ISSN: 2754-4516

Journal of Medicine and Healthcare

SCIENTIFIC Research and Community

Research Article

Open Access

Causal links between 1,400 Human Blood Metabolites and Non-Alcoholic Fatty Liver Disease Via Mendelian Randomization Study

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ABSTRACT

Background: For safe blood transfusion services, understanding ABO blood group and Rhesus factor distribution at local levels is very essential.

Objective: To determine the frequency of phenotype, allele and genotypes of ABO and Rhesus (D) blood group in South Wollo, Ethiopia.

Materials and Methods: A cross-sectional document review was done using data from September 2019 to March 2023. The Chi-square test was used to assess the variations in the distribution of blood groups based on sex and locations, as well as to compare the observed and expected frequencies with data from various sites in Ethiopia. The frequencies of alleles and genotypes were calculated under Hardy-Weinberg assumption.

Result: 16,318 participants with median age of 26 years were included in the study, 11,924 males. The most common blood groups were O (40.4%) and Rh (D) positive (90.7%). Allele of I^O and I^OI^O were the predominant allelic and genotypic frequency respectively. In the case of Rh the dominant allele D was the most common. ABO and Rh frequency differ significantly across different sites. However, there is no difference in the ABO and Rh blood groups between the current study and other sites of Ethiopia as well as between observed and expected blood groups frequencies.

Conclusion: the most and the least blood groups were O and AB respectively. The distribution of ABO and Rh blood groups varies among different locations. No significance difference of ABO and Rh blood groups between present study and other areas of Ethiopia.

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Received: March 19, 2025; **Accepted:** March 24, 2025; **Published:** March 31, 2025

Keywords: Metabolite, Non-Alcoholic Fatty Liver Disease, Mendelian Randomization

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver condition globally, with an estimated prevalence of approximately 25%, and its morbidity and incidence rates have been rising in recent years. NAFLD is characterized by the accumulation of fat in liver cells, accounting for more than 5% of the liver's total weight, due to altered lipid metabolism in the liver, excluding alcohol and other clear causes of liver damage. It is a disease marked by complex pathophysiology and multiple stages, encompassing a spectrum of conditions including simple steatosis, steatohepatitis, liver fibrosis, cirrhosis, and even liver cancer. The most recent term used to describe this condition is Metabolic-Dysfunction Associated Fatty Liver Disease. Recent observational studies have suggested that the occurrence of NAFLD may be linked to abnormalities in certain specific serum metabolites or associated with changes in endogenous metabolites in the blood. Moreover, due to the lack of universally accepted and reliable pharmacological treatments for NAFLD, research into the relationship between serum metabolites and NAFLD has garnered significant attention [1-5].

Blood metabolites, including amino acids, fatty acids, sugars, and other small molecules, play critical roles in various metabolic pathways. The pathogenesis of NAFLD remains incompletely understood; however, animal experiments and clinical studies have indicated that dysregulations in lipid metabolism, amino acid metabolism, and glucose metabolism may all play extensive roles in the pathophysiology of NAFLD development and progression. Analyzing changes in blood metabolites in humans may offer a promising new tool for diagnosing NAFLD. A deeper understanding of the alterations in blood metabolites can also help identify more effective measures for preventing the onset of NAFLD. For instance, the ratio of urinary caffeine metabolites to caffeine intake, known as the urinary caffeine metabolite index, has been used as a surrogate marker for Cytochrome P450 1A2 (CYP1A2) activity, one of the primary liver metabolizing enzymes, closely associated with the progression of NAFLD [6-9]. Mowry et al. in a cross-sectional clinical study found that phosphatidylcholine and free fatty acids could serve as specific

biomarkers for high risk of NASH and have the potential to be used as non-invasive diagnostic tools for assessing, monitoring, and altering the disease course. Although previous research has explored some connections between 486 blood metabolites and NAFLD and found that biliverdin and myristoleate as risk and protective factors for NAFLD respectively, more extensive studies are required to fully determine the causal relationships between these metabolites and NAFLD [10].

Traditional observational studies are subject to influence by a variety of potential confounding factors, which may lead to potentially misleading inferences. Crucial for investigating the causal link between blood metabolites and NAFLD, Mendelian Randomization (MR) used genetic variations as instrument variables (IVs) to evade the impact of confounding factors. Using information from big biobanks and consortia, this method allows for MR analysis that takes into account the correlations between genetic variations and each exposure and outcome variable [11-14]. A prominent advantage of this method is that it uses genetic variants distributed randomly during fertilization to simulate randomized controlled trials. This reduces bias from various confounding factors, for instance, age, gender, weight, and lifestyle habits in causal analysis, and is unaffected by disease progression. Consequently, it evaluates the causality between metabolites and NAFLD more efficiently and gives a more solid grasp of how exposure factors affect results [15].

Given the incomplete understanding of the causal relationship between blood metabolites and NAFLD, this MR study evaluated the causality between 1,400 human blood metabolites and NAFLD. The aim was to discover more about how NAFLD starts, make better predictions about NAFLD risk, and ultimately enable early intervention [16].

Results

The blood metabolites data used in this study were obtained from research conducted by Dr. Chen et al, which was published in the GWAS catalog (GCST90199621 to GCST90201020) and included 1400 blood metabolites from the European population.

MR analyses were performed on these 1400 blood metabolites after going through rigorous processes in the instrument selection process. The number of SNPs per metabolite ranged from 7 to 32. All SNP instruments had F-statistics greater than the empirical threshold of 10, indicating sufficient validity for all SNPs.

Using the IVW method, we initially identified a total of 71 metabolites significantly associated with NAFLD (GWAS ID: GCST90091033) (Figure 1). To enhance the reliability of our findings, we further validated our results by conducting a replication analysis using another NAFLD dataset from GWAS (GWAS ID: GCST90011885), revealing 21 metabolites potentially causally related to NAFLD.

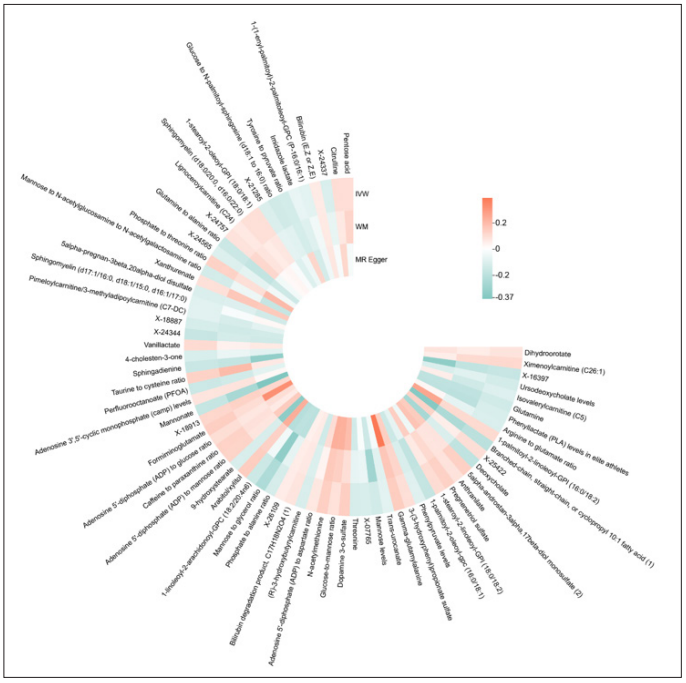

Figure 1: The Circular Heatmap Shows the β values Corresponding to 71 Positive Metabolites.

A comparative analysis of the results from the two MR analyses showed three metabolites (mannose levels, caffeine to paraxanthine ratio, and mannonate levels) with stable causal relationships with NAFLD, all of which are known metabolites (Figure 2). Among these, mannose and mannonate exhibited inverse causal relationships, i.e. acting as protective factors, while caffeine to paraxanthine ratio showed a positive causal relationship with NAFLD, indicating a risk factor (Figure 3, Figure 4). After multiple correction tests for FDR to eliminate false positives, it was confirmed that these three metabolites still showed significant causal relationships with NAFLD: mannose (OR=0.878, 95%CI:0.789-0.977, P=0.017, FDR=0.025), Caffeine to paraxanthine (CAF/PX) ratio (OR=1.348, 95%CI:1.041-1.745, P=0.024, FDR= 0.019), mannonate (OR=0.846, 95%CI: 0.719-0.996, P=0.044, FDR=0.044) (Table S1). MR-Egger intercept tests (all p>0.05) did not detect horizontal pleiotropy in all three metatolites [17]. In MR-PRESSO test, neither CAF/PX ratio (Global test p value=0.084) nor mannonate levels (Global test p value = 0.093) exhibited horizontal pleiotropy. However, three outliers were identified for mannose levels (Global best p value = 0.033). Upon removing three outliers and conducting Mendelian randomization analysis anew to correct for horizontal pleiotropy, it was found that the causality between mannose and NAFLD remains significant (p=0.016). According to the result of the Leave-one-out (Loo) analysis, no single SNP was responsible for the result (Figure S1). There was no violation of estimates, as seen by the symmetrical funnel plots (Figure S2) [18]. Steiger directionality test results refuted the existence of reverse causality between blood metabolites and non-alcoholic fatty liver disease (Table S2).

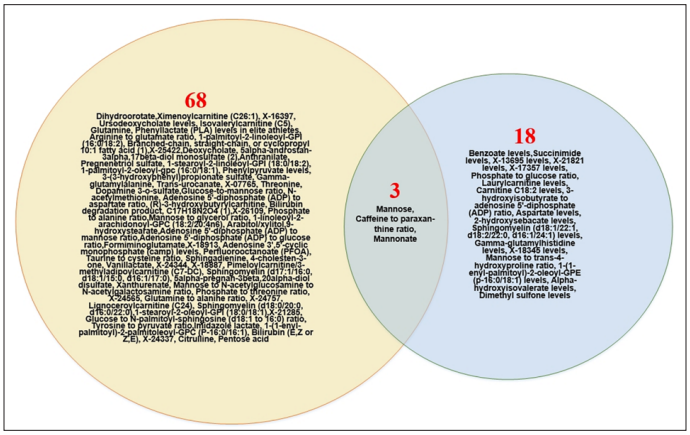

Figure 2: Intersection between Primary and Replication MR Analysis

exposureTrait	outcomeTrait	nsnp	method	pval	OR(95% CI)
Mannose levels	NAFLD	18	MR Egger	0.202	0.865 (0.699 to 1.071)
		18	Weighted median	**<0.001**	0.754 (0.667 to 0.852)
		18	Inverse variance weighted	**0.017**	0.878 (0.789 to 0.977)
		18	Simple mode	0.835	1.034 (0.761 to 1.403)
		18	Weighted mode	**<0.001**	0.760 (0.669 to 0.864)
Caffeine to paraxanthine ratio	NAFLD	20	MR Egger	0.649	1.065 (0.814 to 1.394)
		20	Weighted median	0.102	1.096 (0.982 to 1.222)
		20	Inverse variance weighted	**0.006**	1.144 (1.039 to 1.259)
		20	Simple mode	0.352	1.092 (0.912 to 1.308)
		20	Weighted mode	0.224	1.089 (0.954 to 1.243)
Mannonate levels	NAFLD	13	MR Egger	**0.047**	0.684 (0.491 to 0.954)
		13	Weighted median	**<0.001**	0.774 (0.668 to 0.896)
		13	Inverse variance weighted	**0.044**	0.846 (0.719 to 0.996)
		13	Simple mode	0.330	0.835 (0.590 to 1.183)
		13	Weighted mode	**0.002**	0.739 (0.633 to 0.862)

Figure 3: MR Results for The Causality between Metabolites and NAFLD

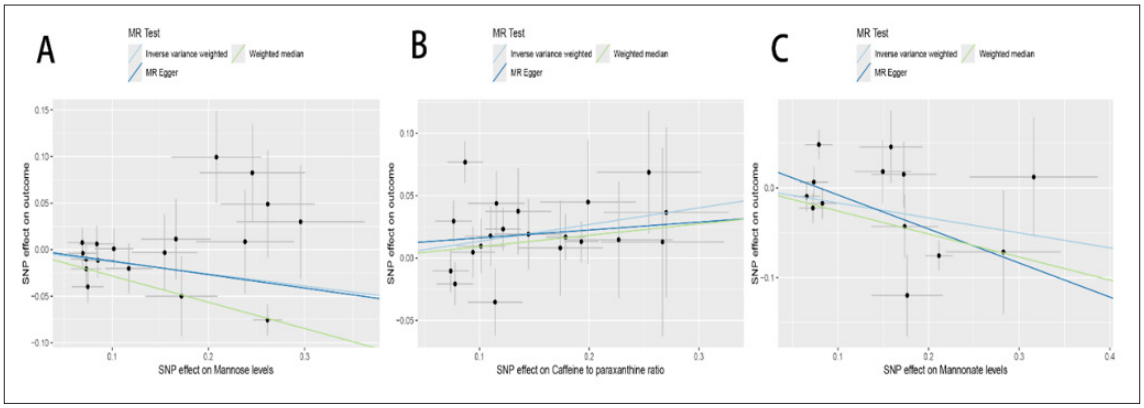

Figure 4: The MR Scatter Plot Shows the Strong link Between Non-Alcoholic Fatty Liver Disease and (A) Mannose; (B) Caffeine to Paraxanthine Ratio; (C) Mannonate.

Metabo Analyst 6.0 was utilized to identify putative metabolic signaling pathways implicated in the pathogenesis of NAFLD through the analysis of these three identified metabolites. Mannose and mannonate are constituents of the fructose and mannose metabolism pathway (p=0.038), whereas caffeine and paraxanthine are components of the metabolism pathway of caffeine (p=0.001). These metabolic pathways may be involved in the onset as well as progression of non-alcoholic fatty liver disease.

Discussion

NAFLD is a highly complex disease resulting from the interaction of genetic, environmental, metabolic, and microbial factors[19]. In this study, we conducted an unbiased two-sample MR analysis to causally assess the risk of 1,400 blood metabolites published by Chen et al. for NAFLD. To further ensure the reliability and stability of the results, replication analysis ultimately confirmed the presence of causal relationships between three metabolites (mannose level, caffeine to paraxanthine ratio[CAF/PX ratio], and mannonate level) and NAFLD, wherein mannose and mannonate exhibit protective effects, while caffeine to paraxanthine ratio is a risk factor for NAFLD. Subsequently, we conducted heterogeneity tests and sensitivity analyses on these metabolites. A study assessed the causality between 486 blood metabolites and NAFLD, identifying two known metabolites significantly associated with NAFLD: biliverdin and myristoleate. However, this is the first systematic and comprehensive MR study to evaluate the causality of 1,400 human blood metabolites on NAFLD.

Currently, there is no universally recognized effective pharmacological treatment for NAFLD, making screening and prevention of NAFLD particularly crucial. Our research findings suggest that mannose is a factor that protects against NAFLD. Mannose, also known as D-mannose, is a C2 epimer of glucose, functioning as a reducing monosaccharide. It serves as a direct precursor for glycoprotein synthesis and plays significant physiological roles in immune modulation and obesity improvement [20-22]. Mannose has been found to regulate gut microbiota, and increase metabolic oxygen consumption, thus reducing weight and improving the risk of fatty liver [22]. Experiments have shown that D-mannose regulates key transcription factors in hepatic lipid metabolism through the PI3K/Akt/mTOR signaling pathway, exhibiting significant protective effects against hepatic steatosis [23]. Specific mechanisms include the upregulation of protein and mRNA levels of ACOX1, CPT1, and PPARα, enhancing fatty acid β-oxidation, and thereby reducing lipid accumulation in hepatocytes. However, recent research has found that inhibiting the fructose metabolism pathway and suppressing the expression of ketohexokinase (KHK) are key mechanisms by which mannose inhibits hepatic steatosis. Clinical trials both in vivo and in vitro have also confirmed mannose's efficacy as a KHK inhibitor in combating hepatic steatosis. Surprisingly, this finding aligns perfectly with our analysis using MetaboAnalyst, which revealed that mannose exerts its anti-hepatic steatosis effects through the fructose metabolism pathway, providing a mutually reinforcing validation.

Mannonate is a derivative of mannose, and currently, existing research on the function of mannonate in NAFLD is limited. However, considering the relationship between mannonate and mannose, it is plausible that mannonate may have similar effects on hepatic lipid metabolism. A recent metabolomics study of 2,535 male NAFLD patients found that the NAFLD susceptibility gene variant GCKR (glucokinase regulatory protein gene) is statistically negatively correlated with both mannonate and mannose, and the GCKR variant increases the risk of NAFLD through increased acetyl-CoA generation and de novo lipogenesis [24]. This study found a negative causality between mannonate and the risk of NAFLD, consistent with the aforementioned research conclusions. However, due to the lack of direct evidence, additional investigation is required to elucidate the potential involvement of mannonate in the occurrence and progression of NAFLD, and specific protective mechanisms necessitate further exploration.

Caffeine is primarily metabolized in the liver through cytochrome p451 1A2 (CYP1A2), forming paraxanthine, also known as 1,7-dimethylxanthine, which is the major metabolite of caffeine in the body [25]. Previous animal experiments have found that coffee consumption can significantly improve and prevent hepatic steatosis, fibrosis, inflammatory infiltration, and swelling. A meta-analysis of clinical studies has also confirmed that regular coffee drinkers have a 29% reduced incidence of NAFLD compared to non-coffee drinkers. However, the mechanism of coffee's protective effect against hepatic steatosis is currently unclear, possibly achieved through its metabolites, with paraxanthine being the primary metabolite of coffee. It's well known that the conversion of caffeine to paraxanthine occurs entirely through the N-3 demethylation pathway mediated by CYP1A2. Studies have found that the activity of CYP1A2 is negatively correlated with the severity of NAFLD [26-30]. Animal experiments have also confirmed that the activity of CYP1A2 is suppressed in animal models of NAFLD. Currently, the determination of paraxanthine to caffeine ratio in blood is widely used to assess the activity of CYP1A2 [31-33]. Thus, the paraxanthine to caffeine ratio is a protective factor for NAFLD. This analysis, from a genetic perspective, found that the caffeine to paraxanthine ratio is a risk factor for NAFLD, which is consistent with the aforementioned findings.

This study has several strengths. Initially, this 1,400 metabolite MR study is the most exhaustive to date in examining the causality between blood metabolites and NAFLD. Furthermore, we performed a replication study using two NAFLD datasets from GWAS, significantly increasing the reliability and accuracy of our findings. Finally, pleiotropy was ruled out through sensitivity analysis, highlighting the statistical robustness.

Nonetheless, we recognize that this study has some inherent limitations. In the first place, all of the datasets were obtained from the European, which largely avoids heterogeneity. However, these conclusions should not be extrapolated to another ethical group without additional validation. Furthermore, although we confirmed the causality between three blood metabolites and NAFLD using MR methods, the specific mechanisms of action require deeper investigation.

In summary, the findings of this research indicate that mannose and mannonate have a protective effect on NAFLD, but CAF/PX ratio acts as a risk factor of NAFLD. This provides valuable clues for early screening, prevention, and treatment of NAFLD.

Materials and Methods

An exhaustive assessment of 1,400 serum metabolites with the risk of NAFLD was carried out based on a rigorously designed Mendelian randomization framework. For an MR study to be scientifically valid, it must follow three main assumptions: Firstly, the genetic instrument must have a strong connection with the exposure; secondly, the genetic variants must not be influenced by any other factors that could affect the outcome; thirdly, the genetic instrument should only impact the outcome through the exposure, and not through other risk factors or biological pathways.

Study population and Selection of Instrumental Variables (IVs)

The dataset for the exposure factor containing 1,400 human blood metabolites was sourced from the most comprehensive blood metabolite data to date, discovered by Chen et al. in 2023 from 8,299 individuals of European descent. A total of 1,091 metabolites (850 known and 241 unknown metabolites) and 309 metabolite

ratios were identified. The data for NAFLD as an outcome factor are derived from GWAS (GCST90091033) based on four European cohorts comprising 8,434 cases and 770,180 controls for primary analysis. To bolster the validity of our findings, we performed a secondary analysis using data from another European cohort for NAFLD, also obtained from GWAS (GCST90011885), comprising 1,483 cases and 17,781 controls.

To address assumptions, the following criteria for selecting instrumental variables related to blood metabolites were established. In light of the restricted quantity of single nucleotide polymorphism (SNPs), we set the significance threshold at 1.00E-05 with a linkage disequilibrium threshold (LD) or R2<0.1 over a 500kb range. Previous studies have extensively utilized and acknowledged these criteria. Furthermore, to validate the results and ascertain the reliability of IVs, we eliminated those lacked strength by computing the F statistic for every SNP. The following equation represents the F statistic: F=(β/SE)2. F statistic values <10 were considered weak IVs and discarded. Finally, we excluded from the dataset the SNPs that were significant about to the outcomes (p<1x10-5). Subsequently, harmonization was employed to synchronize the alleles of the exposure and the outcome SNPs. Eventually, further MR analysis was conducted using these residual metabolites.

MR and Sensitivity Analysis

MR analyses were performed with the "TwoSampleMR" package in R version 4.3.1. A significance level of p<0.05 was deemed to have statistical significance. Odds ratio (OR) and 95% confidence intervals(95%CI) were used as the primary effect measures. The principal analytic strategy used to evaluate the causality between blood metabolites and NAFLD was the inverse variance weighted (IVW) method. The decision to choose IVW is based on its capacity to offer the most accurate estimations by consolidating the Wald ratios of all genetic variations, assuming the efficacy of all SNPs. The study utilized the weighted median (WM) and MR-Egger approaches as additional measurements to corroborate the findings. To account for the possibility of incorrect positive results in multiple hypothesis testing, false discovery rate (FDR) correction was used to adjust the IVW estimates of metabolites. A threshold of FDR <0.05 was utilized to identify metabolites causally linked to NAFLD. Secondary analysis was conducted to enhance the precision and reliability of the results.

Cochran's Q test is employed to evaluate the heterogeneity of SNP estimates. Horizontal pleiotropy is assessed by MR-Egger intercept and MR-Pleiotropy residual sum and outlier (MR-PRESSO) [26]. Horizontal pleiotropy is considered present when the outcome of MR-Egger deviates significantly from 0. If the global p-value of MR-PRESSO < 0.05 indicates horizontal pleiotropy. To determine if MR estimates are influenced by individual SNPs, Loo analysis was also conducted, whereby each SNP is sequentially removed, and MR analysis is performed to assess whether the results are significantly affected by individual SNPs. Furthermore, the Steiger directionality test was employed to confirm whether the observed causal relationship is biased due to reverse causation [34-36]. This test determines if the included SNPs explain variability in NAFLD better than the detected metabolites. An analysis with MetatoAnalyst 6.0 was conducted to explore the correlation between metabolic pathways and NAFLD [37,38].

Acknowledgements

Genetic instruments for all blood metabolites were obtained from Dr. Yiheng Chen's publication in Nature Genetics in 2023. Genetic association estimates for NAFLD were obtained from the published GWASs. The authors are thankful to all the participants and investigators for sharing their data.

Additional Information

Competing interests

The authors declare no conflict of interest.

Funding

This study was supported by the 2024 Zhengzhou Municipal Science and Technology Innovation Guidance Program Project in the Medical and Health Field (Grant No.: 2024YLZDJH385) from the Zhengzhou Science and Technology Bureau References

Author Contributions

D. J., Data curation, software, formal analysis, investigation, visualization, writing-original draft; S. J., Data curation, software, conceptualization, validation.

Ethics

Human subjects: Because Mendelian Randomization analyses used secondary, genome-wide association data from research that had ethical permission from review boards and/or ethics committees and informed consent from all participants, they did not require ethical approval.

Data Availability

We utilized data for 1,400 blood metabolites from the paper published by Dr. Yisheng Chen in Nature Genetics and two data for NAFLDs from GWAS with accession numbers provided in the main text, all of which are publicly available. All analyses were performed using R statistical package freely available at https://cran.r-project.org/ mirrors.html. The CAUSE R package and instructions are available at https://jean997. github.io/cause/. The Two-sample MR package is available at https://mrcieu.github.io/TwoSampleMR /.The code for the current analysis is available by request.

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