

Fruit and Vegetable Consumption and Risk of Coronary Heart Disease: A Meta-Analysis of Cohort Studies¹

Luc Dauchet,^{2,3} Philippe Amouyel,⁴ Serge Hercberg,² and Jean Dallongeville^{4*}

²INSERM U557; INRA U1125; CNAM; University Paris 13, Centre de Recherche en Nutrition Humaine, 93017 Bobigny, France; ³Département d'Epidémiologie et de Santé Publique, 76000 Rouen; and ⁴Service d'Epidémiologie et Santé Publique; INSERM U744; Institut Pasteur de Lille, 59019 Lille Cedex, France

Abstract

The consumption of fruit and vegetables is associated with a reduced rate of coronary heart disease (CHD) in observational cohorts. The purpose of this study was to assess the strength of this association in a meta-analysis. Cohort studies were selected if they reported relative risks (RRs) and 95% CI for coronary heart disease or mortality and if they presented a quantitative assessment of fruit and vegetable intake. The pooled RRs were calculated for each additional portion of fruit and/or vegetables consumed per day, and the linearity of the associations were examined. Nine studies were eligible for inclusion in the meta-analysis that consisted of 91,379 men, 129,701 women, and 5,007 CHD events. The risk of CHD was decreased by 4% [RR (95% CI): 0.96 (0.93–0.99), $P = 0.0027$] for each additional portion per day of fruit and vegetable intake and by 7% [0.93 (0.89–0.96), $P < 0.0001$] for fruit intake. The association between vegetable intake and CHD risk was heterogeneous ($P = 0.0043$), more marked for cardiovascular mortality [0.74 (0.75–0.84), $P < 0.0001$] than for fatal and nonfatal myocardial infarction [0.95 (0.92–0.99), $P = 0.0058$]. Visual inspection of the funnel plot suggested a publication bias, although not statistically significant. Therefore, the reported RRs are probably overestimated. This meta-analysis of cohort studies shows that fruit and vegetable consumption is inversely associated with the risk of CHD. The causal mechanism of this association, however, remains to be demonstrated. *J. Nutr.* 136: 2588–2593, 2006.

Introduction

Consumption of sufficient amounts of fruit and vegetables are recommended as part of a healthy diet. Fruit and vegetables may reduce chronic diseases and more specifically, coronary heart disease (CHD),⁵ by means of their protective constituents such as potassium, folate, vitamins, fiber, and other phenolic compounds (1). These nutrients act through a variety of mechanisms, such as reducing antioxidant stress, improving lipoprotein profile, lowering blood pressure, increasing insulin sensitivity, and improving hemostasis regulation (1–3). However, the recommendation to eat fruit and vegetables to prevent chronic diseases is mainly based on observational epidemiological studies, which leaves much uncertainty regarding the causal mechanism of this association.

Several cohort studies have examined the relation between fruit and vegetable intake and coronary heart disease. The results of these studies have been summarized in previous reviews (4), and an earlier pooled analysis reported an inverse association between intake of fiber from fruit and vegetables and CHD risk (5). In general, these studies report a favorable re-

lation between fruit and vegetable consumption and CHD occurrence, although sometimes the results are inconsistent. Furthermore, the magnitude of the favorable association remains uncertain because of differences in methodological approaches, analytical techniques, and outcome definitions. Two recent meta-analyses have reported an inverse association between fruit and vegetable consumption and the occurrence of stroke (6,7), which supports the idea that fruit and vegetable consumption might protect against cardiovascular events. Therefore, the objective of the present study was to assess, through meta-analysis, the magnitude of the relation between fruit and vegetable consumption and the risk of CHD. Only cohort studies using quantitative methods of dietary intake assessment were used for the present meta-analysis.

Methods

Search. We selected published prospective studies that assessed the relation between CHD and the consumption of fruit and/or vegetables. The prespecified criteria were: 1) prospective studies, 2) coronary heart disease, and 3) quantitative assessment of fruit and vegetable intake.

Searches were conducted in electronic databases (Medline and EMBASE) from 1970 to January 2006. References from the extracted papers, reviews, and previous meta-analysis were also consulted to complete the data bank. The electronic search includes both free-text and

¹ This study was supported by INSERM and Pasteur Institute of Lille.

⁵ Abbreviations used: CHD, coronary heart disease; MI, myocardial infarction; RR, relative risk.

* To whom correspondence should be addressed. E-mail: jean.dallongeville@pasteur-lille.fr.

MeSH terms and was performed with the support of the laboratory librarian. Used terms were: “cardiovascular disease,” “heart disease,” “ischemic heart disease,” “myocardial infarction,” “coronary heart disease,” “cohort studies,” “prospective studies,” “follow-up studies,” “fruit,” and “vegetables.” No attempt was made to contact authors of unpublished works or to find articles in languages other than English. Two investigators (L.D. and J.D.) performed data collection. Disagreements were resolved by consensus.

We included in the analysis the cohorts’ reporting incidence of relative risk (RR) for coronary heart events. When more than one outcome was available we included, by order of priority: 1) fatal and nonfatal myocardial infarction (MI), 2) ischemic heart disease mortality or coronary death, and 3) coronary heart disease incidence. Studies that reported cardiovascular events only, or combined cerebro- and cardiovascular events, were excluded. Inclusion criteria for exposure variables were fruit and/or vegetable consumption per se and not their representative nutrients. Thus, we included in the analysis only the following food groups named in the articles: “vegetables,” “all vegetables,” “vegetables rich in carotenoids,” “fruit,” or “all fruit.” Individual fruit or vegetables, such as tomatoes, garlic, beans, etc. were excluded. There was no restriction on the method of dietary assessment provided that the method involved a computation of the amount of fruit and vegetable intake and not just the frequency of intake. Therefore, food intake was assessed by means of food records, diet history methods, and food frequency questionnaires. As long as the exposure variable was always fruit and/or vegetables, the definition of this variable could vary among studies. For instance, fruit juices were included with fruit in some studies and potatoes were included with vegetables in others.

Literature and reference searches identified 20 studies (8–27). Four were excluded because CHD events were pooled with cardiovascular (8,9) or cerebrovascular events (10), therefore not permitting a separate analysis of CHD events (11). Four studies were excluded because the food frequency questionnaire did not assess the quantity of fruit and/or vegetable intake (12–15). Three were excluded because there were insufficient data to extrapolate the relative risks (17–19). Data from the ATBC study were taken from Hirvonen et al. (21) instead of Pietinen et al. (20). The final data set consisted of 9 independent studies (16,21–27) comprising 221,080 subjects and 5007 events with a follow-up between 5 and 19 y (Table 1).

Statistical methods. The method used in this analysis is described in detail elsewhere (28). Briefly, the RR of CHD for an increment in 1 standard portion/d of fruit and/or vegetable and related CI adjusted for the largest number of potentially confounding variables (except dietary variables such as vitamins, see Table 2 for the confounding variables) were extracted from the original reports. Whenever the RR for a standard portion was not available in the publication, it was calculated from the RR of each category of fruit and/or vegetable intake as described previously (29). The median values of fruit and/or vegetable intake for each class were taken from the individual publication to calculate exposure. If the data were unavailable, the median was estimated as the midpoint of the class using the limits of the class provided in the original article (28). When exposure was expressed in terms of frequency (21), fruit and vegetable quantities were computed from the validation study.

When fruit and vegetable intake was expressed in g/d (11,20), the exposure level was transformed into a standard portion by dividing this quantity by 106 g. For the Health Professionals’ Follow-up Study and the Nurses’ Health Study (24) the CI of RR were calculated from the original article, assuming that the variance of the logarithm of RR was inversely related to the number of events.

Heterogeneity among studies was assessed by the Cochran’s Q test. The pooled estimates of the RRs were computed assuming a log-linear model $\ln RR = \beta X$, where X represents 1 portion of fruit and/or vegetable and β the pooled weighted coefficient of individual studies using a random-effect model. To test the appropriateness of a log-linear model, we plotted for each category of fruit and/or vegetable intake the corresponding logarithm of RR in each individual study. Due to insufficient information, the Baltimore Longitudinal Study of Aging (27) was not included in the plot graph. The possibility of a publication bias was assessed by funnel plot analysis and the Egger test (30). For this analysis the results of individual cohorts presented in the same publication (22,24) were pooled.

Results

Nine cohorts were selected for the meta-analysis (Table 1 and Table 2). Seven cohorts were from the U.S. and 2 were from Finland. The sample size ranged from 501 in the Baltimore Longitudinal Study of Aging to 75,596 in the Nurses’ Health Study for a total number of 91,379 men and 129,701 women. The range of follow-up duration was 5 to 19 y. The analysis included 5007 CHD events.

Six cohorts reported an association between fruit and vegetable intake and risk of CHD. The sample size was 48,039 men and 127,316 women, all of whom were from the U.S. The end-points were: fatal and nonfatal MI in 3 studies, coronary death in 2, and incident CHD in 1 study. The total number of events was 3561. The RRs of CHD for each increment of 1 portion/d of fruits and vegetables varied between 0.79 and 0.97 (Fig. 1A). There was no evidence of heterogeneity among studies ($P = 0.17$). In a random-effect model the pooled RR (95% CI) of CHD was 0.96 (0.93–0.99, $P = 0.0027$).

Six cohorts reported data for fruit intake and CHD; the results of the Mobile Clinic Social Insurance were presented in men and women separately. The sample size was 67,304 men and 117,108 women, of whom 153,907 were from the U.S. and 30,505 were from Finland. The end-points were: fatal and nonfatal MI in 3 studies, coronary death in the others. The total number of events was 3446. The RR of CHD for each increment of 1 portion/d of fruit varied from 0.81 to 0.95 (Fig. 1B). There was no evidence for heterogeneity among studies ($P = 0.91$). In a random-effect model the pooled RR (95% CI) for each increment of 1 portion/d of fruit was 0.93 (0.89–0.96, $P < 0.0001$).

TABLE 1 Description of cohort studies on consumption of fruits and/or vegetables and risk of coronary heart disease

Cohort	Population sample	Authors	Publication date	Location	Men/women, <i>n</i>	Age, <i>y</i>	Follow-up, <i>y</i>
Health professionals follow-up study (24)	Professional	Joshiyura et al.	1999	USA	38,683/—	40 to 75	8
Nurses’ health study (24)	Professional	Joshiyura et al.	1999	USA	—/75,596	34 to 59	14
Women’s health study (23)	Professional	Liu et al.	2000	USA	—/39,127	mean 54	5
Physicians’ health study (25)	Professional	Liu et al.	2001	USA	15,220/—	40–84	12
α -Tocopherol β -carotene cancer prevention study (ATBC) (21)	Smoker population based	Hirvonen et al.	2001	Finland	25,372/—	50–69	6.1
NHANES follow-up study (26)	Population based	Bazzano et al.	2002	USA	3684/5924	25 to 74	19
Atherosclerosis risk in communities (ARIC) (16)	Population based	Steffen et al.	2003	USA	5171/6669	45 to 64	11
Mobile clinic of social insurance (22)	Population based	Knekt et al.	1994	Finland	2748/2385	30 to 69	14
Baltimore longitudinal study of aging (BLSA) (27)	Population based	Tucker et al.	2005	USA	501/—	mean 62	18

TABLE 2 Consumption of fruits and/or vegetables and coronary heart disease

Cohort	End-point	Events, <i>n</i>	Exposure level	Exposure variable ¹	Median of intake	RR of CHD	Adjustment ²
Health professionals follow-up study (24)	Fatal and nonfatal MI	1063	1 Additional portion/d	Fruit	2.1	0.92 (0.87–0.98)	Age, smoking, alcohol, family history of myocardial infarction, BMI, vitamin supplement use, vitamin E use, PA, aspirin use, time periods, hypertension, hypercholesterolemia, total energy intake, PHU.
				Vegetables	2.8	0.97 (0.92–1.02)	
				F + V	5.1	0.96 (0.93–1.00)	
Nurses' health study (24)	Fatal and nonfatal MI	1127	1 Additional portion/d	Fruit	2.3	0.95 (0.89–1.01)	Adjustments as above.
				Vegetables	3.3	0.93 (0.88–0.98)	
				F + V	5.8	0.97 (0.93–1.01)	
Women's health study (23)	Fatal and nonfatal MI	126	5th vs. 1st Quintile	Fruit	1.9	0.66 (0.36–1.22)	Age, smoking, PA alcohol, menopausal status, PHU, BMI, multivitamin use, vitamin C, diabetes, hypertension, high cholesterol, parental history of MI
				Vegetables	3.4	0.88 (0.50–1.58)	
				F + V	5.5	0.63 (0.38–1.17)	
Physicians' health study (25)	Fatal and nonfatal MI	387	≥2,5 Times/d vs. <1 times/d	Vegetables rich in carotenoid	1.3*	0.81 (0.59–1.31)	Age, treatment, smoking, AI, PA, BMI, diabetes, high cholesterol, hypertension, multivitamin use
ATBC (21)	Coronary death	815	5th vs. 1st Quintile	Fruit	0.6*	0.87 (0.70–1.08)	Age, supplementation, blood pressure, cholesterol, HDL, BMI, smoking, diabetes, coronary heart disease, marital status, education, PA
				Vegetables	0.9*	0.68 (0.50–0.95)	
NHANES follow-up study (26)	Ischemic heart disease mortality	639	≥3 Times/d vs. <1 time/d	F + V	3.3 [†]	0.76 (0.56–1.03)	Age, gender, race, history of diabetes, PA, educational level, regular alcohol consumption, current cigarette smoking at baseline, vitamin supplementation, total EI
Altherosclerosis risk in communities (16)	Incident coronary heart disease	535	5th vs. 1st Quintile	F + V	3.5	1.17 (0.82–1.66)	Age, gender, race, EI, education, smoking status, pack-year of smoking, PA, AI, hormone replacement, BMI, waist-to-hip ratio, systolic blood pressure, and antihypertensive medication use.
Mobile clinic of social insurance (22)	Coronary death	186 men/58 women	3rd vs. 1st Tertile	Fruit	Men: 1.1* women: 1.0*	Men: 0.77 (0.52–1.12) women: 0.66 (0.36–1.22)	Age, smoking, cholesterol, hypertension, BMI, EI
				Vegetables	Men: 0.8* women: 1.0*	Men: 0.66 (0.46–0.96) women: 0.66 (0.35–1.23)	
Baltimore longitudinal study of aging (27)	Coronary death	71	1 Additional portion/d	Fruit	2.2**	0.86 (0.70–1.05)	Age, EI, BMI, smoking, alcohol, PA, supplement use
				Vegetables	2.4**	0.60 (0.46–0.78)	
				F + V	4.6**	0.79 (0.69–0.92)	

¹ F + V, fruit and vegetables.

² AI, alcohol intake; EI, energy intake; PA, physical activity; PHU, postmenopausal hormone use.

* Middle of median class; **mean.

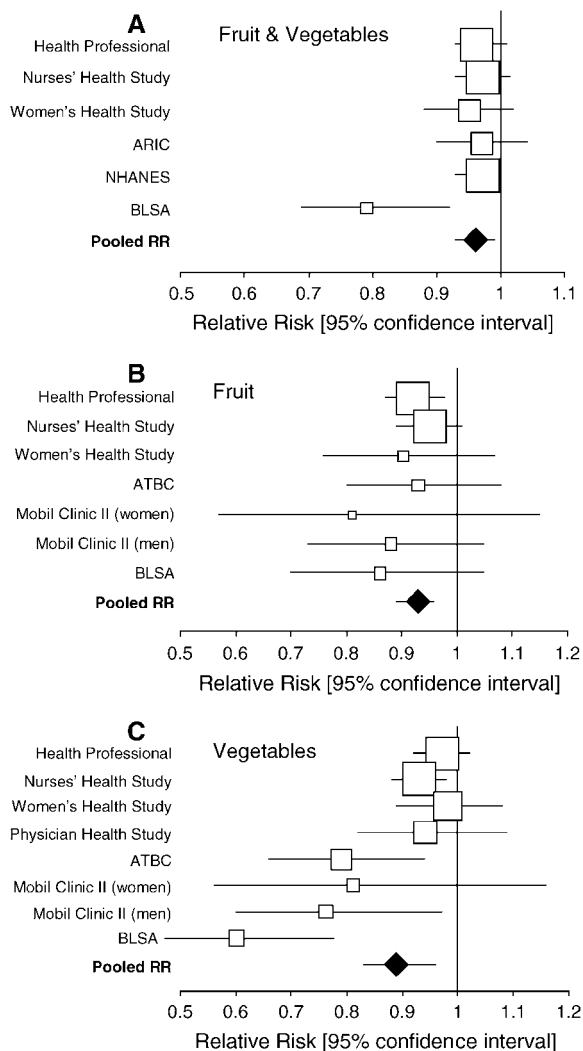


Figure 1 Pooled estimate of relative risk (RR) and 95% CI of ischemic heart disease (IHD) rates for one portion increment per day of "fruit and vegetable" (A), fruit (B) and vegetables (C). Open squares indicate adjusted RR in each study and are inversely related to RRs variance. Filled diamonds are pooled RR. Horizontal line represents 95% CI.

Seven cohorts reported the association between vegetable intake and risk of CHD; the results of the Mobile Clinic Social Insurance were presented in men and women separately. The sample size was 82,524 men and 117,108 women, of whom 169,127 were from the U.S. and 30,505 from Finland. The end-points were: fatal and nonfatal MI in 4 studies and coronary death in the others. The total number of events was 3833. The RRs for each additional portion of vegetable/d varied from 0.60 to 0.98 (Fig. 1C). There was evidence for heterogeneity among studies ($P = 0.004$). In a random-effect model the pooled RR (95% CI) of CHD for each additional portion of vegetables/d was 0.89 (0.83–0.95, $P = 0.0023$). The RR (95% CI) of fatal and nonfatal MI (4 studies) was 0.95 (0.92–0.99, $P = 0.0058$), and the RR for mortality (3 studies) was 0.74 (0.75–0.84, $P < 0.0001$), with no evidence of heterogeneity ($P = 0.66$ and $P = 0.36$, respectively).

The scatter-plots of the association between fruit and fruit and vegetable intake and RRs from the individual studies are compatible with a linear relation (Fig. 2). The results are more heterogeneous for vegetable consumption. Visual inspection of the funnel plot (Fig. 3) suggests a publication bias although, the

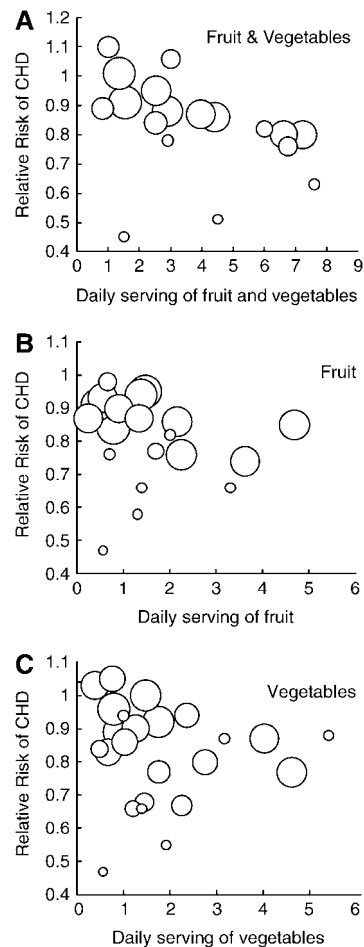


Figure 2 Relation between fruit and vegetable intake and relative risk (RR) of coronary heart disease. The circles represent the RR reported in each class of daily servings in each individual study. The number of portions consumed, in addition to the reference class, is plotted on the X axis and the RR on the Y axis. The size of the circle is inversely proportional to the logarithm of the RR variance.

Egger test, for fruit and vegetables ($P = 0.23$), fruit ($P = 0.11$), and vegetables ($P = 0.08$).

Discussion

The results of the present meta-analysis of cohort studies indicate that fruit and vegetable consumption is inversely

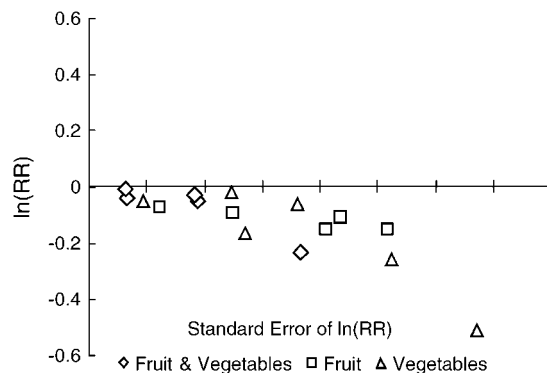


Figure 3 Funnel plot representation of the relation between the relative risks (RRs) of CHD and the SE of the RR. Each point represents the result of 1 study.

associated with the occurrence of CHD. The risk of CHD is decreased by 4% for each additional portion per day of fruit and vegetables and by 7% for fruit consumption. The association between vegetable intake and CHD risk is heterogeneous depending on the outcomes. Finally, visual inspection of the funnel plot suggest a publication bias, thus, the relative risks are probably overestimated.

Clinical and biological investigations support the protective effect of fruit and vegetables against CHD. Firstly, the relation is biologically plausible with abundant clinical and laboratory data demonstrating that the micro- and macro-constituents of fruit and vegetables improve important risk factors of CHD, such as hypertension, dyslipidemia, and diabetes (1–3). Secondly, the association persists after adjustment on these risk factor, suggesting a specific effect of fruit and vegetables. Thirdly, the scatter-plot representation of the relation shows a linear trend between fruit and vegetable intake and RR, which supports a dose-response relation. In contrast, other facts are not in favor of a causal relation. In population studies fruit and vegetable intake correlates with healthy lifestyles, which may explain the lower CHD rates. Generally, consumers of fruit and vegetables smoke less, exercise more, and are better educated than nonconsumers (31). Although most studies adjust for lifestyle factors, residual confounders may still explain part of the favorable association with CHD. High intakes of fruit and vegetables are associated with a prudent diet pattern (32,33) and inversely related to the consumption of saturated fat-rich food (27), which may also contribute to the lower CHD risk (32–34). Furthermore, the hypothetical mechanisms involved in the protective effects of fruit and vegetables have not always been confirmed in randomized clinical trials (35–37). Therefore, the results of the present study support the concept that the regular consumption of fruit and vegetables is associated with low rates of CHD, however, it does not establish a causal relation.

This study has several limitations. First, the finding of a possible publication bias suggests that the values of the RRs are probably overestimated. The reasons for this bias are not known. One possible explanation may be that during the process of selecting the publications we might have excluded a number of critical studies. Among these, 4 presented nonsignificant associations between vegetable intake and CHD (14,17–19) and 3 presented favorable associations (12,13,15). Second, the analysis of the relation between vegetable intake and CHD risk revealed heterogeneity among studies ($P = 0.0043$). Analyses stratified by outcomes gave some clues to explain this heterogeneity. The association between vegetable intake and CHD risk was more pronounced for cardiovascular mortality than for incident CHD. The reason for this difference is not known. One possible explanation may be the publication bias. Because mortality studies have fewer outcomes than studies reporting incident CHD, their 95% CI of RRs are wider. Thus associations (RRs) must be stronger to reach statistical significance. Alternatively, consumption of vegetables might have specific effects on mortality, a hypothesis that needs confirmation in cohorts with large numbers of fatal outcomes. Third, the meta-analysis is based on observational studies, which leaves the possibility that residual confounding factors, including measurement errors, affect the relation between fruit and/or vegetable intake and CHD. Fourth, there were many differences among studies, including dietary assessment methods, the variety of fruit or vegetables investigated, the definition of the reference group, and the choice of exposure categories. These differences could affect the estimation of the true relation. Fifth, due to the limited number of studies, subgroup analyses to test

the possible impact of gender, geographical area, and other factors were not performed. Finally, 7 of 9 studies were conducted in North America. Therefore, the results reflect the association in this country and not necessarily in other parts of the world where dietary habits and background may differ substantially.

In conclusion, this analysis presents evidence of a beneficial association between fruit and vegetable consumption and CHD risk, supporting the recommendation to eat a sufficient amount of fruit and vegetables to lower CHD risk. The strength of this association, however, is still uncertain because of a possible publication or selection bias. Furthermore, because observational studies do not control for unmeasured confounders, the causal mechanisms remain to be established in randomized controlled trials. Finally, this study also points out the limited availability of cohort studies to analyze the relation between fruit and/or vegetable intake and CHD risk in Europe and Asia.

Acknowledgment

The authors thank Sophie Duchaussoy (librarian) for data search.

Literature Cited

1. Van Duyn MA, Pivonka E. Overview of the health benefits of fruit and vegetable consumption for the dietetics professional: selected literature. *J Am Diet Assoc.* 2000;100:1511–21.
2. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH collaborative research group. *N Engl J Med.* 1997;336:1117–24.
3. Bazzano LA, Serdula MK, Liu S. Dietary intake of fruits and vegetables and risk of cardiovascular disease. *Curr Atheroscler Rep.* 2003;5:492–9.
4. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol.* 1997;26:1–13.
5. Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, et al. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. *Arch Intern Med.* 2004;164:370–6.
6. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology.* 2005;65:1193–7.
7. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet.* 2006;367:320–6.
8. Sahyoun NR, Jacques PF, Russell RM. Carotenoids, vitamins C and E, and mortality in an elderly population. *Am J Epidemiol.* 1996;144:501–11.
9. Rissanen TH, Voutilainen S, Virtanen JK, Venho B, Vanharanta M, Mursu J, Salonen JT. Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio ischaemic heart disease risk factor (KIHD) study. *J Nutr.* 2003;133:199–204.
10. Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA.* 2003;289:1659–66.
11. Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H. High fruit intake may reduce mortality among middle-aged and elderly men. The study of men born in 1913. *Eur J Clin Nutr.* 2000;54:337–41.
12. Gaziano JM, Manson JE, Branch LG, Colditz GA, Willett WC, Buring JE. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Ann Epidemiol.* 1995;5:255–60.
13. Key TJ, Thorogood M, Appleby PN, Burr ML. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. *BMJ.* 1996;313:775–9.
14. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart.* 1997;78:450–5.

15. Dauchet L, Ferrieres J, Arveiler D, Yarnell JW, Gey F, Ducimetiere P, Ruidavets JB, Haas B, Evans A, et al. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study. *Br J Nutr*. 2004;92:963-72.
16. Steffen LM, Jacobs DR, Jr., 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;78:383-90.
17. Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, et al. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston diet-heart study. *N Engl J Med*. 1985;312:811-8.
18. 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;152:1416-24.
19. Fehily AM, Yarnell JW, Sweetnam PM, Elwood PC. Diet and incident ischaemic heart disease: the Caerphilly study. *Br J Nutr*. 1993;69:303-14.
20. Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The alpha-tocopherol, beta-carotene cancer prevention study. *Circulation*. 1996;94:2720-7.
21. Hirvonen T, Pietinen P, Virtanen M, Ovaskainen ML, Hakkinen S, Albanes D, Virtamo J. Intake of flavonols and flavones and risk of coronary heart disease in male smokers. *Epidemiology*. 2001;12:62-7.
22. Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ*. 1996;312:478-81.
23. Liu S, Manson JE, Lee IM, Cole SR, Hennekens CH, Willett WC, Buring JE. Fruit and vegetable intake and risk of cardiovascular disease: the women's health study. *Am J Clin Nutr*. 2000;72:922-8.
24. Joshipura KJ, Hu FB, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Colditz G, Ascherio A, Rosner B, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med*. 2001;134:1106-14.
25. 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;30:130-5.
26. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, Whelton PK. 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;76:93-9.
27. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore longitudinal study of aging. *J Nutr*. 2005;135:556-61.
28. Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev*. 2001;10:439-46.
29. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*. 1992;135:1301-9.
30. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34.
31. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA*. 1999;282:1233-9.
32. Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr*. 2000;72:912-21.
33. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. *Arch Intern Med*. 2001;161:1857-62.
34. Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE, Hennekens CH, Willett WC. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr*. 1999;70:1001-8.
35. Leppala JM, Virtamo J, Fogelholm R, Huttunen JK, Albanes D, Taylor PR, Heinonen OP. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol*. 2000;20:230-5.
36. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145-9.
37. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-92.