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Abbreviations:
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBS, fasting blood sugar; GGT, γ-glutamyl transferase; HOMA-IR, homeostatic model assessment for insulin resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; TC, total cholesterol

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Effect of vitamin E on cardiometabolic factors in paediatric metabolic dysfunction-associated steatotic liver disease: a systematic review with meta-analysis

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a serious disease and increasingly prevalent in children. MASLD is associated with health consequences such as type 2 diabetes and CVD. While vitamin E is a potent antioxidant that has been proposed to improve liver function and cardiometabolic health including liver markers, lipid profile, glycaemic control and anthropometric measurements. A comprehensive search was conducted up to March 2025. Data on anthropometric measures, liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT)), glycaemic indices (fasting blood sugar (FBS), insulin, homeostatic model assessment for insulin resistance (HOMA-IR)), lipid profiles (total cholesterol (TC), TAG, LDL-cholesterol, HDL-cholesterol) and serum vitamin E levels were extracted. Statistical analyses were performed using a random-effects model. Eleven randomised controlled trials involving 665 participants were included in this study. Vitamin E significantly reduced ALT (weighted mean difference (WMD) = −5·23 U/L; 95 % CI: −7·72, −2·75; $P < 0·001$) and AST (WMD = −3·00 U/L; 95 % CI: −4·59, −1·41; $P < 0·001$), reflecting improved liver function. It also decreased TC (WMD = −5·77 mg/dl; 95 % CI: −11·46, −0·09; $P = 0·04$) and HOMA-IR (WMD = −0·82; 95 % CI: −1·28, −0·37; $P < 0·001$), while significantly increasing serum vitamin E levels (WMD = 9·16 mg/l; 95 % CI: 3·29, 15·03; $P = 0·002$). No significant changes were observed in the BMI, GGT, FBS, insulin, LDL-cholesterol, HDL-cholesterol or TAG levels. Vitamin E supplementation in paediatric MASLD appears to favourably influence key liver enzymes such as ALT, AST and certain metabolic factors including TC, and HOMA-IR levels, supporting its potential role as adjunctive therapy.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition characterised by fat accumulation in the liver that is not associated with alcohol consumption. MASLD includes a range of liver dysfunctions, from simple steatosis (fat accumulation without inflammation) to metabolic dysfunction-associated steatohepatitis, fibrosis and cirrhosis[1]. Based on latest studies, the average prevalence of MASLD in the paediatric population is approximately 7–14 %[2]. Genetic factors, sedentary lifestyles and unhealthy diets with increased calorie intake may increase the risk of MASLD[3]. Based on previous studies, the main treatment strategy for MASLD is an lifestyle modifications, such as more physical activity and following healthy dietary habits, which cause weight loss and better liver function[4,5]. Drug interventions and supplement consumption may also have positive effects on MASLD. For instance, glucose-lowering medications such as metformin and pioglitazone[4,6], dietary supplements such as *n*-3 that could reduce liver fat due to DHA[7] and vitamin E, due to its antioxidant properties, can decrease liver inflammation and improve liver tissue function, which may have beneficial effects on MASLD[7,8].

Vitamin E is a fat-soluble antioxidant that not only improves cell communication but also modifies gene expression. Furthermore, it protects usual cellular activities and prevents cells oxidative tissues damage made by free radicals[9,10]. Plant-based oils, such as olive oil, sunflower oil and nuts and seed oil, such as hazelnut and almond, are known to be the main sources of vitamin E[11]. However, dietary intake may not always be sufficient to meet the recommended

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dietary allowance for children, which ranges from 7 mg/d for children aged 4–8 years to 11 mg/d for those aged 9–13 years. Accordingly, vitamin E supplementation may be a proper therapeutic option in children with increased oxidative stress or conditions like MASLD to support the daily vitamin E requirements. Some studies have reported that vitamin E supplementation may have positive effects on MASLD. For example, reductions in ballooning, portal inflammation and alkaline phosphatase have been observed in previous studies. However, fibrosis and alanine aminotransferase (ALT) levels have a lower response rate[12,13]. Moreover, vitamin E supplementation may play a role in regulating the glycaemic indices in these patients. However, the outcomes are sparse and inconsistent[14,15]. Similar to glycaemic indices, lipid profile markers may also be influenced by vitamin E consumption. However, the results of studies inconsistent[16,17]. Because of these inconsistencies, the aim of this systematic review and meta-analysis of published randomised controlled trials was to assess the effects of vitamin E supplementation on liver function, glycaemic control and lipid profile markers in children with MASLD.

Method

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol for reporting systematic reviews and meta-analyses[18]. The study was registered with PROSPERO on March 2025 (CRD420251016595).

Search strategy

PubMed, Scopus, Web of Science databases and Google Scholar were searched until March 2025. The search strategy that was performed following the MeSH terms, and keywords are available in online Supplementary File 1.

Study selection, inclusion and exclusion criteria

The PICO criteria for this meta-analysis were as follows: population (P: Children with MASLD or obesity-related liver dysfunction), intervention (I: Vitamin E supplementation, either alone or combined with co-supplements), comparison (C: Placebo, lifestyle modification, or standard care), outcome (O: anthropometric measures (weight and BMI), liver function indices (ALT, aspartate aminotransferase (AST), alkaline phosphatase and γ-glutamyl transferase (GGT)), glycaemic-related parameters (fasting blood sugar (FBS), homeostatic model assessment for insulin resistance (HOMA-IR), and insulin) and lipid profile indicators (total cholesterol (TC), TAG, LDL-cholesterol and HDL-cholesterol). The criteria for inclusion were (1) randomised controlled trials; (2) assessment of the effects of vitamin E supplementation on anthropometric measures, liver function, glycaemic-related parameters or lipid profile in children with MASLD; (3) English language study; (4) children < 18 years old and (5) providing sufficient information of variables on the baseline and end trial in both intervention and control groups. The exclusion criteria were as follows: (1) observational studies, reviews, letters, conference abstracts, case reports and *in vitro* and *ex vivo* studies and (2) insufficient information on outcomes.

Data extraction

Data from the included studies were extracted by two reviewers (PP and MM) separately and then abstracted as follows: (1) author's name; (2) date of publication; (3) origin country; (4) study design; (5) number of participants in both intervention and control groups; (6) dosage and type of vitamin E; (7) duration of intervention; (8) age and sex of study participants and (9) mean changes and SD of outcome measures at baseline, post-intervention and/or changes in outcome measures from baseline to the end of trial. If data were reported in different units, we changed them to the most frequent according to the standard formula.

Quality assessment and certainty assessment

The quality of studies was evaluated by two independent reviewers (PP and MM) using Version 2 of the Cochrane risk-of-bias tool (RoB2), which contains five criteria to evaluate the risk of bias: randomisation process, deviation from inclined interventions, missing outcome data, measurement of the outcome and selection of the reported result[19]. Consequently, terms such as 'Low', 'High' or 'Some concern' were used to indicate the level of each criterion. Finally, all disagreements were resolved by a third author (RZ). Confidence in collective evidence was evaluated in accordance with Grading of Recommendations Assessment, Development, and Evaluation system guidelines[20]. The body of evidence was systematically rated across four quality tiers: high, moderate, low or very low certainty based on predefined assessment criteria.

Statistical analysis

Effect sizes for all variables are reported as weighted mean differences with 95 % CI. A random-effects model was employed to estimate the overall effect size using the restricted maximum likelihood method. To convert the standard error of the mean (SEM) into SD, the following formula was used: $SD = SEM \times \sqrt{n}$ (where n represents the number of participants in each group). To discover the potential origins of heterogeneity, a between-study heterogeneity test using Cochran's Q test was performed and measured using the (I^2) statistic. $I^2 > 50$ % or P value < 0·05 was intended as high between-study heterogeneity[21]. Subgroup analyses were conducted based on pre-specified criteria, including participants' health condition (e.g., MASLD, metabolic dysfunction-associated steatohepatitis and obesity-related hepatic steatosis), vitamin E dosage (< 600 *v.* ≥ 600 IU/d), intervention duration (< 24 *v.* ≥ 24 weeks), type of intervention (vitamin E alone *v.* co-supplementation) and risk of bias rating (low, some concerns and high), in order to explore potential sources of heterogeneity. Sensitivity analysis was applied to predict the effect of each study on the overall estimation[22]. Publication bias was assessed using visual inspection of funnel plots and statistically with Egger's test[23]. Statistical analyses were performed using STATA version 14. Statistical significance was set at $P < 0{\cdot}05$.

Results

Study selection

A total of 1929 records were retrieved through electronic database searches, including PubMed (*n* 276), Scopus (*n* 1090) and Web of Science (*n* 563). After removal of 532 duplicate records, 1397 records remained. During the preliminary review process, 387 articles were excluded for reasons (e.g. irrelevant publication types or titles), leaving 1010 records for title and abstract screening. Of these, 834 records were excluded, and 176 full-text reports were sought for retrieval. Following a thorough full-text review, we excluded 113 articles and proceeded to evaluate the remaining sixty-three studies for eligibility. Based on our inclusion and

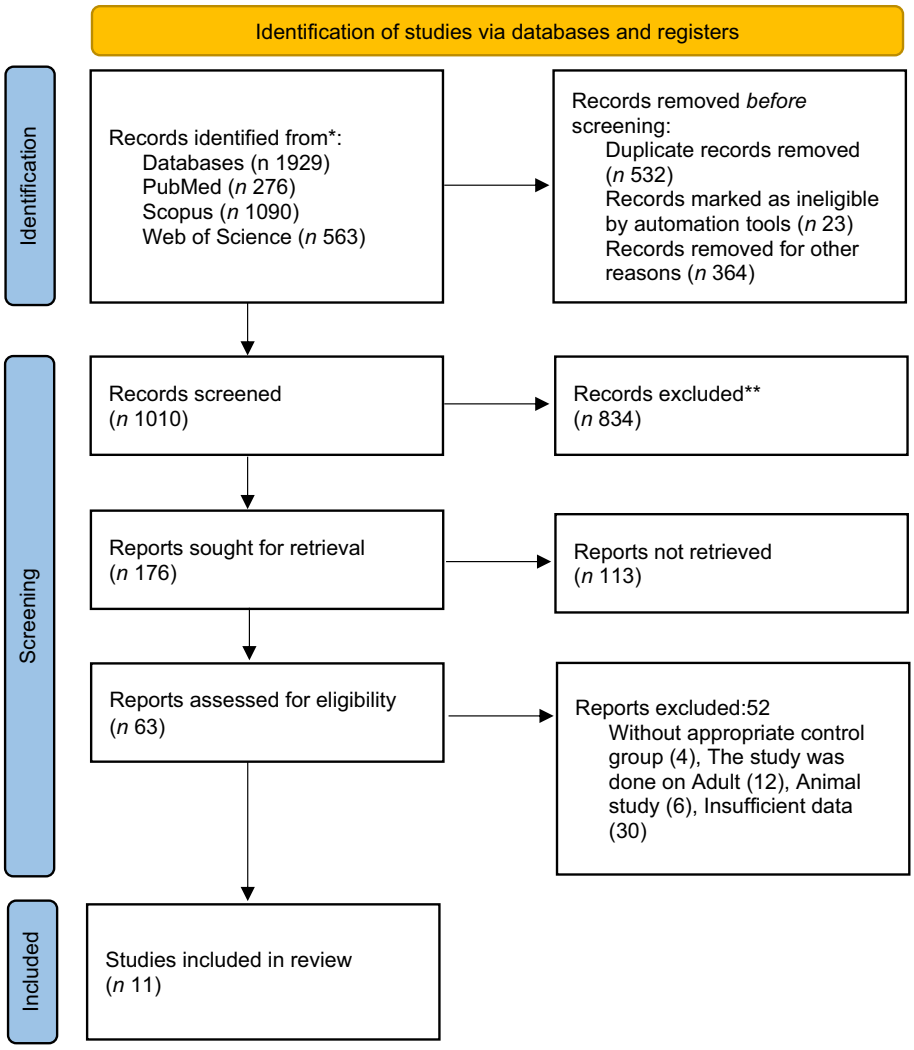


Figure 1. The PRISMA flowchart of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

exclusion criteria, fifty-two articles were excluded for reasons such as being conducted on adults (*n* 12), animal models (*n* 6), insufficient outcome data (*n* 30) or lacking an appropriate control group (*n* 4). Finally, eleven randomised controlled trials were included in the meta-analysis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart is shown in Figure 1.

Study characteristics

The present systematic review and meta-analysis included eleven studies (twelve arms) encompassing 665 children. The included studies were published between 2004 and 2024 time frame. Most of the included studies were conducted in Italy[24–29], one in Malaysia[30], Iran[31], Switzerland[32], Turkey[33] and the USA[34]. All studies were conducted on both girls and boys. The administered vitamin E dose varied from 14·9 to 895 (IU/d). In addition, the treatment duration was between 8 and 96 weeks in the included studies. The baseline BMI values of participants, ranged from approximately 24·5–34 kg/m^2 across studies. The baseline characteristics of the study participants are presented in Table 1.

Risk of bias and quality of evidence

The results of the quality assessment for all included studies, based on RoB2, are summarised in Table 2. Of the studies assessed, three were determined to have a low risk of bias[25,31,34], while four studies were found to have some concerns regarding bias[26,27,29,32] for the quality assessment of the included studies. All of the included studies were done based on randomisation process except Adamo et al.'s[24] and Al-Baiaty et al.'s study[30]. Zohrer et al.,[29], Akcam et al.,[33], Nobili et al.,[27], Nobili et al.,[26], and Vajro et al.[28] got some concern based on possible deviations without clear evidence of impact. Also, the studies by Adamo et al.[24] and Zohrer et al.[29] were flagged for potential selective reporting bias due to inconsistencies between their reported outcomes and pre-specified analysis plans. Al-Baiaty et al.[30] and Zohrer et al.'s study[29] had missing outcome data and scored as some concern. In addition, a Grading of Recommendations Assessment, Development, and Evaluation assessment was performed to evaluate the certainty of the evidence, with the results presented for each outcome in Table 3. Accordingly, the quality of evidence for ALT, AST and serum vitamin E was rated as moderate, supported by acceptable reliability. While, the quality of evidence for weight, BMI, GGT, TC, LDL-cholesterol, HDL-cholesterol, TAG, insulin and HOMA-

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Table 1. Baseline characteristics of study participants

Author name	country	Study design	Sex	Int. mean age	SD	Con. mean age	SD	Int. BMI (kg/m^2)	SD	Con. BMI (kg/m^2)	SD	*n* (Int)	*n* (Con)	Health condition	Intervention type (Int)	Dose (IU/d)	Intervention type (Con)	Side effects	Duration (week)
Al-Baiaty *et al.* 2024	Malaysia	Parallel, R, PC, SB	M/F (NR)	11·8	2·1	12·5	2·6	–		–		15	14	Overweight or obese children with MASLD	Vitamin E	74·6	Placebo	No side effects	24
Homaei *et al.* 2022	Iran	Parallel, R, PC, TB	M/F (F:48, M:52)	12·1	1·7	12·2	1·5	28·5	3·3	28·6	5·3	50	50	Non-diabetic obese children with MASLD	Vitamin E + Diet + exercise	800	Placebo + Diet + exercise	Not mention	12
Nobili *et al.* 2019	Italy	Parallel, R, PC, DB	M/F (NR)	12·5	2·9	12·9	2·7	27·4	4·4	27·4	5·4	35	35	Children with MASLD	Vitamin E + Co-supplements (Hydroxytyrosol) + lifestyle intervention	14·9	Placebo + lifestyle intervention	No side effects	16
Zohrer *et al.* 2017	Italy	Parallel, R, PC, TB	M/F (F:16, M:24)	13·2	2·3	13·2	2·1	27·6	4·0	28·3	5·3	20	20	Children with MASH	Vitamin E + Co-supplements (docosahexaenoic acid-choline) + hypocaloric diet + exercise	39	Placebo + hypocaloric diet + exercise	No side effects	48
Murer *et al.* 2014	Switzerland	Parallel, R, PC, SB	M/F (F:22, M:22)	12·8	1·4	12·7	1·6	31	3	32	4	23	20	Overweight and obese children and adolescents	Vitamin E + Co-supplements (Vitamin C, Se) + lifestyle modification	400	Placebo + lifestyle modification	No side effects	16
Adamo *et al.* 2013	Italy	Parallel, R, PC	M/F (F:26, M:16)	8·3	1·6	8·4	1·3	26·6	2·1	26·0	2·0	21	21	Obese prepubertal children with liver steatosis	Vitamin E + lifestyle intervention	895·5	Lifestyle intervention	No side effects	24
Akcam *et al.* 2011	Turkey	Parallel, R, C, DB	M/F (F:24, M:21)	12·6	2·3	11·3	2·6	27·7	3·2	26·8	4·0	23	22	Obese Adolescents with Fatty Liver	Vitamin E + Diet + exercise	400	Diet + exercise	No side effects	24
Lavine *et al.* 2011	USA	Parallel, R, PC, DD, DB	M/F (F:23, M:93)	13·4	2·3	12·9	2·6	34	7	33	6	50	49	Nondiabetic children with histologically confirmed MASLD	Vitamin E + lifestyle modification	800	Placebo + lifestyle modification	No side effects	96
Nobili *et al.* 2008	Italy	Parallel, R, PC, DB	M/F (F: 16, M:37)	12·8	2·85	11·7	3·15	24·9	2·57	26·8	2·82	25	28	Children with MASLD	Vitamin E + Co-supplements (Vitamin C) + Diet + exercise	600	Placebo + Diet + exercise	Not mention	96
Nobili *et al.* 2006	Italy	Parallel, R, PC, DB	M/F (F:60, M:28)	12·07	3·29	12·36	3·02	26·49	3·57	25·46	3·60	45	43	Children with MASLD	Vitamin E + Co-supplements (Vitamin C) + Diet + exercise	600	Placebo + Diet + exercise	No side effects	48
Vajro *et al.* 2004 (A)	Italy	Parallel, R, PC, SB	M/F (F: 7, M:21)	10·7	3·45	9·88	3·97	24·50	2·78	24·82	2·35	14	14	Obesity-related hyper transaminasemia	Vitamin E + Diet + exercise	597	Placebo + Diet + exercise	No side effects	8
Vajro *et al.* 2004 (B)	Italy	Parallel, R, PC, SB	M/F (F: 7, M:21)	10·7	3·45	9·88	3·97	24·50	2·78	24·82	2·35	14	14	Obesity-related hyper transaminasemia	Vitamin E + Diet + exercise	149·2	Placebo + Diet + exercise	No side effects	12

R, randomised; PC, placebo-controlled; SB, single blind; DB, double-blind; TB , triple-blind; NR , not reported; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; Int , intervention group; Con, control group; IU, international units; M, male; F, female.

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Table 2. Results of risk of bias assessment for randomised clinical trials included in the present study

Author, Year	Randomisation Process	Deviation from Intended Interventions	Selection of the Reported Result	Measurement of the Outcome	Missing Outcome Data	General risk of bias
Al-Baiaty *et al.* 2024	Some Concerns	High	Low	High	Some concerns	High risk
Homaei *et al.* 2022	Low	Low	Low	Low	Low	Low risk
Nobili *et al.* 2019	Low	Low	Low	Low	Low	Low risk
Lavine *et al.* 2011	Low	Low	Low	Low	Low	Low risk
Zohrer *et al.* 2017	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Murer *et al.* 2014	Low	Low	Low	Some concerns	Low	Some concerns
Adamo *et al.* 2013	High	High	Some concerns	Some concerns	Low	High risk
Akcam *et al.* 2011	Low	Some concerns	High	Some concerns	High	High risk
Nobili *et al.* 2008	Low	Some concerns	Low	Some concerns	Low	Some concerns
Nobili *et al.* 2006	Low	Some concerns	Low	Some concerns	Low	Some concerns
Vajro *et al.* 2004 (A)	Low	Some concerns	Low	High	Low	High risk
Vajro *et al.* 2004 (B)	Low	Some concerns	Low	High	Low	High risk

Each study was assessed for risk of bias using the ROB2 tool. Domains of assessment included were Randomisation Process, Deviation from Intended Interventions, Selection of the Reported Result, Measurement of the Outcome, Missing Outcome Data and General Risk of Bias. Each domain was scored as 'high risk' if it contained methodological flaws that may have affected the results, 'low risk' if the flaw was deemed inconsequential and 'some concern' if information was insufficient to determine.

IR were rated as low, due to concerns regarding risk of bias, imprecision and inconsistency. Also, the quality of evidence was very low for FBS.

Vitamin E supplementation and anthropometric measurements

Combining effect sizes from seven eligible studies with containing 465 participants showed no significant changes for weight based on vitamin E supplementation (weighted mean difference (WMD) = −0·17 kg; 95 % CI: −1·74, 1·41, $P = 0·837$), with no significant heterogeneity across the studies ($I^2 = 0·0$ %, P-heterogeneity = 0·768) (Figure 2(a)). Subgroup analyses revealed no significant changes in weight following vitamin E supplementation by health condition, type of supplementation, dosage, period and quality of studies ($P > 0·05$) (Table 4) and the forest plots are available in the online Supplementary File 1. Furthermore, sensitivity analysis showed that omitting any single study did not significantly alter the overall effect size. No small-study effects were observed performing Egger's test ($P = 0·147$).

Combining effect sizes from nine studies encompassing 537 participants demonstrated no significant effect of vitamin E on BMI level (WMD = −0·23 kg/m^2; 95 % CI: −0·61, 0·15, $P = 0·238$; $I^2 = 0·0$ %, P-heterogeneity = 0·516) (Figure 2(b)). Subgroup analysis showed no significant changes based on the health condition, type of supplementation, dosage, duration and quality of the study subgroups ($P > 0·05$) (Table 4). The sensitivity analysis showed no changes in the overall effect size, excluding individual studies. No small-study effects were observed performing Egger's test ($P = 0·651$).

Vitamin E supplementation and liver function tests

The pooled random-effects model of eleven studies (620 participants) revealed that consumption of vitamin E reduced ALT levels significantly (WMD = −5·23 U/L; 95 % CI: −7·72, −2·75, $P < 0·001$) with a low between-study heterogeneity ($I^2 = 23·8$ %, P-heterogeneity = 0·217) (Figure 3(a)). Moreover, subgroup analyses revealed that co-supplementation with vitamin E had a more pronounced effect on ALT levels ($P < 0·001$). The analyses showed that both obese and MASLD patients benefited from vitamin E supplementation. In addition, higher doses (≥ 600 IU/d) with short-term (< 24 weeks) vitamin E treatment significantly affected ALT levels ($P < 0·001$). In the subgroup analysis based on the quality of the studies, we observed a significant difference in ALT outcomes, with different levels of risk of bias. Specifically, in the lower risk of bias ($P = 0·030$) and some concern ($P < 0·001$) subgroups, vitamin E led to a significant reduction in ALT levels (Table 4). Accordingly, 'leave-one-out' approach demonstrated no significant changes based on sensitivity analyses for ALT value. No publication bias was reported based on Egger's test ($P = 0·453$).

The pooled random-effects model of nine studies (564 participants) revealed significant reduction in AST levels following vitamin E treatment (WMD = −3·00 U/L; 95 % CI: −4·59, −1·41, $P < 0·001$) with a lower between-study heterogeneity ($I^2 = 0.0$ %, P-heterogeneity = 0·749) (Figure 3(b)). Moreover, subgroup analyses revealed that co-supplementation with vitamin E had a more pronounced effect on AST levels ($P = 0·001$). In contrast to ALT levels, lower doses (< 600 IU/d) were effective in significantly reducing AST levels ($P < 0·001$). However, short- and long-term treatments were accompanied by a significant reduction in AST

Table 3. Summary of findings and quality of evidence assessment using the GRADE approach

	No of patients	Meta-analysis	WMD	95 % CI	Risk of bias*	Inconsistency†	Indirectness‡	Imprecision§	Publication bias‖	Quality of evidence¶
Weight (kg)	465	7	−0·17	−1·74, 1·41	Serious	Not Serious	Not Serious	Serious	Not Serious	Low
BMI (kg/m^2)	537	9	−0·23	−0·61, 0·15	Serious	Not Serious	Not Serious	Serious	Not Serious	Low
ALT (U/L)	620	11	−5·23	−7·72, −2·75	Serious	Not Serious	Not Serious	Not Serious	Not Serious	Moderate
AST (U/L)	564	9	−3·00	−4·59, −1·41	Serious	Not Serious	Not Serious	Not Serious	Not Serious	Moderate
GGT (U/L)	382	6	0·93	−3·59, 5·45	Not Serious	Serious	Not Serious	Serious	Not Serious	Low
TC (mg/dl)	465	9	−5·77	−11·46, −0·09	Serious	Serious	Not Serious	Not Serious	Not Serious	Low
LDL-cholesterol (mg/dl)	295	6	−1·15	−5·81, 3·51	Serious	Not Serious	Not Serious	Serious	Not Serious	Low
HDL-cholesterol (mg/dl)	295	6	−0·38	−1·85, 1·10	Serious	Not Serious	Not Serious	Serious	Not Serious	Low
TAG (mg/dl)	465	10	−1·85	−10·63, 6·94	Serious	Not serious	Not Serious	Serious	Not Serious	Low
FBS (mg/dl)	609	9	−1·07	−3·06, 0·92	Serious	Serious	Not Serious	Serious	Not Serious	Very Low
Insulin (mU/L)	609	8	−2·71	−5·62, 0·20	Not Serious	Serious	Not Serious	Serious	Not Serious	Low
HOMA-IR	467	6	−4·14	−5·47, −2·81	Serious	Serious	Not Serious	Not Serious	Not Serious	Low
Serum vitamin E (mg/l)	252	4	9·16	3·29, 15·03	Not Serious	Serious	Not Serious	Not Serious	Not Serious	Moderate

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; TC, total cholesterol; FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance.
*Risk of bias based on the Cochrane risk of bias tool.
†Downgraded if there was a substantial unexplained heterogeneity ($I^2 > 50$ %, $P < 0·10$) that was not explained by subgroup analyses.
‡Downgraded if there were factors present relating to the participants, interventions or outcomes which restrict the overall generalisability of the results.
§Downgraded if the 95 % CI crossed the minimally important difference (MID).
‖Downgraded if there was an evidence of publication bias using funnel plot.
¶Since all included studies were randomised controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria.

levels ($P < 0·001$) (Table 4). 'Leave-one-out' approach reported no significant changes based on sensitivity analyses for AST value. No publication bias was reported based on Egger's test ($P = 0·450$).

Additionally, pooled analysis using a random-effects model was performed for GGT as a marker of liver function. In total, six studies involving 382 children assessed the impact of vitamin E supplementation on GGT levels, showing a non-significant effect (WMD = 0·93 U/L; 95 % CI: −3·59, 5·45; $P = 0·688$) (Figure 3(c)). Substantial heterogeneity was observed across studies ($I^2 = 67·6$ %, P for heterogeneity = 0·009). Nevertheless, subgroup analyses did not reveal any significant sources of heterogeneity based on treatment type, participants' health status, supplementation dose or duration or study quality (Table 4). The sensitivity analysis indicated that excluding individual studies did not influence the overall effect estimate for GGT. Furthermore, Egger's test did not reveal any evidence of publication bias ($P = 0·409$).

Vitamin E supplementation and lipid profile

A pooled analysis of nine studies involving 465 participants revealed a significant reduction in TC levels following vitamin E supplementation (WMD = −5·77 mg/dl; 95 % CI: −11·46, −0·09; $P = 0·046$). However, substantial heterogeneity was observed among the studies ($I^2 = 62·1$ %, P for heterogeneity = 0·007) (Figure 4(a)). The subgroup analysis indicated that patients with MASLD experienced a more pronounced decrease in TC levels ($P = 0·013$) (Table 4). Although the pooled estimate for TC showed a significant decrease, the sensitivity analysis suggested that the overall effect size might be influenced by the studies conducted by Al-Baiaty *et al.*[30], Nobili *et al.*[25], Murer *et al.*[32], Adamo *et al.*[24], Nobili *et al.*[26] and Nobili *et al.*[27], which altered the results to a non-significant level. Furthermore, Egger's test showed no evidence of publication bias ($P = 0·979$).

Pooling effect sizes from six studies for LDL-cholesterol and HDL-cholesterol and ten studies for TAG showed a non-significant effect for vitamin E treatment, respectively (WMD = −1·15 mg/dl; 95 % CI: −5·81, 3·51, $P = 0·628$, $I^2 = 38·9$ %, P-heterogeneity = 0·146) (Figure 4(b)), (WMD = −0·38 mg/dl; 95 % CI: −1·85, 1·10, $P = 0·616$, $I^2 = 16·5$ %, P-heterogeneity = 0·307) (Figure 4(c)) and (WMD = −1·85 mg/dl; 95 % CI: −10·63, 6·94, $P = 0·680$, $I^2 = 57·7$ %, P-heterogeneity = 0·012) (Figure 4(d)). Subgroup analyses failed to introduce health conditions, type of treatment, supplementation dosage and duration of treatment as sources of heterogeneity ($P > 0·05$). However, a significant reduction in LDL-cholesterol levels within the higher risk of bias subgroup was observed ($P = 0·016$) (Table 4). In addition, sensitivity analysis demonstrated that the overall WMD does not depend on any single study effect on LDL-cholesterol, HDL-cholesterol and TAG levels. No evidence of

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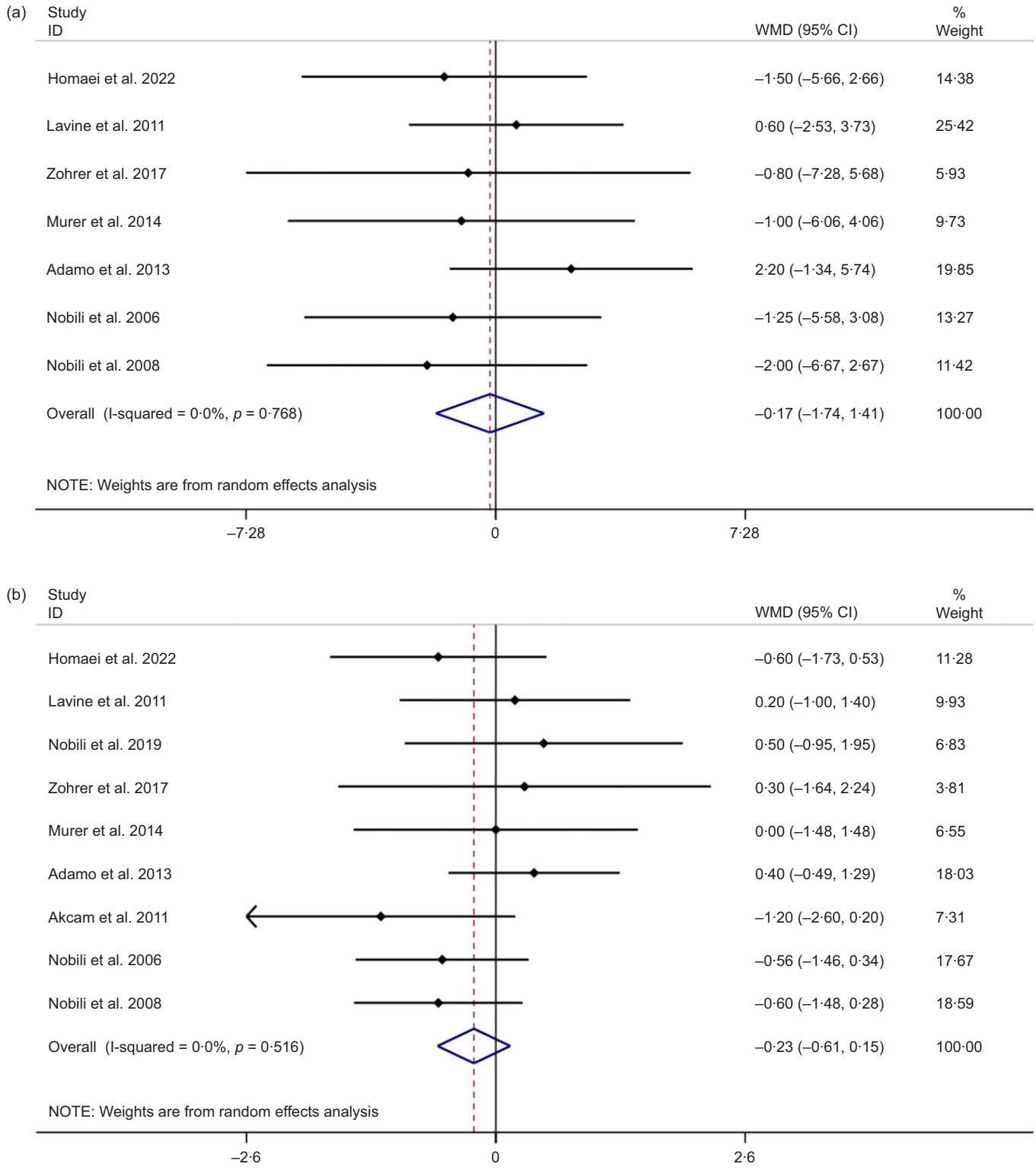


Figure 2. (a) The forest plot of vitamin E treatment on weight value. (b) The forest plot of vitamin E treatment on BMI value.

publication bias was found based on Egger's tests for LDL-cholesterol ($P = 0{\cdot}406$) and HDL-cholesterol ($P = 0{\cdot}729$). The funnel plot for TAG outcomes appeared symmetric, and neither Begg's test ($P = 0{\cdot}929$) nor Egger's test ($P = 0{\cdot}979$) indicated a significant publication bias. These findings suggest a low risk of small study effects that influence the pooled estimate.

Vitamin E supplementation and glycaemic state

Nine studies involving 609 children investigated the effects of vitamin E treatment on FBS. The combined outcome from the random-effects model specified that vitamin E treatment (WMD = −1·07 mg/dl; 95 % CI: −3·06, 0·92, $P = 0{\cdot}294$) with a

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Table 4. Pooled estimate effects of vitamin E treatment on anthropometric measurements, liver function tests, lipid profile, glycAemic markers and serum vitamin E in different subgroups

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
Weight (kg)						
Health condition						
MASLD	5	−0·02	−1·74, 1·69	0·978	0	0·533
MASH	1	−0·80	−7·28, 5·68	0·809	–	–
Obese	1	−1·0	−6·06, 4·06	0·698	–	–
Type of intervention						
Vitamin E	3	0·63	−1·42, 2·67	0·548	0	0·414
Vitamin E + co-supplements	4	−1·34	−3·82, 1·15	0·292	0	0·989
Dose of vitamin E						
< 600 (IU/d)	2	−0·92	−4·91, 3·06	0·649	0	0·962
≥ 600 (IU/d)	5	−0·02	−1·74, 1·69	0·978	0	0·533
Duration of treatment (weeks)						
< 24	2	−1·30	−4·51, 1·91	0·428	0	0·881
≥ 24	5	0·19	−1·62, 2·01	0·833	0	0·616
Quality of studies						
Higher risk of bias	1	2·20	−1·34, 5·74	0·223	–	–
Lower risk of bias	2	−0·16	−2·66, 2·34	0·901	0	0·429
Some concerns	4	−1·34	−3·82, 1·15	0·292	0	0·989
BMI (kg/m^2)						
Health condition						
MASLD	7	−0·27	−0·70, 0·16	0·222	11·5	0·342
MASH	1	0·30	−1·64, 2·24	0·762	–	–
Obese	1	0	−1·48, 1·48	1·00	–	–
Type of intervention						
Vitamin E	4	−0·19	−0·89, 0·50	0·587	33·9	0·209
Vitamin E + co-supplements	5	−0·31	−0·83, 0·21	0·244	0	0·653
Dose of vitamin E						
< 600 (IU/d)	4	−0·17	−0·96, 0·62	0·675	5·2	0·367
≥ 600 (IU/d)	5	−0·25	−0·68, 0·19	0·268	0	0·406
Duration of treatment (weeks)						
< 24	3	−0·14	−0·90, 0·63	0·727	0	0·492
≥ 24	6	−0·26	−0·73, 0·21	0·283	12·3	0·337
Quality of studies						
Higher risk of bias	2	−0·30	−1·86, 1·25	0·701	71·9	0·059
Lower risk of bias	3	−0·05	−0·77, 0·67	0·894	0	0·443
Some concerns	4	−0·43	−0·98, 0·13	0·132	0·	0·780
ALT (U/L)						
Health condition						
MASLD	7	−5·15	−9·17, −1·14	0·012	47·2	0·078
MASH	1	0·50	−18·71, 19·71	0·959	–	–
Obese	3	−5·80	−8·34, −3·25	< 0·001	0	0·511

(*Continued*)

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Table 4. (*Continued*)

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
Type of intervention						
Vitamin E	6	−4·05	−8·79, 0·69	0·094	50·7	0·071
Vitamin E + co-supplements	5	−6·05	−8·43, −3·68	< 0·001	0	0·619
Dose of vitamin E						
< 600 (IU/d)	6	−2·66	−6·86, 1·55	0·215	32·1	0·195
≥ 600 (IU/d)	5	−7·39	−10·24, −4·55	< 0·001	0	0·517
Duration of treatment (weeks)						
< 24	5	−5·43	−7·60, −3·25	< 0·001	0	0·782
≥ 24	6	−5·26	−11·27, 0·76	0·087	55·7	0·046
Quality of studies						
Higher risk of bias	4	−2·78	−10·78, 5·21	0·495	69·5	0·020
Lower risk of bias	3	−4·60	−8·75, −0·45	0·030	0	0·798
Some concerns	4	−6·24	−8·68, −3·79	< 0·001	0	0·521
AST (U/L)						
Health condition						
MASLD	7	−2·41	−4·37, −0·45	0·016	0	0·691
MASH	1	−6·50	−17·86, 4·86	0·262	–	–
Obese	1	−4·0	−6·82, −1·18	0·005	–	–
Type of intervention						
Vitamin E	4	−2·23	−4·67, 0·20	0·072	0	0·590
Vitamin E + co-supplements	5	−3·58	−5·69, −1·47	0·001	0	0·646
Dose of vitamin E						
< 600 (IU/d)	4	−4·11	−6·37, −1·85	< 0·001	0	0·959
≥ 600 (IU/d)	5	−1·90	−4·15, 0·35	0·097	0	0·569
Duration of treatment (weeks)						
< 24	3	−3·18	−5·24, −1·12	0·003	0	0·691
≥ 24	6	−2·74	−5·25, −0·23	0·033	0	0·511
Quality of studies						
Higher risk of bias	2	−2·13	−7·30, 3·03	0·419	47·5	0·168
Lower risk of bias	3	−2·24	−5·21, 0·73	0·139	0	0·981
Some concerns	4	−3·64	−5·84, −1·44	0·001	0	0·483
GGT (U/L)						
Health condition						
MASLD	5	1·64	−3·65, 6·92	0·544	68·2	0·013
Obese	1	−2·0	−7·46, 3·46	0·473	–	–
Type of intervention						
Vitamin E	2	3·30	−8·45, 15·04	0·582	46·3	0·172
Vitamin E + co-supplements	4	0·33	−4·94, 5·60	0·903	77·7	0·004
Dose of vitamin E						
< 600 (IU/d)	3	−0·81	−5·88, 4·26	0·755	44·0	0·168
≥ 600 (IU/d)	3	2·41	−3·55, 8·38	0·428	53·8	0·115
Duration of treatment (weeks)						
< 24	2	−2·60	−6·28, 1·07	0·165	0	0·770
≥ 24	4	3·69	−1·06, 8·44	0·128	37·9	0·185

(*Continued*)

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Table 4. (*Continued*)

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
Quality of studies						
Higher risk of bias	1	9·0	−2·61, 20·61	0·129	–	–
Lower risk of bias	2	−3·09	−7·72, 1·54	0·191	0	0·989
Some concerns	3	1·55	−4·41, 7·50	0·611	74·8	0·019
TC (mg/dl)						
Health condition						
MASLD	7	−7·79	−13·92, −1·66	0·013	61·1	0·017
MASH	1	7·50	−4·36, 19·36	0·215	–	–
Obese	1	−3·08	−15·53, 9·37	0·628	–	–
Type of intervention						
Vitamin E	4	−4·91	−15·00, 5·19	0·341	72·2	0·013
Vitamin E + co-supplements	5	−6·55	−13·88, 0·77	0·080	58·5	0·047
Dose of vitamin E						
< 600 (IU/d)	4	−3·13	−10·62, 4·36	0·412	37·3	0·188
≥ 600 (IU/d)	5	−7·63	−16·10, 0·84	0·077	73·9	0·004
Duration of treatment (weeks)						
< 24	3	−3·21	−8·39, 1·97	0·224	0	0·376
≥ 24	6	−6·97	−15·59, 1·65	0·113	71·4	0·004
Quality of studies						
Higher risk of bias	2	−14·83	−23·17, −6·5	< 0·001	0	0·437
Lower risk of bias	3	−1·35	−8·32, 5·62	0·704	44·4	0·166
Some concerns	4	−5·99	−15·94, 3·96	0·238	68·7	0·022
LDL-cholesterol (mg/dl)						
Health condition						
MASLD	4	−0·60	−6·91, 5·70	0·851	59·6	0·059
MASH	1	−1·60	−14·15, 10·95	0·803	–	–
Obese	1	−5·02,	−16·21, 6·17	0·379	–	–
Type of intervention						
Vitamin E	3	−2·09	−10·41, 6·24	0·623	69·6	0·037
Vitamin E + co-supplements	3	−0·01	−6·05, 6·02	0·996	0	0·458
Dose of vitamin E						
< 600 (IU/d)	3	−0·01	−6·05, 6·02	0·623	0	0·458
≥ 600 (IU/d)	3	−2·09	−10·41, 6·24	0·996	69·6	0·037
Duration of treatment (weeks)						
< 24	3	1·75	−2·42, 5·92	0·247	0	0·428
≥ 24	3	−4·46	−12·00, 3·09	0·410	36·8	0·205
Quality of studies						
Higher risk of bias	1	−10·60	−19·23, −1·97	0·016	–	–
Lower risk of bias	3	2·56	−1·57, 6·69	0·225	0	0·921
Some concerns	2	−3·51	−11·86, 4·85	0·411	0	0·690
HDL-cholesterol (mg/dl)						
Health condition						
MASLD	4	−0·06	−1·90, 1·77	0·946	26·8	0·251

(*Continued*)

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Table 4. (*Continued*)

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
MASH	1	0·35	−3·59, 4·29	0·862	–	–
Obese	1	−2·71	−6·36, 0·94	0·146	–	–
Type of intervention						
Vitamin E	3	−0·98	−2·88, 0·91	0·309	0	0·503
Vitamin E + co-supplements	3	0·0	−2·63, 2·64	0·998	46·7	0·153
Dose of vitamin E						
< 600 (IU/d)	3	0	−2·63, 2·64	0·998	46·7	0·153
≥ 600 (IU/d)	3	−0·98	−2·88, 0·91	0·309	0	0·503
Duration of treatment (weeks)						
< 24	3	−0·82	−3·81, 2·18	0·593	60·3	0·081
≥ 24	3	−0·33	−2·26, 1·60	0·739	0	0·621
Quality of studies						
Higher risk of bias	1	1·30	−3·30, 5·90	0·580	–	–
Lower risk of bias	3	−0·33	−2·59, 1·94	0·778	46·5	0·154
Some concerns	2	−1·27	−4·27, 1·72	0·405	19·7	0·264
TAG (mg/dl)						
Health condition						
MASLD	8	−2·60	−11·48, 6·27	0·566	53·5	0·035
MASH	1	−13·40	−31·78, 4·98	0·153	–	–
Obese	1	32·77	1·47, 64·07	0·040	–	–
Type of intervention						
Vitamin E	5	−4·26	−13·97, 5·46	0·390	19·6	0·290
Vitamin E + co-supplements	5	−0·69	−15·23, 13·85	0·926	73·4	0·005
Dose of vitamin E						
< 600 (IU/d)	5	−5·57	−25·47, 14·33	0·337	69·4	0·011
≥ 600 (IU/d)	5	0·79	−6·92, 8·50	0·841	34·1	0·194
Duration of treatment (weeks)						
< 24	3	−2·03	−30·25, 26·19	0·888	80·0	0·007
≥ 24	7	−0·69	−9·11, 7·74	0·873	42·3	0·109
Quality of studies						
Higher risk of bias	3	−6·80	−21·03, 7·43	0·349	30·8	0·236
Lower risk of bias	3	−7·28	−28·87, 14·31	0·509	66·2	0·052
Some concerns	4	4·65	−7·55, 16·84	0·455	57·0	0·073
FBS (mg/dl)						
Health condition						
MASLD	7	−1·36	−4·10, 1·38	0·330	69·9	0·003
MASH	1	−2·00	−4·77, 0·77	0·157	–	–
Obese	1	1·25	−1·30, 3·80	0·336	–	–
Type of intervention						
Vitamin E	4	−2·42	−5·05, 0·22	0·072	1·6	0·384
Vitamin E + co-supplements	5	−0·74	−3·26, 1·79	0·568	7·1	0·002
Dose of vitamin E						
< 600 (IU/d)	5	0·55	−0·81, 1·91	0·427	10·5	0·346

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Table 4. (*Continued*)

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
≥ 600 (IU/d)	4	−3·17	−6·15, −0·19	0·037	51·1	0·105
Duration of treatment (weeks)						
< 24	2	1·28	−0·14, 2·71	0·077	0	0·975
≥ 24	7	−2·32	−4·35, −0·29	0·025	36·5	0·150
Quality of studies						
Higher risk of bias	3	−1·75	−5·47, 1·97	0·356	33·7	0·221
Lower risk of bias	2	0·83	−1·83, 3·49	0·540	13·4	0·283
Some concerns	4	−1·37	−4·50, 1·75	0·389	75·8	0·006
Insulin (mU/L)						
Health condition						
MASLD	6	−3·12	−6·40, 0·17	0·063	89·9	< 0·001
MASH	1	−5·10	−12·06, 1·86	0·151	–	–
Obese	1	2·74	−3·18, 8·65	0·365	–	–
Type of intervention						
Vitamin E	3	−4·44	−6·81, −2·07	< 0·001	19·6	0·288
Vitamin E + co-supplements	5	−1·91	−5·78, 1·97	0·335	89·6	< 0·001
Dose of vitamin E						
< 600 (IU/d)	4	−3·42	−8·72, 1·88	0·205	78·0	0·003
≥ 600 (IU/d)	4	−2·02	−5·44, 1·40	0·246	89·3	< 0·001
Duration of treatment (weeks)						
< 24	3	−3·91	−10·04, 2·22	0·211	82·8	0·003
≥ 24	5	−1·85	−4·90, 1·20	0·235	85·1	< 0·001
Quality of studies						
Higher risk of bias	2	−4·08	−8·13, −0·03	0·048	59·7	0·715
Lower risk of bias	2	−6·87	−11·12, −2·61	0·002	59·7	0·115
Some concerns	4	0·20	−2·55, 2·95	0·886	73·2	0·011
HOMA-IR						
Health condition						
MASLD	7	−0·80	−1·29, −0·32	0·001	80·3	< 0·001
MASH	1	−1·10	−2·41, 0·21	1·00	–	–
Type of intervention						
Vitamin E	4	−1·12	−1·43, −0·82	< 0·001	0·0	0·498
Vitamin E + co-supplements	4	−0·53	−1·08, 0·03	0·063	77·3	0·004
Dose of vitamin E						
< 600 (IU/d)	3	−1·29	−1·77, −0·80	< 0·001	0	0·556
≥ 600 (IU/d)	5	−0·58	−1·11, −0·05	0·032	81·4	< 0·001
Duration of treatment (weeks)						
< 24	2	−1·08	−1·41, −0·75	< 0·001	0	0·763
≥ 24	6	−0·70	−1·27, −0·13	0·015	75·2	< 0·001
Quality of studies						
Higher risk of bias	2	−1·31	−1·93, −0·68	< 0·001	24·4	0·250
Lower risk of bias	3	−1·08	−1·41, −0·75	< 0·001	0	0·702
Some concerns	3	−0·26	−0·73, 0·21	0·274	60·6	0·079

(*Continued*)

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Table 4. (*Continued*)

Group	No. of comparisons	WMD	95 % CI	*P*-value	I^2 (%)	*P*-heterogeneity
Serum vitamin E (mg/l)						
Health condition						
MASLD	2	5·52	−3·69, 14·72	0·240	95·0	< 0·001
MASH	1	10·26	8·58, 11·94	< 0·001	–	–
Obese	1	15·20	12·87, 17·53	< 0·001	–	–
Type of intervention						
Vitamin E	1	1030	6·87, 13·73	< 0·001	–	–
Vitamin E + co-supplements	3	8·80	1·33, 16·26	0·021	97·4	< 0·001
Dose of vitamin E						
< 600 (IU/d)	3	8·80	1·33, 16·26	0·021	97·4	< 0·001
≥ 600 (IU/d)	1	10·30	6·87, 13·73	< 0·001	–	–
Duration of treatment (weeks)						
< 24	2	8·05	−5·95, 22·06	0·260	98·6	< 0·001
≥ 24	2	10·27	8·76, 11·77	< 0·001	0	0·984
Quality of studies						
Lower risk of bias	2	5·52	−3·69, 14·72	0·240	95·0	< 0·001
Some concerns	2	12·66	7·82, 17·50	< 0·001	91·2	0·001

WMD, weighted mean difference; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HOMA-IR, homeostatic model assessment for insulin resistance.

significant between-study heterogeneity ($I^2 = 65·1$ %, *P*-heterogeneity = 0·003) did not alter FBS level significantly (Figure 5(a)). Subgroup analysis indicated that higher doses of vitamin E (≥ 600 IU/d) ($P = 0·037$) and long-term treatment ($P = 0·025$) with vitamin D significantly decreased FBS levels (Table 4). The sensitivity analysis revealed that the exclusion of individual studies did not lead to any significant changes in the overall effect size. In addition, no evidence of publication bias was found according to Egger's test for FBS value ($P = 0·432$).

Eight studies with 609 participants investigated the effects of vitamin E treatment on insulin levels. The combined effect of the random-effects model indicated that vitamin E treatment (WMD = −2·71 mU/l; 95 % CI: −5·62, 0·20, $P = 0·068$) with a significant between-study heterogeneity ($I^2 = 86·7$ %, *P*-heterogeneity < 0·001) did not alter insulin levels significantly (Figure 5(b)). Subgroup analysis showed that vitamin E treatment alone ($P < 0·001$) had more significant effects on insulin levels in studies with a lower risk of bias ($P = 0·002$). The sensitivity analysis indicated that omitting individual studies did not significantly affect the overall effect size. In addition, no evidence of publication bias was found according to Egger's test for FBS value ($P = 0·290$).

Eight studies (including 537 children) explored the effects of vitamin E on HOMA-IR. The combined effect of the random-effects model indicated that vitamin E significantly reduced the HOMA-IR value significantly (WMD = −0·82; 95 % CI: −1·28, −0·37, $P < 0·001$). Substantial heterogeneity was observed across the included studies ($I^2 = 77·4$ %, *P*-heterogeneity < 0·001) (Figure 5(c)). Subgroup analysis demonstrated that all doses, both short- and long-term treatments, MASLD patients and vitamin E treatment alone could significantly affect HOMA-IR values. In addition, subgroup analysis based on the quality of studies indicated that lower and higher risk of bias subgroups were accompanied by a significant decrease in HOMA-IR level ($P < 0·001$) (Table 4). Sensitivity analysis showed no significant changes in the overall effect size after excluding a single study. In addition, no evidence of publication bias was found according to Egger's test for FBS value ($P = 0·559$).

Vitamin E supplementation and serum level

Pooled effect size of four studies demonstrated that vitamin E treatment could increase serum level of vitamin E significantly (WMD = 9·16 mg/l; 95 % CI: 3·29, 15·03; $P = 0·002$; $I^2 = 96·1$; *P*-heterogeneity < 0·001) (Figure 6). Subgroup analysis was performed, and all doses, long-term treatments and vitamin E treatment, whether used alone or in combination, could significantly affect serum vitamin E levels (Table 4). In addition, sensitivity analysis demonstrated that the overall effect size may be influenced by the study by Zohrer *et al.*[29], as its exclusion shifted the result from statistically significant to non-significant.

Discussion

The current systematic review and meta-analysis summarised the results of 665 children who received vitamin E treatment and evaluated their efficacy in various outcomes. Accordingly, our findings indicated that vitamin E treatment could significantly improve some metabolic factors in children compared with the control group. In addition, vitamin E administration was associated with an increase in serum vitamin E levels.

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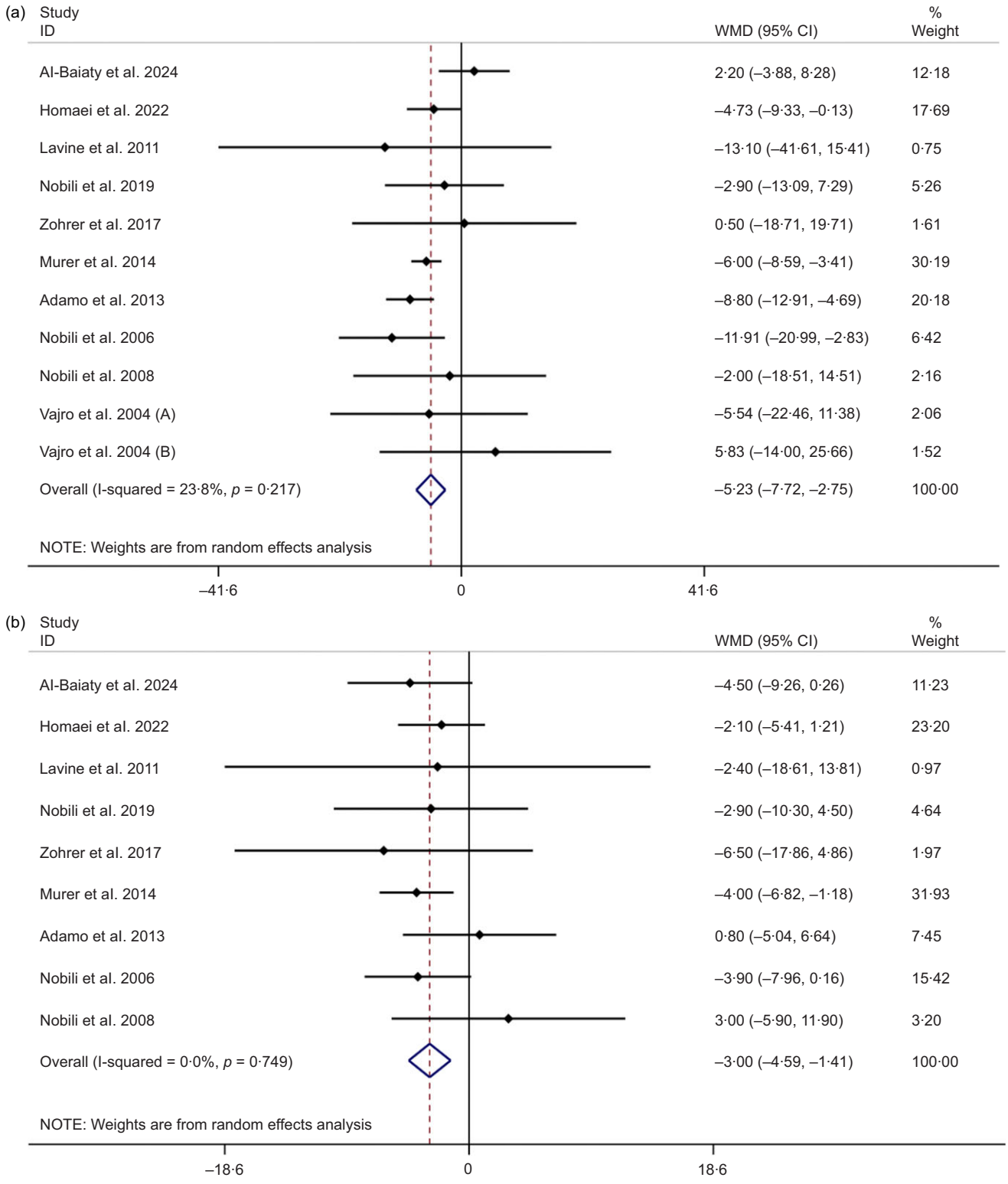


Figure 3. (a) The forest plot of vitamin E treatment on ALT level. (b) The forest plot of vitamin E treatment on AST level. (c) The forest plot of vitamin E treatment on GGT level. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

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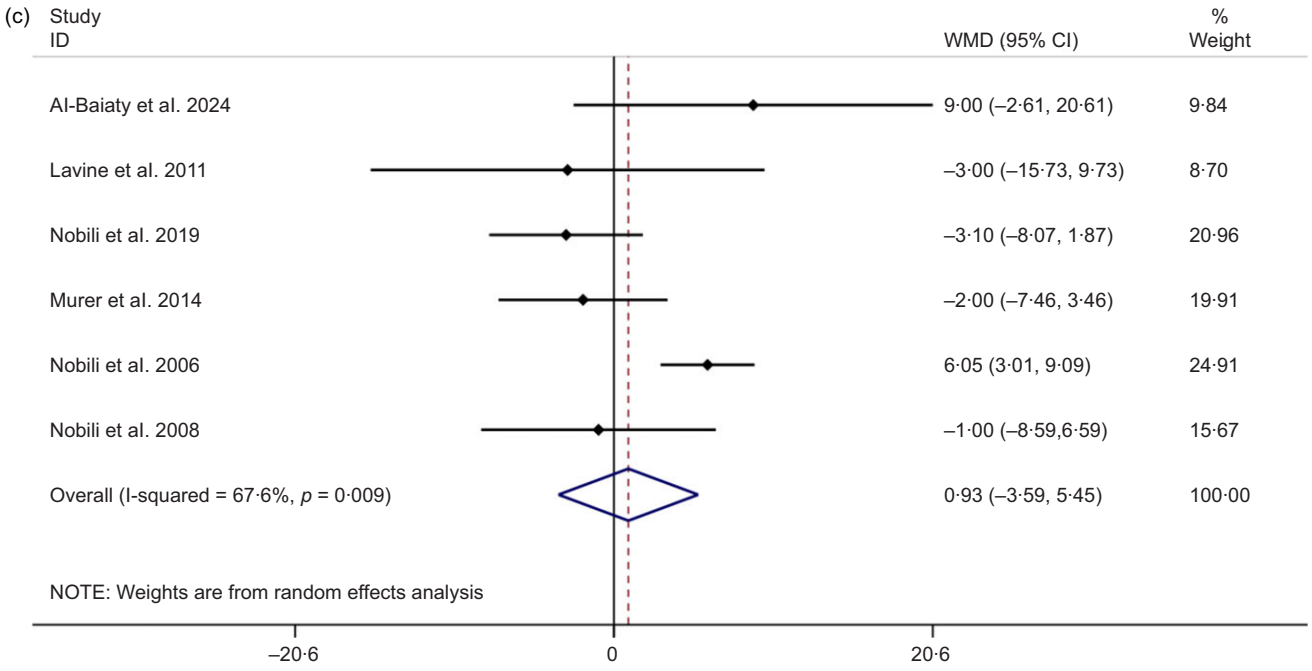


Figure 3. Continued.

According to our findings, vitamin E supplementation led to a significant reduction in ALT and AST levels, but did not significantly affect GGT levels. Several meta-analyses have reported a consistent decrease in ALT levels following vitamin E supplementation in both children and adults[35]. In contrast, AST levels did not show significant changes following vitamin E administration in the paediatric population[35,36]. This discrepancy may be explained by the fact that our meta-analysis included a more comprehensive set of studies, thus providing a broader and more updated perspective. Subgroup analyses indicated that higher doses of vitamin E (> 600 IU/d) significantly reduced ALT levels, whereas lower doses (< 600 IU/d) were effective in reducing AST levels. This differential response may be attributed to the different sensitivities of the liver enzymes to oxidative stress. ALT is primarily localised in hepatocytes, is a more specific marker for liver cell injury and tends to increase in response to liver injury[37,38]. It seems that higher doses of vitamin E are required to exert a sufficient antioxidant effect to decrease ALT levels[39]. AST is found in the liver and other tissues, making it less responsive to liver-targeted therapies, and lower doses are required in the clinical setting. Moreover, our study demonstrated that short-term (< 24 weeks) vitamin E supplementation could have a more pronounced effect on ALT and AST levels in obese children. This highlights the antioxidant and anti-inflammatory properties of vitamin E in children[40]. Similarly, Abdel-Maboud *et al.* 's meta-analysis showed that vitamin E could exert its favourable properties during long-term (> 12 weeks) follow-up in children[41]. Thus, our findings align with this perspective. While a previous study[41] suggested that vitamin E may have beneficial effects in > 12 weeks follow-ups, our analysis indicated that these benefits may also be observed in periods shorter than 24 weeks. In addition, a significant reduction in ALT levels in the lower risk of bias subgroup following vitamin E supplementation supports the idea that high-quality studies yield more consistent and reliable findings regarding the therapeutic potential of vitamin E for liver health. However, vitamin E did not significantly affect the GGT levels. The antioxidative effect of vitamin E may not affect GGT levels, which are involved in biliary function[42]. This finding may be explained by the fact that GGT is primarily a biliary dysfunction and oxidative stress marker, which suggests that the included participants had minimally biliary dysfunction and the GGT level remained unaffected subsequently. Previous evidence supports that vitamin E treatment may be more effective in liver diseases rather than biliary dysfunction.

In addition, our study demonstrated that vitamin E treatment significantly reduced TC levels in the paediatric population compared with the control group. However, the observed reduction in TC levels within the subgroup with a higher risk of bias following vitamin E supplementation suggests that these findings should be interpreted with caution. The methodological limitations of these studies may have influenced the reliability of this outcome, and further high-quality research is needed to confirm the true effects of vitamin E on TC. The antioxidant properties of vitamin E help alleviate oxidative stress, which in turn improves lipid metabolism and reduces lipid peroxidation[43–45]. Similarly, vitamin E mitigates lipid peroxidation to lower cholesterol levels in the liver[46]. Subgroup analysis further indicated that children with MASLD experienced greater benefits from vitamin E supplementation in terms of TC reduction compared with the control group. As oxidative stress and chronic inflammation are key hallmarks of MASLD, vitamin E may exert greater therapeutic effects in this population. In contrast, Lin *et al.* 's meta-analysis demonstrated that vitamin E did not have any significant effect on TC levels in paediatric patients with MASLD[47]. This discrepancy may be attributed to study heterogeneity, variations in sample sizes, differences in disease severity and baseline cholesterol levels, all of which can influence outcomes. Although vitamin E exerts favourable effects on Tc level, its impact on other lipid parameters is limited and LDL-cholesterol, HDL-cholesterol and TAG levels remained unaffected.

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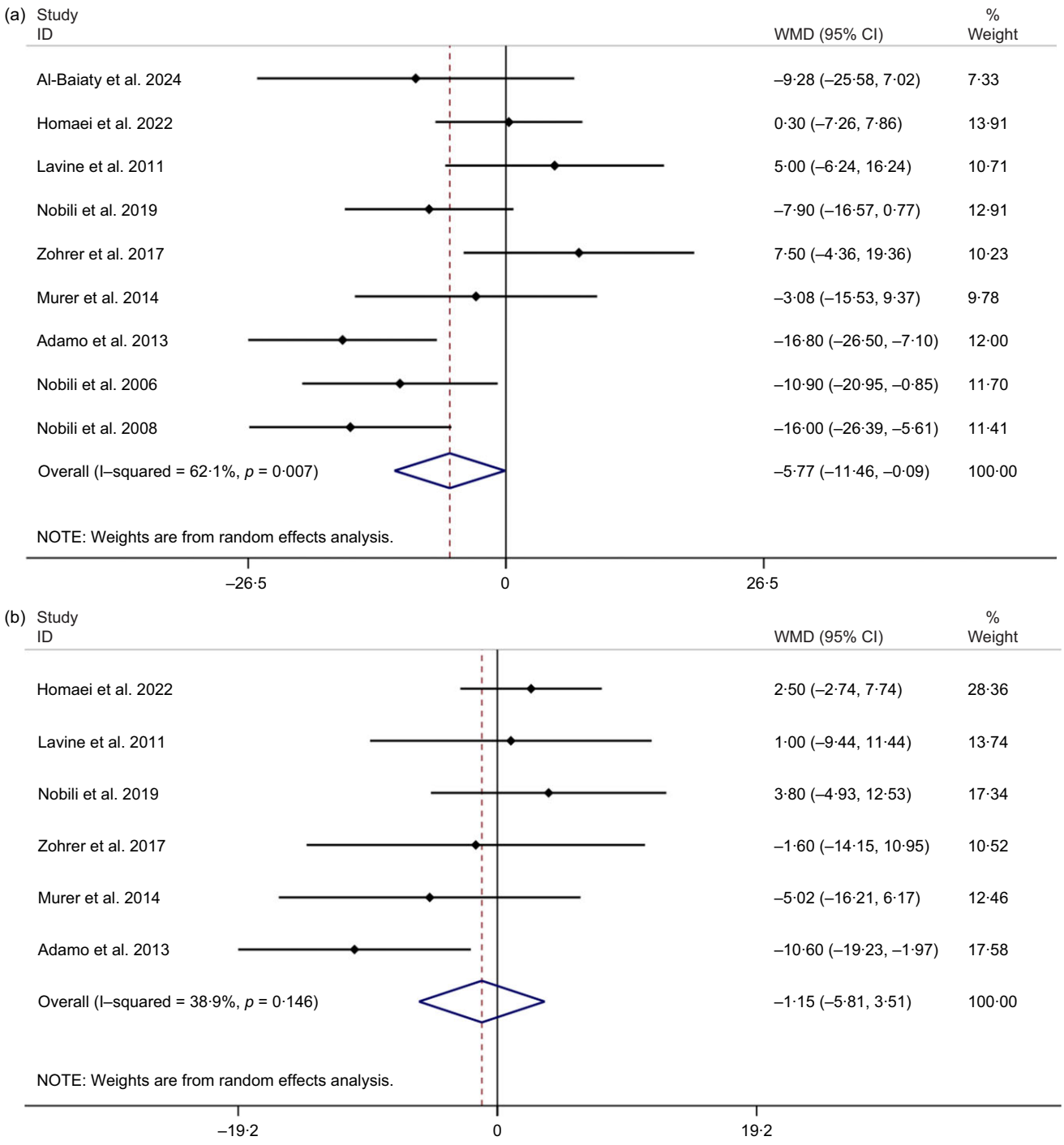


Figure 4. (a) The forest plot of vitamin E treatment on TC level. (b) The forest plot of vitamin E treatment on LDL-cholesterol level. (c) The forest plot of vitamin E treatment on HDL-cholesterol level. (d) The forest plot of vitamin E treatment on TAG level.

This finding may be explained by variations in the treatment dosage and duration which is insufficient to influence these parameters.

Furthermore, vitamin E supplementation had beneficial effects on the HOMA-IR levels. However, it is important to note that both lower- and higher-quality studies reported reductions in HOMA-IR, warranting cautious interpretation of these findings. The presence of studies with a higher risk of bias highlights the need for further investigation using more rigorous methodology. Subgroup analysis revealed that improvements in HOMA-IR were observed across all dosage ranges and durations of supplementation. Moreover, vitamin E treatment alone exhibited favourable effects on HOMA-IR across different health conditions. The underlying mechanism for these effects may involve the reduction of oxidative stress and low-grade inflammation, both of which are known contributors to insulin resistance[48,49]. Vitamin E, a potent antioxidant, may mitigate oxidative stress and ameliorate inflammation, thereby improving insulin sensitivity and lowering

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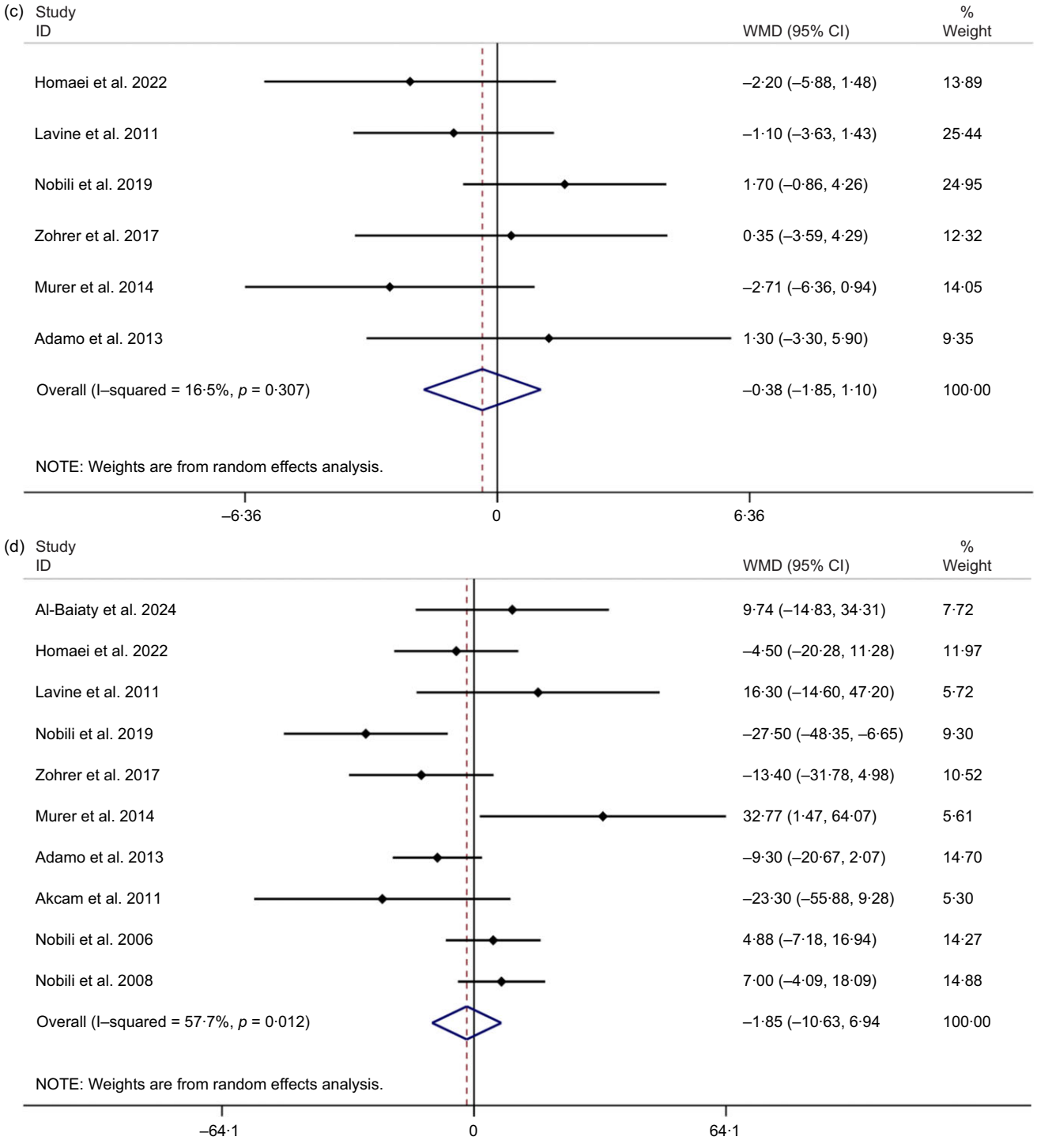


Figure 4. Continued.

HOMA-IR levels[48,50]. Since FBS is affected by multiple factors, vitamin E treatment may not efficiently affect FBS levels. It has been shown that FBS levels are regulated by hepatic glucose uptake involving glucagon, cortisol and glycogenolysis that are not influenced by vitamin E's antioxidant and anti-inflammatory properties, directly. While HOMA-IR reflects insulin sensitivity in muscle and adipose tissue, that vitamin E's antioxidant and anti-inflammatory effects may directly modulate insulin resistance.

Furthermore, vitamin E supplementation contributed to elevated level of serum vitamin E as it is expected that an increased adherence to vitamin E supplementation is accompanied with elevated serum vitamin E level. Given the small number of studies assessing serum vitamin E levels, subgroup analyses were underpowered and may not accurately represent the intervention's effect. Furthermore, variation in the assay methods, baseline vitamin E status could contribute to inconsistent results.

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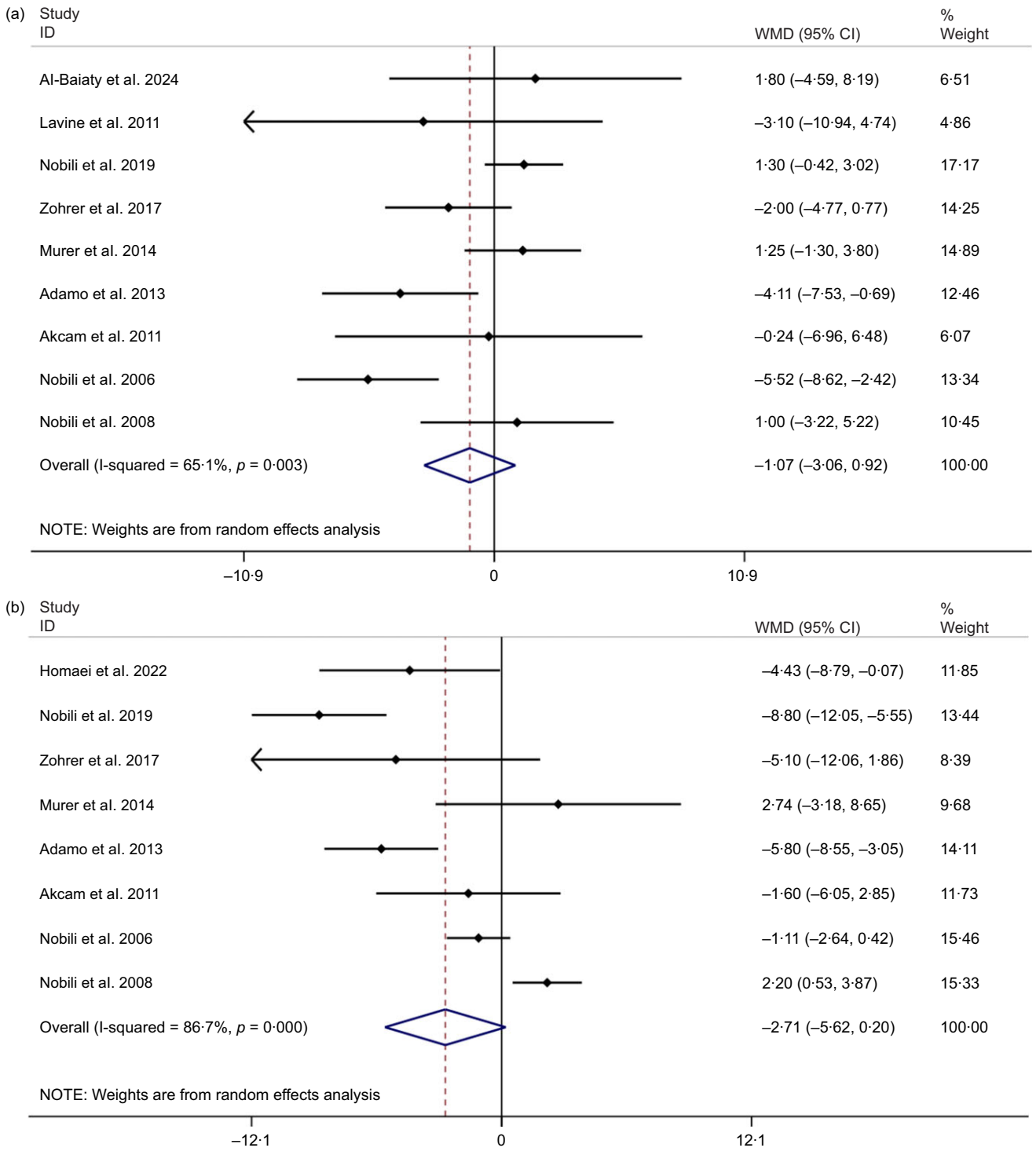


Figure 5. (a) The forest plot of vitamin E treatment on FBS level. (b) The forest plot of vitamin E treatment on insulin level. (c) The forest plot of vitamin E treatment on HOMA-IR level. FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment for insulin resistance.

A notable strength of our study is the incorporation of subgroup analyses, which allowed for the exploration of potential sources of heterogeneity. Moreover, this study presents a comprehensive evaluation focused exclusively on the effects of vitamin E supplementation in paediatric populations. However, this study had certain limitations. The use of different forms and formulations of vitamin E across the included trials may have influenced our findings. Additionally, the limited number of clinical trials investigating the efficacy of vitamin E in children restricts the generalisability of the results.

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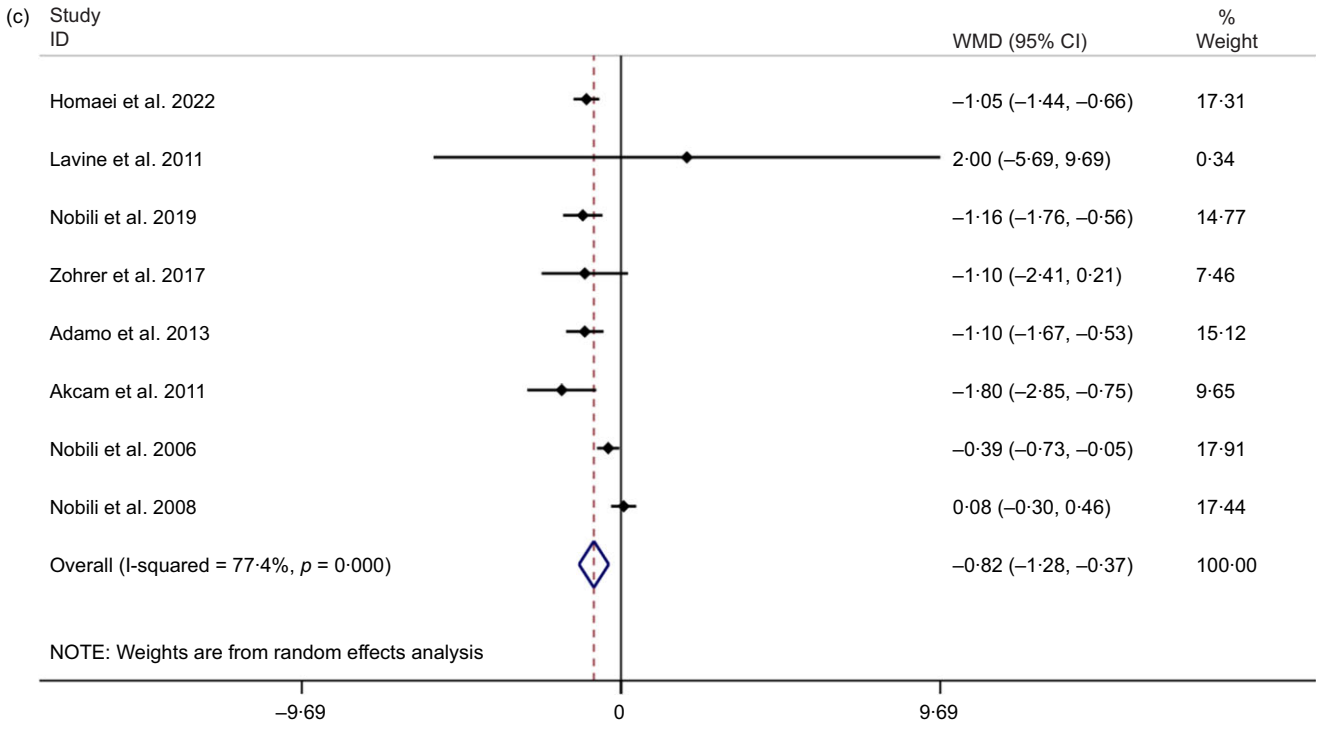


Figure 5. Continued.

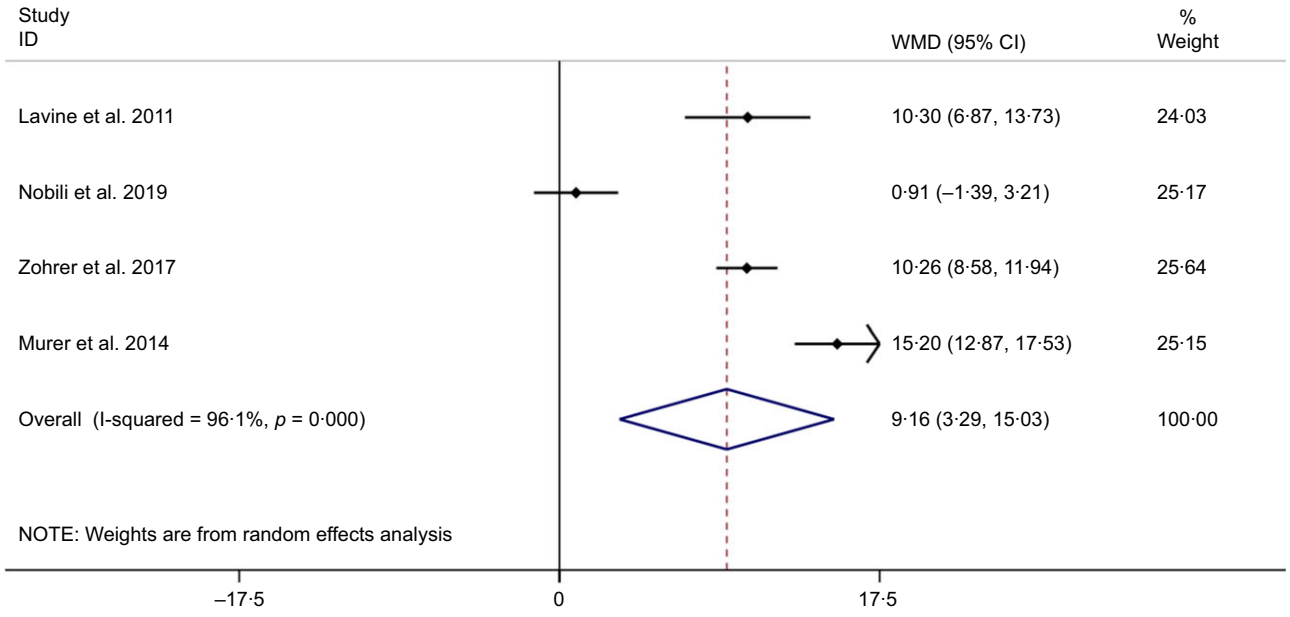


Figure 6. The forest plot of vitamin E treatment on serum vitamin E level.

Conclusion

This updated systematic review and meta-analysis provides a comprehensive approach to vitamin E treatment and its effect on cardiometabolic factors and liver function tests. The current meta-analysis of randomised controlled trials provides evidence of the reducing effects of vitamin E on TC, HOMA-IR, ALT and AST levels in children with MASLD.

Supplementary material. For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114525105400

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References

1. Pouwels S, Sakran N, Graham Y, *et al.* (2022) Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocr Disord* **22**, 63.
2. Younossi ZM, Kalligeros M & Henry L (2025) Epidemiology of metabolic dysfunction-associated steatotic liver disease. *Clin Mol Hepatol* **31**, S32–S50.
3. Vos MB, Abrams SH, Barlow SE, *et al.* (2017) NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr* **64**, 319–334.
4. Lee HS (2024) Nonalcoholic fatty liver disease in children and adolescents. *Clin Exp Pediatr* **67**, 90–91.
5. Utz-Melere M, Targa-Ferreira C, Lessa-Horta B, *et al.* (2018) Non-alcoholic fatty liver disease in children and adolescents: lifestyle change – a systematic review and meta-analysis. *Ann Hepatol* **17**, 345–354.
6. Soliman A, De Sanctis V, Alaaraj N, *et al.* (2020) The clinical application of metformin in children and adolescents: a short update. *Acta Biomed* **91**, e2020086.
7. Sobhani Shahmirzadi M & Barati L (2018) Treatment of nonalcoholic fatty liver disease in children: a systematic review. *J Pediatr Rev* **6**, 21–28.
8. Shah J, Okubote T & Alkhouri N (2018) Overview of updated practice guidelines for pediatric nonalcoholic fatty liver disease. *Gastroenterol Hepatol* **14**, 407–414.
9. Rizvi S, Raza ST, Ahmed F, *et al.* (2014) The role of vitamin E in human health and some diseases. *Sultan Qaboos Univ Med J* **14**, e157–165.
10. Song Y, Ni W, Zheng M, *et al.* (2025) Vitamin E (300 mg) in the treatment of MASH: a multi-center, randomized, double-blind, placebo-controlled study. *Cell Rep Med* **6**, 101939.
11. Shim JS, Kim KN, Lee JS, *et al.* (2022) Dietary intake and major source foods of vitamin E among Koreans: findings of the Korea National Health and Nutrition Examination Survey 2016–2019. *Nutr Res Pract* **16**, 616–627.
12. Yodoshi T, Orkin S, Arce-Clachar AC, *et al.* (2020) Identifying predictors of response to vitamin E for the treatment of pediatric nonalcoholic steatohepatitis. *JPEN J Parenter Enteral Nutr* **44**, 1301–1307.
13. Pacana T & Sanyal AJ (2012) Vitamin E and nonalcoholic fatty liver disease. *Curr Opin Clin Nutr Metab Care* **15**, 641–648.
14. Basu P, Shah N, Aloysius M, *et al.* (2014) Effect of vitamin E and α lipoic acid in nonalcoholic fatty liver disease: a randomized, placebo-controlled, open-label, prospective clinical trial (VAIN trial). *Open J Gastroenterol* **04**, 199–207.
15. Abdel-Maboud M, Menshawy A, Menshawy E, *et al.* (2020) The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Therap Adv Gastroenterol* **13**, 1756284820974917.
16. Lin M, Zeng H, Deng G, *et al.* (2021) Vitamin E in paediatric non-alcoholic fatty liver disease: a meta-analysis. *Clin Res Hepatol Gastroenterol* **45**, 101530.
17. Al-Baiaty FDR, Ismail A, Abdul Latiff Z, *et al.* (2021) Possible hepatoprotective effect of tocotrienol-rich fraction vitamin E in non-alcoholic fatty liver disease in obese children and adolescents. *Front Pediatr* **9**, 667247.
18. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* **6**, e1000097.
19. Sterne JAC, Savović J, Page MJ, *et al.* (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* **366**, l4898.
20. Guyatt GH, Oxman AD, Vist GE, *et al.* (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926.
21. Higgins J (2008) *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: Cochrane Collaboration and John Wiley & Sons Ltd.
22. Tobias A (1999) Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull* **47**, 15–17.
23. Begg CB & Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biom* **50**, 1088–1101.
24. D'Adamo E, Marcovecchio ML, Giannini C, *et al.* (2013) Improved oxidative stress and cardio-metabolic status in obese prepubertal children with liver steatosis treated with lifestyle combined with Vitamin E. *Free Radical Res* **47**, 146–153.
25. Nobili V, Alisi A, Mosca A, *et al.* (2019) The antioxidant effects of hydroxytyrosol and vitamin E on pediatric nonalcoholic fatty liver disease, in a clinical trial: a new treatment? *Antioxid Redox Signaling* **31**, 127–133.
26. Nobili V, Manco M, Devito R, *et al.* (2006) Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* **24**, 1553–1561.
27. Nobili V, Manco M, Devito R, *et al.* (2008) Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. *Hepatology* **48**, 119–128.
28. Vajro P, Mandato C, Franzese A, *et al.* (2004) Vitamin E treatment in pediatric obesity-related liver disease: a randomized study. *J Pediatr Gastroenterol Nutr* **38**, 48–55.
29. Zöhrer E, Alisi A, Jahnel J, *et al.* (2017) Efficacy of docosahexaenoic acid-choline-vitamin E (DHA-CHO-VE) in paediatric NASH: a randomized controlled clinical trial. *Appl Physiol Nutr Metab* **42**, 948–954.
30. Al-Baiaty FD, Ishak S, Mohd Zaki F, *et al.* (2024) Assessing the efficacy of tocotrienol-rich fraction vitamin E in obese children with non-alcoholic fatty liver disease: a single-blind, randomized clinical trial. *BMC Pediatr* **24**, 529.
31. Homaei A, Alhadad M, Arad B, *et al.* (2022) Effect of metformin or vitamin E on ultrasonographic grade and biochemical findings of children and adolescents with nonalcoholic fatty liver disease: a randomized clinical trial. *J Compr Ped* **13**, e123944.
32. Murer SB, Aeberli I, Braegger CP, *et al.* (2014) Antioxidant supplements reduced oxidative stress and stabilized liver function tests but did not reduce inflammation in a randomized controlled trial in obese children and adolescents. *J Nutr* **144**, 193–201.
33. Akcam M, Boyaci A, Pirgon O, *et al.* (2011) Therapeutic effect of metformin and vitamin E *v.* prescriptive diet in obese adolescents with fatty liver. *Int J Vitam Nutr Res* **81**, 398.
34. Lavine JE, Schwimmer JB, Van Natta ML, *et al.* (2011) Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. *JAMA* **305**, 1659–1668.
35. Vogli S, Naska A, Marinos G, *et al.* (2023) The effect of vitamin E supplementation on serum aminotransferases in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. *Nutrients* **15**, 3733.
36. Amanullah I, Khan YH, Anwar I, *et al.* (2019) Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. *Postgraduate Med J* **95**, 601–611.
37. McGill MR (2016) The past and present of serum aminotransferases and the future of liver injury biomarkers. *EXCLI J* **15**, 817.
38. Senior J (2012) Alanine aminotransferase: a clinical and regulatory tool for detecting liver injury–past, present, and future. *Clin Pharmacol Ther* **92**, 332–339.
39. Manning PJ, Sutherland WH, Walker RJ, *et al.* (2004) Effect of high-dose vitamin E on insulin resistance and associated parameters in overweight subjects. *Diabetes Care* **27**, 2166–2171.
40. Jiang Q (2014) Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radical Biol Med* **72**, 76–90.
41. Abdel-Maboud M, Menshawy A, Menshawy E, *et al.* (2020) The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Ther Adv Gastroenterol* **13**, 1756284820974917.

https://doi.org/10.1017/S0007114525105400 Published online by Cambridge University Press

42. Singh M, Tiwary S, Patil D, *et al.* (2007) Gamma-Glutamyl Transpeptidase (GGT) as a marker in obstructive jaundice. *Internet J Surg* **9**. https://doi.org/10.5580/102f
43. Abdelqader A, Obeidat M, Al-Rawashdeh M, *et al.* (2023) The role of vitamin E as an antioxidant and preventing damage caused by free radicals. *J Life Sci Appl Res* **4**, 88–95.
44. Meagher EA, Barry OP, Lawson JA, *et al.* (2001) Effects of vitamin E on lipid peroxidation in healthy persons. *JAMA* **285**, 1178–1182.
45. Viitala P & Newhouse I (2004) Vitamin E supplementation, exercise and lipid peroxidation in human participants. *Eur J Appl Physiol* **93**, 108–115.
46. Wang Y, Li H, Zhang Z, *et al.* (2024) The association between vitamin E intake and remnant cholesterol, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol in US adults: a cross-sectional study. *Lipids Health Dis* **23**, 325.
47. Lin M, Zeng H, Deng G, *et al.* (2021) Vitamin E in paediatric non-alcoholic fatty liver disease: a meta-analysis. *Clin Res Hepatol Gastroenterol* **45**, 101530.
48. Fang F, Kang Z & Wong C (2010) Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors. *Mol Nutr Food Res* **54**, 345–352.
49. Lewis ED, Meydani SN & Wu D (2019) Regulatory role of vitamin E in the immune system and inflammation. *IUBMB life* **71**, 487–494.
50. Gray B, Swick J & Ronnenberg AG (2011) Vitamin E and adiponectin: proposed mechanism for vitamin E-induced improvement in insulin sensitivity. *Nutr Rev* **69**, 155–161.

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