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Supplemental Material

Associations between the Maternal Exposome and Metabolome during Pregnancy

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Figure S2. The models for integration of the literature search with our results for use in explaining the pathway: exposome-metabolome-outcome. (A) Positive associations between maternal exposure to exogenous chemicals and outcome from literature, between maternal metabolite and outcome from literature, and between maternal exposure to exogenous chemicals and metabolite identified in our study. In this scenario, a previous study reported that exogenous chemical exposure is positively related to health outcomes, and our study found that exogenous chemical exposure might increase one metabolite reported to be positively related to health outcomes in a previous study. (B) Negative associations between maternal exposure to exogenous chemicals and outcome from literature, and between maternal metabolite and outcome from literature; positive association between maternal exposure to exogenous chemicals and metabolite identified in our study. In this scenario, a previous study reported that exogenous chemical exposure is negatively related to health outcomes, and our study found that exogenous chemical exposure might increase one metabolite reported to be negatively related to health outcomes in a previous study. (C) Negative associations between maternal exposure to exogenous chemicals and outcome from literature, and between maternal exposure to exogenous chemicals and metabolite identified in our study; positive association between maternal metabolite and outcome from literature. In this scenario, a previous study reported that exogenous chemical exposure is negatively related to health outcomes, and our study found that exogenous chemical exposure might decrease one metabolite reported to be positively related to health outcomes in a previous study. (D) Positive association between maternal exposure to exogenous chemicals and outcome from literature; negative associations between maternal metabolite and outcome from literature, between maternal exposure to exogenous chemicals and metabolite identified in our study. In this scenario, a previous study reported that exogenous chemical exposure is positively related to health outcomes, and our study found that exogenous chemical exposure might decrease one metabolite reported to be negatively related to health outcomes in a previous study.

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Figure S4. Network of environmentally determined urinary metabotypes of pregnant women in Jiangsu province from April 2013 to July 2016 in the KEGG general metabolic pathway map. The figure was built by ipath (https://pathways.embl.de/). The sample size for the environmentally determined urinary metabotypes according to the organic exposome was 1,024; the sample size for the environmentally determined urinary metabotypes according to the inorganic exposome was 963. The pie chart named "original proportion" shows the original constituent ratios of numbers of profiled chemicals in the exposome classified into macro and trace essential element, potential toxic and other element, organic pollutant, and plant metabolite and phytoestrogen. The pie charts in the pathway were built based on constituent ratios of numbers of chemicals in the exposome that were significantly associated with this metabolite classified into macro and trace essential element, potential toxic and other element, organic pollutant, and plant metabolite and phytoestrogen, and the size of pie charts reflects by the number of chemicals in the exposome that were significantly associated with this metabolite. Other profiled metabolites without significant association with any exposome chemical in our study were colored purple in the pathway map. Metabolites not included in the general metabolic pathway map are not shown. The original general metabolic pathway map is available at https://pathways.embl.de/ipath3.cgi. KEGG, Kyoto Encyclopedia of Genes and Genomes. The data underlying this figure can be found in **Figure S3** and **Excel Table S2**.

Excel Table S1. List of the exposome and metabolome metabolites and their classifications.

Excel Table S2. Statistical analysis results of associations between exposome and urinary metabolome among pregnant women in Jiangsu province, China from April 2013 to July 2016 (n=1,024 for organic exposome and metabolome; n=963 for inorganic exposome and metabolome).

Excel Table S3. Information on the associations between exposome and outcomes during pregnancy mediated by environmentally determined urinary metabotypes.

References

Additional File- Excel Document

Table S1. Demographic information of pregnant women without inclusion in Jiangsu province from April 2013 to July 2016 (n=508).

Maternal characteristic [a].	
Maternal age (year, mean ± SD)	28.8 ± 3.7
Ethnicity [Number (%)]	
Han	498(98.0%)
Other	10(2.0%)
Maternal height (cm, mean ± SD)	162.1 ± 4.9
Weight before pregnancy (kg, mean ± SD)	55.2 ± 8.2
BMI before pregnancy (kg/m^2, mean ± SD)	21.0 ± 2.8
Parity [No.(%)]	
0	413(81.3%)
⩾1	95(18.7%)
Education (years) [No.(%)]	
⩽ 12	190(37.4%)
⩾ 13	318(62.6%)
Smoking [No.(%)][b]	
Yes	8(1.6%)
No	500(98.4%)
Alcohol consumption [No.(%)][b]	
Yes	19(3.7%)
No	489(96.3%)

Note: [a]These data were complete for all participants.
[b]reported “Yes” at least one time in the first, second or third trimester.

Table S2. Element concentrations in urine samples in the first trimester (ng/mL) from 963 women in Jiangsu province, China from April 2013 to July 2016.

Element	Detectable rate(%)	Limit of detection	Geometric Mean	Percentile				
				Min	25	50	75	90
Magnesium	100	0.038	35.477	1.923	19.219	42.121	70.418	110.444
Calcium	89.1	3.954	79.343	<LOD	47.885	128.598	233.509	370.413
Boron	99.69	2.115	1358.191	<LOD	897.382	1476.694	2356.717	3251.343
Vanadium	64.69	0.028	0.095	<LOD	<LOD	0.128	0.396	0.724
Chromium	48.81	0.39	0.659	<LOD	<LOD	<LOD	1.991	4.839
Manganese[a]	57.94	0.885	2.563	<LOD	<LOD	7.569	8.5	10.704
Iron	58.26	18.839	49.903	<LOD	<LOD	91.101	160.964	240.678
Cobalt[b]	92	0.007	0.307	<LOD	0.192	0.402	0.807	1.556
Nickel	54.21	0.681	2.823	<LOD	<LOD	12.827	15.228	19.304
Copper	87.33	0.744	14.274	<LOD	15.67	21.215	30.036	40.405
Zinc	72.9	44.3	283.368	<LOD	<LOD	558.221	812.256	1169.406
Selenium	95.53	0.231	4.392	<LOD	2.663	5.529	9.756	15.164
Molybdenum[b]	100	0.01	29.622	0.475	19.258	32.515	48.391	70.199
Arsenic[a]	100	0.04	24.040	5.429	15.491	23.078	34.944	55.659
Cadmium[b]	48.29	0.075	0.153	<LOD	<LOD	<LOD	0.596	1.844
Mercury	83.39	0.014	1.508	<LOD	1.827	3.131	5.352	11.459
Lead[a]	63.55	1.39	3.304	<LOD	<LOD	4.877	7.471	14.366
Lithium	80.69	0.323	0.538	<LOD	0.376	0.583	0.9	1.253
Beryllium	78.19	0.016	0.610	<LOD	1.579	2.038	2.038	2.619
Aluminum	58.36	35.035	63.635	<LOD	<LOD	118.184	146.587	204.376
Titanium	99.38	2.239	97.436	<LOD	59.645	111.151	175.716	269.97
Gallium	48.81	0.025	0.050	<LOD	<LOD	<LOD	0.204	0.591
Germanium	67.6	0.132	0.249	<LOD	<LOD	0.317	0.544	0.805
Rubidium	100	0.075	1812.053	82.691	1228.024	1966.355	3005.827	3963.881
Strontium[a]	99.58	1.781	124.408	<LOD	70.026	136.968	230.393	342.785
Zirconium	53.17	0.054	0.162	<LOD	<LOD	0.563	0.725	0.915
Rhodium	74.04	0.001	0.010	<LOD	<LOD	0.029	0.03	0.031
Palladium	50.16	0.86	1.077	<LOD	<LOD	1.791	2.627	3.054
Tin[b]	69.47	0.081	0.370	<LOD	<LOD	0.607	1.01	2.116
Antimony[c]	29.8	0.014	0.013	<LOD	<LOD	<LOD	0.022	0.081
Cesium[a]	100	0.009	12.025	1.363	8.171	12.634	18.186	25.329
Barium[a]	87.12	1.091	18.702	<LOD	14.242	23.517	45.499	82.118
Lanthanum	68.85	0.015	0.083	<LOD	<LOD	0.139	0.275	0.583
Cerium	42.68	0.024	0.103	<LOD	<LOD	<LOD	1.351	7.204
Samarium	65.32	0.009	0.021	<LOD	<LOD	0.027	0.046	0.094
Dysprosium	64.38	0.003	0.014	<LOD	<LOD	0.034	0.045	0.074
Holmium	60.96	0.001	0.009	<LOD	<LOD	0.038	0.045	0.07
Erbium	20.77	0.004	0.004	<LOD	<LOD	<LOD	<LOD	0.164
Thulium	30.53	0.001	0.002	<LOD	<LOD	<LOD	0.008	0.079

Ytterbium	58.57	0.005	0.022	<LOD	<LOD	0.04	0.108	0.299
Lutetium	46.21	3.628	5.044	<LOD	<LOD	<LOD	16.066	16.511
Hafnium	54.41	0.002	0.012	<LOD	<LOD	0.051	0.093	0.231
Tantalum	52.44	0.0003	0.002	<LOD	<LOD	0.006	0.019	0.042
Gold	69.89	0.006	0.213	<LOD	<LOD	1.248	1.329	1.501
Thallium[a]	99.17	0.002	0.313	<LOD	0.212	0.354	0.551	0.826
Thorium	55.24	0.006	0.028	<LOD	<LOD	0.032	0.19	0.501
Uranium[a]	75.08	0.002	0.018	<LOD	0.002	0.027	0.066	0.174

Note: LOD, limit of detection.

The value < LOD was imputed with the value of LOD/2 for calculation. The unit for magnesium and calcium in this table is mg/L.

[a]The geometric mean in our study was above the 95% confidence intervals (CIs) of corresponding element in female nonsmokers reported in US CDC Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019, Volume Two (US National Exposure Report). Urinary geometric mean and its CIs (ng/mL) was reported as 0.122 (0.109-0.137) in 2011-2012, not available in 2013-2014, not available in 2015-2016 for manganese; 6.75 (5.79-7.87) in 2011-2012, 6.06 (5.07-7.24) in 2013-2014, 5.85 (5.19-6.59) in 2015-2016 for arsenic; 0.321 (0.288-0.359) in 2011-2012, 0.237 (0.219-0.257) in 2013-2014, 0.260 (0.229-0.296) in 2015-2016 for lead; 74.9 (69.1-81.3) in 2011-2012, 72.7 (67.9-77.9) in 2013-2014, 77.5 (70.3-85.5) in 2015-2016 for strontium; 3.48 (3.22-3.75) in 2011-2012, 3.60 (3.37-3.84) in 2013-2014, 3.63 (3.27-4.03) in 2015-2016 for cesium; 1.04 (0.928-1.17) in 2011-2012, 0.921 (0.838-1.01) in 2013-2014, 0.963 (0.887-1.05) in 2015-2016 for barium; 0.132 (0.121-0.143) in 2011-2012, 0.130 (0.121-0.139) 2013-2014, 0.139 (0.126-0.153) in 2015-2016 for thallium; 0.005 (0.005-0.006) in 2011-2012, 0.005 (0.004-0.006) in 2013-2014, 0.005 (0.004-0.006) in 2015-2016 for uranium.

[b]The geometric mean in our study was within the 95% CIs of corresponding urinary element reported in US National Exposure Report. Urinary geometric mean and its CIs (ng/mL) was reported as 0.313 (0.282-0.348) in 2011-2012, 0.374 (0.342-0.410) in 2013-2014, 0.401 (0.370-0.435) in 2015-2016 for cobalt; 30.2 (27.1-33.6) in 2011-2012, 27.6 (25.1-30.4) in 2013-2014, 29.0 (25.5-33.1) in 2015-2016 for molybdenum; 0.181 (0.160-0.205) in 2011-2012, 0.139 (0.126-0.155) in 2013-2014, 0.161 (0.138-0.189) in 2015-2016 for cadmium; 0.574 (0.506-0.651) in 2011-2012, 0.405 (0.342-0.481) in 2013-2014, 0.467 (0.405-0.539) in 2015-2016 for tin.

[c]The geometric mean in our study was below the 95% CIs of corresponding urinary element reported in US National Exposure Report. Urinary geometric mean and its CIs (ng/mL) was reported as not available in 2011-2012, 0.036 (0.032-0.040) in 2013-2014, 0.038 (0.036-0.041) in 2015-2016 for antimony.

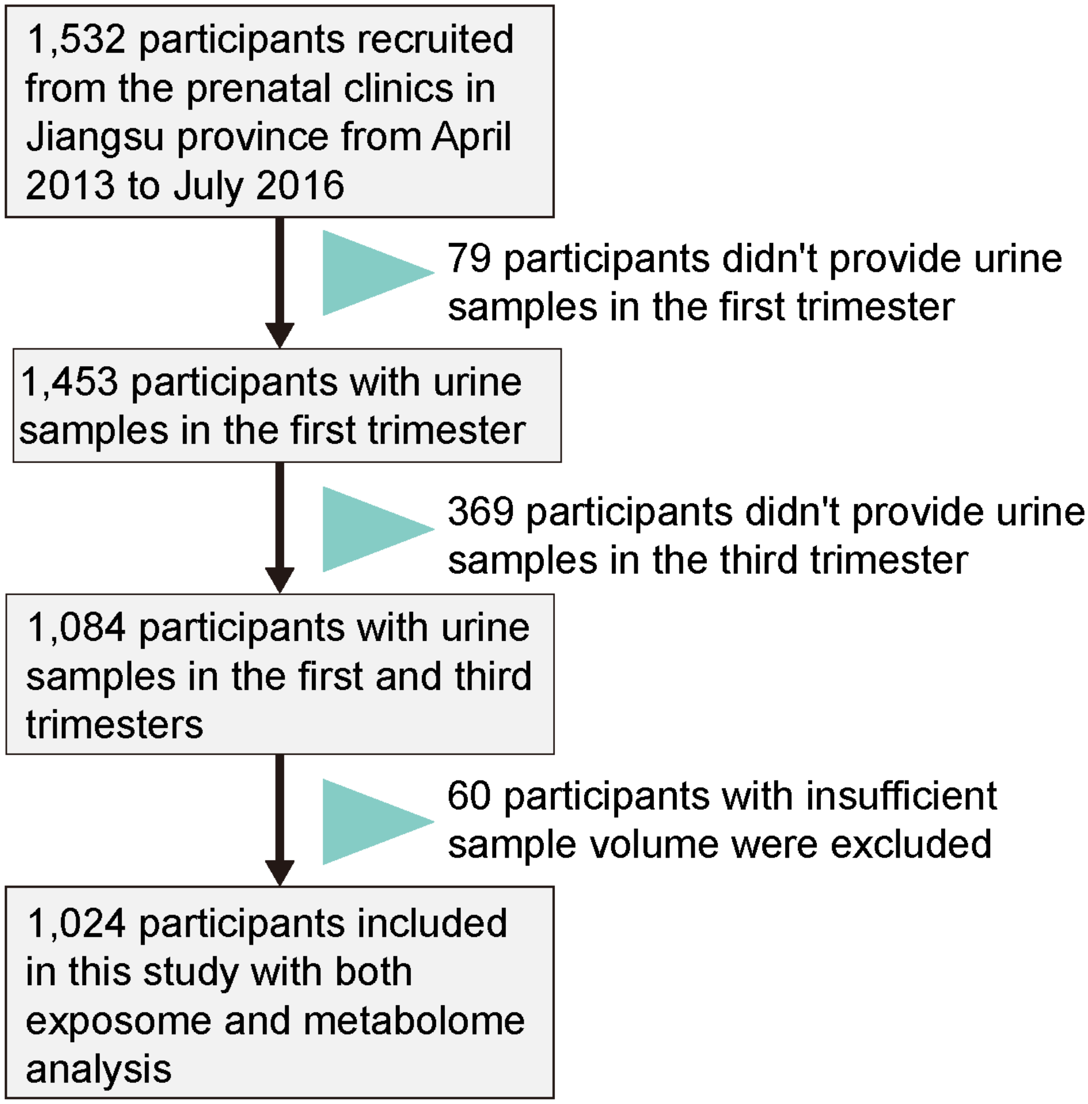
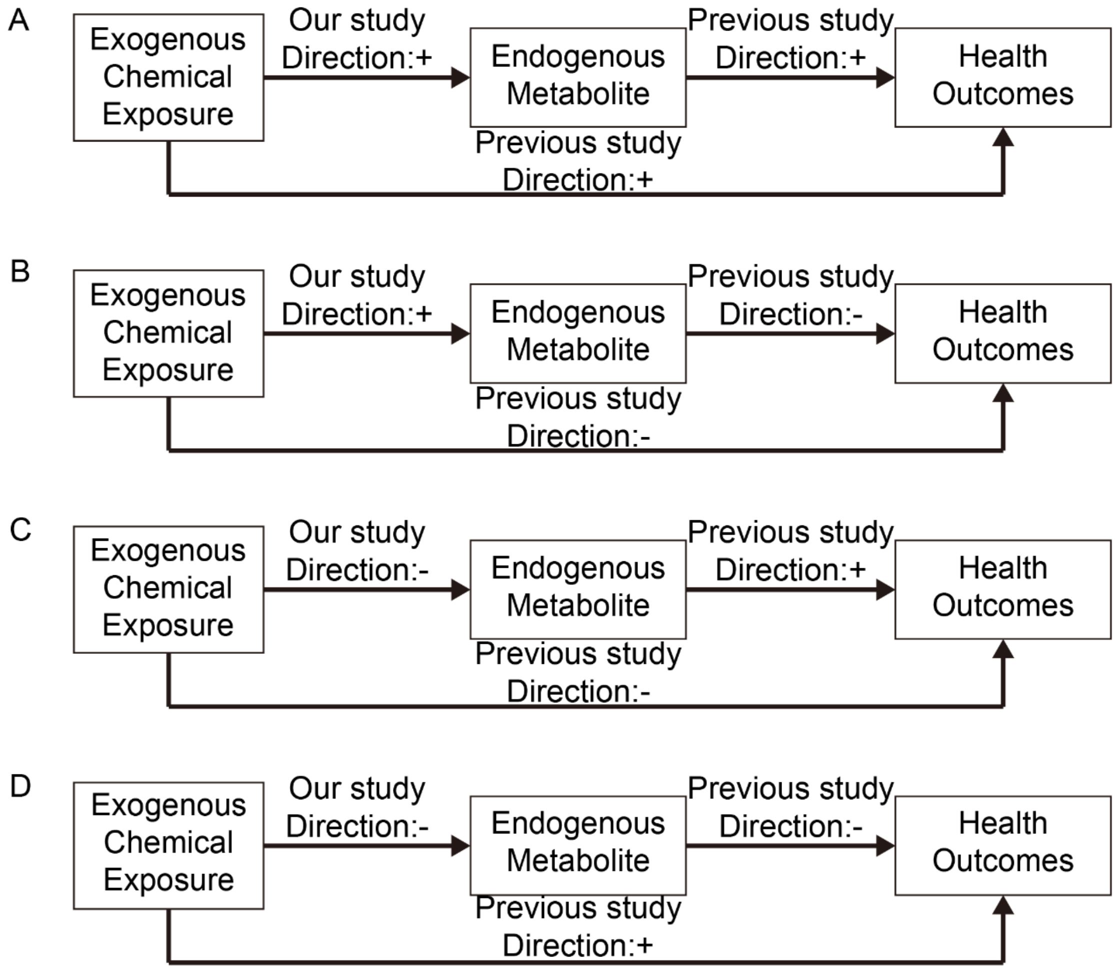


Figure S1. Flow diagram of the participant inclusion process.



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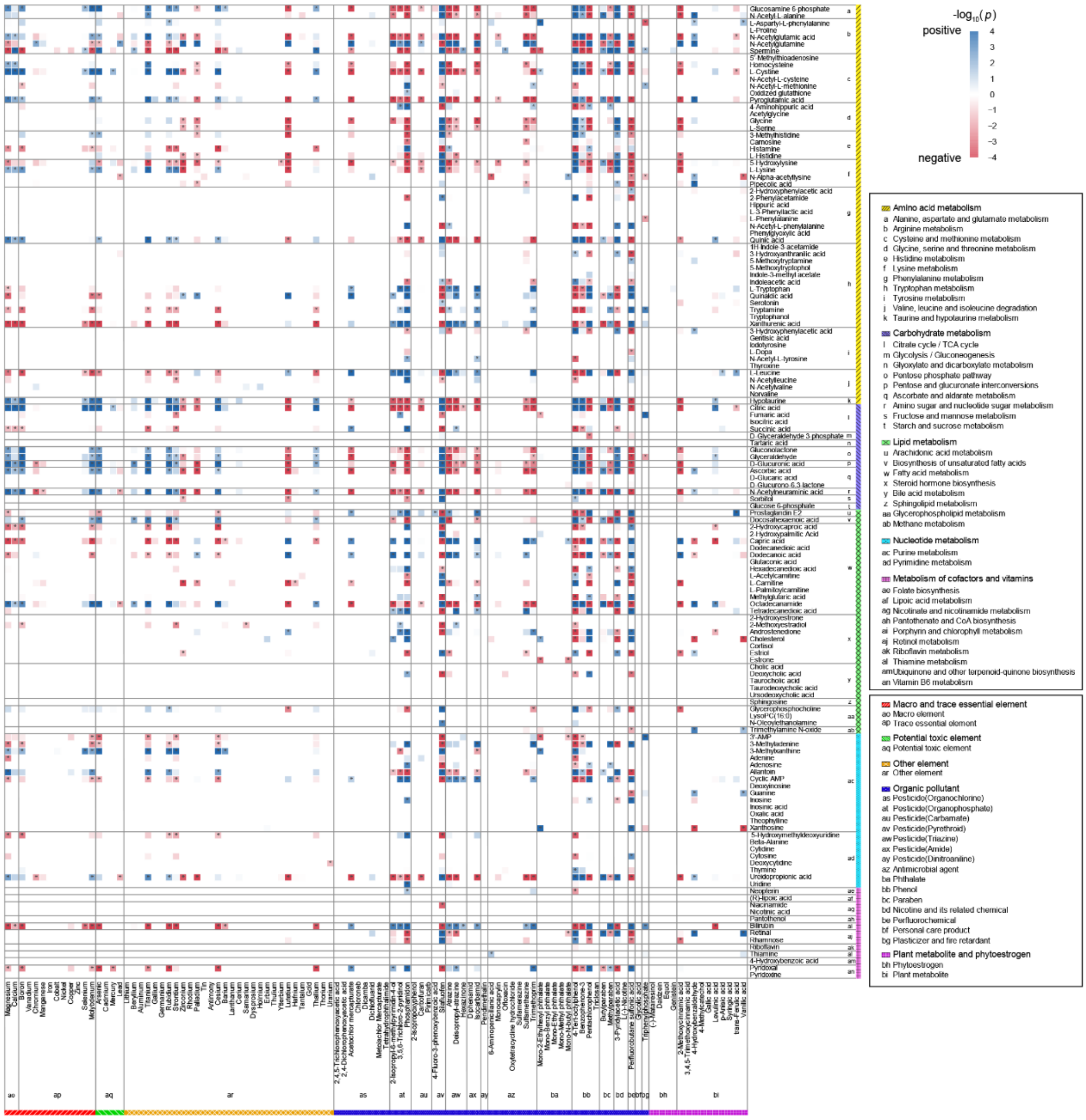

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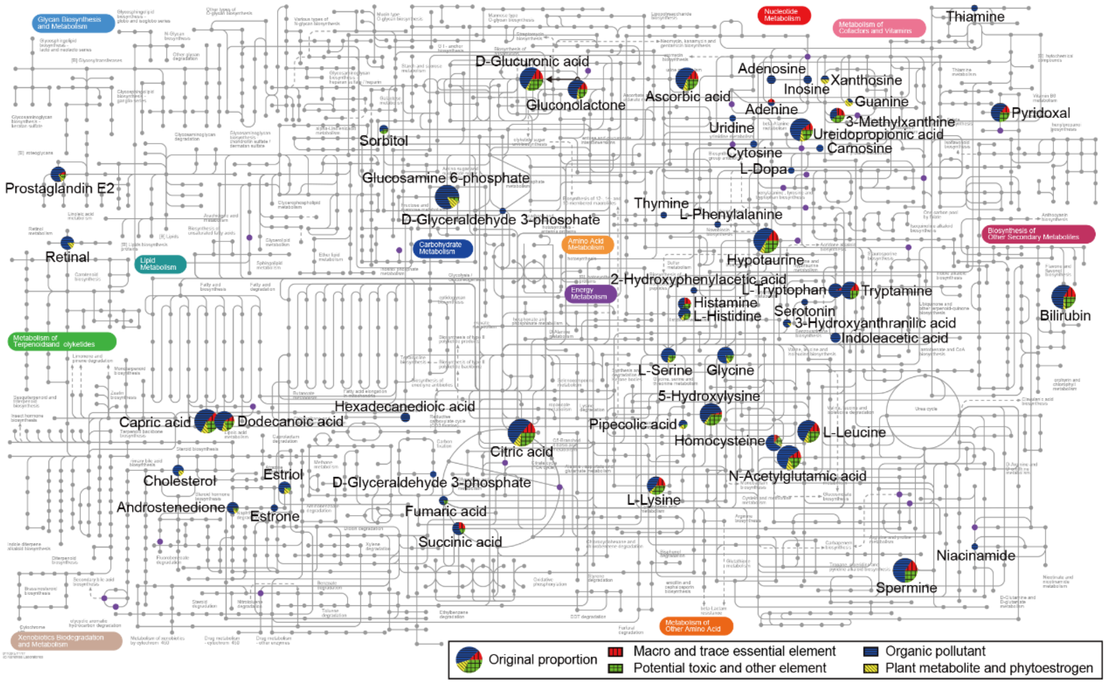

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