# Diet and Amyotrophic Lateral Sclerosis

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**Background:** Several dietary factors have been associated with risk of amyotrophic lateral sclerosis (ALS) in case-control studies, but no prospective studies have investigated diet and ALS.

**Methods:** We prospectively assessed the association of selected foods and beverages with ALS mortality among participants of the Cancer Prevention Study II, a cohort of over 1 million men and women enrolled in 1982. Habitual diet was assessed with a 44-item food frequency questionnaire. Participant follow-up was conducted from 1989 through 2002 for ALS mortality.

**Results:** During the follow-up period, 862 cohort participants died of ALS. The strongest finding was an inverse association between chicken consumption and risk of ALS (*P* for trend = 0.0006). We also observed an increased risk of ALS among study participants with a high consumption of brown rice/whole wheat/barley (*P* for trend = 0.006) and decaffeinated coffee (*P* for trend = 0.01), and a decreased risk of ALS for high consumption of tea (*P* for trend = 0.02) and French fries (*P* for trend = 0.02); however, none of these latter associations remained significant after adjusting for multiple comparisons.

**Conclusions:** Overall, these results do not provide convincing evidence that the investigated food items are related to ALS mortality. The association observed between chicken consumption and ALS mortality should be assessed in other studies.

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The majority of amyotrophic lateral sclerosis (ALS) cases are sporadic, with familial cases accounting for only about 10% of all ALS cases.[1] Occupational exposure to neurotoxins,[1,2] cigarette smoking,[1,3,4] and dietary factors[5] are possible risk factors for ALS, but none of these is well established.[6] Comprehensive case-control studies of diet and ALS have reported several associations with diet, including decreased risk associated with dietary intake of fiber,[5] magnesium,[7] and lycopene,[7] polyunsaturated fatty acids,[8] and vitamin E,[8] and an increase in risk associated with dietary intake of fat and glutamate.[5] The limitations of case-control studies in assessing relationships between diet and chronic disease are, however, well known.[9] To date, no case-control studies have looked at foods or food groups; only individual nutrients have been studied in relation to ALS. Studies of nutrients are easiest to interpret biologically. Studies of foods and food groups, such as this one, however, are more practical because they enable exploratory analyses of disease for which few specific dietary hypotheses have been developed.[9]

We examined prospectively the relation between diet and risk of ALS among participants in the Cancer Prevention Study II cohort, comprising nearly 1.2 million men and women. We have previously reported an inverse association between use of vitamin E supplements and ALS mortality among participants of this cohort.[10] Here we present the results of a comprehensive analysis of foods and beverages.

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## METHODS

### Study Population

The Cancer Prevention Study II is a prospective study that began in 1982 when 77,000 American Cancer Society volunteers recruited 508,334 men and 676,288 women from 50 states, the District of Columbia, and Puerto Rico.[11] Eligible households had to have at least 1 member over the age of 45 years; all members over the age of 30 were invited to participate. Participants completed a 4-page questionnaire on diet, smoking history, alcohol intake, physical activity, height, weight, medical history, and other factors.

Participants were not given an opportunity specifically to report a history of ALS at baseline. Consequently, we excluded 65,836 participants who reported "any other serious disease" in their baseline 1982 questionnaire because they may have had ALS at baseline. We also excluded from food and food-group analyses those individuals who left all of 28 food questions blank or indicated consuming fewer than 5 of the 28 items listed on the questionnaire. From the beverage analysis, we excluded those who left the entire beverage section blank and those who reported more than 10 servings of 2 or more beverages per day. Otherwise, blank values for a beverage were considered as zero consumption. We intended to exclude all participants who left the entire fried foods section blank, but after all other exclusions, there were no such participants in the analysis.

## Case Ascertainment

The National Death Index was used to determine the vital status of the study participants through December 31, 2002.[12] We were able to obtain death certificates or codes for the cause of death for over 98% of known deaths. The International Classification of Diseases, 9th[13] or 10th[14] revision (ICD-9 or ICD-10), as appropriate, was used to code the underlying and contributing cause of death.[15] We excluded follow-up time before January 1, 1989 because deaths from ALS were not coded separately before that date.[3]

For follow-up from January 1989 through the end of 1998, we considered as eligible cases all individuals who had ICD-9 code 335.20 (motor neuron disease) listed as either the underlying or contributing cause of death. For this segment of follow-up, we had 183 death certificates coded 335.2 available to us for review (108 for men and 75 for women); 164 (90%) were specified as ALS (ICD-9 code 335.20); 13 (7.1%) were specified only as motor neuron disease (ICD-9 code 335.2); 3 (1.6%) were illegible; 2 (1.1%) were specified as bulbar palsy; and 1 (0.6%), as progressive muscular dystrophy. Thus, only a small number of death certificates with ICD-9 code 335.2 did not have a diagnosis of ALS. Likewise, for follow-up from January 1999 through December 2002, ICD-10 code G12.2 (motor neuron disease) was used to identify the cases.

## Assessment of Exposure and Other Covariates

The dietary questionnaire used in this study has been described previously.[16] Participants were asked to report how many days per week they consumed each of the 34 foods listed on the questionnaire. For the present study, foods were grouped in a manner analogous to that used in prior work on this cohort.[16] Food groups considered in the analyses included vegetables only, citrus fruits/juices, vegetables and citrus fruits, high fiber grains, low fiber grains, fatty meats, dairy, other fats, and fried foods. To construct food groups, aggregate measures were obtained by summing the contributions from the individual foods, treating all foods equivalently. Participants were also asked how many times per day they consumed 10 beverages at the time of the study and in the past. Therefore, in addition to considering beverage consumption at the time of the study, we also estimated the relative risk of ALS comparing individuals with consistently high (more then 1 serving/d both in the past and at the time of the study) versus those with consistently low (less then 1 serving/d both in the past and at the time of the study) consumption of individual beverages. Components of each food group and the beverages are listed in eTable 1 (available with the online version of this article).

Participants were instructed to write "1/2" if they consumed foods less than once a week, but at least twice a month, and if they consumed beverages less than once a day, but at least 3 times a week. Unless all items were left blank, we assumed that blanks in the questionnaire represented nonconsumption, as there were no instructions to include a zero for nonconsumption.

## Statistical Analysis

Follow-up of the study participants lasted from January 1, 1989 to the date of death or December 31, 2002, whichever came first.

We analyzed foods individually as well as grouped in the categories described above. Within strata of individual foods and beverages, we combined data from men and women, adjusting for sex. To examine possible differences in results between men and women, we repeated all analyses among men and women separately and verified that there were no significant differences (at the 95% confidence level) between the combined and sex-specific results. For food groups, to avoid an uneven distribution by sex across quintiles, we first created sex-specific consumption quintiles. All food group results were then pooled across sex. We performed tests of heterogeneity for the *P* for trend for each food group. With the exception of pooling, which was done using Stata 9.0 (StataCorp, College Station, TX), SAS version 8.2 (SAS Institute, Cary, NC) was used for all analyses.

For each individual food, we created categories of consumption based on distribution of intakes, collapsing categories until no group had fewer than 10 cases. We calculated relative risks (RRs) of ALS, adjusted for age (in 5-year age groups), by dividing ALS mortality rates among study participants in each consumption category by the corresponding mortality rate in the reference category (lowest consumption category), using Mantel-Haenszel weights. We estimated multivariate RRs and 95% confidence intervals (CIs) using Cox proportional hazards regression, adjusted for age, smoking (never, past, current),[3] and vitamin E[10] [categorized into nonusers, occasional users ($<15$ times per month), regular users ($\geq 15$ times per month) for less than 10 years, regular users for 10 years or longer, and missing or incomplete data]. The Cox models were stratified by age in single years to obtain a better adjustment.

We also considered the possibility that body mass index (BMI) or education could confound the diet-ALS association. Neither of these variables, however, was related to ALS mortality. In men, the RR for BMI comparing persons with BMI ranging from 24.7 to 27.8 kg/m$^2$and from 27.8 to 31.3 kg/m$^2$ to those with a reference BMI (20.7–24.7 kg/m$^2$) was 0.97 (95% CI = 0.79–1.20) and 0.99 (0.76–1.29), respectively. In women, these relative risks were 0.78 (0.60–1.04) and 0.95 (0.68–1.32) for the BMI categories above. Likewise, for education, the RR comparing those with some college or more education to a reference category comprising those with high school diploma or less education was, in men, 1.08 (0.86–1.36) and, in women, 1.13 (0.89–1.45). The associations reported in this manuscript did not materially change when BMI or education were added to the models. Thus, we did not include BMI or education in our final models.

After exclusions, our dietary analyses included 891,920 participants (383,683 men and 508,237 women); 96,475 participants were excluded because they left all of 28 food questions blank or indicated consuming less than 5 of the 28 items listed on the questionnaire. Our beverage analysis included 956,918 participants; 28,201 respondents were excluded because they left the entire beverage section blank; and 3276 participants were excluded for having reported consumption of more than 10 servings per day of 2 or more beverages. This latter exclusion was because we thought it unlikely that a person would consume more than 10 servings per day of one beverage. We were concerned that respondents may have misinterpreted our beverage question and thus reported beverage consumption in days per week, as was the timeframe for foods, whereas for beverages the question on beverages asked about times per day.

In analysis of beverages, we partitioned beverage consumption into the following categories: 0, <1, 1, 2, 3, and 4 or more cups/d. For beverages, the tests for trend were based on these 6 categories.

Because of the exploratory nature of the study and the multiple analyses conducted, significant associations could easily arise by chance. To assist in the interpretation of the data, in addition to the unadjusted $P$ values (defined as significant if <0.05), we have also reported whether associations were significant after Bonferroni correction (based on a total of 44 comparisons, and thus significant if $P < 0.001$).

## RESULTS

The mean age of study participants in 1989 was 63.5 years for men and 63.0 years for women. During the follow-up period, we documented 862 ALS deaths among participants included in the dietary analyses (474 deaths among men and 388 deaths among women).

As expected, consumption of healthy foods such as citrus fruits and vegetables and whole fiber grains was associated with a higher education and a lower prevalence of smoking. More than 75% of men and 68% of women in the top quintile of fruit and vegetable consumption had completed college as compared with only 48% of men and 40% of women in the lowest consumption quintile. Only 14% of men and 16% of women in the highest fruit and vegetable consumption quintile were current smokers as compared with 28% of men and 25% of women in the bottom quintile. Opposite associations were found for fried foods and fatty meats. For example, 27% of men and 21% of women in the highest quintile of fried food consumption were smokers as compared with only 13% of men and 18% of women in the bottom quintile. Major changes in diet in the past 10 years were reported more often by individuals in the top quintile of consumption of healthy foods (40% of men and 50% of women in the highest vegetable consumption quintile reported such changes as compared with only 23% of men and 31% of women in the bottom quintile), and by those in the bottom quintile of fried foods (49% of men and 53% of women) and fatty meats (42% of men and 51% of women), a result consistent with improvement in diet over time among participants of this cohort. These results are presented in eTable 2.

Overall, intakes of dairy, dairy and eggs, fatty meats, low fat meats, fried foods, high fiber grains, low fiber grains, other fats, vegetables, and citrus fruit were not associated with risk of ALS (Table 1). The tests for heterogeneity by sex were not significant for any of the food groups; therefore, we also present results combining men and women.

Results from our analysis of individual foods are presented in Table 2. High intake of brown rice/whole wheat/barley was associated with an increased risk of ALS ($P$ for trend = 0.006), whereas high consumption of chicken ($P$ for trend = 0.0006) and French fries ($P$ for trend = 0.02) was associated with a decreased risk. Only the association with chicken remained significant after adjusting for multiple comparisons.

Our beverage analysis was based on 932 ALS cases. The number of cases in the beverage analysis was different from that in the food analysis because of nonoverlapping exclusions in the 2 analyses, as described above. Among beverages (Table 3), high consumption of tea was associated with a decreased risk of ALS ($P$ for trend = 0.02). In contrast, consumption of decaffeinated coffee was associated with an increased risk of ALS ($P$ for trend = 0.01).

In combined analyses of past and current beverage consumption, individuals who reported consistently high wine consumption had a higher risk of ALS than those reporting a consistently low consumption (RR = 2.06; 95% CI = 1.20–3.45); no similar evidence for an association, however, was found for consumption of liquor (1.30; 0.85–1.98). None of the nonalcoholic beverages was related to ALS mortality in these analyses.

Because the accuracy of ALS diagnosis may decline with age, we repeated the analyses censoring participants who were more than 65 years old in 1989. For foods and food groups, the analysis included 514,675 subjects, of whom 393 were ALS cases. The main change in results after the exclusion of these older subjects was the disappearance of the positive trend associated in the overall cohort with the consumption of brown rice/whole wheat/barley ($P$ for trend = 0.31) and French fries ($P$ for trend = 0.54). In contrast, the

**TABLE 1.** Relative Risk of ALS Death According to Consumption of Various Food Groups by Quantities

| | Men | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Foods | Quantile Range (times/wk) | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | Quantile Rangey (times/wk) | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | Pooled RR (95%CI) |
| Dairy | | | | | | | | | | | |
| Q1† | 0–2.50 | 75,654 | 81 | 895,550 | 1.00 | 0–2.0 | 100,175 | 71 | 1,261,347 | 1.00 | 1.00 |
| Q2 | 2.75–5.25 | 73,477 | 93 | 901,039 | 1.17 (0.87–1.58) | 2.25–4.75 | 102,852 | 78 | 1,339,072 | 1.11 (0.80–1.53) | 1.14 (0.92–1.42) |
| Q3 | 5.50–8.75 | 73,371 | 95 | 902,604 | 1.20 (0.89–1.62) | 5.0–7.25 | 95,402 | 71 | 1,249,133 | 1.10 (0.79–1.53) | 1.15 (0.92–1.44) |
| Q4 | 9.0–14.75 | 83,593 | 104 | 1,030,563 | 1.18 (0.88–1.57) | 7.50–11.75 | 105,227 | 89 | 1,368,795 | 1.26 (0.92–1.73) | 1.22 (0.98–1.51) |
| Q5 | 15.0–91.0 | 77,588 | 101 | 948,588 | 1.27 (0.95–1.70) | 12.0–89.0 | 104,581 | 79 | 1,351,131 | 1.14 (0.83–1.58) | 1.21 (0.98–1.50) |
| *P* for trend | | | | | 0.18 | | | | | 0.38 | 0.11 |
| *P* for heterogeneity | | | | | | | | | | | 0.94 |
| Dairy and Eggs | | | | | | | | | | | |
| Q1† | 0–4.25 | 73,149 | 99 | 872,267 | 1.00 | 0–3.75 | 93,678 | 74 | 1,180,435 | 1.00 | 1.00 |
| Q2 | 4.5–7.75 | 72,506 | 75 | 890,261 | 0.76 (0.56–1.03) | 4.0–6.75 | 98,838 | 73 | 1,284,624 | 0.96 (0.70–1.33) | 0.85 (0.68–1.06) |
| Q3 | 8.0–11.75 | 82,395 | 98 | 1,010,949 | 0.88 (0.67–1.17) | 7.0–9.75 | 103,537 | 68 | 1,348,452 | 0.86 (0.62–1.20) | 0.87 (0.70–1.08) |
| Q4 | 12.0–17.75 | 78,568 | 109 | 964,269 | 1.04 (0.79–1.36) | 10.0–14.50 | 109,762 | 95 | 1,433,316 | 1.15 (0.85–1.57) | 1.09 (0.89–1.33) |
| Q5 | 18.0–98.0 | 77,068 | 93 | 940,600 | 0.93 (0.70–1.24) | 14.75–92.0 | 102,422 | 78 | 1,322,653 | 1.04 (0.75–1.43) | 0.98 (0.79–1.21) |
| *P* for trend | | | | | 0.66 | | | | | 0.45 | 0.42 |
| *P* for heterogeneity | | | | | | | | | | | 0.73 |
| Fatty Meats | | | | | | | | | | | |
| Q1† | 0–3.75 | 59,964 | 85 | 711,822 | 1.00 | 0–3.25 | 99,030 | 76 | 1,245,711 | 1.00 | 1.00 |
| Q2 | 4.0–5.75 | 71,894 | 102 | 872,891 | 1.03 (0.77–1.37) | 3.5–4.75 | 76,641 | 59 | 984,573 | 1.03 (0.73–1.44) | 1.03 (0.83–1.28) |
| Q3 | 6.0–7.75 | 81,307 | 101 | 997,220 | 0.93 (0.70–1.25) | 5.0–6.75 | 120,934 | 99 | 1,573,233 | 1.12 (0.83–1.52) | 1.02 (0.83–1.25) |
| Q4 | 8.0–10.75 | 88,615 | 108 | 1,091,675 | 0.94 (0.70–1.25) | 7.0–8.75 | 96,369 | 71 | 1,261,021 | 1.05 (0.76–1.45) | 0.99 (0.80–1.23) |
| Q5 | 11.0–56.0 | 81,903 | 78 | 1,004,738 | 0.75 (0.55–1.03) | 9.0–56.0 | 115,263 | 83 | 1,504,942 | 1.04 (0.76–1.43) | 0.88 (0.71–1.10) |
| *P* for trend | | | | | 0.05 | | | | | 0.83 | 0.16 |
| *P* for heterogeneity | | | | | | | | | | | 0.15 |
| Low Fat Meats | | | | | | | | | | | |
| Q1† | 0 | 27,657 | 36 | 325,050 | 1.00 | 0–0.75 | 33,456 | 25 | 416,581 | 1.00 | 1.00 |
| Q2 | 0.25–0.75 | 116,505 | 150 | 1,426,844 | 0.97 (0.67–1.39) | 1.0–1.50 | 135,529 | 96 | 1,759,126 | 0.96 (0.62–1.50) | 0.97 (0.73–1.28) |
| Q3 | 1.0–2.75 | 77,580 | 114 | 949,597 | 1.08 (0.74–1.57) | 2.0–2.50 | 125,232 | 97 | 1,630,370 | 1.04 (0.67–1.61) | 1.06 (0.80–1.41) |
| Q4 | 3.0–6.75 | 78,240 | 84 | 958,577 | 0.78 (0.53–1.15) | 3.0–3.50 | 84,890 | 75 | 1,099,440 | 1.17 (0.75–1.85) | 0.93 (0.69–1.24) |
| Q5 | 7.0–21.0 | 83,701 | 90 | 1,018,278 | 0.76 (0.52–1.12) | 4.0–14.0 | 129,130 | 95 | 1,663,962 | 0.95 (0.61–1.48) | 0.84 (0.63–1.12) |
| *P* for trend | | | | | 0.02 | | | | | 0.92 | 0.11 |
| *P* for heterogeneity | | | | | | | | | | | 0.08 |
| Fried Foods | | | | | | | | | | | |
| Q1† | 0–1.75 | 64,708 | 96 | 766,794 | 1.00 | 0–0.75 | 92,665 | 74 | 1,165,756 | 1.00 | 1.00 |
| Q2 | 2–3.75 | 75,992 | 113 | 929,828 | 1.03 (0.78–1.35) | 1.0–2.25 | 102,591 | 74 | 1,328,224 | 0.94 (0.68–1.30) | 0.99 (0.80–1.22) |
| Q3 | 4–5.75 | 73,381 | 83 | 903,043 | 0.80 (0.60–1.08) | 2.5–3.75 | 84,742 | 73 | 1,104,711 | 1.15 (0.83–1.59) | 0.94 (0.76–1.17) |
| Q4 | 6–9.25 | 92,766 | 101 | 1,139,566 | 0.80 (0.60–1.06) | 4.0–6.75 | 125,378 | 99 | 1,632,494 | 1.08 (0.79–1.46) | 0.92 (0.75–1.13) |
| Q5 | 9.5–42.0 | 76,836 | 81 | 939,115 | 0.80 (0.59–1.08) | 7.0–42.0 | 102,861 | 68 | 1,338,294 | 0.92 (0.66–1.29) | 0.85 (0.68–1.07) |
| *P* for trend | | | | | 0.06 | | | | | 0.78 | 0.09 |
| *P* for heterogeneity | | | | | | | | | | | 0.38 |

(*Continued*)

**TABLE 1.** (*Continued*)

| Foods | Men: Quantile Range (times/wk) | Men: No. Persons | Men: No. Cases | Men: No. Person-Years | Men: RR (95% CI)* | Women: Quantile Rangey (times/wk) | Women: No. Persons | Women: No. Cases | Women: No. Person-Years | Women: RR (95% CI)* | Pooled RR (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| High Fiber Grains | | | | | | | | | | | |
| Q1† | 0 | 92,293 | 103 | 1,120,989 | 1.00 | 0 | 1,10,207 | 67 | 1,410,529 | 1.00 | 1.00 |
| Q2 | 0.25–0.75 | 34,965 | 46 | 420,520 | 1.16 (0.82–1.64) | 0.25–0.75 | 53,353 | 39 | 684,156 | 1.20 (0.81–1.78) | 1.18 (0.91–1.53) |
| Q3 | 1.0–2.75 | 86,422 | 96 | 1,065,674 | 0.97 (0.73–1.28) | 1.0–3.25 | 1,41,333 | 103 | 1,842,124 | 1.22 (0.90–1.66) | 1.08 (0.88–1.33) |
| Q4 | 3.00–6.75 | 91,300 | 116 | 1,122,311 | 1.04 (0.79–1.35) | 3.50–6.75 | 93,958 | 79 | 1,226,387 | 1.37 (0.99–1.90) | 1.16 (0.95–1.43) |
| Q5 | 7.0–21.0 | 78,703 | 113 | 948,852 | 1.10 (0.84–1.45) | 7.0–21.0 | 1,09,386 | 100 | 1,406,283 | 1.44 (1.05–1.97) | 1.24 (1.01–1.52) |
| *P* for trend | | | | | 0.51 | | | | | 0.03 | 0.05 |
| *P* for heterogeneity | | | | | | | | | | | 0.25 |
| Low Fiber Grains | | | | | | | | | | | |
| Q1† | 0–1.75 | 60,678 | 80 | 718,652 | 1.00 | 0–1.25 | 84,155 | 72 | 1,064,351 | 1.00 | 1.00 |
| Q2 | 2.0–4.75 | 75,364 | 107 | 931,321 | 1.09 (0.82–1.46) | 1.5–3.75 | 1,00,310 | 70 | 1,306,101 | 0.85 (0.61–1.18) | 0.98 (0.79–1.22) |
| Q3 | 5.0–7.25 | 81,030 | 86 | 998,163 | 0.82 (0.60–1.11) | 4.0–6.75 | 1,10,104 | 83 | 1,440,668 | 0.94 (0.69–1.29) | 0.88 (0.70–1.09) |
| Q4 | 7.5–9.25 | 83,626 | 98 | 1,018,779 | 0.91 (0.67–1.22) | 7.0–8.50 | 98,922 | 72 | 1,274,685 | 0.89 (0.64–1.24) | 0.90 (0.72–1.13) |
| Q5 | 9.5–21.0 | 82,985 | 103 | 1,011,430 | 0.94 (0.70–1.26) | 9.0–21.0 | 1,14,746 | 91 | 1,483,675 | 1.00 (0.73–1.36) | 0.97 (0.78–1.20) |
| *P* for trend | | | | | 0.33 | | | | | 0.79 | 0.58 |
| *P* for heterogeneity | | | | | | | | | | | 0.4 |
| Other Fats | | | | | | | | | | | |
| Q1† | 0–1.75 | 66,266 | 91 | 785,979 | 1.00 | 0–1.25 | 90,186 | 64 | 1,131,774 | 1.00 | 1.00 |
| Q2 | 2.0–4.75 | 72,226 | 93 | 891,733 | 0.97 (0.72–1.29) | 1.5–4.75 | 1,01,626 | 73 | 1,327,049 | 1.08 (0.77–1.51) | 1.02 (0.82–1.27) |
| Q3 | 5–7.25 | 81,349 | 95 | 986,119 | 0.86 (0.64–1.14) | 5.0–7.25 | 1,08,117 | 84 | 1,384,448 | 1.13 (0.82–1.57) | 0.97 (0.78–1.20) |
| Q4 | 7.5–8.75 | 65,750 | 85 | 797,089 | 0.91 (0.68–1.22) | 7.5–8.75 | 98,418 | 83 | 1,276,990 | 1.19 (0.86–1.66) | 1.02 (0.82–1.27) |
| Q5 | 9.0–28.0 | 98,092 | 110 | 1,217,426 | 0.84 (0.64–1.11) | 9.0–28.0 | 1,09,890 | 84 | 1,449,218 | 1.18 (0.85–1.63) | 0.97 (0.78–1.19) |
| *P* for trend | | | | | 0.18 | | | | | 0.26 | 0.8 |
| *P* for heterogeneity | | | | | | | | | | | 0.08 |
| Vegetables | | | | | | | | | | | |
| Q1† | 0–5.25 | 73,919 | 90 | 869,553 | 1.00 | 0–6.25 | 1,01,204 | 58 | 1,268,324 | 1.00 | 1.00 |
| Q2 | 5.5–8.75 | 74,637 | 77 | 912,462 | 0.83 (0.61–1.12) | 6.5–9.75 | 94,401 | 76 | 1,222,007 | 1.44 (1.02–2.03) | 1.06 (0.84–1.33) |
| Q3 | 9.0–11.75 | 78,127 | 95 | 962,193 | 0.94 (0.70–1.25) | 10.0–12.75 | 97,531 | 76 | 1,270,355 | 1.37 (0.97–1.93) | 1.10 (0.88–1.37) |
| Q4 | 12.0–14.75 | 67,088 | 90 | 827,562 | 1.00 (0.75–1.35) | 13.0–16.25 | 1,08,418 | 88 | 1,414,265 | 1.38 (0.99–1.93) | 1.15 (0.92–1.44) |
| Q5 | 15.0–35.0 | 89,912 | 122 | 1,106,575 | 0.99 (0.75–1.30) | 16.5–35.0 | 1,06,683 | 90 | 1,394,528 | 1.41 (1.01–1.97) | 1.14 (0.92–1.41) |
| *P* for trend | | | | | 0.64 | | | | | 0.09 | 0.13 |
| *P* for heterogeneity | | | | | | | | | | | 0.37 |
| Vegetables and Citrus Fruit | | | | | | | | | | | |
| Q1† | 0–7.75 | 73,206 | 88 | 866,226 | 1.00 | 0–8.75 | 92,754 | 53 | 1,167,137 | 1.00 | 1.00 |
| Q2 | 8.0–12.25 | 77,785 | 80 | 951,511 | 0.83 (0.61–1.12) | 9–13.75 | 98,477 | 74 | 1,274,161 | 1.35 (0.95–1.92) | 1.02 (0.81–1.29) |
| Q3 | 12.5–15.75 | 66,548 | 73 | 818,265 | 0.85 (0.62–1.16) | 14–17.75 | 1,04,089 | 84 | 1,353,332 | 1.41 (1.00–1.99) | 1.07 (0.85–1.35) |
| Q4 | 16.0–20.25 | 85,706 | 117 | 1,055,122 | 1.01 (0.76–1.34) | 18–21.75 | 97,521 | 83 | 1,271,905 | 1.44 (1.01–2.03) | 1.16 (0.93–1.45) |
| Q5 | 20.5–42.0 | 80,438 | 116 | 987,221 | 1.03 (0.78–1.36) | 22.0–42.0 | 1,15,396 | 94 | 1,502,944 | 1.34 (0.96–1.89) | 1.15 (0.92–1.42) |
| *P* for trend | | | | | 0.43 | | | | | 0.12 | 0.1 |
| *P* for heterogeneity | | | | | | | | | | | 0.53 |

*Adjusted for age (one year categories), vitamin E use, and smoking (never, past, current).
†Reference category.

**TABLE 2.** Relative Risk of ALS According to Consumption of Individual Foods

| Food Servings/wk | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| Tomato | | | | | |
| <1‡ | 266,552 | 220 | 2,317,306 | 1.00 | 1.00 |
| 2 to 3 | 274,377 | 267 | 2,430,450 | 1.17 (0.98–1.40) | 1.16 (0.97–1.38) |
| 4 to 5 | 224,903 | 258 | 1,995,934 | 1.34 (1.12–1.61) | 1.35 (1.13–1.62) |
| 6 or more | 126,088 | 117 | 1,107,934 | 1.04 (0.83–1.30) | 1.07 (0.86–1.34) |
| *P* for trend | | | | | 0.17 |
| Cabbage | | | | | |
| Never‡ | 170,101 | 151 | 1,464,381 | 1.00 | 1.00 |
| <2 | 445,540 | 449 | 3,936,794 | 1.13 (0.94–1.36) | 1.16 (0.96–1.40) |
| 2 to 3 | 205,900 | 206 | 1,825,642 | 1.10 (0.89–1.36) | 1.16 (0.94–1.43) |
| 4 or more | 70,379 | 56 | 624,807 | 0.87 (0.64–1.18) | 0.95 (0.70–1.29) |
| *P* for trend | | | | | 0.87 |
| Green leafy vegetables | | | | | |
| <1‡ | 159,973 | 140 | 1,364,420 | 1.00 | 1.00 |
| 2 to 3 | 170,089 | 156 | 1,493,820 | 1.07 (0.85–1.35) | 1.06 (0.84–1.33) |
| 4 to 5 | 232,863 | 224 | 2,071,195 | 1.09 (0.88–1.35) | 1.09 (0.88–1.35) |
| 6 or more | 328,995 | 342 | 2,922,189 | 1.13 (0.93–1.38) | 1.15 (0.94–1.40) |
| *P* for trend | | | | | 0.16 |
| Carrots | | | | | |
| Never‡ | 145,048 | 117 | 1,246,569 | 1.00 | 1.00 |
| <1 | 440,322 | 442 | 3,891,218 | 1.22 (1.00–1.50) | 1.26 (1.03–1.55) |
| 2 to 3 | 207,891 | 198 | 1,835,147 | 1.11 (0.88–1.40) | 1.17 (0.93–1.48) |
| 4 or more | 98,659 | 105 | 878,690 | 1.25 (0.96–1.62) | 1.34 (1.03–1.75) |
| *P* for trend | | | | | 0.18 |
| Squash/corn | | | | | |
| Never‡ | 155,612 | 147 | 1,336,446 | 1.00 | 1.00 |
| <1 | 497,520 | 500 | 4,404,222 | 1.08 (0.90–1.29) | 1.09 (0.90–1.31) |
| 2 to 3 | 200,507 | 178 | 1,773,226 | 0.96 (0.77–1.19) | 0.97 (0.78–1.20) |
| 4 or more | 38,281 | 37 | 337,730 | 1.03 (0.72–1.48) | 1.07 (0.75–1.54) |
| *P* for trend | | | | | 0.70 |
| Potatoes | | | | | |
| Never‡ | 59,730 | 52 | 518,018 | 1.00 | 1.00 |
| <1 | 237,258 | 236 | 2,089,383 | 1.16 (0.86–1.56) | 1.15 (0.85–1.55) |
| 2 to 3 | 318,982 | 305 | 2,825,933 | 1.13 (0.85–1.52) | 1.08 (0.81–1.45) |
| 4 to 5 | 204,654 | 203 | 1,803,150 | 1.15 (0.85–1.57) | 1.10 (0.81–1.49) |
| 6 or more | 71,296 | 66 | 615,138 | 1.08 (0.75–1.55) | 0.98 (0.68–1.41) |
| *P* for trend | | | | | 0.52 |
| Raw vegetables | | | | | |
| Never‡ | 150,620 | 119 | 1,272,786 | 1.00 | 1.00 |
| <1 | 223,196 | 234 | 1,959,091 | 1.34 (1.07–1.67) | 1.40 (1.12–1.74) |
| 2 to 3 | 182,502 | 168 | 1,622,342 | 1.17 (0.93–1.48) | 1.23 (0.97–1.56) |
| 4 to 5 | 143,664 | 143 | 1,285,073 | 1.23 (0.96–1.56) | 1.34 (1.05–1.72) |
| 6 or more | 191,938 | 198 | 1,712,331 | 1.22 (0.97–1.53) | 1.36 (1.08–1.72) |
| *P* for trend | | | | | 0.11 |
| Citrus fruit | | | | | |
| Never‡ | 110,824 | 104 | 953,178 | 1.00 | 1.00 |
| <1 | 154,826 | 131 | 1,359,507 | 0.92 (0.71–1.19) | 0.93 (0.72–1.21) |
| 2 to 3 | 120,226 | 105 | 1,072,122 | 0.94 (0.72–1.24) | 0.97 (0.74–1.27) |
| 4 to 5 | 120,686 | 109 | 1,079,170 | 0.97 (0.74–1.27) | 0.99 (0.75–1.30) |
| 6 or more | 385,358 | 413 | 3,387,647 | 1.08 (0.87–1.34) | 1.12 (0.90–1.39) |
| *P* for trend | | | | | 0.06 |

(*Continued*)

**TABLE 2.** (*Continued*)

| Food Servings/wk | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| Brown rice/whole wheat/barley | | | | | |
| Never‡ | 441,905 | 384 | 3,848,651 | 1.00 | 1.00 |
| <1 | 212,858 | 214 | 1,891,619 | 1.15 (0.98–1.36) | 1.17 (0.99–1.38) |
| 2 to 3 | 91,291 | 86 | 816,415 | 1.08 (0.85–1.36) | 1.09 (0.86–1.38) |
| 4 to 5 | 61,532 | 84 | 551,749 | 1.53 (1.21–1.94) | 1.56 (1.23–1.98) |
| 6 or more | 84,334 | 94 | 743,189 | 1.20 (0.96–1.51) | 1.22 (0.97–1.53) |
| *P* for trend | | | | | 0.006 |
| Bran/corn muffins | | | | | |
| Never‡ | 561,179 | 537 | 4,923,607 | 1.00 | 1.00 |
| <1 | 255,898 | 253 | 2,271,638 | 1.04 (0.89–1.20) | 1.06 (0.91–1.23) |
| 2 to 3 | 47,196 | 46 | 414,793 | 1.00 (0.74–1.35) | 1.02 (0.75–1.37) |
| 4 to 5 | 27,647 | 26 | 241,585 | 0.93 (0.63–1.39) | 0.94 (0.63–1.39) |
| *P* for trend | | | | | 0.98 |
| Oatmeal/shredded wheat/bran cereals | | | | | |
| Never‡ | 364,084 | 326 | 3,204,503 | 1.00 | 1.00 |
| <1 | 222,100 | 231 | 1,968,443 | 1.15 (0.97–1.36) | 1.16 (0.98–1.38) |
| 2 to 3 | 138,130 | 126 | 1,219,038 | 0.96 (0.78–1.18) | 0.96 (0.78–1.19) |
| 4 to 5 | 83,340 | 88 | 734,480 | 1.07 (0.84–1.36) | 1.08 (0.85–1.37) |
| 6 or more | 84,266 | 91 | 725,158 | 1.07 (0.84–1.35) | 1.06 (0.83–1.34) |
| *P* for trend | | | | | 0.84 |
| Bread/rolls/biscuits | | | | | |
| Never‡ | 156,087 | 179 | 1,357,787 | 1.00 | 1.00 |
| <1 | 210,247 | 196 | 1,855,677 | 0.85 (0.69–1.04) | 0.84 (0.68–1.03) |
| 2 to 3 | 149,260 | 137 | 1,332,354 | 0.86 (0.69–1.08) | 0.84 (0.67–1.05) |
| 4 to 5 | 122,855 | 109 | 1,095,594 | 0.84 (0.66–1.07) | 0.82 (0.64–1.04) |
| 6 or more | 253,471 | 241 | 2,210,210 | 0.89 (0.74–1.09) | 0.83 (0.69–1.01) |
| *P* for trend | | | | | 0.19 |
| Spaghetti/macaroni/white rice | | | | | |
| Never‡ | 122,698 | 107 | 1,049,248 | 1.00 | 1.00 |
| <1 | 515,696 | 536 | 4,543,286 | 1.24 (1.01–1.53) | 1.25 (1.01–1.54) |
| 2 to 3 | 203,138 | 178 | 1,808,703 | 1.10 (0.86–1.41) | 1.13 (0.89–1.44) |
| 4 or more | 50,388 | 41 | 450,386 | 1.10 (0.76–1.59) | 1.10 (0.77–1.58) |
| *P* for trend | | | | | 0.94 |
| Cold (dry) cereals | | | | | |
| Never‡ | 370,657 | 336 | 3,259,574 | 1.00 | 1.00 |
| <1 | 201,304 | 182 | 1,782,099 | 1.00 (0.84–1.20) | 1.01 (0.84–1.21) |
| 2 to 3 | 147,856 | 143 | 1,306,612 | 1.03 (0.84–1.25) | 1.02 (0.84–1.24) |
| 4 to 5 | 89,647 | 104 | 791,535 | 1.21 (0.97–1.51) | 1.17 (0.94–1.46) |
| 6 or more | 82,456 | 97 | 711,803 | 1.18 (0.94–1.49) | 1.12 (0.89–1.41) |
| *P* for trend | | | | | 0.16 |
| Beef | | | | | |
| Never‡ | 19,782 | 19 | 169,945 | 1.00 | 1.00 |
| <1 | 233,136 | 234 | 2,016,705 | 1.02 (0.64–1.64) | 0.97 (0.61–1.54) |
| 2 to 3 | 412,217 | 395 | 3,638,530 | 0.99 (0.63–1.58) | 0.94 (0.59–1.48) |
| 4 to 5 | 194,439 | 187 | 1,738,060 | 1.08 (0.68–1.74) | 0.97 (0.60–1.56) |
| 6 or more | 32,346 | 27 | 288,383 | 0.88 (0.49–1.60) | 0.82 (0.45–1.48) |
| *P* for trend | | | | | 0.68 |
| Pork | | | | | |
| Never‡ | 196,827 | 186 | 1,710,966 | 1.00 | 1.00 |
| <1 | 566,512 | 573 | 5,015,605 | 1.12 (0.95–1.32) | 1.10 (0.93–1.30) |
| 2 to 3 | 105,932 | 87 | 928,205 | 0.93 (0.72–1.20) | 0.89 (0.69–1.15) |
| 4 or more | 22,649 | 16 | 196,847 | 0.78 (0.47–1.30) | 0.71 (0.43–1.18) |
| *P* for trend | | | | | 0.12 |

(*Continued*)

**TABLE 2.** (*Continued*)

| Food Servings/wk | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| Ham | | | | | |
| Never‡ | 285,851 | 262 | 2,505,555 | 1.00 | 1.00 |
| <1 | 544,944 | 549 | 4,814,607 | 1.12 (0.97–1.30) | 1.11 (0.95–1.28) |
| 2 ore more | 61,125 | 51 | 531,462 | 0.93 (0.69–1.26) | 0.89 (0.66–1.20) |
| *P* for trend | | | | | 0.98 |
| Liver | | | | | |
| Never‡ | 549,673 | 529 | 4,855,355 | 1.00 | 1.00 |
| Ever | 342,247 | 333 | 2,996,268 | 0.98 (0.85–1.12) | 0.99 (0.87–1.14) |
| *P* for trend | | | | | 0.92 |
| Bacon | | | | | |
| Never‡ | 359,519 | 349 | 3,149,696 | 1.00 | 1.00 |
| <1 | 360,953 | 349 | 3,209,643 | 1.04 (0.89–1.20) | 1.03 (0.89–1.20) |
| 2 to 3 | 122,022 | 120 | 1,067,225 | 1.04 (0.84–1.28) | 1.04 (0.84–1.28) |
| 4 or more | 49,426 | 44 | 425,060 | 0.92 (0.67–1.25) | 0.92 (0.67–1.26) |
| *P* for trend | | | | | 0.29 |
| Sausage | | | | | |
| Never‡ | 314,001 | 306 | 2,740,286 | 1.00 | 1.00 |
| <1 | 502,794 | 506 | 4,456,475 | 1.09 (0.94–1.25) | 1.06 (0.91–1.22) |
| 2 or more | 75,125 | 50 | 654,862 | 0.74 (0.55–0.99) | 0.69 (0.51–0.94) |
| *P* for trend | | | | | 0.12 |
| Smoked meat | | | | | |
| Never‡ | 589,793 | 549 | 5,179,577 | 1.00 | 1.00 |
| <1 | 257,118 | 265 | 2,279,110 | 1.11 (0.96–1.29) | 1.11 (0.96–1.28) |
| 2 or more | 45,009 | 48 | 392,937 | 1.14 (0.85–1.53) | 1.09 (0.81–1.46) |
| *P* for trend | | | | | 0.24 |
| Fried hamburgers or beef | | | | | |
| Never‡ | 268,760 | 254 | 2,340,909 | 1.00 | 1.00 |
| <1 | 396,127 | 392 | 3,505,374 | 1.09 (0.93–1.27) | 1.08 (0.92–1.27) |
| 2 to 3 | 190,717 | 190 | 1,684,223 | 1.13 (0.93–1.37) | 1.15 (0.95–1.38) |
| 4 or more | 36,316 | 26 | 321,118 | 0.86 (0.57–1.29) | 0.87 (0.58–1.31) |
| *P* for trend | | | | | 0.60 |
| Fried eggs | | | | | |
| Never‡ | 338,577 | 297 | 2,972,769 | 1.00 | 1.00 |
| <1 | 326,146 | 356 | 2,895,068 | 1.28 (1.09–1.49) | 1.28 (1.10–1.49) |
| 2 to 3 | 157,788 | 144 | 1,384,259 | 1.07 (0.88–1.30) | 1.07 (0.88–1.31) |
| 4 to 5 | 39,391 | 36 | 343,975 | 1.08 (0.76–1.53) | 1.09 (0.77–1.54) |
| 6 or more | 30,018 | 29 | 255,553 | 1.10 (0.75–1.61) | 1.11 (0.76–1.63) |
| *P* for trend | | | | | 0.33 |
| Fried chicken | | | | | |
| Never‡ | 353,262 | 351 | 3,090,418 | 1.00 | 1.00 |
| <1 | 413,429 | 403 | 3,667,198 | 1.02 (0.88–1.17) | 1.02 (0.88–1.17) |
| 2 or more | 125,229 | 108 | 1,094,008 | 0.89 (0.72–1.11) | 0.90 (0.73–1.12) |
| *P* for trend | | | | | 0.18 |
| Butter | | | | | |
| Never‡ | 569,547 | 545 | 4,985,818 | 1.00 | 1.00 |
| <1 | 112,504 | 11 | 997,741 | 1.08 (0.88–1.32) | 1.08 (0.88–1.33) |
| 2 to 3 | 48,429 | 46 | 433,784 | 1.07 (0.79–1.45) | 1.05 (0.78–1.42) |
| 4 to 5 | 40,631 | 38 | 365,650 | 1.09 (0.78–1.51) | 1.07 (0.77–1.48) |
| 6 or more | 120,809 | 122 | 1,068,632 | 1.10 (0.91–1.34) | 1.10 (0.91–1.34) |
| *P* for trend | | | | | 0.32 |
| Cheese | | | | | |
| <1‡ | 316,736 | 289 | 2,739,608 | 1.00 | 1.00 |
| 2 to 3 | 288,998 | 303 | 2,560,203 | 1.16 (0.99–1.37) | 1.18 (1.00–1.39) |

(*Continued*)

 

**TABLE 2.** (*Continued*)

| Food Servings/wk | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| 4 to 5 | 193,218 | 189 | 1,725,981 | 1.11 (0.92–1.33) | 1.14 (0.95–1.37) |
| 6 or more | 92,968 | 81 | 825,831 | 0.98 (0.77–1.26) | 1.01 (0.79–1.30) |
| *P* for trend | | | | | 0.69 |
| Ice cream | | | | | |
| Never‡ | 183,799 | 158 | 1,598,351 | 1.00 | 1.00 |
| <1 | 375,825 | 378 | 3,325,841 | 1.17 (0.97–1.41) | 1.15 (0.96–1.39) |
| 2 to 3 | 208,142 | 190 | 1,840,479 | 1.04 (0.84–1.29) | 0.98 (0.79–1.21) |
| 4 to 5 | 89,928 | 94 | 792,237 | 1.17 (0.91–1.51) | 1.08 (0.84–1.40) |
| 6 or more | 34,226 | 42 | 294,716 | 1.38 (0.98–1.94) | 1.23 (0.87–1.73) |
| *P* for trend | | | | | 0.77 |
| Chocolate | | | | | |
| Never‡ | 345,808 | 332 | 2,979,484 | 1.00 | 1.00 |
| <1 | 352,158 | 350 | 3,136,100 | 1.06 (0.91–1.23) | 1.07 (0.92–1.24) |
| 2 to 3 | 129,176 | 118 | 1,156,962 | 0.99 (0.80–1.23) | 1.00 (0.81–1.23) |
| 4 or more | 64,778 | 62 | 579,077 | 1.07 (0.82–1.41) | 1.08 (0.83–1.42) |
| *P* for trend | | | | | 0.69 |
| Margarine | | | | | |
| Never‡ | 184,305 | 168 | 1,617,332 | 1.00 | 1.00 |
| <1 | 116,499 | 116 | 1,014,986 | 1.09 (0.86–1.38) | 1.11 (0.88–1.41) |
| 2 to 3 | 86,206 | 84 | 769,955 | 1.11 (0.85–1.44) | 1.11 (0.85–1.44) |
| 4 to 5 | 103,363 | 94 | 926,364 | 1.03 (0.80–1.33) | 1.03 (0.80–1.33) |
| 6 or more | 401,547 | 400 | 3,522,985 | 1.05 (0.88–1.26) | 1.06 (0.89–1.27) |
| *P* for trend | | | | | 0.81 |
| French fries | | | | | |
| Never‡ | 435,237 | 454 | 3,792,399 | 1.00 | 1.00 |
| <1 | 358,964 | 332 | 3,191,572 | 0.97 (0.84–1.11) | 0.96 (0.84–1.11) |
| 2 or more | 97,719 | 76 | 867,653 | 0.86 (0.67–1.11) | 0.89 (0.70–1.14) |
| *P* for trend | | | | | 0.02 |
| Other fried foods | | | | | |
| Never‡ | 580,501 | 574 | 5,078,567 | 1.00 | 1.00 |
| <1 | 194,478 | 185 | 1,734,236 | 1.00 (0.84–1.17) | 0.99 (0.84–1.17) |
| 2 to 3 | 91,720 | 86 | 814,598 | 1.01 (0.80–1.26) | 1.02 (0.81–1.28) |
| 4 or more | 25,221 | 17 | 224,222 | 0.75 (0.46–1.22) | 0.77 (0.47–1.24) |
| *P* for trend | | | | | 0.26 |
| Chicken | | | | | |
| Never‡ | 28,623 | 33 | 244,919 | 1.00 | 1.00 |
| <1 | 460,236 | 488 | 4,054,162 | 0.91 (0.64–1.30) | 0.94 (0.66–1.34) |
| 2 to 3 | 349,570 | 308 | 3,082,028 | 0.76 (0.53–1.08) | 0.79 (0.55–1.13) |
| 4 or more | 53,491 | 33 | 470,514 | 0.52 (0.32–0.85) | 0.58 (0.36–0.94) |
| *P* for trend | | | | | 0.0006 |
| Fish | | | | | |
| Never‡ | 135,950 | 130 | 1,180,120 | 1.00 | 1.00 |
| <1 | 579,483 | 554 | 5,116,423 | 0.98 (0.81–1.18) | 0.97 (0.80–1.18) |
| 2 to 3 | 152,977 | 156 | 1,347,115 | 0.98 (0.78–1.24) | 1.01 (0.80–1.28) |
| 4 or more | 23,510 | 22 | 207,966 | 0.92 (0.59–1.45) | 0.97 (0.62–1.53) |
| *P* for trend | | | | | 0.89 |
| Eggs | | | | | |
| <1‡ | 364,563 | 365 | 3,196,299 | 1.00 | 1.00 |
| 2 to 3 | 334,447 | 323 | 2,961,705 | 0.97 (0.83–1.12) | 0.98 (0.84–1.14) |
| 4 to 5 | 120,040 | 110 | 1,064,071 | 0.94 (0.76–1.16) | 0.94 (0.76–1.17) |
| 6 or more | 72,870 | 64 | 629,548 | 0.87 (0.67–1.14) | 0.83 (0.64–1.09) |
| *P* for trend | | | | | 0.18 |

*Adjusted for age (5-year categories).
†Adjusted for age (1-year categories), smoking (never, past, current), and vitamin E use.
‡Reference category.

**TABLE 3.** Relative Risk of ALS According to Current Beverage Consumption

| Beverage | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| Tea | | | | | |
| 0 cups‡ | 466,914 | 495 | 5,827,186 | 1.00 | 1.00 |
| Seasonal/occasional | 12,316 | 7 | 146,560 | 0.54 (0.25 – 1.13) | 0.58 (0.28–1.23) |
| 3–6 cups/wk | 160,535 | 156 | 2,044,525 | 0.90 (0.75–1.07) | 0.95 (0.80–1.14) |
| 1 cup/d | 137,151 | 132 | 1,729,783 | 0.90 (0.74–1.09) | 0.93 (0.77–1.13) |
| 2 cups/d | 96,045 | 87 | 1,219,526 | 0.85 (0.68–1.07) | 0.89 (0.71–1.12) |
| 3 cups/d | 37,820 | 29 | 483,540 | 0.73 (0.50–1.07) | 0.78 (0.54–1.13) |
| 4 or more cups/d | 46,137 | 32 | 585,285 | 0.68 (0.48–0.97) | 0.71 (0.49–1.01) |
| *P* for trend | | | | | 0.02 |
| Diet soda or diet iced tea | | | | | |
| 0 cups | 669,351 | 671 | 8,321,550 | 1.00 | 1.00 |
| Seasonal/occasional | 8047 | 5 | 97,572 | 0.61 (0.25–1.48) | 0.70 (0.29–1.68) |
| 3–6 cups/wk | 113,940 | 115 | 1,474,518 | 1.01 (0.83–1.24) | 1.11 (0.91–1.36) |
| 1 cup/d | 84,109 | 77 | 1,091,402 | 0.97 (0.77–1.23) | 1.04 (0.82–1.32) |
| 2 cups/d | 44,172 | 34 | 571,380 | 0.84 (0.59–1.19) | 0.91 (0.64–1.29) |
| 3 cups/d | 16,842 | 16 | 217,585 | 1.06 (0.65–1.75) | 1.16 (0.70–1.90) |
| 4 or more cups/d | 20,457 | 20 | 262,399 | 1.09 (0.70–1.70) | 1.17 (0.75–1.83) |
| *P* for trend | | | | | 0.62 |
| Nondiet colas | | | | | |
| 0 cups | 738,708 | 724 | 9,225,297 | 1.00 | 1.00 |
| Seasonal/occasional | 7557 | 11 | 92,796 | 1.50 (0.83–2.73) | 1.61 (0.89–2.92) |
| 3–6 cups/wk | 117,046 | 114 | 1,513,285 | 1.07 (0.87–1.30) | 1.04 (0.85–1.27) |
| 1 cup/d | 55,482 | 49 | 714,968 | 1.03 (0.77–1.37) | 0.96 (0.72–1.29) |
| 2 cups/d | 21,469 | 23 | 276,572 | 1.30 (0.86–1.97) | 1.23 (0.81–1.86) |
| 3 cups/d | 7535 | 7 | 97,054 | 1.15 (0.55–2.43) | 1.10 (0.52–2.32) |
| 4 or more cups/d | 9121 | 10 | 116,434 | 1.38 (0.74–2.58) | 1.31 (0.70–2.46) |
| *P* for trend | | | | | 0.33 |
| Other nondiet soft drinks | | | | | |
| 0 cups | 835,993 | 816 | 10,495,992 | 1.00 | 1.00 |
| Seasonal/occasional | 6697 | 7 | 81,434 | 1.04 (0.49–2.18) | 1.12 (0.53–2.36) |
| 3–6 cups/wk | 72,529 | 68 | 931,883 | 0.96 (0.75–1.23) | 0.97 (0.76–1.24) |
| 1 cup/d | 25,112 | 25 | 319,281 | 1.07 (0.72–1.59) | 1.03 (0.69–1.53) |
| 2 cups/d | 9084 | 12 | 114,326 | 1.44 (0.82–2.55) | 1.39 (0.79–2.47) |
| 3 cups/d | 3249 | 5 | 41,061 | 1.70 (0.70–4.09) | 1.65 (0.69–3.98) |
| 4 or more cups/d | 4254 | 5 | 52,429 | 1.33 (0.55–3.20) | 1.29 (0.54–3.11) |
| *P* for trend | | | | | 0.18 |
| Milk | | | | | |
| 0 cups | 570,585 | 576 | 7,207,486 | 1.00 | 1.00 |
| Seasonal/occasional | 7332 | 8 | 86,880 | 1.10 (0.55–2.22) | 1.14 (0.56–2.28) |
| 3–6 cups/wk | 142,063 | 105 | 1,802,196 | 0.75 (0.61–0.93) | 0.74 (0.60–0.91) |
| 1 cup/d | 144,431 | 145 | 1,806,030 | 1.02 (0.85–1.22) | 0.96 (0.80–1.15) |
| 2 cups/d | 60,153 | 68 | 738,788 | 1.16 (0.90–1.49) | 1.07 (0.83–1.38) |
| 3 cups/d | 17,086 | 23 | 210,812 | 1.42 (0.94–2.16) | 1.30 (0.85–1.97) |
| 4 or more cups/d | 15,268 | 13 | 184,215 | 0.90 (0.52–1.56) | 0.80 (0.46–1.39) |
| *P* for trend | | | | | 0.99 |
| Coffee | | | | | |
| 0 cups | 348,531 | 347 | 4,319,863 | 1.00 | 1.00 |
| Seasonal/occasional | 10,711 | 12 | 129,620 | 1.20 (0.67–2.13) | 1.16 (0.65–2.07) |
| 3–6 cups/wk | 50,992 | 33 | 641,756 | 0.64 (0.45–0.92) | 0.64 (0.45–0.91) |
| 1 cup/d | 102,500 | 97 | 1,278,665 | 0.93 (0.74–1.17) | 0.91 (0.73–1.14) |
| 2 cups/d | 151,305 | 127 | 1,917,171 | 0.82 (0.67–1.01) | 0.80 (0.65–0.98) |
| 3 cups/d | 110,903 | 120 | 1,420,351 | 1.09 (0.89–1.35) | 1.05 (0.85–1.29) |
| 4 or more cups/d | 181,976 | 202 | 2,328,978 | 1.16 (0.98–1.39) | 1.09 (0.91–1.31) |
| *P* for trend | | | | | 0.28 |

(*Continued*)

**TABLE 3.** (*Continued*)

| Beverage | No. Persons | No. Cases | No. Person-Years | RR (95% CI)* | RR (95% CI)† |
|---|---|---|---|---|---|
| Decaffeinated coffee | | | | | |
| 0 cups | 621,323 | 594 | 7,849,364 | 1.00 | 1.00 |
| Seasonal/occasional | 7737 | 7 | 89,773 | 0.94 (0.44–1.97) | 1.00 (0.47–2.11) |
| 3–6 cups/wk | 59,050 | 60 | 745,701 | 1.01 (0.77–1.32) | 1.07 (0.82–1.39) |
| 1 cup/d | 91,357 | 81 | 1,134,012 | 0.86 (0.68–1.08) | 0.89 (0.71–1.12) |
| 2 cups/d | 81,205 | 71 | 1,014,425 | 0.86 (0.67–1.10) | 0.88 (0.69–1.13) |
| 3 cups/d | 42,469 | 46 | 531,216 | 1.07 (0.79–1.45) | 1.09 (0.81–1.47) |
| 4 or more cups/d | 53,777 | 79 | 671,914 | 1.49 (1.18–1.89) | 1.48 (1.17–1.88) |
| *P* for trend | | | | | 0.01 |
| Beer | | | | | |
| 0 cups | 739,346 | 722 | 9,289,226 | 1.00 | 1.00 |
| Seasonal/occasional | 11,703 | 15 | 143,077 | 1.34 (0.80–2.23) | 1.27 (0.76–2.12) |
| 3–6 cups/wk | 112,507 | 103 | 1,435,483 | 0.96 (0.78–1.18) | 0.82 (0.67–1.02) |
| 1 cup/d | 37,348 | 44 | 473,168 | 1.25 (0.92–1.69) | 1.02 (0.75–1.38) |
| 2 cups/d | 25,066 | 24 | 313,851 | 1.05 (0.70–1.58) | 0.84 (0.56–1.27) |
| 3 cups/d | 11,843 | 13 | 148,105 | 1.22 (0.71–2.12) | 0.97 (0.56–1.69) |
| 4 or more cups/d | 19,105 | 17 | 233,495 | 1.03 (0.64–1.66) | 0.80 (0.49–1.30) |
| *P* for trend | | | | | 0.30 |
| Wine | | | | | |
| 0 cups | 718,784 | 666 | 8,957,406 | 1.00 | 1.00 |
| Seasonal/occasional | 14,640 | 13 | 181,617 | 0.93 (0.54–1.61) | 1.01 (0.58–1.75) |
| 3–6 cups/wk | 139,944 | 165 | 1,817,383 | 1.26 (1.07–1.50) | 1.30 (1.09–1.54) |
| 1 cup/d | 44,244 | 46 | 572,661 | 1.11 (0.82–1.49) | 1.12 (0.83–1.51) |
| 2 cups/d | 23,814 | 29 | 307,884 | 1.32 (0.91–1.91) | 1.36 (0.93–1.97) |
| 3 cups/d | 6578 | 9 | 85,074 | 1.50 (0.78–2.90) | 1.52 (0.79–2.94) |
| 4 or more cups/d | 8914 | 10 | 114,381 | 1.21 (0.65–2.26) | 1.24 (0.66–2.32) |
| *P* for trend | | | | | 0.07 |
| Liquor | | | | | |
| 0 cups | 705,039 | 652 | 8,872,153 | 1.00 | 1.00 |
| Seasonal/occasional | 16,027 | 19 | 198,289 | 1.23 (0.78–1.95) | 1.27 (0.80–2.01) |
| 3–6 cups/wk | 123,244 | 131 | 1,575,138 | 1.12 (0.93–1.36) | 1.06 (0.88–1.28) |
| 1 cup/d | 45,878 | 55 | 574,153 | 1.24 (0.94–1.63) | 1.13 (0.86–1.49) |
| 2 cups/d | 38,363 | 36 | 474,229 | 0.95 (0.68–1.33) | 0.87 (0.62–1.22) |
| 3 cups/d | 13,538 | 25 | 164,955 | 1.94 (1.30–2.90) | 1.73 (1.16–2.59) |
| 4 or more cups/d | 14,829 | 20 | 177,489 | 1.45 (0.93–2.26) | 1.28 (0.82–2.00) |
| *P* for trend | | | | | 0.10 |

*Adjusted for age (5-year categories).
†Adjusted for age (1-year categories), smoking (never, past, current), Vitamin E use, and gender (male, female).
‡Reference category.

inverse trend for chicken (*P* for trend = 0.0007) remained strong. A marginally significant positive trend with the consumption of tomatoes (*P* for trend = 0.03) was also present in this subgroup. In the beverage analysis, excluding participants over 65 years old at baseline resulted in 544,473 participants and 422 ALS cases. The decreased risk associated with consumption of tea (*P* for trend = 0.005) and the increased risk associated with consumption of decaffeinated coffee (*P* for trend = 0.03) remained marginally significant. As in the main analysis, only the association with chicken was significant after we applied the Bonferroni correction.

Contrary to a prior observation of an association between high fat consumption and increased risk of ALS,[5] fatty meat, dairy, and other sources of fat were not associated with risk of ALS in our study.

## DISCUSSION

To our knowledge, this is the first prospective study of diet and ALS. Other exposures, such as military service,[17] occupation,[18] smoking,[3] and vitamin E consumption,[10] have been studied with relation to ALS in the Cancer Prevention Study II cohort, but this is the first analysis of foods and food groups as potential risk factors for ALS in this cohort. We found an inverse association between frequency of chicken consumption and ALS mortality. Consumption of tea and French fries was also associated with decreased ALS mortality, whereas consumption of brown rice/whole wheat/barley and decaffeinated coffee were associated with increased risk. However, only the association with chicken consumption was significant at a level $<0.001$, the level that corrects for multiple comparisons.

The most important factor that constrains the interpretation of our findings is that our dietary questionnaire assessed only a limited number of foods. Thus, we could not provide accurate estimates of nutrient intakes to directly refute or support those of other studies. For the same reason, we also could not adjust for total caloric intake when examining the individual food item/group associations. Further, although the questionnaire adopted in this study has not been directly validated, the instrument replicates known associations of diet and colon cancer.[16]

The hypotheses generated by previous studies on diet and ALS include potential adverse effects of glutamate and high fat intake, and possible protective effects of high fiber, omega-3 fatty acids, and vitamin E. Although these hypotheses cannot be directly assessed in our study, we examined whether intake of foods rich in these nutrients was related to risk of ALS. Glutamate is the primary excitatory neurotransmitter in the brain. According to the "glutamate hypothesis," overexcitation of glutamate receptors leads to an elevation of intracellular calcium, which can cause the selective neuron death characteristic of ALS.[19,20] Glutamate is found in most foods that contain protein, but is particularly high in tomatoes, mushrooms, milk, and cheese.[5] It is unknown whether dietary glutamate affects neurotransmission. In most areas of the brain, glutamate does not normally cross the blood-brain barrier.[21] However, there exist areas of the brain called the "circumventricular organs" that are vulnerable to large fluctuations in plasma glutamate.[21] In a population-based case-control study in western Washington State, Nelson et al[5] reported a dose-response association of glutamate with risk of ALS. Subjects in the highest quartile of glutamate or fat intake had approximately a 3-fold higher risk of ALS compared with those in the bottom quartile. In our study, we did not see significant associations with meats, vegetables, or dairy products, which are the primary sources of glutamate; in fact, some protein sources (eg, chicken) were strongly inversely related to risk. In the same case-control study, high fat intake was found to be associated with an increased risk of ALS, whereas high fiber intake was associated with a reduced risk.[5] In our cohort, we did not find an association between intake of fatty or high fiber foods and ALS. In contrast, brown rice/whole wheat/barley was associated with higher risk, but this finding may have been due to chance; it did not remain significant after adjustment for multiple comparisons.

In a separate case-control study, dietary polyunsaturated fatty acids and vitamin E intake were found to be associated with a reduced risk of ALS[8]; the risk was 50% to 60% lower comparing highest with lowest tertiles of intake. The 2 nutrients appeared to be acting synergistically, and the interaction between them was statistically significant. Omega 3 polyunsaturated fatty acids (eicosapentanoic acid, docosahexanoic acid, and alpha-linolenic acid) are known to have anti-inflammatory properties,[22] whereas vitamin E could be beneficial because of its antioxidant effects.[23] Results of several studies suggest that oxidative damage may increase the risk of ALS mortality[10,24–26] and that antioxidants may be protective.[5] We did not observe a decreased risk of ALS for any of the foods that are high in omega 3 polyunsaturated fatty acids (fish, green leafy vegetables). We also did not see a decreased risk of ALS in foods potentially high in vitamin E (mainly green leafy vegetables, of which some are high in this vitamin, as intake of nuts or vegetable oils was not measured in this study). However, as previously reported,[10] regular use of vitamin E supplements was strongly associated with a decreased risk of ALS in this cohort.

Previous studies have not reported specific associations between individual foods or beverages and risk of ALS. We observed an association between high tea consumption and decreased risk of ALS. Ho et al[27] reported that treatment of ALS model mice with epigallocatechin gallate, a constituent of green tea, significantly prolonged the symptom onset and lifespan. In humans, Kuriyama et al[28] reported an inverse association between higher consumption of green tea and cognitive impairment. Consumption of vegetables and citrus fruit, however, which are the primary sources of dietary antioxidants such as carotenoids and flavonoids, was not associated with a reduction in ALS risk.

A case-control study by Nelson et al,[4] looked at alcohol intake in relation to risk of ALS, but found no association. We did not find any relation between ALS and consumption of beer, wine, or liquor.

The strong inverse association between chicken consumption and ALS mortality was not expected a priori. The remaining associations were not statistically robust or supported by a biologic hypothesis, and most likely were due to chance.

There are 2 important limitations of this study. One is that we used ALS mortality as an end point because we did not have data on ALS incidence. Although this may introduce some misclassification of outcome, mortality is considered a reasonable proxy, for incidence, due to the highly fatal prognosis of ALS, and bias from this source is probably modest. Several authors[29–31] have pointed out the limitations of using death certificate data to ascertain ALS, such as regional variability and the inability of some clinicians to distinguish ALS from other neurologic disorders. However, death certificates remain a valuable tool for large epidemiologic studies of ALS, and are widely used.[17,32–35] Also, although the questionnaire used in this study has not been validated using an independent method of dietary assessment, a subset comprising 184,194 participants completed a more detailed and validated food frequency questionnaire in 1992. The correlations between the food intakes reported in 1982 (used in this study) and the corresponding intakes in 1992 were as follows—in men: carrots 0.31, high fiber grains 0.16, chicken 0.19, fried chicken 0.32, and tomatoes 0.30; correlations in women: carrots 0.30, high fiber grains 0.15, chicken 0.18, fried chicken 0.35, and tomatoes 0.30. Tea and coffee were not included in the 1992 questionnaire, but for liquor, a beverage recorded in both questionnaires, the correlation coefficient was 0.53 in men and 0.52 in women.

The other, more important, limitation is that not all foods were included in the dietary questionnaire, and we were thus unable to accurately estimate nutrient intakes. A nutrient analysis would have been very useful for comparing our results with previous work on diet and ALS[5,7] and to address specific hypotheses based on experimental findings and biologic mechanisms. Although studies of nutrients contribute most directly to our knowledge of biologic processes, studies that focus on foods and food groups give an opportunity to explore the data when a specific hypothesis has not been formulated.[9] Additionally, foods are inherently more than just their nutrient composition, as exemplified by the difference in the physiologic effects of milk and yogurt.[9] Additionally, studies of foods rather than specific nutrients are more practical, as they can be linked directly to dietary recommendations.[9] Finally, as in all observational studies, confounding by unmeasured factors is a possibility. These limitations are in part compensated for by the unique strength of a prospective design, which minimizes the possibility of recall and selection bias. Both recall and selection bias may have affected the results of previous investigations, which relied on a case-control design with retrospective assessment of dietary habits.

In summary, in this large prospective study, we did not find convincing evidence that the investigated food items are related to ALS mortality. Although the results suggested a possible protective effect of high chicken consumption, studies in other populations are needed to determine whether this association is reproducible.

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