Chapter 5
Associations with diseases other than cancer

This chapter briefly reviews associations between fruit and vegetable intake and chronic diseases other than cancer, summarizing findings from the main epidemiological studies that have assessed fruit and vegetables directly or through an indicator of fruit and vegetable intake. The relationship between fruit and vegetables in the diet and chronic diseases has been reviewed recently by a joint FAO/WHO Expert Consultation panel (WHO, 2003), which rated the evidence to be convincing for a protective effect of fruit and vegetables against cardiovascular diseases (the panel defined convincing as epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary).

The beneficial effects of dietary fruit and vegetables are clearly demonstrated by scurvy, a well documented, dramatic consequence of a dietary deficiency in these foods (Passmore & Eastwood, 1986). Two main lines of research have drawn increasing attention to other long-term beneficial effects of fruit and vegetables. One line of research is based on knowledge, derived from the study of clinical deficiency conditions, of the physiological functions of specific components of fruit and vegetables, such as individual vitamins. The antioxidant, free radical-scavenging properties of fruit and vegetables have prompted investigations of cardiovascular diseases in relation to intake of single vitamins, and, more recently, of fruit and vege-tables as complex mixtures of naturally occurring chemicals that may have beneficial effects because of the simultaneous presence of several active components. A second line of research has developed from the "Seven Countries" investigation of coronary heart disease (Keys, 1983). The observation of the rarity of myocardial infarction cases in the late 1940s in areas of southern Italy, Spain and Greece led to the idea that diets low in saturated fat and rich in vegetables were cardio-protective (Keys, 1980). While this line of research focused mainly on the adverse role of saturated fats, it also provided the basis for more recent work on the possible protective role of omega-3 fatty acids of vegetable or marine-fish origin. It has in fact been hypothesized that the markedly low rate of coronary heart disease in the Greek island of Crete (Renaud *et al.*, 1995) could be mainly due to a diet rich in the omega-3 α-linolenic acid of vegetable origin, a conjecture that has received some recent support (Renaud & Lanzmann-Petithory, 2002).

These different lines of investigation are now converging in studies of how fruit and vegetables, with their micronutrient components, may influence not only the different pathogenetic steps of cardiovascular disease but also steps in the development of other chronic diseases.

Cardiovascular diseases

A number of ecological studies (Ness & Powles, 1997) have reported inverse correlations between mortality rates for coronary heart disease or stroke and the consumption of fruit and vegetables, assessed through food balance sheets or household surveys. This suggestive evidence is reinforced by the results of analytical studies of individuals. Several methodological considerations are relevant to the evaluation of such studies. Case–control studies of cardiovascular disease are few in number, while cohort studies often use only cursory measures of diet. Biomarkers of cardiovascular disease risk are also amenable to study: hypertension, hypercholesterolaemia and obesity can be regarded as intermediate steps linking diet to cardiovascular disease. Behavioural factors such as alcohol and tobacco use should be taken into account as confounding factors.

Tables 121 and 122 summarize the key findings of case–control and cohort studies on the association between fruit and vegetables (or dietary indices closely related to fruit and vegetables) and coronary heart disease; Tables 123 and 124 summarize the studies for stroke; and Table 125 summarizes the studies for total cardiovascular disease. Overall the results of these studies, on either coronary heart disease or stroke, are not entirely consistent. However, the inverse associations found in the larger studies, with better control for confounding factors, provide evidence supporting a protective effect.

Blood pressure was significantly reduced in both normotensive and hypertensive subjects in two randomized controlled trials of vegetarian diets, in which animal products were replaced with vegetable products. In an eight-week randomized controlled trial on adults with mild hypertension, a diet enriched with fruit and vegetables (and less snacks and sweets) reduced both systolic and diastolic blood pressure (Appel *et al.*, 1997). In another six-month trial, participants randomly assigned to an intervention to increase consumption of fruit and vegetables up to at least five daily portions showed a greater reduction in systolic and diastolic blood pressure than the control group (John *et al.*, 2002). These studies indicate the potential effectiveness of a diet rich in fruit and vegetables in lowering blood pressure over intervals of weeks and months. In contrast, however, increasing fruit and vegetable consumption up to at least eight servings per day over one year in subjects with a recent history of adenomas did not reduce blood pressure or body weight, despite a modest reduction in serum cholesterol level (Smith-Warner *et al.*, 2000).

Other diseases

Two recent randomized trials (Tuomilehto *et al.*, 2001; Lindstrom *et al.*, 2003) have shown that lifestyle and diet changes, including substitution of energy-dense dietary fats with fruit and vegetables, can improve glucose tolerance and prevent the onset of type II diabetes. Although these trials featured increased intake of fruit and vegetables, they were not designed to assess the independence of these changes from the effects of other factors, including physical activity and weight loss. Virtually all diets that aim at avoiding excess weight, an established risk factor for diabetes as well as coronary heart disease, involve replacing high-fat foods with low-energy density foods, such as fruit and vegetables. Higher intake of some fruits and vegetables rich in carotenoids, or a higher estimated level of dietary carotenoids, has been associated with decreased risk of cataracts in some studies, in particular two large prospective studies (Hankinsson *et al.*, 1992; Brown *et al.*, 1999). Less data are available on associations of fruit and vegetable consumption with other chronic conditions such as osteoporosis, senile macular degeneration, Alzheimer disease and Parkinson disease.

Table 121. Case-control studies reporting measures of association between intake of fruit and vegetables and coronary heart disease

Author, year country	Cases/controls, gender	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Gramenzi *et al.*, 1990, Italy	287 Acute MI/649 hospital controls, F	FFQ (10)	Carrots: > 1 vs < 1 portion/wk (3)	0.5	$p < 0.01$	Age, education, area of residence, smoking, CHD risk factors, other foods	Crude dietary measure
			Green veg.: > 7 vs < 7 portion/w (3)	0.7	NS		
			Fresh fruit: > 13 vs < 7 portion/w (3)	0.6	NS		
Tzonou *et al.*, 1993, Greece	329 first MI or positive angiogram/570 hospital controls, M, F	FFQ (110)	Estimated vitamin C: highest vs lowest (5)	1.14 (0.67–1.95)		Gender, age, interviewer, education, BMI, exercise, siesta, smoking, alcohol, coffee, energy	No food-based analyses

*p for trend when applicable

BMI, body mass index; CHD, coronary heart disease; FFQ, food frequency questionnaire, MI, myocardial infarction; NS not significant.

Adapted and updated from Ness & Powles, 1997

Table 122. Cohort studies reporting measures of association between intake of fruit and vegetables and coronorary heart disease

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Morris *et al.*, 1977, UK	45 cases of CHD (26 CHD deaths)/337, M (10–20y)	7-day weighed diary		No association with fibre from fruit, nuts, pulses, veg.		Age, occupation, follow-up	High energy intake cereal fibre protective
Vollset & Bjelke, 1983, Norway	No. ischaemic heart disease not reported/ 16 713, M, F (11.5y)	Postal dietary survey (20)	Estimated vitamin C index	No association		Age, sex, region, urbanization	Three subcohorts

Table 122 (contd)

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hirayama, 1990, Japan	Deaths – numbers not given/ 265 118, M, F (17 y)	FFQ (7)	Green and yellow veg.: daily vs not (2)	No association			Census-based cohort Crude diet measure
Lapidus *et al.*, 1986, Sweden	23 MI (8 fatal; 15 non-fatal)/ 1462 F (12 y)	24-h recall	Estimated vitamin C	No association		Age, obesity, smoking, CHD risk factors, exercise	Energy negatively associated with MI
Fraser *et al.*, 1992, USA	134 non-fatal MI, 260 fatal CHD/26 473 M, F (6 y)	FFQ (65)	Fruit index: > 2 vs < 1/d (3)	Non-fatal MI: 1.07 (0.58–1.96) Fatal CHD: 1.08 (0.67–1.75)		Age, sex, smoking, exercise, weight, blood pressure	Seventh-Day Adventists Low-risk cohort High fruit intake not well discriminated
Manson *et al.*, 1992, USA	437 non-fatal MI, 115 CHD deaths/87 245, F (8 y)	FFQ	Estimated vitamin C: Highest vs lowest (5)	0.80 (0.58–1.10)		Age, smoking, CHD risk factors, vitamin supplements	Nurses' Health Study Only reported as abstract
Fehily *et al.*, 1993, Wales	148 CHD events/2423, M (5 y)	FFQ	Estimated vitamin C: ≥ 66.5 vs ≤ 34.7 mg/d (5)	[0.63]	NS	Age, BMI, smoking, CHD at baseline	25% had CHD at baseline
Rimm *et al.*, 1993, USA	667 CHD/ 39 910, M (4 y)	FFQ (131)	Estimated vitamin C (median values: 1162 vs 92 mg/day) (5)	1.25 (0.91–1.71)	$p = 0.98$	Age, smoking, diet, aspirin, exercise, BMI, energy, fibre, alcohol, parental history of MI, other antioxidants	Health professionals study Main finding was for vitamin E High vitamin C ranges
			Estimated β-carotene (median values: 190.34 vs 3969 mg/day) (5)	Smokers: 0.30 (0.11–0.82) Former smokers: 0.60 (0.38–0.94) Non-smokers: 1.09 (0.66–1.79)	$p = 0.02$ $p = 0.04$ $p = 0.64$		

Table 122 (contd)

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Hertog *et al.*, 1993, Netherlands	43 CHD deaths/805 M (5 y)	Cross-check diet history interview	Apples: ≥110 vs <18 g/d (3)	0.51 (0.23–1.16)	$p = 0.12$	Age, diet, BMI, exercise, CHD risk factors, energy, saturated fatty acids, smoking, history of MI	Main focus on flavonoids
Knekt *et al.*, 1994, Finland	244 CHD deaths/5133, M, F (14 y)	Diet history interview	Fruit: > 159 vs ≤ 75 g/d (M) and > 137 vs ≤ 77 g/d (F) (3)	M: 0.77 (0.52–1.12)	$p = 0.28$	Age, smoking, CHD risk factors, BMI, energy	Main focus on antioxidants. Similar effects in F but NS
			Veg.: > 117 vs ≤ 61 g/d (M) and > 137 vs ≤ 77 (F) (3)	M: 0.66 (0.46–0.96)	p=0.02		
Gaziano *et al.*, 1995, USA	48 fatal MI/ 1299, M, F (4.75 y)	FFQ (43)	Estimated β-carotene index	0.27 (0.10–0.74)	p =0.005	Age, sex, smoking, cholesterol intake, alcohol, activities of daily living	Cause of death not confirmed in 15%
Gale *et al.*, 1995, UK	182 CHD deaths/730, M, F (20 y)	7-day weighed record	Estimated vitamin C: > 44.9 vs ≤ 27.9 mg/d (3)	0.8 (0.6–1.2)	$p = 0.595$	Age, sex	Low vitamin C intake and infrequent supplement use No food-based analyses
Gillman *et al.*, 1995, USA	CHD numbers. not reported/ 832 M (20 y)	24-h recall		CHD no association		CHD risk factors, left ventricular hypertrophy, BMI, energy, alcohol, exercise	Potatoes included as fruit and veg. Poor exposure measure
Pandey *et al.*, 1995, USA	231 CHD deaths/1556, M (24 y)	Diet history (twice, 1 year apart)	Increment of 19 points in estimated vitamin C + β-carotene index (highest/lowest: vitamin C 138/66, β-carotene 5.3/2.3)	0.70 (0.49–0.98)		Age, family history, CHD risk factors, smoking, BMI, energy, fats, iron, education, alcohol, cholesterol intake	Few supplement takers

Table 122 (contd)

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Knekt *et al.*, 1996, Finland	473 CHD deaths/5133 M, F (26 y)	Diet history interview	Highest vs lowest (4)	RR between 0.50–0.89 for apples, berries (only in women), other fruit, onions and veg.		Age, smoking, CHD risk factors, BMI	Main focus on flavonoids
Kushi *et al.*, 1996, USA	242 CHD deaths/34 486, F (post-menopausal) (7 y)	FFQ (127)	Vitamin C from food and supplements: ≥ 391 vs ≤ 112.3 mg/d (5)	1.49 (0.96–2.30)	$p = 0.02$	Age, energy, BMI, WHR, smoking, hypertension, diabetes, HRT, contraceptive use, physical activity, alcohol, marital status, education	No analysis for fruits and veg. Intake of vitamin C from foods and supplements high Result similar in non supplement takers
			Carotenoids from food and supplements: ≥ 13 465 vs ≤ 4421 IU/d (5)	1.03 (0.63–1.70)	$p = 0.71$		
Liu *et al.*, 2000, USA	126 MI/ 39 127, F (6 y)	FFQ, (131)	Fruit and veg.: highest vs lowest (5) (median values: 10.2 vs 2.6 servings/d)	0.63 (0.38–1.17)	$p = 0.21$	Age, smoking, physical activity, alcohol, menopausal status, HRT use, BMI, vitamin supplement use, parental history MI, history of MI, diabetes, hypertension, hypercholesterolaemia	Women's Health Study
Liu *et al.*, 2001, USA	1148 incident CHD/15 220, M (12 y)	FFQ (8 veg.)	Veg.: > 2.5 vs < 1 serving/d (5)	0.77 (0.60–0.98)	$p = 0.03$	Age, randomization assigment, BMI, smoking, alcohol, physical activity, history of hypercholesterolaemia, hypertension and diabetes, multivitamin supplements	Physicians' Health Study end-points: MI plus coronary artery bypass grafting plus percutaneous transluminal angioplasty

Table 122 (contd)

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Joshipura *et al.*, 2001, USA	CHD 1063 M, 1127 F (fatal and non-fatal)/ 42 148 M, 84 251 F (M: 8 y F: 14 y)	FFQ (126, 15 fruits, 28 veg.)	Fruit and veg.: highest vs lowest (5) (median values: 9.15 vs 2.54 servings/d)	0.80 (0.69–0.93)		Age, smoking, alcohol, family history of MI, BMI, energy, multi-vitamins and vitamin E supplements, aspirin, physical activity, HRT, hypertension, hypercholesterolaemia	Nurses' and Health Professionals' studies Main contributors: green leafy veg. and vitamin C-rich fruits and veg.
Bazzano *et al.*, 2002, USA	1786 CHD (639 deaths)/ 9608, M, F (19 y)	FFQ (13, 3 fruits and veg.)	Fruit and veg.: > 3 vs < 1 times/d (4)	Mortality 0.76 (0.56–1.03) Incidence: 1.01 (0.84–1.21)	$p = 0.07$ $p = 0.8$	Age, sex, race, education, physical activity, alcohol, smoking, history of diabetes, energy, vitamin supplements	National Health and Nutrition Examination Survey Study
Michels & Wolk, 2002, Sweden	1558 CHD deaths/ 59 038, F (9.9 y)	FFQ (60) Creation of categories of 'good' diet or RFS (recommended foods score) and 'bad; or NRFS (non-recommended foods score)	RFS: highest vs lowest (5)	0.47 (0.33–0.68)	$p < 0.0001$	Age, height, BMI, parity, age at first birth, education, marital status, alcohol, energy	Mammography cohort No association with NRFS

**p* for trend when applicable

BMI, body mass index; CHD, coronary heart disease; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; MI, myocardial infarction; NS, not significant; WHR, waist-to-hip ratio

Adapted and updated from Ness & Powles, 1997

Table 123. Case–control study reporting measures of association between intake of fruit and vegetables and stroke

Author, year country	Cases/ controls, gender	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Barer *et al.*, 1989, UK	63 thrombotic stroke/91, M, F	Questionnaire	Estimated vitamin C index	No association		Age, sex, socioeconomic status, smoking, alcohol, non-steroidal anti-inflammatory drugs, build	Hospital cases and controls Crude measure of habitual diet

*p for trend when applicable

Adapted and updated from Ness & Powles, 1997

Table 124. Cohort studies reporting measures of association between intake of fruit and vegetables and stroke

Author, year country	Cases/cohort-size, gender, (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Vollset & Bjelke, 1983, Norway	438 cerebrovascular deaths/16 713, M, F (11.5 y)	Postal dietary survey (20)	Estimated vitamin C index: highest vs lowest (3)	0.67 (0.52–0.87)	$p = 0.0005$	Age, sex, region, urbanization	3 subcohorts Negative association with fruit and veg.
Hirayama, 1990, Japan	Deaths – numbers not given/ 265 118, M, F (17 y)	FFQ (7)	Green and yellow veg.: daily vs not (2)	No association			Census-based cohort Crude diet measure
Lapidus *et al.*, 1986, Sweden	13 strokes/ 1462 F (12 y)	24-h recall	Estimated vitamin C	No association		Age, obesity, smoking, CHD risk factors, exercise	
Manson *et al.*, 1994, USA	345 stroke cases/ 87 245, F (8 y)	FFQ	Veg. score: highest vs lowest (5) Carrots, spinach ≥ 5/wk vs < 1/mo	0.74 Carrots: 0.32 Spinach: 0.57	$p = 0.03$	Age, smoking	Nurses' Health Study No association for fruit
Gale *et al.*, 1995, UK	124 stroke deaths/730, M, F (20) y	7-day weighed diet record	Estimated vitamin C: > 44.9 vs ≤ 27.9 mg/d (3)	0.5 (0.3–0.8)	$p = 0.003$	Age, sex, CHD risk factors	Low vitamin C intake and infrequent supplement use No food-based analyses

Table 124 (contd)

Author, year country	Cases/ cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Gillman *et al.*, 1995, USA	97 strokes (14 deaths)/832 M (20 y)	24-h recall	Fruit and veg.: increment of 3 servings/d	0.77 (0.60–0.98)		Age, CHD risk factors, BMI, exercise, left ventricular hypertrophy, energy, fat, alcohol	Potatoes included in fruit and vegetables Poor exposure measure Same association for mortality
Joshipura *et al.*, 1999, USA	Ischaemic stroke: 204 (M), 366 (F)/ 38 683 (M), 75 596 (F) (M: 8 y F: 14 y)	FFQ (116, 15 fruits, 28 veg.)	Fruit and veg.: highest vs lowest (5) (median values: 9.15 vs 2.54 servings/d)	0.69 (0.52–0.92)		Age, smoking, alcohol, family history of MI, BMI, energy, multivitamin and vitamin E supplements, aspirin use, physical activity, HRT, hypertension, hypercholesterolaemia	Nurses' and Health Professionals' Studies Most contribution from cruciferous veg., green leafy veg., citrus fruits, including juice
Bazzano *et al.*, 2002, USA	888 stroke, 218 fatal/ 9608, M, F (19 y)	FFQ (13, 3 fruits and veg.)	Fruit and veg.: > 3 vs < 1 time/d (4)	Mortality: 0.58 (0.33–1.02) Incidence: 0.73 (0.57–0.95)	$p = 0.05$ $p = 0.01$	Age, sex, race, education, physical activity, history of diabetes, alcohol, smoking, energy, vitamin supplements	National Health and Nutrition Examination Survey Study
Michels & Wolk, 2002, Sweden	684 stroke/ 59 038, F (9.9 y)	FFQ (60) Creation of categories of 'good' diet or RFS (recommended foods score) and 'Bad' or NRFS (non-recommended foods score)	RFS: highest vs lowest (5)	0.40 (0.22–0.73)	$p = 0.007$	Age, height, BMI, parity, age first birth, education, marital status, alcohol, energy	Mammography cohort No association with NRFS

**p* for trend when applicable

BMI, body mass index, CHD, coronary heart disease; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; MI, myocardial infarction

Adapted and updated from Ness & Powles, 1997

Table 125. Cohort studies reporting measures of association between intake of fruit and vegetables and total circulatory disease

Author, year country	Cases/cohort size, gender (years follow-up)	Exposure assessment (no. of items)	Range contrast (no. of categories)	Relative risk (95% CI)	Stat. sign.*	Adjustment for confounding	Comments
Enstrom *et al.*, 1992, USA	929 cardiovascular disease deaths/11 348, M, F (10 y)	24-h recall and FFQ	Estimated vitamin C index: ≥ 50 vs < 50 mg/d (2)	SMR (relative to US whites): No regular supplement: 0.90 (0.82–0.99) Regular supplements: 0.66 (0.53–0.82)		Age, sex, smoking, education, race, disease, exercise, alcohol, energy, nutrients	National Health and Nutrition Examination Survey
Gaziano *et al.*, 1995, USA	161 fatal cardiovascular disease/1299, M, F (4.75 y)	FFQ (43)	≥ 1 vs < 1/d	Carrots: 0.40 (0.17–0.98) Salads: 0.49 (0.31–0.77)		Age, sex	Cause of death not confirmed in 15%. Significant inverse association with estimated β-carotene index
Cox *et al.*, 2000, UK	392 cardiovascular events (162 fatal)/3389, M, F (7 y)	FFQ (31, considering seasons)	Daily vs never (5)	Salads: inverse association (consumption either in winter and summer for F; only in winter for M). Fruit: inverse association (consumption either in winter and summer only in F)	$p < 0.001$	Age, smoking, socioeconomic status	
Strandhagen *et al.*, 2000, Sweden	209 non-fatal cardio-vascular events, 226 deaths/730 M (26 y)	FFQ	6–7 vs 0–1 times/wk (4)	Fruit (M) 16 y follow-up: 0.87 (0.76–0.96) 26 y follow-up: 0.92 (0.84–1.00) Veg.: no association	$p = 0.051$	Smoking, hypertension, serum cholesterol (no age control, since all men were born same year)	
Rissanen *et al.*, 2003, Finland	115 cardiovascular disease deaths/1950, M (12.8 y)	Food record	Fruits, berries and vegetables: > 408 vs < 133 g/d (5)	0.66 (0.28–1.55)	$p = 0.13$	Age, examination year, BMI, CHD risk factors, energy, intake of vitamins C and E, β-carotene, lycopene, folate, fibre	

*p for trend when applicable
BMI, body mass index; CHD, coronary heart disease; FFQ, food frequency questionnaire
Adapted and updated from Ness & Powles, 1997