

Supplementary Material for the article

Wolters et al. Effects of n-3 polyunsaturated fatty acid supplementation in the prevention and treatment of depressive disorders – a systematic review and meta-analysis

Supplementary Table S1. Search strategy used in current review. All searches were conducted on January 1, 2020.

MEDLINE via Ovid	
1. (depression* or "depressive disorder*" or dysthymia or blues or dejection or despondency or disconsolate or dumps or gloom or joylessness or mournfulness or sadness or sorrowfulness or unhappiness).ti,ab.	
2. exp depression/ or exp depressive disorder/ or exp depressive disorder, major/ or exp dysthymia/ or exp sadness/	
3. 1 or 2	
4. ("omega 3 fatty acid*" or "omega-3 fatty acid*" or "n 3 fatty acid*" or "n-3 fatty acid*" or "w 3 fatty acid*" or "w-3 fatty acid*" or "ω 3 fatty acid*" or "ω-3 fatty acid*" or "eicosapentaenoic acid*" or EPA or "alpha linolenic acid" or ALA or "docosahexaenoic acid*" or DHA or "fish oil" or "cod liver oil" or PUFA or "polyunsaturated fatty acid*").ti,ab.	
5. exp acids, omega 3 fatty/ or exp fatty acids, unsaturated/ or exp eicosapentaenoic acid/ or exp alpha linolenic acid/ or exp docosahexaenoic acid/ or exp fish oils/ or exp cod liver oil/	
6. 4 or 5	
7. 3 and 6	
8. limit 7 to (humans and yr="2010 - 2020")	
9. limit 8 to randomized controlled trial	
PSYCINFO via Ovid	
1. (depression* or "depressive disorder*" or dysthymia or blues or dejection or despondency or disconsolate or dumps or gloom or joylessness or mournfulness or sadness or sorrowfulness or unhappiness).ti,ab.	
2. exp "Major Depression"/ or exp "Depression (Emotion)"/ or exp "Dysthymic Disorder"/ or exp "Sadness"/	
3. 1 or 2	
4. ("omega 3 fatty acid*" or "omega-3 fatty acid*OR n 3 fatty acid*" or "n-3 fatty acid*" or "w 3 fatty acid*" or "w-3 fatty acid*" or "ω 3 fatty acid*" or "ω-3 fatty acid*" or "eicosapentaenoic acid*" or EPA or "alpha linolenic acid" or ALA or "docosahexaenoic acid*" or DHA or "fish oil" or "cod liver oil" or PUFA or "polyunsaturated fatty acid*").ti,ab.	
5. exp "Fatty Acids"/	
6. 4 or 5	
7. 3 and 6	
8. limit 7 to (human and "0300 clinical trial" and yr="2010 - 2020")	
CENTRAL via the Cochrane Library	
ID	Search Hits
#1	MeSH descriptor: [Depression] explode all trees 10762
#2	MeSH descriptor: [Depressive Disorder] explode all trees 11061
#3	MeSH descriptor: [Dysthymic Disorder] explode all trees 168
#4	MeSH descriptor: [Sadness] explode all trees 3
#5	(depression* OR "depressive disorder*" OR dysthymia OR blues OR dejection OR despondency OR disconsolate OR dumps OR gloom OR joylessness OR mournfulness OR sadness OR sorrowfulness OR unhappiness):ti,ab 63158
#6	MeSH descriptor: [Fatty Acids, Omega-3] explode all trees 2933
#7	MeSH descriptor: [Eicosapentaenoic Acid] explode all trees 991

#8	MeSH descriptor: [Docosahexaenoic Acids] explode all trees	1125
#9	MeSH descriptor: [alpha-Linolenic Acid] explode all trees	227
#10	MeSH descriptor: [Fish Oils] explode all trees	3252
#11	MeSH descriptor: [Cod Liver Oil] explode all trees	34
#12	MeSH descriptor: [Fatty Acids, Unsaturated] explode all trees	12050
#13	("omega 3 fatty acid*" OR "omega-3 fatty acid*" OR "n 3 fatty acid*" OR "n-3 fatty acid*" OR "w 3 fatty acid*" OR "w-3 fatty acid*" OR "ω 3 fatty acid*" OR "ω-3 fatty acid*" OR "eicosapentaenoic acid*" OR EPA OR "alpha linolenic acid" OR ALA OR "docosahexaenoic acid*" OR DHA OR "fish oil" OR "cod liver oil" OR PUFA OR "polyunsaturated fatty acid*"):ti,ab	8798
#14	((#1 OR #2 OR #3 OR #4) OR #5) AND ((#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12) OR #13) with Publication Year from 2010 to 2020, in Trials	313

Supplementary Table S2: Baseline and end-study estimates and/or mean changes of trials included in the systematic review (Studies in lines marked in light grey were not included in the meta-analysis)

Lead author, publication date	Intervention (n-3 PUFA dosage/d)	Outcome assessment score	Intervention group			Placebo group		
			Sample size	Baseline mean \pm SD	End study mean \pm SD and/or mean change \pm SD	Sample size	Baseline mean \pm SD	End study mean \pm SD
Andrieu et al. 2017¹	Group 1: capsule: 800mg DHA 225mg EPA + multidomain intervention	Geriatric Depression Scale (GDS)	374	3.17 \pm 2.47	mean change: -0.280 \pm 2.659	390	3.2 \pm 2.58	mean change: -0.126 \pm 1.265
	Group 2: capsule: 800mg DHA 225mg EPA		381	3.27 \pm 2.67	mean change: -0.444 \pm 2.694	380	3.21 \pm 2.7	mean change: -0.295 \pm 2.660
Antypa et al. 2011	fish oil capsule: 1740mg EPA 250mg DHA	Beck Depression Inventory II (BDI-II)	36	5.7 \pm 5.0	6.6 \pm 7.3	35	7.7 \pm 5.9	6.5 \pm 6.4
Bot et al. 2010	capsule: 1000mg E-EPA	Montgomery Asberg Depression Rating Scale (MADRS)	12	26.3 \pm 8.2	14.0 \pm 6.9	12	26.4 \pm 8.7	11.6 \pm 9.1
Carney et al. 2019 (pers. commun.)	capsule: 2000mg EPA + 50mg Sertraline	Beck Depression Inventory II (BDI-II)	71	29.9 \pm 9.0	11.0 \pm 9.0; mean change: -18.9 \pm 12.9	73	29.1 \pm 8.8	9.1 \pm 7.7; mean change: -9.7 \pm 9.7

		Hamilton Depression Rating Scale (HDRS)		17.4 ±5.4	7.1±7; mean change: -11.3±8.7		17.0 ±5.0	6.2±5.5; mean change: -11.3±6.9
		Patient Health Questionnaire (PHQ-9)		15.9 ±4.6	5.4±5.2; mean change: -11.2±8.1		15.4 ±4.1	4.9±4.7; mean change: -10.8±5.4
Chang et al. 2019² (pers. commun.)	capsule: 2000mg EPA 1000mg DHA	Hamilton Depression Rating Scale (HDRS)		19 ±4.21	13.90 ±4.44 mean change: -5.10 ±4.05		19.17 ±3.58	15.07± 3.90 mean change: -4.10 ±3.42
		Beck Depression Inventory (BDI)	30	17.67 ±9.08	14.73 ± 10.75 mean change: -3.07 ±5.44	29	17.72 ±6.31	14.17± 7.76 mean change: -2.97 ±7.47
Gabbay et al. 2019	capsule: starting with 1200mg, which was increased 600mg every 2 weeks, up to a maximum of 3600mg (2400mg EPA, 1200mg DHA)	Children's Depression Rating Scale-Revised (CDRS-R)		49.5 ±8.20	36.5 ±10.01		50.2 ± 8.91	35.2 ±10.57
		Beck Depression Inventory-II (BDI-II)	21	24.2 ±13.70	16.9 ±13.21	27	22.4 ±12.65	14.8 ±11.97
Gharekhani et al. 2014 (pers. commun.)	capsules: 1080mg EPA 720mg DHA	Beck Depression Inventory (BDI)	27		14.56 ±6.8 mean change: -10.68 ±8.28	27		20.4 ±6.69 mean change: -0.98 ±8.71

Giltay et al. 2011 (pers. commun.)	Group 1: Magarine spread: 400mg EPA + DHA 2mg ALA/d	Geriatric Depression Scale (GDS)	1021		2.1060 ± 2.4106 mean change (N=170): 0.2342 ±2.1352			
	Group 2: Magarine spread: 400mg EPA + DHA		1015		2.0161± 2.3252 mean change (N=146): 0.3064 ±1.7676			
	Group 3: Magarine spread: 2mg ALA		1034		2.0466 ± 2.3597 mean change (N=162): 0.0770 ±2.2588	1046		2.1631 ± 2.4591 mean change (N=173): -0.0127 ±1.8416
Ginty et al. 2015	capsule: 1000mg EPA 400mg DHA	Beck Depression Inventory (BDI)	12	15.58 ±5.21	NA	9	15.89 ±5.46	NA
Haberka et al. 2013	capsule: 465mg EPA 375mg DHA	Beck Depression Inventory (BDI)	26	11.1 ±6.8	9.3	26	11.7 ±6.8	11.3

		Beck Depression Inventory (BDI)		36.36 ±6.0	7.16 ±1.70		35.44 ±6.24	15.44 ±3.62
Jahangard et al. 2018	capsule: 1000mg n3-PUFA + 50-200mg Sertraline	Montgomery Asberg Depression Rating Scale (MADRS)	25	37.2 ±7.57	6 ±2.38	25	32.60 ±7.53	17.20 ±3.52
				Group 1: 22.22 ±3.78	15.1 ±5.4			
	Group 1: capsule: 2000mg 2:1 EPA:DHA	Hamilton Depression Scale (HDRS)	Group 1: 36	Group 2: 22.67 ±4.24	15.7 ±5.4		23.56 ±4.53	14.9 ±5.4
				Group 1: 19 ±7.58	13.3 ±7.8			
Jiang et al. 2018²	Group 2: capsule: 2000mg EPA	Beck Depression Inventory II (BDI-II)	Group 2: 36	Group 2: 20 ±8.45	13.6 ±7.8	36	21.53 ±8.47	14.3 ±7.8
	Group 1: softgel: 360 mg EPA 240mg DHA + capsule: 500mg Vit.C		34	14.242 ±3.71	11.18±5.31 mean change: -3.061 ±6.83	34	14.133 ±4.37	10.90±5.90 mean change: -3.233 ±7.08
Khajehnasiri et al. 2012²	Group 2: softgel: 360 mg EPA 240mg DHA	Beck Depression Inventory (BDI)	34	13.903 ±4.63	7.61±5.16 mean change: -6.29 ±6.82	34	14.090 ±3.42	11.75±5.55 mean change: -2.34 ±5.88

Lespérance et al. 2011 (pers. commun.)	capsule: 1050mg EPA 150mg DHA	Inventory of Depressive Symptomatology (IDS-SR)	218	43.8 ±8.75	30.93 ±12.12 ³	214	43.3 ±8.88	32.26 ±12.16 ³
		Montgomery Asberg Depression Rating Scale (MADRS)		17.9 ±8.9 ⁴	18.8 ±8.9 ⁴			
Mazereeuw et al. 2016	capsule: 1200mg EPA 600mg DHA 100mg other n-3 PUFA	Hamilton Depression Rating Scale (HDRS)	45	6.5 ±6.3	mean change: -1.1 ±4.6	47	7.4 ±5.6	NA
		Beck Depression Inventory II (BDI-II)		12.2 ±11.5	NA		12.4 ±10.5	NA
Mischoulon et al. 2015^{2,3} (pers. commun.)	Group 1: capsule: 1060mg EPA 274mg DHA Group 2: capsule: 900mg DHA 180mg EPA	Hamilton Depression Rating Scale (HDRS)	Group 1: 60 Group 2: 60	Group 1: 19.3 ±3.8	8.96 (6.9) ⁴ mean change: -10.34±4.8025	59	19.2 ±3.1	group 1 (N30), group 2 (N29): 9.71 (6.4) ⁴ mean change: -9.49±4.6855
		Group 2: 19.8 ±3.2		10.54 (6.9) ⁴ mean change: -9.26±4.7218				
		Clinical Global Impression (CGI-S)		Group 1: 4.2 ±0.6	mean change: -1.46 ±0.8521		4.0 ±0.6	mean change: -1.41±0.8449
		Quick Inventory of Depressive		Group 1: 12.9 ±3.9	mean change: -5.01±3.6406		13.5 ±3.8	mean change: -5.54±3.6101

		Symptomatology (QIDS-SR)	58	Group 2: 13.3 ±4.5	mean change: -4.79±3.5794			
Mozaffari-Khosravi et al. 2013²	Group 1: capsule: 1000mg EPA	Hamilton Depression Rating Scale (HDRS)	21	15.9 ±2	10.3 ± 3.208			
	Group 2: capsule: 1000mg DHA		20	15.7 ±2.4	13.7 ±2.683	21	15.5 ±2.3	13.7 ±2.750
Ravi et al. 2016	capsule: 720mg EPA 480mg DHA	Beck Depression Inventory II (BDI-II)	50	28.42 ±8.51	14.30 ±5.78	50	27.20 ±5.86	26.70 ±5.95
		Depression subscale of the Hospital Anxiety and Depression scale (HADS-D)		13.04 ±2.51	7.54 ±1.99		12.98 ±2.66	12.68 ±2.64
		Patient Health Questionnaire (PHQ-9)		16.16 ±4.03	7.8 ±2.61		15.42 ±4.20	15.14 ±4.08
Rondanelli et al. 2010	fish oil capsule: 1670mg EPA 830mg DHA	Geriatric Depression Scale (GDS)	22	17.1 ±3.6	12.6 ±4.3	24	16.7 ±4.3	15.9 ±5.4
Shinto et al. 2016 (pers. commun.)	fish oil capsule: 1950mg EPA 1350mg DHA	Montgomery Asberg Depression Rating Scale (MADRS)	15	18.4 ±5.3	10.9 ±7.4 mean change: -6.9 ±8.3	16	19.1 ±4	9.0 ±5.2 mean change: -9.7 ±6.0
		Beck Depression Inventory (BDI)		20.1 ±8	10.6 ±5.8 mean change: -8.2 ±6.5		19.6 ±5.7	8.9 ±6.6 mean change: -11.1 ±5.8

Sinn et al. 2012	Group 1: fish oil capsule: 1670mg EPA 160mg DHA	Geriatric Depression Scale (GDS)	17	4.40 ±2.92	NA	15	3.15 ±2.08	NA
	Group 2: fish oil capsule: 1550mg DHA 400mg EPA		18	3.19 ±3.17	NA			
Tajalizadekhoob et al. 2011	fish oil capsule: 180mg EPA 120mg DHA	Geriatric Depression Scale (GDS)	33	7.24 ±1.95	6.00 ±2.92	33	7.21 ±1.83	6.91 ±3.98
Tayama et al. 2019	capsule: 1064mg EPA 558mg DHA + psychoeducation	Beck Depression Inventory II (BDI-II)	47	12.3 ±6.1	8.4 ±5.1	43	12.2 ±7.7	8.0 ±4.5
Trebaticka et al. 2020 (pers. commun.)	fish oil emulsion: 1000mg EPA 750mg DHA	Children's Depression Inventory (CDI)	29	27.8 ±9.0	21.34±11.7; mean change:- -7.6±7.1	29	24.9 ±8.5	22.24 ±10.1; mean change:-2.9±7.8
Watanabe et al. 2018¹	Group 1: capsule: 1200mg EPA 600mg DHA + stressmanagement program	Hospital Anxiety and Depression scale (HADS)	40	Group 1 and 2: 7.4 ±4.8	Week 13: 6.40 ±3.872 Week 26: 6.32 ±3.856 Week 52: 5.85 ±3.872	40	7.11 ± 4.55	Week 13: 7.60±3.985 Week 26: 6.81±4.001 Week 52: 8.32±4,050
		Hospital Anxiety and Depression scale (HADS), depression score		Group 1 and 2: 3.3 ±2.8	Week 13: 2.84 ±2.194 Week 26: 2.69 ±2.194 Week 52: 2.36 ±2.194			Week 13: 3.54 ±2.259 Week 26: 3.05 ±2.259 Week 52: 3.80 ±2.291

	Group 2: capsule: 1200mg EPA 600mg DHA + psychoeducation	Patient Health Questionnaire (PHQ-9)	Group 1 and 2: 5.1 ±3.4	Week 13: 5.42 ±2.953	4.7 ±3.4	Week 13: 5.83 ±3.388
				Week 26: 5.39 ±2.969		Week 26: 5.31 ±3.082
				Week 52: 5.42 ±2.953		Week 52: 4.79 ±3.114

¹To calculate the SD from 95% CI we used the following formula: $SD = \sqrt{N} * (\text{upper limit} - \text{lower limit}) / 3.92$

²To calculate the SD from standard error we used the following formula: $SD = \sqrt{N} * SE$

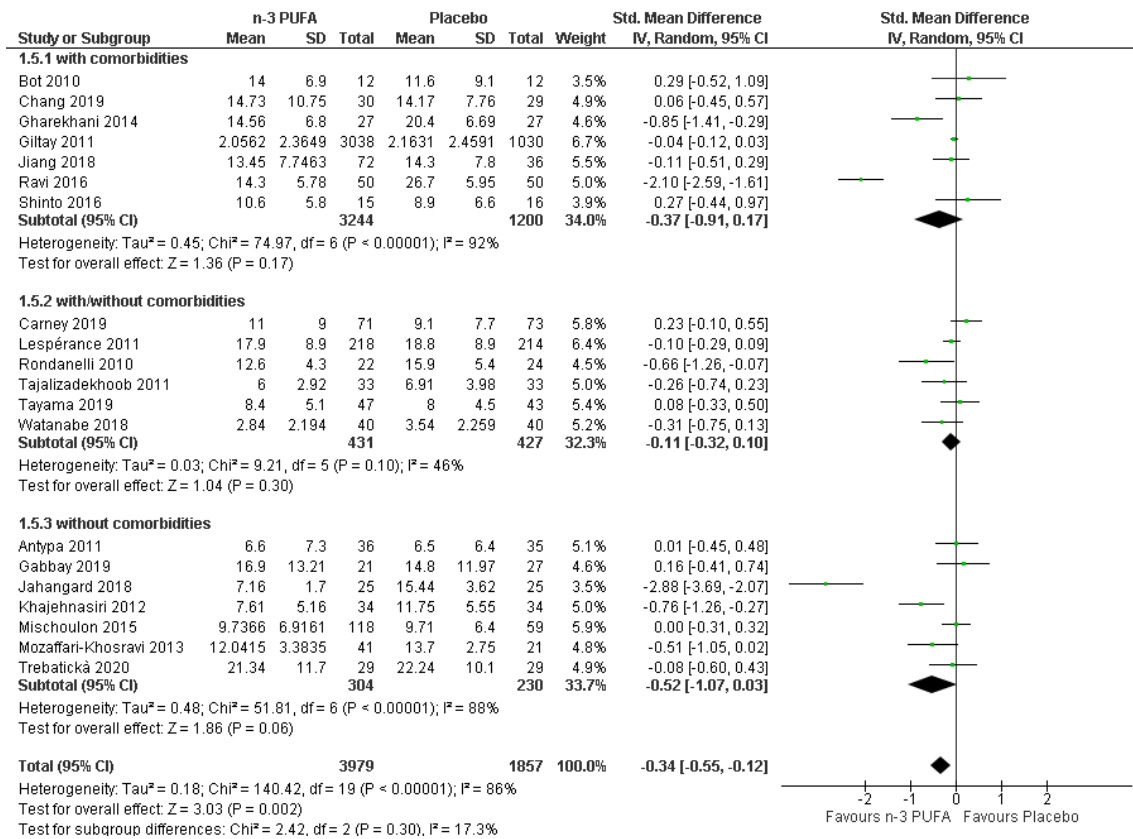
³For changes: Least squares means with adjustments are given

⁴Data taken from Appleton et al. 2015

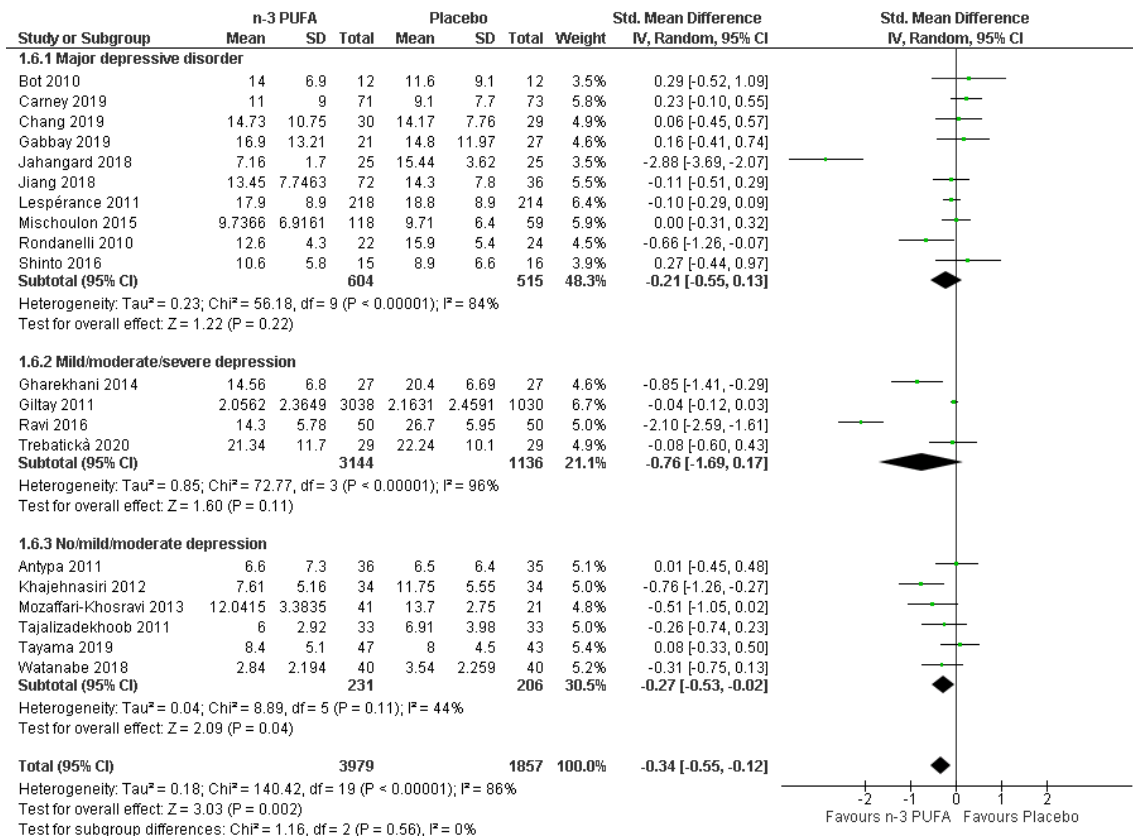
Abbreviations: ALA, alpha-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentanoic acid; ITT, intention to treat; MDD, major depressive disorder; NA, not available; pers. commun., personal communication; SD, standard deviation

Supplementary Table S3. Leave-one-out sensitivity analyses

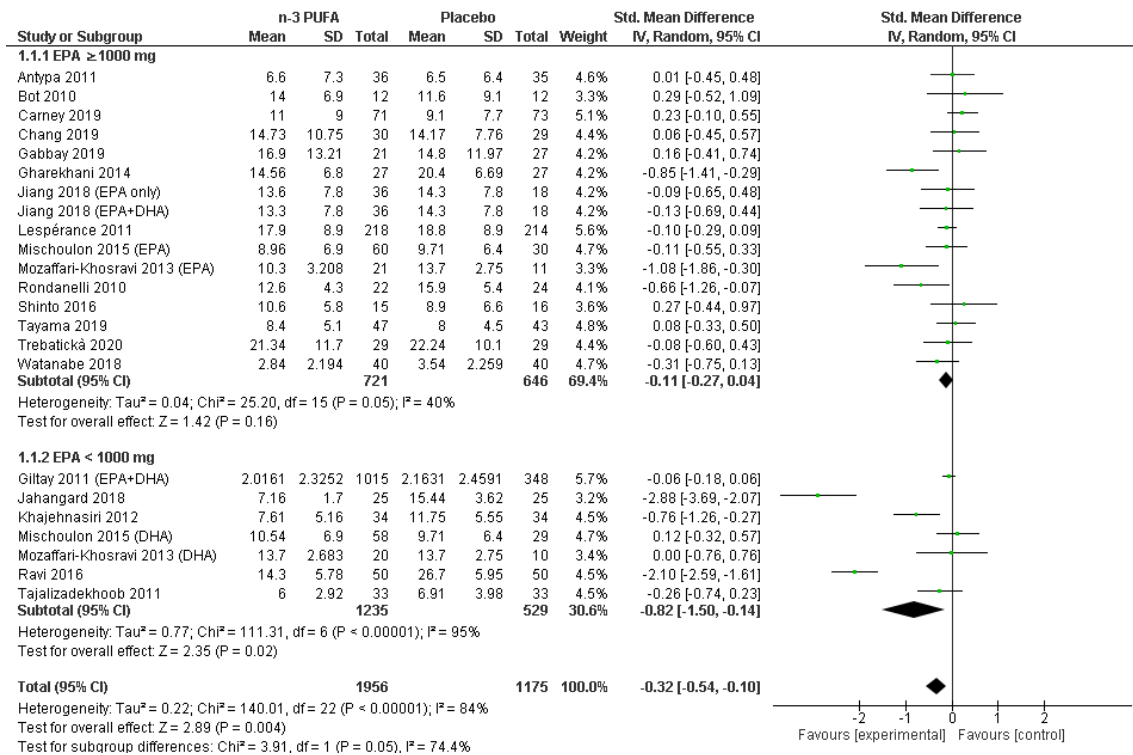
Study	Standardized mean difference, given named study is omitted	95% Confidence interval	<i>I</i>² estimate
Antypa 2011	-0.36	-0.58, -0.13	87%
Bot 2010	-0.36	-0.58, -0.14	87%
Carney 2019	-0.37	-0.60, -0.14	87%
Chang 2019	-0.36	-0.58, -0.13	87%
Gabbay 2019	-0.36	-0.58, -0.14	87%
Gharekhani 2014	-0.31	-0.53, -0.09	87%
Giltay 2011	-0.37	-0.64, -0.09	86%
Jahangard 2018	-0.24	-0.43, -0.05	81%
Jiang 2018	-0.35	-0.58, -0.12	87%
Khajehnasiri 2012	-0.31	-0.53, -0.09	87%
Lespérance 2011	-0.36	-0.61, -0.11	87%
Mischoulon 2015	-0.36	-0.59, -0.13	87%
Mozzafari-Khosravi 2013	-0.33	-0.55, -0.10	87%
Ravi 2016	-0.22	-0.39, -0.05	77%
Rondanelli 2010	-0.32	-0.54, -0.10	87%
Shinto 2016	-0.36	-0.58, -0.14	87%
Tajalizadekhoob 2011	-0.34	-0.57, -0.11	87%
Tayama 2019	-0.36	-0.59, -0.13	87%
Trebatickà 2020	-0.35	-0.58, -0.12	87%
Watanabe 2018	-0.34	-0.56, -0.11	87%



Supplementary Figure S1: Effect of n-3 PUFA on depressive symptoms by subgroup of studies including participants with comorbidities, without comorbidities or with and without comorbidities



Supplementary Figure S2: Effect of n-3 PUFA on depressive symptoms by subgroup of studies including participants with major depression only, with mild to moderate and severe depression, without depression and mild to moderate depression.



Supplementary Figure S3: Effect of n-3 PUFA on depressive symptoms by subgroup of studies with high or low EPA dosage (\geq versus <1000 mg/d)

References

Andrieu, S., S. Guyonnet, N. Coley, C. Cantet, M. Bonnefoy, S. Bordes, L. Bories, M. N. Cufi, T. Dantoine, J. F. Dartigues, F. Desclaux, A. Gabelle, Y. Gasnier, A. Pesce, K. Sudres, J. Touchon, P. Robert, O. Rouaud, P. Legrand, P. Payoux, J. P. Caubere, M. Weiner, I. Carrié, P. J. Ousset and B. Vellas (2017). "Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial." *Lancet Neurol* **16**(5): 377-389.

Appleton, K. M., H. M. Sallis, R. Perry, A. R. Ness and R. Churchill (2015). "Omega-3 fatty acids for depression in adults." *Cochrane Database Syst Rev*(11): Cd004692.