Dietary protein and risk of ischemic heart disease in middle-aged men

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ABSTRACT

Background: Prospective studies in US women have suggested an inverse relation between dietary protein and risk of ischemic heart disease (IHD). However, no large-scale prospective studies have been conducted in US men.

Objective: The objective was to examine the association between dietary protein and risk of IHD in a prospective study of US men.

Design: Intakes of protein and other nutrients were assessed by using a validated food-frequency questionnaire at 4 time points during follow-up of 43,960 men participating in the Health Professionals Follow-Up Study. Cox proportional hazards models were used to calculate multivariable-adjusted relative risks (RRs) and 95% CIs.

Results: During 18 y of follow-up, we documented 2959 incident cases of IHD. The RR of IHD was 1.08 (95% CI: 0.95, 1.23; P for trend = 0.30) comparing the top with the bottom quintile of percentage of energy from total protein. RRs for animal and vegetable protein were 1.11 (95% CI: 0.97, 1.28; P for trend = 0.18) and 0.93 (95% CI: 0.78, 1.12; P for trend = 0.49), respectively. When the population was restricted to “healthy” men (those free of hypertension, hypercholesterolemia, and diabetes at baseline), the RR of IHD was 1.21 (95% CI: 1.01, 1.44; P for trend = 0.02) for total protein, 1.25 (95% CI: 1.04, 1.51; P for trend = 0.02) for animal protein, and 0.93 (95% CI: 0.72, 1.19; P for trend = 0.65) for vegetable protein.

Conclusions: We observed no association between dietary protein and risk of total IHD in this group of men aged 40–75 y. However, higher intake of animal protein may be associated with an increased risk of IHD in “healthy” men.

INTRODUCTION

Several studies have suggested that a higher dietary intake of protein in conjunction with a low- or moderate-carbohydrate diet may be associated with lower blood pressure and cholesterol concentrations and with short-term weight loss (1–3). However, the relation between dietary protein and long-term risk of ischemic heart disease (IHD) has not been thoroughly studied. With the current emphasis on higher-protein diets and weight loss, it is important to determine the long-term ramifications of such diets on chronic disease risk. Although previous results from studies in US women suggest that higher-protein diets are associated with a lower risk of IHD (4, 5), similar results have not been confirmed in US men. We examined the association between dietary protein and risk of IHD in men participating in the Health Professionals Follow-Up Study.

SUBJECTS AND METHODS

Study population

The Health Professionals Follow-Up Study is an ongoing prospective cohort study of 51,529 men aged 40–75 y at baseline in 1986. The cohort participants are sent a biennial questionnaire regarding diseases and lifestyle characteristics, such as smoking status, medication use, and physical activity. Every 4 y, the participants are sent a food-frequency questionnaire (FFQ) to assess their diet composition. Approximately 94% of the cohort has completed at least one follow-up questionnaire. We excluded those who reported a history of myocardial infarction (MI), angina, coronary artery bypass graft, other heart conditions, stroke, pulmonary embolism, or cancer on the baseline questionnaire. In addition, those who had an implausible caloric intake (<800 or >4200 kcal/d; cutoffs for extreme intake values (±4 SD) derived from the baseline FFQ) or had >70 missing responses to food items were excluded, which resulted in a baseline population of 43,960 for the current analysis. This study was approved by the Harvard Institutional Review Board.

Dietary assessment

Diet was assessed at baseline in 1986 and in 1990, 1994, 1998, and 2002 by using a 131-item FFQ. Details of the method of calculating nutrient intakes from the FFQ were previously described (6). Intakes of total, animal, and vegetable protein were calculated for each participant. Protein intake was expressed as a percentage of energy by multiplying the grams of protein consumed per day by the number of kilocalories in 1 g of protein (4 kcal/g) and then dividing by the subject’s total caloric intake (7). The other macronutrients, carbohydrate, and fats (saturated, monounsaturated, polyunsaturated, and trans) were also ex-

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pressed as a percentage of energy, assuming 4 kcal per gram of carbohydrate and 9 kcal per gram of fat. In addition to the macronutrients, nutrient intakes were calculated for glycemic index, fiber, folate, vitamin C, magnesium, total omega-3 (n3) fatty acids, and alcohol. With the exception of alcohol, all nutrients were energy-adjusted by using the residual method (8).

The validity of the 131-item FFQ was assessed in a subsample of the baseline study population (9). The validity of the FFQ was assessed by comparing the nutrient intakes estimated by the questionnaire with the intakes calculated from an average of the 2 weighed 1-wk diet records. The deattenuated energy-adjusted Pearson correlation coefficient for the macronutrients between the diet records and the FFQ was 0.67 for fat, 0.73 for carbohydrate, and 0.44 for protein.

Assessment of IHD endpoints

The primary endpoints of interest were incident nonfatal MI and fatal IHD occurring between the return of the 1986 questionnaire and 31 January 2004. Nonfatal MI was assessed biennially with a mailed questionnaire. If a participant reported a diagnosis and hospitalization for MI, we first obtained confirmation of the event and consent by letter or by phone to review their medical records. A physician blinded to exposure status verified the report of MI through a review of medical or hospital records using the World Health Organization criteria of symptoms and either typical electrocardiographic changes or elevated cardiac enzymes (10).

Deaths were ascertained by contact with family members or through the National Death Index. Fatal IHD was confirmed from the medical records or autopsy reports or if IHD was listed as the cause of death on the death certificate and there was evidence of previous IHD in the records.

Statistical analysis

A multivariate nutrient density model was used to analyze the association between protein intake and risk of IHD (8, 11). Our purpose in using the percentage of energy from protein instead of grams of protein was to examine the effect of increasing protein intake independent of increases in total energy intake. The coefficient for protein reflects the substitution of an equal amount of energy from protein for carbohydrate rather than an absolute increase in protein intake. The age-adjusted nutrient density model contains quintiles of percentage of energy from protein, percentage of energy from saturated fat, percentage of energy from monounsaturated fat, percentage of energy from polyunsaturated fat, percentage of energy from trans fat, and total energy intake. The multivariate nutrient density model contains all variables in the age-adjusted model plus variables for other established risk factors for IHD including body mass index (BMI, in kg/m2; <23, 23–24.9, 25–28.9, or ≥29), cigarette smoking (never smoker, nonsmoker with unknown past history, past smoker, or current smoker of 1–14, 15–24, ≥25, or an unknown number of cigarettes daily), parental history of MI before age 65 y (yes or no), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/d), multivitamin use (yes or no), and quintiles of physical activity (metabolic equivalents/d), glycemic index, folate (µg/d), fiber (g/d), vitamin C (mg/d), magnesium (mg/d), and total omega-3 fatty acids (g/d) (12, 13). Because protein intake was shown to be inversely associated with IHD mortality in a previous study, we repeated our main analysis examining nonfatal and fatal IHD endpoints separately (5).

Because the participants who developed hypertension, diabetes, or hypercholesterolemia before the start of the study may have altered their diet after their diagnosis, we fit an alternative multivariate nutrient-density model that contained baseline (1986) status of hypertension, diabetes, and hypercholesterolemia in addition to all of the abovementioned variables. We did not control for the development of hypertension, diabetes, and hypercholesterolemia during the study because these variables are potential intermediates in the causal pathway between dietary protein intake and IHD (14).

Each participant contributed person-time to the analysis, starting from the date of the return of their 1986 questionnaire until 31 January 2004, death, loss to follow-up, diagnosis of cancer or stroke, or development of IHD, whichever occurred first. Incidence rates for MI were calculated for each quintile of percentage of energy from protein. A Cox proportional hazards regression model, stratified jointly by age in months and by each of the eight 2-y follow-up time periods, was fit by using PROC PHREG in SAS (version 9.1; SAS Institute Inc, Cary, NC) to calculate incidence rate ratios (relative risks; RRs) and 95% CIs. To assess the presence of a linear trend, a median score variable was constructed by using the median protein intake of each quintile and its significance was assessed by using a Wald test. All P values are 2-sided.

For the repeated measurements of dietary protein, we used the cumulative average approach to assign an individual’s intake at each time period, which gives greater weight to more recent diet (11). The cumulative average approach minimizes measurement error because it uses all previous dietary assessments during follow-up (11). If a person developed an intermediate event that could alter their diet (eg, hypercholesterolemia, hypertension, angina, diabetes, and cancer), only their diet before the development of the event was considered in the analysis.

The interaction of total protein intake with traditional cardiovascular disease (CVD) risk factors was examined by including a cross-product term for percentage of energy from protein multiplied by the risk factor, and its significance was assessed by using a likelihood ratio test. The risk factors considered were hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no), BMI (in kg/m2; ≥25 or <25), and glycemic index (≥55 or <55).

RESULTS

Baseline characteristics

During the 18 y (688,455 person-years) of follow-up, we documented 2959 incident IHD events (1804 nonfatal MIs and 1155 fatal cases of IHD) among the 43,960 participants included in the analysis. Baseline characteristics of the study population according to quintile of percentage of energy from total protein are presented in Table 1. Men with a higher percentage of energy from protein were more likely to have reported a diagnosis of hypertension, hypercholesterolemia, and diabetes and also had higher average folate, vitamin C, magnesium, and omega-3 fatty acid intakes (P for linear trend <0.0001 for all variables). Those in the top quintile also had lower alcohol consumption and lower total energy intake (P for linear trend <0.0001 for both variables).
TABLE 1
Distribution of ischemic heart disease risk factors according to quintile (Q) of percentage of energy from total protein at baseline (1986): Health Professionals Follow-Up Study (n = 43,960), 1986–2004

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Q1</th>
<th>Q3</th>
<th>Q5</th>
<th>P for linear trend2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>55 ± 104</td>
<td>53 ± 9</td>
<td>55 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Past</td>
<td>3993 (45.2)</td>
<td>4007 (47.5)</td>
<td>4409 (44.9)</td>
<td>Referent</td>
</tr>
<tr>
<td>History of diabetes [n (%)]</td>
<td>3405 (38.6)</td>
<td>3336 (39.5)</td>
<td>4126 (42.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>History of hypercholesterolemia [n (%)]</td>
<td>262 (3.0)</td>
<td>216 (2.6)</td>
<td>251 (2.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>History of MI [n (%)]</td>
<td>334 (3.8)</td>
<td>294 (3.5)</td>
<td>276 (2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exercise (METs)</td>
<td>390 (4.4)</td>
<td>214 (2.5)</td>
<td>209 (2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>105 (1.2)</td>
<td>72 (0.9)</td>
<td>96 (1.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Missing</td>
<td>337 (3.8)</td>
<td>301 (3.6)</td>
<td>446 (4.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of hypertension [n (%)]</td>
<td>1822 (20.6)</td>
<td>1812 (21.5)</td>
<td>2512 (25.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypercholesterolemia [n (%)]</td>
<td>807 (9.1)</td>
<td>873 (10.3)</td>
<td>1227 (12.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of diabetes [n (%)]</td>
<td>114 (1.3)</td>
<td>147 (1.7)</td>
<td>506 (5.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parental history of MI &lt;65 y [n (%)]</td>
<td>1025 (11.6)</td>
<td>975 (11.6)</td>
<td>1283 (13.1)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Parental history of MI &gt;65 y [n (%)]</td>
<td>975 (11.6)</td>
<td>975 (11.6)</td>
<td>1283 (13.1)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Exercise (METs)</td>
<td>20.9 ± 30.1</td>
<td>20.8 ± 27.4</td>
<td>21.1 ± 29.1</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 3.2</td>
<td>25.5 ± 3.3</td>
<td>25.9 ± 3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calories (kcal/d)</td>
<td>2137 ± 664</td>
<td>2024 ± 597</td>
<td>1780 ± 574</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total protein (% of energy)</td>
<td>14.2 ± 1.4</td>
<td>18.2 ± 0.4</td>
<td>23.2 ± 2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Animal protein (% of energy)</td>
<td>9.3 ± 1.8</td>
<td>13.2 ± 1.2</td>
<td>18.4 ± 2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vegetable protein (% of energy)</td>
<td>4.9 ± 1.3</td>
<td>5.0 ± 1.2</td>
<td>4.9 ± 1.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Carbohydrates (% of energy)</td>
<td>50.9 ± 9.3</td>
<td>46.9 ± 7.5</td>
<td>42.9 ± 7.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Saturated fat (% of energy)</td>
<td>10.5 ± 2.8</td>
<td>11.2 ± 2.7</td>
<td>11.1 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Monounsaturated fat (% of energy)</td>
<td>11.8 ± 2.8</td>
<td>12.5 ± 2.6</td>
<td>12.2 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polyunsaturated fat (% of energy)</td>
<td>5.9 ± 1.8</td>
<td>6.0 ± 1.5</td>
<td>6.0 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trans Fat (% of energy)</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol (% of energy)</td>
<td>5.0 ± 7.4</td>
<td>3.9 ± 4.8</td>
<td>2.7 ± 3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>17.5 ± 22.0</td>
<td>10.9 ± 13.5</td>
<td>6.8 ± 9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Folate, energy-adjusted (µg/d)</td>
<td>442 ± 255</td>
<td>476 ± 262</td>
<td>520 ± 312</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fiber, energy-adjusted (g/d)</td>
<td>19.9 ± 7.6</td>
<td>21.0 ± 6.6</td>
<td>21.6 ± 7.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin C, energy-adjusted (mg/d)</td>
<td>389 ± 423</td>
<td>421 ± 469</td>
<td>488 ± 532</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Magnesium, energy-adjusted (mg/d)</td>
<td>324 ± 81</td>
<td>351 ± 75</td>
<td>382 ± 92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Omega-3 fatty acids, energy-adjusted (g/d)</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycemic index</td>
<td>54.0 ± 3.8</td>
<td>53.3 ± 3.3</td>
<td>52.0 ± 3.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 METs, metabolic equivalent tasks; MI, myocardial infarction.  
2 P value for linear trend was calculated across all 5 quintiles by using logistic regression for dichotomous variables and linear regression for continuous variables.  
3 Mean ± SD (all such values).

Substitution of protein for carbohydrate

The association between quintile of percentage of energy from protein and risk of IHD is shown in Table 2. For total protein, the RR for the comparison of those in the top total protein quintile (median: 22.5% of energy) with those in the bottom quintile (median: 14.6% of energy) was 1.22 (95% CI: 1.08, 1.38) after adjustment for age, dietary fat, and total energy intake. This model substituted protein for an isocaloric amount of carbohydrate. Additional adjustment for BMI; quintiles of fiber, folate, vitamin C, magnesium, and omega-3 fatty acids; glycemic index; physical activity; family history of MI; cigarette smoking; and alcohol and multivitamin use resulted in an RR of 1.20 (95% CI: 1.05, 1.37; P for trend = 0.006). After additional adjustment for baseline status of hypertension, hypercholesterolemia, and diabetes, the RR decreased to 1.08 (95% CI: 0.95, 1.23), and the P for trend was 0.30.

The Cox proportional hazards models for animal protein showed results similar to those for total protein. The age- and macronutrient-adjusted RR for the comparison of those in the top quintile of animal protein (median: 17.7% of energy) intake with those in the bottom (median: 9.3% of energy) was 1.27 (95% CI: 1.12, 1.44). In the fully adjusted model, the RR for the top quintile was 1.11 (95% CI: 0.97, 1.28), and the P for trend was 0.18. For vegetable protein, the age- and macronutrient-adjusted RR for the comparison of those in the top quintile (median: 6.5% of energy) with those in the bottom quintile (median: 3.7% of energy) was 0.86 (95% CI: 0.75, 0.98). In the fully adjusted model, the RR for the top quintile was 0.93 (95% CI: 0.78, 1.12), and the P for trend was 0.49.

Exclusion of participants with baseline conditions

Some participants had hypertension, diabetes, and hypercholesterolemia at baseline, which may have led to a change in their diet before the onset of the study. Control for these potential confounders attenuated the main results (Table 2). However, it is unclear whether the attenuation was due to the removal of
Dietary protein and fatal and nonfatal IHD

We conducted further subanalyses to examine the association between dietary protein intake and risk of nonfatal MI and fatal IHD separately (Table 3). For both nonfatal MI and fatal IHD, the results for total protein and animal protein were similar to those for total IHD. For vegetable protein, the RR for the comparison of those in the top quintile with those in the bottom quintile was 1.18 (95% CI: 0.93, 1.48) in the fully adjusted model for nonfatal MI and 0.66 (95% CI: 0.49, 0.88) with a P for trend of 0.005 for fatal IHD.

Effect modification by CVD risk factors

No statistically significant interaction between diabetes, hypercholesterolemia, or high BMI and total, animal, or vegetable protein on the risk of IHD was observed. However, we did find significant differences between protein and risk of IHD by baseline hypertension and average glycemic index of the diet. The increased risk of IHD associated with higher total and animal protein was strongest among men without hypertension (Table 4). Total and animal protein were more strongly associated with risk of MI among men consuming a diet with a lower glycemic index (<55) (Table 4).

DISCUSSION

In this study we examined the risk of IHD associated with the substitution of an equal percentage of energy from total, animal, and vegetable protein for carbohydrate in a large prospective cohort of US men. We found no association between quintiles of percentage of energy from total, animal, or vegetable protein and risk of IHD across the range of intakes. We found a significant inverse association between higher intake of vegetable protein and risk of fatal IHD. In addition, when the study population was restricted to men free of diabetes, hypertension, and hypercholesterolemia, a higher intake of total and animal protein was associated with an increased risk of IHD. Finally, total and animal protein...
protein intakes were more strongly associated with risk of MI among men without hypertension and among men consuming a diet with a lower glycemic index (<55).

In the context of the current literature

The Kuopio Ischemic Heart Disease Risk Factor Study, which was conducted in a Finnish cohort of ~2000 men, reported on the association between dietary protein and risk of IHD (15). The age- and examination year–adjusted RR for the comparison of extreme quartiles of percentage of energy from total protein was 0.78 (95% CI: 0.56, 1.09). Consistent with their age-adjusted RR, our multivariate results also showed no statistically significant association between total protein and IHD risk. Multivariate RRs are not presented in their article.

The association between dietary protein and risk of IHD has been investigated in 2 prior cohort studies in all-female US populations. In 20 y of follow-up in the Nurses’ Health Study, the authors found a RR of 1.06 (95% CI: 0.86, 1.30) for total IHD when comparing extreme deciles of percentage energy from total protein (16). The corresponding RR for animal protein was 1.13 (95% CI: 0.91, 1.41) and 1.08 (95% CI: 0.82, 1.43) for vegetable protein. Our results are consistent with those from the Nurses’ Health Study cohort which had a similar range of protein intake as our cohort.
TABLE 4
Relative risks (and 95% CIs) of ischemic heart disease according to quintile (Q) of percentage of energy from protein, stratified by hypertension and glycemic index: Health Professionals Follow-Up Study, 1986–2004

<table>
<thead>
<tr>
<th>Total protein</th>
<th>Hypertension</th>
<th>Q1 (referent)</th>
<th>Q2 (0.85, 1.22)</th>
<th>Q3 (0.94, 1.36)</th>
<th>Q4 (0.86, 1.27)</th>
<th>Q5 (1.02, 1.53)</th>
<th>P for trend</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>1.00 (0.70, 1.42)</td>
<td>1.03 (0.88, 1.20)</td>
<td>1.03 (0.67, 1.61)</td>
<td>0.99 (0.64, 1.55)</td>
<td>0.78 (0.53, 1.11)</td>
<td>0.74</td>
<td>0.42</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>1.00 (0.69, 1.39)</td>
<td>1.01 (0.74, 1.39)</td>
<td>1.06 (0.73, 1.57)</td>
<td>0.89 (0.56, 1.42)</td>
<td>0.83 (0.51, 1.36)</td>
<td>0.54</td>
<td>0.42</td>
</tr>
</tbody>
</table>

The association between dietary protein and risk of IHD mortality was also examined in the Iowa Women’s Health Study (5). In a comparison of extreme quintiles of protein intake, the RR of fatal IHD was 0.84 (95% CI: 0.39, 1.79) for total protein (22.0% compared with 14.1% of energy), 0.88 (95% CI: 0.42, 1.86) for animal protein (17.5% compared with 8.9% of energy), and 0.70 (95% CI: 0.49, 0.99) for vegetable protein (6.1% compared with 3.7% of energy). Our results for fatal IHD were similar to the results found in the Iowa Women’s Health Study, in which we found a significant inverse association for vegetable protein and no association of fatal IHD with total or animal protein.

Potential biological mechanisms

If dietary protein intake, especially vegetable protein intake, reduces the risk of IHD, it may be mediated through beneficial effects on blood pressure, cholesterol, and body weight. Randomized clinical trials have shown an inverse association between higher vegetable protein intake and blood pressure (1, 17–20). Observational studies have also shown an inverse relation between nonanimal protein intake and blood pressure (21, 22). In addition, the effect of protein may depend on the quality of carbohydrates that is being replaced, because we observed a differential effect of total and animal protein depending on the average glycemic index of a participant’s diet.

With respect to dietary protein and plasma cholesterol, in a meta-analysis of 38 clinical trials of soy-protein diets, there was an average decrease of 9.3% for total cholesterol, 12.9% for LDL cholesterol, and 10.5% for triglycerides and an increase of 2.4% for HDL cholesterol when compared with subjects consuming a control diet (high animal protein) (23). However, more recent studies have suggested that the effect of soy on LDL cholesterol is much smaller (24). Other randomized trials that compared high-protein diets found that individuals assigned to a low-carbohydrate, high-protein diet had a greater weight loss than did those assigned to a low-fat diet; however, few studies found statistically significant differences between groups after long-term follow-up (2, 25, 26, 30–34). Foods high in vegetable protein, such as nuts and legumes, have been shown to be inversely associated with risk of IHD (35, 36). These sources of protein also have a high content of unsaturated fatty acids, which have been shown to be especially beneficial at preventing sudden cardiac death (37). However, we controlled for both fats and omega-3 fatty acids in our analysis and still found an inverse association between vegetable protein and fatal IHD. In general, vegetable protein has a lower content of saturated and total fats, trans fatty acids; glycemic index; physical activity; family history of myocardial infarction (yes or no); BMI (in kg/m²; <23, 23–24.9, 25–28.9, or ≥29); cigarette smoking (never, nonsmoker with unknown past history, past smoker, or current smoker of 1–14, 15–24, 25–28.9, or ≥29); alcohol use (0, 0.1–4.9, 5–14.9, or ≥15 g/d); multivitamin use (yes or no); and baseline status of hypercholesterolemia and diabetes.

1. A Cox proportional hazards model was used to calculate RRs and 95% CIs, and P values were derived from a Wald test. The number of cases is 1318 for nonhypertensive, 1638 for hypertensive, 2104 for low glycemic index, and 852 for high glycemic index. All models were adjusted for age; quintiles of percentage of energy from saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, calories, fiber, folate, vitamin C, magnesium, and total omega-3 fatty acids; glycemic index; physical activity; family history of myocardial infarction (yes or no); BMI (in kg/m²; <23, 23–24.9, 25–28.9, or ≥29); cigarette smoking (never, nonsmoker with unknown past history, past smoker, or current smoker of 1–14, 15–24, ≥25, or an unknown number of cigarettes daily); alcohol use (0, 0.1–4.9, 5–14.9, or ≥15 g/d); multivitamin use (yes or no); and baseline status of hypercholesterolemia and diabetes.

2. Additionally adjusted for baseline hypertension status. Model was adjusted for glycemic index (continuous) instead of glycemic index in quintiles.

3. Additionally adjusted for quintiles of percentage of energy from vegetable protein.

4. Additionally adjusted for quintiles of percentage of energy from animal protein.
of essential amino acids—namely methionine, lysine, and tryptophan—than does animal protein (38). Vegetable protein contains a higher content of the nonessential amino acids arginine, glycine, alanine, and serine. Intake of essential amino acids results in increased insulin release to stimulate protein synthesis and storage, whereas intake of nonessential amino acids results in gluconeogenesis (38). However, a higher intake of the amino acid arginine may increase concentrations of the vasodilator nitric oxide and decrease blood pressure (1). Also, arginine has been shown to have a powerful depressor effect when administered intravenously (39). One study suggested that higher intakes of glutamic acid, the primary amino acid found in vegetable protein, were associated with lower blood pressure (40). Thus, the stronger beneficial effects of vegetable protein on risk of IHD may be explained through these mechanisms.

Although it is biologically plausible that a higher intake of dietary protein, especially from vegetable sources, may decrease the risk of IHD, it is unclear why we observed an inverse association only for fatal MI and not for total or nonfatal IHD. Our results are consistent with a previous study that showed a statistically significant inverse association between vegetable protein and IHD mortality; however, the biological mechanism to explain this inverse association is unclear (5). It is important to note that we were unable to control for several factors related to health consciousness (e.g., such as medication compliance and behavior change after nonfatal disease), which may have confounded the results for fatal IHD. It is also possible that this relation may have arisen by chance; therefore, confirmation in other prospective studies is men is necessary.

Limitations

We recognize that assessment of dietary protein through self-administered FFQs has limitations. Misclassification could occur if there were dietary changes that were not captured during the 4-y period between the FFQ administrations. This misclassification is likely to be nondifferential, causing the effect estimates to be biased toward the null. In our dietary validation study, the correlation between protein intake estimated from the FFQ and protein intake estimated from the diet records was relatively low (0.44), which suggested that the FFQ may not be an ideal measure of protein intake (9). However, in the validation study, the range of protein intakes was limited (10–25% of energy), which also likely contributed to the modest correlation. The same FFQ was used in previous studies among female populations, which reported inverse associations between dietary protein and MI risk (4, 5). Dietary protein measured with an FFQ has been validated against a urinary nitrogen biomarker (41). Our study population consisted of white male health professionals; thus, it is unclear whether the results are generalizable to other groups of men.

Conclusions

We observed no association between quintiles of percentage of energy from dietary protein and risk of total IHD at the protein levels consumed in the cohort of US men participating in the Health Professionals Follow-Up Study. We observed a significant inverse association between higher vegetable protein intake and risk of fatal IHD. Studies that focus on the health effects of specific amino acids are warranted.

The authors’ responsibilities were as follows—SRP: study design, data analysis, and writing of manuscript; MJS: study design, data collection, and critical revision of manuscript; DS: data analysis and revision of manuscript; WCW: study design, data collection, and critical revision of manuscript; and EBR: study design, data collection, and critical revision of manuscript. There were no conflicts of interest to disclose.

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