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Original Article

Assessing the causal relationship between blood metabolites and low back pain: a Mendelian randomization study

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Abstract: Aim: Low back pain (LBP) is one of the most common health problems worldwide. This study aimed to determine whether blood metabolites were causally linked to the risk of LBP. Methods: Based on summary-level genome-wide association studies, we designed a Mendelian randomization (MR) study. Instrumental variables were selected for each blood metabolite with the following criteria: genome-wide significance levels of $< 5e^{-8}$ and independent clumping ($r^2 < 0.001$, distance < 10,000 kb). Inverse-variance weighting (IVW) was used as the primary statistical method. The weighted median (WM) method and MR-Egger regression were implemented to complement IVW. Subsequently, sensitivity analyses were conducted, including Cochran's Q test, MR-Egger intercept analysis, scatter plots, leave-one-out analysis, and funnel plots. Results: IVW revealed that higher levels of lactate (odds ratio [OR] = 0.974, 95% confidence interval [CI] 0.953-0.995, P = 0.017), medium low-density lipoprotein triglycerides (OR = 0.990, 95% CI 0.983-0.997, P = 0.005) and albumin (OR = 0.985, 95% CI 0.973-0.998, P = 0.019) had a causal effect on decreased risk of LBP, whereas positive causality was detected between genetic predisposition to tyrosine and LBP (OR = 1.016, 95% CI 1.001-1.032, P = 0.043). Estimates from WM and MR-Egger were consistent with the direction of the IVW method. Additionally, there was no evidence of heterogeneity or pleiotropy in this study. Conclusion: This MR study demonstrated that four blood metabolites were causally related to LBP. It is possible to enhance the diagnosis of LBP, prognostic outcome predictions, and the personalization of therapy by analyzing novel signatures of metabolites.

Keywords: Metabolites, low back pain, Mendelian randomization, causality

Introduction

Low back pain (LBP), one of the non-specific consequences of musculoskeletal diseases, presents with diverse pain types, such as nociceptive, neuropathic, and nociplastic pain [1]. Originating from the lumbar area components, untreated LBP hinders daily activities, causing reduced mobility and chronic discomfort [1]. The 2019 Global Burden of Disease study emphasized LBP's consistent rank among the top 10 health concerns for 30 years, affecting people of all ages [2, 3]. Back pain could result in billions of dollars in economic costs along with intangible expenses, such as difficulties performing household duties, caring for others, and participating in recreational activities as well as relationship crises, despair, and anxiety [4-6]. This underlines the importance of early diagnosis, intervention, and sustained research to address its prevalence and impact.

In light of the established understanding of blood circulation, it is pertinent to note that the influence of blood metabolites on the inception and evolution of diseases has emerged as a salient topic in contemporary research. Leveraging high-throughput techniques, metabolomics has identified a wide range of small molecules, including amino acids, carbohydrates, lipids, peptides, and organic acids, among others [7]. Concurrently, as information technology advances, metabolomics may provide insights into physiologic conditions and aberrant processes. Notably, recent findings emphasize the pivotal influence of specific metabolites in the pathogenesis of LBP [8-10]. For instance, meta-analyses have identified an

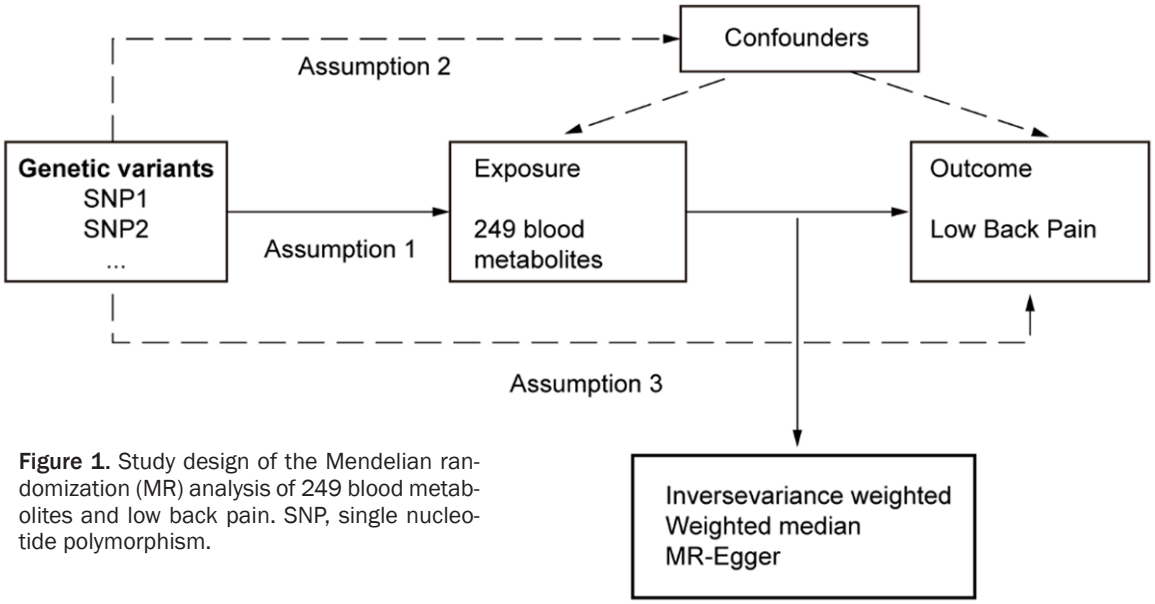

Figure 1. Study design of the Mendelian randomization (MR) analysis of 249 blood metabolites and low back pain. SNP, single nucleotide polymorphism.

association between significant reductions in 25(OH)D concentrations and a variety of chronic pain conditions [9]. Additionally, the Mendelian randomization (MR) method has been used to demonstrate that in the European population, genetically higher levels of omega-3 fatty acids are associated with a reduced risk of LBP [10]. As far as we know, however, there is a dearth of systematic and comprehensive studies evaluating the causal effects of blood metabolites on LBP.

Although randomized controlled trials (RCTs) have been widely regarded as the gold standard for determining causal relationships, they may not eliminate confounding factors and reverse causality [11, 12]. Furthermore, RCTs are often impractical, expensive, and even unethical due to their duration, cost, and time constraints. Utilizing genetic instrumental variables, MR serves as an analytical method to assess causality that might be obscured by confounders or vulnerable to reverse causality. MR provides an effective and reliable way to investigate the causal association between blood metabolites and LBP by leveraging environmental exposure-related genetic variations (instrumental variables, IVs).

Using the summary data from published genome-wide association studies (GWAS) in conjunction with MR analysis, we investigated the potential causal relationship between blood metabolites and the risk of LBP in this study.

Methods

Study design

In this MR study, the aim was to examine whether blood metabolites contribute to LBP development based on the summarized GWAS datasets in order to determine the causal effects. Three presumptions must be met for this MR design to work: (i) genetic instruments predict the interest exposure ($P = 5 \times 10^{-8}$), (ii) genetic instruments are not linked to possible confounders, and (iii) genetic instruments only have an impact on the outcome through risk factors. Inverse-variance weighting (IVW) was used for the main analysis to evaluate the causal effects of blood metabolites on LBP, along with the weighted median (WM) method, MR-Egger regression, and WM-Egger regression to increase the robustness of the causal findings. Additionally, the above results were subjected to sensitivity analyses, such as Cochran's Q test, MR-Egger intercept analysis, scatter plots, leave-one-out (LOO) analyses, and funnel plots. The study frame chart in **Figure 1** illustrates the process.

Data sources

For the primary analysis, a total of 249 metabolite GWAS datasets were extracted from the Nightingale Health Metabolic Biomarkers Phase 1 Study, including 115,078 randomly selected participants from the UK Biobank

cohort. The MR Base website and the IEU GWAS project website provide a complete list of summary statistics using the accessing ID (met-d). In total, over 12.3 million single nucleotide polymorphisms (SNPs) were preserved for downstream analysis. In addition, GWAS summary data were retrieved with the accessing ID from the MRC-IEU consortium, which represents a large private-public partnership encompassing 461,857 European participants, including 118,471 LBP cases and 343,386 controls.

IV selection

SNPs associated with metabolites required *p*-values < 5×10^{-8}, linkage disequilibrium (r^2 < 0.001), Hardy-Weinberg equilibrium, and genetic distance < 10,000 kb. Each SNP was then genotyped to determine its major alleles, allele frequencies, *p*-values, and standard errors. Previous MR studies demonstrated the effectiveness and accuracy of model estimation when IVs are applied to high-strength models. As a precaution against bias caused by weak proxies, the F-statistic was calculated for each instrument. An F-statistic of 10 was not found for any IV. Finally, Table S1 summarizes all the data related to the SNPs in detail. The selected procedures were similar to those of a previous study [13].

Mendelian randomization (MR) analyses

Three MR analytical methods were used in this study to assess the causal effects of blood metabolites on LBP in order to address the potential pleiotropy of genetic variants. A detailed MR analysis was carried out by using the IVW method as the primary analysis. As complementary methods in case the IV assumptions could not be fully satisfied, the WM and MR-Egger methods were also used to provide more robust estimations [14, 15]. There is considerable heterogeneity and unbalanced pleiotropy in the MR-Egger regression; however, it requires a larger sample size for the same underexposure variation [16]. If horizontal pleiotropy is valid for at least half of the variance of the data set, then a WM method can be used to estimate the effect consistently [17]. Furthermore, a strict threshold was set for the instrument *p*-value, and the results of different MR analyses were recalculated if the results of the different analyses were inconsistent [18].

Several sensitivity analyses, including Cochran's Q statistic, funnel plots, LOO analyses, and MR-Egger intercept tests, were performed to determine whether any pleiotropic effects were present in the MR studies and to assess the robustness of the results. To detect heterogeneity in the IVW approach, Cochran's Q test was used, and the intercept from the MR-Egger regression was used as an indicator of horizontal pleiotropy (the intercept with a *p*-value of 0.05 was taken as a sign of horizontal pleiotropy) [15, 16]. A LOO analysis was performed to determine whether a single SNP is driving the MR estimate in one direction or the other. To satisfy presumption iii, we conducted a SNP search with a phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk) for the significant estimates. We removed the SNPs associated with LBP confounders (obesity and bone diseases) and re-performed MR without those SNPs associated with the confounders.

The MR estimates presented in the paper were expressed in the form of odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The analyses were conducted using TwoSampleMR (version 0.4.25) in R (version 3.6.1).

Results

Primary analysis

Four kinds of blood metabolites were causally associated with the development of LBP in the univariable MR with 249 metabolic traits. As shown in **Table 1**, the presence of lactate was universally inversely associated with the risk of LBP based on the IVW estimates (OR = 0.974, 95% CI 0.953-0.995, P = 0.017) and WM methods (OR = 0.961, 95% CI 0.932-0.990, P = 0.009). The MR-Egger estimates (OR = 0.988, 95% CI 0.879-1.111, P = 0.851) also exhibited a direction consistent with that of the IVW estimates. Moreover, medium low-density lipoprotein triglycerides (M-LDL-TG) were also found to decrease the risk of LBP using IVW analysis (OR = 0.990, 95% CI 0.983-0.997, P = 0.005). Estimates from the WM (OR = 0.994, 95% CI 0.986-1.002, P = 0.162) and MR-Egger methods (OR = 0.991, 95% CI 0.980-1.003, P = 0.138) were consistent with the direction of the IVW method (**Table 1**). In addition, using 24 SNPs as IVs, the MR analysis from the three models supported the notion that albumin

Table 1. Significant MR estimates from 123 blood metabolites on low back pain experienced

Exposure	Methods	nSNP	MR estimates		Heterogeneity		Pleiotropy	
			OR (95% CI)	P	Cochran Q	P	Intercept	P
Lactate	IVW	7	0.9744 (0.953-0.995)	0.017	6.126	0.409	-0.0005	0.813
	WM	7	0.961 (0.932-0.990)	0.009				
	MR Egger	7	0.988 (0.879-1.111)	0.851				
M_LDL_TG	IVW	54	0.990 (0.983-0.997)	0.005	92.960	0.0006	-6.85e-05	0.842
	WM	54	0.994 (0.986-1.002)	0.162				
	MR Egger	54	0.991 (0.980-1.003)	0.138				
Tyrosine	IVW	26	1.016 (1.001-1.032)	0.043	74.299	8.68E-07	0.0001	0.840
	WM	26	1.011 (0.997-1.024)	0.115				
	MR Egger	26	1.014 (0.988-1.040)	0.315				
Albumin	IVW	24	0.985 (0.973-0.998)	0.019	44.392	0.005	0.0005	0.227
	WM	24	0.980 (0.967-0.993)	0.003				
	MR Egger	24	0.976 (0.957-0.995)	0.022				

nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; M-LDL-TG, medium low-density lipoprotein triglycerides; IVW, inverse-variance weighting; WM, weighted mean; MR, Mendelian randomization.

might be a protective factor for LBP (IVW OR = 0.985, 95% CI 0.973-0.998, P = 0.019; WM OR = 0.980, 95% CI 0.967-0.993, P = 0.003; Egger OR = 0.976, 95% CI 0.957-0.995, P = 0.022). Notably, the IVW estimates showed that there is a positive causal relationship between genetic predisposition to tyrosine and LBP (OR = 1.016, 95% CI 1.001-1.032, P = 0.043). The *p*-value was very close to 0.05, and conclusions of causality should be made with caution. As for the other MR methods, the results showed a consistent but non-significant direction (WM OR = 1.011, 95% CI 0.997-1.024, P = 0.115; Egger OR = 1.014, 95% CI 0.988-1.040, P = 0.315). The calculated estimates about other blood metabolites are shown in Table S2.

Sensitivity analyses

Sensitivity analyses, including Cochran's Q test for heterogeneity and MR-Egger regression for pleiotropy, were conducted to evaluate whether the results described above were robust (**Table 1**). All of the *p*-values for the MR-Egger intercept tests were greater than 0.05, indicating that there was no horizontal pleiotropy present in the dataset. Although the heterogeneity between lactate and LBP (Q = 6.126, P = 0.409) was not present in our outcomes, heterogeneity was present in the Q test analysis between LBP and M-LDL-TG (Q = 92.960, P = 0.0006), tyrosine (Q = 74.299, P = 0.01), and albumin (Q = 44.392, P = 0.005). Tables S3 and S4 summarize the results of the pleiotropy test and the heterogeneity test. Despite the heterogeneity detected in some of the results, the MR estimates as random-effect IVW were not invalidated by heterogeneity, which may have balanced the pooled heterogeneity. The scatter plots in **Figure 2** illustrate the estimates of four kinds of blood metabolites. The LOO analysis found that no SNP was driving the results, and the funnel plots were symmetrical, indicating that none of the estimates were violated, which is consistent with the results of our previous analysis (**Figures 3** and **4**). The phenoscanner results of the IVs of significant estimates are presented in Table S5. Twenty-eight SNPs correlated with confounders were removed (Table S6). The MR estimates after removing the outliers remained significant, consistent with previous findings (Table S7).

Discussion

In this study, multiple MR approaches were implemented to assess whether blood metabolites may be causally associated with LBP using data collected from GWAS in the UK Biobank. MR estimates of lactate, M-LDL-TG, and albumin levels in this study showed a causal effect on lowering the risk of LBP. By contrast, genetic predisposition to tyrosine had a positive causal effect on LBP development. As far as we know, this is the first MR study that systematically assessed the causal role of human blood metabolites in LBP.

In light of the heavy burden of back pain and the unclear pathophysiological cause, there are

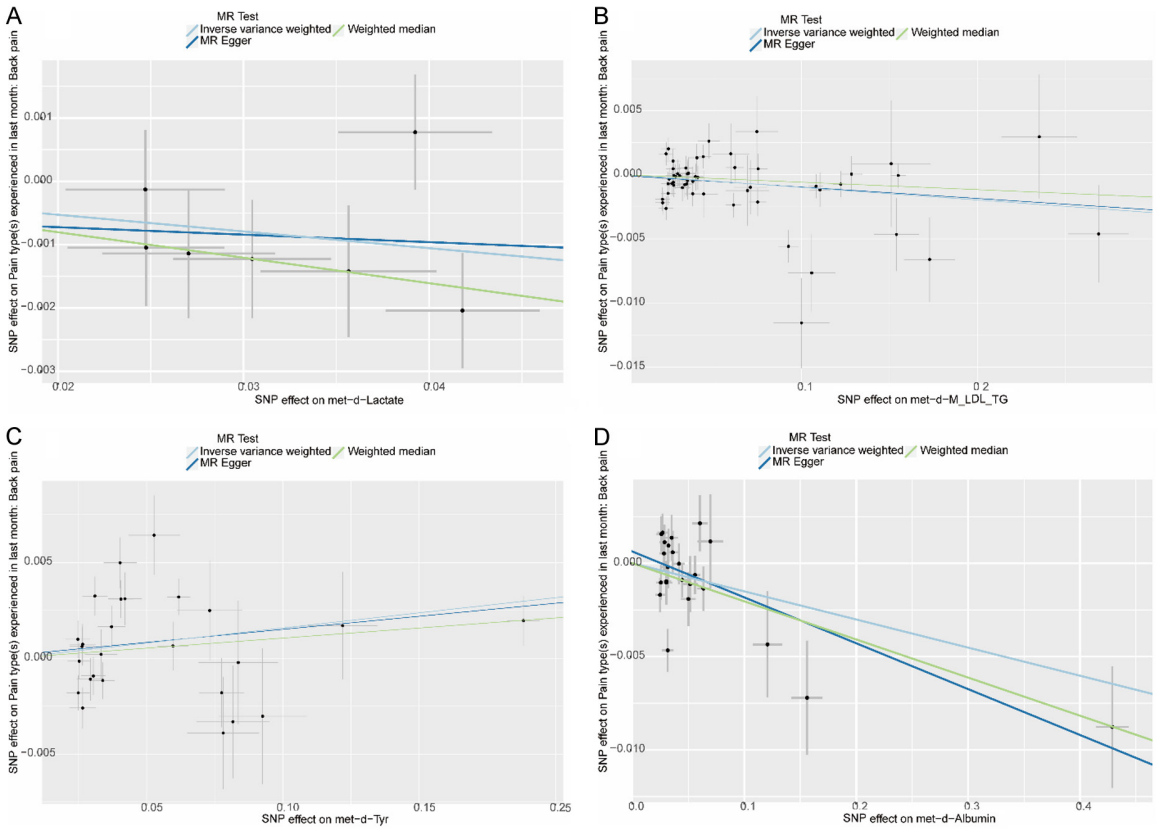

Figure 2. Scatter plots and leave-one-out analysis of the effect of (A) lactate, (B) medium low-density lipoprotein triglycerides (M-LDL-TG), (C) tyrosine, and (D) albumin on low back pain. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

still no specific treatments. To prevent LBP and diagnose it early, it is imperative to discover its modifiable risk factors. Recent noteworthy advancements in high-throughput technologies and the ability to perform genotyping in parallel on large populations have allowed us to measure hundreds of circulating metabolites and determine their genotype with great accuracy [19, 20]. Multiple studies have also underscored the association between blood metabolites and LBP. Silva et al., analyzing over 9,000 participants, linked inadequate vitamin D levels with higher LBP incidence, advocating for the benefits of 25(OH)D in LBP treatment [21]. Using MR analyses, another study found that genetically increased plasma omega-3 concentrations in a European population were associated with a reduced risk of LBP but did not propose a causal association, further supporting the theory that omega-3 supplementation can reduce systemic inflammation in the body and thus protect against the progression of LBP [10]. Overall, metabolomics has emerged as a field of research that is rapidly advancing the diagnosis and treatment of LBP. Although the literature indicates that metabolic disturbances contribute to the development of LBP, evidence of the causal involvement of circulating metabolites cannot conclusively be established. Metabolomics is a field of study that explores the changes that high-molecular-weight molecules undergo under physiological and disease conditions as well as after treating those conditions with drugs. In metabolic profiling, plasma has been the main source of metabolites because it is commonly considered a pool of metabolites [22]. To unravel the metabolic coding that underlies the pathogenesis of LBP and find a novel direction for identifying and treating LBP in the future, we conducted this MR study to investigate the causal connection between blood metabolites and LBP on a systematic basis.

Intriguingly, integrating metabolomics and GWAS, our results first provided a systematic

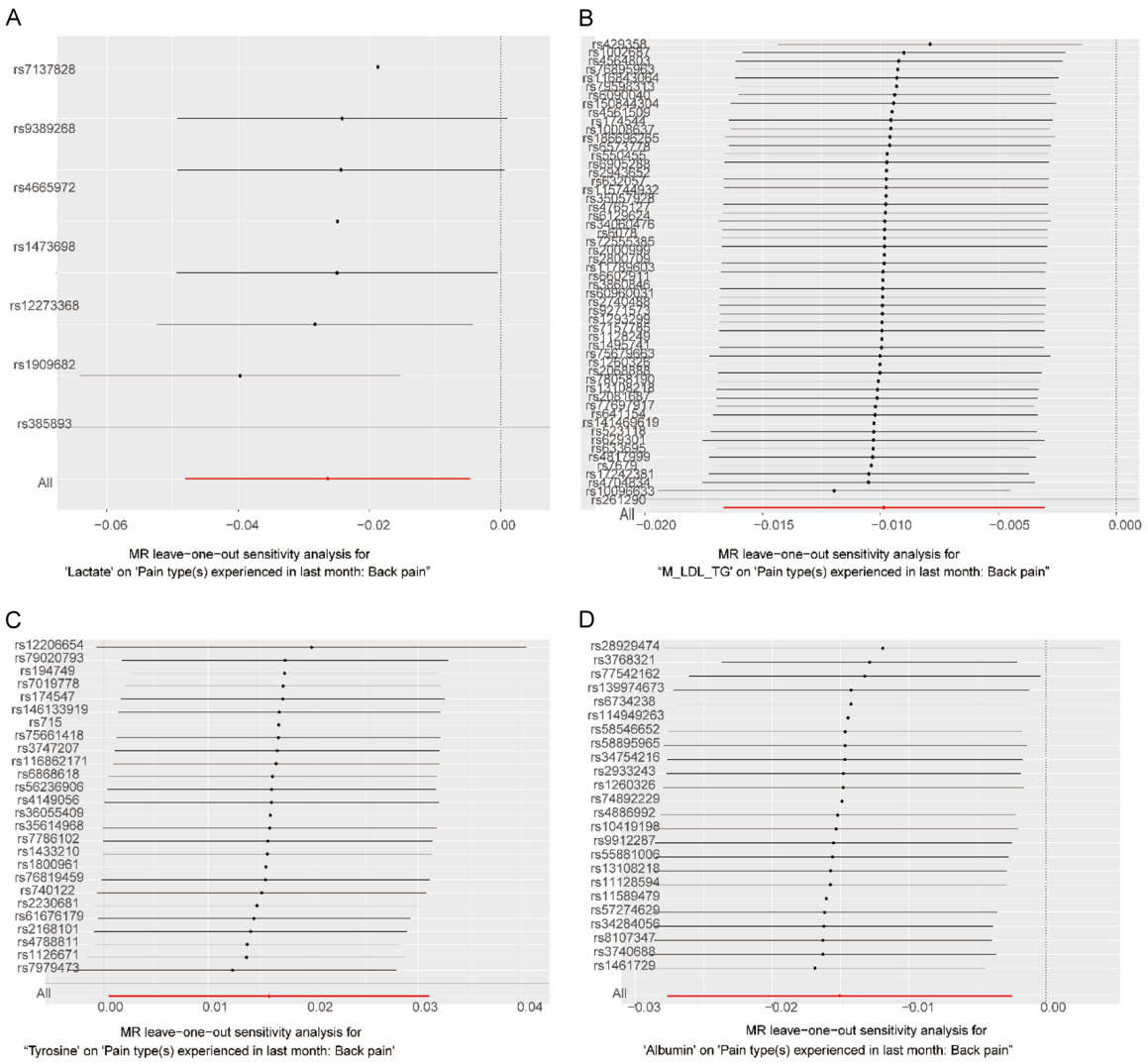

Figure 3. Leave-one-out analysis of the effect of (A) lactate, (B) medium low-density lipoprotein triglycerides (M-LDL-TG), (C) tyrosine, and (D) albumin on low back pain. MR, Mendelian randomization.

demonstration that blood metabolites are causally associated with LBP. According to the current study, higher levels of triglycerides in the blood are causally associated with a decreased risk of LBP. It should be noted, however, that several other studies have provided evidence to the contrary. Using large-scale data from annual health checkups in Japan, Takahiko et al. found that low levels of high-density lipoprotein cholesterol were significantly associated with LBP [23]. Many confounding factors may have been responsible for the inconsistent findings in these studies, such as the design of the studies and the populations studied. MR analysis allows for the inference of causal relationships by using genetic instruments in a potential causal mode of inference to avoid bias associated with confounding factors and estimate the magnitude of the putative causal relationship in the context of different circumstances while minimizing the impact of confounding factors. Further, multiple studies have demonstrated that obesity and overweight play a significant role in the onset of intervertebral disc degeneration in the spine, the causality of which was confirmed by MR analysis [24]. A meta-analysis of 10 cohort studies that included 29,748 subjects showed that overweight and obesity are risk factors for the development of LBP in both male and female individuals [25]. This difference indicates that we should be more careful in interpreting and

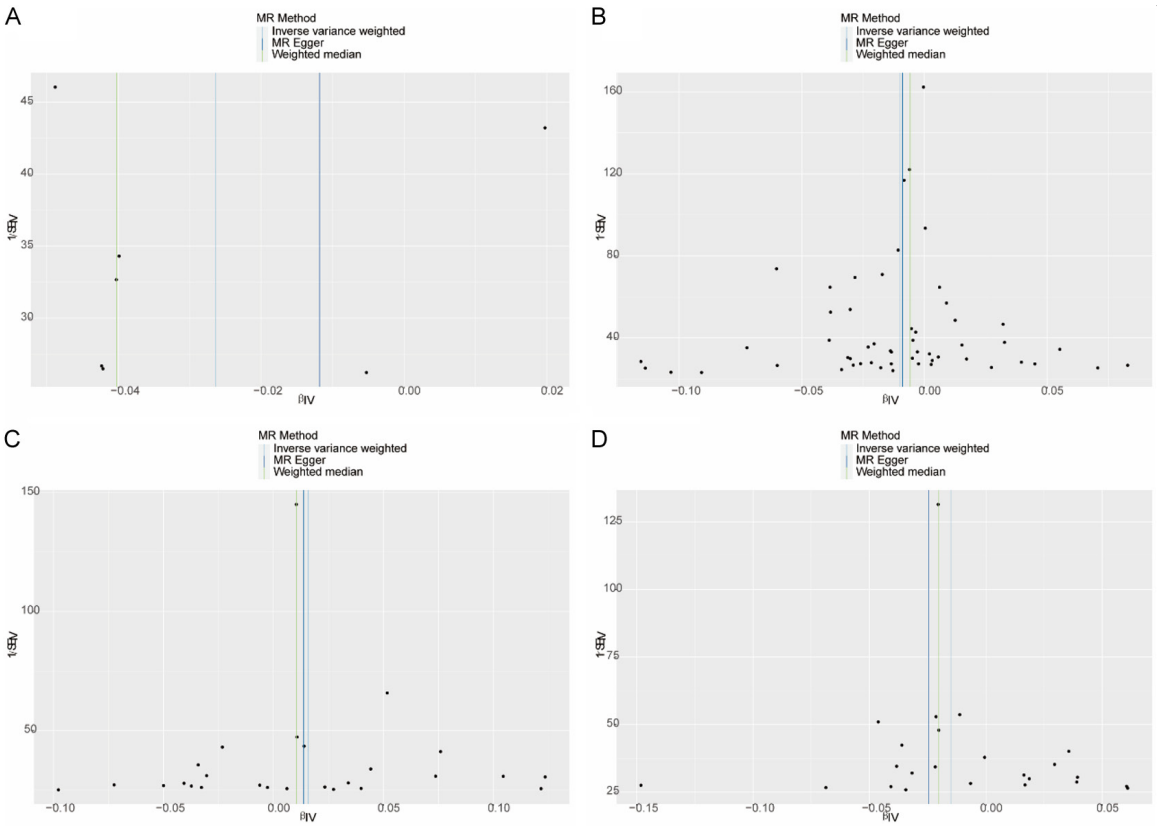

Figure 4. Funnel plots of the effect of (A) lactate, (B) medium low-density lipoprotein triglycerides (M-LDL-TG), (C) tyrosine, and (D) albumin on low back pain. MR, Mendelian randomization.

applying the negative causality between triglycerides and LBP. It is a pity that little research has focused on the relationship between these metabolites - lactate, albumin, and tyrosine - in LBP development; thus, further work is warranted to decipher the underlying mechanisms. In general, we would like to introduce the field of "LBP metabolomics" and show how the application of integrative "omics" approaches can lead to the discovery of biomarkers for complex traits, thus paving the way for future studies to investigate how diseases are induced and how patients can be provided with a more personalized form of care. In particular, comprehensive metabolomics profiles not only elucidate the etiology of LBP but also enhance the early diagnosis, prognosis prediction, and personalized treatment of LBP. In addition, potential targets and drug treatments can be identified by regulating metabolic indicators and their regulated enzymes.

This study has several strengths. To the best of our knowledge, by exploring the extensive variety of blood metabolites, this study provides novel information on the regional alterations associated with LBP markers as it is the first comprehensive and systematic exploration of the causal relationship between blood metabolites and LBP. Second, the GWAS datasets for LBP and serum metabolite genetic IVs come from a European population, thereby avoiding the effects of population stratification. Moreover, a series of methods were incorporated in our study to eliminate reverse causality and residual confounding factors as a result of the MR design. Last but not least, another advantage of the chosen GWAS dataset is its large sample size, with millions of detected SNPs, representing a substantial statistical enhancement over previous GWAS datasets.

Nevertheless, several potential limitations should also be considered. First, because most of our GWAS summary statistics were derived from patients of European ancestry, we can not necessarily generalize our findings to those of other ancestries. Second, we only analyzed one GWAS dataset for LBP. It would be better to collect a large number of GWAS datasets regard-

ing LBP in order to prove our conclusion. Further disadvantages of the MR method include the assumption that each patient was exposed to radiation for the entirety of their life, which might not be the case in the real world. This means that it may be necessary to value the direction of the causal effect more than its magnitude and that the magnitude of the estimated levels should not be overestimated or underestimated. In addition, our findings would be strengthened by larger GWAS and RCTs conducted in the context of LBP and metabolic measurements in an effort to identify more potential risk factors. Moreover, the underlying mechanisms that are connected to blood metabolites and LBP need to be explored further to establish a clearer picture of their role. Lastly, we unfortunately did not identify previously reported LBP-related metabolites. This may be due to disagreement regarding the standard diagnostic criteria between our study and previous studies, which would have led to different results.

Overall, the results of the present study suggest that genetic factors could be involved in the association between LBP and blood metabolites. For LBP screening and prevention in clinical practice, lactate, triglycerides, albumin, and tyrosine may be useful circulating metabolic biomarkers for providing insights into the treatment and prevention of LBP. The underlying mechanisms that relate metabolites to LBP must still be elucidated, and future research may be necessary to continue this study.

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Disclosure of conflict of interest

None.

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