Effect of sodium-glucose cotransporter-2 inhibitor on metabolic syndrome in people with prediabetes and obesity: A systematic review and meta-analysis

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Systematic Review / Meta-analysis

Effect of sodium-glucose cotransporter-2 inhibitor on metabolic syndrome in people with prediabetes and obesity: A systematic review and meta-analysis

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a novel therapeutic approach for managing type 2 diabetes mellitus (T2DM), offering benefits that extend beyond glycaemic control. This systematic review aims to examine the effects of SGLT2 inhibitors on metabolic syndrome in individuals with prediabetes and obesity. We conducted a comprehensive search across PubMed, EMBASE, Cochrane Library, Web of Science (Core Collection), and Scopus. Title and abstract screening, data extraction, and risk of bias (ROB) assessment were performed independently by two reviewers. ROB was assessed using the Cochrane Risk of Bias tool. A meta-analysis was conducted using a random-effects model.

Our meta-analysis did not show statistically significant reductions in body weight (mean difference: –3.05 kg; 95 % CI: –8.18 to 2.09), BMI (mean difference: –1.43 kg/m^2; 95 % CI: –4.11 to 1.25), systolic blood pressure (mean difference: –2.12 mmHg; 95 % CI: –7.39 to 3.16), or diastolic blood pressure (mean difference: –1.04 mmHg; 95 % CI: –5.07 to 2.99) with dapagliflozin. However, a reduction was observed in fasting plasma glucose (mean difference: –0.47 mmol/L; 95 % CI: –0.90 to –0.05).

Although current findings suggest that SGLT2 inhibitors (dapagliflozin) may have little to no impact on individual components of metabolic syndrome, the evidence remains limited. Further well-powered clinical trials are warranted to validate these observations. Future research should focus on comparing the efficacy of different SGLT2 inhibitors and exploring their potential synergistic effects when combined with other pharmacological agents in the treatment of metabolic syndrome.

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as novel agents offering multiple metabolic benefits, including reduced insulin resistance, preservation of pancreatic β-cell function, improvement in hepatic steatosis, reduction in visceral fat mass, and enhanced glucose uptake in skeletal muscle [1]. Their distinctive mechanism of action—increasing urinary glucose excretion and thereby inducing a net calorie deficit—makes them promising candidates for weight reduction [2].

Several studies have supported these benefits across various populations. A 2014 study reported that canagliflozin significantly reduced body weight in overweight or obese individuals without diabetes [3]. In 2018, another study demonstrated that dapagliflozin significantly

Abbreviations: ADA, American Diabetes Association; AUC, Area Under the Curve; BMI, Body Mass Index; CI, Confidence Interval; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; HDL-C, High-Density Lipoprotein-Cholesterol; IDF, International Diabetes Federation; IFG, Impaired Fasting Glucose; LDL-C, Low-Density Lipoprotein-Cholesterol; MetS, Metabolic Syndrome; SBP, Systolic Blood Pressure; SGLT2 inhibitors, Sodium Glucose Cotransporter-2 Inhibitors; Type 2 DM, Type 2 Diabetes Mellitus.

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reduced body weight, body mass index (BMI), waist circumference, total cholesterol, triglycerides, and insulin secretion in patients with metabolic syndrome [4]. Similarly, a separate study found that dapagliflozin reduced body weight, BMI, waist circumference, fasting glucose, and uric acid levels, while showing a non-significant trend toward improved insulin sensitivity [5].

In 2020, dapagliflozin was shown to significantly reduce body weight, BMI, fasting blood glucose, haemoglobin A1c, and both night-time and 24-hour systolic blood pressure in individuals with prediabetes and prehypertension [6]. A 2021 study further reported that dapagliflozin modestly improved glycaemic variability in overweight or obese individuals with prediabetes [7].

According to the International Diabetes Federation (IDF), metabolic syndrome is defined as the presence of central obesity (waist circumference >90 cm in men and >80 cm in women) along with any two of the following criteria: elevated triglycerides (≥1.7 mmol/L or 150 mg/dL), reduced high-density lipoprotein (HDL) cholesterol (<1.03 mmol/L or 40 mg/dL in men and <1.29 mmol/L or 50 mg/dL in women), elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg) or a previous diagnosis of hypertension, and elevated fasting plasma glucose (FPG ≥5.6 mmol/L or 100 mg/dL) [8].

The primary approach to managing metabolic syndrome is lifestyle modification. However, pharmacological treatment is often required to address individual components of the syndrome. This multi-drug approach increases treatment costs and may raise the risk of adverse effects and drug–drug interactions. Therefore, there is a need for therapeutic agents that can target multiple components of metabolic syndrome simultaneously.

This systematic review and meta-analysis aims to examine the effects of SGLT2 inhibitors on various components of metabolic syndrome.

Method

This systematic review was conducted in accordance with established methodological guidelines and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [9]. The review protocol was registered with PROSPERO (registration ID: CRD42023491681).

Data resources

We developed a comprehensive search strategy to identify relevant studies across several electronic sources, including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (Core Collection), and Scopus. The search included terms such as *"Sodium-Glucose Transporter 2 Inhibitors", "Gliflozin", "Gliflozins", "SGLT-2 inhibitor", "SGLT-inhibitors", "Metabolic Syndromes", "Metabolic Syndrome", "Syndrome X", "Dysmetabolic Syndrome"*, and *"Insulin Resistance Syndrome"*. The initial search was conducted on 6 January 2024 and updated in April 2025. Full search strategies for each database are provided in Supplementary File 1.

Study selection

We targeted studies evaluating the effects of SGLT2 inhibitors on various components of metabolic syndrome, with particular emphasis on their impact in individuals with prediabetes and obesity. Eligible study designs included randomised controlled trials (RCTs), quasi-experimental studies, non-randomised studies, and controlled before–-after studies. We limited inclusion to articles published in English and excluded studies that: (i) did not specifically evaluate SGLT2 inhibitors; (ii) focused solely on type 2 diabetes; or (iii) were animal studies, laboratory experiments, non-human research, incomplete or ongoing studies, case reports, case series, modelling studies, review articles, systematic reviews, editorials, commentaries, letters, book chapters, conference abstracts, or opinion pieces.

Two reviewers independently screened titles and abstracts using the online platform *Rayyan* [10], with disagreements resolved by a third reviewer. Full-text screening was then conducted independently by two reviewers, and any conflicts were adjudicated by the lead reviewer. A 'prioritisation and sequential exclusion' approach was applied for study selection [11]. Reasons for exclusion were recorded and are reported.

Data extraction

Data were extracted on study population characteristics, intervention duration, dosage, and the effects of SGLT2 inhibitors on body weight, BMI, waist circumference, fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), insulin sensitivity, and fasting plasma glucose. Two reviewers independently performed the data extraction, and any discrepancies were resolved through cross-checking by the lead reviewer.

Data analyses

We conducted a meta-analysis when outcomes were measured in a comparable manner across studies for the same intervention. As all outcomes were continuous variables, results were summarised using mean differences with corresponding 95 % confidence intervals (CIs). Owing to statistical heterogeneity among the included studies, a random-effects model was applied. All analyses were performed using RevMan software (Version 5.4).

Risk of bias assessment

The Cochrane Risk of Bias (ROB) tool was used to assess the risk of bias in the included studies. Two reviewers independently conducted the assessments, with disagreements resolved through discussion with the lead reviewer. The evaluation covered domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.

Results

Search outcome

A total of 1204 records were identified through the database search. After removing 483 duplicates, 721 unique articles remained for title and abstract screening. Of these, 714 were excluded for not meeting the inclusion criteria. During full-text screening, four articles were further excluded as they were not relevant to the intervention of interest. Additionally, one eligible article was identified through citation searching. In total, four RCTs were included in the final analysis. The study selection process is summarised in the PRISMA flow diagram (Fig. 1).

Risk of bias in the included studies

The risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool. Among the four studies analysed, two lacked sufficient information on random sequence generation and were therefore rated as having an unclear risk of bias [4,12]. Allocation concealment was also unclear in two studies [4,12], while the remaining two studies were considered to have a low risk of bias in these domains [5,6] (Fig. 2).

Blinding of participants and personnel was reported in three studies, indicating a low risk of performance bias [4–6]. However, no studies reported blinding of outcome assessment, resulting in an unclear risk of detection bias [4–6,12].

All studies were rated as having a low risk of attrition bias, with no evidence of selective reporting, thus suggesting a low risk of reporting

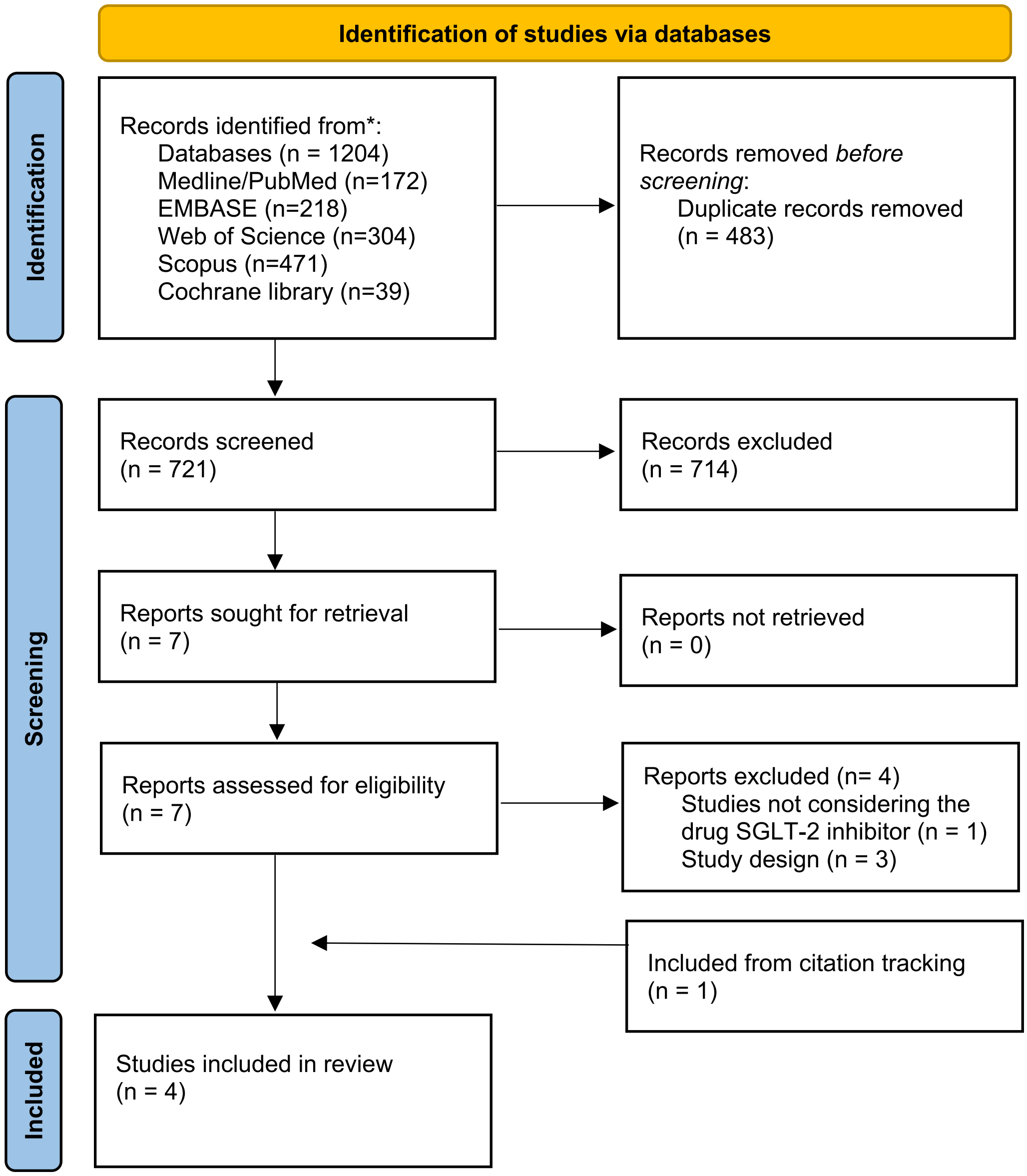


Fig. 1. Flow diagram of study selection process.

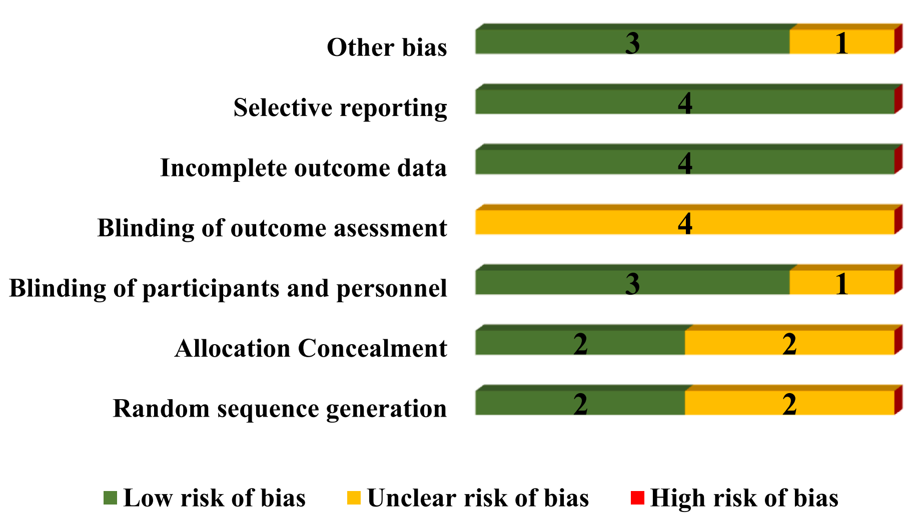


Fig. 2. Risk of bias in the included studies.

bias in those studies [4–6,12].

Regarding other potential sources of bias, three studies were assessed as having a low risk [4–6], while one was rated as unclear due to insufficient methodological detail [12].

Characteristics of included studies

All studies included in this review were published between 2018 and 2021. Three studies were conducted in Mexico [4–6], and one in China [12]. All employed a randomised controlled trial (RCT) design and included participants of both sexes. The age range of participants varied across studies: three trials enrolled individuals aged 30 to 60 years [4–6], while one included participant aged 40 to 60 years [12].

Three studies evaluated the efficacy of dapagliflozin compared to placebo [4–6], whereas one study included 3 arms comparing dapagliflozin, metformin (Glucophage), and a combination of both agents [12]. The intervention duration was three months in three studies [4–6], and one study had a 12-month follow-up period [12].

All studies assessed multiple components of metabolic syndrome. A summary of the key characteristics and outcomes of the included studies is provided in Table 1.

Description of the intervention

Gonzalez et al. [4] evaluated the effect of dapagliflozin (10 mg once daily before breakfast) versus placebo in 24 individuals with metabolic syndrome, diagnosed according to International Diabetes Federation (IDF) criteria. The intervention lasted 90 days.

Alejandra et al. [5] assessed the impact of dapagliflozin (10 mg once daily before breakfast for 12 weeks) compared to placebo in 24 individuals with prediabetes, diagnosed based on the American Diabetes Association (ADA) criteria.

Díaz-Cruz et al. [6] compared dapagliflozin (10 mg once daily before breakfast) with placebo in 30 patients diagnosed with both prediabetes and prehypertension. The intervention period was 12 weeks.

Cheng et al. [12] investigated the effects of three treatment arms in patients with metabolic syndrome: dapagliflozin alone (10 mg once daily before breakfast), metformin (Glucophage) alone (850 mg twice daily), and a combination of both drugs. The intervention lasted for one year.

Table 1
Characteristics of included studies.

Author	Year	Country	Study design	Sample size	Age, years	Sex	Intervention	Dose of intervention	Duration of intervention	Outcome
Gonzalez-Ortiz et al.[4]	2018	Mexico	Randomized controlled trial	Control = 12 Intervention = 12	30–60	Male & Female	Dapagliflozin	10 mg once daily	90 days	Dapagliflozin decreased body weight, BMI, waist circumference, total cholesterol, and triglycerides, AUC of insulin and total insulin secretion, with a remission of Metabolic syndrome in 58.3 %.
Alejandra et al. [5]	2018	Mexico	Randomized controlled trial	Control = 12 Intervention = 12	30–60	Male & Female	Dapagliflozin	10 mg once daily	12 weeks	Dapagliflozin decreased body weight, body mass index, waist circumference, fasting glucose, and uric acid, with a tendency to increase the insulin sensitivity without changes in insulin secretion.
Cheng et al. [12]	2021	China	Randomized controlled trial	Dapagliflozin = 89, metformin (Glucophage) = 82, Dapagliflozin + metformin (Glucophage) = 77	50.3 ± 8.2	Male & Female	Dapagliflozin, metformin (Glucophage), Dapagliflozin+ metformin (Glucophage)	Dapaglifozin 10 mg once daily; metformin (Glucophage) 850 mg twice daily; Dapaglifozin 10 mg once daily combined with metformin (Glucophage) 850 mg twice daily	1 year	Dapaglifozin improved all components of metabolic syndrome in patients with metabolic syndrome. Furthermore, dapaglifozin combined with metformin (Glucophage) showed more meaningful improvements in any of components of metabolic syndrome than dapaglifozin or metformin (Glucophage) monotherapy.
Díaz-Cruz et al. [6]	2020	Mexico	Randomized controlled trial	Control = 12 Intervention = 12	30–60	Male & Female	Dapagliflozin	10 mg once daily	12 weeks	Dapagliflozin decreased body weight, BMI, fasting plasma glucose, hemoglobin A1C, and both office and 24-hour systolic and diastolic pressure.

Abbreviations: BMI- Body Mass Index, AUC- Area under the curve.

Description of outcomes

The effects of dapagliflozin on various components of metabolic syndrome—including body weight, body mass index (BMI), fat mass, waist circumference, systolic and diastolic blood pressure, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c, fasting plasma glucose, fasting insulin, insulinogenic index, Stumvoll index, and Matsuda index—are summarised in Tables 2–5.

Effectiveness of intervention

Gonzalez-Ortiz et al. [4] reported that treatment with dapagliflozin led to significant reductions in body weight, waist circumference, BMI, insulin area under the curve (AUC), overall insulin secretion, and triglyceride levels. Additionally, a 58.3 % remission rate of metabolic syndrome was observed among participants.

Alejandra et al. [5] found that dapagliflozin significantly reduced body weight, BMI, waist circumference, fasting plasma glucose, and uric acid levels.

Díaz-Cruz et al. [6] observed that dapagliflozin reduced blood pressure variability by lowering 24-hour and nighttime systolic blood pressure (SBP) and improving the dipper circadian blood pressure pattern. Additional reductions were noted in BMI, body weight, office blood pressure, fasting plasma glucose, HbA1c, mean arterial pressure (MAP), and nocturnal hypertensive load.

Cheng et al. [12] found that dapagliflozin improved all components of metabolic syndrome. The combination of dapagliflozin and metformin (Glucophage) yielded greater improvements compared to either monotherapy. After one year of treatment, remission rates for metabolic syndrome were 46.1 % for dapagliflozin, 57.3 % for metformin (Glucophage), and 76.6 % for the combination therapy.

Effect of Dapagliflozin on body weight

Compared to placebo, dapagliflozin did not result in a statistically significant reduction in body weight (mean difference: –3.05 kg; 95 % CI: –8.18 to 2.09; 3 trials; 78 participants) (Fig. 3). There was no evidence of heterogeneity among the included studies ($I^2 = 0$ %, $p = 0.54$).

Effect of Dapagliflozin on body mass index

Compared to placebo, dapagliflozin was not associated with a statistically significant reduction in BMI (mean difference: –1.43 kg/m^2; 95 % CI: –4.11 to 1.25; 3 trials; 78 participants) (Fig. 4). However, the results showed substantial heterogeneity ($I^2 = 60$ %; $p = 0.07$).

Effect of Dapagliflozin on waist circumference

Compared to placebo, dapagliflozin was not associated with a statistically significant reduction in waist circumference (mean difference: –1.85 cm; 95 % CI: –7.06 to 3.37; 2 trials; 48 participants) (Fig. 5). The results showed low heterogeneity ($I^2 = 11$ %; $p = 0.29$).

Effect of Dapagliflozin on total cholesterol

Compared to placebo, dapagliflozin was not associated with a statistically significant change in total cholesterol (mean difference: 0.21 mmol/L; 95 % CI: –0.24 to 0.66; 2 trials; 48 participants) (Fig. 6). There was no evidence of heterogeneity ($I^2 = 0$ %; $p = 0.67$).

Effect of Dapagliflozin on triglycerides

Compared to placebo, dapagliflozin was not associated with a statistically significant reduction in triglyceride levels (mean difference: 0.08 mmol/L; 95 % CI: –0.20 to 0.35; 2 trials; 48 participants) (Fig. 7). There was no evidence of heterogeneity ($I^2 = 0$ %; $p = 0.76$).

Effect of Dapagliflozin on systolic blood pressure

Compared to placebo, dapagliflozin was not associated with a statistically significant reduction in systolic blood pressure (mean difference: –2.12 mmHg; 95 % CI: –7.39 to 3.16; 3 trials; 78 participants) (Fig. 8). There was no evidence of heterogeneity ($I^2 = 0$ %; $p = 0.74$).

Effect of Dapagliflozin on diastolic blood pressure

Compared to placebo, dapagliflozin was not associated with a statistically significant reduction in diastolic blood pressure (mean difference: –1.04 mmHg; 95 % CI: –5.07 to 2.99; 3 trials; 78 participants) (Fig. 9). There was no evidence of heterogeneity ($I^2 = 0$ %; $p = 0.51$).

Effect of Dapagliflozin on fasting plasma glucose

Compared to placebo, dapagliflozin was associated with a statistically significant reduction in fasting plasma glucose (mean difference: –0.47 mmol/L; 95 % CI: –0.90 to –0.05; 3 trials; 78 participants). The results showed moderate heterogeneity ($I^2 = 58$ %; $p = 0.09$) (Fig. 10).

Adverse effects of intervention

None of the four studies reported any serious adverse events. However, Gonzalez-Ortiz et al. noted that one participant in the dapagliflozin group experienced a urinary tract infection [4]. In the study by Alejandra et al., two participants in the dapagliflozin group developed urinary tract infections, with one also reporting mild lower back pain

Table 2
Effects of intervention in anthropometric measurements.

Author	Body weight (Mean changes)		BMI (Mean changes)		Fat mass (Mean changes)		Waist circumference (Mean changes)	
	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention
Gonzalez-Ortiz et al. [4]	−1.5 kg ($p <$ 0.001)	−0.4 kg	−0.7 kg/m^2 ($p <$ 0.001)	0.6 kg/m^2	0.5 kg	1.8 kg	3.9 cm ($p <$ 0.001)	1.1 cm
Alejandra et al. [5]	−3 kg ($p =$ 0.019)	−1 kg	−1.1 kg/m^2 ($p =$ 0.023)	−0.4 kg/m^2	1.1 %	0.1 %	4.4 cm ($p =$ 0.003)	−0.4 cm
Cheng et al.* [12]	−3.7 kg	−3.6 kg	−1.0 kg/m^2	−1.0 kg/m^2	–		−3.1 cm	−3.0 cm
Díaz-Cruz et al. [6]	−1 kg	−2 kg	−2 kg/m^2	−2 kg/m^2	–		–	–

* This study has multiple arms (Dapagliflozin, metformin (Glucophage), and Dapagliflozin in combined with Metformin). We reported the results of metformin (Glucophage) in other intervention group.

Abbreviations: BMI- Body Mass Index.

Table 3
Effects of intervention in blood pressure and lipid profile.

Author	Systolic blood pressure (Mean changes)		Diastolic blood pressure (Mean changes)		Triglycerides (Mean changes)		Total cholesterol (Mean changes)		HDL-C (Mean changes)		LDL-C (Mean changes)	
	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention
Gonzalez-Ortiz et al. [4]	−4 mmHg	−5 mmHg	−2 mmHg	0 mmHg	−1 mmol/L ($p < 0.01$)	−0.3 mmol/L	−0.2 mmol/L ($p < 0.05$)	0 mmol/L	0.1 mmol/L	0.1 mmol/L	0.2 mmol/L	0 mmol/L
Alejandra et al. [5]	0 mmHg	−3 mmHg	−1 mmHg	−3 mmHg	−0.2 mmol/L	−0.2 mmol/L	−0.2 mmol/L	0 mmol/L	−0.1 mmol/L	0.1 mmol/L	−0.2 mmol/L	−0.2 mmol/L
Cheng et al.* [12]	−3.4 mmHg ($p < 0.05$)	−1.1 mmHg	−2.0 mmHg ($p < 0.05$)	−0.6 mmHg	−0.69 mmol/L	−0.86 mmol/L	–	–	0.05 mmol/L	0.04 mmol/L	0.07 mmol/L	0.06 mmol/L
Díaz-Cruz et al. [6]	−4 mmHg	1 mmHg	0 mmHg	1 mmHg	–	–	–	–	–	–	–	–

* This study has multiple arms (Dapagliflozin, metformin (Glucophage), and Dapagliflozin in combined with Metformin). We reported the results of metformin (Glucophage) in other intervention group.
Abbreviations: HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol.

that resolved within a day without discontinuation of treatment [5]. Diaz-Cruz et al. reported three cases of cervicovaginal infection and two cases of urinary tract infection in the dapagliflozin group; all cases resolved without complications or treatment withdrawal [6].

Discussion

Metabolic syndrome encompasses a constellation of interrelated conditions, including central obesity, hypertension, impaired fasting glucose, and dyslipidemia. Its pathophysiology involves several mechanisms, most notably insulin resistance coupled with altered fatty acid flux. Chronic low-grade inflammation and oxidative stress also contribute significantly to its development and progression [13]. This systematic review was conducted to assess the potential of SGLT2 inhibitors as therapeutic agents targeting multiple components of metabolic syndrome.

The benefits of SGLT2 inhibitors in metabolic syndrome are largely attributed to their unique mechanism of action. These drugs enhance urinary glucose excretion, resulting in decreased plasma glucose levels, osmotic diuresis, and an overall net energy loss. This contributes to improvements in glycemic control, body weight reduction, and lowered blood pressure [4]. Agents such as canagliflozin, dapagliflozin, and empagliflozin have shown clinical efficacy in treating type 2 diabetes and have demonstrated favorable impacts on weight reduction [14].

Zheng et al. reported in a meta-analysis that SGLT2 inhibitors significantly reduced body weight and BMI in obese adults without diabetes; however, they found no significant effect on waist circumference [15]. Gonzalez-Ortiz and Alejandra et al. found dapagliflozin significantly reduced body weight, BMI, and waist circumference [4,5]. Similarly, Diaz-Cruz et al. reported notable reductions in body weight and BMI [6]. However, our meta-analysis showed no statistically significant changes in body weight or waist circumference and only a slight reduction in BMI. This discrepancy is likely due to the small sample sizes in the included trials.

Cheng et al. found that both dapagliflozin and metformin (Glucophage) similarly affected anthropometric components, though the combination therapy showed superior benefits [12]. Napolitano et al. further reported that remegliflozin, through glycosuria-induced weight loss and a reduction in the leptin-adiponectin ratio, improved metabolic parameters in non-diabetic obese individuals [16]. These findings collectively underscore the need for larger-scale studies to assess the effects of SGLT2 inhibitors on anthropometric parameters more definitively.

Some studies suggest that SGLT2 inhibitors exert antihypertensive effects comparable to low-dose hydrochlorothiazide [17]. However, Gonzalez-Ortiz and Alejandra et al. did not observe significant changes in blood pressure with dapagliflozin [4,5], while Diaz-Cruz et al. reported reductions in 24-hour and nighttime SBP [6]. Cheng et al. noted that combination therapy with metformin (Glucophage) enhanced blood pressure reduction compared to either drug alone [12]. These findings highlight the need for larger, population-diverse trials to validate the antihypertensive effects of SGLT2 inhibitors in individuals with metabolic syndrome.

Regarding lipid profiles, Gonzalez-Ortiz et al. found reductions in total cholesterol and triglycerides, which they attributed to weight loss [4]. Conversely, Alejandra et al. observed no significant lipid changes [5], while Cheng et al. reported improved triglyceride and HDL-C levels with combination therapy [12]. However, our meta-analysis found no consistent effect on lipid parameters. Further investigations are necessary to determine the impact of SGLT2 inhibitors on lipid metabolism.

Mechanistically, SGLT2 inhibitors lower serum glucose via urinary excretion, promote fat utilization, and enhance the browning of white adipose tissue, thereby improving insulin sensitivity [18]. Gonzalez-Ortiz et al. reported reductions in insulin secretion, likely due to decreased adiposity and improved insulin sensitivity [4]. Alejandra et al. found dapagliflozin contributed to remission of prediabetes

Table 4
Effects of intervention in blood glucose level.

Author	HbA1C (Mean changes)		Fasting plasma glucose (Mean changes)		Fasting plasma insulin (Mean changes)	
	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention
Gonzalez-Ortiz et al. [4]	–	–	−0.4mmol/L	0	–	–
Alejandra et al. [5]	−0.1 %	0.1 %	−0.8 mmol/L ($p < 0.001$)	−0.1mmol/L	−33pmol/L	−31pmol/L
Cheng et al.* [12]	−0.8 %	−0.8 %	−1.2 mmol/L	−1.0 mmol/L	−1.0mIU/L	−1.2mIU/L
Díaz-Cruz et al. [6]	−0.5 %	0.1 %	−0.5 mmol/L	0.1 mmol/L	–	–

* This study has multiple arms (Dapagliflozin, metformin (Glucophage), and Dapagliflozin in combined with Metformin). We reported the results of metformin (Glucophage) in other intervention group.

Abbreviations: HbA1C- Haemoglobin A1C.

Table 5
Effects of intervention in insulin secretion and sensitivity.

Author	Insulinogenic index (Mean changes)		Stumvoll index (Mean changes)		Matsuda index (Mean changes)	
	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention	Dapagliflozin	Placebo/ other intervention
Gonzalez-Ortiz et al. [4]	−0.48 ($p < 0.001$)	0.1	−103	523	0.7	−0.2
Alejandra et al. [5]	0.01	−0.02	−30	−329	0.69	0.16
Cheng et al.* [12]	–	–	–	–	–	–
Díaz-Cruz et al.* [6]	–	–	–	–	–	–

* These studies did not report those specific results.

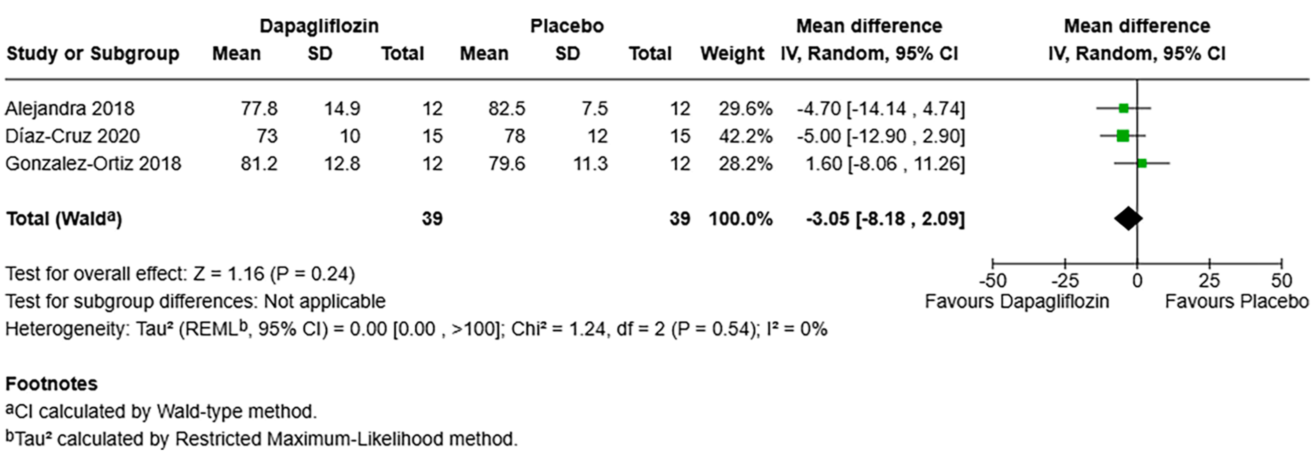


Fig. 3. Effect of Dapagliflozin on body weight.

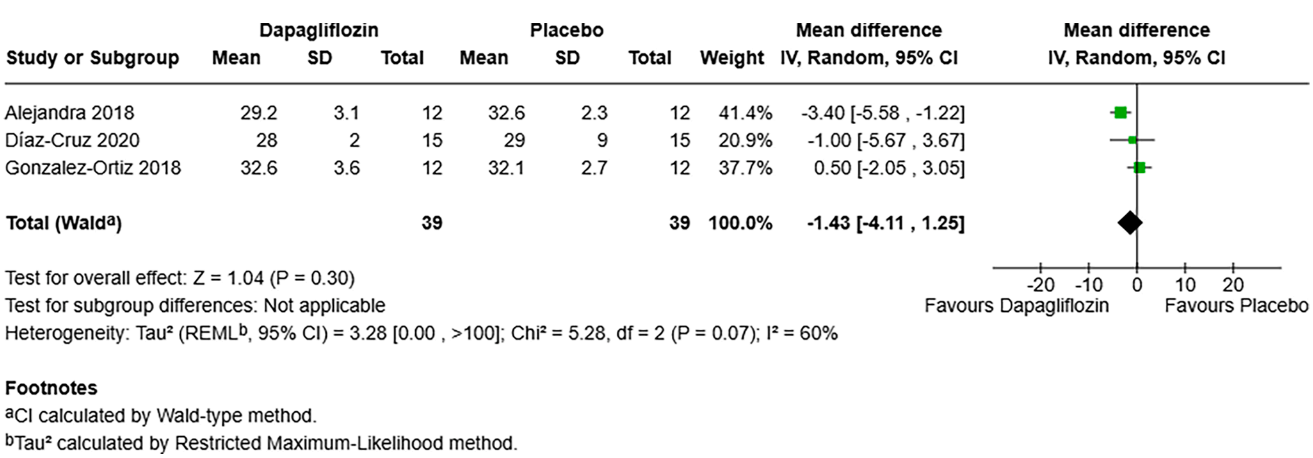


Fig. 4. Effect of Dapagliflozin on Body Mass Index.

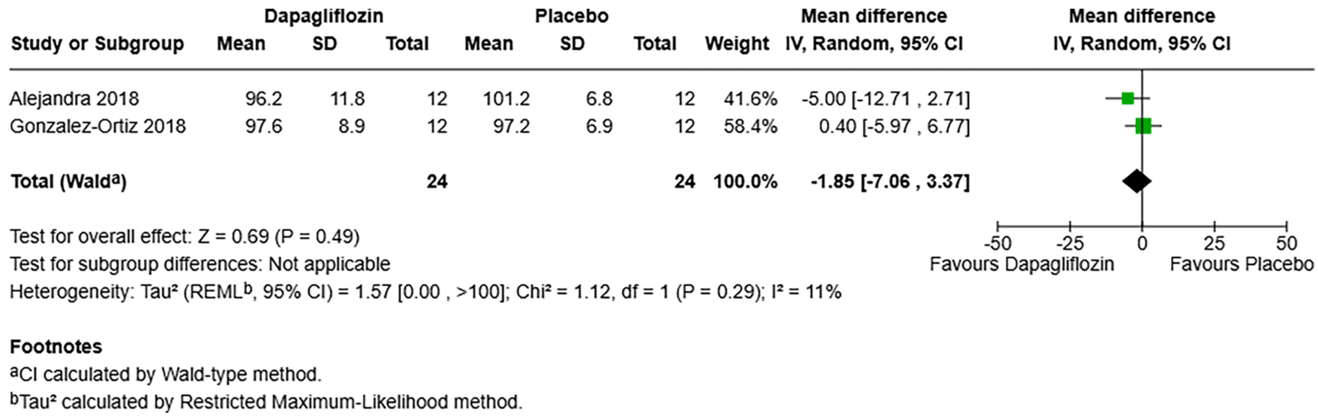


Fig. 5. Effect of Dapagliflozin on waist circumference.

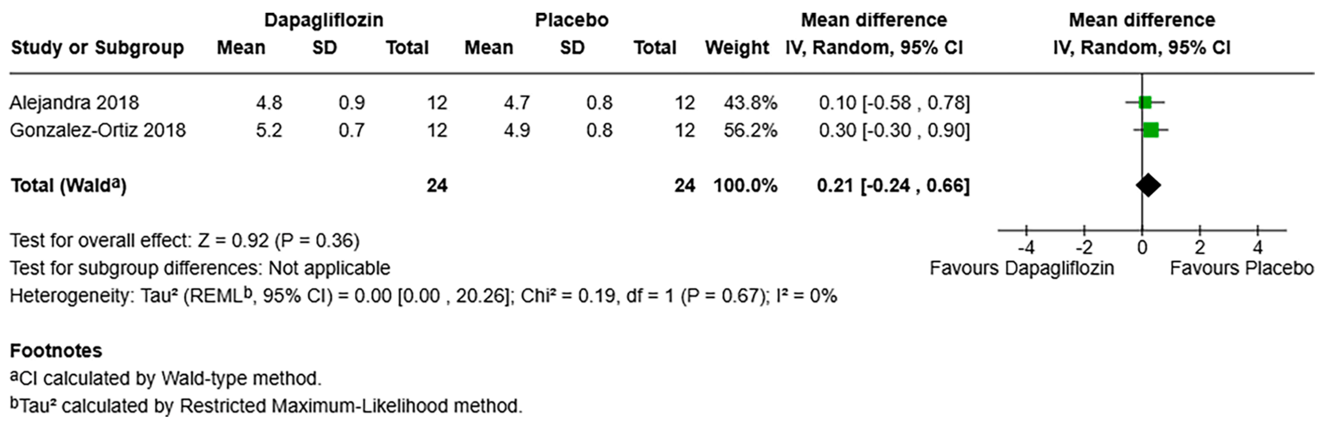


Fig. 6. Effect of Dapagliflozin on total cholesterol.

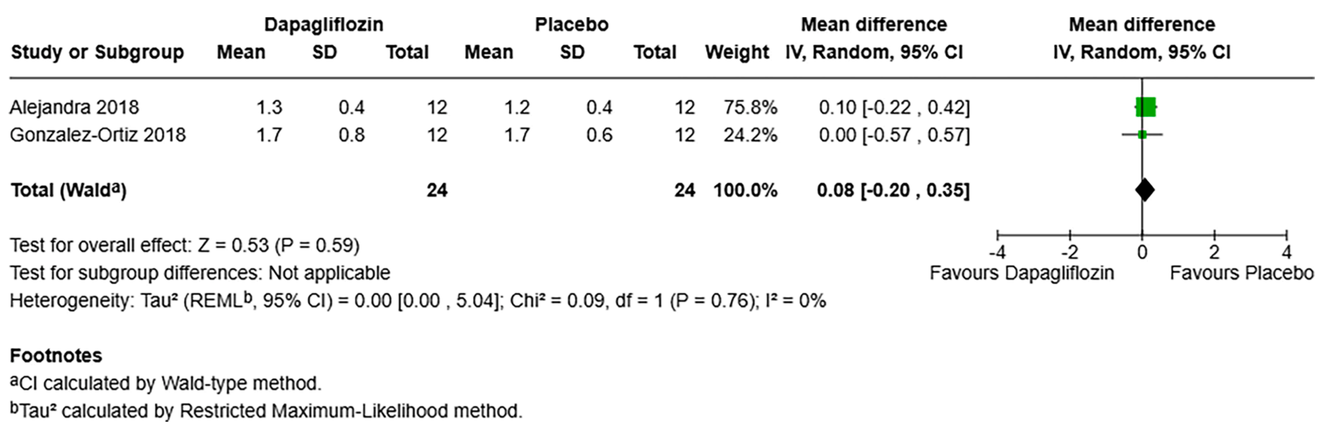


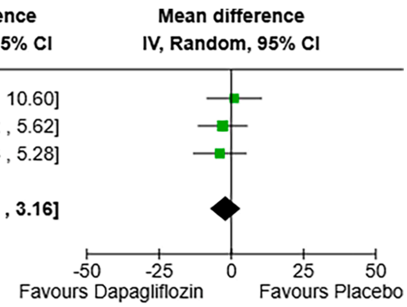
Fig. 7. Effect of Dapagliflozin on triglycerides.

through improved impaired fasting glucose and trends toward enhanced insulin sensitivity [5]. Diaz-Cruz et al. also found that dapagliflozin significantly reduced fasting plasma glucose [6], a finding that was further supported by our meta-analysis.

Cheng et al. found similar effects of dapagliflozin and metformin (Glucophage) monotherapies on fasting plasma glucose and HbA1c, while the combination therapy yielded superior glycemic outcomes [12]. Lundkvist et al. demonstrated that dapagliflozin combined with exenatide led to sustained improvements in body weight, SBP, and prediabetes frequency, and was well tolerated [19].

SGLT2 inhibitors target multiple key components of metabolic syndrome, including glycemic control, blood pressure regulation, and weight management. While our systematic review did not demonstrate a definitive therapeutic effect of SGLT2 inhibitors (dapagliflozin) on metabolic syndrome among people with prediabetes and obesity, the limited number of RCTs and small study populations highlight the need for well-powered, long-term trials across diverse populations. Our study contributes important evidence supporting the continued evaluation of SGLT2 inhibitors as a multi-target treatment strategy for metabolic syndrome.

Study or Subgroup	Dapagliflozin Mean	Dapagliflozin SD	Dapagliflozin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Alejandra 2018	124	12	12	123	12	12	30.2%	1.00 [-8.60 , 10.60]
Díaz-Cruz 2020	117	11	15	120	13	15	37.5%	-3.00 [-11.62 , 5.62]
Gonzalez-Ortiz 2018	117	10	12	121	13	12	32.3%	-4.00 [-13.28 , 5.28]
Total (Wald[a])			**39**			**39**	**100.0%**	**-2.12 [-7.39 , 3.16]**

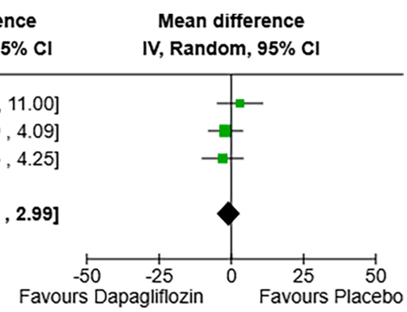


Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b], 95% CI) = 0.00 [0.00 , >100]; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Fig. 8. Effect of Dapagliflozin on Systolic Blood Pressure.

Study or Subgroup	Dapagliflozin Mean	Dapagliflozin SD	Dapagliflozin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Alejandra 2018	77	10	12	74	10	12	25.4%	3.00 [-5.00 , 11.00]
Díaz-Cruz 2020	73	8	15	75	9	15	43.7%	-2.00 [-8.09 , 4.09]
Gonzalez-Ortiz 2018	76	8	12	79	10	12	30.9%	-3.00 [-10.25 , 4.25]
Total (Wald[a])			**39**			**39**	**100.0%**	**-1.04 [-5.07 , 2.99]**

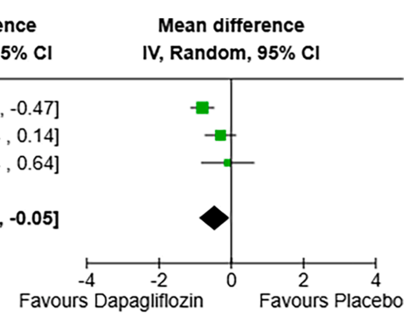


Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b], 95% CI) = 0.00 [0.00 , >100]; Chi² = 1.36, df = 2 (P = 0.51); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Fig. 9. Effect of Dapagliflozin on Diastolic Blood Pressure.

Study or Subgroup	Dapagliflozin Mean	Dapagliflozin SD	Dapagliflozin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Alejandra 2018	5.1	0.3	12	5.9	0.5	12	43.0%	-0.80 [-1.13 , -0.47]
Díaz-Cruz 2020	5.8	0.5	15	6.1	0.7	15	36.0%	-0.30 [-0.74 , 0.14]
Gonzalez-Ortiz 2018	5.7	1.1	12	5.8	0.7	12	21.0%	-0.10 [-0.84 , 0.64]
Total (Wald[a])			**39**			**39**	**100.0%**	**-0.47 [-0.90 , -0.05]**



Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b], 95% CI) = 0.08 [0.00 , 5.07]; Chi² = 4.90, df = 2 (P = 0.09); I² = 58%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Fig. 10. Effect of Dapagliflozin on Fasting Plasma Glucose.

Strength and limitations

This systematic review was rigorously conducted in accordance with established guidelines, focusing exclusively on RCTs. Each included study was assessed using the Cochrane Risk of Bias tool.

However, several limitations should be noted. First, the review was restricted to English-language publications, which may have led to the exclusion of relevant studies published in other languages. Second, the number of eligible RCTs was limited, and most had relatively small sample sizes. This may affect the generalizability of the findings and could potentially inflate the magnitude of observed effects.

Conclusion

As metabolic syndrome comprises a cluster of interrelated conditions, identifying a single, effective treatment remains a significant challenge. Although all included studies reported beneficial effects of SGLT2 inhibitors (dapagliflozin) on various components of metabolic syndrome, our meta-analysis did not reveal statistically significant improvements across most outcomes. A key limitation underlying this finding is the small number of eligible studies, each with a limited sample size.

Despite the limitations, the distinct mechanism of action of SGLT2 inhibitors—targeting glucose reabsorption in the kidneys and promoting caloric loss—positions them as promising therapeutic candidates in the management of metabolic syndrome.

To strengthen the evidence base, further high-quality studies with larger sample sizes, longer follow-up durations, and direct comparisons between different SGLT2 inhibitors and combination therapies are essential. Such studies would help clarify their role in the comprehensive management of metabolic syndrome and inform clinical decision-making.

Supporting information: Supplementary file 1

Disclosure of ethical statements

Author's contribution:
Study conceptualization: SB, KMSUR.
Literature search and screening: AR., MAH, SB, KMSUR.
Data extraction: AR., MAH, SB, KMSUR.
Quality assessment: AR., MAH, SB, KMSUR.
Data synthesis and analysis: AR., MAH, SB, KMSUR.
First draft of the article: SB, AR., KMSUR.
Review and editing: KMSUR
Final draft of the article: The final script was reviewed and approved by all the authors. The review's guarantee is provided by its corresponding author.

Conflict of interest

There is no conflict of interest.

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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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hsr.2025.100229.

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