Web Appendix 1

Study populations

Three-City Study

The 3C study is a prospective cohort initiated in 1999-2000 of 9,294 non-institutionalized community dwellers aged ≥65 years from 3 French cities (Bordeaux, Dijon, and Montpellier) (1). The protocol of the 3C study was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital, Paris, France. Data collected at baseline included socio-demographic, lifestyle and health information, a brief food frequency questionnaire (FFQ) (2), neuropsychological testing and blood samples. Participants have been followed every two to three years during in-home interviews. Among the 7,899 3C participants who answered the baseline FFQ and had at least one repeated cognitive evaluation, 5,641 Caucasian participants were genotyped for *APOE* and had genome-wide genotyping (3).

Nurses' Health Study

The NHS began in 1976 when 121,700 female registered nurses aged 30–55 years, residing in 11 U.S. states, completed a mailed questionnaire about their health and lifestyle. Follow-up questionnaires are sent every 2 years; follow-up of the cohort remains ~90% to date. In 1980, participants completed a semi-quantitative FFQ (4). In 1984, the FFQ was expanded and similar FFQs were sent in 1986 and every 4 y thereafter. From 1995 to 2001, a cognitive sub-study was initiated in participants who were ≥70 y and free of stroke. Among eligible women, 19,415 (93%) completed the first telephone-based cognitive assessment. Follow-up telephone assessments were performed three times at 2-y intervals, with a high participation rate (>90% among those remaining alive at each follow-up point). The study was

approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). In 2002, a buccal sample was collected from willing participants of the NHS cognitive study, allowing *APOE* genotyping for 4,304 participants. In addition, genome-wide genotypes were available in subsamples from the cognitive sub-study as part of nine previous independent case-control GWAS (5-12); the subset consisted of 14,061 Caucasian Nurses with at least one FFQ and one repeated cognitive evaluation after baseline.

Women's Health Study

The WHS was a randomized controlled factorial 2x2 trial of low dose aspirin and vitamin E supplements for the primary prevention of cardiovascular disease and cancer in women. Briefly, between 1992 and 1995, 39,876 US female health professionals aged ≥45 years and with no history of coronary heart disease, cerebrovascular disease, cancer, or chronic liver or kidney disease were randomized. At trial baseline, participants completed a questionnaire about medical history and lifestyle, including a semi-quantitative FFQ (13). Annual mailed questionnaires were subsequently sent to participants to update health and medical information. Follow-up was >99% through the scheduled end of the trial, in 2004. In 1998, an average 5.6 years after trial baseline, a sub-study of cognitive function was initiated among participants aged ≥65 years. This study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). Among age-eligible women, 6,377 (89%) completed the initial cognitive assessment by telephone. Participants underwent two follow-up telephone cognitive assessments at approximately 2-year intervals, with 80% participation rate (14). Among the 5,677 WHS participants who completed the baseline FFQ and had at least two repeated cognitive evaluations, *APOE* and genome-wide genotyping were available among 3,173 Caucasians who provided blood samples at baseline (15, 16).

Chicago Health and Aging Project

The CHAP is a longitudinal population study of older persons aged 65 years and older (17). Age eligible residents were identified in a door-to-door census of three south side neighborhoods of Chicago, and 79% participated in baseline in-home interviews and cognitive assessments conducted from 1993-1997. The institutional review board of Rush University Medical Center (Chicago, Ill) approved the study. Follow-up in-home interviews and cognitive assessments were conducted every 3 years. Study participants completed a validated 139-item FFQ (18) a median of 1.2 years from the baseline; 86% of survivors with nutrition data had at least one follow-up for cognition. Among the 2,782 CHAP Caucasian participants who completed at least one cognitive examination after baseline, 1201 individuals completed the FFQ and 943 were also genotyped for *APOE* and had GWAS data.

Rush Memory and Aging Project

The MAP is a study of volunteers living in retirement communities, senior public housing or individual homes in the Chicago area aged >55 and free of known dementia at inclusion. The ongoing cohort started in 1997 and includes annual clinical neurological examinations, as previously described (19). The study was approved by the institutional review board of Rush University Medical Center. The follow-up rate of survivors exceeds 90%. From 2004 to 2013, participants were invited to participate in a dietary survey and completed a 139-item FFQ (18). Among the 1,825 participants who completed a baseline cognitive evaluation, 1,064 also completed a FFQ, among whom 831 were Caucasians and had APOE and GWAS data (20).

In the present study, we included reported Caucasian participants across the five cohorts, who *(i)* completed at least one FFQ before initial cognitive assessment; *(ii)* had at least one repeated cognitive evaluation; (*iii*) had available data for *APOE* genotype and other AD

SNPs; and (*iv*) had no missing information for fish intake and educational level. In the NHS where *APOE* and genome-wide genotyping were performed in <25% of those included in the cognitive sub-study, to retain study power, primary analyses of fish and cognitive function were conducted on the total sample rather than only the genotyped sample. Overall, there was no relation between diet, cognition, and selection into the genotyped subsets within any of the cohorts, and thus meaningful selection bias in these analyses is unlikely.

Web Appendix 2

Assessment of cognitive function

Cognitive testing was performed by trained, in-person interviewers in the 3C study, CHAP and MAP and validated telephone interviews in NHS and WHS. Although the cognitive tests differed across cohorts, the overall batteries reflected similar cognitive constructs. In particular, the telephone instrument used in the NHS and WHS was designed to be similar to the two Rush cohorts (CHAP and MAP); in a validation study in which a group of participants was administered both the Rush battery in-person and the NHS battery by phone, a high correlation ($\rho>0.80$) was found between overall performance on the two (averaging together all component tests), demonstrating high comparability of the two assessment batteries and methods.

We defined composite scores of global cognition and episodic memory as primary outcomes. A global cognitive score was computed in each cohort as the mean of Z-scores of cognitive tests assessing (*i*) global cognition, (*ii*) verbal fluency/semantic memory, and (*iii*) working memory and attention. For global cognition, we used the Mini-Mental State Examination (MMSE) (21) in the 3C study, CHAP and MAP; and the Telephone Interview for Cognitive Status (TICS) (22) in the NHS and WHS. For verbal fluency/semantic memory, we used the Isaacs' Set Test (23) in the 3C study; a category fluency test in NHS and WHS (24); and a composite measure of semantic memory (25) combining a category fluency test, the Boston naming test and the National Adult Reading Test in MAP. For working memory and attention, we used the Benton Visual Retention Test (26) in the 3C study; Digit Span

Backward Test in NHS; Symbol Digits Modalities Test (27) in CHAP; and Digit Span Backward, Digit Span Forward and Digit Ordering Tests in MAP (25).

In addition, episodic memory tests were combined in a composite score (calculated as the mean of Z-scores of tests assessing episodic memory). In the NHS and WHS, we combined immediate and delayed recalls of the East Boston Memory test (28) and the TICS 10-word list. In MAP, episodic memory was assessed by: word list memory, recognition and recall from CERAD, immediate and delayed recall of Story A from the logical memory subset of the Wechsler Memory Scale-Revised, and immediate and delayed recall of the East Boston Memory test (25). In CHAP, episodic memory was assessed by immediate and delayed recall of the East Boston Memory Test (25, 29). In the 3C study, we computed an episodic memory score using a subset of the MMSE, defined as the sum of items related to orientation to time and the 3-word recall task. In a validation study (30), this sub-score correlated reasonably well ($\rho>0.40$) with scores obtained on the Free and Cued Selective Reminding Test (FCSRT, a validated test of episodic memory (31)), and was equivalent to the FCSRT in predicting incident AD in the 3C study (30), demonstrating its validity for use as a proxy of episodic memory in that cohort.

Web Appendix 3

Assessment of diet

For control of other dietary variables (meat, fruit and vegetables), we used either categorical variables (meat intake ≤ 1 time/week, 2 to 3 times/week, and ≥ 4 times/week; raw and/or cooked fruits/vegetables ≤3 times/week, 4 to 6 times/week, and ≥ daily in: 3C study, NHS and WHS) or continuous variables in servings/week (in CHAP and MAP). Total energy intake was estimated from the FFQs in the 4 US cohorts. In the 3C study, energy was available only in the Bordeaux center where a 24h dietary recall was administered. For participants of the 2 other 3C centers (Dijon and Montpellier), total energy intake was imputed with multiple imputations, using a methodology described in a previous publication (32).

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Web Table 1. Candidate single nucleotide polymorphisms previously associated with the risk of Alzheimer's disease included in this analysis

SNP	Chromosome	Closest gene	Allele coded	Number of studies genotyped	Number of studies imputed
rs11136000	**8**	**CLU**	T	4	1
rs9331888	**8**	**CLU**	G	1	4
rs6656401	**1**	**CR1**	A	5	0
rs744373	**2**	**BIN1**	G	3	2
rs12989701	**2**	**BIN1**	A	2	3
rs541458	**11**	**PICALM**	C	3	2
rs3764650	**19**	**ABCA7**	G	3	2
rs610932	**11**	**MS4A6A**	T	3	2
rs670139	**11**	**MS4A4E**	T	2	3
rs4938933	**11**	**MS4A4A**	C	1	4
rs9349407	**6**	**CD2AP**	C	0	5
rs3865444	**19**	**CD33**	A	2	3
rs11767557	**7**	**EPHA1**	C	4	1

Web Table 2. Minor allele frequencies for candidate single nucleotide polymorphisms across the 5 cohorts included

	3C	NHS	WHS	CHAP	MAP
rs11136000	0.39	0.41	0.41	0.41	0.41
rs9331888	0.27	0.27	0.29	0.28	0.30
rs6656401	0.19	0.18	0.18	0.17	0.18
rs744373	0.28	0.28	0.28	0.29	0.29
rs12989701	0.14	0.15	0.15	0.16	0.16
rs541458	0.31	0.30	0.32	0.30	0.34
rs3764650	0.10	0.10	0.08	0.09	0.08
rs610932	0.45	0.42	0.42	0.44	0.42
rs670139	0.38	0.41	0.41	0.40	0.43
rs4938933	0.42	0.40	0.41	0.41	0.41
rs9349407	0.28	0.27	0.26	0.26	0.27
rs3865444	0.31	0.32	0.31	0.31	0.32
rs11767557	0.21	0.21	0.20	0.20	0.21

Abbreviations: 3C: Three-City study; CHAP: Chicago Health and Aging Project; NHS: Nurses' Health Study; MAP: Memory and Aging Project; WHS: Women's Health Study.

Web Table 3. Multivariate Associations Between Fish Intake and Change in Global Cognition Across all 5 Cohort Studies Included

Cohort	Weekly servings of fish (n)		Global cognitive change (standard units/year)					
			Model 3[a]			Model 4[b]		
			β	95% CI	*P-trend*	β	95% CI	*P-trend*
3C study	< 1	(629)	Ref			Ref		
(N=5,641)	1	(2,178)	-0.002	-0.013, 0.009		-0.003	-0.010, 0.022	
	2 to 3	(2,519)	0.000	-0.010, 0.011	0.364	-0.000	-0.011, 0.010	0.407
	≥ 4	(315)	0.007	-0.010, 0.023		0.006	-0.013, 0.008	
NHS	< 1	(8,502)	Ref			Ref		
(N=13,129)	1	(3,099)	0.002	-0.003, 0.008	0.097	0.002	-0.003, 0.008	0.115
	2 to 3	(1,184)	0.007	-0.001, 0.015		0.007	-0.001, 0.015	
	≥ 4	(344)	0.003	-0.011, 0.018		0.003	-0.011, 0.017	
WHS	< 1	(1,586)	Ref			Ref		
(N=3,170)	1	(987)	-0.018	-0.035, -0.001	0.608	-0.018	-0.035, -0.001	0.700
	2 to 3	(367)	-0.013	-0.037, 0.012		-0.013	-0.038, 0.011	
	≥ 4	(230)	0.022	-0.008, 0.051		0.019	-0.010, 0.049	
CHAP	< 1	(327)	Ref			Ref		
(N=932)	1	(250)	0.005	-0.015, 0.025	0.060	0.005	-0.016, 0.025	0.057

	2 to 3	(338)	0.018	-0.001, 0.038		0.018	-0.001, 0.038	
	≥ 4	(17)	0.020	-0.050, 0.091		0.021	-0.049, 0.091	
MAP	< 1	(204)	Ref		0.732	Ref		0.788
(N=816)	1	(206)	0.053	0.001, 0.105		0.049	-0.003, 0.100	
	2 to 3	(354)	0.032	-0.018, 0.082		0.031	-0.019, 0.080	
	≥ 4	(52)	0.002	-0.086, 0.091		-0.005	-0.093, 0.083	
Pooled	< 1	(11,248)	Ref			Ref		
(N=23,688)	1	(6,720)	-0.001	-0.010, 0.009	0.021	-0.001	-0.010, 0.009	0.028
	2 to 3	(4,762)	0.005	-0.002, 0.013		0.005	-0.004, 0.014	
	≥ 4	(958)	0.007	-0.003, 0.016		0.006	-0.004, 0.016	

Abbreviations: 3C study: Three-City study; CHAP: Chicago Health and Aging Project; NHS: Nurses' Health Study; MAP: Memory and Aging Project; WHS: Women's Health Study.

Estimates were computed in each cohort using linear mixed models and further pooled using inverse-variance weighted meta-analysis. P-for-trends were computed using fish intake as a discrete variable variable taking 4 possible values (0, 1, 2.5 or 4 servings / week).

[a] model 3 was adjusted for age, education, sex (in 3C study, CHAP and MAP only, where applicable), study center (3C study only) and treatment allocation arm (WHS only), income, smoking, regular exercise, total energy intake, fruits and vegetables and meat intakes, and moderate alcohol, history of heart disease, hypertension, hypercholesterolemia, and type 2 diabetes

[b] model 4 included covariates from model 3 and BMI and depression

Web Table 4. Multivariate Associations Between Fish Intake and Change in Episodic Memory Across all 5 Cohort Studies Included

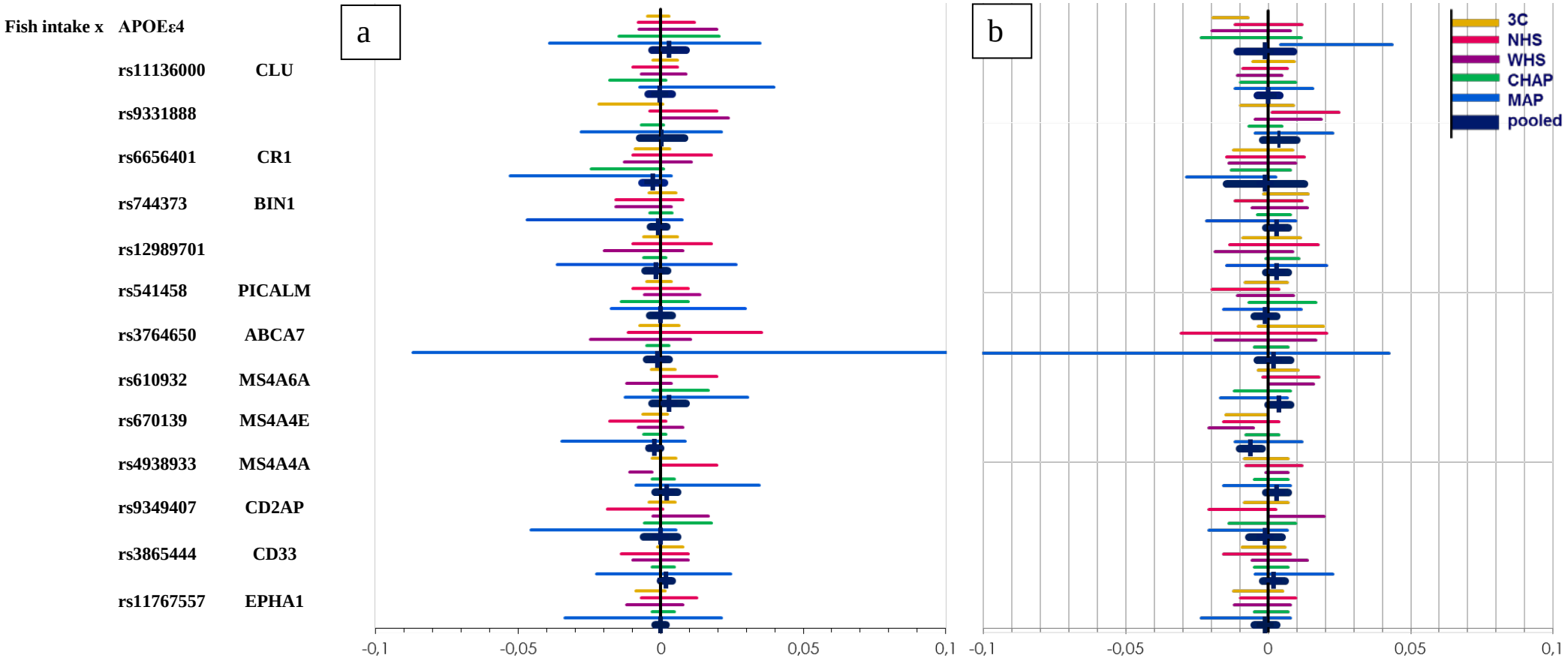
	Weekly servings of fish (n)		**Episodic memory change (standard units/year)**					
			Model 3[a]			**Model 4[b]**		
			β	**95% CI**	***P-trend***	**β**	**95% CI**	***P-trend***
3C study	< 1	(629)	Ref			Ref		
(N=5,641)	1	(2,178)	0.001	-0.017, 0.019	0.115	0.001	-0.017, 0.019	0.114
	2 to 3	(2,519)	0.006	-0.011, 0.024		0.006	-0.011, 0.024	
	≥ 4	(315)	0.022	-0.006, 0.049		0.022	-0.006, 0.049	
NHS	< 1	(8,502)	Ref			Ref		
(N=13,129)	1	(3,099)	0.000	-0.006, 0.006	0.143	0.000	-0.006, 0.006	0.163
	2 to 3	(1,184)	0.005	-0.004, 0.014		0.005	-0.004, 0.013	
	≥ 4	(344)	0.010	-0.006, 0.026		0.009	-0.006, 0.025	
WHS	< 1	(1,586)	Ref			Ref		
(N=3,170)	1	(987)	-0.001	-0.018, 0.016	0.004	-0.001	-0.017, 0.016	0.004
	2 to 3	(367)	0.017	-0.007, 0.041		0.017	-0.007, 0.041	
	≥ 4	(230)	0.043	0.014, 0.073		0.043	0.014, 0.072	
CHAP	< 1	(327)	Ref			Ref		
(N=932)	1	(250)	0.000	-0.020, 0.020	0.766	0.001	-0.018, 0.021	0.661
	2 to 3	(338)	0.001	-0.018, 0.020		0.003	-0.017, 0.022	

	≥ 4	(17)	0.023	-0.048, 0.093		0.022	-0.049, 0.093	
MAP	< 1	(204)	Ref		0.898	Ref		0.873
(N=816)	1	(206)	0.020	-0.009, 0.049		0.021	-0.008, 0.050	
	2 to 3	(354)	0.007	-0.020, 0.035		0.008	-0.020, 0.035	
	≥ 4	(52)	-0.005	-0.056, 0.046		-0.006	-0.057, 0.045	
Pooled	< 1	(11,248)	Ref			Ref		
(N=23,688)	1	(6,720)	0.001	-0.004, 0.006	0.021	0.001	-0.004,0.006	0.021
	2 to 3	(4,762)	0.006	-0.001, 0.012		0.006	-0.001,0.012	
	≥ 4	(958)	0.018	0.004, 0.032		0.018	0.004,0.033	

Abbreviations: 3C study: Three-City study; CHAP: Chicago Health and Aging Project; NHS: Nurses' Health Study; MAP: Memory and Aging Project; WHS: Women's Health Study.
Estimates were computed in each cohort using linear mixed models and further pooled using inverse-variance weighted meta-analysis. P-for-trends were computed using fish intake as a discrete variable variable taking 4 possible values (0, 1, 2.5 or 4 servings / week).

[a] model 3 was adjusted for age, education, sex (in 3C study, CHAP and MAP only, where applicable), study center (3C study only) and treatment allocation arm (WHS only), income, smoking, regular exercise, total energy intake, fruits and vegetables and meat intakes, and moderate alcohol, history of heart disease, hypertension, hypercholesterolemia, and type 2 diabetes
[b] model 4 included covariates from model 3 and BMI and depression

Web Figure 1. Gene-environment interactions between Alzheimer's disease candidate single nucleotide polymorphisms and fish intake on change in global cognition (panel a) and episodic memory (panel b) across all 5 cohort studies included.



The figure represents annual change in global cognition (panel a) and episodic memory (panel b) summary scores (point estimates and 95% confidence intervals, in standard units/year) for the effect of SNP-by-fish intake-by time interaction term (with SNPs coded as count of minor allele and fish as a continuous variable represented by medians of fish intake categories). Estimates were computed in each cohort using linear mixed models adjusted for age, education, sex (in 3C study, CHAP and MAP only), study center (3C study only) and treatment allocation arm (WHS only), and further pooled using inverse-variance weighted meta-analysis.
Abbreviations: 3C study: Three-City study; CHAP: Chicago Health and Aging Project; NHS: Nurses' Health Study; MAP: Memory and Aging Project; SNP: single nucleotide polymorphism; WHS: Women's Health Study.