

Figure 1. Forest plot of random effects meta-analysis on effects of LCn3 on relapse in CD and ulcerative colitis.

CD: Crohn's Disease, LCn3: long-chain omega-3, EPA: Eicosapentaenoic acid, M-H: Mantel–Haenszel, MUFA: mono-unsaturated fatty acid.

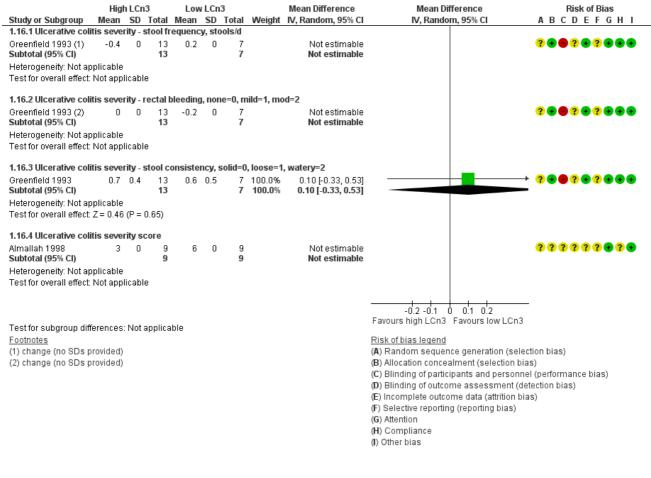


Figure 2. Forest plot of meta-analysis on effects of LCn3 on relapse in UC severity. LCn3: long-chain omega-3, IV: inverse variance, SD: standard deviation, UC: ulcerative colitis.

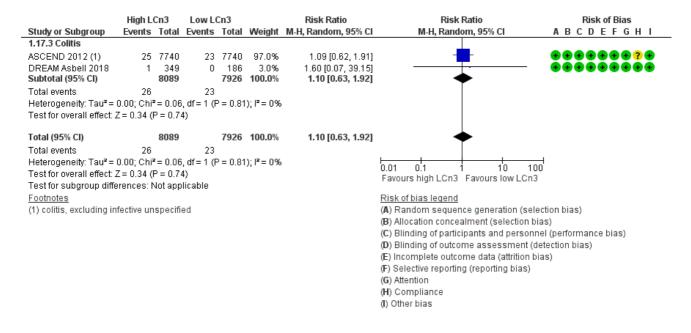


Figure 3. Forest plot of meta-analysis on effects of LCn3 on diagnosis of IBD. IBD: inflammatory bowel disease, LCn3: long-chain omega-3, M-H: Mantel–Haenszel.

	Hi	gh LCn3		Lo	ow LCn3			Std. Mean Difference	Std. Mean Difference	Risk of Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFGHI	
1.17.1 CRP mg/l											
Belch 1988 (1)	-2.6	0	15	3.8	0	16	4.000	Not estimable		???? . ? . ? .	
Berbert 2005 de Luis 2016	19.5 2.1	22.3 1.2	13 14	18.1 1.9	15.8 1.4	13 15	1.8% 1.9%	0.07 [-0.70, 0.84] 0.15 [-0.58, 0.88]		· • ? ? ? • ? • ? • . • • •	
DO IT - Einvik 2010 (2)	2.92	1.2	247	3.04	1.4	239	1.370	Not estimable			
FISHGASTRO - Pot 2009	1.31	0.88	54	1.47	0.93	51	4.0%	-0.18 [-0.56, 0.21]			
Kristensen 2016 (3)	0.22		67	0.67	9.3708	63	4.3%	-0.06 [-0.41, 0.28]			
Li 2015	7.6	0.4	39	9.2	0.8	39	2.5%	-2.50 [-3.10, -1.91]	•	220000200	
Nogueira 2016	2.92	2.65	26	2.28	2.38	23	2.7%	0.25 [-0.31, 0.81]		$\bullet ? ? ? \bullet ? \bullet \bullet \bullet$	
Patch 2005	5.6	6.2	38	5.1	4.8	36	3.4%	0.09 [-0.37, 0.55]			
Sawada 2016	0.06	0	54	0.06	0	53	0.50	Not estimable			
Skoldstam 1992 Tardivo 2015	0.7 0.7	2 0.5	22 44	1.3 0.8	3.9 0.6	21 43	2.5% 3.7%	-0.19 [-0.79, 0.41]			
Veleba 2015 (4)	-0.11	0.5	44	-0.13	0.0	43	3.770	-0.18 [-0.60, 0.24] Not estimable			
Veleba 2015 (5)	-0.08	Ő	14	0.11	Ő	17		Not estimable			
Subtotal (95% CI)	0.00	Ŭ	663	0.11	Ŭ	642	26.7%	-0.28 [-0.75, 0.19]			
Heterogeneity: Tau ² = 0.44; Chi	= 62.60), df = 8 (F	o < 0.00	0001); P	= 87%						
Test for overall effect: Z = 1.18 (P = 0.24))									
1 17 2 bc CPD mg/											
1.17.2 hs-CRP mg/l	0.00		1.4.4	-0.22	0	153		Not active all -		?????	
AFFORD 2014 (6) AlphaOmega - EPA+DHA (7)	-0.23 1.88	0 2.11	144 594	-0.22	U 1.9	153 621	6.5%	Not estimable 0.01 [-0.10, 0.13]	<u> </u>		
AlphaOmega - EPA+DHA (7) AlphaOmega - EPA+DHA (8)	1.88	2.11	594 601	1.85	2.14	609	0.5% 6.5%	-0.13 [-0.24, -0.01]			
Balfego 2016	0.2	0	17	0.2	0.3873	15	0.370	Not estimable			
Clark 2016 (9)	-0.155	2.26	16	0.249	1.81	17	2.1%	-0.19 [-0.88, 0.49]	←───		
Derosa 2009 (10)	0.8	5.1	164	1.5	8.9	162	5.6%	-0.10 [-0.31, 0.12]	- _	• ? • ? ? ? • ? •	
Derosa 2011 (11)	1.1	1.8	78	1.7	4.4	79	4.6%	-0.18 [-0.49, 0.14]		• ? ? • ? ? ? ? •	
Ebrahimi 2009 (12)	3.12	0	47	6.8	0	42		Not estimable		?? @ ? @ ? @ ? @	
ELIA - Takaki 2011	3.93	9.18	23	0.96	1.55	23	2.6%	0.44 [-0.14, 1.03]		• • ? • • ? • ? • •	
EPE-A 2014 (13)	-0.6	0	64	0	0	55		Not estimable			
Eschen 2010 (14)	-0.47	0	69	-0.4	0	69		Not estimable		??? ** ? **	
Kanorsky 2007	3.7		45	4.4	3.5	49	3.8%	-0.22 [-0.63, 0.18]		330333330	
Krebs 2006 MARINA - Sanders 2011 (15)	2.26	3.21 3.4044	35 72	3.04 0.9	3.8 3.6321	32 65	3.2% 4.4%	-0.22 [-0.70, 0.26]			
MARINA - Sanders 2011 (15) MARINA - Sanders 2011 (16)	0.8 0.5	4.3463	75	0.9	2.9357	70	4.4%	-0.03 [-0.36, 0.31] 0.00 [-0.33, 0.33]			
Martinez 2014 (17)	0.5	4.5405	7	0.5	2.3337	,0	4.570	Not estimable			
Niki 2016	0.1	0.2	29	0.1	0.1	30	3.0%	0.00 [-0.51, 0.51]			
Nishio 2014	0.6	0.5	15	1.2	1.1	15	1.9%	-0.68 [-1.42, 0.06]	←	22020200	
OFAMI - Nilsen 2001 (18)	1.5	0	124	1.5	0	129		Not estimable		? • • • ? ? • ? •	
OMEGA-Remodel 2016 (19)	1.95	0	180	2.4	0	178		Not estimable			
OmegAD 2008	0.8	5.7	89	0.6	5.1	85	4.8%	0.04 [-0.26, 0.33]		• ? ? ? • • • • ?	
ORL 2013 (20)	0.009	0.15	168	0	0.15	165	5.6%	0.06 [-0.16, 0.27]			
REDUCE-IT 2018 (21)	2.2	0	4089	2.1	0	4090		Not estimable		• ? • • • • • • •	
SO927 Hershman 2015	4	5.5	74	4.3	5.6	72	4.5%	-0.05 [-0.38, 0.27]			
Tande 2016	0.99	11.5	50	-0.64	3.24	50	3.9%	0.19 [-0.20, 0.58]			
Tani 2017 (22) THIS DIET 2008	0.6 0.29	0 0.31	53 37	0.35 0.22	0 0.19	53 34	3.3%	Not estimable			
Witte 2012	0.29	3.6	22	1.8	2.1	22	2.5%	0.27 [-0.20, 0.73] 0.07 [-0.52, 0.66]			
Subtotal (95% CI)	2	5.0	6981	1.0	2.1	6992	73.3%	-0.04 [-0.10, 0.02]	•		
Heterogeneity: Tau ² = 0.00; Chi	r= 15.43	8, df = 17	(P = 0.6	56); l² = l	0%				-		
Test for overall effect: Z = 1.35 (P = 0.18)									
Total (95% CI)			7644			7634	100.0%	-0.09 [-0.21, 0.03]			
Heterogeneity: Tau ² = 0.05; Chi	² = 87.49	df= 26		100011	I ² = 68%	1034	100.070	-0.03 [-0.2 1, 0.03]		-	
Test for overall effect: Z = 1.52 (0.0.0						-0.5 -0.25 0 0.25 0.5		
Test for subgroup differences:			(P = 0.	32), I ² =	0%				Favours high LCn3 Favours low LCn3		
Footnotes		•							Risk of bias legend		
(1) fish oil plus EPO vs EPO									(A) Random sequence generation (selec	ction bias)	
(2) medians only provided									(B) Allocation concealment (selection bia	is)	
(3) Change data used									(C) Blinding of participants and personne	el (performance bias)	
(4) median change from baseli									(D) Blinding of outcome assessment (de		
(5) median change from baseli		pio vs pio	D						(E) Incomplete outcome data (attrition bia	is)	
(6) change data, no SDs provid	ed								(F) Selective reporting (reporting bias)		
(7) EPA+DHA+ALA vs ALA									(G) Attention		
(8) EPA+DHA vs control (9) Change data used									(H) Compliance (I) Other bias		
(9) Change data used (10) Reported as SDs but assu	imed to P	ne SMDe							w oner blas		
(11) Reported as SDs but assu											
(12) Medians only provided											
(13) median change from base	line, hial	h EPA vs	control								
(14) difference in medians											
(15) 0.9g/d arm compared to pl	acebo ai	rm as bai	anced	atbase	line						
(16) 1.8g/d arm compared to 0.											
(17) change in medians over 1	2 months	s (no cha	nge in	either gr	roup)						
(18) Medians provided only											
(19) estimated as baseline medians minus difference in percent in intervention arm											
(20) Estimated from data in page (21) Data is proported as mod		OB									
(21) Data is presented as med (22) Medians presented	ian and I	ыĸ									
(22) medians presented											

Figure 4. Forest plot of meta-analysis on effects of LCn3 on CRP using SMD in random effects meta-analysis, subgrouping by reported CRP test.

LCn3: long-chain omega-3, CRP: C-reactive protein, SMD: standardized mean difference, SD: standard deviation, EPA: Eicosapentaenoic acid, DHA: docosahexaenoic acid, ALA: alpha-linolenic acid, EPO: evening primrose oil

Study or Subgroup	High Mean	omega 3 SD	Total		omega SD		Weight	Std. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl	Risk of Bias ABCDEFGHI
1.32.1 IBD patients Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect. Not applica			0			0		Not estimable		
1.32.2 Rheumatoid Arthritis pati Belch 1988 (1) Berbert 2005 Skoldstam 1992 Subtotal (95% C1) Heterogeneity: Tau* = 0.00; Chi* Test for overall effect. Z = 0.38 (P	-2.6 19.5 0.7 = 0.28, d	0 22.3 2 f = 1 (P = 1	15 13 22 50 0.60); F	3.8 18.1 1.3 = 0%	0 15.8 3.9	16 13 21 50	1.8% 2.5% 4.2 %	Not estimable 0.07 (-0.70, 0.84) -0.19 (-0.79, 0.41) - 0.09 (-0.57, 0.38)	•	2 2 2 2 • 2 • 2 • 2 • 7 2 2 2 • 2 • 2 • 2 •
1.32.3 Systematic Lupus Erythe Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Not applica		s patients	0			0		Not estimable		
1.32.4 NASH & NAFLD patients EPE-A 2014 (2) Li 2015 Nogueira 2016 Subtotal (95% CI) Heterogeneily: Tau ² = 3.70; Chi ² Test for overall effect Z = 0.82 (P		0 0.4 2.65 df=1 (P =	64 39 26 129 0.000	0 9.2 2.28 101); I ² =	0 0.8 2.38	55 39 23 117	2.5% 2.7% 5.2 %	Not estimable -2.50 [-3.10, -1.91] 0.25 [-0.31, 0.81] - 1.13 [-3.82, 1.57]		
1.32.5 Metabolic syndrome & Da		itients								
Balfego 2016 Clark 2016 (3) Ebrahimi 2009 (4) Krebs 2006 REDUCE-IT 2018 (5) Savada 2016 Tardivo 2015 Veleba 2015 (7) Subtotal (95% CI) Heterogeneity: Tau? = 0.00; Chi ² Test for overail effect. Z = 1.34 (P	0.2 -0.155 3.12 2.26 2.2 0.06 0.7 -0.11 -0.08 = 0.02, df	0 2.26 0 3.21 0 0.5 0.5 0	47 35 4089 54 44 16 14 4332	0.249 6.8 3.04 2.1 0.06 0.8 -0.13 0.11	0.3873 1.81 0 3.8 0 0 0.6 0 0	15 17 42 32 4090 53 43 13 17 4322	2.1% 3.2% 3.7% 9.0%	Not estimable -0.19 [-0.88, 0.49] Not estimable -0.22 [-0.70, 0.26] Not estimable -0.18 [-0.60, 0.24] Not estimable Not estimable -0.20 [-0.48, 0.09]	 •	
1.32.6 Patients at risk for CVD										
AFFORD 2014 (8) AlphaOmega - EPA+DHA (9) AlphaOmega - EPA+DHA (10) Derosa 2009 (11) Derosa 2009 (11) Dorosa 2011 (12) DO IT - Einvik 2010 (13) ELIA - Takaki 2011 Eschen 2010 (14) Kanorsky 2007 Niki 2016 Nishio 2014 OFAMI - Nilsen 2001 (15) OMEGA-Remodel 2016 (16) ORL 2013 (17) Patch 2005 Tani 2017 ThilS DIET 2008 Subtotal (95% C1) Heterogeneily: Tau ^a = 0.00; Chi ² Test for overail effect Z = 0.83 (P	0.1 0.6 1.5 1.95 0.009 5.6 0.6 0.29 = 13.18,		144 594 601 164 247 23 69 45 29 15 124 180 168 38 53 37 2609 = 0.21	-0.22 1.85 1.98 1.5 1.7 3.04 0.96 -0.4 4.4 0.1 1.2 1.5 2.4 0.35 0.22); $I^2 = 2$	0 1.9 2.14 8.9 4.4 0 1.55 0.1 1.55 0.1 1.1 0 0.15 4.0 0.19	153 621 609 162 79 23 69 49 30 129 178 165 36 53 34 2644	6.5% 6.5% 4.6% 2.6% 3.8% 3.0% 1.9% 5.6% 3.4% 3.3% 46.7%	Not estimable 0.01 [0.01,0,013] 0.13 [0.024,-0.01] 0.10 [0.31,0,12] 0.18 [0.49,0,14] Not estimable 0.24 [0.14,1.03] Not estimable 0.00 [0.51,0,51] 0.08 [1.12,0,00,1,0,1] 0.08 [1.12,0,0,1,0,1] 0.08 [1.12,0,0,1,0,1] Not estimable 0.05 [0.16,0,27] Not estimable 0.27 [0.20,0,73] 0.04 [-0.13,0,05]		
1.32.7 Healthy individuals de Luis 2016 MARINA - Sanders 2011 (18) MARINA - Sanders 2011 (19) OmegAD 2008 Tande 2016	2.1 0.8 0.5 0.8 0.99	1.2 3.4044 4.3463 5.7 11.5	14 72 75 89 50	1.9 0.9 0.5 0.6 -0.64	1.4 3.6321 2.9357 5.1 3.24	15 65 70 85 50	1.9% 4.4% 4.5% 4.8% 3.9%	0.15 [-0.58, 0.88] -0.03 [-0.36, 0.31] 0.00 [-0.33, 0.33] 0.04 [-0.26, 0.33] 0.19 [-0.20, 0.58]		
Witte 2012 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² Test for overall effect: Z = 0.57 (P	2 = 0.88, d	3.6	22 322	1.8	2.1	22 307	2.5% 22.1%	0.07 [-0.52, 0.66] 0.05 [-0.11, 0.20]	•	.
1.32.8 Others FISHOASTRO - Pot 2009 Kristensen 2016 (20) Martinez 2014 (21) S0827 Herstman 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Chi ² Test for overall effect Z = 0.88 (P	0 4 = 0.27, d	0.88 4.3867 0 5.5 f= 2 (P = 1	54 67 7 202 0.88); F	0 4.3	0.93 9.3708 0 5.6	51 63 8 72 194	4.0% 4.3% 4.5% 12.9 %	-0.18 [-0.56, 0.21] -0.06 [-0.41, 0.28] Not estimable -0.05 [-0.38, 0.27] - 0.09 [-0.29, 0.11]		
Total (95% CI) Heterogeneily: Tau ² = 0.05; Chi ² Test for overall effect. Z = 1.52 (P Test for subgroup differences: C Footnotes (1) fish oil plus EPO vs EPO (2) median change from baselin (3) Change data used (4) Medians only provided (5) Data is presented as mediar (6) median change from baselin (7) median change from baselin (8) change data, no SDs provided (9) EPA+DHA+ALAvs ALA (10) EPA+DHA+Vs control (11) Reported as SDs but assur (12) Reported as SDs but assur (13) medians only provided (14) difference in medians (15) Medians provided only (16) estimated as baseline med (17) Estimated from data in pape (18) 0.9g/a arm compared to pla (19) 1.8g/a arm compared to pla (20) Change data used (21) change in medians over 12	= 82.49, = 0.13) hi ² = 3.20 e, high E i and IQR e, n3 vs; e, n3 + p d ned to be ned to be ned to be sians min ar cebo arm 5g/d arm	df = 26 (P), df = 5 (F PA vs con)))))))))))))))))))	r = 0.67 ntrol nce in nced at	7), Iª = 0 percent baseli baselir	r% t in interv ne ne		100.0%	-0.09 [-0.21, 0.03]	Favours high omega 3 Favours low or <u>Risk of bias legend</u> (A) Random sequence generation (sele (B) Allocation concealment (selection bi (C) Blinding of outcome assessment (d) (E) Incomplete outcome data (attrition bi (F) Selective reporting (reporting bias) (G) Attention (H) Compliance (t) Other bias	ection bias) as) iel (performance bias) etection bias)

Figure 5. Forest plot of meta-analysis on effects of LCn3 on CRP using SMD in random effects

meta-analysis, subgrouping by baseline health status of participants. LCn3: long-chain omega-3, CRP: C-reactive protein, SMD: standardized mean difference, SD: standard deviation, NASH: non-alcoholic steatohepatitis, NAFLD: non-alcoholic fatty

liver disease, CVD: cardiovascular disease, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, ALA: alpha-linolenic acid, EPO: evening primrose oil.

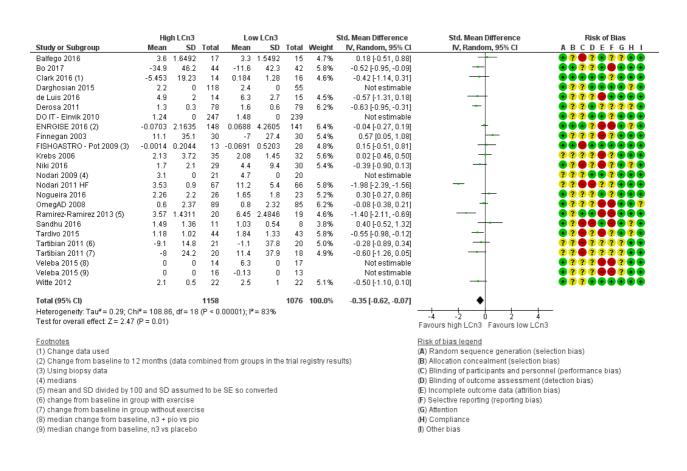


Figure 6. Forest plot of meta-analysis on effects of LCn3 on IL-6 using SMD in random effects meta-analysis.

LCn3: long-chain omega-3, IL-6: interleukin 6, SMD: standardized mean difference, SD: standard deviation, SE: standard error

	Highe	r total PU	IFA	Lowe	r total PL	JFA		Std. Mean Difference	Std. Mean Difference	Risk of Bias
Study or Subgroup 27.10.1 CRP or hs-CRI	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFGHI
Belch 1988 (1) Belch 1988 (2) MENU - Rock 2016 MUFFIN Miller 2016	- 2.6 3.8 2.94 4.8	0 0 3.628 4	15 16 65 16	-0.38 -0.38 2.89 5.1	0 0 3.827 7.5047	18 18 61 22	30.1% 17.6%	Not estimable Not estimable 0.01 [-0.34, 0.36] -0.05 [-0.69, 0.60]		???? @ ? @ ? @ ???? @ ? @ ? @ @? @ ? @ ? @ ? @ ???? @ ? @ ? @
PREDIMED 2013 (3) PREDIMED 2013 (4) PREDIMED 2013 Subtotal (95% CI)	-0.15 2.8 -0.065	0.18 0.4 0.54	189	-0.2 2.3 -0.243	0.26 0.3 0.61	54 12 11 196	28.7% 11.2% 12.4% 100.0 %	0.22 [-0.16, 0.60] 1.37 [0.46, 2.27] 0.30 [-0.54, 1.14] 0.25 [-0.10, 0.60]		
Heterogeneity: Tau² = (Test for overall effect: 2			lf = 4 (P	= 0.09);	I² = 50%					
27.10.2 ESR Belch 1988 (5) Subtotal (95% CI) Heterogeneity: Not app	-6.5 Nicable	0	15 15	9	0	18 18		Not estimable Not estimable		2 2 2 2 8 2 8 2 8
Test for overall effect: N	lot applic	able								
27.10.3 IL-6, pg/ml MENU - Rock 2016 PREDIMED 2013 (6) PREDIMED 2013 (7) PREDIMED 2013 Subtotal (95% CI)	0.6 -0.6	1.6125 0.15 1.0991 1.8097	65 12 54 175 306	0.68 -0.6	2.8117 0.12 1.0991 1.1493	61 12 54 178 305	20.6% 3.8% 17.7% 57.9% 100.0 %	-0.13 [-0.48, 0.22] -0.57 [-1.39, 0.25] 0.00 [-0.38, 0.38] -0.07 [-0.27, 0.14] -0.09 [-0.24, 0.07]		
Heterogeneity: Tau² = (Test for overall effect: 2			lf= 3 (P	= 0.65);	I ^z = 0%					
27.10.4 faecal calprot Subtotal (95% Cl)			0			0		Not estimable		
Heterogeneity: Not app Test for overall effect: N		able								
27.10.5 TNF-alpha, pg/ MUFFIN Miller 2016 PREDIMED 2013 (8) PREDIMED 2013 Subtotal (95% CI)	2 -1.2 -3.3	0.8 2.93 24	16 54 50 120	-1.9 1.7	0.9381 2.93 23.3	22 54 74 150	21.8% 38.4% 39.8% 100.0 %	-0.44 [-1.10, 0.21] 0.24 [-0.14, 0.62] -0.21 [-0.57, 0.15] - 0.09 [-0.47, 0.29]		
Heterogeneity: Tau² = (Test for overall effect: 2			lf = 2 (P	= 0.11);	I²= 54%					
27.10.6 ICAM-1 PREDIMED 2013 Subtotal (95% CI)	-13.3	7	379 379	-10.8	5	379 379	100.0% 100.0 %	-0.41 [-0.55, -0.27] - 0.41 [-0.55, -0.27]	‡	
Heterogeneity: Not app Test for overall effect: 2		♀ < 0.000	01)							
27.10.7 VCAM-1 PREDIMED 2013 (9) Subtotal (95% CI) Heterogeneity: Not app	-8.13	5	379 379	-8.78	7	379 379	100.0% 100.0 %	0.11 [-0.04, 0.25] 0.11 [-0.04, 0.25]	‡	
Test for overall effect: 2		P = 0.14)								
Test for subgroup diffe <u>Footnotes</u>	rences: C	Chi² = 29.1	75, df=	4 (P < 0	.00001), I	² = 86.6	ì%		-1 -0.5 0 0.5 1 Favours high total PUFA Favours low total PUFA Risk of bias legend	-
 EPO plus fish oil vs No measures of va Barcelona Hospital Sevilla & Malaga co EPO plus fish oil vs Sevilla & Malaga co Sevilla & Malaga co Barcelona hospital Barcelona hospital 	riance pro cohort at horts at 1 paraffin, horts at 1 cohort at	ovided t 5 years, I year no SDs p I year 5 years, i	change provideo Casa 2	e,-1.5Ca d 016	sas 2016	ĵ			 (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (perform (D) Blinding of outcome assessment (detection bi (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Attention (H) Compliance 	nance bias)
(9) PREDIMED cohort					1 379 per	arm, 1	year, Med	ina-Remon 2017	(I) Other bias	

Figure 7. Forest plot of meta-analysis on effects of total PUFA on inflammatory markers using SMD in random effects meta-analysis.

PUFA: polyunsaturated fatty acids, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TNF-alpha: tumor necrosis factor alpha, ICAM-1: intercellular adhesion molecule 1, VCAM-1: vascular cell adhesion molecule 1, IL-6: interleukin 6, SMD: standardized mean difference, SD: standard deviation, EPO: evening primrose oil.