Title

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ORIGINAL RESEARCH

Association of Major Dietary Protein Sources With All-Cause and Cause-Specific Mortality: Prospective Cohort Study

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BACKGROUND: Dietary recommendations regarding protein intake have been focused on the amount of protein. However, such recommendations without considering specific protein sources may be simplistic and insufficient.

METHODS AND RESULTS: We included 102 521 postmenopausal women enrolled in the Women's Health Initiative between 1993 and 1998, and followed them through February 2017. During 1 876 205 person-years of follow-up, 25 976 deaths occurred. Comparing the highest with the lowest quintile, plant protein intake was inversely associated with all-cause mortality (hazard ratio [HR], 0.91 [0.86, 0.96]), cardiovascular disease mortality (HR, 0.88 [0.79, 0.97]), and dementia mortality (HR, 0.79 [0.67, 0.94]). Among major protein sources, comparing the highest with the lowest quintile of consumption, processed red meat (HR, 1.06 [1.01, 1.10]) or eggs (HR, 1.14 [1.10, 1.19]) was associated with higher risk of all-cause mortality. Unprocessed red meat (HR, 1.12 [1.02, 1.23]), eggs (HR, 1.24 [1.14, 1.34]), or dairy products (HR, 1.11 [1.02, 1.22]) was associated with higher risk of cardiovascular disease mortality. Egg consumption was associated with higher risk of cancer mortality (HR, 1.10 [1.02, 1.19]). Processed red meat consumption was associated with higher risk of dementia mortality (HR, 1.20 [1.05, 1.32]), while consumption of poultry (HR, 0.85 [0.75, 0.97]) or eggs (HR, 0.86 [0.75, 0.98]) was associated with lower risk of dementia mortality. In substitution analysis, substituting of animal protein with plant protein was associated with a lower risk of all-cause mortality, cardiovascular disease mortality, and dementia mortality, and substitution of total red meat, eggs, or dairy products with nuts was associated with a lower risk of all-cause mortality.

CONCLUSIONS: Different dietary protein sources have varying associations with all-cause mortality, cardiovascular disease mortality, and dementia mortality. Our findings support the need for consideration of protein sources in future dietary guidelines.

Key Words: all-cause mortality ■ cause-specific mortality ■ dietary protein intake ■ dietary protein sources ■ postmenopausal women

Dietary guidelines in the United States and around the world usually recommend consumption of a sufficient amount of protein given its critical role in human growth, development, and health.[1–3] However, previous studies investigating the health effects of dietary protein have yielded inconsistent results. For example, some studies have shown favorable associations of plant protein[4,5] and inverse associations of animal protein with health,[5,6] while other studies have found no significant associations[4] or have even found associations in the opposite direction.[7,8] These discrepancies may be in part because of variations in animal or plant protein sources in different populations. Therefore, dietary recommendations for human health focusing on total protein intake without considering specific protein sources may be simplistic and

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CLINICAL PERSPECTIVE

What Is New?

- Different dietary protein sources have varying associations with all-cause mortality, cardiovascular disease mortality, and dementia mortality.
- Higher plant protein intake and substitution of animal protein with plant protein were associated with lower risk of all-cause mortality, cardiovascular disease mortality, and dementia mortality.

What Are the Clinical Implications?

- Our findings support the need for consideration of protein sources, in addition to the amount of protein intake, in future dietary guidelines.

Nonstandard Abbreviations and Acronyms

CT	Clinical Trials
FFQ	food frequency questionnaire
OS	Observational Study
WHI	Women's Health Initiative

insufficient. A thorough investigation regarding the impact of different dietary protein sources, beyond total protein intake, on human health is warranted to inform future dietary guidelines.

Although previous studies have shown a significant association between red meat consumption and mortality, studies examining the associations of other major dietary protein sources with risk of all-cause and cause-specific mortality are sparse and/or inconclusive. On the basis of recent findings about dietary protein sources in relation to coronary heart disease,[7] stroke,[9] and certain types of cancers (eg, breast cancer),[10] we hypothesized that different dietary protein sources would be differentially associated with mortality risk. We used data from a large prospective cohort study with up to 18 years of follow-up to investigate the risks of all-cause and cause-specific mortality in relation to animal and plant protein intake, and major sources of dietary protein. Furthermore, we estimated whether replacement of selected protein source with other alternatives was associated with mortality risk.

METHODS

This study used data from the Women's Health Initiative (WHI), which was initiated by the National Institutes of Health (NIH) in 1991. The WHI is a long-term national health study that focuses on strategies for preventing heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women. Because of the nature of the data collected for this study, the WHI data are accessible to qualified researchers trained in human subject confidentiality protocols. Requests to access the data set may be sent to the WHI Publications and Presentations Committee.

Study Population

The WHI study design has been previously described in detail.[11] Briefly, between 1993 and 1998, postmenopausal women aged 50 to 79 years old at study entry were recruited through 40 clinical centers into either a Clinical Trials (CT) component (n=68 132), or an Observational Study (OS) component (n=93 676 women). The CT consisted of 4 trials including a dietary modification (DM) trial, 2 hormonal therapy trials, and a calcium and vitamin D clinical trial. The CT and OS were closed in 2004 to 2005 and participants were invited to continue being followed in the WHI Extension Studies, which currently have follow-up data through February 2017. Written informed consent was obtained from each subject. Institutional review board approval was obtained from all participating institutions.

In the present study, we included participants in both the OS component and CT components with the exception of the DM trial intervention arm, because participants in the DM trial intervention arm were randomized to evaluate the effects of a low-fat diet,[12] which may affect their intake of proteins. Of the 142 267 (OS=93 676; CT=48 591) eligible participants, 137 481 women (OS=90 009 [96%]; CT=47 472 [98%]) had valid food frequency questionnaire (FFQ) data defined by reported energy intake between 600 and 5000 kcal/d. We excluded 137 women who had missing data on postmenopausal hormone therapy use, 24 427 women who had a history of cardiovascular disease (CVD) at baseline, and 10 366 women who had a history of cancer at baseline, leaving 102 521 women in the final analyses (OS=63 593; CT=38 928).

Dietary Assessment

A standardized written protocol, centralized training of staff, and quality assurance visits by the Clinical Coordinating Center were used to ensure uniform administration of data collection. Diet was measured at baseline in the WHI using a self-administered FFQ developed and validated,[13] adapted from the Health Habits and Lifestyle Questionnaire.[14] The 3 sections of the WHI FFQ included 122 composite and single food line items asking about frequency of consumption and portion size, 19 adjustment questions related to type of fat intake, and 4 summary questions asking about the usual intake of fruits and vegetables and added fats for comparison with information

gathered from the line items. The WHI-FFQ was designed to capture foods relevant for multiethnic and geographically diverse population groups. The reliability of the FFQ has been previously assessed. The mean correlation of 30 nutrients estimated by FFQ and 8 days of dietary intake from a 4-day food record and four 24-hour dietary recalls was 0.57. The correlations of energy, percent energy from fat, carbohydrate, and protein estimated from FFQ and 4-day food records were 0.37, 0.62, 0.41, and 0.36, respectively.[13] These estimates are similar to the estimates in other cohorts.[15,16]

The nutrient database used to analyze the WHI-FFQ is derived from the Nutrition Data Systems for Research (http://www.ncc.umn.edu/products/ndsr-user-manual/),[17] which provides nutrient information for >140 nutrients and compounds, including energy, saturated fat, sodium, and others.[17–19] Animal protein is protein from animal products, including red meat, poultry, fish/shellfish, eggs, and dairy foods, while plant protein is protein contributed by plant products. In our analyses, animal and plant protein intake was expressed as a percentage of energy from animal and plant protein, respectively, divided by total energy intake.

The MyPyramid Equivalents Database version 2.0, developed by the United States Department of Agriculture,[20] was used to obtain food group intakes in MyPyramid equivalents per 100 g of food. Major dietary animal protein sources included unprocessed red meat (beef, pork, veal, lamb, and game), processed red meat (franks, sausages, luncheon meats), poultry (chicken, turkey, and other poultry), fish/shellfish (fish, and other seafood), eggs, and dairy products (milk, yogurt, and cheese). Major dietary plant protein sources included nuts (nuts and seeds) and legumes (soy product, beans and peas). In MyPyramid Equivalents Database, they have been computed into ounce equivalent or cup equivalent of protein food according to their content of protein. For example, 1 oz cooked meat, or 1 egg, or 0.5 oz of nuts, or one quarter cups of beans, counts as 1 oz equivalent of protein food, while 1 cup of milk or yogurt, or 1.5 oz of hard cheese, counts as 1 cup equivalent.

Ascertainment of Death

Deaths were ascertained by reviewing death certificates, medical records, autopsy reports, or by linkage to the National Death Index.[21] Death certificates and hospital records were obtained and adjudicated by physician adjudicators who were unaware of study component or randomization assignment. Deaths in the CT component of the WHI were centrally adjudicated, as were major causes of CVD death and the 5 main WHI cancer outcomes. Other deaths were adjudicated locally.[21] For deaths occurring in the hospital, records from the most relevant hospitalization preceding death and from the time of death, autopsy records, and the death certificate were used by adjudicators in determining the causes of death. For many deaths occurring out-of-hospital, documentation was limited to the death certificate and records of the most recent hospitalization before death. In these instances, the immediate and underlying causes of death were abstracted from the death certificate.[21] Ascertainment of outcomes was complete as of February 28, 2017. Mortality end points for this study included all-cause mortality (primary outcome), CVD mortality, cancer mortality, and dementia mortality. CVD mortality included deaths from atherosclerotic cardiac, definite coronary heart disease, possible coronary heart disease, cerebrovascular disease, pulmonary embolism, and other or unknown cardiovascular disease. Cancer mortality include deaths from all types of cancer.

Other Covariate Assessments

Information on demographic characteristics, lifestyle, disease history, medication use, family history of disease, and past hormone use was collected at baseline through self-reporting. Recreational moderate–vigorous intensity physical activity, including walking, was assessed by questionnaire, and metabolic equivalent task hours/wk of physical activity for each participant were calculated, as described previously.[11,22] Weight and height were measured during clinic visits using standard methods at baseline. We calculated body mass index as weight (kg)/height $(m)^2$.

Statistical Analysis

Comparisons of covariates among different groups were performed using ANOVA for continuous variables and χ^2 test for categorical variables.

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for mortality associated with protein intake and major protein source consumption. We have tested the proportional hazard assumption by examining the Kaplan–Meier curves. Person-years were calculated from the date of baseline FFQ until the date of death, the last National Death Index search date, or the end of the previously described WHI-Extension Study 2 on February 28, 2017, whichever came first. Multivariable models were constructed in several stages. In the minimally adjusted model we adjusted for age at baseline and race/ethnicity. For animal and plant protein intake, in multivariable model 1 we additionally adjusted for socioeconomic status (education level and annual income), whether the participant was from the OS or CT component, hormone use history (unopposed estrogen use, and estrogen+progesterone use), lifestyle (smoking status, physical activity, and alcohol intake),

Table 1. Baseline Characteristics According to Quintiles of Dietary Animal Protein Intake and Plant Protein Intake Among 102 521 Women from WHI

Variables	Animal Protein Intake, % of Total Energy			Plant Protein Intake, % of Total Energy		
	Q1	Q3	Q5	Q1	Q3	Q5
Number of participants	20 504	20 505	20 504	20 504	20 505	20 504
Age at baseline, y	62.8 (7.4)	62.7 (7.1)	62.8 (7.0)	62.1 (7.1)	63.0 (7.2)	63.1 (7.3)
Race/ethnicity, %						
White	76.4	84.5	85.6	79.8	85.6	80.7
Black	11.3	7.3	8.5	12.9	6.7	6.5
Hispanic	5.0	4.0	4.1	4.6	4.1	4.2
Others*	6.9	4.0	3.0	2.6	3.5	8.2
Missing	0.3	0.3	0.3	0.2	0.2	0.3
Education, %						
High school or less	33.6	30.7	30.5	38.4	30.9	26.1
Some college	26.0	27.5	28.2	28.2	27.6	25.7
College	10.7	11.1	11.9	10.2	11.7	12.0
Postgraduate	29.0	29.9	28.6	22.2	29.1	35.6
Missing	0.8	0.8	0.7	0.9	0.7	0.7
Income, %						
<20 000	17.4	13.4	13.0	17.6	13.2	13.4
20 000–49 999	41.2	42.1	40.9	42.3	42.0	39.7
>50 000	34.4	38.1	39.4	33.5	38.1	40.0
Missing	7.2	6.3	6.8	6.6	6.7	6.9
WHI component/arm, %						
WHI clinical trials	34.2	39.4	38.1	47.1	40.1	24.5
WHI observational study	65.8	60.6	61.9	52.9	60.0	75.6
Unopposed estrogen usage status, %						
Never used	66.3	65.7	66.3	67.2	65.3	66.1
Past user	12.1	12.1	12.1	12.3	12.1	11.8
Current user	21.7	22.3	21.5	20.5	22.6	22.1
Estrogen+progestin use status, %						
Never used	72.9	70.9	72.6	75.7	71.3	69.7
Past user	8.5	8.8	8.7	7.9	8.6	8.9
Current user	18.6	20.3	18.8	16.4	20.1	21.5
Smoking status, %						
Never smoked	51.3	50.9	50.1	46.2	52.0	53.5
Past smoker	40.3	41.1	41.7	40.5	40.6	41.4
Current smoker	7.0	6.8	6.9	11.9	6.0	3.7
Missing	1.3	1.2	1.4	1.5	1.3	1.4
Physical activity (MET-h/wk), %						
<10	48.7	49.2	49.4	60.8	49.5	38.5
≥10	46.9	45.6	46.0	33.7	45.2	58.1
Missing	4.4	5.2	4.6	5.6	5.3	3.4
Alcohol intake, %						
Nondrinker	42.7	37.3	41.2	39.0	37.4	44.6
Moderate drinking	42.9	48.8	49.5	41.2	49.9	49.1
Heavy drinking	14.4	13.9	9.3	19.8	12.7	6.3
Total energy intake, kcal/d	1555 (640)	1673 (639)	1581 (602)	1771 (727)	1627 (605)	1460 (532)
Baseline diabetes mellitus, %	3.4	4.5	6.7	4.5	4.5	5.2

(*Continued*)

Table 1. Continued

Variables	Animal Protein Intake, % of Total Energy			Plant Protein Intake, % of Total Energy		
	Q1	Q3	Q5	Q1	Q3	Q5
Baseline high blood cholesterol, %	11.3	10.7	11.9	9.1	11.4	13.3
Family history of heart attack, %	46.1	48.1	48.9	46.4	48.1	48.1
Family history of stroke, %	35.1	36.4	35.5	34.5	35.4	36.0
Glycemic load	106.2 (45.8)	100.4 (39.5)	84.7 (34.2)	95.6 (47.1)	97.8 (38.3)	100.5 (38.3)
Percent energy from SFA, %	9.7 (3.5)	11.0 (3.2)	10.9 (3.3)	13.1 (3.4)	10.8 (2.6)	7.9 (2.5)
Percent energy from MUFA, %	11.8 (3.8)	12.4 (3.4)	12.0 (3.5)	14.1 (3.4)	12.3 (3.0)	9.8 (3.2)
Percent energy from PUFA, %	7.0 (2.6)	6.8 (2.0)	6.2 (1.9)	7.2 (2.5)	6.8 (2.0)	6.0 (2.0)
Percent energy from TFA, %	2.2 (1.3)	2.3 (1.1)	2.0 (0.9)	2.6 (1.2)	2.3 (1.1)	1.6 (0.9)
Dietary fiber, g/d	17.3 (7.7)	16.4 (6.7)	14.5 (6.1)	11.7 (5.1)	16.1 (5.9)	20.7 (7.7)
BMI	26.6 (5.5)	27.7 (5.7)	28.7 (6.0)	29.1 (6.4)	27.7 (5.7)	26.3 (5.3)

BMI indicates body mass index; MET, metabolic equivalent task; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TFA, *trans*-fatty acid; and WHI, Women's Health Initiative.

*Others included American Indian or Alaskan Native, Asian or Pacific Islander, and others.

baseline health status (baseline diabetes mellitus status, and baseline high blood cholesterol status), family history of heart attack/stroke, and dietary factors (total energy intake, percentage of energy from saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and *trans*-fatty acids, dietary fiber intake, and glycemic load). For animal and plant protein intake, their mutual adjustment was also added. For the consumption of major protein sources, in multivariable model 1 we additionally adjusted for socioeconomic status, if the participant was from OS or CT component, hormone use history, lifestyle, baseline health status, family history of heart attack/stroke, and dietary factors (total energy intake, whole grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption), and mutual adjustment for other protein sources. In multivariable model 2 we additionally adjusted for body mass index. Considering that dementia generally occurs at older ages than CVD and cancer, and deaths that occur before dementia onset in individuals who would have developed dementia (had they lived long enough) have the effect of censoring the latent failure time to dementia, we additionally performed a competing risk analysis for dementia mortality. In this competing risk analysis, participants who died of causes other than dementia were not censored but were considered as a competitive event.

We evaluated whether the associations of protein sources with mortality varied by age (<65 years versus ≥65 years), race/ethnicity (White versus non-White), smoking status (never smoked versus ever smoked), and physical activity (<10 versus ≥10 metabolic equivalent task hours per week). We first conducted interaction tests via multiplicative interaction terms in the multivariable models, and when significant interactions were detected, we showed data in different strata. For sensitivity analyses, we repeated the analyses by (1) excluding women in the CT; and (2) excluding deaths within 3 years after baseline.

Finally, we estimated the effect of substituting 5% of energy of animal protein with an equivalent amount of energy from plant protein. In order to identify the healthy alternatives associated with lower mortality risk for total red meat, we also estimated the effect of substituting 2 oz equivalent/d of total red meat with other protein sources, by simultaneously including these protein items as continuous variables in the multivariable model. The HRs and 95% CIs for the substitution effect were derived from the difference among the regression coefficients, variance, and covariance.[23]

All statistical tests were based on a priori hypotheses, and thus there was no adjustment for multiple testing. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided with statistical significance set at $P < 0.05$.

RESULTS

Baseline Characteristics

During 1 876 205 person-years of follow-up (18.1 years on average), 25 976 deaths occurred, including 6993 deaths from CVD, 7516 deaths from cancer, and 2734 from dementia. CVD deaths included 776 deaths from definite coronary heart disease, 1808 deaths from cerebrovascular diseases, 140 deaths from pulmonary embolism, 2120 deaths from possible coronary heart disease, and 2149 deaths from other or unknown cardiovascular diseases. Cancer deaths including 1724 deaths from lung cancer, 684 deaths from breast cancer, 699 deaths from pancreatic cancer, 615 deaths from colorectal cancer, 532 deaths from ovarian cancer,

Table 2. Association of Animal Protein Intake and Plant Protein Intake With All-Cause Mortality Among 102 521 Women From WHI

	Quintiles of Protein Intake, % of Total Energy					*P* Value for Trend	HR for Every 5% of Total Energy
	Q1	Q2	Q3	Q4	Q5		
Animal protein							
Median intake	7.5	9.8	11.5	13.2	16.0		
N of cases/person-y	5099/374 345	5151/375 718	5190/376 529	5166/376 131	5370/373 481		
Minimal adjusted Model	1.00 (Ref)	0.99 (0.96, 1.03)	1.00 (0.97, 1.04)	0.99 (0.95, 1.03)	1.01 (0.97, 1.05)	0.92	1.00 (0.98, 1.02)
Multivariable Model 1	1.00 (Ref)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	1.00 (0.96, 1.04)	1.01 (0.96, 1.05)	0.99	0.99 (0.97, 1.02)
Multivariable Model 2	1.00 (Ref)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	0.99 (0.95, 1.03)	0.99 (0.95, 1.04)	0.56	0.99 (0.97, 1.01)
Plant protein							
Median intake	3.5	4.3	4.9	5.6	6.8		
N of cases/person-y	5574/370 108	5248/374 893	5214/376 059	5103/376 931	4837/378 214		
Minimal adjusted Model	1.00 (Ref)	0.88 (0.84, 0.91)	0.83 (0.80, 0.86)	0.80 (0.77, 0.83)	0.75 (0.72, 0.78)	<0.001	0.68 (0.65, 0.72)
Multivariable Model 1	1.00 (Ref)	0.95 (0.92, 0.99)	0.95 (0.91, 0.99)	0.93 (0.89, 0.98)	0.91 (0.86, 0.96)	0.001	0.86 (0.80, 0.92)
Multivariable Model 2	1.00 (Ref)	0.95 (0.92, 0.99)	0.95 (0.91, 0.99)	0.93 (0.89, 0.98)	0.91 (0.86, 0.96)	0.002	0.86 (0.80, 0.93)

Minimal adjusted Model: age at baseline, and race/ethnicity. Multivariable Model 1: age at baseline, race/ethnicity, education, income, Observational Study/Clinical Trials, unopposed estrogen use, estrogen+progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack/stroke, percentage of energy from saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and *trans*-fatty acids, dietary fiber intake, and glycemic load. For animal and plant protein, their mutual adjustment was also added. Multivariable Model 2: Multivariable Model 1+BMI. HR indicates hazard ratio; and WHI, Women's Health Initiative.

Table 3. Association of Animal Protein Intake and Plant Protein Intake With Cause-Specific Mortality Among 102 521 Women From WHI

	Quintiles of Protein Intake, % of Total Energy					*P* Value for Trend	HR for Every 5% of Total Energy
	Q1	Q2	Q3	Q4	Q5		
Animal protein							
CVD mortality	1.00 (Ref)	1.00 (0.93, 1.08)	1.05 (0.97, 1.13)	1.03 (0.95, 1.11)	1.05 (0.96, 1.15)	0.24	1.02 (0.98, 1.07)
Cancer mortality	1.00 (Ref)	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)	0.98 (0.91, 1.06)	0.99 (0.91, 1.07)	0.73	0.98 (0.94, 1.03)
Dementia mortality	1.00 (Ref)	1.01 (0.90, 1.14)	0.98 (0.87, 1.11)	0.93 (0.82, 1.06)	0.90 (0.78, 1.04)	0.10	0.94 (0.88, 1.01)
Plant protein							
CVD mortality	1.00 (Ref)	0.94 (0.87, 1.01)	0.93 (0.86, 1.01)	0.90 (0.82, 0.98)	0.88 (0.79, 0.97)	0.01	0.82 (0.72, 0.95)
Cancer mortality	1.00 (Ref)	0.98 (0.91, 1.06)	0.99 (0.91, 1.06)	1.06 (0.97, 1.16)	1.06 (0.96, 1.18)	0.11	1.05 (0.92, 1.19)
Dementia mortality	1.00 (Ref)	1.05 (0.92, 1.19)	0.93 (0.81, 1.06)	0.91 (0.78, 1.05)	0.79 (0.67, 0.94)	0.003	0.72 (0.58, 0.90)

Adjustment: age at baseline, race/ethnicity, education, income, Observational Study/Clinical Trials, unopposed estrogen use, estrogen+progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack/stroke, percentage of energy from saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and *trans*-fatty acids, dietary fiber intake, and glycemic load. For animal and plant protein, their mutual adjustment was also added. CVD indicates cardiovascular disease; HR, hazard ratio; and WHI, Women's Health Initiative.

and 3262 deaths from other types of cancer. As shown in Table 1, compared with women with a lower percent of energy from animal protein intake, those with a higher percent of energy from animal protein intake were more likely to be White and have higher education and higher income. They were more likely to be past smokers, and have less heavy alcohol intake. They were also more likely to have diabetes mellitus at baseline, and have a family history of heart attack. They tended to have a higher percent of energy from saturated fatty acid, lower percent of energy from polyunsaturated fatty acid, lower intake of dietary fiber, have lower glycemic load, and have higher body mass index.

The patterns for plant protein intake were similar, except that women with a higher percent of energy from plant protein intake were more likely to be older, have less total energy intake, a lower percent of energy from saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, and *trans*-fatty acid, have higher intake of dietary fiber, have higher glycemic load, and have lower body mass index.

Dietary Protein Intake and Mortality

In these 102 521 postmenopausal women, 16.8% (SD=3.2%) of total energy was from protein intake, among which 68.6% (SD=10.3) was from animal protein intake. The median percent intake of total energy from animal protein in this population was 7.5% in the lowest quintile and 16.0% in the highest quintile. The median percent intake of total energy from plant protein in this population was 3.5% in the lowest quintile and 6.8% in the highest quintile. After adjustment for age, race/ethnicity, socioeconomic status, dietary and lifestyles factors, and baseline and family history of diseases, animal protein intake was not associated with all-cause or cause-specific mortality, comparing the highest with the lowest quintile (Tables 2 and 3). Comparing the highest with the lowest quintile, plant protein intake was inversely associated with all-cause mortality (HR, 0.91; 95% CI, 0.86–0.96), CVD mortality (HR, 0.88; 95% CI, 0.79–0.97), and dementia mortality (HR, 0.79; 95% CI, 0.67–0.94) (Table 2). Plant protein intake was not associated with cancer mortality (Table 3). Competing risk analysis for dementia mortality revealed similar results (Table S1).

Substituting 5% energy of animal protein with plant protein was associated with a lower risk of all-cause mortality (HR, 0.86; 95% CI, 0.81–0.91), CVD mortality (HR, 0.78, 95% CI, 0.70–0.87), and dementia mortality (HR, 0.81, 95% CI, 0.68–0.97) (Figure 1). Substituting 5% energy of animal protein with plant protein was not associated with cancer mortality. The results of sensitivity analyses were similar when women in the CT were excluded or deaths occurring within 3 years after baseline were excluded (Tables S2 and S3). The associations of protein intake with all-cause and cause-specific

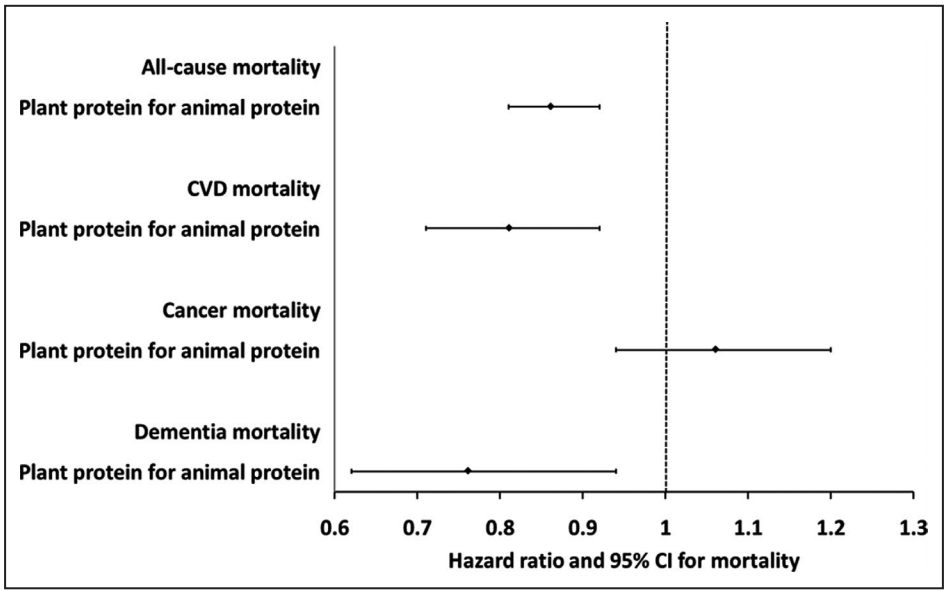

Figure 1. Hazard ratios of all-cause and cause-specific mortality associated with replacement of 5% energy of animal protein with plant protein.
CVD indicates cardiovascular disease.

mortality did not vary by age, race/ethnicity, smoking status, physical activity levels, or hormone use (data not shown).

Major Dietary Protein Sources and Mortality

Comparing the highest with the lowest quintile, consumption of total red meat (HR, 1.10; 95% CI, 1.05–1.15), processed red meat (HR, 1.06; 95% CI, 1.01–1.10), or eggs (HR, 1.14; 95% CI, 1.10–1.19) was each associated with higher risk of all-cause mortality (Table 4). Consumption of unprocessed red meat, poultry, fish/shellfish, dairy products, or legumes or nuts was not associated with mortality. Furthermore, substituting 2 oz equivalent/d of total red meat (HR, 0.89; 95% CI, 0.81–0.98), eggs (HR, 0.53; 95% CI, 0.45–0.61), dairy products (HR, 0.88; 95% CI, 0.80–0.97), or legumes (HR, 0.86; 95% CI, 0.74–0.99) with nuts was associated with lower risk of all-cause mortality (Figures 2 and 3).

Comparing the highest with the lowest quintile, total red meat (HR, 1.14; 95% CI, 1.04–1.25), unprocessed red meat (HR, 1.12; 95% CI, 1.02–1.23), egg (HR, 1.24; 95% CI, 1.14–1.34) or dairy product consumption (HR, 1.11; 95% CI, 1.02–1.22) was each associated with higher risk of CVD mortality. Processed red meat, poultry, fish/shellfish, legume, or nut consumption was not associated with CVD mortality (Table 5). Substituting 2 oz equivalent/d of eggs (HR, 0.44; 95% CI, 0.33–0.58), dairy products (HR, 0.81; 95% CI, 0.67–0.97), or legumes (HR, 0.70; 95% CI, 0.53–0.92) with nuts was associated with lower risk of CVD mortality (Figure 3).

Major protein sources were not associated with cancer mortality, except that egg consumption was associated with higher risk of cancer mortality (HR, 1.10; 95% CI, 1.02–1.19), comparing the highest with the lowest quintile (Table 5). Substituting 2 oz equivalent/d of eggs (HR, 0.59; 95% CI, 0.45–0.78) with nuts was associated with lower risk of cancer mortality (Figure 3).

Comparing the highest with the lowest quintile, consumption of processed red meat (HR, 1.20; 95% CI, 1.05–1.36) was associated with higher risk of dementia mortality, while consumption of poultry (HR, 0.85; 95% CI, 0.75–0.97) or eggs (HR, 0.86; 95% CI, 0.75–0.98) was each associated with lower risk of dementia mortality. Unprocessed red meat, fish/shellfish, dairy product, legume, or nut consumption was not associated with dementia mortality. Competing risk analysis for dementia mortality revealed similar results. Furthermore, substituting 2 oz equivalent/d of dairy products with nuts (HR, 0.70; 95% CI, 0.51–0.96) was associated with lower risk of dementia mortality (Figure 3).

The results were robust in sensitivity analyses by excluding women in the CT or women who died within 3 years after baseline (Tables S4 and S5). The associations of major protein sources with all-cause mortality did not vary by age, race/ethnicity, smoking status, physical activity levels, or hormone use, except that unprocessed and processed red meat was associated with higher risk of all-cause and CVD mortality and poultry consumption was associated with lower

Table 4. Association of Major Protein Sources With All-Cause Mortality Among 102 521 Women From WHI

	Quintiles of Protein Intake					*P* Value for Trend	HR for 1 oz Equivalent/d
	Q1	Q2	Q3	Q4	Q5		
Total red meat							
Median intake	0.4	1.0	1.5	2.4	3.9		
N of cases/person-y	4997/376 020	5264/374 527	5383/374 928	5184/375 547	5148/375 183		
Minimal adjusted Model	1.00 (Ref)	1.06 (1.02, 1.11)	1.13 (1.09, 1.18)	1.15 (1.10, 1.19)	1.22 (1.17, 1.27)	<0.001	1.03 (1.03, 1.04)
Multivariable Model 1	1.00 (Ref)	1.03 (0.99, 1.08)	1.08 (1.04, 1.13)	1.08 (1.03, 1.13)	1.10 (1.05, 1.15)	<0.001	1.01 (1.01, 1.02)
Multivariable Model 2	1.00 (Ref)	1.03 (0.99, 1.07)	1.07 (1.03, 1.12)	1.07 (1.03, 1.12)	1.08 (1.03, 1.12)	0.004	1.01 (1.01, 1.02)
Unprocessed red meat							
Median intake	0.3	0.7	1.2	1.8	3.2		
N of cases/person-y	5073/375 022	5305/374 702	5313/374 989	5235/375 380	5050/376112		
Minimal adjusted Model	1.00 (Ref)	1.04 (1.01, 1.09)	1.06 (1.02, 1.10)	1.10 (1.06, 1.15)	1.11 (1.06, 1.16)	<0.001	1.02 (1.01, 1.03)
Multivariable Model 1	1.00 (Ref)	1.03 (0.99, 1.07)	1.04 (1.01, 1.09)	1.07 (1.02, 1.12)	1.05 (0.99, 1.10)	0.11	1.01 (0.99, 1.02)
Multivariable Model 2	1.00 (Ref)	1.03 (0.99, 1.07)	1.04 (0.99, 1.08)	1.06 (1.02, 1.11)	1.04 (0.99, 1.09)	0.23	1.00 (0.99, 1.02)
Processed red meat							
Median intake	0.01	0.1	0.2	0.5	1.0		
N of cases/person-y	5023/375 921	5132/375 449	5180/376 655	5228/374 391	5413/373 788		
Minimal adjusted Model	1.00 (Ref)	1.02 (0.98, 1.06)	1.06 (1.02, 1.11)	1.11 (1.06, 1.15)	1.15 (1.10, 1.20)	<0.001	1.09 (1.07, 1.12)
Multivariable Model 1	1.00 (Ref)	1.00 (0.96, 1.04)	1.01 (0.97, 1.06)	1.03 (0.99, 1.08)	1.06 (1.01, 1.10)	0.01	1.05 (1.02, 1.07)
Multivariable Model 2	1.00 (Ref)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	1.03 (0.99, 1.07)	1.05 (1.01, 1.10)	0.02	1.04 (1.02, 1.07)
Poultry							
Median intake	0.2	0.4	0.7	1.1	1.9		
N of cases/person-y	5690/368 948	5405/373 287	5218/376 480	4993/378 371	4760/379 119		
Minimal adjusted Model	1.00 (Ref)	0.95 (0.92, 0.99)	0.92 (0.88, 0.95)	0.92 (0.89, 0.96)	0.93 (0.89, 0.97)	<0.001	0.98 (0.97, 0.99)
Multivariable Model 1	1.00 (Ref)	0.97 (0.93, 1.01)	0.94 (0.91, 0.98)	0.97 (0.93, 1.01)	0.97 (0.93, 1.01)	0.22	0.99 (0.98, 1.02)
Multivariable Model 2	1.00 (Ref)	0.97 (0.93, 1.01)	0.94 (0.91, 0.98)	0.96 (0.93, 1.01)	0.97 (0.93, 1.01)	0.15	1.00 (0.98, 1.01)
Fish/shellfish							
Median intake	0.1	0.3	0.5	0.7	1.3		
N of cases/person-y	5699/369 506	5439/373 858	5173/376 704	4892/378 008	4773/378 129		
Minimal adjusted Model	1.00 (Ref)	0.95 (0.92, 0.99)	0.90 (0.87, 0.94)	0.88 (0.85, 0.92)	0.87 (0.83, 0.91)	<0.001	0.94 (0.91, 0.96)
Multivariable Model 1	1.00 (Ref)	1.00 (0.96, 1.03)	0.97 (0.93, 1.01)	0.97 (0.94, 1.01)	0.97 (0.93, 1.01)	0.07	0.99 (0.97, 1.02)
Multivariable Model 2	1.00 (Ref)	1.00 (0.96, 1.03)	0.97 (0.93, 1.07)	0.97 (0.93, 1.01)	0.97 (0.93, 1.01)	0.04	0.99 (0.97, 1.02)

(*Continued*)

Table 4. Continued

	Quintiles of Protein Intake					*P* Value for Trend	HR for 1 oz Equivalent/d
	Q1	Q2	Q3	Q4	Q5		
Eggs							
Median intake	0.03	0.1	0.2	0.3	0.7		
N of cases/person-y	5017/377 757	5094/376 870	5001/377 542	5182/374 989	5682/369 046		
Minimal adjusted Model	1.00 (Ref)	1.00 (0.96, 1.04)	1.04 (1.01, 1.09)	1.05 (1.01, 1.09)	1.24 (1.19, 1.29)	<0.001	1.24 (1.21, 1.28)
Multivariable Model 1	1.00 (Ref)	0.99 (0.96, 1.04)	1.02 (0.98, 1.06)	1.03 (0.98, 1.07)	1.14 (1.10, 1.19)	<0.001	1.16 (1.12, 1.19)
Multivariable Model 2	1.00 (Ref)	0.99 (0.96, 1.03)	1.01 (0.97, 1.06)	1.02 (0.98, 1.06)	1.13 (1.08, 1.18)	<0.001	1.15 (1.11, 1.18)
Dairy products							
Median intake	0.5	0.9	1.4	2.0	3.3		
N of cases/person-y	5299/370 823	5233/374 298	5184/375 885	5054/378 162	5206/377 038		
Minimal adjusted Model	1.00 (Ref)	0.95 (0.92, 0.99)	0.95 (0.91, 0.98)	0.93 (0.89, 0.97)	0.95 (0.91, 0.99)	0.02	0.99 (0.98, 1.00)
Multivariable Model 1	1.00 (Ref)	0.99 (0.95, 1.03)	1.00 (0.96, 1.04)	1.01 (0.96, 1.05)	1.04 (0.99, 1.09)	0.08	1.02 (1.01, 1.03)
Multivariable Model 2	1.00 (Ref)	0.99 (0.95, 1.03)	1.00 (0.96, 1.04)	1.00 (0.96, 1.05)	1.04 (0.99, 1.09)	0.11	1.02 (1.01, 1.03)
Legumes							
Median intake	0.02	0.1	0.2	0.4	0.9		
N of cases/person-y	5738/370 602	5499/373 523	5211/375 094	4941/377 833	4587/379 153		
Minimal adjusted Model	1.00 (Ref)	0.96 (0.93, 0.99)	0.92 (0.89, 0.96)	0.93 (0.89, 0.97)	0.93 (0.89, 0.97)	<0.001	0.97 (0.95, 1.00)
Multivariable Model 1	1.00 (Ref)	0.99 (0.96, 1.03)	0.98 (0.94, 1.02)	1.00 (0.96, 1.04)	1.02 (0.97, 1.06)	0.62	1.03 (0.99, 1.06)
Multivariable Model 2	1.00 (Ref)	0.99 (0.96, 1.03)	0.98 (0.94, 1.02)	1.00 (0.96, 1.04)	1.02 (0.98, 1.06)	0.52	1.03 (1.01, 1.06)
Nuts							
Median intake	0	0.1	0.2	0.3	1.0		
N of cases/person-y	5200/372 991	5083/367 640	4920/361 055	4764/355 564	6009/418 956		
Minimal adjusted Model	1.00 (Ref)	0.94 (0.91, 0.97)	0.94 (0.91, 0.97)	0.92 (0.89, 0.96)	0.93 (0.90, 0.96)	<0.001	0.97 (0.95, 0.99)
Multivariable Model 1	1.00 (Ref)	0.97 (0.93, 1.01)	0.98 (0.94, 1.02)	0.96 (0.92, 0.99)	0.97 (0.93, 1.01)	0.05	0.99 (0.96, 1.01)
Multivariable Model 2	1.00 (Ref)	0.97 (0.93, 1.01)	0.98 (0.95, 1.02)	0.96 (0.93, 1.01)	0.97 (0.94, 1.01)	0.11	0.99 (0.97, 1.01)

Unit used was oz equivalent/d for red meat, poultry, fish, eggs, legumes and nuts, and cup equivalent/d for dairy products. Minimal adjusted Model: age at baseline, and race/ethnicity. Multivariable Model 1: age at baseline, race/ethnicity, education, income, Observational Study/Clinical Trials, unopposed estrogen use, estrogen+progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack/stroke, whole grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption, and mutual adjustment for other protein sources. Multivariable Model 2: Multivariable Model 1+body mass index. HR indicates hazard ratio; and WHI, Women's Health Initiative.

risk of all-cause mortality among those younger than 65 years; poultry consumption was associated with lower risk of CVD mortality among White women; dairy product consumption was associated with higher risk of CVD mortality among women who ever smoked or were current smokers; and nut consumption was associated with higher risk of cancer mortality among women who ever used hormone or were current users, but lower risk of cancer mortality among women who never used hormones (data not shown).

DISCUSSION

In this large prospective cohort study of 102 521 women followed for 18 years on average, we found that intake of plant protein, and substitution of animal protein with plant protein, were associated with lower risk of all-cause, CVD, and dementia mortality. The associations were independent of age, race/ethnicity, socioeconomic status, dietary and lifestyles factors, baseline disease status, and family history of diseases. For specific major proteins sources, processed red meat was associated with higher risk of all-cause and dementia mortality; poultry was associated with lower risk of dementia mortality; eggs were associated with higher risk of all-cause, CVD, and cancer mortality and lower risk of dementia mortality; and unprocessed red meat and dairy products were associated with higher risk of CVD mortality. Substitution of red meat, eggs, dairy products, or legumes with nuts was associated with lower risk of all-cause mortality.

A limited number of studies have examined long-term risk of mortality in relation to specific animal and plant protein sources, except red meat, and they have yielded inconsistent results.[24–29] Consistent with our study, previous studies showed that major animal protein sources such as red meats and eggs were associated with higher risk of all-cause and CVD mortality,[24,25,28] and dairy products were associated with higher risk of CVD mortality.[25] There was only 1 previous study investigating the associations of all major protein sources and mortality, and the effects of substitution of animal proteins with nuts in Americans, using data from the Nurses' Health Study and the Health Professionals Follow-up Study.[28] However, the lack of analysis on other protein alternatives for red meat besides nuts, and the lack of data on dementia mortality, made it more difficult to have a conclusion on the role of major protein sources on mortality and various underlying causes. Two previous studies reported inverse associations of major plant protein intake including legumes and nuts with CVD or cancer mortality.[24,27]

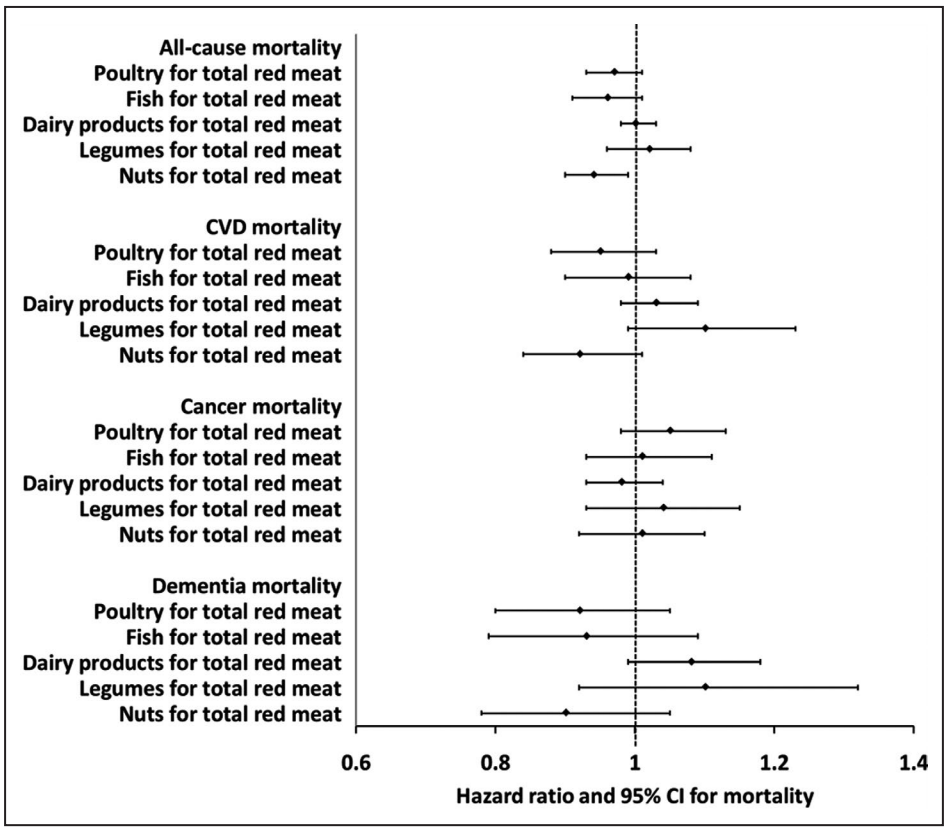

Figure 2. Hazard ratios of mortality associated with replacement of 2 oz equivalent/d of total red meat with various protein sources.
CVD indicates cardiovascular disease.

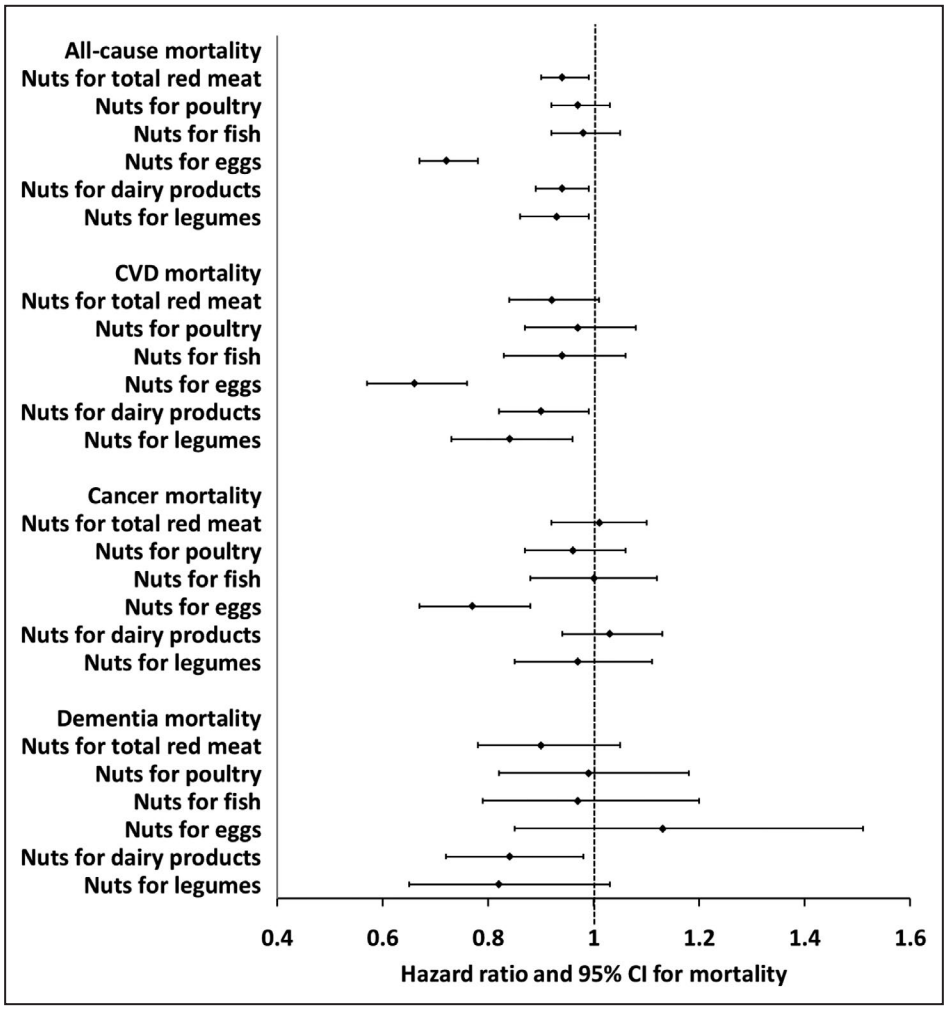

Figure 3. Hazard ratios of mortality associated with replacement of 2 oz equivalent/d of various protein sources with nuts.
CVD indicates cardiovascular disease.

However, legumes or nuts were not significantly associated with mortality risk in our study, consistent with a study in Finland.[29] Nonetheless, we found that substitution of total red meat with nuts was associated with lower risk of all-cause mortality. Although it is difficult to compare these studies because of differences in study methods and populations, these studies together with ours emphasized the importance of not only the need for categorization of overall animal and plant proteins, but also the specific protein sources, for the long-term health outcome. Additionally, our substitution analysis expanded the current evidence by offering protein alternatives from plant sources for animal proteins, which have been shown to be associated with higher risk of mortality.[6,30,31] Furthermore, our study is to our knowledge the first to report the association of major animal and plant protein sources with dementia mortality.

There are several explanations for the divergent associations of specific animal and plant protein sources with mortality in our study. First, the different associations of animal and plant protein intake with mortality could be explained by the amino acid contained in or factors uniquely associated with animal and plant protein foods, which may affect health by their specific physiological effects. For example, heterocyclic aromatic amines, which were uniquely associated with animal proteins, may be involved in the development of atherosclerosis, and thus CVD.[32] On the other hand, glutamic acid and L-arginine, which are predominant in plant proteins,[33–35] were both associated with lower CVD risk factors, possibly through anti-oxidation.[36,37] Second, the distinct risk of mortality between animal and plant protein sources and between different animal protein sources could be attributable to other nutrients coexistent in these foods. For example, nuts contain less saturated and more unsaturated fatty acids compared with red meat, and were associated with lower risk of mortality.[38,39] Dietary cholesterol and choline, which are mainly from red meat and eggs, have been shown to be

Table 5. Association of Major Protein Sources With Cause-Specific Mortality Among 102 521 Women From WHI

	Quintiles of Protein Intake					*P* Value for Trend	HR for 1 oz Equivalent/d
	Q1	Q2	Q3	Q4	Q5		
Total red meat							
CVD mortality	1.00 (Ref)	1.05 (0.98, 1.14)	1.13 (1.04, 1.22)	1.07 (0.99, 1.17)	1.14 (1.04, 1.25)	0.02	1.02 (1.01, 1.04)
Cancer mortality	1.00 (Ref)	1.01 (0.94, 1.09)	1.01 (0.94, 1.10)	1.06 (0.97, 1.15)	1.01 (0.92, 1.10)	0.92	0.99 (0.97, 1.01)
Dementia mortality	1.00 (Ref)	0.98 (0.88, 1.10)	1.00 (0.88, 1.13)	1.01 (0.88, 1.15)	1.04 (0.89, 1.20)	0.92	1.01 (0.98, 1.05)
Unprocessed red meat							
CVD mortality	1.00 (Ref)	1.14 (1.06, 1.23)	1.15 (1.06, 1.24)	1.11 (1.02, 1.21)	1.12 (1.02, 1.23)	0.11	1.01 (0.99, 1.04)
Cancer mortality	1.00 (Ref)	0.96 (0.89, 1.04)	1.02 (0.95, 1.11)	1.05 (0.97, 1.04)	0.98 (0.90, 1.08)	0.96	0.99 (0.97, 1.01)
Dementia mortality	1.00 (Ref)	0.99 (0.88, 1.11)	0.87 (0.77, 0.99)	0.97 (0.85, 1.10)	0.98 (0.84, 1.13)	0.30	1.00 (0.97, 1.04)
Processed red meat							
CVD mortality	1.00 (Ref)	0.97 (0.90, 1.04)	0.95 (0.88, 1.03)	0.98 (0.90, 1.06)	0.99 (0.91, 1.07)	0.84	1.05 (0.99, 1.10)
Cancer mortality	1.00 (Ref)	0.96 (0.89, 1.03)	0.97 (0.90, 1.04)	0.99 (0.92, 1.07)	1.00 (0.92, 1.08)	0.95	1.00 (0.96, 1.05)
Dementia mortality	1.00 (Ref)	1.05 (0.93, 1.18)	1.04 (0.92, 1.18)	1.11 (0.97, 1.26)	1.20 (1.05, 1.36)	0.01	1.06 (0.98, 1.16)
Poultry							
CVD mortality	1.00 (Ref)	1.01 (0.94, 1.09)	0.97 (0.90, 1.05)	1.03 (0.95, 1.11)	0.99 (0.91, 1.08)	0.97	0.99 (0.96, 1.03)
Cancer mortality	1.00 (Ref)	0.99 (0.92, 1.06)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)	1.01 (0.93, 1.09)	0.94	1.02 (0.98, 1.05)
Dementia mortality	1.00 (Ref)	0.87 (0.78, 0.97)	0.77 (0.69, 0.87)	0.86 (0.76, 0.97)	0.85 (0.75, 0.97)	0.01	0.97 (0.91, 1.03)
Fish/shellfish							
CVD mortality	1.00 (Ref)	1.04 (0.97, 1.12)	0.95 (0.88, 1.02)	1.05 (0.97, 1.14)	1.00 (0.93, 1.09)	0.84	1.01 (0.97, 1.06)
Cancer mortality	1.00 (Ref)	1.04 (0.97, 1.11)	0.98 (0.91, 1.06)	0.96 (0.89, 1.04)	1.03 (0.95, 1.11)	0.70	1.00 (0.96, 1.04)
Dementia mortality	1.00 (Ref)	0.94 (0.84, 1.05)	0.90 (0.80, 1.02)	0.94 (0.83, 1.06)	0.92 (0.81, 1.05)	0.16	0.98 (0.90, 1.05)
Eggs							
CVD mortality	1.00 (Ref)	1.0540.96, 1.12)	1.08 (0.99, 1.17)	1.13 (1.03, 1.20)	1.24 (1.14, 1.34)	<0.001	1.21 (1.14, 1.28)
Cancer mortality	1.00 (Ref)	0.97 (0.90, 1.04)	1.00 (0.93, 1.08)	0.95 (0.88, 1.03)	1.10 (1.02, 1.19)	0.05	1.13 (1.07, 1.20)
Dementia mortality	1.00 (Ref)	0.99 (0.88, 1.10)	0.89 (0.89, 1.01)	0.88 (0.78, 0.99)	0.86 (0.75, 0.98)	0.002	0.90 (0.80, 1.03)
Dairy products							
CVD mortality	1.00 (Ref)	0.99 (0.92, 1.07)	1.02 (0.94, 1.11)	0.99 (0.91, 1.08)	1.11 (1.02, 1.22)	0.04	1.03 (1.01, 1.06)
Cancer mortality	1.00 (Ref)	0.98 (0.91, 1.05)	0.98 (0.91, 1.06)	0.98 (0.90, 1.06)	0.95 (0.87, 1.04)	0.33	0.98 (0.96, 1.01)
Dementia mortality	1.00 (Ref)	1.06 (0.93, 1.20)	1.04 (0.92, 1.19)	1.15 (1.01, 1.31)	1.11 (0.97, 1.29)	0.09	1.05 (1.02, 1.09)
Legumes							
CVD mortality	1.00 (Ref)	0.99 (0.92, 1.06)	0.96 (0.89, 1.03)	1.04 (0.96, 1.12)	1.07 (0.98, 1.16)	0.09	1.07 (1.02, 1.13)
Cancer mortality	1.00 (Ref)	0.96 (0.89, 1.03)	0.98 (0.92, 1.06)	0.94 (0.88, 1.02)	0.97 (0.89, 1.04)	0.25	1.01 (0.96, 1.06)
Dementia mortality	1.00 (Ref)	1.01 (0.90, 1.14)	0.97 (0.86, 1.09)	0.99 (0.88, 1.12)	1.06 (0.93, 1.21)	0.63	1.07 (0.98, 1.16)
Nuts							
CVD mortality	1.00 (Ref)	0.97 (0.90, 1.04)	0.98 (0.91, 1.06)	0.94 (0.87, 1.01)	0.94 (0.87, 1.01)	0.06	0.98 (0.94, 1.02)
Cancer mortality	1.00 (Ref)	0.95 (0.88, 1.02)	0.94 (0.87, 1.01)	0.95 (0.89, 1.03)	0.99 (0.92, 1.06)	0.72	1.00 (0.95, 1.04)
Dementia mortality	1.00 (Ref)	1.00 (0.89, 1.13)	1.00 (0.88, 1.13)	1.06 (0.94, 1.20)	0.99 (0.87, 1.12)	0.96	0.96 (0.90, 1.04)

Adjustment: age at baseline, race/ethnicity, education, income, Observational Study/Clinical Trials, unopposed estrogen use, estrogen+progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack/stroke, whole grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption, and mutual adjustment for other protein sources. CVD indicates cardiovascular disease; HR, hazard ratio; and WHI, Women's Health Initiative.

associated with higher risk of mortality.[31,40] The positive association of processed red meat with dementia mortality and the inverse associations of poultry and eggs with dementia mortality could be because of the lower amount of saturated fatty acids in poultry, and the higher amount of beneficial lutein in eggs, which have been associated with less cognitive decline.[41–43] Nevertheless, it is notable that dietary proteins are not consumed in isolation, so that interpretation of the findings could be difficult and should be based on consideration of the overall diet.

The strengths of our study included the large sample size, the prospective cohort study design that allows temporal direction of the associations, and the long-term follow-up. The dietary information was collected by 40 clinical centers across the United States, which allowed

a diversity of dietary habits in this population to identify a wide range of protein food sources. Additionally, the geographical, socioeconomic, and racial/ethnic diversity of the WHI participants may improve the generalizability of the findings to other populations with similar characteristics. We also had detailed data on a variety of confounders that could potentially alter the association of protein intake with mortality; thus, we could explore the role of protein intake thoroughly by adjusting for a wide spectrum of potential confounders. Lastly, in addition to protein intake calculated according to food sources, we assessed the substitution effect of less healthy protein sources (eg, total red meat in this study) with relatively healthier alternatives, to provide more information for public health recommendations. We acknowledge that there are several limitations. First, as in all observational studies, even though we have adjusted for a wide variety of covariates that relate to mortality, residual confounding by unidentified confounders is still possible. Second, measurement errors in dietary assessment and covariates data were possible. However, these errors would be expected to be nondifferential given the nature of prospective cohort study design; therefore our observed associations may underestimate the true risks. Third, diet was assessed only at baseline and may have changed over time. Fourth, lack of more detailed information regarding protein sources such as high-fat dairy products or low-fat dairy products, or how nuts were prepared (eg, raw, or salted) made it impossible to further investigate the associations of more specific dietary sources or their preparations with mortality. Further studies with more details about protein food sources or food preparation methods are needed to help facilitate the translation of this information into practice more effectively. Fifth, although most of the frankfurters, sausages, and luncheon meats were made from red meat, it is possible that some of them were made from poultry such as turkey. Furthermore, MyPyramid Equivalents Database did not include bacon in processed red meat. Sixth, because our participants were postmenopausal women, our findings may not apply to women at a younger age, or premenopausal and perimenopausal women, or men. Seventh, according to the WHI's standard definition, CVD mortality in this study included deaths from all types of CVD instead of mortality from atherosclerotic CVD only. Different types of CVD and cancers might have divergent associations with protein intake. However, as our study was aimed at deaths from all CVD and cancers, future studies are needed to capture the associations of protein intake with specific types of CVD or cancer. Lastly, despite the additional information provided by the substitution analysis, they do not reflect real substitution but rather a mimic of such replacement.

Our findings have potentially significant public health implications. Dietary guidelines worldwide do not distinguish healthier choices for dietary protein from unhealthier choices. For example, the 2015–2020 Dietary Guidelines for Americans recommend ≈5 oz equivalents of protein food including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products, and 3-cup equivalents of dairy products daily for female adults.[1] Moreover, as a visual illustration of the Dietary Guidelines, the MyPlate figure simply reads "protein" as one quarter of the plate with "dairy" in the corner, without specification of different dietary sources. Our findings highlight the need to consider healthier protein sources in future dietary guidelines.

CONCLUSIONS

In this large prospective cohort study, we found that higher plant protein intake and substitution of animal protein with plant protein were associated with lower risk of all-cause mortality, CVD mortality, and dementia mortality. Furthermore, we identified nuts as potential healthier alternatives for red meat, eggs, dairy products, and legumes. Our findings support the need for consideration of protein sources, in addition to the amount of protein intake, in future dietary guidelines.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Association of animal protein intake and plant protein intake with all-cause and cause-specific mortality among 63,593 women from WHI Observational Study.

	Quintiles of protein intake, % of total energy					*P*-value for trend
	Q1	Q2	Q3	Q4	Q5	
Animal protein						
All-cause mortality	1.00(Ref)	1.01(0.96, 1.06)	1.04(0.99, 1.09)	0.99(0.94, 1.05)	1.02(0.96, 1.08)	0.84
CVD mortality	1.00(Ref)	1.03(0.93, 1.13)	1.06(0.96, 1.17)	1.05(0.95, 1.17)	1.07(0.96, 1.19)	0.22
Cancer mortality	1.00(Ref)	0.96(0.87, 1.05)	1.00(0.91, 1.01)	0.92(0.83, 1.01)	0.96(0.86, 1.07)	0.27
Dementia mortality	1.00(Ref)	1.03(0.89, 1.20)	1.03(0.89, 1.20)	0.98(0.83, 1.15)	0.93(0.78, 1.11)	0.39
Plant protein						
All-cause mortality	1.00(Ref)	0.97(0.92, 1.02)	0.94(0.89, 0.99)	0.91(0.86, 0.97)	0.90(0.84, 0.96)	<0.001
CVD mortality	1.00(Ref)	0.93(0.84, 1.03)	0.95(0.85, 1.06)	0.85(0.75, 0.96)	0.84(0.73, 0.96)	0.01
Cancer mortality	1.00(Ref)	0.98(0.89, 1.09)	0.96(0.86, 1.07)	1.07(0.95, 1.20)	1.05(0.92, 1.19)	0.26
Dementia mortality	1.00(Ref)	1.03(0.88, 1.22)	0.91(0.76, 1.09)	0.87(0.72, 1.05)	0.78(0.63, 0.97)	0.01

Adjustment: age at baseline, race/ethnicity, education, income, unopposed estrogen use, estrogen + progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes status, baseline high blood cholesterol status, family history of heart attack/stroke, percentage of energy from saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and *trans*-fatty acids, dietary fiber intake, and glycemic load. For animal and plant protein, mutual adjustment for each other was also added.

Table S2. Association of animal protein intake and plant protein intake with all-cause and cause-specific mortality among 101,733 women from WHI excluding women who died within 3 years after baseline.

	Quintiles of protein intake, % of total energy					*P*-value for trend
	Q1	Q2	Q3	Q4	Q5	
Animal protein						
All-cause mortality	1.00(Ref)	1.00(0.96, 1.04)	1.02(0.98, 1.06)	1.00(0.96, 1.04)	1.00(0.96, 1.05)	0.99
CVD mortality	1.00(Ref)	1.00(0.93, 1.08)	1.05(0.97, 1.14)	1.02(0.94, 1.11)	1.05(0.96, 1.14)	0.28
Cancer mortality	1.00(Ref)	0.98(0.91, 1.06)	1.00(0.93, 1.08)	1.00(0.92, 1.08)	0.98(0.90, 1.07)	0.79
Dementia mortality	1.00(Ref)	1.01(0.90, 1.14)	0.98(0.87, 1.11)	0.93(0.82, 1.06)	0.90(0.78, 1.03)	0.09
Plant protein						
All-cause mortality	1.00(Ref)	0.95(0.92, 0.99)	0.94(0.90, 0.98)	0.93(0.88, 0.97)	0.91(0.86, 0.96)	0.001
CVD mortality	1.00(Ref)	0.94(0.87, 1.02)	0.93(0.86, 1.01)	0.89(0.81, 0.98)	0.88(0.79, 0.98)	0.02
Cancer mortality	1.00(Ref)	0.98(0.91, 1.06)	0.97(0.89, 1.05)	1.06(0.97, 1.16)	1.06(0.95, 1.17)	0.13
Dementia mortality	1.00(Ref)	1.05(0.92, 1.19)	0.93(0.81, 1.07)	0.91(0.78, 1.06)	0.80(0.67, 0.95)	0.003

Adjustment: age at baseline, race/ethnicity, education, income, OS/CT, unopposed estrogen use, estrogen + progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes status, baseline high blood cholesterol status, family history of heart attack/stroke, percentage of energy from saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and *trans*-fatty acids, dietary fiber intake, and glycemic load. For animal and plant protein, mutual adjustment for each other was also added.

Table S3. Association of major protein sources with all-cause and cause-specific mortality among 63,593 women from WHI Observational Study.

	Quintiles of protein intake					*P*-value for trend	HR for 1 oz equivalent/day
	Q1	Q2	Q3	Q4	Q5		
Total red meat							
All-cause mortality	1.00(Ref)	1.02(0.97, 1.07)	1.06(1.01, 1.11)	1.08(1.02, 1.14)	1.10(1.04, 1.17)	0.002	1.02(1.01, 1.04)
CVD mortality	1.00(Ref)	1.00(0.92, 1.10)	1.08(0.98, 1.19)	1.04(0.93, 1.15)	1.11(0.99, 1.26)	0.16	1.03(1.01, 1.05)
Cancer mortality	1.00(Ref)	1.01(0.93, 1.11)	0.99(0.90, 1.09)	1.02(0.93, 1.13)	1.01(0.90, 1.13)	0.94	0.99(0.97, 1.01)
Dementia mortality	1.00(Ref)	1.03(0.90, 1.18)	1.06(0.92, 1.23)	1.10(0.94, 1.30)	1.12(0.93, 1.35)	0.29	1.04(0.99, 1.08)
Unprocessed red meat							
All-cause mortality	1.00(Ref)	1.04(0.99, 1.09)	1.03(0.98, 1.08)	1.06(1.01, 1.12)	1.05(0.99, 1.12)	0.19	1.01(0.99, 1.03)
CVD mortality	1.00(Ref)	1.13(1.03, 1.24)	1.08(0.98, 1.20)	1.10(0.99, 1.23)	1.09(0.97, 1.22)	039	1.02(0.99, 1.05)
Cancer mortality	1.00(Ref)	0.99(0.91, 1.09)	1.03(0.94, 1.13)	1.03(0.93, 1.14)	0.99(0.88, 1.11)	0.87	0.99(0.96, 1.02)
Dementia mortality	1.00(Ref)	1.06(0.92, 1.22)	0.98(0.84, 1.14)	1.02(0.87, 1.20)	1.03(0.85, 1.23)	0.67	1.01(0.96, 1.06)
Processed red meat							
All-cause mortality	1.00(Ref)	0.97(0.93, 1.02)	0.99(0.94, 1.04)	1.03(0.98, 1.09)	1.04(0.99, 1.10)	0.04	1.01(0.99, 1.030
CVD mortality	1.00(Ref)	0.98(0.90, 1.08)	0.95(0.86, 1.04)	0.98(0.89, 1.09)	0.98(0.89, 1.09)	0.73	1.07(1.01, 1.15)
Cancer mortality	1.00(Ref)	0.91(0.83, 0.99)	0.93(0.85, 1.02)	0.94(0.86, 1.04)	0.95(0.86, 1.05)	0.44	0.99(0.92, 1.06)
Dementia mortality	1.00(Ref)	0.98(0.87, 1.13)	0.99(0.85, 1.16)	1.14(0.98, 1.33)	1.23(1.05, 1.45)	0.003	1.15(1.03, 1.28)
Poultry							
All-cause mortality	1.00(Ref)	0.98(0.93, 1.03)	0.95(0.91, 1.01)	0.95(0.91, 1.01)	0.97(0.92, 1.03)	0.18	0.99(0.97, 1.01)
CVD mortality	1.00(Ref)	1.00(0.91, 1.09)	0.99(0.90, 1.09)	0.99(0.90, 1.10)	1.04(0.93, 1.15)	0.59	1.01(0.97, 1.06)
Cancer mortality	1.00(Ref)	1.03(0.94, 1.13)	1.00(0.91, 1.10)	0.98(0.88, 1.08)	1.01(0.91, 1.12)	0.79	1.00(0.96, 1.05)
Dementia mortality	1.00(Ref)	0.89(0.77, 1.02)	0.78(0.67, 0.90)	0.87(0.75, 1.02)	0.83(0.71, 0.98)	0.03	0.95(0.88, 1.02)
Fish/shellfish							
All-cause mortality	1.00(Ref)	0.98(0.94, 1.03)	0.97(0.92, 1.02)	0.97(0.92, 1.02)	0.97(0.92, 1.02)	0.19	1.01(0.98, 1.04)
CVD mortality	1.00(Ref)	1.04(0.94, 1.14)	0.96(0.87, 1.06)	1.06(0.96, 1.17)	1.00(0.90, 1.11)	0.98	1.02(0.96, 1.08)
Cancer mortality	1.00(Ref)	1.01(0.92, 1.11)	0.95(0.86, 1.04)	0.91(0.82, 0.99)	1.01(0.91, 1.11)	0.40	1.01(0.95, 1.06)
Dementia mortality	1.00(Ref)	0.95(0.82, 1.10)	0.98(0.85, 1.13)	0.92(0.79, 1.08)	0.91(0.78, 1.08)	0.22	1.00(0.91, 1.09)
Eggs							
All-cause mortality	1.00(Ref)	0.99(0.95, 1.04)	1.03(0.98, 1.09)	1.04(0.99, 1.10)	1.16(1.10, 1.23)	<0.001	1.17(1.12, 1.22)
CVD mortality	1.00(Ref)	1.07(0.97, 1.18)	1.12(1.01, 1.24)	1.18(1.07, 1.30)	1.36(1.23, 1.51)	<0.001	1.25(1.16, 1.35)
Cancer mortality	1.00(Ref)	0.94(0.86, 1.03)	1.03(0.93, 1.13)	0.93(0.85, 1.03)	1.04(0.95, 1.15)	0.60	1.10(1.02, 1.19)
Dementia mortality	1.00(Ref)	0.98(0.85, 1.12)	0.91(0.78, 1.06)	0.87(0.74, 1.01)	0.85(0.72, 1.01)	0.01	0.87(0.73, 1.03)
Dairy products							

All-cause mortality	1.00(Ref)	1.00(0.95, 1.06)	1.03(0.97, 1.08)	1.04(0.98, 1.10)	1.05(0.99, 1.12)	0.06	1.02(1.01, 1.03)
CVD mortality	1.00(Ref)	0.99(0.89, 1.09)	1.00(0.90, 1.11)	1.02(0.91, 1.14)	1.10(0.98, 1.23)	0.10	1.03(1.01, 1.06)
Cancer mortality	1.00(Ref)	1.00(0.91, 1.10)	0.98(0.88, 1.08)	0.99(0.89, 1.10)	0.95(0.85, 1.06)	0.34	0.98(0.95, 1.01)
Dementia mortality	1.00(Ref)	1.00(0.86, 1.17)	0.99(0.84, 1.16)	1.16(0.98, 1.38)	1.14(0.96, 1.36)	0.05	1.07(1.02, 1.11)
Legumes							
All-cause mortality	1.00(Ref)	0.97(0.93, 1.02)	0.98(0.93, 1.02)	0.96(0.91, 1.01)	0.99(0.93, 1.04)	0.41	1.02(0.99, 1.06)
CVD mortality	1.00(Ref)	0.94(0.85, 1.03)	0.96(0.87, 1.06)	1.03(0.93, 1.13)	1.05(0.94, 1.16)	0.17	1.07(1.01, 1.15)
Cancer mortality	1.00(Ref)	0.96(0.87, 1.05)	0.98(0.89, 1.07)	0.95(0.86, 1.04)	0.94(0.85, 1.04)	0.23	1.02(0.95, 1.08)
Dementia mortality	1.00(Ref)	1.03(0.89, 1.19)	1.01(0.87, 1.17)	1.00(0.85, 1.17)	1.10(0.93, 1.29)	0.47	1.08(0.97, 1.19)
Nuts							
All-cause mortality	1.00(Ref)	0.96(0.92, 1.01)	0.99(0.94, 1.04)	0.95(0.90, 1.01)	0.96(0.91, 1.01)	0.07	0.98(0.95, 1.01)
CVD mortality	1.00(Ref)	1.00(0.91, 1.09)	0.93(0.84, 1.03)	0.94(0.85, 1.04)	0.97(0.88, 1.07)	0.26	1.00(0.95, 1.06)
Cancer mortality	1.00(Ref)	0.96(0.87, 1.05)	1.02(0.93, 1.12)	0.97(0.87, 1.07)	1.01(0.92, 1.11)	0.91	0.99(0.94, 1.05)
Dementia mortality	1.00(Ref)	0.90(0.78, 1.05)	0.91(0.78, 1.06)	1.02(0.87, 1.18)	0.94(0.80, 1.09)	0.80	0.96(0.87, 1.06)

Adjustment: age at baseline, race/ethnicity, education, income, unopposed estrogen use, estrogen + progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes status, baseline high blood cholesterol status, family history of heart attack/stroke, whole grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption, and mutual adjustment for other protein sources.

Table S4. Association of major protein sources with all-cause and cause-specific mortality among 101,733 women from WHI excluding women who died within 3 years after baseline.

	Quintiles of protein intake					*P*-value for trend	HR for 1 oz equivalent/day
	Q1	Q2	Q3	Q4	Q5		
Total red meat							
All-cause mortality	1.00(Ref)	1.04(0.99, 1.08)	1.09(1.04, 1.14)	1.09(1.04, 1.13)	1.10(1.05, 1.16)	<0.001	1.02(1.01, 1.03)
CVD mortality	1.00(Ref)	1.05(0.97, 1.13)	1.14(1.05, 1.23)	1.08(0.99, 1.17)	1.15(1.05, 1.27)	0.01	1.02(1.01, 1.04)
Cancer mortality	1.00(Ref)	1.02(0.95, 1.10)	1.02(0.94, 1.11)	1.07(0.99, 1.16)	1.00(0.92, 1.10)	0.99	0.99(0.97, 1.01)
Dementia mortality	1.00(Ref)	0.98(0.88, 1.10)	0.99(0.88, 1.12)	1.01(0.88, 1.15)	1.04(0.89, 1.20)	0.93	1.01(0.98, 1.05)
Unprocessed red meat							
All-cause mortality	1.00(Ref)	1.03(0.99, 1.08)	1.05(1.01, 1.10)	1.07(1.02, 1.12)	1.05(0.99, 1.10)	0.11	1.01(0.99, 1.02)
CVD mortality	1.00(Ref)	1.14(1.05, 1.23)	1.16(1.07, 1.25)	1.11(1.01, 1.21)	1.12(1.02, 1.23)	0.10	1.02(0.99, 1.04)
Cancer mortality	1.00(Ref)	0.97(0.90, 1.05)	1.03(0.95, 1.12)	1.05(0.97, 1.14)	0.98(0.89, 1.07)	0.81	0.98(0.96, 1.01)
Dementia mortality	1.00(Ref)	0.99(0.88, 1.11)	0.87(0.77, 0.99)	0.97(0.85, 1.10)	0.98(0.84, 1.13)	0.30	1.00(0.97, 1.04)
Processed red meat							
All-cause mortality	1.00(Ref)	1.00(0.96, 1.04)	1.02(0.98, 1.06)	1.03(0.99, 1.08)	1.07(1.02, 1.12)	0.002	1.05(1.02, 1.08)
CVD mortality	1.00(Ref)	0.97(0.90, 1.05)	0.95(0.88, 1.03)	0.97(0.90, 1.05)	1.00(0.92, 1.09)	0.98	1.05(1.01, 1.11)
Cancer mortality	1.00(Ref)	0.97(0.90, 1.05)	0.98(0.91, 1.06)	0.99(0.91, 1.07)	1.01(0.93, 1.10)	0.77	1.00(0.96, 1.05)
Dementia mortality	1.00(Ref)	1.05(0.93, 1.18)	1.04(0.92, 1.18)	1.10(0.97, 1.25)	1.20(1.08, 1.36)	0.01	1.06(0.98, 1.16)
Poultry							
All-cause mortality	1.00(Ref)	0.97(0.93, 1.01)	0.94(0.90, 0.98)	0.97(0.93, 1.01)	0.97(0.93, 1.01)	0.27	1.00(0.98, 1.02)
CVD mortality	1.00(Ref)	1.02(0.94, 1.09)	0.97(0.90, 1.05)	1.04(0.96, 1.12)	0.99(0.91, 1.08)	0.94	0.99(0.96, 1.03)
Cancer mortality	1.00(Ref)	0.99(0.92, 1.07)	0.96(0.89, 1.04)	0.97(0.89, 1.04)	1.02(0.94, 1.10)	0.91	1.02(0.99, 1.05)
Dementia mortality	1.00(Ref)	0.87(0.78, 0.97)	0.77(0.69, 0.87)	0.86(0.76 ,0.97)	0.85(0.75, 0.97)	0.01	0.97(0.91, 1.03)
Fish/shellfish							
All-cause mortality	1.00(Ref)	1.00(0.96, 1.04)	0.97(0.93, 1.01)	0.97(0.93, 1.01)	0.97(0.93, 1.01)	0.04	0.99(0.97, 1.02)
CVD mortality	1.00(Ref)	1.05(0.97, 1.12)	0.94(0.87, 1.01)	1.05(0.97, 1.13)	1.01(0.93, 1.09)	0.93	1.01(0.97, 1.06)
Cancer mortality	1.00(Ref)	1.04(0.97, 1.12)	0.98(0.91, 1.05)	0.95(0.88, 1.02)	1.03(0.95, 1.11)	0.59	1.00(0.96, 1.05)
Dementia mortality	1.00(Ref)	0.94(0.84, 1.05)	0.90(0.80, 1.02)	0.94(0.83, 1.06)	0.92(0.81, 1.05)	0.16	0.98(0.90, 1.05)
Eggs							
All-cause mortality	1.00(Ref)	0.99(0.95, 1.03)	1.02(0.98, 1.06)	1.03(0.99, 1.07)	1.14(1.09, 1.19)	<0.001	1.15(1.12, 1.19)
CVD mortality	1.00(Ref)	1.04(0.96, 1.12)	1.07(0.99, 1.16)	1.12(1.03, 1.21)	1.23(1.13, 1.33)	<0.001	1.21(1.14, 1.28)
Cancer mortality	1.00(Ref)	0.96(0.89, 1.03)	1.01(0.93, 1.09)	0.96(0.89, 1.04)	1.10(1.02, 1.19)	0.04	1.13(1.06, 1.20)
Dementia mortality	1.00(Ref)	0.98(0.88, 1.10)	0.89(0.79, 1.01)	0.88(0.78, 0.99)	0.86(0.75, 0.98)	0.002	0.91(0.80, 1.03)

Dairy products							
All-cause mortality	1.00(Ref)	0.99(0.95, 1.03)	1.00(0.96, 1.04)	1.00(0.96, 1.05)	1.03(0.98, 1.08)	0.17	1.01(1.01, 1.03)
CVD mortality	1.00(Ref)	1.00(0.92, 1.08)	1.02(0.95, 1.11)	1.00(0.92, 1.09)	1.10(1.01, 1.21)	0.05	1.03(1.01, 1.06)
Cancer mortality	1.00(Ref)	0.98(0.90, 1.05)	0.98(0.90, 1.06)	0.96(0.99, 1.05)	0.94(0.86, 1.02)	0.15	0.98(0.95, 0.99)
Dementia mortality	1.00(Ref)	1.06(0.94, 1.20)	1.05(0.92, 1.19)	1.15(1.01, 1.31)	1.11(0.96, 1.28)	0.10	1.05(1.02, 1.09)
Legumes							
All-cause mortality	1.00(Ref)	0.99(0.95, 1.03)	0.98(0.94, 1.01)	1.00(0.96, 1.04)	1.01(0.97, 1.06)	0.62	1.03(0.99, 1.06)
CVD mortality	1.00(Ref)	1.00(0.93, 1.07)	0.96(0.89, 1.04)	1.04(0.96, 1.13)	1.07(0.98, 1.16)	0.10	1.07(1.02, 1.13)
Cancer mortality	1.00(Ref)	0.94(0.87, 1.01)	0.98(0.91, 1.05)	0.94(0.88, 1.02)	0.97(0.89, 1.05)	0.36	1.02(0.97, 1.08)
Dementia mortality	1.00(Ref)	1.01(0.90, 1.14)	0.97(0.86, 1.09)	1.00(0.88, 1.13)	1.06(0.93, 1.21)	0.61	1.07(0.98, 1.16)
Nuts							
All-cause mortality	1.00(Ref)	0.97(0.93, 1.01)	0.99(0.95, 1.03)	0.95(0.92, 0.99)	0.96(0.93, 1.01)	0.03	0.98(0.96, 1.01)
CVD mortality	1.00(Ref)	0.97(0.90, 1.05)	1.00(0.92, 1.08)	0.94(0.87, 1.02)	0.95(0.88, 1.02)	0.09	0.98(0.94, 1.02)
Cancer mortality	1.00(Ref)	0.94(0.87, 1.01)	0.94(0.87, 1.01)	0.93(0.86, 1.01)	0.97(0.90, 1.04)	0.32	0.99(0.95, 1.03)
Dementia mortality	1.00(Ref)	1.00(0.89, 1.13)	1.00(0.88, 1.13)	1.06(0.94, 1.20)	0.99(0.87, 1.12)	0.96	0.96(0.90, 1.04)

Adjustment: age at baseline, race/ethnicity, education, income, OS/CT, unopposed estrogen use, estrogen + progesterone use, smoking status, physical activity, alcohol intake, total energy intake, baseline diabetes status, baseline high blood cholesterol status, family history of heart attack/stroke, whole grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption, and mutual adjustment for other protein sources.

Table S5. Competing risk analysis for dement mortality in relation to dietary protein intake and major protein sources.

	Quintiles of protein intake					*P*-value for trend
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	
Animal protein	1.00(Ref)	1.01(0.90, 1.14)	0.99(0.88, 1.12)	0.93(0.82, 1.06)	0.90(0.78, 1.04)	0.10
Plant protein	1.00(Ref)	1.06(0.93, 1.21)	0.94(0.82, 1.08)	0.92(0.79, 1.08)	0.82(0.69, 0.98)	0.01
Total red meat	1.00(Ref)	0.97(0.86, 1.09)	0.98(0.87, 1.11)	0.97(0.85, 1.11)	1.00(0.86, 1.15)	0.68
Unprocessed red meat	1.00(Ref)	0.98(0.87, 1.10)	0.85(0.75, 0.97)	0.94(0.82, 1.07)	0.95(0.82, 1.10)	0.17
Processed red meat	1.00(Ref)	1.05(0.93, 1.18)	1.05(0.92, 1.19)	1.11(0.98, 1.26)	1.19(1.04, 1.35)	0.01
Poultry	1.00(Ref)	0.80(0.79, 0.99)	0.80(0.71, 0.91)	0.88(0.78, 0.99)	0.88(0.77, 1.01)	0.06
Fish/shellfish	1.00(Ref)	0.94(0.84, 1.06)	0.92(0.81, 1.04)	0.94(0.83, 1.07)	0.93(0.82, 1.07)	0.27
Eggs	1.00(Ref)	0.98(0.87, 1.10)	0.88(0.78, 0.99)	0.86(0.76, 0.97)	0.82(0.72, 0.94)	0.002
Dairy products	1.00(Ref)	1.08(0.95, 1.22)	1.04(0.91, 1.19)	1.14(0.99, 1.31)	1.10(0.95, 1.27)	0.15
Legumes	1.00(Ref)	1.03(0.92, 1.16)	0.99(0.88, 1.12)	1.01(0.89, 1.14)	1.06(0.93, 1.21)	0.59
Nuts	1.00(Ref)	1.04(0.92, 1.18)	1.03(0.90, 1.16)	1.10(0.97, 1.25)	1.02(0.90, 1.16)	0.67