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**APPENDIX DOCUMENTS A**

**Table A. 1. Search terms across databases**

| **Database name** | **Keyword search** |
| --- | --- |
| **Cochrane** | (Krill oil OR Fish oil) AND (LIPID OR TRIGLYCERIDE OR HDL OR LDL) |
| **Pubmed** | ((((((((Oils, Fish) OR (Fish Oil)) OR (Oil, Fish)) OR (Fish Liver Oils)) OR (Liver Oils, Fish)) OR (Fish Liver)) OR (Krill oil))) AND (((((((lipid) OR (triglyceride)) OR (Triacylglycerol)) OR (Triacylglycerols)) OR (HDL)) OR (LDL))) AND ((((((((((((Cardiovascular Disease) OR (Disease, Cardiovascular)) OR (Major Adverse Cardiac Events)) OR (Cardiac Events)) OR (Cardiac Event)) OR (Event, Cardiac)) OR (Adverse Cardiac Event)) OR (Adverse Cardiac Events)) OR (Cardiac Event, Adverse)) OR (Cardiac Events, Adverse)) OR (Healthy))) |
| **Embase** | 'cardiovascular disease'/exp AND ('fish oil'/exp OR 'ameu' OR 'efamed' OR 'epax' OR 'epax 5000' OR 'feniko' OR 'fish oil' OR 'fish oils' OR 'himega' OR 'k 85' OR 'k 85 fish oil preparation' OR 'lachs 550' OR 'lipitac' OR 'maxepa' OR 'olemar' OR 'omegaven' OR 'optimepa' OR 'pikasol' OR 'promega' OR 'super epa' OR 'superepa' OR 'tuna oil' OR 'krill oil'/exp) AND ('high density lipoprotein cholesterol'/exp OR 'low density lipoprotein cholesterol'/exp OR 'ldl cholesterol' OR 'cholesterol, ldl' OR 'lipoproteins, ldl cholesterol' OR 'low density lipoprotein cholesterol' OR 'triacylglycerol'/exp OR 'acylglycerol, tri' OR 'fatty acid triglyceride' OR 'triacyl glyceride' OR 'triacylglycerol' OR 'triglyceride' OR 'triglycerides' OR 'tryglyceride') |
| **ClinicalTrials** | (Krill oil OR Fish oil) AND (LIPID OR TRIGLYCERIDE OR HDL OR LDL) |
| **ICTRP** | (Krill oil OR Fish oil) AND Cardiovascular Disease) AND (Lipid) |

**Table A. 2. Selected research**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Author,year of publication** | **Research article name** | **TC** | **TG** | **HDL -C** | **LDL - C** |
| 1 | Saleh AA. Alkhedhairi, 2022 | The effect of krill oil supplementation on skeletal muscle function and size in older adults: A randomised controlled trial | - | x | x | x |
| 2 | Joel L. Ramirez, 2019 | Fish Oil Increases Specialized Pro-resolving Lipid Mediators in PAD (The OMEGA-PAD II Trial) | - | x | x | x |
| 3 | S. Marlene Grenon, 2015 | Short-Term, High-Dose Fish Oil Supplementation Increases the Production of Omega-3 Fatty Acid-Derived Mediators in Patients With Peripheral Artery Disease (the OMEGA-PAD I Trial) | - | x | x | x |
| 4 | Michael R. Flock, 2013 | Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose–Response Randomized Controlled Trial | - | x | x | x |
| 5 | Berge K, 2014 | Krill oil supplementation lowers serum triglycerides without increasing low-density lipoprotein cholesterol in adults with borderline high or high triglyceride levels | - | x | - | - |
| 6 | Heather E.C. Hanwell, 2009 | Acute fish oil and soy isoflavone supplementation increase postprandial serum (n-3) polyunsaturated fatty acids and isoflavones but do not affect triacylglycerols or biomarkers of oxidative stress in overweight and obese hypertriglyceridemic men | - | - | x | - |
| 7 | Vanu R Ramprasath, 2013 | Enhanced increase of omega-3 index in healthy individuals with response to 4-week n-3 fatty acid supplementation from krill oil versus fish oil | - | x | x | x |
| 8 | VR Ramprasath, 2015 | Supplementation of krill oil with high phospholipid content increases sum of EPA and DHA in erythrocytes compared with low phospholipid krill oil | - | x | x | x |
| 9 | Jan Philipp Schuchardt, 2014 | Associations between Omega-3 Index increase and triacylglyceride decrease in subjects with hypertriglyceridemia in response to six month of EPA and DHA supplementation | - | x | x | x |
| 10 | Peter Angerer, 2002 | Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries | - | x | x | x |
| 11 | Barbosa MMDAL, 2017 | The benefits of ω-3 supplementation depend on adiponectin basal level and adiponectin increase after the supplementation: A randomized clinical trial. | - | x | x | x |
| 12 | PN Durrington, 2001 | An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia | - | x | x | x |
| 13 | Mahmoud Ebrahimi, 2009 | Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity | - | x | x | x |
| 14 | Samuel S. Gidding MD, 2014 | A double-blind randomized trial of fish oil to lower triglycerides and improve cardiometabolic risk in adolescents | - | x | x | x |
| 15 | Hill Alison M, 2007 | Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors | - | x | x | - |
| 16 | Syrah Khan, 2002 | Dietary long-chain n-3 PUFAs increase LPL gene expression in adipose tissue of subjects with an atherogenic lipoprotein phenotype | - | x | - | - |
| 17 | Tammy C Lee, 2014 | The impact of polyunsaturated fatty acid-based dietary supplements on disease biomarkers in a metabolic syndrome/diabetes population | - | x | x | x |
| 18 | Meilin Liu, 2001 | Effect of bread containing stable fish oil on plasma phospholipid fatty acids, triglycerides, HDL-cholesterol, and malondialdehyde in subjects with hyperlipidemia | - | x | x | - |
| 19 | Kevin C Maki, 2009 | Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women | - | x | x | x |
| 20 | Kevin C Maki, 2014 | A new, microalgal DHA- and EPA-containing oil lowers triacylglycerols in adults with mild-to-moderate hypertriglyceridemia | - | x | x | - |
| 21 | Barbara J Meyer, 2007 | Dose-Dependent Effects of Docosahexaenoic Acid Supplementation on Blood Lipids in Statin-Treated Hyperlipidaemic Subjects | - | x | x | x |
| 22 | Martin Petersen, 2002 | Effect of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients | - | x | x | x |
| 23 | Thomas AB Sanders, 2011 | Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial | - | x | x | x |
| 24 | Schuchardt JP, 2011 | Moderate doses of EPA and DHA from re-esterified triacylglycerols but not from ethyl-esters lower fasting serum triacylglycerols in statin-treated dyslipidemic subjects: Results from a six-month randomized controlled trial | - | x | x | x |
| 25 | Simao AN, 2014 | Effect of soy product kinako and fish oil on serum lipids and glucose metabolism in women with metabolic syndrome | - | x | x | x |
| 26 | P Singer, 2004 | Can n-3 PUFA reduce cardiac arrhythmias? Results of a clinical trial | - | x | x | x |
| 27 | Stine M Ulven, 2011 | Metabolic Effects of Krill Oil are Essentially Similar to Those of Fish Oil but at Lower Dose of EPA and DHA, in Healthy Volunteers | - | x | x | x |
| 28 | Venturini D, 2015 | Effects of extra virgin olive oil and fish oil on lipid profile and oxidative stress in patients with metabolic syndrome | - | x | x | x |
| 29 | Wu SY, 2014 | Fish-oil supplementation alters numbers of circulating endothelial progenitor cells and microparticles independently of eNOS genotype | - | x | - | x |
| 30 | Bo Yang, 2019 | Effects of n-3 fatty acid supplements on cardiometabolic profiles in hypertensive patients with abdominal obesity in Inner Mongolia: a randomized controlled trial | - | x | x | x |
| 31 | Welma Stonehouse, 2022 | Krill oil improved osteoarthritic knee pain in adults with mild to moderate knee osteoarthritis: a 6-month multicenter, randomized, double-blind, placebo-controlled trial | - | x | x | x |
| 32 | Dariush Mozaffarian, 2022 | Effectiveness of a Novel ω-3 Krill Oil Agent in Patients With Severe Hypertriglyceridemia: A Randomized Clinical Trial | - | x | - | - |
| 33 | Jessika M Lobraico, 2015 | Effects of krill oil on endothelial function and other cardiovascular risk factors in participants with type 2 diabetes, a randomized controlled trial | - | x | x | x |
| 34 | Essi S. Sarkkinen, 2018 | Prospective, randomized, double-blinded, placebo-controlled study on safety and tolerability of the krill powder product in overweight subjects with moderately elevated blood pressure | - | x | x | x |
| 35 | Suzuki Yoshio, 2016 | Krill Oil Improves Mild Knee Joint Pain: A Randomized Control Trial | - | x | x | x |
| 36 | Luke J Laffin, 2023 | Comparative Effects of Low-Dose Rosuvastatin, Placebo, and Dietary Supplements on Lipids and Inflammatory Biomarkers | - | x | x | x |
| 37 | Zhi-Hong Yang, 2020 | Supplementation with saury oil, a fish oil high in omega-11 monounsaturated fatty acids, improves plasma lipids in healthy subjects | - | x | x | x |
| 38 | F Sacks, 1995 | Controlled trial of fish oil for regression of human coronary atherosclerosis | - | x | x | x |
| 39 | D Franzen, 1993 | A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following ptca | - | x | x | x |
| 40 | C von Schacky, 1999 | The Effect of Dietary ω-3 Fatty Acids on Coronary Atherosclerosis A Randomized, Double-Blind, Placebo-Controlled Trial | - | x | x | x |
| 41 | Asma Zamanian, 2020 | The Effect of Omega-3 Fatty Acids Supplementation on the Improvement of Metabolic Syndrome in Patients with Ischemic Heart Disease: A Double-blind, Randomised, Placebo-controlled Trial | - | x | x | x |
| 42 | M C E Bragt, 2013 | Comparison of the effects of n-3 long chain polyunsaturated fatty acids and fenofibrate on markers of inflammation and vascular function, and on the serum lipoprotein profile in overweight and obese subjects | - | - | x | x |
| 43 | Amanda Rundblad, 2018 | Effects of krill oil and lean and fatty fish on cardiovascular risk markers: a randomised controlled trial | - | - | x | x |
| 44 | Mohammad Javad Zibaeenezhad, 2017 | Comparison of the effect of omega-3 supplements and fresh fish on lipid profile: a randomized, open-labeled trial | - | x | x | x |
| 45 | Dr Xiao Su, 2018 | Comparison of a 30-day krill oil and fish oil supplementation on plasma omega-3 polyunsaturated fatty acids, triglycerides and inflammatory biomarkers in healthy women | - | x | - | - |
| 46 | Dick C Chan, 2012 | ω-3 Fatty Acid Ethyl Esters Diminish Postprandial Lipemia in Familial Hypercholesterolemia | - | x | x | x |
| 47 | Cicero AFG, 2015 | Lipid-lowering and anti-inflammatory effects of omega 3 ethyl esters and krill oil: a randomized, cross-over, clinical trial | - | x | x | x |
| 48 | Ian G. Davies, 2012 | A Comparison Of Krill And Fish Oils In Metabolic Syndrome | - | x | x | x |
| 49 | Liania Alves Luzia, 2015 | Fish oil and vitamin E change lipid profiles and anti-LDL-antibodies in two different ethnic groups of women transitioning through menopause | x | x | x | x |
| 50 | Inar A Castro, 2007 | Effect of eicosapentaenoic/docosahexaenoic fatty acids and soluble fibers on blood lipids of individuals classified into different levels of lipidemia | x | x | x | x |
| 51 | Irina Ciubotaru, 2003 | Dietary fish oil decreases C-reactive protein, interleukin-6, and triacylglycerol to HDL-cholesterol ratio in postmenopausal women on HRT | x | x | x | x |
| 52 | Sani Hlais, 2013 | Combined Fish Oil and High Oleic Sunflower Oil Supplements Neutralize their Individual Effects on the Lipid Profile of Healthy Men | x | x | x | x |
| 53 | Nalini Kaul, 2008 | A Comparison of Fish Oil, Flaxseed Oil and Hempseed Oil Supplementation on Selected Parameters of Cardiovascular Health in Healthy Volunteers | x | x | x | x |
| 54 | Samantha L Logan, 2015 | Omega-3 Fatty Acid Supplementation for 12 Weeks Increases Resting and Exercise Metabolic Rate in Healthy Community-Dwelling Older Females | - | x | - | - |
| 55 | Inger Ottestad, 2012 | Fish Oil Supplementation Alters the Plasma Lipidomic Profile and Increases Long-Chain PUFAs of Phospholipids and Triglycerides in Healthy Subjects | x | x | x | x |
| 56 | Raija L Tahvonen, 2005 | Black currant seed oil and fish oil supplements differ in their effects on fatty acid profiles of plasma lipids, and concentrations of serum total and lipoprotein lipids, plasma glucose and insulin | x | x | x | x |
| 57 | Baukje de Roos, 2020 | The nutritional and cardiovascular health benefits of rapeseed oil-fed farmed salmon in humans are not decreased compared with those of traditionally farmed salmon: a randomized controlled trial | x | x | x | x |
| 58 | Barbora K, 2020 | Lipid Profile, Lipoprotein Subfractions, and Fluidity of Membranes in Children and Adolescents with Depressive Disorder: Effect of Omega-3 Fatty Acids in a Double-Blind Randomized Controlled Study | x | x | x | x |
| 59 | Sebastian Jannas-Vela, 2020 | Resting metabolic rate and skeletal muscle SERCA and Na+/K+ ATPase activities are not affected by fish oil supplementation in healthy older adults | x | x | x | x |
| 60 | Cassandra Sparkes, 2018 | Effect of Low Dose Docosahexaenoic Acid-Rich Fish Oil on Plasma Lipids and Lipoproteins in Pre-Menopausal Women: A Dose–Response Randomized Placebo-Controlled Trial | - | x | - | - |
| **TOTAL** | | | | | | |
| **60** |  |  | **10** | **57** | **53** | **50** |

**Table A. 3. Expected analysis methods**

|  |  |  |
| --- | --- | --- |
| **Analysis step** | **Tool/function (#) used** | **Tool/function (#) used** |
| Sort data / Calculate comparison in pairs | **pairwise ()** | Convert datasets from long branch format to contrast-based format and to calculate all comparison processing. |
| Multi-branch testing processing | **subset ()** | Handling multi-branch tests, variance structure: A random impact model can be defined with the assumption of general heterogeneous variance τ2 for each intervention comparison. These estimates are similar to those obtained by weighted maximum probability1.2) [1] [2]. |
| Key analysis | **netmeta ()** | To build NMA graphical network results (graph network), which gives continuous results - TC, TG, HDL - C, LDL - C. Crippa and Orsini methods [3] for continuous analysis of data. |
| Additional analysis | **decomp.design ()\*** | Assessing heterogeneity and inconsistency Mantel and Haenszel's meta-methodology [4] for the team's binary variable analysis for estimation  Relative treatment efficacy (OR) and corresponding error standard number from each study.  Overall measurement statistics heterogeneity/inconsistency in the network through Q-total separation [5]. |
| **netsplit ()\*/forest.nets**  **plit () netheat () give 'netmeta' object** | Forest plot generation gives evaluation inconsistent results – Net heat graph [5] in randomization.  The model was evaluated using a node decomposition design model [6]. |
| **funnel.netmeta ()** | Create funnel charts [7] of published results that bias evaluation. Egger test regression testing [8] is used to test asymmetries in funnel diagrams. When z has a score of ≥ 1.96 or ≤ -1.96, the impact is significant (p < 0.05). |
| Presentation of results | **netgraph ()** | Evidence visualization. |
|  | **direct.evidence.plot ()** | Visualization of direct and indirect evidence. |
|  | **forest.netmeta ()/fores t.netcomb ()**  **netleague ()\*** | Create forest plots and League tables [9] to analyze the network chart. |
|  | **netrank ()\***  **rankogram ()\*** | Treatment ratings indicate which treatments are used that are likely to be beneficial. The P-score is equivalent to the SUCRA score [10]. |
| #: Use the functions of R, in the {netmeta} package described in the tutorial  \*: At least one of the print/chart/summary functions available [11] | | |

**References Table A.3**

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**Table A. 4. Research features**

Notes: Triglyceride (TG), Low-density lipoprotein cholesterol (LDL), High-density lipoprotein cholesterol (HDL), Total-cholesterol (TC)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Author Name, year of release** | **Location** | **Time** | **Intervention 1** | **Intervention 2** | **Intervention 3** | **Result** |
| 1 | Saleh AA. Alkhedhairi, 2022 [1] | Glasgow  (Scotland, England) | 6 months | Oil Testimony  (mixed vegetable oils (a mixture of olive oil (pure, cold-pressed), corn oil (refined), palm kernel oil (refined) and medium-chain triglycerides, in a ratio of 4:4:3:2). The total LCn-3PUFA content of the control supplement was 4 mg/g,  EPA + DHA intake < 1mg/g | Krill oil  (SuperbaBoost™)  Dosage form: capsules  The total LCn-3PUFA content of krill oil supplements are 322 mg/g  Dosage  EPA + DHA intake: 289 mg/g |  | TG  LDL  HDL |
| 2 | Joel L. Ramirez, 2019 [2] | San Francisco  (US) | 3 months | Fish oil  ProOmega Capsules (Ultimate Omega)  Dosage  EPA+DHA 550mg | Placebo  Soybeans (Nordic Naturals) |  | TG  LDL  HDL |
| 3 | S. Marlene Grenon, 2015  [3] | San Francisco  (US) | 1 months | Fish oil  (Capsules Pro‐Omega)  Dosage  EPA + DHA  550mg | Placebo  (capsule) |  | TG  LDL  HDL |
| 4 | Michael R. Flock, 2013 [4] | America | 5 months | Fish oil  Dosage  EPA + DHA absorption 33%  (20% EPA (20:5, n-3), 13% DHA (22:6, n-3), 17% palmitic acid (16:0), 14% oleic acid (18:1, n-9), 8% palmitoleic acid (16:1, n-7), 8% myristic acid (14:0), 4% stearic acid (18:0), 4% eicosadienoic acid (20:2, n-6), and small amounts of other fatty acids.) | Soybean oil  (53% linoleic acid (18:2, n-6), 23% oleic acid, 10% palmitic acid, 6% alpha-linolenic acid (18:3, n-3), 4% stearic acid (18:0) and another small amount of FA.) |  | TG  LDL  HDL |
| 5 | Berge K, 2014  [5] | America | 12 weeks | 0.5g; 1g; 2g; 4g Krill oil  Daily intake of EPA + DHA: 100, 200, 400 and 800 mg/day | placebo  Daily intake of EPA + DHA: 0mg/day |  | TG |
| 6 | Heather E.C. Hanwell 2009 [6] | Canada | 4 days | fish oil (FO)  A total dose of 7.0 g of refined fish oil contains 2.8 g of EPA and 1.4 g of DHA | Placebo |  | HDL |
| 7 | Vanu R Ramprasath, 2013 [7] | Canada | 30 weeks | Fish oil  The daily dose of both krill and fish oil treatments provides 600 mg of n-3 PUFAs (of which EPA 337mg + DHA 188mg) | Krill oil  The daily dose of both krill and fish oil treatments provides 600 mg n-3 PUFA (including EPA 320mg + DHA 207mg) | Corn oil (Placebo) | TG  LDL  HDL |
| 8 | VR Ramprasath, 2015 [8] | Canada | 4 weeks | Low Phospholipid Krill Oil  1.5 g/day (including 320mg EPA + 207mg DHA | High Phospholipid Krill Oil  3 g/day (including 337mg EPA + 188mg DHA | Placebo  (corn oil) | TG  LDL  HDL |
| 9 | Jan Philipp Schuchardt, 2014 [9] | Germany | 6 months | EE fish oil  Dose: EPA + DHA: 1008 mg EPA and 672 mg DHA | Corn Oil (Placebo Capsules  contains corn oil and is superficially identical to n-3 PUFA capsules in all respects) | rTAG fish oil  Dose: 1008 mg EPA and 672 mg DHA | TG  LDL  HDL |
| 10 | Peter Angerer, 2002 [10] | Munich, Germany | 2 years | Fish oil  In the first 3 months, six tablets,  EPA + DHA dosage consumed: 3.3g  and for the next 21 months, 3 capsules, EPA+DHA dosage of 1.65g | Placebo  Each capsule contains 1 g of fatty acid mixture.  (Placebo) |  | TG  LDL  HDL |
| 11 | Barbosa MMDAL, 2017  [11] | São Paulo, Brazil | 2 months | Fish oil  (3.0 grams/day; EPA+DHA intake dose  37% EPA + DHA 23%) | Placebo  (3.0 grams/day; sunflower oil, with 65% linoleic acid [ω-6]) |  | TG  LDL  HDL |
| 12 | PN Durrington, 2001 [12] | Manchester, English | 48 weeks | Fish oil  (a concentrated preparation of  omega-3 PUFA)  Dosage of EPA+DHA absorbed  44% EPA and  36% DHA with a dose of 2g x 2 times  daily | Corn Oil |  | TG  LDL  HDL |
| 13 | Mahmoud Ebrahimi, 2009 [13] | Mashhad, Iran | 6 months | Fish Oil Capsules  Dosage of EPA+DHA absorbed  300mg | Placebo  (do the same but do not add ω-3 fatty acids) |  | TG  LDL  HDL |
| 14 | Samuel S. Gidding MD, 2014 [14] | US | 8 weeks | EE Fish Oil Capsules  Dosage: 4g per day including 1.5g DHA + 1.86 g EPA | Corn oil |  | TG  LDL  HDL |
| 15 | Hill Alison M, 2007 [15] | Australia | 12 weeks | Tuna oil (Hi-DHA; Nu-Mega Ingredients Pty Ltd, Brisbane, Australia)  Dose: total EPA+DHA  is 320 mg in each 1 g capsule | Sunflower oil  6g/day |  | TG  HDL |
| 16 | Syrah Khan, 2002 [16] | West Berkshire, English | 6 weeks | Fish oil  (Pikasol, EPAX 5500 TG, Pronova, Norway)  6g in six 1g capsules  Dosage of EPA+DHA absorbed  50% EPA+DHA | Olive Oil  (Pronova, Norway)  6g/day |  | TG |
| 17 | Tammy C Lee, 2014 [17] | US | 8 weeks | Corn oil  (control group) |  | Fish oil  9 FO tablets daily | TG  LDL  HDL |
| 18 | Meilin Liu, 2001 [18] | Sweden | 4 weeks | The bread contains fish oil with oat fiber  (LEVA, Pågens, Malmo¨, Sweden) daily contains 1.3 g  Completely stabilized fish oil (0.5 g omega-3 fatty acids).  Dosage of EPA+DHA absorbed  31% EPA+DHA | The bread has only oat fiber  The amount of fiber in bread is 10g per 100g of bread |  | TG  HDL |
| 19 | Kevin C Maki, 2009 [19] | US | 4 weeks | PL krill oil (Superba krill oil, Aker  BioMarine ASA, Oslo, Norway)  2g/day  Dosage: total EPA+DHA 306mg | Olive oil  (control group)  Consume four 500 mg capsules per day |  | TG  LDL  HDL |
| 20 | Kevin C Maki, 2014 [20] | US | 14 weeks | Corn/soybean oil (ratio 1:1)  Each tablet is administered as 4 - 1 g soft capsules at a time  day  (vegetable oil mixture) | Fish oil (EPAX™6000 AS, Oslo,  Norway)  Each tablet is administered as 4 - 1 g soft capsules at a time  day  Dosage: EPA+DHA 494mg |  | TG  HDL |
| 21 | Barbara J Meyer 2007 [21] | Australia | 6 months | Tuna oil rich in DHA (HiDHA, Clover Cor-  meal; 7% EPA, 27% DHA; 4g/day, providing 1.08g/day DHA) | DHA-rich tuna oil (8g/day, pro-  providing 2.16g/day DHA) | olive oil (control), half on 4g/day and half on 8g/day) | TG  LDL  HDL |
| 22 | Martin Petersen 2002 [22] | Denmark | 8 weeks | Fish oil:  4 capsules daily (Futura 1000; Dansk Droge) (4 g fish oil contains 2.6 g [EPA] and [DHA]) | corn oil  4 tablets per day. |  | TG  LDL  HDL |
| 23 | Thomas AB Sanders 2011 [23] | London, England | 12 months | n−3 LC-PUFA (Fish Oil) packaged in 3 different doses (0.45, 0.9 and 1.8 g/day) | Placebo: Olive oil |  | TG  LDL  HDL |
| 24 | Schuchardt JP, 2011 (2) [24] | Germany | 6 months | Fish oil (EE form)  Dosage: 1.01 g EPA + 0.67 g DHA | Fish oil (rTAG form)  Dosage: 1.01 g EPA + 0.67 g DHA | Placebo (corn oil)  Dosage: 1.01 g EPA + 0.67 g DHA | TG  LDL  HDL |
| 25 | Simao AN 2014  [25] | Brazil | 90 days | Fish oil: get 3 g/day of fish oil n-3 fatty acids (10 capsules)  Each fish oil capsule contains 180 mg EPA and 120 mg DHA derived from sardines. | Control group: only eat a normal diet |  | TG  LDL  HDL |
| 26 | P Singer 2004 [26] | Germany | 6 months | Fish oil: 3g/day  fish oil; 18% eicosapentaenoic acid (EPA), 12%  docosahexaenoic acid (DHA) | Placebo: Olive oil 3g/day |  | TG  LDL  HDL |
| 27 | Stine M Ulven 2011 [27] | Norway | 7 weeks | Krill Oil PL: The daily study dose was six capsules (500 mg oil capsule each); Each capsule provides 90.5 mg EPA and DHA, and a total of 103.5 mg n-3 PUFA | Fish Oil: The daily study dose was three capsules, each containing 600 mg of fish oil providing 288 mg of EPA and DHA, and a total of 330 mg of n-3 PUFA. | Control (no additions) | TG  LDL  HDL |
| 28 | Venturini D 2015 [28] | Brazil | 90 days | Fish oil: get 3 g/day of fish oil n-3 fatty acids (10 capsules)  Each fish oil capsule contains 180 mg EPA and 120 mg DHA derived from sardines | Control group: only instructed to maintain a normal diet. |  | TG  LDL  HDL |
| 29 | Wu SY 2014 [29] | London, England | 8 weeks | Fish oil in TG form  Dosage: 3 tablets/day (EPAX 6000 TG; EPAX), providing a total daily dose of 0.9 g EPA + 0.6 g DHA) | Placebo capsules:  corn oil (mainly composed of 54% linoleic, 29% oleic and 12% palmitic acid) (EPAX) |  | TG  LDL |
| 30 | Bo Yang 2019 [30] | China | 12 weeks | Fish oil (FO) 2g/day  Dosage: total EPA + DHA is 2000mg/day | Flaxseed oil (FLO) 2.5g/day  Each FLO tablet contains 630 mg of ALA |  | TG  LDL  HDL |
| 31 | Welma Stonehouse 2022 [31] | Australia | 6 months | 4 capsules/day krill oil [providing a total of 0.88g/day EPA + DHA (0.60g EPA, 0.28g DHA) and 0.45g astaxanthin] | Placebo: contained 1g of mixed vegetable oil (olive oil, corn oil, palm oil and medium-chain triglycerides) consisting of 31% SFAs, 46% MUFA and 22% PUFA, with no possible EPA or DHA detectable |  | TG  LDL  HDL |
| 32 | Dariush Mozaffarian, 2022 [32] | US, Canada, Mexico | 26 weeks | Krill oil  Dosage: total 1.24 g/day EPA + DHA as FFA or PL | Placebo |  | TG |
| 33 | Jessika M Lobraico, 2015  [33] | US | 17 weeks | daily krill oil capsule contains 1000 mg of ω-3 fatty acids | Placebo: olive oil capsules |  | TG  LDL  HDL |
| 34 | Essi S. Sarkkinen, 2018  [34] | Finland | 8 weeks | Krill oil  FFA form (4 tablets/day, providing a dose of 4 g per day) | Placebo  (corn flour) |  | TG  LDL  HDL |
| 35 | Suzuki Yoshio, 2016 [35] | Japan | 30 days | Krill oil - PL  Dosage: 8 tablets/day, each day providing 240 mg EPA + 110 mg DHA) | Placebo capsules 9  (safflower oil) |  | TG  LDL  HDL |
| 36 | Luke J Laffin, 2023 [36] | US | 10 years | Fish oil  Dosage: Nature Made™ 1200mg, 2 soft gels/days) | Placebo  rosuvastatin 5 mg daily |  | TG  LDL  HDL |
| 37 | Zhi-Hong Yang, 2020 [37] | US | 8 weeks | Mackerel oil  Dosage: per day 0.76g EPA + 1.41 DHA | Control oil (sardine and olive oil blend; 4.9 g shorter chain MUFA oleate and 3 g omega-3 FA) |  | TG  LDL  HDL |
| 38 | F M Sacks, 1995  [38] | US | 28 months | Fish oil  Dosage: 12 tablets/days, Each tablet contains a total of 400mg EPA + DHA | Placebo capsules (olive oil) |  | TG  LDL  HDL |
| 39 | D Franzen, 1993 [39] | Germany | 4 months | fish oil  3.15 g omega-3 fatty acids | Placebo capsules contained olive oil |  | TG  LDL  HDL |
| 40 | C von Schacky, 1999 [40] | Germany | 24 months | Fish oil form EE  Dosage: 9 capsules per day = 9 g fish oil/days, 3.15 g omega-3 fatty acids days, 19 +15) | Placebo  Dosage: 70% oleic acid, 15% linoleic and palmitic acids |  | TG  LDL  HDL |
| 41 | Asma Zamanian, 2020 [41] | Iran | 12 weeks | Fish oil  Dosage: 3 tablets per day, each tablet includes  180 mg EPA and 120 mg DHA | Placebo:  Capsules contain gelatin |  | TG  LDL  HDL |
| 42 | M C E Bragt, 2013 [42] | Netherlands | 6 weeks | Fish oil  Dosage: 8 tablets per day (Marinol C-38™, Lipid Nutrition, Wormerveer, Netherlands), providing approximately 3.7 g/days n-3 LCPUFA (1.7 g/days EPA and 1.2 g/days DHA,) and 2 placebo-like fenofibrate tablets (200 mg/days cellulose | fenofibrate capsules matched to placebo (200 mg/days cellulose) |  | LDL  HDL |
| 43 | Amanda Rundblad 2018  [43] | Norway | 8 weeks | Krill oil  8 capsules per day (RIMFROST Sublime ®, lot 11335; Rimblast AS)  The amount of n -3 marine fatty acids consumed per week from krill oil was 4654 mg | Lean fish meal (140g cod fillet, fatty fish containing 140g salmon fillet and a fatty fish sandwich containing 66g mackerel)  The amount of marine n -3 fatty acids consumed per week from fish provided was 4103 mg | high oleic sunflower oil (HOSO) | LDL  HDL |
| 44 | Mohammad Javad Zibaeenezhad, 2017 [44] | Iran |  | Dietary fish requires consuming 250 g of farmed salmon (contains 1.4 g omega-3 (280 mg EPA and 160 mg DHA) per 100 g)  Consumed 14 g omega-3 [2.8 g EPA and 1.6 g DHA] per weeks) while they were advised not to take fish oil supplements during the intervention period. | Fish oil  2 g omega-3 supplement (containing 180 mg EPA and 120 mg DHA per softgel) per day (Equivalent to consuming 14 g omega-3 [2.5 g EPA and 1.7 g DHA] per week) |  | TG  LDL  HDL |
| 45 | Dr Xiao Su, 2018 [45] | Australia | 30 days | Krill oil  Dose: 1,269 mg total LC n-3 PUFA (EPA, DHA and DPA) | Fish oil  Dose: 1,441 mg total LC n-3 PUFA (EPA, DHA and DPA) |  | TG |
| 46 | Dick C Chan, 2012 [46] | Australia | 8 weeks | Fish oil ethyl ester form  Dose: 4 g/days ω-3 FAEE (Omacor, 46% EPA and 38% DHA in ethyl ester form; Abbott Products Pty Ltd) | Do not interfere |  | TG  LDL  HDL |
| 47 | Cicero AFG, 2015 [47] | Italy | 4 weeks | Fish oil ethyl ester form  Each 1000 mg omega 3 ethyl ester PUFAs capsule contains at least 85% EPA and DHA, with an EPA/DHA ratio of 0.9–1.5; | Krill oil  Dosage: 2 capsules per day, each krill oil capsule has 75mg EPA and 45mg DHA. |  | TG  LDL  HDL |
| 48 | Ian G. Davies, 2012 [48] | England | 6 weeks | Fish oil  Dose received: 390 mg EPA/DHA (4 capsules) | Krill oil - PL  Dose received: 580 mg EPA/DHA (1 capsule) |  | TG  LDL  HDL |
| 49 | Liania Alves Luzia, 2015 [49] | Brazil | 3 months | Fish oil (600 mg EPA and 400 mg DHA per day) | Placebo (contains mineral oil) |  | TG  LDL  HDL  TC |
| 50 | Inar A Castro, 2007 [50] | Brazil | 6 weeks | Fish oil (460 mg EPA + DHA) | Placebo |  | TG  LDL  HDL  TC |
| 51 | Irina Ciubotaru, 2003 [51] | Greensboro (US) | 5 weeks | Fish oil (EPA +DHA 2,18 g) | Placebo (Safflower Oil) |  | TG  LDL  HDL  TC |
| 52 | Sani Hlais, 2013 [52] | England | 6 weeks và 12 weeks | Fish oil (1382 mg EPA + DHA | Placebo (High oleic sunflower oil (8 g/days)) |  | TG  LDL  HDL  TC |
| 53 | Nalini Kaul, 2008 [53] | Canada | 6 weeks và 12 weeks | Fish oil (594 mg EPA + DHA) | Placebo included: sunflower oil (2g/days), flaxseed oil (2g/days), hempseed oil (2g/days) |  | TG  LDL  HDL  TC |
| 54 | Samantha L, Logan 2015 [54] | Canada |  | Fish oil (3000 mg EPA + DHA) | Placebo (olive oil) |  | TG |
| 55 | Inger Ottestad, 2012 [55] | Norway | 3 weeks | Fish oil (0,7 g EPA + 0,9 g DHA) | Sunflower oil (8g/days) |  | TG  LDL  HDL  TC |
| 56 | Raija L, Tahvonen 2005 [56] | Finland | 4 weeks | Fish oil (644 mg DHA + EPA) | Black currant seed oil (3g/days: 500mg capsules, 6 capsules/days) |  | TG  LDL  HDL  TC |
| 57 | Baukje de Roos, 2020 [57] | England | 18 weeks | Fish oil (900mg/days EPA + DHA) | Canola oil (400mg/days) |  | TG  LDL  HDL  TC |
| 58 | Barbora K, 2020 [58] | Slovakia | 6 weeks và 12 weeks | Fish oil (1000mg EPA + 750 mg DHA) | Sunflower oil (2467 mg omega-6 linoleic acid) |  | TG  LDL  HDL  TC |
| 59 | Sebastian Jannas-Vela, 2020 [59] | Canada | 12 weeks | Fish oil (2g EPA + 1g DHA/days | Olive oil (5g/days: 1g contains 66% oleic acid, 9% palmitic acid and 4% linoleic acid |  | TG  LDL  HDL  TC |
| 60 | Cassandra Sparkes, 2018 [60] | Australia |  | Fish oil triglycerides (810 mg DHA and 210 mg EPA) | Placebo (Sunola oil) |  | TG |

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**Table A. 5. Research quality**

| **Pedro criteria**  **Research rescue** | **Total score Pedro** | **Quality** | **1/ Eligibility\*** | **2/ Random allocation** | **3/ Concealed allocation** | **4/ Baseline comparability** | **5/ Blind subject** | **6/ Blind therapist** | **7/ Blind assessor** | **8/ Adequate follow-up** | **9/Intention-to-treat analysis** | **10/ Between-group comparisons** | **11/ Point estimate variability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Saleh AA. Alkhedhairi, 2022 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Joel L. Ramirez, 2019 | 8/10 | Good | X | X | X | X | X | X | O | O | X | X | X |
| S. Marlene Grenon, 2015 | 8/10 | Good | X | X | O | X | X | X | O | X | X | X | X |
| Michael R. Flock, 2013 | 7/10 | Good | X | O | X | X | X | X | O | X | O | X | X |
| Berge K, 2014 | 7/10 | Good | X | X | O | X | X | X | O | X | O | X | X |
| Heather E.C. Hanwell 2009 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Vanu R Ramprasath, 2013 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| VR Ramprasath, 2015 | 7/10 | Good | X | X | X | O | X | X | O | X | O | X | X |
| Jan Philipp Schuchardt, 2014 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |
| Peter Angerer, 2002 | 9/10 | Excellent | X | X | X | X | X | X | X | O | X | X | X |
| Barbosa MMDAL, 2017 | 9/10 | Excellent | X | X | X | X | X | X | X | X | O | X | X |
| P N Durrington, 2001 | 8/10 | Good | X | X | X | X | X | X | O | O | X | X | X |
| Mahmoud Ebrahimi, 2009 | 7/10 | Good | X | X | X | X | O | O | O | X | X | X | X |
| Samuel S. Gidding MD, 2014 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Alison M Hill, 2007 | 5/10 | Fair | X | O | X | X | O | O | O | X | O | X | X |
| Syrah Khan, 2002 | 7/10 | Good | X | O | O | X | X | X | O | X | X | X | X |
| Tammy C Lee, 2016 | 6/10 | Good | X | X | X | X | X | O | O | O | O | X | X |
| Meilin Liu, 2001 | 7/10 | Good | X | X | X | X | O | O | O | X | X | X | X |
| Kevin C Maki, 2009 | 8/10 | Good | X | X | O | X | X | X | O | X | X | X | X |
| Kevin C Maki, 2014 | 8/10 | Good | X | X | O | X | X | X | O | X | X | X | X |
| Barbara J Meyer 2007 | 5/10 | Fair | X | X | O | X | O | O | O | X | O | X | X |
| Martin Petersen 2002 | 7/10 | Good | X | X | X | O | X | X | O | X | O | X | X |
| Thomas A B Sanders 2011 | 9/10 | Excellent | X | X | X | X | X | X | X | O | X | X | X |
| Simao AN 2014 | 6/10 | Good | X | X | X | O | X | O | O | X | O | X | X |
| P Singer 2004 | 7/10 | Good | X | X | O | O | X |  | O | X | X | X | X |
| Stine M Ulven 2011 | 6/10 | Good | X | X | O | X | O | O | O | X | X | X | X |
| Venturini D 2015 | 6/10 | Good | X | X | X | X | X | O | O | O | O | X | X |
| Wu SY 2014 | 8/10 | Good | X | X | X | X | X | X | O | X | O | X | X |
| Bo Yang 2019 | 10/10 | Excellent | X | X | X | X | X | X | X | X | X | X | X |
| Welma Stonehouse 2022 | 10/10 | Excellent | X | X | X | X | X | X | X | X | X | X | X |
| Dariush Mozaffarian, 2022 | 8/10 | Good | X | X | O | X | X | X | O | X | X | X | X |
| Jessika M Lobraico, 2015 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |
| Essi S. Sarkkinen, 2018 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |
| Yoshio Suzuki, 2016 | 8/10 | Good | X | X | X | X | X | X | O | X | O | X | X |
| Luke J Laffin, 2023 | 8/10 | Good | X | X | X | X | X | O | O | X | X | X | X |
| Zhi-Hong Yang, 2020 | 7/10 | Good | X | X | O | X | X | X | O | O | X | X | X |
| F M Sacks, 1995 | 10/10 | Excellent | X | X | X | X | X | X | X | X | X | X | X |
| D Franzen, 1993 | 9/10 | Excellent | X | X | X | X | X | O | X | X | X | X | X |
| C von Schacky, 1999 | 8/10 | Good | X | X | X | X | X | X | O | O | X | X | X |
| Asma Zamanian 2020 | 10/10 | Excellent | X | X | X | X | X | X | X | X | X | X | X |
| M C E Bragt, 2013 | 7/10 | Good | X | X | X | O | X | X | O | O | X | X | X |
| J P Schuchardt 2011 (2) | 10/10 | Excellent | X | X | X | X | X | X | X | X | X | X | X |
| Amanda Rundblad 2018 | 4/10 | Fair | X | X | O | O | O | O | O | X | O | X | X |
| Mohammad Javad Zibaeenezhad, 2017 | 6/10 | Good | X | X | O | O | O | X | X | X | O | X | X |
| Dr Xiao Su, 2018 | 5/10 | Fair | X | X | O | X | O | O | O | X | O | X | X |
| Dick C Chan, 2012 | 5/10 | Fair | X | X | O | O | X | O | O | X | O | X | X |
| Cicero AFG, 2015 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Ian G. Davies, 2012 | 4/10 | Fair | X | X | O | O | X | O | O | O | O | X | X |
| Liania Alves Luzia 2015 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |
| Inar A Castro 2007 | 8/10 | Good | X | X | X | X | X | X | O | O | X | X | X |
| Irina Ciubotaru 2003 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Sani Hlais 2013 | 7/10 | Good | X | X | X | X | X | O | O | X | O | X | X |
| Nalini Kaul 2008 | 9/10 | Excellent | X | X | X | X | X | X | O | X | X | X | X |
| Samantha L Logan 2015 | 6/10 | Good | X | O | O | X | X | O | O | X | X | X | X |
| Inger Ottestad 2012 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |
| Raija L Tahvonen 2005 | 7/10 | Good | X | X | O | X | X | X | O | X | O | X | X |
| Baukje de Roos 2020 | 5/10 | Fair | X | O | O | X | X | O | O | X | O | X | X |
| Barbora K, 2020 | 9/10 | Excellent | X | X | X | X | X | X | X | X | O | X | X |
| Sebastian Jannas-Vela 2020 | 7/10 | Good | X | X | O | X | X | X | O | X | O | X | X |
| Cassandra Sparkes 2018 | 7/10 | Good | X | X | X | X | X | X | O | O | O | X | X |

**Table A. 6. Net graph results of TC index**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of studies: k = 66  Number of pairwise comparisons: m = 84  Number of treatments: n = 13  Number of designs: d = 16  Random effects model  Treatment estimate (sm = 'MD', comparison: other treatments vs 'Placebo'): | | | | |
|  | MD | 95%-CI | z | p-value |
| FO - EE <2 | 0.0473 | [-0.1522; 0.2468] | 0.46 | 0.6424 |
| FO - EE >3 | -0.5161 | [-0.7878; -0.2443] | -3.72 | 0.0002 |
| FO - EM <2 | -0.0556 | [-0.4306; 0.3195] | -0.29 | 0.7716 |
| FO - rTAG <2 | -0.2143 | [-0.5010; 0.0724] | -1.47 | 0.1429 |
| FO - TG <2 | -0.0649 | [-0.2789; 0.1490] | -0.59 | 0.5520 |
| FO - TG <3 | -0.1600 | [-1.4549; 1.1349] | -0.24 | 0.8086 |
| FO <2 | -0.0127 | [-0.1180; 0.0926] | -0.24 | 0.8128 |
| FO <3 | 0.0315 | [-0.1376; 0.2006] | 0.37 | 0.7150 |
| FO >3 | 0.2289 | [-0.0299; 0.4878] | 1.73 | 0.0830 |
| KO - HPL <2 | 0.2600 | [-0.3535; 0.8735] | 0.83 | 0.4061 |
| KO - LPL <2 | 0.2100 | [-0.4559; 0.8759] | 0.62 | 0.5365 |
| KO <2 | 0.0707 | [-0.0738; 0.2151] | 0.96 | 0.3378 |
| Placebo | . | . | . | . |
| Quantifying heterogeneity / inconsistency: | | | | |
| **tau2 = 0.0347** | **tau = 0.1864** | **I2= 59.5% [46.7%; 69.2%]** | | |
| Tests of heterogeneity (within designs) and inconsistency (between designs): | | | | |
|  | | Q | d.f. | p-value |
| Total | | **155.43** | 63 | < 0.0001 |
| Within designs | | 85.71 | 55 | 0.0050 |
| Between designs | | 69.72 | 8 | < 0.0001 |

**Table A. 7. Net graph results of TG index**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of studies: k = 57  Number of pairwise comparisons: m = 98  Number of treatments: n = 14  Number of designs: d = 18  Random effects model  Treatment estimate (sm = 'MD', comparison: other treatments vs 'Placebo'): | | | | |
|  | MD | 95%-CI | z | p-value |
| FO - EE < 2 | -0.2509 | [-0.4067; -0.0952] | -3.16 | 0.0016 |
| FO - EE > 3 | -0.4310 | [-0.6510; -0.2110] | -3.84 | 0.0001 |
| FO - EM < 2 | -0.0191 | [-0.2532; 0.2150] | -0.16 | 0.8730 |
| FO - rTAG < 2 | -0.1685 | [-0.3703; 0.0333] | -1.64 | 0.1017 |
| FO - TG < 2 | -0.2022 | [-0.3650; -0.0395] | -2.44 | 0.0149 |
| FO - TG < 3 | -0.4400 | [-0.8524; -0.0276] | -2.09 | 0.0365 |
| FO < 2 | -0.1966 | [-0.2704; -0.1228] | -5.22 | < 0.0001 |
| FO < 3 | -0.2677 | [-0.4033; -0.1320] | -3.87 | 0.0001 |
| FO > 3 | -0.1692 | [-0.3665; 0.0280] | -1.68 | 0.0927 |
| KO - HPL < 2 | -0.0800 | [-0.4961; 0.3361] | -0.38 | 0.7063 |
| KO - LPL < 2 | -0.0100 | [-0.4174; 0.3974] | -0.05 | 0.9616 |
| KO – PL/FFA <3 | -1.2400 | [-2.1991; -0.2809] | -2.53 | 0.0113 |
| KO < 2 | -0.2500 | [-0.3238; -0.1763] | -6.64 | < 0.0001 |
| Placebo | . | . | . | . |
| Quantifying heterogeneity / inconsistency: | | | | |
| tau2 = 0.0189 | tau = 0.1375 | **I2= 84.3% [80.9%; 87.0%]** | | |
| Tests of heterogeneity (within designs) and inconsistency (between designs): | | | | |
|  | | Q | d.f. | p-value |
| Total | | **489.09** | 77 | **< 0.0001** |
| Within designs | | **449.18** | 68 | **< 0.0001** |
| Between designs | | **39.92** | 9 | **< 0.0001** |

**Table A. 8. Rankogram results of TC index**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| FO - EE <2 | 0.00 | 0.01 | 0.03 | 0.06 | 0.09 | 0.09 | 0.10 | 0.11 | 0.15 | 0.20 | 0.10 | 0.05 | 0.01 |
| **FO - EE >3** | **0.63** | 0.31 | 0.04 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - EM <2** | 0.02 | 0.09 | 0.15 | **0.16** | 0.09 | 0.08 | 0.05 | 0.07 | 0.08 | 0.10 | 0.07 | 0.04 | 0.02 |
| **FO - rTAG <2** | 0.04 | **0.31** | 0.34 | 0.14 | 0.06 | 0.04 | 0.02 | 0.02 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 |
| **FO - TG <2** | 0.00 | 0.07 | 0.18 | **0.20** | 0.17 | 0.11 | 0.07 | 0.08 | 0.05 | 0.04 | 0.03 | 0.01 | 0.00 |
| **FO - TG <3** | **0.29** | 0.13 | 0.08 | 0.04 | 0.02 | 0.02 | 0.02 | 0.02 | 0.03 | 0.04 | 0.05 | 0.09 | 0.18 |
| FO <2 | 0.00 | 0.01 | 0.03 | 0.13 | 0.19 | 0.19 | 0.18 | 0.13 | 0.09 | 0.04 | 0.02 | 0.01 | 0.00 |
| FO <3 | 0.00 | 0.01 | 0.03 | 0.07 | 0.11 | 0.12 | 0.11 | 0.12 | 0.16 | 0.13 | 0.09 | 0.04 | 0.00 |
| FO >3 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.01 | 0.02 | 0.03 | 0.06 | 0.10 | 0.25 | 0.31 | 0.21 |
| KO - HPL <2 | 0.01 | 0.02 | 0.04 | 0.05 | 0.03 | 0.03 | 0.04 | 0.03 | 0.04 | 0.07 | 0.12 | 0.21 | 0.31 |
| KO - LPL <2 | 0.01 | 0.05 | 0.07 | 0.07 | 0.04 | 0.04 | 0.04 | 0.03 | 0.04 | 0.06 | 0.11 | 0.17 | 0.27 |
| KO <2 | 0.00 | 0.00 | 0.01 | 0.03 | 0.04 | 0.07 | 0.11 | 0.15 | 0.20 | 0.20 | 0.14 | 0.05 | 0.01 |
| Placebo | 0.00 | 0.00 | 0.01 | 0.05 | 0.14 | 0.21 | 0.26 | 0.21 | 0.09 | 0.03 | 0.01 | 0.00 | 0.00 |

**Table A. 9. Rankogram results of TG index**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
| FO - EE < 2 | 0.00 | 0.02 | 0.09 | 0.18 | 0.14 | 0.14 | 0.12 | 0.13 | 0.10 | 0.06 | 0.03 | 0.01 | 0.00 | 0.00 |
| **FO - EE > 3** | 0.03 | **0.40** | 0.36 | 0.11 | 0.04 | 0.03 | 0.02 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| FO - EM < 2 | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.01 | 0.02 | 0.02 | 0.04 | 0.09 | 0.12 | 0.21 | 0.20 | 0.26 |
| FO - rTAG < 2 | 0.00 | 0.01 | 0.03 | 0.04 | 0.07 | 0.08 | 0.08 | 0.10 | 0.12 | 0.16 | 0.16 | 0.09 | 0.04 | 0.01 |
| **FO - TG < 2** | 0.00 | 0.01 | 0.04 | 0.07 | 0.11 | 0.12 | 0.11 | 0.13 | **0.14** | 0.14 | 0.08 | 0.04 | 0.01 | 0.00 |
| **FO - TG < 3** | 0.06 | **0.43** | 0.20 | 0.06 | 0.04 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.02 | 0.01 | 0.01 |
| **FO < 2** | 0.00 | 0.00 | 0.00 | 0.02 | 0.06 | 0.10 | 0.17 | **0.22** | 0.21 | 0.14 | 0.06 | 0.01 | 0.00 | 0.00 |
| **FO < 3** | 0.00 | 0.03 | 0.12 | **0.21** | 0.18 | 0.14 | 0.12 | 0.09 | 0.06 | 0.04 | 0.02 | 0.00 | 0.00 | 0.00 |
| FO > 3 | 0.00 | 0.01 | 0.03 | 0.06 | 0.07 | 0.08 | 0.09 | 0.10 | 0.14 | 0.15 | 0.15 | 0.08 | 0.04 | 0.01 |
| KO - HPL < 2 | 0.00 | 0.03 | 0.06 | 0.05 | 0.04 | 0.04 | 0.04 | 0.04 | 0.05 | 0.08 | 0.13 | 0.11 | 0.15 | 0.21 |
| KO - LPL < 2 | 0.00 | 0.02 | 0.02 | 0.04 | 0.02 | 0.03 | 0.02 | 0.03 | 0.04 | 0.07 | 0.11 | 0.12 | 0.14 | 0.34 |
| **KO – PL/FFA <3** | **0.90** | 0.04 | 0.01 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 |
| **KO < 2** | 0.00 | 0.00 | 0.05 | 0.15 | **0.23** | 0.21 | 0.18 | 0.10 | 0.06 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 |
| Placebo | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.12 | 0.31 | 0.40 | 0.16 |

**APPENDIX DOCUMENTS B**

**1. 1. Research results of TG**

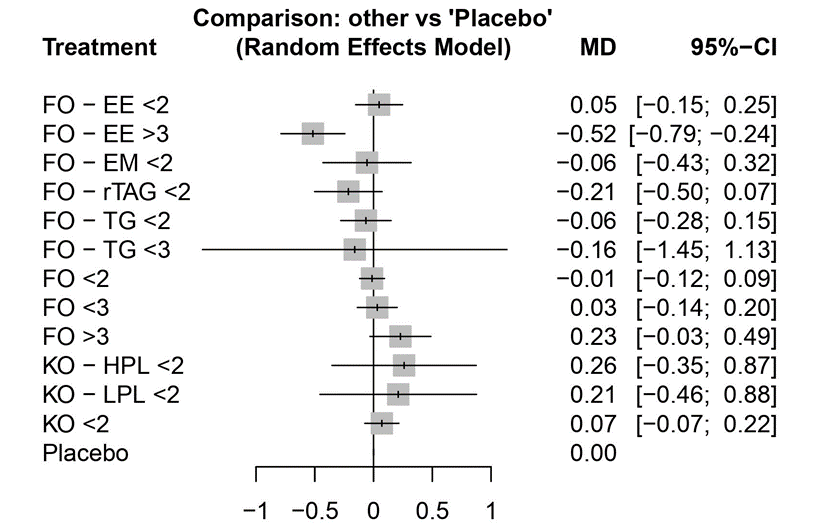
A comparison of a number of objects

Description automatically generated with medium confidence

**Figure B. 1. Forest plot of TG**

The forest plot (**Figure B. 1.**) and the results of Table A.7 show that the therapies are effective in reducing TG compared to placebo, including: KO – PL/FFA < 3 (MD = -1.24, 95% CI = [-2.1991; -0.2809], z = -2.53 < -1.96, p = 0.0113), FO - TG < 3 (MD = -0.44, 95%CI = [-0.8524; -0.0276], z = -2.09, p = 0.0365), FO - EE > 3 (MD = -0.43, 95%CI = [-0.6510; -0.2110], z = -3.84, p = 0.0001), FO - EE < 2 (MD = -0.25, 95 %CI = [-0.4067; -0.0952], z = -3.16, p = 0.0016), KO < 2 (MD = -0.25, 95%CI = [-0.3238; -0.1763], z = -6.64, p = < 0.0001), FO <3 (MD = -0.26, 95%CI = [-0.4033; -0.1320], z = -3.87, p = 0.0001), FO < 2 (MD = -0.20, 95%CI = [-0.2704 ; -0.1228], z = -5.22, p = < 0.0001) and FO - TG < 2 (MD = -0.20, 95%CI = [-0.3650; -0.0395], z = -2.44, p = 0.0149) with z values < -1.96 and p < 0.05 show that these results are highly reliable and statistically significant. Besides, there are interventions that show treatment effectiveness but are not statistically significant: FO > 3, FO - EM < 2, KO - HPL < 2, KO - LPL < 2 and FO - rTAG < 2

**1. 2. Research results of TC**



**Figure B. 2.** **Forest plot of TC**

Based on the Forest chart and the results in Table A.6, it shows that most of the results are not statistically significant, except for intervention FO - EE > 3. Interventions FO - EE > 3 (MD = -0.52, 95%CI = [-0.79; - 0.24], p = 0.0002, z = -3.71); FO - rTAG < 2 (MD = -0.21, 95%CI = [-0.50; 0.07], p = 0.1429, z = -1.47); FO - TG < 3 (MD = -0.16, 95%CI = [-1.45; 1.13], p = 0.8086, z = -0.24) was effective in reducing TC concentrations compared to placebo. Interventions FO - EE > 3 are most effective and highly reliable based on z and p values.

**1. 3. Results of checking the consistency of NMA TG**

**A. Cochrane Q' decomposition of TG**

**Table B. 1.** Cochrane Q' analysis on TG

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Q statistics to assess homogeneity / consistency** | | | | | |
|  | | | **Q** | **df** | **p-value** |
| Total | | | **489.09** | **77** | **< 0.0001** |
| Within designs | | | 449.18 | 68 | < 0.0001 |
| Between designs | | | 39.92 | 9 | < 0.0001 |
| **Design-specific decomposition of within-designs Q statistic** | | | | | |
| **Design** | | | **Q** | **df** | **p-value** |
| Placebo: KO < 2 | | | **195.92** | 14 | **< 0.0001** |
| Placebo: FO < 2 | | | **206.39** | 22 | **< 0.0001** |
| Placebo: FO < 3 | | | **29.48** | 11 | **0.0019** |
| Placebo: FO > 3 | | | **7.12** | 2 | **0.0284** |
| Placebo: FO - EM < 2 | | | 1.26 | 1 | 0.2620 |
| Placebo: FO - EE > 3 | | | 5.02 | 4 | 0.2848 |
| Placebo: FO < 2:KO < 2 | | | 0.85 | 2 | 0.6536 |
| Placebo: FO < 2:FO < 3 | | | 0.76 | 2 | 0.6853 |
| Placebo: FO - TG < 2 | | | 2.21 | 4 | 0.6964 |
| Placebo: FO - EE < 2 | | | 0.01 | 2 | 0.9970 |
| Placebo: FO - EE < 2: FO - rTAG < 2 | | | 0.15 | 4 | 0.9972 |
| **Between-designs Q statistic after detaching of single designs (influential designs have p-value markedly different from < 0.0001)** | | | | | |
| **Detached design** | | | **Q** | **df** | **p-value** |
| Placebo: KO < 2 | | | 24.02 | 8 | 0.0023 |
| Placebo: FO < 2: KO < 2 | | | 24.01 | 7 | 0.0011 |
| FO - EE < 2: KO < 2 | | | 34.40 | 8 | < 0.0001 |
| Placebo: FO - EE < 2 | | | 35.01 | 8 | < 0.0001 |
| FO - TG < 2: FO < 2 | | | 37.70 | 8 | < 0.0001 |
| Placebo: FO - TG < 2 | | | 39.19 | 8 | < 0.0001 |
| **Placebo: FO < 3** | | | **39.47** | 8 | < 0.0001 |
| FO < 2: KO < 2 | | | 39.71 | 8 | < 0.0001 |
| FO - TG < 2: KO < 2 | | | 39.77 | 8 | < 0.0001 |
| **Placebo: FO < 2** | | | **39.86** | 8 | < 0.0001 |
| Placebo: FO < 2: FO < 3 | | | 38.56 | 7 | < 0.0001 |
| **Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model** | | | | | |
|  | **Q** | **df** | **p-value** | **tau.within** | **tau2.within** |
| Between designs | **17.99** | 9 | **0.0353** | 0.1337 | 0.0179 |

The results of the Cochrane Q' decomposition (Table 1) show that the cause of this heterogeneity of NMA TG is due to the results from the comparisons between Placebo and: KO < 2, FO < 2, FO < 3, FO > 3 (p < 0.05). After performing the decomposition, the inconsistency between study designs decreased significantly (Q = 489.09 decreased to 17.99), however the p value = 0.0353 < 0.05 shows that significant inconsistency still exists. between comparisons affects the NMA TG results.

**B. SIDE analysis**

**Table B. 2.** Results of SIDE analysis on TG

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **comparison** | **k** | **prop** | **nma** | **direct** | **indir.** | **Diff** | **z** | **p-value** |
| 1 | FO - EE < 2: FO - EE > 3 | 0 | 0 | 0.1801 | . | 0.1801 | . | . | . |
| 2 | FO - EE < 2: FO - EM < 2 | 0 | 0 | -0.2318 | . | -0.2318 | . | . | . |
| 3 | FO - EE < 2: FO - rTAG < 2 | 3 | **0.82** | -0.0824 | 0.0633 | -0.7637 | **0.8270** | 3.01 | **0.0026** |
| 4 | FO - EE < 2: FO - TG < 2 | 0 | 0 | -0.0487 | . | -0.0487 | . | . | . |
| 5 | FO - EE < 2: FO - TG < 3 | 0 | 0 | 0.1891 | . | 0.1891 | . | . | . |
| 6 | FO - EE < 2: FO < 2 | 0 | 0 | -0.0543 | . | -0.0543 | . | . | . |
| 7 | FO - EE < 2: FO < 3 | 0 | 0 | 0.0167 | . | 0.0167 | . | . | . |
| 8 | FO - EE < 2: FO > 3 | 0 | 0 | -0.0817 | . | -0.0817 | . | . | . |
| 9 | FO - EE < 2: KO - HPL < 2 | 0 | 0 | -0.1709 | . | -0.1709 | . | . | . |
| 10 | FO - EE < 2: KO - LPL < 2 | 0 | 0 | -0.2409 | . | -0.2409 | . | . | . |
| 11 | **FO - EE < 2: KO - PLFFA <3** | 0 | 0 | 0.9891 | . | 0.9891 | . | . | . |
| 12 | FO - EE < 2: KO < 2 | 1 | 0.28 | -0.0009 | -0.1100 | 0.0417 | -0.1517 | -0.81 | 0.4161 |
| **13** | **FO - EE < 2: Placebo** | 6 | **0.76** | -0.2509 | -0.2147 | -0.3665 | 0.1518 | 0.81 | 0.4156 |
| 14 | **FO - EE > 3: FO - EM < 2** | 0 | 0 | -0.4119 | . | -0.4119 | . | . | . |
| 15 | FO - EE > 3: FO - rTAG < 2 | 0 | 0 | -0.2625 | . | -0.2625 | . | . | . |
| 16 | FO - EE > 3: FO - TG < 2 | 0 | 0 | -0.2287 | . | -0.2287 | . | . | . |
| 17 | FO - EE > 3: FO - TG < 3 | 0 | 0 | 0.0090 | . | 0.0090 | . | . | . |
| 18 | FO - EE > 3: FO < 2 | 0 | 0 | -0.2344 | . | -0.2344 | . | . | . |
| 19 | FO - EE > 3: FO < 3 | 0 | 0 | -0.1633 | . | -0.1633 | . | . | . |
| 20 | FO - EE > 3: FO > 3 | 0 | 0 | -0.2617 | . | -0.2617 | . | . | . |
| 21 | FO - EE > 3: KO - HPL < 2 | 0 | 0 | -0.3510 | . | -0.3510 | . | . | . |
| 22 | FO - EE > 3: KO - LPL < 2 | 0 | 0 | -0.4210 | . | -0.4210 | . | . | . |
| 23 | FO - EE > 3: KO - PLFFA <3 | 0 | 0 | 0.8090 | . | 0.8090 | . | . | . |
| 24 | FO - EE > 3: KO < 2 | 0 | 0 | -0.1810 | . | -0.1810 | . | . | . |
| 25 | **FO - EE > 3: Placebo** | 5 | **1.00** | -0.4310 | -0.4310 | . | . | . | . |
| 26 | FO - EM < 2: FO - rTAG < 2 | 0 | 0 | 0.1494 | . | 0.1494 | . | . | . |
| 27 | FO - EM < 2: FO - TG < 2 | 0 | 0 | 0.1832 | . | 0.1832 | . | . | . |
| 28 | FO - EM < 2: FO - TG < 3 | 0 | 0 | 0.4209 | . | 0.4209 | . | . | . |
| 29 | FO - EM < 2: FO < 2 | 0 | 0 | 0.1775 | . | 0.1775 | . | . | . |
| 30 | FO - EM < 2: FO < 3 | 0 | 0 | 0.2486 | . | 0.2486 | . | . | . |
| 31 | FO - EM < 2: FO > 3 | 0 | 0 | 0.1502 | . | 0.1502 | . | . | . |
| 32 | FO - EM < 2: KO - HPL < 2 | 0 | 0 | 0.0609 | . | 0.0609 | . | . | . |
| 33 | FO - EM < 2: KO - LPL < 2 | 0 | 0 | -0.0091 | . | -0.0091 | . | . | . |
| 34 | **FO - EM < 2: KO - PLFFA <3** | 0 | 0 | 1.2209 | . | 1.2209 | . | . | . |
| 35 | FO - EM < 2: KO < 2 | 0 | 0 | 0.2309 | . | 0.2309 | . | . | . |
| 36 | FO - EM < 2: Placebo | 2 | **1.00** | -0.0191 | -0.0191 | . | . | . | . |
| 37 | FO - rTAG < 2: FO - TG < 2 | 0 | 0 | 0.0337 | . | 0.0337 | . | . | . |
| 38 | FO - rTAG < 2: FO - TG < 3 | 0 | 0 | 0.2715 | . | 0.2715 | . | . | . |
| 39 | FO - rTAG < 2: FO < 2 | 0 | 0 | 0.0281 | . | 0.0281 | . | . | . |
| 40 | FO - rTAG < 2: FO < 3 | 0 | 0 | 0.0992 | . | 0.0992 | . | . | . |
| 41 | FO - rTAG < 2: FO > 3 | 0 | 0 | 0.0007 | . | 0.0007 | . | . | . |
| 42 | FO - rTAG < 2: KO - HPL < 2 | 0 | 0 | -0.0885 | . | -0.0885 | . | . | . |
| 43 | FO - rTAG < 2: KO - LPL < 2 | 0 | 0 | -0.1585 | . | -0.1585 | . | . | . |
| 44 | **FO - rTAG < 2: KO - PLFFA <3** | 0 | 0 | 1.0715 | . | 1.0715 | . | . | . |
| 45 | FO - rTAG < 2: KO < 2 | 0 | 0 | 0.0815 | . | 0.0815 | . | . | . |
| 46 | FO - rTAG < 2: Placebo | 3 | **0.85** | -0.1685 | -0.0376 | -0.9090 | **0.8714** | 3.02 | **0.0025** |
| 47 | FO - TG < 2: FO - TG < 3 | 0 | 0 | 0.2378 | . | 0.2378 | . | . | . |
| 48 | FO - TG < 2: FO < 2 | 1 | 0.12 | -0.0056 | -0.3300 | 0.0397 | -0.3697 | -1.36 | 0.1750 |
| 49 | FO - TG < 2: FO < 3 | 0 | 0 | 0.0654 | . | 0.0654 | . | . | . |
| 50 | FO - TG < 2: FO > 3 | 0 | 0 | -0.0330 | . | -0.0330 | . | . | . |
| 51 | FO - TG < 2: KO - HPL < 2 | 0 | 0 | -0.1222 | . | -0.1222 | . | . | . |
| 52 | FO - TG < 2: KO - LPL < 2 | 0 | 0 | -0.1922 | . | -0.1922 | . | . | . |
| 53 | **FO - TG < 2: KO - PLFFA <3** | 0 | 0 | 1.0378 | . | 1.0378 | . | . | . |
| 54 | FO - TG < 2: KO < 2 | 1 | 0.11 | 0.0478 | 0.2200 | 0.0258 | 0.1942 | 0.69 | 0.4915 |
| 55 | **FO - TG < 2: Placebo** | 5 | **0.80** | -0.2022 | -0.1804 | -0.2904 | 0.1100 | 0.53 | 0.5972 |
| 56 | FO - TG < 3: FO < 2 | 0 | 0 | -0.2434 | . | -0.2434 | . | . | . |
| 57 | FO - TG < 3: FO < 3 | 0 | 0 | -0.1723 | . | -0.1723 | . | . | . |
| 58 | FO - TG < 3: FO > 3 | 0 | 0 | -0.2708 | . | -0.2708 | . | . | . |
| 59 | FO - TG < 3: KO - HPL < 2 | 0 | 0 | -0.3600 | . | -0.3600 | . | . | . |
| 60 | FO - TG < 3: KO - LPL < 2 | 0 | 0 | -0.4300 | . | -0.4300 | . | . | . |
| 61 | FO - TG < 3: KO - PLFFA <3 | 0 | 0 | 0.8000 | . | 0.8000 | . | . | . |
| 62 | FO - TG < 3: KO < 2 | 0 | 0 | -0.1900 | . | -0.1900 | . | . | . |
| 63 | **FO - TG < 3: Placebo** | 1 | **1.00** | -0.4400 | -0.4400 | . | . | . | . |
| 64 | FO < 2: FO < 3 | 2 | 0.09 | 0.0711 | 0.2626 | 0.0530 | 0.2097 | 0.75 | 0.4510 |
| 65 | FO < 2: FO > 3 | 0 | 0 | -0.0274 | . | -0.0274 | . | . | . |
| 66 | FO < 2: KO - HPL < 2 | 0 | 0 | -0.1166 | . | -0.1166 | . | . | . |
| 67 | FO < 2: KO - LPL < 2 | 0 | 0 | -0.1866 | . | -0.1866 | . | . | . |
| 68 | **FO < 2: KO - PLFFA <3** | 0 | 0 | 1.0434 | . | 1.0434 | . | . | . |
| 69 | FO < 2: KO < 2 | 3 | 0.22 | 0.0534 | -0.0312 | 0.0771 | -0.1083 | -0.89 | 0.3761 |
| 70 | **FO < 2: Placebo** | **27** | **0.92** | -0.1966 | -0.1943 | -0.2219 | 0.0276 | 0.20 | 0.8388 |
| 71 | FO < 3: FO > 3 | 0 | 0 | -0.0984 | . | -0.0984 | . | . | . |
| 72 | FO < 3: KO - HPL < 2 | 0 | 0 | -0.1877 | . | -0.1877 | . | . | . |
| 73 | FO < 3: KO - LPL < 2 | 0 | 0 | -0.2577 | . | -0.2577 | . | . | . |
| 74 | **FO < 3: KO - PLFFA <3** | 0 | 0 | 0.9723 | . | 0.9723 | . | . | . |
| 75 | FO < 3: KO < 2 | 0 | 0 | -0.0177 | . | -0.0177 | . | . | . |
| 76 | **FO < 3:Placebo** | **14** | **0.98** | -0.2677 | -0.2598 | -0.7129 | 0.4531 | 0.86 | 0.3915 |
| 77 | FO > 3: KO - HPL < 2 | 0 | 0 | -0.0892 | . | -0.0892 | . | . | . |
| 78 | FO > 3: KO - LPL < 2 | 0 | 0 | -0.1592 | . | -0.1592 | . | . | . |
| 79 | **FO > 3: KO - PLFFA <3** | 0 | 0 | 1.0708 | . | 1.0708 | . | . | . |
| 80 | FO > 3: KO < 2 | 0 | 0 | 0.0808 | . | 0.0808 | . | . | . |
| 81 | FO > 3:Placebo | 3 | **1.00** | -0.1692 | -0.1692 | . | . | . | . |
| 82 | KO - HPL < 2: KO - LPL < 2 | 1 | **1.00** | -0.0700 | -0.0700 | . | . | . | . |
| **83** | **KO - HPL < 2: KO - PLFFA <3** | 0 | 0 | 1.1600 | . | 1.1600 | . | . | . |
| 84 | KO - HPL < 2: KO < 2 | 0 | 0 | 0.1700 | . | 0.1700 | . | . | . |
| 85 | KO - HPL < 2:Placebo | 1 | **1.00** | -0.0800 | -0.0800 | . | . | . | . |
| 86 | **KO - LPL < 2: KO - PLFFA <3** | 0 | 0 | 1.2300 | . | 1.2300 | . | . | . |
| 87 | KO - LPL < 2: KO < 2 | 0 | 0 | 0.2400 | . | 0.2400 | . | . | . |
| 88 | KO - LPL < 2: Placebo | 1 | **1.00** | -0.0100 | -0.0100 | . | . | . | . |
| 89 | **KO - PLFFA <3: KO < 2** | 0 | 0 | -0.9900 | . | -0.9900 | . | . | . |
| **90** | **KO - PLFFA <3: Placebo** | 1 | **1.00** | -1.2400 | -1.2400 | . | . | . | . |
| **91** | **KO < 2: Placebo** | **17** | **0.88** | -0.2500 | -0.2522 | -0.2340 | -0.0182 | -0.16 | 0.8756 |

Legend:

comparison - Treatment comparison

k - Number of studies providing direct evidence

prop - Direct evidence proportion

nma - Estimated treatment effect (MD) in network meta-analysis

direct - Estimated treatment effect (MD) derived from direct evidence

indir. - Estimated treatment effect (MD) derived from indirect evidence

Diff - Difference between direct and indirect treatment estimates

z - z-value of test for disagreement (direct versus indirect)

p-value - p-value of test for disagreement (direct versus indirect)

The SIDE analysis aimed to assess inconsistency between study designs including direct and indirect evidence (Table 2), a total of 91 comparisons were made between interventions, of which 20 were Research designs have direct evidence (accounting for 21.98%), and up to 83 research designs have indirect evidence (accounting for 91.21%). While there are only 12 research designs that have both indirect and direct evidence (accounting for 13.19%), of which: only diff, z-value and p-value (<0.05) of 2 pairs FO - EE < 2: FO - rTAG < 2 and FO - rTAG < 2: Placebo shows that the difference between the evidence is significant. Additionally, according to k values, only three comparisons between Placebo and: KO < 2, FO < 3, and FO < 2 had multiple studies providing direct evidence (prop from 0.88 to 0.98); There were also 8 comparisons where most of the evidence was provided directly (prop = 1.00), increasing the reliability of the results. However, for the 4 comparison pairs with negative diff numbers such as: FO - EE < 2: KO < 2, FO - TG < 2: FO < 2, FO < 2: KO < 2, KO < 2: Placebo has an effect treatment estimates from indirect evidence are greater than from direct evidence. Therefore, after further consideration of the effectiveness estimate, the treatment intervention is not as effective as the comparison intervention (in pairs FO - EE < 2: KO < 2, FO - TG < 2: FO < 2), but not significant (p>0.05)

In the pairwise treatment comparisons in the league table, compared with the SIDE analysis, KO < 2:Placebo, KO - PLFFA <3:Placebo, FO < 3:Placebo, FO < 2:Placebo, FO - TG < 2:Placebo, FO - EE > 3:Placebo, FO - EE < 2:Placebo, FO - TG < 3:Placebo has direct evidence, and the remaining pairs (statistically significant) only have evidence Indirect.

According to the top 8 effective interventions to reduce TG in the SUCRA scoreboard, there are only: KO < 2:Placebo, KO - PLFFA <3:Placebo, FO < 3:Placebo, FO < 2:KO < 2, FO < 2 :FO < 3, FO - TG < 3:Placebo, FO - TG < 2:KO < 2, FO - EE > 3:Placebo, FO - EE < 2:KO < 2, FO - TG < 2: FO < 2 , FO – EE < 2: FO – rTAG < 2, FO – EE < 2: Placebo, FO - TG < 2: Placebo, FO < 2: Placebo with direct evidence.

**1. 4. Results of checking the consistency of the NMA TC**

**A. Decomposition of Q'Cochrane**

**Table B.3: Decomposition of Q'Cochrane on TC**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Q statistics to assess homogeneity / consistency | | | | | |
|  | | | Q | d.f. | p-value |
| Total | | | **155.43** | 63 | **< 0.0001** |
| Within designs | | | 85.71 | 55 | 0.0050 |
| Between designs | | | 69.72 | 8 | < 0.0001 |
| Design-specific decomposition of within-designs Q statistic | | | | | |
| Design | | | Q | df | p-value |
| Placebo:FO <2 | | | **48.20** | 18 | **0.0001** |
| Placebo:FO - EE >3 | | | **21.58** | 4 | **0.0002** |
| Placebo:FO >3 | | | 4.62 | 2 | 0.0992 |
| Placebo:FO - EM <2 | | | 0.38 | 1 | 0.5401 |
| Placebo:KO <2 | | | 3.50 | 5 | 0.6237 |
| Placebo:FO <2:KO <2 | | | 1.63 | 4 | 0.8028 |
| Placebo:FO - TG <2 | | | 1.35 | 4 | 0.8521 |
| Placebo:FO <2:FO <3 | | | 0.19 | 2 | 0.9115 |
| Placebo:FO <3 | | | 3.83 | 9 | 0.9225 |
| Placebo:FO - EE <2 | | | 0.16 | 2 | 0.9237 |
| Placebo:FO - EE <2:FO - rTAG <2 | | | 0.27 | 4 | 0.9914 |
| Between-designs Q statistic after detaching of single designs  (influential designs have p-value markedly different from < 0.0001) | | | | | |
| Detached design | | | Q | df | p-value |
| Placebo:FO <2:KO <2 | | | 46.32 | 6 | < 0.0001 |
| FO - EE <2:KO <2 | | | 49.53 | 7 | < 0.0001 |
| FO - TG <2:FO <2 | | | 51.07 | 7 | < 0.0001 |
| Placebo:FO <2 | | | 53.22 | 7 | < 0.0001 |
| Placebo:FO - TG <2 | | | 61.07 | 7 | < 0.0001 |
| Placebo:FO <3 | | | 67.69 | 7 | < 0.0001 |
| FO - TG <2:KO <2 | | | 68.54 | 7 | < 0.0001 |
| Placebo:FO - EE <2 | | | 68.96 | 7 | < 0.0001 |
| Placebo:KO <2 | | | 69.72 | 7 | < 0.0001 |
| Placebo:FO <2:FO <3 | | | 67.50 | 6 | < 0.0001 |
| Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model | | | | | |
|  | Q | df | p-value | tau.within | tau2.within |
| Between designs | **29.08** | 8 | **0.0003** | 0.1318 | 0.0174 |

Based on the results of Q'Cochrane decomposition on the TC index presented in Table 1 to evaluate the inconsistency between studies. The results show that the inconsistency of NMA TC comes from 2 pairs of comparisons FO < 2 and FO - EE > 3 compared to placebo, with p values of 0.0001 and 0.0002, respectively. After separation, the Q value was significantly reduced from 155.43 to 29.08 with p = 0.0003 but the heterogeneity between studies was not eliminated (p < 0.05).

**B. SIDE analysis**

**Table B. 4: Results of SIDE analysis on TC**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| comparison | k | prop | nma | direct | indir. | Diff | z | p-value |
| FO - EE <2:FO - EE >3 | 0 | 0 | 0.5634 | . | 0.5634 | . | . | . |
| FO - EE <2:FO - EM <2 | 0 | 0 | 0.1028 | . | 0.1028 | . | . | . |
| **FO - EE <2:FO - rTAG <2** | 3 | 0.84 | 0.2616 | 0.0958 | 1.1266 | **-1.0308** | -2.57 | **0.0101** |
| FO - EE <2:FO - TG <2 | 0 | 0 | 0.1122 | . | 0.1122 | . | . | . |
| FO - EE <2:FO - TG <3 | 0 | 0 | 0.2073 | . | 0.2073 | . | . | . |
| FO - EE <2:FO <2 | 0 | 0 | 0.0600 | . | 0.0600 | . | . | . |
| FO - EE <2:FO <3 | 0 | 0 | 0.0158 | . | 0.0158 | . | . | . |
| FO - EE <2:FO >3 | 0 | 0 | -0.1817 | . | -0.1817 | . | . | . |
| FO - EE <2:KO - HPL <2 | 0 | 0 | -0.2127 | . | -0.2127 | . | . | . |
| FO - EE <2:KO - LPL <2 | 0 | 0 | -0.1627 | . | -0.1627 | . | . | . |
| FO - EE <2:KO <2 | 1 | 0.36 | -0.0234 | 0.2400 | -0.1708 | 0.4108 | 1.74 | 0.0811 |
| FO - EE <2:Placebo | 6 | 0.75 | 0.0473 | -0.0547 | 0.3553 | **-0.4100** | -1.74 | 0.0817 |
| FO - EE >3:FO - EM <2 | 0 | 0 | -0.4605 | . | -0.4605 | . | . | . |
| FO - EE >3:FO - rTAG <2 | 0 | 0 | -0.3018 | . | -0.3018 | . | . | . |
| FO - EE >3:FO - TG <2 | 0 | 0 | -0.4512 | . | -0.4512 | . | . | . |
| FO - EE >3:FO - TG <3 | 0 | 0 | -0.3561 | . | -0.3561 | . | . | . |
| FO - EE >3:FO <2 | 0 | 0 | -0.5034 | . | -0.5034 | . | . | . |
| FO - EE >3:FO <3 | 0 | 0 | -0.5476 | . | -0.5476 | . | . | . |
| FO - EE >3:FO >3 | 0 | 0 | -0.7450 | . | -0.7450 | . | . | . |
| FO - EE >3:KO - HPL <2 | 0 | 0 | -0.7761 | . | -0.7761 | . | . | . |
| FO - EE >3:KO - LPL <2 | 0 | 0 | -0.7261 | . | -0.7261 | . | . | . |
| FO - EE >3:KO <2 | 0 | 0 | -0.5867 | . | -0.5867 | . | . | . |
| FO - EE >3:Placebo | 5 | **1.00** | -0.5161 | -0.5161 | . | . | . | . |
| FO - EM <2:FO - rTAG <2 | 0 | 0 | 0.1588 | . | 0.1588 | . | . | . |
| FO - EM <2:FO - TG <2 | 0 | 0 | 0.0094 | . | 0.0094 | . | . | . |
| FO - EM <2:FO - TG <3 | 0 | 0 | 0.1044 | . | 0.1044 | . | . | . |
| FO - EM <2:FO <2 | 0 | 0 | -0.0428 | . | -0.0428 | . | . | . |
| FO - EM <2:FO <3 | 0 | 0 | -0.0871 | . | -0.0871 | . | . | . |
| FO - EM <2:FO >3 | 0 | 0 | -0.2845 | . | -0.2845 | . | . | . |
| FO - EM <2:KO - HPL <2 | 0 | 0 | -0.3156 | . | -0.3156 | . | . | . |
| FO - EM <2:KO - LPL <2 | 0 | 0 | -0.2656 | . | -0.2656 | . | . | . |
| FO - EM <2:KO <2 | 0 | 0 | -0.1262 | . | -0.1262 | . | . | . |
| FO - EM <2:Placebo | 2 | **1.00** | -0.0556 | -0.0556 | . | . | . | . |
| FO - rTAG <2:FO - TG <2 | 0 | 0 | -0.1494 | . | -0.1494 | . | . | . |
| FO - rTAG <2:FO - TG <3 | 0 | 0 | -0.0543 | . | -0.0543 | . | . | . |
| FO - rTAG <2:FO <2 | 0 | 0 | -0.2016 | . | -0.2016 | . | . | . |
| FO - rTAG <2:FO <3 | 0 | 0 | -0.2458 | . | -0.2458 | . | . | . |
| FO - rTAG <2:FO >3 | 0 | 0 | -0.4432 | . | -0.4432 | . | . | . |
| FO - rTAG <2:KO - HPL <2 | 0 | 0 | -0.4743 | . | -0.4743 | . | . | . |
| FO - rTAG <2:KO - LPL <2 | 0 | 0 | -0.4243 | . | -0.4243 | . | . | . |
| FO - rTAG <2:KO <2 | 0 | 0 | -0.2850 | . | -0.2850 | . | . | . |
| **FO - rTAG <2:Placebo** | 3 | 0.85 | -0.2143 | -0.3719 | 0.6848 | -1.0567 | -2.57 | **0.0101** |
| FO - TG <2:FO - TG <3 | 0 | 0 | 0.0951 | . | 0.0951 | . | . | . |
| **FO - TG <2:FO <2** | 1 | 0.18 | -0.0522 | -0.8400 | 0.1205 | -0.9605 | -3.14 | **0.0017** |
| FO - TG <2:FO <3 | 0 | 0 | -0.0964 | . | -0.0964 | . | . | . |
| FO - TG <2:FO >3 | 0 | 0 | -0.2939 | . | -0.2939 | . | . | . |
| FO - TG <2:KO - HPL <2 | 0 | 0 | -0.3249 | . | -0.3249 | . | . | . |
| FO - TG <2:KO - LPL <2 | 0 | 0 | -0.2749 | . | -0.2749 | . | . | . |
| FO - TG <2:KO <2 | 1 | 0.13 | -0.1356 | 0.3000 | -0.2011 | 0.5011 | 1.33 | 0.1840 |
| FO - TG <2:Placebo | 5 | 0.76 | -0.0649 | 0.0406 | -0.3986 | 0.4392 | 1.72 | 0.0856 |
| FO - TG <3:FO <2 | 0 | 0 | -0.1473 | . | -0.1473 | . | . | . |
| FO - TG <3:FO <3 | 0 | 0 | -0.1915 | . | -0.1915 | . | . | . |
| FO - TG <3:FO >3 | 0 | 0 | -0.3889 | . | -0.3889 | . | . | . |
| FO - TG <3:KO - HPL <2 | 0 | 0 | -0.4200 | . | -0.4200 | . | . | . |
| FO - TG <3:KO - LPL <2 | 0 | 0 | -0.3700 | . | -0.3700 | . | . | . |
| FO - TG <3:KO <2 | 0 | 0 | -0.2307 | . | -0.2307 | . | . | . |
| FO - TG <3:Placebo | 1 | **1.00** | -0.1600 | -0.1600 | . | . | . | . |
| FO <2:FO <3 | 2 | 0.17 | -0.0442 | 0.1618 | -0.0871 | 0.2489 | 0.95 | 0.3421 |
| FO <2:FO >3 | 0 | 0 | -0.2416 | . | -0.2416 | . | . | . |
| FO <2:KO - HPL <2 | 0 | 0 | -0.2727 | . | -0.2727 | . | . | . |
| FO <2:KO - LPL <2 | 0 | 0 | -0.2227 | . | -0.2227 | . | . | . |
| FO <2:KO <2 | 3 | 0.35 | -0.0834 | -0.1069 | -0.0708 | -0.0361 | -0.20 | 0.8402 |
| **FO <2:Placebo** | 24 | 0.92 | -0.0127 | -0.0448 | 0.3654 | -0.4102 | -2.05 | **0.0404** |
| FO <3:FO >3 | 0 | 0 | -0.1974 | . | -0.1974 | . | . | . |
| FO <3:KO - HPL <2 | 0 | 0 | -0.2285 | . | -0.2285 | . | . | . |
| FO <3:KO - LPL <2 | 0 | 0 | -0.1785 | . | -0.1785 | . | . | . |
| FO <3:KO <2 | 0 | 0 | -0.0392 | . | -0.0392 | . | . | . |
| FO <3:Placebo | 12 | 0.95 | 0.0315 | 0.0410 | -0.1375 | 0.1785 | 0.46 | 0.6421 |
| FO >3:KO - HPL <2 | 0 | 0 | -0.0311 | . | -0.0311 | . | . | . |
| FO >3:KO - LPL <2 | 0 | 0 | 0.0189 | . | 0.0189 | . | . | . |
| FO >3:KO <2 | 0 | 0 | 0.1583 | . | 0.1583 | . | . | . |
| FO >3:Placebo | 3 | **1.00** | 0.2289 | 0.2289 | . | . | . | . |
| KO - HPL <2:KO - LPL <2 | 1 | **1.00** | 0.0500 | 0.0500 | . | . | . | . |
| KO - HPL <2:KO <2 | 0 | 0 | 0.1893 | . | 0.1893 | . | . | . |
| KO - HPL <2:Placebo | 1 | **1.00** | 0.2600 | 0.2600 | . | . | . | . |
| KO - LPL <2:KO <2 | 0 | 0 | 0.1393 | . | 0.1393 | . | . | . |
| KO - LPL <2:Placebo | 1 | **1.00** | 0.2100 | 0.2100 | . | . | . | . |
| **KO <2:Placebo** | 9 | 0.78 | 0.0707 | 0.1580 | -0.2410 | 0.3989 | 2.24 | **0.0253** |

Legend:

comparison - Treatment comparison

k - Number of studies providing direct evidence

prop - Direct evidence proportion

nma - Estimated treatment effect (MD) in network meta-analysis

direct - Estimated treatment effect (MD) derived from direct evidence

indir. - Estimated treatment effect (MD) derived from indirect evidence

Diff - Difference between direct and indirect treatment estimates

z - z-value of test for disagreement (direct versus indirect)

p-value - p-value of test for disagreement (direct versus indirect)

The SIDE analysis aimed to assess inconsistency between study designs including direct and indirect evidence (Table 2), 78 comparisons were made between interventions, of which 19 were paired comparisons. providing direct evidence accounted for 24.36%, 71 pairs provided indirect evidence accounting for 91.03% and 12 comparisons providing both direct and indirect evidence accounted for 15.38%.

However, there is evidence showing inconsistency stemming from 5 pairs: FO - EE <2: FO - rTAG < 2, FO - rTAG < 2: Placebo, FO - TG < 2: FO < 2, FO < 2:Placebo and KO < 2:Placebo both have p values < 0.05. According to the k value, there are 6 pairs of comparisons FO - EE < 2:FO – rTAG < 2, FO – rTAG < 2:Placebo, FO – TG < 2:Placebo, FO < 2:Placebo, FO < 3:Placebo and KO < 2:Placebo are the studies that provide the most direct evidence (from 0.76 - 0.93 according to prop value), besides there are 7 pairs of comparisons that also provide the most direct evidence (prop = 1.00) increases the reliability of the results. However, some comparisons have negative diff values such as FO - EE < 2:Placebo or FO - TG < 2:Placebo, so it is necessary to consider the feasibility and reliability of the indirect evidence. This comparison is based on indir values because they have larger treatment effects estimated from indirect evidence than direct evidence.

When comparing treatment pairs in the league table and side analysis, we found that there are 3 pairs of comparisons: FO - EE > 3: Placebo, FO - rTAG < 2: Placebo and FO - TG < 2: FO < 2 provides direct evidence, the remaining treatment pairs presented in Table 3 provide only indirect evidence. When comparing interventions that are effective in reducing TC with SUCRA, there are 4 interventions ranked highest: FO - EE > 3: Placebo, FO - rTAG < 2: Placebo, FO - TG < 2: Placebo and FO - TG < 3: Placebo has direct evidence.

**1. 5. Net graph of HDL - C**

A diagram of a sphere with lines and dots

Description automatically generated

**Figure B.3. Net graph estimating the effect of intervention oils on HDL-C**

The yellow buttons in the graph layout correspond to treatments. Edges show observed treatment comparisons. Edges in the graph have different thicknesses. Thickness represents how often we find a particular comparison in the network. Interventions include:

|  |  |
| --- | --- |
| 1. FO - EE < 2 | * Ethyl ester fish oil, (dha+epa) 300 - 2000 mg |
| 1. FO - EE < 3 | * Ethyl ester fish oil, (dha+epa) 2000-3000 mg |
| 1. FO - EE > 3 | * Ethyl ester fish oil, (dha+epa) > 3000 mg |
| 1. FO - EM < 2 | * Emulsified fish oil, (DHA+EPA) 300 - 2000 mg |
| 1. FO - rTAG < 2 | * Re-esterified triacylglycerole fish oil, (dha+epa) 300 - 2000 mg |
| 1. FO - TG < 2 | * Triglyceride fish oil, (dha+epa) 300 - 2000 mg |
| 1. FO - TG < 3 | * Triglyceride fish oil, (dha+epa) 2000-3000 mg |
| 1. FO < 2 | * Fish oil capsule, (dha+epa) 300 - 2000 mg |
| 1. FO < 3 | * Fish oil capsule, (dha+epa) 2000-3000 mg |
| FO > 3 | * Fish oil capsule, (dha+epa) > 3000 mg |
| KO - HPL < 2 | Krill oil with high phospholipid, (dha+epa) 300 - 2000 mg |
| KO - LPL < 2 | Krill oil with low phospholipid, (dha+epa) 300 - 2000 mg |
| KO < 2 | * Krill oil, (dha+epa) 300 - 2000 mg |
| Placebo | * Placebo |

Network geometry to visualize the estimated effects of oils as intervention agents, compared with each other on HDL-C index results in subjects at risk of cardiovascular diseases or healthy (Figure 1). In this NMA (Table 1), we searched for 53 studies related to HDL-C index, including 78 pairs of specific comparisons between 14 dosage forms with different doses of fish oil and krill oil. The majority of studies compared the effectiveness of FO < 2, FO < 3, and KO < 2 compared with placebo, with the number of pairs of comparisons up to 22, 12, and 9. The remaining interventions had a number of comparisons. Compare less, all below 5.

In particular, there were no obvious differences between intervention comparisons (Table 1), tau^2 = 0.0009 represents the level of variability between study results. This value is low, showing consistency between research results. tau = 0.0299 is the square root of tau2, used to compare with the effect size. This value is also low, indicating that the heterogeneity between study results does not greatly affect the pooled results. I2 = 17.1% [0.0%; 40.9%] indicates the percentage of heterogeneity between study results. With a value of 17.1%, this level of heterogeneity is considered low. In summary, there were no significant differences between intervention comparisons in this NMA, with Q total = 67.59 (p = 0.138)

**Table B.5: net graph results of HDL-C**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of studies:k = 53  Number of pairwise comparisons:m = 78  Number of treatments:n = 14  Number of designs:d = 17  Random effects model  Treatment estimate (sm = 'MD'  comparison:other treatments vs 'Placebo'): | | | | |
|  | MD | 95%-CI | *z* | p-value |
| FO - EE < 2 | -0.0396 | [-0.0970; 0.0178] | -1.35 | 0.1761 |
| FO - EE < 3 | 0.0500 | [-0.0718; 0.1718] | 0.80 | 0.4209 |
| **FO - EE > 3** | **-0.1443** | **[-0.2633; -0.0253]** | **-2.38** | **0.0175** |
| FO - EM < 2 | -0.0725 | [-0.2140; 0.0689] | -1.01 | 0.3148 |
| FO - rTAG < 2 | -0.0702 | [-0.1597; 0.0193] | -1.54 | 0.1243 |
| FO - TG < 2 | 0.0426 | [-0.0212; 0.1063] | 1.31 | 0.1904 |
| FO - TG < 3 | 0.2900 | [-0.0770; 0.6570] | 1.55 | 0.1214 |
| **FO < 2** | **0.0580** | **[0.0294; 0.0867]** | **3.97** | **< 0.0001** |
| **FO < 3** | **0.0734** | **[0.0256; 0.1211]** | **3.01** | **0.0026** |
| **FO > 3** | **-0.1142** | **[-0.1780; -0.0505]** | **-3.51** | **0.0004** |
| KO - HPL < 2 | 0.0700 | [-0.1607; 0.3007] | 0.59 | 0.5520 |
| KO - LPL < 2 | 0.0300 | [-0.2293; 0.2893] | 0.23 | 0.8206 |
| **KO < 2** | **0.0437** | **[-0.0053; 0.0926]** | **1.75** | **0.0803** |
| Placebo | . | . | . | . |
| **Quantifying heterogeneity / inconsistency:**  **tau2 =0.0009; tau =0.0299; I2 = 17.1% [0.0%; 40.9%]**  **Tests of heterogeneity (within designs) and inconsistency (between designs):** | | | | |
|
|
|  | Q | d.f. | p-value | |
| Total | 67.59 | 56 | 0.1380 | |
| Within designs | 57.90 | 48 | 0.1551 | |
| Between designs | 9.69 | 8 | 0.2875 | |

**1. 6. Research results of HDL-C**

A close-up of a chart

Description automatically generated  
**Figure B.4. Forest plot of HDL-C**

The forest chart (Figure 2) and the results in Table 1 show that most of the meta-analysis results have not shown clear, statistically significant results. Using FO < 3 (MD = 0.0734, 95%CI = [0.0256; 0.1211], p = 0.0026, z = 3.01 >1.96), and FO < 2 (MD = 0.0580, 95%CI = [0.0294; 0.0867], z = 3.97 > 1.96, p < 0.0001) is effective in increasing HDL-C, with these z and p values showing high reliability, however FO - TG < 3 is the most effective, but not yet effective. High reliability (z = 1.55 < 1.96 and p = 0.1214 > 0.5). On the contrary, using FO > 3, FO – EE > 3 and < 2, FO – rTAG < 2, FO – EM < 2 did not increase HDL-C, while the remaining oils also showed therapeutic effects. but not statistically significant.

**1. 7. Results of treatment ranking according to rankogram and SUCRA score of HDL-C**

**Table B.6. Rankogram results of HDL-C**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
| **FO - EE < 2** | 0.00 | 0.02 | 0.10 | 0.23 | **0.32** | 0.19 | 0.09 | 0.03 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - EE < 3** | 0.00 | 0.00 | 0.01 | 0.03 | 0.06 | 0.07 | 0.11 | 0.10 | 0.10 | 0.08 | 0.12 | 0.13 | **0.15** | 0.03 |
| **FO - EE > 3** | **0.50** | 0.22 | 0.14 | 0.08 | 0.04 | 0.02 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - EM < 2** | **0.16** | **0.16** | 0.14 | **0.16** | 0.12 | 0.09 | 0.06 | 0.04 | 0.02 | 0.01 | 0.02 | 0.01 | 0.01 | 0.00 |
| **FO - rTAG < 2** | 0.05 | 0.13 | 0.24 | **0.25** | 0.17 | 0.10 | 0.03 | 0.02 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - TG < 2** | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.05 | 0.11 | 0.17 | **0.18** | 0.17 | 0.14 | 0.10 | 0.06 | 0.01 |
| **FO - TG < 3** | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.02 | 0.01 | 0.01 | 0.01 | 0.02 | 0.09 | **0.77** |
| **FO < 2** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.08 | 0.19 | 0.24 | **0.26** | 0.16 | 0.06 | 0.00 |
| **FO < 3** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.06 | 0.09 | 0.17 | 0.21 | **0.27** | 0.16 | 0.03 |
| **FO > 3** | 0.20 | **0.38** | 0.27 | 0.11 | 0.04 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **KO - HPL < 2** | 0.03 | 0.02 | 0.03 | 0.05 | 0.06 | 0.06 | 0.07 | 0.07 | 0.05 | 0.05 | 0.05 | 0.10 | **0.27** | 0.09 |
| **KO - LPL < 2** | 0.06 | 0.06 | 0.06 | 0.08 | 0.06 | 0.07 | 0.06 | 0.06 | 0.04 | 0.05 | 0.04 | 0.10 | **0.18** | 0.07 |
| **KO < 2** | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.03 | 0.08 | 0.18 | **0.22** | 0.19 | 0.15 | 0.10 | 0.03 | 0.00 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  |  | | --- | --- | |  | SUCRA (%) | | **FO - EE > 3** | 91.99 | | **FO > 3** | 88.85 | | **FO - rTAG < 2** | 77.21 | | **FO - EM < 2** | 75.61 | | **FO - EE < 2** | 68.95 | | **Placebo** | 55.35 | | **KO - LPL < 2** | 44.55 | | **FO - TG < 2** | 35.78 | | **FO - EE < 3** | 34.96 | | **KO < 2** | 34.78 | | **KO - HPL < 2** | 33.70 | | **FO < 2** | 28.02 | | **FO < 3** | 22.52 | | **FO - TG < 3** | 7.72 | |
|  |  |

**Figure B.5. Rankogram and SUCRA results for HDL-C**

Based on Figure B. 3 and Table B.2 of rankogram and SUCRA treatment ranking results, it shows that FO - TG < 3 (SUCRA = 7.72%), FO < 3 (SUCRA = 22.52%), FO < 2 (SUCRA = 28.02% ), KO - HPL < 2 (SUCRA = 33.70%), and KO < 2 (SUCRA = 34.78%) are the top 5 interventions showing the most effectiveness in increasing HDL-C with the highest probability of 0.77, respectively. 0.27, 0.27, 0.26 and 0.22.

While different dosage forms and doses of FO - EE > 3, FO > 3, FO - rTAG < 2, FO - EM < 2, FO - EE < 2 all had lower therapeutic ratings than placebo. . Thereby, we see that using fish oil in triglyceride form with a dose of (DHA + EPA) from 2000 - 3000 mg per day and has the highest HDL-C increasing effect. At the same time, high doses of fish oil from 2000 - 3000 mg are more effective than fish oils with lower doses. Only EE dosage form fish oil has been studied at doses > 3000 mg, but has not shown effectiveness compared to TG and rTAG dosage forms of fish oil, even at the highest dose, but compared to FO – EE and FO – rTAG at the same dose, EE is more effective than rTAG. Krill oil has been studied mainly at doses below 2000 mg per day, however has been found to be highly effective in the 4th and 5th positions of the treatment chart, so it should be used preferentially. KO – HPL and KO are better than fish oil dosage forms such as EE, rTAG or KO – LPL.

**1. 8. Results of paired treatment ranking of HDL-C**

**Table B.7. Paired treatment comparison league tables on net estimates of HDL-C**

The results of each comparison will be expressed with MD [95% CI], where MD: mean difference, 95% CI: 95% confidence interval. Statistically significant results are shown in bold. Upper triangle (blue shows pooled effect size of direct comparisons. Lower triangle (pink): estimated effect size for each comparison. MD > 0 favors treatment intervention in column than intervention in row, “.” There is no direct comparison.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **FO - EE < 2** | . | . | . | 0.00  [-0.10; 0.10] | . | . | . | . | . | . | . | **-0.09**  **[-0.17; -0.01]** | -0.03  [-0.11; 0.04] |
| -0.09  [-0.22; 0.04] | **FO - EE < 3** | . | . | . | . | . | . | . | . | . | . | . | 0.05  [-0.07; 0.17] |
| 0.10  [-0.03; 0.24] | **0.19**  **[ 0.02; 0.36]** | **FO - EE > 3** | . | . | . | . | . | . | . | . | . | . | **-0.14**  **[-0.26; -0.03]** |
| 0.03  [-0.12; 0.19] | 0.12  [-0.06; 0.31] | -0.07  [-0.26; 0.11] | FO - EM < 2 | . | . | . | . | . | . | . | . | . | -0.07  [-0.21; 0.07] |
| 0.03  [-0.06; 0.12] | 0.12  [-0.03; 0.27] | -0.07  [-0.22; 0.07] | -0.00  [-0.17; 0.17] | **FO - rTAG < 2** | . | . | . | . | . | . | . | . | -0.10  [-0.20; 0.00] |
| -0.08  [-0.17; 0.00] | 0.01  [-0.13; 0.14] | **-0.19**  **[-0.32; -0.05]** | -0.12  [-0.27; 0.04] | -0.11  [-0.22; 0.00] | **FO - TG < 2** | . | -0.02  [-0.09; 0.05] | . | . | . | . | 0.10  [-0.07; 0.27] | -0.01  [-0.17; 0.14] |
| -0.33  [-0.70; 0.04] | -0.24  [-0.63; 0.15] | **-0.43**  **[-0.82; -0.05]** | -0.36  [-0.76; 0.03] | -0.36  [-0.74; 0.02] | -0.25  [-0.62; 0.13] | **FO - TG < 3** | . | . | . | . | . | . | 0.29  [-0.08; 0.66] |
| **-0.10**  **[-0.16; -0.03]** | -0.01  [-0.13; 0.12] | **-0.20**  **[-0.32; -0.08]** | -0.13  [-0.27; 0.01] | **-0.13**  **[-0.22; -0.03]** | -0.02  [-0.08; 0.04] | 0.23  [-0.14; 0.60] | **FO < 2** | -0.01  [-0.14; 0.12] | . | . | . | -0.06  [-0.18; 0.05] | **0.06**  **[ 0.03; 0.09]** |
| **-0.11**  **[-0.19; -0.04]** | -0.02  [-0.15; 0.11] | **-0.22**  **[-0.35; -0.09]** | -0.15  [-0.30; 0.00] | **-0.14**  **[-0.24; -0.04]** | -0.03  [-0.11; 0.05] | 0.22  [-0.15; 0.59] | -0.02  [-0.07; 0.04] | **FO < 3** | . | . | . | . | **0.07**  **[ 0.02; 0.12]** |
| 0.07  [-0.01; 0.16] | **0.16**  **[ 0.03; 0.30]** | -0.03  [-0.17; 0.10] | 0.04  [-0.11; 0.20] | 0.04  [-0.07; 0.15] | **0.16**  **[ 0.07; 0.25]** | **0.40**  **[ 0.03; 0.78]** | **0.17**  **[ 0.10; 0.24]** | **0.19**  **[ 0.11; 0.27]** | **FO > 3** | . | . | . | **-0.11**  **[-0.18; -0.05]** |
| -0.11  [-0.35; 0.13] | -0.02  [-0.28; 0.24] | -0.21  [-0.47; 0.05] | -0.14  [-0.41; 0.13] | -0.14  [-0.39; 0.11] | -0.03  [-0.27; 0.21] | 0.22  [-0.21; 0.65] | -0.01  [-0.24; 0.22] | 0.00  [-0.23; 0.24] | -0.18  [-0.42; 0.06] | KO - HPL < 2 | 0.04  [-0.22; 0.30] | . | 0.07  [-0.16; 0.30] |
| -0.07  [-0.34; 0.20] | 0.02  [-0.27; 0.31] | -0.17  [-0.46; 0.11] | -0.10  [-0.40; 0.19] | -0.10  [-0.37; 0.17] | 0.01  [-0.25; 0.28] | 0.26  [-0.19; 0.71] | 0.03  [-0.23; 0.29] | 0.04  [-0.22; 0.31] | -0.14  [-0.41; 0.12] | 0.04  [-0.22; 0.30] | KO - LPL < 2 | . | 0.03  [-0.23; 0.29] |
| **-0.08**  **[-0.14; -0.02]** | 0.01  [-0.12; 0.14] | **-0.19**  **[-0.32; -0.06]** | -0.12  [-0.27; 0.03] | **-0.11**  **[-0.21; -0.02]** | -0.00  [-0.08; 0.07] | 0.25  [-0.12; 0.62] | 0.01  [-0.04; 0.07] | 0.03  [-0.04; 0.10] | **-0.16**  **[-0.24; -0.08]** | 0.03  [-0.21; 0.26] | -0.01  [-0.28; 0.25] | **KO < 2** | 0.04  [-0.02; 0.10] |
| -0.04  [-0.10; 0.02] | 0.05  [-0.07; 0.17] | **-0.14**  **[-0.26; -0.03]** | -0.07  [-0.21; 0.07] | -0.07  [-0.16; 0.02] | 0.04  [-0.02; 0.11] | 0.29  [-0.08; 0.66] | **0.06**  **[ 0.03; 0.09]** | **0.07**  **[ 0.03; 0.12]** | **-0.11**  **[-0.18; -0.05]** | 0.07  [-0.16; 0.30] | 0.03  [-0.23; 0.29] | 0.04  [-0.01; 0.09] | Placebo |

The League Table B.(Table B.3) shows statistically significant pairwise treatment comparisons including: FO - EE < 2 is more effective in increasing HDL-C than (FO < 3, FO < 2, KO < 2) ; At the same time, FO - EE < 3 is more effective (FO - EE > 3, FO > 3, FO - TG < 2, FO - TG < 3, FO < 2). Using FO < 3 is more effective than FO > 3, similarly (FO - TG < 2, FO - TG < 3, FO < 2, FO < 3, KO < 2) is more effective than FO - EE > 3 Between KO < 2 and FO > 3, KO < 2 is preferred. In addition, in 20 pairs of comparisons with direct evidence, there are 5 comparisons between: (FO - EE > 3, FO < 2, FO < 3, FO > 3) compared to Placebo and FO - EE < 2 with KO < 2 only contributed to a statistically significant pooled effect size for the HDL-C network model.

**1. 9. The results of testing the minimum properties of the insect network are consistent on the HDL-C**

**A. Cochrane Q' decomposition**

**Table B.8:** Cochrane Q' analysis on HDL-C index

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Q statistics to assess homogeneity / consistency** | | | | | |
|  | | | **Q** | **df** | **p-value** |
| Total | | | 67.59 | 56 | 0.1380 |
| Within designs | | | 57.90 | 48 | 0.1551 |
| Between designs | | | 9.69 | 8 | 0.2875 |
| **Design-specific decomposition of within-designs Q statistic** | | | | | |
| **Design** | | | **Q** | **df** | **p-value** |
| Placebo: FO > 3 | | | **6.07** | 2 | 0.0480 |
| Placebo: FO < 2 | | | **26.39** | 16 | 0.0487 |
| Placebo: KO < 2 | | | 9.61 | 5 | 0.0870 |
| Placebo: FO - EE > 3 | | | 4.84 | 3 | 0.1839 |
| Placebo: FO < 3 | | | 8.77 | 9 | 0.4588 |
| Placebo: FO < 2: FO < 3 | | | 0.86 | 2 | 0.6497 |
| Placebo: FO - EM < 2 | | | 0.08 | 1 | 0.7739 |
| Placebo: FO < 2: KO < 2 | | | 0.69 | 4 | 0.9532 |
| Placebo: FO - EE < 2: FO - rTAG < 2 | | | 0.53 | 4 | 0.9706 |
| Placebo: FO - TG < 2 | | | 0.05 | 2 | 0.9757 |
| **Between-designs Q statistic after detaching of single designs**  **(influential designs have p-value markedly different from 0.2875)** | | | | | |
| **Detached design** | | | **Q** | **df** | **p-value** |
| Placebo: FO - EE < 2 | | | **4.89** | **7** | **0.6739** |
| FO - TG < 2: KO < 2 | | | 7.42 | 7 | 0.3864 |
| Placebo: FO < 2: KO < 2 | | | 7.88 | 6 | 0.2472 |
| Placebo: FO - TG < 2 | | | 9.34 | 7 | 0.2293 |
| FO - TG < 2: FO < 2 | | | 9.35 | 7 | 0.2285 |
| Placebo: FO < 2 | | | 9.48 | 7 | 0.2202 |
| FO - EE < 2: KO < 2 | | | 9.49 | 7 | 0.2196 |
| Placebo: KO < 2 | | | 9.52 | 7 | 0.2176 |
| Placebo: FO < 3 | | | 9.52 | 7 | 0.2171 |
| Placebo: FO < 2: FO < 3 | | | 9.52 | 6 | 0.1465 |
| **Q statistic to assess consistency under the assumption of**  **a full design-by-treatment interaction random effects model** | | | | | |
|  | **Q** | **df** | **p-value** | **tau.within** | **tau2.within** |
| Between designs | **8.64** | 8 | **0.3734** | 0.0302 | 0.0009 |

Q' Cochrane dissociation results (Table B.1) show that the cause of this heterogeneity of this HDL-C NMA is the results of comparisons between placebo with: FO < 2, FO > 3, (*p =*0.048). However, this p-value was close to 0.05 and the comparative designs of these interventions did not significantly affect the entire NMA after implementing the Q node separation method, resulting in negligible heterogeneity of HDL-C NMAs (Q decreased significantly from 57.90 to 8.64, *p =*0.3734).

**B. Visualization using a net heat chart:**A chart with different colored squares

Description automatically generated with medium confidence

**Figure B. 6. Net heat chart of HDL-C index**

The net heat chart is a visualization from performing a Q' Cochrane split, the area of the gray square showing the contribution of a direct estimate of a design in the column to the network estimate in the row, the larger the gray cell, the more important the comparison. Background color was associated with a change in inconsistency between direct and indirect evidence in in-row network estimates, after loosening consistent assumptions about the impact of a design in the column. The metrics 0, 1, 2, 3 next to the chart can indicate the extent of the difference or the impact of the comparison: 0 may indicate no difference, while 3 indicates a larger difference.

Observing the net heat chart (Figure B. 4), there are 12 study designs that affect the inconsistency of the HDL-C NMA. In terms of the contribution of the estimates directly to the network estimate, we see that the large gray cells are mostly concentrated diagonally, the vertical axis of Placebo: FO < 2 and the upper right corner of the netheat, so these cells have a strong direct estimate of the network estimate (Placebo: FO < 2 had a large impact on the majority of network estimates (*6th vertical column from left*), similarly in Placebo: FO < 3 major contributors to Placebo network estimates: FO < 3\_Placebo:FO < 2: FO < 3). At the same time, the main diagonal consists entirely of the light gray cell, suggesting that the comparison of each group with itself will have no difference (in the study designs: Placebo: KO < 2, Placebo: FO < 2, FO - EE < 2: KO < 2, FO - TG < 2: FO < 2 and Placebo: FO < 3).

In terms of inconsistency, only the comparison pair "FO – EE < 2" and "Placebo" in the top left corner are dark yellow in color range number 3, suggesting that the difference between these conditions is probably the most significant and recognizable (however unaffected because p = 0.6739 > 0.05, Table B.4). Other comparisons show no inconsistencies.

**C. SIDE Analysis**

**Table B.9:**SIDE analysis results on HDL-C index

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No | Comparison | k | prop | nma | direct | indir. | Diff | z | p-value |
| 1 | FO - EE < 2:FO - EE < 3 | 0 | 0 | -0.0896 | . | -0.0896 | . | . | . |
| 2 | FO - EE < 2:FO - EE > 3 | 0 | 0 | 0.1046 | . | 0.1046 | . | . | . |
| 3 | FO - EE < 2:FO - EM < 2 | 0 | 0 | 0.0329 | . | 0.0329 | . | . | . |
| 4 | FO - EE < 2:FO - rTAG < 2 | 3 | **0.85** | 0.0306 | 0.0000 | 0.1981 | -0.1981 | -1.56 | 0.1185 |
| 5 | FO - EE < 2:FO - TG < 2 | 0 | 0 | -0.0822 | . | -0.0822 | . | . | . |
| 6 | FO - EE < 2:FO - TG < 3 | 0 | 0 | -0.3296 | . | -0.3296 | . | . | . |
| 7 | **FO - EE < 2: FO < 2** | 0 | 0 | -0.0977 | . | -0.0977 | . | . | . |
| 8 | **FO - EE < 2: FO < 3** | 0 | 0 | -0.1130 | . | -0.1130 | . | . | . |
| 9 | FO - EE < 2:FO > 3 | 0 | 0 | 0.0746 | . | 0.0746 | . | . | . |
| 10 | FO - EE < 2:KO - HPL < 2 | 0 | 0 | -0.1096 | . | -0.1096 | . | . | . |
| 11 | FO - EE < 2:KO - LPL < 2 | 0 | 0 | -0.0696 | . | -0.0696 | . | . | . |
| 12 | **FO - EE < 2: KO < 2** | 1 | **0.56** | -0.0833 | -0.0900 | -0.0748 | -**0.0152** | -0.25 | 0.8046 |
| 13 | FO - EE < 2:Placebo | 4 | **0.65** | -0.0396 | -0.0344 | -0.0493 | **0.0149** | 0.24 | 0.8079 |
| 14 | **FO - EE < 3: FO - EE > 3** | 0 | 0 | 0.1943 | . | 0.1943 | . | . | . |
| 15 | FO - EE < 3:FO - EM < 2 | 0 | 0 | 0.1225 | . | 0.1225 | . | . | . |
| 16 | FO - EE < 3:FO - rTAG < 2 | 0 | 0 | 0.1202 | . | 0.1202 | . | . | . |
| 17 | **FO - EE < 3: FO - TG < 2** | 0 | 0 | 0.0074 | . | 0.0074 | . | . | . |
| 18 | **FO - EE < 3: FO - TG < 3** | 0 | 0 | -0.2400 | . | -0.2400 | . | . | . |
| 19 | **FO - EE < 3: FO < 2** | 0 | 0 | -0.0080 | . | -0.0080 | . | . | . |
| 20 | **FO - EE < 3: FO < 3** | 0 | 0 | -0.0234 | . | -0.0234 | . | . | . |
| 21 | FO - EE < 3:FO > 3 | 0 | 0 | 0.1642 | . | 0.1642 | . | . | . |
| 22 | FO - EE < 3:KO - HPL < 2 | 0 | 0 | -0.0200 | . | -0.0200 | . | . | . |
| 23 | FO - EE < 3:KO - LPL < 2 | 0 | 0 | 0.0200 | . | 0.0200 | . | . | . |
| 24 | FO - EE < 3:KO < 2 | 0 | 0 | 0.0063 | . | 0.0063 | . | . | . |
| 25 | FO - EE < 3:Placebo | 1 | **1.00** | 0.0500 | 0.0500 | . | . | . | . |
| 26 | FO - EE > 3:FO - EM < 2 | 0 | 0 | -0.0717 | . | -0.0717 | . | . | . |
| 27 | FO - EE > 3:FO - rTAG < 2 | 0 | 0 | -0.0741 | . | -0.0741 | . | . | . |
| 28 | **FO - EE > 3: FO - TG < 2** | 0 | 0 | -0.1869 | . | -0.1869 | . | . | . |
| 29 | **FO - EE > 3: FO - TG < 3** | 0 | 0 | -0.4343 | . | -0.4343 | . | . | . |
| 30 | **FO - EE > 3: FO < 2** | 0 | 0 | -0.2023 | . | -0.2023 | . | . | . |
| 31 | FO - EE > 3:FO < 3 | 0 | 0 | -0.2176 | . | -0.2176 | . | . | . |
| 32 | FO - EE > 3:FO > 3 | 0 | 0 | -0.0300 | . | -0.0300 | . | . | . |
| 33 | FO - EE > 3:KO - HPL < 2 | 0 | 0 | -0.2143 | . | -0.2143 | . | . | . |
| 34 | FO - EE > 3:KO - LPL < 2 | 0 | 0 | -0.1743 | . | -0.1743 | . | . | . |
| 35 | FO - EE > 3:KO < 2 | 0 | 0 | -0.1879 | . | -0.1879 | . | . | . |
| 36 | FO - EE > 3:Placebo | 4 | **1.00** | -0.1443 | -0.1443 | . | . | . | . |
| 37 | FO - EM < 2:FO - rTAG < 2 | 0 | 0 | -0.0024 | . | -0.0024 | . | . | . |
| 38 | FO - EM < 2:FO - TG < 2 | 0 | 0 | -0.1151 | . | -0.1151 | . | . | . |
| 39 | FO - EM < 2:FO - TG < 3 | 0 | 0 | -0.3625 | . | -0.3625 | . | . | . |
| 40 | FO - EM < 2:FO < 2 | 0 | 0 | -0.1306 | . | -0.1306 | . | . | . |
| 41 | FO - EM < 2:FO < 3 | 0 | 0 | -0.1459 | . | -0.1459 | . | . | . |
| 42 | FO - EM < 2:FO > 3 | 0 | 0 | 0.0417 | . | 0.0417 | . | . | . |
| 43 | FO - EM < 2:KO - HPL < 2 | 0 | 0 | -0.1425 | . | -0.1425 | . | . | . |
| 44 | FO - EM < 2:KO - LPL < 2 | 0 | 0 | -0.1025 | . | -0.1025 | . | . | . |
| 45 | FO - EM < 2:KO < 2 | 0 | 0 | -0.1162 | . | -0.1162 | . | . | . |
| 46 | FO - EM < 2:Placebo | 2 | **1.00** | -0.0725 | -0.0725 | . | . | . | . |
| 47 | FO - rTAG < 2:FO - TG < 2 | 0 | 0 | -0.1128 | . | -0.1128 | . | . | . |
| 48 | FO - rTAG < 2:FO - TG < 3 | 0 | 0 | -0.3602 | . | -0.3602 | . | . | . |
| 49 | FO - rTAG < 2:FO < 2 | 0 | 0 | -0.1282 | . | -0.1282 | . | . | . |
| 50 | FO - rTAG < 2:FO < 3 | 0 | 0 | -0.1435 | . | -0.1435 | . | . | . |
| 51 | FO - rTAG < 2:FO > 3 | 0 | 0 | 0.0441 | . | 0.0441 | . | . | . |
| 52 | FO - rTAG < 2:KO - HPL < 2 | 0 | 0 | -0.1402 | . | -0.1402 | . | . | . |
| 53 | FO - rTAG < 2:KO - LPL < 2 | 0 | 0 | -0.1002 | . | -0.1002 | . | . | . |
| 54 | FO - rTAG < 2:KO < 2 | 0 | 0 | -0.1138 | . | -0.1138 | . | . | . |
| 55 | FO - rTAG < 2:Placebo | 3 | **0.85** | -0.0702 | -0.0998 | 0.1027 | -0.2025 | -1.57 | 0.1173 |
| 56 | FO - TG < 2:FO - TG < 3 | 0 | 0 | -0.2474 | . | -0.2474 | . | . | . |
| 57 | FO - TG < 2:FO < 2 | 1 | **0.75** | -0.0154 | -0.0200 | -0.0019 | **-0.0181** | -0.25 | 0.7992 |
| 58 | FO - TG < 2:FO < 3 | 0 | 0 | -0.0308 | . | -0.0308 | . | . | . |
| 59 | FO - TG < 2:FO > 3 | 0 | 0 | 0.1568 | . | 0.1568 | . | . | . |
| 60 | FO - TG < 2:KO - HPL < 2 | 0 | 0 | -0.0274 | . | -0.0274 | . | . | . |
| 61 | FO - TG < 2:KO - LPL < 2 | 0 | 0 | 0.0126 | . | 0.0126 | . | . | . |
| 62 | FO - TG < 2:KO < 2 | 1 | **0.19** | -0.0011 | 0.1000 | -0.0245 | 0.1245 | 1.27 | 0.2055 |
| 63 | FO - TG < 2:Placebo | 3 | **0.17** | 0.0426 | -0.0147 | 0.0545 | -**0.0692** | -0.80 | 0.4227 |
| 64 | FO - TG < 3:FO < 2 | 0 | 0 | 0.2320 | . | 0.2320 | . | . | . |
| 65 | FO - TG < 3:FO < 3 | 0 | 0 | 0.2166 | . | 0.2166 | . | . | . |
| 66 | FO - TG < 3:FO > 3 | 0 | 0 | 0.4042 | . | 0.4042 | . | . | . |
| 67 | FO - TG < 3:KO - HPL < 2 | 0 | 0 | 0.2200 | . | 0.2200 | . | . | . |
| 68 | FO - TG < 3:KO - LPL < 2 | 0 | 0 | 0.2600 | . | 0.2600 | . | . | . |
| 69 | FO - TG < 3:KO < 2 | 0 | 0 | 0.2463 | . | 0.2463 | . | . | . |
| 70 | FO - TG < 3:Placebo | 1 | **1.00** | 0.2900 | 0.2900 | . | . | . | . |
| 71 | FO < 2:FO < 3 | 2 | 0.17 | -0.0153 | -0.0109 | -0.0163 | **0.0054** | 0.07 | 0.9412 |
| 72 | FO < 2:FO > 3 | 0 | 0 | 0.1723 | . | 0.1723 | . | . | . |
| 73 | FO < 2:KO - HPL < 2 | 0 | 0 | -0.0120 | . | -0.0120 | . | . | . |
| 74 | FO < 2:KO - LPL < 2 | 0 | 0 | 0.0280 | . | 0.0280 | . | . | . |
| 75 | FO < 2:KO < 2 | 3 | 0.23 | 0.0144 | -0.0641 | 0.0375 | -0.1016 | -1.55 | 0.1219 |
| 76 | FO < 2:Placebo | **22** | **0.92** | 0.0580 | 0.0587 | 0.0508 | **0.0079** | 0.15 | 0.8831 |
| 77 | FO < 3:FO > 3 | 0 | 0 | 0.1876 | . | 0.1876 | . | . | . |
| 78 | FO < 3:KO - HPL < 2 | 0 | 0 | 0.0034 | . | 0.0034 | . | . | . |
| 79 | FO < 3:KO - LPL < 2 | 0 | 0 | 0.0434 | . | 0.0434 | . | . | . |
| 80 | **FO < 3: KO < 2** | 0 | 0 | 0.0297 | . | 0.0297 | . | . | . |
| 81 | FO < 3:Placebo | **12** | **0.90** | 0.0734 | 0.0738 | 0.0693 | **0.0045** | 0.06 | 0.9557 |
| 82 | FO > 3:KO - HPL < 2 | 0 | 0 | -0.1842 | . | -0.1842 | . | . | . |
| 83 | FO > 3:KO - LPL < 2 | 0 | 0 | -0.1442 | . | -0.1442 | . | . | . |
| 84 | FO > 3:KO < 2 | 0 | 0 | -0.1579 | . | -0.1579 | . | . | . |
| 85 | FO > 3:Placebo | 3 | **1.00** | -0.1142 | -0.1142 | . | . | . | . |
| 86 | KO - HPL < 2:KO - LPL < 2 | 1 | **1.00** | 0.0400 | 0.0400 | . | . | . | . |
| 87 | KO - HPL < 2:KO < 2 | 0 | 0 | 0.0263 | . | 0.0263 | . | . | . |
| 88 | KO - HPL < 2:Placebo | 1 | **1.00** | 0.0700 | 0.0700 | . | . | . | . |
| 89 | KO - LPL < 2:KO < 2 | 0 | 0 | -0.0137 | . | -0.0137 | . | . | . |
| 90 | KO - LPL < 2:Placebo | 1 | **1.00** | 0.0300 | 0.0300 | . | . | . | . |
| 91 | KO < 2:Placebo | **9** | **0.67** | 0.0437 | 0.0389 | 0.0535 | -0.0146 | -0.27 | 0.7845 |

Comment:

|  |  |
| --- | --- |
| comparison | Treatment comparison |
| k | Number of studies that provide direct evidence |
| prop | The ratio of direct evidence to the total amount of evidence available |
| nma | Estimated Treatment Effect (MD) in Network Meta-Analysis |
| direct | Estimated treatment efficacy (MD) derives from direct evidence |
| indir. | Estimated treatment efficacy (MD) derived from circumstantial evidence |
| Diff | The difference between direct and indirect processing estimates |
| *z* | * The *z-value* of the test disagrees between estimates from direct and indirect evidence |
| p-value | The *p-value* of the test disagrees between estimation from direct and indirect evidence |

The SIDE analysis aimed at assessing inconsistencies between study designs including both direct and indirect evidence (Table B.2), had a total of 91 comparisons made between interventions, of which 20 study designs had direct evidence (21.98%), and 83 study designs with circumstantial evidence (91.21%). While only 12 study designs had both indirect and direct evidence (13.19 percent), the diff, *z-value* and p-value (>0.05) values of these 12 comparable stars all showed negligible differences between the evidence. In addition, according to the k-value, there are only 3 comparisons between placebo and: KO < 2, FO < 3, and FO < 2 that there are many studies that provide direct evidence (prop*=*0.67 to 0.92), there are also 8 comparisons where most of the evidence is provided directly (prop = 1.00), increases the reliability of the results. However, for comparisons with negative diff numbers such as: FO - EE < 2:FO - rTAG < 2, FO - EE < 2:KO < 2, FO - rTAG < 2:Placebo, FO - TG < 2:FO < 2, FO - TG < 2:Placebo, FO < 2:KO < 2, KO < 2:Placebo has a greater estimated therapeutic effect from indirect evidence than direct evidence, further consideration should be given to the feasibility and reliability of circumstantial evidence of these comparative pairs (indir).

In pair-to-pair treatment comparisons in the league table, compared with the SIDE analysis, only FO - EE < 2 versus KO < 2 had direct evidence, while the remaining treatment effects as stated in the **Table B.3** results had only indirect evidence.

Comparisons of highly effective interventions (according to SUCRA) show that only: KO < 2:Placebo, FO - TG < 3:Placebo, FO < 2:Placebo, FO < 3:Placebo, KO - HPL < 2:KO - LPL < 2, KO - HPL < 2:Placebo, KO - LPL < 2:Placebo have direct evidence.

**1. 10. Results of testing publication bias of the HDL-C network model**

A diagram of a graph

Description automatically generated with medium confidence

**Figure B.7. Results of published bias analysis for HDL-C**

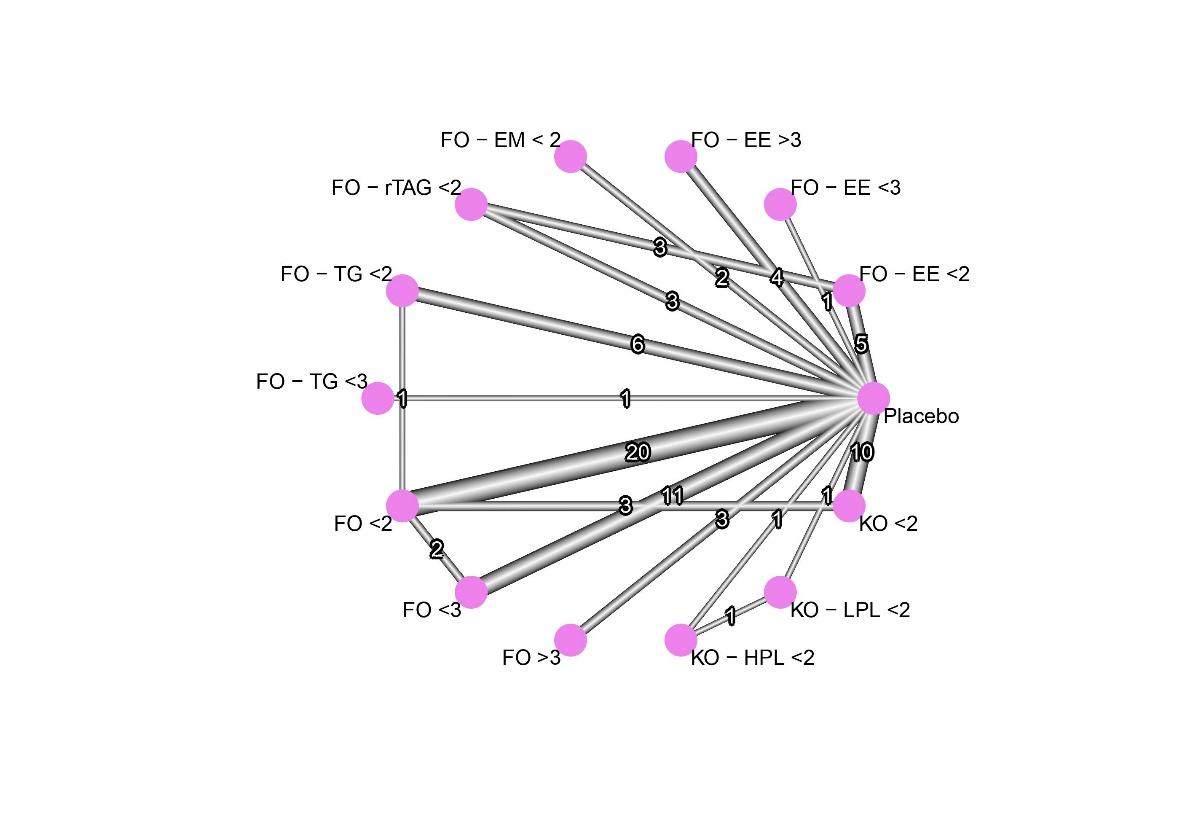
*The standard error (SE) of the intervention estimation is expressed on the vertical axis, the mean differential of the specific comparison effect (horizontal axis). 2 The Triangular edge represents the 95% confidence interval of the studies, the more concentrated the studies above and fit within the 95% CI, the higher the confidence.*

There are 20 direct comparison pairs presented as funnel charts to assess publishing bias (Fig. 5). Observations of the graph are quite symmetrical, showing that no publication bias or small-sized studies tend to report larger or smaller effects than large studies. At the same time, the results of testing the asymmetry of funnel graphs (Table B.6) after linear regression to assess the uniformity of the data and the reliability of the NMA HDL-C analysis were also conducted. There is insufficient statistical evidence that there is an asymmetry of the graph, most measures of the effectiveness of intervention pairs are within confidence intervals, which are highly accurate *(with a value t = 1.69 (range: -1.96 à 1.96) with degrees of freedom df = 76 and p-value = 0.0957 < 0.05).* The deviation estimate is 0.2913 with a standard deviation (SE) of 0.1727, indicating a degree of certainty of this HDL-C NMA result. In summary, the NMA HDL-C results based on our analysis have uniformity and reliable results.

**Table B.10:** Asymmetry test results of funnel chart after linear regression

|  |  |  |
| --- | --- | --- |
| **Linear regression test of funnel plot asymmetry** | | |
| Test result:t = 1.69 | df = 76 | p-value = 0.0957 |
| Bias estimate: | 0.2913 | (SE = 0.1727) |
| Details:  - multiplicative residual heterogeneity variance (tau^2 = 0.8501)  - predictor:standard error  - weight:inverse variance  - reference:Egger et al. (1997)- BMJ | | |

**1. 11. Net graph results of LDL-C**



**Figure B.8. Net graph estimates the effect of interfering oils on LDL**

**Three-cell interventionsinclude:**

|  |  |
| --- | --- |
| 1.FO - EE < 2 | Ethyl ester fish oil (DHA + EPA) 300 - 1900 mg |
| 2.FO - EE < 3 | Ethyl ester fish oil (DHA + EPA) 2000 - 2900 mg |
| 3.FO - EE > 3 | Ethyl ester fish oil (DHA + EPA) > 3000 mg |
| 4.FO < 2 | Fish oil capsules (DHA + EPA) 300 – 1900 mg |
| 5.FO < 3 | Fish oil capsules (DHA + EPA) 2000 - 2900 mg |
| 6.FO > 3 | Fish oil capsules (DHA + EPA) > 3000mg |
| 7.FO - EM < 2 | Emulsified fish oil (DHA + EPA) 300 – 1900 mg |
| 8.FO - rTAG < 2 | Re-esterified triacylglycerole (DHA+EPA) fish oil between 300 and 1900 mg |
| 9.FO - TG < 2 | Triglyceride fish oil, (DHA + EPA) between 300 and 1900 mg |
| 10.FO - TG < 3 | Triglyceride fish oil, (DHA + EPA) from 2000 to 2900 mg |
| 11.KO - HPL < 2 | Krill oil has a high phospholipid content (DHA + EPA) of 300 - 1900 mg |
| 12.KO - LPL < 2 | Krill oil has a low phospholipid content (DHA + EPA) of 300 – 1900 mg |
| 13.KO < 2 | Krill oil capsules, (DHA + EPA) between 300 - 1900 mg |
| 14.Placebo | Placebo |

LDL network geometry (Figure B. 1) shows a total of 60 studies involving LDL-C - index, which included 78 pair-specific comparisons between 14 dosage forms with different doses of fish oil and krill oil. The most numerous comparisons were in FO <2, FO < 3, and KO < 2 pairs versus placebo (20, 11, and 10, respectively). The remaining interventions, with relatively few comparisons, were all below 6.

There are three indicators used to assess heterogeneity/inconsistency in data as follows:

1. tau2 = 0.0751: Used to evaluate heterogeneity/inconsistency in data.

2. tau = 0.2741: Used to measure the degree of heterogeneity/inconsistency.

3.I2= 87.9% [85.1%; 90.2%]: Denotes the percentage of variance between the study results due to the difference between them, rather than by random variation. The higher this value, the greater the variability between studies.

From the above 3 indicators, tau and tau2are quite high, indicating a large degree of heterogeneity / inconsistency of the regression model with the data. The I2value is high, indicating a large heterogeneity between studies in the analysis.

**Table B.11:** Net graph results of LDL-C

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number of studies: k = 60  Number of pairwise comparisons: m = 78  Number of treatments: n = 14  Number of designs: d = 15  Random effects model  Treatment estimate (sm = 'MD', comparison: other treatments vs 'Placebo'): | | | | |
|  | MD | 95%-CI | z | p-value |
| **FO - EE < 2** | **-0.3077** | **[-0.5804; -0.0351]** | **-2.21** | **0.0270** |
| FO - EE < 3 | 0.1000 | [-0.5016; 0.7016] | 0.33 | 0.7446 |
| **FO - EE > 3** | **-0.5970** | **[-1.0462; -0.1479]** | **-2.61** | **0.0092** |
| FO - EM < 2 | -0.0381 | [-0.4964; 0.4201] | -0.16 | 0.8704 |
| **FO - rTAG < 2** | **-0.3171** | **[-0.6550; 0.0208]** | **-1.84** | **0.0659** |
| FO - TG < 2 | -0.0010 | [-0.2699; 0.2680] | -0.01 | 0.9945 |
| FO - TG < 3 | -0.2600 | [-1.4172; 0.8972] | -0.44 | 0.6597 |
| FO < 2 | -0.0320 | [-0.1701; 0.1060] | -0.45 | 0.6494 |
| FO < 3 | 0.1190 | [-0.0931; 0.3310] | 1.10 | 0.2715 |
| FO > 3 | 0.2520 | [-0.1132; 0.6172] | 1.35 | 0.1763 |
| KO - HPL < 2 | 0.2400 | [-0.4655; 0.9455] | 0.67 | 0.5049 |
| KO - LPL < 2 | 0.2000 | [-0.5379; 0.9379] | 0.53 | 0.5953 |
| KO < 2 | 0.1022 | [-0.0995; 0.3039] | 0.99 | 0.3207 |
| Placebo | . | . | . | . |
| Quantifying heterogeneity / inconsistency: | | | | |
| tau2 = 0.0751 | tau = 0.2741 | **I2= 87.9% [85.1%; 90.2%]** | | |
| Tests of heterogeneity (within designs) and inconsistency (between designs): | | | | |
|  | | Q | d.f. | p-value |
| Total | | **462.14** | 56 | **< 0.0001** |
| Within designs | | 386.55 | 50 | < 0.0001 |
| Between designs | | 75.59 | 6 | < 0.0001 |

**1. 12. Research results of LDL-C**

A close-up of a graph

Description automatically generated

**Figure B.9. LDL–C forest chart**

The forest chart (Figure B. 2) and Table B.1 results show that most studies using fish oil have yielded positive effects. In particular, FO – EE > 3 (MD = -0.5970, 95% CI = [-1.0462; -0.1479], z = -2.61 < - 1.96, p = 0.0092) and FO – EE < 2 (MD = -0.3077, 95%CI = [-0.5804; -0.0351], z = -2.21 < - 1.96, p = 0.0270) bring the highest LDL - C reduction effect. Meanwhile, using the following forms: FO - rTAG < 2, FO - TG < 3, FO - TG < 2, FO - EM < 2 or FO < 2 for therapeutic effect but not statistically significant. The use of fish oil in doses above 2000 mg per day (even the EE 2000 - 3000 mg form) and krill oil forms have no effect on LDL-C - as shown by MD > 0.

**1. 13. Rankogram and SUCRA scores of LDL-C**

**Table B.12. Rankogram results of LDL - C index**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| **FO - EE < 2** | 0.06 | 0.22 | **0.33** | 0.23 | 0.11 | 0.04 | 0.01 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - EE < 3** | 0.01 | 0.03 | 0.04 | 0.07 | 0.09 | 0.06 | 0.05 | 0.05 | 0.07 | 0.07 | 0.08 | 0.13 | **0.14** | 0.12 |
| **FO - EE > 3** | **0.54** | 0.28 | 0.10 | 0.05 | 0.02 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - EM < 2** | 0.01 | 0.04 | 0.08 | 0.12 | **0.14** | 0.09 | 0.07 | 0.06 | 0.08 | 0.08 | 0.08 | 0.07 | 0.06 | 0.03 |
| **FO - rTAG < 2** | 0.08 | 0.25 | **0.26** | 0.21 | 0.11 | 0.04 | 0.02 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FO - TG < 2** | 0.00 | 0.01 | 0.02 | 0.08 | 0.12 | **0.14** | 0.11 | 0.11 | 0.12 | 0.10 | 0.10 | 0.05 | 0.02 | 0.01 |
| **FO - TG < 3** | **0.27** | 0.13 | 0.09 | 0.07 | 0.05 | 0.03 | 0.02 | 0.03 | 0.02 | 0.04 | 0.03 | 0.05 | 0.07 | 0.11 |
| **FO < 2** | 0.00 | 0.00 | 0.01 | 0.06 | 0.14 | **0.25** | 0.20 | 0.14 | 0.11 | 0.05 | 0.02 | 0.01 | 0.01 | 0.00 |
| FO < 3 | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.04 | 0.08 | 0.10 | 0.13 | 0.19 | **0.21** | 0.14 | 0.08 | 0.02 |
| FO > 3 | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.02 | 0.03 | 0.03 | 0.06 | 0.08 | 0.13 | 0.19 | **0.24** | 0.18 |
| KO - HPL < 2 | 0.01 | 0.03 | 0.03 | 0.04 | 0.05 | 0.03 | 0.03 | 0.04 | 0.06 | 0.06 | 0.07 | 0.12 | 0.15 | **0.27** |
| KO - LPL < 2 | 0.02 | 0.03 | 0.04 | 0.04 | 0.06 | 0.05 | 0.04 | 0.04 | 0.04 | 0.05 | 0.07 | 0.11 | 0.17 | **0.25** |
| KO < 2 | 0.00 | 0.00 | 0.00 | 0.01 | 0.03 | 0.05 | 0.09 | 0.12 | 0.14 | **0.19** | 0.17 | 0.11 | 0.06 | 0.02 |
| Placebo | 0.00 | 0.00 | 0.00 | 0.01 | 0.05 | 0.16 | 0.26 | 0.26 | 0.16 | 0.08 | 0.03 | 0.00 | 0.00 | 0.00 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  |  | | --- | --- | |  | SUCRA | | **FO - EE > 3** | **93.80** | | **FO - EE < 2** | **81.98** | | **FO - rTAG < 2** | **81.49** | | **FO - TG < 3** | **63.15** | | **FO < 2** | **54.15** | | **FO - EM < 2** | **50.57** | | **Placebo** | 48.63 | | **FO - TG < 2** | 48.14 | | **FO - EE < 3** | 36.95 | | **KO < 2** | 34.02 | | **FO < 3** | 31.06 | | **KO - LPL < 2** | 29.36 | | **KO - HPL < 2** | 27.18 | | **FO > 3** | 19.53 | |

**Figure B.10. Rankogram and SUCRA results for LDL-C**

Based on the analysis of rankogram ratings and SUCRA scores, FO - EE > 3 (SUCRA = 93.80%), FO - EE < 2 (SUCRA = 81.98%), FO - rTAG < 2 (SUCRA = 81.49%), FO - TG < 3 (SUCRA = 63.15%), FO < 2 (SUCRA = 54.15%), FO - EM < 2 (SUCRA = 50.57%) has the highest LDL concentration reduction effect, with probabilities of 0.54, 0.33, 0.26, 0.27, 0.25 and 0.14, respectively. While different dosage forms and dosages of FO – TG < 2, FO – EE < 3, FO < 3, FO > 3 all have lower treatment ratings than placebo.

Thereby, we see that the use of ethyl ester fish oil with doses (DHA + EPA) < 2000 mg (from 300 - 1900mg) and > 3000 mg per day, or FO - rTAG low doses of less than 2000 mg (from 300 - 1900mg) is the highest LDL-C reduction effect. While the interventional forms of krill oil did not show positive effects, they ranked low (12 and 13 in SUCRA).

**1. 14. Results of paired treatment rankings of the LDL–C**

**Table B.13. League Table B. comparing treatment in pairs on network estimates of LDL-C**

The results of each comparison will be shown with MD [95% CI], where MD: mean differential error, 95% CI: 95% confidence interval. Statistically significant results are in bold. The upper triangle (blue) shows the pooled effect size of direct comparisons. Bottom triangle (pink): estimated effect size for each comparison. MD < 0 prefers processing intervention in column over intervention in row, "." There is no direct comparison.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FO - EE < 2 | . | . | . | 0.07  [-0.29; 0.42] | . | . | . | . | . | . | . | . | **-0.31**  **[-0.58; -0.04]** |
| -0.41  [-1.07; 0.25] | FO - EE < 3 | . | . | . | . | . | . | . | . | . | . | . | 0.10  [-0.50; 0.70] |
| 0.29  [-0.24; 0.81] | 0.70  [-0.05; 1.45] | FO - EE > 3 | . | . | . | . | . | . | . | . | . | . | **-0.60**  **[-1.05; -0.15]** |
| -0.27  [-0.80; 0.26] | 0.14  [-0.62; 0.89] | -0.56  [-1.20; 0.08] | FO - EM < 2 | . | . | . | . | . | . | . | . | . | -0.04  [-0.50; 0.42] |
| 0.01  [-0.33; 0.35] | 0.42  [-0.27; 1.11] | -0.28  [-0.84; 0.28] | 0.28  [-0.29; 0.85] | FO - rTAG < 2 | . | . | . | . | . | . | . | . | -0.26  [-0.62; 0.10] |
| -0.31  [-0.69; 0.08] | 0.10  [-0.56; 0.76] | **-0.60**  **[-1.12; -0.07]** | -0.04  [-0.57; 0.49] | -0.32  [-0.75; 0.12] | FO - TG < 2 | . | -0.25  [-0.80; 0.30] | . | . | . | . | . | 0.08  [-0.22; 0.39] |
| -0.05  [-1.24; 1.14] | 0.36  [-0.94; 1.66] | -0.34  [-1.58; 0.90] | 0.22  [-1.02; 1.47] | -0.06  [-1.26; 1.15] | 0.26  [-0.93; 1.45] | FO - TG < 3 | . | . | . | . | . | . | -0.26  [-1.42; 0.90] |
| -0.28  [-0.58; 0.03] | 0.13  [-0.49; 0.75] | **-0.57**  **[-1.03; -0.10]** | -0.01  [-0.48; 0.47] | -0.29  [-0.65; 0.08] | 0.03  [-0.26; 0.32] | -0.23  [-1.39; 0.94] | FO < 2 | -0.09  [-0.61; 0.43] | . | . | . | -0.07  [-0.47; 0.32] | -0.06  [-0.21; 0.08] |
| **-0.43**  **[-0.77; -0.08]** | -0.02  [-0.66; 0.62] | **-0.72**  **[-1.21; -0.22]** | -0.16  [-0.66; 0.35] | **-0.44**  **[-0.84; -0.04]** | -0.12  [-0.46; 0.22] | -0.38  [-1.56; 0.80] | -0.15  [-0.39; 0.09] | FO < 3 | . | . | . | . | 0.11  [-0.11; 0.33] |
| **-0.56**  **[-1.02; -0.10]** | -0.15  [-0.86; 0.55] | **-0.85**  **[-1.43; -0.27]** | -0.29  [-0.88; 0.30] | **-0.57**  **[-1.07; -0.07]** | -0.25  [-0.71; 0.20] | -0.51  [-1.73; 0.70] | -0.28  [-0.67; 0.11] | -0.13  [-0.56; 0.29] | FO > 3 | . | . | . | 0.25  [-0.11; 0.62] |
| -0.55  [-1.30; 0.21] | -0.14  [-1.07; 0.79] | -0.84  [-1.67; 0.00] | -0.28  [-1.12; 0.56] | -0.56  [-1.34; 0.23] | -0.24  [-1.00; 0.51] | -0.50  [-1.86; 0.86] | -0.27  [-0.99; 0.45] | -0.12  [-0.86; 0.62] | 0.01  [-0.78; 0.81] | KO - HPL < 2 | 0.04  [-0.72; 0.80] | . | 0.24  [-0.47; 0.95] |
| -0.51  [-1.29; 0.28] | -0.10  [-1.05; 0.85] | -0.80  [-1.66; 0.07] | -0.24  [-1.11; 0.63] | -0.52  [-1.33; 0.29] | -0.20  [-0.99; 0.58] | -0.46  [-1.83; 0.91] | -0.23  [-0.98; 0.52] | -0.08  [-0.85; 0.69] | 0.05  [-0.77; 0.88] | 0.04  [-0.72; 0.80] | KO - LPL < 2 | . | 0.20  [-0.54; 0.94] |
| **-0.41**  **[-0.75; -0.07]** | -0.00  [-0.64; 0.63] | **-0.70**  **[-1.19; -0.21]** | -0.14  [-0.64; 0.36] | **-0.42**  **[-0.81; -0.03]** | -0.10  [-0.44; 0.23] | -0.36  [-1.54; 0.81] | -0.13  [-0.36; 0.10] | 0.02  [-0.27; 0.31] | 0.15  [-0.27; 0.57] | 0.14  [-0.60; 0.87] | 0.10  [-0.67; 0.86] | KO < 2 | 0.11  [-0.10; 0.32] |
| **-0.31**  **[-0.58; -0.04]** | 0.10  [-0.50; 0.70] | **-0.60**  **[-1.05; -0.15]** | -0.04  [-0.50; 0.42] | -0.32  [-0.66; 0.02] | -0.00  [-0.27; 0.27] | -0.26  [-1.42; 0.90] | -0.03  [-0.17; 0.11] | 0.12  [-0.09; 0.33] | 0.25  [-0.11; 0.62] | 0.24  [-0.47; 0.95] | 0.20  [-0.54; 0.94] | 0.10  [-0.10; 0.30] | Placebo |

Table B.League (Table B.3) shows statistically significant pairing treatment comparisons: FO - EE < 2 and FO - rTAG < 2 were more effective at reducing LDL - C than (FO < 3, FO > 3, KO < 2); similarly FO – EE > 3 is more effective (FO – TG < 2, FO < 2, FO < 3, FO > 3, and KO < 2). In addition, in 18 pairs of comparisons with direct evidence, two comparisons between: (FO – EE < 2, FO – EE > 3) versus the new placebo contributed to the pool-effect size for the statistically significant LDL-C network model.

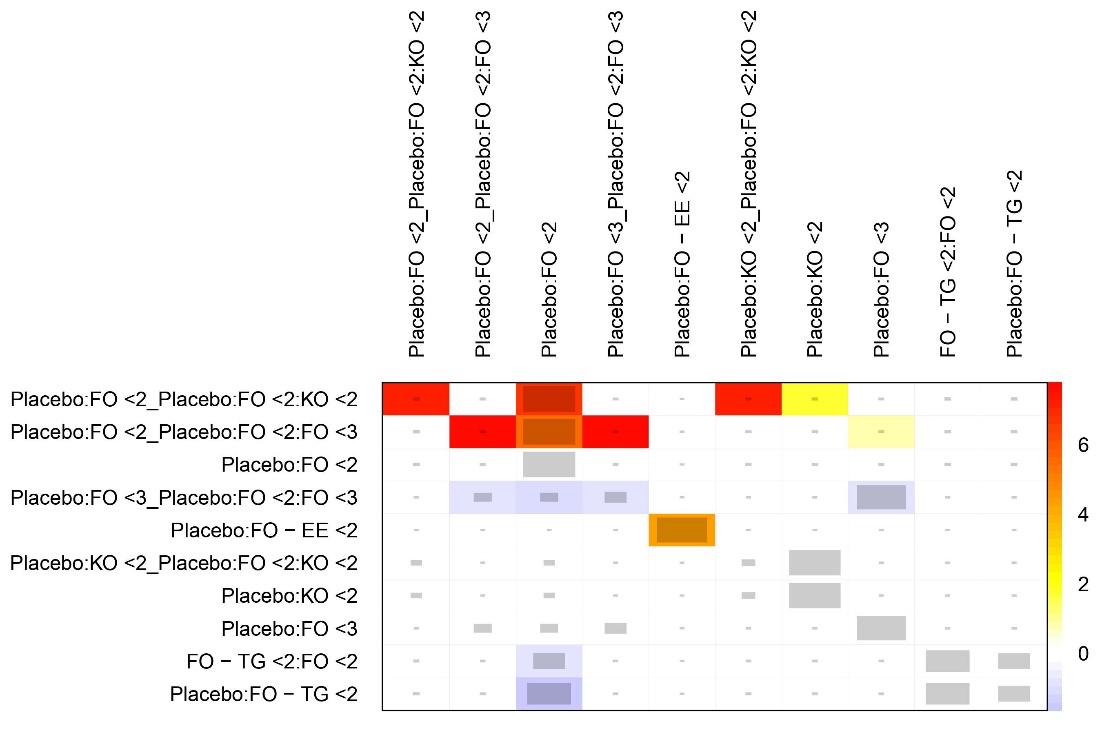
**1. 15. Results of testing the consistency of the mesh effect on LD-C**

**A. Q' Cochrane decomposition**

**Table B.14. Cochrane Q' analysis on LDL-C index**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Q statistics to assess homogeneity / consistency | | | | | |
|  | | | Q | df | p-value |
| Total | | | **462.14** | 56 | < 0.0001 |
| Within designs | | | 386.55 | 50 | < 0.0001 |
| Between designs | | | 75.59 | 6 | < 0.0001 |
| Design-specific decomposition of within-designs Q statistic | | | | | |
| Design | | | Q | df | p-value |
| Placebo: FO < 2 | | | **267.60** | 14 | **< 0.0001** |
| Placebo: FO - EE < 2 | | | **90.39** | 1 | **< 0.0001** |
| Placebo: FO - EE > 3 | | | 7.18 | 3 | 0.0664 |
| Placebo: FO > 3 | | | 2.58 | 2 | 0.2755 |
| Placebo: FO < 2: KO < 2 | | | 3.24 | 4 | 0.5178 |
| Placebo: FO - EM < 2 | | | 0.33 | 1 | 0.5673 |
| Placebo: FO < 3 | | | 6.48 | 8 | 0.5933 |
| Placebo: FO - TG < 2 | | | 3.58 | 5 | 0.6115 |
| Placebo: KO < 2 | | | 4.04 | 6 | 0.6707 |
| Placebo: FO < 2: FO < 3 | | | 0.57 | 2 | 0.7509 |
| Placebo: FO - EE < 2: FO - rTAG < 2 | | | 0.55 | 4 | 0.9679 |
| Between-designs Q statistic after detaching of single designs  (influential designs have p-value markedly different from < 0.0001) | | | | | |
| Detached design | | | Q | df | p-value |
| Placebo: FO - EE < 2 | | | 14.08 | 5 | 0.0151 |
| Placebo: FO < 2 | | | 67.09 | 5 | < 0.0001 |
| Placebo: FO < 2: FO < 3 | | | 68.51 | 4 | < 0.0001 |
| Placebo: FO < 2: KO < 2 | | | 68.64 | 4 | < 0.0001 |
| Placebo: KO < 2 | | | 73.93 | 5 | < 0.0001 |
| Placebo: FO < 3 | | | 75.35 | 5 | < 0.0001 |
| FO - TG < 2: FO < 2 | | | 75.57 | 5 | < 0.0001 |
| Placebo: FO - TG < 2 | | | 75.57 | 5 | < 0.0001 |
| Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model | | | | | |
|  | Q | df | p-value | tau.within | tau2.within |
| Between designs | **3.43** | 6 | **0.7529** | 0.2627 | 0.0690 |

Q' Cochrane dissociation results (**Table B.1**) show that the cause of this heterogeneity of LDL-C NMAs is the results of comparisons between placebo with: FO < 2, FO - EE < 2, (*p*< 0.0001). After separation, inconsistencies between study designs decreased significantly (Q decreased from **386.55**to **3.43,** *p****=*0.7529**).

**B. Visualize using net heat chart:**

**Figure B.11. Net heat graph of LDL-C index**

The net heat chart is a visualization from performing a Q' Cochrane split, the area of the gray square showing the contribution of a direct estimate of a design in the column to the network estimate in the row, the larger the gray cell, the more important the comparison. Background color was associated with a change in inconsistency between direct and indirect evidence in in-row network estimates, after loosening consistent assumptions about the impact of a design in the column. The Figure B.s 0, 2, 4, 6 next to the chart can indicate the degree of difference or impact of the comparison corresponding to blue for negative values, yellow for values near 0, and red for high positive values. The blue boxes represent interventions that support reliable evidence for NMAs, while yellow indicates a small disparity, while red represents a larger disparity.

Figure B. 4 results show that there are 10 study designs impacting inconsistencies in the LDL-C network pooling effect. In terms of the contribution of direct estimates to network estimates, we see that the large gray cells are mostly concentrated diagonally, the vertical axis of Placebo: FO < 2, so these cells have strong direct estimates on network estimates (Placebo: FO < 2 has a large impact on the majority of network estimates (*3rd vertical column from left*), similar in Placebo: KO < 2 major contributors to network estimates Placebo: KO < 2\_Placebo FO < 2: KO < 2), and Placebo: FO < 3 to Placebo: FO < 3\_Placebo: FO < 2: FO < 3. At the same time, the main diagonal consists entirely of light gray cells, suggesting that the comparison of each group to itself will not differ (in the study designs: Placebo: FO < 2, Placebo: FO - EE < 2, Placebo: KO < 2, Placebo: FO < 3, and FO - TG < 2: FO< 2).

In terms of inconsistencies, the results show evidence due to Placebo: FO < 2\_Placebo: FO < 2: KO < 2, Placebo: FO < 2, and Placebo: KO < 2\_Placebo: KO < 2: KO < 2 impacts on network estimates Placebo: FO < 2\_Placebo: FO < 2: KO < 2; similar to Placebo: FO < 2\_Placebo: FO < 2: FO < 3, Placebo: FO < 2 and Placebo: FO < 3\_Placebo: FO < 2: FO < 3 impacts on Placebo: FO < 3\_Placebo: FO < 2: FO < 3, which demonstrates that the inconsistencies in these comparisons are most significant and pronounced However, the red band in these cells corresponds to the color range in the column, so separating the effect of the above designs solves all inconsistencies in the network. In addition, the net heat chart shows evidence of Placebo design: FO < 2\_Placebo: FO < 2: FO < 3, Placebo: FO < 2, Placebo: FO < 3\_Placebo: FO < 2: FO < 3 and Placebo: FO < 3 contribute evidence to Placebo: FO < 3\_Placebo: FO < 2: FO < 3; similar to Placebo: FO < 2 contributed to FO – TG < 2: FO< 2 and Placebo: FO – TG < 2.

**C. SIDE Analysis**

**Table B.15:**SIDE analysis results on LDL-C index

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | | **Comparison** | **k** | **prop** | **nma** | **direct** | **indir.** | **Diff** | **z** | **p-value** |
| 1 | | FO - EE < 2: FO - EE < 3 | 0 | 0 | -0.4077 | . | -0.4077 | . | . | . |
| 2 | | FO - EE < 2: FO - EE > 3 | 0 | 0 | 0.2893 | . | 0.2893 | . | . | . |
| 3 | | FO - EE < 2: FO - EM < 2 | 0 | 0 | -0.2696 | . | -0.2696 | . | . | . |
| 4 | | FO - EE < 2: FO - rTAG < 2 | 3 | **0.88** | 0.0094 | 0.0663 | -0.4151 | 0.4814 | 0.90 | 0.3657 |
| 5 | | FO - EE < 2: FO - TG < 2 | 0 | 0 | -0.3068 | . | -0.3068 | . | . | . |
| 6 | | FO - EE < 2: FO - TG < 3 | 0 | 0 | -0.0477 | . | -0.0477 | . | . | . |
| 7 | | FO - EE < 2: FO < 2 | 0 | 0 | -0.2757 | . | -0.2757 | . | . | . |
| 8 | | **FO - EE < 2: FO < 3** | 0 | 0 | -0.4267 | . | -0.4267 | . | . | . |
| 9 | | **FO - EE < 2: FO > 3** | 0 | 0 | -0.5597 | . | -0.5597 | . | . | . |
| 10 | | FO - EE < 2: KO - HPL < 2 | 0 | 0 | -0.5477 | . | -0.5477 | . | . | . |
| 11 | | FO - EE < 2: KO - LPL < 2 | 0 | 0 | -0.5077 | . | -0.5077 | . | . | . |
| 12 | | **FO - EE < 2: KO < 2** | 0 | 0 | -0.4099 | . | -0.4099 | . | . | . |
| 13 | | **FO - EE < 2: Placebo** | **5** | **1.00** | -0.3077 | -0.3077 | . | . | . | . |
| 14 | | FO - EE < 3: FO - EE > 3 | 0 | 0 | 0.6970 | . | 0.6970 | . | . | . |
| 15 | | FO - EE < 3: FO - EM < 2 | 0 | 0 | 0.1381 | . | 0.1381 | . | . | . |
| 16 | | FO - EE < 3: FO - rTAG < 2 | 0 | 0 | 0.4171 | . | 0.4171 | . | . | . |
| 17 | | FO - EE < 3: FO - TG < 2 | 0 | 0 | 0.1010 | . | 0.1010 | . | . | . |
| 18 | | FO - EE < 3: FO - TG < 3 | 0 | 0 | 0.3600 | . | 0.3600 | . | . | . |
| 19 | | FO - EE < 3: FO < 2 | 0 | 0 | 0.1320 | . | 0.1320 | . | . | . |
| 20 | | FO - EE < 3: FO < 3 | 0 | 0 | -0.0190 | . | -0.0190 | . | . | . |
| 21 | | FO - EE < 3: FO > 3 | 0 | 0 | -0.1520 | . | -0.1520 | . | . | . |
| 22 | | FO - EE < 3: KO - HPL < 2 | 0 | 0 | -0.1400 | . | -0.1400 | . | . | . |
| 23 | | FO - EE < 3: KO - LPL < 2 | 0 | 0 | -0.1000 | . | -0.1000 | . | . | . |
| 24 | | FO - EE < 3: KO < 2 | 0 | 0 | -0.0022 | . | -0.0022 | . | . | . |
| 25 | | FO - EE < 3: Placebo | 1 | **1.00** | 0.1000 | 0.1000 | . | . | . | . |
| 26 | | FO - EE > 3: FO - EM < 2 | 0 | 0 | -0.5589 | . | -0.5589 | . | . | . |
| 27 | | FO - EE > 3: FO - rTAG < 2 | 0 | 0 | -0.2799 | . | -0.2799 | . | . | . |
| 28 | | **FO - EE > 3: FO - TG < 2** | 0 | 0 | -0.5961 | . | -0.5961 | . | . | . |
| 29 | | FO - EE > 3: FO - TG < 3 | 0 | 0 | -0.3370 | . | -0.3370 | . | . | . |
| 30 | | **FO - EE > 3: FO < 2** | 0 | 0 | -0.5650 | . | -0.5650 | . | . | . |
| 31 | | **FO - EE > 3: FO < 3** | 0 | 0 | -0.7160 | . | -0.7160 | . | . | . |
| 32 | | **FO - EE > 3: FO > 3** | 0 | 0 | -0.8490 | . | -0.8490 | . | . | . |
| 33 | | FO - EE > 3: KO - HPL < 2 | 0 | 0 | -0.8370 | . | -0.8370 | . | . | . |
| 34 | | FO - EE > 3: KO - LPL < 2 | 0 | 0 | -0.7970 | . | -0.7970 | . | . | . |
| 35 | | **FO - EE > 3: KO < 2** | 0 | 0 | -0.6992 | . | -0.6992 | . | . | . |
| 36 | | **FO - EE > 3: Placebo** | 4 | **1.00** | -0.5970 | -0.5970 | . | . | . | . |
| 37 | FO - EM < 2: FO - rTAG < 2 | | 0 | 0 | 0.2790 | . | 0.2790 | . | . | . |
| 38 | | FO - EM < 2: FO - TG < 2 | 0 | 0 | -0.0372 | . | -0.0372 | . | . | . |
| 39 | | FO - EM < 2: FO - TG < 3 | 0 | 0 | 0.2219 | . | 0.2219 | . | . | . |
| 40 | | FO - EM < 2: FO < 2 | 0 | 0 | -0.0061 | . | -0.0061 | . | . | . |
| 41 | | FO - EM < 2: FO < 3 | 0 | 0 | -0.1571 | . | -0.1571 | . | . | . |
| 42 | | FO - EM < 2: FO > 3 | 0 | 0 | -0.2901 | . | -0.2901 | . | . | . |
| 43 | | FO - EM < 2: KO - HPL < 2 | 0 | 0 | -0.2781 | . | -0.2781 | . | . | . |
| 44 | | FO - EM < 2: KO - LPL < 2 | 0 | 0 | -0.2381 | . | -0.2381 | . | . | . |
| 45 | | FO - EM < 2: KO < 2 | 0 | 0 | -0.1403 | . | -0.1403 | . | . | . |
| 46 | | FO - EM < 2: Placebo | 2 | **1.00** | -0.0381 | -0.0381 | . | . | . | . |
| 47 | | FO - rTAG < 2: FO - TG < 2 | 0 | 0 | -0.3162 | . | -0.3162 | . | . | . |
| 48 | | FO - rTAG < 2: FO - TG < 3 | 0 | 0 | -0.0571 | . | -0.0571 | . | . | . |
| 49 | | FO - rTAG < 2: FO < 2 | 0 | 0 | -0.2851 | . | -0.2851 | . | . | . |
| 50 | | **FO - rTAG < 2: FO < 3** | 0 | 0 | -0.4361 | . | -0.4361 | . | . | . |
| 51 | | **FO - rTAG < 2: FO > 3** | 0 | 0 | -0.5691 | . | -0.5691 | . | . | . |
| 52 | | FO - rTAG < 2: KO - HPL < 2 | 0 | 0 | -0.5571 | . | -0.5571 | . | . | . |
| 53 | | FO - rTAG < 2: KO - LPL < 2 | 0 | 0 | -0.5171 | . | -0.5171 | . | . | . |
| 54 | | **FO - rTAG < 2: KO < 2** | 0 | 0 | -0.4193 | . | -0.4193 | . | . | . |
| 55 | | FO - rTAG < 2: Placebo | 3 | **0.88** | -0.3171 | -0.2591 | -0.7353 | 0.4762 | 0.90 | 0.3662 |
| 56 | | FO - TG < 2: FO - TG < 3 | 0 | 0 | 0.2590 | . | 0.2590 | . | . | . |
| 57 | | FO - TG < 2: FO < 2 | 1 | 0.27 | 0.0311 | -0.2500 | 0.1344 | -0.3844 | -1.16 | 0.2450 |
| 58 | | FO - TG < 2: FO < 3 | 0 | 0 | -0.1199 | . | -0.1199 | . | . | . |
| 59 | | FO - TG < 2: FO > 3 | 0 | 0 | -0.2529 | . | -0.2529 | . | . | . |
| 60 | | FO - TG < 2: KO - HPL < 2 | 0 | 0 | -0.2410 | . | -0.2410 | . | . | . |
| 61 | | FO - TG < 2: KO - LPL < 2 | 0 | 0 | -0.2010 | . | -0.2010 | . | . | . |
| 62 | | FO - TG < 2: KO < 2 | 0 | 0 | -0.1031 | . | -0.1031 | . | . | . |
| 63 | | FO - TG < 2: Placebo | 6 | **0.78** | -0.0010 | 0.0841 | -0.3003 | 0.3844 | 1.16 | 0.2450 |
| 64 | | FO - TG < 3: FO < 2 | 0 | 0 | -0.2280 | . | -0.2280 | . | . | . |
| 65 | | FO - TG < 3: FO < 3 | 0 | 0 | -0.3790 | . | -0.3790 | . | . | . |
| 66 | | FO - TG < 3: FO > 3 | 0 | 0 | -0.5120 | . | -0.5120 | . | . | . |
| 67 | | FO - TG < 3: KO - HPL < 2 | 0 | 0 | -0.5000 | . | -0.5000 | . | . | . |
| 68 | | FO - TG < 3: KO - LPL < 2 | 0 | 0 | -0.4600 | . | -0.4600 | . | . | . |
| 69 | | FO - TG < 3: KO < 2 | 0 | 0 | -0.3622 | . | -0.3622 | . | . | . |
| 70 | | FO - TG < 3: Placebo | 1 | **1.00** | -0.2600 | -0.2600 | . | . | . | . |
| 71 | | FO < 2: FO < 3 | 2 | 0.22 | -0.1510 | -0.0892 | -0.1683 | 0.0792 | 0.26 | 0.7925 |
| 72 | | FO < 2: FO > 3 | 0 | 0 | -0.2840 | . | -0.2840 | . | . | . |
| 73 | | FO < 2: KO - HPL < 2 | 0 | 0 | -0.2720 | . | -0.2720 | . | . | . |
| 74 | | FO < 2: KO - LPL < 2 | 0 | 0 | -0.2320 | . | -0.2320 | . | . | . |
| 75 | | FO < 2: KO < 2 | 3 | 0.34 | -0.1342 | -0.0741 | -0.1651 | 0.0910 | 0.37 | 0.7135 |
| 76 | | FO < 2: Placebo | **20** | **0.90** | -0.0320 | -0.0635 | 0.2481 | -0.3115 | -1.33 | 0.1827 |
| 77 | | FO < 3: FO > 3 | 0 | 0 | -0.1330 | . | -0.1330 | . | . | . |
| 78 | | FO < 3: KO - HPL < 2 | 0 | 0 | -0.1210 | . | -0.1210 | . | . | . |
| 79 | | FO < 3: KO - LPL < 2 | 0 | 0 | -0.0810 | . | -0.0810 | . | . | . |
| 80 | | FO < 3: KO < 2 | 0 | 0 | 0.0168 | . | 0.0168 | . | . | . |
| 81 | | FO < 3: Placebo | **11** | **0.94** | 0.1190 | 0.1127 | 0.2121 | -0.0994 | -0.22 | 0.8232 |
| 82 | | FO > 3: KO - HPL < 2 | 0 | 0 | 0.0120 | . | 0.0120 | . | . | . |
| 83 | | FO > 3: KO - LPL < 2 | 0 | 0 | 0.0520 | . | 0.0520 | . | . | . |
| 84 | | FO > 3: KO < 2 | 0 | 0 | 0.1498 | . | 0.1498 | . | . | . |
| 85 | | FO > 3: Placebo | 3 | **1.00** | 0.2520 | 0.2520 | . | . | . | . |
| 86 | | KO - HPL < 2: KO - LPL < 2 | 1 | **1.00** | 0.0400 | 0.0400 | . | . | . | . |
| 87 | | KO - HPL < 2: KO < 2 | 0 | 0 | 0.1378 | . | 0.1378 | . | . | . |
| 88 | | KO - HPL < 2: Placebo | 1 | **1.00** | 0.2400 | 0.2400 | . | . | . | . |
| 89 | | KO - LPL < 2: KO < 2 | 0 | 0 | 0.0978 | . | 0.0978 | . | . | . |
| 90 | | KO - LPL < 2: Placebo | 1 | **1.00** | 0.2000 | 0.2000 | . | . | . | . |
| 91 | | KO < 2: Placebo | **10** | **0.92** | 0.1022 | 0.1081 | 0.0376 | 0.0705 | 0.19 | 0.8498 |

Comment:

|  |  |
| --- | --- |
| comparison | Treatment comparison |
| k | Number of studies that provide direct evidence |
| prop | The ratio of direct evidence to the total amount of evidence available |
| nma | Estimated Treatment Effect (MD) in Network Meta-Analysis |
| direct | Estimated treatment efficacy (MD) derives from direct evidence |
| indir. | Estimated treatment efficacy (MD) derived from circumstantial evidence |
| Diff | The difference between direct and indirect processing estimates |
| *z* | * The *z-value* of the test disagrees between estimates from direct and indirect evidence. |
| p-value | The *p-value* of the test disagrees between estimation from direct and indirect evidence |

The SIDE analysis aimed to assess inconsistencies between study designs including both direct and indirect evidence (Table B.2), a total of 91 comparisons were made between interventions, of which 18 study designs had direct evidence (19.78%), and 82 study designs had circumstantial evidence (90.11%). While only 9 study designs had both indirect and direct evidence (9.89%), the diff, *z-value* and p-value (>0.05) of these 9 comparable stars all showed no significant difference between direct and indirect evidence.

In addition, according to the k-value, there are 5 comparisons between placebo and: KO < 2, FO < 3, FO < 2, FO – TG < 2, and FO – rTAG < 2 that there are many studies that provide direct evidence (prop from 0.78 to 0.94), there are also 9 comparisons where most of the evidence is provided directly (prop*=*1.00), increases the reliability of the results.

However, for comparisons with negative diff numbers such as: FO - TG < 2: FO < 2, FO < 2: Placebo, FO < 3: Placebo has a greater estimated therapeutic effect from indirect evidence than direct evidence, further consideration should be given to the feasibility and reliability of indirect evidence of these comparable pairs (indir).

In the pair treatment comparisons in Table B.3, compared with SIDE analysis, comparisons between statistically significant interventions were not directly evidenced, all were circumstantial evidence. There are only 2 comparisons of FO - EE < 2: Placebo and FO - EE > 3: Placebo is derived from direct evidence, so the results from Table B.3 only provide indirect comparative evidence with each other, but with MD and 95%-CI values there is high reliability.

Comparisons of highly effective interventions (according to SUCRA) are only: FO - EE < 2: FO - rTAG < 2, FO - EE < 2: Placebo, FO - EE > 3: Placebo, FO - EM < 2: Placebo, FO - rTAG < 2: Placebo, FO - TG < 3: Placebo, FO < 2: New placebo with direct evidence, the rest have only circumstantial evidence (k = 0, prop = 0).

**1. 16. Results of testing for publication bias of the LDL-C network model**

A diagram of a graph

Description automatically generated

**Figure B.12. Results of published bias analysis for LDL - C index**

*The standard error (SE) of the intervention estimation is expressed on the vertical axis, the mean differential of the specific comparison effect (horizontal axis). 2 The Triangular edge represents the 95% confidence interval of the studies, the more concentrated the studies above and fit within the 95% CI, the higher the confidence.*

There are 18 pairs of direct comparisons presented as funnel charts to assess publication bias (Figure B. 5). Observations of asymmetric diagrams, when the majority of studies are concentrated at the top inside the triangle,there are still many studies outside the 95% confidence interval, thus suggesting that publication bias may occur or because small studies tend to report larger or smaller effects than larger studies.

With statistical values *t = -4.28, df = 76 and p-value < 0.0001 (< 0.05)),*this indicates that there is a publishing bias.

Deviation estimation, which has a value of -2.6569 with a standard error (SE) of 0.6215. This result suggests that there is a significant discrepancy between the predictive data and the observational data.

The T-test and bias estimate both show significant asymmetry of the funnel chart, with a very small P-value (<< 0.0001). Therefore, control or adjustment of data may be necessary to ensure the objectivity and reliability of research results.

In summary, the LDL-C NMA results based on our analysis have publication bias, the NMA results do not have enough convincing evidence of study parity, and some study results have not produced statistically significant results, so there is insufficient certainty.

**Table B.16: Asymmetry test results of funnel chart after linear regression**

|  |
| --- |
| Linear regression test of funnel plot asymmetry |
|  | t | df | p-value |
| Test result | -4.28 | 76 | < 0.0001 |
| Bias estimate | -2.6569 (SE = 0.6215) | | |
| Details:  - multiplicative residual heterogeneity variance (tau2 = 26.2009)  - predictor: standard error  - weight: inverse variance  - reference: Egger et al. (1997), BMJ | | | |

**Figure B. 1. Forest plot of TG, Figure B. 2. Forest plot of TC, Figure B.3. Net graph estimating the effect of intervention oils on HDL-C, Figure B.4. Forest plot of HDL-C**, **Figure B.5. Rankogram and SUCRA results for HDL-C, Figure B. 6. Net heat chart of HDL-C index**, **Figure B.7. Results of published bias analysis for HDL-C, Figure B.8. Net graph estimates the effect of interfering oils on LDL**, **Figure B.9. LDL–C forest chart, Figure B.10. Rankogram and SUCRA results for LDL-C, Figure B.11. Net heat graph of LDL-C index**, **Figure B.12. Results of published bias analysis for LDL - C index,**

**Table B. 1.** Cochrane Q' analysis on TG , **Table B. 2.** Results of SIDE analysis on TG, **Table B.3: Decomposition of Q'Cochrane on TC , Table B. 4: Results of SIDE analysis on TC , Table B.5: net graph results of HDL-C, Table B.6. Rankogram results of HDL-C , Table B.7. Paired treatment comparison league tables on net estimates of HDL-C, Table B.8:** Cochrane Q' analysis on HDL-C index, **Table B.9:**SIDE analysis results on HDL-C index, **Table B.10:** Asymmetry test results of funnel chart after linear regression, **Table B.11:** Net graph results of LDL-C, **Table B.12. Rankogram results of LDL - C index , Table B.13. League Table B. comparing treatment in pairs on network estimates of LDL-C , Table B.14. Cochrane Q' analysis on LDL-C index, Table B.15:**SIDE analysis results on LDL-C index, **Table B.16: Asymmetry test results of funnel chart after linear regression.**