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META - ANALYSIS

Ge et al: Liver fat reduction via SGLT2 inhibitors

Effect of SGLT2 inhibitors on liver fat content: A meta-analysis

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major metabolic disorder linked to increased morbidity and mortality. Sodium-glucose co-transporter-2 (SGLT2) inhibitors, commonly used to manage type 2 diabetes (T2DM), have shown potential in reducing liver fat content (LFC). However, the magnitude and consistency of this effect remain uncertain. This meta-analysis aimed to evaluate the impact of SGLT2 inhibitors on LFC in adults with metabolic disorders. A systematic search of PubMed, Embase, the Cochrane Library, and Web of Science was conducted up to January 2, 2024, to identify randomized controlled trials (RCTs) assessing the effects of SGLT2 inhibitors on LFC. Studies were included if they reported liver fat changes measured by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) or proton magnetic resonance spectroscopy (^{1}H-MRS). We pooled standardized mean differences (SMDs) and 95% confidence intervals (CIs) using a random-effects model to account for variability across studies. Thirteen RCTs with 14 datasets (n = 791 participants) were included. SGLT2 inhibitors significantly reduced LFC compared to controls (SMD: -0.73, 95% CI: -0.97 to -0.50; $p < 0.001$), with moderate heterogeneity (I^2 = 62%). Subgroup and meta-regression analyses did not identify any study characteristics — such as study design, diabetic status, patient demographics, baseline LFC, type of SGLT2 inhibitor, or treatment duration — as significant contributors to heterogeneity (all $p > 0.05$). In conclusion, SGLT2 inhibitors are associated with a significant reduction in LFC in adults, supporting their potential role in managing MASLD.

Keywords: Sodium-glucose co-transporter-2; SGLT2; liver fat content; LFC; type 2 diabetes; T2DM.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder affecting approximately 32% of the global population (1, 2). It represents a spectrum of liver conditions characterized by excessive hepatic fat accumulation in the absence of significant alcohol consumption (3). Recently, the nomenclature has shifted towards metabolic dysfunction-associated steatotic liver disease (MASLD), which better reflects the metabolic risk factors contributing to the disease (4). While NAFLD and MASLD share similar diagnostic criteria, the latter emphasizes the role of metabolic dysfunction, including obesity, type 2 diabetes (T2D), and dyslipidemia, in disease progression (5). Both conditions increase the risk of nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, hepatocellular carcinoma, and cardiovascular complications, leading to substantial morbidity and mortality (6).

Liver fat content (LFC) is a key pathological feature of NAFLD/MASLD and plays a crucial role in disease progression (7). Excessive hepatic lipid accumulation contributes to insulin resistance, hepatic inflammation, and fibrosis, which are central to the pathogenesis of NAFLD/MASLD (8). Reducing LFC is considered an important therapeutic target to mitigate disease progression and associated metabolic complications (9). The measurement of LFC relies on various imaging techniques and histological assessments (10). While liver biopsy remains the gold standard for diagnosing NAFLD/MASLD and assessing fibrosis, its invasive nature limits widespread use (10). Noninvasive imaging modalities such as magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) and proton magnetic resonance spectroscopy (^{1}H-MRS) have emerged as highly accurate and reproducible methods for quantifying LFC (11-13). Compared to ultrasound-based techniques, MRI-based methods offer superior sensitivity, allowing for precise LFC quantification and longitudinal monitoring of treatment response (14).

Despite the increasing recognition of NAFLD/MASLD as a major health concern, there is no approved pharmacological therapy specifically for reducing LFC (15). Current evidence-based management strategies focus on lifestyle interventions, including weight loss through dietary modifications and exercise, which have been shown to improve hepatic steatosis and insulin sensitivity (16) However, sustained adherence to lifestyle interventions remains challenging, highlighting the need for

targeted pharmacological treatments. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a class of antidiabetic agents that lower blood glucose levels by promoting urinary glucose excretion (17). Initially developed for the management of T2D, these agents have demonstrated additional metabolic and cardiovascular benefits beyond glycemic control (18, 19). SGLT2 inhibitors reduce body weight, improve insulin sensitivity, lower blood pressure, and exert protective effects on the cardiovascular and renal systems (20). Recent studies suggest that SGLT2 inhibitors may also influence hepatic lipid metabolism, making them a promising therapeutic option for reducing LFC in patients with NAFLD/MASLD (21). However, the effects of SGLT2 inhibitors on hepatic fat accumulation appear to vary across studies, with some demonstrating significant LFC reductions (22-32) while others report minimal or inconsistent findings (33, 34). Accordingly, in this study, we performed a meta-analysis of randomized controlled trials (RCTs) aiming to systematically assess the effects of SGLT2 inhibitors on LFC in adults with metabolic disorders using MRI-based measurements.

MATERIAL AND METHODS

This meta-analysis was designed and conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 guidelines (35, 36) and the Cochrane Handbook for Systematic Reviews and Meta-analysis (37). The protocol of the study has been registered prospectively in PROSPERO with the identifier CRD42025632495.

Search strategy

A systematic search was performed across PubMed, Embase, Cochrane Library, and Web of Science databases from their inception to January 02, 2024. The search strategy combined terms related to (1) "sodium glucose transporter 2 inhibitor" OR "sodium glucose transporter ii inhibitor" OR "SGLT 2 inhibitor" OR "SGLT-2 inhibitor" OR "SGLT2" OR "sodium glucose cotransporter 2 inhibitors" OR "canagliflozin" OR "dapagliflozin" OR "empagliflozin" OR "ertugliflozin" OR "tofogliflozin" OR "bexagliflozin" OR "henagliflozin" OR "ipragliflozin" OR "licogliflozin" OR "luseogliflozin" OR "remogliflozin" OR "sergliflozin" OR "sotagliflozin"; (2) "liver" OR "hepatic"; (3) "fat" OR "adipose" OR "adiposity" OR

"lipid"; and (4) "random" OR "randomly" OR "randomized" OR "control" OR "allocated" OR "placebo" OR "controls" OR "RCT". The detailed search strategy for each database is shown in **Supplemental File 1**. Only studies published in peer-reviewed journals as full-length articles in English were considered. We also manually searched the reference lists of relevant articles and reviews to identify additional studies. Duplicate records were removed using EndNote X4 (Thomson Reuters, New York, NY, USA) reference management software.

Inclusion and exclusion criteria

We included studies that met the following criteria, which were designated according to the Population, Intervention, Comparison, Outcomes and Study (PICOS) principle (38).

Population (P): Adults with metabolic disorders or conditions associated with NAFLD or metabolic dysfunction-associated steatotic liver disease, including but not limited to obesity, T2D, and metabolic syndrome.

Intervention (I): SGLT2 inhibitors on the basis of background treatments (such as other concurrent antidiabetic medications for patients with T2D) for at least one week.

Control (C): Placebo or no additional treatments on the basis of background treatments.

Outcomes: The difference for the changes of LFC after treatment between patients allocated to the intervention and control groups, which was evaluated by MRI-based methods, such as MRI-PDFF or ^{1}H-MRS.

Study Design: RCTs, including cross-over studies and parallel-group RCTs.

Reviews, case reports, editorials, animal studies, and observational studies were excluded. Studies involving pediatric populations were excluded. In addition, we also excluded studies with treatment of SGLT2 inhibitors for less than 7 days because we did not want to evaluate the acute influence of SGLT2 inhibitors on LFC. Finally, studies comparing SGLT2 inhibitors with active controls, or studies that did not report the outcome of interest were also excluded. In instances of overlapping study populations, the study with the largest sample size was selected for inclusion in the meta-analysis.

Data extraction

Two independent reviewers screened the titles, abstracts, and full texts of the studies and extracted relevant data using a standardized data extraction form. Discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included study characteristics (author, year of publication, country, and study design), participant characteristics (diagnosis, patient number, mean ages, proportions of men, baseline HbA1c, body mass index [BMI], and duration of diabetes), methods for evaluating LFC, mean LFC at baseline, concurrent antidiabetic treatments, individual medication and dosages of SGLT2 inhibitors, details of controls, and treatment durations.

Quality assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias Tool, which evaluates potential sources of bias across multiple domains (39). These domains include selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. Each study was rated as having a low, high, or unclear risk of bias in each domain (39). Discrepancies were resolved through discussion or consultation with a third reviewer when necessary. A risk-of-bias summary table was generated to visualize the assessment results. In addition, the certainty of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system, which considers factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias (40). The certainty of evidence was thus classified as very low, low, moderate, or high.

Statistical analysis

The difference for the changes of LFC after treatment between patients allocated to the SGLT2 inhibitors and control groups were summarized as the standardized mean differences (SMDs) with corresponding 95% confidence intervals (CIs) (37) because different MRI-based methods were used to evaluate LFC among the included studies. The significance of between-study heterogeneity was evaluated with Cochrane Q test

(37). The severity of statistical heterogeneity was assessed using the I^2 statistic, with I^2 < 25%, 25~75%, and > 75% indicating mild, moderate, and substantial heterogeneity among the included studies (41). The meta-analysis was conducted using the inverse variance (IV) method with a random-effects model to account for potential heterogeneity across studies (37). Sensitivity analyses were conducted by excluding one dataset at a time to evaluate the robustness of the findings (42). Subgroup analyses were performed to explore the influences of the predefined study characteristics on the outcomes, such as countries of the study (Asian or non-Asian), study design (double-blind or open-label), diabetic status of the participants, mean ages, proportions of men, mean HbA1c at baseline, and baseline BMI, methods for measuring LFC, baseline LFC of the included participants, individual medications of SGLT2 inhibitors, and treatment durations. Medians of continuous variables were used as cutoffs for defining subgroups. In addition, a univariate meta-regression analysis was also performed to evaluate the influences of study characteristics in continuous variables on the results of the meta-analysis, such as sample sizes, mean ages of the patients, proportions of men, baseline HbA1c, BMI, and LFC, as well as the treatment durations. Potential publication bias was assessed using funnel plots, and Egger's regression test was conducted to detect small-study effects (43). A p-value < 0.05 in Egger's test was considered indicative of publication bias. The statistical analyses were carried out with RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 17.0; Stata Corporation, College Station, TX).

RESULTS

Literature search and study identification

A detailed PRISMA flow diagram is provided in Figure 1. Briefly, the initial search yielded 983 records across the four databases. After removing 397 duplicates, 586 unique articles remained. Following title and abstract screening, 556 studies were further excluded mainly because they were not relevant to the aim of the meta-analysis. Of the 30 studies undergoing full-text review, 17 studies were subsequently excluded for the reasons listed in Figure 1. Finally, 13 RCTs (22-34) met the inclusion criteria and included for subsequent meta-analysis.

Study characteristics

A summary of study characteristics is shown in Table 1. Overall, 13 RCTs, including two cross-over studies (29, 34) and 11 parallel-group studies (22-28, 30-33) were included in the meta-analysis. Since one study (31) included two datasets in participants with and without diabetes separately, these datasets were independently included in the meta-analysis, making 14 datasets available. The included studies were published between 2018 and 2024, and conducted in India, Sweden, Finland, the United States, Germany, France, Japan, Egypt, the United Kingdom, China, and the Netherlands. Four datasets included T2D patients with NAFLD (22, 23, 27, 30), seven datasets included patients with T2D (24-26, 28, 29, 31, 33), one included prediabetic patients (34), and the other two included non-diabetic overweight participants (31) and non-diabetic patients with MASLD (32). The sample sizes of the included studies were 14 to 160, with the mean ages of the patients varying from 45.0 to 66.3 years, and the proportion of men ranging from 39.2 to 80.6%. The mean HbA1c of the included patients at baseline were 5.5 to 9.1%, and the mean BMI at baseline were 27.4 to 35.2 kg/m^2. The LFC was measured with MRI-PDFF in six studies (22, 23, 25, 27, 30, 32), while with ^{1}H-MRS in the other seven studies (24, 26, 28, 29, 31, 33, 34). The mean LFC at baseline were 6.2 to 26.5%. The interventions of SGLT2 inhibitors including dapagliflozin in six studies (22, 25, 28-30, 34), empagliflozin in six studies (23, 26, 27, 31-33), and canagliflozin in another study (24). The controls were placebo in 11 studies (22-27, 29, 31-34), and none additional treatment besides standard therapy in two studies (28, 30). The treatment durations were two to 52 weeks.

Study quality evaluation

The details of study quality evaluation via the Cochrane Risk of Bias Tool are shown in Table 2. Three of the included studies were open-label RCTs (23, 28, 30), while the other ten were all double-blind RCTs (22, 24-27, 29, 31-34). Details of random sequence generation were adequately reported in nine studies (22-24, 26, 28-30, 32, 33), and the details of allocation concealment were sufficiently addressed in nine studies (22, 24-26, 28-30, 32, 33). No bias related to incomplete outcome data reporting or selective reporting was observed.

Influence of SGLT2 inhibitors on LFC

Overall, 13 RCTs including 14 datasets (22-34) evaluated the influence of SGLT2 inhibitors on LFC. The pooled results showed that compared to controls of placebo or no additional treatment, SGLT2 inhibitors significantly reduced LFC in adults (SMD: -0.73, 95% CI: -0.97 to -0.50; $p < 0.001$; Figure 2) with moderate heterogeneity (I^2 = 62%). Further sensitivity analysis by excluding one dataset at a time did not significantly affect the results (SMD: -0.67 to -0.78, p all < 0.05). Subsequent subgroup analyses showed that the effect of SGLT2 inhibitors on LFC was not significantly affected by study country, design, diabetic status of the participants, mean age, proportion of men, baseline HbA1c, baseline BMI, MRI-based methods for measuring LFC, individual medications of SGLT2 inhibitors, or the treatment durations (p for subgroup difference all > 0.05; Table 3). Moreover, the results of univariate meta-regression analyses also did not show that any of the following characteristics could significantly modify the effect of SGLT2 inhibitors on LFC, which included sample size of the study, mean age, proportion of men, baseline HbA1c, BMI, and LFC, or the treatment duration (p all > 0.05; Table 4). The evidence certainty for the outcome of LFC was rated down for one level (level of evidence: moderate) because of the statistical heterogeneity observed among the included studies (Table 5).

Publication bias

The funnel plots for the meta-analysis evaluating the influence of SGLT2 inhibitors on LFC are shown in Figure 3. A visual inspection revealed no substantial asymmetry of these plots, suggesting low risk of publication bias. Further results of the Egger's regression test also confirmed the low risks of publication bias (p = 0.82).

DISCUSSION

This meta-analysis of 13 RCTs with 14 datasets, involving 791 participants, demonstrated that SGLT2 inhibitors significantly reduce LFC in adults with metabolic disorders. Sensitivity analyses confirmed the robustness of these findings, while subgroup and meta-regression analyses did not identify any significant modifiers of the effect, suggesting that multiple factors may collectively influence the heterogeneity. These results highlight the potential of SGLT2 inhibitors in managing

hepatic steatosis, supporting their role as a therapeutic option for patients with MASLD.

Several mechanisms may underlie the observed reduction in LFC with SGLT2 inhibitors. One proposed pathway is the enhancement of lipid metabolism through increased fatty acid oxidation and reduced hepatic de novo lipogenesis (44). SGLT2 inhibitors promote lipolysis in adipose tissue and shift energy metabolism toward lipid utilization, leading to a decrease in ectopic fat deposition in the liver (45). Additionally, these agents improve insulin sensitivity by reducing hyperinsulinemia, which may attenuate insulin-driven lipogenesis and hepatic fat accumulation (46). At the molecular level, SGLT2 inhibitors have been shown to activate AMP-activated protein kinase (AMPK) (47), a key regulator of cellular energy homeostasis that promotes lipid oxidation and inhibits lipogenesis (48). Moreover, they may modulate peroxisome proliferator-activated receptor alpha (PPAR-α) (49), which enhances fatty acid transport and oxidation in the liver (50). Beyond metabolic effects, SGLT2 inhibitors also exhibit anti-inflammatory properties, reducing systemic and hepatic inflammation, which is critical in preventing the progression of MASLD to more severe stages such as nonalcoholic steatohepatitis (NASH) and fibrosis (51, 52).

Despite the overall positive findings, the presence of moderate heterogeneity (I^2 = 62%) suggests variability in treatment response among the included studies. Subgroup and meta-regression analyses did not identify significant contributors to heterogeneity, indicating that multiple unmeasured factors may influence the effect of SGLT2 inhibitors on LFC. Possible contributors include differences in dietary intake (53), genetic predisposition (54), and other nutritional or lifestyle factors (55), which were not accounted for at the study level. Individual patient characteristics, such as hepatic insulin resistance, baseline metabolic status, or gut microbiome composition, may also affect responsiveness to SGLT2 inhibitors. Additionally, variations in study design, including treatment adherence, concomitant medications, and imaging techniques for LFC assessment, could have influenced the results. These findings underscore the complexity of hepatic fat metabolism and suggest that further research incorporating patient-level data is necessary to identify specific populations that may derive the greatest benefit from SGLT2 inhibitors.

This meta-analysis has several strengths. First, it included only RCTs, providing the highest level of evidence regarding the effect of SGLT2 inhibitors on LFC. Second, an extensive and systematic literature search ensured the inclusion of all relevant studies, making this the most up-to-date synthesis of available evidence. Third, the findings were validated through multiple sensitivity analyses, confirming their robustness. Furthermore, MRI-based techniques, which provide more accurate quantification of LFC compared to ultrasound-based methods, were used across all included studies, enhancing the reliability of the pooled results. However, some limitations should be acknowledged. The presence of moderate heterogeneity limits the certainty of the findings, although no significant sources of heterogeneity were identified through subgroup or meta-regression analyses. Additionally, only three SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) were evaluated among the included studies, leaving the effects of other SGLT2 inhibitors on LFC unclear. While our subgroup analysis did not reveal significant differences between empagliflozin and dapagliflozin, a comparative analysis for canagliflozin was not feasible due to the inclusion of only one study using this agent. Furthermore, we were unable to assess the dose–response relationship due to limited data across specific dosage levels. These findings suggest that although different SGLT2 inhibitors may share similar mechanisms, their comparative efficacy on reducing liver fat content remains uncertain and warrants investigation in future head-to-head RCTs. Moreover, although subgroup analysis by study country (Asian vs. non-Asian) did not reveal significant differences, we could not directly assess the impact of patient ethnicity on treatment outcomes due to the absence of individual-level data. Ethnic differences in genetic background, dietary patterns, and lifestyle factors may potentially influence responsiveness to SGLT2 inhibitors. Future patient-level meta-analyses are needed to explore whether genetic or environmental factors mediate variations in liver fat response across ethnic groups. It is also worth noting that none of the included studies enrolled lean individuals, as all reported mean baseline BMI values in the overweight or obese range. Therefore, the effect of SGLT2 inhibitors on liver fat content in lean individuals remains unclear and requires further investigation. Another limitation is the duration of treatment, which ranged from two to 52 weeks. While a significant reduction in LFC was observed, longer-term studies are needed to assess whether these benefits are sustained over time and whether they translate into improvements in liver histology or clinical outcomes. Importantly, this meta-analysis was based on

study-level data, precluding an individualized assessment of patient or study characteristics that may influence treatment response. Future large-scale RCTs with individual patient-level data are needed to better evaluate the impact of baseline metabolic status, genetic factors, and concurrent lifestyle modifications on the efficacy of SGLT2 inhibitors in reducing hepatic steatosis.

The clinical implications of these findings are significant. Given the growing burden of MASLD and the lack of approved pharmacological treatments, SGLT2 inhibitors represent a promising option for reducing LFC in patients with metabolic disorders. Their ability to improve multiple metabolic parameters, including glycemic control, body weight, and insulin sensitivity, further supports their role in comprehensive metabolic disease management. Future research should explore whether combining SGLT2 inhibitors with other pharmacological agents, such as GLP-1 receptor agonists or PPAR agonists, provides additive benefits in reducing hepatic fat and preventing MASLD progression. Additionally, long-term studies evaluating the impact of SGLT2 inhibitors on liver fibrosis, cardiovascular risk, and overall survival are needed to establish their full therapeutic potential.

CONCLUSION

In conclusion, this meta-analysis provides robust evidence that SGLT2 inhibitors significantly reduce LFC in adults with metabolic disorders, supporting their potential role in MASLD management. While the exact mechanisms remain to be fully elucidated, the observed benefits likely result from improvements in lipid metabolism, insulin sensitivity, and hepatic inflammation. Given the presence of moderate heterogeneity and the study-level nature of the analysis, further large-scale RCTs with long-term follow-up and patient-level data are needed to refine treatment strategies and identify individuals who may benefit the most from SGLT2 inhibitor therapy.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included RCTs

Study	Country	Design	Patient diagnosis	Patient number	Mean age (years)	Male (%)	Baseline HbA1c (%)	Duration of diabetes (years)	Baseline BMI (kg/m^2)	Methods of MR-LFC measurement	Baseline LFC (%)	Concurrent antidiabetic treatment	Intervention	Control	Treatment duration (weeks)
Kuchay 2018	India	R, OL	T2D and NAFLD	42	49.9	59.5	9.1	6.7	29.7	Average MRI-PDFF of 9-segment	16.3	Metformin, DPP-4 inhibitors, SUs, or insulin	Empagliflozin 10 mg/d	No additional treatment	20
Eriksson 2018	Sweden	R, DB, PC	T2D and NAFLD	38	65.3	78.6	7.4	6.6	30.2	MRI-PDFF covering the entire	16.2	Metformin, or SUs, 14% were	Dapagliflozin 10 mg/d	Placebo	12

										liver volume		drug naive			
Latva-Rasku 2019	Finland	R, DB, PC	T2D	31	60.9	80.6	6.9	7.5	32	Median LFC by MRI-PDFF covering the entire liver volume	21.5	Metformin, or DPP-4 inhibitors	Dapagliflozin 10 mg/d	Placebo	8
Cusi 2019	USA	R, DB, PC	T2D	51	58	66.1	7.7	NR	31.5	Liver ^{1}H-MRS	12.3	Metformin, or DPP-4 inhibitors	Canagliflozin 300 mg/d	Placebo	24
Kahl 2020	Germany	R, DB, PC	T2D	84	62.1	69	6.6	3.3	32.2	Liver ^{1}H-MRS	10.4	None	Empagliflozin 25 mg/d	Placebo	24
Gaborit 2021	France	R, DB, PC	T2D	51	56.9	39.2	8.1	11.1	34.9	Liver ^{1}H-MRS	26.5	Metformin, DPP-4 inhibitors,	Empagliflozin 10 mg/d	Placebo	12

												SUs, or insulin			
Horibe 2022	Japan	R, OL	T2D	43	60.9	64	7.7	12.5	27.8	Liver ^{1}H-MRS	22.1	Metformin, DPP-4 inhibitors, SUs, or insulin	Dapagliflozin 5 mg/d	No additional treatment	24
Elhini 2022	Egypt	R, DB, PC	T2D and NAFLD	160	47.5	65	8.5	NR	32.3	Average MRI-PDFF of 9-segment	20.8	Metformin, or SUs	Empagliflozin 25 mg/d	Placebo	24
Rajeev 2023	UK	R, DB, PC, CO	T2D	45	57.3	63	7.7	NR	35.2	Liver ^{1}H-MRS	19.9	Metformin, or SUs	Dapagliflozin 10 mg/d	Placebo	12
Shi 2023	China	R, OL	T2D and NAFLD	78	48.2	69.2	8.5	NR	30.7	Average MRI-PDFF of 9-	14.2	Metformin	Dapagliflozin 10 mg/d	No additional treatment	24

										segment					
Veelen 2023	The Netherlands	R, DB, PC, CO	Prediabetes	14	66.3	57.1	5.5	0	30.3	Liver ^{1}H-MRS	6.2	None	Dapagliflozin 10 mg/d	Placebo	2
Abdelganji 2024 DM	USA	R, DB, PC	T2D	30	55	57	7.6	5.9	32.7	Liver ^{1}H-MRS	13.6	Metformin, or SUs	Empagliflozin 25 mg/d	Placebo	12
Abdelganji 2024 NDM	USA	R, DB, PC	Non-diabetic overweight participants	27	45	52	5.5	0	34.3	Liver ^{1}H-MRS	11.8	None	Empagliflozin 25 mg/d	Placebo	12
Cheung 2024	China	R, DB, PC	Non-diabetic patients with	97	55.7	55.1	5.7	0	27.4	Average MRI-PDFF of 9-segment	9.6	None	Empagliflozin 10 mg/d	Placebo	52

			MASLD												

Table 2. Study quality evaluation via the cochrane risk of bias tool

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other sources of bias
Kuchay 2018	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Eriksson 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Latva-Rasku 2019	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cusi 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kahl 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gaborit 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Horibe 2022	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Elhini 2022	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Rajeev 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shi 2023	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk
Veelen 2023	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk

Abdelgani 2024 DM	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Abdelgani 2024 NDM	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Cheung 2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3. Results of subgroup analyses

	Difference of LFC between patients treated with SGLT2 inhibitors and controls				
Variables	No. of datasets	SMD (95% CI)	I^2	p for subgroup effects	p for subgroup difference
Study country					
Asian	4	-0.79 [-1.31, -0.28]	74%	0.003	
Non-Asian	10	-0.71 [-1.00, -0.43]	60%	< 0.001	0.79
Design					
R, DB, PC	11	-0.67 [-0.93, -0.40]	61%	< 0.001	
R, OL	3	-0.98 [-1.50, -0.46]	58%	< 0.001	0.29
Diabetic status					
T2D	11	-0.82 [-1.07, -0.56]	60%	< 0.001	
Non-diabetic	3	-0.38 [-0.77, -0.01]	19%	0.04	0.07
Mean age (years)					
< 57	7	-0.77 [-1.12, -0.42]	67%	< 0.001	
≥ 57	7	-0.70 [-1.05, -0.35]	61%	< 0.001	0.78

Men (%)					
< 64	7	-0.65 [-1.08, -0.23]	72%	0.003	
≥ 64	7	-0.81 [-1.08, -0.54]	46%	< 0.001	0.54
Baseline HbA1c (%)					
< 7.7	7	-0.54 [-0.78, -0.30]	11%	< 0.001	
≥ 7.7	7	-0.86 [-1.21, -0.50]	70%	< 0.001	0.14
Baseline BMI (kg/m^2)					
< 32	7	-0.63 [-0.97, -0.29]	60%	< 0.001	
≥ 32	7	-0.84 [-1.18, -0.49]	64%	< 0.001	0.40
Methods for LFC measuring					
MRI-PDFF	6	-0.81 [-1.14, -0.48]	61%	< 0.001	
1H-MRS	8	-0.67 [-1.03, -0.31]	65%	< 0.001	0.59
Baseline LFC (%)					
< 15	7	-0.67 [-1.03, -0.30]	65%	< 0.001	

≥ 15	7	-0.80 [-1.12, -0.49]	58%	< 0.001	0.58
SGLT2 inhibitors					
Empagliflozin	7	-0.60 [-0.87, -0.34]	46%	0.09	
Dapagliflozin	6	-0.93 [-1.35, -0.50]	66%	0.01	0.21
Treatment durations (weeks)					
< 24	8	-0.73 [-1.11, -0.35]	62%	< 0.001	
≥ 24	6	-0.74 [-1.06, -0.41]	67%	< 0.001	0.98

Table 4. Results of univariate meta-regression analysis

Variables	SMD for the changes of LFC between patients treated with SGLT2 inhibitors and controls		
	Coefficient	95% CI	P values
Sample size	-0.00095	-0.00806 to 0.00616	0.77
Mean age (years)	0.032	-0.008 to 0.072	0.11
Men (%)	-0.017	-0.042 to 0.008	0.18
Baseline HbA1c (%)	-0.16	-0.39 to 0.07	0.15
Baseline BMI (kg/m^2)	-0.052	-0.166 to 0.062	0.34
Baseline LFC (%)	-0.020	-0.068 to 0.029	0.40
Treatment duration (weeks)	0.0050	-0.0176 to 0.0277	0.64

Table 5. Summarized certainty of evidence using the GRADE system

Outcome	Quality assessment							Absolute effect SMD (95% CI)	Quality
	No. of datasets	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LFC (%)	14	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	None	-0.73 (-0.97 to -0.50)	⊕⊕⊕O MODERATE

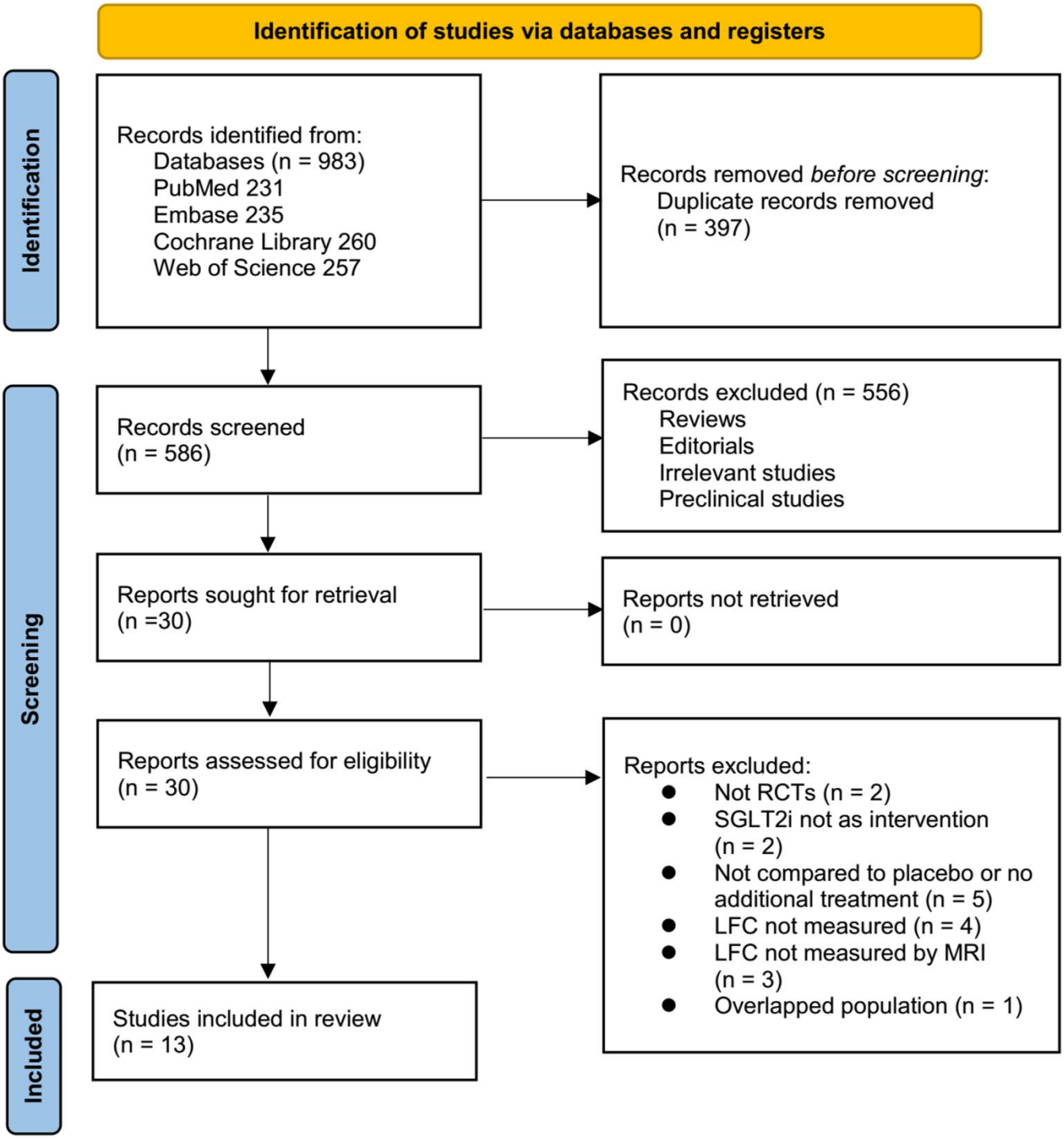

Figure 1. Flowchart of study inclusion

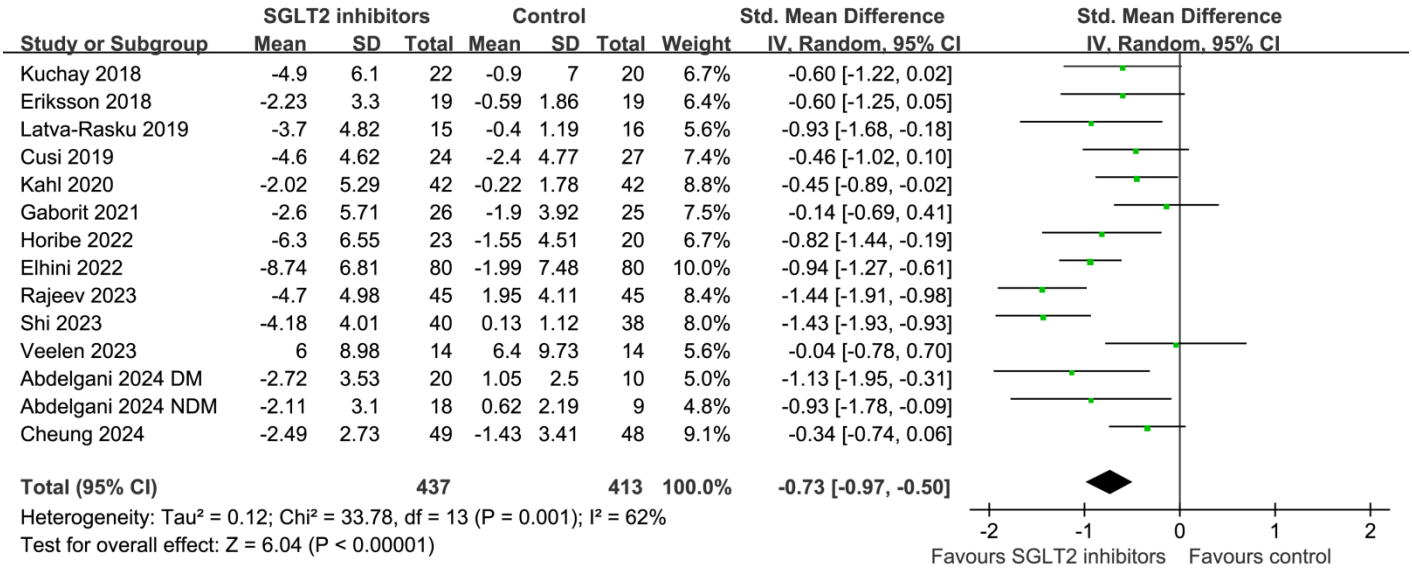

Figure 2. Forest plots for the meta-analysis comparing the influence between SGLT2 inhibitors with controls on LFC

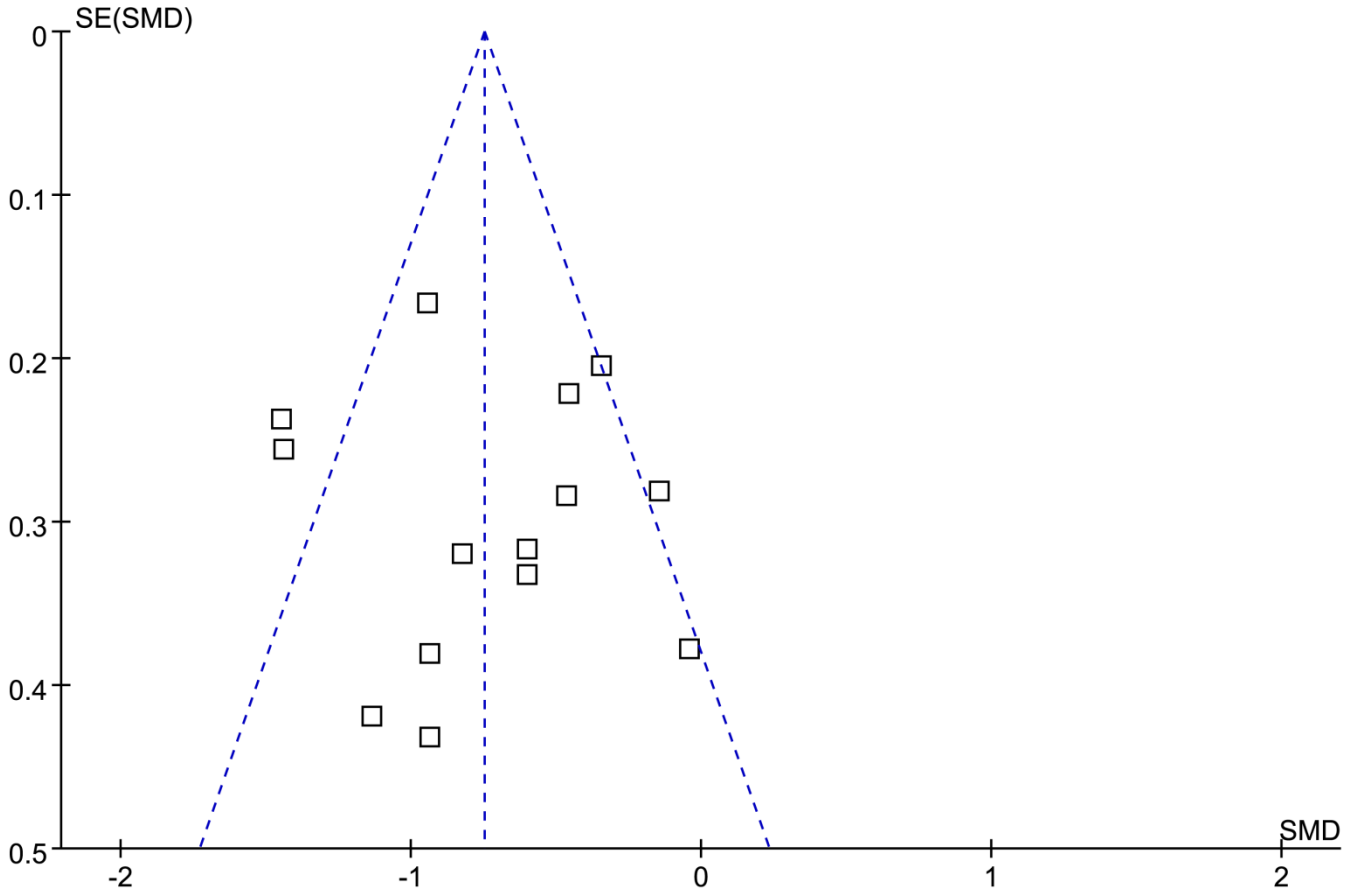

Figure 3. Funnel plots for the publication bias underlying the meta-analysis comparing the influence between SGLT2 inhibitors with controls on LFC

SUPPLEMENTAL DATA

Detailed search strategy for each database

PubMed

("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "sodium glucose transporter 2 inhibitor" OR "sodium glucose transporter ii inhibitor" OR "SGLT 2 inhibitor" OR "SGLT-2 inhibitor" OR "SGLT2" OR "sodium glucose cotransporter 2 inhibitors" OR "canagliflozin" OR "dapagliflozin" OR "empagliflozin" OR "ertugliflozin" OR "tofogliflozin" OR "bexagliflozin" OR "henagliflozin" OR "ipragliflozin" OR "licogliflozin" OR "luseogliflozin" OR "remogliflozin" OR "sergliflozin" OR "sotagliflozin") AND ("Randomized Controlled Trial"[Publication Type] OR "randomized" OR "randomly" OR "randomization" OR "placebo" OR "control" OR "allocated" OR "RCT") AND ("Liver"[Mesh] OR "Hepatic" OR "Liver") AND ("Fat"[Mesh] OR "adipose" OR "adiposity" OR "lipid")

Embase

('sodium glucose transporter 2 inhibitor'/exp OR 'sodium glucose transporter 2 inhibitor' OR 'sodium glucose transporter ii inhibitor' OR 'sglt 2 inhibitor' OR 'sglt-2 inhibitor' OR 'sglt2' OR 'sodium glucose cotransporter 2 inhibitors' OR 'canagliflozin' OR 'dapagliflozin' OR 'empagliflozin' OR 'ertugliflozin' OR 'tofogliflozin' OR 'bexagliflozin' OR 'henagliflozin' OR 'ipragliflozin' OR 'licogliflozin' OR 'luseogliflozin' OR 'remogliflozin' OR 'sergliflozin' OR 'sotagliflozin') AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomized' OR 'randomly' OR 'randomization' OR 'placebo' OR 'control' OR 'allocated' OR 'rct') AND ('liver'/exp OR 'hepatic' OR 'liver') AND ('fat'/exp OR 'adipose' OR 'adiposity' OR 'lipid')

Cochrane Library

("sodium glucose transporter 2 inhibitor" OR "sodium glucose transporter ii inhibitor" OR "SGLT 2 inhibitor" OR "SGLT-2 inhibitor" OR "SGLT2" OR "sodium glucose cotransporter 2 inhibitors" OR "canagliflozin" OR "dapagliflozin" OR "empagliflozin" OR "ertugliflozin" OR "tofogliflozin" OR "bexagliflozin" OR "henagliflozin" OR "ipragliflozin" OR "licogliflozin" OR "luseogliflozin" OR "remogliflozin" OR "sergliflozin" OR "sotagliflozin") AND ("randomized controlled trial" OR "randomized" OR "randomly" OR "placebo" OR "control" OR "allocated" OR "RCT") AND ("liver" OR "hepatic") AND ("fat" OR "adipose" OR "adiposity" OR "lipid") IN Cochrane Central Register of Controlled Trials (CENTRAL)

Web of Science

TS=("sodium glucose transporter 2 inhibitor" OR "sodium glucose transporter ii inhibitor" OR "SGLT 2 inhibitor" OR "SGLT-2 inhibitor" OR "SGLT2" OR "sodium glucose cotransporter 2 inhibitors" OR "canagliflozin" OR "dapagliflozin" OR "empagliflozin" OR "ertugliflozin" OR "tofogliflozin" OR "bexagliflozin" OR "henagliflozin" OR "ipragliflozin" OR "licogliflozin" OR "luseogliflozin" OR "remogliflozin" OR "sergliflozin" OR "sotagliflozin") AND TS=("randomized controlled trial" OR "randomized" OR "randomly" OR "placebo" OR "control" OR "allocated" OR "RCT") AND TS=("liver" OR "hepatic") AND TS=("fat" OR "adipose" OR "adiposity" OR "lipid")