Title: An updated systematic review and dose-response meta-analysis of the effects of Alpha-Lipoic acid supplementation on inflammatory biomarkers

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Electronic Supplementary Material

https://doi.org/10.1024/0300-9831/a000702

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 1-3
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 1-28
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4; lines 6-14
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 17-19
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 5-20
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 17-28
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 17-28
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 5-20
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 5; lines 21-28 Page 6; lines 1-8

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 1-5
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 10- lines 1-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6; lines 17-28
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 10-28
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 10- lines 1-11
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 10-28
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 2-17
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 18-28 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 8 , 9
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
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
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 13-19 Page 11, 12
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 12; lines 13-20.

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12, line 21-26
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 12; line 28

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 ((((((((((inflammation [Title/Abstract]) OR inflammat* [Title/Abstract]) OR C reactive protein[Title/Abstract]) OR CRP[Title/Abstract]) OR interleukin 6[Title/Abstract]) OR IL-6[Title/Abstract]) OR interleukin*[Title/Abstract]) OR tumor necrosis factor α[Title/Abstract]) OR TNF α[Title/Abstract]) OR TNF-α[Title/Abstract]) Sort by: Best Match	PubMed	462
	Scopus	737
	ProQuest	607
	Embase	482

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
Mendoza-Núñez VM; 2019 [2]	H	L	H	U	H	L	Fair
Sardu C; 2017 [3]	L	L	L	U	U	L	Good
Hong Y; 2017 [4]	L	L	L	U	U	L	Good
Atmaca HU; 2017[5]	L	H	H	U	U	H	Weak
Marfella R; 2016 [6]	L	L	L	H	U	H	Good
Mohammadi V; 2017 [7]	L	L	L	U	U	H	Good
Mirtaheri E; 2015 [8]	L	L	L	U	U	L	Good
Huerta AE; 2015 [9]	L	L	L	U	H	H	Good
Dworacka M; 2015 [10]	L	H	H	H	U	U	Weak
Safa J; 2014 [11]	L	L	L	H	U	L	Good
Khalili M; 2014[12]	L	L	L	H	U	U	Good
Manning PJ; 2014[13]	L	L	L	U	H	U	Good
El-Nakib G; 2013 [14]	L	L	H	H	U	H	Weak
Ahmadi A; 2013 [15]	L	H	H	U	H	U	Weak
Mollo RZ; 2012[16]	L	L	L	U	U	H	Good
Khabbazi RZ; 2012 [17]	L	L	L	L	U	L	Good
Zhang Y; 2011 [18]	L	L	L	U	L	L	Good
Gianturko V; 2009 [19]	L	L	L	U	H	U	Good
Bae SC; 2009 [20]	L	L	L	U	H	U	Good
Xiang GD; 2008 [21]	L	L	L	U	H	L	Good
Vincent H; 2007 [22]	L	L	L	U	H	L	Good
Chang J; 2007 [23]	L	L	H	U	H	H	Weak
Alleva R; 2005 [24]	L	L	L	U	H	L	Good

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

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

Group	No. of trial	WMD (95% CI)	P	P heterogeneity	I^2, %	P for between study heterogeneity
Total	16	-0.692 -1.125 -0.258	0.002	<0.001	83.2	
Study duration, weeks						<0.001
< 10	8	-0.969 -1.715 -0.222	0.011	0.153	34.5	
10-20	4	-0.894 -2.138 0.350	0.159	0.015	71.3	
≥ 20	4	-0.411 -1.273 0.451	0.350	<0.001	95.5	
ALA dose, mg/day						<0.001
> 600	3	-1.107 -2.196 -0.018	0.046	0.670	0	
≥ 600	13	-0.653 -1.115 -0.192	0.006	<0.001	86.1	
Baseline CRP mg/l						<0.001
≤ 2	4	0.114 -0.296 0.523	0.586	0.242	28.3	
2-4	6	-0.844 -1.295 -0.393	<0.001	<0.001	78.8	
≥4	6	-1.585 -3.233 0.063	0.059	0.087	47.9	
CRP type						<0.001
CRP	9	-0.507 -1.019 0.004	0.052	<0.001	88.5	
hs-CRP	7	-1.193 -2.177 -0.209	0.018	0.015	61.8	
Health status						<0.001
Apparently healthy/ obese	4	-0.118 -0.645 0.410	0.661	<0.001	85.6	
Diseased	12	-0.959 -1.344 -0.574	<0.001	0.106	35.5	
Sample size						<0.001
< 40	4	-0.518 -1.083 0.048	0.073	0.504	0.0	
≥ 40	12	-0.706 -1.209 -0.203	0.006	<0.001	87.3	
Region						<0.001
USA/ Europe	9	-0.457 -0.926 0.013	0.057	<0.001	88.4	
Asia	7	-1.492 -2.571 -0.412	0.007	0.076	47.6	
Quality						<0.001
Good	13	-0.592 -1.058 -0.127	0.013	<0.001	85.4	
Weak	3	-1.233 -2.151 -0.315	0.008	0.325	11.1	
Gender						<0.001
Male	2	-9.384 -27.962 9.193	0.322	0.004	87.8	
Female	2	-1.103 -2.148 -0.059	0.038	0.621	0.0	
Both gender	12	-0.532 -0.980 -0.085	0.020	<0.001	79.0	

* Note that the study by Manning PJ et al [13] was included as two independent studies.

Table E5. Results of subgroup analyses for the effects of ALA on IL-6 concentrations according to intervention or participant characteristics

Group	No. of trial	WMD (95% CI)	P	$P_{heterogeneity}$	I^2, %	P for between study heterogeneity
Total	13	-1.830 -2.902 -0.758	0.001	<0.001	98.7	-
Study duration, weeks						<0.001
< 10	6	-2.655 -4.394 -0.915	0.003	<0.001	99.4	
10-20	4	-10.012 -27.08 6.984	0.248	<0.001	94.8	
≥ 20	3	-0.183 -0.427 0.061	0.142	0.955	0.0	
ALA dose, mg/day						<0.001
300	2	-0.774 -2.087 0.538	0.248	0.150	51.6	
600	9	-1.526 -2.748 -0.304	0.014	<0.001	99.0	
1200	2	-24.627 -59.71 10.45	0.169	<0.001	96.8	
Baseline IL-6, pg/ml						<0.001
≤ 10	9	-1.431 -2.485 -0.378	0.008	<0.001	99.1	
> 10	4	-15.56 -38.923 7.810	0.192	<0.001	93.2	
Health status						<0.001
Apparently healthy / obese	4	-0.395 -0.799 0.009	0.055	0.001	80.7	
Diseased	9	-1.830 -2.902 -0.758	0.001	<0.001	99.7	
Sample size						<0.001
≤ 40	6	-2.705 -6.152 0.743	0.124	<0.001	99.3	
> 40	7	-0.438 -1.163 0.288	0.237	<0.001	90.7	
Region						<0.001
USA/ Europe	6	-1.641 -3.479 0.196	0.080	<0.001	99.4	
Asia	7	-6.739 -11.61 -1.870	0.007	<0.001	91.4	
Quality						<0.001
Good	10	-2.487 -4.163 -0.811	0.004	0.024	98.9	
Fair	1	-0.180 -0.297 -0.063	0.003	<0.001	-	
Weak	2	-9.563 -33.582 14.456	0.435	<0.001	80.3	
Gender						<0.001
Male	2	-0.198 -0.592 0.197	0.325	0.760	0.0	
Female	2	-3.182 -8.573 2.210	0.247	0.077	68.0	
Both gender	9	-2.158 -3.505 -0.810	0.002	<0.001	99.7	

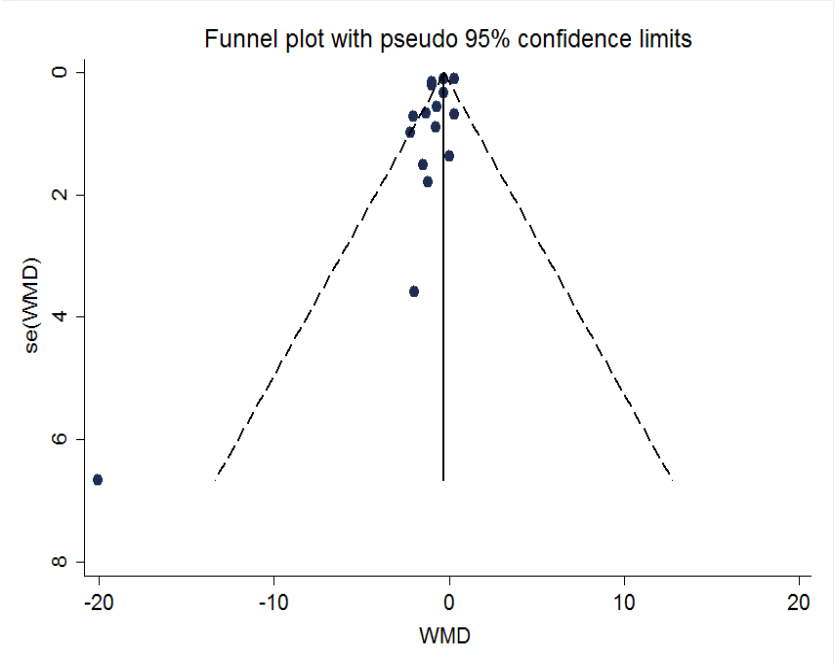
* Note that the study by Manning PJ et al [13] was included as two independent studies.

Table E6. Results of subgroup analyses for the effects of ALA on TNF-α concentrations according to intervention or participant characteristics.

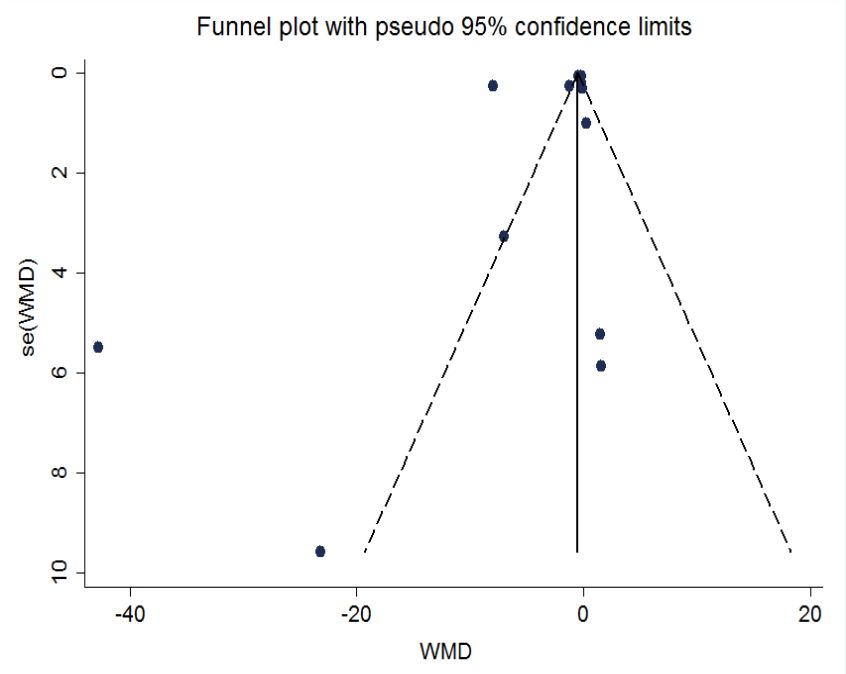
Group	No. of trial	WMD (95% CI)	P	P heterogeneity	I^2, %	P for between study heterogeneity
Total	10	-0.446 -0.853 -0.039	0.032	<0.001	94.9	
Study duration, weeks						<0.001
≤ 10	5	-0.283 -0.846 0.280	0.325	<0.001	80.8	
10-20	5	-0.819 -1.774 0.136	0.093	<0.001	98.9	
ALA dose, mg/day						<0.001
> 1000	8	-0.469 -0.861 -0.077	0.019	<0.001	95.2	
≥ 1000	2	-30.679 -93.33 31.978	0.339	<0.001	96.7	
Baseline TNF-α (pg/ml)						0.008
< 1	5	-0.400 -0.810 0.010	0.056	<0.001	97.0	
1-3	2	-1.091 -2.725 0.544	0.191	0.094	64.4	
≥ 3	3	-6.131 -14.89 2.629	0.170	<0.001	93.8	
Health status						<0.001
Apparently healthy obese	3	0.101 -0.273 0.475	0.597	<0.001	96.8	
Diseased	7	-0.847 -1.963 0.268	0.137	<0.001	88.2	
Sample size						<0.001
≤ 50	4	-1.359 -2.995 0.276	0.103	<0.001	92.4	
≥ 50	6	-0.025 -0.389 0.340	0.894	<0.001	93.4	
Region						0.003
USA/ Europe	5	-0.425 -0.845 -0.005	0.047	<0.001	96.5	
Asia	5	-0.361 -2.468 1.746	0.737	<0.001	89.3	
Gender						<0.001
Male/ Female	2	-0.780 -2.809 1.248	0.451	0.009	85.5	
Both gender	8	-0.376 -0.810 0.058	0.090	<0.001	95.8	

* Note that the study by Manning PJ et al [13] was included as two independent studies. All of the studies had "Good" quality. therefore, subgrouping according to quality of study had not performed.

(A)


Funnel plot with pseudo 95% confidence limits
se(WMD)
0
2
4
6
8
-20
-10
0
10
20
WMD

(B)


Funnel plot with pseudo 95% confidence limits
se(WMD)
0
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4
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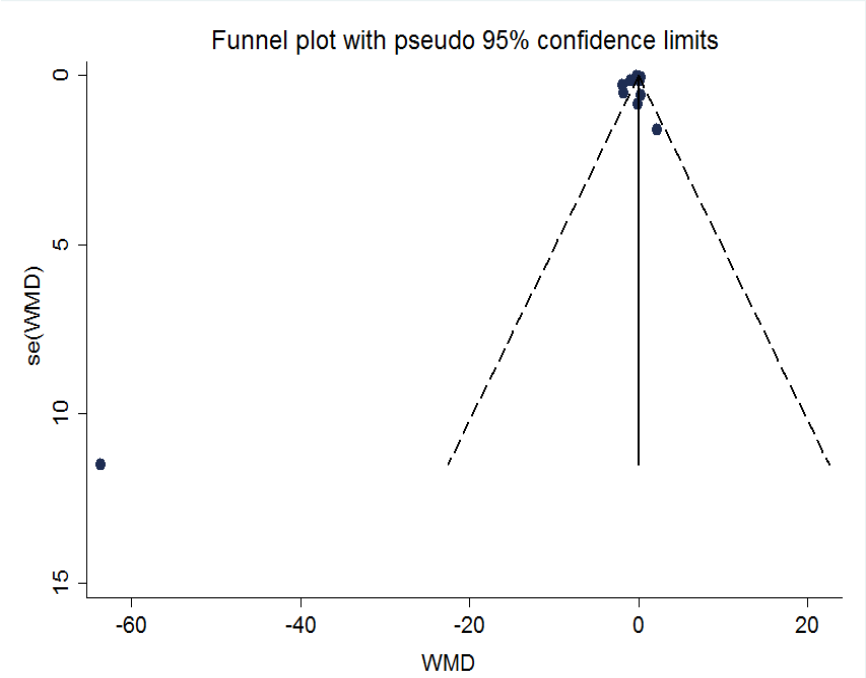
8
10
-40
-20
0
20
WMD



(C)

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) CRP (B) IL-6 and (C) TNF-α concentrations.

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