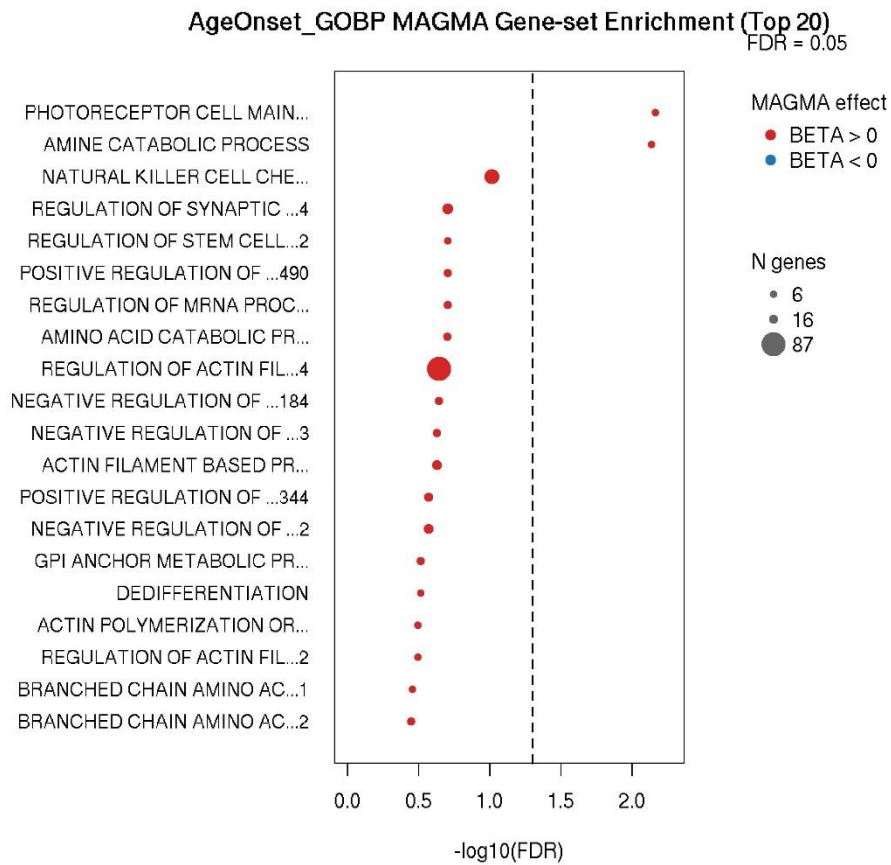
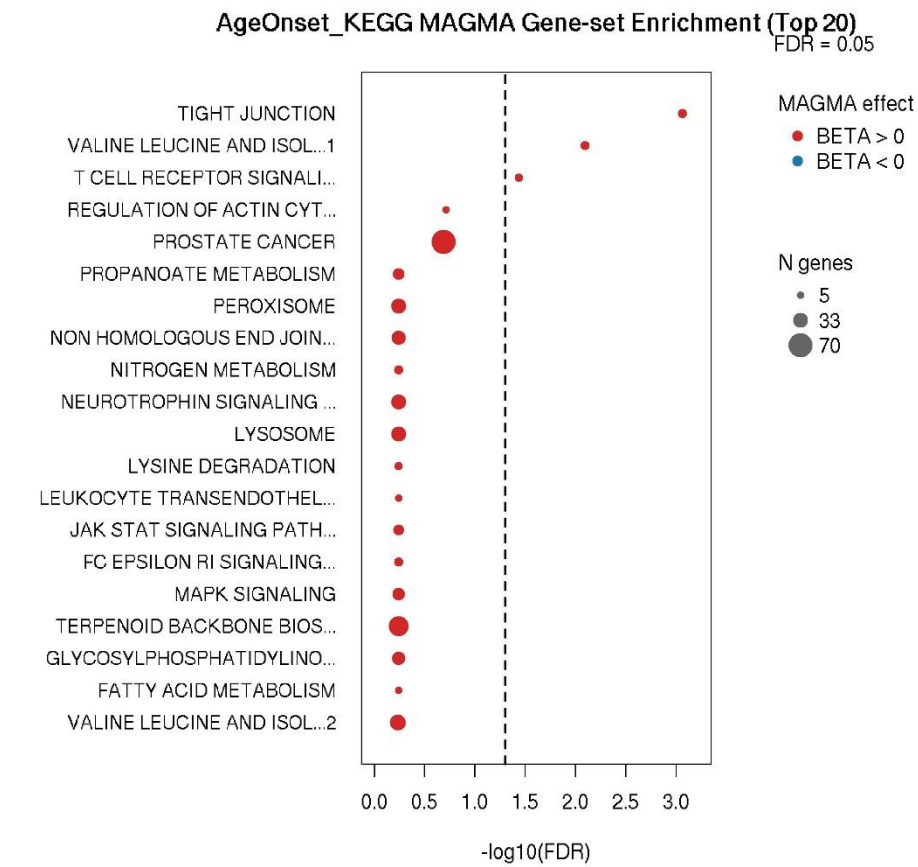
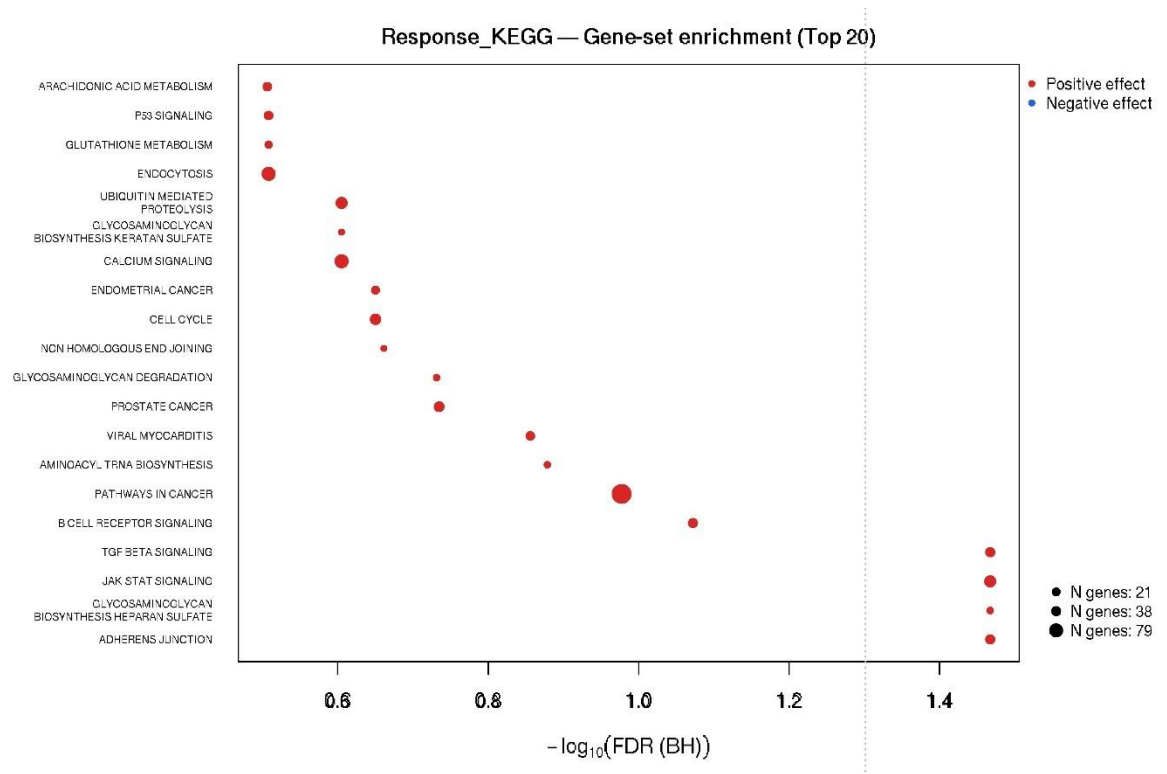




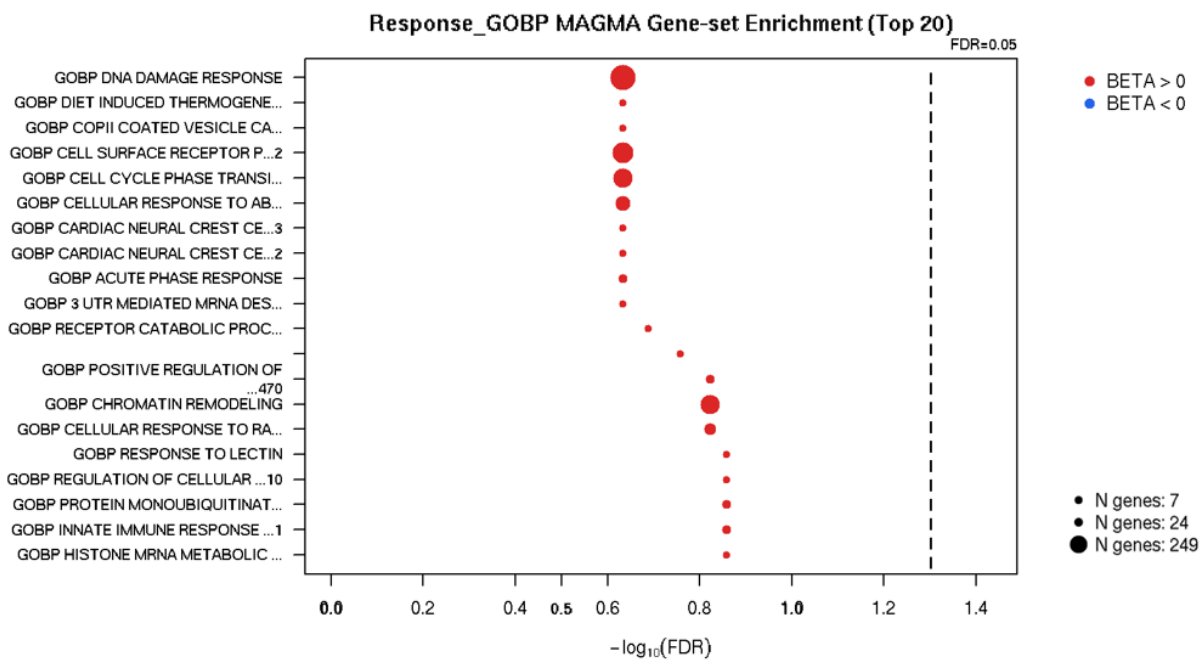
(A)



(B)



(C)



(D)

Supplementary Figure 4 **MAGMA competitive gene-set enrichment for age of onset and methadone response**

Competitive gene-set enrichment analyses were performed in **MAGMA v1.10** using **KEGG** (MSigDB c2.cp.kegg_legacy v2024.1) and **GO Biological Process** (MSigDB c5.go.bp v2024.1), adjusting for MAGMA's standard gene-level covariates (**gene size, gene density, inverse MAC**) and applying **Benjamini–Hochberg (BH)** correction within each analysis. Dot plots show the **top 20 gene sets** ranked by q ; the x-axis is $-\log_{10}(q)$, dot size reflects the **number of genes** in each set, and dot color indicates the **direction of effect** ($\beta > 0$ positive; $\beta < 0$ negative). The dashed vertical line marks the $q = 0.05$ threshold. **(A) Age of onset — KEGG gene-set enrichment (Top 20)**

Age of onset showed reproducible enrichment for **metabolic and intracellular signaling pathways**. Among KEGG (186 gene sets), **five pathways reached $q < 0.25$** , with **three surviving $q < 0.05$** , led by **valine, leucine and isoleucine degradation, fatty acid metabolism, and GPI-anchor biosynthesis**. Two additional pathways (**MAPK signaling and terpenoid backbone biosynthesis**) were enriched at $q < 0.25$, supporting a model in which earlier onset reflects broad metabolic vulnerability with MAPK-related signaling involvement.

(B) Age of onset — GO Biological Process gene-set enrichment (Top 20)

GO BP results reinforced the metabolic signature observed in KEGG. Across GO BP (5,543 gene sets), **eight terms reached $q < 0.25$** and **two survived $q < 0.05$** , with the strongest signals mapping to **branched-chain amino acid catabolic processes** ($\beta \approx 1.43\text{--}1.44$). Additional nominally enriched processes included **amino acid catabolism, GPI-anchor metabolism, and regulation of actin filament organization** ($q < 0.25$), indicating convergent enrichment in amino-acid metabolism and cytoskeletal regulation.

(C) Methadone response — KEGG gene-set enrichment (Top 20)

Methadone response was enriched for pathways implicating **cell–cell adhesion/ECM remodeling and cytokine signaling**. Sixteen KEGG pathways reached $q < 0.25$, with **four surviving $q < 0.05$** : **adherens junction, glycosaminoglycan biosynthesis—chondroitin sulfate, JAK–STAT signaling, and TGF- β signaling**. Additional pathways enriched at $q < 0.25$ included immune-related signatures (e.g., **B-cell receptor signaling**), **proteostasis/ubiquitin, DNA repair/cell cycle, and calcium signaling**, consistent with biologically coherent mechanisms underlying inter-individual variability in treatment response.

(D) Methadone response — GO Biological Process gene-set enrichment (Top 20)

GO BP enrichment for methadone response highlighted broader regulatory programs. **Forty-four GO BP terms survived $q < 0.25$** (none at $q < 0.05$), with prominent categories spanning **innate immune activation, protein monoubiquitination/proteostasis, chromatin/DNA damage response, receptor-linked signaling, and stress-response pathways**. Together, these results support a response-associated axis involving **immune and cytokine signaling, proteostasis and epigenetic regulation, and stress-response programs**.