

Description of Additional Supplementary Files

Supplementary Data 1: Genetic correlations between five metabolic aging clocks and 327 circulating metabolites

We applied linkage disequilibrium score regression (LDSC) to estimate genetic correlations between five metabolic biological age gaps (MetBAGs) and 327 circulating metabolites. The analysis includes both 107 directly measured metabolites and additional composite and derived measures available from the dataset.

Supplementary Data 2: Genetic correlations between five metabolic aging clocks and 545 complex traits

We used linkage disequilibrium score regression (LDSC) to estimate genetic correlations between five metabolic biological age gaps (MetBAGs) and a comprehensive set of 545 traits, including 525 disease endpoints (DEs), 9 phenotype-derived aging clocks (PhenoBAGs), and 11 proteome-derived aging clocks (ProtBAGs). NA/empty values indicate that the LDSC model was not converged.

Supplementary Data 3: Two-sample Mendelian randomization analyses between 525 disease endpoints and five metabolic aging clocks.

We conducted bidirectional Mendelian randomization (MR) analyses to infer potential causal relationships between 525 disease endpoints (DEs) and five metabolic biological age gaps (MetBAGs). Two causal frameworks were examined: (i) DE2MetBAG, where disease endpoints with sufficient instrumental variables were treated as exposures and MetBAGs as outcomes; and (ii) MetBAG2DE, where MetBAGs served as exposures and disease endpoints as outcomes.

Supplementary Data 4: Sensitivity analyses for the DE2MetBAG causal network.

We conducted a series of sensitivity checks for the significant associations identified in the DE2MetBAG Mendelian randomization (MR) analyses: a) Scatter plot showing SNP effect sizes for the exposure (x-axis, log OR) and outcome (y-axis, log OR), with standard error bars. Causal slopes from five MR estimators are overlaid. b) Forest plot of single-SNP MR estimates, where each point represents the MR effect (log OR) and its 95% confidence interval. c) Leave-one-out analysis evaluating the robustness of the causal effect of the exposure on outcome by iteratively removing one SNP at a time. d) Funnel plot displaying individual SNP-level MR effect sizes versus the inverse of their standard errors, to assess potential directional pleiotropy. e) Heterogeneity test and pleiotropy test.

Supplementary Data 5: Sensitivity analyses for the MetBAG2DE causal network.

We conducted a series of sensitivity checks for the significant associations identified in the MetBAG2DE Mendelian randomization (MR) analyses: a) Scatter plot showing SNP effect sizes for the exposure (x-axis, log OR) and outcome (y-axis, log OR), with standard error bars. Causal slopes from five MR estimators are overlaid. b) Forest plot of single-SNP MR estimates, where each point represents the MR effect (log OR) and its 95% confidence interval. c) Leave-one-out analysis evaluating the robustness of the causal effect of the exposure on outcome by iteratively removing one SNP at a time. d) Funnel plot displaying individual SNP-level MR effect sizes versus the inverse of their standard errors, to assess potential directional pleiotropy. e) Heterogeneity test and pleiotropy test.