ORIGINAL ARTICLE

Efficacy and safety of sitagliptin and insulin for latent autoimmune diabetes in adults: A systematic review and meta-analysis

Tong Lin[1], Yinhe Cai[1], Liting Tang[2], Youwei Lian[1], Min Liu[2], Chaonan Liu[2]* ID

[1]The First School of Clinical Medical Sciences, Guangzhou University of Chinese, Medicine, Guangzhou, China, and [2]Department of Endocrinology, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

ABSTRACT

Aims/Introduction: The optimal therapy for latent autoimmune diabetes in adults (LADA) remains undefined. Increasing evidence has shown that sitagliptin and insulin treatment can benefit patients with LADA, but the efficacy still lacks systematic evaluation. We carried out this systematic review and meta-analysis to summarize the current data on the efficacy and safety of sitagliptin combined with insulin on LADA, providing a reliable reference for the effective therapeutic treatment of LADA patients.

Materials and Methods: We retrieved the literature in PubMed, Cochrane Library, Embase, Web of Science and CNKI from inception to August 2021. Randomized controlled trials comparing the effects of sitagliptin plus insulin with insulin alone in LADA patients were identified. The outcome measures included parameters of glycemic control, β-cell function, body mass index and adverse events. The Review Manager 5.2 and Stata 14.0 were utilized for data analysis.

Results: Eight randomized controlled trials involving 295 participants were identified. Sitagliptin and insulin treatment lowered hemoglobin A1c (weighted mean difference −0.36, 95% confidence interval −0.61 to −0.10, $I^2 = 91.6\%$), increased fasting C-peptide (weighted mean difference 0.08, 95% confidence interval −0.02 to 0.17, $I^2 = 88.8\%$) and had fewer adverse events compared with insulin alone. The inter-study heterogeneity, potential publication bias and other factors might interpret asymmetrical presentation of funnel plots. There was no significant association between sitagliptin plus insulin treatment and levels of hemoglobin A1c or fasting C-peptide, regardless of the duration of intervention and sample size.

Conclusions: Sitagliptin combined with insulin can achieve better glycemic control and improve islet β-cell function with lower incidence of hypoglycemia compared with insulin alone, which provides an effective and tolerated therapeutic regimen for LADA patients. However, further well-designed and rigorous randomized controlled trials are required to validate this benefit due to the limited methodology quality of included trials.

INTRODUCTION

Latent autoimmune diabetes in adults (LADA) is an autoimmune diabetes that shares common clinical manifestations with type 2 diabetes mellitus, and has the same immunological characteristics as type 1 diabetes mellitus[1]. Characterized by slow progression of islet β-cell failure and the presence of diabetes associated autoantibodies, patients with LADA usually show older age at diabetes onset compared with type 1 diabetes mellitus patients[2]. Patients with LADA show high levels of insulin resistance and do not require insulin therapy at the initial diagnosis, which often contribute to a high misdiagnosis rate of 5–10% among patients with type 2 diabetes mellitus[3,4].

A previous study showed that diabetes duration and worse glycemic control might account for microvascular complications in LADA[5]. In this case, therapeutic strategies for LADA include preserving β-cell function, improving insulin sensitivity, achieving good glycemic control and preventing complications. The optimal therapy for LADA has not been recommended in guidelines so far, and recent studies gradually focus on exploring promising LADA treatments. The C-peptide levels show a further progressive decline after onset of LADA, leading to the occurrence of insulin dependence. Exogenous insulin therapy not only produces glucose-lowering effects, but also ameliorate inflammation of islets[6]. As previously reported[7, 8], early insulin treatment in LADA patients is essential and effective regardless of residual β-cell function and C-peptide levels. In recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic agents frequently used to produce protective effects on islet β-cell function, as well as decrease blood glucose levels. Evidence from animal models showed that DPP-4 inhibitors can reverse new-onset diabetes by stimulating β-cell regeneration, modulating the inflammatory response and ameliorating the autoimmune response[9]. Sitagliptin, a representative drug of DPP-4 inhibitors, has the effects of reducing hemoglobin A1c (HbA1c) levels, ameliorating β-cell function and improving in insulin sensitivity, which might also benefit patients with LADA[10, 11]. The optimal treatment strategies for patients with LADA have not been identified and require further exploration.

Increasing evidence supports that sitagliptin and insulin can benefit patients with LADA, but the efficacy still lacks systematic evaluation. Therefore, we carried out the present systematic review and meta-analysis to summarize current data on the efficacy and safety of sitagliptin combined with insulin on LADA, providing a reliable reference for the effective therapeutic treatment of LADA patients.

MATERIALS AND METHODS

The protocol for this meta-analysis has been registered with the PROSPERO registry (CRD42021254508).

Search strategy

We retrieved articles in the following databases: PubMed, Web of Science, Embase, Cochrane Library and Chinese National Knowledge Infrastructure from their inception to August 2021 without restriction of language or type of publication. Search strategies carried out in English databases are listed in Table 1, and corresponding terms in Chinese translations were also applied for the Chinese database.

Eligibility and exclusion criteria

Only randomized controlled trials (RCTs) for evaluating the efficacy and safety of sitagliptin and insulin in LADA treatment were considered. Patients included in the present study met the following criteria: diabetes diagnosed according to the World Health Organization 1999 criteria; with an adult age of onset >30 years, insulin independence for at least 6 months at initial

diagnosis, presence of β-cell antibodies, mostly glutamic acid decarboxylase antibodies and fasting C-peptide (FCP) ≥ 0.2 nmol/L[12]. The exclusion criteria were: (i) evidence of other autoimmune diseases; (ii) chronic or acute infection; (iii) a history of any malignancy; and (iv) the studies were animal experiments, conference references, case reports or duplicated publication. There was no restriction on sex or region. In all included trials, the intervention group was treated with sitagliptin combined with insulin or sitagliptin monotherapy, and the control group was given insulin treatment alone. The primary outcomes were HbA1c and FCP, and the secondary outcomes were 2-h postprandial C-peptide (2hCP), changes in C-peptide levels ($\triangle CP$; $\triangle CP = 2hCP - FCP$), fasting blood glucose (FBG), 2-hour postprandial glucose (2hBG), body mass index (BMI) and adverse events.

Study selection and data extraction

Two reviewers independently screened the titles and abstracts to select potential studies on the basis of the inclusion and exclusion criteria, and then scanned all full articles for eligibility. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was adapted for study selection process. Discrepancies were resolved by achieving a consensus with a third author.

Two researchers extracted data from included trials using a self-designed data extraction form. The following information was included: author, year, region, sample size, age, intervention, follow up, outcome measures, adverse events and so on. Discrepancies were discussed with a third author.

Quality assessment of included studies

Two reviewers independently evaluated the risk of bias of included studies with the Cochrane Collaboration's tool, which mainly contained random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Our judgment on each domain was classified as low, unclear or high risk of bias.

Statistical analysis

The Stata version 14.0 software (StataCorp, College Station, TC, USA) was utilized for data analysis. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated. The heterogeneity of included studies was assessed using Q and I^2 statistics. For Q statistics, $P < 0.05$ was considered high heterogeneity. As for I^2 statistics, $I^2 < 25\%$ showed no significant heterogeneity, $I^2 = 25–50\%$ was considered moderate heterogeneity and $I^2 > 50\%$ represented high heterogeneity. Random effects models were used when there was high heterogeneity, otherwise fixed effects models were applied. The reporting bias was examined by funnel plot to evaluate symmetry and more objectively through the Egger's test. A contour-enhanced funnel plot was used to visibly assess the publication bias. Potential treatment–effect modifiers on HbA1c and FCP

Table 1 | Search strategies for English databases

Databases	Strategies
PubMed	((((Sitagliptin[Title/Abstract]) OR (dipeptidylpeptidase-4 inhibitor[Title/Abstract])) OR (DPP-4 inhibitor[Title/Abstract])) AND (insulin[Title/Abstract]) AND ((((((((latent autoimmune diabetes in adults[Title/Abstract]) OR (LADA[Title/Abstract])) OR (Diabetes Mellitus Type 1.5[Title/Abstract])) OR (Type 1.5 Diabetes Mellitus[Title/Abstract])) OR (Type 1.5 Diabetes[Title/Abstract])) OR (Diabetes, Type 1.5[Title/Abstract])) OR (latent autoimmune diabetes of adults[Title/Abstract]))
Cochrane Library	#1 (Sitagliptin):ti,ab,kw OR (dipeptidylpeptidase-4 inhibitor):ti,ab,kw OR (DPP-4 inhibitor):ti,ab,kw
	#2 (insulin):ti,ab,kw
	#3 (latent autoimmune diabetes in adults):ti,ab,kw OR (LADA):ti,ab,kw OR (diabetes mellitus type 1.5):ti,ab,kw OR (type 1.5 diabetes mellitus):ti,ab,kw OR (type 1.5 diabetes):ti,ab,kw
	#4 (diabetes, type 1.5):ti,ab,kw OR (latent autoimmune diabetes of adults):ti,ab,kw
	#5 #1 AND #2 AND (#3 OR #4)
EMBASE	#1 sitagliptin:ab,ti OR 'dipeptidylpeptidase-4 inhibitor':ab,ti OR 'dpp-4 inhibitor':ab,ti
	#2 insulin:ab,ti
	#3 'latent autoimmune diabetes in adults':ab,ti OR lada:ab,ti OR 'diabetes mellitus type 1.5':ab,ti OR 'type 1.5 diabetes mellitus':ab,ti OR 'type 1.5 diabetes':ab,ti OR 'diabetes, type 1.5':ab,ti OR 'latent autoimmune diabetes of adults':ab,ti
	#4 #1 AND #2 AND #3
Web of Science	#1 TS = "Sitagliptin" OR "dipeptidylpeptidase-4 inhibitor" OR "DPP-4 inhibitor"
	#2 TS = "insulin"
	#3 TS = "latent autoimmune diabetes in adults" OR "LADA" OR "Diabetes Mellitus Type 1.5" OR "Type 1.5 Diabetes Mellitus" OR "Type 1.5 Diabetes" OR "Diabetes, Type 1.5" OR "latent autoimmune diabetes of adults"
	#4 #1 AND #2 AND #3

levels were further investigated by meta-regression analysis, including duration and sample size. A *P*-value <0.05 showed statistical significance.

RESULTS
Study selection
We identified 389 potentially relevant articles, of which 64 were removed due to duplicate publication. Through screening titles and abstracts, 137 studies were excluded because they were review articles, experimental researches, case reports, conference abstracts, letters or irrelevant studies. Of the remaining 188 articles, 180 articles were excluded by reading the full texts, of which four had no useful outcomes, 166 were not related to sitagliptin or LADA and 10 were non-RCTs. Finally, eight eligible trials[13–20] involving 295 participants that met our inclusion criteria were included in the present study. The flowchart of the study selection process is summarized in Figure 1.

Study characteristics
A total of 295 patients were included in the eight studies[13–20], 148 patients underwent insulin treatment in the control group, and 147 patients received sitagliptin combined with insulin therapy in the experimental group. The duration of the included studies lasted from 12 weeks to 24 months. Seven studies[13–15, 17–20] described HbA1c. Both FCP and 2hCP levels were measured in six studies[13–16, 18, 20]. Five studies included △CP as an outcome measure[13–16, 20]. Five studies[14, 15, 18–20] reported FBG and 2hBG levels. BMI was observed in four studies[13–15, 18]. Adverse events were reported in four included studies[13, 14, 18, 19], whereas the other four studies[15–17, 20] did

not mention adverse events. The basic characteristics of all included studies were listed in Table 2.

Risk of bias assessment
The quality of the eligible studies was assessed using the Cochrane Collaboration's tool. All included studies reported randomization, but just four trials[13, 16, 18, 19] provided concrete randomization methods. Only one study[13] mentioned allocation concealment and evaluated patients with sequentially numbered envelopes. With respect to blinding of participants and personnel, all included studies[13–20] without available evidence were assessed to be unclear risk of bias. No trials described the detailed information about blinding of outcome assessment and other bias, thus these two domains were judged as an unclear risk of bias. All of the studies[13–20] showed a low risk of bias in relation to incomplete outcome data and selective reporting. The risk of bias of included studies was shown in Figure 2.

Efficacy assessment
HbA1c levels
A total of seven studies evaluated the effect of sitagliptin plus insulin treatment on HbA1c levels[13–15, 17–20]. Significant heterogeneity was seen among the trials ($I^2 = 89.0\%$, $P < 0.05$), therefore a random effects model was used. The combined effect showed that sitagliptin plus insulin intervention significantly decreased HbA1c levels compared with the insulin therapy alone (WMD −0.36, 95% CI −0.61 to −0.10, $I^2 = 91.6\%$, $P = 0.0001$; Figure 3a). Furthermore, patients with LADA receiving sitagliptin plus insulin treatment had a better effect
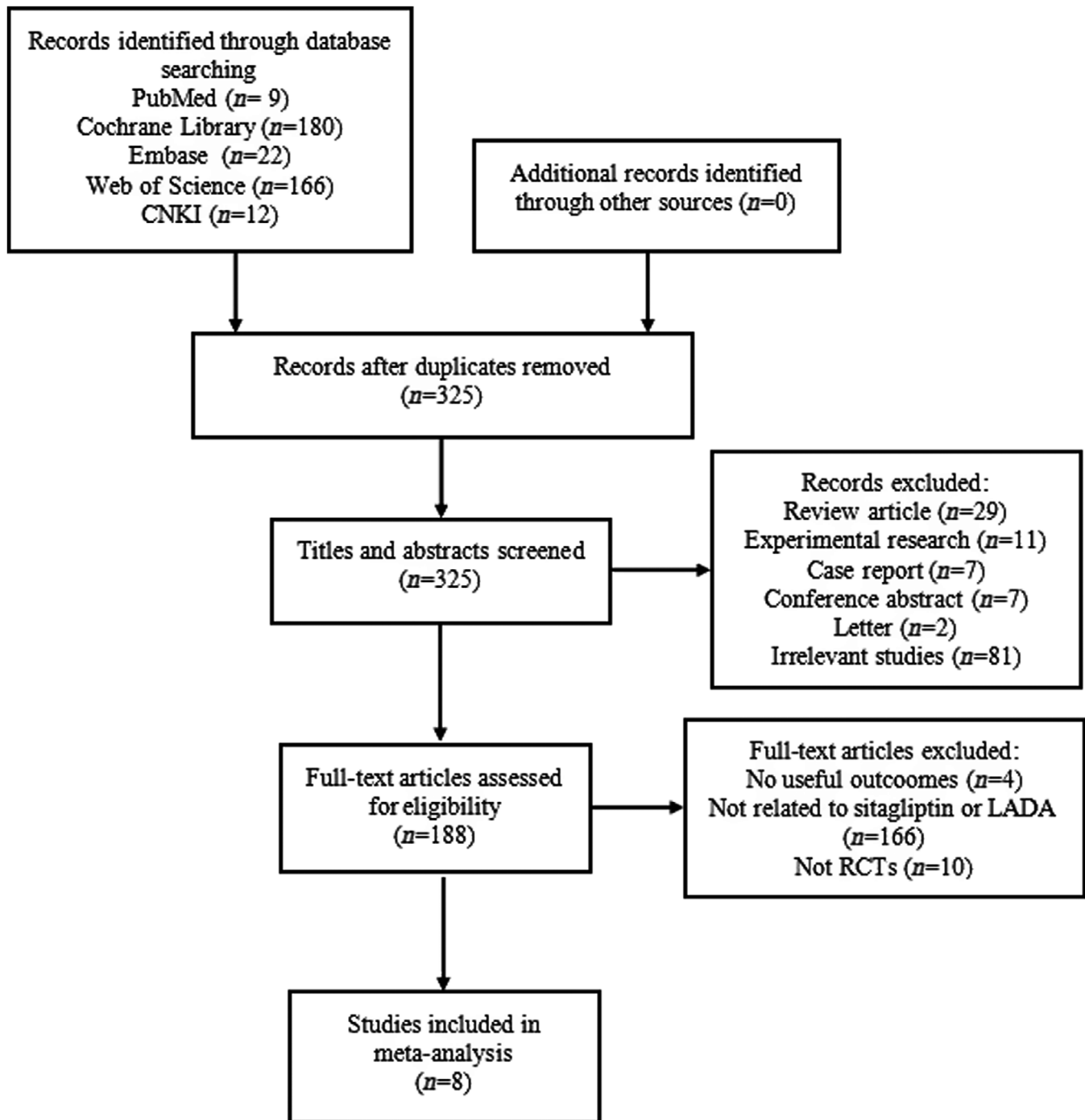
Figure 1 | Flowchart of the study selection process. LADA, latent autoimmune diabetes in adults; RCTs, randomized controlled trials.

on HbA1c levels than insulin alone in the 3-month follow up subgroups (WMD −0.42, 95% CI −0.76 to −0.08, P = 0.0001). Sitagliptin plus insulin therapy showed similar reductions on HbA1c levels at 6 months (WMD −0.32, 95% CI −0.85 to 0.21, P = 0.0001) and 12 months (WMD −0.26, 95% CI −0.75 to 0.24, P = 0.0001; Figure 3b).

FCP
FCP was assessed in six included RCTs[13–16, 18, 20] with significant heterogeneity (I^2 = 82.2%, P < 0.05). The meta-analysis showed that sitagliptin plus insulin described a clinical increase on FCP (WMD 0.08, 95% CI −0.02 to 0.17; I^2 = 88.8%, P = 0.0001; Figure 4a). The subgroup analyses were carried out

Table 2 | Characteristics of included studies

Included trials	Year	Region	Study design	Sample size	Age (years)	Intervention	Control	Follow-up	Outcome measures	Adverse events
Yang *et al.*[13]	2021	China	RCT	51	I:48.2 ± 11.5 C:48.2 ± 12.3	Sitagliptin (100 mg/day) + insulin (10.9 ± 10.6 U)	Insulin (13.4 ± 9.3 U)	24 months	①②③④⑤	One participant in the intervention group had severe elevation of transaminase. Three participants in two groups had detected hypoglycemia
Zhao *et al.*[14]	2014	China	RCT	30	I:48.0 ± 2.8 C:46.9 ± 3.7	Sitagliptin (100 mg/day) + insulin (14.9 ± 1.5, U)	Insulin (17.9 ± 1.9, U)	12 months	①②③⑤⑥⑦	The incidence of hypoglycemia was low and no other severe side effects
Wang *et al.*[15]	2019	China	RCT	40	I:47.8 ± 13.1 C:51.9 ± 10.2	Sitagliptin (100 mg/day) + insulin (premixed insulin twice or three times daily)	Insulin (premixed insulin twice or three times daily)	12 months	①②③④⑤⑥⑦	Not mentioned
Yuan *et al.*[16]	2020	China	RCT	30	48.2 ± 12.0	Sitagliptin (100 mg/d) + insulin	Insulin	12 months	③④⑤	Not mentioned
Chen *et al.*[17]	2017	China	RCT	30	I: 32.08 ± 10.76 C: 30.48 ± 12.23	Sitagliptin (100 mg/day) + insulin	Insulin	12 weeks	②	Not mentioned
Huang *et al.*[18]	2017	China	RCT	50	I: 53.9 ± 4.8 C:54.1 ± 5.0	Sitagliptin (100 mg/day) + insulin	Insulin	12 weeks	①②③④⑥⑦	The incidence of hypoglycemia was lower in the intervention group compared with the control group
Zhang[19]	2019	China	RCT	50	I: 48 ± 9 C: 47 ± 10	Sitagliptin (100 mg/day) + insulin	Insulin	12 weeks	②⑥⑦	No adverse events
Lai *et al.*[20]	2017	China	RCT	14	I:47.8 ± 2.8 C:46.9 ± 3.7	Sitagliptin (100 mg/day) + insulin (14.9 ± 1.5 U)	Insulin (13.8 ± 2.1 U)	9 months	②③④⑤⑥⑦	Not mentioned

This study was carried out to assess the efficacy and safety of sitagliptin and insulin for latent autoimmune diabetes in adults. Our findings showed that sitagliptin and insulin treatment achieved better glycemic control, improve islet β-cell function and had fewer adverse events compared with insulin alone, providing a promising therapeutic strategy for latent autoimmune diabetes in adults treatment. More rigorous and well-designed studies are required to validate our results. ①Body mass index; ②hemoglobin A1c (HbA1c); ③Fasting C-peptide (FCP); ④2-h postprandial C-peptide (2hCP); ⑤ΔCP = 2hCP − FCP; ⑥fasting blood glucose; ⑦2-h postprandial blood glucose. C, control group; I, intervention group; RCT, randomized controlled trials.

Figure 2 | Summary of risk of bias of included studies.

according to different treatment duration. After 6 months, a significant improvement of FCP in favor of sitagliptin treatment was identified (WMD 0.03, 95% CI −0.08 to 0.14; $P = 0.0001$). However, sitagliptin combined with insulin for 3 months (WMD 0.14, 95% CI 0.10 to 0.18; $P = 0.985$) or 9 months (WMD 0.10, 95% CI −0.05 to 0.24; $P = 0.195$) showed clinical improvement of FCP in comparison with the control group, which was not statistically significant. Meaningfully, sitagliptin combined with insulin treatment for 12 months significantly increased FCP levels compared with insulin therapy (WMD

0.05, 95% CI −0.05 to 0.16; $P = 0.0001$; Figure 4b). However, a clinically meaningful increase on FCP levels was found in LADA patients with sitagliptin plus insulin treatment in comparison with insulin treatment alone, and long-term efficacy was identified.

2hCP
Data were extracted from six trials[13–16, 18, 20] to assess 2hCP. The random effects model was used due to significant heterogeneity ($I^2 = 82.8\%$, $P < 0.05$). Sitagliptin treatment showed a significant effect on increasing 2hCP levels compared with insulin therapy (WMD 0.31, 95% CI 0.11 to 0.51; $I^2 = 87.5\%$, $P = 0.0001$; Figure 5).

△CP
Changes in C-peptide levels were presented as △CP. Five trials[13–16, 20] evaluated the effect of sitagliptin plus insulin on △CP with high heterogeneity ($I^2 = 84.7\%$, $P < 0.05$). The results found that △CP of sitagliptin plus insulin intervention was higher than that of the control group (WMD 0.22, 95% CI 0.14 to 0.31; $I^2 = 53.9\%$, $P = 0.070$; Figure 6).

FBG
Regarding FBG, data extracted from five studies[14, 15, 18–20] showed high heterogeneity ($I^2 = 91.3\%$, $P < 0.05$), thus the random effects model was used for statistical analysis. The combined effects showed that FBG was lower in LADA patients using sitagliptin plus insulin or sitagliptin than in the control group (WMD −0.58, 95% CI −0.95 to −0.21; $I^2 = 88.3\%$, $P = 0.0001$; Figure 7).

2hBG
Five trials[14, 15, 18–20] included 2hBG outcomes. There was significant heterogeneity among these trials ($I^2 = 74.2\%$, $P < 0.05$), consequently a random effects model was developed. Sitagliptin combined with insulin significantly decreased 2hBG levels compared with insulin alone (WMD −1.62, 95% CI −2.43 to −0.82; $I^2 = 89.6\%$, $P = 0.0001$; Figure 8).

BMI
Four studies[13–15, 18] reported BMI. The random effects model was utilized for data analysis due to the high heterogeneity ($I^2 = 79.0\%$, $P = 0.003$). The results showed that sitagliptin combined with insulin showed a significant reduction on BMI levels (WMD −1.20, 95% CI −1.53 to −0.86; $I^2 = 0\%$, $P = 0.996$) compared with insulin treatment (Figure 9).

Adverse events
Three trials[13, 14, 18] reported hypoglycemia, two of which showed that the incidence of hypoglycemia was lower in the intervention group compared with the control group. One trial[19] reported that there was no adverse event, whereas the remaining four studies[15–17, 20] did not mention adverse events.
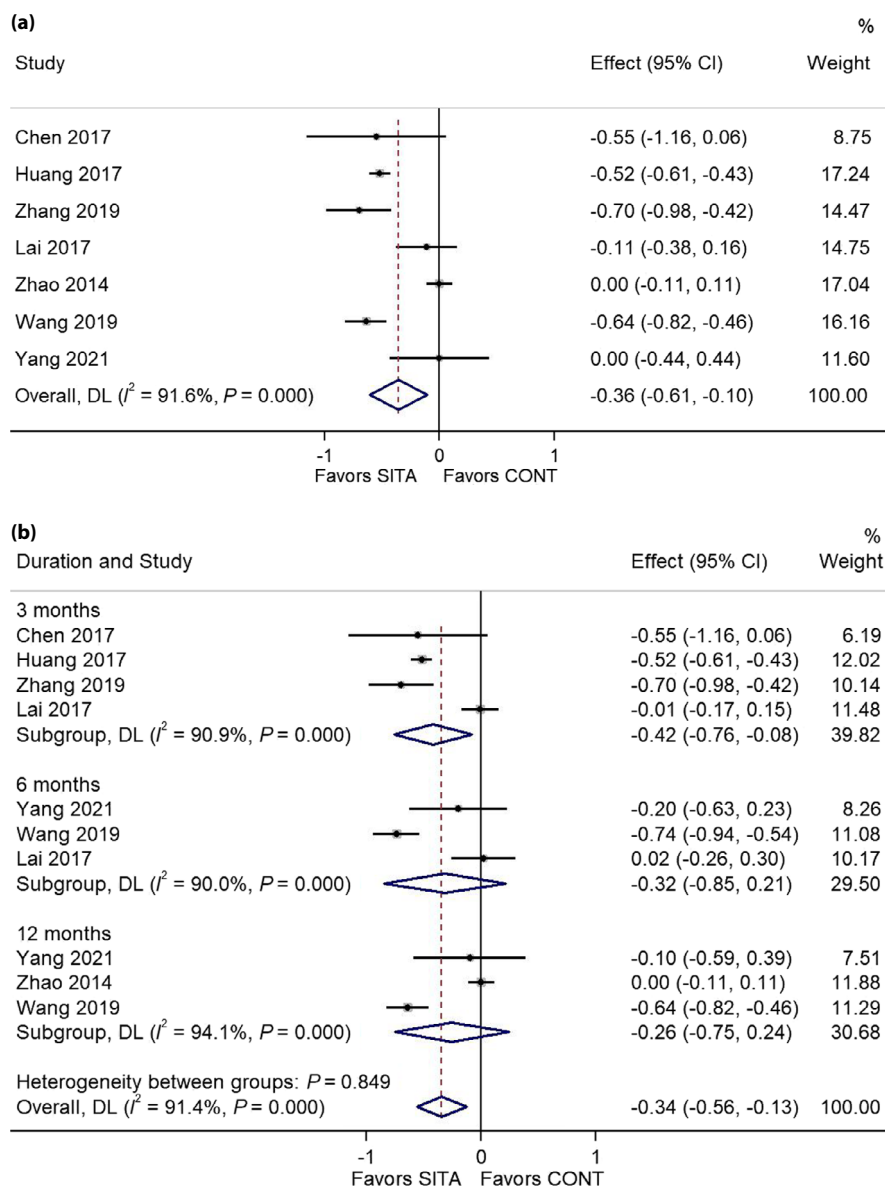
Figure 3 | (a) Hemoglobin A1c levels at the longest follow-up. (b) Hemoglobin A1c levels at different follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.

Publication bias

A funnel plot was carried out to assess publication bias of included studies. The asymmetrical presentation of HbA1c and FCP levels showed that the publication bias might influence the results of meta-analysis (Figure 10). The Egger's test showed no significant publication bias in FCP ($P = 0.680 > 0.05$) and HbA1c levels ($P = 0.979 > 0.05$; Figure 11). The results of the contour-enhanced funnel plot showed the included studies were found not only in the area of significant difference, but also in the area of non-significant difference (Figure 12). Therefore, the interstudy heterogeneity was not the only factor interpreting asymmetrical presentation, potential publication bias and other factors might also contribute to it.

Meta-regression analysis

A meta-regression analysis was carried out to explore the potential correlation between treatment duration, as well as sample size and the effectiveness of intervention. For HbA1c levels, there was no significant relationship for duration (slope 0.03, 95% CI −0.014 to 0.07, $P = 0.147$) or sample size (slope −0.02, 95% CI −0.036 to 0.005, $P = 0.114$). The heterogeneity of FCP was not associated with the duration of intervention (slope
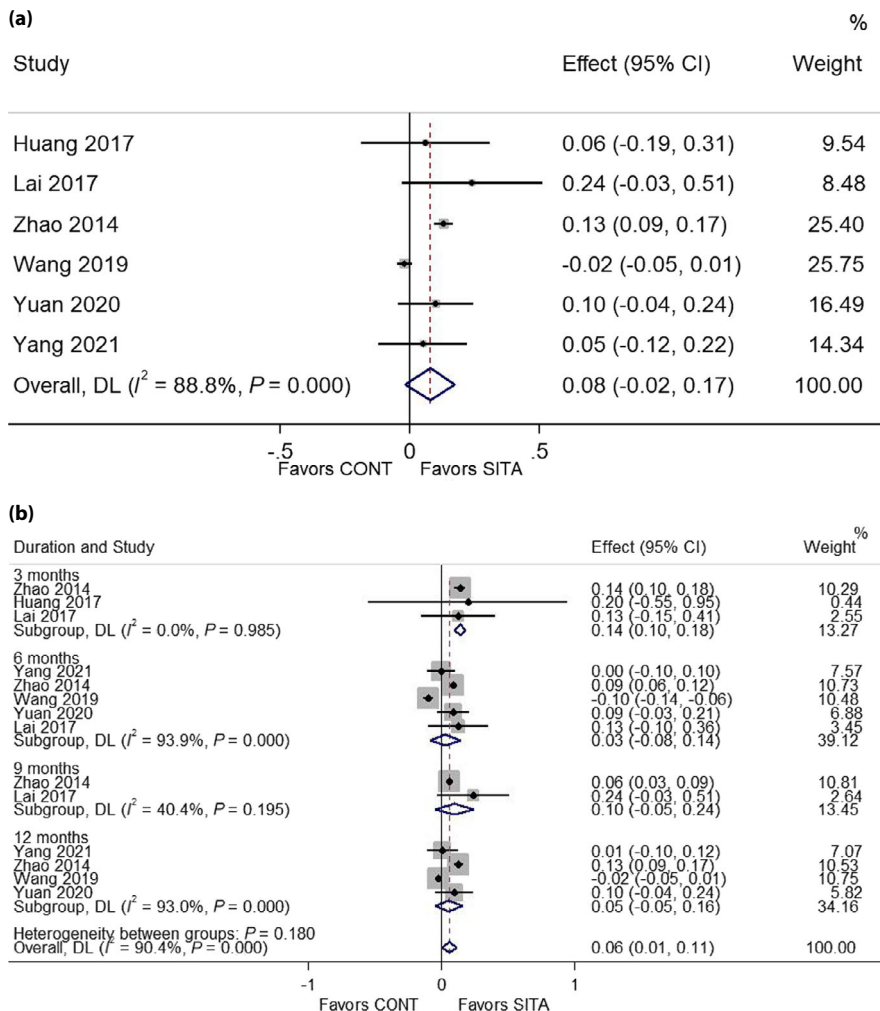
Figure 4 | (a) Fasting C-peptide levels at the longest follow-up. (b) Fasting C-peptide levels at different follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.

−0.002, 95% CI −0.025 to 0.02, $P = 0.782$) and the sample size of each individual study (slope −0.009, 95% CI −0.019 to 0.0006, $P = 0.060$; Figure 13).

DISCUSSION

In the present meta-analysis of the effects and safety of sitagliptin combined with insulin on LADA, our findings showed that compared with insulin treatment, sitagliptin combined with insulin could decrease HbA1c levels, lower fasting blood glucose levels and increase C-peptide levels. This suggested that sitagliptin combined with insulin therapy could improve glycemic control and islet β-cell function in patients with LADA. Thus, sitagliptin combined with insulin therapy might be a better choice for LADA treatment.

As previously reported[21], during the first 3 years after type 1 diabetes mellitus is diagnosed, achieving better glycemic control is related to preserve C-peptide levels. Patients with LADA have low C-peptide levels and show slower progression in islet cell destruction than those with type 1 diabetes mellitus[22]. C-peptide is a marker secreted by islet β-cells, and is not affected by exogenous insulin, which can reflect insulin content in the body and residual function of islet β-cells[23]. Therefore, it is crucial for LADA patients to improve glycemic control and preserve β-cell function. Good glucose control is beneficial for maintaining islet β-cell function and reducing the risk of chronic diabetic complications, as well as diabetes-related deaths[22, 24].

For decades, insulin has been recommended as an essential treatment for β-cell loss to supplement endogenous insulin secretion. It is acknowledged that insulin has the potential to lower blood glucose levels and inhibit inflammatory response by suppressing autoreactive T cells and regulatory cytokines[25]. In addition, some reviews have summarized the mechanisms that exogenous insulin can reverse glucotoxicity, promote β-cell
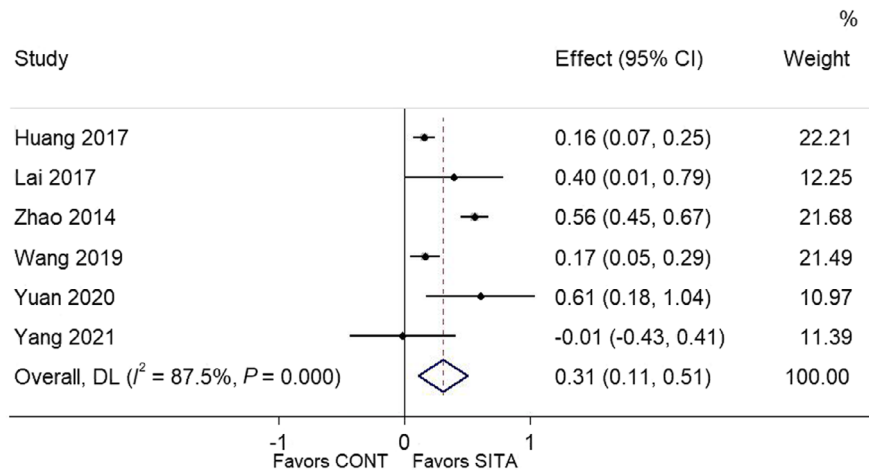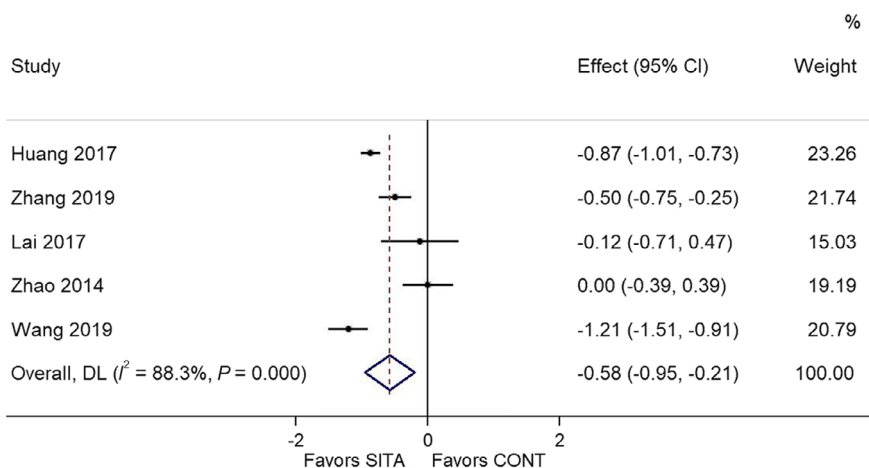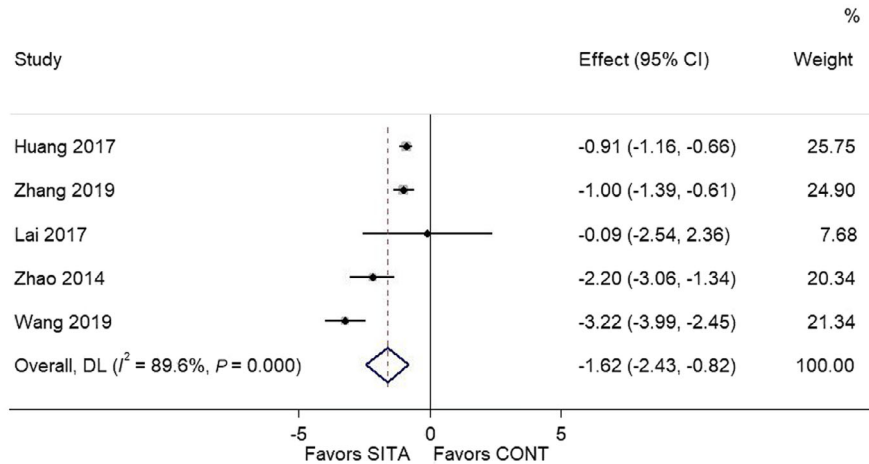
Figure 5 | Levels of 2-hour postprandial C-peptide at the longest follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.
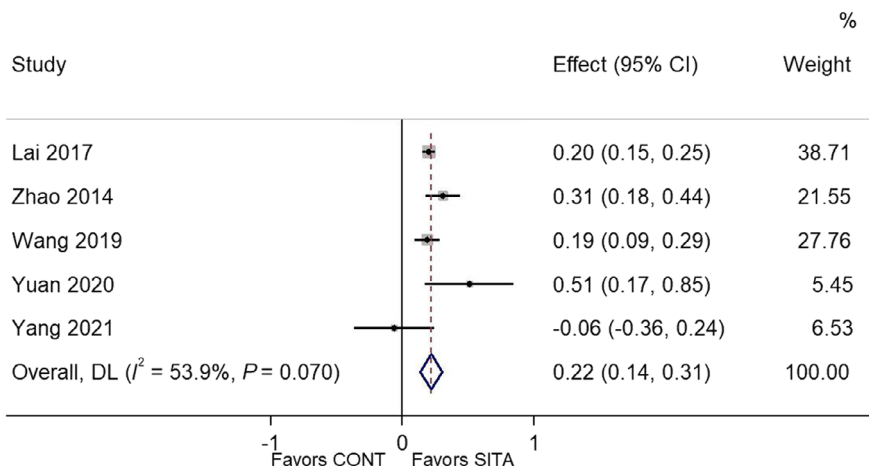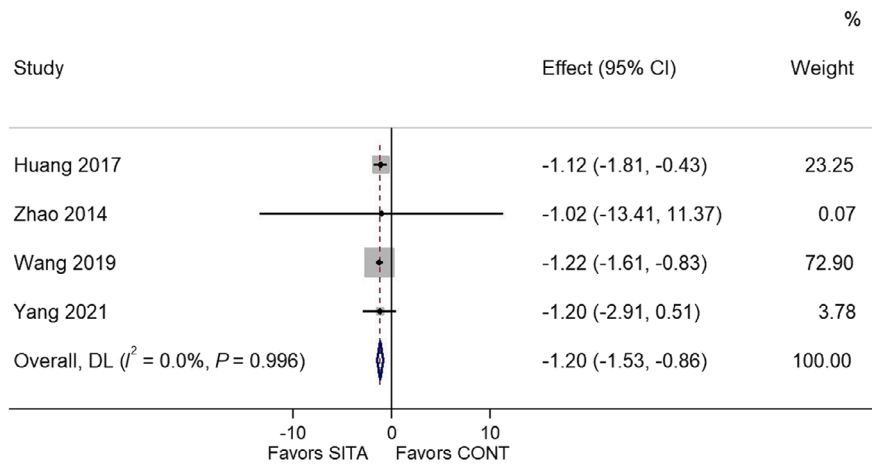

Figure 6 | Changes in C-peptide levels at the longest follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.

Figure 7 | Fasting blood glucose levels at the longest follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.

Figure 8 | Levels of 2-hour postprandial blood glucose at the longest follow-up. CI, confidence interval; CONT, control; SITA, sitagliptin.


Figure 9 | Body mass index levels at the longest fo. CI, confidence interval; CONT, control; SITA, sitagliptin.

rest, leading to endogenous insulin generation, thus achieving glycemic control and improving islet β-cell function[26, 27]. Increasing evidence has emphasized that it is important to initiate early insulin treatment in LADA patients, regardless of endogenous insulin secretion[28]. A previous study proved that LADA patients given insulin treatment could better preserve C-peptide levels and metabolic control than those that received conventional therapy after a 3-year follow-up[29]. DPP-4 inhibitors are oral antidiabetic agents widely used for diabetes treatment. A recent meta-analysis[30] has confirmed that adding DPP-4 inhibitors to existing insulin treatment can significantly reduce HbA1c levels (WMD −0.61, 95% CI −0.74 to −0.48) without increasing the incidence of hypoglycemia. Sitagliptin, a classic DPP-4 inhibitor, has the ability of slowing β-cell reduction, promoting insulin production, as well as decreasing insulin requirements[31]. Current clinical studies on sitagliptin combined with insulin treatment for LADA are increasing.

The present study is the first systematic review and meta-analysis to evaluate the efficacy and safety of sitagliptin plus insulin for the management of LADA by integrating data from eight RCTs. Our systematic review and meta-analysis showed similar results that sitagliptin combined with insulin treatment exerted better effects on downregulating HbA1c levels than insulin therapy alone (WMD −0.36, 95% CI −0.61 to −0.10, $I^2 = 91.6\%$) and preserving islet β-cell function through increasing fasting C-peptide levels (WMD 0.08, 95% CI −0.02 to 0.17, $I^2 = 88.8\%$). The results of this meta-analysis support evidence from previous research[32], which proved that insulin treatment is effective for LADA patients, and DPP-4 inhibitors play a protective role on β-cell function.

Pooled results showed significant heterogeneity ($I^2 > 50\%$, $P < 0.05$) when analyzing the outcome measures, except for BMI levels. The confounding factors, such as the dosage and frequency of insulin treatment, varied between studies.
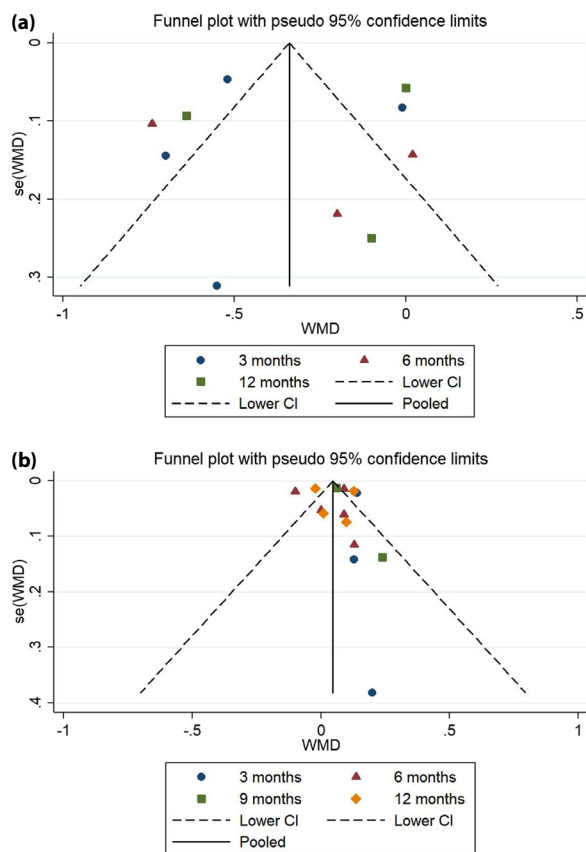
Figure 10 | (a) Funnel plot of hemoglobin A1c. (b) Funnel plot of fasting C-peptide. CI, confidence interval; se(WMD), standard error of the weighted mean difference.
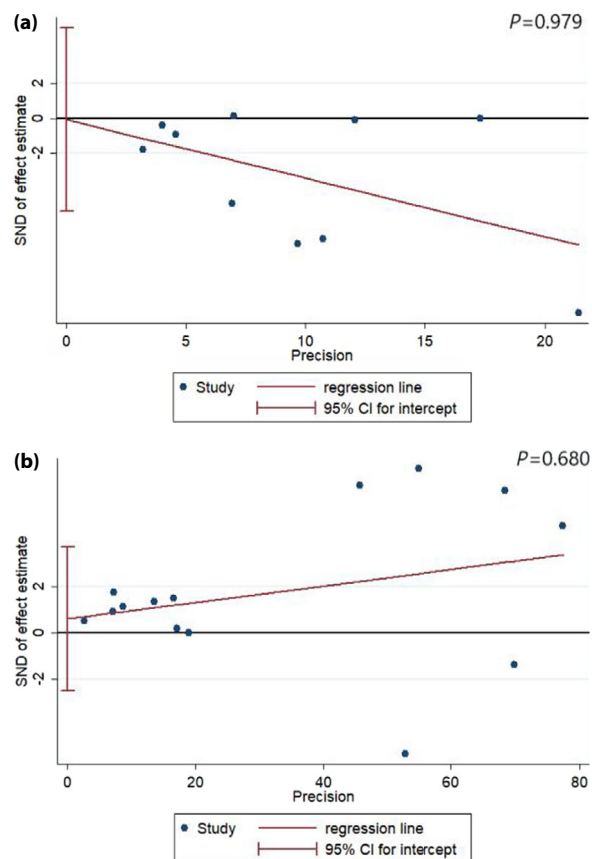
Figure 11 | (a) Egger's funnel plot of hemoglobin A1c. (b) Egger's funnel plot of fasting C-peptide. CI, confidence interval; SND, standard normal deviate.

Furthermore, the duration ranged from 3 to 24 months, thus it is difficult to determine whether the length of follow-up is associated with the improvement of blood glucose levels and β-cell function. The subgroup analyses suggested that longer treatment duration might produce better therapeutic effects, whereas treatment duration and sample size could not adequately interpret heterogeneity in meta-regression analysis.

Several limitations need to be taken into account when further interpreting these results. First, just four included studies have their protocols registered. Prior clinical trial registration can strengthen research transparency, and increase the integrity and authenticity of literature. Second, all included trials mentioned randomization, whereas just four RCTs provided a concrete randomization method, which might lead to selection bias. Most trials did not report allocation concealment and detailed information about blinding, thus influencing the validity of results. Third, significant heterogeneity is presented in the present results, probably due to the limited number of included studies, small sample size, different duration and dosage of insulin. The duration of included trials ranged from 3 months to 24 months. More clinical studies are warranted to assess sitagliptin and insulin treatment for LADA with longer follow-up.

The dosage of insulin for each individual trial was not coincident, depending on judgments of physicians. However, the subgroup analysis of different duration was carried out to minimize the heterogeneity. Fourth, all included studies were from China, which might result in publication bias. Fifth, a few false positive results might be recorded in autoantibody-positive cases due to the detection method variability or limited predictive ability in insulin dependence. A previous study concluded that approximately 4–14% of patients diagnosed as type 2 diabetes are positive for diabetes-related autoantibodies[22]. Thus, the C-peptide levels require long-term follow-up, which providing evidence for the following treatments and the results should be interpreted with cautious.

In summary, the present study provides the latest comprehensive evidence for sitagliptin plus insulin in treating LADA patients, whereas large-scale and well-designed RCTs are required to verify our results, and LADA complications still require further exploration.

In general, the combined therapy of sitagliptin and insulin can lower blood glucose levels, improve islet β cell function and reduce adverse events, which provide an effective and tolerated therapeutic regimen for patients with LADA. However,
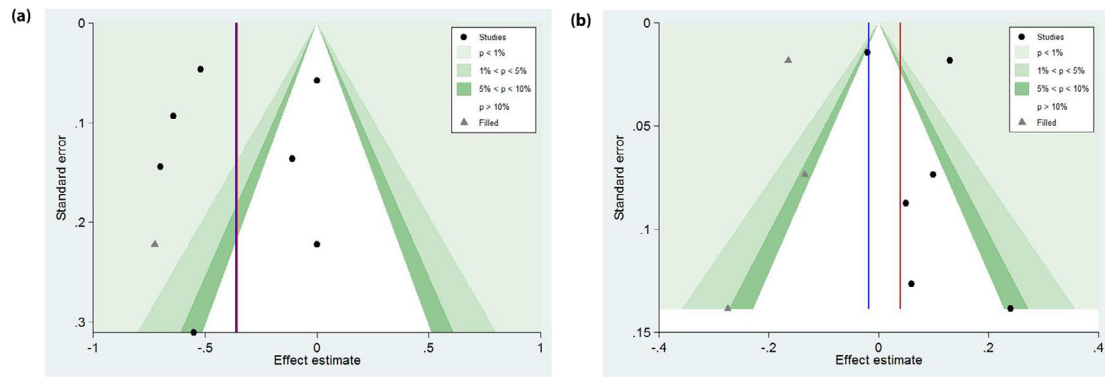
Figure 12 | (a) Contour-enhanced funnel plot assessing publication bias reporting hemoglobin A1c levels in latent autoimmune diabetes in adults patients treated with insulin plus sitagliptin compared to controls. (b) Contour-enhanced funnel plot assessing publication bias reporting FCP levels in latent autoimmune diabetes in adults patients treated with insulin plus sitagliptin compared to controls.
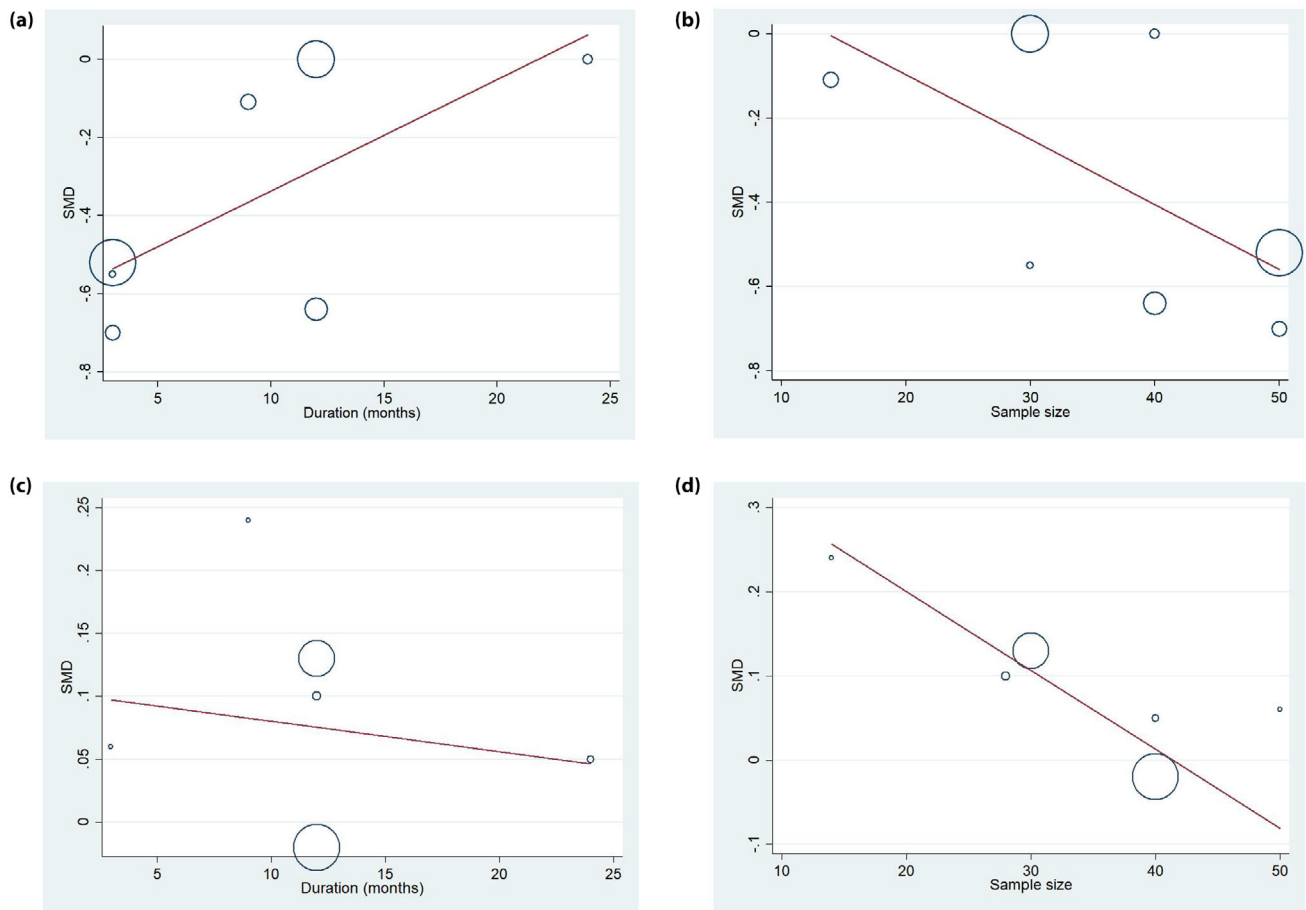
Figure 13 | (a) Average hemoglobin A1c levels during the overall duration. (b) Average hemoglobin A1c levels for sample size of each included study. (c) Average fasting C-peptide levels during the overall duration. (d) Average fasting C-peptide levels for sample size of each included study. SMD, stand mean difference.

more rigorous and well-designed RCTs are required to further validate the present results.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: We registered our protocol in PROSPERO (approval date: 12/06/2021; registration number: CRD42021254508).

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included in the tables and figures.

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