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Original article

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Nut consumption and total and cause-specific mortality: results from the Golestan Cohort Study

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Abstract

Background: A number of prospective studies have observed inverse associations between nut consumption and chronic diseases. However, these studies have predominantly been conducted in Western countries, where nut consumption tends to be more common among individuals with healthier lifestyles. It is important to examine the association in other parts of the world, and particularly among populations with different patterns of disease, socioeconomic status, lifestyles and disease risk factors. Our objective was to examine the association between nut consumption and mortality in a population whose nut consumption does not track with a healthy lifestyle.

Methods: We examined the association between nut consumption and all-cause and cause-specific mortality in the 50 045 participants of the Golestan Cohort Study. Participants were aged 40 and older at baseline in 2004, and have been actively followed since that time. Dietary data were collected using a validated semi-quantitative food frequency questionnaire that was administered at baseline.

Results: During 349 677 person-years of follow-up, 3981 cohort participants died, including 1732 women and 2249 men. Nut consumption was associated inversely with

all-cause mortality. The pooled multivariate adjusted hazard ratios for death among participants who ate nuts, as compared with those who did not, were 0.89 [95% confidence interval (CI), 0.82-0.95] for the consumption of less than one serving of nuts per week, 0.75 (95% CI, 0.67-0.85) for one to less than three servings per week and 0.71 (95% CI, 0.58-0.86) for three or more servings per week ($P < 0.001$ for trend). Among specific causes, significant inverse associations were observed between nut consumption and deaths due to cardiovascular disease, all cancers and gastrointestinal cancers.
Conclusions: This study provides evidence for an inverse association between nut consumption and mortality in a developing country, where nut consumption does not track with a healthy lifestyle. Further work is needed to establish the underlying mechanisms responsible for this association.

Key words: Nuts, mortality, cardiovascular, cancer, Golestan Cohort Study

Key Message

- This study provides evidence for an inverse association between nut consumption and mortality in a developing country, where nut consumption does not track with a healthy lifestyle.

Introduction

Nuts are an important component of the Mediterranean diet. Nutritionally rich,[1,2] nuts have been inversely associated with chronic diseases in a number of complementary studies.[3–10] Epidemiological and clinical studies suggest that nut consumption is inversely related to several mediators of chronic diseases, including visceral adiposity, insulin resistance, hyperglycaemia, oxidative stress and inflammation.[6–10] Nut consumption has also been associated inversely with cardiovascular disease (CVD), cancer, diabetes mellitus, metabolic syndrome and hypertension,[5,8,11–13] which are the main causes of death. Inverse associations between nut consumption and total and cause-specific mortality have also been reported in a few prospective cohorts in Western countries.[4,14] Among these populations, however, nut consumption tends to be associated with a healthy lifestyle. Therefore, prospective studies of nut consumption and mortality are needed in geographical regions with different lifestyle patterns and chronic disease risk factors. The aim of our study was to evaluate the associations of nut consumption with total and cause-specific mortality in a large, cohort study from Iran.

Methods

Study population

The design of the Golestan Cohort Study has been reported previously.[15] This cohort was launched in 2004 in Golestan Province, in north-eastern Iran, by the recruitment of 50 045 adults, aged between 40 and 87 years, from Gonbad city and 326 rural villages (a 20% urban, 80% rural cohort). This study was approved by the institutional review boards of the Digestive Disease Research Center of Tehran University of Medical Sciences, the US National Cancer Institute (NCI) and the World Health Organization International Agency for Research on Cancer (IARC). All participants provided written informed consent before enrolment.

Dietary assessment

Dietary information was collected using a validated food frequency questionnaire (FFQ) that was specifically developed for this population.[16] Information on typical portion size, consumption frequency and servings consumed each time was collected for each food item at enrolment. Daily intake of each food item was calculated by multiplying the consumption frequency by the typical portion size and the number of servings per day. Participants reported their frequency of consumption of a given serving of each food item during the previous year on a daily (e.g. bread), weekly (e.g. rice, meat), or monthly (e.g. fish) basis. For our analysis, daily intake of all food items was computed from the FFQ and then consumed foods were converted to grams. Total energy intake was computed by summing energy intakes from all foods. In the case of nut consumption, we evaluated consumption of peanuts, tree nuts and overall nuts consumption, and categorized the participants according to the frequency of their 28-g servings of nuts

during the preceding year: never, less than one (< 1) serving per week, one or less than three (1 to < 3) servings per week and three or more (≥ 3) than three servings per week.

Assessment of potential confounders

All participants underwent interviews by trained physicians and/or technicians, and information on demographics and baseline lifestyle behaviours were collected using a structured lifestyle questionnaire. Anthropometric indices were measured after the interviews by trained technicians. Weight was measured using digital scales with the participants wearing minimal clothing and no shoes, and was recorded to the nearest 100 g. Height was measured using a tape measure while the participants were standing in a normal position with no shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (metres). Other potential confounders assessed in this cohort study included age, sex, smoking status and physical activity.[17] Information on wealth score [a surrogate of socioeconomic status (SES)[18] calculated from appliance ownership], opium and alcohol consumption, diabetes and hypertension was also assessed.

Cause of death ascertainment

Details of the follow-up procedures of this cohort study have been described previously.[19] During the period of analysis, only 364 participants (0.7% of the cohort) were lost to follow-up). Our primary end point was death from any cause. Any reported death was followed by a physician visit and completion of a verbal autopsy questionnaire, validated for this population,[20] which was administered to the closest relative of the deceased. At the same time, death certificates and all available medical documents were collected and evaluated. Two internists independently reviewed all documents, including the verbal autopsy information and medical records, and determined the cause of death. In case of disagreement between the two internists, all documents and the two initial diagnoses were reviewed by a third more experienced internist who made the final diagnosis. For this analysis, causes of death were categorized as cardiovascular disease, all cancers together, gastrointestinal (GI) cancers (including alimentary tract, liver and pancreas) and other causes.

Statistical analysis

Cox proportional hazard models were used to estimate overall and cause-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs). Age at the date of death, loss to follow-up or end of follow-up (30 December 2013), whichever occurred first, was considered as the time scale, and age at enrolment considered as time zero. Proportional hazard assumption was tested based on Schoenfeld-residual and -ln survival plots, and it was not violated. Multivariable models were adjusted for all variables which were significantly different between people with different nut consumption levels or were known as risk factors for death, e.g. age at enrolment, sex, BMI, level of education, place of residence, smoking status, opium and alcohol consumption, physical activity level, wealth score (WS), diabetes, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetable, dairy product, egg and total fibre), magnesium (Mg), zinc (Zn) and copper (Cu).

Nut consumption was divided into four categories according to the number of servings consumed weekly (1 serving = 28 g): never, less than one (< 1) serving per week, one or less than three (1 to < 3) servings per week, and three or more (≥ 3) than three servings per week. The median number of servings of nut consumption was calculated for each category and linear trends were tested using the Wald test. Further analyses were performed on data stratified by subgroups of the other known risk factors. To maintain statistical power for these analyses, we combined the two highest categories of nut consumption, and compared this new category (> 1 serving of nuts per week) with participants who never ate nuts. Interactions between each stratified factor and the amount of nut consumption were tested by likelihood-ratio tests.

To test the stability of the results, we performed several sensitivity analyses. To reduce the potential influence of possible confounders including wealth score, BMI, smoking, opium use and alcohol consumption, we excluded participants in the first and last deciles of WS, participants who had extreme BMI (< 18.5 or > 35), or those who were opium users, alcohol users or smokers. We also excluded participants with chronic diseases at baseline, including a previous cancer, CVD, diabetes or hypertension, because these disorders may have changed the patient's dietary patterns. In addition, we excluded events occurring in the first 2 years of follow-up, to examine the potential influence of reverse causation by preclinical disorders. Analyses were performed using STATA software, version 12.0 (Stata Corp., College Station, TX, USA).

Results

Nut consumption and baseline characteristics

After those subjects with incomplete dietary data at baseline (n = 933) were excluded, 49 112 individuals were

Table 1. Baseline characteristics of participants according to nut consumption categories

	Servings of nut consumption				
	Never	**<1 serving per week**	**1 to < 3 servings per week**	**≥3 servings per week**	**Total**
n (%)	13 491 (27.5)	25 494 (51.9)	7 846 (16.0)	2 281 (4.6)	49 112
Men *n* (%)	5 410 (40.1)	10 428 (40.9)	3 793 (48.3)	1 224 (53.7)	20 855 (42.5)
Age mean±SD	55.8±9.4	51.2±8.4	49.4±7.6	48.7±7.6	52.07±8.9
BMI (kg/m^2) mean±SD	25.6±5.5	26.9±5.4	27.4±5.2	27.8±5.1	26.69±5.4
Education *n* (%)					
• No formal	11 435 (84.8)	17 520 (68.7)	4 409 (56.2)	1 039 (45.5)	34 403 (70.1)
• Up to high school	2 021 (15.0)	7 471 (29.3)	3 083 (39.3)	1 083 (47.5)	13 658 (27.8)
• University	35 (0.3)	503 (2.0)	354 (4.5)	159 (7.0)	1 051 (2.1)
Place of residence					
• Rural	12 082 (89.6)	19 699 (77.3)	5 828 (74.3)	1 495 (65.5)	39 104 (79.6)
• Urban	1 409 (10.4)	5 795 (22.7)	2 018 (25.7)	786 (34.5)	10 008 (20.4)
Smoking status *n* (%)					
• Never	11 138 (82.6)	21 366 (83.8)	6 385 (81.4)	1 731 (75.9)	40 620 (82.7)
• Current	1 373 (10.2)	2 591 (10.2)	999 (12.7)	379 (16.6)	5 342 (10.9)
• Former	980 (7.2)	1 537 (6.0)	462 (5.9)	171 (7.5)	3 150 (6.4)
Alcohol ever used *n* (%)	304 (2.2)	827 (3.2)	380 (4.8)	200 (8.8)	1 711 (3.5)
Opiate ever use *n* (%)]	2 782 (20.6)	3 944 (15.5)	1 205 (15.4)	411 (18.0)	8 342 (17.0)
Diabetes *n* (%)	1 115 (8.3)	1 756 (6.9)	484 (6.2)	171 (7.5)	3 526 (7.2)
Hypertension *n* (%)]	6 638 (49.2)	10 642 (41.7)	2 888 (36.8)	837 (36.7)	21 005 (42.8)
Wealth score *n* (%)					
• 1st quartile	4 041 (29.9)	4 380 (17.2)	920 (11.7)	181 (7.9)	9 522 (19.4)
• 2nd quartile	4 812 (35.7)	7 586 (29.8)	1 918 (24.5)	467 (20.5)	14 783 (30.1)
• 3rd quartile	3 051 (22.6)	6 654 (26.1)	2 095 (26.7)	568 (24.9)	12 368 (25.2)
• 4th quartile	1 587 (11.8)	6 874 (27.0)	2 913 (37.1)	1 065 (46.7)	12 439 (25.3)
Physical activity *n* (%)					
• Low	9 750 (72.3)	15 617 (61.3)	4 168 (53.1)	1 021 (44.8)	30.556 (62.22)
• Moderate	3 147 (23.3)	8.690 (34.1)	3 230 (41.2)	1 131 (49.6)	16.198 (33.0)
• High	594 (4.4)	1 187 (4.7)	448 (5.7)	129 (5.7)	2 358 (4.8)
Nutritional characteristics mean±SD					
• Energy intake	1964±1150	2180±862	2446±1338	2666±951	2186±1054
• Fish (g/d)	5.5±11.8	7.7±13.7	11.2±16.7	16.3±23.9	8.06±14.6
• Red meat (g/d)	10.2±14.4	15.2±17.9	23.2±92.8	27.9±68.9	15.70±42.9
• Chicken (g/d)	67.4±110.5	64.4±217.7	69.7±250.6	72.4±162.4	66.47±198.1
• Vegetable (g/d)	158.4±79.5	184.8±82.4	211.9±87.4	241.8±123.4	184.52±87.4
• Fruit (g/d)	102.0±97.3	149.1±120.2	208.7±142.3	275.4±212.1	151.58±131.7
• Dairy products (g/d)	157.5±131.4	195.3±136.4	233.5±143.8	276.9±181.2	194.80±142.0
• Egg (g/d)	8.0±12.6	11.4±13.4	13.9±14.2	16.1±18.8	11.06±13.8
• Total fibre (g/d)	20.4±16.8	22.7±7.2	25.3±7.9	28.7±11.6	22.77±11.2
• Mg	418.5±338.9	450.8±148.1	490.8±162.3	544.3±231.6	452.68±224.9
• Zn	9.1±6.2	10.0±5.2	11.3±7.3	12.6±6.1	10.11±6.0
• Cu	1.5±0.98	1.7±0.56	1.9±0.65	2.2±1.00	1.69±0.76

All variables were different at levels of nut consumption ($P < 0.001$).
1 serving = 28 g.

available for the present analysis, including 20 855men and 28 257 women. The mean ± SD age of the participants at enrolment was 52 ± 8.9 years. The mean (SD) intake of total nuts was 3.5 (31.8) g/day in men and 2.6 (9.5) g/day in women. Table 1 shows the baseline characteristics of the study participants, overall and by servings of total nut consumption. More than 70% of our cohort reported consuming nuts in the past year. A number of examined baseline characteristics varied by level of nut consumption at baseline. Those who ate more nuts were more likely to live in urban areas, less likely to exercise and more likely to smoke or drink alcohol. Also, participants who consumed more nuts had a higher wealth score, higher BMI and more energy intake, and they were younger. In the highest category of nut consumption, there were fewer individuals with diabetes mellitus or hypertension than among those

who did not eat nuts. In addition, frequent nut consumption was associated with a higher intake of total energy and higher intake of other foods and nutrients.

Nut consumption and total mortality

During a median of 7 years of follow-up (349 677 person-years), we documented 3981 deaths including 2016 cardiovascular deaths, 887 cancer deaths and 515 GI cancer deaths. Table 2 shows HRs for total mortality by servings of total nut consumption. The multivariate-adjusted hazard ratios for death among participants who ate nuts, as compared with those who did not, were 0.89 (95% CI, 0.82-0.95) for the consumption of less than one serving per week, 0.75 (95% CI, 0.67-0.85) for one to less than three servings per week and 0.71 (95% CI, 0.58-0.86) for three or more servings per week ($P < 0.001$ for trend). This inverse association was stronger in women than men, and did not remain statistically significant in men after multivariate adjustment (P for trend $= 0.060$) although, even in men, the risk estimates for each category of nut consumption remained below one.

Nut consumption and cause-specific mortality

In multivariate analyses, nut consumption was inversely associated with the risk of most major causes of death among women (Table 3). In men, HRs for each examined cause of death was also below one, although in each case they were far from significant. In the pooled analysis of women and men, significant inverse associations were observed for deaths due to heart disease, all cancer and GI cancers. For example, the HR for GI cancer mortality in the pooled analysis was 0.56 (95% CI: 0.28-1.00) for individuals who consumed three or more servings of nuts per week compared with those who did not eat nuts (Table 3).

Subgroup analyses

Similar associations were found for both peanuts and tree nuts. The adjusted hazard ratios for total mortality were0.74 (95% CI: 0.62-0.89, $P = 0.002$) for peanuts and 0.76 (95% CI: 0.66-0.88, $P < 0.001$) for tree nuts, when consumption of one or more servings per week was compared with no consumption. In analyses stratified by other potential risk factors of death, the significant inverse relationship between nut consumption and mortality was observed in nearly every examined subgroup (Table 4).

Sensitivity analyses

The HRs for mortality in all nut consumption groups remained consistent when we excluded participants with the lowest and highest wealth scores, those who had ever smoked or used opium or consumed alcohol, those with chronic disease at baseline and those with extreme BMI, and when we excluded deaths occurring in the first 2 years of follow-up (Table 5).

Discussion

In this large population-based cohort study, we found an inverse association of nut consumption with total and

Table 2. Hazard ratios for total mortality, according to serving of nut consumption[a]

	Serving of nut consumption				*P*-value for trend
	Never	<1 serving per week	1 to,<3 servings per week	≥3 servings per week	
Women					
No. of person-years	55 137	109 921	30 069	8 167	
No. of deaths	767	792	141	32	
Age-adjusted hazard ratio (95% CI)	1.00	0.74 (0.67-0.82)	0.57 (0.47-0.68)	0.48 (0.34-0.69)	<0.001
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.82 (0.74-0.91)	0.65 (0.54-0.79)	0.49 (0.34-0.71)	<0.001
Men					
No. of person-years	35 544	74 112	27 552	9 606	
No. of deaths	878	1 033	255	83	
Age-adjusted hazard ratio (95% CI)	1.00	0.85 (0.77-0.93)	0.69 (0.60-0.80)	0.72 (0.58-0.91)	<0.001
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.94 (0.85-1.03)	0.82 (0.70-0.96)	0.84 (0.66-1.07)	0.060
Pooled					
Age-adjusted hazard ratio (95% CI)	1.00	0.81 (0.75-0.86)	0.67 (0.60-0.75)	0.67 (0.56-0.82)	<0.001
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.89 (0.82-0.95)	0.75 (0.67-0.85)	0.71 (0.58-0.86)	<0.001

[a]Multivariable models were adjusted for age, sex, BMI, level of education, place of residence, smoking status, opium and alcohol consumption, physical activity, wealth score, diabetes, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetable, dairy product, egg, and total fibre), magnesium, zinc and copper.

1 serving = 28 g.

Table 3. Hazard ratios for cause-specific mortality, according to serving of nut consumption[a]

	Serving of nut consumption				*P*-value for trend
	Never	<1 serving per week	1 to < 3 serving per week	≥3 serving per week	
Cardiovascular disease					
Women					
No. of deaths	412	412	69	18	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.83 (0.71-0.96)	0.65 (0.49-0.86)	0.55 (0.33-0.91)	0.004
Men					
No. of deaths	439	497	124	45	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.92 (0.80-1.05)	0.83(0.66-1.03)	0.90 (0.66-1.26)	0.411
Pooled					
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.87 (0.79-0.97)	0.75 (0.63-0.89)	0.77 (0.58-1.01)	0.018
All cancer					
Women					
No. of deaths	156	194	36	6	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.91 (0.73-1.14)	0.72 (0.48-1.07)	0.43 (0.18-1.01)	0.022
Men					
No. of deaths	196	229	57	13	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.98 (0.80-1.20)	0.90 (0.65-1.25)	0.73 (0.41-1.33)	0.268
Pooled					
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.96 (0.82-1.11)	0.84 (0.65-1.07)	0.62 (0.38-1.01)	0.029
GI cancer					
Women					
No. of deaths	87	99	12	2	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.91 (0.67-1.25)	0.51 (0.27-0.96)	0.30 (0.07-1.31)	0.020
Men					
No. of deaths	128	146	34	7	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.98 (0.76-1.26)	0.87 (0.57-1.32)	0.69 (0.31-1.54)	0.296
Pooled					
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.96 (0.79-1.17)	0.75 (0.53-1.05)	0.56 (0.28-1.00)	0.035
Other cause					
Women					
No. of deaths	199	186	36	8	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.74 (0.60-0.92)	0.62 (0.42-0.91)	0.43 (0.20-0.89)	0.013
Men					
No. of deaths	243	307	74	26	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.98 (0.81-1.17)	0.79 (0.59-1.05)	0.85 (0.55-1.32)	0.231
Pooled					
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.87 (0.76-1.00)	0.72 (0.57-0.90)	0.69 (0.47-1.00)	0.019

[a]Multivariable models were adjusted for age, sex, BMI, level of education, place of residence, smoking status, opium and alcohol consumption, physical activity, wealth score, diabetes, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetable, dairy product, egg, and total fibre), magnesium, zinc and copper.

1 serving = 28 g.

cause-specific mortality, after adjusting for potential confounders. Relative to those who did not eat nuts, women who ate three or more servings of nuts per week had a 51% lower risk of death, whereas men in this consumption category had 16% lower risk. Inverse associations were observed for most major causes of death, including cardiovascular disease, all cancers and GI cancers. Similar findings were observed for peanuts and tree nuts, and the inverse association persisted among participants with and without a broad range of chronic disease risk factors at baseline.

Our results are in line with the findings in previous cohort studies[4,14,21,22] which have all been conducted in Western countries. Furthermore, clinical trials have shown that nut consumption has beneficial effects on some intermediate markers of chronic diseases, such as hyperglycaemia, high cholesterol levels, insulin resistance, oxidation and endothelial dysfunction.[5–7,9,10,13,14,23–26] Such findings may be due to the healthy nutrient content of nuts, including high levels of polyunsaturated fatty acids, especially n-3 fatty acids, high-quality protein, fibre, vitamins (e.g. folate, niacin and vitamin E), minerals (e.g.

Table 4. Hazard ratios for total mortality for those eating ≥ 1 serving of nuts per week vs those not eating nuts, stratified by subgroups of other potential risk factors[a]

	Women		Men		Pooled	
	HR (95% CI)	***P*-value for interaction**	**HR (95% CI)**	***P*-value for interaction**	**HR (95% CI)**	***P*-value for interaction**
Age		0.312		0.456		0.239
• <50 yr.	0.62 (0.42-0.91)		0.82 (0.60-1.12)		0.73 (0.57-0.92)	
• ≥50 yr.	0.66 (0.53- 0.81)		0.8 (0.73-1.02)		0.78 (0.68-0.88)	
BMI		0.901		0.420		0.742
• <25	0.67 (0.49-0.92)		0.78 (0.64-0.96)		0.76 (0.64-0.90)	
• 25 to < 30	0.62 (0.45-0.86)		0.90 (0.70-1.16)		0.78 (0.64-0.95)	
• ≥30	0.55 (0.40-0.77)		0.95 (0.64-1.40)		0.68 (0.53-0.87)	
Education		0.243		0.555		0.867
No formal	0.63 (0.52-0.77)		0.76 (0.62-0.92)		0.70 (0.61-0.80)	
Formal	0.42 (0.19-0.91)		0.97 (0.80-1.19)		0.88 (0.70-1.11)	
Place of residence		0.019		0.542		0.117
Rural	0.62 (0.50-0.77)		0.76 (0.64-0.89)		0.71 (0.62-0.81)	
Urban	0.55 (0.39-0.79)		1.06 (0.77-1.44)		0.80 (0.63-1.00)	
Smoking		0.352		0.881		0.469
• Never	0.61 (0.50-0.73)		0.89 (0.73-1.08)		0.73 (0.64-0.84)	
• Ever	1.02 (0.34-3.06)		0.74 (0.60-0.92)		0.75(0.61-0.93)	
Opiate ever use		0.015		0.548		0.173
• Never	0.59 (0.47-0.70)		0.88 (0.73-1.06)		0.72 (0.63-0.82)	
• Ever	0.88 (0.57-1.34)		0.76 (0.61-0.96)		0.79 (0.65-0.97)	
Wealth score		0.461		0.924		0.868
• Below median	0.67 (0.51-0.87)		0.78(0.63-0.95)		0.73 (0.62-0.86)	
• Above median	0.56 (0.43-0.73)		0.89 (0.72-1.11)		0.75 (0.64-0.89)	
Physical activity		0.475		0.751		0.875
• Low	0.58 (0.47-0.72)		0.87 (0.72-1.07)		0.72 (0.63-0.84)	
• Moderate and high	0.79 (0.52-1.19)		0.80 (0.65-0.99)		0.79 (0.65-0.95)	
Energy intake		0.791		0.483		0.547
• Below median	0.63 (0.48-0.82)		0.79 (0.60-1.05)		0.71 (0.59-0.87)	
• Above median	0.62 (0.48-0.81)		0.83 (0.70-0.99)		0.77 (0.66-0.89)	
Fish (g/d)		0.953		0.195		0.326
• Below median	0.60 (0.45-0.81)		0.69 (0.55-0.88)		0.66 (0.55-0.79)	
• Above median	0.62 (0.48-0.79)		0.95 (0.78-1.16)		0.80 (0.69-0.94)	
Red meat (g/d)		0.246		0.992		0.679
• Below median	0.64 (0.48-0.85)		0.83 (0.64-1.07)		0.74 (0.61-0.90)	
• Above median	0.60 (0.46-0.77)		0.81 (0.67-0.97)		0.74 (0.63-0.85)	
Chicken (g/d)		0.033		0.148		0.212
• Below median	0.70 (0.54-0.90)		0.74 (0.60-0.92)		0.73 (0.62-0.86)	
• Above median	0.55 (0.42-0.72)		0.91 (0.75-1.11)		0.76 (0.65-0.89)	
Vegetable (g/d)		0.907		0.430		0.683
• Below median	0.60 (0.45-0.80)		0.79 (0.63-1.00)		0.72 (0.60-0.86)	
• Above median	0.64 (0.50-0.83)		0.86 (0.71-1.04)		0.77 (0.66-0.89)	
Fruit (g/d)		0.873		0.519		0.785
• Below median	0.61 (0.44-0.83)		0.89 (0.68-1.17)		0.76 (0.62-0.93)	
• Above median	0.67 (0.52-0.85)		0.82 (0.68-0.98)		0.76 (0.66-0.88)	
Dairy products (g/d)		0.319		0.286		0.673
• Below median	0.75 (0.57-0.99)		0.79 (0.61-1.02)		0.77 (0.64-0.93)	
• Above median	0.55 (0.43-0.71)		0.82 (0.68-0.98)		0.72 (0.62-0.83)	
Egg (g/d)		0.750		0.983		0.765
• Below median	0.61 (0.49-0.75)		0.84 (0.70-1.00)		0.73 (0.64-0.84)	
• Above median	0.66 (0.44-0.99)		0.80 (0.62-1.03)		0.78 (0.63-0.96)	

(Continued)

Table 4. Continued

	Women		Men		Pooled	
	HR (95% CI)	*P*-value for interaction	HR (95% CI)	*P*-value for interaction	HR (95% CI)	*P*-value for interaction
Total fibre (g/d)		0.235		0.943		0.541
• Below median	0.69 (0.54-0.89)		0.97 (0.75-1.24)		0.83 (0.69-0.99)	
• Above median	0.57 (0.43-0.75)		0.77 (0.64-0.92)		0.71 (0.61-0.82)	
Mg		0.746		0.780		0.603
• Below median	0.58 (0.45-0.75)		0.89 (0.69-1.15)		0.72 (0.59-0.86)	
• Above median	0.70 (0.53-0.93)		0.80 (0.67-0.95)		0.77 (0.67-0.90)	
Zn		0.319		0.315		0.311
• Below median	0.64 (0.50-0.84)		0.78 (0.58-1.05)		0.71 (0.58-0.86)	
• Above median	0.62 (0.47-0.81)		0.83 (0.70-0.99)		0.77 (0.67-0.89)	
Cu		0.358		0.796		0.751
• Below median	0.68 (0.52-0.89)		0.96 (0.72-1.28)		0.79 (0.65-0.97)	
• Above median	0.61 (0.47-0.80)		0.80 (0.67-0.94)		0.74 (0.65-0.86)	

[a]Multivariable models were adjusted for all covariates except the one that was stratified.
1 serving = 28 g.

potassium, calcium, magnesium and zinc), and phytochemicals (e.g. carotenoids, flavonoids and phytosterols), each of which could potentially mediate the associations in our study.[27,28–30].

In our study, participants provided detailed data on their lifestyle and diet, which allowed us to control for a variety of potential confounding factors such as age, sex, BMI, smoking status, opium and alcohol consumption, physical activity level, wealth score (WS), education level, place of residence, diabetes, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetable, dairy product, egg and total fibre), magnesium (Mg), zinc (Zn) and copper (Cu). The inverse associations between nut consumption and total mortality persisted across subgroups of these potential confounding factors. Together, these results suggest an independent association between nut consumption and mortality, although we cannot rule out the possibility of confounding by unknown factors. Reverse causality is another possible explanation for our findings, as participants with chronic disorders and poor health might abstain from nut consumption. However, the associations in our study were similar in analyses in which we excluded participants with hypertension or diabetes at baseline, or those who died in the first 2 years of follow-up.

In most previous reports from Western populations, people consuming more nuts were more likely to have healthier diets and lifestyles. For example, some of these studies have reported that increased nut intake was associated with less weight gain and waist circumference.[3,4] In our study, however, participants who ate more nuts were more likely to smoke, drink alcohol or be obese and less likely to exercise. As a result, the observed inverse association between nut intake and mortality is unlikely to be due to confounding by an overall healthy lifestyle; however, those who consumed more nuts were younger and had a higher SES or educational level. This group, on the other hand, smoked more. The inverse association between nut consumption and mortality did not change after adjustments for multiple SES indicators and other potential confounders, suggesting that this association was independent from other known confounding and risk factors.

One intriguing finding in our study was that we observed stronger associations in women than in men. Such a finding in our study may be due to chance, as inverse associations between nut consumption and mortality have been observed in both men and women in previous studies such as the Southern Community Cohort Study (SCCS) in the USA and the Shanghai Women's Health Study (SWHS) in China.[31]

In our study, inverse associations were observed for deaths due to cancer, which is consistent with the finding of the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) in the USA.[4] However, no association was observed for deaths due to cancer in Americans of European descent or in the Asian populations in a recent study.[31] This inconsistency may be the result of differences in the major types of cancer death distributed in different study populations. In our population, the most common types of cancers are GI cancers (gastric cancer and oesophageal cancer). Nuts are rich in phytosterols, which inhibit cancer cells proliferation.[32] The anti-inflammatory and antioxidant effects of nuts also may protect against malignancies[33]; however, more studies are needed to explore the exact mechanism of action of nuts in inhibition of cancers.

Table 5. Sensitivity analyses of the inverse association of nut consumption and total mortality[a]

	Serving of nut consumption				*P*-value for trend
	Never	<1 serving per week	1 to < 3 serving per week	≥3 serving per week	
First and last deciles of WS were excluded					
No. of person-years	73 064	149 477	43 789	12 145	
No. of deaths	1 212	1 451	312	90	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.92 (0.84-0.99)	0.80 (0.70-0.92)	0.78 (0.62-0.97)	0.006
Patients with chronic diseases[b] were excluded					
No. of person-years	43 255	101 788	34 670	10 288	
No. of deaths	515	599	149	41	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.85 (0.75-0.97)	0.74 (0.61-0.91)	0.71 (0.50-1.00)	0.026
Participants with extreme BMI[c] were excluded					
No. of person-years	78 682	162 650	51 487	15 500	
No. of deaths	1 388	1 577	344	102	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.89 (0.82-0.96)	0.75 (0.65-0.85)	0.72 (0.58-0.89)	<0.001
Smokers, opium users and alcohol drinkers were excluded					
No. of person-years	65 989	141 123	42 794	11 690	
No. of deaths	934	1 067	216	53	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.88 (0.80-0.96)	0.73 (0.62-0.85)	0.62 (0.47-0.84)	<0.001
First 2 years of follow-up were excluded					
No. of person-years	64 038	133 390	41 994	12 784	
No. of deaths	1 282	1,461	321	99	
Multivariable-adjusted hazard ratio (95% CI)	1.00	0.88 (0.82-0.96)	0.76 (0.66-0.87)	0.75 (0.60-0.93)	0.001

[a]Multivariable models were adjusted for age, sex, BMI, level of education, place of residence, smoking status, opium and alcohol consumption, physical activity, wealth score, diabetes, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetable, dairy product, egg, and total fibre), magnesium, zinc and copper.

[b]Chronic disease including a previous cancer, CVD, diabetes or hypertension.

[c]Extreme BMIs were considered as < 18.5 or > 35 kg/m^2.

1 serving = 28 g.

We found an inverse association between nut intake and cardiovascular mortality, which was seen in the other recent studies. Peanuts are good sources of resveratrol, which can reduce cardiovascular diseases risk[34] due to its hypocholesterolaemic, antioxidant, and anti-inflammatory effects.[33,35–37]. Some recent studies have reported that the most difference occurred between individuals who consume no or low peanut and those who consume some peanut, with little changes in mortality with increasing nut consumption thereafter.[31,38] The difference between our pattern and the flatness of the dose-response trends in these studies could be the result of low intake levels in our population. (The mean intakes were 3.5 (31.8) g/day in men and 2.6 (9.5) g/day in women in our population, vs 8.1 (14.5) g/day in men and 4.4 (8.5) g/day in women in the Netherlands Cohort Study.)[38] The results of a recent study on Americans of African and European descent, and a Chinese population who consumed low amounts of nut, were similar to our study, and showed an inverse dose-dependent association between nut consumption and mortality risk,[31] which confirms our hypothesis that this relation might be seen only in low amounts of nut consumption.

The present study has several strengths, including its large sample size, its prospective design, its high participation rate and a relatively long follow-up with an excellent retention rate (99.3%). In addition, one of the most important strengths of this analysis was being the first study to assess the association of nut consumption with mortality in a country in economic transition. Studies in less developed countries can provide unique opportunities to test for associations between diet and disease within the context of different lifestyle patterns. People in developing countries tend to have different socioeconomic backgrounds from those in the developed Western world, and these differences can help establish the independence of a putative association.[39]

Our study also has several limitations. Given its observational nature, it is not possible to conclude that the observed association reflects cause and effect. There remains the possibility of residual confounding and other non-causal explanations. However, after adjusting for a large number of predictors of death, the associations remained strong. Also, this study was conducted in an older population in a high-risk region for cancer, so the results cannot necessarily be extrapolated to other populations. However, we do note

that previous studies in Western countries have found similar results. Consistency of association, particularly, in the presence of different confounding structures, may suggest causality. In addition, we found a dose-response which strengthens the argument for a causal relationship. Finally, since dietary intakes were self-reported, some measurement error is inevitable. It has been shown that obesity, dietary restraint, gender, socioeconomic status, motivation and social expectations play a role in under-reporting.[40,41] We adjusted our analysis for dietary energy intake to reduce the effects of this limitation.

In conclusion, our study provides evidence of an inverse association between nut consumption and mortality in a developing country, where nut consumption does not track with a healthy lifestyle. Further research directed at understanding the underlying mechanisms by which nuts protect against chronic diseases may also lead to the development of novel preventive strategies.

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