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Comments

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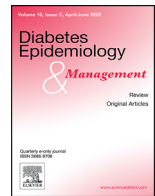
Original article

The glycemic, cholesterol, and weight effects of L-carnitine in diabetes: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: L-carnitine possibly impacts insulin sensitivity and glucose metabolism. However, its therapeutic role in diabetes is poorly understood.

Methods: A systematic review and meta-analysis were conducted using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through June 30, 2021. Included studies evaluated the use of L-carnitine in diabetes on fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), weight, or body mass index (BMI). Weighted mean difference (WMD) and 95% confidence intervals (CI) were calculated using the DerSimonian and Laird random-effects model.

Results: Seventeen studies involving 1622 patients were included. Reductions in FBG (WMD = -0.46 mmol/L, 95% CI = -0.68 to -0.23 mmol/L), HbA1c (WMD = -0.5%, 95% CI = -0.8 to -0.1%), TC (WMD = -0.29 mmol/L, 95% CI = -0.42 to -0.16 mmol/L), and LDL-C (WMD = -0.23 mmol/L, 95% CI = -0.39 to -0.07 mmol/L) were significant. Effects on HDL-C, TG, weight, or BMI were insignificant. Doses between 1001 to 2000 mg showed greatest benefit ($p < 0.02$ for all).

Discussion/Conclusion: L-carnitine plays a potential role as adjunctive therapy in diabetes. Additional research is necessary for patients with higher baseline HbA1c and type 1 diabetes.

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Introduction

Carnitine is a water-soluble amino acid derivative found in many cells of the body. It exists as L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine, and is commonly supplemented in the form of L-carnitine. According to animal and human studies, excess dietary fat contributes to insulin resistance through lipotoxicity [1]. Specifically, fatty acyl CoA derivatives accumulate in muscles and impact glucose oxidation and insulin signaling [2]. Carnitine plays a primary role in transporting long-chain fatty acids into the mitochondria to produce cellular energy as well as fatty acyl-CoA derivatives out of the mitochondria to prevent accumulation [3]. Carnitine helps the mitochondria regulate processes involved in fatty acid oxidation and gluconeogenesis [4]. L-carnitine supplementation possibly impacts glucose metabolism by improving glucose uptake, storage, and oxidation in individuals with diabetes [5–7]. These antioxidant and anti-inflammatory properties play a beneficial role in dyslipidemia, insulin sensitivity, and protein nutrition [8]. L-carnitine may prove useful for individualizing the therapeutic approach for patients with diabetes by improving diabetes control. In addition, L-carnitine may help address the reduced insulin sensitivity and insulin resistance that underlies type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), respectively.

Previous meta-analyses exploring the metabolic impact of L-carnitine in patients with diabetes are limited [9]. Few studies have assessed the dosage and duration of L-carnitine supplementation required to achieve metabolic outcomes or the impact of baseline diabetes severity and body weight. Further studies are necessary to better elucidate its clinical significance in diabetes. Therefore, this study aimed to explore the current evidence on the glycemic, cholesterol, and weight impacts of L-carnitine supplementation in diabetes through meta-analysis.

Methods

Literature search

A comprehensive literature search using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases

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was conducted from inception through June 30, 2021. The search strategy combined Medical Subject Headings and keywords related to L-carnitine ("carnitine" OR "L-carnitine" OR "acetylcarnitine" OR "acetyl-L-carnitine" OR "propionyl-L-carnitine") AND diabetes mellitus ("diabetes mellitus" OR "type 2 diabetes" OR "type ii diabetes" OR "t2dm" OR "NIDDM" OR "non insulin dependent diabetes"). Results were limited to clinical studies conducted in humans and published in English. Results were reported in accordance with the *Preferred Reporting Items for Systematic Review and Meta-Analysis: the PRISMA Statement* [10].

Study eligibility and selection

Randomized controlled trials that evaluated the effect of L-carnitine or its derivatives in patients with diabetes mellitus and reported metabolic outcomes including fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), weight, or body mass index (BMI) were included in the meta-analysis. Unless otherwise stated, the term L-carnitine refers to L-carnitine and its derivatives collectively in this analysis. Studies were excluded if they 1) contained data that was already published in another included study, 2) studied an L-carnitine-containing combination product where the effect of treatment cannot be attributed only to L-carnitine, 3) had an active comparator, or 4) contained no usable data for meta-analysis. Two study investigators independently reviewed all potentially relevant abstracts, and discrepancies were resolved by a third investigator.

Data abstraction and risk of bias assessment

All data were extracted by two independent investigators using a standardized form, with discrepancies resolved by discussion until a consensus was reached. The following information was retrieved from each study: author identification; year of publication; country of publication; study design; study duration; sample size; patient population, details of the intervention and comparator arm, clinical outcomes including FBG, HbA1c, TC, LDL-C, HDL-C, TG, weight, and BMI; as well as information for the assessment of bias. When applicable, efforts were made to contact investigators for clarification or additional data.

Risk of Bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [11,12]. Five domains were assessed by two independent investigators as either having a low, some concerns, or high risk of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was also assigned an overall risk of bias, which corresponds to the worst risk of bias in any of the five domains. Discrepancies were resolved through discussion until a consensus was reached.

Data synthesis and statistical analysis

The DerSimonian and Laird random-effects model was used to calculate the weighted mean difference (WMD) in all reported outcomes as well as their accompanying 95% confidence intervals. When appropriate, reported 95% confidence intervals were converted to standard deviations by dividing the length of the confidence interval by 3.92 and then multiplying by the square root of the sample size [13].

The Mantel-Haenszel fixed-effects model was used to evaluate the robustness of treatment effects. A sensitivity analysis was also performed by limiting the analysis to L-carnitine supplementation (no derivatives) and T2DM patients only as well as excluding studies determined to have an overall high risk of bias. Consistency of treatment effect was assessed among 4 subgroups based on administered dose, baseline HbA1c, baseline BMI, and study duration. A p-value of <0.05 was considered statistically significant for all analyses.

Statistical heterogeneity between trials was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively [14]. Publication bias was assessed using the Egger's statistic and visual inspection of funnel plots. All statistical analyses were completed using StatsDirect Version 3.2.8 (StatsDirect Ltd, Merseyside, England).

Results

Study characteristics

Of the 884 initial citations, 33 full-text articles were screened for eligibility, and 17 studies involving 1622 patients were ultimately included in the meta-analysis (Fig. 1, Table 1) [15−31]. Nine of the 17 studies were conducted in Italy [18−21,23,25−27,29], and remaining trials were conducted in Iran, Egypt, Korea, and Mexico [15−17,22,24,28,30,31]. A parallel-group study design was employed in all studies. Ten of the 17 studies were conducted in a double-blinded manner [15,17,19−21,23,24,27,28,30], whereas two studies were conducted in an open-label fashion [18,29]. Blinding status was not reported in the remaining 5 studies [16,22,25,26,31]. Sixteen studies were conducted in patients with T2DM [15,17−31], and one was conducted in patients with T1DM [16]. L-carnitine was used in 16 studies, (15-26, 28-31) whereas acetyl-L-carnitine was used in one [27]. The duration of intervention ranged from 4 weeks to 12 months. With the exception of one pediatric study that utilized weight-based L-carnitine dosing [16], the total daily L-carnitine dose ranged from 900 mg to 3000 mg. When assessed for risk of bias, 3, 4, and 10 studies were rated as having a low, some concerns, and high risk of bias based on the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [12]. A summary of the revised Cochrane risk of bias assessment is provided in Fig. 2.

Glycemic endpoints

Compared to control, L-carnitine was associated with a statistically significant reduction in FBG (n = 1366, WMD = -0.46 mmol/L, 95% CI = -0.68 to -0.23 mmol/L). A low degree of heterogeneity was present (I^2 = 23.5%). The Egger statistic showed no publication bias (p = 0.17), although bias cannot be ruled out based on visual inspection of the funnel plot. Similarly, a modest reduction in HbA1c was also observed with L-carnitine administration (n =1236, WMD = -0.5%, 95% CI = -0.8 to -0.1%). Although no publication bias was seen (Egger's p = 0.81), a high degree of heterogeneity was present (I^2 = 77.6%).

Cholesterol endpoints

L-carnitine supplementation was also associated with a statistically significant reduction in TC (n = 1422, WMD = -0.29 mmol/L, 95% CI = -0.42 to -0.16 mmol/L) and LDL-C (n = 1414, WMD = -0.23 mmol/L, 95% CI = -0.39 to -0.07 mmol/L) levels compared to control. A statistically significant change in HDL-C (n = 1446, WMD = 0.06 mmol/L, 95% CI = 0 to 0.13 mmol/L) or TG (n = 1281, WMD = -0.17 mmol/L, 95% CI = -0.36 to 0.02 mmol/L) levels was not seen. A low degree of heterogeneity (I^2 = 19.8%) was present for TC, and high degrees of heterogeneity were present for LDL-C, HDL-C, and TG (I^2 = 79.2%, 87.1%, and 85.4%, respectively). A review of funnel plots and Egger statistics suggested low likelihood for publication bias in all cholesterol endpoints evaluated (p > 0.49 for all).

Weight and body mass index

L-carnitine was not associated with changes in weight (n = 877, WMD = 0.1 kg, 95% CI = -0.5 to 0.7 kg) or BMI (n = 1276, WMD = 0, 95% CI = -0.2 to 0.2) upon meta-analysis. Statistical heterogeneity

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┌─────────────────────────────────┐   ┌─────────────────────────────────┐
│ 884 records identified through  │   │ 0 record identified through other│
│       database searching        │   │            sources              │
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                 │ 728 records after duplicates removed│
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                 ┌──────────────────────────┐      ┌──────────────────────────┐
                 │   728 records screened   │─────▶│ 695 records excluded      │
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                 ┌──────────────────────────┐      ┌──────────────────────────────────┐
                 │ 33 full-text articles    │─────▶│ 16 full-text articles excluded   │
                 │  assessed for eligibility│      │   3 were duplicate data          │
                 └──────────────────────────┘      │   1 used a combination product   │
                                    │              │   containing l-carnitine         │
                                    ▼              │   1 had active l-carnitine       │
                 ┌──────────────────────────┐      │   comparator                     │
                 │ 17 studies included for  │      │   2 did not have usable data     │
                 │     meta-analysis        │      │   9 did not meet inclusion       │
                 └──────────────────────────┘      │   criteria                       │
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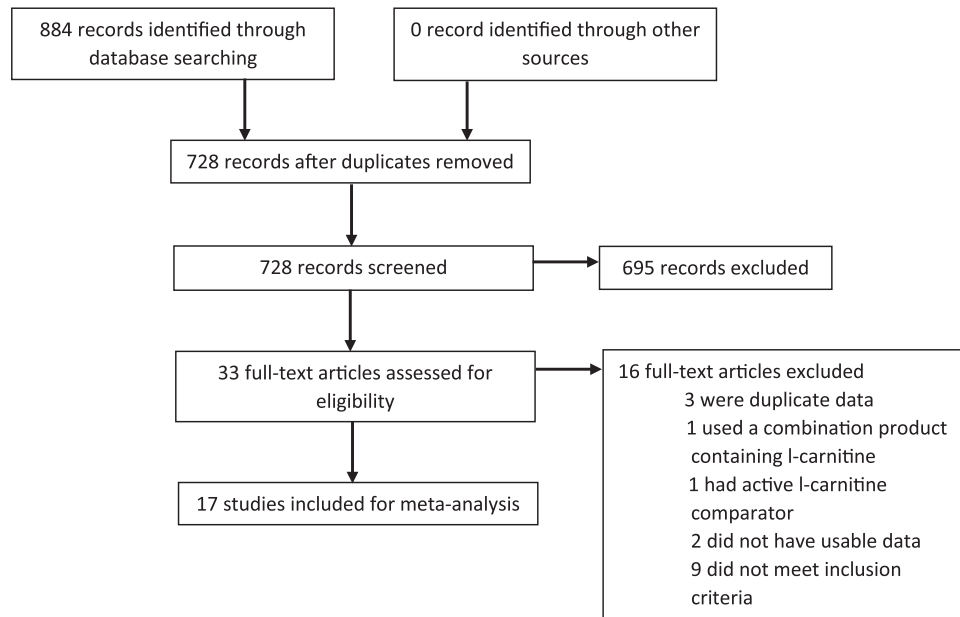
Fig. 1. PRISMA literature search and study selection flow diagram.

was not detected in both endpoints (I^2 = 0% for both). Egger statistics suggested potential publication bias for BMI (p = 0.05) but not for weight (p = 0.13).

Sensitivity and subgroup analysis

L-carnitine was associated with an increase in HDL-C (n = 1446, WMD = 0.04 mmol/L, 95% CI = 0.02 to 0.06 mmol/L) and a reduction in TG (n = 1281, WMD = -0.20 mmol/L, 95% CI = -0.27 to -0.14 mmol/L) when a fixed-effects model was used. No significant change from baseline results was found when analysis was limited to L-carnitine

supplementation (no L-carnitine derivatives) or T2DM patients. When studies with high risk of bias were excluded, a reduction in FBG, HbA1c, and TC was still observed with L-carnitine supplementation (p < 0.05 for all) but not LDL-C. At doses between 1001 to 2000 mg per day, L-carnitine administration was associated with favorable outcomes on FBG, HbA1c, TC, LDL-C, and TG (p < 0.02 for all). No significant effect was seen at daily doses of ≤ 1000 mg or between 2001 to 3000 mg. Patients with baseline HbA1c of 7-9% experienced a reduction in FBG, HbA1c, TC, and LDL-C similar to the entire study cohort (p < 0.005 for all). On the contrary, no signal for benefit was observed in patients with baseline HbA1c of less than 7%.

Table 1
Study characteristics

Author, Year	Study Design	Sample Size	Study Duration	Intervention	Comparator
Alavinejad, 2016 [15]	P, DB	54	3 months	L-carnitine 2250mg/day	Placebo
Badreldeen, 2021 [16]	P, NR	100	4 months	L-carnitine tartrate 50mg/kg/day	No L-carnitine
Bae, 2015 [17]	P, DB	78	3 months	Carnitine-orotate complex 900mg/day	Placebo
Brescia, 2002 [18]	P, UB	32	2 months	L-carnitine 2000mg/day + simvastatin 20mg/day	Simvastatin 20mg/day
Derosa, 2003 [19]	P, DB	94	6 months	L-carnitine 2000mg/day	Placebo
Derosa, 2010 (1) [20]	P, DB	258	12 months	L-carnitine 2000mg/day + orlistat 360mg/day	Orlistat 360mg/day
Derosa, 2010 (2) [21]	P, DB	254	12 months	L-carnitine 2000mg/day + sibutramine 10mg/day	Sibutramine 10mg/day
El-sheikh, 2019 [22]	P, NR	58	6 months	L-carnitine 2000mg/day + glimepiride 4mg/day	Glimepiride 4mg/day
Galvano, 2009 [23]	P, DB	75	4 months	L-carnitine 2000mg/day + simvastatin 20mg/day	Simvastatin 20mg/day
Gonzalez-Ortiz, 2008 [24]	P, DB	12	1 month	L-carnitine 3000mg/day	Placebo
Malaguarnera, 2009 (1) [25]	P, NR	80	3 months	L-carnitine 2000mg/day + simvastatin 20mg/day	Simvastatin 20mg/day
Malaguarnera, 2009 (2) [26]	P, NR	81	3 months	L-carnitine 2000mg/day	Placebo
Parvanova, 2018 [27]	P, DB	229	6 months	Acetyl-L-carnitine 2000mg/day + simvastatin 10-20mg/day	Placebo + simvastatin 10-20mg/day
Rahbar, 2005 [28]	P, DB	35	3 months	L-carnitine 3000mg/day	Placebo
Solfrizzi, 2006 [29]	P, UB	52	2 months	L-carnitine 2000mg/day + simvastatin 20mg/day	Simvastatin 20mg/day
Talenezhad, 2002 [30]	P, DB	70	3 months	L-carnitine 1000mg/day	Placebo
Alipour, 2014 [31]	P, NR	60	2 months	L-carnitine 2000mg + low calorie diet (500kcal below required energy)	Placebo + low calorie diet (500kcal below required energy)

DB: Double blind
NR: No report
P: Parallel RCT
UB: Unblinded

	D1	D2	D3	D4	D5	Overall
Alavinejad, 2016	!	+	-	+	!	-
Badreldeen, 2021	!	+	+	+	+	!
Bae, 2015	!	+	+	+	+	!
Brescia, 2002	!	-	-	-	!	-
Derosa, 2003	!	-	-	+	+	-
Derosa, 2010 (1)	+	+	+	+	+	+
Derosa, 2010 (2)	+	+	!	+	+	!
El-sheikh, 2019	!	-	!	-	+	-
Galvano, 2009	!	+	-	+	+	-
Gonzalez-Ortiz, 2008	!	+	+	+	-	-
Malaguarnera, 2009 (1)	!	+	+	-	-	-
Malaguarnera, 2009 (2)	!	+	+	+	-	-
Parvanova, 2018	+	+	+	+	+	+
Rahbar, 2005	!	+	+	+	+	!
Solfrizzi, 2005	!	-	-	-	+	-
Talenezhad, 2020	+	+	+	+	+	+
Alipour, 2014	!	+	+	-	!	-

Legend:
+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Fig. 2. Revised Cochrane Risk of Bias (RoB 2.0) assessment.

Those with baseline HbA1c of greater than 9% experienced a reduction in TG (n = 112, WMD = -0.42 mmol/L, 95% CI = -0.61 to -0.22 mmol/L) but no improvement in other study endpoints. When analyzed by the patient's baseline BMI, L-carnitine administration was associated with a reduction in FBG, HbA1c, and TC in patients with baseline BMI between 25 to 29.9 and 30 or greater (p < 0.05 for all). In addition, patients with baseline BMI of 30 or greater also experienced a reduction in LDL-C, TG, and BMI (p < 0.05 for all). Only one study was conducted in patients with BMI of less than 25 [16], therefore a subgroup analysis was not performed in this patient group. No significant change from baseline results was found in studies with duration of greater than 6 months. In studies of less than 6 months duration, L-carnitine administration was associated with a decrease in FBG, HbA1c, and TC levels along with a modest increase in HDL-C (p < 0.05 for all). Subgroup analyses results are summarized in Table 2.

Discussion/conclusion

The metabolic effects of L-carnitine in T2DM have been evaluated in prior meta-analyses but these studies were either limited by small sample size or number of endpoints [9,32]. Additional randomized controlled trials have since been conducted to further assess the glycemic and metabolic effects of L-carnitine supplementation in diabetes. L-carnitine also plays a potential role in T1DM by targeting insulin sensitivity, which contributes to the development of microvascular and macrovascular complications in T1DM [33,34]. This current meta-analysis adds to existing literature by comprehensively evaluating the metabolic effects of L-carnitine supplementation in diabetes and assessing its treatment effect across different patient subgroups.

L-carnitine supplementation was associated with a significant reduction in glycemic endpoints in patients with diabetes. The modest reduction in FBG observed in this study (-0.46 mmol/L) is comparable to a prior meta-analysis conducted in patients with T2DM [9]. However, the current study observed a significant reduction in HbA1c (-0.5%), although no significant differences were observed in the prior meta-analysis [9]. This discrepancy may be due to limited research available at the time of the prior meta-analysis, resulting in including fewer studies. The moderate degree of HbA1c reduction found in the present study is comparable to the HbA1c reduction observed with oral antidiabetic drug classes such as dipeptidyl peptidase-4 (DPP-4) inhibitors (-0.75%), meglitinides (-0.75%) [35] and sodium glucose transporter-2 (SGLT-2) inhibitors (-0.5% to -0.7%).[36 −38] L-carnitine supplementation was similarly found to have a statistically significant reduction in HbA1c (-0.3%) in a meta-analysis that included patients with or without diabetes [39]. However, no subgroup analysis was conducted in patients with T2DM; therefore the actual treatment effect may be higher than reported. The results from the included studies suggest that L-carnitine may be considered as adjuvant therapy in addition to current pharmacotherapy, although further studies are necessary.

The effect of L-carnitine on cholesterol levels is mixed. Significant reductions were observed in TC and LDL-C (-0.29 mmol/L and -0.23 mmol/L, respectively). In a subgroup analysis in patients with T2DM, significant reductions in TC and LDL-C were seen (-0.26 mmol/L and -0.18 mmol/L, respectively), and these results are consistent with earlier meta-analyses on lipid concentrations in patients with T2DM [9,32]. One study was conducted on T1DM and

A. Fasting Blood Glucose

Study	L-carnitine			Control			WMD (95% CI)
	N	Mean	SD	N	Mean	SD	
Alavinejad 2016	28	-0.39	4.64	26	-0.33	4.72	-0.06 (-2.55 to 2.44)
Bae 2015	39	-0.12	1.91	39	-0.94	3.62	0.82 (-0.47 to 2.10)
Derosa 2003	46	-0.50	2.20	48	-0.33	1.78	-0.17 (-0.97 to 0.64)
Derosa 2010 (1)	114	-1.55	1.11	113	-0.83	1.06	-0.72 (-1.00 to -0.44)
Derosa 2010 (2)	113	-1.78	1.21	110	-1.33	1.21	-0.44 (-0.76 to -0.13)
El-Sheikh 2019	31	-0.88	0.90	27	-0.10	2.19	-0.77 (-1.62 to 0.07)
Galvano 2009	38	-1.72	2.00	37	-0.50	1.79	-1.22 (-2.08 to -0.36)
Gonzalez-Ortiz 2008	6	-0.10	1.20	6	-0.40	1.22	0.30 (-1.07 to 1.67)
Malaguarnera 2009 (1)	40	-1.45	1.78	40	-0.61	1.64	-0.84 (-1.59 to -0.09)
Malaguarnera 2009 (2)	41	-0.73	1.79	40	-0.47	1.80	-0.27 (-1.05 to 0.51)
Parvanova 2018	109	-0.18	3.29	110	-0.47	3.47	0.29 (-0.60 to 1.19)
Rahbar 2005	19	-0.75	2.70	16	0.36	3.04	-1.11 (-3.01 to 0.80)
Talenezhad 2020	35	-0.09	1.92	35	0.22	1.93	-0.31 (-1.21 to 0.59)
Alipour 2014	30	-0.66	1.45	30	-0.46	1.51	-0.20 (-0.94 to 0.55)
Combined	689			677			-0.46 (-0.68 to -0.23)

I^2 = 23.5%; Egger's P = 0.17
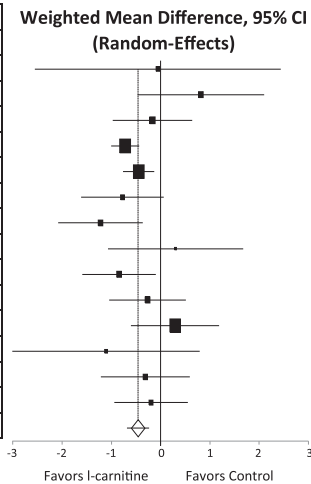
B. Hemoglobin A1c

Study	L-carnitine			Control			WMD (95% CI)
	N	Mean	SD	N	Mean	SD	
Alavinejad 2016	28	-0.3	1.8	26	-0.3	2.5	0.0 (-1.2 to 1.2)
Bae 2015	39	-0.3	0.8	39	-0.1	1.0	-0.2 (-0.6 to 0.2)
Derosa 2003	46	-0.5	1.0	48	-0.6	1.4	0.1 (-0.4 to 0.6)
Derosa 2010 (1)	114	-2.2	1.6	113	-1.4	1.5	-0.8 (-1.2 to -0.4)
Derosa 2010 (2)	113	-2.4	1.6	110	-1.4	1.6	-1.0 (-1.4 to -0.6)
El-Sheikh 2019	31	-2.3	1.0	27	-0.3	1.3	-1.9 (-2.5 to -1.3)
Galvano 2009	38	-0.5	0.9	37	-0.3	1.1	-0.2 (-0.6 to 0.2)
Gonzalez-Ortiz 2008	6	-0.4	1.1	6	-0.7	1.8	0.3 (-1.4 to 2.0)
Malaguarnera 2009 (1)	40	-0.3	0.9	40	-0.2	0.6	-0.1 (-0.4 to 0.2)
Malaguarnera 2009 (2)	41	-0.7	1.1	40	-0.1	1.1	-0.6 (-1.1 to -0.1)
Parvanova 2018	109	0.3	1.9	110	0.2	1.7	0.1 (-0.4 to 0.6)
Rahbar 2005	19	-0.1	2.6	16	0.8	3.2	-0.9 (-2.8 to 1.0)
Combined	624			612			-0.5 (-0.8 to -0.1)

I^2 = 77.6%; Egger's P = 0.81
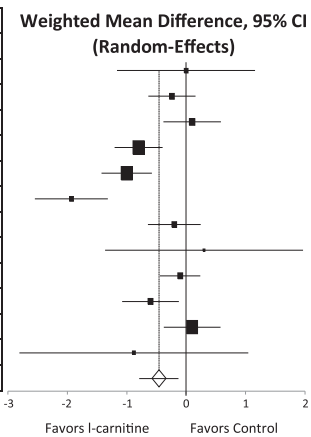
C. Total Cholesterol

Study	L-carnitine			Control			WMD (95% CI)
	N	Mean	SD	N	Mean	SD	
Alavinejad 2016	28	-0.62	1.36	26	-0.80	1.53	0.18 (-0.59 to 0.95)
Badreldeen 2021	25	-1.26	1.40	25	0.01	1.71	-1.26 (-2.13 to -0.40)
Brescia 2002	16	-2.09	1.44	16	-1.52	1.41	-0.57 (-1.55 to 0.42)
Derosa 2003	46	-0.26	1.06	48	0.16	1.33	-0.41 (-0.90 to 0.07)
Derosa 2010 (1)	114	-1.14	0.67	113	-0.88	0.66	-0.26 (-0.43 to -0.09)
Derosa 2010 (2)	113	-0.96	0.75	110	-0.70	0.81	-0.26 (-0.46 to -0.05)
El-Sheikh 2019	31	-0.76	1.16	27	-0.03	0.90	-0.73 (-1.28 to -0.19)
Galvano 2009	38	-1.71	1.25	37	-1.29	1.13	-0.41 (-0.95 to 0.13)
Gonzalez-Ortiz 2008	6	-0.20	1.36	6	0.50	1.78	-0.70 (-2.49 to 1.09)
Malaguarnera 2009 (1)	40	-2.07	1.20	40	-1.45	1.06	-0.62 (-1.12 to -0.12)
Malaguarnera 2009 (2)	41	-0.72	1.17	40	-0.30	1.17	-0.42 (-0.93 to 0.09)
Parvanova 2018	109	0.05	1.15	110	0.14	1.19	-0.09 (-0.40 to 0.22)
Rahbar 2005	19	-0.12	1.39	16	-0.16	1.50	0.04 (-0.92 to 1.00)
Solfrizzi 2006	26	-1.14	1.07	26	-1.40	1.80	0.27 (-0.54 to 1.07)
Talenezhad 2020	35	-0.08	1.17	35	-0.27	1.24	0.19 (-0.38 to 0.75)
Alipour 2014	30	-0.61	1.20	30	-0.27	1.16	-0.33 (-0.93 to 0.26)
Combined	717			705			-0.29 (-0.42 to -0.16)

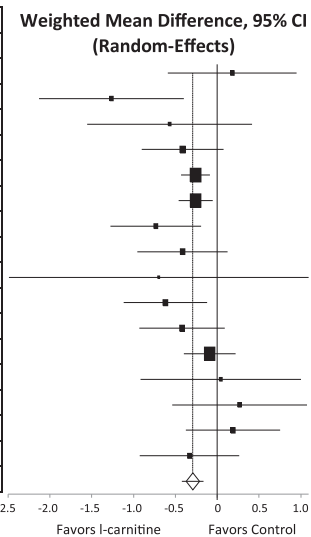I^2 = 19.8%; Egger's P = 0.50

Fig. 3. Forest plot depicting meta-analyses results.

observed significant improvements in TC, LDL-C, and HDL-C (-1.26 mmol/L, -1.45 mmol/L, and 0.43 mmol/L, respectively) [16]. Interestingly, the lipid effects observed in T1DM appear to be more pronounced compared to improvements observed in T2DM, which may be related to differing serum acylcarnitine profiles observed among patients with T1DM, T2DM, and metabolic syndrome. Serum acylcarnit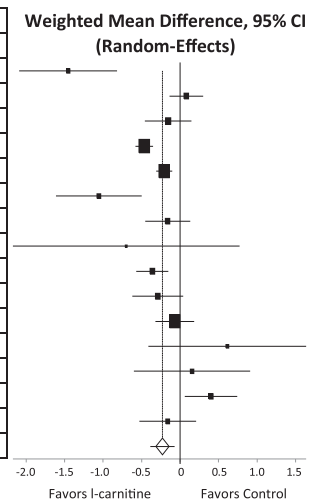ine profiles are indirect indicators of mitochondrial dysfunction [40] and further studies are necessary to elucidate its role in distinguishing metabolic features [41]. L-carnitine supplementation was not associated with beneficial effects in HDL-C or TG in this present study. T2DM and insulin resistance may cause postprandial hypertriglyceridemia despite normal fasting TG levels [42,43]. As a result, the effect of L-carnitine on TG levels may not be fully appreciated when measured while fasting, and it is uncertain if each of the

D. Low-density Lipoprotein Cholesterol

Study	L-carnitine			Control			WMD (95% CI)
	N	Mean	SD	N	Mean	SD	
Badreldeen 2021	25	-1.48	0.74	25	-0.02	1.44	-1.45 (-2.09 to -0.82)
Bae 2015	39	0.09	0.60	39	0.01	0.36	0.08 (-0.14 to 0.30)
Derosa 2003	46	-0.08	0.66	48	0.08	0.81	-0.16 (-0.46 to 0.15)
Derosa 2010 (1)	114	-1.16	0.46	113	-0.70	0.41	-0.47 (-0.58 to -0.35)
Derosa 2010 (2)	113	-0.78	0.39	110	-0.57	0.41	-0.21 (-0.31 to -0.10)
El-Sheikh 2019	31	-1.14	1.17	27	-0.08	0.97	-1.06 (-1.61 to -0.50)
Galvano 2009	38	-1.40	0.65	37	-1.24	0.65	-0.16 (-0.46 to 0.13)
Gonzalez-Ortiz 2008	6	-0.40	1.17	6	0.30	1.42	-0.70 (-2.17 to 0.77)
Malaguarnera 2009 (1)	40	-1.65	0.45	40	-1.29	0.50	-0.36 (-0.57 to -0.15)
Malaguarnera 2009 (2)	41	-0.45	0.75	40	-0.16	0.77	-0.29 (-0.62 to 0.04)
Parvanova 2018	109	0.02	0.98	110	0.09	0.93	-0.07 (-0.32 to 0.18)
Rahbar 2005	19	-0.11	1.44	16	-0.72	1.65	0.61 (-0.41 to 1.64)
Solfrizzi 2006	26	-1.02	1.01	26	-1.18	1.68	0.16 (-0.60 to 0.91)
Talenezhad 2020	35	-0.04	0.76	35	-0.44	0.69	0.40 (0.06 to 0.74)
Alipour 2014	30	-0.37	0.76	30	-0.21	0.69	-0.16 (-0.53 to 0.21)
Combined	712			702			-0.23 (-0.39 to -0.07)

I^2 = 79.2%; Egger's P = 0.71

Weighted Mean Difference, 95% CI (Random-Effects). X-axis: -2.0 -1.5 -1.0 -0.5 0 0.5 1.0 1.5. Favors l-carnitine / Favors Control

E. High-density Lipoprotein Cholesterol

Study	L-carnitine			Control			WMD (95% CI)
	N	Mean	SD	N	Mean	SD	
Badreldeen 2021	25	0.39	0.45	25	-0.04	0.49	0.43 (0.17 to 0.69)
Bae 2015	39	0.02	0.14	39	0.01	0.14	0.01 (-0.06 to 0.07)
Brescia 2002	16	0.05	0.45	16	-0.09	0.46	0.14 (-0.17 to 0.45)
Derosa 2003	46	-0.05	0.17	48	0.03	0.17	-0.08 (-0.14 to -0.01)
Derosa 2010 (1)	114	0.00	0.21	113	0.03	0.27	-0.03 (-0.09 to 0.04)
Derosa 2010 (2)	113	-0.03	0.27	110	-0.05	0.23	0.03 (-0.04 to 0.09)
El-Sheikh 2019	31	0.52	0.25	27	0.00	0.15	0.52 (0.42 to 0.63)
Galvano 2009	38	0.21	0.14	37	0.13	0.18	0.09 (0.01 to 0.16)
Gonzalez-Ortiz 2008	6	-0.10	0.28	6	0.10	0.32	-0.20 (-0.54 to 0.14)
Malaguarnera 2009 (1)	40	0.20	0.11	40	0.11	0.17	0.09 (0.03 to 0.15)
Malaguarnera 2009 (2)	41	0.07	0.09	40	0.04	0.08	0.03 (-0.01 to 0.07)
Parvanova 2018	109	-0.04	0.50	110	-0.04	0.45	0.00 (-0.12 to 0.13)
Rahbar 2005	19	-0.20	0.49	16	-0.14	0.39	-0.07 (-0.36 to 0.23)
Solfrizzi 2006	26	0.02	0.45	26	0.03	0.43	-0.01 (-0.25 to 0.23)
Talenezhad 2020	35	-0.05	0.42	35	-0.04	0.43	-0.01 (-0.21 to 0.19)
Alipour 2014	30	0.11	0.13	30	0.09	0.14	0.02 (-0.05 to 0.08)
Combined	728			718			0.06 (0.00 to 0.13)

I^2 = 87.1%; Egger's P = 0.50

Weighted Mean Difference, 95% CI (Random-Effects). X-axis: -0.6 -0.4 -0.2 0 0.2 0.4 0.6. Favors Control / Favors l-carnitine
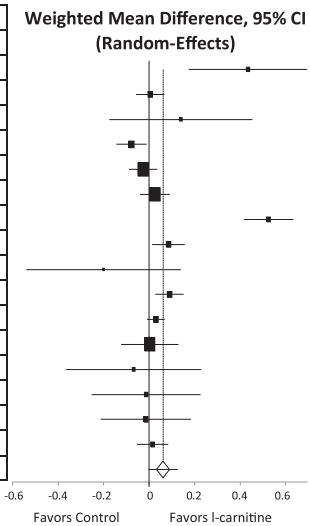
Fig. 3. Continued.

included studies assessed lipid profiles during fasting state. High quality trials are needed to clarify L-carnitine's effects on non-fasting lipid parameters.

No significant changes in weight or BMI were seen in the overall patient cohort. This differs from the significant reduction in weight and BMI observed in a prior meta-analysis [44]. The discrepancy may be attributed to differences in study inclusion, as only three studies involving diabetes were included in the prior meta-analysis. In the present subgroup analysis, BMI decreased with L-carnitine supplementation in patients with baseline BMI ≥ 30. A trend towards reduction in weight was observed in this patient population although no effect on weight or BMI was seen with other baseline BMI subgroups. Together, these results suggest that L-carnitine may have beneficial weight-reducing effect in patients with higher baseline BMI. Additional studies are needed to validate these findings.

Limited research exists regarding the optimal dosing required for L-carnitine supplementation to achieve glycemic and lipid effects; therefore, an analysis was conducted to assess the impact of dosing. The majority (11 out of 17) of included studies assessed L-carnitine supplementation at a dose of 2000 mg per day [18–23,25–27,29,31]. L-carnitine was associated with favorable improvements in FBG, A1c, TC, LDL-C, and TG at the 1001 mg to 2000 mg dose range, however no significant glycemic or lipid effects were observed at other

doses. This could be due to including fewer studies that evaluated doses ≤ 1000 mg per day and 2001 mg to 4000 mg per day. In a prior meta-analysis in patients with or without diabetes, a minimum dose of 1000 mg per day was also necessary to show significant reductions in FBG, TG, and HDL-C. However, the authors ultimately recommended a dose range of 2000 mg to 3000 mg per day [45]. Based on subgroup analysis, our study provides additional support for L-carnitine supplementation at a dose of 2000 mg per day.

The consistency of L-carnitine treatment effect was evaluated across various diabetes populations. In this study, significant improvements in FBG, HbA1c, TC, and LDL-C were seen in patients who had a higher baseline HbA1c of 7-9%, but not if HbA1c was < 7%. Oral antidiabetic agents have been associated with greater reduction in HbA1c when initiated at higher baseline HbA1c,[35] a finding that is highlighted in our present study. Contrarily, patients with baseline HbA1c > 9% did not observe a statistically significant improvement in most study endpoints, possibly due to including fewer studies with patients at higher baseline HbA1c. Importantly, when compared to patients with baseline HbA1c of 7-9%, there is a trend towards greater FBG (-0.69 mmol/L) and HbA1c reduction (-1.03%) in those with baseline HbA1c > 9%. Additional studies in this patient population are needed to shed light on the effect of L-carnitine in patients with higher baseline HbA1c.

F. Triglycerides

Study	L-carnitine N	L-carnitine Mean	L-carnitine SD	Control N	Control Mean	Control SD	WMD (95% CI)
Alavinejad 2016	28	-0.15	1.31	26	-0.07	1.29	-0.08 (-0.77 to 0.62)
Badreldeen 2021	25	-0.06	0.35	25	0.02	0.61	-0.08 (-0.36 to 0.20)
Bae 2015	39	0.05	2.49	39	0.08	0.95	-0.03 (-0.87 to 0.81)
Brescia 2002	16	-1.28	1.37	16	-0.82	1.46	-0.46 (-1.44 to 0.52)
Derosa 2003	46	0.11	0.52	48	-0.07	0.42	0.18 (-0.01 to 0.37)
Derosa 2010 (1)	114	-0.42	0.52	113	-0.42	0.60	0.00 (-0.15 to 0.15)
Derosa 2010 (2)	113	-0.36	0.56	110	-0.16	0.61	-0.20 (-0.36 to -0.05)
El-Sheikh 2019	31	-0.31	0.30	27	0.14	0.47	-0.45 (-0.65 to -0.24)
Galvano 2009	38	-1.11	0.54	37	-0.40	0.50	-0.71 (-0.95 to -0.47)
Gonzalez-Ortiz 2008	6	0.20	1.35	6	0.00	1.28	0.20 (-1.29 to 1.69)
Malaguarnera 2009 (1)	40	-1.36	0.50	40	-0.41	0.50	-0.95 (-1.17 to -0.73)
Malaguarnera 2009 (2)	41	-1.01	0.47	40	-0.97	0.52	-0.04 (-0.25 to 0.17)
Rahbar 2005	19	0.42	1.48	16	-0.34	1.63	0.76 (-0.27 to 1.80)
Solfrizzi 2006	26	-0.19	1.11	26	-0.56	0.95	0.37 (-0.19 to 0.93)
Talenezhad 2020	35	0.06	0.78	35	0.08	0.92	-0.02 (-0.43 to 0.38)
Alipour 2014	30	-0.29	0.47	30	-0.17	0.57	-0.12 (-0.39 to 0.14)
Combined	647			634			-0.17 (-0.36 to 0.02)

I² = 85.4%; Egger's P = 0.74
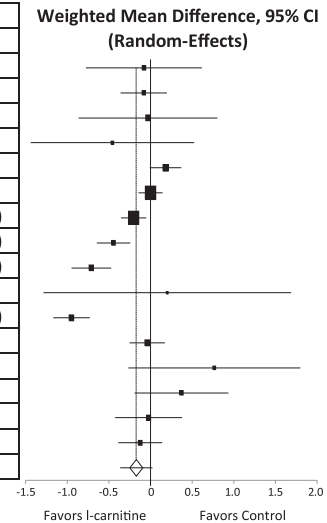
G. Body Weight

Study	L-carnitine N	L-carnitine Mean	L-carnitine SD	Control N	Control Mean	Control SD	WMD (95% CI)
Bae 2015	39	-0.4	1.6	39	-0.7	1.4	0.3 (-0.4 to 1.0)
Derosa 2010 (1)	114	-11.3	11.0	113	-9.5	11.1	-1.8 (-4.7 to 1.1)
Derosa 2010 (2)	113	-10.9	11.8	110	-9.1	12.7	-1.8 (-5.0 to 1.4)
Parvanova 2018	109	0.1	20.6	110	-0.2	22.0	0.3 (-5.4 to 6.0)
Talenezhad 2020	35	0.4	17.4	35	0.1	16.7	0.3 (-7.7 to 8.3)
Alipour 2014	30	-4.7	11.2	30	-2.7	10.6	-2.0 (-7.5 to 3.5)
Combined	440			437			0.1 (-0.5 to 0.7)

I² = 0%; Egger's P = 0.13
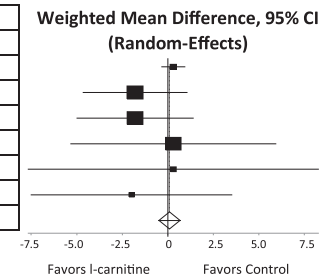
H. Body Mass Index

| Study	L-carnitine N	L-carnitine Mean	L-carnitine SD	Control N	Control Mean	Control SD	WMD (95% CI)
Bae 2015	39	-0.1	0.6	39	-0.3	0.5	0.1 (-0.1 to 0.3)
Derosa 2003	46	-1.1	3.3	48	-1.3	3.0	0.2 (-1.1 to 1.5)
Derosa 2010 (1)	114	-3.9	3.1	113	-3.3	3.1	-0.6 (-1.4 to 0.2)
Derosa 2010 (2)	113	-3.8	3.9	110	-3.1	3.7	-0.7 (-1.7 to 0.3)
El-Sheikh 2019	31	-0.8	7.4	27	-0.3	7.8	-0.4 (-4.4 to 3.5)
Galvano 2009	38	-1.1	3.1	37	-0.7	2.7	-0.4 (-1.7 to 0.9)
Gonzalez-Ortiz 2008	6	-0.3	3.6	6	-0.3	3.8	0.0 (-4.2 to 4.2)
Malaguarnera 2009 (1)	40	-1.2	3.3	40	-0.8	3.7	-0.4 (-1.9 to 1.1)
Malaguarnera 2009 (2)	41	-0.6	2.2	40	-0.6	2.4	0.0 (-1.0 to 1.0)
Parvanova 2018	109	0.1	6.9	110	0.0	7.3	0.1 (-1.8 to 2.0)
Talenezhad 2020	35	0.2	4.9	35	0.5	6.9	-0.3 (-3.1 to 2.5)
Alipour 2014	30	-1.8	4.6	30	-0.8	3.9	-1.0 (-3.1 to 1.2)
Combined	641			635			0.0 (-0.2 to 0.2)

I² = 0%; Egger's P = 0.05
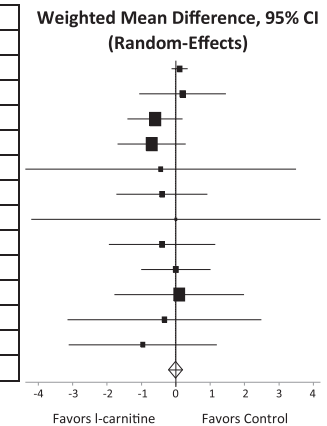
Fig. 3. Continued.

Several limitations should be noted when interpreting the results of this meta-analysis. First, many of the included studies had some concerns or high risk for bias. However, when studies with a high risk of bias were excluded, reductions in FBG, HbA1c, and TC remained significant. Second, there was a high degree of heterogeneity with many of the glycemic and cholesterol endpoints, which limits our ability to conclusively determine the effect of L-carnitine in diabetes. Additionally, the included studies did not address the safety of L-carnitine supplementation when used in diabetes. When studied in other clinical contexts, L-carnitine supplementation was likely safe with appropriate use. Total doses of 3000 mg per day may cause gastrointestinal adverse effects, including nausea, vomiting, abdominal cramps, and diarrhea [46]. Further research is necessary to better understand the safety of L-carnitine in diabetes. Lastly, the included studies were conducted in Italy, Iran, Egypt, Korea, and Mexico, which may limit application to other geographic locations and populations.

In conclusion, L-carnitine supplementation is associated with improvements in FBG, HbA1c, TC, and LDL-C in patients with diabetes. Supplementation at 1001 to 2000 mg per day in patients with HbA1c of 7-9% and BMI of 25 to 29.9 and 30 or greater have the strongest data for benefit. The results from this study suggest that L-carnitine supplementation may play a role as adjunctive therapy in diabetes by improving insulin sensitivity. Further studies are necessary to clarify the effects of L-carnitine supplementation in patients with higher baseline HbA1c and in patients with T1DM.

Funding

Table 2
Subgroup analyses results.

	FBG	HbA1c	TC	LDL-C	HDL-C	TG	Weight	BMI
Random-effects	-0.46	-0.5	-0.29	-0.23	0.06	-0.17	0.1	0.0
	(-0.68 to -0.23)	(-0.8 to -0.1)	(-0.42 to -0.16)	(-0.39 to -0.07)	(0.00 to 0.13)	(-0.36 to 0.02)	(-0.5 to 0.7)	(-0.2 to 0.2)
Fixed-effects	-0.51	-0.4	-0.28	-0.26	0.04	-0.20	0.1	0.0
	(-0.68 to -0.34)	(-0.6 to -0.3)	(-0.38 to -0.18)	(-0.32 to -0.20)	(0.02 to 0.06)	(-0.27 to -0.14)	(-0.5 to 0.7)	(-0.2 to 0.2)
L-carnitine only	-0.52	-0.5	-0.32	-0.24	0.06	-0.17	0.1	0.0
	(-0.72 to -0.31)	(-0.9 to -0.2)	(-0.46 to -0.18)	(-0.42 to -0.07)	(0.00 to 0.13)	(-0.36 to 0.02)	(-0.5 to 0.7)	(-0.2 to 0.2)
T2DM only	-0.51	-0.5	-0.26	-0.18	0.05	-0.18	0.1	0.0
	(-0.68 to -0.23)	(-0.8 to -0.1)	(-0.36 to -0.16)	(-0.33 to -0.03)	(-0.02 to 0.11)	(-0.38 to 0.03)	(-0.5 to 0.7)	(-0.2 to 0.2)
Exclude high RoB	-0.37	-0.5	-0.22	-0.17	0.02	-0.08	0.1	-0.1
	(-0.74 to 0.00)	(-1.0 to -0.1)	(-0.41 to -0.03)	(-0.43 to 0.09)	(-0.04 to 0.07)	(-0.20 to 0.04)	(-0.5 to 0.8)	(-0.5 to 0.3)
Dose								
≤ 1000 mg	0.16	-	-	0.22	0.00	-0.02	0.3	0.1
	(-0.93 to 1.24)			(-0.09 to 0.53)	(-0.06 to 0.06)	(-0.39 to 0.34)	(-0.4 to 1.0)	(-0.1 to 0.3)
1001 to 2000 mg	-0.53	-0.5	-0.29	-0.28	0.07	-0.24	-1.6	-0.4
	(-0.75 to -0.30)	(-0.9 to -0.1)	(-0.40 to -0.19)	(-0.41 to -0.15)	(-0.01 to 0.14)	(-0.48 to 0.00)	(-3.5 to 0.3)	(-0.8 to 0.1)
2001 to 3000 mg	-0.16	-0.1	0.04	0.06	-0.12	0.18	-	-
	(-1.18 to 0.87)	(-1.0 to 0.8)	(-0.53 to 0.62)	(-1.21 to 1.33)	(-0.34 to 0.10)	(-0.35 to 0.72)		
Baseline HbA1c								
< 7%	0.05	0.1	-0.08	0.09	-0.01	-0.07	0.3	0.0
	(-0.53 to 0.62)	(-0.3 to 0.6)	(-0.34 to 0.18)	(-0.35 to 0.53)	(-0.10 to 0.09)	(-0.43 to 0.29)	(-4.3 to 4.9)	(-1.5 to 1.4)
7-9%	-0.55	-0.4	-0.32	-0.26	0.03	-0.15	-0.5	0.00
	(-0.83 to -0.27)	(-0.7 to -0.1)	(-0.47 to -0.18)	(-0.43 to -0.09)	(-0.02 to 0.07)	(-0.41 to 0.11)	(-2.0 to 1.1)	(-0.2 to 0.2)
> 9%	-0.69	-1.0	-0.32	-	-	-0.42	-	-
	(-1.53 to 0.14)	(-2.9 to 0.9)	(-1.22 to 0.57)			(-0.61 to -0.22)		
Baseline BMI								
< 25	-	-	-	-	-	-	-	-
25-29.9	-0.41	-0.2	-0.25	-0.06	0.02	-0.11	0.3	0.1
	(-0.79 to -0.01)	(-0.4 to 0.0)	(-0.48 to -0.03)	(-0.26 to 0.14)	(-0.03 to 0.06)	(-0.47 to 0.25)	(-0.4 to 1.0)	(-0.1 to 0.3)
≥ 30	-0.48	-0.9	-0.26	-0.32	0.11	-0.19	-1.6	-0.6
	(-0.77 to -0.20)	(-1.6 to -0.2)	(-0.39 to -0.14)	(-0.54 to -0.11)	(-0.06 to 0.27)	(-0.38 to 0.00)	(-3.5 to 0.3)	(-1.2 to 0.0)
Study duration								
< 6 months	-0.41	-0.2	-0.31	-0.16	0.05	-0.18	0.3	0.1
	(-0.79 to -0.02)	(-0.4 to 0.0)	(-0.56 to -0.06)	(-0.42 to 0.10)	(0.00 to 0.09)	(-0.46 to 0.10)	(-0.4 to 0.9)	(-0.2 to 0.3)
≥ 6 months	-0.48	-0.7	-0.27	-0.32	0.09	-0.11	-1.5	-0.4
	(-0.77 to -0.19)	(-1.3 to 0.0)	(-0.40 to -0.14)	(-0.52 to -0.11)	(-0.09 to 0.26)	(-0.35 to 0.12)	(-3.5 to 0.5)	(-1.0 to 0.1)

T2DM=type 2 diabetes mellitus

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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