Supplementary Table S1. Compounds Identified as Markers (Partial Least-Squares Discriminant Analysis Variable Importance in Projection ≥1) When Analyzing the Two-Dimensional Gas Chromatography Time-of-Flight Mass Spectrometer (GCxGC-TOFMS) Generated Metabolome Profiles of Serum Collected from Combined Oral Contraceptive Users and Controls

Detected compound	*Control average concentration (standard deviation)*	*COC users average concentration (standard deviation)*	*Increased (↑) or decreased (↓) with COC*	*FC*	*Effect size (Cohen's* d*-value)*	t-*Test (BH FDR adjusted* p*-value)*	*PLS-DA (VIP)*
Pyroglutamic acid	233.03 (25.50)	177.40 (22.23)	↓	1.31	2.23	0.0000	3.24
Oxazole, 2-(3Z,6Z,9Z,12Z,15Z,18Z)-3,6,9,12,15,18-heneicosahexaen-1-yl-4,5-dihydro-	0.2041 (0.123)	0.4709 (0.135)	↑	2.31	2.01	0.0000	3.23
α-Ketoglutaric acid	0.2295 (0.168)	0.0486 (0.057)	↓	4.72	1.12	0.0008	3.20
Proline	274.53 (75.18)	174.92 (51.61)	↓	1.57	1.65	0.0000	2.91
Glutamine	28.198 (3.296)	22.241 (3.852)	↓	1.27	1.41	0.0000	2.72
2,3-Dihydroxybutanoic acid	0.9263 (0.351)	1.8856 (0.898)	↑	2.04	1.25	0.0000	2.66
Dodecane, 1-isocyanat	0.2198 (0.053)	0.2905 (0.048)	↑	1.32	1.28	0.0003	2.58
Campesterol	0.2650 (0.164)	0.1240 (0.111)	↓	2.14	0.95	0.0061	2.40
2-[(4Z,7Z,10Z,13Z)-Nonadeca-4,7,10,13-tetraen-1-yl]-4,5-dihydrooxazole	0.8416 (0.281)	1.2963 (0.370)	↑	1.54	1.30	0.0001	2.32
L-Rhamnose	1.2258 (0.497)	1.9025 (0.581)	↑	1.55	1.22	0.0005	2.31
Ornithine	7.7852 (2.707)	4.9821 (1.544)	↓	1.56	1.32	0.0002	2.30
Acetic acid, 2-(dimethylamino)ethyl ester	3.6830 (1.348)	6.3445 (2.579)	↑	1.72	1.20	0.0002	2.25
3-Amino-2-piperidone	0.3508 (0.145)	0.2225 (0.092)	↓	1.58	0.95	0.0058	2.23
Caffeine	1.7203 (1.657)	5.3217 (4.068)	↑	3.09	1.03	0.0007	2.17
Doconexent	2.1594 (0.664)	3.0752 (0.833)	↑	1.42	1.28	0.0004	2.17
Serinyl-leucine	0.0197 (0.014)	0.0392 (0.013)	↑	1.99	1.34	0.0002	2.07
Serine	30.873 (6.353)	24.303 (8.412)	↓	1.27	0.96	0.0008	2.03
Methionine	11.829 (2.929)	9.3029 (2.459)	↓	1.27	0.96	0.0056	2.01
11,14-Eicosadienoic acid	0.4118 (0.247)	0.7255 (0.305)	↑	1.76	1.08	0.0011	2.00
Glycine	61.909 (23.26)	38.899 (17.68)	↓	1.59	1.22	0.0002	1.99
Hydroxyproline	5.9259 (3.888)	3.5707 (1.571)	↓	1.66	0.74	0.0303	1.97
Tyrosine	43.935 (11.01)	34.411 (9.584)	↓	1.28	0.94	0.0087	1.93
N-acetylglutamine	1.2193 (0.510)	0.8600 (0.342)	↓	1.42	0.74	0.0362	1.87
Dodecanamide, N-(2-hydroxyethyl)	0.0355 (0.010)	0.0502 (0.014)	↑	1.41	1.00	0.0005	1.87
Galactaric acid	0.2407 (0.063)	0.3722 (0.208)	↑	1.55	0.76	0.0005	1.84
Propanamide, 2-amino-3-phenyl	0.0489 (0.046)	0.1595 (0.164)	↑	3.26	0.73	0.0005	1.82
Decanamide, N-(2-hydroxyethyl)	2.4754 (0.590)	3.1022 (0.571)	↑	1.25	1.01	0.0040	1.77
1,2,4,5-Tetrazine-3,6-diamine	0.0695 (0.044)	0.1312 (0.079)	↑	1.89	0.81	0.0017	1.77
Octanoic acid	3.7674 (0.976)	3.0745 (0.771)	↓	1.23	0.83	0.0210	1.77

(*continued*)

SUPPLEMENTARY TABLE S1. (CONTINUED)

Detected compound	*Control average concentration (standard deviation)*	*COC users average concentration (standard deviation)*	*Increased (↑) or decreased (↓) with COC*	*FC*	*Effect size (Cohen's* d*-value)*	t-*Test (BH FDR adjusted* p*-value)*	*PLS-DA (VIP)*
3-Methylhistidine	0.8058 (0.689)	1.6335 (1.368)	↑	2.03	0.69	0.0192	1.73
Ribofuranose	0.1289 (0.049)	0.1832 (0.072)	↑	1.42	0.78	0.0071	1.72
2,2-Dimethyl-3-hydroxybutanoic acid	0.1031 (0.045)	0.1802 (0.099)	↑	1.75	0.82	0.0005	1.70
α-Linolenic acid	3.1468 (0.942)	4.0770 (1.016)	↑	1.30	0.92	0.0090	1.67
Glycolic acid	0.7162 (0.156)	0.5871 (0.107)	↓	1.22	0.86	0.0127	1.65
Octopamine	0.1423 (0.093)	0.0814 (0.053)	↓	1.75	0.67	0.0493	1.59
Myo-inositol 3-phosphate	0.1376 (0.048)	0.1972 (0.080)	↑	1.43	0.74	0.0058	1.59
5-Hydroxynorvaline	4.1331 (0.442)	3.9852 (0.342)	↓	1.04	0.52	0.1649	1.57
Rhamnose	1.6531 (0.539)	1.3427 (0.380)	↓	1.23	0.59	0.1079	1.57
Isopropylamine	1.7252 (0.783)	1.1562 (0.772)	↓	1.49	0.79	0.0245	1.57
Cholest-7-en-3-ol, (3á,5à)-	0.0669 (0.025)	0.1094 (0.069)	↑	1.63	0.62	0.0056	1.56
Hexanoic acid	3.4185 (0.548)	2.9934 (0.705)	↓	1.14	0.61	0.0380	1.55
Butylated Hydroxytoluene	0.2371 (0.110)	0.3465 (0.176)	↑	1.46	0.67	0.0192	1.55
α-Tocopherol	0.0481 (0.021)	0.0362 (0.014)	↓	1.33	0.56	0.1169	1.52
Myo-Inositol	9.0987 (1.492)	10.432 (2.110)	↑	1.15	0.66	0.0362	1.51
Pipecolic acid	3.3419 (1.471)	4.3881 (2.278)	↑	1.31	0.59	0.0796	1.51
Uridine	0.7747 (0.229)	0.6082 (0.236)	↓	1.27	0.72	0.0432	1.50
Asparagine	5.2294 (1.093)	4.6092 (0.744)	↓	1.13	0.61	0.0962	1.47
Alanine	384.34 (120,6)	303.31 (63.33)	↓	1.27	0.67	0.0499	1.47
Diethylene glycol	0.9234 (0.631)	0.9555 (0.733)	↑	1.03	0.03	0.9529	1.46
Erythrono-1,4-lactone	1.6140 (0.901)	0.9638 (0.483)	↓	1.67	0.79	0.0215	1.46
2-Hydroxy-2-methylbutyric acid	0.0885 (0.066)	0.1351 (0.063)	↑	1.53	0.70	0.0521	1.46
Bis(2-chloroethyl)methylamine	0.1786 (0.092)	0.2624 (0.095)	↑	1.47	0.90	0.0128	1.45
4,7,10,13,16,19-Docosahexaenoic acid	0.0282 (0.016)	0.0584 (0.026)	↑	2.07	1.13	0.0000	1.45
Ribitol	293.61 (160.5)	345.94 (171.5)	↑	1.18	0.48	0.2051	1.42
Malic acid	1.4416 (0.399)	1.2131 (0.392)	↓	1.19	0.53	0.1384	1.42
Diethylene glycol, isobutyl ether	44.515 (13.06)	42.221 (10.80)	↓	1.05	0.11	0.8221	1.39
2,3,4-Trihydroxybutyric acid	5.4738 (1.843)	4.7758 (1.508)	↓	1.15	0.45	0.2840	1.39
Citrulline	1.7464 (0.732)	1.3144 (0.479)	↓	1,33	0,63	0.0755	1,38
Dimethylaminoethyl palmitate	13.727 (5.460)	9.4698 (2.812)	↓	1.45	0.83	0.0143	1.38
Arabinonic acid gamma lactone	0.7798 (0.848)	1.8155 (2.056)	↑	2.33	0.59	0.0380	1.37
2-Aminobutanoic acid	21.608 (5.870)	17.690 (6.297)	↓	1.22	0.63	0.0455	1.37
3,6-Dihydro-pyrazine-2,5-diol	0.1154 (0.097)	0.1662 (0.077)	↑	1.44	0.55	0.1363	1.36
Furfuryl alcohol	7.3396 (1.339)	6.3874 (1.426)	↓	1.15	0.59	0.0328	1.36

(*continued*)

SUPPLEMENTARY TABLE S1. (CONTINUED)

Detected compound	*Control average concentration (standard deviation)*	*COC users average concentration (standard deviation)*	*Increased (↑) or decreased (↓) with COC*	*FC*	*Effect size (Cohen's* d*-value)*	t*-Test (BH FDR adjusted* p*-value)*	*PLS-DA (VIP)*
2-hydroxyisobutryric acid	1.3642 (0.720)	1.7338 (0.572)	↑	1.27	0.64	0.0769	1.36
Citric acid	0.4947 (0.150)	0.6902 (0.322)	↑	1.40	0.66	0.0102	1.34
Heptanoic acid	0.0557 (0.042)	0.0550 (0.048)	↓	1.01	0.10	0.8485	1.33
Arachidonic acid	5.2915 (1.372)	6.2959 (1.402)	↑	1.19	0.74	0.0385	1.32
Isoleucine	60.223 (16.62)	50.432 (13.30)	↓	1.19	0.65	0.0796	1.32
L-Ribulose	0.1500 (0.089)	0.1529 (0.085)	↑	1.02	0.00	0.9946	1.32
2-Aminomalonic acid	18.903 (9.161)	13.576 (5.735)	↓	1.39	0.71	0.0459	1.31
Stearic acid hydrazide	0.0460 (0.024)	0.0269 (0.011)	↓	1.71	0.79	0.0181	1.30
Octadecanamid	0.1193 (0.076)	0.1026 (0.056)	↓	1,16	0,44	0.2803	1,30
9,12-Octadecadienoyl chloride	0.2257 (0.144)	0.1277 (0.050)	↓	1.77	0.72	0.0285	1.30
Dicyclopentadiene	0.1042 (0.025)	0.0974 (0.022)	↓	1.07	0.32	0.4330	1.29
L-Glutamic acid	0.3348 (0.083)	0.2841 (0.094)	↓	1.18	0.52	0.1673	1.29
Ribose	1.4055 (0.793)	1.9172 (1.119)	↑	1.36	0.53	0.1815	1.27
Fucose	0.1076 (0.026)	0.0968 (0.018)	↓	1.11	0.40	0.3302	1.26
Dihydroxybutanoic acid	0.2145 (0.129)	0.1730 (0.118)	↓	1.24	0.45	0.2630	1.24
tert-Butylhydroquinone	0.0331 (0.023)	0.0445 (0.024)	↑	1.34	0.41	0.2803	1.24
Oxazole, 2-(8Z)-8-heptadecen-1-yl-4,5-dihydro-	0.4055 (0.128)	0.4789 (0.107)	↑	1.18	0.58	0.1173	1.22
Gluconic acid	1.4498 (0.385)	1.9325 (0.825)	↑	1.33	0.63	0.0181	1.22
1,1,1-Trifluoroheptadecen-2-one	0.4780 (0.151)	0.5841 (0.163)	↑	1.22	0.67	0.0725	1.21
Urea	0.7094 (0.118)	0.7032 (0.170)	↓	1.01	0.28	0.5147	1.21
Linolenic acid	0.1238 (0.079)	0.1837 (0.124)	↑	1.48	0.55	0.0791	1.21
Octadecanoic acid	4.7647 (1.594)	4.0473 (1.290)	↓	1.18	0.51	0.1809	1.19
Leucine	123.33 (33.98)	106.06 (22.23)	↓	1.16	0.53	0.1664	1.18
L-Cysteine	0.1948 (0.213)	0.1626 (0.230)	↓	1.20	0.25	0.6188	1.18
3-Indoleacetic acid	1.6751 (0.564)	1.3893 (0.557)	↓	1.21	0.53	0.1673	1.18
Hexadecane-1,2-diol	0.0682 (0.020)	0.0531 (0.017)	↓	1.28	0.75	0.0362	1.17
Threonic acid	0.4224 (0.255)	0.3496 (0.194)	↓	1.21	0.52	0.1274	1.17
N-Methyl-L-proline	0.0340 (0.008)	0.0301 (0.008)	↓	1.13	0.45	0.2803	1.16
3-Indolepropionic acid	0.1909 (0.226)	0.2167 (0.206)	↑	1.14	0.34	0.4511	1.16
Lactic acid	1.1399 (0.900)	0.9998 (0.715)	↓	1.14	0.44	0.0923	1.14
Homoserine	0.0352 (0.008)	0.0306 (0.006)	↓	1.15	0.53	0.1624	1.13
1,2-Cyclohexanedicarboxylic acid, 2-methylpent-3-yl nonyl ester	39.872 (17.41)	31.058 (8.691)	↓	1.28	0.41	0.3058	1.13
Talofuranose	0.0938 (0.030)	0.1056 (0.075)	↑	1.13	0.34	0.4677	1.12
Hexanedioic acid	3.5772 (0.258)	3.5073 (0.210)	↓	1.02	0.48	0.1804	1.12
Succinic anhydride	0.0159 (0.004)	0.0143 (0.003)	↓	1.11	0.41	0.2006	1.12
Dodecanamide	0.1649 (0.137)	0.1469 (0.162)	↓	1.12	0.36	0.3775	1.11

(*continued*)

SUPPLEMENTARY TABLE S1. (CONTINUED)

Detected compound	*Control average concentration (standard deviation)*	*COC users average concentration (standard deviation)*	*Increased (↑) or decreased (↓) with COC*	*FC*	*Effect size (Cohen's* d*-value)*	t-*Test (BH FDR adjusted* p*-value)*	*PLS-DA (VIP)*
Glycylglycine	0.0603 (0.022)	0.0520 (0.014)	↓	1.16	0.43	0.2756	1.11
3-Hydroxyisovaleric acid	0.0941 (0.036)	0.0973 (0.048)	↑	1.03	0.24	0.5818	1.11
Lanthionine	0.4641 (0.393)	0.5728 (0.491)	↑	1.23	0.25	0.5748	1.11
Creatinine	0.0286 (0.027)	0.0200 (0.006)	↓	1.43	0.40	0.2482	1.10
2-Amino-1-methyl-1H-imidazol-4-ol	0.0345 (0.054)	0.0577 (0.072)	↑	1.67	0.22	0.6619	1.10
3-Hydroxy-2-methyl-butyric acid	0.3422 (0.179)	0.2796 (0.117)	↓	1.22	0.49	0.1658	1.09
Diacetin	0.0467 (0.043)	0.0559 (0.045)	↑	1.20	0.29	0.5283	1.07
Decanoic acid	1.3817 (0.532)	1.6360 (0.628)	↑	1.18	0.39	0.3164	1.07
Pentadecanoic acid, 14-methyl-, methyl ester	0.5007 (0.106)	0.5974 (0.141)	↑	1.19	0.70	0.0264	1.06
Catechol	0.0155 (0.004)	0.0160 (0.017)	↑	1.03	0.42	0.3009	1.06
L-Cysteine	0.0204 (0.011)	0.0265 (0.011)	↑	1.30	0.38	0.3775	1.06
Paraxanthine	2.0042 (2.878)	4.3094 (5.116)	↑	2.15	0.47	0.1673	1.05
1,2-Benzenedicarboxylic-Acid-(2-ethylhexyl) ester	0.2143 (0.074)	0.2264 (0.053)	↑	1.06	0.40	0.2994	1.04
Allonic acid, γ-lactone	0.1062 (0.125)	0.1280 (0.203)	↑	1.21	0.13	0.7852	1.04
Quininic acid	0.0794 (0.061)	0.0711 (0.065)	↓	1.12	0.38	0.2756	1.03
Leucylglycine	9.4661 (9.135)	5.4753 (5.368)	↓	1.73	0.31	0.4814	1.02
Oxalic acid	0.2979 (0.110)	0.2314 (0.080)	↓	1.29	0.62	0.0888	1.02
1-Monoacetin	0.0374 (0.058)	0.0297 (0.052)	↓	1.26	0.38	0.3935	1.01
2,3,4-Trihydroxy-butyraldehyde oxime	2.7166 (0.443)	2.6889 (0.462)	↓	1.01	0.04	0.9427	1.00
Succinic acid	0.0957 (0.063)	0.1200 (0.093)	↑	1.25	0.22	0.6706	1.00

COC, combined oral contraceptive; FC, fold change; PLS-DA, partial least-squares discriminant analysis; VIP, variable importance in projection.