Red Meat Intake and Risk of Coronary Heart Disease Among US Men

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Keywords:	Red meat, plant protein, coronary heart disease, substitution analysis

Red Meat Intake and Risk of Coronary Heart Disease Among US Men

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Abstract

Objectives: To study total, processed and unprocessed red meat in relation to risk of coronary heart disease (CHD) and estimate the effects of substituting other protein sources for red meat with CHD risk.

Design: Prospective cohort study with repeated measures of diet and lifestyle factors.

Setting: Health Professionals Follow Up Study cohort, United States, 1986-2016.

Participants: 43,272 men without cardiovascular disease or cancer at baseline.

Exposure: Total, processed, and unprocessed red meat consumption.

Main Outcome Measures: Total CHD, comprised of acute non-fatal myocardial infarction or fatal CHD. Cox models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) across categories of red meat consumption. Substitution analyses were conducted by comparing coefficients for red meat and the alternative food in models including red meat and alternative foods as continuous variables.

Results: During 1,023,872 person-years of follow-up, we documented 4,456 cases of incident CHD of which 1,860 were fatal. After multivariate adjustment for dietary and nondietary risk factors, total, unprocessed, and processed red meat intake were each associated with a modestly higher risk of CHD (HR for a one serving/day increment: 1.12; 95% CI, 1.06-1.18 for total, HR=1.11; 95% CI, 1.02-1.21 for unprocessed, and HR=1.15; 95% CI, 1.06-1.25 for processed red meat). Compared to red meat, plant protein sources (nuts, legumes, and soy) were associated with lower risk of CHD. The HR's (95% CI's)

were 0.86 (0.80, 0.93) for 1 serving per day of plant protein sources compared with total red meat, 0.87 (0.79, 0.95) compared with unprocessed red meat, and 0.83 (0.76, 0.91) compared with processed red meat.

Conclusions: Substituting high-quality plant foods such as legumes, nuts, soy for red meat may reduce risk of CHD.

Key words:

Red meat, plant protein, coronary heart disease, substitution analysis.

Introduction

Substantial evidence from randomized trials of meat consumption with cardiovascular risk factors as the outcome[1] and from observational studies with clinical endpoints suggests that high consumption of red meat, especially processed red meat, is associated with increased risk of mortality[2-4] and major chronic diseases[5-10] including the coronary heart disease (CHD)[11-13]. Consequently, the 2015-2020 US Dietary Guidelines for Americans[14] encourage dietary patterns that are low in red and processed meat intake. However, increases in risk were not seen a population with low consumption of red meat[3] and in Asian populations in which consumption of red meat has recently increased[15]. These inconsistencies may be due to the variable amounts and duration of red meat consumed in different populations, inadequate differentiation between processed and unprocessed red meat, incomplete control of confounding, and importantly, differences in the comparison sources of calories. In particular, in most populations, the majority of calories come from refined starches, sugar, potatoes, and fats that are highly saturated or partially hydrogenated. Thus, analyses that fail to specify comparison foods are by default mainly comparing red meat with these suboptimal sources of calories. Therefore, lack of an association of red meat with disease outcomes simply implies that red meat is similarly unhealthy as these alternative foods.

To address these issues, we examined the relationship of total, processed and unprocessed red meat to risk of CHD in the large prospective Health Professionals Follow-up Study cohort with repeated measures of diet during 30 years of follow-up. We estimated the effects of substituting other protein sources for red meat with CHD risk and evaluated the temporal relation of red meat consumption to risk of developing CHD.

Methods

Study Population:

The Health Professionals Follow-up Study (HPFS) started in 1986 when 51,529 US male health professionals, aged 40 to 75 years provided detailed information on their medical history, lifestyle, and habitual diet. Questionnaires have been completed biennially to update information on potential risk factors and occurrence of new diseases.

Dietary data were not included if participants left more than 70 items blank in the FFQ or had implausible total energy intake (<800 kcal or > 4200 kcal per day). Participants were excluded if they had a history of cancer (n=1645), myocardial infarction, angina, coronary artery bypass graft (n=3696), or stroke (n=221). A total of 43, 272 participants were included and subsequently followed up.

The study protocol was approved by the institutional review board of the Harvard T.H. Chan School of Public Health.

Dietary Assessment:

Participants completed a semiquantitative food frequency questionnaire in 1986 and every 4 years thereafter. Participants were asked how often, on average, they had consumed a standard portion of food in the past year (for portion sizes, see Supplement Table 1). Nine responses were possible and ranged from "never" to "> 6 times per day". The items on processed red meat included beef or pork hotdogs, bacon, salami, bologna, or other processed meat sandwiches, in addition to other processed meats such as sausages and kielbasa. Items on unprocessed red meat included hamburger (lean or extra lean), regular hamburgers, beef, pork, or lamb as a main or mixed dish or sandwich. Total red meat included processed and unprocessed red meat. Other protein sources, apart from red meat, included fish, eggs, high- and low-fat dairy, nuts, legumes, soy, and whole grains (Supplement Table 1).

The reproducibility and validity of the FFQs in measuring food intake have been described previously in detail[16]. The correlation coefficients between the FFQ and multiple dietary records were 0.59 for unprocessed red meat, 0.52 for processed red meat, 0.48 for poultry, 0.74 for fish, 0.56 for eggs, 0.62 for

each of high- and low-fat dairy, 0.46 for legumes including soybeans and tofu, 0.45 for nuts, 0.27 for whole grains[17].

Ascertainment of outcome:

The primary outcome for this study was total CHD, comprised of acute non-fatal myocardial infarction or fatal CHD, occurring after the return of the 1986 FFQ questionnaire but before January 31, 2016. Myocardial infarction was initially self-reported and confirmed by medical records documenting symptoms and either diagnostic electrocardiographic changes or elevated cardiac specific enzymes. Medical records were reviewed by physicians blinded to the participants' exposure status. For those whose medical records were unavailable, the diagnosis was considered probable (10.3% of total cases) if supported by telephone interview or other supplemental information. Deaths were identified from searches of vital records, the National Death Index, and reports by the participant's next of kin or the postal system[13 18]. Using these methods, at least 98% of deaths were ascertained[18]. Fatal CHD included fatal myocardial infarction, or if CHD was listed as cause of death on the death certificate and there was an evidence of a previous coronary disease. Sudden death within one hour of the onset of symptoms in men with no other plausible cause of death (other than coronary disease) was considered as fatal CHD.

Assessment of covariates:

In the biennial follow-up questionnaires, we inquired about and updated information on known or potential risk factors for CHD, including body mass index (BMI; < 21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33-34.9, 35-39.9, ≥ 40 in kg/m2;), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, and ≥ 27 in metabolic equivalents per week), cigarette smoking (never smoker, past smoker, current 1 to 14 cigarettes per day, current 15 to 24 cigarettes per day, current ≥ 25 cigarettes per day), alcohol consumption (0, 0.1-4.9, 5.0-9.9, 10-14.9, or ≥ 15.0 g per day), total energy intake (in quintiles), family history of MI (defined as infarction before age 65 years for a participant's mother or before age 55 years for a participant's father), multivitamin use (yes/no), aspirin use (yes/no), race/ethnicity (white, black, Asian, other), work status (full time, part time, retired), profession (dentist, pharmacist, optometrist, podiatrist, veterinary), living

arrangement (lives with family, lives alone, other arrangements), and marital status (married, divorced, widowed, never married). In case of missing data, the last value was carried forward for one 2-year cycle. If the last value was missing, then a missing indicator was created.

Statistical Analysis:

Age- and multivariate-adjusted Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals across the quintiles of total, processed, and unprocessed red meat consumption in relation to CHD risk. Person years of follow up were calculated from the return of the 1986 FFQ to the date of first CHD event, death, or end of follow up, whichever came first. The main models were adjusted for age in months and calendar time (2-year follow up periods), and energy intake, in addition to the above-mentioned list of covariates. We further adjusted for other dietary variables including poultry (unprocessed), fish, egg, high fat dairy, low fat dairy, nuts, legumes, soy, whole grains, fruits, vegetables, coffee, and glycemic index. To check for possible confounding by other aspects of diet, we conducted a sensitivity analysis adjusting for a modified diet score of the Alternative Healthy Eating Index (AHEI) that excluded the red meat components. In another sensitivity analysis, we included as covariates baseline history of diabetes, hypertension, and hypercholesterolemia, which might act as intermediates on the pathway linking red meat consumption and risk of CHD. Sensitivity analyses after excluding probable cases were similar, so only total cases of acute myocardial infarction were presented.

To better represent long-term diet and minimize within-person variation, we calculated the cumulative average of food intake from baseline up to the beginning of each 2-year follow up interval. We then investigated the cumulative average intake in relation to risk of CHD from the beginning of each follow-up interval until the next follow up interval. To minimize the possibility of reverse causation bias, we stopped updating diet after the participant's diagnosis of cancer or stroke, or after reporting diabetes, angina, or coronary artery bypass grafting.

We investigated the associations of substituting a single serving of alternative foods for red meat (total, processed, or unprocessed) with CHD risk by including the alternative foods as continuous variables in the same multivariable model and accounting for other dietary and non-dietary variables as well as total energy

intake. The difference in the beta coefficients of the two foods being compared, and their variances and covariances, were used to estimate the HR and 95% CI for the substitution[13]. Stratified analysis by age (<65, ≥ 65 years) and calendar time (before 2000, 2000 or later) were also conducted. Effect modification was tested after including the multiplicative interaction term between the continuous dietary variables included in the substitution model and each of age and calendar time.

Time-lagged analysis with varying lag-time periods (0-4 years, 4-8 years, 8-12 years, 12-16 years, 16-20 years, or 20-24 years) was conducted to predict the risk of CHD. For example, for latency of 4-8 years, we used dietary intake of 1986 to predict CHD risk during 1990 to 1994, the dietary intake of 1994 for CHD events occurring from 1998 to 2002, dietary intake in 1998 for CHD events occurring from 2002 to 2006, and so forth. The lagged analyses allow an evaluation of the latency between consumption of a dietary factor and occurrence of the outcome but does not account for correlation of intakes over time.

We also conducted several sensitivity analyses to test the robustness of our results. In addition to using the cumulative average intake updated until the development of major diseases (i.e. incidence of cancer, stroke, diabetes, or angina or performing a coronary artery bypass grafting, CABG) , we used a) baseline diet, b) most recent diet, c) cumulative average which was continually updated even after the diagnosis of a major disease, and d) cumulative updated average adjusted for the incidence of major diseases (cancer, stroke, diabetes, angina, or performing CABG) in the multivariate model.

The proportional hazards assumption was tested by including an interaction term between red meat intake and months to events. To test for linear trend, the median intakes for each quintile were modeled as a single continuous variable. Data were analyzed in SAS software, (version 9.4-SAS institute) at a two-tailed alpha level of 0.05.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. No plans exist to involve patients in dissemination.

Results

During 1,023,872 person-years of follow-up, we documented 4,456 incident CHD events of which 1,860 were fatal CHD cases. Participants with higher total red meat consumption were more likely to be current smokers, alcohol drinkers, diabetic, and aspirin users. They had higher intakes of total energy and trans-fat but were less physically active and less likely to have hypercholesterolemia or a family history of cardiovascular diseases. They had lower intakes of multivitamins, fruits, vegetables and cereal fiber, as compared to those in the lower quintiles of total red meat intake. Similar distributions were observed with processed and unprocessed red meat consumption (Table 1).

In age-adjusted analyses, higher intakes of total red meat, unprocessed red meat, and processed red meat were each positively associated with higher risk of CHD (Table 2). After further adjustment for non-dietary cardiovascular disease risk factors and energy intake, the associations of total, processed and unprocessed red meat consumption with CHD risk each remained significant but attenuated. Adjusting for other major dietary variables such as poultry, fish, egg, high and low fat dairy products, nuts, legumes, soy, and whole grains in addition to fruits, vegetables, coffee, and glycemic index further attenuated the associations, but total, unprocessed, and processed red meat remained significantly associated with risk of CHD (comparing the fifth to first quintile, HR=1.28, (95% CI, 1.14-1.45, P_{trend}<0.001) for total red meat, HR=1.18, (95% CI, 1.05-1.32, P_{trend}=0.01) for unprocessed red meat and HR=1.19, (95% CI, 1.07-1.33, P_{trend}=0.001) for processed red meat consumption, see Table 2). A one serving per day greater intake of total red meat was associated with a 12% (95% CI, 6%-18%) higher risk of CHD. Similar associations were observed for unprocessed and processed red meat (see Table 2).

Associations of each of total red meat, unprocessed, and processed red meat with fatal CHD were slightly stronger (see Supplementary Table 2).

In sensitivity analyses, the associations between meat and CHD risk became slightly weaker after including baseline history of diabetes, hypertension, and hypercholesterolemia in the model, or after adjusting for the modified AHEI score (Supplementary Table 3).

When compared with total, unprocessed, or processed red meat, intakes of nuts, legumes, soy, and combined plant protein sources (nuts, legumes, and soy), were each associated with a significantly lower risk of CHD (Figure 1). Specifically, the HR's (95% CI's) were 0.86 (0.80, 0.93) for 1 serving per day of combined plant protein sources when compared with 1 serving/day of total red meat, 0.87 (0.79, 0.95) when compared with unprocessed red meat, and 0.83 (0.75, 0.91) when compared with processed red meat (Figure 1). High- and low-fat dairy products, and whole grains were also associated with a lower CHD risk as compared with total red meat, unprocessed, and processed red meat (Figure 1, Supplementary Table 4). Egg intake was additionally associated with lower CHD risk as compared with processed red meat intake (Figure 1).

Milk (both skim and whole milk), yogurt, and cheese were each associated with lower risk of CHD as compared with red meat. These associations were more pronounced when replacing 1 serving of processed red meat with 1 serving of each of these dairy products (Supplementary Table 5).

Replacement of red meat with total fish intake was not associated with CHD risk. In a more detailed analysis according to the different types of fish (dark-meat fish, canned tuna fish , and other fish), we found that upon stratifying by calendar year of follow-up (before 2000, 2000 or later), dark meat fish intake was observed to be associated with a lower CHD risk as compared to total red meat, unprocessed and processed red meat (Supplementary Table 5), in the period of 2000 or later but not earlier. Other fish intake was however associated with higher CHD risk as compared to total, unprocessed, and processed red meat.

The associations comparing specific protein sources in relation to risk of CHD did not differ by age (< 65, ≥ 65 years) or period (before 2000, 2000 or later), (*P >0.05 for interaction),* except the comparisons for nuts and plant-based proteins versus red meat which showed stronger associations among older men. The associations comparing red meat with egg intake were stronger among younger men in which the

replacement of red meat with egg was associated with 20% (2%-35%) lower risk of CHD. (Supplementary Figure 1).

Results were comparable to our primary analysis (in which we stopped updating diet after the incidence of intermediate outcomes), when we continued to use cumulatively updated average diet through-out follow-up, with and without adjusting for the incidence of major diseases (Supplementary Figure 2). Weaker associations were observed when analyzing the most recent diet alone (except for poultry), as compared to cumulative updated diet (Supplementary Figure 2).

We also conducted latency analyses to further evaluate the temporal relationship between assessment of diet and diagnosis of CHD. Overall, the associations we observed in the substitution analyses did not appear to diminish with up to 20 years of latency; with greater than 20 years, the associations tended to be weaker but the number of events was relatively small (Supplementary Figure 3).

Discussion

In this prospective cohort study of men with up to 30 years of follow up, greater intakes of total, unprocessed, and processed red meat were associated with a higher risk of CHD, independent of other dietary and nondietary cardiovascular disease risk factors. When compared with total, unprocessed or processed red meat, intakes of high-quality plant-based protein foods such as nuts, legumes, and soy in addition to whole grains and dairy foods were each associated with a lower risk of CHD. The latency analyses suggested that the inverse associations of substituting red meat intake with major protein sources did not diminish with lags up to 20 years before the diagnosis of CHD. Also, associations were stronger using cumulative average intakes than with single dietary assessments, likely reflecting the less precise measurement of long-term diet when using a single questionnaire compared with using the cumulative average of repeated assessments.

Strengths and weaknesses in relation to other studies

Our finding of red meat consumption being associated with increased risk of CHD is in line of several previous studies. We previously found that higher intake of total red meat was significantly associated with elevated risk of CHD among 84,136 women of the Nurses' Health Study (NHS) cohort, especially when compared with alternative protein sources [13]. In 25,153 California Seventh Day Adventists, daily meat consumption (type not specified) was associated with 70% higher risk in fatal ischemic heart disease[19]. In a prospective study of 409,885 men and women in 9 European countries, the ischemic heart disease (IHD) risk was 19% greater for every 100g/day increment in the intake of total and processed red meat[20]. Substituting 100 kcal/d of fatty fish, yogurt, cheese, and eggs for 100 kcal/d of red and processed meat was associated with 15-24% lower IHD risk[20]. Also, in a recent analysis of individual-level data of 6 prospective US cohort studies, an additional 2 servings of unprocessed red meat per week was associated with 3% greater risk of cardiovascular diseases (CVD). Participants who consumed 2 servings per week of processed meat were also at a 7% higher risk of CVD as compared to non-consumers[21].

In a meta-analysis of observational studies, processed meat intake was associated with increased risk of CHD[12] and increased risk of death from any cause and CVD [22]. Although the comparison food was not specified, in a recent meta-analysis of prospective cohorts, lower intakes of unprocessed and processed red meat were each associated with lower risk of all-cause and CVD mortality, and a lower risk of MI [23].

Possible explanations and implications

Several mechanisms may contribute to an adverse effect of red meat intake on the risk of CHD. Consistent with its high content in saturated fat and cholesterol, in a meta-analysis of randomized clinical trials, consumption of red meat increased blood levels of low density lipoprotein (LDL) cholesterol when compared with plant based protein sources[1]. In a network meta-analysis of randomized trials, nuts, legumes, and whole grains were each more effective in reducing LDL cholesterol when compared with red meat[24]. In addition, polyunsaturated fat is very low in red meat, and reduction of risk of CHD by replacement of saturated fat with polyunsaturated fat has been supported by both observational cohort studies and randomized trials[25]. Dietary heme iron found in red meat has been associated with myocardial infarction

and fatal CHD in many epidemiologic studies[26-28]. Excessive iron may catalyze several cellular reactions involved in the production of reactive oxygen species, thus increasing the levels of oxidative stress[29]. L-carnitine, relatively high in red meat, may be also metabolized by intestinal microbiota into proatherogenic compounds, trimethylamine-N-oxide (TMAO), promoting atherosclerosis[30]. Also, the sialic acid N-glycolylneuraminic acid (Neu5Gc) in red meat has been hypothesized to generate a pro-inflammatory, atherogenic state in humans [31]. The high sodium content of processed meats is likely to increase risk of CHD by increasing blood pressure[32 33] and vascular resistance. Preservatives in processed red meat such as nitrates and their by-products have been associated with endothelial dysfunction, atherosclerosis, and insulin resistance in some animal models[34 35].

In our analysis, high quality plant-based protein foods such as nuts, legumes, and soy foods were associated with lower risk of CHD when compared with red meat. Such replacement would not only decrease the amounts of saturated fats, cholesterol, and heme iron, but also increase intake of unsaturated fat, fiber, and many constituents that could reduce risk of CHD. A reduction in CHD risk with such substitution could be therefore due to multiple changes in intakes of nutrients and phytochemicals.

In this study, the replacement of red meat with total fish intake was not associated with CHD risk. However, upon analyzing the different types of fish, intake of dark meat fish was inversely associated with CHD risk as compared to red meat in the period of 2000 and later. This could be due to the variation in the method of food preparation over time, as fish were mostly consumed as deep fried in the earlier years. Other fish intake was positively associated with CHD risk, possibly because this food group also included processed breaded fish, fish cakes, fish pieces, and fish sticks.

Strengths and weaknesses of this study

Our study has multiple strengths and limitations. The 30 years of follow up, the large number of CHD cases, and the availability of updated dietary data and other risk factors, provided a unique opportunity to evaluate processed and unprocessed red meat and potential replacements with alternative foods in relation with CHD. The cumulative averages of repeated assessments of intake were used to minimize random

measurement error caused by within-person variation and to account for real changes in diet over time. The use of isocaloric models enabled us to interpret food substitution analyses by specification of the comparison foods. Although the observational nature of the study doesn't enable us to assume causality of the observed relationships, the consistency with randomized studies documenting benefits on blood lipids when red meat is replaced by plant protein sources supports causality. Inevitable measurement error in dietary assessment, even though reduced by using the average of repeated assessments, would have tended to underestimate the true effects of red meat. Residual and unmeasured confounding cannot be excluded despite the adjustment for important demographic and lifestyle factors. Finally, our patients are mostly non-Hispanic white men, drawn from a cohort of health professionals whose socioeconomic status may not represent the overall population, thus affecting the generalizability of the results to other populations. However, this homogeneity can help reduce unmeasured confounding related to socioeconomic status.

Conclusion

We found that greater intakes of total, unprocessed, and processed red meat were each associated with a higher risk of CHD. Compared with total, unprocessed, or processed red meat, other dietary components such as soy, nuts, and legumes were associated with lower risk of CHD. These findings are consistent with the effects of these foods on LDL cholesterol and support a benefit of limiting red meat consumption and replacement with plant protein sources.

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We would like to thank the participants and staff of the Health Professionals Study for their valuable contributions. The results of the study are presented clearly, honestly, and without

fabrication, falsification, or inappropriate data manipulation. The authors assume full responsibility for analyses and interpretation of these data.

Contributors: LA, AS, DW, and WCW had the idea for the study.LA and AS did the data analysis. LA, AS, DW and WCW provided statistical expertise. LA wrote the first draft of the paper. WCW, EBR, and MJS obtained funding. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of Interest

The authors have no conflict of interest.

Summary boxes

What is already known on this topic

- The relation of red meat to risk of coronary heart disease (CHD) has long been debated.
- Discrepant results may partly be due to non-specific characterization of the alternatives to meat sources of protein and calories.

What this study adds

- Greater intakes of total, unprocessed, and processed red meat were each associated with a higher risk of CHD.
- Compared with total, unprocessed, or processed red meat, other dietary components such as soy, nuts, and legumes were associated with lower risk of CHD.

Table 1: Age-standardized baseline characteristics* of participants (n=43,272) by quintiles of total, unprocessed, and processed red meat intake

	Total Red Meat Intake			Unprocessed Red Meat Intake			Processed Red Meat Intake		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Number participants	8,599	8,331	8,640	9,063	9,955	9,840	11,069	9,503	8,754
Median intake (servings/d)	0.21	0.85	1.93	0.14	0.50	1.29	0.00	0.21	0.93
Age (years)	54 (10)	53 (10)	52 (9)	55 (10)	53 (10)	52 (9)	54 (10)	52 (10)	53 (9)
Caucasian (%)	93	95	96	93	95	96	94	95	96
Current smoker (%)	5	9	14	5	10	12	5	9	14
Physical activity (MET-h/wk)	26 (30)	19 (23)	17 (22)	26 (30)	19 (24)	17 (22)	24 (29)	20 (24)	17 (22)
BMI (kg/m^2)	25 (3.1)	26 (3.2)	26 (3.4)	25 (3.2)	26 (3.2)	26 (3.4)	25 (3.1)	26 (3.2)	26 (3.6)
Family history of CVD	14	12	11	13	12	12	14	12	11
History of diabetes (%)	2	2	4	2	2	3	2	2	3
History of hypertension (%)	20	20	20	20	20	20	20	20	20
History of hypercholesterolemia (%)	15	10	8	14	10	9	14	10	8
Current multivitamin use (%)	50	42	38	50	41	38	48	41	38
Current aspirin use (%)	25	26	28	25	27	28	25	27	29
Alcohol intake (g/d)	9 (13)	12 (15)	14 (18)	9 (13)	12 (16)	13 (17)	9 (13)	12 (15)	14 (18)
Total energy intake (kcal/d)	1,684 (544)	1,906 (521)	2,502 (605)	1,680 (543)	1,899 (530)	2,441 (613)	1,772 (560)	1,943 (569)	2,365 (633)
Fruit intake (servings/d)†	2.2 (1.6)	1.5 (1.1)	1.2 (1.1)	2.1 (1.6)	1.5 (1.1)	1.2 (1.1)	2.1 (1.5)	1.5 (1.1)	1.2 (1.0)
Vegetable intake (servings/d)†	3.8 (2.2)	3.1 (1.7)	2.7 (1.7)	3.7 (2.2)	3.1 (1.7)	2.8 (1.8)	3.7 (2.2)	3.0 (1.6)	2.7 (1.7)
Trans-fat intake (g/d)†	2.1 (1.1)	3.0 (1.1)	3.3 (1.0)	2.2 (1.2)	2.9 (1.1)	3.2 (1.0)	2.3 (1.2)	2.9 (1.0)	3.3 (1.0)
Cereal fiber intake (g/d)†	7.4 (5.4)	5.6 (3.4)	4.8 (2.6)	7.1 (5.1)	5.6 (3.5)	5.0 (2.8)	7.0 (5.1)	5.6 (3.5)	5.0 (2.7)
Glycemic index†	53 (4.0)	53 (3.5)	54 (3.4)	53 (4.0)	53 (3.6)	54 (3.4)	53 (4.0)	53 (3.4)	53 (3.4)

* Values are means (SD) for continuous variables, and percentages for categorical variables

† Energy-adjusted

Abbreviations: MET, metabolic equivalent of task; BMI, Body Mass Index; CVD, Cardiovascular Disease

Table 2: Hazard Ratios (95% CI) for total CHD associated with quintiles of total, unprocessed, and processed red meat intake (N=43,272).

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	HR per 1 serving/d	P-trend*
Total red meat							
Median servings/d	0.21	0.52	0.78	1.14	1.72		
Cases/PY	811/203879	833/206108	859/203718	865/206087	1087/204079		
Age-adjusted Model	1	1.08 (0.98, 1.19)	1.15 (1.04, 1.27)	1.15 (1.04, 1.27)	1.47 (1.34, 1.61)	1.20 (1.16, 1.26)	<0.001
Multivariable-adjusted Model 1	1	1.06 (0.96, 1.17)	1.11 (1.00, 1.23)	1.09 (0.97, 1.21)	1.34 (1.21, 1.49)	1.15 (1.09, 1.21)	<0.001
Multivariable-adjusted Model 2	1	1.06 (0.96, 1.18)	1.11 (0.99, 1.23)	1.08 (0.97, 1.21)	1.28 (1.14, 1.45)	1.12 (1.06, 1.18)	< 0.001
Unprocessed red meat							
Median servings/d	0.14	0.35	0.5	0.71	1.09		
Cases/PY	847/205918	875/199361	840/207111	877/201942	1016/209540		
Age-adjusted Model	1	1.13 (1.02, 1.24)	1.08 (0.98, 1.19)	1.17 (1.06, 1.28)	1.36 (1.24, 1.49)	1.27 (1.18, 1.35)	<0.001
Multivariable-adjusted Model 1	1	1.12 (1.01, 1.23)	1.05 (0.95, 1.16)	1.12 (1.01, 1.23)	1.24 (1.12, 1.37)	1.17 (1.08, 1.26)	< 0.001
Multivariable-adjusted Model 2	1	1.11 (1.01, 1.22)	1.04 (0.94, 1.16)	1.09 (0.98, 1.22)	1.18 (1.05, 1.32)	1.11 (1.02, 1.21)	0.01
Processed red meat							
Median servings/d	0.02	0.14	0.21	0.38	0.71		
Cases/PY	889/224469	734/181661	883/211353	843/201440	1107/204950		
Age-adjusted Model	1	1.05 (0.95, 1.15)	1.14 (1.04, 1.25)	1.12 (1.02, 1.24)	1.39 (1.27, 1.52)	1.32 (1.24, 1.41)	<0.001
Multivariable-adjusted Model 1	1	1.02 (0.93, 1.13)	1.09 (0.99, 1.20)	1.06 (0.96, 1.16)	1.24 (1.12, 1.36)	1.20 (1.12, 1.30)	<0.001
Multivariable-adjusted Model 2	1	1.02 (0.92, 1.13)	1.09 (0.98, 1.20)	1.05 (0.95, 1.17)	1.19 (1.07, 1.33)	1.15 (1.06, 1.25)	0.001

Age-adjusted Model: Adjusted for age and year of questionnaire return

Multivariable-adjusted Model 1: Adjusted for variables in Age-adjusted Model + race/ethnicity (white, black, Asian, other), marital status (married, divorced, widowed, never married), living arrangement (lives with family, lives alone, other arrangements), profession (dentist, pharmacist, optometrist, podiatrist, veterinary), work status (full time, part time, retired), smoking status (never smoker, past smoker, current 1 to 14 cigarettes per day, current 15 to 24 cigarettes per day, current ≥ 25 cigarettes per day), physical activity(< 3, 3-8.9, 9-17.9, 18-26.9, and ≥ 27 in metabolic equivalents per week), body mass index;(< 21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33-34.9, 35-39.9, ≥ 40 in kg/m2), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10-14.9, or ≥ 15.0 g per day), multivitamin use (yes, no), aspirin use (yes, no), family history of early CHD or stroke (diagnosis before 60 years of age; yes, no), and total energy intake (in quintiles).

Multivariable-adjusted Model 2: Adjusted for variables in Model 1 + intakes of poultry, fish, egg, high fat dairy, low fat dairy, nuts, legumes, soy, whole grains, fruits, vegetables, and coffee, and glycemic index

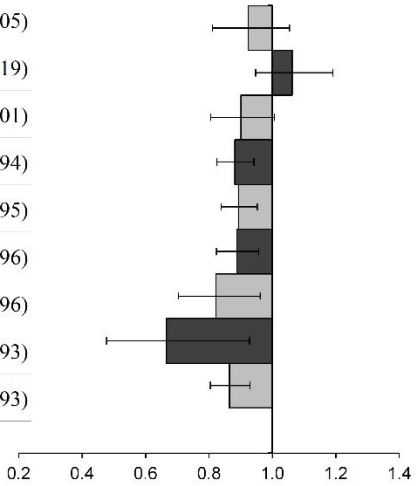
* P-value when each quintile was assigned the median value and treated as a continuous variable

Abbreviations: CHD, Coronary Heart Disease; PY, Person-Years; HR, Hazard Ratio; CI, Confidence Interval

Figure 1: Hazard Ratios (95% CI) for total CHD associated with replacement of 1 serving/day of total, unprocessed, and processed red meat with 1 serving/day of other protein sources or whole grains.

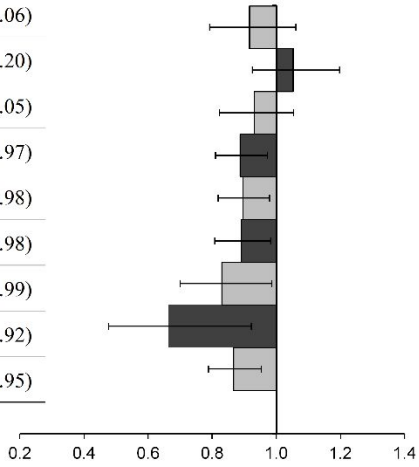
A. Total red meat

	HR (95% CI)
Poultry	0.92 (0.81, 1.05)
Fish	1.06 (0.95, 1.19)
Eggs	0.90 (0.81, 1.01)
High-fat dairy	0.88 (0.82, 0.94)
Low-fat dairy	0.89 (0.84, 0.95)
Nuts	0.89 (0.82, 0.96)
Legumes	0.82 (0.70, 0.96)
Soy*	0.67 (0.48, 0.93)
Plant-based proteins	0.86 (0.80, 0.93)



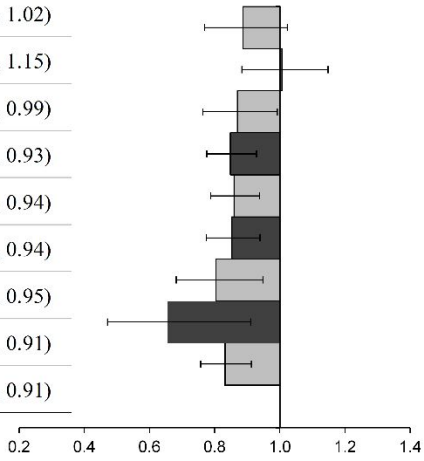
B. Unprocessed red meat

	HR (95% CI)
Poultry	0.92 (0.79, 1.06)
Fish	1.05 (0.93, 1.20)
Eggs	0.93 (0.82, 1.05)
High-fat dairy	0.89 (0.81, 0.97)
Low-fat dairy	0.90 (0.82, 0.98)
Nuts	0.89 (0.81, 0.98)
Legumes	0.83 (0.70, 0.99)
Soy*	0.66 (0.48, 0.92)
Plant-based proteins	0.87 (0.79, 0.95)



C. Processed red meat

	HR (95% CI)
Poultry	0.89 (0.77, 1.02)
Fish	1.01 (0.88, 1.15)
Eggs	0.87 (0.76, 0.99)
High-fat dairy	0.85 (0.78, 0.93)
Low-fat dairy	0.86 (0.79, 0.94)
Nuts	0.85 (0.77, 0.94)
Legumes	0.80 (0.68, 0.95)
Soy*	0.66 (0.47, 0.91)
Plant-based proteins	0.83 (0.76, 0.91)



* Replacing ≥2 servings/week of red meat with ≥2 servings/week of soy
One daily serving of nuts (28g); low-fat dairy products (240 ml skimmed or 1-2% milk, 28g low-fat or fat-free cheese, or 120 ml yogurt); high fat dairy product (240 ml whole milk, 28g cream cheese, or 1 cup of regular ice cream); legumes (1/2 cup); whole grains (32 g (1 slice) of bread or 200 g (1 cup) of cooked brown rice or cereals). Models were adjusted for age, year of questionnaire return,, race/ethnicity (white, black, Asian, other), marital status (married, divorced, widowed, never married), living arrangement (lives with family, lives alone, other arrangements), profession (dentist, pharmacist, optometrist, podiatrist, veterinary), work status (full time, part time, retired), smoking status (never smoker, past smoker, current 1 to 14 cigarettes per day, current 15 to 24 cigarettes per day, current ≥ 25 cigarettes per day), physical activity(< 3, 3-8.9, 9-17.9, 18-26.9, and ≥ 27 in metabolic equivalents per week), body mass index;(< 21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33-34.9, 35-39.9, ≥ 40 in kg/m2), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10-14.9, or ≥ 15.0 g per day), multivitamin use (yes, no), aspirin use (yes, no), family history of early CHD or stroke (diagnosis before 60 years of age; yes, no), and total energy intake (in quintiles), and intakes of poultry, fish, egg, high fat dairy, low fat dairy, nuts, legumes, soy (or combined plant protein sources of nuts, legumes, and soy), whole grains, fruits, vegetables, and coffee, and glycemic index.
Abbreviations: CHD, Coronary Heart Disease; HR, Hazard Ratio; CI, Confidence Interval

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