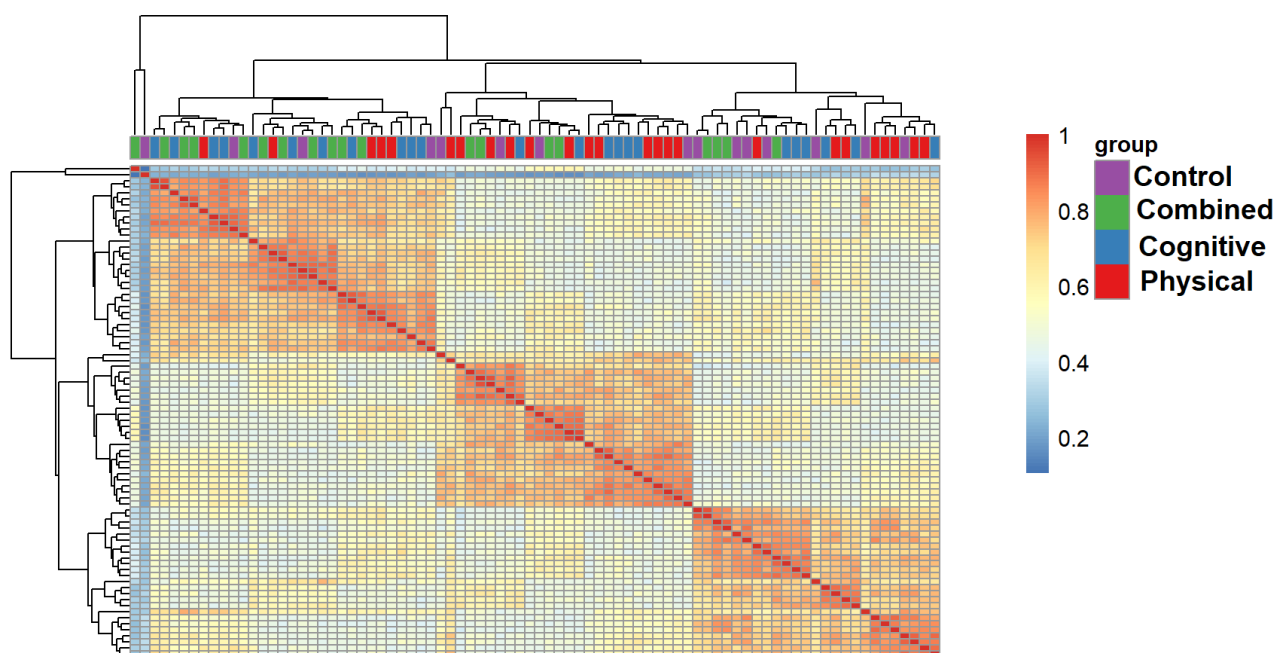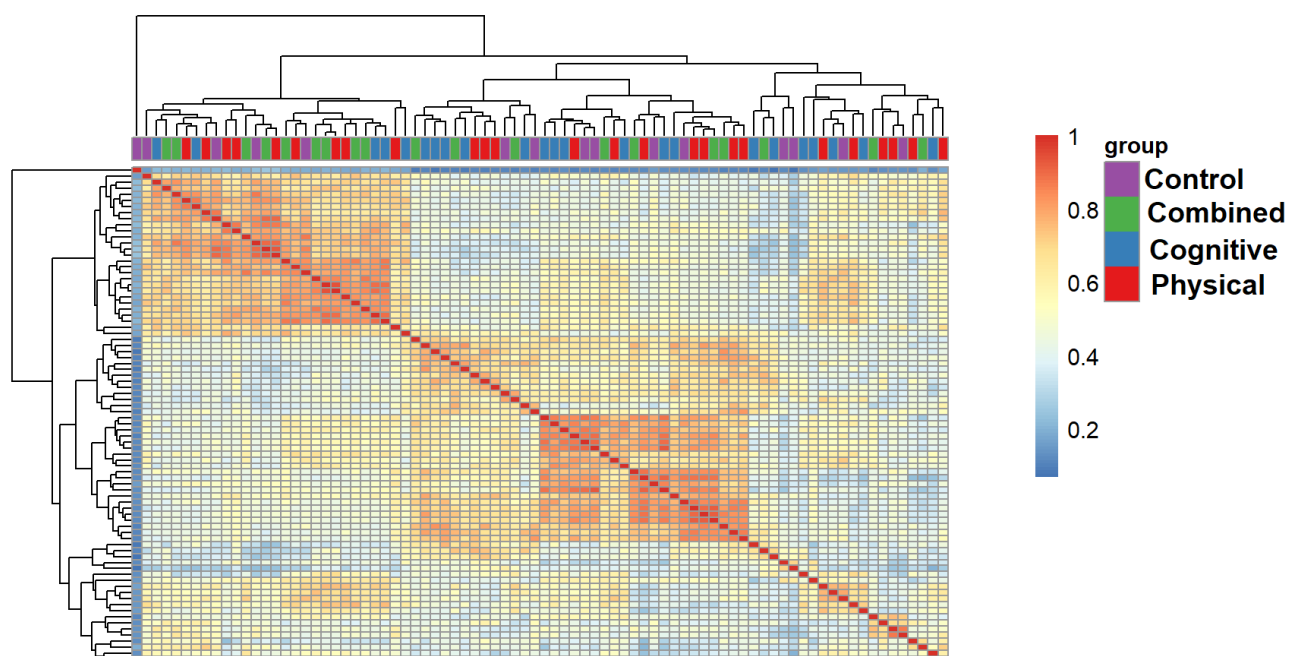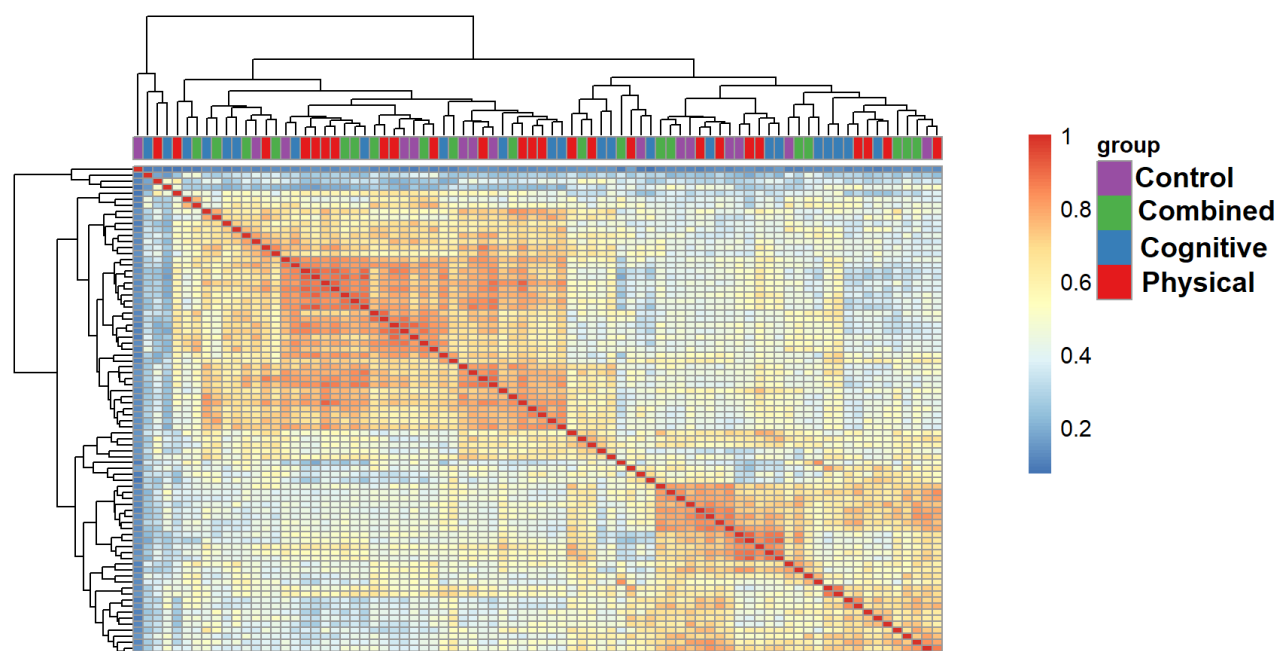**SFigure 1.** Grouping of samples based on similarity of their base peak chromatogram for the pre-intervention period and the positive ionization.

SFigure 2. Grouping of samples based on similarity of their base peak chromatogram for the post-intervention period and the positive ion mode.

SFigure 3. Grouping of samples based on similarity of their base peak chromatogram for the pre-intervention period and the negative ion mode.
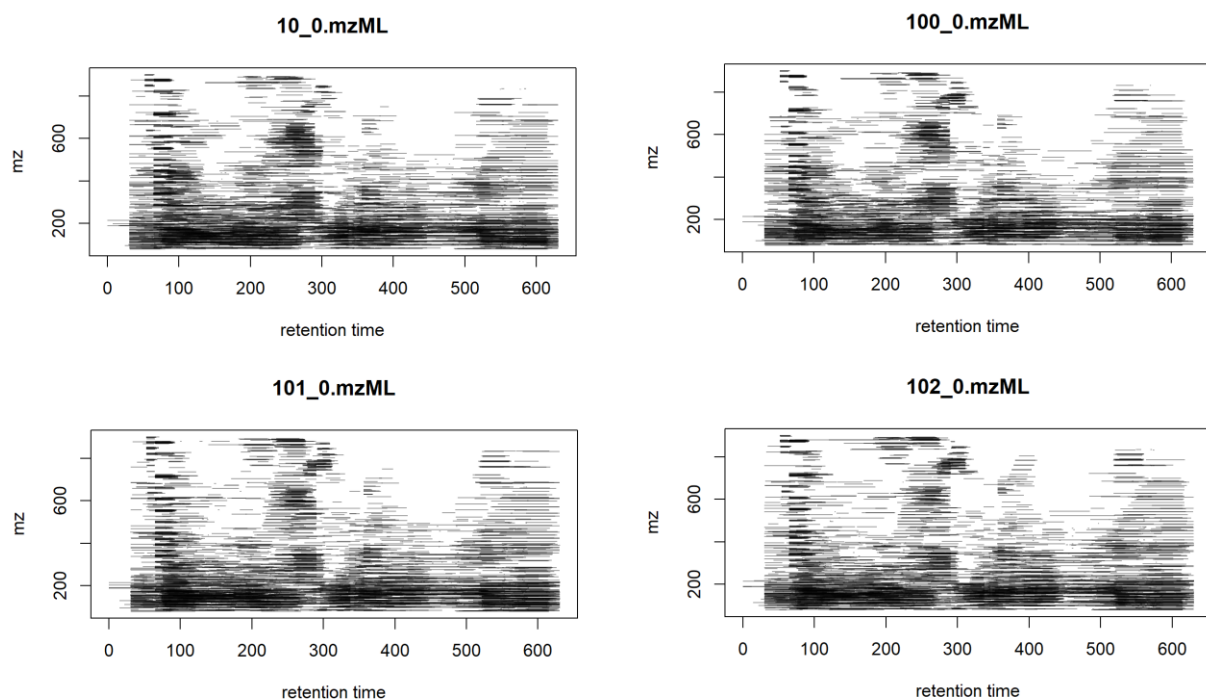

SFigure 4. Grouping of samples based on similarity of their base peak chromatogram for the post-intervention period and the negative ion mode.

SFigure 5. Identified chromatographic peaks in the m/z by retention time space for one sample per group for the pre-intervention period of positive ionization.
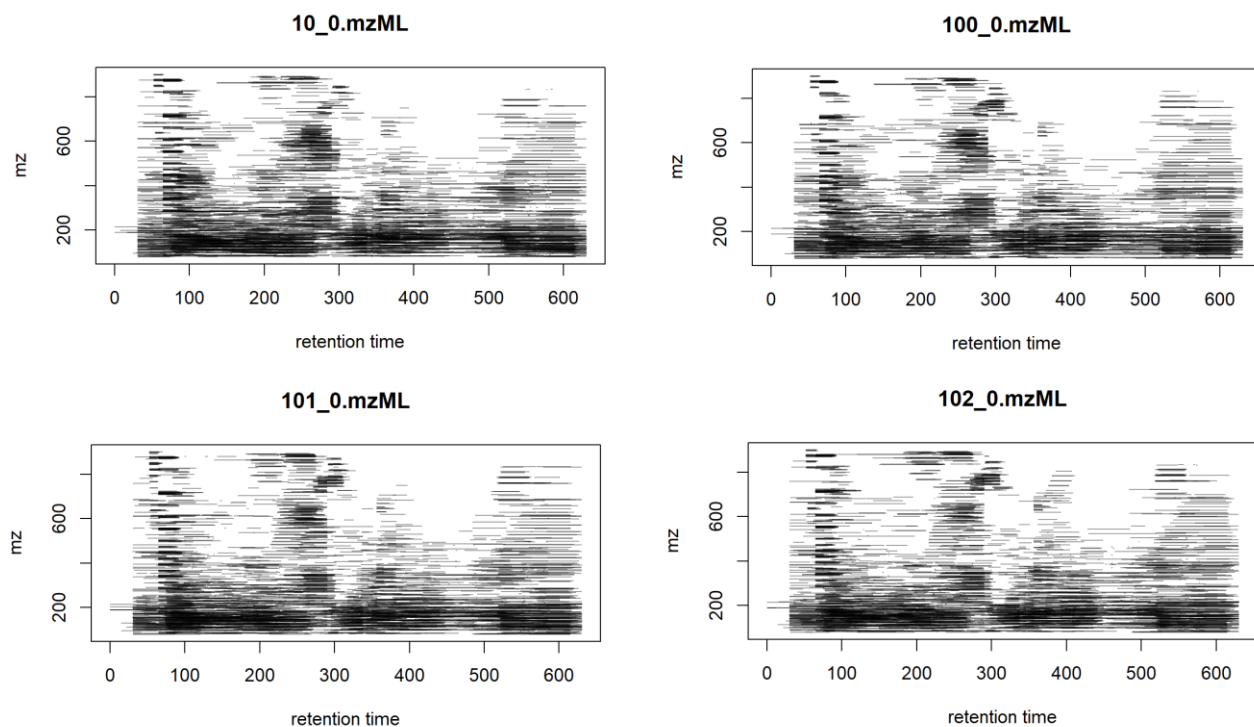
SFigure 6. Identified chromatographic peaks in the m/z by retention time space for one sample per group for the post-intervention period of positive ion mode.
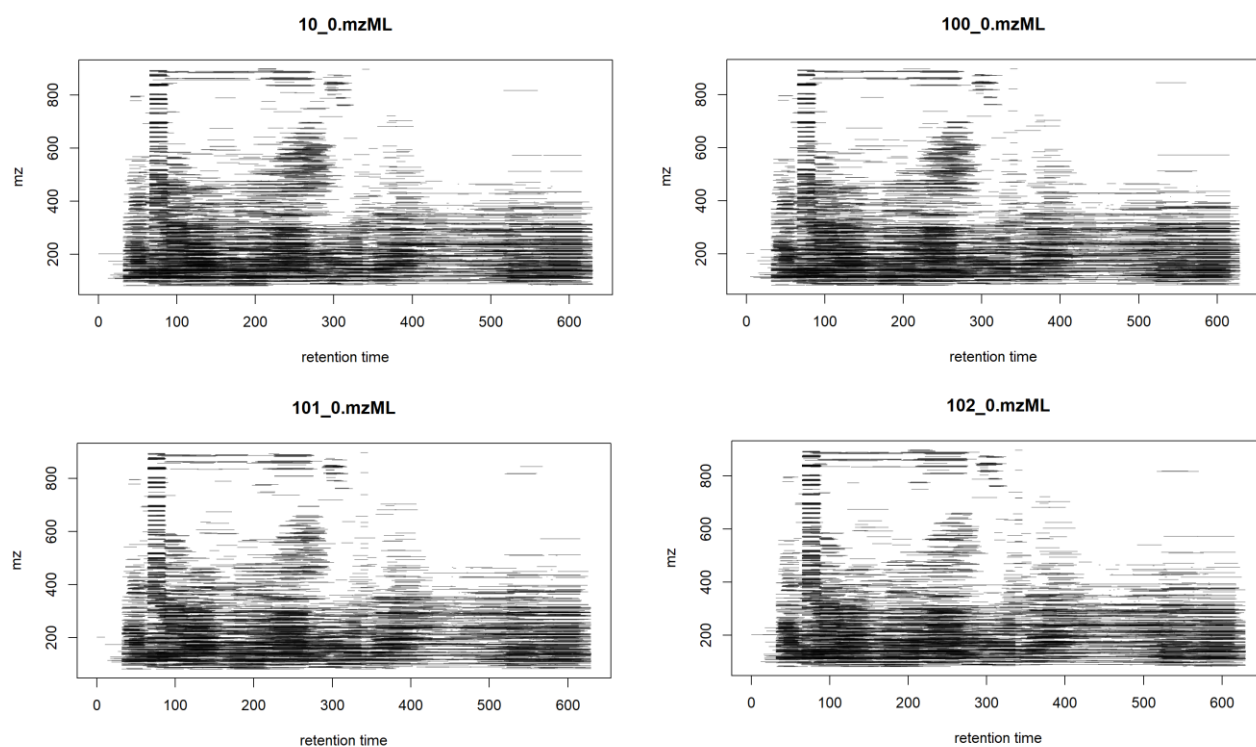
SFigure 7. Identified chromatographic peaks in the m/z by retention time space for one sample per group for the pre-intervention period of negative ion mode.
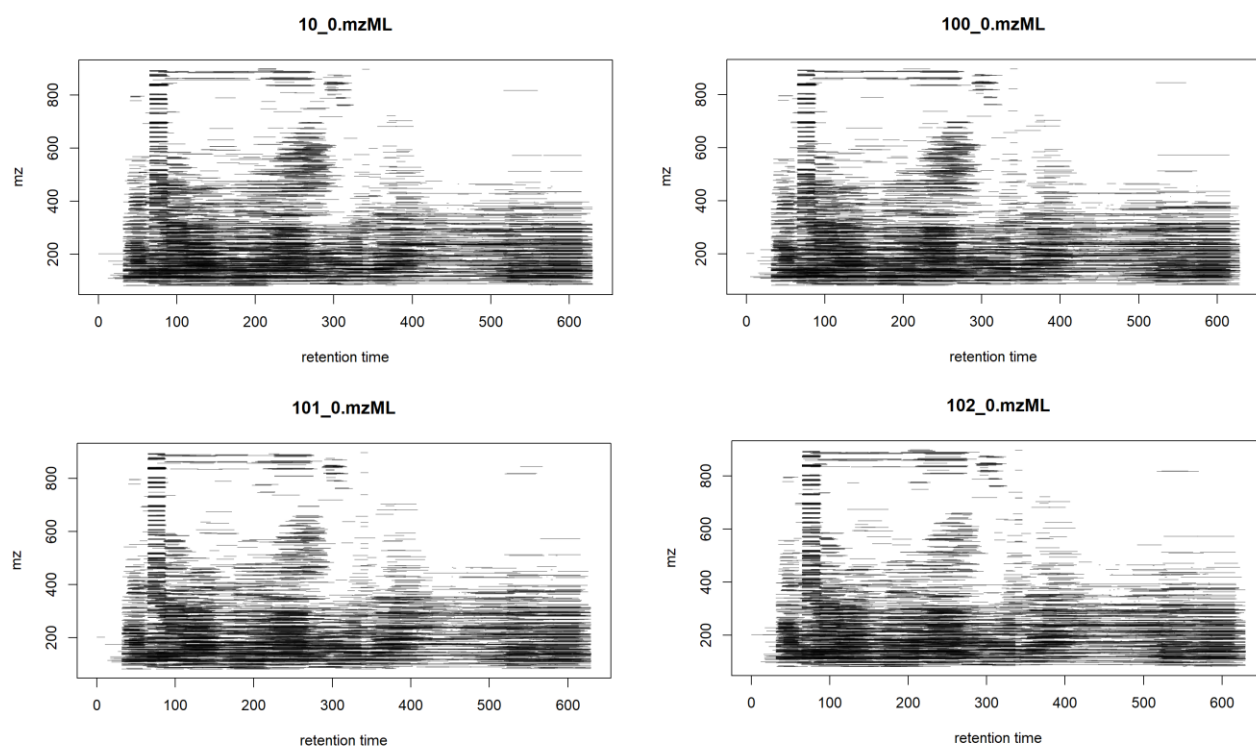
SFigure 8. Identified chromatographic peaks in the m/z by retention time space for one sample per group for the post-intervention period of negative ion mode.
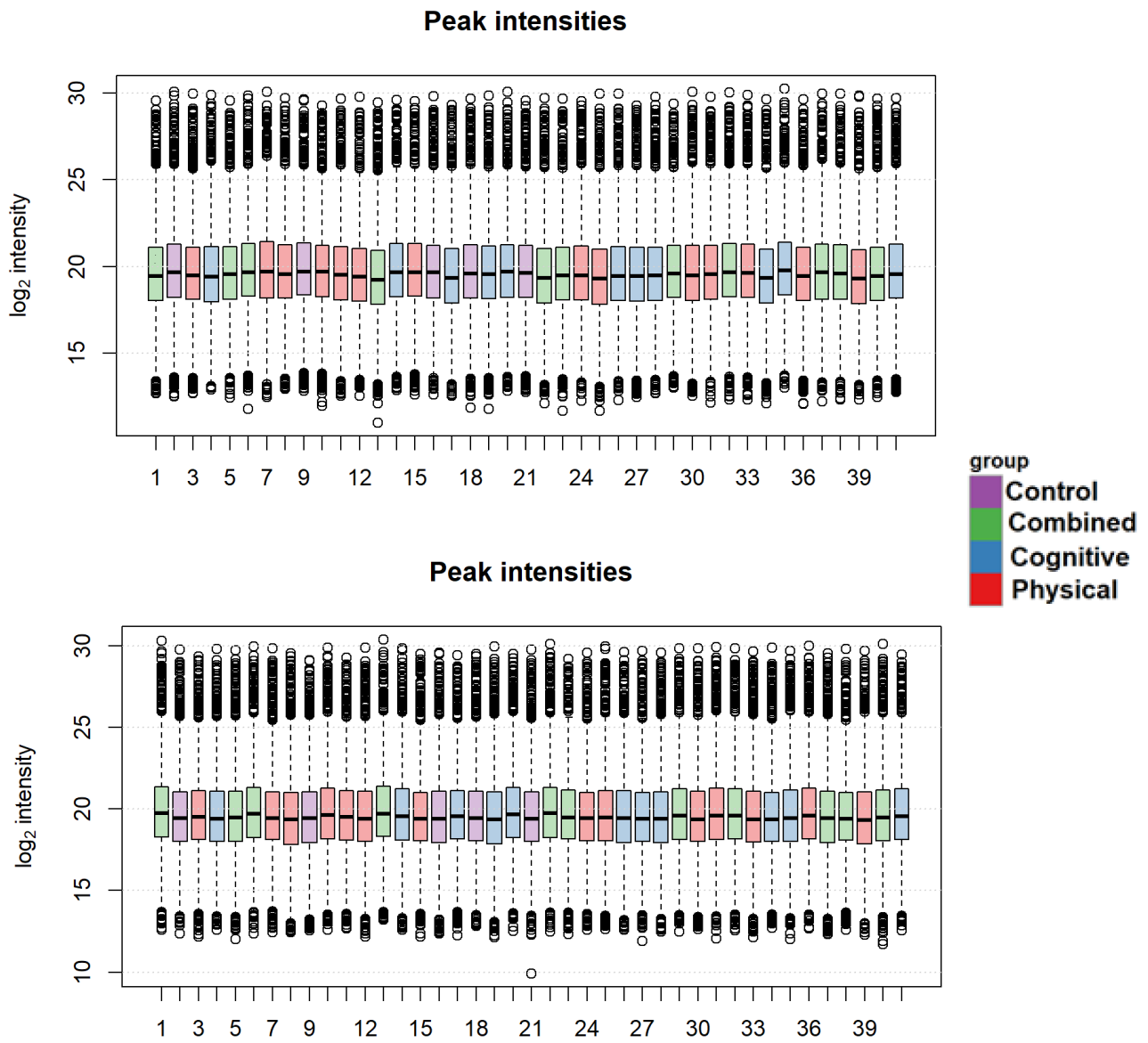
SFigure 9. Peak intensity distribution per sample for the pre-intervention period of positive ionization. I splitted the demonstration of peak intensities in two sub-figures of 41 samples each one.
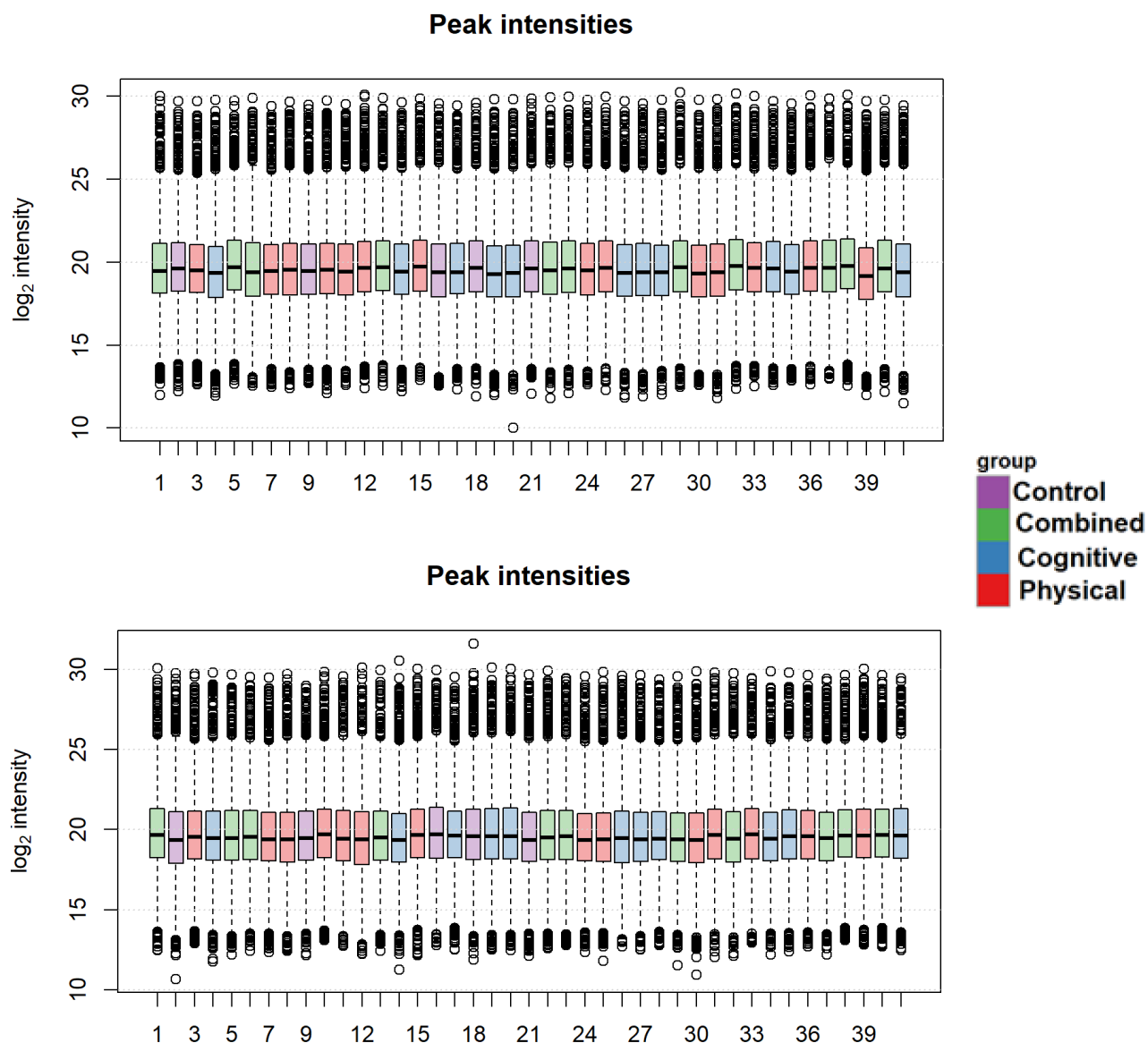
SFigure 10. Peak intensity distribution per sample for the post-intervention period of positive ionization. I splitted the demonstration of peak intensities in two sub-figures of 41 samples each one.
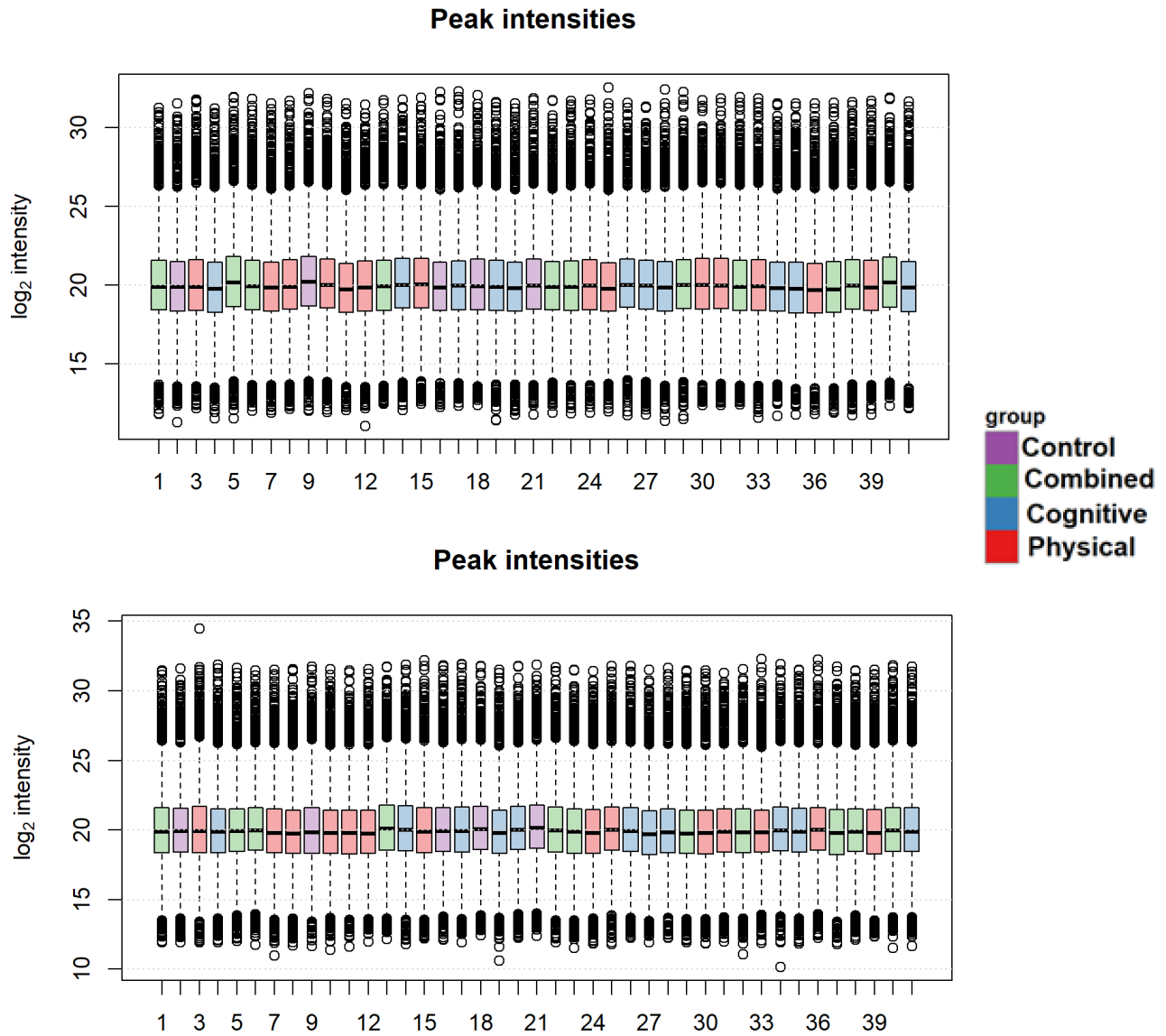
SFigure 11. Peak intensity distribution per sample for the pre-intervention period of negative ionization. I splitted the demonstration of peak intensities in two sub-figures of 41 samples each one.
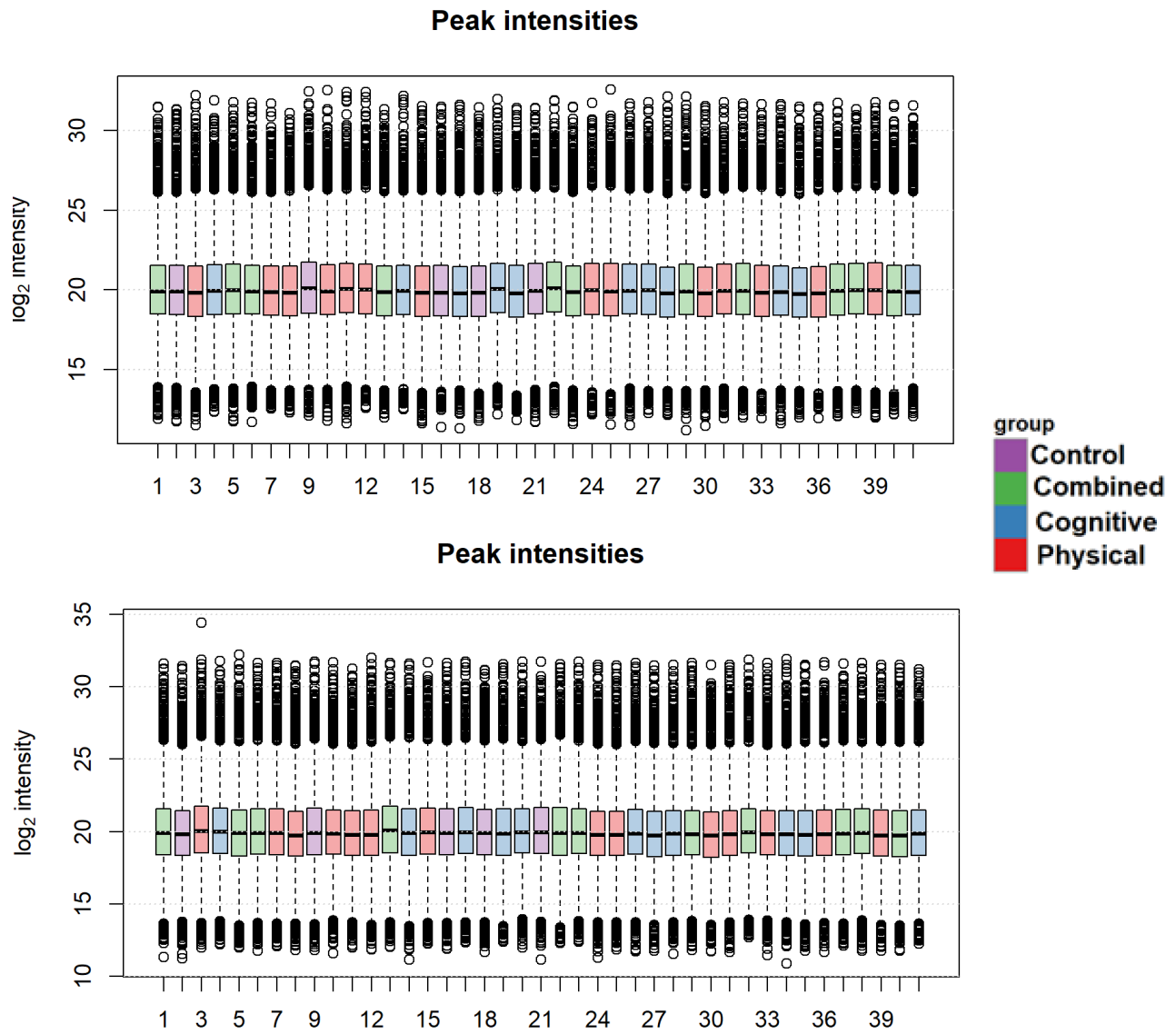
SFigure 12. Peak intensity distribution per sample for the post-intervention period of negative ionization. I splitted the demonstration of peak intensities in two sub-figures of 41 samples each one.

SFigure 13. Obiwarp aligned data example from the pre-intervention period of positive ionization. Base peak chromatogram before (top) and after alignment (middle) and difference between adjusted and raw retention times along the retention time axis (bottom).

SFigure 14. Obiwarp aligned data example from the post-intervention period of positive ioniz ation. Base peak chromatogram before (top) and after alignment (middle) and difference between a djusted and raw retention times along the retention time axis (bottom).

**SFigure 15. Obiwarp aligned data example from the pre-intervention period of negative ioniz
ation.** Base peak chromatogram before (top) and after alignment (middle) and difference between a
djusted and raw retention times along the retention time axis (bottom).

**SFigure 16. Obiwarp aligned data example from the post-intervention period of negative ioniz
ation.** Base peak chromatogram before (top) and after alignment (middle) and difference between a
djusted and raw retention times along the retention time axis (bottom).

STable 1. Inclusion and exclusion criteria for Projecte Moviment.

Inclusion criteria	Exclusion criteria
Aged 50–70 years	Current participation in any cognitive training activity or during last 6 months > 2 h/week
$\leq$120 min/week of physical activity during last 6 months	Diagnostic of dementia or mild cognitive impairment
Mini-Mental State Examination (MMSE) $\geq$ 24	Diagnostic of neurological disorder: stroke, epilepsy, multiple sclerosis, traumatic brain injury, brain tumor
Montreal Cognitive Assessment 5-min (MoCA 5-min) $\geq$ 6	Diagnostic of psychiatric illness current or during last 5 years
Competency in Catalan or Spanish	Geriatric Depression Scale (GDS-15) > 9
Adequate visual, auditory, and fine motor skills	Consumption of psychopharmacological drugs current or during last 5 years; or more than 5 years throughout life
Acceptance of participation in the study and signature of the informed consent	History of drug abuse or alcoholism current or during last 5 years; or more than 5 years throughout life; >28 men and >18 woman unit of alcohol/week
	History of chemotherapy
	Contraindication to magnetic resonance imaging

MMSE (Blesa et al., 2001); MoCA 5-min (Wong et al., 2015); GDS-15 (Martínez et al., 2002).

STable 2 (Positive mode pre): Summary statistics on identified chromatographic peaks. Show n are number of identified peaks per sample and widths/duration of chromatographic peaks.

	peak_count	rt.0%	rt.25%	rt.50%	rt.75%	rt.100%
10_0.mzML	3361	0.4071	22.98	34.27	45.8	239.1
100_0.mzML	3052	0.7646	21.98	33.91	45.26	220.3
101_0.mzML	3286	0.4048	22.7	33.99	45.78	317.3
102_0.mzML	3219	0.7719	22.97	34.13	45.01	224.6
104_0.mzML	3077	0.7763	21.95	33.87	45.31	231.9
105_0.mzML	3004	0.7842	21.88	33.51	45.59	209.4
11_0.mzML	3119	0.4037	21.41	33.22	45.22	219.4
13_0.mzML	3094	0.7742	21.08	32.95	44.97	321.2
15_0.mzML	3147	0.7594	22.58	33.74	45.08	268.8
17_0.mzML	3012	0.3911	22.94	34.14	45.54	280.3
18_0.mzML	3125	0.7648	23.17	34.34	46.66	305.4
19_0.mzML	3142	0.7712	22.95	33.82	45.72	245.6
2_0.mzML	3318	0.7814	23.48	34.39	46.07	223.8
21_0.mzML	3023	0.7848	22.53	34.6	45.54	321.5
22_0.mzML	2997	0.7718	22.62	34.62	45.74	230.5
24_0.mzML	3045	0.7726	21.98	33.4	45.29	239.8
25_0.mzML	3285	0.7844	22.64	33.89	46.05	308.4
26_0.mzML	3163	0.3977	22.62	33.22	45.4	272.1
27_0.mzML	3284	0.3913	22.41	33.29	44.91	221.8
29_0.mzML	2925	0.4146	21.89	33.25	44.63	318.1
30_0.mzML	3053	0.3975	22.72	34.27	45.16	274.2
31_0.mzML	3338	0.7603	22.85	33.76	45.11	244.2
32_0.mzML	3099	0.7735	23.3	34.49	46.96	314.9
33_0.mzML	3284	0.7651	23.65	34.52	46.01	213.2
34_0.mzML	3573	0.7648	22.5	33.28	44.46	318.3
35_0.mzML	3276	0.4187	22.17	33.5	44.71	304.3
36_0.mzML	3286	0.7646	23.65	34.16	45.47	242.2
37_0.mzML	3375	0.7841	22.92	33.64	44.62	319.9
38_0.mzML	2999	0.7641	22.63	34.26	45.07	230.6
39_0.mzML	3256	0.773	22.35	33.3	44.81	278
40_0.mzML	3008	0.7818	21.85	33.19	45.43	310.3
41_0.mzML	2987	0.3944	21.86	33.52	45.02	318.4
43_0.mzML	3060	0.7722	22.54	33.75	45.45	309.2

44_0.mzML	3264	0.4152	23.42	33.98	45.58	308.5
46_0.mzML	2917	0.7704	21.36	34.17	45.8	249.3
47_0.mzML	3175	0.7821	23.4	34.65	46.26	317.5
49_0.mzML	3054	0.4035	21.58	32.96	44.84	307.3
5_0.mzML	3190	0.7829	22.03	33.57	44.48	318.7
50_0.mzML	3317	0.7616	22.61	33.84	46.04	280.8
52_0.mzML	3280	0.7766	22.57	33.7	45.48	320.1
53_0.mzML	3081	0.7485	21.41	32.47	44.27	227.5
55_0.mzML	3033	0.7628	21.92	33.09	44.49	309.8
56_0.mzML	3276	0.763	22.4	33.67	45.8	231.3
57_0.mzML	3172	0.3807	22.96	34.16	45.24	242.8
58_0.mzML	3293	0.7718	22.74	34.25	46.02	232.5
6_0.mzML	3250	0.3918	23.07	33.85	45.17	194.6
60_0.mzML	2997	0.7621	22.23	33.59	44.89	309.1
61_0.mzML	3204	0.414	23.02	34.1	45.63	320.6
63_0.mzML	3430	0.7643	21.68	33.15	44.75	320.6
65_0.mzML	3513	0.7645	22.35	33.63	45.06	238
66_0.mzML	3059	0.4244	22.28	33.59	45.4	248.3
67_0.mzML	3117	0.7474	22.63	34.35	45.49	232.5
68_0.mzML	3293	0.4031	23.46	34.98	45.91	319.3
69_0.mzML	3002	0.7767	21.82	32.92	44.44	258.5
7_0.mzML	3069	0.7615	21.16	33.3	44.81	230.2
70_0.mzML	3268	0.4144	23.06	34.49	45.94	302.9
71_0.mzML	3376	0.7653	22.51	33.83	46.38	255.9
73_0.mzML	3191	0.7619	23.82	34.63	45.9	309.1
74_0.mzML	3204	0.7824	23.5	34.3	46.07	315.6
75_0.mzML	3450	0.7647	22.09	33.07	45.07	228.1
76_0.mzML	2991	0.7827	22.28	33.73	45.46	305.8
77_0.mzML	3260	0.4251	22.87	34.06	45.47	315
78_0.mzML	3073	0.3931	22.2	33.47	45.11	279.3
79_0.mzML	2933	0.7854	22.66	34.19	46.73	280.6
80_0.mzML	3311	0.7589	23.44	34.85	46.44	319.6
81_0.mzML	3252	0.4193	22.94	33.77	46.18	322
83_0.mzML	3305	0.3931	22.77	33.89	46.01	318.1
84_0.mzML	3253	0.7603	23	34.18	45.73	253.3
85_0.mzML	3253	0.7715	22.33	34.08	45.2	228
86_0.mzML	3195	0.4032	21.19	32.85	44.88	245

87_0.mzML	3341	0.7614	22.65	34.11	45.11	227.1
89_0.mzML	3205	0.3924	22.19	33.09	44.87	239.7
9_0.mzML	3103	0.7616	21.81	33.33	45.18	229
90_0.mzML	3218	0.3927	22.93	33.82	45.79	319.7
91_0.mzML	3339	0.7759	22.96	34.21	44.92	243.2
92_0.mzML	3273	0.4022	22.31	33.54	44.58	317.9
93_0.mzML	3137	0.7488	22.27	33.82	45.69	223.5
94_0.mzML	3228	0.7648	22.68	33.48	44.99	268.9
95_0.mzML	3120	0.4144	23.44	34.26	45.59	292.6
96_0.mzML	3223	0.7642	22.73	33.79	46.14	234.7
98_0.mzML	3178	0.3847	22.63	33.69	45.37	320.4
99_0.mzML	3026	0.7723	21.32	32.89	44.97	237.4

STable 3 (Negative mode – pre): Summary statistics on identified chromatographic peaks. Shown are number of identified peaks per sample and widths/duration of chromatographic peaks.

	peak_count	rt.0%	rt.25%	rt.50%	rt.75%	rt.100%
10_0.mzML	4484	0.4398	22.49	34.15	45.98	202.7
100_0.mzML	4330	0.3928	22.43	34.56	46.27	315.2
101_0.mzML	4263	0.4355	21.92	33.48	45.38	312.8
102_0.mzML	4324	0.7601	22.19	33.8	45.38	268
104_0.mzML	4276	0.4138	22.39	34.11	45.97	312.4
105_0.mzML	4367	0.759	22.51	33.52	45.39	265.7
11_0.mzML	4375	0.7659	22.4	34.12	45.83	249.8
13_0.mzML	4346	0.4352	22.47	34.45	46.02	253.8
15_0.mzML	4448	0.4342	22.06	34.21	45.31	305
17_0.mzML	4362	0.4348	22.66	33.93	46.33	313.8
18_0.mzML	4190	0.4354	22.48	34.61	47.12	298.9
19_0.mzML	4401	0.4351	22.52	34.22	46.28	253
2_0.mzML	4261	0.7495	21.88	34.03	46	304.3
21_0.mzML	4234	0.3983	22.87	33.89	45.76	271.9
22_0.mzML	4308	0.7541	22.82	33.72	44.84	251.2
24_0.mzML	3830	0.7608	21.29	33.59	46.84	312.9
25_0.mzML	3835	0.4352	21.08	33.73	45.77	254.1
26_0.mzML	3840	0.7398	20.53	33.13	45.57	241.6
27_0.mzML	4355	0.4455	22.96	33.92	46.01	312.5
29_0.mzML	4167	0.7623	23.35	34.38	46.71	250.1
30_0.mzML	4295	0.7599	22.55	33.4	46.25	303.7
31_0.mzML	4321	0.4351	22.99	34.26	46.37	247.2
32_0.mzML	4253	0.4352	22.89	34.42	46.1	313.4
33_0.mzML	4191	0.3923	22.47	33.74	46.42	253.2
34_0.mzML	4516	0.4457	23.88	34.11	45.71	253.6
35_0.mzML	4390	0.7636	22.85	33.57	45.58	253.5
36_0.mzML	4247	0.7598	23.32	34.07	46.32	299.4
37_0.mzML	4418	0.4505	23.33	33.38	45.25	283.4
38_0.mzML	4339	0.392	22.83	33.12	45.43	311.9
39_0.mzML	4126	0.3922	22.87	34.08	45.78	225
40_0.mzML	4249	0.7496	22.92	33.48	46.51	268
41_0.mzML	4209	0.44	22.92	34.34	46.67	250.5

43_0.mzML	4306	0.76	23.56	34.35	46.55	258.2
44_0.mzML	4368	0.3994	22.97	34.28	45.83	316.1
46_0.mzML	4231	0.4457	23.42	34.81	47.09	313.1
47_0.mzML	4366	0.7398	22.6	33.97	46.03	253.9
49_0.mzML	4190	0.4359	23.54	34.46	46.78	311.4
5_0.mzML	4305	0.4357	22.59	34.49	46.99	266.7
50_0.mzML	4259	0.749	22.53	33.95	45.64	257.6
52_0.mzML	4193	0.7603	23.29	33.88	45.82	300
53_0.mzML	4281	0.764	22.54	34.04	45.82	253.4
55_0.mzML	4330	0.4099	22.49	32.89	45.38	255
56_0.mzML	4388	0.4452	22.66	33.41	45.86	265.4
57_0.mzML	4063	0.754	23.17	33.75	46.24	312.6
58_0.mzML	4334	0.7599	22.91	34.35	46.22	354.7
6_0.mzML	4382	0.7601	22.09	34.2	46.15	311.6
60_0.mzML	4346	0.76	22.84	34.03	46.22	256.5
61_0.mzML	4345	0.7643	22.93	34.2	46.62	313.4
63_0.mzML	4375	0.408	22.97	33.83	46.02	303.5
65_0.mzML	4325	0.7504	22.05	33.83	46.37	311.8
66_0.mzML	4434	0.4401	22.9	34.44	45.93	253
67_0.mzML	4409	0.3903	22.95	33.84	46.29	236.8
68_0.mzML	4327	0.7598	22.71	34.14	45.93	315.9
69_0.mzML	4359	0.3918	22.77	33.01	45.32	313.1
7_0.mzML	4287	0.393	22.28	33.64	45.71	266.5
70_0.mzML	4331	0.4043	22.9	33.99	46.24	304.9
71_0.mzML	4222	0.4346	22.37	34.42	46.47	311.9
73_0.mzML	4272	0.4454	22.74	34.43	47.12	271.2
74_0.mzML	4182	0.4241	22.92	33.63	46.13	305
75_0.mzML	4340	0.4404	24	34.12	46.13	224
76_0.mzML	4351	0.76	22.82	33.73	45.52	269.2
77_0.mzML	4356	0.7495	22.89	34.15	45.45	220
78_0.mzML	4187	0.76	22.47	34.05	47	222.9
79_0.mzML	4341	0.3996	22.94	33.95	46.61	312.2
80_0.mzML	4384	0.4086	23.09	33.64	46.5	230.5
81_0.mzML	4252	0.4254	23.41	34.13	46.32	266.2
83_0.mzML	4462	0.7519	21.64	33.34	46.13	202.3
84_0.mzML	4324	0.7601	22.54	34.02	46.35	250.8
85_0.mzML	4310	0.4355	22.14	34.06	45.9	267.2

86_0.mzML	4310	0.7619	22.49	34.48	46.83	216.3
87_0.mzML	4434	0.391	22.5	34.31	45.74	251.9
89_0.mzML	4289	0.4393	22.79	34.6	46.07	197.4
9_0.mzML	4296	0.3802	22.12	34.25	46.41	245.8
90_0.mzML	4390	0.7596	22.19	34.06	45.45	255.5
91_0.mzML	4293	0.4244	22.09	33.86	46.15	311.4
92_0.mzML	4404	0.4348	22.12	34.01	45.71	311.9
93_0.mzML	4434	0.7595	22.42	33.67	44.9	268.4
94_0.mzML	4342	0.7591	21.86	34.12	46.47	305.7
95_0.mzML	4357	0.7598	22.22	34.32	45.37	303.6
96_0.mzML	4314	0.4398	22.09	33.92	45.45	267.2
98_0.mzML	4321	0.7596	21.69	33.86	45.62	266.7
99_0.mzML	4243	0.75	21.66	34.59	46.26	301.8

STable 4 **(Positive mode – post): Summary statistics on identified chromatographic peaks. Shown are number of identified peaks per sample and widths/duration of chromatographic peaks.**

	peak_count	rt.0%	rt.25%	rt.50%	rt.75%	rt.100%
10_1.mzML	3311	0.7862	22.95	33.62	45.25	309.2
100_1.mzML	3042	0.7819	21.92	33.53	45.05	279.1
101_1.mzML	3271	0.7825	23.19	34.7	46.93	258.1
102_1.mzML	3353	0.7613	22.25	33.47	44.71	243.7
104_1.mzML	2930	0.7483	22.31	33.52	45.61	281.5
105_1.mzML	3355	0.7646	22.93	33.46	44.55	218.9
11_1.mzML	3259	0.7577	22.93	34.93	46.19	306.1
13_1.mzML	3322	0.7827	22.73	33.28	44.46	258.6
15_1.mzML	3371	0.7599	22.3	33.64	45.05	259.7
17_1.mzML	3207	0.4035	23.61	34.32	45.7	310.8
18_1.mzML	3301	0.7829	22.86	33.85	46.35	313.3
19_1.mzML	2964	0.7824	21.62	33.88	45.22	239.9
2_1.mzML	2932	0.783	22.19	33.77	45.47	229.6
21_1.mzML	3310	0.7888	21.94	33.65	45.59	321.2
22_1.mzML	2897	0.7847	21.63	33.02	44.35	282
24_1.mzML	3283	0.7688	23.13	33.64	45.49	307.6
25_1.mzML	3141	0.7626	22.82	34.55	46.6	312.6
26_1.mzML	3016	0.4036	21.69	33.75	45.02	240.5
27_1.mzML	3392	0.7656	22.85	33.83	45.76	235.2
29_1.mzML	3357	0.4368	23.5	34.33	46.07	229.6
30_1.mzML	2976	0.782	21.67	32.62	45.12	293.4
31_1.mzML	3209	0.4142	23	34.14	46.15	310.2
32_1.mzML	3054	0.408	21.94	34.15	45.82	252
33_1.mzML	3115	0.7728	22.48	33.67	44.89	320.1
34_1.mzML	3120	0.7851	22.3	33.76	44.8	230.6
35_1.mzML	3474	0.4145	23.03	33.47	44.5	241.4
36_1.mzML	3300	0.3908	23.12	34.05	45.52	217.7
37_1.mzML	3275	0.7724	23.68	34.46	46.62	317.9
38_1.mzML	3099	0.4034	21.68	32.66	43.98	316.4
39_1.mzML	3457	0.7753	22.71	34.82	46.62	254
40_1.mzML	3385	0.391	22.5	33.03	44.46	234.5

41_1.mzML	2936	0.7655	22.09	33.12	44.52	305.5
43_1.mzML	3014	0.7846	22.72	33.81	45.14	252.8
44_1.mzML	3052	0.7819	22.84	34.58	46.25	244.3
46_1.mzML	3236	0.7854	23.15	34.6	45.72	261.4
47_1.mzML	3041	0.783	21.43	33.75	45.95	242.5
49_1.mzML	3003	0.7581	22.98	34.29	46.33	213
5_1.mzML	2976	0.384	22.25	33.66	46.13	246
50_1.mzML	3464	0.7476	23.33	34.67	46.24	229
52_1.mzML	3174	0.4035	21.53	33.36	44.62	259.2
53_1.mzML	3312	0.403	22.23	33.93	46.21	306.5
55_1.mzML	3135	0.3822	22.18	33	44.64	237.7
56_1.mzML	3412	0.7643	22.14	33.38	45.28	227.9
57_1.mzML	3031	0.3946	21.6	33.44	44.88	252.7
58_1.mzML	3353	0.4186	23.4	34.09	45.47	321.4
6_1.mzML	3160	0.7719	23.2	34.39	46.07	297.8
60_1.mzML	3132	0.7579	21.3	33.1	44.29	252.4
61_1.mzML	3200	0.7721	23.95	34.64	46.15	276.2
63_1.mzML	3255	0.7818	22.85	33.74	44.76	235.6
65_1.mzML	3304	0.4247	23.52	34.23	45.67	281.1
66_1.mzML	2966	0.7824	21.65	33.5	45.22	272.9
67_1.mzML	3162	0.7657	24.06	34.33	45.82	317.6
68_1.mzML	3310	0.7606	23.15	33.72	45.5	274.1
69_1.mzML	3245	0.7424	23.18	34.18	45.53	311.2
7_1.mzML	3331	0.7637	23.34	33.81	44.99	257
70_1.mzML	3193	0.3909	21.46	33.07	45.26	241.4
71_1.mzML	3000	0.404	21.51	33.24	45.27	241.7
73_1.mzML	2886	0.7619	22.26	33.92	44.83	278.6
74_1.mzML	3190	0.4044	21.87	33.69	45.82	320.4
75_1.mzML	3043	0.4037	22.79	34.52	46.05	230.2
76_1.mzML	3112	0.7828	22.18	33.72	44.87	244.1
77_1.mzML	3272	0.4238	22.58	33.6	45.13	272
78_1.mzML	3398	0.7732	23.47	34.32	45.84	238
79_1.mzML	3100	0.7703	22.31	33.78	45.26	313.9
80_1.mzML	3289	0.7813	23.42	34.53	45.63	319.5
81_1.mzML	3375	0.3688	22.7	34.05	45.49	308.9
83_1.mzML	3264	0.3789	22.69	33.71	45.83	273.9
84_1.mzML	3212	0.7817	22.68	33.59	45.27	280.5
85_1.mzML	3235	0.4028	23.01	34.49	45.7	221

86_1.mzML	3258	0.4018	22.47	33.75	46.04	293.1
87_1.mzML	3423	0.4257	23.24	34.32	46.06	320.2
89_1.mzML	3023	0.4244	21.2	32.95	44.73	223.6
9_1.mzML	3272	0.7858	22.72	33.84	44.99	305.6
90_1.mzML	2973	0.4074	22.35	33.72	44.56	286.7
91_1.mzML	3229	0.7774	22.56	34.08	45.77	310.9
92_1.mzML	3160	0.7808	22.28	33.66	45.43	231.9
93_1.mzML	3103	0.7727	22.4	34.08	45.45	230.9
94_1.mzML	3203	0.7812	22.88	34.11	45.78	231
95_1.mzML	3064	0.762	22.66	34.29	44.99	244.3
96_1.mzML	3058	0.7721	21.8	33.68	44.86	231.6
98_1.mzML	3001	0.7619	21.53	33.23	45.01	289.8
99_1.mzML	3041	0.759	22.34	33.48	45.85	235

STable 5 (Negative mode – post): Summary statistics on identified chromatographic peaks. Shown are number of identified peaks per sample and widths/duration of chromatographic peaks.

	peak_count	rt.0%	rt.25%	rt.50%	rt.75%	rt.100%
10_1.mzML	4527	0.3992	22.88	33.91	45.31	273.4
100_1.mzML	4398	0.3809	22.59	34.02	45.15	302.5
101_1.mzML	4347	0.4358	22.07	33.88	46.24	313.9
102_1.mzML	4220	0.3852	22.51	34.29	46.05	313.3
104_1.mzML	4305	0.7588	22.05	33.75	46.02	253.9
105_1.mzML	4265	0.7596	22.99	34.02	46.02	266.3
11_1.mzML	4379	0.436	22.72	34.07	45.78	202
13_1.mzML	4275	0.7472	22.55	33.76	46.78	315.7
15_1.mzML	4335	0.3801	22.06	33.43	45.48	247.1
17_1.mzML	4477	0.3831	22.87	34.12	45.84	250.2
18_1.mzML	3746	0.7601	20.81	33.23	45.46	264
19_1.mzML	3884	0.3816	20.33	32.62	45.25	244.1
2_1.mzML	4411	0.7498	22.3	34.03	45.92	235.8
21_1.mzML	3858	0.7601	20.66	33.57	45.98	254
22_1.mzML	4324	0.3904	23.27	33.73	45.93	255.1
24_1.mzML	4233	0.4097	23.05	34.15	45.64	216.4
25_1.mzML	4325	0.3923	23.03	34.6	46.2	250.5
26_1.mzML	4288	0.7397	22.89	34.21	46.14	321.9
27_1.mzML	4281	0.3976	22.53	33.57	45.25	306.4
29_1.mzML	4281	0.769	22.47	33.76	45.59	313.1
30_1.mzML	4300	0.4294	22.89	33.99	45.65	235.5
31_1.mzML	4193	0.391	23	34.19	45.99	319
32_1.mzML	4319	0.3732	23.59	34.65	47.01	312.7
33_1.mzML	4316	0.3867	22.41	33.41	45.67	207.7
34_1.mzML	4312	0.7598	22.93	33.77	45.08	214.2
35_1.mzML	4359	0.4135	23.62	33.95	45.81	313
36_1.mzML	4322	0.3981	22.87	33.63	45.88	265.9
37_1.mzML	4392	0.7599	22.92	34.24	46.13	200.5
38_1.mzML	4306	0.7594	22.58	33.4	45.14	302.8
39_1.mzML	4243	0.7589	22.54	34.14	45.79	325.2
40_1.mzML	4281	0.7594	22.85	33.65	45.93	266
41_1.mzML	4207	0.7594	23.26	34.12	46.61	265.8

43_1.mzML	4350	0.7615	22.91	34.12	45.53	308
44_1.mzML	4335	0.4356	22.91	33.64	45.7	265.8
46_1.mzML	4288	0.7597	22.89	34.51	46.4	267.1
47_1.mzML	4380	0.7603	22.93	34.21	45.6	315.3
49_1.mzML	4296	0.7607	22.84	34.09	45.6	328.7
5_1.mzML	4359	0.435	22.07	33.73	45.87	216
50_1.mzML	4225	0.4359	22.52	33.37	45.37	310.8
52_1.mzML	4292	0.7708	23.03	33.81	45.72	202.7
53_1.mzML	4299	0.4098	23.24	34.8	47.6	304.8
55_1.mzML	4391	0.4348	22.52	33.97	46.27	268.8
56_1.mzML	4473	0.4456	23.04	33.86	46.1	242
57_1.mzML	4022	0.4248	23.16	34.28	47.13	267.3
58_1.mzML	4424	0.7692	22.9	34.09	46.07	310.5
6_1.mzML	4428	0.7512	23.07	33.6	45.91	206.7
60_1.mzML	4373	0.7622	23.24	33.89	46.06	269.3
61_1.mzML	4294	0.7599	22.97	33.73	46.06	315.4
63_1.mzML	4327	0.7596	22.84	34.06	45.75	204.7
65_1.mzML	4216	0.7649	22.47	34.42	46.98	214.6
66_1.mzML	4372	0.7374	23.31	34.24	46.33	299.7
67_1.mzML	4376	0.446	23.39	34.01	46.7	315.2
68_1.mzML	4373	0.4022	22.55	34.22	45.68	298.9
69_1.mzML	4305	0.7604	22.51	33.69	46.14	199.2
7_1.mzML	4356	0.4458	23.06	34.88	46.74	312.2
70_1.mzML	4328	0.4231	22.18	33.49	45.32	251
71_1.mzML	4261	0.7622	22.69	34.4	46.65	268.6
73_1.mzML	4232	0.7593	23.27	33.78	45.88	203.7
74_1.mzML	4255	0.7598	22.58	34.03	46.6	313.4
75_1.mzML	4254	0.7596	22.96	33.79	45.67	213.3
76_1.mzML	4440	0.7602	22.96	33.93	45.76	266.2
77_1.mzML	4329	0.3805	22.6	33.93	45.92	242
78_1.mzML	4325	0.4351	21.96	34.21	46.68	202
79_1.mzML	4134	0.7605	22.69	34.09	46.23	226
80_1.mzML	4351	0.782	22.76	34.51	46.17	304.9
81_1.mzML	4343	0.7615	22.05	34.27	45.95	312.6
83_1.mzML	4330	0.3688	22.1	34.31	46.59	267.2
84_1.mzML	4234	0.762	22.95	34.77	46.17	314.4
85_1.mzML	4415	0.3928	22.98	34.52	46.42	265.3

86_1.mzML	4216	0.76	22.32	34.04	46.06	452.6
87_1.mzML	4387	0.76	22.58	34.44	45.4	304.4
89_1.mzML	4367	0.7452	22.09	34.37	45.83	303.5
9_1.mzML	4242	0.3981	22.6	34.27	46.04	254.6
90_1.mzML	4449	0.4498	22.06	33.81	45.92	266.3
91_1.mzML	4437	0.3998	22.5	33.98	45.52	314.9
92_1.mzML	4457	0.7605	22.77	34.07	45.22	312.4
93_1.mzML	4320	0.7592	22.94	34.23	45.79	208.2
94_1.mzML	4204	0.7436	21.92	34.07	45.96	296.6
95_1.mzML	4283	0.7474	22.16	34.29	45.75	314
96_1.mzML	4315	0.3975	22.49	34.53	46.63	314.6
98_1.mzML	4401	0.4398	22.16	34.09	45.96	282.2
99_1.mzML	4223	0.7639	22.52	34.35	46.49	275.1

Pathway Enrichment Analysis

STables 6-7 tabulate the pathways, and modules extracted by the FELLA R package and the diffusion methodology commonly adopted for groups and conditions in both positive, and negative ionization modes.

STables 8-9 tabulate the pathways, and modules extracted by the FELLA R package and the pagerank methodology commonly adopted for groups and conditions in both positive, and negative ionization modes.

STable 6. Pathways extracted with FELLA R package and diffusion method across groups and conditions on positive ionization mode (I = Intervention).

Conditions & Groups	KEGG id & Pathway name						
	hsa00280 Valine, leucine and isoleucine degradation	hsa00340 Histidine metabolism	hsa00380 Tryptophan metabolism	hsa04024 cAMP signaling pathway	hsa04621 NOD-like receptor signaling pathway	hsa05230 Central carbon metabolism in cancer	
HC pre-I	✔	✔	✔	✔	✔		
HC post-I	✔	✔	✔	✔	✔	✔	
PHY pre-I	✔	✔	✔	✔	✔		
PHY post-I	✔	✔	✔	✔	✔	✔	
COG pre-I		✔	✔	✔	✔	✔	
COG post-I	✔	✔	✔	✔	✔	✔	
COMB pre-I	✔	✔	✔	✔	✔		
COMB post-I	✔	✔	✔	✔	✔	✔	

Table 7. Pathways extracted with FELLA R package and diffusion method across groups and conditions on negative ionization mode (I = Intervention).

Conditions & Groups	KEGG id & Pathway name						
	hsa00280 Valine, leucine and isoleucine degradation	hsa00340 Histidine metabolism	hsa00380 Tryptophan metabolism	hsa04024 cAMP signaling pathway	hsa04621 NOD-like receptor signaling pathway	hsa05230 Centralcarbon metabolism in cancer	
HC pre-I		✔	✔	✔	✔		
HC post-I			✔	✔	✔	✔	
PHY pre-I		✔	✔	✔	✔		
PHY post-I			✔	✔	✔	✔	

COG pre-I	✓	✓	✓	✓		
COG post-I		✓	✓	✓	✓	
COMB pre-I	✓	✓	✓	✓		
COMB post-I		✓	✓	✓	✓	

STable 8. Pathways extracted with FELLA R package and pagerank method across groups and conditions on positive ionization mode (I = Intervention).

Conditions & Groups	KEGG id & Pathway/modules name							
	hsa00340 Histidine metabolism	hsa00380 Tryptophan metabolism	M00038 Tryptophan metabolism, tryptophan => kynurenine => 2-aminomuconate	M00078 Heparan sulfate degradation	M00115 NAD biosynthesis, aspartate => quinolinate => NAD	M00129 Ascorbate biosynthesis, animals, glucose-1P => ascorbate	M00338 Cysteine biosynthesis, homocysteine + serine => cysteine	M00376 3-Hydroxypropionate bi-cycle
HC pre-I	✓	✓	✓		✓	✓	✓	
HC post-I			✓				✓	✓
PHY pre-I			✓				✓	✓
PHY post-I			✓				✓	✓
COG pre-I			✓				✓	✓
COG post-I			✓				✓	✓
COMB pre-I			✓				✓	✓
COMB post-I			✓				✓	✓

STable 9. Pathways extracted with FELLA R package and pagerank method across groups and conditions on negative ionization mode (I = Intervention).

Conditions & Groups	KEGG id & Pathway/modules name								
	hsa00340 Histidine metabolism	hsa00380 Tryptophan metabolism	M00038 Tryptophan metabolism, tryptophan => kynurenine => 2-aminomuconate	M00078 Heparan sulfate degradation	M00115 NAD biosynthesis, aspartate => quinolinate => NAD	M00129 Ascorbate biosynthesis, animals, glucose-1P => ascorbate	M00338 Cysteine biosynthesis, homocysteine + serine => cysteine	M00376 3-Hydroxypropionate bi-cycle	M00912 NAD biosynthesis, tryptophan => quinolinate => NAD
HC pre-I	✔	✔	✔				✔		✔
HC post-I	✔	✔	✔		✔	✔	✔		
PHY pre-I	✔	✔	✔				✔		✔
PHY post-I	✔	✔	✔		✔	✔	✔		
COG pre-I	✔	✔	✔				✔		✔
COG post-I	✔	✔	✔		✔	✔	✔		
COMB pre-I	✔	✔	✔				✔		✔
COMB post-I	✔	✔	✔		✔	✔	✔		

Below, I give brief descriptions of the following detected metabolic pathways in my study.

hsa00280 - Valine, leucine and isoleucine degradation,

hsa00340 - Histidine metabolism,

hsa00380 - Tryptophan metabolism,

hsa04024 - cAMP signaling pathway,

hsa04621 - NOD-like receptor signaling pathway, and

hsa05230 - Central carbon metabolism in cancer.

Metabolic pathways:

**Valine, leucine and isoleucine degradation (hsa00280)**

Valine, isoleucine, and leucine are essential amino acids and are identified as the branched-chain amino acids (BCAAs). The catabolism of all three amino acids starts in muscle and yields NADH and FADH2 which can be utilized for ATP generation.

Histidine metabolism (has00340) :

Histidine is a dietary essential amino acid because it cannot be synthesized in humans. The WHO/FAO requirement for adults for histidine is 10 mg · kg body weight-1 · d-1. Histidine is required for synthesis of proteins. It plays particularly important roles in the active site of enzymes, such as serine proteases (e.g., trypsin) where it is a member of the catalytic triad. Excess histidine may be converted to trans-urocanate by histidine ammonia lyase (histidase) in liver and skin. UV light in skin converts the trans form to cis-urocanate which plays an important protective role in skin. Liver is capable of complete catabolism of histidine by a pathway which requires folic acid for the last step, in which glutamate formiminotransferase converts the intermediate N-formiminoglutamate to glutamate, 5,10 methenyl-tetrahydrofolate, and ammonia. Inborn errors have been recognized in all of the catabolic enzymes of histidine. Histidine is required as a precursor of carnosine in human muscle and parts of the brain where carnosine appears to play an important role as a buffer and antioxidant. It is synthesized in the tissue by carnosine synthase from histidine and β-alanine, at the expense of ATP hydrolysis. Histidine can be decarboxylated to histamine by histidine decarboxylase. This reaction occurs in the enterochromaffin-like cells of the stomach, in the mast cells of the immune system, and in various regions of the brain where histamine may serve as a neurotransmitter.

Tryptophan metabolism (hsa00380):

Metabolism of tryptophan results in the neurotransmitters serotonin and melatonin and, via the kynurenine pathway (KP), to nicotinamide adenine dinucleotide. Indoleamine 2,3-dioxygenase (IDO) catalyzes the first step in the KP and is upregulated in the setting of HIV infection (see SFig.13).
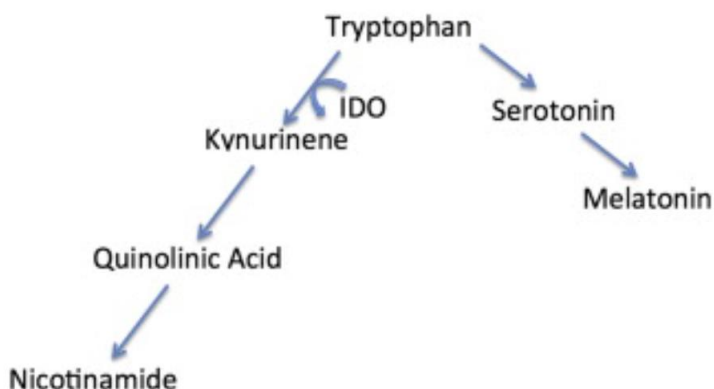
SFigure 13. Overview of tryptophan metabolism

cAMP signaling pathway (hsa04024)

cAMP-dependent pathway is necessary for many living organisms and life processes. Many different cell responses are mediated by cAMP; these include increase in heart rate, cortisol secretion, and breakdown of glycogen and fat. cAMP is essential for the maintenance of memory in the brain, relaxation in the heart, and water absorbed in the kidney. This pathway can activate enzymes and regulate gene expression. The activation of preexisting enzymes is a much faster process, whereas regulation of gene expression is much longer and can take up to hours. The cAMP pathway is studied through loss of function (inhibition) and gain of function (increase) of cAMP.

If cAMP-dependent pathway is not controlled, it can ultimately lead to hyper-proliferation, which may contribute to the development and/or progression of cancer.

NOD-like receptor signaling pathway (hsa04621)

The innate immune system is the first line of defense against microbial invasion, relying on pattern recognition receptors to recognize external pathogenic microorganisms and then remove them. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) are important receptors that mediate immune recognition. By identifying pathogen-associated molecular patterns, they not only initiate innate immune responses, but also activate adaptive immune responses. These processes are bridges between innate immunity and adaptive immunity.

Nucleotide-binding oligomerization domain-like receptors, in short NOD-like receptors (NLRs), are intracellular sensors of pathogen-associated molecular patterns (PAMPs) that enter the cell via phagocytosis or pores and damage-associated molecular patterns (DAMPs) that are associated with cell stress. The Nod-like receptor is a cytoplasmic recognition receptor that specifically recognizes "non-self-components" such as pathogenic microorganisms, non-microorganisms, and some dangerous signals in different parts of the organism with TLR, and interacts with each other to regulate the immune response in the body.

Central carbon metabolism in cancer (hsa05230)

Malignant transformation of cells requires specific adaptations of cellular metabolism to support growth and survival. In the early twentieth century, Otto Warburg established that there are fundamental differences in the central metabolic pathways operating in malignant tissue. He showed that cancer cells consume a large amount of glucose, maintain high rate of glycolysis and convert a majority of glucose into lactic acid even under normal oxygen concentrations (Warburg's Effects). More recently, it has been recognized that the 'Warburg effect' encompasses a similarly increased utilization of glutamine. From the intermediate molecules provided by enhanced glycolysis and glutaminolysis, cancer cells synthesize most of the macromolecules required for the duplication of their biomass and genome. These cancer-specific alterations represent a major consequence of genetic mutations and the ensuing changes of signalling pathways in cancer cells. Three transcription factors, c-MYC, HIF-1 and p53, are key regulators and coordinate regulation of cancer metabolism in different ways, and many other oncogenes and tumor suppressor genes cluster along the signaling pathways that regulate c-MYC, HIF-1 and p53.
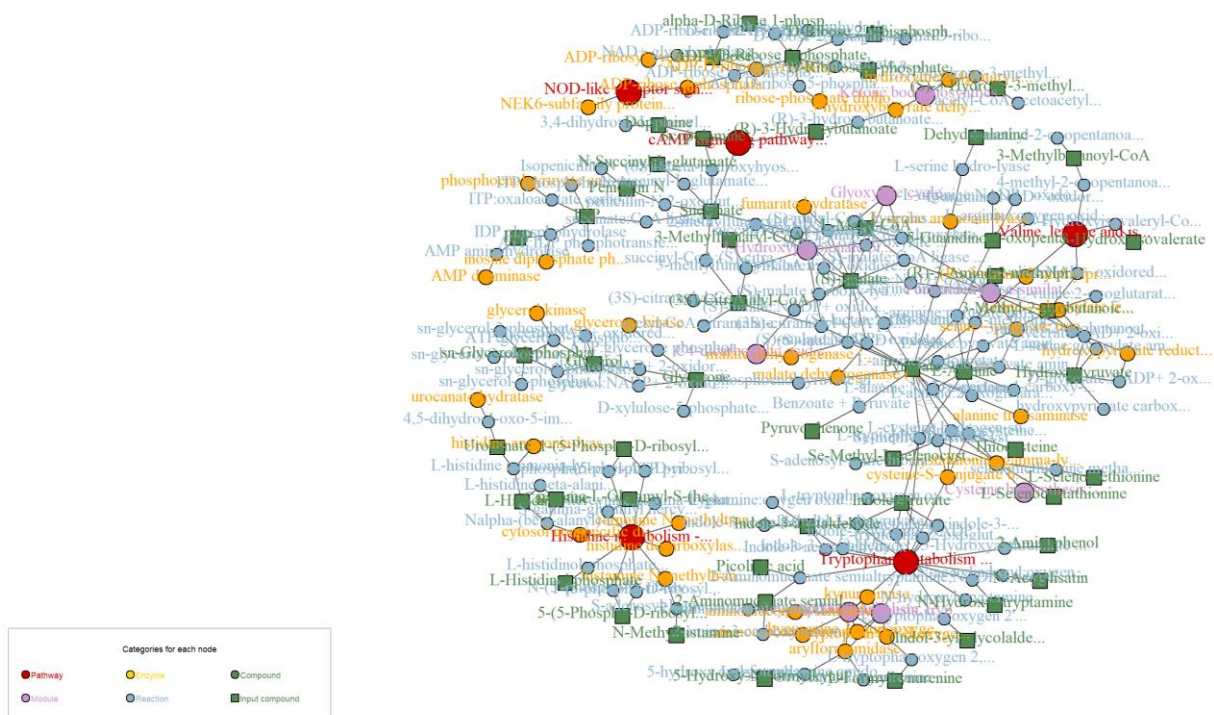
SFigure 17. A subgraph reported for the HC group on pre-intervention period, and on positive ionization mode. Compounds are green, reactions are blue, enzymes are orange, modules are purple and pathways are red.

CODE EXAMPLE

The code applied to my analysis is given below with the relevant parametrization:

```
Annotated.List.control <- mWISE.annotation(Peak.List =Peak.List.new.feat,
                    polarity = "positive",
                    force.mass.range = TRUE,
                    mass.range.type = "ppm.mode",
                    mz.range = NULL,
                    ppm =10,
                    Add.List=NULL,
                    diffusion.input.type = "probability",
                    use = "everything",
                    method = "pearson",
                    Freq = 0.5,
                    Rt.05 = 5,
                    score = "z",
                    Cpd.Add = Cpd.Add,
                    graph = g.metab,
                    Unique.Annotation = TRUE,
                    graph.name = "fella",
                    Intensity.idx = Intensity.idx,
                    do.Par = FALSE,
                    nClust =2)
```

where Peak.List.new.feat represents the peak intensity table or peak matrix which refer to tables containing peaks or features defined by their mass-to-charge ratios (m/z), retention times (rt), and intensities for each group, periods, and polarity.

The outcome of the mWISE software is the following dataframe:

View(Annotated.List.control$Ranked.Tab)

	Compound	Peak.Id	mz	rt	exact_mass	Add.name	pcgroup	Input.Score	z	Ranking
1	C00015	1931	302.97382	331.54608	404.00220	2M+Na+2K	684	NA	NA	
2	C12829	1931	302.97382	331.54608	222.00040	M+H+HPO3	684	NA	NA	
3	C00020	2185	292.01014	368.48706	347.06310	M+H-C4H8	663	NA	NA	
4	C00946	2185	292.01014	368.48706	347.06310	M+H-C4H8	663	NA	NA	
5	C01691	2185	292.01014	368.48706	250.04420	2M+2Na+K-H	663	NA	NA	
6	C04378	2185	292.01014	368.48706	347.06310	M+H-C4H8	663	NA	NA	
7	C15566	2185	292.01014	368.48706	193.03750	M+H+H2SO4	663	NA	NA	
8	C18264	2185	292.01014	368.48706	234.06810	2M+3K-H	663	NA	NA	
9	C00104	2324	331.04502	370.38675	428.01340	M+H-H3PO4	79	1	0.9958798	
10	C00104	2630	331.04482	533.46191	428.01340	M+H-H3PO4	723	1	0.9958798	
11	C00020	6732	366.08168	78.45921	347.06310	M+H+H2O	21	NA	NA	
12	C00130	6732	366.08168	78.45921	348.04710	M+H+NH3 | M+NH4	21	NA	NA	