Supplementary File 4: supplementary materials

(Supplementary File 4 for Hooper et al "Creation of a database to assess effects of omega-3, omega-6 and total polyunsaturated fats on health: methodology for a set of systematic reviews")

Supplementary Table 1. Risk of bias assessment methods in detail

Risk of bias element	Criteria for low risk of bias	Criteria for unclear	Criteria for high risk of bias
Selection bias: random sequence generation	The study authors needed to have described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. For example "the randomisation sequence was computer generated". We allowed that a good method of randomisation was strongly implied if the authors discussed stratification and/or blocking. Therefore, if the authors were not explicit about their randomisation method but did describe stratification or blocking we assessed this as corresponding to low risk.	The study authors have not described their method in sufficient detail for the assessment of whether it would produce comparable groups. For example, the authors state "the trial was randomised" and provide no further information.	The randomisation method was assessed as not truly random, and may not produce comparable groups.
Selection bias: allocation concealment	The study authors needed to have described the method used to conceal allocation sequence in sufficient detail to determine whether the allocations could have been foreseen in advance of, or during, enrolment. Good methods included putting allocation codes in opaque sealed envelopes (ideally prepared by someone outside the treatment or assessment teams and sequentially numbered), using a telephone allocation system after the participants had consented to participate or providing a random number that links to a specific set of capsules prepared and distributed centrally or by an arms-length pharmacist.	The authors gave insufficient detail as to method.	The allocation was known in advance of participants consenting to take part in the study.
Performance bias: blinding of participants and personnel	The study authors needed to have described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective. For example, the authors could say "both the intervention and placebo capsules looked and tasted the same." However, if the study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding, then it was assumed that the blinding was effective and the risk of bias was low.	Insufficient methodological details were provided e.g. "the study was blinded."	The study was unblinded or where blinding was broken, e.g. "the capsules were visually identical but the participants reported a strong fishy flavour in the intervention group only."
Detection bias: blinding of outcome assessment	Study authors needed to have described measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Ideally, they should also have provided information relating to whether the intended blinding was effective.	Insufficient methodological details were provided e.g. "the study was blinded."	The study was unblinded or blinding was broken, e.g. for a self-assessment measure "the capsules were visually identical but the participants reported a

	For example, the authors could say "the outcome assessors had no knowledge of the group allocation, and both the intervention and placebo capsules looked and tasted the same so the self-assessment scales were also blinded." However if the study authors did not provide information on whether the blinding was effective, but sufficient detail was given on a good method of blinding of the assessors, then it was assumed that the blinding was effective and the risk of bias is low. All biochemical assessment (lipids, glucose, CRP, insulin, PSA, etc.) were considered at low risk of detection bias if outcome assessor blinding or double blinding was stated.		strong fishy flavour in the intervention group only." Because the level of blinding could vary by outcome assessment of risk of bias was based on blinding of the review's primary outcome(s). Where primary outcomes had different assessments we opted for the higher risk of bias but noted that that risk of bias was lower for other outcomes.
Attrition bias: incomplete outcome data	The study authors needed to describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. They needed to report the number of attrition/exclusions, the numbers in each group at each time point, reasons for attrition/exclusion and any re-inclusions in analyses. Ideally, they would report how they imputed any missing data e.g. last observation carried forward. There needed to be a reasonable balance of attrition/exclusions between study arms and ≤ 20% of the sample should be lost over a year.	The authors didn't state reasons for attrition/exclusion, or were unclear about the numbers lost to attrition/exclusion in each study arm.	The authors demonstrated a substantial difference in the rates of attrition/exclusions between the study arms and/or > 20% of the baseline sample was lost over a year (> 10% over 6 months).
Reporting bias: selective outcome reporting	The study authors needed to have published their trial protocol or trials registry entry before the end of the study's recruitment period i.e. prospectively. They needed to have reported on all of the primary and secondary outcomes listed in the protocol/registry entry. Reporting additional secondary outcomes in the results paper(s), although not ideal, was deemed to still be low risk.	No trial protocol or trials registry entry was found, it was registered retrospectively, or the dates of registration and participant recruitment were unclear.	The study authors did not report at least one primary or secondary outcome listed in the protocol/registry entry *or* the results paper(s) reported a primary outcome that was not listed at all in the protocol or not listed as a primary outcome in the protocol.
Other sources of bias: attention bias	The study authors needed to have reported that participants in all study arms received the same amount of attention and time from researchers and clinical teams. For example, "All participants attended the clinic for a baseline assessment which took 2 hours. They were then followed with monthly telephone calls, and finally attended for a 6 month assessment at the clinic which took 1 hour." If the study only differed by the content of the capsules, and the assessment schedule was not stated to differ between the two arms, it was assumed to be at low risk.	The authors did not state the attention each arm received.	Participants in different arms received different amounts of attention. For example "the intervention group only attended for additional assessments at months 2, 4, and 6" or "the rates of relapse differed substantially between the groups which led to differing amounts of treatment time and attention," or "the intervention group received a 40 minute dietary education session."

Other sources of bias: limited compliance	The study authors needed to have reported on the level of compliance in all arms in sufficient detail to determine whether the study results were robust. We followed a flow chart to make this determination. A statistically significant difference between the intervention and control groups in a body measure of ≥ 50% of the text fatty acids. Where no body measures were reported then estimated compliance needed to be greater than 64% (proportion complying multiplied by compliance threshold). Or (for the review assessing effects of total PUFA on CVD only[1]) the higher PUFA arm had to demonstrate an increase in PUFA fats over control in a body biomarker (total PUFA had to be assessed by at least LA plus one or more further components of PUFA), or greater reduction in TC in the higher PUFA arm.	Compliance not reported or not in a way that could be interpreted.	Measures of compliance were reported but fell below the appropriate thresholds.
Other sources of bias: other	In the absence of any additional issues this item was coded "low risk of bias"	—	If fraud concerns had been raised and the paper had been withdrawn, or the author had been found guilty of fraud by a legal or medical entity the paper was excluded from the review. However if fraud concerns were raised, but the journal had not withdrawn the paper, and the author had not been formally sanctioned; then the study was included in the review, but concerns were raised here, and the risk of bias for this item was high.

Footnotes

CRP: C-reactive protein; **PSA**: prostate specific antigen.

Supplementary Table 2. Table of which of the 216 included trials are included in which reviews

		N3 & CVD[2]	N6 & CVD[3]	PUFA & CVD[1]	N3, n6, PUFA & DM[4]	N3, n6, PUFA & depression[5]	N3, n6, PUFA & cognition[6]	N3, n6, PUFA & IBD[7]	N3, n6, PUFA & functional[8]	N3, n6, PUFA & cancers[9]
ADCS 2010	NCT00440050	X					X			
AFFORD 2013	NCT01235130; ISRCTN52203885	X						X		
Ahn 2016		X		X						
Almallah 1998								X		
AlphaOmega - ALA 2010	NCT00127452	X		X	X	X	X	X		X
AlphaOmega - EPA+DHA 2010		X			X	X	X	X		X
Araujo 2014								X		
AREDS2 2014	NCT00345176	X			X	X	X			X
ASCEND 2018	NCT00135226	X			X	X	X	X		X
Baldassarre 2006		X								
Baleztena 2015	NCT01817101						X			
Balfego 2016	NCT02294526				X			X		
Bassey 2000-Post				X					X	
Bassey 2000-Pre				X						
Bates 1977			X	X						
Bates 1978			X	X						
Bates 1989		X		X						
Baxheinrich 2012					X				X	
Belch 1988			X					X		
Belluzzi 1996								X		
Berbert 2005								X		
Berson 2004		X								X
Black 1994			X	X						X
Bo 2017	ChiCTR-TRC-14004625						X	X		
Boespflug 2016	NCT01746303						X			
Bonnema 1995					X					
Brox 2001		X		X				X		
Brzeski 1991								X		
Caldwell 2011	NCT00681408	X			X					

Chiu 2008	**NCT00628017**					X	X			
Clark 2016	**NCT01241474**				X			X	X	
Connor 1993					X					
Darghosian 2015	**NCT00552084**							X		
DART2 2003		X			X	X				X
DART fat 1989			X	X	X		X			X
DART fish 1989		X			X		X			X
Dasarathy 2015	**NCT00323414**				X				X	
DeFina 2010					X					
Delamaire 1991					X					
de Luis 2016	**NCT01865448**				X			X		
Derosa 2009					X			X		
Derosa 2011					X			X		
Derosa 2016		X			X	X				
Deslypere 1992		X			X			X		
DIPP 2015	**UMIN000000461**	X		X	X	X				X
DISAF 2003		X								
Dodin 2005		X		X	X				X	
Doi 2014	**UMIN000016723**	X		X						
DO IT 2010	**NCT00764010**	X			X	X		X		X
Dullaart 1992			X	X	X					
Ebrahimi 2009					X			X		
ELIA - Takaki 2011	**UMIN000002171**							X		
EPE-A 2014	**NCT01154985**	X			X	X		X		X
EPIC-1 2008	**NCT00613197**	X		X				X		X
EPIC-2 2008	**NCT00074542**	X		X				X		X
EPOCH 2014	**ACTRN2607000278437**	X		X	X	X	X	X	X	
Erdogan 2007		X								
Eschen 2010								X		
FAAT 2005	**NCT00004559**	X		X						
Fakhrzadeh 2010					X					
Ferrara 2000					X					
Ferreira 2015						X				
Finnegan 2003					X			X		
FISHGASTRO - Pot 2009								X		
FLAX-PAD 2013	**NCT00781950**	X						X		
FORWARD 2013	**NCT00597220**	X								

FOSTAR 2016	**ACTRN12607000415404**	X							X	X
Franzen 1993		X								
Gill 2012	**NCT00350194**	X			X					
GISSI-HF 2008		X								X
GISSI-P 1999		X			X					X
GLAMT 1993			X	X	X				X	X
Greenfield 1993								X		
Gruenwald 2009									X	
HARP 1995	**NCT00000461**	X		X						X
Hashimoto 2012							X			
Hashimoto 2016						X	X			
Hawthorne 1992								X		
Heine 1989					X					
HERO 2009	**ACTRN12607000600448**	X		X	X					
Higashihara 2010										X
Houtsmuller 1979			X	X	X					
Huang 1996										X
Hutchins-Wiese 2013	**NCT00634686**								X	
IFOMS- Sirtori 1997					X					
Jackson 2016	**NCT01185379**					X	X			
JELIS 2007	**NCT00231738**	X			X					X
Kanorsky 2007								X		
Krebs 2006					X			X		
Kremer 1995								X		
Kristensen 2016								X		
Kruger 1998									X	
Kumar 2008								X		
Kumar 2012	**NCT00232219**	X		X						
Kumar 2013	**NCT00232245**	X		X						
Lalia 2015	**NCT01686568**				X			X		
Lau 1993								X		
Lee 2012						X	X			
Leventhal 1993								X		
Leventhal 1994								X		
Ley 2004				X						X
Li 2015								X		
Loeschke 1996								X		

Lorenz-Meyer 1996		X						X		
Macsai 2005										X
Mansel 1990			X							X
Mantzaris 1996								X		
MAPT 2017	**NCT00672685**	X				X	X		X	
MARGARIN 2002		X						X		
MARINA 2011	**ISRCTN66664610**	X		X				X		
Martinez 2014					X			X		
Mate 1991								X		
McIllmurray 1987			X	X						X
MEMO 2008						X	X		X	
Mendis 2001			X	X						
MENU 2016	**NCT01424007**	X			X			X		
MIDAS 2010	**NCT0027813**					X	X			
Mita 2007		X		X	X					X
Moore 2006					X			X		
MRC 1968			X	X						X
MUFFIN Miller 2016					X			X		
NAT2 2013	**ISRCTN98246501**	X								
NDHS Faribault 1968			X	X						
NDHS Open 1st 1968			X	X						X
NEURAPRO 2017	**ACTRN12608000475347**					X				
Nigam 2014					X					
Niki 2016					X			X		
Nishio 2014								X		
Nodari 2009								X		
Nodari 2011 AF	**NCT01198275**	X		X						
Nodari 2011 HF	**NCT01223703**	X		X	X			X		
Nogueira 2016	**NCT01992809**				X			X		
Nomura 2009					X					
Norouzi 2014	**NCT01311375**	X							X	
Norwegian 1968		X			X					
Nutristroke 2009		X					X		X	
Nye 1990		X		X						
OFAMI 2001	**NCT01422317**	X			X			X		X
OFAMS 2012	**NCT00360906**					X	X			
OFFER 2015	**NCT02210962**					X				

OMEGA 2009	**NCT00251134**	X				X				X
OmegAD 2008						X	X	X	X	
OMEGA-Remodel 2016	**NCT00729430**							X		
OPAL 2010	**ISRCTN: 72331636**	X			X	X	X			
OPTILIP 2006					X					
ORIGIN 2012	**NCT00069784**	X			X		X			X
ORL 2013	**NCT01350999**	X		X	X			X		X
Özaydin 2011		X								
Palma 2015						X				
Patch 2005					X			X		
Paty 1978							X			
Pomponi 2014						X	X			
Pratt 2009					X	X				
PREDIMED 2013				X	X	X	X	X	X	X
Proudman 2015	**ACTRN12613000579796**	X		X	X					
Puri 2005	**ISRCTN: 79170611**	X		X			X			X
Raitt 2005	**NCT00004558**	X		X			X			X
Ramirez-Ramirez 2013		X						X		
Rebello 2015	**NCT01669200**						X			
REDUCE-IT	**NCT01492361**	X								
Reed 2014	**NCT00072982**	X						X		
Risk & Prevention 2013	**NCT00317707**	X			X					X
Romero 2013							X			
Rose 1965			X	X	X					
Rossing 1996		X		X	X					X
Salari 2010									X	
Sandhu 2016	**NCT00723398**	X			X			X		X
Sasaki 2012	**UMIN000005783**				X					
Sawada 2016	**UMIN000011265**				X			X		
Schattin 2016						X	X			
Schirmer 2007			X		X					
SCIMO 1999		X					X			X
seAFOod Hull 2018	**ISRCTN05926847**									X
Shimizu 1995					X					
Shinto 2014	**NCT00090402**	X					X			
SHOT 1996		X			X					
Sianni 2013		X								

Simon 1997				X						X
Sinn 2012	**ACTRN 12609000167268**					X	X		X	
Skoldstam 1992								X		
SMART 2013	**ACTRN12608000425392**	X			X					
Smith 2015	**NCT01308957**				X				X	
SO927 Hershman 2015	**NCT01385137**							X		
SOFA 2006	**NCT00110838**	X								X
Sofi 2010		X			X					
Spadaro 2008					X					
Stammers 1992									X	
Stonehouse 2013							X			
SU.FOL.OM3 2010	**ISRCTN: 41926726**	X				X	X		X	X
Sydney Diet-Heart 1978			X	X						
Tajalizadekhoob 2011						X				
Tande 2016		X			X			X		
Tani 2017	**UMIN000010452**							X		
Tapsell 2004					X					
Tardivo 2015	**RBR-5668v4**				X			X	X	
Tartibian 2011								X	X	
Terano 1999							X			
THIS DIET 2008	**NCT00269425**	X			X	X		X		X
TREND-HD 2008	**NCT00146211**					X				
Vanlint 2012									X	
Varghese 2000								X		
Veleba 2015	**EudraCT 2009-011106-42**				X			X		
Veterans Admin 1969			X	X						X
Vijayakumar 2014			X	X	X			X		
VITAL Manson 2018	**NCT01169259**	X								X
WAHA 2016	**NCT01634841**	X		X						X
Wang 2016	**ChiCTR-TRC-14005084**				X				X	
Weinstock-Guttman 2005		X								
WELCOME 2015	**NCT00760513**	X		X	X				x	
Westberg 1990								X		
WINS 2006				X						X
Witte 2012	**NCT00996229**				X			X		

Wright 2008								X		
Zhang 2017	**ChiCTR-IOR-15006058**	x					X			
Zheng 2016	**NCT01857167**				X					

Supplementary Table 3. Interventions in 311 included studies (included in reviews or not) - omega-3 (ALA or LCn3), omega-6 and/or total PUFA interventions

Trial name	Registry number (if found)	Omega-3 LCn3*	Omega-3 ALA*	Omega-6	Total PUFA
ADCS 2010	NCT00440050	X			
AFFORD 2013	NCT01235130; ISRCTN52203885	X			
Ahn 2016		X			X
Almallah 1998		X			
AlphaOmega - ALA 2010	NCT00127452		X		X
AlphaOmega - EPA+DHA 2010		X			
Annuzzi 2014	NCT01154478	X			
Araujo 2014		NR	NR		
AREDS2 Pilot - Huang 2008	NCT00121589	X			
AREDS2 2014	NCT00345176	X			
ASCEND 2018	NCT00135226	X			
Bairati 1992		X			
Baldassarre 2006		X			
Baleztena 2015	NCT01817101	X			
Balfego 2016	NCT02294526	X			
Bassey 2000-Post					X
Bassey 2000-Pre					X
Bates 1977				X	X
Bates 1978				X	X
Bates 1989		X			X
Baxheinrich 2012			X		
Belch 1988				X	
Bellamy 1992		X			
Belluzzi 1996		X			
Berbert 2005		X			
Berson 2004		X			
Bhargava 2015		X			
Bhargava 2016		X			
Bianconi 2011		X			
Bierenbaum 1963					X
Black 1994				X	X
Blommers 2002		X			X
Bo 2017	ChiCTR-TRC-14004625	X			
Boespflug 2016	NCT01746303	X			
Bonnema 1995		X			
Borchgrevink 1966			X		
Brox 2001		X			X
Brzeski 1991				X	
Caldwell 2011	NCT00681408	X			
CART - Johansen 1999		X			
Chen 2008		NR	NR		
Chiu 2008	NCT00628017	X			
CHOICE - Peters 2014			X		
Chrysohoou 2016		NR	NR		
Clark 2016	NCT01241474	X			
Cod-Fish - Thomashow 2014		NR	NR		

Colli 2012			X		
Connor 1993		X			
Darghosian 2015	NCT00552084	X			
DART2 2003		X			
DART fat 1989				X	X
DART fish 1989		X			
Dasarathy 2015	NCT00323414	X			
DeFina 2010		X			
Delamaire 1991		X			
de Luis 2016	NCT01865448	X			
Derosa 2009		X			
Derosa 2011		X			
Derosa 2016		X			
Deslypere 1992		X			
DIPP 2015	UMIN000000461	X			X
DISAF 2003		X			
Dodin 2005			X		X
Doi 2014	UMIN000016723	X			X
DO IT 2010	NCT00764010	X			
DREAM 2018	NCT02128763	X			
Dry 1991		X			
Duffy 2004		X			
Dullaart 1992				X	X
Ebrahimi 2009		X			
El Khouli 2014		X			
ELIA - Takaki 2011	UMIN000002171	X			
EPE-A 2014	NCT01154985	X			
EPIC-1 2008	NCT00613197	X			X
EPIC-2 2008	NCT00074542	X			X
EPOCH 2014	ACTRN2607000278437	X			X
Erdogan 2007		X			
Eschen 2010		X			
ESPRIT - Maresta 2002		X			
FAAT 2005	NCT00004559	X			X
Fakhrzadeh 2010		X			
Ferrara 2000				X	
Ferreira 2015		X			
Finnegan 2003		X	X		
FISHGASTRO - Pot 2009		X			
FLAX-PAD 2013	NCT00781950		X		
FORCE - Harper 2006			X		
FORT - Leaf 1994		X			
FORWARD 2013	NCT00597220	X			
FOSTAR 2016	ACTRN12607000415404	X			
Franzen 1993		X			
Galarraga 2008		X			
Garcia-Medina 2011		X			
Geusens 1994		X			
Ghadian 2017		NR	NR		
Gill 2012	NCT00350194	X			
GISSI-HF 2008		X			
GISSI-P 1999		X			
GLAMT 1993				X	X
Greenfield 1993		X		X	
Gruenwald 2009		X			
Hamazaki 2006			X		

Hansen 2010		X			
Harbige 2007				X	
HARP 1995	NCT00000461	X			X
Harris 1991		X			
Hashimoto 2012		X			
Hashimoto 2016		X			
Hawthorne 1992		X			
Heine 1989				X	
Henz 1999				X	
HERO 2009	ACTRN12607000600448		X		X
Higashihara 2010		X			
Holguin 2005		X			
Horrobin 1997				X	
Houtsmuller 1979				X	X
Huang 1996		X			
Hutchins-Wiese 2013	NCT00634686	X			
IFOMS- Sirtori 1997		X			
Jackson 2016	NCT01185379	X			
Jamal 1986				X	
J-EACH - Domei 2013		X			
JELIS 2007	NCT00231738	X			
Jenkins 1996				X	
Kanorsky 2007		NR	NR		
Khan 2003		X		X	X
Kojuri 2013	NCT01227837	NR	NR		
Kokke 2008				X	
Koziolova 2015		NR	NR		
Krebs 2006		X			
Kremer 1990		X			
Kremer 1995		X			
Kristensen 2016		X			
Kruger 1998					X
Kumar 2008				X	
Kumar 2012	NCT00232219	X			X
Kumar 2013	NCT00232245	X			X
Kurabayashi 2000		X			
Lalia 2015	NCT01686568	X			
Lau 1993		X			
Lau 1995		X			
Lee 2012		X			
Leventhal 1993				X	
Leventhal 1994			X	X	
Ley 2004					X
Li 2015		X			
Loeschke 1996		X			
Lorenz-Meyer 1996		X			
Macsai 2005			X		
Malaguarnera 1999		X			
Mansel 1990				X	
Mantzaris 1996		X			
MAPT 2017 & MAPT plus	NCT00672685, NCT01513252	X			
MARGARIN 2002			X		
MARINA 2011	ISRCTN66664610	X			X
Martinez 2014		X			
Masterton 2015		NR	NR		

Mate 1991		X			
McIllmurray 1987				X	X
McKew 2012		X			
Mehta 2008		X			
MEMO 2008		X			
Mendis 2001				X	X
MENU 2016	NCT01424007		X		
Meyer 2007		X			
Meymandi 2007	NCT00454493	X			
MIDAS 2010	NCT0027813	X			
Millar 1973				X	
Milner 1989		X			
Mita 2007		X			X
Moore 2006			X		X
MRC 1968				X	X
MUFFIN Miller 2016				X	
NAT-1 Querques 2009		X			
NAT2 2013	ISRCTN98246501	X			
NDHS Faribault 1968				X	X
NDHS Open 1st 1968				X	X
Neubronner 2011		X			
NEURAPRO 2017	ACTRN12608000475347	X			
Nigam 2014			X	X	
Niki 2016		X			
Nishio 2014		X			
Njike 2016			X		
Nodari 2009		X			
Nodari 2011 AF	NCT01198275	X			X
Nodari 2011 HF	NCT01223703	X			X
Nogueira 2016	NCT01992809	X			
Nomura 2009		X			
Norouzi 2014	NCT01311375	X			
Norwegian 1968			X		
Nostratzehi 2016		NR	NR		
Nutristroke 2009		X			
Nye 1990		X			X
OFAMI 2001	NCT01422317	X			
OFAMS 2012	NCT00360906	X			
OFFER 2015	NCT02210962	X			
Oliwiecki 1994					X
OMEGA 2009	NCT00251134	X			
OmegAD 2008		X			
OMEGA-Remodel 2016	NCT00729430	X			
OPAL 2010	ISRCTN: 72331636	X			
OPTILIP 2006		X	X		
ORIGIN 2012	NCT00069784	X			
ORL 2013	NCT01350999	X			X
Özaydin 2011		X			
Palma 2015		X			
Palozza 1996		X			
Parulkar 2009		NR	NR		
Patch 2005		X			
Paty 1978				X	
PEACH - Urakawa 2014		X			
Pinheiro 2007			X		
Pinna 2007				X	

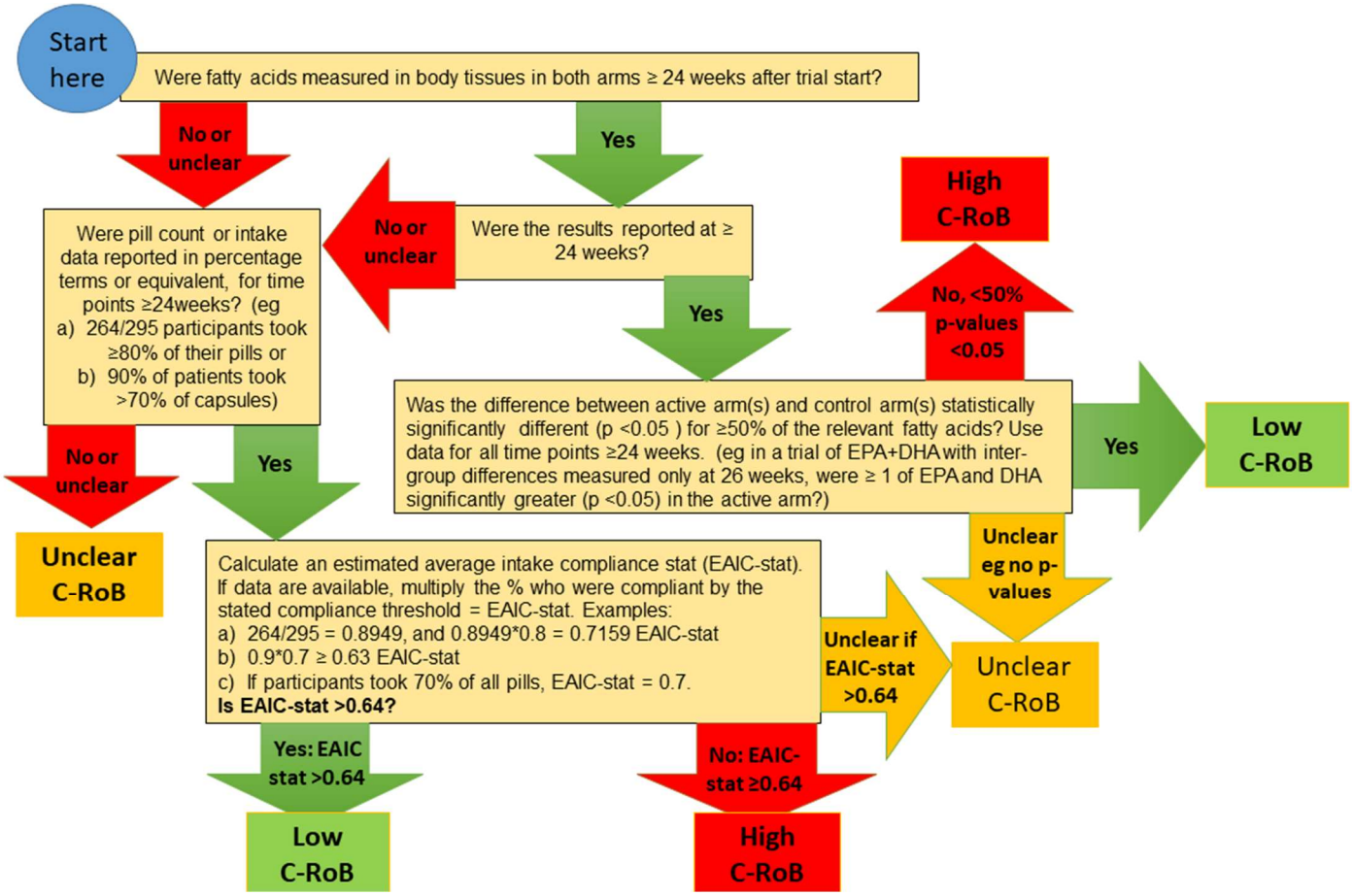
Pomponi 2014		X			
Pratt 2009		X			
PREDIMED 2013					X
Proudman 2015	ACTRN12613000579796	X			X
Purewal 1997				X	
Puri 2002		X			
Puri 2005	ISRCTN: 79170611	X			X
Raitt 2005	NCT00004558	X			X
Ramirez-Ramirez 2013		X			
Rebello 2015	NCT01669200		X		
REDUCE-IT Bhatt 2018	NCT01492361	X			
Reed 2014	NCT00072982	X			
Reis 1991		X			
Rezapour-Firouzi 2013					X
Risk & Prevention 2013	NCT00317707	X			
Romero 2013		X			
Rocha Filho 2011				X	
Rodrigues 2015		X			
Rose 1965				X	X
Rossing 1996		X			X
Sabate 2005			X		
Safarinajad 2009		X			
Salari 2010		NR	NR		
Sandhu 2016	NCT00723398	X			
Sasaki 2012	UMIN000005783	X			
Sarkkinen 1998			X		
Sawada 2016	UMIN000011265	X			
Schaefer 1996		X			
Schattin 2016		X			
Schirmer 2007				X	
SCIMO 1999		X			
seAFOod Hull 2018	ISRCTN05926847	X			
Selvais 1995		X			
Sheppard 2013	NCT00883649	X			
Shevelyok 2013		NR	NR		
Shimizu 1995		X			
Shinto 2014	NCT00090402	X			
SHOT 1996		X			
Sianni 2013		X			
Simon 1997					X
Singer 2004		X			
Sinn 2012	ACTRN 12609000167268	X			
Skoldstam 1992		X			
Slack 1987		X			
SMART 2013	ACTRN12608000425392	X			
Smith 2015	NCT01308957	X			
SO927 Hershman 2015	NCT01385137	X			
SOFA 2006	NCT00110838	X			
Sofi 2010		X			
Spadaro 2008		X			
Stainforth 1996					X
Stammers 1992		X			
Stonehouse 2013		X			
SU.FOL.OM3 2010	ISRCTN41926726	X			
Sydney Diet-Heart 1978				X	X

Tajalizadekhoob 2011		X			
Tande 2016		X			
Tani 2013		X			
Tani 2017	UMIN000010452	X			
Tapsell 2004			X		
Tardivo 2015	RBR-5668v4	X			
Tartibian 2011		X			
Terano 1999		X			
Theander 2002				X	
Thien 1993		X			
THIS DIET 2008	NCT00269425	X			
Tobin 1988		X			
TOHP 1 - Sacks 1994		X			
Tomer 2001		X			
Tremoli 1994		NR	NR		
TREND-HD 2008	NCT00146211	X			
Uehara 2013		X			
Vaddadi 2002					X
Vanlint 2012		X			
Varghese 2000		NR	NR		
Veale 1994					X
Veleba 2015	EudraCT 2009-011106-42	X			
Veterans Admin 1969				X	X
Vijayakumar 2014				X	X
VITAL Manson 2018	NCT01169259	X			
WAHA 2016	NCT01634841		X		X
Wakita 2013		X			
Wang 2016	ChiCTR-TRC-14005084	X			
Weinstock-Guttman 2005		X			
Weisman 2011		X			
WELCOME 2015	NCT00760513	X			X
West 2010	NCT00510692	X			
Westberg 1990		X			
WINS 2006					X
Witte 2012	NCT00996229	X			
Wolf-Schnurrbusch 2015	NCT00563979	X			
Wright 2008		X			
Yamano 2012		X			
Yee 2010		X			
Yoon 2015		NR	NR		
Zhang 2017	ChiCTR-IOR-15006058	X			
Zheng 2016	NCT01857167	X	X		
Zhu 2008		X			
Totals:		**217**	**27**	**41**	**59**
		Plus 16 omega-3 RCTs (unclear whether LCn3 or ALA)			

*Trials of omega-3 vs omega-6 are classified as omega-3 trials.

NR trials reported an omega-3 intervention, but it was unclear whether the intervention was of LCn3 or ALA or both.

Supplementary Figure. Decision tree for use in assessing compliance risk of bias (C-RoB).



Supplementary Text 1. Background information on types of omega-3 and omega-6, and potential mechanisms of omega-3, omega-6 and total polyunsaturated fats

Polyunsaturated fatty acids (PUFAs) include at least two double (unsaturated) carbon-to-carbon bonds in their hydrocarbon chains. Because double bonds introduce "kinks" into hydrocarbon chains they pack less well, tending to be liquid at room temperature, rather than solid like more saturated fats. PUFAs can be omega-3 (where the first double bond is three carbons away from the methyl-carbon chain end), omega-6 or omega-9. Plant and fish oils are often rich in PUFAs. Two PUFAs, alpha-linolenic acid (ALA, 18:3n3) and linoleic acid (LA, 18:2n6), are essential nutrients in humans – we are unable to synthesise them ourselves so must obtain them through the diet.

The main dietary omega-6 is LA, available from a wide variety of foods including vegetable and nut oils, nuts, poultry, meat, egg, milk, margarines, and spreads. Omega-6 fats include GLA (gamma linoleic acid, 18:3n6) and AA (arachidonic acid, 20:4n6). Omega-3 fats include long-chain omega-3s (from fish sources including eicosapentaenoic acid (EPA, 20:5n3), docosahexaenoic acid (DHA, 22:6n3) and docosapentaenoic acid (DPA, 22:5n3)) and ALA (from plant oils) which is partially converted to long-chain omega-3 fatty acids (LCn3) within our bodies, though there is debate about the completeness of this conversion, so ALA impacts in body may differ from LCn3[10 11].

Dietary fats have been implicated in cardiovascular health since the 1950s when Keys published ground-breaking research linking plasma cholesterol and dietary saturated fat [12], and Oliver reported higher levels of low-density lipoprotein (LDL) cholesterol in those surviving myocardial infarction than healthy controls [13]. In 1965 Hegsted quantified the relationship between dietary fat and serum total cholesterol, suggesting that increasing saturated fats increased serum cholesterol, while increasing PUFAs reduced serum cholesterol [14]. More recently there has been discussion about protective types of PUFA, with interest in omega-3 following Bang's suggestion that abundant LCn3 in Innuit diets was responsible for their low ischaemic heart disease (IHD) mortality [15 16]. Two positive randomized controlled trials (RCTs) in 1989 and 1999 providing dietary fish and fish oil supplementation raised excitement about LCn3 and coronary heart disease [17 18], although subsequent trials have been equivocal [19].

While the total PUFA mechanism, especially higher intakes of LA, mainly involves reduced serum total and LDL cholesterol, slowing atherosclerosis to delay or prevent onset of cardiovascular and cerebrovascular disease [20], proposed omega-3 mechanisms are broader. They include: lowering blood pressure; altered lipid profile, especially reduced serum triglyceride concentration; reduced thrombotic tendency; anti-inflammatory effects; anti-arrhythmic effects including reduction in heart rate; improved vascular endothelial function; increased plaque stability through increased plaque calcification); increased paraoxonase levels and improved insulin sensitivity [21-26]. Omega-3 and omega-6 may also exhibit harm. Omega-3 fats could extend bleeding times and suppress normal immune responses [27]. Omega-6 may be pro-inflammatory by increasing production of 2-series prostaglandins and 4-series leukotrienes, rather than the 3-series prostaglandins and 5-series leukotrienes associated with omega-3 intake [28 29]. As the 2-series prostaglandins and 4-series leukotrienes exert a more potent pro-inflammatory effect, and inflammation leads to increased blood clotting, omega-6 could increase cardiovascular disease risk via this mechanism [30].

Proposed effects of omega-3 and omega-6 fats on inflammatory processes have spurred exploration of effects on inflammatory diseases such as inflammatory bowel disease (IBD) [7 22], and discussion of omega-3/omega-6 ratios. High LCn3 concentrations in brain tissues suggest importance of omega-3 in cognition and mental health[5 6], and proposed modification of insulin-sensitivity has hypothesised effects in glucose metabolism and diabetes[4 31]. The enthusiasm for health effects of omega-3 and omega-6 fats has generated research assessing effects on cancers although mechanisms are being sought[9 32 33].

Supplementary Text 2. MEDLINE Ovid search strategy used to find omega-6 and total PUFA trials

1. exp fatty acids, essential/
2. fatty acids, unsaturated/
3. ((polyunsaturat* or poly-unsaturat*) adj3 fat*).ti,ab.
4. (poly* adj4 unsat* adj4 fatty acid*).ti,ab.
5. PUFA.ti,ab.
6. exp fatty acids, omega-6/
7. omega-6.ti,ab.
8. (n-6 adj4 acid*).ti,ab.
9. linoleic acid*.ti,ab.
10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/
11. ((corn or maize or mazola) adj4 oil*).ti,ab.
12. (cottonseed* or (cotton adj seed*)).ti,ab.
13. (olive adj4 oil*).ti,ab.
14. (safflower adj4 oil*).ti,ab.
15. (sesame adj4 oil*).ti,ab.
16. ((soy bean or soybean) adj4 (oil* or fat*)).ti,ab.
17. (so?a adj4 oil*).ti,ab.
18. so?aoil*.ti,ab.
19. (soy adj4 oil*).ti,ab.
20. (sunflower adj4 oil*).ti,ab.
21. helianth*.ti,ab.
22. (grapeseed adj4 oil*).ti,ab.
23. (canola adj4 oil*).ti,ab.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 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 or 21 or 22 or 23
25. randomized controlled trial.pt.
26. controlled clinical trial.pt.
27. randomized.ab.
28. placebo.ab.
29. clinical trials as topic.sh.
30. randomly.ab.
31. trial.ti.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. exp animals/ not humans.sh.
34. 32 not 33
35. 24 and 34

Supplementary Text 3. MEDLINE Ovid search strategy used to find omega-3 RCTs

1. exp Fish Oils/
2. Linseed Oil/
3. linolenic acids/ or alpha-linolenic acid/
4. Flax/
5. exp Fatty Acids, Omega-3/
6. (fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
7. (oil* adj3 (cod* or marin*)).ti,ab.
8. (omega-3 or omega3 or (omega* adj5 fat*)).ti,ab.
9. eicosapentaen*.ti,ab.
10. docosahexaen*.ti,ab.
11. (oil* adj3 (flax* or rapeseed* or canola*)).ti,ab.
12. (Linolen* or alpha-linolen* or alphalinolen*).ti,ab.
13. (perilla* or linseed* or maxepa*).ti,ab.
14. (oil* adj3 (rape or colza)).ti,ab.
15. (marin* adj3 lipid*).ti,ab.
16. (naudicelle* or herring* or sild).ti,ab.
17. (clupe* adj3 hareng*).ti,ab.
18. (whitebait or sardine* or sardina* or pilchard* or sprat* or brisling*).ti,ab.
19. (salmo* adj3 trut*).ti,ab.
20. (trout or bloater or kipper* or salmon or mackerel* or scomb* or conger* or tuna or tunny or tunafish or tuna-fish).ti,ab.
21. (thunnus* or swordfish* or xiphias* or dogfish or scyliorrhinus* or laks or lax).ti,ab.
22. (crab or crabs or cancer pagarus).ti,ab.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 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 or 21 or 22
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. randomized.ab.
27. placebo.ab.
28. clinical trials as topic.sh.
29. randomly.ab.
30. trial.ti.
31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. exp animals/ not humans.sh.
33. 31 not 32
34. 23 and 33
35. exp salmoniformes/ or tuna/
36. (fish adj3 capsul*).ti,ab.
37. icosapentaen*.ti,ab.
38. docosapentaen*.ti,ab.
39. (oil* adj3 (purslane or mustard* or candlenut* or stillingia or walnut*)).ti,ab.
40. 35 or 36 or 37 or 38 or 39
41. 33 and 40
42. 34 or 41

References

1. Abdelhamid AS, Martin N, Bridges C, et al. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;7:CD012345. doi: https://dx.doi.org/10.1002/14651858.CD012345.pub2
2. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;7:CD003177. doi: https://dx.doi.org/10.1002/14651858.CD003177.pub3
3. Hooper L, Al-Khudairy L, Abdelhamid AS, et al. Omega-6 fats for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;7:CD011094. doi: https://dx.doi.org/10.1002/14651858.CD011094.pub3
4. Brown TJ, Brainard JS, Song F, et al. Omega-3, omega-6 and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review of randomised controlled trials. *Br Med J* 2018;submitted
5. Deane KHO, Jimoh OF, Biswas P, et al. Omega-3, omega-6 and total polyunsaturated fat for prevention and severity of depression and anxiety: a systematic review and meta-analysis of RCTs *Br Med J* 2018;submitted
6. Jimoh OF, Brainard J, Deane KA, et al. Dietary polyunsaturated fat for prevention and treatment of neurocognitive disorders. *PROSPERO* 2017:CRD42017019049.
7. Thorpe G, Ajabnoor S, Ahmed Z, et al. Dietary polyunsaturated fat for prevention and treatment of inflammatory bowel disease. *PROSPERO* 2017:CRD42017068704.
8. Abdelhamid AS, Hooper L, Sivakaran R, et al. Omega-3, omega-6 and total polyunsaturated fat for musculoskeletal health and functional status in older adults: a systematic review and meta-analysis of RCTs. *Br Med J* 2018;submitted
9. Hanson S, Thorpe G, Winstanley L, et al. Effects of supplementary dietary polyunsaturated fat on cancer incidence. *PROSPERO* 2017:CRD42017056109.
10. Li D, Sinclair A, Wilson A, et al. Effect of dietary alpha-linolenic acid on thrombotic risk factors in vegetarian men. *Am J Clin Nutr* 1999;69:872-82.
11. Pawlosky RJ, Hibbeln JR, Novotny JA, et al. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *J Lipid Res* 2001;42:1257-65.
12. Keys A, Mickelsen O, Miller EVO, et al. The relation in man between cholesterol levels in the diet and in the blood. *Science* 1950;112:79-81.
13. Oliver MF, Boyd GS. The plasma lipids in coronary artery disease. *Br Heart J* 1953;15:387-90.
14. Hegsted DM, McGandy RB, Myers ML, et al. Quantitative effects of dietary fat on serum cholesterol in man. *Am J Clin Nutr* 1965;17(5):281-95.
15. Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast eskimos. *Acta Med Scand* 1972;192:85-94.
16. Bang HO, Dyerberg J, Hjorne N. The composition of food consumed by Greenland Eskimos. *Acta Med Scand* 1976;200:69-73.
17. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2(8666):757-61.
18. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.
19. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *Br Med J* 2006;322:752-52.
20. Hooper L, Martin N, Abdelhamid A, et al. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* 2015;6:CD011737.
21. Calabresi L, Villa B, Canavesi M, et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. *Metabolism* 2004;53(2):153-58.
22. Bhatnagar D, Durrington PN. Omega-3 fatty acids: their role in the prevention and treatment of atherosclerosis related risk factors and complications. *Int J Clin Pract* 2003;57(4):305-14.
23. British Nutrition Foundation. n-3 fatty acids and health: briefing paper. London: British Nutrition Foundation 1999.

24. Geelen A, Brouwer IA, Zock PL, et al. Antiarrhythmic effects of n-3 fatty acids: evidence from human studies. *Curr Opin Lipidol* 2004;15:25-30.
25. Calder PC. Mechanisms of action of (n-3) fatty acids. *J Nutr* 2012;142(3):592S-99S.
26. Ohwada T, Yokokawa T, Kanno Y, et al. Vascular composition data supporting the role of N-3 polyunsaturated fatty acids in the prevention of cardiovascular disease events. *Data Brief* 2016;7:1237-47.
27. US Food and Drug Administration. Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. US FDA web site, wwwfdagov, 2000.
28. Siriwardhana N, Kalupahana NS, Fletcher S, et al. N-3 and n-6 polyunsaturated fatty acids differentially regulate adipose angiotensinogen and other inflammatory adipokines in part via NF-κB-dependent mechanisms. *J Nutr Biochem* 2012;23(12):1661-67.
29. Tortosa-Caparrós E, Navas-Carrillo D, Marín F, et al. Anti-inflammatory effects of omega 3 and omega 6 polyunsaturated fatty acids in cardiovascular disease and metabolic syndrome. *Crit Rev Food Sci Nutr* 2017;57(16):3421-29.
30. Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. *Biochem Pharmacol* 2009;77(6):937-46.
31. Lalia AZ, Johnson ML, Jensen MD, et al. Effects of Dietary n-3 Fatty Acids on Hepatic and Peripheral Insulin Sensitivity in Insulin-Resistant Humans. *Diabetes Care* 2015;38(7):1228-37.
32. Gu Z, Suburu J, Chen H, et al. Mechanisms of Omega-3 Polyunsaturated Fatty Acids in Prostate Cancer Prevention. *Biomed Res Int* 2013;2013:824563. doi: 10.1155/2013/824563
33. Jing K, Wu T, Lim K. Omega-3 polyunsaturated fatty acids and cancer. *Anticancer Agents Med Chem* 2013;13:1162-77.