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Research Article

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Nut Consumption and Lung Cancer Risk: Results from Two Large Observational Studies

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Abstract

Background: Epidemiologic evidence on the association between nut consumption and lung cancer risk is limited.

Methods: We investigated this relationship in the Environment and Genetics in Lung Cancer Etiology (EAGLE) study, a population-based case–control study, and the National Institutes of Health (NIH) American Association of Retired Persons (AARP) Diet and Health Study, a prospective cohort. We identified 2,098 lung cases for EAGLE and 18,533 incident cases in AARP. Diet was assessed by food frequency questionnaire for both studies. Multivariable ORs and HRs and respective 95% confidence intervals (CI) were calculated using unconditional logistic regression and Cox proportional hazards regression for EAGLE and AARP, respectively.

Results: Higher frequency of intake of nut consumption was inversely associated with overall lung cancer risk (highest vs. lowest quintile, $OR_{EAGLE} = 0.74$; 95% CI, 0.57–0.95; $HR_{AARP} = 0.86$; 95% CI, 0.81–0.91), regardless of smoking status. Results from the prospective cohort showed similar associations across histologic subtypes and a more pronounced benefits from nut consumption for those who smoked 1 to 20 cigarettes/day ($OR_{EAGLE} = 0.61$; 95% CI, 0.39–0.95; $HR_{AARP} = 0.83$; 95% CI, 0.74–0.94).

Conclusions: Nut consumption was inversely associated with lung cancer in two large population-based studies, and associations were independent of cigarette smoking and other known risk factors.

Impact: To our knowledge, this is the first study that examined the association between nut consumption and lung cancer risk by histologic subtypes and smoking intensity. *Cancer Epidemiol Biomarkers Prev; 26(6); 826–36. ©2017 AACR.*

Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide (1). Cigarette smoking is the established primary risk factor for lung cancer. However, other factors, such as dietary intakes, may modify smoking-associated lung cancer risk (2).

Nut intake has been associated with lower risk of several chronic diseases, including cardiovascular disease (3, 4) and diabetes (5). There is also a growing body of evidence suggesting that nut consumption may be associated inversely with cancer mortality (6–9) and incidence (10, 11). To date, just a few studies have investigated associations between nut consumption and lung cancer and have observed evidence for an inverse association (12–14). However, these studies had small sample sizes (number of cases range from 178 to 342), and as such were unable to examine associations with lung cancer histologic subtypes or examine associations separately in current, former, and never-smokers. A recent prospective study (number of cases = 9,272) based on the National Institutes of Health (NIH) American Association of Retired Persons (AARP) Diet and Health Study (15) showed that several index-based dietary patterns, for which intake of nuts was a component but was not specifically examined in this study, were associated with modest reduction of lung cancer risk. This study focuses on nut consumption and its relationship with lung cancer in this cohort.

Here, we investigated the association between nut consumption and lung cancer risk in the Environment and Genetics in Lung Cancer Etiology (EAGLE), a population-based case–control study of more than 2,000 cases and 2,000 controls (16), and further validated our findings in a large prospective cohort study, the AARP Diet and Health Study (17). Our large sample size allowed us to explore the association with major lung cancer histology subtypes, and by stratification of smoking status.

Materials and Methods

Study population

The EAGLE study is a large population-based case–control study conducted in the Lombardy region of Italy. Details of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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the study have been described previously (16). Between April 2002 and February 2005, primary lung cancer cases (n = 2,098) were identified from 13 hospitals, which covered approximately 80% of incident lung cancer cases in the catchment area, and consist of 216 municipalities, including five cities (Milan, Monza, Brescia, Pavia, and Varese) and surrounding towns and villages. Inclusion criteria for both cases and controls were Italian nationality between the ages of 35 and 79 years, official residents of the municipalities, and no severe disease that could impede participation. Case response rate was 86.6%. Approximately 95% of cases were confirmed pathologically or cytologically, and the remaining 5% were confirmed on the basis of clinical history and imaging. Detailed histologic classification was recorded for all cases. Controls were randomly selected from the Lombardy Regional Health Service database, which contains demographic information for virtually all Italians from the catchment area, and were frequency-matched to cases based on sex, 5-year age group, and area of residence. Family physicians for the potential controls were asked to verify the absence of lung cancer history or any advanced diseases that would impede participation. At study completion, 2,120 controls were enrolled with an overall participation rate of 72.4%.

The EAGLE analysis excluded 582 participants (380 cases and 202 controls) who did not complete the food frequency questionnaire (FFQ), resulting in a study population of 1,721 cases and 1,918 controls. The study protocol was approved by the Institutional Review Board of the NCI (Rockville, MD) and the involved institutions in Italy. Informed consent was obtained for all subjects prior to study participation.

The AARP Diet and Health Study is a large prospective study of members of AARP, formally the American Association of Retired Persons, established in 1995 to 1996. Details of the study design have been described previously (17). AARP members (n = 617,119) ages 50 to 71 years and residing in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed a self-administered questionnaire where demographics, health-related behaviors, and diet were queried. The study cohort included 566,398 participants who satisfactorily completed the baseline questionnaire and provided informed consent. We excluded individuals with prevalent cancer except nonmelanoma skin cancer ($n = 52{,}708$), proxy respondents (n = 14,398), those with missing information on nut consumption and with log-transformed total energy intake of more than two interquartile ranges from the median ($n = 3{,}437$), and individuals with 0 years of follow-up (n = 70); 495,785 individuals were included in our analysis. This study was approved by the Special Studies Institutional Review Board at the NCI.

Incident lung cancer cases were identified through linkage with 11 state cancer registry databases, which included the eight original and three additional states (Arizona, Texas, and Nevada) that a number of participants moved during follow-up (18). Lung cancer cases were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, third edition; ref. 19). As previously described, total lung cancer category included carcinoma of the bronchus and lung (ICD 34.0–34.9; 20). Examined histologic subtypes included adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma.

Exposure assessment

In EAGLE, tobacco exposure was categorized into active smoking (number of cigarettes per day averaged over a lifetime, age at initiation/quit, pack-years) and passive smoking (during childhood, at workplace, and at home during adulthood). Diet over the year prior to diagnosis for the cases and enrolment for the controls (cases were enrolled at diagnosis) was collected at baseline via a self-administered 58-item FFQ specific to this Italian population. There was one question on total consumption of nuts (walnuts, hazelnuts, almonds, and peanuts), 41 on fruits and vegetables, nine on processed meats, one on pizza, and six on other meats and poultry. The FFQ queried frequency of consumption using 11 possible responses ("never" to "2 or more times per day") in the year prior to the study. Alcoholic beverage consumption was assessed using three possible response categories (yes, in the past, and never) in the year prior to the study, and 10 possible response categories ("never" to "6 or more times per day") for different age categories. Portion size was not queried.

At baseline, participants in the AARP cohort completed a 124-item FFQ (21) that queried typical diet, including consumption of nuts (peanuts, walnuts, seeds, or other nuts) over the past year. The food items were constructed on the basis of the method developed by Subar (22) with national dietary data from the U.S. Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (23). Participants answered one question on their frequency of nut consumption using 10 categories, ranging from "never" to "2 or more times per day," and 3 categories for portion size.

Statistical analysis

In EAGLE, nut consumption was categorized by sex-specific quintiles based on distribution of frequency of consumption from the controls for each sex (Q1–Q5): Q1 (never), Q2 (1–6 times/year), Q3 (7–11 times/year), Q4 (1–3 times/month), and Q5 (1–5 times/week, and $\geq$1 time/day) during the past year. Frequency of nut consumption in AARP was categorized by quintiles based on distribution of frequency of consumption from the controls: Q1 (never), Q2 (1–6 times/year), Q3 (7–11 times/year), Q4 (1–3 time/month), and Q5 (1–6 times/week, and $\geq$1 time/day) during the past year.

The correlation between nut consumption and selected factors was examined by Pearson product–moment correlation coefficients. In EAGLE, ORs and 95% confidence intervals (CI) within sex-specific quintiles of nut consumption were obtained using logistic regression. In AARP, we used Cox proportional hazards regression (24) to estimate HRs and 95% CIs for nut consumption and total lung cancer, with nonconsumers as the referent group and person-year as the underlying time metric. Person-years were calculated beginning on the date of questionnaire return until cancer diagnosis, movement out of the registry area, loss to follow-up, death, or the end of follow-up (December 31, 2011), whichever came first.

For EAGLE, models were adjusted for matching variables (age, sex, area of residence) and cumulative pack-years of cigarette smoking (continuous and 0 for never-smokers), and for AARP, age, sex, and cigarette smoking dose (categorical and 0 for never-smokers), but not residence. Both studies also adjusted for body mass index (BMI), education, cigarette smoking status, and years since last cigarette smoked for former smokers (continuous in EAGLE, 0 for current smokers and highest years for never-smokers;

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categorical in AARP, 0 for never-smokers, 1 for ≥10 years, 2 for 5–9 years, 3 for 1–4 years, 4 for within last year, and 5 for current smokers). AARP additionally adjusted for energy intake. The analyses were further adjusted for selected dietary intakes (fruits, vegetables, red and processed meat, and alcohol), which have been hypothesized to be associated with lung cancer (25–27). Variables for family history of lung cancer, previous lung diseases, and passive smoke exposures were not included in the final model as they did not substantially alter our results.

Subgroup analyses were conducted separately by smoking status (never, former, and current), smoking intensity (quintiles based on distribution of cigarettes per day in controls), sex, and major histologic subtypes (adenocarcinoma, squamous cell carcinoma, and small-cell lung cancer). For sensitivity analyses, we conducted an analysis by tertiles of nut consumption. We further conducted lag analyses by 5 years and 10 years in AARP.

Analyses in EAGLE were conducted using STATA 9.1 and in the AARP cohort using SAS 9.3 (SAS Institute). For all comparisons, P values were two-sided and α <0.05 indicated statistical significance.

Results

In EAGLE, cases (n = 1,721) and controls (n = 1,918) were similarly distributed by age, sex, and BMI (Table 1). Compared with controls, cases were likely to be less educated, more likely to be current smokers, and among ever-smokers, smoked more intensely. Cases had a lower average weekly consumption of nuts than controls. Overall, the proportion of participants was similarly distributed by smoking status across all categories of nut consumption in both cases and controls. In AARP (n = 495,785), we identified 18,533 incident lung cancer cases during up to 16 years of follow-up (Table 2). A majority of lung cancer cases were diagnosed in current (38%) and former (52%) smokers at baseline. In general, cases ate more red meat and processed meat, less fruits and vegetables, and drank more alcohol in both EAGLE and AARP. Nut consumption was not correlated with any smoking-related factors, intakes of fruits and vegetables, red meat, processed meat, or lifetime alcohol consumption (Supplementary Table S1).

Table 3 presented results showing that individuals in the highest quintile of frequency of nut consumption had a 26% (OR_{EAGLE} = 0.74; 95% CI, 0.57–0.95; P_{trend} = 0.017) and 14% (HR_{AARP} = 0.86; 95% CI, 0.81–0.91; P_{trend} < 0.001) lower risk of developing lung cancer compared with those in the lowest quintile of intake. Similar inverse associations were observed in sex-stratified (data not shown) analyses that examined tertiles of nut consumption (Supplementary Tables S2–S4), and in analyses excluding frequent (2 or more times a day) nut consumption (data not shown). Across several lag-analyses in AARP, similar statistically significant inverse associations were observed (Supplementary Tables S5 and S6).

When stratified by smoking status (Table 3), significant inverse associations for nut consumption were observed for lung cancer cross all smoking status in AARP ($HR_{current}$ = 0.88; 95% CI, 0.80–0.96; P_{trend} = 0.004; HR_{former} = 0.85; 95% CI, 0.79–0.92; P_{trend} < 0.001; HR_{never} = 0.77; 95% CI, 0.62–0.96; P_{trend} = 0.02). Data from EAGLE showed significant inverse association for only current smokers (OR_{EAGLE} = 0.68; 95% CI, 0.47–1.00, P_{trend} = 0.05) with inverse associations that were not significant for former smokers (OR_{EAGLE} = 0.81; 95% CI, 0.57–1.13, P_{trend} = 0.213) and never-smokers (OR_{EAGLE} = 0.91; 95% CI, 0.43–1.90; P_{trend} = 0.796), likely because of the small numbers in this category.

When we stratified by smoking intensity, the inverse associations were most pronounced among participants who smoked between 1 to 20 cigarettes/day among (OR_{EAGLE} = 0.67; 95% CI, 0.50–0.90; P_{trend} = 0.008; HR_{AARP} = 0.84; 95% CI, 0.77–0.91; P_{trend} < 0.001). Similar analyses within smoking-stratified categories showed that this more pronounced benefit from higher nut consumption was driven by the strong inverse associations observed for current smokers who smoked 1 to 20 cigarettes/day (Table 4). A sensitivity analysis excluding those with missing smoking information showed similar results (data not shown).

We observed borderline or significant inverse associations in analyses stratified by histology subtypes (Table 5) in AARP ($HR_{adenocarcinoma}$ = 0.93; 95% CI, 0.85–1.03; P_{trend} = 0.151; $HR_{squamous}$ = 0.83; 95% CI, 0.72–0.94; P_{trend} = 0.004; and $HR_{small\text{-}cell}$ = 0.76; 95% CI, 0.65–0.90; P_{trend} = 0.002). Conversely, probably due to smaller number of subjects across categories in EAGLE, we did not observe similar findings across histology groups in the case–control study.

Discussion

In this study, we observed that higher frequent consumption of nuts was associated with a statistically significant (26% in EAGLE and 14% in AARP) reduced risk of lung cancer in both a large population-based case–control study from Northern Italy and in a large prospective cohort from the United States, respectively. The inverse associations between nut consumption and lung cancer were independent of smoking characteristics. Moreover, lighter smokers (1–20 cigarettes/day) may benefit the most from higher consumption of nuts.

The body of evidence on nut consumption and lung cancer risk is scarce. Of the three published studies, two reported estimates and corresponding 95% CI on nut consumption and lung cancer risk (13, 14); the remaining third did not report actual estimate but stated that a nonsignificant inverse association was observed (12). Of the two with reported estimates, the older hospital-based case–control study (number of cases = 342) did not find an association ($OR_{\geq weekly+\text{-}versus\text{-}<weekly}$ = 1.15; 95% CI, 0.66–2.02; ref. 14). Analyses from the Continuing Observation of Smoking Subjects (COSMOS) screening program (number of cases = 178) showed a nonsignificant inverse association ($OR_{Q4\text{-}VS\text{-}Q1}$ = 0.76; 95% CI, 0.48–1.21; ref. 13). Both studies had limited power to fully assess the relationship between nut consumption and lung cancer risk. Findings from the COSMOS suggested a stronger inverse association for increased consumption among the studied population of heavy smokers (smoking ≥1 pack/day). In this study, when the analyses were restricted to participants who smoked ≥1 pack/year, we observed a nonsignificant 9% and a significant 10% reduction in lung cancer risk for EAGLE and AARP, respectively.

Although we observed evidence for an association among former and current smokers, associations appeared strongest among participants who smoked fewer than 20 cigarettes per day. A plausible explanation for this observation is that smokers may be exposed to free radicals, and cellular damage from oxidative stress caused by cigarette smoke and the carcinogenic damage caused by high exposure among heavy smokers may overwhelm the potential protective effects derived from nut

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Table 1. Selected baseline characteristics of the EAGLE study by lung cancer cases and controls of nut consumption

			Quintile of total nut consumption (frequency/d) in controls[a]				
Characteristics	**Controls (n = 1,918)**	**Cases (n = 1,721)**	**1 (n = 748)**	**2 (n = 122)**	**3 (n = 291)**	**4 (n = 397)**	**5 (n = 360)**
Sex, %							
Male	1,387 (80.59)	1,485 (77.42)	652 (87.17)	0 (0)	240 (82.47)	319 (80.45)	274 (76.11)
Age,[b] y	65.49 (8.60)	66.31 (8.33)	66.96 (8.36)	64.10 (10.94)	63.78 (8.40)	64.92 (8.05)	64.93 (8.52)
BMI,[b] kg/m^2	26.00 (3.85)	25.81 (4.18)	26.30 (4.11)	25.15 (4.07)	25.80 (3.49)	26.18 (3.76)	25.64 (3.50)
Education, n (%)							
Elementary	642 (38.12)	519 (27.07)	231 (30.97)	39 (31.97)	69 (23.71)	94 (23.68)	86 (23.89)
Middle school	484 (28.91)	555 (29.00)	209 (28.02)	37 (30.33)	103 (35.40)	103 (25.94)	103 (28.61)
≥High school	468 (27.44)	771 (40.22)	268 (35.92)	42 (34.43)	110 (37.80)	185 (46.60)	166 (46.11)
Smoking status, n (%)							
Never[c]	110 (6.33)	604 (31.52)	212 (28.42)	59 (48.36)	90 (30.93)	132 (33.25)	111 (30.83)
Former	761 (43.84)	838 (43.74)	344 (46.11)	29 (23.77)	128 (43.99)	171 (43.07)	166 (46.11)
Current	846 (48.73)	473 (24.69)	190 (25.47)	34 (27.87)	73 (25.09)	93 (23.43)	83 (23.06)
Cumulative pack-years of cigarette smoking[b]							
Ever	48.29 (27.45)	26.83 (21.37)	30.51 (23.41)	17.03 (16.69)	26.41 (20.52)	24.67 (19.74)	24.11 (18.64)
Former	43.54 (28.82)	22.62 (20.27)	25.92 (22.03)	6.87 (8.66)	23.33 (19.48)	20.13 (18.44)	20.53 (18.48)
Current	52.60 (25.41)	34.39 (21.22)	38.90 (23.59)	25.69 (17.08)	31.80 (21.30)	33.28 (19.23)	31.26 (16.92)
Smoking intensity (packs/d)[b,d]	0.79 (0.51)	1.12 (0.55)	0.86 (0.55)	0.51 (0.38)	0.79 (0.49)	0.76 (0.48)	0.73 (0.46)
Cigarettes smoking duration,[b,d] y	31.78 (15.00)	42.91 (11.71)	33.54 (14.65)	28.48 (17.14)	31.76 (14.41)	30.30 (15.03)	30.57 (15.27)
Lifetime alcohol,[b] g/wk	162.51 (152.59)	203.71 (197.40)	172.15 (171.12)	71.35 (87.24)	169.44 (139.0)	158.90 (143.74)	171.88 (139.04)
Total red meat,[b] servings/wk	1.86 (1.59)	2.36 (1.99)	1.77 (1.60)	1.57 (1.37)	1.80 (1.51)	2.05 (1.54)	1.98 (1.73)
Total processed meat consumption,[b] servings/wk	4.89 (3.87)	5.87 (4.86)	4.45 (3.87)	3.99 (3.52)	4.82 (3.65)	5.39 (3.89)	5.62 (3.98)
Total fruit and vegetables,[b] servings/wk	26.70 (12.76)	24.45 (12.82)	24.31 (12.40)	28.04 (13.39)	25.75 (12.38)	28.04 (12.38)	30.44 (12.89)
Total quercetin,[b] servings/wk	6.62 (4.68)	5.66 (4.42)	6.43 (4.85)	6.31 (4.60)	6.36 (4.38)	6.82 (4.56)	7.08 (4.65)
Total nut consumption,[b] servings/wk	0.68 (1.52)	0.55 (1.44)	0.04 (0.03)	0.07 (0.00)	0.17 (0.00)	0.41 (0.13)	2.90 (2.47)

NOTE: Some percentages do not sum to 100 due to missing data.

[a]Nut consumption in sex-specific quintiles based on distribution of controls for each sex: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day).

[b]Values are shown in mean (SD).

[c]Never smokers of any tobacco products (cigarettes, pipes, cigars).

[d]Current smokers and former smokers.

Table 2. Selected baseline characteristics of the AARP Diet and Health Study by cohort and lung cancer cases of nut consumption

			Quintile of total nut consumption (frequency/d) in cohort[a]				
			1	2	3	4	5
Characteristics	**Cohort (*n* = 495,785)**	**Cases (*n* = 18,533)**	**(*n* = 51,217)**	**(*n* = 122,447)**	**(*n* = 147,636)**	**(*n* = 87,389)**	**(*n* = 87,096)**
Sex, *n* (%)							
Male	295,953 (59.69)	11,717 (63.22)	28,459 (55.57)	66,745 (54.51)	87,902 (59.54)	55,280 (63.26)	57,567 (66.10)
Age,[b] y	62.02 (5.37)	63.58 (4.86)	62.72 (5.30)	61.90 (5.40)	61.74 (5.38)	61.89 (5.36)	62.37 (5.31)
BMI,[b] kg/m^2	27.11 (5.08)	26.57 (4.87)	27.18 (5.64)	27.37 (5.33)	27.30 (5.03)	27.10 (4.81)	26.41 (4.64)
Education, *n* (%)							
<High school	27,854 (5.84)	1,830 (9.87)	5,446 (10.63)	8,543 (6.98)	8,098 (5.49)	4,022 (4.60)	3,575 (4.10)
Completed high school	145,770 (29.40)	6,253 (33.74)	18,175 (35.49)	40,701 (33.24)	43,196 (29.25)	23,156 (26.50)	20,542 (23.58)
Post-high school training	110,262 (23.10)	4,663 (25.16)	10,897 (21.28)	29,370 (23.99)	34,658 (23.48)	20,296 (23.22)	19,704 (22.62)
Completed college	185,751 (38.92)	5,140 (27.73)	14,106 (27.54)	40,098 (32.75)	57,775 (39.13)	37,726 (43.17)	41,186 (47.29)
Smoking status, *n* (%)							
Never[c]	173,887 (35.07)	1,196 (6.45)	16,489 (32.19)	41,765 (34.11)	52,250 (35.39)	31,112 (35.60)	32,271 (37.05)
Former	243,703 (49.15)	9,607 (51.84)	24,228 (47.30)	60,458 (49.37)	72,592 (49.17)	43,404 (49.67)	43,021 (49.39)
Current	59,353 (11.97)	7,043 (38.00)	7,603 (14.84)	15,801 (12.90)	17,391 (11.78)	9,712 (11.11)	8,846 (10.16)
Cigarettes smoked per day, *n* (%)[d]							
1–10	75,002 (15.72)	2,081 (11.23)	7,659 (14.95)	19,164 (15.65)	22,928 (15.53)	13,569 (15.53)	13,763 (15.80)
11–20	93,390 (19.57)	5,378 (29.02)	10,151 (19.82)	25,265 (20.63)	29,386 (19.90)	17,114 (19.58)	16,852 (19.35)
21–40	98,133 (19.79)	6,972 (37.62)	10,539 (20.58)	24,579 (20.07)	29,119 (19.72)	17,418 (19.93)	16,478 (18.92)
>41	29,072 (5.86)	2,219 (11.97)	3,482 (6.79)	7,251 (5.92)	8,550 (5.79)	5,015 (5.74)	4,774 (5.48)
Years since quitting smoking, *n* (%)[e]							
≥10	180,197 (36.35)	5,117 (27.61)	16,342 (31.91)	43,254 (35.32)	54,231 (36.73)	32,907 (37.66)	33,463 (38.42)
5–9	34,584 (6.98)	2,139 (11.54)	4,019 (7.85)	9,465 (7.73)	10,089 (6.83)	5,725 (6.55)	5,286 (6.07)
1–4	20,074 (4.05)	1,576 (8.50)	2,707 (5.29)	5,478 (4.47)	5,697 (3.86)	3,258 (3.73)	2,934 (3.37)
0–1	8,848 (1.78)	775 (4.18)	1,160 (2.26)	2,261 (1.85)	2,575 (1.74)	1,514 (1.73)	1,338 (1.54)
Lifetime alcohol,[c] g/wk	12.67 (34.14)	18.64 (47.16)	10.06 (34.36)	10.79 (32.26)	12.34 (33.26)	13.89 (34.15)	16.19 (37.53)
Energy intake,[b] cal/wk	1,851.81 (840.20)	1,931.67 (916.68)	1,719.07 (865.53)	1,642.54 (754.49)	1,792.58 (786.51)	1,995.83 (832.03)	2,179.96 (910.00)
Total red meat,[b] g/wk	66.28 (57.75)	75.57 (62.90)	56.95 (58.50)	56.61 (51.37)	66.16 (54.87)	76.16 (60.30)	75.64 (64.38)
Total processed meat,[b] g/wk	20.00 (23.00)	23.14 (24.94)	19.20 (25.57)	18.06 (22.31)	19.59 (22.13)	21.89 (22.63)	22.03 (23.88)
Total fruits,[b] g/wk	371.26 (343.66)	311.24 (308.95)	372.49 (384.26)	345.66 (333.00)	356.55 (328.32)	383.39 (334.45)	419.31 (361.77)
Total vegetables,[b] g/wk	300.49 (209.25)	288.02 (204.05)	293.01 (243.81)	269.93 (192.24)	288.67 (195.17)	320.04 (201.94)	248.29 (229.34)
Total nut consumption,[b] g/wk	20.14 (59.44)	19.64 (61.59)	0.00 (0.00)	1.75 (1.82)	7.08 (6.60)	17.80 (16.15)	82.34 (122.05)

NOTE: Some percentages do not sum to 100 due to missing data.

[a]Nut consumption in sex-specific quintiles based on distribution of controls: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[b]Values are shown in mean (SD).

[c]Never smokers of any tobacco products (cigarettes, pipes, cigars).

[d]Current smokers and former smokers.

[e]Former smokers.

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Table 3. ORs and HRs (95% CIs) for lung cancer and nut consumption in EAGLE and AARP, by smoking status

	Quintile of total nut consumption (frequency/d) in EAGLE						Quintile of total nut consumption (frequency/d) in AARP					
Nut consumption[a]	1	2	3	4	5	P_{trend}	1	2	3	4	5	P_{trend}
All participants												
Cases/Controls	821/748	121/122	217/291	311/397	251/360		2,484/48,733	4,834/117,613	5,270/142,366	3,053/84,336	2,892/84,204	
Crude	1.00	0.90	0.68	0.71	0.64	*<0.001*	1.00	0.78	0.70	0.69	0.65	*<0.001*
(95% CI)	(reference)	(0.69–1.18)	(0.56–0.83)	(0.60–0.85)	(0.53–0.77)		(reference)	(0.74–0.82)	(0.67–0.73)	(0.65–0.72)	(0.62–0.69)	
Multivariable[b]	1.00	0.92)	0.76	0.90	0.74	*0.017*	1.00	0.93	0.89	0.89	0.86	*<0.001*
(95% CI)	(reference)	(0.58–1.45)	(0.59–0.99)	(0.71–1.14)	(0.57–0.95)		(reference)	(0.89–0.98)	(0.85–0.94)	(0.84–0.94)	(0.81–0.91)	
Current smokers												
Cases/Controls	423/190	58/34	107/73	138/93	120/83		992/6,611	1,855/13,946	2,033/15,358	1,141/8,571	1,022/7,824	
Crude	1.00	0.77	0.66	0.67	0.65	*0.010*	1.00	0.85	0.84	0.84	0.83	*<0.001*
(95% CI)	(reference)	(0.49–1.21)	(0.47–0.93)	(0.49–0.91)	(0.47–0.90)		(reference)	(0.79–0.92)	(0.78–0.90)	(0.78–0.92)	(0.76–0.90)	
Multivariable[b]	1.00	0.91	0.74	0.70	0.68	*0.050*	1.00	0.94	0.93	0.92	0.88	*0.004*
(95% CI)	(reference)	(0.50–1.65)	(0.50–1.10)	(0.49–1.00)	(0.47–1.00)		(reference)	(0.87–1.02)	(0.86–1.01)	(0.85–1.01)	(0.80–0.96)	
Former smokers												
Cases/Controls	367/344	33/29	97/128	150/171	114/166		1,233/22,995	2,560/57,898	2,661/69,931	1,583/41,821	1,570/41,451	
Crude	1.00	1.07	0.71	0.82	0.64	*0.002*	1.00	0.79	0.68	0.68	0.68	*<0.001*
(95% CI)	(reference)	(0.63–1.79)	(0.53–0.96)	(0.63–1.07)	(0.49–0.85)		(reference)	(0.74–0.85)	(0.64–0.73)	(0.63–0.73)	(0.63–0.73)	
Multivariable[b]	1.00	0.93	0.78	1.11	0.81	*0.213*	1.00	0.93	0.85	0.86	0.85	*<0.001*
(95% CI)	(reference)	(0.45–1.91)	(0.55–1.11)	(0.81–1.52)	(0.57–1.13)		(reference)	(0.87–1.00)	(0.80–0.92)	(0.79–0.92)	(0.79–0.92)	
Never smokers												
Cases/Controls	29/212	30/59	13/90	21/132	17/111		143/16,346	262/41,503	363/51,887	212/30,900	216/32,055	
Crude	1.00	3.72	1.06	1.16	1.12	*0.730*	1.00	0.70	0.78	0.77	0.76	*0.010*
(95% CI)	(reference)	(2.07–6.68)	(0.52–2.12)	(0.64–2.12)	(0.59–2.13)		(reference)	(0.57–0.86)	(0.64–0.94)	(0.62–0.95)	(0.61–0.93)	
Multivariable[b]	1.00	1.43	1.10	1.09	0.91	*0.796*	1.00	0.75	0.84	0.80	0.77	*0.020*
(95% CI)	(reference)	(0.71–2.89)	(0.51–2.36)	(0.56–2.11)	(0.43–1.90)		(reference)	(0.61–0.92)	(0.69–1.02)	(0.65–1.00)	(0.62–0.96)	

NOTE: Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

[a]Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); nut consumption in sex-specific quintiles based on distribution of controls for AARP: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[b]Adjusted for age, sex, area of residence, education, BMI, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never smokers), years since last cigarette smoked (continuous, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; adjusted for age, sex, education, BMI, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never smokers), years since last cigarette smoked (categorical, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.

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Table 4. ORs and HRs (95% CIs) for lung cancer and nut consumption in EAGLE and AARP, by smoking intensity in ever smokers

	Quintile of total nut consumption (frequency/day) in EAGLE						Quintile of total nut consumption (frequency/day) in AARP					
Nut consumption[a]	1	2	3	4	5	P_{trend}	1	2	3	4	5	P_{trend}
Ever smokers												
Smoked 1–20 cigarettes/d												
Cases/Controls	517/422	72/61	140/166	188/222	158/211		1,026/16.784	2,011/42,418	2,086/50,228	1,211/29,472	1,125/29,490	
Crude	1.00	0.96	0.69	0.69	0.61	*<0.001*	1.00	0.75	0.65	0.65	0.61	*<0.001*
(95% CI)	(reference)	(0.67–1.39)	(0.53–0.89)	(0.55–0.87)	(0.48–0.78)		(reference)	(0.69–0.81)	(0.61–0.70)	(0.60–0.71)	(0.56–0.66)	
Multivariable[b]	1.00	0.74	0.77	0.78	0.67	*0.008*	1.00	0.92	0.85	0.86	0.84	*<0.001*
(95% CI)	(reference)	(0.45–1.22)	(0.57–1.04)	(0.60–1.03)	(0.50–0.90)		(reference)	(0.85–0.99)	(0.79–0.92)	(0.79–0.93)	(0.77–0.91)	
Smoked ≥21 cigarettes/d												
Cases/Controls	273/112	19/2	64/35	100/43	76/38		1,199/12,822	2,404/29,426	2,608/35,061	1,513/20,920	1,467/19,785	
Crude	1.00	3.90	0.75	0.95	0.82	*0.386*	1.00	0.84	0.76	0.74	0.76	*<0.001*
(95% CI)	(reference)	(0.89–17.01)	(0.47–1.20)	(0.63–1.45)	(0.52–1.28)		(reference)	(0.78–0.90)	(0.71–0.81)	(0.69–0.80)	(0.70–0.82)	
Multivariable[b]	1.00	3.72	0.70	1.13	0.91	*0.723*	1.00	0.96	0.93	0.91	0.89	*0.003*
(95% CI)	(reference)	(0.65–21.13)	(0.41–1.19)	(0.69–1.84)	(0.55–1.52)		(reference)	(0.89–1.03)	(0.86–0.99)	(0.84–0.98)	(0.82–0.97)	
Current smokers												
Smoked 1–20 cigarettes/d												
Cases/Controls	273/153	43/32	70/61	77/78	74/72		587/4,343	1,039/9,300	1,092/10,181	616/5,649	535/5,003	
Crude	1.00	0.79	0.67	0.61	0.62	*0.012*	1.00	0.80	0.76	0.77	0.76	*<0.001*
(95% CI)	(reference)	(0.48–1.30)	(0.46–1.00)	(0.42–0.87)	(0.42–0.90)		(reference)	(0.72–0.88)	(0.69–0.84)	(0.69–0.86)	(0.68–0.86)	
Multivariable[b]	1.00	0.81	0.80	0.61	0.61	*0.030*	1.00	0.90	0.86	0.85	0.83	*0.003*
(95% CI)	(reference)	(0.42–1.58)	(0.51–1.25)	(0.40–0.93)	(0.39–0.95)		(reference)	(0.81–1.00)	0.77–0.95)	(0.76–0.96)	(0.74–0.94)	
Smoked ≥21 cigarettes/d												
Cases/Controls	148/35	13/2	34/12	54/15	41/11		405/2,268	816/4,646	941/5,177	525/2,922	487/2,821	
Crude	1.00	1.54	0.67	0.85	0.88	*0.745*	1.00	0.93	0.94	0.95	0.90	*0.117*
(95% CI)	(reference)	(0.33–7.12)	(0.32–1.42)	(0.43–1.68)	(0.41–1.89)		(reference)	(0.82–1.04)	(0.83–1.05)	(0.84–1.08)	(0.79–1.03)	
Multivariable[b]	1.00	1.74	0.59	0.79	0.94	*0.897*	1.00	1.01	1.05	1.04	0.94	*0.401*
(95% CI)	(reference)	(0.23–12.96)	(0.26–1.39)	(0.36–1.72)	(0.40–2.24)		(reference)	(0.90–1.14)	(0.93–1.18)	(0.91–1.18)	(0.82–1.08)	
Former smokers												
Smoked 1–20 cigarettes/d												
Cases/Controls	242/267	27/29	67/105	104/143	79/139		439/12,441	972/33,118	994/40,047	595/23,823	590/24,487	
Crude	1.00	1.03	0.70	0.80	0.63	*0.005*	1.00	0.80	0.67	0.68	0.66	*<0.001*
(95% CI)	(reference)	(0.59–1.78)	(0.49–1.00)	(0.59–1.09)	(0.45–0.87)		(reference)	(0.72–0.90)	(0.60–0.75)	(0.60–0.77)	(0.59–0.75)	
Multivariable[b]	1.00	0.72	0.74	0.99	0.75	*0.162*	1.00	0.94	0.84	0.86	0.84	*0.008*
(95% CI)	(reference)	(0.33–1.54)	(0.48–1.12)	(0.68–1.43)	(0.50–1.12)		(reference)	(0.84–1.06)	(0.74–0.94)	(0.76–0.98)	(0.74–0.96)	
Smoked ≥21 cigarettes/d												
Cases/Controls	125/77	6/0	30/23	46/28	35/27		794/10,554	1,588/24,780	1,667/29,884	988/17,998	980/16,964	
Crude	1.00	NA	0.80	1.01	0.80	*0.445*	1.00	0.82	0.71	0.70	0.73	*<0.001*
(95% CI)	(reference)		(0.44–1.48)	(0.58–1.75)	(0.45–1.42)		(reference)	(0.76–0.90)	(0.65–0.77)	(0.64–0.77)	(0.67–0.81)	
Multivariable[b]	1.00	NA	0.79	1.46	0.95	*0.882*	1.00	0.93	0.86	0.85	0.86	*0.002*
(95% CI)	(reference)		(0.39–1.60)	(0.75–2.85)	(0.48–1.87)		(reference)	(0.85–1.01)	(0.79–0.94)	(0.77–0.94)	(0.78–0.95)	

NOTE: Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

Abbreviation: NA, not applicable.

[a]Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); nut consumption in sex-specific quintiles based on distribution of controls for AARP: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[b]Adjusted for age, sex, area of residence, education, BMI, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never smokers), years since last cigarette smoked (continuous, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; adjusted for age, sex, education, BMI, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never smokers), years since last cigarette smoked (categorical, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.

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Table 5. ORs and HRs (95% CIs) for lung cancer and nut consumption in EAGLE and AARP, by histologic subtypes

	Quintile of total nut consumption (frequency/d) in EAGLE						Quintile of total nut consumption (frequency/d) in AARP					
Nut consumption[a]	**1**	**2**	**3**	**4**	**5**	***p*-trend**	**1**	**2**	**3**	**4**	**5**	***p*-trend**
Adenocarcinoma												
Cases/controls	316/748	60/122	87/291	129/397	110/360		760/49,023	1,703/118,080	1,823/142,904	1,111/84,631	1,022/84,503	
Crude	1.00	1.16	0.71	0.77	0.72	*0.011*	1.00	0.89	0.79	0.81	0.75	*<0.001*
(95% CI)	(reference)	(0.83–1.63)	(0.54–0.93)	(0.61–0.98)	(0.56–0.93)		reference	(0.82–0.97)	(0.72–0.85)	(0.74–0.89)	(0.68–0.82)	
Multivariable[b]	1.00	0.89	0.71	0.87	0.79	*0.136*	1.00	1.02	0.95	0.99	0.93	*0.151*
(95% CI)	(reference)	(0.52–1.55)	(0.51–1.00)	(0.65–1.18)	(0.58–1.08)		reference	(0.93–1.11)	(0.87–1.04)	(0.90–1.09)	(0.85–1.03)	
Squamous cell carcinoma												
Cases/Controls	228/748	11/122	61/291	83/397	65/360		462/49,023	734/118,080	927/142,904	505/84,631	497/84,503	
Crude	1.00	0.30	0.69	0.69	0.59	*0.001*	1.00	0.63	0.66	0.61	0.60	*<0.001*
(95% CI)	(reference)	(0.16–0.56)	(0.50–0.94)	(0.52–0.91)	(0.44–0.80)		(reference)	(0.57–0.71)	(0.59–0.73)	(0.54–0.69)	(0.53–0.68)	
Multivariable[b]	1.00	1.08	0.81	0.96	0.74	*0.125*	1.00	0.79	0.87	0.81	0.83	*0.004*
(95% CI)	(reference)	(0.44–2.68)	(0.54–1.20)	(0.67–1.38)	(0.50–1.09)		(reference)	(0.70–0.89)	(0.78–0.98)	(0.71–0.93)	(0.72–0.94)	
Small cell carcinoma												
Cases/Controls	87/748	12/122	21/291	31/397	26/360		310/49,023	578/118,080	625/142,904	344/84,631	284/84,503	
Crude	1.00	0.85	0.62	0.67	0.62	*0.040*	1.00	0.75	0.66	0.62	0.51	*<0.001*
(95% CI)	(reference)	(0.45–1.59)	(0.38–1.02)	(0.44–1.03)	(0.39–0.98)		(reference)	(0.65–0.86)	(0.58–0.76)	(0.53–0.72)	(0.44–0.60)	
Multivariable[b]	1.00	1.41	0.91	0.89	0.96	*0.887*	1.00	0.95	0.92	0.88	0.76	*0.002*
(95% CI)	(reference)	(0.56–3.58)	(0.52–1.59)	(0.53–1.49)	(0.56–1.65)		(reference)	(0.83–1.10)	(0.80–1.06)	(0.75–1.03)	(0.65–0.90)	

NOTE: Unless otherwise indicated, data are reported as OR (95% CI) for EAGLE and HR (95% CI) for AARP.

[a]Nut consumption in sex-specific quintiles based on distribution of controls for each sex for EAGLE: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 3 times a month), and quintile 5 (once a week up to 5 times a week, and once a day up to 2 or more times a day); nut consumption in sex-specific quintiles based on distribution of controls for AARP: quintile 1 (nonconsumers), quintile 2 (1–6 times/y), quintile 3 (7–11 times/y), quintile 4 (once a month up to 2–3 times a month), and quintile 5 (once a week up to 6 times a week, and once a day up to 2 or more times a day).

[b]Adjusted for age, sex, area of residence, education, BMI, cigarette smoking status, cumulative pack-years of cigarette smoking (continuous, 0 for never smokers), years since last cigarette smoked (continuous, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol in EAGLE; adjusted for age, sex, education, BMI, energy intake, cigarette smoking status, cigarette smoking dose (categorical, 0 for never smokers), years since last cigarette smoked (categorical, 0 for never smokers), and intakes of red and processed meat, fruits, vegetables, and alcohol for AARP.

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intake. More prospective studies are needed to confirm this finding in light smokers.

Our finding of an inverse association for nut intake for lung cancer risk might be explained by the bioactive constituents found in nuts. For example, tree nut extracts were found to be protective against oxidative damage (28), although results from animal studies and human clinical trials have shown mixed results (29, 30). Studies on healthy male smokers consuming a diet enriched with powdered almonds showed a significant decrease in oxidative DNA damage and lipid peroxidation (31, 32). This suggests nut consumption may decrease oxidative stress mediated by tobacco smoking (31).

Several other bioactive constituents of nuts may contribute to the associations observed here. Most nuts are high in n-3 polyunsaturated fatty acids (PUFA) and monounsaturated fatty acid (mainly oleic acid, which is more resistant to oxidation than PUFAs) known to have beneficial anti-inflammatory properties (4). Recent studies have further linked inflammation to cellular mechanisms and to genomic pathways involved in carcinogenesis (33) with some epidemiologic evidence of a protective effect by dietary n-3 PUFAs (derived from fish/fish oil) on lung carcinogenesis (34, 35). Nuts also provide a rich source of phytochemicals (polyphenols, phytoestrogens, and flavonoids), which are potent scavengers that may reduce oxidative stress and inhibit neutrophils respiratory burst to prevent carcinogenesis (36). Previous studies have looked at polyphenols in relation to lung cancer risk in consumption of tea (37), and olive oil (14), and found mixed results. Higher intake of dietary flavonoids was associated with significantly reduced risk (17%–76%) of lung cancer (38, 39), particularly among smokers (38), although some studies did not find an association (40, 41). Antitumor activities by other components naturally found in nuts, such as inositol (42), magnesium (43), and selenium (44), have also been evaluated, but findings are inconsistent. Emerging evidence suggests that phytochemicals and antioxidants may act synergistically to decrease oxidative damage (45).

Our study has several strengths, as it includes results from both a large population-based retrospective case–control study and a well-characterized prospective cohort. As the EAGLE study is more prone to bias due to its case-control study design, the similar results in a prospective cohort study validates and strengthen the inverse associations between nut consumption and lung cancer risk. It is the largest study to date, permitting analyses that were stratified by histologic subtypes, smoking status, and smoking intensity. Sensitivity analyses using lag showed persisted protective associations that further buttress the benefits observed for nut consumption and lung cancer.

Our study also has some limitations such as the possibility of recall bias due to the retrospective nature inherent in case–control study design in EAGLE. However, it is unlikely that our participants would consider nut eating to be a healthy choice, as the study was conducted in 2003 to 2005, when the potential health benefits of nut consumption were not widely hypothesized. Moreover, it is reassuring that we observed a similar association in our large prospective cohort. As the FFQ queried about nut consumption at a single point, we lack data on the cumulative exposure of nut consumption. Furthermore, information on intake of individual type of nuts was not available for analyses. Nevertheless, studies that looked at differences between specific nuts (46, 47) suggested that consumption of a mixed type of nuts is important for a robust level of antioxidants. In addition, no validation study has been conducted to investigate the FFQ's ability to reflect nuts intake, and thus, this precluded the possibility to estimate measurement error. Nut consumption may be associated with aspects of a healthy lifestyle, such as lower exposures to tobacco and alcohol, lower BMI, lower intakes of red and processed meat, higher intakes of fruits and vegetables, and higher physical activity, but we observed no correlations between these factors and nut consumption. We adjusted for all important potential confounders in our analyses; nevertheless, we cannot exclude the possibility of residual confounding from smoking and dietary intake or additional unmeasured confounding that may affect our results. It is possible that changing smoking status could have a more profound effect, such as that current smokers may quit smoking during follow-up. Although we are unable to examine changing smoking status during follow-up, results from several lag analyses [by 5 years (for all smoking status and histologic subtypes) and 10 years (for current and former smokers, and for squamous cell and small cell carcinoma)] in AARP showed that the inverse associations associated with higher nut consumption and lung cancer risk remained consistent (Supplementary Tables S5 and S6). In particular, the results for small cell carcinoma were persistent across lag-analyses, suggesting that nut consumption may be more protective in this group. Because small cell carcinoma is more associated with smoking-related lung cancer, this observation may provide further evidence to support our hypothesis that smokers may benefit from higher nut consumption.

Altogether, the findings of this study show that nut consumption is inversely related to all of the major histologic subtypes of lung cancer. The results of this present study add to the emerging body of literature that investigates the potential protective effect of nut consumption on cancer risk and mortality, which may lead to evidence-based public health recommendations in the future. Further studies are needed to confirm these results in additional populations and to examine specific types of nuts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the DOH. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

Authors' Contributions

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