Efficacy and safety of resmetirom for the treatment of nonalcoholic steatohepatitis: a GRADE assessed systematic review and meta-analysis

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There are no Food and Drug Administration (FDA)-approved treatment options for nonalcoholic steatohepatitis (NASH) which is a prevailing disease that leads to fibrosis, cirrhosis, or hepatocellular carcinoma. Hence, this systematic review and meta-analysis aims to determine the efficacy and safety of resmetirom, the first FDA-approved drug, for the treatment of NASH. A Grading of Recommendations, Assessment, Development, and Evaluation assessed systematic search of *Cochrane Library*, *MEDLINE*, *Scopus*, *and Google Scholar* database was conducted from inception till 31 March 2024. Meta-analyses were carried out in accordance with the PRISMA statement. Heterogeneity was determined to be significant if found above 50%. This meta-analysis encompasses three randomized clinical trials, including a total of 2231 patients. The findings show resmetirom's significant efficacy in several key outcomes, including improvement in fibrosis risk ratios, 1.67 [95% confidence intervals (CI), 1.26–2.20], reductions in liver fat content (95% CI, –39.58 to –23.5), and enhanced liver fibrosis score (95% CI, –0.37 to –0.13) along with improved levels of liver enzymes. Resmetirom was found to be associated with nausea and diarrhea. This is the first systematic review and meta-analysis to determine the safety and efficacy of resmetirom which showed significant positive results in fibrosis improvement, liver fat content, lipid profiles, and liver enzymes in comparison to placebo. Moreover, moderate side effects, such as diarrhea and nausea, were seen in few patients indicating a satisfactory safety profile. Eur J Gastroenterol Hepatol XXX: XXXX–XXXX

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition characterized by fat accumulation in the liver cells, leading to inflammation and potentially progressing to fibrosis and cirrhosis. Its global prevalence has surged from 25.5% before 2005 to 37.8% after 2016 [1], with projections indicating that nearly one-third of the US population may be affected by 2030 [2]. In fact, a study found that 51% of NAFLD patients also suffer from obesity, while 22% have type 2 diabetes mellitus (T2DM) [3]. Another study reported a staggering 59.67% prevalence of NAFLD among T2DM patients [4].

NAFLD represents a spectrum of liver diseases, ranging from simple steatosis to more severe nonalcoholic steatohepatitis (NASH), which can lead to serious complications such as fibrosis, cirrhosis, or hepatocellular carcinoma [5]. Moreover, NAFLD is intricately linked with cardiovascular disease, further underscoring its impact on overall health [6].

Studies show a wide variation in NAFLD prevalence, with biopsy-confirmed NASH observed in 15.9–68.3% of NAFLD cases, and particularly high rates (65.26%) among individuals with T2DM [7]. Projections suggest a significant rise in NASH prevalence in the coming years, with estimates indicating a potential 63% increase between 2015 and 2030, necessitating urgent attention and effective prevention and management strategies [8].

Despite the concerning increase in the occurrence of NASH, there had not been any officially approved pharmacotherapy for the condition until resmetirom (Rezdiffra) which was approved recently. As there is a connection between metabolic health and NASH, lifestyle adjustments and shedding weight have become the primary approach to treatment, showing enhancements in liver tissue examination. Nevertheless, because responses to these adjustments can differ, there is a need for pharmaceutical substances that support weight loss. Antioxidants and medications that enhance insulin sensitivity are also employed in managing NASH [9].

Resmetirom is a selective agonist targeting thyroid hormone receptor β (THR-β), which is prominently expressed in hepatocytes. THR-β plays a crucial role in regulating metabolic pathways within the liver, often compromised in NAFLD and NASH [10]. In individuals with NASH,

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liver thyroid hormone activity is diminished, leading to impaired hepatic function. Preclinical studies indicate that THR-β activation contributes to the reduction of triglycerides and cholesterol levels, enhances insulin sensitivity, fosters liver regeneration, and diminishes apoptosis [10,11].

Understanding the safety and efficacy of resmetirom is crucial for addressing the need for a novel therapy for this condition. Despite the availability of ample data from clinical trials, there has been no comprehensive meta-analysis conducted to assess the drug's performance in these regards. Thus, our objective was to carry out a systematic review and meta-analysis to determine the efficacy and safety of resmetirom in patients suffering from NASH.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [12] and carried out using the Cochrane Handbook for Systematic Reviews of Interventions criteria. Under the identification CRD42024529676, this review has been registered with the International Prospective Register of Systematic Reviews. Ethical permission was not needed for this study as the analysis was performed with already available data.

Eligibility criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs); (2) patients with a biopsy-confirmed diagnosis of NASH; (3) resmetirom was used as an intervention; and (4) outcomes of interest such as fibrosis improvement and NASH resolution, enhanced liver fibrosis (ELF) score, fibrosis improvement with no worsening of NASH, change in liver fat content, enzymes such as gamma-glutamyl transferase (GGT), absolute aspartate aminotransferase (AST), and absolute alanine aminotransferase (ALT) and so on were reported.

The exclusion criteria were as follows: (1) non-RCTs; (2) patients not suffering from NASH; (3) abstracts, correspondence, conference presentations, review articles, research-in-progress studies, nonexperimental, and preclinical studies, and so on; and (4) articles not in english.

Information sources

Without regard to language, the following worldwide registers and databases were searched from their creation to 31st March 2024: the Cochrane Central Register of Controlled Trials (via The *Cochrane Library*), *MEDLINE* (via *PubMed*), *Scopus*, and *Google Scholar*. To find other possibly suitable research, we reviewed the reference lists of the included publications and pertinent systematic reviews as well. A keyword-rich search technique was employed, along with Medical Subject Headings phrases related to NASH and resmetirom. Supplementary Table S1, Supplemental digital content 1, *http://links.lww.com/EJGH/B92* provides a detailed search technique applied to each database.

Study selection process

We used Rayyan software [13] to both screen and deduplicate all the articles that came up in our online literature search. Following the deduplication procedure, the initial screening of titles and abstracts was carried out independently by two authors. Subsequently, the authors performed a thorough full-text screening of the remaining selected articles. If there was any disagreement between them, a third reviewer would resolve the conflict.

Data collection and data items

Two reviewers were assigned to extract the relevant information items from the included studies and enter them into an Excel sheet following the screening and selection procedure. Study IDs, the last names of the first authors, the study design, the nation in which the research was carried out, the length of the intervention, the total number of participants, mean age, sex, body weight, BMI, hypertension, ALT, alkaline phosphatase, GGT, and AST levels, the number of individuals with T2DM, lipid parameters such as total cholesterol, low-density lipoprotein (LDL)-C, high-density lipoprotein-C, triglycerides, hepatic fat fraction, use of statins, efficacy outcomes such as fibrosis improvement and NASH resolution, and the ELF score, fibrosis improvement with no worsening of NASH, absolute neoepitope specific *N*-terminal pro-peptide of type III collagen (Pro C3), absolute AST and absolute ALT, and so on and adverse events such as headache, urinary tract infection, diarrhea, nausea, fatigue, and so on were among the pertinent data items.

Risk of bias assessment

A revised Cochrane risk-of-bias tool for randomized trials or risk of bias 2 (RoB2) was used to determine the risk of bias of each RCT [14], which evaluates bias in the following five domains: (1) the randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome, and (5) selection of the reported result. Two authors independently rated the risk of bias for each included study as low, high, or some concerns. A third reviewer arbitrated any disputes between them.

Data synthesis

Review Manager (RevMan, version 5.4; The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. The random effects model was employed to calculate the mean differences and risk ratios (RRs), and their corresponding 95% confidence intervals (95% CI). The random-effects model was used because of the estimated heterogeneity of the true effect sizes. For each synthesis, the I^2 index and the χ^2 test were used for the assessment of heterogeneity, and a value less than 50% was deemed acceptable for the heterogeneity of the included studies. For outcomes with less than 10 studies, Doi plots were constructed, and the Luis Furuya-Kanamori (LFK) index was used to assess publication bias using MetaXL version 5.3 (EpiGear International Pty, Sunrise Beach, Queensland, Australia). The LFK index has greater sensitivity and power than the Egger

test and, hence, is suitable for a lower number of studies [15]. In all instances, a *P* value of less than 0.05 was considered significant.

Certainty of evidence assessment

The The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group classified the quality of evidence of the pooled estimates as high, moderate, low, or very poor. The GRADE approach was used to assess the certainty of the evidence [16,17]. It can be seen in Table 1.

Results

Study selection and characteristics of included studies

A total of 1753 results were obtained after the first screening, of which *MEDLINE* (*PubMed*) comprised 44 results, *Scopus* yielded 163, *Cochrane Library* showed 56 results, and *Google Scholar* displayed 1490 results. Three articles were included in this systematic review and meta-analysis after titles and abstracts were checked and duplicates were removed [18–20]. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram illustrating the research selection process summary is presented in Figure 1.

In these included studies, 1551 NASH patients received resmetirom, out of 2231 patients in total. Furthermore, among the participants receiving resmetirom, 666 were males while 885 were females. Patients in the resmetirom intervention arm ranged in age from 51.8 to 57.0 years in terms of mean. The patients' mean BMI varied between 93.4 kg and 109.2 kg. The patients' mean ELF scores varied from 9.2 to 9.8. Further summary of additional baseline characteristics of included studies can be seen in Table 2.

Risk of bias assessment

Supplementary Figure 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B92* indicates the quality of the assessment found. According to the RoB2 tool, all the included studies were deemed to have an overall low risk of bias in the respective domains.

Results of the meta-analysis

Fibrosis improvement of ≥1 with no worsening of nonalcoholic steatohepatitis

Two studies reported data for the number of patients showing fibrosis improvement of ≥1 with no worsening of NASH. Moderate certainty evidence suggested that resmetirom significantly increased the number of individuals showing fibrosis improvement of ≥1 with no worsening of NASH compared to placebo (RR, 1.67; 95% CI, 1.26–2.20; I^2 = 0%; *P* = 0.0003; Fig. 2).

Nonalcoholic steatohepatitis resolution with no worsening of fibrosis

Two studies reported data for the number of patients showing NASH resolution with no worsening of fibrosis. We observed low certainty evidence that resmetirom was not associated with any change in the number of individuals showing NASH resolution with no worsening of fibrosis compared to placebo (RR, 2.09; 95% CI, 0.96–4.55; I^2 = 68%; *P* = 0.06; Fig. 3).

Liver fat content by MRI-proton density fat fraction

Two studies reported the difference in percentage of liver fat content by MRI-proton density fat fraction. Moderate certainty evidence suggested that resmetirom significantly decreased liver fat content by 31.41% (95% CI, −39.58 to −23.5; I^2 = 69%; *P* < 0.00001; Fig. 4) compared to placebo, with no publication bias (LFK index: −0.92, no asymmetry; Supplementary Figure 15, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Enhanced liver fibrosis score

Two studies reported the difference in ELF score. Moderate certainty evidence suggested that resmetirom significantly decreased ELF score by 0.25 points (95% CI, −0.37 to −0.13; I^2 = 0%; *P* < 0.0001; Supplementary Figure 2, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, possibly subject to publication bias (LFK index −2.91, major asymmetry; Supplementary Figure 16, Supplemental digitalcContent 1, *http://links.lww.com/EJGH/B92*).

Alanine aminotransferase

Two studies reported the difference in ALT levels. Moderate certainty evidence suggested that resmetirom significantly reduced ALT by 12.12 U/L (95% CI, −18.25 to −5.99; I^2 = 44%; *P* = 0.0001; Supplementary Figure 3, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some observed publication bias (LFK index: −3.22, major asymmetry; Supplementary Figure 17, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Aspartate aminotransferase

Two studies reported the difference in AST levels. Moderate certainty evidence suggested that resmetirom significantly reduced AST by 6.06 U/L (95% CI, −9.61 to −2.51; I^2 = 33%; *P* = 0.0008; Supplementary Figure 4, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: −2.12, major asymmetry; Supplementary Figure 18, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Gamma-glutamyl transferase

Two studies reported the difference in GGT levels. Low certainty evidence suggested that resmetirom significantly reduced GGT by 13.99 U/L (95% CI, −26.46 to −1.53; I^2 = 71%; *P* = 0.03; Supplementary Figure 5, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with evident publication bias (LFK index: −4.18, major asymmetry; Supplementary Figure 19, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Table 1. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) summary of findings

Summary of findings						
Resmetirom compared to placebo for nonalcoholic steatohepatitis						
Patient or population: nonalcoholic steatohepatitis Intervention: resmetirom Comparison: placebo						
Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without resmetirom	With resmetirom	Difference		
Fibrosis improvement № of participants: 1062 (2 RCTs)	RR 1.67 (1.26–2.20)	15.1%	25.1% (19–33.1)	10.1% more (3.9 more to 18.1 more)	⨁⨁⨁◯ Moderate[a]	Resmetirom likely increases fibrosis improvement.
NASH resolution № of participants: 1059 (2 RCTs)	RR 2.09 (0.96–4.55)	10.6%	22.2% (10.2–48.2)	11.6% more (0.4 fewer to 37.6 more)	⨁⨁◯◯ Low[a,b,c]	Resmetirom may increase NASH resolution.
Liver fat content assessed with: MRI-PDFF № of participants 1074: (2 RCTs)	-		-	MD 31.41% lower (39.58 lower to 23.25 lower)	⨁⨁⨁◯ Moderate[b]	Resmetirom likely reduces liver fat content.
ELF score № of participants: 1027 (2 RCTs)	-		-	MD 0.25 points lower (0.37 lower to 0.13 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely results in a slight reduction in ELF score.
Alanine aminotransferase № of participants: 1061 (2 RCTs)	-		-	MD 12.12 U/L lower (18.25 lower to 5.99 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely reduces alanine aminotransferase.
Aspartate aminotransferase № of participants: 1061 (2 RCTs)	-		-	MD 6.06 U/L lower (9.61 lower to 2.51 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely reduces aspartate aminotransferase.
Gamma-glutamyl transferase № of participants: 1061 (2 RCTs)	-		-	MD 13.99 U/L lower (26.46 lower to 1.53 lower)	⨁⨁◯◯ Low[b,d]	Resmetirom may reduce gamma-glutamyl transferase.
LDL cholesterol № of participants: 2027 (3 RCTs)	-		-	MD 14.07 mg/dL lower (17.67 lower to 10.47 lower)	⨁⨁⨁◯ Moderate[b]	Resmetirom likely reduces LDL cholesterol.
Triglycerides № of participants: 1965 (3 RCTs)	-		-	MD 22.82 mg/dL lower (27.04 lower to 18.61 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely reduces triglycerides.
Apolipoprotein B № of participants: 1980 (3 RCTs)	-		-	MD 19.06 U/L lower (23.03 lower to 15.09 lower)	⨁⨁◯◯ Low[b,d]	Resmetirom may reduce apolipoprotein B.
Lipoprotein(a) № of participants: 1969 (3 RCTs)	-		-	MD 27.72 nmol/L lower (33.18 lower to 22.26 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely reduces lipoprotein(a).
Adiponectin № of participants: 2024 (3 RCTs)	-		-	MD 0.9 µg/mL higher (0.62 higher to 1.18 higher)	⨁⨁⨁⨁ High	Resmetirom increases adiponectin slightly.
CK-18/M30 № of participants: 2020 (3 RCTs)	-		-	MD 123.03 U/L lower (157.72 lower to 88.33 lower)	⨁⨁⨁⨁ High	Resmetirom results in large reduction in CK-18/M30.
Reverse T3 № of participants: 2021 (3 RCTs)	-		-	MD 4.17 ng/dL lower (4.92 lower to 3.42 lower)	⨁⨁◯◯ Low[b,d]	Resmetirom may reduce reverse T3 slightly.
FibroScan CAP Score № of participants: 1909 (2 RCTs)	-		-	MD 23.75 dB/m lower (28.44 lower to 19.07 lower)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely reduces FibroScan CAP score.
Apolipoprotein CIII № of participants: 1056 (2 RCTs)	-		-	MD 23.53 mg/dL lower (31.77 lower to 15.28 lower)	⨁⨁◯◯ Low[b,d]	Resmetirom may reduce apolipoprotein CIII.
Diarrhea № of participants: 2231 (3 RCTs)	RR 2.03 (1.65–2.50)	14.3%	29.0% (23.5–35.7)	14.7% more (9.3 more to 21.4 more)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely increases diarrhea.
Nausea № of participants: 2231 (3 RCTs)	RR 1.76 (1.37–2.27)	9.9%	17.3% (13.5–22.4)	7.5% more (3.6 more to 12.5 more)	⨁⨁⨁◯ Moderate[d]	Resmetirom likely increases nausea.
Fatigue № of participants: 2231 (3 RCTs)	RR 1.09 (0.77–1.55)	6.6%	7.2% (5.1–10.3)	0.6% more (1.5 fewer to 3.6 more)	⨁⨁◯◯ Low[c,d]	Resmetirom may result in little to no difference in fatigue.
Back pain № of participants: 2106 (2 RCTs)	RR 0.90 (0.65–1.24)	8.1%	7.3% (5.3–10.1)	0.8% fewer (2.8 fewer to 2 more)	⨁⨁⨁◯ Moderate[c]	Resmetirom likely results in little to no difference in back pain.
Arthralgia № of participants: 2106 (2 RCTs)	RR 1.10 (0.83–1.46)	9.5%	10.5% (7.9–13.9)	1.0% more (1.6 fewer to 4.4 more)	⨁⨁⨁◯ Moderate[c]	Resmetirom likely results in little to no difference in arthralgia.
Headache № of participants: 1265 (2 RCTs)	RR 0.98 (0.65–1.47)	8.4%	8.2% (5.4–12.3)	0.2% fewer (2.9 fewer to 3.9 more)	⨁⨁⨁◯ Moderate[a,c]	Resmetirom likely results in little to no difference in headache.
UTI № of participants: 2231 (3 RCTs)	RR 0.99 (0.72–1.34)	7.9%	7.9% (5.7–10.6)	0.1% fewer (2.2 fewer to 2.7 more)	⨁⨁◯◯ Low[c,d]	Resmetirom may not reduce UTIs.
Covid № of participants: 2106 (2 RCTs)	RR 0.97 (0.77–1.21)	14.6%	14.1% (11.2–17.6)	0.4% fewer (3.3 fewer to 3.1 more)	⨁⨁⨁◯ Moderate[c]	Resmetirom probably does not reduce covid.

CI, confidence interval; ELF, enhanced liver fibrosis; LDL, low-density lipoprotein; MD, mean difference; NASH, nonalcoholic steatohepatitis; PDFF, proton density fat fraction; RCT, randomized controlled trials; RR, risk ratio; UTI, urinary tract infection.

GRADE Working Group grades of evidence.

⨁⨁⨁⨁High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

⨁⨁⨁◯Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⨁⨁◯◯Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

⨁◯◯◯Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations.

[a]Number of participants less than the optimal information size.

[b]High heterogeneity.

[c]Confidence interval overlaps no effect.

[d]Doi plot asymmetry.

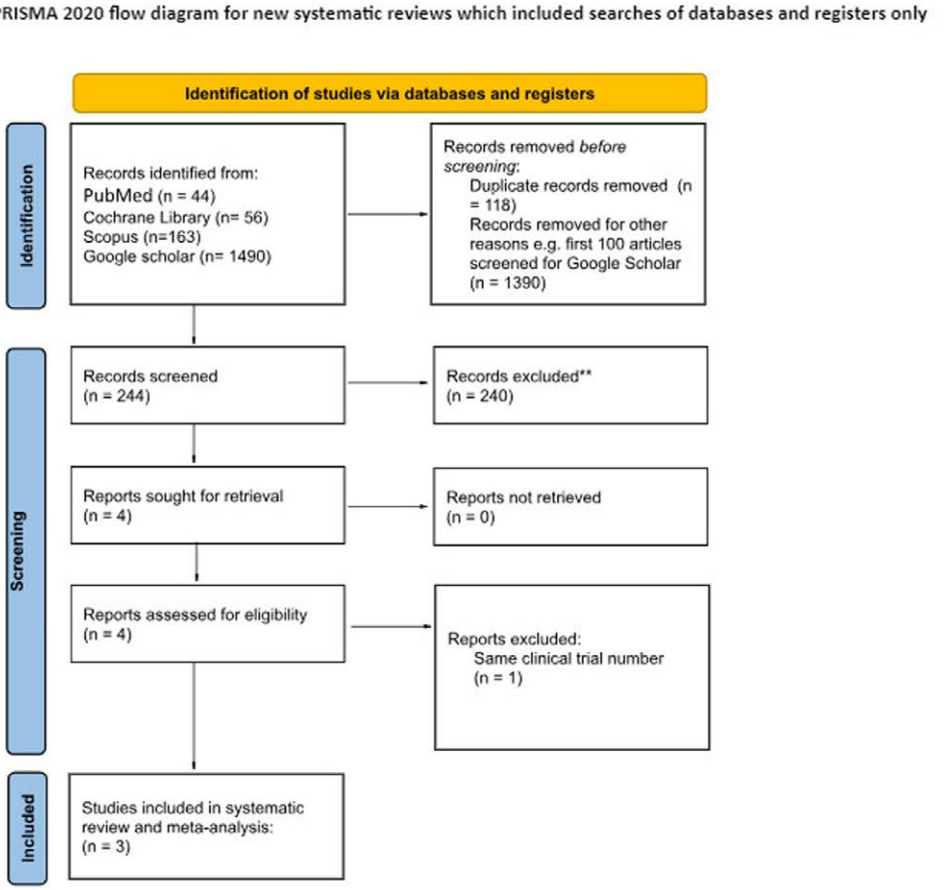

Fig. 1. PRISMA flowchart

LDL cholesterol

Three studies reported the difference in LDL cholesterol levels. Moderate certainty evidence suggested that resmetirom significantly reduced LDL cholesterol by 14.07 mg/dl (95% CI, −17.67 to −10.47; $I^2 = 64\%$; $P < 0.00001$; Supplementary Figure 6, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with no publication bias (LFK index: −0.36, no asymmetry; Supplementary Figure 20, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Triglycerides

Three studies reported the difference in triglyceride levels. Moderate certainty evidence suggested that resmetirom significantly reduced triglyceride by 22.82 mg/dl (95% CI, −27.04 to −18.61; $I^2 = 0\%$; $P < 0.00001$; Supplementary Figure 7, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: −1.63, minor asymmetry; Supplementary Figure 21, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Apolipoprotein B

Three studies reported the difference in percentage of apolipoprotein B. Low certainty evidence suggested that resmetirom significantly reduced apolipoprotein B by 19.06% (95% CI, −23.03 to −15.09; $I^2 = 78\%$; $P < 0.00001$; Supplementary Figure 8, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: −1.95, minor asymmetry; Supplementary Figure 22, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Lipoprotein(a)

Three studies reported the difference in the percentage of lipoprotein(a). Moderate certainty evidence suggested that resmetirom significantly reduced lipoprotein(a) by 22.72% (95% CI, −33.18 to −22.26; $I^2 = 30\%$; $P < 0.00001$; Supplementary Figure 9, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: −1.49, minor asymmetry; Supplementary Figure 23, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Table 2. Baseline characteristics of the included studies

	Harrison *et al*. 2024			Harrison *et al*. 2023				Harrison *et al*. 2019	
	Resmetirom			Resmetirom				Resmetirom	
	80 mg Dose	100 mg Dose	Placebo	100 mg OL Dose	100 mg DB Dose	80 mg DB Dose	Placebo	80 mg Dose	Placebo
Location	15 countries			USA and Puerto Rico				USA	
Sample size	322	323	321	171	325	327	320	84	41
Age [years]*	55.9 (11.5)	57.0 (10.8)	57.1 (10.5)	55.6 (11.5)	55.9 (11.7)	56.2 (11.7)	55.7 (12.1)	51.8 (10.4)	47.3 (11.7)
Males (n)	140	141	143	55	147	145	150	38	24
Body weight [kg]*	100.1 (22.3)	101.9 (22.9)	100.2 (23.1)	-	-	-	-	101.0 (21.2)	97.5 (22.5)
BMI [kg/m^2]*	35.5 (6.4)	36.2 (7.4)	35.3 (6.5)	36.1 (6.3)	35.4 (6.4)	35.3 (5.9)	35.2 (5.8)	35.8 (6.2)	33.6 (5.8)
T2DM [n]*	224	213	210	83	156	160	159	36	13
ALT [U/L]*	52.8 (27.3)	56.3 (34.0)	54.7 (34.8)	36.9 (24.2)	36.2 (25.2)	37.1 (23.9)	37.9 (30.4)	50·0 (29.2)	60.1 (32.2)
AST [U/L]*	38.2 (19.3)	42.5 (25.2)	40.7 (24.6)	26.4 (15.3)	24.9 (12.4)	25.3 (13.3)	26.4 (16.4)	35·1 (17.7)	38.0 (20.7)
ALP [U/L]*	74.9 (27.1)	73.9 (23.0)	71.5 (23.7)	72.8 (23.8)	70.8 (22.3)	71.6 (23.8)	71.3 (24.8)	68·8 (19.9)	80·1 (30.9)
ELF*	9.7 (0.89)	9.8 (0.86)	9.7 (0.86)	-	-	-	-	9·2 (0.9)	9.2 (1.0)
Apolipoprotein B [mg/dL]*	98.4 (27.8)	95.9 (27.8)	97.8 (32.0)	101.1 (28.4)	95.5 (25.0)	98.1 (26.3)	95.1 (27.1)	103.5 (22.8)	104.1 (21.7)
Lp (a) [nmol/L]*	44.7 (61.1)	43.8 (60.8)	42.2 (62.7)	48.5 (73.1)	57.6 (77.6)	60.8 (77.5)	49.0 (70.2)	29.1 (44.7)	36.9 (50.0)
FibroScan CAP [dBm]*	346.1 (37.2)	349.4 (38.7)	347.2 (37.0)	342.3 (35.6)	341.4 (34.0)	339.5 (32.9)	344.1 (34.0)	-	-
MRI-PDFF [%]*	18.2 (6.8)	17.2 (6.6)	17.8 (6.8)	17.9 (7.1)	18.1 (7.3)	17.7 (6.7)	17.8 (6.9)	20.2 (6.8)	19.6 (8.2)
Total cholesterol [mg/dL]*	179.6 (43.4)	176.9 (46.0)	180.0 (50.0)	186.9 (47.9)	178.1 (42.9)	181.0 (44.2)	176.8 (43.4)	193.0 (39.3)	198.4 (37.3)
HDL Cholesterol [mg/dL]*	43.8 (12.6)	44.0 (12.9)	43.8 (13.3)	45.1 (14.5)	43.8 (13.0)	43.6 (14.7)	43.2 (13.6)	43.8 (12.5)	45.2 (13.4)
LDL Cholesterol [mg/dL]*	106.6 (37.4)	103.0 (36.8)	106.8 (41.1)	115.2 (41.0)	109.1 (36.4)	111.7 (37.6)	106.8 (37.2)	111.3 (30.4)	116.9 (30.0)
Triglycerides [mg/dL]*	189.2 (112.5)	188.7 (153.8)	184.1 (125.8)	183.6 (86.2)	174.1 (93.5)	177.6 (94.4)	186.8 (119.2)	178.5 (82.4)	161.1 (75.2)
Prior statin therapy [n]	149	166	158	75	143	138	164	19	4

*Reported as Mean (SD).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; MRI-PDFF, MRI-proton density fat fraction; T2DM, type 2 diabetes mellitus.

Adiponectin

Three studies reported the difference in adiponectin levels. High certainty evidence suggested that resmetirom significantly increased adiponectin by 0.90 µg/ml (95% CI, 0.62 to 1.18; $I^2 = 44\%$; $P < 0.00001$; Supplementary Figure 10, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with no publication bias (LFK index: −0.40, no asymmetry; Supplementary Figure 24, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

CK-18/M30

Three studies reported the difference in CK-18/M30 levels. High certainty evidence suggested that resmetirom significantly reduced CK-18/M30 by 123.03 U/L (95% CI, −157.72 to −88.33; $I^2 = 18\%$; $P < 0.00001$; Supplementary Figure 11, Supplemental Digital Content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with no publication bias (LFK index: −0.20, no asymmetry; Supplementary Figure 25, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Reverse T3

Three studies reported the difference in reverse T3 levels. Low certainty evidence suggested that resmetirom significantly reduced reverse T3 by 4.17 ng/dl (95% CI, −4.92 to −3.42; $I^2 = 75\%$; $P < 0.00001$; Supplementary Figure 12, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with evident publication bias (LFK index: 3.29, major asymmetry; Supplementary Figure 26, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

FibroScan controlled attenuation parameter

Two studies reported the difference in FibroScan controlled attenuation parameter scores. Moderate certainty evidence suggested that resmetirom significantly reduced FibroScan controlled attenuation parameter scores by 23.75 dB/m (95% CI, −28.44 to −19.07; $I^2 = 0\%$; $P < 0.00001$; Supplementary Figure 13, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: 1.03, minor asymmetry; Supplementary Figure 27, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Apolipoprotein CIII

Two studies reported the difference in the percentage of apolipoprotein CIII. Low certainty evidence suggested that resmetirom significantly reduced apolipoprotein

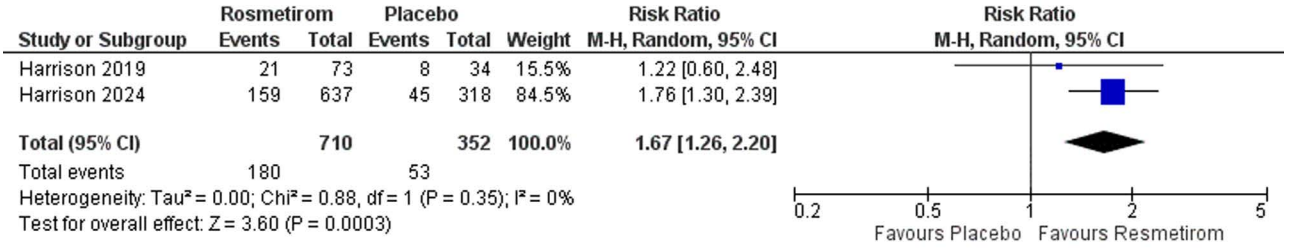

Fig. 2. Forest plot of fibrosis improvement of ≥1 with no worsening of NASH. NASH, nonalcoholic steatohepatitis.

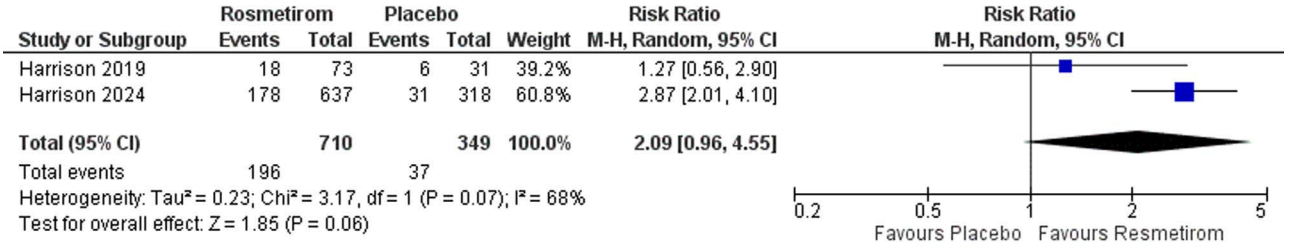

Fig. 3. Forest plot of NASH resolution with no worsening of fibrosis. . NASH, nonalcoholic steatohepatitis.

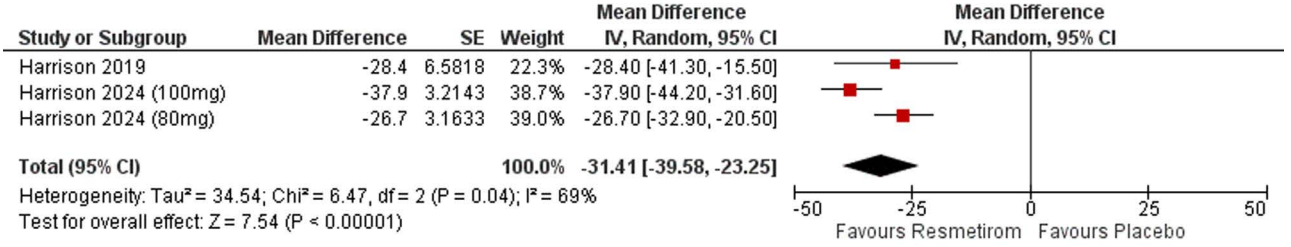

Fig. 4. Forest plot of Liver fat content by MRI-PDFF. PDFF, proton density fat fraction.

CIII by 23.53% (95% CI, −31.77 to −15.28; I^2 = 70%; P < 0.00001; Supplementary Figure 14, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) compared to placebo, with some evidence of publication bias (LFK index: −1.95, minor asymmetry; Supplementary Figure 28, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Adverse events

Resmetirom was associated with significantly increased events of diarrhea and nausea. Patients receiving resmetirom were more likely to experience diarrhea (RR, 2.03; 95% CI, 1.65–2.50; I^2 = 4%; P < 0.00001; Supplementary Figure 29, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) with evident publication bias (LFK index: 3.91, major asymmetry; Supplementary Figure 37, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), and nausea (RR, 1.76; 95% CI, 1.37–2.27; I^2 = 0%; P < 0.0001; Supplementary Figure 30, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) with evident publication bias (LFK index: 4.79, major asymmetry; Supplementary Figure 38, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

No significant association was found between resmetirom and fatigue (RR, 1.09; 95% CI, 0.77–1.55; I^2 = 4%; P = 0.62; Supplementary Figure 31, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) with evident publication bias (LFK index: 2.06, major asymmetry; Supplementary Figure 39, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), back pain (RR, 0.90; 95% CI, 0.65–1.24; I^2 = 0%; P = 0.53; Supplementary Figure 35, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), arthralgia (RR, 1.10; 95% CI, 0.83–1.46; I^2 = 0%; P = 0.51; Supplementary Figure 36, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), headache (RR, 0.98; 95% CI, 0.65–1.47; I^2 = 0%; P = 0.92; Supplementary Figure 32, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), urinary tract infection (RR, 0.99; 95% CI, 0.72–1.34; I^2 = 0%; P = 0.93; Supplementary Figure 34, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*) with some publication bias (LFK index: 1.38, minor asymmetry; Supplementary Figure 40, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*), or COVID (RR: 0.97, 95% CI: 0.77 to 1.21, I^2 = 0%, P = 0.78; Supplementary Figure 33, Supplemental digital content 1, *http://links.lww.com/EJGH/B92*).

Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis that evaluated the efficacy and safety of resmetirom in treating NASH and related parameters. Resmetirom demonstrated significant improvements across multiple endpoints compared to placebo. Notably, it increased fibrosis improvement without worsening NASH, reduced liver fat content, improved liver enzymes (ALT and AST), lowered LDL cholesterol and triglycerides, and decreased levels of apolipoproteins B and CIII as well as lipoprotein(a). It also increased adiponectin, reduced CK-18/M30, and reversed T3 levels. While some evidence suggested publication bias in certain outcomes, overall, resmetirom showed promise in ameliorating key markers of NASH and associated metabolic dysregulation.

On the safety aspect of the drug, it was found that patients receiving resmetirom were significantly more likely to experience diarrhea and nausea compared to those on placebo. However, no significant associations were observed between resmetirom and adverse effects such as fatigue, back pain, arthralgia, headache, urinary tract infection, or COVID-19 incidence, which were minor or moderate in nature. Therefore, proving resmetirom was well tolerated and safe for use in people suspected of having NASH.

As mentioned earlier, lifestyle management has been the mainstay treatment for NASH, also referred to as metabolic-dysfunction-associated steatohepatitis (MASH). Pharmacotherapy targeting NASH is still a future promise. Historically, NASH treatment has depended on the theory of removing metabolic injury, intrahepatic or extrahepatic, and reducing proinflammatory processes that lead to hepatocyte injury [21]. Interestingly, hypothyroidism was an important comorbidity that was observed with NASH [22]. The Rotterdam study revealed a negative linear relationship between free T4 activity and NAFLD [23]. It was later found that the hepatic stellate cells express a multitude of nuclear receptors that are potential interventional targets for pharmacotherapy.

Resmetirom, a THR agonist that targets fatty acid handling, is one of the promising drugs that ongoing trials are focused on [18]. Agencies such as the Food and Drug Administration (FDA) and European Medicines Agency have approved resmetirom on the basis of the MAESTRO-NASH trial [24]. These THR-β receptors regulate lipid activity, leading to control over LDL, Apo B, and Lp(a) levels [25]. Resimetirom, a THR-β agonist, reduces fibrosis as a result of a reduction in metabolic injury, reduces lipotoxicity, and increases fat metabolism [21,26]. Resimetrom was observed to decrease free T4 levels with minimal effect on free T3 and consequently thyrotropin [18,27]. Resmetirom is also found to have added cardiovascular benefits [28].

Mice models have shown strong anti-steatotic activity, and the mechanism behind it is suspected to involve signal transducer and activator of transcription 3 and nuclear factor-kappa B signaling pathways [25,29]. Being a strong contender among pharmacotherapeutic options, the three trials that have been conducted so far have assessed the safety, efficacy, and side effects associated with the drug. Serum fibrosis markers were found to be decreasing, even though histological evidence showed no progress [25]. Moderate side effects found included nausea and diarrhea in the MAESTRO-NAFLD-1 trial. Notably, most trials have been conducted on white females. This seriously affects the generalizability of the findings to everyone else.

The trials were directed toward a decrease in liver fatty tissues as their primary outcome. An assessment of the health-related quality of life [HRQL] revealed that patients responding to resmetirom therapy, evident via a decrease in MRI-proton density fat fraction, had expressed a higher quality of life. This was most pronounced in week 12 of therapy and continued to increase thereafter [30].

Our meta-analysis reveals significant fibrosis improvement and decreased levels of liver fat content, liver function panel values, reverse T3, and a significant increase in adiponectin. These are essential targets for NASH management and are consistent with the available trials [21].

THR-β receptors are the primary liver thyroid receptors. However, thyroid receptors do exist in other tissues, such as cardiac and bone tissues, due to the existence of the THR-α receptors [22]. The selective agonist action of resimetrom and its rate of uptake by hepatic stellate cells lead to an effective solution for NASH. Any interaction with THR-α receptors was not found in the available trials. Relative to the rate of recovery with respect to fibrosis, Resmetirom is also assessed to be cost-effective for the management of NASH [31]. With the upcoming transition to MASH and metabolic dysfunction-associated steatotic liver disease, the diagnostic criteria for indicating resimetrom as a drug of choice is still contested. Resimetrom is provided without the riskier test on the criteria: liver biopsy. It is imperative to figure out noninvasive tests and biomarkers that can help assess and quantify MASH. These tests in turn can help in the appropriate identification of the candidate for treatment [27,32,33]. Coupled with the discovery of such noninvasive biomarkers, continuing education of practitioners, and the emphasis on their cost-effectiveness is crucial to primary care providers [34].

NASH is the result of a web of causes ranging from metabolic injury to pro-fibrotic processes. It is imperative to tackle the whole web, depending on the stressors causing it for every patient. Drugs that target obesity, lifestyle changes that promote better lipid handling, pharmacotherapy, and possible gene silencing/therapy may lead to better management of the condition. Drug interactions and adverse effects with maximal combinations are yet to be tested and are vital considering the constant co-morbid nature of NASH. This encompasses thyroid, cardiovascular, and diabetic disorders. Future research and focus, with the help of integrative models, should try to achieve the balance of all the mechanisms our bodies have evolved to maintain homeostasis or prevent the initiation of the event from the first step.

It is imperative to acknowledge any potential limitations that may have arisen during the course of our study. First, as our meta-analysis only included three RCTs, it indicates the need for working on further trials for more robust and reliable results. Furthermore, upon a closer look, our GRADE summary findings concluded that due to smaller sample sizes than recommended in the respective studies, there was moderate potential of bias being present in the studies. Another significant concern was the variation in certain research characteristics, such as different primary endpoints between

the studies, too many outcomes reported, and outcomes measured at different weeks thus making the comparison between studies complex, and so on. Additionally, in a few outcomes, noticeable asymmetry was highlighted by the doi plots, indicating a potential publication bias in our research.

Consequently, more investigations are required to have a deeper comprehension of resmetirom's effectiveness in treating NASH. Longer follow-up periods and a larger sample size should be key features of future research. Future research should also aim to demonstrate high-yield outcomes across secondary outcomes while maintaining similar primary objectives across all investigations. To determine the most effective dose, results should also be reported at weeks that are comparable to those of earlier experiments and at varied dosages. Nonetheless, these trials along with the FDA approval finally showcase a medication for relief of patients suffering from NASH.

In conclusion, the recent approval of resmetirom marks a significant breakthrough as the first treatment for NASH. This meta-analysis showcased significant improvements in key outcomes related to NASH, such as fibrosis improvement, liver fat content, lipid profiles, and liver enzymes. With mild side effects such as diarrhea and nausea, the drug maintains a satisfactory and favorable safety profile, further cementing its place as a viable treatment option for NASH. Moving forward, further research is needed to address the remaining questions regarding the long-term efficacy, safety, most effective dose, and optimal patient selection criteria for resmetirom therapy in NASH management.

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Conflicts of interest

There are no conflicts of interest.

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