International Journal of Epidemiology
Vol. 26, No. 1

Printed in Great Britain

REVIEW ARTICLES

Fruit and Vegetables, and Cardiovascular Disease: A Review

ANDREW R NESS AND JOHN W POWLES

Ness A R (Institute of Public Health, University Forvie Site, Cambridge CB2 2SR, UK) and Powles J W. Fruit and vegetables, and cardiovascular disease: A review. *International Journal of Epidemiology* 1997; **26:** 1–13.
Background. Increased interest in the potential cardio-protective effects of fruit and vegetables is currently unsupported by systematic reviews of the reported associations of these foods with risk.
Method. All ecological, case-control, cohort studies and unconfounded trials in humans were eligible for inclusion. Eligible outcomes were symptomatic coronary heart disease, stroke and total circulatory disease. Only studies of diet that reported on fresh fruit and vegetables or a nutrient which could serve as a proxy (reversing the usual direction of inference) were included. MEDLINE (1966–1995) and EMBASE (1980–1995) were searched using the terms cerebrovascular disorder, coronary heart disease, fruit(s) and vegetable(s) as keywords. Personal bibliographies, books and reviews were also searched, as were citations in located reports.
Results. For coronary heart disease nine of ten ecological studies, two of three case-control studies and six of 16 cohort studies found a significant protective association with consumption of fruit and vegetables or surrogate nutrients. For stroke three of five ecological studies, none (of one) case-control study and six of eight cohort studies found a significant protective association with consumption of fruit and vegetables or surrogate nutrients. For total circulatory disease, one of two cohort studies reported a significant protective association. No attempt was made to arrive at a summary measure of the association because of the differences in study type, study quality and the different exposure measures used.
Conclusions. Although null findings may be underreported the results are consistent with a strong protective effect of fruit and vegetables for stroke and a weaker protective effect on coronary heart disease. Greater use of food-based hypotheses and analyses, would complement existing nutrient-based analyses and help guide the search for underlying causes.
Keywords: fruit, vegetables, coronary heart disease, stroke, systematic review

Heart attack and stroke are major causes of mortality and morbidity in industrialized countries (outside of East Asia); for example within the UK 26% of deaths in 1992 were attributed to ischaemic heart disease[1] and 12% of deaths to stroke.[2] Diet is believed to be a major factor in the aetiology of cardiovascular disease[3] but there is still considerable scientific uncertainty about the relationship between specific dietary components and cardiovascular disease risk[4] and epidemiological doubts about the adequacy of the classic diet-heart hypothesis.[5]

In contrast to the literature on diet and cancer risk,[6] most studies of cardiovascular disease have reported the associations of risk with nutrients rather than with foods.[3] In retrospect, a more complete understanding of the causal links between diet and vascular disease was assumed than actually existed: recent reports on plasma homocysteine and cardiovascular risk, for example, suggest a newly appreciated connection between fresh foods—as sources of folate—and cardiovascular risk.[7]

Institute of Public Health, University Forvie Site, Cambridge CB2 2SR, UK

Increased interest in putative protective dietary factors in coronary heart disease, such as antioxidants,[8] has generated increased interest in foods which are rich in these substances, such as fruit and vegetables.

Confirmation of the associations between foods and disease risk also provides support for formulating public health messages in terms of foods.

An increase in consumption of fruit and vegetables to 400 g or five portions a day has been advocated by national and international bodies[4,9–11] on the assumption that such a change would reduce the incidence both of cancer and of cardiovascular disease. Systematic reviews of the association between the consumption of fresh fruit and vegetables and the risk of heart attack and stroke are however lacking. This contribution aims to fill that gap.

METHOD

We sought to include all relevant reports (including abstracts) of ecological, case-control, cohort studies and trials in humans. Eligible outcomes were symptomatic ischaemic heart disease, cerebrovascular disease and

total circulatory disease. We excluded studies of peripheral vascular disease, all-cause mortality or cardiovascular risk factors.

We included only studies that measured diet as such and not those that relied on biological markers and intermediate variables. We included studies of vegetarians that measured food intake but excluded those that merely classified people according to whether they ate meat or not. We have focused on studies that reported associations of risk with foods though, for completeness, we have included studies reporting certain nutrient associations where these were highly suggestive of associations with foods. Nutrients included on this basis were vitamin C (from diet as opposed to supplements), β-carotene, folate, flavonoids, potassium and dietary fibre from vegetables. The nutrient categories vegetable protein, the percentage of fats from fruit and vegetables, other carbohydrates (excluding starch and refined sucrose composed mainly of monosaccharides and disaccharides) and dietary fibre were not included. We included ecological studies only where there was explicit comparison with disease rates between populations and where more than two populations were compared.

We searched MEDLINE (1966–1995) using the keyword search terms 'cerebrovascular disorder' and 'coronary heart disease', as exploded terms, and fruit and vegetable, as both single and plural text words. We searched EMBASE (1980–1995) using the search terms cerebrovascular and coronary and fruit and vegetable, as both single and plural text words. We complemented this computer search with a search of personal bibliographic files, books and reviews [3,6,12–16] and followed up citations in references already located. We continued this process of cross-referencing until no new references were identified.

RESULTS

We identified ten ecological studies, three case-control studies and 16 cohort studies that reported the relationship between intake of fruit and vegetables and coronary heart disease. The methods and results of these studies are summarized in Tables 1–3.

We identified five ecological studies, one case-control study and eight prospective studies that reported the relationship between intake of fruit and vegetables and stroke. The methods and results of these studies are summarized in Tables 4–6.

We identified two prospective studies that reported the relationship between intake of fruit and vegetables and total circulatory disease. The methods and results of these studies are summarized in Table 7.

We made no attempt to arrive at a summary statistic for the association between the intake of fresh fruit and vegetables and cardiovascular disease as the measures of exposure and disease varied considerably between studies. We have, however, produced two summary tables, Table 8 (coronary heart disease) and Table 9 (stroke).

The presentation of risk in the Tables is standardized —higher number quartiles represent higher intake and the highest quantiles are compared with the lowest. This is denoted as Q5/1 for quintiles, Q4/1 for quartiles and T3/1 for tertiles.

DISCUSSION

We found nine of 10 ecological studies, two of three case-control studies and six of 16 cohort studies to report a significant protective association of consumption of fruit and vegetables or surrogate nutrients with coronary heart disease. We found no trials that just gave advice to eat more fruit and vegetables. But three trials of dietary advice,[55–57] which included advice to eat more fresh fruit and vegetables and were unconfounded by other lifestyle interventions, reported a survival benefit and are thus consistent with the observed protective association. We found three of five ecological studies, none of one case-control study and six of eight cohort studies to report a significant protective association of consumption of fruit and vegetables or surrogate nutrients with stroke. We found one of two cohort studies to report a significant protective association for all cardiovascular disease.

The studies included differed in: the type of study, the measurement and reporting of exposure, the period of follow-up and outcome selected. For these reasons no attempt was made to arrive at a summary statistic.

We have attempted to review published reports of associations between fruit and vegetable intake and cardiovascular disease. We made no attempt to search for unpublished studies or analyses and a bias against the publication of null or positive associations is possible. We found a number of cohort studies that measured diet and followed the participants up for cardiovascular disease which have not published data on this relationship. Our search strategy, by using a number of different approaches, allowed cross-checking of sources and thereby made omission of published studies unlikely. Our inclusion and exclusion criteria were clearly specified in advance. If one or two cohort studies for coronary heart disease or stroke have been missed or excluded in error, their findings would be unlikely to materially alter our conclusions.

Exposures have been poorly measured in most studies. The resulting exposure misclassification would

TABLE 1 *Ecological studies reporting measures of association between intake of fruit and vegetables and coronary heart disease (CHD)*

Population(s)	Author and year	Age, sex	Measure of fruit and vegetables	Potential confounders considered	Measure of CVD[a]	Dietary association (values are for r)	Notes
8 regions of England and Wales 1964–1969	Knox E G, 1973[17]	All M + F	Household survey	–	CHD (standardized mortality ratio)	Vitamin C: univariate correlation –0.49	Focus of write up: calcium
9 regions of Great Britain 1950–1967 30 countries 1968 or 1969	Armstrong B K *et al.*, 1975[18]	35–64 M + F	Food balance and household survey	Other dietary variables	Age standardized deaths	Univariate correlations in Great Britain fresh green vegetables in men: –0.83 ($P < 0.05$), in women –0.91 ($P < 0.05$). In 30 countries vegetables in men –0.39 ($P < 0.05$) and in women –0.22 (NS). Null for fruit	Flour and coffee most strongly correlated
19 countries 1960–68	Knox E G *et al.*, 1977[19]	55–64 (most) M + F	Food balance sheets 1960–1968	Latitude of the capital city	Age specific death rates ICD-8	Correlation CHD and fruit (non citrus) –0.71; CHD and vegetables –0.64	Table difficult to interpret. Associations in opposite directions for CHD and stroke for most exposures.
20 countries 1954–1965	Byington R *et al.*, 1979[20]	35–74 M + F	Food balance sheets 1954–1965	–	CHD mortality 1971–1973	Univariate fruit and non starchy vegetables 1971 in men –0.50 ($P < 0.05$), in women = –0.23 (NS) Similar for 1973	Correlations weaker than those for dairy and animal products.
49 regions of Japan 1969–78	Ikeda M *et al.*, 1986[21]	most 20–59 M + F	1072 24hr duplicate diet 1977–81 K+ measured by spectrometry	Age, sex, season	Regional CHD standardized mortality ratio	27 regions men, 39 regions women IHD[d] men K+: 0.10 (NS) IHD women K+: 0.27 ($P < 0.05$)	Sampling process not described.
22 districts of Scotland	Crombie I K *et al.*, 1990[22]	40–59 M + F	FFQ[b] in random sample of 10 359 from 22 local government districts	Age, sex, CHD risk factors, BMI,[c] alcohol, smoking, exercise, other blood measures	CHD (standardized mortality ratio)	Men univariate correlation: % no fruit: 0.59 ($P < 0.05$) % no green vegetables: 0.50 ($P < 0.05$) Women univariate correlation: % no fruit: 0.54 ($P < 0.05$) % no green vegetables: 0.43 ($P < 0.05$)	Multivariate analysis uses vitamin C.
40 countries, 1975–1977	Artaud-Wild S M *et al.*, 1993[23]	45–64 M	Food balance sheets	Dietary cholesterol, saturated fat	CHD death rates	Univariate correlations: folic acid –0.46 ($P < 0.01$); vitamin C –0.19 (NS); K+ –0.05 (NS)	Study aimed to explain 'French paradox'.
19 countries 1985–1987 Longitudinal 1970–1987	Bellizzi M C *et al.*, 1994[24]	<65 M	Food balance sheets	Latitude	Age standardized mortality rates	Cross sectional: vegetable –0.65 Longitudinal median: –0.36; Correlation coefficient -ve in 16 of 24	Focus of write up: vitamin E. Very low α-tocopherol intakes estimated for Japan.
21 countries 1965; 1970; 1980; 1988	Criqui M H, Ringel B L, 1994[25]	35–74 M + F	Food balance sheets	Age, calories, alcohol, animal fat	Directly age adjusted mortality rates	For CHD mortality 1988: vegetables (%kcal) = –0.43 fruit (%kcal) = –0.57	Focus of write up: alcohol. Inconsistent for fruit and vegetables. Analysis adjusted for energy intake.
12 Caribbean countries 1984–1988	Sinha D P, 1995[26]	All M + F	Food balance sheets 1979–1981	Age	Age adjusted CHD mortality	Correlation between per capita availability of fruits and vegetables and CHD: –0.46	Calories and CHD = 0.64 Fat and CHD = 0.54

[a] Cardiovascular disease.
[b] Food frequency questionnaire.
[c] Body mass index.
[d] Ischaemic heart disease.
cont. overleaf

TABLE 2 *Case control studies reporting measures of association between intake of fruit and vegetables and coronary heart disease*

Population	Author and year	Age, sex	Cases	Controls	Exclusions	Exposure measure	Potential confounders considered	Association with CVD	Notes
Northern Italy	Gramenzi A *et al.*, 1990[27]	21–69 F	287 Acute MI 1983–1989	649 hospital controls	Systemic disease	FFQ[a] for 10 food groups per week	Age, education, area of residence, smoking, CHD risk factors, foods.	Carrots OR = 0.4 (<1 vs.>1) Green veg OR = 0.6 (< 7 vs.>7) Fresh fruit OR = 0.4 (<7 vs. >13)	Crude dietary measure. Models mix social and food variables.
Athens, Greece	Tzonou A *et al.*, 1993[28]	All ages M + F	329 first MI or angiogram 1990–1991	570 hospital controls	Systemic disease	Vitamin C estimated from 110 item FFQ at interview.	Calories nutrients	No association with vitamin C.	No food based analyses.
Sofia, Bulgaria	Georgieva L M *et al.*, 1995[29]	45–70 M + F	154 admissions cardiology unit	155 hospital controls		Interview on ward Frequency of fruit and vegetable consumption.	Sociodemographic, family history, tobacco, alcohol and coffee use, physical activity.	Daily vs. ⩽ 2 days per week: fruit OR = 0.33 (CI : 0.17–0.64); vegetables OR = 0.44 (CI : 0.21–0.81)	Crude measure of intake.

[a] Food frequency questionnaire.

TABLE 3 *Prospective studies reporting measures of association between intake of fruit and vegetables and coronary heart disease (CHD)*

Population/ location	Author and year	No.	Age, sex	Eligible, recruitment period	Exclusions	Exposure measure	Potential confounders considered	Follow up: duration, completeness	Case identification	Number of events	Association with CVD	Notes
Bank and bus workers, England	Morris J N *et al.*, 1977[30]	337	30–67 M	Healthy middle aged men 1956–1966	CHD, pescribed diet	7 day weighed diary	Age, occupation, follow-up	10–20 years	Survey, letter, employer, record linkage	45 cases of CHD (26 CHD deaths)	No association with fibre from fruit, nuts, pulses, vegetables	High calorie intake cereal fibre protective.
Norwegian postal survey	Vollset S E, Bjelke E, 1983[31]	16 713	45–74 M + F	Response postal survey in 1967 three sub cohorts	No dietary information	Postal dietary survey	Age, sex, region, urbanization	11.5 years	Record linkage	438 deaths	No association between vitamin C and CHD.	Actual strength of association not reported.
Japanese	Hirayama T, 1986[32]	265 118	40 + M + F	Census-based cohort 1965	–	Measurement tool not well described	Age, smoking, alcohol, meat	16 years	Record linkage	Deaths—numbers not given	Green and yellow vegetables daily vs. not: no association	Crude diet measure.
Women in Gothenburg, Sweden	Lapidus L *et al.*, 1986[33]	1462	38–60 F	Women in Gothenburg 1968–1969	CHD, refusal, unsatisfactory interview	24 hr recall	Age, obesity, CHD risk factors, exercise	12 years 99.7%	Re exams, letter, phone	23 MI (8 fatal; 15 non fatal) 75 deaths	No association between vitamin C and MI	Energy negatively associated with MI.
Southern California	Khaw K-T *et al.*, 1987[34]	859	50–79 M + F	Residents of Rancho Bernardo, 1972–1974	MI,[a] CVA,[b] heart failure	24 hr recall	Age, sex, obesity, CHD risk factors, calories, nutrients	12 years 99.8%	Death certificates, questionnaire	65 CHD deaths 26 non fatal MI	K+ protective on univariate analysis but not significant	Calories, dietary fibre protective.
Seventh Day Adventists, California	Fraser G E *et al.*, 1992[35]	26 473	25 + M + F	Adventists in California 1976	CHD, diabetes Hispanic, non white	65 item FFQ[d]	Age, sex, smoking, exercise, BMI,[e] BP,[f] vegetarian, bread	6 years 97%	Questionnaire, hospital notes	134 MI definite, 260 definite CHD deaths	No association with risk for fruit index or legumes	Low risk cohort. High fruit intake not well discriminated.
Nurses, USA	Manson J E *et al.*, 1992[36]	87 245	34–59 F	Examined in 1980	CHD, cancer	FFQ	Age, CHD risk factors, vitamin supplements	8 years	Biennial questionnaire	437 non fatal MI; 115 CHD deaths	Adjusted RR Q5/1 for vitamin C: 0.80 (CI : 0.58–1.10)	Only reported as abstract.
Caerphilly, Wales	Fehily A M *et al.*, 1993[37]	2512	45–59 M	Male residents in Caerphilly and five villages	–	FFQ	Age, BMI, smoking, CHD, calories, nutrients	5 years 99.7%	Re exam 5 yrs	148 CHD events, 132 deaths	Adjusted RR Q5/1 vitamin C: 0.63 (NS)	25% had IHD[h] at baseline.
Health professionals, USA	Rimm E B *et al.*, 1993[38]	39 910	40–75 M	Health professionals recruited 1986	CVD,[c] diabetes ↑cholesterol, poor diet data	FFQ 131 item	Age, smoking, diet, aspirin, exercise	4 years 96%	Biennial questionnaire	667 CHD, 360 CABG,[g] 201 MI, 106 fatal MI	Vitamin C no association, β-carotene reduced risk in smokers	Main finding was for vitamin E. High vitamin C ranges.
–	Rimm E B *et al.*, 1995[39]	43 757	–	–	–	–	Age, saturated fat, vitamin E	6 years	–	229 fatal MI, 505 non fatal MI	Age adjusted RR total fibre Q5/1 0.59 (CI : 0.46–0.76)	Abstract report. *'No single fibre source … more protective.'*
Residents of Zutphen, East Netherlands	Hertog M G L *et al.*, 1993[40]	805	65–84 M	Survivors of 1960 cohort and new recruits in 1985	–	Cross-check diet history method (1 hr interview)	Age, BMI, exercise CHD risk factors, nutrients, calories	5 years 100%	5 yr re-exam, municipality registers	38 cases of MI (13 fatal), 43 CHD deaths	RR CHD death apples (g/d) tertiles T3/1 0.51 (NS)	Main focus of report: flavonoids-protective association. Tertiles of apple intake g/day T3/1: ⩾110/<18.

Cont. overleaf

TABLE 3 (*cont.*)

Population/ location	Author and year	No.	Age, sex	Eligible, recruitment period	Exclusions	Exposure measure	Potential confounders considered	Follow up: duration, completeness	Case identification	Number of events	Association with CVD	Notes
Several regions of Finland	Knekt P *et al.*, 1994[41]	5133	30–69 M + F	Finnish regions 1966–1972	CHD	Diet history method	Age, sex, smoking, CHD risk factors, obesity, calories	14 years	Record linkage	244 CHD deaths (186 men, 58 women)	RR T3/1 men for vegetables 0.66 (P = 0.02). T3/1 men for fruit: 0.77 (P = 0.28) Women similar effects but (NS)	Focus of write up: antioxidants. Vegetable and fruit intake g/day T3/1 >117/⩽61 in men and >159/⩽75 in women.
–	Knekt P *et al.*, 1996[42]	–	–	–	–	–	–	26 years	–	473 CHD deaths	Protective association Q4/1 RR between 0.50–0.89 for apples, berries (only in women), other fruit, onions and vegetables	Focus of write up: flavonoids. Vegetable intake Q4/1 (g/day) in men ⩾458 vs. <262, ?includes potatoes).
Elderly Massachusetts residents	Gaziano J M *et al.*, 1995[43]	1299	> 66 M + F	State-wide area sample 1976	Living in a nursing home	43 category FFQ	Age, sex, smoking, cholesterol intake, alcohol, activites of daily living	4.75 years 96% f/u	Mailings, interview	48 fatal MI	Adjusted RR for β-carotene Q4/1: 0.27 (P = 0.005)	Cause of death not confirmed in 15%.
Elderly, eight areas of Britain	Gale C R *et al.*, 1995[44]	730	65 + M + F	Elderly living in the community 1973–1974	CVD, no diet data	7 day weighed record	Age, sex, CHD risk factors, social class, nutrients, obesity, smoking	20 years 93%	Record linkage	182 CHD deaths	Adjusted RR CHD death, vitamin C T3/1 0.8 (CI : 0.6–1.2)	Low vitamin C intake and infrequent supplement use. No food based analyses.
Residents in Framingham, USA	Gillman M W *et al.*, 1995[45]	832	45–65 M	Framingham men examined 1966–1969	CVD	24 hr recall	CHD risk factors, left ventricular hypertrophy, BMI, energy, alcohol, exercise	20 years 98%	Biennial exam	CHD nos. not reported	CHD no association	Potatoes included as fruit and vegetables. Poor exposure measure.
Working men in the Chicago area	Pandey D K *et al.*, 1995[46]	1556	40–55 M	Employees for 2 years+ Western Electric, Chicago 1957–1959	CHD, cancer, diabetes, missing data	Diet history ×2 (1 year apart)	Age, family history, CHD risk factors, smoking, BMI, energy, fats, iron, education, alcohol, cholesterol intake	24 years complete	Annual exam until 1969, vital status after 25 years	231 CHD deaths	Adjusted RR for T3/1 in vitamin C + β-carotene index 0.70 (CI : 0.49–0.98)	Few supplement takers. T3/1 mg/day vitamin C 138/66, β-carotene 5.3/2.3.
Post-menopausal women in Iowa	Kushi L H *et al.*, 1996[47]	34 486	55–69 F	Random sample with valid drivers licence. Mailed in 1986	Pre menopause, low reported energy intake, CHD, FFQ incomplete	127 item FFQ	Age, energy, BMI, WHR,[i] smoking, hypertension, diabetes, HRT,[j] contraceptive use, physical activity, alcohol, marital status, education	7 years	Iowa death register, biennial questionnaire, national death index	242 CHD deaths	Adjusted RR Q5/1 vitamin C food and supplements 1.49 (CI : 0.96–2.30) Adjusted RR Q5/1 carotenoids food and supplements 1.03 (CI : 0.63–1.70)	No analysis for fruits and vegetables. Intake of vitamin C from foods and supplements high. Result similar in non supplement takers.

[a] Myocardial infarction.
[b] Cerebrovascular accident.
[c] Cerebrovascular disease.
[d] Food frequency questionnaire.
[e] Body mass index.
[f] Blood pressure.
[g] Coronary artery bypass graft.
[h] Ischaemic heart disease.
[i] Waist-hip ratio.
[j] Hormone replacement therapy.

TABLE 4 *Ecological studies reporting measures of association between intake of fruit and vegetables and stroke*

Population(s)	Author and year	Age, sex	Measure of fruit and vegetables	Potential confounders considered	Measure of CVD[a]	Effect on CVD (values are for r)	Notes
8 regions of England and Wales 1964–1969	Knox E G, 1973[17]	All M + F	Household survey	–	CVA standardized mortality ratio	Vitamin C: –0.68	Focus of write up: calcium
19 countries 1960–1968	Knox E G *et al.*, 1977[19]	55–64 (most) M + F	Food balance sheets 1960–1968	Latitude of the capital city	Age specific death rates	Non citrus fruit 0.30 Vegetables 0.38 Potatoes 0.18	Difficult to interpret. Associations in opposite directions for CHD and stroke for most exposures.
16 regions of England, Wales, Scotland	Acheson R M and Williams D R R, 1983[48]	45–64 M + F	Household survey	Age, sex	CVA death rate 1970–1972	Fruit: men –0.67 ($P = 0.04$); women –0.74 ($P = 0.02$) Vegetables: men –0.55 ($P = 0.12$); women –0.80 ($P = 0.01$)	Similar correlations when restricted to England and Wales and for different types of vegetable.
49 regions of Japan	Ikeda M *et al.*, 1986[21]	most 20–59 M + F	1072 24 hr duplicate diets 1977–1981 K+ by spectrometry	Age, sex, season	Regional standardized mortality ratios	27 regions men, 39 regions women CVA men K+: 0.19 (NS) CVA women K+: 0.39 ($P < 0.01$)	Sampling process not described.
22 districts of Scotland	Starr J M *et al.*, 1996[49]	40–59 M + F	FFQ in random sample of 10 359 from 22 local government districts.	Age, sex	Age specific hospital admission rates for CVA 1984–1986	Men % not eating fruit: 0.56 ($P < 0.01$) % not eating vegetables: 0.30 Women % not eating fruit: 0.47 ($P < 0.05$) % not eating vegetables: 0.25	Multivariate include socioeconomic variables along with risk factors and exposure measures making interpretation difficult.

[a] For abbreviations see footnote to Table 3.

TABLE 5 *Case control studies reporting measures of association between intake of fruit and vegetables and stroke*

Population	Author and year	Age, sex	Cases	Controls	Exclusions	Exposure measure	Potential confounders considered	Association with CVD[a]	Notes
Nottingham, UK	Barer D *et al.*, 1989[50]	All ages M + F	63 thrombotic stroke 1984	47 chest pain, 44 acute other	Embolic stroke, CVA, systemic disease, too ill	Questionnaire vitamin C index from foods	Socioeconomic, smoking, alcohol, non steroidal anti-inflammatory drugs, build	No association with vitamin C intake	Hospital cases and controls. Crude measure of habitual diet.

[a] For abbreviations see footnotes to Table 3.

TABLE 6 *Prospective studies reporting measures of association between intake of fruit and vegetables and stroke*

Population/ location	Author and year	No.	Age, sex	Eligible, recruitment period	Exclusions	Exposure measure	Potential confounders considered	Follow up: duration, completeness	Case identification	Number of events	Association with CVD[a]	Notes
Norwegian postal survey	Vollset S E, Bjelke E, 1983[31]	16 713	45–74 M + F	Response postal survey in 1967 three sub cohorts	No dietary information	Postal dietary survey	Age, sex, region, urbanization	11.5 years	Record linkage	438 deaths	Vitamin C RR T3/1 CVA death 0.67 (CI : 0.52–0.87)	Protective effect potatoes, vegetables, fruits, estimates for other exposures not cited.
Japanese	Hirayama T, 1986[32]	265 118	40+ M + F	Census based cohort 1965	–	Measurement tool not described	Age, smoking, alcohol, meat	16 years	Record linkage	Deaths—numbers not given	Green and yellow vegetables daily vs. not: no association	Crude diet measure.
Women in Gothenburg, Sweden	Lapidus L *et al*., 1986[33]	1462	38–60 F	Women in Gothenburg 1968–1969	CHD, refusal, unsatisfactory interview	24 hr recall	Age, obesity, CHD risk factors, exercise	12 years 99.7%	Re exams, letter, phone	13 CVA (75 deaths)	No association vitamin C and CVA	–
Southern California	Khaw K-T, Barrett-Connor E, 1987[51]	859	50–79 M + F	Residents of Rancho Bernardo, 1972–1974	MI, CVA, heart failure	24 hr recall	Age, sex, obesity, CHD risk factors, calories, nutrients	12 years 99.8%	Death certificates, questionnaire	24 stroke deaths 17 non fatal strokes	Adjusted RR CVA death ↑10 mmol intake ↓40% ($P < 0.001$)	Non significant associations with calcium, fibre, magnesium.
Hawaiian men of Japanese ancestry	Lee C N *et al*., 1987[52]	7591	45–68 M	Men of Japanese ancestry resident in Oaku 1965–1968	CVD	24 hr recall	Age, calories, nutrients, glucose, BP, smoking	16 years	Surveillance of hospitals, death registrations	408 CVA; 254 thrombotic; 111 haemorrhagic	K+ protective for fatal thrombotic CVA. NS for non fatal thrombotic	No association with haemorrhagic CVA.
Nurses, USA	Manson J E *et al*., 1994[53]	87 245	34–59 F	US nurses recruited 1980	CVD, cancer	FFQ	Age, smoking	8 years	Biannual questionnaire	Incident CVA 345 cases	Q5/1 of veg score adjusted 0.74 ($P = 0.03$)	Null for fruit. RR carrots 0.32 RR spinach 0.57 5+/wk vs. <1 mth.
Elderly, eight areas of Britain	Gale C R *et al*., 1995[44]	730	65+ M + F	Elderly in the community 1973–1974	CVD, no diet data	7 day weighed diet record	Age, sex, CHD risk factors, social class, nutrients, obesity, smoking	20 years 93%	Record linkage	124 deaths CVA	Adjusted RR stroke death and vitamin C T3/1: 0.5 (CI : 0.3–0.8)	Low vitamin C intake and infrequent supplement use. No food based analysis.
Residents in Framingham USA	Gillman M W *et al*., 1995[45]	832	45–65 M	Framingham men examined 1966–1969	CVD	24 hr recall	CHD risk factors, BMI, exercise, left ventricular hypertrophy, energy, fat, alcohol	20 years 98%	Biennial exam	73 CVA, 24 TIA[b] 14 deaths CVA	RR per 3 servings/ day: 0.78 (CI : 0.62–0.98). Same association for fruit, vegetables and death	Potatoes included as fruit and vegetables. Poor exposure measure.

[a] For abbreviations see footnotes to Table 3.
[b] Trans-ischaemic attack.

TABLE 7 *Prospective studies reporting measures of association between intake of fruit and vegetables and total circulatory disease*

Population/ location	Author and year	No.	Age, sex	Eligible, recruitment period	Exclusions	Exposure measure	Potential confounders considered	Follow up: duration, completeness	Case identification	Number of events	Association with CVD[a]	Notes
Representa-tive sample of US population	Enstrom J E *et al.*, 1992[54]	11 348	25–74 M + F	Sample of US civilians 1971–1975 NHANES 1	In institution	Vitamin C (24 hr recall and FFQ)	Age, sex, smoking, education, race, disease, exercise, alcohol, calories, nutrients	10 years 93%	Re interview, death certificates	1809 deaths; (929 circulatory)	No association when vitamin C intake of <50 mg/d vs. ⩾50mg/d compared	Effect only in supplement group, null for food.
Elderly Massachusetts residents	Gaziano J M *et al.*, 1995[43]	1299	>66 M + F	State-wide area sample 1976	Living in a nursing home	43 category FFQ	Age, sex, smoking, cholesterol intake, alcohol, activities of daily living	4.75 years 96%	Mailings, interview	317 deaths (161 CVD)	RR ⩾ 1/day vs. <1/day carrots 0.40 (CI : 0.17–0.98) salads 0.49 (CI : 0.31–0.71).	Cause of death not confirmed in 15%. Broccoli 0.29 (NS) tomatoes 0.73 (NS) strawberries/melon 0.70 (NS) dried fruit 1.13 (NS).

[a] For abbreviations see footnote to Table 3.

TABLE 8 *Summary of studies reporting measures of association between intake of fruit and vegetables and coronary heart disease*

Study type	Study population(s)	Association with food	Association with proxy[b]
Ecological	8 regions of England and Wales[17]	–	neg[a]
	30 countries and Great Britain over time[18]	neg	–
	19 countries[19]	neg	–
	20 countries[20]	neg	–
	49 regions of Japan[21]	–	pos
	22 districts of Scotland[22]	neg	–
	40 countries and each country over time[23]	–	neg
	19 countries[24]	neg	–
	21 countries[25]	neg	–
	12 Caribbean countries[26]	neg	–
Case control	Italian women[27]	neg	–
	Greece[28]	–	null
	Bulgaria[29]	neg	–
Cohort	London bus and bank workers[30]	–	null
	Norwegian postal survey[31]	–	null
	Japanese general poulation[32]	null	–
	Gothenburg women[33]	–	null
	Rancho Bernardo[34]	–	null
	Seventh Day Adventists[35]	null	–
	US nurses[36]	–	neg
	Caerphilly[37]	–	null
	US Health professionals[38,39]	–	neg
	Zutphen[40]	–	neg
	Finnish regions[41,42]	neg	–
	Boston elderly[43]	–	neg
	UK elderly[44]	–	null
	Framingham[45]	null	–
	Western Electric[46]	–	neg
	Iowa women[47]	–	null

[a] Association neg = statistically significant negative association, pos = statistically significant positive association and null = no significant association. A negative association implies a protective effect.
[b] Proxy indicates that associations were only reported for nutrients – taken here as proxies for fruit and vegetables.

be unlikely to produce spurious significant associations but may have obscured important underlying associations. We chose to include surrogate or proxy nutrients where no food based analyses were presented. This approach was necessitated by the large number of studies that framed their hypotheses in terms of nutrients and reported only on associations with nutrients. We accept that these surrogate measures are far from ideal, and that they would tend to underestimate the underlying true specific association if this was with an associated constituent.

An important justification for this review is that major ecological differences between countries and within countries and also secular trends in vascular disease are inadequately explained by differences in established risk factors.[58] The justification for our 'exposure based' approach, is not that it can point directly to underlying causes but rather that it can help to mark out the territory in which the search for new causes is most likely to be profitable.

For coronary heart disease, roughly equal numbers of studies reported a negative association as reported null. This apparently unimpressive result needs to be interpreted in the light of similar findings for more favoured hypotheses. Willet, in his review of the epidemiological evidence in favour of the classic diet heart hypothesis,[3] found a positive association with saturated fat intake in only two of the 12 cohort studies reviewed, a positive association with cholesterol intake in two and a negative relationship with polyunsaturated fat in one. Though we have made no formal attempt to gauge study quality, the single most informative study on fruit and vegetables and coronary heart disease to date is that reported by Knekt *et al.*[41] because of its combination of dietary history measure (with better validity than food frequency questionnaires and 24-h recalls) and a large person-time of follow up (5000 subjects followed for 14 years). This found a negative association with coronary death for both fruit and vegetables. In the studies we have reviewed, significant

TABLE 9 *Summary of studies reporting measures of association between intake of fruit and vegetables and stroke*

Study type	Study population(s)	Association with food	Association with proxy[b]
Ecological	8 regions of England and Wales[17]	–	neg[a]
	19 countries[19]	pos	–
	16 regions of England, Wales and Scotland[48]	neg	–
	49 regions of Japan[21]	–	pos
	22 districts of Scotland[49]	neg	–
Case control	Nottingham[50]	–	null
Cohort	Norwegian postal survey[31]	–	neg
	Japanese general population[32]	null	–
	Gothenburg women[33]	–	null
	Rancho Bernardo[51]	–	neg
	Honolulu heart[52]	–	neg
	US nurses[53]	neg	–
	UK elderly[44]	–	neg
	Framingham[45]	neg	–

[a] Association neg = statistically significant negative association, pos = statistically significant positive association and null = no significant association. A negative association implies a protective effect.
[b] Proxy indicates that associations were only reported for nutrients – taken here as proxies for fruit and vegetables.

associations are not more common where study quality is poor.

There were fewer studies of stroke than of coronary heart disease; with the majority reporting a negative association. These protective associations contrast with the null association between blood cholesterol concentration and stroke risk (which is suggestive of a null association also with saturated fat intake) revealed by a recent meta-analysis.[59] The single most informative study on fruit and vegetables and stroke to date is that reported by Manson *et al.*[53] because of its combination of food frequency questionnaire (better able to characterize usual intake than 24-h recall) and large person-time of follow up (87 000 nurses for 8 years). This reported a negative association between stroke incidence and vegetables but was null for fruit.

The observed protective association for fruit and vegetables and cardiovascular disease may be explained by confounding. This may be because high intake of fruit and vegetables is associated with other healthy behaviours[60] or because high intake of fruits and vegetables are associated with reduced intake of putative harmful substances such as salt or saturated fat. We found very few studies that adequately addressed the issue of confounding and cannot discount this as an explanation, at least in part, for the observed association.

A number of mechanistic hypotheses invoking specific constituents of fruits and vegetables have been proposed. The antioxidant hypothesis[8] suggests antioxidant vitamins such as C and E, β-carotene and other carotenoids; antioxidant minerals such as selenium and zinc and other antioxidant compounds such as flavonoids are protective. The homocysteine hypothesis[7] suggests substances such as folate and vitamins B6 and B12 that modify blood levels of homocysteine are protective. The tendency of researchers to pursue hypotheses based on single nutrients, may underestimate the possibilities with exposures as chemically complex as foods. The fate, so far, of the β-carotene and α-tocopherol hypotheses may be instructive.[61,62]

The current literature did not allow us to examine the association of cardiovascular risk with specific fruits and vegetables or with fruit and vegetable groups, or to examine the effect of seasonal deficits in intake; nor could we examine the effects of secular changes in diet.

Those conducting epidemiological studies of diet and vascular disease should be encouraged to formulate and test hypotheses in terms of foods as well as specific food constituents (whether nutrients or non-nutrients). Standard food groups would help such analyses. International collaboration for food based analyses of existing cohort studies, where the data is available, could help refine the current state of knowledge.

The public health importance of international differences in cardiovascular mortality is highlighted by the recent work of Peto[63] which suggests that, once the effect of smoking is removed, populations differ little in their overall cancer death rates but continue to differ considerably in their rates of vascular mortality. Results from the WHO MONICA study[58] show that these interpopulation differences are very inadequately

explained by the conventional risk factors—suggesting that the search for new determinants of vascular risk should be continued.

ACKNOWLEDGEMENTS

Dr Ness is supported by a Wellcome Research Training Fellowship in Clinical Epidemiology.

REFERENCES

[1] *Coronary Heart Disease. An Epidemiological Overview*. Central Health Monitoring Unit Overview series. London: HMSO, 1994.

[2] *Stroke. An Epidemiological Overview*. Central Health Monitoring Unit Overview series. London: HMSO, 1994.

[3] Willett W. *Nutritional Epidemiology*. New York: Oxford University Press, 1990.

[4] Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy. *Nutritional Aspects of Cardiovascular Disease*. London: HMSO, 1994.

[5] James W P T, Duthie G G, Wahle K W J. The Mediterranean diet: protective or simply non-toxic? *Eur J Clin Nutr* 1989; **43 (Suppl. 2):** 31–41.

[6] Steinmetz K A, Potter J D. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991; **2:** 325–57.

[7] Boushey C J, Beresford S A A, Omenn G S, Motulsky A G. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA* 1995; **274:** 1049–57.

[8] Wiztum J L. The oxidation hypothesis of atherosclerosis. *Lancet* 1994; **344:** 793–95.

[9] James W P T in collaboration with Ferro-Luzzi A, Isakson B, Szostak W B. *Healthy Nutrition: Preventing Nutrition-related Diseases in Europe*. Copenhagen: WHO Regional publications, European Series, No. 24, 1988.

[10] Committee on Diet and Health. *Diet and Health: Implications for Reducing Chronic Disease Risk*. Washington DC: National Academy Press, 1989.

[11] Report of WHO Study Group. *Diet, Nutrition, and the Prevention of Chronic Diseases*. Technical Report Series 797. Geneva: World Health Organization, 1990.

[12] Powles J W, Ruth D. Diet-mortality associations: an overview. In: Wahlqvist M L, Vobecky J S (eds). *Medical Practice of Preventive Nutrition*. London: Smith Gordon, 1992.

[13] Marmot M, Elliott P. *Coronary Heart Disease Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press, 1992.

[14] Marmot M G, Poulter N R. *The Prevention of Stroke in Stroke Octet*. London: The Lancet, 1992.

[15] Klag M J, Whelton P K. The decline in stroke mortality: an epidemiologic perspective. *Ann Epidemiol* 1993; **3:** 571–55.

[16] Bronner L L, Kanter D S, Manson J E. Primary prevention of stroke. *N Engl J Med* 1995; **333:** 1392–1400.

[17] Knox E G. Ischaemic heart disease mortality and dietary intake of calcium. *Lancet* 1973; **i:** 1465–67.

[18] Armstrong B K, Mann J I, Adelstein A M, Eskin F. Commodity consumption and ischaemic heart disease mortality, with special reference to dietary practices. *J Chron Dis* 1975; **28:** 455–69.

[19] Knox E G. Foods and diseases. *Br J Prev Soc Med* 1977; **31:** 71–80.

[20] Byington R, Dyer A R, Garside D *et al*. Recent trends of major coronary risk factors and CHD mortality in the United States and other industrialised countries. In: Proceedings of the Conference on the decline of coronary heart disease mortality. Washington: NIH publication No 79-1610., US Department of Health, 1979.

[21] Ikeda M, Kasahara M, Koizumi A, Watanabe T. Correlation of cerebrovascular disease standardised mortality ratios with dietary sodium and the sodium/potassium ratio among the Japanese population. *Prev Med* 1986; **15:** 46–59.

[22] Crombie I K, Smith W C S, Tavendale R, Tunstall-Pedoe H. Geographical clustering of risk factors for coronary heart disease in the Scottish Heart Health Study. *Br Heart J* 1990; **64:** 199–203.

[23] Artaud-Wild S M, Connor S L, Sexton G, Connor W E. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland: A paradox. *Circulation* 1993; **88:** 2771–79.

[24] Bellizzi M C, Franklin M F, Duthie G G, James W P T. Vitamin E and coronary heart disease: The European paradox. *Eur J Clin Nutr* 1994; **48:** 822–31.

[25] Criqui M H, Ringel B L. Does diet or alcohol explain the French paradox. *Lancet* 1994; **344:** 1719–23.

[26] Sinha D P. Changing patterns of food, nutrition and health in the Caribbean. *Nutr Res* 1995; **15:** 899–938.

[27] Gramenzi A, Gentile A, Fasoli M, Negri E, Parazzini F, La Vecchia C. Association between certain foods and risk of myocardial infarction in women. *Br Med J* 1990; **300:** 771–73.

[28] Tzonou A, Kalandidi A, Trichopoulou A *et al*. Diet and coronary heart disease: a case-control study in Athens, Greece. *Epidemiology* 1993; **4:** 511–16.

[29] Georgieva L M, Powles J, Ness A R, Penev B, Dragoichev T, Popova S. Negative association of fruit and vegetable consumption with ischaemic heart disease: a case control study from Sofia, Bulgaria. Poster at conference: IEA regional meeting in The Hague in August 1995.

[30] Morris J N, Marr J W, Clayton D G. Diet and heart: a postscript. *Br Med J* 1977; **2:** 308–14.

[31] Vollset S E, Bjelke E. Does consumption of fruit and vegetables protect against stroke? *Lancet* 1983; **ii:** 742.

[32] Hirayama T. Nutrition and cancer — a large scale cohort study. *Prog Clin Biol Res* 1986; **206:** 299–311.

[33] Lapidus L, Anderson H, Bengtsson C, Bosaeus I. Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Am J Clin Nutr* 1986; **44:** 444–48.

[34] Khaw K-T, Barrett-Connor E. Dietary fibre and reduced ischaemic heart disease mortality rates in men and women: a 12-year prospective study. *Am J Epidemiol* 1987; **126:** 1093–102.

[35] Fraser G E, Sabate J, Beeson W L, Stahan T M. A possible protective effect of nut consumption on risk of coronary heart disease: the Adventist health study. *Arch Intern Med* 1992; **152:** 1416–24.

[36] Manson J E, Stampfer M J, Willett W *et al*. A prospective study of vitamin C and incidence of coronary heart disease in women. *Circulation* 1992; **85:** 865.

[37] Fehily A M, Yarnell J W G, Sweetnam P M, Elwood P C. Diet and incident ischaemic heart disease. The Caerphilly Study. *Br J Nutr* 1993; **69:** 303–14.

[38] Rimm E B, Stampfer M J, Ascherio A, Giovannucci E, Colditz G A, Willett W C. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993; **328:** 1450–56.

[39] Rimm E, Ascherio A, Giovannucci E, Stampfer M, Willett W. Dietary fibre intake and coronary heart disease among a large population of US men. *Am J Epidemiol* 1995; **141 (Suppl.):** S17.

[40] Hertog M G L, Feskens E J M, Hollman P C H, Katan M B, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet* 1993; **342:** 1007–11.

[41] Knekt P, Reunanen A, Jarvinen R, Seppanen R, Hellovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal study. *Am J Epidemiol* 1994; **139:** 180–89.

[42] Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *Br Med J* 1996; **312:** 478–81.

[43] Gaziano J M, Manson J E, Branch L G, Colditz G A, Willett W C, Buring J E. A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the elderly. *Ann Epidemiol* 1995; **5:** 255–60.

[44] Gale C R, Martyn C N, Winter P, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in a cohort of elderly people. *Br Med J* 1995; **310:** 1563–66.

[45] Gillman M W, Cupples L A, Gagnon D *et al*. Protective effect of fruits and vegetables on development of stroke in men. *JAMA* 1995; **273:** 1113–17.

[46] Pandey D K, Shekelle R, Selwyn B J, Tangney C, Stamler J. Dietary vitamin C and β-carotene and risk of death in middle-aged men: The Western Electric study. *Am J Epidemiol* 1995; **142:** 1269–78.

[47] Kushi L H, Folsom A R, Prinaes R J, Mink P J, Ying W, Bostick R M. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med* 1996; **334:** 1156–62.

[48] Acheson R M, Williams D R R. Does consumption of fresh fruit and vegetables protect against stroke? *Lancet* 1983; **i:** 1191–93.

[49] Starr J M, Thomas B, Whalley L J. Population risk factors for hospitalisation for stroke in Scotland. *Int J Epidemiol* 1996; **25:** 276–81.

[50] Barer D, Leibowitz R, Ebrahim S, Pengally D, Neale R. Vitamin C status and other nutritional indices in patients with stroke and other acute illnesses: a case-control study. *J Clin Epidemiol* 1989; **42:** 625–31.

[51] Khaw K-T, Barrett-Connor E B. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. *N Engl J Med* 1987; **316:** 235–40.

[52] Lee C N, Reed D M, MacLean C J, Yano K, Chiu D. Dietary potassium and stroke. *N Engl J Med* 1988; **318:** 995–96.

[53] Manson J E, Willett W C, Stampfer M J, Colditz G A, Speizer F E, Hennekens C H. Vegetable and fruit consumption and incidence of stroke in women. *Circulation* 1994; **89:** 932 (Abstract).

[54] Enstrom J E, Kanim L E, Klein M A. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992; **3:** 194–202.

[55] Rinzler S H. Primary prevention of coronary heart disease by diet. *Bull N Y Acad Med* 1968; **44:** 936–49.

[56] Singh R B, Rastogi S S, Verma R *et al*. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow-up. *Br Med J* 1992; **304:** 1015–19.

[57] de Lorgeril M, Renauld S, Mamelle N *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994; **343:** 1454–59.

[58] WHO MONICA project. Ecological analysis of the association between mortality and major risk factors of cardiovascular disease. *Int J Epidemiol* 1994; **23:** 505–16.

[59] Prospective studies collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995; **346:** 1647–53.

[60] Serdula M K, Byers T, Mokdad A H, Simoes E, Mendlein J M, Coates R J. The association between fruit and vegetable intake and chronic disease risk factors. *Epidemiology* 1996; **7:** 161–65.

[61] Rowe P M. Beta-carotene takes a collective beating. *Lancet* 1996; **347:** 249.

[62] Greenberg E R, Sporn M B. Antioxidant vitamins, cancer, and cardiovascular disease. *N Engl J Med* 1996: **334:** 1189–90.

[63] Peto R, Lopez A D, Boreham J, Thun M, Heath C Jnr. Mortality from smoking in developed countries 1950–2000. Oxford: Oxford University Press, 1994.

(Revised version received June 1996)