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The Effects of Combination Therapy with Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Co-Transporters 2 Inhibitors on Cardiometabolic Indices: A GRADE Assessed Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose transporter 2 inhibitors (SGLT2i) are a relatively new class of drugs used to improve cardiometabolic risk factors. The aim of this meta-analysis was to systematically evaluate the effects of combination therapy of GLP-1RAs and SGLT2i on cardiometabolic markers in adults.

Methods: MEDLINE, SciVerse Scopus, and Clarivate Analytics Web of Science were thoroughly searched using relevant keywords and MeSH-terms from inception until September 2023 for randomized trials addressing the effects of GLP-1Ras and SGLT2 inhibitors on cardiometabolic markers. Only English-language randomized clinical trials involving adults (≥18 years) treated with GLP-1Ras and SGLT2is, with cardiometabolic outcomes and placebo controls, were included. A random-effects meta-analysis was performed to assess changes in glucose hemostasis, lipid profile, blood pressure, and anthropometric parameters. Subgroup analyses were conducted to assess the impact of the study on health status, intervention types, concurrent diets, study design and blinding, participant age, and treatment duration. PROSPERO registration: CRD42023471047.

Results: Four studies (5 arms) involving 249 patients were analyzed, which showed that treatment with GLP-1RA and SGLT2 inhibitors reduced fasting plasma glucose (FPG) by an average of -11.8 mg/dL (95% confidence interval [CI]: -16.7 to -6.9; p<0.001), systolic blood pressure (SBP) by an average of -7.4 mmHg (95% CI: -10.6 to -4.1; p<0.001), body weight by an average of -3.8 kg (95% CI: -5.2 to -2.4; p<0.001), and waist circumference by an average of -3.5 cm (95% CI: -5.8 to -1.1; p=0.003).

Conclusion: GLP-1RA and SGLT2 inhibitor therapy improve cardiometabolic outcomes by lowering FPG, SBP, BW, and WC, which may alleviate downstream complications. Further research is needed to characterize the long-term effects on cardiometabolic markers.

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1. Introduction

Cardiometabolic diseases, including hypertension, type 2 diabetes (T2D), coronary heart disease (CHD), and obesity, are now recognized as a growing health challenge globally with almost 18 million deaths reported in 2019. [1] In the United States, obesity affects 41.9% of adults, while T2D impacts approximately 463 million people worldwide, with risk factors including glucose intolerance, hypertension, and dyslipidemia.[2-4] Globally, hypertension affects 26% of the population, with ongoing efforts to reduce its prevalence.[2] Global burden of CVD predicts 20.5 million cardiovascular deaths by 2025, indicating the increasing trend of these conditions.[5]

Recent pharmacological advancements have shown glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors as promising therapies for cardiometabolic diseases management.[6-10] Moreover, recent evidence has unveiled numerous pleiotropic action for these classes of drugs.[11-15] SGLT2 inhibitors, such as empagliflozin and canagliflozin, block glucose reabsorption in the renal proximal tubule, increasing urinary glucose excretion, which promotes weight loss and blood pressure reduction.[16, 17] Although human studies have not been conducted, these findings are in line with animal studies that represent compensatory hyperphagia in response to SGLT2 inhibition.[18, 19] To optimize treatment, it is crucial to study this issue in humans and gain insight into the mechanisms through which SGLT2 inhibitors may affect appetite regulation and food consumption. GLP-1RAs, such as liraglutide and dulaglutide, enhance glucose-dependent insulin synthesis and secretion, stimulate beta-cell proliferation, suppress appetite signaling in the brain and increase satiety, leading to significant weight loss and improved glycemic control.[20, 21] As the impact of GLP-1RAs on central nervous system (CNS), combining GLP-1RAs and SGLT2i may enhance cardiometabolic outcomes by increasing weight loss. Evidence from three studies demonstrated that this combination leads to more significant reductions in both body weight and blood glucose levels compared to using each treatment alone.[22-24]

Despite the established benefits of combination therapies, comprehensive studies on the combined use of GLP-1RAs and SGLT2i are limited. Preliminary evidence, including a phase 2 study demonstrating weight loss with combined dapagliflozin and exenatide in obese adults without diabetes, and preclinical data suggesting GLP-1RAs may counteract SGLT2i-induced hyperphagia, indicate potential synergistic effects.[25] However, large-scale, long-term human trials are sparse, leaving a critical evidence gap given the high prevalence of cardiometabolic multimorbidity and the need for effective, durable interventions.

Therefore, this systematic review and meta-analysis aims to evaluate the efficacy of combining GLP-1RAs and SGLT2 inhibitors on cardiometabolic indices. By synthesizing data from clinical trials, this study seeks to provide a comprehensive assessment of the combined therapy's impact on outcomes such as glycemic control, weight loss, and cardiovascular risk factors, thereby informing future therapeutic strategies for managing cardiometabolic diseases.

2. Method:

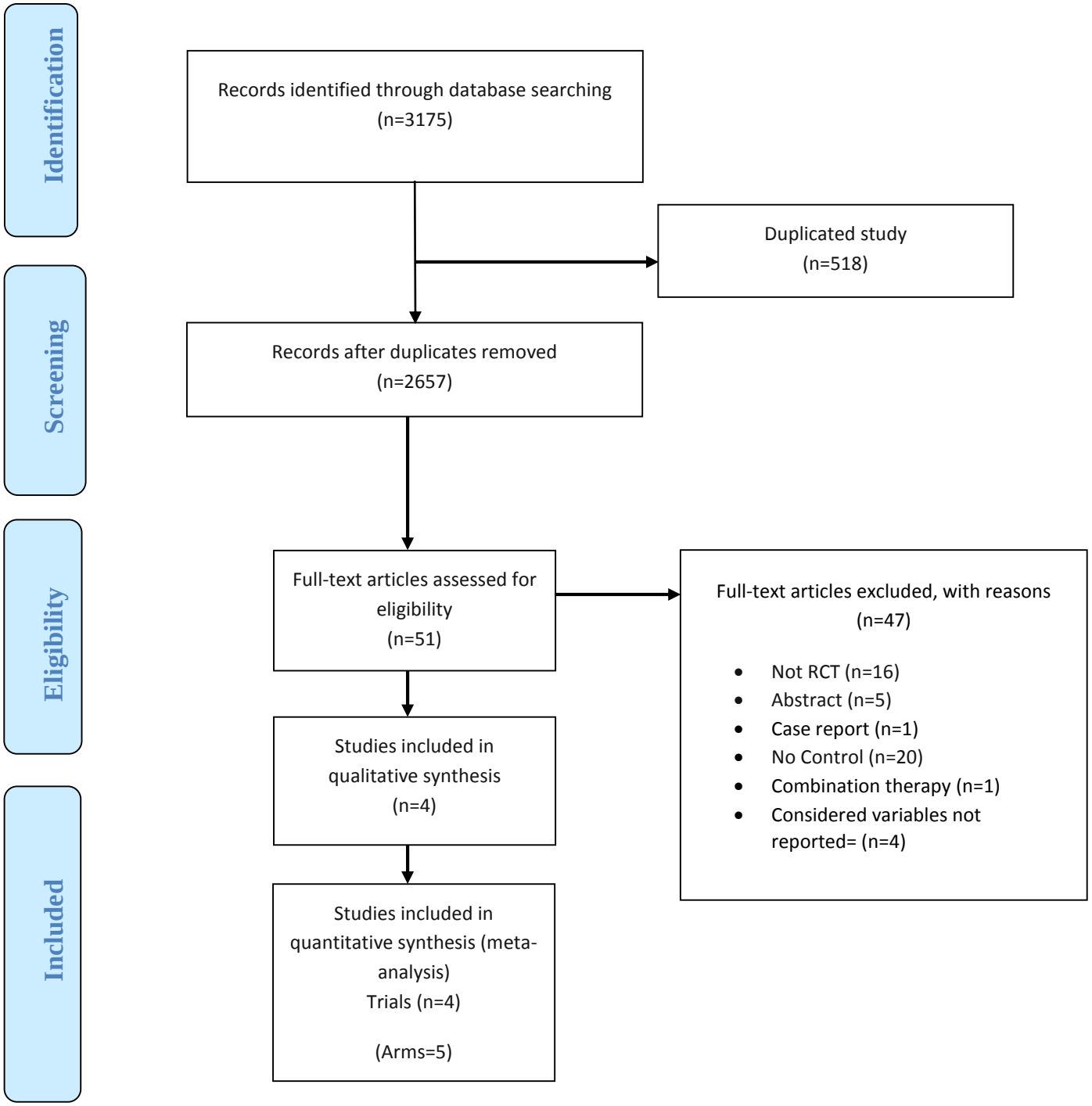
We use the PRISMA method, which includes evidence-based elements for the documentation of systematic reviews and meta-analyses, to ensure transparency, completeness and adherence to best practice in our research endeavors.[26]

2.1. Search strategy:

To identify all relevant clinical trials up to September 2023, a comprehensive search was conducted in various online databases, including SCOPUS (http://www.scopus.com), MEDLINE (http://www.ncbi.nlm.nih.gov/PubMed) and Web of Science (https://clarivate.com/scientific-and-academic-research/). The searches in these databases were performed using the specified keywords and MeSH terms (the search strategy is shown in Supplementary **Table S1**). The results from these databases were then collated and

organized using the Reference Manager software; careful screening was then performed to eliminate duplicate studies. In addition, the reference lists of relevant papers were thoroughly checked and previous reviews and search strategies were analyzed to ensure that all potentially overlooked studies were included. Only articles written in English were included in the study. The entire literature search process is visualized in **Figure 1**.

Figure 1. PRISMA flow diagram



1.1. Inclusion criteria

Studies were included independently by two authors based on the PICOS framework. The population included adults aged 18 years and above who received treatment with GLP-1RAs and SGLT2 inhibitors for any medical indication. The intervention consisted of a combination of GLP-1 RAs and SGLT2 inhibitors, with comparison to placebo or control groups. Outcomes of interest included cardiometabolic indices including glucose hemostasis, lipid profile, blood pressure and anthropometric parameters. Only randomized controlled trials (RCTs), including both parallel and crossover designs, were considered. Additionally, only studies published in English were included.

1.2. Exclusion criteria

The studies that did not fulfill the following criteria were excluded: A) studies that were not conducted in non-clinical subjects; B) studies that were duplicates; C) studies that involved animals, in vitro experiments, observational studies and reviews; D) studies that did not measure cardiometabolic indices; E) studies that involved children; F) studies that did not involve treatment with glucagon-like peptide one receptor agonists and sodium-glucose co-transporters.

1.3. Data extraction

Information including the first author's name, year of publication, study location, study design, participant characteristics, sample size, intervention details including dose, duration, supplementation, and mean ± standard deviation (7) and changes of outcomes including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), body weight and waist circumference (WC) before and after intervention in both treatment and control groups were obtained from all studies by two independent authors (S. M. and MS. M.).

1.4. Risk of bias assessment:

To assess the risk of bias for each study included in the current meta-analysis, we used the Cochrane Risk of Bias Tool (ROB 2).[27] This tool included five components: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. If a study had methodological concerns that could have affected its results, a “high risk” was assigned for each area. If there were no deficiencies in this area, a “low risk” rating was assigned. If the information was insufficient to determine the impact of the study, an “some concerns” rating was assigned. However, if the study met the criteria for “low risk” in all dimensions, it was rated as high quality and had a low overall risk of bias. Two researchers worked independently to assess the potential for bias: I. R. and M. H.

1.5. Statistical analysis:

We plan to conduct a random effects analysis on the effects of the combination treatment on outcomes in the intervention and control groups. The SD was calculated in research projects reporting the standard error of the mean[28] by multiplying the SEM by the square root of the sample size as follows: $SD = SEM \times \sqrt{n}$. We used a random effects model that accounted for differences from one study to the next to obtain an accurate picture of the overall effect sizes. The I^2 statistic and Cochrane's Q test were used to determine the presence of heterogeneity. It was determined that there was significant heterogeneity between studies if the I^2 value was $> 50\%$ or $P < 0.05$.[29] To assess the influence of confounding factors on the overall effect size and to identify potential sources of heterogeneity, we conducted a subgroup analysis. Factors for inclusion in the subgroup analysis were selected based on predefined criteria outlined in the study protocol, prioritizing feasibility, consistency, and their potential

to significantly impact the effect size. Subgroup analyses were performed considering variables such as mean age, health status, study type and design, follow-up duration, intervention type, and study quality. To evaluate the influence of individual studies in our analysis, we will employ the leave-one-out method to assess the impact of each study on the overall effect size.[30] Stata was used for the meta-analysis, and a P value < 0.05 was considered a significant.

1.6. Grading the evidence

To evaluate and summarize the body of evidence related to each outcome analyzed in the meta-analysis, we employed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. This framework categorizes evidence obtained from systematic reviews and meta-analyses into four distinct categories: "high," "moderate," "low," or "very low." The quality of the reported effect size can be upgraded or downgraded based on the study's design, as well as other methodological and statistical limitations. Two independent reviewers (LS. B and AM. A), took into consideration factors for each outcome to assess the certainty of the estimate. These factors included study design, risk of bias, consistency, precision, directness, presence of a substantial effect, dose-response gradient, and publication bias.[31]

3. Results:

3.1. Study selection

The systematic review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes), the methodology of which is shown in **Figure 1**. Initially, a total of 3175 studies were identified, which were reduced to 2657 articles after elimination of duplicates. Subsequent screening of titles and abstracts led to the exclusion of 2606 articles, leaving 51 studies for a comprehensive review. Ultimately, 4 of these studies met the criteria for inclusion in the systematic review.[25,32-34]

3.2. Study characteristics

This meta-analysis includes four studies from the Netherlands,[34] Sweden,[25] the USA,[33] and one multicenter study.[32] The studies were published between 2016[32] and 2022,[33,34] and included a total of 5 arms. The number of participants in these studies ranged from 32 to 65,[33,34] and most of them had diabetes mellitus,[32,34] with the exception of one study that included healthy obese individuals. The average age of participants ranged from 50.4 years to 63.5 years.[33,34] All RCTs had a parallel design, with the exception of one study that used a cross-over design.[34] In three of the studies, dapagliflozin was administered,[25,33,34] while in one study canagliflozin was used as an SGLT2 inhibitor.[32] All studies used exenatide as the GLP-1 agonist receptor drug. The dosage of the SGLT2 inhibitor was uniformly 10 mg/day in all studies, while the dosage of exenatide in the treatment group ranged from 5 µ/day to 2 mg/week.[25,33] In the control group, all participants received the placebo, and the intervention studies lasted between 16 and 24 weeks.[25,34] **Table 1** summarizes all experimental characteristics of the studies.

Table 1. Characteristics of included studies

First author, year, country	Design	Participants(n) Int/con	Health condition	Age means (year) Int/con	Intervention			Duration of intervention [23]	Outcomes (Changes, mg/dl, kg, mmHg, cm, %)	
					Treatment group	Control group	Dose		Treatment group	Control group
Van Ruiten, 2022, Netherlands	RCT-DB-Crossover	16/16	T2DM	63.5	SGLT2 inhibitor (Dapagliflozin)+GLP-1 RA (Exenatide)	Placebo	10 mg/day Dapagliflozin+10 µg twice daily Exenatide	16	BW -3.2±2 HbA1c -1.48±1.08	BW -0.25±2.2 HbA1c -0.2±0.84
López-Cano, 2022, USA	RCT-NB-Parallel	24/25	T2DM Obesity awaiting bariatric surgery	50.4	SGLT2 inhibitor (Dapagliflozin)+GLP-1 RA (Exenatide)	Placebo	10 mg/day Dapagliflozin+ exenatide twice daily (weeks 1-4; 5 µg/day, weeks 5 - 16; 10 µg/day)	24	BMI -2.7±2.12 BW -6.6±4.87 LDL -15.7±28.6 HDL 1.2±4.99 TG -55.8±123.12 FPG -51.6±72.98 HbA1c -1.6±0.87 SBP -13.2±17.74 DBP -1.1±11.99 WC -3.6±6.12	BMI 0.6±2.04 BW 1.5±5.48 LDL -0.2±31.37 HDL 2.2±5.99 TG 11.51±100.09 FPG -44±33.62 HbA1c -1.5±1.14 SBP -7.2±21.42 DBP -4.8±11.6 WC 0.8±6.25
Fulcher, 2016, multi center	RCT-DB-Parallel	35/30	T2DM	60.8	Canagliflozin (SGLT2) +GLP1	Placebo	100 mg	18	BW -3.3±2.48 LDL 0.22±21.32 HDL 1.65±5.77 TG 2.35±63.68 HbA1c 0.16±0.82 SBP -7±12 DBP -2.8±7.39	BW -0.6±3.3 LDL 5.1±22.65 HDL 0.97±6.62 TG 4.71±63.33 HbA1c -0.9±0.76 SBP 1.1±11.99 DBP -0.8±7.39
Fulcher, 2016, multi center	RCT-DB-Parallel	30/30	T2DM	61.2	Canagliflozin (SGLT2) +GLP1	Placebo	300mg	18	BW -3.7±2.13 LDL 11.9±22.42 HDL 2.29±5.86	BW -0.6±3.3 LDL 5.1±22.65 HDL 0.97±6.62

									TG 8.12±60.3 HbA1c -0.83±0.67 SBP -6.9±11.99 DBP -2.4±7.22	TG 4.71±63.33 HbA1c -0.9±0.76 SBP 1.1±11.99 DBP -0.8±7.39
Lundkvist, 2017, Sweden	RCT-DB-Parallel	23/20	Obese adults without diabetes	51.75	Dapagliflozin (SGLT2) +Exenatide (GLP1)	Placebo	SGLT2 10 mg/day - GLP1 2 mg/week	24	BW -4.47±3.85 LDL -6.57±20.11 HDL 0.38±6.96 TG -8.85±15.94 TC -6.19±23.97 FPG -7.40±8.30 HbA1c -0.36±0.19 SBP -9.8±9.66 DBP 1.6±10.76 HR 2.7±6.6 WC -5.3±5.26	BW -0.27±3.74 LDL -8.5±19.33 HDL -3.09±6.96 TG -0.26±39.86 TC -10.05±23.97 FPG 4.5±8.1 HbA1c -0.15±0.18 SBP -3.1±9.46 DBP 2.4±10.83 HR 0.5±6.61 WC -2.5±5.24

Abbreviations: RCT: randomized clinical trial, Int: Intervention, Con: Control, SB: Single-Blind, DB: Double-Blind, TB: Triple-Blind, NR: Not Reported T2DM: Type 2 diabetes mellitus, SGLT-2: Sodium-glucose co-transporter-2, GLP-1: Glucagon-like peptide-1, BW: Body Weight, BMI: Body mass index, LDL: low-Density Lipoproteins, HDL: high-Density Lipoprotein, TG: Triglycerides, FPG: Fasting plasma glucose, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, WC: Waist Circumference

3.3. Quality assessment

Following evaluation using the ROB 2 tool, three of the four studies demonstrated a low risk of bias in the randomization process, while one study raised some concerns in this area. The Lopez-Cano study exhibited a high risk of bias in both the domains of deviations from the intended intervention and outcome measurement, alongside concerns regarding missing outcome data.[33] Similarly, in the studies by Ruiten and Lundkvist, issues were identified in the outcome measurement domain.[25,34] Overall, among the four randomized controlled trials (RCTs) assessed, one study was deemed to be of low quality,[33] while the remaining three presented varying levels of concern.[25,32,34] A comprehensive overview of the experimental characteristics of these studies can be found in Table 2.

Table 2. Risk of bias for analysis

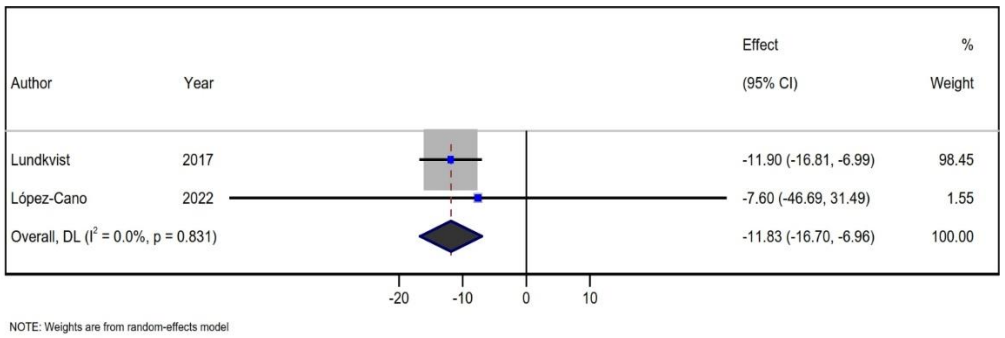
	Bias						
Study	**Randomization process**	**Deviations from intended interventions**	**Missing outcome data**	**Outcome measurement**	**Selection of reported results**	**Overall**	**Comment for overall bias**
Ruiten, 2022	✓	✓	✓	~	✓	~	It is unclear whether the outcome assessors were blinded, as this information was not mentioned.
López-Cano, 2022	✓	✗	~	✗	✓	✗	Patients who are not blind and the individual responsible for assessing outcomes.
Fulcher, 2016	✓	✓	✓	~	✓	~	Patients without blindness, healthcare personnel, and the individual responsible for assessing outcomes.
Lundkvist, 2017	~	✓	✓	✓	✓	~	The method used to perform randomization was not clearly described.

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

3.4. Primary outcomes

3.4.1. Glucose hemostasis

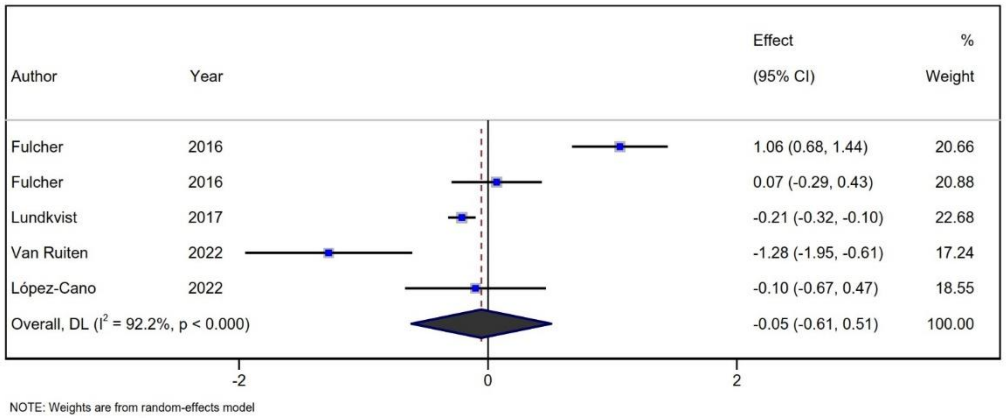
A meta-analysis of two studies with 92 participants showed that combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist significantly lowered FPG levels (WMD: -11.8 mg/dL; 95% confidence interval [CI]: -16.7 to -6.9; p<0.001) without significant heterogeneity (I^2=0%, p=0.8), as illustrated in **Figure 2A.**[25,33]



(A)

Figure 2A. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on FPG (A), and HbA1c (B) levels in trials.

Furthermore, a pooled analysis of four studies (with 5 arms) comprising 249 participants indicated that treatment with SGLT2 inhibitor and GLP-1 receptor agonist versus placebo did not significantly reduce the levels of HbA1c (WMD: -0.05%; 95% CI: -0.6 to 0.5; p=0.8); however, considerable heterogeneity was observed (I^2=92.2%, p<0.001) as presented in **Figure 2B.**[25,32-34]



(B)

Figure 2B. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on HbA1c levels in trials.

3.4.2. Lipid profile

In a comprehensive evaluation of the combination therapy of SGLT2 inhibitors and GLP-1 receptor agonists on TG levels, the results of three studies (with 4 arms) with 217 participants showed a non-significant reduction in TG levels (WMD: -8.4 mg/dL; 95% CI: -26.03 to 9.05; p=0.3). In addition, the analysis revealed non-significant heterogeneity (I^2=25.9%, p=0.2; **Figure 3A**).[25,32,33]

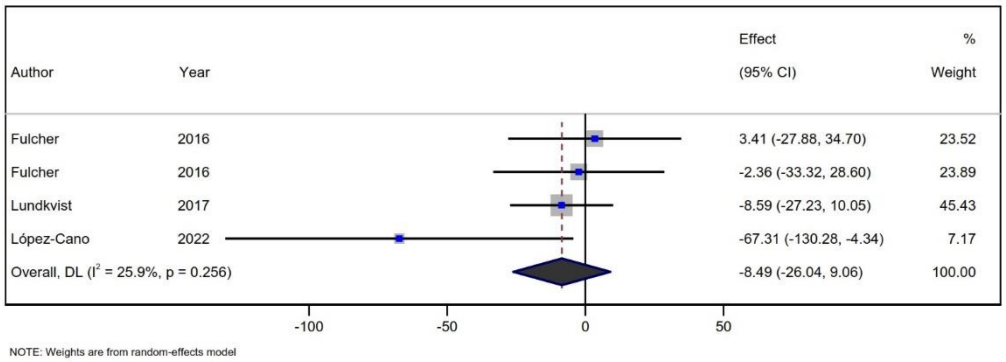


Figure 3A. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on TG levels in trials.

Based on a meta-analysis of data from three different studies (4 arms) with 217 participants, it can be concluded that the joint use of SGLT2 inhibitors and GLP-1 receptor agonists does not significantly increase HDL levels (WMD: 0.8 mg/dL; 95% CI: -0.8 to 2.4; p=0.3; **Figure 3B**).[25,32,33]

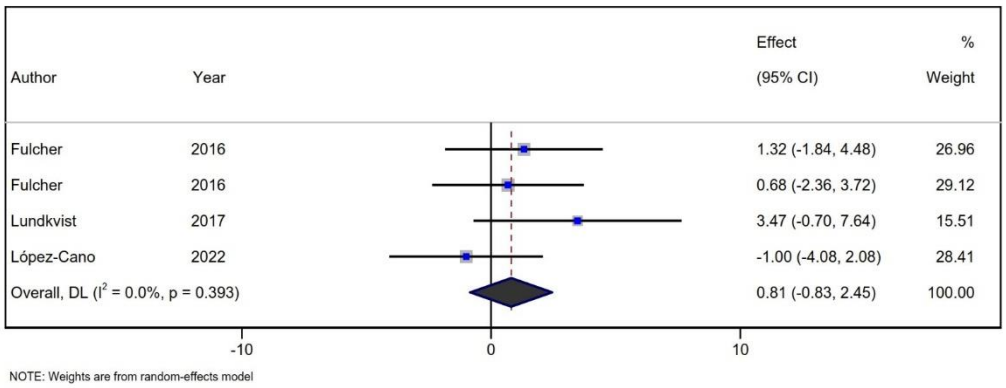


Figure 3B. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on HDL levels in trials.

There is no appreciable heterogeneity in the results (I^2: 0%, p= 0.3). A pooled analysis of three RCTs (4 arms) with 217 subjects also shows that these treatment methods have no significant effect on LDL levels (WMD: -1.7 mg/dL; 95% CI: -10.01 to 6.6; p=0.6; **Figure 3C**).[25,32,33] However, there is moderate heterogeneity (I^2: 44.6%, p=0.1) between the results.

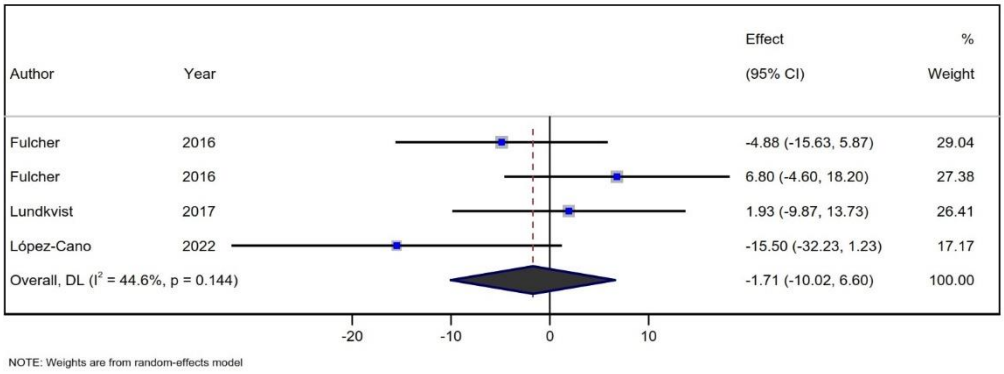


Figure 3C. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on LDL levels in trials.

3.4.3. Blood pressure

According to a meta-analysis of data from three different studies (4 arms) with 217 participants, a combination therapy of SGLT2 inhibitors and GLP-1 receptor agonists significantly SBP (WMD: -7.4 mmHg; 95% CI: -10.6 to -4.2; p<0.001) without significant heterogeneity (I^2=0%, p=0.9; **Figure 4A**).[25,32,33]

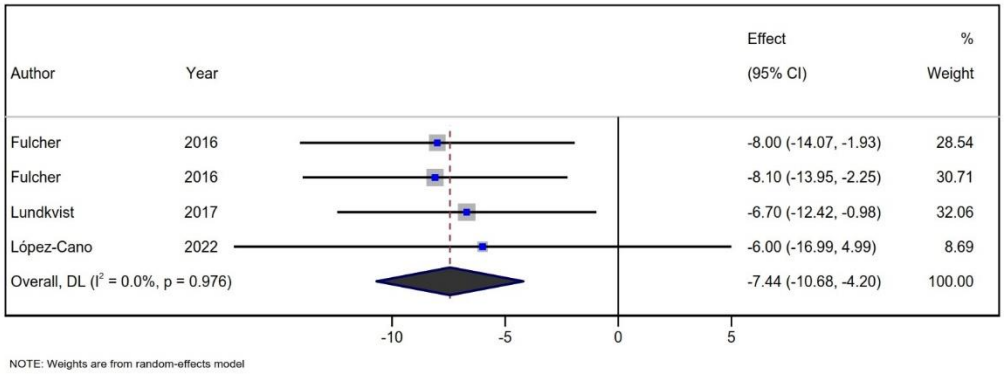


Figure 4A. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on SBP levels in trials.

After analyzing data from four different studies with 217 participants, it was found that the combined use of SGLT2 inhibitors and GLP-1 receptor agonists resulted in a non-significant reduction in DBP (WMD: -1.04 mmHg; 95% confidence interval: -3.2 to 1.2; p=0.3; **Figure 4B**).[25,32,33] The results were consistent across studies (I^2: 0%, p= 0.5), indicating no significant heterogeneity in the results.

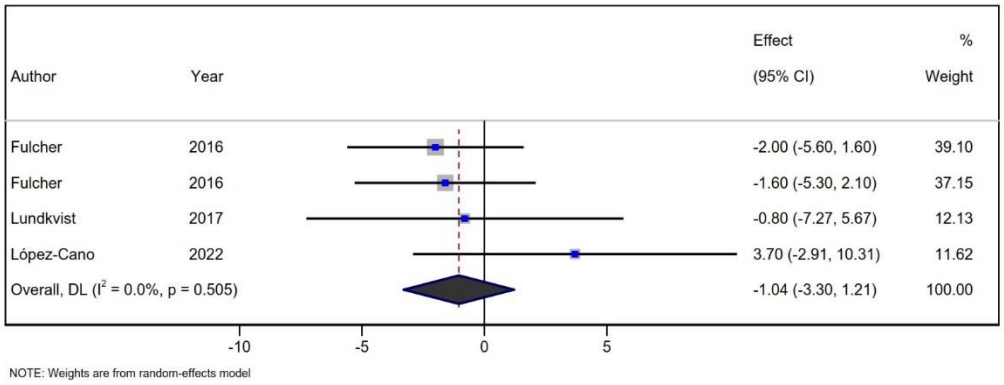


Figure 4B. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on DBP levels in trials.

3.4.4. Anthropometric parameters

A combination therapy of SGLT2 inhibitors and GLP-1 receptor agonists can significantly reduce body weight (WMD: -3.8 kg; 95% CI: -5.2 to -2.4; p<0.001). This was the result of a meta-analysis of data from four separate studies with 249 participants (5 arms). However, the heterogeneity of the results was remarkable (I^2=67.9%, p=0.01; **Figure 5A**).[25,32-34]

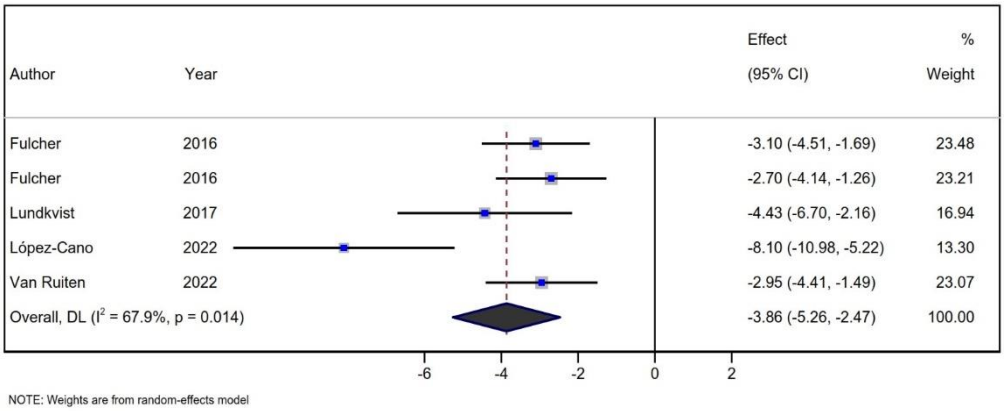


Figure 5A. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on BW levels in trials.

Further analysis of data from two studies with 92 participants showed a significant reduction in waist circumference when SGLT inhibitors and GLP-1 receptor agonists were used together (WMD: -3.5 cm; 95% CI: -5.8 to -1.1; p=0.003; **Figure 5B**). The results showed no significant heterogeneity across studies (I^2: 0%, p= 0.5), suggesting that the results are consistent.

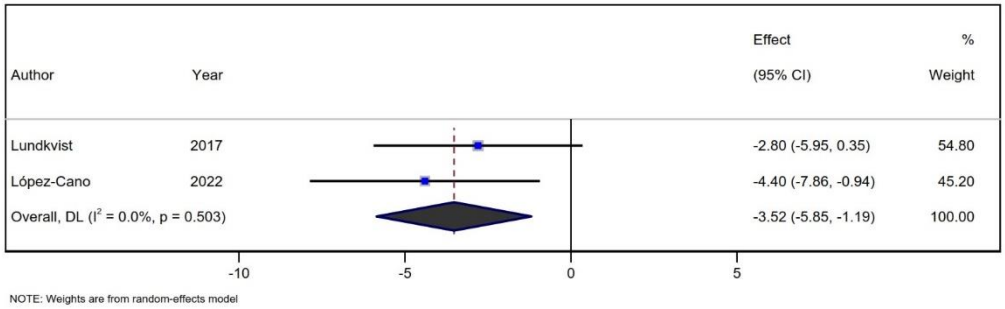


Figure 5B. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of combination therapy with GLP-1RAs and SGLT2 inhibitor treatment on WC levels in trials.

3.5. Subgroup analysis

Subgroup analysis revealed that the duration of the intervention could contribute to heterogeneity in the effect size of HbA1c. Interventions lasting more than 20 weeks demonstrated a greater reduction in HbA1c levels compared to those lasting less than 20 weeks. Additionally, the quality of the included RCTs may influence the effect size observed for SBP. Studies categorized as having "some concerns" regarding bias were associated with a reduction in SBP, whereas those identified as having a high risk of bias showed less pronounced effects (**Table 3**).

Table 3. Description of subgroup analyses of Glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter 2 inhibitors as combination therapy for cardiometabolic risk factors.

	Number of studies	WMD (95%CI)	P-value	heterogeneity	
				P heterogeneity	I^2
Subgroup analyses of GLP & SGLT supplementation on HbA1c					
Overall effect	5	-0.05 (-0.6, 0.5)	0.8	<0.001	92.2%
Blinding					
RCT-DB	4	-0.04 (-0.7, 0.6)	0.8	<0.001	94.2%
RCT-NB	1	-0.1 (-0.6, 0.4)	0.7	-	-
Study design					
Parallel	4	0.2 (-0.3, 0.7)	0.4	<0.001	92.4%
Crossover	1	-1.2 (-1.5, -0.6)	<0.001	-	-
Intervention type					
Conogliflozin	2	0.5 (-0.4, 1.5)	0.2	<0.001	92.6%
Dapagliflozin	3	-0.4 (-1.04, 0.1)	0.1	0.008	79.5%
Duration of intervention (weeks)					
<20	3	-0.01 (-1.1, 1.1)	0.9	<0.001	94.7%
>20	2	-0.2 (-0.3, -0.09)	<0.001	0.7	0.0%
Health Status					
T2DM	4	-0.03 (-0.8, 0.8)	0.9	<0.001	92.4%
Obese Adult	1	-0.2 (-0.3, -0.09)	<0.001	-	-
Study quality					
Some concerns	3	-0.2 (-0.3, 0.7)	0.4	<0.001	92%

High risk of bias	1	-1.2 (-1.9, -0.6)	<0.001	-	-
Baseline mean age (years)					
>60	3	-0.01 (-1.1, 1.1)	0.9	<0.001	94.7%
<60	2	-0.2 (-0.6, 0.5)	<0.001	0.7	0.0%
Subgroup analyses of GLP & SGLT supplementation on SBP					
Overall effect	4	-7.4 (-10.6, -4.1)	<0.001	0.9	0.0%
Blinding					
RCT-DB	3	-7.5 (-10.6, -4.1)	<0.001	0.9	0.0%
RCT-NB	1	-6 (-16.9, 4.9)	0.2	-	-
Study design					
Parallel	4	-7.4 (-10.6, -4.1)	<0.001	0.9	0.0%
Intervention type					
Conogliflozin	2	-8.05 (-12.2, -3.8)	<0.001	0.9	0.0%
Dapagliflozin	2	-6.5 (-11.6, -1.4)	0.01	0.9	0.0%
Duration of intervention (weeks)					
<20	2	-8.05 (-12.2, -3.8)	<0.001	0.9	0.0%
>20	2	-6.5 (-11.6, -1.4)	0.01	0.9	0.0%
Health Status					
T2DM	3	-7.7 (-11.7, -3.8)	<0.001	0.9	0.0%
Obese Adult	1	-6.7 (-12.4, -0.9)	0.02	-	-
Study quality					
Some concerns	3	-7.5 (-10.9, -4.1)	<0.001	0.9	0.0%
High risk of bias	1	-6 (-16.9, 4.9)	0.2	-	-
Baseline mean age (years)					
>60	2	-8.05 (-12.2, -3.8)	<0.001	0.9	0.0%
<60	2	-6.5 (-11.6, -1.4)	0.01	0.9	0.0%
Subgroup analyses of GLP & SGLT supplementation on DBP					
Overall effect	4	-1.04 (-3.2, 1.2)	0.3	0.5	0.0%
Blinding					
RCT-DB	3	-1.6 (-4.06, 0.7)	0.1	0.9	0.0%
RCT-NB	1	3.7 (-2.9, 10.3)	0.2	-	-
Study design					
Parallel	4	-1.04 (-3.2, 1.2)	0.3	0.5	0.0%
Intervention type					
Conogliflozin	2	-1.8 (-4.3, 0.7)	0.1	0.8	0.0%
Dapagliflozin	2	1.4 (-3.2, 6.02)	0.5	0.3	0.0%
Duration of intervention (weeks)					
<20	2	-1.8 (-4.3, 0.7)	0.1	0.8	0.0%

>20	2	1.4 (-3.2, 6.02)	0.5	0.3	0.0%
Health Status					
T2DM	2	-1.8 (-4.3, 0.7)	0.1	0.8	0.0%
Obese adults without diabetes	1	-0.8 (-7.2, 5.6)	0.8	-	-
T2DM Obesity awaiting bariatric	1	3.7 (-2.9, 10.3)	0.2	-	-
Study quality					
Some concerns	3	-1.6 (-4.06, 0.7)	0.1	0.9	0.0%
High risk of bias	1	3.7 (-2.9, 10.3)	0.2	-	-
Baseline mean age (years)					
>60	2	-1.8 (-4.3, 0.7)	0.1	0.8	0.0%
<60	2	1.4 (-3.2, 6.02)	0.5	0.3	0.0%
Subgroup analyses of GLP & SGLT supplementation on TG					
Overall effect	4	-8.4 (-26.03, 9.05)	0.3	0.2	25.9%
Blinding					
RCT-DB	3	-4.7 (-19.02, 9.4)	0.5	0.8	0.0%
RCT-NB	1	-67.3 (-130.2, -4.3)	0.03	-	-
Study design					
Parallel	4	-8.4 (-26.03, 9.05)	0.3	0.2	25.9%
Intervention type					
Conogliflozin	2	0.4 (-21.5, 22.5)	0.9	0.7	0.0%
Dapagliflozin	2	-29.9 (-85.2, 25.4)	0.2	0.08	67.4%
Duration of intervention (weeks)					
<20	2	0.4 (-21.5, 22.5)	0.9	0.7	0.0%
>20	2	-29.9 (-85.2, 25.4)	0.2	0.08	67.4%
Health Status					
T2DM	3	-11.9 (-43.6, 19.7)	0.4	0.1	50.4%
Obese adults	1	-8.5 (-27.2, 10.05)	0.3	-	-
Study quality					
Some concerns	3	-4.7 (-19.02, 9.4)	0.5	0.8	0.0%
High risk of bias	1	-67.3 (-130.2, -4.3)	0.03	-	-
Baseline mean age (years)					
>60	2	0.4 (-21.5, 22.5)	0.9	0.7	0.0%
<60	2	-29.9 (-85.2, 25.4)	0.2	0.08	67.4%
Subgroup analyses of GLP & SGLT supplementation on LDL					
Overall effect	4	-1.7 (-10.01, 6.6)	0.6	0.1	44.6%
Blinding					
RCT-DB	3	1.03 (-5.7, 7.8)	0.7	0.3	7.7%
RCT-NB	1	-15.5 (-32.2, 1.2)	0.06	-	-

Study design					
Parallel	4	1.7 (-10.01, 6.6)	0.6	0.1	44.6%
Intervention type					
Conogliflozin	2	0.7 (-10.6, 12.2)	0.8	0.1	53.1%
Dapagliflozin	2	-5.7 (-22.6, 11.2)	0.5	0.09	64.1%
Duration of intervention (weeks)					
<20	2	0.7 (-10.6, 12.2)	0.8	0.1	53.1%
>20	2	-5.7 (-22.6, 11.2)	0.5	0.09	64.1%
Health Status					
T2DM	3	-3.3 (-15.04, 8.2)	0.5	0.08	60.5%
Obese adults	1	1.9 (-9.8, 13.7)	0.7	-	-
Study quality					
Some concerns	3	1.09 (-5.7, 7.8)	0.7	-	-
High risk of bias	1	-15.5 (-32.2, 1.2)	0.06	0.3	7.7%
Baseline mean age (years)					
>60	2	0.7 (-10.6, 12.2)	0.8	0.1	53.1%
<60	2	-5.7 (-22.6, 11.2)	0.5	0.09	64.1%
Subgroup analyses of GLP & SGLT supplementation on HDL					
Overall effect	4	0.8 (-0.8, 2.4)	0.3	0.3	0.0%
Blinding					
RCT-DB	3	1.5 (-0.4, 3.4)	0.1	0.5	0.0%
RCT-NB	1	-1 (-4.08, 2.08)	0.5	-	-
Study design					
Parallel	4	0.8 (-0.8, 2.4)	0.3	0.3	0.0%
Intervention type					
Conogliflozin	2	0.9 (-1.2, 3.1)	0.3	0.7	0.0%
Dapagliflozin	2	1 (-3.3, 5.3)	0.6	0.09	65.0%
Duration of intervention (weeks)					
<20	2	0.9 (-1.2, 3.1)	0.3	0.7	0.0%
>20	2	1 (-3.3, 5.3)	0.6	0.09	65.0%
Health Status					
T2DM	3	0.3 (-1.4, 2.1)	0.7	0.5	0.0%
Obese adults	1	3.4 (-0.7, 7.6)	0.1	-	-
Study quality					
Some concerns	3	1.5 (-0.4, 3.4)	0.1	0.5	0.0%
High risk of bias	1	-1 (-4.08, 2.08)	0.5	-	-
Baseline mean age (years)					
>60	2	0.9 (-1.2, 3.1)	0.3	0.7	0.0%

<60	2	1 (-3.3, 5.3)	0.6	0.09	65.0%
Subgroup analyses of GLP & SGLT supplementation on BW					
Overall effect	5	-3.8 (-5.2, -2.4)	<0.001	0.01	67.9%
Blinding					
RCT-DB	4	-3.09 (-3.8, -2.3)	<0.001	0.6	0.0%
RCT-NB	1	-8.1 (-10.9, -5.2)	<0.001	-	-
Study design					
Parallel	4	-4.2 (-6.1, -2.3)	<0.001	0.008	74.7%
Crossover	1	-2.9 (-4.4, -1.4)	<0.001	-	-
Intervention type					
Conogliflozin	2	-2.9 (-3.9, -1.8)	<0.001	0.6	0.0%
Dapagliflozin	3	-4.9 (-7.7, -2.1)	<0.001	0.007	79.8%
Duration of intervention (weeks)					
<20	3	-2.9 (-3.74, -2.09)	<0.001	0.9	0.0%
>20	2	-6.1 (-9.7, -2.5)	0.001	0.05	74.0%
Health Status					
T2DM	4	-3.7 (-5.4, -2.1)	<0.001	0.009	74.2%
Obese adults	1	-4.4 (-6.7, -2.1)	<0.001	-	-
Study quality					
Some concerns	4	-3.09 (-3.8, -2.3)	<0.001	0.9	0.0%
High risk of bias	1	-8.1 (-10.9, -5.2)	<0.001	-	-
Baseline mean age (years)					
>60	3	-2.9 (-3.7, -2.09)	<0.001	0.9	0.0%
<60	2	-6.1 (-9.7, -2.5)	0.001	0.05	74.0%

Legends: T2DM: type 2 diabetes mellitus, AHA: American Heart Association, RCT: randomized controlled trials, DB: double-blind, SB: single-blind, NB: non-blind.

3.6. Influence analysis

A thorough examination using influence analysis revealed that the overall effect of the combined treatment on cardiometabolic risk factors remained consistent even when individual studies were removed from the analysis. These results provide strong evidence for the reliability and validity of the observed effects of the treatments on cardiometabolic risk factors.

3.7. Grading of the evidence

From the assessment using the GARDE criteria, there is low certainty for the measurements of body weight, HDL, LDL, TG, SBP and DBP. However, the certainty of evidence for waist circumference, FPG and HbA1c was remarkably low. The details can be found in **Table 4**.

Table 4. GRADE evidence table for GLP-1RAs and SGLT2 inhibitor treatment compared to control for cardiometabolic parameters.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects Risk difference with GLP-1 and SGLTi
Waist circumference	92 (2 RCTs)	⊕◯◯◯ Very low[a,b]	MD **3.5 cm lower** (5.8 lower to 1.1 lower)
Body weight	249 (5 RCTs)	⊕⊕◯◯ Low[b,c]	MD **3.8 kg lower** (5.2 lower to 2.4 lower)
Fasting plasma glucose	92 (2 RCTs)	⊕◯◯◯ Very low[a,b]	MD **11.8 mg.dl lower** (16.7 lower to 6.9 lower)
HbA1c	249 (5 RCTs)	⊕◯◯◯ Very low[b,d,e]	MD **0.05 % lower** (0.6 lower to 0.5 higher)
High density lipoprotein	217 (4 RCTs)	⊕⊕◯◯ Low[a,b]	MD **0.8 mg/dl higher** (0.8 lower to 2.4 higher)
Low density lipoprotein	217 (4 RCTs)	⊕⊕◯◯ Low[a,b]	MD **1.7 mg/dl lower** (10.01 lower to 6.6 higher)
Triglyceride	217 (4 RCTs)	⊕⊕◯◯ Low[a,b]	MD **8.4 mg.dl lower** (26.03 lower to 9.05 higher)
Systolic blood pressure	217 (4 RCTs)	⊕⊕◯◯ Low[a,b]	MD **7.4 mmHg lower** (10.6 lower to 4.1 lower)
Diastolic blood pressure	217 (4 RCTs)	⊕⊕◯◯ Low[a,b]	MD **1.04 mmHg lower** (3.2 lower to 1.2 higher)

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. There is a significant risk of bias due to two trials being categorized as high risk. As a result, it is necessary to downgrade the overall reliability of the findings.
b. The optimal information size was not reached and has been downgraded.
c. A serious inconsistency has been noted, as I2=67.9%. As a result, it is necessary to initiate a downgrade.
d. A serious inconsistency has been noted, as I2=92.2%. As a result, it is necessary to initiate a downgrade.
e. Due to the significant presence of publication bias, it is necessary to downgrade.

4. Discussion

The above meta-analysis study shows that combined treatment with an SGLT2 inhibitor and a GLP-1 receptor agonist is associated with a significant decrease in plasma glucose level, SBP, DBP, weight and waist circumference. A subgroup analysis comparing individual SGLT2 inhibitors showed that dapagliflozin resulted in greater weight loss than canagliflozin, while canagliflozin resulted in greater reductions in SBP. According to the subgroup analysis, an intervention lasting more than 20 weeks may lead to a greater reduction in HbA1c levels compared to a shorter duration.

Previous studies have shown that GLP-1 receptor agonists reduce the incidence of HF through their effect on indirect cardiometabolic factors such as weight and inflammation.[35] A network meta-analysis among 23,209

patients with T2DM showed that GLP-1 receptor agonists improve HbA1c, lipid profile, blood pressure and weight.[36] Studies have shown that SGLT2 inhibitor improve cardiovascular disease prevention indicators.[37] A systematic review and network meta-analysis conducted in 2018 showed that SGLT2 inhibitor lowered basal insulin, weight and HbA1c in two RCTs examined.[38] The results of the earlier studies are consistent with the current study showing the positive effect of SGLT2 inhibitor and GLP-1 receptor agonists on improving cardiometabolic indicators.

Combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist has gained attention in recent years due to its potential synergistic effects on cardiometabolic indices. Here are some of the mechanisms related to this combination therapy:

Improved Glycemic Control: Both GLP-1 RAs and SGLT2 inhibitors improve glycemic control through different mechanisms. GLP-1 RAs stimulate insulin secretion, inhibit glucagon secretion, slow gastric emptying and promote satiety.[39] SGLT2 inhibitors, on the other hand, reduce renal glucose reabsorption, which leads to increased glucose excretion in the urine.[40] When used together, they can lead to additive or synergistic effects in lowering blood glucose levels, thus improving glycemic control.

Weight Loss: GLP-1 RAs are associated with weight loss due to their effects on reducing appetite and slowing gastric emptying.[39] SGLT2 inhibitors also contribute to weight loss by promoting urinary excretion of glucose and associated calories.[40] Although SGLT2 inhibitors promote weight loss primarily by increasing urinary glucose excretion, evidence suggests that their weight-reducing effects may plateau over time and are generally less pronounced than those achieved with GLP-1 receptor agonists, which act by suppressing appetite, enhancing satiety, and delaying gastric emptying.[41,42] Therefore, in clinical practice, GLP-1 receptor agonists may be more suitable for patients prioritizing significant weight loss, while SGLT2 inhibitors may be favored for those needing additional cardiovascular or renal benefits. A combination therapy approach may offer synergistic advantages depending on the patient's overall health goals.

Blood Pressure Reduction: SGLT2 inhibitors have been shown to reduce SBP, likely through osmotic diuresis and natriuresis. Other proposed mechanisms, such as reductions in arterial stiffness, have been suggested but require further evidences.[43] GLP-1 RAs may also have modest SBP lowering effects by approximately 2–4 mmHg and based on the results from a meta-analysis SBP lowering effect of GLP-1 RAs is an indirect effect and it is associated with weight/body mass index reduction and better glycemic control.[38] Therefore, the combination therapy can lead to additional reductions in SBP, which is beneficial for patients with hypertension and those at risk of cardiovascular events.

4.1. *Clinical insight*

Clinical studies have shown that the minimum clinically important difference (MCID) for FPG in patients with type 2 diabetes is 10 to 20 mg/dL.[44] The present meta-analysis study showed that combination therapy with GLP-1 RAs and SGLT2 inhibitors lowers FBG (WMD: -11.8 mg/dL; 95% CI: -16.7 to -6.9; $p<0.001$). The MCID for blood pressure is considered to be around 5 mmHg for both SBP and DBP.[45] Combination therapy with GLP-1 RAs and SGLT2 inhibitors reduced SBP (WMD: -7.4 mmHg; 95% CI: -10.6 to -4.1; $p<0.001$) and DBP (WMD: -1.04 mmHg; 95% CI: -3.2 to 1.2; $p=0.3$). The MCID for WC can also vary but is typically considered to be around 1 to 2 cm.[46] SGLT2 inhibitors and GLP-1 receptor agonists together reduced WC (WMD: -3.5 cm; 95%

CI: -5.8 to -1.1). This means that a decrease in FBG, SBP and WC is considered clinically meaningful and indicative of treatment efficacy. For other variables the change shown in this meta was less than their MCID.

4.2. Side effects

Although safety outcomes were not evaluated in this meta-analysis, the known class-related side effects should be considered in clinical decision-making.

4.2.1. Short-Term Tolerability

GLP-1 Agonists:

Gastrointestinal (GI) side effects such as nausea and diarrhea are common, particularly at treatment initiation or with combination therapy. These GI events are more frequent with GLP-1 agonists than with SGLT-2 inhibitors, and the risk increases when both agents are used together.[28,47]

SGLT-2 Inhibitors:

SGLT-2 inhibitors are less likely to cause GI upset but are associated with an increased risk of genital infections, which is a well-established short-term side effect.[47]

4.2.2. Long-Term Safety Signals

GLP-1 Agonists:

Pancreatitis: GLP-1 agonists should be used with caution in patients with a history of pancreatitis, as there is a potential risk, though the absolute risk appears low.[48]

Other Risks: GLP-1 agonists are contraindicated in those with a history of medullary thyroid cancer.[47]

SGLT-2 Inhibitors:

Diabetic Ketoacidosis (DKA): SGLT-2 inhibitors can increase the risk of DKA, particularly in situations of reduced insulin or acute illness, and should be avoided in patients at high risk for DKA.[47]

Renal Safety: SGLT-2 inhibitors are generally safe but should be used with caution in patients with low estimated glomerular filtration rate (eGFR), as efficacy and safety may be reduced.[47]

4.3. Limitation

To the best of our knowledge, few systematic reviews have comprehensively analyzed the combination therapy of GLP-1 RAs and SGLT2 inhibitors on cardiometabolic parameters.[49] The limitation of the above study is the small number of RCTs and the low quality of the reviewed RCTs. As mentioned in Table 4, outcomes including WC and FPG had very low certainty as the result of low number of participants and risk of bias, and HbA1c outcome had also very low certainty due to high heterogeneity and number of participants. A key limitation of our meta-analysis on FPG is the inclusion of only two studies, with the Lundkvist 2017 study contributing 98% of the weight to the pooled effect estimate due to its larger sample size or lower variance. This over-reliance on a single study raises concerns about the robustness of the findings, as the results may be heavily influenced by the characteristics of that study. Additionally, the limited number of studies restricted our ability to reliably assess heterogeneity, potentially masking variations in effect sizes across different populations or study designs.

Furthermore, the short intervention duration and inclusion of non-diabetic populations may limit the generalizability of the results to long-term clinical outcomes. For these reasons, the results should be interpreted with caution.

4.4. Conclusion

Overall, combination therapy with GLP-1 RAs and SGLT2 inhibitors may improve fasting glucose, systolic blood pressure, body weight, and waist circumference. However, effects on HbA1c, lipid profile, and diastolic blood pressure were not significant. The overall certainty of evidence was low to very low, with limitations including heterogeneity, small sample sizes, short intervention durations, and risk of bias. These findings highlight the need for more rigorous, long-term RCTs to confirm the clinical value of this combination therapy.

Declarations

Acknowledgments

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Competing interests

All authors declare that they have no conflicts of interest.

Study Highlights

1. What is current knowledge?

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose transporter 2 inhibitors (SGLT2i) are relatively new drugs used to improve cardiometabolic risk factors.

Previous research has explored the effects of GLP-1RAs on cardiometabolic markers in adults.

2. What is new here?

Our systematic review and meta-analysis assessed the impact of combination therapy with GLP-1RAs and SGLT2 inhibitors on various cardiometabolic indices.

Treatment with GLP-1RA and SGLT2 inhibitors resulted in significant reductions in fasting plasma glucose, systolic blood pressure, body weight, and waist circumference.

These findings suggest that combination therapy may alleviate downstream complications related to cardiometabolic health.

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Availability of data and materials

The data are available upon request

Registrations

The protocol of the study has been registered in PROSPERO (CRD42023471047).

Author Contributions

AS and SMA contributed to the study conception, literature search, data extraction, data analysis, and manuscript drafting. SM, MMM, and IR contributed to the literature search, data extraction, and manuscript drafting. MM, MH, and LSB contributed to the study manuscript drafting. AS critically revised the manuscript. All authors take full responsibility for the analyses and interpretation of the report. All authors read and approved the final manuscript.

Statement:

During the preparation of this work, the author(s) utilized the Grammarly tool and Monika artificial intelligence (AI) for proofreading and enhancing the English language proficiency of our manuscript. This helped in improving the readability of our work and made it more accessible to a wider audience. After using these tools, the author(s) carefully reviewed and edited the content as required and took complete responsibility for the publication's content.

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