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Dietary Protein Sources and All-Cause and Cause-Specific Mortality: The Golestan Cohort Study in Iran

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Abstract

Introduction—Dietary protein comes from foods with greatly different compositions that may not relate equally with mortality risk. Few cohort studies from non-Western countries have examined the association between various dietary protein sources and cause-specific mortality.

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Therefore, the associations between dietary protein sources and all-cause, cardiovascular disease, and cancer mortality were evaluated in the Golestan Cohort Study in Iran.

Methods—Among 42,403 men and women who completed a dietary questionnaire at baseline, 3,291 deaths were documented during 11 years of follow up (2004–2015). Cox proportional hazards models estimated age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% CIs for all- cause and disease-specific mortality in relation to dietary protein sources. Data were analyzed from 2015 to 2016.

Results—Comparing the highest versus the lowest quartile, egg consumption was associated with lower all-cause mortality risk (HR=0.88, 95% CI=0.79, 0.97, p_{trend}=0.03). In multivariate analysis, the highest versus the lowest quartile of fish consumption was associated with reduced risk of total cancer (HR=0.79, 95% CI=0.64, 0.98, p_{trend}=0.03) and gastrointestinal cancer (HR=0.75, 95% CI=0.56, 1.00, p_{trend}=0.02) mortality. The highest versus the lowest quintile of legume consumption was associated with reduced total cancer (HR=0.72, 95% CI=0.58, 0.89, p_{trend}=0.004), gastrointestinal cancer (HR=0.76, 95% CI=0.58, 1.01, p_{trend}=0.05), and other cancer (HR=0.66, 95% CI=0.47, 0.93, p_{trend}=0.04) mortality. Significant associations between total red meat and poultry intake and all- cause, cardiovascular disease, or cancer mortality rate were not observed among all participants.

Conclusions—These findings support an association of higher fish and legume consumption with lower cancer mortality, and higher egg consumption with lower all-cause mortality.

INTRODUCTION

Red meat and processed meat consumption may contribute to increased risk of several chronic diseases such as diabetes,[1] cardiovascular disease (CVD)[1], and certain cancers.[2–6] Prospective studies have noted increased mortality risk among men and women with high total and processed red meat consumption,[7,8] whereas poultry and fish are often considered healthier substitutes for red meat. Current evidence supports the relationship between fish consumption and lower all-cause or coronary heart disease (CHD) mortality risk,[9,10] whereas the role of fish intake in cancer mortality is unclear.[11–13] Findings from prospective studies relating poultry to mortality risk are inconsistent.[12,14,15] The roles of other dietary protein sources such as eggs or legumes in mortality risk are less clear.[16,17] Further, most of the results in relation to red meat consumption and mortality were from Western countries, where high red meat consumption is common. However, Iranian people consume less red meat: 9.2 kg per capita compared with 65.3 and 58.3 kg per capita among American or European populations, respectively.[18] Therefore, to examine the association between red meat and mortality and to show the effect of other protein sources on mortality, the association of red meat, poultry, fish, eggs, and legumes consumption with mortality risk from all and specific causes was investigated, using data from a prospective cohort study of adult men and women in Golestan, Iran.

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METHODS

Study Population

The Golestan Cohort Study is an ongoing prospective population- based study established in 2004 in Iran with enrollment of 50,045 participants (21,234 men and 28,811 women) aged 36–85 years, without previous history of upper gastrointestinal cancer, from Gonbad city and 326 villages in Golestan province. The study design is described in further detail elsewhere.[19] This analysis included participants who had data on dietary intake (*n*=49,112) at baseline. Participants were excluded owing to loss of follow up (*n*=63); extreme total energy intake (<600 or >4,200 kcal/day, *n*=436); or prior diagnosis of chronic disease, including cancer, diabetes, CHD, or stroke (*n*=6,210), leaving 42,403 participants (18,261 men and 24,142 women).

This study was approved by the IRBs of the Digestive Disease Research Center of Tehran University of Medical Sciences, the U.S. National Cancer Institute, the WHO International Agency for Research on Cancer, and the Harvard T.H. Chan School of Public Health. All participants gave written informed consent before enrollment.

Measures

At enrollment, dietary intake was measured by face-to-face interviews using a validated, 116-item food frequency questionnaire specifically designed for this population.[20] Total red meat items listed on the food frequency questionnaire included unprocessed (beef or lamb, hamburger) and processed (sausage) red meat; poultry included chicken; fish included tuna, stellate sturgeon, carp, smoked fish, salted fish, and other fish; and legumes included soybeans, beans, lentils, peas, and split peas. Participants were asked about the frequency of food item consumption per day, week, month, or year. The standard serving sizes for these food items were 85 g for cooked beef, lamb, hamburger, chicken, and fish; 45 g for sausage; 100 g for cooked beans, lentils, peas, split peas, and soybeans; and 54 g for eggs. Iranian[21] and U.S. Department of Agriculture[22] databases were used to calculate daily energy intake.

Data on lifestyle variables and medical history were obtained through face-to-face interviews using a general questionnaire at the beginning of the study. Participants were asked about gender, age, ethnicity, residential history, occupation, education, smoking habits, opium use, alcohol consumption, indicators of SES, and medical history including self-reports of medically diagnosed diabetes mellitus, heart disease, stroke, and cancer. Height and weight were then measured. Blood pressure in both arms was also measured twice at a 10-minute interval. Occupational physical activity was measured in four levels: Level 1 activities defined as sedentary work mostly done while sitting (e.g., driving); Level 2 activities defined as standing or occasional walking (e.g., teaching); Level 3 activities defined as mainly indoor activities causing a mild increase in heart rate and sweating (e.g., housekeeping); and Level 4 activities defined as those causing a significant increase in heart rate and sweating usually performed outdoors (e.g., farming).[23] Using multiple correspondence analysis, the wealth score was created based on occupation, house ownership, house structure, house size, having a bath in the residence, as well as a personal

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car, motorbike, black/white TV, color TV, refrigerator, freezer, vacuum, and washing machine.[24]

Deaths were reported by family members, friends, or local health workers during annual telephone calls. When a death was reported, a physician visited the house to complete a validated verbal autopsy questionnaire by interviewing the next of kin.[25] Relevant medical documents including medical charts, radiography and pathology reports, and hospital discharge reports were gathered from the hospitals or pathology centers. All collected documents were reviewed, and the cause of death was coded according to the ICD-10. In this analysis, deaths were classified as due to CVD (ICD-I00–I99); CHD (ICD-I20–I52); stroke (ICD- I60–I69); cancer (ICD-C00–D48); gastrointestinal cancers (ICD- C15–26); and other cancers (ICD-C00–14, ICD-C30–97, and ICD- D00–48). If a final diagnosis could not be determined for any reason, the cause of death was classified as "unknown."

Statistical Analysis

Data were analyzed from 2015 to 2016. Person-years of follow up were calculated from the date of completed questionnaires at baseline until death, or last follow-up date (until June 1, 2015), which ever came first. Participants were divided into quintiles according to food group intake. Because of the low consumption of fish and eggs, participants who did not eat fish or eggs were assigned to the first category, and others were divided into tertiles. Cox proportional hazards regression was used to estimate age- adjusted and multivariate-adjusted hazard ratios (HRs) and 95% CIs for all-cause and disease-specific mortality in relation to total red meat, poultry, fish, egg, and legume consumption. Multivariate models were adjusted for age, gender, place of residence, marital status, educational level, ethnicity, cigarette smoking, opium use, BMI, systolic blood pressure, family history of cancer, occupational physical activity, medication, wealth score, alcohol consumption, and total energy intake (footnotes in Tables 2–4 list categorizations). Tests for linear trend were carried out by assigning a median value for each quintile (or quartile) and modeling this as a continuous variable in the model. Missing covariate data, which included five participants for BMI and eight participants for systolic blood pressure, were replaced with median values. To address whether the observed associations were independent of other dietary intake, the analysis additionally controlled for fruit and vegetable or total grain intake. Furthermore, a previous study using data from the Golestan Cohort Study indicated that high consumption of low-fat dairy was associated with reduced mortality risk,[26] so the associations were evaluated after additional adjustment for intake of low-fat dairy foods. By including a cross-product interaction term for gender, age, BMI, smoking, or wealth score, and dietary protein sources in the multivariate-adjusted model, this study examined whether the associations between dietary protein sources and all-cause mortality were modified by other mortality risk factors.[27–29] The effect of substituting one serving/day of poultry, fish, legumes, or eggs for one serving/day of total red meat was estimated by including these food items simultaneously as continuous variables in the multivariate-adjusted model. The HRs and 95% CIs for the substitution effect were estimated from the difference between the regression coefficients, variances, and covariance.[30] Stata, version 12, was used for all analyses. All *p*-values were two-sided.

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RESULTS

During 339,867 person-years of follow up (2004–2015; total, 11 years; median, 8.1 years), 3,291 deaths were documented (1,938 deaths among men and 1,353 deaths among women) in the Golestan Cohort Study. A total of 1,467 deaths were from CVD (764 CHD deaths, 507 stroke deaths, and 196 other CVD deaths) and 859 deaths were caused by cancer (509 gastrointestinal cancer deaths and 350 other cancer deaths). Mean consumption of total red meat was 0.19 serving/day, which included 0.04 serving/day of processed red meat. Participants with higher total red meat intake were more likely to be male, Turkmen, married, and smokers, and to have higher BMI. Also, they were less likely to live in rural areas and perform higher levels of occupational physical activity (Table 1). The percentage of energy intake from each food group according to tertiles of total red meat intake was used to show changes in dietary habits by increasing consumption of total red meat: the higher total red meat intake, the lower percentage of energy intake from grains (Appendix Figure 1, available online).

Higher intake of total red meat as well as poultry, fish, and legumes was not associated with all-cause mortality risk (Table 2). The wealth score was responsible for most of the differences in HRs between age-adjusted and multivariate-adjusted models (data not shown). Higher egg consumption was associated with a lower all-cause mortality risk (HR [highest versus lowest] =0.88, 95% CI=0.79, 0.97, p_{trend}=0.03). Similar point estimates were observed after additional adjustment for fruit and vegetable, total grain food, or low-fat dairy food intake (data not shown). With mutual adjustment for dietary protein sources, a non-significant positive association for total red meat intake was observed (HR=1.08, 95% CI=0.96, 1.22, p_{trend}=0.08). The association of egg intake was not changed materially (HR=0.88, 95% CI=0.80, 0.98, p_{trend}=0.045). Significant associations with poultry, legume, or fish intake were not noted.

Furthermore, substituting one serving/day of legumes for one serving/day of total red meat was associated with a lower risk of all-cause mortality (HR=0.68, 95% CI=0.50, 0.93). Substituting one serving/day of eggs for one serving/day of total red meat was associated with a lower risk of all-cause mortality (HR=0.65, 95% CI=0.43, 0.98). Further, substituting one serving/day of fish for one serving/day of total red meat was associated with lower risk of all-cause mortality (HR=0.63, 95% CI=0.47, 0.84). Substituting one serving/day of poultry for one serving/day of total red meat was not significantly associated with risk of all-cause mortality (data not shown).

Total red meat intake was not associated with CVD, CHD, or stroke mortality risk. After additional adjustment for low-fat dairy food consumption, higher red meat consumption was somewhat associated with increased CHD mortality (HR [highest versus lowest] = 1.29, 95% CI=1.00, 1.66, p_{trend}=0.14), but not CVD mortality (HR=1.12, 95% CI=0.94, 1.34, p_{trend}=0.08) or stroke mortality risk (HR=1.05, 95% CI=0.78, 1.42, p_{trend}=0.25). No significant association was observed between poultry, fish, egg, or legume intake and CVD, CHD, or stroke mortality risk (Table 3).

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Higher intake of total red meat and poultry was not associated with total cancer, gastrointestinal, or other cancer mortality (Table 4). In multivariate analysis, high fish consumption was associated with reduced total cancer mortality risk (HR [highest versus lowest] =0.79, 95% CI=0.64, 0.98, p_{trend}=0.03). This association was unchanged with adjustment for total red meat (HR=0.79, 95% CI=0.64, 0.98, p_{trend}=0.03); fruit and vegetable (HR=0.81, 95% CI=0.66, 1.01, p_{trend}=0.07); or low-fat dairy food intake (HR=0.79, 95% CI=0.64, 0.99, p_{trend}=0.03). Fish intake was also associated with lower gastrointestinal cancer mortality risk (HR [highest versus lowest]=0.75, 95% CI=0.56, 1.00, p_{trend}=0.02). Intake of eggs was somewhat associated with a reduced risk of total cancer mortality (HR=0.81, 95% CI=0.67, 0.99, p_{trend}=0.17). The highest versus the lowest quintile of legume intake was associated with 28% lower risk of total cancer mortality (HR=0.72, 95% CI=0.58, 0.89, p_{trend}=0.004), 24% lower risk of gastrointestinal cancer mortality (HR=0.76, 95% CI=0.58, 1.01, p_{trend}=0.05), and 34% lower risk of other cancer mortality (HR=0.66, 95% CI=0.47, 0.93, p_{trend}=0.04). Similar estimates for total cancer mortality were noted after additional adjustment for fruit and vegetable intake (data not shown).

Sensitivity Analysis

In sensitivity analyses, participants who died as a result of external events (i.e., accidents, intoxication, suicide, or other types of injury; n=217) were excluded. The results were similar to total mortality (data not shown). Further, the authors evaluated whether the association between protein-rich food intake and all-cause mortality risk was modified by gender, age, BMI, smoking, and wealth score. The associations between dietary protein sources and all-cause mortality did not differ by gender (Appendix Figure 2, available online), age, or BMI (data not shown). A significant interaction between red meat intake and smoking status was noted ($p_{interaction}$=0.04). Red meat consumption was significantly associated with higher all-cause mortality risk in current smokers (HR [highest versus lowest] =1.43, 95% CI=1.11, 1.82, p_{trend}=0.006) compared with never smokers (HR [highest versus lowest]=0.93, 95% CI=0.80, 1.07,p_{trend}=0.64) or former smokers (HR [highest versus lowest]=1.06, 95% CI=0.63, 1.78, p_{trend}=0.87). An inverse association between fish intake and all-cause mortality was also observed among non-smokers ($p_{interaction}$=0.05; Appendix Figure 3, available online). Furthermore, the association between red meat intake and all-cause mortality was modified by the wealth score. Comparing the highest versus the lowest consumption of total red meat, all-cause mortality risk was 34% higher among participants who had a higher wealth score (HR=1.34, 95% CI=1.09, 1.65, p_{trend}=0.02), with no association among participants with a lower wealth score (HR=0.93, 95% CI=0.80, 1.08, p_{trend}=0.67; $p_{interaction}$=0.02; Appendix Figure 4, available online). No other significant interaction was observed.

DISCUSSION

In this prospective community-based cohort study in Iran, high consumption of fish and legumes was associated with lower cancer mortality risk, independent of other dietary factors. Lowered all-cause mortality risk was observed among participants with high egg consumption. Furthermore, high red meat intake was associated with higher mortality risk among current smokers as well as participants with higher SES. Poultry, fish, and legume

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consumption was not related to reduced CVD or all-cause mortality risk among all participants. However, replacement of red meat with fish, eggs, or legumes was associated with lower risk of all-cause mortality.

Based on data from American and European cohort studies, high red meat consumption, with more emphasis on processed meat, has been reported to be associated with all-cause and specific-cause mortality.[17,31–33] However, similar to the results from a pooled analysis of eight Asian prospective cohort studies,[12] the current study showed that high total red meat intake was not associated with all-cause, CVD, or cancer mortality risk. Wide variation in the amount of red meat and processed meat intake among studies may lead to a difference in risk. Although two servings/day of total red meat is common in most Western countries, mean consumption of total red meat was only 0.19 serving/day in the current study, with a very small amount of processed red meat (mean intake, 0.04 serving/day). A small amount of red meat intake has been reported in Asian prospective cohort studies as well.[12] However, within smoking subgroups, similar to the European Prospective Investigation into Cancer and Nutrition study,[31] increased mortality risk was observed among current smokers with high total red meat consumption in the current study. Current smokers might be more susceptible to adverse health effects of red meat than never or former smokers. Smoking may accelerate the carcinogenic effect of red meat owing to its induction of *CYP1A2* activity,[34] however, residual confounding from smoking could not be ruled out.

Although high fish consumption has been associated with reduced all-cause mortality[9] and CHD mortality risk[10] in meta-analyses of prospective studies, significant associations were not observed in the multivariate-adjusted model. Differences in fish intake may partly explain disparities in results, and SES may play an important role in mediating the association between fish intake and mortality. In the current study, high fish consumption was associated with lower cancer mortality risk, even after adjusting for the wealth score. Prospective studies show a very wide range of results.[11–13] While high fish consumption was not associated with cancer mortality risk in the European Prospective Investigation into Cancer and Nutrition study,[11] high fish consumption was associated with increased cancer mortality risk among men in a pooled analysis of eight Asian cohorts[12] and decreased cancer mortality risk in British men and women.[13] Fish contributing to high intake of n-3 fatty acids may suppress the carcinogenesis process and inhibit tumor growth.[35]

The relation between bean and soybean consumption and cancer risk has been reported in some cohort studies.[36–39] As an important dietary source of fiber, flavonols, and other bioactive constituents, legumes may regulate cell proliferation[40] and contribute to the prevention of cancer.[41]

Eggs are a diverse food consisting of several factors that may potentially influence risk of chronic diseases. Cholesterol that is found in eggs has been hypothesized to increase risk of CHD,[42] whereas other nutrients such as vitamins, minerals, carotenoids, and monounsaturated fatty acids in eggs may have beneficial health effects.[43–45] In general, there is no consistent association across epidemiologic studies in terms of CVD or overall mortality and egg consumption. Although egg consumption was not associated with CVD and all-cause mortality risk in a recent meta-analysis,[16] in the current study, high egg

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consumption was associated with reduced mortality risk. The inconsistencies among cohort studies might be due to chance or differences in intake. In the Physicians' Health Study, consuming at least one egg/day was significantly associated with higher all-cause mortality risk,[46] whereas the median egg intake in the highest quartile in the current study population was less than half an egg/day.

Limitations

The results need to be interpreted in the context of several limitations. Residual confounding is always of concern in any observational study, as participants with high consumption of red meat or other dietary protein sources may have different lifestyles and SES compared with other participants. Although controlling for potential confounders (except the wealth score) had minimal effects on associations, the possibility of residual confounding by unmeasured or unknown confounders could not be ruled out. Moreover, random measurement error due to within-person variation is possible from use of food frequency questionnaires to assess dietary intake. Further, in the current study, the dietary protein sources were only evaluated at enrollment and it is likely that participants might have altered dietary habits during the follow-up period.

This study has several strengths. The prospective population-based cohort study with a high rate of follow up (> 99%) reduced the potential risk of selection bias. To minimize the possibility of recall bias, participants with pre-existing diabetes, CVD, or cancer at time of enrollment were excluded from the analyses. Furthermore, to the best of the authors' knowledge, this is the first cohort study in the Middle East that prospectively evaluated the role of dietary protein sources in mortality risk among a population with different socioeconomic and lifestyle patterns.

CONCLUSIONS

The present findings suggest that a high intake of fish and legumes might be associated with decreased cancer mortality risk. In addition, lower mortality risk with egg consumption was observed. Although there was no significant association between total red meat intake and all-cause mortality, the association differed by smoking and SES with increased risk in current smokers and in individuals with higher wealth score. Further studies are needed to investigate underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Participants According to Quintile of Total Red Meat Consumption

	Total red meat				
Potential risk factors	**Q1 (*n*=8,480)**	**Q2 (*n*=8,481)**	**Q3 (*n*=8,480)**	**Q4 (*n*=8,481)**	**Q5 (*n*=8,481)**
M±SD					
Total red meat intake, serving/day	0.02±0.01	0.07±0.02	0.14±0.02	0.23±0.04	0.52±0.30
Poultry intake, serving/day	0.8±0.8	0.7±0.6	0.7±0.6	0.7 ±0.6	0.6±0.6
Fish intake, serving/day	0.06±0.13	0.08±0.15	0.09±0.18	0.10±0.15	0.12±0.19
Egg intake, serving/day	0.14±0.20	0.18±0.22	0.21±0.25	0.23 ±0.25	0.28±0.31
Legume intake, serving/day	0.13±0.11	0.13 ±0.10	0.13±0.10	0.14±0.10	0.15±0.13
Total dairy food intake, serving/day	0.9±0.7	1.2±0.8	1.3±0.8	1.5±0.9	1.7±1.0
Total grain intake, serving/day	12.1±5.0	12.4±4.8	12.7±4.8	12.9±4.8	13.4±4.9
Total fruit intake, serving/day	1.1±1.0	1.6±1.3	1.9±1.5	2.1±1.7	2.7±1.9
Total vegetable intake, serving/day	1.1±0.8	1.3±0.8	1.4±0.9	1.6±0.9	1.8±1.1
Total energy intake, kcal/day	1,891±542	2,060±525	2,174±528	2,265±525	2,471±565
Age (years)	53.1±9.2	52.0±8.8	51.4±8.7	51.0±8.6	50.6±8.4
BMI (kg/m^2)	25.6±5.4	26.4±5.4	26.7±5.4	26.7 ±5.3	26.9±5.3
Percentage					
Gender (male)	37	39	42	45	53
Ethnicity (Turkmen)	54	77	81	82	82
Marital status (married)	85	88	89	90	91
Current smokers	12	12	14	15	18
Opium use	18	15	16	16	17
Place of residence (rural)	89	84	81	76	73
Occupational physical activity, %					
Level 1	3	3	2	2	3
Level 2	3	4	5	7	8
Level 3	51	57	58	56	51
Level 4	43	36	35	35	38

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Table 2

Risk for All-cause Mortality According to Quintile of Dietary Protein Sources Consumption

Dietary protein sources	Quintile of intake: 1	2	3	4	5	*p* trend	3 servings/week
Total red meat							
Median intake, serving/day	0.02	0.07	0.13	0.23	0.43		
No. of deaths/person-year	775/65,241	655/67,685	617/68,133	618/68,990	626/69,818		
Age-adjusted HR (95% CI)[a]	1	0.90 (0.81, 1.00)	0.89 (0.80, 0.99)	0.91 (0.82, 1.01)	0.95 (0.86, 1.06)	0.82	1.01 (0.94, 1.08)
Multivariate-adjusted HR (95% CI)[b]	1	0.96 (0.86, 1.07)	0.98 (0.88, 1.09)	1.01 (0.90, 1.13)	1.04 (0.93, 1.17)	0.25	1.02 (0.96, 1.09)
Poultry							
Median intake, serving/day	0.11	0.33	0.54	0.78	1.33		
No. of deaths/person-year	706/70,172	654/68,732	614/67,769	617/67,029	700/66,165		
Age-adjusted HR (95% CI)[a]	1	0.95 (0.86, 1.06)	0.90 (0.81, 1.00)	0.89 (0.80, 0.99)	0.90 (0.81, 1.00)	0.06	0.97 (0.93, 1.00)
Multivariate-adjusted HR (95% CI)[b]	1	0.97 (0.87, 1.08)	0.96 (0.86, 1.07)	0.98 (0.88, 1.10)	1.02 (0.91, 1.14)	0.54	1.01 (0.98, 1.05)
Fish[c]							
Median intake, serving/day	0	0.01	0.06	0.19			
No. of deaths/person-year	883/68,316	910/90,608	790/90,242	708/90,701			
Age-adjusted HR (95% CI)[a]	1	0.88 (0.81, 0.97)	0.82 (0.75, 0.90)	0.77 (0.69, 0.85)		**<0.0001**	0.61 (0.49, 0.75)
Multivariate-adjusted HR (95% CI)[b]	1	0.94 (0.86, 1.04)	0.93 (0.84, 1.02)	0.93 (0.83, 1.03)		0.32	0.89 (0.71, 1.12)
Eggs[c]							
Median intake, serving/day	0	0.06	0.18	0.48			
No. of deaths/person-year	905/69,165	804/82,907	798/95,280	784/92,515			
Age-adjusted HR (95% CI)[a]	1	0.88 (0.80, 0.97)	0.86 (0.79, 0.95)	0.89 (0.81, 0.98)		0.12	0.94 (0.86, 1.02)
Multivariate-adjusted HR (95% CI)[b]	1	0.92 (0.84, 1.02)	0.90 (0.82, 0.99)	0.88 (0.79, 0.97)		**0.03**	0.91 (0.84, 0.99)
Legumes							
Median intake, serving/day	0.03	0.08	0.12	0.17	0.26		
No. of deaths/person-year	787/69,186	622/68,484	581/67,714	619/67,013	682/67,470		
Age-adjusted HR (95% CI)[a]	1	0.87 (0.78, 0.96)	0.82 (0.73, 0.91)	0.87 (0.79, 0.97)	0.85 (0.77, 0.94)	**0.01**	0.80 (0.66, 0.95)

Dietary protein sources	Quintile of intake					p trend	3 servings/week
	1	2	3	4	5		
Multivariate-adjusted HR (95% CI)[b]	1	0.92 (0.83, 1.02)	0.89 (0.80, 0.99)	0.95 (0.85, 1.06)	0.94 (0.84, 1.04)	0.45	0.93 (0.77, 1.13)

Note: Bold values were statistically significant (p<0.05).

[a]Age-adjusted model was adjusted for age (years).

[b]Multivariate-adjusted model was adjusted for gender; age (years); ethnicity (Turkmen, Persian, others); education (illiterate, ≤5 years, 6–8 years, high school, academic); marital status (married, other); residency (rural, urban); smoking (never, former, current <20 p/year, current 20–30 p/year, current ≥30 p/year); opium use (user, non-user); alcohol (user, non-user); BMI (<18.5,18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0); systolic blood pressure (quintile); occupational physical activity (sedentary, standing or occasional walking, causing mild increase in heart rate and sweating, causing significant increase in heart rate and sweating); family history of cancer (yes, no); wealth score (quintile); medication (using a fixed-dose combination pill consisting of aspirin, valsartan, atorvastatin, and hydrochlorothiazide; yes/no); and energy intake (quintile).

[c]Quartile.

HR, hazard ratio.

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Table 3

Risk for Cardiovascular Disease, Coronary Heart Disease, and Stroke Mortality According to Quintile of Dietary Protein Sources Consumption

Dietary protein sources	Quintile of intake 1	2	3	4	5	*p* trend	3 servings/week
Total red meat							
Cardiovascular disease							
Median intake, serving/day	0.02	0.07	0.13	0.23	0.43		
No. of deaths/person-year	339/65,241	271/67,685	295/68,133	291/68,990	271/69,818		
Age-adjusted HR (95% CI)[a]	1	0.86 (0.73, 1.01)	0.99 (0.85, 1.16)	1.00 (0.86, 1.17)	0.96 (0.82, 1.13)	0.74	1.03 (0.94, 1.13)
Multivariate-adjusted HR (95% CI)[b]	1	0.93 (0.79, 1.09)	1.11 (0.94, 1.31)	1.12 (0.95, 1.33)	1.07 (0.90, 1.28)	0.20	1.04 (0.95, 1.15)
Coronary heart disease							
No. of deaths/person-year	153/65,241	145/67,685	170/68,133	143/68,990	153/69,818		
Age-adjusted HR (95% CI)[a]	1	1.01 (0.80, 1.27)	1.24 (1.00, 1.55)	1.07 (0.85, 1.34)	1.17 (0.94, 1.47)	0.19	1.08 (0.96, 1.21)
Multivariate-adjusted HR (95% CI)[b]	1	1.09 (0.86, 1.38)	1.37 (1.09, 1.73)	1.16 (0.91, 1.48)	1.22 (0.95, 1.56)	0.29	1.04 (0.91, 1.18)
Stroke							
No. of deaths/person-year	131/65,241	90/67,685	96/68,133	102/68,990	88/69,818		
Age-adjusted HR (95% CI)[a]	1	0.75 (0.58, 0.99)	0.86 (0.66, 1.12)	0.94 (0.73, 1.23)	0.85 (0.65, 1.11)	0.71	0.99 (0.83, 1.18)
Multivariate-adjusted HR (95% CI)[b]	1	0.78 (0.60, 1.03)	0.96 (0.73, 1.26)	1.07 (0.81, 1.41)	1.00 (0.74, 1.34)	0.41	1.05 (0.89, 1.24)
Poultry							
Cardiovascular disease							
Median intake, serving/day	0.11	0.33	0.54	0.78	1.33		
No. of deaths/person-year	310/70,172	277/68,732	295/67,769	266/67,029	319/66,165		
Age-adjusted HR (95% CI)[a]	1	0.92 (0.78, 1.08)	0.98 (0.83, 1.15)	0.87 (0.73, 1.02)	0.92 (0.79, 1.08)	0.33	0.97 (0.93, 1.03)
Multivariate, adjusted HR (95% CI)[b]	1	0.93 (0.79, 1.10)	1.04 (0.89, 1.22)	0.95 (0.80, 1.12)	1.03 (0.87, 1.21)	0.63	1.01 (0.96, 1.07)
Coronary heart disease							
No. of deaths/person-year	164/70,172	131/68,732	162/67,769	140/67,029	167/66,165		
Age-adjusted HR (95% CI)[a]	1	0.82 (0.65, 1.03)	1.02 (0.82, 1.26)	0.87 (0.69, 1.08)	0.93 (0.75, 1.16)	0.79	0.99 (0.92, 1.06)
Multivariate-adjusted HR (95% CI)[b]	1	0.83 (0.66, 1.04)	1.06 (0.85, 1.32)	0.92 (0.73, 1.15)	0.97 (0.77, 1.22)	0.90	1.00 (0.93, 1.08)

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Dietary protein sources	Quintile of intake 1	2	3	4	5	*p* trend	3 servings/week
Stroke							
No. of deaths/person-year	109/70,172	93/68,732	97/67,769	96/67,029	112/66,165		
Age-adjusted HR (95% CI)[a]	1	0.88 (0.66, 1.15)	0.91 (0.69, 1.19)	0.88 (0.67, 1.16)	0.89 (0.68, 1.16)	0.53	0.97 (0.89, 1.06)
Multivariate-adjusted HR (95% CI)[b]	1	0.89 (0.68, 1.18)	0.98 (0.75, 1.30)	0.99 (0.75, 1.31)	1.06 (0.80, 1.39)	0.47	1.03 (0.94, 1.13)
Fish[c]							
Cardiovascular disease							
Median intake, serving/day	0	0.01	0.06	0.19			
No. of deaths/person-year	386/68,316	396/90,608	356/90,242	329/90,701			
Age-adjusted HR (95% CI)[a]	1	0.89 (0.77, 1.02)	0.86 (0.74, 0.99)	0.83 (0.71, 0.96)		0.04	0.73 (0.54, 0.99)
Multivariate-adjusted HR (95% CI)[b]	1	0.95 (0.82, 1.09)	0.95 (0.82, 1.10)	0.96 (0.82, 1.13)		0.88	0.98 (0.70, 1.36)
Coronary heart disease							
No. of deaths/person-year	198/68,316	192/90,608	188/90,242	186/90,701			
Age-adjusted HR (95% CI)[a]	1	0.83 (0.68, 1.01)	0.86 (0.70, 1.05)	0.89 (0.72, 1.08)		0.72	0.93 (0.61, 1.40)
Multivariate-adjusted HR (95% CI)[b]	1	0.85 (0.70, 1.04)	0.90 (0.73, 1.10)	0.93 (0.75, 1.16)		0.94	1.02 (0.65, 1.59)
Stroke							
No. of deaths/person-year	131/68,316	145/90,608	129/90,242	102/90,701			
Age-adjusted HR (95% CI)[a]	1	0.99 (0.78, 1.25)	0.95 (0.74, 1.21)	0.79 (0.61, 1.03)		0.05	0.58 (0.34, 1.00)
Multivariate-adjusted HR (95% CI)[b]	1	1.11 (0.87, 1.41)	1.15 (0.89, 1.47)	1.03 (0.78, 1.36)		0.90	0.96 (0.54, 1.70)
Eggs[c]							
Cardiovascular disease							
Median intake, serving/day	0	0.06	0.18	0.48			
No. of deaths/person-year	396/69,165	374/82,907	348/95,280	349/92,515			
Age-adjusted HR (95% CI)[a]	1	0.95 (0.82, 1.09)	0.88 (0.76, 1.02)	0.93 (0.80, 1.07)		0.41	0.95 (0.84, 1.07)
Multivariate-adjusted HR (95% CI)[b]	1	1.01 (0.87, 1.16)	0.93 (0.80, 1.08)	0.92 (0.79, 1.07)		0.22	0.92 (0.81, 1.05)
Coronary heart disease							
No. of deaths/person-year	190/69,165	192/82,907	193/95,280	189/92,515			

Dietary protein sources	Quintile of intake					*p* trend	3 servings/week
	1	2	3	4	5		
Age-adjusted HR (95% CI)[a]	1	1.00 (0.82, 1.22)	0.98 (0.80, 1.20)	1.01 (0.82, 1.24)		0.90	1.01 (0.86, 1.20)
Multivariate-adjusted HR (95% CI)[b]	1	1.03 (0.84, 1.26)	0.99 (0.80, 1.21)	0.92 (0.74, 1.14)		0.31	0.91 (0.77, 1.09)
Stroke							
No. of deaths/person-year	152/69,165	134/82,907	104/95,280	117/92,515			
Age-adjusted HR (95% CI)[a]	1	0.91 (0.72, 1.14)	0.72 (0.56, 0.92)	0.86 (0.67, 1.09)		0.27	0.89 (0.72, 1.10)
Multivariate-adjusted HR (95% CI)[b]	1	1.00 (0.79, 1.26)	0.80 (0.62, 1.04)	0.94 (0.73, 1.21)		0.56	0.94 (0.75, 1.17)
Legumes							
Cardiovascular disease							
Median intake, serving/day	0.03	0.08	0.12	0.17	0.26		
No. of deaths/person-year	330/69,186	279/68,484	247/67,714	285/67,013	326/67,470		
Age-adjusted HR (95% CI)[a]	1	0.93 (0.80, 1.09)	0.83 (0.70, 0.98)	0.96 (0.82, 1.12)	0.97 (0.83, 1.13)	0.98	1.00 (0.76, 1.31)
Multivariate-adjusted HR (95% CI)[b]	1	0.99 (0.84, 1.16)	0.89 (0.76, 1.06)	1.03 (0.88, 1.21)	1.05 (0.89, 1.23)	0.40	1.13 (0.85, 1.51)
Coronary heart disease							
No. of deaths/person-year	160/69,186	155/68,484	127/67,714	149/67,013	173/67,470		
Age-adjusted HR (95% CI)[a]	1	1.06 (0.85, 1.32)	0.87 (0.69, 1.10)	1.02 (0.82, 1.28)	1.06 (0.86, 1.32)	0.57	1.12 (0.77, 1.62)
Multivariate-adjusted HR (95% CI)[b]	1	1.10 (0.88, 1.37)	0.92 (0.72, 1.16)	1.06 (0.85, 1.33)	1.08 (0.86, 1.36)	0.57	1.12 (0.75, 1.67)
Stroke							
No. of deaths/person-year	120/69,186	86/68,484	88/67,714	109/67,013	104/67,470		
Age-adjusted HR (95% CI)[a]	1	0.81 (0.61, 1.06)	0.83 (0.63, 1.09)	1.02 (0.79, 1.33)	0.84 (0.65, 1.09)	0.58	0.88 (0.55, 1.39)
Multivariate-adjusted HR (95% CI)[b]	1	0.86 (0.65, 1.14)	0.91 (0.69, 1.20)	1.15 (0.88, 1.50)	0.99 (0.75, 1.30)	0.55	1.16 (0.71, 1.89)

[a] Age-adjusted model was adjusted for age (years).

[b] Multivariate-adjusted model was adjusted for gender; age (years); ethnicity (Turkmen, Persian, others); education (illiterate, ≤5 years, 6–8 years, high school, academic); marital status (married, other); residency (rural, urban); smoking (never, former, current <20 p/year, current 20–30 p/year, current ≥30 p/year); opium use (user, non-user); alcohol (user, non-user); BMI (<18.5,18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0); systolic blood pressure (quintile); occupational physical activity (sedentary, standing or occasional walking, causing mild increase in heart rate and sweating, causing significant increase in heart rate and sweating); family history of cancer (yes, no); wealth score (quintile); medication (using a fixed-dose combination pill consisting of aspirin, valsartan, atorvastatin, and hydrochlorothiazide; yes/no); and energy intake (quintile).

[c] Quartile.

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HR, hazard ratio.

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Table 4

Risk for Total Cancer, Gastrointestinal Cancer, and Other Cancer Mortality According to Quintile of Dietary Sources of Protein Consumption

Dietary protein sources	Quintile of intake 1	2	3	4	5	p trend	3 servings/week
Total red meat							
Total cancer							
Median intake, serving/day	0.02	0.07	0.13	0.23	0.43		
No. of deaths/person-year	191/65,241	193/67,685	153/68,133	156/68,990	166/69,818		
Age-adjusted HR (95% CI)[a]	1	1.07 (0.87, 1.31)	0.89 (0.72, 1.10)	0.93 (0.75, 1.14)	1.01 (0.82, 1.25)	0.85	1.05 (0.93, 1.18)
Multivariate-adjusted HR (95% CI)[b]	1	1.09 (0.89, 1.34)	0.92 (0.73, 1.15)	0.96 (0.76, 1.20)	1.03 (0.82, 1.30)	1.00	1.04 (0.92, 1.17)
Gastrointestinal cancer							
No. of deaths/person-year	108/65,241	110/67,685	98/68,133	92/68,990	101/69,818		
Age-adjusted HR (95% CI)[a]	1	1.09 (0.84, 1.42)	1.03 (0.78, 1.36)	0.99 (0.75, 1.31)	1.12 (0.85, 1.47)	0.57	1.06 (0.91, 1.23)
Multivariate-adjusted HR (95% CI)[b]	1	1.12 (0.85, 1.47)	1.08 (0.81, 1.43)	1.05 (0.78, 1.41)	1.17 (0.87, 1.59)	0.43	1.05 (0.89, 1.22)
Other cancer							
No. of deaths/person-year	83/65,241	83/67,685	55/68,133	64/68,990	65/69,818		
Age-adjusted HR (95% CI)[a]	1	1.04 (0.76, 1.41)	0.71 (0.51, 1.01)	0.84 (0.61, 1.17)	0.87 (0.63, 1.21)	0.33	1.04 (0.86, 1.26)
Multivariate-adjusted HR (95% CI)[b]	1	1.05 (0.77, 1.44)	0.72 (0.51, 1.03)	0.85 (0.60, 1.20)	0.85 (0.60, 1.22)	0.34	1.03 (0.84, 1.25)
Poultry							
Total cancer							
Median intake, serving/day	0.11	0.33	0.54	0.78	1.33		
No. of deaths/person-year	200/70,172	169/68,732	152/67,769	159/67,029	179/66,165		
Age-adjusted HR (95% CI)[a]	1	0.87 (0.71, 1.07)	0.78 (0.64, 0.97)	0.81 (0.66, 1.00)	0.82 (0.67, 1.01)	0.10	0.94 (0.88, 1.01)
Multivariate-adjusted HR (95% CI)[b]	1	0.88 (0.72, 1.08)	0.83 (0.67, 1.03)	0.90 (0.73, 1.11)	0.93 (0.75, 1.15)	0.75	0.99 (0.92, 1.06)
Gastrointestinal cancer							
No. of deaths/person-year	110/70,172	111/68,732	92/67,769	90/67,029	106/66,165		
Age-adjusted HR (95% CI)[a]	1	1.04 (0.80, 1.35)	0.86 (0.65, 1.14)	0.83 (0.63, 1.09)	0.87 (0.67, 1.14)	0.16	0.94 (0.86, 1.03)
Multivariate-adjusted HR (95% CI)[b]	1	1.05 (0.81, 1.38)	0.93 (0.70, 1.22)	0.94 (0.70, 1.24)	1.04 (0.78, 1.37)	0.95	1.00 (0.91, 1.10)

Dietary protein sources	Quintile of intake 1	2	3	4	5	*p* trend	3 servings/week
Other cancer							
No. of deaths/person-year	90/70,172	58/68,732	60/67,769	69/67,029	73/66,165		
Age-adjusted HR (95% CI)[a]	1	0.66 (0.48, 0.92)	0.69 (0.50, 0.96)	0.79 (0.57, 1.08)	0.77 (0.56, 1.05)	0.36	0.95 (0.85, 1.06)
Multivariate-adjusted HR (95% CI)[b]	1	0.67 (0.48, 0.93)	0.72 (0.52, 1.00)	0.85 (0.62, 1.17)	0.81 (0.58, 1.12)	0.61	0.97 (0.87, 1.09)
Fish[c]							
Total cancer							
Median intake, serving/day	0	0.01	0.06	0.19			
No. of deaths/person-year	240/68,316	253/90,608	203/90,242	163/90,701			
Age-adjusted HR (95% CI)[a]	1	0.90 (0.75, 1.07)	0.76 (0.63, 0.92)	0.64 (0.52, 0.78)		<0.0001	0.38 (0.25, 0.59)
Multivariate-adjusted HR (95% CI)[b]	1	0.96 (0.80, 1.14)	0.87 (0.72, 1.06)	0.79 (0.64, 0.98)		**0.03**	0.60 (0.38, 0.94)
Gastrointestinal cancer							
No. of deaths/person-year	147/68,316	160/90,608	117/90,242	85/90,701			
Age-adjusted HR (95% CI)[a]	1	0.94 (0.75, 1.17)	0.73 (0.58, 0.94)	0.56 (0.43, 0.73)		<0.0001	0.26 (0.15, 0.47)
Multivariate-adjusted HR (95% CI)[b]	1	1.03 (0.82, 1.29)	0.88 (0.68, 1.12)	0.75 (0.56, 1.00)		**0.02**	0.49 (0.26, 0.89)
Other cancer							
No. of deaths/person-year	93/68,316	93/90,608	86/90,242	78/90,701			
Age-adjusted HR (95% CI)[a]	1	0.83 (0.62, 1.11)	0.81 (0.60, 1.09)	0.76 (0.56, 1.03)		0.17	0.64 (0.34, 1.20)
Multivariate-adjusted HR (95% CI)[b]	1	0.85 (0.64, 1.14)	0.87 (0.64, 1.18)	0.84 (0.60, 1.17)		0.52	0.80 (0.40, 1.58)
Eggs[c]							
Total cancer							
Median intake, serving/day	0	0.06	0.18	0.48			
No. of deaths/person-year	235/69,165	189/82,907	239/95,280	196/92,515			
Age-adjusted HR (95% CI)[a]	1	0.79 (0.65, 0.96)	0.98 (0.82, 1.17)	0.84 (0.69, 1.02)		0.35	0.93 (0.79, 1.09)
Multivariate-adjusted HR (95% CI)[b]	1	0.81 (0.67, 0.99)	0.99 (0.83, 1.20)	0.81 (0.67, 0.99)		0.17	0.89 (0.75, 1.05)
Gastrointestinal cancer							
No. of deaths/person-year	143/69,165	113/82,907	136/95,280	117/92,515			

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Dietary protein sources	Quintile of intake 1	2	3	4	5	*p* trend	3 servings/week
Age-adjusted HR (95% CI)[a]	1	0.79 (0.62, 1.01)	0.95 (0.75, 1.20)	0.86 (0.67, 1.09)		0.56	0.94 (0.76, 1.16)
Multivariate-adjusted HR (95% CI)[b]	1	0.82 (0.64, 1.05)	0.97 (0.76, 1.23)	0.84 (0.65, 1.08)		0.39	0.91 (0.73, 1.13)
Other cancer							
No. of deaths/person-year	92/69,165	76/82,907	103/95,280	79/92,515			
Age-adjusted HR (95% CI)[a]	1	0.79 (0.58, 1.07)	1.03 (0.77, 1.36)	0.82 (0.61, 1.11)		0.44	0.91(0.71, 1.17)
Multivariate-adjusted HR (95% CI)[b]	1	0.80 (0.59, 1.09)	1.03 (0.77, 1.37)	0.78 (0.57, 1.07)		0.26	0.86 (0.66, 1.12)
Legumes							
Total cancer							
Median intake, serving/day	0.03	0.08	0.12	0.17	0.26		
No. of deaths/person-year	232/69,186	178/68,484	136/67,714	161/67,013	152/67,470		
Age-adjusted HR (95% CI)[a]	1	0.84 (0.69, 1.02)	0.64 (0.52, 0.79)	0.77 (0.63, 0.94)	0.65 (0.53, 0.79)	<0.0001	0.47 (0.32, 0.68)
Multivariate-adjusted HR (95% CI)[b]	1	0.88 (0.73, 1.08)	0.70 (0.57, 0.87)	0.84 (0.68, 1.03)	0.72 (0.58, 0.89)	**0.004**	0.57 (0.39, 0.84)
Gastrointestinal cancer							
No. of deaths/person-year	136/69,186	112/68,484	79/67,714	94/67,013	88/67,470		
Age-adjusted HR (95% CI)[a]	1	0.91(0.71, 1.17)	0.64 (0.49, 0.85)	0.77 (0.59, 1.00)	0.63 (0.48, 0.83)	0.001	0.43 (0.27, 0.70)
Multivariate-adjusted HR (95% CI)[b]	1	0.96 (0.75, 1.24)	0.72 (0.54, 0.95)	0.86 (0.66, 1.13)	0.76 (0.58, 1.01)	**0.05**	0.60 (0.37, 1.00)
Other cancer							
No. of deaths/person-year	96/69,186	66/68,484	57/67,714	67/67,013	64/67,470		
Age-adjusted HR (95% CI)[a]	1	0.74 (0.54, 1.01)	0.64 (0.46, 0.89)	0.76 (0.55, 1.04)	0.66 (0.48, 0.91)	0.03	0.53 (0.30, 0.94)
Multivariate-adjusted HR (95% CI)[b]	1	0.78 (0.57, 1.06)	0.68 (0.49, 0.95)	0.80 (0.58, 1.10)	0.66 (0.47, 0.93)	**0.04**	0.52 (0.29, 0.96)

[a]Age-adjusted model was adjusted for age (years).

[b]Multivariate-adjusted model was adjusted for gender; age (years); ethnicity (Turkmen, Persian, others); education (illiterate, ≤5 years, 6–8 years, high school, academic); marital status (married, other); residency (rural, urban); smoking (never, former, current <20 p/year, current 20–30 p/year, current ≥30 p/year); opium use (user, non-user); alcohol (user, non-user); BMI (<18.5,18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0); systolic blood pressure (quintile); occupational physical activity (sedentary, standing or occasional walking, causing mild increase in heart rate and sweating, causing significant increase in heart rate and sweating); family history of cancer (yes, no); wealth score (quintile); medication (using a fixed-dose combination pill consisting of aspirin, valsartan, atorvastatin, and hydrochlorothiazide; yes/no); and energy intake (quintile).

[c]Quartile.

HR, hazard ratio.

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