Relationship of omega-3 fatty acids with dementia and cognitive decline: cohort evidence from perspective of supplementation, dietary intake, and blood markers Bao-Zhen Wei & Lin Li

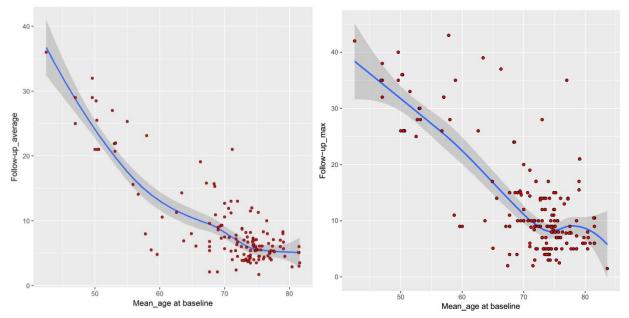
# Supplementary Table 1. Predesigned templates for data extraction

first author,	cohort	study	mean age	female	sample size	number	of	follow- uj	р	attrition rate	cognitive	;	exposure	outcome	confounders	multivaria	able-
publication	name,	design		percentage		incident		duration		during	status	at	measureme	definition		adjusted	risk
year	country					cases				follow-up	baseline		nt			estimates	

#### Supplementary Table 2. Newcastle-Ottawa Quality Assessment Scale- Cohort Studies (involving version) &.

Risk of bias	Questions	Scores	Standards
			a) randomly selected or
			b) database covering very large population or
		\$	c) participation rate (PR) is $\ge 90\%$ or
	Q1. representativeness of the		d) reported there is no difference in important characteristics between those who agreed to participate and those who did
	exposed cohort		not
		0.5☆	PR varies from 70% to 90% with no reporting of significant difference in important characteristics between those who
Selection		0.3 x	agreed to participate and those who did not
(generalisability,		0	Selected group of users e.g. nurses, volunteers or no description
assessment bias	Q2. selection of the	☆	Drawn from the same community as the exposed cohort
and potential	non-exposed cohort	0.5☆	Self-report to simple question with potential recall bias
reverse causality)	non-exposed conort	0	Drawn from a different source or no description of the derivation of the non-exposed cohort
		☆	Questionnaire or interview based on self-report to series questions or database
	Q3. ascertainment of exposure	0.5☆	Self-report to simple question with potential recall bias
		0	No description
	Q4. demonstration that	☆	Cognitively intact for outcome as dementia or MCI; Free of dementia for population with MCI at baseline
	outcome of interest was not	0.5☆	Free of dementia (cognitively intact & cognitive impairment no dementia (CIND)) for outcome of dementia
	present at baseline	0	No description
	Q5. comparability of cohorts	**	Except for age, sex, and education, the analysis still controls forat least another two domains of AD risk factors, including
Confounding bias	on the basis of the design or	AA	APOE4, pre-existing disease, lifestyle, medical exposure, biochemical exposure, occupation, diet, etc.
Comounding bias	analysis	☆	Controls for age, sex and education
	anarysis	0	No description
		☆	Independent or blind assessment
	Q6. assessment of outcome	0.5☆	Record linkage (e.g. identified through ICD codes on database records or claim data)
0.4		0	Self-report or no description
Outcome	Q7. follow-up long enough for	\$	The average or max duration reached the lower 95% CI.
(assessment bias	outcomes to occur?#	0	The average or max duration did not reach the lower 95% CI.
and attrition bias)		☆	Attrition rate $\leq 5\%$
	Q8. adequacy of follow up of cohorts <sup>*</sup>	0.5☆	$5\% \leq \text{Attrition rate} \leq 20\%$
	conorts	0	Attrition rate $> 20\%$ and no description of those lost or no description

& A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. In the involving version, an assignment of a half point (0.5) is permitted.



**#Figure**: It is obviously absurd to define a common period for population with diverse age range at baseline. A presumable negative correlation was reasonably supposed to exist between so-called adequate follow-up period and average age of population at baseline. Here, we will draw the nonlinear regression line with its 95% confidence interval (CI) for the association between the mean/max follow-up duration and mean age of population at baseline for AD cohorts (unpublished data). We will predefine that the follow-up is adequate if the average or max duration reach the lower 95% CI [1]. \*It has been indicated that a rate of loss < 5% probably leads to little bias, whereas a rate of loss that is greater than 20% potentially poses serious threats to validity [2].

#### Reference

[1] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603-5.
[2] Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. NewYork: Churchill Livingstone, 1997.

#### Supplementary Table 3. Assessment of credibility of meta-analyses

The evidence robustness of meta-analysis was assessed by summing five domains: risk of bias, heterogeneity, publication bias, effect size, and imprecision. Scores in each domain ranged from 0 to 10, and a score of 50 represents the highest level of evidence. Scores were summed up for each exposure and then we ranked them in descending order, the top third of evidence rating is categorized into high level (H), the middle third is moderate level (M), and the bottom third is low level (L).

(1) Risk of bias: We calculated the weighted quality score (WQS)=QS (study 1) × weight% (study 2) + QS (study 2) × weight% (study 2) + .....QS (study n) × weight% (study n), "QS" means NOS score; "Weight" means weight value in the random model.

(2) Heterogeneity: we assigned scores 10 to 0 points in proportion to I<sup>2</sup> 0-100% in the random model.

(3) Publication bias:

If study number  $(n) \ge 10$ , and no publication bias exists, score 10.

If publication bias exists, but results remained significant/non-significant after trim and fill, score 5.

If  $n \le 10$ , a quarter of full score will be deducted correspondingly.

Regardless of the number of studies, once publication bias exists and results significantly changed after trim and fill, no score was assigned.

(4) Effect size: RR=0.75 or 1.25 is representative of the rough cutoff of evident benefits or harm. If RR > 1.25 or RR < 0.75, full score 10 was assigned. Otherwise, scored assigned based on the calculation formula |RR-1|\*40.

(5) Imprecision: A 95% prediction interval (PI) was calculated for rating imprecision [1].

If neither 95%CI nor 95% PI contained RR=1, score 10.

If both contained RR=1 but didn't contain RR=0.75 or 1.25, score 7.5.

If 95%CI didn't contain RR=1, but 95% PI contained RR=1, score 5.

If both contained RR=1 but only 95% PI contained RR=0.75 or 1.25, score 2.5.

If both contained RR=1 & 0.75 or 1.25, or PI was unavailable, score 0.

#### Reference

[1] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. Bmj. 2011;342:d549. doi:10.1136/bmj.d549

#### Supplementary Table 4. Index S (Systematic review index).

This index was designed weighing up both the study quality and the direction of research conclusion: L = 0 (2) O(2) U = 0 (2) O(2) (2) O(2)

The "N" refers to the total number of studies included in the meta-analysis.

We calculated both index  $S_{for}$  and index  $S_{against}$ . As for the former index, when the research conclusion is consistent with that of meta-analysis, the value of "P" is equal to 1; Otherwise, the P-value is equal to zero. The opposite is true for the index  $S_{against}$ . The indexes range from 1% to 100%. A higher index  $S_{for}$  or index  $S_{against}$  respectively represents that there are more high-quality studies supportive of or opposed to the meta-analysis conclusions. The difference between the index  $S_{for}$  and index  $S_{against}$  was also calculated as index  $S_{difference}$ . The larger the difference, the more current research supports the pooled results of this factor. If the difference tends to zero or even less than zero, it indicates that there is great controversy about the predictive role of this factor in current studies.

	index S <sub>for</sub>	index S <sub>against</sub>	index S <sub>difference</sub>
D-PUFA	0.339	0.428	-0.089
D-omega3	0.176	0.534	-0.358
D-DHA	0.372	0.350	0.022
D-EPA	0.321	0.401	-0.08
D-ALA	0.722	0	0.722
P-omega3	0.5	0.208	0.292
P-EPA	0.259	0.5	-0.241
P-DHA	0.278	0.457	-0.179
P-ALA	0.380	0.370	0.01
E-omega3	0.644	0.111	0.533
E-EPA	0.789	0	0.789
E-DHA	0.0926	0.657	-0.5644

		Model 1		Model 2		Model 3	
	n./total	HR	р	HR	р	HR	р
Omega-3 supplemen	tation						
non-exposure (N)	164/779	1 (reference)		1 (reference)		1 (reference)	
exposure (Y)	35/248	0.64 (0.45-0.93)	0.018	0.62 (0.43-0.90)	0.011	0.65 (0.45-0.94)	0.023
medium exposure	28/181	0.72 (0.48-1.08)	0.109	0.70 (0.47-1.04)	0.079	0.72 (0.48-1.08)	0.112
long-term exposure	7/67	0.45 (0.21-0.96)	0.039	0.43 (0.20-0.92)	0.030	0.47 (0.22-1.02)	0.055
<b>Blood markers</b>							
omega-3	187/767	0.93 (0.46-1.89)	0.848	1.33 (0.65-2.70)	0.433	1.47 (0.72-3.02)	0.295
DHA	187/767	0.92 (0.55-1.53)	0.739	1.20 (0.72-1.98)	0.481	1.28 (0.76-2.14)	0.349
ALA	187/767	0.84 (0.43-1.61)	0.594	0.98 (0.52-1.83)	0.944	1.00 (0.52-1.92)	0.997

Supplementary Table 5. Sensitivity analyses for the association of dietary omega-3 supplementation use and its blood biomarkers with risk of AD.

Abbreviations: Sensitivity analyses were conducted by excluding those who progressed to dementia within 1 year follow-up;

ALA = alpha linolenic acid; DHA = docosahexaenoic acid;

Model 1: crude HR with no covariates adjusted;

Model 2: HR adjusted for age, sex, education, clinical diagnosis and APOE ε4;

Model 3: HR adjusted for model 2 plus insomnia, depression, anxiety, hypertension, diabetes mellitus, hyperlipidemia, smoking, BMI, stroke, and coronary heart disease, multivitamins, vitamin B12, folate, anti-hypertensive drugs and anti-diabetic drugs;

Supplementary Table 6. Subgroup analyses for association between exposure measurement and cognitive decline.

			D-PUFA			D-omega3			D-EPA			D-DHA	
Strata	Subgroup	N	Pooled results	I <sup>2</sup> (p value)	Ν	<b>Pooled results</b>	I <sup>2</sup> (p value)	Ν	Pooled results	I <sup>2</sup> (p value)	Ν	Pooled results	I <sup>2</sup> (p value)
Total		10	0.91(0.81-1.02)	18.4% 0.274	18	0.91(0.82-1.00)	60.0% 0.001	9	1.02(0.88-1.19)	65.6% 0.003	13	0.82 (0.72-0.93)	63.6% 0.001
	Europe	8	0.98(0.86-1.12)	2.4% 0.411	9	0.95(0.77-1.16)	58.3% 0.014	2	1.01(0.84-1.21)	0 0.527	2		0 0.446
Region	North	1	0.76(0.55-1.07)		5	0.91(0.80-1.02)	59.4% 0.043	5	1.05(0.82-1.33)	78.1% 0.001	9	0.78(0.69-0.87)	42.4% 0.085
	Asia	1	0.84(0.73-0.96)		4	0.77(0.52-1.12)	77.1% 0.004	2	0.77(0.32-1.83)	78.1% 0.032	2	0.61(0.16-2.26)	89.7% 0.002
	Male				1	0.81(0.39-1.56)							
Sex	Female	1	1.03(0.86-1.25)		1	0.81(0.66-0.98)							
	Mixed	9	0.87(0.78-0.98)	7.0% 0.377	16	0.92(0.82-1.02)	62.0% 0.001	9	1.02(0.88-1.19)	65.6% 0.003	13	0.82 (0.72-0.93)	63.6% 0.001
	<1000	1	0.65(0.43-0.98)		3	1.02(0.35-3.00)	79.1% 0.008	2	0.94(0.82-1.08)	0 0.923	6	0.63(0.46-0.88)	59.0% 0.032
Sample size	1000-5000	5	0.92(0.77-1.10)	6.7% 0.369	9	0.86(0.76-0.98)	67.7% 0.002	5	1.03(0.78-1.35)	79.8% 0.001	5	0.83(0.70-0.99)	72.6% 0.006
	>5000	4	0.94(0.81-1.1)	26% 0.255	6	0.98(0.83-1.15)	35.3% 0.172	2	1.01(0.84-1.22)	0 0.527	2	1.04(0.87-1.25)	0 0.446
Cognitive	Not mentioned	4	0.88(0.74-1.04)	43.1% 0.153	6	0.86(0.73-1.03)	52.4% 0.062	2	0.77(0.32-1.83)	78.1% 0.032	4	0.61(0.36-1.04)	84.9% 0.000
status at baseline	Free of dementia	6	0.96(0.81-1.13)	2.5% 0.400	12	0.93(0.81-1.05)	63.3% 0.002	7	1.04(0.88-1.23)	67.9% 0.005	9	0.86(0.78-0.96)	38.4% 0.112
A go stago	Midlife	2	0.84(0.74-0.97)	0 0.757	4	0.86(0.67-1.11)	67% 0.028	3	0.94(0.73-1.21)	60.6% 0.079	3	0.84(0.58-1.23)	80.5% 0.006
Age stage	Latelife	8	0.93(0.80-1.08)	23.2% 0.245	14	0.91(0.81-1.02)	60.8% 0.002	6	1.07(0.87-1.31)	69.2% 0.006	10	0.80(0.70-0.91)	52.9% 0.024
Follow-up	< 10y	5	0.91(0.74-1.12)	36.7% 0.176	13	0.92(0.82-1.05)	60.3% 0.003	7	1.04(0.88-1.23)	67.9% 0.005	11	0.82(0.73-0.92)	51.2% 0.025
(max)	≥ 10y	5	0.90(0.79-1.03)	12.9% 0.332	5	0.86(0.71-1.04)	61.6% 0.034	2	0.77(0.32-1.83)	78.1% 0.032	2	0.61(0.16-2.26)	89.7% 0.002
Adjusted for	Yes	4	0.76(0.57-1.01)	0.0% 0.769	8	0.83(0.71-0.97)	65% 0.006	5	1.05(0.82-1.33)	78.1% 0.001	9	0.78(0.69-0.87)	42.4% 0.085
APOE4	No	6	0.94(0.82-1.08)	39.3% 0.144	10	0.96(0.83-1.12)	60.0% 0.007	4	1.00(0.85-1.18)	40% 0.172	4	0.95(0.71-1.28)	70.9% 0.016
	Dementia	2	0.84(0.42-1.68)	51.2% 0.152	5	0.96(0.82-1.11)	66.6% 0.030	3	0.98(0.66-1.45)	77.8% 0.011	5	0.73(0.56-0.96)	69.5% 0.011
	AD	3	0.90(0.69-1.18)	19.6% 0.288	7	0.91(0.77-1.06)	58.3% 0.035	4	1.01(0.73-1.40)	74.2% 0.009	6	0.76(0.61-0.95)	56.9% 0.041
Outcome	Cognitive decline but not dementia	2	0.92(0.76-1.12)	66.4% 0.085	5	0.89(0.73-1.09)	66.7% 0.010	1	0.94(0.81-1.08)		2	1.00(0.83-1.21)	
Effect	HR/RR	5	0.91(0.74-1.12)	36.7% 0.176	10	0.93(0.84-1.04)	47.7% 0.045	6	1.07(0.87-1.31)	69.2% 0.006	8	0.85(0.75-0.96)	42.5% 0.095
estimate	tRR	5	0.97(0.79-1.03)	12.9% 0.332	8	0.86(0.68-1.09)	70.4% 0.001	3	0.94(0.73-1.21)	60.6% 0.079	5	0.71(0.51-0.99)	80.5% 0.000
NOS score	<7	6	1.00(0.88-1.14)	0 0.428	12	0.91(0.80-1.03)	67.2% 0.000	6	1.09(0.89-1.33)	67.2% 0.009	8	0.78(0.66-0.92)	72.1% 0.001
INOS SCORE	≥7	4	0.82(0.72-0.93)	0% 0.706	6	0.90(0.75-1.06)	40.0% 0.139	3	0.92(0.73-1.14)	52.3% 0.123	5	0.89(0.71-1.11)	44.2% 0.127

			D-ALA			P-omega3			P-EPA			P-DHA	
Strata	Subgroup	Ν	<b>Pooled results</b>	I <sup>2</sup> (p value)	N	<b>Pooled results</b>	I <sup>2</sup> (p value)	N	<b>Pooled results</b>	I <sup>2</sup> (p value)	Ν	Pooled results	I <sup>2</sup> (p
Total		8	0.93(0.85-1.01)	0 0.998	3	0.94(0.63,1.42)	75.2% 0.018	8	0.88(0.78-0.995)	38.1% 0.126	12	0.88(0.76-1.03)	63.6%
	Europe	1	0.91(0.76-1.1)		1	0.62(0.42-0.9)		4	0.86(0.71-1.05)	69.3% 0.021	3	0.94(0.76-1.18)	67.6%
Region	North America	4	0.92(0.79-1.07)	0 0.911	2	1.11(0.96-1.28)	0 0.64	1	0.96(0.81-1.15)	64.7% 0.023	6	0.89(0.73-1.08)	60.0%
	Asia	3	0.94(0.83-1.06)	0 0.942				3	0.77(0.52-1.14)	0 0.895	3	0.47(0.15-1.50)	80.6%
	Male							1	1.12(0.92-1.38)				
Sex	Female	1	0.91(0.76-1.1)										
	Mixed	7	0.93(0.85-1.02)	0 0.994	3	0.94(0.63,1.42)	75.2% 0.018	7	0.85(0.78-0.93)	0.0% 0.484	12	0.88(0.76-1.03)	63.6%
	<1000	1	0.93(0.8-1.09)		1	1.27(0.71-2.28)		2	0.61(0.31-1.47)	0 0.776	7	0.75(0.59-0.94)	45.8%
Sample size	1000-5000	6	0.90(0.78-1.04)	0 0.994	2	0.85(0.49-1.49)	86.7% 0.006	5	0.89(0.77-1.03)	61.8% 0.033	5	1.01(0.86-1.18)	61.7%
	>5000	1	0.95(0.82-1.09)					1	0.8(0.5-1.25)		1	1.17(0.73-1.87)	
Cognitive	Not mentioned	4	0.93(0.84-1.03)	0 0.978	1	1.1(0.95-1.28)		2	1.03(0.89-1.19)	21.3% 0.26	5	0.999(0.88-1.13)	45.4%
status at baseline	Free of dementia	4	0.92(0.79-1.07)	0 0.911	2	0.86(0.43-1.72)	75.4% 0.044	6	0.81(0.73-0.91)	0.0% 0.712	7	0.75(0.56-0.998)	59.6% 0.021
A an ata an	Midlife	4	0.94(0.85-1.03)	0 0.998	1	1.1(0.95-1.28)		2	1.03(0.89-1.19)	21.3% 0.26	3	0.84(0.58-1.23)	80.5%
Age stage	Latelife	4	0.90(0.75-1.07)	0 0.932	2	0.86(0.43-1.72)	75.4% 0.044	6	0.81(0.73-0.91)	0.0% 0.712	9	0.77(0.63-0.94)	46.5%
Follow-up	< 10y	4	0.92(0.79-1.07)	0 0.911	3	0.94(0.63,1.42)	75.2% 0.018	4	0.85(0.74-0.96)	39.6%	7	0.85(0.70-1.03)	63.5%
(max)	≥10y	4	0.94(0.84-1.05)	0 0.718				4	1.03(0.85-1.24)	1.4% 0.385	5	0.92(0.69-1.22)	68.0%
Adjusted for	Yes	4	0.92(0.79-1.07)	0 0.911	3	0.94(0.63,1.42)	75.2% 0.018	4	0.85(0.74-0.96)	39.6% 0.174	7	0.85(0.70-1.03)	63.5%
APOE4	No	4	0.94(0.84-1.05)	0 0.718				4	1.03(0.85-1.24)	1.4% 0.385	5	0.92(0.69-1.22)	68.0%
	Dementia	2	0.93(0.52-1.67)	0 0.943	1	0.62(0.42-0.9)		3	0.84(0.73-0.96)	0.0% 0.385	5	0.86(0.72-1.03)	53.6%
	AD	2	0.72(0.37-1.42)	0 0.91	1	1.27(0.71-2.28)		2	0.92(0.63-1.35)	86.3% 0.007	4	0.96(0.75-1.21)	40.0%
Outcome	Cognitive decline but not dementia	3	0.93(0.85-1.02)	0 0.935	1	1.1(0.95-1.28)		3	0.94(0.80-1.12)	0 0.658	3	0.47(0.15-1.50)	84.3% 0.002
Effect	HR/RR	3	0.80(0.48-1.33)	0 0.902	2	0.86(0.43-1.72)	75.4% 0.044	4	0.86(0.71-1.05)	69.3% 0.021	6	0.91(0.77-1.08)	56.6%
estimate	tRR	5	0.93(0.85-1.01)	0 0.995	1	1.1(0.95-1.28)		4	0.93(0.79-1.09)	0 0.735	6	0.80(0.57-1.10)	72.8%
NOS score	<7	6	0.92(0.82-1.02)	0 0.999	2	1.11(0.96-1.28)	0.0%	2	1.03(0.89-1.19)	21.3%	6	1.01(0.90-1.13)	33.6%
	≥7	2	0.94(0.82-1.08)	0 0.481	1	0.62(0.42-0.9)		6	0.81(0.73-0.91)	0 0.712	6	0.68(0.49-0.94)	57.4%

			P-ALA			E-omega3	}		E-EPA			E-DHA	
Strata	Subgroup	Ν	<b>Pooled results</b>	I <sup>2</sup> (p value)	Ν	<b>Pooled results</b>	I <sup>2</sup> (p value)	N	Pooled results	I <sup>2</sup> (p value)	Ν	Pooled results	I <sup>2</sup> (p value)
Total		6	0.96(0.85-1.08)	45% 0.106	5	0.96(0.90-1.02)	34.5% 0.191	5	0.95(0.89-1.00)	0 0.740	6	0.94(0.89-0.98)	0.4% 0.413
	Europe	4	0.98(0.91-1.07)	0 0.469	1	0.59(0.38-0.93)					1	0.6(0.39-0.93)	
Region	North America	1	1.29(0.76-2.19)		4	0.97(0.92-1.01)	0 0.685	5	0.95(0.89-1.00)	0 0.740	5	0.94(0.90-0.99)	0 0.920
	Asia	1	0.62(0.42-0.9)										
	Male	1	1.00(0.82-1.23)										
Sex	Female				2	0.96(0.99-1.04)	26.6% 0.244	2	0.95(0.90-1.01)	0 0.500	2	0.95(0.89-1.004)	0 0.383
	Mixed	5	0.95(0.82-1.10)	55.4% 0.062	3	0.94(0.83-1.07)	57.8% 0.093	3	0.90(0.73-1.10)	0 0.549	4	0.91(0.82-1.01)	24.0%
	<1000	1	0.62(0.42-0.9)		3	0.94(0.83-1.07)	57.8% 0.093	3	0.90(0.73-1.10)	0 0.549	4	0.91(0.82-1.01)	24.0%
Sample size	1000-5000	4	1.05(0.93-1.19)	0 0.551									
	>5000	1			2	0.96(0.88-1.04)	26.6% 0.244	2	0.95(0.90-1.01)	0 0.500	2	0.95(0.89-1.004)	0 0.383
Cognitive	Not mentioned	1	1.00(0.82-1.23)		1	0.59(0.38-0.93)					1	0.6(0.39-0.93)	
status at baseline	Free of dementia	5	0.95(0.82-1.10)	55.4% 0.062	4	0.97(0.92-1.01)	0 0.685	5	0.95(0.89-1.00)	0 0.740	5	0.94(0.90-0.99)	0 0.920
A ga staga	Midlife	1	1.00(0.82-1.23)					1	0.97(0.75-1.24)		1	0.6(0.39-0.93)	
Age stage	Latelife	5	0.95(0.82-1.10)	55.4% 0.062	5	0.96(0.90-1.02)	34.5% 0.191	4	0.95(0.89-1.004)	0 0.585	5	0.94(0.90-0.99)	0 0.920
Follow-up	< 10y	4	0.99(0.89-1.10)	14.3% 0.321	5	0.96(0.90-1.02)	34.5% 0.191	5	0.95(0.89-1.00)	0 0.740	6	0.94(0.89-0.98)	0.4% 0.413
(max)	≥10y	2	0.81(0.51-1.29)	78.8% 0.030									
Adjusted for	Yes	4	0.99(0.89-1.10)	14.3% 0.321	5	0.96(0.90-1.02)	34.5% 0.191	5	0.95(0.89-1.00)	0 0.740	6	0.94(0.89-0.98)	0.4% 0.413
APOE4	No	2	0.81(0.51-1.29)	78.8% 0.030									
	Dementia	3	0.91(0.73-1.14)	72.9% 0.025	2	0.95(0.89-1.01)	0 0.43	2	0.92(0.84-1.01)	0 0.397	2	0.93(0.86-0.999)	0 0.697
	AD	3	0.97(0.85-1.10)	0 0.432	1	0.98(0.88-1.08)		1	0.76(0.43-1.34)		1	0.93(0.79-1.10)	
Outcome	Cognitive decline but not dementia				1	0.59(0.38-0.93)		1	0.97(0.75-1.24)		2	0.78(0.52-1.18)	70.5% 0.066
Effect	HR/RR	5	0.99(0.91-1.08)	0 0.476	5	0.96(0.90-1.02)	34.5% 0.191	4	0.95(0.89-1.004)	0 0.585	1	0.6(0.39-0.93)	
estimate	tRR	1	0.62(0.42-0.9)					1	0.97(0.75-1.24)		5	0.94(0.90-0.99)	0 0.920
NOS score	<7	3	1.06(0.94-1.20)	0 0.636	1	0.59(0.38-0.93)		1	0.97(0.75-1.24)		2	0.78(0.52-1.18)	70.5%
	≥7	3	0.87(0.73-1.03)	49.9% 0.136	4	0.97(0.92-1.01)	0 0.685	4	0.95(0.89-1.004)	0 0.585	4	0.95(0.90-0.995)	0 0.848

#### Supplementary Figure 1. Forest plot for dietary omega-3 fatty acid intake and risk of dementia, AD, and cognitive decline but not dementia

Study	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Subgroup = Dementia	4				
Nozaki ( 2021 )	· ]	0.37	[0.17; 0.80]	0.3%	0.8%
Koch (2021)			[0.92; 1.06]	34.9%	16.4%
Devore (2009)	Ŧ		[0.77; 1.22]	3.4%	6.6%
Barberger-gateau ( 2007 ) —			[0.19; 1.11]	0.2%	0.6%
Engelhart ( 2002 )	1		[0.94; 1.22]	10.3%	
Common effect model	5		[0.94; 1.06]	49.1%	
Random effects model			[0.94: 1.06]		36.3%
Heterogeneity: $l^2 = 62\%$ , $\tau^2 = < 0.0001$ , $p = 0.03$			[]		
Subgroup = AD					
Li ( 2021 )		0.72	[0.54; 0.96]	2.1%	4.7%
Koch ( 2021 )	1	0.97	[0.89; 1.06]	22.9%	15.1%
Gustafson(2020)		0.72	[0.51; 1.01]	1.5%	3.5%
Devore ( 2009 )	4-	1.16	[0.84; 1.60]	1.7%	3.9%
Barberger-gateau ( 2007 ) ———	·	0.43	[0.14; 1.34]	0.1%	0.4%
Morris ( 2003 )	• <del>• • •</del>	0.40	[0.13; 1.20]	0.1%	0.4%
Engelhart(2002)	+	1.07	[0.91; 1.25]	6.9%	9.9%
Common effect model	4	0.96	[0.90; 1.03]	35.4%	-
Random effects model	-	0.89	[0.75; 1.07]	-	37.9%
Heterogeneity: $l^2 = 58\%$ , $\tau^2 = 0.0284$ , $p = 0.03$					
Subgroup = Cognitive decline but not	t dementia				
Nozaki ( 2021 )		1.11	[0.88; 1.39]	3.4%	6.6%
Jiang ( 2020 )	+	0.92	[0.79; 1.08]	7.2%	10.1%
Gao ( 2011 )		0.23	[0.07; 0.75]	0.1%	0.4%
Vercambre ( 2009 )	-	0.81	[0.66; 0.99]	4.5%	7.8%
Kalmijn(2) ( 1997 )		0.81	[0.41; 1.62]	0.4%	1.0%
Common effect model	•	0.91	[0.82; 1.01]	15.5%	
Random effects model	•	0.90	[0.77; 1.06]		25.8%
Heterogeneity: $l^2 = 58\%$ , $\tau^2 = 0.0122$ , $p = 0.05$					
Common effect model		0.97	[0.93; 1.01]	100.0%	
Random effects model	•	0.94	[0.88; 1.01]		100.0%
Heterogeneity: $I^2 = 56\%$ , $\tau^2 = 0.0068$ , $p < 0.01$ 0.1	0.5 1 2	10			

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplementary Figure 2. Forest plot for dietary DHA intake and risk of dementia, AD, and cognitive decline but not dementia

.29 .57 .99 .56 .84 .69 .80 .73 .55 .15 .30	[0.79; 1.24] [0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	12.7% 2.9% 7.3% 10.6% 2.4% 35.9% 12.5% 10.0% 6.4% 8.8% 1.8%
.29 .57 .99 .56 .84 .69 .80 .73 .55 .15 .30	[0.13; 0.66] [0.38; 0.85] [0.79; 1.24] [0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.48; 0.99] [0.57; 0.94] [0.55; 0.86] [0.84; 1.57] [0.10; 0.90]	0.6% 2.5% 7.9% 0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	2.9% 7.3% 10.6% 2.4%  35.9% 12.5% 10.0% 6.4% 8.8%
.29 .57 .99 .56 .84 .69 .80 .73 .55 .15 .30	[0.13; 0.66] [0.38; 0.85] [0.79; 1.24] [0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.48; 0.99] [0.57; 0.94] [0.55; 0.86] [0.84; 1.57] [0.10; 0.90]	0.6% 2.5% 7.9% 0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	2.9% 7.3% 10.6% 2.4%  35.9% 12.5% 10.0% 6.4% 8.8%
.57 .99 .56 .84 .69 .80 .73 .55 .15 .30	[0.38; 0.85] [0.79; 1.24] [0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	2.5% 7.9% 0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	7.3% 10.6% 2.4%  35.9% 12.5% 10.0% 6.4% 8.8%
.99 .56 .84 .69 .80 .73 .55 .15 .30	[0.79; 1.24] [0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	7.9% 0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	2.4%  35.9% 12.5% 10.0% 6.4% 8.8%
.56 .84 .69 .73 .55 .15 .30	[0.23; 1.38] [0.76; 0.93] [0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	0.5% 40.8%  23.2% 6.1% 2.0% 4.1%	35.9% 12.5% 10.0% 6.4% 8.8%
.84 .69 .73 .55 .15 .30	[0.76; 0.93] [0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	40.8%  23.2% 6.1% 2.0% 4.1%	35.9% 12.5% 10.0% 6.4% 8.8%
.69 .80 .73 .55 .15 .30	[0.48; 0.99] [0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	23.2% 6.1% 2.0% 4.1%	12.5% 10.0% 6.4% 8.8%
.80 .73 .55 .15 .30	[0.70; 0.91] [0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	6.1% 2.0% 4.1%	10.0% 6.4% 8.8%
.73 .55 .15 .30	[0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	6.1% 2.0% 4.1%	10.0% 6.4% 8.8%
.73 .55 .15 .30	[0.57; 0.94] [0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	6.1% 2.0% 4.1%	10.0% 6.4% 8.8%
.55 .15 .30	[0.35; 0.86] [0.84; 1.57] [0.10; 0.90]	2.0% 4.1%	6.4% 8.8%
.15 .30	[0.84; 1.57] [0.10; 0.90]	4.1%	8.8%
.30	[0.10; 0.90]		
		0.3%	1.8%
.63	15		
	[0.23; 1.72]	0.4%	2.0%
.79	[0.72; 0.88]	36.2%	
.75	[0.59; 0.97]		41.5%
.12	[0.89; 1.40]	7.9%	10.7%
.92	[0.78; 1.08]	15.1%	11.9%
,98	[0.86; 1.12]	23.0%	
.00	[0.83; 1.21]		22.6%
.86	[0.80; 0.91]	100.0%	
.80	[0.68; 0.93]		100.0%
0	0.92 0.98 1.00 <b>0.86</b>	0.92 [0.78; 1.08] 0.98 [0.86; 1.12] 1.00 [0.83; 1.21]	0.92 [0.78; 1.08] 15.1% 0.98 [0.86; 1.12] 23.0% 1.00 [0.83; 1.21] 0.86 [0.80; 0.91] 100.0%

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplementary Figure 3. Forest plot for dietary EPA intake and risk of dementia, AD, and cognitive decline but not dementia

Study	Risk Ratio	RR	95%-CI	Weight (common)	-
Subgroup = Dementia	l				
Koch ( 2021 )		1.34	[1.07; 1.68]	14.5%	15.6%
Nozaki (2021)+		0.45	[0.20; 1.00]	1.2%	4.2%
Devore ( 2009 )		0.97	[0.77; 1.22]	14.5%	15.6%
Common effect model	-	1.10	[0.94; 1.29]	30.2%	
Random effects model		0.94	[0.56; 1.56]	-	35.4%
Heterogeneity: $l^2 = 78\%$ , $r^2 = 0.1598$ , $p = 0.01$					
Subgroup = AD					
Koch ( 2021 )		1.33	[1.06; 1.67]	14.5%	15.6%
Gustafson ( 2020 )		0.74	[0.57; 0.96]	11.3%	14.6%
Devore ( 2009 )		1.10	[0.80; 1.51]	7.3%	12.6%
Morris ( 2003 )		0.90	[0.38; 2.16]	1.0%	3.6%
Common effect model	<b>\</b>	1.04	[0.90; 1.20]	34.1%	
Random effects model	-	1.02	[0.75; 1.38]		46.4%
Heterogeneity: $l^2 = 74\%$ , $r^2 = 0.0632$ , $p < 0.01$					
Subgroup = Cognitive decline but i	not dementia				
Bigornia ( 2018 )	-	0.94	[0.81; 1.09]	35.7%	18.2%
Common effect model	\$	1.02	[0.94; 1.11]	100.0%	
Random effects model	-	1.00	[0.84; 1.21]		100.0%
Heterogeneity: $l^2 = 69\%$ , $\tau^2 = 0.0422$ , $p < 0.07$					

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplementary Figure 4. Forest plot for plasma DHA and risk of dementia, AD, and cognitive decline but not dementia

				Weight	Weight
Study	Risk Ratio	RR	95%-CI	(common)	(random)
Subgroup = Dementia	1				
Thomas ( 2020 )		0.64	[0.44; 0.94]	3.9%	8.0%
Yamagishi(2017)		1.17	[0.73; 1.87]	2.5%	6.2%
Ronnemaa (2012)		1.00	[0.87; 1.15]	27.1%	14.6%
Lopez ( 2011 )		0.75	[0.54; 1.05]	4.9%	9.0%
Schaefer ( 2006 )	-	0.80	[0.64; 0.99]	12.1%	12.5%
Common effect model	•	0.90	[0.81; 1.00]	50.6%	-
Random effects model		0.86	[0.72; 1.02]	-	50.2%
Heterogeneity: $t^2 = 54\%$ , $r^2 = 0.0190$ , $p = 0$	).07				
Subgroup = AD					
Li ( 2021 )		1.13	[0.74; 1.72]	3.2%	7.1%
Ronnemaa ( 2012 )	1	1.10	[0.90; 1.34]	14.2%	13.0%
Lopez ( 2011 )		0.78	[0.54; 1.13]	4.0%	8.1%
Schaefer ( 2006 )		0.61	[0.31; 1.19]	1.3%	3.8%
Common effect model	<b>\</b>	1.01	[0.86; 1.18]	22.7%	
Random effects model	+	0.96	[0.76; 1.21]		31.9%
Heterogeneity: $l^2 = 40\%$ , $r^2 = 0.0209$ , $p = 0$	0.17				
Subgroup = Cognitive decline bu	ut not dementia				
Otsuka ( 2014 ) —		0.33	[0.14; 0.80]	0.7%	2.3%
Otsuka ( 2014 )		0.18	[0.04; 0.78]	0.3%	0.9%
Beydoun(2007)	+-	1.12	[0.97; 1.30]	25.7%	14.5%
Common effect model	•	1.06	[0.92; 1.23]	26.7%	
Random effects model		0.48	[0.16; 1.43]		17.8%
Heterogeneity: $l^2 = 84\%$ , $\tau^2 = 0.7245$ , $p < 0$	0.01				
Common effect model		0.96	[0.89; 1.04]	100.0%	
Random effects model	•	0.88	[0.76; 1.02]		100.0%
Heterogeneity: $l^2 = 64\%$ , $r^2 = 0.0329$ , $b < 0.0.1$		つ 10	4859 - 86 - 1179		

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplementary Figure 5. Forest plot for plasma EPA and risk of dementia, AD, and cognitive decline but not dementia

Study	Risk Ratio	RR	95%-CI	Weight (common)	Weight (random)
Subgroup = Dementia					
Thomas ( 2021 )		0.66	[0.45; 0.97]	4.9%	9.0%
MelovanLent (2021)		0.88	[0.75; 1.03]	30.5%	22.6%
Yamagishi ( 2017 )		0.80	[0.51; 1.26]	3.4%	6.9%
Common effect model		0.84	[0.73; 0.96]	38.8%	
Random effects model	•	0.83	[0.70; 0.98]		38.5%
Heterogeneity: $l^2 = 0\%$ , $z^2 = 0.0044$ , p	= 0.38				
Subgroup = AD					
MelovanLent(2021)		0.76	[0.63; 0.92]	19.0%	19.3%
Ronnemaa ( 2012 )		1.12	[0.91; 1.37]	17.5%	18.6%
Common effect model	•	0.92	[0.80; 1.05]	36.5%	
Random effects model	<b></b>	0.92	[0.63; 1.35]		37.9%
Heterogeneity: $l^2 = 86\%$ , $r^2 = 0.0649$ ,	p < 0.01				
Subgroup = Cognitive declin	e but not dementia				
Otsuka ( 2014 )		0.71	[0.30; 1.69]	1.0%	2.3%
Otsuka (2014)	•	0.53	[0.09; 3.25]	0.2%	0.5%
Beydoun (2007)		0.96	[0.81; 1.14]	23.5%	20.8%
Common effect model	-	0.94	[0.80; 1.12]	24.6%	
Random effects model	-	0.94	[0.80; 1.12]		23.6%
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.6$	6				
Common effect model	•	0.89	[0.82; 0.97]	100.0%	
			[0.76; 1.00]		100.0%

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplementary Figure 6. Forest plot for erythrocyte DHA and risk of dementia, AD, and cognitive decline but not dementia

Study	Risk Ratio	RR	95%-CI	Weight (common)	10 N 33
Subgroup = Dementia	4 4				
Ammann ( 2017 )		0.92	[0.84; 1.00]	47.3%	47.3%
(roger ( 2009 )		0.95	[0.83; 1.09]	19.0%	19.0%
Common effect model	<b></b>	0.93	[0.86; 1.00]	66.3%	100.000
Random effects model leterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.70$	•	0.93	[0.86; 1.00]		66.3%
Subgroup = AD	and the late of				
Kroger ( 2009 )		0.93	[0.79; 1.10]	12.8%	12.8%
Subgroup = Cognitive decline but	not dementia				
Bigornia ( 2018 )	-	0.92	[0.80; 1.05]	19.0%	19.0%
Heude (2003)+		0.60	[0.39; 0.93]	1.9%	1.9%
Common effect model		0.89	[0.78; 1.01]	20.9%	
Random effects model		0.78	[0.52; 1.17]		20.9%
Heterogeneity: $I^2 = 70\%$ , $\tau^2 = 0.0644$ , $p = 0.0644$	)7				
Common effect model	•	0.92	[0.87; 0.98]	100.0%	
Random effects model	•	0.92	[0.87; 0.98]		100.0%
Random effects model leterogeneity: $l^2 = 0\%$ , $\tau^2 < 0.0001$ , $\rho = 0.41$ 0.5	•	0.92 7 2	[0.87; 0.98]		

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

# Supplemental Figure 7. Forest plot for erythrocyte EPA and risk of dementia, AD, and cognitive decline but not dementia

Study	Risk Ratio	RR	95%-CI	Weight (common)	
Subgroup = Dementia					
Ammann ( 2017 )		0.93	[0.85; 1.02]	83.6%	83.6%
Kroger ( 2009 )		0.76	[0.48; 1.20]	3.3%	3.3%
Common effect model	-	0.92	[0.84; 1.01]	86.9%	
Random effects model	-	0.92	[0.84; 1.01]	-	86.9%
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.40$					
Subgroup = AD					
Kroger ( 2009 )		0.76	[0.43; 1.34]	2.1%	2.1%
Subgroup = Cognitive decline b	ut not dementia				
Bigornia(2018)		0.97	[0.75; 1.25]	11.0%	11.0%
Common effect model	•	0.92	[0.85; 1.00]	100.0%	
Random effects model	-	0.92	[0.85; 1.00]		100.0%
Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.73$ 0.5	1	2			

The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.

Supplementary Table 7. Comparison between previous SR & MA and the present study.

Author & Year	Dataset	Search endpoint	Exposure	Outcome	Studies included	Inconsistency	Risk of bias (NOS)	Publication bias	Directness	Imprecision
Kosti, 2022	PubMed, Scopus and Web of Science databases	2021.3	Fish, EPA/DHA	all-cause dementia, AD	11 cohort and 9 RCT	significant	study quality is moderate to excellent	no	yes	no PI
Wu, 2015	PubMed, EmBase,, and Web of Science	2013.6	Dietary intake of omega-3 fatty acid, or fish	dementia, AD	6 prospective cohort	significant	study quality is moderate to excellent	yes	yes	no PI
Zhang, 2016	PubMed, Embase, and Cochrane Library databases	2015.5	Fish, PUFA, Omega-3 fatty acid, DHA, EPA, ALA	Mild-to-severe cognitive impairment	21 cohort studies	significant	study quality is moderate to excellent	no	mixed but subgroup	no PI
The present study	PubMed, Embase, and Cochrane library	2022.3	PUFA, Omega-3 fatty acid, DHA, EPA, and ALA from diet, plasma, and erythrocyte concentration	cognitive decline and its subtypes (dementia, AD, cognitive decline but not dementia)	48 longitudinal cohort studies	Low inconsistency for most analyses	study quality is deemed moderate, possibly because we adopted refined rating criteria	no publicatio n bias after trim and fill methods	mixed outcome & subgroup analyses	PI was calculated