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ORIGINAL RESEARCH

Causal Relationships Between Plasma Metabolites and Risk of Dermatomyositis

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Purpose: This exploratory study aimed to investigate the potential causal relationships between plasma metabolites and dermatomyositis using Mendelian randomization (MR), with the goal of generating hypotheses for future research.

Patients and Methods: We screened well-established metabolite GWAS databases and a comprehensive dermatomyositis patient database, starting with 1,400 metabolites. Suitable instrumental variables (IVs) were selected based on genome-wide significance, LD independence ($r^2 < 0.01$), and F-statistics > 10 to minimize weak instrument bias and pleiotropy. These IVs were then integrated with dermatomyositis patient data for MR analysis, employing techniques such as inverse-variance weighting (IVW), MR-Egger regression, and weighted median approaches. Sensitivity analyses were conducted to ensure result robustness, and findings were visualized using forest plots, scatter plots, and funnel plots.

Results: The IVW method revealed 53 metabolites and metabolic ratios significantly associated with dermatomyositis. Specifically, 20 metabolites and 8 metabolic ratios were linked to a decreased risk, while 17 metabolites and 8 ratios indicated increased risk. However, none of these associations remained statistically significant after false discovery rate (FDR) correction. Notable heterogeneity was observed in Lactosyl-N-palmitoyl-sphingosine levels, and pleiotropy was evident with 3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP). Robustness was confirmed through MR-PRESSO and leave-one-out analyses.

Conclusion: This study conducted the first exploratory Mendelian randomization analysis to investigate potential causal links between plasma metabolites and dermatomyositis. Although no statistically significant causal relationships were identified after multiple testing correction, this study provides preliminary evidence and valuable hypotheses for further research into metabolic pathways underlying dermatomyositis.

Keywords: dermatomyositis, metabolites, metabolomics, mendelian randomization, genetic association studies, inverse variance weighted, instrumental variables

Introduction

Dermatomyositis is an idiopathic inflammatory myopathy characterized by muscle weakness and distinctive skin rashes.[1] It can also impact other organs like the lungs, heart, and joints, making it a multifaceted condition.[2] Dermatomyositis is rare, with an incidence of about 1 in 100,000 people annually, and it affects both children and adults, most commonly those between 5 to 15 years and 40 to 60 years.[3,4] Despite treatment, up to 80% of dermatomyositis patients experience long-term disability and their overall mortality rate remains three times higher than the general population, primarily due to complications from cancer, lung and cardiac issues, and infections.[5] Symptoms typically include progressive muscle weakness and skin rashes with violet or dusky red patches on the face, eyelids, and other body parts.[6] Complications can be severe, ranging from difficulty swallowing and interstitial lung disease to calcinosis and an elevated cancer risk, especially in adults.[6,7] The exact causes of dermatomyositis remain unknown, which underscores the importance of identifying potential risk factors to enhance preventive and therapeutic strategies. Given the serious nature of its complications and unknown risk factors, prompt diagnosis and proactive management are vital to reduce the risks associated with dermatomyositis.

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Metabolomics, the comprehensive analysis of metabolites within a biological system, has become a vital tool for elucidating disease etiology and pathogenesis.[8] By offering a detailed snapshot of biochemical activities and metabolic states, metabolomics facilitates the identification of potential biomarkers and therapeutic targets.[9,10] In the context of dermatomyositis, investigating the plasma metabolome can provide valuable insights into the metabolic changes associated with the disease, highlighting underlying mechanisms and uncovering novel risk factors. Although prior research has focused on specific metabolites related to certain dermatomyositis subtypes, there remains a significant gap in systematic, large-scale metabolomic studies that encompass all forms of dermatomyositis.[11,12]

Mendelian randomization (MR) is a research method that uses genetic variants as instrumental variables to infer causal relationships between exposures and outcomes.[13] By mimicking the randomization process in controlled trials, MR helps determine causal effects while minimizing confounding and reverse causation.[14] Compared to traditional observational studies, MR provides higher evidence levels and is cost-effective for large-scale research due to its reliance on existing genetic and epidemiological data.[15] The increasing availability of genetic data from biobanks and genome-wide association studies (GWAS) enhances MR's feasibility in diverse populations.[16] In dermatomyositis research, MR can investigate causal relationships between plasma metabolites and onset risk of diseases. Metabolomic MR integrates metabolomic and genetic data, revealing whether specific metabolites causally contribute to dermatomyositis.[17,18] This approach identifies potential biomarkers and therapeutic targets, advancing disease understanding and informing regimen and prevention for dermatomyositis.

This study is the first, to our knowledge, to apply a MR framework to systematically investigate the potential causal relationships between plasma metabolites and the risk of dermatomyositis. By utilizing genetic instruments, we aim to generate hypothesis-driven insights into metabolic pathways potentially involved in disease pathogenesis, with the ultimate goal of identifying candidate biomarkers and therapeutic targets that may inform future prevention and treatment strategies.

Materials and Methods

Study Design

This study employed a MR design to investigate the causal relationships between plasma metabolites and the risk of dermatomyositis. We utilized well-established metabolite GWAS databases and a comprehensive database of dermatomyositis patients to conduct this analysis. From an initial pool of 1,400 metabolites, we screened for suitable instrumental variables (IVs) based on their robust genetic associations with the metabolites of interest, ensuring minimal pleiotropic effects. These IVs were then matched and integrated with the dermatomyositis patient data to perform the MR analysis. The primary MR analysis was conducted using established methods, including inverse-variance weighting (IVW), MR-Egger regression, and weighted median approaches, to ensure robust and reliable causal inference. To assess the robustness of the findings, sensitivity analyses were conducted, including tests for horizontal pleiotropy, heterogeneity, and leave-one-out analysis. The results were visualized using forest plots, scatter plots, and funnel plots, providing a clear and comprehensive presentation of the causal effects, thus facilitating the interpretation of data and highlighting significant findings for further investigation.

Data Sources

We sourced our outcome data from the R10 version of the FinnGene database.[19] This dataset includes GWAS data from 3,921 dermatomyositis patients and 403,213 controls, providing a robust foundation for our analysis (Table S1). The cohort comprised 1,642 females and 2,279 males. The unadjusted period prevalence was 1.03%, with a prevalence of 0.71% in females and 1.25% in males. The median age at the first event was 57.07 years overall, 55.05 years for females, and 58.52 years for males.

For exposure data, we referred the study published by Chen et al, which aimed to create a comprehensive genomic atlas of the plasma metabolome and identify key metabolites associated with various human diseases. The authors analyzed a total of 1,400 metabolites, which included 1,091 identified metabolites and 309 unclassified metabolic ratios. Their research not only established an extensive database of gene-metabolite associations but also highlighted the potential roles of specific metabolites in diseases.[20]

Selection of Instrumental Variables

In this study, the selection of IVs followed stringent criteria to ensure their validity and strength. First, single nucleotide polymorphisms (SNPs) significantly associated with plasma metabolites at a genome-wide significance level ($P < 5\times10^{-6}$) were identified. Second, only SNPs with a minor allele frequency (MAF) greater than 0.01 were included to ensure sufficient allele representation in the population. Third, Linkage Disequilibrium Score Regression (LDSC) was performed to exclude the SNPs with an LD threshold of $R^2 < 0.001$ within a 10,000 kb window, which confirm the absence of horizontal pleiotropy and to validate the genetic instruments' relevance to the exposures. Fourth, in cases where the selected IVs were not present in the outcome summary data, proxy SNPs with a high LD ($R^2 > 0.8$) with the original IVs were used as substitutes. Lastly, the F-statistic for each SNP was calculated to evaluate the strength of the IVs and exclude those potentially biased by weak instrument variables. The F-statistic was determined using the formula: $F = R^2 * (N - 2) / (1 - R^2)$, where R^2 represents the proportion of variance in the exposure explained by the SNP, and N is the sample size. An F-value greater than 10 was required to ensure the strength and reliability of the IVs. These thresholds were selected to optimize IV validity, minimize pleiotropy, and strengthen the robustness of causal inference.

MR Analysis

The MR analysis in this study utilized several established methods to infer causal relationships between plasma metabolites and the risk of dermatomyositis. The primary methods employed were IVW, MR-Egger regression, and the weighted median approach.

The IVW method, which combines the effect estimates of each instrumental variable (IV) in a meta-analysis framework, was used as the primary analysis tool.[21] This method assumes that all IVs are valid and provides a weighted average of the causal effect estimates, offering high precision and reliability. MR-Egger regression was used as a secondary method to detect and correct for pleiotropy, where the intercept can provide an estimate of the presence of horizontal pleiotropy.[22] The weighted median approach, which can provide a consistent estimate even if up to 50% of the IVs are invalid, was also applied to ensure robustness of the results.[23] Additionally, the Simple mode and Weighted mode methods were used to support and validate the findings.

After performing the initial MR analyses, the IVW method was primarily utilized to select significant associations. Positive results from the IVW analysis ($P_{IVW}<0.05$) were further examined, and metabolites (1091 in total) and metabolic ratios (309 in total) were analyzed separately. To account for multiple testing, false discovery rate (FDR) correction was applied to the results.[24] The corrected p-values were calculated to identify statistically significant metabolites and metabolic ratios associated with the risk of dermatomyositis, ensuring that the findings were both robust and reliable.

Sensitivity Testing

To ensure the robustness of the MR findings, a series of sensitivity tests were conducted. Leave-one-out analysis was performed to assess the influence of each individual IV on the overall causal estimate by systematically removing one IV at a time and recalculating the MR estimate.[25] This helped identify any single IV that might disproportionately influence the results. Cochran's Q test was used to evaluate the heterogeneity among the IVs.[26] Significant heterogeneity might indicate the presence of pleiotropy or other biases, prompting further investigation. MR-Egger regression was also employed in the sensitivity analysis to detect and correct for horizontal pleiotropy, with the intercept term providing an indication of directional pleiotropy.[27] Additionally, the MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) test was used to identify and correct for pleiotropic outliers.[28] MR-PRESSO performs a global test for horizontal pleiotropy, identifies outlier IVs, and provides a corrected causal estimate after removing these outliers. These sensitivity tests collectively ensured that the MR results were robust and reliable, accounting for potential biases and confirming the validity of the identified causal relationships between plasma metabolites and the risk of dermatomyositis.

Visualization

The results of the MR analysis were visualized using several R packages to ensure clear and comprehensive presentation. The "TwoSampleMR" package was used for performing the MR analyses and generating scatter plots, forest plots, and funnel plots. Scatter plots illustrated the causal relationships between the genetic variants and the metabolites, while

forest plots provided a clear summary of the effect estimates for each IV, highlighting the overall causal effects. Funnel plots were utilized to assess potential biases and the presence of horizontal pleiotropy. The "MR-PRESSO" package was employed to identify and correct for pleiotropic outliers, with results visualized to demonstrate the impact of outlier removal on causal estimates. Additionally, "ggplot2" was used to create high-quality graphical representations of the data, including detailed plots of the corrected p-values after false discovery rate (FDR) adjustment.

Results

Selection of Instrumental Variables

In this study, the selection of IVs for each exposure followed stringent criteria to ensure their validity and strength (Table S2). After initial selection and refinement using MR-KEEP and linkage disequilibrium score regression (LDSC), the number of single nucleotide polymorphisms (SNPs) used as IVs ranged from 16 to 37 across exposures. To assess instrument strength, we calculated the F-statistic for each SNP based on GWAS summary statistics of carnitine levels. Among a total of 34,843 SNPs, the F-statistics ranged from 19.503 to 5308.355, with a mean of 30.93 and a median of 21.20. Notably, no SNP had an F-statistic below the conventional threshold of 10, indicating a low risk of weak instrument bias in subsequent Mendelian randomization analyses.

MR Analysis

The MR analysis identified multiple significant associations between serum metabolites and the risk of dermatomyositis via multiple methods (Table S3 and Figures S1–S4). In total, there were 53 metabolites and metabolic ratios that showed significant associations with dermatomyositis at the IVW significance level ($P_{IVW}<0.05$) (Table 1, Figures 1 and 2). These results were categorized based on whether they indicated a decreased or increased risk of dermatomyositis and were further classified into metabolites and metabolic ratios.

Table 1 Serum Metabolites and Dermatomyositis Risk by Mendelian Randomization Analysis (IVW)

Outcome	Exposure	Method	nsnp	P value	OR (95% CI)
Dermatomyositis	Quinate levels	IVW	20	0.049933	0.908930 (0.829674–0.995758)
Dermatomyositis	DHEAS levels	IVW	44	0.025198	1.142212 (1.039393–1.255203)
Dermatomyositis	1-linoleoylglycerol (18:2) levels	IVW	18	0.009267	0.827879 (0.685419–0.999949)
Dermatomyositis	Docosatrienoate (22:3n3) levels	IVW	23	0.01166	1.117757 (1.006549–1.241251)
Dermatomyositis	N-methyl-2-pyridone-5-carboxamide levels	IVW	16	0.031149	1.108920 (1.012595–1.214408)
Dermatomyositis	Hexanoylglycine levels	IVW	26	0.038023	0.923958 (0.870654–0.980526)
Dermatomyositis	Glycerophosphoethanolamine levels	IVW	25	0.02977	1.142911 (1.016499–1.285044)
Dermatomyositis	Androstenediol (3beta,17beta) monosulfate (1) levels	IVW	32	0.038606	1.151945 (1.035483–1.281506)
Dermatomyositis	Indole-3-carboxylate levels	IVW	15	0.032776	1.136067 (1.002912–1.286901)
Dermatomyositis	Sulfate levels	IVW	29	0.021929	1.126636 (1.012621–1.253489)
Dermatomyositis	Carboxyethyl-gaba levels	IVW	22	0.035697	0.900264 (0.824591–0.982881)
Dermatomyositis	Guaiacol sulfate levels	IVW	24	0.030823	0.864166 (0.756721–0.986866)
Dermatomyositis	Methionine sulfone levels	IVW	33	0.038109	1.107726 (1.023404–1.198996)
Dermatomyositis	Methyl glucopyranoside (alpha + beta) levels	IVW	27	0.019004	1.073841 (1.016484–1.134433)
Dermatomyositis	1-dihomo-linolenylglycerol (20:3) levels	IVW	24	0.019314	1.154095 (1.029322–1.293992)
Dermatomyositis	1,2,3-benzenetriol sulfate (2) levels	IVW	23	0.029137	0.903029 (0.829064–0.983593)
Dermatomyositis	5-hydroxyindole sulfate levels	IVW	18	0.040235	1.190560 (1.047658–1.352954)
Dermatomyositis	Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels	IVW	24	0.016718	1.145441 (1.002605–1.308626)
Dermatomyositis	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6) levels	IVW	31	0.025201	0.878218 (0.777990–0.991359)
Dermatomyositis	Catechol glucuronide levels	IVW	18	0.009089	0.884792 (0.791753–0.988763)
Dermatomyositis	Linoleoylcholine levels	IVW	21	0.010926	0.867517 (0.758210–0.992582)
Dermatomyositis	Cerotoylcarnitine (C26) levels	IVW	30	0.045863	1.102892 (1.014103–1.199455)
Dermatomyositis	2-hydroxyarachidate levels	IVW	22	0.010965	0.930066 (0.879560–0.983472)
Dermatomyositis	3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels	IVW	25	0.017645	0.889595 (0.796472–0.993607)
Dermatomyositis	Glycine conjugate of C10H14O2 (1) levels	IVW	23	0.011257	0.872790 (0.770296–0.988920)
Dermatomyositis	Gamma-glutamylcitrulline levels	IVW	27	0.034467	1.090525 (1.019841–1.166108)

(*Continued*)

Table 1 (Continued).

Outcome	Exposure	Method	nsnp	P value	OR (95% CI)
Dermatomyositis	Delta-CEHC levels	IVW	20	0.022194	1.144958 (1.024457–1.279632)
Dermatomyositis	3,5-dichloro-2,6-dihydroxybenzoic acid levels	IVW	20	0.011319	0.848709 (0.750060–0.960332)
Dermatomyositis	2,4-di-tert-butylphenol levels	IVW	19	0.025749	0.859517 (0.764126–0.966816)
Dermatomyositis	Creatine levels	IVW	25	0.037334	0.913324 (0.843617–0.988790)
Dermatomyositis	1-palmitoyl-2-oleoyl-GPE (16:0/18:1) levels	IVW	32	0.018152	0.912140 (0.845955–0.983502)
Dermatomyositis	Eicosapentaenoate (EPA; 20:5n3) levels	IVW	25	0.04807	1.124330 (1.020166–1.239130)
Dermatomyositis	Cholesterol levels	IVW	18	0.028495	0.844440 (0.728231–0.979193)
Dermatomyositis	Threonine levels	IVW	31	0.037243	1.126382 (1.001009–1.267459)
Dermatomyositis	Caprylate (8:0) levels	IVW	22	0.044887	0.947973 (0.899534–0.999020)
Dermatomyositis	Bilirubin (E,E) levels	IVW	28	0.005731	1.078267 (1.013201–1.147513)
Dermatomyositis	Adenosine 5'-monophosphate (AMP) to palmitate (16:0) ratio	IVW	18	0.025506	1.173255 (1.014922–1.356288)
Dermatomyositis	Serine to alpha-tocopherol ratio	IVW	28	0.017038	1.135899 (1.007558–1.280587)
Dermatomyositis	5-methylthioadenosine (MTA) to phosphate ratio	IVW	25	0.045686	0.873777 (0.778540–0.980665)
Dermatomyositis	Spermidine to phosphate ratio	IVW	19	0.00929	1.180861 (1.041670–1.338652)
Dermatomyositis	Carnitine to ergothioneine ratio	IVW	21	0.014086	1.165286 (1.012296–1.341398)
Dermatomyositis	Tyrosine to pyruvate ratio	IVW	23	0.033157	1.185393 (1.042899–1.347355)
Dermatomyositis	Acetylcarnitine (C2) to propionylcarnitine (C3) ratio	IVW	19	0.047457	1.187602 (1.029129–1.370478)
Dermatomyositis	Succinate to proline ratio	IVW	16	0.030753	0.865418 (0.754952–0.992047)
Dermatomyositis	Phosphate to EDTA ratio	IVW	20	0.009377	1.166076 (1.001722–1.357395)
Dermatomyositis	Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	IVW	35	0.009245	1.101163 (1.007069–1.204049)
Dermatomyositis	Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	IVW	31	0.018626	0.906022 (0.829147–0.990024)
Dermatomyositis	Salicylate to citrate ratio	IVW	22	0.007503	0.867172 (0.762572–0.986119)

Among the findings, 20 metabolites were associated with a decreased risk of dermatomyositis, including 1-linoleoyl-glycerol (18:2) levels (OR = 0.8279, 95% CI: 0.6854–0.9999, P = 0.0499), cholesterol levels (OR = 0.8444, 95% CI: 0.7282–0.9792, P = 0.0252), 3,5-dichloro-2,6-dihydroxybenzoic acid levels (OR = 0.8487, 95% CI: 0.7501–0.9603, P = 0.0093), 2,4-di-tert-butylphenol levels (OR = 0.8595, 95% CI: 0.7641–0.9668, P = 0.0117), and guaiacol sulfate levels (OR = 0.8642, 95% CI: 0.7567–0.9869, P = 0.0311). Additionally, 8 metabolic ratios were associated with a decreased risk of dermatomyositis, such as the succinate to proline ratio (OR = 0.8654, 95% CI: 0.7550–0.9920, P = 0.0380), and the salicylate to citrate ratio (OR = 0.8672, 95% CI: 0.7626–0.9861, P = 0.0298).

Conversely, 17 metabolites were associated with an increased risk of dermatomyositis, including methyl glucopyranoside (alpha + beta) levels (OR = 1.0738, 95% CI: 1.0165–1.1344, P = 0.0110), bilirubin (E,E) levels (OR = 1.0783, 95% CI: 1.0132–1.1475, P = 0.0176), gamma-glutamylcitrulline levels (OR = 1.0905, 95% CI: 1.0198–1.1661, P = 0.0113), cerotoyl-carnitine (C26) levels (OR = 1.1029, 95% CI: 1.0141–1.1995, P = 0.0222), and androstenediol (3beta,17beta) monosulfate (1) levels (OR = 1.1519, 95% CI: 1.0355–1.2815, P = 0.0093). Similarly, 8 metabolic ratios were associated with an increased risk of dermatomyositis, such as the cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio (OR = 1.1012, 95% CI: 1.0071–1.2040, P = 0.0345), and the spermidine to phosphate ratio (OR = 1.1809, 95% CI: 1.0417–1.3387, P = 0.0094).

Following the initial MR analysis, the metabolites (1091 in total) and metabolic ratios (309 in total) were subjected to FDR correction to account for multiple testing. After applying the FDR adjustment, no metabolites or metabolic ratios had a P_{FDR} value less than 0.05 (Table S4). The power analysis revealed that, at the nominal significance level (α=0.05), the study had moderate power to detect larger effect sizes (OR=1.20) for metabolites with relatively high explained variance. However, the power to detect modest effects (OR=1.10) was limited, particularly for exposures with lower R^2 values. When considering the FDR correction for multiple testing, statistical power was similarly reduced, especially under the more stringent significance threshold typically required to control FDR in high-dimensional data.

Sensitivity Testing

Sensitivity testing was conducted to confirm the robustness of our MR findings. The primary approach involved a leave-one-out analysis, which assessed the impact of each IV on the overall causal estimate. The results of this analysis did not show any single IV disproportionately affecting the overall results, indicating robustness in the causal inferences drawn from the study.

exposure	OR(95%CI)	pval
DHEAS levels	1.14(1.04 to 1.26)	0.005731010
5-hydroxyindole sulfate levels	1.19(1.05 to 1.35)	0.007502994
Hexanoylglycine levels	0.92(0.87 to 0.98)	0.009089114
Tyrosine to pyruvate ratio	1.19(1.04 to 1.35)	0.009245378
3,5-dichloro-2,6-dihydroxybenzoic acid levels	0.85(0.75 to 0.96)	0.009267157
Androstenediol (3beta,17beta) monosulfate (1) levels	1.15(1.04 to 1.28)	0.009289929
Spermidine to phosphate ratio	1.18(1.04 to 1.34)	0.009376853
2-hydroxyarachidate levels	0.93(0.88 to 0.98)	0.010925552
Methyl glucopyranoside (alpha + beta) levels	1.07(1.02 to 1.13)	0.010965250
Gamma-glutamylcitrulline levels	1.09(1.02 to 1.17)	0.011256887
Methionine sulfone levels	1.11(1.02 to 1.20)	0.011318783
2,4-di-tert-butylphenol levels	0.86(0.76 to 0.97)	0.011660299
1-dihomo-linolenylglycerol (20:3) levels	1.15(1.03 to 1.29)	0.014085631
1-palmitoyl-2-oleoyl-GPE (16:0/18:1) levels	0.91(0.85 to 0.98)	0.016717880
Delta-CEHC levels	1.14(1.02 to 1.28)	0.017038334
Bilirubin (E,E) levels	1.08(1.01 to 1.15)	0.017645230
Eicosapentaenoate (EPA; 20:5n3) levels	1.12(1.02 to 1.24)	0.018151916
Acetylcarnitine (C2) to propionylcarnitine (C3) ratio	1.19(1.03 to 1.37)	0.018625940
Carboxyethyl-gaba levels	0.90(0.82 to 0.98)	0.019003630
1,2,3-benzenetriol sulfate (2) levels	0.90(0.83 to 0.98)	0.019314142
5-methylthioadenosine (MTA) to phosphate ratio	0.87(0.78 to 0.98)	0.021928619
Cerotoylcarnitine (C26) levels	1.10(1.01 to 1.20)	0.022194120
Cholesterol levels	0.84(0.73 to 0.98)	0.025197558
Creatine levels	0.91(0.84 to 0.99)	0.025200643
Glycerophosphoethanolamine levels	1.14(1.02 to 1.29)	0.025506436
N-methyl-2-pyridone-5-carboxamide levels	1.11(1.01 to 1.21)	0.025748936
Sulfate levels	1.13(1.01 to 1.25)	0.028495291
Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	0.91(0.83 to 0.99)	0.029136601
Salicylate to citrate ratio	0.87(0.76 to 0.99)	0.029769792
Adenosine 5'-monophosphate (AMP) to palmitate (16:0) ratio	1.17(1.01 to 1.36)	0.030752961
Catechol glucuronide levels	0.88(0.79 to 0.99)	0.030822703
Guaiacol sulfate levels	0.86(0.76 to 0.99)	0.031148644
Glycine conjugate of C10H14O2 (1) levels	0.87(0.77 to 0.99)	0.032776484
Carnitine to ergothioneine ratio	1.17(1.01 to 1.34)	0.033156623
Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	1.10(1.01 to 1.20)	0.034467420
1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6) levels	0.88(0.78 to 0.99)	0.035696742
Serine to alpha-tocopherol ratio	1.14(1.01 to 1.28)	0.037242555
Docosatrienoate (22:3n3) levels	1.12(1.01 to 1.24)	0.037333885
Succinate to proline ratio	0.87(0.75 to 0.99)	0.038023432
3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels	0.89(0.80 to 0.99)	0.038109240
Linoleoylcholine levels	0.87(0.76 to 0.99)	0.038606068
Quinate levels	0.91(0.83 to 1.00)	0.040234617
Indole-3-carboxylate levels	1.14(1.00 to 1.29)	0.044886837
Caprylate (8:0) levels	0.95(0.90 to 1.00)	0.045863314
Phosphate to EDTA ratio	1.17(1.00 to 1.36)	0.047457124
Threonine levels	1.13(1.00 to 1.27)	0.048070049
1-linoleoylglycerol (18:2) levels	0.83(0.69 to 1.00)	0.049933406

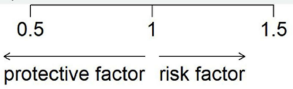

Figure 1 Forest Plot of Causal Associations Between Metabolites and Dermatomyositis (dermatomyositis). This forest plot illustrates the 53 significant associations between metabolites and metabolic ratios with the risk of dermatomyositis, identified using the IVW method (P<0.05). The x-axis represents the odds ratio (OR) with 95% confidence intervals (CI), where values less than 1 indicate a protective effect and values greater than 1 indicate an increased risk. Each row corresponds to a specific metabolite or metabolic ratio, with the effect size and significance level annotated on the right. The red dashed line indicates an OR of 1, separating protective factors from risk factors.

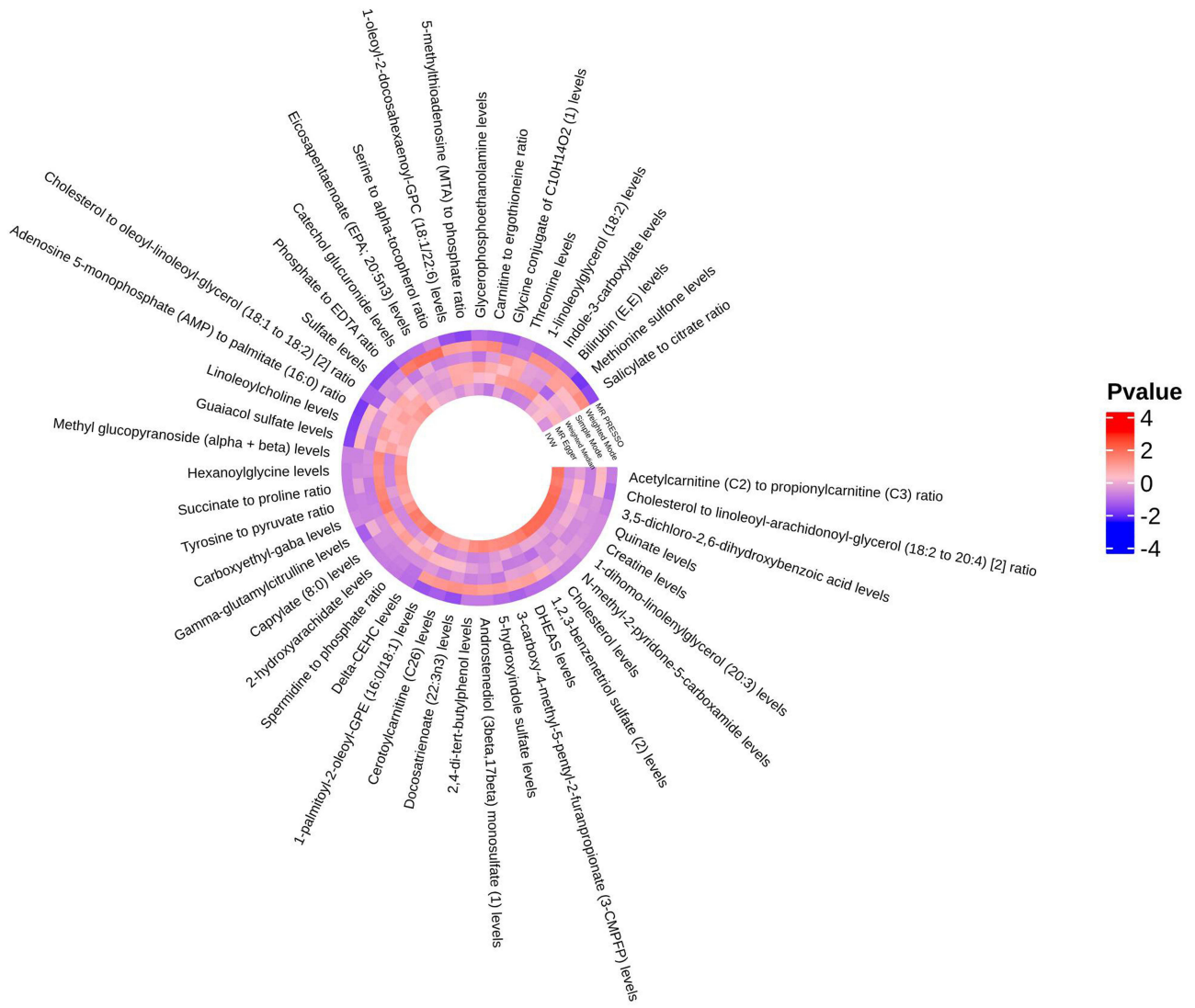

Figure 2 Heatmap of Metabolites and Metabolic Ratios Causally Associated with dermatomyositis. This heatmap visualizes the 53 metabolites and metabolic ratios that showed significant associations with dermatomyositis at the IVW significance level (P<0.05). The color gradient represents the -log10(p-value) of the associations, with darker shades indicating stronger associations. The metabolites and ratios are categorized along the vertical axis, highlighting the variation in significance levels across different metabolic features.

The tests included Cochran's Q for heterogeneity (Table 2) and MR-Egger regression for pleiotropy (Table 3). Among the exposures analyzed, the majority of the results indicated no significant heterogeneity or pleiotropy, suggesting that the selected IVs were appropriate and robust for the MR analysis, except following metabolites. Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels showed significant heterogeneity by Cochran's Q test, detected using both the IVW (Q = 37.12356, P = 0.031558) and MR-Egger methods (Q = 0.016349475, P = 0.032348). 3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels exhibited significant pleiotropy with an MR-Egger intercept of −0.032209452 (P = 0.038368), indicating potential pleiotropic effects that need to be considered in the interpretation of the results. Full details of the heterogeneity and pleiotropy test results are presented in Table S5 and Table S6, respectively.

The MR-PRESSO results across all analyzed metabolites consistently showed non-significant outcomes, further indicating no presence of pleiotropic outliers that could potentially skew the causal relationships between various plasma metabolites and the risk of dermatomyositis (Table 4).

Table 2 Validating Heterogeneity of Instrumental Variable by Cochran's Q Test (By IVW and MR-Egger Methods)

Outcome	Exposure	Cochran's Q Pleiotropy			
		IVW	P value	MR-Egger	P value
Dermatomyositis	Quinate levels	10.86079	0.928432	10.15656	0.926676
Dermatomyositis	DHEAS levels	44.10538	0.424653	43.57772	0.404146
Dermatomyositis	1-linoleoylglycerol (18:2) levels	23.29698	0.13983	23.10343	0.110997
Dermatomyositis	Docosatrienoate (22:3n3) levels	25.03279	0.295509	24.8833	0.252254
Dermatomyositis	N-methyl-2-pyridone-5-carboxamide levels	20.03702	0.170517	19.7127	0.139463
Dermatomyositis	Hexanoylglycine levels	19.64221	0.765333	19.51434	0.724032
Dermatomyositis	Glycerophosphoethanolamine levels	33.15424	0.100861	32.66453	0.087093
Dermatomyositis	Androstenediol (3beta,17beta) monosulfate (1) levels	23.71942	0.821825	22.20989	0.8463
Dermatomyositis	Indole-3-carboxylate levels	20.90056	0.104208	19.38476	0.111649
Dermatomyositis	Sulfate levels	19.61965	0.877931	19.61908	0.846355
Dermatomyositis	Carboxyethyl-gaba levels	22.7113	0.359562	18.9587	0.524512
Dermatomyositis	Guaiacol sulfate levels	17.81331	0.767536	15.69433	0.830761
Dermatomyositis	Methionine sulfone levels	28.9892	0.619712	26.74025	0.685156
Dermatomyositis	Methyl glucopyranoside (alpha + beta) levels	28.14094	0.351558	26.45524	0.383634
Dermatomyositis	1-dihomo-linolenylglycerol (20:3) levels	18.52903	0.728196	17.46094	0.737428
Dermatomyositis	1,2,3-benzenetriol sulfate (2) levels	15.64657	0.833031	14.05269	0.867326
Dermatomyositis	5-hydroxyindole sulfate levels	13.8543	0.677387	13.14415	0.66219
Dermatomyositis	**Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels**	**37.12356**	**0.031558**	**35.74295**	**0.032348**
Dermatomyositis	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6) levels	33.06791	0.319603	32.65845	0.291728
Dermatomyositis	Catechol glucuronide levels	17.59289	0.414948	16.81064	0.397951
Dermatomyositis	Linoleoylcholine levels	18.73136	0.539345	18.71503	0.47525
Dermatomyositis	Cerotoylcarnitine (C26) levels	24.24191	0.716916	22.88114	0.738965
Dermatomyositis	2-hydroxyarachidate levels	19.64566	0.543794	19.64195	0.480518
Dermatomyositis	3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels	21.94276	0.582683	17.11637	0.803502
Dermatomyositis	Glycine conjugate of C10H14O2 (1) levels	28.73202	0.152672	27.61044	0.151549
Dermatomyositis	Gamma-glutamylcitrulline levels	23.15458	0.624188	21.39292	0.670509
Dermatomyositis	Delta-CEHC levels	11.07039	0.921448	9.218236	0.954471
Dermatomyositis	3,5-dichloro-2,6-dihydroxybenzoic acid levels	8.660149	0.978708	8.447125	0.97121
Dermatomyositis	2,4-di-tert-butylphenol levels	14.4927	0.696455	13.60622	0.694753
Dermatomyositis	Creatine levels	14.18839	0.94228	13.68484	0.935542
Dermatomyositis	1-palmitoyl-2-oleoyl-GPE (16:0/18:1) levels	27.79334	0.631813	24.40736	0.75329
Dermatomyositis	Eicosapentaenoate (EPA; 20:5n3) levels	30.07546	0.182263	26.3862	0.282975
Dermatomyositis	Cholesterol levels	8.544215	0.953486	8.48255	0.933187
Dermatomyositis	Threonine levels	43.32787	0.054805	41.3837	0.063727
Dermatomyositis	Caprylate (8:0) levels	14.43372	0.850258	14.40893	0.809172
Dermatomyositis	Bilirubin (E,E) levels	25.5973	0.541026	21.87877	0.695311
Dermatomyositis	Adenosine 5'-monophosphate (AMP) to palmitate (16:0) ratio	13.76799	0.683452	13.71037	0.620281
Dermatomyositis	Serine to alpha-tocopherol ratio	34.57581	0.14994	33.57107	0.146168
Dermatomyositis	5-methylthioadenosine (MTA) to phosphate ratio	25.34949	0.386973	23.17436	0.450628
Dermatomyositis	Spermidine to phosphate ratio	10.33092	0.920568	9.406708	0.926632
Dermatomyositis	Carnitine to ergothioneine ratio	30.1477	0.067495	29.90632	0.053003
Dermatomyositis	Tyrosine to pyruvate ratio	20.74197	0.53673	18.48112	0.618387
Dermatomyositis	Acetylcarnitine (C2) to propionylcarnitine (C3) ratio	20.82234	0.288471	20.71463	0.239316
Dermatomyositis	Succinate to proline ratio	12.90562	0.609587	12.77097	0.544632
Dermatomyositis	Phosphate to EDTA ratio	13.21269	0.827507	12.99338	0.791966
Dermatomyositis	Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	25.91405	0.838567	24.39846	0.860777
Dermatomyositis	Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	23.84887	0.778819	23.82767	0.737382
Dermatomyositis	Salicylate to citrate ratio	23.36282	0.324943	20.99661	0.397332

Notes: Bolded values indicate p-values < 0.05, suggesting significant heterogeneity according to Cochran's Q test.

Table 3 Pleiotropy Test Results Through MR-Egger Method

Outcome	Exposure	Egger_intercept	P value
Dermatomyositis	Quinate levels	0.012284673	0.412374
Dermatomyositis	DHEAS levels	0.007054799	0.479709
Dermatomyositis	1-linoleoylglycerol (18:2) levels	−0.011007361	0.719078
Dermatomyositis	Docosatrienoate (22:3n3) levels	0.004801807	0.725984
Dermatomyositis	N-methyl-2-pyridone-5-carboxamide levels	−0.007316431	0.638691
Dermatomyositis	Hexanoylglycine levels	0.00536448	0.723777
Dermatomyositis	Glycerophosphoethanolamine levels	0.008699357	0.562781
Dermatomyositis	Androstenediol (3beta,17beta) monosulfate (1) levels	0.012991591	0.228762
Dermatomyositis	Indole-3-carboxylate levels	0.021482878	0.331741
Dermatomyositis	Sulfate levels	0.000371317	0.981071
Dermatomyositis	Carboxyethyl-gaba levels	0.023422658	0.066979
Dermatomyositis	Guaiacol sulfate levels	−0.023010798	0.159606
Dermatomyositis	Methionine sulfone levels	0.015867962	0.143822
Dermatomyositis	Methyl glucopyranoside (alpha + beta) levels	−0.011959627	0.21855
Dermatomyositis	1-dihomo-linolenylglycerol (20:3) levels	−0.018211293	0.312606
Dermatomyositis	1,2,3-benzenetriol sulfate (2) levels	−0.014718619	0.220613
Dermatomyositis	5-hydroxyindole sulfate levels	0.01604083	0.411813
Dermatomyositis	Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels	0.016349475	0.366617
Dermatomyositis	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6) levels	−0.011006628	0.55121
Dermatomyositis	Catechol glucuronide levels	−0.019878586	0.400964
Dermatomyositis	Linoleoylcholine levels	−0.002350391	0.899655
Dermatomyositis	Cerotoylcarnitine (C26) levels	0.013105375	0.253244
Dermatomyositis	2-hydroxyarachidate levels	0.000601385	0.952054
Dermatomyositis	**3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels**	**−0.032209452**	**0.038368**
Dermatomyositis	Glycine conjugate of C10H14O2 (1) levels	0.015962766	0.366182
Dermatomyositis	Gamma-glutamylcitrulline levels	0.012242661	0.196412
Dermatomyositis	Delta-CEHC levels	−0.02039062	0.19033
Dermatomyositis	3,5-dichloro-2,6-dihydroxybenzoic acid levels	0.007640547	0.649936
Dermatomyositis	2,4-di-tert-butylphenol levels	−0.01604974	0.359622
Dermatomyositis	Creatine levels	0.007229645	0.485076
Dermatomyositis	1-palmitoyl-2-oleoyl-GPE (16:0/18:1) levels	−0.022199804	0.075666
Dermatomyositis	Eicosapentaenoate (EPA; 20:5n3) levels	0.019848006	0.086091
Dermatomyositis	Cholesterol levels	0.00420076	0.807043
Dermatomyositis	Threonine levels	−0.019168943	0.252632
Dermatomyositis	Caprylate (8:0) levels	−0.001421714	0.876484
Dermatomyositis	Bilirubin (E,E) levels	0.018423901	0.064799
Dermatomyositis	Adenosine 5'-monophosphate (AMP) to palmitate (16:0) ratio	0.00472022	0.813355
Dermatomyositis	Serine to alpha-tocopherol ratio	0.013940262	0.385792
Dermatomyositis	5-methylthioadenosine (MTA) to phosphate ratio	−0.021573199	0.155305
Dermatomyositis	Spermidine to phosphate ratio	−0.015035206	0.349848
Dermatomyositis	Carnitine to ergothioneine ratio	0.009114555	0.699707
Dermatomyositis	Tyrosine to pyruvate ratio	−0.027200375	0.147572
Dermatomyositis	Acetylcarnitine (C2) to propionylcarnitine (C3) ratio	−0.005618225	0.769829
Dermatomyositis	Succinate to proline ratio	0.006520896	0.719139
Dermatomyositis	Phosphate to EDTA ratio	−0.011059796	0.645186
Dermatomyositis	Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	−0.014375268	0.226992
Dermatomyositis	Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	−0.001819128	0.885268
Dermatomyositis	Salicylate to citrate ratio	−0.02788759	0.148903

Notes: Bolded values indicate p-values < 0.05, suggesting evidence of horizontal pleiotropy based on the MR-Egger intercept test.

Table 4 MR-PRESSO Analysis Results for Assessing Pleiotropic Outliers

Outcome	Exposure	Raw P value	Global P value
Dermatomyositis	Quinate levels	0.01379061	0.921
Dermatomyositis	DHEAS levels	0.008399596	0.439
Dermatomyositis	1-linoleoylglycerol (18:2) levels	0.066531077	0.138
Dermatomyositis	Docosatrienoate (22:3n3) levels	0.04917419	0.344
Dermatomyositis	N-methyl-2-pyridone-5-carboxamide levels	0.041450033	0.318
Dermatomyositis	Hexanoylglycine levels	0.006920754	0.809
Dermatomyositis	Glycerophosphoethanolamine levels	0.035087805	0.121
Dermatomyositis	Androstenediol (3beta,17beta) monosulfate (1) levels	0.005652176	0.854
Dermatomyositis	Indole-3-carboxylate levels	0.064611194	0.141
Dermatomyositis	Sulfate levels	0.01415173	0.878
Dermatomyositis	Carboxyethyl-gaba levels	0.028903724	0.36
Dermatomyositis	Guaiacol sulfate levels	0.022369004	0.771
Dermatomyositis	Methionine sulfone levels	0.012079611	0.599
dermatomyositis	Methyl glucopyranoside (alpha + beta) levels	0.017252606	0.321
dermatomyositis	1-dihomo-linolenylglycerol (20:3) levels	0.011793642	0.742
dermatomyositis	1,2,3-benzenetriol sulfate (2) levels	0.011068939	0.849
dermatomyositis	5-hydroxyindole sulfate levels	0.008739721	0.699
dermatomyositis	Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels	0.044208015	0.327
Dermatomyositis	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6) levels	0.045403103	0.445
Dermatomyositis	Catechol glucuronide levels	0.045114208	0.588
Dermatomyositis	Linoleoylcholine levels	0.018265147	0.755
Dermatomyositis	Cerotoylcarnitine (C26) levels	0.015605222	0.759
Dermatomyositis	2-hydroxyarachidate levels	0.040238464	0.575
Dermatomyositis	3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP) levels	0.044163517	0.175
Dermatomyositis	Glycine conjugate of C10H14O2 (1) levels	0.01243453	0.676
Dermatomyositis	Gamma-glutamylcitrulline levels	0.00556698	0.927
Dermatomyositis	Delta-CEHC levels	0.001069111	0.985
Dermatomyositis	3,5-dichloro-2,6-dihydroxybenzoic acid levels	0.011562313	0.695
Dermatomyositis	2,4-di-tert-butylphenol levels	0.007657297	0.947
Dermatomyositis	Creatine levels	0.016816251	0.684
Dermatomyositis	1-palmitoyl-2-oleoyl-GPE (16:0/18:1) levels	0.026599617	0.22
Dermatomyositis	Eicosapentaenoate (EPA; 20:5n3) levels	0.005751863	0.964
Dermatomyositis	Cholesterol levels	0.057325506	0.058
Dermatomyositis	Threonine levels	0.025293827	0.899
Dermatomyositis	Caprylate (8:0) levels	0.021673415	0.383
Dermatomyositis	Bilirubin (E,E) levels	0.028100415	0.691
Dermatomyositis	Adenosine 5'-monophosphate (AMP) to palmitate (16:0) ratio	0.046841594	0.176
Dermatomyositis	Serine to alpha-tocopherol ratio	0.031003985	0.428
Dermatomyositis	5-methylthioadenosine (MTA) to phosphate ratio	0.00299088	0.941
Dermatomyositis	Spermidine to phosphate ratio	0.045761397	0.1
Dermatomyositis	Carnitine to ergothioneine ratio	0.013659339	0.57
Dermatomyositis	Tyrosine to pyruvate ratio	0.030199296	0.309
Dermatomyositis	Acetylcarnitine (C2) to propionylcarnitine (C3) ratio	0.040926127	0.64
Dermatomyositis	Succinate to proline ratio	0.028116647	0.84
Dermatomyositis	Phosphate to EDTA ratio	0.020912201	0.814
Dermatomyositis	Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	0.020485178	0.802
Dermatomyositis	Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	0.041358366	0.308
Dermatomyositis	Salicylate to citrate ratio	0.01379061	0.921

Discussion

In this study, we explored the causal relationships between various plasma metabolites and the risk of dermatomyositis using MR techniques, identifying several potential causal relationships according to the IVW method. This study represents the first exploratory Mendelian randomization analysis investigating potential causal relationships between plasma metabolites and dermatomyositis. While none of the identified associations remained statistically significant after FDR correction, the analysis revealed several nominal associations that may serve as hypotheses for future investigation.

Although 53 metabolites and metabolic ratios showed nominal associations with dermatomyositis under the IVW method, none remained statistically significant after FDR correction. This suggests that some initial signals may represent false positives. Alternatively, the study may have been underpowered to detect small but biologically relevant effects, especially under stringent multiple testing correction.

Although 53 metabolites and metabolic ratios showed nominal associations with dermatomyositis under the IVW method, including 20 metabolites and 8 ratios linked to decreased risk, and 17 metabolites and 8 ratios linked to increased risk, none of these associations remained statistically significant after FDR correction. This outcome suggests that the initial findings may include false positives, which is a common challenge in high-dimensional exploratory studies. Alternatively, the study may have lacked sufficient statistical power to detect small but biologically meaningful effects under stringent multiple testing conditions. The use of FDR correction is essential to control type I error in large-scale screening, but it may increase the risk of overlooking real associations (type II error), especially when effect sizes are modest. Notably, we observed significant heterogeneity in Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) and evidence of pleiotropy in 3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP), underscoring the complex metabolic architecture of dermatomyositis. Heterogeneity may reflect true biological variation across subgroups, while pleiotropy indicates that certain genetic variants may influence multiple traits, potentially biasing causal estimates. Despite these complexities, the robustness of our results was supported by sensitivity analyses, including MR-PRESSO and leave-one-out testing, both of which showed no influential outliers or substantial bias, thereby reinforcing the internal consistency of our nominal associations.

Previous study conducted by Zhang et al has also employed metabolomics to explore the pathogenesis of dermatomyositis.[29] The researchers conducted a metabolomic analysis on a relatively small sample size of 26 patients with dermatomyositis and 26 controls. Their study primarily focused on identifying potential biomarkers by comparing metabolite levels between the two groups, indicating differences that may suggest biomarker potential for dermatomyositis. Our study expands significantly on this earlier research by leveraging a much larger sample size derived from GWAS databases, enhancing the statistical power and reliability of our findings. Furthermore, our research takes a critical step forward by examining the causal relationships between specific metabolites and dermatomyositis. Additionally, Zhang et al utilized broader categories of metabolites, whereas our study delves deeper by subdividing metabolites into more specific categories. Among the findings, Methionine was highlighted in Zhang et al's patient data for elevated expression, and in our analysis, Methionine sulfone also demonstrated a significant potential causal relationship with dermatomyositis, showing an odds ratio of 1.1077 with a 95% confidence interval of 1.0234 to 1.1990. Methionine sulfone is an oxidative metabolite of methionine, often considered a marker of oxidative stress.[30] Elevated levels of methionine sulfone have been reported in inflammatory states, and oxidative stress is a known contributor to muscle damage and immune activation in dermatomyositis.[31]

Similarly, while elevated levels of Indole were reported in Zhang et al's patient data, our study identified a nominal association between Indole-3-carboxylate and dermatomyositis ($p = 0.0449$; OR = 1.1361). Although this association did not remain significant after multiple testing correction, the consistency in findings across different approaches may warrant further investigation. Indole-3-carboxylate is a tryptophan metabolite derived from gut microbial metabolism and has been shown to interact with the aryl hydrocarbon receptor (AhR), which plays a role in modulating immune responses and maintaining epithelial barrier function.[32] Dysregulation of the tryptophan–AhR pathway has been implicated in various autoimmune and inflammatory diseases, and its nominal association in our study suggests a possible link with immune dysfunction in dermatomyositis.[33–35]

Additionally, there has been notable research on specific metabolites and their roles in dermatomyositis, such as glycerophosphoethanolamine, which plays a part in cellular signaling and membrane composition.[36,37] This may influence the inflammatory processes seen in dermatomyositis, as alterations in phospholipid metabolism are known to affect immune cell function, which is critical in autoimmune pathologies.[38] Creatine, typically linked with energy metabolism in muscle cells, also has implications for dermatomyositis due to its role in muscle energy homeostasis and potentially in muscle repair and inflammation.[39] Research has suggested that creatine supplementation could aid muscle strength and recovery in diseases affecting muscles.[40] Cholesterol levels, particularly high-density lipoprotein (HDL) or "good" cholesterol, have been associated with various systemic inflammatory diseases and possess anti-inflammatory properties that could be protective against autoimmune reactions.[41] Caprylate, a medium-chain fatty acid known for its anti-inflammatory and antimicrobial properties, might play a role in modulating immune function and inflammation, a common element in autoimmune disease pathology.[42] DHEA affects the regulation of various immune cells, including T cells, B cells, and monocytes.[43,44] This regulation is crucial as it can alter the immune response in ways that may exacerbate or ameliorate autoimmune conditions like dermatomyositis. Notably, elevated serum BAFF (B-cell activating factor) levels in dermatomyositis patients, especially those with anti-MDA5 antibodies, have been connected to interstitial lung disease (ILD), a serious complication of dermatomyositis.[45] High BAFF levels correlate with increased disease activity and poor prognosis, emphasizing the role of BAFF in the immune dysregulation observed in dermatomyositis. These findings collectively underscore the significant impact that metabolic alterations can have on the progression and pathogenesis of dermatomyositis, highlighting the need for further research into these connections.

After adjusting for multiple testing using the FDR correction, all initially significant associations lost statistical significance. This outcome indicates that the observed nominal associations do not meet the statistical threshold required to confidently reject the null hypothesis when accounting for the large number of comparisons. In other words, these associations are not statistically robust under stringent correction and should not be interpreted as definitive evidence of causality. FDR correction is essential in large-scale MR studies to reduce the likelihood of false positives, especially when testing hundreds of exposures. However, this stringency inevitably reduces statistical power and increases the risk of Type II errors — failing to detect true associations with small effect sizes or limited genetic variance explained. This is a known trade-off in exploratory, hypothesis-generating research. Despite the lack of FDR-significant findings, the nominal associations observed in our study may still offer preliminary insights. While not conclusive, they highlight potential metabolic signals that warrant further investigation in larger and more powered studies. We emphasize that the current results should be viewed as hypothesis-generating, rather than confirmatory.

Given the severity and complications associated with dermatomyositis, identifying potential metabolic markers remains clinically important. Although our study did not yield statistically significant associations after multiple testing correction, the nominal findings offer preliminary clues that may guide future research. Metabolomic profiling has the potential to improve early detection, particularly in atypical cases, and to enhance understanding of disease-related metabolic disturbances. The metabolites identified in this study—if validated through experimental and longitudinal research—may contribute to the development of biomarkers for disease risk assessment, prognosis, or therapeutic targeting. Moreover, these findings may help prioritize candidates for functional studies, ultimately advancing efforts toward more personalized and mechanism-based approaches in dermatomyositis management.

This study has several limitations. First, inherent to Mendelian randomization, the results may be affected by residual horizontal pleiotropy, measurement error in GWAS summary statistics, and unmeasured population stratification, all of which could bias causal estimates. Second, our analysis was based on individuals of predominantly European ancestry, which limits the generalizability of findings to other populations with different genetic backgrounds. Third, many of the identified metabolites are not routinely measured in clinical settings, posing challenges for direct translation. Moreover, while MR can suggest potential causal relationships, it cannot uncover underlying biological mechanisms. Future studies should aim to replicate these findings in larger and more diverse populations, apply longitudinal designs, and perform experimental validation to better understand the functional roles of key metabolites. These efforts are essential to confirm our exploratory results and guide biomarker discovery and therapeutic development in dermatomyositis.

Future studies should aim to replicate these findings in larger, multi-ethnic cohorts, integrate functional omics data, and perform experimental validation of metabolite-disease pathways. Longitudinal metabolomic profiling and functional assays could confirm the biological relevance of the identified candidates.

Conclusion

This study performed an exploratory Mendelian randomization analysis to investigate potential causal links between plasma metabolites and dermatomyositis. While 51 metabolites and metabolic ratios showed nominal associations, none remained significant after FDR correction. These findings should be interpreted with caution but may offer preliminary hypotheses for future validation. As the first MR study focusing on dermatomyositis and metabolomics, this work provides a foundation for hypothesis generation and future research into the metabolic underpinnings of the disease.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and supplementary information files.

Ethics Approval and Consent to Participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Ethic Committee of Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2024-029-01). The study did not involve human participants, so consent to participate was not required.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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