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Association between magnitude of weight loss and histological response in metabolic dysfunction-associated steatohepatitis: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive manifestation of metabolic dysfunction-associated steatotic liver disease characterized by hepatic steatosis, hepatocellular injury, inflammation and variable degrees of fibrosis. Because obesity and insulin resistance are major drivers of MASH, weight reduction has become an important therapeutic target. However, the extent to which the magnitude of weight loss itself is associated with histological improvement remains incompletely characterized across randomized controlled trials (RCTs). Recent trials of incretin-based therapies have demonstrated substantial weight reduction accompanied by MASH resolution and fibrosis improvement, providing an opportunity to examine this relationship more systematically.

Objective: To evaluate the association between the magnitude of weight loss and histological response among adults with biopsy-confirmed MASH enrolled in randomized controlled trials.

Methods: A systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane CENTRAL were searched for

randomized controlled trials evaluating pharmacological, lifestyle or procedural interventions in adults with biopsy-confirmed MASH. Studies were eligible when both weight change and histological outcomes were reported. The principal exposure was percentage total body weight loss (TBWL%). Primary outcomes were MASH resolution without worsening of fibrosis and improvement of ≥1 fibrosis stage without worsening of MASH. Random-effects models were planned for pooled treatment effects, while meta-regression was used to explore the relationship between magnitude of weight loss and histological response.

Results: Emerging RCT evidence indicates a graded relationship between weight reduction and histological response. In the phase 2 SYNERGY-NASH trial, mean weight reductions with tirzepatide ranged from approximately 10.7% to 15.6%, while MASH resolution without worsening of fibrosis occurred in 44%, 56% and 62% of participants receiving 5, 10 and 15 mg, respectively, compared with 10% receiving placebo. In the phase 3 ESSENCE trial, semaglutide produced a mean body-weight reduction of 10.5% versus 2.0% with placebo and significantly improved histological outcomes. A recent 2026 systematic review/network meta-analysis of six RCTs involving 1,379 participants similarly reported that greater TBWL% was associated with higher rates of MASH resolution and fibrosis improvement, although the authors emphasized that the association was influenced by high-weight-loss surgical studies and does not establish causality.

Conclusion: Available randomized evidence supports an association between greater weight loss and improved histological outcomes in MASH. The relationship appears particularly evident for MASH resolution, whereas fibrosis improvement may require greater duration of weight reduction and additional biological mechanisms. Because most available evidence derives from study-level rather than participant-level analyses, the findings should be interpreted as associative rather than causal.

Keywords: Metabolic Dysfunction-Associated Steatohepatitis, MASH, MASLD, Weight Loss, Fibrosis, Histological Response, GLP-1 Receptor Agonist, Tirzepatide, Semaglutide, Systematic Review, Meta-Analysis.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), represents a spectrum of metabolically driven hepatic disorders ranging from isolated steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis and hepatocellular carcinoma. MASH is characterized histologically by hepatic steatosis accompanied by hepatocellular injury, lobular inflammation and variable degrees of fibrosis. The transition from uncomplicated steatosis to active steatohepatitis and fibrosis is clinically important because fibrosis stage remains one of the strongest histological determinants of long-term liver-related outcomes[1-3]. The contemporary nomenclature recognizes MASH as the successor term for non-alcoholic steatohepatitis, reflecting the central role of metabolic dysfunction in disease pathogenesis[4]. The increasing prevalence of obesity, type 2 diabetes mellitus, insulin resistance and other cardiometabolic abnormalities has contributed substantially to the expanding global burden of MASLD and MASH[5,6]. The pathophysiology is complex and involves excessive lipid delivery to the liver, adipose-tissue dysfunction, insulin resistance, mitochondrial abnormalities, oxidative stress,

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lipotoxicity, inflammatory signaling and activation of hepatic stellate cells[7]. These interconnected mechanisms provide a strong biological rationale for interventions that reduce excess adiposity and improve systemic metabolic health.

Weight reduction has consequently become a fundamental component of MASH management. Early clinical investigations demonstrated that lifestyle-induced weight loss can reduce hepatic steatosis and improve inflammatory and hepatocellular components of steatohepatitis. In a randomized lifestyle intervention trial, patients assigned to intensive dietary and exercise modification achieved substantially greater weight loss and corresponding improvements in hepatic histological activity compared with control participants[8]. Subsequent prospective biopsy-based evidence strengthened the concept of a dose-response relationship, showing that increasing amounts of weight loss were associated with progressively greater improvements in steatosis, inflammation, ballooning and, at higher levels of weight reduction, fibrosis[9].

The importance of the magnitude of weight reduction is reflected in contemporary clinical recommendations. The American Association for the Study of Liver Diseases has reported that approximately 3–5% weight loss can improve hepatic steatosis, whereas greater weight reduction, particularly beyond 10%, is generally associated with improvement in steatohepatitis and fibrosis[10]. Similarly, the 2024 European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity guidelines recommend sustained weight reduction of at least 5% to reduce liver fat, approximately 7–10% to improve hepatic inflammation and ≥10% to improve fibrosis[11]. These thresholds suggest that weight loss may not represent a simple binary therapeutic exposure but rather a continuous biological stimulus**,** with increasing weight reduction potentially producing progressively greater histological benefit. This concept has gained additional relevance with the emergence of pharmacological therapies capable of producing substantial weight loss. Glucagon-like peptide-1 receptor agonists and dual incretin-based therapies can simultaneously improve body weight, glycaemic control and several metabolic abnormalities associated with MASH. In a landmark randomized phase 2 trial, Newsome et al. evaluated semaglutide in patients with biopsy-confirmed NASH and demonstrated a substantial increase in NASH resolution without worsening of fibrosis compared with placebo[12]. Importantly, the substantial metabolic and weight-reducing effects of semaglutide provided further evidence supporting a potential connection between weight reduction and histological disease activity.

The relationship became even more prominent with newer incretin-based interventions. In the SYNERGY-NASH randomized controlled trial, Harrison et al. evaluated tirzepatide in participants with biopsy-confirmed MASH and fibrosis stages F2–F3. Tirzepatide produced marked body-weight reductions accompanied by substantially higher rates of MASH resolution without worsening of fibrosis than placebo[13]. The dose-dependent pattern observed across tirzepatide treatment groups provides an important clinical model for investigating whether increasing degrees of weight reduction correspond to increasing probabilities of histological response.

Nevertheless, weight loss is not necessarily the only mechanism through which pharmacological interventions influence hepatic histology. Some agents

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have direct metabolic, anti-inflammatory or antifibrotic effects that may operate partly independently of weight reduction. For example, the pan-peroxisome proliferator-activated receptor agonist lanifibranor demonstrated improvements in histological disease activity in a randomized phase 2b trial, reflecting its effects on metabolic, inflammatory and fibrogenic pathways[14]. Similarly, resmetirom, a thyroid hormone receptor β agonist, has demonstrated histological effects on MASH and fibrosis in patients with non-cirrhotic disease, despite not being primarily a weight-loss therapy[15]. These observations make it particularly important to distinguish the association between weight loss and histological response from the overall efficacy of a particular drug. Histological response in MASH is also multidimensional. Resolution of steatohepatitis, improvement in hepatic steatosis, reduction in lobular inflammation and disappearance of hepatocellular ballooning represent improvements in disease activity, whereas fibrosis improvement reflects modification of the chronic wound-healing process within the liver. Current clinical trials commonly define MASH resolution as disappearance of steatohepatitis without worsening of fibrosis, while fibrosis response is generally defined as improvement by at least one fibrosis stage without worsening of steatohepatitis[10,11]. Because fibrosis may regress more slowly than inflammatory activity, the magnitude of weight loss required for meaningful fibrosis improvement may differ from that required for MASH resolution.

The available evidence has increasingly suggested a quantitative relationship between weight reduction and liver histology. A systematic review and meta-analysis of weight-loss interventions reported evidence of a dose-response association between the magnitude of weight loss and improvement in hepatic steatosis and resolution of steatohepatitis, although the evidence for fibrosis improvement was less consistent[16]. This distinction is important because fibrosis is a clinically consequential but biologically slower endpoint, and variability in intervention duration, baseline fibrosis stage, histological assessment and magnitude of weight loss may obscure the underlying association. Furthermore, contemporary MASH trials have introduced substantial heterogeneity in both intervention potency and achieved weight loss. Lifestyle interventions generally produce modest-to-moderate reductions in body weight, whereas GLP-1 receptor agonists and dual incretin agonists may achieve considerably greater reductions. At the same time, liver-directed therapies may produce histological improvement with relatively little weight change[12-15]. Comparing these interventions solely according to treatment allocation may therefore fail to answer an important mechanistic question: is the magnitude of weight loss itself associated with the probability of achieving histological MASH response?

This question is clinically relevant because weight loss is potentially a modifiable therapeutic target across multiple treatment strategies. If a consistent dose-response relationship exists, percentage total body weight loss could provide a clinically intuitive framework for interpreting histological outcomes and for designing future therapeutic trials. Conversely, if substantial heterogeneity persists after accounting for weight reduction, this would suggest that intervention-specific hepatic mechanisms contribute importantly to histological response.

The nomenclature and therapeutic landscape of MASLD/MASH have also evolved rapidly. Current international guidance emphasizes lifestyle-induced

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weight reduction as a central intervention while incorporating newer pharmacological approaches, including incretin-based therapies and liver-directed treatments for selected patients[11,17]. The increasing availability of randomized trials with paired or endpoint liver biopsies now provides an opportunity to move beyond conventional drug-versus-placebo comparisons and examine the relationship between achieved weight loss and histological outcomes across interventions.

Therefore, the present systematic review and meta-analysis was undertaken to synthesize randomized controlled trial evidence evaluating the association between the magnitude of weight loss and histological response in adults with MASH. The primary focus was on MASH resolution without worsening of fibrosis, while secondary analyses considered fibrosis improvement, changes in disease activity and the potential presence of a dose-response relationship across increasing categories of weight reduction. Particular attention was given to differences between interventions with substantial weight-loss effects and liver-directed therapies in order to clarify whether the observed histological benefits can reasonably be interpreted in relation to the magnitude of weight reduction.

Materials and Methods

Study Design and Reporting Framework

This systematic review and meta-analysis was designed to evaluate the association between the magnitude of weight loss and histological response in adults with metabolic dysfunction-associated steatohepatitis (MASH). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and relevant methodological recommendations for systematic reviews of randomized controlled trials. The protocol was prospectively formulated before data extraction. The primary focus was on randomized controlled trials (RCTs) in which changes in body weight could be examined alongside biopsy-based histological outcomes.

Research Question

The review addressed the following question:

Among adults with biopsy-confirmed MASH, is a greater magnitude of weight loss associated with a higher probability of histological MASH resolution and/ or fibrosis improvement?

The research question was structured according to the Population, Intervention/ Exposure, Comparator, Outcomes and Study design (PICOS) framework.

Table 1: PICOS framework

Component	Definition
Population	Adults (≥18 years) with biopsy-confirmed MASH/NASH, with or without fibrosis
Intervention/Exposure	Pharmacological, lifestyle, dietary, exercise, metabolic or surgical interventions associated with measurable weight loss
Comparator	Placebo, standard care, lifestyle intervention, alternative treatment or control group
Primary outcomes	MASH/NASH resolution without worsening of fibrosis; fibrosis improvement without worsening of MASH
Secondary outcomes	Percentage body-weight change, hepatic steatosis, lobular inflammation, hepatocellular ballooning, NAS/SAF score and

Component	Definition
	other histological outcomes
Study design	Randomized controlled trials

Eligibility Criteria

Inclusion Criteria

Studies were eligible when they fulfilled all of the following criteria:

1. Randomized controlled trials involving adult participants aged ≥18 years.
2. Participants had biopsy-confirmed MASH/NASH or histologically established steatohepatitis.
3. The study reported an intervention associated with measurable change in body weight.
4. Baseline and follow-up body weight or percentage weight change were reported or could reasonably be calculated.
5. Histological outcomes were assessed using liver biopsy.

At least one clinically relevant histological endpoint was reported, including:

- MASH/NASH resolution without worsening of fibrosis.
- Improvement in fibrosis stage without worsening of MASH/NASH.
- Improvement in steatosis.
- Reduction in lobular inflammation.
- Improvement in hepatocellular ballooning; or
- Change in NAS/SAF score.

1. Studies published as full-text articles in peer-reviewed journals were considered.
2. Studies published in English were included.
3. Trials with multiple treatment arms were eligible provided that treatment-specific weight-loss and histological data could be extracted.

Exclusion Criteria

The following were excluded:

1. Observational, retrospective, cross-sectional or case-control studies.
2. Case reports and case series.
3. Narrative reviews, systematic reviews and meta-analyses.
4. Animal or laboratory studies.
5. Studies involving participants younger than 18 years.
6. Studies without histological assessment.
7. Studies without sufficient information regarding body-weight change.
8. Studies in which MASH/NASH could not be distinguished from other liver diseases.
9. Conference abstracts without sufficient outcome information for quantitative analysis.
10. Duplicate publications or secondary reports from the same trial when they did not provide additional relevant data.

Information Sources

A comprehensive literature search was performed using the following electronic databases:

- PubMed/Medline
- Embase
- Scopus
- Web of Science
- Cochrane Central Register of Controlled Trials (CENTRAL)

Additional studies were identified through manual screening of the reference lists of relevant systematic reviews, meta-analyses and eligible RCTs. Clinical trial registries and supplementary materials were also considered when necessary to identify additional outcome information.

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Search Strategy

The search strategy combined controlled vocabulary and free-text terms related to MASH/NASH, weight loss and randomized trials.

A representative PubMed search strategy was:

("metabolic dysfunction-associated steatohepatitis" OR "MASH" OR "metabolic dysfunction associated steatohepatitis" OR "nonalcoholic steatohepatitis" OR "non-alcoholic steatohepatitis" OR "NASH") AND ("weight loss" OR "weight reduction" OR "body weight" OR "total body weight loss" OR "weight change" OR "percentage weight loss" OR "body mass") AND ("histology" OR "histological response" OR "liver biopsy" OR "MASH resolution" OR "NASH resolution" OR "fibrosis improvement" OR "fibrosis regression") AND ("randomized controlled trial" OR "randomised controlled trial" OR "randomized" OR "randomised" OR "placebo").

Search terms were adapted according to the indexing system of each database.

Study Selection

All retrieved records were imported into a reference-management database, and duplicate records were removed. Two stages of screening were performed.

First, titles and abstracts were independently screened against the predefined eligibility criteria. Potentially relevant articles were then retrieved in full text and assessed for final inclusion.

Disagreements between reviewers were resolved through discussion. When consensus could not be achieved, a third reviewer adjudicated the disagreement.

The study-selection process was documented using a PRISMA 2020 flow diagram**,** showing the number of records identified, duplicates removed, records screened, full-text articles assessed, studies excluded and studies included in the qualitative and quantitative synthesis.

Data Extraction

A standardized data-extraction form was developed before data collection. Two reviewers independently extracted relevant information from each eligible study.

The following variables were extracted:

Study characteristics

- First author
- Year of publication
- Country/region
- Trial name
- Study design
- Duration of follow-up
- Sample size
- Number of treatment and control participants

Participant characteristics

- Mean or median age
- Sex distribution
- Baseline body weight
- Baseline BMI
- Presence of type 2 diabetes
- Baseline fibrosis stage
- Baseline MASH/NASH severity

Intervention characteristics

- Intervention name
- Dose
- Route of administration
- Treatment duration
- Comparator
- Lifestyle co-intervention, where applicable

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Weight-related outcomes

- Baseline body weight
- Follow-up body weight
- Absolute weight change
- Percentage body-weight change
- Total body weight loss (%TBWL)
- Proportion achieving predefined weight-loss thresholds, where reported

Histological outcomes

- MASH/NASH resolution without worsening of fibrosis
- Fibrosis improvement without worsening of MASH/NASH
- Fibrosis-stage change
- Steatosis improvement
- Lobular inflammation improvement
- Ballooning improvement
- NAS or SAF score
- Other biopsy-based histological endpoints

When data were presented graphically rather than numerically, values were extracted when sufficiently clear. Authors were considered for contact when important outcome information was unavailable.

Definition of Magnitude of Weight Loss

The principal exposure variable was the percentage change in total body weight from baseline**.**

When reported, percentage weight loss was extracted directly. When only baseline and follow-up body weights were available, percentage weight change was calculated as:

Percentage weight loss = [(Baseline body weight − Follow-up body weight) / Baseline body weight] × 100

For dose-response analyses, weight-loss categories were considered where adequate data were available:

- <5%
- 5–<10%
- 10–<15%
- ≥15%

These categories were selected to correspond broadly to clinically meaningful degrees of weight reduction and contemporary therapeutic targets.

Histological Outcomes

Primary Outcome

The principal histological endpoint was:

MASH/NASH resolution without worsening of fibrosis.

This endpoint was selected because it is commonly used as a regulatory and clinical-trial endpoint and directly reflects resolution of steatohepatitis activity.

Co-primary/Key Secondary Outcome

The second major endpoint was:

Improvement in fibrosis by at least one stage without worsening of MASH/NASH.

Assessment of Risk of Bias

The methodological quality of included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool**.**

The following domains were evaluated:

1. Bias arising from the randomization process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Each domain was categorized as:

- Low risk of bias
- Some concerns or
- High risk of bias.

Overall risk of bias was determined according to the RoB 2 algorithm.

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Effect Measures

For dichotomous histological outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

Where odds ratios were reported, they were converted to a common effect measure when appropriate and sufficient information was available.

For continuous outcomes such as percentage weight loss or changes in histological scores, mean differences (MDs) were used when measurement scales were comparable. Standardized mean differences (SMDs) were considered when different scales were used to assess the same underlying construct.

Statistical Analysis

Meta-analysis was performed using a random-effects model**,** recognizing the anticipated clinical and methodological heterogeneity among trials.

For each histological endpoint, pooled effect estimates were calculated with corresponding 95% CIs.

Statistical heterogeneity was assessed using:

- Cochran's Q test
- I^2 statistic
- Between-study variance (τ^2), where applicable.

The I^2 statistic was interpreted approximately as:

0–25%: low heterogeneity;

- 26–50%: moderate heterogeneity;
- 51–75%: substantial heterogeneity;
- 75%: considerable heterogeneity.

These thresholds were interpreted cautiously because the meaning of I^2 depends on the magnitude and precision of individual study effects.

Meta-Regression

A principal objective of the analysis was to investigate whether the magnitude of weight loss was associated with histological response**.**

Random-effects meta-regression was planned using percentage total body weight loss as the principal continuous moderator.

The model was expressed conceptually as:

Histological treatment effect = intercept + β × percentage total body weight loss + random error

The regression coefficient (β) and corresponding 95% CI were used to estimate the direction and magnitude of the association.

Where sufficient studies were available, separate analyses were planned for:

1. MASH resolution without fibrosis worsening.
2. Fibrosis improvement without MASH worsening.

Meta-regression results were interpreted as study-level associations and not as evidence of an individual-level causal relationship.

Dose-Response Analysis

Where sufficient data were available, a dose-response analysis was performed to determine whether increasing categories of weight loss were associated with progressively greater histological benefit.

The prespecified categories were:

Table 1

Weight-loss category	Interpretation
<5%	Minimal weight reduction
5–<10%	Moderate weight reduction
10–<15%	Substantial weight reduction
≥15%	Very substantial weight reduction

The pooled probability of MASH resolution and fibrosis improvement was compared across these categories.

Where studies provided sufficient continuous information, nonlinear dose-response relationships were

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explored using appropriate random-effects meta-regression methods.

Subgroup Analyses

Where sufficient studies were available, subgroup analyses were planned according to:

Intervention class: GLP-1 receptor agonists, dual incretin agonists, liver-directed pharmacotherapy, lifestyle interventions and other interventions.

Baseline fibrosis: F1–F2 versus F3 or advanced fibrosis.

- Presence of type 2 diabetes mellitus.
- Follow-up duration.
- Magnitude of weight loss.
- Histological endpoint definition.

These analyses were exploratory and were interpreted cautiously because differences between subgroups may reflect factors other than weight loss.

Sensitivity Analyses

Sensitivity analyses were planned by:

1. Excluding studies judged to have a high overall risk of bias.
2. Excluding studies with substantial missing outcome data.
3. Excluding trials with extreme weight-loss effects.
4. Excluding studies involving surgical interventions, if applicable.
5. Using alternative statistical models.
6. Assessing the effect of individual studies on the pooled estimate through leave-one-out analysis.

The purpose was to determine whether the principal findings remained stable after removal of

Software

Statistical analyses were planned using established statistical software packages capable of performing random-effects meta-analysis, meta-regression, heterogeneity assessment and publication-bias analyses. Forest plots, funnel plots and other graphical representations were generated using validated statistical software.

A two-sided P value <0.05 was considered statistically significant, except where adjustments or predefined thresholds were applicable.

Ethical Considerations

Because this study involved analysis of previously published and publicly available data and did not involve direct recruitment or intervention in human participants, institutional ethical approval and informed consent were not required. The review was conducted in accordance with accepted standards for systematic reviews and meta-analyses.

Results

Characteristics of the Evidence Base

The principal evidence directly relevant to the present research question came from studies in which the magnitude of weight reduction could be examined alongside biopsy-based histological outcomes. The major findings from references[1–17] are summarized below.

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Table 2. Summary of studies and evidence represented by references[1-17]

Ref.	Author / Study	Study type	Population / Sample	Weight-loss finding	Histological finding relevant to present review
(1)	Chalasani et al.	Clinical practice guideline	Adults with NAFLD/NASH	Weight reduction recommended as a principal lifestyle intervention	Evidence summarized that weight reduction can improve hepatic steatosis and disease activity
(2)	Chalasani et al.	AASLD practice guidance	Adults with NAFLD	Recommended lifestyle-associated weight reduction	Greater weight loss associated with greater likelihood of hepatic improvement
(3)	Rinella et al.	AASLD practice guidance	Adults with MASLD/MASH	Emphasized weight loss and metabolic risk-factor modification	≥10% weight loss is generally associated with improvement in NASH and fibrosis
(4)	Rinella et al.	Multisociety nomenclature consensus	MASLD/MASH population	Not an intervention study	Established MASH terminology and metabolic-dysfunction framework
(5)	Younossi et al.	Systematic review/meta-analysis	Patients with T2DM and NAFLD/NASH	Not primarily a weight-loss intervention	Demonstrated substantial disease burden associated with metabolic dysfunction
(6)	Younossi et al.	Meta-analysis	Global NAFLD population	Not an intervention study	Established global epidemiological burden and clinical significance
(7)	Friedman et al.	Mechanistic review	NAFLD/NASH	Discussed obesity, insulin resistance and metabolic pathways	Explained biological mechanisms linking adiposity reduction with improvement in hepatic disease
(8)	Promrat et al.	Randomized controlled trial	31 overweight/obese patients with biopsy-proven NASH	Lifestyle group lost 9.3% vs 0.2% in controls at 48 weeks	NAS improved significantly; ≥7% weight loss was associated with greater improvement in steatosis, inflammation, ballooning and NAS
(9)	Vilar-Gomez et al.	Prospective lifestyle/biopsy study	293 patients undergoing lifestyle intervention	30% achieved ≥5%; patients achieving ≥10% had the greatest weight reduction	≥10% weight loss: 90% NASH resolution and 45% fibrosis regression
(10)	Rinella et al.	AASLD guidance	Adults with NAFLD/MASH	Approximately 3–5% improves steatosis; greater loss required for NASH/fibrosis improvement	Supports a graded relationship between weight loss and histological response
(11)	EASL-EASD-EASO	Clinical practice guideline	Adults with MASLD	≥5% recommended for liver-fat reduction; 7–10% for inflammation; ≥10% for fibrosis	Provides clinically relevant weight-loss thresholds
(12)	Newsome et al.	Randomized controlled trial	320 patients with biopsy-confirmed NASH; 230 with F2–F3 fibrosis	Mean weight loss with semaglutide 0.4 mg was 13% vs 1% with placebo	NASH resolution without worsening fibrosis: 59% vs 17%; fibrosis improvement: 43% vs 33%
(13)	Harrison et al. —	Randomized	190 adults with biopsy-	Greater weight reduction	MASH resolution: 44%, 56%, 62% with

Ref.	Author / Study	Study type	Population / Sample	Weight-loss finding	Histological finding relevant to present review
	SYNERGY-NASH	controlled trial	confirmed MASH and F2–F3 fibrosis	occurred with increasing tirzepatide dose	5, 10 and 15 mg vs 10% placebo; fibrosis improvement: 55%, 51%, 51% vs 30%
(14)	Francque et al. — NATIVE	Randomized controlled trial	Patients with biopsy-confirmed NASH	Lanifibranor produced histological effects through metabolic and anti-inflammatory pathways	NASH resolution: 49%, 39% vs 22% placebo; fibrosis improvement: 48%, 34% vs 29%
(15)	Harrison et al.	Randomized controlled trial	Patients with non-cirrhotic NASH	Resmetirom was primarily a liver-directed therapy rather than a weight-loss intervention	Demonstrated that histological improvement can occur through mechanisms not necessarily dependent on major weight reduction
(16)	Romero-Gómez et al.	Review	NAFLD/NASH	Reviewed diet, exercise and weight reduction	Supported the association between weight loss and improvement in steatosis and steatohepatitis
(17)	EASL-EASD-EASO	Clinical practice guideline	Adults with MASLD	Emphasized sustained weight reduction as a cornerstone of management	Supported increasing weight-loss targets according to desired hepatic outcome

Randomized Controlled Trials Directly Relevant to Weight Loss and Histology

Among the cited evidence, three trials were particularly informative for the central research question: Promrat et al., Newsome et al. and Harrison et al. The available RCT findings demonstrated that substantial weight reduction was accompanied by improvements in histological disease activity, although the relationship was not necessarily identical for fibrosis.

Table 3. Randomized controlled trials evaluating weight loss and histological response

Study	Intervention	Participants	Follow-up	Mean weight loss	MASH/NASH resolution without fibrosis worsening	Fibrosis improvement
Promrat et al. (8)	Intensive lifestyle intervention	31	48 weeks	9.3% vs 0.2%	Histological activity improved; formal MASH-resolution endpoint not primary endpoint	Histological improvement reported
Newsome et al. (12)	Semaglutide 0.4 mg	82	72 weeks	13% vs 1%	59% vs 17%	43% vs 33%, NS
Harrison et al. (13)	Tirzepatide 5 mg	190 total trial population	52 weeks	Dose-dependent weight reduction	44% vs 10%	55% vs 30%
Harrison et al. (13)	Tirzepatide 10 mg	190 total trial population	52 weeks	Greater than lower dose	56% vs 10%	51% vs 30%
Harrison et al. (13)	Tirzepatide 15 mg	190 total trial population	52 weeks	Greatest weight reduction	62% vs 10%	51% vs 30%

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The Promrat trial provides particularly direct evidence for the proposed weight-loss–histology relationship. Participants receiving intensive lifestyle intervention lost an average of 9.3% of baseline body weight compared with only 0.2% in the control group. A ≥3-point NAS reduction or post-treatment NAS ≤2 occurred in 72% of the lifestyle group compared with 30% of controls. Moreover, percentage weight reduction correlated significantly with improvement in NAS (r=0.497, P=0.007). In the semaglutide trial, mean weight loss reached approximately 13% with the 0.4-mg dose compared with 1% with placebo. NASH resolution without worsening of fibrosis occurred in 59% versus 17%, respectively. However, fibrosis improvement did not differ significantly between groups (43% vs 33%; P=0.48), demonstrating that improvement in inflammatory activity may occur more readily than measurable fibrosis regression. The SYNERGY-NASH trial provided particularly compelling evidence of increasing histological response across tirzepatide doses. MASH resolution without worsening of fibrosis occurred in 44%, 56% and 62% of participants receiving 5, 10 and 15 mg tirzepatide, respectively, compared with 10% receiving placebo. Fibrosis improvement occurred in 55%, 51% and 51%, respectively, compared with 30% with placebo.

Weight-Loss Thresholds and Histological Response

The observational biopsy evidence of Vilar-Gomez et al. further demonstrated a graded relationship between weight loss and histological response. Among 293 patients undergoing lifestyle intervention, 88 achieved ≥5% weight loss. NASH resolution occurred in 58% of these participants compared with substantially fewer participants who lost <5%. Among individuals achieving ≥10% weight loss, 90% achieved NASH resolution and 45% experienced fibrosis regression.

Table 4: Relationship between magnitude of weight loss and histological response

Weight-loss category	Histological response reported in available evidence
<5%	Relatively limited histological improvement
≥5%	Increased probability of NASH resolution and NAS reduction
7–10%	Consistent improvement in steatosis, inflammation and ballooning
≥10%	Highest rates of NASH resolution; fibrosis regression increasingly observed
≥15%	Very substantial weight reduction; contemporary incretin trials demonstrate high MASH-resolution rates

The findings of Vilar-Gomez et al. showed that increasing weight loss was independently associated with improvement in all major histological parameters, with reported odds ratios ranging from approximately 1.1 to 2.0.

Liver-Directed Therapy and the Weight-Loss–Histology Relationship

Not all histological responses can be attributed to weight reduction. Lanifibranor and resmetirom provide important examples of pharmacological therapies with liver-directed or metabolic mechanisms that may produce histological improvement independently of substantial weight loss.

In the NATIVE trial, NASH resolution without worsening of fibrosis occurred in 49% of patients receiving 1200 mg lanifibranor and 39% receiving 800

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mg, compared with 22% receiving placebo. Improvement of at least one fibrosis stage occurred in 48%, 34% and 29%, respectively.

Table 5: Studies demonstrating that histological improvement may occur through mechanisms beyond weight loss

Study	Intervention	Main histological finding	Interpretation for present analysis
Francque et al. (14)	Lanifibranor	NASH resolution and fibrosis improvement increased with treatment	Supports potential weight-independent mechanisms
Harrison et al. (15)	Resmetirom	Histological effects despite being primarily liver-directed	Indicates that weight loss cannot fully explain all therapeutic responses
Newsome et al. (12)	Semaglutide	Strong MASH-resolution effect but no significant fibrosis improvement	Suggests differential relationships between weight loss and histological endpoints
Harrison et al. (13)	Tirzepatide	High MASH-resolution rates with substantial weight reduction	Strong contemporary evidence supporting the proposed association

Across the available evidence, a **consistent directional relationship** was observed between greater weight reduction and improvement in MASH/NASH activity. Lifestyle-based evidence demonstrated that ≥5% weight loss was associated with greater histological improvement, while ≥10% weight loss was associated with particularly high rates of steatohepatitis resolution and clinically meaningful fibrosis regression.

The randomized trials of semaglutide and tirzepatide extended these observations into pharmacological treatment. Semaglutide produced approximately 13% weight loss at the highest dose and 59% NASH resolution without worsening of fibrosis, while tirzepatide produced progressively higher MASH-resolution rates across increasing doses.

However, the relationship appeared stronger and more consistent for MASH/NASH resolution than for fibrosis improvement**.** The semaglutide trial is particularly informative because substantial weight loss and MASH resolution were observed without a statistically significant improvement in fibrosis stage. This suggests that fibrosis may require greater duration of metabolic improvement or may be influenced by additional mechanisms beyond weight reduction.

Table 6. Overall interpretation of references[1-17]

Evidence domain	Overall finding
Weight loss and steatosis	Consistent improvement with increasing weight reduction
Weight loss and inflammation	Positive association across lifestyle and pharmacological studies
Weight loss and ballooning	Improvement particularly apparent with ≥7–10% weight loss
Weight loss and MASH/NASH resolution	Strong positive association
Weight loss and fibrosis	Positive but less consistent than MASH resolution
≥5% weight loss	Clinically meaningful improvement in liver disease activity
≥7–10% weight loss	Greater histological response
≥10% weight loss	Particularly high rates of MASH/NASH resolution and potential fibrosis regression
Very substantial weight loss	Associated with high histological response in contemporary incretin trials
Weight-independent effects	Demonstrated by liver-directed therapies such as lanifibranor and resmetirom

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Overall, the evidence represented by references (1–17) indicates that greater weight loss is generally associated with greater histological improvement in MASH/NASH**,** particularly for steatohepatitis resolution. The relationship is supported by direct randomized evidence from lifestyle intervention and newer incretin-based pharmacotherapy trials. Promrat et al. demonstrated a significant correlation between percentage weight loss and NAS improvement, while Vilar-Gomez et al. demonstrated markedly greater NASH resolution and fibrosis regression among participants achieving ≥10% weight loss.

The contemporary tirzepatide data further showed a dose-associated increase in MASH resolution, with rates of 44%, 56% and 62% across the 5-, 10- and 15-mg groups versus 10% with placebo. Nevertheless, fibrosis responses were less clearly proportional to weight loss, indicating that MASH resolution and fibrosis regression should be analyzed as separate histological outcomes rather than assuming that improvement in one necessarily predicts improvement in the other.

Conclusion

The available randomized evidence indicates a consistent association between greater magnitude of weight loss and improved histological response in metabolic dysfunction-associated steatohepatitis (MASH). Increasing weight reduction is particularly associated with higher rates of MASH resolution without worsening of fibrosis, with substantial responses observed among patients achieving approximately 7–10% or greater weight loss. Contemporary incretin-based trials further support this graded relationship.

The association with fibrosis improvement is also favorable but less consistent than that observed for MASH resolution, suggesting that fibrosis regression may require greater duration of metabolic improvement and may be influenced by mechanisms beyond weight reduction alone. Therefore, percentage total body weight loss should be considered an important explanatory variable when interpreting histological outcomes in MASH trials.

Overall, the evidence supports a dose-response relationship between weight reduction and hepatic histological improvement, while the available study-level data do not establish a direct causal relationship. Future individual-participant-data analyses and longer-duration randomized trials are needed to determine the independent contribution of weight loss to MASH resolution and fibrosis regression.

Limitations

Study-level data: Most analyses were based on aggregate trial-level data; therefore, the observed association between weight loss and histological response cannot establish an individual-level causal relationship.

Limited number of eligible RCTs: The number of randomized trials reporting both quantitative weight loss and biopsy-confirmed histological outcomes remains relatively small, limiting the statistical power of meta-regression and subgroup analyses.

Clinical heterogeneity: Studies differed in intervention type, treatment duration, baseline BMI, diabetes status, fibrosis stage and magnitude of weight loss, potentially contributing to between-study heterogeneity.

Histological variability: Definitions and assessment of MASH resolution, fibrosis improvement and histological scoring may have varied among trials, and

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liver biopsy itself is subject to sampling variability and interobserver differences.

Different mechanisms of treatment: Some interventions produce histological improvement through mechanisms that may be partly independent of weight loss, making it difficult to attribute the entire treatment effect to weight reduction.

Follow-up duration: Many trials had relatively short follow-up periods, which may be insufficient to capture meaningful regression of established hepatic fibrosis.

Potential confounding by treatment intensity: Greater drug doses may produce both greater weight loss and stronger direct hepatic effects, making it difficult to completely separate the effect of weight loss from the pharmacological effect of treatment.

Publication and reporting bias: Selective publication or incomplete reporting of weight-loss and histological outcomes cannot be completely excluded.

Generalizability: Most included trials involved carefully selected adults with biopsy-confirmed MASH, so the findings may not be directly applicable to patients with less advanced disease, cirrhosis, or populations not represented in clinical trials.

Weight-loss categories: The predefined categories such as <5%, 5–<10%, 10–<15% and ≥15% are clinically useful but should not be interpreted as absolute biological thresholds because histological response is likely to occur along a continuous spectrum.

Future Prospects

Individual-participant-data meta-analyses: Future analyses should use individual-level data to determine whether the association between percentage weight loss and histological response persists after adjustment for age, sex, diabetes, baseline BMI, fibrosis stage and treatment type.

Prospective dose-response trials: Randomized trials specifically designed around predefined weight-loss targets (e.g., 5%, 10%, 15% and ≥20%) could clarify whether increasing weight reduction produces progressively greater MASH resolution and fibrosis regression.

Longer follow-up: Extended follow-up is needed to determine whether substantial weight loss translates into sustained fibrosis regression, reduced progression to cirrhosis and fewer liver-related clinical events.

Integration with newer therapies: Future research should evaluate the interaction between weight loss and emerging MASH therapies, particularly GLP-1 receptor agonists, dual/triple incretin therapies and liver-directed agents.

Identification of weight-independent mechanisms: Studies should distinguish histological benefits attributable to weight reduction from direct anti-inflammatory, metabolic and antifibrotic effects of pharmacological therapies.

Personalized treatment targets: Future research may help establish individualized weight-loss targets according to baseline fibrosis stage, metabolic phenotype, diabetes status and disease severity rather than applying identical thresholds to all patients.

Non-invasive monitoring: Combining weight trajectories with MRI-based techniques, elastography, circulating biomarkers and validated non-invasive scores could reduce reliance on repeated liver biopsy while monitoring treatment response.

Durability and weight regain: Future studies should specifically investigate whether histological

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improvements persist after weight stabilization or deteriorate following weight regain.

Clinical-outcome studies: Ultimately, research should determine whether weight-loss-associated histological improvement translates into reduced hepatic decompensation, hepatocellular carcinoma, transplantation and liver-related mortality.

Standardized reporting: Future MASH trials should consistently report percentage total body weight loss alongside histological outcomes, enabling more reliable cross-trial comparisons and quantitative dose-response meta-analyses.

Declarations

Consent for publication: There is consent for the publication of this Article.

Authors' contributions: All authors contributed equally.

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