Title: Alpha lipoic acid supplementation affects serum lipids in a dose and duration-dependent manner in different health status: an updated systematic review and dose-response meta-analysis of randomized controlled trials

Authors: **Mahsa Mahmoudinezhad [1], Mahdieh Abbasalizad Farhangi *[2]**

[1] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.

[3] Department of Community Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.

Electronic Supplementary Material

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Table E1. PRISMA Checklist [1]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1; line 1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2; lines 1-18
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4; lines 11-18
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4 lines 20-21
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5; lines 9-16
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4, line 23-25
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4, line 23-25 Page 5, line 1-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5; lines 8-23
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6; lines 1-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5; lines 4-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6- lines 7-13

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Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6; lines 16-24
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6; lines 16-24
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 15; Figure 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6; lines 16-24
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7, line 7-11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 7, lines 12-21 And Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Sup. Tables 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 1-3 Page 16-27
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 1-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Sup. Figure 1A, B, C, D
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Sup. Tables 4, 5, 6 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 10; lines 5-7 Page 11; lines 3-6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11; lines 7-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 11, line 12-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11; line 23

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Table E2. Search strategies and the number of records according to different electronic database

Search strategy	**Database**	**Num. of records**
Search (((((alpha lipoic acid[Title/Abstract]) OR α lipoic acid[Title/Abstract]))))) AND ((((((((((serum lipids[Title/Abstract]) OR plasma lipids[Title/Abstract]) OR low density lipoprotein cholesterol[Title/Abstract]) OR LDL[Title/Abstract]) OR high density lipoprotein cholesterol[Title/Abstract]) OR HDL[Title/Abstract]) OR total cholesterol[Title/Abstract]) OR TC[Title/Abstract]) OR triglyceride[Title/Abstract]) OR TG[Title/Abstract]) Sort by: Best Match	PubMed	118
	Scopus	125
	ProQuest	460
	Embase	144

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Table E3. Quality of bias assessment of the included studies according to the Cochrane guidelines.

Author name, year of publication, references	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Baziar N; 2020 (1)	L	L	L	U	L	L	Good
Mohammadi V; 2017 (2)	L	L	L	U	L	L	Good
Vidovic B; 2014 (3)	H	H	H	U	U	L	Weak
Udupa, A. S; 2012 (4)	L	L	L	L	L	H	Good
Ying-Dong S; 2012 (5)	L	H	U	U	H	L	Fair
Khabbazi T; 2012 (6)	L	H	L	L	L	L	Good
Zhang, Y; 2011 (7)	L	L	L	U	L	L	Good
de Oliveira AM; 2011(8)	L	U	H	U	L	L	Good
El-Nabarawy SK; 2010 (9)	H	H	H	U	U	L	Weak
Gianturco V; 2009 (10)	L	H	L	U	U	L	Good
Lukaszuk JM; 2009 (11)	L	U	L	U	L	L	Good
Xiang GD; 2008 (12)	L	H	L	U	U	L	Good

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

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Table E4. Results of subgroup analyses for the effects of ALA on TC according to intervention or participant characteristics

Group	No. of trial	WMD (95% CI)	P	P heterogeneity	I^2 %	P between study heterogeneity
Total	11	-10.781 -20.813 -0.749	0.035	0.002	63.6%	
Study duration, weeks						<0.001
1-10	5	-9.472 -27.980 9.036	0.316	0.002	76.7%	
≥ 10	6	-13.052 -23.860 -2.243	0.018	0.172	35.2%	
ALA dose, mg/day						<0.001
< 600	4	-13.876 -24.131 -3.622	0.008	0.758	0.0%	
=600	6	-13.104 -30.770 4.563	0.146	0.001	75.2%	
>600	1	0.050 -9.305 9.405	0.992	.	.%	
Baseline TC mg/dl						<0.001
<200	6	-5.205 -16.848 6.438	0.381	0.044	56.2%	
≥200	5	-19.010 -33.692 -4.328	0.011	0.098	49.0%	
Sample type						<0.001
Serum	8	-9.012 -17.910 -0.114	0.047	0.077	45.3%	
Plasma	3	-12.673 -49.421 24.075	0.499	0.003	83.2%	
Health status						<0.001
obese / over weight	1	-42.530 -61.718 -23.342	0.000	.	.%	
IGT, diabetes	6	-6.852 -17.635 3.932	0.213	0.112	43.9%	
Other disease	4	-7.853 -23.350 7.644	0.321	0.103	51.4%	
Sample size						<0.001
≤ 50	5	-13.794 -32.396 4.808	0.146	0.012	69.0%	
>50	6	-7.413 -18.202 3.376	0.178	0.087	47.9%	
Design						<0.001
RCT	1	-6.960 -38.714 24.794	0.667	.	.%	
CT	10	-11.017 -21.697 -0.338	0.043	0.001	67.2%	
Continent						<0.001
USA	2	-4.671 -43.281 33.938	0.813	0.049	74.1%	
Europe	2	-7.037 -33.483 19.410	0.602	0.993	0.0%	
Asia	7	-12.417 -24.662 -0.172	0.047	0.001	74.3%	
Quality						<0.001
Good	9	-11.831 -23.584 -0.078	0.048	0.001	70.5%	
Fair	1	-3.480 -24.974 18.014	0.751	.	.%	
Weak	1	-6.960 -38.714 24.794	0.667	.	.%	

ALA, alpha lipoic acid; CI, confidence interval; IGT, impaired glucose tolerance.

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Table E5. Results of subgroup analyses for the effects of ALA on LDL according to intervention or participant characteristics

Group	No. of trial	WMD (95% CI)	P	P Heterogeneity	I^2 %	P Between study heterogeneity
Total	11	-10.884 -19.526 -2.241	0.014	0.000	78.1%	
Study duration, weeks						<0.001
1-10	5	-9.076 -21.354 3.202	0.147	0.000	87.5%	
≥ 10	6	-16.003 -24.959 -7.047	0.000	0.417	0.0%	
ALA dose, mg/day						<0.001
< 600	3	4.350 -4.571 13.271	0.195	0.132	50.7%	
=600	7	-13.107 -24.079 -2.135	0.019	0.000	79.8%	
>600	1	-12.679 -31.854 6.496	0.339	.	.%	
Baseline lDL mg/dl						<0.001
<110	6	-2.656 -14.021 8.708	0.647	0.014	64.8%	
≥110	5	-20.367 -33.980 -6.754	0.003	0.000	80.6%	
Sample type						<0.001
Serum	8	-7.365 -15.334 0.605	0.070	0.004	66.8%	
Plasma	3	-18.627 -43.530 6.277	0.143	0.017	75.5%	
Health status						<0.001
obese / over weight	1	-35.190 -45.769 -24.611	0.000	.	.%	
IGT, diabetes	4	-5.148 -14.554 4.257	0.283	0.016	64.2%	
Other disease	6	-11.012 -26.294 4.271	0.158	0.033	65.7%	
Sample size						<0.001
≤ 50	5	-13.766 -28.605 1.073	0.069	0.000	84.0%	
>50	6	-8.065 -20.013 3.883	0.186	0.008	68.1%	
Design						<0.001
RCT	2	-6.960 -38.714 24.794	0.667	.	.%	
CT	9	-11.017 -21.697 -0.338	0.043	0.001	67.2%	
Continent						<0.001
USA	2	-4.950 -28.257 18.357	0.677	0.228	31.2%	
Europe	2	-23.597 -42.254 -4.939	0.013	0.744	0.0%	
Asia	7	-9.709 -20.166 0.747	0.069	0.000	85.7%	
Quality						<0.001
Good	8	-9.945 -24.102 4.212	0.169	0.000	84.5%	
Fair	1	-11.220 -30.165 7.725	0.246	.	.%	
Weak	2	-10.516 -13.895 -7.138	0.000	0.455	0.0%	

ALA, alpha lipoic acid; CI, confidence interval.

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Table E6. Results of subgroup analyses for the effects of ALA on HDL according to intervention or participant characteristics

Group	No. of trial	WMD (95% CI)			P	P heterogeneity	I^2 %	P for between study heterogeneity
Total	11	2.858	-0.692	6.408	0.115	0.000	85.7%	
Study duration, weeks								<0.001
1-10	6	2.572	-0.463	5.607	0.097	0.002	73.5%	
≥ 10	5	1.023	-9.553	11.598	0.850	0.000	90.5%	
ALA dose, mg/day								<0.001
< 600	3	-0.127	-11.115	10.861	0.982	0.002	84.4%	
=600	7	4.352	-0.889	9.593	0.104	0.000	88.9%	
>600	1	2.030	-1.374	5.434	0.242	.	.%	
Baseline HDL mg/dl								<0.001
≤45	6	3.101	-0.566	6.769	0.097	0.002	73.6%	
>45	5	0.951	-7.782	9.684	0.831	0.000	91.1%	
Sample type								<0.001
Serum	8	3.024	-0.710	6.757	0.112	0.000	85.8%	
Plasma	3	2.156	-12.731	17.044	0.776	0.000	90.4%	
Health status								<0.001
obese / over weight	1	14.310	6.695	21.925	0.000	.	.%	
IGT, diabetes	6	1.491	-0.007	2.988	0.051	0.306	16.6%	
Other disease	4	-0.190	-12.202	11.821	0.975	0.000	94.0%	
Sample size								<0.001
≤ 50	5	4.692	0.057	9.327	0.047	0.002	76.2%	
>50	6	0.567	-6.510	7.643	0.875	0.000	90.3%	
Design								<0.001
RCT	2	-4.265	-16.568	8.037	0.497	0.002	89.6%	
CT	9	4.558	-0.370	9.485	0.070	0.000	85.0%	
Continent								<0.001
USA	2	1.914	-3.883	7.710	0.518	0.661	0.0%	
Europe	2	1.047	-23.706	25.801	0.934	0.000	91.9%	
Asia	3	3.739	-0.400	7.879	0.077	0.000	89.2%	
Quality								<0.001
Good	1	5.420	0.241	10.598	0.040	0.000	86.2%	
Fair	8	-4.250	-14.379	5.879	0.411	.	.%	
Weak	2	-4.265	-16.568	8.037	0.497	0.002	89.6%	

ALA, alpha lipoic acid; CI, confidence interval

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Table E7. Results of subgroup analyses for the effects of ALA on TG according to intervention or participant characteristics

Group	No. of trial	WMD (95% CI)	P	P heterogeneity	I^2 %	P for between study heterogeneity
Total	12	-31.029 -49.632 -12.425	0.001	0.000	79.0%	
Study duration, weeks						<0.001
1-10	6	-38.740 -62.309 -15.171	0.001	0.003	71.9%	
≥ 10	6	-18.454 -55.776 18.867	0.332	0.000	85.5%	
ALA dose, mg/day						<0.001
< 600	3	11.772 -27.954 51.497	0.005	0.272	23.3%	
=600	8	-42.219 -62.051 -22.386	0.000	0.000	77.8%	
>600	1	-31.080 -52.708 -9.452	0.005	.	.%	
Baseline glucose mg/dl						<0.001
≤150	4	-20.765 -39.317 -2.212	0.028	0.520	0.0%	
150-200	4	-3.719 -37.847 30.408	0.831	0.067	58.1%	
≥200	4	-64.068 -80.212 -47.925	0.000	0.058	59.9%	
Sample type						<0.001
Serum	9	-34.764 -53.100 -16.427	0.000	0.000	76.8%	
Plasma	3	-4.268 -99.453 90.918	0.930	0.000	88.6%	
Health status						<0.001
obese / over weight	1	-80.610 -112.371 -48.849	0.000	.	.%	
IGT, diabetes	7	-43.362 -62.637 -24.088	0.000	0.003	70.3%	
Other disease	4	-4.114 -32.434 24.207	0.776	0.090	53.7%	
Sample size						<0.001
≤ 50	5	-39.841 -70.648 -9.034	0.011	0.016	67.3%	
>50	7	-23.439 -51.679 4.801	0.104	0.000	84.4%	
Design						<0.001
RCT	3	-25.884 -45.340 -6.428	0.001	0.001	86.5%	
CT	9	-48.231 -76.693 -19.769	0.009	0.029	53.1%	
Continent						<0.001
USA	2	-14.422 -87.807 58.963	0.700	0.162	48.9%	
Europe	3	-12.613 -89.729 64.504	0.749	0.000	88.9%	
Asia	7	-34.782 -55.944 -13.620	0.001	0.000	76.1%	
Quality						<0.001
Good	8	-29.459 -50.466 -8.452	0.006	0.044	51.6%	
Fair	1	-4.430 -36.951 28.091	0.789	.	.%	
Weak	3	-48.231 -76.693 -19.769	0.001	0.001	86.5%	

ALA, alpha lipoic acid; CI, confidence interval

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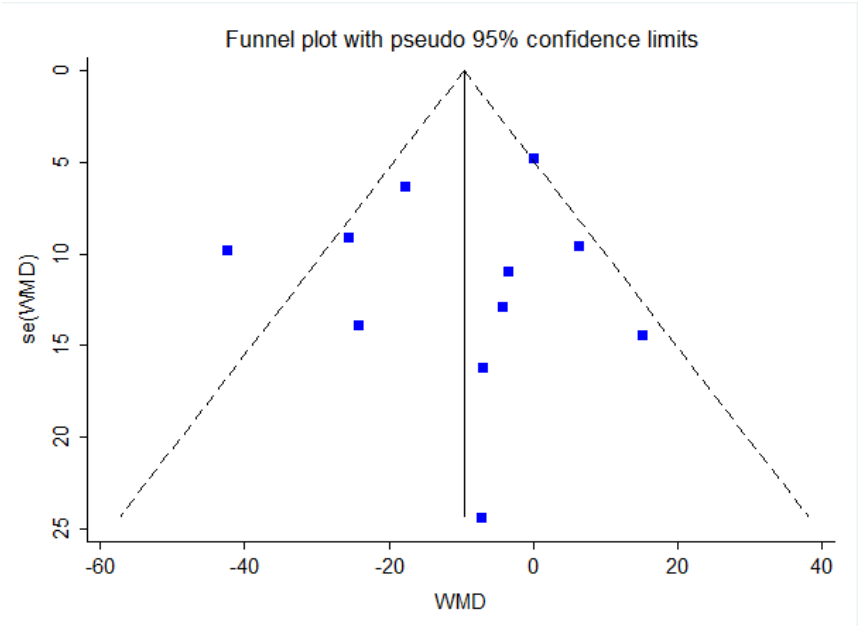
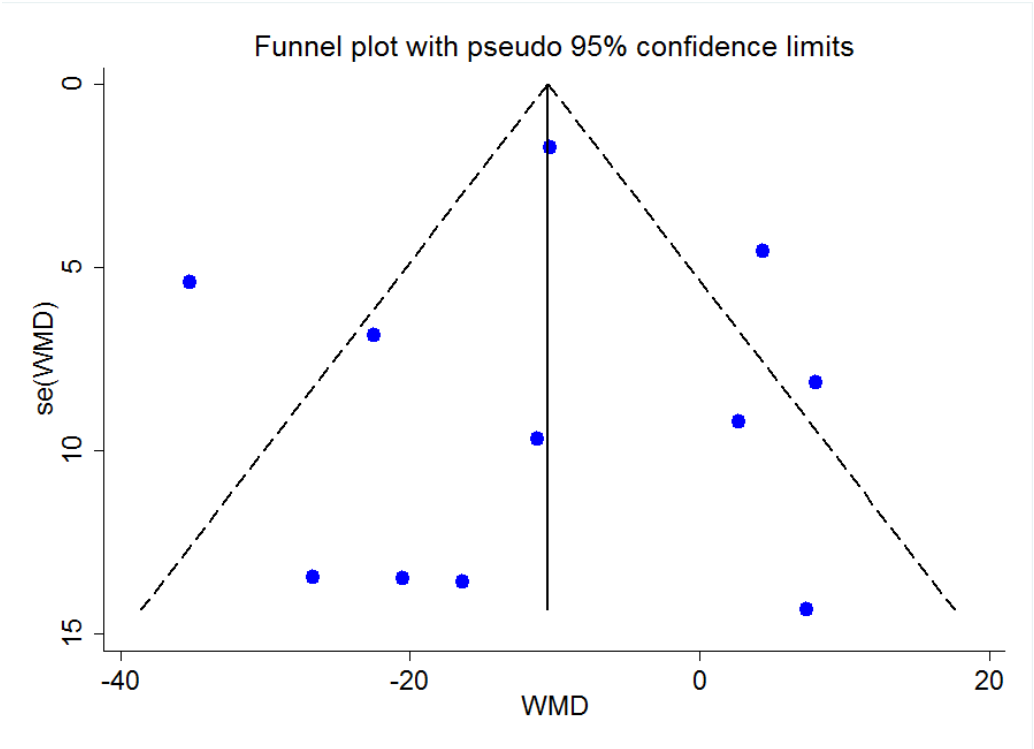
(A)



(B)



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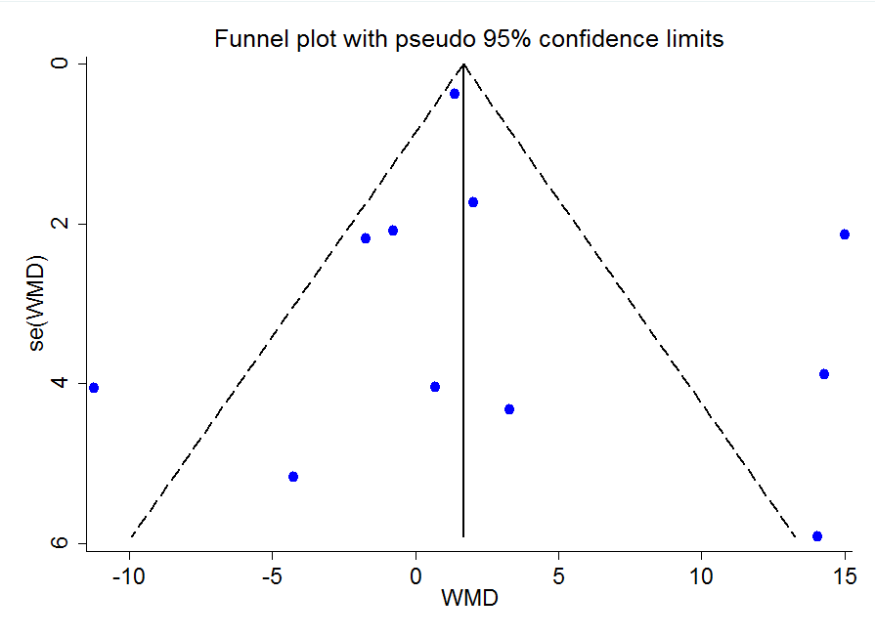
(C)



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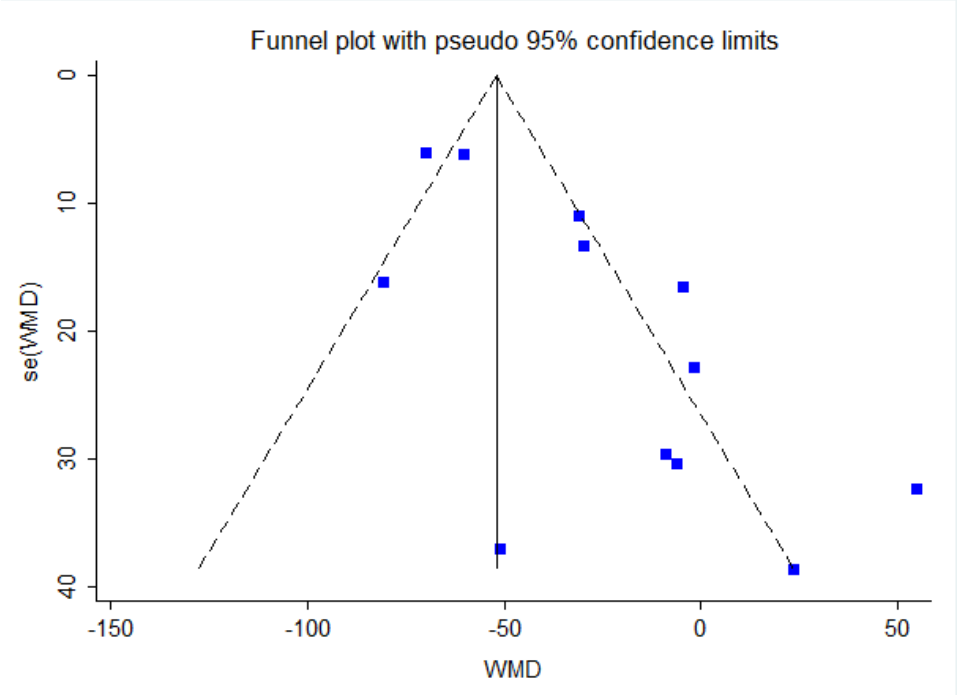

Figure E1. Begg's funnel plot (with pseudo 95% CIs) of the WMD versus the se (WMD) for studies evaluating the association between ALA supplementation and (A) TC (B) LDL (C) HDL and (D) TG values.

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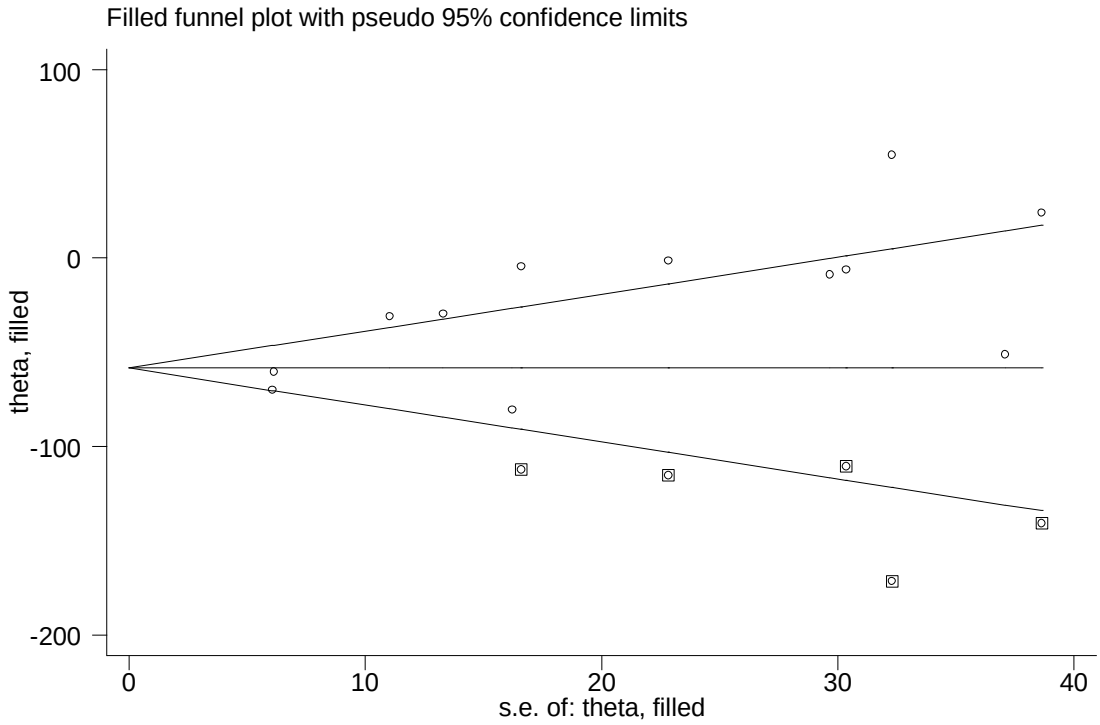

Figure E2. Filled funnel plot with pseudo 95% confidence limits for studies evaluating the association between ALA supplementation and TG values (WMD: -54.106 CI: -73.084 -35.128 ; P <0.001)

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