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Nut and peanut butter consumption and the risk of lung cancer and its subtypes: A prospective cohort study

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ABSTRACT

Objectives: Nut consumption has been associated with reduced cancer-related mortality, but evidence for a relation between nut intake and lung cancer risk is limited. We investigated the association between total nut, tree nut, peanut, and peanut butter intake and the risk of lung cancer and its subtypes in the Netherlands Cohort Study.

Materials and Methods: In 1986, dietary and lifestyle habits of 120,852 participants, aged 55–69 years, were measured with a questionnaire. After 20.3 years of follow-up, 3720 subcohort members and 2861 lung cancer cases were included in multivariable case-cohort analyses.

Results: Total nut intake was not significantly associated with total lung cancer risk in men or women. For small cell carcinoma, a significant inverse association with total nut intake was observed in men after controlling for detailed smoking habits (HR (95%CI) for 10+ g/day vs. nonconsumers: 0.62 (0.43-0.89), p-trend: 0.024). Inverse relations with small cell carcinoma were also found for tree nut and peanut intake in men in continuous analyses (HR (95%CI) per 5 g/day increment: 0.70 (0.53-0.93) and 0.93 (0.88-0.98), respectively). For the other lung cancer subtypes, no significant associations were seen in men. Nut intake was not related to the risk of lung cancer subtypes in women, and no associations were found for peanut butter in both sexes.

Conclusion: Increased nut intake might contribute to the prevention of small cell carcinoma in men. No significant associations were found in men for the other subtypes or total lung cancer, in women, or for peanut butter intake.

1. Introduction

In 2012, 1.8 million people were diagnosed with lung cancer worldwide, which accounted for 13% of all cancer diagnoses [1]. Survival rates of lung cancer are still poor, despite advances in its detection and treatment: the 5-year survival rate in the USA was 18% for total lung cancer and 4% for advanced lung cancer [2]. Unfortunately, minimally 50% of the patients are diagnosed when at an advanced disease stage [2].

The primary causative factor of lung cancer is tobacco smoking. Other factors, like age, sex, ethnicity, lung diseases, environmental and occupational exposures, and genetic factors may also influence lung cancer risk, as well as diet [3,4]. Nuts have recently been hypothesized to conduct cancer-chemopreventive activities because of their antioxidant and anti-inflammatory effects [5]. Several studies have demonstrated inverse associations of nut intake with cancer-related mortality [6–9]. Nevertheless, evidence regarding the relation between nut consumption and lung cancer risk is limited to three cohort [10–12] and three case-control studies [12–14], and is inconclusive.

In two cohort studies, nut consumption was not significantly associated with lung cancer risk [10,11]. A third cohort study, the NIH-AARP, observed inverse relations between nut consumption frequency and lung cancer risk across three major histologic subtypes [12]. In an accompanying Italian case-control study, nut consumption frequency was also significantly associated with a decreased lung cancer risk [12]. Two other case-control studies found no effects of nut consumption frequency, peanut consumption, or peanut butter consumption on lung cancer risk [13,14].

Recently, we observed nonsignificant inverse associations between adherence to the Mediterranean diet and lung cancer risk [15]. Nut

Abbreviations: AIC, Akaike Information Criterion; aMED, alternate Mediterranean diet score; BMI, body mass index; CI, confidence intervals; FFQ, food frequency questionnaire; HR, hazard ratio; NLCS, Netherlands Cohort Study; PALGA, Dutch Pathology Registry; SD, standard deviation

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consumption appeared to contribute to this protective effect, especially in men, but was not studied thoroughly. Therefore, in this paper, we investigated in detail the relation between total nut, tree nut, peanut, and peanut butter consumption and the risk of lung cancer in men and women in the Netherlands Cohort Study (NLCS). Moreover, we examined whether this relation differs across the four major histologic lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma) and across never, former, and current smokers.

2. Materials and methods

2.1. Study design and cancer follow-up

The NLCS is a Dutch prospective population-based cohort study. At baseline (September 1986), 58,279 men and 62,573 women, aged 55–69, were included [16]. Participants agreed to participate by completing and returning a mailed, self-administered questionnaire on diet and other cancer risk factors. To improve the efficiency of the follow-up and data processing, a case-cohort method was applied by drawing a random subcohort (n = 5000) from the total cohort directly after baseline. Person-years at risk were calculated in the subcohort, whereas cases originated from the entire cohort. The NLCS was approved by the institutional review boards of the Maastricht University and the Netherlands Organization for Applied Scientific Research.

Vital status information of the subcohort members was obtained biennially, and was 100% complete after 20.3 years of follow-up. Incident cancer cases were detected through record linkage with the Netherlands Cancer Registry and the Dutch Pathology Registry (PALGA), with a completeness > 95% after the follow-up period [17,18].

In the current analyses, 3720 subcohort members and 2861 incident lung cancer cases (ICD-O-3 code C34) diagnosed between September 1986 and December 2006 were included after applying the exclusion criteria: participants with prevalent cancer (except skin cancer), with inconsistent or incomplete dietary data, or with missing data on confounding variables were excluded, as were cases with non-carcinoma, in situ lung cancers, or lung cancers without microscopic confirmation (Supplementary Figure S1).

2.2. Exposure assessment

The 11-page self-administered baseline questionnaire measured dietary factors and other cancer risk factors, e.g. detailed smoking habits, physical activity, and anthropometrics. Habitual diet in the year preceding baseline was assessed using a validated 150-item semi-quantitative food frequency questionnaire (FFQ) [19]. Participants filled in how often they consumed 'peanuts', 'other, mixed nuts' (tree nuts), and 'peanut butter', which could range from 'never or less than 1x/month' to '6-7x/week'. Participants also filled in the number of standard portions sizes they consumed per intake. The assumed standard portion sizes were 28 g for tree nuts and peanuts, and 15 g per slice of bread for peanut butter. Mean daily intakes were calculated by multiplying intake frequencies and portion sizes. Total nut intake was the sum of tree nut and peanut intake.

2.3. Statistical analysis

To evaluate the relation between nut consumption and the risk of total lung cancer, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma, we estimated hazard ratios (HRs) and 95% confidence intervals (95%CIs) using age-adjusted and multivariable-adjusted Cox proportional hazards models. Person-years in the subcohort were calculated from baseline until cancer diagnosis, death, emigration, loss to follow-up, or end of follow-up. Standard errors were calculated using the robust Huber-White sandwich estimator to account for the additional variance introduced by sampling from the entire cohort [20]. Schoenfeld residuals, log-log survival plots, and time-varying covariates were used to test the proportional hazard assumption, which was met for the exposure variables. If the assumption was violated for confounders, time-varying covariates were included in the model.

The associations between nut and peanut butter consumption and lung cancer risk were analyzed on a categorical and continuous scale, for men and women separately. Total nut consumption was categorized into 0, 0.1- < 5, 5- < 10, and 10 + g/day, peanut and peanut butter consumption into 0, 0.1- < 5, and 5 + g/day, and tree nut intake into 0 and 0.1 + g/day, because of the limited number of cases in the higher intake categories. Intake of 0 g/day was the reference category. Sex-specific median values per intake category in the subcohort were fitted as continuous variables in regression models to perform trend tests. Continuous analyses were performed per 5 g/day increment.

We ran three models per nut exposure to correct for predefined confounders, which were literature-based and included in the models independent of their effect on the estimates: in the age-adjusted model, we adjusted for age at baseline (years; continuous). In the smoking-adjusted model, we additionally adjusted for cigarette smoking status (never, former, current), frequency (n /day; continuous, centered), and duration (years; continuous, centered). In the fully adjusted model, we additionally adjusted for body mass index (BMI; < 18.5, 18.5- < 25, 25- < 30, ≥30 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), educational level (primary or lower vocational (low), secondary or medium vocational (medium), higher vocational or university (high)), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥30 g/day), and alternate Mediterranean (aMED) diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points). Other considered potential confounders were height, nutritional supplement use, and history of tuberculosis and asthma. Because these variables did not change the HRs with ≥10% when using a backward stepwise selection procedure, they were not included in the final model.

Restricted cubic spline analyses with three fixed knots at 0, 5, and 10 g nut intake/day were performed to evaluate the linearity of the exposure-response relation between nut intake and lung cancer risk. Heterogeneity in associations with nut intake across the four histologic lung cancer subtypes was tested using a competing risk procedure [21], which estimates standard errors using a bootstrapping method designed for the case-cohort approach [22].

To investigate interactions by cancer risk factors and potential residual confounding, we stratified the associations by cigarette smoking status (never, former, current) and frequency (1- < 20 or 20 + cigarettes/day). In an additional analysis, we stratified the results by BMI (18.5- < 25, ≥25 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), alcohol consumption (0, 0.1–15, ≥15 g/day), educational level (low, medium, high), aMED score excluding alcohol and nuts (0–2, 3–4, 5–7 points), and family history of lung cancer (yes, no). Participants with a BMI < 18.5 kg/m^2 were excluded from the latter analysis, because of their limited numbers. Interactions were tested by including cross-product terms in the models and performing Wald tests.

In sensitivity analyses, we excluded the first two years of follow-up to investigate potential reversed causation, and we restricted the analysis of peanut butter to those with a constant peanut butter intake in the five years before baseline. To investigate potential residual confounding, we adjusted the associations for intake of fruits, vegetables, milk, milk products, cheese, and red and processed meat instead of for the aMED score excluding alcohol and nuts. Moreover, tree nut, peanut, and peanut butter intakes were mutually adjusted in additional analyses.

All analyses were performed in Stata 14 software (StataCorp. 2015. College Station, TX). P-values were tested two-sided, with values <

Table 1
Baseline characteristics (mean (SD) or %) of subcohort members and lung cancer cases in the Netherlands Cohort Study.1986–2006.

	Subcohort	Total lung cancer	Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma
Men						
N	1,834	2,413	535	933	395	376
Age (years)	61.2 (4.2)	61.7 (4.2)	61.4 (3.9)	61.8 (4.3)	61.7 (4.1)	61.9 (4.2)
Body mass index (kg/m^2)	24.9 (2.6)	24.9 (2.7)	24.7 (2.6)	25.0 (2.6)	25.1 (2.6)	24.8 (2.8)
Never cigarette smoker (%)	13.6	3.9	3.0	4.5	3.3	4.8
University or higher vocational education (%)	20.3	13.8	18.1	12.2	12.2	11.2
Non-occupational physical activity (min/day)	81.0 (67.4)	78.9 (68.4)	76.0 (63.3)	77.7 (68.1)	81.9 (76.2)	80.6 (67.6)
Family history of lung cancer (%)	9.4	12.9	9.9	14.8	13.4	12.8
History of chronic bronchitis (%)	7.3	10.3	9.0	12.1	9.1	8.2
Daily energy intake (kcal)	2,167 (499)	2,185 (500)	2,192 (519)	2,181 (501)	2,175 (486)	2,191 (492)
Total nut intake (g/day)	7.9 (13.7)	7.1 (13.1)	7.7 (14.4)	7.6 (13.4)	5.4 (9.4)	6.3 (9.7)
Tree nut intake (g/day)	1.0 (3.4)	0.8 (2.8)	0.8 (2.5)	0.9 (3.6)	0.5 (1.3)	0.7 (2.3)
Peanut intake (g/day)	6.9 (13.0)	6.4 (12.4)	6.9 (13.7)	6.7 (12.4)	4.9 (9.0)	5.6 (9.4)
Peanut butter intake (g/day)	1.4 (4.2)	1.2 (4.0)	1.5 (4.6)	1.3 (4.3)	1.0 (2.7)	1.3 (3.4)
Alcohol intake (g/day)	15.1 (17.1)	19.2 (19.7)	19.0 (19.4)	19.7 (20.2)	19.0 (19.0)	18.6 (19.8)
aMED score (excl. alcohol and nuts) of 5-7 pts (%)	22.6	18.1	18.9	18.0	14.4	20.7
Women						
N	1,886	448	150	104	83	69
Age (years)	61.4 (4.2)	60.7 (4.0)	61.0 (4.2)	60.1 (3.9)	60.1 (3.9)	61.2 (4.1)
Body mass index (kg/m^2)	25.0 (3.5)	24.3 (3.4)	24.3 (3.1)	24.4 (3.6)	25.0 (3.6)	23.3 (3.4)
Never cigarette smoker (%)	58.9	23.0	41.3	12.5	6.0	15.9
University or higher vocational education (%)	9.5	9.2	12.7	6.7	7.2	7.3
Non-occupational physical activity (min/day)	65.5 (50.6)	64.3 (59.1)	57.3 (50.8)	75.7 (68.4)	72.4 (72.3)	63.3 (53.0)
Family history of lung cancer (%)	10.5	13.6	13.3	15.4	14.5	11.6
History of chronic bronchitis (%)	5.1	8.9	8.7	17.3	2.4	7.3
Daily energy intake (kcal)	1,684 (389)	1,700 (385)	1,724 (383)	1,716 (379)	1,642 (399)	1,706 (396)
Total nut intake (g/day)	4.4 (8.5)	4.9 (10.8)	4.8 (10.9)	4.6 (8.5)	3.7 (7.5)	6.9 (16.3)
Tree nut intake (g/day)	1.1 (4.0)	0.9 (2.9)	1.2 (3.8)	1.0 (2.9)	0.5 (1.6)	0.9 (2.4)
Peanut intake (g/day)	3.3 (7.0)	4.0 (9.5)	3.6 (8.1)	3.6 (7.7)	3.2 (7.1)	6.0 (15.8)
Peanut butter intake (g/day)	1.2 (3.6)	1.0 (2.9)	0.8 (2.5)	1.2 (3.1)	1.2 (3.8)	1.3 (2.9)
Alcohol intake (g/day)	6.0 (9.5)	9.4 (14.4)	9.4 (13.5)	10.9 (16.9)	8.5 (13.6)	8.6 (13.7)
aMED score (excl. alcohol and nuts) of 5-7 pts (%)	25.8	17.9	20.7	17.3	16.9	15.9

0.05 considered statistically significant.

3. Results

Squamous cell carcinoma was the most commonly diagnosed lung cancer subtype in men (38.7%), followed by adenocarcinoma (22.2%). In women, the most commonly diagnosed subtype was adenocarcinoma (33.5%), followed by squamous cell carcinoma (23.2%) (Table 1). Histology was unspecified in 7.2% and 9.4% of the male and female cases, respectively.

The mean (SD) total nut intake was 7.1 (13.1) g/day in male lung cancer cases, which was somewhat lower than in the subcohort (7.9 (13.7) g/day) (Table 1). In women, the mean (SD) total nut intake in cases was 4.9 (10.8) g/day, which was slightly higher than in the subcohort (4.4 (8.5) g/day). In men, the median (IQR) total nut intake was 2.0 (0.0–8.5) in lung cancer cases and 2.8 (0.0–9.0) in subcohort members. In women, these values were 1.0 (0.0–4.9) and 1.6 (0.0–4.9), respectively. Tree nut, peanut, and peanut butter consumption was, on average, lower in male cases than in the subcohort. In female cases, tree nut and peanut butter intake was somewhat lower than in the subcohort, whereas peanut intake was higher.

Regarding other baseline characteristics (Table 1), male cases were, on average, older than subcohort members, whereas female cases were younger. Only 13.6% of the male subcohort members had never smoked. Cases were more often former or current smokers, more often reported a positive family history of lung cancer, consumed more alcohol, and had a lower aMED score (excluding alcohol and nuts) than subcohort members. In addition, cases, except female small cell carcinoma cases, more often reported a history of chronic bronchitis and had a higher average daily energy intake than the subcohort. Furthermore, cases, except female adenocarcinoma cases, were more often lower educated than subcohort members.

Age-adjusted and multivariable-adjusted associations between nut consumption and total lung cancer risk are presented in Table 2. In the age-adjusted analyses, statistically significant inverse associations with total lung cancer risk were found for total nuts, tree nuts, and peanuts in men, and non-statistically significant inverse associations in women. For peanut butter intake, nonsignificant inverse associations were observed in both sexes. When additionally adjusting for cigarette smoking status, frequency, and duration, most associations became weaker. After full adjustment, the associations attenuated even more, and some became positive in women.

Total nut intake was not significantly associated with total lung cancer risk in men and women (HR (95%CI) for 10+ g/day vs. non-consumers: 0.83 (0.67–1.04), p-trend: 0.184, and 0.91 (0.58–1.43), p-trend: 0.720, respectively). For tree nut and peanut intake, non-significant inverse associations were found in men, and no relations in women. Peanut butter intake was not associated with total lung cancer risk in both sexes. Although we found no significant interactions between the nut variables and sex (p-interaction $\geq$0.403), we chose to present the results for men and women separately because of the substantial differences in estimates between the sexes.

In restricted cubic spline analyses with fixed knots at 0, 5, and 10 g nut intake/day, the exposure-response relations with total lung cancer risk were linear for all nut variables in both sexes (Fig. 1). Based on the Akaike Information Criterion (AIC) score, the model fit did not improve when using additional knots or different knot positions.

Across the four histologic lung cancer subtypes, the multivariable-adjusted associations with nut intake varied slightly in strength (Table 3), but the heterogeneity tests were not significant in men and women (p-heterogeneity = 0.090 and 0.998, respectively). For small cell carcinoma, a significant inverse association with total nut intake

Table 2
Age- and sex-adjusted and multivariable-adjusted HRs (and 95%CIs) for total lung cancer according to nut consumption; NLCS.1986–2006.

Food item	Median intake[a]		Men					Women				
	Men	Women	Person-years	Cases	Age-adjusted HR (95%CI)	Multivariable-adjusted HR[b] (95%CI)	Multivariable-adjusted HR[c] (95%CI)	Person-years	Cases	Age-adjusted HR (95%CI)	Multivariable-adjusted HR[b] (95%CI)	Multivariable-adjusted HR[c] (95%CI)
Total nuts (g/day)												
0	0.0	0.0	8,696	897	1.00 (reference)	1.00 (reference)	1.00 (reference)	13,308	196	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1- < 5	2.5	2.1	9,613	733	0.76 (0.65-0.88)	0.89 (0.74-1.07)	0.87 (0.72-1.06)	12,257	150	0.81 (0.63-1.02)	1.04 (0.77-1.39)	1.10 (0.81-1.49)
5- < 10	8.5	7.8	3,931	285	0.73 (0.60-0.90)	0.89 (0.70-1.15)	0.91 (0.70-1.19)	3,794	49	0.82 (0.58-1.18)	1.01 (0.66-1.57)	1.17 (0.73-1.87)
10 +	21.4	15.7	6,965	498	0.73 (0.62-0.87)	0.80 (0.66-0.98)	0.83 (0.67-1.04)	4,280	53	0.80 (0.57-1.13)	0.85 (0.56-1.29)	0.91 (0.58-1.43)
P_{trend}					0.007	0.058	0.184			0.273	0.455	0.720
Continuous, per 5 g/day increment					0.98 (0.95-1.00)	0.97 (0.95-1.00)	0.98 (0.95-1.01)			1.02 (0.96-1.08)	1.02 (0.95-1.09)	1.02 (0.95-1.10)
Tree nuts (g/day)												
0	0.0	0.0	21,040	1,892	1.00 (reference)	1.00 (reference)	1.00 (reference)	23,457	332	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1 +	1.6	2.1	8,165	521	0.72 (0.62-0.83)	0.83 (0.70-0.99)	0.87 (0.72-1.04)	10,182	116	0.79 (0.62-1.00)	0.95 (0.71-1.26)	1.01 (0.74-1.37)
Continuous, per 5 g/day increment					0.83 (0.73-0.95)	0.89 (0.77-1.03)	0.90 (0.78-1.05)			0.90 (0.74-1.10)	0.93 (0.74-1.17)	0.92 (0.72-1.17)
Peanuts (g/day)												
0	0.0	0.0	9,802	963	1.00 (reference)	1.00 (reference)	1.00 (reference)	15,693	217	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1- < 5	2.5	2.1	10,477	786	0.80 (0.68-0.92)	0.89 (0.74-1.06)	0.88 (0.73-1.06)	12,519	156	0.87 (0.69-1.10)	1.06 (0.80-1.40)	1.15 (0.86-1.55)
5 +	12.8	10.7	8,926	664	0.81 (0.69-0.95)	0.85 (0.70-1.02)	0.89 (0.72-1.08)	5,427	75	0.95 (0.71-1.28)	0.96 (0.67-1.39)	1.05 (0.70-1.56)
P_{trend}					0.051	0.119	0.371			0.833	0.808	0.886
Continuous, per 5 g/day increment					0.99 (0.96-1.01)	0.98 (0.95-1.00)	0.98 (0.95-1.01)			1.05 (0.97-1.12)	1.03 (0.96-1.11)	1.04 (0.96-1.13)
Peanut butter (g/day)												
0	0.0	0.0	20,916	1,809	1.00 (reference)	1.00 (reference)	1.00 (reference)	24,516	334	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1- < 5	1.2	1.2	5,067	366	0.87 (0.73-1.03)	0.91 (0.75-1.11)	0.98 (0.79-1.20)	5,927	79	0.96 (0.73-1.26)	0.99 (0.71-1.38)	1.03 (0.72-1.45)
5 +	9.6	6.9	3,223	238	0.89 (0.72-1.09)	0.91 (0.71-1.17)	0.92 (0.70-1.19)	3,197	35	0.78 (0.53-1.15)	0.91 (0.58-1.41)	1.03 (0.65-1.62)
P_{trend}					0.258	0.470	0.519			0.205	0.668	0.906
Continuous, per 5 g/day increment					0.95 (0.87-1.03)	0.98 (0.88-1.08)	0.98 (0.88-1.10)			0.89 (0.75-1.06)	0.91 (0.76-1.09)	0.95 (0.79-1.13)

[a] Median intake in the subcohort.
[b] Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)).
[c] Adjusted for [b] and body mass index (< 18.5, 18.5- < 25, 25- < 30, ≥30 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), educational level (low, medium, high), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥30 g/day), and alternate Mediterranean diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points).

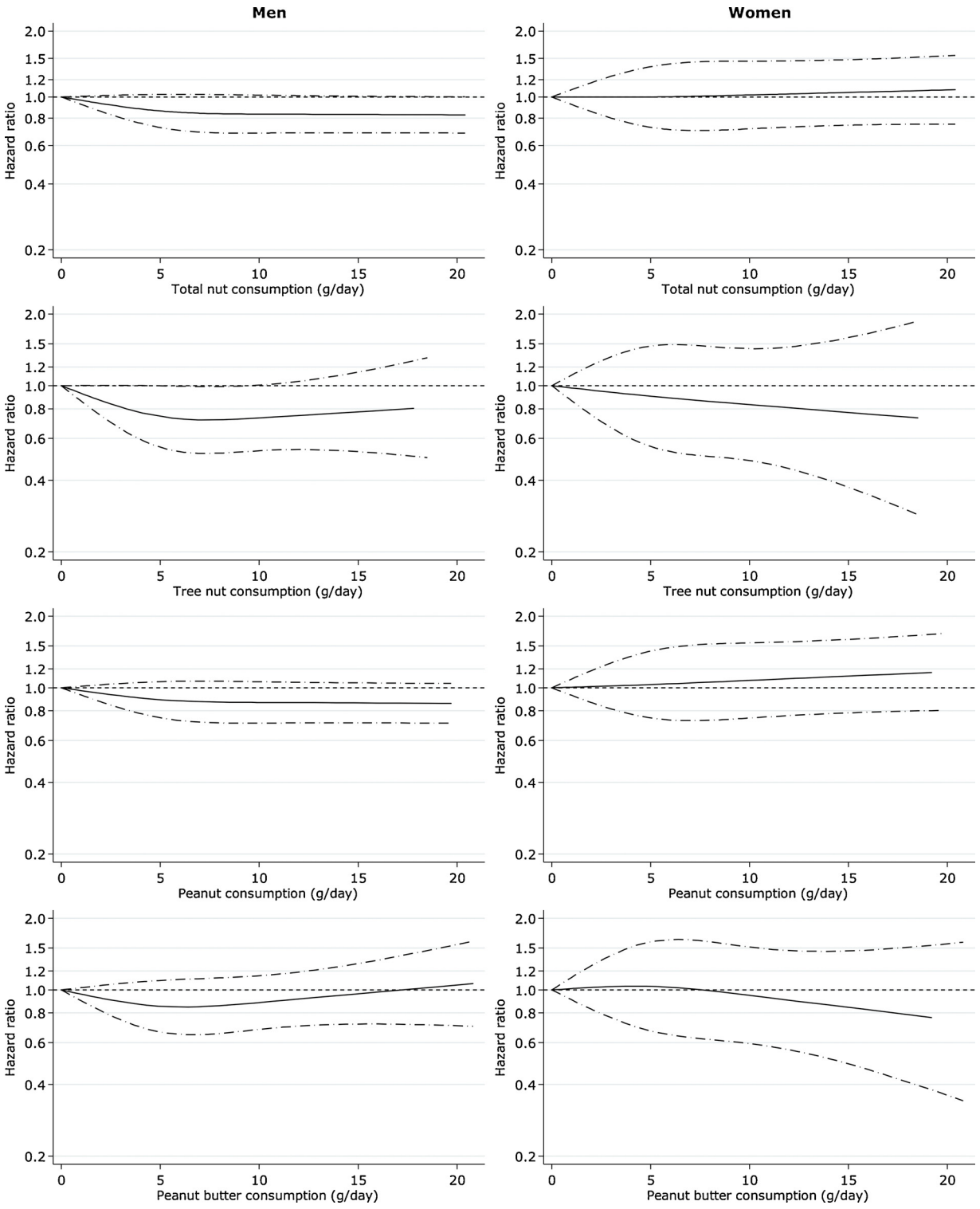

Fig. 1. Nonparametric regression curves for the associations between total lung cancer risk and intake of total nuts, tree nuts, peanuts, and peanut butter in men and women separately. Solid lines represent multivariable-adjusted HRs; dashed lines represent 95%CIs. HRs were calculated using restricted cubic spline models with three fixed knots at intakes of 0, 5, and 10 g/day, and were adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered) and duration (years; continuous, centered)), body mass index (< 18.5, 18.5- < 25, 25- < 30, ≥30 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), educational level (low, medium, high), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥30 g/day), and alternate Mediterranean diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points). P-values for nonlinearity for total nut, tree nut, peanut, and peanut butter intake were 0.143, 0.110, 0.257, and 0.185 in men, and 0.888, 0.946, 0.959, and 0.625 in women, respectively.

Table 3
Multivariable-adjusted HRs (and 95%CIs) for the four major histologic lung cancer subtypes according to nut consumption; NLCS.1986–2006.

			Adenocarcinoma		Squamous cell carcinoma		Small cell carcinoma		Large cell carcinoma	
	Median intake[a]	Person-years	N cases	Multivariable-adjusted HR[b] (95%CI)	N cases	Multivariable-adjusted HR[b] (95%CI)	N cases	Multivariable-adjusted HR[b] (95%CI)	N cases	Multivariable-adjusted HR[b] (95%CI)
Men										
Total nuts (g/day)										
0	0.0	8,696	195	1.00 (reference)	347	1.00 (reference)	162	1.00 (reference)	137	1.00 (reference)
0.1- < 5	2.5	9,613	169	0.90 (0.69-1.18)	274	0.85 (0.67-1.08)	116	0.82 (0.60-1.12)	118	0.89 (0.65-1.21)
5- < 10	8.5	3,931	52	0.71 (0.48-1.05)	109	0.91 (0.66-1.26)	56	1.12 (0.75-1.67)	44	0.91 (0.59-1.38)
10+	21.4	6,965	119	0.84 (0.62-1.14)	203	0.91 (0.70-1.19)	61	0.62 (0.43-0.89)	77	0.82 (0.57-1.18)
P_{trend}				0.317		0.783		0.024		0.373
Continuous, per 5 g/day increment				0.99 (0.95-1.03)		1.00 (0.96-1.03)		0.92 (0.87-0.98)		0.95 (0.90-1.00)
Tree nuts (g/day)										
0	0.0	21,040	417	1.00 (reference)	729	1.00 (reference)	308	1.00 (reference)	300	1.00 (reference)
0.1+	1.6	8,165	118	0.84 (0.65-1.09)	204	0.89 (0.71-1.12)	87	0.98 (0.72-1.32)	76	0.79 (0.58-1.07)
Continuous, per 5 g/day increment				0.89 (0.72-1.10)		1.01 (0.84-1.21)		0.70 (0.53-0.93)		0.83 (0.63-1.09)
Peanuts (g/day)										
0	0.0	9,802	206	1.00 (reference)	373	1.00 (reference)	171	1.00 (reference)	153	1.00 (reference)
0.1- < 5	2.5	10,477	181	0.93 (0.71-1.20)	295	0.86 (0.68-1.08)	129	0.87 (0.65-1.18)	120	0.82 (0.61-1.10)
5+	12.8	8,926	148	0.86 (0.65-1.15)	265	0.94 (0.74-1.21)	95	0.77 (0.55-1.07)	103	0.85 (0.61-1.18)
P_{trend}				0.357		0.928		0.144		0.503
Continuous, per 5 g/day increment				0.99 (0.95-1.04)		1.00 (0.96-1.03)		0.93 (0.88-0.98)		0.96 (0.91-1.01)
Peanut butter (g/day)										
0	0.0	20,916	381	1.00 (reference)	712	1.00 (reference)	305	1.00 (reference)	275	1.00 (reference)
0.1- < 5	1.2	5,067	93	1.10 (0.82-1.46)	134	0.94 (0.72-1.23)	50	0.85 (0.60-1.22)	64	1.13 (0.81-1.60)
5+	9.6	3,223	61	1.14 (0.80-1.62)	87	0.85 (0.61-1.18)	40	0.97 (0.64-1.48)	37	0.91 (0.59-1.41)
P_{trend}				0.488		0.336		0.903		0.675
Continuous, per 5 g/day increment				1.07 (0.93-1.23)		0.99 (0.85-1.15)		0.89 (0.73-1.08)		0.98 (0.82-1.17)
Women										
Total nuts (g/day)										
0	0.0	13,308	65	1.00 (reference)	43	1.00 (reference)	40	1.00 (reference)	28	1.00 (reference)
0.1- < 5	2.1	12,257	51	0.98 (0.64-1.49)	36	1.31 (0.73-2.37)	28	1.15 (0.64-2.06)	22	1.26 (0.67-2.37)
5- < 10	7.8	3,794	17	1.02 (0.54-1.90)	12	1.64 (0.68-3.97)	8	0.92 (0.33-2.56)	9	1.74 (0.68-4.46)
10+	15.7	4,280	17	0.72 (0.38-1.35)	13	1.13 (0.48-2.69)	7	0.73 (0.28-1.94)	10	1.28 (0.54-3.03)
P_{trend}				0.338		0.693		0.473		0.509
Continuous, per 5 g/day increment				0.99 (0.88-1.12)		1.02 (0.90-1.15)		0.98 (0.84-1.15)		1.10 (0.97-1.25)
Tree nuts (g/day)										
0	0.0	23,457	107	1.00 (reference)	76	1.00 (reference)	68	1.00 (reference)	48	1.00 (reference)
0.1+	2.1	10,182	43	1.01 (0.66-1.55)	28	1.13 (0.62-2.08)	15	0.70 (0.35-1.39)	21	1.40 (0.75-2.59)
Continuous, per 5 g/day increment				0.99 (0.78-1.27)		0.92 (0.61-1.39)		0.63 (0.30-1.36)		0.93 (0.63-1.38)
Peanuts (g/day)										
0	0.0	15,693	72	1.00 (reference)	46	1.00 (reference)	42	1.00 (reference)	35	1.00 (reference)
0.1- < 5	2.1	12,519	54	1.07 (0.71-1.59)	41	1.67 (0.92-3.02)	29	1.18 (0.65-2.13)	20	1.01 (0.56-1.83)
5+	10.7	5,427	24	0.85 (0.49-1.48)	17	1.27 (0.57-2.82)	12	1.05 (0.47-2.34)	14	1.26 (0.58-2.74)
P_{trend}				0.526		0.664		0.943		0.545
Continuous, per 5 g/day increment				0.99 (0.87-1.13)		1.04 (0.92-1.18)		1.01 (0.87-1.18)		1.12 (0.98-1.28)
Peanut butter (g/day)										
0	0.0	24,516	117	1.00 (reference)	73	1.00 (reference)	63	1.00 (reference)	47	1.00 (reference)
0.1- < 5	1.2	5,927	22	0.83 (0.50-1.38)	23	1.28 (0.70-2.35)	13	0.84 (0.39-1.80)	13	1.29 (0.63-2.68)
5+	6.9	3,197	11	0.79 (0.40-1.56)	8	1.17 (0.48-2.84)	7	1.00 (0.39-2.59)	9	1.92 (0.81-4.54)
P_{trend}				0.475		0.647		0.967		0.130
Continuous, per 5 g/day increment				0.83 (0.60-1.15)		1.02 (0.78-1.35)		0.97 (0.66-1.42)		1.06 (0.81-1.38)

[a] In the subcohort.

[b] Adjusted for age (years; continuous), cigarette smoking (status (never, former, current), frequency (n/day; continuous, centered), and duration (years; continuous, centered)), body mass index (< 18.5, 18.5- < 25, 25- < 30, ≥ 30 kg/m^2), nonoccupational physical activity (≤ 30, > 30-60, > 60-90, > 90 min/day), educational level (low, medium, high), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥ 30 g/day), and alternate Mediterranean diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points).

was observed in men (HR (95%CI) for 10+ g/day vs nonconsumers: 0.62 (0.43-0.89), p-trend: 0.024). For adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, nonsignificant inverse trends with total nut intake were seen in men. In continuous analyses, a (borderline) significant association with large cell carcinoma was found (HR (95%CI) per 5 g/day increment: 0.95 (0.90–1.00)). In women, no or nonsignificant positive associations with total nut intake were found for the four subtypes. For tree nut intake, nonsignificant inverse associations with all lung cancer subtypes were observed in men. In continuous analyses, the HR (95%CI) per 5 g tree nuts/day increment was 0.70 (0.53-0.93) for small cell carcinoma. No significant associations were found for tree nut intake for the four subtypes in women. For peanut intake, nonsignificant inverse associations with all lung cancer subtypes were seen in men, and a significant inverse association for small cell

Table 4
Total lung cancer risk according to total nut intake, in multivariable adjusted analyses[a], in strata of smoking status and smoking frequency; the Netherlands Cohort Study.1986–2006.

	Total nut consumption (g/day)			P_{trend}	$P_{interaction}$
	0 g/day	0.1- < 5 g/day	5+ g/day		
Total lung cancer					
Men					
Smoking status					
Never					
Cases/person-time at risk (years)	44/1,296	21/1,598	30/1,451		
HR (95%CI)	1 (ref)	0.34 (0.15-0.75)	0.63 (0.27-1.46)	0.854	0.042
Former					
Cases/person-time at risk (years)	291/4,433	256/5,194	269/6,164		
HR (95%CI)	1 (ref)	0.91 (0.68-1.20)	0.68 (0.51-0.91)	0.007	
Current					
Cases/person-time at risk (years)	562/2,967	456/2,822	484/3,280		
HR (95%CI)	1 (ref)	0.91 (0.68-1.20)	0.99 (0.75-1.31)	0.843	
Smoking frequency					
Former cigarette smokers					
1- < 20 cigarettes/day					
Cases/person-time at risk (years)	119/2,350	91/3,225	106/3,071		
HR (95%CI)	1 (ref)	0.56 (0.36-0.85)	0.61 (0.39-0.96)	0.164	0.005
20+ cigarettes/day					
Cases/person-time at risk (years)	172/2,083	165/1,969	163/3,093		
HR (95%CI)	1 (ref)	1.22 (0.82-1.81)	0.71 (0.47-1.06)	0.021	
Current cigarette smokers					
1- < 20 cigarettes/day					
Cases/person-time at risk (years)	259/1,638	213/1,841	222/1,839		
HR (95%CI)	1 (ref)	0.68 (0.47-0.99)	0.89 (0.61-1.32)	0.935	0.111
20+ cigarettes/day					
Cases/person-time at risk (years)	303/1,329	243/981	262/1,441		
HR (95%CI)	1 (ref)	1.16 (0.76-1.78)	0.94 (0.63-1.42)	0.585	
Women					
Smoking status					
Never					
Cases/person-time at risk (years)	47/8,430	30/7,502	26/4,226		
HR (95%CI)	1 (ref)	0.75 (0.46-1.23)	1.14 (0.66-1.96)	0.452	0.387
Former					
Cases/person-time at risk (years)	23/1,957	27/2,736	20/2,249		
HR (95%CI)	1 (ref)	0.88 (0.41-1.91)	0.75 (0.30-1.88)	0.549	
Current					
Cases/person-time at risk (years)	126/2,921	93/2,019	56/1,600		
HR (95%CI)	1 (ref)	1.39 (0.87-2.21)	1.03 (0.59-1.80)	0.937	
Smoking frequency					
Former cigarette smokers					
1- < 20 cigarettes/day					
Cases/person-time at risk (years)	12/1,494	16/2,228	8/1,844		
HR (95%CI)	1 (ref)	1.98 (0.68-5.78)	0.81 (0.23-2.86)	0.350	0.676
20+ cigarettes/day					
Cases/person-time at risk (years)	11/462	11/508	12/405		
HR (95%CI)	1 (ref)	0.92 (0.13-6.59)	0.27 (0.03-2.22)	0.208	
Current cigarette smokers					
1- < 20 cigarettes/day					
Cases/person-time at risk (years)	53/2,018	47/1,514	30/1,190		
HR (95%CI)	1 (ref)	1.36 (0.70-2.64)	1.26 (0.58-2.74)	0.672	0.797
20+ cigarettes/day					
Cases/person-time at risk (years)	73/903	46/505	26/410		
HR (95%CI)	1 (ref)	1.50 (0.72-3.12)	1.09 (0.39-3.06)	0.893	

[a] Adjusted for age (years; continuous), cigarette smoking (frequency (n/day; continuous, centered) and duration (years; continuous, centered)), body mass index (< 18.5, 18.5- < 25, 25- < 30, ≥30 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), educational level (low, medium, high), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥30 g/day), and alternate Mediterranean diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points).

carcinoma in continuous analyses (HR (95%CI) per 5 g/day increment: 0.93 (0.88-0.98)). In women, no or nonsignificant positive associations were found for all subtypes for peanut intake. Peanut butter intake was not significantly associated with the lung cancer subtypes in both sexes.

Stratification of the relation between total nut intake and total lung cancer by smoking status in men showed nonsignificant inverse associations in never smokers, significant inverse associations in former smokers, and no relation in current smokers (p-trend: 0.854, 0.007, and 0.843, respectively) (Table 4). To increase statistical power, the two highest intake categories were merged into one category of 5+ g/day for these stratified analyses. The test for interaction by smoking status was significant in men (p-interaction: 0.042). In women, the relation between total nut intake and total lung cancer was unclear in never smokers, non-significantly inverse in former smokers, and non-significantly positive in current smokers (p-trend: 0.452, 0.549, and 0.937, respectively).The test for interaction was not significant (p-interaction:

Table 5
Small cell carcinoma risk according to total nut intake in men, in multivariable adjusted analyses[a], in strata of smoking status and smoking frequency; the Netherlands Cohort Study.1986–2006.

	Total nut consumption (g/day) per 5 g/day increment	$P_{interaction}$
Small cell carcinoma		
Men		
Smoking status		
Never		
Cases/person-time at risk (years)	13/4,345	
HR (95%CI)	0.45 (0.10-1.93)	0.574
Former		
Cases/person-time at risk (years)	110/15,791	
HR (95%CI)	0.88 (0.79-0.99)	
Current		
Cases/person-time at risk (years)	272/9,069	
HR (95%CI)	0.93 (0.87-1.00)	
Smoking frequency		
Former cigarette smokers		
1- < 20 cigarettes/day		
Cases/person-time at risk (years)	31/8,647	
HR (95%CI)	1.00 (0.86-1.15)	0.075
20+ cigarettes/day		
Cases/person-time at risk (years)	79/7,145	
HR (95%CI)	0.82 (0.69-0.98)	
Current cigarette smokers		
1- < 20 cigarettes/day		
Cases/person-time at risk (years)	113/5,318	
HR (95%CI)	0.96 (0.86-1.06)	0.332
20+ cigarettes/day		
Cases/person-time at risk (years)	159/3,751	
HR (95%CI)	0.90 (0.80-1.01)	

[a] Adjusted for age (years; continuous), cigarette smoking (frequency (n/day; continuous, centered) and duration (years; continuous, centered)), body mass index (< 18.5, 18.5- < 25, 25- < 30, ≥30 kg/m^2), nonoccupational physical activity (≤30, > 30-60, > 60-90, > 90 min/day), educational level (low, medium, high), family history of lung cancer (yes, no), history of chronic bronchitis (yes, no), daily energy intake (kcal/day; continuous), alcohol consumption (0, 0.1- < 5, 5- < 15, 15- < 30, ≥30 g/day), and alternate Mediterranean diet score excluding alcohol and nuts (0–2, 3–4, 5–7 points).

0.387). After further stratification by smoking frequency, the HRs in male former smokers were stronger inverse in lighter smokers (1- < 20 cigarettes/day) than in heavy smokers (20+ cigarettes/day) (p-interaction: 0.005). In male current smokers, there was no significant interaction by smoking frequency (p-interaction: 0.111), although stronger inverse associations were seen in lighter smokers. In female former and current smokers, no interactions by smoking frequency were found.

Interactions between nut intake and smoking characteristics were also investigated for the lung cancer subtypes. Because of the low number of never smoking male cases, interactions by smoking habits for the subtypes were tested on a continuous scale. (Borderline) significant inverse associations of total nut intake with small cell carcinoma were observed in male former and current smokers, and a stronger, but nonsignificant inverse association in male never smokers (p-interaction: 0.574) (Table 5). When additionally stratifying by smoking frequency, no association was observed in male former lighter smokers, and a significant inverse association in male former heavy smokers (p-interaction: 0.075). In male current smokers, nonsignificant inverse associations were found in both strata of smoking frequency (p-interaction: 0.332). For small cell carcinoma, also no significant interactions between smoking frequency and tree nut or peanut intake were observed in male former and current smokers (data not shown). The associations with small cell carcinoma risk in male former heavy smokers and male current lighter and heavy smokers were stronger inverse for tree nut intake than for total nut intake (data not shown). For peanut intake, comparable estimates as for total nut intake were found when stratifying by smoking frequency in male current and former smokers (data not shown). No significant interactions by smoking characteristics were found for small cell carcinoma in women or for the other subtypes in both sexes, although the number of female cases in each stratum of smoking frequency was very small (data not shown).

For the other considered lung cancer risk factors we observed no significant interactions in both sexes (Supplementary Table S1). In sensitivity analyses, adjustment for fruit, vegetable, milk, milk product, cheese, and red and processed meat intake resulted in similar associations as when adjusting for the aMED score excluding alcohol and nuts (data not shown). Mutual adjustment for tree nut, peanut, and peanut butter intake also did not change the estimates (data not shown). Excluding the first two years of follow-up did not importantly alter the estimates, and neither did restricting the analyses to participants with a constant peanut butter intake in the five years before baseline (data not shown).

4. Discussion

In this large prospective cohort study, increased total nut, tree nut, and peanut intake was associated with a non-significantly decreased lung cancer risk in men. The inverse relation for total nut intake in men differed significantly across strata of smoking characteristics, and was strongest in never and former lighter smokers (1- < 20 cigarettes/day). The risk of small cell carcinoma was significantly reduced in men with increasing nut intake, after controlling for smoking status, frequency, and duration. Significant inverse relations with small cell carcinoma in men were also seen for tree nut and peanut intake in continuous analyses. For adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, nonsignificant inverse associations were found for all nut exposures in men. In women, nut intake was not related to the risk of lung cancer, nor its subtypes. Peanut butter was also not associated with lung cancer risk in both sexes.

In contrast to our study, no relation between nut intake and lung cancer risk was found in the Adventist Health Study, although no estimates were reported [10]. In the COSMOS lung cancer screening study, a nonsignificant inverse relation was observed among heavy smokers [11]. However, these cohort studies had small sample sizes and relatively short follow-up periods, and they did not stratify by sex or histologic subtype.

A third cohort study, the NIH-AARP, with 18,533 incident lung cancer cases found significant inverse associations between nut consumption frequency and risk of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma in both sexes combined, after controlling for smoking characteristics [12]. They also observed that lighter smokers may benefit most from higher nut consumption, and sensitivity analyses suggested that nut intake might be most protective against small cell carcinoma. Furthermore, the authors stated that similar associations were found in men and women. These results largely correspond with our findings, although we observed substantial differences between the sexes, and nonsignificant inverse associations for adenocarcinoma and squamous cell carcinoma in men. The latter might be explained by the higher statistical power in the NIH-AARP.

In an accompanying Italian case-control study, nut consumption frequency was also significantly associated with a decreased lung cancer risk [12]. A Hawaiian case-control study found no association between peanut and peanut butter intake and lung cancer risk [14], and another Italian case-control study also observed no effect of nut consumption frequency on lung cancer risk [13].

In our study, the relation between nut intake and lung cancer risk differed substantially between the sexes. This might be explained by the lower mean nut intake in women (4.4 g/day) than in men (7.9 g/day). Only one other cohort [12] and two case-control studies [12,14] performed sex-stratified analyses, and observed no differences between men and women. Because these studies did not report sex-specific mean nut intakes, it is difficult to compare them to our study. Other possible

explanations for the observed differences between men and women might be residual confounding by smoking characteristics or hormonal mechanisms that might contribute to lung carcinogenesis [23,24]. Because there is no clear explanation for the observed dissimilarities, additional research investigating sex-differences in the relation between nut intake and lung cancer risk is required.

The inverse relation with nut intake in men was strongest for small cell carcinoma, after controlling for smoking habits. This finding is important, because small cell carcinoma is characterized by its rapid growth and early metastatic spread [25]. Moreover, it has the strongest relation with smoking of all subtypes [26–28].

For total lung cancer and small cell carcinoma, the inverse association with total nut intake in men was strongest in never and former smokers. Moreover, for total lung cancer, the inverse association was stronger in lighter smokers than in heavy smokers. Stronger inverse relations in lighter smokers (1–20 cigarettes/day) were also observed in the NIH-AARP [12]. A possible explanation for these observations is the high amount of antioxidants in nuts, e.g. vitamin E, selenium, proanthocyanidins, flavonoids, resveratrol, and carotenoids [29,30]. In a crossover trial, almond supplementation significantly reduced biomarkers of oxidative stress and increased antioxidant defenses in men smoking 5–20 cigarettes/day [31]. The large amount of reactive oxygen species generated by heavy smoking (20+ cigarettes/day) might exceed the antioxidant capacity of nuts, possibly explaining the weaker associations in this subgroup. Nonetheless, no studies have investigated the relation of nut intake with oxidation status in heavy smokers. Moreover, in vivo studies, animal experiments, and human randomized controlled trials have not consistently observed beneficial effects of nut consumption on antioxidant status [30].

Another hypothesized mechanism relates to the anti-inflammatory and immune modulating effects of nuts, by compounds like α-linolenic acid, magnesium, L-arginine, flavonoids, and resveratrol [5,25,32]. Nevertheless, a recent meta-analysis of 23 randomized clinical trials found that, out of six inflammatory markers, nut consumption only significantly reduced the levels of intercellular adhesion molecule-1 [32]. Other potential mechanisms relate to the reduction of tumor initiation or promotion, regulation of DNA damage repair, metabolic enzyme activity, and hormonal mechanisms [5,33]. Because the exact biological mechanism remains unclear, further research is warranted.

The (nonsignificant) inverse relations between nut intake and lung cancer risk were somewhat stronger for tree nut intake than for peanut intake, whereas no relations were observed for peanut butter intake. One possible explanation for these differences is the different nutrient composition of the nut types: peanuts, which are botanically legumes, contain less total fat than almonds, hazelnuts, and walnuts, whereas the amount of saturated fatty acids, proteins, carbohydrates, folate, and phytosterols is higher [34,35]. Almonds, cashew nuts, and hazelnuts contain more monounsaturated fatty acids than peanuts, and walnuts contain more polyunsaturated fatty acids [35]. Moreover, almonds are better sources of fiber, magnesium, and calcium than peanuts [35]. Peanut butter that was sold in the Netherlands in 1986 contained more vitamin B6, sodium, and partially hydrogenated fatty acids, and less niacin than peanuts [34]. However, because the exact mechanism by which nuts might reduce the risk of lung cancer is unclear, we can only speculate about the differences between the observed relations for tree nuts, peanuts, and peanut butter. Furthermore, the food frequency questionnaire did not include questions about the consumption of specific tree nut subtypes. According to FAO trade data, tree nut subtypes that were imported into the Netherlands in 1986 included almonds, hazelnuts, walnuts, and cashew nuts [36]. These trade data give an indication of the tree nut subtypes that were available in the Netherlands at that time. Because the nutrient composition differs between tree nut subtypes [34], we recommend to further investigate their differential effects on lung cancer risk in future studies.

The prospective design of the NLCS and its long and complete follow-up make information and selection bias unlikely. The large number of cases enabled us to stratify the results by the four lung cancer subtypes, by smoking characteristics, and by sex. Moreover, we were able to distinguish between tree nut, peanut, and peanut butter intake. Another advantage is the relatively high average nut intake in our study compared to most other cohort studies which investigated the relation between nut intake and lung cancer risk [11,12]. Potential weaknesses include the single exposure measurement at baseline and possible measurement error, which may have attenuated our results. Residual confounding might be another limitation, although we extensively adjusted for potential confounders.

In conclusion, our cohort study showed that increased total nut, tree nut, and peanut intake is related to a significantly reduced risk of small cell carcinoma in men, after controlling for detailed smoking habits. Inverse, but nonsignificant associations were also seen for total lung cancer and the other histologic lung cancer subtypes in men. Nut intake was not related to lung cancer risk in women, and no significant associations were found for peanut butter intake in both sexes. Based on the overall body of evidence from the few prospective cohort studies investigating the relation between nut consumption and lung cancer risk, nut intake might be associated with a reduced risk of lung cancer, in particular the small cell carcinoma subtype. Cigarette smoking possibly modifies this relation. However, the evidence regarding this topic is still very limited and more prospective evidence is required before firm conclusions can be drawn. In addition, the exact biological mechanism that explains the observed relations has to be elucidated yet.

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Competing interests

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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