Published in final edited form as:
J Nutr Health Aging. 2014 May ; 18(5): 496–502. doi:10.1007/s12603-014-0014-6.

LONG-TERM INTAKE OF NUTS IN RELATION TO COGNITIVE FUNCTION IN OLDER WOMEN

J. O'BRIEN[1,2], **O. OKEREKE**[1,2,3], **E. DEVORE**[1], **B. ROSNER**[1,4], **M. BRETELER**[2,5], and **F. GRODSTEIN**[1,2]

[1]Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[3]Department of Psychiatry, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

[4]Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA

[5]German Center for Neurodegenerative Diseases, Bonn, Germany

Abstract

Objective—Nuts contain nutrients that may benefit brain health; thus, we examined long-term intake of nuts in relation to cognition in older women.

Design—Population-based prospective cohort study.

Setting—Academic research using data from the Nurses' Health Study.

Participants—Nut intake was assessed in a food-frequency questionnaire beginning in1980, and approximately every four years thereafter. Between 1995–2001, 16,010 women age 70 or older (mean age = 74 years) without a history of stroke were administered 4 repeated telephone-based cognitive interviews over 6 years. Our final sample included 15,467 women who completed an initial cognitive interview and had complete information on nut intake.

Main Outcome Measures—The Telephone Interview for Cognitive Status (TICS), a global score averaging the results of all tests (TICS, immediate and delayed verbal recall, category fluency, and attention), and a verbal memory score averaging the results of tests of verbal recall.

Results—In multivariable-adjusted linear regression models, higher long-term total nut intake was associated with better average cognitive status for all cognitive outcomes. For the global composite score combining all tests, women consuming at least 5 servings of nuts/week had higher scores than non-consumers (mean difference=0.08 standard units, 95% confidence interval 0.00–0.15; p-trend=0.003). This mean difference of 0.08 is equivalent to the mean difference we

Corresponding author: Jacqueline O'Brien, Brigham and Women's Hospital, Channing Division of Network Medicine, 181 Longwood Avenue, Boston MA 02115, Phone: 617-240-0097, Fax: 617-525-4597, jlo391@mail.harvard.edu.

The authors responsibilities were as follows – JLO and FG: design of experiment, data analysis, manuscript preparation; FG: collection of the data; JLO, OIO, EED, BR, MMBB, FG: significant manuscript revisions, consultation, and advice.

None of the authors report a conflict of interest.

find between women 2 years apart in age. Long-term intake of nuts was not associated with rates of cognitive decline.

Conclusions—Higher nut intake may be related to better overall cognition at older ages, and could be an easily-modifiable public health intervention.

Keywords

Cognition; cognitive decline; cognitive function; cohort study; diet; epidemiology; nutrition

Introduction

Nuts contain both monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA), and are low in saturated fats (1). Short-term randomized trials have shown that nut intake decreases total cholesterol and LDL cholesterol (2), and in observational epidemiologic studies, nuts have been associated with reduced risk of cardiovascular disease (3–5) and type 2 diabetes (6, 7). Because all of these vascular factors have been related to cognition, nuts may also have the potential to prevent or slow cognitive decline in older adults. Moreover, walnuts in particular are high in α-linolenic acid (ALA), an essential fatty acid important for brain function (8), and thus merit focused research.

Despite a clear rationale for the hypothesis that nut intake may be related to better cognitive function in late life, and the relative ease of modifying nut intake in the population, few studies have investigated nut intake in relation to cognitive outcomes (9–11). These existing studies have largely focused on broad dietary patterns (10, 11) (including one study of Mediterranean diet in the Nurses' Health Study (11)), with only one study carefully examining nuts in particular (9). Thus, we utilized the Nurses' Health Study to investigate in detail how long-term dietary intake of nuts is related to cognitive outcomes in later life.

Subjects and methods

The Nurses' Health Study (NHS) began in 1976, when 121,700 female registered nurses, aged 30–55 years, completed a mailed questionnaire on their health and lifestyle. Similar questionnaires have been mailed to participants every two years thereafter. Beginning in 1980, a food-frequency questionnaire (FFQ) was included in this assessment (12); food frequency data are collected approximately every four years. Between 1995–2001, a telephone-based sub-study of cognitive function was started, and women age 70 or over, without a history of stroke, were invited to participate; 93% of eligible women completed an initial interview (n = 19,415). A total of four telephone cognitive assessments were administered, at approximately two-year intervals. Over 90% follow-up was maintained in the cognitive sub-study, among those who remained alive at each interview. The Institutional Review Board of Brigham and Women's Hospital (Boston, MA) approved this study.

Diet Assessment

Dietary information was assessed with the Willett semi-quantitative food frequency questionnaire. The 1980 questionnaire contained 61 items, and an expanded 130-item

version was used in 1984, 1986, and every subsequent four years. Participants reported their average frequency of food consumption during the previous year, by specified units or portion sizes (e.g., 1 small packet or 1 oz of nuts). There were nine response choices: never/almost never, one to three times a month, once a week, two to four times a week, five to six times a week, once a day, two to three times a day, four to six times a day, or more than six times a day. Reproducibility and validity of the dietary questionnaires has been documented (13).

In 1980 and 1984, participants were asked, "How often, on average, did you consume nuts (serving size, 28g [1 oz]) during the previous year?" In 1986, 1990, and 1994, the question for nuts was split into two categories: one for peanuts, and one for other nuts. In 1998, the questionnaire was expanded to include a question for peanuts, other nuts, and walnuts, since the fat content of walnuts is distinct from other nuts (they are particularly high in alpha-linolenic acid). Total nut consumption for each year was calculated as the sum of intakes of peanuts and other nuts. In a validation study, nut intake from the FFQ correlated well with intakes based on four, one-week dietary records collected over one year ($r = 0.57–0.75$ for nuts, corrected for within-person variation in dietary records) (14).

Cognitive Assessment

Our cognitive interview consisted of six tests; the Telephone Interview for Cognitive Status (TICS), a modified version of the Mini-Mental State Examination; immediate and delayed recalls of the East Boston Memory Test; a test of category fluency (i.e., naming as many animals as possible in one minute); a delayed recall of the TICS 10-word list (given at the end of the interview, approximately 15 minutes later); and the digit span backwards test.

In analyses, we focused on three primary outcomes encompassing global cognition and verbal memory: (1) the TICS; (2) a composite score of global cognition (i.e., an average of all cognitive tests); and (3) a composite score of verbal memory (i.e., an average of the immediate and delayed recalls of the East Boston Memory Test and the 10-word list). We chose to consider verbal memory since it is an important predictor of Alzheimer's disease (15). Since the individual cognitive tests are scaled differently, we used z-scores to create the composite global and verbal memory scores. Specifically, we subtracted the mean of each test at the initial assessment from the individual's score and divided the difference by the standard deviation at the initial assessment. Composite scores were calculated only for women who completed all contributing tests. We considered the results of the individual tests in the cognitive battery as secondary outcomes.

In a previous validation study of the telephone cognitive testing, the correlation between the global composite score from the telephone interview versus an extensive in-person assessment was 0.81. There was also high reliability of TICS performance between 35 women who were given the test twice, 31 days apart (test-retest correlation = 0.7), as well as high inter-rater reliability across 10 interviewers who scored the same interview ($r > 0.95$ for each cognitive test).

Population for analysis

Of the 19,415 women who completed the initial cognitive interview, we excluded 3,405 participants from our analysis because they did not provide dietary data at the initial dietary assessment. Of the 16,010 remaining women, 15,467 had complete information on total nut intake and were thus part of our analytic sample for total nuts. Women included in our analysis were similar to those who were excluded (e.g., mean age = 74.2 v. 74.5 years; 17% v. 18% with BMI > 30 kg/m^2; 77% v. 80% with an associate's degree, 23% v. 20% with a bachelor's degree or higher, respectively).

Because walnuts were only included on the FFQ beginning in 1998, analyses of walnuts are based on the 16,995 people who completed the 1998 FFQ.

Statistical analysis

Because cognitive decline develops over many years, long-term exposures are probably most relevant for prevention. Thus, to obtain a stable measure of long-term nut intake beginning in mid-life, we averaged total nut intake from 1980 through the dietary assessment immediately before the first cognitive interview. Since walnut intake was not available prior to 1998, analyses of walnut intake are based only on that single measure.

We divided total nut intake into five categories: never or < 1/month, 1–3/month, 1/week, 2–4/week, ≥ 5/week. Although there were relatively few people in the highest intake categories for nuts, we specified these categories a priori based on previous research in the NHS on other health outcomes (e.g., type 2 diabetes (6), CHD (4)), which has demonstrated that inverse associations are strongest in these highest intake categories. Nonetheless, walnut intake had a particularly limited distribution, prohibiting us from examining categories beyond ≥ 1/week; thus, our ability to examine walnut intake separately was somewhat limited.

We analyzed the cognitive outcomes with two different, complementary approaches. First, we averaged the four repeated measures of cognitive function taken over 6 years to create an outcome representing overall cognitive status at older ages, and modeled the association of long-term nut intake to cognitive status using linear regression (with separate models for the TICS, global composite and verbal memory composite scores). Such averaging of repeated measures of cognition has some advantages, since it attenuates variability in each single cognitive assessment, which may be helpful when cognition is measured in a population of well-educated women with moderate follow-up time. Furthermore, given the long exposure period over which we measured nut intake (approximately 15–20 years) prior to our first cognitive assessment, it is possible that any influence of nut intake on cognitive decline was initiated prior to our first assessment of cognitive function, and thus it is important to capture relations of nut consumption to "average" cognition in late life.

At the same time, it is of interest to assess the trajectory of the four repeated cognitive scores and their relation to nut consumption, and we have seen significant relationships between dietary factors and cognitive change in some of our previous research (16–18). Thus, in our second approach we used multivariable-adjusted, linear mixed effects models to estimate mean differences in rates of cognitive decline over the follow-up period, across categories of

nut intake. We observed a non-linear pattern of test scores over time (e.g., mean scores improved from the first to second administration likely due to learning effects, and generally declined subsequently as subjects aged and as learning effects diminished). Thus, for models of cognitive decline we used an average of the cognitive scores from the first two timepoints, or a "robust baseline", and then applied the linear mixed effects model on three data points (i.e., an average of timepoints one and two; timepoint three; and timepoint four). By using a robust baseline, the relation of cognitive change and time was linear. These models included randomly varying intercepts and slopes to allow for description of individual cognitive trajectories over time, as well as explicit tests for the relationship of nut intake to rates of cognitive decline. Tests for trend were calculated using a continuous variable of servings per week.

We adjusted for the following potential confounders in our models: age (continuous), education (registered nurse, bachelor's degree, graduate degree), time span between cognitive interviews (continuous; for models of average cognition only), body mass index (BMI) (<22, 22–24, 25–30, 30+ kg/m2), use of antidepressants (yes, no), smoking status (never, past, current), physical activity (quintiles), total energy intake (quintiles), alcohol intake (none, 0–14 g/day, 15+ g/day), use of multivitamins (yes, no), history of high blood pressure (yes, no), high cholesterol (yes, no), myocardial infarction (yes, no), and type 2 diabetes (yes, no). All covariates were determined as of the time of the initial cognitive interview, except that total caloric intake was averaged to correspond with the method used to calculate nut intake. In some analyses, we also considered tooth loss as a potential confounding variable, utilizing an item on the 1996 Nurses' Health Study mailed questionnaire inquiring about the number of teeth lost.

All analyses were performed with SAS software (version 9.2; SAS, Cary, NC).

Results

The characteristics of study participants at the initial cognitive interview are presented in Table 1, according to long-term total nut intake. Women who consumed nuts most frequently had slightly higher educational attainment, tended to be more physically active, and were more likely to use multivitamins and have a lower BMI. Higher frequency nut consumers were less likely to be smokers, or have a history of high blood pressure.

After adjusting for potential confounding factors, increasingly higher total nut intake was related to increasingly better overall cognition at older ages, as assessed by the TICS (P-trend = 0.02; Table 2), global composite score (P - trend = 0.003), and the verbal composite score (P- trend = 0.005). For example, for the global score, the mean difference in cognitive scores comparing the highest to the lowest categories of nut intake was 0.08 standard units (95% CI: 0.004, 0.15), and for the verbal score this difference was 0.09 standard units (95% CI: 0.01, 0.17). To help interpret these mean differences, we derived the effect of aging directly from this cohort. In this population, we find that one year of age is associated with a mean decline of 0.04 standard units on both the global and verbal composite scores. Therefore, the mean differences reported here comparing the highest to lowest categories of nut intake are equivalent to approximately two years of cognitive aging. When we examined

the individual tests in the cognitive battery as secondary outcomes (supplementary table 1), we saw the general pattern that higher intakes of total nuts were associated with better scores, with statistically significant or borderline significant results for the 10-word list immediate recall (p-trend=0.0015), 10-word list delayed recall (p-trend=0.07), and digit span backwards test (p-trend=0.01).

Furthermore, there was a suggestion that those who consumed walnuts 1 to 3 times per month had better cognition than those who consumed walnuts less than once per month, on all three cognitive outcomes, with statistically significant findings on the global and verbal memory composite scores; for example, on the global composite score, those with moderate walnut intake of 1–3 servings per month scored higher by 0.03 standard units (95% CI 0.01–0.06) than women with lower walnut intake. However, findings should be interpreted cautiously, since results were unstable in the highest category of walnut intake (>1 serving/week), due to the small sample in that group, and we found no overall trend of increasingly better cognitive performance with increasing walnut intake.

When comparing rates of cognitive decline over the follow-up period according to total nut intake, nut intake was not significantly associated with rate of decline on any of the tests (P-trends = 0.61 for TICS, 0.21 for global composite score, and 0.26 for verbal composite score in fully adjusted models) (Table 3), although there was less decline in the highest category of total nut intake (i.e., ≥ 5/week). When we examined the individual tests in the cognitive battery as secondary outcomes (supplementary table 2), we also found no relations of nut intake to decline on the cognitive tests. There was no significant difference in rates of decline over the follow-up period for walnut intake (p-trends = 0.42 for TICS, 0.27 for global composite score, and 0.29 for verbal composite score for fully adjusted models).

In additional analyses, we removed cardiovascular risk factors (i.e., history of high cholesterol, high blood pressure, myocardial infarction, type 2 diabetes, depression) because these covariates could possibly mediate the association of interest, but results remained essentially unchanged. Moreover, the exclusion of women with clinical diagnosis of type 2 diabetes or myocardial infarction as of the initial cognitive interview (who may have changed their diet due to diagnosis) did not change these results meaningfully either. To evaluate the influence of other potentially confounding dietary components, we adjusted for total red meat, fruit, vegetable and fish intake. Although the overall pattern of results did not change, estimates were slightly attenuated (e.g., the mean difference in the global score (i.e., where the average of the four repeated scores was the outcome) comparing the highest to lowest categories of nut intake was 0.06 standard units (95% CI: −0.02, 0.13, p-trend = 0.03). Finally, additional adjustment for tooth loss did not change our findings.

Discussion

Higher total nut intake over the long term was associated with modestly better cognitive performance at older ages across all three of our cognitive outcomes in this cohort. There was a suggestion that walnut intake may be related to better cognitive performance, although it is difficult to draw conclusions since very few women consumed walnuts more than 1 to 3 times per month. Neither total nut intake nor walnut intake was related to rates of decline in

cognitive function over the follow-up period, although our follow-up period for measuring cognitive decline was relatively short compared to the long period over which we measured dietary exposures.

The largest mean differences in analyses of average cognition were observed between the highest total nut intake categories (e.g., 2–4 times per week, or ≥ 5 times per week) and the non-consumers, despite the limited sample size in the high frequency intake categories. These findings are consistent with those we observe for other chronic health conditions in this cohort (eg, type 2 diabetes, coronary heart disease), and future research should probably focus on these higher intake categories. We did not have adequate distribution of walnut intake in our sample to separately consider higher levels of intake, and clearly research is merited in investigations which can also focus on broader distributions of walnut intake due to their particular biologic interest, with high levels of ALA.

To our knowledge, only one detailed prospective study has focused on the relation of nut intake to cognition. A study from the Doetinchem Cohort with 2613 participants reported that total nut intake was associated with better cognitive function at their initial assessment, but not with decline over five years of follow-up (9). Likewise, our data suggest that nut intake is related to overall level of cognition at older ages, but not with cognitive decline over 6 years; thus, their results were fairly consistent with ours.

Several lines of evidence support the hypothesis that nut intake is related to cognitive function. Nuts are nutrient-dense (e.g., high in protein, unsaturated fat, dietary fiber, antioxidants, phyto-estrogens and other phytochemicals (19)), and inverse associations have been identified involving nut intake and numerous vascular outcomes (e.g., non-fatal myocardial infarction (3, 4), fatal coronary heart disease (3, 4, 20), and type 2 diabetes (6, 7)). Randomized clinical trials have demonstrated vascular benefits of nuts (e.g., lipid lowering effects (21), improved inflammatory markers (22), decreased insulin resistance (22), and improved endothelial function (23)), which all appear to contribute to improved cognitive function (24). Additionally, while most nuts are high in monounsaturated fatty acids, walnuts are unique because they are composed largely of polyunsaturated fatty acids, especially ALA, and studies have shown that rodents given diets rich in α – linolenic acid have improved learning and memory (25).

Strengths of the current study include the prospective study design, multiple dietary assessments over approximately 15–20 years, and repeated measurements of cognition. Our study also has several limitations. Since it is an observational study, uncontrolled or residual confounding could explain the relation between frequent nut intake and improved cognitive performance. Specifically, if eating more nuts clusters with higher educational attainment, better health behaviors and health awareness, these factors could explain part of the observed association between nut intake and better cognitive function. That said, detailed information on the health and lifestyle of the participants permitted adjustment for many potential confounders, and the medical knowledge of the Nurses improves the accuracy of self-reported medical information. We also considered the possibility that poor tooth health could make nut consumption difficult, as research has demonstrated that poor oral health predicts poor diet quality [26], and can be a reflection of overall health. However, our study

design, with multiple assessments of nut intake over many years, from mid-life through older ages, would limit such biases. In addition, over 90% of participants reported having lost fewer than two teeth in the years immediately preceding the baseline cognitive assessment; furthermore, to address this limitation, we tried to adjust for tooth loss in our models and this did not change our results.

Secondly, diet assessments are subject to misclassification. However, since data on dietary intake was collected prospectively, any misreporting of diet information should be random, and would result in the underestimation of associations. Furthermore, we were able to reduce random measurement error by averaging together total nut intake from multiple time-points, and our validation data indicate that nut intake is reasonably well-measured. Thus, such bias is likely to be minimal. Of note, walnut intake was evaluated from a single food frequency questionnaire, and thus those results are more likely to underestimate true relations.

In conclusion, we found a modest relationship between long-term total nut intake and cognitive function. Nut intake could potentially represent a fairly simple dietary modification if future research confirms our findings. Additional investigations- particularly with a focus on those who consume nuts frequently - is warranted.

Acknowledgments

We acknowledge the substantial scientific contribution made by women participating in the Nurses' Health Study.

Financial support: This work was supported by grants P01 CA87969 and T32-AG000158 (JO) from the National Institute of Health, grant K08029813 (OO) from the National Institute on Aging, and the California Walnuts Commission.

Abbreviations

ALA	α-linolenic acid
BMI	body mass index
CI	confidence interval
FFQ	food-frequency questionnaire
MET-h	metabolic equivalence hour
MUFA	monounsaturated fatty acid
NHS	Nurses' Health Study
PUFA	polyunsaturated fatty acid
SD	standard deviation
TICS	Telephone Interview for Cognitive Status

References

1. Brufau G, Boatella J, Rafecas M. Nuts: source of energy and macronutrients. The British journal of nutrition. 2006; 96 (Suppl 2):S24–28. [PubMed: 17125529]

2. Mukuddem-Petersen J, Oosthuizen W, Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. The Journal of nutrition. 2005; 135:2082–2089. [PubMed: 16140880]

3. Fraser GE, Sabate J, Beeson WL, Strahan TM. The Adventist Health Study. A possible protective effect of nut consumption on risk of coronary heart disease. Archives of Internal Medicine. 1992; 152:1416–1424. [PubMed: 1627021]

4. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, Speizer FE, Hennekens CH, Willett WC. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ (Clinical research ed). 1998; 317:1341–1345.

5. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. The New England journal of medicine. 1996; 334:1156–1162. [PubMed: 8602181]

6. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA: the journal of the American Medical Association. 2002; 288:2554–2560.

7. Jenkins DJ, Hu FB, Tapsell LC, Josse AR, Kendall CW. Possible benefit of nuts in type 2 diabetes. The Journal of nutrition. 2008; 138:1752S–1756S. [PubMed: 18716181]

8. Yehuda S, Rabinovitz S, Mostofsky DI. Essential fatty acids and the brain: from infancy to aging. Neurobiology of aging. 2005; 26 (Suppl 1):98–102. [PubMed: 16226347]

9. Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP, van Gelder BM, Verhagen H, Verschuren WM. Fruit and vegetable intake and cognitive decline in middle-aged men and women: the Doetinchem Cohort Study. The British journal of nutrition. 2011; 106:752–761. [PubMed: 21477405]

10. Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, Buring JE, Willett WC, Okereke OI. Mediterranean diet and cognitive function in older age. Epidemiology. 2013; 24:490–499. [PubMed: 23676264]

11. Samieri C, Okereke OI, EED, Grodstein F. Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. J Nutr. 2013; 143:493–499. [PubMed: 23365105]

12. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. American Journal of Epidemiology. 1988; 127:188–199. [PubMed: 3337073]

13. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. American Journal of Epidemiology. 1985; 122:51–65. [PubMed: 4014201]

14. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. International journal of epidemiology. 1989; 18:858–867. [PubMed: 2621022]

15. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, Zamora D, Goodkind M, Bell K, Stern Y, Devanand DP. Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. Archives of General Psychiatry. 2006; 63:916–924. [PubMed: 16894068]

16. Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. The New England journal of medicine. 2005; 352:245–253. [PubMed: 15659724]

17. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Annals of Neurology. 2005; 57:713–720. [PubMed: 15852398]

18. Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. Annals of Neurology. 2012

19. Alexiadou K, Katsilambros N. Nuts: anti-atherogenic food? European journal of internal medicine. 2011; 22:141–146. [PubMed: 21402243]

20. Ellsworth JL, Kushi LH, Folsom AR. Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's Health Study. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2001; 11:372–377.

21. Griel AE, Kris-Etherton PM. Tree nuts and the lipid profile: a review of clinical studies. The British journal of nutrition. 2006; 96 (Suppl 2):S68–78. [PubMed: 17125536]

22. Casas-Agustench P, Bullo M, Salas-Salvado J. Nuts, inflammation and insulin resistance. Asia Pacific Journal of Clinical Nutrition. 2010; 19:124–130. [PubMed: 20199997]

23. Casas-Agustench P, Lopez-Uriarte P, Ros E, Bullo M, Salas-Salvado J. Nuts, hypertension and endothelial function. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2011; 21 (Suppl 1):S21–33.

24. Grodstein F. Cardiovascular risk factors and cognitive function. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2007; 3:S16–22.

25. Haider S, Batool Z, Tabassum S, Perveen T, Saleem S, Naqvi F, Javed H, Haleem DJ. Effects of Walnuts (Juglans regia) on Learning and Memory Functions. Plant Foods for Human Nutrition (Dordrecht, Netherlands). 2011

26. Shatenstein B, Gauvin L, Keller H, Richard L, Gaudreau P, Giroux F, Gray-Donald K, Jabbour M, Morais JA, Payette H. Baseline determinants of global diet quality in older men and women from the NuAge cohort. J Nutr Health Aging. 2013; 17:419–425. [PubMed: 23636542]

Table 1

Characteristics of women at the initial cognitive interview (1995–2001) in the Nurses' Health Study cognitive substudy by total nut intake*

	Never, <1/mo	1–3/month	1/week	2–4/week	≥5/week
n (% of study population)	7211 (46.6)	3590(23.2)	3671(23.7)	738 (4.8)	257 (1.7)
Mean age, years (SD)	74.2 (2.3)	74.2 (2.3)	74.3 (2.3)	74.4 (2.4)	74.5 (2.2)
Education (%)					
Registered Nurse degree	79.9	76.9	74.5	72.8	63.4
Bachelor's degree	14.5	17.1	18.7	18.3	25.7
Graduate degree	5.6	6.0	6.9	8.9	10.9
Antidepressant use (%)	6.1	6.2	5.1	5.3	5.1
Total calories (kcal/d)	1566.5	1695.3	1800.5	1951.1	2040.3
Smoking (%)					
Never	46.0	46.6	46.9	47.3	43.6
Former	45.1	45.7	46.1	46.2	50.2
Current	8.9	7.8	7.0	6.4	6.2
High blood pressure (%)	57.3	54.9	52.4	52.2	44.8
High cholesterol (%)	65.1	65.5	65.7	64.4	65.0
Myocardial infarction (%)	6.3	5.8	5.8	4.2	5.1
Type 2 diabetes (%)	10.8	9.2	9.3	9.9	9.3
Physical activity (MET-h/wk)†	14.9	16.1	17.3	19.8	17.5
BMI (%)					
<22	20.0	20.8	20.3	24.9	29.1
22–24	25.9	25.9	28.1	31.2	29.1
25–29	34.9	35.4	36.1	31.2	26.2
30+	19.1	17.9	15.6	12.7	15.6
Alcohol intake (%)					
None	55.8	46.2	42.9	41.6	49.6
1–14 g/d	38.3	44.5	46.8	43.0	41.0
≥ 15 g/d	7.0	9.4	10.4	15.4	9.5
Multivitamin use (%)	60.9	64.3	67.6	69.2	68.4
Cognitive Performance, Mean (SD)					

	Never, <1/mo	1–3/month	1/week	2–4/week	≥5/week
TICS (n= 15467)‡	33.7 (2.8)	33.8 (2.6)	33.9 (2.7)	33.9 (2.6)	33.9 (3.0)
Global Score (n=13432)‡	−0.02 (0.61)	0.01 (0.59)	0.01 (0.60)	−0.00(0.60)	0.02(0.62)
Verbal Score (n=13447)‡	−0.02 (0.69)	0.01 (0.69)	0.00 (0.69)	−0.02(0.72)	0.01(0.72)

*Serving of nuts is 28 g, or 1 ounce; total nut intake averaged from 1980 until the initial cognitive interview and includes all nut types.

†MET-h, metabolic equivalence hour (i.e., the amount of energy expended during 1 hour of sitting).

‡TICS = Telephone Interview for Cognitive Status; Global score is an average of the z-scores of six tests among those with complete data on all tests (TICS, East Boston Immediate recall, East Boston Delayed recall, 10 words list Delayed recall, verbal/category function, digit backwards); Verbal memory score is an average of the z-scores of four tests among those with complete data on all tests (10 word list Immediate recall, East Boston Immediate recall, East Boston Delayed recall, 10 words list Delayed recall).

Table 2

Mean differences in cognitive status in older age (the average of all 4 timepoints of cognitive tests), by long-term total nut intake and walnut intake

Total Nuts*	**Never, <1/mo**	**1–3/month**	**1/week**	**2–4/week**	**≥ 5/week**	**P-trend§**
TICS (n = 15,467)						
Model 1†	0.00	0.07 (−0.03, 0.17)	0.08 (−0.02, 0.18)	0.14 (−0.05, 0.33)	0.21 (−0.10, 0.52)	0.004
Model 2‡	0.00	0.05 (−0.05, 0.15)	0.04 (−0.06, 0.14)	0.13 (−0.06, 0.32)	0.21 (−0.10, 0.52)	0.02
Global (n = 15,168)						
Model 1	0.00	0.03 (0.00, 0.05)	0.01 (−0.01, 0.04)	0.04 (−0.01, 0.08)	0.07 (0.00, 0.15)	0.001
Model 2	0.00	0.02 (0.00, 0.05)	0.01 (−0.02, 0.03)	0.04 (−0.01, 0.09)	0.08 (0.00, 0.15)	0.003
Verbal (n =15,170)						
Model 1	0.00	0.02 (0.01, 0.04)	0.01 (−0.02, 0.03)	0.02 (−0.03, 0.07)	0.08 (−0.01, 0.16)	0.009
Model 2	0.00	0.02 (−0.01, 0.04)	0.01 (−0.02, 0.03)	0.03 (−0.02, 0.08)	0.09 (0.01, 0.17)	0.005
Walnuts¶	Never, <1/mo	1–3/month	≥ 1/week#			
TICS (n = 16,995)						
Model 1	0.00	0.12 (0.02, 0.22)	0.11 (−0.05, 0.27)			0.46
Model 2	0.00	0.05 (−0.05, 0.16)	0.09 (−0.07, 0.25)			0.66
Global (n = 16,720)						
Model 1	0.00	0.05 (0.02, 0.07)	0.00 (−0.04, 0.04)			0.96
Model 2	0.00	0.03 (0.01, 0.06)	0.00 (−0.04, 0.04)			0.90
Verbal (n = 16,721)						
Model 1	0.00	0.04 (0.01, 0.07)	−0.01 (−0.06, 0.03)			0.43
Model 2	0.00	0.03 (0.00, 0.06)	−0.01 (−0.05, 0.03)			0.51

*Sample sizes differ for each cognitive outcome, since tests included in the global and verbal scores were added gradually throughout the initial cognitive assessment period. Covariates determined as of the initial cognitive interview.

†Model 1: Adjusted for age, education (registered nurse, bachelor's degree, and graduate degree), time span between cognitive interviews (continuous).

‡Model 2: Adjusted for Model 1 variables and use of antidepressant medication, smoking (never, former, current), physical activity (quintiles - MET-h/wk), total calories (quintiles), body mass index (< 22, 22–24, 25–29, ≥ 30 kg/m2), alcohol intake (0, 1–14, ≥15 g/d), multivitamin use (yes/no), history of high blood pressure (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), and type 2 diabetes (yes/no).

§P-trend is from analysis using total nuts (or walnuts) in servings per day as a continuous variable.

¶Sample sizes differ for the walnut analysis because subjects were only asked about walnuts on the diet questionnaire in 1998 and thus the sample is based on women who answered the 1998 questionnaire.

[#]The highest frequency categories for walnut consumption were collapsed due to low numbers (never, <1/mo = 13,687; 1–3/mo = 2,420; 1/wk = 571; 2–4/wk = 239; ≥ 5/wk = 78).

J Nutr Health Aging. Author manuscript; available in PMC 2015 May 01.

Table 3

Mean differences in slopes of cognitive decline by long-term total nut intake and walnut intake

Total nuts*	**Never, <1/mo**	**1–3/month**	**1/week**	**2–4/week**	**≥ 5/week**	**P-trend§**
TICS						
Model 1†	0.00	0.07 (−0.09, 0.23)	−0.12 (−0.28, 0.03)	0.03 (−0.26, 0.32)	0.11 (−0.41, 0.63)	0.92
Model 2‡	0.00	0.08 (−0.08, 0.24)	−0.11 (−0.27, 0.05)	0.09 (−0.21, 0.38)	0.17 (−0.35, 0. 70)	0.61
Global						
Model 1	0.00	−0.00 (−0.04, 0.03)	−0.00 (−0.04, 0.04)	0.02 (−0.05, 0.09)	0.08 (−0.05, 0.21)	0.18
Model 2	0.00	−0.01 (−0.05, 0.03)	−0.01 (−0.04, 0.03)	0.02 (−0.06, 0.09)	0.08 (−0.05, 0.21)	0.21
Verbal						
Model 1	0.00	−0.00 (−0.05, 0.04)	−0.01 (−0.05, 0.04)	0.03 (−0.06, 0.11)	0.11 (−0.04, 0.26)	0.24
Model 2	0.00	−0.01 (−0.05, 0.04)	−0.01 (−0.06, 0.03)	0.03 (−0.06, 0.12)	0.11 (−0.04, 0.27)	0.26
Walnuts	Never, <1/mo	1–3/month	≥ 1/week¶			
TICS						
Model 1	0.00	0.13 (−0.04, 0.29)	−0.11 (−0.36, 0.15)			0.36
Model 2	0.00	0.11 (−0.06, 0.27)	−0.08 (−0.34, 0.18)			0.42
Global						
Model 1	0.00	0.04 (0.00, 0.08)	−0.03 (−0.09, 0.03)			0.31
Model 2	0.00	0.03 (−0.01, 0.07)	−0.03 (−0.09, 0.03)			0.27
Verbal						
Model 1	0.00	0.02 (−0.03, 0.07)	−0.07 (−0.14, 0.01)			0.28
Model 2	0.00	0.01 (−0.04, 0.06)	−0.06 (−0.14, 0.01)			0.29

*Covariates calculated at time of first cognitive interview.

†Model 1: Adjusted for age, education (registered nurse, bachelor's degree, and graduate degree).

‡Model 2: Adjusted for Model 1 variables and use of antidepressant medication, smoking (never, former, current), physical activity (quintiles -MET-h/wk), total calories (quintiles), body mass index (< 22, 22–24, 25–29, ≥ 30 kg/m2), alcohol intake (0, 1–14, ≥15 g/d), multivitamin use (yes/no,), history of high blood pressure (yes/no), high cholesterol (yes/no), myocardial infarction (yes/no), and type 2 diabetes (yes/no).

§P-trend is from analysis using total nuts (or walnuts) in servings per day as a continuous variable.

¶The highest frequency categories for walnut consumption were collapsed due to low numbers (never, <1/mo = 13,687; 1–3/mo = 2,420; 1/wk = 571; 2–4/wk = 239; ≥ 5/wk = 78).