Phenylalanine is a novel marker for radiographic knee osteoarthritis progression: the MOST study

Running title: Phenylalanine and knee OA progression

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The sources of support: The current study was supported by Canadian Institutes of Health Research (FRN153298) and the original study of the MOST was supported by National Institutes of Health and National Institute on Aging (Felson – U01 AG18820; Lewis – U01 AG18947; Nevitt – U01 AG19069; Torner – U01 AG18832).

Conflicts of interest: Both AG and FR are shareholders of Boston Imaging Core Lab (BIC), LLC. All other authors have no conflict of interest to declare.

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Supplementary Table 1. List of metabolite concentrations determined using the Biocrates AbsoluteIDQ kit

Metabolite class	Number	Metabolite name or abbreviation	Biological relevance (selected examples)
Amino acids	21	Alanine, arginine, asparagine, aspartate, citrulline, glutamine, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine	Amino acid metabolism, urea-cycle, activity of gluconeogenesis and glycolysis, insulin sensitivity, neurotransmitter metabolism, oxidative stress
Carnitine	1	C0	
Acylcarnitine	25	C2, C3, C3:1, C4, C4:1, C5, C5:1, C6(or C4:1-DC), C6:1, C8, C9, C10, C10:1, C10:2, C12, C12:1, C14, C14:1, C14:2, C16, C16:1, C16:2, C18, C18:1, C18:2	Energy metabolism, fatty acid transport and mitochondrial fatty acid oxidation, ketosis, oxidative stress, mitochondrial membrane damage
Hydroxy- and dicarboxyacylcarnitines	14	C3-OH, C4-OH(or C3-DC), C5:1-DC, C5-DC(or C6-OH), C5-M-DC, C5-OH(or C3-DC-M), C7-DC, C12-DC, C14:1-OH, C14:2-OH, C16:1-OH, C16:2-OH, C16-OH, C18:1-OH	
Biogenic amines	19	acetylornithine, asymmetric dimethylarginine, total dimethylarginine, alpha-Aminoadipic acid, carnosine, creatinine, histamine, kynurenine, methioninesulfoxide, nitrotyrosine,hydroxyproline, phenylethylamine, putrescine, sarcosine, serotonin, spermidine, spermine, taurine	
Lyso-phosphatidylcholines	14	lysoPC a C14:0/C16:0/C16:1/C17:0/C18:0/C18:1/C18:2/ C20:3/C20:4/C26:0/C26:1/C28:0/C28:1	Degradation of phospholipids, membrane damage, signalling cascades, fatty acid profi le
Diacyl-phosphatidylcholines	38	PC aa C24:0/C26:0/C28:1/C30:0/C30:2/C32:0/C32:1/C32:2/ C32:3/C34:1/C34:2/C34:3/C34:4/C36:0/C36:1/C36:2/C36:3/C36:4/C 36:5/C36:6/C38:0/C38:1/C38:3/C38:4/C38:5/C38:6/C40:1/C40:2/C4 0:3/C40:4/C40:5/C40:6/C42:0/C42:1/C42:2/C42:4/C42:5/C42:6	Dyslipidaemia, membrane composition and damage, fatty acid profi le, activity of desaturases
Acyl-alkyl-phosphatidylcholines	38	PC ae C30:0/C30:2/C32:1/C32:2/C34:0/C34:1/C34:2/C34:3/ C36:0/C36:1/C36:2/C36:3/C36:4/C36:5/C38:0/C38:1/C38:2/C38:3/C 38:4/C38:5/C38:6/C40:1/C40:2/C40:3/C40:4/C40:5/C40:6/C42:0/C4 2:1/C42:2/C42:3/C42:4/C42:5/C44:3/C44:4/C44:5/C44:6	
Sphingomyelines	10	SM C16:0, SM C16:1, SM C18:0, SM C18:1, SM C20:2, SM C22:3, SM C24:0, SM 24:1, SM C26:0, SM C26:1	Signalling cascades, membrane damage (eg, neurodegeneration)
Hydroxysphingomyelines	5	SM (OH) C14:1, SM (OH) C16:1, SM (OH) C22:1, SM (OH) C22:2, SM (OH) C24:1	
Hexose	1	H1	Carbohydrate metabolism
Total	186		

aa, acyl-acyl; ae, acyl-alkyl; a, lyso; Cx:y, where x is the number of carbons in the fatty acid side chain; y is the number of double bonds in the fatty acid side chain; DC, decarboxyl; M, methyl; OH, hydroxyl; PC, phophatidylcholine; SM, sphingomyelin

Supplementary Table 2. The association between knee progression and each of the 157 metabolites.
Note: 1 - group 1; 2 - group 2; 3 - the combined of the group 1 and 2. Beta and SE were logistic regression coefficients and standard error.

Metabolites	Beta 1	SE 1	P value 1	Beta 2	SE 2	P value 2	Beta 3	SE 3	P value 3
Phenylalanine	0.51	0.17	0.0036	0.31	0.12	0.0089	0.38	0.10	0.0001
Serine	0.23	0.16	0.1593	0.35	0.13	0.0077	0.30	0.10	0.0034
PC_ae_C36_2	0.16	0.15	0.2953	0.36	0.13	0.0060	0.27	0.10	0.0064
Arginine	0.39	0.16	0.0135	0.18	0.12	0.1289	0.25	0.10	0.0075
C0	0.53	0.18	0.0026	0.12	0.12	0.3257	0.26	0.10	0.0100
Leucine	0.39	0.18	0.0332	0.22	0.13	0.0928	0.26	0.10	0.0120
PC_ae_C40_6	0.21	0.17	0.2166	0.30	0.13	0.0207	0.24	0.10	0.0157
Asparagine	0.20	0.16	0.2215	0.25	0.12	0.0378	0.23	0.10	0.0164
PC_ae_C34_0	0.20	0.16	0.1932	0.24	0.13	0.0542	0.23	0.10	0.0172
PC_ae_C34_2	0.11	0.16	0.4753	0.33	0.13	0.0141	0.23	0.10	0.0204
PC_ae_C36_1	0.21	0.15	0.1754	0.25	0.13	0.0565	0.22	0.10	0.0245
PC_ae_C34_3	0.11	0.16	0.4642	0.31	0.13	0.0219	0.22	0.10	0.0272
PC_ae_C38_4	0.10	0.15	0.5042	0.31	0.13	0.0165	0.21	0.10	0.0280
PC_ae_C34_1	0.17	0.16	0.2855	0.27	0.13	0.0434	0.22	0.10	0.0303
Histidine	0.08	0.16	0.6099	0.29	0.13	0.0230	0.20	0.10	0.0357
Glycine	0.17	0.17	0.3144	0.23	0.12	0.0598	0.21	0.10	0.0364
PC_ae_C36_3	0.04	0.15	0.8052	0.34	0.13	0.0110	0.21	0.10	0.0385
PC_ae_C38_5	0.10	0.15	0.5148	0.28	0.13	0.0346	0.19	0.10	0.0500
Threonine	0.31	0.16	0.0556	0.12	0.12	0.3004	0.18	0.09	0.0528
Tyrosine	0.34	0.18	0.0630	0.13	0.11	0.2534	0.19	0.10	0.0528
Isoleucine	0.38	0.18	0.0368	0.11	0.13	0.3976	0.21	0.11	0.0563
Ornithine	0.10	0.15	0.5294	0.27	0.13	0.0295	0.18	0.10	0.0627
Methionine	0.29	0.17	0.0771	0.13	0.12	0.2693	0.18	0.10	0.0693
Hexose	0.16	0.14	0.2536	0.17	0.13	0.2082	0.17	0.10	0.0768
PC_ae_C38_6	0.14	0.16	0.4032	0.22	0.14	0.0972	0.18	0.10	0.0855
Valine	0.21	0.17	0.2012	0.16	0.13	0.2205	0.18	0.10	0.0872
PC_aa_C40_6	0.20	0.15	0.2048	0.18	0.13	0.1670	0.17	0.10	0.0920
PC_aa_C36_2	0.09	0.15	0.5175	0.23	0.13	0.0782	0.16	0.10	0.0939
Tryptophan	-0.07	0.15	0.6242	0.31	0.12	0.0097	0.15	0.09	0.0968
PC_ae_C36_4	0.09	0.15	0.5329	0.20	0.13	0.1167	0.16	0.10	0.1053

PC_aa_C38_0	0.13	0.16	0.4191	0.22	0.14	0.1097	0.16	0.10	0.1065
PC_aa_C32_0	0.20	0.16	0.2175	0.14	0.13	0.2901	0.16	0.10	0.1113
PC_aa_C42_0	0.21	0.16	0.1763	0.14	0.13	0.2497	0.15	0.10	0.1124
C5	0.62	0.18	0.0005	-0.09	0.13	0.4658	0.16	0.10	0.1161
Lysine	-0.03	0.15	0.8196	0.26	0.12	0.0270	0.14	0.09	0.1241
PC_ae_C38_3	0.14	0.15	0.3461	0.17	0.13	0.1954	0.15	0.10	0.1268
PC_ae_C40_5	0.05	0.15	0.7531	0.24	0.13	0.0611	0.15	0.10	0.1294
PC_ae_C38_2	0.07	0.15	0.6416	0.24	0.14	0.0766	0.15	0.10	0.1325
PC_ae_C40_4	0.01	0.15	0.9553	0.25	0.13	0.0529	0.14	0.10	0.1529
Glutamine	0.01	0.16	0.9299	0.21	0.12	0.0817	0.13	0.09	0.1557
Kynurenine	0.15	0.15	0.3054	0.16	0.13	0.2116	0.13	0.10	0.1593
PC_ae_C44_3	0.08	0.16	0.6208	0.17	0.12	0.1501	0.13	0.10	0.1610
PC_ae_C30_1	0.01	0.16	0.9338	0.18	0.12	0.1250	0.13	0.10	0.1666
PC_ae_C42_4	0.06	0.15	0.6996	0.19	0.13	0.1303	0.13	0.10	0.1706
PC_ae_C36_5	0.14	0.15	0.3664	0.13	0.13	0.3086	0.13	0.10	0.1714
PC_ae_C32_1	0.09	0.16	0.5798	0.18	0.13	0.1725	0.14	0.10	0.1721
PC_aa_C42_4	0.21	0.16	0.1954	0.12	0.13	0.3700	0.14	0.10	0.1725
PC_aa_C38_6	0.12	0.16	0.4604	0.17	0.13	0.1798	0.13	0.10	0.1756
Alanine	0.05	0.16	0.7809	0.17	0.12	0.1503	0.13	0.09	0.1821
lysoPC_a_C17_0	0.20	0.20	0.3308	0.10	0.10	0.3297	0.12	0.09	0.1857
PC_ae_C44_6	0.06	0.16	0.7100	0.20	0.13	0.1239	0.13	0.10	0.1967
PC_aa_C42_6	0.15	0.15	0.3437	0.16	0.14	0.2379	0.13	0.10	0.2119
trans_hydroxyprolin	0.05	0.17	0.7809	0.18	0.13	0.1619	0.12	0.10	0.2170
PC_ae_C42_3	0.09	0.16	0.5885	0.18	0.13	0.1650	0.12	0.10	0.2180
PC_ae_C42_5	0.05	0.15	0.7503	0.20	0.13	0.1299	0.12	0.10	0.2185
PC_aa_C32_3	0.12	0.17	0.4801	0.14	0.14	0.2980	0.13	0.11	0.2291
PC_aa_C34_2	0.05	0.15	0.7182	0.17	0.13	0.1909	0.12	0.10	0.2297
PC_ae_C44_4	0.13	0.16	0.4213	0.11	0.11	0.3301	0.11	0.09	0.2335
Proline	0.32	0.16	0.0425	-0.01	0.12	0.9229	0.11	0.09	0.2352
PC_aa_C40_1	0.13	0.16	0.4039	0.14	0.13	0.2825	0.12	0.10	0.2509
PC_ae_C42_0	0.21	0.16	0.1883	0.11	0.13	0.4276	0.11	0.10	0.2510

C12_1	-0.26	0.16	0.1084	0.01	0.13	0.9366	-0.11	0.10	0.2646
PC_aa_C38_4	0.15	0.16	0.3466	0.11	0.13	0.4103	0.11	0.10	0.2838
Citruline	0.22	0.16	0.1710	0.04	0.12	0.7441	0.10	0.09	0.2869
PC_ae_C40_2	0.14	0.15	0.3595	0.10	0.14	0.4548	0.10	0.10	0.3051
PC_aa_C38_5	0.11	0.16	0.5045	0.13	0.13	0.3244	0.10	0.10	0.3086
PC_aa_C36_1	0.09	0.14	0.5392	0.11	0.13	0.4125	0.09	0.10	0.3245
PC_aa_C28_1	0.08	0.16	0.6163	0.12	0.13	0.3469	0.10	0.10	0.3329
PC_ae_C42_2	0.14	0.16	0.3881	0.10	0.13	0.4430	0.10	0.10	0.3336
C14_1	-0.22	0.18	0.2137	-0.02	0.11	0.8433	-0.08	0.09	0.3473
lysoPC_a_C18_0	0.17	0.22	0.4256	0.06	0.10	0.5314	0.08	0.09	0.3535
PC_aa_C36_3	0.01	0.15	0.9466	0.16	0.13	0.2029	0.09	0.10	0.3569
PC_ae_C44_5	0.06	0.15	0.6795	0.13	0.13	0.3207	0.09	0.10	0.3711
PC_aa_C36_0	0.10	0.17	0.5489	0.09	0.12	0.4444	0.08	0.10	0.3900
lysoPC_a_C20_4	0.21	0.20	0.2938	0.04	0.10	0.6861	0.08	0.09	0.3922
PC_aa_C36_4	0.11	0.16	0.5064	0.08	0.13	0.5117	0.09	0.10	0.3932
PC_aa_C36_6	0.15	0.16	0.3566	0.05	0.12	0.6823	0.08	0.10	0.3979
C5_1_DC	0.20	0.15	0.2018	0.01	0.12	0.9541	0.08	0.10	0.4035
C16_2	-0.08	0.18	0.6383	-0.06	0.10	0.5716	-0.07	0.09	0.4175
PC_aa_C40_3	0.05	0.15	0.7384	0.12	0.13	0.3607	0.08	0.10	0.4181
C18_1	-0.05	0.17	0.7850	0.15	0.12	0.1977	0.07	0.09	0.4215
PC_ae_C38_0	0.06	0.17	0.7079	0.12	0.13	0.3479	0.08	0.10	0.4278
SM_C26_1	-0.24	0.21	0.2442	-0.01	0.11	0.9390	-0.07	0.09	0.4384
C16	0.15	0.19	0.4343	0.06	0.12	0.6275	0.08	0.10	0.4415
lysoPC_a_C18_2	0.15	0.20	0.4581	0.05	0.11	0.6456	0.07	0.09	0.4442
C14_2	-0.20	0.18	0.2641	-0.01	0.10	0.9281	-0.07	0.09	0.4443
PC_ae_C32_2	0.10	0.17	0.5492	0.08	0.13	0.5471	0.08	0.10	0.4476
C7_DC	0.08	0.16	0.6006	0.07	0.12	0.5600	0.07	0.10	0.4502
PC_aa_C30_0	0.16	0.15	0.2818	-0.01	0.13	0.9554	0.07	0.10	0.4513
lysoPC_a_C16_0	0.13	0.21	0.5259	0.05	0.10	0.6159	0.06	0.09	0.4606
C16_1	-0.17	0.20	0.3955	-0.03	0.10	0.7583	-0.06	0.09	0.4632
C14_1_OH	-0.14	0.17	0.4152	-0.03	0.10	0.7552	-0.06	0.09	0.4662

PC_ae_C40_1	0.10	0.17	0.5626	0.08	0.13	0.5219	0.07	0.10	0.4671
lysoPC_a_C18_1	0.15	0.21	0.4781	0.04	0.10	0.6648	0.06	0.09	0.4779
PC_aa_C42_2	0.05	0.16	0.7366	0.09	0.12	0.4503	0.07	0.10	0.4836
Spermidine	-0.18	0.22	0.4164	-0.04	0.16	0.8288	-0.09	0.13	0.4859
PC_ae_C42_1	0.16	0.16	0.3146	0.03	0.13	0.8184	0.07	0.10	0.4921
PC_aa_C40_5	0.06	0.15	0.6650	0.09	0.13	0.4860	0.06	0.10	0.5017
C3	0.27	0.15	0.0749	-0.06	0.13	0.6519	0.07	0.10	0.5035
SM_C26_0	-0.27	0.22	0.2210	0.00	0.11	0.9695	-0.06	0.09	0.5153
PC_aa_C40_2	0.10	0.16	0.5187	0.08	0.13	0.5656	0.06	0.10	0.5265
PC_aa_C40_4	0.08	0.15	0.5857	0.07	0.13	0.5869	0.06	0.10	0.5348
C18_2	-0.02	0.15	0.8957	0.11	0.12	0.3287	0.05	0.09	0.5525
Acetylornithoine	-0.18	0.15	0.2204	0.05	0.12	0.7069	-0.05	0.09	0.5629
PC_aa_C42_1	0.06	0.16	0.7239	0.08	0.12	0.4707	0.05	0.09	0.5812
C6__C4_1_DC_	-0.09	0.17	0.5730	-0.02	0.13	0.8578	-0.05	0.10	0.5821
SM_C24_1	-0.22	0.20	0.2814	0.01	0.11	0.9166	-0.05	0.09	0.5823
C10_2	-0.22	0.16	0.1540	0.08	0.12	0.5148	-0.05	0.10	0.5963
PC_aa_C32_1	0.00	0.15	0.9812	-0.08	0.13	0.5106	-0.05	0.10	0.6006
PC_aa_C38_1	0.19	0.16	0.2492	-0.03	0.13	0.8088	0.05	0.10	0.6047
Spermine	-0.09	0.15	0.5380	-0.01	0.12	0.9274	-0.04	0.09	0.6386
C12	-0.13	0.17	0.4516	0.02	0.12	0.8860	-0.05	0.10	0.6434
C10_1	-0.07	0.16	0.6537	-0.01	0.12	0.9589	-0.05	0.10	0.6460
C4	0.23	0.15	0.1338	-0.22	0.13	0.0814	-0.04	0.10	0.6475
Creatinine	0.15	0.16	0.3631	-0.01	0.13	0.9221	0.04	0.10	0.6526
lysoPC_a_C20_3	0.19	0.21	0.3556	-0.01	0.10	0.9401	0.04	0.09	0.6571
PC_aa_C34_3	0.04	0.16	0.8019	0.06	0.14	0.6849	0.04	0.10	0.6630
C16_1_OH	-0.03	0.17	0.8768	-0.04	0.11	0.7003	-0.04	0.09	0.6659
PC_ae_C40_3	0.02	0.15	0.8983	0.08	0.14	0.5685	0.04	0.10	0.6842
C18	-0.14	0.17	0.4241	0.13	0.12	0.2523	0.04	0.09	0.6874
Serotonin	0.25	0.17	0.1479	-0.07	0.12	0.5293	0.04	0.09	0.6877
PC_aa_C34_1	0.01	0.15	0.9278	0.07	0.13	0.6060	0.04	0.10	0.6905
SM_C16_1	-0.24	0.22	0.2815	0.03	0.11	0.7817	-0.03	0.09	0.7024

SM_C24_0	-0.19	0.20	0.3379	0.02	0.11	0.8429	-0.03	0.09	0.7056
SM_C18_0	-0.31	0.24	0.1973	0.04	0.10	0.7248	-0.03	0.09	0.7131
SM__OH__C24_1	-0.13	0.19	0.4848	0.01	0.10	0.9554	-0.03	0.09	0.7219
C14	-0.09	0.17	0.5972	0.00	0.11	0.9901	-0.03	0.09	0.7318
C10	-0.01	0.15	0.9689	0.07	0.13	0.5714	0.03	0.10	0.7326
PC_aa_C36_5	0.09	0.16	0.5714	0.00	0.12	0.9912	0.03	0.10	0.7441
SM_C16_0	-0.25	0.23	0.2845	0.03	0.10	0.7590	-0.03	0.09	0.7474
lysoPC_a_C14_0	0.06	0.19	0.7309	0.01	0.10	0.8976	0.03	0.09	0.7664
Glutamic_acid	0.01	0.17	0.9744	0.05	0.14	0.7293	0.03	0.11	0.7667
C8	0.05	0.16	0.7565	0.03	0.12	0.8202	0.03	0.10	0.7812
PC_aa_C38_3	0.00	0.15	0.9745	0.07	0.13	0.6202	0.03	0.10	0.7848
lysoPC_a_C28_1	0.00	0.16	0.9879	-0.03	0.11	0.7737	-0.02	0.09	0.7861
Methioninesulfoxide	0.11	0.18	0.5488	-0.03	0.11	0.8057	0.02	0.09	0.7879
Putrescine	0.05	0.17	0.7630	-0.07	0.13	0.6047	-0.03	0.10	0.7994
Asymmetric_dimethy	0.26	0.16	0.1092	-0.11	0.13	0.4001	0.02	0.10	0.8008
SM_C20_2	-0.21	0.19	0.2601	0.06	0.11	0.5944	-0.02	0.09	0.8056
Aspartic_acid	0.08	0.17	0.6246	-0.08	0.12	0.4854	-0.02	0.09	0.8109
alpha_Aminoadipic_	-0.05	0.16	0.7413	0.00	0.12	0.9927	-0.02	0.10	0.8246
SM_C18_1	-0.28	0.23	0.2244	0.06	0.11	0.6042	-0.02	0.09	0.8316
Taurine	0.27	0.17	0.1059	-0.10	0.12	0.3851	0.02	0.09	0.8531
PC_aa_C42_5	0.02	0.16	0.9186	0.00	0.14	0.9934	-0.02	0.10	0.8784
SM_C22_3	0.02	0.16	0.9079	0.03	0.11	0.7559	0.01	0.09	0.8786
PC_ae_C36_0	0.01	0.15	0.9261	-0.03	0.13	0.8307	-0.01	0.10	0.8927
PC_ae_C30_2	-0.06	0.16	0.6872	0.02	0.12	0.8540	-0.01	0.10	0.9108
SM__OH__C22_1	-0.14	0.19	0.4668	0.04	0.11	0.7026	-0.01	0.09	0.9234
PC_aa_C34_4	0.11	0.17	0.5197	-0.05	0.13	0.6884	0.01	0.10	0.9316
PC_ae_C30_0	0.06	0.16	0.7219	-0.06	0.12	0.6522	-0.01	0.10	0.9332
lysoPC_a_C16_1	0.02	0.16	0.9108	-0.01	0.11	0.9263	0.00	0.09	0.9621
PC_aa_C32_2	0.04	0.15	0.7881	-0.04	0.13	0.7669	0.00	0.10	0.9747
PC_ae_C38_1	-0.03	0.16	0.8680	0.04	0.12	0.7157	0.00	0.09	0.9874
SM__OH__C16_1	-0.18	0.20	0.3745	0.06	0.11	0.5693	0.00	0.09	0.9967

C2	0.15	0.15	0.3288	-0.07	0.12	0.5491	0.00	0.09	0.9974
SM__OH__C14_1	-0.14	0.20	0.4639	0.05	0.11	0.6274	0.00	0.09	0.9977
SM__OH__C22_2	-0.12	0.19	0.5157	0.06	0.11	0.6137	0.00	0.09	0.9990

Supplementary Table 3. Mean concentrations of phenylalanine in non-progressors, progressors, and the in-betweeners*

	Non-progressors**	In-betweeners**	Progressors**
Group 1	65.48±0.76	67.46±1.54	72.13±2.08
Group 2	64.28±1.12	67.51±3.37	68.00±0.96
Combined	65.04±0.63	67.44±1.45	69.00±0.89

*Figures are mean±SE and the measurement unit is μMol.

**For group 1, participants were classified as progressors if they had radiographic progression in the knee with baseline OA and the contralateral knee developed OA (KL >=2); for group 2, progressors were participants with both knees with OA showed progression at follow-up. Non-progressors were defined as subjects in groups 1 and 2 in whom neither knee progressed nor developed OA. The in-betweeners in group 1 was subjects who had radiographic progression in the knee with baseline OA but the contralateral knee did not develop OA; for group 2, the in-betweeners were subjects who only had one OA knee progressed. While the mean concentration of phenylalanine was statistically significant between non-progressors and progressors as presented in Table 1 in the text of the manuscript, it was not significantly different between non-progressors and in-betweeners.