

Supplementary Information

The following tables can be found in the Supplementary Data.

Supplementary Data Table S1

Table S1a. Differentially Expressed Genes for the Horvath Clock at FDR<.01

Table S1b. Differentially Expressed Genes for the Hannum Clock at FDR<.01

Table S1c. Differentially Expressed Genes for the PhenoAge Clock at FDR<.01

Table S1d. Differentially Expressed Genes for the GrimAge Clock at FDR<.01

Table S1e. Differentially Expressed Genes for the DunedinPACE Clock at FDR<.01

Supplementary Data Table S2

Table S2a. Results of Gene Set Enrichment Analysis (GSEA) at FDR<.25 for Horvath Clock

Table S2b. Results of Gene Set Enrichment Analysis (GSEA) at FDR<.25 for Hannum Clock

Table S2c. Results of Gene Set Enrichment Analysis (GSEA) at FDR<.25 for PhenoAge Clock

Table S2d. Results of Gene Set Enrichment Analysis (GSEA) at FDR<.25 for GrimAge Clock

Table S2e. Results of Gene Set Enrichment Analysis (GSEA) at FDR<.25 for DunedinPACE Clock

Supplementary Data Table S3

Table S3a. Groupings for the 75 Gene Ontology Clusters, Across all Five Epigenetic Clocks

Table S3b. Groupings for the 4 Gene Ontology Themes, Across all Five Epigenetic Clocks

Supplemental Tables

Table S4. Test sample characteristics for health phenotypes (n=645)

	Mean (SD)	Range	N (%)
Grip strength	30.6 (11.0)	8-100	
Walking speed	3.5 (1.3)	2-12	
ADLs	0.3 (0.9)	0-5	
Frailty index	22.4 (14.9)	0-39	
Cognitive functioning	15.1	0-26	
BMI	30.1 (6.3)	16.5-58.2	
Interkeukin-6	6.6 (11.6)	0.8-177.4	
Interkeukin-10	4.4 (2.8)	1.1-34.2	
Telomere length	1.3 (0.4)	0.1-3.3	
6-year mortality			123 (19.0%)
Heart problems			198 (30.7%)
Diabetes diagnosis			184 (28.5%)
Lung problems			87 (13.5%)
Psychological problems			149 (23.1%)

Table S5. Regression results showing standardized effect sizes when both epigenetic and transcriptomic clocks are in the same model predicting health outcomes

Grip Strength	Estimate	Std. Error	p-value	95% CI Lower Bound	95% CI Upper Bound	p<.05 when both in the model	p<.05 when alone in the model
DNAmHorvath	0.05	0.03	8.4E-02	-0.01	0.10		
TAGSHorvath	-0.11	0.04	9.6E-03	-0.20	-0.03	*	*
DNAmHannum	-0.01	0.03	6.3E-01	-0.07	0.04		
TAGSHannum	-0.07	0.05	1.0E-01	-0.16	0.02		
DNAmPhenoAge	-0.03	0.03	3.4E-01	-0.08	0.03		
TAGSPhenoAge	-0.01	0.03	8.0E-01	-0.08	0.06		
DNAmGrimAge	-0.02	0.03	5.3E-01	-0.09	0.04		
TAGSGrimAge	-0.05	0.03	1.6E-01	-0.12	0.02		
DNAmDunedinPACE	-0.03	0.03	4.3E-01	-0.09	0.04		
TAGSDunedinPACE	-0.01	0.04	7.2E-01	-0.09	0.06		
Cognitive Function							
DNAmHorvath	-0.02	0.04	6.8E-01	-0.09	0.06		
TAGSHorvath	0.03	0.06	6.2E-01	-0.09	0.15		
DNAmHannum	-0.10	0.04	1.3E-02	-0.18	-0.02	*	
TAGSHannum	0.14	0.06	3.0E-02	0.01	0.26	*	
DNAmPhenoAge	-0.04	0.04	3.6E-01	-0.12	0.04		
TAGSPhenoAge	0.10	0.05	4.4E-02	0.00	0.19	*	
DNAmGrimAge	0.10	0.05	2.2E-02	0.02	0.19	*	*
TAGSGrimAge	0.08	0.05	9.7E-02	-0.01	0.17		*
DNAmDunedinPACE	0.10	0.05	2.3E-02	0.01	0.20	*	*
TAGSDunedinPACE	0.04	0.05	4.1E-01	-0.06	0.15		*
BMI							
DNAmHorvath	0.07	0.04	1.2E-01	-0.02	0.15		*
TAGSHorvath	0.01	0.07	8.8E-01	-0.12	0.14		
DNAmHannum	0.11	0.04	1.1E-02	0.03	0.19	*	*
TAGSHannum	0.22	0.07	1.3E-03	0.09	0.35	*	*
DNAmPhenoAge	0.03	0.04	4.6E-01	-0.05	0.12		*
TAGSPhenoAge	0.28	0.05	6.6E-08	0.18	0.37	*	*
DNAmGrimAge	0.03	0.05	5.7E-01	-0.07	0.13		*
TAGSGrimAge	0.18	0.05	7.1E-04	0.08	0.28	*	*
DNAmDunedinPACE	0.17	0.05	3.4E-04	0.08	0.27	*	*
TAGSDunedinPACE	0.25	0.06	1.2E-05	0.14	0.37	*	*
Mortality							
DNAmHorvath	0.01	0.10	9.4E-01	-0.19	0.21		
TAGSHorvath	0.51	0.16	1.4E-03	0.20	0.82	*	*
DNAmHannum	-0.13	0.10	2.0E-01	-0.33	0.07		
TAGSHannum	0.69	0.15	3.9E-06	0.39	0.98	*	*
DNAmPhenoAge	0.02	0.09	8.2E-01	-0.16	0.20		*
TAGSPhenoAge	0.42	0.11	1.7E-04	0.20	0.64	*	*
DNAmGrimAge	0.52	0.12	1.3E-05	0.29	0.76	*	*

TAGSGrimAge	0.37	0.12	2.4E-03	0.13	0.61	*	*
DNAmDunedinPACE	0.39	0.12	1.1E-03	0.16	0.63	*	*
TAGSDunedinPACE	0.30	0.14	3.3E-02	0.02	0.57	*	*
Diabetes							
DNAmHorvath	-0.01	0.10	9.4E-01	-0.20	0.19		
TAGSHorvath	0.31	0.15	4.1E-02	0.01	0.61	*	*
DNAmHannum	0.15	0.11	1.6E-01	-0.06	0.36		*
TAGSHannum	0.98	0.17	4.0E-09	0.66	1.32	*	*
DNAmPhenoAge	0.03	0.11	8.1E-01	-0.18	0.23		*
TAGSPHenoAge	0.85	0.13	9.1E-11	0.60	1.11	*	*
DNAmGrimAge	0.03	0.11	7.9E-01	-0.20	0.25		*
TAGSGrimAge	0.54	0.12	8.8E-06	0.31	0.78	*	*
DNAmDunedinPACE	0.32	0.12	7.3E-03	0.09	0.56	*	*
TAGSDunedinPACE	0.62	0.15	2.1E-05	0.34	0.92	*	*
Frailty							
DNAmHorvath	-0.04	0.04	2.7E-01	-0.12	0.03		
TAGSHorvath	0.16	0.06	1.2E-02	0.03	0.28	*	*
DNAmHannum	0.07	0.04	9.4E-02	-0.01	0.14		*
TAGSHannum	0.34	0.06	6.8E-08	0.22	0.46	*	*
DNAmPhenoAge	0.00	0.04	9.4E-01	-0.08	0.08		*
TAGSPHenoAge	0.31	0.05	4.7E-11	0.22	0.41	*	*
DNAmGrimAge	0.18	0.04	4.2E-05	0.10	0.27	*	*
TAGSGrimAge	0.23	0.05	1.3E-06	0.14	0.32	*	*
DNAmDunedinPACE	0.20	0.05	1.3E-05	0.11	0.29	*	*
TAGSDunedinPACE	0.21	0.05	1.3E-04	0.10	0.31	*	*
Heart Disease							
DNAmHorvath	-0.15	0.10	1.4E-01	-0.34	0.04		
TAGSHorvath	0.22	0.15	1.5E-01	-0.08	0.51		
DNAmHannum	-0.10	0.10	3.1E-01	-0.30	0.09		
TAGSHannum	0.39	0.15	1.2E-02	0.09	0.70	*	*
DNAmPhenoAge	0.01	0.10	9.1E-01	-0.19	0.21		
TAGSPHenoAge	0.42	0.12	4.9E-04	0.19	0.66	*	*
DNAmGrimAge	0.17	0.11	1.3E-01	-0.05	0.39		*
TAGSGrimAge	0.34	0.12	4.4E-03	0.11	0.58	*	*
DNAmDunedinPACE	0.28	0.12	1.8E-02	0.05	0.51	*	*
TAGSDunedinPACE	0.34	0.14	1.7E-02	0.06	0.62	*	*
Interleukin-6							
DNAmHorvath	0.01	0.03	8.1E-01	-0.05	0.06		
TAGSHorvath	-0.01	0.04	8.6E-01	-0.09	0.08		
DNAmHannum	0.03	0.03	3.1E-01	-0.03	0.08		
TAGSHannum	0.15	0.04	6.1E-04	0.06	0.23	*	*
DNAmPhenoAge	0.00	0.03	9.2E-01	-0.06	0.05		*
TAGSPHenoAge	0.21	0.03	4.4E-11	0.15	0.27	*	*
DNAmGrimAge	0.00	0.03	9.6E-01	-0.06	0.06		*
TAGSGrimAge	0.29	0.03	1.7E-20	0.23	0.35	*	*

DNAmDunedinPACE	0.11	0.03	3.5E-04	0.05	0.16	*	*
TAGSDunedinPACE	0.22	0.03	9.3E-10	0.15	0.29	*	*
Interleukin-10							
DNAmHorvath	0.02	0.01	2.2E-01	-0.01	0.04		
TAGSHorvath	0.04	0.02	6.6E-02	0.00	0.08		*
DNAmHannum	0.04	0.01	6.3E-03	0.01	0.06	*	*
TAGSHannum	0.09	0.02	1.5E-05	0.05	0.14	*	*
DNAmPhenoAge	0.03	0.01	1.2E-02	0.01	0.06	*	*
TAGSPhenAge	0.11	0.02	8.2E-11	0.07	0.14	*	
DNAmGrimAge	-0.04	0.02	2.1E-02	-0.07	-0.01	*	*
TAGSGrimAge	0.11	0.02	1.1E-11	0.08	0.14	*	*
DNAmDunedinPACE	0.01	0.02	6.4E-01	-0.02	0.04		*
TAGSDunedinPACE	0.11	0.02	2.4E-09	0.08	0.15	*	*
Lung Problems							
DNAmHorvath	-0.27	0.13	4.3E-02	-0.54	-0.01	*	
TAGSHorvath	0.65	0.20	1.4E-03	0.25	1.05	*	*
DNAmHannum	-0.06	0.14	6.5E-01	-0.35	0.21		
TAGSHannum	0.67	0.20	9.6E-04	0.28	1.08	*	*
DNAmPhenoAge	-0.18	0.14	2.0E-01	-0.46	0.09		
TAGSPhenAge	0.47	0.16	2.9E-03	0.16	0.78	*	*
DNAmGrimAge	0.68	0.15	1.2E-05	0.38	0.99	*	*
TAGSGrimAge	0.13	0.16	4.0E-01	-0.18	0.45		*
DNAmDunedinPACE	0.42	0.15	5.9E-03	0.12	0.72	*	*
TAGSDunedinPACE	0.12	0.19	5.3E-01	-0.25	0.49		*
Psychological Problems							
DNAmHorvath	-0.11	0.11	3.1E-01	-0.32	0.10		
TAGSHorvath	0.23	0.16	1.6E-01	-0.09	0.55		
DNAmHannum	0.22	0.11	3.9E-02	0.01	0.44	*	*
TAGSHannum	0.16	0.17	3.5E-01	-0.17	0.48		
DNAmPhenoAge	0.01	0.11	9.4E-01	-0.22	0.23		
TAGSPhenAge	0.09	0.13	5.0E-01	-0.17	0.33		
DNAmGrimAge	0.20	0.12	1.0E-01	-0.04	0.44		*
TAGSGrimAge	0.12	0.13	3.7E-01	-0.14	0.37		
DNAmDunedinPACE	0.10	0.12	4.1E-01	-0.14	0.34		
TAGSDunedinPACE	0.00	0.15	1.0E+00	-0.29	0.29		
Telomere Length							
DNAmHorvath	0.02	0.04	5.4E-01	-0.06	0.11		
TAGSHorvath	0.02	0.06	7.3E-01	-0.10	0.15		
DNAmHannum	-0.05	0.04	2.0E-01	-0.13	0.03		
TAGSHannum	-0.11	0.06	1.0E-01	-0.23	0.02		
DNAmPhenoAge	-0.01	0.04	7.7E-01	-0.09	0.07		
TAGSPhenAge	-0.17	0.05	6.6E-04	-0.26	-0.07	*	*
DNAmGrimAge	-0.02	0.05	6.8E-01	-0.11	0.07		
TAGSGrimAge	-0.13	0.05	1.1E-02	-0.22	-0.03	*	*

DNAmDunedinPACE	-0.02	0.05	7.5E-01	-0.11	0.08		*
TAGSDunedinPACE	-0.19	0.06	5.8E-04	-0.30	-0.08	*	*
Walking Speed							
DNAmHorvath	0.03	0.02	6.2E-02	0.00	0.06		
TAGSHorvath	0.04	0.02	1.2E-01	-0.01	0.09		*
DNAmHannum	0.02	0.02	1.1E-01	-0.01	0.06		*
TAGSHannum	0.08	0.02	1.9E-03	0.03	0.13	*	*
DNAmPhenoAge	0.00	0.02	8.9E-01	-0.03	0.03		*
TAGSPhenAge	0.06	0.02	4.3E-03	0.02	0.09	*	*
DNAmGrimAge	0.06	0.02	5.1E-04	0.03	0.10	*	*
TAGSGrimAge	0.03	0.02	2.0E-01	-0.01	0.06		*
DNAmDunedinPACE	0.03	0.02	1.5E-01	-0.01	0.06		*
TAGSDunedinPACE	0.05	0.02	2.5E-02	0.01	0.09	*	*
ADLs							
DNAmHorvath	-0.12	0.08	1.2E-01	-0.27	0.03		
TAGSHorvath	0.39	0.11	7.2E-04	0.16	0.61	*	*
DNAmHannum	0.17	0.08	2.1E-02	0.03	0.32	*	*
TAGSHannum	0.30	0.10	3.4E-03	0.10	0.50	*	*
DNAmPhenoAge	0.04	0.08	6.1E-01	-0.11	0.18		
TAGSPhenAge	0.27	0.08	9.8E-04	0.11	0.43	*	*
DNAmGrimAge	0.16	0.09	5.4E-02	0.00	0.33	*	*
TAGSGrimAge	0.27	0.09	1.9E-03	0.10	0.44	*	*
DNAmDunedinPACE	0.27	0.08	1.6E-03	0.10	0.43	*	*
TAGSDunedinPACE	0.17	0.10	9.2E-02	-0.03	0.38		*

Note. Colors help to distinguish epigenetic and transcriptomic clock pairs visually with Horvath clocks in violet, Hannum in green, PhenoAge in gold, GrimAge in orange, and DunedinPACE in purple.

Table S6. Model Discrimination and Performance Metrics when DNAm and TAGS predict health outcomes, separately and in the same model

		TAGS or DNAm Clock in Separate Models										Both TAGS + DNAm Clocks in the Same Model				
Model	Measure	TAGS Horvath	DNAm Horvath	TAGS Hannum	DNAm Hannum	TAGS Pheno Age	DNAm Pheno Age	TAGS GrimAge	DNAm GrimAge	TAGS Dunedin PACE	DNAm Dunedin PACE	TAGS + DNAm Horvath	TAGS + DNAm Hannum	TAGS + DNAm Pheno Age	TAGS + DNAm GrimAge	TAGS + DNAm Dunedin PACE
Linear																
BMI	R2	0.14	0.08	0.17	0.10	0.19	0.09	0.17	0.08	0.22	0.14	0.21	0.22	0.23	0.22	0.23
Cognitive Function		0.21	0.14	0.21	0.14	0.21	0.14	0.22	0.15	0.21	0.15	0.21	0.22	0.21	0.22	0.22
Frailty Index		0.15	0.06	0.18	0.08	0.19	0.08	0.21	0.14	0.19	0.15	0.15	0.18	0.19	0.23	0.22
Gait Speed		0.28	0.23	0.30	0.23	0.30	0.22	0.30	0.26	0.30	0.23	0.29	0.31	0.30	0.32	0.30
Grip Strength		0.63	0.59	0.63	0.59	0.63	0.59	0.63	0.59	0.63	0.59	0.64	0.63	0.63	0.63	0.63
Interleukin-6		0.06	0.08	0.08	0.08	0.13	0.11	0.22	0.09	0.18	0.17	0.11	0.13	0.18	0.25	0.24
Interleukin-10		0.08	0.06	0.11	0.08	0.16	0.06	0.13	0.09	0.15	0.09	0.11	0.15	0.20	0.17	0.18
Telomere Length		0.21	0.09	0.21	0.10	0.23	0.10	0.22	0.10	0.23	0.10	0.21	0.22	0.23	0.22	0.23
Logistic																
Diabetes diagnosis	McFadden's pseudo-R2	0.06	0.01	0.11	0.03	0.13	0.02	0.09	0.03	0.11	0.05	0.06	0.12	0.13	0.09	0.12
Heart problems		0.09	0.04	0.09	0.03	0.10	0.04	0.10	0.05	0.11	0.06	0.09	0.09	0.10	0.11	0.11
Lung problems		0.14	0.01	0.15	0.01	0.14	0.01	0.14	0.08	0.14	0.04	0.15	0.15	0.14	0.18	0.15
Psych. problems		0.08	0.05	0.08	0.05	0.07	0.05	0.08	0.05	0.07	0.05	0.08	0.08	0.07	0.08	0.08
Diabetes diagnosis	AUC	0.67	0.60	0.73	0.62	0.74	0.61	0.71	0.63	0.73	0.66	0.67	0.74	0.74	0.71	0.73
Heart problems		0.69	0.63	0.70	0.62	0.71	0.63	0.71	0.65	0.72	0.66	0.70	0.70	0.71	0.72	0.73
Lung problems		0.76	0.56	0.77	0.57	0.76	0.57	0.77	0.70	0.76	0.64	0.77	0.77	0.77	0.79	0.77
Psych. problems		0.68	0.64	0.68	0.65	0.68	0.64	0.68	0.65	0.68	0.64	0.68	0.69	0.68	0.69	0.68
Cox																
Mortality	Cox-Snell R2	0.24	0.20	0.25	0.20	0.25	0.21	0.27	0.23	0.25	0.23	0.24	0.26	0.25	0.29	0.27
Mortality	Concordance	0.82	0.77	0.82	0.77	0.82	0.78	0.83	0.81	0.82	0.80	0.82	0.82	0.82	0.84	0.82
Negative Binomial																
ADLs	McFadden's pseudo-R2	0.05	0.01	0.06	0.01	0.06	0.01	0.06	0.01	0.06	0.02	0.06	0.06	0.06	0.06	0.06

Note. Column colors help to distinguish epigenetic and transcriptomic clock pairs visually with Horvath clocks columns in violet, Hannum in green, PhenoAge in gold, GrimAge in orange, and DunedinPACE in purple. Bolded, red text indicates where the estimate measure is larger for the model when both epigenetic and transcriptomic clocks are in the model compared to only one version being in the model.

Table S7. Model Diagnostics

Model type	Metric	Summary
Linear		
Interleukin-6	Max VIF	1.0-2.9
Interleukin-10	Max VIF	1.0-2.9
BMI	Max VIF	1.0-2.2
Grip Strength	Max VIF	1.0-2.2
Walking Speed	Max VIF	1.0-2.3
Telomere Length	Max VIF	1.0-2.1
Frailty Index	Max VIF	1.0-2.0
Cognitive Function	Max VIF	1.0-1.9
Logistic		
Diabetes	Max VIF	1.0-2.2
Lung Problems	Max VIF	1.0-2.2
Heart Problems	Max VIF	1.0-2.0
Psych Problems	Max VIF	1.0-4.7
Linear and Logistic	Max Cook's D	< 0.15
Negative Binomial	Dispersion parameter	0.9–1.0
Cox	Global PH test p-values	0.31–0.87

Table S8. Results of CpG to gene mapping

	# of CpGs in the clock	# of clock CpGs in HRS dataset	# of CpGs mapped to cis-gene	# of CpGs-gene pairs with $ r > .25$	# CpG-gene pairs with $ r > .25$ and identified as a DEG (% of mapped)
Horvath	353	334	305	5	0 (0.00%)
Hannum	71	65	41	4	3 (7.31%)
PhenoAge	513	512	478	11	3 (0.63%)
GrimAge	1030	1025	611	26	7 (1.15%)
DunedinPACE	173	173	101	6	1 (0.99%)

Notes. DEG = differentially expressed gene

Table S9. CpG-cis expression quantitative trait methylation (EQTM) pairs where correlations are $|r| > .25$

CpG	Gene	correlation
Horvath		
cg20240860	ACCS	-0.47
cg07730301	ALDH3B1	-0.32
cg07770222	C8orf31	-0.64
cg16899442	CCDC78	0.25
cg05921699	CD79A	-0.26
cg08771731	LOC285696	-0.25
cg17338403	SLCO3A1	-0.36
cg09646392	TNFSF13B	-0.37
Hannum		
cg10501210	C1orf132	-0.34
cg06419846	CD248*	-0.28
cg11067179	CD248*	-0.28
cg22213242	CD248*	-0.28
PhenoAge		
cg10636246	AIM2*	-0.39
cg08529529	ALOX5AP	-0.29
cg24921089	AMPD3	-0.34
cg23159337	ATP13A4	0.54
cg23668631	CAMKK1	-0.34
cg22194129	CLEC4C	-0.37
cg23234999	MKRN3*	-0.61
cg19566405	SLFN12	-0.37
cg09045681	TCF19	0.27
cg01626227	TRIM4	-0.25
cg08668790	ZNF154*	-0.49
GrimAge		
cg06500161	ABCG1	-0.28
cg27243685	ABCG1	-0.28
cg12020464	ABO	-0.29
cg03604011	AHRR*	-0.40
cg05575921	AHRR*	-0.40
cg11554391	AHRR*	-0.40
cg17287155	AHRR*	-0.40
cg10636246	AIM2	-0.39
cg10224107	C5AR1	-0.34
cg25939861	CD8A	-0.66
cg14928764	CD93*	-0.35
cg00959259	DTX3L	-0.41
cg08122652	DTX3L	-0.41
cg22930808	DTX3L	-0.41
cg21584251	FAM153B	-0.26
cg09899215	LDHD	-0.49

cg24429836	LDHD	-0.49
cg06806711	MS4A1	-0.27
cg14592365	POU2AF1	-0.30
cg01256539	PRR16	-0.27
cg15947697	PSORS1C3	-0.38
cg05174890	SLFN12	-0.33
cg10431713	SLFN12	-0.33
cg10130564	TAGLN*	0.42
cg12051762	TAGLN*	0.42
cg07973162	UGT2B17	0.40
DunedinPACE		
cg06500161	ABCG1*	-0.34
cg05991820	ECHDC3	-0.37
cg11103390	ECHDC3	-0.37
cg17460386	FAIM3	-0.35
cg04927537	LGALS3BP	-0.29
cg11202345	LGALS3BP	-0.29

* indicates the gene was identified as a differentially expressed gene in association with the clock.

Supplementary Figures

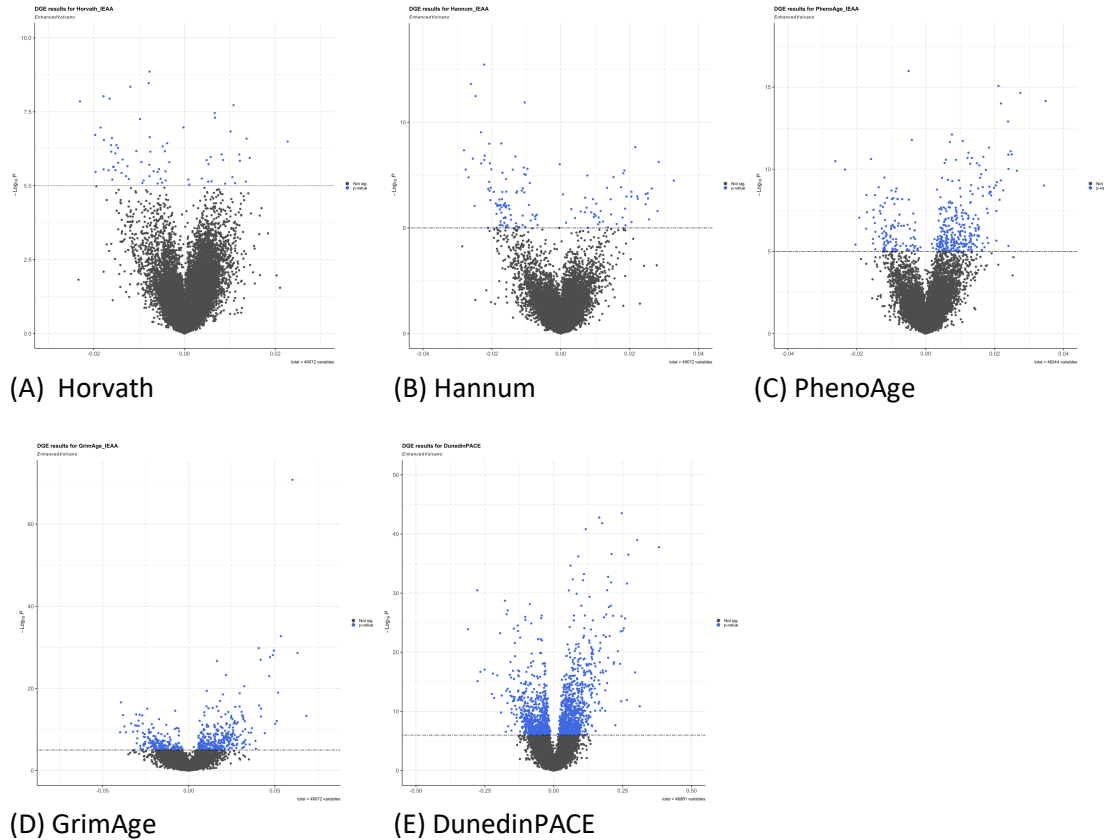
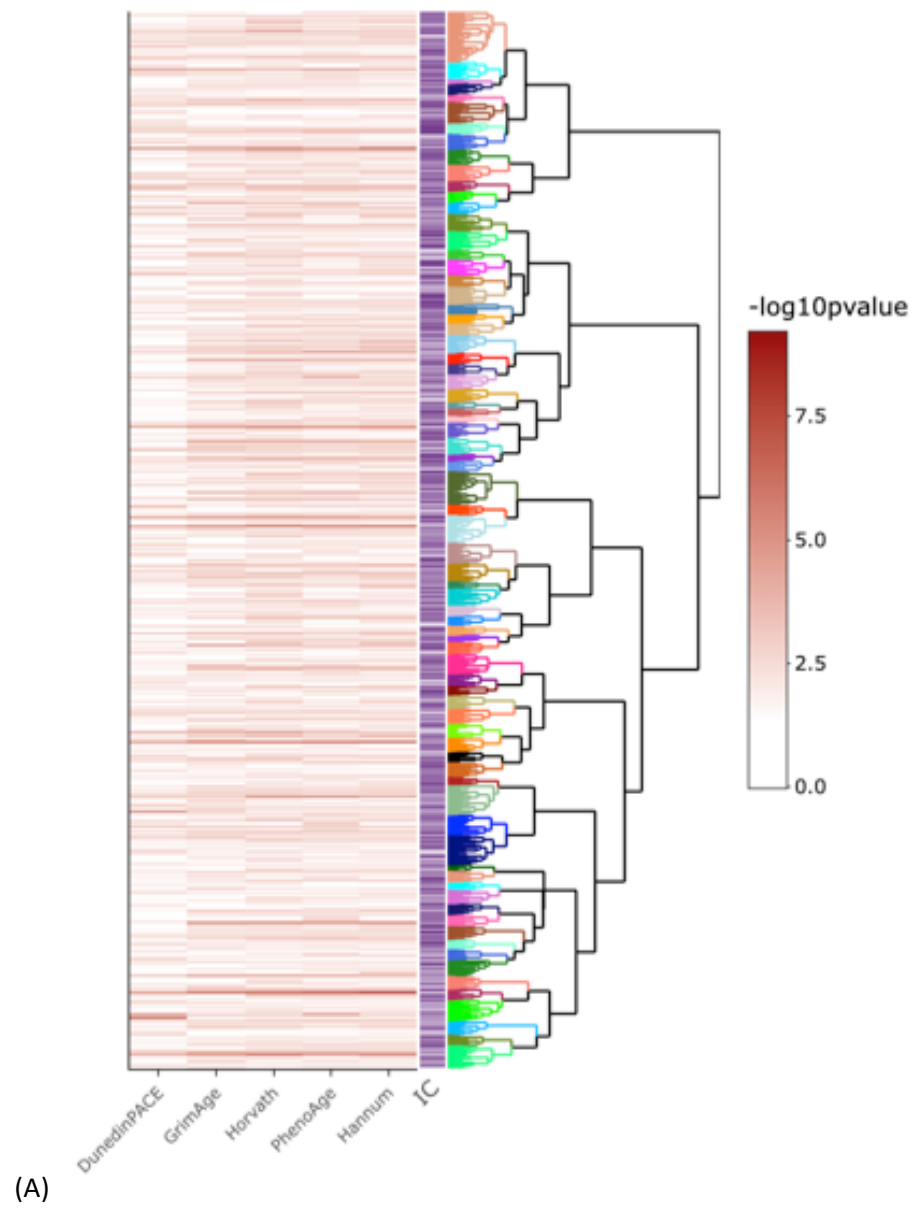
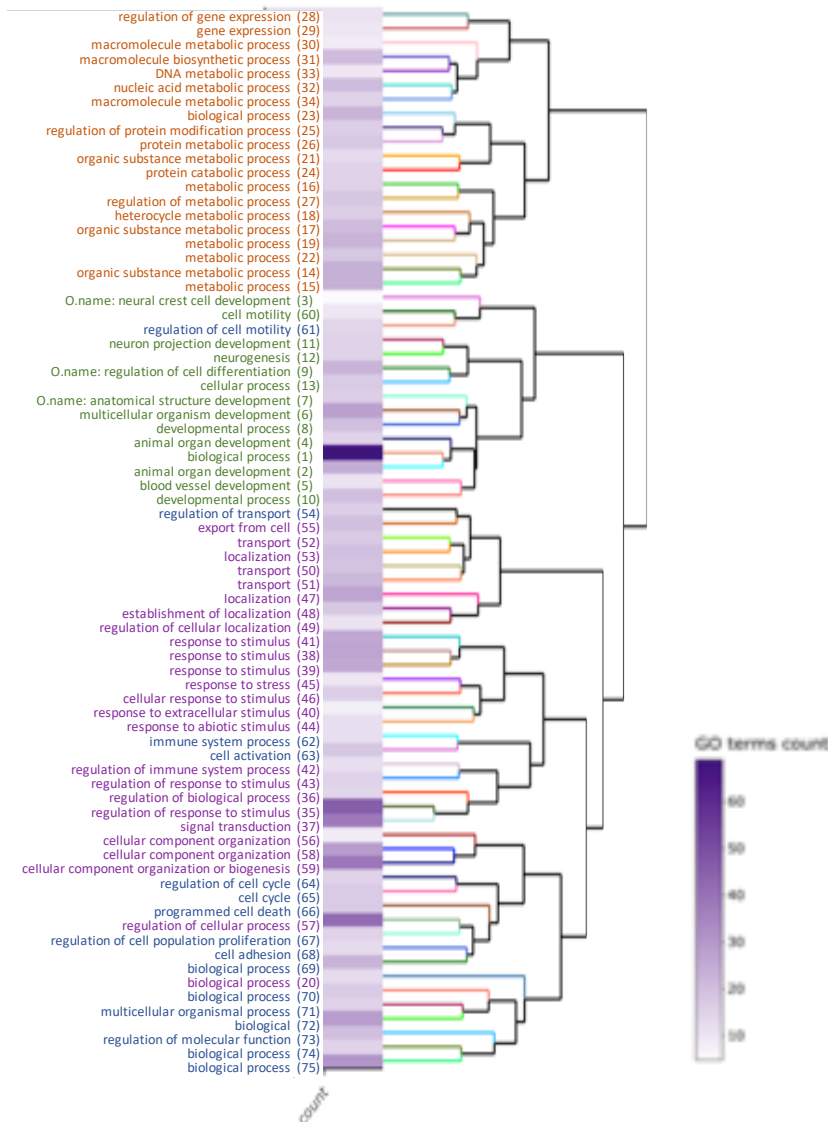


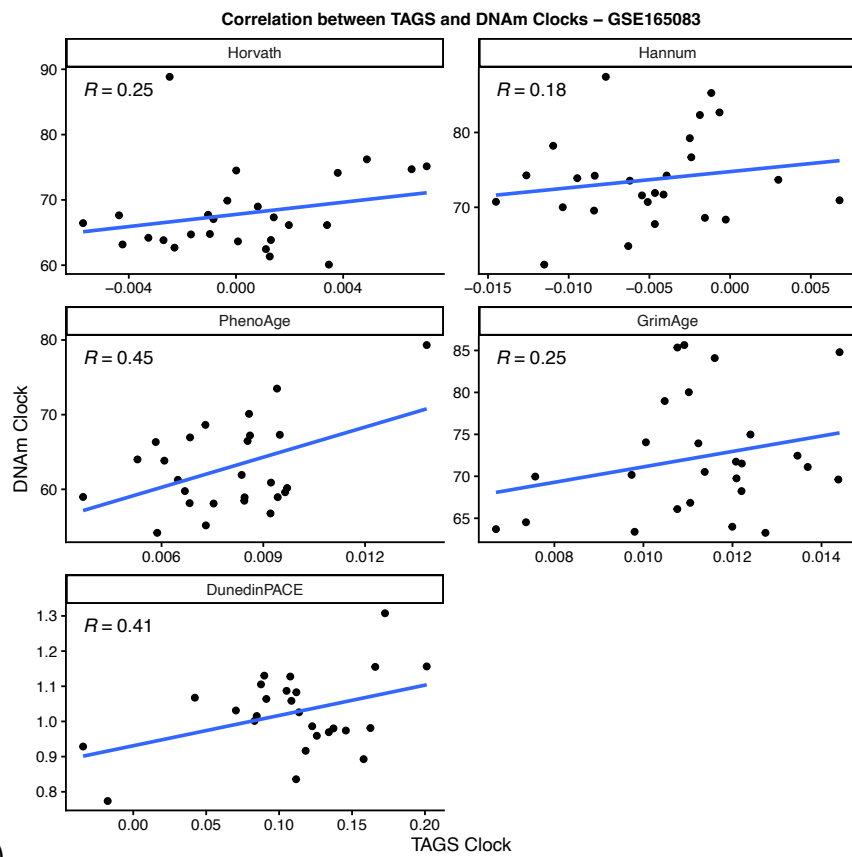
Figure S1. Volcano plots show the pattern of upregulated and downregulated genes for each epigenetic clock: (A) Horvath, (B) Hannum, (C) PhenoAge, (D) GrimAge, and (E) DunedinPACE. Volcano plots show the pattern of upregulated and downregulated genes for each epigenetic clock. Plots show unadjusted $-\log_{10} p$ -values on the y-axis and magnitude of the regression coefficient on the x-axis. Because the differential gene expression models used the predictors that were $\log_2$ -transformed, a one-unit increase corresponds to a doubling of its expression level and thus the regression coefficient represents the expected change in the age acceleration clock value per two-fold increase in predictor, or gene expression level, adjusted for covariates. The blue dots correspond to the genes in each clock that surpass the Bonferroni multiple testing p-value threshold of $p < 1e-06$ and black dots indicate genes under that threshold.





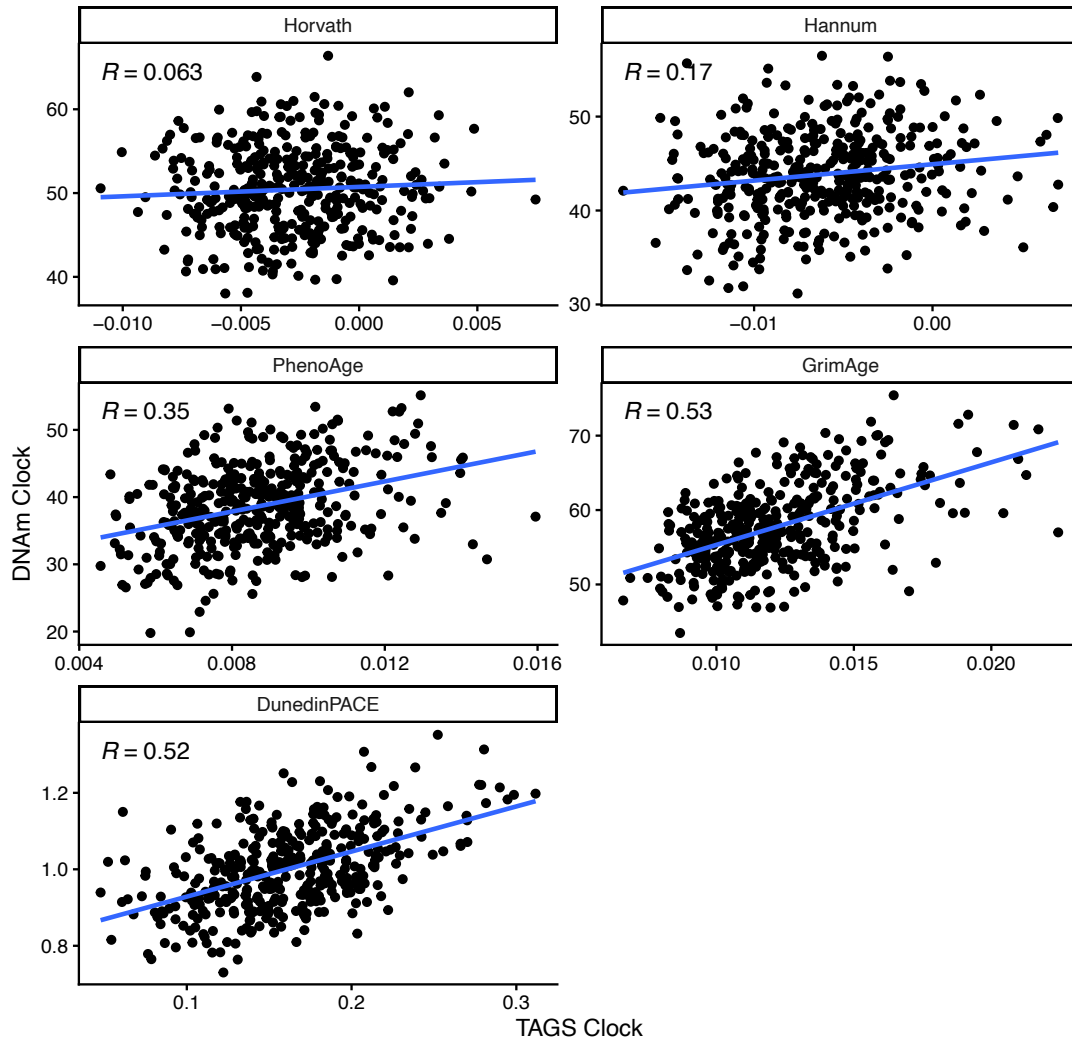
(B)

Figure S2. Gene Ontologies (GO) across clocks. (A) A clustering heatmap plot that combines a dendrogram based on Wang's semantic similarity distance method, which uses graph-based similarity, and Ward D2 aggregation criterion yielding 75 clusters of biological processes across the clocks from the 1,453 enriched GO terms (Table S3a). The branches are colored according to cluster membership. The $-\log_{10}(p\text{-value})$ from functional enrichment tests uses the DEGs from the 5 clocks and information content (IC) of the GO term. The IC is computed as the probability of occurrence of the term in a set of GO terms. (B) The IC and 75 functional clusters are listed.

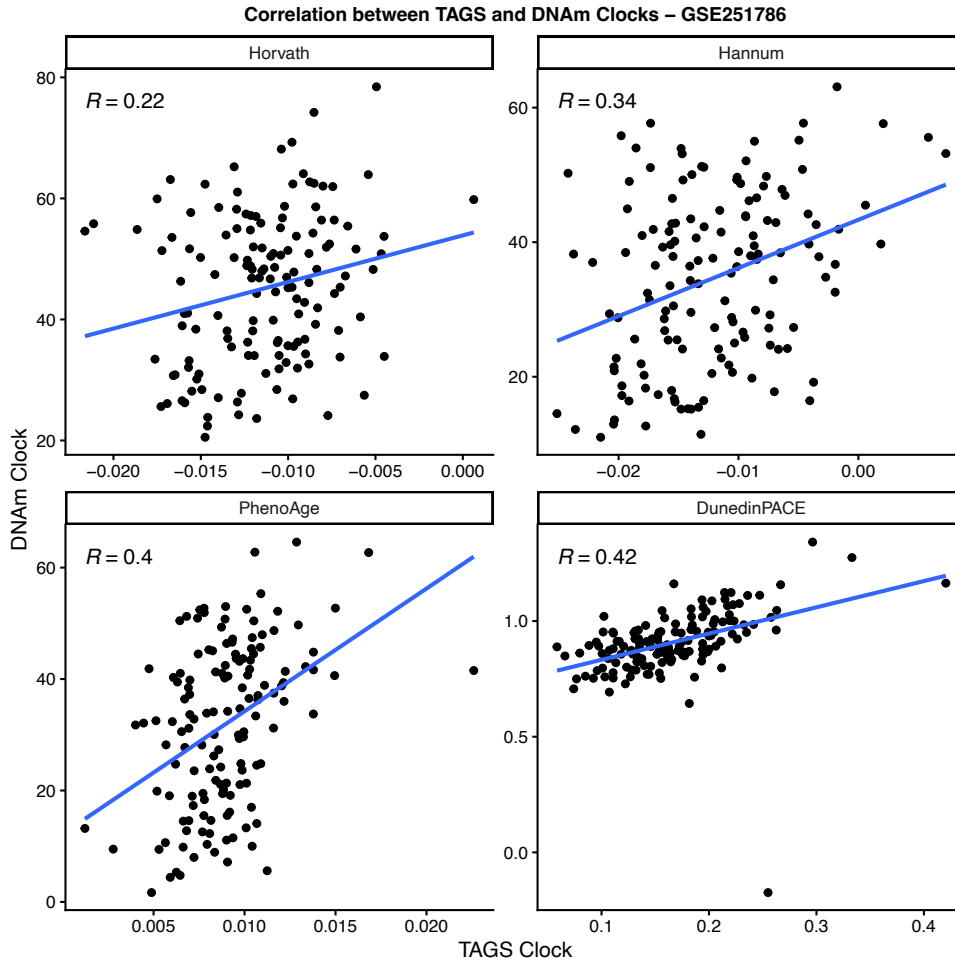


(A)

Correlation between TAGS and DNAm Clocks – GSE224624

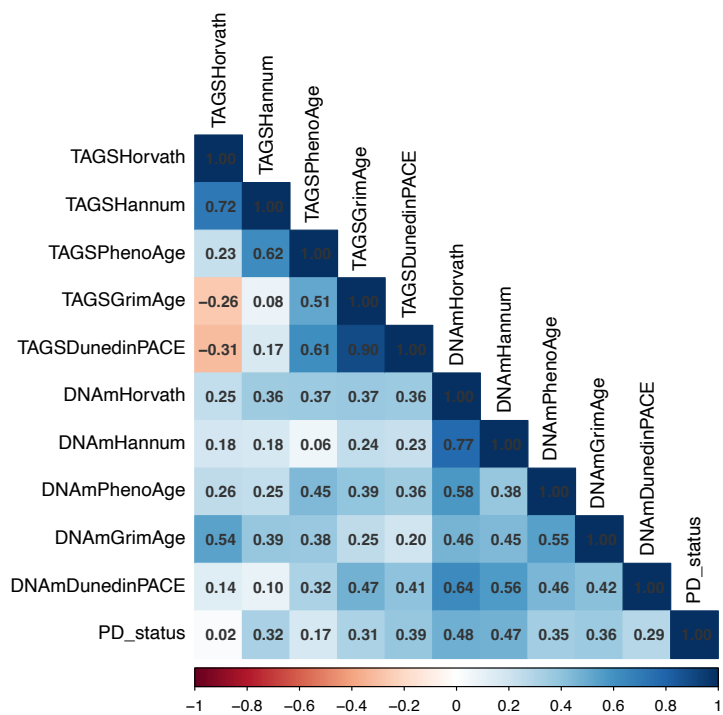


(B)

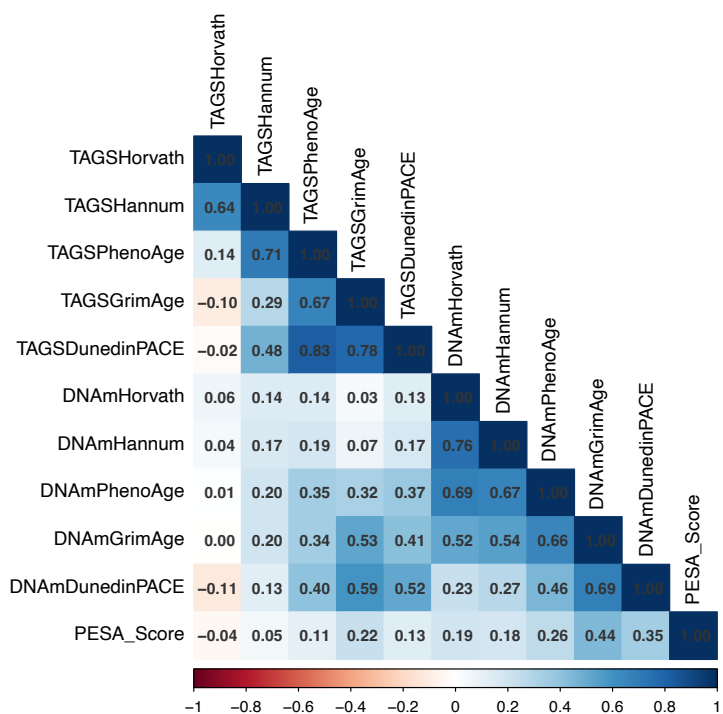


(C)

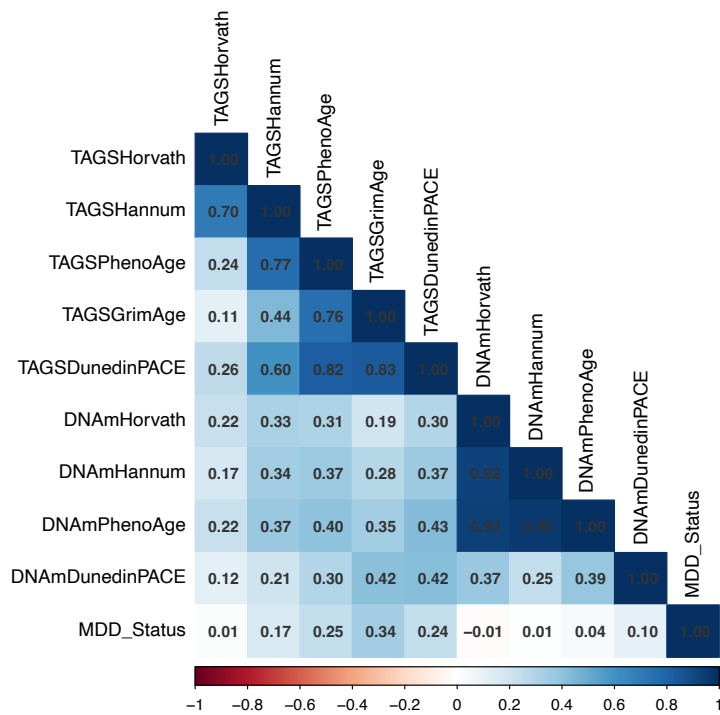
Figure S3. Correlations between Epigenetic Clocks and their respective TAGS in external datasets (A) GSE165083, (B) GSE224624, and (C) GSE251786. Datasets GSE165083 and GSE224624 provided an age phenotype which is needed to calculate the epigenetic version of GrimAge, but GSE251786 did not and thus DNAmGrimAge is not included in the comparison.



(A)



(B)



(C)

Figure S4. Correlations between Epigenetic Clocks, TAGS, and the primary study outcome of the external dataset. Primary outcomes included (A) Parkinson’s Disease (PD) diagnosis in GSE165083 where PD present is coded as 1 vs 0 for controls; (B) Progression of Early Subclinical Atherosclerosis (PESA) score in GSE224624 where a higher score indicates greater risk for cardiovascular disease; and (C) Major Depressive Disorder (MDD) in GSE251786 where MDD present is coded as 1 vs 0 for controls. Datasets GSE165083 and GSE224624 provided an age phenotype which is needed to calculate the epigenetic version of GrimAge, but GSE251786 did not and thus DNAmGrimAge is not included in the comparison.

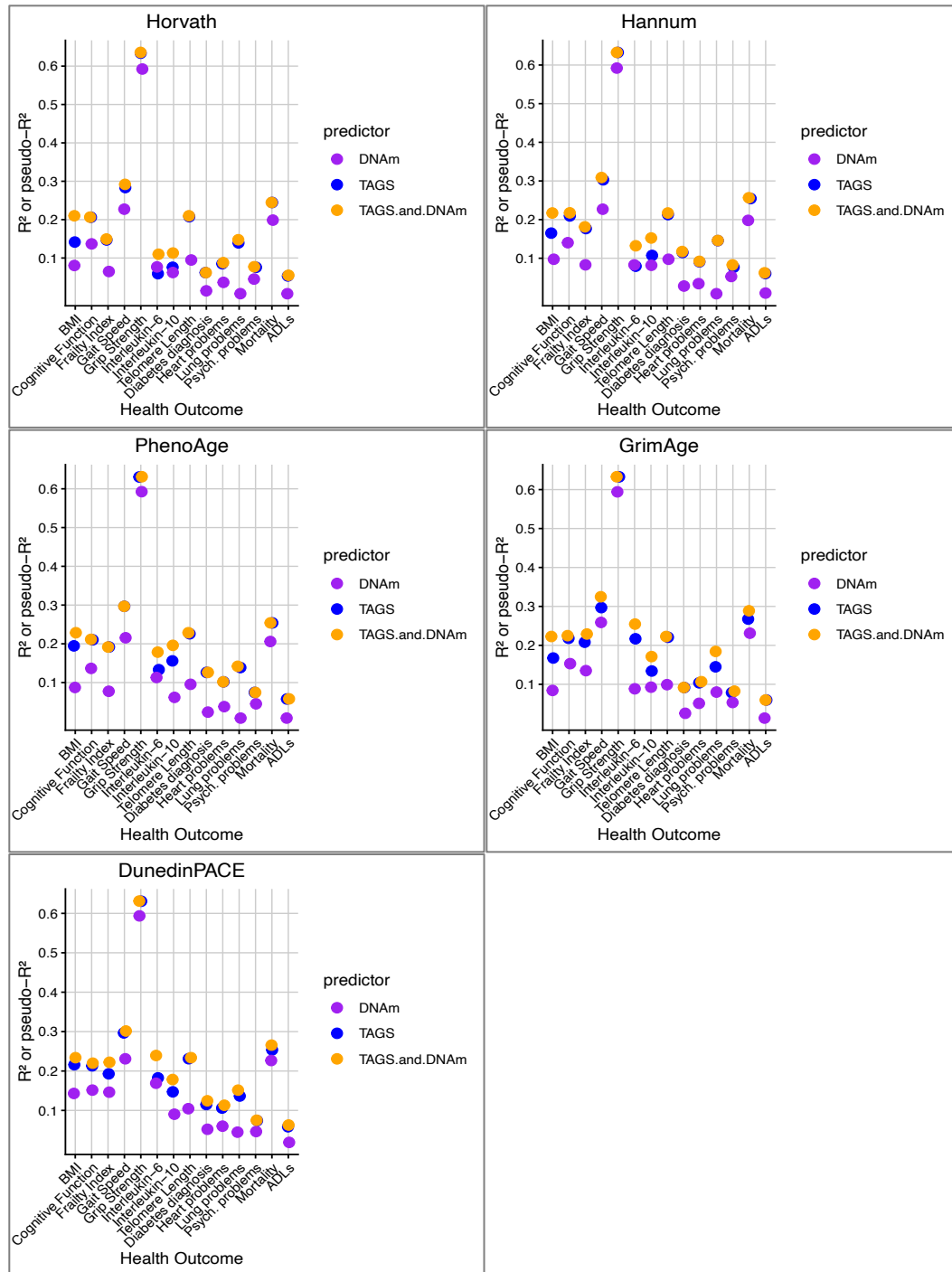


Figure S5. Comparisons of model fit when DNAm and TAGS are alone in a model or together in predicting a health outcome. R² or pseudo-R² values (y-axis) for each model predicting the health outcome (x-axis) is shown by clock for (A) Horvath, (B) Hannum, (C) PhenoAge, (D), GrimAge, and (E) DunedinPACE. The dot color indicates when the model includes only the DNAm (purple) or transcriptomic (blue) clock in the model, or both (gold) in the same model.

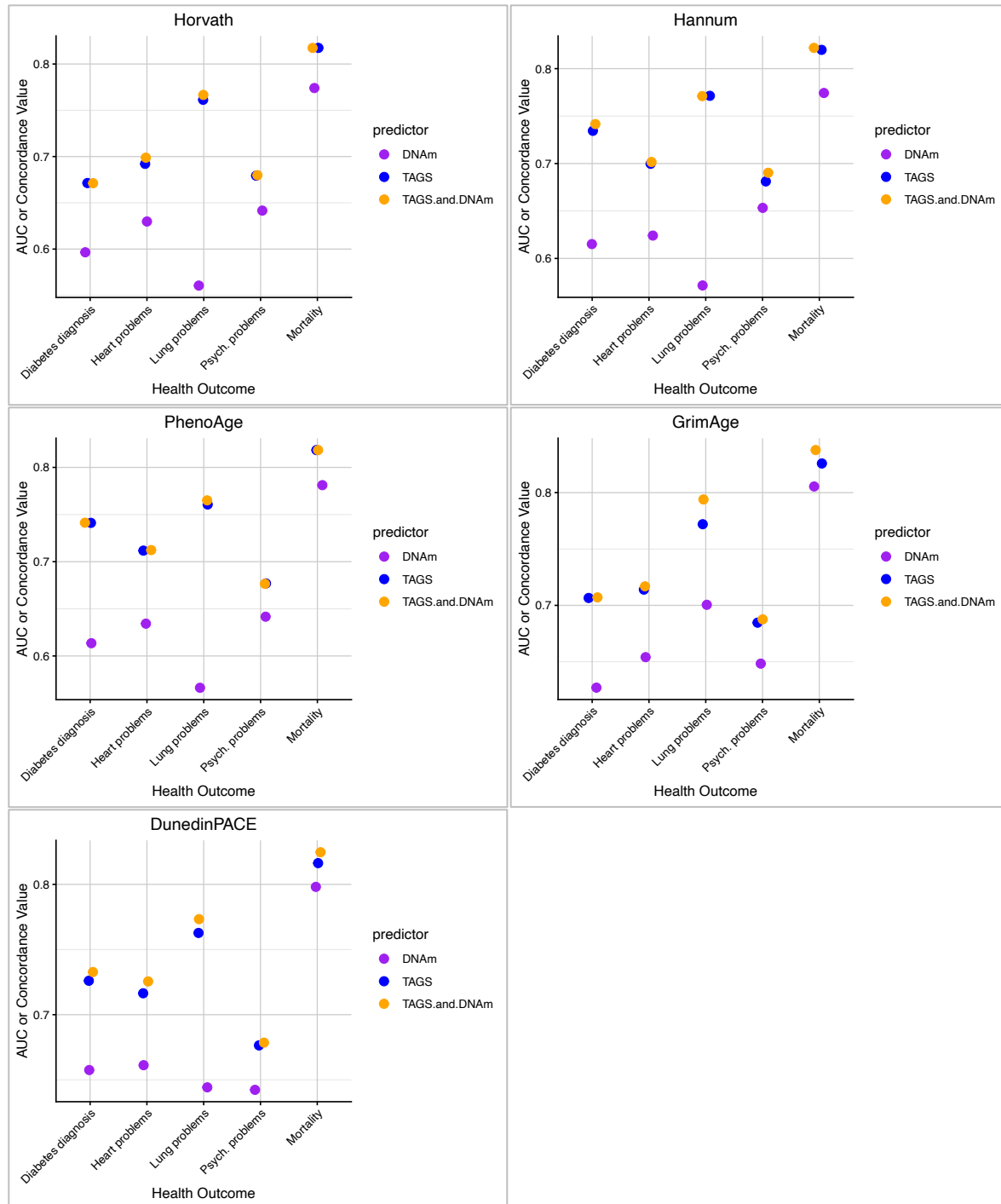


Figure S6. Comparisons of discrimination metrics for models when DNAm and TAGS are alone in a model or together in predicting the health outcome. Area Under the Curve (AUC) or Concordance Value (C-statistic) on the y-axis for each model predicting the health outcome (x-axis) is shown by clock for (A) Horvath, (B) Hannum, (C) PhenoAge, (D), GrimAge, and (E) DunedinPACE. The dot color indicates when the model includes only the DNAm (purple) or transcriptomic (blue) clock in the model, or both (gold) in the same model.

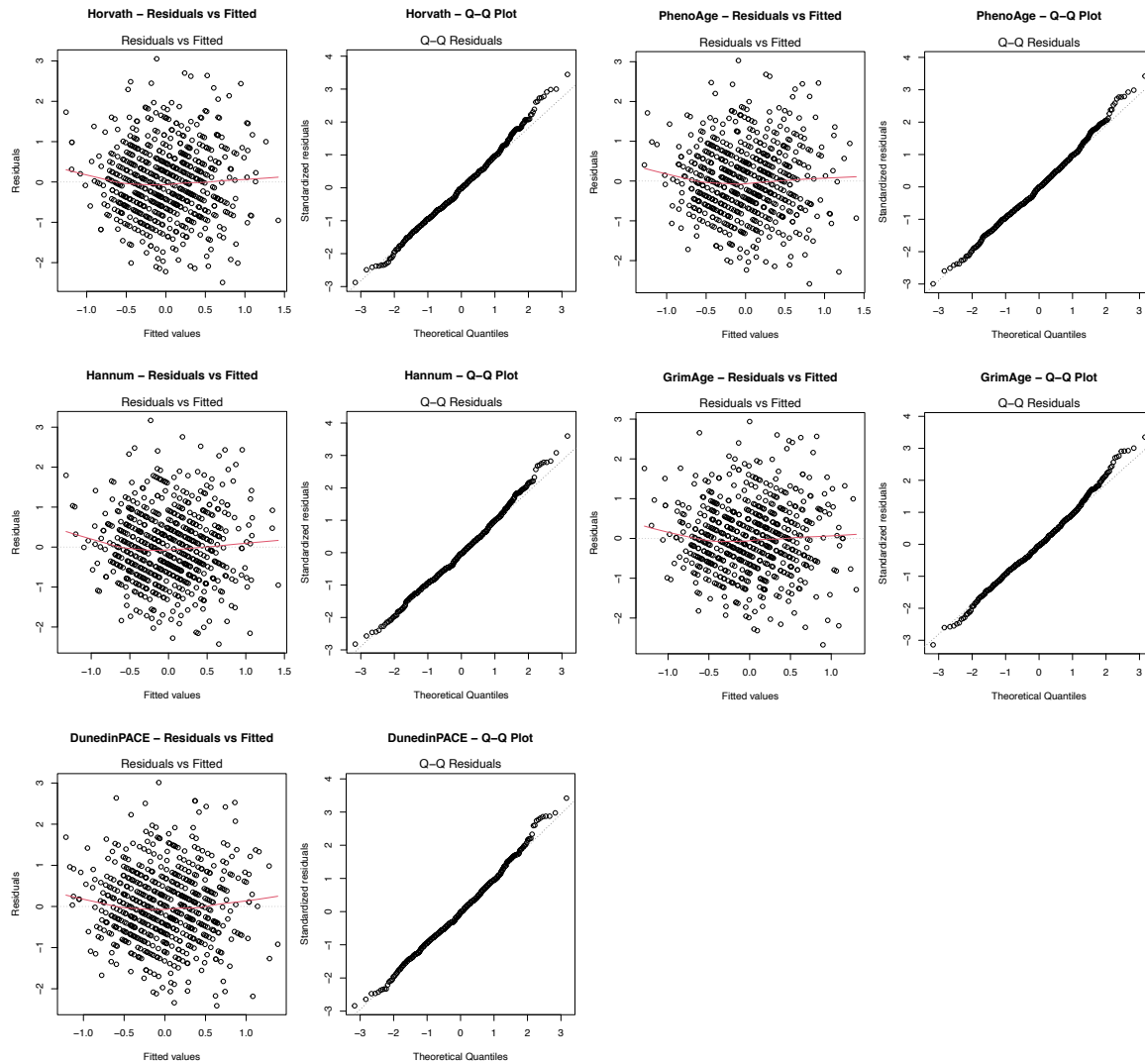


Figure S7. Regression diagnostics for epigenetic clock models. Residuals versus fitted values (left panels) and Q-Q plots of standardized residuals (right panels) are shown for models including Horvath, Hannum, PhenoAge, GrimAge and DunedinPACE clocks when predicting cognitive function. Residuals are centered around zero with no strong evidence of heteroscedasticity or non-linearity, and Q-Q plots demonstrate approximate normality with minor deviations in the tails, supporting the validity of model assumptions. Similar diagnostic patterns were observed for models of other outcomes.

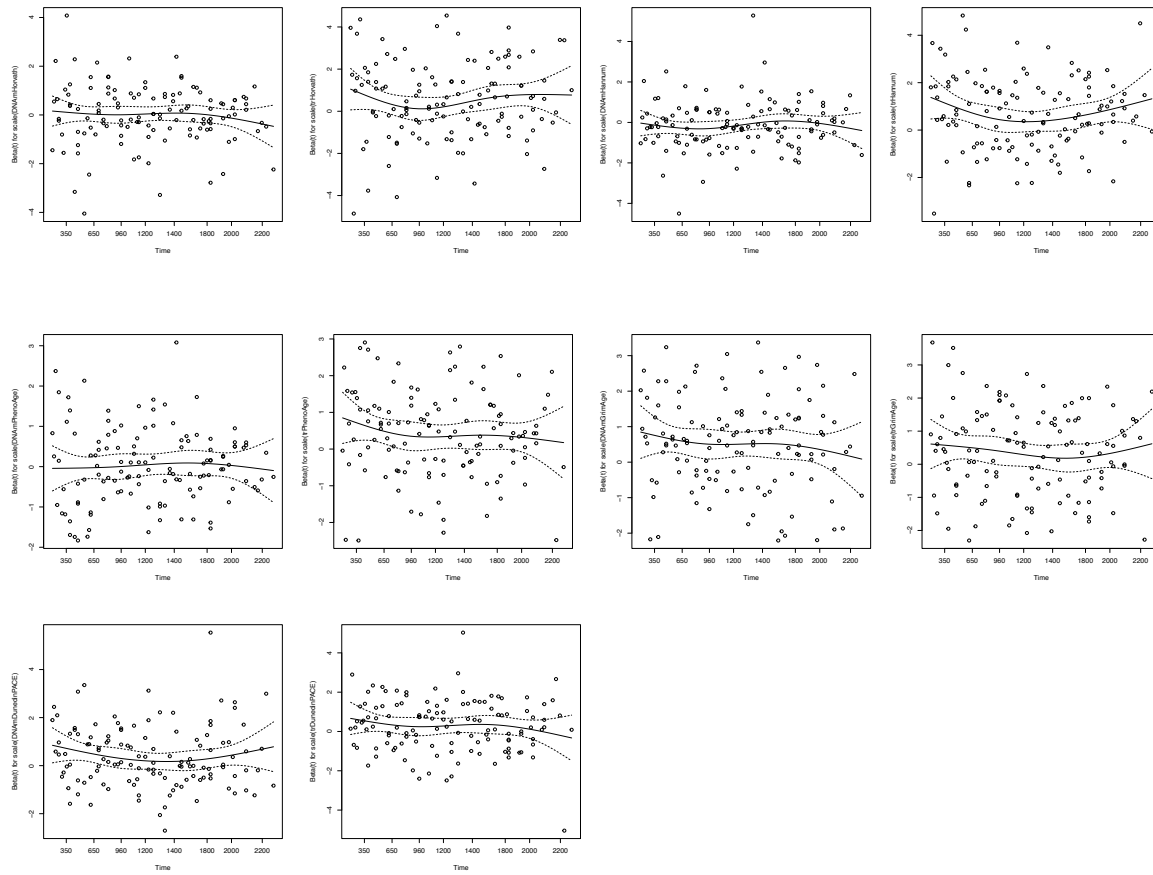


Figure S8. Assessment of proportional hazards assumptions. Scaled Schoenfeld residuals are shown for predictors (DNAm and TAGS clocks) in the Cox proportional hazards models. Solid lines represent smoothed estimates of time-varying coefficients and dashed lines indicate approximate 95% confidence intervals. Across covariates, effects were generally stable over time with no consistent evidence of violation of the proportional hazards assumption, although minor deviations were observed at the extremes of follow-up.