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Non-communicable Disease Risk Factors

Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis

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Abstract

Background: Nut intake has been associated with lower mortality, but few studies have investigated causes of death other than cardiovascular disease, and dose-response relationships remain unclear.

Methods: We investigated the relationship of nut (tree nut, peanut) and peanut butter intake with overall and cause-specific mortality. In the Netherlands Cohort Study, 120 852 men and women aged 55–69 years provided information on dietary and lifestyle habits in 1986. Mortality follow-up until 1996 consisted of linkage to Statistics Netherlands. Multivariate case-cohort analyses were based on 8823 deaths and 3202 subcohort members with complete data on nuts and potential confounders. We also conducted meta-analyses of our results with those published from other cohort studies.

Results: Total nut intake was related to lower overall and cause-specific mortality (cancer, diabetes, cardiovascular, respiratory, neurodegenerative diseases, other causes) in men and women. When comparing those consuming 0.1−<5, 5−<10 and 10+ g nuts/day with non-consumers, multivariable hazard ratios for total mortality were 0.88, 0.74 and 0.77 [95% confidence interval (CI), 0.66–0.89], respectively ($P_{trend} = 0.003$). Cause-specific hazard ratios comparing 10+ vs 0 g/day varied from 0.56 for neurodegenerative to 0.83 for cardiovascular disease mortality. Restricted cubic splines showed nonlinear dose-response relationships with mortality. Peanuts and tree nuts were inversely related to mortality, whereas peanut butter was not. In meta-analyses, summary hazard ratios for highest vs lowest nut consumption were 0.85 for cancer, and 0.71 for respiratory mortality.

Conclusions: Nut intake was related to lower overall and cause-specific mortality, with evidence for nonlinear dose-response relationships. Peanut butter was not related to mortality.

Key words: Nuts, peanuts, mortality, neoplasms, respiratory tract diseases, cohort studies

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Key Messages

- Intake of nuts was associated in a nonlinear fashion with lower overall and cause-specific mortality (cancer, diabetes, cardiovascular, respiratory, neurodegenerative diseases, other causes excluding external injuries).
- Peanuts showed at least as strong inverse associations with mortality as tree nuts, but peanut butter did not.
- Meta-analyses of published cohort studies on cancer and respiratory mortality showed consistent risk reductions with increasing nut intake, in a nonlinear fashion.

Introduction

Interest in the health effects of nut intake is growing rapidly. Tree nuts are defined as dry fruits with one seed in which the ovary wall becomes hard at maturity, but the consumer definition of nuts also includes peanuts which are groundnuts or legumes.[1] Interest in the prevention of non-communicable diseases emerged after a publication on nut intake and cardiovascular disease (CVD) risk.[2] Subsequent publications on nuts and CVD, or blood lipid levels, have led to a qualified health claim, published by the Food and Drug Administration in 2003, stating that 'Eating 43 g/day (1.5 oz) of most nuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease'.[3] Apart from CVD, interest is growing in mortality and other health effects as well, stimulated by the PREDIMED trial showing effects of Mediterranean diet supplemented with mixed nuts or olive oil on CVD and depression.[4,5] In two cohort studies, nut intake was related to reduced total, CVD and cancer mortality,[6,7] and respiratory mortality.[6] In the Netherlands Cohort Study (NLCS), an inverse association between nut intake as a component of the Mediterranean diet and overall mortality in both men and women was found.[8] Recent meta-analyses showed inverse associations between nut consumption and total mortality, (non)fatal ischaemic heart disease (IHD), CVD and diabetes.[9,10]

Little is known about differences between tree nuts and peanuts, and whether peanut butter shows similar associations with mortality as peanuts. In addition, dose-response relationships remain unclear. We investigated the dose-response relationship between intake of nuts (total, peanuts, tree nuts and peanut butter) and overall and cause-specific mortality in the NLCS. We also conducted meta-analyses on nuts and mortality due to cancer and respiratory diseases.

Methods

Study design and mortality follow-up

The NLCS started in September 1986 and includes 58 279 men and 62 573 women aged 55–69 years.[11] At baseline (September 1986), they completed a mailed, self-administered 11-page questionnaire on cancer risk factors. The NLCS study was approved by the Maastricht University institutional review board. For efficiency, we applied the nested case-cohort method,[12] requiring only data-entry of questionnaires (which could not be scanned) of cases and a random subcohort. Following this method,[11] cases were enumerated from the NLCS cohort of 120 852 (numerator information of mortality rates), whereas the accumulated person-years at risk in the cohort were estimated using a subcohort of 5000 subjects (denominator information). Immediately after baseline, the subcohort (2411 men, 2589 women) was randomly sampled from the cohort and has been actively followed up since 1986 for vital status and migration. Data on mortality and causes of death in the cohort-at-large were obtained from the Dutch Central Bureau of Genealogy and Statistics Netherlands. Through this linkage, 18 091 deaths were identified between January 1987 and December 1996. The completeness of the mortality follow-up was 99%.[8] Overall mortality follow-up was not available for the NLCS after this period. Causes of death were coded according to the International Classification of Disease, Ninth Revision (ICD-9) for 1987–95 and ICD-10 for 1996. Besides total mortality, the following primary causes of death were separately investigated: cancer, CVD, IHD, stroke, respiratory disease, diabetes, neurodegenerative disease and all other causes excluding external injuries (see ICD codes, Supplementary Table 1, available as Supplementary data at *IJE* online).

Exposure assessment

The baseline questionnaire measured dietary intake (150 items), detailed smoking habits and many other lifestyle factors and medical conditions.[11] Habitual consumption of food and beverages during the year preceding baseline was assessed using a semi-quantitative food-frequency questionnaire, which was validated against a 9-day diet record.[13] Nut and peanut butter consumption was assessed by asking frequency and portion size of intake of 'peanuts', 'other nuts, mixed nuts' and 'peanut butter'. Total nut

intake was calculated as the sum of peanuts and other nuts. Nutrient intakes were calculated using the computerized Dutch food composition table.[14]

Population for analysis

From the 18 091 deaths in the cohort, subjects who reported a history of cancer (excluding skin cancer) or CVD (myocardial infarction, angina pectoris, stroke) at baseline were excluded from this mortality analysis, leaving 12 386 deaths. A similar exclusion applied to the subcohort yielded 4193 subcohort members available. Additionally, subjects with inconsistent dietary data were excluded,[8] leaving 10 382 deaths (6701 men, 3681 women) and 3693 subcohort members (1743 men, 1950 women) available for analysis. Cause-specific numbers are presented in Supplementary Figure 1 (available as Supplementary data at *IJE* online).

Statistical analysis

All analyses were first done for men and women separately, and combined when there was no significant interaction by sex. For the intakes of nuts and peanut butter, the mean (SD) values were calculated in the subcohort. Associations between nut intake and various (non)dietary characteristics were examined by cross-tabulations, after standardization for age. The relationship between intake of nuts and overall mortality and cause-specific mortality was evaluated using Cox proportional hazards models. It was verified that the proportional hazards assumption was not violated, using Schoenfeld residuals[15] and -ln(-ln) survival plots. Standard errors were estimated using the robust Hubert–White sandwich estimator to account for additional variance introduced by the subcohort sampling.[16]

In age- and multivariable-adjusted survival analyses, total nut intake was evaluated and tested on categorical (0, 0.1–<5, 5–<10, 10+ g/day) and continuous scales. In multivariable analyses, hazard ratios (HRs) were corrected for potential confounders. Analyses were repeated after excluding deaths occurring in the first 2 years of follow-up. Tests for trends were assessed using Wald tests, by fitting ordinal exposure variables as continuous terms. We tested for nonlinearity in the associations with mortality using restricted cubic splines, using three knots (10th, 50th and 90th percentiles). These survival analyses (for total nut intake) were conducted for overall mortality, followed by cause-specific analyses. Analyses were also done for peanuts and tree nuts separately, and peanut butter; because of lower numbers in the high intake categories, we used categories 0, 0.1–<5 and 5+ g/day.

To evaluate potential residual confounding by mortality risk factors, and interactions, analyses of nut intake and overall mortality rate were also conducted within strata of other risk factors. Interactions with these factors were tested using Wald tests and cross-product terms. In sensitivity analyses, we additionally adjusted for adherence to the Mediterranean diet as measured with the alternate Mediterranean Diet Score (aMED).[8,17,18] This is an adapted version of the original Mediterranean Diet Score created by Trichopoulou *et al.*[19]

Meta-analyses

Using PubMed with search terms 'nuts' or 'peanuts', and 'mortality', cohort studies of the association between nut consumption and mortality (various causes of death) were identified as of August 2014. Considering recent meta-analyses on total mortality, CVD, IHD, stroke and diabetes,[9,10] we limited our meta-analyses to cancer and respiratory disease mortality. Two articles on cancer mortality,[6,7] representing three cohorts [PREDIMED, Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)] were identified and combined with NLCS data in the meta-analysis. For respiratory disease, data from NHS and HPFS[6] were used together with NLCS data in the meta-analysis. HRs for the contrast between highest vs lowest nut intake from each study were pooled using random-effects models. In these analyses, the HR estimate for each study was weighted by the inverse of the variance of the log HR to calculate the summary HR and its 95% confidence interval (CI). Heterogeneity between studies was estimated using the Cochran's Q test and I^2 (the proportion of variation in HRs attributable to heterogeneity[20]). Publication bias was assessed by the Begg test.[21] In addition, we performed dose-response meta-analyses using generalized least squares regression described by Orsini *et al.*,[22] with restricted cubic splines (four knots, at 5th, 35th, 65th and 95th percentiles) to investigate potential nonlinearity in the dose-response relationship. We used the median per reported intake category as dose level; when this was not available, we assigned the midpoint of the lower and upper boundaries in each category as median consumption. For the highest intake category, we assumed that the lower boundary plus a 25% increment was the median intake.[9] Nut intake in servings per day was converted into grams/day using the standard conversion (1 serving = 28 g).

All analyses were performed using Stata version 10; presented *P*-values are two-sided.

Results

The mean (SD) intake of total nuts was 8.1 (14.5) g/day in men and 4.4 (8.5) g/day in women; for peanut butter, these

values were 1.4 (4.1) and 1.2 (3.6) g/day, respectively. Nut consumers were on average somewhat younger (Table 1), leaner (in women), drank more alcohol, ate more vegetables and fruits, were less often hypertensive or never smokers (women), but were higher educated and more often used supplements, or postmenopausal hormone replacement therapy (HRT). Women with the highest nut consumption less often reported diabetes. Peanut butter intake was positively associated with nut intake in women.

Table 2 shows data on the relationship of overall mortality with total nut intake in men and women. Of the 8823 deaths with complete information on nut consumption and potential confounders, 5797 occurred in men and 3026 in women. In age-sex-adjusted and multivariable-adjusted Cox regression analyses, total nut consumption was inversely related to overall mortality. Compared with nonconsumers of nuts, the HRs (95% CIs) of overall death for those consuming 0.1–<5, 5–<10 or at least 10 g nuts/day were 0.88 (0.78–0.99), 0.74 (0.63–0.88) and 0.77 (0.66–0.89), respectively ($P_{trend} = 0.003$) in multivariable analyses. Comparable results were found in sex-specific analyses with a somewhat stronger inverse association in men ($P = 0.770$ for heterogeneity tests between men and women). Analyses excluding the first 2 years of follow-up showed similar results (data not shown). Restricted cubic splines (Figure 1A) showed deviations from linearity between nuts and mortality (Table 2, P for nonlinearity $= 0.016$ in men, $P = 0.013$ in women).

In multivariable cause-specific analyses, total nut intake was inversely related to death due to cancer, CVD, IHD, stroke, respiratory disease, diabetes, neurodegenerative diseases and other causes of death, with P-values for trend < 0.05 (Table 2). The inverse association with diabetes mortality was strongest in lower intake categories ($P_{trend} = 0.063$), but numbers were low for diabetes. Compared with nonconsumers, the HRs in the highest consumption category of $10 + $ g nuts/day varied from 0.53 for neurodegenerative mortality to 0.83 for CVD mortality. There was no statistical evidence for heterogeneity by sex in the categorical analyses in any cause-specific analyses. Restricted cubic splines analyses showed evidence for nonlinear associations for death due to CVD ($P_{nonlinearity} = 0.027$), respiratory disease ($P = 0.023$), diabetes ($P = 0.002$) and other causes of death ($P = 0.007$). Figure 1B shows cause-specific nonparametric regression curves from these analyses.

In sensitivity analyses with adjustment for Mediterranean diet adherence (excluding nuts) instead of adjusting for alcohol, vegetables and fruit, essentially similar results were seen. For example, compared with nonconsumers of nuts, the HRs (95% CIs) of overall death for those consuming 0.1–<5, 5–<10 or at least 10 g nuts/day

Table 1. Baseline characteristics [age-standardized means (SD), or percent] according to total nut intake in male and female subcohort members

Characteristic	Men Total nut intake (g/day) (median)				Women Total nut intake (g/day) (median)			
	0 g/d (0)	0.1–<5 g/d (2.5)	5–<10 g/d (8.5)	10+ g/d (21.4)	0 g/d (0)	0.1–<5 g/d (2.1)	5–<10 g/d (8.0)	10+ g/d (15.7)
N	552	554	234	403	795	700	216	239
Age, mean (SD) (yr)	62.0 (4.4)	61.4 (4.1)	61.1 (4.2)	60.7 (3.9)	62.3 (4.3)	61.4 (4.2)	60.4 (4.0)	60.8 (3.9)
BMI (kg/m²)	24.9 (2.8)	24.8 (2.6)	24.9 (2.8)	25.0 (2.6)	25.3 (3.9)	25.1 (3.4)	24.4 (3.4)	24.5 (3.6)
Physical activity, nonoccupational (min/day)	81.6 (75.4)	82.0 (69.0)	68.6 (57.1)	84.7 (70.7)	63.1 (57.5)	67.4 (50.5)	72.2 (58.9)	60.7 (39.3)
Alcohol intake (g/day)	12.5 (16.7)	13.5 (16.9)	16.7 (19.0)	20.1 (17.7)	5.3 (11.0)	5.9 (9.0)	7.4 (9.7)	8.3 (10.8)
Vegetable intake (g/day)	183.8 (84.1)	188.4 (73.2)	187.0 (75.9)	186.3 (75.1)	183.6 (78.7)	195.3 (79.4)	201.6 (80.4)	204.5 (75.9)
Fruit intake (g/day)	147.4 (124.5)	153.0 (102.9)	161.4 (139.1)	162.6 (124.3)	181.9 (132.8)	200.1 (116.7)	210.1 (126.5)	209.9 (130.8)
Peanut butter intake (g/day)	1.4 (5.4)	1.5 (3.8)	1.6 (4.3)	1.2 (3.4)	1.1 (4.2)	1.2 (3.4)	1.3 (3.7)	1.4 (3.4)
Never smoker (%)	13.0	14.5	15.3	11.8	60.1	61.5	49.9	50.8
University or higher vocational education (%)	14.8	20.1	24.5	24.0	6.6	11.2	13.2	12.7
Diabetes (%)	3.0	2.6	3.9	3.5	3.2	4.1	3.2	0.9
Hypertension (%)	23.7	19.7	22.7	19.7	31.6	25.5	24.0	26.1
Nutritional supplement user (%)	21.2	21.8	28.1	24.6	32.4	37.1	40.9	42.7
Ever used hormone replacement therapy (%)					11.1	13.4	13.1	16.3

Table 2. Overall and cause-specific mortality according to total nut intake in men and women, in multivariable-adjusted[a] analyses

Cause of death	Total nut intake (g/day) (median)				P trend	P heterogeneity by sex	P non-linearity
	0 g/d (0)	0.1–<5 g/d (2.5)	5–<10 g/d (8.5)	10+ g/d (19.6)			
All causes							
Men and women							
No. of deaths	3732	2843	853	1395			
Person-years in subcohort	10518	10489	3771	5542			
Age-sex-adjusted HR	1.00	0.80	0.67	0.69	<0.001	0.938	
(95% CI)		(0.72–0.90)	(0.57–0.78)	(0.61–0.79)			
Multivariable-adjusted HR	1.00	0.88	0.74	0.77	0.003	0.770	0.004
(95% CI)		(0.78–0.99)	(0.63–0.88)	(0.66–0.89)			
Men							
No. of deaths	2254	1842	611	1090			
Person-years in subcohort	4264	4600	1976	3450			
Age-adjusted HR	1.00	0.81	0.66	0.70	< 0.001		
(95% CI)		(0.70–0.95)	(0.54–0.80)	(0.59–0.82)			
Multivariable-adjusted HR	1.00	0.86	0.71	0.76	0.001		0.016
(95% CI)		(0.72–1.02)	(0.57–0.88)	(0.63–0.92)			
Women							
No. of deaths	1478	1001	242	305			
Person-years in subcohort	6253	5888	1795	2092			
Age-adjusted HR	1.00	0.78	0.69	0.70	< 0.001		
(95% CI)		(0.68–0.90)	(0.55–0.85)	(0.57–0.86)			
Multivariable-adjusted HR	1.00	0.87	0.79	0.79	0.016		0.013
(95% CI)		(0.74–1.02)	(0.61–1.01)	(0.63–1.00)			
Cause-specific, men and women							
Cancer							
No. of deaths	1556	1299	411	651			
Multivariate-adjusted HR	1.00	0.92	0.82	0.79	0.002	0.849	0.092
(95% CI)		(0.81–1.05)	(0.68–0.98)	(0.67–0.93)			
Cardiovascular disease							
No. of deaths	1281	947	276	481			
Multivariable-adjusted HR	1.00	0.89	0.74	0.83	0.013	0.770	0.027
(95% CI)		(0.76–1.03)	(0.59–0.91)	(0.69–1.00)			
Ischaemic heart disease							
No. of deaths	636	483	126	243			
Multivariable-adjusted HR	1.00	0.90	0.67	0.83	0.026	0.542	0.065
(95% CI)		(0.76–1.07)	(0.52–0.88)	(0.67–1.04)			
Stroke							
No. of deaths	260	168	50	87			
Multivariable-adjusted HR	1.00	0.80	0.68	0.76	0.029	0.709	0.060
(95% CI)		(0.63–1.01)	(0.48–0.97)	(0.56–1.02)			
Respiratory disease							
No. of deaths	284	152	45	69			
Multivariable-adjusted HR	1.00	0.67	0.58	0.61	0.001	0.146	0.023
(95% CI)		(0.52–0.88)	(0.39–0.87)	(0.43–0.87)			
Diabetes							
No. of deaths	85	46	8	19			
Multivariable-adjusted HR	1.00	0.45	0.22	0.70	0.063	0.915	0.002
(95% CI)		(0.24–0.83)	(0.08–0.63)	(0.32–1.51)			

(Continued)

Table 2. Continued

Cause of death	Total nut intake (g/day) (median)				P trend	P heterogeneity by sex	P non-linearity
	0 g/d (0)	0.1–<5 g/d (2.5)	5–<10 g/d (8.5)	10+ g/d (19.6)			
Neurodegenerative disease							
No. of deaths	47	25	5	10			
Multivariable-adjusted HR (95% CI)	1.00	0.64 (0.38–1.09)	0.36 (0.13–0.97)	0.53 (0.25–1.14)	0.035	0.096	0.115
Other causes excl. external							
No. of deaths	430	318	89	141			
Multivariable-adjusted HR (95% CI)	1.00	0.85 (0.70–1.02)	0.67 (0.51–0.89)	0.70 (0.54–0.89)	0.001	0.502	0.007

[a]Multivariable analyses were adjusted for: age at baseline (continuous, in years), sex, cigarette smoking (coded as current vs never/former smoker), number of cigarettes smoked per day, and years of smoking (both continuous)), history of physician-diagnosed hypertension (no, yes) and diabetes (no, yes), body height (continuous, m), BMI (<18.5, 18.5–<25, 25–<30, $\geq$30 kg/m^2), non-occupational physical activity (<30, 30–60, 61–90, $\geq$90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), intake of alcohol (0, 0.1–<5, 5–<15, 15–<30, 30+ g/day), vegetables and fruit (both continuous, g/day), energy (continuous, kcal/day), use of nutritional supplements (no, yes), and, in women, postmenopausal HRT (never, ever). Sex-specific results for nuts and total mortality differed somewhat from those reported earlier[8] because the earlier results were not adjusted for alcohol, vegetables, fruit and supplement intake, height and HRT.

were 0.86 (0.77–0.97), 0.72 (0.61–0.86) and 0.75 (0.65–0.87), respectively, with P_{trend} <0.001 (data not shown).

Table 3 shows results of multivariable analyses in men and women combined, separately for peanuts and tree nuts. For peanuts, inverse associations were observed for total mortality (HR: 0.76; 95% CI: 0.66–0.87) for 5+ vs 0 g peanuts/day; P_{trend} < 0.001), and all causes except neurodegenerative diseases. The latter may be due to the small number of cases of neurodegenerative disease, because the estimated HR is quite low (0.56). In categorical analyses, the strongest association with peanuts was seen for diabetes mortality: HR (95% CI): 0.45 (0.21–0.96). HRs for the other causes of death ranged from 0.56 for neurodegenerative diseases to 0.80 for cancer. For tree nuts, inverse associations were seen for total mortality and most causes of death, but these were non-significant, possibly due to the lower consumption levels than for peanuts. The P-value for trend was 0.050 for other causes of death, and 0.072 for overall mortality. There was no heterogeneity between men and women (data not shown).

Apart from peanuts, we conducted analyses for peanut butter. Peanut butter intake was not associated with total mortality (P_{trend} = 0.884; HR: 0.97; (95% CI: 0.81–1.15) for 5+ g/day peanut butter vs none), nor with any cause of death. In additional analyses using frequency of total nut intake per week instead of amount per day, those who consumed nuts 2+ times per week showed a multivariable HR (95% CI) for total mortality of 0.74 (0.62–0.88); P_{trend} < 0.001) compared with those who never consumed nuts. For peanuts and tree nuts, these HRs (95% CIs) were 0.80 (0.67–0.96), P_{trend} = 0.002, and 0.77 (0.54–1.10),

P_{trend} = 0.037, respectively. Cause-specific analyses generally showed similar results as for analyses using amount per day, but the associations with tree nut frequency were in addition significant for respiratory diseases and other causes (data not shown).

In Supplementary Table 2 (available as Supplementary data at *IJE* online), associations between total nut intake and overall mortality are presented, in subgroups of potential effect modifiers. Inverse associations with nut intake were seen in most subgroups. There was only clear interaction between nut intake and alcohol intake level ($P_{interaction}$ = 0.005): no association was seen in non-drinkers, but an increasingly inverse association within strata of increasing alcohol consumption.

Meta-analyses

Forest plots and summary estimates for highest vs lowest consumption of total nuts are presented in Figure 2, for mortality due to cancer and respiratory disease. For cancer mortality, estimates are based on 14 340 deaths in four cohorts, comprising 247 030 men and women. The summary HR (95% CI) was 0.85 (0.77–0.93), with no evidence of between-study heterogeneity (P = 0.305). For respiratory mortality (based on 2551 deaths in three cohorts with 239 814 participants), the common HR (95% CI) was 0.71 (0.58–0.86), with no evidence for between-study heterogeneity. Whereas the lowest consumption category was always zero, the highest consumption category reported was 5+ times per week in NHS/HFPS (corresponding to 20+ g/day, assuming standard serving size 28 g), > three times per week (> 12 g/day) in PREDIMED, and 10+ g/day in
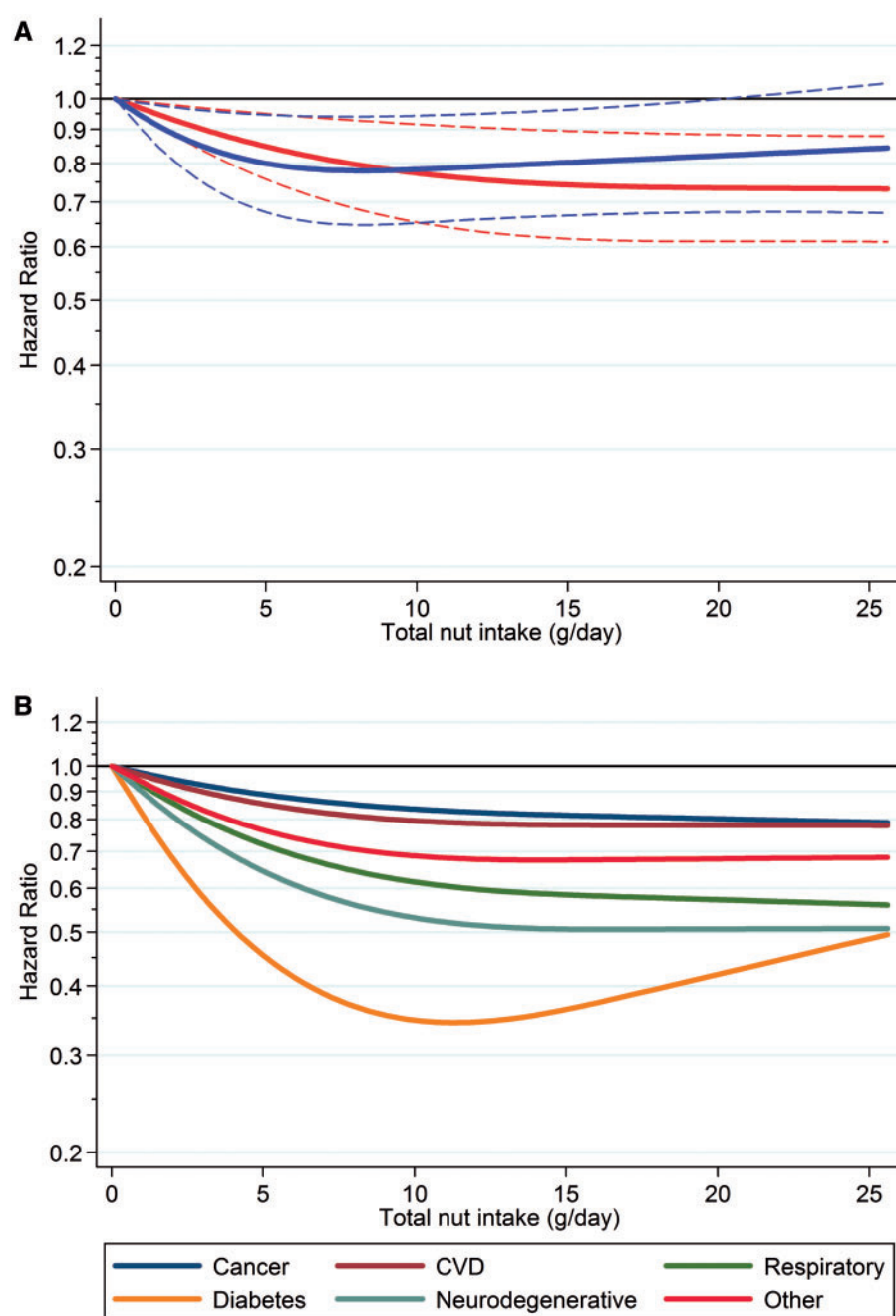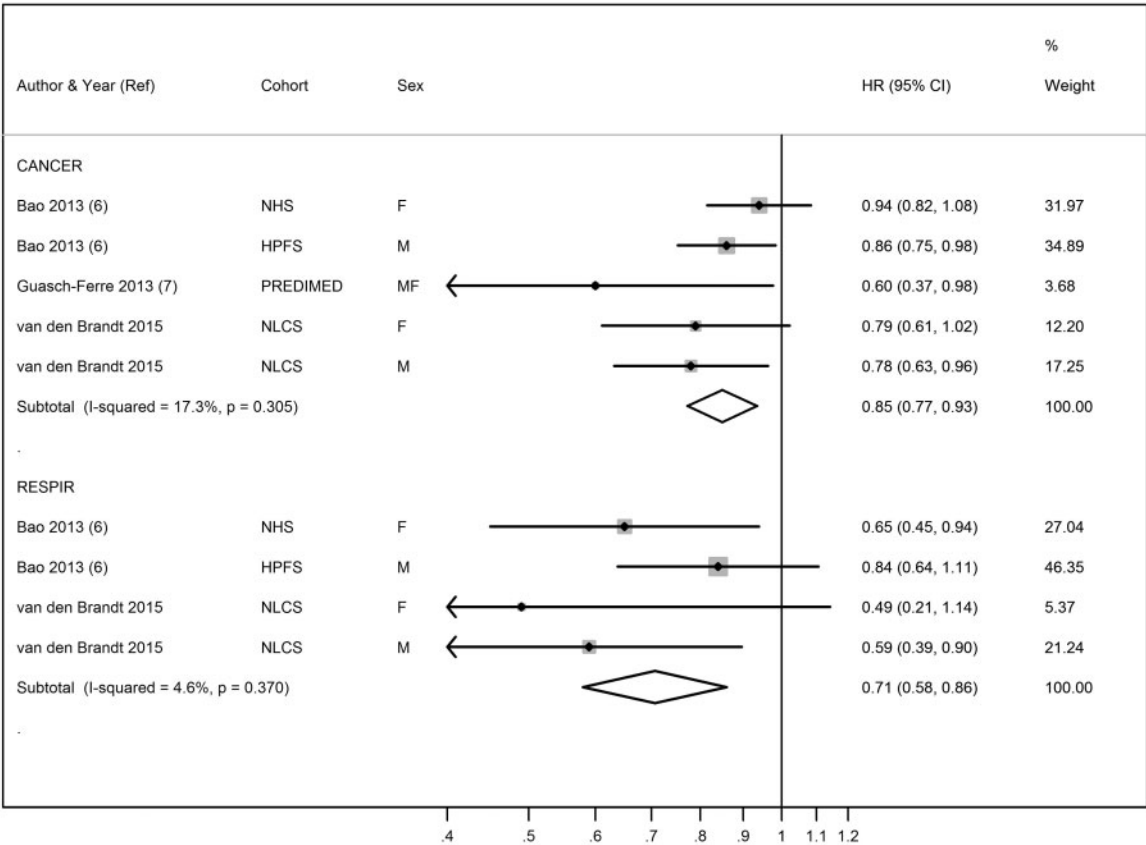
Figure 1. (A) Nonparametric regression curves for the association between total nut intake and total mortality. Red lines: men. Blue lines: women. Solid lines represent point estimates and dashed lines represent 95% confidence intervals. Multivariate HRs are calculated by restricted cubic spline regression (using three knots at 10th, 50th and 90th percentiles) adjusting for: age at baseline (continuous, years), sex, cigarette smoking (coded as current vs never/former smoker), number of cigarettes smoked per day and years of smoking (both continuous), history of physician-diagnosed hypertension (no, yes) and diabetes (no, yes), body height (continuous, m), BMI (<18.5, $18.5–<25$, $25–<30$, ≥30 kg/m^2), non-occupational physical activity (<30, $30–60$, $61–90$, ≥90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), intake of alcohol (0, $0.1–<5$, $5–<15$, $15–<30$, $30+$ g/day), vegetables and fruit (both continuous, g/day), energy (continuous, kcal/day), use of nutritional supplements (no, yes), and, in women, postmenopausal HRT (never, ever). To test for non-linearity, the model including the linear and cubic spline terms was compared with the model with only the linear term using a Wald test. *P*-values for non-linearity were 0.016 in men and 0.013 in women. (B) Nonparametric regression curves for the association between total nut intake and cause-specific mortality (cancer, CVD, respiratory disease, diabetes, neurodegenerative disease, other causes excluding external injuries). *P*-values for non-linearity were 0.092 for cancer, 0.027 for CVD, 0.023 for respiratory disease, 0.002 for diabetes, 0.115 for neurodegenerative disease and 0.007 for other causes excluding external injuries.

Table 3. Total and cause-specific mortality according to intake of peanuts, tree nuts and peanut butter in men and women, in multivariable-adjusted[a] analyses

Cause of death	Intake of peanuts (g/day) (median)			P trend	Tree nuts (g/day) (median)			P trend	Peanut butter (g/day) (median)			P trend
	0 g/d (0)	0.1–<5 g/d (2.5)	5+ g/d (10.7)		0 g/d (0)	0.1–<5 g/d (1.6)	5+ g/d (8.9)		0 g/d (0)	0.1–<5 g/d (1.2)	5+ g/d (9.6)	
Total												
Person-years in subcohort	12186	10972	7162		21411	7280	1629		21956	5264	3099	
No. of deaths	4155	2902	1766		6782	1719	322		6589	1420	814	
Multivariable-adjusted HR	1.00	0.87	0.76	<0.001	1.00	0.93	0.83	0.072	1.00	1.03	0.97	0.884
(95% CI)		(0.77–0.98)	(0.66–0.87)			(0.82–1.05)	(0.66–1.06)			(0.90–1.17)	(0.81–1.15)	
Cancer												
No. of deaths	1736	1343	838		2942	830	145		2906	646	365	
Multivariable-adjusted HR	1.00	0.93	0.80	0.004	1.00	0.97	0.81	0.190	1.00	1.04	0.98	0.977
(95% CI)		(0.82–1.05)	(0.69–0.93)			(0.85–1.11)	(0.62–1.05)			(0.90–1.20)	(0.82–1.17)	
Cardiovascular disease												
No. of deaths	1434	956	595		2317	552	116		2240	461	284	
Multivariable-adjusted HR	1.00	0.86	0.78	0.003	1.00	0.91	0.91	0.252	1.00	1.00	0.99	0.956
(95% CI)		(0.74–0.99)	(0.66–0.93)			(0.78–1.07)	(0.68–1.23)			(0.85–1.17)	(0.80–1.23)	
Ischaemic heart disease												
No. of deaths	707	482	299		1161	264	63		1110	241	137	
Multivariable-adjusted HR	1.00	0.86	0.79	0.014	1.00	0.88	1.03	0.440	1.00	1.04	0.97	0.968
(95% CI)		(0.73–1.03)	(0.64–0.96)			(0.74–1.06)	(0.72–1.46)			(0.86–1.26)	(0.75–1.24)	
Stroke												
No. of deaths	290	170	105		439	106	20		440	76	49	
Multivariable-adjusted HR	1.00	0.79	0.71	0.010	1.00	0.90	0.74	0.186	1.00	0.84	0.86	0.222
(95% CI)		(0.62–0.99)	(0.54–0.94)			(0.70–1.15)	(0.44–1.24)			(0.64–1.11)	(0.60–1.23)	
Respiratory disease												
No. of deaths	307	156	87		453	82	15		410	100	40	
Multivariable-adjusted HR	1.00	0.68	0.61	0.001	1.00	0.75	0.82	0.083	1.00	1.23	0.77	0.701
(95% CI)		(0.52–0.88)	(0.44–0.83)			(0.56–1.01)	(0.44–1.54)			(0.92–1.64)	(0.50–1.18)	
Diabetes												
No. of deaths	93	43	22		129	23	6		129	20	9	
Multivariable-adjusted HR	1.00	0.40	0.45	0.009	1.00	0.79	2.00	0.826	1.00	0.68	0.56	0.162
(95% CI)		(0.22–0.75)	(0.21–0.96)			(0.38–1.64)	(0.76–5.27)			(0.29–1.60)	(0.22–1.45)	
Neurodegenerative disease												
No. of deaths	50	25	12		66	18	3		65	13	9	
Multivariable-adjusted HR	1.00	0.70	0.56	0.077	1.00	0.97	0.68	0.617	1.00	1.01	0.98	0.979
(95% CI)		(0.41–1.18)	(0.28–1.15)			(0.56–1.68)	(0.20–2.37)			(0.53–1.91)	(0.44–2.19)	
Other causes excl. external												
No. of deaths	481	317	180		767	177	34		730	154	94	
Multivariable-adjusted HR	1.00	0.82	0.69	0.001	1.00	0.84	0.79	0.050	1.00	1.00	1.03	0.877
(95% CI)		(0.69–0.99)	(0.55–0.86)			(0.69–1.02)	(0.52–1.18)			(0.81–1.23)	(0.79–1.34)	

[a]Multivariable analyses were adjusted for: age at baseline (continuous, in years), sex, cigarette smoking (coded as current vs never/former smoker), number of cigarettes smoked per day, and years of smoking (both continuous), history of physician-diagnosed hypertension (no, yes) and diabetes (no, yes), body height (continuous, m), BMI (<18.5, 18.5–<25, 2.5–<30, ≥30 kg/m²), non-occupational physical activity (<30, 30–60, 61–90, ≥90 min/day), highest level of education (primary school or lower vocational, secondary or medium vocational, and higher vocational or university), intake of alcohol (0, 0.1–<5, 5–<15, 15–<30, 30+ g/day), vegetables and fruit (both continuous, g/day), energy (continuous, kcal/day), use of nutritional supplements (no, yes), and, in women, postmenopausal HRT (never, ever)

Figure 2. Forest plots of mortality HRs and 95% CIs comparing highest vs lowest intake of nuts, from random-effects meta-analyses. Separate plots are presented for cancer and respiratory mortality. Studies are referred to by first author, year of publication, and cohort abbreviation (NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; PREDIMED, Prevención con Dieta Mediterránea; NLCS, Netherlands Cohort Study). M: males, F: females. Studies are weighted according to the inverse of the variance of the log hazard ratio estimate. The HRs are represented by the squares (the size is proportional to the weights used in the meta-analysis) and confidence intervals are represented by the error bars. Diamonds represent the summary HR estimates and 95% confidence interval per endpoint.
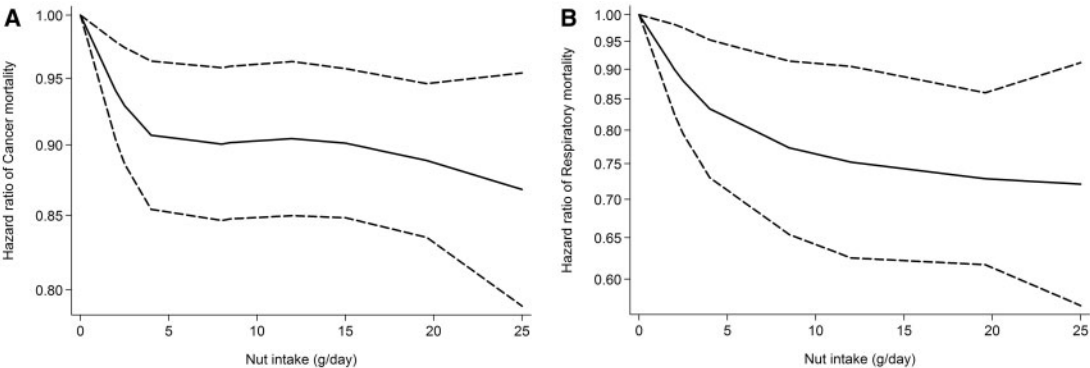
Figure 3. Dose-response relations in meta-analyses between nut intake (g/day) and hazard ratios of (A) cancer mortality (*P* for nonlinearity $= 0.036$) and (B) respiratory mortality (*P* for nonlinearity $= 0.142$). Lines with dashes represent the 95% CIs for the fitted nonlinear trend (solid line).

NLCS. No publication bias was evident in these meta-analyses. In the dose-response meta-analyses with the cubic spline model, we found a nonlinear association between nut intake and cancer mortality (Figure 3A, $P_{\text{nonlinearity}} = 0.036$); for respiratory mortality, $P_{\text{nonlinearity}}$ was 0.142 (Figure 3B).

Discussion

In this prospective cohort study, total nut intake was related to lower overall and cause-specific mortality (cancer, CVD, respiratory, diabetes, neurodegenerative, other causes) during 10 years of follow-up in men and women aged 55–69 years at baseline. When comparing those

consuming 10+ g nuts/day with non-consumers, the HR for total mortality was 0.77. Cause-specific HRs for this contrast varied from 0.53 for neurodegenerative diseases to 0.83 for CVD mortality. There was evidence of nonlinear dose-response relationships with mortality. Intake of peanuts and tree nuts separately were also inversely related to mortality. No associations were found with peanut butter intake. There was no evidence for heterogeneity between men and women in any analysis. There was significant interaction between total nut and alcohol intake. In meta-analyses, summary HRs for highest vs lowest total nut consumption were 0.85 for cancer mortality and 0.71 for respiratory mortality. Dose-response meta-analyses suggested nonlinear associations with cancer and respiratory mortality.

A recent meta-analysis reported a summary HR for total mortality of 0.85, comparing highest with lowest nut consumption.[9] For cancer mortality, our meta-analysis summary HR was 0.85. For respiratory mortality, our summary HR of 0.71 suggests equally strong associations as with fatal IHD.[10] The associations between nut intake and total mortality, and deaths due to cancer, stroke, respiratory disease, diabetes and neurodegenerative disease, were stronger in the NLCS than in American cohorts,[6,23,24] but weaker than in the Spanish PREDIMED cohort.[7] Consumption of tree nuts was low in the NLCS, compared with Mediterranean countries,[25] but higher amounts of peanuts (and peanut butter) were consumed in The Netherlands,[25] as in the USA.[26] The percentages of subjects reporting total nut consumption 2+ times/week were 10% in Iowa women,[24] 18% in the Harvard cohorts[6] and 32% (consuming 3+ times/week) in PREDIMED,[7] compared with 15% in the NLCS. The NLCS results suggest that nut intake may offer protection against CVD and various non-cardiovascular causes of death, at lower intake levels than previously reported.[7] Our results from restricted cubic splines indicate that the maximum reduction in mortality was reached at intake levels of around 10 (women) to 15 (men) grams nuts/day. In the NHS, the nonparametric regression curve levelled off around 0.5 serving/day, or 14 g/day (standard serving size 28 g). It is also comparable to recent meta-analyses indicating nonlinearity for total mortality.[9]

Tree nuts have received more attention recently, but our results, like those of others,[6,27] show that peanuts may confer equivalent protection. Peanuts were also inversely related to colorectal cancer risk in Taiwan.[28] We found no association between mortality and peanut butter intake, consistent with the absence of associations in the NHS with (non)fatal CVD,[27] but not with an inverse association with diabetes risk.[29] Peanut butter in The Netherlands is 20-fold higher in sodium content but lower in niacin than peanuts.[14] Other possible reasons for the differences in mortality associations between peanuts and peanut butter may be the addition of partially hydrogenated vegetable fats (*trans* fats) to peanut butter.[30] Additional NLCS analyses of lifestyle differences revealed only that peanut butter users do not consume more alcohol, unlike frequent peanut/nut users (data not shown). When peanuts are compared with walnuts, it can be concluded that both are good sources of magnesium, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), but that walnuts contain more alpha-linolenic acid; peanuts are richer in MUFA, protein, niacin and potassium. The antioxidant capacity of walnuts is higher than that of peanuts or peanut butter.[31,32] Peanuts, grapes and red wine are primary sources of resveratrol, which is suggested to reduce chronic disease risk.[33] Peanuts and walnuts are also sources of phytosterols, that inhibit colon, prostate and breast cancer cells *in vitro*,[34] and are implicated in CVD because of their hypocholesterolaemic action. Other mechanisms (e.g. anti-inflammatory, antioxidant) by which nuts may protect against cancer have been suggested as well.[35] To our knowledge, this is the first report of a significant and rather strong interaction between nuts and alcohol intake. Nevertheless, subgroup findings are to be interpreted with caution because of possible chance findings; they need to be verified first in other studies.

The prospective design and highly complete follow-up of the NLCS make information and selection bias unlikely. We minimized possible reverse causation due to changes in diet or lifestyle by excluding prevalent CVD or cancer cases.[8] Exclusion of early deaths from follow-up also did not change our results. The NLCS also has some limitations. Although many possible confounders were accounted for, the possibility of residual confounding or confounding by unmeasured factors remains. Although peanut butter and peanuts show differences in nutrient composition, the absence of associations with peanut butter intake may also indicate uncontrolled confounding in the findings on nuts and mortality. The validation study of the food frequency questionnaire has shown that it performs relatively well,[13] but measurement error may still have attenuated associations. No specific validation study results were available relating to nuts. Because there was no possibility to update dietary or other lifestyle data during follow-up, this may have resulted in some attenuated associations too. However, analyses in other cohorts showed that nut consumption is a stable habit.[6] The percentage of subjects with missing values on diet or covariates was only slightly lower among deaths than among subcohort members, which makes the possibility of bias less likely. The quality of the Dutch cause of death information for deaths under 80 years of age can be regarded as high.[36]

In conclusion, this study provides evidence on beneficial effects of nuts on lower overall and cause-specific mortality. Peanuts showed at least as strong inverse associations as tree nuts, but peanut butter did not. Meta-analyses showed consistent risk reductions for cancer and respiratory mortality.

Supplementary Data

Supplementary data are available at *IJE* online.

Acknowledgements

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Commentary: Frequent nut consumption protects against cardiovascular and cancer mortality, but the effects may be even greater if nuts are included in a healthy diet

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Cardiovascular disease and cancer are the common causes of death worldwide, and worrisomely their incidence will continue to increase in the near future. Fortunately, both diseases can be largely preventable through a healthy lifestyle, particularly a healthy diet. To date, several studies have evaluated the potential beneficial effects of different dietary patterns, foods and nutrients on the prevention of cardiovascular disease and cancer as well as on increasing longevity. However, analysis of dietary patterns rather than single foods or nutrients may be a more useful option since it examines the effects of the overall diet with the synergistic interaction of its food and nutrient components. In this respect, a systematic review of the evidence supporting the causal link between dietary factors and cardiovascular disease ranked the Mediterranean diet as the most likely dietary model to provide protection against disease.[1] Moreover, researchers have demonstrated increased interest in analysing the protective effects of key foods of healthy diets, such as nuts.

In this issue of the *International Journal of Epidemiology*, van den Brandt and Schouten[2] make a relevant contribution to this field by analysing the relationship of tree nut and peanut intake with total and cause-specific mortality in 120 852 men and women included in the Netherlands Cohort Study. The authors used a nested case-cohort design in which a random subsample of the baseline study participants ($n = 5000$) was chosen. Random selection of a subcohort allows variables to be measured in a subsample rather than the entire study population, yet the findings are still generalizable to the full cohort. Noticeably, tree nut and peanut intakes were inversely related to all-cause mortality, whereas peanut butter was not. In addition, in those participants who reported an intake of 10 g/day or more of nuts, neurodegenerative disease, respiratory disease, cancer and cardiovascular mortalities were reduced by 46%, 39%, 21% and 17%, respectively, compared with non-consumers. They also observed an interesting interaction between nut and alcohol intakes.

Nuts are nutrient-dense fruits characterized by a hard shell and dry seed rich in unsaturated fatty acids, high-quality protein, fibre, vitamins (folate, niacin, vitamin E), minerals (potassium, calcium, magnesium), carotenoids, phytosterols and phenolic compounds such as ellagic acid and urolithins. The food matrix plays a crucial role in determining accessibility and extractability of these bioactive compounds and hence their absorption, metabolism and final biological action in the human body. In addition, some important compounds such as polyphenols and other antioxidants are mainly in the skin of nuts. All these facts may explain, at least in part, why peanut butter use does not confer protection, whereas peanuts and tree nuts do.

Two observational studies, the Doetinchem Cohort Study[3] and the Nurses' Health Study[4], found that long-term nut consumption was related to better overall cognition at older age, but not to cognitive decline during follow-up for 5 to 6 years. Likewise, in a long-term