Supplemental information

Figures S1-S5 and Tables S1-S20.

Supplementary Figures

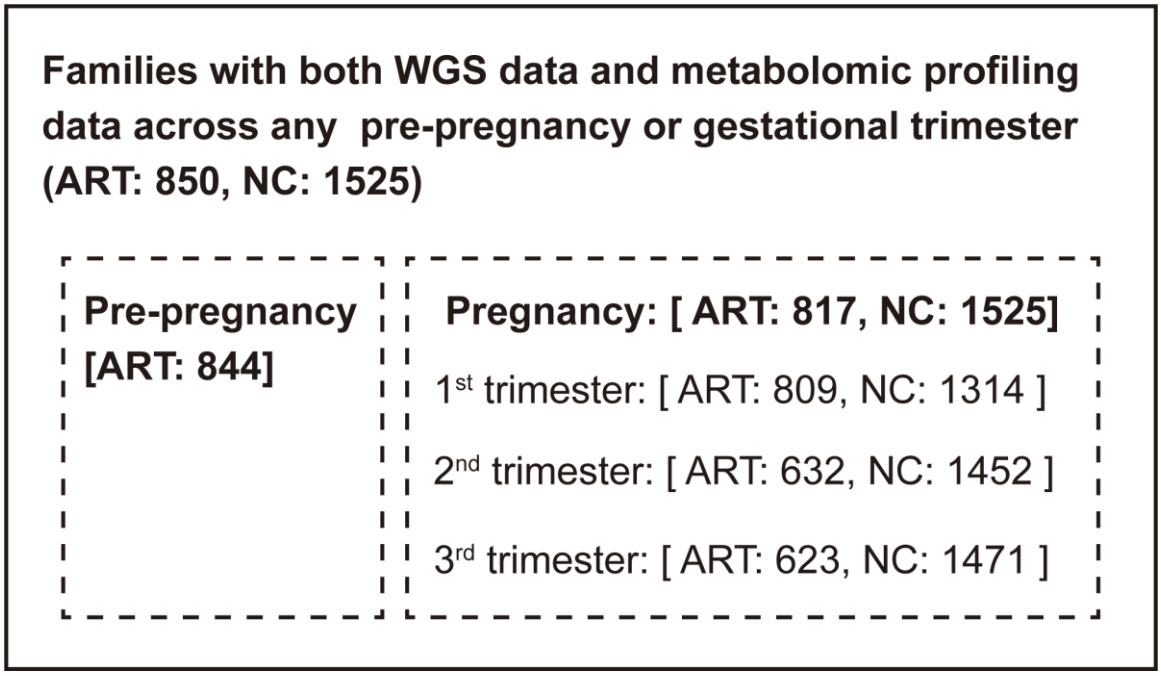

Fig. S1. Sample distribution of NC and ART participants across pre-pregnancy and gestational stages.

NC, naturally conceived; ART, assisted reproductive technology.

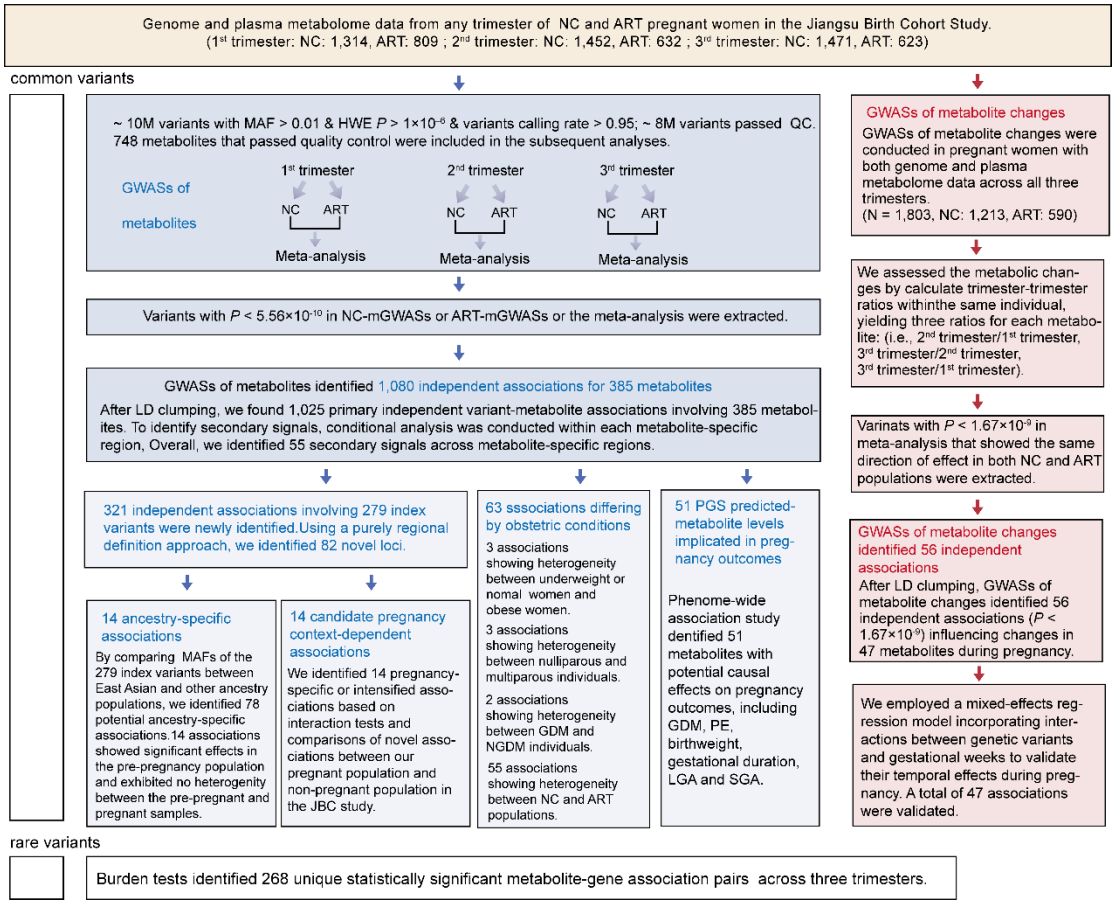

Fig. S2. Study design and workflow.

NC, naturally conceived; ART, assisted reproductive technology; MAF, minor allele frequency; HWE: Hardy-Weinberg equilibrium; QC: quality control; GWAS, genome-wide association study; LD, linkage disequilibrium; FDR, false discovery rate; PGS: polygenic score, GDM, gestational diabetes mellitus; PE, preeclampsia; LGA, large for gestational age; SGA, small for gestational age.

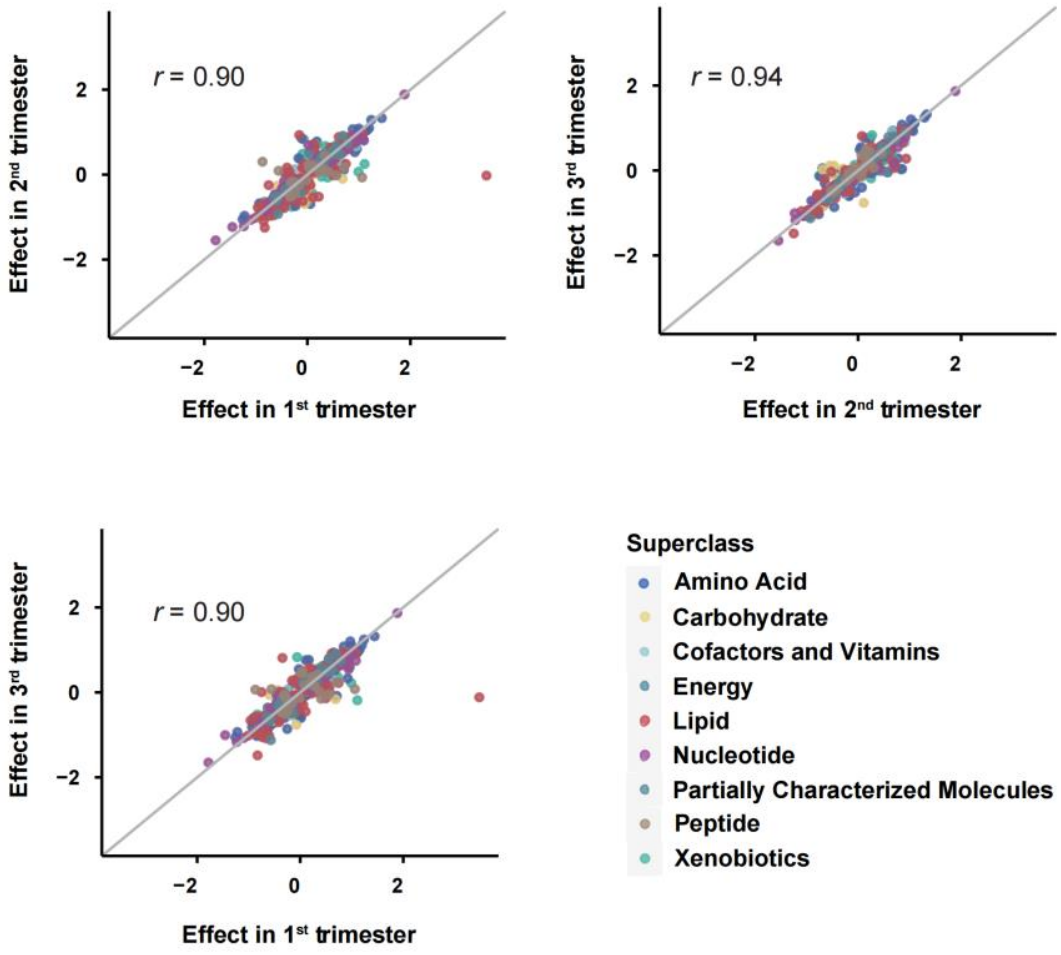

Fig. S3. Comparison of the effects for 1,080 significant independent associations across three trimesters.

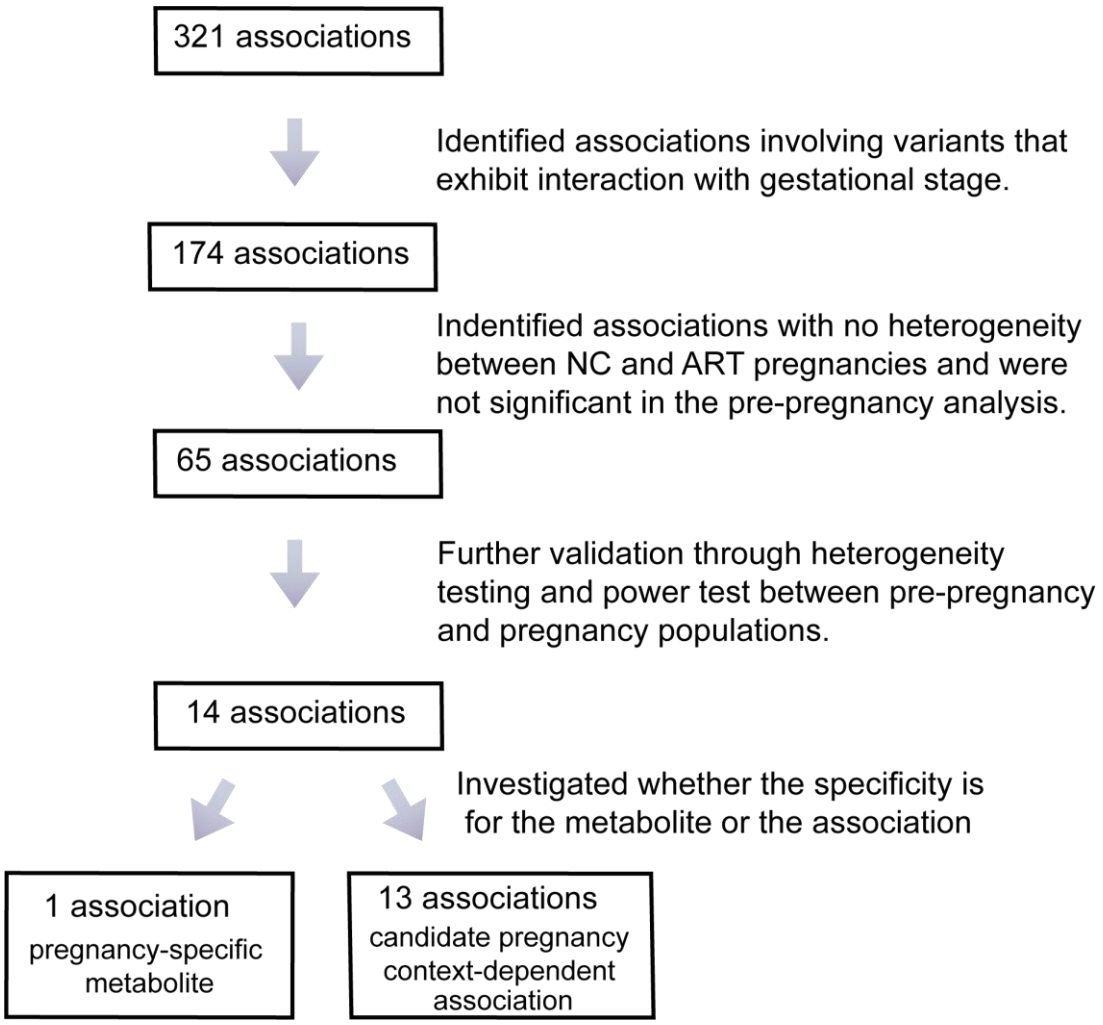

Fig. S4. Flow diagram illustrates the pipeline for identifying candidate pregnancy context-dependent associations.

NC, naturally conceived; ART, assisted reproductive technology.

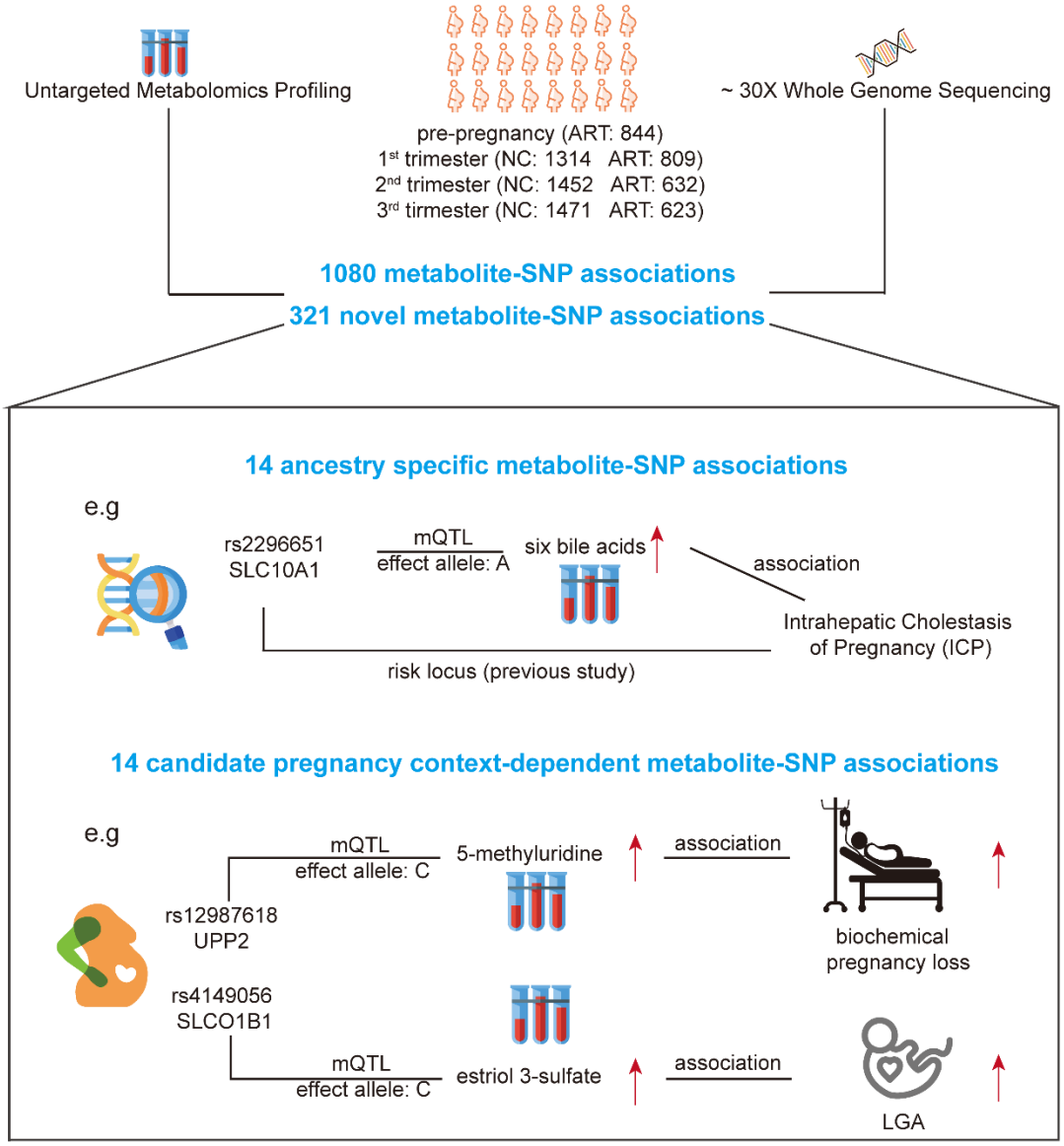

Fig. S5. Conceptual diagram summarizing the key findings of this study.

NC, naturally conceived; ART, assisted reproductive technology; mQTL metabolic quantitative trait locus; LGA, large for gestational age.

Supplementary Tables

Table S1. Characteristics of the study populations.

Table S2. Information on the metabolites analyzed in the present study.

Table S3. Summary of variant-metabolite associations (primary plus secondary) identified in the present study, related to **Figs. 1-2**.

Table S4. Genomic inflation factor for each metabolite in the present study.

Table S5. Conditional analysis within each metabolite-specific region to identify secondary signals.

Table S6. Putative causal genes nominated in this study and related information (i.e., type of encoded proteins, Gene function summary, and Gene-Phenotype Relationships from OMIM), related to **Figs. 1-2**.

Table S7. Study information of the 12 published mGWASs.

Table S8. Novel variant-metabolite associations in the present study.

Table S9. The significant variant-metabolite associations reported in the 12 published mGWASs (modified from Supplementary Data 6 of Yin et al., 2022, PMID: 35347128).

Table S10. Validation of the variant-metabolite associations reported in the 12 published mGWASs using the metabolon.

Table S11. Validation of the variant-metabolite associations reported in the 24_Cell Genomics.

Table S12. MAFs of the 279 index variants in East Asian and other ancestries using 1KGP3 genotype data, related to **Fig. 3a**.

Table S13. Ancestry-specific associations, related to **Fig. 3b**.

Table S14. Candidate pregnancy context-dependent associations, related to **Figs. 4-5**.

Table S15. Genomic inflation factor of trimester-trimester ratio for each metabolite in the present study.

Table S16. Summary of the significant associations between variant and trimester-trimester ratio for each metabolite, related to **Figs. 6**.

Table S17. Strata analyses according to obstetric factors, related to **Fig. 7**.

Table S18. The variant-metabolites associations stratified by the ART procedures or medications, related to **Fig. 7**.

Table S19. Results of burden tests.

Table S20. PheWAS analyses demonstrate potential causal effects of metabolites on birthweight, gestational age, GDM, preeclampsia, preterm birth, LGA and SGA.