Comparing the effects of docosahexaenoic and eicosapentaenoic acids on inflammation markers using pairwise and network meta-analyses of randomized controlled trials.
Vors *et al.* Online Supplementary Material

Supplementary data

Supplementary Table 1. Search strategy

Database	MEDLINE	EMBASE	The Cochrane Library
Search Period	1946 to September 27, 2019	1946 to September 27, 2019	1946 to September 27, 2019
Search Terms	1. EPA.mp. 2. eicosapenta*.mp. 3. icosapentaenoic.mp. 4. exp Docosahexaenoic Acids/ 5. DHA.mp. 6. Fatty acids, Unsaturated/ 7. exp Fatty Acids, Omega-3/ 8. exp INTERLEUKINS/ 9. interleukin-6.mp. 10. IL-6.mp. 11. C-reactive protein.mp. 12. CRP.mp. 13. Tumor Necrosis Factor-alpha.mp. 14. tnf-alpha.mp. 15. adiponectin.mp 16. 1 or 2 or 3 or 4 or 5 or 6 or 7 17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 18. 16 and 17 19. limit 18 to *all adult (19 plus years)* 20. limit 19 to (english or french)	1. eicosapenta* 2. icosapenta* 3. epa 4. docosahexa* 5. dha 6. 'unsaturated fatty acid*' 7. 'omega 3 fatty acid*' 8. 'interleukins'/exp 9. 'interleukins' 10. 'interleukin 6' 11. 'il-6'/exp 12. 'il-6' 13. 'c reactive protein' 14. 'crp'/exp 15. 'crp' 16. 'tumor necrosis factor alpha'/exp 17. 'tumor necrosis factor alpha' 18. 'tnf-alpha'/exp 19. 'tnf-alpha' 20. 'adiponectin' 21. 1 or 2 or 3 or 4 or 5 or 6 or 7 22. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 23. 21 and 22 24. 21 and 22 and ((english)/lim or (french)/lim) and ((adult)/lim or (aged)/lim)	1. eicosapenta* 2. icosapenta* 3. "EPA" 4. docosahexa* 5. "DHA" 6. MeSH descriptor: [Fatty Acids, Unsaturated] this term only 7. MeSH descriptor: [Fatty Acids, Omega-3] explode all trees 8. MeSH descriptor: [Interleukins] explode all trees 9. "interleukins" 10. "interleukin-6" 11. "IL-6" 12. "C-reactive protein" 13. "CRP" 14. "tumor necrosis factor-alpha" 15. "TNF-alpha" 16. "adiponectin" 17. 1 or 2 or 3 or 4 or 5 or 6 or 7 18. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 19. 17 and 18 in Trials

Supplementary data

Supplementary Table 2. Side-splitting approach[1] for inconsistency for plasma CRP

Side	Direct		Indirect		Difference		
	Estimate	SE	Estimate	SE	Estimate	SE	P value
Canola - EPA	0.222	1.092	0.577	0.439	-0.355	1.186	0.76
Canola - DHA	0.210	0.351	0.094	2.156	0.116	2.202	0.96
Coconut - EPA	-0.400	0.251	1.113	238.769	-1.513	238.769	0.99
Corn - EPA	0.115	0.390	-0.445	0.472	0.559	0.611	0.36
Corn - DHA	-0.472	0.265	-0.033	0.993	-0.439	1.039	0.67
Oil mixture[2] - DHA	1.220	2.486	0.484	4686.976	0.736	4686.976	0.99
Olive - EPA	0.271	0.283	0.029	0.480	0.242	0.557	0.66
Olive - DHA	-0.094	0.270	-0.102	0.549	0.008	0.619	0.99
EPA - DHA	-0.102	0.294	-0.757	0.407	0.655	0.518	0.21

[1] The side-splitting detects comparisons for which direct estimates disagree with indirect estimates from the entire network (statistical difference).
[2] Mix of palm, olive, soy, canola, and coco butter oils.
CRP: C-reactive protein; SE: standard error.

Supplementary data

Supplementary Table 3. Side-splitting approach[1] for inconsistency for plasma IL-6

Side	Direct		Indirect		Difference		
	Estimate	SE	Estimate	SE	Estimate	SE	P value
Canola - DHA	-0.010	0.162	-0.107	72.045	0.097	72.046	0.99
Coconut - EPA	0.150	0.187	-0.346	669.428	0.496	669.428	0.99
Corn - EPA	0.020	0.229	-0.283	0.250	0.303	0.339	0.37
Corn - DHA	-0.069	0.162	0.301	0.471	-0.370	0.498	0.46
Oil mixture[2] - EPA	-0.134	1.255	0.335	0.432	-0.469	1.327	0.72
Oil mixture[2] - DHA	0.420	0.418	-0.049	1.259	0.469	1.327	0.72
Olive - EPA	-0.164	0.119	-0.120	0.213	-0.045	0.246	0.86
Olive - DHA	-0.053	0.081	-0.207	0.275	0.154	0.286	0.59
Sunflower - DHA	-2.990	0.820	2.965	631.901	-5.955	631.902	0.99
EPA - DHA	0.109	0.143	0.056	0.178	0.053	0.234	0.82

[1] The side-splitting detects comparisons for which direct estimates disagree with indirect estimates from the entire network (statistical difference).
[2] Mix of palm, olive, soy, canola, and coco butter oils.
IL-6: interleukin-6; SE: standard error.

Supplementary data

Supplementary Table 4. Side-splitting approach[1] for inconsistency for plasma TNF-α

Side	Direct		Indirect		Difference		
	Estimate	SE	Estimate	SE	Estimate	SE	P value
Corn - EPA	-0.110	0.218	-0.322	0.487	0.212	0.515	0.68
Corn - DHA	-0.190	0.204	0.022	0.506	-0.212	0.515	0.68
Oil mixture[2] - EPA	-0.042	1.071	-0.714	0.372	0.672	1.134	0.55
Oil mixture[2] - DHA	-0.730	0.353	-0.058	1.077	-0.672	1.134	0.55
Olive - EPA	-0.124	0.134	0.135	0.251	-0.259	0.277	0.35
Olive - DHA	-0.020	0.169	-0.214	0.218	0.195	0.280	0.49
EPA - DHA	-0.079	0.133	0.129	0.228	-0.208	0.263	0.43

[1] The side-splitting detects comparisons for which direct estimates disagree with indirect estimates from the entire network (statistical difference).
[2] Mix of palm, olive, soy, canola, and coco butter oils.
TNF-α: tumor necrosis factor-alpha; SE: standard error.

Supplementary data

Supplementary Table 5. Loop-specific approach for inconsistency for plasma CRP, IL-6 and TNF-α.

Loop	IF	95% CI (truncated)	Loop heterogeneity (τ^2)
Outcome: CRP			
Corn-EPA-DHA	0.875	(0.00,2.47)	0.204
Olive-EPA-DHA	0.457	(0.00,1.27)	0.000
Canola-EPA-DHA	0.167	(0.00,2.73)	0.156
Outcome: IL-6			
Oil mixture[1]-EPA-DHA	0.460	(0.00,3.07)	0.000
Corn-EPA-DHA	0.260	(0.00,0.93)	0.000
Olive-EPA-DHA	0.024	(0.00,0.44)	0.000
Outcome: TNF-α			
Oil mixture[1]-EPA-DHA	0.604	(0.00,2.81)	0.000
Olive-EPA-DHA	0.257	(0.00,0.83)	0.022
Corn-EPA-DHA	0.005	(0.00,0.49)	0.000

[1] Mix of palm, olive, soy, canola, and coco butter oils.

CI: confidence interval; CRP: C-reactive protein; IF: inconsistency factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

Supplementary data

Supplementary Table 6. Results of the *a priori* sensitivity analysis by the systematic removal of each trial, one by one, for pairwise meta-analysis comparing directly the effect of DHA and EPA on CRP[a]

Outcome: CRP Removal of	**DHA vs. EPA MD**	**95% CI**	**P value[b]**	**I^2**	**$P_{heterogeneity}$[c]**	**Comment**
Allaire 2016 (1)	0.32	[-0.74, 1.39]	0.55	64%	0.03	MD not significant after trial removal
Asztalos 2016 (2) a*	0.15	[-0.63, 0.94]	0.70	69%	0.01	MD not significant after trial removal
Asztalos 2016 (2) b*	0.08	[-0.69, 0.85]	0.83	67%	0.02	MD not significant after trial removal
Azizi-Soleiman 2013 (3)	0.25	[-0.56, 1.05]	0.55	68%	0.01	MD not significant after trial removal
Mori 2003 (4)	-0.26	[-0.54, 0.02]	0.07	0%	0.82	Heterogeneity was explained after trial removal
Tsunoda 2015 (5)	0.36	[-0.62, 1.34]	0.47	67%	0.02	MD not significant after trial removal

[a] Sensitivity analysis included the removal of a single study from the pairwise meta-analysis one at a time and the summary effect was recalculated. All comparisons after systematic removal of each trial are presented in this table.
[b] For the pooled effect estimates, $P < 0.05$ is considered significant.
[c] $P_{heterogeneity} < 0.10$ is considered significant.
* Study was divided into two (a, b), as Asztalos *et al*. (2) studied two doses of EPA compared to DHA.
CI: confidence interval; CRP: C-reactive protein; I^2: heterogeneity; MD: mean difference.

Supplementary data

Supplementary Table 7. GRADE assessment of the certainty of evidence for pairwise meta-analysis comparing DHA and EPA directly

Quality assessment[1]							Effect	Certainty
No of trial comparisons	**Design**	**Risk of bias[2]**	**Inconsistency**	**Indirectness[3]**	**Imprecision**	**Publication bias[4]**	**DHA vs. EPA MD (95% CI)**	
CRP								
6	RCTs	no serious	no serious[a]	no serious	serious[c]	none	0.14 mg/L (-0.57, 0.85)	MODERATE because of imprecision
IL-6								
4	RCTs	no serious	no serious[b]	no serious	no serious[d]	none	0.10 pg/mL (-0.15, 0.34)	HIGH
TNF-α								
4	RCTs	no serious	no serious[b]	no serious	no serious[e]	none	-0.10 pg/mL (-0.37, 0.18)	HIGH

[1]All outcomes started with high quality evidence since all studies were randomized controlled trials. Risk of Bias –We rated down for risk of bias if the majority of studies were considered to be at high risk of bias. Inconsistency – We assessed inconsistency using I^2 estimates where an $I^2 \geq 50\%$, $P<0.10$ indicates substantial heterogeneity. I^2 is the percentage of variability in the treatment estimate that is attributable to heterogeneity between studies. We rated down for inconsistency if there was substantial heterogeneity that was unexplained by any *a priori* sensitivity or subgroup analysis. Indirectness – We rated down for indirectness if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results. Imprecision – We rated down for imprecision if the 95% confidence interval (95% CI) crossed the Minimally Important Difference (MID). MIDs used for each outcome were: 0.5 mg/L for CRP, 0.5 pg/mL for IL-6, and 0.6 pg/mL for TNF-α.

[2] Risk of bias was not downgraded for since there was no 'high risk of bias' study in the pairwise meta-analysis.

[3] No downgraded for indirectness because there were only direct comparisons of DHA vs. EPA as well as no difference in interventions and outcome measures, and studies included relatively diverse populations with different characteristics.

[4] Not downgraded for publication bias, because publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects (<10 trials included in the pairwise meta-analysis).

[a] We did not downgrade for serious inconsistency, since all of the heterogeneity in the analysis was due to the study by Mori *et al.* (4) (Original: I^2=61%, $P_{heterogeneity}$=0.02; after study removal: I^2=0%, $P_{heterogeneity}$=0.82).
[b] We did not downgrade for serious inconsistency as there was evidence of low heterogeneity (I^2=40%, P-heterogeneity=0.17) for both IL-6 and TNF-α outcomes.
[c] Downgraded for serious imprecision, because the 95% confidence interval (-0.57 to 0.85 mg/L) overlapped the MID (0.5 mg/L).
[d] No downgraded for serious imprecision, because the 95% confidence interval (-0.15 to 0.34 pg/mL) did not overlap the MID (0.5 pg/mL).
[e] Not downgraded for serious imprecision, because the 95% confidence interval (-0.37 to 0.18 pg/mL) did not overlap the MID (0.6 pg/mL).
CI: Confidence interval; CRP: C-reactive protein; IL-6: interleukin-6; MD: Mean difference; RCTs: randomized controlled trials; TNF-α: tumor necrosis factor-alpha.

Supplementary data

Supplementary Table 8. GRADE approach for the assessment of the certainty of evidence from the network meta-analysis for plasma CRP.

Comparison	Direct estimate	Certainty direct estimate[1]	Indirect estimate	Certainty indirect estimate[2]	Network estimate	Certainty network estimate[3]
Coconut vs. Canola	NA	-	0.93 (0.02, 1.85)	High	0.93 (0.02, 1.85)	High
Corn vs. Canola	NA	-	0.62 (-0.14, 1.38)	High	0.62 (-0.14, 1.38)	Moderate[a]
Mix vs. Canola	NA	-	-1.01 (-5.93, 3.91)	High	-1.01 (-5.93, 3.91)	Moderate[a]
Olive vs. Canola	NA	-	0.32 (-0.45, 1.08)	High	0.32 (-0.45, 1.08)	Moderate[a]
EPA vs. Canola	0.22 (-1.92, 2.36)	Moderate[a]	0.58 (-0.28, 1.44)	High	0.53 (-0.24, 1.31)	Moderate[a]
DHA vs. Canola	0.21 (-0.48, 0.90)	Moderate[a]	0.09 (-4.13, 4.32)	High	0.21 (-0.44, 0.86)	Moderate[a]
Corn vs. Coconut	NA	-	-0.31 (-1.06, 0.44)	High	-0.31 (-1.06, 0.44)	Moderate[a]
Oil mixture vs. Coconut	NA	-	-1.95 (-6.86, 2.97)	High	-1.95 (-6.86, 2.97)	Moderate[a]
Olive vs. Coconut	NA	-	-0.62 (-1.26, 0.03)	High	-0.62 (-1.26, 0.03)	Moderate[a]
EPA vs. Coconut	-0.40 (-0.89, 0.09)	Moderate[a]	NA	-	-0.40 (-0.89, 0.09)	Moderate[a]
DHA vs. Coconut	NA	-	-0.73 (-1.38, -0.07)	High	-0.73 (-1.38, -0.07)	High
Mix vs. Corn	NA	-	-1.63 (-6.52, 3.26)	High	-1.63 (-6.52, 3.26)	Moderate[a]
Olive vs. Corn	NA	-	-0.31 (-0.87, 0.26)	High	-0.31 (-0.87, 0.26)	Moderate[a]
EPA vs. Corn	0.11 (-0.65, 0.88)	Moderate[a]	-0.45 (-1.37, 0.48)	High	-0.09 (-0.65, 0.47)	Low[a,b]
DHA vs. Corn	-0.47(-0.99, 0.05)	Moderate[a]	-0.03 (-1.98, 1.91)	High	-0.41 (-0.84, 0.01)	Low[a,b]
Olive vs. Oil mixture	NA	-	1.33 (-3.56, 6.22)	High	1.33 (-3.56, 6.22)	Moderate[a]
EPA vs. Oil mixture	NA	-	1.55 (-3.35, 6.44)	High	1.55 (-3.35, 6.44)	Moderate[a]
DHA vs. Oil mixture	1.22 (-3.65, 6.09)	Moderate[a]	NA	-	1.22 (-3.65, 6.09)	Moderate[a]
EPA vs. Olive	0.27(-0.28, 0.82)	Moderate[a]	0.03 (-0.91, 0.97)	High	0.22 (-0.20, 0.63)	Moderate[a]
DHA vs. Olive	-0.09 (-0.62, 0.44)	Moderate[a]	-0.10 (-1.18, 0.97)	High	-0.11 (-0.51, 0.30)	Moderate[a]
DHA vs. EPA	-0.10 (-0.68, 0.48)	Moderate[a]	-0.76 (-1.55, 0.04)	High	-0.33 (-0.75, 0.10)	Moderate[a]

[1] The rating of the certainty of the direct estimates considers risk of bias, indirectness, inconsistency, imprecision and publication bias. The rating was not downgraded based on risk of bias, indirectness and inconsistency. The ratings were downgraded for imprecision when confidence intervals were wide and included or were close to null effect. Finally, there was no evidence of publication bias to justify downgrading the rating of the certainty of the evidence.

[2] Only intransitivity was assessed from the indirect estimates. Not downgraded for intransitivity because there was no evidence for an uneven distribution of effect modifiers.
[3] Incoherence was assessed from the network estimates.
[a] Downgraded because of imprecision.
[b] Downgraded because of incoherence.
CRP: C-reactive protein; Oil mixture: mix of palm, olive, soy, canola, and coco butter oils.

Supplementary data

Supplementary Table 9. GRADE approach for the assessment of the certainty of evidence from the network meta-analysis for plasma IL-6.

Comparison	Direct estimate	Certainty direct estimate[1]	Indirect estimate	Certainty indirect estimate[2]	Network estimate	Certainty network estimate[3]
Coconut vs. Canola	NA	-	-0.25 (-0.78, 0.28)	High	-0.25 (-0.78, 0.28)	Moderate[a]
Corn vs. Canola	NA	-	0.02 (-0.42, 0.46)	High	0.02 (-0.42, 0.46)	Moderate[a]
Oil mixture vs. Canola	NA	-	-0.38 (-1.22, 0.46)	High	-0.38 (-1.22, 0.46)	Moderate[a]
Olive vs. Canola	NA	-	0.06 (-0.30, 0.41)	High	0.06 (-0.30, 0.41)	Moderate[a]
Sunflower vs. Canola	NA	-	2.98 (1.34, 4.62)	High	2.98 (1.34, 4.62)	Moderate[a]
EPA vs. Canola	NA	-	-0.10 (-0.48, 0.28)	High	-0.10 (-0.48, 0.28)	Moderate[a]
DHA vs. Canola	-0.01 (-0.33, 0.31)	Moderate[a]	NA	-	-0.01 (-0.33, 0.31)	Moderate[a]
Corn vs. Coconut	NA	-	0.27 (-0.22, 0.76)	High	0.27 (-0.22, 0.76)	Moderate[a]
Oil mixture vs. Coconut	NA	-	-0.14 (-1.02, 0.75)	High	-0.14 (-1.02, 0.75)	Moderate[a]
Olive vs. Coconut	NA	-	0.30 (-0.11, 0.72)	-	0.30 (-0.11, 0.72)	Moderate[a]
Sunflower vs. Coconut	NA	-	3.23 (1.57, 4.89)	High	3.23 (1.57, 4.89)	Moderate[a]
EPA vs. Coconut	0.15 (-0.22, 0.52)	Moderate[a]	NA	-	0.15 (-0.22, 0.52)	Moderate[a]
DHA vs. Coconut	NA	-	0.24(-0.19, 0.66)	High	0.24 (-0.19, 0.66)	Moderate[a]
Oil mixture vs. Corn	NA	-	-0.40 (-1.24, 0.43)	High	-0.40 (-1.24, 0.43)	Moderate[a]
Olive vs. Corn	NA	-	0.04 (-0.29, 0.36)	High	0.04 (-0.29, 0.36)	Moderate[a]
Sunflower vs. Corn	NA	-	2.96 (1.31, 4.60)	High	2.96 (1.31, 4.60)	Moderate[a]
EPA vs. Corn	0.02 (-0.43, 0.47)	Moderate[a]	-0.28 (-0.77, 0.21)	High	-0.12 (-0.45, 0.21)	Low[a,c]
DHA vs. Corn	-0.07 (-0.39, 0.25)	Moderate[a]	0.30 (-0.62, 1.22)	High	-0.03(-0.33, 0.27)	Low[a,c]
Olive vs. Oil mixture	NA	-	0.44 (-0.35, 1.23)	High	0.44 (-0.35, 1.23)	Moderate[a]
Sunflower vs. Mix	NA	-	3.36 (1.58, 5.15)	High	3.36 (1.58, 5.15)	Moderate[a]
EPA vs. Oil mixture	-0.13 (-2.59, 2.32)	Moderate[a]	0.34 (-0.51, 1.18)	High	0.29 (-0.52, 1.09)	Low[a,c]
DHA vs. Oil mixture	0.42 (-0.40, 1.24)	Moderate[a]	-0.05 (-0.21, 0.11)	High	0.37 (-0.40, 1.15)	Low[a,c]
Sunflower vs. Olive	NA	-	2.92 (1.31, 4.54)	High	2.92 (1.31, 4.54)	Moderate[a]

EPA vs. Olive	-0.16 (-0.40, 0.07)	Moderate[a]	-0.12 (-0.54, 0.30)	High	-0.15 (-0.35, 0.05)	Moderate[a]
DHA vs. Olive	-0.05 (-0.21, 0.11)	Low[a,b]	-0.21 (-0.75, 0.33)	High	-0.07 (-0.22, 0.09)	Moderate[a]
EPA vs. Sunflower	NA	-	-3.08 (-4.70, -1.46)	High	-3.08 (-4.70, -1.46)	Moderate[a]
DHA vs. Sunflower	-2.99 (-4.60, -1.38)	Moderate[a]	NA	-	-2.99 (-4.60, -1.38)	Moderate[a]
DHA vs. EPA	0.11 (-0.17, 0.39)	Moderate[a]	0.06 (-0.29, 0.40)	High	0.09 (-0.12, 0.30)	Moderate[a]

[1] The rating of the certainty of the direct estimates considers risk of bias, indirectness, inconsistency, imprecision and publication bias. The rating was not downgraded based on risk of bias, indirectness and inconsistency. The ratings were downgraded for imprecision when confidence intervals were wide and included or were close to null effect. Finally, there was no evidence of publication bias to justify downgrading the rating of the certainty of the evidence.

[2] Only intransitivity was assessed from the indirect estimates. No downgrades were made for intransitivity, as there was no evidence for an uneven distribution of effect modifiers.

[3] Incoherence was assessed from the network estimates. Not downgraded for incoherence.

[a] Downgraded because of imprecision.

[b] Downgraded because of publication bias (asymmetry visually identified on comparison-adjusted funnel plot).

[c] Downgraded because of incoherence.

IL-6: interleukin-6; Oil mixture: mix of palm, olive, soy, canola, and coco butter oils.

Supplementary data

Supplementary Table 10. GRADE approach for the assessment of the certainty of evidence from the network meta-analysis for plasma TNF-α.

Comparison	Direct estimate	Certainty direct estimate[1]	Indirect estimate	Certainty indirect estimate[2]	Network estimate	Certainty network estimate[3]
Oil mixture vs. Corn	NA	-	0.50 (-0.25, 1.24)	High	0.50 (-0.25, 1.24)	Moderate[a]
Olive vs. Corn	NA	-	-0.07 (-0.49, 0.34)	High	-0.07 (-0.49, 0.34)	Moderate[a]
EPA vs. Corn	-0.11 (-0.54, 0.32)	Moderate[a]	-0.32 (-1.28, 0.63)	High	-0.15 (-0.52, 0.23)	Moderate[a]
DHA vs. Corn	-0.19 (-0.59, 0.21)	Moderate[a]	0.02 (-0.97, 1.01)	High	-0.17 (-0.53, 0.19)	Low[a,b]
Olive vs. Oil mixture	NA	-	-0.57 (-1.27, 0.13)	High	-0.57 (-1.27, 0.13)	Moderate[a]
EPA vs. Oil mixture	-0.04 (-2.14, 2.06)	Moderate[a]	-0.71 (-1.44, 0.01)	High	-0.64 (-1.33, 0.05)	Moderate[a]
DHA vs. Oil mixture	-0.73 (-1.42, -0.04)		-0.06 (-2.17, 2.05)	High	-0.67 (-1.32, -0.01)	High
EPA vs. Olive	-0.12 (-0.39, 0.14)		0.14 (-0.36, 0.63)	High	-0.07 (-0.30, 0.15)	Low[a,b]
DHA vs. Olive	-0.02 (-0.35, 0.31)		-0.21 (-0.64, 0.21)	High	-0.09 (-0.35, 0.16)	Moderate[a]
DHA vs. EPA	-0.08 (-0.34, 0.18)	Moderate[a]	0.13 (-0.32, 0.58)	High	-0.02 (-0.25, 0.20)	Low[a,b]

[1] The rating of the certainty of the direct estimates considers risk of bias, indirectness, inconsistency, imprecision and publication bias. The rating was not downgraded based on risk of bias, indirectness and inconsistency. The ratings were downgraded for imprecision when confidence intervals were wide and included or were close to null effect. Finally, there was no evidence of publication bias to justify downgrading the rating of the certainty of the evidence.

[2] Only intransitivity was assessed from the indirect estimates. Not downgraded for intransitivity, because there was no evidence for an uneven distribution of effect modifiers.

[3] Incoherence was assessed from the network estimates.

[a] Downgraded because of imprecision.

[b] Downgraded because of incoherence.

Oil mixture: mix of palm, olive, soy, canola, and coco butter oils; TNF-α: tumor necrosis factor-alpha.

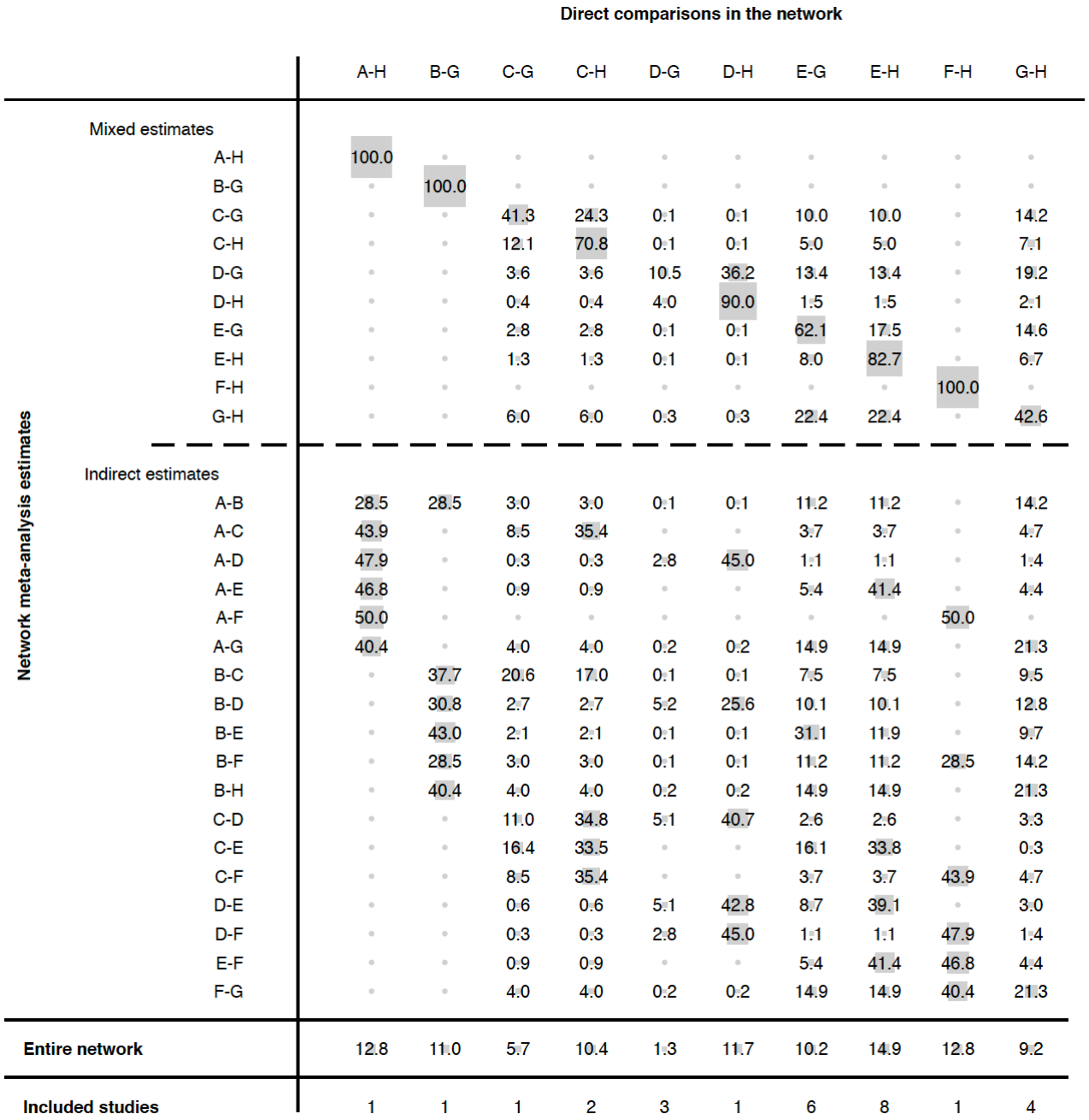
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Supplementary Figure 1. Contribution plot for the C-reactive protein (CRP) network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. (A=canola oil, B=coconut oil, C=corn oil, D=oil mixture (palm, olive, soy, canola, and coco butter oils), E=olive oil, F=EPA, G=DHA).

Network meta-analysis estimates	Direct comparisons in the network								
	A-F	A-G	B-F	C-F	C-G	D-G	E-F	E-G	F-G
Mixed estimates									
A-F	10.5	36.0	·	8.0	8.0	·	9.6	9.6	18.4
A-G	2.8	93.0	·	0.6	0.6	·	0.7	0.7	1.4
B-F	·	·	100.0	·	·	·	·	·	·
C-F	0.6	0.6	·	64.2	15.1	·	5.0	5.0	9.6
C-G	0.6	0.6	·	16.2	61.7	·	5.3	5.3	10.3
D-G	·	·	·	·	·	99.7	·	·	·
E-F	0.4	0.4	·	2.9	2.9	·	76.6	10.0	6.7
E-G	0.8	0.8	·	5.7	5.7	·	19.6	54.4	13.1
F-G	1.7	1.7	·	12.9	12.9	·	15.5	15.5	39.7
Indirect estimates									
A-B	5.2	25.4	30.7	6.0	6.0	·	7.2	7.2	12.3
A-C	4.4	39.2	·	13.7	29.9	·	3.4	3.4	5.9
A-D	1.9	46.5	·	0.4	0.4	48.4	0.5	0.5	0.9
A-E	4.6	37.7	·	3.8	3.8	·	16.2	26.1	7.8
B-C	0.4	0.4	42.6	32.1	10.6	·	3.7	3.7	6.4
B-D	0.9	0.9	28.2	6.4	6.4	28.2	7.7	7.7	13.2
B-E	0.3	0.3	45.3	2.2	2.2	·	38.3	7.0	4.5
B-G	1.2	1.2	39.9	8.6	8.6	·	10.3	10.3	19.8
C-D	0.4	0.4	·	11.2	30.8	42.0	4.0	4.0	6.8
C-E	0.1	0.1	·	27.7	21.2	·	29.7	19.2	1.9
D-E	0.6	0.6	·	4.3	4.3	40.7	13.5	27.1	8.7
D-F	1.1	1.1	·	8.6	8.6	39.8	10.3	10.3	19.8
Entire network	1.8	13.7	13.7	11.2	11.4	14.2	13.2	10.8	9.9
Included studies	1	2	1	1	3	1	5	8	6

Supplementary data

Supplementary Figure 2. Contribution plot for the interleukin-6 (IL-6) network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. (A=canola oil, B=coconut oil, C=corn oil, D=oil mixture (palm, olive, soy, canola, and coco butter oils), E=olive oil, F=sunflower oil, G=EPA, H=DHA).



Supplementary data

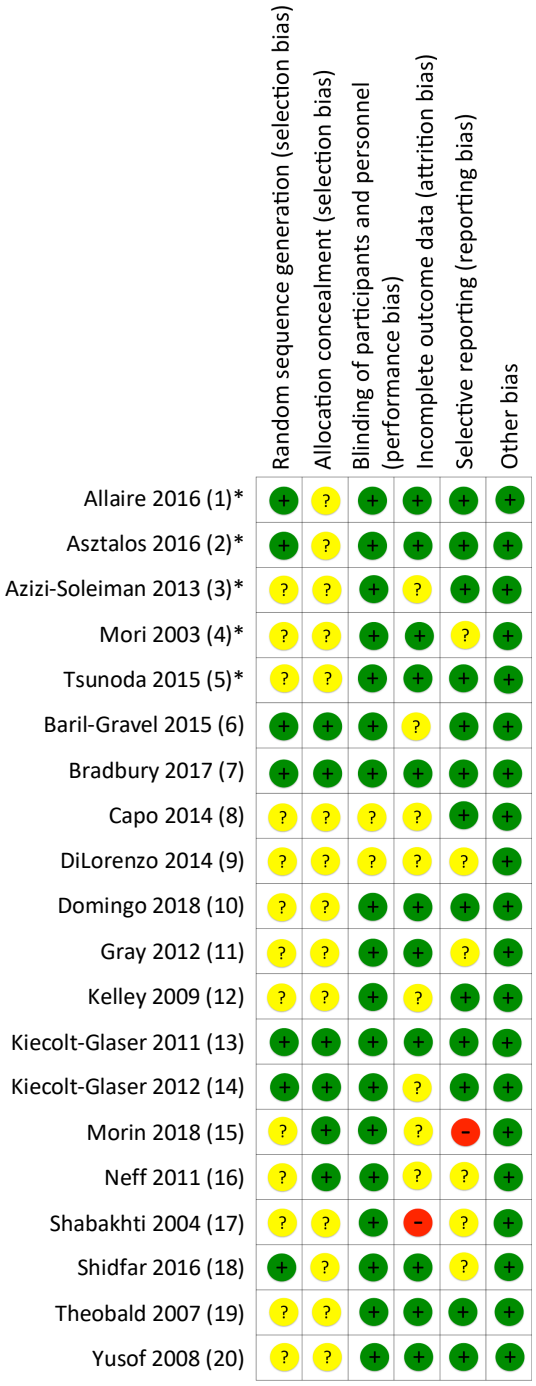
Supplementary Figure 3. Contribution plot for the tumor necrosis factor-alpha (TNF-α) network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. A=corn oil, B=oil mixture (palm, olive, soy, canola, and coco butter oils), C=olive oil, D=EPA, E=DHA).

Direct comparisons in the network

Network meta-analysis estimates		A-D	A-E	B-D	B-E	C-D	C-E	D-E
Mixed estimates								
	A-D	51.9	22.6	0.1	0.1	2.8	2.8	19.6
	A-E	17.7	62.3	0.1	0.1	2.2	2.2	15.4
	B-D	4.3	4.3	9.4	40.8	4.6	4.6	31.9
	B-E	0.4	0.4	4.0	91.2	0.4	0.4	3.1
	C-D	2.9	2.9	0.1	0.1	47.5	24.8	21.7
	C-E	1.8	1.8	0.1	0.1	15.2	67.7	13.3
	D-E	7.1	7.1	0.3	0.3	7.6	7.6	70.1
Indirect estimates								
	A-B	14.1	30.5	4.5	40.0	1.3	1.3	8.2
	A-C	20.9	28.4	·	·	19.5	29.8	1.4
	B-C	1.0	1.0	4.5	41.0	12.4	33.2	6.8
Entire network		12.2	16.1	2.3	21.4	11.4	17.4	19.2
Included studies		1	1	3	1	5	5	4

Supplementary data

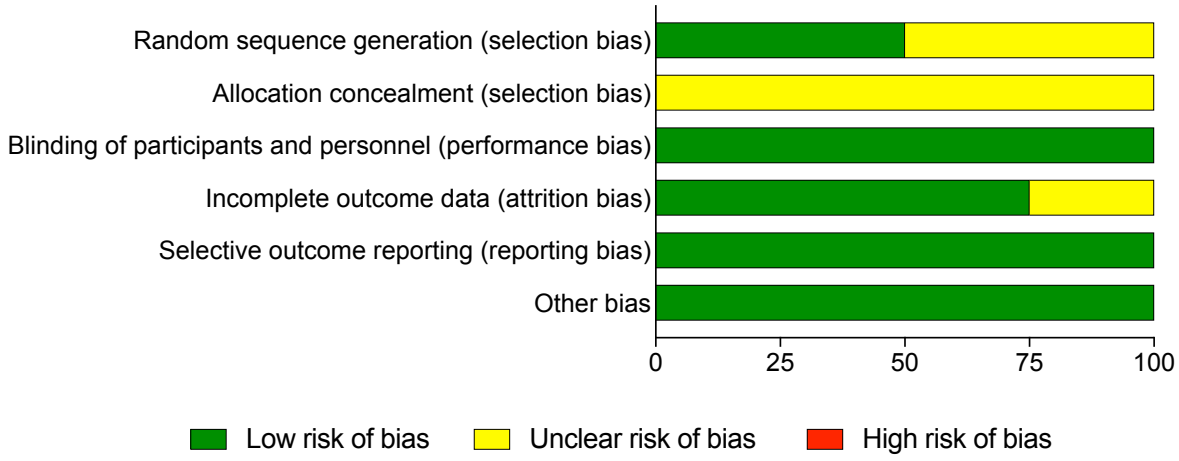
Supplementary Figure 4. Cochrane risk of bias summary for RCTs included in the pairwise and network meta-analyses



Studies with an asterisk are common to both meta-analyses; studies without asterisk were not included in pairwise meta-analysis. Each risk of bias was rated as low (+), high (-), or unclear (?).

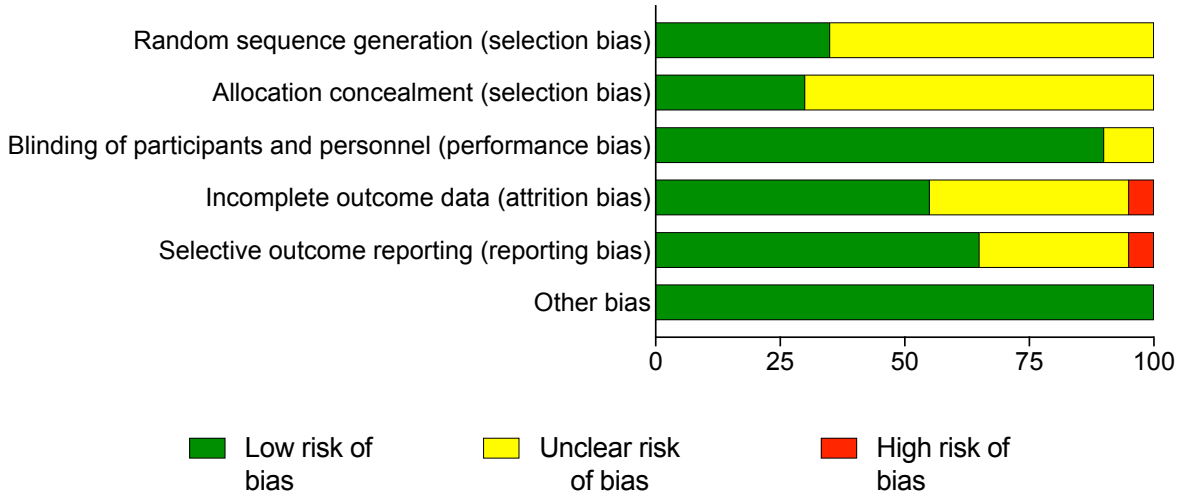
Supplementary data

Supplementary Figure 5. Risk of bias proportion for all trials included in pairwise meta-analysis comparing DHA and EPA directly



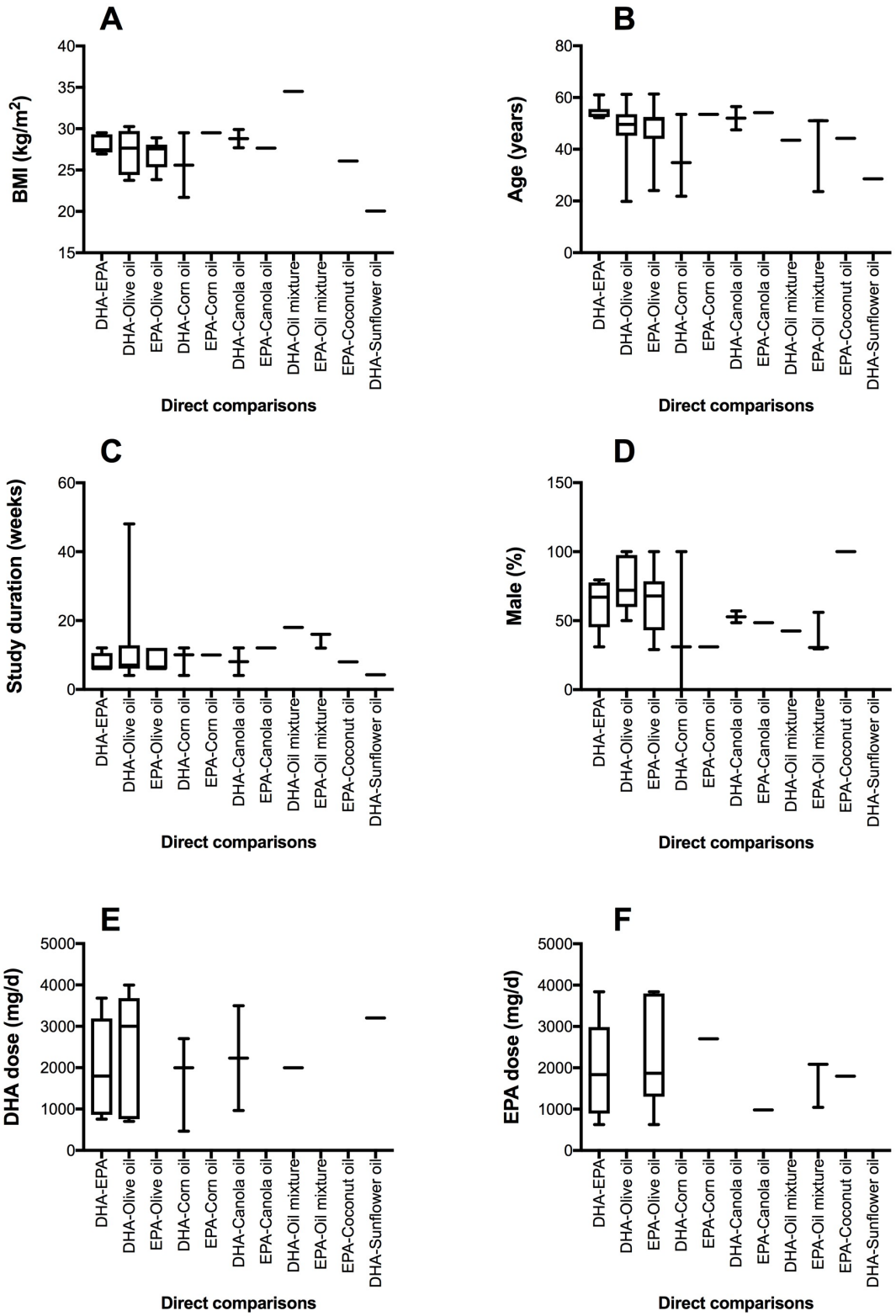
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Supplementary Figure 6. Risk of bias proportion for all trials included in network meta-analysis combining direct and indirect comparisons of DHA and EPA



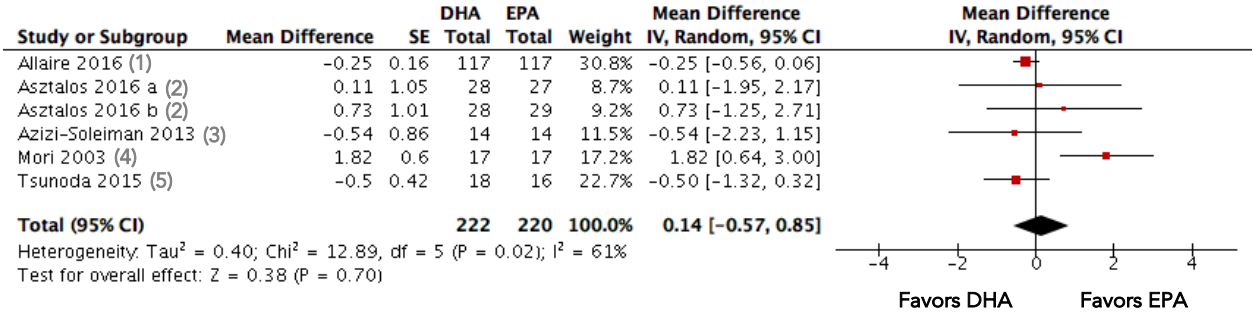
Supplementary data

Supplementary Figure 7. Box plots showing the distributions of BMI (A), age (B), study duration (C), % male participants (D), DHA dose (E) and EPA dose (F) across the available direct comparisons in the network meta-analysis. Oil mixture: mix of palm, olive, soy, canola, and coco butter oils.



Supplementary data

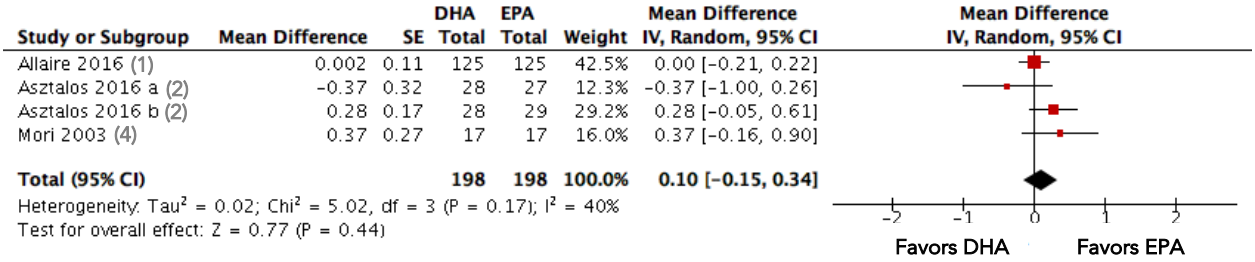
Supplementary Figure 8. Forest plot of randomized controlled trials having compared the effect of DHA and EPA directly on plasma C-reactive protein (CRP) (mg/L); data from the pairwise meta-analysis.



Data are expressed as mean differences represented by a square and 95% CIs by the line through the square. Pooled effect estimates are represented by diamonds and were estimated with the use of generic inverse random effects model. Between-study heterogeneity was assessed by the Cochran Q statistic (where P<0.10 is considered statistically significant) and quantified by the I^2 statistic (where $I^2 \geq 50\%$ is considered evidence by substantial heterogeneity).
CI: confidence interval; IV: inverse variance; SE: standard error.

Supplementary data

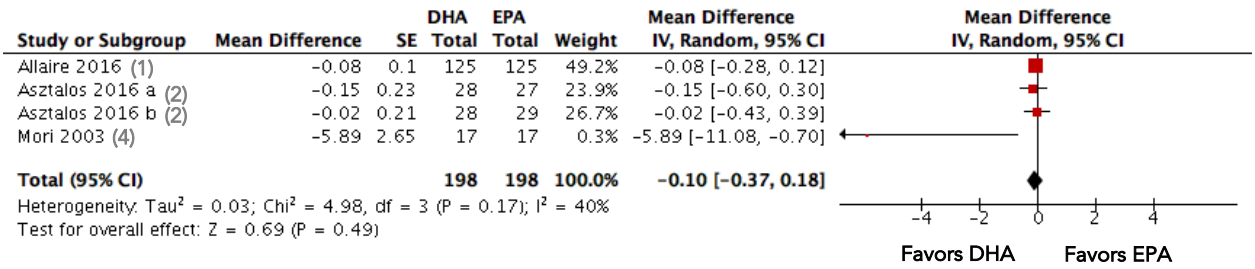
Supplementary Figure 9. Forest plot of randomized controlled trials having compared the effect of DHA and EPA directly on plasma interleukin-6 (IL-6) (pg/mL); data from the pairwise meta-analysis.



Data are expressed as mean differences represented by a square and 95% CIs by the line through the square. Pooled effect estimates are represented by diamonds and were estimated with the use of generic inverse random effects model. Between-study heterogeneity was assessed by the Cochran Q statistic (where P<0.10 is considered statistically significant) and quantified by the I^2 statistic (where $I^2 \geq 50\%$ is considered evidence by substantial heterogeneity).
CI: confidence interval; IV: inverse variance; SE: standard error.

Supplementary data

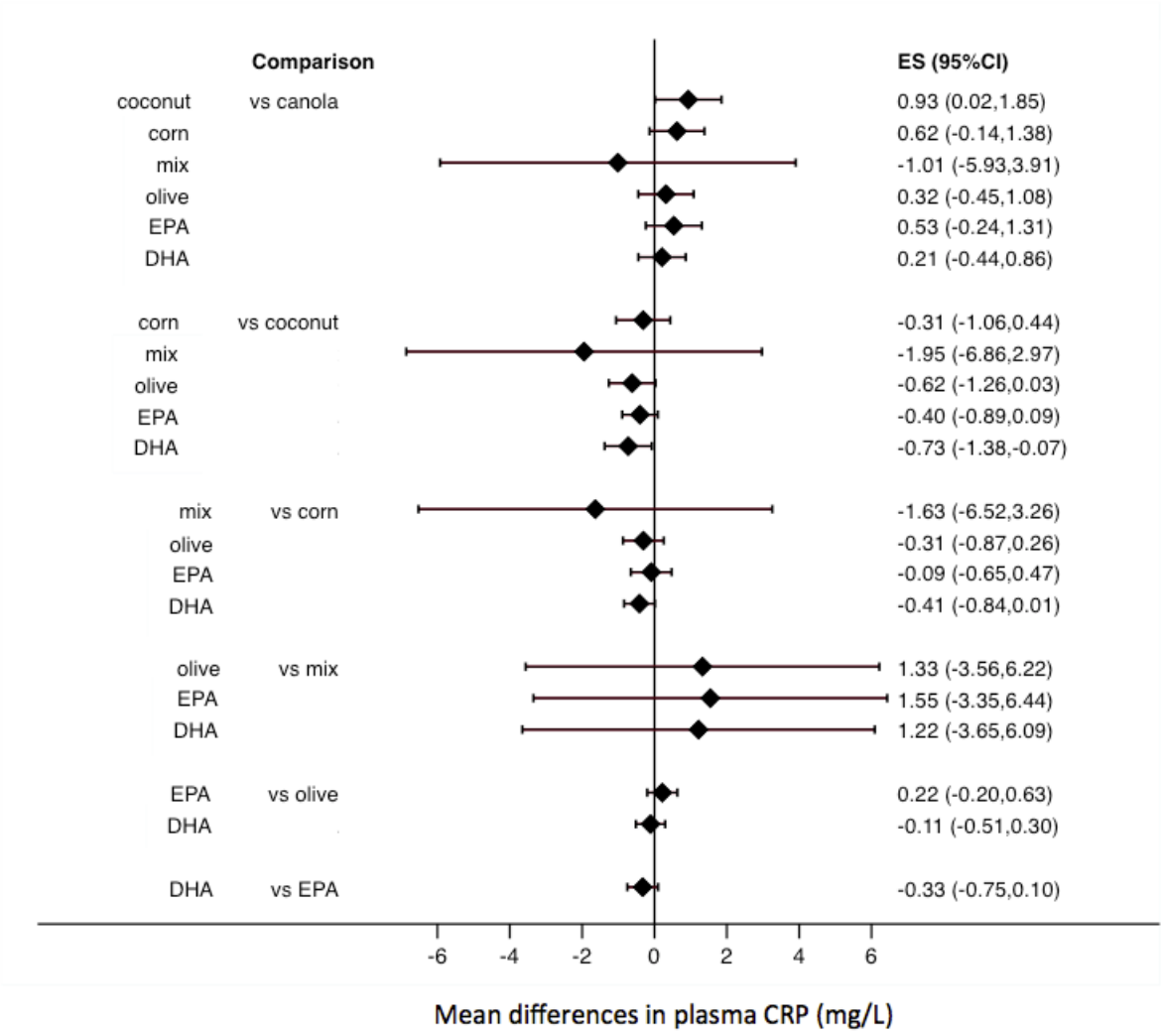
Supplementary Figure 10. Forest plot of randomized controlled trials having compared the effect of DHA and EPA directly on plasma tumor necrosis factor-alpha (TNF-α) (pg/mL); data from the pairwise meta-analysis.



Data are expressed as mean differences represented by a square and 95% CIs by the line through the square. 95% CI exceeding the plot's bound is represented by an arrowhead. Pooled effect estimates are represented by diamonds and were estimated with the use of generic inverse random effects model. Between-study heterogeneity was assessed by the Cochran Q statistic (where P<0.10 is considered statistically significant) and quantified by the I^2 statistic (where $I^2 \geq 50\%$ is considered evidence by substantial heterogeneity).
CI: confidence interval; IV: inverse variance; SE: standard error.

Supplementary data

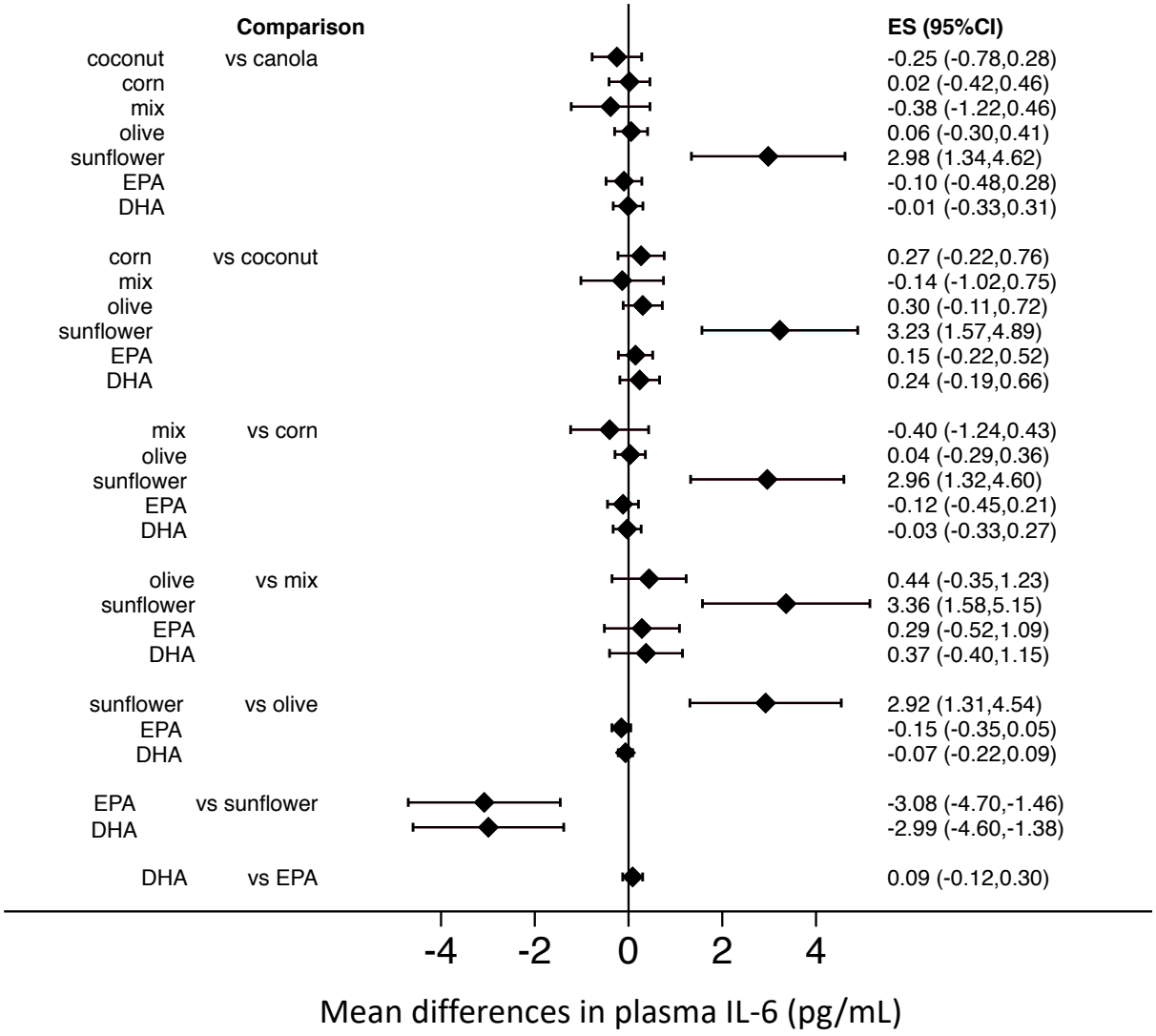
Supplementary Figure 11. Interval-plot showing the mean differences (95% CI) for plasma C-reactive protein (CRP) from the network meta-analysis for each pair of comparisons



Data are expressed as mean differences represented by a diamond. Solid lines represent 95% CIs. ES: effect size; CI: confidence interval. Mix= palm, olive, soy, canola, and coco butter oils. It is stressed here that data comparing DHA to other oils or EPA to other oils cannot be used to infer differences in effects, as the search strategy was not designed to include all comparisons of DHA with other oils and all comparisons of EPA with other oils. Indeed, as indicated in the main body of the paper, only studies that were relevant to the comparison of DHA to EPA were included in this analysis.

Supplementary data

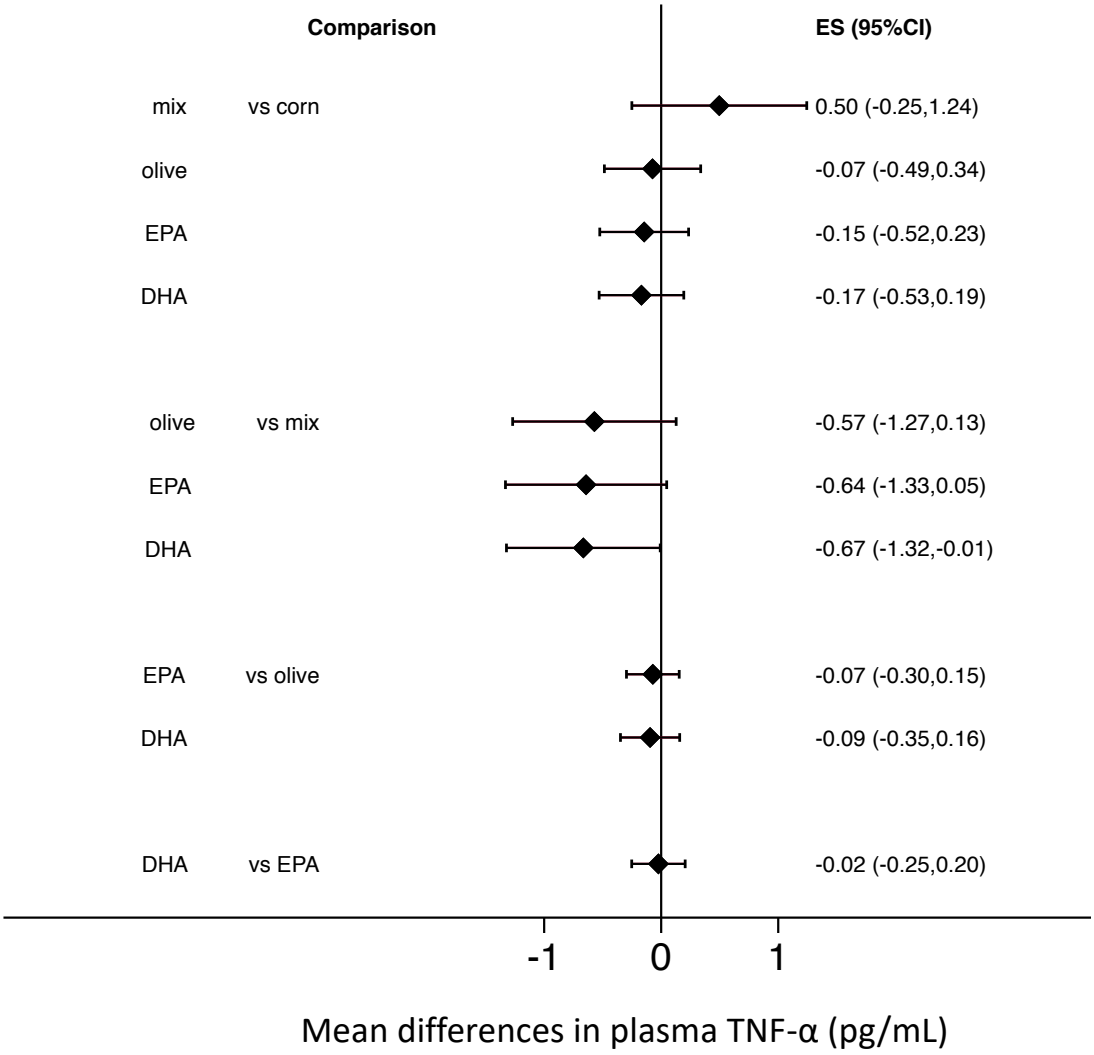
Supplementary Figure 12. Interval-plot showing the mean differences (95% CI) for plasma interleukin-6 (IL-6) from the network meta-analysis for each pair of comparisons



Data are expressed as mean differences represented by a diamond. Solid lines represent 95% CIs. ES: effect size; CI: confidence interval. Mix= palm, olive, soy, canola, and coco butter oils. It is stressed here that data comparing DHA to other oils or EPA to other oils cannot be used to infer differences in effects, as the search strategy was not designed to include all comparisons of DHA with other oils and all comparisons of EPA with other oils. Indeed, as indicated in the main body of the paper, only studies that were relevant to the comparison of DHA to EPA were included in this analysis.

Supplementary data

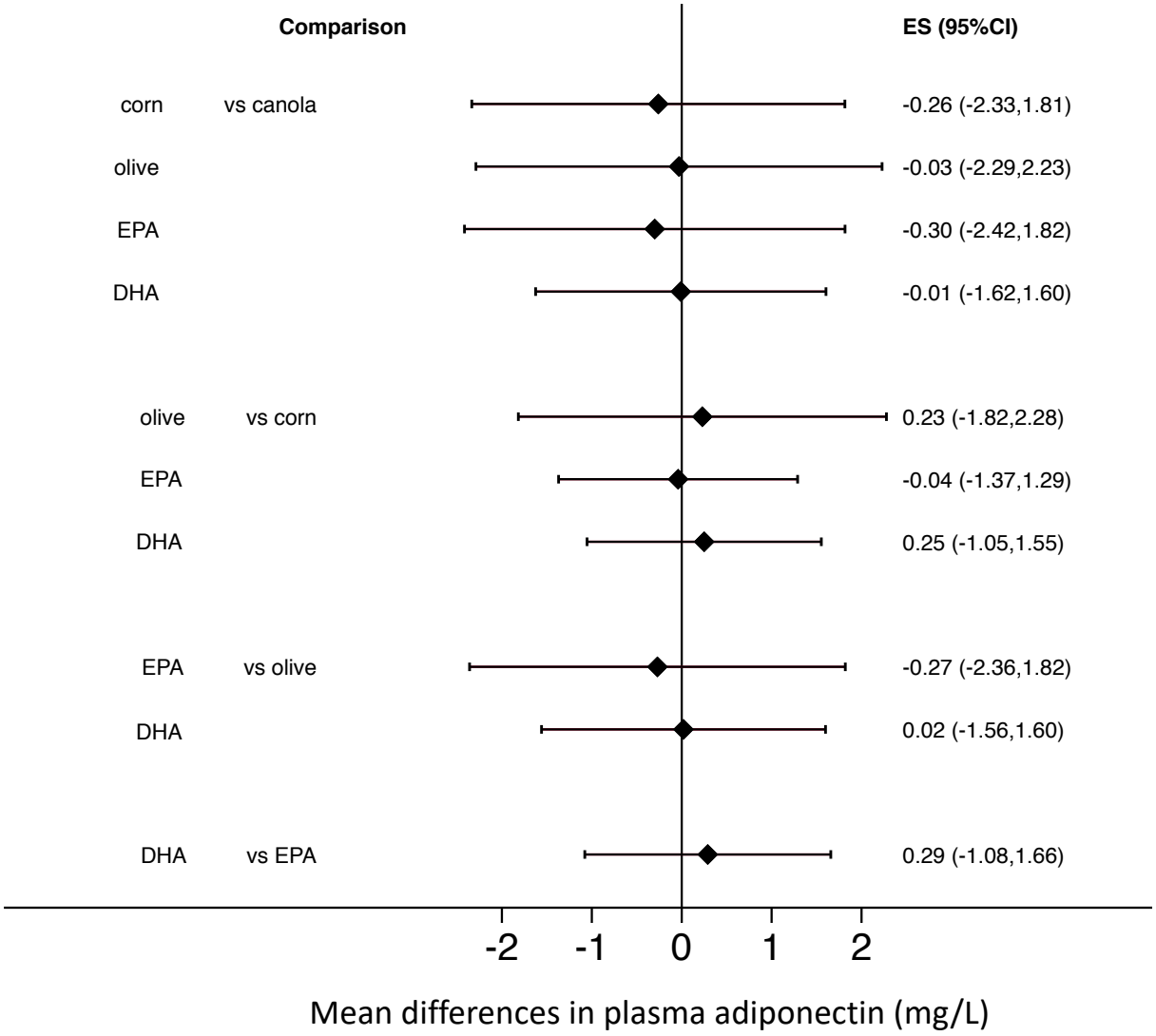
Supplementary Figure 13. Interval-plot showing the mean differences (95% CI) for plasma tumor necrosis factor-alpha (TNF-α) from the network meta-analysis for each pair of comparisons



Data are expressed as mean differences represented by a diamond. Solid lines represent 95% CIs. ES: effect size; CI: confidence interval. Mix= palm, olive, soy, canola, and coco butter oils. It is stressed here that data comparing DHA to other oils or EPA to other oils cannot be used to infer differences in effects, as the search strategy was not designed to include all comparisons of DHA with other oils and all comparisons of EPA with other oils. Indeed, as indicated in the main body of the paper, only studies that were relevant to the comparison of DHA to EPA were included in this analysis.

Supplementary data

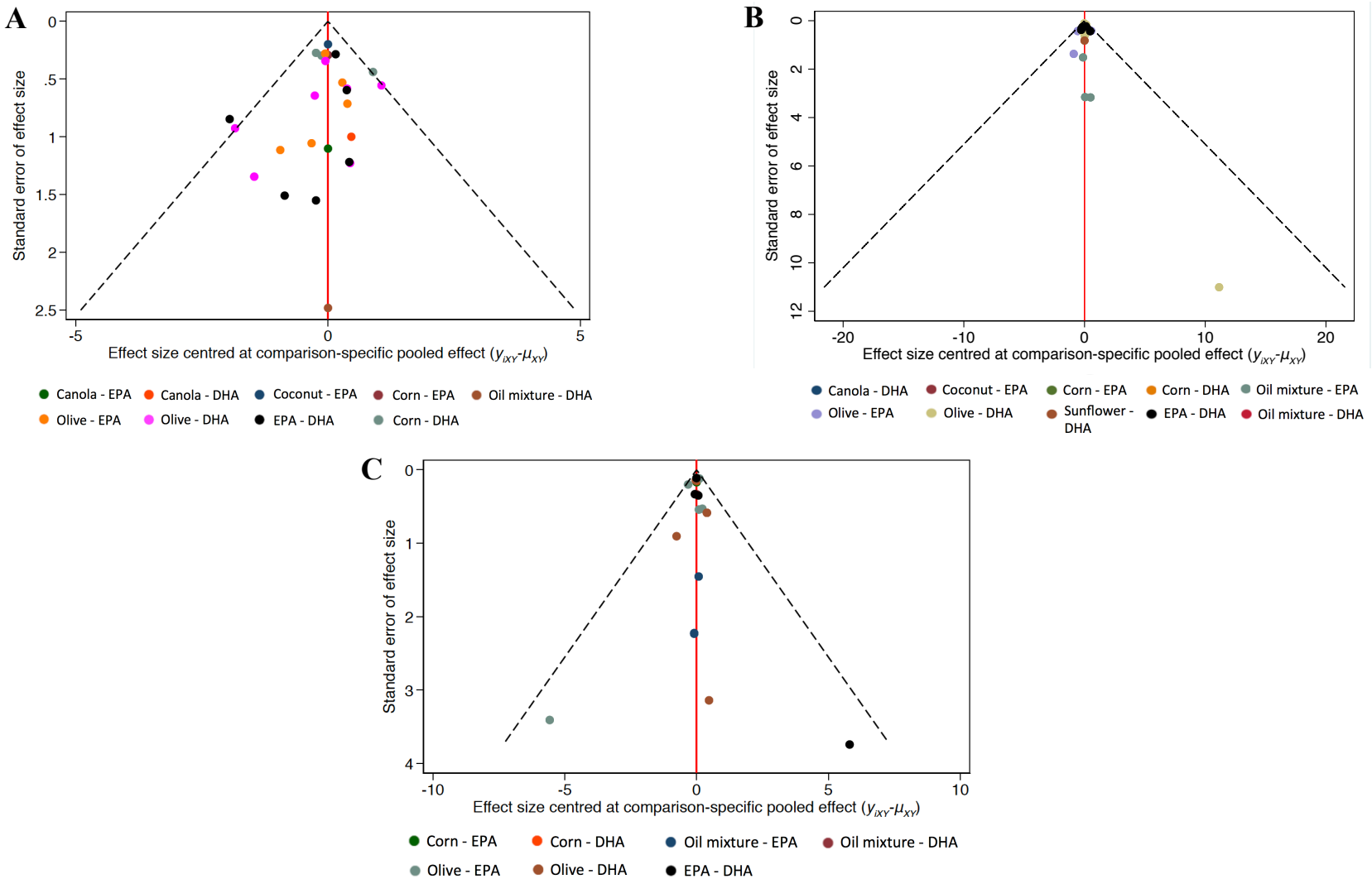
Supplementary Figure 14. Interval-plot showing the mean differences (95% CI) for plasma adiponectin from the network meta-analysis for each pair of comparisons



Data are expressed as mean differences represented by a diamond. Solid lines represent 95% CIs. ES: effect size; CI: confidence interval. It is stressed here that data comparing DHA to other oils or EPA to other oils cannot be used to infer differences in effects, as the search strategy was not designed to include all comparisons of DHA with other oils and all comparisons of EPA with other oils. Indeed, as indicated in the main body of the paper, only studies that were relevant to the comparison of DHA to EPA were included in this analysis.

Supplementary data

Supplementary Figure 15. Comparison-adjusted funnel plots for plasma CRP (A), IL-6 (B) and TNF-α (C) including all studies of the network meta-analysis. The horizontal axis represents an adjusted effect size, presenting the difference between each observed effect size and the mean effect size for the specific comparison being made. The dashed lines represent pseudo 95% confidence intervals.



Supplementary data

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