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Supplemental Material

Associations between the Maternal Exposome and Metabolome during Pregnancy

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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.

Figure S1. Flow diagram of the participant inclusion process.

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.

Figure S3. Heatmap of Bonferroni-14,734 corrected p value regarding associations between exposome and metabolome in urine from pregnant women in Jiangsu province from April 2013 to July 2016. When the association was in the positive direction, the blue scale was used for visualizing $-\log_{10}(p)$ value. When the association was in the negative direction, the red scale was used for visualizing $-\log_{10}(p)$ value. The association was adjusted by maternal age, BMI before pregnancy, parity, and education using polytomous logistic regression with Bonferroni correction. “*” indicates Bonferroni corrected p value < 0.05. The sample size for the association analysis between organic exposome and metabolome was 1,024; the sample size for the association analysis between inorganic exposome and metabolome was 963. The data underlying this figure can be found in **Excel Table S2**.

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