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ORIGINAL RESEARCH

The Impact of the Trajectory of the Monocyte-to-High-Density Lipoprotein Cholesterol Ratio on the Incidence of Metabolic Dysfunction-Associated Fatty Liver Disease: Random Forest Anaylsis, Trajectory Anaylsis, and Mendelian Randomization Study

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Background and Aims: The monocyte-to-high-density lipoprotein cholesterol ratio (MHR) has emerged as a novel biomarker integrating inflammation and lipid metabolism, but its longitudinal association with metabolic dysfunction-associated fatty liver disease (MAFLD) remains unclear. This study aimed to investigate the impact of MHR trajectories on MAFLD risk using multi-disciplinary approaches.

Methods: We conducted a comprehensive anaylsis combining: (1) machine learning-based random forest modeling to evaluate feature importance; (2) prospective cohort anaylsis with repeated MHR measurements to identify trajectory patterns; and (3) Mendelian randomization (MR) to infer causality.

Results: Three distinct MHR trajectories were identified in the cohort. Compared to the low-stable group, both moderate-increasing (HR 1.17, 95% CI 1.04–1.32) and high-fluctuating (HR 1.24, 95% CI1.03–1.49) trajectories showed significantly higher MAFLD incidence. Random forest ranked MHR among top 5 predictors, and MR analyses supported a causal relationship.

Conclusion: This multimodal study demonstrates that longitudinal MHR elevation precedes and predicts MAFLD development, implicating compounded inflammatory-lipid pathways. MHR trajectory anaylsis may enhance early risk stratification, particularly in metabolically compromised individuals.

Keywords: The monocyte-to-high-density lipoprotein cholesterol ratio, metabolic dysfunction-associated fatty liver disease, trajectory anaylsis, Mendelian randomization

Introduction

Metabolic-associated fatty liver disease (MAFLD) has become the most common chronic liver disease globally, affecting more than 25% of adults. Its disease spectrum ranges from simple steatosis to cirrhosis and even liver cancer, while early intervention can significantly improve the prognosis.[1–3] With the update of the disease concept in 2020, the naming of "MAFLD" places more emphasis on the central role of metabolic disorders in the pathogenesis.[4–6] Meanwhile, chronic inflammation has been proven to be a key driving factor for the progression of this disease.[7] In recent years, inflammatory markers based on routine blood tests have demonstrated diagnostic and risk prediction values for MAFLD. Among them, the

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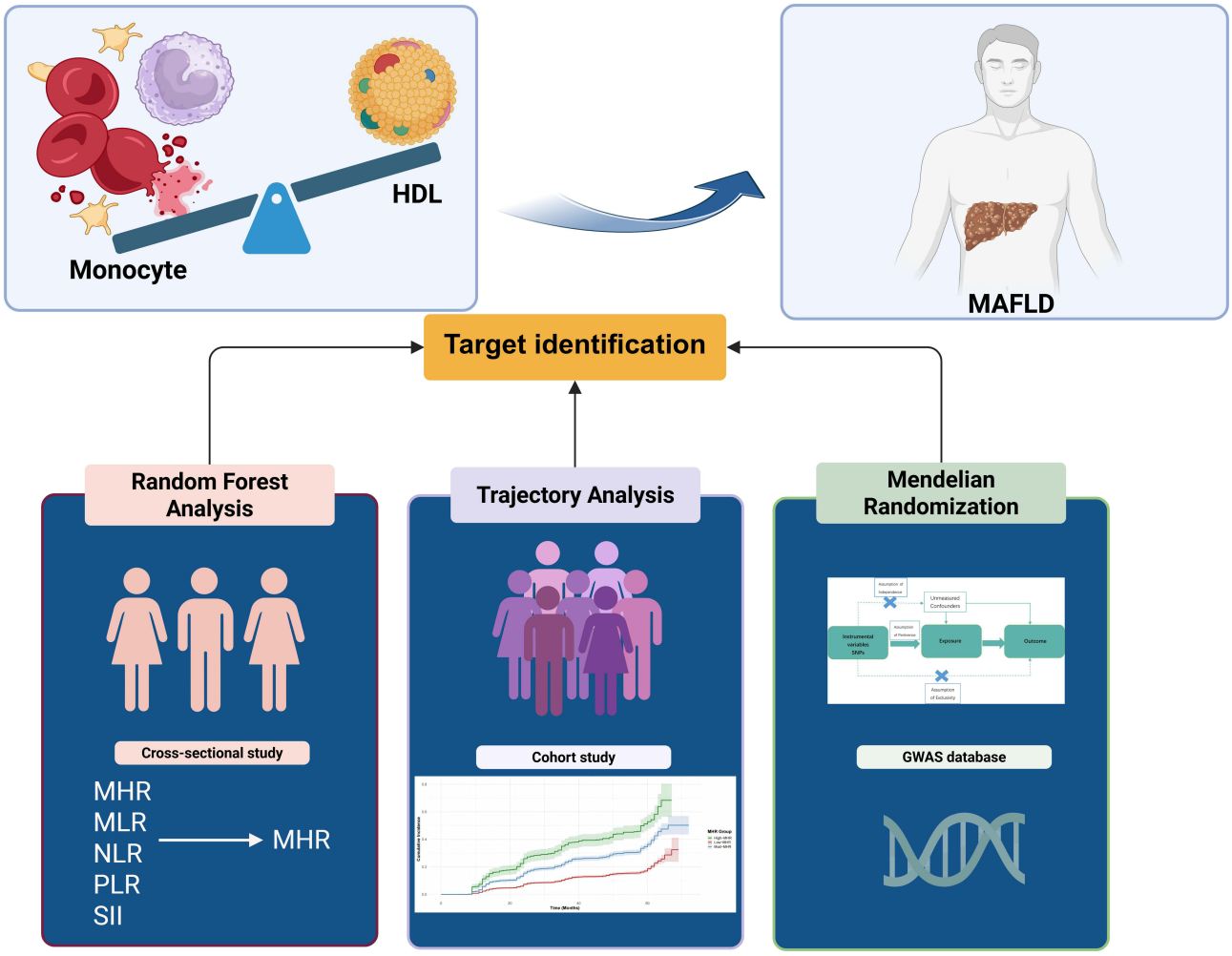
Graphical Abstract



Monocyte/HDL-C ratio (MHR) integrates the dual signals of immune activation and lipid metabolism protection, and has shown better diagnostic efficacy than other indicators in cross-sectional studies[8–10] However, there are important gaps in existing research: (1) There is a lack of longitudinal evidence on the association between the dynamic trajectories of inflammatory markers (especially MHR) and the incidence of MAFLD; (2) It has not been clarified how metabolic factors such as BMI interact with inflammatory trajectories to affect disease risk; (3) The relative contribution values of inflammatory indicators and their gender differences have not been systematically evaluated.

This study, conducted within a community-based prospective cohort, is the first to utilize Group-Based Trajectory Modeling (GBTM) to analyze the dynamic patterns of the MHR,[11] uncovering its temporal association with MAFLD development. Causal inference was further validated through Mendelian randomization (MR), while stratified analyses explored the moderating effects of BMI and sex on the "inflammatory-metabolic crosstalk". The aim of this study is to determine whether longitudinal MHR trajectories are predictive of incident MAFLD, and to explore how metabolic and sex-specific factors modulate this association. The findings of this study could substantially improve population health by providing novel dynamic biomarkers for early risk prediction of MAFLD. Additionally, these insights could enhance clinical decision-making, enabling precision interventions targeted at the immunometabolic regulatory axis to effectively manage and prevent MAFLD progression.

Methods

Population Characteristics

Population for Cross-Sectional Study

This study was initially analyzed based on an independent cross-sectional databases: the Chinese Health Check-up Cohort - 32996 Han Chinese adults who underwent abdominal ultrasound examinations at the Health Management Center of the Third Affiliated Hospital of Southern Medical University were included. All participants were from Guangdong Province of China and its surrounding areas, and they had a highly homogeneous genetic background.

Population for Longitudinal Trajectory Study

Dynamic follow-up cohort - 20186 adult physical examinees (from June 2017 to June 2021) were included, and they were required to complete at least three annual follow-up examinations (including questionnaires, routine blood tests, blood lipid tests, and abdominal ultrasound examinations).

Participants were excluded from both the cross-sectional and longitudinal analyses if they had any of the following:

(1) Serious liver or chronic systemic conditions, including hepatocellular carcinoma (confirmed by CT/MRI), a history of coronary heart disease, heart failure, stroke, chronic kidney disease, malignant tumors, or end-stage liver disease (Child-Pugh Class C);

(2) Special conditions such as pregnancy or lactation;

(3) Evidence of fatty liver on baseline ultrasound examination;

(4) Conditions or medication use potentially affecting hepatic fat accumulation, such as viral hepatitis, corticosteroids, or weight-loss agents (eg, GLP-1 receptor agonists).

Diagnostic Criteria for MAFLD

Hepatic steatosis was assessed using standardized abdominal ultrasonography performed with a Siemens ACUSON X300 diagnostic ultrasound system. All scans were conducted by experienced radiologists who were blinded to clinical information. The diagnosis was based on established echogenic criteria, including increased liver-kidney contrast, blurring of intrahepatic vascular margins, and posterior beam attenuation. These criteria align with recognized guidelines for the noninvasive detection of hepatic steatosis. According to the consensus definition proposed by international expert panels, MAFLD diagnosis required evidence of hepatic steatosis plus one of the following:

(1) Overweight or obesity (BMI $\geq$ 23 kg/m^2 for Asian adults);

(2) Type 2 diabetes mellitus (based on self-reported history, fasting glucose $\geq$ 7.0 mmol/L, or use of glucose-lowering medications);

(3) Presence of metabolic dysfunction, defined as having at least two of the following metabolic risk abnormalities:

- Waist circumference $\geq$ 90 cm (men) or $\geq$ 80 cm (women);
- Blood pressure $\geq$ 130/85 mmHg or current antihypertensive therapy;
- Plasma triglycerides $\geq$ 1.70 mmol/L;
- HDL-C $<$ 1.0 mmol/L (men) or $<$ 1.3 mmol/L (women);
- Prediabetes (fasting glucose 5.6–6.9 mmol/L);
- HOMA-IR $\geq$ 2.5;
- hs-CRP level $>$ 2 mg/L.[12]

After recording baseline data, participants underwent four subsequent annual follow-up visits. At each follow-up visit, both MHR values and MAFLD status were assessed. The median duration from the last follow-up used to determine longitudinal MHR trajectories (ie, the third follow-up visit) to the visit at which MAFLD outcomes were finally evaluated (ie, the fourth follow-up visit) was 12 months (range: 11–13 months).

Data Collection

Through the compilation of questionnaires during each medical visit, information was gathered on age, gender, smoking status, alcohol consumption habits, family medical history, and diagnoses of hypertension, diabetes, and metabolic fatty liver. Smoking was defined as smoking more than one cigarette per day for at least six months. Weight and height were measured to the nearest 0.1kg and 0.1cm, respectively, with participants wearing lightweight clothing and no shoes. BMI was calculated as weight divided by the square of height. Blood pressure (BP) was measured three times with a one-minute interval using a validated digital automatic blood pressure analyzer, by trained personnel after a resting period of 10 minutes. The average of the three BP measurements was recorded as the final blood pressure value. Hypertension was defined as follows: (i) systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg; (ii) self-reported history of physician-diagnosed hypertension; and/or (iii) use of antihypertensive medication. Diabetes was defined as follows: (i) fasting blood glucose ≥ 7.0 mmol/L or glycated hemoglobin (HbA1c) ≥ 6.5 mmol/L; (ii) self-reported history of physician-diagnosed diabetes; and/or (iii) use of antidiabetic medication.

According to the principles of the Declaration of Helsinki, this research protocol was approved by the Institutional Review Board (IRB) of the Third Affiliated Hospital of Southern Medical University (Project Identification Code: 2022-ER-020). We received approval for informed consent exemption, as the study involved retrospective analysis of anonymized data and posed minimal risk to participants. No identifiable personal information was accessible to the researchers, and strict measures were taken to ensure the confidentiality and security of all patient data.

Laboratory Testing

After fasting for at least 10 hours, experienced nurses collected blood samples from the antecubital vein in the morning (between 07:00 and 09:00a.m). All samples were transferred to vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) and analyzed in the clinical laboratory of the Third Affiliated Hospital of Southern Medical University. Enzymatic methods were used to analyze serum markers, triglycerides(TG), total cholesterol(CHOL), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C),and uric acid (UA). Monocyte counts were determined, and fasting blood glucose concentrations were measured using the glucose oxidase method with a diagnostic kit. Automated biochemistry analyzers (Hitachi 7600–110; Hitachi Ltd., Tokyo, Japan) or Sysmex XE-2100 automated hematology analyzers (Sysmex, Kobe, Japan) were used for these measurements. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC).

Formula for inflammatory indicators: the calculation methods for the inflammation indicators are as follows:

$$\mathrm{MHR} = \mathrm{Monocyte\ count}\,(10^9/\mathrm{L})/\mathrm{HDL-C}\,(\mathrm{mmol/L})$$

$$\mathrm{MLR} = \mathrm{Monocyte\ count}\,(10^9/\mathrm{L})/\mathrm{Lymphocyte\ count}\,(10^9/\mathrm{L})$$

$$\mathrm{NLR} = \mathrm{Neutrophil\ count}\,(10^9/\mathrm{L})/\mathrm{Lymphocyte\ count}\,(10^9/\mathrm{L})$$

$$\mathrm{PLR} = \mathrm{Platelet\ count}\,(10^9/\mathrm{L})/\mathrm{Lymphocyte\ count}\,(10^9/\mathrm{L})$$

$$\mathrm{SII} = \mathrm{Neutrophil\ count}\,(10^9/\mathrm{L}) * \mathrm{Platelet\ count}\,(10^9/\mathrm{L})/\mathrm{Lymphocyte\ count}\,(10^9/\mathrm{L})$$

Statistical Methods

The normally distributed data were presented as (Mean±Standard Deviation). Student's *t*-test, anaylsis of variance (ANOVA), and Pearson's chi-square test with Bonferroni correction were used to determine intergroup differences. Population characteristics were analyzed using SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA).

The variable importance of five inflammatory markers, and their partial trajectories was determined using a random forest approach. In this study, we utilized a set of 500 trees (ntree = 500) for the random forest anaylsis, as we found that this setting was sufficient and increasing the ntree value did not further improve predictions. Another parameter in random forest anaylsis was "mtry" which represented the number of variables considered at each split in a tree. The quantity of mtry was determined using a grid search method, utilizing the mtry value from the minimum error estimate. The final value of variable importance was

obtained as the average of 3-fold cross-validation. Random forest anaylsis were performed using the R language with the randomForest packages, respectively.

The participants were initially grouped into four categories based on their gender and BMI status. Trajectories of inflammatory markers were analyzed using Stata software (version 17.0; StataCorp LLC, Texas, USA) and the traj plugin. Inflammatory marker trajectories were modelled using a censored normal distribution. Each trajectory group was assessed based on the following criteria: highest Bayesian Information Criterion (BIC), average posterior probability >70%, and appropriate sample size >5.0%.[13,14]

The findings indicated that the optimal number of trajectories was three. Ultimately, different combinations (quadratic, quadratic, quadratic) were employed to ascertain the best-fitting model, resulting in an average probability of 0.89 (Table S1).

The Cox proportional hazards model was employed to assess the association between MHR trajectories/baseline/variation trajectory and the onset of MAFLD. Baseline MHR was stratified based on tertiles. Several covariates were included in the model to explore the association between MHR trajectories and MAFLD development, including age, sex, body mass index (BMI), waist circumference (WC), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hypertension status, diabetes status, smoking history, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), hemoglobin (Hb), and platelet count.[15,16] The multiplicative interaction of MHR trajectory/variation trajectory and overweight/obese was explored in both genders.

Furthermore, the additive interaction of MHR trajectory/variation trajectory and overweight/obese was also investigated by adjusting the aforementioned variables. The epiR package in R was utilised for calculations.[17]

Mendelian Randomization

We employed multiple analytical methods to study the causal relationships between the key genes and MAFLD. These methods included the inverse variance-weighted (IVW) method, weighted median estimator MR-Egger regression, weighted mode and simple mode, with the results from IVW being considered the primary evidence and the results from other methods serving as supplementary evidence and validation.22 Univariate MR anaylsis was used to calculate the odds ratios (OR) and 95% confidence intervals (CIs), along with sensitivity analyses. The heterogeneity in MR anaylsis was assessed using the Cochrane Q-statistic with both the MR-Eggerr[18,19] and IVW methods,[20] with a $p < 0.05$ indicating the presence of heterogeneity. If heterogeneity existed, a random-effects IVW model was used to consider potential heterogeneity among different SNPs; otherwise, a fixed-effects model was employed. We used the MR-Egger intercept and the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods to test for horizontal pleiotropy.[21] An MR-Egger intercept value close to zero indicates a low likelihood of horizontal pleiotropy, whereas a significant deviation from zero ($p<0.05$) indicates the presence of horizontal pleiotropy. Additionally, MR-PRESSO serves as another tool to detect and correct for horizontal pleiotropy and outliers. MR-PRESSO identifies and excludes outliers that may bias the MR estimates by examining the correlation between each genetic variant and other variants. This process helps to ensure the reliability of the MR results. Specifically, MR-PRESSO not only detects pleiotropy but also identifies and addresses outliers caused by pleiotropy, thereby enhancing the robustness of the MR anaylsis. We used scatterplots to show the data, corrected for pleiotropy using MR-PRESSO. The leave-one-out approach involved sequentially excluding individual SNPs to assess the impact of each SNP on the outcomes. Following prior research, IVs were selected using a threshold of $p < 1*10^5$. To ensure their independence, linkage disequilibrium (LD) was evaluated using PLINK, with an LD $r2 < 0.01$ within a 10,000-kb window. An F-statistic of ≥10 indicates strong evidence against weak instrument bias[22,23] (Figure 1).

Results

Baseline Characteristics

In the domestic cross-sectional population, there were a total of 8826 MAFLD patients (49.4±12.0) and 20486 control individuals (46.5±13.2). In the longitudinal cohort, there were a total of 1984 MAFLD patients (47.9±11.2) and 6540 control individuals (45.3±11.6) (Figure 2). Based on a sample size of 8,524 and an incidence rate of 23% for MAFLD, the study had over 90% statistical power to detect an odds ratio greater than 1.3 at a significance level of 0.05.

The MAFLD group showed significantly higher proportions of males, diabetes, higher BMI, and higher levels of ALT, AST, GGT, triglycerides(TG), and LDL-C, with lower levels of HDL-C, compared to the control group (Table S2). MHR variation was

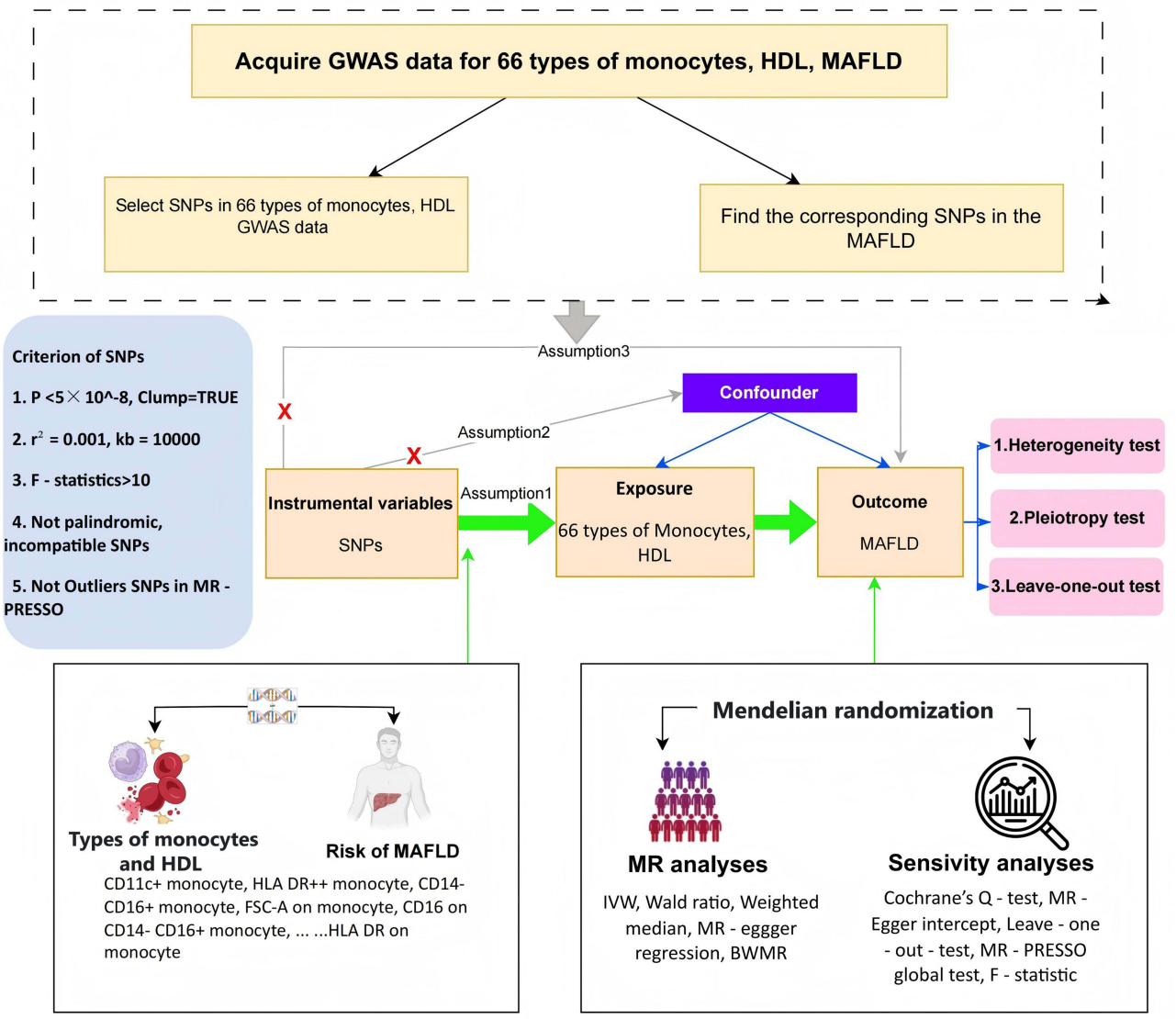


Figure 1 Flow chart of Mendelian randomization.

defined as the difference between each follow-up value and the baseline MHR (ΔMHR = MHR_follow-up − MHR_baseline). The distribution of MHR variation trajectory can be seen in Figure 3. Intra-individual variability analysis indicated Participants in the higher MHR trajectory group had not only higher mean MHR levels but also lower intra-individual variability, suggesting more stable and persistently elevated inflammation. In contrast, the lower trajectory groups exhibited greater MHR fluctuations over time (Table S3).

Random Forest Prediction for MAFLD

Both cross-sectional health examination data revealed that the three most significant predictors identified by random forest for MAFLD were BMI, ALT, and WC. Similarly, MHR demonstrated significantly higher importance compared to the other four inflammation-related indicators. In the longitudinal health examination data, random survival anaylsis determined that several of the most important predictors for MAFLD were BMI, TG, WC, and MHR trajectory (Figure 4).

Association of MHR Trajectories with MAFLD Incidence and Subgroup Anaylsis

Following a 5-year follow-up, 1,984 study participants developed MAFLD. Significant P-value trends were observed across all four gender-BMI subgroups ($P < 0.05$ for trend). The cumulative incidence of MAFLD in the subgroups of

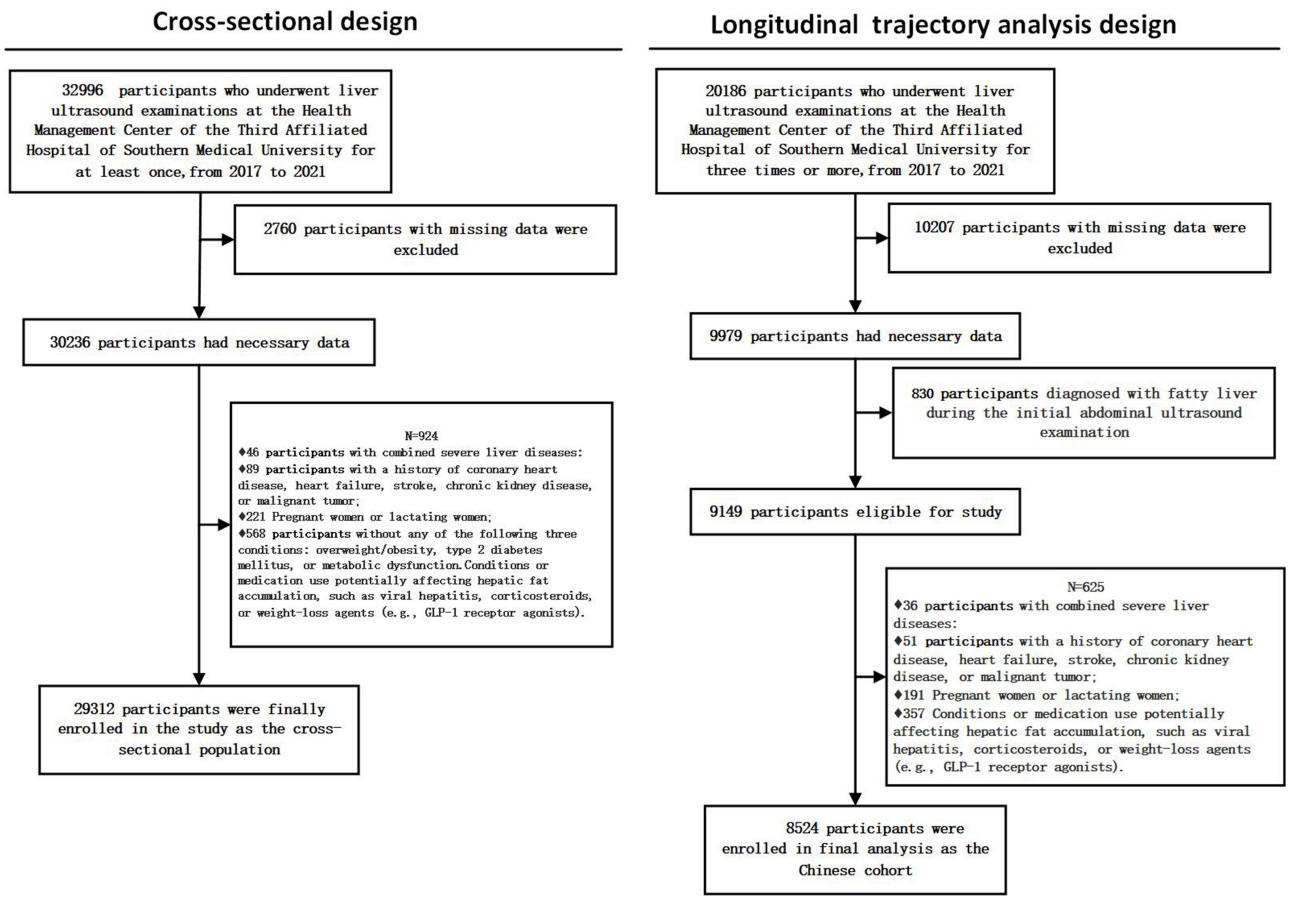


Figure 2 Flow diagram of participant inclusion throughout a cross-section studies and a cohort study.

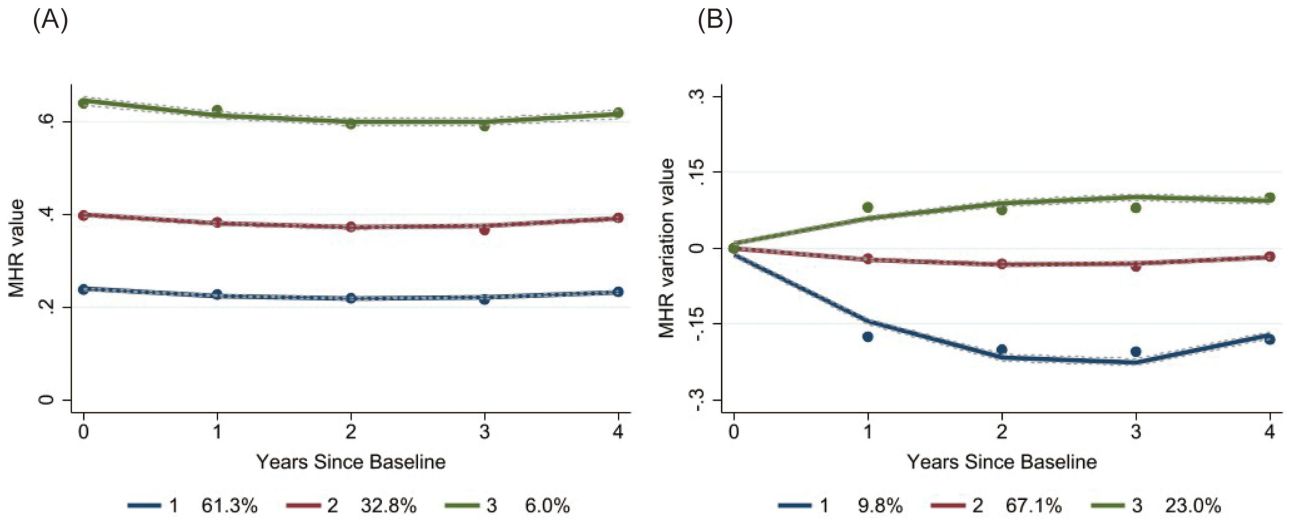


Figure 3 Visualize trajectory distribution (**A**) MHR trajectories and (**B**) the trajectories of MHR variation during 2017–2021.

non-overweight females, non-overweight males, overweight/obese females, and overweight/obese males was 10.48%, 19.73%, 38.79%, and 49.34% respectively. Figure 5 illustrates the cumulative incidence of MAFLD across different MHR trajectory groups. During the follow-up period, individuals in the high MHR trajectory group exhibited a markedly higher cumulative incidence of MAFLD compared to those in the medium and low trajectory groups. The cumulative incidence increased most rapidly in the high MHR group, with a clear separation of curves over time. This trend

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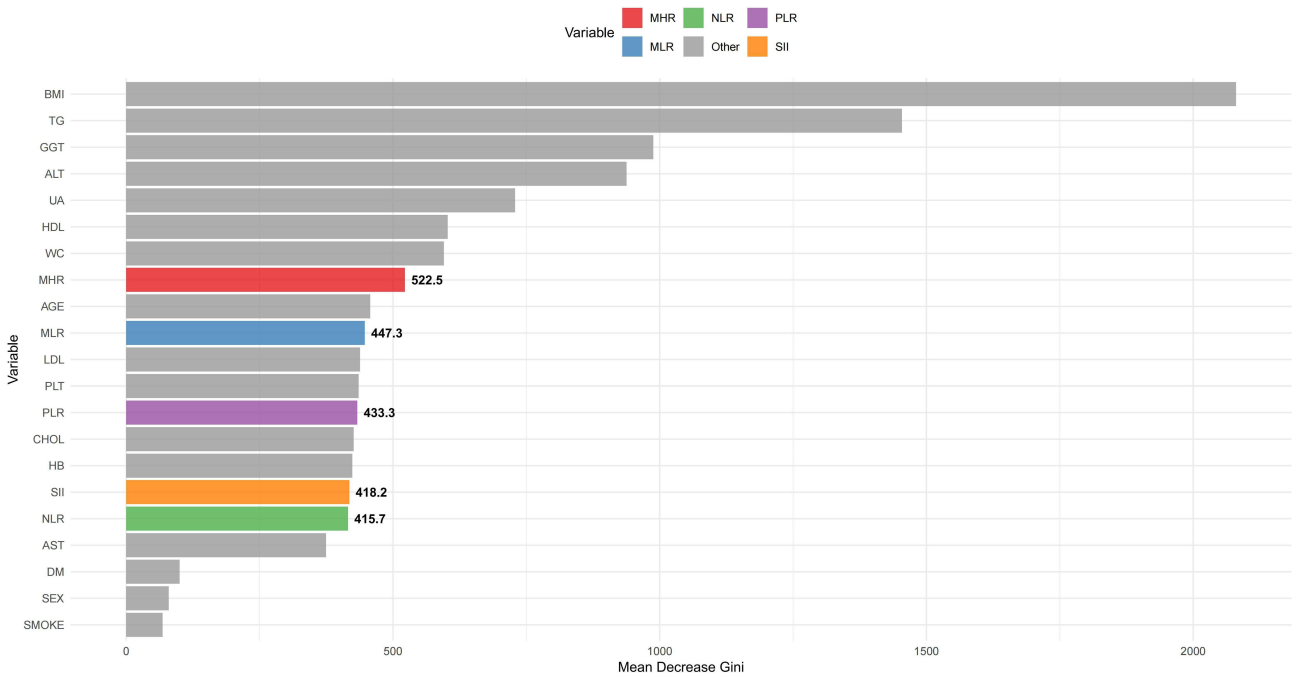

Figure 4 Random forest anaylsis of the domestic cross-section studies.

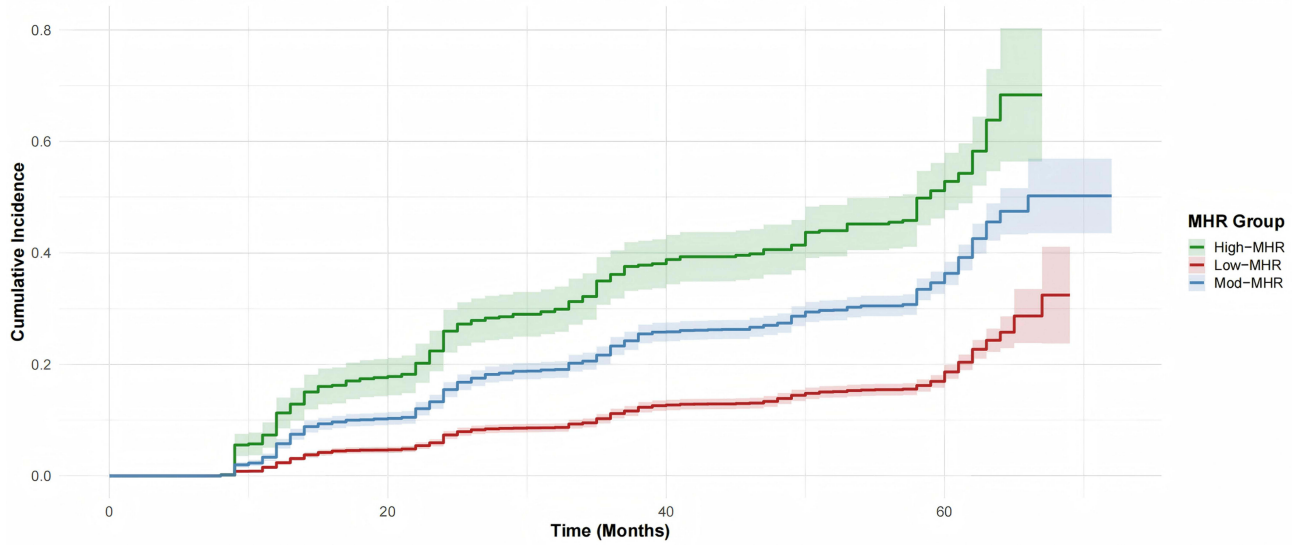

Figure 5 Cumulative incidence curves of MAFLD by MHR trajectory groups.

remained consistent throughout the entire observation period, indicating a strong temporal association between elevated long-term MHR and MAFLD onset. Hazard ratios (HRs) and 95% confidence intervals (CIs) were 0.71 (0.30–1.68) in Group 1, 1.16 (0.80–1.69) in Group 2, 1.41 (0.75–2.64) in Group 3, and 1.59 (1.21–2.10) in Group 4 (Table S4).

The baseline level of MHR (Table S5) and the variation trajectory of MHR (Table S6) were associated with the incidence of MAFLD. Interaction analysis showed that MHR variation trajectory and overweight/obesity exhibited antagonistic multiplicative interactions (Table S7). In additive interaction analysis (Tables S8 and S9), significant synergistic effects were observed in the total population and both sexes under Models 1 and 2 (RERI > 0, AP > 0, SI > 1; 95% CIs excluding null). In Model 3, additive interaction remained borderline significant in the total population.

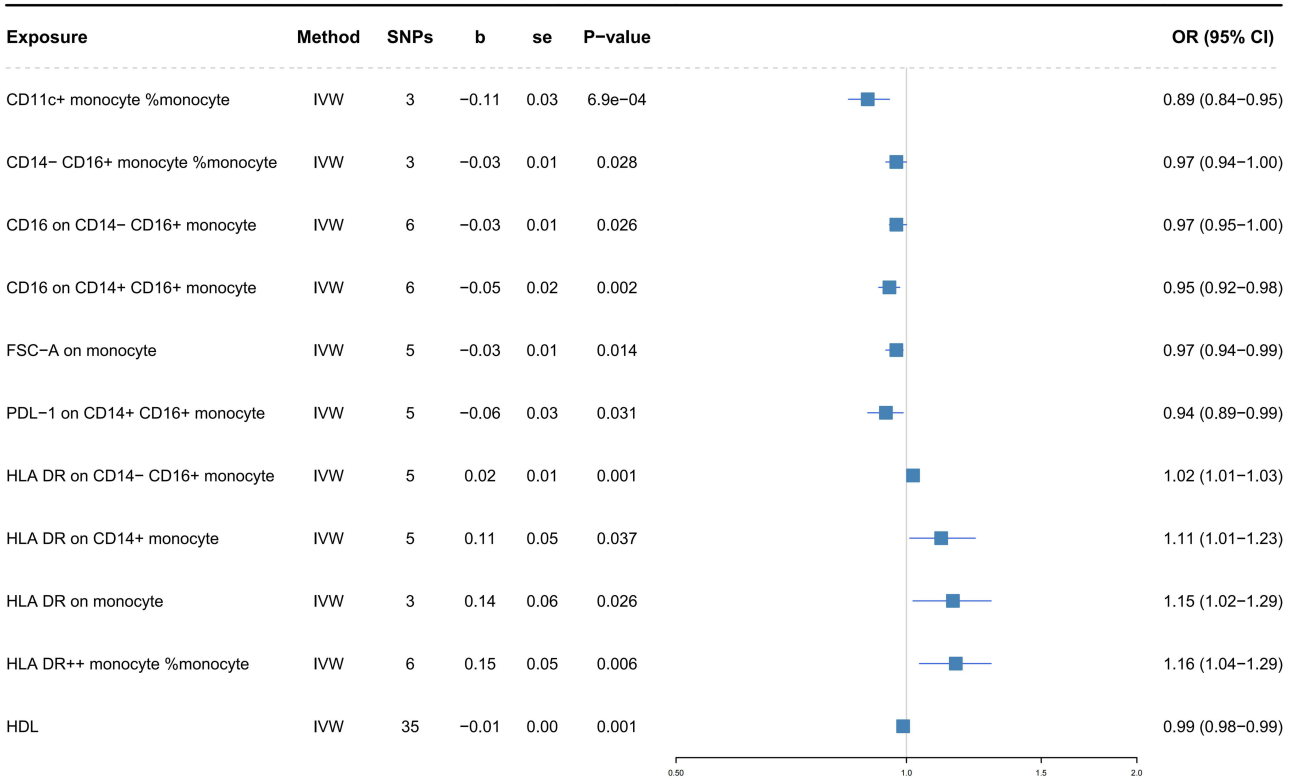

Figure 6 Forest plots of the causal relationship between Types of monocytes and HDL and MAFLD in the result of IVW in the forward MR anaylsis.

Mendelian Randomization Between MHR Phenotype, HDL and MAFLD

By the IVW anaylsis, we found that there was no significant correlation between the number of monocytes and MAFLD ($p > 0.05$) (Table S10). In addition to HDL, 11 monocyte phenotypes were significantly associated with MAFLD (Figure 6). HDL was negatively correlated with MAFLD, and the following phenotypes were also negatively correlated with MAFLD: the percentage of CD11c+ monocytes among total monocytes, the percentage of CD14- CD16+ monocytes among total monocytes, the expression level of CD16 on CD14- CD16+ monocytes, the expression level of CD16 on CD14+ CD16+ monocytes, the forward scatter area (FSC-A) value of monocytes, and the expression level of programmed death-ligand 1 (PDL-1) on CD14+ CD16+ monocytes. The remaining phenotypes, namely, the expression level of human leukocyte antigen DR (HLA DR) on CD14- CD16+ monocytes, the expression level of HLA DR on CD14+ monocytes, the expression level of HLA DR on monocytes, and the percentage of HLA DR++ monocytes among total monocytes, were positively correlated with MAFLD. The scatter plot (Figure S1) and the leave-one-out plot (Figure S2) also support the above conclusions. After multiple testing correction, $CD11c^+$ monocyte %, HLA DR^+ on $CD14^+$ monocyte, and HDL remained significantly associated with the outcome (FDR-adjusted $p < 0.05$) (Table S11). p value of the MR-Egger intercept >0.05, indicating no evidence of horizontal pleiotropy. The Cochran's Q test suggested no significant heterogeneity among SNPs ($p > 0.05$). Given the absence of pleiotropy, we did not conduct MVMR analysis incorporating (Table S12).

Discussion

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a complex multisystem disorder,[24,25] with its pathogenesis involving mechanisms such as adipose tissue dysfunction, gut microbiota imbalance, and abnormal hepatic immune responses.[26–29] In recent years, increasing attention has been paid to the critical role of inflammation in the development and progression of MAFLD. Multiple studies have reported associations between fatty liver and inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII).[2] However, due to sample heterogeneity, the limitations of cross-sectional designs, and a lack of longitudinal data, their predictive

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value has not been systematically evaluated. This study is the first to use a random forest algorithm to compare the predictive power of five commonly used inflammatory markers, revealing that the monocyte-to-HDL cholesterol ratio (MHR) demonstrates the strongest performance in predicting future MAFLD risk. By applying trajectory modeling to five-year follow-up data, we identified three distinct dynamic patterns of MHR. Individuals in the high-trajectory group exhibited a significantly elevated risk of developing MAFLD, with the risk being especially pronounced in overweight or obese men. Compared to conventional static indicators, our findings highlight the predictive significance of temporal trends in MHR itself—an aspect not previously addressed in existing research. Mendelian randomization analysis further supports a causal relationship, showing that higher levels of high-density lipoprotein cholesterol (HDL-C) are protective against MAFLD, whereas monocytes with specific activated phenotypes (eg, high HLA-DR expression) are positively associated with disease risk. These results suggest that it may be the activation state of monocytes, rather than merely their count, that plays a key role in disease progression.

As a ratio that integrates pro-inflammatory monocytes and anti-inflammatory HDL-C, the monocyte-to-HDL cholesterol ratio (MHR) can dynamically reflect shifts in the immune-metabolic balance.[30–32] Activated monocytes release various inflammatory cytokines (such as IL-1β and TNF-α), which promote hepatic inflammation and lipid accumulation.[33] In contrast, HDL-C exerts anti-inflammatory and lipid-modulating effects, offering protection by inhibiting monocyte chemotaxis and attenuating TLR signaling pathways.[34–37]

Furthermore, our Mendelian randomization analysis revealed that higher HDL-C levels have a protective effect, while monocytes with activated phenotypes are positively associated with MAFLD risk. These findings suggest that MHR is not only a predictive marker but may also play a causal role in the development of MAFLD.

Previous studies have established the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) as an independent predictor for the presence and prognosis of cardiovascular diseases.[38] A nationwide cohort study in the United States confirmed the contribution of MHR to the risk of all-cause and cardiovascular mortality. MHR has also been shown to predict metabolic syndrome[39] and vitamin D deficiency.[40] Blood lipids—particularly high-density lipoprotein (HDL)—play a crucial role in linking cardiovascular conditions with metabolic syndrome and fatty liver disease.[41]

Compared with existing literature, this study offers several innovative contributions. First, most previous studies were based on cross-sectional designs and overlooked the temporal dynamics of inflammatory markers; in contrast, we used trajectory modeling to reveal the impact of long-term MHR trends on disease risk. Second, while prior research often focused on a single inflammatory marker, our study systematically compared five markers and validated the robustness of MHR through multiple analytical methods. Third, our Mendelian randomization analysis is the first to suggest a potential causal link between monocytes, HDL-C, and the etiology of MAFLD, providing a theoretical foundation for future exploration of therapeutic targets.

This study also has several limitations. Due to practical constraints of the cohort study, lifestyle factors such as diet and physical activity, as well as indicators of insulin resistance, were not included in the model; instead, BMI and waist circumference were used as proxy variables.[41] The follow-up period was relatively short, and detailed information on the exact timing of MAFLD diagnosis was limited. Moreover, Mendelian randomization (MR) analysis inherently reflects the effect of lifelong exposure on disease risk, making it difficult to capture short-term fluctuations or identify critical thresholds. As the UK Biobank sample is predominantly composed of individuals of European ancestry, the generalizability of the findings to other populations needs to be further validated in multi-center, multi-ethnic cohorts.

Future studies should aim to elucidate the dynamic regulatory mechanisms of MHR as a predictive marker and explore its potential as a therapeutic target, in order to provide new avenues for individualized risk prediction and precise prevention of MAFLD.

Conclusions

In conclusion, our study demonstrates that longitudinal trajectories of the monocyte-to-HDL-C ratio (MHR) are significantly associated with incident MAFLD risk, particularly among overweight and obese males. These findings, further supported by Mendelian randomization, suggest a potential causal role of immunometabolic imbalance in MAFLD development. While the study leverages a large sample size and robust analytical methods, limitations such as unmeasured lifestyle confounders and the lack of mechanistic validation should be noted. Given its availability in routine blood tests, MHR may serve as a promising biomarker for early risk stratification of MAFLD. Future clinical research is warranted to validate its predictive value and explore its utility in personalized prevention strategies.

Data Sharing Statement

The datasets generated and/or analyzed in this study are not publicly available due to concerns about participants' privacy. However, they can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

According to the principles of the "Helsinki Declaration," this research protocol has been approved by the Institutional Review Board (IRB) of the Third Affiliated Hospital of Southern Medical University (Project Identification Code: 2022-ER-020). We received approval for informed consent exemption.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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

All authors disclosed no relevant conflicts of interest for this work.

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