SUPPLEMENTAL MATERIAL

Table S1. Checklist: PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 3-4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 66-81
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 95-102
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 114-121
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 110-112
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 110-112
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 112-113
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 129-128
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 140-142
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 143-149
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 122-126
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 140-149

Topic	No.	Item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Line 163-168, Table S3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 142-147
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 142-147
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 142-147 and Line 157-169
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 163-168
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 154-155
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 151-153
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 172-175 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Line 72-175, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Supp. references and Table S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Line 195-218 and Table 1, S4, S5; Figures S2, S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Line 220-259
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Line 195-259 Table S4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 264-267

Topic	No.	Item	Location where item is reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Line 267-270
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Line 261-264
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	No
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 278-336
	23b	Discuss any limitations of the evidence included in the review.	Line 353-370
	23c	Discuss any limitations of the review processes used.	Line 353-370
	23d	Discuss implications of the results for practice, policy, and future research.	Line 372-377
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 384-386
Competing interests	26	Declare any competing interests of review authors.	Line 388
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

PRISMA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Table S2. Literature retrieval strategies for online databases

Database	Search Strategy
PubMed	#1 (“Dietary fats, unsaturated” [MH] OR “fish oils” [MH] OR “fish oil” [tiab] OR “fatty acids, omega-3”[MH] OR “docosahexaenoic acid” [tiab] OR "Docosahexaenoic Acids" [tiab] OR “PUFA” [tiab] OR “DHA” [tiab] OR “EPA” [tiab] OR “long chain omega-3 fatty acids” [tiab] OR “polyunsaturated fatty acid” [tiab] OR "Docosahexaenoic Acids" [tiab] OR “eicosapentaenoic acid” [tiab]) #2 (“Hyperlipidemias”[MH] OR “Hyperlipemia”[tiab] OR “Lipidemia”[tiab] OR “Hypolipidemic Agents”[MH] OR “Antihyperlipemics”[tiab] OR “antilipemic”[tiab] OR “Hypolipidemic Drug”[tiab] OR “hyperlipoproteinemia”[tiab] OR “dyslipidemic”[tiab] OR “hypercholesterolemia”[tiab] OR “hypertriglyceridemic”[tiab]) #1 AND #2 AND “human study”
Embase	#1 (‘fish oils’:ab,ti) OR (‘omega-3 fatty acids’:ab,ti) OR (‘docosahexaenoic acids’:ab,ti) OR (‘PUFA’:ab,ti) OR (‘DHA’:ab,ti) OR (‘EPA’:ab,ti) OR (‘ALA’:ab,ti) OR (‘long chain omega-3 fatty acids’:ab,ti) OR (‘polyunsaturated fatty acid’:ab,ti) OR (‘eicosapentaenoic acid’:ab,ti) OR (‘alpha linolenic acid’:ab,ti) #2 (‘Hyperlipemia’:ab,ti) OR (‘Lipidemia’:ab,ti) OR (‘Antihyperlipemics’:ab,ti) OR (‘Hyperlipidemias’:ab,ti) OR (‘dyslipidemic’:ab,ti) OR (‘hypercholesterolemia’:ab,ti) OR (‘hypertriglyceridemic’:ab,ti) OR (‘Hypolipidemic Drug’:ab,ti) OR (‘Hypolipidemic Agents’:ab,ti) #1 AND #2 AND 'human'/de

Table S3. Summary of study characteristics of 90 trials in the lipid profile study

Author	Year	Country	n, M/F	Age, y Mean (SE/SD)	BMI, kg/m^2 Mean (SE/SD)	HL	Lipid-lowering	CHD	DHA dose g/d	EPA dose g/d	Total dose g/d	Control	Duration, week
Flaten[57]	1990	Norway	M56	t39.9 ± 2.4 c39.3 ± 2.7	NR	no	no	no	2.87	3.59	6.46	olive oil	6
Hendra[58]	1990	UK	M55F25	t56.0 c55.8	NR	no	no	mixed	1.20	1.80	3.00	olive oil	6
Reis[59]	1990	USA	NR89	t60±10 c57±9	NR	mixed	mixed	yes	2.50	3.70	6.20	olive oil	26
				t60±10 c57±9	NR	mixed	mixed	yes	1.40	3.40	4.80	olive oil	26
Bonaa[60]	1992	Norway	M95F61	49±7	26±3.3	no	no	no	1.80	3.30	5.10	corn oil	10
Kaul[61]	1992	India	M91F16	t56±11 c59±9	NR	NR	NR	yes	1.20	1.80	3.00	Conventional treatment	26
Leaf[62]	1994	USA	M353F94	t57.9 c57.6	NR	NR	NR	yes	2.80	4.10	6.90	corn oil	13
Sacks[63]	1995	USA	M55F4	t62 ± 7 c62 ± 7	NR	NR	mixed	yes	1.92	2.88	4.80	olive oil	120
Shimizu[64]	1995	Japan	M22/F23	t66.3±2.5 c58.6±1.8	t23.9 ± 1 c22.8 ±1.2	NR	NR	NR	0.00	0.90	0.90	Routine treatment	52
Eritsland[65]	1996	Norway	M530F80	t60 c60	t25 c25	NR	NR	yes	1.28	2.04	3.32	Aspirin or warfarin	52
Grimsgaard[66]	1997	Norway	M224	44± 5	t24.9 ±2.6 c24.6±2.7	no	no	no	3.60	—	3.60	corn oil	7
				44± 5	t25.6 ±2.9 c24.6±2.7	no	no	no	—	3.80	3.80	corn oil	7
Harris[67]	1997	USA	M30F12	t46± 11 c45 ± 9	t28 ± 4 c29± 5	yes	no	no	1.56	1.80	3.36	corn oil	16
Sirtori[68]	1997	Italy	M583F352	t58.2± 9.1 c58.8 ± 9	NR	yes	no	no	1.05	1.53	2.58	olive oil	9
Borthwick[69]	1998	UK	M44F11	t54.1± 9.2 c52.8 ± 9.2	NR	yes	no	no	1.56	1.80	3.36	corn oil	12
Nordoy[70]	1998	Norway	M29F12	t46.8± 9.2 c46.7 ± 7.8	t27.6 ± 4 c28.8± 3.7	yes	yes	mixed	1.56	1.80	3.36	corn oil	5
Johansen[71]	1999	Norway	M301F87	t60.3± 9.3 c59.1 ± 9.3	t25.6 ± 3 c26.3± 3.5	NR	mixed	yes	2.34	2.70	5.04	corn oil	26
von Schacky[72]	1999	Germany	M179F44	t57.8± 9.7 c58.9 ± 8.1	NR	mixed	mixed	yes	0.65	1.06	1.71	Non-ω3 fatty acid mixture	104
Mori[73]	2000	Australia	M56	t49.1 ±2.2 c48.4±2	t24.9 ±2.6 c 24.6±2.7	yes	no	no	3.68	—	3.68	olive oil	6
				t 48.9 ± 1.7 c48.4±2	t25.6 ±2.9 c 24.6±2.7	yes	no	no	—	3.84	3.84	olive oil	6
Durrington[74]	2001	UK	M43F16	t55.2± 7 c54.8 ± 10.2	t28.8± 2.8 c28.4 ±4.2	yes	yes	yes	1.44	1.76	3.20	corn oil	24

Finnegan[75]	2003	UK	M53F38	t53± 2 c55 ± 2	t27.2±0.6 c25.8 ±0.6	yes	no	no	0.22	0.33	0.55	sunflower and safflower oils	26
				t54± 2 c55 ± 2	t26.1±0.6 c25.8 ±0.6	yes	no	no	0.66	0.75	1.40	sunflower and safflower oils	26
Hamazaki[76]	2003	Japan	M25F16	t44± 11 c48 ± 11	t25±3 c24 ±3	mixed	no	NR	0.26	0.60	0.86	olive oil	12
Dyerberg[77]	2004	Denmark	M51	t39.2± 10.5 c37.6 ± 10.6	t24.9±3.2 c24.1 ±3.7	no	no	no	0.50	0.79	1.30	palm oil	8
Hjerkinn[78]	2005	Norway	M563	70 (64-76)	26.5±3.5	yes	mixed	mixed	0.80	1.40	2.20	corn oil	156
				70 (64-76)	26.5±3.5	yes	mixed	mixed	0.80	1.40	2.20	corn oil	156
Maki[79]	2005	USA	M31F26	t55.8±2.3 c51.4±2.6	t29.6±0.9 c30.5±0.9	NR	no	NR	1.52	—	1.52	olive oil	6
Geppert[80]	2006	Germany	M87F27	t25.7± 5.4 c26.1 ± 5.8	t21.4±1.8 c21.2±2	no	no	no	0.94	—	0.94	olive oil	8
Lee[81]	2006	UK	M71F6	t59± 10 c55 ±10	t28±4 c27±4	mixed	mixed	yes	0.39	0.45	0.84	"usual care"	13
Sanders[82]	2006	UK	M39F40	29.8-35.2	23-24	no	no	no	1.52	0.00	1.52	olive oil	4
Davidson[83]	2007	USA	M146F108	t60.3± 10.1 c59.3±10.8	t31±5.4 c31.5±5.5	yes	yes	no	1.50	1.86	3.36	vegetable oil	8
Mita[84]	2007	Japan	M36F24	t59± 11.2 c61.2 ±8.4	t25±5.4 c24.5±3	mixed	mixed	no	—	1.80	1.80	Routine treatment	110
Satoh[85]	2007	Japan	M16F28	t51.6± 2.8 c51.6 ±3.2	t31±1.2 c29.2±0.9	mixed	no	NR	0.00	1.80	1.80	Diet alone	13
Kaul[86]	2008	Canada	M34F54	t34.4±1.8 c32.9 ±2.0	t25.1±0.6 c24.4±0.8	no	no	no	0.24	0.35	0.59	sunflower oil	12
Saito[87]	2008	Japan	M486F471	58± 9	25± 3	yes	yes	no	—	1.80	1.80	statin only	239.2
Shidfar[88]	2008	Iran	M24F26	t53.4±11.7 c54.1±11.1	t28.4±0.5 c29±0.7	NR	no	no	0.96	1.04	2.00	mixed oil	10
Ebrahimi[89]	2009	Iran	M11F79	t53.5±12.7 c52.3±11.1	t30.3±5.2 c30.4±6.1	NR	NR	NR	0.12	0.18	0.30	Routine treatment	26
Hartwich[90]	2009	Poland	M14F27	t54.5±1.2 c55.5±1.4	t34.5±0.6 c34.6±0.6	NR	no	NR	0.52	0.72	1.24	sunflower oil	12
Khandelwal[91]	2009	India	M79F7	t48.2±0.9 c46.1±0.9	t25.7±0.6 c24.3±0.5	yes	no	no	0.63	1.26	1.89	safflower oil	4
Nomura[92]	2009	Japan	M101F90	65±3	27.3±3.9	yes	yes	mixed	—	1.80	1.80	Routine treatment	26
Rizza[93]	2009	Italy	M25F25	31.1 ± 5.8	t26.1±5.9 c25.8±4.6	NR	no	no	0.76	0.94	1.70	olive oil	12
Satoh[94]	2009	Japan	M39F53	t51.3±2.1 c52.2±2.1	t30±0.6 c30±0.7	yes	no	NR	—	1.80	1.80	Diet alone	13
Bays[95]	2010	USA	M142F103	t56.3±9.6 c56±10.8	t30.2±4.6 c31.0±4.0	yes	yes	NR	1.50	1.86	3.36	corn oil	16
Hallund[96]	2010	Denmark	M68	t52±9 c53±9	t24.2±2.3 c25.0±2.1	no	no	no	2.00	0.90	2.90	chicken	8
				t54±7 c53±9	t25±2.4 c25±2.1	no	no	no	0.47	0.21	0.68	chicken	8

Kromhout[97]	2010	Netherlands	M1904F524	t69.1±5.6 c68.9±5.6	NR	mixed	mixed	yes	0.15	0.23	0.38	oleic acid in the margarine	175
Neil[98]	2010	UK	M187F139	t63±12 c64±11	t30.7±6.2 c30.6±6	NR	no	no	0.76	0.92	1.68	olive oil	17
			M194F138	t65±11 c63±12	t30.8±6.4 c30.8±5.9	NR	yes	no	0.76	0.92	1.68	olive oil	17
Zhang[99]	2010	China	M62	t49.8±8.5 c51.1±6.2	t26.7±2.8 c26.9±3.5	yes	no	no	1.72	1.11	2.83	pork, chicken, beef	8
Bays[100]	2011	USA	M175F54	t53.4±9.3 c53.4±8.3	t30.8±4.2 c31±4.3	yes	yes	no	—	2.00	2.00	liquid paraffin	12
				t51.9±10.3 c53.4±8.3	t30.4±4.3 c31±4.3	yes	yes	no	—	4.00	4.00	liquid paraffin	12
Itakura[101]	2011	Japan	M5150F11247	t61±8 c61±9	t24±3.2 c24.1±3.3	yes	yes	no	—	1.80	1.80	statin only	239.2
Kim[102]	2011	Korea	M25F36	t56.7±13 c59.4±10.3	t25.9±3.1 c25.7±3.3	yes	yes	mixed	1.50	1.86	3.36	statin only	6
Krysiak[103]	2011	Poland	M43F23	t53.1±3.5 c52.5±3.1	t28.6±2.8 c28.3±2.4	yes	no	no	0.75	0.93	1.68	Placebo	12
Krysiak[104]	2011	Poland	M34F20	t52.9±2.6 c53.1±2.4	t28.4±2.2 c28.7±2.9	yes	no	no	0.75	0.93	1.68	Placebo	13
Nodari[105]	2011	Italy	M120F13	t61±11 c64±9	t25.9±2.3 c25.7±2.2	mixed	mixed	no	1.97	2.36	4.33	olive oil	52
Sanders[106]	2011	UK	M142F225	55 (53-57)	25-27	NR	mixed	no	0.18	0.27	0.45	olive oil and peppermint oil	52
				55 (53-57)	25-27	NR	mixed	no	0.36	0.54	0.90	olive oil and peppermint oil	52
				55 (53-57)	25-27	NR	mixed	no	0.72	1.08	1.80	olive oil and peppermint oil	52
Schuchardt[107]	2011	Germany	M45F53	t61±10.1 c62±8.2	t26±2.7 c26±3.3	yes	yes	no	0.67	1.01	1.68	corn oil	26
				t61.6±7.5 c62±8.2	t26±2.7 c25.8±3.0	yes	yes	no	0.67	1.01	1.68	corn oil	26
Takaki[108]	2011	Japan	M41F9	t61.6±5.6 c60.9±7	t25.1±2.3 c24±3.6	yes	yes	yes	0.00	1.80	1.80	statin only	48
Tierney[109]	2011	Europe	NR	t55.4±1 c54.7±0.9	t32.4±0.4 c32.5±0.4	NR	no	NR	0.52	0.72	1.24	sunflower oil	12
Agouridis[110]	2012	Greece	M22F26	c58±11 t57±16	t30±5 c30±4	yes	yes	no	0.38	0.47	0.84	statin only	12
Ballantyne[111]	2012	USA	M287F179	t61.1±10.0 c61.2±10.0	t32.7±4.9 c33.0±5.0	yes	yes	no	0.00	4.00	4.00	Placebo with statin	12
			M289F180	t61.8±9.42 c61.2±10.05	t32.9±4.9 c33.0±5.0	yes	yes	no	0.00	2.00	2.00	Placebo with statin	12
Derosa[112]	2012	Italy	M79F78	NR	t26.0±1.3 c27.2±1.9	yes	no	NR	1.35	1.20	2.55	sucrose, mannitol, and mineral salts	24
Bosch[20]	2012	USA	M8150F4386	t63.5±7.8 c63.6±7.9	t29.8±5.3 c29.9±5.2	mixed	mixed	NR	0.38	0.47	0.84	olive oil	16
Koh[113]	2012	Korea	M57F40	t55±1 c54±1	t25.5±0.3 c25.1±0.3	yes	no	yes	0.76	0.92	1.68	Placebo	8

Satoh-Asahara[114]	2012	Japan	M48F34	t52.3 ± 13 c54.0 ± 13	t29.9± 4.9 c29.1± 5.3	yes	no	NR	—	1.80	1.80	control	12
Flock[115]	2013	USA	M60F55	t25.8 ± 1.5 c25.7 ± 1.4	t23.4± 0.5 c24.6± 0.6	no	no	no	0.12	0.19	0.31	placebo	21
				t27.1 ± 1.6 c25.7 ± 1.4	t24.5± 0.6 c24.6± 0.6	no	no	no	0.24	0.37	0.61	placebo	21
				t25.8 ± 1.3 c25.7 ± 1.4	t24.0± 0.4 c24.6± 0.6	no	no	no	0.35	0.56	0.91	placebo	21
				t26.0 ± 1.2 c25.7 ± 1.4	t25.4± 0.6 c24.6± 0.6	no	no	no	0.70	1.10	1.80	placebo	21
Roncaglioni[21]	2013	Italy	M7687F4823	t63.9±9.3 c64.0±9.6	t29.3±4.9 c29.4±5.0	mixed	mixed	NR	0.38	0.46	0.84	olive oil	152
Hlais[116]	2013	USA	M112	NR	t25.3±2.6 c26.4±3.0	no	no	no	0.39	0.99	1.38	sunflower oil	12
Maki[47]	2013	USA	M259F172	t60.1±9.2 c61.5±9.6	t33.3±6.6 c32.7±5.3	yes	yes	NR	0.80	2.20	3.00	olive oil	6
Tani[117]	2013	Japan	M106F38	t62±10 c63±10	t25.3±3.7 c26.3±4.0	yes	mixed	no	0.00	1.80	1.80	Non-EPA treatment	24
Maki[118]	2014	USA	M36F37	t52.6±1.7 c52.5±2.0	t32.7±1.0 c31.2±0.7	yes	mixed	NR	1.77	0.66	2.43	corn/soy oil	14
			M26F30	t54.5±2.0 c52.5±2.0	t31.9±1.6 c31.2±0.7	yes	mixed	NR	0.82	1.16	1.98	corn/soy oil	14
Oh[119]	2014	Korea	M45F41	t55±9 c54±9	t26.3±3.2 c26.5± 2.7	yes	no	no	0.38	0.47	0.84	placebo	8
			M46F39	t54±9 c54±9	t26.3±3.2 c26.5± 2.7	yes	no	no	0.75	0.93	1.68	placebo	8
			M46F40	t55±8 c54±9	t26.3±3.2 c26.5± 2.7	yes	no	no	1.50	1.86	3.36	placebo	8
Scorletti[120]	2014	UK	M60F43	t48.6±11.1 c54.0±9.6	t34.3±5.8 c32.0±4.3	NR	no	NR	1.52	1.84	3.36	olive oil	66
Toyama[121]	2014	Japan	M67F13	t65.9±8.2 c68.7±10.6	t24.3±2.9 c24.8±2.9	yes	yes	yes	0.00	1.80	1.80	statin only	12
Mansoori[122]	2015	Iran	NR	t55.8±7.6 c56.0±7.0	t29.2±2.8 c27.4±3.7	yes	NR	NR	1.45	0.40	1.85	paraffin oil	8
Qin[48]	2015	China	M51F19	t46.0±10.6 c44.3±10.9	t26.4±3.9 c26.0±2.8	yes	no	NR	0.52	0.73	1.24	corn oil	12
Ahn[123]	2016	Korea	M50F24	t59.6±9.1 c60.7±0.8	t24.8±2.4 c24.5±2.5	yes	yes	yes	1.13	1.40	2.52	placebo	48
Bays[124]	2016	USA	M60F27	t53.5±8.8 c51.6±11.4	t31.7±4.4 c32.3±4.5	yes	mixed	no	—	0.60	0.60	Miglyol: medium-chain fatty acid	12
Derosa[125]	2016	Italy	M131F127	t53.4±11.2 c54.8±12.1	t28.9±2.4 c28.9±2.4	yes	NR	no	1.36	1.64	3.00	sucrose, mannitol, etc	72
Koh[126]	2016	Korea	M78F68	t54±1 c54±1	t25.4±0.4 c25.3±0.4	yes	yes	no	0.76	0.92	1.68	fenofibrate only	8
Sawada[127]	2016	Japan	M87F20	t67.8±9.1 c68.9±8.8	t25.3±2.9 c25.4±2.4	yes	mixed	NR	—	1.80	1.80	Non-EPA placebo	24
Su[128]	2017	Taiwan	M166F87	t54.7 c54.4	t26.61 c26.66	yes	no	no	0.76	0.92	1.68	olive oil	8

				t53.7 c54.4	t26.63, c26.66	yes	no	no	1.52	1.86	3.38	olive oil	8
Tani[129]	2017	Japan	M88F12	t67.5±10.1 c67.3±10.4	t24.6±3.2 c24.8±4.0	yes	yes	yes	—	1.80	1.80	standard statin only	26
Tani[130]	2017	Japan	M93F13	t68 ± 11 c66 ± 11	t24.2±2.7 c24.7±4.1	yes	yes	yes	0.00	1.80	1.80	standard statin only	26
Toth[131]	2017	Slovakia	M52F53	60.7±12.3	28.3± 3.8	yes	yes	no	1.56	0.47	2.03	statins only	12
Watanabe[132]	2017	Japan	M159F34	t67±10 c68±10	t23.7±3.1 c23.9±2.9	yes	yes	yes	—	1.80	1.80	pitavastatin only	28
Group[133]	2018	UK	M9684F5796	t63.3±9.2 c63.3±9.2	t30.7±6.3 c30.8±6.2	NR	mixed	no	0.38	0.46	0.84	olive oil	130
Kim[134]	2018	Korea	M126F75	t59.7±10.8 c56.6±10.5	t27.4±3.7 c27.6±3.6	yes	yes	no	1.52	1.84	3.36	rosuvastatin only	8
Oscarsson[135]	2018	Sweden	M30F21	t60.0 c59.5	t30.0 c29.7	yes	mixed	no	0.80	2.20	3.00	placebo	12
Stroes[136]	2018	USA	M127F35	t50.3±10.6 c50.0±10.9	NR	yes	mixed	no	0.40	1.10	1.50	olive oil	12
Zhou[137]	2019	China	M49F74	t53.9±6.7 c53.6±4.2	t25.1±1.3 c26.3±1.6	yes	no	NR	0.62	1.23	1.85	corn oil	12
				t54.8±4.7 c53.6±4.2	t25.4±1.6 c26.3±1.6	yes	no	NR	1.21	2.33	3.54	corn oil	12
Fukumoto[138]	2020	Japan	M71F20	t59±13 c60±10	t26.2±3.6 c25.9±3.9	yes	NR	no	—	1.80	1.80	placebo	26
Jun[139]	2020	Korea	M129F71	t58.7±10.1 c58.0±11.4	t27.3±3.5 c27.0±3.4	yes	yes	no	1.50	1.86	3.36	olive oil +atorvastatin	8
Kita[140]	2020	Japan	M79F18	t66 c63	t24.3 c24.7	yes	yes	yes	—	1.80	1.80	statins only	34
				t67 c63	t25.0 c24.7	yes	yes	yes	0.75	0.93	1.68	statins only	34
Nicholls[141]	2020	USA	M8510F4568	t62.5±9.0 c62.5±9.0	t32.2±5.7 c32.2±5.6	yes	yes	no	0.80	2.20	3.00	corn oil	52
Guo[142]	2022	China	M41F33	t54.7±16.6 c56.3±15.2	t27.6±4.0 c26.7±2.4	mixed	mixed	mixed	1.61	0.74	2.34	corn oil	13

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HL, hyperlipidemia; NR, not reported; —, not administered. t, treatment; c, control; SD, standard deviation; and SE, standard error.

Table S4. Estimated average dose-response relationship between DHA+EPA consumption (g/d) and lipid reduction (mg/dL)

Lipid	Participants	N*	1.0 g/d		2.0 g/d		3.0 g/d		4.0 g/d		5.0 g/d	
			MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)
TG	All	86	-19.21	(-32.01, -6.41)	-42.61	(-53.41, -31.80)	-68.90	(-98.40, -39.40)	-96.05	(-155.17, -36.94)	-123.22	(-212.86, -33.58)
LDL-C	All	80	2.91	(0.34, 5.47)	3.48	(1.09, 5.86)	2.43	(-0.36, 5.22)	0.90	(-4.93, 6.73)	-0.64	(-9.97, 8.70)
HDL-C	All	87	1.36	(0.47, 2.25)	1.69	(0.78, 2.61)	1.32	(-0.97, 3.60)	0.73	(-3.65, 5.10)	0.14	(-6.40, 6.68)
Non-HDL-C	All	22	-1.18	(-6.24, 3.89)	-4.13	(-9.20, 0.95)	-8.31	(-11.78, -4.83)	-12.85	(-19.49, -6.20)	-17.40	(-28.95, -5.84)
Hyperlipidemia status												
TG	Yes	49	-23.05	(-43.59, -2.51)	-49.89	(-63.28, -36.49)	-80.58	(-150.43, -10.74)	-112.44	(-259.00, 34.11)	-144.33	(-368.35, 79.69)
	No	11	-17.24	(-31.01, -3.48)	-27.36	(-45.82, -8.89)	-32.58	(-50.72, -14.43)	-35.80	(-53.93, -17.67)	-38.87	(-59.78, -17.97)
LDL-C	Yes	48	2.82	(-1.25, 6.90)	4.17	(0.09, 8.24)	4.01	(0.50, 7.51)	3.39	(-5.43, 12.21)	2.76	(-12.24, 17.77)
	No	10	7.79	(1.83, 13.75)	7.64	(1.15, 14.14)	2.48	(-6.33, 11.29)	-4.17	(-19.57, 11.23)	-10.85	(-33.93, 12.22)
HDL-C	Yes	51	1.96	(0.59, 3.34)	2.38	(0.62, 4.13)	1.15	(0.05, 2.26)	-0.57	(-1.03, -0.11)	-2.30	(-3.43, -1.18)
	No	10	3.43	(1.22, 5.63)	2.92	(-0.84, 6.69)	-0.30	(-10.56, 9.96)	-4.68	(-23.44, 14.09)	-9.16	(-36.70, 18.37)
Non-HDL-C§	Yes	21	-0.89	(-6.37, 4.58)	-3.74	(-9.57, 2.09)	-8.24	(-11.80, -4.68)	-13.24	(-20.14, -6.33)	-18.24	(-30.72, -5.76)
Participants with hyperlipidemia taking lipid-lowering medication												
TG	Yes	22	1.93	(-15.04, 18.90)	-27.96	(-44.08, -11.84)	-98.23	(-201.25, 4.79)	-181.48	(-391.95, 28.99)	-264.99	(-583.40, 53.43)
	No	17	-18.97	(-46.12, 8.19)	-52.75	(-71.38, -34.12)	-100.71	(-160.80, -40.61)	-152.93	(-285.76, -20.09)	-205.23	(-412.34, 1.88)
LDL-C	Yes	24	1.21	(-1.49, 3.92)	1.06	(-2.79, 4.91)	-0.83	(-3.84, 2.17)	-3.29	(-4.85, -1.72)	-5.75	(-6.36, -5.14)
	No	15	-0.41	(-3.77, 2.95)	3.02	(-0.07, 6.12)	10.13	(5.57, 14.70)	18.36	(7.93, 28.80)	26.62	(9.85, 43.38)
HDL-C	Yes	24	-0.56	(-2.92, 1.79)	0.64	(-1.41, 2.69)	4.09	(-9.20, 17.38)	8.26	(-19.07, 35.59)	12.44	(-29.00, 53.89)
	No	17	4.15	(0.63, 7.66)	4.98	(0.64, 9.32)	2.65	(0.01, 5.28)	-0.64	(-1.55, 0.27)	-3.94	(-6.74, -1.15)
Non-HDL-C	Yes	13	1.44	(-7.38, 10.27)	-1.90	(-11.46, 7.67)	-9.59	(-13.90, -5.27)	-18.58	(-27.04, -10.11)	-27.59	(-44.86, -10.32)
	No	3	-1.87	(-7.72, 3.98)	-3.52	(-11.49, 4.46)	-4.88	(-10.31, 0.55)	-6.16	(-8.21, -4.11)	-7.43	(-11.26, -3.61)
Baseline mean BMI												
TG	≥25 kg/m^2	53	-25.54	(-42.03, -9.04)	-46.86	(-58.64, -35.08)	-65.27	(-91.38, -39.17)	-82.82	(-140.21, -25.43)	-100.35	(-190.25, -10.45)
	<25 kg/m^2	22	-5.76	(-24.62, 13.10)	-9.23	(-23.58, 5.12)	-11.47	(-82.65, 59.72)	-13.53	(-146.12, 119.06)	-15.60	(-209.67, 178.47)
LDL-C	≥25 kg/m^2	52	4.15	(0.41, 7.89)	5.00	(1.74, 8.27)	3.56	(0.34, 6.79)	1.45	(-6.15, 9.04)	-0.69	(-13.28, 11.91)
	<25 kg/m^2	20	1.00	(-2.62, 4.62)	-1.42	(-3.50, 0.67)	-5.83	(-13.76, 2.10)	-10.62	(-26.60, 5.36)	-15.41	(-39.54, 8.71)

Lipid	Participants	N*	1.0 g/d		2.0 g/d		3.0 g/d		4.0 g/d		5.0 g/d	
			MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)
HDL-C	≥25 kg/m^2	55	1.56	(0.76, 2.36)	1.78	(0.82, 2.75)	1.08	(0.15, 2.01)	0.10	(-1.12, 1.33)	-0.88	(-2.64, 0.88)
	<25 kg/m^2	21	1.76	(-5.20, 8.73)	4.69	(-1.47, 10.85)	8.20	(-12.01, 28.41)	11.77	(-25.14, 48.67)	15.33	(-38.48, 69.14)
Non-HDL-C§	≥25 kg/m^2	18	1.19	(-5.32, 7.69)	-1.78	(-8.32, 4.76)	-7.61	(-11.31, -3.90)	-14.29	(-21.21, -7.36)	-20.99	(-33.82, -8.15)
With or without CHD												
TG	Yes	18	16.89	(-8.14, 41.92)	-10.83	(-34.21, 12.54)	-74.19	(-169.03, 20.65)	-160.47	(-362.13, 41.19)	-256.94	(-579.14, 65.26)
	No	44	-29.63	(-51.31, -7.94)	-48.07	(-65.01, -31.13)	-58.77	(-90.41, -27.13)	-67.17	(-136.20, 1.87)	-75.53	(-184.02, 32.97)
LDL-C	Yes	17	-1.64	(-4.42, 1.13)	-1.55	(-4.99, 1.89)	-0.46	(-3.48, 2.56)	0.91	(-1.73, 3.54)	2.27	(-0.49, 5.03)
	No	40	6.11	(1.56, 10.67)	7.36	(2.99, 11.74)	5.24	(1.29, 9.19)	2.12	(-6.04, 10.29)	-1.01	(-14.50, 12.47)
HDL-C	Yes	18	-0.71	(-2.10, 0.67)	-1.08	(-3.03, 0.88)	-1.16	(-3.11, 0.79)	-1.06	(-2.82, 0.71)	-0.88	(-2.74, 0.99)
	No	44	2.92	(1.57, 4.28)	3.21	(1.65, 4.77)	1.67	(0.69, 2.66)	-0.41	(-0.91, 0.09)	-2.50	(-3.52, -1.47)
Non-HDL-C§	No	15	0.22	(-6.89, 7.34)	-2.87	(-10.07, 4.33)	-8.27	(-12.81, -3.73)	-14.35	(-22.66, -6.04)	-20.44	(-35.28, -5.60)
Baseline mean age												
TG	≥50 years	69	-20.60	(-35.58, -5.62)	-42.12	(-54.61, -29.63)	-64.29	(-95.15, -33.43)	-86.64	(-149.26, -24.02)	-109.00	(-204.58, -13.43)
	<50 years	16	-23.52	(-34.09, -12.95)	-50.55	(-81.90, -19.20)	-80.00	(-162.64, 2.63)	-110.48	(-255.66, 34.70)	-141.05	(-350.06, 67.96)
LDL-C	≥50 years	64	2.77	(-0.22, 5.77)	3.06	(0.23, 5.90)	1.66	(-0.71, 4.03)	-0.22	(-5.24, 4.81)	-2.10	(-10.50, 6.30)
	<50 years	15	6.48	(1.36, 11.61)	8.11	(1.81, 14.42)	6.43	(-4.92, 17.79)	3.44	(-16.87, 23.76)	0.36	(-29.73, 30.45)
HDL-C	≥50 years	69	1.05	(0.33, 1.77)	1.17	(0.29, 2.06)	0.64	(-0.20, 1.48)	-0.08	(-1.12, 0.96)	-0.81	(-2.26, 0.65)
	<50 years	17	5.48	(0.82, 10.15)	5.43	(-0.09, 10.95)	1.57	(-4.91, 8.05)	-3.88	(-14.33, 6.57)	-9.46	(-25.15, 6.23)
Duration												
TG	>13 weeks	39	-0.40	(-16.57, 15.78)	-28.66	(-41.94, -15.38)	-74.43	(-123.53, -25.32)	-124.43	(-219.29, -29.57)	-174.45	(-315.62, -33.28)
	≤13 weeks	47	-41.97	(-58.15, -25.78)	-59.49	(-77.77, -41.22)	-60.11	(-73.76, -46.46)	-55.71	(-72.21, -39.20)	-51.21	(-77.77, -24.65)
LDL-C	>13 weeks	34	0.63	(-2.07, 3.33)	0.40	(-2.08, 2.89)	-0.30	(-5.65, 5.06)	-1.07	(-11.00, 8.86)	-1.85	(-16.57, 12.86)
	≤13 weeks	46	4.36	(0.64, 8.09)	5.31	(0.98, 9.63)	3.88	(0.73, 7.03)	1.75	(-1.22, 4.72)	-0.39	(-5.02, 4.23)
HDL-C	>13 weeks	39	0.70	(-1.08, 2.49)	1.06	(-0.27, 2.39)	1.23	(-4.61, 7.07)	1.36	(-9.74, 12.45)	1.49	(-14.89, 17.87)
	≤13 weeks	48	2.31	(0.95, 3.67)	2.50	(0.94, 4.07)	1.23	(0.23, 2.22)	-0.50	(-0.95, -0.04)	-2.23	(-3.19, -1.26)
Non-HDL-C	>13 weeks	8	-3.95	(-7.74, -0.16)	-5.94	(-9.03, -2.84)	-6.95	(-8.50, -5.39)	-7.89	(-11.91, -3.87)	-8.83	(-16.02, -1.64)
	≤13 weeks	14	0.06	(-8.17, 8.30)	-3.07	(-11.52, 5.38)	-8.40	(-13.21, -3.59)	-14.39	(-22.45, -6.34)	-20.40	(-35.47, -5.32)
Individual effect of DHA or EPA												

Lipid	Participants	N*	1.0 g/d		2.0 g/d		3.0 g/d		4.0 g/d		5.0 g/d	
			MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)
TG	EPA only	20	-14.37	(-26.82, -1.91)	-22.52	(-31.45, -13.59)	-29.72	(-40.58, -18.85)	-36.92	(-55.49, -18.35)	-44.12	(-71.69, -16.56)
	DHA only	5	-17.96	(-28.19, -7.72)	-29.61	(-41.78, -17.45)	-37.18	(-56.32, -18.04)	-43.17	(-76.58, -9.76)	-49.07	(-98.57, 0.44)
LDL-C	EPA only	20	4.26	(-2.96, 11.48)	3.15	(-4.13, 10.43)	0.35	(-4.73, 5.44)	-2.44	(-5.36, 0.47)	-5.24	(-6.15, -4.33)
	DHA only	5	10.63	(8.88, 12.38)	12.73	(9.04, 16.42)	9.29	(-0.82, 19.40)	3.72	(-14.32, 21.76)	-1.98	(-28.09, 24.13)
HDL-C	EPA only	22	1.18	(-0.48, 2.83)	0.96	(-0.20, 2.11)	0.45	(-0.96, 1.86)	-0.06	(-2.61, 2.49)	-0.56	(-4.43, 3.30)
	DHA only	5	3.17	(0.69, 5.65)	4.57	(1.83, 7.30)	4.81	(1.61, 8.00)	4.61	(-0.85, 10.06)	4.38	(-3.96, 12.72)

CI indicates the confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglyceride.

Note: *Numbers may not be added to group totals due to missing data or unspecified subgroups in the trials.

§Due to the unavailability of data, only one subgroup estimate was performed in the absence or presence of hyperlipidemia, overweight/obesity (≥25 kg/m^2), and pre-existing CHD.

Table S5. Estimated average dose-response relationship between the achieved changes of red blood cell (RBC) index and lipid level reduction

BP	Participants	N	Index increased by 50%		Index increased by 100%		Index increased by 150%		Index increased by 200%		Index increased by 250%	
			MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)	MD	(95 % CI)
TG	All	28	-24.97	(-35.61, -14.33)	-43.62	(-58.50, -28.74)	-58.72	(-93.76, -23.69)	-73.32	(-133.37, -13.26)	-87.91	(-173.63, -2.18)
LDL-C	All	26	1.50	(-0.52, 3.52)	1.34	(-0.89, 3.57)	0.26	(-4.35, 4.86)	-0.97	(-9.08, 7.15)	-2.19	(-13.98, 9.60)
HDL-C	All	28	1.49	(0.30, 2.69)	2.59	(0.32, 4.85)	3.46	(-2.84, 9.76)	4.30	(-6.49, 15.10)	5.15	(-10.19, 20.48)
Non-HDL-C	All	4	-1.35	(-10.05, 7.34)	-2.85	(-13.35, 7.66)	-4.50	(-11.18, 2.19)	-6.20	(-15.85, 3.45)	-7.90	(-25.65, 9.85)

CI, confidence interval; DHA, docosahexaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; Non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglyceride.

Table S6: Risk of bias of included 90 trials in lipid profile study

Author	Year	Randomization	Blinding	Missing outcome	Measurement	Selection of results	Overall
Flaten[57]	1990	some concern	some concern	low	medium	medium	medium
Hendra[58]	1990	some concern	some concern	low	low	medium	low
Reis[59]	1990	some concern	medium	low	low	low	low
Bonaa[60]	1992	some concern	some concern	low	some concern	low	low
Kaul[61]	1992	high	high	low	low	low	low
Leaf[62]	1994	low	low	low	low	low	low
Sacks[63]	1995	some concern	low	some concern	low	low	low
Shimizu[64]	1995	medium	medium	low	low	medium	medium
Eritsland[65]	1996	low	medium	low	low	low	low
Grimsgaard[66]	1997	low	low	low	low	low	low
Harris[67]	1997	low	some concern	low	low	low	low
Sirtori[68]	1997	low	low	low	low	low	low
Borthwick[69]	1998	some concern	low	low	low	low	low
Nordoy[70]	1998	some concern	low	low	low	low	low
Johansen[71]	1999	low	low	low	low	low	low
von Schacky[72]	1999	low	low	low	low	low	low
Mori[73]	2000	some concern	low	low	low	low	low
Durrington[74]	2001	some concern	some concern	low	low	low	low
Finnegan[75]	2003	some concern	medium	low	low	low	low
Hamazaki[76]	2003	some concern	low	low	low	low	low
Dyerberg[77]	2004	medium	medium	low	low	low	low
Hjerkinn[78]	2005	low	low	low	low	low	low
Maki[79]	2005	some concern	medium	low	low	low	low
Geppert[80]	2006	medium	medium	low	low	low	low
Lee[81]	2006	low	high	low	low	low	low
Sanders[82]	2006	medium	medium	low	low	low	low
Davidson[83]	2007	medium	medium	low	low	low	low
Mita[84]	2007	high	low	low	low	low	low
Satoh[85]	2007	medium	medium	low	low	low	low
Kaul[86]	2008	medium	medium	low	low	low	low
Saito[87]	2008	low	low	low	low	low	low
Shidfar[88]	2008	high	high	low	low	low	low
Ebrahimi[89]	2009	high	high	medium	low	low	high
Hartwich[90]	2009	medium	medium	low	low	low	low
Khandelwal[91]	2009	low	medium	low	low	low	low
Nomura[92]	2009	low	medium	low	low	low	low
Rizza[93]	2009	medium	low	low	low	low	low
Satoh[94]	2009	medium	medium	low	low	low	low
Bays[95]	2010	medium	medium	medium	low	low	medium
Hallund[96]	2010	medium	medium	low	low	low	low

Kromhout[97]	2010	low	low	low	low	low	low
Neil[98]	2010	low	low	low	low	low	low
Zhang[99]	2010	some concern	medium	low	low	low	low
Bays[100]	2011	some concern	high	low	low	low	low
Itakura[101]	2011	low	low	low	low	low	low
Kim[102]	2011	some concern	high	low	low	low	low
Krysiak[103]	2011	some concern	high	low	low	low	low
Krysiak[104]	2011	some concern	high	low	low	low	low
Nodari[105]	2011	low	low	low	low	low	low
Sanders[106]	2011	low	low	medium	low	low	low
Schuchardt[107]	2011	low	low	medium	low	low	low
Takaki[108]	2011	low	medium	low	low	low	low
Tierney[109]	2011	low	medium	low	low	low	low
Agouridis[110]	2012	low	high	medium	low	low	high
Ballantyne[111]	2012	low	low	low	low	low	low
Derosa[112]	2012	low	low	low	low	low	low
Bosch[20]	2012	low	low	low	low	low	low
Koh[113]	2012	low	medium	low	low	low	low
Satoh-Asahara[114]	2012	some concern	some concern	low	low	low	low
Flock[115]	2013	some concern	some concern	low	medium	low	low
Roncaglioni[21]	2013	low	low	low	low	low	low
Hlais[116]	2013	low	medium	low	low	low	low
Maki[47]	2013	low	low	low	low	low	low
Tani[117]	2013	low	medium	low	low	low	low
Maki[118]	2014	low	some concern	low	low	low	low
Oh[119]	2014	low	medium	low	low	low	low
Scorletti[120]	2014	some concern	some concern	low	low	low	low
Toyama[121]	2014	some concern	medium	low	low	low	low
Mansoori[122]	2015	some concern	some concern	low	low	low	low
Qin[48]	2015	low	some concern	low	low	low	low
Ahn[123]	2016	low	low	low	low	low	low
Bays[124]	2016	low	low	low	low	low	low
Derosa[125]	2016	low	low	low	low	low	low
Koh[126]	2016	low	medium	low	low	low	low
Sawada[127]	2016	low	medium	low	low	low	low
Su[128]	2017	low	low	low	low	low	low
Tani[129]	2017	low	medium	low	low	low	low
Tani[130]	2017	low	medium	low	low	low	low
Toth[131]	2017	low	some concern	low	low	medium	low
Watanabe[132]	2017	low	high	low	low	low	low
Group[133]	2018	low	low	low	low	low	low
Kim[134]	2018	low	some concern	low	low	low	low

Oscarsson[135]	2018	low	low	some concern	low	some concern	low
Stroes[136]	2018	low	low	low	low	low	low
Zhou[137]	2019	low	low	low	low	low	low
Fukumoto[138]	2020	high	high	low	low	medium	high
Jun[139]	2020	low	low	low	low	low	low
Kita[140]	2020	low	high	low	low	low	low
Nicholls[24]	2020	low	low	low	low	low	low
Guo[141]	2022	low	low	low	low	low	low

Note: Two review authors independently assessed the risk of bias of each included trial in the domains of randomization (random sequence generation); blinding (allocation concealment, blinding of participants and personnel, and blinding of outcome assessors); missing outcome (incomplete outcome data); measurement (method and measurement bias); and selection of results (reporting bias).

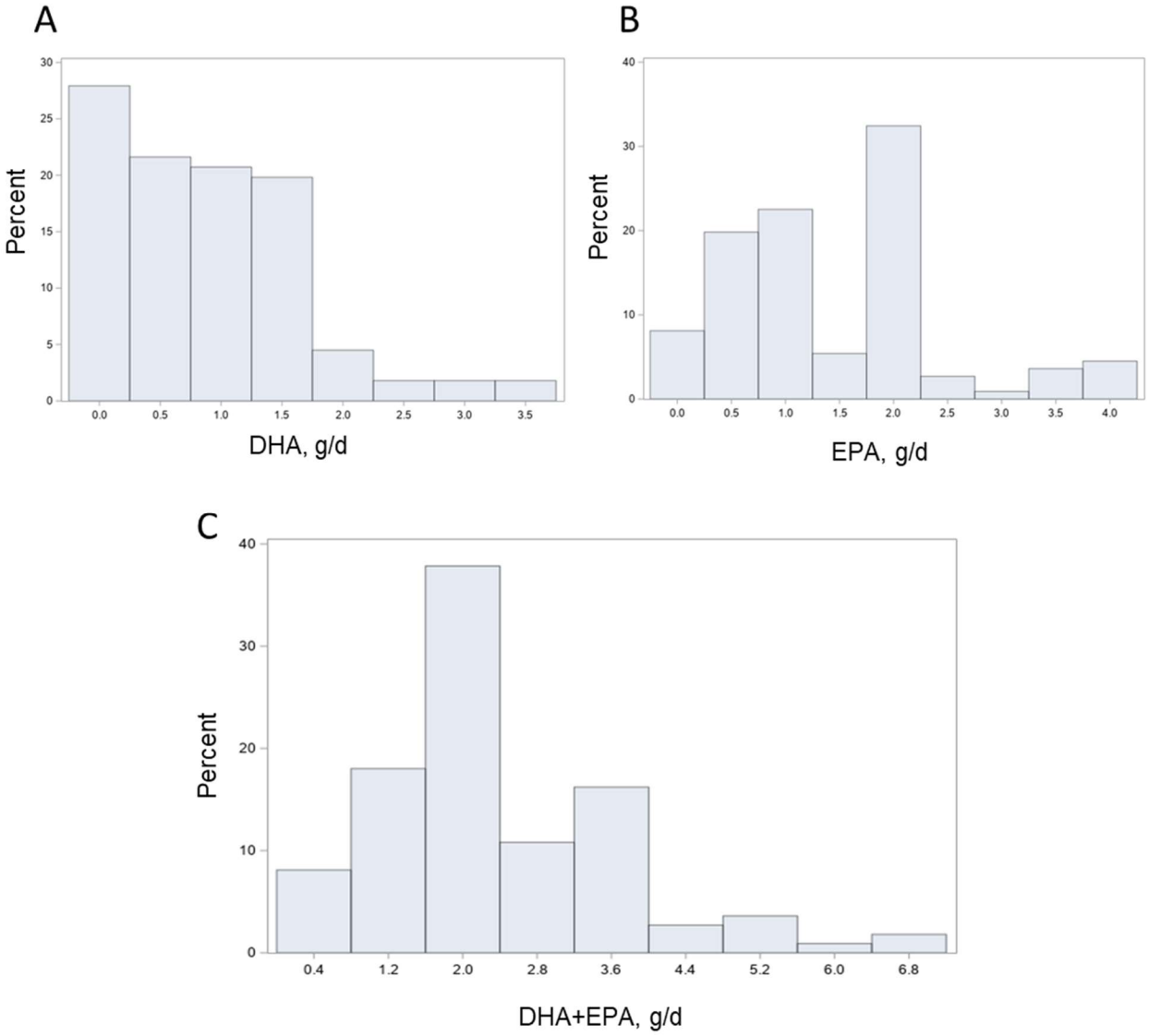

Figure S1: Histogram of dose distribution of 90 RCTs. A, Histogram of docosahexaenoic acid (DHA) dose (g/d). B, Histogram of eicosapentaenoic acid (EPA) dose (g/d). C, Histogram of the total dose (DHA+EPA, g/d).

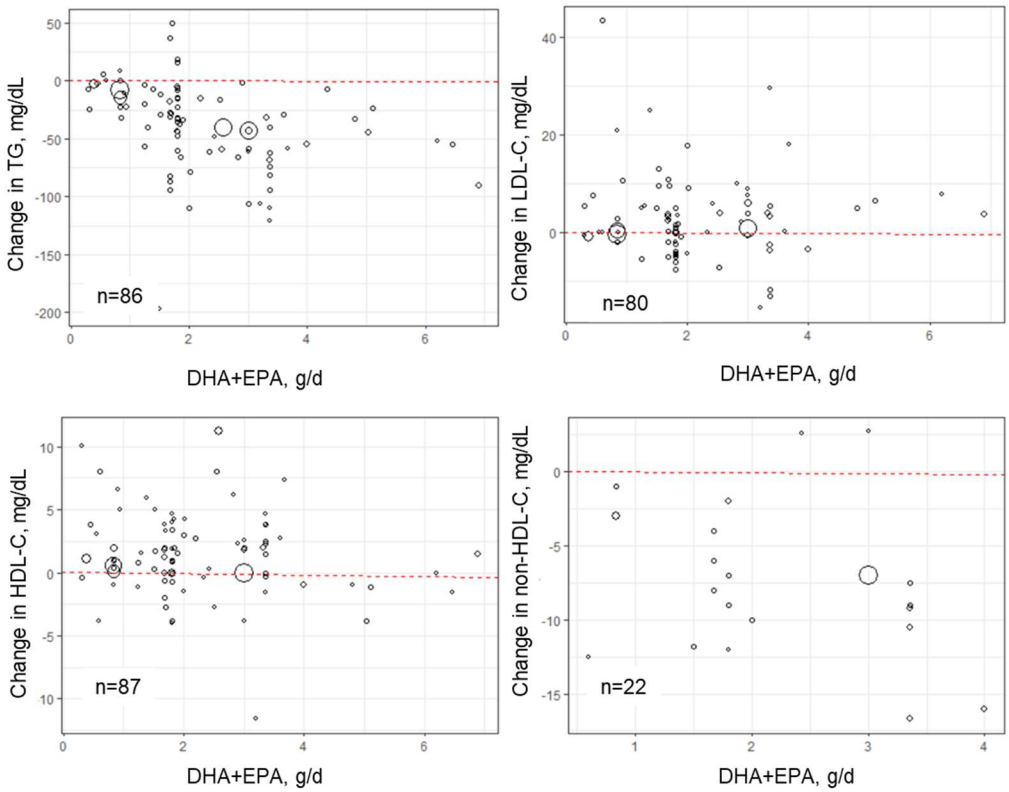

Figure S2. Scatterplot of the included trials. Studies included n=86 for triglyceride (TG), n=80 for low-density lipoprotein cholesterol (LDL-C), n=87 for high-density lipoprotein cholesterol (HDL-C), and n=22 for non-high-density lipoprotein cholesterol (non-HDL-C). Dashed red lines indicate referent changes and the bubble size is the inverse of the standard error of each exposure level.

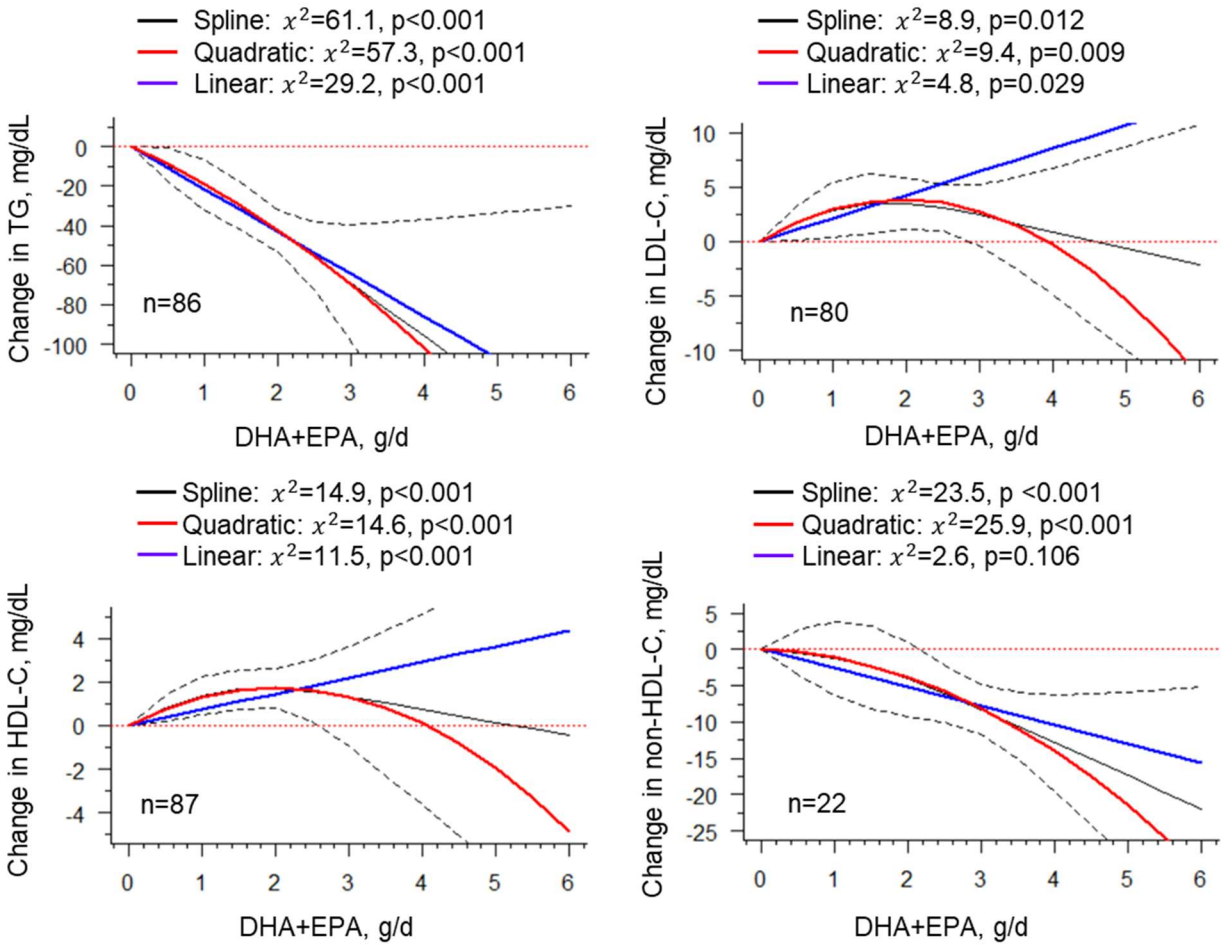

Figure S3. Model comparison. In each panel, the solid black line indicates the restricted cubic spline model, the red solid line indicates the quadratic model, and the blue solid line indicates the linear model, respectively. Dashed black lines are 95% point-wise CIs estimated by a 1-stage random-effects restricted cubic spline model.

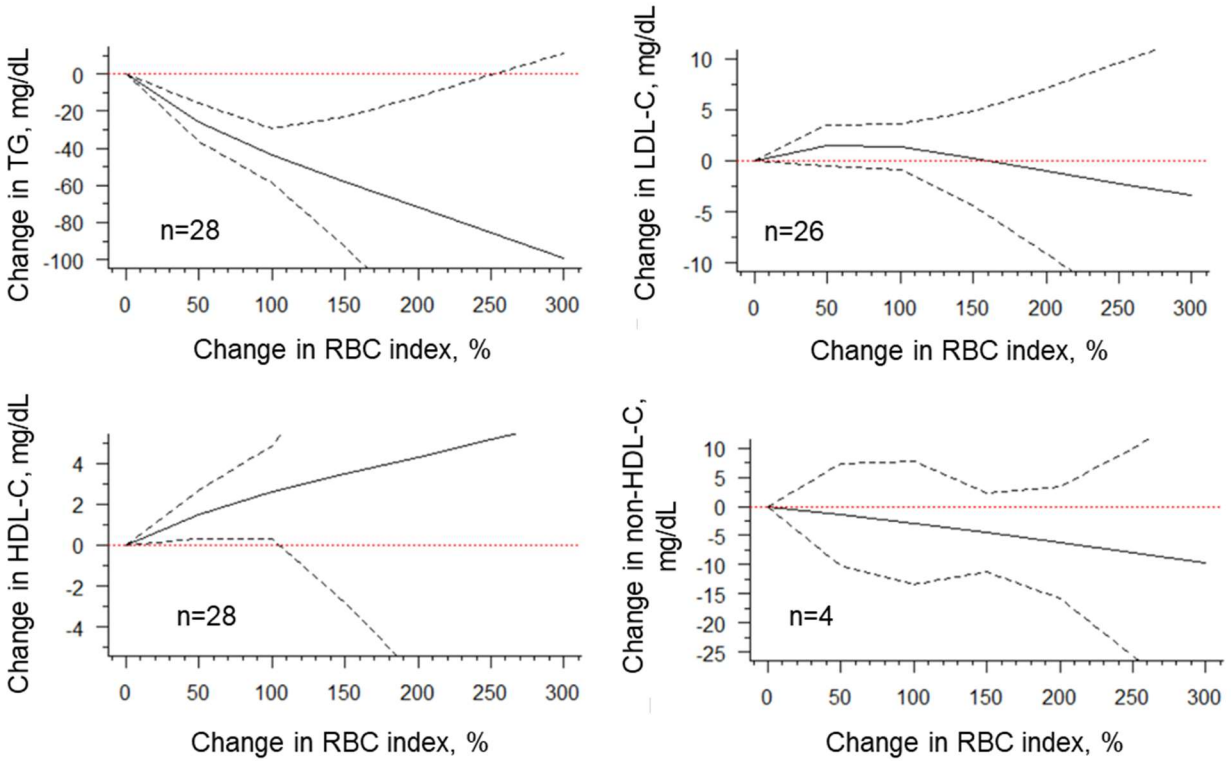

Figure S4: Dose-response relationship between changes in lipids and achieved increment of red blood cell (RBC) omega index.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/d as the referent. RBC omega index change is the achieved increment of EPA+DHA percentage in total fatty acids integrated into the RBC membrane. Studies included n=28 for triglyceride (TG), n=26 for low-density lipoprotein cholesterol (LDL-C), n=28 for high-density lipoprotein cholesterol (HDL-C), and n=4 for non-high-density lipoprotein cholesterol (non-HDL-C). Non-HDL-C analysis only includes the trials that reported non-HDL-C data.

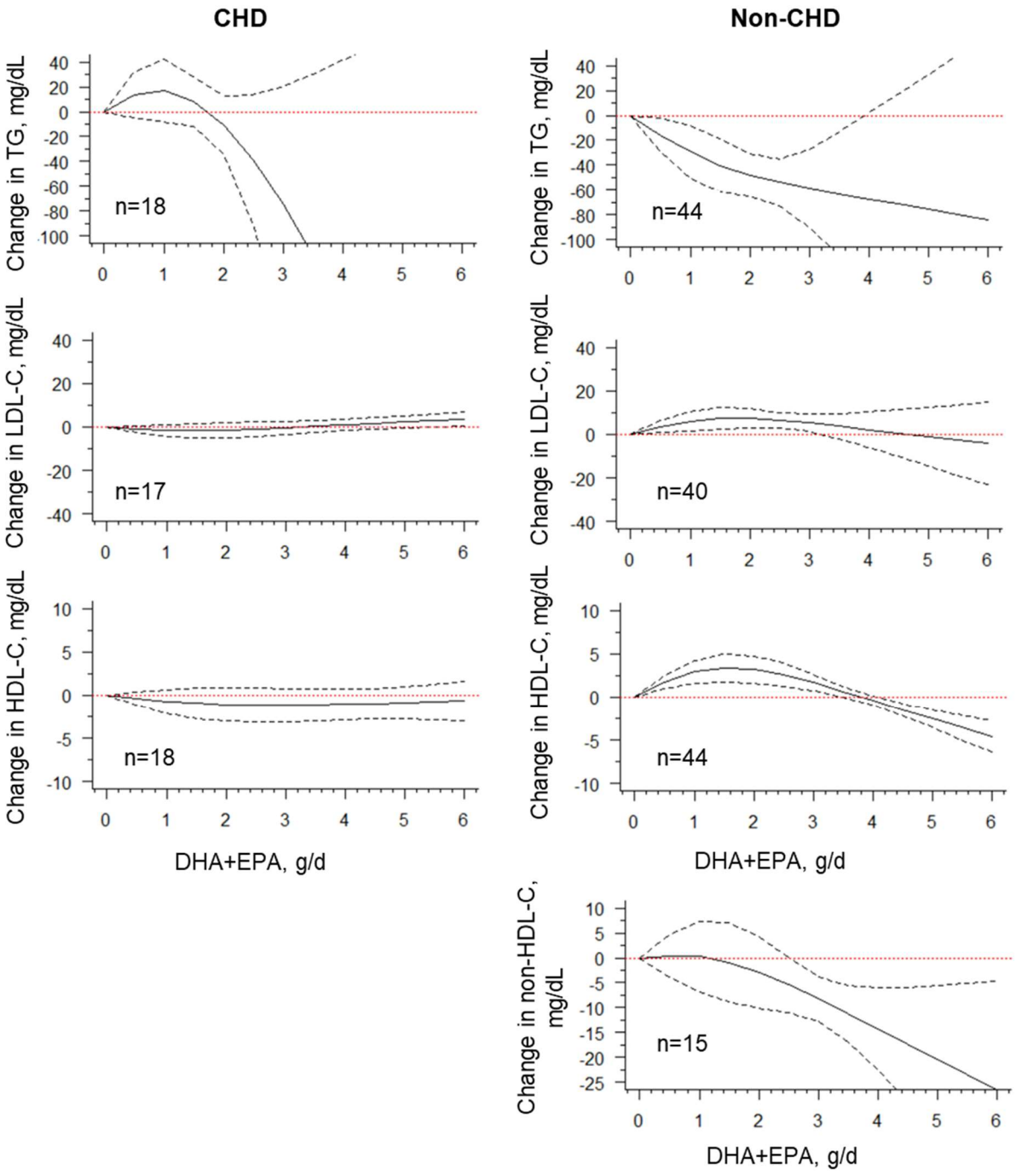

Figure S5: Dose-response relationship between changes in lipids and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by pre-existing coronary heart diseases.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with or without coronary heart diseases. CHD indicates coronary heart disease. n indicates the number of the included study.

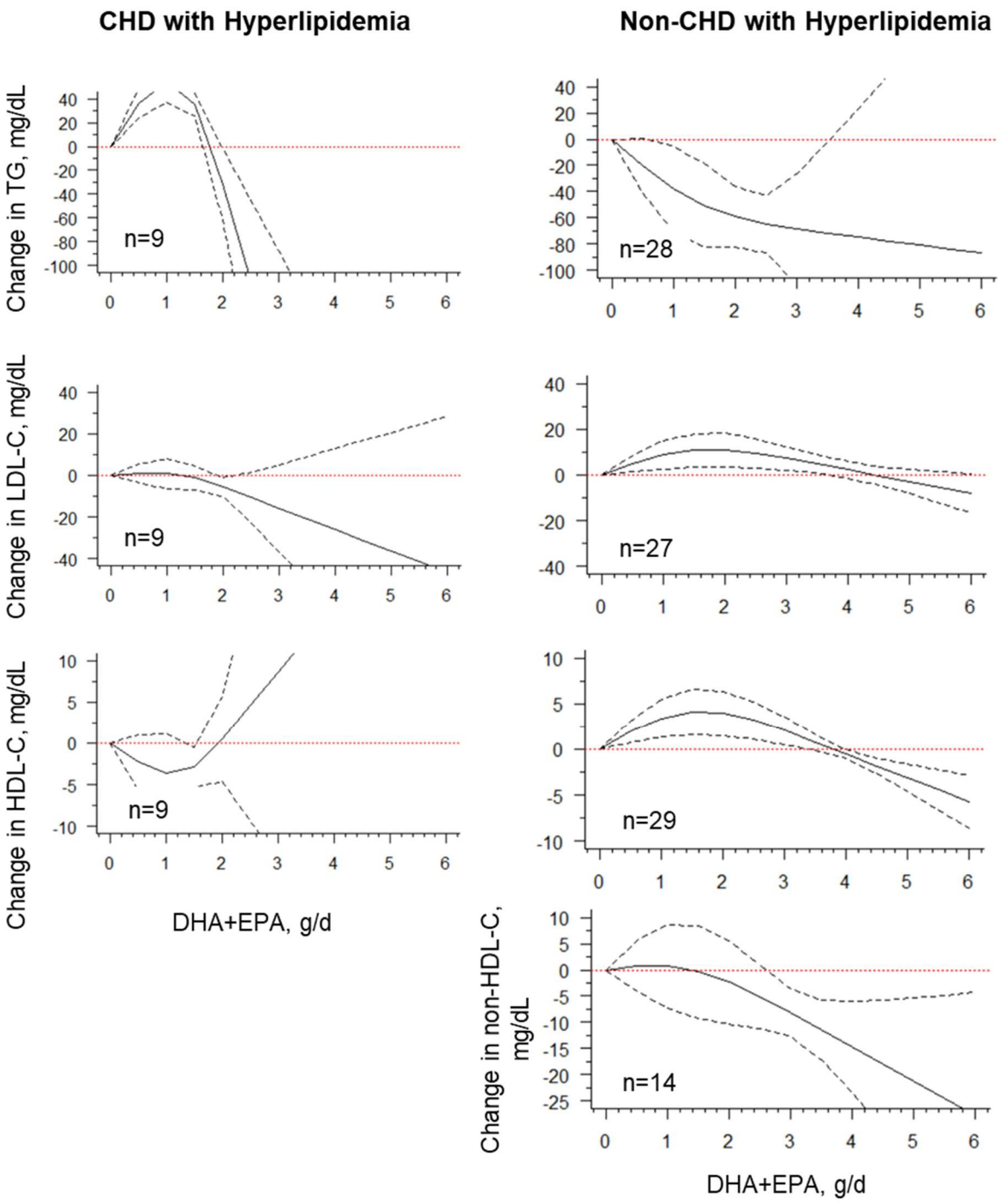

Figure S6: Dose-response relationship between changes in lipids and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified in patients with hyperlipidemia with or without pre-existing coronary heart diseases.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with or without coronary heart diseases. CHD indicates coronary heart disease. n indicates the number of the included study.

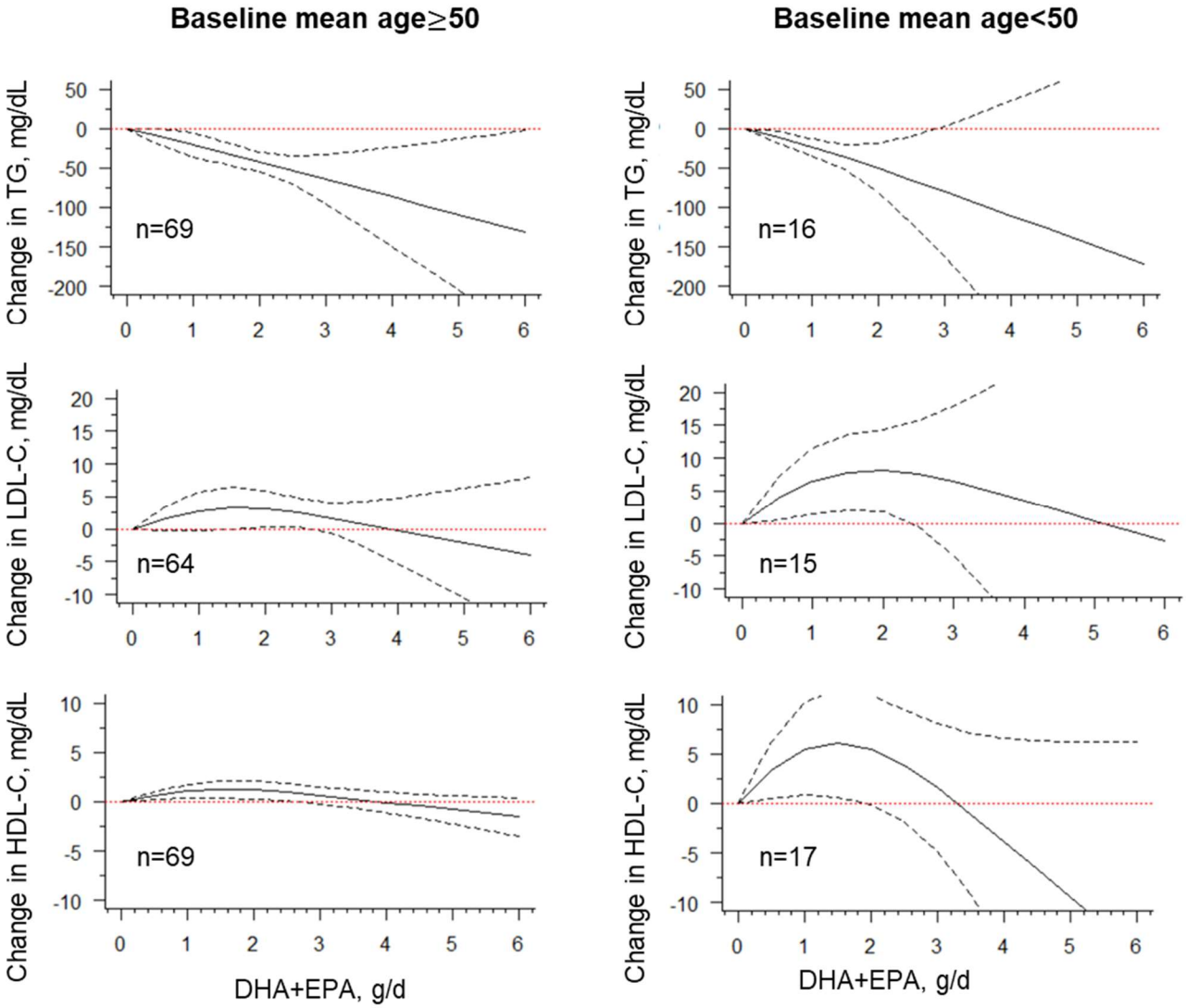

Figure S7. Dose-response relation between changes in lipids and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by baseline mean of age.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants of baseline mean of age ≥ 50 or <50 years. n indicates the number of the included study.

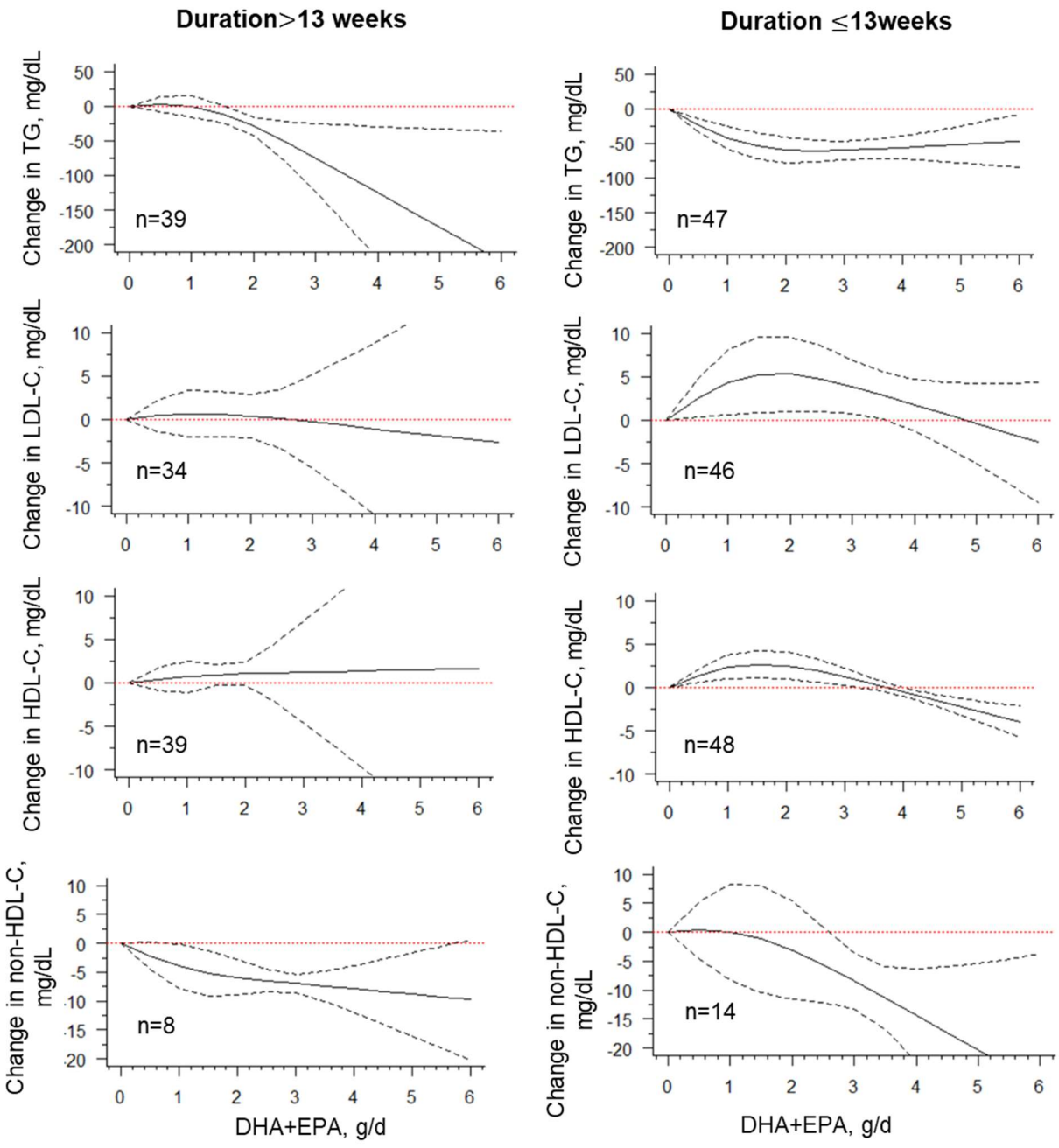

Figure S8. Dose-response relationship between changes in lipids and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by trial duration.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with trial duration ≤ 13 or >13 weeks. n indicates the number of the included study.

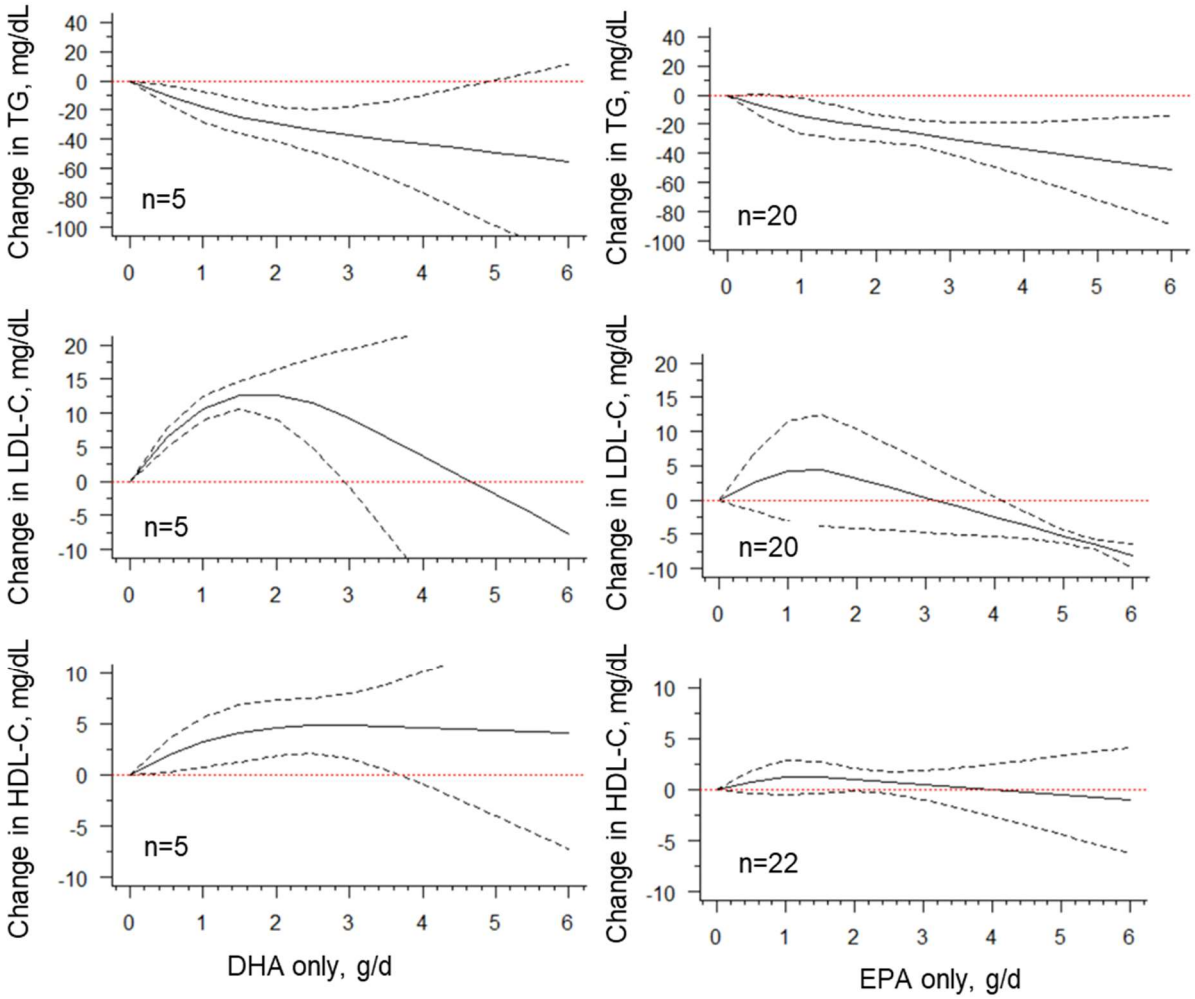

Figure S9: Dose-response relationship between changes in lipids and docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by the individual fish oils, either DHA or EPA only.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in studies using DHA or EPA alone. n indicates the number of the included study.

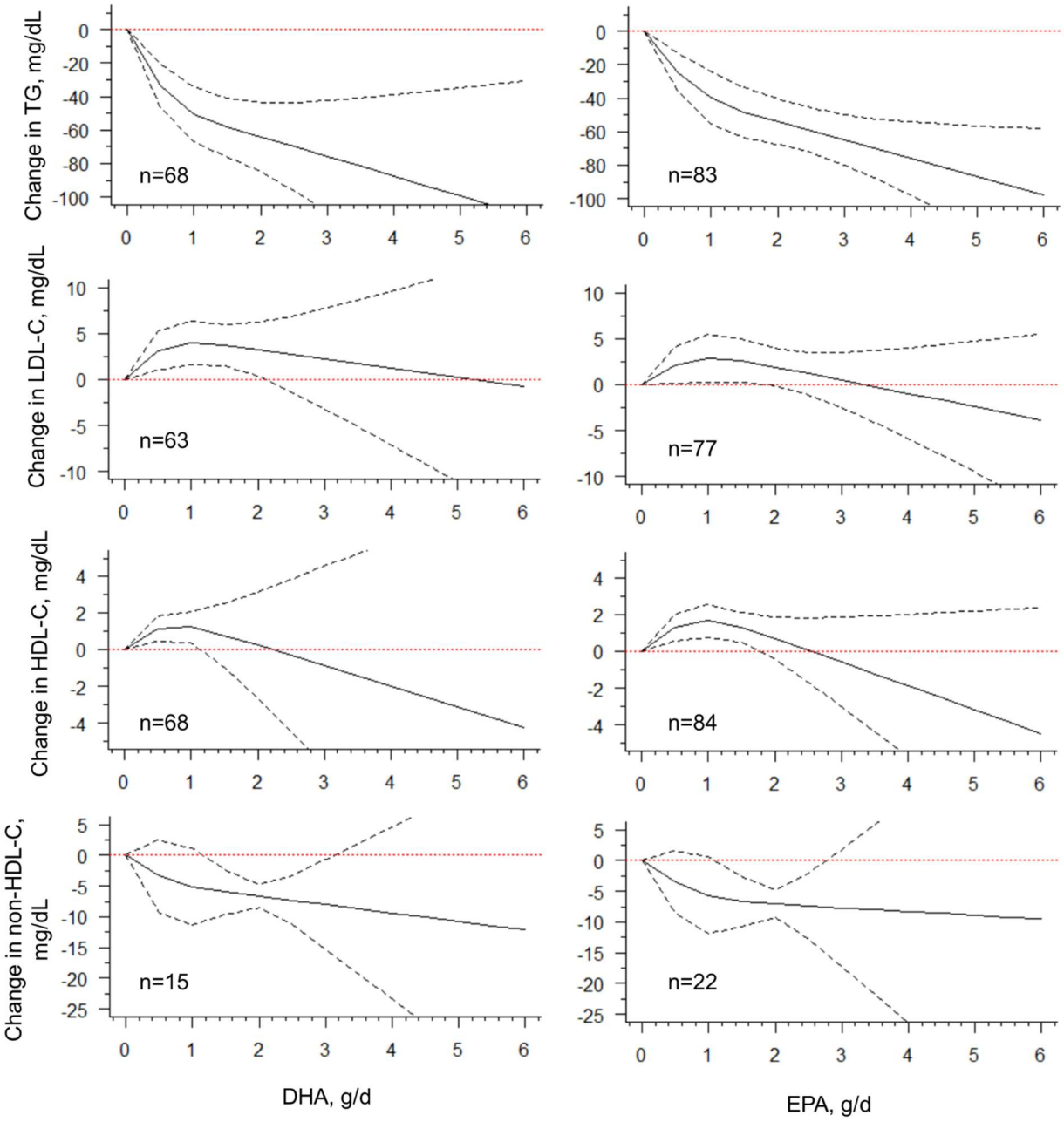

Figure S10: Dose-response relationship between changes in lipids and separate docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) intake.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent. n indicates the number of the included study.

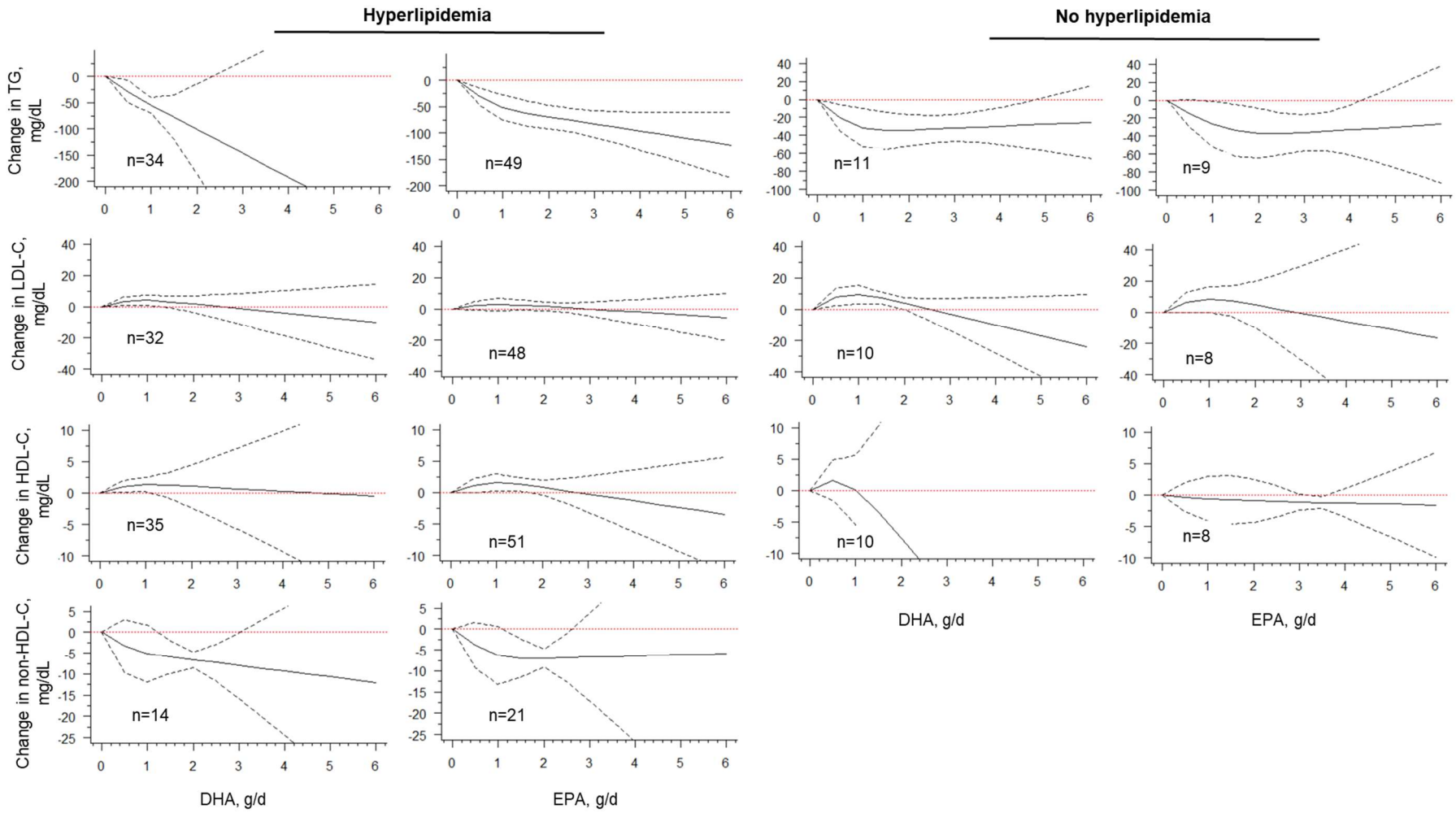

Figure S11. Dose-response relationship between changes in lipids and separate intake of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) of studies stratified by hyperlipidemia status.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as a reference, in participants with or without hyperlipidemia. n indicates the number of the included study.

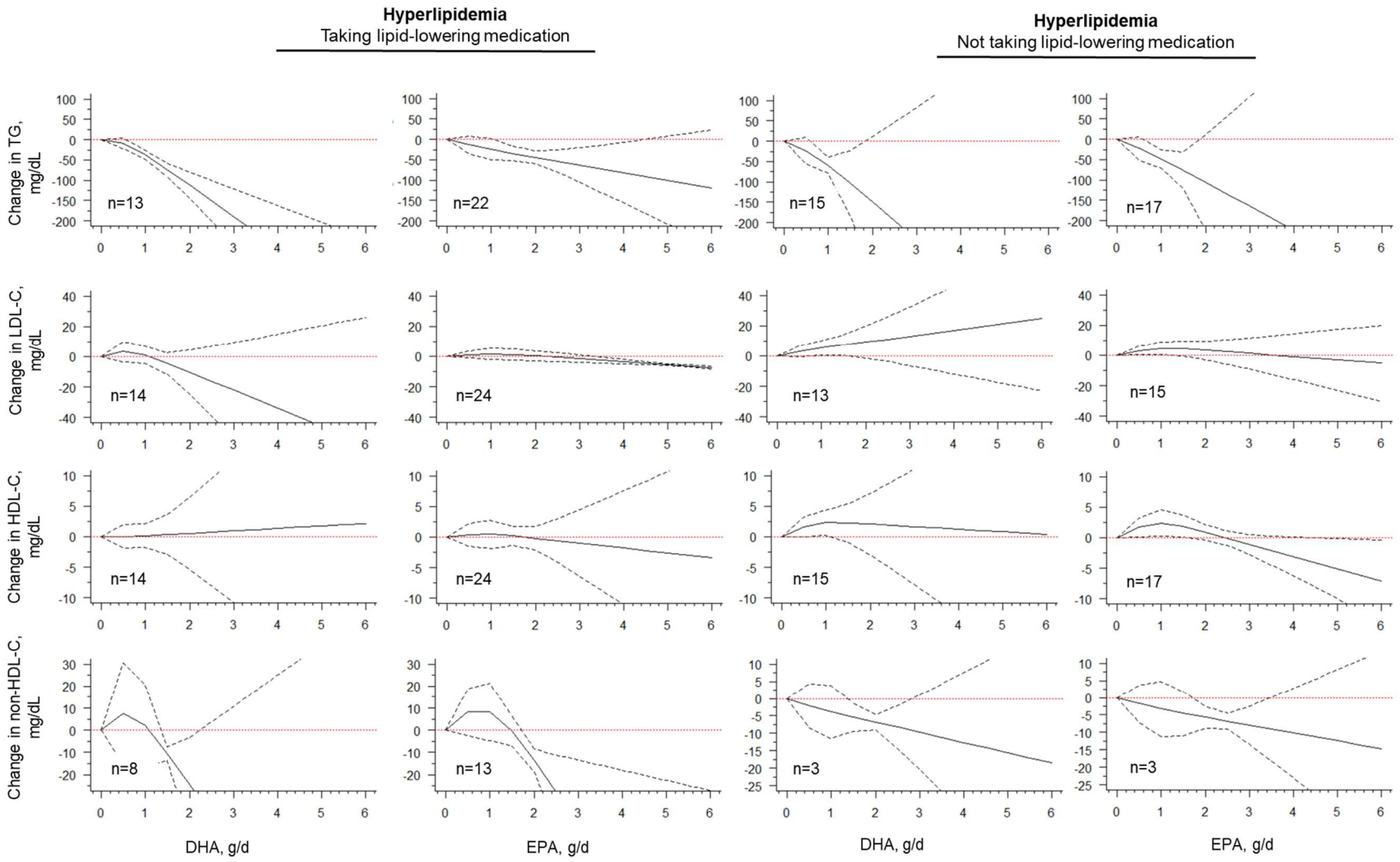

Figure S12. Subgroup analysis for changes in lipids and separate intake of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) among hyperlipidemic participants. Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as a reference, in participants taking or not taking lipid-lowering medications. n indicates the number of the included study.

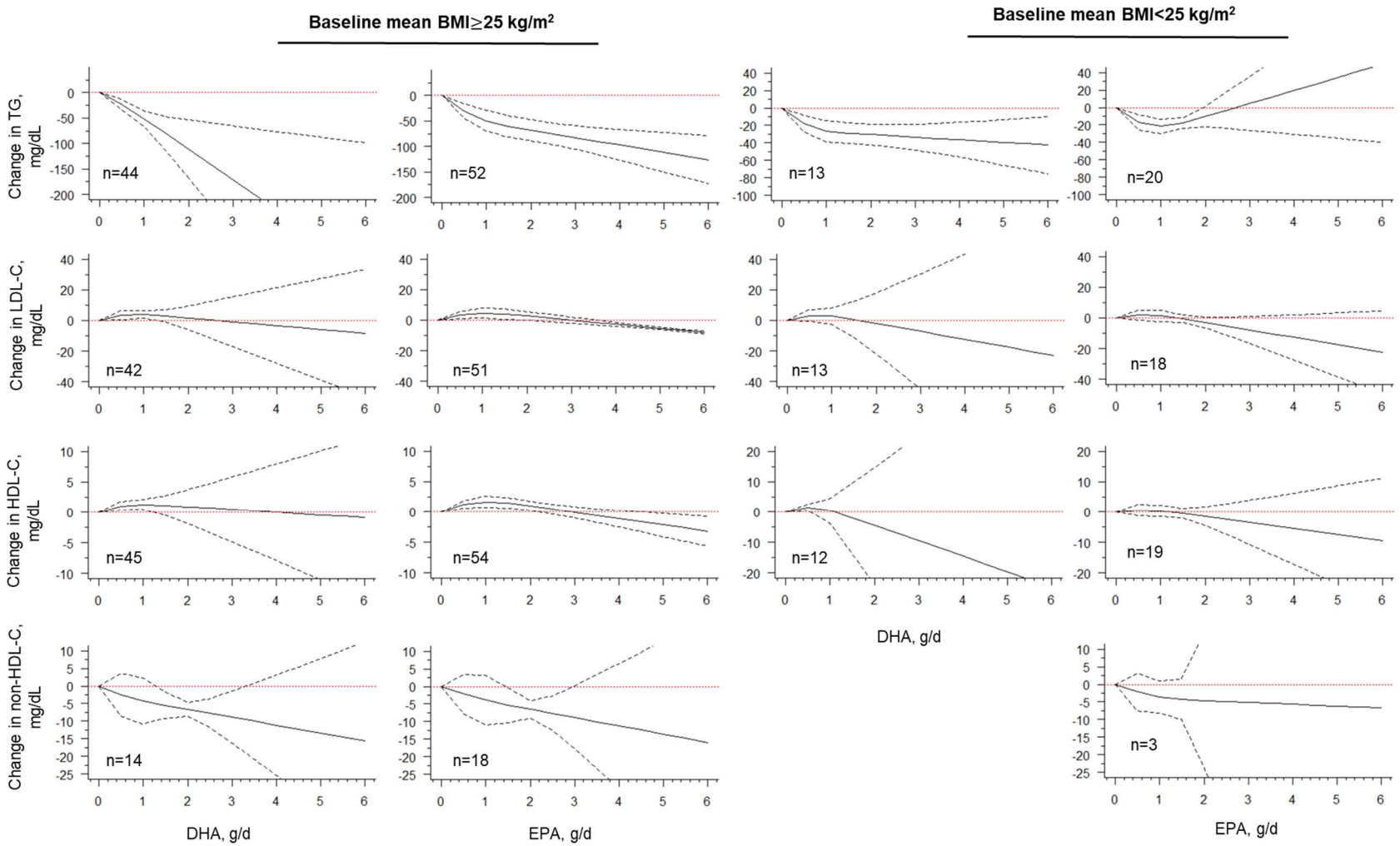

Figure S13. Dose-response relationship between changes in lipids and separate intake of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) of the studies stratified by overweight/obesity classified by the baseline mean of body mass index (BMI). Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as a reference, among participants with a mean BMI≥ 25 or <25 kg/m^2. n indicates the number of the included study.

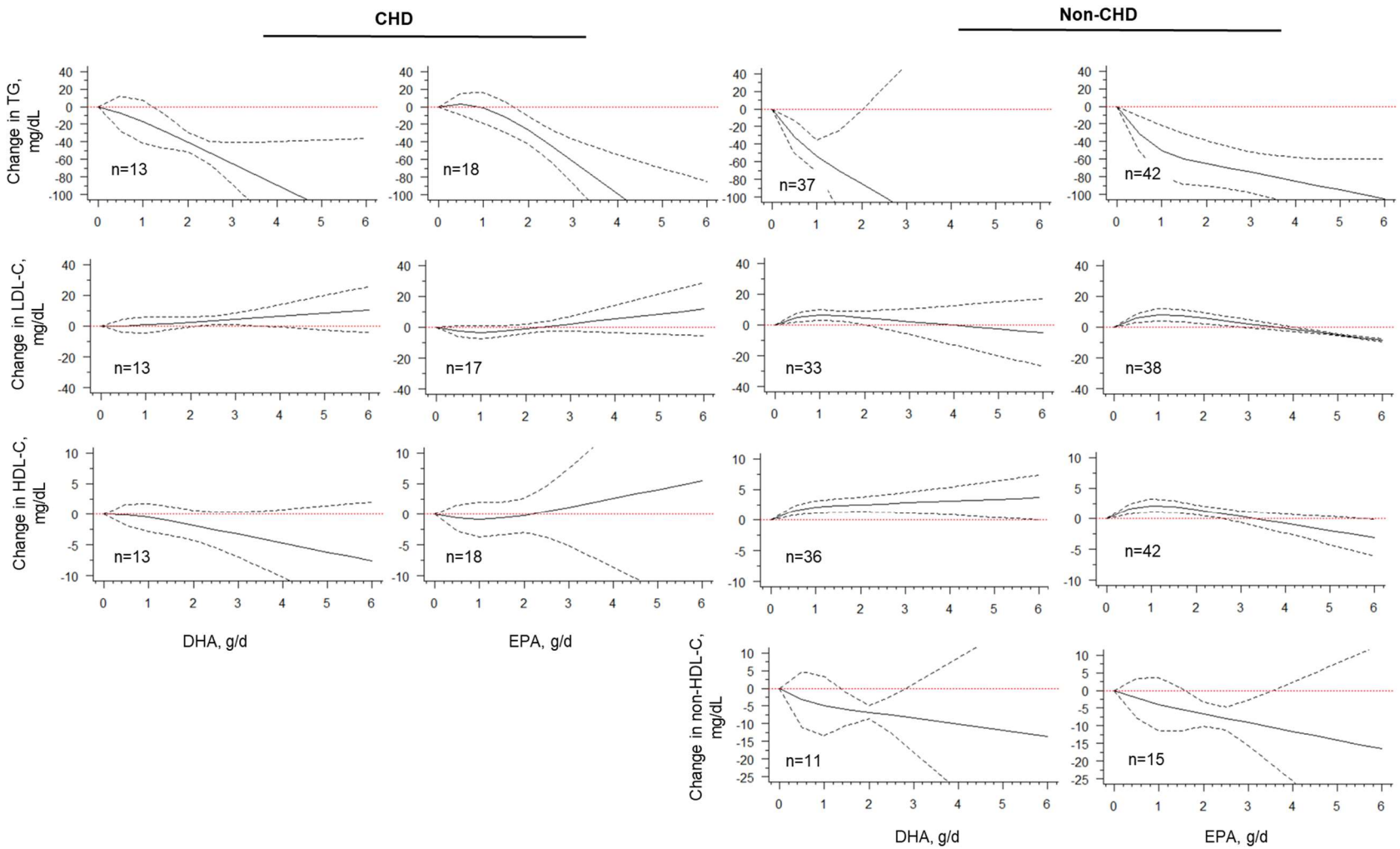

Figure S14: Dose-response relationship between changes in lipids and separate intake of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) stratified by pre-existing coronary heart diseases.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with or without coronary heart diseases. CHD indicates coronary heart disease. n indicates the number of the included study.

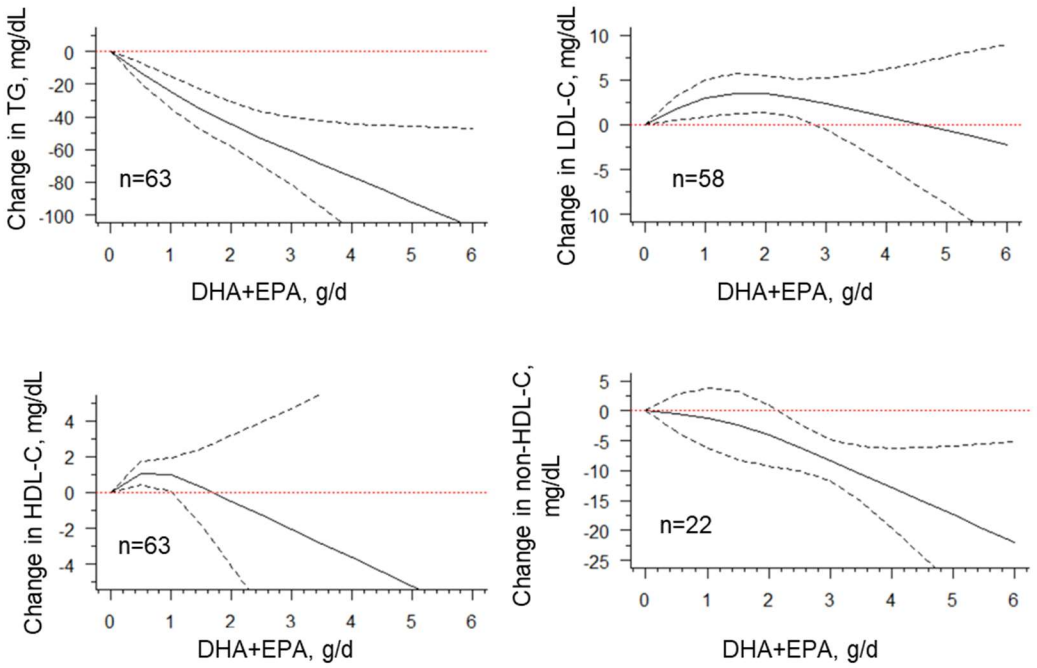

Figure S15: Dose-response relationship between changes in lipids and combined docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intake dosage, with the removal of DHA/EPA monotherapy.

Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent. n indicates the number of the included study.

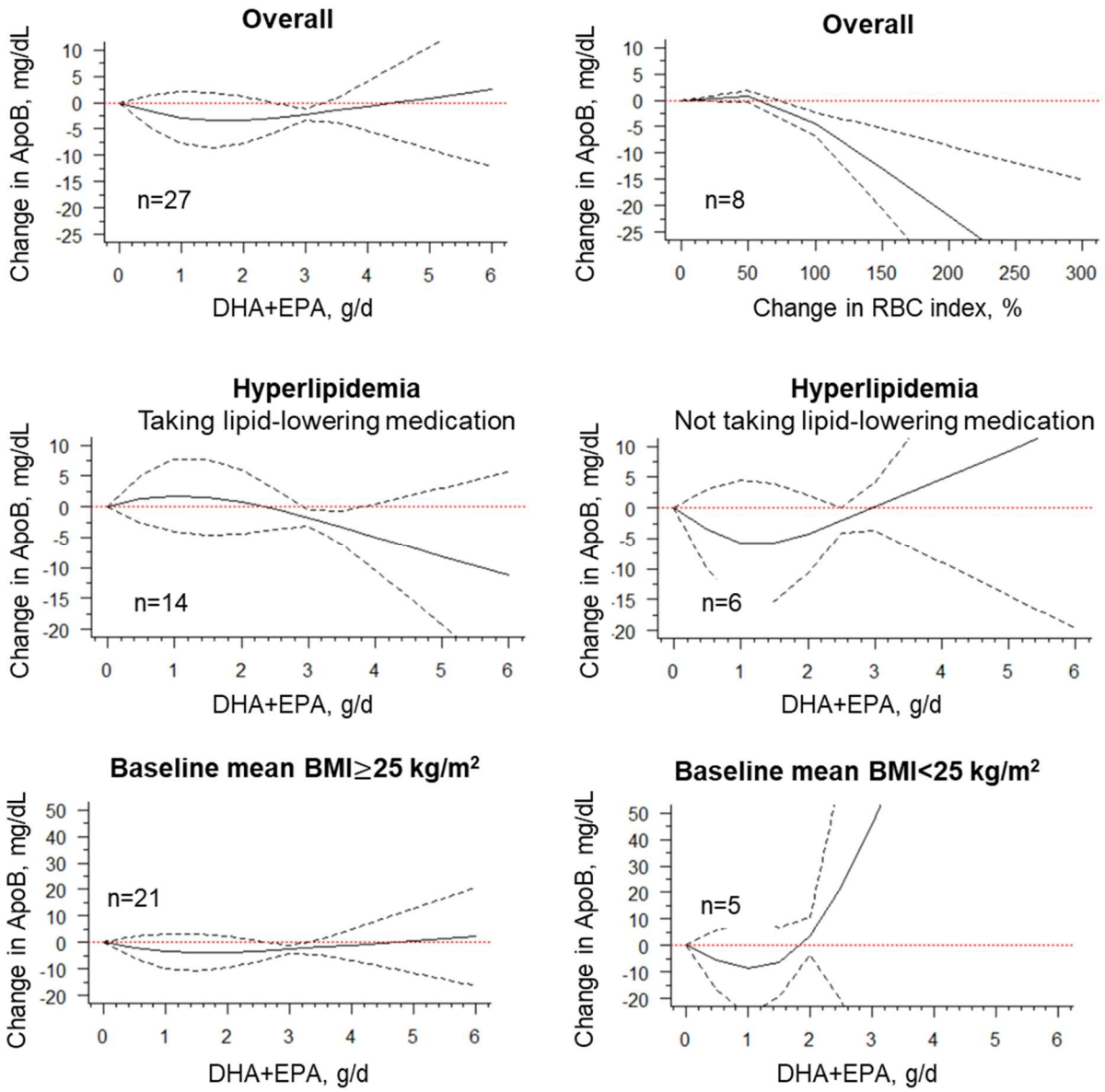

Figure S16: Dose-response relationship between changes in ApoB and docosahexaenoic acid (DHA)+eicosapentaenoic acid (an EPA) intake or red blood cells (RBC) omega index. Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day or 0 % RBC omega change as the referent. n indicates the number of the included study.

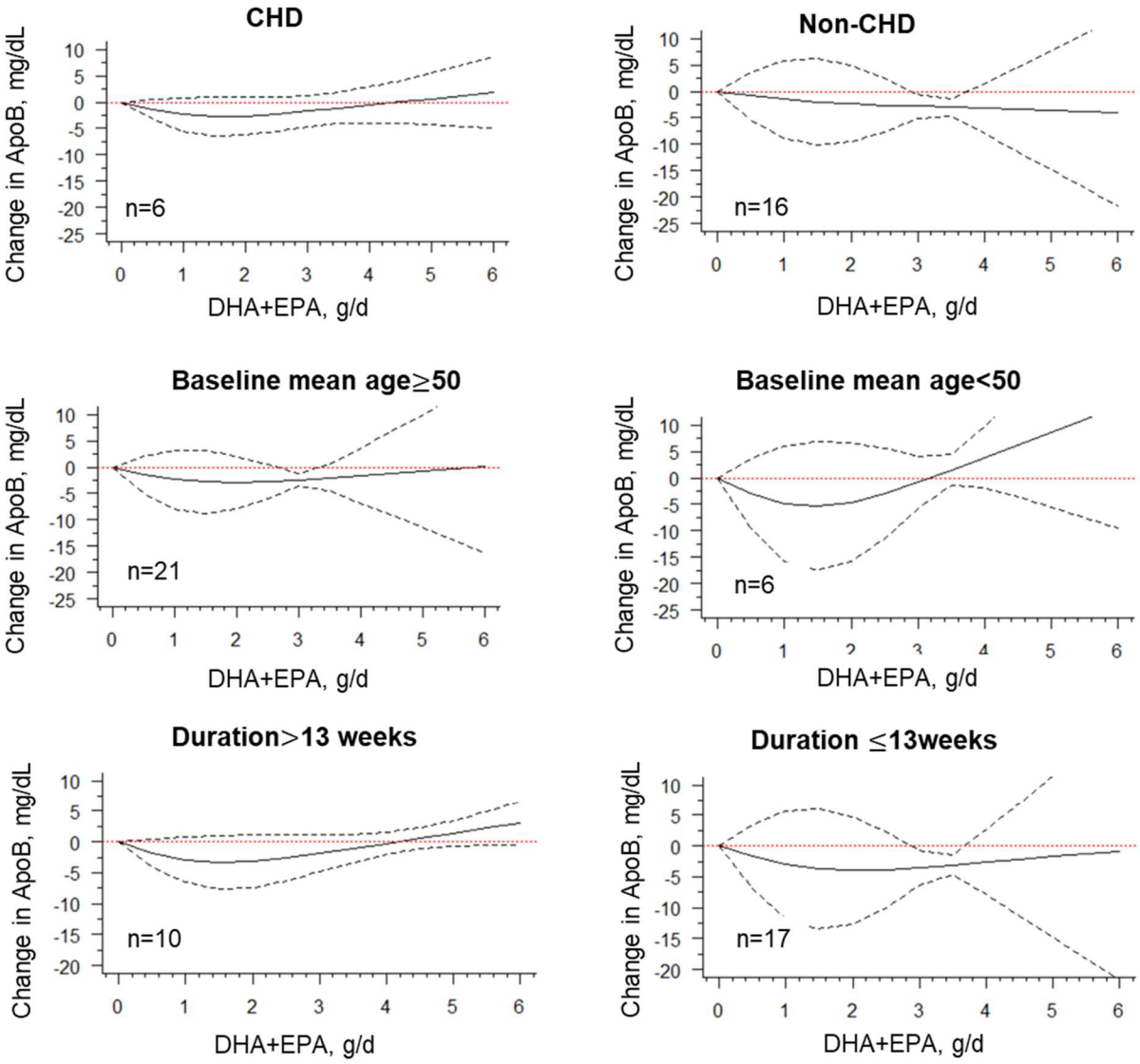

Figure S17: Dose-response relationship between changes in ApoB and docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/day as the referent. n indicates the number of the included study.

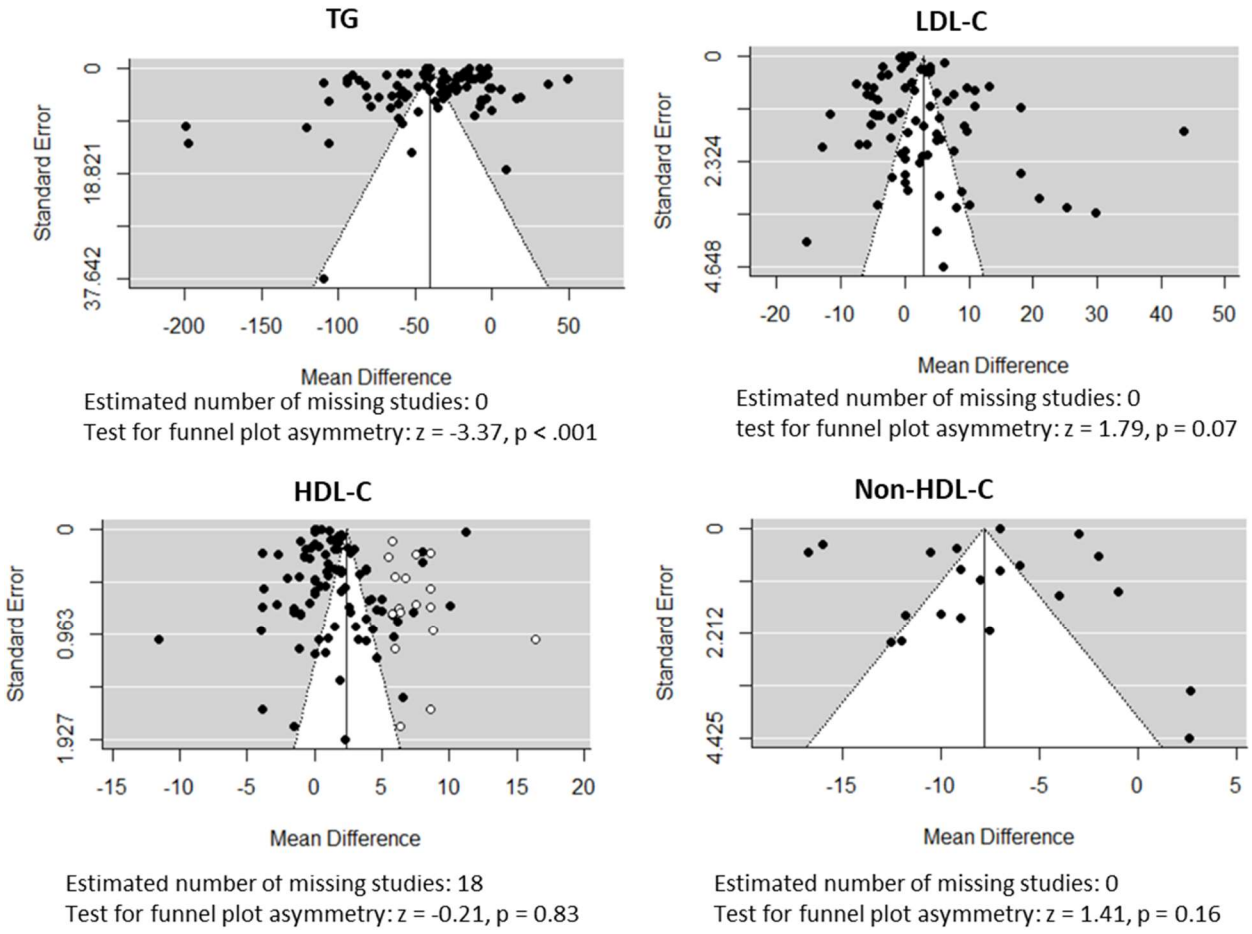

Figure S18: Funnel plots for assessment of overall publication bias.
The plots are generated for the mean difference of changes in TG, LDL-C, HDL-C, and non-HDL-C levels as mg/dL and its standard error using the trim-and-fill method. Filled and unfilled dots indicate observed and imputed studies, respectively. The grey area indicates $p \leq 0.05$. The plot asymmetry analysis was performed by Egger's regression test.

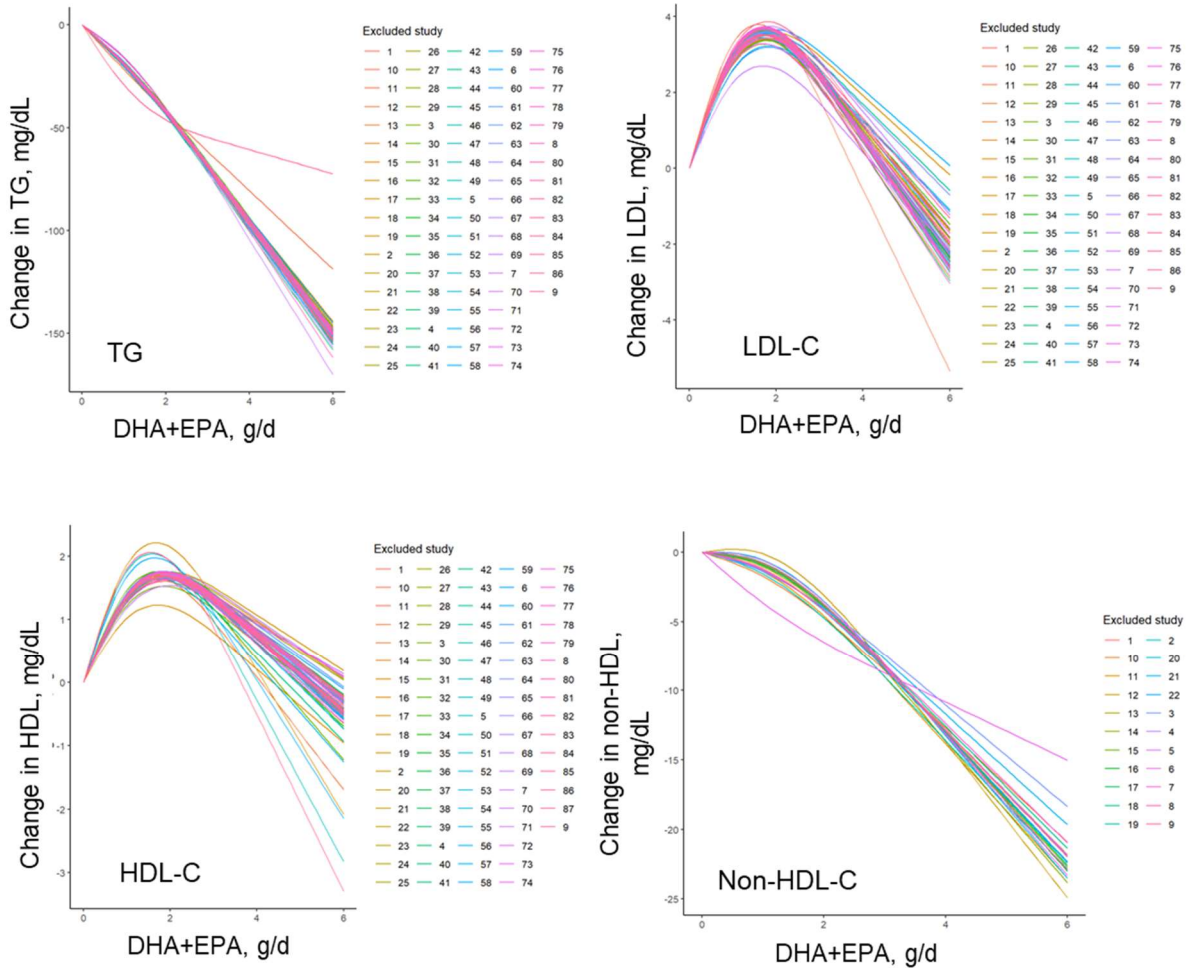

Figure S19: Sensitivity analysis of overall effects of docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) on lipids

Sensitivity analysis of mean difference for changes in TG, LDL-C, HDL-C, and non-HDL-C levels between DHA+EPA treatment and placebo groups, using the leave-one-out method where each time one study is omitted to compute the pooled estimate in the 1-stage regression model.