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Original Article

Comparative Efficacy of Promising Targets in the Treatment of Metabolic Dysfunction-associated Steatotic Liver Disease and Steatohepatitis: A Systematic Review and Network Meta-analysis

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Abstract

Background and Aims: Randomized controlled trials (RCTs) have been conducted to evaluate treatment efficacy for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis. This study aimed to compare the effectiveness and safety of 11 promising targets among adults with MASLD. ***Methods:*** PubMed, Web of Science, the Cochrane Central Register of Controlled Trials, Scopus, and Embase were searched from inception to November 20, 2024. The primary outcomes were fibrosis improvement ≥1 stage without worsening of steatohepatitis and steatohepatitis resolution without worsening of fibrosis. Additional outcomes included reductions in liver fat content, liver enzymes, metabolic profiles, and selected safety outcomes. The surface under the cumulative ranking curve (SUCRA) was used to rank efficacy. ***Results:*** Of 11,584 articles screened, 44 eligible RCTs (11,410 participants, 33 medications) were included. For fibrosis improvement, d-(R)-pioglitazone (SUCRA: 79.3) and fibroblast growth factor (FGF) 21 analogs (SUCRA: 71.9) ranked higher. For steatohepatitis resolution, glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists (RAs) (SUCRA: 91.7) ranked higher. Co-agonists of GLP-1/GIP/GCG and GLP-1/GCG receptors ranked higher for relative and absolute changes in liver fat content, respectively. For liver enzymes and glucose improvement, the combination of a GLP-1 RA and an acetyl-coenzyme A carboxylase inhibitor ranked higher. GLP-1 RAs, peroxisome proliferator-activated RAs, and FGF21 analogs showed favorable effects on lipid profile improvement. ***Conclusions:*** Incretin-based co-agonists and FGF21 analogs showed favorable profiles across key endpoints, while d-(R)-pioglitazone and GLP-1/GIP dual RAs ranked higher for fibrosis improvement and steatohepatitis resolution, respectively. SUCRA rankings should be interpreted in conjunction with effect sizes, uncertainty, and available safety data.

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Keywords: Metabolic dysfunction-associated steatotic liver disease; Randomized controlled trials; Fibrosis improvement; Steatohepatitis resolution; Metabolic improvement; Non-invasive tests; Safety assessment; Network meta-analysis.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), with its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), is the leading cause of chronic liver diseases globally.[1,2] Substantial efforts have been de-

voted to developing pharmacological therapies to address MASH and MASH-associated fibrosis.

Currently, resmetirom, a thyroid hormone receptor-β (THR-β) agonist, is the only medication approved by the United States Food and Drug Administration for the treatment of individuals with MASH and fibrosis stages F2–F3.[3] Resmetirom achieved significant histological improvements in the liver after 52 weeks of treatment.[4] However, there remains a considerable unmet medical need for effective MASH therapies.

Several pharmacological therapies targeting different mechanisms have shown promising efficacy in the treatment of MASH, such as GLP-1 receptor agonists (RAs), fibroblast growth factor (FGF) 21 analogues, and peroxisome proliferator-activated receptor (PPAR) agonists, which act on metabolism, fibrosis, and inflammation through distinct pathways. These emerging therapies represent promising interventions for managing MASH. In this systematic review and network meta-analysis, we aimed to compare the efficacy of key candidate interventions targeting distinct mechanisms across a comprehensive range of endpoints beyond liver fat content (LFC), including fibrosis improvement, steatohepatitis resolution, liver enzyme improvement, and changes in metabolic parameters such as weight, glucose, and lipid profiles. We also assessed selected safety outcomes reported in the included trials. The results of this study provide a critical summary and appraisal of current progress in MASH treatment and may inform future clinical development and the therapeutic landscape of MASH.

Methods

The protocol for this systematic review and network meta-analysis has been registered with PROSPERO (CRD4202 4625681). This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement and the extension for network meta-analyses (PRISMA-NMA).[5,6]

Data sources and search strategy

We searched PubMed, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Embase for randomized controlled trials (RCTs) in adults with MASLD/MASH (previously known as NAFLD/MAFLD/NASH) from inception to November 20, 2024, as well as abstracts presented at the annual meetings of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) between 2020 and 2024. Six paired reviewers (WJN, XYW, SSZ, XB, ML, and ZRJ) independently conducted the first-round screening based on abstracts and titles, cross-checking their results sequentially. Any studies with uncertainty or inconsistencies were retained for further review. Subsequently, the second-round screening was conducted independently by the same six reviewers using full texts and/or trial protocols, with results also checked in sequence. Any remaining inconsistencies were resolved by a seventh reviewer (JL). Comprehensive search strategies for each of the five databases are provided in the Supplementary File 1.

Study selection

The inclusion criteria were as follows: (1) RCTs enrolling participants aged 18 years or older; (2) MASLD diagnosed by liver histology and/or magnetic resonance imaging proton density fat fraction (MRI-PDFF); (3) interventions targeting THR-β agonists, GLP-1 RAs, GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual RAs, GLP-1/GIP/glucagon (GCG) triple RAs, GLP-1/GCG dual RAs, farnesoid X receptor (FXR) agonists, FGF21 analogues, FGF19 analog, acetyl-coenzyme A carboxylase (ACC) inhibitors, and PPAR agonists or PPAR-related isomers.

The exclusion criteria included: (1) review articles, meta-analyses, letters, comments, editorials, animal studies, practice guidelines, consensus statements, case reports, protocols, or other forms of gray literature, including preprints not formally published, unpublished reports, regulatory documents, theses, or dissertations. Conference proceedings were not routinely included, except for abstracts presented at the annual meetings of AASLD and EASL between 2020 and 2024; (2) observational, cross-sectional, case-control, or single-arm studies; (3) phase 1 trials; (4) trials enrolling a majority of participants with cirrhosis (F4); (5) trials using lifestyle interventions as the comparator; (6) trials reporting treatments involving traditional Chinese medicine, probiotics, or lifestyle interventions (diet and/or physical exercise); (7) trials conducted in pediatric or adolescent populations (younger than 18 years); and (8) trials written in languages other than English; or (9) studies without available data for extraction and analysis.

Data extraction

Data extraction from eligible studies included study characteristics (title, authors, year of publication, trial registration number, and country/region), participant baseline characteristics, including age, sex, sample size, body mass index (BMI), glycated hemoglobin (HbA1c), LFC assessed by MRI-PDFF, liver stiffness measurement (LSM) assessed by magnetic resonance elastography, prevalence of diabetes, hypertension, and dyslipidemia, distributions of fibrosis stages (F1–F3) diagnosed by liver biopsy, intervention details (medication name, therapeutic target, duration, dose, dosing frequency, and route of administration), relevant liver histological outcomes at the end of treatment, other outcome changes from baseline, and prespecified safety outcomes. Continuous variables were extracted only when each arm included sample size, mean, and standard deviation (SD), or when SD could be calculated. For each intervention, the dose and frequency associated with the most favorable estimate for the corresponding outcome were selected. If multiple published reports were identified from the same clinical trial, the most recent and most complete dataset was used for data extraction and analysis. When certain outcomes were not available in the most recent publication, relevant data from earlier reports of the same trial were used, ensuring each outcome was included only once per trial in the meta-analysis. Plot Digitizer was used to extract values when data were presented only in figures.[7,8]

Outcomes

The primary outcomes were: (1) fibrosis improvement of at least one stage without worsening of steatohepatitis; and (2) steatohepatitis resolution without worsening of fibrosis. Secondary outcomes included relative and absolute changes from baseline in LFC assessed by MRI-PDFF; absolute changes in liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]); body weight; lipid and glucose parameters (triglycerides, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], HbA1c, and fasting blood glucose [FBG]); as well as non-invasive tests (NITs), including the enhanced liver fibrosis (ELF) score, N-terminal type III collagen propeptide (PRO-C3), and LSM assessed by vibration-controlled transient elastography (VCTE). Safety outcomes included any adverse events (AEs), serious adverse events (SAEs), discontinuation due to AEs, three common gastrointestinal

(GI) events (nausea, diarrhea, and vomiting), cardiovascular events, and pruritus (specifically for FXR agonists).

Quality assessment

The Cochrane Risk of Bias tool for randomized trials (version 2.0, RoB 2) was used to assess risk of bias in eligible studies.[9] RoB 2 includes five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall risk of bias was categorized as low, some concerns, or high. Two investigators (WJN and SSZ) independently assessed each domain, and inconsistencies were resolved through discussion. Funnel plots were used to evaluate publication bias. The Confidence in Network Meta-Analysis (CINeMA) framework was used to assess certainty of evidence.[10,11] This framework evaluates six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency. Certainty of evidence was classified as high, moderate, low, or very low.

Data synthesis and analysis

For lipid and glucose variables, mean and SD of absolute changes were converted from millimoles per liter (mmol/L) to milligrams per deciliter (mg/dL). When studies reported separate results for participants with and without diabetes for glucose-related variables, the formula provided below was used to calculate combined results according to Cochrane Handbook guidance[12]:

$$\sqrt{\frac{\left(N_1-1\right)SD_1^2+\left(N_2-1\right)SD_2^2+\frac{N_1N_2}{N_1+N_2}\left(M_1^2+M_2^2-2M_1M_2\right)}{N_1+N_2-1}}$$

Network meta-analyses of RCTs were conducted using Stata version 17 (StataCorp LLC) within a frequentist framework. Liver histological and safety outcomes, treated as binary variables, were measured using odds ratios (ORs). Absolute risk differences (ARDs) for histological outcomes were derived from ORs estimated in the network meta-analysis. The pooled placebo event risk, calculated as the weighted mean event rate across placebo arms of included trials for each outcome, was used as the assumed comparator risk (ACR).[13] The corresponding intervention risk ($Risk_{intervention}$) was calculated as:

$$\text{Corresponding intervention risk}=\frac{\text{OR}\times\text{ACR}}{1-\text{ACR}+(\text{OR}\times\text{ACR})}$$

The ARD was then calculated as: ARD = $Risk_{intervention}$ − ACR. A positive ARD indicated a higher event probability in the intervention group than in the placebo group, representing an absolute increase in treatment benefit. The 95% confidence intervals (CIs) for ARDs were derived by applying the same transformation to the upper and lower limits of the OR 95% CIs. Secondary continuous outcomes were calculated as mean differences with 95% CIs. Subgroup analyses by treatment duration and leave-one-out sensitivity analyses were performed to evaluate liver histological improvement. Network diagrams and surface under the cumulative ranking curve (SUCRA) plots were generated for ranking assessments. SUCRA values range from 0% to 100%, with higher values indicating a greater probability of ranking among more effective interventions, and lower values indicating less effective interventions. Rankograms were also generated to display full ranking probability distributions across all possible ranks for both primary outcomes and for relative and absolute changes in LFC, with rank 1 indicating the most favorable outcome. Global inconsistency was assessed using an inconsistency model when network geometry allowed. Inconsistency testing was not performed when insufficient indirect evidence was available. Evidence contribution matrices were generated for the two primary outcomes and for relative and absolute changes in LFC to quantify the contribution of each direct comparison to network estimates. Meta-regression was conducted to explore the impact of treatment duration on histological outcomes. Forest plots were generated using R software version 4.3.1 (http://www.R-project.org) and GraphPad Prism version 10.1.2.

Results

Characteristics of eligible studies

A total of 18,237 records were retrieved from five databases, with 1,038 studies selected for full-text screening. Finally, 44 studies (11,410 randomized participants, 11 targets, 33 medications) that met the study eligibility criteria were included (Fig. 1). A summary of these eligible studies is provided in Supplementary Table 1. At baseline, the mean age of participants across the included RCTs ranged from 37.0 to 59.4 years, indicating that most study populations were middle-aged. The reported mean or median BMI generally ranged from 28.4 to 39.7 kg/m^2, except for one study that enrolled participants with a mean BMI of 18–22 kg/m^2.[14] Within individual RCTs, the distributions of key baseline characteristics, including sex, metabolic comorbidities, and fibrosis stage, were generally balanced across randomized treatment arms. However, between-trial variations were observed in baseline BMI, metabolic profiles, fibrosis stage distributions, and intervention durations. A summary of key baseline characteristics of the study populations is provided in Supplementary Table 2.

Analysis for PPAR agonists included the most medications (pioglitazone, pemafibrate, lanifibranor, elafibranor, rosiglitazone, saroglitazar, and chiglitazar). PXL065, a deuterium-stabilized R-pioglitazone (d-(R)-pioglitazone), was included as a separate target for analysis, as it is developed with deuterium added to its chiral center and does not activate PPAR.[15] Analysis of THR-β agonists included two medications (resmetirom and VK2809). Analysis of FXR agonists included five medications (obeticholic acid, EDP-305, vonafexor, cilofexor, and FXR314), while analysis of the FGF19 analogue included only aldafermin (also known as NGM282 or M70). Analysis of FGF21 included four medications (pegozafermin, pegbelfermin, efruxifermin, and efimosfermin alfa [BOS-580]), and analysis of ACC inhibitors included two medications (PF-05221304 and firsocostat [GS-0976]). As for GLP-1 RA, dulaglutide, semaglutide, and liraglutide were included. Analysis of GLP-1/GCG dual RA included four medications (efinopegdutide, pemvidutide, survodutide, and cotadutide); analysis of GLP-1/GIP dual RA included tirzepatide; and analysis of GLP-1/GCG/GIP triple RA included retatrutide.

Regarding route of administration, PPAR agonists, d-(R)-pioglitazone, THR-β agonists, FXR agonists, and ACC inhibitors were administered orally once daily, whereas FGF19 analogue, FGF21 analogue, GLP-1 RA, GLP-1/GIP dual RA, and GLP-1/GCG/GIP triple RA were administered subcutaneously. The duration of intervention in the included studies ranged from 12 to 72 weeks. Specifically, the intervention durations of the included RCTs contributing to histological outcomes ranged from 16 to 72 weeks.

Risk of bias, publication bias, and global consistency

The details of the risk of bias assessment for each included

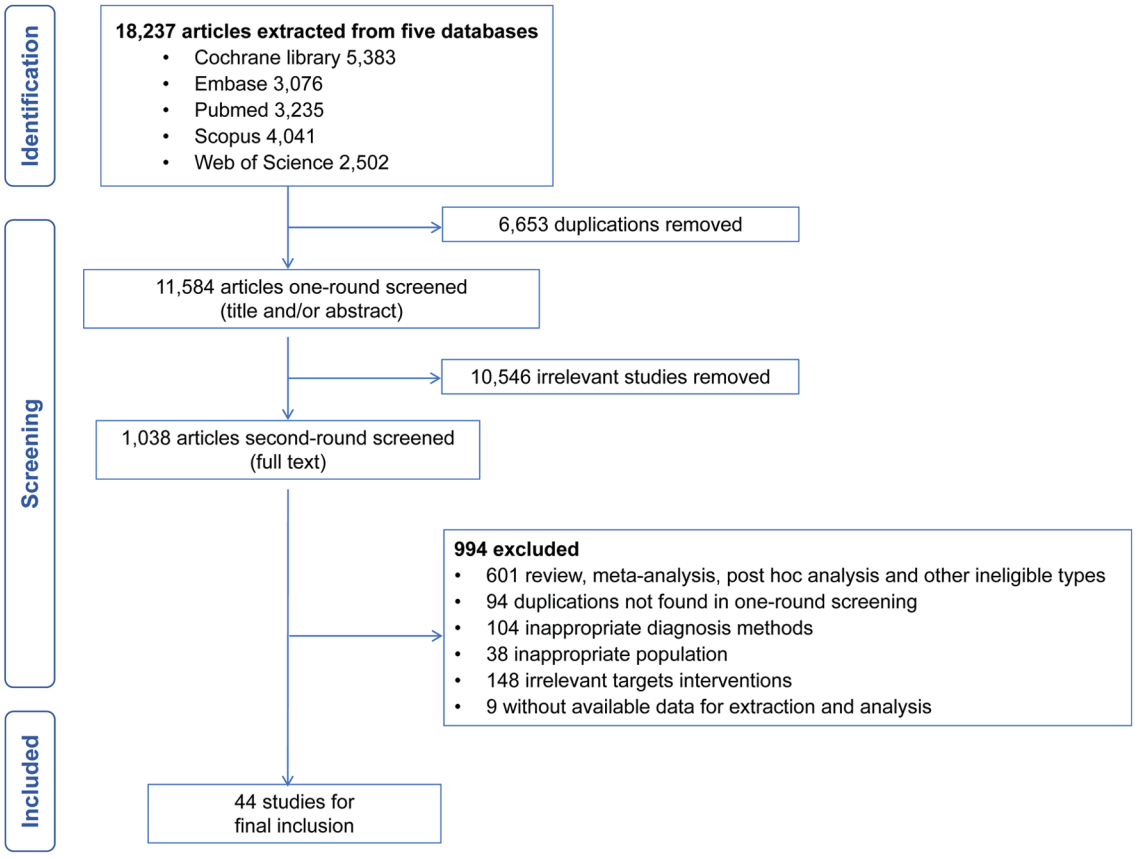

Fig. 1. Flow diagram for systematic reviews and meta-analyses (PRISMA).

study are presented in Supplementary Figure 1 and Supplementary Table 3. Briefly, 84.0% of included studies had a low risk of bias for the randomization process. The majority of studies [34 (77.2%), 41 (93.1%), 42 (95.4%), and 42 (95.4%)] were considered at low risk for deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result, respectively. Funnel plots showed no significant asymmetry, suggesting no evidence of publication bias (Supplementary Figs. 2 and 3). Global inconsistency tests were largely not applicable for most outcomes due to insufficient indirect evidence, and no inconsistency was detected where testing was possible for relative change from baseline in LFC, liver enzymes, and certain safety outcomes (Supplementary Table 4).

Liver histology improvement

Fibrosis improvement at least one stage without steatohepatitis worsening: A total of 17 studies with 3,300 participants reported the outcome of fibrosis improvement of at least one stage without steatohepatitis worsening. Nine targets comprising 14 medications were included for comparison (Fig. 2A). The network was predominantly placebo-centered, with interventions connected through placebo and no direct head-to-head comparisons among active interventions. Compared with placebo, d-(R)-pioglitazone (OR: 4.75, 95% CI: 1.21 to 18.58), FGF21 analogue (OR: 3.52, 95% CI: 1.81 to 6.85), GLP-1/GCG dual RA (OR: 3.40, 95% CI: 1.53 to 7.56), and GLP-1/GIP dual RA (OR: 3.01, 95% CI: 1.29 to 7.02) showed favorable signals, with ORs greater than 3 for this outcome (Fig. 3A). The SUCRA scores showed that d-(R)-pioglitazone (SUCRA: 79.3), FGF21 analogue (SUCRA: 71.9), and GLP-1/GCG dual RA (SUCRA: 69.5) ranked higher than the other interventions, followed by PPAR agonists (SUCRA: 61.3), GLP-1/GIP dual RA (SUCRA: 59.7), and FXR agonists (SUCRA: 55.5) (Supplementary Table 5.1). Because SUCRA summarizes ranking probabilities rather than the magnitude of effect, rankings should be interpreted together with effect estimates, 95% CIs, and the certainty of evidence. The rankograms showed a ranking pattern broadly aligned with the SUCRA estimates, while also illustrating uncertainty in ranking probabilities across targets (Supplementary Fig. 4A).

In the CINeMA assessment, the certainty of evidence for most target comparisons was rated as low or very low, mainly due to small sample sizes, single-trial evidence, imprecision, and limited direct comparative evidence. Comprehensive comparisons between targets and the CINeMA assessment are provided in Supplementary Table 6.1. In addition, given the placebo-centered network structure, an evidence contribution matrix was generated. The results showed that active-versus-placebo estimates were mainly informed by the corresponding direct placebo-controlled comparisons, whereas most active-versus-active estimates were primarily derived from indirect evidence through the common placebo comparator (Supplementary Table 7.1).

We further evaluated the ARDs across targets. Using the pooled placebo event risk of 17.41% as the ACR, the estimated ARDs across targets ranged from 12.30 to 32.30 percentage points versus placebo, indicating an absolute

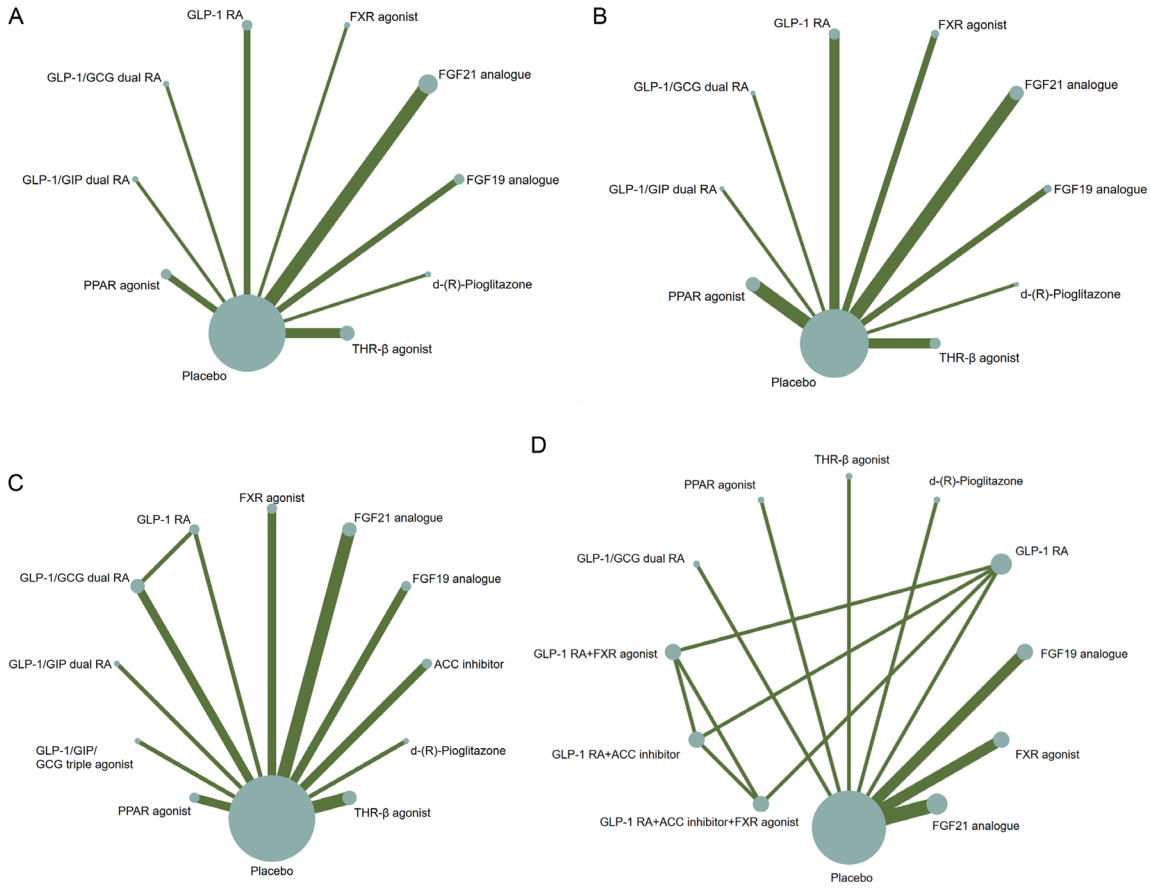

Fig. 2. Network maps of available comparisons of targets and placebo for liver histology and liver fat content. (A) Fibrosis improvement of at least one stage without steatohepatitis worsening; (B) Steatohepatitis resolution without fibrosis worsening; (C) Relative change from baseline in liver fat content; (D) Absolute change from baseline in liver fat content. ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

increase in the probability of achieving the histological outcome (Supplementary Table 8.1).

As for medications, 30 mg/day pioglitazone[16] ranked highest, followed by 44 mg every two weeks of pegozafermin[17] and 50 mg/week efruxifermin[18] (Supplementary Fig. 5A). However, liver biopsy results from efruxifermin were flagged for high risk of bias due to missing outcome data caused by the COVID-19 pandemic and patient-specific issues.[18]

Steatohepatitis resolution without fibrosis worsening: A total of 21 studies evaluating 9 targets in 3,768 participants were analyzed for the outcome of steatohepatitis resolution without fibrosis worsening (Fig. 2B). Compared with placebo, GLP-1/GIP dual RA, the highest-ranking target according to SUCRA (91.7), had an OR of 14.33 (95% CI: 3.39 to 60.57) for achieving this outcome, followed by GLP-1/GCG dual RA (OR: 10.67, 95% CI: 3.07 to 37.04) (Supplementary Table 5.2). All of these targets, except for d-(R)-pioglitazone, showed favorable efficacy signals compared with placebo (Fig. 3B and Supplementary Table 6.2). In addition, because the LEAN trial enrolled a small proportion of patients with cirrhosis, as assessed by the Kleiner scoring system,[19] a sensitivity analysis was conducted excluding liraglutide. The ranking order remained unchanged, and a similar SUCRA value (59.7) was observed for GLP-1 RA compared with placebo (OR: 4.35, 95% CI: 1.91–9.87). In the CINeMA assessment, many comparisons were downgraded due to imprecision, as reflected by wide 95% CIs and limited sample sizes. Detailed comparisons and certainty of evidence are provided in Supplementary Table 6.2. The rankogram was generally consistent with the SUCRA-based ranking pattern (Supplementary Fig. 4B). The contribution matrix showed that most active-versus-active estimates were primarily informed by indirect evidence through placebo, highlighting the limited direct comparative evidence within the network and suggesting caution when comparing active targets (Supplementary Table 7.2).

In addition, using the pooled placebo event risk of 15.59% as the ACR, the estimated ARDs across targets ranged from 5.10 to 57.00 percentage points, suggesting varying absolute increases in the probability of achieving steatohepatitis resolution (Supplementary Table 8.2).

For specific medications, 15 mg/week pegozafermin[17] and 15 mg/week tirzepatide[20] showed favorable signals compared with placebo (Supplementary Fig. 5B).

LFC as assessed by MRI-PDFF

There were 21 studies involving 2,296 participants, and 16 studies comprising 1,127 participants were analyzed to evaluate the relative and absolute changes in LFC from baseline, respectively. For relative change in LFC from baseline, 11 targets were compared with placebo in double-blind trials (Fig.

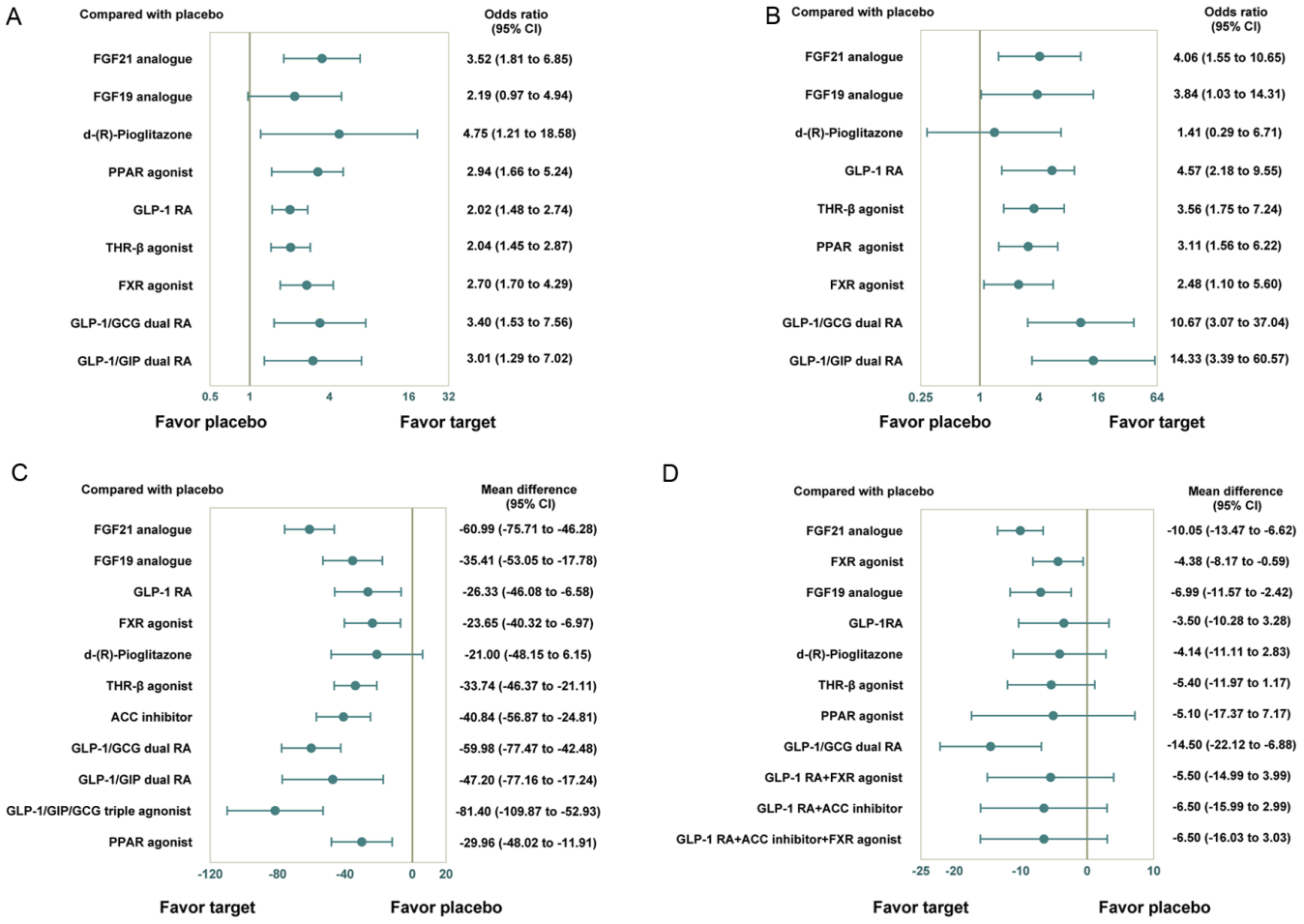

Fig. 3. Forest plots of network effect sizes between targets and placebo for liver histology and liver fat content. (A) Fibrosis improvement of at least one stage without steatohepatitis worsening; (B) Steatohepatitis resolution without fibrosis worsening; (C) Relative change from baseline in liver fat content; (D) Absolute change from baseline in liver fat content. ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

2C). GLP-1/GIP/GCG triple RA demonstrated a favorable effect estimate (mean difference: −81.40%, 95% CI: −109.87 to −52.93, SUCRA: 97.5) (Fig. 3C and Supplementary Table 5.3). GLP-1 RA (semaglutide) and GLP-1/GCG dual RA (efinopegdutide) were compared in an open-label RCT,[21] with low to very low certainty of evidence (Supplementary Table 6.3). Regarding absolute change in LFC from baseline, GLP-1/GCG dual RA was associated with a relatively larger estimated treatment effect (mean difference: −14.50, 95% CI: −22.12 to −6.88, SUCRA: 94.3) (Fig. 3D and Supplementary Table 5.4).

For both outcomes, the rankograms showed patterns generally aligned with the corresponding SUCRA estimates (Supplementary Figs. 4C and D). The contribution matrix indicated that the evidence structure was not purely star-shaped, as a few active-comparator trials contributed to selected network estimates. However, the network remained predominantly placebo-centered, and most active-versus-active estimates were still primarily informed by indirect evidence via placebo (Supplementary Tables 7.3 and 7.4).

Among specific medications, 12 mg/week retatrutide,[22] 70 mg/week efruxifermin,[18] and 1.8 mg/week pemvidutide[23] exhibited favorable signals in reducing relative change in LFC from baseline (Supplementary Fig. 5C), and 70 mg/week efruxifermin,[18] 1.8 mg/week pemvidutide,[23] and 27 mg/week pegozafermin[17,24] ranked higher for reducing absolute change in LFC from baseline (Supplementary Fig. 5D).

Liver enzyme improvement

The effects of different targets on ALT improvement were analyzed using data from 23 studies with 3,176 participants. Combination therapy of GLP-1 RA + ACC inhibitor + FXR agonist yielded a favorable point estimate for reducing ALT levels (mean difference: −46.31, 95% CI: −67.96 to −24.67; SUCRA: 91.7) (Fig. 4A and Supplementary Table 6.5). For AST reduction, data from 3,058 participants in 21 studies were analyzed. GLP-1 RA + ACC inhibitor had a comparatively favorable point estimate (mean difference: −30.54, 95% CI: −49.48 to −11.61; SUCRA: 89) (Fig. 4B and Supplementary Table 6.6). Additional details of target and medication comparisons for ALT and AST are provided in Supplementary Tables 6.5–6.6 and Supplementary Figures 6A–B.

Body weight

A total of 11 targets in 21 studies involving 3,375 par-

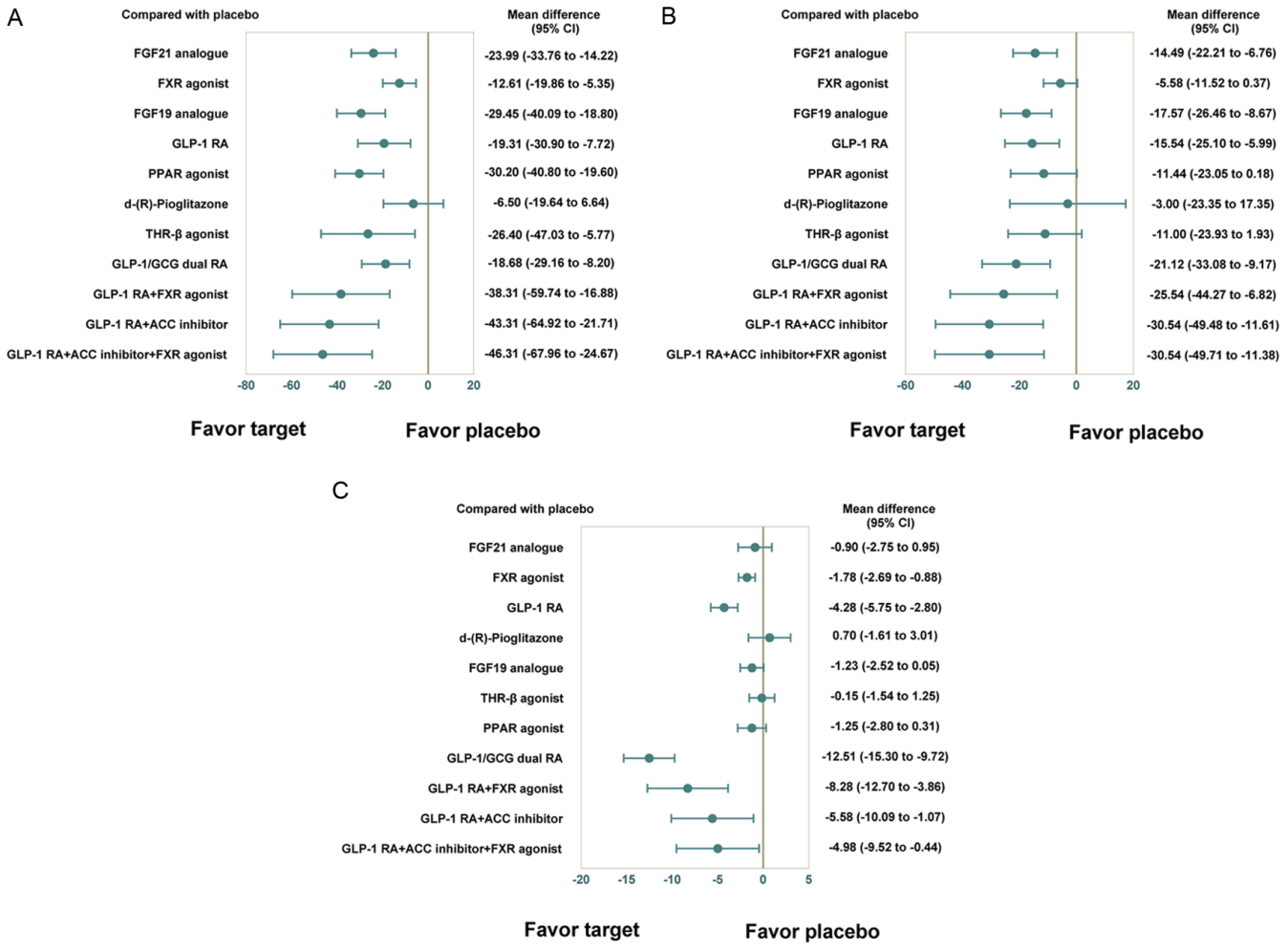

Fig. 4. Forest plots of network effect sizes between targets and placebo for liver enzymes and body weight. (A) ALT; (B) AST; (C) Body weight. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

ticipants were analyzed to evaluate the effects of interventions on body weight. GLP-1/GCG dual RA showed a favorable point estimate for body weight reduction (mean difference: −12.51, 95% CI: −15.30 to −9.72; SUCRA: 99.4) (Fig. 4C and Supplementary Table 5.7). Comparisons of targets for body weight reduction are detailed in Supplementary Table 5.7. These findings were generally aligned with the results for specific interventions (Supplementary Fig. 6C).

Metabolic profiles

Lipid parameters: TG, LDL-C, HDL-C, and TC were selected as key parameters for assessing improvements in lipid profiles. Among these targets, PPAR agonists showed a favorable point estimate for reducing TG levels (mean difference: −53.36, 95% CI: −72.98 to −33.74; SUCRA: 86.2). For LDL-C reduction, GLP-1 RA displayed the highest SUCRA value (78.7). However, the reduction was not statistically significant compared with placebo (mean difference: −21.13, 95% CI: −52.64 to 10.38). The FGF21 analogue showed a favorable point estimate for increasing HDL-C (mean difference: 7.66, 95% CI: 3.13 to 12.20; SUCRA: 94.5) and for lowering TC (mean difference: −34.33, 95% CI: −68.15 to −0.16; SUCRA: 86.4) (Figs. 5A–D and Supplementary Tables 5.8–5.11). Comparisons of lipid profiles across different targets and specific medications are provided in Supplementary Tables 6.8–6.11 and Supplementary Figures 6D–G.

Glucose parameters: HbA1c and FBG were selected as representative parameters for evaluating improvements in glucose profiles. Although GLP-1 RA + ACC inhibitor had the highest SUCRA score (77.5) for lowering HbA1c (Supplementary Table 6.12), its effect did not reach statistical significance (mean difference: −0.73, 95% CI: −1.60 to 0.13) (Fig. 5E). For FBG, GLP-1 RA + ACC inhibitor showed a relatively larger estimated effect (mean difference: −24.92, 95% CI: −41.98 to −7.86; SUCRA: 84.1) (Fig. 5F and Supplementary Table 6.13). Comparisons of targets and medications for glucose profiles are provided in Supplementary Tables 6.12–6.13 and Supplementary Figures 6H–I.

Three representative NITs

We analyzed ELF score, PRO-C3, and LSM-VCTE. GLP-1/GIP dual RA showed favorable point estimates for decreas-

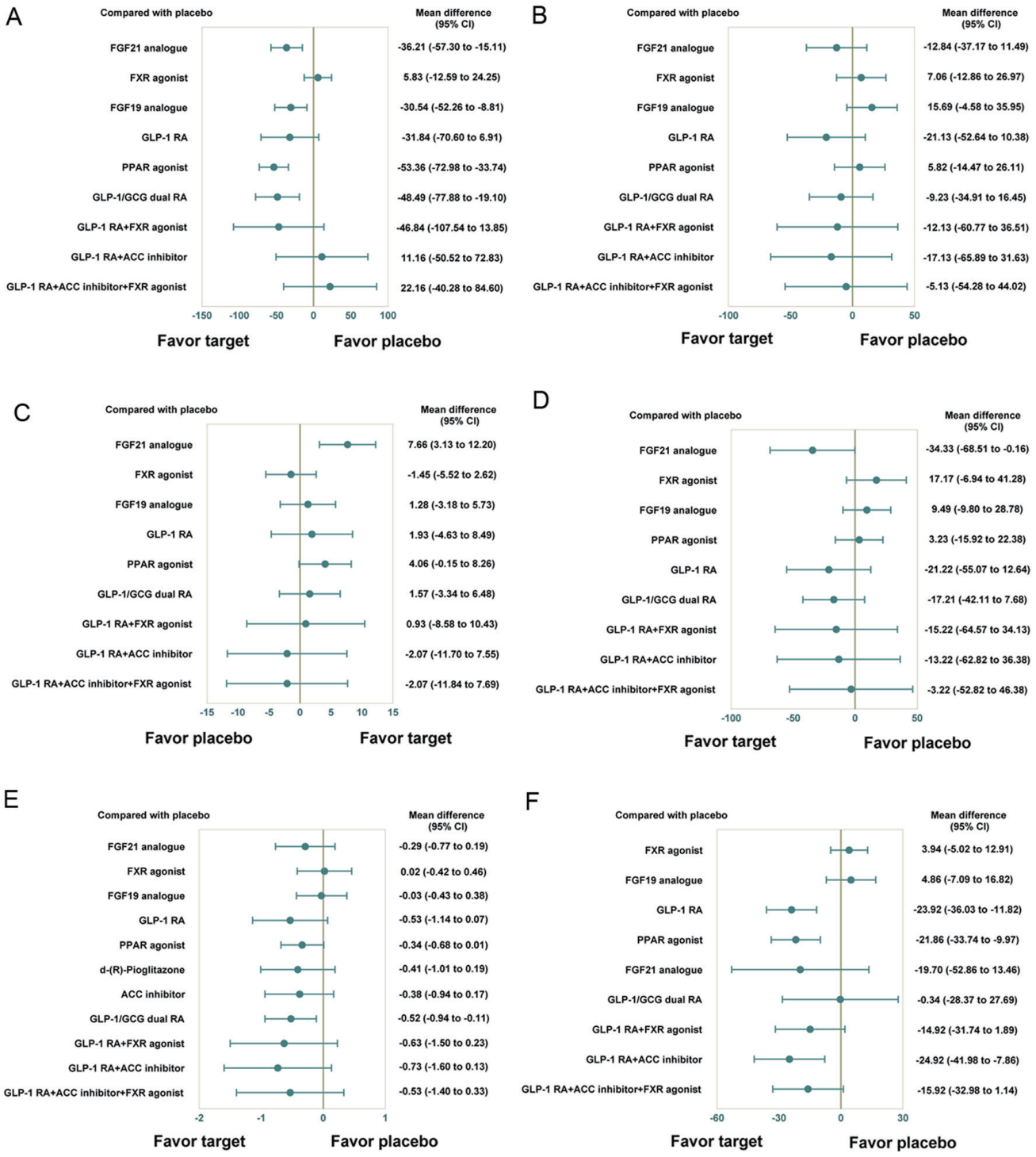

Fig. 5. Forest plots of network effect sizes between targets and placebo for metabolic profiles. (A) Triglyceride; (B) LDL-C; (C) HDL-C; (D) Total cholesterol; (E) HbA1c; (F) Fasting blood glucose. ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

ing both ELF score (mean difference: −0.66, 95% CI: −1.06 to −0.26; SUCRA: 87.50) and PRO-C3 (mean difference: −50.90, 95% CI: −69.57 to −32.23; SUCRA: 100) (Figs. 6A–B and Supplementary Tables 5.14–5.15), with tirzepatide also ranking higher in analyses of individual medications (Supplementary Fig. 6J). For LSM-VCTE, the FGF21 analogue showed a more favorable point estimate (Fig. 6C and Supplementary Table 5.16). Detailed compar-

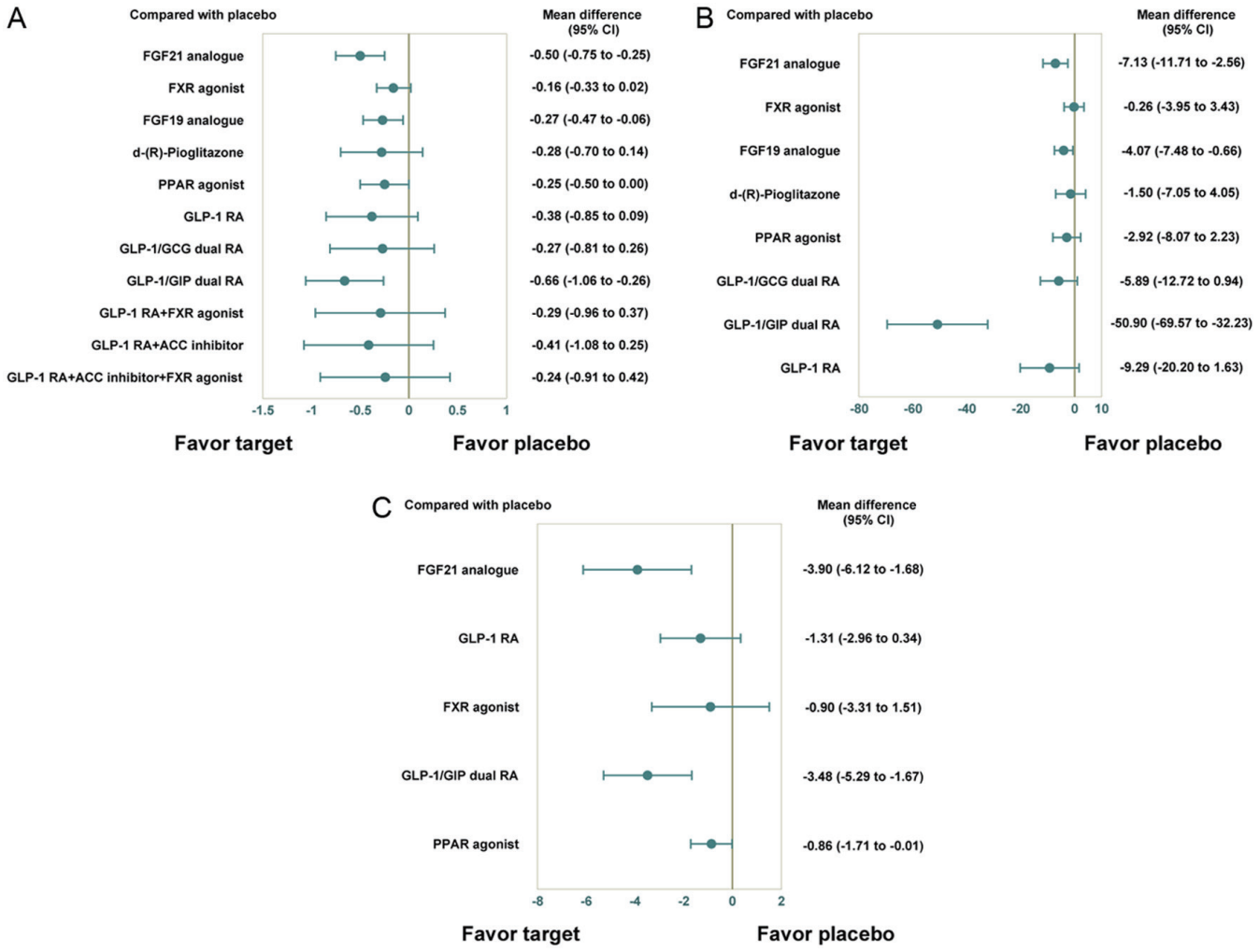

Fig. 6. Forest plots of network effect sizes between targets and placebo for non-invasive tests. (A) ELF score; (B) PRO-C3; (C) LSM-VCTE. ACC, acetyl-coenzyme A carboxylase; ELF, enhanced liver fibrosis; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; LSM, liver stiffness measurement; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist; VCTE, vibration-controlled transient elastography; PRO-C3, N-terminal type III collagen propeptide.

isons among targets are provided in Supplementary Tables 6.14–6.16.

Subgroup analyses of intervention duration in liver histology outcomes

In the included trials, intervention duration ranged from 16 to 72 weeks; therefore, subgroup analyses were conducted according to intervention duration (≤36 or >36 weeks) across targets. For trials with intervention durations ≤36 weeks, five targets from nine trials were analyzed. d-(R)-pioglitazone and the FGF21 analogue ranked higher for fibrosis improvement (Supplementary Table 9.1), and FGF21 and FGF19 analogues showed favorable signals for steatohepatitis resolution (Supplementary Table 9.3).

For trials with durations >36 weeks, six and seven targets were available for analyzing fibrosis improvement and steatohepatitis resolution, respectively. GLP-1/GCG dual RA appeared to have a favorable profile for fibrosis improvement (Supplementary Table 9.2), while GLP-1/GIP dual RA showed a favorable signal for steatohepatitis resolution (Supplementary Table 9.4).

Sensitivity analyses and meta-regression analyses of intervention duration in liver histology outcomes

We conducted leave-one-out sensitivity analyses to assess the robustness of target hierarchy and effect estimates for liver histological outcomes. For fibrosis improvement by ≥1 stage without worsening of steatohepatitis, d-(R)-pioglitazone, GLP-1/GCG dual RA, and the FGF21 analogue generally remained among the higher-ranked interventions based on SUCRA values, including when data from the 16-week efruxifermin trial were omitted (Supplementary Table 10.1).[18] Because data for d-(R)-pioglitazone were based on only a single 36-week trial,[25] omitting this trial removed d-(R)-pioglitazone from the network, and it could not be ranked. When the 24-week lanifibranor trial was omitted,[26] the SUCRA value for PPAR agonists increased and ranked highest, while the OR changed from 2.94 (95% CI: 1.66 to 5.24) to 7.00 (95% CI: 1.98 to 24.75) compared with placebo. Estimates for the other targets showed no substantial changes (Supplementary Table 10.2).

For steatohepatitis resolution without worsening of fibrosis, GLP-1/GIP dual RA, GLP-1/GCG dual RA, GLP-1 RA, and

the FGF21 analogue consistently ranked among the higher-ranked interventions based on SUCRA values, with only minor changes in ORs, consistent with the primary results (Supplementary Tables 10.3 and 10.4).

In addition, meta-regression using intervention duration as a continuous variable was performed to assess whether intervention duration modified relative treatment effects on histological outcomes. The results did not detect a statistically significant modifying effect of intervention duration for either histological outcome, with coefficients of 0.0007 (95% CI: −0.0429 to 0.0443, $P = 0.974$) and 0.0021 (95% CI: −0.0283 to 0.0326, $P = 0.891$) for fibrosis improvement without worsening of steatohepatitis and steatohepatitis resolution without fibrosis worsening, respectively (Supplementary Table 11). However, these findings should not be interpreted as definitive evidence that intervention duration does not modify treatment effects, given the limited number of trials and potential lack of statistical power.

Safety outcomes assessment

We analyzed selected safety outcomes among different pharmacologic targets. For any AEs during treatment, GLP-1 RA and GLP-1/GCG dual RA were associated with a significantly higher risk compared with placebo (GLP-1 RA: OR: 1.61, 95% CI: 1.21 to 2.14; GLP-1/GCG dual RA: OR: 3.07, 95% CI: 1.53 to 6.15; both $P < 0.001$) (Fig. 7A). For SAEs, none of the targets showed a statistically significant increase in risk compared with placebo (Fig. 7B). Numerically, FXR agonists and GLP-1/GCG dual RA were associated with higher risks of treatment discontinuation due to AEs compared with placebo (FXR agonists: OR: 1.63, 95% CI: 1.28 to 2.07; GLP-1/GCG dual RA: OR: 5.67, 95% CI: 1.98 to 16.23; both $P < 0.001$) (Fig. 7C). Specifically, we evaluated pruritus, a target-specific and commonly reported AE for FXR agonists. The OR for pruritus was 3.61 (95% CI: 1.15 to 11.34, $P = 0.03$), significantly higher than that of placebo. Given the clinical relevance of GI tolerability, we assessed three common GI-related AEs, including nausea, diarrhea, and vomiting. The results showed that GLP-1 RA, GLP-1/GCG dual RA, and FGF21 analogues all had significantly higher risks of these GI-related AEs compared with placebo (Figs. 7D–F). Furthermore, considering the clinical importance of cardiovascular safety, we also analyzed cardiovascular events in trials with clearly reported data. No statistically significant increase in cardiovascular event risk was observed for any of these targets compared with placebo (Fig. 7G).

Discussion

This network meta-analysis evaluated 11 therapeutic targets across 33 medications to assess their efficacy in improving hepatic histology, liver function, body weight, metabolic profiles, NITs, and certain safety outcomes in MASLD/MASH. Based on SUCRA rankings, d-(R)-pioglitazone and FGF21 analogues ranked higher for fibrosis improvement, whereas GLP-1/GIP dual agonists ranked higher for steatohepatitis resolution. Across secondary outcomes, incretin-based co-agonists and the FGF21 analogue showed favorable effects on LFC and metabolic profiles. Subgroup analyses based on treatment duration and leave-one-out sensitivity analyses for liver histological outcomes were largely consistent with the main findings. For safety outcomes, GLP-1 RA and GLP-1/GCG dual RA were associated with higher risks of any AEs during treatment, whereas evidence from available trials did not suggest a significant increase in SAEs or cardiovascular events for any pharmacologic target. FXR agonists and GLP-1/GCG dual agonists were associated with higher risks of medication discontinuation due to AEs, and incretin-based agents showed higher risks of nausea, diarrhea, and vomiting. Overall, our findings highlight the importance of balancing potential efficacy with tolerability in clinical decision-making.

In this study, SUCRA was applied to assess the hierarchy of different treatments. While a key advantage of SUCRA is that it makes complex ranking information easier to interpret, SUCRA does not capture the magnitude of treatment effects, does not incorporate the certainty of evidence, and rankings may be highly sensitive to the precision of estimates and the specific geometry of the treatment network.[27] In our analyses, THR-β agonists did not rank among the top interventions for the prespecified outcomes, but this should not be interpreted as a lack of clinical value. Resmetirom (Rezdiffra), a THR-β agonist, was the first therapy to receive accelerated approval from the U.S. Food and Drug Administration (FDA) for adults with MASH with moderate-to-advanced fibrosis (F2–F3),[3,28] supported by large phase 2–3 trials. Thus, resmetirom represents an approved, evidence-based option for non-cirrhotic MASH, whereas several higher-ranked targets in our analyses remain earlier in clinical development and require confirmation in larger and longer-term studies.

More recently, semaglutide (Wegovy), a GLP-1 RA, received accelerated approval from the FDA for the treatment of MASH in adults with moderate-to-advanced fibrosis (F2–F3).[29] Incretin-based medications have demonstrated pleiotropic benefits for MASLD/MASH, with several trials showing the glycemic and weight-reducing efficacy of GLP-1 RA in T2DM and overweight/obesity,[8,30–32] while also reducing LFC and resolving steatohepatitis, as shown for liraglutide in the LEAN trial in 2016.[19,33,34] A series of clinical trials investigating long-acting GLP-1 RA, particularly semaglutide, further highlighted its efficacy in improving liver histology.[35] GLP-1 RA can stimulate insulin secretion to regulate glucose levels and interact with GLP-1 receptors located in circumventricular organs to enhance satiety and reduce food intake.[36] Although no evidence has confirmed GLP-1 receptor expression on hepatocytes, these agents are believed to exert their effects through indirect mechanisms. In this study, GLP-1 RA showed favorable signals in lowering LDL-C levels and promoting steatohepatitis resolution. Of note, because the combination of semaglutide and resmetirom has not yet been studied for safety or efficacy, no specific recommendation can be made for their concomitant use in MASH treatment according to the updated AASLD guidance for the management of MASH.[29]

Advancements in GCG biology have led to the development of GLP-1 co-agonists targeting GIP or GCG receptors, as well as GLP-1/GIP/GCG triple RAs. These novel agents have shown promising results in the treatment of T2DM, obesity, and MASLD.[20,37–39] We found that GLP-1/GIP dual RA was associated with favorable effects on steatohepatitis resolution, along with reductions in ELF score and PRO-C3. GIP can stimulate insulin secretion in the pancreas, improve insulin sensitivity in white adipose tissue, suppress appetite by acting on the central nervous system, and reduce ectopic lipid accumulation in the liver and skeletal muscle.[40] However, the evidence base for these multi-agonist strategies in histology-proven MASLD trials remains relatively limited, and the ranking hierarchy may be sensitive to relatively small sample sizes and the small number of contributing trials. Therefore, these findings should be interpreted with caution.

GLP-1/GCG dual RA showed promise in reducing the absolute change from baseline in LFC and body weight, while also showing favorable signals for improvements in liver histology, glucose, and lipid profiles. Evidence indicates that GCG

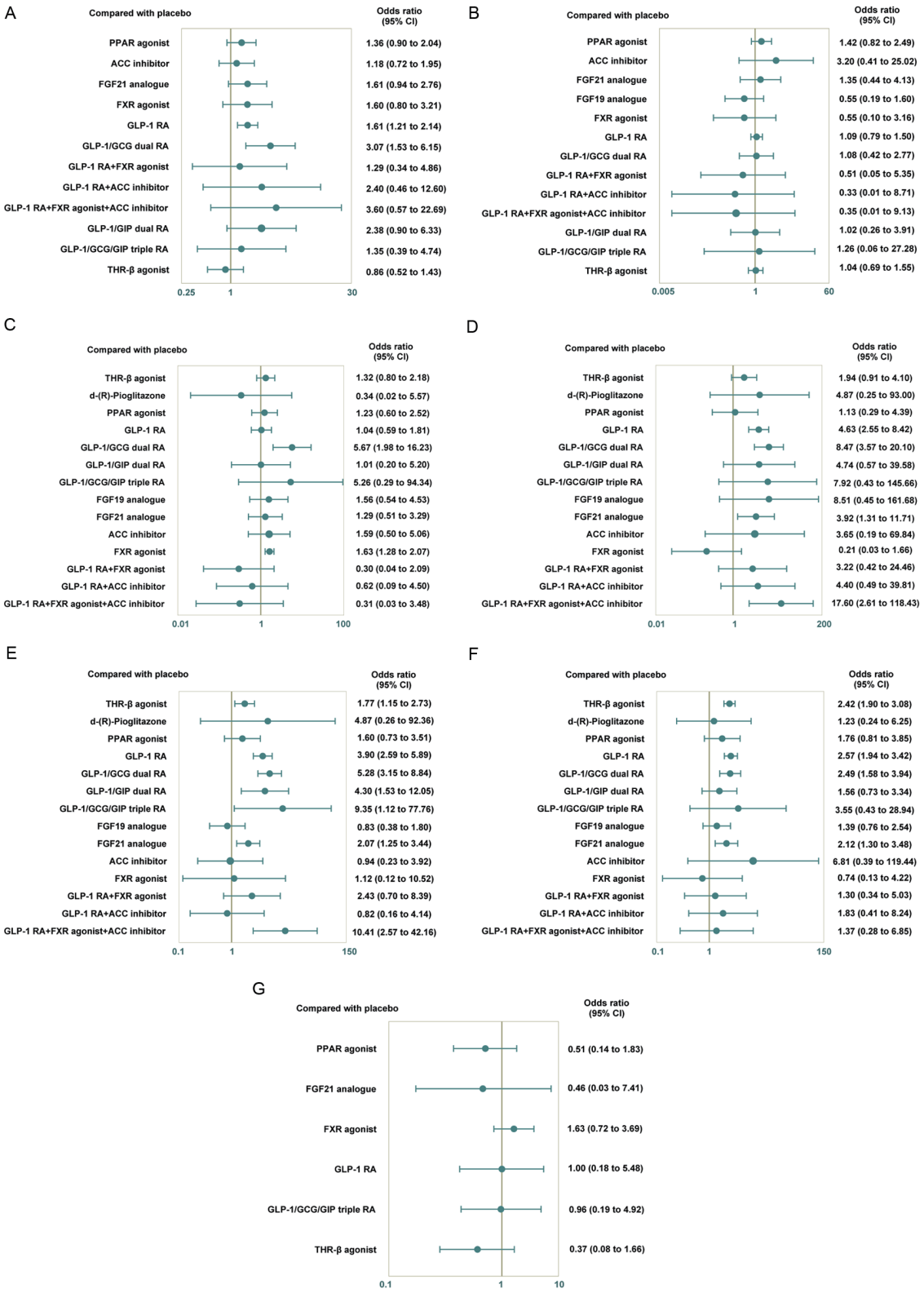

Fig. 7. Forest plots of estimates in network meta-analysis for adverse events of different targets compared with placebo. (A) Any adverse events during treatment; (B) Serious adverse events; (C) Discontinuation due to adverse events; (D) Vomiting; (E) Nausea; (F) Diarrhea; (G) Cardiovascular events. ACC, acetyl-coenzyme A carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor; RA, receptor agonist.

enhances hepatic lipolysis, facilitates clearance of circulating cholesterol, and contributes to appetite suppression.[41] However, it is important to note that trials of GLP-1 dual or triple co-agonists remain limited, and results from ongoing studies are still emerging. Confirmation in larger-sample and longer-duration trials will be essential before firm conclusions can be drawn for routine practice.

FGF21 analogue demonstrated potential for improving liver fibrosis or steatohepatitis resolution, reducing LFC, and improving lipid and glucose metabolism, particularly HDL-C and TG. FGF21 exerts hepatoprotective effects by promoting fatty acid oxidation, inhibiting de novo lipogenesis, and through other mechanisms.[42] d-(R)-pioglitazone is a unique agent, as despite lacking PPARγ activity, it demonstrated a favorable signal in reducing liver fibrosis, likely via its effects on the mitochondrial pyruvate carrier and acyl-CoA synthetase long chain family member 4, as well as the non-genomic effects of pioglitazone.[15,43] In the DESTINY-1 trial, 50% of individuals in the 15 mg PXL065 group achieved fibrosis improvement without steatohepatitis worsening.[25] However, this analysis was conducted in a small subset of patients who completed serial liver biopsies, which may have introduced selection bias, limited generalizability, and increased imprecision. Importantly, estimates based on small biopsy subsets tend to be less precise, and this imprecision can translate into more variable ranking probabilities. Consequently, SUCRA values may appear inflated even when the underlying evidence is uncertain. Indeed, although d-(R)-pioglitazone had a high SUCRA ranking for fibrosis improvement, the certainty of evidence assessed by CINeMA was very low. Therefore, interpretation of d-(R)-pioglitazone requires caution, and SUCRA should be considered alongside effect estimates and their uncertainty rather than as a standalone measure. Meanwhile, leave-one-out sensitivity analyses showed that omitting the d-(R)-pioglitazone trial removed this node from the network, while the overall hierarchy of the remaining targets remained largely unchanged, supporting the robustness of our primary findings.

Treatment duration is an important consideration when interpreting histological outcomes in MASLD/MASH trials. Fibrosis regression is a slow biological process and may require longer treatment exposure than changes in biochemical markers. Therefore, shorter-duration trials may have limited ability to capture meaningful fibrosis or steatohepatitis improvement. In our current analysis, trials contributing to histological outcomes ranged from 16 to 72 weeks. Although subgroup analyses, leave-one-out sensitivity analyses, and network meta-regression using treatment duration as a continuous covariate did not detect statistically significant evidence that the main findings were driven by intervention duration, these negative findings should not be interpreted as evidence of the absence of duration-related effect modification. The limited number of included trials, sparse network structure, and potential correlation between intervention duration and trial design may have reduced statistical power to detect such effects. Currently, the optimal treatment duration for achieving and sustaining liver histological benefits remains uncertain.[44] Longer-duration trials and longitudinal follow-up studies are needed to better clarify whether and how treatment duration modifies histological responses and to inform treatment strategies.

For safety assessment, we focused on a prespecified set of clinically relevant safety outcomes, including any AEs during treatment, SAEs, discontinuation due to AEs, three common GI-related AEs across different targets, pruritus for FXR agonists, and cardiovascular safety. Overall, most pharmacologic targets did not show a statistically significant increase in AEs compared with placebo based on available data. However, some incretin-based therapies were associated with increased risks of any AEs during treatment and GI events, highlighting the importance of tolerability in clinical decision-making. Although most reported AEs in the included trials were not considered treatment-related, longer-term safety and tolerability beyond the intervention period still require further investigation.

The findings of our study may inform clinical decision-making by providing a comparative overview of the potential benefits and safety outcomes of these emerging pharmacologic targets. However, treatment selection in clinical practice should not be based solely on ranking metrics or isolated efficacy outcomes. Instead, clinicians should consider clinical phenotype, including fibrosis stage, presence of T2DM, obesity, and other comorbidities, cardiometabolic risk profiles, long-term tolerability, contraindications, and individual preferences. In this context, given the limited direct head-to-head evidence and the low or very low certainty of evidence for histological comparisons, our findings should be viewed as supportive evidence for individualized treatment considerations rather than direct guidance for treatment selection.

The strengths of this study lie in the comprehensive and updated nature of the therapeutic interventions included and the endpoints analyzed. The study evaluated several promising therapeutic targets currently under investigation in high-quality RCTs with comparative data not only for the major therapeutic target classes but also for individual medications within each class. The current study evaluated fibrosis reduction and steatohepatitis resolution as primary endpoints, along with several other metabolic parameters and safety profiles as secondary endpoints. The primary endpoints analyzed in this study are highly relevant outcomes, as liver fibrosis is a well-recognized independent factor associated with both liver-related and non–liver-related mortality among people with MASLD, with steatohepatitis considered its "prodrome".[45,46] It is also highly relevant to evaluate the therapeutic impacts of MASH interventions on metabolic parameters, as these are underlying factors in the pathogenesis of MASLD.[47,48]

We also note several limitations. First, the primary efficacy outcomes relied heavily on liver biopsy results, which may have led to the inclusion of participants with more severe disease states. Second, although our predefined eligibility criteria and the use of placebo-controlled RCTs with broadly accepted histological endpoints provide partial support for the clinical plausibility of the transitivity assumption, transitivity should not be considered fully established across all treatment nodes. Residual clinical heterogeneity remained. The included trials varied in baseline fibrosis stage distributions, metabolic comorbidity burden, BMI, and other key clinical factors, all of which may influence histological treatment responses. We therefore added a summary of key baseline characteristics to facilitate assessment of comparability across trials. These characteristics showed variability, although we did not observe an obvious separation of target nodes by markedly distinct patient populations. However, the possibility of residual intransitivity cannot be fully excluded. Therefore, indirect active-versus-active comparisons should be interpreted cautiously, particularly when estimates are mainly derived from a common placebo comparator rather than direct head-to-head evidence. Accordingly, these findings should be interpreted in light of the observed clinical heterogeneity and the structure of the evidence network. Future studies with arm-level subgroup-specific events and denominators, or preferably individual participant data, are warranted to better evaluate whether baseline characteristics modify treatment responses.

Third, although SUCRA was used to summarize treatment rankings, these rankings should be interpreted cautiously, as some data were extracted from single trials with relatively small sample sizes. SUCRA does not account for the magnitude or certainty of treatment effects and may be unstable in sparse or placebo-centered networks. In our analysis, several higher-ranked targets were supported by limited trial evidence, wide 95% CIs, or low to very low CINeMA certainty ratings. Therefore, SUCRA-based rankings and active-versus-active estimates should be interpreted cautiously, particularly when supported primarily by indirect evidence, and should be considered together with evidence contribution and certainty of evidence.

Fourth, not all medications and interventions were included for comparison. Due to the large number of treatments in the development pipeline, we focused on the most promising targets. Furthermore, our analyses focused on absolute changes from baseline for body weight, metabolic profiles, and NITs. The lack of separate analysis of percent change outcomes due to inconsistent reporting across trials is also a limitation. In addition, this study did not evaluate the efficacy of different treatments in MASH-related cirrhosis (F4), which remains a major unmet medical need. Considering that there are substantial differences in trial design, patient risk profiles, stratification factors, and endpoint settings between trials conducted in individuals with cirrhosis and those in the non-cirrhotic MASLD/MASH population (F1–F3), we excluded cirrhotic MASLD/MASH clinical trials to minimize clinical heterogeneity and improve comparability across studies. Therefore, our findings should not be extrapolated to patients with cirrhosis. Future studies should evaluate whether the treatment effects observed in the F1–F3 population translate into clinically meaningful benefits in patients with cirrhosis.

Finally, although our safety analyses focused on a prespecified set of safety outcomes, the assessment of safety remained limited by the availability and consistency of reported data. In particular, longer-term tolerability could not be formally evaluated because follow-up durations varied across trials and safety outcomes beyond the trial period were rarely reported. Therefore, our safety findings should not be interpreted as definitive evidence of longer-term safety or tolerability.

Conclusions

This network meta-analysis provides hypothesis-generating evidence on the comparative efficacy and selected safety outcomes of emerging therapeutic targets for MASLD/MASH. Co-agonists of GLP-1, GCG, and/or GIP receptors, as well as FGF21 analogues, showed promising signals across several endpoints. However, given the predominantly placebo-centered network, limited head-to-head comparisons, and variable certainty of evidence, these findings should not be interpreted as definitive guidance for treatment selection. Rather, our study may support the generation of future research hypotheses and inform the design of larger, longer-duration comparative trials with clinically meaningful endpoints and comprehensive safety assessment.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2025.00596.

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Conflict of interest

Mindie H. Nguyen reports receiving research support from Pfizer, Enanta, AstraZeneca, Glycotest, GSK, Delfi, Innogen, Exact Science, CurveBio, Gilead, Helio Health, the National Institutes of Health, and Roche, and serving as a consultant and/or advisory board member for GSK and Exelixis. JL has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2024. The other authors have no conflict of interests related to this publication.

Author contributions

Study conception and design (JL, MHN), article collection and selection (WN, XB, SZ, XW, ML, ZJ), data extraction (WN, XB, SZ, XW, LJ, ZJ), assessment of bias risk (WN, SZ), data analysis (JL, WN), rating of evidence certainty (WN, SZ), data interpretation, drafting of the manuscript (JL, WN), study supervision, and revision of the manuscript (MHN). All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have approved the final version and publication of the manuscript.

Data sharing statement

The analytic dataset is available on request by contacting the corresponding authors.

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