Journal of Pain Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Carnitine and Other Metabolites in Fibromyalgia a Clinical Perspective on a Mendelian Randomization Study

Minping Hong[1,*], Jianguo Wang[2,*], Xiaowen Huang[1], Qin Xu[1], Yujin Xiao[1], Keng Ling[2]

[1]Department of Radiology, Jiaxing Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical Universityl, Jiaxing, People's Republic of China; [2]Clinical laboratory, Jiaxing Maternity and Children Health Care Hospital, Jiaxing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Keng Ling, Clinical Laboratory, Jiaxing University, Jiaxing Maternity and Children Health Care Hospital, No. 2468 Zhonghuan East Road, Nanhu District, Jiaxing, Zhejiang Province, 314000, People's Republic of China, Email 450620239@qq.com; Yujin Xiao, Jiaxing Hospital of Traditional Chinese Medical, No. 1501 Zhongshan East Road, Nanhu District, Jiaxing, Zhejiang Province, 314000, People's Republic of China, Email 249877814@qq.com

Background: Fibromyalgia (FM) is a chronic pain disorder lacking reliable biomarkers. While metabolomic studies have suggested associations with various metabolites, including carnitine, establishing causality remains a challenge. This study integrates clinical metabolomic profiling with a Mendelian Randomization (MR) framework to investigate the potential causal influence of blood metabolites on FM.

Methods: In this study, 96 patients with Fibromyalgia and normal controls were recruited, and the carnitine level in peripheral blood was detected by ELISA method. And then, a two-sample Mendelian randomization (MR) method was used to test the potential causal relationship between 1400 metabolite biomarkers, including the level of carnitine, and Fibromyalgia. Additionally, for those metabolites demonstrating a causal link to Fibromyalgia in the initial MR analysis, a reverse Mendelian Randomization analysis was conducted to further validate these findings.

Results: Carnitine levels were markedly decreased in patients with fibromyalgia compared with healthy controls. The MR analysis identified 10 metabolites potentially causally linked to fibromyalgia. Among them, carnitine has a causal relationship with Fibromyalgia and is a protective factor (OR 0.73, 95% CI: 0.59–0.91, p = 0.004). There are others, 4 metabolites showed protective effects, whereas 5 were linked to an elevated risk of the condition. The results were consistent among various MR methods, suggesting a strong correlation.

Conclusion: Our findings provide novel evidence supporting a potential causal, protective role of carnitine in FM pathogenesis, alongside other implicated metabolites. These results highlight the promise of metabolic pathways as targets for intervention, but future studies in larger, diverse populations are warranted to confirm these relationships.

Keywords: fibromyalgia, carnitine, metabolomics, Mendelian randomization

Introduction

Fibromyalgia (FM), characterized by chronic and widespread pain, remains an elusive condition in contemporary medicine. The pathogenesis and etiology of FM are still largely unexplored, and its diagnosis is complicated by the absence of specific biomarkers and significant symptomatic overlap with other disorders.[1–5] Recent advances in metabolomics have opened new avenues for investigating the biological underpinnings of FM by profiling small molecular metabolites in blood samples.[6–8]

Plasma metabolomic studies have consistently identified alterations in amino acid, lipid, and energy metabolism in FM patients.[8–11] Among the dysregulated pathways, mitochondrial function and fatty acid oxidation are frequently implicated. Additionally, perturbations in the neuroendocrine and immune systems—such as dysregulated cortisol levels

Received: 28 September 2025
Accepted: 18 December 2025
Published: 25 December 2025

and inconsistent alterations in inflammatory markers including C-reactive protein (CRP)—have been documented, further illustrating the systemic complexity of FM.[12] Carnitine, a crucial metabolite for mitochondrial fatty acid transport, sits at the nexus of these processes. Its recognized role in modulating oxidative stress and energy production.[13–15] coupled with preliminary clinical observations of its alteration in FM, made it a primary candidate for a causal investigation in this study. The potential of metabolomics to shed light on the complex metabolic landscape of FM is immense. By offering a dynamic snapshot of the body's physiological state, metabolomics helps to uncover the disrupted biochemical pathways that contribute to FM's clinical manifestations.[16,17]

To further elucidate the causal relationships between these metabolic abnormalities and FM, this study uses a Mendelian Randomization (MR) approach.[18–20] Using genetic variants as instrumental variables, MR allows for the assessment of potential causal links between plasma metabolite levels and FM, while minimizing the confounding factors inherent in observational studies. This innovative approach not only deepens our understanding of FM pathogenesis but also lays the groundwork for future research into targeted metabolic interventions.

Materials and Methods

Study Population Recruitment and Ethical Approval

This study employed a two-phase, hierarchical design. In the first phase, we conducted a focused clinical investigation in a well-phenotyped, modestly sized cohort comprising 96 fibromyalgia (FM) patients (diagnosed according to the 2016 American College of Rheumatology criteria)[21] and 96 matched controls. The control group consisted of non-pregnant, non-postpartum females recruited from health check-up centers, with all participants confirming no pregnancy for at least one year prior to sample collection. All individuals underwent comprehensive screening, including laboratory assessments of thyroid, renal, and hepatic function, and were free from medications known to affect carnitine metabolism (eg, valproic acid). Specifically, patients with comorbid osteoarthritis were excluded, and the use of FM-specific medications (including duloxetine) was prohibited for at least two weeks prior to enrollment. The principal aim of this clinical stage was to test the specific hypothesis regarding carnitine levels in FM, which was quantitatively assessed using ELISA. In the second phase, this clinically derived hypothesis was rigorously evaluated for causality within a two-sample MR framework. This MR approach leveraged large-scale, independent GWAS datasets, which provide superior statistical power and minimize confounding biases inherent in observational studies. The research was approved by the hospital's ethical review board and conducted in accordance with the ethical guidelines of the Helsinki Declaration. All participants were fully informed about the research objectives and methods, and they provided written informed consent. All patients were free from major comorbidities (eg, cardiovascular disease, diabetes, autoimmune disorders) and had not taken any medications that could affect metabolism in the two weeks prior to enrollment. Inclusion criteria were ages 18–65, with the exclusion of other chronic pain or metabolic disorders. Healthy controls were matched strictly to the patient group by age and gender, with the patient group having a mean age of 45.3 ± 10.2 years and approximately 99.5% being female.

Plasma Carnitine Quantification (ELISA Method)

We used ELISA to quantify plasma carnitine levels (Coibo Biotechnology Cat#CB11833-Hu). Blood samples were first collected and centrifuged to separate the plasma, which was then stored at −80°C. Following the manufacturer's instructions for the ELISA kit, the samples were incubated at 37°C, and a standard curve was generated using a quadratic polynomial fit. Absorbance was measured at 450 nm, and carnitine concentrations were calculated based on the standard curve. Each sample was assayed in triplicate.

Overview of Mendelian Randomization Methodology

Utilizing a two-sample MR technique, we investigated a potential causal relationship between 1091 blood metabolites and 309 metabolite ratios and FM.[22] In our data processing, we adopted a listwise deletion strategy for missing genetic and phenotypic data. Given the minimal amount of missing data, this approach effectively avoids potential bias that may be introduced by imputation, thereby ensuring the stability and reliability of subsequent analyses. In the context of MR,

genetic variations serve as proxies for risk factors. To ensure a valid causal interpretation using instrumental variables (IVs), three essential criteria must be met:

A direct correlation exists between genetic variation and exposure.

This genetic variation must be independent of any confounding factors that could influence the exposure-outcome relationship.

Consequently, the outcome is exclusively determined by the exposure linked to genetic variation.

All included studies obtained the required ethical approvals, and informed consent was obtained from all participants.

Fibromyalgia GWAS Data Sources and Definitions

Summary statistics pertinent to FM was sourced from the GWAS database (https://gwas.mrcieu.ac.uk/). For FM, the sample consisted of 168,378 individuals (737 cases and 167,641 controls), evaluating around 16,380,308 single nucleotide polymorphisms (SNPs). The study's population was composed of people of European descent. FM was defined using endpoint definitions approved by the FinnGen study's clinical expert groups, which included leading experts in their respective medical fields (RRID: SCR_022254). The FinnGen study established a strong framework for defining medical conditions, ensuring consistency and reliability in our diagnostic criteria.

GWAS Data Sources: 1091 Blood Metabolites and 309 Metabolite Ratios

The GWAS database (https://gwas.mrcieu.ac.uk/) provided summary statistics for a range of conditions (RRID: SCR_012745). GWAS summary datasets for 1400 metabolites were detached from the study by Chen et al[22] which has been the most comprehensive investigation of the genetic effects on human serum metabolism so far. The detailed names of 1400 metabolites are presented in Supplemental Table S1. The participants in the study were all of European ancestry.

Instrumental Variable (IV) Selection Criteria and Procedure

Guided by recent scientific findings, we set a significance level for IVs associated with each characteristic at 1×10^{-5}.[23,24] By utilizing the R package TwoSampleMR[25](RRID: SCR_019010), we optimized the selection of SNPs. The clumping parameter was activated, with a secondary significance level set at 1×10^{-5}. We delineated a criterion for linkage disequilibrium (LD) r^2 at 0.001 and demarcated a clumping proximity of 10,000 kb. To eliminate the bias induced by poor instruments, we calculated R^2 and F statistics for each SNP. R^2 and F statistics are calculated as follows:

$$R^2 = \frac{2\beta^2_{exposure} eaf_{exposure}\left(1 - eaf_{exposure}\right)}{2\beta^2_{exposure} eaf_{exposure}\left(1 - eaf_{exposure}\right) + 2se^2_{exposure} samplesize_{exposure} eaf_{exposure}\left(1 - eaf_{exposure}\right)}$$

$$F = \frac{R^2\left(samplesize_{exposure} - 2\right)}{1 - R^2}$$

In these formulas:

- $\beta_{exposure}$ represents the beta coefficient of exposure.
- $eaf_{exposure}$ is the effect allele frequency of exposure.
- $se_{exposure}$ is the standard error of exposure.
- $samplesize_{exposure}$ is the sample size of the exposure group.

SNPs with $F < 10$ were defined as poor genetic variants and were removed.

KEGG Pathway Enrichment Analysis

To further explore the potential biological roles of metabolites, we conducted KEGG pathway enrichment analysis using the MetaboAnalyst online tool (https://www.metaboanalyst.ca). First, we uploaded the selected metabolite list to the MetaboAnalyst platform and selected the KEGG database as the reference for the enrichment analysis.

Statistical Analysis Methods

In this study, the R programming environment (version 4.3.1) was utilized for all evaluations. We investigated the causal relationship between 1400 metabolites and FM using a range of statistical methods, primarily through the TwoSampleMR package. These methods included inverse variance weighting (IVW),[26] weighted median,[27] and mode-based techniques,[28] primarily through the TwoSampleMR package. To address heterogeneity among IVs, Cochran's Q statistic was employed. When significant heterogeneity was detected, a shift from a fixed-effects to a random-effects IVW model was made. Additionally, the MR-Egger method was utilized to probe potential horizontal pleiotropy; the presence of which was indicated by a significant intercept.[29] The MR-PRESSO technique was also applied to refine the analysis by identifying and excluding potential pleiotropic outliers.[30] The robustness and consistency of the results were further corroborated through funnel plots.

For the selection of blood metabolites potentially causing FM, we applied stringent criteria: (1) In this study, we employ the conventional p-value threshold of < 0.05 as the criterion for statistical significance, a standard widely acknowledged in the biomedical field. In the initial screening phase, we applied a more lenient $P < 0.05$ This choice was made to increase sensitivity and reduce the likelihood of missing metabolites with small effect sizes that could still hold biological relevance. Although this relaxed threshold may increase the risk of false positives, it allows us to retain signals that may be biologically meaningful but have smaller effects.[19] (2) results had to show consistent direction and magnitude across all five MR methods, and (3) there should be no evidence of heterogeneity or horizontal pleiotropy in the MR outcomes.

Furthermore, for metabolites identified as causally related to FM in the forward MR analysis, a reverse MR analysis was conducted to strengthen the causal inference. The methodology and parameters for the reverse MR were aligned with those used in the forward MR process.

Results

ELISA results

A standard curve for carnitine quantification was established with known concentrations, yielding a high degree of linearity (R^2 =0.99037) across the concentration range of 0 to 360 μM. This curve facilitated the precise quantification of carnitine levels in the serum samples (Figure 1A).

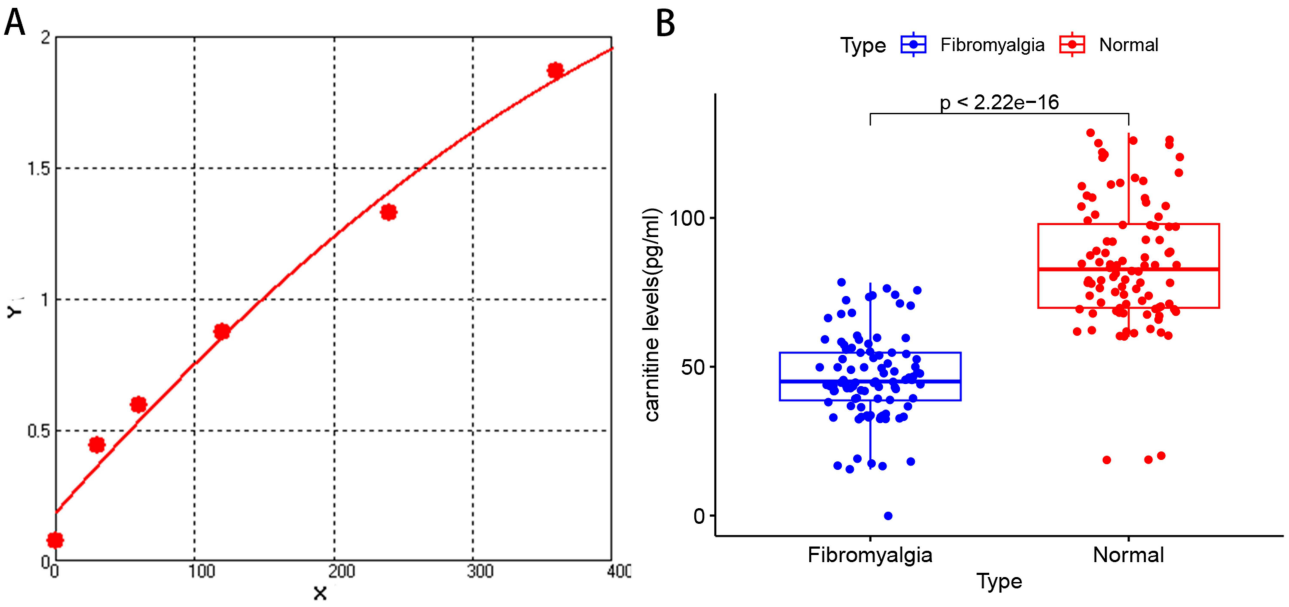

Figure 1 Quantitative Analysis of Carnitine Concentrations in FM. (**A**) displays the ELISA standard curve for accurate carnitine quantification; (**B**) shows a box plot of carnitine levels in FM patients compared to healthy controls.

The average serum carnitine level in the control group (84.6 ± 20.4 pg/mL) was significantly higher than that in the FM group (46.2 ± 16.8 pg/mL) ($p < 0.001$). The magnitude of this difference was very large, as indicated by Cohen's d = 2.07 (95% CI: 1.66 to 2.47). The distribution of carnitine levels across both groups is illustrated in Figure 1B, highlighting the marked decrease in the FM cohort. Statistical analysis employing an independent samples *t*-test confirmed the significant difference in serum carnitine levels between the two groups ($p < 0.001$).

Probing the Impact of Metabolites on FM

Based on the predefined criteria for selecting IVs, a comprehensive set of 33267 SNPs were employed as IVs in this study. Detailed information regarding these chosen SNPs and their characteristics can be found in Supplemental Table S2.

In a MR study, 11 metabolites were identified. Among these, five metabolites exhibited protective effects against FM, while six metabolites were found to have potential pathogenic roles. The IVW analysis for these metabolites yielded an aggregated score of Carnitine levels (OR 0.73, 95% CI: 0.59–0.91, p = 0.004), Iminodiacetate (IDA) levels (OR 1.59, 95% CI: 1.16–2.17, p = 0.004), Deoxycarnitine levels (OR 0.75, 95% CI: 0.61–0.92, p = 0.006), (R)-3-hydroxybutyrylcarnitine levels (OR 0.62, 95% CI: 0.45–0.84, p = 0.002), 1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (p-16:0/20:4) levels (OR 1.56, 95% CI: 1.17–2.08, p = 0.002), Oleoylcholine levels (OR 1.58, 95% CI: 1.14–2.19, p = 0.006), N-acetyl leucine levels (OR 0.57, 95% CI: 0.40–0.83, p = 0.003), 3-ethylcatechol sulfate (1) levels (OR 1.67, 95% CI: 1.21–2.29, p = 0.002), Metabolonic lactone sulfate levels (OR 0.84, 95% CI: 0.74–0.95, p = 0.005), Pentadecanoate (15:0) levels (OR 1.54, 95% CI: 1.15–2.07, p = 0.003), Alpha-ketoglutarate to kynurenine ratio (OR 1.42, 95% CI: 1.12–1.79, p = 0.004). Notably, estimates derived from the IVW analysis were significant ($p < 0.05$), and the direction and magnitude of the estimates were consistent across four other analytical methods. (Figures 2–4).

The results of the Cochran's IVW Q test, detailed in Supplemental Table S3, indicated a lack of significant heterogeneity in the IVs. Furthermore, the MR-Egger regression intercept analysis, as shown in Supplemental Table S4, did not reveal any significant directional horizontal pleiotropy. Additionally, the MR-PRESSO global test (results in Supplemental Table S5) failed to identify any significant outliers, suggesting a negligible presence of horizontal pleiotropy in the association between the metabolites and FM.

In the reverse MR analysis, a suggestive but not definitive association was observed between FM and IDA levels (IVW OR = 0.98, 95% CI: 0.954–0.998, P = 0.04), as detailed in Supplemental Tables S6 and S7. For other metabolites, no significant causal relationships with FM were found. Furthermore, the Cochran's IVW Q test results for FM IVs, shown in Supplemental Table S8, indicated an absence of significant heterogeneity. The results of the MR-Egger regression intercept item analysis (Supplemental Table S9) and MR-PRESSO analysis (Supplemental Table S10) also supported the lack of significant horizontal pleiotropy in these findings.

KEGG pathway enrichment analysis revealed significant enrichment in the Lysine degradation pathway, suggesting that this pathway may play a key role in the metabolic mechanisms underlying fibromyalgia. Detailed results can be found in Supplemental Table S11.

Discussion

In this study, we integrated original clinical metabolomic data from a well-phenotyped FM cohort with a rigorous MR design to investigate the causal effects of blood metabolites on FM. To our knowledge, this is one of the first studies to apply such an integrated approach in FM research. We found that lower levels of metabolomic lactone sulfate, deoxycarnitine, carnitine, (R)-3-hydroxybutyrylcarnitine, and N-acetyl leucine are associated with a lower risk of FM. Conversely, a genetic predisposition to higher levels of 3-ethylcatechol sulfate, oleoylcholine, 1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (p-16:0/20:4), pentadecanoate (15:0), and an increased alpha-ketoglutarate to kynurenine ratio is linked to an elevated risk of FM. These findings offer a new perspective on the pathophysiology of FM, particularly regarding the connection between metabolic pathways and disease risk. Notably, we observed significantly lower levels of carnitine in peripheral blood samples from patients with FM compared to those from healthy individuals, offering a comprehensive perspective from molecular mechanisms to clinical manifestations.

In our study, we observed results that align with previous research, particularly regarding the vital role of carnitine and its derivatives in energy metabolism.[31–33] Carnitine, a crucial biomolecule, plays an essential role in the

Figure 2 Forest plots showed the causal associations between metabolites on FM. Method: Mendelian randomization method applied. Bold values indicate statistical significance ($p < 0.05$). An OR < 1 indicates a protective effect, while an OR > 1 indicates a risk factor.

Abbreviations: IVW, inverse variance weighting; WM, weighted median; pval, P-value for the causal estimate; OR (95% CI), Odds ratio and 95% confidence interval; id. exposure, Identifies the blood metabolite under investigation; nsnp, Number of single-nucleotide polymorphisms used as instrumental variables for each metabolite.

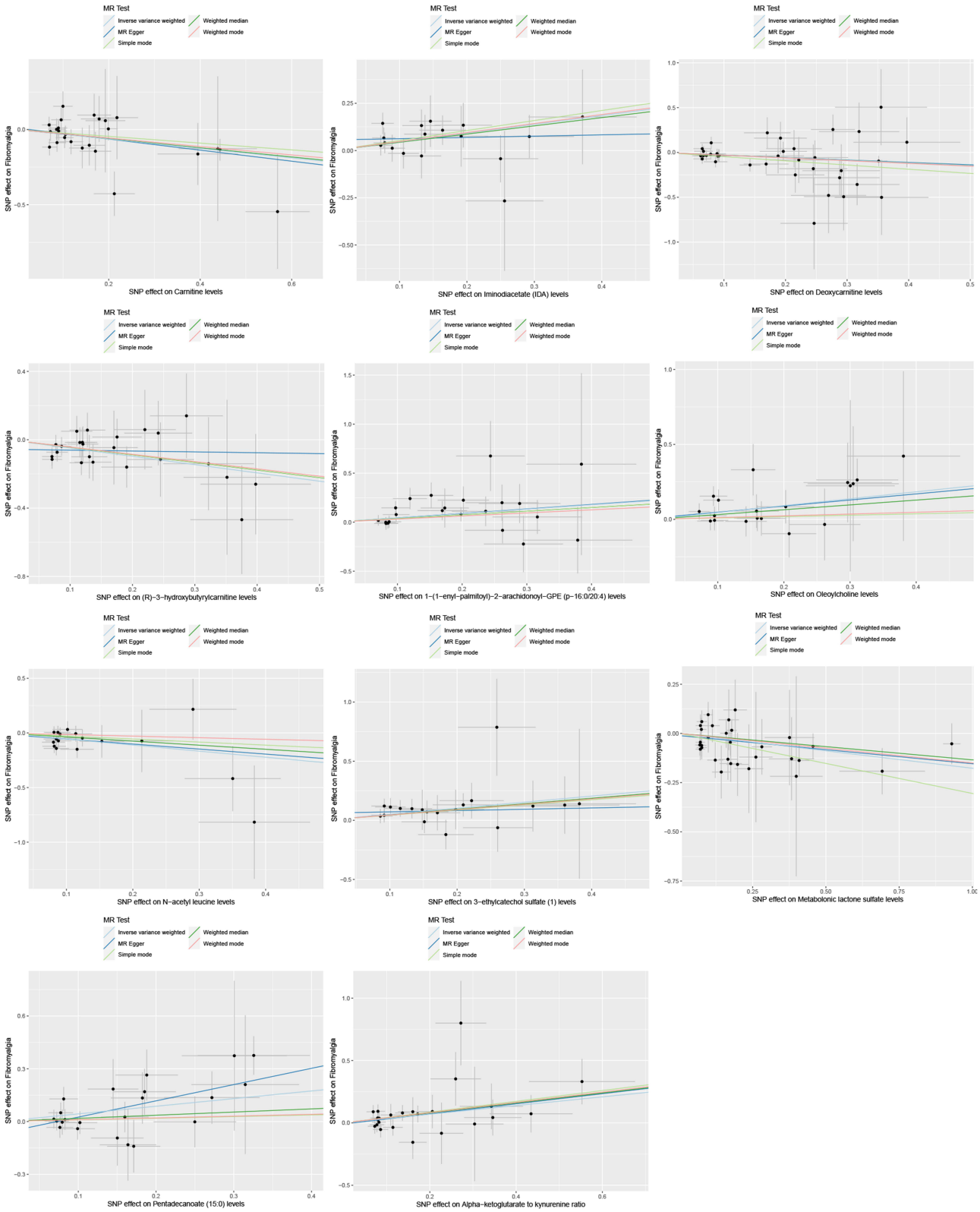

Figure 3 Scatter plots for the causal association between metabolites and FM.

https://doi.org/10.2147/JPR.S569174

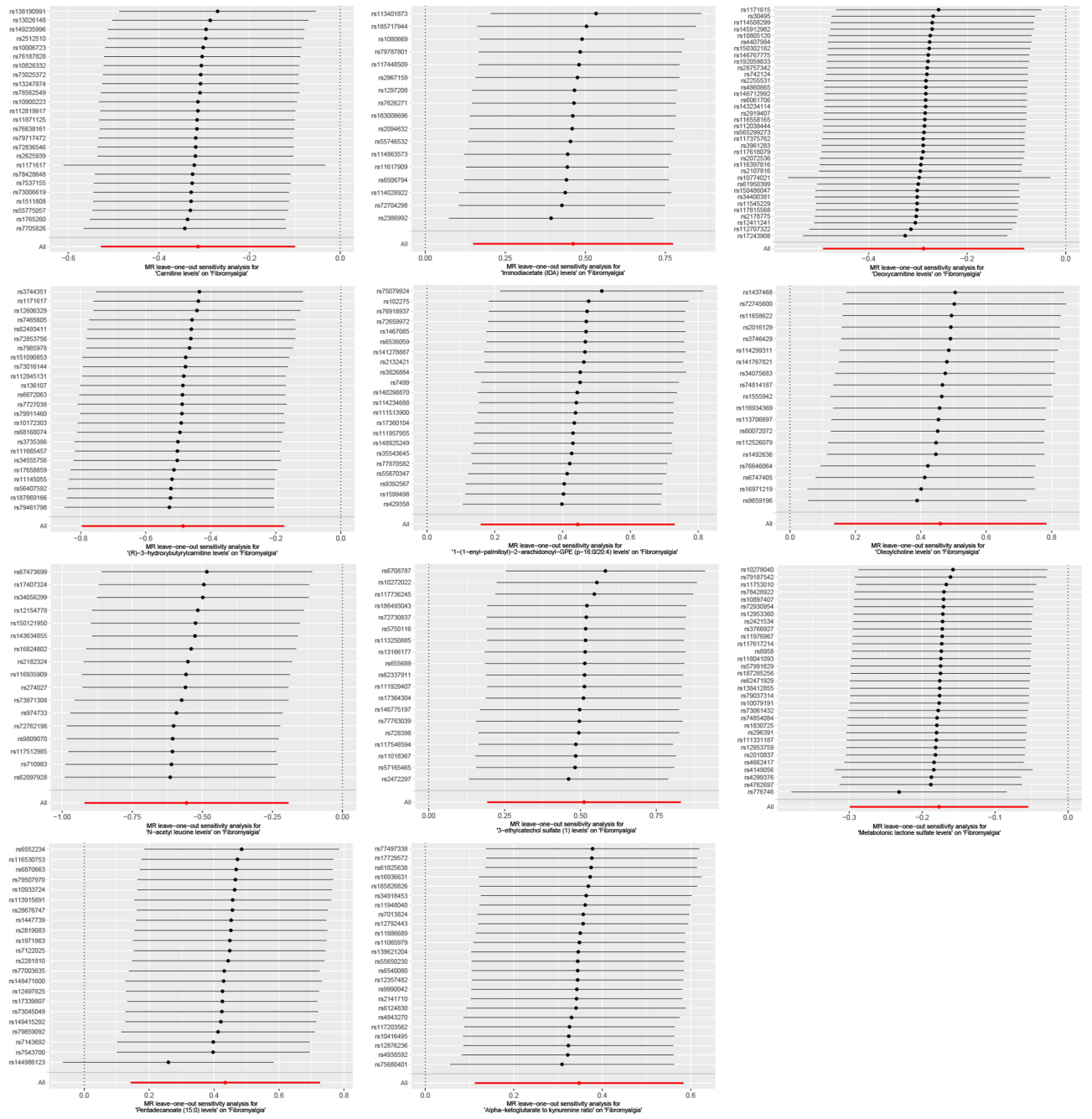

Figure 4 Leave-one-out plots for the causal association between metabolites and FM.

transportation and metabolism of fatty acids, which is vital for maintaining cellular energy balance.[34] In the context of FM, this finding may indicate that abnormalities in energy metabolism play a key role in the disease's progression. Recent research has shown that FM is often linked to oxidative stress.[35] Elevated levels of pro-oxidants, including nitric oxide, lipid peroxidation, and mitochondrial autophagy, can contribute to heightened pain sensitivity in FM. Conversely, carnitine acts as an antioxidant, helping to neutralize free radicals and mitigate cellular damage caused by oxidative stress.[36,37] Thus, the antioxidant properties of carnitine may play a protective role in the development of FM. This discovery offers new insights for further exploration into therapeutic approaches for FM.

Recent metabolomic studies have identified six key metabolites that play critical roles in chronic pain conditions. Carnitine and its derivatives, including deoxycarnitine and (R)-3-hydroxybutyrylcarnitine, are frequently dysregulated,

reflecting altered energy metabolism and impaired fatty acid β-oxidation.[38,39] For example, in ME/CFS patients, reduced acetylcarnitine levels accompanied by increased short-chain acylcarnitines indicate a hypometabolic state.[38,39] Similarly, disturbed carnitine profiles in rheumatoid arthritis underscore their role in immune-inflammatory regulation, with emerging evidence supporting their use as diagnostic biomarkers and therapeutic targets.[40] Additionally, alterations in amino acid derivatives such as N-acetyl-leucine correlate with pain severity in FM, suggesting that imbalanced BCAA metabolism may contribute to chronic pain via reduced energy supply and increased oxidative stress.[41] Furthermore, 3-ethylcatechol sulfate—a gut microbiota-derived catechol metabolite—has been linked to oxidative stress and aberrant neurotransmitter metabolism, while diminished oleoylcholine may impair the cholinergic anti-inflammatory pathway.[41,42] Collectively, these findings point to convergent pathogenic mechanisms—including mitochondrial dysfunction, lipid and amino acid metabolic imbalances, neuroinflammation, and autonomic dysregulation—that underpin various chronic pain states and highlight the potential of these metabolites as biomarkers and therapeutic targets.

Reverse MR analysis revealed a borderline association between fibromyalgia and iminodiacetate (IDA) levels (IVW OR = 0.98, 95% CI: 0.954–0.998; P = 0.04). Although IDA is biologically plausible given its roles in mitochondrial function and inflammatory regulation, we cannot exclude potential bias from residual confounding or weak instrument strength.[43] Future studies should independently replicate this finding in larger, multi-ancestry cohorts using stronger genetic instruments to confirm the validity of this reverse causal association.

A distinctive feature of our study was the utilization of comprehensive blood metabolite GWAS data, which is relatively rare in previous FM research. Furthermore, our MR approach provided robust evidence for analyzing the causal relationship between metabolites and FM. The application of this method not only deepened our understanding of the disease but also offered new directions for future treatment strategies.

Our study has several limitations. First, the modest clinical sample size, while sufficient for detecting large effect sizes as in the case of carnitine, limits the generalizability of our findings and the power to identify subtler associations. Second, the unique source of our control group from a maternity center, despite strict exclusion criteria for pregnancy and postpartum status, may affect the representativeness of the baseline carnitine levels and necessitates cautious interpretation. Third, the lack of systematically collected detailed clinical phenotypes, such as disease-specific symptom scores, precluded deeper clinical correlation analyses. Finally, while the MR design strengthens causal inference, potential residual confounding such as horizontal pleiotropy, coupled with the limited ancestral diversity of both our clinical and GWAS cohorts, underscores the need for replication in larger, more diverse, and deeply phenotyped populations.

In summary, our research provides new insights into understanding the metabolic mechanisms of FM and may indicate directions for future treatment strategies. Future studies should concentrate on confirming the role of these metabolites in the onset of FM and investigating their potential therapeutic applications. Moreover, research efforts should be broadened to include diverse populations and a wider array of metabolites to fully grasp the biological underpinnings of this complex disease.

Conclusions

In conclusion, by integrating clinical and genetic data, our study provides novel evidence supporting a potential causal, protective role of carnitine in FM pathogenesis. While these findings highlight the promise of targeting metabolic pathways for FM management, they also necessitate confirmation through larger, multi-ancestry studies and ultimately, interventional trials.

Informed Consent Statement

All individuals involved in the study were thoroughly educated on the research objectives and methods, and they gave their written informed consent.

Data Sharing Statement

The datasets analyzed during the current study are available in the GWAS repository. The specific datasets used are:

Fibromyalgia: finn-b-M13_FIBROMYALGIA

Blood Metabolomic: Supplemental Table S1

All R scripts and analysis pipelines used in this study are publicly available at GitHub: https://github.com/lingkeng23/Fibromyalgia_MR_study.git.

Please specify from whom the data is available upon request from the two Corresponding authors.

Ethics Approval and Consent to Participate

This research was approved by the ethics review board of the Jiaxing Maternity and Children Health Care Hospital, and all procedures were complied with the ethical principal of Helsinki Declaration. All the participants fully understood the goals and process of the research and provided the written informed consent.

Author Contributions

All authors made a significantontribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysisnd 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 beccountable for all aspects of the work.

Funding

This work was supported by Medical Health Science and Technology Project Zhejiang Provincial Health Commission (Grant No. 2024KY454, 2025KY366), Zhejiang Traditional Chinese Medicine Administration (2024ZL1058) and Zhejiang Provincial Natural Science Foundation of China (No.LQN25H180008).

Disclosure

The authors declare no conflict of interest.

References

1. Sarzi-puttini P, Giorgi V, Marotto D, et al. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat Rev Rheumatol*. 2020;16(11):645–660. doi:10.1038/s41584-020-00506-w
2. Hackshaw KV. The search for biomarkers in fibromyalgia. *Diagnostics*. 2021;11(2):156. doi:10.3390/diagnostics11020156
3. Qureshi AG, Jha SK, Iskander J, et al. Diagnostic challenges and management of fibromyalgia. *Cureus*. 2021;13(10):e18692. doi:10.7759/cureus.18692
4. Berwick R, Barker C, Goebel A. The diagnosis of fibromyalgia syndrome. *Clin Med*. 2022;22(6):570–574. doi:10.7861/clinmed.2022-0402
5. Giorgi V, Sirotti S, Romano ME, et al. Fibromyalgia: one year in review 2022. *Clin Exp Rheumatol*. 2022;40(6):1065–1072. doi:10.55563/clinexprheumatol/if9gk2
6. Kumbhare D, Hassan S, Diep D, et al. Potential role of blood biomarkers in patients with fibromyalgia: a systematic review with meta-analysis. *Pain*. 2022;163(7):1232–1253. doi:10.1097/j.pain.0000000000002510
7. Piras C, Conte S, Pibiri M, et al. Metabolomics and psychological features in fibromyalgia and electromagnetic sensitivity. *Sci Rep*. 2020;10(1):20418. doi:10.1038/s41598-020-76876-8
8. Piras C, Pibiri M, Conte S, et al. Metabolomics analysis of plasma samples of patients with fibromyalgia and electromagnetic sensitivity using GC-MS technique. *Sci Rep*. 2022;12(1):21923. doi:10.1038/s41598-022-25588-2
9. Menzies V, Starkweather A, Y Yao, et al. Metabolomic differentials in women with and without fibromyalgia. *Clin Transl Sci*. 2020;13(1):67–77. doi:10.1111/cts.12679
10. Zhang D, Jiang L, Li L, et al. Integrated metabolomics revealed the fibromyalgia-alleviation effect of Mo(2)C nanozyme through regulated homeostasis of oxidative stress and energy metabolism. *Biomaterials*. 2022;287:121678. doi:10.1016/j.biomaterials.2022.121678
11. Zetterman T, Nieminen AI, Markkula R, et al. Machine learning identifies fatigue as a key symptom of fibromyalgia reflected in tyrosine, purine, pyrimidine, and glutaminergic metabolism. *Clin Transl Sci*. 2024;17(3):e13740. doi:10.1111/cts.13740
12. Dirawi N, Habib G. Effect of intramuscular depot betamethasone injection in patients with fibromyalgia and elevated C-reactive protein levels. *J Investig Med*. 2022;70(7):1553–1556. doi:10.1136/jim-2021-002293
13. Li N, Zhao H. Role of carnitine in non-alcoholic fatty liver disease and other related diseases: an update. *Front Med*. 2021;8:689042. doi:10.3389/fmed.2021.689042
14. Virmani MA, Cirulli M. The role of l-Carnitine in mitochondria, prevention of metabolic inflexibility and disease initiation. *Int J Mol Sci*. 2022;23(5). doi:10.3390/ijms23052717
15. El-hattab AW, Scaglia F. Disorders of carnitine biosynthesis and transport. *Mol Gene Metabol*. 2015;116(3):107–112. doi:10.1016/j.ymgme.2015.09.004
16. Aroke EN, Powell-roach KL. The metabolomics of chronic pain conditions: a systematic review. *Biol Res Nurs*. 2020;22(4):458–471. doi:10.1177/1099800420941105
17. Menzies V, Starkweather A, Y YAO, et al. Exploring associations between metabolites and symptoms of fatigue, depression and pain in women with fibromyalgia. *Biol Res Nurs*. 2021;23(1):119–126. doi:10.1177/1099800420941109

18. Hong M, Wang J, L Jin, et al. The impact of creatine levels on musculoskeletal health in the elderly: a mendelian randomization analysis. *BMC Musculoskel Disorders*. 2024;25(1):1004. doi:10.1186/s12891-024-08140-3
19. Ling K, Hong M, L Jin, et al. Blood metabolomic and postpartum depression: a mendelian randomization study. *BMC Pregnancy Childbirth*. 2024;24(1):429. doi:10.1186/s12884-024-06628-3
20. Ling K, Zhang S, L Jin, et al. Potential association between mobile phone usage duration and postpartum depression risk: evidence from a Mendelian randomization study. *Medicine*. 2024;103(41):e39973. doi:10.1097/MD.0000000000039973
21. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46 (3):319–329. doi:10.1016/j.semarthrit.2016.08.012
22. Chen Y, Lu T, Pettersson-kymmer U, et al. Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases. *Nature Genet*. 2023;55(1):44–53. doi:10.1038/s41588-022-01270-1
23. Orrù V, Steri M, Sidore C, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. *Nature Genet*. 2020;52 (10):1036–1045. doi:10.1038/s41588-020-0684-4
24. Yu XH, Yang YQ, Cao RR, et al. The causal role of gut microbiota in development of osteoarthritis. *Osteoarthritis Cartilage*. 2021;29 (12):1741–1750. doi:10.1016/j.joca.2021.08.003
25. Kurilshikov A, Medina-gomez C, Bacigalupe R, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nature Genet*. 2021;53(2):156–165. doi:10.1038/s41588-020-00763-1
26. Burgess S, small SS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Meth Med Res*. 2017;26 (5):2333–2355. doi:10.1177/0962280215597579
27. Bowden J, Davey Smith G, Haycock PC, et al. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
28. Hartwig FP, G Daveysmith, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46(6):1985–1998. doi:10.1093/ije/dyx102
29. Burgess S, G Thompsons. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. doi:10.1007/s10654-017-0255-x
30. Verbanck M, Y Chenc, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
31. Bene J, Hadzsiev K, Melegh B. Role of carnitine and its derivatives in the development and management of type 2 diabetes. *Nut Diabetes*. 2018;8 (1):8. doi:10.1038/s41387-018-0017-1
32. Sawicka AK, Renzi G, Olek RA. The bright and the dark sides of L-carnitine supplementation: a systematic review. *J Int Soc Sports Nutr*. 2020;17 (1):49. doi:10.1186/s12970-020-00377-2
33. Alhasaniah AH. l-carnitine: nutrition, pathology, and health benefits. *Saudi J Biol Sci*. 2023;30(2):103555. doi:10.1016/j.sjbs.2022.103555
34. Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *BBA*. 2016;1863(10):2422–2435. doi:10.1016/j.bbamcr.2016.01.023
35. Assavarittirong C, Samborski W, Grygiel-górniak B. Oxidative stress in fibromyalgia: from pathology to treatment. *Oxid Med Cell Longev*. 2022;2022:1582432. doi:10.1155/2022/1582432
36. Gülçin I. Antioxidant and antiradical activities of L-carnitine. *Life Sci*. 2006;78(8):803–811. doi:10.1016/j.lfs.2005.05.103
37. Wang W, D Pan, Q Liu, et al. L-carnitine in the treatment of psychiatric and neurological manifestations: a systematic review. *Nutrients*. 2024;16 (8):1232.
38. N Baraniukj. Cerebrospinal fluid metabolomics, lipidomics and serine pathway dysfunction in myalgic encephalomyelitis/chronic fatigue syndroome (ME/CFS). *Sci Rep*. 2025;15(1):7381. doi:10.1038/s41598-025-91324-1
39. Hoel F, Hoel A, Pettersen IK, et al. A map of metabolic phenotypes in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *JCI Insight*. 2021;6(16). doi:10.1172/jci.insight.149217
40. Zhang R, Wang J, Zhai X, et al. Targeted detection of 76 carnitine indicators combined with a machine learning algorithm based on HPLC-MS/MS in the diagnosis of rheumatoid arthritis. *Metabolites*. 2025;15(3):205. doi:10.3390/metabo15030205
41. L Fernandessilva, Hokkanen J, Vangipurapu J, et al. Metabolites as risk factors for diabetic retinopathy in patients with type 2 diabetes: a 12-year follow-up study. *J Clin Endocrinol Metab*. 2023;109(1):100–106. doi:10.1210/clinem/dgad452
42. Hu J, Melchor GS, Ladakis D, et al. Myeloid cell-associated aromatic amino acid metabolism facilitates CNS myelin regeneration. *NPJ Regen Med*. 2024;9(1):1. doi:10.1038/s41536-023-00345-9
43. Wajner M, U AMARALA. Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animal studies. *Biosci Rep*. 2015;36(1):e00281. doi:10.1042/BSR20150240