Mastering the Market: Stress and Mental Wellness

Join us virtually September 30th - October 2nd

Omega-3 PUFAs and depression: what's going on?

Dr Simon Dyall

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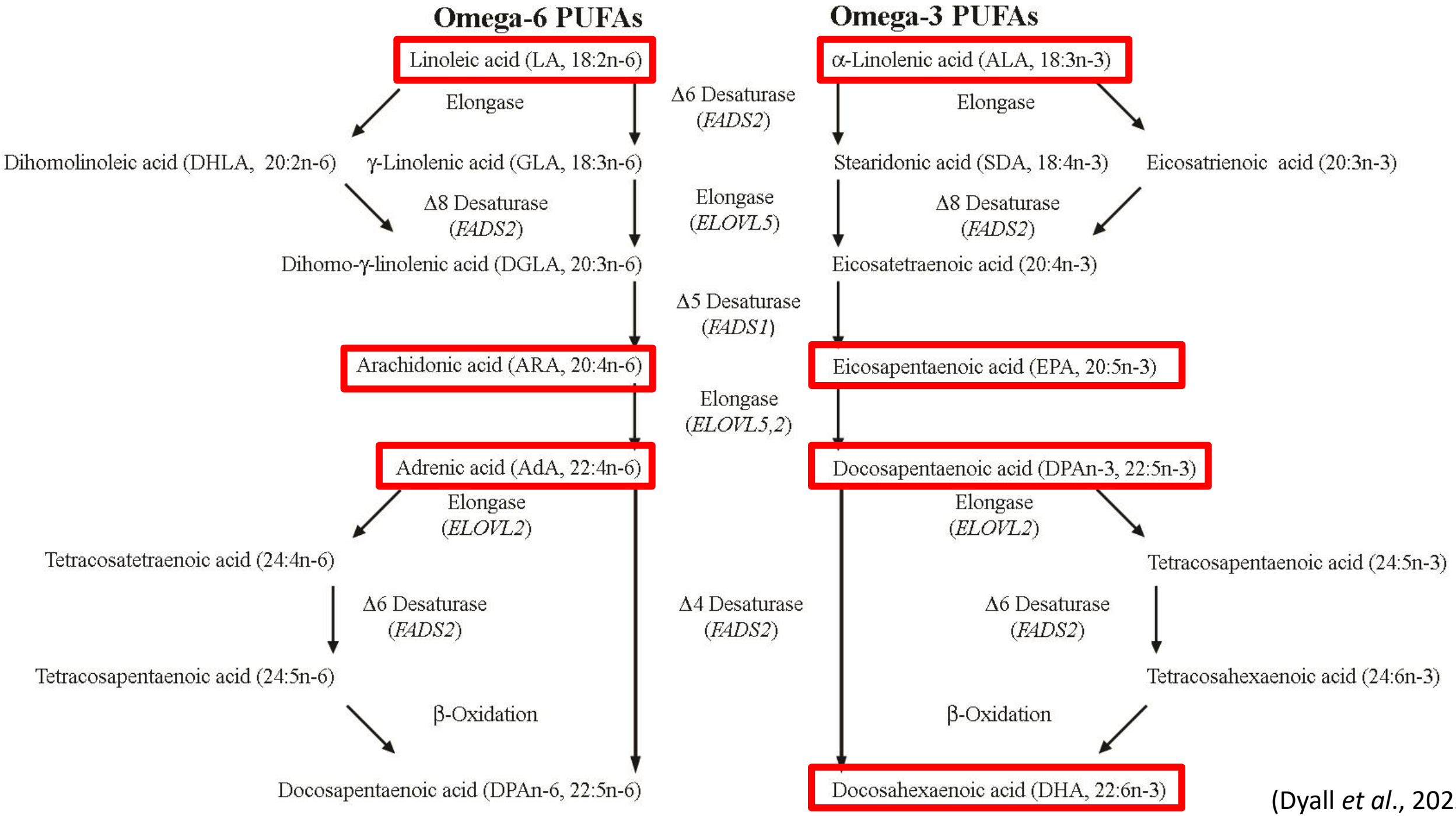
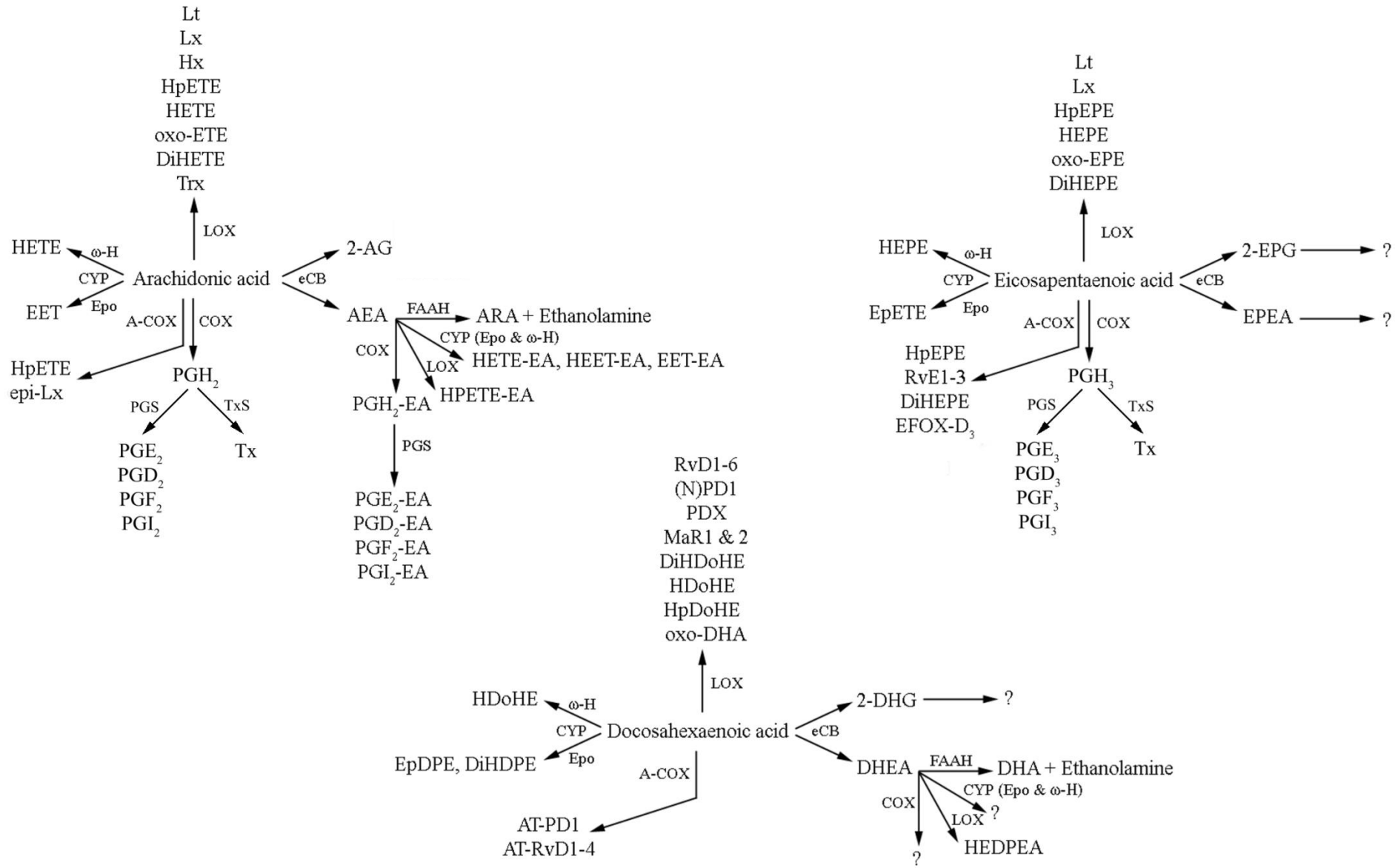


(Dyall *et al.*, 2022)


Lt
Lx
Hx
HpETE
HETE
oxo-ETE
DiHETE
Trx
LOX
HETE
ω-H
CYP
Arachidonic acid
eCB
2-AG
EET
Epo
A-COX
COX
AEA
FAAH
ARA + Ethanolamine
CYP (Epo & ω-H)
HpETE
epi-Lx
PGH2
COX
LOX
HETE-EA, HEET-EA, EET-EA
HPETE-EA
PGS
TxS
PGH2-EA
PGE2
PGD2
PGF2
PGI2
Tx
PGS
PGE2-EA
PGD2-EA
PGF2-EA
PGI2-EA
Lt
Lx
HpEPE
HEPE
oxo-EPE
DiHEPE
LOX
HEPE
ω-H
CYP
Eicosapentaenoic acid
eCB
2-EPG
?
EpETE
Epo
A-COX
COX
EPEA
?
HpEPE
RvE1-3
DiHEPE
EFOX-D3
PGH3
PGS
TxS
PGE3
PGD3
PGF3
PGI3
Tx
RvD1-6
(N)PD1
PDX
MaR1 & 2
DiHDoHE
HDoHE
HpDoHE
oxo-DHA
LOX
HDoHE
ω-H
CYP
Docosahexaenoic acid
eCB
2-DHG
?
EpDPE, DiHDPE
Epo
A-COX
DHEA
FAAH
DHA + Ethanolamine
CYP (Epo & ω-H)
AT-PD1
AT-RvD1-4
COX
LOX
?
?
HEDPEA

(Dyall 2017)

Medical Hypotheses

Medical Hypotheses (1991) 35, 298–306

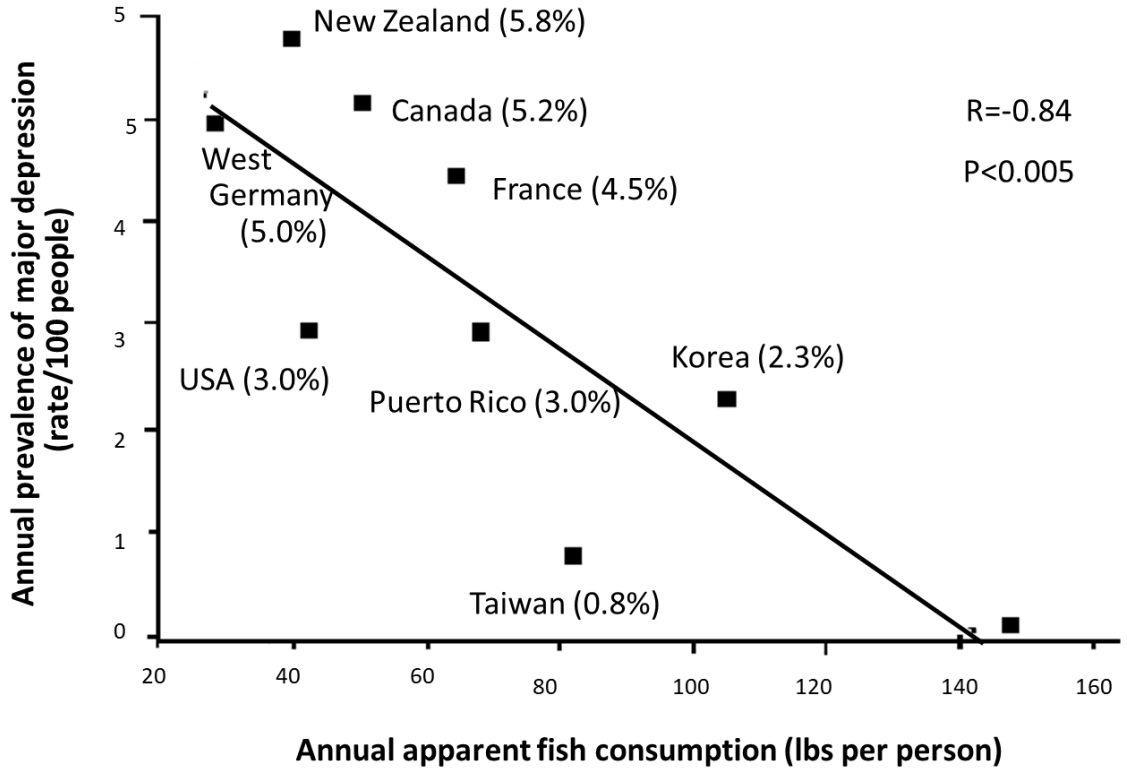
The Macrophage Theory of Depression

R. S. SMITH

4718 Meridian Avenue, Suite 208, San Jose, CA 95118, USA

"The extraordinary low rate of depression in Japan is consistent with the suppressive effect of eicosapentaenoic acid on macrophages. Fish oil is proposed as a prophylaxis against depression and omega-6 fat as a promoter"

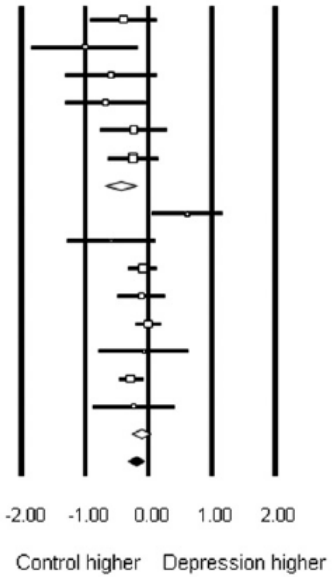
promoter. Infection, tissue damage, respiratory allergies and antigens found in food are some of the possible causes of macrophage activation triggering depression.



(Hibbeln *et al.,* 1998)

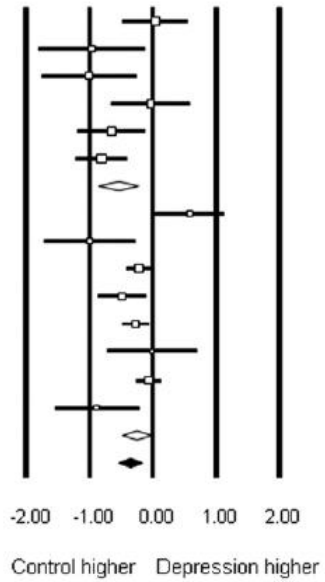
EPA

Group by study type	Study name	Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
	Maes 1996 (30)	-0.39	-0.90	0.13	-1.48	0.1397
	Edwards 1998 (32)	-1.00	-1.83	-0.17	-2.35	0.0187
	Peet 1998 (33)	-0.58	-1.29	0.13	-1.59	0.1115
	Maes 1999 (34)	-0.67	-1.29	-0.04	-2.08	0.0372
	Dinan 2009 (43)	-0.23	-0.75	0.28	-0.88	0.3770
	Riemer (in press)(45)	-0.24	-0.63	0.16	-1.17	0.2413
DSM-defined MDD vs. healthy controls-pooled		**-0.42**	**-0.67**	**-0.18**	**-3.36**	**0.0008**
	Fehily 1981 (29)	0.61	0.06	1.16	2.18	0.0296
	De Vriese 2003 (35)	-0.59	-1.28	0.11	-1.65	0.0984
	Tiemeier 2003 (36)	-0.09	-0.30	0.12	-0.84	0.3998
	Frasure-Smith 2004 (38)	-0.11	-0.48	0.27	-0.57	0.5684
	Amin 2008 (40)	0.00	-0.20	0.20	0.00	1.0000
	Aupperle 2008 (41)	-0.07	-0.78	0.64	-0.20	0.8435
	Feart 2008 (42)	-0.27	-0.46	-0.09	-2.84	0.0045
	Rees 2009 (44)	-0.23	-0.86	0.40	-0.71	0.4787
Studies NOT using DSM criteria and healthy controls-pooled		**-0.10**	**-0.25**	**0.05**	**-1.32**	**0.1877**
Overall		**-0.18**	**-0.31**	**-0.06**	**-2.85**	**0.0044**



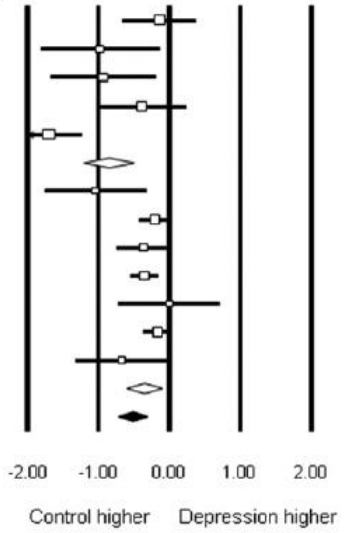
DHA

Group by study type	Study name	Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
	Maes 1996 (30)	0.04	-0.47	0.55	0.14	0.8897
	Edwards 1998 (32)	-0.96	-1.79	-0.13	-2.27	0.0231
	Peet 1998 (33)	-1.00	-1.74	-0.26	-2.65	0.0080
	Maes 1999 (34)	-0.03	-0.65	0.58	-0.11	0.9122
	Dinan 2009 (43)	-0.65	-1.18	-0.13	-2.42	0.0153
	Riemer (in press)(45)	-0.81	-1.22	-0.40	-3.89	0.0001
DSM-defined MDD vs. healthy controls-pooled		**-0.54**	**-0.85**	**-0.22**	**-3.35**	**0.0008**
	Fehily 1981 (29)	0.58	0.03	1.12	2.07	0.0383
	De Vriese 2003 (35)	-0.99	-1.71	-0.28	-2.73	0.0063
	Tiemeier 2003 (36)	-0.21	-0.42	-0.00	-1.96	0.0499
	Frasure-Smith 2004 (38)	-0.49	-0.87	-0.11	-2.51	0.0121
	Amin 2008 (40)	-0.27	-0.47	-0.08	-2.73	0.0063
	Aupperle 2008 (41)	-0.01	-0.72	0.70	-0.03	0.9800
	Feart 2008 (42)	-0.06	-0.25	0.13	-0.65	0.5186
	Rees 2009 (44)	-0.88	-1.54	-0.22	-2.62	0.0089
Studies NOT using DSM criteria and healthy controls-pooled		**-0.25**	**-0.48**	**-0.02**	**-2.11**	**0.0347**
Overall		**-0.35**	**-0.53**	**-0.16**	**-3.68**	**0.0002**



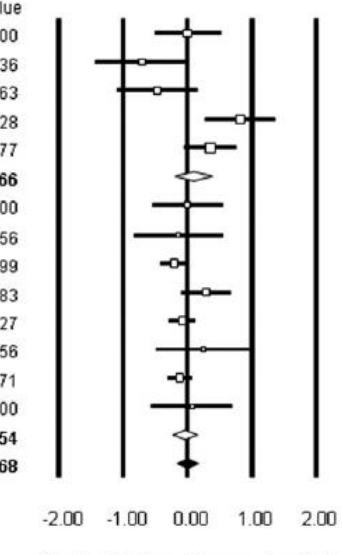
N-3 PUFAs

Group by study type	Study name	Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
	Maes 1996 (30)	-0.15	-0.66	0.36	-0.57	0.5718
	Edwards 1998 (32)	-0.98	-1.81	-0.15	-2.31	0.0207
	Peet 1998 (33)	-0.93	-1.67	-0.20	-2.49	0.0127
	Maes 1999 (34)	-0.39	-1.01	0.22	-1.25	0.2117
	Riemer (in press)(45)	-1.70	-2.15	-1.25	-7.37	0.0000
DSM-defined MDD vs. healthy controls-pooled		**-0.85**	**-1.21**	**-0.49**	**-4.62**	**0.0000**
	De Vriese 2003 (35)	-1.04	-1.76	-0.32	-2.85	0.0044
	Tiemeier 2003 (36)	-0.20	-0.41	0.01	-1.88	0.0599
	Frasure-Smith 2004 (38)	-0.37	-0.75	0.01	-1.92	0.0551
	Amin 2008 (40)	-0.35	-0.55	-0.16	-3.53	0.0004
	Aupperle 2008 (41)	-0.01	-0.71	0.70	-0.02	0.9859
	Feart 2008 (42)	-0.17	-0.36	0.02	-1.79	0.0734
	Rees 2009 (44)	-0.67	-1.32	-0.03	-2.04	0.0418
Studies NOT using DSM criteria and healthy controls-pooled		**-0.35**	**-0.60**	**-0.09**	**-2.69**	**0.0071**
Overall		**-0.51**	**-0.72**	**-0.30**	**-4.85**	**0.0000**



ARA

Group by study type	Study name	Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
	Maes 1996 (30)	0.00	-0.51	0.51	0.00	1.0000
	Peet 1998 (33)	-0.71	-1.43	0.01	-1.93	0.0536
	Maes 1999 (34)	-0.46	-1.08	0.16	-1.45	0.1463
	Dinan 2009 (43)	0.82	0.28	1.35	2.99	0.0028
	Riemer (in press)(45)	0.36	-0.04	0.75	1.76	0.0777
DSM-defined MDD vs. healthy controls-pooled		**0.10**	**-0.19**	**0.39**	**0.66**	**0.5066**
	Fehily 1981 (29)	0.00	-0.54	0.54	0.00	1.0000
	De Vriese 2003 (35)	-0.14	-0.82	0.55	-0.39	0.6956
	Tiemeier 2003 (36)	-0.21	-0.42	-0.00	-1.96	0.0499
	Frasure-Smith 2004 (38)	0.29	-0.08	0.67	1.52	0.1283
	Amin 2008 (40)	-0.08	-0.28	0.12	-0.80	0.4227
	Aupperle 2008 (41)	0.24	-0.47	0.95	0.67	0.5056
	Feart 2008 (42)	-0.12	-0.31	0.07	-1.21	0.2271
	Rees 2009 (44)	0.07	-0.56	0.70	0.21	0.8300
Studies NOT using DSM criteria and healthy controls-pooled		**-0.03**	**-0.22**	**0.16**	**-0.35**	**0.7254**
Overall		**0.01**	**-0.15**	**0.16**	**0.07**	**0.9468**



(Lin *et al*., 2010)

So, what do they do?

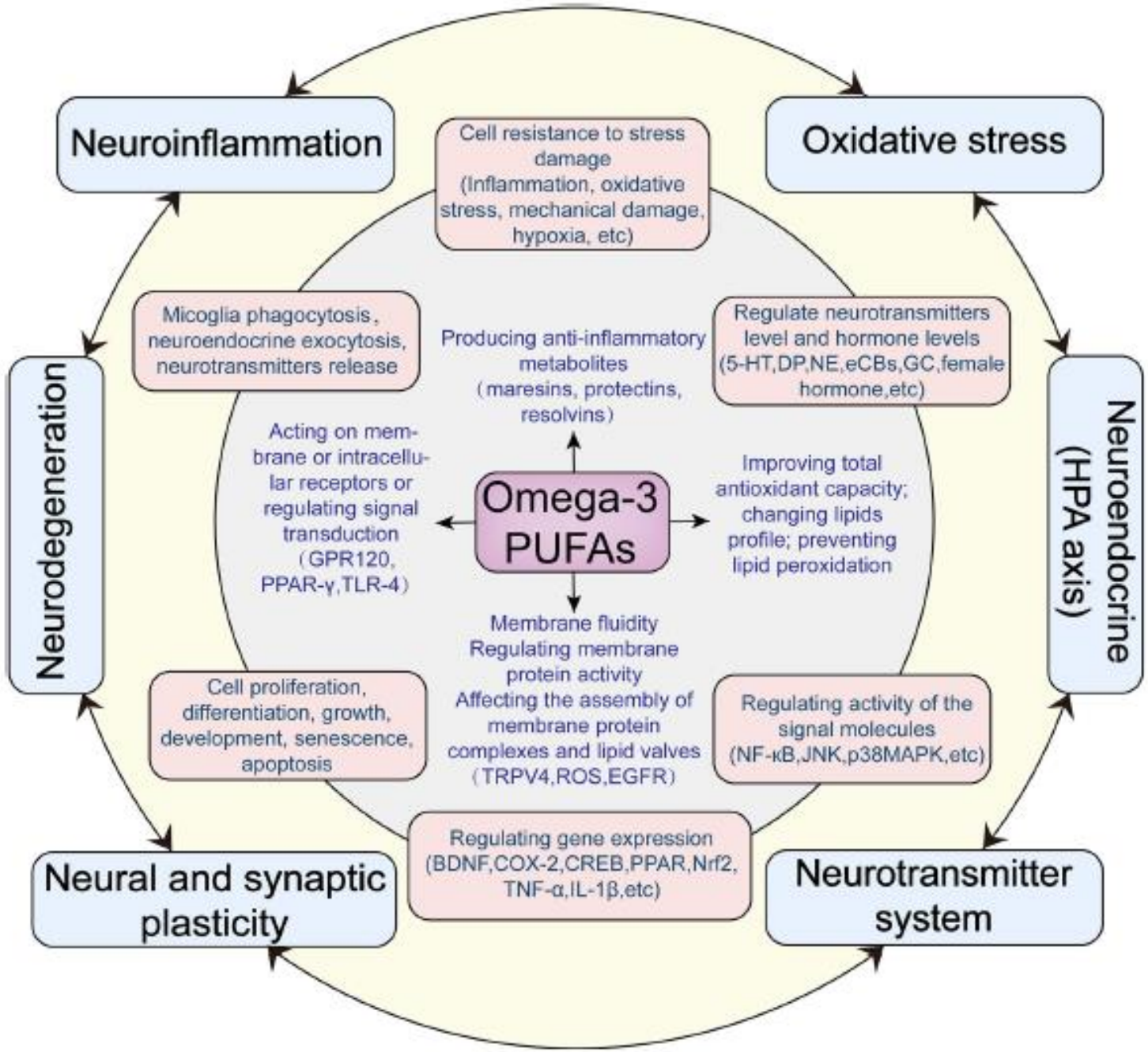
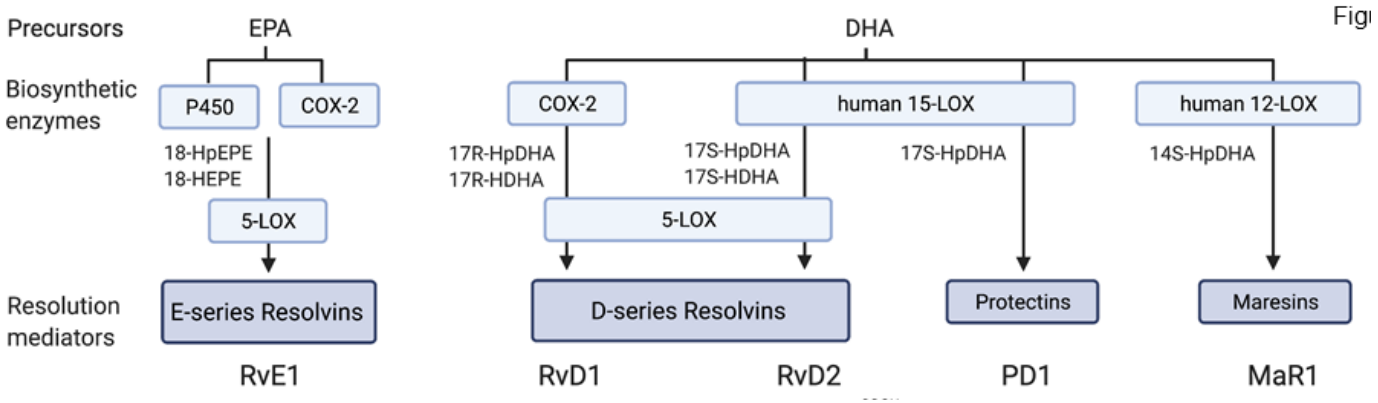
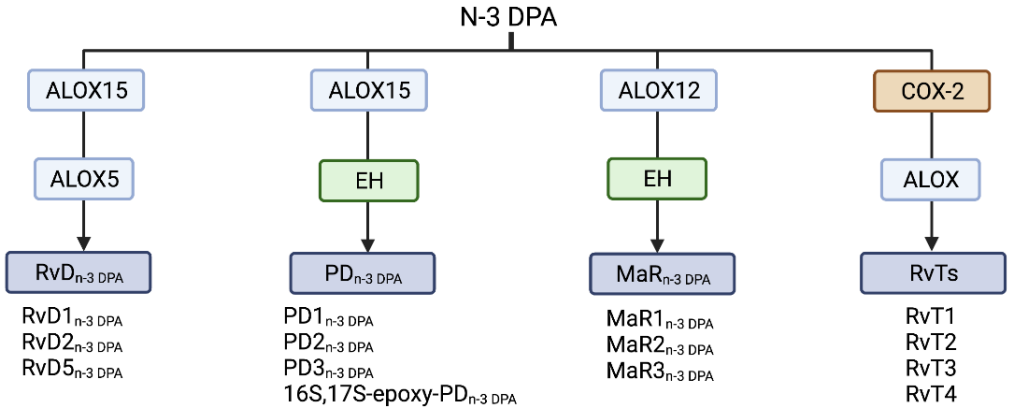
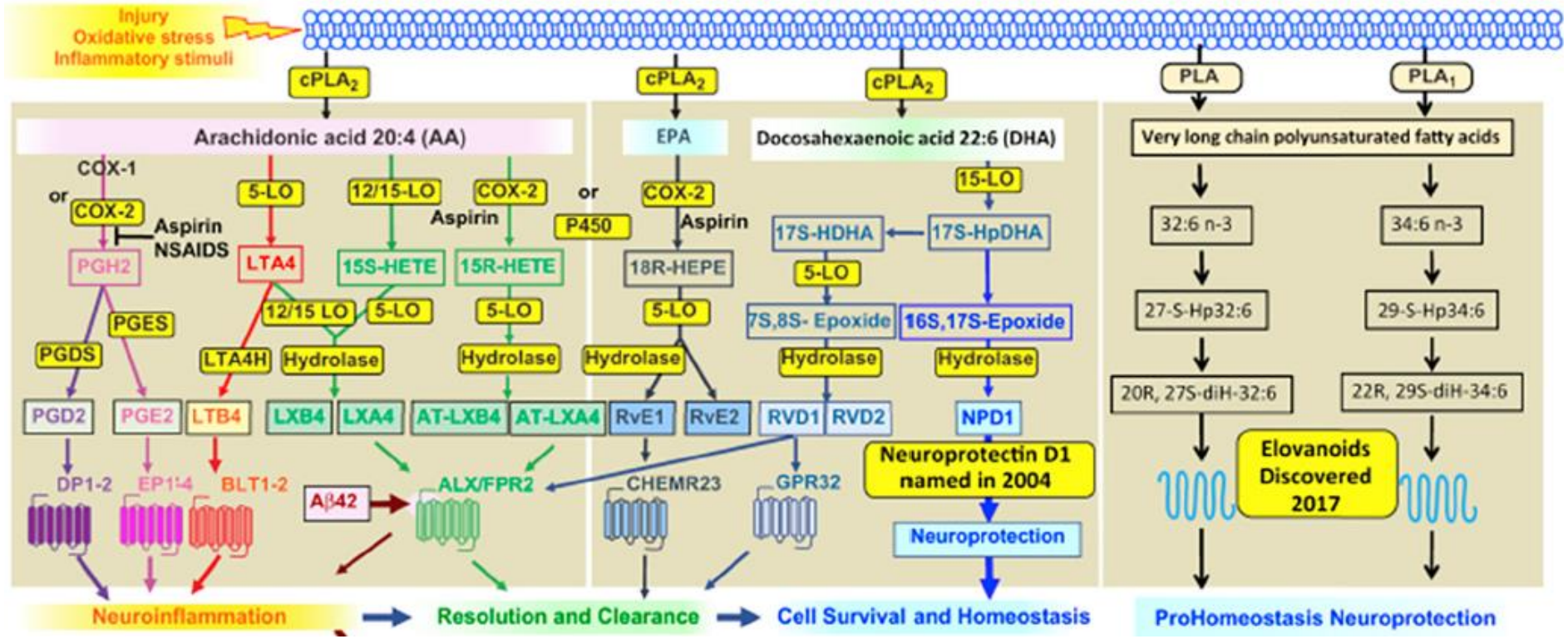


FIGURE 1
Hypothesized antidepressant mechanisms of omega-3 PUFAs acting on the central nervous system.

(Zhou *et al.*, 2022)







(Dyall *et al.*, 2022)

Omega-3 Fatty Acids: Evidence Basis for Treatment and Future Research in Psychiatry

Marlene P. Freeman, M.D.; Joseph R. Hibbeln, M.D.; Katherine L. Wisner, M.D., M.S.; John M. Davis, M.D.; David Mischoulon, M.D., Ph.D.; Malcolm Peet, M.B., F.R.C.Psych.; Paul E. Keck, Jr., M.D.; Lauren B. Marangell, M.D.; Alexandra J. Richardson, Ph.D.; James Lake, M.D.; and Andrew L. Stoll, M.D.

(J Clin Psychiatry 2006;67:1954–1967)

Participants: The authors of this article were invited participants in the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association (APA).

All adults should eat fish ≥ 2 times per week
Patients with mood, impulse-control, or psychotic disorders should consume 1 g EPA + DHA per day
A supplement may be useful in patients with mood disorders (1–9 g per day). Use of > 3 g per day should be monitored by a physician

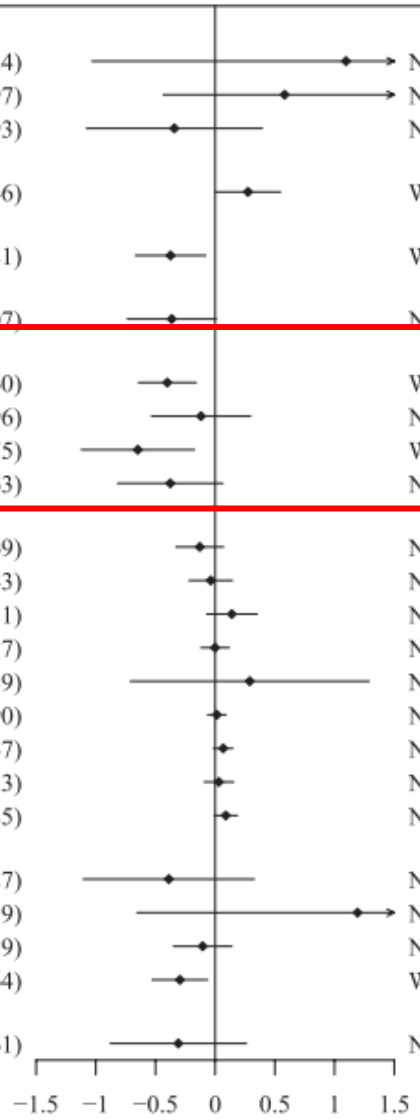
[a]Adapted from the American Heart Association recommendations[5] to provide guidelines on omega-3 fatty acid use in the context of treating psychiatric disorders.

(Yetley *et al.*, 2018)

Unsaturated Fatty Acids in Mental Disorders: An Umbrella Review of Meta-Analyses

Xuping Gao,[1,2] Xin Su,[1] Xue Han,[1] Huiyan Wen,[1] Chen Cheng,[1] Shiwen Zhang,[1] Wanlin Li,[1] Jun Cai,[1] Lu Zheng,[1] Junrong Ma,[1] Minqi Liao,[3] Wanze Ni,[1] Tao Liu,[1] Dan Liu,[1] Wenjun Ma,[1] Shasha Han,[4] Sui Zhu,[1] Yanbin Ye,[5] and Fang-fang Zeng[1]

Outcomes	SMD (95% CI)	Evidence grading
Alzheimer's disease		
Alzheimer's Disease Assessment Scale–Cognitive section	1.096 (−1.031, 3.224)	Not significant
Mini-mental State Examination	0.582 (−0.434, 1.597)	Not significant
Narcissistic Personality Inventor	−0.342 (−1.077, 0.393)	Not significant
Mild cognitive impairment		
Mini-mental State Examination	0.275 (0.005, 0.546)	Weak
Anxiety		
Anxiety symptoms	−0.374 (−0.666, −0.081)	Weak
Bipolar depression		
Depressive symptoms	−0.364 (−0.735, 0.007)	Not significant
Depression		
Depressive symptoms	−0.401 (−0.642, −0.160)	Weak
Depressive symptoms in children	−0.119 (−0.533, 0.296)	Not significant
Depressive symptoms in women	−0.648 (−1.120, −0.175)	Weak
Quality of life	−0.376 (−0.816, 0.063)	Not significant
Attention-deficit/hyperactivity disorder		
Attention (omission errors)	−0.129 (−0.327, 0.069)	Not significant
Inhibition	−0.037 (−0.217, 0.143)	Not significant
IQ	0.139 (−0.07, 0.351)	Not significant
Mean reaction time	−0.001 (−0.118, 0.117)	Not significant
Reaction time variability	0.290 (−0.709, 1.289)	Not significant
Reading	0.014 (−0.062, 0.090)	Not significant
Short-term memory	0.067 (−0.013, 0.147)	Not significant
Spelling	0.031 (−0.090, 0.153)	Not significant
Working memory	0.089 (−0.007, 0.185)	Not significant
Schizophrenia		
Positive and Negative Syndrome Scale–General Psychopathology scale	−0.388 (−1.103, 0.327)	Not significant
Positive and Negative Syndrome Scale–Negative scale	1.193 (−0.654, 3.039)	Not significant
Positive and Negative Syndrome Scale–Positive scale	−0.105 (−0.349, 0.139)	Not significant
Positive and Negative Syndrome Scale–Total scores	−0.295 (−0.527, −0.064)	Weak
Psychosis		
Attenuated psychotic symptoms	−0.309 (−0.878, 0.261)	Not significant

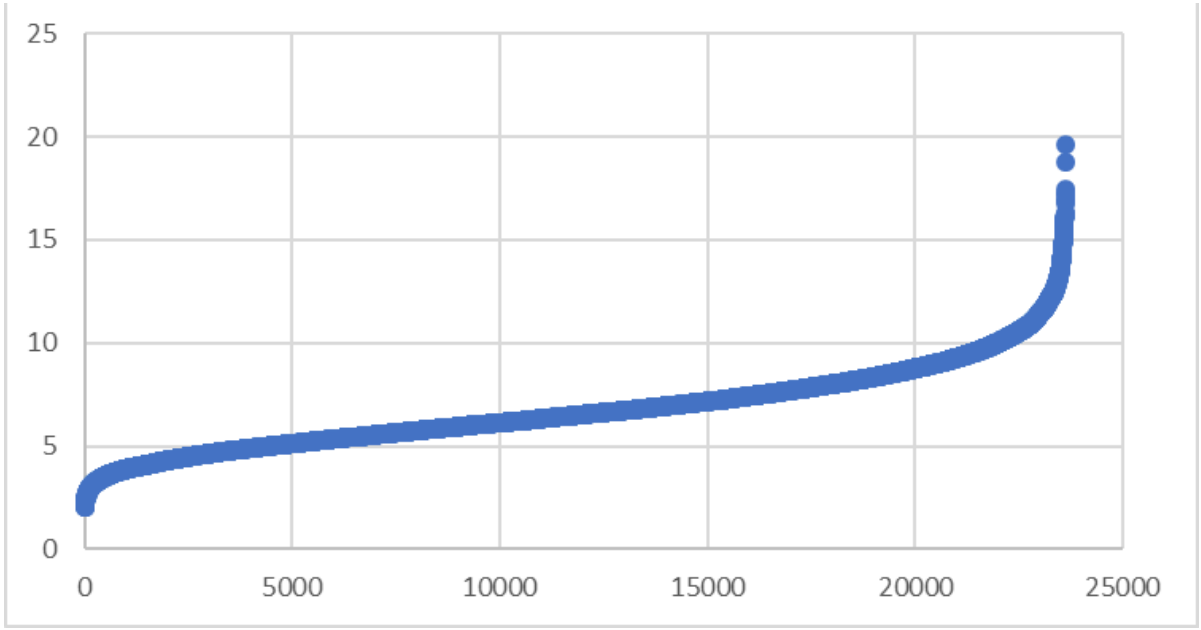


(Gao *et al.*, 2022)

Limitations of RCTS with Omega-3 PUFAs

- Nutrients ≠ Drugs
- Nutrients vs. foods
- Increasing one dietary component usually changes others
- Duration of intervention
- Compliance
- Double blinding not always possible
- Effect sizes generally smaller
- Background levels
- All omega-3 PUFAs are not equal
- Gestational age at birth
- Appropriate placebo

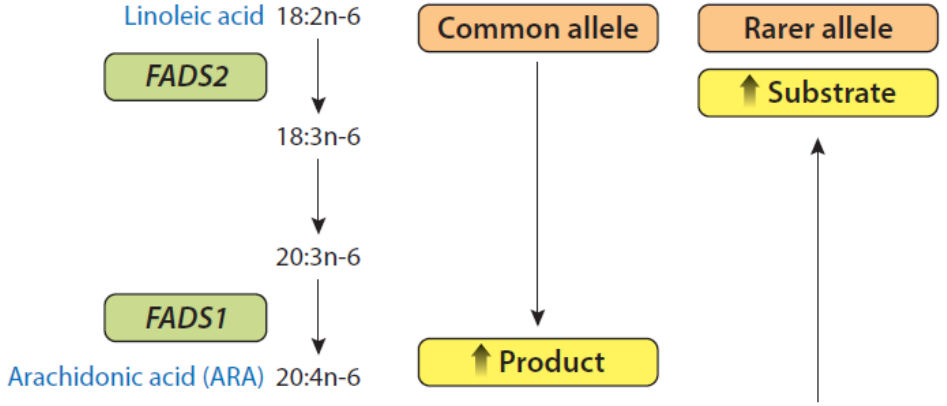
HS-Omega-3 Index of 23615 RBC Samples



n <2% = 0; n >18% = 2

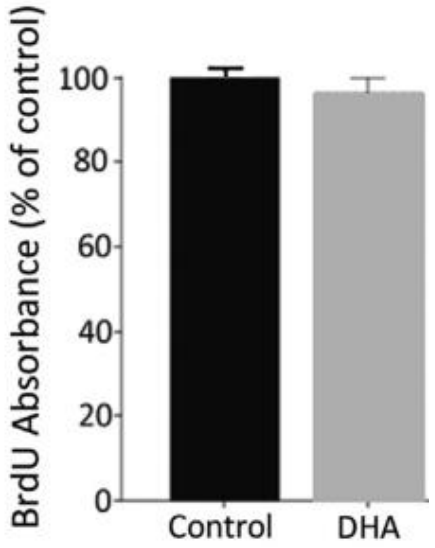
(von Schacky 2019)

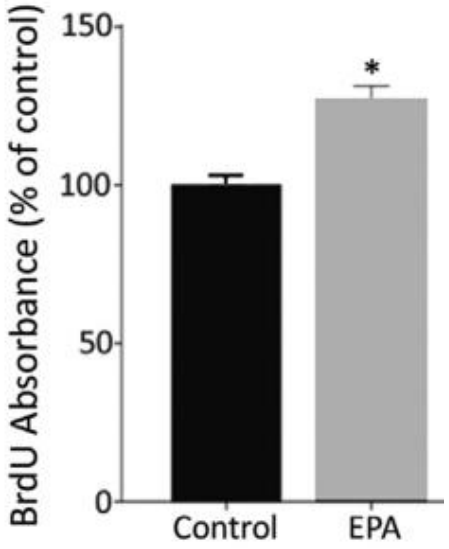
FADS1 and *FADS2* SNPs



SNP	Location of study (reference) and % of population with SNP				
	Indonesia (78)	Mexico (27)	Germany (64)	United Kingdom (64)	Australia (54)
FADS1					
rs174548	27	22	ND	70	67
rs174556	27	24	73	70	72
rs174561	27	24	72	70	ND
FADS2					
rs174570	23	27	87	87	77
rs174574	22	20	ND	66	53
rs174576	22	21	ND	66	64
rs174578	22	21	ND	66	61
rs174579	28	38	ND	79	87
rs174602	41	37	82	66	58
rs498793	15	35	ND	60	69

(Koletzko *et al.*, 2019)





Neuropharmacology 107 (2016) 387–395

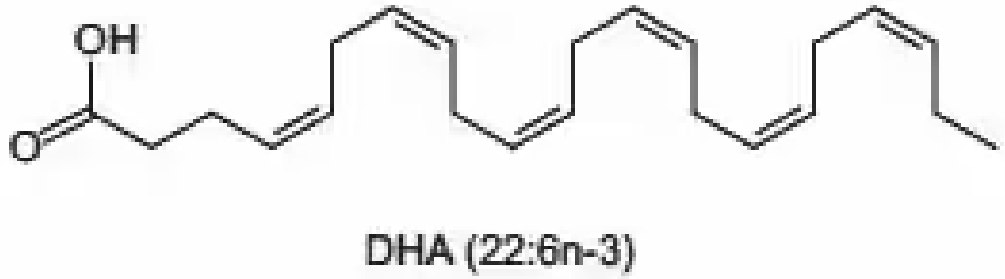
Contents lists available at ScienceDirect

Neuropharmacology

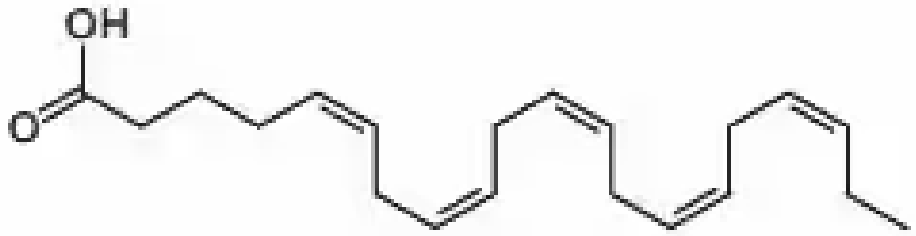
journal homepage: www.elsevier.com/locate/neuropharm

Distinctive effects of eicosapentaenoic and docosahexaenoic acids in regulating neural stem cell fate are mediated via endocannabinoid signalling pathways

S.C. Dyall [a, b, *], H.K. Mandhair [a], R.E.A. Fincham [a], D.M. Kerr [c, d, e], M. Roche [c, e], F. Molina-Holgado [a]



DHA (22:6n-3)



EPA (20:5n-3)

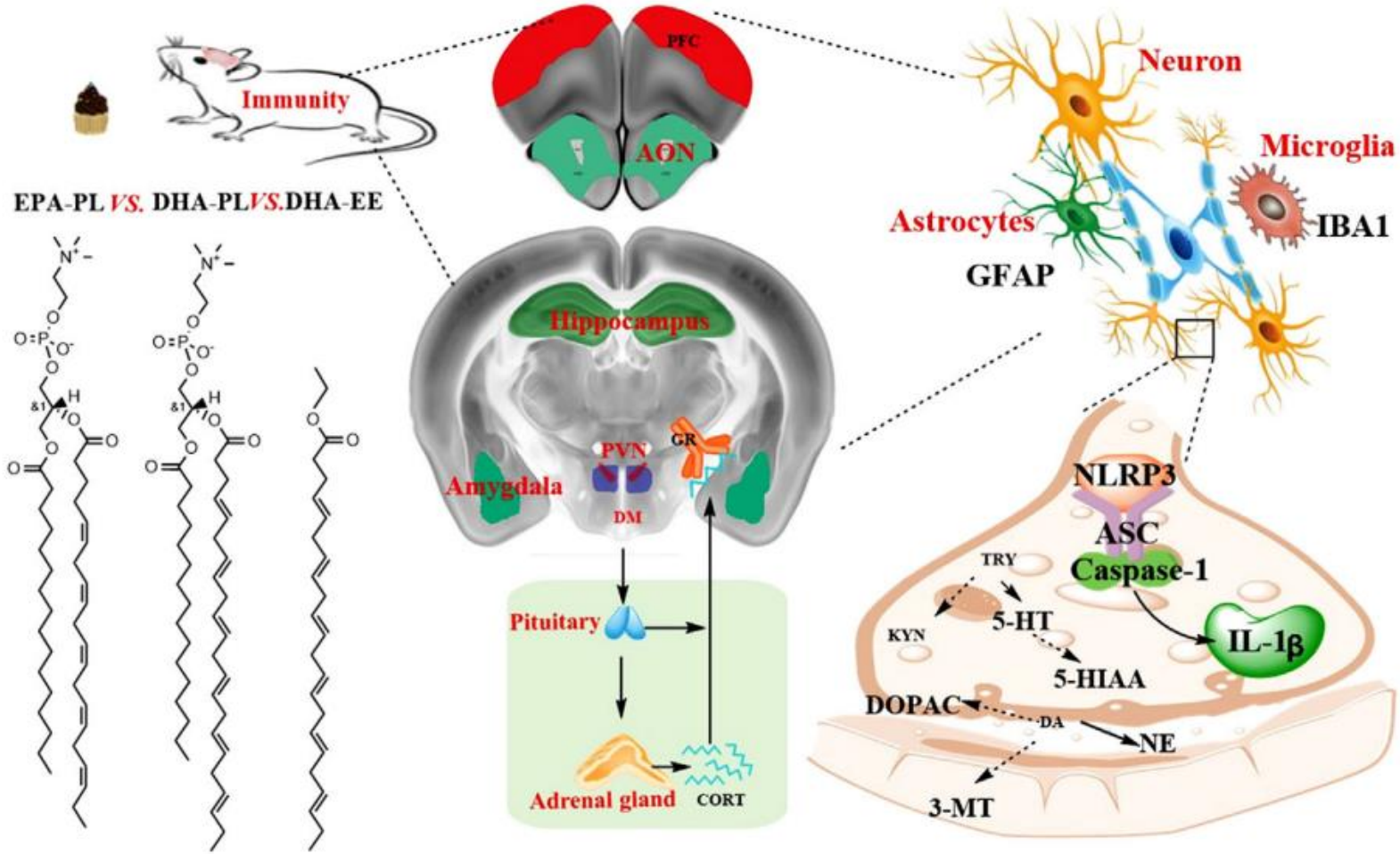
RESEARCH ARTICLE

Molecular Nutrition & Food Research
www.mnf-journal.com

Mol. Nutr. Food Res. 2022, 2200089

DHA-Enriched Phospholipids Exhibit Anti-Depressant Effects by Immune and Neuroendocrine Regulation in Mice: A Study on Dose- and Structure-Activity Relationship

Cheng-Cheng Wang, Jun-Yi Wang, Hao-Hao Shi, Ying-Cai Zhao, Jin-Yue Yang, Yu-Ming Wang, Teruyoshi Yanagita, Chang-Hu Xue, and Tian-Tian Zhang**



0.2% EPA-PL = 0.6% DHA-PL > 0.6% DHA-EE >> 0.2% DHA-PL

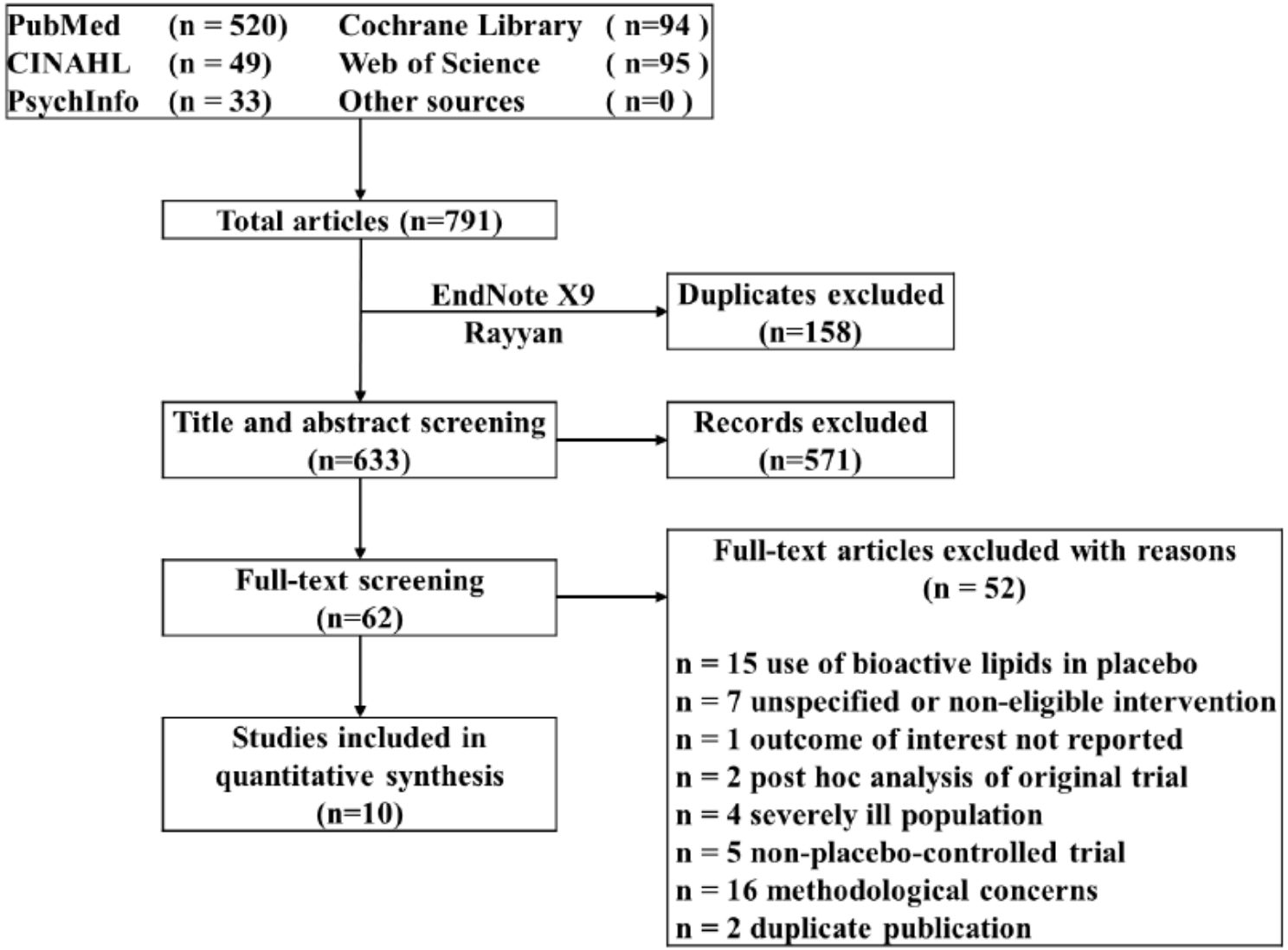
Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Effects of long-chain omega-3 polyunsaturated fatty acids on reducing anxiety and/or depression in adults; A systematic review and meta-analysis of randomised controlled trials

Christos F. Kelaiditis [a,*], E.Leigh Gibson [b], Simon C. Dyall [a]



Depression: 10 RCTs (n = 1426)

Anxiety: 1 RCT (n = 68)

DPAn-3: 0

(Kelaiditis *et al.*, 2023)

Table 1. Eligible Studies Characteristics

Study	Duration (weeks)	Mean Age (years)	Sample Size (n)	Female (%)	Population	Intervention	Comparator	Outcome
Frangou 2006	12	47.0	75	76.0	Adults with bipolar depression	1 g EPA-EE or 2 g EPA-EE	paraffin oil	HDRS
Ginty 2017	18	43.1	255	50.7	Healthy adults	1 g EPA-TG and 0.4 g DHA-TG	soybean oil	BDI
Kiecolt-Glaser 2011	12	23.6	68	44.1	Healthy university students	2.1 g EPA-FO and 0.3 g DHA-FO	mixture of palm, olive, soy, canola, and coco butter oils	BAI, CES-D
Kiecolt-Glaser 2012	16	51.1	133	67.4	Healthy, sedentary, overweight, middle-aged, and older adults	2.1 g EPA-FO and 0.3 g DHA-FO or 1 g EPA-FO and 0.2 g DHA-FO	mixture of palm, olive, soy, canola, and coco butter oils	CES-D
Lespérance 2011	8	46.0	432	68.5	Patients experiencing a major depressive episode	1.1 g EPA-EE and 0.2 g DHA-EE	sunflower oil	IDS, MADRS
Lucas 2009	8	48.8	106	100.0	Women with moderate-to-severe psychological distress	1.1 g EPA-EE and 0.2 g DHA-EE	sunflower oil	HSCL, HDRS
Mischoulon 2015	8	44.7	177	53.0	Adult outpatients with major depressive disorder	1.1 g EPA-TG and 0.3 g DHA-TG or 0.2 g EPA-TG and 0.9 g DHA-TG	soybean oil	HDRS
Mozaffari-Khosravi 2013	12	35.1	62	61.3	Adult outpatients with mild-to-moderate depression	1 g EPA-EE or 1 g DHA-FO	coconut oil	HDRS
Rapaport 2016	8	46.1	155	58.7	Adult outpatients with major depressive disorder	1.1 g EPA-TG and 0.3 g DHA-TG or 0.2 g EPA-TG and 0.9 g DHA-TG	soybean oil	HDRS
Rondanelli 2010	8	83.9	46	100.0	Older-adult depressed females (nursing home residents)	1.7 g EPA-FO and 0.8 g DHA-FO	paraffin oil	GDS

EPA eicosapentaenoic acid; **DHA** docosahexaenoic acid; **HDRS** Hamilton Rating Scale for Depression; **BDI** Beck Depression Inventory; **BAI** Beck Anxiety Inventory; **CES-D** Center for Epidemiological Studies Depression Scale; **IDS** Inventory of Depressive Symptomatology; **MADRS** Montgomery-Asberg Depression Rating Scale; **HSCL** Hopkins Symptom Checklist Depression Scale; **GDS** Geriatric Depression Scale; **EE** ethyl ester; **TG** triacylglycerols; **FO** fish oil.

Reference	Age (years)	Diagnosis	MDD Criteria	Participants	Intervention (g/day)	Placebo	Gender	Duration (weeks)	Summary
Mischoulon *et al.* [19▪▪]	18–80	MDD	DSM-VI	61 randomized (N=15–16 per group)	(1) 1.18 g EPA, 0.254 g DHA (2) 2.36 g EPA, 0.51 g DHA (3) 4.27 g EPA, 1.16 g DHA	Matched dose soybean oil (51% LA, 25% OA, 6% ALA)	M (25%) F (75%)	12	Higher dose of EPA showed promise in treating MDD with reduced inflammation level
Chang *et al.* [20▪]	60±9	MDD	DSM-VI	40 randomized (N=20 per group)	2 g EPA, 1 g DHA	Soybean oil 3 g/d	M (58%) F (42%)	12	N-3 PUFAs improved the fatigue symptoms in patients with CVDs comorbid MDD
Lin *et al.* [21]	>60	LLD	DSM-VI	29 randomized (N=9 or 11 per group)	1.2 g EPA, 1 g DHA	Soybean oil	M (15%) F (85%)	52	N-3 PUFAs supplement may alleviate cognitive decline in LLD through anti-inflammatory mechanisms and modulation of brain entropy
Amminger *et al.* [22]	15-25	MDD	DSM-VI	233 randomized (N=88–93 per group)	0.84 g EPA, 0.56 g DHA	Paraffin oil	M (31%) F (69%)	12	No evidence to support the use of N-3 PUFAs for treatment in young people with MDD
Xue *et al.* [44]	18-45	Drug-naive depressed patient	DSM-VI	72 randomized (N=36 per group)	Venlafaxine + 1.44 g EPA, 0.96 g DHA 0	Venlafaxine + 8 g soybean oil	M (36%) F (64%)	12	N-3 PUFAs yielded a small but statistically significant improvement on immediate memory in first-diagnosed, drug-naive depressed patients
Ilavská *et al.* [23▪]	10-18	Depressed children and adolescent	ICD-10	60 randomized (N=29 per group)	1.00 g EPA, 0.75 g DHA	Sunflower oil (2.47 g/d LA)	M (26%) F (74%)	12	Standard SSRI treatment N-3 PUFAs increased the production of serotonin that helps regulate mood and behavior
Lamon-Fava *et al.* [41]	18-80	Nonpsychotic MDD	M.I.N.I.	N=10–13 per group	(1) 1.18 g EPA, 0.254 g DHA (2) 2.36 g EPA, 0.51 g DHA (3) 4.27 g EPA, 1.16 g DHA	Matched dose soybean oil (51% LA, 25% OA, 6% ALA)	M (29%) F (71%)	12	Secondary analysis of Mischoulon *et al.*, 2022 MDD patients taking highest dose had greatest increases in EPA and DHA-derived mediators
McNamara *et al.* [24]	9–21	MDD	DSM-VI	56 randomized (N=18 or 21 per group)	1.35 g EPA, 0.12 g DPAn-3, and 0.78 g DHA	Olive oil	M (23%) F (77%)	12	N-3 PUFAs improved brain communication linked to emotions in unmedicated adolescent at high risk for depression
Tabasi *et al.* [45]	18-60	Depression	DSM-VI	73 randomized (N=15–17 per group)	tDCS or sham + 0.62 g EPA, 0.55 g DHA	tDCS or sham + 5 ml soybean oil	F (100%)	3	Significant interaction effect of tDCS and N-3 PUFAs in reducing the weight of women with depression and overweight
Li *et al.* 2024	13–24	Depression	ICD-10	71 randomized (N=34 or 37 per group)	Paxil + 1.94 g EPA, 0.76 g DHA	Paxil	M (41%) F (59%)	12	Paxil open label study. Adjuvant N-3 PUFAs is effective for reducing depressive symptoms

CVD, cardiovascular disease; DHA, docosahexaenoic acid; DSM-VI, Diagnostic and Statistical Manual of Mental Disorders; EPA, eicosapentaenoic acid; ICD, International Classification of Diseases; L
depression; M.I.N.I, Mini International Neuropsychiatric Interview; MDD, major depressive disorder; N-3 PUFAs; NSFR, niacin skin flushing response; tDCS, transcranial direct current stimulation.

(Dyall *et al.*, 2025)

Omega-3 PUFAs and Depression

- **EPA at ≥60% total EPA+DHA (>1 g/d) show promise in treating depression, especially with inflammatory subtypes**
- **Methodological considerations in omega-3 PUFA research**
  - Dose and timing of treatment, blood levels, placebo, background diet, interaction with other nutrients, genotype, GA at birth…
  - *Responders vs. non-responders*

International Society for Nutritional Psychiatry Research Practice Guidelines for Omega-3 Fatty Acids in the Treatment of Major Depressive Disorder

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Categories	Clinical recommendations
General concepts	Clinicians who use n -3 PUFA treatments in major depressive disorder (MDD) should do so only after applying a clinical interview to confirm the diagnosis and assess mental status and relevant physical conditions, including fish hypersensitivities n–3 PUFAs are better used as an adjunctive treatment than monotherapy for adult MDD n–3 PUFAs can be efficacious and safe, both for acceleration and augmentation – Acceleration = adding n–3 at the beginning of treatment concurrently with another antidepressant – Augmentation = adding n–3 when a prior antidepressant's effect is inadequate Both pure EPA and EPA/DHA (ratio >2:1) combinations are effective as a potential treatment of MDD n–3 PUFAs are considered effective as an adjunctive treatment for acute major depressive episodes, but more evidence is needed for recurrent major depressive episodes
Acute treatment strategy	The recommended therapeutic dosages should aim for 1–2 g/day of total EPA from pure EPA or 1–2 g/day EPA from an EPA/DHA (>2:1) combination The dose is recommended to be increased in 2 weeks for non- or partial responders, and titrated up to the maximum dose in 4–6 weeks if tolerable For nonresponders, it is recommended to evaluate the quality of n–3 PUFA supplementary products