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ORIGINAL RESEARCH

Weight Regain after Lifestyle Interventions is Associated with Higher Risk of Liver Inflammation: A Retrospective Observational Study

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Background: Lifestyle-induced weight loss improves metabolic health, but weight regain is common. Its hepatic consequences, particularly in relation to metabolic dysfunction–associated steatotic liver disease (MASLD), remain insufficiently characterized.

Methods: This retrospective observational study included 213 patients categorized as weight regain (≥5% lifestyle-induced weight loss followed by return to or exceeding baseline weight) or weight sustain (weight change within ±5% of baseline) over 3 years. Propensity score matching (PSM) balanced age, sex, weight, and body mass index. Clinical, biochemical, and noninvasive liver indices were compared. In a bariatric surgery subset, liver histology, transcriptomics, quantitative PCR, and immunohistochemistry were performed.

Results: No significant differences were found in metabolic parameters between groups. After PSM, the weight regain group showed higher alanine aminotransferase (ALT) (median 59.00 vs 41.00 IU/L, P=0.007) and aspartate aminotransferase (AST) (33.50 vs 26.00 IU/L, P=0.041). In males, ALT (88.00 vs 47.00 IU/L, P<0.001) and AST (46.00 vs 30.00 IU/L, P=0.004) remained higher. Noninvasive indices of hepatic steatosis (Dallas Steatosis Index, DSI) and fibrosis (NFS, FIB-4) did not differ. In male patients with liver biopsy samples available, liver histology showed comparable NAFLD Activity Scores (NAS) and fibrosis stages, whereas transcriptomic analysis revealed immune-related pathway enrichment. Increased hepatic CD11B and CD68 expression was confirmed by quantitative PCR and immunohistochemistry.

Conclusion: Weight regain after lifestyle-induced weight loss is associated with early liver-related biochemical abnormalities and hepatic innate immune activation in the absence of advanced fibrosis, underscoring the need for early liver risk assessment in individuals with weight cycling.

Keywords: weight regain, obesity, lifestyle modifications, masld, inflammation

Introduction

Obesity is a major risk factor for a wide spectrum of chronic diseases, including type 2 diabetes, cardiovascular disease, and metabolic dysfunction–associated steatotic liver disease (MASLD), and its global prevalence continues to rise.[1] MASLD, recently redefined to emphasize its close link with metabolic dysfunction, has become the most prevalent chronic liver disease globally, affecting approximately 30% of the adult population.[2–4] Beyond progressive liver injury—ranging from steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma—MASLD is also strongly

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associated with extrahepatic complications, particularly cardiovascular disease,[5] type 2 diabetes,[6] stroke,[7] and chronic kidney disease.[8]

MASLD represents hepatic manifestation of systemic metabolic dysfunction and is closely intertwined with obesity, insulin resistance, dyslipidemia, and chronic low-grade inflammation.[9] Sustained weight management is therefore a cornerstone of both obesity- and MASLD-related disease prevention and treatment. Considerable weight loss can be achieved through diverse approaches such as lifestyle modifications,[10,11] pharmaceutical interventions,[12,13] or bariatric surgical procedure.[14,15] A weight loss of 5% has proved to be a benchmark of enhancements in health outcomes, including cardiovascular benefits[16] and liver steatosis improvements,[17] making it currently the first goal in weight management interventions.[18] However, weight loss via different strategies is often followed by a subsequent weight regain among most individuals,[19] which poses a complex challenge for long-term weight management.

The metabolic consequences of weight regain remain incompletely understood. While some studies, including reanalysis of the Look AHEAD trial, suggest that the benefits of weight loss persist despite subsequent regain,[20,21] others have linked weight regain to increased mortality and cardiovascular risk.[22,23] Importantly, existing evidence is largely derived from cardiovascular or diabetes-focused outcomes, with limited attention to liver-related endpoints or validated noninvasive indices of MASLD severity. Moreover, obesity is characterized by chronic low-grade inflammation, raising concern that weight regain may reactivate inflammatory pathways and accelerate metabolic deterioration, potentially exacerbating insulin resistance and MASLD progression.[24] Whether weight regain ultimately confers net metabolic harm compared with weight stability in individuals with obesity therefore remains an unresolved clinical question.

Notably, data are particularly scarce regarding the long-term metabolic and hepatic impact of weight regain following lifestyle-induced weight loss, despite lifestyle intervention being the most widely recommended first-line therapy. This lack of clarity represents a critical gap in knowledge with direct implications for patient counseling, long-term management strategies, and risk stratification in obesity and MASLD. To address this gap, the present study investigates whether weight regain after achieving ≥5% weight loss through lifestyle interventions is associated with adverse metabolic outcomes, compared with sustained weight stability over a three-year follow-up period. By comprehensively evaluating metabolic parameters and noninvasive indices related to MASLD, this study aims to clarify the clinical significance of weight regain and inform long-term weight management strategies in individuals with obesity.

Methods

Study Population

The retrospective study included patients exhibiting either weight regain or sustained weight over a continuous period of 3 years before their initial diagnosis of obesity (BMI ≥ 30 kg/m^2). These patients were sourced from the specialized department of obesity of Ruijin Hospital, affiliated to Shanghai Jiao Tong University School of Medicine, from September 2018 to September 2023. All participants were Han Chinese aged 18–45 years. In this study, "weight regain" was defined as a documented history of losing at least 5% of their initial weight by means of lifestyle intervention (including cognitive restraint and exercise) followed by a return to or exceeding their initial weight, and "weight sustain" was defined as experiencing weight fluctuations within a range of 5% (steady-obese state of patients). The exclusion criteria were as follows: 1) obesity secondary to known genetic syndromes (for example, Prader–Willi syndrome), endocrine disorders (for example, Cushing's syndrome), or medication use (for example, corticosteroids, antidepressants); 2) use of any pharmacologic treatment within three months preceding the study visit; 3) documented history of alcohol, tobacco, or substance abuse; 4) body-weight trajectories inconsistent with the above definitions; or 5) individuals without reliable weight trajectory history. Conduction of the study along with the waiver of informed consent were approved by the Institutional Review Board of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Approval number: Ethics 2023[411]).

Sample Size

Sample size was estimated based on preliminary findings from the Genetics of Obesity in Chinese Youngs (GOCY) cohort (ClinicalTrials.gov identifier: NCT01084967). The mean ALT concentrations were approximately 65 ± 45 IU/L among individuals with weight regain and 45 ± 45 IU/L among those with sustained obesity. Assuming $\alpha = 0.05$, power = 0.80, and a 2:1 allocation ratio, the minimum required sample sizes were calculated as 120 and 60 for the two groups, respectively (total = 180).

Measurements

Clinical information was retrieved from electronic medical records. Height and body weight were measured with participants wearing light clothing and no shoes, recorded to the nearest 0.1 cm and 0.1 kg, respectively. BMI (kg/m^2) was calculated as body weight divided by the square of height.All participants underwent an oral glucose tolerance test (OGTT). Fasting and 2-hour glucose values were determined using an automated analyzer (AU5800; Beckman Coulter, CA, USA). The same system measured liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AKP], and γ-glutamyl transpeptidase [GGT]), creatinine, uric acid, and serum lipids (triglycerides [TG], total cholesterol [TC], high-density cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]). Fasting and 2-hour insulin concentrations were measured by double-antibody radioimmunoassay (DSL, Webster, TX, USA). Hemoglobin A1c (HbA1c) was quantified by high-performance liquid chromatography using the VARIANT II analyzer (Bio-Rad Laboratories). Thyroid hormones—free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH)—were determined using chemiluminescent immunoassay (Architect i2000sr; Abbott Laboratories, IL, USA).

Assessment of Insulin Resistance, Insulin Sensitivity, and β-Cell Function

Insulin resistance and insulin sensitivity were assessed using both fasting- and OGTT-derived indices. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma glucose (mmol/L) × fasting insulin (μU/mL) / 22.5. Homeostasis model assessment of β-cell function (HOMA-β) was calculated as 20 × fasting insulin (μU/mL) / [fasting plasma glucose (mmol/L) − 3.5]. Whole-body insulin sensitivity was estimated using the Matsuda insulin sensitivity index (ISI), also referred to as ISI (0, 120), calculated using the Matsuda formula based on glucose and insulin values obtained during OGTT.[25] The disposition index (DI) was calculated as the ratio of HOMA-β to HOMA-IR and was used to assess β-cell function adjusted for insulin resistance, reflecting the ability of pancreatic β-cells to compensate for insulin resistance.

Non-Invasive Tests Evaluating Liver Steatosis and Liver Fibrosis

The Dallas Steatosis Index (DSI),[26] Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS) and Fibrosis-4 (FIB-4) index were calculated according to validated formulas (NFS and FIB-4 formulas see Supplementary Table 1). Established cutoff values were applied to identify advanced fibrosis, with NFS ≥ −1.45 and FIB-4 ≥ 1.3, in accordance with current clinical guidelines.[27]

Acquisition and Preservation of Liver Specimens

Liver biopsy samples were obtained from participants who also took part in the clinical trial Efficacy and Mechanism Study of Bariatric Surgery to Treat Moderate to Severe Obesity in Han Chinese Population (ClinicalTrials.gov identifier: NCT02653430). Written informed consent was obtained from all donors. Biopsy specimens collected during laparoscopic sleeve gastrectomy were immediately snap-frozen in liquid nitrogen and stored until RNA isolation.

Liver Histology and NAFLD Activity Score (NAS)

Liver biopsy specimens were evaluated by two blinded hepatopathologists. Steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2) were scored to calculate the NAS, with fibrosis assessed separately (0–4) according to the NASH Clinical Research Network criteria. Discrepancies were resolved by consensus.

RNA Extraction and cDNA Preparation

Total RNA was extracted from liver tissue using the Eastep Super Total RNA Extraction Kit (Promega, ls1040). Complementary DNA (cDNA) was synthesized from 1 μg of total RNA using the HiScript III All-in-One RT SuperMix (Vazyme, China) according to the manufacturer's instructions.

Bulk-RNA Sequencing and Analysis

RNA integrity was verified using an Agilent 2100 Bioanalyzer (Agilent Technologies, CA, USA) and agarose gel electrophoresis. Poly(A) mRNA was isolated from total RNA using Oligo(dT) magnetic beads and fragmented into short pieces prior to reverse transcription with the NEBNext Ultra RNA Library Prep Kit for Illumina (NEB #7530). The resulting cDNA fragments underwent end-repair, A-tailing, and adaptor ligation, followed by purification with AMPure XP beads and PCR amplification. Sequencing was performed on an Illumina NovaSeq 6000 platform (Gene Denovo Biotechnology, Guangzhou, China). Principal component analysis (PCA) was conducted using the R package gmodels. Differentially expressed genes were identified with DESeq2 using a false discovery rate (FDR) < 0.05 and absolute fold change ≥ 2. Gene set enrichment analysis (GSEA) was performed with MSigDB to determine significantly enriched Gene Ontology (GO) terms.

Real-Time PCR

Real-time PCR was performed on an ABI system (Life Technologies) using ChamQ Universal SYBR qPCR Master Mix (Vazyme, China). Reactions were run in duplicate in 384-well plates. Relative expression levels were calculated using the 2^−ΔΔCt method after normalization to the GAPDH housekeeping gene. Primer sequences are listed in Supplementary Table 2.

Immunohistochemistry (IHC) Staining

Immunohistochemical staining was performed with primary monoclonal antibodies targeting CD11b (ab133357, Abcam, UK), CD68 (76437S, Cell Signaling Technology, USA), and IL-6 (ab233706, Abcam, UK) and Anti-alpha smooth muscle Actin (ab7817, Abcam, UK). Formalin-fixed, paraffin-embedded liver sections were dewaxed, subjected to antigen retrieval, and blocked for 1 h in phosphate-buffered saline containing 5% bovine serum albumin (BSA; Sigma, USA). Primary antibodies were incubated overnight at 4 °C, followed by washing and incubation with HRP-conjugated secondary antibodies for 30 min at room temperature. Visualization was performed using the REAL™ EnVision™ system (DAKO, Denmark). Slides were examined under a light microscope (TissueFAXS viewer). The integrated optical densities (IODs) of target proteins calculated by ImageJ software.

Statistical Analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation; non-normally distributed data are presented as median (interquartile range). Between-group comparisons were performed using the *t*-test or the Mann–Whitney *U*-test, as appropriate. Categorical data were expressed as counts (percentages) and compared using the chi-square test.

To minimize confounding from demographic factors, propensity score matching (PSM) was conducted using nearest-neighbor matching without replacement, adjusting for age, sex, body weight, and BMI. An absolute standardized mean difference (SMD) < 0.2 was considered indicative of adequate balance. Subgroup analyses were further conducted according to sex.

Data analysis was performed with R version 4.2.0 and GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA). Propensity score matching was done with the R package "Matching".[28] A two-sided P value of less than 0.05 was regarded as being statistically significant.

Results

Recruitment

A total of 1068 patients aged 18–45 years were initially diagnosed with obesity at the specialized department of obesity of Ruijin Hospital, affiliated with Shanghai Jiao Tong University School of Medicine, from September 2018 to September 2023, a total of 213 patients were included in this study. Figure 1 showed the flow diagram of the study protocol.

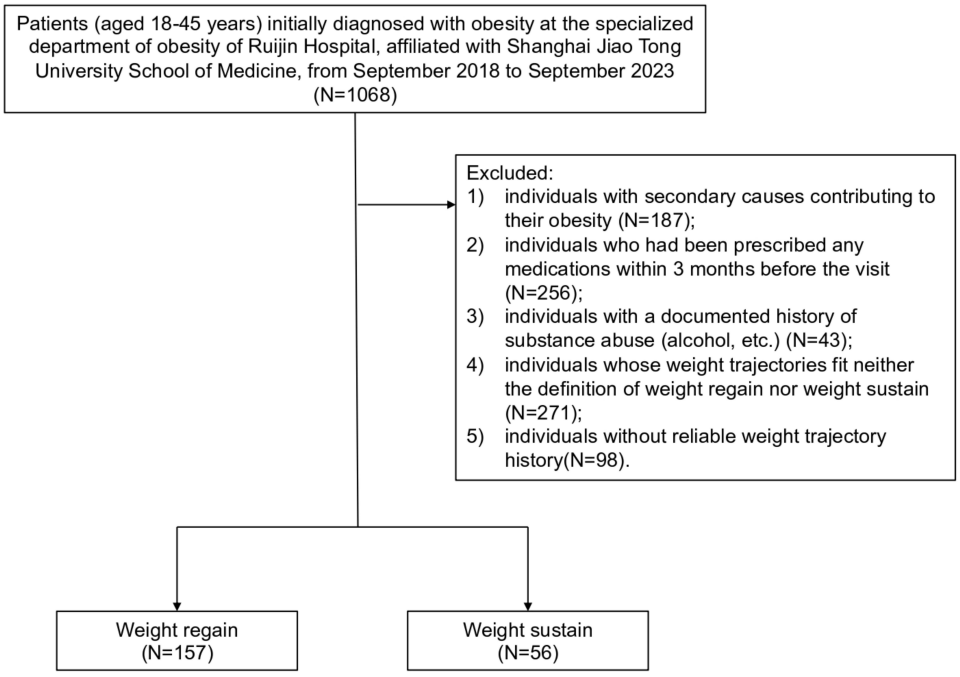

Figure 1 Patient flow chart.

Basic Characteristics and Clinical Assessments of All Participants

A total of 157 patients with weight regain and 56 patients with weight sustain were included in this study. Patients in the weight regain group were younger [mean age, 27.32 (5.28) vs 29.82 (6.58), P=0.006]. No significant differences were observed between the two groups in metabolic and endocrine parameters, including glycemic indices, insulin resistance and sensitivity, lipid profiles, and thyroid function (Table 1). In addition, liver and renal function parameters as well as inflammatory markers were comparable between the two groups (Table 2).

After PSM of age, sex, weight, and BMI, 50 cases were matched each group. SMDs of the matched variables were all below 0.2, indicating a balanced match. Among all the matched patients, the weight regain group showed significantly higher ALT levels [median (IQR), 59.00 (40.25, 94.00) IU/L vs 41.00 (29.50, 58.00) IU/L, P=0.007] and higher AST levels [median (IQR), 33.50 (24.25, 55.00) IU/L vs 26.00 (21.00, 35.75) IU/L, P=0.041] (Table 2). No statistically significant difference was demonstrated between the two groups in terms of other biochemical indexes.

Subgroup Analysis of Clinical Characteristics

We further analyzed the characteristics categorized by sex. Male patients (Table 3) showed higher weight at baseline in the weight regain group [mean weight (SD), 125.83 (17.26) kg vs 116.40 (19.89) kg, P=0.015], while female patients (Table 4) were younger in the weight regain group [mean age (SD), 27.31 (5.06) vs 30.38 (7.45), P=0.025]. Also, male patients in the weight regain group showed higher level of ALT [median (IQR), 64.00 (42.00, 109.00) IU/L vs 47.00 (35.00, 65.00) IU/L, P=0.017]. The two groups were comparable with respect to other biochemical indices in both male and female patients before matching (Supplementary Tables 3 and 4).

After PSM, 31 male patients from each group were matched (Table 3). In the subgroup analysis, a stronger trend was observed in the measurement of ALT level [median (IQR), 88.00 (57.00, 137.50) IU/L vs 47.00 (35.00, 65.00) IU/L, P<0.001] and AST level [median (IQR), 46.00 (31.50, 60.00) IU/L vs 30.00 (23.00, 36.50) IU/L, P=0.004] in male patients. In female patients, 30 patients from the weight regain group and 15 patients from the weight sustain group were matched (Table 4). Unlike the male patients, female patients with weight regain showed higher uric acid level [mean (SD), 429.70 (74.05) μmol/L vs 380.87 (66.15) μmol/L, P=0.037] than those with sustained weight. Other metabolic parameters did not differ significantly between the two groups in both sexes after matching (Supplementary Tables 3 and 4).

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Table 1 Metabolic and Endocrine Parameters of Weight Regain and Sustain Group, Raw and Propensity Score-Matched Data

n	Raw Data			Propensity Score-Matched Data			
	Weight Regain 157	Weight Sustain 56	P	Weight Regain 50	Weight Sustain 50	P	SMD
Sex (Female, n, %)	90 (57.3)	21 (37.5)	0.013	19 (38.0)	20 (40.0)	1.000	0.041
Age (years)	27.32 (5.48)	29.82 (6.58)	0.006	28.94 (5.46)	28.98 (6.31)	0.973	0.007
Height (m)	1.71 (0.09)	1.72 (0.08)	0.462	1.73 (0.08)	1.71 (0.08)	0.443	
Weight (kg)	110.79 (20.59)	108.92 (20.50)	0.561	110.17 (15.45)	109.65 (20.64)	0.888	0.028
BMI (kg/m^2)	37.85 (5.11)	36.80 (5.43)	0.197	36.91 (4.26)	37.16 (5.45)	0.804	0.050
HbA1c (%)	5.50 [5.30, 5.90]	5.50 [5.25, 5.95]	0.927	5.40 [5.30, 5.90]	5.60 [5.20, 6.00]	0.860	
Fasting plasma glucose (mmol/L)	5.41 [5.03, 6.00]	5.46 [5.13, 5.95]	0.521	5.48 [5.06, 6.01]	5.46 [5.12, 6.03]	0.839	
2-h plasma glucose (mmol/L)	7.72 [6.63, 9.48]	7.54 [6.40, 10.39]	0.671	7.56 [6.68, 9.00]	7.54 [6.42, 10.50]	0.997	
Fasting serum insulin (μIU/mL)	23.20 [15.11, 33.88]	22.18 [17.72, 26.59]	0.667	26.35 [15.38, 34.69]	22.18 [17.75, 26.49]	0.457	
2-h serum insulin (μIU/mL)	143.95 [98.86, 212.05]	125.45 [90.13, 182.65]	0.237	148.30 [108.70, 216.40]	121.30 [92.11, 175.28]	0.095	
HOMA-IR	5.59 [3.75, 8.90]	5.55 [4.36, 6.93]	0.944	6.12 [3.83, 9.83]	5.55 [4.41, 6.93]	0.614	
HOMA-β	241.78 [157.57, 343.05]	221.62 [169.29, 302.82]	0.405	240.06 [146.04, 353.07]	218.65 [168.92, 295.47]	0.360	
ISI (0,120)	8.77 [5.87, 12.42]	8.91 [6.94, 11.41]	0.779	7.92 [5.70, 12.64]	8.76 [7.03, 11.10]	0.475	
DI	43.55 [30.00, 57.74]	41.76 [30.18, 53.60]	0.388	40.77 [29.92, 56.53]	41.48 [29.22, 53.93]	0.798	
Triglyceride (mmol/L)	1.56 [1.19, 2.21]	1.61 [1.24, 2.21]	0.828	1.63 [1.24, 2.35]	1.65 [1.31, 2.22]	0.817	
Total cholesterol (mmol/L)	4.98 (1.16)	4.88 (0.82)	0.560	5.26 (1.65)	4.91 (0.84)	0.186	
HDL-C (mmol/L)	1.10 (0.28)	1.04 (0.19)	0.175	1.11 (0.36)	1.05 (0.20)	0.325	
LDL-C (mmol/L)	3.18 (0.93)	3.14 (0.69)	0.772	3.36 (1.30)	3.15 (0.72)	0.333	
Free triiodothyronine (pmol/L)	4.61 (0.49)	4.58 (0.52)	0.650	4.68 (0.49)	4.58 (0.53)	0.327	
Free tetraiodothyronine (pmol/L)	12.84 [11.98, 13.84]	13.18 [12.46, 14.21]	0.096	12.79 [11.85, 13.86]	13.18 [12.45, 14.17]	0.122	
Thyroid stimulating hormone (μIU/mL)	2.06 [1.58, 2.94]	2.05 [1.65, 3.09]	0.960	2.00 [1.59, 2.73]	2.00 [1.65, 3.27]	0.567	

Notes: Continuous variables with normal distribution are presented as mean (standard deviation), while other continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).
Abbreviations: SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; HbA1c, glycosylated hemoglobin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HOMA-β, Homeostasis Model Assessment of β-cell Function; ISI (0,120), insulin sensitivity index derived from 0- and 120-min OGTT values; DI, disposition indices; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

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Table 2 Organ Function and Inflammatory Parameters of Weight Regain and Sustain Group, Raw and Propensity Score-Matched Data

n	Raw Data			Propensity Score-Matched Data			
	Weight Regain 157	Weight Sustain 56	P	Weight Regain 50	Weight Sustain 50	P	SMD
Sex (Female, n, %)	90 (57.3)	21 (37.5)	0.013	19 (38.0)	20 (40.0)	1.000	0.041
Age (years)	27.32 (5.48)	29.82 (6.58)	0.006	28.94 (5.46)	28.98 (6.31)	0.973	0.007
Height (m)	1.71 (0.09)	1.72 (0.08)	0.462	1.73 (0.08)	1.71 (0.08)	0.443	
Weight (kg)	110.79 (20.59)	108.92 (20.50)	0.561	110.17 (15.45)	109.65 (20.64)	0.888	0.028
BMI (kg/m^2)	37.85 (5.11)	36.80 (5.43)	0.197	36.91 (4.26)	37.16 (5.45)	0.804	0.050
ALT (IU/L)	46.00 [26.00, 84.00]	43.00 [31.00, 63.25]	0.534	59.00 [40.25, 94.00]	41.00 [29.50, 58.00]	0.007	
AST (IU/L)	29.00 [20.00, 46.00]	28.00 [22.50, 37.25]	0.856	33.50 [24.25, 55.00]	26.00 [21.00, 35.75]	0.041	
GGT (IU/L)	31.50 [22.00, 49.25]	37.00 [23.75, 59.00]	0.272	35.50 [24.25, 67.25]	35.50 [23.00, 56.50]	0.649	
AKP (IU/L)	74.64 (19.90)	73.59 (19.08)	0.733	74.50 (20.09)	73.18 (19.69)	0.741	
DSI	−0.06 [−0.96, 0.55]	−0.35 [−0.88, 0.30]	0.511	0.04 [−0.78, 0.66]	−0.21 [−0.80, 0.40]	0.385	
Serum creatinine (μmol/L)	69.95 (13.34)	73.55 (15.42)	0.098	72.78 (14.19)	72.26 (14.59)	0.857	
Uric acid (μmol/L)	443.47 (100.03)	435.22 (90.02)	0.588	446.18 (103.64)	433.97 (94.77)	0.540	
WBC count (10^9/L)	8.02 (2.01)	7.62 (1.65)	0.203	7.38 (1.73)	7.65 (1.49)	0.439	
Neutrophil percentage (%)	57.69 (7.83)	56.58 (7.60)	0.380	57.34 (8.57)	56.10 (7.73)	0.471	
C-reactive protein (mg/L)	4.49 [2.02, 7.13]	4.26 [1.95, 7.01]	0.609	3.21 [1.57, 5.61]	4.25 [1.74, 7.04]	0.340	

Notes: Continuous variables with normal distribution are presented as mean (standard deviation), while other continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; AKP, alkaline phosphatase; DSI, Dallas Steatosis Index; WBC, white blood cell.

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Table 3 Subgroup Analysis of Organ Function Parameters of Male Patients, Raw and Propensity Score-Matched Data

n	Raw Data			Propensity Score-Matched Data			
	Weight Regain 67	Weight Sustain 35	P	Weight Regain 31	Weight susTain 31	P	SMD
Age (years)	27.33 (6.03)	29.49 (6.09)	0.091	29.65 (6.60)	29.23 (6.06)	0.795	0.066
Height (m)	1.79 (0.06)	1.76 (0.06)	0.063	1.78 (0.06)	1.77 (0.06)	0.391	
Weight (kg)	125.83 (17.26)	116.40 (19.89)	0.015	118.50 (13.97)	119.16 (19.43)	0.879	0.039
BMI (kg/m^2)	39.46 (4.92)	37.39 (5.72)	0.058	37.38 (4.29)	38.05 (5.74)	0.604	0.132
ALT (IU/L)	64.00 [42.00, 109.00]	47.00 [35.00, 65.00]	0.017	88.00 [57.00, 137.50]	47.00 [35.00, 65.00]	<0.001	
AST (IU/L)	36.00 [25.50, 55.50]	30.00 [23.00, 38.50]	0.111	46.00 [31.50, 60.00]	30.00 [23.00, 36.50]	0.004	
GGT (IU/L)	42.00 [29.00, 69.50]	40.00 [32.50, 55.00]	0.554	52.00 [33.50, 73.50]	40.00 [32.50, 51.50]	0.065	
AKP (IU/L)	77.10 (19.44)	72.46 (19.64)	0.256	76.81 (21.00)	71.19 (19.74)	0.283	
DSI	0.20 [−0.38, 0.72]	−0.19 [−0.88, 0.34]	0.043	0.35 [−0.38, 0.72]	−0.17 [−0.88, 0.58]	0.127	
Serum creatinine (μmol/L)	79.09 (12.52)	80.97 (13.05)	0.479	77.61 (12.06)	80.48 (12.67)	0.364	
Uric acid (μmol/L)	486.00 (108.03)	466.13 (87.81)	0.351	449.74 (110.89)	475.79 (86.50)	0.307	

Notes: Continuous variables with normal distribution are presented as mean (standard deviation), while other continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; AKP, alkaline phosphatase; DSI, Dallas Steatosis Index.

Table 4 Subgroup Analysis of Organ Function Parameters of Female Patients, Raw and Propensity Score-Matched Data

n	RAW Data			Propensity Score-Matched Data			
	Weight Regain 90	Weight Sustain 21	P	Weight Regain 30	Weight Sustain 15	P	SMD
Age (years)	27.31 (5.06)	30.38 (7.45)	0.025	26.53 (4.34)	26.60 (4.81)	0.963	0.015
Height (m)	1.65 (0.06)	1.64 (0.05)	0.544	1.65 (0.07)	1.65 (0.05)	0.799	
Weight (kg)	99.60 (15.00)	96.46 (14.90)	0.390	99.87 (13.55)	100.78 (14.80)	0.838	0.064
BMI (kg/m^2)	36.65 (4.94)	35.84 (4.90)	0.497	36.59 (4.16)	37.15 (4.98)	0.693	0.122
ALT (IU/L)	32.00 [20.00, 61.50]	35.00 [21.00, 59.00]	0.994	27.00 [18.00, 74.50]	35.00 [24.00, 45.50]	0.990	
AST (IU/L)	24.00 [18.00, 38.50]	24.00 [21.00, 36.00]	0.603	22.50 [19.00, 51.75]	24.00 [20.00, 31.50]	0.894	
GGT (IU/L)	27.00 [19.00, 37.00]	23.00 [17.00, 64.00]	0.770	26.00 [18.00, 33.00]	23.00 [19.50, 58.00]	0.435	
AKP (IU/L)	72.80 (20.14)	75.48 (18.44)	0.579	74.60 (23.25)	72.40 (16.22)	0.745	
DSI	−0.37 [−1.19, 0.29]	−0.38 [−0.88, 0.30]	0.655	−0.34 [−1.17, 0.07]	−0.36 [−0.62, 0.28]	0.560	
Serum creatinine (μmol/L)	63.07 (9.17)	61.19 (10.38)	0.413	63.40 (9.17)	62.20 (11.81)	0.709	
Uric acid (μmol/L)	411.45 (80.35)	383.71 (68.71)	0.147	429.70 (74.05)	380.87 (66.15)	0.037	

Notes: Continuous variables with normal distribution are presented as mean (standard deviation), while other continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; AKP, alkaline phosphatase; DSI, Dallas Steatosis Index.

Non-Invasive Scoring Systems (DSI, NFS, FIB-4) Evaluating Hepatic Dysfunction

Since ALT and AST levels differed between the two groups, we also calculated DSI, NFS and FIB-4 scores to further evaluate hepatic dysfunction associated with steatosis or fibrosis.

DSI is a validated tool for the accurate detection of early-grade hepatic steatosis.[26] In the overall population, DSI values did not differ significantly between the two groups, before or after PSM (Table 2). In male patients, higher DSI was found in weight regain group [median (IQR), 0.20 [−0.38, 0.72] vs −0.19 [−0.88, 0.34], P=0.043] (Table 3). However, this difference was no longer observed after PSM. Also, DSI was found comparable between groups in female patients, before and after matching (Table 4).

NFS and FIB-4 are classic non-invasive scoring systems evaluating liver fibrosis. Among those with available data, 23.5% in the weight regain group and 27.5% in the weight sustain group had NFS values above the cutoff. Meanwhile, 4.4% in the weight regain group and 3.9% in the weight sustain group had FIB-4 values above the cutoff. There were no

significant differences in the positive rates between the groups for either scoring system (Supplementary Table 5). Additionally, no differences were observed between the groups after matching (Supplementary Table 6).

In male patients, among those with data, 26.3% in the weight regain group and 29.0% in the weight sustain group had NFS values above the cutoff. 8.5% in the weight regain group had FIB-4 values above the cutoff, compared to 6.5% in the weight sustain group. No significant differences were found between the groups, before or after matching (Supplementary Tables 7 and 8).

Sensitivity Analysis Assessing the Impact of Excess Weight Gain

Notably, the process of weight gain itself may contribute to hepatic alterations.[29] In our study, some individuals in the weight regain group experienced weight gain that exceeded their baseline levels, which may have contributed to the observed liver dysfunction. Hence, we conducted a one-way sensitivity analysis to assess the impact of the excess weight gain on the reliability of our findings.

We excluded patients whose weight exceeded more than 5% of baseline after weight regain. After the adjustment, a total of 106 patients (54.7% female) were included in the weight regain group. ALT and AST levels were not significantly higher in the weight regain group, before or after PSM, in the overall sample. However, ALT level remained significantly higher in the male patients of weight regain group [median (IQR), 60.00 (41.00, 126.00) IU/L vs 43.00 (32.50, 54.50) IU/L, P=0.015] after PSM (weight regain: weight sustain= 27:27) (Table 5), while the levels of liver enzymes remained equivalent in female patients of both groups, before and after matching (Supplementary Table 9).

Correlation of Liver Dysfunction and Inflammatory Status in Weight Regain Group

To gain a deeper understanding of the relationship between weight regain and liver metabolism, we conducted further analyses in a subset of bariatric surgery patients who underwent liver biopsy. A total of 19 male patients (weight regain: weight sustain=13:6) and 23 female patients (weight regain: weight sustain=20:3) had undergone bariatric surgery and

Table 5 Clinical Features of Weight Regain and Sustain Group in Sensitivity Analysis

	Raw Data			**Propensity Score-Matched Data**			
Overall n	Weight Regain 106	Weight Sustain 56	p	Weight Regain 49	Weight Sustain 49	p	SMD
Sex (Female, n, %)	58 (54.7)	21 (37.5)	0.047	20 (40.8)	21 (42.9)	1.000	0.041
Age (years)	27.62 (5.43)	29.82 (6.58)	0.024	29.10 (6.17)	29.14 (6.53)	0.975	0.006
Weight (kg)	109.19 (21.05)	108.92 (20.50)	0.938	109.76 (17.77)	108.47 (20.42)	0.739	0.068
BMI (kg/m^2)	37.37 (5.15)	36.80 (5.43)	0.513	37.12 (4.84)	36.88 (5.10)	0.813	0.048
ALT (IU/L)	43.50 [25.00, 83.50]	43.00 [31.00, 63.25]	0.912	45.00 [25.00, 85.00]	39.00 [29.00, 63.00]	0.321	
AST (IU/L)	28.00 [19.25, 45.75]	28.00 [22.50, 37.25]	0.914	29.00 [22.00, 45.00]	26.00 [21.00, 36.00]	0.382	
GGT (IU/L)	31.00 [22.00, 50.00]	37.00 [23.75, 59.00]	0.220	36.00 [21.00, 52.00]	35.00 [23.00, 58.00]	0.918	
AKP (IU/L)	72.44 (20.57)	73.59 (19.08)	0.730	73.33 (22.01)	72.88 (19.76)	0.916	
Male n	Weight regain 48	Weight sustain 35	p	Weight regain 27	Weight sustain 27	p	SMD
Age (years)	27.67 (5.76)	29.49 (6.09)	0.169	29.37 (6.36)	28.56 (6.01)	0.631	0.132
Weight (kg)	124.60 (18.71)	116.40 (19.89)	0.058	121.40 (19.04)	119.19 (19.45)	0.674	0.115
BMI (kg/m^2)	38.99 (5.24)	37.39 (5.72)	0.190	38.57 (5.78)	37.98 (5.40)	0.701	0.105
ALT (IU/L)	60.50 [40.00, 115.00]	47.00 [35.00, 65.00]	0.056	60.00 [41.00, 126.00]	43.00 [32.50, 54.50]	0.015	
AST (IU/L)	36.50 [25.50, 56.25]	30.00 [23.00, 38.50]	0.140	34.00 [26.00, 59.50]	29.00 [22.00, 36.00]	0.088	
GGT (IU/L)	43.00 [29.00, 68.25]	40.00 [32.50, 55.00]	0.504	48.00 [29.00, 71.00]	38.00 [30.50, 51.50]	0.303	
AKP (IU/L)	74.06 (20.69)	72.46 (19.64)	0.722	75.11 (23.97)	71.19 (21.27)	0.527	

Notes: Continuous variables with normal distribution are presented as mean (standard deviation), while other continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; AKP, alkaline phosphatase.

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provided liver biopsy samples. We matched liver specimen providers' basic characteristics to avoid confounding factors. First, we performed histopathological assessment using NAS on the matched biopsy samples. Scores for steatosis, lobular inflammation, ballooning, and fibrosis stage were comparable between groups in male patients (individual data for all participants, including a limited number of female samples, are provided in Supplementary Table 10), indicating no major disparity in structural liver injury at the time of biopsy.

Given the absence of pronounced histopathological divergence in this analyzable cohort yet persistent clinical biochemical differences, we performed RNA-seq analysis on liver samples of matched male patients to identify earlier, pathway-level alterations that might explain the observed phenotype (Figure 2A). PCA was applied to visualize the sample distribution patterns (Figure 2B). Among the genes that were identified, 296 were upregulated and 201 were downregulated in the weight regain group (Figure 2C). Furthermore, analysis of the gene transcription profiles through Gene Ontology revealed that the differential genes in the two groups were mainly enriched in immune-related pathways (Figure 2D). GSEA analysis of different genes indicated that most of the upregulated pathways in the weight regain group were associated with macrophage activation as well as monocyte chemotaxis (Figure 2E and F). We subsequently verified that the expression of immune-related gene CD11B (P=0.016) was up-regulated in liver tissues of the weight regain group by mRNA quantification; while expression of CD68 tended to be higher in the weight regain group (P=0.0536) (Figure 2G). Additionally, the mRNA expression of α-SMA, a marker for hepatic stellate cell activation and fibrosis, showed no significant difference between the two groups. Immunohistochemical staining was performed to detect the expression of CD11B, CD68, IL-6 and α-SMA in liver tissues (Figure 2H). As shown, the expression of CD11B, CD68 and IL-6 was higher in the weight regain group compared with the weight sustain group. Consistently, immunohistochemical analysis of α-SMA also revealed no obvious difference in staining between the groups (Figure 2I).

Discussion

Weight loss is actively pursued by a substantial proportion of the global population, with an estimated 42% of adults attempting to lose weight each year.[30] However, long-term weight maintenance remains challenging, and most individuals ultimately experience partial or complete weight regain.[31] While sustained weight loss of ≥5% through lifestyle interventions improves metabolic health and quality of life,[32] the biological consequences of subsequent weight regain remain incompletely understood.

In our current pilot study, after adjustment for confounders, individuals with weight regain exhibited comparable glycemic indices, insulin resistance, lipid profiles, and endocrine parameters relative to those with sustained weight status. In contrast, hepatic transaminase levels were modestly but consistently higher in the weight regain group. These findings suggest that, in the short term, weight regain may not lead to broad deterioration of classical metabolic biomarkers but may reflect early liver-related biochemical alterations.

Elevated liver enzymes are commonly interpreted as indicators of hepatocellular stress or injury. Although these changes do not necessarily indicate overt liver disease, they may reflect subclinical hepatic vulnerability. Our findings extend observations from animal models,[33–35] in which weight cycling has been associated with hepatic inflammation and injury, to a human cohort. Importantly, this association was observed in the absence of significant differences in glucose homeostasis or lipid metabolism, highlighting the liver as a potentially sensitive organ in the context of weight regain.

Sex-stratified analyses after propensity score matching revealed distinct patterns: men with weight regain showed higher hepatic enzyme levels, whereas women exhibited higher serum uric acid concentrations. These differences suggest sex-specific biochemical responses, though underlying mechanisms cannot be determined from the current dataset. Also, sex-stratified findings are reported descriptively and should be interpreted cautiously given limited female sample size.

At the tissue level, individuals with weight regain exhibited increased hepatic expression of macrophage markers CD68 and CD11B, while established indices of steatosis and fibrosis—including NAS score, Dallas Steatosis Index, NFS, FIB-4 index, and α-SMA—did not differ significantly. This pattern is consistent with early hepatic alterations characterized by innate immune activation, preceding detectable steatosis or fibrotic remodeling. Innate immunity plays a central role in liver inflammation, with Kupffer cells and monocyte-derived macrophages contributing to pro-inflammatory signaling and immune recruitment.[36,37] Experimental studies show that macrophage activation markers

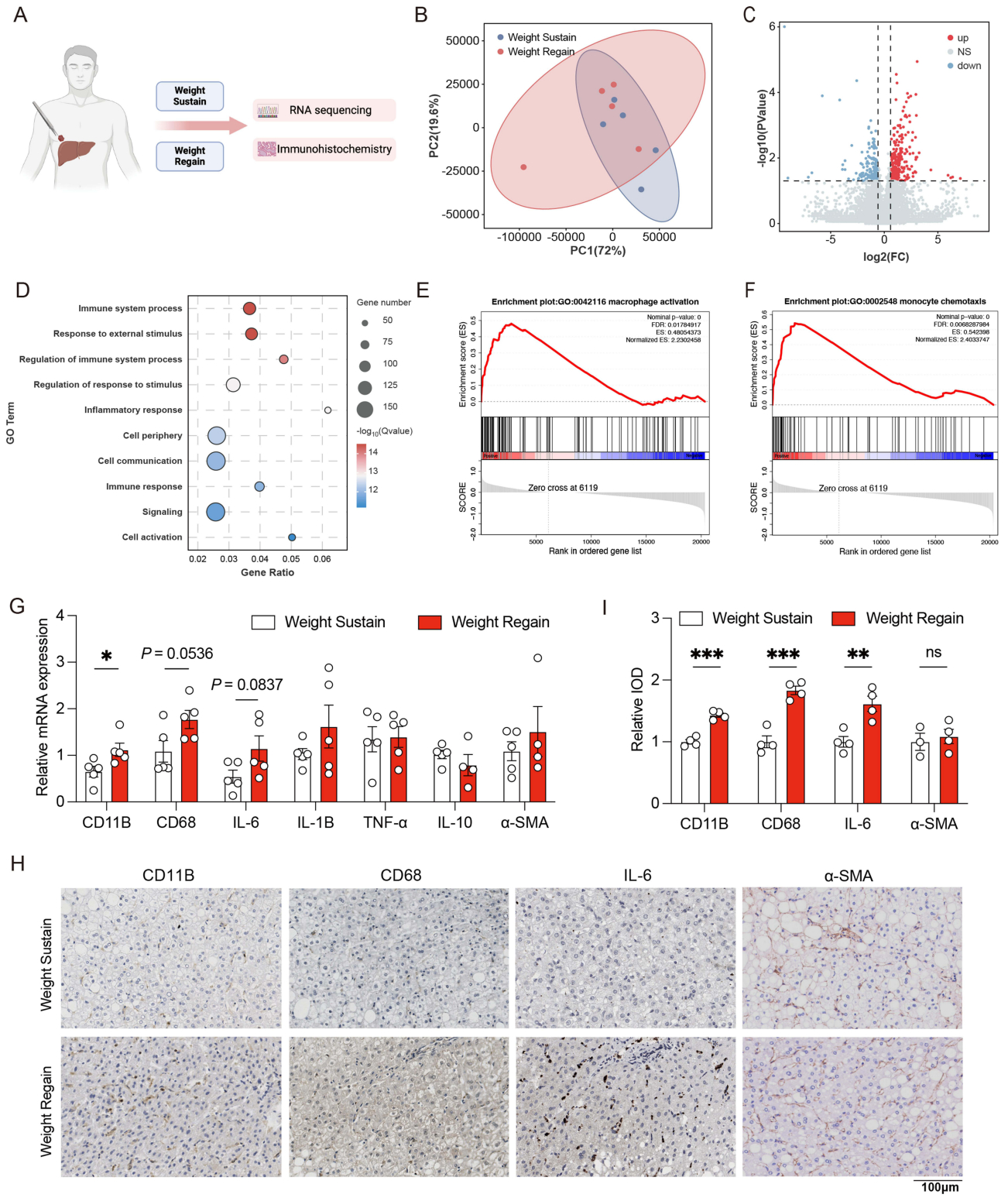

Figure 2 Correlation of liver dysfunction and inflammatory status in male patients of weight regain group. (**A**) Flow chart of the experiment. (**B**) Principal component analysis (PCA) of the transcriptome profiles between weight sustain and weight regain group. (**C**) Volcano plot of differentially expressed genes between weight sustain and weight regain group. (**D**) The top10 regulated GO pathways between weight sustain and weight regain group. (**E**) and (**F**) GSEA results of microphage activation (**E**) and monocyte chemotaxis (**F**). (**G**) The mRNA expression of pro-inflammatory cytokines and fibrosis related genes between male subgroups. (**H**) Immunohistochemistry (IHC) staining representative images of CD11B, CD68, IL6 and α-SMA in male liver tissues (scale bar = 100 μm). (**I**) Quantitative analysis of images from (**H**). n=4. Data are shown as mean ± SEM. Statistical significance was assessed by unpaired two-sided Student's *t*-test.

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such as CD68 and CD11b increase during early diet-induced liver injury before significant fibrosis develops,[38] and human studies similarly associate macrophage activation with hepatic injury metrics in MASLD.[39] Thus, the selective upregulation of macrophage-related genes observed in the weight regain group is compatible with an early inflammatory response, consistent with models proposing that immune activation precedes structural pathology.[40]

Emerging evidence on innate immune memory in metabolic tissues provides additional context. Prior exposure to obesity-associated inflammatory stimuli has been proposed to induce durable functional reprogramming of innate immune cells, resulting in heightened responsiveness upon renewed metabolic challenge.[41] In adipose tissue, such imprinting persists despite weight loss and can be reactivated upon renewed challenge.[42,43] In the present study, increased hepatic macrophage marker expression, alongside trends toward higher IL-6 and IL-1B and lower IL-10, is compatible with—but does not prove—the hypothesis that prior obesity primes hepatic innate immune cells. This interpretation should be considered hypothesis-generating, with longitudinal studies needed to clarify whether immune memory contributes to liver vulnerability during weight regain.

The current study was designed as a pilot investigation to explore the metabolic and hepatic consequences of weight regain in comparison with sustained obesity. A major strength lies in the use of a rigorous propensity score matching strategy, which minimized baseline confounding and enabled a balanced comparison between groups. In addition, the integration of clinical, biochemical, and liver tissue data provided a unique opportunity to examine hepatic inflammatory signatures associated with weight regain, a context that remains insufficiently characterized in existing literature. Beyond mechanistic considerations, early hepatic inflammatory alterations may have clinical implications in MASLD, a leading cause of liver-related morbidity and mortality.[44] Macrophage activation, in particular, has been implicated as a central mediator linking metabolic stress to hepatic injury and disease progression in MASLD.[45] In this context, the observation of elevated transaminases and macrophage-related gene expression despite absence of fibrosis or advanced histological changes may represent a window of early hepatic vulnerability. While causality cannot be inferred, repeated episodes of weight regain could contribute to MASLD progression via recurrent hepatic inflammation.

Several limitations should be noted. First, mechanistic interpretations are derived from a male-predominant cohort. While this design reduced biological heterogeneity and strengthened internal validity, it limits the generalizability of our findings to female patients. Although all available female participants with liver biopsy samples are transparently reported (Supplementary Table 10), the small number of female samples precluded statistically or biologically meaningful subgroup analyses; thus, whether similar macrophage-associated inflammatory signatures exist in females remains an open question. Second, despite systematic EMR-based data collection, recall bias related to long-term weight trajectories cannot be fully excluded, particularly regarding the timing and magnitude of weight regain. Third, the cohort was restricted to individuals undergoing lifestyle-based weight loss to avoid heterogeneity introduced by anti-obesity pharmacotherapies; consequently, the hepatic effects of weight regain following pharmacological interventions remain unexplored. Finally, due to the observational design, causal relationships cannot be established. Given the multifaceted and personalized determinants influencing weight fluctuations,[46] it is impractical to randomize participants into the groups capable of maintaining or regaining reduced body weight. Therefore, the current observational study may emphasize the necessity for designing studies of higher level of evidence.

Conclusions

In conclusion, our study provides novel evidence that benefits achieved through lifestyle-induced weight loss may not be sustained after subsequent weight regain. Compared with individuals who maintained a stable state of obesity, those experiencing weight regain showed modest but consistent elevations in hepatic transaminases and increased hepatic expression of macrophage-related markers, despite the absence of advanced steatosis or fibrosis. By integrating biochemical and liver tissue data, our findings extend current knowledge by indicating that weight regain may preferentially affect hepatic inflammatory pathways before overt metabolic dysfunction or structural liver abnormalities become apparent.

Clinically, these results suggest that achieving weight loss alone may be insufficient to ensure durable hepatic health. Individuals with a history of weight regain following lifestyle interventions may benefit from continued monitoring of liver-related biochemical parameters, even in the absence of established liver disease. Collectively,

our findings underscore the importance of early liver risk assessment in long-term weight management and highlight the need for longitudinal studies to determine whether repeated weight regain contributes to progressive hepatic injury.

Abbreviations

MASLD, Metabolic dysfunction–associated steatotic liver disease; PSM, Propensity score matching; PCR, Polymerase chain reaction; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DSI, Dallas Steatosis Index; NFS, Nonalcoholic fatty liver disease fibrosis score; FIB-4, Fibrosis-4 index; NAS, NAFLD Activity Scores; NAFLD, Non-alcoholic associated fatty liver disease; BMI, Body mass index; GOCY, Genetics of Obesity in Chinese Youngs; OGTT, Oral glucose tolerance test; AKP, Alkaline phosphatase; GGT, γ-Glutamyl transpeptidase; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; HbA1c, Glycosylated hemoglobin; fT3, Free triiodothyronine; fT4, Free tetraiodothyronine; TSH, Thyroid-stimulating hormone; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; ISI, Insulin sensitivity index; DI, Disposition index; cDNA, Complementary deoxyribonucleic acid; PCA, Principal component analysis; FDR, False discovery rate; GSEA, Gene Set Enrichment Analysis; GO, Gene Ontology; IHC, Immunohistochemistry; BSA, Bovine serum albumin; IODs, Integrated optical densities; SMD, Standardized mean difference; SD, Standard deviation; WBC, White blood cell; IQR, Interquartile range; EMR, Electronic medical records; SEM, Standard error of the mean.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Conduction of the study along with the waiver of informed consent were approved by the Institutional Review Board of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Approval number: Ethics 2023[411]). Our study complies with the Declaration of Helsinki.

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Author Contributions

Y.Z., Z.C. and Y.C. are co-first authors. Conceptualization: J.H., J.W., S.Z.; Methodology: Z.C., M.Y.; Investigation: Y.Z., Y.C., Z.Z., Z.C., M.Y.; Data Curation: Y.Z., Z.C., Y.C. W.G.; Formal Analysis: Y.Z., Y.C., Z.Z.; Resources: W.G., S.Z., J. H.; Supervision: J.H., J.W., S.Z., W.G.; Writing – Original Draft: J.H., Y.Z.; Writing – Review & Editing: all authors. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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