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, I² = 0%, n = 15] for coronary heart disease, 0.84 (95% CI: 0.76–0.92, I² = 73%, n = 10) for stroke, 0.92 (95% CI: 0.90–0.95, I² = 31%, n = 13) for cardiovascular disease, 0.97 (95% CI: 0.95–0.99, I² = 49%, n = 12) for total cancer and 0.90 (95% CI: 0.87–0.93, I² = 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.

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**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. 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, coronary heart disease and stroke. 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). Data regarding fruit and vegetable intake and cancer risk are less clear-cut today than a decade or two ago. A modest association between fruit and vegetable intake of specific subtypes of fruits and vegetables and total cancer risk cannot yet be excluded, but the available studies have been inconsistent. Some studies reported inverse associations, whereas other studies found no clear association; however, some of these may have had statistical power too low to detect a modest association. Cohort studies have been more consistent in finding an inverse association between fruit and vegetable intake and risk of coronary heart disease and stroke than for cancer, and this has also been shown in meta-analyses as well as in several additional studies that have been published since these meta-analyses. In addition, several but not all 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.
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, the review missed or excluded a large number of publications on all-cause mortality 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 recalculated the confidence intervals from 99% to 95%.43,60
We conducted linear dose-response analyses using the method by Greenland and Longnecker\textsuperscript{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.\textsuperscript{72,73} For specific fruit and vegetable types we used serving sizes as provided in a pooled analysis of cohort studies,\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{77,78} We conducted a sensitivity analysis using fractional polynomial models for the nonlinear analysis as well,\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{33,84} We used data on mortality from the Global Burden of Disease Study 2013.\textsuperscript{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.\textsuperscript{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\textsuperscript{7–40,42–68,75,76,86–164} (Figure 1; Supplementary Tables 3–7, available at IJE online); 44,49772 records identified in total: 40744 records identified in the PubMed database 9028 records identified in the Embase database 48386 records excluded based on title or abstract 1386 records given detailed assessment Updated search: 4 publications 370 records on fruit and vegetable intake 1020 reported on other exposures than fruit and vegetable intake 228 publications excluded: 45 case-control studies 41 reviews 33 duplicates 23 not relevant exposure/outcome 17 abstract only publications 16 no risk estimates, confidence intervals, or not usable result 14 meta-analyses 10 comments/news/editorials 7 studies in subjects with diabetes 7 not original data 3 household intake (not individual) 3 cross-sectional studies 3 ecological studies 2 secondary prevention study 2 unadjusted risk estimates 2 only 1 study for F&V subtype 95 cohort studies (142 publications) included

**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. 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), 23,29,31,32,56,58,64,86,88,90,91,93,94,96,100,101,103,104,108,110,118,120,122 and 26 studies (26 publications), 9–11,22,23,27,29,36,35,36,56,60,62–64,86,88,91,92,94,95,98–100,104,132 were included in the analyses of fruit and vegetables combined, fruits alone and vegetable alone and coronary heart disease, respectively. The summary RR per 200 g/day was 0.92 (95% CI: 0.76–0.92, I² = 73%) for fruits and vegetables (Figure 2; Table 1), 0.90 (95% CI: 0.86–0.94, I² = 44%) for fruits (Figure 2c, d; Table 1; Supplementary Figure 2), and 0.84 (95% CI: 0.79–0.90, I² = 61%) for vegetables (Figure 2e, f; 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 apples/ pears, citrus fruits, fruit juices, green leafy vegetables, betacarotene-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), 31,36,58,64,108–110,118,120,122 and 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, I² = 73%) for fruits and vegetables (Figure 3a, b; Table 1; Supplementary Figure 4), 0.82 (95% CI: 0.74–0.90, I² = 73%) for fruits (Figure 3c, d; Table 1; Supplementary Figure 5), and 0.87 (95% CI: 0.79–0.96, I² = 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 and nine studies (eight 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, I² = 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, I² = 58%) for fruits (Supplementary Figures 10–12, Supplementary Tables 12, 29) and 0.86 (95% CI: 0.76–0.97, I² = 55%) for vegetables (Supplementary Figures 13–15, Supplementary Tables 12,
<table>
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<th>Food group</th>
<th>Comparison</th>
<th>n</th>
<th>Cases</th>
<th>Participants</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>Heterogeneity</th>
<th>Egger</th>
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<td><strong>Coronary heart disease</strong></td>
<td>Fruit and vegetables</td>
<td>High vs low</td>
<td>16</td>
<td>18516</td>
<td>792197</td>
<td>0.87 (0.83–0.91)</td>
<td>0</td>
<td>0.52</td>
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<td></td>
<td>Per 200 g/d</td>
<td>15</td>
<td>17742</td>
<td>775132</td>
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<td>0</td>
<td>0.96</td>
<td>0.12</td>
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<td>25</td>
<td>40229</td>
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<td>Per 200 g/d</td>
<td>24</td>
<td>43336</td>
<td>1555553</td>
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<td>43.3</td>
<td>0.01</td>
<td>0.04</td>
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<td>Vegetables</td>
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<td>22</td>
<td>34754</td>
<td>2123415</td>
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<td>1.9</td>
<td>0.43</td>
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<tr>
<td></td>
<td>Per 200 g/d</td>
<td>20</td>
<td>20853</td>
<td>1047071</td>
<td>0.84 (0.79–0.90)</td>
<td>60.6</td>
<td>&lt; 0.0001</td>
<td>0.001</td>
<td></td>
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<td>Fruit and vegetables</td>
<td>High vs low</td>
<td>8</td>
<td>10560</td>
<td>226910</td>
<td>0.79 (0.71–0.88)</td>
<td>37.6</td>
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<td>Per 200 g/d</td>
<td>10</td>
<td>11644</td>
<td>303338</td>
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<td>73.3</td>
<td>&lt; 0.0001</td>
<td>0.08</td>
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<td>Fruit</td>
<td>High vs low</td>
<td>17</td>
<td>46951</td>
<td>960337</td>
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<td>36.3</td>
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<td>Per 200 g/d</td>
<td>16</td>
<td>46203</td>
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<td>60.6</td>
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<td>High vs low</td>
<td>13</td>
<td>14519</td>
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<td>High vs low</td>
<td>16</td>
<td>27842</td>
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<td>13</td>
<td>20329</td>
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<td>31.3</td>
<td>0.13</td>
<td>0.99</td>
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<td>Fruit</td>
<td>High vs low</td>
<td>21</td>
<td>81807</td>
<td>1605227</td>
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<td>70.9</td>
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<td>Per 200 g/d</td>
<td>17</td>
<td>72648</td>
<td>1492617</td>
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<td>79.1</td>
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<td>Vegetables</td>
<td>High vs low</td>
<td>18</td>
<td>32049</td>
<td>101118</td>
<td>0.89 (0.85–0.94)</td>
<td>43.2</td>
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<td>Per 200 g/d</td>
<td>14</td>
<td>23857</td>
<td>1009038</td>
<td>0.90 (0.87–0.93)</td>
<td>11.5</td>
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<td>Fruit and vegetables</td>
<td>High vs low</td>
<td>13</td>
<td>54123</td>
<td>904300</td>
<td>0.93 (0.87–0.98)</td>
<td>53.5</td>
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<td>Per 200 g/d</td>
<td>12</td>
<td>52872</td>
<td>902065</td>
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<td>48.7</td>
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<td>21</td>
<td>105401</td>
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<td>Per 200 g/d</td>
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<td>1648240</td>
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<td>52.1</td>
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<td>Per 200 g/d</td>
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<td>1579722</td>
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<td>55.2</td>
<td>0.003</td>
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<td>Fruit and vegetables</td>
<td>High vs low</td>
<td>22</td>
<td>87574</td>
<td>1035556</td>
<td>0.82 (0.79–0.86)</td>
<td>62.3</td>
<td>&lt; 0.0001</td>
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<tr>
<td></td>
<td>Per 200 g/d</td>
<td>15</td>
<td>71160</td>
<td>950893</td>
<td>0.90 (0.87–0.93)</td>
<td>82.5</td>
<td>&lt; 0.0001</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fruit</td>
<td>High vs low</td>
<td>30</td>
<td>93473</td>
<td>&gt;1144194</td>
<td>0.87 (0.84–0.90)</td>
<td>60.2</td>
<td>&lt; 0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Per 200 g/d</td>
<td>27</td>
<td>94235</td>
<td>&gt;1104255</td>
<td>0.85 (0.80–0.91)</td>
<td>89.5</td>
<td>&lt; 0.0001</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vegetables</td>
<td>High vs low</td>
<td>24</td>
<td>82904</td>
<td>1082960</td>
<td>0.87 (0.82–0.92)</td>
<td>78.6</td>
<td>&lt; 0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Per 200 g/d</td>
<td>22</td>
<td>86264</td>
<td>1050795</td>
<td>0.87 (0.82–0.92)</td>
<td>82.3</td>
<td>&lt; 0.0001</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
### Fruits and vegetables and coronary heart disease, per 200 g/d

#### Study
- Buil-Cosiales, 2016
- Stefler, 2015
- Hjartåker, 2015
- Kobylecki, 2015
- Yu, 2014, SMHS
- Yu, 2014, NHS
- Bhupatiraju, 2013, HPFS
- Bhupatiraju, 2013, NHS
- Rosvold, 2012
- Crowe, 2011
- Dauchet, 2010
- Tuder, 2005
- Stefler, 2003
- Bazano, 2002
- Liu, 2000

#### Relative Risk (95% CI)
- Buil-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: 0.84 (0.71, 1.00)
- Yu, 2014, NHS: 0.92 (0.80, 1.05)
- Bhupatiraju, 2013, HPFS: 0.76 (0.54, 1.07)
- Bhupatiraju, 2013, NHS: 0.91 (0.77, 1.08)
- Rosvold, 2012: 0.75 (0.69, 0.81)
- Crowe, 2011: 0.79 (0.72, 0.87)
- Dauchet, 2010: 0.77 (0.70, 0.84)
- Tuder, 2005: 0.77 (0.70, 0.84)
- Stefler, 2003: 0.77 (0.70, 0.84)
- Bazano, 2002: 0.77 (0.70, 0.84)
- Liu, 2000: 0.77 (0.70, 0.84)

#### Overall
- 0.92 (0.90, 0.94)

### Vegetables and coronary heart disease, per 200 g/d

#### Study
- Buil-Cosiales, 2016
- Stefler, 2015
- Hjartåker, 2015
- Kobylecki, 2015
- Yu, 2014, SMHS
- Yu, 2014, NHS
- Bhupatiraju, 2013, HPFS
- Bhupatiraju, 2013, NHS
- Rosvold, 2012
- Crowe, 2011
- Dauchet, 2010
- Tuder, 2005
- Stefler, 2003
- Bazano, 2002
- Liu, 2000

#### Relative Risk (95% CI)
- Buil-Cosiales, 2016: 0.76 (0.54, 1.07)
- Stefler, 2015: 0.85 (0.79, 0.91)
- Hjartåker, 2015: 0.72 (0.53, 0.97)
- Kobylecki, 2015: 0.76 (0.63, 0.90)
- Yu, 2014, SMHS: 0.85 (0.71, 1.01)
- Yu, 2014, NHS: 0.89 (0.76, 1.05)
- Bhupatiraju, 2013, HPFS: 0.79 (0.70, 0.89)
- Bhupatiraju, 2013, NHS: 0.84 (0.74, 0.96)
- Rosvold, 2012: 0.76 (0.63, 0.91)
- Crowe, 2011: 0.79 (0.69, 0.90)
- Dauchet, 2010: 0.78 (0.67, 0.90)
- Tuder, 2005: 0.77 (0.67, 0.88)
- Stefler, 2003: 0.77 (0.67, 0.88)
- Bazano, 2002: 0.77 (0.67, 0.88)
- Liu, 2000: 0.77 (0.67, 0.88)

#### Overall
- 0.84 (0.79, 0.90)

---

**Figure 2.** Fruits, vegetables and coronary heart disease, linear and nonlinear dose-response.
Table 2. Fruit and vegetable subtypes and coronary heart disease

<table>
<thead>
<tr>
<th>Fruit, vegetable subtype</th>
<th>High vs low analysis</th>
<th>Dose-response analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Apples, pears</td>
<td>10</td>
<td>0.85 (0.79–0.93)</td>
</tr>
<tr>
<td>Bananas</td>
<td>3</td>
<td>0.90 (0.67–1.20)</td>
</tr>
<tr>
<td>Berries</td>
<td>6</td>
<td>0.94 (0.81–1.08)</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>14</td>
<td>0.91 (0.86–0.96)</td>
</tr>
<tr>
<td>Dried fruits</td>
<td>2</td>
<td>0.93 (0.78–1.11)</td>
</tr>
<tr>
<td>Fruit juices</td>
<td>2</td>
<td>0.79 (0.63–0.98)</td>
</tr>
<tr>
<td>Grapes</td>
<td>4</td>
<td>0.91 (0.76–1.10)</td>
</tr>
<tr>
<td>Strawberries</td>
<td>2</td>
<td>1.17 (0.71–1.91)</td>
</tr>
<tr>
<td>Watermelon</td>
<td>2</td>
<td>0.87 (0.64–1.18)</td>
</tr>
<tr>
<td>Allium vegetables</td>
<td>3</td>
<td>0.98 (0.79–1.20)</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>7</td>
<td>1.01 (0.90–1.13)</td>
</tr>
<tr>
<td>Green leafy vegetables</td>
<td>10</td>
<td>0.83 (0.75–0.91)</td>
</tr>
<tr>
<td>Onions</td>
<td>3</td>
<td>0.75 (0.56–1.02)</td>
</tr>
<tr>
<td>Potatoes</td>
<td>5</td>
<td>0.92 (0.79–1.07)</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>5</td>
<td>0.90 (0.80–1.00)</td>
</tr>
<tr>
<td>Beta-carotene rich F&amp;V</td>
<td>3</td>
<td>0.83 (0.75–0.92)</td>
</tr>
<tr>
<td>Lutein rich F&amp;V</td>
<td>3</td>
<td>0.97 (0.89–1.05)</td>
</tr>
<tr>
<td>Lycopene rich F&amp;V</td>
<td>3</td>
<td>1.01 (0.93–1.09)</td>
</tr>
<tr>
<td>Vitamin C rich F&amp;V</td>
<td>3</td>
<td>0.86 (0.78–0.95)</td>
</tr>
<tr>
<td>Raw F&amp;V</td>
<td>2</td>
<td>0.89 (0.61–1.30)</td>
</tr>
</tbody>
</table>

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.
86–88, 98, 125 25 studies (22 publications) 11, 15, 16, 19, 25–56, 60–64, 75, 76, 88, 98, 124, 125, 127 high intakes of apples/pears, citrus fruits, carrot 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).

Of specific types of fruit and vegetables, 11, 15, 16, 19, 25–56, 60–64, 109, 112, 119, 141–144, 146, 148–150, 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).

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 cardiovascular disease, respectively. The summary RR was 0.92 (95% CI: 0.90–0.95, I2 = 31%) for fruits and vegetables (Figure 4a, b, Table 1; Supplementary Figure 23), 0.87 (95% CI: 0.82–0.92, I2 = 79%) for fruits (Figure 4c, d, Table 1; Supplementary Figure 24), and 0.90 (95% CI: 0.87–0.93, I2 = 12%) for vegetables (Figure 4e, f, 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, 25–56, 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, 33, 34, 36, 37, 39, 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, I2 = 49%) for fruits and vegetables combined (Figure 5a, b, Table 1; Supplementary Figure 26), 0.96 (95% CI: 0.94–0.99, I2 = 52%) for fruits (Figure 5c, d, Table 1; Supplementary Figure 27) and 0.96 (95% CI: 0.93–0.99, I2 = 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

<table>
<thead>
<tr>
<th>Fruit, vegetable subtype</th>
<th>Ischaemic stroke</th>
<th>Haemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berries</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Citrus fruit juices</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Allium vegetables</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Green leafy vegetables</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Potatoes</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Root vegetables</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vitamin C-rich F&amp;V</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Fruit, vegetable subtype</th>
<th>n</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>( p_h )</th>
<th>References</th>
<th>n</th>
<th>Increment</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>( p_h )</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apples, pears</td>
<td>7</td>
<td>0.86 (0.80–0.93)</td>
<td>0</td>
<td>0.74</td>
<td>56,60,61,64,129,142,152</td>
<td>7</td>
<td>Per 100 g/d</td>
<td>0.92 (0.82–1.03)</td>
<td>46.9</td>
<td>0.08</td>
<td>56,60,61,64,129,142,152</td>
</tr>
<tr>
<td>Berries</td>
<td>2</td>
<td>1.02 (0.94–1.11)</td>
<td>0</td>
<td>0.44</td>
<td>56,60</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>1.13 (0.88–1.46)</td>
<td>0</td>
<td>0.68</td>
<td>56,60</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>6</td>
<td>0.78 (0.66–0.92)</td>
<td>72.3</td>
<td>0.003</td>
<td>16,56,60,64,124,146</td>
<td>8</td>
<td>Per 100 g/d</td>
<td>0.92 (0.84–1.00)</td>
<td>65.8</td>
<td>0.005</td>
<td>15,16,56,60–62,64,146</td>
</tr>
<tr>
<td>Citrus fruit juice</td>
<td>2</td>
<td>0.88 (0.53–1.46)</td>
<td>48.3</td>
<td>0.16</td>
<td>60,124</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.98 (0.95–1.02)</td>
<td>6.9</td>
<td>0.30</td>
<td>15,60</td>
</tr>
<tr>
<td>Dried fruits</td>
<td>3</td>
<td>0.94 (0.83–1.06)</td>
<td>0</td>
<td>0.80</td>
<td>11,60,151</td>
<td>1</td>
<td>Per 100 g/d</td>
<td>0.66 (0.33–1.26)</td>
<td>-</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>Fruit juice</td>
<td>1</td>
<td>0.67 (0.41–1.10)</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.99 (0.93–1.06)</td>
<td>0</td>
<td>0.58</td>
<td>60,154</td>
</tr>
<tr>
<td>Grapes</td>
<td>3</td>
<td>0.86 (0.70–1.05)</td>
<td>62.3</td>
<td>0.07</td>
<td>56,60,142</td>
<td>3</td>
<td>Per 100 g/d</td>
<td>0.83 (0.48–1.45)</td>
<td>66.7</td>
<td>0.05</td>
<td>56,60,142</td>
</tr>
<tr>
<td>Strawberries</td>
<td>1</td>
<td>1.02 (0.79–1.32)</td>
<td>57.2</td>
<td>0.10</td>
<td>142,144,151</td>
<td>1</td>
<td>Per 100 g/d</td>
<td>1.06 (0.95–1.17)</td>
<td>-</td>
<td>-</td>
<td>144</td>
</tr>
<tr>
<td>Tinned fruits</td>
<td>3</td>
<td>1.23 (1.06–1.43)</td>
<td>0</td>
<td>0.51</td>
<td>159</td>
<td>4</td>
<td>Per 100 g/d</td>
<td>1.30 (0.81–2.08)</td>
<td>66.0</td>
<td>0.03</td>
<td>154,159</td>
</tr>
<tr>
<td>Broccoli</td>
<td>3</td>
<td>0.87 (0.67–1.13)</td>
<td>25.0</td>
<td>0.26</td>
<td>142,144,151</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.75 (0.49–1.14)</td>
<td>0</td>
<td>0.57</td>
<td>142,144</td>
</tr>
<tr>
<td>Carrots</td>
<td>2</td>
<td>0.81 (0.70–0.93)</td>
<td>0</td>
<td>0.73</td>
<td>56,123</td>
<td>1</td>
<td>Per 100 g/d</td>
<td>0.97 (0.72–1.30)</td>
<td>-</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>8</td>
<td>0.88 (0.73–1.05)</td>
<td>77.5</td>
<td>&lt; 0.0001</td>
<td>16,19,56,64,87,124,151</td>
<td>9</td>
<td>Per 100 g/d</td>
<td>0.89 (0.77–1.02)</td>
<td>65.1</td>
<td>0.003</td>
<td>15,16,19,56,62,64,87,154</td>
</tr>
<tr>
<td>Green leafy vegetables</td>
<td>5</td>
<td>0.84 (0.71–0.99)</td>
<td>74.0</td>
<td>0.004</td>
<td>16,56,64,124,151</td>
<td>5</td>
<td>Per 100 g/d</td>
<td>0.83 (0.65–1.08)</td>
<td>66.7</td>
<td>0.02</td>
<td>15,16,56,64</td>
</tr>
<tr>
<td>Noncruciferous vegetables</td>
<td>2</td>
<td>0.76 (0.59–0.97)</td>
<td>50.1</td>
<td>0.16</td>
<td>19</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.91 (0.82–1.01)</td>
<td>74.5</td>
<td>0.05</td>
<td>19</td>
</tr>
<tr>
<td>Potatoes</td>
<td>3</td>
<td>1.01 (0.91–1.13)</td>
<td>60.0</td>
<td>0.08</td>
<td>12,166</td>
<td>4</td>
<td>Per 100 g/d</td>
<td>1.01 (0.97–1.04)</td>
<td>13.4</td>
<td>0.33</td>
<td>15,154,164</td>
</tr>
<tr>
<td>Raw vegetables</td>
<td>2</td>
<td>0.83 (0.66–1.05)</td>
<td>88.0</td>
<td>0.004</td>
<td>11,175</td>
<td>1</td>
<td>Per 100 g/d</td>
<td>0.86 (0.81–0.90)</td>
<td>-</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>4</td>
<td>0.94 (0.86–1.02)</td>
<td>0</td>
<td>0.43</td>
<td>56,141,142,151</td>
<td>4</td>
<td>Per 100 g/d</td>
<td>0.92 (0.80–1.07)</td>
<td>52.6</td>
<td>0.10</td>
<td>56,141,142,148</td>
</tr>
<tr>
<td>Beta-carotene rich F&amp;V</td>
<td>2</td>
<td>0.96 (0.89–1.03)</td>
<td>0</td>
<td>0.77</td>
<td>64,124</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.94 (0.89–0.99)</td>
<td>0</td>
<td>0.55</td>
<td>64,124</td>
</tr>
<tr>
<td>Vitamin C rich F&amp;V</td>
<td>1</td>
<td>0.91 (0.44–1.90)</td>
<td>-</td>
<td>-</td>
<td>64</td>
<td>2</td>
<td>Per 100 g/d</td>
<td>0.95 (0.92–0.98)</td>
<td>0</td>
<td>0.88</td>
<td>15,64</td>
</tr>
</tbody>
</table>

F&V, fruit and vegetables.
\( p_h = \) P-value for heterogeneity.
Figure 5. Fruits and vegetables and total cancer, linear and nonlinear dose-response.
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, I² = 83%) for fruits and vegetables (Figure 6a, b, Table 1; Supplementary Figure 29), 0.85 (95% CI: 0.80–0.91, I² = 90%) for fruits (Figure 6c, d, Table 1; Supplementary Figure 30), and 0.87 (95% CI: 0.82–0.92, I² = 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, 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

<table>
<thead>
<tr>
<th>Fruit, vegetable subtype</th>
<th>RR (95% CI)</th>
<th>I²</th>
<th>$P_{\text{h}}$</th>
<th>$P_{\text{nonlinearity}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrus fruits</td>
<td>0.97 (0.90–1.04)</td>
<td>61.0</td>
<td>0.04</td>
<td>-</td>
</tr>
<tr>
<td>Dried fruits</td>
<td>0.89 (0.61–1.28)</td>
<td>0</td>
<td>0.22</td>
<td>-</td>
</tr>
<tr>
<td>Tinned fruits</td>
<td>0.92 (0.72–1.17)</td>
<td>0</td>
<td>0.49</td>
<td>-</td>
</tr>
<tr>
<td>Fruit juice</td>
<td>0.98 (0.90–1.05)</td>
<td>0</td>
<td>0.80</td>
<td>-</td>
</tr>
<tr>
<td>Cooked vegetables</td>
<td>0.98 (0.73–1.28)</td>
<td>0</td>
<td>0.72</td>
<td>-</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>1.03 (0.75–1.40)</td>
<td>0</td>
<td>0.51</td>
<td>-</td>
</tr>
<tr>
<td>Green vegetables</td>
<td>0.99 (0.79–1.25)</td>
<td>0</td>
<td>0.49</td>
<td>-</td>
</tr>
<tr>
<td>Green yellow vegetables</td>
<td>0.97 (0.76–1.23)</td>
<td>0</td>
<td>0.50</td>
<td>-</td>
</tr>
<tr>
<td>Mushrooms</td>
<td>1.09 (0.85–1.38)</td>
<td>0</td>
<td>0.01</td>
<td>-</td>
</tr>
<tr>
<td>Noncruciferous vegetables</td>
<td>0.79 (0.60–1.02)</td>
<td>0</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Onions</td>
<td>0.73 (0.61–0.88)</td>
<td>0</td>
<td>0.01</td>
<td>-</td>
</tr>
<tr>
<td>Pickled vegetables</td>
<td>0.94 (0.74–1.19)</td>
<td>0</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>0.86 (0.67–1.10)</td>
<td>70.1</td>
<td>0.04</td>
<td>-</td>
</tr>
<tr>
<td>Yellow vegetables</td>
<td>0.97 (0.86–1.09)</td>
<td>0</td>
<td>0.71</td>
<td>-</td>
</tr>
</tbody>
</table>

$P_{\text{h}}$ = $P$-value for heterogeneity. $P_{\text{nonlinearity}}$ = $P$-value for nonlinearity.
### Table 1: Studies on Fruits and All-Cause Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgson, 2016</td>
<td>0.85 (0.73, 0.99)</td>
</tr>
<tr>
<td>Nguyen, 2016</td>
<td>0.89 (0.83, 0.95)</td>
</tr>
<tr>
<td>Stefler, 2016</td>
<td>1.00 (0.92, 1.08)</td>
</tr>
<tr>
<td>Wang, 2016</td>
<td>0.92 (0.71, 1.18)</td>
</tr>
<tr>
<td>Boggs, 2015</td>
<td>1.07 (0.94, 1.21)</td>
</tr>
<tr>
<td>Hjartåker, 2015</td>
<td>0.84 (0.70, 1.00)</td>
</tr>
<tr>
<td>Kobylecki, 2015</td>
<td>0.80 (0.78, 0.82)</td>
</tr>
<tr>
<td>Shi, 2015</td>
<td>0.70 (0.57, 0.87)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.86 (0.69, 1.07)</td>
</tr>
<tr>
<td>Oyebode, 2014</td>
<td>0.89 (0.84, 0.95)</td>
</tr>
<tr>
<td>Leenders, 2013</td>
<td>1.00 (0.98, 1.02)</td>
</tr>
<tr>
<td>Regidor, 2012</td>
<td>0.36 (0.20, 0.66)</td>
</tr>
<tr>
<td>Zhang, 2011, SMHS</td>
<td>0.82 (0.74, 0.90)</td>
</tr>
<tr>
<td>Zhang, 2011, SWHS</td>
<td>0.91 (0.87, 0.96)</td>
</tr>
<tr>
<td>van den Brandt, 2011</td>
<td>0.94 (0.86, 1.03)</td>
</tr>
<tr>
<td>Nagura, 2009</td>
<td>0.63 (0.50, 0.81)</td>
</tr>
<tr>
<td>Gonzalez, 2008</td>
<td>0.70 (0.50, 0.98)</td>
</tr>
<tr>
<td>Tucker, 2005</td>
<td>0.83 (0.65, 1.08)</td>
</tr>
<tr>
<td>Kouris-Blazos, 1999</td>
<td>0.60 (0.35, 0.90)</td>
</tr>
<tr>
<td>Whiteman, 1999</td>
<td>0.44 (0.21, 0.96)</td>
</tr>
<tr>
<td>Fraser, 1997, blacks</td>
<td>0.71 (0.51, 1.00)</td>
</tr>
<tr>
<td>Fraser, 1997, whites</td>
<td>0.92 (0.72, 1.18)</td>
</tr>
<tr>
<td>Mann, 1999</td>
<td>0.93 (0.58, 1.50)</td>
</tr>
<tr>
<td>Osler, 1997</td>
<td>1.22 (0.74, 2.16)</td>
</tr>
<tr>
<td>Sahyoun, 1996</td>
<td>0.90 (0.73, 1.12)</td>
</tr>
<tr>
<td>Trichopoulou, 1995</td>
<td>1.10 (0.74, 1.48)</td>
</tr>
<tr>
<td>Kahn, 1984</td>
<td>0.61 (0.50, 0.73)</td>
</tr>
<tr>
<td>Fraser, 1997, blacks</td>
<td>0.71 (0.51, 1.00)</td>
</tr>
<tr>
<td>Fraser, 1997, whites</td>
<td>0.92 (0.72, 1.18)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.85 (0.80, 0.91)</td>
</tr>
</tbody>
</table>

### Table 2: Studies on Vegetables and All-Cause Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen, 2016</td>
<td>0.97 (0.95, 1.00)</td>
</tr>
<tr>
<td>Stefler, 2016</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>Wang, 2016</td>
<td>0.85 (0.65, 1.09)</td>
</tr>
<tr>
<td>Boggs, 2015</td>
<td>1.09 (0.95, 1.26)</td>
</tr>
<tr>
<td>Hjartåker, 2015</td>
<td>0.94 (0.81, 1.10)</td>
</tr>
<tr>
<td>Kobylecki, 2015</td>
<td>0.79 (0.72, 0.88)</td>
</tr>
<tr>
<td>Shi, 2015</td>
<td>0.47 (0.36, 0.63)</td>
</tr>
<tr>
<td>Buil-Cosiales, 2014</td>
<td>0.89 (0.73, 1.08)</td>
</tr>
<tr>
<td>Oyebode, 2014</td>
<td>0.74 (0.67, 0.81)</td>
</tr>
<tr>
<td>Leenders, 2013</td>
<td>0.94 (0.92, 0.96)</td>
</tr>
<tr>
<td>Regidor, 2012</td>
<td>0.28 (0.16, 0.49)</td>
</tr>
<tr>
<td>Van den Brandt, 2011</td>
<td>0.82 (0.73, 0.91)</td>
</tr>
<tr>
<td>Zhang, 2011, SMHS</td>
<td>0.87 (0.82, 0.93)</td>
</tr>
<tr>
<td>Zhang, 2011, SWHS</td>
<td>0.95 (0.89, 1.00)</td>
</tr>
<tr>
<td>Nagura, 2009</td>
<td>0.94 (0.71, 1.24)</td>
</tr>
<tr>
<td>Gonzalez, 2008</td>
<td>1.54 (0.82, 2.91)</td>
</tr>
<tr>
<td>Tucker, 2005</td>
<td>0.86 (0.67, 1.10)</td>
</tr>
<tr>
<td>Seccareccia, 2003</td>
<td>0.74 (0.54, 0.90)</td>
</tr>
<tr>
<td>Kouris-Blazos, 1999</td>
<td>1.22 (0.90, 1.97)</td>
</tr>
<tr>
<td>Osler, 1997</td>
<td>0.90 (0.60, 1.48)</td>
</tr>
<tr>
<td>Sahyoun, 1996</td>
<td>0.55 (0.38, 0.79)</td>
</tr>
<tr>
<td>Trichopoulou, 1995</td>
<td>0.74 (0.48, 1.22)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.82, 0.92)</td>
</tr>
</tbody>
</table>

### Figure 6: Fruits, vegetables and all-cause mortality, linear and nonlinear dose-response.
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), 8.0 (8.0), and 8.1 (8.0) for stroke, 7.8 (8.0), 7.7 (8.0), 7.7 (8.0) for cardiovascular disease, 7.9 (8.0), 8.0 (8.0) for total cancer, and 7.7 (8.0), 8.0 (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, $P_{\text{heterogeneity}} = 0.003$, compared to studies without such adjustment. In the analysis of fruits and vegetables and cardiovascular disease there was a weaker association among studies with BMI than among studies without BMI adjustment for smoking. However, there was more indication of nonlinearity (results not shown).

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

<table>
<thead>
<tr>
<th>Fruit, vegetable subtype</th>
<th>$n$</th>
<th>RR (95% CI)</th>
<th>$I^2$</th>
<th>$P_{h}$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apples, pears</td>
<td>5</td>
<td>0.80 (0.70–0.91)</td>
<td>84.9</td>
<td>&lt;0.0001</td>
<td>34,56,67,134</td>
</tr>
<tr>
<td>Bananas</td>
<td>2</td>
<td>0.91 (0.80–1.03)</td>
<td>0.07</td>
<td>0.27</td>
<td>56,61</td>
</tr>
<tr>
<td>Berries</td>
<td>3</td>
<td>0.92 (0.88–0.97)</td>
<td>0.34</td>
<td>0.34</td>
<td>34,56,75</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>6</td>
<td>0.90 (0.86–0.94)</td>
<td>12.3</td>
<td>0.34</td>
<td>9,36,38,75</td>
</tr>
<tr>
<td>Fruit juice</td>
<td>1</td>
<td>0.87 (0.83–0.91)</td>
<td>-</td>
<td>-</td>
<td>143</td>
</tr>
<tr>
<td>Tinned fruits</td>
<td>3</td>
<td>1.11 (1.04–1.23)</td>
<td>0.72</td>
<td>0.72</td>
<td>159</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>6</td>
<td>0.88 (0.80–0.97)</td>
<td>78.9</td>
<td>&lt;0.0001</td>
<td>19,56,67,138</td>
</tr>
<tr>
<td>Mushrooms</td>
<td>2</td>
<td>0.93 (0.84–1.01)</td>
<td>73.9</td>
<td>0.03</td>
<td>34,56,75</td>
</tr>
<tr>
<td>Noncruciferous vegetables</td>
<td>2</td>
<td>0.85 (0.67–1.07)</td>
<td>82.7</td>
<td>0.02</td>
<td>19</td>
</tr>
<tr>
<td>Onions, allium vegetables</td>
<td>3</td>
<td>0.85 (0.69–1.06)</td>
<td>84.0</td>
<td>0.02</td>
<td>34,56,75</td>
</tr>
<tr>
<td>Potatoes</td>
<td>4</td>
<td>0.78 (0.74–0.83)</td>
<td>2.8</td>
<td>0.38</td>
<td>43,44,67,75</td>
</tr>
<tr>
<td>Root vegetables</td>
<td>2</td>
<td>0.93 (0.77–1.15)</td>
<td>89.2</td>
<td>0.02</td>
<td>75,139</td>
</tr>
<tr>
<td>Green leafy vegetables, salads</td>
<td>7</td>
<td>0.92 (0.86–0.97)</td>
<td>39.5</td>
<td>0.13</td>
<td>11,30,37,43,56,75,138</td>
</tr>
<tr>
<td>Cooked vegetables</td>
<td>5</td>
<td>0.87 (0.80–0.94)</td>
<td>66.4</td>
<td>0.02</td>
<td>30,38,43,68,75</td>
</tr>
<tr>
<td>Raw vegetables</td>
<td>2</td>
<td>0.88 (0.79–0.98)</td>
<td>74.4</td>
<td>0.05</td>
<td>48,75</td>
</tr>
</tbody>
</table>

$P_{h} = P$-value for heterogeneity.
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)

<table>
<thead>
<tr>
<th>Region</th>
<th>Coronary heart disease</th>
<th>Stroke</th>
<th>Cardiovascular disease</th>
<th>Total cancer</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 g/d</td>
<td>800 g/d</td>
<td>500 g/d</td>
<td>800 g/d</td>
<td>500 g/d</td>
</tr>
<tr>
<td>America A</td>
<td>9.1</td>
<td>16.9</td>
<td>10.3</td>
<td>14.8</td>
<td>11.2</td>
</tr>
<tr>
<td>America B</td>
<td>12.5</td>
<td>20.7</td>
<td>9.7</td>
<td>14.4</td>
<td>11.7</td>
</tr>
<tr>
<td>America D</td>
<td>8.5</td>
<td>16.5</td>
<td>8.0</td>
<td>14.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Europe A</td>
<td>4.5</td>
<td>10.2</td>
<td>8.6</td>
<td>14.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Europe B</td>
<td>8.4</td>
<td>15.6</td>
<td>6.2</td>
<td>14.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Europe C</td>
<td>12.3</td>
<td>21.5</td>
<td>26.9701</td>
<td>30.9</td>
<td>11.7</td>
</tr>
<tr>
<td>South East Asia B</td>
<td>12.2</td>
<td>21.9</td>
<td>60.025</td>
<td>30.6</td>
<td>11.7</td>
</tr>
<tr>
<td>South East Asia D</td>
<td>11.4</td>
<td>20.9</td>
<td>291326</td>
<td>28.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Eastern Mediterranean B</td>
<td>7.1</td>
<td>15.5</td>
<td>19630</td>
<td>19.9</td>
<td>14.075</td>
</tr>
<tr>
<td>Eastern Mediterranean D</td>
<td>6.8</td>
<td>13.9</td>
<td>54293</td>
<td>21.6</td>
<td>51.646</td>
</tr>
<tr>
<td>Africa A</td>
<td>7.0</td>
<td>14.2</td>
<td>17381</td>
<td>24.2</td>
<td>46.683</td>
</tr>
<tr>
<td>Africa E</td>
<td>10.3</td>
<td>19.5</td>
<td>27864</td>
<td>25.7</td>
<td>57.088</td>
</tr>
<tr>
<td>Western Pacific A</td>
<td>5.9</td>
<td>12.3</td>
<td>22357</td>
<td>15.0</td>
<td>30.799</td>
</tr>
<tr>
<td>Western Pacific B</td>
<td>7.9</td>
<td>16.9</td>
<td>238931</td>
<td>19.6</td>
<td>43.7848</td>
</tr>
<tr>
<td>Globally</td>
<td>9.3</td>
<td>17.7</td>
<td>1345327</td>
<td>22.9</td>
<td>1468264</td>
</tr>
</tbody>
</table>

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; 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, stroke and mortality, 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-anal-
ysis 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 cardiovascu-
lar disease, but only modestly associated with cancer. One
explanation may be that the studies included in each anal-
ysis 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 dis-
eases,168–175 and recently in the EPIC study inverse associ-
atations 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 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 dis-
eases and premature mortality.176 Dietary fibre and fruit
and vegetable intakes have been shown to reduce cholesterol
levels, blood pressure, inflammation and platelet aggrega-
tion, and to improve vascular and immune function,177–180
and recent meta-analyses showed inverse associations be-
tween 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 enzymes183 and
intake of fruits, vegetables and fibre may modulate steroid
hormone concentrations and hormone metabolism178 and
may have a beneficial effect on gut microbiota.172 In addi-
tion, fruit and vegetable intake has been inversely associ-
ated with risk of developing overweight or obesity and with
weight gain184–186 although data are not entirely consist-
ent;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 indi-
crectly, 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 ad-
justed for dietary fat or meat intake.

Our analysis has several limitations. Combining studies
from different populations increases the sample size and sta-
tistical power, but also results in heterogeneity because of dif-
fferences in the characteristics of the study populations.
Heterogeneity was low in the analyses of coronary heart dis-
ease, moderate to high for stroke, cardiovascular disease and
total cancer and high for all-cause mortality. The heterog-
enity 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 associ-
ations. Some heterogeneity is expected as the studies varied
by the age groups included, duration of follow-up, geographi-
cal 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 vege-
tables 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 con-
ducted subgroup analyses to investigate sources of the het-
erogeneity, 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 sub-
groups, 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 substan-
tially whether or not adjustment for most of these con-
founders 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 treat-
ment, 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 num-
ber of studies in each subgroup. The possibility of residual
confounding by imprecisely measured, unknown or un-
measured confounders cannot be entirely excluded.

Measurement error in the assessment of fruit and vege-
table intake and changes in fruit and vegetable intake during
follow-up may have influenced the results, but to date only
the EPIC study23,75 and the China Kadoorie Cohort Study63
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, 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), 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, and a second study reporting no clear association. An analysis from the Latin American countries in the INTERHEART study suggested a similar association between fruit and vegetable intake and coronary heart disease as in the overall study.

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). 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. 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/day). 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. 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. 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 benefits as well as environmental benefits. 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.

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Author Contributions


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