Relationship of omega-3 fatty acids with dementia and cognitive decline: cohort evidence from perspective of supplementation, dietary intake, and blood markers

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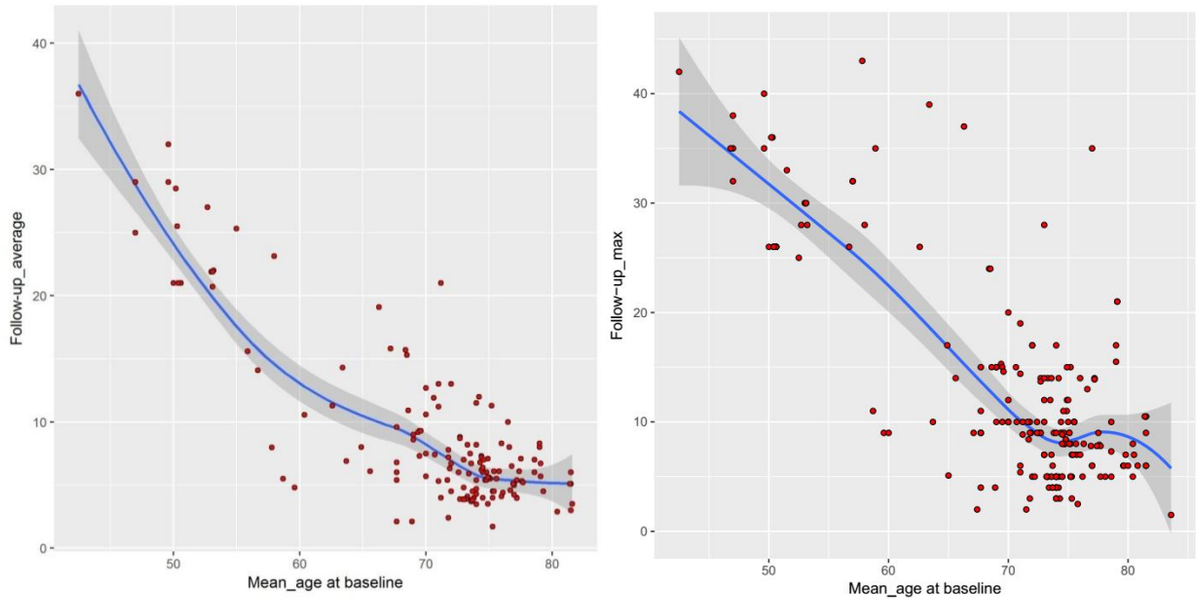
Supplementary Table 1. Predesigned templates for data extraction

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

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

Risk of bias	Questions	Scores	Standards
Selection (generalisability, assessment bias and potential reverse causality)	Q1. representativeness of the exposed cohort	☆	a) randomly selected or b) database covering very large population or c) participation rate (PR) is ≥ 90% or d) reported there is no difference in important characteristics between those who agreed to participate and those who did not
		0.5☆	PR varies from 70% to 90% with no reporting of significant difference in important characteristics between those who agreed to participate and those who did not
		0	Selected group of users e.g. nurses, volunteers or no description
	Q2. selection of the non-exposed cohort	☆	Drawn from the same community as the exposed cohort
		0.5☆	Self-report to simple question with potential recall bias
		0	Drawn from a different source or no description of the derivation of the non-exposed cohort
	Q3. ascertainment of exposure	☆	Questionnaire or interview based on self-report to series questions or database
		0.5☆	Self-report to simple question with potential recall bias
		0	No description
	Q4. demonstration that outcome of interest was not present at baseline	☆	Cognitively intact for outcome as dementia or MCI; Free of dementia for population with MCI at baseline
		0.5☆	Free of dementia (cognitively intact & cognitive impairment no dementia (CIND)) for outcome of dementia
		0	No description
Confounding bias	Q5. comparability of cohorts on the basis of the design or analysis	☆☆	Except for age, sex, and education, the analysis still controls forat least another two domains of AD risk factors, including *APOE4*, pre-existing disease, lifestyle, medical exposure, biochemical exposure, occupation, diet, etc.
		☆	Controls for age, sex and education
		0	No description
Outcome (assessment bias and attrition bias)	Q6. assessment of outcome	☆	Independent or blind assessment
		0.5☆	Record linkage (e.g. identified through ICD codes on database records or claim data)
		0	Self-report or no description
	Q7. follow-up long enough for outcomes to occur?[#]	☆	The average or max duration reached the lower 95% CI.
		0	The average or max duration did not reach the lower 95% CI.
	Q8. adequacy of follow up of cohorts[*]	☆	Attrition rate ≤ 5%
		0.5☆	5% ≤ Attrition rate ≤ 20%
		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 1) + 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^2 0-100% in the random model.

(3) Publication bias:

If study number (n) ≥ 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＜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:

Index S = {(NOS score [study_1] /9)*P + (NOS score [study_2]/9)*P+...+ (NOS score [study_N]/9)*P} / N

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_{for}	index $S_{against}$	index $S_{difference}$
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

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

		Model 1		Model 2		Model 3	
	n./total	HR	*p*	HR	*p*	HR	*p*
Omega-3 supplementation							
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
Blood markers							
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

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;

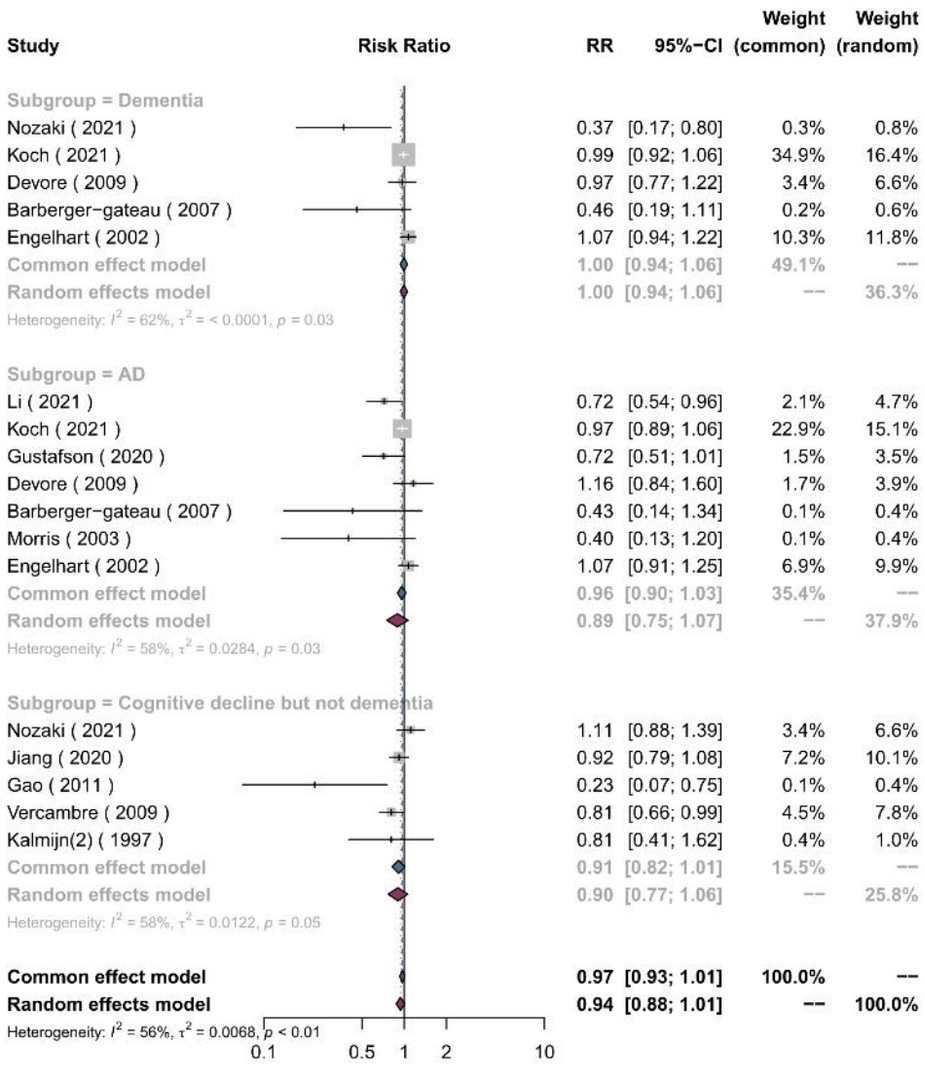
Supplementary Table 6. Subgroup analyses for association between exposure measurement and cognitive decline.

		D-PUFA			D-omega3			D-EPA			D-DHA		
Strata	**Subgroup**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (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
Region	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
	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
Sex	Male				1	0.81(0.39-1.56)							
	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
Sample size	<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
	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 status at baseline	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
	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
Age stage	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
	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 (max)	< 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
	≥ 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 *APOE*4	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
	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
Outcome	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
	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 estimate	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
	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
	≥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**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (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%
Region	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%
	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%
Sex	Male							1	1.12(0.92-1.38)				
	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%
Sample size	<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%
	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 status at baseline	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%
	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
Age stage	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%
	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 (max)	< 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%
	≥ 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 *APOE4*	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%
	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%
Outcome	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%
	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 estimate	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%
	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**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (p value)**	**N**	**Pooled results**	**I^2 (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
Region	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)	
	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)										
Sex	Male	1	1.00(0.82-1.23)										
	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%
Sample size	<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%
	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 status at baseline	Not mentioned	1	1.00(0.82-1.23)		1	0.59(0.38-0.93)					1	0.6(0.39-0.93)	
	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
Age stage	Midlife	1	1.00(0.82-1.23)					1	0.97(0.75-1.24)		1	0.6(0.39-0.93)	
	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 (max)	< 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
	≥ 10y	2	0.81(0.51-1.29)	78.8% 0.030									
Adjusted for *APOE*4	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
	No	2	0.81(0.51-1.29)	78.8% 0.030									
Outcome	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)	
	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 estimate	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)	
	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

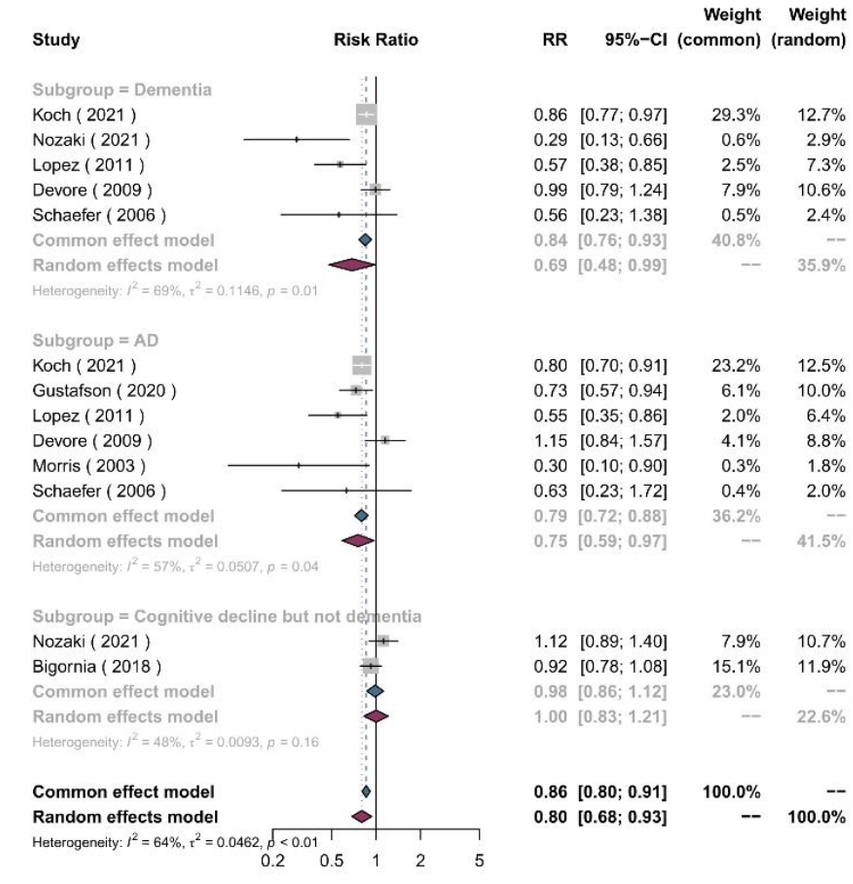
Supplementary Figure 1. Forest plot for dietary omega-3 fatty acid intake and risk of dementia, AD, and cognitive decline but not dementia



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

AD, Alzheimer's disease; RR, risk ratio

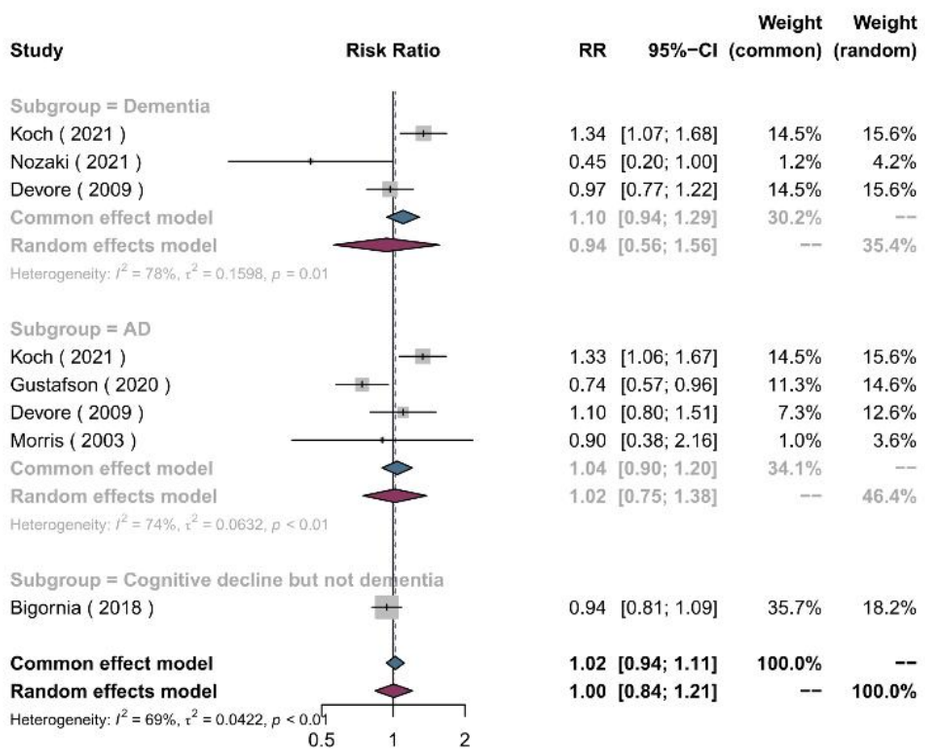
Supplementary Figure 2. Forest plot for dietary DHA intake and risk of dementia, AD, and cognitive decline but not dementia



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

AD, Alzheimer's disease; RR, risk ratio

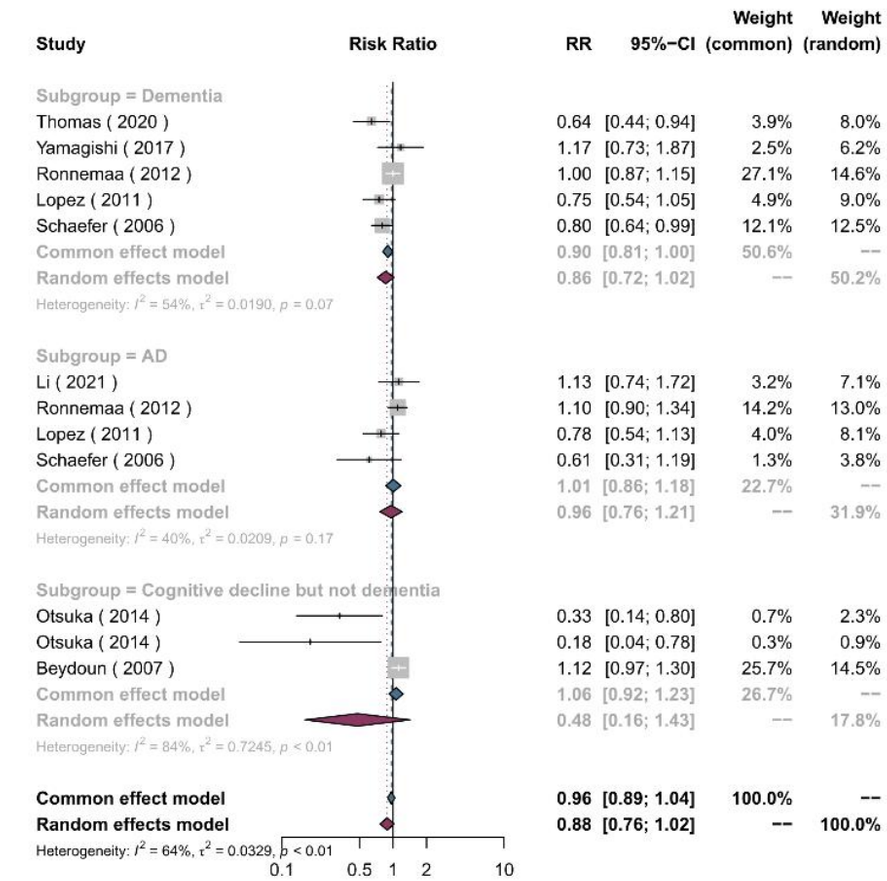
Supplementary Figure 3. Forest plot for dietary EPA intake and risk of dementia, AD, and cognitive decline but not dementia



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

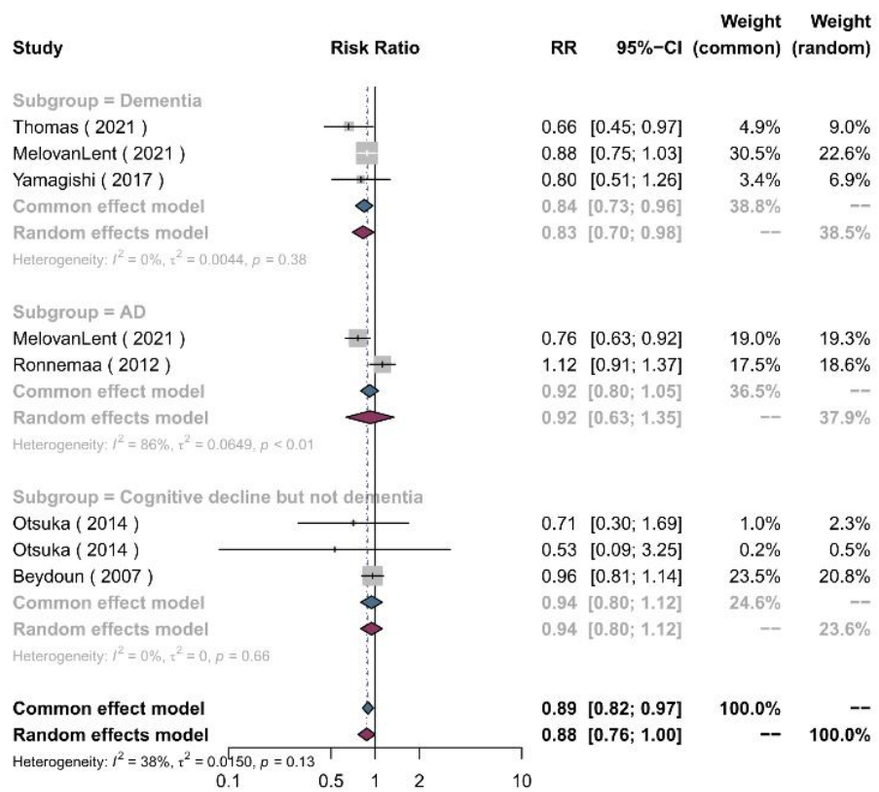
AD, Alzheimer's disease; RR, risk ratio

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



The rhombus represents overall estimate effects and solid lines represent 95% confidence intervals.
AD, Alzheimer's disease; RR, risk ratio

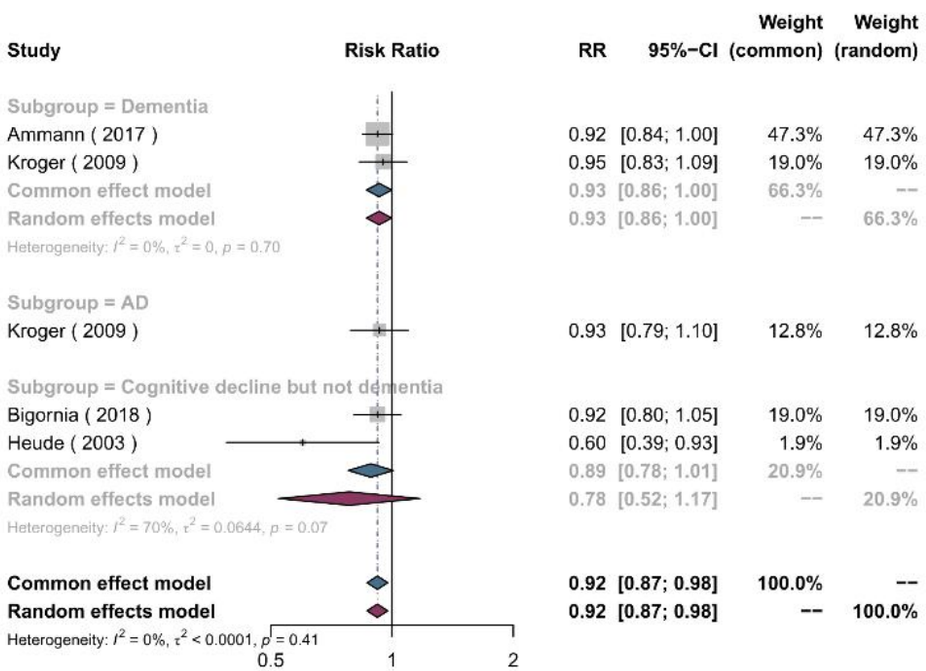
Supplementary Figure 5. Forest plot for plasma EPA and risk of dementia, AD, and cognitive decline but not dementia



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

AD, Alzheimer's disease; RR, risk ratio

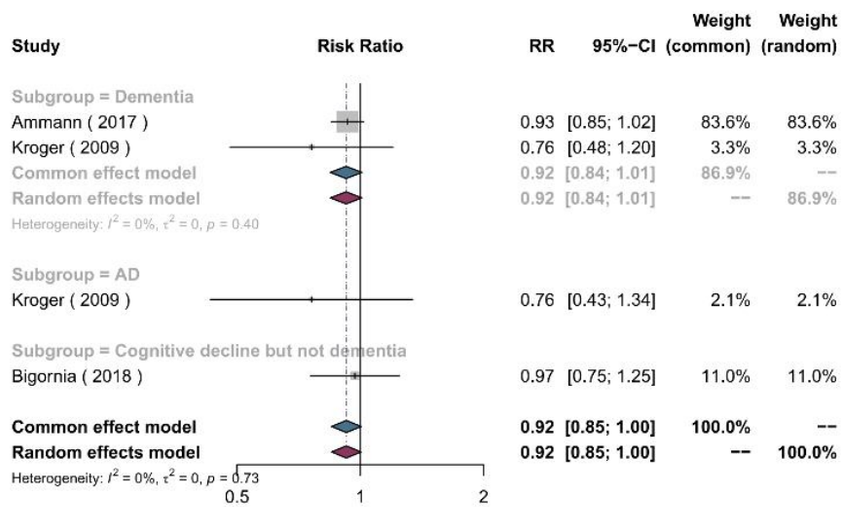
Supplementary Figure 6. Forest plot for erythrocyte DHA and risk of dementia, AD, and cognitive decline but not dementia



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

AD, Alzheimer's disease; RR, risk ratio

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



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

AD, Alzheimer's disease; RR, risk ratio

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 publication bias after trim and fill methods**	**mixed outcome & subgroup analyses**	**PI was calculated**