (iii) 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 and experimental evidence (on intermediate risk markers).[190] However, 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 all-cause mortality comparing an intake of 800 g/day with no intake, weak or moderate associations should not be dismissed as non-causal.[190] 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 a low fruit and vegetable intake. As already mentioned, the association between fruit and vegetable intake and cardiovascular disease, cancer and all-cause mortality persisted in many subgroup analyses when stratified by adjustment for confounding factors. 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. Confounding might exaggerate the observed associations but measurement errors would most likely tend to attenuate the observed associations. Because the distributions of causes of death differ substantially in sub-Saharan Africa compared with other regions, the results from existing cohort studies on all-cause mortality may not be generalizable to this region. 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 g/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 geographical 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 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.

Strengths of this analysis include the wide search terms used, the large number of studies included from various geographical locations and the large number of cases and deaths (up to 43 000 coronary heart disease cases, 47 000 stroke cases, 81 000 cardiovascular disease cases, 112 000 cancer cases and >71 000–94 000 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 geographical regions which have 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 geographical 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 all-cause 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 g/day (7.5 servings/day), whereas for coronary heart disease, stroke, cardiovascular disease and all-cause mortality the lowest risk was observed at 800 g/day (10 servings/day), a level of intake that is double the five servings per day (400 g/day) currently recommended by the World Cancer Research Fund, the WHO, and in England.[5] In 2013, an estimated 1 340 000 coronary heart disease deaths, 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 g/day globally. A change in the diet towards a higher intake of fruit and vegetables and other plant foods could also have other important health[168–175,192,193] as well as environmental benefits.[194] 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.

Supplementary Data

Supplementary data are available at *IJE* online.

Author Contributions

D.A. 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: D.A., E.G., P.B., S.T. Acquisition, analysis or interpretation of data: D.A., E.G., P.B., N.K., L.T.F., T.N., D.C.G., E.R., L.J.V., S.T. Drafting of manuscript: D.A. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: D.A., D.C.G.. Obtained funding: D.A., E.G., P.B., E.R., L.J.V., S.T. Study supervision: S.T.

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