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Dietary fat types and 4-year cognitive change in community-dwelling older women

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Abstract

Objective—To relate dietary fat types to cognitive change in healthy community-based elders.

Methods—Among 6,183 older participants in the Women's Health Study, we related intake of major fatty acids (FAs) (saturated [SFA], mono-unsaturated [MUFA], total poly-unsaturated [PUFA], *trans*-unsaturated) to late-life cognitive trajectory. Serial cognitive testing, conducted over 4 years, began 5 years post-dietary assessment. Primary outcomes were global cognition (averaging tests of general cognition, verbal memory and semantic fluency) and verbal memory (averaging tests of recall). We used analyses of response profiles and logistic regression to estimate multivariable-adjusted differences in cognitive trajectory and risk of worst cognitive change (worst 10%) by fat intake.

Results—Higher SFA intake was associated with worse global cognitive (p-linear-trend=0.008) and verbal memory (p-linear-trend=0.01) trajectories. There was a higher risk of worst cognitive change, comparing highest vs. lowest SFA quintiles: the multivariable-adjusted odds ratio (OR) (95% confidence interval, CI) was 1.64 (1.04,2.58) for global cognition and 1.65 (1.04,2.61) for verbal memory. By contrast, higher MUFA intake was related to better global cognitive (p-linear-trend<0.001) and verbal memory (p-linear-trend=0.009) trajectories, and lower OR (95% CI) of worst cognitive change in global cognition (0.52 [0.31,0.88]) and verbal memory (0.56 [0.34,0.94]). Total fat, PUFA, and *trans* fat intakes were not associated with cognitive trajectory.

Interpretation—Higher SFA intake was associated with worse global cognitive and verbal memory trajectories, while higher MUFA intake was related to better trajectories. Thus, different

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consumption levels of the major specific fat types, rather than total fat intake itself, appeared to influence cognitive aging.

INTRODUCTION

The continuum of cognitive decline is important in dementia research; early decline is likely more amenable than clinical-level impairments to preventive or disease-modifying interventions.[1–3] Emerging evidence links dietary fat to late-life cognition; mechanisms may involve lipid profiles,[4, 5] inflammation[6–8], cardiovascular health[9–14] or neuroprotection[15, 16]. While these potential links are compelling, it is challenging to implement long-term randomized trials of varying intakes of major fatty acids (FA). Thus, consensus has emerged that more well-conducted, large-scale prospective studies with serial cognitive assessments are needed to address long-term relations of fats to cognitive aging.[17]

We examined relations of major fat types to cognitive change over 4 years among ~6,000 older, community-dwelling participants of the Women's Health Study (WHS). We hypothesized: worse cognitive trajectories among women with higher vs. lower consumption of saturated FA (SFA) and *trans* fats ("bad fats") and better trajectories among women with higher vs. lower intake of monounsaturated FA (MUFA) and polyunsaturated FA (PUFA) ("good fats").

METHODS

Participants

Women's Health Study—The WHS was a randomized, double-blind, placebo-controlled 2×2 trial of aspirin and vitamin E supplements for primary prevention of heart disease and cancer[18]. From 1992–1995, 39,876 US female health professionals, aged ≥45 years, were randomized to one of four factorial groups. All were initially free of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, transient cerebral ischemia, liver disease, renal disease, peptic ulcer, and gout; women using corticosteroids, anticoagulants, or vitamin A and E supplements were excluded. Participants completed annual questionnaires updating information on health and lifestyle factors and clinical outcomes. The trial was completed on March 31, 2004; total follow-up was >99%.[19]

The Cognitive Sub-study—In 1998, cognitive testing began among WHS participants aged ≥65 years. Of 7,175 age-eligible participants, 6,377 (89%) completed the initial assessment. Follow-up assessments occurred in 2000 and 2002: 5,692 (89%) of those who completed the initial assessment also participated in a second wave of assessment; 5,226 women (82%) participated in wave 3. The mean duration was 2 years between each wave. This study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA).

The Cognitive Function Assessment

Cognitive exams were conducted via telephone by hypotheses-blind interviewers and consisted of: (1) Telephone Interview for Cognitive Status (TICS); (2) immediate and (3) delayed recall trials of the East Boston Memory Test; (4) delayed recall trial of the TICS 10-word list; and (5) category fluency. The TICS[20] (range: 0–41 points) is a test of general cognitive function, similar to the Mini-Mental State Examination[21], and has high reliability and validity. The East Boston Memory Test (EBMT)[22] is a verbal (episodic) memory task of paragraph recall (range: 0–12 points) and involves immediate and 15-minute delayed recalls. The 15-minute delayed recall of the TICS 10-word list (range: 0–10 points) also assesses verbal memory. Lastly, category fluency (naming as many different animals as possible in

one minute) captures language and executive functions such as abstract conceptualization and use of strategy.[23]

Reliability and Validity of Telephone Cognitive Assessments

To examine test-retest reliability, we administered the TICS twice after a one-month interval among 35 similar older women; the Pearson correlation was 0.7 ($p<0.001$). Regarding inter-rater reliability, intraclass correlations were >0.95 on each test. In a validity study, 61 well-educated older women completed both telephone-based and comprehensive (21-test) in-person assessments; the Pearson correlation was 0.81 between the global scores based on telephone vs. in-person tests. Also, expected relations of age and *APOE* ε4[24] to telephone-based cognition have been observed. In a further validation, cognitive impairment determined by telephone assessment was strongly associated with clinically-diagnosed dementia three years later[25].

Ascertainment of Diet

A 131-item, semi-quantitative food-frequency questionnaire (FFQ) was administered at WHS baseline. For each item, portion size was specified, and participants were asked how often, on average, during the past year they consumed that amount. We computed nutrient scores by multiplying the frequency of consumption of each food unit by the nutrient content of that portion size according to US Department of Agriculture food composition tables, supplemented with information from manufacturers. Details on development, use, reproducibility and validity of the FFQ have been published previously.[26, 27]

Ascertainment of covariates

Information on covariates was obtained from annual questionnaires. Validation work demonstrated high accuracy of self-reported conditions (e.g., diabetes)[28].

Population for Analysis

We excluded 194 women from the cognitive sub-study (n=6,377) with incomplete FFQ data. Thus, there were 6,183 participants for the analysis who completed initial testing; of these, 5,532 (89%) completed wave 2; 5,084 (82%) completed wave 3 (Supplemental Fig. 1).

Statistical Analysis

We categorized SFA, MUFA, PUFA (primarily comprised of linolenic acid), *trans* fat and total fat into quintiles. We conducted analyses using the multivariate nutrient density method,[29] in which fats are expressed as percentages of total energy and analyzed in the same model, along with protein as a percentage of energy and total energy intake (i.e., isocaloric); coefficients can be interpreted as the effect of substituting a specific amount of energy from fat for the same amount of energy from carbohydrates. This is the preferred analytic method for dietary components comprising relatively large proportions of calories[27, 29]. Primary outcomes were: global score, calculated by averaging z-scores from the TICS, delayed 10-word recall, immediate and delayed EBMT and category fluency tests; verbal memory, calculated by averaging z-scores of the EBMT and 10-word immediate and delayed recall trials. Outcomes were normally-distributed.

First, we examined mean scores across the three assessments, by fat quintiles, while adjusting for trial design variables (aspirin/vitamin E randomization status) as well as socio-demographic factors (age at initial testing, education, high household income, race) found to be the greatest potential confounders. Scores were repeated continuous outcomes, and we modeled the effect of fat intake using time-by-fat quintile interaction terms. Because the pattern of scores was non-linear (likely due to learning effects typically concentrated in the

early test administrations, such as between the first and second interviews[30]), we used general linear models of response profiles to estimate the means, and modeled timepoints as binary indicator variables (i.e., time 1, 2 or 3)[30, 31]. This approach imposes minimal structure on outcome trends, permits valid estimation of effects in non-linear data and can handle unbalanced patterns of longitudinal observations due to missing responses. We fitted models by maximum likelihood, incorporating longitudinal correlations within participants, using unstructured covariance matrices. For statistical testing, we used Wald tests[31], and examined linear trends for fat quintiles continuously (participants in a given quintile were assigned the median value). Secondarily, because initial cognitive score was related to performance during follow-up, we repeated the above approach including interaction terms of initial (time 1) score-x-follow-up period (i.e., time 2 or 3). Analyses were conducted utilizing PROC MIXED in SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

We considered other variables (based on the literature and distributions in our sample) for the multivariable-adjusted models. Thus, for primary analysis, fully-adjusted models included: age at first cognitive interview (years), highest attained education (bachelor's degree or above vs. associate's degree), aspirin and vitamin E randomization assignment, race (white/non-white), household income (≥$50,000 per year/less), body mass index (BMI) (<25, 25.0–29.9, or ≥30 kg/m2), current smoking (yes/no), postmenopausal hormone use (ever/never), hypertension (self-reported history, use of antihypertensive medications, or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; yes/no), elevated cholesterol (self-reported history, use of lipid-lowering medications, or blood cholesterol >240 mg/dL; yes/no), depression (self-reported history; yes/no), diabetes (self-reported history; yes/no), daily alcohol consumption (≥1 drinks/day), and moderate or above frequency of exercise (≥1 times/week). Of note, self-reported household income (reported in categories as high as $100K+/yr or as low as <$10K/yr) was not available in 400 women; as our objective was to account for higher vs. lower income, these participants were placed in the reference (under $50K) group. Similarly, women missing self-reported white race or depression information (53 and 74, respectively) were placed in the non-white race (reference) and non-depressed (reference) categories, rather than excluded.

In a secondary analysis, we calculated odds ratios (ORs) of worst change in cognitive performance over 4 years (i.e., between the first and third testing waves). This was defined as being in the bottom 10% of the distributions of the global or verbal memory change scores. Such a population-based 10% cutpoint is common in cognitive research[32] and has high sensitivity and specificity for impairment.[33] Logistic regression models adjusted for covariates described above as well as the time between assessments (years). However, given the influence of initial score on the amount of absolute change that can be observed, we constructed an additional model including a term for residual initial score (after adjustment for intake of fats, protein, energy and the other covariates in linear regression), to account for initial performance while reducing bias. These analyses were restricted to the subset within our study population who completed both first and third testing waves (n=5,072 for global score; n=5,069 for verbal memory). We also addressed effects of substituting energy (e.g., 5%) from "good" fat (MUFA, PUFA) for that same energy amount from "bad" fat (SFA, *trans* fat) on the ORs (with confidence limits) of worst change, using the estimates, standard errors and covariances for the different fats obtained directly from the multivariate nutrient density models[27].

We repeated the primary analysis models after excluding 455 women who developed cardiovascular disease (from the beginning of the WHS parent study to the end of the cognitive sub-study), as CVD is a major risk factor for late-life cognitive dysfunction[34] and strongly related to fat intake.[14, 35, 36] CVD included all medical record-confirmed non-fatal myocardial infarction, non-fatal stroke, cardiovascular-related deaths, or vascular disease as

evidenced by coronary artery bypass graft or percutaneous transluminal coronary angioplasty or stenting.[19]

Finally, we addressed possible interactions by two key factors: 1) age, as prior work[37] in a similar cohort revealed significant interactions between age and fat intake on cognitive decline; 2) history of elevated cholesterol, due to its central relation to fat intake.

RESULTS

Baseline characteristics

Women with higher intakes of all fats had higher BMI, higher prevalence of current smoking, and lower prevalence of moderate-or-above exercise. Women with higher SFA and MUFA intakes had lower prevalence of hypercholesterolemia and higher prevalence of daily alcohol consumption. Those with higher PUFA intake had higher prevalence of daily alcohol and lower prevalence of high income. Finally, women with higher *trans* fat intake had lower prevalence of high income and education (Table 1).

Prospective analyses of cognitive change

Lower SFA and higher MUFA intakes were significantly related to more favorable global and verbal memory scores over time, after adjusting for socio-demographic variables (data not shown). Multivariable-adjusted results were similar (Figures 1 and 2). Wald p-values for linear trends of time-by-fat quintiles interactions illustrated significantly worse trajectories with higher SFA intakes for global score (p=0.008) and verbal memory (p=0.01). Similarly, trajectories were more favorable among those with higher MUFA intake, for global score (p<0.001) and verbal memory (p=0.009). There were no associations of PUFA, *trans* fat or total fat with cognitive change. Results were similar when models included adjustment for initial score-by-follow-up time interactions (Supplemental Figure 2, results shown for SFA and MUFA only).

For further illustration of differences in cognitive outcomes by fat consumption, the mean differences in change over 4 years can be obtained directly from the models (Table 2). For example, multivariable-adjusted mean differences (95% confidence intervals [CI]) in 4-year change were −0.12 (−0.20, −0.03) standard units for global score and −0.13 (−0.23, −0.03) standard units for verbal memory, comparing the highest vs. lowest SFA quintiles. Comparing women in the highest vs. lowest MUFA quintile, the adjusted mean differences (95% CI) in change were 0.17 (0.07,0.26) standard units for global score and 0.16 (0.04,0.27) standard units for verbal memory. To help interpret these differences, we contrasted them with the estimate for the relation of age to cognitive change. Estimates for 4-year cognitive change comparing women in the highest vs. lowest SFA quintiles were similar to those for women 5-to-6 years apart at the start of testing (i.e., 5–6 added years of aging). By contrast, mean differences in change comparing the extreme MUFA quintiles were equivalent to 6-to-7 fewer years of aging.

Findings from analyses addressing worst cognitive change were consistent with results from primary analyses (Table 3). Women with the highest vs. lowest SFA intake had 60–70% greater odds of worst change on global score and verbal memory. By contrast, women with the highest vs. lowest MUFA intake had 40–50% lower odds of worst change. Results were the same in models that adjusted for residual initial cognitive scores (data not shown). Finally, when estimating impacts of “good” fat vs. “bad” fat substitutions, we found that replacing 5% of energy from SFA with the same amount of energy from MUFA was associated with significantly lower odds of worst change: ORs were 0.47 (95% CI=0.25,0.89) for global score and verbal memory. There were no significant associations of

substituting *trans* fat with MUFA or PUFA for either outcome. (Substitution data shown in Supplemental Table 1).

In analyses excluding women with CVD, results were similar to those from the primary analyses: i.e., better trajectories in global score (n=5,717) and verbal memory (n=5,721) with lower SFA and higher MUFA intakes (p-linear-trends≤0.01; data not shown).

There were no significant three-way-interactions for age (above/below median age-at-initial testing [71 years]) or hypercholesterolemia with fat intake and time (data not shown). Of note, there appeared to be differences in initial global scores by SFA and MUFA intakes – driven by performance among persons below median age (e.g., p-interaction<0.01 for age-x-SFA intake on initial global score only; data not shown in Figure 1); no such differences or interactions were observed for verbal memory.

DISCUSSION

In this study of community-dwelling older women, higher saturated fat intake was associated with a poorer 4-year trajectory of global cognition and verbal memory. By contrast, higher MUFA intake was related to better global cognitive and verbal memory trajectory. The magnitude of relations found for extreme fat quintiles and cognitive change were equivalent to ~6 years of aging. Regarding worst global cognitive or verbal memory 4-year change, there was a 60–70% higher risk comparing the highest vs. lowest SFA quintiles, but a 40–50% lower risk comparing the highest vs. lowest MUFA quintiles. There were no associations of PUFA, *trans* fat or total fat with cognitive change.

The results regarding SFA are similar to those from prior large-scale studies[38–40] that examined "bad" fats with comparable methodology (e.g., adjusting for presence of other fats). For example, Morris et al.[38] observed that increasing SFA (p-trend=0.04) and t*rans* fat intakes (p-trend=0.07) were linearly associated with faster global cognitive decline over 5.6 years among 2,560 age-65+ participants. Similarly, among 1,486 older women of the Nurses' Health Study with type 2 diabetes, higher SFA and *trans* intakes were associated with worse cognitive decline.[40] Finally, Eskelinen et al.[39] reported a 2-fold elevated risk of MCI (mild cognitive impairment) among 1,341 participants with high vs. low mid-life SFA intake; although the analysis was cross-sectional, the 21-year interval between diet assessment (mean age=50 years) and cognitive examination may have approximated prospective development of MCI. Regarding our null findings for *trans* fats, a potential explanation is their narrower distribution among these generally healthy women, compared to that in other cohorts[38, 40]. Although *trans* fat intake can be quite high among Americans,[41] the median percentage of energy from *trans* fat in the highest quintile for our cohort was 1.8%.

There are limited data available from larger-scale prospective studies regarding "good" fats. Solfrizzi et al.[42, 43] identified significant relations of higher MUFA and PUFA intakes to better cognitive aging. Devore et al.[40] observed inverse associations of higher MUFA consumption (p-trend=0.06) and higher intake of PUFA relative to SFA (p-trend=0.03) with global cognitive change among older diabetic women. Navqi et al. found significantly less 3-year memory decline among 482 Women's Health Initiative participants in the highest vs. lowest MUFA intake quartiles (SFA and *trans* fat were not significantly related to cognitive change; associations for PUFAs were not reported)[44]. Morris et al.[38] did not find significant associations of MUFA or PUFA with global cognitive decline, but estimates suggested inverse relations. Vercambre and colleagues[37] reported inverse relations of MUFA and PUFA to 5-year global cognitive decline among 2,551 women with CVD or risk factors – but only among the oldest (73–91 years). Variability in study designs may partly explain

inconsistency in findings. For example, investigators used different methods for defining fat types (e.g., total PUFA, PUFA from spreads[45], linolenic acid (n-6 PUFA) only[46]), may address different sub-groups (e.g., those with diabetes[40]), or may not account for other fat types – as is recommended by experts in the field.[38] Finally, unsaturated fats may be more susceptible to random misclassification when using only a one-time or a lower-precision diet instrument.

Strengths of this study include its prospective design, large sample, well-validated FFQ, availability of numerous health and lifestyle covariates, high follow-up and focus on late-life cognitive change. Limitations should also be considered. First, repeated diet assessments were not available – increasing random measurement error, which could attenuate associations. Second, reverse causation is possible; however, there was a 5-year lag between the FFQ and initial cognitive assessment, and it seems unlikely that many women had substantial cognitive impairment at study entry, as all WHS participants had successfully completed a pre-randomization run-in phase that scrutinized compliance to assigned treatment. Third, generalizability of findings among these mostly Caucasian women is an issue. Although it seems unlikely that basic biological relations would differ greatly, further research on dietary fat and cognition among racial/ethnic minorities and men is needed. Lastly, residual confounding is possible, and the data should be interpreted with appropriate caution.

In conclusion, these data suggest that elevated SFA intake is related to worse late-life cognitive trajectory, and increased MUFA intake is related to better cognitive aging. Thus, decreasing SFA and increasing MUFA merit further consideration in promoting healthy cognitive aging, and dietary patterns that incorporate higher intake of “good” fats (e.g., Mediterranean)[47] should be further addressed in cognitive aging research. Findings from this large-scale prospective study help to address the identified need for an expanded, stronger evidence base on dietary factors and cognitive decline.[17, 48]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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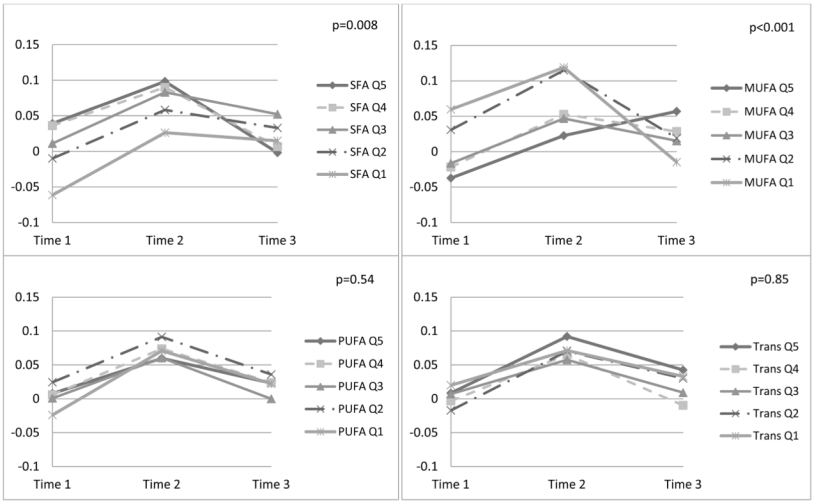

Figure 1. Multivariable-adjusted Least-squares Means Global Cognitive* Scores over 4 years, by Quintiles of Fat Types (n=6,172)†

* Global score combines results of the TICS (Telephone Interview for Cognitive Status), category fluency, immediate and delayed recall trials of East Boston Memory Test (EBMT), and delayed recall trial of the TICS 10-word list; verbal memory score combines results of the immediate and delayed recall trials of EBMT and the TICS 10-word list; mean (SD) span between the 1st and 3rd assessments was 4.0 (0.3) years. Adjusted least-squares means were obtained from the repeated measures analysis models involving N=6,172 participants.

† SFA = saturated fatty acid; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; Trans = *trans* fatty acid; Q1 = lowest quintile of intake; Q5 = highest quintile of intake; models adjusted for mean-centered age at initial cognitive assessment (continuous, in years), educational attainment (bachelor's degree or above versus associate's degree), race (white/non-white), annual household income (≥$50,000/less), randomized treatment assignment (aspirin, vitamin E), other fat intake, protein intake, total energy intake, body mass index (<25, 25.0–29.9, or ≥30 kg/m^2), current cigarette smoking (yes/no), postmenopausal hormone use (ever/never), history of hypertension (yes/no), history of elevated cholesterol (yes/no), history of depression (yes/no), history of diabetes (yes/no), daily alcohol consumption (yes/no), exercise (≥1 times per week/less), and all covariate-by-time interactions. P-values are from the Wald tests of interactions between fat type consumption level (medians-per-quintile) and time. N.B.: N=11 women were missing data at initial cognitive testing on components tests required to compute the global score.

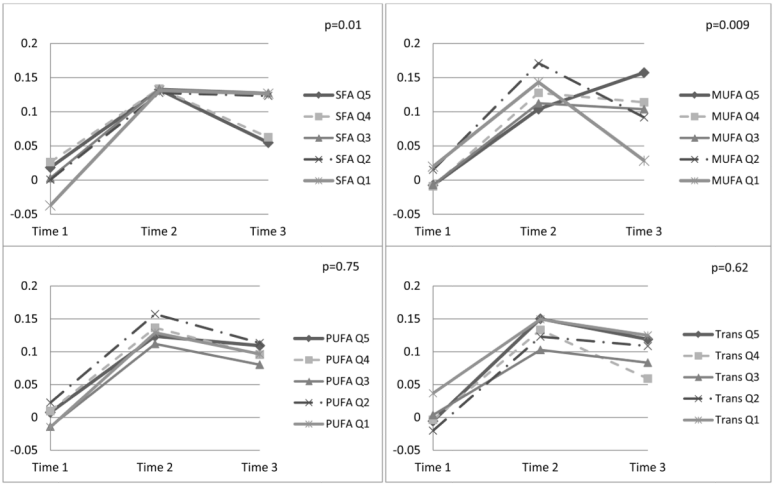

Figure 2. Multivariable-adjusted Least-squares Means Verbal Memory* Scores over 4 years, by Quintiles of Fat Types (n=6,176)†

* Global score combines results of the TICS (Telephone Interview for Cognitive Status), category fluency, immediate and delayed recall trials of East Boston Memory Test (EBMT), and delayed recall trial of the TICS 10-word list; verbal memory score combines results of the immediate and delayed recall trials of EBMT and the TICS 10-word list; mean (SD) span between the 1st and 3rd assessments was 4.0 (0.3) years. Adjusted least-squares means were obtained from the repeated measures analysis models involving N=6,176 participants.

† SFA = saturated fatty acid; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; Trans = *trans* fatty acid; Q1 = lowest quintile of intake; Q5 = highest quintile of intake; models adjusted for mean-centered age at initial cognitive assessment (continuous, in years), educational attainment (bachelor's degree or above versus associate's degree), race (white/non-white), annual household income (≥$50,000/less), randomized treatment assignment (aspirin, vitamin E), other fat intake, protein intake, total energy intake, body mass index (<25, 25.0–29.9, or ≥30 kg/m^2), current cigarette smoking (yes/no), postmenopausal hormone use (ever/never), history of hypertension (yes/no), history of elevated cholesterol (yes/no), history of depression (yes/no), history of diabetes (yes/no), daily alcohol consumption (yes/no), exercise (≥1 times per week/less), and all covariate-by-time interactions. P-values are from the Wald tests of interactions between fat type consumption level (medians-per-quintile) and time. N.B.: N=7 women were missing data at initial cognitive testing on components tests required to compute the verbal memory composite.

Table 1

Characteristics of the Sample at Dietary Assessment, by Quintiles of Major Fat Types (n=6,183)*

	Saturated fat Quintiles			Mono-unsaturated fat Quintiles			Poly-unsaturated fat Quintiles			*Trans* fat Quintiles		
	1	3	5	1	3	5	1	3	5	1	3	5
Mean age at study entry (years)	66.5	66.3	65.9	66.4	66.1	66.1	66.5	66.1	66.3	66.6	66.1	66.0
Mean age at initial cognitive testing (years)	72.1	71.9	71.6	72.0	71.7	71.8	72.1	71.8	72.0	72.3	71.7	71.6
Mean body mass index (kg/m^2)	24.8	25.9	26.3	25.1	25.8	26.1	25.4	25.7	25.8	25.1	25.8	26.2
Household income ≥$50,000/year	26	23	23	26	25	25	29	23	23	29	26	21
Caucasian race	94	97	97	95	97	97	96	97	96	95	97	97
Randomized to aspirin	52	50	50	51	49	50	52	50	52	50	52	50
Randomized to vitamin E	53	50	48	52	50	49	49	50	50	52	51	51
Bachelor's degree or higher education	39	31	30	38	34	31	37	34	31	40	35	28
History of hypertension	39	41	41	39	39	42	39	41	42	40	39	44
History of elevated cholesterol	54	42	35	50	42	39	43	43	41	48	42	42
History of diabetes	4	3	4	5	4	3	4	3	4	4	4	3
Current smoking	5	9	19	5	9	18	8	9	13	6	11	14
Current hormone use	43	42	36	43	42	38	41	41	40	44	41	37
History of depression	6	7	7	6	6	6	7	5	6	5	6	6
Exercise level												
≥4 times per week	19	10	7	18	11	8	14	12	11	21	11	7
1–3 times per week	36	29	22	34	29	20	32	28	25	35	28	23
Rare or never	45	61	71	48	61	71	55	60	63	44	61	71
Alcohol use												
1 or more drinks/day	10	12	16	10	11	18	11	12	16	12	13	12
1–6 drinks/week	23	31	29	23	31	30	26	31	28	27	31	28
1–3 drinks/month or less, or never	67	57	55	67	58	52	64	57	56	61	57	60
Mean total calories (kcal/day)	1769	1753	1744	1768	1754	1740	1761	1754	1750	1765	1752	1747
Total fat (median % energy)	22.4	29.5	36.4	22.1	29.5	37.1	24.3	29.7	34.4	23.8	30.0	33.9
Protein (median % energy)	17.9	18.5	18.5	18.5	18.4	18.2	18.5	18.5	17.7	19.0	18.6	17.0
Carbohydrate (median % energy)	59.3	51.9	44.7	59.3	52.0	44.3	56.8	51.8	47.5	56.6	51.1	48.7
SFA† (median % energy)	7.0	9.8	13.1	7.3	9.9	12.3	8.8	9.9	10.5	7.7	10.2	11.2

	Saturated fat Quintiles			Mono-unsaturated fat Quintiles			Poly-unsaturated fat Quintiles			*Trans* fat Quintiles		
	1	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**	**1**	**3**	**5**
MUFA[†] (median % energy)	8.0	11.0	13.6	7.8	11.0	14.4	8.9	11.1	12.8	8.4	11.1	12.9
PUFA[†] (median % energy)	5.1	5.8	6.0	4.6	5.7	6.8	4.1	5.7	7.7	5.1	5.7	6.2
***Trans* fat**[†] (median % energy)	0.65	1.06	1.37	0.64	1.07	1.46	0.84	1.10	1.20	0.55	1.04	1.84
Median PUFA/SFA[†] **ratio**	0.75	0.59	0.45	0.66	0.58	0.55	0.45	0.57	0.77	0.69	0.56	0.56

[*] Figures are percentages of respondents, unless stated otherwise. Due to rounding, percentages may not add to 100.

[†] SFA = saturated fatty acid; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; Trans = *trans*-unsaturated fatty acid.

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Table 2

Multivariable-adjusted* Mean Differences (95% Confidence Intervals) in 4-year Cognitive Change†, by Fat Quintiles.

	GLOBAL SCORE† (in standard units)	VERBAL MEMORY† (in standard units)
SFA‡		
Quintile 1	0.00	0.00
Quintile 2	−0.03 (−0.10, 0.03)	−0.04 (−0.12, 0.04)
Quintile 3	−0.04 (−0.11, 0.04)	−0.04 (−0.12, 0.05)
Quintile 4	−0.11 (−0.19, −0.03)	−0.13 (−0.22, −0.03)
Quintile 5	−0.12 (−0.20, −0.03)	−0.13 (−0.23, −0.03)
MUFA‡		
Quintile 1	0.00	0.00
Quintile 2	0.06 (−0.00, 0.13)	0.07 (−0.01, 0.15)
Quintile 3	0.11 (0.03, 0.18)	0.10 (0.01, 0.19)
Quintile 4	0.12 (0.04, 0.21)	0.11 (0.02, 0.21)
Quintile 5	0.17 (0.07, 0.26)	0.16 (0.04, 0.27)
PUFA‡		
Quintile 1	0.00	0.00
Quintile 2	−0.03 (−0.09, 0.02)	−0.02 (−0.09, 0.05)
Quintile 3	−0.05 (−0.11, 0.01)	−0.02 (−0.09, 0.05)
Quintile 4	−0.03 (−0.09, 0.03)	−0.03 (−0.10, 0.05)
Quintile 5	−0.03 (−0.10, 0.04)	−0.01 (−0.09, 0.07)
***Trans*‡**		
Quintile 1	0.00	0.00
Quintile 2	0.03 (−0.03, 0.10)	0.04 (−0.03, 0.11)
Quintile 3	−0.01 (−0.08, 0.05)	−0.01 (−0.09, 0.07)
Quintile 4	−0.02 (−0.09, 0.05)	−0.03 (−0.11, 0.06)
Quintile 5	0.02 (−0.05, 0.09)	0.04 (−0.05, 0.12)

*Models adjusted for age at 1st cognitive assessment (years), educational attainment (bachelor's degree or above vs. associate's degree), race (white/non-white), annual household income (≥$50,000/less), randomized treatment assignment (aspirin, vitamin E), other fat intake, protein intake, total energy intake, body mass index (<25, 25.0–29.9, or ≥30 kg/m^2), current cigarette smoking (yes/no),

postmenopausal hormone use (ever/never), history of hypertension (yes/no), history of elevated cholesterol (yes/no), history of depression (yes/no), history of diabetes (yes/no), daily alcohol consumption (yes/no), exercise (≥1 times per week/less), and all covariate-by-time interactions. For all fat types, the reference category=quintile 1 (lowest quintile of intake).

†Global score combines results of TICS (Telephone Interview for Cognitive Status), category fluency, immediate and delayed recall trials of East Boston Memory Test (EBMT), and delayed recall trial of the TICS 10-word list. Verbal memory score combines results of the immediate and delayed recall trials of the EBMT and the TICS 10-word list. Mean (SD) interval between first and third waves of cognitive assessment = 4.0 (0.3) years. Adjusted mean differences were obtained from the repeated measures analysis models involving N=6,172 participants for the global score and N=6,176 participants for verbal memory.

‡SFA = saturated fatty acid; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; Trans = *trans*-unsaturated fatty acid.

Table 3

Multivariable-adjusted Odds Ratios (95% CI) of Worst Cognitive Change over 4 years, by Quintiles of Major Fats*

Fat Type and Cognitive Outcome	Quintile of Fat Intake					Linear Trend
	1st	2nd	3rd	4th	5th	P-value
Saturated fat						
Global score†	1.0	1.23 (0.88, 1.71)	1.28 (0.88, 1.87)	1.54 (1.02, 2.33)	1.64 (1.04, 2.58)	0.02
Verbal memory†	1.0	1.35 (0.97, 1.89)	1.39 (0.95, 2.02)	1.63 (1.08, 2.47)	1.65 (1.04, 2.61)	0.02
Mono-unsaturated fat						
Global score†	1.0	0.96 (0.68, 1.34)	0.73 (0.49, 1.08)	0.66 (0.42, 1.03)	0.52 (0.31, 0.88)	0.006
Verbal memory†	1.0	0.89 (0.64, 1.24)	0.65 (0.44, 0.97)	0.67 (0.43, 1.04)	0.56 (0.34, 0.94)	0.02
Poly-unsaturated fat						
Global score†	1.0	1.28 (0.95, 1.73)	1.23 (0.90, 1.69)	1.33 (0.96, 1.85)	1.37 (0.97, 1.94)	0.09
Verbal memory†	1.0	1.11 (0.83, 1.49)	0.93 (0.68, 1.27)	1.11 (0.80, 1.53)	1.03 (0.73, 1.46)	0.82
***Trans* fat**						
Global score†	1.0	0.90 (0.66, 1.23)	0.94 (0.68, 1.32)	1.08 (0.76, 1.52)	0.76 (0.52, 1.11)	0.49
Verbal memory†	1.0	0.85 (0.62, 1.17)	1.05 (0.75, 1.45)	1.00 (0.71, 1.41)	0.72 (0.49, 1.06)	0.32

*Models adjusted for mean-centered age at initial cognitive assessment (continuous, in years), educational attainment (bachelor's degree or above versus associate's degree), aspirin and vitamin E randomization assignment, race (white/non-white), household income level (≥$50,000 per year/less), body mass index (kg/m^2), cigarette smoking (current/past/never), postmenopausal hormone use (ever/never), history of hypertension (yes/no), history of elevated cholesterol (yes/no), history of depression (yes/no), history of diabetes (yes/no), alcohol consumption (none/rare, 1–6 per week, >=7 per week), exercise frequency (never/rare, 1–3 times per week, >=4 times per week), other fat intake, protein intake, total energy intake, and time span between 1st and 3rd cognitive assessment (years). For all fat types, the reference category=lowest (1st) quintile of intake.

†Global score combines results of the TICS (Telephone Interview for Cognitive Status), category fluency, immediate and delayed recall trials of East Boston Memory Test (EBMT), and delayed recall trial of the TICS 10-word list; verbal memory score combines results of the immediate and delayed recall trials of EBMT and the TICS 10-word list; mean (SD) span between the 1st and 3rd assessments was 4.0 (0.3) years. Of 5,084 women who participated in waves 1 and 3, there were 12 missing data on components tests required to compute the global score (N=5,072 for analysis) and 15 missing data on components tests required to compute the verbal memory composite (N=5,069 for analysis).