International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Physiotherapy Reduces Pain and Alters Fatty Acid Biomarkers in Women with Chronic Non-Specific Low Back Pain

Zhou Zhang[1,2,*], Xin Li[1,*], Wen Tang[1], Hao Xie[1], Hong-Jiang Wang[1], Hao-Yu Xie[1,3], Chu-Huai Wang[1]

[1]Department of Rehabilitation Medicine, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, 510275, People's Republic of China; [2]Guangdong Provincial Clinical Research Center for Rehabilitation Medicine, Guangzhou, 510275, People's Republic of China; [3]Department of Rehabilitation Medicine, Suzhou Municipal Hospital, Gusu School of Nanjing Medical University, Suzhou, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chu-Huai Wang; Hao-Yu Xie, Email wangchuh@mail.sysu.edu.cn; xiehy55@mail.sysu.edu.cn

Background: Chronic nonspecific low back pain (cNLBP) represents the most prevalent musculoskeletal disorder encountered in clinical practice, constituting approximately two-thirds of all chronic low back pain cases. Epidemiological studies have identified significant gender differences in the incidence of cNLBP, with women exhibiting a slightly higher prevalence and reporting greater pain severity compared to men. However, the underlying mechanisms contributing to the increased severity of cNLBP in women remain largely unexplored. Our research is the first to explore fatty acid biomarkers in female patients with cNLBP undergoing physiotherapy from the perspectives of metabolomics and lipidomics.

Methods: The study comprised 13 healthy female volunteers and 15 women diagnosed with cNLBP. Metabolomic and lipidomic analyses were employed to identify lipid metabolites closely associated with cNLBP in women. Subsequently, the 15 patients with cNLBP underwent manual therapy and exercise therapy, which incorporated both manual therapy and exercise therapy. Each therapy session lasted 50 minutes and was conducted over six sessions, occurring every two days. The Visual Analog Scale (VAS) scores of the patients were evaluated before and after treatment, and serum samples were collected for lipid determination at both pre- and post-treatment intervals.

Results: Our metabolomic and lipidomic analyses revealed significantly elevated levels of three fatty acids (FAs): C14:0 FA (P=0.046), C20:0 FA (P=0.000001), and C20:1 FA (P=0.0007)), alongside significantly reduced levels of C20:5 (P=0.021) FA in women with cNLBP compared to healthy female volunteers. Receiver Operating Characteristic (ROC) curve analyses demonstrated that the Area Under the Curve (AUC) for these FAs exceeded 75%, indicating robust diagnostic performance. Notably, C20:0 FA exhibited an AUC greater than 95%, suggesting its potential as the most effective biomarker for diagnosing female patients with cNLBP. Additionally, physiotherapy significantly reduced pain levels in these women and was associated with a substantial decrease in blood FA levels.

Conclusion: The study revealed a significant correlation between FA levels and female patients with cNLBP undergoing physiotherapy, thereby providing valuable insights for the development of personalized treatment approaches.

Trial Registration: (Chinese Clinical Trial Registry (https://www.chictr.org.cn), No.ChiCTR2300076620, 10/13/2023).

Keywords: fatty acid, metabolome, lipidome, chronic nonspecific low back pain

Introduction

Chronic nonspecific low back pain (cNLBP) represents a widespread clinical challenge affecting a substantial portion of the global population.[1] The *Guidelines for the Diagnosis and Treatment of Chronic Low Back Pain in China*, published in 2024, indicate that the prevalence of cNLBP consistently ranks among the top three conditions worldwide. Furthermore, it is listed as one of the five leading causes of reduced disability-adjusted life years, significantly contributing to disability and diminished productivity.[2] The healthcare expenditures associated with cNLBP have surpassed those of other

Received: 2 July 2025
Accepted: 6 September 2025
Published: 15 September 2025

common chronic conditions, including hypertension, diabetes, and coronary heart disease, thereby imposing a considerable economic burden on both society and affected individuals.[3]

cNLBP represents a multifaceted syndrome with a complex pathogenesis involving mechanical, chemical, psychosocial, biomechanical, and neurobiological factors.[4] The suggested approach for managing cNLBP evolves from simpler, conservative treatments to more advanced, higher-risk, and costlier options. This progression typically begins with conservative medical management, advances to percutaneous interventional techniques aimed at alleviating persistent pain, and ultimately culminates in surgical interventions that address underlying issues or modify the chronic pain mechanism.[5] Conservative medical management encompasses exercise, physical rehabilitation, and various non-pharmacological strategies, alongside pharmacological options such as analgesics, non-steroidal anti-inflammatory drugs, and, for select patients, opioids. Physiotherapy is a critical component of conservative medical management and is regarded as the initial treatment choice for chronic low back pain.[6] Among the numerous physiotherapy techniques, exercise therapy and manual therapy have demonstrated efficacy in managing chronic low back pain. These methods are associated with a decreased likelihood of exacerbating future back problems or leading to work absences, making them preferable treatment alternatives to medication or surgical interventions. Furthermore, these therapies can be administered in rehabilitation facilities.[7] Furthermore, a significant sex disparity exists in both the prevalence and experience of low back pain. Studies demonstrate that females have a higher prevalence of cNLBP than males.[8,9] Moreover, females with back pain report greater pain intensity compared to males.[10] Nevertheless, the underlying mechanisms contributing to the increased severity of cNLBP in women remain largely unexplored.

Recent research has increasingly focused on the role of lipid molecules in pain regulation.[11,12] Studies indicate that aberrant lipid metabolism and inflammatory responses significantly contribute to pain onset and progression.[13–15] A recent investigation demonstrated a significant association between abdominal adipose tissue and chronic musculoskeletal pain, suggesting that excess ectopic fat deposition may significantly contribute to the pathogenesis of multisite, generalized chronic musculoskeletal pain, with a notably stronger effect in women compared to men.[16] ω-6 polyunsaturated fatty acids (PUFAs) represent a significant risk factor for both inflammatory and neuropathic pain. In patients with type 2 diabetic neuropathic pain, skin levels of omega-6 lipids are strongly correlated with reported pain levels and analgesic requirements. Furthermore, reducing ω-6 PUFAs while increasing ω-3 PUFA intake result in a substantial decrease in pain levels.[17] Additionally, lipid metabolites, including prostaglandins and leukotrienes, activate inflammatory signaling pathways that promote the release of inflammatory mediators, thereby exacerbating pain.[18–20] Our previous studies have shown that levels of monacylglycerol (MAG) and diacylglycerol (DAG) are significantly elevated, while triacylglycerol (TAG) levels are markedly decreased in patients with cNLBP compared to healthy individuals. This finding suggests that lipid molecules may significantly contribute to cNLBP development.[21] However, the study did not account for sex disparity in cNLBP within the population. Consequently, the association between specific lipids and the increased occurrence and intensity of pain in women with cNLBP remains uncertain. Our research is the first to explore fatty acid biomarkers in female cNLBP patients undergoing physiotherapy from the perspective of lipidomics.

Materials and Methods

Participants

This study recruited 13 healthy female participants and 15 female patients with chronic nonspecific low back pain (cNLBP) through advertisements. Eligibility criteria included individuals aged between 18 and 40 years with radiating pain from the lower rib to the inferior gluteal fold for at least three months continuously or intermittently for over six months.[22] Two qualified medical professionals confirmed the cNLBP diagnosis using criteria established by the American Pain Society and the American College of Physicians.[23,24] Only individuals with a Visual Analog Scale (VAS) score of 2 or higher were included.[25] Additional requirements encompassed right-hand dominance, absence of neurological disorders or intracranial lesions, and no back pain treatment in the preceding three months.

Individuals who did not meet specific health criteria were excluded from the research. Notably, those who had recently been pregnant or were currently expecting, those experiencing back pain extending to other regions, or those

facing postpartum lower back pain or menstrual complications were disqualified from selection. Furthermore, individuals diagnosed with known inflammatory diseases of the spine, vertebral fractures, advanced osteoporosis, autoimmune arthritis, or cancer were also excluded. Participants with cardiovascular or cerebrovascular diseases, as well as those suffering from endocrine disorders, were deemed ineligible for the study. Subjects who had taken anti-inflammatory drugs or received any other form of intervention were also excluded. Furthermore, individuals facing mental health challenges requiring medication, those unwilling to provide consent or comply with the study protocol, and people struggling with alcohol or substance dependence were also excluded from participation.

Pain levels were assessed in each participant using the VAS, and blood samples were collected for omics analyses. The First Affiliated Hospital of Sun Yat-sen University granted ethical approval for the study (no. [2023]596). Before the experiment, informed consent was obtained from all participants, evidenced by their signatures.

Therapy of Subjects

Therapeutic interventions for women experiencing cNLBP incorporated both manual therapy and exercise therapy. Manual therapy interventions consisted of joint mobilization or manipulation (thrust) and mobilization with movement techniques targeting the spine or pelvis, in accordance with the physiotherapy protocol described in the literature.[26] Each session lasted approximately 20 minutes. Subsequently, patients engaged in exercise therapy for 30 minutes, emphasizing motor control and core stabilization exercises. Motor control exercises included stretching of trunk and limb muscles, flexibility training, trunk and hip rotation, and flexion activities. Stability exercises encompassed the bridge movement, leg-raising bridge, side plank, two-point bird-dog stance with opposite arms and legs elevated, bear crawls, and the dead bug exercise. VAS scores before and after physiotherapy in female patients with cNLBP were evaluated employing the Student's *t*-test ($P < 0.05$). The results are expressed as mean ± standard error of the mean (SD).

Metabolomic Analysis

Venous blood underwent centrifugation at 4°C for 15 minutes to obtain serum. A 100 μL aliquot of the serum sample received an extraction solution, followed by sonication in a 4°C water bath for 10 minutes. The samples were then incubated for one hour at −20°C before centrifugation. The resulting supernatant was transferred to a fresh centrifuge tube and subjected to nitrogen drying. After drying, the samples were reconstituted and applied to a C18 column (2.1 × 100 mm, 1.7 μm particle size; Waters, USA) for mass spectrometry analysis. The metabolomic analysis employed an AB SCIEX Mass Spectrometer QTRAP 4500, with mass spectrometry settings adjusted according to the methodologies described in this article.[21,27]

Lipidomic Analysis

Following venous blood collection, serum was separated through centrifugation at 4°C for 15 minutes. A lipid internal standard and extraction solution were added to 200 μL serum sample, followed by vortex mixing and subsequent centrifugation. The resulting supernatant was transferred to a fresh centrifuge tube and evaporated under nitrogen. The dried samples were then reconstituted and injected into a C18 column (dimensions: 2.1×100 mm, particle size: 1.7 μm) manufactured by Waters (USA) for analysis via mass spectrometry. Lipid analysis was conducted using the AB SCIEX Mass Spectrometer QTRAP 6500, with mass spectrometry parameters configured in accordance with the methodologies outlined in this article.[21,28] Biomarkers were identified through classical univariate Receiver Operating Characteristic (ROC) curve analysis, conducted using the web-based tool METPA (https://www.metaboanalyst.ca/).[29]

Results

Metabolomic Profiling of Women with cNLBP

The study comprised 13 healthy female participants in the Healthy Female Volunteers (HFV) group and 15 female patients diagnosed with cNLBP in the cNLBP group. The cNLBP cohort reported substantial pain levels, as measured by the VAS score. The two groups exhibited no significant differences in age, height, weight, or body mass index (BMI). Detailed demographic information is presented in Table 1. To investigate potential pathogenic factors associated with

Table 1 Demographic Information, M±SD

	Healthy Female Volunteers	Female Patients with cNLBP	P
N (female)	13	15	
Age (years)	23.38±4.52	25.67±3.05	0.1388
Height (m)	1.60±5.89	1.63±6.13	0.2295
Weight (kg)	51.07±4.60	55.80±7.29	0.0634
BMI (kg/m^2)	19.93±1.75	20.94±2.17	0.2088
VAS	0	4.20±1.32	<0.001

Abbreviations: BMI, body mass index; VAS, visual analogue scale.

cNLBP in females, serum metabolite profiles from both groups were analyzed. A Partial Least Squares Discriminant Analysis (PLS-DA) was employed to assess the model's validity. The PLS-DA score plot results revealed a clear separation between healthy female participants and women with cNLBP (Figure 1A). Of the 520 metabolites identified, 15 demonstrated significant changes, characterized by a fold change of ≥ 1.5 and a *p*-value of less than 0.05. Among these metabolites, 10 were upregulated, while 5 were downregulated in female cNLBP patients (Figure 1B).

The metabolites underwent enrichment analysis, which revealed that those exhibiting differential changes were primarily associated with FA metabolism, amino acid metabolism, and energy production. The significant enrichment of amino acid metabolism pathways, including glutamate, cysteine, and glycine/serine metabolism, in conjunction with the urea cycle, likely reflects active nitrogen metabolism and ammonia detoxification processes. Additionally, the enrichment of ubiquinone biosynthesis and glutathione metabolism may indicate the activation of antioxidant defense systems in response to oxidative stress. Notably, there was a marked enrichment of mitochondrial beta-oxidation pathways for long-chain, very long-chain, and short-chain saturated FAs, with enrichment ratios reaching up to 12-fold. This substantial difference in these processes between the two groups suggests that FA catabolism plays a significant role in the pathogenesis of chronic low back pain in women (Figure 2).

Lipidomic Profiling of Women with cNLBP

Following the metabolomic analysis, this study sought to identify specific lipid components associated with cNLBP in women by comparing the lipid composition of women with cNLBP to that of healthy women. The lipid analysis identified 17 lipid species, including phospholipids, sphingolipids, and triglycerides. PLS-DA was employed to elucidate distinct lipidomic profiles between healthy women and those with cNLBP. As depicted in Figure 3A, a notable separation trend was observed in the component 1

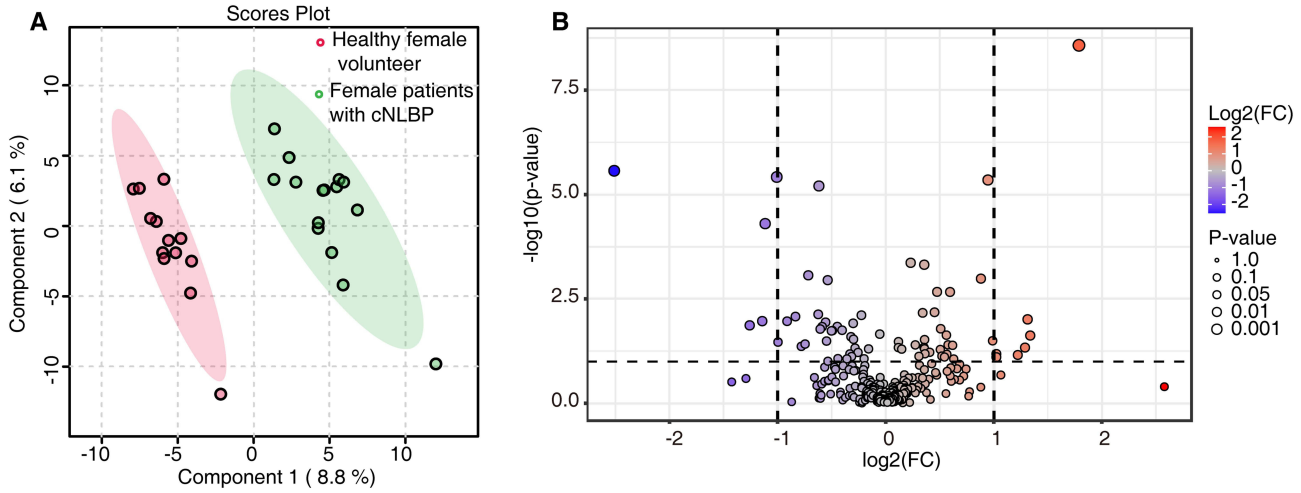

Figure 1 Metabolomic analysis of healthy female participants and female patients with cNLBP (**A**) PLS-DA score plots were generated to illustrate the differences between healthy female participants and female patients with cNLBP (**B**) A volcano plot illustrated the differential metabolites identified between healthy female participants and female patients with cNLBP.

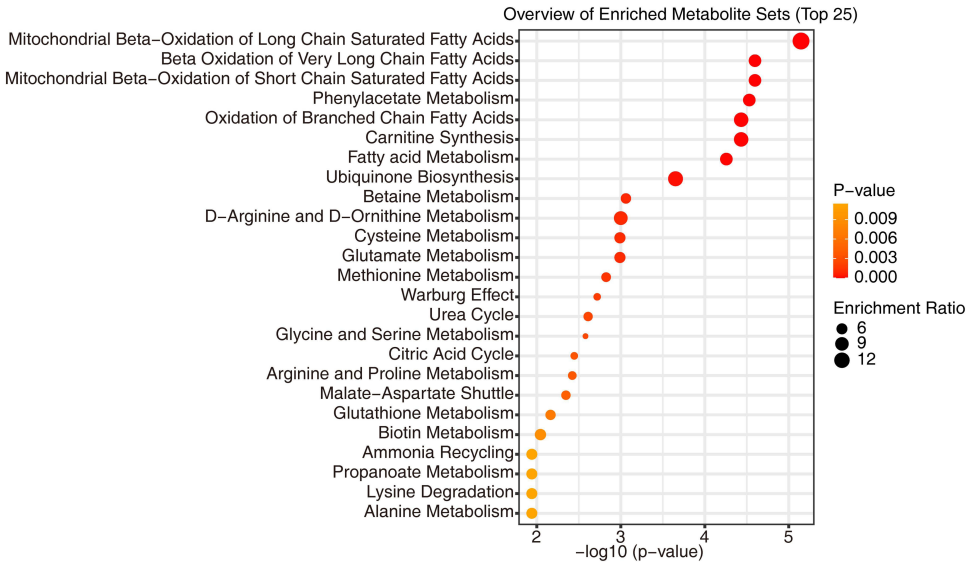

Figure 2 Pathway enrichment analysis of differential metabolites observed between healthy female participants and female patients with cNLBP.

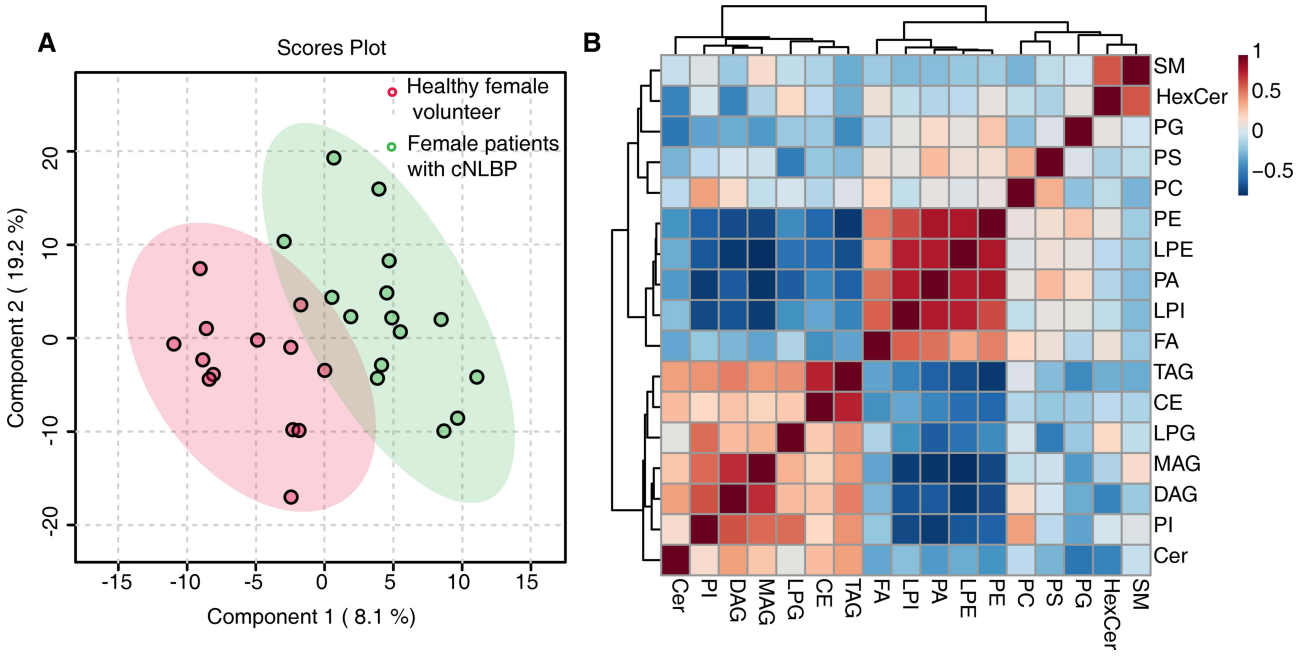

Figure 3 Lipidome analysis in healthy female participants and female patients with cNLBP (**A**) PLS-DA score plots were generated to illustrate the differences between healthy female participants and female patients with cNLBP (**B**) A correlation analysis was conducted on the lipids exhibiting significant differences, employing diverse colors to represent the magnitude of the Pearson correlation coefficient.

scores between healthy female volunteers and female patients with cNLBP. This distinction reveals significant differences in the characteristics or variables represented by component 1 between the two groups. The analysis of correlations among the 17 lipid types was conducted using the Pearson correlation coefficient, demonstrating the degree of association between various lipid species. Positive correlations are indicated in red, while negative correlations are shown in blue; additionally, a deeper shade represents a stronger correlation (Figure 3B).

https://doi.org/10.2147/IJWH.S551117

FA Levels Were Significantly Elevated in Women with cNLBP Compared to Their Healthy Counterparts

We conducted a comparative analysis of 17 lipid levels between healthy women and those with cNLBP. Our results indicated significantly elevated levels of FA, MAG, and DAG in women with cNLBP compared to healthy controls. In a previous investigation, we observed a similar significant increase in MAG and DAG levels in cNLBP patients, regardless of gender. Based on these findings, we propose that FA may represent a class of lipid molecules specifically associated with cNLBP in women (Figure 4).

Changes in FA Levels of Female Patients with cNLBP

Our comprehensive analysis of specific FA components revealed notable increases in the levels of C14:0, C20:0, and C20:1 FAs, while C20:5 FA showed a significant decrease in female patients with cNLBP compared to healthy women (Figure 5). To evaluate the efficacy of these four FAs as biomarkers for diagnosing cNLBP in women, we conducted ROC curve analyses. The ROC curves displayed the False Positive Rate (FPR) on the horizontal axis and the True Positive Rate (TPR) on the vertical axis. The shape and position of each curve illustrated the diagnostic capability of the respective biomarker in distinguishing between healthy women and female patients with cNLBP. The AUC is a crucial metric for assessing diagnostic test performance, with values closer to one indicating superior classification ability. Our results demonstrated that the AUC for these four FAs exceeded 75%, indicating good diagnostic performance. Notably, C20:0 FA exhibited an AUC greater than 95%, suggesting it as the most effective biomarker for diagnosing cNLBP in women (Figure 6).

Physiotherapy Demonstrated Efficacy in Reducing Serum FA Levels Among Female Patients with cNLBP

To corroborate our findings, we administered physiotherapy to 15 patients in the female cNLBP group. Serum samples were obtained before and after treatment. The results demonstrated a significant reduction in pain levels following physiotherapy (Figure 7A). Moreover, analysis of FA content in the serum samples revealed a marked decrease in the levels of 20 FAs post-treatment (Figure 7B). These observations suggest that physiotherapy may mitigate chronic low back pain in women by reducing serum FA levels.

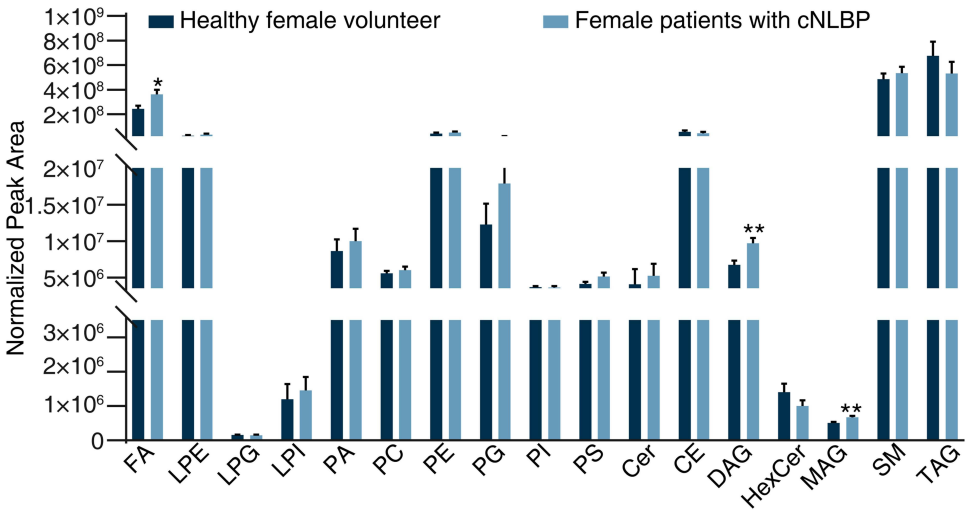

Figure 4 Identification of changes in lipid components in healthy female participants and female patients with cNLBP Lipid analysis was performed on samples obtained from healthy female participants and female patients diagnosed with cNLBP. Significant differences in lipid levels were observed between the two groups, as determined by Student's *t*-test. *p<0.05; **p<0.01.

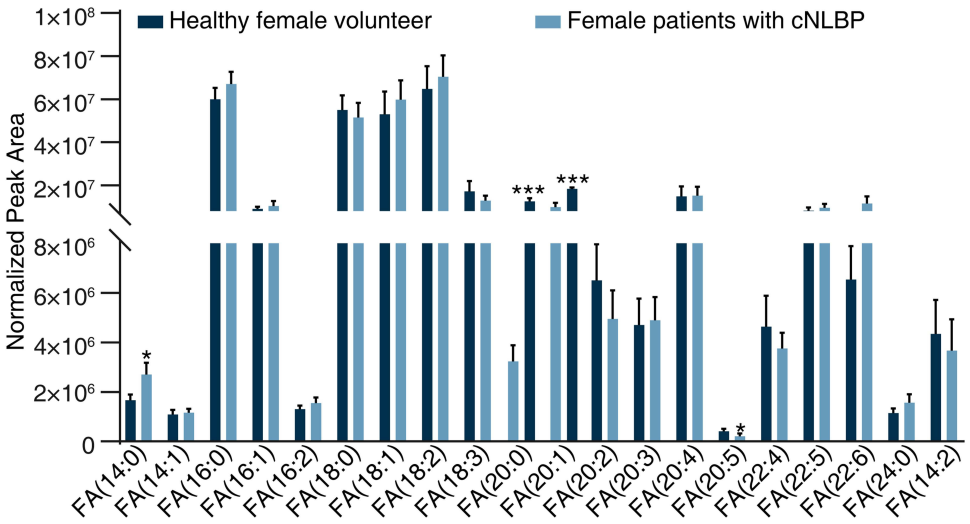

Figure 5 Comparing the variations in the constituents of fatty acid in healthy female participants and female patients with cNLBP To assess differences in fatty acid concentrations between healthy female participants and female patients with cNLBP, a Student's *t*-test was employed. *$p<0.05$; ***$p<0.001$.

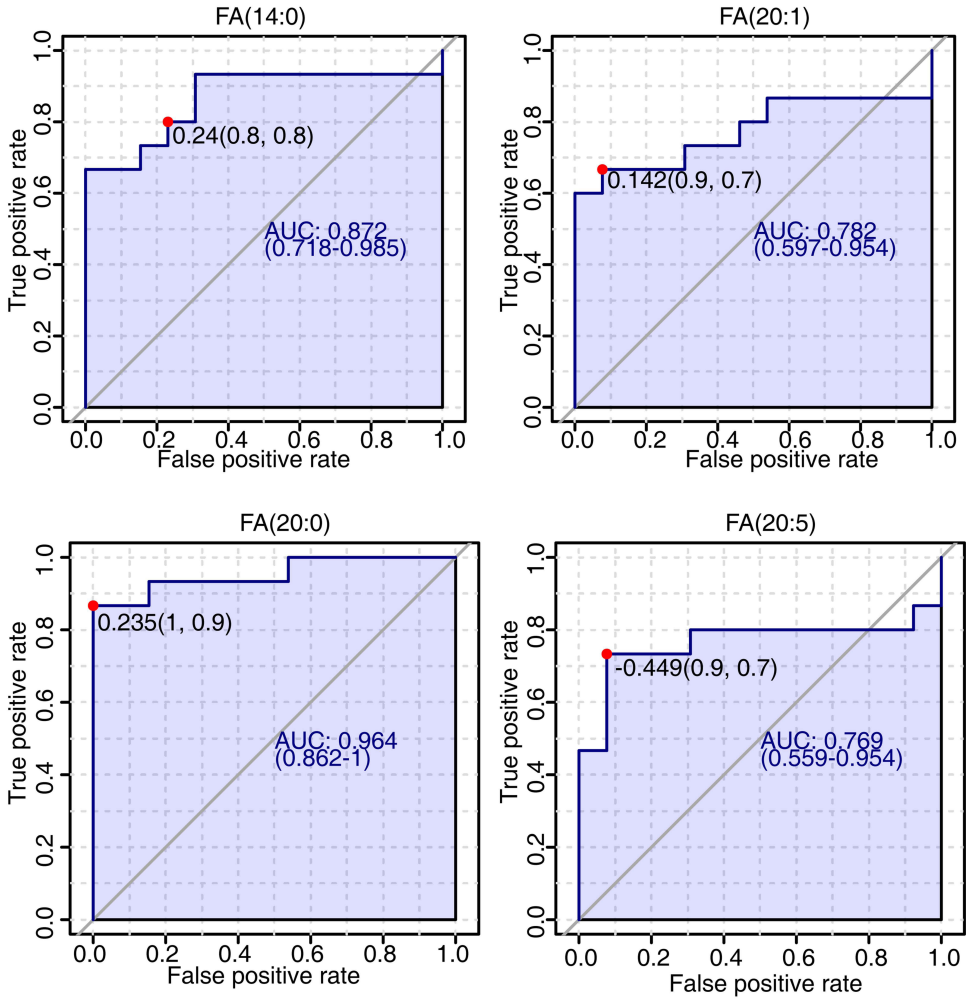

Figure 6 Classical univariate ROC curve analysis of the 4 fatty acids that exhibited significant differences between healthy female participants and female patients with cNLBP.

https://doi.org/10.2147/IJWH.S551117

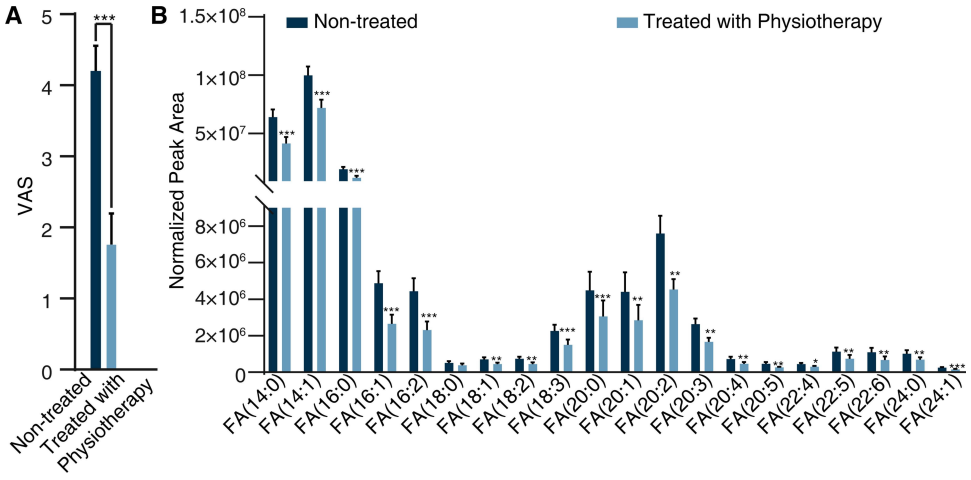

Figure 7 Physiotherapy demonstrated significant efficacy in pain alleviation and serum fatty acid level reduction among women with cNLBP.(**A**) Comparison of VAS scores before and after physiotherapy in female patients with cNLBP (**B**) Comparative analysis of fatty acid composition in female patients with cNLBP pre- and post-physiotherapyA Student's *t*-test was performed. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

Discussion

cNLBP represents the most prevalent musculoskeletal disorder encountered in clinical practice, comprising approximately two-thirds of all chronic low back pain cases.[30] Epidemiological studies have revealed that between 65% and 80% of adults will experience low back pain at least once in their lifetime, with nonspecific cases accounting for nearly 90% of all low back pain occurrences.[31] cNLBP imposes a significant economic burden on society, with healthcare expenditures exceeding USD 100 billion annually in the United States alone.[32] The global burden of LBP is projected to increase, as the number of adults aged 60 and above experiencing cNLBP is expected to double from its 2015 figures, reaching 2.1 billion by 2050.[33] Notable gender disparities exist in the incidence of cNLBP, with women demonstrating a slightly higher prevalence than men and reporting more severe pain.[34] Some studies suggest that these differences may be associated with hormonal fluctuations, such as changes in estrogen levels, reduced core muscle strength, and psychosocial stress.[35–37] However, the underlying molecular mechanisms contributing to the greater impact of cNLBP on women remain unexplored.

The initial stage of FA synthesis begins with the carboxylation of acetyl-CoA, resulting in the formation of malonyl-CoA. This reaction, catalyzed by acetyl-CoA carboxylase (ACCase), is considered the rate-limiting step in the process.[38] In eukaryotes, long-chain FAs, including palmitic acid (C16:0), are synthesized from malonyl-CoA by the enzyme fatty acid synthase (FASN).[39] Unsaturated FAs, characterized by varying carbon chain lengths and numbers of double bonds—such as oleic and arachidonic acids—are produced through the action of desaturases, including Δ9 desaturase, and elongation enzymes.[40–42] Our metabolomic analysis and lipid profiling of serum samples from healthy women and those with cNLBP revealed significantly elevated levels of FAs, MAG, and DAG in women with cNLBP compared to healthy controls. A previous study, which did not consider gender differences, found elevated MAG and DAG levels in individuals with cNLBP compared to healthy subjects.[21] This suggests a notable association between MAG and DAG levels and cNLBP, with the elevated FA content identified as a specific contributing factor to cNLBP in women. Moreover, physiotherapy has been shown to significantly reduce pain scores and serum FA levels in women with cNLBP, further substantiating the correlation between FA levels and cNLBP in this population. Previous studies have demonstrated that exercise can facilitate the transport of fatty acids into mitochondria by activating the "AMPK-ACC-CPT-1" pathway, thereby promoting fatty acid oxidation and reducing their concentration in serum.[43,44] Furthermore, exercise may also contribute to the long-term restructuring of the oxidation system through the "SIRT1-PGC-1α-PPAR" axis, ultimately leading to a reduction in circulating fatty acids.[45] We propose two mechanisms by which FAs may contribute to cNLBP in women. The first involves pain transmission, which is influenced by the activity of transient receptor potential (TRP) ion channels.[46] The TRP channel family acts as a crucial sensor for pain signaling, with its activity being highly dependent on the lipid environment.[47] FA metabolites, such as prostaglandins and leukotrienes, directly activate channels like TRPV1 and TRPA1, facilitating Ca^{2+}influx and initiating pain signaling pathways.[48,49]

The second mechanism suggests that a higher proportion of saturated FAs relative to unsaturated FAs stimulates an inflammatory reaction, resulting in pain. Studies have shown that saturated FAs can exacerbate inflammation and neuropathic pain by activating Toll-like receptor 4 (TLR4).[50,51] Conversely, polyunsaturated FAs, such as 20:5 FA, can competitively inhibit arachidonic acid metabolism and generate anti-inflammatory lipid mediators, including resolvins, which may alleviate chronic pain.[52,53] Our findings indicate that levels of polyunsaturated 20:5 FA were significantly lower in women with cNLBP compared to healthy women, whereas levels of saturated FAs, such as 20:0 FA and 14:0 FA, were significantly higher in women with cNLBP, potentially promoting inflammatory responses and exacerbating pain. This study employed metabolomic and lipomic analyses to demonstrate that alterations in FA levels may contribute to cNLBP in women, thereby offering novel insights for personalized treatment strategies.

Study Strengths and Limitations

The primary strength of this study lies in its identification of elevated FA levels as a significant risk factor for cNLBP in women. Furthermore, it establishes that physical therapy can mitigate chronic low back pain in this demographic by reducing FA concentrations. However, the precise mechanisms through which FAs contribute to cNLBP in women remain to be elucidated.

Conclusions and Clinical Perspective

This study pioneered the establishment of a robust association between FAs and cNLBP in women, utilizing both metabolomic and lipidomic approaches. Moreover, it elucidates how physical therapy can mitigate cNLBP in women by down-regulating FA levels, thus offering novel insights for personalized treatment strategies. The development of new therapeutic agents targeting these FA alterations may prove advantageous in the treatment of cNLBP in women. In the next phase of our study, we will increase our clinical sample size and specify the follow-up duration and sustained outcomes to enhance the rigor of our investigation.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (ethics: no. [2023]596). Written informed consent was obtained from all the participants prior to the experiment.

Acknowledgments

We would like to thank the Changsha SmallAnt Biotechnology Co., Ltd. (Changsha, China) for providing the technical support.

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.

Funding

This work was supported by the Traditional Chinese Medicine Research Projects of Guangdong province (20251057); National Natural Science Foundation of China (82302851); Program of Guangdong Provincial Clinical Research Center for Rehabilitation Medicine (2023B110003).

Disclosure

All authors approved the manuscript and declared no competing interests.

References

1. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet*. 2017;389(10070):736–747. doi:10.1016/S0140-6736(16)30970-9
2. Ma K, Zhuang ZG, Wang L, et al. The Chinese Association for the Study of Pain (CASP): consensus on the assessment and management of chronic nonspecific low back pain. *Pain Res Manag*. 2019;2019:8957847. doi:10.1155/2019/8957847
3. Fatoye F, Gebrye T, Ryan CG, Useh U, Mbada C. Global and regional estimates of clinical and economic burden of low back pain in high-income countries: a systematic review and meta-analysis. *Front Public Health*. 2023;11:1098100. doi:10.3389/fpubh.2023.1098100
4. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012;379:482–491. doi:10.1016/S0140-6736(11)60610-7
5. Mekhail N, Eldabe S, Templeton E, Costandi S, Rosenquist R. Pain management interventions for the treatment of chronic low back pain: a systematic review and meta-analysis. *Clin J Pain*. 2023;39:349–364. doi:10.1097/AJP.0000000000001116
6. Nicol V, Verdaguer C, Daste C, et al. Chronic low back pain: a narrative review of recent international guidelines for diagnosis and conservative treatment. *J Clin Med*. 2023;13:12. doi:10.3390/jcm13010012
7. Hidalgo B, Detrembleur C, Hall T, Mahaudens P, Nielens H. The efficacy of manual therapy and exercise for different stages of non-specific low back pain: an update of systematic reviews. *J Man Manip Ther*. 2014;22:59–74. doi:10.1179/2042618613Y.0000000041
8. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: systematic review. *Rev Saude Publica*. 2015;49:1. doi:10.1590/S0034-8910.2015049005874
9. Meints SM, Wang V, Edwards RR. Sex and race differences in pain sensitization among patients with chronic low back pain. *J Pain*. 2018;19:1461–1470. doi:10.1016/j.jpain.2018.07.001
10. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine*. 2003;28:143–150. doi:10.1097/00007632-200301150-00010
11. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. 2014;510:92–101. doi:10.1038/nature13479
12. Chávez-Castillo M, Ortega Á, Cudris-Torres L, et al. Specialized pro-resolving lipid mediators: the future of chronic pain therapy? *Int J Mol Sci*. 2021;23:22. doi:10.3390/ijms23010022
13. Wagner KM, Gomes A, McReynolds CB, Hammock BD. soluble epoxide hydrolase regulation of lipid mediators limits pain. *Neurotherapeutics*. 2020;17:900–916. doi:10.1007/s13311-020-00916-4
14. Miller YI, Navia-Pelaez JM, Corr M, Yaksh TL. Lipid rafts in glial cells: role in neuroinflammation and pain processing. *J Lipid Res*. 2020;61:655–666. doi:10.1194/jlr.TR119000468
15. Ueda H. Pathogenic mechanisms of lipid mediator lysophosphatidic acid in chronic pain. *Prog Lipid Res*. 2021;81:101079. doi:10.1016/j.plipres.2020.101079
16. Kifle ZD, Tian J, Aitken D, et al. MRI-derived abdominal adipose tissue is associated with multisite and widespread chronic pain. *Reg Anesth Pain Med*. 2025. doi:10.1136/rapm-2024-105535
17. Boyd JT, LoCoco PM, Furr AR, et al. Elevated dietary ω-6 polyunsaturated fatty acids induce reversible peripheral nerve dysfunction that exacerbates comorbid pain conditions. *Nat Metab*. 2021;3:762–773. doi:10.1038/s42255-021-00410-x
18. Hedenberg-Magnusson B, Ernberg M, Alstergren P, Kopp S. Pain mediation by prostaglandin E2 and leukotriene B4 in the human masseter muscle. *Acta Odontol Scand*. 2001;59:348–355. doi:10.1080/000163501317153185
19. Devi NS, Doble M.: leukotriene c4 synthase: upcoming drug target for inflammation. *Curr Drug Targets*. 2012;13:1107–1118. doi:10.2174/138945012802009053
20. Rondina MT. Targeting prostacyclin: all gain with no pain? *Blood*. 2023;142:1506–1507. doi:10.1182/blood.2023022227
21. Tang W, Wang HJ, Luo SY, et al. Lipid alterations in chronic nonspecific low back pain in the chinese population: a metabolomic and lipidomic study. *Bioengineering*. 2024;11.
22. Meints SM, Mawla I, Napadow V, et al. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. *Pain*. 2019;160:833–843. doi:10.1097/j.pain.0000000000001461
23. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. 2007;30:77–94. doi:10.1007/s10865-006-9085-0
24. van Dieën JH, Reeves NP, Kawchuk G, van Dillen LR, Hodges PW, Van Dillen LR. Motor control changes in low back pain: divergence in presentations and mechanisms. *J Orthop Sports Phys Ther*. 2019;49:370–379. doi:10.2519/jospt.2019.7917
25. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science*. 2000;288:1769–1772. doi:10.1126/science.288.5472.1769
26. Castro J, Correia L, BdS D, et al. Cognitive functional therapy compared with core exercise and manual therapy in patients with chronic low back pain: randomised controlled trial. *PAIN*. 2022;163:2430–2437. doi:10.1097/j.pain.0000000000002644
27. Wang J, Zhang T, Shen X, et al. Serum metabolomics for early diagnosis of esophageal squamous cell carcinoma by UHPLC-QTOF/MS. *Metabolomics*. 2016;12:116. doi:10.1007/s11306-016-1050-5
28. Xuan Q, Zheng F, Yu D, et al. Rapid lipidomic profiling based on ultra-high performance liquid chromatography-mass spectrometry and its application in diabetic retinopathy. *Anal Bioanal Chem*. 2020;412:3585–3594. doi:10.1007/s00216-020-02632-6
29. Xia J, Wishart DS. Web-based inference of biological patterns, functions and pathways from metabolomic data using MetaboAnalyst. *Nat Protoc*. 2011;6:743–760. doi:10.1038/nprot.2011.319
30. Alonso-Sal A, Alonso-Perez JL, Sosa-Reina MD, et al. Effectiveness of physical activity in the management of nonspecific low back pain: a systematic review. *Medicina*. 2024;60:2065. doi:10.3390/medicina60122065
31. Rubin DI. Epidemiology and risk factors for spine pain. *Neurol Clin*. 2007;25:353–371. doi:10.1016/j.ncl.2007.01.004
32. Hayden JA, Ellis J, Ogilvie R, Malmivaara A, van Tulder MW. Exercise therapy for chronic low back pain. *Cochrane Database Syst Rev*. 2021;9:Cd009790.

33. Gill TK, Mittinty MM, March LM, et al. Global, regional, and national burden of other musculoskeletal disorders, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5:e670–e682. doi:10.1016/S2665-9913(23)00232-1
34. Chenot JF, Becker A, Leonhardt C, et al. Sex differences in presentation, course, and management of low back pain in primary care. *Clin J Pain*. 2008;24:578–584. doi:10.1097/AJP.0b013e31816ed948
35. Inman SL, Faut-Callahan M, Swanson BA, Fillingim RB. Sex differences in responses to epidural steroid injection for low back pain. *J Pain*. 2004;5:450–457. doi:10.1016/j.jpain.2004.07.004
36. Lee HI, Lee ST, Kim M, Ryu JS. Sex differences in predicting chronicity of low-back pain after acute trauma using lumbar muscle area. *Am J Phys Med Rehabil*. 2015;94:123–130. doi:10.1097/PHM.0000000000000149
37. Rathbone T, Truong C, Haldenby H, et al. Sex and gender considerations in low back pain clinical practice guidelines: a scoping review. *BMJ Open Sport Exerc Med*. 2020;6:e000972.
38. Mashima T, Seimiya H, Tsuruo T. De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy. *Br. J. Cancer*. 2009;100:1369–1372. doi:10.1038/sj.bjc.6605007
39. Menendez JA, Lupu R. Fatty acid synthase (FASN) as a therapeutic target in breast cancer. *Expert Opin Ther Target*. 2017;21:1001–1016. doi:10.1080/14728222.2017.1381087
40. Hou CT. New bioactive fatty acids. *Asia Pac J Clin Nutr*. 2008;17 Suppl 1:192–195.
41. Satogami K, Tseng PT, Su KP, et al. Relationship between polyunsaturated fatty acid and eating disorders: systematic review and meta-analysis. *Prostaglandins Leukot Essent Fatty Acids*. 2019;142:11–19. doi:10.1016/j.plefa.2019.01.001
42. Hayashi S, Satoh Y, Ogasawara Y, Dairi T. Recent advances in functional analysis of polyunsaturated fatty acid synthases. *Curr Opin Chem Biol*. 2020;59:30–36. doi:10.1016/j.cbpa.2020.04.015
43. Richter EA, Ruderman NB. AMPK and the biochemistry of exercise: implications for human health and disease. *Biochem J*. 2009;418:261–275. doi:10.1042/BJ20082055
44. Steinberg GR, Carling D. AMP-activated protein kinase: the current landscape for drug development. *Nat Rev Drug Discov*. 2019;18:527–551. doi:10.1038/s41573-019-0019-2
45. Philp A, Chen A, Lan D, et al. Sirtuin 1 (SIRT1) deacetylase activity is not required for mitochondrial biogenesis or peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) deacetylation following endurance exercise. *J Biol Chem*. 2011;286:30561–30570. doi:10.1074/jbc.M111.261685
46. Zhang M, Ma Y, Ye X, Zhang N, Pan L, Wang B. TRP (transient receptor potential) ion channel family: structures, biological functions and therapeutic interventions for diseases. *Signal Transduct Target Ther*. 2023;8:261. doi:10.1038/s41392-023-01464-x
47. Bobkov D, Semenova S. Impact of lipid rafts on transient receptor potential channel activities. *J Cell Physiol*. 2022;237:2034–2044. doi:10.1002/jcp.30679
48. Startek JB, Talavera K, Antonio L. Lipid raft destabilization impairs mouse TRPA1 responses to cold and bacterial lipopolysaccharides. *Int J Mol Sci*. 2020;22:21. doi:10.3390/ijms22010021
49. Birkic N, Visentin D, Ž S, Reynolds CA. Binding interactions of fatty acyl lipid mediators within the vanilloid pocket of TRPV1: a molecular dynamics study. *Prostaglandins Other Lipid Mediat*. 2023;169:106771. doi:10.1016/j.prostaglandins.2023.106771
50. Olona A, Hateley C, Muralidharan S, Wenk MR, Torta F, Behmoaras J. Sphingolipid metabolism during Toll-like receptor 4 (TLR4)-mediated macrophage activation. *Br J Pharmacol*. 2021;178:4575–4587. doi:10.1111/bph.15642
51. Jin X, Dong X, Sun Y, Liu Z, Liu L, Gu H. Dietary fatty acid regulation of the NLRP3 inflammasome via the TLR4/NF- κ B signaling pathway affects chondrocyte pyroptosi. *Oxid Med Cell Longev*. 2022;2022:3711371. doi:10.1155/2022/3711371
52. Ping Z, Lang H, Yuliang Z, Xiao H, Shao L. ω-3 fatty acid alleviates virus-induced myocardial injury by regulating TLR4 and TLR3 expression. *Int Immunopharmacol*. 2021;99:107973. doi:10.1016/j.intimp.2021.107973
53. Dyall SC, Balas L, Bazan NG, et al. Polyunsaturated fatty acids and fatty acid-derived lipid mediators: recent advances in the understanding of their biosynthesis, structures, and functions. *Prog Lipid Res*. 2022;86:101165. doi:10.1016/j.plipres.2022.101165