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

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Abstract

Background: Diet is one of the modifiable risk factors for cognitive decline. However, studies on dietary protein intake and cognitive decline have remained limited and inconclusive.

Objectives: In this study, we aimed 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). For the NHS, average dietary intake was calculated from 7 repeated semiquantitative FFQs (SFFQs), and SCD was assessed in 2012 and 2014. For the HPFS, average dietary intake was calculated from 5 repeated SFFQs, and SCD was assessed in 2008 and 2012. Poisson regression was used to examine the associations between dietary protein, amino acids, and various protein food sources with subsequent SCD.

Results: Higher protein intake compared with total carbohydrates was associated with lower odds of SCD. When substituting 5% energy from protein for the equivalent percentage of energy from total carbohydrates, the pooled multivariable-adjusted ORs (95% CIs) 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 OR was 0.84 (95% CI: 0.72, 0.97). For protein food sources, higher intakes of beans/legumes, fish, and lean poultry were significantly associated with lower odds of SCD, but higher intake of hotdogs was associated with higher odds of SCD.

Conclusions: Higher protein intake was associated with lower odds of SCD when compared isocalorically with carbohydrate. Plant protein sources were also associated with lower odds when compared with animal protein sources. Our findings suggest that adequate protein intake, and choices of protein sources could play a role in the maintenance of cognition and should be studied further. *Am J Clin Nutr* 2022;115:199–210.

Introduction

In our world of rapid aging, the global prevalence of age-related cognitive decline and dementia is projected to rise exponentially (1). Disability related to cognitive decline and the substantial lifetime costs (2) not only affect patients but also pose great burdens on their families and the whole society (1). 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 (3). Subjective cognitive decline (SCD) is a state of self-perceived cognitive decline without detectable objective cognitive impairments and can precede clinically apparent mild cognitive impairment and dementia (3). SCD has been strongly associated with both concurrent objective cognitive function (4, 5) and subsequent cognitive decline (5), especially for people with higher education (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 modifiable risk factors for cognitive decline and may play an important role in cognitive function (9).

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 (10). In some animal studies, low-calorie and low-protein diets were associated with longer life span and better aging-related outcomes (11, 12), and higher dietary protein intake was associated with increased cardiovascular risk (13). However, inadequate protein intake in the older population could increase risk of sarcopenia and frailty (14), closely linked to cognitive impairment (15). To date, epidemiologic studies on dietary protein intake and cognitive decline have been inconclusive (16, 17). In addition, evidence on the impact of specific protein sources on cognitive function has been mixed (16, 18–20). Therefore, the current study aimed to investigate the relations between long-term dietary protein intake and subsequent SCD with repeated dietary assessments from >20 y of follow-up in 2 large prospective cohorts of men and women.

Methods

Study design

A total of 121,701 female registered nurses aged 30–55 y in the United States were enrolled in the Nurses' Health Study (NHS) in 1976. Participants were followed up biennially via questionnaires that included potential risk factors and newly diagnosed diseases (21). Dietary information has been collected using a semiquantitative FFQ (SFFQ) that has been validated in multiple studies (22), and these data were collected in 1980, 1984, 1986, and then every 4 y thereafter.

Starting in 1986, 51,529 male health professionals aged 40–75 y, residing in the United States, were enrolled in the Health Professionals Follow-up Study (HPFS). Detailed questionnaires regarding information on lifestyle risk factors and medical history have been sent to participants every 2 y (23). Dietary assessments with the SFFQ began in 1986 and have continued every 4 y.

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. Nutrient values were mainly based on the USDA database. Follow-up for this analysis 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 4 y. Cumulative average intakes of the 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 (24). Similarly, in the HPFS, average intakes were calculated from 5 repeated dietary assessments obtained every 4 y since 1986 until 2002. Energy-adjusted total protein intake (i.e., the sum of plant and animal protein intake) from the SFFQs correlated well with multiple dietary records and with protein biomarkers (urine nitrogen adjusted for energy intake using doubly labeled water) (25, 26). The estimated correlation with true protein intake using the combined assessments with dietary records and biomarkers was 0.65 (95% CI: 0.59, 0.72) (25).

Assessment of SCD

The primary outcome of SCD was assessed twice by mailed or online questionnaires (2012 and 2014 for the NHS, 2008 and 2012 for the HPFS; available at www.nurseshealthstudy.org and sites.sph.harvard.edu/hpfs/hpfs-questionnaires) (5). The descriptive term *subjective cognitive function* was used in our previous publications (27), but we have updated our terminology to SCD in keeping with changes in the field (28). SCD was assessed by 6 yes/no questions for the HPFS and 7 questions for the NHS. For each question, every "yes" was assigned the number 1 and every "no" the number 0. Of the participants in the NHS and HPFS, 86% and 72.4%, respectively, completed both SCD questionnaires; 11.4% and 19% completed only the first questionnaire; and 2.6% and 8.7% completed only the second questionnaire (**Table 1**). To minimize random errors, the average of the 2 SCD scores was used, except for participants who completed only 1 of the 2 SCD questionnaires. Dietary data were updated until 6 y prior to SCD assessment to minimize the potential impact of altered cognitive function on diet.

The strong associations between the homozygous *APOE*4 genotype and poor SCD scores in both the NHS and HPFS support the validity of this score (27). Among men, the age-standardized prevalence of the homozygous *APOE* 4 genotype was 1.0% among participants with a good SCD score (0 points) and 4.6% among those with a poor SCD score (≥3 points; *P*-trend < 0.001) (27); among women, the prevalence was 1.3% for those with a good SCD score and 2.4% for those with a poor SCD score (29). 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 (27).

Covariates

Starting from baseline and in follow-up questionnaires, information on covariates was collected prospectively in the NHS and HPFS. These covariates include age, race, BMI (in kg/m^2), physical activity, multivitamin use, smoking status, alcohol consumption, history of cancer, history of cardiovascular disease (CVD), high blood pressure, elevated cholesterol, diabetes, family history of dementia, and depression. For the NHS, additional information on education, husband's education, census tract income, menopausal status and the use of hormone replacement therapy, and parity was obtained. For the HPFS, we also used information on specific health professions.

Population for analysis

For both NHS and HPFS, we excluded participants with extreme energy intakes (<600 or >3500 kcal/d for women and <800 or >4200 kcal/d for men), those with >70 food items blank, and individuals who developed Parkinson disease (PD) prior to SCD assessments because patients with PD may also present with cognitive impairment. The final analysis included

TABLE 1 Characteristics of NHS and HPFS participants by quintiles of total protein intake[1]

Characteristic	Quintile of protein intake				
	Q1	Q2	Q3	Q4	Q5
NHS (49,493 women)	(*n* = 9898)	(*n* = 9899)	(*n* = 9899)	(*n* = 9899)	(*n* = 9898)
Protein intake, % energy, mean ± SD	14.9 ± 1.1	16.8 ± 0.4	17.9 ± 0.3	19.1 ± 0.4	21.4 ± 1.4
Age at study baseline, y, mean ± SD	49.1 ± 6.8	48.5 ± 6.6	48.2 ± 6.6	48.0 ± 6.5	47.9 ± 6.4
BMI, kg/m² mean ± SD	25.0 ± 4.3	25.5 ± 4.4	26.0 ± 4.6	26.6 ± 4.8	27.4 ± 4.9
Total energy intake, kcal/d, mean ± SD	1842 ± 447	1808 ± 421	1751 ± 406	1694 ± 388	1583 ± 377
Total carbohydrate, % energy, mean ± SD	52.7 ± 6.6	51.3 ± 5.8	50.5 ± 5.7	49.8 ± 5.6	48.5 ± 5.9
Total fat, % energy, mean ± SD	31.7 ± 4.7	31.6 ± 4.5	31.5 ± 4.4	31.2 ± 4.6	30.6 ± 4.8
Alcohol, g/d, mean ± SD	7.8 ± 11.3	6.5 ± 8.8	5.8 ± 7.8	4.9 ± 6.7	3.7 ± 5.5
Physical activity, MET-h/wk, mean ± SD	17.5 ± 16.4	18.3 ± 15.4	18.5 ± 16.0	18.9 ± 16.0	19.6 ± 16.8
Smoking pack-years, *n* (%)					
Never smoked	4646 (46.9)	4692 (47.4)	4643 (46.9)	4586 (46.3)	4471 (45.2)
≤4 pack-years	993 (10.0)	1050 (10.6)	1081 (10.9)	1107 (11.2)	1176 (11.9)
5–24 pack-years	2089 (21.1)	2213 (22.4)	2269 (22.9)	2307 (23.3)	2341 (23.6)
≥25 pack-years	2008 (20.3)	1792 (18.1)	1744 (17.6)	1735 (17.5)	1740 (17.6)
Missing	162 (1.6)	152 (1.5)	162 (1.6)	164 (1.7)	170 (1.7)
Cancer, *n* (%)	1724 (17.4)	1859 (18.8)	1855 (18.7)	1855 (18.7)	1859 (18.8)
Depression, *n* (%)	1895 (19.1)	1837 (18.6)	1876 (18.9)	2006 (20.3)	2014 (20.3)
Number of dietary assessments, *n* (%)					
1	40 (0.4)	14 (0.1)	16 (0.2)	15 (0.1)	25 (0.3)
2	93 (0.9)	67 (0.7)	65 (0.7)	57 (0.6)	91 (0.9)
3	162 (1.6)	141 (1.4)	153 (1.5)	135 (1.4)	168 (1.7)
4	357 (3.6)	313 (3.2)	274 (2.8)	284 (2.9)	380 (3.8)
5	812 (8.2)	691 (7.0)	670 (6.8)	686 (6.9)	703 (7.1)
6	1993 (20.1)	1893 (19.1)	1816 (18.3)	1905 (19.2)	1883 (19.0)
7	6441 (65.1)	6780 (68.5)	6905 (69.8)	6817 (68.9)	6648 (67.2)
Missing year of SCD assessment, *n* (%)					
None	8449 (85.4)	8569 (86.6)	8495 (85.8)	8530 (86.2)	8498 (85.9)
2012	282 (2.8)	229 (2.3)	254 (2.6)	269 (2.7)	258 (2.6)
2014	1167 (11.8)	1101 (11.1)	1150 (11.6)	1100 (11.1)	1142 (11.5)
Postmenopause and ever use hormone, *n* (%)	7022 (70.9)	7332 (74.0)	7389 (74.6)	7410 (74.9)	7440 (75.2)
Parity, *n* (%)					
Nulliparous	548 (5.5)	530 (5.4)	511 (5.2)	490 (5.0)	497 (5.0)
1–2	738 (7.5)	608 (6.1)	645 (6.5)	608 (6.1)	690 (7.0)
3+	8440 (85.3)	8572 (86.6)	8589 (86.8)	8633 (87.2)	8498 (85.9)
Missing	172 (1.7)	189 (1.9)	154 (1.5)	168 (1.7)	213 (2.1)
Dietary intake, servings/d, mean ± SD					
Vegetable intake	3.2 ± 1.6	3.4 ± 1.5	3.5 ± 1.5	3.7 ± 1.6	3.9 ± 1.7
Fruit intake	1.5 ± 0.9	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.8
Fruit juice intake	0.8 ± 0.6	0.8 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.5 ± 0.4
Sweets/desserts intake	1.8 ± 1.1	1.4 ± 0.9	1.2 ± 0.7	1.0 ± 0.6	0.7 ± 0.5
SSB intake	0.5 ± 0.6	0.3 ± 0.4	0.2 ± 0.3	0.2 ± 0.2	0.1 ± 0.2
HPFS (27,842 men)	(*n* = 5568)	(*n* = 5569)	(*n* = 5568)	(*n* = 5569)	(*n* = 5568)
Protein intake, % energy, mean ± SD	14.7 ± 1.1	16.6 ± 0.4	17.8 ± 0.3	19.1 ± 0.4	21.5 ± 1.6
Age at study baseline, y, mean ± SD	51.4 ± 8.4	51.1 ± 8.3	50.9 ± 8.2	51.0 ± 8.1	50.8 ± 7.9
BMI, kg/m² mean ± SD	25.2 ± 2.9	25.7 ± 3.1	25.8 ± 3.2	26.2 ± 3.3	26.6 ± 3.6
Total energy intake, kcal/d, mean ± SD	2124 ± 541	2078 ± 514	2034 ± 507	1943 ± 485	1785 ± 460
Total carbohydrate, % energy, mean ± SD	51.9 ± 7.7	50.3 ± 6.8	49.7 ± 6.6	49.0 ± 6.5	47.3 ± 6.9
Total fat, % energy, mean ± SD	30.3 ± 5.2	30.8 ± 5.1	30.8 ± 5.1	30.6 ± 5.2	30.3 ± 5.6
Alcohol, g/d, mean ± SD	15.9 ± 17.4	13.0 ± 13.5	11.0 ± 11.5	9.3 ± 10.0	7.1 ± 8.0
Physical activity, MET-h/wk, mean ± SD	28.4 ± 22.4	29.0 ± 21.3	29.0 ± 21.0	28.4 ± 20.4	27.6 ± 20.3
Smoking pack-years, *n* (%)					
Never smoked	2703 (48.6)	2748 (49.3)	2786 (50.0)	2770 (49.7)	2711 (48.7)
≤24 pack-years	1600 (28.7)	1622 (29.1)	1548 (27.8)	1638 (29.4)	1635 (29.4)
25–44 pack-years	657 (11.8)	622 (11.2)	623 (11.2)	611 (11.0)	654 (11.7)
≥45 pack-years	334 (6.0)	292 (5.3)	305 (5.5)	256 (4.6)	235 (4.2)
Missing	274 (4.9)	285 (5.1)	306 (5.5)	294 (5.3)	333 (6.0)
Cancer, *n* (%)	840 (15.1)	898 (16.1)	891 (16.0)	855 (15.4)	860 (15.4)
Depression, *n* (%)	336 (6.0)	314 (5.6)	314 (5.6)	293 (5.3)	300 (5.4)

(Continued)

TABLE 1 *(Continued)*

	Quintile of protein intake				
Characteristic	Q1	Q2	Q3	Q4	Q5
Number of dietary assessments, *n* (%)					
1	123 (2.2)	82 (1.5)	90 (1.6)	110 (2.0)	223 (4.0)
2	253 (4.5)	232 (4.2)	220 (4.0)	229 (4.1)	349 (6.3)
3	434 (7.8)	449 (8.1)	461 (8.3)	460 (8.3)	568 (10.2)
4	1010 (18.1)	941 (16.9)	983 (17.7)	1040 (18.7)	1128 (20.2)
5	3748 (67.3)	3865 (69.4)	3814 (68.5)	3730 (67.0)	3300 (59.3)
Missing year of SCD assessment, *n* (%)					
None	4131 (74.2)	4122 (74.0)	4050 (72.7)	4002 (71.9)	3846 (69.1)
2008	423 (7.6)	418 (7.5)	463 (8.3)	508 (9.1)	599 (10.8)
2012	1014 (18.2)	1029 (18.5)	1055 (18.9)	1059 (19.0)	1123 (20.2)
Profession, *n* (%)					
Dentist	2874 (51.6)	3013 (54.1)	3207 (57.6)	3336 (59.9)	3535 (63.5)
Pharmacist	653 (11.7)	523 (9.4)	467 (8.4)	376 (6.7)	328 (5.9)
Optometrist	390 (7.0)	381 (6.8)	383 (6.9)	375 (6.7)	360 (6.5)
Osteopath	212 (3.8)	217 (3.9)	187 (3.4)	256 (4.6)	259 (4.7)
Podiatrist	122 (2.2)	107 (1.9)	131 (2.3)	140 (2.5)	197 (3.5)
Veterinarian	1317 (23.7)	1328 (23.8)	1193 (21.4)	1086 (19.5)	889 (16.0)
Dietary intake, servings/d, mean ± SD					
Vegetable	3.2 ± 1.7	3.5 ± 1.7	3.6 ± 1.7	3.7 ± 1.7	3.8 ± 1.9
Fruit	1.7 ± 1.2	1.7 ± 1.1	1.7 ± 1.0	1.7 ± 1.0	1.6 ± 1.0
Fruit juice	0.9 ± 0.8	0.8 ± 0.6	0.8 ± 0.6	0.8 ± 0.6	0.6 ± 0.5
Sweets/desserts	2.0 ± 1.4	1.6 ± 1.1	1.4 ± 0.9	1.2 ± 0.8	0.8 ± 0.6
SSB	0.6 ± 0.7	0.4 ± 0.5	0.3 ± 0.4	0.2 ± 0.3	0.2 ± 0.2

[1]Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population. All values are averages over the follow-up period except for age at baseline. HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; Q, quintile; NHS, Nurses' Health Study; SCD, subjective cognitive decline; SSB, sugar-sweetened beverage.

49,493 women with a mean age of 48 y at baseline in 1984 and 27,842 men with a mean age of 51 y at enrollment in 1986 (**Supplementary Figure 1**). Compared with participants who were excluded, participants included in the analysis were younger (**Supplementary Table 1**).

Statistical analysis

Intake of protein was expressed as the 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. Average SCD score was calculated from the 2 SCD assessments and was used as our primary outcome. 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 3 or more positive SCD questions have been used to indicate poor cognitive function (4, 5). 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 relation between age and SCD was nonlinear. In multivariate analyses, the average age at the 2 SCD assessments, total energy intake, race, smoking history, depression, physical activity level, BMI, alcohol intake, family history of dementia, an indicator for having only 1 of the 2 SCD assessments, number of dietary assessments during the 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, and husband's education were also included in the analyses, whereas specific 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 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, MUFA, and 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 percentage of energy from carbohydrates. For substitution of animal protein with plant protein, the difference between the *β*-coefficients was exponentiated, and the variances and covariance of the 2 types of proteins were used to estimate the 95% CI (30). To examine whether the associations were independent of other dietary factors in our protein analyses, we further adjusted for intakes of carotenoids, anthocyanins, and vitamins C, D, and E. The same dietary factors were controlled in analyses of amino acid intakes. Sensitivity analyses were done by only including participants with both SCD assessments and also adjusting for flavonoid subclasses, which had significant inverse associations with SCD in our cohorts (31).

For food-based analyses, all aforementioned nondietary 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 y, ≥50 y), smoking status (never smokers, past smokers, and current smokers), disease status (self-reported depression, CVD, and type 2 diabetes), and *APOE* 4 allele carrier status (yes/no) in a subgroup of participants who had their *APOE* 4 measured or imputed from a genome-wide association analysis.

Temporal relations between specific sources of protein intake and SCD were evaluated. We estimated the associations between dietary intake at each of the individual years with SCD. Also, both recent (the average intake from 2002–2006 in the NHS and average intake from 1998–2002 for the HPFS) and remote (the average intake from 1984–1990 in the NHS and average 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. Covariates closest in time to the dietary assessments were used in these analyses.

Analyses were performed separately for the NHS and HPFS, and an inverse variance–weighted, meta-analysis was used to combine the results across cohorts. Because our analyses included multiple comparisons, we interpreted our findings using the conservative Bonferroni correction. All analyses were performed using SAS software, version 9.2 (SAS Institute). Figures were generated by Prism, version 8.0.0 (GraphPad Software).

Results

Population characteristics

The characteristics of study participants are shown in Table 1. For both the NHS and HPFS, participants with higher total protein intake (as a percentage of energy) had higher BMI, less alcohol consumption, and a higher vegetable intake but lower intake of sweets/desserts.

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 2). Adjusting for total energy intake (which was positively associated with SCD) and major nondietary factors attenuated the magnitude of these associations. Comparing the highest with the lowest quintiles of intakes, the pooled multivariate ORs (95% CIs) 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.

When substituting each 5% of energy intake from protein for the equivalent percentage of energy from total carbohydrates, the pooled multivariate ORs (95% CIs) 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 from animal protein with plant protein, the pooled multivariable-adjusted OR (95% CI) was 0.84 (0.72, 0.97) (data not shown). Similar results were observed in the sensitivity analysis, which

only included participants with both SCD assessments and when also adjusted for flavonoid subclasses. Results were similar across strata of baseline age, smoking status, disease status, and *APOE* 4 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 (**Supplementary Table 2**).

Amino acids

After adjusting for total energy intake, the 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 (**Supplementary Table 3**). In the pooled results, amino acid intakes were associated with 11–26% lower odds of SCD.

Protein food and food group analysis

In a 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 (95% CIs) for each 3-serving/wk increase in intake were 0.86 (0.81, 0.91) for chicken without skin, 0.93 (0.89, 0.97) for fish, and 0.62 (0.54, 0.70) for beans/legumes; **Figure 1**, **Supplementary Table 4**]. Associations between individual protein foods and SCD are shown in **Figure 2**. Among foods selected as independent prospective predictors of SCD using stepwise regression, shrimp/scallop/lobster [the pooled multivariable-adjusted OR (95% CI) for each 3-serving/wk increase in intake = 0.68 (0.55, 0.84)], peas/lima beans (0.72 [0.66, 0.79]), and string beans (0.79 [0.72, 0.84]) had the strongest inverse associations with SCD. Hotdogs (1.16 [1.06, 1.31]) had a significant positive association with SCD.

Temporal relations

Intakes of total, animal, and plant protein in recent years were associated with lower odds of SCD in both the NHS and HPFS (**Figure 3**). The average intakes had the strongest inverse associations. Dietary intake of protein before and after SCD assessments was compared, and no major dietary change was found.

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. These findings are highly unlikely to be due to chance because of the extreme degree of statistical significance and consistency across the 2 cohorts. For major food sources of protein, higher intakes of beans/legumes, fish, and lean poultry were significantly associated with better late-life subjective cognitive function.

TABLE 2 OR (95% CI) for the associations between specific sources of protein intakes with subjective cognitive decline in the NHS and HPFS[1]

Characteristic	Quintile of protein intake					P-trend	Continuous[2]
	Q1	Q2	Q3	Q4	Q5		5% energy
Total protein							
NHS							
Median intake, % of energy	15.17	16.77	17.92	19.12	20.99		
Age-adjusted model	Reference	0.96 (0.88, 1.03)	0.94 (0.87, 1.02)	0.85 (0.78, 0.92)	0.77 (0.71, 0.84)	<0.0001	0.84 (0.79, 0.89)
Age- and calorie-adjusted model	Reference	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)	Reference	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)	Reference	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	Reference	1.02 (0.90, 1.16)	0.84 (0.74, 0.96)	0.86 (0.75, 0.98)	0.74 (0.64, 0.85)	<0.0001	0.82 (0.75, 0.89)
Age- and calorie-adjusted model	Reference	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)	Reference	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)	Reference	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)	Reference	1.00 (0.94, 1.09)	0.97 (0.89, 1.03)	0.91 (0.86, 0.97)	0.84 (0.76, 0.91)	<0.0001	0.89 (0.85, 0.94)
Animal protein							
NHS							
Median intake, % of energy	9.71	11.35	12.49	13.72	15.61		
Age-adjusted model	Reference	1.07 (0.99, 1.15)	0.98 (0.91, 1.06)	0.92 (0.85, 1.00)	0.80 (0.73, 0.87)	<0.0001	0.84 (0.79, 0.89)
Age- and calorie-adjusted model	Reference	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)	Reference	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)	Reference	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	Reference	1.11 (0.97, 1.26)	0.87 (0.77, 1.00)	0.90 (0.78, 1.03)	0.78 (0.68, 0.90)	<0.0001	0.82 (0.75, 0.89)
Age- and calorie-adjusted model	Reference	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)	Reference	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)	Reference	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)	Reference	1.09 (1.03, 1.16)	1.00 (0.91, 1.06)	0.94 (0.89, 1.03)	0.86 (0.79, 0.94)	<0.0001	0.89 (0.84, 0.94)
Plant protein							
NHS							
Median intake, % of energy	4.43	4.97	5.36	5.77	6.47		
Age-adjusted model	Reference	0.80 (0.73, 0.86)	0.77 (0.71, 0.84)	0.76 (0.70, 0.83)	0.68 (0.62, 0.75)	<0.0001	0.50 (0.41, 0.60)
Age and calorie-adjusted model	Reference	0.80 (0.74, 0.87)	0.78 (0.72, 0.85)	0.77 (0.71, 0.84)	0.71 (0.65, 0.79)	<0.0001	0.55 (0.45, 0.67)
Above + nondietary factors adjusted (MV1)	Reference	0.83 (0.77, 0.90)	0.83 (0.76, 0.91)	0.82 (0.75, 0.90)	0.76 (0.69, 0.84)	<0.0001	0.64 (0.52, 0.79)
Above + dietary factors adjusted (MV2)	Reference	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)

(Continued)

TABLE 2 (*Continued*)

Characteristic	Quintile of protein intake					P-trend	Continuous[2]
	Q1	Q2	Q3	Q4	Q5		
HPFS							
Median intake, % of energy	4.24	4.87	5.35	5.87	6.78		
Age-adjusted model	Reference	0.84 (0.74, 0.96)	0.81 (0.71, 0.93)	0.77 (0.66, 0.89)	0.61 (0.52, 0.73)	<0.0001	0.44 (0.33, 0.58)
Age- and calorie-adjusted model	Reference	0.85 (0.75, 0.97)	0.82 (0.72, 0.95)	0.79 (0.68, 0.91)	0.64 (0.54, 0.76)	<0.0001	0.48 (0.36, 0.64)
Above + nondietary factors adjusted (MV1)	Reference	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)	Reference	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)	Reference	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)

[1]Age-adjusted model: adjusted for age [at subjective cognitive decline (SCD) measurement, continuous, with a linear and a quadratic term, years]. Age- and calorie-adjusted model: adjusted for age and total calorie intake (kcal, continuous). Multivariate model 1 (nondietary factors): NHS: further adjusted for census tract income ($50,000, $50,000–$69,999, or $70,000/y), education (registered nursing degrees, bachelor's degree, master's or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, ≥25 pack-years), depression, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–25, 25–30, >30 kg/m^2) from 1984 to 2006, 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, family history of dementia, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m^2) from 1986 to 2002, multivitamin use (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): in addition to variables adjusted in MV1, further adjusted for carotenoids (quintiles), anthocyanins (quintiles), and vitamins C, D, and E (quintiles). HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; Q, quintile; MV1, multivariate model 1; MV2, multivariate model 2; NHS, Nurses' Health Study.

[2]Indicates OR of 3-unit increments in SCD when replacing each 5% of energy 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. Percentages of energy from animal and plant protein were mutually adjusted. Poisson regression was used for data analysis. Pearson χ^2 for Poisson regression = 74,073.8, degrees of freedom = 74,080.4, degrees of freedom = 49,310; pseudo-R^2 = 0.3655 for NHS animal and plant protein multivariate model 2. Pearson χ^2 for Poisson regression = 74,080.4, degrees of freedom = 49,314; pseudo-R^2 = 0.3655 for NHS total protein multivariate model 2. Pearson χ^2 for Poisson regression = 40,524.2, degrees of freedom = 27,753; pseudo-R^2 = 0.2475 for HPFS animal and plant protein multivariate model 2. Pearson χ^2 for Poisson regression = 40,543.2, degrees of freedom = 27,757; pseudo-R^2 = 0.2475 for HPFS animal and plant protein multivariate model 2.
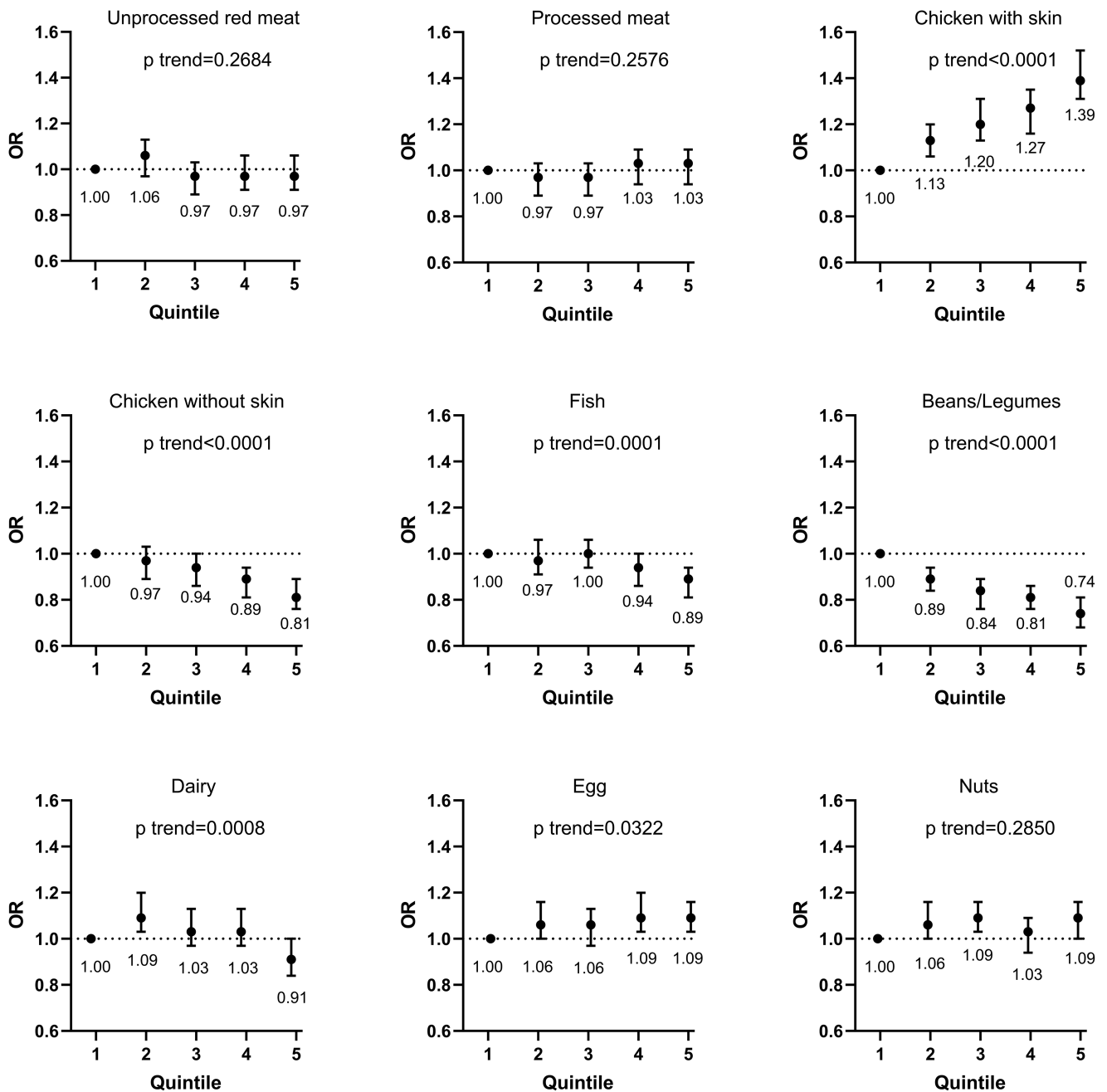
FIGURE 1 ORs of a 3-unit increment in subjective cognitive decline (SCD), associated with protein food groups in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Multivariate model: NHS: adjusted for age (at SCD assessment, continuous, with a linear and a quadratic term, years), total energy intake (kcal, continuous), census tract income ($50,000, $50,000–$69,999, or $70,000/y), education (registered nursing degrees, bachelor's degree, master's or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, ≥25 pack-years), depression, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–25, 25–30, >30 kg/m^2) from 1984 to 2006, 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), and 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, family history of dementia, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m^2) from 1986 to 2002, multivitamin use (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. Poisson regression was used for data analysis.

Current literature on the associations between protein intake and cognitive decline showed mixed results. Some cohort studies suggested that higher protein intake was associated with less cognitive decline (17, 32), whereas other studies found null results (16, 33). In a Chinese cross-sectional study, higher protein intake was associated with an increased risk of mild cognitive impairment (34). We found that substituting each 5% of energy from total protein for the same percentage of energy from total
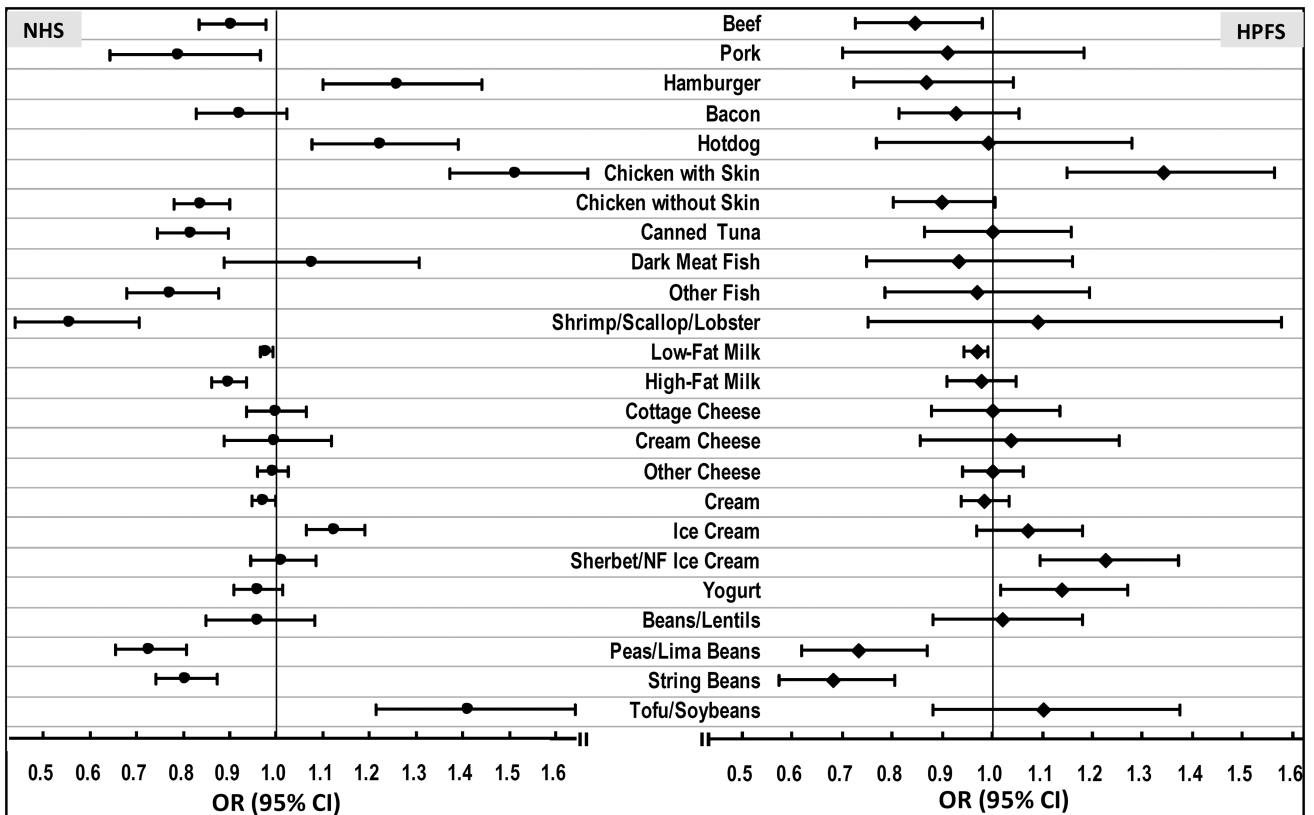
FIGURE 2 ORs (95% CIs) of a 3-unit increment in subjective cognitive decline (SCD), associated with individual protein food sources in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). For each 3-serving/wk of protein foods as continuous variables. Multivariate model: NHS: 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, bachelor's degree, master's or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, ≥25 pack-years), depression, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–25, 25-30, >30 kg/m^2) from 1984 to 2006, 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), and 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, family history of dementia, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m^2) from 1986 to 2002, multivitamin use (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. Poisson regression was used for data analysis.

carbohydrates was associated with 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, for every 5% of energy intake from animal protein replaced with the equivalent amount of energy from plant protein, there was a 16% lower odds of SCD after adjusting for major nondietary factors (including socioeconomic factors) and other dietary factors (including *trans* fat, saturated fat, MUFA, PUFA, carotenoids, flavonoids, and vitamins C, D, and E). Especially in the older population, low protein intake can be associated with a higher risk of sarcopenia (35, 36) and frailty (14), which are closely linked to the development of cognitive impairment (37). 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. 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 (38). 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 acid were mostly short term and limited to only healthy young adults (39). In our analyses, inverse associations of these 2 amino acids with SCD were observed in the NHS but not the HPFS.

Results from other studies on the associations between various protein food sources and cognitive function have been mixed. For legume consumption, suggestions of better cognitive function were reported (19, 40), but no association was also observed (16), and poorer subsequent cognitive function was seen in other studies (20, 41). For fish intake, beneficial associations with cognitive function were reported (16, 42), but in the PAQUID (Personnes Agées QUID) study (42), the association became null after adjusting for education, and null results for fish consumption
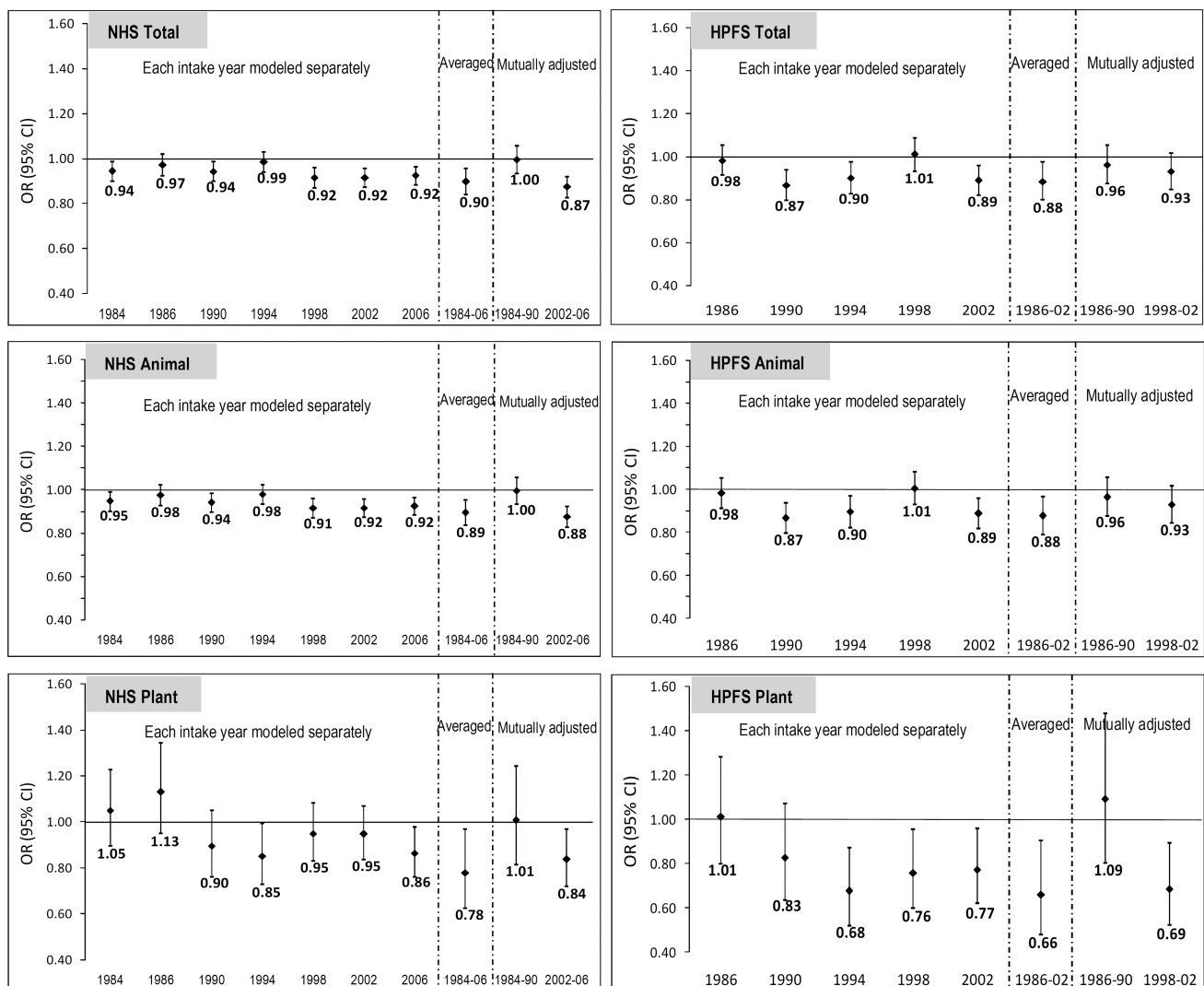
FIGURE 3 Intakes of specific sources of protein at each year of dietary assessment and OR of a 3-unit increment in subjective cognitive decline (SCD). Substituting every 5% of energy intake from each specific protein for the same amount of energy from total carbohydrates. Multivariate model: Nurses' Health Study (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, bachelor's degree, master's or doctorate degree), husband's education (high school or lower education, college, graduate school), race (white, black, other), smoking history (never, ≤4 pack-years, 5–24 pack-years, ≥24 pack-years), depression, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–25, 25–30, >30 kg/m^2) from 1984 to 2006, 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). Health Professionals Follow-up Study (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, family history of dementia, physical activity level (metabolic equivalent–h/wk, quintiles), BMI (<23, 23–24.9, 25–29.9, ≥30 kg/m^2) from 1986 to 2002, multivitamin use (yes/no), intake of alcohol (g/d), profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian), missing indicator for SCD measurement at 2008 or 2012, and the number of dietary assessments during 1986–2002. Both cohorts also adjusted for intakes carotenoids (quintiles), anthocyanins (quintiles), and vitamins C, D, and E (quintiles). All models adjusted for the percentage of energy intake from *trans* fat, saturated fat, MUFA, and PUFA. The percentages of energy from animal and plant protein were mutually adjusted. Poisson regression was used for data analysis.

were also seen in other studies (18, 40) [an inverse association between fish consumption and dementia was seen only among *APOE* 4 noncarriers in the Three-City cohort study (18)]. For other protein food sources, current evidence also remained inconclusive (16, 20, 41, 42). 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 concentrations of AGEs among major protein sources (43). A low-AGE diet was found to be associated with significantly lower brain amyloid protein accumulation (44). 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 (43, 44) on AGEs. Different cooking methods may also affect AGE formation: cooking with high and dry heat such as frying or roasting resulted in significantly higher concentrations of AGE (43), which may have been reflected in the positive association between chicken with skin and SCD seen in our cohorts.

Over 20 y 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 detailed analyses. Dietary intake averaged from multiple dietary assessments over time reduced the effects of random error and within-person variations. Updating dietary data ceased 6 y prior to SCD assessments minimized the impact of altered cognitive function on diet. We also included comprehensive information on many possible confounders, and we adjusted for these variables 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 highly educated participants may also have relatively good insights in reporting subtle cognitive changes (45). Second, objective cognitive assessment was not included in our study. However, SCD has been repeatedly validated and has been found to be strongly associated with both concurrent objective cognitive function (4, 5) and subsequent cognitive decline (5). Moreover, SCD can be more advantageous in detecting subtle cognitive changes (46), especially in those with higher education (6). 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, and in our sensitivity analysis including only participants with both SCD assessments, the results remained similar. Finally, limited generalizability could be an issue, because the study populations were mainly Caucasian and health care 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.

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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