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Flavonoid intake and coronary mortality in Finland: a cohort study

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See editorial

Abstract

***Objective*—To study the association between dietary intake of flavonoids and subsequent coronary mortality.**

***Design*—A cohort study based on data collected at the Finnish mobile clinic health examination survey from 1967-72 and followed up until 1992.**

***Settings*—30 communities from different parts of Finland.**

***Subjects*—5133 Finnish men and women aged 30-69 years and free from heart disease at baseline.**

***Main outcome measure*—Dietary intake of flavonoids, total mortality, and coronary mortality.**

***Results*—In women a significant inverse gradient was observed between dietary intake of flavonoids and total and coronary mortality. The relative risks between highest and lowest quarters of flavonoid intake adjusted for age, smoking, serum cholesterol concentration, blood pressure, and body mass index were 0·69 (95% confidence interval 0·53 to 0·90) and 0·54 (0·33 to 0·87) for total and coronary mortality, respectively. The corresponding values for men were 0·76 (0·63 to 0·93) and 0·78 (0·56 to 1·08), respectively. Adjustment for intake of antioxidant vitamins and fatty acids weakened the associations for women; the relative risks for coronary heart disease were 0·73 (0·41 to 1·32) and 0·67 (0·44 to 1·00) in women and men, respectively. Intakes of onions and apples, the main dietary sources of flavonoids, presented similar associations. The relative risks for coronary mortality between highest and lowest quarters of apple intake were 0·57 (0·36 to 0·91) and 0·81 (0·61 to 1·09) for women and men, respectively. The corresponding values for onions were 0·50 (0·30 to 0·82) and 0·74 (0·53 to 1·02), respectively.**

***Conclusion*—The results suggest that people with very low intakes of flavonoids have higher risks of coronary disease.**

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Introduction

Oxidation of low density lipoproteins by free radicals is thought to play a central part in the development of atherosclerosis.[1] Antioxidants may thus delay the onset of atherogenesis. Flavonoids represent a wide variety of natural polyphenolic structures with ubiquitous distributions in plant foods.[2] Several flavonoid compounds have been shown to have antioxidant properties in vitro, inhibiting the oxidation of low density lipoproteins and reducing thrombotic tendencies by inhibiting platelet aggregation.[3-7] A small cohort study on elderly men demonstrated a significant inverse association between intake of those flavonoids most commonly consumed in the Netherlands and coronary mortality.[8] An ecological study based on middle aged men from 16 different cohorts showed a similar inverse association between flavonoid intake and coronary mortality.[9] In a recent study based on the Finnish mobile clinic health cohort we reported an increased coronary mortality during a 14 year follow up among men and women with very low intakes of the antioxidant vitamins C and E and carotenoids.[10] We have investigated whether low intake of flavonoids would be an independent risk factor for coronary disease in the same cohort by using a 26 year follow up period.

Subjects and methods

The mobile clinic of the Finnish Social Insurance Institution carried out multiphasic health examinations in different regions of Finland in 1966-72.[11] A total of 2748 men and 2385 women aged 30-69 years and free of known heart disease participated in a survey on dietary intake. The food consumption was estimated by using an interview on dietary history, covering the total habitual diet of the subjects during the previous year.[12] The total intake of five major flavonoids—quercetin, kaempferol, myricetin, luteolin, and apigenin—was estimated by using values derived from analyses completed recently in the Netherlands.[13] The reported values for 28 vegetables and nine fruits covered those consumed by the present population with a mean consumption >1 g/day. For berries commonly consumed in Finland but not reported in the Dutch analyses the flavonoid contents were determined from values shown in other previous studies.[14,15] As consumption of berries and berry products was recorded mainly as average figures, the calculations of flavonoids from these foods were less accurate than for other fruits and vegetables. All food composition values for flavonoids were given as aglycons. The estimations of antioxidant vitamins C and E, β carotene, fibre, fatty acids, and energy are presented elsewhere.[10,16]

The median flavonoid intake was 3·4 mg/day and ranged from 0-41·4 mg/day. On average about 95% of the total flavonoid intake was quercetin. The main sources of flavonoids were apples and onions, which

together covered 64% of the total dietary intake. Other notable sources were other fruits, berries, sweetened juices and jams (mainly from berries), and vegetables.

The reproducibility of the dietary history method was estimated by repeating the interviews 4-8 months and 4-7 years apart.[12] The intraclass correlation coefficients for the short term and long term repeatability of flavonoid intake were 0·49 and 0·35, respectively. The coefficients differed significantly from zero and were on a similar level to those for antioxidant vitamins from fruit and vegetable sources.[12]

A questionnaire provided information on sociodemographic background, diseases, medication, and smoking habits. The subjects were classified according to smoking as those who had never smoked, former smokers, cigar or pipe smokers only, smokers of fewer than 15 cigarettes a day, and smokers of 15 or more cigarettes a day. Height and weight were measured and the body mass index (weight (kg)/(height)^2 (m)) was calculated. Casual blood pressure was registered in the sitting position after a five minute rest with the auscultatory method.[17] Subjects with systolic blood pressure $\geq$160 mm Hg and diastolic blood pressure $\geq$95 mm Hg or who used antihypertensive drugs were classified as hypertensive. Serum samples were taken and the cholesterol concentration determined by an autoanalyser modification of the Liebermann-Burchard reaction.[18]

Mortality data from the Central Statistical Office of Finland were linked to the study population by using personal identification numbers.[19] Coverage of the mortality register, based on death certificates, is complete, including the emigrants who died abroad. The codes 410-414 of ICD-8 (international classification of diseases, eighth revision) were used for coronary heart disease as the causes of death. During the 26 years of follow up from 1967 until late 1992 a total of 1364 people died; of these 473 died of coronary heart disease.

Estimations of the adjusted mean levels of different factors in people who died during follow up and among survivors and mean intake of different foodstuffs in quarters of flavonoid concentration were based on multiple regression.[20] Relative risks of mortality between quarters of the dietary flavonoids and their food sources, adjusted for different confounding factors, and the 95% confidence intervals were computed based on Cox's life table regression model.[21]

Table 1—*Mean levels of selected variables adjusted for age and sex of people who died and survived during follow up*

Variable	Deaths: Coronary heart disease (n=473)	Deaths: Other (n=891)	Survivors (n=3769)	P value for heterogenity
Sex (% males)*	74·0	68·7	47·4	<0·001
Age (years)†	53·5	53·4	41·9	<0·001
Serum cholesterol (mmol/l)	7·11	6·67	6·80	<0·001
Body mass index (kg/m^2)	25·9	25·6	25·9	0·10
Smoking (%)	48·2	43·0	30·4	<0·001
Hypertension (%)	13·0	14·2	9·2	<0·001
Dietary intake/day				
Vegetables (g)	339	343	340	0·90
Fruits (g)	96	97	113	<0·001
Berries (g)	16·3	15·0	16·5	0·19
Sweetened juices and jams (g)	35·4	36·0	39·0	0·15
Apple (g)	35·5	39·4	43·5	0·02
Onion (g)	3·54	3·57	3·84	0·05
Flavonoids (mg)	3·73	3·74	4·10	<0·001
β carotene (mg)	1·83	1·86	2·06	0·03
Vitamin E (mg)	7·39	7·36	7·68	0·03
Vitamin C (mg)	77·2	75·9	81·4	0·001
Fibre (g)	28·2	28·7	29·0	0·35
Saturated fatty acids (g)	65·6	64·2	61·6	0·002
Monounsaturated fatty acids (g)	36·6	36·3	35·2	0·06
Polyunsaturated fatty acids (g)	7·49	7·60	7·78	0·33
Polyunsaturated: saturated fat ratio (%)	12·7	12·8	13·7	0·005
Energy (MJ)	11·1	10·9	10·9	0·49

*Adjusted for age.
†Adjusted for sex.

Results

People who died during follow up were older and more often men, hypertensive, and smokers (table 1). The intakes of flavonoids as well as their main food sources—apples and onions—were lower among those who died. They also showed lower total intakes of fruits, vitamins C and E, and β carotene, but higher intakes of saturated and monounsaturated fats and lower ratios of polyunsaturated to saturated fats.

The flavonoid intake was not associated with the non-dietary major risk factors of cardiovascular diseases, smoking, serum cholesterol concentration, hypertension, or body mass index (table 2). Although the major sources of flavonoids—apples and onions—provided only 0·5-2% of the total vitamin C and E and β carotene intakes, the intakes of these antioxidant vitamins significantly increased with flavonoid intake. There was a strong correlation between the intakes of fruits and flavonoids (0·62 in men and 0·70 in women), which was mainly due to the intake of apples. The correlation coefficients for apples were 0·71 in men and 0·84 in women and for other fruits 0·32 and 0·34, respectively; the respective corresponding figures for

Table 2—*Mean levels of selected variables adjusted for age in quarters* of flavonoid intake*

Variable	Men (n=2748): 1 (lowest)	2	3	4 (highest)	P value for trend	Women (n=2385): 1 (lowest)	2	3	4 (highest)	P value for trend
Age (years)†	47·4	44·4	43·6	43·0	<0·001	47·6	45·8	44·2	43·9	<0·001
Serum cholesterol (mmol/l)	6·74	6·80	6·85	6·74	0·48	6·74	6·85	6·83	6·90	0·18
Body mass index (kg/m^2)	25·4	25·6	25·5	25·6	0·27	26·3	26·3	26·0	26·3	0·76
Smoking (%)	57·7	55·6	44·9	46·0	0·09	17·4	13·7	14·2	13·7	0·25
Hypertension (%)	7·3	6·8	6·7	7·3	0·97	13·5	16·7	14·8	15·6	0·24
β carotene (mg)	1·12	1·41	1·82	2·49	<0·001	1·47	2·23	2·60	3·11	<0·001
Vitamin E (mg)	7·1	8·0	8·6	10·2	<0·001	5·5	6·2	6·9	7·8	<0·001
Vitamin C (mg)	53	68	82	108	<0·001	53	74	89	116	<0·001
Fibre (g)	27·3	30·5	33·3	38·1	<0·001	20·7	24·1	25·8	29·3	<0·001
Saturated fatty acids (g)	69	71	74	79	<0·001	47	51	51	52	<0·001
Monounsaturated fatty acids (g)	38	40	42	47	<0·001	26	28	29	31	<0·001
Polyunsaturated fatty acids (g)	7·6	8·5	8·9	10·8	<0·001	5·5	6·0	6·5	7·2	<0·001
Polyunsaturated: saturated fat ratio (%)	11·8	13·1	13·1	14·6	<0·001	12·9	13·0	14·1	15·2	<0·001
Energy (MJ)	11·1	12·0	12·7	14·2	<0·001	8·0	9·0	9·3	9·9	<0·001

*Quarters are <2·1, 2·1-3·2, 3·3-4·8, >4·8 in men and <2·4, 2·4-3·6, 3·7-5·5, >5·5 in women.
†No adjustment.

Table 3—*Relative risks of total mortality and coronary mortality between quarters* of flavonoid intake*

Quarter of flavonoid intake*	Men						Women					
			Adjustment A†		Adjustment B‡				Adjustment A†		Adjustment B‡	
	No of cases	No at risk	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval	No of cases	No at risk	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
Total mortality												
1 (lowest)	291	687	1		1		167	595	1		1	
2	227	686	0·87	(0·73 to 1·03)	0·87	(0·73 to 1·04)	125	595	0·92	(0·73 to 1·16)	0·92	(0·73 to 1·17)
3	206	688	0·87	(0·73 to 1·05)	0·89	(0·74 to 1·09)	97	595	0·78	(0·61 to 1·00)	0·81	(0·61 to 1·06)
4 (highest)	162	685	0·76	(0·63 to 0·93)	0·79	(0·62 to 1·01)	85	595	0·69	(0·53 to 0·90)	0·78	(0·57 to 1·08)
P value for trend			<0·01		0·08				<0·01		0·13	
Coronary mortality												
1 (lowest)	99	687	1		1		58	595	1		1	
2	84	687	0·90	(0·67 to 1·21)	0·86	(0·64 to 1·16)	42	595	0·87	(0·59 to 1·30)	0·95	(0·62 to 1·45)
3	84	686	1·00	(0·75 to 1·35)	0·93	(0·68 to 1·28)	25	595	0·56	(0·35 to 0·90)	0·65	(0·39 to 1·09)
4 (highest)	57	685	0·78	(0·56 to 1·08)	0·67	(0·44 to 1·00)	24	595	0·54	(0·33 to 0·87)	0·73	(0·41 to 1·32)
P value for trend			0·24		0·12				<0·01		0·21	

*Quarters are <2·1, 2·1-3·2, 3·3-4·8, >4·8 in men and <2·4, 2·4-3·6, 3·7-5·5, >5·5 in women.
†Adjusted for age, smoking, serum cholesterol, hypertension, and body mass index.
‡Adjusted for age, smoking, serum cholesterol, hypertension, and body mass index and intakes of β carotene, vitamin E, vitamin C, fibre, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and energy.

Table 4—*Relative risks* of total mortality and coronary mortality between highest and lowest quarters† of intake of sources of flavonoid*

Source	Death	Men (n=2748)		Women (n=2385)	
		Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
Apple	Total	0·84	0·71 to 1·00	0·76	0·59 to 0·97
	Coronary heart disease	0·81	0·61 to 1·09	0·57	0·36 to 0·91
Other fruits	Total	0·77	0·64 to 0·93	0·70	0·54 to 0·91
	Coronary heart disease	0·88	0·65 to 1·20	0·55	0·34 to 0·90
Berries	Total	1·08	0·90 to 1·30	0·70	0·55 to 0·90
	Coronary heart disease	1·21	0·89 to 1·64	0·59	0·36 to 0·94
Sweetened juices and jams	Total	0·95	0·78 to 1·15	0·89	0·69 to 1·15
	Coronary heart disease	1·07	0·78 to 1·47	1·04	0·66 to 1·63
Onion	Total	0·72	0·59 to 0·87	0·80	0·62 to 1·04
	Coronary heart disease	0·74	0·53 to 1·02	0·50	0·30 to 0·82
Vegetables	Total	0·88	0·73 to 1·06	0·97	0·76 to 1·24
	Coronary heart disease	0·89	0·65 to 1·21	0·77	0·49 to 1·21

*Adjusted for age, smoking, serum cholesterol, hypertension, and body mass index.
†Highest/lowest quarters: apple ≥54 g/0 g in men and ≥71 g/0 g in women; other fruits ≥71 g/<7 g in men and ≥117 g/<20 g in women; berries ≥19 g/<3 g in men and ≥24 g/<7 g in women; sweetened juices and jams ≥49 g/<8 g in men and ≥53 g/<11 g in women; onion ≥5 g/0 g in men and women; vegetables ≥458 g/<262 g in men and ≥369 g/<216 g in women.

onion and flavonoid intake were 0·55 and 0·42. The correlation coefficients between intake of flavonoids and vegetables were 0·33 in men and 0·32 in women.

There was an inverse gradient between flavonoid intake and total mortality both in men and women when the major cardiovascular risk factors of smoking, serum cholesterol concentration, blood pressure, and body mass index were adjusted for (table 3). In women coronary mortality was significantly inversely associated with flavonoid intake, but in men the inverse association was not significant. Further adjustment for intake of energy, fatty acids, fibre, and antioxidant vitamins weakened the associations in women.

The consumption of apples and onions was inversely associated with total and coronary mortality (table 4). The relations were again stronger in women than in men. Adjustment for the intake of other fruits and vegetables, not notably including flavonoids, did not materially alter the results (data not shown). The inverse association between flavonoid intake and total and coronary mortality in women was present both at higher and lower intakes of vitamins C and E and β carotene (data not shown).

Discussion

The present cohort study indicated an inverse association between intake of flavonoids and coronary mortality. This finding is in line with the results of a Dutch study in Zutphen, which presented a similar association in elderly men followed for five years.[8] Our results thus support the suggested beneficial effect of flavonoid intake against coronary heart disease. The mechanism of protection may be due to an antioxidant effect[1] or inhibition of thrombogenesis.[3]

Vegetables, fruits, tea, and red wine were the major sources of flavonoids in the Dutch study,[13] and all these foods were associated with a low risk of coronary heart disease.[8] The low coronary mortality in France may be due in part to the high consumption of red wine, which is a rich source of flavonoids.[22] Data on tea and red wine were not available in the present study. As the consumption of tea and red wine is low in Finland their contribution to the flavonoid intake was also small in the present population. The consumption of onions and apples, the main food sources of flavonoids, was also not high during the baseline study, the average intake of flavonoids in our study being much lower than that reported in the Zutphen study. The fact that this and also the intake of the antioxidant vitamins C and E and carotenoids were low in Finland during the baseline study[10] suggests the possibility that even smaller amounts of dietary flavonoids are important in circumstances where the intake of other dietary antioxidant agents is low. We found a stronger association between low dietary flavonoid intake and mortality in women than in men. The results are in line with our previous findings demonstrating the beneficial effects of antioxidants particularly in women.[10]

Several earlier studies have suggested that high dietary intake of fruits and vegetables, strongly correlated with intake of antioxidant vitamins, may protect against cardiovascular diseases.[23] We obtained a similar finding from our population[10]; thus it cannot be excluded that the association in the present study between intake of flavonoids and coronary mortality may be due to other substances in fruits and vegetables—for example, fibre, carotenoids, and vitamin C—or due to differences in intake of fatty acids closely correlated with high flavonoid intake. Adjustment for the intake of vitamins C and E and β carotene and various fatty acids diminished the associations. The main sources of flavonoids in the present study—apples and onions—were inversely associated with coronary mortality. As these foods do not contribute

Key messages

- The incidence of coronary mortality is higher among populations with low dietary intake of flavonoids
- The protective effect of flavonoids was associated with a diet high in intake of apples and onions
- The effect may be mediated through prevention of oxidation of low density lipoproteins but other mechanisms could be involved
- Flavonoids offer an explanation for the suggested beneficial effect of fruits and vegetables in coronary heart disease
- Further studies should concentrate on the effects of various flavonoid compounds and on populations with different intakes

significantly to intake of the antioxidant vitamins C or E or β carotene the association observed for flavonoids was probably not due to these antioxidants.

With the exception of berries in men, foods representing sources of flavonoids were inversely associated with coronary mortality risk. In contrast with fruits and vegetables some berries also contain considerable amounts of flavonoids (for example, myricetin), which, according to in vitro studies, modify low density lipoprotein to increase its uptake by macrophages, thus possibly having an opposite effect on the risk of coronary heart disease.[24] This and the low accuracy of our estimates of flavonoid concentration in berries may explain the absence of an association.

In summary, the results of the present study suggest that people with very low dietary intakes of flavonoids have increased risks of coronary heart disease. This could not, however, be fully distinguished from the possible effects of other dietary substances or lifestyle. Further longitudinal studies of other populations are needed to confirm the importance of flavonoids in the prevention of coronary heart disease.

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Prescribing and hospital admissions for asthma in east London

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Admission rates for asthma in 1991-2 were 80-100% above national averages for all age groups in east London.[1] We have shown in east London general practices that a higher ratio of prophylaxis to bronchodilator prescribing occurs in training practices and those approved for health promotion band 3 and asthma surveillance.[2] We have also explored the relation of appropriate prescribing for asthma to other local practice characteristics.[3] We investigated excessive asthma admission rates in patients from these practices by studying the relation between asthma prescribing and admissions.

Methods and results

Data on asthma admissions by age for east London residents in 134 out of 163 practices covered two years from April 1992 and included some 1602 patients (800 in 1992-3 and 802 in 1993-4). Ninety eight per cent of admissions for asthma were acute and only 3% of all patients admitted were not allocated to a practice. Data were obtained from the integrated district and regional information system with the international classification of disease code 493. Rates per thousand patients per practice were calculated from the average number of patients admitted per year; this excluded readmissions within the same year. The denominators were the resident population of east London in each practice at June 1993 and June 1994. We also investigated admission rates in the age groups under 5, 5-64, and 65 and over.

Our asthma prescribing data have been described elsewhere.[2] While only one year's prescribing data were available (April 1992 to March 1993), our experience from a parallel study in 24 local practices is that the prescribing ratios remained almost constant during our two year study period.

Table 1 presents the mean (SD) asthma admission rates for different categories of the prophylaxis to bronchodilator ratios. These ratios have been divided into four groups by the 25th and 75th percentiles and the median. Statistical significance was determined by Cuszick's test for trend. Table 1 shows that practices prescribing higher ratios of prophylaxis to broncho-