Supplemental Material for

Oxidative stress involves phenotype modulation of morbid soreness symptoms in fibromyalgia

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Supplementary Methods and Materials

Study participants

All participants underwent routine laboratory examination to exclude disorders that would otherwise explain the pain, including testing for erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, thyroid hormone, thyroid-stimulating hormone, alanine and aspartate aminotransferase, creatinine kinase, cortisol, and electrolytes. All participants with a final diagnosis of primary FM were followed for at least 6 months by outpatient services to ensure that no other etiology was identified. We prospectively recruited age- and sex-matched subjects without pain and soreness as healthy controls (HCs). Participants were asked to report their physical exertional events (such as intense labor or exercise) in the last 2 weeks. Exclusion criteria for both groups were the presence of systemic rheumatological or immune disorders (e.g., systemic lupus erythematosus, inflammatory myositis), systemic use of corticosteroids, current statin treatment, pregnancy, chronic diseases under poor control (e.g., diabetes mellitus, or chronic renal failure) and malignancies.

Blood collection and analyses

Venous blood was collected from patients and controls at the first visit before pharmacotherapeutic intervention and placed in EDTA tubes. Blood was centrifuged at 3000 rpm for 15 min at 4o C to obtain plasma. Plasma samples were stored at–80o C.

To assess oxidative stress, thiobarbituric acid reactive substances (TBARS) were

determined in plasma samples with use of a commercial kit (Cayman, Ann Arbor, MI; item 700870). The lipid peroxidation level was expressed as nanomoles of malondialdehyde (MDA) formed per milliliter.

Metabolomics profiling

Metabolomics profiling of plasma samples involved using an Agilent 1290 UHPLC system coupled with Agilent 6540 QTOF (Agilent Technologies, Santa Clara, CA). An amount of 2 μL plasma extract was injected into an Acquity HSS T3 column (2.1×100 mm, 1.8 μm) (Waters, Milford, MA), with the apparatus temperature kept at 40 ° C. The mobile phase involved solvent A (water/0.1% formic acid) and solvent B (acetonitrile/0.1% formic acid). The gradient elution program was 0–1.5 min: 2% B; 1.5–9 min: linear gradient from 2 to 50% B; 9–14 min: linear gradient from 50 to 95% B; and 3 min: maintenance in 95% B. The flow rate was kept at 300 μL/min. For ionization, a Jet Stream electrospray ionization source was used for sample ionization. The following parameters were used throughout the study: 325° C gas temperature, 5 L/min gas flow, 40 psi nebulizer, 325°C sheath gas temperature, 10 L/min sheath gas flow, 40 kV in positive mode capillary voltage, and 120V fragmentation voltage. The mass scan range and acquisition rate were m/z 50–1700 and 2 Hz.

All data obtained with the Bruker system extracted with ion chromatography for

Hexakis (1H,1H,3H-perfluoropropoxy) phosphazene (m/z 922) were generated by using Bruker Data Analysis software. The peak area was then integrated for further analyses. For metabolic profiling, the metabolites were identified by using the in-house library with accurate mass and retention time by using Agilent MassHunter Profinder v6.0. The datasets containing m/z values, retention time and peak area were further analyzed.

Statistical analysis of metabolomics data:

Metabolomics analyses involved using SPSS v20 and the MetaboAnalyst 4.0 website service (www.metaboanalyst.ca/)[1]. Non-parametric tests were used to identify metabolites with significant difference in peak intensities between FM and controls. The resulting *p* values were adjusted by the false discovery rate method of Benjamini–Hochberg for multiple testing [2], with $p < 0.02$ considered statistically significant. Kruskal-Wallis test was used to compare multiple groups (FM-P, FM-PS, and HCs).

PCA was used to evaluate intrinsic clustering and relevant subgroups. Sparse partial least squares discriminant analysis (sPLS-DA) was used to analyze the metabolomic expression for different groups by high-dimensional spectral features with multivariate PCA and further discrimination of inter-class variance between the groups. The variable importance in projection was constructed to provide a quantitative estimation of the importance of prominent metabolites that mostly contributed to the phenotypic

variability, and the score of these metabolites was depicted. Also, a heat map of the identified metabolites of interest was constructed, with hierarchical clustering of Euclidean distance applied to both participants and metabolites.

References

1. Xia J, Wishart DS. Web-based inference of biological patterns, functions and pathways from metabolomic data using MetaboAnalyst. *Nat Protoc* 2011;6(6):743-60. doi: 10.1038/nprot.2011.319

2. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)* 1995;57(1):289-300. doi: 10.1111/j.2517-6161.1995.tb02031.x

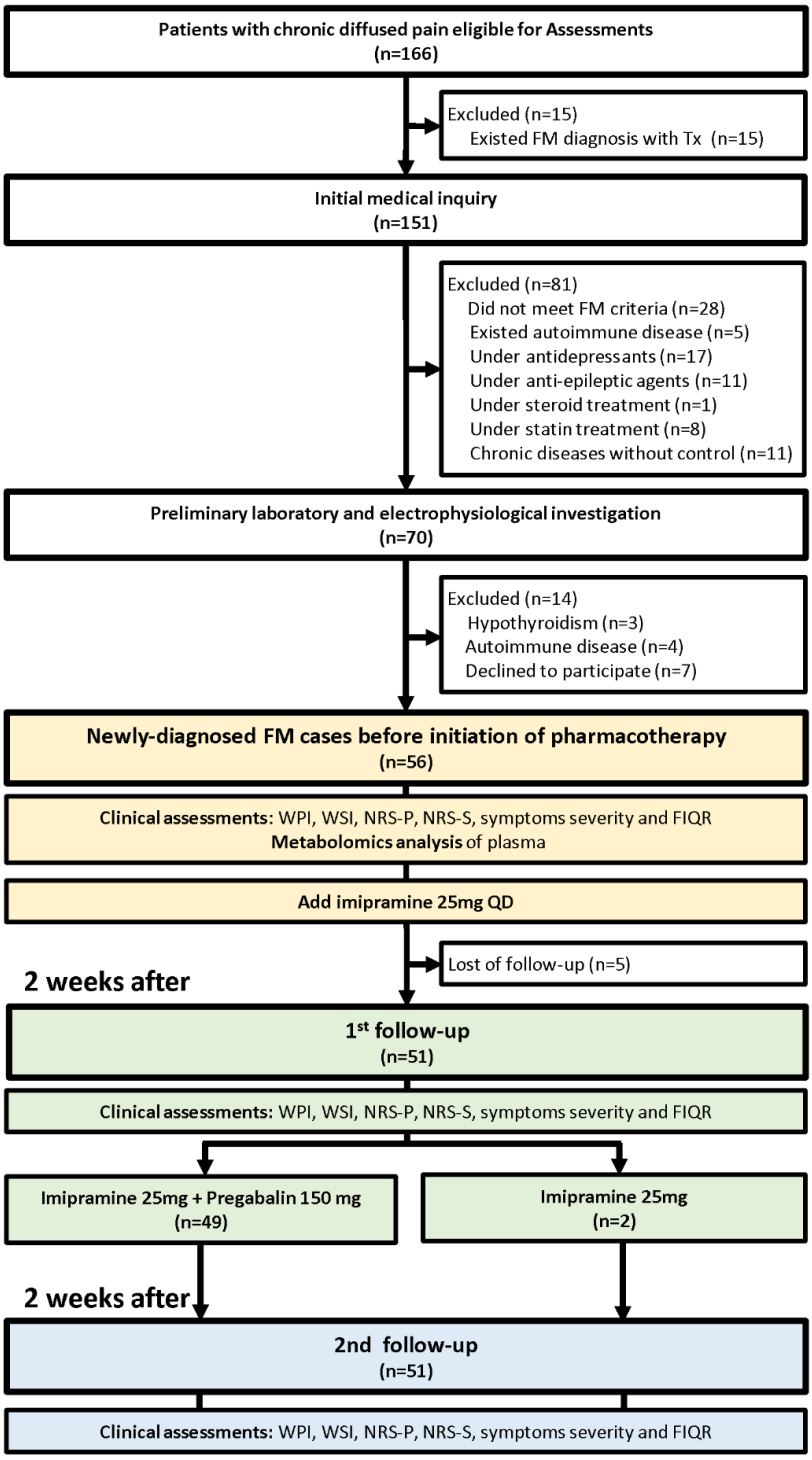

Figure S1. Diagram of patient recruitment. WPI, widespread pain index. WSI, widespread soreness index. NRS-P, numeric rating scale for pain. NRS-S, numeric rating scale for soreness. FIQR, the Revised Fibromyalgia Impact Questionnaire. QD, daily.

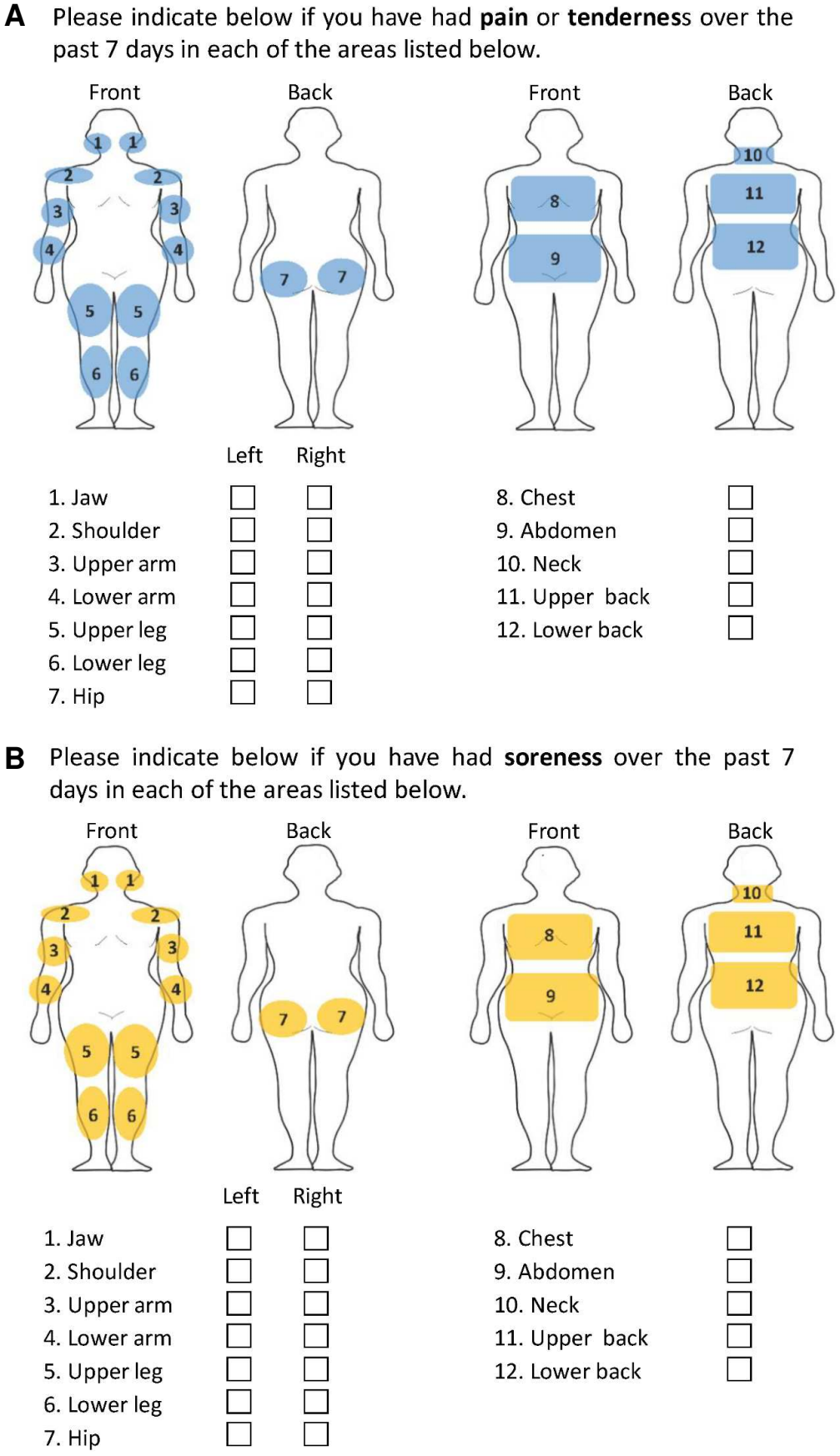

Figure S2. Questionnaires of widespread pain[7] index (**A**) and widespread soreness index (**B**).

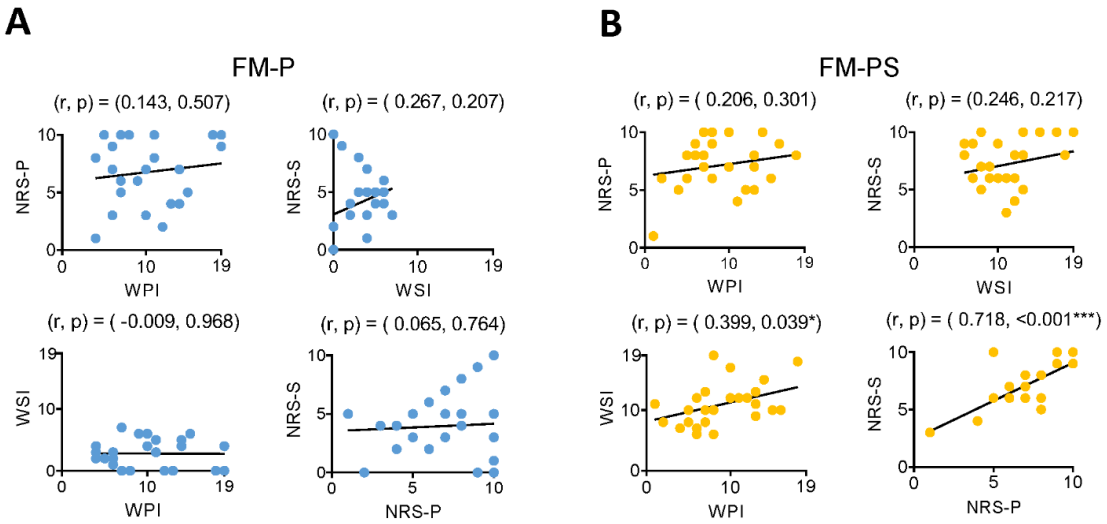

Figure S3. Correlation analysis of NRS-P, NRS-S, WPI and WSI in FM-P (A) and FM-PS (B) (Pearson correlation test).

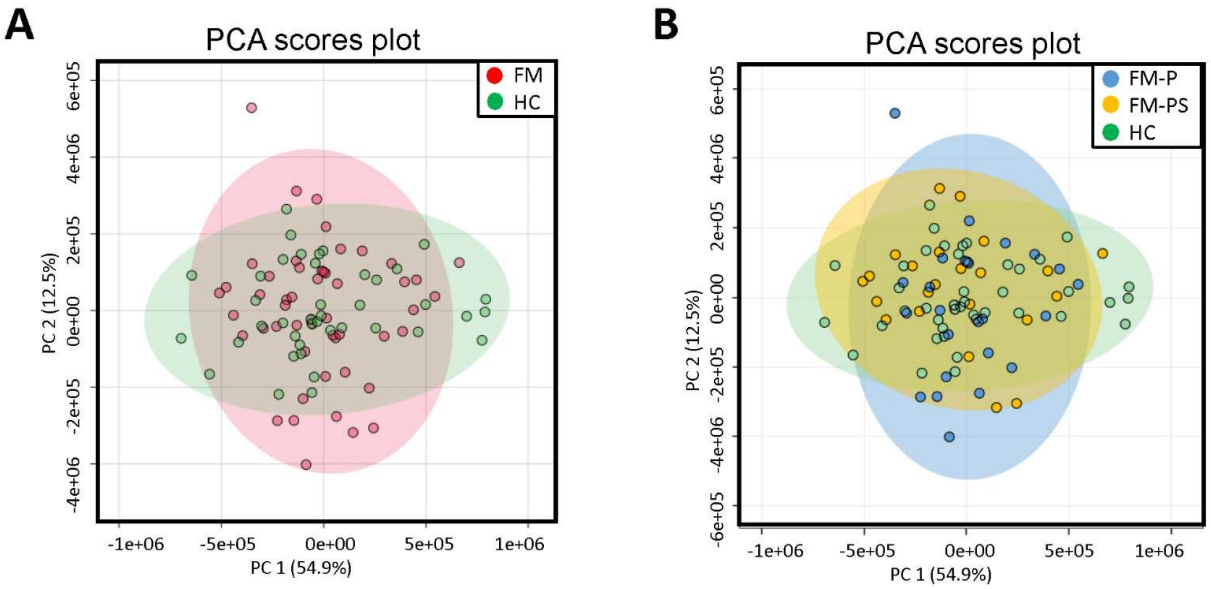

Figure S4. Principal component analysis score plot based on metabolomic analysis of plasma from FM patients and HCs (**A**) and FM-P, FM-PS and HCs (**B**). FM, fibromyalgia. HCs, healthy controls. FM-P, fibromyalgia with pain dominant symptoms. FM-PS, fibromyalgia with mixed pain and soreness symptoms.

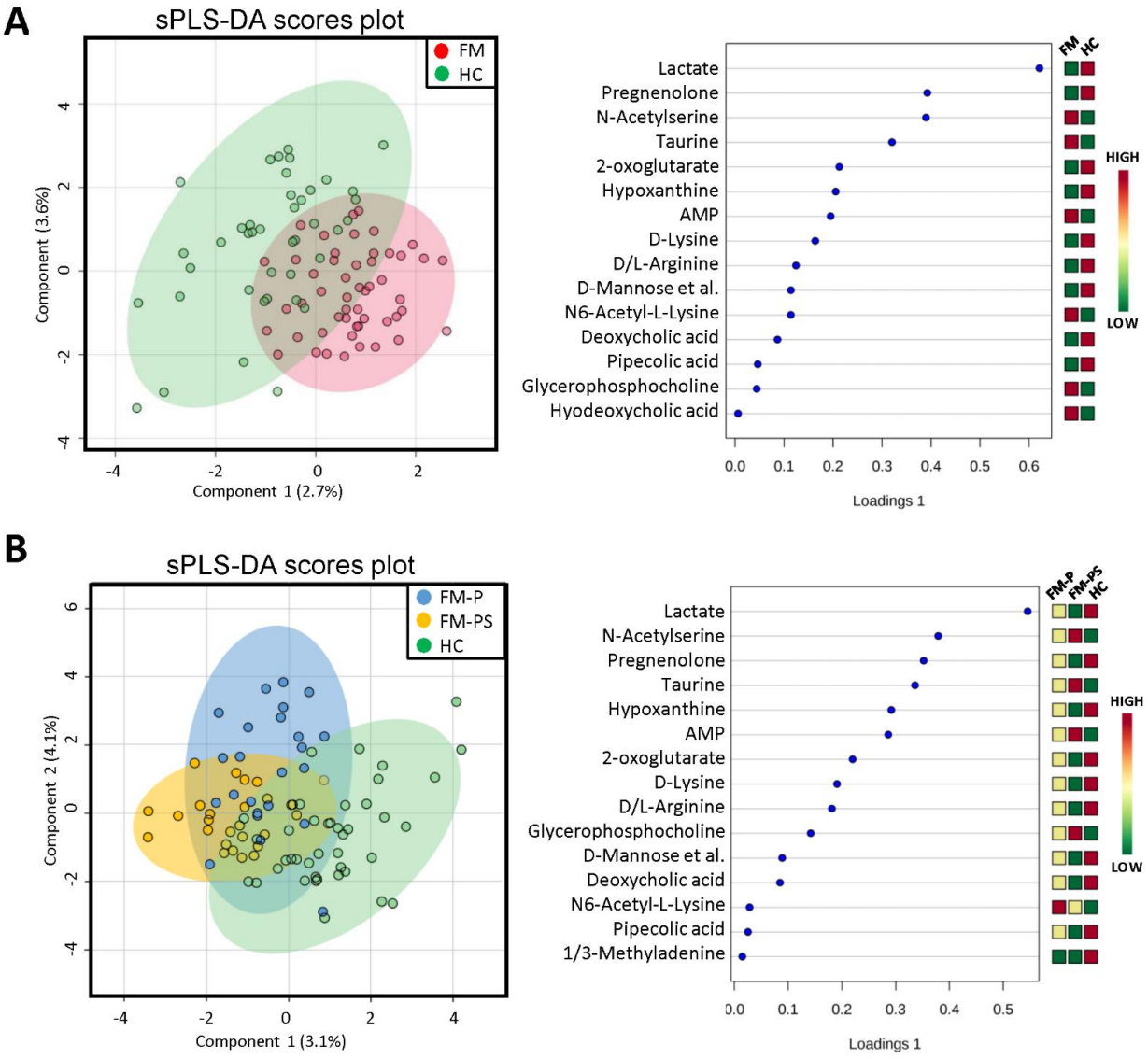

Figure S5. Metabolomic differences in FM-PS but not FM-P groups as compared with HCs. (**A**) Sparse partial least squares discriminant analysis (sPLS-DA) based on metabolomic profiling of plasma from FM patients and HCs. Left, score plot of sPLS-DA. Right, loading plot of sPLS-DA component 1 and the 15 most discriminative variables selected by the sPLS-DA model for this component. (**B**) sPLS-DA based on metabolomic profiling of plasma from FM-P, FM-PS and HC participants. Left, score plot of sPLS-DA. Right, loading plot of sPLS-DA component 1 and the 15 most discriminative variables selected by the sPLS-DA model for this component.

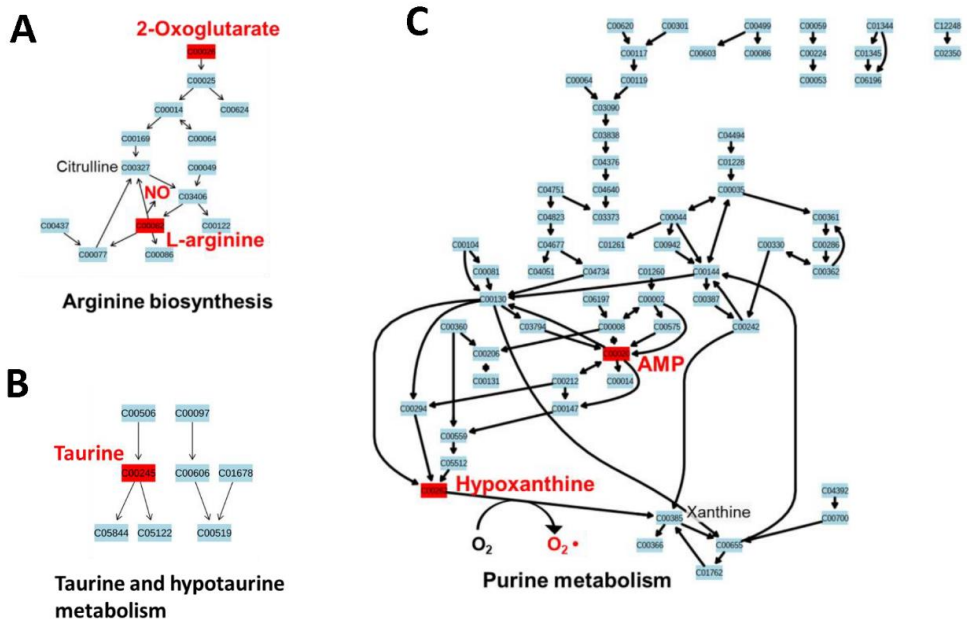

Figure S6. Biologically meaningful pathways selected by pathway analysis and the involved metabolites in FM. Pathways with statistical significance and impact values above the defined threshold (0.05) in the bubble plot (Fig. 3A) were identified as pathway targets, including arginine biosynthesis pathway (**A**), taurine and hypotaurine metabolism pathway (**B**), and purine metabolism pathway **(C)**. Two of the three identified pathways (purine metabolism and arginine biosynthesis) involved cellular oxidative metabolism, such as superoxide (O2—•) and nitric oxide (NO) synthesis.

Table S1. Correlation analysis of pain and soreness manifestation in given regions

	R jaw	L jaw	R shoulder	L shoulder	R arm	L arm	R forearm	L forearm	R hip	L hip
Pearson r value	0.267	0.186	0.048	0.037	0.046	-0.165	0.103	0.038	0.031	0.161
p value	0.058	0.190	0.754	0.749	0.747	0.246	0.471	0.793	0.828	0.258

	R thigh	L thigh	R leg	L leg	Up back	Low back	Neck	Chest	Abd.	
Pearson r value	-0.005	0.131	0.046	0.230	0.005	-0.116	0.188	0.164	0.291	
p value	0.974	0.361	0.751	0.105	0.973	0.058	0.186	0.250	0.038	

Pearson correlation analysis.

Table S2. Clinical impacts of pain and soreness on FM symptoms

	Numeric rating score			
	Pain		Soreness	
FIQR	Item	(r, *p*)	Item	(r, *p*)
Domain 1			Sit for 45 mins	(0.425, 0.002*)
subtotal		(0.146, 0.307)		(0.081, 0.574)
Domain 2				
subtotal		(0.395, 0.004*)		(0.238, 0.092)
Domain 3	Fatigue	(0.469, 0.001*)	Stiffness	(0.317, 0.023*)
	Allodynia	(0.391, 0.005*)		
	Insomnia	(0.307, 0.028*)		
subtotal		(0.520, 0.000*)		(0.220, 0.121)
Sum		(0.434, 0.001*)		(0.216, 0.128)

Pearson correlation analysis. r, Pearson correlation coefficient. p, p-value. *statistically significant. FIQR, the Revised Fibromyalgia Impact Questionnaire. Domain 1, evaluation of function. Domain 2, evaluation of disease overall impact. Domain 3, evaluation of disease symptoms.

Table S3. Therapeutic responses in patients with fibromyalgia

	Rating score (mean ± SD)			
Variable	Basal	1st f/u	2nd f/u	*p* value
Pain / soreness symptoms				
WPI	9.55 ± 4.39	6.96 ± 4.90*	6.90 ± 4.91*	0.007‡
WSI	7.12 ± 5.05	5.57 ± 4.61	5.73 ± 4.55	0.196
NRS-P	6.96 ± 2.47	5.04 ± 2.83**	4.88 ± 2.77***	<0.001‡
NRS-S	5.67 ± 2.88	4.29 ± 2.87*	4.33 ± 2.83	0.024
Symptom severity				
Cognitive disturbance	1.51 ± 0.93	1.12 ± 0.74	1.12 ± 0.86	0.028
Fatigue	2.04 ± 0.80	1.76 ± 0.74	1.78 ± 0.83	0.151
Waking up tired	2.20 ± 0.80	1.63 ± 0.89**	1.73 ± 0.85*	0.002‡
Headache	0.86 ± 0.35	0.90 ± 0.36	0.78 ± 0.42	0.277
GI symptoms	0.61 ± 0.49	0.49 ± 0.54	0.39 ± 0.49	0.105
Depression	0.71 ± 0.46	0.66 ± 0.52	0.61 ± 0.49	0.603
Sum	7.92 ± 2.15	6.55 ± 2.45**	6.41 ± 2.64*	0.003‡
FIQR				
Domain 1	29.06 ± 23.56	24.73 ± 19.87	23.92 ± 20.26	0.426
Domain 2	12.67 ± 6.46	8.90 ± 6.80*	7.92 ± 6.71**	0.001‡
Domain 3	62.61 ± 17.08	57.69 ± 21.93	52.08 ± 21.03*	0.033
Sum	53.66 ± 18.76	45.99 ± 20.43	41.93 ± 20.76*	0.012‡

WPI, widespread pain index. WSI, widespread soreness index. NRS-P, numeric rating scale for pain. NRS-S, numeric rating scale for soreness. FIQR, the Revised Fibromyalgia Impact Questionnaire. SD, standard deviation. f/u, follow-up. The resulting p values for the items of each questionnaire were adjusted by the Bonferroni correction, with p <0.0125 considered statistically significant for pain/soreness symptoms, p <0.0071 for symptom severity and p <0.0125 for FIQR. ‡, statistically significant. One-way ANOVA with post-hoc analysis (Dunnett). * p<0.05, ** p<0.01, ***p<0.001 post-hoc analysis compared with basal.

Table S4. A comparison of comorbidity and disease severity based on the subgroups of fibromyalgia

Variable	FM-P (n=24)	FM-PS (n=27)	*p*-value
Age	54.79 ± 13.76	42.15 ± 11.09	0.001
Gender (F / M)	22 / 2	23 / 4	0.473
NRS-P	6.71 ± 2.93	7.15 ± 2.14	0.540
NRS-S	3.96 ± 2.79	7.19 ± 1.98	<0.001
WPI	9.96 ± 4.71	8.96 ± 4.54	0.446
WSI	2.79 ± 2.32	10.96 ± 3.41	<0.001
Symptom Severity - Sum	8.25 ± 2.21	7.63 ± 2.10	0.309
Cognitive disturbance	1.67 ± 0.92	1.37 ± 0.93	0.257
Fatigue	2.04 ± 0.86	2.04 ± 0.76	0.984
Sleep disturbance	2.33 ± 0.87	2.07 ± 0.73	0.252
Headache	0.92 ± 028	0.81 ± 0.40	0.301
GI symptoms	0.46 ± 0.51	0.74 ± 0.45	0.040
Depression	0.83 ± 0.38	0.59 ± 0.50	0.061
FIQR			
Domain 1	31.75 ± 26.07	26.67 ± 21.29	0.447
Brush or comb hair	0.54 ± 0.98	0.69 ± 1.67	0.837
Walk continuously for 20 mins	3.61 ± 3.84	2.89 ± 3.40	0.485
Prepare a homemade meal	3.17 ± 3.74	3.11 ± 3.86	0.959
Vacuum, scrub or weep floor	4.92 ± 4.15	4.07 ± 3.30	0.424
Lift and carry a bag full of groceries	4.96 ± 4.03	4.44 ± 3.78	0.622
Climb one flight of stairs	3.63 ± 3.40	1.93 ± 2.92	0.061
Change Bedsheets	4.08 ± 4.03	2.96 ± 3.43	0.289
Sit in a chair for 45 minutes	3.00 ± 3.30	3.56 ± 3.68	0.575
Shop for groceries	3.50 ± 3.23	2.63 ± 3.69	0.383
Domain 2	13.13 ± 7.57	12.26 ± 5.42	0.638
Domain 3	63.83 ± 20.14	61.52 ± 14.13	0.634
Sum	55.62 ± 21.20	51.91 ± 16.50	0.486

FM-P, fibromyalgia with pain dominant symptoms. FM-PS, fibromyalgia with mixed pain and soreness symptoms. WPI, widespread pain index. WSI, widespread soreness index. NRS-P, numeric rating scale for pain. NRS-S, numeric rating scale for soreness. FIQR, the Revised Fibromyalgia Impact Questionnaire. Values are mean ± SD. Chi-square test for tests of gender and relieving factors, and unpaired t test for other tests.

Table S5. Presentation of pain and soreness symptoms in the body regions between FM subgroups

Region	Pain (%)			Soreness (%)		
	FM-P	FM-PS	p value	FM-P	FM-PS	p value
Head	45.8	40.7	0.714	8.3	40.7	0.008
Lt upper limb	87.5	85.2	0.811	29.2	96.3	<0.001
Rt upper limb	83.3	85.2	0.856	33.3	92.6	<0.001
Upper back and spine	87.5	77.8	0.363	25	77.8	<0.001
Lower back and spine	75	85.2	0.360	41.7	85.2	0.001
Lt lower limb	50	55.6	0.692	29.2	81.5	<0.001
Rt lower limb	54.2	48.1	0.668	33.3	74.1	0.004
Chest	33.3	44.4	0.417	0	25.9	0.007
Abdomen	25	48.1	0.088	0	18.5	0.026

FM-P, fibromyalgia with pain dominant symptoms. FM-PS, fibromyalgia with mixed pain and soreness symptoms. Chi-squared test.

Table S6. Correlation analysis of regional pain and soreness manifestations in FM-P

	R jaw	L jaw	R shoulder	L shoulder	R arm	L arm	R forearm	L forearm	R hip	L hip
Pearson *r* value	0.078	0.107	0.193	0.194	0.134	—0.312	—0.076	—0.302	0.227	—0.126
p value	0.718	0.620	0.365	0.364	0.533	0.138	0.726	0.151	0.287	0.557

	R thigh	L thigh	R leg	L leg	Up back	Low back	Neck	Chest	Abd.	
Pearson *r* value	0.048	0.098	0.122	0.193	—0.393	—0.449	0.000	1.000	1.000	
p value	0.823	0.650	0.569	0.365	0.058	0.036	1.000	—	—	

FM-P, fibromyalgia with pain dominant symptoms. Pearson correlation analysis.

Table S7. Correlation analysis of regional pain and soreness manifestations in FM-PS

	R jaw	L jaw	R shoulder	L shoulder	R arm	L arm	R forearm	L forearm	R hip	L hip
Pearson *r* value	0.434	0.287	—0.286	—0.025	0.426	0.189	0.377	0.336	0.189	0.373
p value	0.024	0.146	0.149	0.900	0.027	0.345	0.052	0.087	0.345	0.055

	R thigh	L thigh	R leg	L leg	Up back	Low back	Neck	Chest	Abd.	
Pearson *r* value	0.107	0.267	0.052	0.223	0.053	0.067	0.342	0.197	0.304	
p value	0.597	0.179	0.795	0.264	0.792	0.738	0.081	0.323	0.123	

FM-PS, fibromyalgia with mixed pain and soreness symptoms. Pearson correlation analysis.

Table S8. Clinical impacts of pain and soreness on FM symptoms based on the subgroups of fibromyalgia

		FM-P (n=24)			FM-PS (n=27)			
		NRS-P		NRS-S	NRS-P		NRS-S	
FIQR		Item	(*r, p*)	Item	(*r, p*)	Item	(*r, p*)	Item	(*r, p*)
Domain 1				Brush hair	(0.556, 0.007*)				
				Sit for 45 mins	(0.426, 0.048*)			Sit for 45 mins	(0.524, 0.009*)
subtotal			(0.103, 0.649)		(0.117, 0.605)		(0.286, 0.175)		(–0.013, 0.953)
Domain 2									
subtotal			(0.141, 0.532)		(0.293, 0.186)		(0.722, <0.001*)		(0.410, 0.047*)
Domain 3	Fatigue		(0.542, 0.009*)						
	Insomnia		(0.486, 0.022*)						
	Allodynia		(0.476, 0.025*)						
subtotal			(0.605, 0.003*)		(0.388, 0.075)		(0.395, 0.056)		(0.120, 0.576)
Sum			(0.383, 0.078)		(0.341, 0.121)		(0.511, 0.011*)		(0.171, 0.424)

Correlation analyses of symptom intensity and FIQR scores. NRS-P, numeric rating scale for pain. NRS-S, numeric rating scale for soreness. FM-P, fibromyalgia with pain dominant symptoms. FM-PS, fibromyalgia with mixed pain and soreness symptoms. FIQR, the Revised Fibromyalgia Impact Questionnaire. Domain 1, evaluation of function. Domain 2, evaluation of disease overall impact. Domain 3, evaluation of disease symptoms. r, Pearson correlation coefficient r. *p*, p value. *statistically significant.

Table S9. Comparison of therapeutic responses in the subgroups of fibromyalgia

	Rating score (mean ± SD)							
	FM-P (n=24)				FM-PS (n=27)			
	Basal	1st f/u	2nd f/u	*p* value	Basal	1st f/u	2nd f/u	*p* value
Symptom severity								
Cognitive disturbance	1.67 ± 0.92	0.96 ± 0.55*	0.88 ± 0.85*	0.001‡	1.37 ± 0.93	1.26 ± 0.86	1.33 ± 0.83	0.893
Fatigue	2.04 ± 0.86	1.75 ± 0.85	1.67 ± 0.92	0.303	2.04 ± 0.76	1.78 ± 0.64	1.89 ± 0.75	0.417
Waking up tired	2.33 ± 0.87	1.46 ± 1.02**	1.50 ± 0.93**	0.002‡	2.07 ± 0.73	1.78 ± 0.75	1.93 ± 0.73	0.341
Headache	0.92 ± 028	0.83 ± 0.48	0.75 ± 0.44	0.378	0.81 ± 0.40	0.96 ± 0.19	0.81 ± 0.40	0.191
GI symptoms	0.46 ± 0.51	0.38 ± 0.58	0.25 ± 0.44	0.371	0.74 ± 0.45	0.59 ± 0.50	0.52 ± 0.51	0.238
Depression	0.83 ± 0.38	0.74 ± 0.54	0.67 ± 0.48	0.474	0.59 ± 0.50	0.59 ± 0.50	0.56 ± 0.51	0.952
Sum	8.25 ± 2.21	6.08 ± 2.94*	5.71 ± 2.90**	0.003‡	7.63 ± 2.10	6.96 ± 1.87	7.04 ± 2.26	0.439
FIQR								
Domain 1	31.75 ± 26.07	24.88 ± 22.57	24.58 ± 23.11	0.506	26.67 ± 21.29	24.59 ± 17.55	23.33 ± 17.79	0.809
Domain 2	13.13 ± 7.57	8.67 ± 7.35	6.33 ± 6.43**	0.005‡	12.26 ± 5.42	9.11 ± 6.41	9.33 ± 6.77	0.123
Domain 3	63.83 ± 20.14	55.54 ± 25.64	47.67 ± 24.49*	0.066	61.52 ± 14.13	59.59 ± 18.32	56.00 ± 16.90	0.465
Sum	55.62 ± 21.20	44.73 ± 23.74	38.36 ± 23.41*	0.035	51.91 ± 16.50	47.10 ± 17.36	45.11 ±17.93	0.337

One-way ANOVA with post-hoc analysis (Dunnett). The resulting p values for the items of each questionnaire were adjusted by the Bonferroni correction, with p <0.0071 considered statistically significant for symptom severity and p <0.0125 for FIQR. ‡, statistically significant. * p<0.05, ** p<0.05, ***p<0.001 post-hoc analysis (Dunnett) compared with basal. f/u, follow-up. SD, standard deviation. FM-P, fibromyalgia with pain dominant symptoms. FM-PS, fibromyalgia with mixed pain and soreness symptoms. FIQR, the Revised Fibromyalgia Impact Questionnaire.

Table S10 Significantly dysregulated metabolites in patients with fibromyalgia as compared with healthy controls

Metabolites	Adduct	ion (m/z)	Fold change (FM / HC)	*p* value
Upregulation				
Adenosine monophosphate	[M + H]+	348.07	7.96	0.008
N6-Acetyl-L-Lysine	[M + H]+	189.123	1.82	0.014
N-Acetylserine | Glutamic acid	[M + H]+	148.06	1.51	<0.001
Taurine	[M + H]+	126.022	21.33	0.002
Downregulation				
2-Oxoglutarate	[M - H]-	145.014	0.46	0.018
D-Lysine	[M + H]+	147.11	0.33	0.011
D/L-Arginine	[M + H]+	175.119	0.43	0.014
Hypoxanthine	[M + H]+	137.046	0.44	<0.001
Lactate	[M - H]-	89.024	0.78	<0.001
Pregnenolone sulfate	[M - H]-	395.19	0.56	0.001
Pyruvate	[M - H]-	87.007	0.74	0.003

Plasma metabolites were analyzed in fibromyalgia and control groups. The peak intensities of each metabolite were compared using Mann–Whitney U test. Fold changes were calculated by comparing metabolites differing between patients and healthy controls. FM, fibromyalgia. HC, healthy control.

Table S11. Pathway analysis of the selected discriminative metabolites in fibromyalgia

Pathway Name	Total	*p* value	- log(p)	Holm p	FDR	Impact
Arginine biosynthesis	2/14	0.0011137*	6.8	0.093554	0.093554	0.076140
Purine metabolism	2/65	0.023294*	3.7596	1.000000	0.489170	0.080680
Taurine and hypotaurine metabolism	1/8	0.03062*	3.4861	1.000000	0.514410	0.428570
Citrate cycle (TCA cycle)	1/20	0.075082	2.5892	1.000000	0.788360	0.058560
Arginine and proline metabolism	1/38	0.13858	1.9763	1.000000	1.000000	0.057860
Aminoacyl-tRNA biosynthesis	2/48	0.013014*	4.3418	1.000000	0.489170	0.000000
D-Glutamine and D-glutamate metabolism	1/6	0.023039*	3.7706	1.000000	0.489170	0.000000
Biotin metabolism	1/10	0.038151*	3.2662	1.000000	0.534120	0.000000
Butanoate metabolism	1/15	0.056767	2.8688	1.000000	0.681210	0.000000
Lysine degradation	1/25	0.093099	2.3741	1.000000	0.868930	0.000000
Alanine, aspartate and glutamate metabolism	1/28	0.10377	2.2656	1.000000	0.871660	0.048080
Primary bile acid biosynthesis	1/46	0.16561	1.7981	1.000000	1.000000	0.007580

FDR, false discovery rate. TCA cycle, the citric acid cycle. *statistically significant.

Table S12. Phenotypic characteristics of FM with pain dominant symptoms (FM-P) and FM with mixed pain and soreness symptoms (FM-PS)

	FM-P	FM-PS
Number (percentage)	24 (47.1%)	27 (52.9%)
Manifestation		
Correlation of NRS-P and NRS-S	No	Yes
Correlation of WPI and WSI	No	Yes
Therapeutic response		
NRS-P	Yes	Yes
NRS-S	Yes	Delayed response
Symptom severity score	Yes	No
FIQR score	Yes	No
Metabolic expression (vs HCs)		
Metabolomic phenotype	Less distinct	More distinct
Increased MDA level	Nonsignificant	Significant

FIQR, Revised Fibromyalgia Impact Questionnaire. NRS-P, numeric rating score for pain. NRS-S, numeric rating score for soreness. WPI, widespread pain index. WSI, widespread soreness index. MDA, malondialdehyde. HCs, healthy controls.