

Citation:

Li TY, Brennan AM, Wedick NM, Mantzoros C, Rifai N, Hu FB. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr.* Jul 2009; 139(7): 1,333-1,338.

PubMed ID: [19420347](#)

Study Design:

Prospective cohort study.

Class:

B - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To prospectively evaluate the relationship between nut and peanut butter consumption and CVD, including CHD and stroke, among women with type 2 diabetes in the Nurses' Health Study. A secondary objective was to examine whether nuts favorably influence the risk of CVD through modulation of plasma lipids or markers of inflammation.

Inclusion Criteria:

- Were women
- Were participating in the Nurses Health study
- Had type 2 diabetes
- Did not drop from Nurses Health study.

Exclusion Criteria:

- Had any type of cardiovascular disease at baseline
- Had any type of cancer at baseline.

Description of Study Protocol:**Recruitment**

Nurses Health Study, not described here.

Design

Prospective cohort.

Dietary Intake/Dietary Assessment Methodology

- The semi-quantitative FFQ included 61 foods in 1980 and was later revised and expanded
- Participants were asked to report their average frequency of consumption of selected foods and beverages with a specified commonly used unit or portion size during the previous year
- Nutrient intakes were computed by multiplying the consumption frequency of each food by the nutrient content of the specified portion and then summing up the products across all food items. The food composition values were obtained from the Harvard University Food Composition Database derived from the USDA sources and supplemented with manufacturer information.
- In the 1980 and 1984 dietary questionnaires, participants were asked how often, on average, they consumed nuts [serving size, 28g (one ounce)] during the previous year according to the following categories: Never/almost never, one to three servings a month, one serving a week, two to four servings a week, five to six servings a week, one serving a day, two to three servings a day, four to six servings a day or more than six servings a day
- In the 1986, 1990, 1994 and 1998 dietary questionnaires, the question for nuts was divided into two separate questions: Peanuts and other nuts
- Total nut consumption was calculated in the questionnaires since 1986 as the sum of the intake for peanuts and other nuts
- Consumption of peanut butter [serving size, 16g (one tablespoon)] was assessed in 1980, 1984, 1986, 1990, 1994 and 1998 with the same nine responses as those for nut consumption
- To represent long-term intake of nuts and peanut butter most accurately and to reduce measurement error, we calculated the cumulative mean number of servings per week from all available questionnaires.

Blinding Used

Patient physicians were unaware of study purpose.

Statistical Analysis

- All analyses were performed with SAS version 9.1 (SAS Institute)
- All P-values were two-sided
- Women were classified into four exposure categories according to frequency of consumption: almost never, one to three servings a month to less than one serving a week, one to four servings a week and at least five servings a week
- Hazard ratios for CVD endpoints were estimated using Cox proportional hazard models with calendar year as time scales
- Potential confounders included age (five-year categories), BMI (less than 23.0, 23.0 to 24.9, 25.0 to 29.9, 30.0 to 34.9 and 35.0 or more), quintiles of physical activity (hours per week), smoking status [never smoker, past smoker, or current smoker (one to 14 and 15 or more cigarettes a day)], alcohol consumption (non-drinker and zero to 4.9, 5.0 to 9.9, 10 to 14.9 and 15.0g or more a day), current aspirin use, post-menopausal hormone therapy (pre-menopausal and never, past and current user) and total energy intake (kJ per day)
- Further adjustment for nutrients and foods that have previously been found to be associated with CVD risk (trans and saturated fats, glycemic load, cereal fiber, processed meat, fruit and vegetables) was also performed
- Generalized linear regression models were used to calculate the age-adjusted geometric

means and standard errors for lipids among each category of nut consumption. Log transformations were performed to approximate normal distribution of plasma concentrations makers.

- Multiple linear regression analyses were used to assess the relationship between increment of one serving per day of nut and peanut butter consumption and plasma concentrations of lipid and inflammatory markers.

Data Collection Summary:

Timing of Measurements

- Study started in 1980 and ended in 2002
- Food frequency questionnaires were conducted in 1980, 1984, 1986, 1990, 1994, 1998
- Blood sample collection was conducted in a subpopulation (N) from 1989 to 1990
- Blood sample analyses were conducted in 2003
- Participants completed a questionnaire every two years, including assessment of physical activity, cigarette smoking, alcohol consumption, menopausal status and use of post-menopausal hormone therapy. Additional questions included duration of diabetes, family history of MI, hypertension and hypercholesterolemia.

Control Variables

Determined from general surveys, medical records and food frequency questionnaires:

- *Age*: Years
- *BMI*: kg/m²
- *Physical activity*: Hours per week
- *Current smokers*: Percentage
- *Alcohol consumption*: Grams per day
- *Duration of diabetes*: Years
- *Family history of MI*: Percentage
- *Hypertension*: Percentage
- *Hypercholesterolemia*: Percentage
- *Hormone use among post-menopausal women*: Percentage
- *Multivitamin use*: Percentage
- *Vitamin E use*: Percentage
- *Aspirin use*: Percentage
- *Energy intake*: kJ per day
- *Cereal fiber*: Grams per day
- *Polyunsaturated fat*: Grams per day
- *Monounsaturated fat*: Grams per day
- *Saturated fat*: Grams per day
- *Trans fat*: Grams per day
- *Glycemic load*: Grams epr day
- *Red meat*: Servings per day
- *Fruit and vegetables*: Servings per day.

End-point-associated Variables

- Nonfatal MI: It was confirmed by reviewing medical records using the WHO criteria for symptoms plus either typical electrocardiographic changes or elevated cardiac enzyme

levels.

- Fatal CHD: Cardiovascular deaths were confirmed by review of medical records or autopsy reports with the permission of the next of kin. The cause listed on the death certificate was not considered sufficient for documentation of a coronary death. Sudden deaths (i.e., death within one hour of symptom onset in a woman without known disease that could explain death) were considered cardiovascular deaths.
- Stroke: A definite diagnosis of stroke was made when computerized tomography scan, MRI, angiography, surgery or autopsy confirmed the lesion; otherwise, a probable diagnosis was made.
- All causes of deaths: These were reported by next of kin, the postal system and through records of the National Death Index.
- Associated variables determined from food frequency questionnaires and food composition databases:
 - *Nuts*: Servings per day
 - *Peanut butter*: Servings per day
- Associated sensitivity variables determined from blood sample analyses
 - *LDL cholesterol*: mmol per L
 - *Non-HDL cholesterol*: mmol per L
 - *HDL cholesterol*: mmol per L
 - *Total cholesterol*: mmol per L
 - *ApoB*: Grams per L.

Description of Actual Data Sample:

- Initial N: 6,309 women
- Attrition (final N): 6,309 women
- Age: 55.9±9.1 (calculated from averaging baseline values)
- Anthropometrics: BMI was 29.5±6.4kg/m² (calculated from averaging baseline values)
- Location: Research team in Boston, MA.

Summary of Results:

Key Findings:

- During 54,656 person-years of follow-up, there were 452 CHD events (including MI and revascularization) and 182 incident stroke cases. Women at study entry who consumed more nuts and peanut butter were leaner, more physically active, and tended to smoke less. They also reported a slightly longer duration of diabetes and less hypertension. Women consuming at least 5 servings/wk of nuts and peanut butter had higher intakes of total energy, polyunsaturated fat, red meat, fruits, and vegetables and a significantly lower glycemic load than the other exposure categories of nut consumption
- Frequent nut and peanut butter consumption was inversely associated with total CVD risk in age-adjusted analyses.
- After adjustment for conventional CVD risk factors, consumption of at least 5 servings/wk of nuts or peanut butter [serving size, 28 g (1 ounce) for nuts and 16 g (1 tablespoon) for peanut butter] was significantly associated with a lower risk of CVD (relative risk = 0.56; 95% CI: 0.36–0.89).
- Increasing nut consumption was significantly associated with a more favorable plasma lipid profile, including lower LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein-B-100 concentrations; but not significant associations for HDL cholesterol or inflammatory markers.

Other Findings

Plasma lipid concentrations according to consumption of nuts and peanut butter among 1171 women with type 2 diabetes in the NHS who had blood collected in 1989 -1990¹

Nuts and peanut butter consumption	Almost never	1–3 servings/mo to 1 serving/wk	2–4 servings/wk	5 servings/wk	Linear regression coefficients β ± SE	P-value²
n	96	410	504	161		

LDL cholesterol, mmol/L						
Age adjusted	3.6	3.55	3.43	3.3	-0.20 ± 0.06	0.0008
Multivariate adjusted ³	3.66	3.55	3.43	3.31	-0.17 ± 0.17	0.008
Non-HDL cholesterol, mmol/L						
Age adjusted	4.73	4.54	4.37	4.29	-0.25 ± 0.07	0.0003
Multivariate adjusted ³	4.72	4.51	4.38	4.35	-0.18 ± 0.07	0.014
HDL cholesterol, mmol/L						
Age adjusted	1.31	1.24	1.31	1.27	0.03 ± 0.02	0.26
Multivariate adjusted ³	1.34	1.26	1.3	1.24	-0.02 ± 0.02	0.45
Total cholesterol, mmol/L						
Age adjusted	6.09	5.83	5.75	5.62	-0.22 ± 0.07	0.0009
Multivariate adjusted ³	6.11	5.83	5.76	5.65	-0.19 ± 0.07	0.007

1 One serving nuts = 16 g (1 tablespoon) and 1 serving peanut butter = 28 g (1 ounce).

2 P-values are from the multiple linear regression models for the relation between nut and peanut butter consumption (1 serving/d increase) and biomarkers.

3 Multivariate model was adjusted for age, BMI, physical activity, alcohol consumption, family history of MI, hormone use and menopausal status, smoking, aspirin intake, duration of diabetes years, hypertension, total energy intake, cereal fiber, glycemic load, saturated fat, and trans fat.

Author Conclusion:

Frequent nut consumption, especially at least 5 servings/wk, was associated with a reduced risk of CVD and MI among women with type 2 diabetes. These data support a role for regular consumption of nuts in reducing CVD risk among patients with diabetes.

Reviewer Comments:

This was a very well conducted prospective cohort study.

Reviewer agrees with authors that sample size power to conduct more detailed analysis for biomarker associations was not the most ideal.

From Research Design and Implementation Rating Checklist.

4.0. Unclear. Method of handling withdrawals was not described. Nonetheless, authors presented results based on the total initial sample population.

4.2. Unclear. Characteristics of withdrawals, if any, were not described.

8.4 and 8.7. Unclear. Power calculation and intent to treat analysis were not described.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	Was the research question clearly stated?	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	Was the selection of study subjects/patients free from bias?	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	???
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	???
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	Was blinding used to prevent introduction of bias?	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	N/A
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	???
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	???
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes