Long-Term Dietary Intake and Subjective Cognitive Decline

Long-Term Dietary Intake and Subjective Cognitive Decline

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Abstract

Introduction

Dementia is a neurodegenerative disease characterized by progressive decline of cognitive function and performance, leading to disability and functional dependence. In the rapidly aging world, dementia has become a leading public health concern due to the significant health-care costs and caregiver burden it contributes. However, there is still no effective treatment for dementia. To date, diet has been shown as one of the few modifiable risk factors for cognitive decline. Because current evidence on the associations between specific long-term dietary intakes and cognitive function remained inconclusive, we conducted the following research aiming to address this important issue. More than 20 years of long-term dietary intake was assessed by the semi-quantitative food frequency questionnaire (SFFQ). Subjective cognitive decline (SCD), a preclinical phase before dementia, was the outcome. The study population was two large prospective cohorts in the US, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

In Chapter 1, we investigated the associations between long-term dietary intakes of total flavonoids, flavonoid subclass, and flavonoids-containing foods with SCD. The findings from this study provided strong evidence to further support the possible beneficial roles for flavonoids on subsequent cognitive function. To our knowledge, we were the first to report the dose-response relationship for each flavonoid subclass, which could provide important guidance for future interventional studies.

In Chapter 2, the associations between total energy and dietary fat intake with SCD was examined. The results from this study showed positive associations between total energy intake

and SCD, which was supported by numerous animal studies. The associations between specific fatty acid intakes and SCD were inconsistent during the follow-up period and across cohorts. Further research is needed to confirm these findings.

In Chapter 3, the associations between intakes of specific protein sources, amino acids, and protein-containing foods with SCD were assessed. Higher intakes of protein, compared with total carbohydrates, were associated with lower odds of subsequent SCD. Plant-based protein was generally the superior source. Intakes of beans/legume, fish, and chicken without skin were associated with better SCD scores. These findings could have important public health implications.

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CHAPTER 1

Long-term dietary flavonoid intake and subjective cognitive decline in US men and women

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Abstract

Objective: To prospectively examine the associations between long-term dietary flavonoids and subjective cognitive decline (SCD).

Methods: We followed 49,493 women from the Nurses' Health Study (NHS) (1984-2006) and 27,842 men from the Health Professionals Follow-up Study (HPFS) (1986-2002). Poisson regression was used to evaluate the associations between dietary flavonoids (flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, polymeric flavonoids, and proanthocyanidins) and subsequent SCD. For the NHS, long-term average dietary intake was calculated from seven repeated food frequency questionnaires (SFFQs), and SCD was assessed in 2012 and 2014. For the HPFS, average dietary intake was calculated from five repeated SFFQs, and SCD assessed in 2008 and 2012. The validity of the SCD scores was documented by strong associations with *APOE* ε4 genotype.

Results: Higher intakes of total flavonoids and all flavonoid subclasses were significantly associated with lower odds of SCD after adjusting for age, total energy intake, major non-dietary factors, and specific dietary factors. When comparing the highest versus the lowest quintiles of intakes, the pooled multivariable-adjusted odds ratios (ORs) (95% CIs) of 3-unit increments in SCD were 0.62 (0.57, 0.68) for flavones, 0.64 (0.58, 0.70) for flavanones, and 0.79 (0.72, 0.86) for anthocyanins (p trend <0.0001 for all groups). The dose-response curve was steepest for flavones, followed by anthocyanins. Many flavonoid-rich foods, such as strawberries, oranges, grapefruits, citrus juices, apples/pears, celery, peppers, and bananas, were significantly associated with lower odds of SCD.

Conclusion: Our findings support a benefit of higher flavonoid intakes for maintaining cognitive function in US men and women.

Introduction

The world is experiencing rapid aging, and the global prevalence of age-related cognitive decline and dementia is expected to rise substantially.[1-3] The functional disability of cognitive decline and dementia[4] not only impact patients, but also greatly burdens family and society.[2, 5] Effective treatments for dementia are still lacking, highlighting the importance of preventive strategies. Along the continuum from normal cognitive function to dementia, there is a preclinical phase—subjective cognitive decline (SCD)—when self-perceived cognitive decline may be present, but objective cognitive impairments cannot be detected.[6] The cerebral pathologies that contribute to dementia may develop for years or even decades before SCD.[7] The long preclinical phase of dementia may be a critical window for prevention.[8] Among the few modifiable risk factors for cognitive decline, diet has received growing attention. [9-12]

Flavonoids are a group of naturally occurring phytochemicals found in plants[13] and have long been considered to be powerful antioxidants.[14] Considering the likely role of oxidative stress in age-related cognitive decline,[15] flavonoids have been proposed as potentially effective agents for preventing deterioration of cognitive function.[16] Although several small, short-term intervention trials have provided some evidence to support the beneficial role of flavonoids on cognitive decline,[17-20] epidemiological studies have remained inconclusive.[21-28] Further, whether different flavonoid subclasses and specific foods contributing to flavonoid intake possess distinct relationships with cognitive function is unclear. Therefore, we investigated the relationships between intake of flavonoids and subsequent SCD using comprehensive repeated dietary assessments from over 20 years of follow-up in two large prospective cohorts of men and women.

Methods

Study Design

The Nurses' Health Study (NHS) began in 1976 in the United States with 121,701 female registered nurses aged 30-55 years. Participants have been followed up via biennial questionnaires that included information on potential risk factors and newly diagnosed diseases. Dietary information has been collected in 1980, 1984, 1986 and then every 4 years using the semi-quantitative food frequency questionnaire (SFFQ) that has been validated in multiple studies.[29] Starting in 2012, 49,693 women completed questions on subjective cognitive decline (SCD). Follow-up rates have been approximately 90% for each two-year cycle.

The Health Professionals Follow-up Study (HPFS) began in 1986 with 51,529 male US health professionals aged 40-75 years. Detailed questionnaires have been sent biennially to participants to update information on lifestyle risk factors and medical history.[30] Starting in 1986, and continuing every 4 years, participants have been asked to complete the SFFQ.

The study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Assessment of dietary flavonoid intake

Dietary assessments were done with the SFFQs (available at channing.harvard.edu/). Participants were asked how often, on average, they consumed each food of a standard portion size in the previous year (9 response categories for frequency of consumption ranging from "never or less than once per month" to "6 or more times per day"). For the NHS, follow-up began in 1984 when the first comprehensive SFFQ was administered with 131 items. Average intakes of total flavonoids, flavonoids subclasses, other nutrients/foods, and total energy intake were calculated from 7 repeated SFFQs collected in 1984, 1986, and every four years until 2006. This approach can reduce within-subject variation and best represent long-term diet.[31] For the

HPFS, dietary data have been updated every four years since 1986 with the SFFQ. Average dietary intake was calculated from the 5 repeated SFFQs collected in 1986 and every four years until 2002.

A database for the assessment of different flavonoid subclasses intakes was constructed as previously described, using the US Department of Agriculture (USDA) database and a European database (EuroFIR eBASIS) as main sources. [32] In short, the intake of different flavonoid subclasses was calculated by multiplying the flavonoid content of each food by its consumption frequency. We focused on the following 6 subclasses, which are commonly consumed in the western diet: Flavonols (isorhamnetin, kaempferol, quercetin, and myricetin), flavones (apigenin and luteolin), flavanones (eriodictyol, hesperetin, and naringenin), flavan-3-ols monomers (catechins, epicatechins, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, and gallocatechins), anthocyanins (cyanidin, delphinidin, malvidin, pelargonin, peonidin, and petunidin), and polymers (proanthocyanidins, theaflavins, and thearubigins). The sum of all subclasses was defined as "total flavonoids". Proanthocyanidins, the sum of monomers and polymers of the repetitive flavanol units,[33] was also examined, given their possible neuroprotective effects.[34] Intakes of total flavonoids, flavonoid subclasses, and major flavonoid-containing foods measured by the SFFQ were generally highly correlated with weighed dietary records (e.g., correlations were 0.80 for apples, 0.84 for orange juice, and 0.93 for tea).[35]

Assessment of subjective cognitive decline (SCD)

SCD was assessed twice by mailed or online questionnaires (2012 and 2014 for the NHS, 2008 and 2012 for the HPFS). In our prior work,[36, 37] we used the term subjective cognitive function (SCF), but we have updated the terminology in keeping with changes in the field (our outcome assessment met the definition of SCD as self-reported and persistent deterioration in cognitive function).[38] The SCD scores for the HPFS were based on 6 yes/no questions on the recent change in general memory, executive function, attention, and visuospatial skills: (1) "Do you have more trouble than usual remembering recent events?"; (2) "Do you have more trouble than usual remembering a short list of items, such as a shopping list?"; (3) "Do you have trouble remembering things from one second to the next?"; (4) "Do you have any difficulty in understanding things or following spoken instructions?"; (5) "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?"; and (6) "Do you have trouble finding your way around familiar streets?" The SCD scores for the NHS included one additional question: "Have you recently experienced any change in your ability to remember things?"[39] Equal value was assigned to each question, 1 point for every "yes." The average of the two SCD scores was used to reduce random errors. For participants who completed only one of the two SCD questionnaires, that one assessment was then used as their SCD score. We stopped updating dietary data 6 years prior to SCD assessment to minimize reverse causation, i.e., the possible effects of altered cognitive function on diet.

Validity of SCD assessment has been documented by its strong association with both concurrent objective cognitive function[39, 40] and subsequent cognitive decline,[39] especially for those with a high level of education.[41] The strong association between *APOE* ε4 genotype and our SCD score in both the NHS and HPFS further strengthened the validity of this score.[37] Also, risk factors for dementia, such as heavy smoking, cardiovascular disease, high blood pressure, high blood cholesterol, depression, and type 2 diabetes, were all related to low subsequent SCD scores.

Covariates

Information on covariates of interest was collected prospectively in the NHS and HPFS baseline and follow-up questionnaires. Covariates of interest include: Age, body mass index (BMI) (kilograms/meters^2), physical activity (metabolic equivalents, MET-hours/week), race (white, black, other), multivitamin use, smoking status (pack-years), alcohol consumption, diabetes, high blood pressure, elevated cholesterol, cardiovascular disease (stroke, myocardial infarction, angina, or coronary artery surgery), cancer (prostate, colon/rectum, melanoma, lymphoma, leukemia, or other cancer), family history of dementia, and depression (defined as anti-depressant use or self-reported depression). For the NHS, information on postmenopausal status and hormone replacement therapy use, parity, education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), census tract income ($50,000, $50,000–69,999, or $70,000/y) were available; for the HPFS, information on profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian) was obtained.

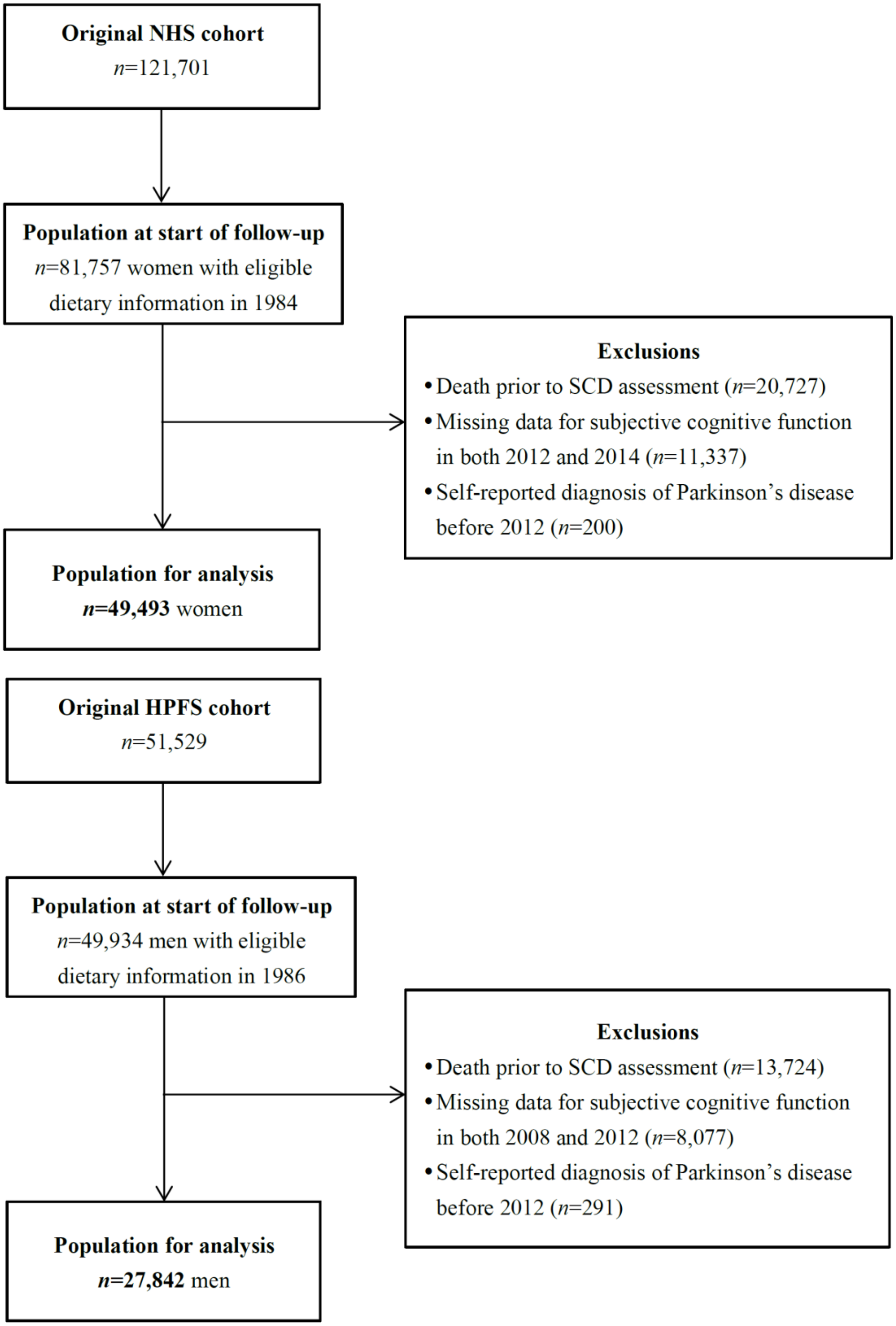
Population for Analysis

For both the NHS and HPFS, we excluded individuals with >70 food items blank, with extreme energy intakes (<600 or >3,500 kcal/day for women and <800 or >4200 kcal/day for men), and participants who developed Parkinson's disease prior to SCD assessments. The final analysis included 49,493 women with a mean age of 48 years at baseline in 1984 and 27,842 men with a mean age of 51 years at enrollment in 1986 (Figure 1).

Statistical analysis

Age-standardized characteristics of participants were calculated according to quintiles of total flavonoid intakes. Because of the distribution and nature of the SCD scores, Poisson

Figure 1. Study population and exclusions in the NHS and HPFS.



regression was used to evaluate the associations between flavonoid intakes and flavonoid-containing foods with SCD. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Because three or more positive SCD questions have been used to indicate poor cognitive function,[39, 40] ORs (95% CIs) for 3-unit increments in SCD were calculated. To be consistent with the time frame of dietary assessments, covariates information from 1984-2006 was used for the NHS; information from 1986-2002 was used for the HPFS. Because the relationship between age and SCD was non-linear, a quadratic term and a linear term for age were included in the model and age-adjusted associations were calculated. In multivariate analyses, age (at SCD measurement, continuous, with a linear and quadratic term, years), total energy intake, race (white, black, other), smoking history (pack-years), depression (defined as use of anti-depressants or self-reported depression), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2), intakes of alcohol, family history of dementia, missing indicator for SCD measurement if one of the two assessments was missing, number of dietary assessments during follow-up period, multivitamin use (yes/no) were included as covariates. For the NHS, the following variables were also included: Parity (nulliparous, 1-2, >2), postmenopausal status and hormone replacement therapy use, census tract income ($50,000, $50,000–69,999, or $70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school); while for the HPFS, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian) was included. Hypertension, diabetes, elevated cholesterol, and CVD were not adjusted in our primary analysis because these variables may be mediators on the causal pathway, although results remained similar when these variables were included. To examine if the associations were independent of other nutrients/antioxidants, we further adjusted for total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid in the final model. Missing indicators were included in the model for variables with missing values. Linear trends were tested by assigning median values within each quintile and modeling these variables continuously.

In the food-based analyses, age, total energy intake, and the above-mentioned non-dietary factors were adjusted. To investigate whether the associations were independent of other major food groups, we also adjusted for sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. Flavonoid-containing foods were treated as continuous variables and ORs for every 3 servings/week were estimated. Spearman correlations were calculated to evaluate correlations between total and each flavonoid subclass, total and individual carotenoids, vitamin C, vitamin E, and folate within foods. The amounts of these nutrients within foods were calculated according to USDA data.

We further investigated whether the associations between flavonoids and SCD differed by baseline age (<50 years, ≥50 years), smoking status (never smokers, past smokers, and current smokers), and *APOE* ε4 allele carrier status (yes/no) in a subgroup of participants who had their *APOE* ε4 measured or imputed from a genome-wide association analysis.

Analyses were done separately for the NHS and HPFS, an inverse-variance-weighted, fixed-effect meta-analysis was then used to combine the results across cohorts. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC) and R version 3.6.2.

Results

The mean age of participants at the initial SCD assessment was 76.4 years for the NHS and 73 years for the HPFS. Among the 49,493 women in the NHS, 41% had good cognitive function (averaged SCD score 0 points), 46.6% had moderate cognitive function (averaged SCD score between 0.5-2.5 points), and 12.4% had poor function (averaged SCD score ≥ 3 points); among the 27,842 men in the HPFS, 54.5% had a good cognitive function (averaged SCD score 0 points), 38% had moderate function (averaged SCD score between 0.5-2.5 points), and 7.5% had poor function (averaged SCD score ≥ 3 points). The median intakes of total flavonoids were 283 mg/d in women and 290 mg/d in men. Among flavonoid subclasses, intake of polymeric flavonoids was the highest, with medians of 166 mg/d and 167 mg/d in the NHS and HPFS, respectively. Intake of flavones was the lowest, with medians of 2 mg/d and 2.5 mg/d in the NHS and HPFS, respectively. Women with higher total flavonoid intakes were more likely to be non-smokers, less likely to have elevated cholesterol, and had higher intakes of coffee and tea; while men with higher intakes of total flavonoids had higher intakes of fruits and vegetables (Table 1).

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Table 1 NHS: Characteristics in 1984-2006 of 49,493 women who completed subjective cognitive decline questions in 2012/2014 by quintiles of total flavonoids intake

	Q1	Q2	Q3	Q4	Q5
Age, y	47.4 (6.4)	48.3 (6.5)	48.8 (6.6)	48.8 (6.7)	48.5 (6.7)
BMI, kg/m2	26.5 (4.9)	26.2 (4.7)	26.1 (4.6)	25.9 (4.5)	25.9 (4.6)
Total energy intake, kcal/d	1,697 (424)	1,749 (414)	1,769 (421)	1,758 (416)	1,699 (409)
Total Flavonoids, mg/d	143 (32)	217 (18)	284 (22)	382 (38)	699 (251)
Flavonols, mg/d	10.5 (3.9)	13.4 (4.0)	15.7 (4.2)	19.0 (4.6)	28.2 (8.5)
Flavones, mg/d	1.6 (0.8)	2.1 (0.9)	2.4 (1.0)	2.5 (1.1)	2.3 (1.1)
Flavanones, mg/d	28.0 (19.0)	40.3 (22.6)	45.2 (25.0)	46.8 (26.5)	44.6 (28.3)
Flavan-3-ols, mg/d	13.4 (5.4)	22.1 (6.9)	32.6 (9.5)	52.7 (14.2)	126 (60.5)
Total Anthocyanins, mg/d	8.3 (5.1)	13.2 (7.2)	16.8 (9.9)	19.2 (13.2)	18.6 (15.7)
Polymeric flavonoids, mg/d	80.3 (25.1)	125 (27.5)	169 (37.2)	243 (62.3)	527 (326)
Proanthocyanidins, mg/d	74.9 (23.0)	106 (26.5)	128 (34.1)	146 (44.0)	177 (56.8)
Total Fat, % energy	33.4 (4.5)	31.6 (4.2)	30.7 (4.3)	30.3 (4.5)	30.7 (4.7)
Total Protein intake, % energy	18.0 (2.4)	18.1 (2.3)	18.0 (2.3)	18.0 (2.3)	18.0 (2.4)
Total Carbohydrate, % energy	47.6 (6.0)	50.1 (5.5)	51.4 (5.7)	51.9 (5.9)	51.7 (6.1)
Alcohol, g/day	6.7 (10.0)	6.0 (8.3)	5.8 (8.2)	5.5 (7.7)	4.8 (7.3)
Physical activity, MET-h/wk	14.8 (13.4)	18.1 (15.0)	19.9 (16.8)	20.8 (17.9)	19.4 (16.7)
Smoking pack-years, 1984-2006, %					
Never smoked	38.9	46.1	48.3	49.1	50.7
<=4 pack-years	8.7	11.0	11.5	12.5	10.9
5-24 pack-years	21.4	24.0	23.5	22.9	21.7
>=25 pack-years	29.5	17.4	15.0	13.8	15.3
Missing	1.6	1.5	1.7	1.7	1.5
High blood pressure, 1984-2006, %	62.0	60.9	60.8	59.0	59.2
Elevated cholesterol, 1984-2006, %	72.7	72.0	71.3	71.1	70.8
Diabetes, 1984-2006, %	11.6	10.8	10.6	9.8	10.5
CVD, 1984-2006, %	10.4	9.5	9.8	9.9	11.2
Cancer, 1984-2006, %	18.2	17.7	19.1	18.5	18.8
Depression diagnosis or anti-depressant use 1996 -2006, %	20.5	19.5	18.9	19.3	18.5
Number of dietary assessment, 1984-2006					
1	0.4	0.1	0.1	0.2	0.1
2	0.9	0.4	0.5	0.6	0.8
3	1.6	1.4	1.1	1.1	1.4
4	3.8	2.9	2.8	2.6	3.0
5	7.5	6.7	6.8	6.9	6.9
6	19.2	18.6	19.8	18.8	18.9
7	66.6	69.8	68.8	69.8	68.9
Missing year of SCD measurement					
None	87.2	88.6	88.5	88.7	88.4
2014	12.8	11.4	11.5	11.3	11.6
Education					
Registered nursing degrees	67.1	63.6	62.3	61.8	62.8
Bachelors degree	18.1	20.6	21.5	21.0	20.3
Masters or doctorate degree	8.3	10.6	10.8	11.8	11.2
Missing	6.5	5.2	5.4	5.4	5.7
Husband's education					
High school or lower education	39.3	34.4	32.5	32.9	34.7
College	23.3	24.3	24.5	25.2	23.7
Graduate school	17.3	21.8	22.9	21.7	21.9
Missing	20.2	19.5	20.1	20.2	19.7
Postmenopausal status & hormone use					
Premenopause	0.4	0.4	0.3	0.5	0.5
Postmenopause & never use hormone therapy	22.6	20.5	19.3	20.1	22.3
Postmenopause & ever use hormone therapy	72.1	74.3	76.2	75.1	72.5
Missing	4.9	4.8	4.1	4.3	4.7
Parity					
Nulliparous	4.6	5.6	5.0	5.3	5.5
1-2	6.5	6.6	6.7	6.7	6.7
3+	87.2	86.3	86.5	86.1	86.0
Missing	1.7	1.5	1.8	1.8	1.8
Dietary intake					
Vegetable intake (servings/d)	3.0 (1.4)	3.5 (1.5)	3.8 (1.6)	3.9 (1.7)	3.6 (1.7)
Fruit intake (servings/d)	1.0 (0.5)	1.5 (0.6)	1.8 (0.8)	1.9 (0.9)	1.8 (1.0)
Fruit juice intake (servings/d)	0.5 (0.4)	0.7 (0.5)	0.8 (0.5)	0.8 (0.6)	0.7 (0.5)

Table 1 NHS (Continued)					
Sweets/desserts intake (servings/d)	1.3 (0.9)	1.3 (0.9)	1.2 (0.8)	1.2 (0.9)	1.2 (0.9)
Misc animal food (servings/d)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)
Whole grain intake (servings/d)	1.2 (0.8)	1.4 (0.8)	1.5 (0.8)	1.5 (0.8)	1.4 (0.8)
Nut intake (servings /d)	0.4 (0.4)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)
Legume intake (servings/d)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.3)	0.4 (0.2)
Vegetable oil dressing intake (servings /d)	0.3 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Tea & coffee intake (servings/d)	2.4 (1.4)	2.4 (1.3)	2.4 (1.3)	2.6 (1.2)	3.4 (1.4)
Potato intake (servings/d)	0.5 (0.3)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Refined grain intake (servings/d)	1.6 (0.9)	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)
SSB intake (servings /d)	0.3 (0.5)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.2 (0.4)
Egg intake (servings /d)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Fish intake (servings/d)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Yogurt intake (servings /d)	0.7 (1.0)	0.8 (1.0)	0.8 (1.0)	0.8 (1.0)	0.8 (1.0)
Dairy minus yogurt intake (servings /d)	1.9 (1.0)	2.0 (0.9)	1.9 (0.9)	1.9 (0.9)	1.8 (0.9)
Dairy intake (servings /d)	2.0 (1.0)	2.1 (1.0)	2.1 (1.0)	2.1 (0.9)	2.0 (0.9)
Diet beverage intake (servings /d)	0.6 (0.8)	0.6 (0.7)	0.5 (0.7)	0.5 (0.6)	0.5 (0.7)
Poultry intake (servings/d)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)
Fresh red Meat intake (servings/d)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)
Processed red Meat intake (servings /d)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)
Total carotenoids (mcg/day)	13,174 (4,580)	14,796 (4,753)	15,714 (5,025)	16278 (5,436)	15,772 (5,431)

Table 1 HPFS: Characteristics in 1986-2002 of 27,842 men who completed subjective cognitive decline questions in 2008/2012 by quintiles of total flavonoids intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Age (y) at study baseline 1986	49.8 (7.9)	50.8 (8.2)	51.1 (8.1)	51.8 (8.3)	51.7 (8.2)
BMI, 1986-2002	26.3 (3.5)	26.0 (3.3)	25.8 (3.2)	25.7 (3.1)	25.8 (3.2)
Total calorie intake (kcal/day), 1986-2002	1,968 (525)	2,018 (524)	2,025 (515)	2,000 (513)	1,956 (499)
Total Flavonoids, mg/d	147 (33.8)	224 (18.3)	291 (20.8)	381 (34.9)	681 (251)
Flavonols, mg/d	11.7 (4.8)	14.8 (5.1)	17.3 (5.2)	20.4 (5.8)	29.7 (9.6)
Flavones, mg/d	1.7 (1.0)	2.5 (1.0)	2.9 (1.3)	3.2 (1.4)	3.2 (1.7)
Flavanones, mg/d	32.0 (21.6)	48.6 (26.6)	57.6 (31.4)	64.7 (37.4)	63.8 (42.1)
Flavan-3-ols, mg/d	14.9 (6.9)	22.8 (8.0)	31.5 (10.3)	46.5 (15.3)	112.8 (61.9)
Total Anthocyanins, mg/d	7.2 (4.8)	11.7 (6.8)	15.4 (8.9)	19.1 (13.2)	21.6 (20.8)
Polymeric flavonoids, mg/d	80.5 (26.6)	126 (29.6)	170 (38.2)	239 (59.5)	506 (296)
Proanthocyanidins, mg/d	78.9 (25.3)	115 (29.2)	144 (38.1)	171 (54.6)	213 (84.1)
Total Fat, % energy	33.2 (5.0)	31.2 (4.7)	30.0 (4.8)	29.2 (5.1)	29.3 (5.5)
Total Protein intake, % energy	18.1 (2.6)	17.9 (2.4)	17.8 (2.4)	17.9 (2.5)	17.9 (2.6)
Total Carbohydrate, % energy	45.8 (6.8)	48.7 (6.2)	50.4 (6.4)	51.6 (6.9)	51.6 (7.3)
Alcohol, g/day	12.5 (14.7)	11.9 (13.3)	11.5 (12.4)	10.5 (11.8)	10.1 (11.9)
Physical activity, MET-h/wk	23.6 (18.5)	28.0 (20.6)	30.3 (21.4)	30.7 (22.3)	30.0 (22.0)
Smoking pack-years, 1986-2002, %					
Never smoked	41.8	49.4	51.3	52.3	51.3
< 24 pack-years	28.6	27.6	29.6	29.5	29.1
25-44 pack-years	14.9	12.0	9.9	10.0	10.0
>=45 pack-years	9.0	5.5	3.7	3.3	4.2
Missing	5.7	5.5	5.4	5.0	5.4
High blood pressure, 1986-2002, %	45.7	44.2	42.8	44.4	45.2
Elevated cholesterol, 1986-2002, %	56.6	56.1	56.8	56.6	56.3
Diabetes, 1986-2002, %	8.6	8.7	6.8	6.8	7.5
CVD, 1986-2002, %	16.8	17.4	16.9	18.1	17.8
Cancer, 1986-2002, %	15.2	15.2	15.9	16.3	15.4
Depression diagnosis or anti-depressant use 1986-2002, %	6.5	5.6	5.9	4.5	5.5
Number of dietary assessment, 1986-2002, %					
1	4.0	2.3	1.4	1.6	1.9
2	6.3	4.4	4.1	4.0	4.3
3	9.3	8.8	8.0	7.6	9.0
4	17.9	18.1	18.5	19.1	17.8
5	62.4	66.5	68.0	67.8	67.0
Missing year of SCD measurement					
None	70.0	71.6	74.5	73.3	72.8
2008	9.8	9.5	7.4	7.9	8.6
2012	20.2	18.9	18.0	18.8	18.6
Profession, %					
Dentist	52.6	55.4	58.8	60.0	59.9
Pharmacist	9.8	9.0	8.0	7.5	7.7
Optometrist	7.6	7.1	6.9	6.4	6.0
Osteopath	4.3	3.9	3.9	4.6	3.7
Podiatrist	3.0	2.5	2.4	2.4	2.2
Veterinarian	22.9	22.1	20.1	19.0	20.5
Dietary intake					

Table 1 HPFS (Continued)					
Vegetable intake (servings/d)	2.8 (1.4)	3.4 (1.5)	3.7 (1.7)	3.9 (1.8)	3.9 (1.9)
Fruit intake (servings/d)	1.0 (0.6)	1.5 (0.7)	1.8 (0.9)	2.1 (1.1)	2.2 (1.4)
Fruit juice intake (servings/d)	0.5 (0.4)	0.8 (0.5)	0.9 (0.6)	1.0 (0.7)	0.9 (0.7)
Whole grain intake (servings/d)	1.4 (1.0)	1.6 (1.1)	1.8 (1.1)	1.8 (1.1)	1.7 (1.1)
Refined grain intake (servings/d)	1.7 (1.1)	1.6 (0.9)	1.6 (0.9)	1.6 (0.9)	1.6 (1.0)
Potato intake (servings/d)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Sweets/desserts intake (servings/d)	1.4 (1.1)	1.5 (1.1)	1.4 (1.1)	1.3 (1.0)	1.3 (1.0)
Fresh red Meat intake (servings/d)	1.2 (1.3)	1.2 (1.3)	1.2 (1.3)	1.1 (1.4)	1.1 (1.4)
Processed red Meat intake (servings/d)	0.4 (1.0)	0.4 (1.0)	0.4 (0.9)	0.4 (0.9)	0.4 (1.0)
Poultry intake (servings/d)	0.8 (1.4)	0.9 (1.4)	0.9 (1.4)	0.9 (1.4)	0.9 (1.4)
Fish intake (servings/d)	0.3 (0.2)	0.3 (0.2)	0.4 (0.2)	0.4 (0.3)	0.4 (0.3)
Legume intake (servings/d)	0.4 (0.3)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
Dairy intake (servings/d)	2.0 (1.2)	1.9 (1.1)	1.9 (1.0)	1.8 (1.0)	1.7 (1.0)
Egg intake (servings/d)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Misc. animal food (servings/d)	0.5 (1.1)	0.5 (1.0)	0.5 (1.1)	0.5 (1.1)	0.5 (1.2)
Nut intake (servings/d)	0.4 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)
Vegetable oil dressing intake (servings/d)	0.3 (0.3)	0.3 (0.3)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Tea & coffee intake (servings/d)	2.1 (1.6)	2.0 (1.5)	2.0 (1.4)	2.1 (1.4)	2.8 (1.5)
SSB intake (servings/d)	0.4 (0.6)	0.4 (0.5)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Diet beverage intake (servings/d)	0.6 (0.9)	0.5 (0.8)	0.5 (0.8)	0.5 (0.7)	0.5 (0.8)
Total carotenoids (mcg/day)	15,176 (6,410)	17,280 (6,420)	18,453 (6,625)	19,635 (7,224)	19,656 (8,174)

Significant inverse associations between total flavonoids and all the flavonoid subclasses with SCD were observed after controlling for age, total energy intake, and major non-dietary factors in both the NHS and HPFS (Table 2). After further adjusting for total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid, associations remained significant for total flavonoids and all subclasses in the NHS. In this multivariable-adjusted model, when comparing the highest with the lowest quintiles of intakes, OR (95% CI) of 3 unit-increments in SCD was 0.82 (0.75, 0.89) for total flavonoids. The strongest associations among flavonoid subclasses were observed for flavones 0.60 (0.55, 0.66) and flavanones 0.63 (0.58, 0.69). Inverse linear trends across quintiles were observed (p trend < 0.0001). Consistent results were found in the HPFS: The multivariate ORs (95% CI) were 0.86 (0.75, 0.99) for total flavonoids, 0.68 (0.58, 0.79) for flavones, and 0.65 (0.56, 0.75) for flavanones. The pooled multivariate ORs (95% CI) were 0.84 (0.76, 0.89) for total flavonoids, 0.62 (0.57, 0.68) for flavones, and 0.64 (0.58, 0.70) for flavanones. Using stepwise regression, flavanones were selected as independent predictors of subsequent SCD in both the NHS and HPFS; flavones, anthocyanins, flavanols, and total flavonoids were also selected in the NHS. The dose-response relationship was steepest for flavones, followed by anthocyanins, and the flattest for polymeric flavonoids (Figure 2). In the sensitivity analysis adjusted for individual carotenoids (β-carotene, α-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin) instead of total carotenoids, the associations were only

Table 2. ORs (95% CI) for associations between flavonoid subclass intakes and SCD in the NHS & HPFS

	Q1	Q2	Q3	Q4	Q5	P trend	Continuous [a]
Total flavonoids							
NHS							
Median intake (mg/d)	149	218	283	377	618		
Age & calorie-adjusted model	Ref	0.81 (0.75, 0.88)	0.68 (0.63, 0.74)	0.68 (0.63, 0.74)	0.64 (0.59, 0.70)	<.0001	0.79 (0.74, 0.83)
Above+Nondietary factors adjusted (MV1)	Ref	0.89 (0.82, 0.96)	0.77 (0.70, 0.83)	0.78 (0.72, 0.85)	0.73 (0.67, 0.80)	<.0001	0.85 (0.80, 0.90)
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.87, 1.03)	0.85 (0.78, 0.92)	0.88 (0.81, 0.96)	0.82 (0.75, 0.89)	<.0001	0.89 (0.84, 0.94)
HPFS							
Median intake (mg/d)	153	224	290	377	601		
Age & calorie-adjusted model	Ref	0.88 (0.78, 1.01)	0.69 (0.61, 0.79)	0.66 (0.58, 0.76)	0.66 (0.58, 0.76)	<.0001	0.80 (0.73, 0.88)
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.83, 1.07)	0.78 (0.68, 0.89)	0.76 (0.67, 0.87)	0.74 (0.65, 0.84)	<.0001	0.84 (0.77, 0.92)
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.88, 1.15)	0.87 (0.76, 0.99)	0.89 (0.78, 1.03)	0.86 (0.75, 0.99)	0.0173	0.91 (0.83, 0.99)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.97 (0.89, 1.03)	0.86 (0.79, 0.91)	0.89 (0.84, 0.94)	0.84 (0.76, 0.89)	<.0001	0.89 (0.86, 0.94)
Flavonols							
NHS							
Median intake (mg/d)	9	13	16	20	28		
Age & calorie-adjusted model	Ref	0.84 (0.77, 0.91)	0.72 (0.67, 0.79)	0.76 (0.70, 0.83)	0.62 (0.57, 0.68)	<.0001	0.73 (0.69, 0.78)
Above+Nondietary factors adjusted (MV1)	Ref	0.88 (0.81, 0.95)	0.79 (0.73, 0.86)	0.86 (0.79, 0.93)	0.72 (0.66, 0.78)	<.0001	0.83 (0.78, 0.89)
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.89, 1.05)	0.92 (0.85, 1.01)	1.03 (0.95, 1.13)	0.89 (0.82, 0.98)	0.0616	0.95 (0.89, 1.02)
HPFS							
Median intake (mg/d)	10	14	17	21	30		
Age & calorie-adjusted model	Ref	0.87 (0.76, 0.99)	0.76 (0.67, 0.87)	0.74 (0.65, 0.84)	0.68 (0.60, 0.78)	<.0001	0.78 (0.71, 0.86)
Above+Nondietary factors adjusted (MV1)	Ref	0.88 (0.77, 1.00)	0.79 (0.69, 0.91)	0.79 (0.70, 0.91)	0.72 (0.63, 0.82)	<.0001	0.83 (0.75, 0.91)
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.85, 1.11)	0.95 (0.83, 1.09)	1.00 (0.87, 1.16)	0.96 (0.83, 1.11)	0.8184	1.01 (0.91, 1.12)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.97 (0.89, 1.03)	0.94 (0.86, 1.00)	1.03 (0.94, 1.09)	0.91 (0.84, 0.97)	0.1151	0.97 (0.91, 1.03)
Flavones							
NHS							
Median intake (mg/d)	1	2	2	3	4		
Age & calorie-adjusted model	Ref	0.74 (0.68, 0.80)	0.66 (0.61, 0.72)	0.50 (0.46, 0.54)	0.43 (0.40, 0.47)	<.0001	0.49 (0.46, 0.53)
Above+Nondietary factors adjusted (MV1)	Ref	0.79 (0.72, 0.85)	0.73 (0.68, 0.80)	0.57 (0.53, 0.62)	0.51 (0.47, 0.55)	<.0001	0.57 (0.54, 0.61)
Above+Dietary factors adjusted (MV2)	Ref	0.83 (0.76, 0.90)	0.80 (0.74, 0.87)	0.64 (0.59, 0.70)	0.60 (0.55, 0.66)	<.0001	0.66 (0.61, 0.71)
HPFS							
Median intake (mg /d)	1	2	3	3	4		
Age & calorie-adjusted model	Ref	0.85 (0.75, 0.97)	0.70 (0.61, 0.79)	0.56 (0.49, 0.64)	0.44 (0.38, 0.50)	<.0001	0.49 (0.44, 0.54)
Above+Nondietary factors adjusted (MV1)	Ref	0.91 (0.80, 1.03)	0.77 (0.67, 0.87)	0.63 (0.55, 0.71)	0.53 (0.46, 0.61)	<.0001	0.57 (0.51, 0.63)
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.86, 1.11)	0.87 (0.76, 1.01)	0.75 (0.65, 0.87)	0.68 (0.58, 0.79)	<.0001	0.68 (0.61, 0.77)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.86 (0.81, 0.94)	0.81 (0.76, 0.89)	0.68 (0.62, 0.72)	0.62 (0.57, 0.68)	<.0001	0.66 (0.62, 0.70)
Flavanones							

Table 2. (Continued)							
NHS							
Median intake (mg /d)	12	25	37	51	74		
Age & calorie-adjusted model	Ref	0.84 (0.77, 0.91)	0.74 (0.68, 0.80)	0.58 (0.53, 0.63)	0.49 (0.45, 0.54)	<.0001	0.53 (0.50, 0.57)
Above+Nondietary factors adjusted (MV1)	Ref	0.89 (0.82, 0.96)	0.80 (0.74, 0.87)	0.67 (0.61, 0.72)	0.58 (0.54, 0.64)	<.0001	0.62 (0.58, 0.66)
Above+Dietary factors adjusted (MV2)	Ref	0.92 (0.85, 1.00)	0.84 (0.78, 0.92)	0.72 (0.66, 0.78)	0.63 (0.58, 0.69)	<.0001	0.66 (0.62, 0.71)
HPFS							
Median intake (mg /d)	15	32	48	66	97		
Age & calorie-adjusted model	Ref	0.81 (0.71, 0.92)	0.73 (0.64, 0.83)	0.57 (0.50, 0.65)	0.46 (0.40, 0.52)	<.0001	0.51 (0.46, 0.56)
Above+Nondietary factors adjusted (MV1)	Ref	0.88 (0.77, 0.99)	0.80 (0.70, 0.91)	0.66 (0.58, 0.75)	0.55 (0.48, 0.63)	<.0001	0.59 (0.53, 0.66)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.79, 1.02)	0.86 (0.76, 0.99)	0.73 (0.63, 0.84)	0.65 (0.56, 0.75)	<.0001	0.68 (0.60, 0.76)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.91 (0.86, 0.97)	0.86 (0.79, 0.91)	0.72 (0.68, 0.76)	0.64 (0.58, 0.70)	<.0001	0.66 (0.62, 0.70)
Flavan-3-ols							
NHS							
Median intake (mg /d)	12	21	32	53	109		
Age & calorie-adjusted model	Ref	0.78 (0.72, 0.85)	0.79 (0.73, 0.85)	0.77 (0.71, 0.84)	0.76 (0.70, 0.83)	<.0001	0.90 (0.86, 0.95)
Above+Nondietary factors adjusted (MV1)	Ref	0.84 (0.78, 0.92)	0.86 (0.79, 0.93)	0.84 (0.78, 0.91)	0.83 (0.76, 0.90)	0.0017	0.93 (0.88, 0.98)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.83, 0.98)	0.92 (0.85, 1.01)	0.91 (0.84, 0.99)	0.88 (0.81, 0.96)	0.0280	0.94 (0.90, 0.99)
HPFS							
Median intake (mg /d)	13	21	31	47	96		
Age & calorie-adjusted model	Ref	0.79 (0.69, 0.90)	0.79 (0.70, 0.90)	0.73 (0.64, 0.83)	0.78 (0.69, 0.89)	0.0137	0.95 (0.88, 1.02)
Above+Nondietary factors adjusted (MV1)	Ref	0.84 (0.74, 0.96)	0.89 (0.78, 1.01)	0.80 (0.70, 0.91)	0.82 (0.72, 0.93)	0.0159	0.94 (0.87, 1.01)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.79, 1.03)	1.00 (0.87, 1.14)	0.90 (0.78, 1.02)	0.90 (0.79, 1.02)	0.1643	0.96 (0.89, 1.04)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.89 (0.84, 0.97)	0.94 (0.89, 1.00)	0.91 (0.84, 0.97)	0.89 (0.84, 0.94)	0.0108	0.94 (0.91, 1.00)
Anthocyanins							
NHS							
Median intake (mg /d)	5	8	12	18	29		
Age & calorie-adjusted model	Ref	0.79 (0.73, 0.86)	0.67 (0.62, 0.72)	0.61 (0.56, 0.66)	0.50 (0.46, 0.54)	<.0001	0.62 (0.59, 0.66)
Above+Nondietary factors adjusted (MV1)	Ref	0.84 (0.78, 0.91)	0.76 (0.70, 0.82)	0.72 (0.66, 0.78)	0.62 (0.57, 0.68)	<.0001	0.72 (0.68, 0.77)
Above+Dietary factors adjusted (MV2)	Ref	0.88 (0.81, 0.95)	0.83 (0.76, 0.90)	0.81 (0.74, 0.88)	0.74 (0.68, 0.81)	<.0001	0.81 (0.76, 0.86)
HPFS							
Median intake (mg /d)	4	8	12	17	29		
Age & calorie-adjusted model	Ref	0.93 (0.82, 1.05)	0.82 (0.72, 0.93)	0.66 (0.58, 0.75)	0.63 (0.55, 0.71)	<.0001	0.75 (0.69, 0.81)
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.85, 1.10)	0.91 (0.80, 1.04)	0.77 (0.67, 0.87)	0.75 (0.66, 0.86)	<.0001	0.85 (0.78, 0.92)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.88, 1.14)	1.00 (0.87, 1.14)	0.87 (0.76, 0.99)	0.91 (0.79, 1.05)	0.0664	0.93 (0.86, 1.01)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.91 (0.86, 0.97)	0.86 (0.81, 0.94)	0.84 (0.76, 0.89)	0.79 (0.72, 0.86)	<.0001	0.86 (0.81, 0.89)
Polymeric flavonoids							
NHS							
Median intake (mg /d)	79	121	166	236	436		
Age & calorie-adjusted model	Ref	0.87 (0.80, 0.94)	0.77 (0.71, 0.83)	0.74 (0.68, 0.80)	0.75 (0.69, 0.81)	<.0001	0.90 (0.86, 0.94)
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.86, 1.02)	0.85 (0.78, 0.92)	0.82 (0.75, 0.89)	0.83 (0.76, 0.90)	<.0001	0.94 (0.90, 0.98)
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.91, 1.07)	0.93 (0.85, 1.01)	0.90 (0.83, 0.98)	0.90 (0.83, 0.98)	0.0103	0.96 (0.91, 1.01)

Table 2. (Continued)							
HPFS							
Median intake (mg /d)	77	122	167	235	424		
Age & calorie-adjusted model	Ref	1.01 (0.89, 1.15)	0.83 (0.73, 0.94)	0.73 (0.64, 0.84)	0.83 (0.72, 0.94)	0.0005	0.94 (0.87, 1.01)
Above+Nondietary factors adjusted (MV1)	Ref	1.09 (0.96, 1.24)	0.93 (0.82, 1.06)	0.84 (0.73, 0.95)	0.88 (0.77, 1.01)	0.0052	0.94 (0.88, 1.01)
Above+Dietary factors adjusted (MV2)	Ref	1.13 (0.99, 1.29)	1.01 (0.88, 1.16)	0.93 (0.81, 1.06)	0.98 (0.86, 1.13)	0.2057	0.97 (0.91, 1.04)
Meta-analyzed results[a]							
Multivariate model 2	Ref	1.06 (1.00, 1.13)	0.97 (0.91, 1.03)	0.91 (0.86, 0.99)	0.94 (0.89, 1.00)	0.0090	0.97 (0.91, 1.00)
Proanthocyanidins							
NHS							
Median intake (mg /d)	68	96	119	146	193		
Age & calorie-adjusted model	Ref	0.80 (0.74, 0.87)	0.78 (0.72, 0.84)	0.67 (0.62, 0.73)	0.57 (0.53, 0.62)	<.0001	0.66 (0.62, 0.70)
Above+Nondietary factors adjusted (MV1)	Ref	0.85 (0.79, 0.93)	0.84 (0.78, 0.91)	0.77 (0.71, 0.84)	0.69 (0.64, 0.76)	<.0001	0.78 (0.73, 0.83)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.83, 0.98)	0.90 (0.83, 0.98)	0.86 (0.79, 0.94)	0.81 (0.74, 0.88)	<.0001	0.87 (0.81, 0.93)
HPFS							
Median intake (mg /d)	72	105	133	166	229		
Age & calorie-adjusted model	Ref	1.09 (0.96, 1.24)	0.91 (0.80, 1.04)	0.78 (0.68, 0.89)	0.70 (0.61, 0.80)	<.0001	0.73 (0.66, 0.81)
Above+Nondietary factors adjusted (MV1)	Ref	1.16 (1.02, 1.32)	1.01 (0.89, 1.15)	0.90 (0.78, 1.02)	0.83 (0.73, 0.96)	<.0001	0.84 (0.76, 0.93)
Above+Dietary factors adjusted (MV2)	Ref	1.23 (1.08, 1.40)	1.10 (0.96, 1.25)	1.00 (0.87, 1.15)	0.99 (0.86, 1.14)	0.1337	0.95 (0.86, 1.05)
Meta-analyzed results[a]							
Multivariate model 2	Ref	0.97 (0.89, 1.03)	0.94 (0.86, 1.00)	0.89 (0.81, 0.94)	0.86 (0.79, 0.91)	<.0001	0.89 (0.84, 0.94)

Age & calorie adjusted model: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years), total calorie intake;
Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (Registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol, postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes, no), intake of alcohol, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2: other than the variables adjusted in MV1, further adjusted for dietary intakes of total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid
[a] Comparing 90th to 10th percentile of intake

modestly attenuated: For total flavonoids, OR=0.89 (0.81, 0.96), for flavones, OR=0.72 (0.62, 0.83), and for flavanones, OR=0.77 (0.66, 0.90) (*p* trend <0.0001). For subgroup analyses, results were similar across strata of smoking status and *APOE* ε4 allele carrier status; the inverse associations for flavones and flavanones were even stronger in younger participants (baseline age < 50 years) (NHS: 0.57 [0.49, 0.65], HPFS: 0.67 [0.51, 0.87] for flavones; NHS: 0.60 [0.52, 0.68], HPFS: 0.60 [0.47, 0.78] for flavonones)

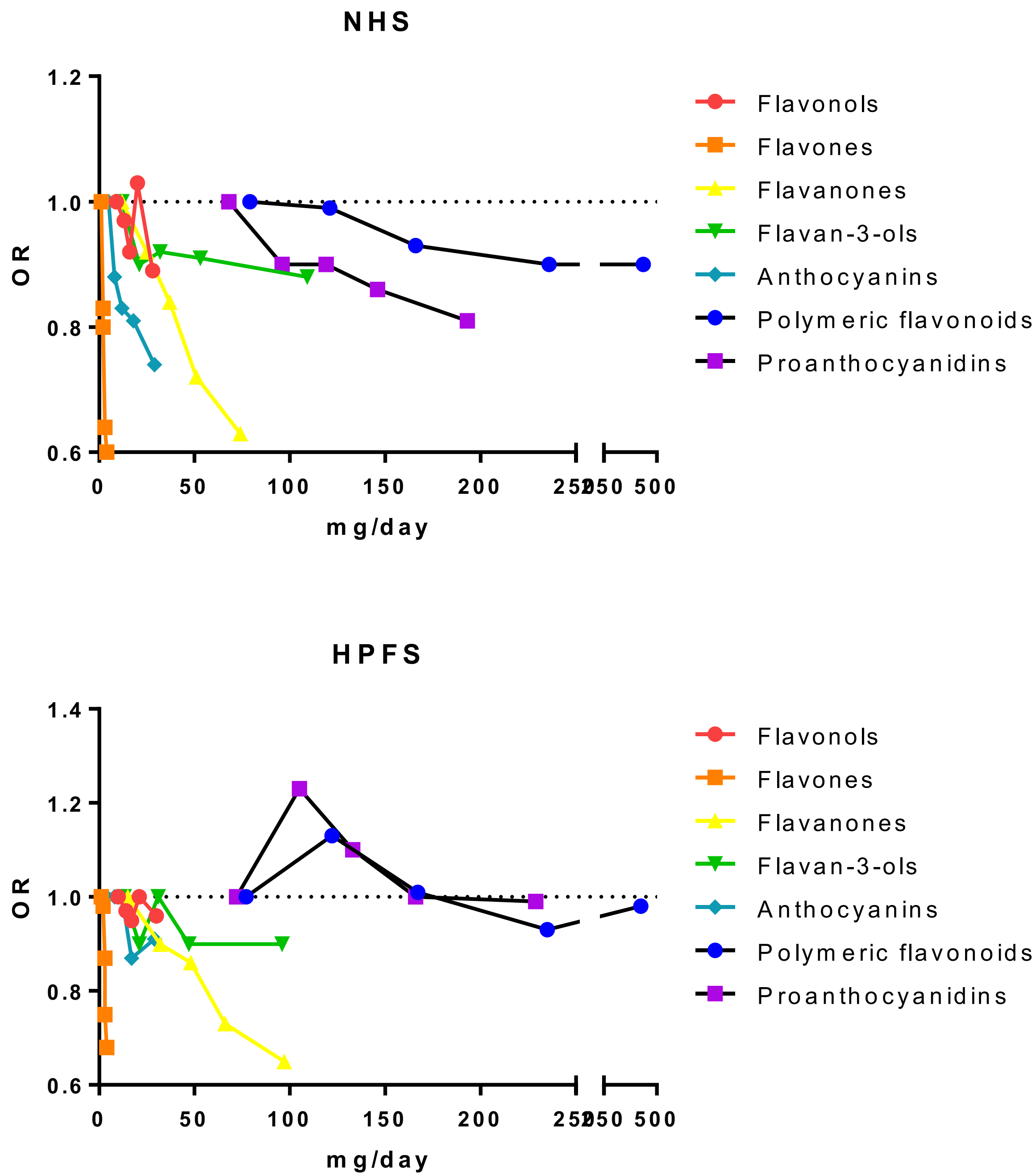

Figure 2. The adjusted dose-response relationship between each flavonoid subclass and OR of 3 unit increments in SCD

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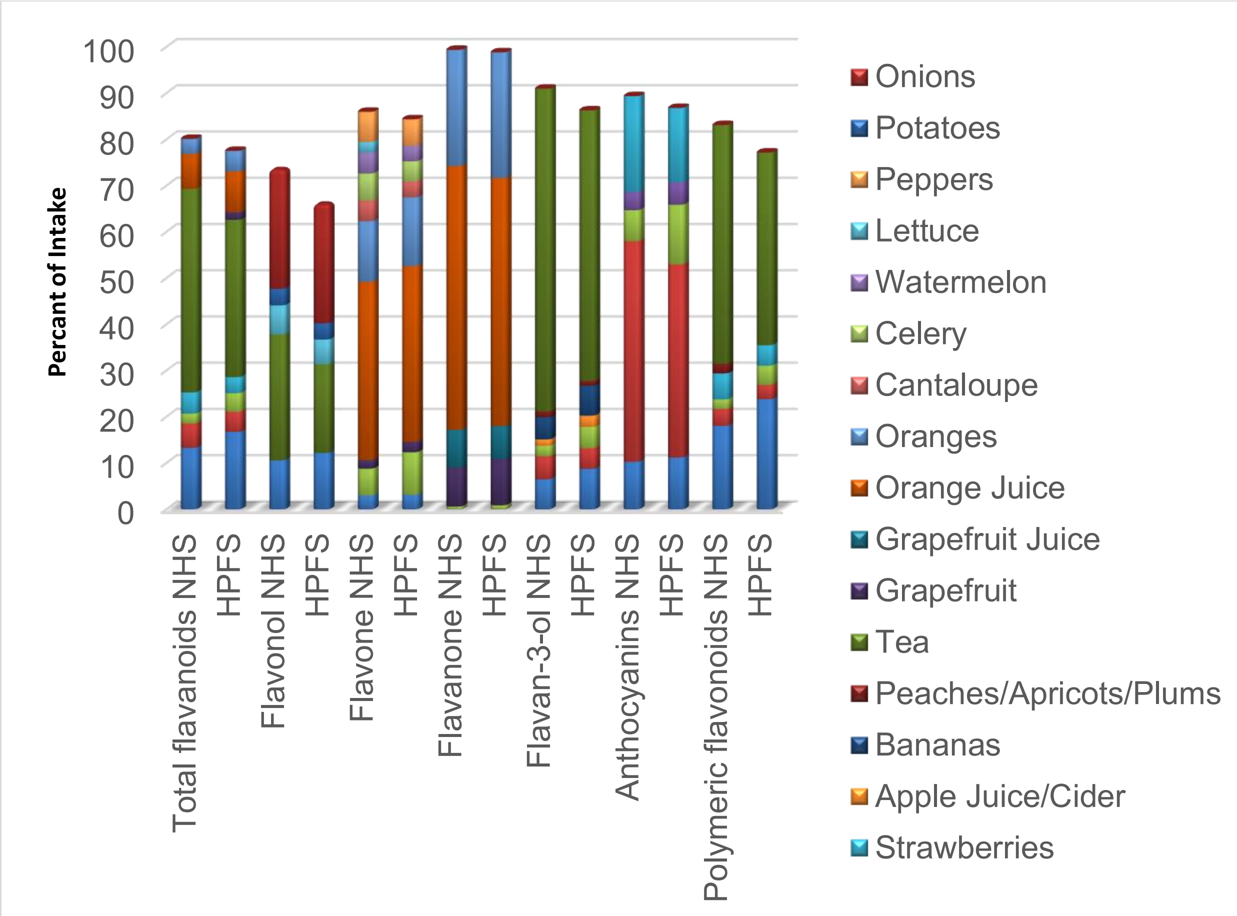


Figure 3. Major food sources of flavonoids by subclass, averaged for 1984-2006 in the NHS and 1986-2002 in the HPFS.

Top food contributors to flavones in our cohorts during the follow-up period were orange juice, oranges, peppers, celery, and red wine. Orange juice, oranges, grapefruits, grapefruit juice, and red wine were the main food sources of flavanones; while blueberries, strawberries, apples, and red wine were major contributors to anthocyanins (Figure 3). In the flavonoid-containing food analyses, we found significant associations for strawberries, grapefruits, grapefruit juice, oranges, orange juice, apples/pears, bananas, celery, peppers, peaches, beets, squash, broccoli, cauliflower, brussels sprouts, raw spinach, lettuce, cantaloupe, and potatoes with SCD for both

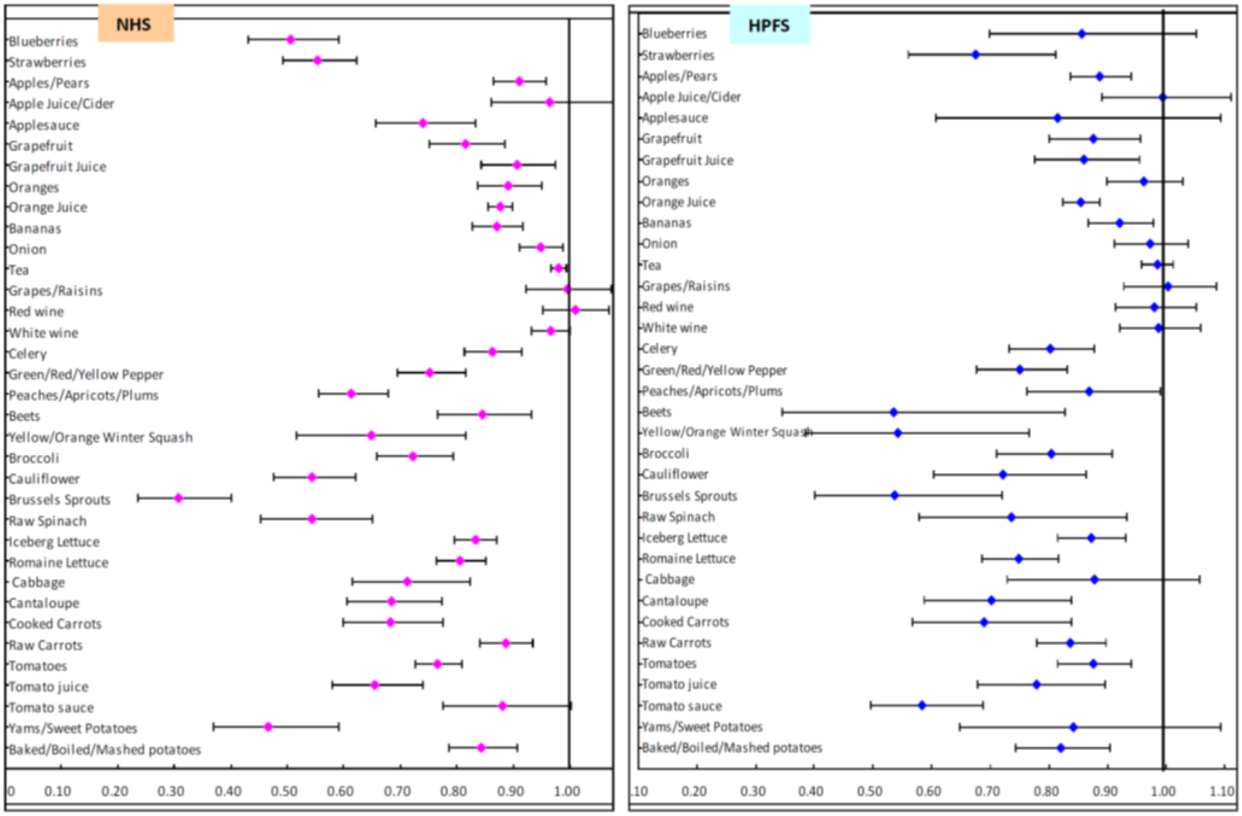
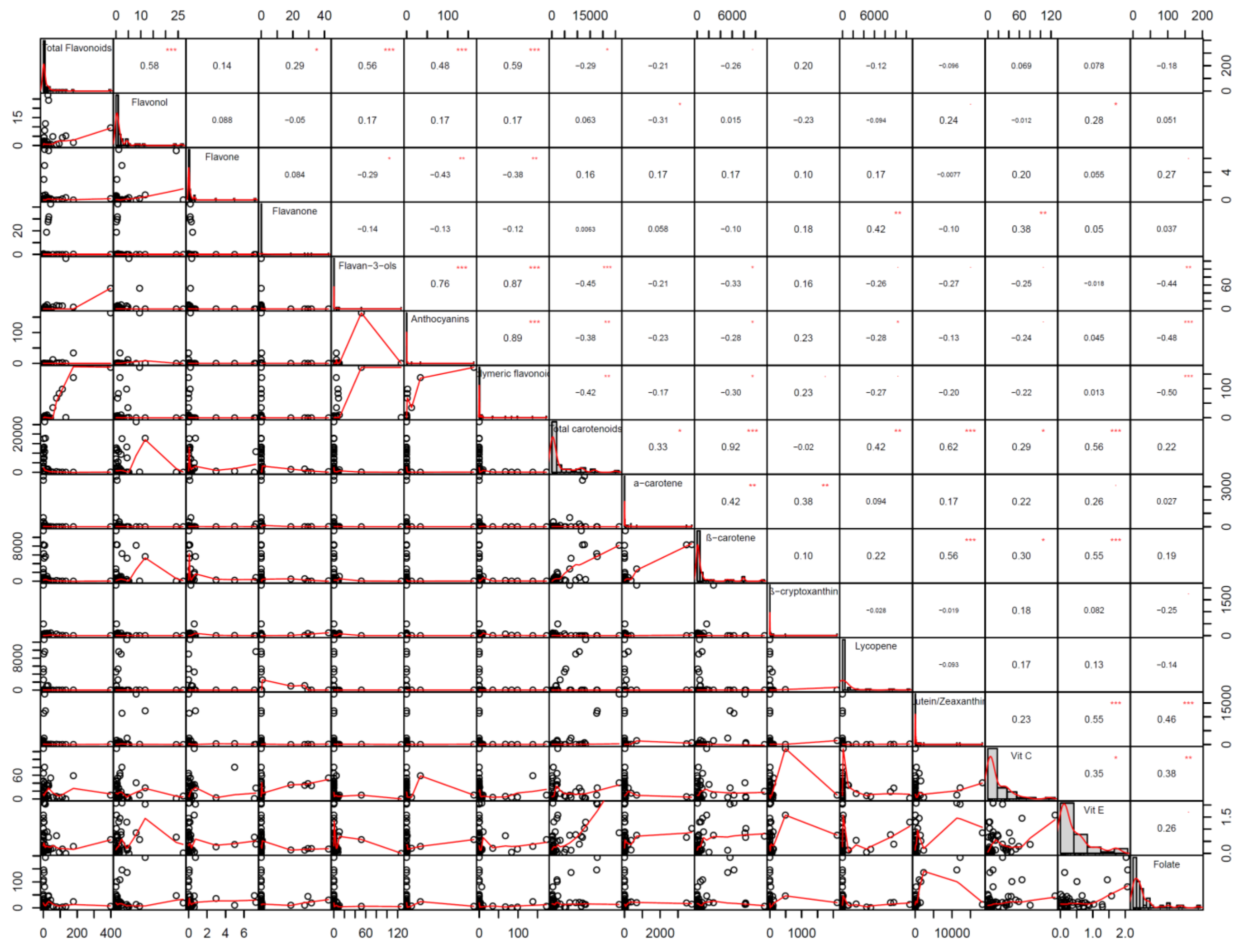


Figure 4. ORs (95% CIs) of 3 unit increments in SCD, associated with individual flavonoid-containing foods in the NHS and HPFS (for every 3 servings/wk as continuous variables)

Multivariate model: NHS: adjusted for age, total energy intake, census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (Registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol, postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2); HPFS: adjusted for age, total energy intake, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, elevated physical activity level (metabolic equivalent-h/wk, quintiles), and body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes, no), intake of alcohol, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002. Both cohorts also adjusted for dietary intakes of sugar-sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat.

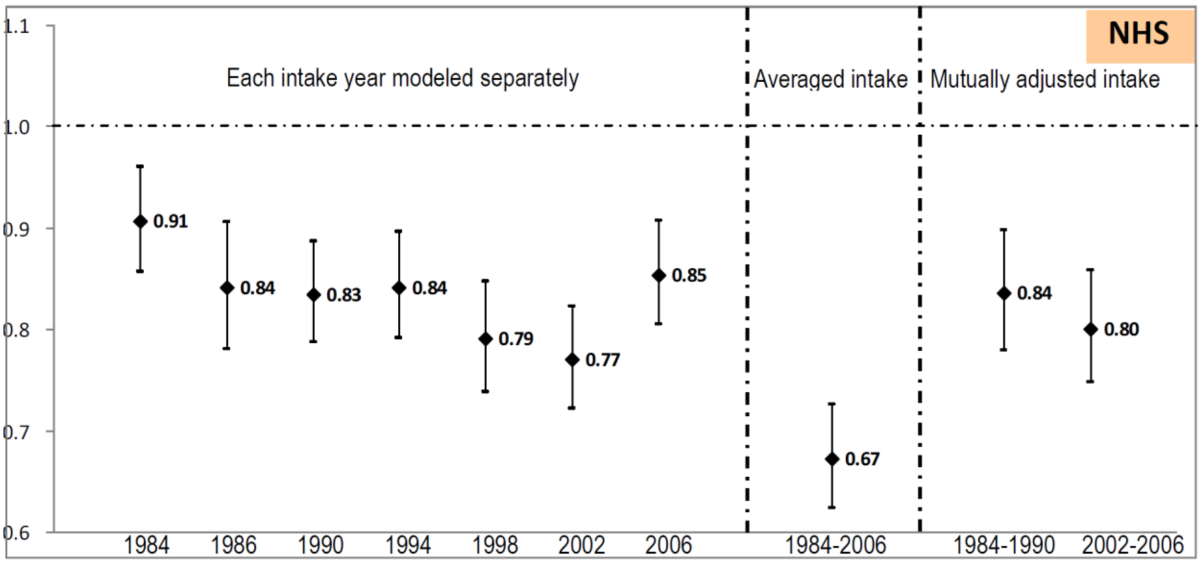
the NHS and HPFS (Figure 4). Blueberries, onions, and tea were only significant in the NHS. No significant associations were observed for grapes and wine. In the analysis using stepwise regression, blueberries, strawberries, apples, orange juice, grapefruit juice, bananas, onions, tea, peaches, cauliflower, brussels sprouts, lettuce, and potatoes were selected as independent predictors of subsequent SCD status. Generally, foods high in flavonoids were low in carotenoids, and vise versa (Figure 5).

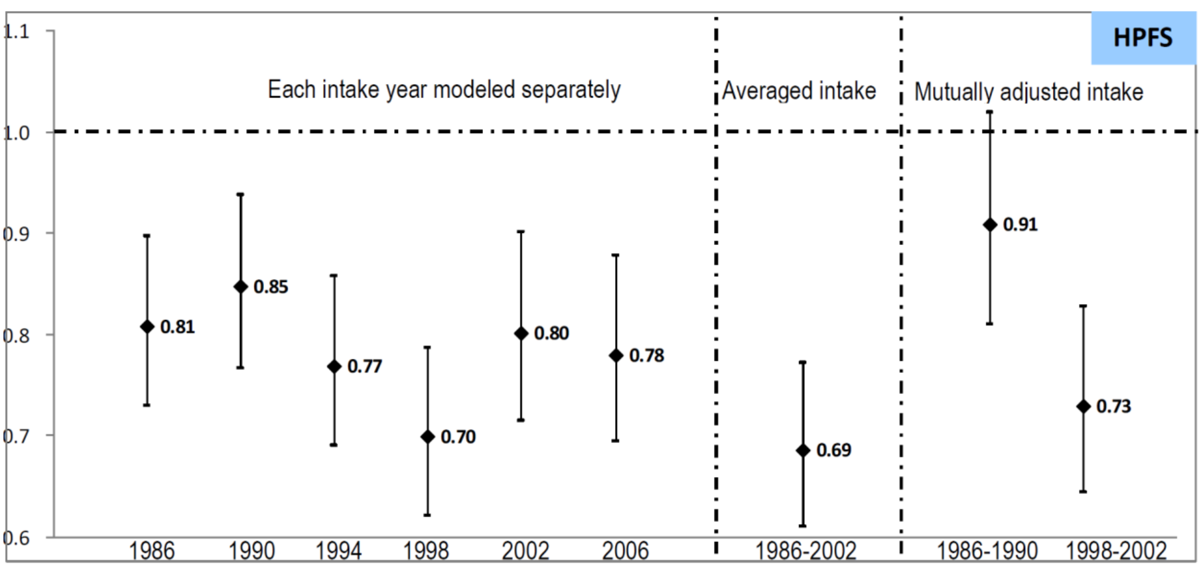
Figure 5. Correlation matrix of total and each flavonoid subclass, total and individual carotenoids, vitamin C, vitamin E, and folate, within foods. Each dot in the scatter plot indicates one type of food, with Spearman correlation coefficients shown.



In the analyses of the temporal relationships, we found that at all of the time points during follow-up (7 times in the NHS and 5 times in the HPFS), higher intakes of flavones were significantly associated with lower odds of SCD (Figure 6). The average of all dietary assessments had the strongest associations in both cohorts. When including both recent (6-10

Figure 6. Intakes of flavones at each year of dietary assessment and odds of 3 unit increments in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) comparing 90th to 10th percentile of intake (NHS: n=49,493 women, HPFS: 27,842 men)





Multivariate model: NHS: adjusted for age, total energy intake, census tract income, education (Registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, family history of dementia, vitamin C, vitamin D, vitamin E supplementation use (yes/no), intakes of alcohol, postmenopausal status and hormone replacement therapy use, missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2), total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid. HPFS: adjusted for age, total energy intake, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), physical activity level (metabolic equivalent-h/wk, quintiles), and body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes, no), intake of alcohol, family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), percentage of energy intake from dietary total protein (quintiles), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002, total carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid.

years before SCD assessment) and remote (22-28 years before SCD assessments in the NHS and 18-22 years before SCD assessments in the HPFS) intakes in the model, the association between recent flavone intakes and SCD was slightly stronger compared to remote intakes in the NHS; the association was only significant for recent intakes in the HPFS. The findings were similar for flavanones (data not shown). For intakes of strawberries (Figure 7), the associations with SCD were significant for almost all the individual years, and both recent and remote intakes were significant when being mutually adjusted in the model. These results were similar for orange juice (data not shown).

Figure 7. Intakes of strawberry at each year of dietary assessment and odds of 3 unit increment in SCD (NHS: SCD assessed in 2012, 2014; HPFS: SCD assessed in 2008, 2012) for every 3 servings/wk as continuous variables (NHS: n=49,493 women, HPFS: 27,842 men)

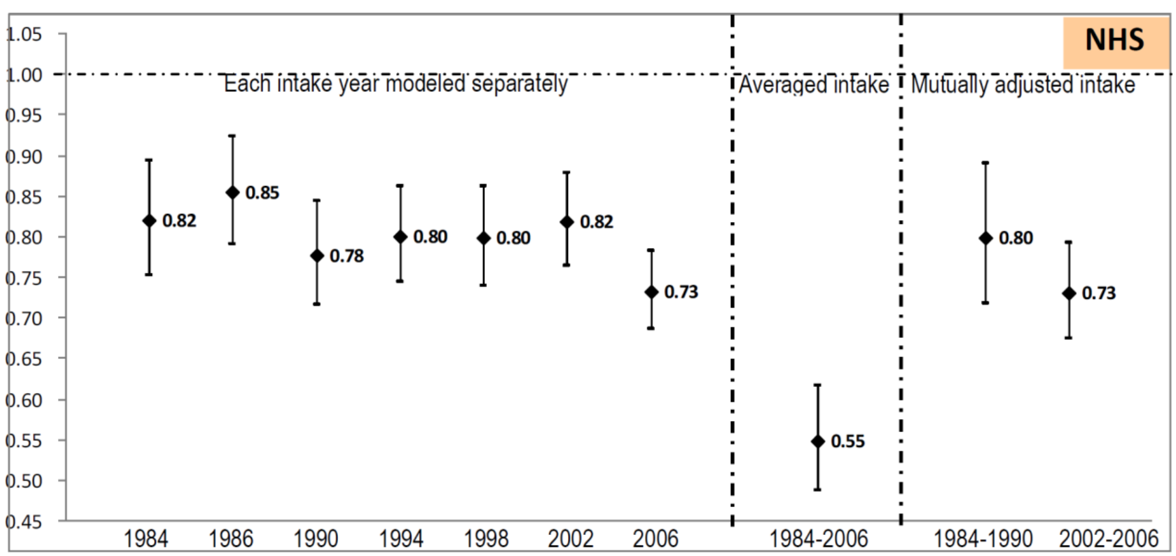
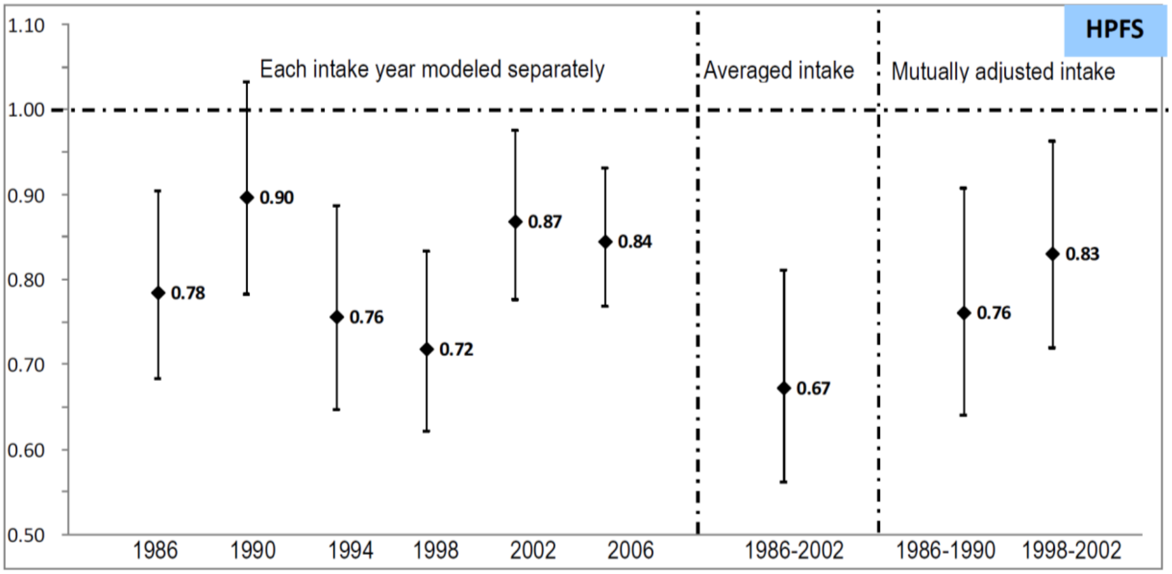


Figure 7. (Continued)



Multivariate model: NHS: adjusted for age, total energy intake, census tract income, education (Registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, family history of dementia, vitamin C, vitamin D, vitamin E supplementation use (yes/no), intakes of alcohol, postmenopausal status and hormone replacement therapy use, missing indicator for SCD measurement at 2008 or 2012, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2), sugar sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat. HPFS: adjusted for age, total energy intake, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), physical activity level (metabolic equivalent-h/wk, quintiles), and body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes, no), intake of alcohol, family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), percentage of energy intake from dietary total protein (quintiles), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002, sugar sweetened beverages, sweets/desserts, whole grains, refined grains, and animal fat.

Discussion

Combining the results from these 2 large prospective cohort studies of US men and women, we found that higher intakes of flavonoids were associated with better later-life SCD. The strongest associations were observed for flavones, flavanones, and anthocyanins. The associations remained statistically significant even after adjusting for carotenoids, vitamin C, vitamin D, vitamin E, and long-chain omega-3 fatty acid SCD.

Although several epidemiologic studies have been conducted on the relationships between flavonoids and cognitive function, results have been inconclusive. In the Rotterdam study, no associations between dietary flavonoids and Alzheimer's disease (AD) were seen[21, 22] (higher flavonoid intakes were related to risk reduction of AD only among current smokers over a 6-year follow-up[21]). In addition, in both the Honolulu-Asia Aging Study and the Zutphen study, no associations between flavonoid intakes and cognitive decline were seen.[23, 24] However, in the PAQUID study, dietary flavonoids were associated with a lower risk of cognitive decline,[25] and did not differ by smoking status.[26] In both the Rush Memory and Aging Project[42] and among participants in our NHS who completed repeated telephone-administered cognitive tests,[27] greater consumption of berries, anthocyanidins, and total flavonoids was associated with less cognitive decline. In contrast, in the Doetinchem Cohort Study, greater intake of flavonoids was associated with larger decline in cognitive flexibility during a 5-year follow-up.[28] In the SU.VI.MAX study, flavonols, proanthocyanidins, and catechins were adversely associated with executive functioning, whereas many polyphenol classes were beneficially associated with language and verbal memory.[43] These inconsistencies may be partly due to the different ages of enrolled participants, different food sources of flavonoids, or chance as some of these studies were modest in size. Studies with older participants have generally appeared to find more favorable effects of antioxidants or flavonoids,[25, 42] while middle-aged individuals appeared less likely to benefit from such dietary intakes.[28] Different follow-up durations may also influence the detection of significant associations; reverse causation, changes in cognitive function may influence diets, is possible in studies with relatively short duration. In addition, substantial differences in the flavonoid intake amounts recorded in various studies were noted. While the flavonoid intakes in the current study (mean 345 mg/d) were similar to those of the SU.VI.MAX study[43] and amounts previously reported,[27, 44] they were considerably higher compared to the Rotterdam study (mean 28.5 mg/d),[22] the PAQUID study (mean 14.4 mg/d),[25, 26] and the Honolulu-Asia Aging Study (mean 4.1 mg/d).[23] These differences may stem from the different flavonoid-containing foods included in the questionnaire, the use of different reference databases, different definitions of total flavonoids, and variation in major sources of flavonoids in different study populations. We note that our study was far larger and had much longer follow-up than previous studies; in addition, most other studies had only a single assessment of diet.

Despite the aforementioned mixed results from epidemiologic studies, several animal and *in vitro* studies, as well as some human interventional studies, have provided insights into the possible mechanisms of flavonoids on cognitive function. The antioxidant properties of flavonoids are one of the many reasons cited for a potential neuroprotective effect.[45] The findings of antioxidant activity were especially noted for flavanones from citrus,[46] which also inhibited β-amyloid induced neurotoxicity,[47] and improved cognitive function and brain blood flow in healthy adults.[19, 48] Flavanones and anthocyanins can also destabilize β-amyloid fibril aggregation[49, 50] and suppress neuroinflammation.[51-53] In murine AD, *in vivo* administration of the flavanone quercetin ameliorated Alzheimer's pathology, including β-amyloidosis, tauopathy, astrogliosis and microgliosis.[54] Flavones also possessed strong antioxidant and anti-inflammatory biologic activities.[55] Apigenin, one of the flavones included in the current study, possessed a potent anti-inflammatory effect and prevented neuronal apoptosis.[56] Another flavone, luteolin, examined in our cohorts, ameliorated spatial learning and memory impairment in the rat AD model,[57] and these beneficial effects could be due to its ability to serve as reactive oxygen species scavenger [58]. Flavanoids could also improve spatial working memory by increasing brain-derived neurotrophic factors, preventing endothelial dysfunction,[59, 60] and facilitating synaptic strength.[61]

Our findings are consistent with the above mechanistic studies of flavones, flavanones, and anthocyanins by showing that among all the flavonoid subclasses, flavones had the strongest inverse associations with SCD (a 38% lower odds of SCD when comparing participants in the highest versus the lowest quintile, equivalent to being 3 to 4 years younger in age) and the steepest dose-response curve. Flavanones possessed the second strongest relationship with SCD (a 36% lower odds of SCD when comparing participants in the highest with the lowest quintile). Anthocyanins had the second steepest dose-response curve. To our knowledge, the current study is the first to present dose-response relationships and compare the associations between various flavonoid subclasses and subsequent cognitive function. Furthermore, the interaction between flavonoid subclasses and age revealed that the magnitude of inverse associations for flavones and flavanones increased 5~6% for every 10 years younger in age for both men and women, suggesting earlier consumption of flavones and flavanones may be related to additional benefits or that the association may be stronger with earlier onset dementia.

We also found significant inverse associations between many flavonoid-containing foods, such as orange juice, oranges, grapefruits, peppers, celery, cantaloupes, apples/pears, blueberries, and strawberries, and SCD; these foods were the major contributors to flavones, flavanones, and anthocyanidins in our cohorts. These findings mirrored our results on the phytochemical level, and added to the existing evidence from some short-term human and animal interventional studies[19, 48, 61-65] that these flavonoid-containing foods may have beneficial roles in cognitive function. Although we cannot be certain whether the flavonoids in these foods are the causal agents for the associations that we observed, low correlations were observed between total and each flavonoid subclass, and total and individual carotenoids, vitamin C, vitamin E, and folate, within these foods. Detailed examination of the scatter plots in the correlation matrix revealed relatively low levels of carotenoids, vitamin C, vitamin E, and folate content in the majority of flavonoid-rich foods (especially flavone- and flavanone-rich foods). These data suggest that the beneficial associations seen with these foods were mostly attributed to the flavonoids we examined. One exception was orange and orange juice: Due to the high amount of their intakes, they were top food contributors to flavones, flavanones, and β-cryptoxanthin in our cohorts. Although both flavonoids and β-cryptoxanthin may contribute to the inverse associations seen in orange and orange juice, the associations between flavones and flavanones with SCD remained significant after adjusting for β-cryptoxanthin. Therefore, our findings on the food level further supported the hypothesis that flavonoids may be beneficial for SCD, although we cannot exclude effects of other phytochemicals.

Strengths of the present study include over 20 years of follow-up, allowing us to capture a range of potential critical exposure windows and minimize potential reverse causation. The large sample size provided great statistical power. Average dietary intakes from multiple dietary assessments over time reduced errors and within-person variations, and best represented long-term diet. To minimize the influence of dietary change due to altered cognitive function, we stopped updating dietary data 6 years prior to SCD assessments. Our data included comprehensive information on possible confounders, and adjusting for these variables minimized residual confounding. Some limitations of the current study include: First, data is lacking on baseline cognitive function. However, all cohort participants are health professionals with relatively high education levels, and high baseline cognitive function can be assumed; they are also more likely to have good insight[66] in reporting subtle cognitive changes. Second, our study does not include objective cognitive assessment and SCD assessment may be subject to errors. However, SCD has been repeatedly validated to demonstrate strong associations with both concurrent objective cognitive function[39, 40] and subsequent cognitive decline.[39] In addition, SCD can be more informative than objective cognitive function assessments because it could be used to detect subtle cognitive change,[67] especially in those with higher education.[41] Third, participants who did not complete the second SCD assessment might have more severe cognitive impairment. However, this scenario would bias our results toward the null. Fourth, generalizability could be limited because our participants were mainly Caucasian healthcare professionals who required relatively high cognitive function for their occupations and may have better health awareness. However, this relatively uniformly high cognitive function may reduce residual confounding.

In conclusion, our study identified flavones, flavanones, and anthocyanins as having the strongest protective associations with SCD. These findings could provide a roadmap for future interventional studies in search of possible therapeutic or preventive strategies for cognitive decline. Future clinical trials are warranted to validate our findings regarding the possible effects of flavonoids on cognitive function and ascertain the effective dosage. Furthermore, consumption of flavonoid-rich foods, such as berries, and citrus fruits and juices, may be beneficial to maintain cognitive function.

CHAPTER 2

Long-term total energy and fat intake on subjective cognitive decline

in US men and women

Tian-Shin Yeh, Changzheng Yuan, Alberto Ascherio, Bernard A. Rosner, Deborah Blacker,

Walter C. Willett

Abstract

Objective: We prospectively examined the associations between long-term intakes of total energy and fat with subsequent subjective cognitive decline (SCD).

Methods: A total of 49,493 women were included from the Nurses' Health Study (NHS), and 27,842 men were included from the Health Professionals Follow-up Study (HPFS). For the NHS, averaged dietary intake from 1984 to 2006 was calculated based on seven repeated food frequency questionnaires (SFFQs) and SCD was assessed in 2012 and 2014. For the HPFS, averaged dietary intake from 1986 to 2002 was calculated based on five repeated SFFQs and SCD was assessed in 2008 and 2012. A strong association with *APOE* Ɛ4 genotype supported the validity of SCD scores. Poisson regression was used to examine associations between total energy, total fat, specific fatty acid, and fat-containing food intakes with subsequent SCD. Odds ratios (ORs) were estimated for a 3-unit increment in SCD from zero as an indication of poor versus good cognitive function.

Results: Higher total energy intake was significantly associated with higher odds of SCD in both the NHS and HPFS. Comparing the highest versus the lowest quintiles of total energy intake, the pooled multivariable-adjusted ORs (95% CIs) of a 3-unit increment in SCD was 1.91 (1.77, 2.05), p trend <0.0001. A positive association was observed between total fat intake and SCD; the pooled multivariable-adjusted OR was 1.14 (1.11, 1.17) when substituting each 5% of energy intake from total fat for the same amount of energy from total carbohydrates. *Trans*-fat and saturated fat were not associated with SCD; the associations for monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) were inconsistent over the follow-up period and across cohorts.

Conclusion: We found that total energy intake and the total fat composition of diet were adversely associated with SCD in US men and women. Whether these association are causal is unclear and deserve further investigation.

Introduction

Dementia has become a leading disease burden in many countries, impacting the rapidly aging world population.[2, 5] To date, there are no effective treatments for dementia,[68] and identification of modifiable risk factors to prevent or delay onset and progression of this disease is of utmost importance. The development of clinical dementia is preceded by a preclinical phase—subjective cognitive decline (SCD)—a state of self-perceived cognitive decline without detectable cognitive impairments by objective measures.[6] Dementia-associated brain pathologies may be found on brain MRI years before SCD,[7] suggesting a long window for potential prevention.[8] Available evidence has suggested that diet is one of the few modifiable risk factors for cognitive decline.[9-12]

Calorie restriction has been used frequently to understand the mechanisms in age-related diseases.[69] In numerous animal studies, calorie restriction has increased longevity,[70] delayed or prevented many chronic diseases, and improved cognitive function and late-life health.[71-74] However, human data on total energy intake and cognitive function remain sparse. Of the three macronutrients, fat, carbohydrates, and proteins, contributing to total energy intake, dietary fat has been of research interest because of the relationship with cholesterol metabolism, which is related to *APOE* ε4, the strongest genetic risk factor for Alzheimer's disease.[75, 76] *APOE* acts as a cholesterol transporter, and possession of *APOE* ε4 alleles is associated with poor cholesterol export, resulting in increased intracellular cholesterol and impaired beta-amyloid clearance.[77] To date, results of studies on the relationship between dietary fat and cognitive function have been inconclusive.[78-81] In some studies, higher intakes of saturated fat[79] and *trans*-fat[82] were associated with higher risk of cognitive impairment,[79, 80] but other studies have found the opposite[78] or null results.[78, 81] In addition, findings on the effects of specific types of unsaturated fats have been conflicting.[83-86] Therefore, in the current study, we examined the relationships between long-term total energy and fat intake and SCD using repeated dietary assessments from over 20 years of follow-up in two large prospective cohorts of US men and women.

Methods

Study Design

A total of 121,701 female registered nurses in the US aged 30 to 55 years were enrolled in the Nurses' Health Study (NHS) in 1976. Questionnaires have been distributed to the participants biennially inquiring about newly diagnosed diseases and potential risk factors. A semi-quantitative food frequency questionnaire (SFFQ), which has been validated in multiple studies,[29] has been used to collect dietary information in 1980, 1984, 1986, and every 4 years thereafter. A total of 51,529 US male health professionals aged 40 to 75 years were enrolled in the Health Professionals Follow-up Study (HPFS) in 1986. Questionnaires regarding lifestyle risk factors and medical history have been sent to participants every two years,[30] and dietary assessments using the SFFQ have been collected from 1986 and every 4 years thereafter. This study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Assessment of dietary intake

Dietary information was assessed by the SFFQs (available at www.nurseshealthstudy.org and sites.sph.harvard.edu/hpfs/hpfs-questionnaires). A standard portion size of each food was defined, and the consumption frequency was divided into 9 categories, ranging from <1 time/month to ≧6 times/day. The total intake amount of nutrients and energy intake were calculated based on the product of consumption frequency of each item and its nutrient and energy composition, summed across all items. Nutrient values were primarily based on the US Department of Agriculture (USDA) database (available at regepi.bwh.harvard.edu/health/nutrition). For the NHS, an expanded SFFQ with 131 items was first distributed in 1984, and repeated in 1986 and then every four years. Averaged intakes of percentage of energy from fat, other nutrients/foods, and total energy were calculated based on the seven repeated SFFQs from 1984 until 2006 to best represent long-term diet and minimize within-subject variation.[31] Updating of intake was stopped in 2006 to provide a lag before the assessment of cognitive decline and thus minimize the effect of cognitive function on diet. Similarly, for the HPFS, the averaged intake from five repeated dietary assessments (starting from 1986 and then every four years until 2002) was used. In both cohorts, SFFQs correlated well with multiple dietary records for total and specific types of fat: the correlations for energy-adjusted intakes were 0.67 for total fat, 0.70 for saturated fatty acids (SFAs), 0.69 for monounsaturated fatty acids (MUFA), and 0.64 for polyunsaturated fatty acids (PUFA).[87, 88] Correlations between energy intake and doubly labeled water measurements were 0.12 among women[89] and 0.25 among men.[90]

Assessment of subjective cognitive decline (SCD)

In both cohorts, SCD was assessed twice by either mail or online questionnaires (2012 and 2014 for the NHS, 2008 and 2012 for the HPFS). In our previous publications, the term subjective cognitive function (SCF) was used,[36, 37] but we have updated the terminology to SCD in line with changes in the field.[38] For the HPFS, the SCD scores were based on six yes/no questions: (1) “Do you have more trouble than usual remembering recent events?”; (2) “Do you have more trouble than usual remembering a short list of items, such as a shopping list?”; (3)

"Do you have trouble remembering things from one second to the next?"; (4) "Do you have any difficulty in understanding things or following spoken instructions?"; (5) "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?"; and (6) "Do you have trouble finding your way around familiar streets?" For the NHS, one additional question: "Have you recently experienced any change in your ability to remember things?" was included.[39] For scoring, one point was given to each positive response for these questions. Two SCD scores were then averaged to minimize random errors, except for participants with only one documented response from the two SCD questionnaires.

Strong associations have been shown between SCD with both concurrent objective cognitive function[39, 40] and subsequent cognitive decline,[39] notably for individuals with higher education.[41] SCD was also strongly associated with homozygous *APOE* Ɛ4 genotype in both the NHS and HPFS.[37] Also, numerous risk factors for dementia, such as high blood pressure, depression, cardiovascular disease (CVD), type 2 diabetes, heavy smoking, and high blood cholesterol, were all associated with SCD,[37] which further supports validity.

Covariates

Information on covariates was prospectively collected in the NHS and HPFS at baseline and on follow-up questionnaires. These included: age (years, continuous), body mass index (BMI) (<23, 23-25, 25-30, >30 kg/m^2), height (inches), physical activity (MET-hours/week), race (white, black, other), the use of multivitamin (yes/no), smoking status (pack-years), amount of alcohol consumption (g/d), cancer, diabetes, high blood pressure, elevated cholesterol, history of CVD (stroke, myocardial infarction, angina, or coronary artery surgery), family history of dementia, and depression (defined as anti-depressant use or self-reported depression). For the

NHS, additional information on menopausal status, use of hormone replacement therapy, parity (nulliparous, 1-2, >2), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), census tract income ($50,000, $50,000–69,999, or $70,000/y) was obtained. For the HPFS, information on profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian) was also collected.

Population for Analysis

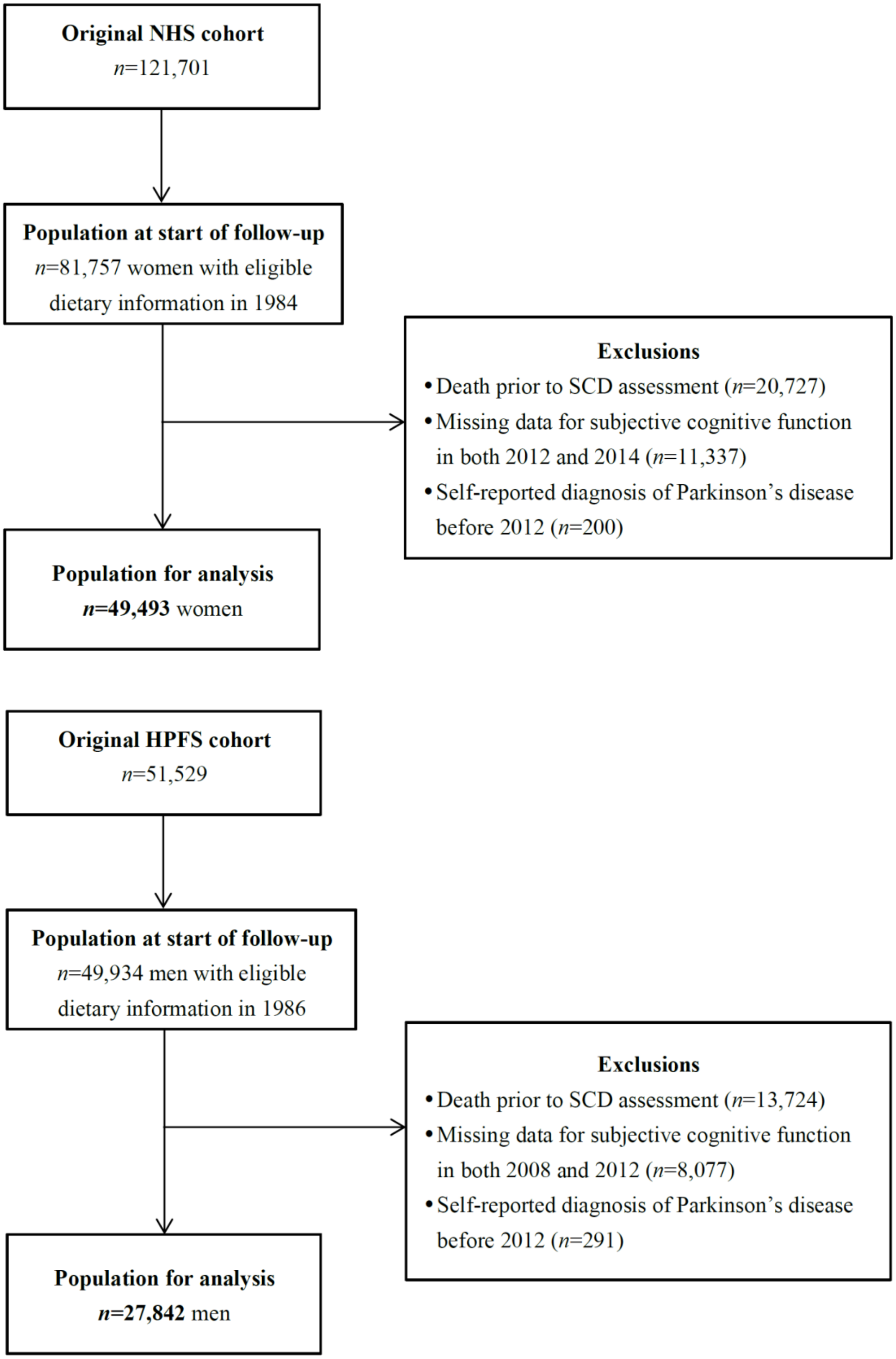
In the NHS, excluding deaths prior to 1984, and individuals with >70 food items blank and extreme energy intake of <600 or >3,500 kcal/day, a total of 81,757 participants with eligible dietary information in 1984 were included at baseline (Figure 8). From the total participants, there were additional exclusions that consisted of 20,727 deaths prior to SCD assessments and 11,337 participants without SCD information. Another 200 participants who developed Parkinson's disease prior to SCD assessment were also excluded, leaving 49,493 women in the final analysis with a mean age of 48 years at baseline in 1984.

Exclusion criteria were the same for the HPFS. After excluding deaths before SCD assessment, individuals without dietary or SCD information, and 291 participants with Parkinson's disease diagnosis before SCD assessment, the final analysis included 27,842 men with a mean age of 51 years at enrollment in 1986.

Statistical analysis

Averaged daily total energy intake was calculated from repeated SFFQs. The percentage of energy from fat was calculated by dividing the energy intake from fat by total energy intake

Figure 8. Study population and exclusions in the NHS and HPFS.



for each SFFQ, and then we calculated the averaged percentage of energy from fat from repeated SFFQs. Intakes of total energy, total fat, and specific fatty acids were divided into quintiles. We calculated age-standardized characteristics for all participants according to quintiles of total energy, total fat, *trans*-fat, SFA, MUFA, and PUFA intakes. The averaged SCD score was calculated from the two SCD assessments. Poisson regression models were used due to the distribution and nature of the SCD scores. ORs and 95% CIs of 3-unit increments in SCD were calculated because three or more positive SCD questions was our definition of poor cognitive function.[39, 40] The associations between total energy, total fat, specific fatty acids, and fat-containing food intakes with SCD were estimated by comparing each quintile of intake with the lowest quintile. Covariate information was used from the same questionnaire as the dietary assessments (1984-2006 for the NHS and 1986-2002 for the HPFS). Due to a non-linear relationship between age and SCD, both a linear and a quadratic term for age were included in all models. In multivariate analyses, the averaged age at the two SCD assessments, total energy intake, race, history of smoking, depression, physical activity level, BMI, alcohol intake, family history of dementia, missing indicator for SCD assessments, number of dietary assessments during follow-up period, and the use of multivitamin were included as covariates. For the NHS, information on parity, postmenopausal status, use of hormone replacement therapy, annual income, education, husband's education was also included in the analyses. For the HPFS, information on profession was additionally included in the analyses. Because hypertension, diabetes, elevated cholesterol, and CVD were potential mediators on a causal pathway, we did not adjust for these variables in our primary analysis, although similar results were observed with or without these variables in the models. For primary fatty acid analyses, all models were mutually adjusted for remaining fatty acid and protein intakes. In the fully adjusted model, intakes of carotenoids, anthocyanins, vitamin C, D, and E were also included. In addition to being categorized as quintiles, total fat and specific fatty acids were also treated as continuous variables. In these isocaloric substitution models, the coefficients can be interpreted as the associations when increasing the percentage of energy from fat while reducing the same percentage of energy from total carbohydrates. In the sensitivity analysis, we adjusted for individual carotenoids (β-carotene, α-carotene, lycopene, lutein/zeaxanthin, and β-cryptoxanthin) instead of total carotenoids. Also, because body size is one of the major determinants of between-person variation in total energy intake, we further adjusted for height when evaluating the association between total energy intake and SCD.

In addition to the aforementioned traditional isocaloric substitution with carbohydrates, we modeled each specific fatty acid as percentage of total fat (fat quality index), also adjusting for total fat and total energy intakes in the same model as secondary analysis. The coefficients from these models can be interpreted as the effect when substituting the specific fatty acid for all other fatty acids. All the aforementioned non-dietary variables and intakes of carotenoids, anthocyanins, vitamin C, D, and E were included in the fully adjusted models in the continuous analyses.

For fat-containing food analysis, all major non-dietary variables and intakes of total vegetables, fruit, fruit juice, and sugar-sweetened beverages were included in the final model. For all analyses, testing for linear trends was conducted by assigning median values within each quintile and modeling these variables as continuous variables.

To investigate whether the associations between total energy and fat intake were modified by variables of interests, additional analyses were conducted by stratifying participants by baseline age (<50 years, ≥50 years), smoking status (never smokers, past smokers, and current smokers), disease status (self-reported CVD, type 2 diabetes, and depression), and *APOE* Ɛ4 allele carrier status (yes/no) in a subgroup of participants who had their APOE Ɛ4 measured or imputed from a genome-wide association analysis.

To evaluate the temporal relationship between total energy and fat with SCD, the associations between dietary intake at each of the individual years with SCD were estimated. We also mutually included both recent (the averaged intake from 2002~2006 in the NHS and averaged intake from 1998~2002 for the HPFS) and remote (the averaged intake from 1984~1990 in the NHS and averaged intake from 1986~1990 for the HPFS) intakes in the same model to examine whether these associations were independent of each other. Covariates closest in time with the dietary assessments were used in these analyses.

Analyses were first performed separately for each cohort, and an inverse-variance-weighted, fixed-effect meta-analysis was used to combine the results across the NHS and HPFS studies. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Population Characteristics

The mean age at the initial SCD assessment was 76.4 years for women and 73 years for men. Participants with higher total energy intake had higher alcohol and percent of energy from total fat intakes, lower percent of energy from protein, carotenoid, and anthocyanin intakes, higher level of physical activity, and higher prevalance of depression in both the NHS and HPFS. In addition, women with higher total energy intake tend to be younger, while lower prevalence of hypercholesterolemia was observed for men (Table 3).

Table 3 NHS: Characteristics[a] in 1984-2006 of 49,493 women who completed SCD questions in 2012/2014 by quintiles of total energy intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Total energy intake, kcal/d	1,191	1,488	1,702	1,935	2,358
Age, y	49.5	48.7	48.4	47.9	47.1
BMI, kg/m^2	26.1	26.0	26.1	26.1	26.3
Alcohol, g/day	4.2	5.3	5.9	6.3	6.9
Total fat intake, % energy	30.9	30.9	31.2	31.5	32.3
Carbohydrate, % energy	50.1	50.5	50.6	50.7	50.7
Protein, % energy	18.8	18.3	18.0	17.7	17.2
Physical activity, MET-h/wk	16.6	17.9	18.3	18.9	21.2
Smoking pack-years, 1984-2006, %					
Never smoked	44.5	45.7	45.6	47.1	49.7
<=4 pack-years	9.9	10.4	11.5	11.3	11.6
5-24 pack-years	23.9	23.0	23.1	22.2	21.3
>=25 pack-years	20.2	19.2	18.2	17.6	15.8
Missing	1.5	1.8	1.5	1.8	1.5
High blood pressure, 1984-2006, %	60.7	60.8	60.6	60.1	60.0
Elevated cholesterol, 1984-2006, %	71.9	71.8	71.2	71.2	71.3
Diabetes, 1984-2006, %	11.6	10.7	10.7	10.0	10.7
CVD, 1984-2006, %	10.0	10.2	9.9	10.0	10.9
Cancer, 1984-2006, %	18.3	18.3	18.2	18.5	19.0
Depression diagnosis or anti-depressant use 1996 - 2006, %	18.7	18.9	19.3	19.8	20.7
Number of dietary assessments, 1984-2006					
1	0.3	0.2	0.2	0.1	0.3
2	1.2	0.7	0.5	0.5	1.0
3	1.9	1.3	1.4	1.4	1.6
4	3.8	2.9	2.8	2.9	3.9
5	8.6	6.4	6.0	6.4	8.6
6	21.3	17.7	17.6	17.6	21.8
7	63.0	70.9	71.5	71.1	62.8
Missing year of SCD measurement					
None	85.2	86.1	86.0	86.2	86.0
2014	12.3	11.5	11.4	11.0	11.3
Postmenopausal status & hormone use					
Postmenopause and never use hormone therapy	21.1	20.5	20.4	20.6	21.6
Postmenopause and ever use hormone therapy	73.0	74.4	74.5	74.3	73.5
Missing	5.5	4.6	4.7	4.6	4.4
Parity					
Nulliparous	5.3	5.3	5.4	5.2	4.9
1-2	7.4	6.6	6.4	6.3	6.6
3+	85.1	86.3	86.4	87.1	86.7
Missing	2.2	1.8	1.7	1.5	1.9
Total carotenoid intake (mcg/day)	15,646	15,236	15,061	14,921	14,879
Total anthocyanin intake (mg/day)	16.8	15.9	15.2	14.5	13.5

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population

Table 3 HPFS (Continued): Characteristics[a] in 1986-2002 of 27,842 men who completed SCD questions in 2008/2012 by quintiles of total energy intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Total energy intake, kcal/d	1,339	1,681	1,939	2,231	2,773
Age, y	51.3	51.4	51.1	51.0	50.5
BMI, kg/m^2	26.0	25.9	25.8	25.9	26.0
Alcohol, g/day	7.7	9.9	11.5	12.7	14.5
Total fat intake, % energy	29.6	29.8	30.5	31.0	32.0
Carbohydrate, % energy	49.8	50.0	49.7	49.6	49.2
Protein, % energy	18.8	18.2	17.8	17.6	17.2

Table 3 (Continued)					
Physical activity, MET-h/wk	24.3	26.6	28.5	30.1	33.0
Smoking pack-years, 1986-2002, %					
Never smoked	48.2	49.2	49.6	50.0	49.2
<=24 pack-years	29.9	29.4	28.7	28.5	28.1
25-44 pack-years	11.3	11.2	11.5	11.3	11.6
>=45 pack-years	4.6	4.7	4.6	5.7	5.9
Missing	6.1	5.5	5.5	4.6	5.1
High blood pressure, 1986-2002, %	46.1	45.1	43.5	44.7	43.2
Elevated cholesterol, 1986-2002, %	60.1	58.0	56.9	55.3	52.6
Diabetes, 1986-2002, %	8.5	7.6	7.3	7.6	7.3
CVD, 1986-2002, %	19.2	17.9	16.8	17.1	16.2
Cancer, 1986-2002, %	15.9	16.2	15.8	15.3	14.7
Depression diagnosis or anti-depressant use 1986-2002, %	4.9	5.2	5.7	5.9	6.1
Number of dietary assessment, 1986-2002					
1	3.6	2.0	1.8	1.6	2.3
2	6.8	4.6	3.8	3.5	4.4
3	10.8	7.3	7.4	7.8	9.4
4	21.1	17.1	17.5	16.8	19.1
5	57.7	69.0	69.5	70.4	64.8
Missing year of SCD measurement					
None	71.0	71.5	73.3	73.4	72.7
2008	9.9	9.1	8.4	8.2	7.7
2012	19.1	19.4	18.3	18.4	19.6
Profession, %					
Dentist	61.7	60.4	58.6	54.6	51.6
Pharmacist	8.2	8.0	8.3	8.7	8.8
Optometrist	7.4	7.1	6.9	6.8	5.8
Osteopath	5.2	4.4	3.7	3.8	3.3
Podiatrist	3.4	2.3	2.4	2.2	2.1
Veterinarian	14.1	17.7	20.1	24.0	28.4
Total carotenoid intake (mcg/day)	18,759	18,416	18,141	17,696	17,250
Total anthocyanin intake (mg/day)	16.3	15.8	15.4	14.3	13.4

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population.

Both male and female participants with higher total fat intake (as percentage of energy) tend to be younger, less physically active, had higher BMI, higher total energy intake, and had lower alcohol, cabohydrate, carotenoid, and anthocyanin intakes. Male participants with higher fat intake were also more likely to be heavy smokers, with higher prevalence of diabetes, but lower prevalence of CVD and hypercholesterolemia (Table 4). For both the NHS and HPFS, participants with higher SFA, *trans*-fatty acid, MUFA, and PUFA intakes (as percentage of

Table 4 NHS: Characteristics[a] in 1984-2006 of 49,493 women who completed SCD questions in 2012/2014 by quintiles of total fat intake (as percentage of energy)					
	Q1	Q2	Q3	Q4	Q5
Total fat intake, % energy	25.1	28.9	31.3	33.7	37.8
Age, y	50.4	48.8	48.0	47.5	46.9
BMI, kg/m^2	25.0	25.8	26.1	26.5	27.1
Alcohol, g/day	6.3	6.2	5.9	5.5	4.8
Total energy intake, kcal/d	1,648	1,719	1,749	1,782	1,782
Carbohydrate, % energy	56.6	52.8	50.5	48.4	44.4
Protein, % energy	18.3	18.1	18.0	17.8	17.7

Table 4 (NHS) (Continued)					
Physical activity, MET-h/wk	23.5	19.7	18.3	16.9	14.9
Smoking pack-years, 1984-2006, %					
Never smoked	47.9	48.1	46.8	46.5	43.6
<=4 pack-years	12.2	11.7	11.0	10.2	9.7
5-24 pack-years	24.1	22.8	23.4	22.0	21.0
>=25 pack-years	14.3	15.7	17.3	19.7	24.0
Missing	1.6	1.8	1.5	1.6	1.8
High blood pressure, 1984-2006, %	58.1	60.7	60.3	61.1	61.5
Elevated cholesterol, 1984-2006, %	72.1	72.8	71.8	71.0	69.5
Diabetes, 1984-2006, %	7.3	9.5	10.9	12.3	13.7
CVD, 1984-2006, %	10.7	9.9	10.2	10.2	9.9
Cancer, 1984-2006, %	18.9	18.3	18.6	17.9	18.6
Depression diagnosis or anti-depressant use 1996 - 2006, %	19.3	19.1	19.9	19.5	19.6
Number of dietary assessments, 1984-2006					
1	0.1	0.1	0.1	0.2	0.6
2	0.5	0.5	0.6	0.8	1.2
3	1.3	1.3	1.5	1.5	2.0
4	3.0	3.0	2.8	3.4	4.0
5	7.0	6.7	6.9	7.2	8.1
6	19.4	19.0	19.2	18.7	19.9
7	68.7	69.4	68.8	68.2	64.2
Missing year of SCD measurement					
None	86.3	86.2	86.7	85.4	85.2
2014	11.4	11.2	10.8	11.8	11.8
Postmenopausal status & hormone use					
Postmenopause and never use hormone therapy	21.3	20.0	20.7	21.3	21.4
Postmenopause and ever use hormone therapy	73.8	75.0	74.0	73.5	73.0
Missing	4.5	4.6	4.7	4.8	5.2
Parity					
Nulliparous	6.1	5.1	5.0	5.0	4.9
1-2	7.2	6.8	6.6	6.1	6.7
3+	85.0	86.4	86.5	87.4	86.2
Missing	1.7	1.6	1.9	1.5	2.2
Total carotenoid intake (mcg/day)	17,081	15,748	15,028	14,332	13,505
Total anthocyanin intake (mg/day)	20.4	16.7	14.8	13.2	11.1

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population.

Table 4 HPFS (Continued): Characteristics[a] in 1986-2002 of 27,842 men who completed SCD questions in 2008/2012 by quintiles of total fat intake (as percentage of energy)					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Total fat intake, % energy	23.2	27.9	30.7	33.3	37.8
Age, y	52.0	51.3	50.9	50.7	50.5
BMI, kg/m^2	24.9	25.6	26.0	26.3	26.8
Alcohol, g/day	12.7	12.3	11.7	10.7	8.9
Total energy intake, kcal/d	1,857	1,932	1,998	2,069	2,110
Carbohydrate, % energy	56.7	52.0	49.5	47.1	42.9
Protein, % energy	18.0	17.9	17.9	17.8	18.0
Physical activity, MET-h/wk	33.9	29.9	28.2	26.4	24.3
Smoking pack-years, 1986-2002, %					
Never smoked	51.9	50.8	49.3	48.9	45.6
<=24 pack-years	30.1	29.7	29.9	28.3	26.4
25-44 pack-years	9.2	10.7	11.0	12.0	13.7
>=45 pack-years	3.5	3.7	4.4	5.2	8.9
Missing	5.3	5.1	5.4	5.6	5.4
High blood pressure, 1986-2002, %	44.1	44.3	45.3	44.9	43.7
Elevated cholesterol, 1986-2002, %	61.4	57.9	57.8	54.4	51.1
Diabetes, 1986-2002, %	5.4	6.3	7.2	8.7	10.7
CVD, 1986-2002, %	22.5	18.2	16.1	15.4	14.6
Cancer, 1986-2002, %	16.1	16.4	16.0	15.0	14.6

Table 4 HPFS (Continued)					
Depression diagnosis or anti-depressant use 1986-2002, %	5.2	4.9	5.5	6.1	6.3
Number of dietary assessment, 1986-2002					
1	2.3	1.7	1.7	2.3	3.2
2	4.0	4.5	4.5	4.3	5.7
3	8.2	7.7	8.3	8.4	10.2
4	18.0	17.8	18.6	18.5	18.6
5	67.5	68.3	66.9	66.6	62.3
Missing year of SCD measurement					
None	74.2	73.8	72.4	72.3	69.2
2008	8.0	8.1	9.0	8.4	9.9
2012	17.8	18.1	18.6	19.3	20.9
Profession, %					
Dentist	64.3	60.4	56.9	55.0	50.3
Pharmacist	6.7	8.2	9.2	9.4	8.5
Optometrist	7.2	6.7	6.7	6.8	6.5
Osteopath	4.6	4.2	3.8	3.5	4.3
Podiatrist	2.4	2.8	2.5	2.4	2.4
Veterinarian	14.8	17.7	20.9	22.8	28.1
Total carotenoid intake (mcg/day)	21,552	19,121	17,759	16,684	15,139
Total anthocyanin intake (mg/day)	20.9	16.9	14.6	12.5	10.1

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population.

participants with higher SFA, *trans*-fatty acid, MUFA, and PUFA intakes (as percentage of energy) had higher total energy intake, lower physical activity level, higher BMI, generally lower alcohol consumption, and lower intakes of carbohydrate, carotenoids, and anthocyanins (Table 5) . In addition, women with higher intakes of SFA, *trans*-fatty acid, MUFA, and PUFA tend to be younger and had higher prevalence of diabetes; while men with higher intakes of SFA, *trans*-fatty acid, MUFA, and PUFA had higher prevalence of depression and higher percentage of multivitamin use.

Table 5 NHS: Age-adjusted characteristics[a] in 1984-2006 of 49,493 women who completed SCD assessments in 2012/2014 across quintiles of fatty acid intakes (as percentage of energy)

	Saturated fat			Trans fat			Polyunsaturated fat			Monounsaturated fat		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Fatty acid intake, % energy	7.9	10.4	13.4	0.8	1.3	1.8	4.7	6.0	7.7	9.2	11.9	14.8
Age, y	50.3	48.1	47.1	49.8	48.1	47.4	49.3	48.1	47.9	50.6	48.0	46.8
BMI, kg/m^2	24.8	26.2	27.2	25.0	26.3	26.9	25.6	26.2	26.4	25.2	26.2	26.8
Alcohol, g/day	6.7	6.0	4.6	7.5	5.8	3.8	6.8	5.6	5.0	5.7	5.7	5.7
Total energy intake, kcal/d	1,668	1,751	1,771	1,670	1,741	1,789	1,656	1,750	1,770	1,635	1,752	1,789
Total fat intake, % energy	25.9	31.4	36.7	27.3	31.4	35.1	27.3	31.3	35.4	25.3	31.4	37.3
Carbohydrate, % energy	55.8	50.3	45.5	53.5	50.3	48.2	53.9	50.5	47.2	56.4	50.5	44.7
Protein, % energy	18.3	18.0	17.7	18.8	18.1	17.1	18.2	18.1	17.7	18.4	18.0	17.7

Table 5 NHS (Continued)												
Physical activity, MET-h/wk	24.4	18.1	14.5	25.6	18.0	13.5	20.2	18.2	17.4	22.8	18.2	16.1
Smoking pack-years, 1984-2006, %												
Never smoked	47.3	45.8	44.8	43.5	46.4	49.8	46.6	47.2	45.6	48.5	47.4	42.6
<=4 pack-years	12.8	11.1	9.0	13.0	10.9	9.3	11.2	11.0	10.5	11.7	11.2	10.3
5-24 pack-years	25.2	23.7	19.6	27.1	22.4	18.6	22.2	22.9	22.6	23.7	22.4	22.7
>=25 pack-years	13.1	17.9	24.9	14.6	18.6	20.9	18.5	17.2	19.5	14.5	17.5	22.7
Missing	1.6	1.5	1.7	1.7	1.6	1.5	1.5	1.6	1.8	1.6	1.4	1.7
High blood pressure, 1984-2006, %	57.2	60.6	61.8	56.6	61.2	62.4	60.3	59.9	59.3	58.5	60.4	60.5
Elevated cholesterol, 1984-2006, %	73.6	72.3	68.3	69.2	72.0	71.8	69.8	72.5	70.8	71.7	71.9	70.4
Diabetes, 1984-2006, %	7.6	11.2	13.1	8.0	10.9	12.3	8.6	10.6	12.3	7.8	11.1	13.1
CVD, 1984-2006, %	10.6	10.1	10.2	9.7	10.7	10.0	10.3	10.7	9.9	10.6	10.6	9.8
Cancer, 1984-2006, %	18.9	17.8	17.9	19.1	18.4	18.1	18.8	18.4	18.4	18.7	18.3	18.7
Depression diagnosis or anti-depressant use 1996 -2006, %	18.6	20.1	19.9	18.6	19.3	19.7	19.8	19.8	19.0	19.4	19.5	19.3
Number of dietary assessment, 1984-2006												
1	0.1	0.1	0.6	0.0	0.1	0.8	0.2	0.2	0.5	0.1	0.1	0.4
2	0.5	0.5	1.5	0.4	0.6	1.5	0.8	0.5	1.2	0.7	0.7	1.0
3	1.3	1.6	2.1	1.3	1.5	2.2	1.4	1.4	2.0	1.4	1.6	1.8
4	3.0	2.8	4.2	3.0	3.1	4.2	3.6	2.8	4.2	3.3	2.9	3.7
5	6.8	7.1	7.9	7.2	6.8	7.9	7.1	6.6	8.3	7.1	7.0	7.8
6	19.7	19.1	19.8	20.4	19.2	19.2	19.2	19.1	18.9	19.2	18.5	20.1
7	68.6	68.8	63.8	67.8	68.7	64.3	67.8	69.4	65.0	68.3	69.1	65.2
Missing year of SCD measurement												
None	87.3	85.8	84.2	87.3	86.3	83.9	85.4	85.9	86.3	85.9	86.1	85.9
2014	10.5	11.6	12.7	10.5	11.3	12.6	11.8	11.5	11.0	11.5	11.3	11.2
Postmenopausal status & hormone use												
Postmenopause and never use hormone therapy	19.9	19.8	24.1	19.6	20.5	23.7	22.7	21.0	19.4	21.8	20.3	20.6
Postmenopause and ever use hormone therapy	75.3	75.4	69.9	75.7	74.7	69.9	71.6	74.1	75.5	73.2	74.6	74.0
Missing	4.4	4.5	5.6	4.3	4.5	6.0	5.2	4.4	4.7	4.6	4.7	5.0
Parity												
Nulliparous	6.5	5.2	4.7	6.7	4.7	4.7	5.6	5.0	5.3	6.2	5.0	5.2
1-2	7.2	6.6	6.4	7.0	6.5	6.5	7.0	6.7	6.6	7.3	6.6	6.9
3+	84.6	86.4	86.7	84.6	87.2	86.6	85.5	86.6	85.9	84.6	86.8	85.8
Missing	1.7	1.8	2.2	1.6	1.6	2.2	1.8	1.7	2.1	1.9	1.6	2.0
Total carotenoid intake (mcg/day)	18,140	14,957	12,766	18,938	14,859	12,042	15,145	15,232	14,954	16,734	14,869	14,338
Total anthocyanin intake (mg/day)	21.6	14.7	10.5	22.6	14.4	9.9	17.1	15.0	13.5	19.6	14.6	12.4

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population.

Table 5 HPFS (Continued): Age-adjusted characteristics[a] in 1986-2002 of 27,842 men who completed SCD assessments in 2008/2012 across quintiles of fatty acid intakes (as percentage of energy)

	Saturated fat			Trans fat			Polyunsaturated fat			Monounsaturated fat		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Fatty acid intake, % energy	6.9	10.2	13.5	0.7	1.3	1.9	4.4	5.7	7.5	8.8	12.0	15.3
Age, y	52.3	50.8	50.3	51.9	51.1	50.1	51.5	50.9	51.0	51.8	50.9	50.5
BMI, kg/m^2	24.8	26.0	26.8	25.0	26.1	26.3	25.5	26.0	26.0	25.0	25.9	26.6
Alcohol, g/day	5.4	4.6	3.3	5.5	4.7	3.2	6.2	4.5	3.5	5.1	4.7	3.8
Total energy intake, kcal/d	1,950	2,072	2,154	1,961	2,057	2,146	1,969	2,060	2,124	1,908	2,071	2,164
Total fat intake, % energy	25.9	31.4	36.7	27.3	31.4	35.1	27.3	31.3	35.4	25.3	31.4	37.3
Carbohydrate, % energy	56.2	49.1	43.6	54.2	48.9	46.6	53.5	49.5	46.3	56.7	49.4	42.9
Protein, % energy	17.9	17.9	18.0	18.5	18.0	17.1	17.7	18.0	17.9	18.2	17.8	17.9
Physical activity, MET-h/wk	34.3	27.3	23.9	35.3	27.8	23.0	30.1	28.0	27.2	33.6	27.9	24.7
Smoking pack-years, 1986-2002, %												
Never smoked	52.3	50.0	46.4	50.5	48.8	49.4	50.3	48.6	47.8	53.3	50.0	44.3
<=24 pack-years	30.9	29.1	25.7	31.7	28.5	25.7	28.6	29.8	29.6	29.3	29.6	28.0
25-44 pack-years	8.7	11.7	14.6	9.4	12.5	12.6	11.3	11.7	12.2	9.1	11.1	14.7

Table 5 HPFS (Continued)												
>=45 pack-years	2.8	4.0	7.8	3.0	4.9	6.9	4.3	4.5	5.4	3.3	4.0	7.6
Missing	5.3	5.2	5.4	5.4	5.2	5.4	5.6	5.4	5.0	5.1	5.3	5.5
High blood pressure, 1986-2002, %	43.4	44.3	44.2	42.5	45.6	44.7	46.3	45.4	42.5	44.2	44.7	43.6
Elevated cholesterol, 1986-2002, %	62.4	56.7	48.6	57.0	57.3	53.8	55.9	57.3	55.0	60.5	58.3	52.3
Diabetes, 1986-2002, %	5.3	7.5	10.3	6.6	8.8	8.1	5.8	7.2	9.6	5.4	7.4	10.1
CVD, 1986-2002, %	4.5	3.1	2.8	3.9	3.1	3.3	4.0	3.2	3.1	4.3	3.2	3.0
Cancer, 1986-2002, %	13.5	13.7	13.2	13.6	14.1	13.3	14.0	14.1	13.1	13.8	13.9	12.9
Depression diagnosis or anti-depressant use 1986-2002, %	5.0	5.4	6.2	4.9	5.3	6.5	5.5	5.6	5.9	5.0	5.2	6.3
Number of dietary assessment, 1986-2002												
1	1.9	1.7	3.5	3.0	2.2	1.9	3.0	2.0	3.1	2.9	1.8	2.6
2	4.1	4.5	6.0	5.2	4.3	4.8	5.2	4.0	5.2	4.9	4.3	5.4
3	8.4	7.7	10.3	9.0	8.2	8.9	8.2	7.6	10.3	8.4	7.7	10.1
4	17.6	18.1	18.0	19.6	17.0	17.4	18.2	18.3	18.9	18.0	18.0	18.9
5	67.9	68.0	62.1	63.1	68.3	67.1	65.3	68.2	62.5	65.8	68.2	62.9
Missing year of SCD measurement												
None	74.1	72.3	69.9	72.3	72.3	71.8	72.3	72.8	70.8	73.6	73.2	70.0
2008	8.1	8.4	9.6	9.5	8.5	8.9	8.9	8.4	9.3	8.7	8.6	9.7
2012	17.8	19.3	20.5	18.2	19.1	19.2	18.7	18.8	19.8	17.6	18.2	20.3
Profession, %												
Dentist	66.6	57.7	46.8	67.6	57.5	46.2	56.8	57.1	59.4	64.0	56.2	52.2
Pharmacist	6.0	9.2	9.1	5.2	8.8	12.1	9.2	8.8	7.6	6.7	9.4	8.4
Optometrist	6.5	6.7	5.8	6.0	7.1	7.3	6.5	6.6	7.0	6.7	6.9	6.4
Osteopath	4.7	3.9	4.0	4.7	4.1	3.9	4.5	4.1	3.9	4.9	3.8	4.2
Podiatrist	2.4	2.3	2.6	2.7	2.2	2.7	2.9	2.2	2.5	2.7	2.5	2.2
Veterinarian	13.7	20.3	31.7	13.8	20.4	28.0	20.0	21.2	19.6	15.1	21.2	26.7
Total carotenoid intake (mcg/day)	15,171	10,876	8,325	15,685	10,796	8,211	11,836	11,345	11,135	14,332	11,072	9,302
Total anthocyanin intake (mg/day)	20.7	14.1	9.5	22.7	14.1	9.3	17.4	14.7	13.0	20.6	14.3	10.8

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population.

Total Energy

For both the NHS and HPFS, higher total energy intake was significantly associated with higher odds of SCD after adjusting for age and major non-dietary factors (Table 6). In the pooled analysis, when comparing the highest with the lowest quintiles of total energy intake, the multivariate OR of a 3 unit-increment in SCD was 1.91 (95% CI: 1.77, 2.05), *p* trend <0.0001; each 500 kcal/day greater intake was associated with a 30% higher odds of SCD. In the sensitivity analysis when height was additionally adjusted, the positive associations were strengthened.

Table 6: Associations (ORs (95% CI) between total energy intake and 3-unit increments in SCD in the NHS & HPFS							
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P trend**	**Continuous[a]**
Total energy							(500 kcal/day)
NHS							
Median intake (kcal/day)	1,196	1,472	1,687	1,923	2,301		
Age-adjusted model	Ref	1.36 (1.25, 1.47)	1.44 (1.33, 1.57)	1.62 (1.49, 1.76)	1.81 (1.67, 1.96)	<.0001	1.27 (1.23, 1.30)
Multivariate model(MV)	Ref	1.40 (1.29, 1.52)	1.49 (1.38, 1.62)	1.68 (1.55, 1.83)	1.92(1.77, 2.09)	<.0001	1.30 (1.26, 1.34)
HPFS							
Median intake (kcal/day)	1,366	1,683	1,938	2,224	2,693		
Age-adjusted model	Ref	1.05 (0.92, 1.20)	1.40 (1.22, 1.60)	1.58 (1.38, 1.80)	2.01 (1.76, 2.29)	<.0001	1.29 (1.24, 1.35)
Multivariate model (MV)	Ref	1.03 (0.90, 1.19)	1.35 (1.18, 1.54)	1.48 (1.29, 1.69)	1.90 (1.66, 2.18)	<.0001	1.27 (1.22, 1.32)
Meta-analyzed results(MV)	Ref	1.30 (1.26, 1.33)	1.44 (1.37, 1.56)	1.64 (1.52, 1.73)	1.91 (1.77, 2.05)	<.0001	1.30 (1.26, 1.33)

Age-adjusted model: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years);
Multivariate model: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as the use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as the use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
[a] Indicates OR of SCD for each 500 kcal increase in daily total energy intake.

Fatty Acid Analysis

Total fat intake (as percentage of energy) was positively associated with SCD in both cohorts (Table 7). The magnitude of these associations was attenuated after adjusting for total energy, and further attenuated after adjusting for major non-dietary factors and dietary factors. In the final multivariate model comparing extreme quintiles, the pooled OR (95% CI) of a 3-unit increment in SCD was 1.40 (1.30, 1.52), *p* trend <0.0001. When replacing each 5% of energy intake from total fat with the same amount of energy from total carbohydrates, the pooled ORs were 1.14 (1.11, 1.17). Results were similar in the sensitivity analysis when we adjusted for individual carotenoids instead of total carotenoids.

Table 7: OR (95% CI) for the associations between total and specific types of fat intakes (mutually adjusted for all FA) with SCD in the NHS and HPFS (comparison is isocaloric substitution for total carbohydrates)							
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P trend**	**Continuous[a]**
Total Fat							5% Energy
NHS							
Median intake (% of energy)	25.52	28.96	31.29	33.65	37.16		
Age-adjusted model	Ref	1.17 (1.08, 1.27)	1.43 (1.32, 1.55)	1.55 (1.43, 1.69)	1.89 (1.74, 2.05)	<.0001	1.28 (1.25, 1.32)
Age & Calorie-adjusted model	Ref	1.14 (1.05, 1.24)	1.39 (1.28, 1.50)	1.49 (1.37, 1.62)	1.81 (1.67, 1.96)	<.0001	1.26 (1.23, 1.30)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (1.03, 1.22)	1.32 (1.22, 1.44)	1.39 (1.28, 1.52)	1.66 (1.53, 1.81)	<.0001	1.22 (1.19, 1.26)
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.98, 1.16)	1.23 (1.13, 1.34)	1.26 (1.16, 1.37)	1.45 (1.33, 1.58)	<.0001	1.16 (1.13, 1.20)
HPFS							
Median intake (% of energy)	23.86	27.89	30.67	33.28	37.11		
Age-adjusted model	Ref	1.21 (1.05, 1.38)	1.58 (1.38, 1.80)	1.78 (1.56, 2.03)	2.05 (1.80, 2.34)	<.0001	1.29 (1.24, 1.35)
Age & Calorie-adjusted model	Ref	1.17 (1.02, 1.34)	1.49 (1.31, 1.71)	1.63 (1.43, 1.87)	1.84 (1.61, 2.11)	<.0001	1.25 (1.20, 1.30)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (0.98, 1.29)	1.38 (1.20, 1.58)	1.44 (1.25, 1.65)	1.51 (1.31, 1.73)	<.0001	1.16 (1.11, 1.21)
Above+Dietary factors adjusted (MV2)	Ref	1.06 (0.92, 1.21)	1.24 (1.08, 1.42)	1.24 (1.08, 1.43)	1.24 (1.07, 1.44)	0.0008	1.09 (1.04, 1.14)
Meta-analyzed results(MV2)	Ref	1.06 (1.00, 1.12)	1.23 (1.16, 1.33)	1.26 (1.16, 1.37)	1.40 (1.30, 1.52)	<.0001	1.14 (1.11, 1.17)
Trans fat							2% Energy
NHS							
Median intake (% of energy)	0.87	1.11	1.28	1.46	1.76		
Age-adjusted model	Ref	1.24 (1.14, 1.35)	1.29 (1.17, 1.41)	1.36 (1.23, 1.50)	1.46 (1.31, 1.61)	<.0001	2.11 (1.75, 2.55)
Age & Calorie-adjusted model	Ref	1.24 (1.14, 1.36)	1.29 (1.18, 1.42)	1.37 (1.24, 1.51)	1.47 (1.33, 1.63)	<.0001	2.18 (1.80, 2.63)
Above+Nondietary factors adjusted (MV1)	Ref	1.19 (1.09, 1.30)	1.20 (1.09, 1.32)	1.22 (1.10, 1.34)	1.30 (1.17, 1.45)	<.0001	1.69 (1.38, 2.06)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (1.02, 1.21)	1.07 (0.97, 1.18)	1.04 (0.94, 1.15)	1.04 (0.93, 1.17)	0.9529	1.11 (0.89, 1.37)
HPFS							
Median intake (% of energy)	0.90	1.23	1.48	1.75	2.17		
Age-adjusted model	Ref	1.07 (0.92, 1.24)	1.14 (0.98, 1.33)	1.15 (0.98, 1.36)	1.17 (0.98, 1.39)	0.0693	1.29 (1.03, 1.61)
Age & Calorie-adjusted model	Ref	1.07 (0.93, 1.24)	1.14 (0.98, 1.34)	1.16 (0.98, 1.36)	1.19 (0.99, 1.41)	0.0495	1.33 (1.07, 1.67)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.89, 1.20)	1.06 (0.90, 1.24)	1.05 (0.89, 1.24)	1.06 (0.89, 1.27)	0.5161	1.17 (0.92, 1.47)
Above+Dietary factors adjusted (MV2)	Ref	0.96 (0.83, 1.12)	0.94 (0.80, 1.11)	0.89 (0.75, 1.06)	0.86 (0.71, 1.03)	0.0937	0.87 (0.68, 1.11)
Meta-analyzed results(MV2)	Ref	1.06 (1.00, 1.16)	1.03 (0.94, 1.12)	1.00 (0.91, 1.09)	1.00 (0.91, 1.09)	0.2825	1.00 (0.85, 1.17)
Saturated fat							5% Energy
NHS							
Median intake (% of energy)	8.04	9.45	10.44	11.46	13.03		
Age-adjusted model	Ref	1.07 (0.97, 1.17)	1.16 (1.05, 1.29)	1.09 (0.98, 1.22)	1.16 (1.03, 1.31)	0.0133	1.12 (1.01, 1.23)
Age & Calorie-adjusted model	Ref	1.06 (0.97, 1.16)	1.15 (1.04, 1.27)	1.08 (0.97, 1.20)	1.15 (1.02, 1.30)	0.0211	1.10 (1.00, 1.22)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.95, 1.14)	1.07 (0.97, 1.19)	1.01 (0.91, 1.13)	1.07 (0.95, 1.21)	0.3229	1.03 (0.93, 1.14)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.91, 1.10)	1.01 (0.91, 1.12)	0.92 (0.83, 1.03)	0.94 (0.83, 1.06)	0.1553	0.89 (0.81, 0.99)
HPFS							
Median intake (% of energy)	7.05	8.76	9.91	11.04	12.79		
Age-adjusted model	Ref	1.15 (0.99, 1.35)	1.22 (1.02, 1.46)	1.38 (1.14, 1.67)	1.56 (1.27, 1.93)	<.0001	1.36 (1.16, 1.60)
Age & Calorie-adjusted model	Ref	1.15 (0.98, 1.34)	1.21 (1.01, 1.44)	1.35 (1.11, 1.63)	1.50 (1.22, 1.85)	<.0001	1.30 (1.10, 1.53)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (0.95, 1.30)	1.13 (0.95, 1.35)	1.22 (1.01, 1.48)	1.32 (1.07, 1.64)	0.0075	1.16 (0.98, 1.37)
Above+Dietary factors adjusted (MV2)	Ref	1.04 (0.89, 1.22)	1.03 (0.86, 1.23)	1.07 (0.88, 1.30)	1.11 (0.89, 1.38)	0.3356	0.99 (0.83, 1.18)
Meta-analyzed results(MV2)	Ref	1.00 (0.94, 1.09)	1.00 (0.94, 1.09)	0.97 (0.86, 1.06)	0.97 (0.88, 1.09)	0.5839	0.92 (0.84, 1.01)

Table 7 (Continued)							
Total MUFA							5% Energy
NHS							
Median intake (% of energy)	9.41	10.87	11.88	12.89	14.47		
Age-adjusted model	Ref	0.93 (0.84, 1.02)	1.09 (0.99, 1.21)	1.09 (0.98, 1.22)	1.31 (1.16, 1.49)	<.0001	1.24 (1.11, 1.38)
Age & Calorie-adjusted model	Ref	0.91 (0.83, 0.99)	1.07 (0.96, 1.18)	1.05 (0.94, 1.18)	1.26 (1.12, 1.43)	<.0001	1.20 (1.08, 1.33)
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.86, 1.03)	1.12 (1.01, 1.24)	1.11 (0.99, 1.24)	1.33 (1.18, 1.51)	<.0001	1.27 (1.14, 1.42)
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.87, 1.05)	1.16 (1.05, 1.29)	1.16 (1.04, 1.31)	1.42 (1.25, 1.61)	<.0001	1.39 (1.24, 1.54)
HPFS							
Median intake (% of energy)	9.11	10.85	12.02	13.17	14.83		
Age-adjusted model	Ref	1.13 (0.97, 1.33)	1.14 (0.95, 1.36)	1.13 (0.93, 1.38)	1.23 (0.98, 1.54)	0.1145	1.20 (1.00, 1.44)
Age & Calorie-adjusted model	Ref	1.10 (0.94, 1.29)	1.08 (0.90, 1.30)	1.06 (0.86, 1.29)	1.13 (0.90, 1.42)	0.4218	1.13 (0.93, 1.36)
Above+Nondietary factors adjusted (MV1)	Ref	1.09 (0.93, 1.28)	1.11 (0.92, 1.33)	1.04 (0.85, 1.28)	1.10 (0.87, 1.38)	0.6097	1.09 (0.90, 1.32)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.95, 1.30)	1.15 (0.96, 1.38)	1.09 (0.89, 1.33)	1.15 (0.92, 1.45)	0.3344	1.18 (0.98, 1.43)
Meta-analyzed results(MV2)	Ref	1.00 (0.91, 1.06)	1.16 (1.06, 1.26)	1.16 (1.03, 1.26)	1.37 (1.23, 1.52)	<.0001	1.33 (1.21, 1.46)
PUFA							5% Energy
NHS							
Median intake (% of energy)	4.79	5.48	5.99	6.54	7.46		
Age-adjusted model	Ref	1.03 (0.95, 1.12)	1.20 (1.10, 1.31)	1.11 (1.01, 1.22)	1.16 (1.06, 1.28)	0.0025	1.27 (1.10, 1.48)
Age & Calorie-adjusted model	Ref	1.02 (0.93, 1.11)	1.18 (1.08, 1.29)	1.09 (0.99, 1.19)	1.15 (1.04, 1.27)	0.0053	1.26 (1.08, 1.46)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.95, 1.13)	1.18 (1.08, 1.28)	1.09 (0.99, 1.20)	1.17 (1.06, 1.29)	0.0032	1.25 (1.08, 1.46)
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.98, 1.16)	1.21 (1.11, 1.32)	1.13 (1.03, 1.24)	1.20 (1.09, 1.32)	0.0006	1.28 (1.10, 1.48)
HPFS							
Median intake (% of energy)	4.57	5.27	5.77	6.32	7.26		
Age-adjusted model	Ref	1.12 (0.97, 1.28)	1.16 (1.00, 1.34)	1.18 (1.02, 1.37)	1.32 (1.13, 1.55)	0.0005	1.25 (0.98, 1.59)
Age & Calorie-adjusted model	Ref	1.10 (0.96, 1.27)	1.15 (0.99, 1.33)	1.16 (1.01, 1.35)	1.32 (1.13, 1.54)	0.0005	1.26 (0.99, 1.61)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (0.97, 1.29)	1.16 (1.01, 1.34)	1.17 (1.01, 1.36)	1.33 (1.14, 1.56)	0.0004	1.32 (1.03, 1.69)
Above+Dietary factors adjusted (MV2)	Ref	1.14 (0.99, 1.31)	1.19 (1.03, 1.38)	1.21 (1.04, 1.40)	1.35 (1.15, 1.58)	0.0003	1.29 (1.00, 1.65)
Meta-analyzed results(MV2)	Ref	1.09 (1.00, 1.16)	1.19 (1.12, 1.30)	1.16 (1.06, 1.26)	1.23 (1.12, 1.37)	<.0001	1.28 (1.12, 1.45)
MUFA Plant							5% Energy
NHS							
Median intake (% of energy)	4.19	5.24	6.08	7.01	8.75		
Age-adjusted model	Ref	1.21 (1.11, 1.31)	1.32 (1.21, 1.44)	1.25 (1.15, 1.37)	1.33 (1.22, 1.45)	<.0001	1.17 (1.09, 1.26)
Age & Calorie-adjusted model	Ref	1.18 (1.09, 1.29)	1.27 (1.17, 1.38)	1.20 (1.10, 1.31)	1.27 (1.17, 1.39)	<.0001	1.14 (1.06, 1.22)
Above+Nondietary factors adjusted (MV1)	Ref	1.18 (1.09, 1.28)	1.28 (1.18, 1.39)	1.24 (1.14, 1.35)	1.36 (1.25, 1.48)	<.0001	1.22 (1.13, 1.31)
Above+Dietary factors adjusted (MV2)	Ref	1.19 (1.10, 1.30)	1.31 (1.20, 1.42)	1.28 (1.18, 1.40)	1.47 (1.35, 1.61)	<.0001	1.33 (1.24, 1.43)
HPFS							
Median intake (% of energy)	4.26	5.33	6.12	6.98	8.41		
Age-adjusted model	Ref	1.10 (0.96, 1.26)	1.22 (1.07, 1.40)	1.28 (1.12, 1.47)	1.24 (1.08, 1.43)	0.0017	1.24 (1.09, 1.41)
Age & Calorie-adjusted model	Ref	1.07 (0.94, 1.23)	1.19 (1.04, 1.36)	1.22 (1.07, 1.41)	1.19 (1.03, 1.37)	0.0109	1.19 (1.05, 1.36)
Above+Nondietary factors adjusted (MV1)	Ref	1.07 (0.94, 1.23)	1.18 (1.02, 1.35)	1.22 (1.06, 1.40)	1.23 (1.07, 1.42)	0.0019	1.27 (1.11, 1.44)
Above+Dietary factors adjusted (MV2)	Ref	1.08 (0.94, 1.24)	1.20 (1.05, 1.38)	1.25 (1.08, 1.44)	1.28 (1.10, 1.48)	0.0003	1.33 (1.16, 1.52)
Meta-analyzed results(MV2)	Ref	1.16 (1.09, 1.26)	1.30 (1.19, 1.37)	1.26 (1.19, 1.33)	1.40 (1.33, 1.52)	<.0001	1.33 (1.24, 1.42)
MUFA Animal							5% Energy
NHS							
Median intake (% of energy)	3.56	4.56	5.26	5.97	7.09		

Table 7 (Continued)

Age-adjusted model	Ref	1.14 (1.05, 1.23)	1.12 (1.03, 1.21)	1.23 (1.13, 1.34)	1.27 (1.15, 1.39)	<.0001	1.34 (1.20, 1.49)
Age & Calorie-adjusted model	Ref	1.13 (1.04, 1.22)	1.11 (1.02, 1.21)	1.23 (1.13, 1.34)	1.28 (1.17, 1.40)	<.0001	1.35 (1.21, 1.50)
Above+Nondietary factors adjusted (MV1)	Ref	1.11 (1.02, 1.20)	1.04 (0.95, 1.13)	1.11 (1.02, 1.22)	1.14 (1.04, 1.26)	0.0169	1.15 (1.03, 1.29)
Above+Dietary factors adjusted (MV2)	Ref	1.05 (0.96, 1.14)	0.96 (0.88, 1.04)	0.99 (0.91, 1.09)	0.98 (0.88, 1.08)	0.3069	0.92 (0.82, 1.04)
HPFS							
Median intake (% of energy)	3.40	4.62	5.45	6.31	7.69		
Age-adjusted model	Ref	1.22 (1.06, 1.39)	1.25 (1.09, 1.44)	1.23 (1.07, 1.43)	1.36 (1.16, 1.59)	0.001	1.30 (1.12, 1.51)
Age & Calorie-adjusted model	Ref	1.20 (1.05, 1.38)	1.23 (1.07, 1.41)	1.21 (1.05, 1.40)	1.32 (1.13, 1.54)	0.004	1.26 (1.08, 1.46)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (0.97, 1.28)	1.12 (0.97, 1.30)	1.05 (0.90, 1.22)	1.07 (0.91, 1.26)	0.9012	0.98 (0.84, 1.15)
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.90, 1.19)	1.01 (0.87, 1.17)	0.92 (0.79, 1.08)	0.90 (0.76, 1.07)	0.0748	0.82 (0.69, 0.97)
Meta-analyzed results(MV2)	Ref	1.00 (0.97, 1.12)	0.97 (0.91, 1.06)	0.97 (0.88, 1.06)	0.97 (0.88, 1.03)	0.0479	0.88 (0.80, 0.98)

Age-adjusted model: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2: other than variables adjusted in MV1, further adjusted for carotenoids (quintiles), anthocyanins (quintiles), vitamin c, d, and e (quintiles)
[a] Indicates OR of 3-unit increments in SCD when replacing each 5% of energy intake from specific fatty acids with the same amount of energy from total carbohydrates (except for *trans*-fat, which was when replacing each 2% of energy intake from *trans*-fat for energy equivalent of total carbohydrates).
Abbreviations: FA: fatty acids; MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids;

All models adjusted for percentage of energy intake from total protein. All models (except models for total fat intake) also included percentages of energy intake from remaining fatty acids.

For both *trans*-fat and SFA, although positive associations with SCD were observed in the age-adjusted and age-and-calorie-adjusted models, associations became null in the fully-adjusted models; the greatest magnitude of attenuation occurred when adjusting for carotenoid and anthocyanin intakes. Comparing the highest versus the lowest quintiles, the pooled multivariate ORs (95% CI) of 3 unit-increments in SCD were 1.00 (0.91, 1.09), *p* trend=0.28 for trans-fat and 0.97 (0.89, 1.09), *p* trend =0.58 for SFA.

For MUFA intake, positive associations with SCD were found in the NHS, while null associations were found in the HPFS. For PUFA intake, positive associations with SCD were observed in both the NHS and HPFS. In both cohorts, for MUFA and PUFA, adjusting for total energy intake attenuated the magnitude of associations, whereas adjusting for carotenoids and anthocyanins strengthened the associations. The pooled multivariate OR (95% CI) comparing extreme quintiles were 1.37 (1.23, 1.52), *p* trend <0.0001 for MUFA and 1.23 (1.12, 1.37), *p* trend <0.0001 for PUFA.

When replacing each 5% of energy intake from specific fatty acids with the same amount of energy from total carbohydrates, the pooled ORs were 0.92 (0.84, 1.01) for SFA, 1.33 (1.21, 1.46) for MUFA, and 1.28 (1.12, 1,45) for PUFA. When replacing each 2% of energy intake from *trans*-fat with equivalent energy from total carbohydrates, the pooled OR was 1.00 (0.85, 1.17). Results were similar across strata of baseline age, smoking status, disease status, and *APOE* ε4 allele carrier status.

Secondary analysis for specific fatty acids

When modeling specific fatty acids as percentage of total fat and also adjusting for total fat in the same model, results for *trans*-fat, SFA, MUFA, and PUFA (Table 8) had generally similar trends as the aforementioned substitution for total carbohydrates.

Table 8: ORs (95% CI) for the associations between specific types of fat Intake and SCD in the NHS and HPFS (Each fatty acid as percentage of total fat, all models adjusted for total fat)

	Q1	Q2	Q3	Q4	Q5	P trend
Trans fat						
NHS						
Median intake (% of energy)	0.03	0.04	0.04	0.05	0.05	
Age-adjusted model	Ref	1.18 (1.09, 1.28)	1.29 (1.19, 1.40)	1.37 (1.26, 1.48)	1.43 (1.31, 1.55)	<.0001
Age & Calorie-adjusted model	Ref	1.18 (1.08, 1.28)	1.28 (1.18, 1.39)	1.35 (1.25, 1.47)	1.40 (1.29, 1.52)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (1.03, 1.22)	1.19 (1.09, 1.29)	1.22 (1.12, 1.32)	1.25 (1.15, 1.36)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.04 (0.96, 1.13)	1.06 (0.97, 1.16)	1.05 (0.96, 1.14)	1.02 (0.93, 1.12)	0.8441
HPFS						
Median intake (% of energy)	0.03	0.04	0.04	0.05	0.06	
Age-adjusted model	Ref	1.17 (1.03, 1.34)	1.19 (1.04, 1.36)	1.27 (1.11, 1.45)	1.37 (1.20, 1.56)	<.0001
Age & Calorie-adjusted model	Ref	1.16 (1.01, 1.32)	1.17 (1.02, 1.34)	1.24 (1.09, 1.42)	1.33 (1.16, 1.52)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.10 (0.96, 1.26)	1.06 (0.93, 1.22)	1.11 (0.96, 1.27)	1.20 (1.05, 1.38)	0.0132
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.89, 1.17)	0.95 (0.83, 1.09)	0.95 (0.82, 1.09)	0.99 (0.86, 1.15)	0.7171
Meta-analyzed results(MV2)	Ref	1.03 (0.97, 1.12)	1.03 (0.94, 1.12)	1.03 (0.94, 1.09)	1.00 (0.94, 1.09)	0.9232
Saturated fat						
NHS						
Median intake (% of total fat)	0.29	0.32	0.33	0.35	0.37	
Age-adjusted model	Ref	1.02 (0.94, 1.10)	1.09 (1.01, 1.18)	1.05 (0.96, 1.13)	0.99 (0.91, 1.07)	0.9721
Age & Calorie-adjusted model	Ref	1.01 (0.93, 1.10)	1.08 (1.00, 1.18)	1.04 (0.96, 1.13)	0.99 (0.91, 1.08)	0.9431
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.90, 1.05)	1.02 (0.94, 1.10)	0.97 (0.89, 1.05)	0.90 (0.83, 0.98)	0.0179

Table 8 (Continued)						
Above+Dietary factors adjusted (MV2)	Ref	0.91 (0.84, 0.99)	0.92 (0.85, 1.00)	0.86 (0.79, 0.94)	0.77 (0.71, 0.84)	<.0001
HPFS						
Median intake (% of total fat)	0.28	0.31	0.33	0.34	0.37	
Age-adjusted model	Ref	1.01 (0.88, 1.15)	1.23 (1.08, 1.41)	1.13 (0.99, 1.29)	1.12 (0.97, 1.28)	0.0448
Age & Calorie-adjusted model	Ref	1.01 (0.89, 1.16)	1.23 (1.08, 1.41)	1.12 (0.98, 1.28)	1.10 (0.96, 1.26)	0.0888
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.84, 1.10)	1.14 (0.99, 1.30)	1.02 (0.89, 1.17)	0.98 (0.86, 1.13)	0.9647
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.78, 1.03)	1.03 (0.90, 1.18)	0.90 (0.79, 1.04)	0.85 (0.73, 0.98)	0.0354
Meta-analyzed results(MV2)	Ref	0.91 (0.86, 0.97)	0.94 (0.88, 1.03)	0.88 (0.80, 0.94)	0.80 (0.73, 0.86)	<.0001
Total MUFA						
NHS						
Median intake (% of total fat)	0.35	0.37	0.38	0.39	0.41	
Age-adjusted model	Ref	1.07 (0.99, 1.16)	1.08 (0.99, 1.17)	1.20 (1.11, 1.30)	1.01 (0.93, 1.09)	0.4128
Age & Calorie-adjusted model	Ref	1.05 (0.96, 1.13)	1.04 (0.96, 1.13)	1.15 (1.06, 1.25)	0.97 (0.89, 1.05)	0.8842
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.95, 1.12)	1.05 (0.97, 1.14)	1.15 (1.06, 1.24)	1.04 (0.95, 1.13)	0.1203
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.95, 1.11)	1.05 (0.97, 1.14)	1.17 (1.08, 1.27)	1.14 (1.04, 1.24)	0.0002
HPFS						
Median intake (% of total fat)	0.37	0.38	0.39	0.40	0.42	
Age-adjusted model	Ref	1.06 (0.92, 1.21)	1.16 (1.01, 1.32)	1.11 (0.97, 1.27)	1.07 (0.94, 1.22)	0.2901
Age & Calorie-adjusted model	Ref	1.02 (0.90, 1.17)	1.10 (0.96, 1.26)	1.05 (0.91, 1.20)	1.02 (0.89, 1.16)	0.7972
Above+Nondietary factors adjusted (MV1)	Ref	1.01 (0.88, 1.16)	1.07 (0.93, 1.22)	1.03 (0.90, 1.18)	1.04 (0.90, 1.19)	0.5719
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.87, 1.14)	1.06 (0.93, 1.22)	1.04 (0.91, 1.19)	1.10 (0.95, 1.26)	0.1593
Meta-analyzed results(MV2)	Ref	1.03 (0.94, 1.09)	1.06 (0.97, 1.12)	1.12 (1.06, 1.23)	1.12 (1.03, 1.23)	<.0001
PUFA						
NHS						
Median intake (% of total fat)	0.16	0.18	0.19	0.21	0.23	
Age-adjusted model	Ref	1.14 (1.05, 1.24)	1.11 (1.03, 1.21)	1.11 (1.02, 1.21)	1.07 (0.99, 1.16)	0.2828
Age & Calorie-adjusted model	Ref	1.12 (1.03, 1.22)	1.09 (1.01, 1.19)	1.09 (1.00, 1.18)	1.06 (0.98, 1.16)	0.3585
Above+Nondietary factors adjusted (MV1)	Ref	1.13 (1.04, 1.23)	1.11 (1.02, 1.20)	1.14 (1.05, 1.24)	1.11 (1.02, 1.21)	0.0254
Above+Dietary factors adjusted (MV2)	Ref	1.16 (1.07, 1.26)	1.15 (1.05, 1.24)	1.20 (1.10, 1.30)	1.21 (1.11, 1.32)	<.0001
HPFS						
Median intake (% of total fat)	0.16	0.18	0.19	0.21	0.24	
Age-adjusted model	Ref	1.17 (1.03, 1.34)	1.10 (0.96, 1.26)	1.18 (1.03, 1.34)	0.96 (0.83, 1.11)	0.5301
Age & Calorie-adjusted model	Ref	1.19 (1.04, 1.35)	1.10 (0.97, 1.26)	1.20 (1.05, 1.37)	0.98 (0.85, 1.13)	0.7761
Above+Nondietary factors adjusted (MV1)	Ref	1.23 (1.08, 1.41)	1.16 (1.02, 1.33)	1.27 (1.11, 1.45)	1.11 (0.96, 1.28)	0.1685
Above+Dietary factors adjusted (MV2)	Ref	1.26 (1.11, 1.44)	1.21 (1.06, 1.39)	1.35 (1.18, 1.55)	1.24 (1.07, 1.44)	0.0033
Meta-analyzed results(MV2)	Ref	1.19 (1.12, 1.26)	1.16 (1.09, 1.26)	1.23 (1.16, 1.33)	1.23 (1.12, 1.33)	<.0001
MUFA plant						
NHS						
Median intake (% of total fat)	0.15	0.18	0.20	0.22	0.27	
Age-adjusted model	Ref	1.15 (1.06, 1.25)	1.24 (1.15, 1.35)	1.28 (1.18, 1.39)	1.08 (0.99, 1.17)	0.0413
Age & Calorie-adjusted model	Ref	1.12 (1.03, 1.21)	1.19 (1.09, 1.29)	1.21 (1.12, 1.31)	1.02 (0.94, 1.11)	0.596
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (1.03, 1.21)	1.19 (1.09, 1.29)	1.23 (1.13, 1.34)	1.12 (1.03, 1.22)	0.0037
Above+Dietary factors adjusted (MV2)	Ref	1.13 (1.04, 1.22)	1.21 (1.12, 1.32)	1.28 (1.18, 1.39)	1.24 (1.14, 1.35)	<.0001
HPFS						
Median intake (% of total fat)	0.15	0.18	0.20	0.23	0.27	
Age-adjusted model	Ref	1.26 (1.10, 1.44)	1.15 (1.00, 1.31)	1.16 (1.02, 1.33)	1.16 (1.02, 1.33)	0.1329
Age & Calorie-adjusted model	Ref	1.23 (1.08, 1.40)	1.10 (0.97, 1.26)	1.11 (0.97, 1.26)	1.10 (0.96, 1.25)	0.5764
Above+Nondietary factors adjusted (MV1)	Ref	1.24 (1.09, 1.42)	1.14 (0.99, 1.30)	1.16 (1.01, 1.32)	1.22 (1.07, 1.40)	0.0272
Above+Dietary factors adjusted (MV2)	Ref	1.25 (1.09, 1.43)	1.16 (1.02, 1.33)	1.20 (1.05, 1.37)	1.33 (1.15, 1.52)	0.0007
Meta-analyzed results(MV2)	Ref	1.16 (1.09, 1.26)	1.19 (1.12, 1.30)	1.26 (1.16, 1.33)	1.26 (1.16, 1.37)	<.0001
MUFA animal						
NHS						
Median intake (% of total fat)	0.13	0.16	0.17	0.19	0.21	
Age-adjusted model	Ref	1.06 (0.98, 1.15)	1.04 (0.96, 1.13)	0.98 (0.91, 1.06)	0.90 (0.83, 0.97)	0.0028
Age & Calorie-adjusted model	Ref	1.06 (0.98, 1.15)	1.05 (0.97, 1.14)	1.01 (0.93, 1.09)	0.95 (0.87, 1.03)	0.1327
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.95, 1.12)	0.99 (0.92, 1.08)	0.95 (0.87, 1.03)	0.88 (0.81, 0.96)	0.001
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.08)	0.95 (0.88, 1.03)	0.91 (0.83, 0.98)	0.83 (0.76, 0.90)	<.0001
HPFS						
Median intake (% of total fat)	0.13	0.16	0.18	0.20	0.22	
Age-adjusted model	Ref	1.06 (0.93, 1.20)	0.96 (0.84, 1.09)	0.88 (0.77, 1.01)	0.96 (0.84, 1.10)	0.1208
Age & Calorie-adjusted model	Ref	1.06 (0.93, 1.21)	0.98 (0.86, 1.12)	0.91 (0.80, 1.04)	1.01 (0.88, 1.16)	0.486
Above+Nondietary factors adjusted (MV1)	Ref	1.02 (0.89, 1.16)	0.92 (0.81, 1.05)	0.85 (0.74, 0.97)	0.88 (0.76, 1.01)	0.0098

Table 8 (Continued)						
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.86, 1.12)	0.88 (0.77, 1.01)	0.81 (0.70, 0.93)	0.82 (0.72, 0.95)	0.0006
Meta-analyzed results(MV2)	Ref	1.00 (0.94, 1.06)	0.94 (0.86, 1.00)	0.88 (0.83, 0.94)	0.83 (0.78, 0.88)	<.0001

Age-adjusted model: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2: other than variables adjusted in MV1, further adjusted for carotenoids (quintiles), anthocyanins (quintiles), vitamin c, d, and e (quintiles)

All models adjusted for total fat intake.

For ω-3 PUFA intake, although inverse associations with SCD were observed when adjusting for age and total energy intake, the associations generally became null after further adjusting for carotenoids and anthocyanins (Table 9). The pooled multivariate ORs (95% CI) comparing extreme quintiles were 1.06 (0.97, 1.12) for alpha-linolenic acid (ALA), 1.06 (0.97, 1.16) for eicosapentaenoic acid (EPA), and 1.00 (0.94, 1.09) for docosahexaenoic acid (DHA). For ω-6 PUFA intake, adjusting for carotenoids and anthocyanins generally increased the associations (i.e., brought the inverse associations to null and strengthened the magnitude of positive associations.) The pooled multivariate ORs (95% CI) comparing the highest versus the lowest quintiles were 1.23 (1.12, 1.30) for linoleic acid (LA) and 0.97 (0.88, 1.03) for arachidonic acid (AA).

Table 9: OR (95% CI) for the associations between specific PUFA intakes and SCD in the NHS& HPFS
(Each fatty acid as percentage of total fat, all models adjusted for total fat)

	Q1	Q2	Q3	Q4	Q5	P trend
Omega-3						
NHS						
Median intake (%of total fat)	0.02	0.02	0.02	0.03	0.03	
Age-adjusted model	Ref	0.94 (0.86, 1.01)	0.89 (0.82, 0.97)	0.89 (0.82, 0.97)	0.77 (0.71, 0.84)	<.0001
Age & Calorie-adjusted model	Ref	0.94 (0.86, 1.01)	0.90 (0.83, 0.97)	0.90 (0.83, 0.98)	0.80 (0.73, 0.88)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.04)	0.94 (0.87, 1.02)	0.96 (0.88, 1.04)	0.89 (0.82, 0.98)	0.0246
Above+Dietary factors adjusted (MV2)	Ref	1.05 (0.96, 1.14)	1.07 (0.98, 1.17)	1.13 (1.04, 1.24)	1.14 (1.04, 1.26)	0.0039
HPFS						
Median intake (%of total fat)	0.02	0.02	0.02	0.03	0.03	
Age-adjusted model	Ref	0.98 (0.86, 1.12)	1.03 (0.90, 1.18)	0.86 (0.75, 0.99)	0.79 (0.68, 0.92)	0.0004
Age & Calorie-adjusted model	Ref	1.01 (0.88, 1.15)	1.08 (0.94, 1.23)	0.92 (0.80, 1.06)	0.87 (0.75, 1.02)	0.0293
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.91, 1.18)	1.16 (1.01, 1.32)	1.02 (0.88, 1.17)	0.99 (0.84, 1.16)	0.6582
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.97, 1.27)	1.30 (1.14, 1.50)	1.21 (1.04, 1.41)	1.29 (1.08, 1.53)	0.007
Meta-analyzed results(MV2)	Ref	1.06 (1.00, 1.12)	1.12(1.06, 1.23)	1.16 (1.06, 1.26)	1.19(1.09, 1.30)	<.0001

Table 9 (Continued)						
Omega-6						
NHS						
Median intake (%of total fat)	0.14	0.16	0.17	0.18	0.20	
Age-adjusted model	Ref	1.12 (1.03, 1.22)	1.18 (1.09, 1.28)	1.16 (1.07, 1.26)	1.20 I1.11, 1.31)	<.0001
Age & Calorie-adjusted model	Ref	1.10 (1.02, 1.20)	1.15 (1.06, 1.25)	1.13 (1.04, 1.23)	1.19 (1.09, 1.29)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.10 (1.01, 1.20)	1.15 (1.06, 1.25)	1.15 (1.06, 1.25)	1.19 (1.10, 1.29)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.11 (1.02, 1.20)	1.18 (1.09, 1.28)	1.17 (1.08, 1.27)	1.23 (1.13, 1.34)	<.0001
HPFS						
Median intake (%of total fat)	0.14	0.16	0.17	0.18	0.21	
Age-adjusted model	Ref	1.02 (0.90, 1.17)	1.17 (1.02, 1.33)	1.17 (1.03, 1.34)	1.06 (0.93, 1.22)	0.1487
Age & Calorie-adjusted model	Ref	1.01 (0.89, 1.16)	1.15 (1.01, 1.31)	1.15 (1.01,1.31)	1.05 (0.92, 1.20)	0.2152
Above+Nondietary factors adjusted (MV1)	Ref	1.06 (0.93, 1.21)	1.18 (1.04, 1.35)	1.20 (1.05, 1.37)	1.15 (1.00, 1.32)	0.0151
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.94, 1.22)	1.21 (1.06, 1.38)	1.23 (1.08, 1.41)	1.20 (1.04, 1.38)	0.0026
Meta-analyzed results(MV2)	Ref	1.09 (1.03, 1.19)	1.19(1.12, 1.26)	1.19(1.09, 1.26)	1.23 (1.12, 1.33)	<.0001
Long-chain omega-3						
NHS						
Median intake (%of total fat)	0.002	0.003	0.004	0.006	0.009	
Age-adjusted model	Ref	0.97 (0.90,1.05)	0.89 (0.83, 0.97)	0.79 (0.73, 0.86)	0.76 (0.70, 0.83)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.89, 1.05)	0.89 (0.83, 0.97)	0.81 (0.74, 0.88)	0.80 (0.73, 0.87)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.90, 1.06)	0.91 (0.84, 0.99)	0.85 (0.78, 0.92)	0.87 (0.79, 0.95)	0.0002
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.95, 1.11)	0.99 (0.91, 1.07)	0.95 (0.87, 1.04)	1.02 (0.92, 1.12)	0.9466
HPFS						
Median intake (%of total fat)	0.002	0.003	0.005	0.007	0.012	
Age-adjusted model	Ref	0.96 (0.84, 1.09)	0.87 (0.77, 1.00)	0.85 (0.74, 0.98)	0.75 (0.65, 0.86)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.84, 1.09)	0.90 (0.79, 1.03)	0.90 (0.79, 1.03)	0.82 (0.71, 0.95)	0.0094
Above+Nondietary factors adjusted (MV1)	Ref	0.99 (0.87, 1.13)	0.96 (0.84, 1.10)	0.99 (0.86, 1.14)	0.95 (0.81, 1.10)	0.4951
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.90, 1.17)	1.05 (0.91, 1.20)	1.12 (0.97, 1.30)	1.14 (0.96, 1.34)	0.1044
Meta-analyzed results(MV2)	Ref	1.03 (0.97, 1.09)	1.00 (0.94, 1.06)	1.00 (0.91, 1.06)	1.06(0.97, 1.16)	0.4512
LA						
NHS						
Median intake (%of total fat)	0.14	0.15	0.17	0.18	0.20	
Age-adjusted model	Ref	1.17 (1.08, 1.27)	1.12 (1.03, 1.22)	1.18 (1.08, 1.28)	1.16 (1.07, 1.26)	0.0015
Age & Calorie-adjusted model	Ref	1.15 (1.06, 1.25)	1.09 (1.01, 1.19)	1.14 (1.05, 1.24)	1.14 (1.05, 1.23)	0.0083
Above+Nondietary factors adjusted (MV1)	Ref	1.14 (1.05, 1.24)	1.10 (1.01, 1.20)	1.17 (1.07, 1.27)	1.16 (1.07, 1.26)	0.0009
Above+Dietary factors adjusted (MV2)	Ref	1.16 (1.07, 1.26)	1.12 (1.03, 1.22)	1.20 (1.10, 1.30)	1.21 (1.11, 1.32)	<.0001
HPFS						
Median intake (%of total fat)	0.13	0.15	0.16	0.18	0.20	
Age-adjusted model	Ref	1.17 (1.02, 1.33)	1.11 (0.97, 1.27)	1.18 (1.03, 1.35)	1.07 (0.94, 1.23)	0.3668
Age & Calorie-adjusted model	Ref	1.17 (1.02, 1.33)	1.10 (0.96, 1.25)	1.18 (1.03, 1.34)	1.07 (0.94, 1.23)	0.3753
Above+Nondietary factors adjusted (MV1)	Ref	1.18 (1.04, 1.35)	1.13 (0.99, 1.29)	1.24 (1.09, 1.42)	1.17 (1.02, 1.34)	0.0264
Above+Dietary factors adjusted (MV2)	Ref	1.21 (1.06, 1.38)	1.17 (1.02, 1.33)	1.29 (1.13, 1.48)	1.25 (1.09, 1.44)	0.0014
Meta-analyzed results(MV2)	Ref	1.16 (1.09, 1.26)	1.12(1.06, 1.23)	1.23 (1.12, 1.33)	1.23 (1.12, 1.30)	<.0001
AA						
NHS						
Median intake (%of total fat)	0.002	0.002	0.002	0.003	0.003	
Age-adjusted model	Ref	0.96 (0.89, 1.04)	0.92 (0.85, 1.00)	0.87 (0.80, 0.95)	0.74 (0.68, 0.81)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.90, 1.05)	0.95 (0.88, 1.03)	0.92 (0.85, 1.00)	0.82 (0.75, 0.89)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.04)	0.94 (0.86, 1.02)	0.91 (0.84, 0.99)	0.84 (0.77, 0.92)	0.0002
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.08)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)	0.96 (0.87, 1.05)	0.4466
HPFS						
Median intake (%of total fat)	0.002	0.002	0.002	0.003	0.004	
Age-adjusted model	Ref	0.93 (0.82, 1.06)	0.86 (0.75, 0.98)	0.82 (0.72, 0.93)	0.70 (0.61, 0.81)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.84, 1.08)	0.90 (0.79, 1.03)	0.89 (0.77, 1.01)	0.81 (0.70, 0.93)	0.0031
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.82, 1.06)	0.91 (0.80, 1.04)	0.92 (0.80, 1.05)	0.87 (0.75, 1.01)	0.0819
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.84, 1.08)	0.95 (0.83, 1.08)	0.98 (0.86, 1.13)	0.95 (0.82, 1.11)	0.6899
Meta-analyzed results(MV2)	Ref	0.97 (0.91, 1.06)	0.97 (0.91, 1.03)	1.00 (0.94, 1.09)	0.97 (0.88, 1.03)	0.3802
ALA						
NHS						
Median intake (%of total fat)	0.01	0.02	0.02	0.02	0.02	
Age-adjusted model	Ref	0.96 (0.88, 1.04)	0.91 (0.84, 0.99)	0.86 (0.79, 0.93)	0.76 (0.70, 0.83)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.87, 1.03)	0.90 (0.83, 0.98)	0.85 (0.78, 0.92)	0.77 (0.71, 0.84)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.89, 1.05)	0.96 (0.88, 1.04)	0.92 (0.84, 1.00)	0.87 (0.79, 0.94)	0.0005

Table 9 (Continued)						
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.95, 1.12)	1.07 (0.99, 1.17)	1.06 (0.98, 1.16)	1.07 (0.98, 1.18)	0.122
HPFS						
Median intake (%of total fat)	0.01	0.02	0.02	0.02	0.02	
Age-adjusted model	Ref	0.89 (0.78, 1.02)	0.93 (0.82, 1.06)	0.83 (0.72, 0.95)	0.71 (0.62, 0.82)	<.0001
Age & Calorie-adjusted model	Ref	0.90 (0.79, 1.02)	0.95 (0.84, 1.09)	0.85 (0.74, 0.97)	0.75 (0.65, 0.86)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.91 (0.80, 1.04)	0.96 (0.84, 1.10)	0.87 (0.76, 1.00)	0.81 (0.70, 0.93)	0.0041
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.85, 1.11)	1.06 (0.93, 1.22)	1.01 (0.88, 1.16)	1.00 (0.86, 1.17)	0.8538
Meta-analyzed results(MV2)	Ref	1.00 (0.94, 1.09)	1.06 (1.00, 1.16)	1.06 (0.97, 1.12)	1.06 (0.97, 1.12)	0.1547
EPA						
NHS						
Median intake (%of total fat)	0.000	0.001	0.001	0.002	0.003	
Age-adjusted model	Ref	0.95 (0.88, 1.03)	0.91 (0.84, 0.99)	0.81 (0.75, 0.88)	0.79 (0.73, 0.86)	<.0001
Age & Calorie-adjusted model	Ref	0.94 (0.87, 1.02)	0.89 (0.82, 0.97)	0.81 (0.75, 0.88)	0.82 (0.75, 0.89)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.89, 1.04)	0.92 (0.84, 0.99)	0.85 (0.78, 0.93)	0.89 (0.81, 0.97)	0.0029
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.93, 1.09)	0.99 (0.91, 1.07)	0.95 (0.87, 1.03)	1.02 (0.93, 1.12)	0.8647
HPFS						
Median intake (%of total fat)	0.000	0.001	0.001	0.002	0.004	
Age-adjusted model	Ref	0.95 (0.83, 1.08)	0.86 (0.76, 0.99)	0.86 (0.75, 0.98)	0.80 (0.69, 0.92)	0.0018
Age & Calorie-adjusted model	Ref	0.93 (0.82, 1.06)	0.87 (0.76, 0.99)	0.89 (0.77, 1.02)	0.86 (0.74, 0.99)	0.064
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.85, 1.10)	0.94 (0.82, 1.08)	0.97 (0.84, 1.11)	0.97 (0.84, 1.12)	0.7968
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.89, 1.15)	1.02 (0.89, 1.17)	1.10 (0.95, 1.27)	1.17 (0.99, 1.37)	0.0323
Meta-analyzed results(MV2)	Ref	1.00 (0.94, 1.09)	1.00 (0.94, 1.06)	0.97 (0.91, 1.06)	1.06 (0.97, 1.16)	0.1716
DHA						
NHS						
Median intake (%of total fat)	0.001	0.002	0.002	0.003	0.005	
Age-adjusted model	Ref	0.98 (0.91, 1.06)	0.88 (0.81, 0.95)	0.81 (0.74, 0.88)	0.73 (0.66, 0.79)	<.0001
Age & Calorie-adjusted model	Ref	0.98 (0.91, 1.06)	0.89 (0.82, 0.96)	0.83 (0.76, 0.90)	0.76 (0.70, 0.83)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.92, 1.08)	0.90 (0.83, 0.98)	0.87 (0.80, 0.94)	0.83 (0.76, 0.91)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.05 (0.97, 1.14)	0.97 (0.90, 1.06)	0.98 (0.90, 1.07)	0.98 (0.89, 1.08)	0.4064
HPFS						
Median intake (%of total fat)	0.001	0.002	0.003	0.004	0.007	
Age-adjusted model	Ref	0.98 (0.86, 1.11)	0.84 (0.73, 0.96)	0.85 (0.75, 0.98)	0.73 (0.63, 0.84)	<.0001
Age & Calorie-adjusted model	Ref	0.98 (0.86, 1.11)	0.87 (0.76, 1.00)	0.91 (0.80, 1.05)	0.81 (0.70, 0.94)	0.0037
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.88, 1.14)	0.93 (0.82, 1.07)	1.00 (0.87, 1.15)	0.93 (0.80, 1.09)	0.4086
Above+Dietary factors adjusted (MV2)	Ref	1.04 (0.91, 1.18)	1.01 (0.88, 1.16)	1.13 (0.97, 1.30)	1.11 (0.94, 1.31)	0.171
Meta-analyzed results(MV2)	Ref	1.06 (0.97, 1.12)	0.97 (0.91, 1.06)	1.03 (0.94, 1.09)	1.00 (0.94, 1.09)	0.8556

Age-adjusted model: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2: other than variables adjusted in MV1, further adjusted for carotenoids (quintiles), anthocyanins (quintiles), vitamin c, d, and e (quintiles)
Abbreviations: LA: Linoleic acid, AA: Arachidonic acid; ALA: α-Linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid;

All models adjusted for total fat intake.

Fat-Containing Food Analysis

The associations between fat-containing foods and SCD are shown in Table 10. Inverse associations with SCD were observed for olive oil, salad dressing, and oil and vinegar dressing after adjusting for age, total energy, and major non-dietary factors; however, the associations became null after further adjusting for total vegetables, fruit, fruit juice, and sugar-sweetened beverage intakes. Peanut butter was significantly associated with lower odds of SCD in the fully adjusted model. The pooled multivariate OR (95% CI) for each three servings/week increase in intake was 0.97 (0.94, 0.99) for peanut butter.

Table 10. ORs (95% CI) for the association between Fat-Containing Foods and SCD in the NHS & HPFS

	Q1	Q2	Q3	Q4	Q5	P Trend	Continuous[a]
Olive oil							(3 servings /wk)
NHS							
Median intake (% of energy)	0	0.03	0.11	0.25	0.57		
Age-adjusted model	Ref	1.08 (1.00, 1.17)	1.14 (1.05, 1.24)	1.14 (1.05, 1.24)	1.00 (0.93, 1.10)	0.2737	1.00 (0.96, 1.03)
Age & Calorie-adjusted model	Ref	1.06 (0.98, 1.15)	1.10 (1.01, 1.19)	1.06 (0.98, 1.15)	0.89 (0.82, 0.97)	<.0001	0.94 (0.90, 0.97)
Above+Nondietary factors adjusted (MV1)	Ref	1.10 (1.01, 1.19)	1.16 (1.06, 1.26)	1.14 (1.05, 1.25)	1.03 (0.94, 1.12)	0.3424	0.99 (0.95, 1.03)
Above+Dietary factors adjusted (MV2)	Ref	1.15 (1.06, 1.24)	1.27 (1.17, 1.38)	1.31 (1.20, 1.44)	1.24 (1.13, 1.37)	0.0032	1.06 (1.02, 1.10)
HPFS							
Median intake (% of energy)	0	0.02	0.07	0.19	0.48		
Age-adjusted model	Ref	1.00 (0.87, 1.13)	0.94 (0.82, 1.07)	0.85 (0.75, 0.96)	0.81 (0.71, 0.92)	.0012	0.98 (0.92, 1.05)
Age & Calorie-adjusted model	Ref	0.99 (0.87, 1.13)	0.93 (0.81, 1.06)	0.82 (0.72, 0.93)	0.74 (0.65, 0.85)	<.0001	0.93 (0.87, 1.00)
Above+Nondietary factors adjusted (MV1)	Ref	1.05 (0.92, 1.19)	0.96 (0.84, 1.10)	0.86 (0.76, 0.98)	0.83 (0.73, 0.95)	.0017	0.97 (0.91, 1.04)
Above+Dietary factors adjusted (MV2)	Ref	1.08 (0.95, 1.24)	1.04 (0.91, 1.19)	0.98 (0.86, 1.12)	1.03 (0.89, 1.18)	0.9541	1.07 (1.00, 1.15)
Meta-analyzed results(MV2)	Ref	1.13 (1.06, 1.20)	1.20 (1.13, 1.27)	1.20 (1.13, 1.31)	1.16 (1.09, 1.27)	0.0087	1.06 (1.02, 1.10)
Salad dressing							
NHS							
Median intake (% of energy)	0.07	0.22	0.34	0.50	0.75		
Age-adjusted model	Ref	0.99 (0.91, 1.07)	0.95 (0.88, 1.03)	0.92 (0.85, 1.00)	0.92 (0.85, 0.99)	0.0113	0.95 (0.92, 0.99)
Age & Calorie-adjusted model	Ref	0.95 (0.88, 1.03)	0.88 (0.81, 0.96)	0.82 (0.76, 0.89)	0.78 (0.72, 0.85)	<.0001	0.88 (0.85, 0.92)
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.90, 1.05)	0.94 (0.87, 1.02)	0.90 (0.83, 0.97)	0.90 (0.83, 0.98)	0.005	0.94 (0.90, 0.98)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.08)	0.98 (0.90, 1.07)	0.96 (0.89, 1.05)	1.02 (0.94, 1.12)	0.7646	1.00 (0.96, 1.04)
HPFS							
Median intake (% of energy)	0.05	0.19	0.33	0.48	0.81		
Age-adjusted model	Ref	1.13 (0.99, 1.29)	1.17 (1.02, 1.34)	1.04 (0.91, 1.18)	1.07 (0.94, 1.22)	0.8901	1.01 (0.96, 1.06)
Age & Calorie-adjusted model	Ref	1.10 (0.96, 1.26)	1.10 (0.96, 1.26)	0.95 (0.83, 1.08)	0.93 (0.81, 1.07)	0.0332	0.95 (0.90, 1.00)
Above+Nondietary factors adjusted (MV1)	Ref	1.08 (0.95, 1.24)	1.08 (0.94, 1.24)	0.96 (0.85, 1.10)	0.98 (0.85, 1.12)	0.2605	0.97 (0.93, 1.03)
Above+Dietary factors adjusted (MV2)	Ref	1.08 (0.95, 1.24)	1.12 (0.98, 1.29)	1.01 (0.89, 1.16)	1.12 (0.97, 1.29)	0.3591	1.03 (0.98, 1.09)
Meta-analyzed results(MV2)	Ref	1.03 (0.94, 1.09)	1.03 (0.94, 1.09)	0.97 (0.91, 1.06)	1.06 (0.97, 1.13)	0.4373	1.01 (0.98, 1.04)
Oil & vinegar dressing							
NHS							
Median intake (% of energy)	0.07	0.17	0.33	0.549	1.12		
Age-adjusted model	Ref	1.00 (0.92, 1.08)	0.91 (0.84, 0.99)	0.95 (0.88, 1.03)	0.90 (0.83, 0.97)	0.0051	0.97 (0.95, 0.99)
Age & Calorie-adjusted model	Ref	0.98 (0.91, 1.06)	0.87 (0.80, 0.94)	0.88 (0.81, 0.95)	0.80 (0.74, 0.87)	<.0001	0.94 (0.92, 0.96)
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.92, 1.08)	0.90 (0.83, 0.97)	0.94 (0.87, 1.02)	0.90 (0.83, 0.98)	0.0072	0.97 (0.95, 1.00)
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.95, 1.12)	0.95 (0.88, 1.04)	1.03 (0.95, 1.12)	1.05 (0.96, 1.14)	0.2854	1.01 (0.99, 1.04)
HPFS							

Table 10 (Continued)							
Median intake (% of energy)	0	0.07	0.11	0.29	0.53		
Age-adjusted model	Ref	0.94 (0.82, 1.08)	0.89 (0.78, 1.02)	0.92 (0.81, 1.06)	0.76 (0.67, 0.87)	0.0001	0.89 (0.84, 0.95)
Age & Calorie-adjusted model	Ref	0.96 (0.84, 1.09)	0.88 (0.77, 1.01)	0.91 (0.79, 1.04)	0.72 (0.63, 0.82)	<.0001	0.86 (0.81, 0.91)
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.85, 1.11)	0.92 (0.81, 1.06)	0.94 (0.82, 1.08)	0.78 (0.69, 0.89)	0.0002	0.89 (0.84, 0.95)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.87, 1.14)	0.98 (0.86, 1.13)	1.05 (0.91, 1.21)	0.93 (0.81, 1.07)	0.4566	0.97 (0.91, 1.04)
Meta-analyzed results(MV2)	Ref	1.03 (0.94, 1.09)	0.97 (0.89, 1.03)	1.03 (0.97, 1.09)	1.03 (0.97, 1.09)	0.4440	1.01 (0.99, 1.03)
Peanut							
NHS							
Median intake (% of energy)	0.02	0.04	0.08	0.14	0.29		
Age-adjusted model	Ref	1.18 (1.09, 1.28)	1.21 (1.12, 1.31)	1.22 (1.13, 1.32)	1.38 (1.27, 1.49)	<.0001	1.21 (1.14, 1.29)
Age & Calorie-adjusted model	Ref	1.14 (1.05, 1.24)	1.14 (1.05, 1.23)	1.10 (1.02, 1.20)	1.17 (1.08, 1.27)	0.0133	1.07 (1.00, 1.14)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (1.03, 1.21)	1.13 (1.04, 1.23)	1.12 (1.03, 1.21)	1.21 (1.11, 1.31)	0.0003	1.12 (1.05, 1.19)
Above+Dietary factors adjusted (MV2)	Ref	1.12 (1.03, 1.22)	1.14 (1.05, 1.23)	1.13 (1.04, 1.23)	1.21 (1.11, 1.32)	0.0003	1.11 (1.04, 1.18)
HPFS							
Median intake (% of energy)	0	0.04	0.07	0.14	0.34		
Age-adjusted model	Ref	1.23 (1.07, 1.41)	1.43 (1.24, 1.65)	1.51 (1.32, 1.73)	1.45 (1.27, 1.67)	<.0001	1.13 (1.05, 1.21)
Age & Calorie-adjusted model	Ref	1.17 (1.02, 1.34)	1.30 (1.13, 1.50)	1.32 (1.15, 1.52)	1.17 (1.01, 1.35)	0.1676	1.00 (0.93, 1.08)
Above+Nondietary factors adjusted (MV1)	Ref	1.16 (1.01, 1.33)	1.30 (1.13, 1.50)	1.29 (1.12, 1.48)	1.19 (1.03, 1.37)	0.0958	1.02 (0.95, 1.11)
Above+Dietary factors adjusted (MV2)	Ref	1.14 (0.99, 1.31)	1.27 (1.10, 1.47)	1.26 (1.10, 1.46)	1.16 (1.00, 1.34)	0.177	1.00 (0.93, 1.08)
Meta-analyzed results(MV2)	Ref	1.13 (1.06, 1.20)	1.16 (1.09, 1.27)	1.16 (1.09, 1.23)	1.20 (1.13, 1.27)	0.0003	1.06 (1.01, 1.11)
Peanut butter							
NHS							
Median intake (% of energy)	0.03	0.10	0.18	0.31	0.61		
Age-adjusted model	Ref	0.96 (0.88, 1.04)	1.05 (0.97, 1.14)	1.05 (0.96, 1.13)	1.11 (1.03, 1.21)	0.001	1.08 (1.04, 1.12)
Age & Calorie-adjusted model	Ref	0.93 (0.86, 1.01)	0.99 (0.91, 1.07)	0.94 (0.86, 1.02)	0.94 (0.87, 1.02)	0.2442	1.00 (0.97, 1.04)
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.87, 1.02)	0.98 (0.90, 1.07)	0.91 (0.84, 0.99)	0.93 (0.86, 1.02)	0.1016	0.99 (0.96, 1.03)
Above+Dietary factors adjusted (MV2)	Ref	0.93 (0.86, 1.01)	0.97 (0.89, 1.05)	0.89 (0.82, 0.97)	0.88 (0.81, 0.96)	0.0032	0.96 (0.93, 0.99)
HPFS							
Median intake (% of energy)	0	0.04	0.11	0.24	0.54		
Age-adjusted model	Ref	1.17 (1.02, 1.34)	1.21 (1.06, 1.38)	1.32 (1.15, 1.50)	1.20 (1.05, 1.37)	0.0577	1.11 (1.05, 1.17)
Age & Calorie-adjusted model	Ref	1.15 (1.00, 1.32)	1.14 (1.00, 1.31)	1.19 (1.04, 1.36)	0.99 (0.87, 1.14)	0.1433	1.02 (0.97, 1.08)
Above+Nondietary factors adjusted (MV1)	Ref	1.13 (0.98, 1.30)	1.11 (0.97, 1.27)	1.13 (0.99, 1.29)	0.95 (0.83, 1.09)	0.06	1.01 (0.96, 1.07)
Above+Dietary factors adjusted (MV2)	Ref	1.10 (0.96, 1.27)	1.08 (0.94, 1.24)	1.09 (0.96, 1.25)	0.90 (0.78, 1.03)	0.007	0.98 (0.93, 1.04)
Meta-analyzed results(MV2)	Ref	0.97 (0.91, 1.03)	1.00 (0.94, 1.06)	0.94 (0.89, 1.00)	0.89 (0.84, 0.94)	<.0001	0.97 (0.94, 0.99)
Other nuts							
NHS							
Median intake (% of energy)	0.01	0.02	0.04	0.09	0.21		
Age-adjusted model	Ref	1.08 (1.00, 1.18)	1.33 (1.23, 1.44)	1.28 (1.18, 1.39)	1.32 (1.21, 1.43)	<.0001	1.23 (1.14, 1.33)
Age & Calorie-adjusted model	Ref	1.06 (0.97, 1.15)	1.25 (1.15, 1.35)	1.16 (1.07, 1.26)	1.13 (1.04, 1.23)	0.1119	1.07 (0.98, 1.16)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.96, 1.13)	1.23 (1.14, 1.34)	1.18 (1.08, 1.28)	1.19 (1.09, 1.29)	0.002	1.14 (1.05, 1.23)
Above+Dietary factors adjusted (MV2)	Ref	1.06 (0.97, 1.15)	1.25 (1.16, 1.36)	1.21 (1.12, 1.32)	1.24 (1.13, 1.35)	<.0001	1.16 (1.07, 1.26)
HPFS							
Median intake (% of energy)	0	0.02	0.05	0.09	0.24		
Age-adjusted model	Ref	1.50 (1.30, 1.73)	1.48 (1.27, 1.72)	1.89 (1.64, 2.19)	1.78 (1.54, 2.06)	<.0001	1.26 (1.14, 1.39)

Table 10 (Continued)							
Age & Calorie-adjusted model	Ref	1.44 (1.25, 1.66)	1.35 (1.16, 1.56)	1.66 (1.43, 1.92)	1.48 (1.27, 1.72)	0.0004	1.11 (0.99, 1.23)
Above+Nondietary factors adjusted (MV1)	Ref	1.38 (1.20, 1.59)	1.35 (1.16, 1.57)	1.62 (1.39, 1.88)	1.50 (1.29, 1.75)	<.0001	1.15 (1.03, 1.28)
Above+Dietary factors adjusted (MV2)	Ref	1.40 (1.21, 1.61)	1.38 (1.19, 1.60)	1.67 (1.44, 1.94)	1.58 (1.36, 1.84)	<.0001	1.19 (1.07, 1.32)
Meta-analyzed results(MV2)	Ref	1.13 (1.06, 1.23)	1.27 (1.20, 1.39)	1.31 (1.23, 1.43)	1.31 (1.23, 1.43)	<.0001	1.17 (1.09, 1.24)
Walnut							(1 serving/ wk)
NHS							
Median intake (% of energy)	0	0.07					
Age-adjusted model	Ref	1.08 (1.03, 1.14)				0.0018	0.98 (0.96, 1.01)
Age & Calorie-adjusted model	Ref	1.00 (0.94, 1.05)				0.9767	0.95 (0.93, 0.98)
Above+Nondietary factors adjusted (MV1)	Ref	1.07 (1.02, 1.13)				0.01	0.98 (0.96, 1.00)
Above+Dietary factors adjusted (MV2)	Ref	1.12 (1.06, 1.18)				<.0001	1.00 (0.97, 1.02)
HPFS							
Median intake (% of energy)	0	0.07					
Age-adjusted model	Ref	1.01 (0.92, 1.10)				0.837	0.98 (0.94, 1.03)
Age & Calorie-adjusted model	Ref	0.92 (0.84, 1.00)				0.0246	0.95 (0.91, 0.99)
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.05)				0.3522	0.97 (0.93, 1.02)
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.94, 1.13)				0.6497	1.00 (0.95, 1.04)
Meta-analyzed results(MV2)	Ref	1.09 (1.06, 1.16)				0.0001	1.00 (0.98, 1.02)
Avocado							(1 serving/ wk)
NHS							
Median intake (% of energy)	0	0.02	0.05				
Age-adjusted model	Ref	1.03 (0.95, 1.12)	1.13 (1.03, 1.23)			0.0005	1.04 (0.98, 1.10)
Age & Calorie-adjusted model	Ref	1.02 (0.94, 1.11)	1.09 (0.99, 1.19)			0.0135	1.00 (0.94, 1.06)
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.90, 1.10)	1.07 (0.97, 1.18)			0.0281	1.01 (0.95, 1.07)
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.88, 1.08)	1.11 (1.01, 1.22)			0.0002	1.06 (1.00, 1.13)
HPFS							
Median intake (% of energy)	0	0.02	0.07				
Age-adjusted model	Ref	1.09 (0.95, 1.24)	1.16 (1.06, 1.28)			0.0023	1.05 (0.97, 1.14)
Age & Calorie-adjusted model	Ref	1.07 (0.94, 1.22)	1.11 (1.01, 1.22)			0.0473	1.00 (0.92, 1.09)
Above+Nondietary factors adjusted (MV1)	Ref	1.06 (0.92, 1.21)	1.14 (1.04, 1.26)			0.0095	1.05 (0.97, 1.14)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.97, 1.27)	1.23 (1.12, 1.36)			<.0001	1.11 (1.02, 1.20)
Meta-analyzed results(MV2)	Ref	1.03 (0.94, 1.09)	1.16 (1.09, 1.23)			<.0001	1.08 (1.02, 1.13)
French Fried Potatoes							(3 servings/ wk)
NHS							
Median intake (% of energy)	0.02	0.04	0.06	0.09	0.18		
Age-adjusted model	Ref	1.10 (1.02, 1.19)	1.20 (1.11, 1.30)	1.31 (1.21, 1.42)	1.50 (1.38, 1.64)	<.0001	2.34 (2.00, 2.74)
Age & Calorie-adjusted model	Ref	1.08 (1.00, 1.17)	1.14 (1.05, 1.24)	1.22 (1.12, 1.32)	1.32 (1.21, 1.45)	<.0001	1.81 (1.54, 2.13)
Above+Nondietary factors adjusted (MV1)	Ref	1.01 (0.94, 1.10)	1.03 (0.95, 1.12)	1.08 (0.99, 1.17)	1.14 (1.04, 1.24)	0.0025	1.40 (1.18, 1.65)
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.90, 1.05)	0.95 (0.88, 1.04)	0.97 (0.89, 1.05)	0.96 (0.88, 1.06)	0.5719	1.02 (0.86, 1.22)
HPFS							
Median intake (% of energy)	0	0.03	0.07	0.10	0.22		
Age-adjusted model	Ref	1.04 (0.91, 1.19)	1.07 (0.94, 1.22)	1.31 (1.15, 1.50)	1.81 (1.58, 2.08)	<.0001	2.56 (2.12, 3.07)
Age & Calorie-adjusted model	Ref	1.01 (0.89, 1.15)	1.01 (0.88, 1.15)	1.19 (1.04, 1.36)	1.51 (1.31, 1.74)	<.0001	1.94 (1.59, 2.35)

Table 10 (Continued)							
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.82, 1.07)	0.92 (0.80, 1.05)	1.06 (0.92, 1.21)	1.27 (1.10, 1.47)	<.0001	1.58 (1.29, 1.92)
Above+Dietary factors adjusted (MV2)	Ref	0.88 (0.77, 1.01)	0.81 (0.71, 0.93)	0.91 (0.79, 1.05)	1.04 (0.89, 1.21)	0.1903	1.23 (1.00, 1.52)
Meta-analyzed results(MV2)	Ref	0.94 (0.89, 1.00)	0.91 (0.86, 0.97)	0.94 (0.89, 1.03)	0.97 (0.91, 1.06)	0.6892	1.10 (0.96, 1.26)
Mayonnaise							
NHS							
Median intake (% of energy)	0.06	0.14	0.22	0.32	0.55		
Age-adjusted model	Ref	1.09 (1.00, 1.18)	1.17 (1.08, 1.27)	1.36 (1.25, 1.47)	1.55 (1.43, 1.67)	<.0001	1.30 (1.25, 1.36)
Age & Calorie-adjusted model	Ref	1.05 (0.97, 1.14)	1.09 (1.01, 1.19)	1.22 (1.12, 1.32)	1.32 (1.22, 1.44)	<.0001	1.18 (1.13 1.24)
Above+Nondietary factors adjusted (MV1)	Ref	1.01 (0.92, 1.09)	1.03 (0.95, 1.12)	1.13 (1.04, 1.23)	1.19 (1.09, 1.29)	<.0001	1.12 (1.06, 1.17)
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.91, 1.07)	1.00 (0.92, 1.08)	1.08 (0.99, 1.17)	1.11 (1.02, 1.21)	0.0008	1.07 (1.02, 1.13)
HPFS							
Median intake (% of energy)	0.01	0.06	0.11	0.20	0.40		
Age-adjusted model	Ref	1.35 (1.18, 1.55)	1.40 (1.22, 1.61)	1.68 (1.47, 1.92)	1.92 (1.68, 2.19)	<.0001	1.45 (1.33, 1.57)
Age & Calorie-adjusted model	Ref	1.32 (1.15, 1.51)	1.32 (1.15, 1.51)	1.51 (1.32, 1.73)	1.60 (1.39, 1.84)	<.0001	1.28 (1.17, 1.39)
Above+Nondietary factors adjusted (MV1)	Ref	1.25 (1.09, 1.43)	1.23 (1.08, 1.41)	1.35 (1.18, 1.55)	1.38 (1.20, 1.58)	0.0001	1.18 (1.08 1.29)
Above+Dietary factors adjusted (MV2)	Ref	1.19 (1.03, 1.36)	1.17 (1.02, 1.34)	1.27 (1.11, 1.46)	1.26 (1.09, 1.45)	0.0061	1.13 (1.03 1.23)
Meta-analyzed results(MV2)	Ref	1.03 (0.97, 1.13)	1.03 (0.97, 1.13)	1.13 (1.06, 1.20)	1.16 (1.06, 1.23)	<.0001	1.08 (1.04, 1.13)
Margarine							
NHS							
Median intake (% of energy)	0.07	0.38	0.73	1.18	1.99		
Age-adjusted model	Ref	1.07 (0.99, 1.17)	1.16 (1.07, 1.26)	1.32 (1.22, 1.43)	1.45 (1.34, 1.58)	<.0001	1.08 (1.07, 1.10)
Age & Calorie-adjusted model	Ref	1.08 (1.00, 1.18)	1.13 (1.04, 1.23)	1.25 (1.15, 1.35)	1.29 (1.19, 1.40)	<.0001	1.05 (1.04, 1.07)
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.95, 1.12)	1.05 (0.96, 1.14)	1.14 (1.05, 1.24)	1.13 (1.04, 1.23)	0.001	1.03 (1.01, 1.04)
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.95, 1.12)	1.04 (0.96, 1.14)	1.12 (1.03, 1.22)	1.07 (0.98, 1.16)	0.085	1.01 (1.00, 1.03)
HPFS							
Median intake (% of energy)	0	0.15	0.36	0.64	1.36		
Age-adjusted model	Ref	1.15 (1.01, 1.33)	1.19 (1.04, 1.37)	1.22 (1.07, 1.40)	1.48 (1.29, 1.69)	<.0001	1.06 (1.03, 1.09)
Age & Calorie-adjusted model	Ref	1.18 (1.03, 1.36)	1.19 (1.03, 1.36)	1.17 (1.02, 1.33)	1.27 (1.11, 1.46)	0.0188	1.01 (0.98, 1.04)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (0.98, 1.29)	1.10 (0.96, 1.27)	1.04 (0.91, 1.19)	1.11 (0.97, 1.27)	0.7038	0.98 (0.96, 1.01)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.97, 1.27)	1.07 (0.93, 1.23)	1.00 (0.87, 1.15)	1.02 (0.89, 1.17)	0.3499	0.96 (0.93, 0.99)
Meta-analyzed results(MV2)	Ref	1.06 (0.97, 1.13)	1.06 (0.97, 1.13)	1.09 (1.00, 1.16)	1.06 (0.97, 1.13)	0.2373	1.00 (0.99, 1.02)
Chocolate Bars							
NHS							
Median intake (% of energy)	0.02	0.05	0.08	0.14	0.32		
Age-adjusted model	Ref	1.10 (1.02, 1.20)	1.27 (1.16, 1.37)	1.34 (1.23, 1.45)	1.61 (1.49, 1.75)	<.0001	1.35 (1.28, 1.43)
Age & Calorie-adjusted model	Ref	1.07 (0.99, 1.16)	1.20 (1.10, 1.30)	1.23 (1.14, 1.34)	1.41 (1.30, 1.54)	<.0001	1.23 (1.16, 1.30)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.95, 1.12)	1.13 (1.04, 1.23)	1.13 (1.04, 1.23)	1.27 (1.16, 1.38)	<.0001	1.16 (1.09, 1.23)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.08)	1.05 (0.97, 1.15)	1.02 (0.94, 1.12)	1.08 (0.99, 1.18)	0.0495	1.04 (0.98, 1.10)
HPFS							
Median intake (% of energy)	0	0.03	0.07	0.11	0.29		
Age-adjusted model	Ref	1.41 (1.23, 1.61)	1.40 (1.22, 1.60)	1.76 (1.54, 2.01)	1.79 (1.56, 2.04)	<.0001	1.36 (1.24, 1.50)
Age & Calorie-adjusted model	Ref	1.35 (1.18, 1.55)	1.30 (1.14, 1.49)	1.58 (1.38, 1.81)	1.49 (1.30, 1.71)	<.0001	1.18 (1.07, 1.31)
Above+Nondietary factors adjusted (MV1)	Ref	1.29 (1.12, 1.47)	1.23 (1.07, 1.41)	1.47 (1.29, 1.69)	1.39 (1.21, 1.60)	<.0001	1.13 (1.02, 1.25)
Above+Dietary factors adjusted (MV2)	Ref	1.23 (1.07, 1.41)	1.13 (0.99, 1.30)	1.32 (1.15, 1.52)	1.21 (1.05, 1.39)	0.0385	1.02 (0.92, 1.14)

Table 10 (Continued)							
Meta-analyzed results(MV2)	Ref	1.06 (0.97, 1.13)	1.06 (1.00, 1.16)	1.09 (1.03, 1.20)	1.13 (1.03, 1.20)	0.0060	1.04 (0.98, 1.09)
Crackers							
NHS							
Median intake (% of energy)	0.05	0.12	0.21	0.34	0.72		
Age-adjusted model	Ref	1.02 (0.94, 1.11)	1.01 (0.94, 1.10)	1.04 (0.96, 1.13)	1.14 (1.05, 1.24)	0.0003	1.06 (1.03, 1.10)
Age & Calorie-adjusted model	Ref	0.97 (0.90, 1.06)	0.93 (0.86, 1.01)	0.91 (0.84, 0.99)	0.95 (0.88, 1.04)	0.3929	1.00 (0.97, 1.03)
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.86, 1.02)	0.90 (0.83, 0.98)	0.88 (0.81, 0.95)	0.92 (0.85, 1.00)	0.1711	0.99 (0.95, 1.02)
Above+Dietary factors adjusted (MV2)	Ref	0.93 (0.86, 1.01)	0.89 (0.82, 0.97)	0.85 (0.78, 0.93)	0.87 (0.80, 0.95)	0.0086	0.96 (0.93, 0.99)
HPFS							
Median intake (% of energy)	0.03	0.07	0.14	0.26	0.57		
Age-adjusted model	Ref	1.15 (1.00, 1.33)	1.18 (1.02, 1.35)	1.19 (1.04, 1.36)	1.39 (1.22, 1.59)	<.0001	1.12 (1.07, 1.16)
Age & Calorie-adjusted model	Ref	1.09 (0.95, 1.25)	1.06 (0.92, 1.22)	1.01 (0.88, 1.16)	1.10 (0.95, 1.26)	0.289	1.05 (1.00, 1.09)
Above+Nondietary factors adjusted (MV1)	Ref	1.07 (0.93, 1.23)	0.98 (0.86, 1.13)	0.95 (0.82, 1.09)	0.98 (0.85, 1.13)	0.54	1.02 (0.98, 1.06)
Above+Dietary factors adjusted (MV2)	Ref	1.05 (0.91, 1.21)	0.95 (0.82, 1.09)	0.91 (0.79, 1.05)	0.93 (0.80, 1.07)	0.1936	1.00 (0.96, 1.04)
Meta-analyzed results(MV2)	Ref	0.97 (0.89, 1.03)	0.91 (0.84, 0.97)	0.86 (0.81, 0.94)	0.89 (0.84, 0.94)	0.0034	0.98 (0.95, 1.00)
Potato Chips or Corn Chips							
NHS							
Median intake (% of energy)	0.02	0.05	0.10	0.18	0.35		
Age-adjusted model	Ref	1.19 (1.10, 1.28)	1.24 (1.14, 1.34)	1.30 (1.20, 1.41)	1.50 (1.38, 1.64)	<.0001	1.31 (1.22, 1.40)
Age & Calorie-adjusted model	Ref	1.15 (1.06, 1.25)	1.17 (1.08, 1.26)	1.19 (1.10, 1.29)	1.30 (1.19, 1.42)	<.0001	1.15 (1.07, 1.24)
Above+Nondietary factors adjusted (MV1)	Ref	1.11 (1.02, 1.20)	1.08 (1.00, 1.17)	1.08 (0.99, 1.17)	1.15 (1.06, 1.26)	0.0109	1.05 (0.97, 1.12)
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.99, 1.16)	1.02 (0.94, 1.11)	0.99 (0.91, 1.08)	1.00 (0.91, 1.09)	0.4163	0.92 (0.86, 0.99)
HPFS							
Median intake (% of energy)	0	0.04	0.08	0.15	0.33		
Age-adjusted model	Ref	1.20 (1.05, 1.37)	1.36 (1.18, 1.55)	1.59 (1.39, 1.82)	1.92 (1.67, 2.20)	<.0001	1.58 (1.42, 1.76)
Age & Calorie-adjusted model	Ref	1.15 (1.01, 1.31)	1.25 (1.09, 1.43)	1.41 (1.23, 1.62)	1.57 (1.36, 1.81)	<.0001	1.33 (1.18, 1.49)
Above+Nondietary factors adjusted (MV1)	Ref	1.09 (0.96, 1.25)	1.17 (1.02, 1.34)	1.28 (1.12, 1.48)	1.39 (1.20, 1.60)	<.0001	1.23 (1.09, 1.38)
Above+Dietary factors adjusted (MV2)	Ref	1.04 (0.91, 1.19)	1.07 (0.93, 1.23)	1.16 (1.00, 1.33)	1.19 (1.02, 1.38)	0.035	1.09 (0.96, 1.23)
Meta-analyzed results(MV2)	Ref	1.06 (1.00, 1.13)	1.03 (0.97, 1.13)	1.03 (0.97, 1.13)	1.03 (0.97, 1.13)	0.6552	0.96 (0.91, 1.03)
Butter							
NHS							
Median intake (% of energy)	0.02	0.05	0.17	0.44	1.19		
Age-adjusted model	Ref	1.10 (1.02, 1.19)	1.02 (0.94, 1.10)	1.08 (0.99, 1.17)	1.19 (1.10, 1.30)	<.0001	1.04 (1.02, 1.06)
Age & Calorie-adjusted model	Ref	1.08 (1.00, 1.17)	0.99 (0.91, 1.07)	1.02 (0.94, 1.11)	1.07 (0.98, 1.16)	0.2864	1.01 (0.99, 1.03)
Above+Nondietary factors adjusted (MV1)	Ref	1.06 (0.98, 1.15)	0.98 (0.90, 1.07)	1.02 (0.94, 1.11)	1.08 (0.99, 1.17)	0.1137	1.01 (0.99, 1.03)
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.98, 1.16)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)	1.03 (0.94, 1.12)	0.876	0.99 (0.97, 1.01)
HPFS							
Median intake (% of energy)	0	0.02	0.08	0.23	0.69		
Age-adjusted model	Ref	1.34 (1.17, 1.53)	1.16 (1.02, 1.33)	1.18 (1.04, 1.34)	1.21 (1.06, 1.37)	0.3707	1.03 (0.99, 1.07)
Age & Calorie-adjusted model	Ref	1.32 (1.15, 1.51)	1.13 (0.99, 1.28)	1.11 (0.97, 1.26)	1.03 (0.90, 1.17)	0.0551	0.98 (0.94, 1.02)
Above+Nondietary factors adjusted (MV1)	Ref	1.32 (1.15, 1.51)	1.13 (0.99, 1.29)	1.11 (0.97, 1.27)	1.00 (0.88, 1.15)	0.0184	0.96 (0.92, 1.00)
Above+Dietary factors adjusted (MV2)	Ref	1.29 (1.13, 1.48)	1.10 (0.97, 1.26)	1.09 (0.95, 1.24)	0.94 (0.82, 1.07)	0.0007	0.94 (0.90, 0.97)
Meta-analyzed results(MV2)	Ref	1.13 (1.06, 1.20)	1.03 (0.94, 1.09)	1.03 (0.97, 1.09)	1.00 (0.94, 1.06)	0.3090	0.98 (0.96, 1.00)
Cake							

Table 10 (Continued)							
NHS							
Median intake (% of energy)	0.02	0.03	0.05	0.07	0.13		
Age-adjusted model	Ref	1.22 (1.12, 1.32)	1.31 (1.21, 1.43)	1.43 (1.32, 1.55)	1.62 (1.49, 1.76)	<.0001	2.44 (2.06, 2.89)
Age & Calorie-adjusted model	Ref	1.18 (1.09, 1.28)	1.22 (1.13, 1.33)	1.28 (1.17, 1.39)	1.35 (1.24, 1.47)	<.0001	1.61 (1.34, 1.94)
Above+Nondietary factors adjusted (MV1)	Ref	1.16 (1.07, 1.26)	1.22 (1.12, 1.33)	1.24 (1.14, 1.35)	1.37 (1.25, 1.50)	<.0001	1.73 (1.43, 2.09)
Above+Dietary factors adjusted (MV2)	Ref	1.14 (1.05, 1.23)	1.16 (1.07, 1.27)	1.15 (1.06, 1.26)	1.21 (1.11, 1.33)	0.0028	1.29 (1.07, 1.57)
HPFS							
Median intake (% of energy)	0	0.02	0.03	0.05	0.10		
Age-adjusted model	Ref	1.07 (0.93, 1.22)	1.25 (1.09, 1.43)	1.53 (1.33, 1.75)	1.52 (1.33, 1.73)	<.0001	2.27 (1.73, 2.97)
Age & Calorie-adjusted model	Ref	1.03 (0.90, 1.19)	1.16 (1.01, 1.33)	1.33 (1.16, 1.53)	1.22 (1.06, 1.40)	0.0004	1.42 (1.06, 1.91)
Above+Nondietary factors adjusted (MV1)	Ref	1.02 (0.89, 1.17)	1.15 (1.00, 1.33)	1.31 (1.14, 1.51)	1.25 (1.08, 1.44)	<.0001	1.51 (1.12, 2.04)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.87, 1.15)	1.11 (0.96, 1.27)	1.22 (1.06, 1.41)	1.15 (0.99, 1.33)	0.0092	1.28 (0.94, 1.74)
Meta-analyzed results(MV2)	Ref	1.09 (1.03, 1.20)	1.16 (1.06, 1.23)	1.16 (1.09, 1.27)	1.20 (1.09, 1.27)	<.0001	1.29 (1.09, 1.52)
Chowder or Cream Soup							
NHS							
Median intake (% of energy)	0.02	0.03	0.05	0.08	0.14		
Age-adjusted model	Ref	1.10 (1.01, 1.19)	1.26 (1.16, 1.36)	1.27 (1.17, 1.38)	1.42 (1.31, 1.54)	<.0001	1.96 (1.65, 2.32)
Age & Calorie-adjusted model	Ref	1.07 (0.98, 1.16)	1.19 (1.09, 1.29)	1.15 (1.06, 1.25)	1.22 (1.12, 1.32)	<.0001	1.35 (1.13, 1.62)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.96, 1.13)	1.12 (1.04, 1.22)	1.10 (1.01, 1.19)	1.16 (1.06, 1.26)	0.0015	1.28 (1.06, 1.54)
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.94, 1.11)	1.10 (1.02, 1.20)	1.07 (0.98, 1.16)	1.13 (1.03, 1.23)	0.014	1.20 (1.00, 1.45)
HPFS							
Median intake (% of energy)	0	0.02	0.04	0.07	0.12		
Age-adjusted model	Ref	1.18 (1.03, 1.36)	1.39 (1.22, 1.60)	1.32 (1.15, 1.52)	1.63 (1.43, 1.86)	<.0001	2.20 (1.69, 2.88)
Age & Calorie-adjusted model	Ref	1.15 (1.00, 1.32)	1.31 (1.14, 1.50)	1.19 (1.03, 1.37)	1.35 (1.17, 1.54)	<.0001	1.41 (1.06, 1.87)
Above+Nondietary factors adjusted (MV1)	Ref	1.14 (0.99, 1.31)	1.27 (1.11, 1.45)	1.18 (1.02, 1.37)	1.27 (1.11, 1.46)	0.0012	1.28 (0.96, 1.70)
Above+Dietary factors adjusted (MV2)	Ref	1.12 (0.97, 1.29)	1.25 (1.09, 1.44)	1.14 (0.98, 1.32)	1.23 (1.07, 1.42)	0.0055	1.20 (0.90, 1.61)
Meta-analyzed results(MV2)	Ref	1.06 (0.97, 1.13)	1.13 (1.06, 1.23)	1.09 (1.00, 1.16)	1.16 (1.06, 1.23)	0.0004	1.20 (1.03, 1.40)

Age-adjusted model: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years);

Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);

Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.

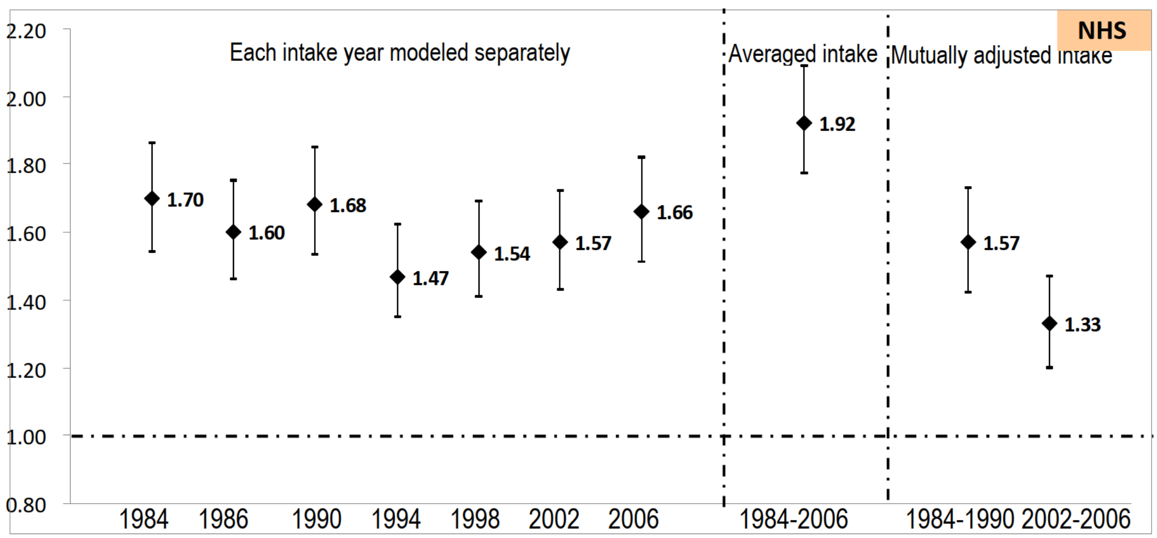
Multivariate model 2: other than variables adjusted in MV1, further adjusted for dietary intakes of total vegetables, fruit, fruit juice, and sugar-sweetened beverages (all in quintiles)

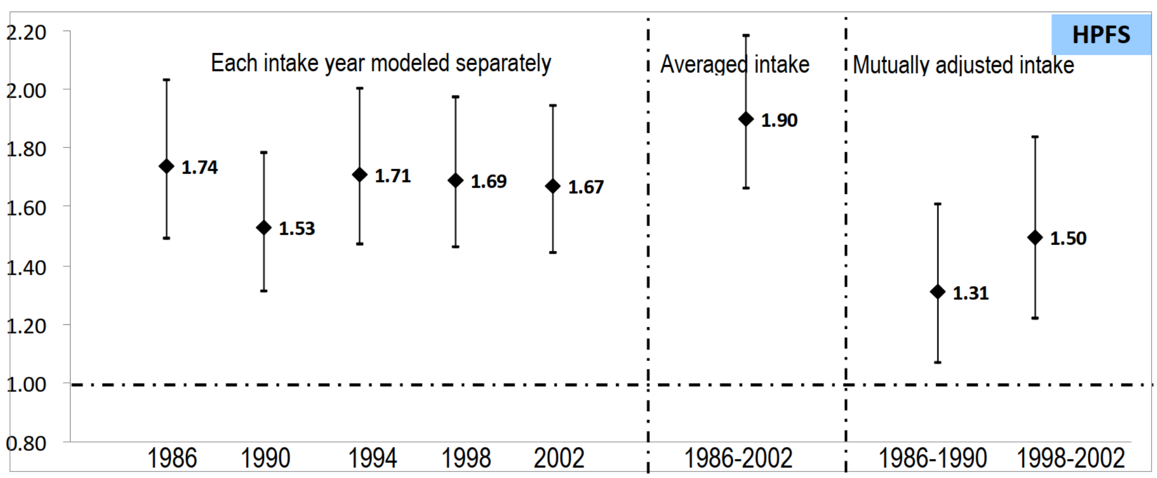
[a]Indicates ORs of 3-unit increments in SCD for each 3 servings/week increase in food intakes (except for walnuts and avocado, which were ORs for each 1 serving/week increase in intakes).

Temporal Relationships

Higher total energy and total fat intakes were significantly associated with higher odds of SCD at all time points during follow-up (7 times in the NHS and 5 times in the HPFS) (Figures 9 and 10); the average of all dietary assessments had the strongest associations in both cohorts. When both recent (6-10 years before SCD assessment) and remote (22-28 years before SCD assessments in the NHS and 18-22 years before SCD assessments in the HPFS) intakes were mutually included in the model, the association between remote total energy intake and SCD was stronger compared to recent intake in the NHS; while in the HPFS, recent intake had a stronger association compared with remote intake. Similar findings were observed for total fat. For *trans*-fat and SFA intakes, associations with SCD were mostly null in both cohorts. For MUFA and PUFA intakes, temporal relationships were relatively inconsistent over time and across cohorts, and associations were mainly null in the HPFS (Figure 11).

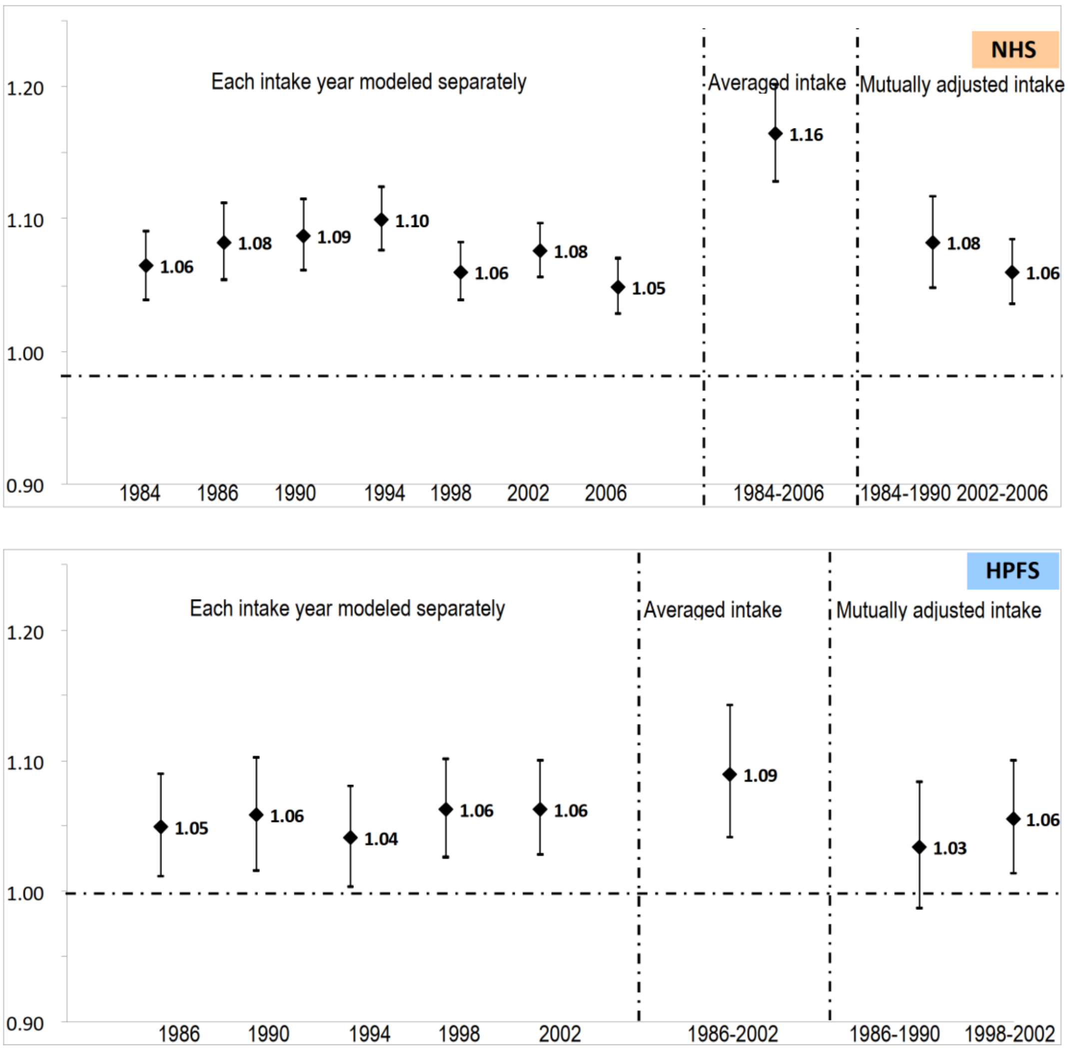
Figure 9. Total energy intake at each year of dietary assessment and odds of 3-unit increments in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) comparing the highest versus the lowest quintiles of intake (NHS: n=49,493 women, HPFS: 27,842 men)





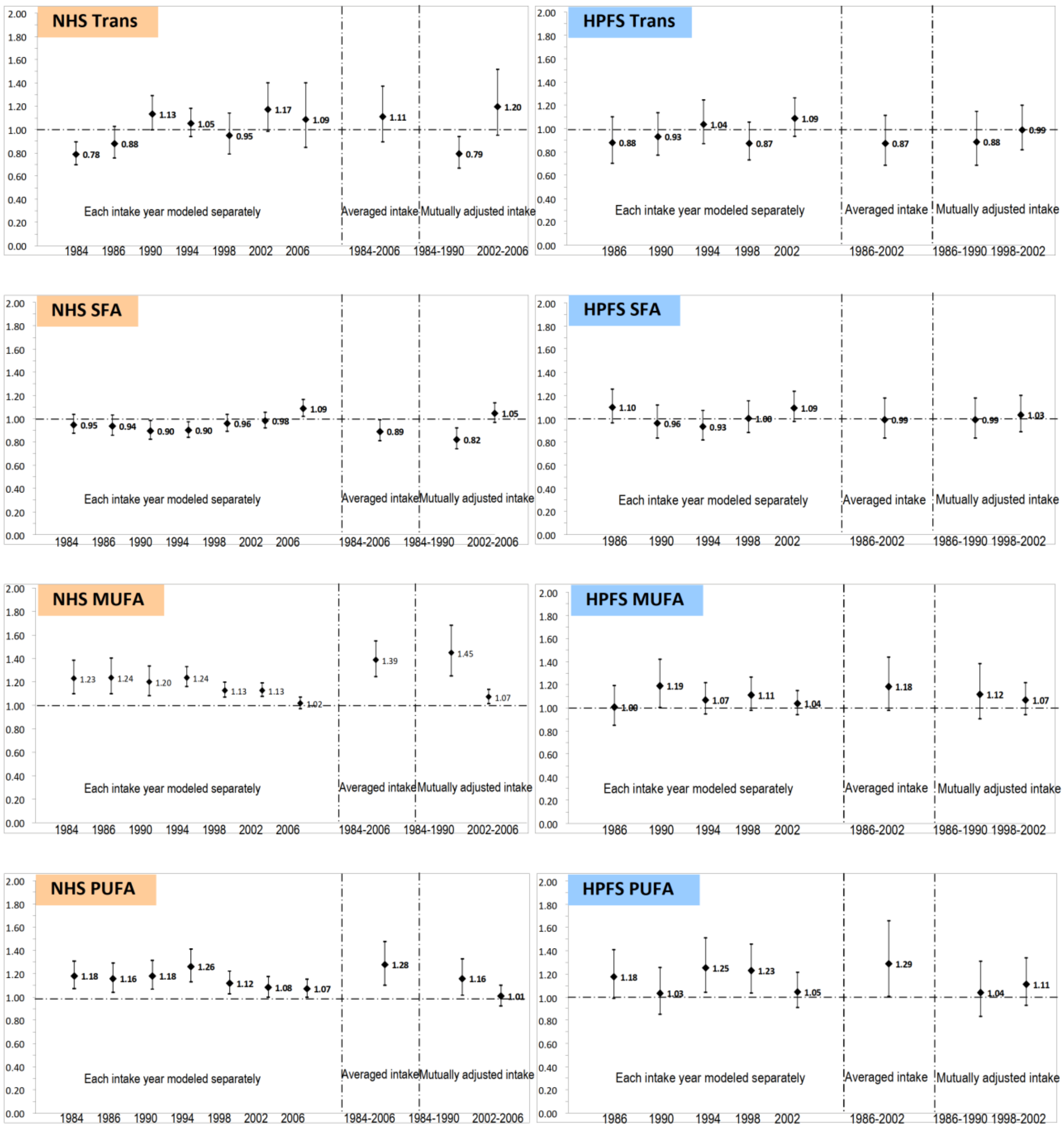
Multivariate model: NHS: adjusted for age, census tract income, education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, family history of dementia, multivitamin use (yes/no), intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, parity (nulliparous, 1-2, >2).
HPFS: adjusted for age, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002

Figure 10. Intake of total fat at each year of dietary assessment and odds of 3-unit increment in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) substituting every 5% of energy intake from total fat for the same amount of energy from total carbohydrates (NHS: n=49,493 women, HPFS: 27,842 men)



Multivariate model: NHS: adjusted for percentage of energy intake from dietary total protein (quintiles), age, total energy intake, census tract income, education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, family history of dementia, multivitamin use (yes/no), intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, parity (nulliparous, 1-2, >2), intakes ofvitamin c, d, e (quintiles), carotenoids (quintiles), and anthocyanins (quintiles).
HPFS: adjusted for percentage of energy intake from dietary total protein (quintiles), age, total energy intake, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002, intakes of vitamin c, d, e (quintiles), carotenoids (quintiles), and anthocyanins (quintiles)

Figure 11. Intakes of specific fatty acids at each year of dietary assessment and odds of 3-unit increment in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) substituting every 5% of energy intake from each specific fatty acid for the same amount of energy from total carbohydrates (NHS: n=49,493 women, HPFS: 27,842 men) (mutually adjusted for all FA)



Multivariate model: NHS: adjusted for age, total energy intake, census tract income, education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking

history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, family history of dementia, multivitamin use (yes/no), intake of alcohol (g/d), postmenopausal status and hormone replacement therapy use, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, parity (nulliparous, 1-2, >2), intakes of vitamin c, d, e (quintiles), carotenoids (quintiles), and anthocyanins (quintiles).
HPFS: adjusted for age, total energy intake, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), family history of dementia, profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002, intakes of vitamin c, d, e (quintiles), carotenoids (quintiles), and anthocyanins (quintiles)

All models adjusted for percentages of energy intakes from total protein and remaining fatty acids.

Discussion

Higher total energy intake was significantly associated with greater odds of SCD in two large prospective cohort studies of US men and women. Each 500 kcal increase in daily total energy intake was associated with 30% higher odds of SCD, and the positive associations persisted across more than 20 years of follow-up. Also, replacing total carbohydrates with the same amount of energy from total fat was associated with poorer subsequent subjective cognitive function.

Lower total energy intake was related to increased life span and more favorable aging-related outcomes in numerous experimental animal studies.[71-74, 91, 92] Lower calorie intake reversed the accumulation of pro-inflammatory cells across various tissues, dampening the aging-associated cell-cell interaction.[92] Although similar experiments have been hard to conduct in humans, a study on the Okinawan diet suggested a link between lower calorie intake and longer lifespan as well as better later-life outcomes.[93] To date, human studies on total energy intake and cognitive function remain limited. In a study with 980 participants followed-up for a mean of 4 years, Luchsinger et al. reported that higher calorie intake was associated with a higher risk of Alzheimer's disease among *APOE* ε4 carriers.[94] With a population-based case-control study, Geda et al. showed that high caloric intake was associated with an increased risk of having mild cognitive impairment (MCI) compared with the reference group (those who consumed 600 to <1,526 kcals per day), whereas moderate caloric intake was not associated with MCI.[95] One randomized controlled trial involving 50 participants concluded that caloric restriction over a period of 3 months had beneficial effects on memory performance in healthy elderly subjects.[96] The results of the current study support and strengthen the hypothesis that lower total energy intake could be related to better cognitive function. Major determinants of between-person variation in total energy intake include physical activity, body size, and metabolic efficiency.[97] Although we were unable to measure metabolic efficiency, many studies have indicated improvement of energy efficiency in those who practice calorie restriction. In an 11-year follow-up study of rhesus monkey, caloric restriction led to 17% reduction of total energy expenditure (measured by doubly labeled water), 20% reduction in resting energy expenditure (by indirect calorimetry), and no change in the nonbasal energy expenditure.[98] In the CALERIE study, non-obese human calorie-restricted participants did not have reduction in daily activity as determined by accelerometry and 7-day physical activity recall (PAR), indicating the reduction in the activity energy expenditure was most likely attributed to increased muscle efficiency.[99] The result of metabolic slowing likely benefits those under caloric restriction by reducing oxidative stress,[100] which has been one of the major mechanisms proposed for the association between lower calorie intake and better age-related outcomes.[101-103] Lower calorie intake increased neurotrophic factors expression and decrease neuron death in the brain of rats,[104] and may improve brain plasticity in older humans.[96] Calorie restriction also changed body composition, including weight loss (especially fat mass) and waist circumference reduction; such changes can be seen within the first two years of dietary intervention.[105] These changes in body composition and reduction in central obesity also partly contributed to the protective effect against dementia development.[106, 107] However, such reduction in body weight will most likely not persist over time. In aging monkeys, continuous calorie restriction for more than 10 years did not result in further weight loss.[108] In the current study, as we adjusted for BMI, physical activity, and body size (height) in our analyses, the association between total energy intake and SCD was independent of these factors.

As for dietary fat and cognitive function, current literature showed mixed results. Regarding total fat intake, in the Rotterdam study, higher total fat intake was linked to increased risk of dementia with a 2.1 year of follow-up,[109] but the association became null after extending the follow-up period to 6 years.[78] Luchsinger et al. reported that higher fat intake was related to higher risk of AD only among *APOE* ε4 carriers.[94] In contrast, higher fat intake was related to reduced risk of MCI or dementia in a prospective cohort study from the Mayo Clinic.[110] In the current study, compared with total carbohydrate, higher total fat intake was positively associated with SCD throughout the follow-up period in both cohorts. While still inconclusive, in an animal study, fat appeared to be the driving force for microglia activation, suggesting that a high-fat diet may lead to detrimental neuroinflammation in the brain.[111]

Regarding specific fatty acid intakes, Devore et al. reported that higher *trans*-fat and SFA intakes were associated with worse cognitive trajectory among participants with type 2 diabetes.[112] In the Women's Health Study, higher SFA and lower MUFA intakes were associated with worse cognitive function.[79] However, in the Rotterdam study, higher intakes of *trans*-fat and SFA were related to lower risk of AD, whereas no associations were found for MUFA and PUFA intakes; no association was observed for *trans*-fat, SFA, MUFA, and PUFA when the outcome was total dementia.[78] The inconsistencies across studies may arise from, different definitions of cognitive impairment, various lengths of study follow-up and different time points of dietary assessment, as the amount of specific dietary fatty acids changed over time. Also, many studies did not adjust for other dietary fat intake and had only a single dietary assessment, which may not represent long-term diet.

One major difference between the current study and previous studies was that we additionally adjusted for carotenoids and anthocyanins, two dietary variables with strong inverse associations with SCD in our cohorts and also significantly related to fat intakes. After adjusting for these two dietary variables, the inverse associations between specific ω-3 PUFA intakes (ALA, EPA, and DHA) with SCD, and the positive associations between *trans*-fat and SFA with SCD became null. Although the null results for these specific fatty acids have been reported in other epidemiological studies[78, 79, 109, 112] and intervention trials for ω-3 PUFA,[113, 114] future studies are warranted to confirm these findings. Overall, interpreting findings for fatty acids in the current study is difficult because there have been great changes in fat processing over our follow-up period (e.g., policy changes related decrease in *trans*-fat intake[115]), which might cause confounding and may be related to the inconsistencies of the associations observed over time.

Two major strengths of the current study were more than 20 years of long-term follow-up and large sample sizes in both cohorts, allowing for the capture of possible critical exposure windows, reducing reverse causation, and providing great statistical power for analysis. Averaged dietary information from multiple dietary assessments over time best represents long-term diet, and reduces errors due to within-person variation in diet. Dietary data were updated to only 6 years before SCD assessments to minimize the impact of reverse causation, which would be an effect of altered cognitive function on diet. To lessen residual confounding, a comprehensive list of possible confounders collected from our biannual questionnaires were used for adjustment. However, there are some limitations in the present study. First, baseline cognitive functions of our study participants were not available in our cohorts. However, a general high baseline cognitive function can be assumed in these participants during their early adulthood to be able to enter professional schools and pass board exams. These highly educated participants generally have better health awareness and better insights to report subtle cognitive changes.[66] Second, no objective cognitive assessment was included in either cohort and differential reporting of SCD could have occurred. However, the validity of SCD has been repeatedly tested and was strongly related to both concurrent objective cognitive function[39, 40] and subsequent cognitive decline.[39] Moreover, SCD can be used to detect more subtle cognitive changes,[67] especially in higher educated participants.[41] Third, participants who only completed the first but not the second SCD assessment might have more severe cognitive impairment. However, the results would be biased toward the null in this scenario. Fourth, although we adjusted for total energy intake in all analyses, residual confounding could still have existed because of a strong positive association between total energy and SCD. Finally, our study results could have limited generalizability, because the study populations were mainly Caucasian, relatively highly educated healthcare professionals with better health awareness. However, the relatively high and uniform cognitive function in our study participants may reduce residual confounding.

In conclusion, the results from the current study support the hypothesis that lower total energy intake could be beneficial for subsequent cognitive function. Total fat compared with total carbohydrate intake may be related to greater SCD. Future studies are needed to confirm these findings.

CHAPTER 3

Long-term dietary protein intake and subjective cognitive decline in US men and women

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Abstract

Objective: To investigate the associations between long-term dietary protein intake and subsequent subjective cognitive decline (SCD).

Methods: We included 49,493 women from the Nurses' Health Study (NHS) (1984-2006) and 27,842 men from the Health Professionals Follow-up Study (HPFS) (1986-2002) in this analysis. For the NHS, averaged dietary intake was calculated from seven repeated food frequency questionnaires (SFFQs), and SCD was assessed in 2012 and 2014. For the HPFS, averaged dietary intake was calculated from five repeated SFFQs, and SCD was assessed in 2008 and 2012. The validity of SCD scores was supported by strong associations with *APOE* ε4 genotype. Poisson regression was used to examine the associations between dietary protein, amino acids, and various protein food sources with subsequent SCD; a 3-unit increment in SCD from zero was considered poor versus good function.

Results: Higher protein intake compared with total carbohydrates was associated with lower odds of SCD. When substituting 5% energy from protein for the equivalent amount of energy from total carbohydrates, the pooled multivariable-adjusted ORs were 0.89 (0.85, 0.94) for total protein, 0.89 (0.84, 0.94) for animal protein, and 0.74 (0.62, 0.88) for plant protein. When substituting 5% of energy from animal protein with plant protein, the ORs were 0.87 (0.80, 0.94) for the NHS and 0.75 (0.70, 0.80) for the HPFS. For protein food sources, higher intakes of beans/legumes, fish, and chicken without skin were significantly associated with lower odds of SCD, but higher intakes of hotdogs and chicken with skin were associated with higher odds of SCD.

Conclusion: We found that total protein intake was associated with a modestly lower risk of SCD when compared isocalorically with carbohydrate, and that replacement of animal protein sources with plant protein sources was also associated with lower risk.

Introduction

In our world of rapid aging, the global absolute prevalence of age-related cognitive decline and dementia is projected to rise exponentially.[1-3] Disability related to cognitive decline[4] not only impacts patients, but also poses great burdens on patient families and the whole society.[2, 5] Due to the lack of effective treatments for dementia, disease prevention is of great importance. The clinical course of dementia is generally viewed as a continuum of decline from normal cognitive function, through a preclinical phase, then objective cognitive impairment, and finally dementia.[6] The preclinical phase——subjective cognitive decline (SCD) ——is a state of self-perceived cognitive decline without detectable objective cognitive impairments.[6] Dementia-associated brain pathologies may develop years before SCD,[7] making the long preclinical phase of dementia a critical period for prevention.[8] Substantial literature has indicated that diet is one of the very few modifiable risk factors for cognitive decline and may play an important role in cognitive function.[9-12]

Proteins and amino acids are important nutrients for normal functioning of the human body, are the building blocks for muscles and organs, and are essential for tissue/cell repair and production of neurotransmitters.[116] In some animal studies, low calorie and low protein diets were associated with longer life span and better aging-related outcomes,[117, 118] and higher dietary protein intake was associated with increased cardiovascular risk[119, 120]; however, inadequate protein intake in the older population could increase risk of sarcopenia and frailty,[121] closely linked to cognitive impairment.[122] To date, epidemiological studies on dietary protein intake and cognitive decline have remained inconclusive. [110, 123-125] Additionally, evidence on the impact of specific protein sources on cognitive function has been mixed.[125-128] Therefore, the aim of the current study was to investigate the relationships between long-term dietary protein intake and subsequent SCD with repeated dietary assessments from over 20 years of follow-up in two large prospective cohorts of men and women.

Methods

Study Design

The Nurses' Health Study (NHS) enrolled 121,701 female registered nurses aged 30 to 55 years in 1976 in the United States. Participants were followed up biennially via questionnaires which included potential risk factors and newly diagnosed diseases. Dietary information has been collected using a semi-quantitative food frequency questionnaire (SFFQ) that has been validated in multiple studies,[29] and these data were collected in 1980, 1984, 1986 and then every 4 years.

The Health Professionals Follow-up Study (HPFS) started in 1986 and consists of 51,529 male US health professionals aged 40 to 75 years at baseline. Detailed questionnaires regarding information on lifestyle risk factors and medical history have been sent to participants every two years.[30] Dietary assessments with the SFFQ began in 1986 and have continued every 4 years.

The study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Assessment of dietary intake

The SFFQ (available at www.nurseshealthstudy.org and sites.sph.harvard.edu/hpfs/hpfs-questionnaires) was used for dietary assessments. Each SFFQ contained 9 categories for consumption frequency, ranging from <1 time/month to ≧6 times/day. A standard portion size was specified for each food. Intake of nutrients and energy were calculated by multiplying the frequency of consumption of each item by its nutrient and energy content and summing across all items. Nutrient values were based primarily on the US Department of Agriculture (USDA) database (regepi.bwh.harvard.edu/health/nutrition). Information on amino acids was based on gene sequencing.[129] Follow-up began in 1984 for the NHS, when the first expanded SFFQ with 131 items was administered. Repeated dietary assessments were done in 1986 and then every four years. Cumulative averaged intakes of percentage of energy from protein, amino acids, protein foods, other nutrients/foods, and total energy were calculated from these repeated SFFQs (from 1984 until 2006). This approach best represents a long-term diet and can reduce within-subject variation.[31] Similarly, averaged intakes were calculated from 5 repeated dietary assessments done every four years since 1986 until 2002 for the HPFS. The correlation between the SFFQ and multiple dietary records for energy-adjusted total protein intake was 0.54 in women and similar in men.[87, 88] The correlations between the averaged SFFQ energy-adjusted protein intake and a biomarker for protein (urine nitrogen adjusted for energy intake using doubly labeled water) were 0.46 for women[89] and 0.47 for men.[90]

Assessment of subjective cognitive decline (SCD)

SCD was assessed twice by mailed or online questionnaires (2012 and 2014 for the NHS, 2008 and 2012 for the HPFS). Subjective cognitive function (SCF) was used in our previous publications,[36, 37] but we have updated our terminology to SCD in keeping with changes in the field.[38] The SCD scores for the HPFS were based on six yes/no questions on the recent change in general memory, executive function, attention, and visuospatial skills: (1) “Do you have more trouble than usual remembering recent events?”; (2) “Do you have more trouble than usual remembering a short list of items, such as a shopping list?”; (3) “Do you have trouble remembering things from one second to the next?”; (4) “Do you have any difficulty in understanding things or following spoken instructions?"; (5) "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?"; and (6) "Do you have trouble finding your way around familiar streets?" One additional question: "Have you recently experienced any change in your ability to remember things?" was included for the NHS.[39] For each question, every "yes" was assigned the number 1 and every "no" the number 0. To minimize random errors, the average of the two SCD scores was used, except for participants who completed only one of the two SCD questionnaires. We stopped updating dietary data 6 years prior to SCD assessment to minimize the possible effects of altered cognitive function on diet.

Subjective cognitive decline, broadly defined, has been strongly associated with both concurrent objective cognitive function[39, 40] and subsequent cognitive decline,[39] especially for people with higher education.[41] As for our specific SCD measure, t In multivariate analyses, he strong associations between the homozygous *APOE* Ɛ4 genotype and poor SCD scores in both the NHS and HPFS further support the validity of this score.[37] Also, numerous known risk factors for dementia, such as high blood pressure, high blood cholesterol, depression, cardiovascular disease, type 2 diabetes, and heavy smoking, were all associated with poor subsequent SCD scores in our studies.[37]

Covariates

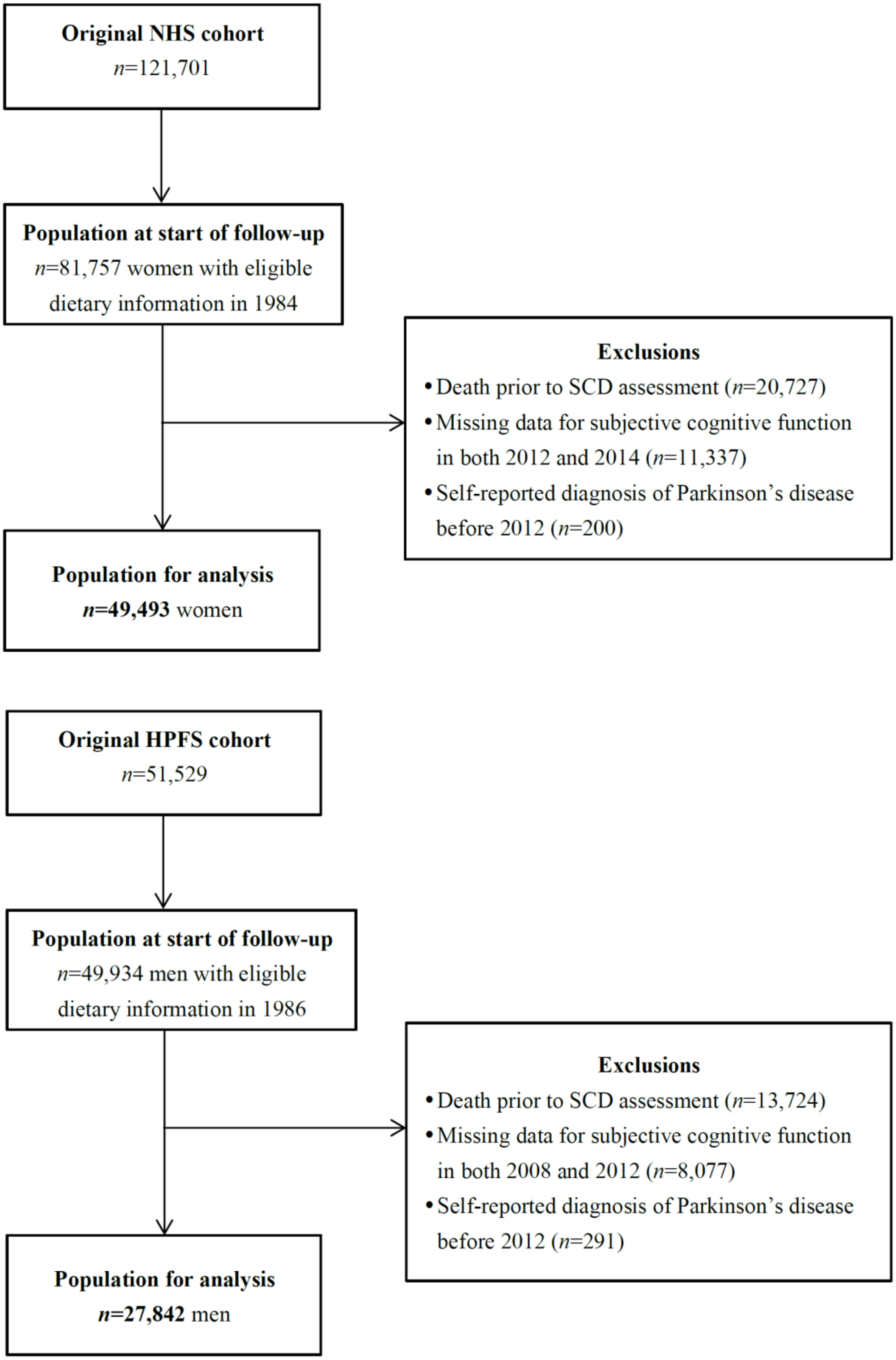
Starting from baseline and in follow-up questionnaires, information on covariates was collected prospectively in the NHS and HPFS. These covariates of interest include: age (years, continuous), race (white, black, other), body mass index (BMI) (<23, 23-25, 25-30, >30 kg/m^2), physical activity (MET-hours/week), multivitamin use (yes/no), smoking status (pack-years), alcohol consumption (g/d), cancer, history of CVD (stroke, myocardial infarction, angina, or coronary artery surgery), high blood pressure, elevated cholesterol, diabetes, family history of dementia, and depression (anti-depressant use or self-reported depression). For the NHS, additional information on education (registered nursing degrees, bachelors degree, master or doctorate degree), husband's education (high school or lower education, college, graduate school), census tract income ($50,000, $50,000–69,999, or $70,000/y), menopausal status and the use of hormone replacement therapy, and parity (nulliparous, 1-2, >2) were obtained. For the HPFS, we also used information on profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian).

Population for Analysis

In the NHS, a total of 81,757 participants with eligible dietary information in 1984 were included at baseline (excluding deaths prior to 1984, and individuals with >70 food items blank and extreme energy intake of <600 or >3,500 kcal/day) (Figure 12). Of these participants, additional exclusions consisted of 20,727 deaths occurring prior to SCD assessment, 11,337 participants not responding to either SCD questionnaire, and 200 participants who developed Parkinson's disease before outcome assessment. The final analysis included 49,493 women with a mean age of 48 years at baseline in 1984.

The same exclusion criteria were applied for the HPFS. After excluding deaths prior to SCD assessment, individuals missing dietary or SCD information, and 291 participants who developed Parkinson's disease prior to SCD assessment, a total of 27,842 men were included with a mean age of 51 years at enrollment in 1986.

Figure 12: Study population and exclusions in the NHS and HPFS



Statistical analysis

Intake of protein was expressed as percentage of total energy and was classified into quintiles in each cohort. Age-standardized characteristics of participants were calculated according to quintiles of total protein intake. Averaged SCD score was calculated from the two SCD assessments. Due to the distribution and nature of the SCD scores, Poisson regression was used to estimate the associations between protein, amino acids, and protein food intakes with SCD. ORs (95% CIs) for a 3-unit increment in SCD were calculated because three or more positive SCD questions have been used to indicate poor cognitive function.[39, 40] Covariate information from the same time frame as dietary assessments was used (1984-2006 for the NHS and 1986-2002 for the HPFS). Both a quadratic term and linear term for age were included in all models because the relationship between age and SCD was non-linear. In multivariate analyses, average age at the two SCD assessments, total energy intake, race, smoking history, depression, physical activity level, BMI, alcohol intake, family history of dementia, an indicator for having only one of the two SCD assessments, number of dietary assessments during follow-up period, and use of multivitamin were included as covariates. For the NHS, parity, postmenopausal status and hormone replacement therapy use, census tract income, education, husband's education were also included in the analyses, while profession was included in the HPFS. Potential mediators on the causal pathway, including hypertension, diabetes, elevated cholesterol, and CVD, were not adjusted in our primary analysis, although the results remained similar when these variables were included in the models.

For protein substitution analysis, isocaloric substitution models were built, which simultaneously included total energy intake, percentage of energy intake from protein, percentage of energy from *trans-* fat, saturated fat, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA). The coefficients from the substitution models can be interpreted as the associations when replacing the percentage of energy intake from protein for the same amount of energy from carbohydrates. To examine whether the associations were independent of other dietary factors in our protein analyses, we further adjusted for intakes of carotenoids, anthocyanins, vitamin C, D, and E. The same dietary factors were controlled in analyses of amino acid intakes. We also performed a sensitivity analysis only including participants with both SCD assessments.

For food-based analyses, all aforementioned non-dietary factors and intakes of total vegetables, fruit, fruit juice, sugar-sweetened beverages, and sweets/desserts were adjusted in the final model. Linear trends were tested by assigning median values within each quintile and modeling these variables continuously.

We further investigated whether the associations between protein and protein-containing food intakes with SCD differed by baseline age (<50 years, ≥50 years), smoking status (never smokers, past smokers, and current smokers), disease status (self-reported depression, cardiovascular disease, and type 2 diabetes), and *APOE* Ɛ4 allele carrier status (yes/no) in a subgroup of participants who had their APOE Ɛ4 measured or imputed from a genome-wide association analysis.

Temporal relationships between specific sources of protein intakes with SCD were evaluated. We estimated the associations between dietary intake at each of the individual years with SCD. Also, both recent (the averaged intake from 2002~2006 in the NHS and averaged intake from 1998~2002 for the HPFS) and remote (the averaged intake from 1984~1990 in the NHS and averaged intake from 1986~1990 for the HPFS) intakes were mutually included in the same model to examine whether these associations were independent of each other. In these analyses, covariates closest in time to the dietary assessments were used.

Analyses were performed separately for the NHS and HPFS, and an inverse-variance-weighted, fixed-effect meta-analysis was used to combine the results across cohorts. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Population Characteristics

The characteristics of study participants are shown in Table 11. The mean age of participants at the initial SCD assessment was 76.4 years for the NHS and 73 years for the HPFS. The mean percentage of energy intake from total protein, animal protein, and plant protein was 18%, 12.6%, and 5.4%, respectively for women, and 17.9%, 12.5%, and 5.5%, respectively for men. For both the NHS and HPFS, participants with higher total protein intake (as percentage of energy) had higher BMI, less alcohol consumption, were more likely to have type 2 diabetes, and had a higher vegetable intake but lower intake of sweets/desserts. In addition, women with higher intake of total protein tend to be younger, had a higher prevalence of metabolic disorders (including high blood pressure, elevated blood cholesterol, and cardiovascular diseases), were more physically active, and had higher dairy intake.

Table 11 NHS: Characteristics[a] in 1984-2006 of 49,493 women who completed SCD questions in 2012/2014 by quintiles of total protein intake

	Q1	Q2	Q3	Q4	Q5
Protein intake, % energy	14.9 (1.1)	16.7 (0.6)	18.0 (0.6)	19.3 (0.7)	21.5 (1.4)
Age, y (at study baseline 1984)	49.2 (6.8)	48.5 (6.6)	48.1 (6.6)	48.0 (6.5)	47.9 (6.4)
BMI, kg/m2	24.9 (4.2)	25.4 (4.4)	26.0 (4.6)	26.6 (4.8)	27.6 (5.0)
Alcohol, g/day	7.7 (11.3)	6.5 (8.9)	5.8 (7.8)	5.1 (6.9)	3.7 (5.5)
Total energy intake, kcal/d	1,735 (439)	1,761 (424)	1,756 (417)	1,736 (404)	1,679 (405)
Total carbohydrate, % energy	51.7 (6.7)	49.9 (5.7)	49.1 (5.5)	48.2 (5.6)	47.2 (5.7)
Total fat, % energy	32.3 (4.7)	32.7 (4.4)	32.6 (4.4)	32.3 (4.5)	31.7 (4.8)
Physical activity, MET-h/wk	16.7 (15.6)	18.2 (15.9)	18.5 (15.5)	19.1 (16.0)	20.3 (17.5)
Smoking pack-years, 1984-2006, %					
Never smoked	46.0	47.3	47.1	45.7	46.3
<=4 pack-years	9.6	10.5	10.8	11.8	11.9
5-24 pack-years	21.2	22.0	23.0	23.6	23.4
>=25 pack-years	21.5	18.6	17.4	17.4	16.6
Missing	1.7	1.6	1.6	1.6	1.8

Table 11 NHS (Continued)					
High blood pressure, 1984-2006, %	57.7	58.7	60.2	61.0	65.0
Elevated cholesterol, 1984-2006, %	69.8	70.6	72.1	72.1	73.4
Diabetes, 1984-2006, %	6.5	8.5	10.0	12.5	16.5
CVD, 1984-2006, %	9.4	9.5	9.7	10.8	11.8
Cancer, 1984-2006, %	17.2	18.7	18.5	18.8	19.1
Depression diagnosis or anti-depressant use, %	19.0	18.4	19.3	19.4	21.4
Number of dietary assessment, 1984-2006, %					
1	0.4	0.2	0.1	0.2	0.3
2	1.0	0.5	0.6	0.7	1.0
3	1.6	1.3	1.5	1.5	1.7
4	3.6	3.1	2.9	2.9	3.8
5	8.1	7.2	6.7	6.7	7.5
6	20.2	19.2	18.7	18.8	19.2
7	65.1	68.4	69.4	69.2	66.5
Missing year of SCD assessment					
None	84.9	86.9	85.8	86.5	85.4
2014	12.3	10.8	11.6	10.9	11.9
Postmenopausal status & hormone use					
Postmenopause & never use hormone therapy	24.0	21.3	20.3	19.9	19.2
Postmenopause & ever use hormone therapy	70.5	73.6	75.0	75.0	75.2
Missing	5.1	4.5	4.3	4.8	5.2
Parity					
Nulliparous	5.8	5.1	5.1	5.1	5.0
1-2	7.4	6.4	6.6	5.8	7.2
3+	85.0	86.8	86.6	87.3	85.7
Missing	1.8	1.8	1.6	1.9	2.1
Dietary intake					
Vegetable intake (servings/d)	2.9 (1.4)	3.3 (1.5)	3.5 (1.5)	3.8 (1.6)	4.2 (1.8)
Fruit intake (servings/d)	1.4 (0.9)	1.5 (0.8)	1.6 (0.8)	1.7 (0.8)	1.7 (0.8)
Fruit juice intake (servings/d)	0.8 (0.6)	0.8 (0.5)	0.7 (0.5)	0.7 (0.5)	0.6 (0.4)
Whole grain intake (servings/d)	1.2 (0.8)	1.3 (0.8)	1.4 (0.8)	1.5 (0.8)	1.5 (0.8)
Refined grain intake (servings/d)	1.7 (0.9)	1.6 (0.8)	1.5 (0.8)	1.4 (0.7)	1.3 (0.7)
Potato intake (servings/d)	0.5 (0.3)	0.5 (0.3)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)
Sweets/desserts intake (servings/d)	1.6 (1.1)	1.4 (0.9)	1.3 (0.8)	1.1 (0.7)	0.8 (0.6)
Fresh red Meat intake (servings/d)	0.8 (0.9)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)
Processed red Meat intake (servings /d)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	0.3 (0.6)
Poultry intake (servings/d)	0.4 (0.8)	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.6 (0.8)
Fish intake (servings/d)	0.2 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.2)	0.4 (0.2)
Legume intake (servings/d)	0.3 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.3)
Dairy intake (servings /d)	1.7 (0.9)	1.9 (0.9)	2.1 (0.9)	2.2 (1.0)	2.3 (1.0)
Egg intake (servings /d)	0.2 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Misc animal food (servings/d)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)
Nut intake (servings /d)	0.4 (0.4)	0.4 (0.4)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)
Vegetable oil dressing intake (servings /d)	0.4 (0.5)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Tea & coffee intake (servings/d)	2.5 (1.4)	2.7 (1.3)	2.7 (1.4)	2.7 (1.4)	2.6 (1.4)
SSB intake (servings /d)	0.5 (0.6)	0.3 (0.4)	0.2 (0.3)	0.2 (0.2)	0.1 (0.2)
Diet beverage intake (servings /d)	0.4 (0.6)	0.5 (0.7)	0.5 (0.7)	0.6 (0.7)	0.7 (0.8)

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population

Table 11 HPFS (Continued): Characteristics[a] in 1986-2002 of 27,842 men who completed SCD questions in 2008/2012 by quintiles of total protein intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Protein intake, % energy	14.7 (1.1)	16.6 (0.4)	17.8 (0.3)	19.1 (0.4)	21.5 (1.6)
Age, y (at study baseline 1986)	50.7 (8.3)	50.5 (8.1)	50.9 (8.1)	51.1 (8.0)	52.0 (8.3)
BMI, kg/m2	25.5 (3.0)	25.7 (3.1)	25.9 (3.3)	26.0 (3.2)	26.5 (3.7)
Alcohol, g/day	14.4 (16.4)	12.4 (13.3)	11.1 (12.0)	9.8 (11.0)	8.6 (9.9)
Total energy intake, kcal/d	1,972 (516)	2,020 (515)	2,034 (512)	2,010 (520.3)	1,928 (509)
Total carbohydrate, % energy	51.9 (7.7)	50.3 (6.8)	49.7 (6.6)	49.0 (6.5)	47.3 (6.9)
Total fat, % energy	30.3 (5.2)	30.8 (5.1)	30.8 (5.1)	30.6 (5.2)	30.3 (5.6)
Physical activity, MET-h/wk	27.3 (21.2)	28.6 (21.3)	28.7 (20.3)	29.2 (21.7)	28.7 (21.1)
Smoking pack-years, 1986-2002, %					
Never smoked	48.6	48.8	51.0	49.6	48.0
Less 24 pack-years	28.2	29.7	28.3	29.3	29.3
25-44 pack-years	11.7	11.3	10.7	11.6	11.6
45 or more pack-years	6.0	5.3	5.0	4.4	4.8
Missing	5.4	4.9	5.0	5.1	6.3
High blood pressure, 1986-2002, %	43.2	43.6	42.7	46.2	46.9
Elevated cholesterol, 1986-2002, %	54.6	56.0	57.1	56.9	58.4
Diabetes, 1986-2002, %	6.1	6.4	7.0	8.0	10.7
CVD, 1986-2002, %	16.7	16.6	16.6	17.7	19.4
Cancer, 1986-2002, %	15.6	15.9	15.6	15.4	15.5
Depression diagnosis or anti-depressant use, %	5.7	5.8	5.4	5.4	5.6
Number of dietary assessment, 1986-2002, %					
1	2.1	2.0	2.0	2.4	2.8
2	5.1	4.5	4.3	4.4	4.8

Table 11 HPFS (Continued)					
3	8.4	8.0	8.4	8.5	9.3
4	18.6	18.0	17.2	17.7	20.1
5	65.9	67.5	68.2	67.0	63.0
Missing year of SCF measurement, %					
None	73.0	72.9	73.3	72.3	70.3
2008	8.3	7.7	8.6	8.9	10.0
2012	18.7	19.4	18.2	18.8	19.7
Profession, %					
Dentist	51.9	54.6	56.8	60.0	63.5
Pharmacist	12.6	9.0	7.9	6.8	5.8
Optometrist	7.2	7.2	6.9	6.1	6.5
Osteopath	3.9	3.9	3.8	4.1	4.7
Podiatrist	2.2	2.2	2.1	2.8	3.2
Veterinarian	22.0	23.0	22.5	20.1	16.4
Dietary intake					
Vegetable intake (servings/d)	3.1 (1.6)	3.4 (1.6)	3.5 (1.6)	3.7 (1.7)	4.0 (2.0)
Fruit intake (servings/d)	1.6 (1.2)	1.7 (1.0)	1.7 (1.0)	1.8 (1.0)	1.8 (1.1)
Fruit juice intake (servings/d)	0.8 (0.7)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	0.7 (0.6)
Whole grain intake (servings/d)	1.5 (1.1)	1.6 (1.1)	1.7 (1.1)	1.7 (1.1)	1.7 (1.1)
Refined grain intake (servings/d)	1.7 (1.0)	1.7 (1.0)	1.7 (0.9)	1.6 (0.9)	1.5 (0.9)
Potato intake (servings/d)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.5 (0.3)	0.5 (0.3)
Sweets/desserts intake (servings/d)	1.7 (1.3)	1.6 (1.2)	1.4 (1.0)	1.3 (0.9)	1.0 (0.8)
Fresh red Meat intake (servings/d)	1.1 (1.4)	1.1 (1.3)	1.2 (1.3)	1.2 (1.3)	1.2 (1.4)
Processed red Meat intake (servings/d)	0.4 (1.0)	0.4 (0.9)	0.4 (1.0)	0.4 (1.0)	0.4 (1.1)
Poultry intake (servings/d)	0.9 (1.5)	0.8 (1.4)	0.9 (1.4)	0.9 (1.4)	0.9 (1.4)
Fish intake (servings/d)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.4 (0.2)	0.5 (0.3)
Legume intake (servings/d)	0.4 (0.3)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
Dairy intake (servings/d)	1.6 (1.0)	1.8 (1.0)	1.9 (1.1)	2.0 (1.2)	1.9 (1.2)
Egg intake (servings/d)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Misc. animal food (servings/d)	0.5 (1.2)	0.5 (1.1)	0.5 (1.1)	0.5 (1.1)	0.6 (1.2)
Nut intake (servings/d)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.4 (0.5)
Vegetable oil dressing intake (servings/d)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.3)	0.4 (0.4)
Tea & coffee intake (servings/d)	2.2 (1.5)	2.2 (1.5)	2.2 (1.5)	2.2 (1.5)	2.2 (1.5)
SSB intake (servings/d)	0.5 (0.7)	0.4 (0.5)	0.3 (0.4)	0.3 (0.4)	0.2 (0.3)
Diet beverage intake (servings/d)	0.4 (0.7)	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)	0.7 (0.9)

[a]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population

Protein Analysis

Higher intakes of total protein, animal protein, and plant protein were significantly associated with lower odds of SCD in both the NHS and HPFS (Table 12). Adjusting for total energy intake (which was positively associated with SCD) and major non-dietary factors attenuated the magnitude of these associations; adjusting for carotenoids and anthocyanins further attenuated the associations for plant protein, whereas associations for total and animal protein were slightly strengthened. Comparing the highest with the lowest quintiles of intakes, the pooled multivariate ORs of a 3 unit-increment in SCD were 0.84 (0.76, 0.91), p trend<0.0001 for total protein, 0.86 (0.79, 0.94), p trend<0.0001 for animal protein, and 0.84 (0.76, 0.91), p trend=0.0007 for plant protein.

Table 12: OR (95% CI) for the associations between total energy and specific sources of protein intakes with SCD in the NHS and HPFS (Comparison is isocaloric substitution of protein for total carbohydrates)							
	Q1	Q2	Q3	Q4	Q5	P trend	Continuous[a]
Total Energy							500 kcal/day
NHS							
Median intake (kcal/day)	1,196	1,472	1,687	1,923	2,301		
Age-adjusted model	Ref	1.36 (1.25, 1.47)	1.44 (1.33, 1.57)	1.62 (1.49, 1.76)	1.81 (1.67, 1.96)	<.0001	1.27 (1.23, 1.30)
Above+Nondietary factors adjusted (MV)	Ref	1.40 (1.29, 1.52)	1.49 (1.38, 1.62)	1.68 (1.55, 1.83)	1.92 (1.77, 2.09)	<.0001	1.30 (1.26, 1.34)
HPFS							
Median intake (kcal/day)	1,366	1,683	1,938	2,224	2,693		
Age-adjusted model	Ref	1.05 (0.92, 1.20)	1.40 (1.22, 1.60)	1.58 (1.38, 1.80)	2.01 (1.76, 2.29)	<.0001	1.29 (1.24, 1.35)
Above+Nondietary factors adjusted (MV)	Ref	1.03 (0.90, 1.19)	1.35 (1.18, 1.54)	1.48 (1.29, 1.69)	1.90 (1.66, 2.18)	<.0001	1.27 (1.22, 1.32)
Meta-analyzed results (MV)	Ref	1.30 (1.26, 1.33)	1.44 (1.37, 1.56)	1.64 (1.52, 1.73)	1.91 (1.77, 2.05)	<.0001	1.30 (1.26, 1.33)
Total Protein							5% Energy
NHS							
Median intake (% of energy)	15.17	16.77	17.92	19.12	20.99		
Age-adjusted model	Ref	0.96 (0.88, 1.03)	0.94 (0.87, 1.02)	0.85 (0.78, 0.92)	0.77 (0.71, 0.84)	<.0001	0.84 (0.79, 0.89)
Age & Calorie-adjusted model	Ref	0.96 (0.89, 1.04)	0.97 (0.90, 1.05)	0.89 (0.82, 0.97)	0.84 (0.77, 0.92)	0.0002	0.90 (0.85, 0.95)
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.91, 1.06)	0.98 (0.90, 1.06)	0.89 (0.82, 0.97)	0.85 (0.77, 0.92)	0.0002	0.90 (0.84, 0.95)
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)	0.91 (0.83, 0.99)	0.84 (0.77, 0.93)	0.0003	0.90 (0.84, 0.96)
HPFS							
Median intake (% of energy)	14.93	16.61	17.79	19.05	21.06		
Age-adjusted model	Ref	1.02 (0.90, 1.16)	0.84 (0.74, 0.96)	0.86 (0.75, 0.98)	0.74 (0.64, 0.85)	<.0001	0.82 (0.75, 0.89)
Age & Calorie-adjusted model	Ref	1.04 (0.92, 1.18)	0.87 (0.77, 1.00)	0.92 (0.81, 1.05)	0.84 (0.73, 0.96)	0.0062	0.90 (0.82, 0.98)
Above+Nondietary factors adjusted (MV1)	Ref	1.05 (0.92, 1.19)	0.87 (0.76, 0.99)	0.92 (0.81, 1.06)	0.84 (0.73, 0.97)	0.008	0.90 (0.82, 0.99)
Above+Dietary factors adjusted (MV2)	Ref	1.06 (0.93, 1.20)	0.87 (0.76, 1.00)	0.93 (0.81, 1.07)	0.82 (0.71, 0.96)	0.0055	0.88 (0.80, 0.98)
Meta-analyzed results (MV2)	Ref	1.00 (0.94, 1.09)	0.97 (0.89, 1.03)	0.91 (0.86, 0.97)	0.84 (0.76, 0.91)	<.0001	0.89 (0.85, 0.94)
Animal Protein							5% Energy
NHS							
Median intake (% of energy)	9.71	11.35	12.49	13.72	15.61		
Age-adjusted model	Ref	1.07 (0.99, 1.15)	0.98 (0.91, 1.06)	0.92 (0.85, 1.00)	0.80 (0.73, 0.87)	<.0001	0.84 (0.79, 0.89)
Age & Calorie-adjusted model	Ref	1.07 (0.99, 1.16)	1.01 (0.93, 1.09)	0.97 (0.89, 1.05)	0.88 (0.80, 0.96)	0.0015	0.90 (0.85, 0.96)
Above+Nondietary factors adjusted (MV1)	Ref	1.07 (0.99, 1.16)	1.01 (0.93, 1.10)	0.94 (0.86, 1.02)	0.87 (0.79, 0.95)	0.0007	0.89 (0.84, 0.95)
Above+Dietary factors adjusted (MV2)	Ref	1.08 (1.00, 1.17)	1.02 (0.94, 1.11)	0.95 (0.87, 1.03)	0.86 (0.79, 0.95)	0.0009	0.89 (0.84, 0.96)
HPFS							
Median intake (% of energy)	9.35	11.11	12.36	13.65	15.78		
Age-adjusted model	Ref	1.11 (0.97, 1.26)	0.87 (0.77, 1.00)	0.90 (0.78, 1.03)	0.78 (0.68, 0.90)	<.0001	0.82 (0.75, 0.89)
Age & Calorie-adjusted model	Ref	1.12 (0.98, 1.27)	0.91 (0.80, 1.04)	0.96 (0.83, 1.09)	0.89 (0.77, 1.02)	0.0344	0.90 (0.82, 0.98)
Above+Nondietary factors adjusted (MV1)	Ref	1.11 (0.97, 1.26)	0.89 (0.78, 1.02)	0.94 (0.82, 1.08)	0.86 (0.74, 0.99)	0.0145	0.89 (0.81, 0.97)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.98, 1.27)	0.90 (0.78, 1.03)	0.94 (0.82, 1.09)	0.84 (0.72, 0.98)	0.0094	0.88 (0.79, 0.97)
Meta-analyzed results (MV2)	Ref	1.09 (1.03, 1.16)	1.00 (0.91, 1.06)	0.94 (0.89, 1.03)	0.86 (0.79, 0.94)	<.0001	0.89 (0.84, 0.94)
Plant Protein							5% Energy
NHS							
Median intake (% of energy)	4.43	4.97	5.36	5.77	6.47		
Age-adjusted model	Ref	0.80 (0.73, 0.86)	0.77 (0.71, 0.84)	0.76 (0.70, 0.83)	0.68 (0.62, 0.75)	<.0001	0.50 (0.41, 0.60)
Age & Calorie-adjusted model	Ref	0.80 (0.74, 0.87)	0.78 (0.72, 0.85)	0.77 (0.71, 0.84)	0.71 (0.65, 0.79)	<.0001	0.55 (0.45, 0.67)

Table 12 (Continued)							
Above+Nondietary factors adjusted (MV1)	Ref	0.83 (0.77, 0.90)	0.83 (0.76, 0.91)	0.82 (0.75, 0.90)	0.76 (0.69, 0.84)	<.0001	0.64 (0.52, 0.79)
Above+Dietary factors adjusted (MV2)	Ref	0.89 (0.81, 0.96)	0.90 (0.83, 0.98)	0.91 (0.83, 1.00)	0.85 (0.76, 0.94)	0.0069	0.78 (0.63, 0.97)
HPFS							
Median intake (% of energy)	4.24	4.87	5.35	5.87	6.78		
Age-adjusted model	Ref	0.84 (0.74, 0.96)	0.81 (0.71, 0.93)	0.77 (0.66, 0.89)	0.61 (0.52, 0.73)	<.0001	0.44 (0.33, 0.58)
Age & Calorie-adjusted model	Ref	0.85 (0.75, 0.97)	0.82 (0.72, 0.95)	0.79 (0.68, 0.91)	0.64 (0.54, 0.76)	<.0001	0.48 (0.36, 0.64)
Above+Nondietary factors adjusted (MV1)	Ref	0.88 (0.77, 1.01)	0.85 (0.74, 0.98)	0.83 (0.71, 0.97)	0.71 (0.59, 0.85)	0.0004	0.54 (0.40, 0.74)
Above+Dietary factors adjusted (MV2)	Ref	0.94 (0.82, 1.08)	0.94 (0.82, 1.09)	0.94 (0.80, 1.10)	0.82 (0.68, 0.98)	0.0422	0.66 (0.48, 0.91)
Meta-analyzed results (MV2)	Ref	0.91 (0.84, 0.97)	0.91 (0.84, 0.97)	0.91 (0.84, 1.00)	0.84 (0.76, 0.91)	0.0007	0.74 (0.62, 0.88)

Age-adjusted model: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1 (non-dietary factors): NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (METs-hr/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2 (dietary factors): other than variables adjusted in MV1, further adjusted for carotenoids (quintiles), anthocyanins (quintiles), vitamin c, d, and e (quintiles)
[a]Indicates OR of 3-unit increments in SCD when replacing each 5% of energy intake from specific protein with the same amount of energy from total carbohydrates.
All models for protein adjusted for percentage of energy intake from trans-fat, saturated fat, MUFA, and PUFA. Percentage of energy from animal and plant protein were mutually adjusted.
Abbreviations: MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids

When substituting each 5% of energy intake from protein for equivalent percentage of energy from total carbohydrates, the pooled multivariate ORs were 0.89 (0.85, 0.94) for total protein, 0.89 (0.84, 0.94) for animal protein, and 0.74 (0.62, 0.88) for plant protein. When substituting every 5% of energy intake from animal protein with plant protein, the ORs were 0.87 (0.80, 0.94) in the NHS and 0.75 (0.70, 0.80) in the HPFS. Similar results were observed in the sensitivity analysis which only included participants with both SCD assessments. When total fat was adjusted instead of four types of fat, the associations for total and animal protein remained similar, whereas the association for plant protein was shifted to null. Results were similar across strata of baseline age, smoking status, disease status, and *APOE* Ɛ4 allele carrier status.

Top food contributors to total protein and animal protein in our cohorts during the follow-up period were chicken without skin, fish, low-fat milk, and beef. Nuts, beans/legumes, dark bread, and cold breakfast cereal were major contributors to plant protein (Table 13).

Table 13: Major food sources of protein, averaged for 1984-2006 in the NHS and 1986-2002 in the HPFS.

	Total Protein		Animal Protein		Plant Protein	
	NHS	**HPFS**	**NHS**	**HPFS**	**NHS**	**HPFS**
1	Chicken without skin (9.51%)	Chicken without skin (10.01%)	Chicken without skin (12.74%)	Chicken without skin (14.39%)	Nuts (8.72%)	Nuts (10.07%)
2	Low-fat milk (9.07%)	Fish (9.17%)	Low-fat milk (12.27%)	Fish (13.21%)	Dark bread (6.41%)	Bean/Legu me (7.11%)
3	Beef (8.41%)	Low-fat milk (7.70%)	Beef (11.84%)	Low-fat milk (11.13%)	Cold breakfast cereal (5.5%)	Dark bread (6.76%)
4	Fish (8.40%)	Beef (7.50%)	Fish (10.40%)	Beef (10.77%)	Bean/Legum e (5.13%)	Cold breakfast cereal (5.94%)
5	Hamburger (5.13%)	Hamburger (5.05%)	Hamburger (7.61%)	Hamburger (7.32%)	Pasta (5%)	Pasta (5.03%)
6	Pork (4.00%)	Chicken sandwich (4.78%)	Pork (5.81%)	Chicken sandwich (7.16%)	Potato (3.67%)	Potato (4.10%)
7	Beef sandwich (3.87%)	Chicken with skin (4.3%6)	Cheese (cheddar) (5.71%)	Chicken with skin (6.24%)	English muffins bagels roll (3.51%)	English muffins bagels roll (3.83%)
8	Chicken sandwich (3.70%)	Pork (3.72%)	Chicken sandwich (5.54%)	Pork (5.46%)	Cooked oatmeal (3.34%)	Pizza (3.65%)
9	Cheese (cheddar) (3.46%)	Beef sandwich (3.48%)	Beef sandwich (5.47%)	Beef sandwich (5.00%)	White bread (2.92%)	White bread (3.01%)
10	Chicken with skin (3.06%)	Cheese (cheddar) (2.80%)	Chicken with skin (4.05%)	Cheese (cheddar) (4.04%)	Pizza (2.75%)	Cooked oatmeal (3.00%)

Amino Acids

In age-adjusted models, amino acid intakes were positively associated with SCD, but after adjusting for total energy intake, these positive associations between amino acid intakes and SCD became inverse or null. In both the NHS and HPFS, higher intake of proline was significantly associated with lower odds of SCD in the fully adjusted model (the pooled multivariable-adjusted OR comparing extreme quintiles was 0.74 [0.66, 0.84]) (Table 14). In the pooled results, amino acid intakes were associated with 11~26% lower odds of SCD.

Table 14: OR (95% CI) for the associations between amino acid intakes and SCD in the NHS and HPFS						
	Q1	Q2	Q3	Q4	Q5	P trend
Alanine						
NHS						
Median intake (g/d)	2.39	3.12	3.65	4.20	5.05	
Age-adjusted model	Ref	1.16 (1.07, 1.25)	1.27 (1.17, 1.37)	1.29 (1.19, 1.40)	1.39 (1.28, 1.51)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.89, 1.05)	0.94 (0.86, 1.03)	0.84 (0.75, 0.92)	0.71 (0.63, 0.81)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.89, 1.05)	0.94 (0.86, 1.04)	0.83 (0.75, 0.92)	0.70 (0.62, 0.80)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.90, 1.07)	0.98 (0.89, 1.07)	0.87 (0.78, 0.97)	0.76 (0.67, 0.87)	<.0001
HPFS						
Median intake (g/d)	3.00	3.72	4.30	4.93	6.02	
Age-adjusted model	Ref	1.18 (1.04, 1.35)	1.20 (1.05, 1.37)	1.40 (1.23, 1.60)	1.88 (1.65, 2.14)	<.0001
Age & Calorie-adjusted model	Ref	1.02 (0.89, 1.17)	0.93 (0.80, 1.08)	0.96 (0.81, 1.13)	1.02 (0.83, 1.24)	0.9721
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.87, 1.14)	0.91 (0.78, 1.06)	0.94 (0.79, 1.10)	0.96 (0.78, 1.18)	0.5885
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.85, 1.13)	0.90 (0.77, 1.04)	0.90 (0.76, 1.07)	0.94 (0.76, 1.16)	0.4766
Meta-analyzed results (MV2)	Ref	0.98 (0.91, 1.06)	0.94 (0.89, 1.03)	0.89 (0.81, 0.97)	0.81 (0.72, 0.91)	0.0002
Arginine						
NHS						
Median intake (g/d)	2.64	3.44	4.01	4.60	5.55	
Age-adjusted model	Ref	1.21 (1.11, 1.31)	1.29 (1.19, 1.39)	1.28 (1.18, 1.39)	1.41 (1.30, 1.53)	<.0001
Age & Calorie-adjusted model	Ref	1.00 (0.92, 1.09)	0.94 (0.85, 1.03)	0.81 (0.73, 0.90)	0.70 (0.61, 0.79)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.01 (0.92, 1.09)	0.98 (0.89, 1.08)	0.84 (0.75, 0.93)	0.74 (0.65, 0.85)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.05 (0.96, 1.14)	1.06 (0.96, 1.17)	0.93 (0.83, 1.04)	0.86 (0.75, 0.99)	0.0145
HPFS						
Median intake (g/d)	3.36	4.14	4.77	5.46	6.65	
Age-adjusted model	Ref	1.12 (0.98, 1.28)	1.20 (1.05, 1.38)	1.36 (1.19, 1.55)	1.73 (1.52, 1.97)	<.0001
Age & Calorie-adjusted model	Ref	0.94 (0.82, 1.08)	0.88 (0.76, 1.02)	0.85 (0.72, 1.00)	0.82 (0.67, 1.01)	0.0527
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.82, 1.08)	0.89 (0.77, 1.04)	0.88 (0.75, 1.04)	0.85 (0.69, 1.04)	0.1238
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.84, 1.11)	0.92 (0.79, 1.07)	0.92 (0.77, 1.10)	0.92 (0.73, 1.15)	0.4453
Meta-analyzed results (MV2)	Ref	1.03 (0.94, 1.09)	1.03 (0.94, 1.09)	0.91 (0.84, 1.03)	0.89 (0.79, 1.00)	0.0151
Asparagine						
NHS						
Median intake (g/d)	1.71	2.21	2.57	2.96	3.55	
Age-adjusted model	Ref	1.17 (1.08, 1.27)	1.23 (1.13, 1.33)	1.29 (1.19, 1.40)	1.26 (1.16, 1.36)	<.0001
Age & Calorie-adjusted model	Ref	0.93 (0.85, 1.01)	0.82 (0.75, 0.90)	0.72 (0.65, 0.80)	0.52 (0.46, 0.59)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.87, 1.03)	0.86 (0.78, 0.95)	0.76 (0.68, 0.85)	0.57 (0.50, 0.65)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.94, 1.12)	0.99 (0.89, 1.09)	0.92 (0.82, 1.04)	0.77 (0.66, 0.89)	0.0003
HPFS						
Median intake (g/d)	2.12	2.60	2.99	3.42	4.14	
Age-adjusted model	Ref	1.11 (0.97, 1.26)	1.21 (1.06, 1.38)	1.30 (1.14, 1.49)	1.68 (1.47, 1.91)	<.0001
Age & Calorie-adjusted model	Ref	0.90 (0.79, 1.04)	0.84 (0.72, 0.98)	0.76 (0.65, 0.90)	0.72 (0.58, 0.88)	0.001
Above+Nondietary factors adjusted (MV1)	Ref	0.92 (0.80, 1.06)	0.86 (0.74, 1.00)	0.81 (0.68, 0.96)	0.77 (0.62, 0.96)	0.0123
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.85, 1.13)	0.94 (0.80, 1.10)	0.91 (0.76, 1.09)	0.95 (0.75, 1.20)	0.5639
Meta-analyzed results (MV2)	Ref	1.00 (0.94, 1.09)	0.97 (0.89, 1.06)	0.91 (0.84, 1.00)	0.81 (0.72, 0.91)	0.0010
Aspartic Acid						
NHS						
Median intake (g/d)	2.12	2.78	3.24	3.74	4.51	
Age-adjusted model	Ref	1.22 (1.12, 1.32)	1.23 (1.13, 1.33)	1.32 (1.22, 1.43)	1.39 (1.28, 1.51)	<.0001
Age & Calorie-adjusted model	Ref	1.03 (0.94, 1.12)	0.92 (0.85, 1.01)	0.88 (0.79, 0.97)	0.74 (0.66, 0.84)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.95, 1.12)	0.94 (0.86, 1.04)	0.88 (0.80, 0.98)	0.75 (0.66, 0.85)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.98, 1.16)	1.01 (0.92, 1.11)	0.96 (0.86, 1.07)	0.85 (0.74, 0.97)	0.006
HPFS						
Median intake (g/d)	2.68	3.33	3.85	4.41	5.40	
Age-adjusted model	Ref	1.08 (0.94, 1.23)	1.15 (1.01, 1.31)	1.25 (1.10, 1.43)	1.78 (1.56, 2.02)	<.0001
Age & Calorie-adjusted model	Ref	0.93 (0.81, 1.06)	0.88 (0.76, 1.02)	0.84 (0.71, 0.98)	0.94 (0.78, 1.14)	0.4879
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.81, 1.06)	0.88 (0.76, 1.01)	0.85 (0.73, 1.00)	0.92 (0.75, 1.12)	0.3656
Above+Dietary factors adjusted (MV2)	Ref	0.93 (0.81, 1.07)	0.89 (0.76, 1.03)	0.87 (0.74, 1.03)	0.97 (0.79, 1.19)	0.7354
Meta-analyzed results (MV2)	Ref	1.03 (0.98, 1.09)	0.98 (0.89, 1.06)	0.94 (0.86, 1.03)	0.89 (0.79, 0.98)	0.0157
Cysteine						
NHS						
Median intake (g/d)	0.83	1.07	1.24	1.43	1.72	
Age-adjusted model	Ref	1.22 (1.12, 1.32)	1.25 (1.15, 1.35)	1.31 (1.21, 1.42)	1.37 (1.26, 1.48)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.89, 1.05)	0.84 (0.76, 0.92)	0.74 (0.66, 0.82)	0.57 (0.50, 0.65)	<.0001

Table 14 (Continued)						
Above+Nondietary factors adjusted (MV1)	Ref	0.99 (0.91, 1.08)	0.90 (0.82, 0.99)	0.78 (0.70, 0.87)	0.64 (0.55, 0.74)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.07 (0.98, 1.17)	1.02 (0.92, 1.13)	0.94 (0.83, 1.05)	0.84 (0.72, 0.98)	0.0102
HPFS						
Median intake (g/d)	1.04	1.28	1.46	1.68	2.03	
Age-adjusted model	Ref	1.06 (0.93, 1.21)	1.30 (1.14, 1.48)	1.34 (1.18, 1.53)	1.64 (1.44, 1.87)	<.0001
Age & Calorie-adjusted model	Ref	0.84 (0.73, 0.97)	0.86 (0.74, 1.01)	0.73 (0.62, 0.87)	0.63 (0.50, 0.79)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.85 (0.74, 0.98)	0.89 (0.77, 1.04)	0.78 (0.65, 0.93)	0.70 (0.55, 0.88)	0.0029
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.78, 1.04)	0.97 (0.83, 1.14)	0.89 (0.73, 1.07)	0.85 (0.67, 1.09)	0.2546
Meta-analyzed results (MV2)	Ref	1.03 (0.94, 1.09)	1.00 (0.91, 1.09)	0.91 (0.84, 1.03)	0.84 (0.74, 0.98)	0.0058
Glutamine						
NHS						
Median intake (g/d)	4.47	5.79	6.74	7.74	9.31	
Age-adjusted model	Ref	1.21 (1.12, 1.32)	1.31 (1.21, 1.42)	1.32 (1.22, 1.44)	1.47 (1.35, 1.60)	<.0001
Age & Calorie-adjusted model	Ref	0.98 (0.90, 1.07)	0.91 (0.82, 1.00)	0.78 (0.70, 0.87)	0.65 (0.56, 0.75)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	1.01 (0.93, 1.10)	0.97 (0.88, 1.07)	0.83 (0.74, 0.93)	0.74 (0.64, 0.86)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.08 (0.99, 1.18)	1.08 (0.97, 1.19)	0.96 (0.85, 1.09)	0.93 (0.79, 1.09)	0.182
HPFS						
Table 14 (Continued)						
Median intake (g/d)	5.47	6.81	7.85	9.04	10.97	
Age-adjusted model	Ref	1.17 (1.03, 1.34)	1.29 (1.13, 1.47)	1.52 (1.33, 1.73)	1.59 (1.39, 1.81)	<.0001
Age & Calorie-adjusted model	Ref	0.90 (0.78, 1.03)	0.81 (0.69, 0.94)	0.76 (0.64, 0.90)	0.53 (0.42, 0.66)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.92 (0.80, 1.06)	0.85 (0.73, 1.00)	0.82 (0.69, 0.99)	0.62 (0.49, 0.78)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.82, 1.10)	0.89 (0.76, 1.05)	0.87 (0.72, 1.05)	0.68 (0.53, 0.88)	0.0036
Meta-analyzed results (MV2)	Ref	1.03 (0.98, 1.13)	1.03 (0.94, 1.13)	0.94 (0.84, 1.03)	0.86 (0.74, 0.98)	0.0055
Glutamic Acid						
NHS						
Median intake (g/d)	4.29	5.64	6.59	7.61	9.21	
Age-adjusted model	Ref	1.18 (1.09, 1.27)	1.22 (1.12, 1.32)	1.29 (1.19, 1.40)	1.29 (1.19, 1.40)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.89, 1.05)	0.88 (0.80, 0.96)	0.80 (0.73, 0.89)	0.62 (0.55, 0.70)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.90, 1.07)	0.90 (0.82, 0.99)	0.82 (0.74, 0.90)	0.64 (0.57, 0.73)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.93, 1.11)	0.97 (0.88, 1.06)	0.90 (0.81, 1.00)	0.75 (0.65, 0.85)	<.0001
HPFS						
Median intake (g/d)	5.29	6.60	7.64	8.78	10.73	
Age-adjusted model	Ref	1.16 (1.01, 1.32)	1.23 (1.08, 1.41)	1.38 (1.21, 1.58)	1.79 (1.57, 2.04)	<.0001
Age & Calorie-adjusted model	Ref	1.00 (0.87, 1.14)	0.94 (0.81, 1.08)	0.92 (0.78, 1.08)	0.92 (0.76, 1.13)	0.341
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.85, 1.12)	0.93 (0.80, 1.07)	0.90 (0.77, 1.07)	0.90 (0.73, 1.10)	0.2456
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.84, 1.12)	0.93 (0.80, 1.08)	0.90 (0.76, 1.07)	0.91 (0.73, 1.13)	0.3549
Meta-analyzed results (MV2)	Ref	1.00 (0.94, 1.09)	0.98 (0.89, 1.03)	0.89 (0.81, 1.00)	0.79 (0.70, 0.89)	<.0001
Glycine						
NHS						
Median intake (g/d)	1.89	2.49	2.90	3.34	4.04	
Age-adjusted model	Ref	1.15 (1.06, 1.25)	1.26 (1.17, 1.37)	1.23 (1.14, 1.34)	1.44 (1.33, 1.56)	<.0001
Age & Calorie-adjusted model	Ref	0.99 (0.91, 1.07)	0.97 (0.89, 1.07)	0.84 (0.76, 0.93)	0.81 (0.71, 0.91)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.99 (0.91, 1.07)	0.98 (0.90, 1.08)	0.84 (0.76, 0.93)	0.80 (0.71, 0.90)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.93, 1.10)	1.02 (0.93, 1.12)	0.89 (0.80, 0.99)	0.86 (0.76, 0.98)	0.0062
HPFS						
Median intake (g/d)	2.42	3.01	3.48	4.00	4.89	
Age-adjusted model	Ref	1.13 (0.99, 1.29)	1.23 (1.07, 1.40)	1.34 (1.18, 1.53)	1.79 (1.57, 2.04)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.85, 1.12)	0.94 (0.82, 1.09)	0.91 (0.78, 1.07)	0.96 (0.79, 1.16)	0.5923
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.84, 1.11)	0.94 (0.81, 1.09)	0.92 (0.79, 1.08)	0.96 (0.79, 1.16)	0.5995
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.84, 1.11)	0.96 (0.82, 1.11)	0.93 (0.79, 1.09)	0.99 (0.81, 1.21)	0.8672
Meta-analyzed results (MV2)	Ref	0.94 (0.94, 1.06)	1.00 (0.94, 1.09)	0.89 (0.81, 0.98)	0.89 (0.81, 1.00)	0.0214
Histidine						
NHS						
Median intake (g/d)	1.38	1.80	2.10	2.41	2.90	
Age-adjusted model	Ref	1.19 (1.10, 1.29)	1.28 (1.18, 1.38)	1.34 (1.24, 1.46)	1.36 (1.25, 1.47)	<.0001
Age & Calorie-adjusted model	Ref	0.98 (0.90, 1.06)	0.91 (0.83, 1.00)	0.82 (0.74, 0.92)	0.64 (0.56, 0.73)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.90, 1.06)	0.94 (0.85, 1.03)	0.83 (0.75, 0.93)	0.66 (0.58, 0.75)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.01 (0.93, 1.10)	0.99 (0.90, 1.10)	0.91 (0.81, 1.02)	0.76 (0.66, 0.87)	<.0001
HPFS						
Median intake (g/d)	1.73	2.13	2.46	2.81	3.42	
Age-adjusted model	Ref	1.15 (1.01, 1.32)	1.25 (1.09, 1.42)	1.38 (1.21, 1.58)	1.78 (1.56, 2.03)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.84, 1.11)	0.91 (0.79, 1.06)	0.87 (0.73, 1.03)	0.85 (0.69, 1.04)	0.0852
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.83, 1.10)	0.91 (0.78, 1.06)	0.87 (0.74, 1.03)	0.84 (0.68, 1.04)	0.0882
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.82, 1.09)	0.91 (0.78, 1.07)	0.87 (0.73, 1.04)	0.85 (0.68, 1.07)	0.1355
Meta-analyzed results (MV2)	Ref	1.00 (0.91, 1.06)	0.98 (0.89, 1.06)	0.89 (0.81, 1.00)	0.79 (0.70, 0.89)	<.0001
Isoleucine						

Table 14 (Continued)						
NHS						
Median intake (g/d)	2.30	2.99	3.48	4.01	4.81	
Age-adjusted model	Ref	1.15 (1.07, 1.25)	1.26 (1.17, 1.37)	1.28 (1.18, 1.39)	1.31 (1.21, 1.42)	<.0001
Age & Calorie-adjusted model	Ref	0.92 (0.84, 1.00)	0.85 (0.77, 0.93)	0.72 (0.65, 0.80)	0.54 (0.47, 0.62)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.86, 1.02)	0.87 (0.79, 0.95)	0.74 (0.66, 0.82)	0.58 (0.50, 0.66)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.90, 1.07)	0.94 (0.85, 1.04)	0.83 (0.74, 0.93)	0.69 (0.60, 0.80)	<.0001
HPFS						
Median intake (g/d)	2.83	3.49	4.03	4.61	5.60	
Age-adjusted model	Ref	1.16 (1.01, 1.32)	1.26 (1.10, 1.44)	1.42 (1.24, 1.62)	1.81 (1.59, 2.06)	<.0001
Age & Calorie-adjusted model	Ref	0.96 (0.84, 1.11)	0.91 (0.78, 1.06)	0.87 (0.74, 1.04)	0.84 (0.67, 1.04)	0.0922
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.83, 1.10)	0.92 (0.78, 1.07)	0.87 (0.73, 1.04)	0.85 (0.68, 1.06)	0.1276
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.83, 1.10)	0.93 (0.79, 1.09)	0.88 (0.74, 1.06)	0.89 (0.70, 1.13)	0.2902
Meta-analyzed results (MV2)	Ref	0.98 (0.91, 1.03)	0.94 (0.86, 1.03)	0.84 (0.76, 0.94)	0.74 (0.66, 0.84)	<.0001
Leucine						
NHS						
Median intake (g/d)	4.26	5.56	6.47	7.46	8.97	
Age-adjusted model	Ref	1.14 (1.05, 1.23)	1.24 (1.14, 1.34)	1.29 (1.19, 1.40)	1.30 (1.20, 1.41)	<.0001
Age & Calorie-adjusted model	Ref	0.92 (0.85, 1.00)	0.86 (0.78, 0.94)	0.77 (0.69, 0.85)	0.58 (0.51, 0.66)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.85, 1.01)	0.87 (0.80, 0.96)	0.77 (0.69, 0.86)	0.61 (0.53, 0.70)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.89, 1.06)	0.95 (0.86, 1.04)	0.87 (0.77, 0.97)	0.73 (0.63, 0.84)	<.0001
HPFS						
Median intake (g/d)	5.23	6.47	7.47	8.56	10.41	
Age-adjusted model	Ref	1.16 (1.02, 1.33)	1.28 (1.12, 1.46)	1.40 (1.22, 1.59)	1.81 (1.59, 2.06)	<.0001
Table 14 (Continued)						
Age & Calorie-adjusted model	Ref	0.98 (0.85, 1.12)	0.93 (0.80, 1.09)	0.88 (0.75, 1.04)	0.86 (0.70, 1.07)	0.1229
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.83, 1.10)	0.93 (0.79, 1.08)	0.87 (0.73, 1.03)	0.85 (0.68, 1.06)	0.1096
Above+Dietary factors adjusted (MV2)	Ref	0.95 (0.83, 1.10)	0.93 (0.79, 1.09)	0.87 (0.73, 1.04)	0.87 (0.69, 1.10)	0.1866
Meta-analyzed results (MV2)	Ref	0.98 (0.89, 1.03)	0.94 (0.86, 1.03)	0.86 (0.79, 0.94)	0.76 (0.68, 0.86)	<.0001
Lysine						
NHS						
Median intake (g/d)	3.10	4.08	4.77	5.51	6.65	
Age-adjusted model	Ref	1.18 (1.09, 1.27)	1.22 (1.13, 1.32)	1.28 (1.18, 1.39)	1.32 (1.22, 1.43)	<.0001
Age & Calorie-adjusted model	Ref	0.99 (0.91, 1.07)	0.91 (0.84, 1.00)	0.83 (0.76, 0.92)	0.69 (0.61, 0.77)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.99 (0.91, 1.07)	0.92 (0.84, 1.01)	0.84 (0.76, 0.92)	0.69 (0.61, 0.77)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.94, 1.11)	0.98 (0.89, 1.08)	0.91 (0.82, 1.01)	0.78 (0.68, 0.89)	<.0001
HPFS						
Median intake (g/d)	3.85	4.81	5.57	6.41	7.84	
Age-adjusted model	Ref	1.20 (1.05, 1.37)	1.23 (1.08, 1.40)	1.35 (1.18, 1.54)	1.83 (1.61, 2.09)	<.0001
Age & Calorie-adjusted model	Ref	1.04 (0.91, 1.19)	0.95 (0.83, 1.10)	0.92 (0.79, 1.08)	1.00 (0.82, 1.20)	0.6572
Above+Nondietary factors adjusted (MV1)	Ref	1.03 (0.90, 1.18)	0.95 (0.82, 1.10)	0.91 (0.78, 1.07)	0.95 (0.78, 1.15)	0.3565
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.89, 1.18)	0.96 (0.83, 1.12)	0.92 (0.78, 1.08)	0.98 (0.80, 1.20)	0.6015
Meta-analyzed results (MV2)	Ref	1.03 (0.94, 1.09)	0.98 (0.91, 1.06)	0.91 (0.84, 1.00)	0.84 (0.74, 0.94)	0.0004
Methionine						
NHS						
Median intake (g/d)	1.18	1.54	1.80	2.07	2.49	
Age-adjusted model	Ref	1.17 (1.08, 1.26)	1.25 (1.15, 1.35)	1.32 (1.21, 1.43)	1.35 (1.25, 1.47)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.87, 1.03)	0.87 (0.80, 0.96)	0.79 (0.71, 0.87)	0.61 (0.54, 0.70)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.04)	0.90 (0.82, 0.99)	0.80 (0.72, 0.89)	0.63 (0.55, 0.72)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.91, 1.08)	0.95 (0.86, 1.05)	0.87 (0.77, 0.97)	0.71 (0.62, 0.83)	<.0001
HPFS						
Median intake (g/d)	1.47	1.82	2.10	2.41	2.93	
Age-adjusted model	Ref	1.21 (1.06, 1.38)	1.25 (1.10, 1.43)	1.39 (1.22, 1.59)	1.89 (1.66, 2.15)	<.0001
Age & Calorie-adjusted model	Ref	1.03 (0.89, 1.18)	0.93 (0.80, 1.08)	0.89 (0.75, 1.06)	0.93 (0.75, 1.16)	0.3315
Above+Nondietary factors adjusted (MV1)	Ref	1.00 (0.87, 1.15)	0.92 (0.79, 1.08)	0.88 (0.74, 1.05)	0.91 (0.73, 1.13)	0.2608
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.85, 1.13)	0.91 (0.78, 1.06)	0.86 (0.71, 1.02)	0.88 (0.70, 1.11)	0.1945
Meta-analyzed results (MV2)	Ref	1.00 (0.91, 1.06)	0.94 (0.86, 1.03)	0.86 (0.79, 0.94)	0.76 (0.68, 0.86)	<.0001
Phenylalanine						
NHS						
Median intake (g/d)	2.36	3.05	3.53	4.06	4.86	
Age-adjusted model	Ref	1.16 (1.07, 1.26)	1.30 (1.20, 1.41)	1.26 (1.16, 1.37)	1.40 (1.29, 1.52)	<.0001
Age & Calorie-adjusted model	Ref	0.94 (0.86, 1.02)	0.90 (0.82, 0.99)	0.74 (0.66, 0.82)	0.61 (0.54, 0.70)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.86, 1.02)	0.92 (0.83, 1.01)	0.75 (0.67, 0.83)	0.63 (0.55, 0.73)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.90, 1.07)	1.00 (0.90, 1.10)	0.84 (0.75, 0.94)	0.76 (0.65, 0.88)	0.0001
HPFS						
Median intake (g/d)	2.94	3.61	4.15	4.74	5.73	
Age-adjusted model	Ref	1.10 (0.96, 1.26)	1.28 (1.12, 1.46)	1.42 (1.24, 1.62)	1.73 (1.52, 1.97)	<.0001
Age & Calorie-adjusted model	Ref	0.90 (0.79, 1.04)	0.90 (0.77, 1.05)	0.84 (0.71, 1.00)	0.75 (0.60, 0.93)	0.0124
Above+Nondietary factors adjusted (MV1)	Ref	0.90 (0.78, 1.04)	0.89 (0.76, 1.04)	0.84 (0.70, 1.00)	0.74 (0.59, 0.93)	0.0119

Table 14 (Continued)						
Above+Dietary factors adjusted (MV2)	Ref	0.91 (0.78, 1.04)	0.90 (0.77, 1.05)	0.85 (0.71, 1.02)	0.77 (0.60, 0.98)	0.0379
Meta-analyzed results (MV2)	Ref	0.97 (0.89, 1.03)	0.97 (0.89, 1.06)	0.84 (0.76, 0.94)	0.76 (0.68, 0.86)	<.0001
Proline						
NHS						
Median intake (g/d)	3.42	4.46	5.20	5.98	7.20	
Age-adjusted model	Ref	1.17 (1.08, 1.27)	1.26 (1.16, 1.36)	1.33 (1.22, 1.44)	1.36 (1.25, 1.48)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.87, 1.03)	0.88 (0.80, 0.97)	0.80 (0.72, 0.89)	0.62 (0.54, 0.71)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.04)	0.89 (0.81, 0.98)	0.80 (0.72, 0.89)	0.64 (0.56, 0.73)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.91, 1.09)	0.95 (0.86, 1.05)	0.89 (0.79, 0.99)	0.74 (0.64, 0.86)	<.0001
HPFS						
Median intake (g/d)	4.22	5.22	6.02	6.91	8.39	
Age-adjusted model	Ref	1.03 (0.90, 1.17)	1.25 (1.10, 1.43)	1.34 (1.17, 1.52)	1.71 (1.50, 1.95)	<.0001
Age & Calorie-adjusted model	Ref	0.85 (0.74, 0.97)	0.89 (0.76, 1.03)	0.80 (0.68, 0.95)	0.76 (0.61, 0.94)	0.0186
Above+Nondietary factors adjusted (MV1)	Ref	0.83 (0.72, 0.96)	0.88 (0.76, 1.03)	0.79 (0.66, 0.94)	0.75 (0.60, 0.93)	0.0165
Above+Dietary factors adjusted (MV2)	Ref	0.82 (0.71, 0.94)	0.87 (0.74, 1.02)	0.77 (0.64, 0.92)	0.73 (0.58, 0.93)	0.017
Meta-analyzed results (MV2)	Ref	0.94 (0.89, 1.00)	0.91 (0.86, 1.00)	0.86 (0.76, 0.94)	0.74 (0.66, 0.84)	<.0001
Serine						
NHS						
Median intake (g/d)	2.75	3.57	4.16	4.78	5.73	
Age-adjusted model	Ref	1.16 (1.07, 1.25)	1.27 (1.17, 1.37)	1.30 (1.20, 1.41)	1.33 (1.23, 1.45)	<.0001
Age & Calorie-adjusted model	Ref	0.93 (0.85, 1.01)	0.87 (0.79, 0.96)	0.76 (0.68, 0.84)	0.58 (0.51, 0.66)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.86, 1.02)	0.89 (0.81, 0.98)	0.77 (0.69, 0.86)	0.61 (0.53, 0.70)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.90, 1.07)	0.96 (0.87, 1.06)	0.86 (0.77, 0.96)	0.72 (0.62, 0.83)	<.0001
HPFS						
Median intake (g/d)	3.41	4.20	4.84	5.54	6.73	
Age-adjusted model	Ref	1.18 (1.03, 1.35)	1.27 (1.11, 1.45)	1.48 (1.30, 1.69)	1.84 (1.62, 2.10)	<.0001
Age & Calorie-adjusted model	Ref	1.00 (0.87, 1.15)	0.94 (0.81, 1.09)	0.95 (0.80, 1.12)	0.90 (0.72, 1.12)	0.2965
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.85, 1.13)	0.94 (0.80, 1.09)	0.93 (0.78, 1.11)	0.88 (0.70, 1.10)	0.2411
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.86, 1.14)	0.95 (0.81, 1.11)	0.95 (0.79, 1.13)	0.92 (0.72, 1.16)	0.4469
Meta-analyzed results (MV2)	Ref	0.98 (0.91, 1.06)	0.94 (0.89, 1.03)	0.89 (0.81, 0.97)	0.76 (0.68, 0.86)	<.0001
Threonine						
NHS						
Median intake (g/d)	2.07	2.70	3.15	3.62	4.34	
Age-adjusted model	Ref	1.13 (1.04, 1.22)	1.24 (1.14, 1.34)	1.29 (1.19, 1.39)	1.35 (1.24, 1.47)	<.0001
Age & Calorie-adjusted model	Ref	0.92 (0.85, 1.00)	0.87 (0.80, 0.96)	0.78 (0.70, 0.86)	0.62 (0.55, 0.71)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.85, 1.01)	0.88 (0.80, 0.97)	0.77 (0.70, 0.86)	0.63 (0.55, 0.72)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.96 (0.88, 1.05)	0.93 (0.84, 1.02)	0.83 (0.74, 0.93)	0.70 (0.61, 0.81)	<.0001
HPFS						
Median intake (g/d)	2.58	3.18	3.68	4.22	5.13	
Age-adjusted model	Ref	1.14 (0.99, 1.30)	1.23 (1.08, 1.40)	1.37 (1.20, 1.56)	1.81 (1.59, 2.06)	<.0001
Age & Calorie-adjusted model	Ref	0.96 (0.83, 1.10)	0.91 (0.78, 1.05)	0.87 (0.73, 1.03)	0.87 (0.71, 1.08)	0.1646
Above+Nondietary factors adjusted (MV1)	Ref	0.94 (0.82, 1.08)	0.90 (0.77, 1.04)	0.85 (0.71, 1.00)	0.84 (0.68, 1.05)	0.0921
Above+Dietary factors adjusted (MV2)	Ref	0.93 (0.80, 1.07)	0.88 (0.76, 1.03)	0.82 (0.69, 0.98)	0.83 (0.66, 1.04)	0.0798
Meta-analyzed results (MV2)	Ref	0.94 (0.89, 1.03)	0.91 (0.84, 1.00)	0.84 (0.76, 0.91)	0.74 (0.66, 0.84)	<.0001
Tryptophan						
NHS						
Median intake (g/d)	0.61	0.79	0.92	1.06	1.27	
Age-adjusted model	Ref	1.16 (1.07, 1.25)	1.25 (1.16, 1.36)	1.34 (1.24, 1.46)	1.32 (1.22, 1.44)	<.0001
Age & Calorie-adjusted model	Ref	0.95 (0.87, 1.03)	0.90 (0.82, 0.98)	0.83 (0.75, 0.92)	0.63 (0.56, 0.72)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.87, 1.03)	0.91 (0.83, 0.99)	0.83 (0.75, 0.92)	0.64 (0.56, 0.73)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	0.98 (0.90, 1.06)	0.96 (0.87, 1.06)	0.90 (0.81, 1.01)	0.73 (0.63, 0.84)	<.0001
HPFS						
Median intake (g/d)	0.75	0.92	1.07	1.22	1.49	
Age-adjusted model	Ref	1.19 (1.04, 1.36)	1.25 (1.09, 1.43)	1.40 (1.23, 1.60)	1.84 (1.62, 2.10)	<.0001
Age & Calorie-adjusted model	Ref	1.02 (0.89, 1.17)	0.94 (0.81, 1.09)	0.91 (0.77, 1.08)	0.93 (0.76, 1.14)	0.3315
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.85, 1.13)	0.92 (0.79, 1.06)	0.88 (0.75, 1.04)	0.87 (0.71, 1.08)	0.1477
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.84, 1.11)	0.91 (0.78, 1.07)	0.87 (0.73, 1.04)	0.88 (0.70, 1.10)	0.195
Meta-analyzed results (MV2)	Ref	0.98 (0.91, 1.06)	0.94 (0.86, 1.03)	0.89 (0.81, 0.97)	0.76 (0.68, 0.86)	<.0001
Tyrosine						
NHS						
Median intake (g/d)	1.88	2.46	2.87	3.30	3.98	
Age-adjusted model	Ref	1.20 (1.11, 1.30)	1.29 (1.19, 1.40)	1.32 (1.22, 1.43)	1.35 (1.24, 1.46)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.89, 1.05)	0.89 (0.81, 0.98)	0.77 (0.70, 0.86)	0.59 (0.52, 0.68)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.89, 1.06)	0.91 (0.82, 1.00)	0.78 (0.70, 0.87)	0.62 (0.54, 0.71)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.09)	0.96 (0.87, 1.06)	0.85 (0.76, 0.95)	0.69 (0.60, 0.81)	<.0001
HPFS						
Median intake (g/d)	2.34	2.89	3.33	3.83	4.67	

Table 14 (Continued)						
Age-adjusted model	Ref	1.17 (1.02, 1.34)	1.34 (1.18, 1.53)	1.45 (1.27, 1.65)	1.92 (1.68, 2.18)	<.0001
Age & Calorie-adjusted model	Ref	1.00 (0.87, 1.15)	1.02 (0.87, 1.18)	0.96 (0.81, 1.14)	1.00 (0.80, 1.24)	0.8665
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.85, 1.13)	1.00 (0.86, 1.17)	0.96 (0.80, 1.14)	0.98 (0.78, 1.22)	0.7995
Above+Dietary factors adjusted (MV2)	Ref	0.96 (0.84, 1.11)	0.98 (0.84, 1.15)	0.93 (0.78, 1.12)	0.95 (0.75, 1.21)	0.6568
Meta-analyzed results (MV2)	Ref	1.00 (0.91, 1.06)	0.98 (0.89, 1.06)	0.86 (0.79, 0.98)	0.76 (0.68, 0.86)	<.0001
Valine						
NHS						
Median intake (g/d)	2.59	3.37	3.92	4.52	5.43	
Age-adjusted model	Ref	1.19 (1.09, 1.28)	1.29 (1.19, 1.39)	1.34 (1.23, 1.45)	1.34 (1.24, 1.46)	<.0001
Age & Calorie-adjusted model	Ref	0.96 (0.88, 1.05)	0.90 (0.82, 0.99)	0.80 (0.72, 0.89)	0.61 (0.54, 0.70)	<.0001
Above+Nondietary factors adjusted (MV1)	Ref	0.96 (0.88, 1.05)	0.91 (0.83, 1.00)	0.81 (0.72, 0.90)	0.63 (0.55, 0.72)	<.0001
Above+Dietary factors adjusted (MV2)	Ref	1.00 (0.92, 1.09)	0.97 (0.88, 1.07)	0.89 (0.80, 1.00)	0.73 (0.64, 0.85)	<.0001
HPFS						
Median intake (g/d)	3.19	3.94	4.55	5.21	6.34	
Age-adjusted model	Ref	1.15 (1.01, 1.32)	1.28 (1.12, 1.47)	1.42 (1.25, 1.62)	1.82 (1.60, 2.08)	<.0001
Age & Calorie-adjusted model	Ref	0.97 (0.85, 1.12)	0.94 (0.81, 1.10)	0.90 (0.76, 1.07)	0.88 (0.71, 1.10)	0.2208
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.83, 1.10)	0.93 (0.80, 1.09)	0.90 (0.76, 1.06)	0.87 (0.70, 1.08)	0.1898
Above+Dietary factors adjusted (MV2)	Ref	0.94 (0.82, 1.08)	0.93 (0.79, 1.08)	0.89 (0.74, 1.06)	0.87 (0.68, 1.09)	0.2226
Meta-analyzed results (MV2)	Ref	0.98 (0.91, 1.06)	0.97 (0.89, 1.03)	0.89 (0.81, 0.97)	0.76 (0.68, 0.86)	<.0001

Age-adjusted model: adjusted for age (at SCD measurement, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1 (non-dietary factors): NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (METs-hr/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2 (dietary factors): other than variables adjusted in MV1, further adjusted for trans-fat, saturated fat, MUFA, PUFA, carotenoids, anthocyanins, vitamin c, d, and e (quintiles)
Abbreviations: MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids;

Protein Food Group Analysis

Although positive associations were observed for unprocessed red meat, processed meat, chicken with skin, dairy, eggs, and nuts in the age-adjusted models, further adjustment of total energy intake and major dietary factors attenuated these associations (Table 15). In the fully adjusted model, chicken with skin remained positively associated with SCD in both the NHS and HPFS (the pooled multivariable-adjusted OR for each three servings/week increase in intake was 1.46 [1.35, 1.59]). In contrast, adjusting for total energy intake strengthened the inverse associations for chicken without skin, fish, and beans/legumes. In the fully adjusted model, higher intakes of chicken without skin, fish, and beans/legumes were significantly associated with lower odds of SCD in the pooled results (multivariable-adjusted ORs for each three servings/week increase in intake were 0.86 [0.81, 0.91] for chicken without skin, 0.93 [0.89, 0.97] for fish, and 0.63 [0.54, 0.70] for beans/legumes.)

Table 15: OR (95% CI) for the associations between intakes of protein food groups and SCD in the NHS and HPFS							
	Q1	Q2	Q3	Q4	Q5	P trend	Continuous [a]
Unprocessed red meat							
NHS							
Median intake (servings/d)	0.42	0.69	0.89	1.10	1.46		
Age-adjusted model	Ref	1.17 (1.08, 1.27)	1.23 (1.13, 1.33)	1.39 (1.28, 1.51)	1.65 (1.52, 1.79)	<.0001	1.19 (1.16, 1.22)
Age & Calorie-adjusted model	Ref	1.12 (1.03, 1.21)	1.13 (1.04, 1.22)	1.22 (1.12, 1.33)	1.35 (1.23, 1.47)	<.0001	1.12 (1.09, 1.15)
Above+Nondietary factors adjusted (MV1)	Ref	1.09 (1.00, 1.18)	1.05 (0.96, 1.14)	1.11 (1.02, 1.21)	1.16 (1.05, 1.27)	0.0034	1.06 (1.03, 1.09)
Above+Dietary factors adjusted (MV2)	Ref	1.03 (0.95, 1.12)	0.96 (0.88, 1.05)	0.99 (0.91, 1.09)	0.98 (0.89, 1.08)	0.5670	1.00 (0.97, 1.04)
HPFS							
Median intake (servings/d)	0.20	0.44	0.64	0.89	1.33		
Age-adjusted model	Ref	1.38 (1.21, 1.58)	1.35 (1.18, 1.54)	1.54 (1.35, 1.76)	2.15 (1.88, 2.45)	<.0001	1.26 (1.21, 1.31)
Age & Calorie-adjusted model	Ref	1.33 (1.16, 1.52)	1.22 (1.07, 1.40)	1.32 (1.15, 1.51)	1.63 (1.41, 1.88)	<.0001	1.15 (1.10, 1.20)
Above+Nondietary factors adjusted (MV1)	Ref	1.23 (1.07, 1.40)	1.10 (0.96, 1.26)	1.10 (0.96, 1.27)	1.22 (1.05, 1.42)	0.0736	1.05 (1.00, 1.10)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.97, 1.27)	0.95 (0.82, 1.09)	0.92 (0.79, 1.06)	0.97 (0.83, 1.14)	0.2459	0.98 (0.93, 1.03)
Meta-analyzed results (MV2)	Ref	1.06 (0.97, 1.13)	0.97 (0.89, 1.03)	0.97 (0.91, 1.06)	0.97 (0.91, 1.06)	0.2684	1.00 (0.97, 1.02)
Processed Meat							
NHS							
Median intake (servings/d)	0.10	0.19	0.29	0.42	0.67		
Age-adjusted model	Ref	1.05 (0.96, 1.14)	1.22 (1.13, 1.33)	1.42 (1.31, 1.54)	1.62 (1.50, 1.76)	<.0001	1.34 (1.28, 1.39)
Age & Calorie-adjusted model	Ref	1.02 (0.94, 1.10)	1.16 (1.07, 1.26)	1.30 (1.19, 1.41)	1.39 (1.27, 1.51)	<.0001	1.22 (1.17, 1.28)
Above+Nondietary factors adjusted (MV1)	Ref	0.97 (0.89, 1.05)	1.04 (0.96, 1.13)	1.13 (1.04, 1.23)	1.17 (1.07, 1.28)	<.0001	1.13 (1.07, 1.18)
Above+Dietary factors adjusted (MV2)	Ref	0.92 (0.85, 1.00)	0.96 (0.88, 1.04)	1.01 (0.93, 1.11)	1.00 (0.91, 1.10)	0.2714	1.04 (0.99, 1.09)
HPFS							
Median intake (servings/d)	0.03	0.11	0.21	0.35	0.64		
Age-adjusted model	Ref	1.34 (1.17, 1.53)	1.34 (1.17, 1.53)	1.64 (1.44, 1.88)	2.08 (1.82, 2.37)	<.0001	1.40 (1.32, 1.48)
Age & Calorie-adjusted model	Ref	1.29 (1.13, 1.48)	1.25 (1.09, 1.43)	1.45 (1.26, 1.66)	1.67 (1.45, 1.91)	<.0001	1.25 (1.18, 1.33)
Above+Nondietary factors adjusted (MV1)	Ref	1.20 (1.05, 1.38)	1.09 (0.95, 1.25)	1.23 (1.07, 1.41)	1.30 (1.13, 1.51)	0.0012	1.12 (1.06, 1.20)
Above+Dietary factors adjusted (MV2)	Ref	1.11 (0.96, 1.27)	0.96 (0.83, 1.10)	1.04 (0.90, 1.20)	1.05 (0.91, 1.23)	0.6946	1.04 (0.97, 1.11)
Meta-analyzed results (MV2)	Ref	0.97 (0.89, 1.03)	0.97 (0.89, 1.03)	1.03 (0.94, 1.09)	1.03 (0.94, 1.09)	0.2576	1.04 (1.00, 1.08)
Chicken with Skin							
NHS							
Median intake (servings/d)	0.02	0.04	0.10	0.17	0.29		
Age-adjusted model	Ref	1.12 (1.03, 1.21)	1.27 (1.17, 1.37)	1.37 (1.26, 1.49)	1.64 (1.51, 1.78)	<.0001	1.86 (1.70, 2.04)
Age & Calorie-adjusted model	Ref	1.11 (1.03, 1.21)	1.25 (1.16, 1.36)	1.32 (1.22, 1.44)	1.51 (1.39, 1.64)	<.0001	1.66 (1.51, 1.82)
Above+Nondietary factors adjusted (MV1)	Ref	1.08 (1.00, 1.17)	1.21 (1.12, 1.32)	1.25 (1.15, 1.36)	1.43 (1.31, 1.56)	<.0001	1.56 (1.42, 1.72)
Above+Dietary factors adjusted (MV2)	Ref	1.06 (0.98, 1.15)	1.17 (1.08, 1.27)	1.19 (1.10, 1.30)	1.38 (1.26, 1.50)	<.0001	1.51 (1.37, 1.67)
HPFS							
Median intake (servings/d)	0	0.03	0.08	0.14	0.27		
Age-adjusted model	Ref	1.51 (1.32, 1.72)	1.60 (1.40, 1.83)	1.77 (1.55, 2.03)	1.89 (1.66, 2.16)	<.0001	1.71 (1.48, 1.97)
Age & Calorie-adjusted model	Ref	1.48 (1.30, 1.69)	1.54 (1.35, 1.76)	1.65 (1.44, 1.88)	1.63 (1.42, 1.87)	<.0001	1.40 (1.21, 1.63)

Table 15 (Continued)							
Above+Nondietary factors adjusted (MV1)	Ref	1.43 (1.25, 1.63)	1.42 (1.24, 1.62)	1.53 (1.34, 1.76)	1.55 (1.35, 1.78)	<.0001	1.37 (1.17, 1.59)
Above+Dietary factors adjusted (MV2)	Ref	1.36 (1.19, 1.56)	1.31 (1.15, 1.50)	1.44 (1.25, 1.65)	1.49 (1.29, 1.71)	<.0001	1.34 (1.15, 1.56)
Meta-analyzed results (MV2)	Ref	1.13 (1.06, 1.20)	1.20 (1.13, 1.31)	1.27 (1.16, 1.35)	1.39 (1.31, 1.52)	<.0001	1.46 (1.35, 1.59)
Chicken without Skin							
NHS							
Median intake (servings/d)	0.11	0.20	0.30	0.39	0.52		
Age-adjusted model	Ref	0.93 (0.86, 1.00)	0.93 (0.86, 1.01)	0.82 (0.76, 0.89)	0.76 (0.70, 0.82)	<.0001	0.81 (0.76, 0.86)
Age & Calorie-adjusted model	Ref	0.90 (0.84, 0.98)	0.89 (0.82, 0.96)	0.76 (0.71, 0.83)	0.68 (0.62, 0.73)	<.0001	0.73 (0.68, 0.78)
Above+Nondietary factors adjusted (MV1)	Ref	0.91 (0.84, 0.98)	0.90 (0.83, 0.98)	0.79 (0.73, 0.86)	0.70 (0.64, 0.76)	<.0001	0.75 (0.70, 0.80)
Above+Dietary factors adjusted (MV2)	Ref	0.94 (0.87, 1.02)	0.96 (0.88, 1.04)	0.87 (0.80, 0.94)	0.79 (0.73, 0.87)	<.0001	0.84 (0.78, 0.90)
HPFS							
Median intake (servings/d)	0.05	0.12	0.21	0.30	0.43		
Age-adjusted model	Ref	0.93 (0.82, 1.06)	0.78 (0.69, 0.89)	0.77 (0.68, 0.88)	0.71 (0.62, 0.81)	<.0001	0.77 (0.69, 0.86)
Age & Calorie-adjusted model	Ref	0.93 (0.82, 1.06)	0.76 (0.67, 0.87)	0.74 (0.65, 0.85)	0.65 (0.57, 0.74)	<.0001	0.71 (0.64, 0.79)
Above+Nondietary factors adjusted (MV1)	Ref	0.98 (0.86, 1.12)	0.82 (0.72, 0.93)	0.81 (0.71, 0.92)	0.74 (0.65, 0.84)	<.0001	0.78 (0.70, 0.87)
Above+Dietary factors adjusted (MV2)	Ref	1.02 (0.90, 1.16)	0.88 (0.77, 1.00)	0.90 (0.79, 1.03)	0.87 (0.75, 0.99)	0.0097	0.90 (0.80, 1.01)
Meta-analyzed results (MV2)	Ref	0.97 (0.89, 1.03)	0.94 (0.86, 1.00)	0.89 (0.81, 0.94)	0.81 (0.76, 0.89)	<.0001	0.86 (0.81, 0.91)
Fish							
NHS							
Median intake (servings/d)	0.20	0.32	0.43	0.57	0.81		
Age-adjusted model	Ref	0.98 (0.91, 1.06)	0.93 (0.86, 1.01)	0.88 (0.81, 0.96)	0.76 (0.70, 0.82)	<.0001	0.86 (0.82, 0.90)
Age & Calorie-adjusted model	Ref	0.93 (0.86, 1.01)	0.86 (0.79, 0.93)	0.78 (0.72, 0.85)	0.63 (0.58, 0.69)	<.0001	0.78 (0.74, 0.81)
Above+Nondietary factors adjusted (MV1)	Ref	0.95 (0.88, 1.03)	0.89 (0.83, 0.97)	0.84 (0.77, 0.91)	0.69 (0.63, 0.75)	<.0001	0.81 (0.78, 0.85)
Above+Dietary factors adjusted (MV2)	Ref	0.99 (0.91, 1.07)	0.97 (0.89, 1.05)	0.94 (0.86, 1.02)	0.83 (0.75, 0.90)	<.0001	0.90 (0.86, 0.94)
HPFS							
Median intake (servings/d)	0.11	0.22	0.32	0.46	0.74		
Age-adjusted model	Ref	0.94 (0.83, 1.08)	1.01 (0.88, 1.15)	0.77 (0.67, 0.87)	0.75 (0.66, 0.86)	<.0001	0.85 (0.80, 0.91)
Age & Calorie-adjusted model	Ref	0.91 (0.80, 1.03)	0.95 (0.83, 1.08)	0.70 (0.61, 0.80)	0.66 (0.58, 0.76)	<.0001	0.79 (0.74, 0.85)
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.81, 1.06)	1.02 (0.89, 1.16)	0.77 (0.68, 0.88)	0.80 (0.70, 0.91)	<.0001	0.88 (0.82, 0.94)
Above+Dietary factors adjusted (MV2)	Ref	0.97 (0.85, 1.10)	1.11 (0.98, 1.27)	0.90 (0.78, 1.03)	1.01 (0.88, 1.17)	0.8328	1.00 (0.93, 1.07)
Meta-analyzed results (MV2)	Ref	0.97 (0.91, 1.06)	1.00 (0.94, 1.06)	0.94 (0.86, 1.00)	0.89 (0.81, 0.94)	0.0001	0.93 (0.89, 0.97)
Bean/Legume							
NHS							
Median intake (servings/d)	0.08	0.13	0.17	0.21	0.29		
Age-adjusted model	Ref	0.92 (0.85, 0.99)	0.87 (0.81, 0.95)	0.87 (0.80, 0.94)	0.80 (0.74, 0.87)	<.0001	0.74 (0.65, 0.84)
Age & Calorie-adjusted model	Ref	0.85 (0.78, 0.92)	0.76 (0.70, 0.83)	0.70 (0.65, 0.77)	0.59 (0.54, 0.64)	<.0001	0.42 (0.36, 0.48)
Above+Nondietary factors adjusted (MV1)	Ref	0.87 (0.80, 0.94)	0.77 (0.71, 0.83)	0.72 (0.66, 0.79)	0.62 (0.57, 0.67)	<.0001	0.45 (0.39, 0.52)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.83, 0.97)	0.83 (0.76, 0.90)	0.80 (0.73, 0.87)	0.72 (0.66, 0.79)	<.0001	0.60 (0.51, 0.70)
HPFS							
Median intake (servings/d)	0.05	0.09	0.12	0.17	0.25		
Age-adjusted model	Ref	0.94 (0.83, 1.08)	0.92 (0.81, 1.05)	0.94 (0.82, 1.07)	0.90 (0.79, 1.03)	0.1979	0.79 (0.64, 0.96)
Age & Calorie-adjusted model	Ref	0.85 (0.75, 0.97)	0.78 (0.69, 0.90)	0.75 (0.66, 0.86)	0.63 (0.55, 0.73)	<.0001	0.43 (0.35, 0.54)

Table 15 (Continued)							
Above+Nondietary factors adjusted (MV1)	Ref	0.84 (0.74, 0.96)	0.79 (0.69 0.90)	0.77 (0.67, 0.88)	0.66 (0.58, 0.76)	<.0001	0.48 (0.39, 0.60)
Above+Dietary factors adjusted (MV2)	Ref	0.87 (0.76, 0.99)	0.84 (0.73, 0.96)	0.85 (0.74, 0.98)	0.79 (0.68, 0.92)	0.0104	0.65 (0.51, 0.82)
Meta-analyzed results (MV2)	Ref	0.89 (0.84, 0.94)	0.84 (0.76, 0.89)	0.81 (0.76, 0.86)	0.74 (0.68, 0.81)	<.0001	0.63 (0.54, 0.70)
Dairy							
NHS							
Median intake (servings/d)	1.30	1.96	2.54	3.23	4.34		
Age-adjusted model	Ref	1.18 (1.09, 1.28)	1.14 (1.05, 1.24)	1.22 (1.12, 1.32)	1.18 (1.08, 1.28)	0.0004	1.02 (1.01, 1.03)
Age & Calorie-adjusted model	Ref	1.08 (0.99, 1.17)	0.97 (0.89, 1.06)	0.98 (0.90, 1.07)	0.84 (0.77, 0.92)	<.0001	0.97 (0.96, 0.99)
Above+Nondietary factors adjusted (MV1)	Ref	1.11 (1.02, 1.21)	1.01 (0.92, 1.09)	1.02 (0.93, 1.11)	0.88 (0.80, 0.97)	0.0004	0.98 (0.97, 0.99)
Above+Dietary factors adjusted (MV2)	Ref	1.12 (1.03, 1.22)	1.02 (0.94, 1.11)	1.03 (0.95, 1.13)	0.88 (0.80, 0.97)	0.0007	0.98 (0.97, 0.99)
HPFS							
Median intake (servings/d)	0.71	1.20	1.63	2.22	3.32		
Age-adjusted model	Ref	1.18 (1.03, 1.36)	1.29 (1.13, 1.47)	1.43 (1.25, 1.63)	1.55 (1.36, 1.77)	<.0001	1.05 (1.04, 1.07)
Age & Calorie-adjusted model	Ref	1.10 (0.96, 1.26)	1.11 (0.97, 1.28)	1.15 (1.00, 1.32)	1.11 (0.96, 1.28)	0.2846	1.00 (0.99, 1.02)
Above+Nondietary factors adjusted (MV1)	Ref	1.08 (0.95, 1.24)	1.12 (0.97, 1.28)	1.09 (0.95, 1.26)	1.05 (0.90, 1.21)	0.8476	1.00 (0.98, 1.02)
Above+Dietary factors adjusted (MV2)	Ref	1.06 (0.93, 1.22)	1.09 (0.95, 1.25)	1.06 (0.92, 1.22)	0.98 (0.84, 1.14)	0.4726	0.99 (0.97, 1.01)
Meta-analyzed results (MV2)	Ref	1.09 (1.03, 1.20)	1.03 (0.97, 1.13)	1.03 (0.97, 1.13)	0.91 (0.84, 1.00)	0.0008	0.98 (0.97, 0.99)
Egg							
NHS							
Median intake (servings/d)	0.07	0.15	0.23	0.33	0.46		
Age-adjusted model	Ref	1.20 (1.10, 1.30)	1.24 (1.14, 1.34)	1.32 (1.21, 1.43)	1.41 (1.30, 1.53)	<.0001	1.29 (1.22, 1.37)
Age & Calorie-adjusted model	Ref	1.14 (1.05, 1.24)	1.14 (1.05, 1.24)	1.17 (1.07, 1.27)	1.19 (1.10, 1.30)	0.0003	1.15 (1.08, 1.22)
Above+Nondietary factors adjusted (MV1)	Ref	1.12 (1.03, 1.22)	1.11 (1.02, 1.21)	1.12 (1.03, 1.22)	1.16 (1.06, 1.26)	0.0063	1.12 (1.05, 1.19)
Above+Dietary factors adjusted (MV2)	Ref	1.14 (1.05, 1.24)	1.13 (1.04, 1.23)	1.14 (1.05, 1.24)	1.16 (1.07, 1.27)	0.0056	1.11 (1.05, 1.18)
HPFS							
Median intake (servings/d)	0.04	0.11	0.20	0.31	0.52		
Age-adjusted model	Ref	1.03 (0.90, 1.18)	1.07 (0.93, 1.22)	1.32 (1.15, 1.50)	1.38 (1.21, 1.58)	<.0001	1.20 (1.13, 1.27)
Age & Calorie-adjusted model	Ref	0.98 (0.86, 1.13)	0.98 (0.86, 1.12)	1.15 (1.00, 1.31)	1.13 (0.98, 1.29)	0.0093	1.09 (1.03, 1.16)
Above+Nondietary factors adjusted (MV1)	Ref	0.93 (0.81, 1.07)	0.90 (0.79, 1.03)	1.04 (0.91, 1.19)	0.99 (0.86, 1.14)	0.46	1.03 (0.97, 1.10)
Above+Dietary factors adjusted (MV2)	Ref	0.90 (0.79, 1.03)	0.88 (0.77, 1.01)	1.00 (0.87, 1.15)	0.93 (0.81, 1.07)	0.9465	1.01 (0.94, 1.07)
Meta-analyzed results (MV2)	Ref	1.06 (1.00, 1.16)	1.06 (0.97, 1.13)	1.09 (1.03, 1.20)	1.09 (1.03, 1.16)	0.0322	1.06 (1.02, 1.11)
Nuts							
NHS							
Median intake (servings/d)							
Age-adjusted model	Ref	1.09 (1.00, 1.18)	1.13 (1.04, 1.22)	1.15 (1.06, 1.25)	1.28 (1.18, 1.38)	<.0001	1.10 (1.06, 1.13)
Age & Calorie-adjusted model	Ref	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)	1.00 (0.92, 1.08)	1.02 (0.94, 1.11)	0.8616	1.00 (0.97, 1.04)
Above+Nondietary factors adjusted (MV1)	Ref	1.04 (0.96, 1.13)	1.03 (0.95, 1.12)	1.01 (0.93, 1.10)	1.08 (0.99, 1.17)	0.1766	1.02 (0.99, 1.06)
Above+Dietary factors adjusted (MV2)	Ref	1.04 (0.96, 1.13)	1.03 (0.95, 1.12)	1.00 (0.92, 1.09)	1.05 (0.96, 1.14)	0.5617	1.00 (0.97, 1.04)
HPFS							
Median intake (servings/d)							
Age-adjusted model	Ref	1.25 (1.09, 1.44)	1.53 (1.33, 1.74)	1.35 (1.18, 1.54)	1.58 (1.39, 1.81)	<.0001	1.10 (1.07, 1.14)
Age & Calorie-adjusted model	Ref	1.18 (1.03, 1.35)	1.36 (1.19, 1.56)	1.13 (0.99, 1.30)	1.19 (1.03, 1.37)	0.3332	1.02 (0.99, 1.06)

Table 15 (Continued)							
Above+Nondietary factors adjusted (MV1)	Ref	1.17 (1.02, 1.34)	1.33 (1.16, 1.52)	1.12 (0.97, 1.28)	1.21 (1.05, 1.40)	0.1605	1.03 (1.00, 1.07)
Above+Dietary factors adjusted (MV2)	Ref	1.16 (1.01, 1.33)	1.30 (1.14, 1.49)	1.09 (0.95, 1.26)	1.18 (1.02, 1.36)	0.3275	1.02 (0.99, 1.06)
Meta-analyzed results (MV2)	Ref	1.06 (1.00, 1.16)	1.09 (1.03, 1.16)	1.03 (0.94, 1.09)	1.09 (1.00, 1.16)	0.2850	1.01 (0.99, 1.04)

Age-adjusted model: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years);
Age & calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous);
Multivariate model 1: NHS: further adjusted for census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: further adjusted for smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002.
Multivariate model 2: other than variables adjusted in MV1, further adjusted for dietary intakes of total vegetables, fruit, fruit juice, sweet/desserts, and sugar-sweetened beverages (all in quintiles)
[a] Indicates ORs of 3-unit increments in SCD for each 3 servings/week increase in food intakes

Individual Protein Food Analysis

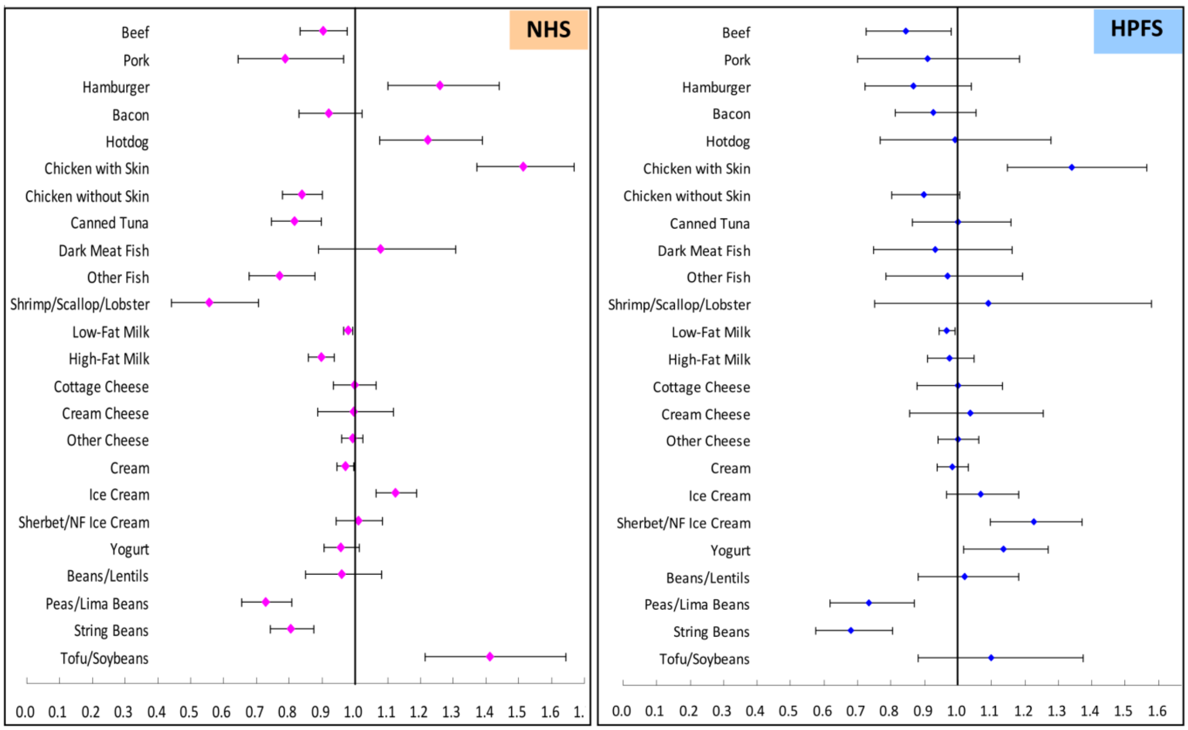
Associations between individual protein foods and SCD are shown in Figure 13. Using stepwise regression, the following foods were selected as independent predictors of prospective SCD in both the NHS and HPFS: peas/lima beans, string beans, low-fat milk, and beef were inversely associated with SCD, whereas chicken with skin was positively associated with SCD.

Temporal Relationships

Intakes of total, animal, and plant protein in recent years were significantly associated with lower odds of SCD in both the NHS and HPFS (Figure 14); the averaged intakes had the strongest inverse associations. Dietary intake of protein before and after SCD assessments was compared, and no major dietary change was found.

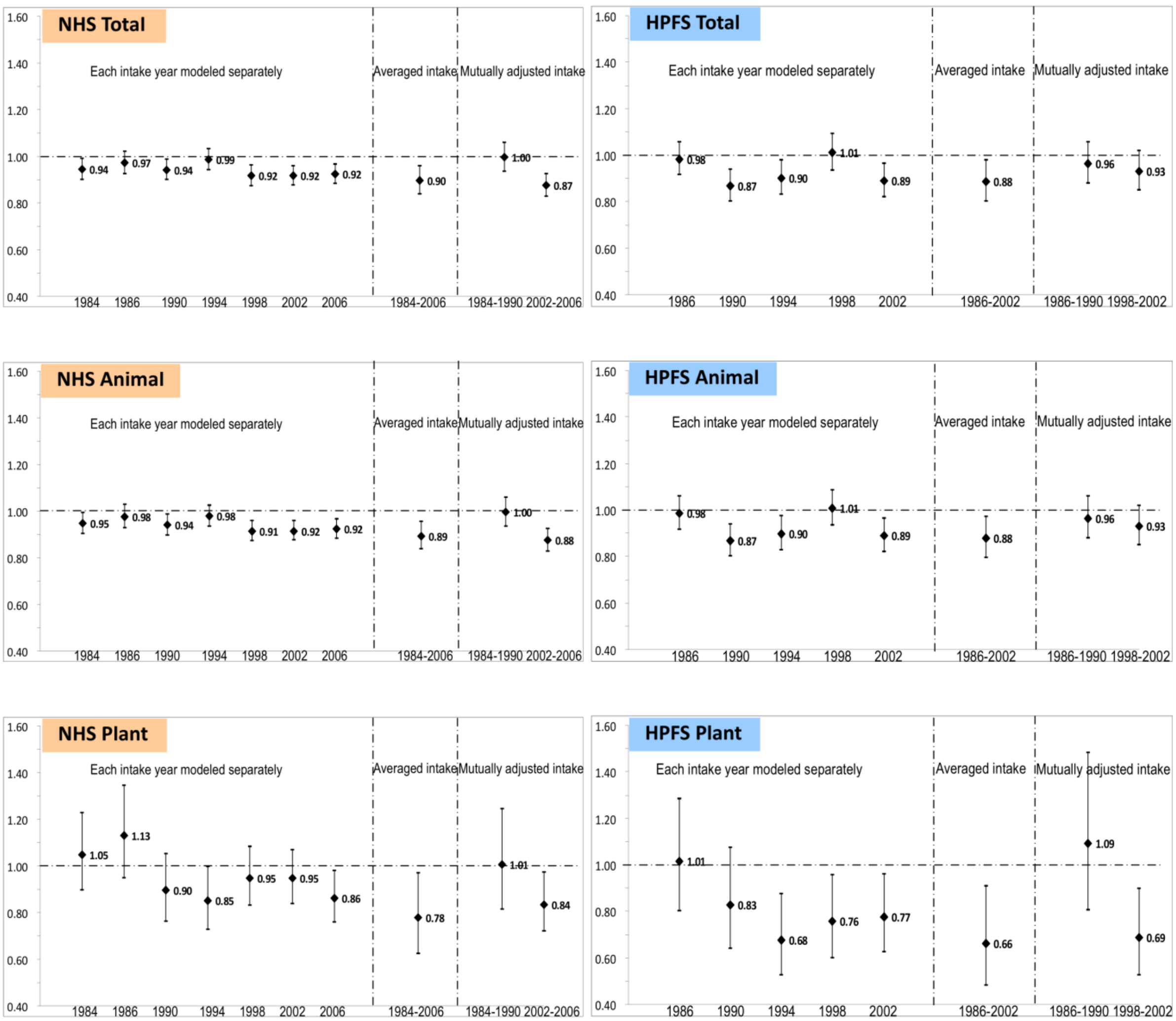
Higher intake of beans/legumes was significantly associated with lower odds of SCD at all 7 time points during follow-up in the NHS (Figure 15); both recent (6-10 years before SCD assessment) and remote (22-28 years before SCD) legume intakes were inversely associated with subsequent SCD when mutually adjusted in the model. For the HPFS, intakes in remote years were significantly associated with lower odds of SCD. The average of all dietary assessments had the strongest associations in both cohorts.

Figure 13. ORs (95% CIs) of a 3-unit increment in SCD, associated with individual protein-containing foods in the NHS and HPFS (for each 3 servings/wk as continuous variables)



Multivariate model: NHS: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years), total energy intake (kcal, continuous), census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: adjusted for age, and total energy, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002. Both cohorts also adjusted for dietary intakes of total vegetables, fruit, fruit juice, sugar sweetened beverages, and sweets/desserts.

Figure 14. Intakes of specific sources of protein at each year of dietary assessment and odds of a 3-unit increment in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) substituting every 5% of energy intake from each specific protein for the same amount of energy from total carbohydrates (NHS: n=49,493 women, HPFS: 27,842 men) (all models adjusted for percentage of energy intake from *trans*-fat, saturated fat, MUFA, and PUFA)



Multivariate model: NHS: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years), total energy intake (kcal, continuous), census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: adjusted for age, and total energy, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (metabolic equivalent-h/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and number of dietary assessments during 1986–2002. Both cohorts also adjusted for intakes carotenoids (quintiles), anthocyanins (quintiles), vit c, d, and e (quintiles).

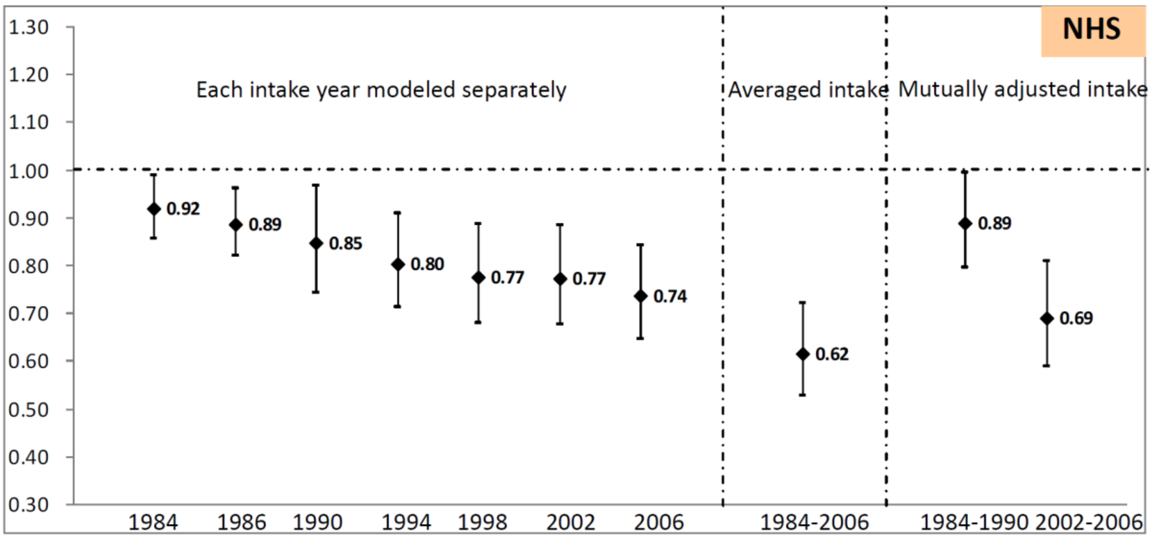
All models adjusted for percentage of energy intake from trans-fat, saturated fat, MUFA, and PUFA. Percentage of energy from animal and plant protein were mutually adjusted.

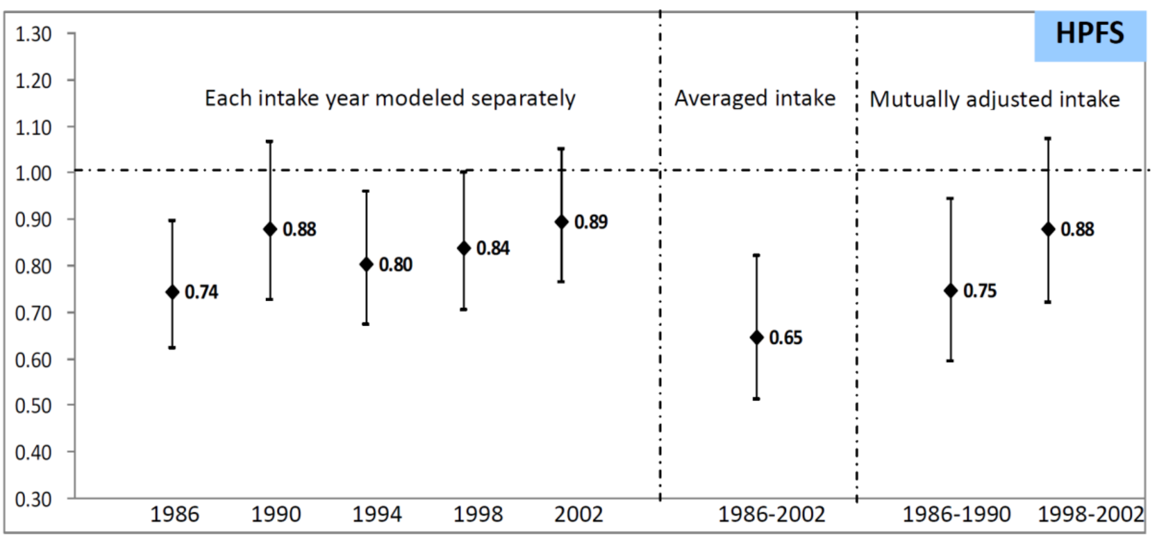
Discussion

Higher total, animal, and plant protein intakes compared with total carbohydrates were associated with lower odds of SCD; substituting animal protein for plant protein was also associated with lower odds. For protein food sources, higher intakes of beans/legumes, fish, and chicken without skin were significantly associated with better late-life SCD.

Current evidence supporting the associations between higher protein intake and less cognitive decline is weak.[110, 123-125] We found that substituting each 5% of energy from total protein for the same percentage of energy from total carbohydrates was related to 11% lower odds of SCD. Plant protein had the strongest inverse association, with a 26% lower odds of SCD compared with total carbohydrates. In addition, replacement of every 5% of energy intake from animal protein with the equivalent amount of energy from plant protein was associated with a 13% lower odds of SCD in the NHS and a 25% lower odds in the HPFS. To our knowledge, the current study was the first to investigate the relationships between dietary protein and cognitive function using isocaloric substitution models, and to examine the differential associations for animal and plant protein with cognitive function. Furthermore, as we adjusted for *trans* fat, saturated fat, MUFA, PUFA, carotenoids, anthocyanins, vitamin C, D, and E in the analyses, we were able to determine the associations for specific types of protein independent of these nutrients. Especially in the older population, low protein intake was associated with a higher risk of sarcopenia[130, 131] and frailty,[121] which were closely linked to the development of cognitive impairment.[132] Our results supported the hypothesis that plant-based protein may be a superior source of protein. We also found many of the amino acids were inversely associated with SCD.

Figure 15. Intake of beans/legumes at each year of dietary assessment and odds of a 3-unit increment in SCD (NHS: assessed in 2012, 2014; HPFS: assessed in 2008, 2012) for each 3 servings/wk as continuous variables (NHS: n=49,493 women, HPFS: 27,842 men)





Multivariate model: NHS: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years), total energy intake (kcal, continuous), census tract income ($50,000, $50,000–69,999, or $$70,000/y), education (registered nursing degrees, bachelors degree, masters or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, 1-24 pack-years, 25-44 pack-years, 45+ pack-years), depression (defined as use of anti-depressants in 1990 or self-reported depression for the last two years in 2008), physical activity level (METs-hr/week, quintiles), BMI (<23, 23-25, 25-30, >30 kg/m2) from 1986-2002, intakes of alcohol (g/d), postmenopausal status and hormone replacement therapy use, family history of dementia, missing indicator for SCD measurement at 2012 or 2014, number of dietary assessments during 1984–2006, multivitamin use (yes/no), parity (nulliparous, 1-2, >2).
HPFS: adjusted for age, and total energy, smoking history (never, 1–24 pack-years, 25–44 pack-years, 45+ pack-years), cancer (yes/no), depression (defined as use of antidepressants in 1990 or self-reported depression for the last 2 years in 2008), family history of dementia, physical activity level (METs-hr/wk, quintiles), body mass index (<23, 23–24.9, 25–29.9, ≥30 kg/m2) from 1986 to 2002, multivitamin use from 1986 to 2002 (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD

measurement at 2008 or 2012, and number of dietary assessments during 1986–2002. Both cohorts also adjusted for dietary intakes of total vegetables, fruit, fruit juice, sugar-sweetened beverages, and sweets/desserts.

Proline was significantly associated with lower odds of SCD in both of our cohorts, although a detailed mechanism is not yet known, a possible protective role has been suggested for a proline-rich polypeptide in preventing dementia progression.[133] Two large neutral amino acids, tyrosine and tryptophan, were suggested to be potentially beneficial because they act as precursors of serotonin and catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine), but dietary supplementation trials with either amino acids were previously short-termed and limited to only healthy young adults.[134] In our analyses, inverse associations of these two amino acids with SCD were only observed in the NHS, but not the HPFS.

Study results on the associations between various protein food sources and cognitive function have been mixed. For legume consumption, although protective associations with cognitive function were reported,[127, 135, 136] no association was also observed,[125] and poorer subsequent cognitive function was seen in other studies.[128, 137, 138] For fish intake, beneficial associations with cognitive function were reported,[109, 125, 139, 140] but the association became null after adjusting for education in the PAQUID study[140]; null results for fish consumption were also seen in other studies[126, 135] (inverse association between fish consumption and dementia was only seen among *APOE* ε4 non-carriers in the Three-City cohort study[53]), and participants with fatty fish intake less than once per week had worse cognitive function compared with participants with no consumption.[141] For other protein food sources, current evidence also remained inconclusive.[125, 128, 137, 140] The discrepancies among these study results may be due to the difference in lengths of study follow-up, ages of the study participants, and dietary patterns in different study populations. Our results support previous studies that showed beneficial associations between beans/legumes, fish, and lean poultry with cognitive function, and those that found harmful associations for processed meat. Plant-based protein foods had the lowest amounts of advanced glycation end products (AGEs), followed by poultry and fish, with processed meat containing the highest levels of AGEs among major protein sources.[142] A low-AGE diet was found to be associated with significantly lower brain amyloid protein accumulation.[143] In our findings, beans/legumes had the strongest inverse association with SCD followed by lean poultry and fish with processed meat having the least favorable association, consistent with these insights[142, 143] on AGEs. Our findings remained robust after adjusting for socioeconomic factors, such as education and income. In addition, to our knowledge, the current study was the first to demonstrate that the associations between these protein foods were independent of total vegetables, fruits, fruit juice, sugar-sweetened beverages, and sweets/desserts intakes.

Over 20 years of follow-up is a major strength of the present study, which allows the capture of potentially important exposure windows and reduces the impact of reverse causation. Large sample sizes in both cohorts provided great power for analyses. Dietary intake averaged from multiple dietary assessments over time reduced errors and within-person variations. Updating dietary data ceased 6 years prior to SCD assessments to minimize the impact of altered cognitive function on diet. We also included comprehensive information on many possible confounders, and these variables were adjusted to minimize residual confounding. There are some limitations in the current study. First, baseline cognitive function was not assessed in our cohorts. However, we can assume generally high baseline cognitive function in these participants during their early adulthood due to multiple admissions and board examinations that were required for practicing health professions. These relatively highly educated participants may also have good insights in reporting subtle cognitive changes.[66] Second, objective cognitive assessment was not included in our study. However, SCD has been repeatedly validated and was found to be strongly associated with both concurrent objective cognitive function[39, 40] and subsequent cognitive decline.[39] Moreover, SCD can be more advantageous in detecting subtle cognitive changes,[67] especially in those with higher education.[41] Third, participants who completed the first but not the second SCD assessment might have more severe cognitive impairment. However, this scenario would bias the results toward the null (in the sensitivity analysis which we only included participants with both SCD assessments, results remained similar.) Finally, limited generalizability could be an issue, because the study populations were mainly Caucasian and healthcare professionals who may have better health awareness and relatively high cognitive function required for their occupations. However, this relatively uniform early-life cognitive function in our study participants may reduce residual confounding.

In conclusion, adequate protein intake may be important for maintaining cognitive function, with plant-based protein being generally a superior source. Choice of protein foods could also be important, in particular, higher intake of beans/legumes, fish, and lean poultry may be beneficial for cognition maintenance. However, processed meat products, such as hotdogs, may be related to poor subsequent cognitive function. These findings could have important public health implications, and future studies are warranted to verify our results.

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