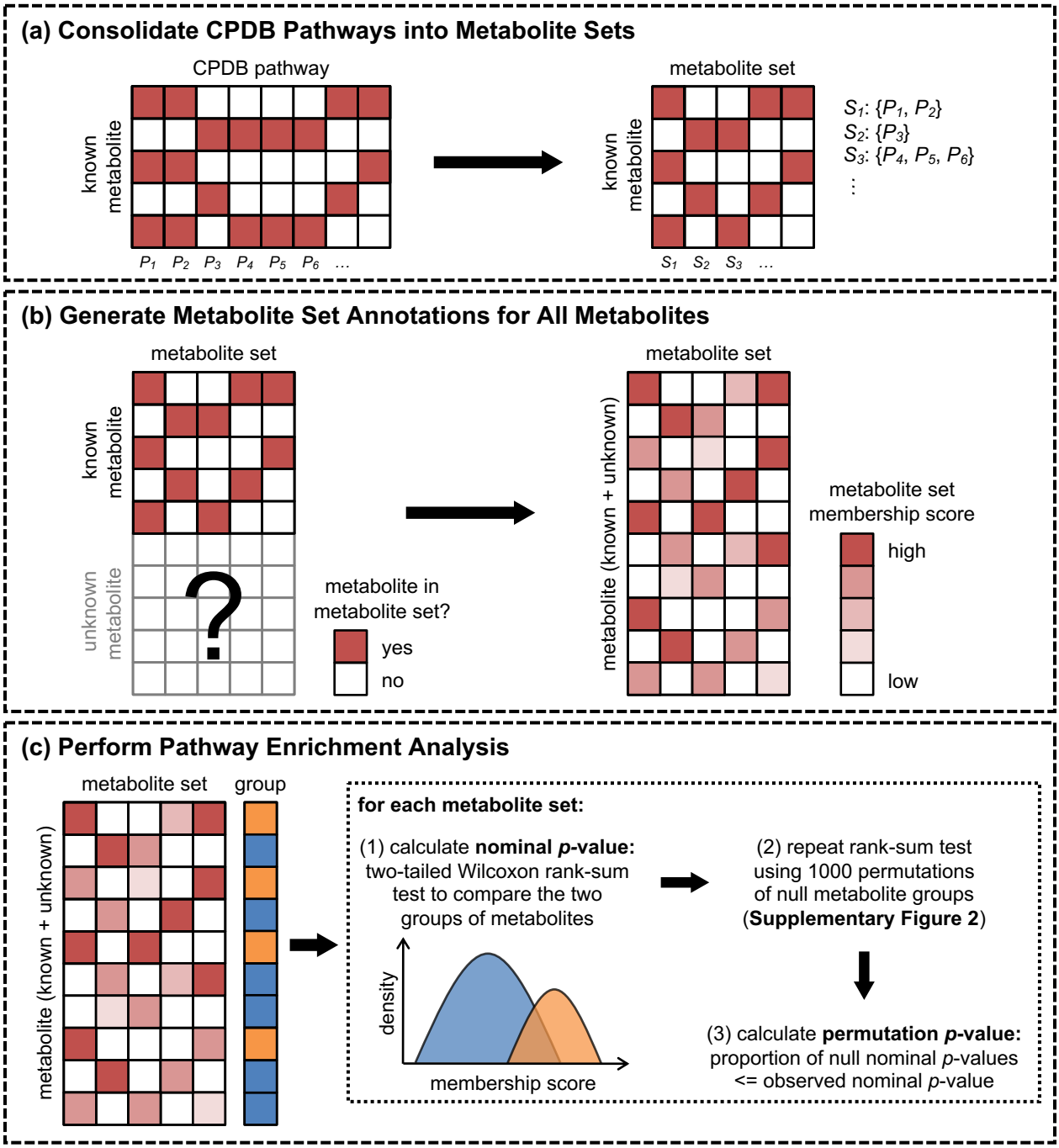
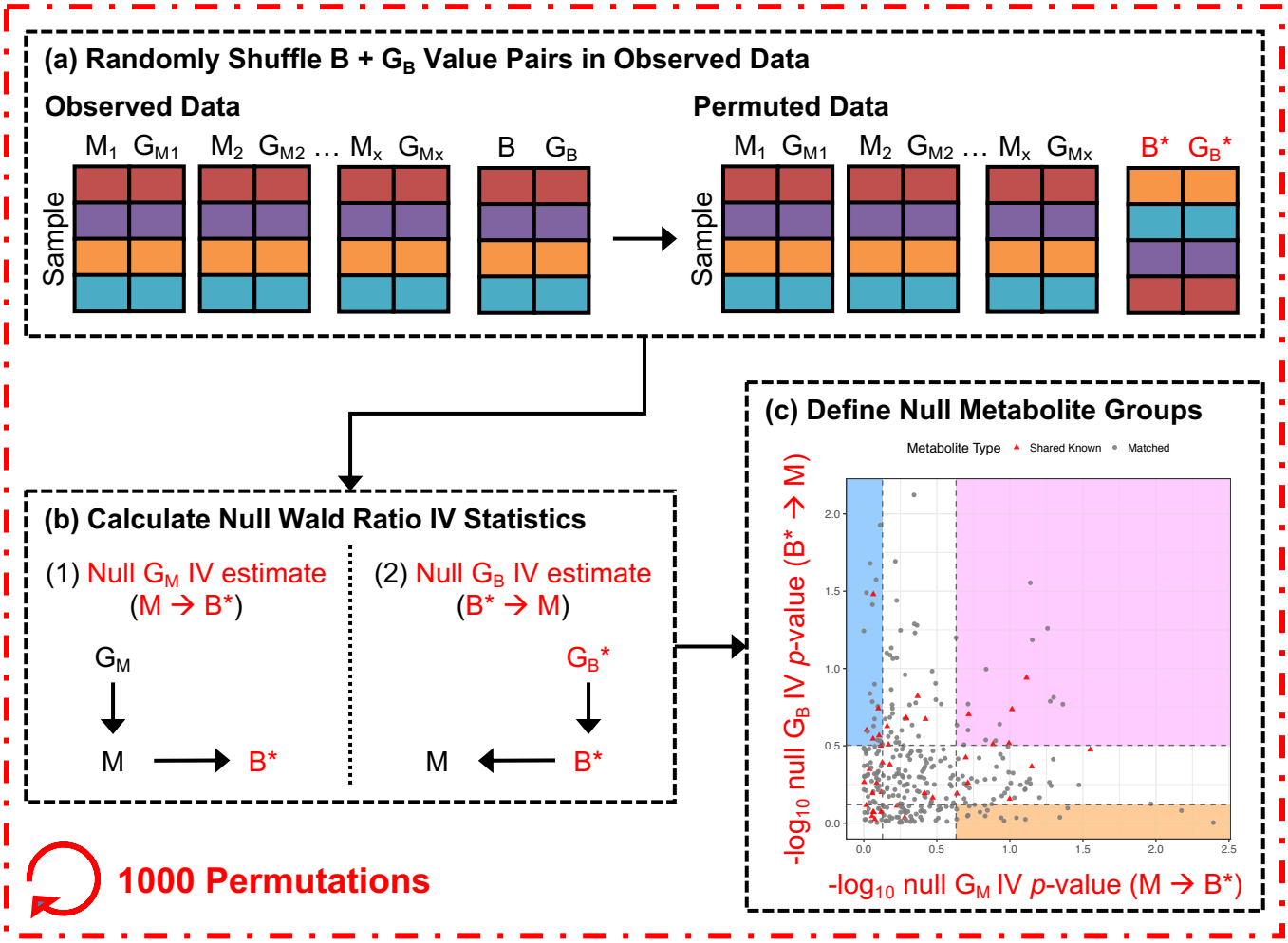
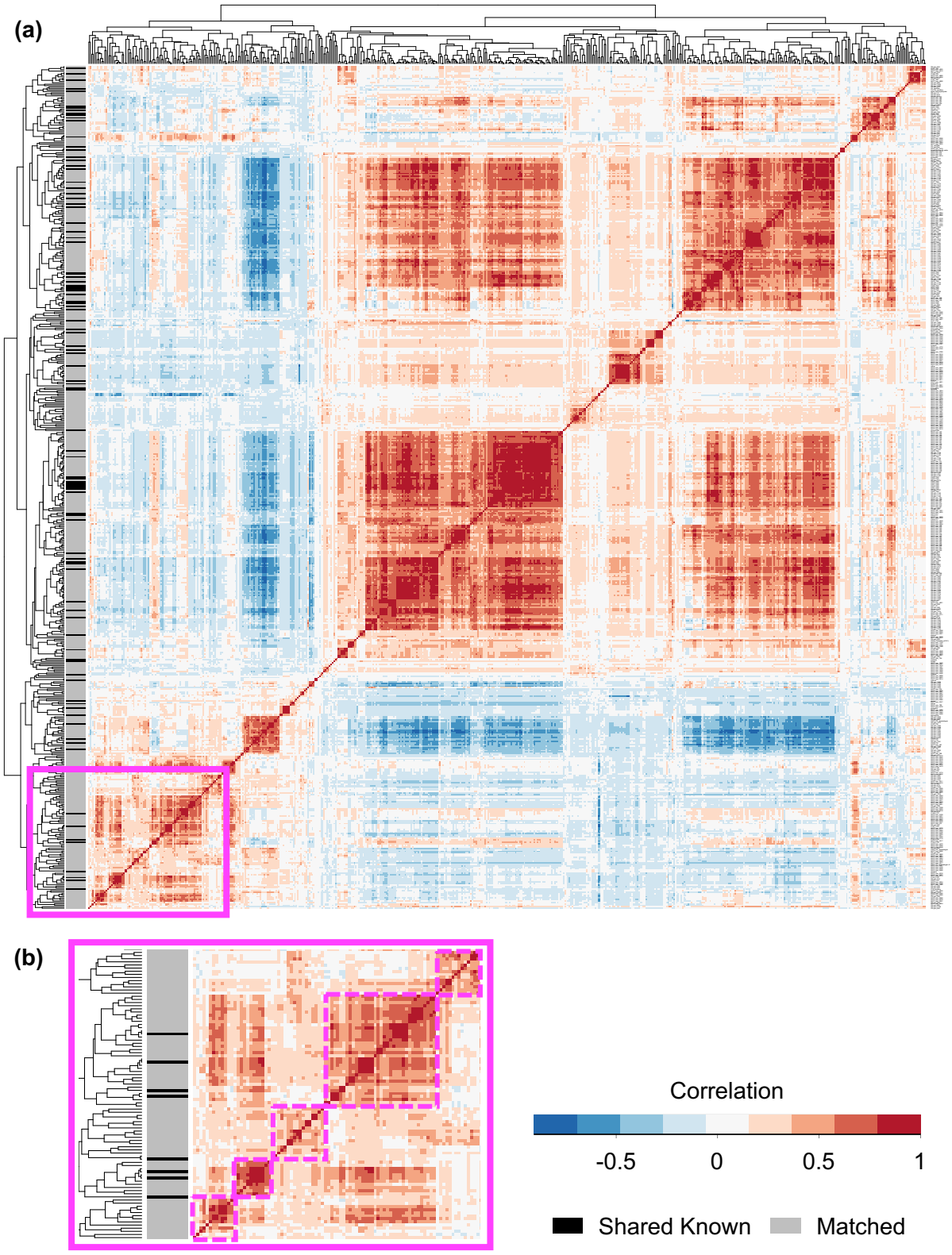


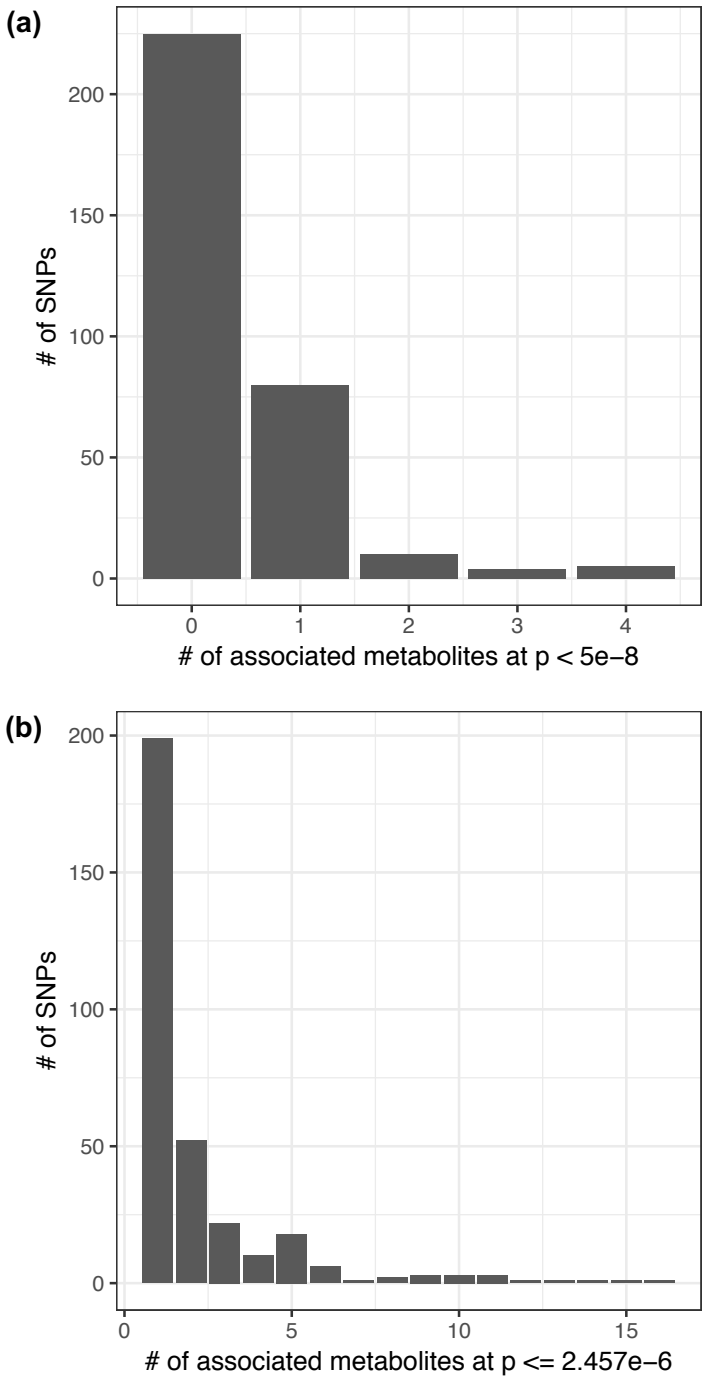
Supplementary Figure 1. PAIRUP-MS pathway annotation and analysis framework. (a) ConsensusPathDB (CPDB) pathways containing at least two known metabolites measured in BioAge data were consolidated into metabolite sets with unique metabolite combinations (e.g. pathways P_1 and P_2 were consolidated into metabolite set S_1). **(b)** Metabolite correlation structure in BioAge data were used to extend (reconstitute) the metabolite sets to include both known and unknown metabolites, calculating a numeric membership score for each metabolite in each metabolite set. **(c)** To identify enriched metabolite sets differing between two groups of metabolites, for each metabolite set: (1) two-tailed Wilcoxon rank-sum test was performed to calculate a nominal *p*-value, (2) the rank-sum test was repeated 1000 times using null metabolite groups (see **Supplementary Figure 2**), and (3) a permutation-based enrichment *p*-value was calculated as the proportion of null nominal *p*-values <= observed nominal *p*-value.



Supplementary Figure 2. Scheme for generating null metabolite groups used in pathway analyses. (a) For each permutation, we randomly shuffled the BMI (B) and G_B value pairs in OE and MCDS data, while leaving the metabolites (M) and G_M data unchanged. Same color shading in the cartoon matrices indicates data that originated from the same sample in observed data. B* and G_B*, permuted BMI and G_B data, respectively. **(b)** We used the permuted data to calculate null Wald ratio IV statistics for both G_M (metabolite-to-BMI direction, M → B*) and G_B (BMI-to-metabolite direction, B* → M). **(c)** We used the top and bottom quartile cutoffs of the null IV *p*-values to define null cause, effect, and bidirectional metabolite groups (mirroring how we defined the observed metabolite groups). The entire permutation procedure (steps (a) – (c)) was repeated 1000 times to generate 1000 sets of null metabolite groups, which were used to calculate the permutation-based pathway enrichment *p*-values in PAIRUP-MS pathway analyses (see **Supplementary Figure 1c**).



Supplementary Figure 3. Clustered correlation heat map of 577 BMI-associated metabolites in OE and MCDS. (a) Heat map of all BMI-associated metabolites. Euclidean distance-based hierarchical clustering was performed on pairwise correlations of the metabolites in OE+MCDS samples. Shared known (black) and matched (grey) metabolites are annotated by side bar on the left. **(b)** Zoomed-in view of a portion of the heat map (solid pink box in (a)), with distinct clusters (as defined by the clustering dendrogram) highlighted by pink dashed boxes.



Supplementary Figure 4. Level of association between the 324 G_M SNPs and the 324 BMI-associated metabolites in OE and MCDS. (a) Histogram showing number of metabolites associated with each SNP at genome-wide significance ($p < 5 \times 10^{-8}$); 19 out of 324 (5.86%) SNPs are associated with > 1 metabolite. **(b)** Histogram showing number of metabolites associated with each SNP at $p <= 2.457 \times 10^{-6}$ (maximum p-value for the selected metabolite-G_M pairs); 125 out of 324 (38.6%) SNPs are associated with > 1 metabolite.