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Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study

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Fruit and vegetable consumption is associated with low CHD risk in the USA and Northern Europe. There is, in contrast, little information about these associations in other regions of Europe. The goal of the present study was to assess the relationship between frequency of fruit and vegetable intake and CHD risk in two European populations with contrasting cardiovascular incidence rates; France and Northern Ireland. The present prospective study was in men aged 50–59 years, free of CHD, who were recruited in France (*n* 5982) and Northern Ireland (*n* 2105). Fruit and vegetable intake was assessed by a food-frequency questionnaire. Incident cases of acute coronary events and angina were recorded over a 5-year follow-up. During follow-up there was a total of 249 ischaemic events. After adjustment on education level, smoking, physical activity, alcohol consumption, employment status, BMI, blood pressure, serum total and HDL-cholesterol, the relative risks (RR) of acute coronary events were 0·67 (95 % CI 0·44, 1·03) and 0·64 (95 % CI 0·41, 0·99) in the 2nd and 3rd tertiles of citrus fruit consumption, respectively (P for trend $<0{\cdot}03$). Similar results were observed in France and Northern Ireland. In contrast, the RR of acute coronary events for 'other fruit' consumption were 0·70 (95 % CI 0·31, 1·56) and 0·52 (95 % CI 0·24, 1·14) respectively in Northern Ireland (trend $P<0{\cdot}05$) and 1·29 (95 % CI 0·69, 2·4) and 1·15 (95 % CI 0·68, 1·94) in France (trend $P=0{\cdot}5$; interaction $P<0{\cdot}04$). There was no evidence for any association between vegetable intake and total CHD events. In conclusion, frequency of citrus fruit, but not other fruits, intake is associated with lower rates of acute coronary events in both France and Northern Ireland, suggesting that geographical or related factors might affect the relationship between fruit consumption and CHD risk.

Fruit: Vegetable: Coronary heart disease: Epidemiological cohort study

The consumption of nutrients from fruit and vegetables, such as dietary fibre, K and antioxidant vitamins, has been associated with a reduced risk of CVD in prospective studies (Khaw & Barrett-Connor, 1987; Pietinen *et al.* 1996; Rimm *et al.* 1996; Iso *et al.* 1999; Marchioli *et al.* 2001). However, when the cardiovascular protective effect of some of these nutrients, for example antioxidant vitamins, was tested in clinical trials the results were at best non-significant (Marchioli *et al.* 2001). This has led the scientific community to shift its interest to the study of the cardioprotective properties of fruit and vegetables taken as a whole rather than a source of particular micro- or macronutrients.

In this respect, short-term clinical trials have shown that diets supplemented with fruit and vegetables are associated with a lowering of blood pressure and plasma cholesterol (Jenkins *et al.* 1979, 1997; Robertson *et al.* 1979; Stasse-Wolthuis *et al.* 1980; Tinker *et al.* 1991; Singh *et al.* 1992; Wisker *et al.* 1994; Appel *et al.* 1997). In addition, cohort studies have usually shown favourable trends between fruit and vegetable intake and the risk of IHD or stroke (Gaziano *et al.* 1995; Pietinen *et al.* 1996; Joshipura *et al.* 2001; Bazzano *et al.* 2002; Johnsen *et al.* 2003; Rissanen *et al.* 2003; Sauvaget *et al.* 2003) which are, at least in part, independent of classic cardiovascular risk factors. Finally, multifactorial intervention trials including increased fruit and vegetable consumption in survivors of myocardial infarction (MI) events have demonstrated major reductions in the recurrence of cardiac events despite modest changes in cardiovascular risk factors (Singh *et al.* 1993, 2002; Pietinen *et al.* 1996; de Lorgeril *et al.* 1999). This suggests that fruit and vegetables might affect

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Abbreviations: MI, myocardial infarction; PRIME study, Prospective Epidemiological Study of Myocardial Infarction; RR, relative risk.

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cardiovascular risk through other factors than their effects on blood pressure and cholesterol levels.

When setting general dietary guidelines, the reproducibility of results across populations is an important factor to consider (Rimm, 2002). Yet, most data presented to date have been collected in North America or Northern Europe, two regions with elevated CHD rates (Tunstall-Pedoe *et al.* 1999). In Italy, Greece and Spain, low intakes of fruit have been reported in survivors of MI enrolled in case–control studies (Martinez-Gonzalez *et al.* 2002; Negri *et al.* 2003; Panagiotakos *et al.* 2003). To our knowledge, there have been no reports of cohort studies in countries from Central and Southern Europe. Therefore, the goal of the present study was to assess the relationship between frequency of fruit and/or vegetables consumption and the CHD risk in France and Northern Ireland, two countries with contrasting CHD rates and different lifestyles.

Methods

Population recruitment

Cohort recruitment and examination methods have been described previously (Yarnell, 1998). Briefly, the Prospective Epidemiological Study of Myocardial Infarction (PRIME study) was established in 1991 in the populations of four WHO-MONICA centres in Belfast (UK), Lille, Strasbourg and Toulouse (France). The target was to recruit 2500 men, aged 50–59 years, in each centre and to follow them for a minimum of 5 years. The present paper was approved by the local ethics committee (Comité d'Ethique de l'Hôpital Broussais, séance no. 60 du 4 juin 1991, protocol no. 235) according to the regulation in France and Northern Ireland.

Questionnaire

Self-administered questionnaires related to demographic, socio-economic factors and diet were completed at home by the participants and checked with them by survey staff at the clinic. Data on educational level, occupational activity, personal and family history, tobacco and alcohol consumption, drug intake and physical activity were also collected. Physical activity was assessed for work and leisure times, on working days and at weekends. Subjects were classified into three categories: regular physical exercise (if they took intense physical activity more than 20 min, once per week or more); moderate physical activity (light physical activity with no increased heart rate most weeks); no physical activity. Smoking habits were determined from questions on present and past habits, number and type of cigarettes, cigars or pipes smoked per d. Smokers were defined as individuals currently smoking at least one cigarette per d. Alcohol consumption was assessed by a questionnaire in which the subject reported his mean consumption (in units) of wine, beer, cider and spirits for each day of the week. Intake of alcohol was expressed in ml pure ethanol/week. Personal medical history of cardiovascular risk factors was assessed: the subject was first asked whether a medical doctor had ever reported a given risk factor, followed by a question on past and actual treatment. Diabetes was defined by a reported history of diabetes and current blood glucose-lowering therapy by dietary or pharmacological means. During an examination, the questionnaire on personal medical history was completed along with the London School of Hygiene Cardiovascular Questionnaire for Chest Pain on Effort and Possible Infarction (Rose *et al.* 1982), and a standard twelve-lead electrocardiogram was recorded. Of the initial 10 600 subjects, 842 were excluded due to history of CHD. In addition, 1360 men who reported that they were on a diet for hypertension, hypercholesterolaemia or diabetes were excluded from the analyses. Finally, 312 were also excluded due to missing data on fruit and/or vegetable intake and/or adjustment variables, leaving a total of 8087 participants for study. Among the remaining patients, 106 (1·3 %) were lost to follow-up.

Clinical examination

The anthropometric measurements included height (to the nearest cm), body weight (to the nearest 200 g) with subjects in light clothing without their shoes. BMI was computed as weight (kg) divided by height squared (m^2). Blood pressure was measured once at the end of the examination after a 5 min rest in the sitting position. Measurements were performed with an automatic device (Spengler SP9; Spengler, F94230 Cachan, France), which also recorded heart rate. A standard cuff size was used, but a large cuff was available when necessary. The devices were recalibrated every 3 months by the Co-ordinating Centre in Paris. Hypertension was defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current blood pressure-lowering treatment.

Dietary assessment

Dietary information on frequency of fruit and vegetable intake was obtained for four categories of fruit and vegetables ('citrus fruit', 'other fruit', 'raw vegetables' and 'baked vegetables'). Subjects were asked, through a personal interview at their home, to indicate their usual frequency of consumption of a standard portion of fruit or vegetables for the last weeks using the following scale: more than once per d (number per d); daily; three to four times per week; once per week; twice per month; once per month; never. Frequency of total 'fruit', 'vegetables' and 'fruit and vegetables' intake scores were calculated as the sum of number of servings per d of fruit and/or vegetables. Potatoes were not included in the dietary scores because: (a) their vitamin and fibre composition is different from most other leafy vegetables; (b) their carbohydrate content is mostly of high glycaemic index; (c) in France, they are often eaten fried whereas in Northern Ireland they are boiled which adds to the complexity of the analysis. We did not validate the questionnaire against another dietary assessment method. However, a correlation analysis between the frequency of fruit and/or vegetable intake and plasma vitamins was performed in 100 men (twenty-five per centre, of which twenty were not analysed because the subjects were taking vitamin supplements) to assess the ability of the questionnaire to discriminate large *v.* small consumers of fruits and vegetables. Correlation analyses were performed between frequency of fruit and vegetable intake and plasma β-cryptoxanthin, vitamin C, α-carotene, β-carotene and lutein (Zino *et al.* 1997; John *et al.* 2002).

Blood sampling and assay procedures

Venous blood was collected into siliconised vacutainer tubes (Vacutainer; Becton Dickinson, Franklin Lakes, NJ, USA) containing EDTA. Samples of plasma were immediately transferred to plastic tubes and frozen at −80°C. The frozen samples were then shipped in batches to the Central Laboratory in Lille. Plasma total cholesterol and HDL-cholesterol levels were measured by enzymic methods using reagents from Boerhinger-Mannheim (Mannheim, Germany). LDL-cholesterol was calculated according to Friedewald's formula. Hypercholesterolaemia was defined by cholesterol levels >2·4 g/l or lipid-lowering treatment. The inter-assay CV for total cholesterol was 2 %. The liposoluble plasma vitamins were assayed by HPLC (Brubacher & Vuilleumier, 1974) by the Swiss Reference Laboratory, Basel, Switzerland, appointed by the National Institute of Standards and Technology, Gaithersburgh, MD, USA. Vitamin C (sum of ascorbic and dehydroascorbic acid) was measured by automated fluorimetry (Brubacher & Vuilleumier, 1974). The laboratory was blinded to the origin of the samples. The CV for all parameters was ≤3 %; periodic parallel analysis of reference samples controlled for systematic errors.

Follow-up

Briefly, subjects were contacted annually by letter and asked to complete a clinical event questionnaire to be returned to the centre in a pre-paid envelope. For all subjects reporting a possible event, clinical information was sought directly from the hospital or family doctor's notes. All details of electrocardiograms, hospital admissions, enzymes, surgical operations, angioplasty, treatment, etc. were collected. Death certificates were checked for supporting clinical and post-mortem information of cause of death. When necessary, the circumstances of death were obtained from the family doctor or the family. A medical committee was established, comprising one member from each PRIME centre and three independent cardiologists (two from France and one from the UK). Its task was to provide an independent validation of coronary events in the PRIME study. The committee met on four occasions during the 5-year follow-up period. All medical information, including all available electrocardiograms related to events, was sequentially displayed by each centre's representative and the committee assigned a code according to a strict protocol (Ducimetiere *et al.* 2001).

MI was defined as previously described (Ducimetiere *et al.* 2001). Definite coronary death was defined as death with documented coronary event. When significant coronary atheroma was present at autopsy, the death was considered as definite coronary death. When a coronary death was suspected, with no other documentation or explanation, it was labelled possible coronary death. The three death categories were grouped together as coronary death. Angina pectoris was defined by the presence of chest pain as extensively described (Ducimetiere *et al.* 2001). Unstable angina was defined as crescendo pain (change in frequency or severity of chest pain on exertion or appearance of chest pain at rest following pre-existing pain on exertion), with either enzyme changes or electrical changes. In the absence of enzyme or electrical data, the diagnosis was not upheld. Events were grouped in two categories, (1) acute events: MI and CHD death, (2) angina events: stable and unstable angina.

Statistical analysis

Baseline characteristics are presented by tertiles of frequency of fruit and vegetable intake. Linear trend (for continuous variables) and χ^2 tests (for categorical variables) were used to compare values across tertiles. For trend analyses, fruit and vegetable intake was used as a continuous variable in the statistical model. Cox's proportional hazard regression models were used to assess the relationship between categories of frequency of fruit and vegetable intake and CHD. Adjustment variables were centre (four levels), education (three levels), smoking (current, never, former), physical activity (four levels), employment status (two levels), alcohol consumption (four levels) and age, BMI, blood pressure, total and HDL-cholesterol as continuous variables. Three different models were used: (1) adjusted on age and centre; (2) adjusted on age, centre and possible confounding variables (smoking, alcohol consumption, physical activity, educational level and employment status); (3) similar to second model plus explanatory variables (systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes or dyslipidaemia). These models gave similar results and thus only the results with the complete model are presented. An interaction test between country (France or Northern Ireland) and frequency of fruit and/or vegetable intakes (as continuous variables) was performed. Whenever the interaction test was significant at $P<0·10$, further analyses were performed in each country separately. The cut-off value of $P<0·05$ was used for statistical significance.

Results

Spearman's correlation coefficients between selected plasma vitamins and frequency of fruit and/or vegetable intake, assessed by the food-frequency questionnaire, were calculated in a sub-sample of eighty men. Frequency of fruit intake was correlated with β-cryptoxanthin (*r* 0·32; $P<0·005$) and vitamin C (*r* 0·33; $P<0·004$). Frequency of citrus fruit intake was also correlated with β-cryptoxanthin (*r* 0·34; $P<0·002$) and vitamin C (*r* 0·37; $P<0·0007$). Similarly, frequency of vegetable intake was correlated with α-carotene (*r* 0·26; $P<0·03$), β-carotene (*r* 0·29; $P<0·02$), β-cryptoxanthin (*r* 0·32; $P<0·04$) and vitamin C (*r* 0·24; $P<0·04$).

Table 1 shows the frequency of fruit and/or vegetable intake and lifestyle characteristics of the participants in France and Northern Ireland. The frequency of fruit and vegetable intake was lower in Northern Ireland than in

Table 1. Frequency of fruit and/or vegetable intake and lifestyle characteristics by country
(Mean values and standard deviations or percentages)

	France		Northern Ireland		
	Mean	SD	Mean	SD	P*
n	5982		2105		
Fruit (frequency/d)	1·18	0·92	0·89	0·8	<0·001
Q1–Q3	0·5–2·0		0·28–1·28		
Vegetables (frequency/d)	1·24	0·68	0·98	0·78	<0·001
Q1–Q3	0·79–1·5		0·57–1·28		
Fruit and vegetables (frequency/d)	2·42	1·28	1·86	1·21	<0·001
Q1–Q3	1·5–3·14		1·07–2·43		
Age (years)	54·8	2·9	54·7	2·9	<0·08
Education level (%)					
Elementary school or less	29·0		38·3		
High school	54·6		49·9		<0·001
University	16·4		11·8		
Currently employed (%)	78·3		87·6		<0·001
Tobacco (%)					
Non-smoker	28·0		35·5		
Ex-smoker	45·0		32·1		<0·001
Current smoker	27·1		32·4		
Physical activity (%)					
No	15·4		6·9		<0·001
Light	52·0		80·1		
Regular	24·7		10·2		
Frequent	7·9		2·8		
Alcohol consumption (%)					
Non-consumer	8·9		39·9		<0·001
≤ 171·1 ml/week	29·4		23·0		
171·1 to 374·1 ml/week	30·9		19·0		
≥ 374·1 ml/week	30·8		18·1		
Vitamin supplements (% ≥1/week)	12·7		20·8		<0·001

Q1–Q3, quartiles 1–3.
* The general linear procedure was used for continous variables and the χ^2 test for categorical variables.

France. The level of education ($P<0·001$), of physical activity ($P<0·001$) and of alcohol consumption ($P<0·001$) was higher in France than in Northern Ireland. Inversely, the rate of men currently employed ($P<0·001$), of smokers ($P<0·001$) and of vitamin supplement consumers ($P<0·001$) was lower in France than in Northern Ireland.

Table 2 shows the clinical, biological and lifestyle characteristics of men according to frequency of fruit and vegetable intake and country. In both France and Northern Ireland, men in the 3rd tertile of frequency of fruit and vegetable intake were more educated ($P<0·001$), currently employed ($P<0·01$), non-smokers ($P<0·001$), physically active ($P<0·001$), moderate alcohol consumers ($P<0·001$) and users of vitamin supplements ($P<0·001$) than men in the lowest tertile of the distribution. In France, BMI ($P=0·03$), systolic blood pressure ($P<0·001$) and total cholesterol were lower in the upper than in the lower tertile of fruit and vegetable distribution (data not shown). In Ireland, BMI was higher in men from the 3rd tertile than in the lower tertile ($P<0·03$).

Over the first 5 years of follow-up, 249 events occurred; 102 in Northern Ireland (incidence 1·0 ‰ per year) and 147 in France (0·5 ‰ per year), including fifty-three acute events in Northern Ireland (0·51 ‰ per year) and eighty in France (0·27 ‰ per year). Three models were used to assess the relationship between frequency of fruit and vegetable intake and CHD: (1) adjusting for age and centre; (2) adjusting for age, centre and lifestyle variables; (3) a complete model adjusting for centre, age, smoking, alcohol consumption, physical activity, education level, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes and dyslipidaemia. Since these analyses yielded similar results, only the results of the complete model are presented in Table 3. There was no evidence for a significant association between frequency of vegetable intake and acute coronary events or for an interaction between country. There was in contrast a significant association between citrus fruit intake and acute coronary events ($P<0·03$) with a 36 % lower risk (relative risk (RR) 0·64 (95 % CI 0·41, 0·99)) of incident acute coronary events in the upper tertile of citrus fruit distribution compared with the lower tertile. There was a statistically significant interaction between countries and frequency of ‘other fruit’ ($P<0·04$), total fruit intake ($P<0·03$) and frequency of fruit and vegetable intake ($P<0·07$) on acute coronary event risk, thus suggesting a different association in France and Northern Ireland.

In order to investigate this interaction, further analyses were performed in both countries separately (Table 4). In Northern Ireland, other fruit ($P<0·05$), total fruit ($P<0·01$) and all fruit and vegetables ($P<0·02$) were

Table 2. Lifestyle characteristics according to frequency of fruit and vegetable intake and country
(Mean values and standard deviations or percentages)

Fruit and vegetable intake (servings per d)...	France							Northern Ireland							Both countries						
	≤1·57		1·6–2·57		≥2·6			≤1·57		1·6–2·57		≥2·6			≤1·57		1·6–2·57		≥2·6		
	Mean	SD	Mean	SD	Mean	SD	*P**	Mean	SD	Mean	SD	Mean	SD	*P**	Mean	SD	Mean	SD	Mean	SD	*P**
n	1755		1975		2252			984		709		412			2739		2684		2664		
Fruit (frequency/d)	0·40		0·95		1·99		<0·001	0·33		0·99		2·02		<0·001	0·37		0·96		1·99		<0·001
Vegetables (frequency/d)	0·70		1·15		1·74		<0·001	0·67		1·08		1·53		<0·001	0·69		1·13		1·70		<0·001
Fruit and vegetables (frequency/d)	1·09		2·10		3·73			1·00		2·07		3·55			1·00		2·09		3·70		
Age (years)	54·7	2·9	54·8	2·9	54·9	2·9	0·05	54·6	2·9	54·6	2·9	54·7	2·8	0·77	54·7	2·9	54·8	2·9	54·9	2·9	<0·001
Education level (%)																					
Elementary or less	30·4		27·6		29·2		<0·001	46·4		32·7		28·4		<0·001	36·1		29·0		29·1		<0·001
High school	57·9		55·8		50·8			46·1		54·0		51·9			53·7		55·4		51·0		
University	11·7		16·5		20·0			7·4		13·3		19·7			10·1		15·6		19·9		
Currently employed (%)	76·3		77·9		80·3		0·01	82·5		90·6		94·7		<0·001	78·5		81·2		82·5		<0·001
Tobacco (%)																					
Non-smoker	23·2		28·1		31·6		<0·001	29·4		37·8		46·1		<0·001	25·4		30·6		33·9		<0·001
Ex-smoker	42·7		44·6		47·0			27·4		35·7		36·9			37·2		42·2		45·5		
Current smoker	34·1		27·4		21·4			43·2		26·5		17·0			37·3		27·2		20·7		
Physical activity (%)																					
No	19·7		15·5		12·0		<0·001	9·1		5·6		3·9		<0·001	15·9		12·9		10·7		<0·001
Light	53·8		52·8		49·9			81·5		79·8		77·2			63·7		59·9		54·1		
Regular	21·4		23·9		28·0			7·6		11·1		14·8			16·4		20·5		26·0		
Frequent	5·1		7·7		10·1			1·7		3·4		4·1			3·9		6·6		9·2		
Alcohol intake (%)																					
Non-consumer	8·4		8·0		10·1		<0·001	36·9		39·9		46·8		<0·001	18·7		16·4		15·8		<0·001
≤ 171·1 ml/week	23·0		30·0		33·9			19·2		27·6		24·3			21·6		29·4		32·4		
171·1 to 374·1 ml/week	29·3		31·1		32·0			19·5		19·0		18·0			25·8		27·9		29·8		
≥ 374·1 ml/week	39·3		30·8		24·0			24·4		13·4		10·9			34·0		26·2		22·0		
Vitamin supplements (% ≥1/week)	11·0		12·8		13·8		0·05	15·9		22·8		28·9		<0·001	12·7		15·5		16·1		<0·001

* The general linear procedure was used for continuous variables and the χ^2 test for categorical variables.

Table 3. Multivariate relative risk (RR) for acute coronary event in France and Northern Ireland according to frequency (Freq) of fruit and vegetable intake

		France and Northern Ireland				
Tertile…		1	2	3	*P**	*P*†
Raw vegetables	Freq/d	≤0·29	0·43–0·57	≥1		
	n	3227	2414	2446		
	Events	68	27	38		
	RR	1	0·76	1·17	0·44	0·45
	95 % CI	–	0·46, 1·23	0·71, 1·91		
Baked vegetables	Freq/d	≤0·29	0·43–0·57	≥1		
	n	2465	2916	2706		
	Events	48	38	47		
	RR	1	0·69	0·93	0·49	0·29
	95 % CI	–	0·45, 1·07	0·61, 1·42		
All vegetables	Freq/d	≤0·79	1–1·29	≥1·5		
	n	3023	2513	2551		
	Events	57	37	39		
	RR	1	0·81	0·98	0·98	0·93
	95 % CI	–	0·54, 1·23	0·82, 1·18		
Citrus fruit	Freq/d	≤0·07	0·14–0·29	≥0·5		
	n	2434	2472	3181		
	Events	59	35	39		
	RR	1	0·66	0·64	<0·03	0·63
	95 % CI	–	0·44, 1·03	0·41, 0·99		
Other fruit	Freq/d	≤0·29	0·43–0·57	≥1		
	n	3253	1582	3252		
	Events	98	69	82		
	RR	1	0·99	0·85	0·61	<0·04
	95 % CI	–	0·61, 1·59	0·56, 1·29		
All fruit	Freq/d	≤0·57	0·64–1·14	≥1·29		
	n	2909	2322	2856		
	Events	64	31	38		
	RR	1	0·68	0·74	<0·05	<0·03
	95 % CI	–	0·44, 1·05	0·48, 1·14		
Fruit and vegetables	Freq/d	≤1·57	1·6–2·57	≥2·60		
	n	2725	2575	2787		
	Events	68	26	39		
	RR	1	0·43	0·75	<0·09	<0·07
	95 % CI	–	0·27, 0·69	0·49, 1·15		

**P* for trend. Adjustment on centre, age, smoking, alcohol consumption, physical activity, education level, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes or dyslipidaemia.
† Interaction between frequency of consumption and country.

associated with a lower risk of acute coronary events. In France, there was no evidence for any statistically significant association between other fruit ($P<0{\cdot}50$), total fruit ($P<0{\cdot}57$) and all fruit and vegetables ($P<0{\cdot}60$) and acute coronary events.

Finally, there was no evidence for any association between vegetable, fruit, and fruit and vegetable intake and total events (combined acute coronary events and angina) in France or in Northern Ireland or in both countries (Table 5). Although there was a tendency to lower total event rate across tertiles of citrus fruit intake (RR 0·77 (95 % CI 0·56, 1·05) and RR 0·76 (95 % CI 0·56, 1·04)) for the middle and upper tertile respectively), this reduction did not reach a level of statistical significance (*P* trend <0·14).

Discussion

The objective of our work was to assess the relationship between the frequency of fruit and vegetable intake in two European countries at contrasting CHD risk and different lifestyles. The results showed a favourable association between the frequency of citrus fruit consumption and acute coronary events in France and Northern Ireland. In addition, other fruit intake was also associated with lower rates of acute coronary events in Northern Ireland but not in France, suggesting that geographical or related influences might affect the relationship between the consumption of fruits and CHD risk.

Few epidemiological studies have specifically analysed the effect of the consumption of citrus fruits on cardiovascular events. In the Nurses' Health Study and the Health Professionals' Follow-up Study, based on 126 000 men and women, Joshipura *et al.* (2001) showed a reduction of 12 % in the risk of MI in the top quintile of citrus fruit distribution as compared with the bottom quintile. Similarly, lower stroke rates were reported among consumers of citrus fruit in the USA (Joshipura *et al.* 1999) and Denmark (Johnsen *et al.* 2003). The present results

Table 4. Multivariate relative risk (RR) for acute coronary events in France and Northern Ireland separately according to frequency (Freq) of fruit and fruit and vegetable intake

		France				Northern Ireland			
Tertile…		1	2	3	*P**	1	2	3	*P**
Citrus fruit	Freq/d	≤0·07	0·14–0·29	≥0·5		≤0·07	0·14–0·29	≥0·5	
	n	1584	1840	2558		850	632	623	
	Events	26	23	31		33	12	8	
	RR	1	0·79	0·78	<0·11	1	0·59	0·43	<0·16
	95 % CI	–	0·45, 1·39	0·45, 1·34		–	0·30, 1·15	0·19, 0·98	
Other fruit	Freq/day	≤0·29	0·43–0·57	≥1		≤0·29	0·43–0·57	≥1	
	n	2260	1170	2552		993	412	700	
	Events	28	17	35		36	8	9	
	RR	1	1·29	1·15	0·50	1	0·70	0·52	<0·05
	95 % CI	–	0·69, 2·4	0·68, 1·94		–	0·31, 1·56	0·24, 1·14	
All fruit	Freq/d	≤0·57	0·64–1·14	≥1·29		≤0·57	0·64–1·14	≥1·29	
	n	1939	1722	2321		970	600	535	
	Events	26	23	31		38	8	7	
	RR	1	1·00	1·08	0·57	1	0·39	0·39	<0·01
	95 % CI	–	0·57, 1·77	0·62, 1·87		–	0·18, 0·85	0·17, 0·89	
All fruit and vegetables	Freq/d	≤1·57	1·6–2·57	≥2·6		≤1·57	1·6–2·57	≥2·6	
	n	1755	1975	2252		970	600	535	
	Events	31	17	32		37	9	7	
	RR	1	0·48	0·86	0·60	1	0·39	0·56	<0·02
	95 % CI	–	0·27, 0·87	0·51, 1·44		–	0·18, 0·80	0·25, 1·28	

**P* for trend. Adjustment on centre, age, smoking, alcohol consumption, physical activity, education level, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes or dyslipidaemia.

are in agreement with these findings and with previous studies which had shown a cardioprotective effect for dietary vitamin C (Marchioli *et al.* 2001). However, the latter associations were inconsistent across studies, suggesting that other factors than vitamin C might explain the beneficial effects of citrus fruit. Altogether, these results suggest that citrus fruit might have favourable effects on CHD prevention in countries at contrasting cardiovascular risk and different lifestyles.

The relationship between the frequency of fruit consumption and CHD risk in Northern Ireland is in agreement with findings in other cohorts from Northern Europe and the USA. In Finland, Pietinen *et al.* (1996) reported an RR for fatal MI of 0·60 (95 % CI 0·45, 0·79) in subjects from the top quintile of fruit intake as compared with the bottom quintile. In Denmark, Johnsen *et al.* (2003) reported an RR for ischaemic stroke of 0·60 (95 % CI 0·38, 0·95) in men and women from the top *v.* the bottom quintile of fruit consumption. Similarly, in the NHANES Follow-up Study in North America, the RR for CHD was 0·76 (95 % CI 0·56, 1·03) in subjects consuming fruit and vegetables at least three times per d as compared with those who consumed them less that once per d (Bazzano *et al.* 2002). Finally, in the Nurses' Health Study and the Health Professionals' Follow-up Study, subjects in the highest quintile of fruits had an RR for CHD of 0·80 (95 % CI 0·69, 0·92) compared with those in the lowest quintile (Joshipura *et al.* 2001). In the present study, although a significant trend was found between acute coronary event risk and frequency of fruit consumption in Northern Ireland, there was no visual evidence of a continuous decreasing gradient of risk across categories of frequencies of fruit intake; the risk was already minimum (RR 0·39) in the second tertile of frequency. One possible explanation to this finding is that a dose effect is not detectable due to the small number of events and large variability. Thus, it appears that in countries with high rates of cardiovascular mortality, such as the USA, Northern Europe and Northern Ireland (Tunstall-Pedoe *et al.* 1999), fruit consumption is associated with a reduction in CHD morbidity and mortality.

The association between fruit intake and cardiovascular events differed in Northern Ireland and France; the association was favourable in Northern Ireland but not in France. A similar interaction, although not statistically significant, was reported (Bazzano *et al.* 2002; Rimm, 2002) in the NHANES Survey Follow-up Study. In this survey, vegetable and fruit intake was associated with a reduction in coronary risk in white Americans, but not in non-white. In contrast, Steffen *et al.* (2003) found a stronger association between fruit and vegetable intake and the risk of incident coronary artery disease among African-Americans than among caucasians ($P=0{\cdot}01$ for interaction). Altogether, these data suggest that the relationship between fruit intake and CHD risk could vary across different geographical areas, ethnic groups and/or according to the type of fruit consumed. There are several possible explanations for this interaction. Firstly, the fruit that are usually consumed by men in Northern Ireland might be different from those consumed in France and these differences might be associated with specific protective effects in Northern Ireland. This hypothesis is supported by the analysis of the food-standardised balance sheets. The supply per capita of bananas and apples is large in Ireland, whereas fruit supplies are more diverse in France (Food and Agriculture Organization, 2003). However, this hypothesis also implies that the fruit consumed in Northern Ireland have protective effects, whereas those consumed in

Table 5. Multivariate relative risk (RR) for total coronary events in France and Northern Ireland according to frequency (Freq) of fruit and/or vegetable intake

		France and Northern Ireland				
Tertile...		1	2	3	*P**	*P*†
Raw vegetables	Freq/d	≤0·29	0·43–0·57	≥1		
	n	3227	2414	2446		
	Events	118	67	64		
	RR	1	1·08	1·19	0·59	0·92
	95 % CI	–	0·77, 1·51	0·82, 1·72		
Baked vegetables	Freq/d	≤0·29	0·43–0·57	≥1		
	n	2465	2916	2706		
	Events	77	90	82		
	RR	1	0·96	0·98	0·54	0·54
	95 % CI	–	0·71, 1·30	0·72, 1·34		
All vegetables	Freq/d	≤0·79	1–1·29	≥1·5		
	n	3023	2513	2551		
	Events	107	73	69		
	RR	1	0·84	1·01	0·93	0·66
	95 % CI	–	0·63, 1·13	0·88, 1·15		
Citrus fruit	Freq/d	≤0·07	0·14–0·29	≥0·5		
	n	2434	2472	3181		
	Events	98	69	82		
	RR	1	0·77	0·76	0·14	0·33
	95 % CI	–	0·56, 1·05	0·56, 1·04		
Other fruit	Freq/d	≤0·29	0·43–0·57	≥1		
	n	3253	1582	3252		
	Events	112	47	90		
	RR	1	0·98	0·96	0·58	0·56
	95 % CI	–	0·68, 1·39	0·71, 1·30		
All fruit	Freq/d	≤0·57	0·64–1·14	≥1·29		
	n	2909	2322	2856		
	Events	108	63	78		
	RR	1	0·83	0·90	0·13	0·22
	95 % CI	–	0·60, 1·14	0·66, 1·24		
All fruit and vegetables	Freq/d	≤1·57	1·6–2·57	≥2·60		
	n	2739	2684	2664		
	Events	118	62	69		
	RR	1	0·61	0·78	0·18	0·18
	95 % CI	–	0·45, 0·83	0·56, 1·07		

* *P* for trend. Adjustment on centre, age, smoking, alcohol consumption, physical activity, education level, employment status, systolic blood pressure, total cholesterol, HDL-cholesterol, BMI, treatment for hypertension, diabetes or dyslipidaemia.
† Interaction between frequency of consumption and country.

France are less protective, an assumption which lacks plausibility. Secondly, it is possible that the beneficial effect of fruit is limited to countries with unhealthy dietary habits, and is less pronounced in countries where diets are healthier. Unhealthy dietary patterns are associated with unfavourable risk factor profiles that may be partly corrected by fruit consumption. In agreement with this hypothesis, men in Northern Ireland consumed more fats and saturated fatty acids than French men (Evans *et al.* 1995; Kelleher *et al.* 2002), had a poorer cardiovascular risk profile (Yarnell, 1998) and low levels of plasma vitamins (Evans *et al.* 1995). Therefore the substitution of food items with fruit and vegetables could theoretically be favourable in Northern Ireland and neutral in France, explaining the lack of a significant relationship in France. Moreover, if part of the protective effect of fruits depends on their vitamin content, it is likely that men in Northern Ireland will benefit more from the consumption of fruit than men in France. Lastly, this result might possibly be related to a residual effect of unmeasured confounders which could be more pronounced in Northern Ireland than in France. Since fruit availability is less important and fruit retail prices are higher in Northern Ireland than in France, the frequent consumption of fruit might reflect a great interest for healthy behaviours in Northern Ireland resulting in fewer cardiovascular events.

In the PRIME study there was no significant relationship between cardiovascular risk and vegetable intake. Similarly, in Southern Europe, case–control studies have found favourable relationships between the risk of MI and fruit but not with vegetable intake (Sasazuki, 2001; Martinez-Gonzalez *et al.* 2002; Negri *et al.* 2003). In contrast, Joshipura *et al.* (2001) and Pietinen *et al.* (1996) reported lower coronary risk among vegetable consumers in the USA and Finland, respectively. However, the relatively limited number of events in the present study, in particular in the analysis by country, does not allow us to rule out modest associations between vegetable consumption and coronary risk. Finally, the relationship between fruit and risk was limited to acute coronary events, but not

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angina – and total events –, suggesting a specific effect of fruits on acute events. However, an alternative hypothesis could be that angina and total events make up a heterogeneous group of events, with different pathophysiological background, which creates variability in the data resulting in non-significant results. Therefore, large numbers of events are necessary to confirm these findings.

The present study has a number of limitations. Firstly, the relatively low number of events limits the statistical power of the analyses and allows us to detect only major associations. Secondly, the food-frequency questionnaire is too simple a tool to quantitatively assess food intake. For instance, although a correlation between the frequency of fruit or vegetable consumption and the amount consumed daily is theoretically possible, an alternate possibility is that frequent consumers reduce their portion size. The latter hypothesis would tend to reduce the ability to find a significant effect, if any. Therefore, the results of the present study should be understood as an analysis of the relationship concerning the frequency, rather than with the amount, of fruit or vegetable intake. In this respect, Thompson *et al.* (2002) showed that questionnaires with a restricted number of items and without quantitative assessment of portion size do not affect the ability to rank subjects according to fruit or vegetable intake very much. Moreover, the correlation analysis between frequency of fruit or vegetable intake and plasma vitamin levels observed in the present study suggests that frequency of fruit and vegetable intake assessment was reasonably accurate. For instance, Bingham *et al.* (1997) found correlation values of 0·34, 0·31, 0·21 and 0·48 between vitamin intake assessed with a reference method and plasma α-carotene, β-carotene, β-cryptoxanthin and vitamin C respectively. In addition, food intake was assessed only at entry to the present study. Therefore, changes in dietary habit over time could have weakened the strength of the associations. However, Goldbohm *et al.* (1995) showed in a cohort of Dutch men aged 55 to 68 years that food habits were stable over 5 years, arguing in favour of stability in the dietary practices of men of this age. Lastly, since the food-frequency questionnaire had a limited number of items, it was not possible to adjust for other nutritional factors such as total energy intake, saturated and polyunsaturated fats. Therefore, part of the observed associations between fruit and/or vegetables might be explained by compensatory changes in other nutrients or food items.

In conclusion, the results of the PRIME study show a favourable relationship between the frequency of citrus fruit consumption and the risk of acute coronary events in France and Northern Ireland. In contrast, the association between the consumption of other fruit and risk was observed only in Northern Ireland. Altogether, the present results, together with earlier reports, support the concept that citrus fruit are cardioprotective in populations from Europe and North America. It also suggests that geographical or related influences might affect the relationship between fruit intake and CHD risk. Further studies comparing the possible protective effect of fruit and vegetable intake in Southern Europe are necessary to confirm these results.

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