European Heart Journal (2011) **32**, 1235–1243
doi:10.1093/eurheartj/ehq465

CLINICAL RESEARCH
Prevention and epidemiology

Fruit and vegetable intake and mortality from ischaemic heart disease: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study

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Received 4 September 2010; revised 5 October 2010; accepted 10 November 2010; online publish-ahead-of-print 18 January 2011

See page 1182 for the editorial comment on this article (doi:10.1093/eurheartj/ehq506)

Aims A higher intake of fruits and vegetables has been associated with a lower risk of ischaemic heart disease (IHD), but there is some uncertainty about the interpretation of this association. The objective was to assess the relation between fruit and vegetable intake and risk of mortality from IHD in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study.

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Methods and results After an average of 8.4 years of follow-up, there were 1636 deaths from IHD among 313 074 men and women without previous myocardial infarction or stroke from eight European countries. Participants consuming at least eight portions (80 g each) of fruits and vegetables a day had a 22% lower risk of fatal IHD [relative risk (RR) = 0.78, 95% confidence interval (CI): 0.65–0.95] compared with those consuming fewer than three portions a day. After calibration of fruit and vegetable intake to account for differences in dietary assessment between the participating centres, a one portion (80 g) increment in fruit and vegetable intake was associated with a 4% lower risk of fatal IHD (RR = 0.96, 95% CI: 0.92–1.00, *P* for trend = 0.033).

Conclusion Results from this large observational study suggest that a higher intake of fruits and vegetables is associated with a reduced risk of IHD mortality. Whether this association is causal and, if so, the biological mechanism(s) by which fruits and vegetables operate to lower IHD risks remains unclear.

Keywords Fruits • Vegetables • Coronary disease • Prospective cohort studies

Introduction

Results from observational studies have suggested that a high fruit and vegetable intake reduces the risk of coronary heart disease (CHD).[1–5] In 2003, the World Health Organization (WHO) concluded that there was convincing evidence that fruits and vegetables lower the risk of CHD and recommended an intake of 400–500 g/day—equivalent to five or six portions of about 80 g each.[6] Since then, the results from separate meta-analyses have shown that a higher intake of fruits and vegetables was associated with lower risks of CHD,[7–10] but the presence of considerable between-study heterogeneity has led to uncertainty in the interpretation of this association.[11]

For developing effective public health strategies, it is essential to clarify the possible relation between fruit and vegetable consumption with CHD mortality, so that dietary advice and government policies can target the most important factors for reducing the rate of this major cause of death. In this paper, findings on the relation between fruits and vegetables and risk of mortality from ischaemic heart disease (IHD) are reported using data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study.

Methods

Study participants

The methods of the EPIC study[12] and EPIC-Heart component[13] have been described previously. Briefly, 519 978 men and women were recruited by 23 collaborating centres in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK) between 1992 and 2000. Participants completed questionnaires on their diet, lifestyle, and medical history, and data were centralized at the International Agency for Research on Cancer (IARC) in Lyon, France. This study complies with the Declaration of Helsinki; ethical review boards of IARC and all local institutions where participants had been recruited gave approval for the study, and all participants gave written informed consent.

IHD mortality data were available for 501 089 participants after excluding participants who had missing non-dietary or dietary data, were in the lowest or highest 1% of the distribution of the ratio of reported total energy intake to energy requirement (to minimize the number of extreme under- or over-reporters), or had no follow-up. From the 501 089 participants, the French and Norwegian cohorts were excluded due to a small number of IHD deaths at the end of the available follow-up period (*n* = 33 and *n* = 13, resulting in 68 042 and 36 453 exclusions, respectively). To restrict the analysis to middle-aged people, participants were excluded if they were younger than 40 or 85 years or over at recruitment (*n* = 57 463). Participants with unknown smoking status (*n* = 7749), those who had a self-reported history of myocardial infarction (MI) or stroke at recruitment (*n* = 9727), and participants who did not answer either or both of the questions on prior MI or stroke (*n* = 8467) were also excluded, with the exception of participants recruited in Umeå (Sweden) who were part of a population-based intervention programme on the primary prevention of cardiovascular disease (CVD) and had no history of MI or stroke at baseline. Finally, 114 participants with erroneous data were excluded leaving a total of 313 074 participants, comprising 121 593 men and 191 481 women, the greater number of women partly reflecting the fact that some study centres (Naples in Italy and Utrecht in the Netherlands) recruited women only.

Baseline dietary and lifestyle questionnaires

Dietary intake during the year before enrolment was measured by country-specific food questionnaires, which have been described elsewhere.[12] In order to improve the comparability of dietary data across the participating centres, dietary intakes from the questionnaires were calibrated using a 24 h diet recall method common to all centres; these data were collected from an 8% stratified random sample of the whole EPIC cohort and were available for 26 475 men and women in the current analysis. For the countries included in this analysis, the second dietary measurement was administered via a face-to-face interview using a computerized 24 h diet recall method.[14,15] The groupings for vegetables and fruits were based on the food classification used for EPIC that has been described elsewhere[16] and was updated in January 2009. The grouping for vegetables did not include potatoes or dried beans due to the different carbohydrate and energy compositions of these plant foods. In accordance with the popular perception, the grouping for total fruit included fresh fruit only; nuts and seeds, mixed fruits (comprising partly fresh and partly canned fruits), and olives were not included.

Assessments of the non-dietary variables were based on answers in the baseline questionnaire and categorized into the following groups: smoking (never, former, current <10 or unknown number of cigarettes per day, current 10–19 cigarettes per day, current ≥20 cigarettes per day), alcohol intake (<1, 1–7, 8–19, ≥20 g/day), physical activity (based on quartiles of the combined occupational physical activity and cycling/other physical exercise and characterized as inactive, moderately inactive, moderately active, active, unknown),[17] marital status (married/cohabiting or not married/cohabiting, unknown), highest education level (some secondary school, higher secondary/technical school, university degree, unknown), current employment (yes, no, unknown), hypertension (yes, no, unknown), angina pectoris (yes, no, unknown), and diabetes mellitus (yes, no, unknown). In most centres, height and weight were measured according to standard techniques except for the 'health-conscious' participants who were recruited by postal methods in the Oxford (UK) centre and self-reported their height and weight[18] from which body mass index [BMI; weight (kg)/height (m^2)] was calculated (<20, 20–22.4, 22.5–24.9, 25–27.4, 27.5–29.9, 30–32.4, 32.5–34.9, and ≥35 kg/m^2 and unknown). Not all centres had asked questions pertaining to the presence of certain IHD risk factors in the central database; for example, there was no information on history of hypertension for participants in Utrecht (the Netherlands) and Malmö (Sweden), nor was any information collected on the presence of angina in Heidelberg (Germany) or in the centres in the Netherlands or Sweden. The majority of the participants in this analysis had systolic ($n = 249\,664$) and diastolic ($n = 249\,659$) blood pressures measured at recruitment.[19] Missing values were assigned to separate strata for each variable where applicable, as listed earlier.

Case ascertainment

Information on vital status was collected from mortality registries at the regional or national level in most centres except in Germany and Greece where vital status was ascertained by active follow-up of study participants and next-of-kin. IHD as the cause of death was defined as codes 410–414 of the International Classification of Diseases Ninth Edition (ICD-9) and codes I20–I25 of the Tenth Edition (ICD-10). The last year of record linkage varied between centres and ranged between 2003 and 2006.

Statistical analysis

Follow-up was analysed from recruitment until the date of death from IHD or censoring at the date of death from other causes, emigration, other loss to follow-up, or the date at which follow-up was considered complete in each centre. Hazard ratios as estimates of the relative risks (RRs) for death from IHD and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards regression using age as the underlying time variable. All analyses are stratified by sex and centre and adjusted for smoking, alcohol intake, BMI, physical activity, marital status, highest education level, current employment, hypertension, angina pectoris, diabetes mellitus, and total energy intake (kcal/day) (base model). Analyses were repeated further adjusting for cereal fibre (g/day) and saturated fat intake (% of total energy).

The dietary factors examined in this study were total intake of fruits, total intake of vegetables, and total intake of fruits and vegetables combined. Fruit and vegetable intake was calculated in grams/day and divided by 80 to create an estimate of the number of standard portions of fruits and vegetables consumed per day, which were analysed as a categorical variable (<3, 3–4, 5–7, ≥8 servings per day) and as a continuous variable. To account for systematic and random errors in the measurement of dietary intakes between the centres, the dietary data were calibrated using a multivariable linear calibration model in which fruit and vegetable intakes obtained from the 24 h recall were regressed on that from the main dietary questionnaire for the calibration study participants (see Ferrari *et al.*[20] for more details). The calibration model was used to compute individual predicted values for fruit and vegetable intake separately and combined. Cox regression models were run by using the predicted (calibrated) values of fruit and vegetable intake on a continuous scale. The association between fruit and vegetable intake and the RR of IHD mortality was also investigated after excluding the entire first 2 years of follow-up (271 IHD deaths excluded).

Heterogeneity in the association between the calibrated intake of fruits and vegetables and the RR of fatal IHD by sex, age (<60 and ≥60 years), smoking status (never, past, current), and country was assessed by adding appropriate interaction terms to the regression models and testing for statistical significance using a likelihood ratio test. All analyses were performed using Stata version 9.0 (Stata Corporation, College Station, TX, USA), all tests of significance were two-sided, and a *P*-value less than 0.05 was considered statistically significant.

Results

After an average of 8.4 years of follow-up (SD 2.1 years, range 3 days to 13.2 years; 2 639 257 person-years in total), there were 1636 deaths from IHD among the 313 074 participants included in this analysis. The numbers of participants, person-years of follow-up, and IHD deaths according to sex and country are shown in *Table 1*. For both men and women, the mean age at recruitment was 54 years, and the mean calibrated intake of fruits and vegetables was almost 5 servings per day (median 4.6 and inter-quartile range 3.4–5.9 servings per day), but only three (Greece, Italy, and Spain) of the eight countries had a mean intake greater than 5 servings per day. The mean calibrated intakes were lowest among men and women from Sweden (2.9 and 3.5 servings per day, respectively) and highest among participants in the Italian and Spanish cohorts (greater than 6 servings per day).

The results in *Table 2* show the associations between total fruit and vegetable consumption, as estimated from the dietary questionnaires, and a range of the participant baseline characteristics. Participants consuming the greatest quantity of fruits and vegetables (at least 8 servings per day) were slightly older, had a higher BMI and a greater intake of total energy but had lower systolic and diastolic blood pressures and a lower consumption of alcohol, cereal fibre, and saturated fat compared with those consuming fewer than 3 servings per day. Across the categories of increasing fruit and vegetable intake, the proportion of participants who were never smokers increased considerably and the proportion who smoked more than 10 cigarettes per day decreased by more than half. A lower proportion of participants who consumed at least eight portions of fruits and vegetables per day reported being moderately active or active and had self-reported angina or hypertension, whereas a higher proportion were married or cohabiting and had self-reported diabetes at recruitment compared with those consuming fewer than 3 servings of fruits and vegetables per day.

The association between fruit and vegetable intake and the RR of fatal IHD for all participants is shown in *Table 3*. In the base model, there was a significant association between fruit and vegetable intake and risk of fatal IHD; participants consuming at least eight portions of fruits and vegetables a day had a 22%

Table 1 Characteristics of participants by country in the European Prospective Investigation into Cancer and Nutrition-Heart study

Country	Cohort numbers		Follow-up time (years)		Person-years		Number of IHD deaths		Age at recruitment (years)		Fruit and vegetable intake (portions/day)[a]	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Denmark	24 778	28 281	5.7	5.8	141 692	163 868	106	25	56.0	56.2	3.5	4.2
Germany	21 116	23 217	8.3	8.3	174 917	193 462	136	29	52.0	51.8	4.3	4.9
Greece	7737	12 022	7.1	7.3	54 583	87 913	107	68	56.2	56.8	6.4	5.4
Italy	12 653	27 685	8.3	9.0	105 184	248 825	39	19	50.8	51.8	7.5	6.3
The Netherlands	5830	22 163	9.9	9.4	57 636	208 899	47	59	50.0	54.9	3.6	4.0
Spain	14 727	20 106	10.5	10.1	154 959	202 886	98	24	50.5	50.6	7.1	6.7
Sweden	17 487	24 165	9.1	9.1	159 758	220 999	287	96	54.4	54.2	2.9	3.5
UK	17 265	33 842	9.0	9.1	155 327	308 348	329	167	56.9	54.9	4.1	4.8
Overall	121 593	191 481	8.3	8.5	1 004 056	1 635 201	1149	487	53.7	53.8	4.7	4.9

Values are reported as means, except where indicated otherwise.
IHD, ischaemic heart disease.
[a]Intake calculated from the calibrated dietary information.

lower RR of fatal IHD (RR = 0.78, 95% CI: 0.65–0.95) compared with those consuming fewer than three portions a day. Adjusting for the intake of saturated fat and cereal fibre lead to a very small change in this risk (RR = 0.76, 95% CI: 0.62–0.93). Each portion of fruits and vegetables (80 g) consumed per day (uncalibrated) was associated with an RR of fatal IHD of 0.97 (95% CI: 0.95–0.99), and after accounting for both systematic and random measurement errors in dietary assessment using regression calibration, a one portion increment in fruit and vegetable intake was associated with a 4% lower risk of IHD mortality (RR = 0.96, 95% CI: 0.92–1.00). After adjusting for cereal fibre and saturated fat intake, each portion increase in fruit and vegetable intake was associated with a 5% reduction in the risk of fatal IHD (RR = 0.95, 95% CI: 0.91–0.99). In analyses examining the calibrated intake of fruits and vegetables separately, there were non-significant inverse associations with the RR of IHD mortality (RR = 0.96, 95% CI: 0.91–1.00, P for trend = 0.071 and RR = 0.90, 95% CI: 0.79–1.02, P for trend = 0.098, respectively). Adjusting for cereal fibre and saturated fat intake led to small changes in these RRs, and the inverse association between fruit intake and IHD mortality became statistically significant (RR = 0.95, 95% CI: 0.91–1.00, P for trend = 0.047).

After omitting the first 2 years of follow-up, the RR of fatal IHD (using the base model) was 0.94 (95% CI: 0.90–0.99) for each portion of fruits and vegetables consumed (calibrated intake, data not shown). The association between fruit and vegetable intake and risk of fatal IHD was also examined among participants who had a measurement of systolic blood pressure (n = 249 664); a one portion increase in the calibrated intake of fruits and vegetables was associated with a reduction in the risk of fatal IHD of 4% (using the base model without adjusting for hypertension), but this was not statistically significant (RR = 0.96, 95% CI: 0.91–1.01). Adjusting for systolic blood pressure made very little difference to the association between fruit and vegetable intake and the risk of fatal IHD (RR = 0.97, 95% CI: 0.92–1.02, data not shown).

Results in *Table 4* show significant heterogeneity in the association of combined fruit and vegetable intake with the RR of IHD death by sex (P for heterogeneity = 0.007); each 80 g increase in intake was associated with a significant reduction in the risk of IHD mortality of 15% for women (RR = 0.85, 95% CI: 0.77–0.94), but the RR reduction for men was smaller (2%) and not statistically significant (RR = 0.98, 95% CI: 0.94–1.02). There was no significant heterogeneity in the association between the calibrated intake of fruits and vegetables and the RR of IHD mortality by age (P = 0.481), smoking (P = 0.264), or country (P = 0.097).

Discussion

The results from this study involving over 300 000 participants with 1636 IHD deaths have shown that each portion increment in the consumption of fruits and vegetables was associated with a 4% lower risk of dying from IHD after controlling for established risk factors and 5% lower risk after the additional adjustment for other dietary variables hypothesized to be related to the risk of IHD. Excluding participants who died from IHD in the first 2 years of follow-up did not alter the association between fruit

Table 2 Selected baseline characteristics by category of fruit and vegetable consumption

Characteristic	Number of observations[a]	Whole cohort	Males	Females	Fruit and vegetable intake, portions per day[b]			
					<3	3–4	5–7	≥8
Fruits and vegetables (portions/day)[b]	313 074	5.4 (3.4)	5.0 (3.4)	5.8 (3.3)	2.1 (0.7)	4.0 (0.6)	6.3 (0.8)	11.0 (3.1)
Number of participants	313 074	313 074	121 593	191 481	77 034	90 943	87 530	57 567
Number of IHD deaths	1636	1636	1149	487	506	465	396	269
Age (years)	313 074	53.8 (8.0)	53.7 (8.0)	53.8 (8.0)	53.1 (7.6)	54.0 (7.7)	54.2 (8.1)	53.8 (8.6)
Body mass index (kg/m^2)	311 558	26.4 (4.2)	26.8 (3.6)	26.2 (4.6)	26.1 (4.0)	26.1 (4.1)	26.4 (4.3)	27.2 (4.6)
Systolic blood pressure (mmHg)	249 664	133.8 (19.7)	136.5 (18.6)	132.1 (20.2)	134.6 (19.8)	134.0 (19.7)	133.7 (19.6)	132.3 (19.6)
Diastolic blood pressure (mmHg)	249 659	82.3 (10.7)	84.4 (10.6)	80.9 (10.5)	83.1 (10.8)	82.3 (10.7)	81.9 (10.6)	81.5 (10.5)
Total energy (kcal/day)	313 074	2098 (626)	2408 (656)	1901 (518)	1975 (613)	2060 (605)	2121 (614)	2287 (646)
Alcohol (g/day)	313 074	13.4 (18.6)	21.8 (23.8)	8.2 (11.7)	16.7 (21.9)	13.9 (18.1)	11.9 (16.6)	10.7 (16.8)
Cereal fibre intake (g/day)	313 074	9.1 (5.1)	10.5 (5.6)	8.1 (4.5)	9.2 (5.0)	9.4 (5.2)	9.0 (5.2)	8.4 (4.9)
Saturated fat intake (% total energy)	313 074	13.2 (3.3)	13.1 (3.4)	13.3 (3.2)	14.6 (3.4)	13.7 (3.1)	12.6 (3.0)	11.5 (2.9)
Smoking status	313 074							
Never smoker (%)	146 251	46.7	31.7	56.3	37.4	45.4	51.1	54.7
Former smoker (%)	91 378	29.2	38.4	23.3	28.8	30.6	29.5	27.0
Current smoker <10 cigarettes/day (%)	25 157	8.0	10.6	6.4	8.8	8.5	7.7	6.9
Current smoker 10–19 cigarettes/day (%)	24 626	7.9	7.4	8.1	11.4	8.4	6.3	4.7
Current smoker ≥20 cigarettes/day (%)	25 662	8.2	11.9	5.9	13.7	7.2	5.4	6.6
Moderately active or active (%)	291 713	42.6	49.5	38.3	44.6	44.9	41.4	38.6
Educated to a university degree level (%)	301 531	21.3	26.4	18.1	21.0	23.0	21.1	19.4
Married or cohabiting (%)	223 114	78.5	84.1	75.4	76.3	78.1	78.9	81.7
Diabetes (%)	310 512	3.1	3.7	2.7	2.3	2.7	3.4	4.1
Angina (%)	219 267	2.2	2.6	1.9	2.5	2.3	2.1	2.0
Hypertension (%)	265 986	22.1	21.9	22.3	23.6	22.5	21.1	21.2

Values are mean (SD) except where indicated otherwise.
IHD, ischaemic heart disease.
[a]Known observations for the characteristic variable, i.e. for physical activity.
[b]As assessed by food questionnaires (i.e. observed intake).

and vegetable intake and risk of fatal IHD, reducing the possibility of reverse causality.

The RR after calibration of the food intake data and additional adjustment for dietary variables was 0.95 per portion of fruits and vegetables consumed per day. A larger association was estimated in a report by the WHO, in which a meta-analysis of four prospective studies produced an estimated RR for IHD of 0.90 for an increment of one portion of fruits and vegetables per day,[7,8] but the results from a larger meta-analysis of nine prospective studies showed an overall RR for CHD of 0.96 for each additional portion of fruits and vegetables per day.[9] Some of the differences between these two meta-analyses in part reflect the studies included by the review teams. They may also reflect the differences in the endpoints used within the studies; some studies used incident CVD, whereas others, including the current study, used IHD mortality, and this heterogeneity in the outcome definition could be responsible for the differences in results. For example, it was reported that the association with vegetable intake was stronger for studies that used mortality as an endpoint compared with non-fatal disease.[9] Despite the finding of an inverse association between fruit and vegetable intake and IHD in this and other observational studies, in the Women's Health Initiative, a randomized controlled trial, a small increase in the consumption of fruits and vegetables of approximately 1 serving per day had no significant effect on the risk of incident or fatal IHD.[21]

The possible protective effect of fruit and vegetable intake on IHD mortality might be mediated through well-established IHD risk factors. Results from randomized controlled trials have shown that increased consumption of fruits and vegetables has a negligible

Table 3 **Prospective association between fruit and vegetable intake and risk of fatal ischaemic heart disease**

Fruit and vegetable intake	**Portions/day**[a]				**Per 80 g/day**			
	<3	**3–4**	**5–7**	**≥8**	**Uncalibrated**[a]	***P*-value**	**Calibrated**	***P*-value**
Number of IHD deaths	506	465	396	269	1636		1636	
Base model[b]	1	0.90 (0.79–1.03)	0.79 (0.68–0.92)	0.78 (0.65–0.95)	0.97 (0.95–0.99)	0.010	0.96 (0.92–1.00)	0.033
Further adjusted for cereal fibre and saturated fat intake	1	0.90 (0.78–1.02)	0.78 (0.67–0.91)	0.76 (0.62–0.93)	0.97 (0.95–0.99)	0.005	0.95 (0.91–0.99)	0.018
Fruit intake	Portions/day				Per 80 g/day			
	<1.5	1.5–2.4	2.5–3.9	≥4	Uncalibrated	*P*-value	Calibrated	*P*-value
Number of IHD deaths	613	382	337	304	1636		1636	
Base model	1	0.90 (0.79–1.02)	0.78 (0.68–0.91)	0.80 (0.69–0.94)	0.96 (0.94–0.99)	0.010	0.96 (0.91–1.00)	0.071
Further adjusted for cereal fibre and saturated fat intake	1	0.89 (0.78–1.02)	0.78 (0.67–0.90)	0.79 (0.67–0.92)	0.96 (0.93–0.99)	0.005	0.95 (0.91–1.00)	0.047
Vegetable intake	Portions/day				Per 80 g/day			
	<1.5	1.5–2.4	2.5–3.9	≥4	Uncalibrated	*P*-value	Calibrated	*P*-value
Number of IHD deaths	566	414	355	301	1636		1636	
Base model	1	0.95 (0.83–1.08)	0.95 (0.81–1.11)	0.93 (0.77–1.12)	0.98 (0.94–1.01)	0.213	0.90 (0.79–1.02)	0.098
Further adjusted for cereal fibre and saturated fat intake	1	0.95 (0.83–1.08)	0.95 (0.81–1.11)	0.92 (0.76–1.12)	0.97 (0.94–1.01)	0.165	0.89 (0.78–1.01)	0.074

Values are relative risk and 95% confidence intervals unless indicated otherwise.
IHD, ischaemic heart disease.
[a]As assessed by food questionnaires (i.e. observed intake).
[b]The base model is stratified by sex and centre and adjusted for smoking, alcohol intake, BMI, physical activity, marital status, highest education level, current employment, hypertension, angina pectoris, diabetes mellitus, and total energy intake.

Table 4 Association between the calibrated intake of fruits and vegetables and risk of fatal ischaemic heart disease according to various subgroups

	Number of IHD deaths	Total fruit and vegetable intake (per 80 g/day)		
		RR (95% CI)[a]	χ^2-value	*P*-value for heterogeneity
Sex				
Men	1149	0.98 (0.94, 1.02)	7.17	0.007
Women	487	0.85 (0.77, 0.94)		
Age at recruitment (years)				
<60	618	0.97 (0.92, 1.02)	0.50	0.481
≥60	1018	0.94 (0.90, 1.00)		
Smoking				
Never	473	0.92 (0.87, 0.99)		
Former	549	0.98 (0.93, 1.04)	2.66	0.264
Current	614	0.95 (0.90, 1.00)		
Country				
Denmark	131	0.99 (0.87–1.11)		
Germany	165	0.93 (0.80–1.08)		
Greece	175	0.84 (0.71–0.99)		
Italy	58	1.00 (0.84–1.19)	12.10	0.097
The Netherlands	106	1.04 (0.89–1.23)		
Spain	122	0.95 (0.87–1.03)		
Sweden	383	0.82 (0.73–0.94)		
UK	496	1.01 (0.94–1.08)		

[a]Stratified by sex and centre and adjusted for smoking, alcohol intake, BMI, physical activity, marital status, highest education level, current employment, hypertension, angina pectoris, diabetes mellitus, and total energy intake where appropriate.

impact on the concentrations of plasma cholesterol fractions,[22,23] even though a higher intake of fruits and vegetables has been associated with lower concentrations of plasma low-density lipoprotein cholesterol in observational studies.[24,25] Increased consumption of fruits and vegetables does lead to a small decrease in blood pressure in large randomized controlled trials,[22,26] perhaps due to an increase in the intake of potassium,[27] magnesium,[28] or some other component in fruits and vegetables,[29] or alternatively a reduced intake of sodium. Nevertheless, adjusting for systolic blood pressure in the current study made very little difference to the association between fruit and vegetable intake and the risk of IHD. There is a long-standing hypothesis that various antioxidant micronutrients present in fruits and vegetables lower the risk of heart disease by reducing the degree of atherosclerosis caused by oxidative damage,[30] but this has not been supported by results from large randomized controlled trials of several antioxidant micronutrients.[31,32] It is, however, worth noting that consuming antioxidant supplements is not the same as increasing the consumption of fruits and vegetables because there are many other components in fruits and vegetables that may confer a cardioprotective effect.[33,34]

The main advantages of the current study are the prospective design and using a European-wide sample with large dietary heterogeneity. Additionally, the availability of a large set of known IHD risk factors allowed analyses to be appropriately adjusted, thus minimizing the impact of confounding. Residual confounding by smoking remains a possibility, although the association between fruit and vegetable intake and risk of fatal IHD did not differ between the subgroups of never, former, and current smokers. The finding of a significant association between fruit and vegetable intake and the risk of fatal IHD in women but not men has been reported in one other study, a finding which the authors attributed to higher rates of smoking among men.[35] There is no suggestion of a difference in the association between risk factors such as serum total cholesterol or blood pressure and risk of vascular mortality between men and women,[36] but whether there is a true differential effect in the association between fruit and vegetable intake and risk of IHD mortality between men and women could be clarified in future pooling studies.

This study has some limitations. At present, there are no lipid or apolipoprotein measurements available for the majority of the EPIC cohort, and so results could not be adjusted for these IHD risk factors.[37] It is also possible that a higher fruit and vegetable intake is a marker of healthy eating habits or lifestyle variables associated with a lower risk of fatal IHD. Adjusting for energy, cereal fibre, and saturated fat intakes (none of which made an appreciable difference to the hazard ratios) allowed for the effects of other major dietary factors, although it is difficult to separate the effects of often highly correlated dietary variables in analyses of this nature. These results are also limited by error in the measurement of fruit and vegetable intake and other confounding variables. In an attempt to overcome the problems created by dietary measurement errors of fruit and vegetable intake, data from 24 h recall measurements were used to calibrate the intake data from the dietary questionnaires. However, such calibration methods are not perfect; errors in measurement using the reference method (the 24 h recall) and the dietary questionnaire are assumed to be independent but, in practice, there is some correlation between the measurement errors[38] and this correlation between the measurement errors would lead to an underestimation of the attenuation factor and bias the estimated calibrated RR towards the null. This would suggest that the true association between the intake of fruits and vegetables and IHD mortality may be higher than that reported in the current study. It is also important to note that this study population had a relatively high intake of fruits and vegetables and was made up of a high proportion of women, thus might not be representative of the wider European population. Furthermore, because the French and Norwegian cohorts were excluded due to the small number of IHD deaths in the available follow-up period, the present study sample is not entirely representative of the wider EPIC cohort.

In summary, the results of the current study show that a higher consumption of fruits and vegetables is associated with a reduced risk of fatal IHD in this European population. Whether this association is causal and, if so, the biological mechanism(s) by which fruits and vegetables operate to lower IHD risk remains unclear.

Acknowledgements

We thank all the participants in EPIC for their invaluable contribution to the study, as well as Bertrand Hémon and colleagues at IARC for their expertise in data handling.

Funding

The work described in this article was carried out with the financial support of the Europe Against Cancer Program of the European Commission (SANCO); Deutsche Krebshilfe; Deutsches Krebsforschungszentrum; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; Spanish Regional Governments of Andalucia and Asturias; Basque Country, Murcia, and Navarra; The ISCIII Network RCESP (C03/09) (Spain); Cancer Research UK; Medical Research Council (UK); Stroke Association (UK); British Heart Foundation; Department of Health (UK); Food Standards Agency (UK); Welcome Trust (UK); Italian Association for Research on Cancer (AIRC); Compagnia di San Paolo (Italy); Dutch Ministry of Public Health, Welfare, and Sports; World Cancer Research Fund; Norwegian Cancer Society; Research Council of Norway; French League Against Cancer (LNCC); National Institute for Health and Medical Research (INSERM) (France); Mutuelle Généralede l'Education Nationale (MGEN) (France); 3MCompany, France; Greek Ministry of Health and Social Solidarity; Hellenic Health Foundation and Stavros Niarchos Foundation; Swedish Cancer Society; Swedish Research Council; the Regional Government of Skåne; Swedish Heart and Lung Foundation; and the Västerbotten County Council. This research was conducted during the tenure of a Girdlers' New Zealand Health Research Council Fellowship.

Conflict of interest: none declared.

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