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ORIGINAL ARTICLE

Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies

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Increased consumption of fruit and vegetables has been shown to be associated with a reduced risk of coronary heart disease (CHD) in many epidemiological studies, however, the extent of the association is uncertain. We quantitatively assessed the relation between fruit and vegetable intake and incidence of CHD by carrying out a meta-analysis of cohort studies. Studies were included if they reported relative risks (RRs) and corresponding 95% confidence interval (CI) of CHD with respect to frequency of fruit and vegetable intake. Twelve studies, consisting of 13 independent cohorts, met the inclusion criteria. There were 278 459 individuals (9143 CHD events) with a median follow-up of 11 years. Compared with individuals who had less than 3 servings/day of fruit and vegetables, the pooled RR of CHD was 0.93 (95% CI: 0.86–1.00, $P = 0.06$) for those with 3–5 servings/day and 0.83 (0.77–0.89, $P < 0.0001$) for those with more than 5 servings/day. Subgroup analyses showed that both fruits and vegetables had a significant protective effect on CHD. Our meta-analysis of prospective cohort studies demonstrates that increased consumption of fruit and vegetables from less than 3 to more than 5 servings/day is related to a 17% reduction in CHD risk, whereas increased intake to 3–5 servings/day is associated with a smaller and borderline significant reduction in CHD risk. These results provide strong support for the recommendations to consume more than 5 servings/day of fruit and vegetables.
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Introduction

Although coronary heart disease (CHD) mortality has been falling during the past 30 years, it is still the commonest cause of death in most developed countries. For instance, in the United Kingdom, CHD accounts for about 114 000 deaths a year, and approximately 1.3 million people have had a heart attack and around 2 million people are suffering from angina. CHD costs the UK economy about £7.9 billion a year.[1] Primary prevention of CHD is therefore a major public health priority. An increase in the consumption of fruit and vegetables has been advocated for the prevention of CHD, stroke and some cancers.[2–4] However, there is still considerable uncertainty about the relation between fruit and vegetable intake and CHD. Several systematic reviews of observational studies have been published.[5–7] Ness and Powles[5] reviewed the evidence of ecological, case-control and cohort studies and showed that 6 of 16 cohort studies, 9 of 10 ecological and 2 of 3 case-control studies reported a protective effect of fruit and vegetables or surrogate nutrients of fruit and vegetables on CHD. Owing to the variations between individual studies in the measures of exposure and outcome, no attempt was made to quantify the association between fruit and vegetable intake and CHD risk. Law and Morris[6] carried out a meta-analysis of cohort studies in an attempt to quantify the relationship between fruit and vegetable consumption and CHD. Six markers were used as an index of fruit and vegetable intake (fruit, vegetables, carotenoids, vitamin C, fruit fibre and vegetable fibre). The analysis showed that the risk of CHD is about 15% lower at the ninetieth than at the tenth centile of fruit and vegetable consumption. In another review, Van't Veer *et al.*[7] estimated that an increase of 150 g/day of fruit and vegetables was associated with a 30% reduction in CHD risk (based on best guess), ranging from 20 (conservative

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estimate) to 40% (optimistic estimate). However, the validity of these estimates is questionable.

Both the review by Ness and Powles[5] and the meta-analysis by Law and Morris[6] included only a very small number of studies that reported fruit and vegetable intake, and other included studies looked at some selected nutrients, for example vitamin C, potassium, carotenoids, fruit fibre and vegetable fibre, rather than fruit and vegetables themselves. Nutritional advice is often easier to understand in the context of foods rather than the nutrients contained within them. Therefore, linking foods or food groups to outcomes may be especially important. Additionally, in all of the three reviews,[5–7] only studies published before 1998 were included (that is, literature search date was up to 1998). Since then, there have been a number of cohort studies published that looked at the relationship between fruit and vegetable intake and CHD.[8–15] We therefore carried out a meta-analysis of prospective cohort studies to quantitatively assess the relation between fruit and vegetable intake and the risk of CHD.

Materials and methods

Literature search

We developed a search strategy (Table 1) to search for studies that reported the association between fruit and vegetable intake and CHD. We searched electronic database – MEDLINE (1966 to November 2005) and EMBASE (1980 to November 2005). We also searched the Cochrane Library with terms of 'fruit' or 'vegetables' in all fields. Furthermore, we reviewed reference list of original and review articles to search for more studies. Only studies that were published as full article and in English were considered.

Inclusion/exclusion criteria

For inclusion, studies had to fulfil the following criteria:

(1) have prospective cohort design;
(2) report relative risks (RRs) or hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) of CHD in relation to each category of fruit and vegetable intake;
(3) provide frequency or amount of fruit and vegetable consumption, which allowed for standardized classification of fruit and vegetable intake.

Studies were excluded if

(1) case-control design was used;
(2) mixed healthy diet was reported, where the effect of fruit and vegetables could not be separated;
(3) only surrogate nutrients of fruits or vegetables were reported, whereas fruits or vegetables themselves were not reported;

Table 1 Search strategy to identify studies on fruit and vegetable intake and CHD

1	Fruit (MeSH terms) or fruit (text word)
2	Fruits (text word)
3	Vegetables (MeSH terms) or vegetables (text word)
4	Vegetable (text word)
5	1 or 2 or 3 or 4
6	Heart diseases (MeSH terms) or heart diseases (text word)
7	Heart disease (text word)
8	Coronary disease (MeSH terms) or coronary disease (text word)
9	Ischaemic heart disease (text word)
10	Ischaemic heart disease (text word)
11	Myocardial infarction (MeSH terms) or myocardial infarction (text word)
12	Myocardial ischaemia (MeSH terms) or myocardial ischaemia (text word)
13	Myocardial ischaemia (text word)
14	Angina pectoris (MeSH terms) or angina pectoris (text word)
15	Cardiovascular diseases (MeSH terms) or cardiovascular diseases (text word)
16	Cardiovascular disease (text word)
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	5 and 17

Abbreviations: CHD, coronary heart disease; MeSH, Medical Subject Heading.

(4) only two categories of fruit and vegetable intake (for example daily vs never) were reported, which could not allow for adequate categorization of fruit and vegetable intake.

When multiple publications from the same study cohort were available, we included only the one with the most detailed information for both outcome and fruit and vegetable consumption and with the longest duration of follow-up.

Data extraction

Data were extracted independently by three persons (FJ He, CA Nowson and M Lucas) and differences were resolved by discussion with a fourth reviewer (GA MacGregor). Relevant data recorded were the first author's name, year of publication, country of origin of centres, number of participants, participants' age, duration of follow-up, number of events, methods of measuring fruit and vegetable consumption, frequency or amount of fruit and vegetable intake for each group, outcome assessment, RRs or HRs and the corresponding 95% CIs of CHD for each group of fruit and vegetable intake, and covariates adjusted in the statistical analysis.

Standardization of fruit and vegetable categories

As the studies included in this meta-analysis reported fruit and vegetable consumption using different measurement units (for example, grams/day, servings/day, times/day, tertile, quartile, quintile), and serving sizes also varied between studies, we therefore standardized and grouped fruit and vegetable consumption into three categories: <3

servings/day, 3–5 servings/day and >5 servings/day for each study (equivalent to <235 g/day, 235–391 g/day, >391 g/day for fruit and vegetables combined). This was performed by an experienced nutritionist (CA Nowson) with assistance from M Lucas. We estimated the average weight of a range of commonly consumed fruit and vegetables using serving size weights for a 0.5 cup standard serving, as indicated in the Composition of Foods Raw, Processed, Prepared, USDA Nutrient Database for Standard Reference, Release 18.[16] From this database, the average serving was calculated as 80 g for fruits and 77 g for vegetables.

When we performed subgroup analysis for fruits and vegetables separately or when an individual study reported fruits alone or vegetables alone, the equivalent intake for the three standardized categories was arbitrarily defined as <1.3, 1.3–2.0 and >2.0 servings/day, respectively for fruits, and <1.7, 1.7–3.0 and >3.0 servings/day, respectively for vegetables.

We assigned each standardized category of fruit and vegetable intake based on the median or mean intake reported in individual studies. When median or mean intake was not reported, and only range of fruit and vegetable intake was reported, we used the mean of upper and lower bounds of that group. When an upper bound was not reported for the group with the highest fruit and vegetable intake in individual studies, this group was assigned to the top category in our meta-analysis. One included study[17] reported occasions of eating fruit and vegetables, where serving size was not specified, we assumed '1–2 times/day' of 3–5 servings of fruit and vegetables combined.

Statistical analyses

RR or HR was used as a measure of the relation between fruit and vegetable intake and CHD. RRs and HRs in each study were transformed by taking their natural logarithms (ln), and the standard errors (s.e.) were calculated from ln RRs or ln HRs and their corresponding 95% CIs. We allocated RRs reported in individual studies into the standardized categories in the meta-analysis. If the average consumption of fruit and vegetables from more than one group in a single study fell into the same category of fruit and vegetable intake in our meta-analysis, then we pooled these RRs with inverse variance weight and used the combined RR for that category.[18] The reference category (that is RR = 1) in individual studies cannot be split into groups, nor combined with other groups, except that the authors have kindly re-analysed their data according to our request. Because of this, misclassification may have occurred in six cohorts. In two cohorts,[12,19] the average fruit and vegetable intake in the reference group was slightly higher than the cut-off point for the reference category in our meta-analysis, and in four other cohorts,[9,11,13,14] the group (or groups) next to the reference group should be combined with the reference group. In the latter circumstances, these groups could be either left out or placed under our standardized category 2. We chose the latter option. However, a separate analysis was performed by excluding all of the cohorts where misclassification was likely to have occurred.

Among the 13 cohorts included in our study, 2 reported non-fatal myocardial infarction (MI) and CHD death separately.[9,20] In one study,[9] only first event was registered as endpoint. We therefore combined RRs of non-fatal MI and CHD death with inverse variance weight and used the combined RRs for our main analysis. In the other study,[20] a few participants had both non-fatal MI and subsequently fatal CHD event, and both events were counted as endpoints. We therefore included RRs of CHD death in the main analysis and RRs of MI in a separate analysis for MI in our meta-analysis.

By comparison with the lowest category of fruit and vegetable intake, we estimated the pooled RRs and 95% CIs of CHD for the middle and the highest categories by using random-effects model because of the presence of significant heterogeneity (that is $P<0.1$). Heterogeneity was analysed using the I^2 and Q statistics. I^2 describes the per cent variation across studies that is a result of heterogeneity rather than chance.[21] We used funnel plot asymmetry to detect whether there was publication bias in the meta-analysis and Egger's regression test to measure funnel plot asymmetry.[22,23] Statistical analyses were performed using Cochrane Collaboration Review Manager 4.2 software and the Statistical Package for the Social Sciences.

Results

Figure 1 shows the number of studies assessed and excluded through the stages of the meta-analysis. A total of 12 studies comprising 13 independent cohorts[8-15,17,19,20,24] were found that fitted in the inclusion criteria (one study[10] consisted of two separate cohorts, that is, the Health Professionals' Follow-up Study and the Nurses' Health Study, and they were entered as two independent cohorts). Table 2 summarizes the characteristics of included studies. Among the 13 cohorts included in the meta-analysis, 9 were from the United States and 4 from Europe. The studies combined had a total of 278 459 individuals with 9143 CHD events. The median duration of follow-up was 11 years, ranging from 5 to 26 years.

The RRs of CHD and the corresponding 95% CIs for individual studies included in the meta-analysis are shown in Figure 2. All RRs presented in this paper were adjusted for possible confounding factors (Table 2). The pooled analyses showed that individuals with a higher fruit and vegetable intake had a lower risk of CHD. Compared with individuals who had less than 3 servings/day of fruit and

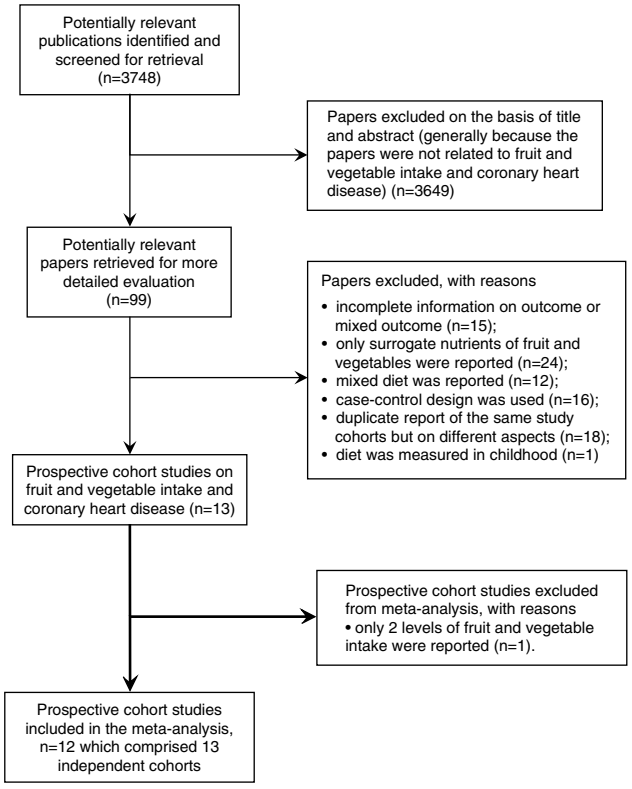

Figure 1 Summary of studies assessed and excluded through the stages of the meta-analysis.

vegetables, the pooled RR of CHD was 0.93 (95% CI: 0.86–1.00, $P=0.06$) for those with 3–5 servings/day and 0.83 (0.77–0.89, $P<0.0001$) for those with more than 5 servings/day (Figure 2).

The subgroup analyses according to gender, duration of follow-up, dietary assessment method and dietary instrument administration are shown in Table 3. Compared with those who had fruit and vegetable intake of less than 3 servings/day, individuals with fruit and vegetable intake of more than 5 servings/day had a significantly lower risk of CHD irrespective of participants' gender, duration of follow-up and method of dietary assessment. However, the association between fruit and vegetable intake and CHD was not significant in studies where dietary assessment was completed via interview. For individuals with fruit and vegetable intake of 3–5 servings/day, the association was only significant in some subgroups (Table 3).

Among the 13 cohorts included in the meta-analysis, 9 reported the association for fruits and vegetables separately.[8-11,14,17,20,24] The equivalent intake for the three categories standardized in our meta-analysis was <1.3, 1.3–2.0 and >2.0 servings/day for fruits and <1.7, 1.7–3.0 and >3.0 servings/day for vegetables. The pooled analysis showed that both fruits and vegetables had a significant protective effect against CHD (Table 3).

Four studies reported the association between fruit and vegetable intake and MI (106 192 individuals with 1769 events).[8,9,11,20] Compared with individuals who had less than 3 servings/day of fruit and vegetables, the pooled RR of MI was 0.94 (95% CI: 0.80–1.10, $P=0.43$) for those with 3–5 servings/day and 0.83 (0.70–0.99, $P=0.04$) for those with more than 5 servings/day.

We performed a separate analysis by excluding the studies,[9,11–14,19] in which misclassification was likely to have occurred, and the study[17] where the classification of fruit and vegetable intake was based on assumption due to lack of details reported. A total of 6 cohorts with 197 633 individuals (3323 events) were included in this analysis. The results showed that, compared with individuals who had less than 3 servings/day of fruit and vegetables, the pooled RR of CHD was 0.88 (95% CI: 0.75–1.02, $P=0.09$) for those with 3–5 servings/day and 0.82 (0.74–0.91, $P=0.0002$) for those with more than 5 servings/day.

Heterogeneity

In our meta-analysis, there was a significant between-study heterogeneity (Table 3). Stratified analysis by gender, duration of follow-up, dietary assessment method and dietary instrument administration did not reduce the heterogeneity consistently. However, the stratified analysis for fruits and vegetables separately, reduced the heterogeneity considerably for most subgroups except for the top category of vegetable intake where significant heterogeneity still existed (Table 3).

Publication bias

We plotted ln RR against the s.e. of ln RR (Figure 3). The funnel plot was slightly asymmetrical, suggesting a possible small publication bias (that is, smaller studies showing no association might be underreported in the literature). Egger's regression test suggested no significant asymmetry of the funnel plot ($P=0.222$ and 0.412 for the middle and highest category of fruit and vegetable intake, respectively). This would indicate that there was no substantial publication bias.

Discussion

Our meta-analysis has quantitatively assessed the relation between fruit and vegetable intake and CHD risk. The study is robust in that the prospective design should eliminate selection bias and recall bias. Furthermore, most studies included in our meta-analysis had a large sample size and long duration of follow-up. Meta-analysis of these studies is a potentially powerful approach to assess the long-term effects of fruit and vegetable intake on CHD risk. Our study shows that an increased consumption of fruit and vegetables is related to a reduced risk of CHD. Compared with those who have less than 3 servings of fruit and vegetables per

Table 2 Characteristics of included studies

Author	*Country*	*No. of participants*	*Age (years)*	*Follow-up (years)*	*No. of events*	*Exposure assessment*	*Outcome assessment*	*Adjusted variables*
Liu *et al.* (2000)[8]	USA. The Women's Health Study	39 127 women	⩾45	5	Incidence of non-fatal MI ($n=126$)	FFQ. Self-administered	MI was diagnosed using WHO criteria: symptoms plus either typical electrocardiographic changes or elevation of cardiac enzymes	Age, smoking, exercise, alcohol, post-menopausal percentage, post-menopausal hormone use, BMI, multivitamin use, vitamin C supplement use, history of diabetes, hypertension or high cholesterol and parental history of MI
Hirvonen *et al.* (2001)[9]	Finland	25 372 male smokers	50–69	6.1	Incidence of nonfatal MI and CHD deaths ($n=1937$)	FFQ. Self-administered, but checked and completed with a nurse	Hospital Discharge Register and Register of Causes of Death. ICD-8: 410-414. The validity of diagnosis was evaluated in random samples using clinical and autopsy data according to FINMONICA criteria[49]	Age, supplementation group, systolic and diastolic blood pressure, serum total and HDL cholesterol, BMI, smoking, history of diabetes or CHD, marital status, education and physical activity
Joshipura *et al.*[10] (2001) (Men)	USA. Health Professionals' Follow-up Study	42 148 men	40–75	8	Incidence of non-fatal MI and fatal CHD ($n=1063$)	FFQ. Self-administered. One repeated measurement during follow-up	Medical records and death certificates. MI was confirmed by using WHO criteria: symptoms plus either diagnostic electrocardiographic changes or elevated levels of cardiac enzymes. Fatal CHD was confirmed by hospital record or autopsy, or CHD was listed the underlying and most plausible cause on the certificate, and evidence of previous CHD was available	Age, smoking, alcohol, family history of MI, BMI, vitamin supplement use, aspirin use, physical activity, hypertension, hypercholesterolemia, caloric intake
Joshipura *et al.*[10] (2001) (Women)	USA. Nurses' Health Study	84 251 women	34–59	14	Incidence of non-fatal MI and fatal CHD ($n=1127$)	FFQ. Self-administered Three repeated measurements during follow-up	Medical records and death certificates. MI was confirmed by using WHO criteria: symptoms plus either diagnostic electrocardiographic changes or elevated levels of cardiac enzymes. Fatal	Age, smoking, alcohol, family history of MI, BMI, vitamin supplement use, aspirin use, physical activity, hypertension, hypercholesterolemia, caloric intake and

Table 2 Continued

Author	*Country*	*No. of participants*	*Age (years)*	*Follow-up (years)*	*No. of events*	*Exposure assessment*	*Outcome assessment*	*Adjusted variables*
							CHD was confirmed by hospital record or autopsy, or CHD was listed the underlying and most plausible cause on the certificate, and evidence of previous CHD was available	post-menopausal hormone use
Liu *et al.* (2001)[11]	USA. The Physicians' Health Study	15 220 men	40–84	12	Incidence of CHD including fatal or non-fatal MI, CABG or PTCA ($n=1148$)	FFQ. Self-administered. Three repeated measurements during follow-up	CABG and PTCA were self-reported. Non-fatal MI was confirmed using WHO criteria. Fatal MI was confirmed by death certificates, hospital records, and observers' accounts	Age, treatment, smoking, alcohol intake, physical activity, BMI, history of diabetes, high cholesterol and hypertension, and use of multivitamins
Bazzano *et al.*, 2002[12]	USA. The first National Health and Nutrition Examination Survey (NHANES I)	9608 men and women	25–74	19	CHD incidence and mortality ($n=1786$)	FFQ. Interviewer-administered	Death certificates and hospital discharge diagnosis. ICD-9: 410–414	Age, sex, race, total energy intake, history of diabetes, physical activity, education, alcohol consumption, smoking and vitamin supplement use
Steffen *et al.* (2003)[13]	USA. The Atherosclerosis Risk in Communities (ARIC)	11 940 men and women	45–64	11	Incidence of fatal or non-fatal CHD including MI and coronary revascularization ($n=535$)	FFQ. Interviewer-administered. One repeated measurement during follow-up	Events were investigated and validated by using hospital records, and deaths were investigated and validated by using physician records and next-of-kin interview. Incidence CHD included first definite or probable MI, silent MI by electrocardiography, definite CHD death and coronary revascularization	Age, sex, race, energy intake, education, smoking, physical activity, alcohol intake, hormone replacement in women, BMI, waist-to-hip ratio, systolic blood pressure, use of antihypertensive medications, HDL and LDL
Dauchet *et al.* (2004)[14]	France and Northern Ireland. The Prospective Epidemiological Study of MI (PRIME study)	7981 men and women	50–59	5	Incidence of fatal and non-fatal CHD including MI and angina pectoris ($n=249$)	FFQ. Self-administered at home, but checked by survey staff at clinic	Medical records and death certificates. The criteria for diagnosing CHD events were described by Ducimetiere *et al.* 2001[50]	Age, centre, smoking, alcohol consumption, physical activity, education, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI,

Table 2 Continued

Author	*Country*	*No. of participants*	*Age (years)*	*Follow-up (years)*	*No. of events*	*Exposure assessment*	*Outcome assessment*	*Adjusted variables*
								treatment for hypertension, diabetes or dyslipidaemia
Tucker *et al.* (2005)[15]	USA. Baltimore Longitudinal Study of Aging (BLSA)	501 men	34–80	18	CHD mortality ($n=71$)	7-day diet record. Self-completed, but ambiguous or incomplete records were clarified by telephone interview	Cause of death was determined by consensus of three physicians using death certificates, hospital and physician records, and autopsy data. CHD mortality included deaths due to acute MI or sudden coronary death	Age, total energy intake, saturate fat, BMI, smoking, alcohol, physical activity, dietary supplement use and secular trend (year of first visit before vs after 1980)
Mann *et al.* (1997)[17]	UK	9980 men and women	16–79	13.3	CHD mortality ($n=64$)	FFQ. Self-administered	Death certificates. ICD-9: 410–414	Age, sex, smoking and social class
Sahyoun *et al.* (1996)[19]	USA	725 men and women	60–101	9–12	Mortality from heart disease ($n=101$)	3-day food record. Self-completed	Death certificates. ICD code was not reported	Age, sex, disease status and disabilities affecting shopping.
Fraser *et al.* (1992)[20]	USA. The Adventist Health Study	26 473 non-Hispanic white Adventists	Mean age: 51 years men; 53 years women	6	Incidence of non-fatal MI and fatal CHD ($n=463$)	FFQ. Self-administered	Medical records and death certificates. ICD: 410–414. Non-fatal MI required diagnostic series of electrocardiographic changes or elevation of cardiac enzyme levels plus either prolonged cardiac pain or static electrocardiographic abnormalities	Age, sex, smoking, exercise, relative weight, high blood pressure
Knekt *et al.* (1996)[24]	Finland. Finnish Mobile clinic health cohort.	5133 men and women	30–69	26	CHD mortality ($n=473$)	Dietary history method. Completed by interview	Death certificates. ICD-8: 410–414	Age, smoking, serum cholesterol, hypertension and BMI

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; ICD, International Classification of Diseases; LDL, low-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

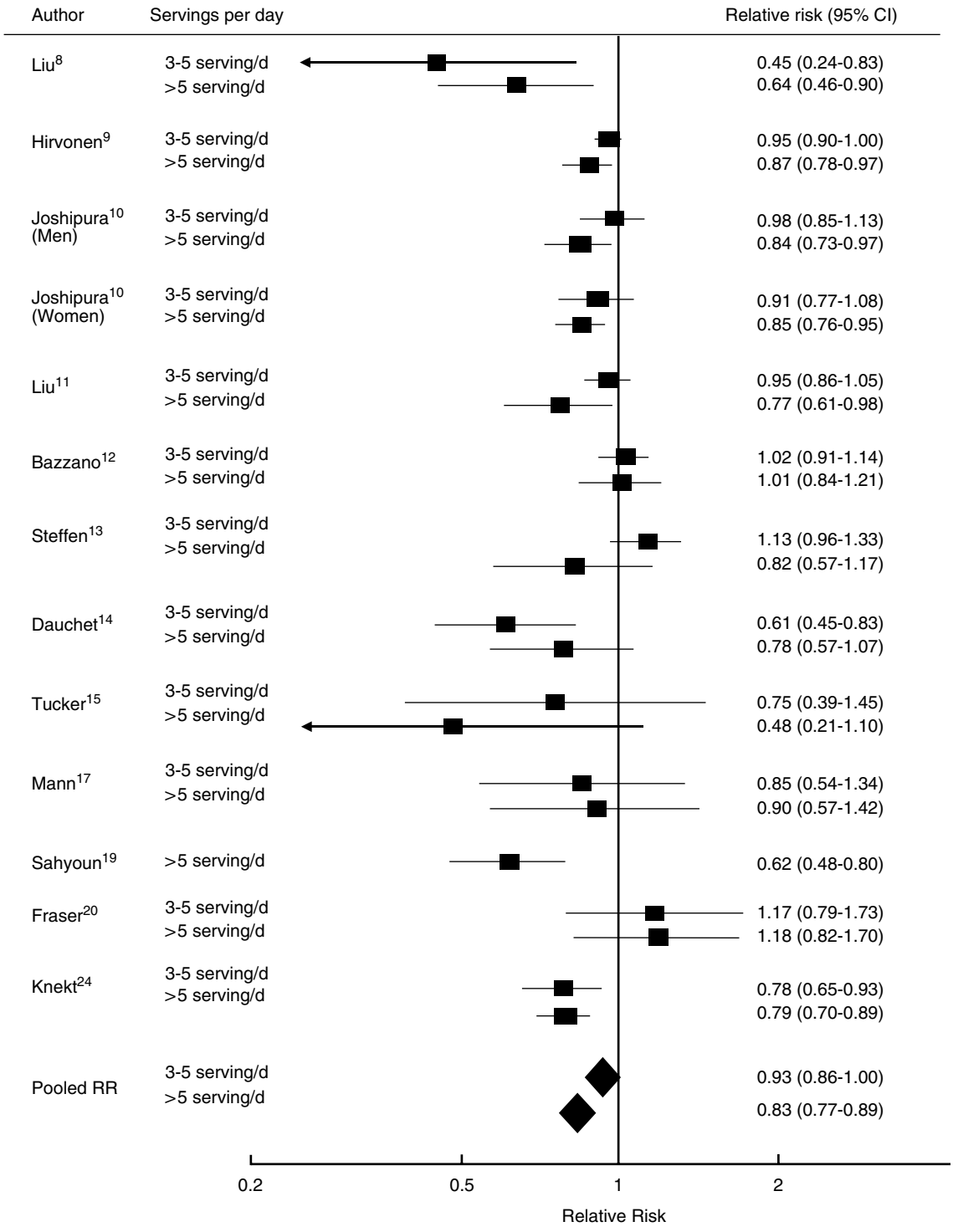

Figure 2 RR and 95% CI of CHD for fruit and vegetable intake of 3–5 servings/day and more than 5 servings/day compared with less than 3 servings/day. The size of the square is in proportion to the weight of each study in the meta-analysis.

day, individuals with more than 5 servings/day have an approximately 17% reduction in CHD risk, whereas individuals with 3–5 servings/day have a smaller and borderline significant reduction in CHD risk (7% reduction). These results provide strong support for the recommendations to consume more than 5 servings/day of fruit and vegetables.

The results of our meta-analysis are in agreement with those from the previous studies.[6,7,25] Law and Morris[6] studied the association of CHD with six dietary markers of fruit and vegetable intake in cohort studies and found that, on average, the risk of CHD is about 15% lower at the 90th than at the 10th centile of fruit and vegetable consumption judged

Table 3 Pooled RRs (95% CI) of CHD and results of heterogeneity test

	No. of cohorts	*No. of participants (events)*	*Fruit and vegetable intake (serving/day)*				
			<3	*3–5*		*>5*	
				RR (95% CI)	I^2, P *for heterogeneity*	*RR (95% CI)*	I^2, P *for heterogeneity*
All studies	13	278 459 (9143)	1	0.93 (0.86–1.00)	58.8%, 0.005	0.83 (0.77–0.89)	37.5%, 0.08
Gender							
Men	6	95 055 (4792)	1	0.90 (0.82–0.98)	58.3%, 0.04	0.84 (0.78–0.90)	0%, 0.72
Women	3	125 763 (1402)	1	0.76 (0.55–1.05)	59.1%, 0.09	0.76 (0.64–0.90)	51.1%, 0.13
Duration of follow-up							
<10 years	5	141 101 (3838)	1	0.87 (0.73–1.04)	73.0%, 0.005	0.85 (0.75–0.95)	35.9%, 0.18
⩾10 years	8	137 358 (5305)	1	0.95 (0.87–1.04)	48.2%, 0.07	0.81 (0.73–0.90)	44.1%, 0.08
Dietary assessment method							
Food frequency questionnaire	10	272 100 (8498)	1	0.95 (0.88–1.03)	57.4%, 0.01	0.86 (0.81–0.92)	12.4%, 0.33
Others[a]	3	6359 (645)	1	0.78 (0.66–0.92)	0%, 0.91	0.70 (0.56–0.88)	49.8%, 0.14
Dietary instrument administration							
Self-administered	10	251 778 (6349)	1	0.91 (0.84–0.99)	48.9%, 0.05	0.81 (0.75–0.89)	36.1%, 0.12
Interview-administered	3	26 681 (2794)	1	0.97 (0.80–1.17)	79.7%, 0.007	0.87 (0.73–1.04)	59.9%, 0.08
Dietary intake[b]							
Fruits	9	241 190 (5603)	1	0.90 (0.83–0.98)	29.4%. 0.20	0.87 (0.80–0.95)	20.1%, 0.27
Vegetables	9	229 937 (6288)	1	0.92 (0.87–0.97)	0%, 0.46	0.84 (0.76–0.92)	49.2%, 0.06

Abbreviations: RR, relative risk; CHD, coronary heart disease; CI, confidence interval.
[a]One study used dietary history method and two used food records.
[b]The equivalent intake for the three categories was <1.3, 1.3 to 2.0 and >2.0 servings/day, respectively for fruits, and <1.7, 1.7 to 3.0 and >3.0 servings/day, respectively for vegetables.

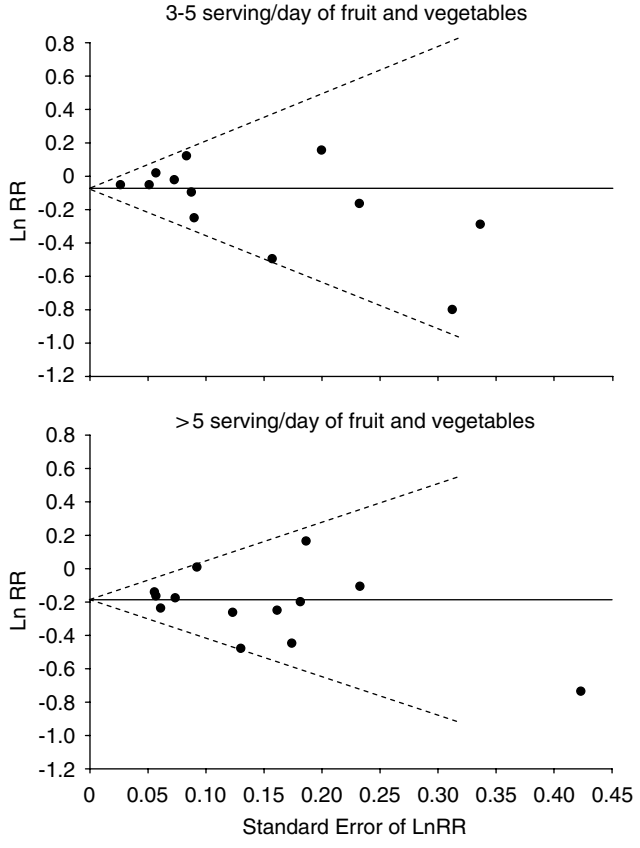

Figure 3 Funnel plot to explore publication bias. The horizontal line is at the mean effect size.

from six dietary markers. However, detailed analysis showed that the association was only significant for carotenoids, vitamin C, fruit fibre and vegetable fibre, whereas there was no significant association of fruits or vegetables with CHD, although the RRs were of similar magnitude for all six dietary markers. These non-significant findings for fruits or vegetables are likely to be due to the small number of studies included (that is, only three studies for fruits and two for vegetables). Another meta-analysis of cohort studies by Van't Veer *et al.* estimated that an increase of 150 g/day of fruit and vegetables was associated with a reduction of 20 to 40% in CHD risk. Lock *et al.*[25] estimated that, worldwide, up to 2.6 million deaths per year were attributable to inadequate consumption of fruit and vegetables, and increasing fruit and vegetable consumption to 600 g/day could reduce the burden of CHD by 31%. A recent meta-analysis of six cohort studies showed that the risk of CHD was decreased by 4% for each additional portion/day of fruit and vegetable intake.[26] Pereira *et al.*[27] pooled the original data of 10 cohort studies and showed that the consumption of dietary fibre from fruit and cereals was inversely associated with CHD risk, but there was no significant association between vegetable fibre and CHD risk. Pereira *et al.* speculated that the beneficial effects of vegetable fibre may be countered by the high glycemic load from starchy and heavily processed vegetables. However, in their analysis, Pereira *et al.* did not look at whether there was an

association between fruits or vegetables themselves and CHD risk.

Case-control studies were excluded from our meta-analysis due to the potential selection bias, recall bias and bias due to the changes in diet and lifestyle following CHD events. However, one large, international, standardized case-control study (that is, the INTERHEART) is worth mentioning. The INTERHEART study[28] enrolled 15 152 cases of acute MI and 14 820 controls from 262 centres in 52 countries. Only first acute MI cases were included in order to minimize the bias due to changes in diet and lifestyle following CHD events. The results showed that individuals who ate fruit and vegetables every day compared with those who did not, had a reduction of 30% (95% CI: 21 to 38%) in the risk of MI (adjusted for possible confounding factors). Several other case-control studies[29–31] generally observed a stronger association between fruit and vegetable intake and CHD than we found in our meta-analysis of prospective cohort studies.

Although there is no outcome of evidence from long-term randomized trials looking at fruit and vegetables alone on the primary prevention of CHD, randomized trials in individuals who had survived CHD showed that increasing fruit and vegetable intake in combination with other diet and lifestyle changes significantly reduced the recurrence of CHD events.[32,33] These results lend further support to the important role of fruit and vegetables in CHD prevention, though the beneficial effects are not solely attributable to fruit and vegetable consumption.

A substantial heterogeneity across studies was apparent in our meta-analysis. The heterogeneity was not accounted by gender, duration of follow-up or the approach used to measure fruit and vegetable intake. However, the stratified analysis for fruits and vegetables separately reduced the heterogeneity. It is possible that variation between study populations on what types of fruits and vegetables and whether cooked or raw vegetables are most commonly consumed may introduce heterogeneity. It is speculated that there will be a stronger association with those vegetables that contain more protective nutrients, for example, potassium, and a weaker association with heavily processed vegetables. Some of the cohort studies included potatoes as vegetables, some excluded potatoes from vegetables, others did not report whether potatoes were included or not. This may also introduce heterogeneity. However, due to the limited information reported in the literature, we did not perform further analyses on this issue.

Our study may have a number of potential limitations. First, we could not exclude potential biases due to other dietary and lifestyle factors. Individuals who eat more fruit and vegetables are likely to have lower rates of smoking, a lower intake of salt and saturated fat, higher levels of physical exercise and are less likely to be overweight.[12] Such healthier diet and lifestyles have been shown to reduce the risk of CHD. A meta-analysis is not able to solve problems with confounding that may be inherent in the included studies. However, the adjustment of major confounding factors in the included studies should reduce the potential bias due to these other dietary and lifestyle factors. Second, we could not exclude the potential bias due to measurement error in the dietary assessment. Among the 12 studies included in our meta-analysis, only 3 took account of the changes of dietary intake over time, and in the majority of the studies dietary assessment was only made at baseline. The inherent measurement error in the dietary assessment would tend to attenuate the protective effect of fruit and vegetables. Therefore, the reductions in CHD risk observed in our study may be a conservative estimate. Finally, we could not exclude potential biases due to misclassification of fruit and vegetable intake as dietary assessment method, the number of groups of fruit and vegetable consumption, and the reference category varied among individual studies. However, our subgroup analyses did not support the presence of major confounding effects by these factors.

The protective effects of fruit and vegetables on CHD have a strong biological basis. Fruit and vegetables are rich sources of potassium, folate, fibre, antioxidants and bioactive phytochemicals. Randomized trials have shown that increasing fruit and vegetable consumption with a subsequent increase in 24 h urinary potassium excretion lowers blood pressure,[34] and potassium supplementation trials also show a significant and similar blood pressure-lowering effect as fruit and vegetables.[35–37] As raised blood pressure throughout its range is a major cause of CHD, it is likely that the blood pressure-lowering effect of potassium is the major mechanism that contributes to a reduced risk of CHD with higher fruit and vegetable consumption.

Dietary folate is a determinant of plasma homocysteine level, and there have been several studies relating plasma homocysteine levels with the risk of CHD.[38,39] Dietary fibre may contribute to the reduction in CHD risk by lowering blood pressure and cholesterol.[40] Phytochemicals (plant sterols, flavonoids and sulphur-containing compounds) found in fruits and vegetables may be important in reducing risk of atherosclerosis.[41] Antioxidants have been shown, in experimental models, to reduce atherosclerosis, mainly through a reduction of the amount of oxidized low-density lipoprotein available to be incorporated into lesions. Increasing fruit and vegetable consumption causes a rise in plasma antioxidants in randomized trials.[42] However, long-term intervention studies of folate, vitamins B, C and E and β-carotene have failed to show any beneficial effect on CHD.[43,44] Therefore, the contributions of folate, fibre, antioxidants and phytochemicals to a

reduced risk of CHD with a higher fruit and vegetable intake are speculative.

In conclusion, our meta-analysis of prospective cohort studies demonstrates that increased consumption of fruit and vegetables from less than 3 to more than 5 servings/day is related to a 17% reduction in CHD risk, whereas increased intake to 3–5 servings/day is associated with a smaller and borderline significant reduction in CHD risk. The average fruit and vegetable intake in most developed countries is approximately 3 servings/day, and it is even less in developing countries. The current recommendations are to increase the intake to 5 or more servings/day. Our results provide strong support for these recommendations. If these were achieved, there would be a large reduction in CHD morbidity and mortality. As raised blood pressure throughout its range is a major cause of CHD, it is likely that the blood pressure-lowering effect of fruit and vegetables is the major mechanism that contributes to a reduced risk of CHD. In addition to its effect on CHD, an increase in the consumption of fruit and vegetables may reduce the risk of strokes[45] and some cancers[46] and may have other health benefits, for example improving bowel function,[47] helping people adhere to weight-reducing diets through improved satiety,[48] however, these outcomes were not the focus of this meta-analysis.

What is known about this topic

- Fruit and vegetable intake is inversely related to the risk of CHD, however, the extent of the quantitative association is uncertain

What this study adds

- Increased consumption of fruit and vegetables from less than 3 to more than 5 servings/day is related to a 17% reduction in CHD risk, whereas increased intake to 3–5 servings/day is associated with a smaller and borderline significant reduction in CHD risk
- Our results provide strong support for the recommendations to consume more than 5 servings/day of fruit and vegetables

Abbreviation: CHD, coronary heart disease.

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References

1 British Heart Foundation Statistics 2005. http://www.bhf.org.uk/professionals/uploaded/factsheet2005finalaw.pdf(accessed 13 January 2006).
2 Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy. Nutritional Aspects of Cardiovascular Disease. 1994. London: HMSO.
3 Joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases, 2003, Geneva. http://www.who.int/hpr/NPH/docs/who_fao_experts_report.pdf(accessed 22 March 2005).
4 US Department of Agriculture. US Department of Health and Human Services. Dietary guidelines for Americans. http://www.health.gov/dietaryguidelines/dga2000/dietgd.pdf(accessed 22 July 2005).
5 Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol* 1997; **26**: 1–13.
6 Law MR, Morris JK. By how much does fruit and vegetable consumption reduce the risk of ischaemic heart disease? *Eur J Clin Nutr* 1998; **52**: 549–556.
7 Van't Veer P, Jansen M, Klerk M, Kok FJ. Fruits and vegetables in the prevention of cancer and cardiovascular disease. *Public Health Nutr* 2000; **3**: 103–107.
8 Liu S, Manson JE, Lee IM, Cole SR, Hennekens CH, Willett WC *et al.* Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr* 2000; **72**: 922–928.
9 Hirvonen T, Pietinen P, Virtanen M, Ovaskainen ML, Hakkinen S, Albanes D *et al.* Intake of flavonols and flavones and risk of coronary heart disease in male smokers. *Epidemiology* 2001; **12**: 62–67.
10 Joshipura KJ, Hu FB, Manson JE, Stampfer MJ, Rimm EB, Speizer FE *et al.* The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med* 2001; **134**: 1106–1114.
11 Liu S, Lee IM, Ajani U, Cole SR, Buring JE, Manson JE. Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. *Int J Epidemiol* 2001; **30**: 130–135.
12 Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L *et al.* Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Am J Clin Nutr* 2002; **76**: 93–99.
13 Steffen LM, Jacobs Jr DR, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2003; **78**: 383–390.
14 Dauchet L, Ferrieres J, Arveiler D, Yarnell JW, Gey F, Ducimetiere P *et al.* Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study. *Br J Nutr* 2004; **92**: 963–972.
15 Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL. The combination of high fruit and vegetable and low saturated fat intake is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. *J Nutr* 2005; **135**: 556–561.
16 USDA Nutrient Database for Standard Reference, Release 18. http://www.ars.usda.gov/Services/docs.htm?docid = 10091&pf = 1&cg_id = 0(accessed 23 December 2005).
17 Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* 1997; **78**: 450–455.
18 He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR *et al.* Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* 2004; **109**: 2705–2711.

19 Sahyoun NR, Jacques PF, Russell RM. Carotenoids, vitamins C and E, and mortality in an elderly population. *Am J Epidemiol* 1996; **144**: 501–511.
20 Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* 1992; **152**: 1416–1424.
21 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
22 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; **323**: 101–105.
23 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
24 Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ* 1996; **312**: 478–481.
25 Lock K, Pomerleau J, Causer L, Altmann DR, McKee M. The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Organ* 2005; **83**: 100–108.
26 Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr* 2006; **136**: 2588–2593.
27 Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL *et al.* Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. *Arch Intern Med* 2004; **164**: 370–376.
28 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**: 937–952.
29 Gramenzi A, Gentile A, Fasoli M, Negri E, Parazzini F, La Vecchia C. Association between certain foods and risk of acute myocardial infarction in women. *BMJ* 1990; **300**: 771–773.
30 Panagiotakos DB, Pitsavos C, Kokkinos P, Chrysohoou C, Vavuranakis M, Stefanadis C *et al.* Consumption of fruits and vegetables in relation to the risk of developing acute coronary syndromes; the CARDIO2000 case-control study. *Nutr J* 2003; **2**: 2–6.
31 Martinez-Gonzalez MA, Fernandez-Jarne E, Martinez-Losa E, Prado-Santamaria M, Brugarolas-Brufau C, Serrano-Martinez M. Role of fibre and fruit in the Mediterranean diet to protect against myocardial infarction: a case-control study in Spain. *Eur J Clin Nutr* 2002; **56**: 715–722.
32 de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; **99**: 779–785.
33 Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA *et al.* Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998; **280**: 2001–2007.
34 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM *et al.* A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**: 1117–1124.
35 Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D *et al.* Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277**: 1624–1632.
36 MacGregor GA, Smith SJ, Markandu ND, Banks RA, Sagnella GA. Moderate potassium supplementation in essential hypertension. *Lancet* 1982; **2**: 567–570.
37 He FJ, Markandu ND, Coltart R, Barron J, MacGregor GA. Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. *Hypertension* 2005; **45**: 571–574.
38 Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002; **325**: 1202–1206.
39 Clarke R, Collins R, Lewington S. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA* 2002; **288**: 2015–2022.
40 He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. *Clin Exp Hypertens* 1999; **21**: 785–796.
41 Howard BV, Kritchevsky D. Phytochemicals and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 1997; **95**: 2591–2593.
42 John JH, Ziebland S, Yudkin P, Roe LS, Neil HAW. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet* 2002; **359**: 1969–1974.
43 Davey Smith G, Ebrahim S. Folate supplementation and cardiovascular disease. *Lancet* 2005; **366**: 1679–1681.
44 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 23–33.
45 He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 2006; **367**: 320–326.
46 World Cancer Research Fund Panel. *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. American Institute for Cancer Research: Washington, DC, 1997.
47 Kelsay JL, Behall KM, Prather ES. Effect of fiber from fruits and vegetables on metabolic responses of human subjects. I. Bowel transit time, number of defecations, fecal weight, urinary excretions of energy and nitrogen and apparent digestibilities of energy, nitrogen, and fat. *Am J Clin Nutr* 1978; **31**: 1149–1153.
48 Rolls BJ, Ello-Martin JA, Tohill BC. What can intervention studies tell us about the relationship between fruit and vegetable consumption and weight management? *Nutr Rev* 2004; **62**: 1–17.
49 Rapola JM, Virtamo J, Korhonen P, Haapakoski J, Hartman AM, Edwards BK *et al.* Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. *Eur J Epidemiol* 1997; **13**: 133–138.
50 Ducimetiere P, Ruidavets JB, Montaye M, Haas B, Yarnell J. Five-year incidence of angina pectoris and other forms of coronary heart disease in healthy men aged 50-59 in France and Northern Ireland: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study. *Int J Epidemiol* 2001; **30**: 1057–1062.