## **Supplementary Figures**



**Figure S1. Validation of platelet EV sample quality. A.** Size distribution of a pooled platelet EV sample was determined by electron microscopy, which indicated the prevalence of small to medium size EVs (pool size, N = 4, total of 364 pEVs). **B.** Western blotting showed the presence of TSG101 in platelet EVs, CD63 in both platelet EVs and platelets, CD9 more in platelets and the absence of TOMM20 from both. **C.** Size distribution by nanoparticle tracking analysis of the same pooled platelet EV sample that was subjected to metabolomics confirmed the prevalence of small-medium size platelet EVs (pool size, N = 4).

CD9 normalization (fmol/OD C Metabolite name	Control 1	Control 2	Control 3	HUB.1 pre	HUB.2 pre	HUB.3 pre	HUB.2 post	HUB.3 post
L-Acetylcamitine	0.3193	0.1328	0.1006	0.0000	0.1396	0.1030	0.2457	0.1316
Adenine	0.0000	0.0000	0.0051	0.0127	0.0175	0.0058	0.0388	0.0371
Adenosine Alanine	25.9214	33.3427	13.8709	0.00025	28,7505	11,1068	100.0048	198.1479
Allantoin	26.4487	0.0000	0.3503	0.0000	1.8268	1.4554	29.6937	111.8033
AMP	0.1717	0.3138	0.2324	0.0817	0.2085	0.1448	0.3060	0.2045
Arginine Asparanine	3.1437	6.2454	1.8532	0.5379	9.2796	1.2558	4 5784	6.0815
Aspartic acid	9.2579	21.6737	5.4381	0.0000	18.3711	2.7171	18.0289	12.5601
Asymmetric dimethylarginine	0.7903	0.0000	0.0456	0.0000	0.2803	0.0848	1.6558	3.6649
Camiline	2.2223	1.5151	0.8394	0.0492	1.2167	0.8596	2.1370	1.4798
Choline	0.5340	0.1324	0.1439	0.0005	0.6681	0.4393	0.8530	2,1397
Citrulline	1.3000	1.6529	0.4077	0.1946	5.4385	0.4569	1.8963	1.7105
Creatine	2.9925	2.6246	1.8306	0.1146	1.8825	1.8038	23.0270	55.6197
Creatinine L-Cvstathionine	135.8859	8.7385	4.9266	0.4539	4 4310	3 9 2 9 6	7 2073	13 6328
Decanoylcamitine	0.0028	0.0000	0.0023	0.0003	0.0000	0.0014	0.0094	0.0181
D-Ribose 5-phosphate	23.7033	36.8885	23.7905	0.4784	10.6830	15.6223	22.8178	19.2863
Folic acid	0.0185	0.0762	0.0142	0.0000	0.0787	0.0081	0.0997	0.0532
Gamma-Glutamylcysteine Glucuronate	2.0084	0.3282	0.4661	0.0343	0.0000	0.2699	2.6608	4,1426
Glutamic acid	3.4830	6.5760	3.7019	0.3354	5.7173	2.0596	6.0509	3.9502
Glutamine	4.8197	0.0000	0.0000	0.0000	0.0000	1.4464	11.9386	15.9571
Giutathione Guanidoscetic acid	0.8423	0.2712	0.7790	0.2164	0.9694	0.3713	1.7767	1.2586
Hexanoylcarnitine	0.0000	0.0000	0.0005	0.0001	0.0006	0.0006	0.0034	0.0063
Hippuric acid	6.7765	1.2113	0.6472	0.0786	1.9684	2.3318	3.8206	4.9995
4-Hydroxyproline	2.6249	5.5931	1.2150	0.5213	3.8391	0.7337	5.1675	5.0234
Hypoxantnine	3,4270	11 2175	2.0962	1.7245	7 3445	1 1404	8,8595	6.0805
Incsine	0.0371	0.0290	0.2433	0.0000	0.0000	0.0384	0.0302	0.0815
Inositol	13.7774	0.0000	7.4996	0.0000	24.4318	4.8828	0.0000	19.1220
Isobutyryi-L-carnitine	0.0210	0.0089	0.0120	0.0003	0.0051	0.0040	0.0153	0.0235
Kynurenic acid	6.8680	0.0089	0.0159	0.00014	0.2308	0.3442	5.6287	14.8754
Leucine	0.9081	0.0000	0.5213	0.0000	3.3033	0.7314	2.7724	1.0403
1-Methylhistamine	0.0152	0.0053	0.0034	0.0000	0.0034	0.0027	0.0397	0.0831
NAD	0.4993	0.5074	0.4135	0.0409	0.4031	0.2396	0.6602	0.5920
Omithine	134,6772	405,2017	61,0995	24,6985	284,3224	47,1520	322,6073	230,2491
Orotic acid	0.2529	0.3891	0.1019	0.0000	0.4133	0.0629	0.6568	0.4552
Pantothenic acid	0.0464	0.0538	0.0113	0.0000	0.0000	0.0204	0.0000	0.0341
Propionylcarnitine	0.0454	0.0113	0.0119	0.0003	0.0109	0.0071	0.1873	0.4406
4-Pyridoxic acid Serine	10.3301	42,6508	7.0563	4.6144	38.0479	4 4172	35 4817	21.0888
Sorbitol	26.4888	0.0000	0.0000	0.0000	21.5789	5.9917	0.0000	47.5618
Spermidine	0.1906	0.3954	0.1208	0.2174	0.2643	0.1581	0.2935	0.2297
Succinic acid	0.0000	7 9935	0.0000	0.0000	2.3927	0.4231	12.8881	31.2228
Symmetric dimethylarginine	0.5744	0.0000	0.0723	0.0000	0.0000	0.0983	0.6056	1.2340
Taurine	20.8605	5.0441	3.0790	0.0000	5.3166	3.3763	21.0273	44.5637
Threonine	0.0000	0.0000	0.0000	0.0000	3.6063	0.4420	3.6054	6.1109
Xanthine	0.0342	0.0204	0.0956	0.0035	0.0277	0.0251	0.0373	0.0328
EV volume permatization (up								
EV volume normalization (µm Metabolite name L-Acetylcamitine	control 1 105.6501	Control 2 21.5948	Control 3 26.9255	HUB.1 pre	HUB.2 pre 27.6760	HUB.3 pre 16.2088	HUB.2 post 29.5041	HUB.3 post 22.2881
EV volume normalization (µm Metabolite name L-Acetylcamitine Adenine Adensine	control 1 105.6501 0.0000 285.0382	Control 2 21.5948 0.0000 199.9857	Control 3 26.9255 1.3552 183.9239	HUB.1 pre 0.0000 2.5929 0.5038	HUB.2 pre 27.6760 3.4769 92.6609	HUB.3 pre 16.2088 0.9152 96.8785	HUB.2 post 29.5041 4.6556 155.1572	HUB.3 post 22.2881 6.2831 115.1227
EV volume normalization (µm Metabolite name L-Acetyic-amitine Adenine Adenine Alanine	control 1 105.6501 0.0000 285.0382 8577.4115	Control 2 21.5948 0.0000 199.9857 5423.5048	Control 3 26.9255 1.3552 183.9239 3711.1010	HUB.1 pre 0.0000 2.5929 0.5038 0.0000	HUB.2 pre 27.6760 3.4759 92.6609 5698.9367	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106	HUB.2 post 29.5041 4.6556 155.1572 12006.6911	HUB.3 post 22.2881 6.2831 115.1227 33555.8515
EV volume normalization (µm Metabolite name L-Acetylcanitine Adenine Adensine Alanine Alanine	0//I) Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 55.0902	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0272	Control 3 26.9255 1.3552 183.9239 3711.1010 93.7188 50.1975	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 0.0000	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.2370	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 20.7723	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3565.0548 26 7415	HUB.3 post 22 2881 6.2831 115.1227 33555.8515 18933.6214 24 6315
EV volume normalization (µm Metabolite name L-Acetylcarnitine Adensine Alanine Allantoin AMP Arolnine	tol/l) Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2605	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790	Control 3 26.9255 1.3552 183.9239 3711.1010 93.7188 62.1875 495.8079	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 0.0000 16.6484 109.5872	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.3270 1839.4129	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3565.0548 36.7415 897.4912	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 18933.6214 34.6315 1029.8808
EV volume normalization (um Metabolite name L-Acetylcamiline Adensine Adensine Alanton Allanton AMP Arginine Asparagine	ol/l) Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2605 643.6850	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000	Control 3 26.9255 1.3562 183.9239 3711.1010 93.7188 62.1875 495.8079 332.9672	HUB.1 pre 0.0000 2.5929 0.6038 0.0000 16.6484 109.5872 0.0000	HUB.2 pre 27.6760 3.4759 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3655.0548 36.7415 897.4912 549.6879	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 18933.6214 34.6315 1029.8808 701.7402
EV volume normalization (µm Metabolite name L-Acetycamitine Adenine Adenine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Asparagine Asparagine Asparate acid	Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2605 643.6850 3053.4478 201.4025	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322	Control 3 26.9255 1.3562 183.9239 3711.1010 93.7188 62.1875 495.8079 332.9672 1454.9521	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 0.0000 16.6484 109.5872 0.0000 0.0000	HUB.2 pre 27.6760 3.4759 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5257	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721 427.4569	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3565.0548 36.7415 897.4912 549.6879 2164.5690	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 18933.6214 34.6315 1029.8008 701.7402 2127.0297
EV volume normalization (µm Metabolite name L-Acetycamitine Adenine Adenine Adamine Adamine Adamine Adamine Adamine Adamine Aspartagine Aspartacid Asymmetric dimethylarginine Gamitine	colrol 1 105 6501 0.0000 285 0382 8577.4115 8571.8780 56.8093 1040.2605 643.6850 3063.4478 261.4975 735.3564	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322 0.0000 246.4400	Control 3 26.9255 1.3552 183.9239 3711.1010 93.7188 62.1875 495.8079 332.9572 1454.9521 12.2097 224.5679	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 16.6484 109.5872 0.0000 0.0000 0.0000 0.0000 10.0327	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5257 55.5601 241.1685	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9570 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312	HUB.2 post 29.5041 4.6555 155.1572 12006.6911 3555.0548 36.7415 549.6879 2164.5690 198.7924 256.5731	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 1029.8808 701.7402 2127.0297 620.6491 250.6042
EV volume normalization (µm Metabolite name L-Acetylcamtine Adentine Adentine Alantine Alantine Alantine Alantion Alantine Aspartagine Aspartagine Aspartic acid Asymetric dimethylarginine Camthine Camthine	coll) Control 1 105 6501 0.0000 285 0382 8577.4115 8751.8780 56.8093 1040.2605 643.6850 3063.4478 261.4975 735.3564 51.4031	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322 0.0000 246.4400 21.5362	Control 3 26.9255 1.3552 183.9239 3711.010 93.7188 62.1875 495.8079 332.9572 1454.9521 12.2097 224.5679 22.3737	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 16.6484 109.5872 0.0000 0.0000 0.0000 10.0327 0.0000	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5257 55.5601 241.1685 44.4387	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312 5.0307	HUB.2 post 29.5041 4.6555 155.1572 12006.6911 3565.0548 36.7415 549.6879 2164.5690 198.7924 256.5731 30.2663	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 1029.8808 701.7402 2127.0297 620.6491 250.6042 29.2615
EV volume normalization (µm Matabolite name L-Actrifycamtine Admotine Alamton Alamton Alamton Appragine Aspanita acid Aspanita acid Camtine Camtine Camtine Camtine	Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2605 643.6850 3063.4478 261.4975 735.3664 51.4031 176.6894 176.6894	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322 0.0000 246.4400 21.5362 36.6571	Control 3 26.9255 1.3502 183.9239 3711.1010 93.7188 62.1875 495.6079 332.9572 1454.9521 12.2097 224.5679 22.3737 38.4959	HUB.1 pre 0.0000 2.5923 0.5038 0.0000 0.0000 16.6484 109.5872 0.0000 0.0000 0.0000 10.0327 0.0000 1.5212	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5287 55.5601 241.1685 44.4387 132.4366	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312 5.0307 69.1075 7.6647	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3565.0548 36.7415 397.4912 549.6879 2164.5690 198.7924 256.5731 30.2663 102.4076	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 18933.6214 34.6315 1029.8808 701.7402 2127.0297 620.6491 250.6042 29.2615 382.2498 392.2498
EV volume normalization (um Matabolite name LAckry(camine Adenine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Alanine Camiline Camiline Cristine Cristine	Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2805 643.6850 3063.4478 261.4975 735.3564 51.4031 176.6894 430.1560 990.2030	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322 0.0000 246.4400 21.5362 36.6571 268.8536 426.9154	Control 3 26.9255 1.3552 183.9239 3711.1010 93.7188 62.1875 495.8079 332.9572 1454.9521 12.2097 224.5679 22.3737 38.4959 109.0820 489.7791	HUB.1 pre 0.0000 2.6523 0.5038 0.0000 16.6484 109.5872 0.0000 0.0000 10.0327 0.0000 1.5212 33.6542 23.3468	HUB.2 pre 27.6760 3.4769 92.6609 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5257 55.6601 241.1685 44.4387 132.4366 1078.0229 373.1594	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312 5.0307 69.1075 71.8847 78.847	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3565.0548 36.7415 897.4912 549.6879 2164.5690 198.7924 256.5731 30.2663 102.4076 227.6714 2764.6478	HUB.3 post 22.2881 6.2831 115.1227 33565.8515 1029.8808 701.7402 2127.0297 620.6491 250.6042 29.2615 362.3498 289.6709 9419.0603
EV volume normalization (um Matabolite name LAcetryicamities Adenine Adenine Adenine Adamote A	Control 1 105.6501 0.0000 285.0382 8577.4115 8751.8780 56.8093 1040.2605 643.6850 3063.4478 261.4975 735.3664 51.4031 176.6894 430.1560 990.2030	Control 2 21.5948 0.0000 199.9857 5423.5048 0.0000 51.0372 1015.8790 0.0000 3525.4322 0.0000 246.4400 246.8400 246.8515 268.8536 426.9154	Control 3 26.9255 1.3552 183.9239 3711.1010 93.7188 62.1875 495.8079 332.9572 1454.9521 12.2097 22.4.5679 22.4.5679 22.4.5679 22.4.5679 109.0620 499.7791 1318.0952	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 0.0000 16.6484 109.8872 0.0000 0.0000 0.0000 0.0000 0.0000 10.0327 0.0000 1.5212 39.6542 23.3488 92.4827	HUB.2 pre 27.6760 3.4769 92.6609 5698.9367 362.1092 41.3270 1839.4129 713.0873 3641.5257 55.5601 241.1685 44.4387 132.4366 1078.0229 373.1594 2533.0441	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9670 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312 5.0307 59.1075 71.6847 283.7702 1952.4863	HUB.2 post 29.5041 4.6556 155.1572 12006.6911 3655.0548 36.7415 897.4912 549.6879 2164.5690 198.7924 256.5731 30.2663 102.4076 227.6714 276.64478 9191.1444	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 18933.6214 34.6315 1029.8808 701.7402 2127.0297 620.6491 250.6042 29.2615 362.2498 289.6709 9419.0603 31828.6521
EV volume normalization (um Matabolite name LAckry(camine Adenine Adenine Adenine Adanos Adanos Agan	Control 1 105 6501 0.0000 285.0382 8771.4115 8771.8780 56.8093 1040.2605 643.6850 3063.4478 261.4975 735.3564 51.4031 176.8894 430.1560 990.2030 44564.6995 1853.29279	Control 2 21:5948 0.0000 199.9857 5423 5045 0.0000 3525 4322 0.0000 246:4000 21:8382 36:6573 228:8573 428:9154 1421:3958 120.0973	Control 3 26 9255 1.3552 133 9239 3711.1010 93.7188 62:1875 495.8079 332.9572 24.5679 22.3737 38.4959 109.0620 499.7791 1318.0652 67.0399	HUB.1 pre 0.0000 2.5929 0.5038 0.0000 0.0000 16.6484 109.5872 0.0000 0.0000 0.0000 0.0000 0.0000 1.5212 239.6542 23.3488 92.4827 18.0599	HUB.2 pre 27,5760 3,4759 92,6609 5698,9367 1639,4159 713,0873 3641,5257 55,5601 241,1685 44,4387 132,4366 1078,0229 373,1594 2533,0441 2533,0441	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 228.9870 22.7782 197.5639 161.3721 427.4569 13.3454 135.2312 5.0307 69.1075 71.8847 283.7702 1952.4863 618.2070	HUB.2 post 29.5041 4.6506 155.1572 12006.6911 3555.0548 36.7415 3897.4912 549.6879 2164.5690 198.7924 256.5731 30.2663 102.4076 227.6714 2764.6478 9151.1444	HUB.3 post 22.2881 6.2831 115.1227 33555.8515 1029.8608 701.7402 2127.0297 620.6491 250.6042 29.2615 362.2498 289.6709 9419.0603 31828.6521 238.6824
EV volume normalization jurn Matabolite name LAcetricemities Adente Aden	oli) Control 1 105 6801 0.0000 285.0382 8577.4115 8574.015 643.6803 1040.2805 643.6805 003.4475 735.3564 735.3564 735.3564 735.3564 735.3564 735.3564 735.3564 735.3564 735.3564 735.3564 735.3574 735.3564 735.357475777777777777777777777777777777	Control 2 21.5948 0.0000 199.9857 423.5048 0.0000 51.0372 1015 8780 0.0000 246.4400 24.5362 246.8571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 36.6571 268.8535 269.8535 269.85555 269.8555 269.85555 269.85555 269.85555 269.85555 269.85555 269.85555 269.85555 269.85555 269.85555 269.85555 269.855555 269.855555 269.8555555 269.8555555555555555555555555555555555555	Control 3 26 9255 1.3652 183.9239 3711.1010 93.7188 62 1875 495.8079 224.5679 224.5679 224.5679 22.3737 18.4659 92.2737 199.0820 499.7791 1318.0952 67 0339 0.6247	HUB 1 pre 0.0000 2.5223 0.5338 0.0000 16.5484 109.5872 0.0000 10.0327 0.0000 1.5212 39.5542 23.348 5428 24.827 18.0899 0.0551 19.7551	HUB.2 pre 27,6760 3,4759 92,6609 92,6609 862,1032 41,3270 1839,4129 713,0673 3641,5257 55,5601 241,1685 44,4387 132,4366 1078,0229 373,1594 12533,0441 878,3223 0,0000	HUB.3 pre 16.2088 0.9152 96.8785 1747.3106 22.89670 22.7822 197.5633 161.3721 13.3454 13.3454 13.3455 0.3377 69.1075 71.88470 28.3770 0.2222 24.76784 195.24663 618.2070 0.22222 24.76784 0.2222 24.76784 0.2222 24.76784 0.2222 24.76784 0.2222 24.76784 0.2222 24.76784 0.2222 24.76784 0.2222 0.2227 0.2278 0.22782 0.2278 0.27787 0.277878 0.277878 0.277878 0.2	HUB.2 post 29:5041 4:6566 155.1872 3565.0546 367.415 837.4912 549.6873 2164.5690 198.7624 256.5731 30.2663 102.4076 227.6714 835.3130 1.1297 2738.5786	HUB.3 post 22.2881 5.2831 115.1227 33555 8515 18933 6214 34.6315 1029.8808 701.7402 2127.0297 620.6491 250.6042 29.2615 362.3498 288.6709 9419.0603 31828.6521 3238.6694 3.0572 3.266.6947
EV volume normalization (um Matabolite name LActryicamine Adenine Adenine Adenine Adenine Adaptagine Appanagin	oli) Control 1 105.6501 0.0000 285.0382 8577.415 8577.415 8577.415 8577.415 8637.415 9637.415 9637.415 9637.415 9635.425 1040.2605 903.2037 900.2030 44964.5995 18533.9279 0.9393 7843.4366 6.1147	Control 2 215948 0.0000 50.0000 50.0372 0.0000 51.0372 0.0000 245.4000 245.400 245.400 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.40000 245.400000000000000000000000000000000000	Control 3 26 9255 1.3662 13.9029 3711.1010 93.7188 62.1875 495.8073 332.9972 1454.9521 12.2087 224.5679 22.3737 38.4956 109.0820 499.7791 1318.0952 67.0339 0.6227 5355.0594 3.8025	HUB.1 pre 0.0000 2.6923 0.5038 0.0000 16.6484 109.5872 0.0000 0.0000 0.0000 0.0000 0.0000 1.6212 39.6542 23.3488 7.4657 0.0561 97.4657	HUB.2 pre 27,6760 3,4789 92,6609 92,6609 92,6609 93,4789 92,6609 41,3270 1439,4129 713,0673 33,41524 713,0673 33,41524 55,6601 241,1655 33,4154 122,4366 1078,0229 373,1594 44,4387 132,4367 253,0441 878,3223 0,0000 2117,6776	HUB.3 pre 16,008 0,9152 223,9570 223,9570 227,752 197,5639 197,5639 197,5639 197,5639 197,5639 197,5639 197,5639 197,5639 197,5639 1952,4663 618,2070 0,2222 2467,6784 1,2795 (76784 (76785) (76785) (76784 (76785) (76784 (76785) (76784 (76785) (76784) (76785) (76784) (76785) (76785) (76785) (76785) (76785) (76785) (76785) (76785) (76785) (76784) (76785) (76784) (76785) (76784)	HUB.2 post 29.5041 4.5056 155.1572 12006.6911 3355.0548 367.415 397.4512 2164.5590 138.7924 256.5731 30.2663 102.4075 227.6714 276.6476 9151.1444 805.3130 1.1257 2738.5285	HUB.3 post 22.2881 6.2831 115.1227 335568.815 1933.5214 33.6315 1029.8803 701.7402 23.2615 382.3483 289.6709 541.90603 31623.6521 230.6694 33.6527 3256.0927 9.0046
EV volume normalization (um Matabolite name LAcetricamite Adenine Aden	olii) Control 1 105.8501 0.0000 285.0382 8577.4115 8577.4115 8571.415 8571.415 8571.415 8571.415 8571.415 857.4015 943.8894 430.1850 950.2030 7843.4356 6.1147 8.20.518	Control 2 21,5948 0.0000 199,9857 5423,5048 0.0000 51,0372 1015,8790 0.0000 246,4400 21,5362 336,6571 258,8535 426,9154 1421,3958 120,0973 0.0000 6000 2663 12,3946	Control 3 26 9255 1.3562 33711.010 93.7185 495.8079 332.9572 1454.9521 12.0097 224.5679 22.3737 38.4999 109.0820 7191.0339 0.9247 3110.0524 567.0339 0.8247 3.80554 3.8025 3.82472	HUB:1 pre 0.0000 2.6923 0.6038 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 10.0327 0.0000 1.6242 23.3468 92.457 0.0001 18.0859 0.0657 0.0002 0.5859	HUB.2 pre 27.6760 3.4769 92.6609 92.6609 93.609 93.609 93.609 93.270 143.3270 143.94129 713.0873 35.41 55.5601 2411.1855 253.0441 273.1594 1533.0441 878.3223 0.0000 2117.6776 15.6044 15.6044 15.604	HUB.3 pre 16.0088 0.9152 228.9570 227.952 197.6539 197.6539 197.6539 197.6539 197.6539 197.6539 197.6539 197.6539 13.3454 135.2312 5.0307 69.1075 71.8847 283.7702 1952.4863 618.2070 0.2222 2457.6784 1.2795 8.5444 8.5444	HUB.2 post 29.5041 4.5556 155.1572 12006.6911 3565.0548 36.7415 49.5673 128.7524 2144.5590 138.7524 2144.5590 138.7524 27.6714 2746.4876 9191.1444 2748.4876 9191.1447 2739.5285 11.9701 52.8827	HUB.3 post 22.2881 6.2831 115.1227 33655 8816 33655 8816 33655 8816 33655 8816 33655 8816 33655 8816 33655 8816 29.2816 3365 8801 29.2816 322.8486 322.8486 33677 31828 6894 33667 336694 33667 30.3846
EV volume normalization (um Matabolite name LActoricamities Adente Adente Adente Adente Adente Adente Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Caractine Crautine C	Jointi     Control 1       105.5801     0.0000       285.0382     0.577.4115       6577.4115     657.6115       677.6125     658.693       1040.2605     643.6550       0033.4475     201.4975       201.4975     201.4975       51.4034     1150       930.2301     1450       930.2303     7483.4985       7483.4985     543.6737       1187.6977     52.0516       654.5737     1187.6977	Control 2 21.5948 0.0000 5423.5048 0.0000 551.0372 242.5048 0.0000 0.0000 0.0000 0.0000 246.4000 246.400 246.400 246.400 246.400 246.8154 246.8450 246.8450 246.8450 268.8555 426.9154 246.8450 268.8555 426.9154 269.8555 279.8555 269.8555 279.8555 269.85555 269.85555 269.85555 269.855555 269.8555555555555555555555555555555555555	Control 3 26 9255 1 3562 13 3562 13 3562 13 3711 60 52 1875 458 6079 332 9872 24 5673 332 9872 24 5673 22 45673 22 4573 22 45673 22 4573 22 4577 22 4577 22 4577 22 45777 22 4577 22 4577 24 4577 24 4577 24 4577 24 4577 24 45777 24 457777 24 4577777777777777777777777777777777777	HUB:1 pre 0.0000 2.622 0.6038 0.0000 16.6444 109.5872 0.0000 0.0000 10.0327 0.0000 10.0327 0.0000 10.0327 2.3348 92.4877 18.0899 92.4877 0.0000 0.5511 97.4657 0.0000	HUB.2 pre 27.6760 3.4769 92.6609 6598 9067 41.3270 83641 5237 713.0873 3641 5237 713.0873 3641 5237 55.6601 241.1685 3641 5237 241.1685 3641 5237 373.1594 241.3673 373.1594 2533.0441 373.593 0.0000 2117.5775 15.6044 73.6530 0.0000	HUB.3 pre 16.0088 0.9152 96.8785 1747 3106 22.8785 1747 3106 22.8782 22.7782 22.7782 22.7782 23.7762 3.3454 13.3454 13.3454 13.3454 13.52312 5.0307 1952.4883 618.2070 0.2222 247.6784 12.7785 8.9444 4.24551 3.240.0785 8.9444 4.24551 3.240.0785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 8.9444 1.2785 1.24651 1.246555555555555555555555555555555555555	HUB.2 post 29.5041 4.5556 155.1572 12006.6911 3056.0548 36.7415 254.5570 138.7524 256.5731 30.2663 102.4075 276.7614 2764.6478 9191.1444 365.3130 1.1297 2739.5285 11.8770 12.855.3130	HUB.3 post 22.2851 5.2831 116,1227 33555,8615 1023,8803 701,7402 2127,0297 250,644 250,6445 250,645 250,645 250,645 250,645 200,865 2120,865 2120,865 2120,865 2120,865 200,85
EV volume normalization jurn Metabolite name LAcetricamite Adenine Adenine Adanine Adanine Adanine Alanton Alanton Alanton Alanton Alanton Alanton Alanton Agentit acid Agentit acid Agentit acid Agentit acid Caractione Caractione Constitute Co	olii) Control 1 105.6501 0.0000 285.0382 8577.4115 8577.4115 8571.415 8571.402 8577.4115 857.403 1040.2605 443.6850 201.4975 735.3564 51.4031 735.3564 51.4031 735.3564 51.4031 735.3564 51.4031 745.3564 30.0518 8332,9279 0.0519 8333,9279 0.0519 7843.3456 6.1147 1152.5217 1152.5217	Control 2 21,5948 0,0000 199,9857 5423,5048 0,0000 551,0372 243,5048 0,0000 246,4400 24,5362 248,8536 0,0000 246,4400 24,5382 20,0973 0,0000 6500,2863 123,946 53,3792 71,7999 1069,6409 0,0000	Control 3 26 9255 1 3562 13 3652 13 3523 13 711.1010 37 711.0 37 711.0 37 711.0 37 711.0 37 711.0 37 711.0 32 9572 24 5679 22 4 5679 22 4 5679 22 4 5679 22 4 5679 22 4 5679 22 4 5679 20 8 267 21 4 5679 22 4 5679 20 8 267 21 4 5679 20 8 267 20 8 2	HUB-1 pre 6.00000 2.5923 0.5038 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.5212 23.3488 92.4827 18.0899 0.0561 97.4857 0.0056 97.4857 0.00000 0.00000 0.00000 0.00000 0.0000 0.0000 0.0000 0	HUB.2 pre 27.6760 3.4769 5658 5957 362.1092 41.3270 55.5601 241.1685 44.3387 132.4366 1078 6229 373.1594 135.4366 1078 6229 1078 6229 1078 6229 1078 6229 115.5044 73.8523 0.0000 115.2776	HUB.3 pre 16.038 0.9152 96.6785 1747.3106 228.9670 22.7782 197.6539 191.3242 191.3242 191.3242 191.3245 192.45555 192.45555 192.45555 192.455	HUB.2 post 29.5041 4.5556 155.1572 12006.6911 3565.0548 36.7415 249.5673 2164.5590 124.4590 2164.5590 102.4076 227.6714 2764.6478 9744.6478 9744.6478 9744.6478 1.1297 2739.5285 1.1297 2739.5285 1.1297 2739.5285 1.1297 2.194.6487 2.194.6487	HUB.3 post 22 281 5 2831 115 1227 33655 8615 1029.8803 701 7402 2127.0297 520.643 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 29.2615 92.2480 20.2659 21.2205 21.2005 21.2
EV volume normalization (um Matabotite name Actenica Actenica Adensine Adensine Adensine Adamite Apparagin	Joint     Constrol 1       Constrol 1     106 3601       0.0000     387 4415       0.001     687 6893       1040 2605     643 6850       0053 4478     261 4976       735 3564     51 4031       176 6894     430 1560       990 2030     44664 6895       14832 9879     0.9393       7843 4386     6.1147       62.0518     62.0518       644 6737     1152 5217       1554 8428     278 8428	Control 2 21.5948 0.0000 5423.5048 0.0000 551.0372 51.0372 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 245.4400 258.8535 458.9154 458.9154 459.9154554 459.9154554459.915455555555555555555555	Control 3 26 9256 1.3552 13.3552 13.35239 3711.1010 5.711.80 62 1875 455.8079 332.9572 24.458 455.8079 332.9572 24.459 22.45679 22.4579 22.45679 22.4579791 23.95679 23.9577979 23.9577979 23.957797979 24.95779797979797979797797797797777777777	HUB-1 pre 0.0000 2.6923 0.6338 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.5212 3.95542 2.33488 92.4827 18.0859 0.0551 97.4857 0.0000 0.5958 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.0000 0.5988 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000000	HUB.2 pre 27,6760 3,4769 92,6609 6588,9367 862,1092 41,3270 241,1685 44,5287 55,5601 241,1685 44,5287 55,5601 241,1685 44,5287 132,4366 1078,0229 373,1594 2233,0441 2233,041 2233,041 2117,5775 135,644 73,6920 0,0000 1133,2760 0,0000	HUB.3 pre 16.0088 0.9152 96.6785 1747.3106 228.9670 22.7782 197.5639 197.5639 191.3241 427.4569 13.3464 15.3212 5.0307 19.13459 13.3464 15.3212 5.0307 19.524 19.77	HUB.2 post 2 95041 4 8565 155, 1572 1 2006,891 2 3063,897 3 307415 8 3074912 5 49,6879 2 744,556 8 307,4912 2 744,5476 9 191,1444 4 855,3130 1,1297 2 746,5476 9 191,1444 4 855,3130 1,1297 2 739,5285 1,13770 1,444 1,455 1,13701 1,228 2,738,5485 1,13701 1,228 2,738,5485 1,238,548 1,444 1,455 1,13701 1,228 1,238,548 1,444 1,455 1,13701 1,228 1,238,548 1,444 1,455 1,144 1,455 1,147 1,455 1,147 1,455 1,147 1,147 1,278 1,278 1,278 1,455 1,147 1,147 1,278 1,278 1,278 1,455 1,147 1,455 1,127 1,127 1,278 1,278 1,455 1,127 1,127 1,278 1,278 1,455 1,127 1,127 1,278 1,278 1,455 1,127 1,278 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,455 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,456 1,127 1,276 1,276 1,476 1,476 1,477 1,456 1,127 1,276 1,276 1,276 1,276 1,276 1,276 1,276 1,376 1,457 1,457 1,4	HUB 5 post 22 2861 5 2833 1355 28415 1355 28415 1353 2814 1353 2814 1353 2814 1353 2814 1353 2814 1353 2814 1353 2814 290 5042 290 5042 290 5042 290 5042 290 5045 290 5045 31628 6821 300 568 30 3284 30572 300 384 30572 300 584 300 572 300 585 570 570 570 570 570 570 570 570 570 57
EV volume normalization jurn Metabolite name LAcetricamine Adenine Adenine Adenine Adanine Alanton Alanton Alanton Alanton Alanton Alanton Alanton Agentit acid Agentit acid Agentit acid Caractione Caractione Caractione Costatione C	Control 1       105 5501       105 5501       20000       285 0382       857 4115       8751 8780       8571 8780       905 0382       937 18780       930 345       946 345       951 8780       951 8780       951 8780       950 2020       4494 8595       1853 9279       0.933       7145 4264 571       1594 8423       278 7134	Control 2 21.5948 0.0000 9423 5048 0.0000 95.0372 2423 5048 0.0000 246.4400 24.536 248.557 20.0373 0.0000 24.63402 248.555 20.0373 0.0000 24.536 253.3154 120.9373 0.0000 253.3154 123.946 53.3759 21.7399 21.1400 21.1400 21.1400	Control 3 26 9255 1 3502 3711.1010 38.7118 495.8079 332.9572 445.8079 332.9572 445.8571 12.2087 1454.9521 12.2087 1454.9521 12.2087 1454.9521 12.2087 1318.0625 67 3339 0.5247 1318.0625 67 3339 0.5247 1318.0625 8.8472 9.9004215 0.204451 2.00451 2.004512 2.004512 2.00451	HUB-1 pro 0.0000 0.0000 0.0000 0.0000 16.5444 109.5872 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 9.4657 0.0561 97.4657 0.0561 97.4657 0.00000 0.000000	HUB.2 pre 27.6760 3.4769 5658 9.367 582.1092 41.3270 55.5601 241.1655 44.387 33.415257 55.5601 241.1655 44.3876 23.33.441 478.5223 0.0000 2117.5776 15.6044 73.6020 2117.5776 15.6044 73.6020 113.2705 15.6044 73.6020 113.2705 15.6044 73.6020 113.2705 15.6044 73.6020 15.6001 15.6044 73.6020 15.6001 15.6044 73.6020 74.60200 74.60200 74.60200 74.60200 74.60200000000000000000000000000000000000	HUB.3 pre 16.2082 0.9152 228.9575 1747.3105 227.752 22.7752 22.7752 22.7752 27.7525 5.0307 69.1075 77.8847 263.7702 1952.4655 618.2070 0.2222 2457.6784 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 8.444 2.24516 1.2755 1.2755 8.444 2.24516 1.2755 1.27	HUB.2 post 29.5041 4.5556 155.1572 12006.6911 2006.6911 2006.6911 2006.6911 2006.6911 2006.6911 2004.691 2014.5900 103.7041 2014.6878 103.7047 2015.2015 11.9701 2015.2015 11.9701 2015.2015	HUB.3 post 22.2881 15.223 15.227 33555.8815 15933.6214 336.315 1029.8803 701.7482 2250.6042 2250.6042 2250.6042 2250.6042 2250.6042 2250.6042 2250.6042 30.6654 30.6654 30.6654 30.6654 30.6654 30.6654 213.4477 213.1477
EV volume normalization (um Matabotite name Actenticamite Actenticamite Adensine Adensine Admannne Admanne Admanne Admanne Admanne Adman	Control 1       Control 1       105x8501       105x8501       285,0382       287,74115       8751,8750       56,033       1040,2605       261,4875       735,3564       51,4031       176,8894       430,1560       990,2030       4454,6995       18532,9277       62,6475       64,6575       54,4575       54,4575       54,4575       54,4571       51,948,4386       278,7134       840,0734       940,0734	Control 2 21:5943 0.0000 51:0372 0.0000 51:0372 0.0000 0.0000 0.0000 2246:400 0.0000 246:400 0.0000 246:400 0.0000 246:400 0.0000 0.0000 211:4002 241:4002 2	Control 3 26 9255 13652 3710552 3711010 337186 521875 4358073 332.9972 1454.9521 12.0097 224.5679 224.5679 224.5679 224.5679 224.5679 224.5679 224.5679 224.5679 22.3737 38.4959 0.6204 459.7791 38.4959 0.6204 459.7791 38.4959 0.6204 459.7791 38.4959 0.6204 459.7914 38.4957 0.6204 459.7914 38.4957 0.6204 459.719 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 3.6225 0.6204 0.6245000000000000000000000000000000000000	HUB.1 pre 0.0000 2.5923 0.5030 0.0000 16.6444 10.95872 0.0000 0.0000 10.0327 0.0000 10.0327 0.0000 10.0327 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000	HUB.2 pro 27.5760 3.4758 92.6067 34.1282 41.2270 41.2770 41.27	HUB.3 pro 16.2088 0.9152 0.9152 0.9152 0.9152 0.9970 12.2792 13.3454 13.3454 13.3454 13.3454 13.3454 13.33454 13.3454 13.5312 0.9272 24.7678 19.22483 1.2756 1.22759 1.22759 1.2755 1.22759	HUB 2 post 29 5041 48 505 48 505 48 505 48 505 48 505 48 505 506 0048 507 415 506 0048 507 415 206 5731 30 5683 102 4076 495 7014 276 4877 519 505 11 2975 519 505 519 505	HUB 3 post 22.281 115.1227 33556 2815 115.127 33556 2815 115.227 33556 2815 115.327 220.6042 22.250.6042 22.250.6042 22.250.6042 22.250.6042 22.250.6042 22.300.6694 31828.6621 3.056.9527 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 9.00451 3.05702 3.05702 3.05702 3.056052 2.131,05702 3.056052 2.131,05702 3.056052 2.131,05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.056052 3.056052 3.05702 3.056052 3.05702 3.056052 3.05702 3.0560552 3.05605555555555555555555555555555555555
EV volume normalization jurn Metabolite name LAcetricamine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Caractione Calactio	Control 1       105 5501       105 5501       285 0382       287 74115       3751 18780       363 245 0382       1040 2603       261 4975       3003 4475       201 4975       31 4051       175 8894       430 1560       0.303 3475       281 4975       31 4051       176 8894       430 1560       0.3933       784 34386       0.1147       450 1560       278 7137       280 0724       0.0000       224 3304       888 8730	Control 2 215948 0.0000 199.9857 5423.5048 0.0000 351,0372 245.4000 215,0372 246.4000 215,032 246.4000 215,032 246.4000 215,032 246.4000 215,032 246.4000 215,032 246.4000 215,032 246.4000 210,0000 2000 2000 2000 2000 2000 20	Control 3 26 9255 1 3862 3711.1010 53.711.010 53.711.010 53.711.010 53.711.010 53.711.010 53.711.010 53.711.010 53.84955 109.0820 499.7791 1318.0952 67.0339 0.8247 5355.0554 3.84957 9.0225 8.9472 2.84770 9.904.2115 0.0000 2.084318 3.84571 0.1305 1.31685 3.345711	HUB-1 pro 0.5000 0.5000 0.5000 0.0000 16.4844 10.95872 0.00000 0.00000 0.00000 0.000000 0.00000 0.00000 0.00000 0.00000000	HUB-2 pro 3/ 3760 3/ 4769 92 6609 5698 5067 362,1092 41,3270 1835 4129 35841 5257 35,6601 35841 5257 36,6601 3641 5257 373,1694 373,1694 373,1694 373,1694 373,1694 373,1694 373,1694 373,1694 373,1694 376,0000 115,6644 7,86001 10,30000 115,6644 7,86001 10,300000 10,300000 10,300000 10,300000 10,300000 10,300000 10,300000 10,300000 10,3000000 10,3000000 10,3000000 10,3000000 10,300000000 10,30000000 10,30000000000	HUB.3 pro 16 5056 16 5057 1747 3105 228,9670 22,7782 197,5539 161,3721 228,9670 227,4556 13,3454 13,3237 27,4556 13,3454 13,3237 28,91075 71,884 1952,4955 1952,4955 1952,4955 1952,4955 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2735 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,2755 8,9444 1,27555 1,27555 1,27555 1,2755 1,27555 1,27555 1,27555 1,	HUB.2 poet 3 5041 4 6505 155, 1572 12006, 6911 3565,0748 367,4415 897,4912 305,073 102,475 205,073 102,475 227,6714 2746,4678 9191,1444 855,3130 1,1297 2739,5285 11,9701 1,1297 1433,3619 273,3626 11,9701 273,3626 213,1890 672,0004 0,4077 485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 630,4157 1485,7742 1485,7742 1495,7744 1495,77445,77445 1495,77445 1495,7745,77451495,7745 1495	HUB.3 post 22.2881 15.1227 33555.8815 1833.5214 33.6315 1029.8803 701.7402 21.27.0297 220.6492 229.6709 229.6709 230.6894 3.0672 230.6694 3.0672 3.0675 3.0675 3.0675 3.071,0676 1.0671 1.0671
EV volume normalization (um Matabotite name LAcetricamitie Adenine Adenine Adenine Admoster Admoster Admoster Admoster Admoster Agantie Aspartige Aspartige Aspartige Aspartige Cambine Cambine Cartuline Cart	Control 1       106:8501       106:8501       285:0382       857:4115       857:16:730       56:8523       107:55:8523       107:55:8523       107:85:8523       107:85:8523       107:85:8523       107:8854       105:8524       107:8854       107:8854       107:8854       107:8854       107:8854       107:8854       107:8854       107:8522       107:8522       107:85233       107:85233	Control 2 2 (1.594) 309,9857 4423,5048 0,0000 51,0372 1015,8790 0,0000 216,5390 246,4400 216,5362 36,6671 423,9158 443,9158 400,0000 444,1105 444,1105 0,0000 0,00000 0,00000 0,00000 0,000000	Control 3 26 9255 135 9239 3711 1010 93 7188 62 1875 4458 8079 332 5572 1454 9521 12 2097 22 4757 34 949 193 0620 449 7771 137 0259 0 6247 585 0654 3 8025 8 9472 124 7039 900 4215 0 0206 208 4318 3 4657 173 1685 173 1685 335 0747	HUB 1 pre 0.0000 2.023 0.0000 1.0200 1.0200 1.0200 0.0000 0.0000 0.0000 1.0327 0.0000 1.0327 2.24877 1.0000 1.0327 0.0000 0.0000 1.0327 0.0000 0.0000 0.0000 1.0327 0.0000 0.0000 1.0327 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 00	HUB 2 pro 27 5763 32 569 32 569 5698 9367 382 1092 41 3270 1839 4129 713 0873 3541 5257 55 5601 241 1685 541 5257 55 5601 241 1685 241 1685 241 1685 253 3641 2533 3642 2533 3642 2534 3642 2533 3642 2534 36444 253444444444444444444444444444444444	HUB.3 pro 16 2082 2082 2089 1747 3106 22789 1975539 1975559 19	HUB.2 poet 29 50/1 155 1572 12006 6911 356 307415 837,415 837,415 837,415 837,415 266,5731 2164,5590 198,7924 256,5731 30,2663 102,4075 405,714 2764,6473 9161,410 2764,6473 9161,410 2764,6473 9161,410 11,92700 11,92700 11,92700 11,92700 11,927000 11,927000 11,92	HUB.3 post 22.2881 115.1227 33955.8815 1953.8214 33.6315 250.6431 250.6431 250.6431 250.643 252.2615 252.2525 252.2555 252.2555 252.2555 252.2555 252.2555 252.25555 252.25555 252.255555 252.255555555
EV volume normalization (um Matabolite name LAcartyicamine Adenine Adenine Adenine Adenine Adenine Adaptagine Apparatine Apparatine Apparatine Apparatine Apparatine Apparatine Apparatine Apparatine Apparatine Apparatine Cartuline Crastin	Control 1       105:5501       105:5501       250:382       857:4115       5751:8780       8575:18780       90:1040       265:3554       90:1040       751:8780       90:1040       90:1040       90:1040       90:1051       90:2030       4436:45951       80:3554       90:2030       44964:45951       820519       1152:5217       154:4828       2242:33549       6:0050       2242:33549       6:0050       90:2224:33549       90:33549       152:5217       54:4394       54:372       152:5217       54:4394       54:372       152:5217       54:4394       55:4394       55:4394       55:4394       55:4394       55:4394       55:4394       55:4394       55:4394       55:4394 <td>Control 2 21 / 5948 0 0000 199,9857 423 5048 0 0000 0 105 6750 0 00000 215 6750 246 4400 21 / 302 248,8535 426,9154 1421 3958 120,0973 0 0,0000 600,2064 53 3792 71,7999 1005 6409 0 0,0000 211,4402 211,402 0 0,0000 0 0,0000 211,4402 211,405 0 0,0000 0 0,00000 0 0,00000000</td> <td>Control 3 26 9255 13562 133,9239 3711,1010 93,7188 495,8073 312,9972 11454,922 23,718 495,8073 22,9773 1454,922 23,713 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,08200 195,08200 195,08200 195,08200 195,08200000000000000000000000000000000000</td> <td>HUB 1 pro 2 0502 2 0523 0 0000 1 05484 1 095872 0 0000 1 0 1095872 0 0000 1 0 1095872 2 3 488 2 4827 1 8 0899 0 0000 6 8 3468 0 0000 0 6 8 3468 0 0000 0 0 10 8 3488 0 0000 0 0 10 9 8 10 10 10 10 10 10 10 10 10 10 10 10 10</td> <td>HUB-2 pro 27,8760 3,4756 92,8609 8698,9367 382,1092 41,3270 1839,4129 8341,5231 8341,5251 8341,5251</td> <td>HUB.3 pre 16 2089 96.8765 1747.3106 228.9570 22.7762 197.5639 197.5639 197.5639 197.5639 197.5639 195.2485 6.0207 1952.4485 1952.</td> <td>HUB.2 poet 3 5041 4 5056 155, 1572 12006, 6911 356, 0744 549, 6673 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5731 30, 2683 102, 4076 2276, 5741 2743, 5476 273, 5747 1, 1297 319, 4661 726, 4637 1433, 3819 622, 0004 0, 4077 485, 7042 630, 411 1053, 5749 3, 5203 4, 5742 4, 5744 4, 5744</td> <td>HUB.3 post 22 2881 15 1227 3355 2815 345315 10528808 701 7402 2127 0297 2520 6492 2127 0297 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 31528 6827 31528 6827 31528 6827 300 652 300 652 300</td>	Control 2 21 / 5948 0 0000 199,9857 423 5048 0 0000 0 105 6750 0 00000 215 6750 246 4400 21 / 302 248,8535 426,9154 1421 3958 120,0973 0 0,0000 600,2064 53 3792 71,7999 1005 6409 0 0,0000 211,4402 211,402 0 0,0000 0 0,0000 211,4402 211,405 0 0,0000 0 0,00000 0 0,00000000	Control 3 26 9255 13562 133,9239 3711,1010 93,7188 495,8073 312,9972 11454,922 23,718 495,8073 22,9773 1454,922 23,713 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,0820 0,6247 195,08200 195,08200 195,08200 195,08200 195,08200000000000000000000000000000000000	HUB 1 pro 2 0502 2 0523 0 0000 1 05484 1 095872 0 0000 1 0 1095872 0 0000 1 0 1095872 2 3 488 2 4827 1 8 0899 0 0000 6 8 3468 0 0000 0 6 8 3468 0 0000 0 0 10 8 3488 0 0000 0 0 10 9 8 10 10 10 10 10 10 10 10 10 10 10 10 10	HUB-2 pro 27,8760 3,4756 92,8609 8698,9367 382,1092 41,3270 1839,4129 8341,5231 8341,5251 8341,5251	HUB.3 pre 16 2089 96.8765 1747.3106 228.9570 22.7762 197.5639 197.5639 197.5639 197.5639 197.5639 195.2485 6.0207 1952.4485 1952.	HUB.2 poet 3 5041 4 5056 155, 1572 12006, 6911 356, 0744 549, 6673 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5580 1264, 5731 30, 2683 102, 4076 2276, 5741 2743, 5476 273, 5747 1, 1297 319, 4661 726, 4637 1433, 3819 622, 0004 0, 4077 485, 7042 630, 411 1053, 5749 3, 5203 4, 5742 4, 5744 4, 5744	HUB.3 post 22 2881 15 1227 3355 2815 345315 10528808 701 7402 2127 0297 2520 6492 2127 0297 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 2520 6492 31528 6827 31528 6827 31528 6827 300 652 300
EV volume normalization (um Matabolite name LActry(camite Adenne A	Control 1       105 6501       105 6501       285 0382       287 18780       285 0382       285 731 8780       100 2003       637 871 8780       100 2003       643 6850       735 3564       51 4203       110 9895       950 2020       44564 8595       118323 927       0.5393       735 3564       51 4231       1153 564       51 4231       6.1147       0.5393       7152 5617       1594 8428       6.1672       1133 5903       1132 6672       1132 6675       4555 8455	Control 2 21.5948 0.0000 5423.5048 0.0000 55.5423.5048 0.0000 2355.4420 0.0000 24.5420 21.5362 21.5362 24.5400 24.5400 24.5400 21.5362 21.5362 21.5362 21.5362 21.5362 21.5362 21.5362 21.5362 21.5362 0.0000 21.5362 21.5362 0.0000 21.5362 0.0000 21.14000 21.1400 21.14000 21.14000 21.14000 21.140	Control 3 26 92/5 13/562 13/562 13/562 13/562 13/562 13/562 13/562 13/562 13/562 13/562 13/562 12/567 22/572 14/5679 22/577 13/5679 22/577 13/5679 22/577 13/5679 22/577 13/5679 22/577 13/5679 22/577 13/5679 20/577 13/5679 20/577 13/5679 20/5779 2	HUB 1 pre 0.0000 2.923 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.5212 2.4877 18.0899 0.0551 97.4857 0.0000 6.3946 0.0000 0.0000 18.0551 0.0000 18.0551 0.0000 18.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 18.0899 0.0551 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0551 0.0000 0	HUB.2 pre 27,6760 3,4769 92,6609 862,1092 41,3270 93,2609 41,3270 93,2609 41,3270 93,200 41,3270 93,200 44,3387 132,4366 133,5270 55,5601 241,1655 44,3387 132,4366 135,644 2533,0441 878,3223 0,0000 1133,2700 0,0000 1132,2700 0,0000 1132,2700 0,0000 1132,2700 0,0000 1132,2700 0,0000 1132,2700 0,0000 1132,2700 1132,2	HUB.3 pre 16.2088 0.9182 96.8785 223.9577 227.782 427.4584 13.3456 13.3456 13.356 13.3576 13.356 13.3576 13.3576 13.3566 13.3576 13.3566 13.3576 13.3566 13.3576 13.3566 13.3576 13.3566 13.3576 13.35766 13.35766 13.3566 13.35766 13.3566 13.35766 13.3566 13.35766 13.3566 13.35766 13.3566 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.35766 13.357666 13.357666 13.357666 13.357666 13.357666 13.357666 13.357666 13.357666 13.357666 13.3576666 13.3576666 13.3576666 13.35766666 13.35766666666666666666666666666666666666	HUB.2 post 29 5041 165.1572 12006 6911 305:0048 307.415 2065.0548 307.415 2065.0548 2164.5690 1187.7924 2164.5690 1187.7924 2164.5690 1187.7924 2164.571 21764.6497 1187.7925 2183.2024 219.1297	HUB.3 post 22 2881 15.127 33555 8815 15.527 7817402 20.642 20.642 20.217 20.642 20.215 20.643 21.27.0297 20.215 20.643 21.27.0297 20.215 20.643 21.230.6694 21.230.6694 21.230.6694 21.230.6694 21.230.6695 21.2702.2884 21.31477 21.219.0673 1.0004 21.31477 21.219.0673 1.0004 21.31477 21.219.0673 1.0004 21.31477 21.219.0673 1.0005 21.219.0673 1.0005 1.0005 21.219.0673 1.0005 21.219.0673 1.0005 21.219.0673 1.0005 22.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 1.0029.7162 21.3375 2.0045 2.0045 2.0
EV volume normalization (um Metabolite name LAcenicamine Adensine Adensine Adensine Adensine Adensine Appragine Citation Ci	Control 1       105 6501       105 6501       285 0382       6071 4170       56 8073       56 8073       104 02005       643 6850       501 4975       501 4975       501 4975       501 4975       501 4975       503 000       430 1560       990 2030       990 2030       0.5031       768 894       776 894       990 2030       0.5031       786 894       790 20518       564 27371       787 438       787 7137       60 0704       0.0005       278 7137       840 0734       0.0006       94 4972       12.2806       12.2805       4555 89485	Control 2 21: 5948 0.0000 50:0000 50:0000 50:0000 245:0000 245:4000 245:4000 245:4000 245:4000 245:4000 245:30154 12:0007 263:9154 12:20973 12:20975 12:20975 12:2097	Control 3 26 9255 13 9522 133 9223 3711 1010 93 7188 458 80773 244 5679 22 4737 244 5679 22 4737 244 5679 22 4737 244 5679 22 4737 199 0820 5 1318 0852 5 1318 0855 5 1318 2 1318 0852 5 1318 2 1318 0852 5 1318 0852 5 1318 2 1318 0852 5 1318 0855 5 1318 2 1318 0852 5 1318 0855 5 1318 0855 5 1318 0855 5 1318 0855 5 1318 0855 5 1318	HUB-1 pre 0.0000 2.9523 0.6000 0.6038 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.5212 3.95542 3.34857 0.0500 0.0000 0	HUB.2 pre       27.6760       3.4769       92.6609       92.6609       1839.4129       1839.4129       241.3270       1839.4129       1839.4129       241.1655       241.1655       243.270       122.4366       1078.6229       273.1694       2533.0441       273.253       2117.5776       2119.5776       2113.2760       0.0000       1133.2700       0.0001       1133.2700       0.0001       1133.2700       0.0001       1133.2700       0.0001       1133.2700       0.0001       1455.5812       0.0004       482.6784       1.0194	HUB.3 pre 16 2069 996.8765 1747.3106 223.9570 22.7762 197.8639 161.37276 233.957 161.37276 161.37276 161.37276 163.3464 155.2312 50.3377 184.47 1952.4651 324.615 324.615 324.615 324.615 324.615 227.554 8.9444 4.2.4651 324.615 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 227.554 8.9444 4.2.4651 324.6152 27.0166 0.6.255 17.33965 6.0.351 17.33965 17.3	HUB.2 post 29.5041 45.507 120.65.8446 35.577 2164.5590 2164.5590 2164.5590 2164.5590 2164.5590 2164.5590 21764.6476 3191.1440 30.24076 211.5701 2.2764.6476 319.1440 31.1297 213.5265 21.3.9506 21.3	HUB.3 post 22.2881 5.22.3861 15.1227 33553.2614 334.5315 1029.8803 701.7402 2.127.0297 22.2015 325.8403 2419.603 31628.8621 32.2015 32
EV volume normalization (um Matabolite name LAcetricamitie Azenne	Control 1       Control 1       105,8201       105,8201       105,8201       105,8201       105,8201       104,8201       8577,4115       8577,4115       8577,4115       8577,4115       751,3564       735,3564       950,201,4976       735,3564       950,2030       4464,4951       80,0731       1832,39279       0,0393       201,147       62,0518       640,6737       1132,8207       1133,8907	Control 2 21.5948 0.0000 5423.5048 0.0000 0.0000 0.0000 0.0000 245.4420 0.0000 245.4420 0.0000 245.4420 21.5362 120.0973 0.0000 245.8535 423.9154 120.0973 0.0000 211.4402 425.9154 120.0973 0.0000 211.4402 44.1105 0.0000 211.4402 44.1105 0.0000 0.0000 211.4402 44.1105 0.0000 0.0000 0.0000 211.4402 44.1105 0.0000 0.0000 0.0000 211.4402 44.1105 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	Control 3 26 9255 13552 133523 2711 1010 53 7186 53 7186 53 7186 53 7186 53 7186 53 7186 53 7186 53 7186 53 7186 53 2977 224 5679 224 5679 224 5679 224 5679 224 5679 23 712 55 7059 0 6247 55 7059 56 7039 0 6247 55 7059 50 7059 0 6247 55 7059 50 7059 0 6247 55 7059 50 7059 7050 7050 7050 7050 7050 7050 7050	HUE.1 pro 0.0000 2.023 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	HUB.2 pre 27.5760 3.4759 92.6609 413.34759 92.6609 55.6601 241.1685 44.3387 55.6601 241.1685 44.3387 55.6601 241.1685 44.3387 578.3223 0.0000 1133.2760 0.0000 1133.2760 0.0000 1133.2760 0.0000 1133.2760 0.0000 1133.2760 0.0000	HUB.3 pre 16.2088 0.9152 96.8785 223.9570 223.9570 223.9570 223.9570 223.9570 233.9570 151.3721	HUB.2 post 29.5041 4.6556 135.1572 12065 0543 307.4912 549.6573 130.2863 130.2863 130.2863 130.2863 130.2863 130.2863 130.2863 130.2863 130.2863 12745 6476 9191.1444 855.3130 1.1297 1274.5476 9191.1444 855.3130 1.1297 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 123.28647 1319.4661 1319.4661 1319.4661 1319.466 13	HUB.3 post 22.2881 4 20317 1 33565 8816 33565 8816 33565 8816 2306 8801 2306 8801 2307 8801 3002 211 1000 211 1000 211000 211 1000 211 10000 211 10000 211 10000 211 10000 211 10000 211 10000 211 10000 211 100000 211 10000000000
EV volume normalization (um Metabolite name LAcetricamities Adente Adente Adente Adente Adente Adente Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Apartagine Circuite Cracitione	Control 1       105,8501       105,8501       280,0382       281,0382       <	Control 2 21.5948 0 0000 5423 0000 5423 0000 551 0372 0 0 0000 2 15 0372 2 8 6671 2 8 8535 4 203 9154 2 8 8535 2 11 400 0 0000 1 8 20 6 6231 2 11 400 0 0 0000 1 8 20 6 6231 2 11 400 1 9 9 8 8 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8	Control 3 26 9255 1 3552 133 9230 3711 1019 62 1875 455 8079 332 9572 24 327 957 24 357 25 555 0594 3 3025 1 9472 9 0 000 9 000 9 0000 9 0000 9 0000 9 0000 9 0000 9 0000 9 0000 9 0000 9 00000 9 00000 9 00000000	HUB-1 pro 0.0000 2.5923 0.6038 0.0000 16.6444 106.8872 0.0000 0.0000 0.0000 0.0000 1.5212 3.96542 23.3485 97.4657 0.00000 0.00000 0.00000 0.0000 0.00000 0.00000 0.00000	HUB2 pre 27.6760 3.4769 92.6609 41.1277 18354129 713.0873 3841 5257 132.4365 24.4387 132.4365 24.4387 132.4365 24.4387 132.4365 24.4387 132.4365 24.4387 132.4365 2117.5776 135.0441 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2533.04413 2535.04413 2535.04413 2555.04413 2555.0120 0.0000	HUB.3 pre 16.2089 0.9152 96.8785 17.87.3108 72.7782 197.5639 191.3221	HUB.2 post 29.5041 455057 155.1572 145 155.1572 145 2006 8446 35.7415 2649.6573 2164.5690 128.7584 120.2675 2764.6474 27764.6474 27764.6474 27764.6474 27764.6474 27764.6474 27764.6474 27764.6474 27764.6474 273.3619 273.	HUB.3 post 22.2881 115.1227 318332414 336334214 336334214 216.270597 100298808 7017462 20.6642 20.6642 20.6642 20.6642 20.6642 20.6645 30.08641 30.0864222 30.0864222 30.0864222 30.08642222322222222222222222
EV volume normalization grm Matabolite name LAcetricamitie Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Cambin	Control 1       105,8201       105,8201       105,8201       105,8201       105,8201       105,8201       104,8201       8577,4115       8577,4115       104,8201       104,2203       104,2203       104,2203       104,2203       104,3203       113,2821       1152,2217       1152,2217       1152,2217       1152,2217       1152,2217       1132,8207       1132,8207       1133,8903       123,826       4558,8482       6,934       22728,875       300,6027       300,6027	Control 2 21.5948 0.0000 51.5948 0.0000 51.0372 0.0000 2.5.0372 2.45.400 2.45.400 2.45.400 2.45.400 2.45.400 2.45.400 0.0000 2.45.400 2.45.400 0.0000 2.5.3752 71.7999 1.008 2.3.9464 5.3.3752 71.7999 1.008 2.3.9464 5.3.3752 71.7999 1.008 2.45.400 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 1.0000 2.1.5464 2.1.5464 1.0000 2.1.7789 2.1.7789 2.1.7789 2.1.778 2.00000 2.1.4400 2.1.4400 2.1.4400 2.1.4400 2.1.4400 2.1.44100 2.1.4400 2.1.4400 2.1.4400 2.1.4400 2.1.4410 2.1.4400 2.1.44100 2.1.4410 2.1.4400 2.1.4410 2.1.4400 2.1.4410 2.1.4410 2.1.4410 2.1.44100 2.1.4410 2.1.4400 2.1.4410 2.1.4400 2.1.44100 2.1.441000 2.1.44100 2.1.441000 2.1	Control 3 26 4255 1 3562 1 3562 1 3112 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	HUE.1 pro 0.0000 2.023 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	HUB2 pre 27.6760 3.4769 30.2600 41.3270 41.3270 41.3270 41.3270 41.3285 41.3285 41.3285 424.1685 5233.0441 573.523 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	HUB.3 pre 16.2088 0.9152 96.4783 17.2088 16.1372 197.6639 16.1372 197.6639 197.6639 197.6639 197.6639 195.2465 1952.4651 202.27762 204.0786 8.9444 4.2.4651 202.7762 8.9444 4.2.4651 202.6785 8.9444 4.2.4651 202.6785 8.9444 4.2.4651 202.6785 8.9444 4.2.4651 202.6785 8.9444 4.2.4651 202.6785 8.9444 195.6635 0.6351 179.3685 6.0351 179.3685 6.0351 179.3685 6.1652 115.6635 0.4314 115.6635 0.455 115.6635 0.04314 115.6635 0.043	HUB.2 poet 29.5041 4.5555 1055157 1055157 1055157 1055157 1055157 1055157 1055157 1055157 1055157 11.25777 11.25777 11.25777 11.25777 11.25777 11.25777 11.2	HUB.3 post 22.2881 4 20317 3 20317 3 20327 3 20327 3 20327 2 2037 2 2
EV volume normalization (um Matabolite name Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Appragine App	Control 1       105,8501       105,8501       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       28,0382       27,033564       390,0303       28,0382       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       290,0303       278,7137       200,0074       200,0074       200,0074       200,0074       200,0074       200,0074       200,0074       200,0075       200,0075       2012,000       200,00007 </td <td>Control 2 21.5948 0.0000 542.0000 542.0000 51.0372 245.4922 0.0000 245.4922</td> <td>Control 3 26 9255 1 3502 1 33 9233 371 1089 52 1878 495 8079 332 9572 1454 9921 124 8071 224 8071 224 8071 224 8071 224 8071 238 4985 109 622 137 824 249 7721 137 0258 0 920 449 7721 137 0258 0 920 440 137 025 0 920 440 130 25 5 1756 139 4657 10 10 10 10 10 10 10 10 10 10 10 10 10</td> <td>HUB-1 pre 8.0000 2.523 0.603 0.600 0.600 0.600 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.5212 3.8652 97.4657 0.0000 0.0000 0.6859 97.4657 0.00000 0.00000 0.0000 0.0000 0.0000 0.00000 0.00000 0.</td> <td>HUB2 pre 27,6760 3,4769 92,6600 41,127 13,0673 3841,527 13,0673 3841,527 13,0673 3841,527 13,0673 3841,527 13,132,4366 44,4387 132,4366 44,4387 132,4366 44,4387 132,4366 41,122,436 10,122,437 10,0000 11,5776 15,0044 7,6000 0,0000 11,32,2700 0,0000 1455,5312 0,0000 1455,5312 0,0000</td> <td>HUB.3 pre 16.2080 0.9152 906.8735 1727.3105 722.7762 127.75633 197.5633 191.3221 191.3221 191.3221 191.3221 191.3221 193.3459 201.778847 203.7702 203.7702 203.7702 204.75784 127.9584 204.421 202.7584 204.421 202.7584 202.7</td> <td>HUB.2 post 29.50/1 455/672 / 12006 804/6 367/412 649.6673 2164.5690 2164.5690 2164.5690 2164.5690 2164.5690 2164.5690 21764.6474 21764.6474 21764.647 21784.6490 211.2297 2133.500 612.0004 0.4077 213.1890 612.0004 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.64000 0.2017 214.64000 0.2017 214.64000 0.2017 214.640000 0.2017 214.6400000000000000000000000000000000000</td> <td>HUB.3 post 22.2881 5.2831 115.1227 31533.5214 33633.5214 336.3315 1029.8808 701.7402 29.2615 326.2615 320.6642 29.2615 3267 3205.6591 30.0673 30.0673 30.0673 30.0673 30.0673 30.0673 30.0673 10.0673 11.0673 11.3603</td>	Control 2 21.5948 0.0000 542.0000 542.0000 51.0372 245.4922 0.0000 245.4922	Control 3 26 9255 1 3502 1 33 9233 371 1089 52 1878 495 8079 332 9572 1454 9921 124 8071 224 8071 224 8071 224 8071 224 8071 238 4985 109 622 137 824 249 7721 137 0258 0 920 449 7721 137 0258 0 920 440 137 025 0 920 440 130 25 5 1756 139 4657 10 10 10 10 10 10 10 10 10 10 10 10 10	HUB-1 pre 8.0000 2.523 0.603 0.600 0.600 0.600 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.5212 3.8652 97.4657 0.0000 0.0000 0.6859 97.4657 0.00000 0.00000 0.0000 0.0000 0.0000 0.00000 0.00000 0.	HUB2 pre 27,6760 3,4769 92,6600 41,127 13,0673 3841,527 13,0673 3841,527 13,0673 3841,527 13,0673 3841,527 13,132,4366 44,4387 132,4366 44,4387 132,4366 44,4387 132,4366 41,122,436 10,122,437 10,0000 11,5776 15,0044 7,6000 0,0000 11,32,2700 0,0000 1455,5312 0,0000 1455,5312 0,0000	HUB.3 pre 16.2080 0.9152 906.8735 1727.3105 722.7762 127.75633 197.5633 191.3221 191.3221 191.3221 191.3221 191.3221 193.3459 201.778847 203.7702 203.7702 203.7702 204.75784 127.9584 204.421 202.7584 204.421 202.7584 202.7	HUB.2 post 29.50/1 455/672 / 12006 804/6 367/412 649.6673 2164.5690 2164.5690 2164.5690 2164.5690 2164.5690 2164.5690 21764.6474 21764.6474 21764.647 21784.6490 211.2297 2133.500 612.0004 0.4077 213.1890 612.0004 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 612.0044 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 213.6200 0.4077 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.6400 0.2017 214.64000 0.2017 214.64000 0.2017 214.64000 0.2017 214.640000 0.2017 214.6400000000000000000000000000000000000	HUB.3 post 22.2881 5.2831 115.1227 31533.5214 33633.5214 336.3315 1029.8808 701.7402 29.2615 326.2615 320.6642 29.2615 3267 3205.6591 30.0673 30.0673 30.0673 30.0673 30.0673 30.0673 30.0673 10.0673 11.0673 11.3603
EV volume normalization (um Matabolite name LAcetricamitie Azenne A	Control 1       Control 1       105,8201       105,8201       105,8201       105,8201       105,8201       105,8201       8577,4115       8577,4115       101,8203       1040,2803       1040,2803       1040,2803       1041,475       735,3564       105,8203       103,8203       103,8203       103,8203       103,8203       103,8203       103,8203       103,8203       103,8203       104,823,9279       0,0004       205,823,9279       0,0004       205,823,9279       0,0004       205,823,9279       205,823,9279       205,823,9279       205,823,9279       205,823,9279       205,823,9279       205,823,9279       205,924,923,929       205,924,923,929       205,924,923,929       207,8275,8278       205,924,929       207,8275,8278	Control 2 21.5948 0.0000 51.5948 0.0000 51.0372 0.0000 245.4000 245.4000 245.4000 245.4000 245.4000 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 21.5948 20.0000 21.5948 20.0000 21.5948 20.0000 21.4002 21.4002 21.4002 21.4002 21.4002 21.40000 21.4000 21.4000 21.4000 21.4000 21.4000	Control 3 26 4255 1 3502 1 3502 1 3112 1 3112 1 3112 1 312 1 31 1 31	HUE.1 pro 0.0000 2.023 0.0000 0.00	HUB2 pre 27.6760 32.6600 41.3270 41.3270 41.3270 41.3270 424.1685 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.1324 300.17345 300.17345 300.17345 300.17345 300.173450	HUB.3 pre 16.2088 0.9152 96.4785 16.3088 10.102 197.5639 10.1372 197.5639 10.1372 197.5639 10.1372 197.5639 10.1372 195.2465 1952.4651 20.2222 24.4276 8.9444 4.2.4651 20.2786 8.9444 4.2.4651 20.2786 8.9444 4.2.4651 20.2786 8.9444 4.2.4651 20.2786 8.9444 4.2.4651 20.2786 8.9444 1952.4653 1952.4552 1952.45	HUB.2 poet 29.5041 4.5555 19.505159 19.505159 19.505159 21.515555 21.5155555 21.515555 21.515555 21.515555 21.515555 21.5155	HUB.3 post 22.2881 4 20317 1 20317 1 20317 1 20317 1 20317 2 2
EV volume normalization (um Matabotite name Acenies Acenies Acenies Acenies Acenies Acenies Acenies Acenies Aparagine Appratine Appratine Appratine Appratine Appratine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Carnosine Containe Carnosine Carnosine Containe Carnosine Carno	Control 1       105,8501       105,8501       287,038,0       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4       287,030,007,4	Control 2 21.5948 0 0000 190.9857 51.0372 0000 51.0372 245.4020 0 0000 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 245.4020 250.772 0.00000 0.0000 0.0000 0.00000	Control 3 26 9255 1 3552 1 33 9233 377 1089 6 21875 4 955 8079 3 323 9572 1 444, 9521 7 445, 8079 3 323 9572 2 4 9577 2 24 9577 2 25757 2 257577 2 2575777 2 257577 2 257577 2 2575777 2 25757777 2 25757777777777	HUB-1 pro 8.0000 2.923 0.6338 0.0000 16.6444 105.8572 0.0000 16.6444 105.8572 0.0000 1.5212 3.95424 2.34857 0.0000 1.5212 3.95424 0.0000 0.6515 0.00000 0.00000 0	HUB2 pre 27.6760 3.4789 92.6600 41.3270 1835 4129 713.0673 3841.5271 44.3270 132.4366 44.3387 132.4366 44.3387 132.4366 44.3387 132.4366 44.3387 132.4366 44.3387 132.4366 45.3373 1078.6229 373.1524 1078.6229 1175.776 136.624 73.6000 1135.2760 0.0000 1135.2760 0.0000 1135.2760 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 0.0000 1145.5312 1.014 1.654.7750 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.7500 1.555.75000 1.555.75000 1.555.75000 1.555.75000 1.555.75000 1.555.75000 1.555.7500000000000000000000000000000000	HUB.3 pre 16.2080 0.9152 96.8785 1747 3160 22.7782 197.5633 191.3721	HUB.2 post 29.50/1 4.5566 155.1572 155.1572 155.1572 155.1572 155.1572 155.1572 155.1572 155.5731 30.5653 102.4076 2764.6473 102.5531 2744.6474 275.5315 11.277 133.5285 11.2774 4.3755 11.277 133.5285 11.277 133.3819 213.1895 123.3819 213.1895 123.3819 213.2856 1.327	HUB.3 post 22.2881 5.2835 115.122 31833.8514 34.6315 2137.0257 2137.0257 220.6042 22.2015 326.6352 220.6042 22.2015 326.60927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3206.69927 3213.410727 313.410727 313.410727 313.410727 313.410727 313.410727 329.5757 329.5757 329.5757 329.5757 329.5757 329.575775
EV volume normalization grm Matabolite name LAcetricamite Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adenine Adamote Adamo	Control 1       Control 1       105,8501       105,8501       105,8501       105,8501       105,8501       8577,4115       8577,4115       8757,4115       751,5640       900,2030       910,2030       910,2030       910,2030       914,2031       1130,1150       920,2030       44964,8995       1132,221,3275       0,0000       224,2339,27137       840,0734       1133,9603       122,222,2330       9,054,7137       9,054,877,113       9,050,807       5,0178       8,0073       1133,9603       1272,8275,876       300,0507       300,0507       300,0507       300,0507       300,8074       300,8074       300,8074       300,8074       300,8074       300,8074       300,8074       300,8074       300,8074 <td>Control 2 21.5948 0.0000 51.5948 0.0000 51.0372 0.0000 245.4000 245.4000 245.4000 245.4000 245.4000 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 23948 53.3792 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 0.9325 0.0000 0.935 0.00000 0.935 0.00000 0.935 0.00000 0.935 0.000000 0.935 0</td> <td>Control 3 26 4255 1 3502 371100 83 7186 62 1875 455 8079 23 7186 62 1875 455 8079 22 3717 345 8057 22 45 8079 22 45 8079 20 45 80 5 3005 8 5 8025 20 45 8057 20 45 451 20 45 8057 20 45 451 20 45 8057 20 45 451 20 45 8057 20 45 8057</td> <td>HUE.1 pro 0.0000 2.023 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0</td> <td>HUB2 pre 27.6760 32.76769 32.6400 41.3270 41.3270 41.3270 55.6601 241.1625 5530.041 3241.1685 5530.041 3241.1685 5530.041 3241.1685 3233.0541 323.31544 32530.0000 152.1511 107.0194 300.17344 300.17344 300.17344 300.17344 300.17344 300.17444 300.1</td> <td>HUB.3 pre 16.2088 0.9152 96.6762 97.6539 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5635 107.575</td> <td>HUB.2 post 29.5041 45556 10000597 10000597 10000597 118000597 118000597 1180005 118005 1180000</td> <td>HUB.3 post 22.2881 4.28317 33565.8815 33565.8815 33565.8815 230.6845 230.6845 230.6451 230.6451 230.6451 230.6451 230.6451 230.6654 230.6654 230.6654 330.6554 230.6654 230.6654 230.6654 230.0454 230.0454 230.258 245.2575 250.0454 200.258 2151.0673 200.457 213.04777 213.04777 213.04777 213.04777 213.04777 213.047777 213.04777777777777777777777777777777777777</td>	Control 2 21.5948 0.0000 51.5948 0.0000 51.0372 0.0000 245.4000 245.4000 245.4000 245.4000 245.4000 245.400 245.400 245.400 245.400 245.400 245.400 245.400 245.400 23948 53.3792 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 211.4002 44.1105 0.0000 0.9325 0.0000 0.935 0.00000 0.935 0.00000 0.935 0.00000 0.935 0.000000 0.935 0	Control 3 26 4255 1 3502 371100 83 7186 62 1875 455 8079 23 7186 62 1875 455 8079 22 3717 345 8057 22 45 8079 22 45 8079 20 45 80 5 3005 8 5 8025 20 45 8057 20 45 451 20 45 8057 20 45 451 20 45 8057 20 45 451 20 45 8057 20 45 8057	HUE.1 pro 0.0000 2.023 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	HUB2 pre 27.6760 32.76769 32.6400 41.3270 41.3270 41.3270 55.6601 241.1625 5530.041 3241.1685 5530.041 3241.1685 5530.041 3241.1685 3233.0541 323.31544 32530.0000 152.1511 107.0194 300.17344 300.17344 300.17344 300.17344 300.17344 300.17444 300.1	HUB.3 pre 16.2088 0.9152 96.6762 97.6539 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5639 107.5635 107.575	HUB.2 post 29.5041 45556 10000597 10000597 10000597 118000597 118000597 1180005 118005 1180000	HUB.3 post 22.2881 4.28317 33565.8815 33565.8815 33565.8815 230.6845 230.6845 230.6451 230.6451 230.6451 230.6451 230.6451 230.6654 230.6654 230.6654 330.6554 230.6654 230.6654 230.6654 230.0454 230.0454 230.258 245.2575 250.0454 200.258 2151.0673 200.457 213.04777 213.04777 213.04777 213.04777 213.04777 213.047777 213.04777777777777777777777777777777777777
EV volume normalization (um Matabotite name Acenies Acenies Acenies Acenies Acenies Acenies Acenies Acenies Acenies Acenies Appragine Appragi	Control 1       105,8501       105,8501       105,8501       105,8501       105,8501       105,8501       104,2503       104,2503       104,2503       104,2503       104,2503       104,2503       104,2503       104,2503       104,2503       1176,8934       1176,8934       1176,8934       1176,8934       1176,8934       1176,8934       1183,823,9279       0,3333       1152,5217       1152,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1132,5217       1134,5934       1144,8873       1155,5254 <td>Control 2 21.5948 0 0000 193.9857 193.9857 1015 6790 0 0000 21.5362 246.4000 247.1399 0.0000 0.</td> <td>Control 3 26 9255 1 3562 1 3562 1 33 9233 377 1788 6 21 1875 23 1788 6 21 1875 23 1788 6 21 1875 23 1878 23 2977 24 5675 24 5675 22 4 5675 23 1924 23 1924 24 5655 0 0000 0 0247 1 3 1000 0 0247 1 3 1000 0 0247 1 3 1000 0 024 1 3 10000 0 024 1 3 10000 0 024 1 3 10000000000000000000000000000000000</td> <td>HUB-1 pro 8.0000 2.923 0.633 0.000 16.844 19.5872 0.0000 16.844 19.5872 0.0000 1.5212 2.4467 0.0001 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000 0.00000 0.00000 0.00000000</td> <td>HUB2 pre 27.6760 3.4789 92.6609 41.3270 1835 4129 713.0673 3841.5271 44.3270 132.41665 241.16555 241.16555 241.16555 241.165555 241.1655555 241.1655555555555555555555555555555555555</td> <td>HUB.3 pre 16.2080 0.9152 96.8785 1747.3170 22.7782 197.5633 191.32711 423.4564 191.32721 423.4564 41.33221 423.4564 42.4561 32.4782 42.4561 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.7052 11.5063 51.5052 52.5052</td> <td>HUB.2 post 29.50/1 4.6505 105.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 125.6731 102.4076 11.227 115.205 11.227 1.</td> <td>HUB.3 post 22.2881 15.227 115.227 115.227 115.227 115.227 23.46315 24.6315 25.8691 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.9705 21.91425 25.96042 25.9575 21.91425 25.95755 25.95755 25.95755 25.95755 25.95755 25.95755 25.957555 25.9575555555555555555555555555555555555</td>	Control 2 21.5948 0 0000 193.9857 193.9857 1015 6790 0 0000 21.5362 246.4000 247.1399 0.0000 0.	Control 3 26 9255 1 3562 1 3562 1 33 9233 377 1788 6 21 1875 23 1788 6 21 1875 23 1788 6 21 1875 23 1878 23 2977 24 5675 24 5675 22 4 5675 23 1924 23 1924 24 5655 0 0000 0 0247 1 3 1000 0 0247 1 3 1000 0 0247 1 3 1000 0 024 1 3 10000 0 024 1 3 10000 0 024 1 3 10000000000000000000000000000000000	HUB-1 pro 8.0000 2.923 0.633 0.000 16.844 19.5872 0.0000 16.844 19.5872 0.0000 1.5212 2.4467 0.0001 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.0000 1.5212 2.4467 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000 0.00000 0.00000 0.00000000	HUB2 pre 27.6760 3.4789 92.6609 41.3270 1835 4129 713.0673 3841.5271 44.3270 132.41665 241.16555 241.16555 241.16555 241.165555 241.1655555 241.1655555555555555555555555555555555555	HUB.3 pre 16.2080 0.9152 96.8785 1747.3170 22.7782 197.5633 191.32711 423.4564 191.32721 423.4564 41.33221 423.4564 42.4561 32.4782 42.4561 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.4051 32.4052 32.7052 11.5063 51.5052 52.5052	HUB.2 post 29.50/1 4.6505 105.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 115.1672 125.6731 102.4076 11.227 115.205 11.227 1.	HUB.3 post 22.2881 15.227 115.227 115.227 115.227 115.227 23.46315 24.6315 25.8691 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.96042 25.9705 21.91425 25.96042 25.9575 21.91425 25.95755 25.95755 25.95755 25.95755 25.95755 25.95755 25.957555 25.9575555555555555555555555555555555555
EV volume normalization grm Matabolite name LAcetricamite Adentine Adentine Adentine Adentine Adentine Adentine Adantonic Adantonic Adantonic Adantonic Adantonic Adantonic Adantonic Adantonic Caractivic C	Control 1       105,8501       105,8501       105,8501       105,8501       105,8501       105,8501       8577,4115       877,115,870       56,8933       104,2605       56,8933       104,2605       51,801,870       73,3564       140,150       90,2030       44964,8955       82,051,873       840,673       113,802       272,873,894       840,073       113,802       28,8373       28,8373       28,40,734       112,822,7137       84,073       113,802       27,834       83,8687       113,802       83,897       300,5027       84,897       44,897       44,897       44,897       44,857       44,857       44,857       44,857       44,857       34,858	Control 2 21.5948 0.0000 51.5948 0.23.5048 0.0000 21.5962 0.25.0000 24.5002 24.5400 24.5402 24.5400 24.5402 24.5400 24.5402 25.3792 21.5402 22.5402 23.5402 25.5202 25.5202 25.5202 25.5202 25.5202 25.5202 25.5202 25.5202 25.5402	Control 3 26 4255 1 38502 1 38502 1 38502 1 38502 1 31512 1 2151 2 3151 2 3151 3151 315151 315151 315151 315151 31515151	HUE.1 pro 0.0000 2.023 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 1.012 2.3486 92.487 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00	HUB2 pre 27.6760 3.4769 92.6607 92.6607 93.2.6007 94.0	HUB.3 pre 16.2089 0.9152 98.6768 16.2089 16.2089 16.2089 16.2089 17.2089 16.2089 19.2089 10	HUB.2 post 29.5041 485856 10056.691 10056.694 36.7415 21.5056.694 11.51526.5731 20.565731 20.565731 20.565731 20.565731 20.70716 21.51270	HUB.3 post 22.2881 72.2881 72.2881 73.257 73.257 70.258 73.257 70.258 71.27.057 72.050 71.27.057 72.0500 72.0500 72.0500 72.0500 72.0500 72.05000 72.0500000000000000000000000000000000000
EV volume normalization (um Matabotite name Actention Actention Actention Activity (Activity) Attention Attention Attention Attention Appendie activity Appendie activity Ap	Control 1       105 8501       105 8501       105 8501       105 8501       105 8501       104 8501       877191       877191       877191       877191       877191       877191       877191       877191       877191       877191       877191       87719       87819 <	Control 2 21.5948 0 0000 193.9857 51.0372 51.0372 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 245.4000 20.0073 0.0000 0.0000 211.4000 0.00000 0.0000 0.00000 0.00000 0.00000 0.0000 0	Control 3 26 9255 1 3562 1 3562 1 33 9233 2 37188 6 21875 4 455.8079 3 32 9572 4 455.8079 3 32 9572 4 455.8079 3 32 9572 2 4 5679 2 2 4 5575 5 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	HUB-1 pro 8.0000 2.923 0.633 0.0000 16.6444 19.5872 0.0000 16.6444 19.5872 0.0000 1.5212 2.4857 10.0859 0.0001 10.0327 10.0859 0.0001 10.0327 10.0859 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.63468 0.0000 0.53457 0.0000 0.63468 0.0000 0.53457 0.0000 0.53457 0.0000 0.63468 0.0000 0.53457 0.00000 0.00000 0.00000 0.00000000	HUB2 pre 27.6760 3.4759 50.8600 50.821002 41.3270 241.1207 241.1207 241.1207 241.1651 122.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 44.4387 132.4366 1078.0223 241.1651 132.4366 0.0000 1117.5776 13.6443 0.0000 1113.2780 0.0000 0.0000 113.6443 0.0000 113.2780 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	HUB.3 pre 16.2088 0.9152 96.8745 170.3172 197.5639 191.322	HUB.2 post 29.50/1 4.65056 105.1672 / 11 105.0672 / 11 105.0672 / 11 105.0674 105.7415 207.6714 205.6731 102.4076 207.6714 205.6731 102.4076 207.6714 205.6731 102.4076 207.6714 205.6731 207.8714 205.6731 207.8714 205.6731 207.8714 2	HUB.3 post 22.2881 15.1227 115.1227 115.1227 115.1227 115.1227 115.1227 115.1227 215.1257 215.1257 215.1257 215.1257 215.1257 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 220.6042 20.0241 2
EV volume normalization grm Matabolite name LAcetricamitient Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Azenne Camoline Camoline Camoline Camoline Camoline Camoline Camoline Creatine Creatine Creatine Creatine Creatine Creatine Creatine Creatine Creatine Camoline Camoline Glucturothe Gluct	Control 1       105,8501       105,8501       105,8501       105,8501       105,8501       105,8501       104,8501       8577,4115       8577,4115       101,820,800       900,2030       910,2030       910,2030       920,2030       44964,8995       820,8731       1824,8373       1834,8373       7433,856       1147       62,0518       840,0734       1139,8902       277,873       858,8770       1139,8902       87,984       858,8770       30,05027       113,9802       87,984       8272,8778       113,9802       87,984       8272,8778       113,9802       87,984       8272,8778       113,9802       87,984       87,973       113,9803       88,8770       30,9027       15,	Control 2 21.5948 0.0000 51.5948 22.5948 22.5948 22.5942 0.0000 21.5962 24.5400 24.5402 24.5400 24.5402 24.5400 25.5372 24.5400 20.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.1402 44.1105 0.0000 21.53782 0.0000 21.1402 44.1105 0.0000 21.1402 44.105 0.0000 1.53782 0.0000 0.0000 1.53782 0.0000 21.53946 0.0000 21.53782 0.0000 21.53946 0.0000 21.53782 0.0000 0.0000 1.53782 0.00000 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000 0.00000000	Control 3 26 225 1 3802 3 3025 1 3802 1 381 1 3812 1 381 1 381	HUE.1 pro 0.0000 2.023 0.00000 0.00000 0.0000 0.0000 0.00000 0.00000000	HUB2 pre 27.6760 3.4769 92.6607 43.276769 92.6607 43.2270 43.2270 43.3270 55.6001 24.1.625 55.30.441 373.5084 373.5084 373.5084 373.5084 373.6084 3	HUB.3 pre 16.2088 0.9152 16.2088 16.2089 16.2089 16.2089 16.2089 17.2089 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 19.2689 27.758 28.9444 24.451 27.758 24.27788 24.277888 24.277888 24.277888 24.27788 24.27	HUB.2 post 29.5041 485856 113056.0048 36.7415 215056.591 2154.5550 2154.5550 11377.6714 2746.478 9191.1444 805.1302 277.6714 2746.478 9191.1444 805.1302 277.6714 805.5130 1137735 2.5827 2739.5265 1137735 2.5827 2139.526 2.5827 2.31.899 6.72.0004 0.4077 2.333.51899 6.72.0004 0.4077 2.333.51899 6.72.0004 0.4077 2.333.51899 6.72.0004 0.4077 2.333.51899 2.33.1899 6.72.0004 0.4077 2.333.51899 1.333.3 3.9391 6.75.7894 1.4333.3 3.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4333.3 2.9391 6.75.7894 1.4335 2.4456 1.4355 1.4355 1.4355 1.4355 1.4355 1.4355 1.4355 1.4355 1.4355 1.4455 1.4555 1.4555 1.4555 1.4555 1.4455 1.45555 1.45555 1.45555 1.45555 1.45555 1.455555 1.4555555 1.45555555555	HUB.3 post 22.2881 6 28317 33558 8815 33558 8815 33558 8815 33558 8815 230 6942 220 6942 230 6949 31628 654 31628 654 30 046 30
EV volume normalization (um Matabotite name Aceniae Aceniae Aceniae Aceniae Aceniae Aceniae Aceniae Aceniae Aceniae Appragine Appra	Control 1       Control 1       105 8501       105 8501       105 8501       105 8501       105 8501       877 4115       877 4115       877 4115       877 4115       877 4115       877 4115       877 4115       877 4115       877 4115       877 4115       877 415       878 43850       978 3480       90 0000       90 0000       91 152 5217       54 4527       91 152 5217       92 43 304       90 0000       2243 3304       91 122 243 3304       91 122 205       4458 5485       93 3827       93 15 3827       93 16 32 244       93 382       93 16 32 244       93 382       93 18 3418       93 382       93 382       93 382       93 382       93 382       93 382       93 382	Control 2 21.5948 0 0000 193.9857 193.9857 1015 6790 0 0000 21.5302 35.0372 246.4000 246.4000 245.4000 246.4000 2.15.302 36.671 120.873 0 0000 0 00000 0 000	Control 3 26 9255 1 3562 1 33 9230 27 37188 62 1875 455.8079 332.9572 445.8079 332.9572 445.8079 332.9572 445.8079 22.3717 38.4959 109.0680 41318 0.6247 10.1080 11318 0.6247 11318 0.6248 0.3257 0.5357 0.5358 0.5478 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.5488 0.54888 0.5488 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.548888 0.5488888 0.5488888 0.5488888 0.5488888 0.54888888888888888888888888888888888888	HUB-1 pro 8.0000 2.923 0.6033 0.0000 16.9434 109.5872 0.0000 16.9444 109.5872 0.0000 1.0337 0.0000 1.0337 0.0000 1.5212 2.4857 10.0859 0.0561 0.0000 0.4000 0.0000 0.4000 0.0000 0.0000 0.0000 0.0152 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000	HUB2 pre 27.6760 3.4759 52.6600 41.3270 1535 4129 713.0873 4129 713.0874	HUB.3 pre 16.2089 0.9152 906.9745 1752.9977 22.7762 197.6533 191.37212 193.76533 191.37212 193.76533 191.37212 22.7762 5.0307 69.1075 69.1075 69.1075 1952.4983 618.276784 1.152.24651 5.24655 5.24655 5.25655 5.25555 5.2555 5.2555 5.2555 5.	HUB.2 post 29.5041 4.50566 195.1672 195.1672 195.1672 195.1672 195.1672 195.1672 205.6731 30.5633 102.4076 102.4076 102.4076 11.1297 213.1695 11.1297 213.1695 11.227 319.4561 12.23.3619 0.0777 485.7042 22.33.3619 0.0777 485.7042 20.4151	HUB.3 post 22.2881 115.221 315.221 315.221 315.221 315.221 32.251 32.551 22.251
EV volume normalization (um Matabolite name LAcetricamitie name Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Constant Amp Amp Appendia Add Appendia Add Add Add Add Add Add Add Add	Control 1       105,8501       105,8501       105,8501       105,8501       105,8501       104,8501       8577,4115       877,8115       8757,8115       900,200,200       901,200,200       901,200,200       902,200,200       903,200,200       904,200,200       904,200,200       905,200,200       905,200,200       906,200,200       906,200,200       906,200,200       906,200,200       906,200,200       906,200,200       906,470,200       906,470,200       906,470,200       907,200,200       908,6970,200       113,9800,200       907,200,200       908,6970,200       150,1050       150,2050       150,2050       150,2050       150,2050       150,2050       150,2050       150,2050       150,2050       150,2050       150,2050	Control 2 21,5948 0,0000 21,5948 0,0000 51,0372 0,0000 21,5423,5048 0,0000 21,5423 0,0000 24,5400 24,5400 24,5400 12,5325 426,9154 12,3946 53,3792 21,1400 21	Control 3 26, 8255 1,3602 1,3602 1,3602 1,3711,610 53,718 62,1875 448,8079 22,3717 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,154,952 1,155 1,1	HUE.1 pro 0.0000 2.023 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	HUB2 pre 27.6760 3.4769 90.2660 41.3270 41.3270 55.6601 241.3270 55.6601 241.3270 55.6601 241.3270 55.6601 241.3270 55.30.441 878.3223 773.1594 573.2023 773.1594 573.2023 773.8280 773.8290 773.8280 773.8290 773.7290 773.7290 773.7290 773.7290 773.7290 773.7290 774.7270 774.7270 774.7270 774.7270 774.7270 774.7270 774.7270 774.7270 774.7270 774.7270 774.77700 774.77700 774.77700 774.77700 774.77700 774.77700 774.77700 774.7	HUB.3 pre 16.2089 0.9152 16.2089 16.2089 16.2089 16.2089 16.2089 17.2089 16.2089 16.2070 17.2089 19.2489 11.2489 11	HUB.2 post 29.5041 4.8585 29.5041 4.8585 4.8585 4.85749 1.2006.6911 305.0448 30.7415 2006.6731 30.2683 11.8724 2745.5780 11.8701 52.6827 312.46476 9191.1444 89.3130 27.78514 27.8574 11.8701 52.6827 312.4657 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.4577 312.45777 312.45777 312.45777 312.457777 312.457777 312.4577777 312.45777777777777777777777777777777777777	HUB.3 post 22.2881 6.28317 33555.8815 33555.8815 33555.8815 23.6315 23.6315 22.50.6442 22.50.6442 22.50.6442 22.50.6442 22.50.6442 22.50.6442 22.50.6442 22.50.6442 22.50.6442 23.05.66441441 23.05.66441444444444444444444444444444444444
EV volume normalization (um Matabotite name Lacktry(camities Adenine Adenine Adenine Adenine Adenine Adaptage Alanto	Control 1       Control 1       105,8501       105,8501       105,8501       105,8501       807,74115       877,4115       877,4115       877,4115       75,35564       93,350,201,4976       73,3556       73,3556       1175,884       490,2030       4496,4895       1152,527,375       540,0734       1152,527,375       576,893       840,0734       1152,527,375       576,893       840,0734       1152,527,375       300,0502       579,892       579,892       300,5027       300,5027       300,5027       53,0178       53,0573       53,0587       15,35877       15,35877       15,35877       15,35877       15,35877       15,35877       15,35877       15,35877       15,35877       15,35877	Control 2 21,5948 0 0000 1939857 19	Control 3 26 225 1 3502 1 33 223 1 33 223 23 25 23 25 24 55 25 27 25 27 27 25 27 27 27 25 27 27 27 25 27 27 27 27 27 27 27 27 27 27 27 27 27 2	HUE 1 pro 8.0000 2.023 2.023 0.0000 16.444 109.5872 0.0000 16.444 109.5872 0.0000 1.5212 2.4857 10.0327 10	HUB2 pre 27.6760 3.4769 30.2600 41.3270 41.3270 41.3270 41.3270 41.324 41.325 424.1685 424.337 132.4366 424.337 132.4366 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.337 424.1685 424.2785 4	HUB.3 pre 16.2080 0.9152 96.4763 176.2087 176.2087 177.3633 181.372197 22.7762 22.7762 22.7762 22.7762 23.7762 23.7762 24.7762 5.0307 195.2465 618.24651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4651 32.4655 32.4651 32.4655 32.4655 32.4655 32.4655 32.4655 32.4655 32.77682 115.6355 0.4314 37.68552 115.6535 0.4314 32.6655 111.64555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.645555 111.6455555555 111.645555555555555555555555555555555555	HUB:2 post 29:5041 29:5041 19:51572 19:51572 29:5045 29:5045 20:5745 20:57452 20:57573 20:5553 20:575475 20:5757475757 20:5757777777777777777777777777777777777	HUB.3 post 22.2881 5 23327 3 25.2881 3355.8815 3355.8815 3355.8815 229.8603 229.5615 220.6642 229.2615 220.6642 229.2615 320.6642 230.66843 3.0677 230.66843 3.0677 230.66843 3.0673 200.461 3.0673 200.461 3.0673 3.0684 3.0273 3.0273 3.0273 1.0601 4.66.8932 3.0387 1.01345 1.001 4.665 3.0273 3.0273 1.001 4.6553 1.001 1.01345 1.0235 1.0237 3.0255 1.0235 1.0235 1.0725 3.07550 3.07255 3.07555 3.07755 3.07555555 3.07555555555555555555555555555555555555
EV volume normalization (um Matabolite name LAcetricamitie name Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Acetrine Canadian Allanton Allanton Allanton Allanton Allanton Allanton Allanton Allanton Allanton Allanton Allanton Canadia Canadia Caratine Creatine Creatine Creatine Creatine Creatine Creatine Creatine Countine Caratine C	Control 1       105 8601       105 8601       105 8601       105 8601       105 8601       8577 4115       8757 4115       8757 4115       8757 4115       900 2005       860 873       901 2005       902 2005       903 2005       903 2005       904 2005       905 2005	Control 2 21,5948 0,0000 21,5948 0,0000 21,5942 0,0000 21,5423,5048 246,4000 21,5325 426,5154 246,400 21,5325 426,9154 122,9325 122,9325 122,9325 122,9325 123,9355 123,9325 123,9355 125	Control 3 26, 8255 1,3602 1,3602 1,3602 1,3711,610 53,718 62,1875 488,8079 22,3737 1,154,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,952 1,155,955 1,155,952 1,155,955 1,155,955 1,155,955 1,155,955 1,1	HUE.1 pro 0.0000 2.023 2.023 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 4.0000 0.0000 0.0000 4.0000 0.0215 0.0223 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	HUB2 pre 27.6760 3.4766 9.5660 9.5660 9.5660 1.327 9.5660 1.327 9.5324 1.3270 9.5330410000000000000000000000000000000000	HUB.3 pre 16.2088 0.9152 16.2088 16.2089 16.2089 16.2089 16.2089 17.2089 19.2489 11.3448 27.0166 27.0166 27.0166 27.0166 27.0389 0.6229 0.6229 0.6228 0.6229 11.1004 37.6689 11.1004 11.100	HUB.2 post 29.5041 48856 21.5006 (301) 2006 (301) 2006 (301) 2006 (301) 2006 (301) 2006 (301) 2006 (301) 2006 (301) 2016	HUB.3 post 22.2881 728377 33555 8815 33555 8815 33555 8815 33555 8815 233555 8815 220,0042 220,014 220,014 220,014 220,014 220,014 220,014 220,014 220,014 220,014 220,014 220,014 230,004 230,004 230,004 230,004 230,004 230,004 230,004 230,004 20,0

EV number normalization (fmol/million particles)									
Metabolite name	Control 1	Control 2	Control 3	HUB.1 pre	HUB.2 pre	HUB.3 pre	HUB.2 post	HUB.3 post	
L-Acetylcarnitine	0.3825	0.1136	0.1165	0.0000	0.1539	0.0886	0.1783	0.1171	
Adenine	0.0000	0.0000	0.0059	0.0155	0.0193	0.0050	0.0281	0.0330	
Adenosine	1.0320	1.0521	0.7957	0.0030	0.5153	0.5296	0.9379	0.6048	
Alanine	31.0562	28,5334	16.0555	0.0000	31.6918	9.5521	72.5778	176.2738	
Allantoin	31.6879	0.0000	0.4055	0.0000	2.0137	1.2517	21,5500	99.4611	
AMP	0.2057	0.2685	0.2690	0.0994	0.2298	0.1245	0.2221	0,1819	
Arginine	3,7665	5.3446	2.1450	0.6541	10.2290	1.0800	5.4251	5.4101	
Asparagine	2.3306	0.0000	1.4405	0.0000	3,9655	0.8822	3.3227	3.6863	
Aspartic acid	11.0918	18.5475	6.2946	0.0000	20.2506	2.3368	13.0843	11.1736	
Asymmetric dimethylarginine	0.9468	0.0000	0.0528	0.0000	0.3090	0.0730	1.2017	3.2604	
Carnitine	2 6625	1,2965	0.9716	0.0599	1.3411	0 7393	1 5509	1.3165	
Carnosine	0.1861	0.1133	0.0968	0.0000	0.2471	0.0275	0.1830	0.1537	
Choline	0.6397	0.1929	0.1666	0.0091	0.7365	0.3778	0.6190	1.9035	
Citrulline	1 5575	1 4145	0.4719	0.2367	5 9949	0.3930	1 3762	1 5217	
Creatine	3.5852	2,2460	2.1189	0.1394	2.0751	1.5513	16,7117	49 4797	
Creatinine	162 8033	7 4780	5 7025	0.5520	14 0863	10.6738	55 5585	167 2006	
L-Cystathionine	67 1020	0.6318	0.2900	0.1080	4 8844	3,3796	5 2306	12 1279	
Decenovicernitine	0.0034	0.0000	0.0027	0.0003	0.0000	0.0012	0.0068	0.0161	
D-Ribose 5-phosphate	28 3987	31 5677	27 5374	0.5818	11 7759	13,4355	16 5599	17 1573	
Eolic acid	0.0221	0.0652	0.0165	0.0000	0.0868	0.0070	0.0724	0.0473	
Commo Olutomideusteine	0.0247	0.0002	0.0397	0.0417	0.4008	0.0490	0.2170	0.1506	
Gamma-Glotamyicysteme	2.4002	0.2000	0.0307	0.0000	0.4090	0.0405	1,0210	2,0952	
Ciutamia asid	4.1700	5.6274	4.3840	0.4070	6 2022	1 7712	4.2014	2 5141	
Clutamine	5 7744	0.0000	4.2045	0.4075	0.0000	1.2420	9.0044	3.0141	
Clutathine	1.0001	1.1124	0.0000	0.0000	1.0000	0.2104	1 2997	4.1500	
Giucadrione	1.0091	0.0004	0.5017	0.2032	1.0000	0.3154	1.2007	1.1157	
Guanicoacetic acid	3.0416	0.2021	0.1455	0.0000	0.0501	0.1500	4.0021	0.0050	
Hexanoyicamitine	0.0000	0.0000	0.0006	0.0001	0.0007	0.0005	0.0025	0.0056	
Hippuric acid	8,1188	1.0366	0.7492	0.0955	2.1698	2.0054	2.7728	4.4475	
4-Hydroxyproline	3.1448	4.7863	1.4064	0.6339	4.2319	0.6310	3.7503	4.4688	
Hypoxantnine	0.1979	0.0000	1.0811	0.0064	0.0000	0.1477	0.1228	0.1573	
IMP .	4.1058	9.5995	2.4264	2.0974	8.0959	0.9807	6.4297	5.4093	
inosine	0.0445	0.0248	0.2817	0.0000	0.0000	0.0330	0.0219	0.0725	
Inositol	16.0065	0.0000	8.6807	0.0000	26.9313	4.1993	0.0000	17.0111	
Isobutyryi-L-carnitine	0.0251	0.0076	0.0138	0.0003	0.0057	0.0034	0.0111	0.0209	
Isovalerylcarnitine	0.0318	0.0076	0.0184	0.0001	0.0082	0.0045	0.0199	0.0756	
Kynurenic acid	8.2285	0.0052	0.0224	0.0017	0.2544	0.2961	4.0850	13.2333	
Leucine	1.0880	0.0000	0.6034	0.0000	3.6412	0.6290	2.0120	0.9255	
1-Methylhistamine	0.0182	0.0045	0.0039	0.0000	0.0037	0.0024	0.0288	0.0739	
NAD	0.5982	0.4342	0.4786	0.0498	0.4443	0.2060	0.4791	0.5267	
Niacinamide	0.1626	0.1221	0.1612	0.0065	0.1111	0.1019	0.0651	0.0579	
Ornithine	161.3552	346.7555	70.7224	30.0370	313.4100	40.5519	234.1301	204.8314	
Orotic acid	0.3030	0.3330	0.1179	0.0000	0.4556	0.0541	0.4767	0.4050	
Pantothenic acid	0.0556	0.0461	0.0131	0.0000	0.0000	0.0176	0.0000	0.0303	
Propionylcarnitine	0.0544	0.0096	0.0137	0.0004	0.0120	0.0061	0.1359	0.3920	
4-Pyridoxic acid	0.0161	0.0296	0.0015	0.0001	0.0020	0.0042	0.0018	0.0040	
Serine	12.3764	36.4988	8.1677	5.6118	41.9404	3.7989	25.7506	18.7608	
Sorbitol	31.7359	0.0000	0.0000	0.0000	23.7865	5.1530	0.0000	42.3114	
Spermidine	0.2284	0.3383	0.1398	0.2643	0.2913	0.1360	0.2130	0.2044	
Succinic acid	0.0000	1.1442	0.0000	0.0000	2.6374	0.3639	9.3535	27.7761	
Sucrose	1.5987	6.7464	0.1667	0.0000	3.3630	0.5240	0.0000	1.6159	
Symmetric dimethylarginine	0.6882	0.0000	0.0837	0.0000	0.0000	0.0845	0.4395	1.0978	
Taurine	24.9928	4.3165	3.5640	0.0000	5.8605	2.9037	15.2605	39.6442	
Threonine	0.0000	0.0000	0.0000	0.0000	3.9752	0.3801	2.6166	5.4363	
Trimethylamine N-oxide	3.4313	0.1253	0.0736	0.3415	1.0073	0.8432	1.6953	7.6334	
Xanthine	0.0410	0.0175	0.1107	0.0043	0.0305	0.0216	0.0271	0.0292	

Figure S2. Heatmaps of the metabolite levels in urinary EVs after normalization to EV-derived parameters.

Normalization to CD9 optical density (OD) from western blotting, EV number from nanoparticle tracking analysis, and EV volume (calculated based on EV number and size) yielded similar results. Patients of Helsinki Urological Biobank project (HUB.1–3), post-prostatectomy (post), pre-prostectomy (pre).

## **Supplementary Tables**

**Table S1. Supplementary clinical and pathological information from the prostate cancer patients.** The table extends the information provided in Table 1 with prostate specific antigen (PSA) values (controls and post (2) measured > 2–3 years after first urine sample donation or prostatectomy) and a list of other follow-up measurements, postoperative treatment, current disease state > 2 years after prostatectomy, age and body-mass index (BMI). Chromogranin A (CGA), gonadotropin releasing hormone (GnRh), positron emission tomography (PET), post-prostatectomy (post), pre-prostatectomy (pre), prostate specific membrane antigen (PSMA).

Patient/sample	Prostatectomy information			PSA	Post-operative	Follow-up	Current disease	Age	BMI
	Gleason score	Stage	Cancer (%)	(µg/l)	treatment		state	(years)	
control 1			1	0.5				30	23.7
control 2				0.9				31	24.8
control 3				0.6				25	28.3
HUB.1/pre	3+4=7	pT2c	5	6.2				56	31.6
HUB.1/post (1)				<0.05	none	Regular PSA follow-up	remission		
HUB.1/post (2)				<0.05					
HUB.2/pre	3+4=7	pT2c	2	0.3				69	23.9
HUB.2/post (1)				<0.05	none	Regular PSA follow-up	remission		
HUB.2/post (2)				<0.05					
HUB.3/pre	4+5=9	pT3b	10	58.2				72	24.8
HUB.3/post (1)				124.0	GnRh antagonist (Firmagon)	Choline PET, PSMA PET, PSA, CGA	castration sensitive stable disease, no metastasis		
HUB.3/post (2)				< 0.05					

**Table S2. List of metabolites in the UPLC-MS-MS analysis panel.** Totally, 102 (urinary EVs and urine) and 111 (platelet EVs and platelets) metabolites were included in the MS-analysis panel. The nine metabolites included only in the panel used for pEVs and platelets are marked with light gray color. Platelet EVs (pEVs), urinary EVs (uEVs).

	Panel for			Panel for	
Metabolite #	uEVs	pEVs	Metabolite #	uEVs	pEVs
1	Acetoacetic acid	Acetoacetic acid	57	Inosine	Hydroxykynurenine
2	L-Acetylcarnitine	L-Acetylcarnitine	58	Isobutvrvl-L-carnitine	4-Hydroxyproline
3	Adenine	Adenine	59	Isoleucine	5-Hydroxy-L-tryptophan
4	Adenosine	Adenosine	60	Isovalervlcarnitine	Hypoxanthine
5	Alanine	S-Adenosylhomocysteine	61	Kynurenic acid	IMP
6	Allantoin	S-5-Adenosyl-L-Methionine Chloride	62		Inosine
7			62	Lousino	Isobutynd L carniting
,	Aminoaupic Aciu	Allantain	63	Leache	Isolousing
•			64	Lysine	Isoleucine
9	AIVIP		65	Methonine	Isovaleryicarnitine
10	Arginine	2-Aminoisobutyric acid	66	1-Methylnistamine	Kynurenic acid
11	Asparagine	AMP	67	Myoinositol	L-Kynurenine
12	Aspartic acid	Arachidyl carnitine	68	NAD	Leucine
14	Asymmetric dimethylarginine	Arginine	69	Neopterin	Lysine
15	Betaine	Asparagine	70	Niacinamide	Methionine
16	Carnitine	Aspartic acid	71	Nicotinic acid	1-Methylhistamine
17	Carnosine	Asymmetric dimethylarginine	72	Normetanephrine	5'-Methylthioadenosine
18	Chenodeoxycholic acid	Betaine	73	L-Octanoylcarnitine	Myoinositol
19	Cholic acid	Carnitine	74	Ornithine	NAD
20	Choline	Carnosine	75	Orotic acid	Neopterin
13	Citrulline	Chenodeoxycholic acid	76	Pantothenic acid	Niacinamide
21	Cotinine	Cholic acid	77	Phenylalanine	Nicotinic acid
22	Creatine	Choline	78	O-Phosphoethanolamine	Normetanephrine
23	Creatinine	Citrulline	79	Proline	L-Octanoylcarnitine
24	Cyclic AMP	Cotinine	80	Propionylcarnitine	Ornithine
25	Cyclic GMP	Creatine	81	4-Pyridoxic acid	Orotic acid
26	L-Cystathionine	Creatinine	82	Pyridoxine	L-Palmitoylcarnitine
27	Cvtidine	Cvclic AMP	83	D-Ribose 5-phosphate	Pantothenic acid
28	, Cvtosine	Cvclic GMP	86	Serine	Phenylalanine
29	Decanovicarnitine	L-Cystathionine	87	Sorbitol	O-Phosphoethanolamine
30	Deoxycytidine	Cysteine	88	Spermidine	Proline
31	Deoxyuridine	Cytidine	89	Succinic acid	Propionylcarnitine
32	Dimethylglycine	Cytosine	90	Sucrose	4-Pyridoxic acid
33	Folic acid	Decanovicarnitine	85	Symmetric dimethylarginine	Pyridoxine
34	Gamma-Aminobutyric acid	Deoxycytidine	91	Taurine	D-Ribose 5-nbosnbate
35	Gamma-Glutamylcysteine	Deoxyeridine	92	Taurochenodesoxycholic acid	Serine
36	Glucuronate	Dimethylglycine	93	Taurocholic acid	Sorbitol
37	Glutamic acid	Dodecanovicarnitine	94	Threonine	Spermidine
57	Clutamino	Folic acid	94	Trimothylamina N. ovida	Stearoulcarniting
29	Clutathiana	Commo Aminohuturio agid	55	Trustenben	Stearbyicarinine
30	Glucathione	Gamma-Aminobutyne aciu	90	Timesia	
39	Giyceraldenyde	Gamma-Giutamyicysteine	97		Sucrose
40	Glycine	Glucuronate	98	UDP-Glucose	Symmetric dimethylarginine
41	Giycocholic acid	Giutamic acid	99	Uracii	Taurine
42	Guanidoacetic acid	Glutamine	100	valine	l'aurochenodesoxycholic acid
43	Guanosine	Glutathione	101	Xanthine	l aurocholic acid
44	Hexanoylcarnitine	Glyceraldehyde	102	Xanthosine	letradecanoylcarnitine
45	Hippuric acid	Glycine	103		Threonine
46	Histidine	Glycocholic acid	104		Trimethylamine N-oxide
47	Homocysteine	Guanidoacetic acid	105		Tryptophan
48	Homogentisic acid	Guanosine	106		Tyrosine
49	Homoserine	Hexanoylcarnitine	107		UDP-Glucose
50	3-Hydroxyanthranilic acid	Hippuric acid	108		Uracil
51	5-Hydroxyindoleacetic acid	Histidine	109		Valine
52	Hydroxykynurenine	Homocysteine	110		Xanthine
53	4-Hydroxyproline	Homogentisic acid	111		Xanthosine
54	5-Hydroxy-L-tryptophan	Homoserine			
55	Hypoxanthine	3-Hydroxyanthranilic acid			
56	IMP	5-Hydroxyindoleacetic acid			

**Table S3. Intra-EV concentrations of metabolites in urinary and platelet EVs.** Calculated average concentrations of metabolites inside the healthy control urinary and platelet EVs were arranged in decreasing order according to the concentrations in the urinary EVs. The concentrations ranged from tens of mM to none. Platelet EVs (pEVs), urinary EVs (uEVs).

		Concentration ins	ide uEVs (μM)		Concentration ins	ide pEVs (μM)	
	Metabolite name	Average	Stdev	CV (%)	Average	Stdev	CV (%)
Above quantificat Metabolite 1	oon iimit in all control uEV samples Ornithine	42273.8	24860.7	58.8	191.0	21.4	11.7
Metabolite _2	Creatinine	15901.4	25169.6	158.3	191.0		
Metabolite _3	D-Ribose 5-phosphate	6736.3	976.0	14.5	68772.0	27514.9	40.0
Metabolite _4	L-Cystathionine	6240.0	10646.0	170.6	575 F	152.9	26.7
Metabolite 6	Serine	4081.2	2589.3	63.4	201.3	73.4	36.5
Metabolite _7	Taurine	2849.0	3510.7	123.2	5275.7	91.8	1.7
Metabolite _8	Aspartic acid	2681.3	1086.9	40.5	49.4	18.3	37.0
Metabolite _9	IMP Clutamic acid	1173.1	632.8	53.9	439.4	16.1	3.7
Metabolite 11	Hippuric acid	870.8	1187.8	136.4	1.6	0.7	40.5
Metabolite _12	Arginine	850.6	307.5	36.2	184.4	1.7	0.9
Metabolite _13	Kynurenic acid	759.6	1310.3	172.5			
Metabolite _14 Metabolite _15	4-Hydroxyproline Creatine	701.1	326.3	46.5	450.3	145.8	32.4
Metabolite _16	Sucrose	587.5	634.6	108.0	67.1	25.1	37.5
Metabolite _17	Carnitine	402.1	288.8	71.8	5.2	1.0	18.5
Metabolite _18	Trimethylamine N-oxide	329.5	535.4	162.5			
Metabolite _19	Guandoacetic acid	306.3	462.3	150.9			
Metabolite _21	Citrulline	269.4	160.5	59.6	71.3	23.3	32.7
Metabolite _22	Glutathione	232.9	39.7	17.1	38.3	3.3	8.6
Metabolite _23	Adenosine	223.0	54.3	24.4	273.2	39.7	14.5
Metabolite _24	Choline	83.9	42.0	35.2	34.8	4.3	6.0
Metabolite _26	Orotic acid	58.1	28.6	49.2	6.4	1.1	16.3
Metabolite _27	AMP	56.7	5.6	9.8	633.1	147.4	23.3
Metabolite _28	Spermidine	53.2	18.1	34.0	17.8	0.8	4.5
Netabolite _29	L-Acetylcamitine Gamma-Glutamvlcvsteine	51.4	47.1	91.6 68.7	5.1	0.1	1.3
Metabolite 31	Niacinamide	35.1	11.0	31.3	46.4	2.2	4.8
Metabolite _32	Carnosine	31.8	17.0	53.5	6.8	3.7	55.2
Metabolite _33	Inosine	27.4	32.9	120.2	13.1	1.2	8.9
Metabolite _34	xantnine Pantothenic acid	13.4	11.3	84.1 69 2	1.2	0.1	11.0
Metabolite 36	Folic acid	7.4	4.4	59.8	0.5	0.2	35.8
Metabolite _37	Propionylcarnitine	6.7	7.3	108.7	0.3	0.0	5.9
Metabolite _38	Isovalerylcarnitine	4.8	3.7	76.6	0.0	0.0	54.4
Metabolite _39	Isobutyryl-L-carnitine	3.9	2.8	72.8	0.6	0.1	9.3
Metabolite _40	1-Methylbistamine	2.3	2.6	105.7			
	,						
One or more sam	ples under quantification/detection l	imit or chromatograp	hy compromized in	control uEVs			
Metabolite _42	Sorbitol	8765.1					
Metabolite _45	Allantoin	4422.8	6122.2	138.4			
Metabolite _45	Myoinositol	3282.7	1804.9	55.0			
Metabolite _46	Glutamine	1594.8			412.1	125.5	30.5
Metabolite _47	Methionine	1155.2					
Metabolite _48	Asparagine	490.9	219.7	45.0	117.8	1.9	1.6
Metabolite _50	Chenodeoxycholic acid	448.0					
Metabolite _51	Histidine	293.9			180.1	69.9	38.8
Metabolite _52	Valine	260.3	40.6	15.6	160.1	1.3	0.8
Metabolite _53	Succinic acid	220.0	113.9	51.8	158.2	24.2	27.0
Metabolite _55	Hypoxanthine	152.3	138.0	90.7	2634.3	43.2	1.6
Metabolite _56	Asymmetric dimethylarginine	136.9	176.3	128.8			
Metabolite _57	Tyrosine	136.4	109.0	79.9	78.0	12.5	16.1
Metabolite _59	Dimethylelycine	79.3	120.7	115.5	0.2	0.1	37.5
Metabolite _60	Gamma-Aminobutyric acid	57.6					
Metabolite _61	Cytosine	55.0					
Metabolite _62	Guanosine	28.2	0.7	2.3			
Metabolite _63	Homogentisic acid	15.5					
Metabolite _65	Cyclic AMP	10.8			2.7	2.7	99.2
Metabolite _66	2-Aminoisobutyric acid	9.3			3.0		
Metabolite _67	L-Octanoylcarnitine	2.6			1.0	0.2	22.6
Metabolite _68	Normetanephrine Taurocholic acid	1.5	1 2	85.6	1 2	0.2	13 5
Metabolite 70	Adenine	1.4	1.2	0.00	0.9	0.1	11.3
Metabolite _71	Decanoylcarnitine	0.8	0.2	28.5	0.8	0.1	11.2
Metabolite _72	Neopterin	0.6					
Metabolite _73	ryridoxine Taurochenodeoxycholic acid	0.2					
Metabolite 75	Hexanoylcarnitine	0.2			0.1	0.0	12.6
Metabolite _76	Acetoacetic acid					-	
Metabolite _77	3-Hydroxyanthranilic acid						
Metabolite _78	Betaine Cuclic GMR						
Metabolite _/9	Cholic Acid						
Metabolite _81	Cotinine						
Metabolite _82	Cytidine				0.2	0.0	5.7
Metabolite _83	Deoxycytidine						
Metabolite 85	Glyceraldehyde						
Metabolite _86	Glycocholic acid						
Metabolite _87	Homocysteine						
Metabolite _88	Homoserine				70.2		
Metabolite _89	Isoleucine Kynurenine				/0.2	U.1 2.1	0.2
Metabolite 91	Hydroxykynurenine				J. 1	2.1	
Metabolite _92	5-Hydroxyindoleacetic acid						
Metabolite _93	5-Hydroxy-L-tryptophan						
Metabolite _94	Lysine Nicotinic Acid				291.7	1.3	U.4
Metabolite 96	Phenylalanine				53.9		
Metabolite _97	O-Phosphoethanolamine				12.6		
Metabolite _98	Proline				233.8	a -	
Metabolite 100	I nreonine Tryptophan				329.1	3.5	1.1
Metabolite 101	UDP-Glucose				33.0	11.4	20.0
Metabolite _102	Xanthosine				31.2	7.1	22.8

**Table S4. Concentrations of metabolites in urine.** Average concentrations of metabolites in the urine samples (filtrates) from the healthy controls were arranged in decreasing order. Most metabolites in the panel were present above the quantification limit. The concentration range was similar as the intra-EV concentrations of the EV samples.

Concentration	n in control urines (μM)				Concentration	in control urines (μM)			
	Metabolite name	Average	Stdev	CV (%)		Metabolite name	Average	Stdev	CV (%)
Above quantifie	cation limit in all control samples				Under quantifica	tion/detection limit in one or more	control samples		
Metabolite_1	Sorbitol	208926.3	335431.8	161	Metabolite_84	Glyceraldehyde	82.7	74.4	90
Metabolite_2	Trimethylamine N-oxide	3891.8	3451.9	89	Metabolite_85	Acetoacetic acid	42.6	38.2	90
Metabolite_3	Glycine	10/0.5	154.1	14	Metabolite_86	4-Hydroxyproline	26.9	26.8	100
Metabolite_4	Creatinine	834.7	480.2	58	Metabolite_87	Isoleucine Chanadaauwahalia aaid	12.3	21.3	1/3
Metabolite_5	Alapina	511.5	2/8.9	55 73	Motabolite 95	2. Hudrowanthranilis asid	2.3	4.0	1/3
Metabolite_6	Alanine	462.7	331.7	72	Motabolite_88	3-Hydroxyanthraniiic acid	1.7	1.7	97
Metabolite_7	Histidine	458.2	328.3	20	Metabolite_90	Deoxyundine Gweecholic acid	1.0	1.5	90 120
Metabolite_8	Serine	205.7	105.0	19	Metabolite_91	Glutathione	1.2	1.7	159
Metabolite_3	Hippuric acid	202.0	50.2	20	Metabolite_85	IMP	1.0	1.2	172
Metabolite_10	Sucrose	252.5	224.9	20	Metabolite_97		0.7	1.2	161
Metabolite_11	Asparagine	225.5	129.9	58	Metabolite_93	5-Hydroxy-L-tryptophan	0.4	0.0	173
Metabolite 13	Betaine	195.8	85.7	44	Metabolite 83	Cotinine	0.2	0.3	155
Metabolite 14	Guanidoacetic acid	165.2	83.3	50	Metabolite 101	Pyridoxine	0.0	0.0	133
Metabolite 15	l vsine	143.1	118.0	82	Metabolite 92	Cholic acid	0.0	0.0	100
Metabolite 16	Asymmetric dimethylarginine	127.1	147.1	116	Metabolite 94	O-Phosphoethanolamine			
Metabolite 17	Symmetric dimethylarginine	121.2	124.0	102	Metabolite 96	Mvoinositol			
Metabolite 18	Tyrosine	113.8	73.2	64	Metabolite 99	Homogentisic acid			
Metabolite 19	Carnitine	108.1	32.9	30	Metabolite 100	Gamma-Glutamvlcvsteine			
Metabolite 20	Creatine	105.9	74.3	70	Metabolite 102	UDP-Glucose			
Metabolite_21	Succinic acid	101.2	11.7	12					
Metabolite 22	Dimethylglycine	68.1	92.9	136					
	Phenylalanine	59.6	40.9	69					
Metabolite 24	Glucuronate	56.0	28.6	51					
Metabolite_25	L-Cystathionine	49.9	47.4	95					
Metabolite_26	Ornithine	49.7	51.2	103					
	Leucine	47.5	35.4	75					
	Tryptophan	41.9	20.0	48					
Metabolite_29	Valine	31.4	20.5	65					
Metabolite_30	D-Ribose 5-phosphate	26.9	33.2	123					
Metabolite_31	Threonine	23.0	23.3	101					
Metabolite_32	Hypoxanthine	20.5	12.7	62					
Metabolite_33	Aminoadipic acid	18.9	12.0	64					
Metabolite_34	Allantoin	18.5	12.3	67					
Metabolite_35	Arginine	18.0	10.3	57					
Metabolite_36	Pantothenic acid	17.6	5.1	29					
Metabolite_37	Deoxycytidine	17.3	6.5	38					
Metabolite_38	Choline	10.4	7.0	67					
Metabolite_39	L-Acetylcarnitine	10.4	7.7	75					
Metabolite_40	Methionine	10.1	6.5	64					
Metabolite_41	Kynurenic acid	9.8	7.7	78					
Metabolite_42	1-Methylhistamine	8.8	7.6	87					
Metabolite_43	Proline	8.0	4.2	53					
Metabolite_44	5-Hydroxyindoleacetic acid	7.4	4.0	54					
Metabolite_45	Glutamic acid	7.2	5.8	81					
Metabolite_46	Aspartic acid	6.7	2.0	30					
Metabolite_47	Cytosine	5.3	4.4	82					
Metabolite_48	Xanthosine	4.9	2.5	51					
Metabolite_49	Xanthine	4.9	4.3	87					
Metabolite_50	Citrulline	4.5	2.1	46					
Metabolite_51	4-Pyridoxic acid	4.1	2.7	67					
Metabolite_52	Carnosine	3.6	2.1	60					
Metabolite_53	Uracil	2.7	1.6	58					
Metabolite_54	Gamma-Aminobutyric acid	2.4	2.8	11/					
Metabolite_55	Homocysteine	2.3	1.5	66					
Metabolite_56	Adenosine	2.2	1.0	49					
Metabolite_57	Propionylcarnitine	2.0	1.0	50					
Metabolite_58	Inosine	1.9	1.0	2/					
Metabolite_59	Isovalery/carnitine	1.5	0.5	54 27					
Metabolite 61	2-Aminoisobutyric acid	1.4 1 4	0.4	57					
Metabolite 67	Homoserine	1.3	0.0	4					
Metabolite_63	Hydroxykynurenine	13	0.6	51					
Metabolite_64	Isobutyryl-I -carnitine	1.3	0.0	21					
Metabolite 65	Nicotinic acid	1.2	0.8	68					
Metabolite 66	Cyclic AMP	0.9	0.3	34					
Metabolite 67	Taurochenodesoxycholic acid	0.8	0.7	79					
Metabolite 68	L-Octanovicarnitine	0.5	0.4	66					
Metabolite 69	Neopterin	0.5	0.1	26					
Metabolite 70	Taurocholic acid	0.4	0.3	63					
Metabolite 71	Decanoylcarnitine	0.3	0.2	64					
	Niacinamide	0.3	0.1	16					
Metabolite_73	Guanosine	0.3	0.3	112					
Metabolite_74	Orotic acid	0.3	0.2	77					
	Folic acid	0.2	0.1	41					
Metabolite_76	NAD	0.2	0.2	92					
Metabolite_77	Normetanephrine	0.2	0.1	74					
Metabolite_78	Cyclic GMP	0.2	0.1	46					
Metabolite_79	Hexanoylcarnitine	0.2	0.1	63					
Metabolite_80	Cytidine	0.1	0.0	31					
Metabolite_81	Adenine	0.1	0.1	50					
Metabolite_82	Spermidine	0.1	0.0	53					

## Supplementary methods

## Ultra performance liquid chromatography-tandem mass spectrometry

EVs from 10–53 ml of urine and 5 ml of platelet concentrate ( $10^9-10^{11}$  particles), 100 µl urine filtrate (from 1.2 µm filtration step of EV isolation) and 1 x  $10^7$  platelets were applied to analysis of 102 (uEVs and urine) or 111 (pEVs and platelets) polar metabolites (Table S21) using ultra performance liquid chromatography-tandem mass spectrometer (UPLC-MS-MS, ACQUITY UPLC<sup>®</sup> with Xevo TQ-S – tandem quadrupole mass spectrometer, Waters) as previously described [27].

All the metabolite standards used in the analyses were purchased from Sigma-Aldrich (Helsinki, Finland). Isotopically labeled internal standards (IS) were obtained from Cambridge Isotope Laboratory. Inc., USA (Ordered from Euroiso-Top, France). Other chemicals like ammonium formate, ammonium acetate and ammonium hydroxide that all are analytical grade were obtained from Sigma-Aldrich (Helsinki, Finland). Formic acid (FA), 2-propanol, acetonitrile (ACN), and methanol (all HiPerSolv CHROMANORM, LCMS grade) were purchased from VWR International (Helsinki, Finland). Deionized water up to a resistivity of 18 M $\Omega$ .cm was purified with a purification system (Barnstead EASYpure RoDi ultrapure water purification system, Thermo scientific, Ohio, USA). Calibration solutions for the calibration curve were prepared in a 96-well plate by serial dilution of the stock calibration mix using Hamilton's MICROLAB® STAR line (Hamilton, Bonaduz AG, Switzerland) liquid handling robot system. Starting from a stock solution mix, 10 additional lower working solutions were prepared using water as the diluent to build the calibration curve. For metabolite extractions, twenty microliters of labeled internal standard mixture was added to the samples. A total of 960  $\mu$ l of extraction solvent (80:20 ACN:H<sub>2</sub>O + 1% FA) was added and three cycles of extraction carried out by vortexing for 2 min and sonicating for 1 min (ultrasonicator settings: sweep mode, frequency 37, power 60, no heating). After this, the tubes were centrifuged at 14000 rpm for 15 min at +4°C. An aliquot of 800 µl of the supernatant was dispensed in OstroTM 96-well plate (Waters Corporation, Milford, USA) and filtered by applying vacuum at a delta pressure of 300–400 mbar for 2.5 min on robot's vacuum station. The clean extract was collected to a 96-well collection plate, placed under OstroTM plate. The collection plate was sealed and centrifuged for 15 min, 4000 rpm, +4°C, and placed in auto-sampler of the liquid chromatography system for the injection.

Sample analysis was performed on an ACQUITY UPLC-MS-MS system (Waters Corporation, Milford, MA, USA). All metabolites were separated using the column, 2.1 x 100 mm Acquity 1.7 $\mu$  BEH amide HILIC column (Waters Corporation, Milford, MA, USA), which was maintained at 45°C temperature. The total run time was 14.5 min including 2.5 min of equilibration step at a flow rate of 600  $\mu$ l/min. Initially the gradient started with a 2.5 min isocratic step at 100% mobile phase B (ACN/ H<sub>2</sub>O, 90/10 (v/v), 20 mM ammonium formate, pH at 3), and then rising to 100% mobile phase A (ACN/H<sub>2</sub>O, 50/50 (v/v), 20 mM ammonium formate, pH at 3) over the next 10 min and maintained for 2 min at 100% A, and finally equilibrated to the initial conditions for 2.5 min. An injection volume of 5  $\mu$ l of sample extract was used and two cycles of 300  $\mu$ l of strong wash and 900  $\mu$ l of weak wash and an additional 2 min of seal wash were carried out after each injection to avoid carry over effect. The auto-sampler was used to perform partial loop with needle overfill injections for the samples and standards and maintained at temperature of 5°C.

The detection system, a Xevo<sup>®</sup> TQ-S tandem triple quadrupole mass spectrometer (Waters, Milford, MA, USA), was operated in both positive and negative polarities with a polarity switching time of 20 msec. Electro spray ionization (ESI) was chosen as the ionization mode with a capillary voltage at 0.6 KV in both polarities. The source temperature and desolvation temperature of 120°C and 650°C, respectively, were maintained constantly throughout the experiment. Cone voltage and collision energy (CE) were optimized for each compound. Highly pure nitrogen and argon gas were used as desolvation gas (1000 l/hr) and collision gas (0.15 ml/min), respectively. Multiple Reaction Monitoring (MRM) acquisition mode was selected for quantification of metabolites with individual span time of 0.1 sec given in their individual MRM channels. The dwell time was calculated automatically by the software based on the region of the retention time window, number of MRM functions and also depending on the number of data points required to form the peak. MassLynx 4.1 software was used for data acquisition, data handling and instrument control. Data processing was done using TargetLynx software and metabolites were quantified using area ratio (area of metabolite/area of IS) standards and external calibration curves.

A peak response giving signal to noise (S/N) ratio of < 3 was considered below the limit of detection. For calculation of average concentrations, concentrations below this limit were assigned as zeros. Lower limit of quantification was defined as the lowest concentration on calibration curve corresponding to S/N of > 6.