Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study[1–3]

Francesca L Crowe, Paul N Appleby, Ruth C Travis, and Timothy J Key

ABSTRACT

Background: Few previous prospective studies have examined differences in incident ischemic heart disease (IHD) risk between vegetarians and nonvegetarians.

Objective: The objective was to examine the association of a vegetarian diet with risk of incident (nonfatal and fatal) IHD.

Design: A total of 44,561 men and women living in England and Scotland who were enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Oxford study, of whom 34% consumed a vegetarian diet at baseline, were part of the analysis. Incident cases of IHD were identified through linkage with hospital records and death certificates. Serum lipids and blood pressure measurements were available for 1519 noncases, who were matched to IHD cases by sex and age. IHD risk by vegetarian status was estimated by using multivariate Cox proportional hazards models.

Results: After an average follow-up of 11.6 y, there were 1235 IHD cases (1066 hospital admissions and 169 deaths). Compared with nonvegetarians, vegetarians had a lower mean BMI [in kg/m^2; −1.2 (95% CI: −1.3, −1.1)], non-HDL-cholesterol concentration [−0.45 (95% CI: −0.60, −0.30) mmol/L], and systolic blood pressure [−3.3 (95% CI: −5.9, −0.7) mm Hg]. Vegetarians had a 32% lower risk (HR: 0.68; 95% CI: 0.58, 0.81) of IHD than did nonvegetarians, which was only slightly attenuated after adjustment for BMI and did not differ materially by sex, age, BMI, smoking, or the presence of IHD risk factors.

Conclusion: Consuming a vegetarian diet was associated with lower IHD risk, a finding that is probably mediated by differences in non-HDL cholesterol, and systolic blood pressure. *Am J Clin Nutr* 2013;97:597–603.

INTRODUCTION

Compared with individuals consuming a nonvegetarian diet (ie, those who eat meat and/or fish), studies have shown that, generally, white vegetarians residing in Western countries have a lower BMI and a higher ratio of polyunsaturated to saturated fat intake (1, 2). Previous studies have shown that vegetarians have lower serum LDL-cholesterol concentrations (3–5), lower blood pressures (6–9), and a lower risk of diabetes than do nonvegetarians (10). As a result of these differences, the risk of developing cardiovascular disease in vegetarians would be expected to be lower. Several studies have investigated the effect of a vegetarian diet on the risk of fatal ischemic heart disease (IHD)[4]. The results from a collaborative analysis of 5 prospective studies showed a 24% lower risk of IHD mortality among vegetarians (11). A more recent analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC)–Oxford cohort also showed a 17% lower risk (albeit nonsignificant) of fatal IHD in vegetarians than in nonvegetarians (12). Few prospective studies have assessed whether rates of incident IHD (ie, both nonfatal and fatal) are lower in vegetarians than in nonvegetarians (13).

The objective of this study was to examine the incidence of IHD in a cohort of British vegetarians and nonvegetarians and to assess whether any associations are mediated through established IHD risk factors, such as serum lipid concentrations and blood pressure.

SUBJECTS AND METHODS

Study population

The EPIC-Oxford study aimed to recruit participants with a wide range of diets and targeted vegetarians and vegans as well as the UK general population. Between 1993 and 1999, 57,446 men and women aged ≥20 were recruited to take part in the EPIC-Oxford cohort and completed a baseline questionnaire (1). Participants were recruited through general practices in Oxfordshire, Buckinghamshire, and Greater Manchester and by postal methods that aimed to recruit health-conscious people living throughout the United Kingdom. Participants were excluded from the analysis if they were older than 90 y at recruitment (n = 56), had no follow-up (n = 711), had a prevalent registered (n = 1370) or self-reported (n = 612) malignant cancer, were of unknown smoking category (n = 295) or un-

[1] From the Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom.

[2] Supported by Cancer Research UK and the UK Medical Research Council.

[3] Address correspondence to FL Crowe, Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, Richard Doll Building, University of Oxford, Roosevelt Drive, Oxford OX3 7LF, UK. E-mail: francesca.crowe@ceu.ox.ac.uk.

[4] Abbreviations used: EPIC, European Prospective Investigation into Cancer and Nutrition; HES, Hospital Episode Statistics; ICD, International Classification of Diseases; IHD, ischemic heart disease; MI, myocardial infarction; MINAP, Myocardial Ischemia National Audit Project; NHS, National Health Service; SMR, Scottish Morbidity Records.

Received June 2, 2012. Accepted for publication December 7, 2012.

First published online January 30, 2013; doi: 10.3945/ajcn.112.044073.

known diet group (n = 239), had unreliable nutrient data (n = 1128), or had a self-reported history of myocardial infarction (MI), stroke, or angina at baseline (n = 6341), which left a total of 46,694 participants available for this analysis.

The protocol was approved by a Multicenter Research Ethics Committee, and all participants provided written informed consent. IHD outcomes were ascertained by linking the participants' National Health Service (NHS) number—a unique personal identifier of NHS records—and other personal information, such as date of birth and information on NHS hospital admission databases [which include inpatient (ie, overnight) and day-case (ie, not overnight) admissions] from the Information Services Division of Scottish Morbidity Records (SMR) in Scotland (14) and from Hospital Episode Statistics (HES) in England (15). After the exclusion of 2128 participants whose nation of residence was Wales or Northern Ireland, linkage to hospital admissions was possible for 44,566 participants from SMR since 1 January 1981 to 31 December 2008 and from HES since 1 April 1997 to 31 March 2009. Five participants were excluded from the analysis because the date of diagnosis of IHD occurred before the date of recruitment, which left 44,561 participants. Record linkage with the UK NHS central register was used to follow participants for cause of death until 30 September 2009. The diagnostic codes used on SMR and HES records or the death certificates were coded by those agencies using the WHO International Classification of Diseases (ICD), 9th revision or, from 1 April 1996, 10th revision for diseases and medical conditions. The SMR records include up to 6 diagnostic codes, and the HES records include up to 7 diagnostic codes from April 1997 to April 2002, 14 diagnostic codes from April 2002 to April 2007, and thereafter up to 20 diagnostic codes per admission.

Assessment of diet and lifestyle variables

At recruitment, participants completed a validated semiquantitative food-frequency questionnaire that estimated the intake of 130 different food items over the past 12 mo (16, 17). Participants were asked whether they ate any meat, fish, eggs, or dairy products (1) and, for the current analysis, were categorized as nonvegetarians if they ate any meat or fish and as vegetarians if they did not eat meat and fish. Time of adherence to a vegetarian diet was calculated by subtracting the age at which the participant last ate meat or fish from the age at the time of recruitment.

Height and weight were measured or self-reported at baseline (18) and were used to calculate BMI [weight (kg)/[height (m)^2]. Cigarette smoking was categorized as never, former, light smoker (<15 cigarettes/d), or heavy smoker (≥15 cigarettes/d), and alcohol consumption was categorized as <1, 1–7, 8–15, or ≥16 g/d. Participants were categorized by their level of educational attainment (some secondary school, higher secondary school, or university degree or equivalent), and socioeconomic status was categorized by using quartiles of the Townsend Deprivation Index (19). Participants were asked about their time spent participating in activities such as walking, cycling, and other physical exercise and were characterized as inactive or active. Current use of oral contraceptives or hormone replacement therapy for menopause among women was categorized as yes or no. Participants were asked to report if they had received a diagnosis of hypertension, hyperlipidemia, or diabetes and whether they were undergoing treatment of any long-term health condition. An "unknown" category was added for each variable for which data were missing or incomplete.

Definition, ascertainment, and validation of IHD

The outcome examined in this analysis was IHD (ICD-9 410–414 and ICD-10 I20-25), which was defined as the earliest diagnosis of IHD from hospital record data (n = 1066) or inclusion as a cause of death or other underlying condition on the death certificate (n = 169). Participants with a diagnosis of IHD in their hospital discharge records were also linked by using their NHS number and date of birth to the Myocardial Ischemia National Audit Project (MINAP) data set, which includes more detailed information on clinical diagnostic criteria for IHD events (mainly MI) in defined areas in England (20). Clinical data were available from 1 January 2003 for participants who had been admitted to hospitals participating in MINAP. There were 127 participants with both a hospital diagnosis of IHD [n = 11 with I20 (angina pectoris), n = 101 with I21 (acute MI), n = 3 with I22 (subsequent MI), n = 12 with I25 (chronic IHD)], and MINAP data for the same event. Of the 127 cases with MINAP data, 120 (94%) had electrocardiographic recordings and troponin measurements (or other cardiac enzymes) indicative of a definite case of IHD (eg, ST elevation and positive for troponin). The diagnosis of IHD was probable for 2 (2%) of the cases (eg, troponin not stated), and 5 (4%) of the suspected IHD cases received some other non-IHD diagnosis.

Blood pressure and serum lipid measurements

At recruitment or shortly after, participants were invited to attend their local general practice surgeries, where a single blood pressure measurement and a blood sample were taken (participants were not required to fast). Blood samples were provided by 19,103 participants (21). Details of the blood pressure measurements were published elsewhere (7). Blood was transported overnight to a laboratory in Norfolk by mail at ambient temperature, where samples were centrifuged and serum was portioned into 0.5-mL plastic straws, which were heat-sealed at both ends and stored in liquid nitrogen (–196°C).

Serum concentrations of lipids and apolipoproteins were measured in a selection of 1546 noncases matched to IHD cases by sex and age. Systolic and diastolic blood pressure measurements were available for 1519 of these participants. Beckman Synchron CX autoanalyzers (Beckman Coulter) were used to measure apolipoproteins A-I and B by immunoturbidimetric assay, HDL cholesterol was measured directly, and total cholesterol was measured by enzymatic assay. Pooled serum samples (n = 196) were included in each run; CVs were 1.9% for total cholesterol, 1.9% for HDL cholesterol, 2.8% for apolipoprotein A-I, and 2.6% for apolipoprotein B.

Statistical analysis

Person-years were calculated from the latest of the beginning of recruitment or the beginning of hospital records until the date of first admission to the hospital for IHD, death from IHD, other death, emigration, or the end of follow-up, whichever occurred first. The exception was for 11 participants with a diagnosis of IHD who were aged ≥90 y who were censored on the day before they turned 90 y.

HRs for IHD and 95% CIs were calculated by using Cox proportional hazards regression, with age as the underlying time variable. All analyses were stratified by sex, method of recruitment, and region and were adjusted for smoking, alcohol intake, physical activity, educational level, and Townsend Deprivation Index and for use of oral contraceptives or hormone therapy for menopause in women. Results were further adjusted for BMI (in kg/m^2; <20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, ≥27.5, or unknown) in a sensitivity analysis. Risk factors such as hypertension, hyperlipidemia, and diabetes may be mediating factors through which vegetarianism affects the risk of IHD; therefore, the analyses were not adjusted for these variables. The test for a difference in the risk of IHD between vegetarians and nonvegetarians was assessed by using a likelihood ratio chi-square test.

In a sensitivity analysis, the effect of vegetarianism on IHD risk was examined after the first 2 y of follow-up were excluded. The effect of vegetarianism was also examined by using an alternative endpoint whereby IHD was the primary hospital diagnosis or the underlying cause of death. Heterogeneity in the association between vegetarianism and risk of IHD by sex, age at recruitment (<60 or ≥60 y), smoking status (never, former, or current), BMI (<25 or ≥25), and presence of IHD risk factors

TABLE 1

Characteristics of men and women participating in the EPIC-Oxford study, by vegetarian status[1]

	Men		Women	
	Nonvegetarians (*n* = 6831)	Vegetarians (*n* = 3771)	Nonvegetarians (*n* = 22,610)	Vegetarians (*n* = 11,349)
Age at recruitment (y)	49.5 ± 13.3[2]	41.8 ± 13.3	46.3 ± 13.2	38.4 ± 12.7
BMI (kg/m^2)	24.5 ± 3.3	23.3 ± 3.2	23.8 ± 3.9	22.6 ± 3.5
Alcohol consumption (g/d)	16.6 ± 18.2	14.1 ± 18.0	8.3 ± 9.9	7.7 ± 9.9
Smoking status [*n* (%)]				
Never	3476 (50.9)	2221 (58.9)	13,824 (61.1)	7337 (64.6)
Former	2328 (34.1)	1121 (29.7)	6362 (28.1)	2877 (25.4)
Light smoker, <15 cigarettes/d	664 (9.7)	282 (7.5)	1445 (6.4)	793 (7.0)
Heavy smoker, ≥15 cigarettes/d	363 (5.3)	147 (3.9)	979 (4.3)	342 (3.0)
Physical activity [*n* (%)][3]				
Inactive	1501 (23.9)	674 (19.4)	4886 (24.6)	2102 (20.7)
Active	4773 (76.1)	2809 (80.6)	14,982 (75.4)	8053 (79.3)
Level of educational attainment [*n* (%)][3]				
Some secondary	2051 (32.3)	951 (26.4)	8767 (41.7)	3472 (32.1)
Secondary	1381 (21.8)	846 (23.5)	5222 (24.8)	2917 (27.0)
Degree or equivalent	2914 (45.9)	1801 (50.1)	7035 (33.5)	4428 (40.9)
Townsend Deprivation Index [*n* (%)][3]				
Rich	1671 (27.8)	685 (20.6)	5124 (26.1)	2128 (21.5)
Less rich	1562 (26.0)	743 (22.4)	5173 (26.4)	2318 (23.4)
Less poor	1453 (24.2)	831 (25.0)	4834 (24.7)	2475 (25.0)
Poor	1318 (22.0)	1059 (31.9)	4475 (22.8)	2991 (30.2)
Self-reported diabetes [*n* (%)][3]	129 (1.9)	37 (1.0)	249 (1.1)	50 (0.4)
Prior hypertension [*n* (%)][3]	767 (11.3)	219 (5.8)	2413 (10.7)	644 (5.7)
Prior hyperlipidemia [*n* (%)][3]	562 (8.3)	100 (2.7)	1159 (5.2)	217 (1.9)
Receiving long-term medical treatment [*n* (%)][3]	1629 (24.1)	627 (16.7)	6098 (27.3)	2175 (19.4)
Use of exogenous hormones [*n* (%)][3,4]	—	—	18,261 (81.4)	9193 (81.7)
Time on vegetarian diet				
<5 y or unknown	—	1256 (33.3)	—	3907 (34.4)
≥5 y	—	2515 (66.7)	—	7442 (65.6)
Diet group at 5-y follow-up [*n* (%)][3]				
Nonvegetarian	4628 (97.2)	250 (10.6)	15,246 (97.4)	1169 (16.3)
Vegetarian	133 (2.8)	2103 (89.4)	407 (2.6)	6004 (83.7)
Intake of selected foods				
Meat (g/d)	64 (21–106)[5]	—	49 (9–87)	—
Fish (g/d)	33 (22–49)	—	34 (21–52)	—
Dairy milk (mL/d)	293 (146–439)	146 (0–439)	293 (146–439)	146 (50–293)
Dairy cheese (g/d)	15 (7–27)	19 (5–35)	19 (9–31)	23 (11–38)
Fresh fruit (g/d)	179 (101–289)	197 (113–328)	238 (146–363)	239 (139–379)
Vegetables (g/d)	206 (147–284)	246 (177–337)	243 (176–329)	267 (192–370)
Whole grains (g/d)	43 (14–109)	99 (38–173)	49 (18–102)	80 (31–132)
Peanuts or other nuts (g/d)	2.1 (0.3–4.2)	4.2 (2.1–12.9)	2.1 (0.3–4.2)	2.1 (0.3–4.2)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition.
[2] Mean ± SD (all such values).
[3] Unknown for some participants.
[4] Defined as oral contraceptives or hormone therapy for menopause; in women only.
[5] Median; IQR in parentheses (all such values).

(hypertension, hyperlipidemia, or diabetes) was assessed by adding appropriate interaction terms to the regression models and testing for statistical significance with the use of a likelihood ratio chi-square test.

All statistical analyses were performed by using Stata statistical software, release 12 (StataCorp). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

There were 1235 cases of IHD (1066 hospital diagnoses and 169 deaths) after a follow-up of 517,960 person-years (mean: 11.6 y). Most (98%) of the diagnoses were angina pectoris (*n* = 332; 27%), acute MI (*n* = 261; 21%), or chronic IHD (*n* = 619; 50%).

The characteristics of the 44,561 participants according to sex and vegetarian status are shown in **Table 1**. Thirty-four percent of the participants reported consuming a vegetarian diet, and 76% were women. Vegetarian participants were younger than nonvegetarians, and, on average, both alcohol consumption and BMI were highest among nonvegetarian men and lowest among vegetarian women. There was a low prevalence of smoking at baseline, ranging from 10% of vegetarian women to 15% of nonvegetarian men. In total, 11.7% of nonvegetarians and 10.3% of vegetarians were current smokers. The overall prevalence of self-reported IHD risk factors was low: 1% had diabetes, 9% had hypertension, and 5% had hyperlipidemia. More than 25% of the nonvegetarians reported receiving long-term medical treatment at recruitment compared with <20% of vegetarians. Two-thirds of the vegetarians had followed their diet for ≥5 y, and data from follow-up showed that most of the vegetarians (∼85%) were still consuming a vegetarian diet 5 y after recruitment. On average, vegetarians had a higher intake of dairy cheese, fruit, vegetables, and whole grains than did nonvegetarians and a lower intake of dairy milk.

The characteristics and serum lipid and apolipoprotein concentrations and systolic and diastolic blood pressures of selected vegetarians and nonvegetarians who provided a blood sample and were sex- and age-matched to IHD cases are shown in **Table 2**. Overall, both the nonvegetarians and the vegetarians in this subgroup were 10 y older at blood sampling, and a higher proportion of the participants were men than in the whole cohort. However, the differences in characteristics between vegetarians and nonvegetarians in this subgroup were similar to those for the whole cohort; compared with nonvegetarians, vegetarians were slightly younger, had a lower BMI, had a lower intake of alcohol, and were less likely to be current smokers. After adjustment for sex and age, serum concentrations of total cholesterol, HDL cholesterol, and the ratio of total to HDL cholesterol were all significantly lower in vegetarians than in nonvegetarians. Non-HDL cholesterol concentrations were 0.45 (95% CI: 0.30, 0.60) mmol/L lower in vegetarians than in nonvegetarians. Apolipoprotein B and the ratio of apolipoprotein B to A-I were both lower in vegetarians, whereas no significant difference in apolipoprotein A-I concentrations was

TABLE 2
Characteristics of vegetarians and nonvegetarians in a subgroup of EPIC-Oxford study participants who provided a blood sample[1]

Characteristic	Nonvegetarians (*n* = 1316)	Vegetarians (*n* = 230)	P^2
Women [*n* (%)]	608 (46.2)	121 (52.6)	0.07
Age at blood sampling (y)	59.4 ± 8.7[3]	57.7 ± 10.5	0.009
BMI (kg/m^2)[4]	24.9 ± 3.7	23.4 ± 3.5	<0.0001
Alcohol consumption (g/d)	10.7 (13.6)	8.6 (13.9)	0.03
Smoking status [*n* (%)]			0.03
Never	686 (52.1)	125 (54.3)	
Former	506 (38.4)	97 (42.2)	
Light smoker, <15 cigarettes/d	83 (6.3)	5 (2.2)	
Heavy smoker, ≥15 cigarettes/d	41 (3.1)	3 (1.3)	
Physical activity [*n* (%)][4]			0.51
Inactive	382 (32.4)	62 (30.1)	
Active	797 (67.6)	144 (69.9)	
IHD risk factor			
Serum total cholesterol (mmol/L)	5.76 (5.70, 5.81)[5]	5.26 (5.13, 5.39)	<0.001
Serum HDL cholesterol (mmol/L)	1.34 (1.32, 1.36)	1.29 (1.24, 1.33)	0.03
Serum total/HDL-cholesterol ratio	4.58 (4.51, 4.66)	4.39 (4.21, 4.56)	0.04
Serum non-HDL cholesterol (mmol/L)	4.42 (4.36, 4.47)	3.97 (3.84, 4.10)	<0.001
Serum apolipoprotein B (mg/dL)	108.3 (107.0, 109.6)	96.4 (93.3, 99.6)	<0.0001
Serum apolipoprotein A-I (mg/dL)	158.8 (157.5, 160.1)	156.8 (153.6, 159.9)	0.25
Serum apolipoprotein B/apolipoprotein A-I ratio	0.70 (0.69, 0.71)	0.63 (0.61, 0.66)	<0.001
Systolic blood pressure (mm Hg)[4]	134.0 (133.0, 134.9)	130.7 (128.4, 133.1)	0.01
Diastolic blood pressure (mm Hg)[4]	79.7 (79.2, 80.3)	79.1 (77.7, 80.5)	0.41

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; IHD, ischemic heart disease.
[2] The differences in characteristic variables between vegetarians and nonvegetarians were assessed by using a chi-square test for categorical variables and an unpaired *t* test for continuous variables.
[3] Mean ± SD (all such values).
[4] Unknown for some participants.
[5] Mean (95% CI) adjusted for sex and age (all such values).

found. Systolic blood pressure was lower in vegetarians by 3.3 (95% CI: 0.7, 5.9) mm Hg, but no significant difference in mean diastolic blood pressure was found between vegetarians and nonvegetarians.

Vegetarians had a 32% lower risk of IHD (HR: 0.68; 95% CI: 0.58, 0.81) than did nonvegetarians after adjustment for age, smoking, alcohol, physical activity, educational level, and Townsend Deprivation Index and use of oral contraceptives or hormone therapy for menopause in women (**Table 3**). On the basis of the absolute rates of hospitalization or death from IHD, the cumulative probability of IHD between ages 50 and 70 y was 6.8% for nonvegetarians compared with 4.6% for vegetarians. Both vegetarians who had adhered to their diet for >5 y (HR: 0.68; 95% CI: 0.56, 0.81) and all other vegetarians (HR: 0.70; 95% CI: 0.52, 0.95) had a lower risk of IHD than did nonvegetarians (data not shown in the table). Further adjustment for BMI led to a small attenuation of the RR; vegetarians had a 28% lower risk of IHD (HR: 0.72; 95% CI: 0.61, 0.85). In a sensitivity analysis that examined the association between vegetarian status and the risk of IHD after exclusion of the first 2 y of follow-up (1133 IHD cases included in the analysis), vegetarians had a 31% (95% CI: 18, 42%) lower risk of IHD than did nonvegetarians. In analyses in which cases were restricted to participants for whom IHD was the primary diagnosis or underlying cause of death (n = 938 cases, including 163 deaths), the risk of IHD for vegetarians compared with nonvegetarians was 28% lower (HR: 0.72; 95% CI: 0.60, 0.87).

The risk of IHD was 19–37% lower in vegetarians than in nonvegetarians in each of the subgroups shown in **Figure 1**. No evidence of heterogeneity was found in the association of vegetarian status and risk of IHD by sex, age at recruitment, BMI, smoking status, or the presence of IHD risk factors.

DISCUSSION

The results from this prospective analysis involving 15,000 vegetarians and 30,000 nonvegetarians with >1200 cases of IHD show that vegetarians in the United Kingdom have a 32% lower risk of developing IHD than do people who consume meat and/or fish. There was no evidence that the association between vegetarianism and IHD differed between smokers and nonsmokers, lean and overweight participants, or those with a low or a high risk of IHD at baseline.

TABLE 3
Risk of IHD in vegetarians compared with nonvegetarians in the EPIC-Oxford study[1]

	No. of cases	HR (95% CI)	P[2]
Overall[3]	1235	0.68 (0.58, 0.81)	<0.001
Further adjusted for BMI	1235	0.72 (0.61, 0.85)	<0.001
Sensitivity analysis[3]			
Excluding first 2 y of follow-up	1133	0.69 (0.58, 0.82)	<0.001
Primary diagnosis of IHD	938	0.72 (0.60, 0.87)	0.001

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; IHD, ischemic heart disease.

[2] The differences in risk of IHD between vegetarians and nonvegetarians were assessed by using a chi-square test.

[3] The analyses were stratified by sex, method of recruitment, and region of residence and were adjusted for age, smoking, alcohol, physical activity, educational level, and Townsend Deprivation Index and the use of oral contraceptives or hormone therapy for menopause in women.

Findings from a previous study showed that male vegetarians from the Adventist Health Study had a 54% lower risk of first definite fatal or nonfatal MI than did participants from the Stanford Five City Project after adjustment for age and education (13). However, because the analyses were not adjusted for smoking and because vegetarians were compared with a different study population (the Stanford Five City Project), it is possible that the lower risk among vegetarians was influenced by differences in confounding variables between the 2 study populations. The lower risk of fatal IHD among vegetarians was previously shown in a combined analysis of 5 prospective studies including 2264 fatal IHD events where, after adjustment for age, sex, and smoking status, vegetarians had a 24% lower risk of fatal IHD than did nonvegetarians (11). A similar result was found in a previous analysis of the EPIC-Oxford cohort when fatal IHD was used as the outcome, although this analysis was probably underpowered to detect a significant difference in the risk of fatal IHD between vegetarians and nonvegetarians (death rate ratio: 0.83; 95% CI: 0.59, 1.18) (12) because of the small number of IHD deaths (n = 213). The current study (which includes most of the 213 cases of fatal IHD from the earlier analysis and additional nonfatal cases) showed a highly significant 32% reduction in the risk of incident IHD in vegetarians than in nonvegetarians, which is of slightly greater magnitude than what was previously reported for the association between vegetarianism and fatal IHD.

The lower risk of IHD among individuals consuming a vegetarian diet can be largely explained through reduced levels of well-established risk factors for IHD, such as non-HDL-cholesterol concentrations and systolic blood pressure. Vegetarians had a better lipid profile than did nonvegetarians, probably because of a higher ratio of polyunsaturated to saturated fat in their diet (22) and a lower BMI. The difference in non-HDL-cholesterol concentrations between vegetarian and nonvegetarian controls was 0.45 mmol/L, which, on the basis of results from the Prospective Studies Collaboration, would predict a 16% lower risk of IHD (23). Vegetarians had a 3.3-mm Hg lower systolic blood pressure (probably because of differences in BMI), which would predict a 10% lower risk of IHD (24). If the combined effects of lower non-HDL-cholesterol concentrations and blood pressure on IHD are taken as being additive (23), it would predict a 24% lower risk of IHD events in vegetarians, which is smaller than the 32% observed in the current analysis but within the 95% CI. Residual confounding by measurement error in variables such as physical activity or smoking may partially explain some of the lower risk among vegetarians, and the lower prevalence of diabetes among vegetarians could contribute to a lower risk of IHD above and beyond the effect on serum lipid fractions and blood pressure (25).

The strengths of this study included the use of a cohort with a large number of vegetarians, which allowed for a reasonably precise estimate of the association between vegetarianism and IHD risk. Adjustment for a range of confounding variables and exclusion of the first 2 y of follow-up also helped to reduce the possibility of a differential healthy volunteer effect among vegetarians, although this cannot be completely ruled out.

Cases of incident IHD were identified by linkage with hospital records; if vegetarians were less likely to be admitted to the hospital, it could bias the results toward a lower risk of IHD for vegetarians. Nevertheless, vegetarians also had a significantly

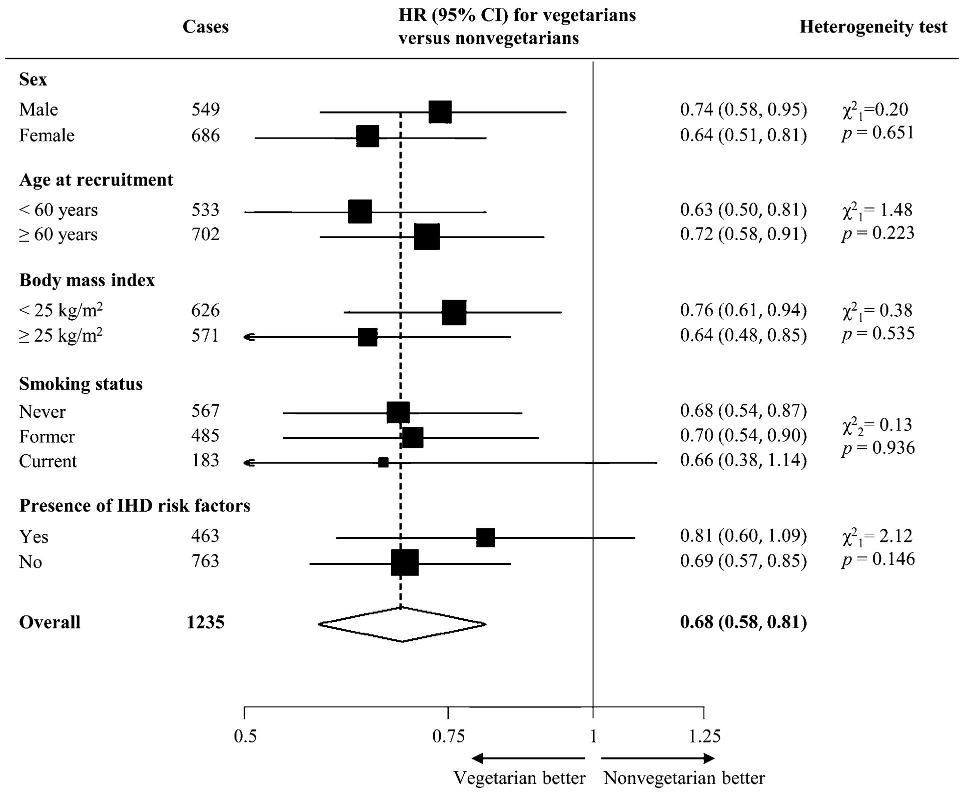

FIGURE 1. Risk of IHD in vegetarians and in nonvegetarians within certain subgroups in the EPIC-Oxford study. Presence of IHD risk factors includes at least one of the following: hypertension, hyperlipidemia, or diabetes. All analyses were stratified by sex, method of recruitment, and region of residence and were adjusted for age, smoking, alcohol, physical activity, educational level, and Townsend Deprivation Index and the use of oral contraceptives or hormone therapy for menopause in women. Tests of heterogeneity were performed by using data for all participants by adding a vegetarian status × sex, age, BMI, smoking, or IHD risk factor group interaction term to the model, as appropriate. EPIC, European Prospective Investigation into Cancer and Nutrition; IHD, ischemic heart disease.

lower risk of IHD in a sensitivity analysis in which IHD was the primary diagnosis on their hospital records, which should reduce the possibility that the higher rate of IHD was due to a greater number of nonvegetarians receiving an incidental diagnosis of IHD while hospitalized. Although only a proportion of the IHD cases in the current analysis were validated, excellent agreement (94%) was found between a hospital diagnosis and clinically confirmed IHD. Moreover, it is unlikely that the validity of a hospital diagnosis of IHD would differ according to whether participants consumed a vegetarian diet or not. Given that the cohort was not a representative sample of UK adults, the absolute rates of IHD in the general population may differ from that of the 6.8% reported for nonvegetarians aged 50–70 y.

In summary, this analysis showed that British vegetarians have a lower risk of hospitalization for or death from IHD than do comparable nonvegetarians. A substantial proportion of the difference in risk was probably mediated through the effect of a vegetarian diet and lifestyle on non-HDL-cholesterol concentrations and systolic blood pressure, which supports the important role of diet in the prevention of IHD.

We thank all the participants in the EPIC-Oxford cohort for their invaluable contribution to the study. The authors acknowledge the MINAP for access to MINAP data.

The authors' responsibilities were as follows—FLC, PNA, RCT, and TJK: responsible for drafting the manuscript; FLC and TJK: responsible for the study concept and design; TJK: responsible for the recruitment and follow-up of the Oxford cohort; and PNA: responsible for the statistical analyses. TJK is a member of the Vegetarian Society, United Kingdom. None of the other authors had financial or nonfinancial interests that might be relevant to the submitted work. The funders played no role in designing or conducting the study or in the collection, management, analysis, or interpretation of the data and had no input into the preparation, review, or approval of the manuscript.

REFERENCES

1. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr 2003;6:259–69.
2. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care 2009;32:791–6.
3. Burslem J, Schonfeld G, Howald MA. Plasma apoprotein and lipoprotein lipid levels in vegetarians. Metabolism 1978;27:711–9.
4. Lock DR, Varhol A, Grimes S. ApoA-I/apoA-II ratios in plasmas of vegetarians. Metabolism 1983;32:1142–5.
5. Thorogood M, Carter R, Benfield L. Plasma lipids and lipoprotein cholesterol concentrations in people with different diets in Britain. Br Med J (Clin Res Ed) 1987;295:351–3.
6. Armstrong B, Van Merwyk AJ, Coates H. Blood pressure in Seventh Day Adventist vegetarians. Am J Epidemiol 1977;105:444–9.
7. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. Public Health Nutr 2002;5:645–54.
8. Fu CH, Yang CCH, Lin C, Kuo TBJ. Effects of long-term vegetarian diets on cardiovascular autonomic functions in healthy postmenopausal women. Am J Cardiol 2006;97:380–3.
9. Pettersen BJ, Anousheh R, Fan J, Jaceldo-Siegl K, Fraser GE. Vegetarian diets and blood pressure among white subjects: results from the Adventist Health Study-2 (AHS-2). Public Health Nutr 2012;15:1909–16).

10. Tonstad S, Stewart K, Oda K, Batech M, Herring RP, Fraser GE. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. Nutr Metab Cardiovasc Dis (Epub ahead of print 7 October 2011).
11. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, Burr ML, Chang-Claude J, Frentzel-Beyme R, Kuzma JW, et al. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr 1999; 70(suppl):516S–24S.
12. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Am J Clin Nutr 2009;89(suppl):1613S–9S.
13. Fraser GE. A comparison of first event coronary heart disease rates in two contrasting California populations. J Nutr Health Aging 2005;9:53–8.
14. NHS National Services Scotland. Information and Services Division Scotland. Available from: http://www.isdscotland.org/isd/1.html (cited 9 October 2011).
15. National Health Service. The Health and Information Centre for Health and Social Care. HESonline Hospital Episodes Statistics. Available from: http://www.hesonline.nhs.uk (cited 9 October 2011).
16. Bingham SA, Cassidy A, Cole TJ, Welch A, Runswick SA, Black AE, Thurnham D, Bates C, Khaw KT, Key TJA, et al. Validation of weighed records and other methods of dietary assessment using the 24h urine nitrogen technique and other biological markers. Br J Nutr 1995;73:531–50.
17. Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, Sneyd MJ, Key TJA, Roe L, Day NE. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. Br J Nutr 1994;72:619–43.
18. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr 2002;5:561–5.
19. Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the north. London, United Kingdom: Croom Helm Ltd, 1988.
20. Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP). Heart 2010;96:1264–7.
21. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
22. Rosell MS, Lloyd-Wright Z, Appleby PN, Sanders TAB, Allen NE, Key TJ. Long-chain n−3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. Am J Clin Nutr 2005; 82:327–34.
23. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet 2007;370:1829–39.
24. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–13.
25. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.