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Assessing the Genetic Causal Effects Between Blood Metabolites and Spinal Pain: A Bidirectional Two-Sample Mendelian Randomization Study

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Background: Previous metabolomics studies have indicated a close association between blood metabolites and pain. However, the causal relationship between blood metabolites and spinal pain (SP) remains unclear. This study employs a bidirectional two-sample Mendelian randomization (MR) analysis to evaluate the causal relationship between 452 blood metabolites and SP.

Methods: We used bidirectional two-sample MR analysis to assess the causal relationship between blood metabolites and SP, including neck pain (NP), thoracic spine pain (TSP), low back pain (LBP), and back pain (BP). Genome-wide association studies (GWAS) data for 452 metabolites (7,824 participants) were used as exposure variables. Summary data for NP were obtained from the UK Biobank, for TSP from the FinnGen Biobank, and for LBP from both the UK Biobank and the FinnGen Biobank. Summary data for BP were obtained from the UK Biobank. Inverse-variance weighting (IVW) was used to estimate the causal relationships between metabolites and SP, complemented by various sensitivity analyses to account for pleiotropy and heterogeneity, ensuring robust results.

Results: The IVW analysis identified 155 metabolites associated with SP risk and 142 metabolites influenced by SP. No significant heterogeneity or horizontal pleiotropy was observed through other analytical methods.

Conclusion: This study demonstrates potential causal effects between blood metabolites and SP, providing new insights into the pathogenesis of SP. These findings lay a theoretical foundation for preventing and treating SP through targeted interventions on specific blood metabolites, potentially elucidating underlying biological mechanisms.

Keywords: spinal pain, neck pain, thoracic spine pain, low back pain, back pain, blood metabolites, Mendelian randomization, causality

Introduction

The spine, as a vital structural pillar of the human body, bears essential functions such as supporting the body, protecting internal organs, and transmitting nerve signals, while also safeguarding the spinal cord, a crucial lifeline. SP is a broad term that typically refers to pain originating from the spine, which may be felt along the axial skeleton or its attachments.[1] SP is associated with substantial healthcare utilization and high disability rates worldwide.[2] Pain can originate from any part of the spine, including the cervical, thoracic, and lumbar regions, as well as the intervertebral discs and soft tissues between them, with a lifetime prevalence of 54–80%.[3] In the United States, the healthcare costs for treating SP have surged, with expenditures for low back pain alone exceeding three times the total costs for all types of cancer.[4,5] By 2020, the estimated healthcare costs for SP reached $134.5 billion.[6] When SP occurs, it not only leads to changes in body posture and limitations in mobility but may also be accompanied by neurological dysfunctions, such as

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sensory abnormalities and muscle weakness. These symptoms not only cause significant suffering for patients but also negatively impact their mental health and social functioning. Therefore, studying the mechanisms of SP, developing prevention strategies, and identifying new therapeutic targets are critically important and urgent in the field of public health.

Metabolites in the blood, as functional intermediates under environmental exposure, are not only products of the body's pathophysiological processes but also functional signaling molecules that participate in regulating cell proliferation, differentiation, and apoptosis. They often reflect the physiological state of an organism in response to genetic or environmental changes and can predict or influence the occurrence and progression of diseases.[7,8] A substantial body of research evidence indicates that dysregulation of blood metabolites is closely related to the development and progression of diseases across various disciplines and can serve as biological markers for disease risk diagnosis and treatment. These diseases include heart failure,[9] stroke,[10,11] fatigue,[12] and pain-related conditions.[13,14]

Previous studies have confirmed a close association between Modic changes (signal intensity variations in the vertebral endplates and adjacent bone marrow on MRI) and the occurrence and severity of low back pain. *Very low-density lipoprotein* in blood metabolites is identified as a potential risk factor for lumbar Modic changes.[15] Disturbances in serum amino acid metabolism are observed in patients with ankylosing spondylitis, thus metabolomics approaches are used to analyze differential metabolites and monitor the onset and progression of the disease.[16] These studies highlight the pathogenic role of blood metabolites in SP, establishing the field of "spine-metabolomics" and applying metabolomics to discover biological markers of spinal diseases. Using systems biology methods to analyze the biological basis of chronic widespread musculoskeletal pain including SP, *epiandrosterone sulfate* has been identified as a potential biological marker.[17] Additionally, exploratory research on chronic neck pain in women found that *plasma lysophosphatidylcholine* derived from *arachidonic acid* concentrations contribute to pain perception.[18] While multiple confounding factors such as age, behavior, and weight contribute to the onset of SP, these findings confirm a deterministic link between blood metabolites and SP occurrence. Metabolomic dysregulation in blood is likely a significant underlying cause of SP, suggesting the need to identify these relevant metabolites to pave the way for more personalized interventions for SP patients.

MR is a statistical method widely used in epidemiology and genetic epidemiology to assess the causal effects of exposure factors (such as lifestyle, environmental factors, or biomarkers) on outcome variables (such as disease or health outcomes), utilizing genetic variations as a basis for natural randomized experimental design.[19] The core advantage of MR lies in its clever utilization of naturally occurring random genetic variations during fertilization. This method essentially mimics a randomized controlled trial, significantly reducing biases from potential confounding factors like gender and age in causal analysis.[20] Additionally, genetic variants are established before disease onset and largely unaffected by disease progression, making them effective for assessing causal relationships between metabolites and SP.[21,22] Currently, while there is evidence suggesting the role of blood metabolites in SP, causal relationships have not yet been established.

In summary, this study collected data on blood metabolites and SP from genome-wide association study (GWAS) databases. Using MR analysis, it investigated the causal relationship between blood metabolites and SP. The study also identified relevant blood metabolites and proposed them as early intervention targets for the prevention and treatment of SP.

Materials and Methods

Study Design

This study employed bidirectional MR analysis to examine potential causal relationships between metabolites and four types of SP. We selected a set of single nucleotide polymorphisms (SNPs) known to indicate genetic variation aFirsts instrumental variables for the bidirectional MR analysis. According to Davies et al, the implementation of bidirectional MR requires strict adherence to three fundamental assumptions., instrumental variables, ie, genetic variations, should exhibit a robust association with the exposure factor. Second, genetic variations must be independent of confounding factors associated with both the exposure and the outcome. Third, genetic variations should affect the outcome (either

blood metabolites or SP) solely through the exposure rather than through other biological pathways.[23] The specific flowchart detailing the MR analysis is presented (Figure 1).

Data Sources

The blood metabolite data were sourced from Shin et al,[24] published in 2014 in the journal Nature Genetics. This study, known as the largest meta-genome-wide association study (mGWAS) to date, consolidated data from 7,824 individuals of European descent. It encompassed approximately 2.1 million single nucleotide polymorphisms and 452 blood metabolites (GWAS ID: met-a).

All GWAS summary statistics related to SP were meticulously obtained from the European OpenGWAS platform. This comprehensive database includes datasets for four main types of SP: NP (neck pain), TSP (thoracic spine pain), LBP (low back pain), and BP (back pain). After thorough review of the relevant datasets, we judiciously selected seven datasets for analysis. Specifically, our study incorporated two GWAS summary statistics for NP, considering durations of 1 month and over 3 months to distinguish between acute and chronic SP and their associations with blood metabolites. These two datasets are sourced from the UK Biobank (ukb-e). The GWAS summary statistics for TSP were obtained from the FinnGen biobank. Similarly, the GWAS summary statistics for LBP were sourced from the Finnish Genetics biobank. Recognizing that patients with low back pain often exhibit sciatica, we expanded our dataset to include one GWAS summary for low back pain with sciatica from the FinnGen biobank. Regarding BP categories, we selected two GWAS summary statistics from the UK Biobank (ukb-e) for analysis, comparing durations of less than 1 month and over 3 months. For detailed categorization of the summary statistics results, please refer to Supplementary Table 1.

Selection of Genetic Instruments

To ensure the accuracy and validity of causal inference between blood metabolites and SP, several steps were taken to select the most appropriate instrumental variables (IVs). Firstly, SNPs that were significantly associated with SP levels ($P<5\times10^{-6}$) were chosen as IVs.[25] Secondly, to address potential pleiotropy, selected SNPs underwent clustering analysis using a linkage disequilibrium threshold of <0.001 and a clustering distance of 10,000 kb to minimize linkage

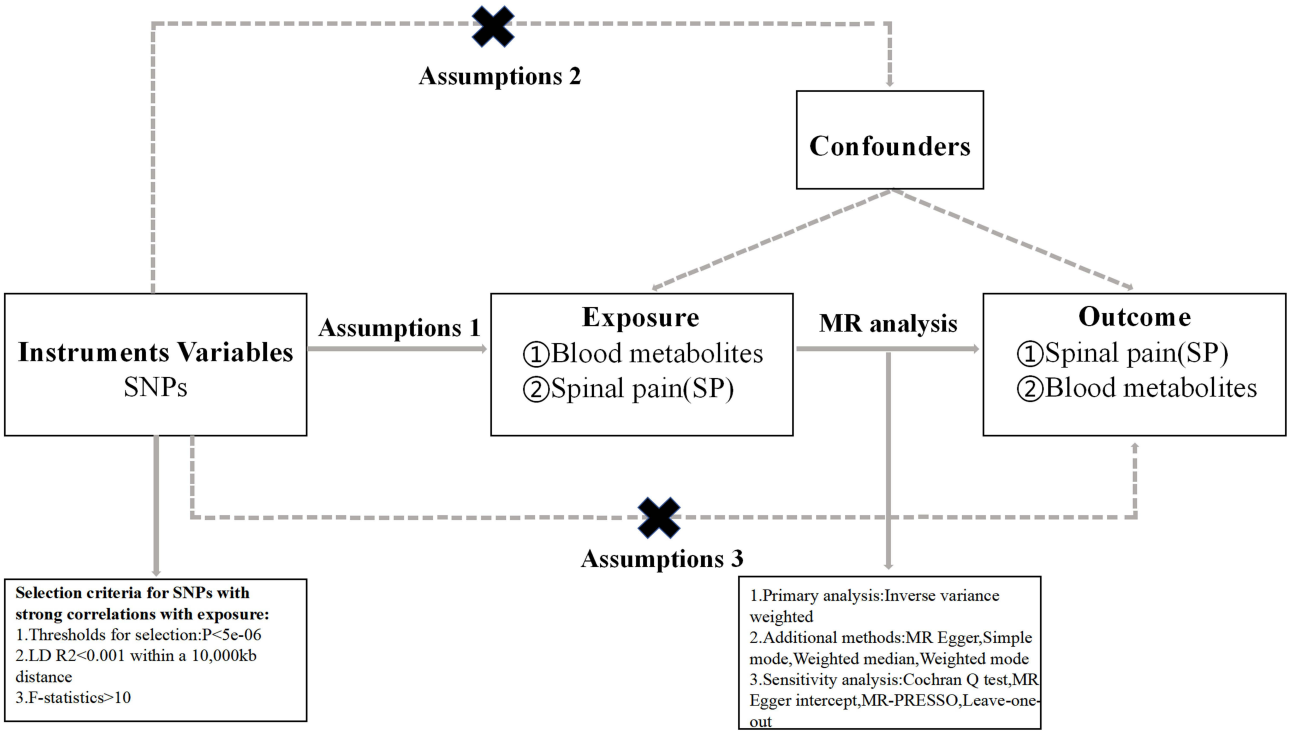


Figure 1 Three assumptions and flow chart for Mendelian randomization study.

disequilibrium.[26] Additionally, SNPs with an F-statistic less than 10 were excluded to eliminate weak instrumental variables. Finally, a meticulous harmonization process aligned the effects of exposure and outcome SNPs. This involved excluding incompatible alleles (eg, A/C paired with A/G) or those showing intermediate allele frequencies. These steps were crucial in ensuring robust MR analysis and minimizing biases in inferring causal relationships between blood metabolites and SP.

Statistical Analysis

The causal relationship between blood metabolites and SP was primarily analyzed using the Inverse Variance Weighted (IVW) method. A P-value less than 0.05 from the IVW analysis suggests a potential causal relationship between blood metabolites and SP. However, the validity of this conclusion relies on the absence of horizontal pleiotropy and heterogeneity.[27] Therefore, various sensitivity analysis methods were employed to examine the potential presence of horizontal pleiotropy and heterogeneity. All statistical analyses mentioned were conducted using the R programming language (version 4.2.3). R packages utilized included "Two sample MR", "forest plot", and "MRPRESSO". These packages were instrumental in performing rigorous statistical analyses to ensure robustness and reliability in inferring the causal relationship between blood metabolites and SP. The results of MR Analysis are shown in Supplementary Tables 2–15.

Sensitivity Analyses

IVW and MR-Egger's Q test were employed to detect heterogeneity in associations among individual IVs, potentially violating assumptions. When the P-value exceeds 0.05, the included instrumental variables are considered non-heterogeneous. In cases where significant heterogeneity ($P < 0.05$) is observed, a random effects model is utilized instead of the default effect model. MR-Egger uses its intercept estimate to gauge horizontal pleiotropy, ensuring genetic variants are independently associated with exposure and outcome. A P-value exceeding 0.05 suggests minimal likelihood of genetic pleiotropy in causal analysis. This study utilized leave-one-out method to assess the likelihood of observed associations being driven by individual SNP drivers.[28]

Results

Causal Effects of Blood Metabolites on SP

Causal Effects of the Blood Metabolites on Neck Pain

Based on the IVW analysis results, we identified 10 blood metabolites that have protective effects against NP in the last month (Figure 2 and Table 1): *Hydroxyisovaleroyl carnitine, X-14205–alpha-glutamyltyrosine, 1-eicosatrienoylglycerophosphocholine*Pyroglutamine*X-12443, X-12441-12-hydroxyeicosatetraenoate (12-HETE), Isobutyrylcarnitine, X-14588, Beta-hydroxyisovalerate, and Choline. Additionally, we identified 18 blood metabolites that act as risk factors for NP in the last month: X-10395, Hexadecanedioate, Docosapentaenoate (n3 DPA; 22:5n3), Allantoin, 1-palmitoylglycerophosphoethanolamine, X-14626, X-12230, Laurate (12:0), Arachidonate (20:4n6), 1-oleoylglycerophosphoethanolamine, X-12680, X-11470, X-12407, Glutamate, X-13658, Androsterone sulfate, Cyclo(leu-pro), and X-13431–nonanoylcarnitine**. Furthermore, IVW estimation indicated that blood metabolites such as *3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF), X-11850, Myristate (14:0), Glycine, Citrate, Deoxycholate, Creatine, X-13741* are associated with increased risk of NP for 3+ months. In contrast, blood metabolites including *X-12029, Hypoxanthine, X-12236, X-14205–alpha-glutamyltyrosine, X-12100–hydroxytryptophan*Glutamate, Eicosenoate (20:1n9 or 11), Choline, X-11793–oxidized bilirubin*X-13671, X-12040, and X-12847* are associated with decreased risk of NP for 3+ months.

Causal Effects of the Blood Metabolites on Thoracic Spine Pain

The IVW screening results reveal that 10 blood metabolites are positively correlated with TSP (Figure 3 and Table 2): *Phenylalanylphenylalanine, Gamma-glutamylglutamate, Cysteine, Hyodeoxycholate, Phenyllactate (PLA), Nonadecanoate (19:0), X-12645, Linoleate (18:2n6), Cysteine-glutathione disulfide, and X-13431–nonanoylcarnitine**. Genetic predictions show that 5 metabolites are negatively correlated with TSP: *X-01911, Phenol sulfate, 1-linoleoylglycerophosphocholine, Stearate (18:0), and Stachydrine*.

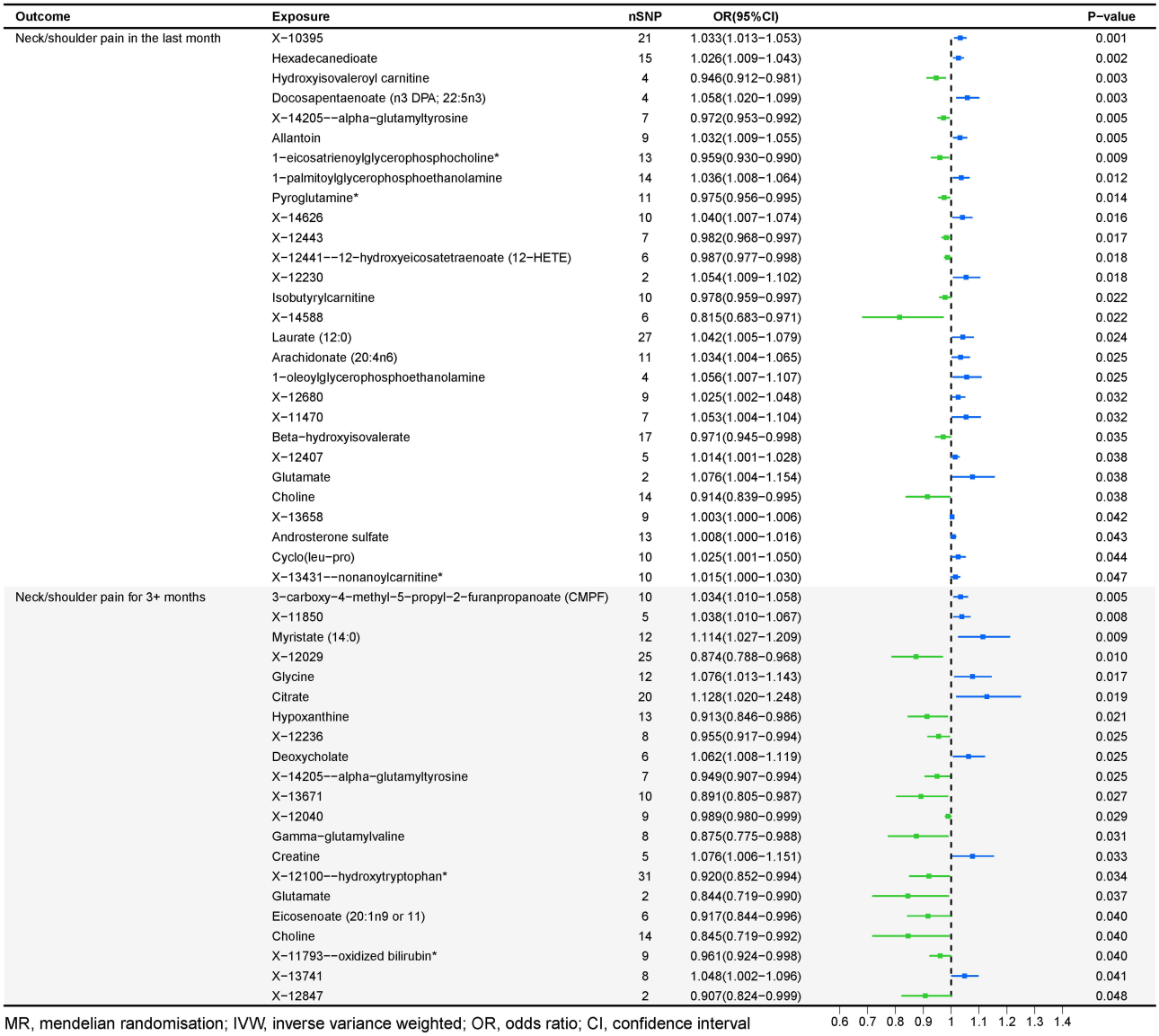


Figure 2 Forest plot of causality of the blood metabolites on neck pain.

Causal Effects of the Blood Metabolites on Back Pain

According to the IVW analysis, specific blood metabolites show unique associations with BP risk at different times (Figure 4 and Table 3). For BP in the last month, the genetically predicted metabolites *Allantoin, X-12645, Linolenate [alpha or gamma; (18:3n3 or 6)], X-05426, X-11546, Arachidonate (20:4n6), X-13549, 1-stearoylglycerol (1-monostearin), Taurodeoxycholate, Cyclo(leu-pro), and X-04498* are positively associated with increased SP risk. Conversely, metabolites such as *Pyroglutamine*1-palmitoylglycerophosphocholine, Succinylcarnitine, X-12556, Isovalerylcarnitine, 1-palmitoleoylglycerophosphocholine*7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca), 4-methyl-2-oxopentanoate, ADpSGEGDFXAEGGGVR*and X-11905* are negatively associated with BP in the last month risk. For Back pain for 3 + months, metabolites associated with increased risk include: *Glycine, N-acetylglycine, X-10429, 4-androsten-3beta,17-beta-diol disulfate 2*Lactate, X-12680, Citrulline, Methionine, 10-undecenoate (11:1n1), X-13741, X-11299, Citrate, Gamma-glutamylglutamine, and X-09026*. Metabolites such as *X-12728, Glutamine, X-12261, X-12040, X-12236, X-11795, Urate, Indolelactate, Gamma-glutamylvaline, 3-phenylpropionate (hydrocinnamate), and Glycerate* are associated with decreased risk of Back pain for 3+ months.

Table 1 Causal Effects of the Blood Metabolites on Neck Pain

Outcome	Exposure	nSNP	IVW		
			OR	(95% CI)	p-value
Neck/shoulder pain in the last month	X-10395	21	1.033	1.013–1.053	0.001
	Hexadecanedioate	15	1.026	1.009–1.043	0.002
	Hydroxyisovaleroyl carnitine	4	0.946	0.912–0.981	0.003
	Docosapentaenoate (n3 DPA; 22:5n3)	4	1.058	1.020–1.099	0.003
	X-14205–alpha-glutamyltyrosine	7	0.972	0.953–0.992	0.005
	Allantoin	9	1.032	1.009–1.055	0.005
	1-eicosatrienoylglycerophosphocholine*	13	0.959	0.930–0.990	0.009
	1-palmitoylglycerophosphoethanolamine	14	1.036	1.008–1.064	0.012
	Pyroglutamine*	11	0.975	0.956–0.995	0.014
	X-14626	10	1.04	1.007–1.074	0.016
	X-12443	7	0.982	0.968–0.997	0.017
	X-12441–12-hydroxyeicosatetraenoate (12-HETE)	6	0.987	0.977–0.998	0.018
	X-12230	2	1.054	1.009–1.102	0.018
	Isobutyrylcarnitine	10	0.978	0.959–0.997	0.022
	X-14588	6	0.815	0.683–0.971	0.022
	Laurate (12:0)	27	1.042	1.005–1.079	0.024
	Arachidonate (20:4n6)	11	1.034	1.004–1.065	0.025
	1-oleoylglycerophosphoethanolamine	4	1.056	1.007–1.107	0.025
	X-12680	9	1.025	1.002–1.048	0.032
	X-11470	7	1.053	1.004–1.104	0.032
	Beta-hydroxyisovalerate	17	0.971	0.945–0.998	0.035
Neck/shoulder pain for 3+ months	X-12407	5	1.014	1.001–1.028	0.038
	Glutamate	2	1.076	1.004–1.154	0.038
	Choline	14	0.914	0.839–0.995	0.038
	X-13658	9	1.003	1.000–1.006	0.042
	Androsterone sulfate	13	1.008	1.000–1.016	0.043
	Cyclo(leu-pro)	10	1.025	1.001–1.050	0.044
	X-13431–nonanoylcarnitine*	10	1.015	1.000–1.030	0.047
	3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	10	1.034	1.010–1.058	0.005
	X-11850	5	1.038	1.010–1.067	0.008
	Myristate (14:0)	12	1.114	1.027–1.209	0.009
	X-12029	25	0.874	0.788–0.968	0.01
	Glycine	12	1.076	1.013–1.143	0.017
	Citrate	20	1.128	1.020–1.248	0.019
	Hypoxanthine	13	0.913	0.846–0.986	0.021
	X-12236	8	0.955	0.917–0.994	0.025
	Deoxycholate	6	1.062	1.008–1.119	0.025
	X-14205–alpha-glutamyltyrosine	7	0.949	0.907–0.994	0.025
	X-13671	10	0.891	0.805–0.987	0.027
	X-12040	9	0.989	0.980–0.999	0.029
	Gamma-glutamylvaline	8	0.875	0.775–0.988	0.031
	Creatine	5	1.076	1.006–1.151	0.033
	X-12100–hydroxytryptophan*	31	0.92	0.852–0.994	0.034
	Glutamate	2	0.844	0.719–0.990	0.037
	Eicosenoate (20:1n9 or 11)	6	0.917	0.844–0.996	0.04
	Choline	14	0.845	0.719–0.992	0.04
	X-11793–oxidized bilirubin*	9	0.961	0.924–0.998	0.04
	X-13741	8	1.048	1.002–1.096	0.041
	X-12847	2	0.907	0.824–0.999	0.048

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

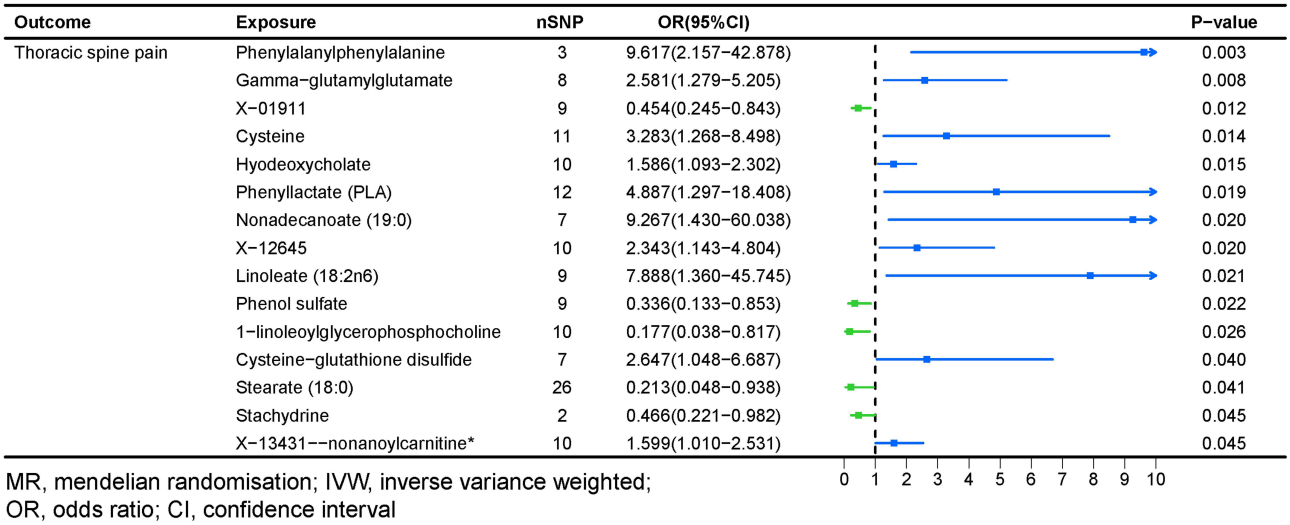


Figure 3 Forest plot of causality of the blood metabolites on thoracic spine pain.

Causal Effects of the Blood Metabolites on Low Back Pain

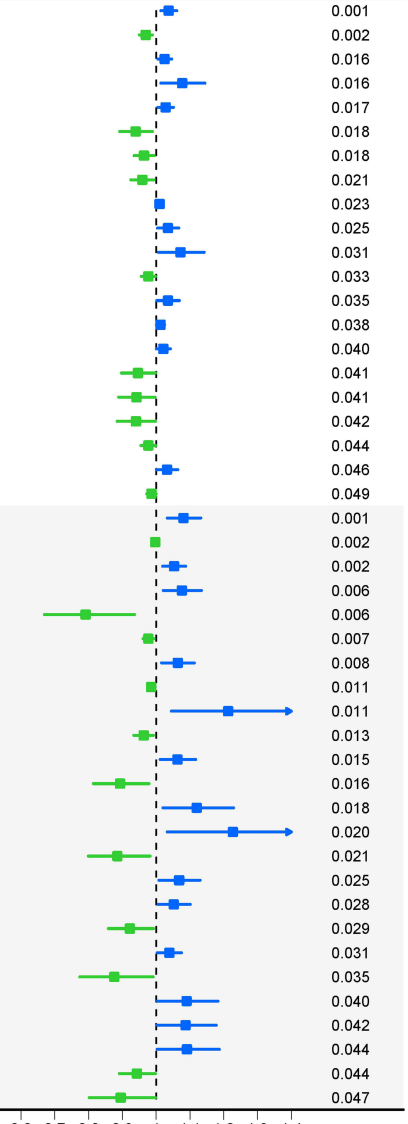
The IVW analysis results describe different associations between blood metabolites and LBP (Figure 5 and Table 4). The genetically predicted blood metabolites associated with increased LBP risk include:*1-oleoylglycerophosphoethanolamine, 2-stearoylglycerophosphocholine*glycine, X-11204, 1-palmitoylglycerol (1-monopalmitin), gamma-glutamylmethionine*tyrosine, X-12094, X-10810, alpha-hydroxyisovalerate, and C-glycosyltryptophan**. In contrast, the metabolites associated with decreased LBP risk include: *X-11852, phenylacetate, threonine, levulinate (4-oxovalerate), X-11795, adrenate (22:4n6), X-04495, 5-oxoproline, and X-12189*. Furthermore, for lower back pain and/or sciatica, the blood metabolites *C-glycosyltryptophan*1-oleoylglycerophosphoethanolamine, Tyrosine, 2-stearoylglycerophosphocholine*Glycine, X-12094, Cholesterol, X-11204, 1-palmitoylglycerophosphoethanolamine, X-11445–5-alpha-pregnan-3beta, 20alpha-disulfate, 1-eicosadienoylglycerophosphocholine, and X-14658* are associated with an increased risk. In contrast, *Adrenate (22:4n6), X-11437, X-11820, X-12441–12-hydroxyeicosatetraenoate (12-HETE), X-12261, X-11852, X-12189, X-11795, Phenylacetate, X-12726,*

Table 2 Causal Effects of the Blood Metabolites on Thoracic Spine Pain

Outcome	Exposure	nSNP	IVW		
			OR	(95% CI)	p-value
Thoracic spine pain	Phenylalanylphenylalanine	3	9.617	2.157–42.878	0.003
	Gamma-glutamylglutamate	8	2.581	1.279–5.205	0.008
	X-01911	9	0.454	0.245–0.843	0.012
	Cysteine	11	3.283	1.268–8.498	0.014
	Hyodeoxycholate	10	1.586	1.093–2.302	0.015
	Phenyllactate (PLA)	12	4.887	1.297–18.408	0.019
	Nonadecanoate (19:0)	7	9.267	1.430–60.038	0.02
	X-12645	10	2.343	1.143–4.804	0.02
	Linoleate (18:2n6)	9	7.888	1.360–45.745	0.021
	Phenol sulfate	9	0.336	0.133–0.853	0.022
	1-linoleoylglycerophosphocholine	10	0.177	0.038–0.817	0.026
	Cysteine-glutathione disulfide	7	2.647	1.048–6.687	0.04
	Stearate (18:0)	26	0.213	0.048–0.938	0.041
	Stachydrine	2	0.466	0.221–0.982	0.045
	X-13431–nonanoylcarnitine*	10	1.599	1.010–2.531	0.045

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

Outcome	Exposure	nSNP	OR(95%CI)	P-value
Back pain in the last month	Allantoin	9	1.037(1.014−1.061)	0.001
	Pyroglutamine*	11	0.969(0.950−0.989)	0.002
	X−12645	10	1.025(1.005−1.046)	0.016
	Linolenate [alpha or gamma;(18:3n3 or 6)]	2	1.077(1.014−1.144)	0.016
	X−05426	7	1.028(1.005−1.051)	0.017
	1−palmitoylglycerophosphocholine	19	0.939(0.892−0.989)	0.018
	Succinylcarnitine	27	0.964(0.935−0.994)	0.018
	X−12556	13	0.959(0.925−0.994)	0.021
	X−11546	11	1.010(1.001−1.018)	0.023
	Arachidonate (20:4n6)	11	1.035(1.004−1.067)	0.025
	X−13549	11	1.072(1.006−1.142)	0.031
	Isovalerylcarnitne	14	0.977(0.956−0.998)	0.033
	1−stearoylglycerol (1−monostearin)	16	1.035(1.002−1.069)	0.035
	Taurodeoxycholate	8	1.013(1.001−1.025)	0.038
	Cyclo(leu−pro)	10	1.021(1.001−1.042)	0.040
	1−palmitoleoylglycerophosphocholine*	8	0.946(0.897−0.998)	0.041
	7−alpha−hydroxy−3−oxo−4−cholestenoate (7−Hoca)	8	0.942(0.889−0.997)	0.041
	4−methyl−2−oxopentanoate	7	0.940(0.885−0.998)	0.042
	ADpSGEGDFXAEGGGVR*	4	0.977(0.955−0.999)	0.044
	X−04498	14	1.032(1.001−1.064)	0.046
	X−11905	12	0.986(0.972−1.000)	0.049
Back pain for 3+ months	Glycine	12	1.081(1.033−1.132)	0.001
	X−12728	32	0.997(0.994−0.999)	0.002
	N−acetylglycine	7	1.053(1.019−1.087)	0.002
	X−10429	15	1.076(1.021−1.134)	0.006
	Glutamine	7	0.791(0.669−0.936)	0.006
	X−12261	7	0.977(0.961−0.994)	0.007
	4−androsten−3beta,17beta−diol disulfate 2*	13	1.064(1.016−1.113)	0.008
	X−12040	9	0.985(0.974−0.997)	0.011
	Lactate	5	1.213(1.045−1.409)	0.011
	X−12236	8	0.963(0.934−0.992)	0.013
	X−12680	9	1.063(1.012−1.117)	0.015
	X−11795	7	0.893(0.814−0.979)	0.016
	Citrulline	23	1.120(1.020−1.229)	0.018
	Methionine	13	1.227(1.033−1.459)	0.020
	Urate	9	0.885(0.799−0.982)	0.021
	10−undecenoate (11:1n1)	12	1.068(1.008−1.130)	0.025
	X−13741	8	1.052(1.006−1.101)	0.028
	Indolelactate	11	0.922(0.858−0.992)	0.029
	X−11299	6	1.039(1.003−1.075)	0.031
	Gamma−glutamylvaline	8	0.876(0.774−0.991)	0.035
	Citrate	20	1.090(1.004−1.183)	0.040
	Gamma−glutamylglutamine	16	1.087(1.003−1.178)	0.042
	X−09026	11	1.091(1.003−1.187)	0.044
	3−phenylpropionate (hydrocinnamate)	4	0.943(0.891−0.998)	0.044
	Glycerate	9	0.895(0.802−0.998)	0.047



MR, mendelian randomisation; IVW, inverse variance weighted;
OR, odds ratio; CI, confidence interval

Figure 4 Forest plot of causality of the blood metabolites on back pain.

7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca), Trans-4-hydroxyproline, and Alpha-tocopherol are associated with a reduced risk of lower back pain and/or sciatica.

Causal Effects of SP on Blood Metabolites

Causal Effects of Neck Pain on Blood Metabolites

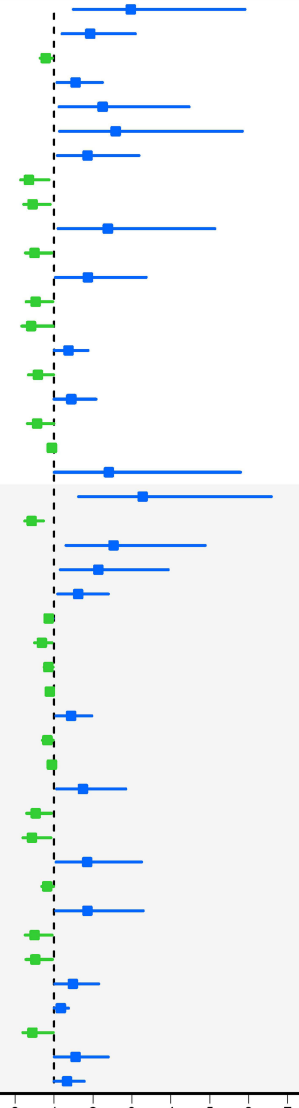
The metabolites positively associated with NP in the last month risk based on genetic prediction include (Figure 6 and Table 5): *X-11381, Taurodeoxycholate, X-12407, X-18601, and 1-stearoylglycerol (1-monostearin)*. Conversely, the metabolites negatively associated with NP in the last month risk include: *Docosahexaenoate (DHA; 22:6n3), Phenyllactate (PLA), X-11315, Phenol sulfate, X-12029, and X-13859*. For Neck/shoulder pain for 3+ months, the metabolites positively associated with risk include: *Octanoylcarnitine, Hexanoylcarnitine, X-11792, Cis-4-decenoyl carnitine, X-11847, Decanoylcarnitine, X-13069, and Acetylcarnitine*. Additionally, the metabolites negatively associated include: *X-12407, X-11444*.

Table 3 Causal Effects of the Blood Metabolites on Back Pain

Outcome	Exposure	nSNP	IVW		
			OR	(95% CI)	p-value
Back pain in the last month	Allantoin	9	1.037	1.014–1.061	0.001
	Pyroglutamine*	11	0.969	0.950–0.989	0.002
	X-12645	10	1.025	1.005–1.046	0.016
	Linolenate [alpha or gamma; (18:3n3 or 6)]	2	1.077	1.014–1.144	0.016
	X-05426	7	1.028	1.005–1.051	0.017
	1-palmitoylglycerophosphocholine	19	0.939	0.892–0.989	0.018
	Succinylcarnitine	27	0.964	0.935–0.994	0.018
	X-12556	13	0.959	0.925–0.994	0.021
	X-11546	11	1.010	1.001–1.018	0.023
	Arachidonate (20:4n6)	11	1.035	1.004–1.067	0.025
	X-13549	11	1.072	1.006–1.142	0.031
	Isovalerylcarnitne	14	0.977	0.956–0.998	0.033
	1-stearoylglycerol (1-monostearin)	16	1.035	1.002–1.069	0.035
	Taurodeoxycholate	8	1.013	1.001–1.025	0.038
	Cyclo(leu-pro)	10	1.021	1.001–1.042	0.040
	1-palmitoleoylglycerophosphocholine*	8	0.946	0.897–0.998	0.041
	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	8	0.942	0.889–0.997	0.041
	4-methyl-2-oxopentanoate	7	0.940	0.885–0.998	0.042
	ADpSGEGDFXAEGGGVR*	4	0.977	0.955–0.999	0.044
	X-04498	14	1.032	1.001–1.064	0.046
	X-11905	12	0.986	0.972–1.000	0.049
Back pain for 3+ months	Glycine	12	1.081	1.033–1.132	0.001
	X-12728	32	0.997	0.994–0.999	0.002
	N-acetylglycine	7	1.053	1.019–1.087	0.002
	X-10429	15	1.076	1.021–1.134	0.006
	Glutamine	7	0.791	0.669–0.936	0.006
	X-12261	7	0.977	0.961–0.994	0.007
	4-androsten-3beta,17beta-diol disulfate 2*	13	1.064	1.016–1.113	0.008
	X-12040	9	0.985	0.974–0.997	0.011
	Lactate	5	1.213	1.045–1.409	0.011
	X-12236	8	0.963	0.934–0.992	0.013
	X-12680	9	1.063	1.012–1.117	0.015
	X-11795	7	0.893	0.814–0.979	0.016
	Citrulline	23	1.120	1.020–1.229	0.018
	Methionine	13	1.227	1.033–1.459	0.020
	Urate	9	0.885	0.799–0.982	0.021
	10-undecenoate (11:1n1)	12	1.068	1.008–1.130	0.025
	X-13741	8	1.052	1.006–1.101	0.028
	Indolelactate	11	0.922	0.858–0.992	0.029
	X-11299	6	1.039	1.003–1.075	0.031
	Gamma-glutamylvaline	8	0.876	0.774–0.991	0.035
	Citrate	20	1.090	1.004–1.183	0.040
	Gamma-glutamylglutamine	16	1.087	1.003–1.178	0.042
	X-09026	11	1.091	1.003–1.187	0.044
	3-phenylpropionate (hydrocinnamate)	4	0.943	0.891–0.998	0.044
	Glycerate	9	0.895	0.802–0.998	0.047

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

Outcome	Exposure	nSNP	OR(95%CI)	P-value
low back pain	1-oleoylglycerophosphoethanolamine	4	2.973(1.497-5.902)	0.002
	2-stearoylglycerophosphocholine*	9	1.931(1.208-3.088)	0.006
	X-11852	6	0.787(0.647-0.957)	0.017
	Glycine	12	1.555(1.079-2.242)	0.018
	X-11204	22	2.249(1.132-4.469)	0.021
	1-palmitoylglycerol (1-monopalmitin)	7	2.584(1.144-5.835)	0.022
	Gamma-glutamylmethionine*	5	1.862(1.089-3.183)	0.023
	Phenylacetate	5	0.356(0.146-0.870)	0.023
	Threonine	13	0.449(0.225-0.900)	0.024
	Tyrosine	21	2.383(1.107-5.130)	0.026
	Levulinate (4-oxovalerate)	22	0.500(0.266-0.939)	0.031
	X-12094	5	1.870(1.040-3.364)	0.037
	X-11795	7	0.527(0.287-0.967)	0.039
	Adrenate (22:4n6)	5	0.410(0.172-0.976)	0.044
	X-10810	12	1.374(1.008-1.874)	0.045
	X-04495	7	0.586(0.347-0.987)	0.045
	Alpha-hydroxyisovalerate	9	1.444(1.003-2.077)	0.048
	5-oxoproline	16	0.565(0.320-0.995)	0.048
	X-12189	20	0.945(0.894-1.000)	0.049
	C-glycosyltryptophan*	15	2.410(1.004-5.787)	0.049
Lower back pain or/and sciatica	C-glycosyltryptophan*	5	3.276(1.631-6.579)	0.001
	Adrenate (22:4n6)	5	0.426(0.249-0.728)	0.002
	1-oleoylglycerophosphoethanolamine	4	2.528(1.309-4.883)	0.006
	Tyrosine	21	2.138(1.162-3.932)	0.015
	2-stearoylglycerop hosphocholine*	9	1.621(1.097-2.395)	0.015
	X-11437	7	0.864(0.765-0.976)	0.019
	X-11820	7	0.688(0.502-0.944)	0.020
	X-12441--12-hydroxyeicosatetraenoate (12-HETE)	6	0.855(0.750-0.976)	0.020
	X-12261	7	0.893(0.811-0.984)	0.022
	Glycine	12	1.438(1.050-1.970)	0.024
	X-11852	6	0.830(0.706-0.977)	0.025
	X-12189	20	0.946(0.900-0.993)	0.026
	X-12094	5	1.742(1.068-2.842)	0.026
	X-11795	7	0.530(0.301-0.933)	0.028
	Phenylacetate	5	0.434(0.205-0.920)	0.029
	Cholesterol	30	1.852(1.056-3.247)	0.032
	X-12726	11	0.823(0.687-0.985)	0.033
	X-11204	22	1.858(1.049-3.291)	0.034
	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	8	0.501(0.263-0.953)	0.035
	Trans-4-hydroxyproline	2	0.519(0.280-0.961)	0.037
	1-palmitoylglycerophosphoethanolamine	14	1.483(1.023-2.148)	0.037
	X-11445--5-alpha-pregnan-3beta,20alpha-disulfate	9	1.175(1.008-1.371)	0.039
	Alpha-tocopherol	5	0.446(0.203-0.978)	0.044
	1-eicosadienoylglycerophosphocholine	6	1.554(1.010-2.392)	0.045
	X-14658	7	1.335(1.003-1.776)	0.047



MR, mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval

Figure 5 Forest plot of causality of the blood metabolites on low back pain.

Causal Effects of Thoracic Spine Pain on Blood Metabolites

The analysis from the IVW test shows unique associations between blood metabolites and TSP risk (Figure 7 and Table 6). Blood metabolites positively associated with TSP include: *Heptanoate (7:0), X-10510, X-12729, palmitoyl sphingomyelin, cholesterol, X-08402, X-11412,4-androsten-3beta,17beta-diol disulfate 2*and 1-stearoylglycerol (1-monostearin)*. Blood metabolites negatively associated with TSP include:*1-eicosadienoylglycerophosphocholine*bilirubin (E,E)*palmitoleate (16:1n7), oleate (18:1n9), 1-palmitoleoylglycerophosphocholine*linoleate (18:2n6), X-12450, 1-arachidonoylglycerophosphocholine*dihomo-linoleate (20:2n6), 2-tetradecenoyl carnitine, myristate (14:0), 10-heptadecenoate (17:1n7), linolenate [alpha or gamma; (18:3n3 or 6)], 1-docosahexaenoylglycerophosphocholine*palmitate (16:0), pyridoxate, 1-heptadecanoylglycerophosphocholine, X-12728, 1-linoleoylglycerophosphocholine, myristoleate (14:1n5), eicosenoate (20:1n9 or 11), 3-methyl-2-oxobutyrate, 1-eicosatrienoylglycerophosphocholine*X-12244–N-acetylcarnosine, X-13183–stearamide, 10-nonadecenoate (19:1n9), oleoylcarnitine, phenylacetate, docosapentaenoate (n3 DPA; 22:5n3), phenol sulfate, X-11820, 2-palmitoylglycerophosphocholine*and X-14473*.

Table 4 Causal Effects of the Blood Metabolites on Low Back Pain

Outcome	Exposure	nSNP	IVW		
			OR	(95% CI)	p-value
Low back pain	1-oleoylglycerophosphoethanolamine	4	2.973	1.497–5.902	0.002
	2-stearoylglycerophosphocholine*	9	1.931	1.208–3.088	0.006
	X-11852	6	0.787	0.647–0.957	0.017
	Glycine	12	1.555	1.079–2.242	0.018
	X-11204	22	2.249	1.132–4.469	0.021
	1-palmitoylglycerol (1-monopalmitin)	7	2.584	1.144–5.835	0.022
	Gamma-glutamylmethionine*	5	1.862	1.089–3.183	0.023
	Phenylacetate	5	0.356	0.146–0.870	0.023
	Threonine	13	0.449	0.225–0.900	0.024
	Tyrosine	21	2.383	1.107–5.130	0.026
	Levulinate (4-oxovalerate)	22	0.500	0.266–0.939	0.031
	X-12094	5	1.870	1.040–3.364	0.037
	X-11795	7	0.527	0.287–0.967	0.039
	Adrenate (22:4n6)	5	0.410	0.172–0.976	0.044
	X-10810	12	1.374	1.008–1.874	0.045
	X-04495	7	0.586	0.347–0.987	0.045
	Alpha-hydroxyisovalerate	9	1.444	1.003–2.077	0.048
	5-oxoproline	16	0.565	0.320–0.995	0.048
	X-12189	20	0.945	0.894–1.000	0.049
	C-glycosyltryptophan*	15	2.410	1.004–5.787	0.049
Lower back pain or/and sciatica	C-glycosyltryptophan*	5	3.276	1.631–6.579	0.001
	Adrenate (22:4n6)	5	0.426	0.249–0.728	0.002
	1-oleoylglycerophosphoethanolamine	4	2.528	1.309–4.883	0.006
	Tyrosine	21	2.138	1.162–3.932	0.015
	2-stearoylglycerop hosphocholine*	9	1.621	1.097–2.395	0.015
	X-11437	7	0.864	0.765–0.976	0.019
	X-11820	7	0.688	0.502–0.944	0.020
	X-12441–12-hydroxyeicosatetraenoate (12-HETE)	6	0.855	0.750–0.976	0.020
	X-12261	7	0.893	0.811–0.984	0.022
	Glycine	12	1.438	1.050–1.970	0.024
	X-11852	6	0.830	0.706–0.977	0.025
	X-12189	20	0.946	0.900–0.993	0.026
	X-12094	5	1.742	1.068–2.842	0.026
	X-11795	7	0.530	0.301–0.933	0.028
	Phenylacetate	5	0.434	0.205–0.920	0.029
	Cholesterol	30	1.852	1.056–3.247	0.032
	X-12726	11	0.823	0.687–0.985	0.033
	X-11204	22	1.858	1.049–3.291	0.034
	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	8	0.501	0.263–0.953	0.035
	Trans-4-hydroxyproline	2	0.519	0.280–0.961	0.037
	1-palmitoylglycerophosphoethanolamine	14	1.483	1.023–2.148	0.037
	X-11445–5-alpha-pregnan-3beta,20alpha-disulfate	9	1.175	1.008–1.371	0.039
	Alpha-tocopherol	5	0.446	0.203–0.978	0.044
	1-eicosadienoylglycerophosphocholine	6	1.554	1.010–2.392	0.045
	X-14658	7	1.335	1.003–1.776	0.047

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

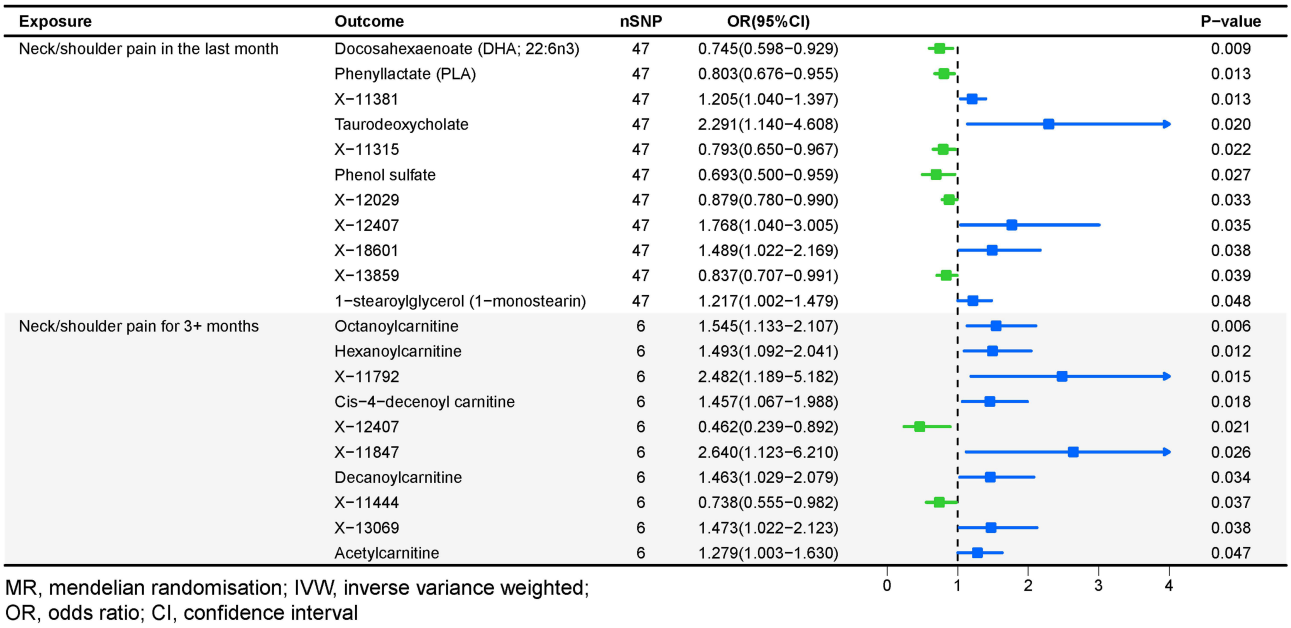


Figure 6 Forest plot of causality of neck pain on blood metabolites.

Causal Effects of Back Pain on Blood Metabolites

Blood metabolites positively associated with the risk of back pain in the last month include (Figure 8 and Table 7): *4-hydroxyhippurate, X-11441, X-11442, X-13619, X-14632, Kynurenine, 3-methyl-2-oxovalerate, X-11852, Leucylleucine, X-11521, Gamma-glutamylphenylalanine*. Conversely, blood metabolites negatively associated with the risk of back pain in the last month include: *X-13215, X-12038, X-11327, X-06307, X-11412, X-11317, X-12847, 1-linoleoylglycerophosphoethanolamine*X-07765, X-06350, Pelargonate (9:0), X-13069, 1,6-anhydroglucose*.

Causal Effects of Low Back Pain on Blood Metabolites

On the one hand, blood metabolites that show increased concentrations associated with the onset of low back pain include (Figure 9 and Table 8): *X-14658, Taurocholate, Cyclo(leu-pro), X-12217, Pseudouridine, Gamma-glutamyltyrosine, Gamma-glutamylphenylalanine, X-13741, Gamma-glutamylmethionine*3-(4-hydroxyphenyl)lactate, Taurolithocholate 3-sulfate, X-04498, ADSGEGDFXAEGGGVR*Threonine*. On the other hand, blood metabolites that show decreased concentrations associated with the onset of low back pain include: *2-stearoylglycerophosphocholine*Choline*. On the other hand, the blood metabolites positively associated with the development of lower back pain and/or sciatica include: *Gamma-*

Table 5 Causal Effects of Neck Pain on Blood Metabolites

Exposure	Outcome	nSNP	IVW		
			OR	(95% CI)	p-value
Neck/shoulder pain in the last month	Docosahexaenoate (DHA; 22:6n3)	47	0.745	0.598–0.929	0.009
	Phenyllactate (PLA)	47	0.803	0.676–0.955	0.013
	X-11381	47	1.205	1.04–1.397	0.013
	Taurodeoxycholate	47	2.291	1.14–4.608	0.020
	X-11315	47	0.793	0.65–0.967	0.022
	Phenol sulfate	47	0.693	0.5–0.959	0.027
	X-12029	47	0.879	0.78–0.99	0.033
	X-12407	47	1.768	1.04–3.005	0.035
	X-18601	47	1.489	1.022–2.169	0.038
	X-13859	47	0.837	0.707–0.991	0.039
	1-stearoylglycerol (1-monostearin)	47	1.217	1.002–1.479	0.048

(*Continued*)

Table 5 (Continued).

Exposure	Outcome	nSNP	IVW		
			OR	(95% CI)	p-value
Neck/shoulder pain for 3+ months	Octanoylcarnitine	6	1.545	1.133–2.107	0.006
	Hexanoylcarnitine	6	1.493	1.092–2.041	0.012
	X-11792	6	2.482	1.189–5.182	0.015
	Cis-4-decenoyl carnitine	6	1.457	1.067–1.988	0.018
	X-12407	6	0.462	0.239–0.892	0.021
	X-11847	6	2.640	1.123–6.21	0.026
	Decanoylcarnitine	6	1.463	1.029–2.079	0.034
	X-11444	6	0.738	0.555–0.982	0.037
	X-13069	6	1.473	1.022–2.123	0.038
	Acetylcarnitine	6	1.279	1.003–1.630	0.047

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

*glutamylisoleucine*Gamma-glutamylphenylalanine, X-12230, Indolelactate, N2,N2-dimethylguanosine, X-11334, and X-12188*. In contrast, the blood metabolites negatively associated with the development of lower back pain and/or sciatica include:*2-hydroxybutyrate (AHB), X-11905, 1-docosahexaenoylglycerophosphocholine*Androsterone sulfate, Epiandrosterone sulfate, Dehydroisoandrosterone sulfate (DHEA-S), 4-androsten-3beta,17beta-diol disulfate 2*2-stearoylglycerophosphocholine*Stearoylcarnitine, 2-palmitoylglycerophosphocholine*1-heptadecanoylglycerophosphocholine, 2-aminobutyrate, and Pantothenate*.

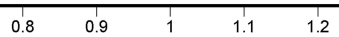
Sensitivity Analysis

Our MR analysis results underwent a comprehensive sensitivity testing to ensure the stability and reliability of the study findings. We employed the IVW test, MR-Egger's intercept test, and the MR-PRESSO global test (Supplementary Table 16). Importantly, the majority of IVW tests relying on Cochran's Q test showed no heterogeneity ($P > 0.05$), indicating consistency in our analyses. Additionally, both MR-Egger's intercept test and MR-PRESSO global test found no evidence of horizontal pleiotropy ($P > 0.05$), further enhancing the reliability of our study results. Scatter plots and leave-one-out analyses for five MR methods assessing the exposure factor (blood metabolites) on the outcome factor (SP) are provided in Supplementary Figures 1–14. Furthermore, Supplementary Figures 15–28 depict scatter plots and leave-one-out analyses for five MR methods assessing the exposure factor (SP) on the outcome factor (blood metabolites). Exclusion of any single SNP did not significantly alter the overall results, confirming the stability and reliability of our study findings.

Discussion

Observational studies have reported associations between blood metabolites and various segments of SP. In this study, we conducted bidirectional two-sample MR analysis using publicly available GWAS summary statistics to investigate causal relationships between human blood metabolites and different segments of SP, including NP, TSP, BP, and LBP. Our research revealed interactions between metabolites and SP. To our knowledge, this study is the first to employ two-sample MR methods to investigate potential causal relationships between blood metabolites in individuals of European ancestry and the risk of SP. We successfully identified 155 metabolites that may have causal relationships with SP, as well as 142 blood metabolite level changes associated with SP onset. Through further exploration of these metabolites, researchers can gain deeper insights into their specific mechanisms of action related to spinal pain, laying a theoretical foundation and providing reference for precise interventions targeting blood metabolites and the treatment and study of SP prevention.

Exposure	Outcome	nSNP	OR(95%CI)	P-value
Thoracic spine pain	1-eicosadienoylglycerophosphocholine*	6	0.967(0.947-0.987)	0.002
	Bilirubin (E,E)*	6	0.949(0.918-0.981)	0.002
	Heptanoate (7:0)	6	1.019(1.007-1.031)	0.003
	Palmitoleate (16:1n7)	6	0.966(0.944-0.988)	0.003
	Oleate (18:1n9)	6	0.981(0.968-0.994)	0.003
	1-palmitoleoylglycerophosphocholine*	6	0.974(0.957-0.992)	0.004
	Linoleate (18:2n6)	6	0.981(0.968-0.994)	0.004
	X-12450	6	0.971(0.952-0.991)	0.004
	1-arachidonoylglycerophosphocholine*	6	0.977(0.961-0.993)	0.005
	Dihomo-linoleate (20:2n6)	6	0.972(0.953-0.992)	0.005
	X-10510	6	1.019(1.005-1.033)	0.007
	X-12729	6	1.083(1.021-1.148)	0.008
	2-tetradecenoyl carnitine	6	0.966(0.942-0.991)	0.008
	Myristate (14:0)	6	0.982(0.968-0.995)	0.009
	Palmitoyl sphingomyelin	6	1.014(1.003-1.025)	0.010
	10-heptadecenoate (17:1n7)	6	0.976(0.957-0.994)	0.011
	Linolenate [alpha or gamma; (18:3n3 or 6)]	6	0.975(0.956-0.994)	0.011
	1-docosahexaenoylglycerophosphocholine*	6	0.976(0.958-0.995)	0.014
	Cholesterol	6	1.011(1.002-1.021)	0.014
	Palmitate (16:0)	6	0.986(0.975-0.997)	0.015
	X-08402	6	1.018(1.003-1.033)	0.016
	X-11412	6	1.020(1.004-1.036)	0.017
	Pyridoxate	6	0.975(0.954-0.996)	0.018
	1-heptadecanoylglycerophosphocholine	6	0.974(0.953-0.996)	0.019
	X-12728	6	0.877(0.786-0.979)	0.019
	1-linoleoylglycerophosphocholine	6	0.985(0.973-0.998)	0.020
	Myristoleate (14:1n5)	6	0.974(0.952-0.996)	0.021
	Eicosenoate (20:1n9 or 11)	6	0.976(0.954-0.997)	0.028
	3-methyl-2-oxobutyrate	6	0.986(0.972-0.999)	0.031
	1-eicosatrienoylglycerophosphocholine*	6	0.980(0.963-0.998)	0.034
	X-12244--N-acetylcarnosine	6	0.986(0.974-0.999)	0.035
	X-13183--stearamide	6	0.957(0.918-0.998)	0.038
	10-nonadecenoate (19:1n9)	6	0.978(0.957-0.999)	0.038
	4-androsten-3beta,17beta-diol disulfate 2*	6	1.032(1.001-1.063)	0.043
	Oleoylcarnitine	6	0.975(0.952-0.999)	0.043
	1-stearoylglycerol (1-monostearin)	6	1.017(1.000-1.033)	0.043
	Phenylacetate	6	0.974(0.948-0.999)	0.044
	Docosapentaenoate (n3 DPA; 22:5n3)	6	0.980(0.960-0.999)	0.044
	Phenol sulfate	6	0.972(0.945-1.000)	0.047
	X-11820	6	0.977(0.955-1.000)	0.047
	2-palmitoylglycerophosphocholine*	6	0.984(0.969-1.000)	0.048
	X-14473	6	0.967(0.935-1.000)	0.048



MR, mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval

Figure 7 Forest plot of causality of thoracic spinepain on blood metabolites.

The potential mechanisms through which blood metabolites contribute to the onset of pain have been discussed in numerous previous studies. According to research by Peng Chen et al, neuropathic pain leads to decreased levels of beta-hydroxybutyrate (BHB), one of the most abundant ketone bodies, in serum and spinal cord. BHB can increase the concentration of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, which helps alleviate neuropathic pain.[29,30] Therefore, in the context of neuropathic pain, dysbiosis of the gut microbiota and disturbances in serum metabolite levels are important factors in pain regulation.[13] In other studies, it has been found that concentrations of glutamate and lactate in the plasma of patients with chronic widespread pain positively correlate with the severity of pain.[31] Metabolites such as amino acids (eg, glutamine, serine, phenylalanine) and intermediate products (eg, succinate, citrate, acetylcarnitine, N-acetylornithine) from pathways involved in the metabolism of various macromolecules are considered potential biological markers in chronic pain individuals compared to healthy individuals, which aligns with our research findings.[32] Furthermore, studies have confirmed that chest pain

Table 6 Causal Effects of Thoracic Spine Pain on Blood Metabolites

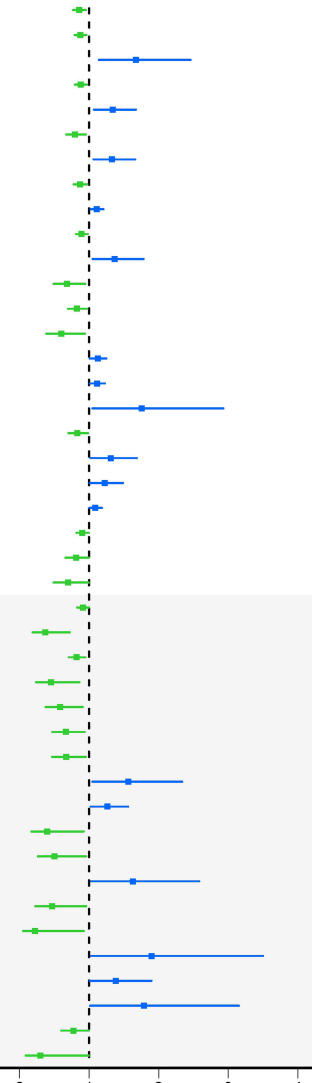
Exposure	Outcome	nSNP	IVW		
			OR	(95% CI)	p-value
Thoracic spine pain	1-eicosadienoylglycerophosphocholine*	6	0.967	0.947–0.987	0.002
	Bilirubin (E,E)*	6	0.949	0.918–0.981	0.002
	Heptanoate (7:0)	6	1.019	1.007–1.031	0.003
	Palmitoleate (16:1n7)	6	0.966	0.944–0.988	0.003
	Oleate (18:1n9)	6	0.981	0.968–0.994	0.003
	1-palmitoleoylglycerophosphocholine*	6	0.974	0.957–0.992	0.004
	Linoleate (18:2n6)	6	0.981	0.968–0.994	0.004
	X-12450	6	0.971	0.952–0.991	0.004
	1-arachidonoylglycerophosphocholine*	6	0.977	0.961–0.993	0.005
	Dihomo-linoleate (20:2n6)	6	0.972	0.953–0.992	0.005
	X-10510	6	1.019	1.005–1.033	0.007
	X-12729	6	1.083	1.021–1.148	0.008
	2-tetradecenoyl carnitine	6	0.966	0.942–0.991	0.008
	Myristate (14:0)	6	0.982	0.968–0.995	0.009
	Palmitoyl sphingomyelin	6	1.014	1.003–1.025	0.01
	10-heptadecenoate (17:1n7)	6	0.976	0.957–0.994	0.011
	Linolenate [alpha or gamma; (18:3n3 or 6)]	6	0.975	0.956–0.994	0.011
	1-docosahexaenoylglycerophosphocholine*	6	0.976	0.958–0.995	0.014
	Cholesterol	6	1.011	1.002–1.021	0.014
	Palmitate (16:0)	6	0.986	0.975–0.997	0.015
	X-08402	6	1.018	1.003–1.033	0.016
	X-11412	6	1.02	1.004–1.036	0.017
	Pyridoxate	6	0.975	0.954–0.996	0.018
	1-heptadecanoylglycerophosphocholine	6	0.974	0.953–0.996	0.019
	X-12728	6	0.877	0.786–0.979	0.019
	1-linoleoylglycerophosphocholine	6	0.985	0.973–0.998	0.02
	Myristoleate (14:1n5)	6	0.974	0.952–0.996	0.021
	Eicosenoate (20:1n9 or 11)	6	0.976	0.954–0.997	0.028
	3-methyl-2-oxobutyrate	6	0.986	0.972–0.999	0.031
	1-eicosatrienoylglycerophosphocholine*	6	0.98	0.963–0.998	0.034
	X-12244–N-acetylcarnosine	6	0.986	0.974–0.999	0.035
	X-13183–stearamide	6	0.957	0.918–0.998	0.038
	10-nonadecenoate (19:1n9)	6	0.978	0.957–0.999	0.038
	4-androsten-3beta,17beta-diol disulfate 2*	6	1.032	1.001–1.063	0.043
	Oleoylcarnitine	6	0.975	0.952–0.999	0.043
	1-stearoylglycerol (1-monostearin)	6	1.017	1.000–1.033	0.043
	Phenylacetate	6	0.974	0.948–0.999	0.044
	Docosapentaenoate (n3 DPA; 22:5n3)	6	0.98	0.960–0.999	0.044
	Phenol sulfate	6	0.972	0.945–1.000	0.047
	X-11820	6	0.977	0.955–1.000	0.047
	2-palmitoylglycerophosphocholine*	6	0.984	0.969–1.000	0.048
	X-14473	6	0.967	0.935–1.000	0.048

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

following myocardial infarction induces comprehensive metabolic changes in glycolysis-related metabolites, malate-aspartate shuttle (MAS) metabolites, and purine metabolites with antioxidant functions.[33]

Given the heavy burden of (SP) and many unknown physiological mechanisms, clinical interventions often face challenges in providing precise and effective targeted therapies, relying frequently on analgesics and muscle relaxants to alleviate symptoms. In this context, early detection of potential risk factors for LBP is crucial for achieving early

Exposure	Outcome	nSNP	OR(95%CI)	P-value
Back pain in the last month	X−13215	71	0.858(0.771−0.955)	0.005
	X−12038	71	0.873(0.793−0.962)	0.006
	4−hydroxyhippurate	71	1.676(1.143−2.457)	0.008
	X−11327	71	0.879(0.797−0.969)	0.010
	X−11441	71	1.339(1.071−1.673)	0.010
	X−06307	71	0.800(0.673−0.952)	0.012
	X−11442	71	1.331(1.065−1.663)	0.012
	X−11412	71	0.871(0.778−0.974)	0.016
	X−13619	71	1.109(1.020−1.207)	0.016
	X−11317	71	0.893(0.813−0.981)	0.019
	X−14632	71	1.369(1.051−1.783)	0.020
	X−12847	71	0.681(0.491−0.945)	0.022
	1−linoleoylglycerophosphoethanolamine*	71	0.825(0.697−0.975)	0.024
	X−07765	71	0.603(0.386−0.942)	0.026
	Kynurenine	71	1.124(1.010−1.250)	0.031
	3−methyl−2−oxovalerate	71	1.114(1.010−1.228)	0.031
	X−11852	71	1.754(1.050−2.929)	0.032
	X−06350	71	0.833(0.704−0.985)	0.033
	Leucylleucine	71	1.312(1.020−1.687)	0.035
	X−11521	71	1.226(1.011−1.487)	0.038
	Gamma−glutamylphenylalanine	71	1.090(1.003−1.185)	0.043
	Pelargonate (9:0)	71	0.904(0.819−0.997)	0.044
	X−13069	71	0.813(0.662−0.998)	0.047
	1,6−anhydroglucose	71	0.699(0.490−0.998)	0.048
	Laurate (12:0)	71	0.911(0.830−0.999)	0.049
Back pain for 3+ months	X−12830	5	0.369(0.188−0.723)	0.004
	X−12776	5	0.819(0.709−0.946)	0.007
	X−12850	5	0.452(0.237−0.862)	0.016
	Homocitrulline	5	0.585(0.377−0.909)	0.017
	Glycerophosphorylcholine (GPC)	5	0.665(0.471−0.938)	0.020
	X−11315	5	0.670(0.470−0.955)	0.027
	Gamma−glutamylmethionine*	5	1.566(1.049−2.340)	0.028
	Citrate	5	1.264(1.023−1.562)	0.030
	Bilirubin (Z,Z)	5	0.398(0.172−0.924)	0.032
	X−11540	5	0.503(0.264−0.956)	0.036
	X−13069	5	1.631(1.030−2.583)	0.037
	5alpha−androstan−3beta,17beta−diol disulfate	5	0.468(0.228−0.959)	0.038
	N−(2−furoyl)glycine	5	0.222(0.053−0.926)	0.039
	Tetradecanedioate	5	1.897(1.028−3.500)	0.040
	1,5−anhydroglucitol (1,5−AG)	5	1.383(1.008−1.897)	0.045
	X−11905	5	1.788(1.014−3.152)	0.045
	Glycerate	5	0.774(0.601−0.996)	0.047
	X−11849	5	0.300(0.090−0.996)	0.049



MR, mendelian randomisation; IVW, inverse variance weighted;
OR, odds ratio; CI, confidence interval

Figure 8 Forest plot of causality of back pain on blood metabolites.

diagnosis and prevention. Metabolomics is a research field exploring changes in high-molecular-weight molecules under physiological conditions, disease states, and after treatment with medications. Over the past decade, metabolomics studies have continuously identified metabolic biomarkers associated with thyroid disease. Tissues, blood, urine, and feces are typical sources of samples for metabolomics analysis. Among these, blood serves as a readily accessible repository of metabolites, making it valuable for identifying blood biomarkers in SP risk screening. According to current research, numerous studies indicate a causal relationship between blood metabolites and SP risk, aligning with our study results. For instance, our research identifies cholesterol as a risk factor for SP. Studies have suggested a 54% increased likelihood of neck pain in patients with hypercholesterolemia, highlighting the potential reduction in degenerative cervical disc disease incidence and progression through preventive and proper management of high cholesterol.[34] Another study has also correlated LDL cholesterol with neck pain.[35] Our study results show a positive correlation between threonine and SP risk. Interestingly, existing research has established that the glycine-serine-threonine metabolic pathway weakens gradually with inflammatory progression, a common cause of discogenic low back pain. Many confounding factors may contribute to inconsistent study results, such as patient sedentary behavior, poor posture, and

Table 7 Causal Effects of Back Pain on Blood Metabolites

Exposure	Outcome	nSNP	IVW		
			OR	(95% CI)	p-value
Back pain in the last month	X-13215	71	0.858	0.771–0.955	0.005
	X-12038	71	0.873	0.793–0.962	0.006
	4-hydroxyhippurate	71	1.676	1.143–2.457	0.008
	X-11327	71	0.879	0.797–0.969	0.010
	X-11441	71	1.339	1.071–1.673	0.010
	X-06307	71	0.800	0.673–0.952	0.012
	X-11442	71	1.331	1.065–1.663	0.012
	X-11412	71	0.871	0.778–0.974	0.016
	X-13619	71	1.109	1.020–1.207	0.016
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	X-12847	71	0.681	0.491–0.945	0.022
	1-linoleoylglycerophosphoethanolamine*	71	0.825	0.697–0.975	0.024
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	X-06350	71	0.833	0.704–0.985	0.033
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	Gamma-glutamylphenylalanine	71	1.090	1.003–1.185	0.043
	Pelargonate (9:0)	71	0.904	0.819–0.997	0.044
	X-13069	71	0.813	0.662–0.998	0.047
	1,6-anhydroglucose	71	0.699	0.490–0.998	0.048
	Laurate (12:0)	71	0.911	0.830–0.999	0.049
Back pain for 3+ months	X-12830	5	0.369	0.188–0.723	0.004
	X-12776	5	0.819	0.709–0.946	0.007
	X-12850	5	0.452	0.237–0.862	0.016
	Homocitrulline	5	0.585	0.377–0.909	0.017
	Glycerophosphorylcholine (GPC)	5	0.665	0.471–0.938	0.020
	X-11315	5	0.670	0.470–0.955	0.027
	Gamma-glutamylmethionine*	5	1.566	1.049–2.340	0.028
	Citrate	5	1.264	1.023–1.562	0.030
	Bilirubin (Z,Z)	5	0.398	0.172–0.924	0.032
	X-11540	5	0.503	0.264–0.956	0.036
	X-13069	5	1.631	1.030–2.583	0.037
	5alpha-androstan-3beta,17beta-diol disulfate	5	0.468	0.228–0.959	0.038
	N-(2-furoyl)glycine	5	0.222	0.053–0.926	0.039
	Tetradecanedioate	5	1.897	1.028–3.500	0.040
	1,5-anhydroglucitol (1,5-AG)	5	1.383	1.008–1.897	0.045
	X-11905	5	1.788	1.014–3.152	0.045
	Glycerate	5	0.774	0.601–0.996	0.047
	X-11849	5	0.300	0.090–0.996	0.049

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

obesity. Therefore, we should interpret the role of metabolites in SP cautiously. Additionally, our research identifies metabolites that play protective or risk roles in SP. Unfortunately, existing research has paid less attention to the roles of these metabolites such as phenyllactate (PLA), androsterone sulfate, and glycerate in SP pathogenesis, warranting further investigation to elucidate their potential mechanisms. Importantly, our study reveals numerous metabolites closely

Exposure	Outcome	nSNP	OR(95%CI)	P-value
low back pain	X-14658	9	1.101(1.031-1.175)	0.004
	Taurocholate	9	1.118(1.028-1.217)	0.009
	2-stearoylglycerophosphocholine*	9	0.957(0.923-0.991)	0.015
	Cyclo(leu-pro)	9	1.074(1.013-1.138)	0.017
	X-12217	9	1.063(1.011-1.118)	0.017
	Pseudouridine	9	1.018(1.003-1.033)	0.022
	Gamma-glutamyltyrosine	9	1.022(1.003-1.041)	0.026
	Gamma-glutamylphenylalanine	9	1.022(1.002-1.042)	0.028
	X-13741	9	1.098(1.007-1.198)	0.035
	Gamma-glutamylmethionine*	9	1.041(1.002-1.082)	0.038
	3-(4-hydroxyphenyl)lactate	9	1.028(1.001-1.055)	0.040
	Taurolithocholate 3-sulfate	9	1.066(1.002-1.134)	0.042
	X-04498	9	1.030(1.001-1.060)	0.042
	ADSGEGDFXAEGGGVR*	9	1.048(1.001-1.098)	0.045
	Threonine	9	1.023(1.001-1.047)	0.045
	Choline	9	0.986(0.973-1.000)	0.045
Lower back pain or/and sciatica	Gamma-glutamylisoleucine*	14	1.047(1.016-1.078)	0.003
	Gamma-glutamylphenylalanine	14	1.028(1.009-1.047)	0.004
	2-hydroxybutyrate (AHB)	14	0.961(0.931-0.992)	0.013
	X-11905	14	0.940(0.894-0.988)	0.014
	1-docosahexaenoylglycerophosphocholine*	14	0.956(0.922-0.991)	0.015
	X-12230	14	1.091(1.017-1.170)	0.016
	Androsterone sulfate	14	0.921(0.861-0.985)	0.016
	Indolelactate	14	1.035(1.006-1.065)	0.017
	Epiandrosterone sulfate	14	0.931(0.877-0.989)	0.020
	Dehydroisoandrosterone sulfate (DHEA-S)	14	0.942(0.895-0.991)	0.021
	4-androsten-3beta,17beta-diol disulfate 2*	14	0.942(0.896-0.991)	0.022
	N2,N2-dimethylguanosine	14	1.031(1.004-1.058)	0.024
	2-stearoylglycerophosphocholine*	14	0.953(0.913-0.995)	0.028
	Stearoylcarnitine	14	0.964(0.932-0.997)	0.035
	2-palmitoylglycerophosphocholine*	14	0.971(0.944-0.998)	0.037
	X-11334	14	1.033(1.002-1.065)	0.038
	1-heptadecanoylglycerophosphocholine	14	0.955(0.914-0.999)	0.045
	2-aminobutyrate	14	0.979(0.959-1.000)	0.045
	Pantothenate	14	0.970(0.942-0.999)	0.046
	X-12188	14	1.117(1.002-1.245)	0.046

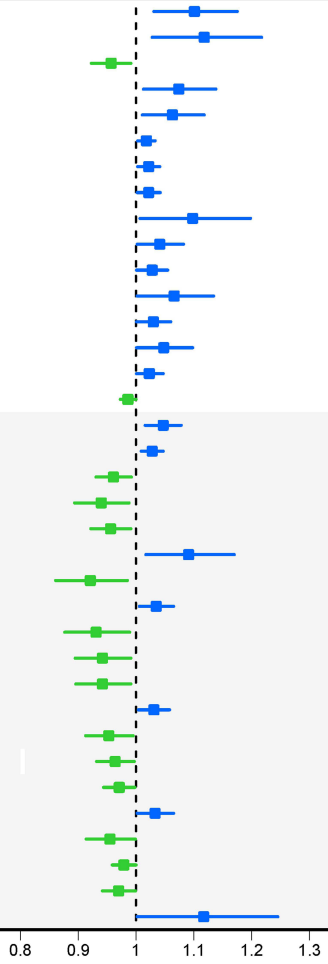

Figure 9 Forest plot of causality of low back pain on blood metabolites.

associated with SP that have not been previously named, laying a foundation for future research in the field of spine-metabolomics.

To carefully study the differences in blood metabolites causally related to acute and chronic SP, we included datasets for SP durations of 1 month and 3 months. As there are currently no datasets available for different durations of TSP and LBP, our study only included datasets for NP and BP lasting 1 month and 3+ months. Interestingly, our research findings indicate that glutamate acts as a protective factor in NP in the last month but becomes a risk factor in NP for 3+ months. In contrast, choline is consistently identified as a risk factor in both NP in the last month and NP for 3+ months. Based on this, we speculate that changes in blood metabolites accompanying the onset and progression of SP play complex cooperative regulatory roles among different spinal segments.

This study has several key strengths. Firstly, it comprehensively and systematically investigates the causal relationships between blood metabolites and SP with the largest sample size to date. Secondly, the GWAS datasets for SP and blood metabolite genetic IVs are derived from European populations, minimizing the influence of racial differences. Thirdly, the combination of bidirectional MR analysis helps to bi-directionally test the causal relationships between blood metabolites and SP.

Nevertheless, this study acknowledges certain limitations. Firstly, due to constraints in achieving genome-wide significant SNP counts, we opted for a lenient P threshold, a common approach in such scenarios. Secondly, drawbacks of the MR method include assuming that each patient has been exposed to factors throughout their entire life, which is

Table 8 Causal Effects of Low Back Pain on Blood Metabolites

Exposure	Outcome	nSNP	IVW		
			OR	(95% CI)	p-value
Low back pain	X-14658	9	1.101	1.031–1.175	0.004
	Taurocholate	9	1.118	1.028–1.217	0.009
	2-stearoylglycerophosphocholine*	9	0.957	0.923–0.991	0.015
	Cyclo(leu-pro)	9	1.074	1.013–1.138	0.017
	X-12217	9	1.063	1.011–1.118	0.017
	Pseudouridine	9	1.018	1.003–1.033	0.022
	Gamma-glutamyltyrosine	9	1.022	1.003–1.041	0.026
	Gamma-glutamylphenylalanine	9	1.022	1.002–1.042	0.028
	X-13741	9	1.098	1.007–1.198	0.035
	Gamma-glutamylmethionine*	9	1.041	1.002–1.082	0.038
	3-(4-hydroxyphenyl)lactate	9	1.028	1.001–1.055	0.04
	Taurolithocholate 3-sulfate	9	1.066	1.002–1.134	0.042
	X-04498	9	1.03	1.001–1.060	0.042
	ADSGEGDFXAEGGGVR*	9	1.048	1.001–1.098	0.045
	Threonine	9	1.023	1.001–1.047	0.045
	Choline	9	0.986	0.973–1.000	0.045
Lower back pain or/and sciatica	Gamma-glutamylisoleucine*	14	1.047	1.016–1.078	0.003
	Gamma-glutamylphenylalanine	14	1.028	1.009–1.047	0.004
	2-hydroxybutyrate (AHB)	14	0.961	0.931–0.992	0.013
	X-11905	14	0.94	0.894–0.988	0.014
	1-docosahexaenoylglycerophosphocholine*	14	0.956	0.922–0.991	0.015
	X-12230	14	1.091	1.017–1.170	0.016
	Androsterone sulfate	14	0.921	0.861–0.985	0.016
	Indolelactate	14	1.035	1.006–1.065	0.017
	Epiandrosterone sulfate	14	0.931	0.877–0.989	0.02
	Dehydroisoandrosterone sulfate (DHEA-S)	14	0.942	0.895–0.991	0.021
	4-androsten-3beta,17beta-diol disulfate 2*	14	0.942	0.896–0.991	0.022
	N2,N2-dimethylguanosine	14	1.031	1.004–1.058	0.024
	2-stearoylglycerophosphocholine*	14	0.953	0.913–0.995	0.028
	Stearoylcarnitine	14	0.964	0.932–0.997	0.035
	2-palmitoylglycerophosphocholine*	14	0.971	0.944–0.998	0.037
	X-11334	14	1.033	1.002–1.065	0.038
	1-heptadecanoylglycerophosphocholine	14	0.955	0.914–0.999	0.045
	2-aminobutyrate	14	0.979	0.959–1.000	0.045
	Pantothenate	14	0.97	0.942–0.999	0.046
	X-12188	14	1.117	1.002–1.245	0.046

Abbreviations: MR, Mendelian randomisation; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; *, the (*) are inherently present as part of the blood metabolite names.

not realistic in the real world. Furthermore, further exploration into the underlying mechanisms linking blood metabolites and LBP is needed to gain a clearer understanding of their roles. Lastly, it is regrettable that after Bonferroni correction, we did not identify significant causal relationships between metabolites and SP. We speculate that shared or different mechanisms may underlie these observations, necessitating further exploration to uncover the potential complexities of this causal association. Nonetheless, the potential SP risk predictors identified in this study provide new insights into understanding the role of genetic-exposure interactions in the pathogenesis of SP.

Finally, this study has important implications for advancing the development of novel chronic pain treatment modalities. We have revealed the association of spinal pain with specific blood metabolites, providing a clear target for research and development by similar investigators. Targeting the modulation of these metabolites may have significant therapeutic effects, and therefore, the development of drugs (eg, inhibitors or activators) targeting these

metabolites may be considered to alleviate spinal pain, ameliorate inflammation, or promote tissue repair. In addition, biomarkers based on metabolic information can be used as diagnostic tools to help physicians accurately determine the type and severity of spinal pain, so that effective treatment plans can be developed. We can further explore the application of these biomarkers to develop more accurate and individualised diagnostic methods. In addition to drugs and biomarkers, we should also consider other innovative therapeutic strategies, such as gene therapy, cell therapy or biotherapy, to treat spinal pain by modulating the synthesis or degradation pathways of metabolites or affecting related signalling pathways. However, it is worth noting that there are still many unknown and unnamed blood metabolites with unclear roles and mechanisms in spinal pain. Therefore, such studies need to be further deepened to reveal more potential targets and therapeutic strategies, so as to better fit the needs of clinical treatments and advance the field of chronic pain treatment. Although research in this area is still in its infancy, we believe that with technological advances and in-depth studies, therapeutic tools based on metabolic information will gradually become a reality. In the future, industry will be able to leverage these innovative strategies to provide more effective, safe and personalised treatments for chronic pain patients, thereby improving their quality of life.

Conclusion

In summary, this study established bidirectional causal relationships between human blood metabolites and SP. Our forward MR analysis identified 155 metabolites that could potentially influence SP, while reverse analysis pinpointed 142 blood metabolites likely affected by SP development. It is noteworthy that subgroup analyses based on different durations of spinal pain (within 1 month and over 3 months) contribute meaningfully to future interventions targeting specific blood metabolites to address SP at different time scales. Additionally, this study provides valuable insights into the complex mechanisms between blood metabolites and SP, laying the foundation for blood metabolomics research in SP. These findings not only provide important references for understanding these intricate connections but also pave the way for future efforts in preventing and treating SP through targeted interventions on blood metabolites. To fully validate our research findings, further comprehensive mechanistic studies and subsequent investigations involving larger sample sizes and multiple research centers are necessary. It is crucial to acknowledge that our MR analysis focused solely on genetic inheritance relationships and did not elucidate other potential causal relationships.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s. According to the National Health Commission of the People's Republic of China, the Ministry of Education, the Ministry of Science and Technology, the State Administration of Traditional Chinese Medicine issued the "Notice on the issuance of Human Life Sciences and medical research ethical Review Measures" Article 32: Using legally available public data, Or by observing and does not interfere with the study on the data of public behavior of exempt from ethical review (https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm) and according to the health committee of the People's Republic of China Article 9 of the document interpretation of "Measures for the Ethical Review of Life Sciences and Medical Research Involving Humans": Using public data gained legally, or by observing and does not interfere with public behavior of data for research involving human life science and medical research can be exempt from ethical review (https://www.gov.cn/zhengce/2023-02/28/content_5743660.htm).

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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

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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