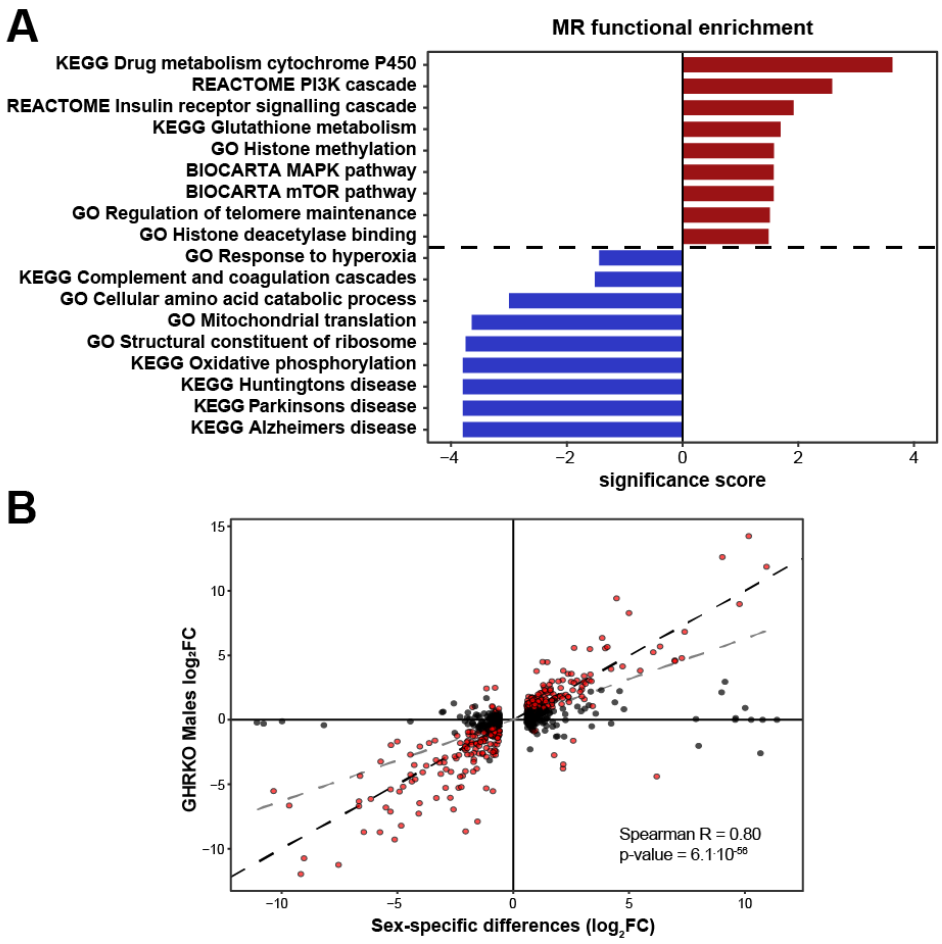

Figure S1, related to Figures 1 and 2. Functional enrichment of methionine restriction (A) and the feminizing effect of GHRKO (B).

(A) Significantly enriched functions in response to MR based on GSEA. Statistically significantly enriched functions (FDR q-value < 0.1) are shown. Significance score, calculated as $\log_{10}$(FDR q-value) corrected by the sign of regulation, is presented on x-axis. Presented functions were selected manually. The whole list of enriched functions can be found in Table S2.

(B) Correlation between feminizing changes and changes induced by GHRKO in males. $\log_2$FC of genes differentially expressed between males and females (BH adjusted p-value < 0.05 and FC > 1.5 in any direction) aggregated across age groups are shown. Genes statistically significantly changed in response to GHRKO (BH adjusted p-value < 0.05 and FC > 1,5 in any direction) are colored in red. Regression and identity lines are shown as grey and black dotted line, respectively.

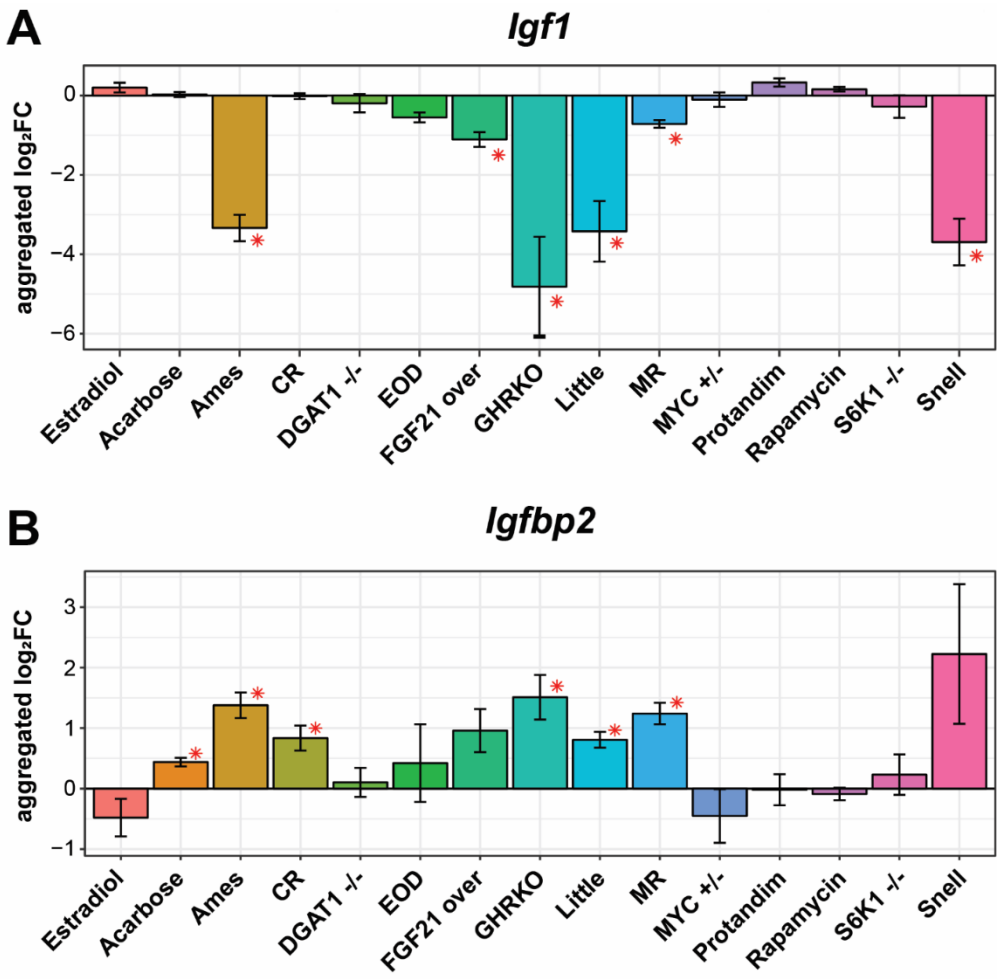

Figure S2, related to Figure 3. *Igf1* (A) and *Igfbp2* (B) fold change across different lifespan-extending interventions.

(A) *Igf1* fold change across lifespan-extending interventions. Insulin-like growth factor 1 (*Igf1*) is significantly downregulated in response to all GH deficiency interventions (Ames and Snell dwarf mice, GHRKO and Little mice) as well as FGF21 overexpression and methionine restriction (BH adjusted p-value < 0.1). Red asterisk denotes interventions with BH adjusted p-value < 0.1.

(B) *Igfbp2* fold change across lifespan-extending interventions. Insulin-like growth factor binding protein 2 (*Igfbp2*), being *Igf1* inhibitor, is significantly upregulated in response to GH deficiency interventions (Ames dwarf mice, GHRKO and Little mice) as well as dietary interventions (MR and CR) and acarbose (BH adjusted p-value < 0.1). Red asterisk denotes interventions with BH adjusted p-value < 0.1.

Estradiol: 17-α-estradiol; Snell: Snell dwarf mice; Ames: Ames dwarf mice; Little: Little mice; CR: Caloric restriction; MR: Methionine Restriction; EOD: Every-other-day feeding; FGF21 over: FGF21 overexpression; GHRKO: Growth Hormone Receptor Knockout.

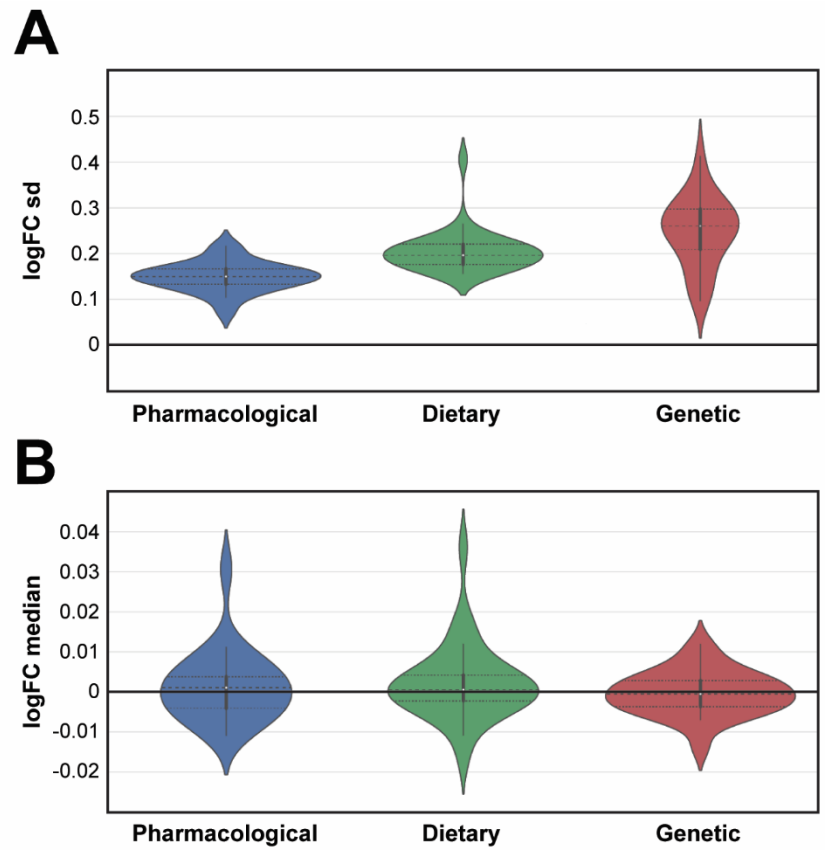

Figure S3, related to Figure 3. Amplitude of gene expression changes induced by different types of interventions.

(A) Standard deviations of gene expression changes (log_2FC) across three main types of interventions. Different intervention types lead to a different scale of gene expression changes, with pharmacological interventions being the mildest and genetic interventions being the most affected. All differences are statistically significant (Mann-Whitney test p-value is equal to $1.71 \cdot 10^{-6}$ between pharmacological and dietary and 0.003 between dietary and genetic).

(B) Medians of gene expression changes (log_2FC) across three main types of interventions. Medians of gene expression changes are distributed similarly across different types of interventions (Mann-Whitney test p-value > 0.05 for all three comparisons).

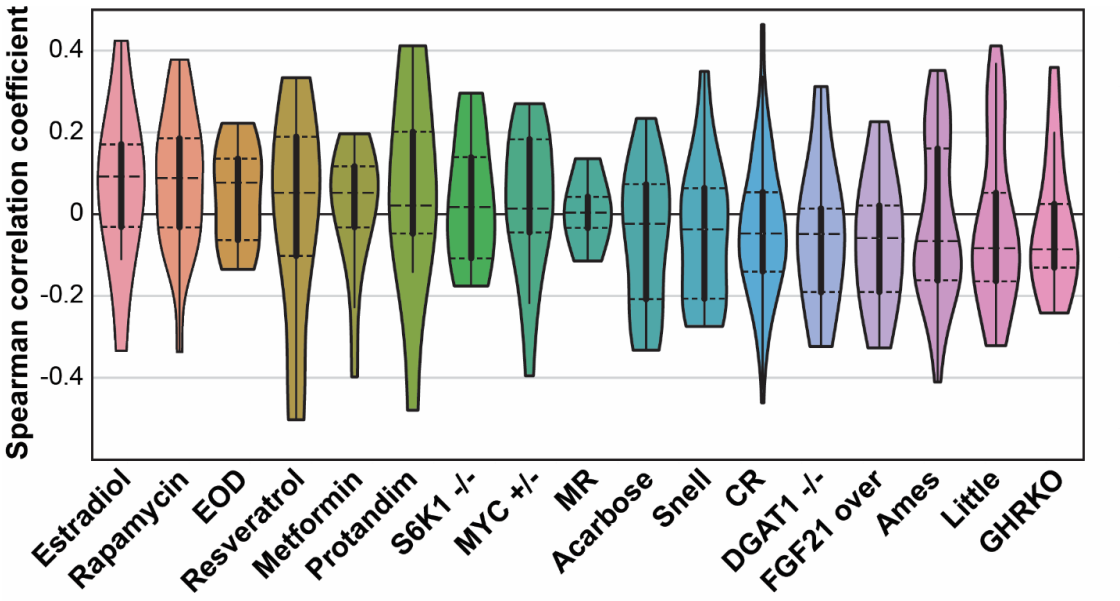

Figure S4, related to Figure 4. Spearman correlation coefficient distribution between gene expression profiles of rapamycin and other interventions.

At the level of gene expression change, rapamycin shows significant positive correlation only with itself (median Spearman correlation coefficient = 0.088; BH adjusted Mann-Whitney test p-value = $2.8 \cdot 10^{-3}$). Although thought to be CR mimetic, rapamycin shows slight (median Spearman correlation coefficient = -0.049) but significant (BH adjusted Mann-Whitney test p-value = $2 \cdot 10^{-3}$) negative correlation with CR at the level of gene expression. For every intervention, violinplot shows the distribution of Spearman correlation coefficient between gene expression changes of every dataset of rapamycin and the corresponding intervention. 250 genes consisting of 125 genes with the lowest p-value in each pair of datasets were used for calculation.

Estradiol: 17-α-estradiol; Snell: Snell dwarf mice; Ames: Ames dwarf mice; Little: Little mice; CR: Caloric restriction; MR: Methionine Restriction; EOD: Every-other-day feeding; FGF21 over: FGF21 overexpression; GHRKO: Growth Hormone Receptor Knockout.

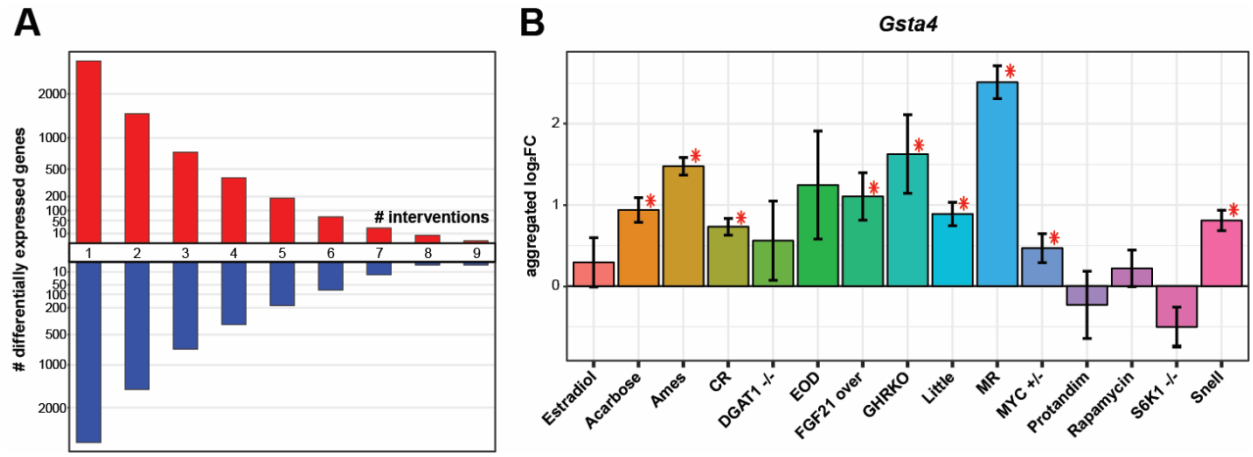

Figure S5, related to Figure 5. Distribution of the number of differentially expressed genes shared across interventions (A) and *Gsta4* fold change across lifespan-extending interventions (B).

(A) Number of genes identified as statistically significantly up- (red) and downregulated (blue) in response to different lifespan-extending interventions. Genes affected by the largest number of individual interventions encode cytochrome P450s and glutathione metabolism proteins. FDR threshold of 0.1 was used to select significant genes within each intervention.

(B) Gsta4 fold change across lifespan-extending interventions. Glutathione S-transferase A4 (*Gsta4*) gene is one of significant commonly upregulated genes across lifespan-extending interventions (BH adjusted robust p-value = 0.013). In addition to being common signature, it is significantly upregulated in response to 9 individual interventions (BH adjusted p-value < 0.1). Red asterisk denotes interventions with BH adjusted p-value < 0.1.

Estradiol: 17-α-estradiol; Snell: Snell dwarf mice; Ames: Ames dwarf mice; Little: Little mice; CR: Caloric restriction; MR: Methionine Restriction; EOD: Every-other-day feeding; FGF21 over: FGF21 overexpression; GHRKO: Growth Hormone Receptor Knockout.

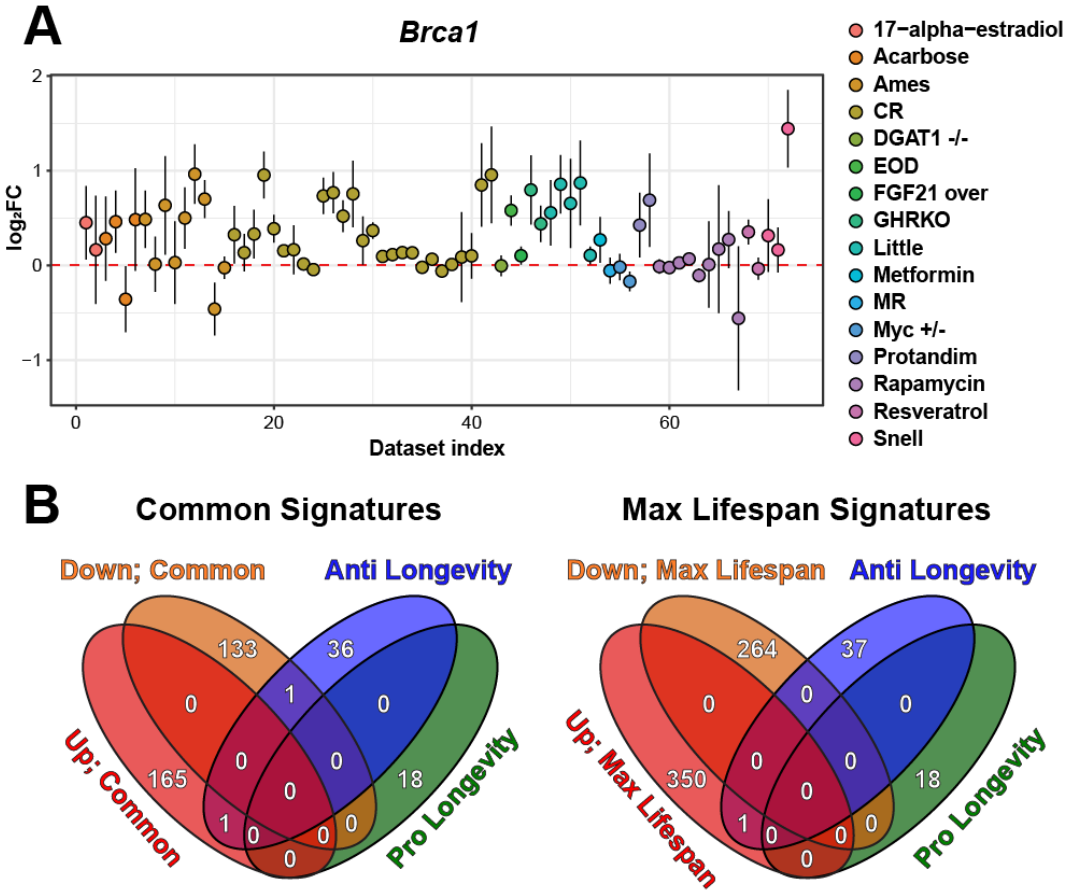

Figure S6, related to Figures 5 and 6. Expression change of genes, whose alterations lead to lifespan extension or shortening in mouse models.

(A) ***Brca1*** **is one of commonly upregulated genes across lifespan-extending interventions (BH adjusted p-value = 0.04).** Snell: Snell dwarf mice; Ames: Ames dwarf mice; Little: Little mice; CR: Caloric restriction; MR: Methionine Restriction; EOD: Every-other-day feeding; FGF21 over: FGF21 overexpression; GHRKO: Growth Hormone Receptor Knockout.

(B) Overlap of gene signatures associated with lifespan extension and genes, whose alteration affects mouse lifespan. Overlap of longevity signatures and genes with the effect on lifespan is not significant for all pairwise comparisons (Fisher exact test p-value > 0.33 for all comparisons). Common: Common signatures; Max Lifespan: signatures associated with maximum lifespan increase; Pro Longevity: Genes, whose overexpression extends lifespan; Anti Longevity: Genes, whose depletion extends lifespan.