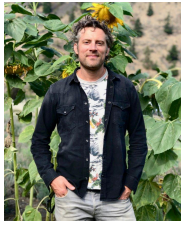
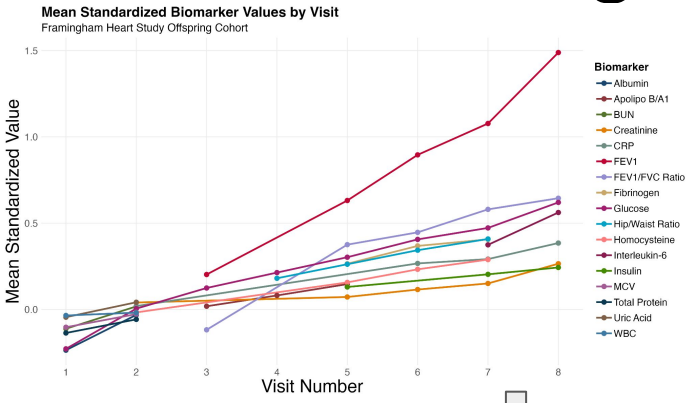
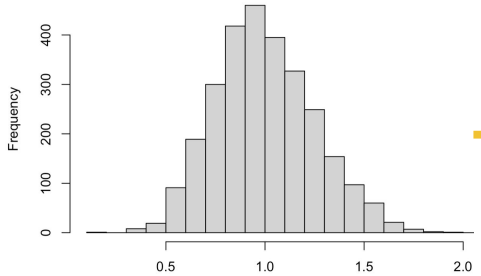
FraminghamPACE: a new DNA methylation biomarker of the Pace of Aging

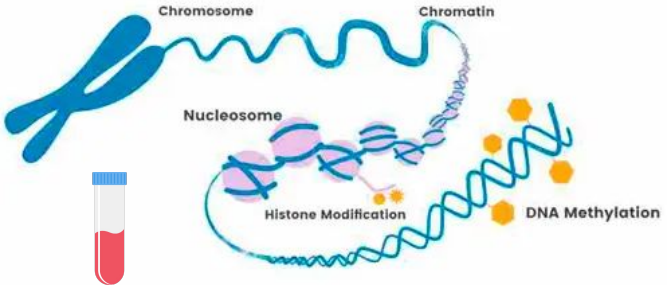


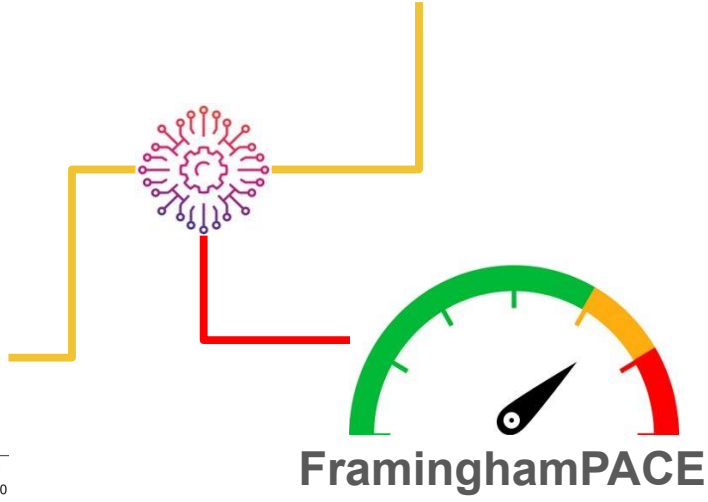


$$y_{ijk} = \beta_{0ik} + \beta_{1ik} t_j + \beta_{2ik} t_j{}^2 + \epsilon_{ijk}$$

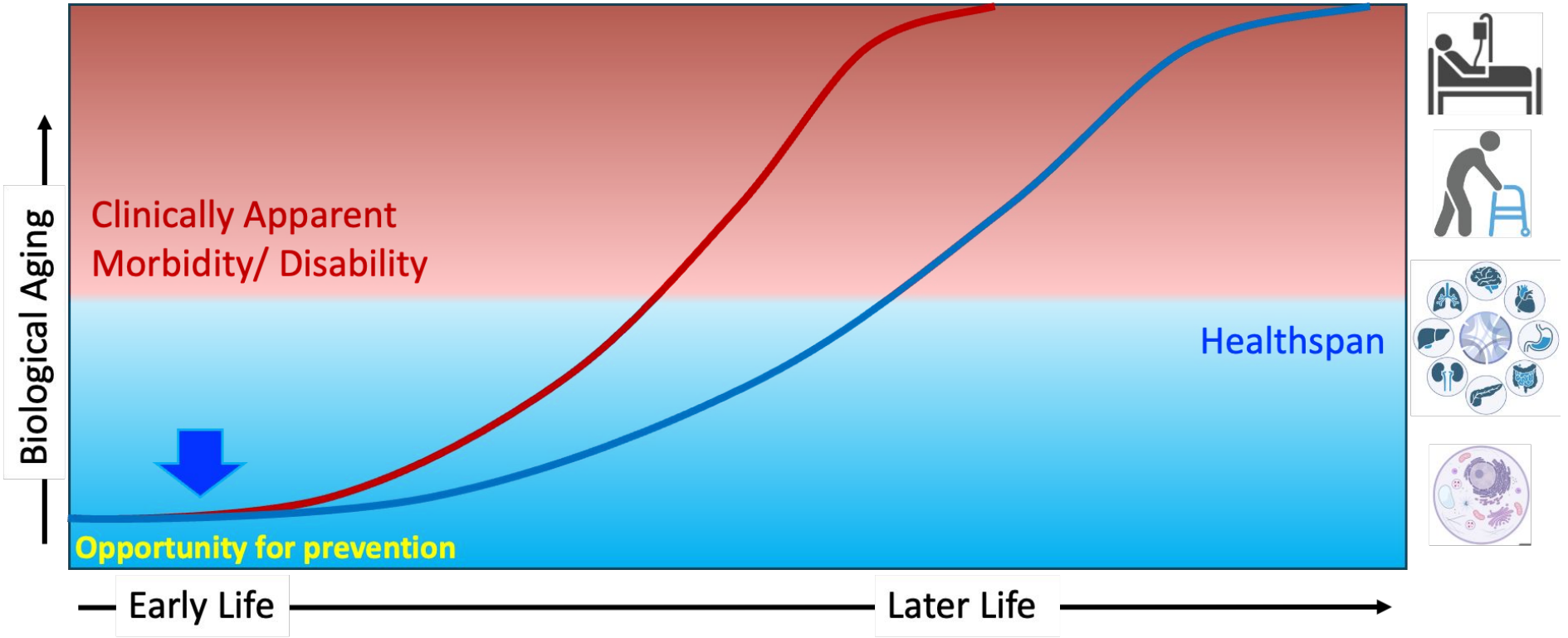
$$\beta_{xik} = \theta_{xi} + \delta_{xik}$$







Geroscience needs sensitive biomarkers



Belsky & Baccarelli 2023 *Nat Aging*
Belsky & Ferrucci 2025 *HBLCE*

Epigenetic clocks are leading aging biomarkers

Epigenetic clocks are leading aging biomarkers

	Predictive	Survival Bias	Cohort Effects	Timing
Gen 1: Predict Age (Horvath, Hannum)	~	✗	✗	✗

Epigenetic clocks are leading aging biomarkers

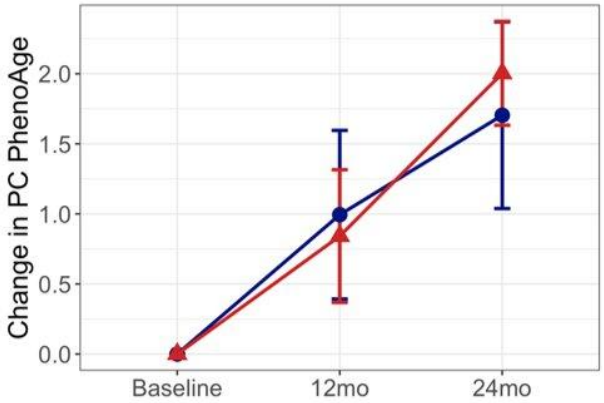
	Predictive	Survival Bias	Cohort Effects	Timing
Gen 1: Predict Age (Horvath, Hannum)	~	✗	✗	✗
Gen 2: Predict Survival (GrimAge, PhenoAge)	✓	✓	✓	✗

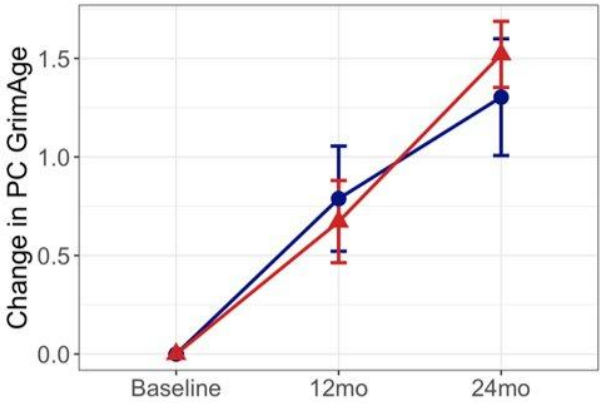
Epigenetic clocks are leading aging biomarkers

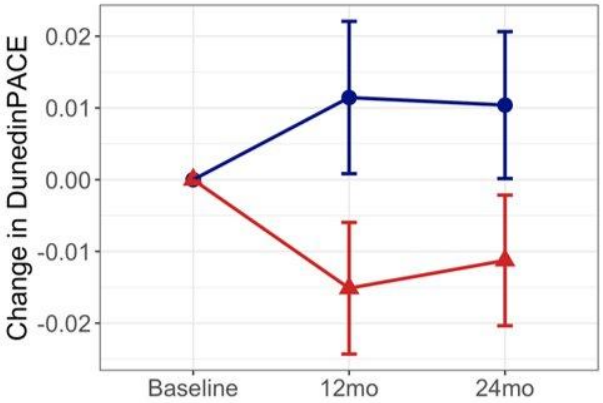
	Predictive	Survival Bias	Cohort Effects	Timing
Gen 1: Predict Age (Horvath, Hannum)	~	✗	✗	✗
Gen 2: Predict Survival (GrimAge, PhenoAge)	✓	✓	✓	✗
Gen 3: Predict Pace of Aging (DunedinPACE)	✓	✓	✓	✓

Epigenetic clocks are leading aging biomarkers

calerie







Waziry, Ryan et al. 2023 *Nat Aging*

Creating Pace of Aging in the FHS Offspring Cohort

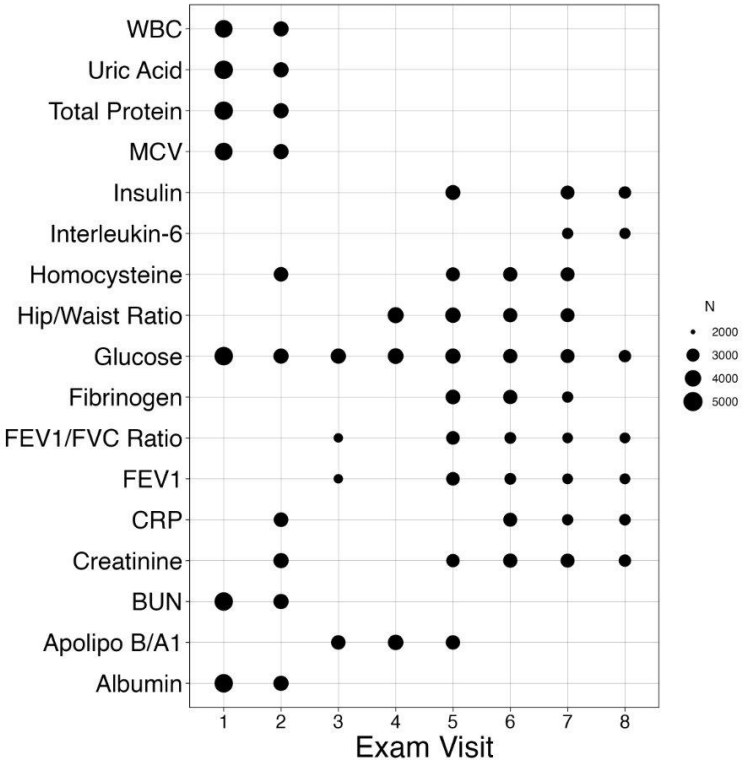
Initiated in 1971

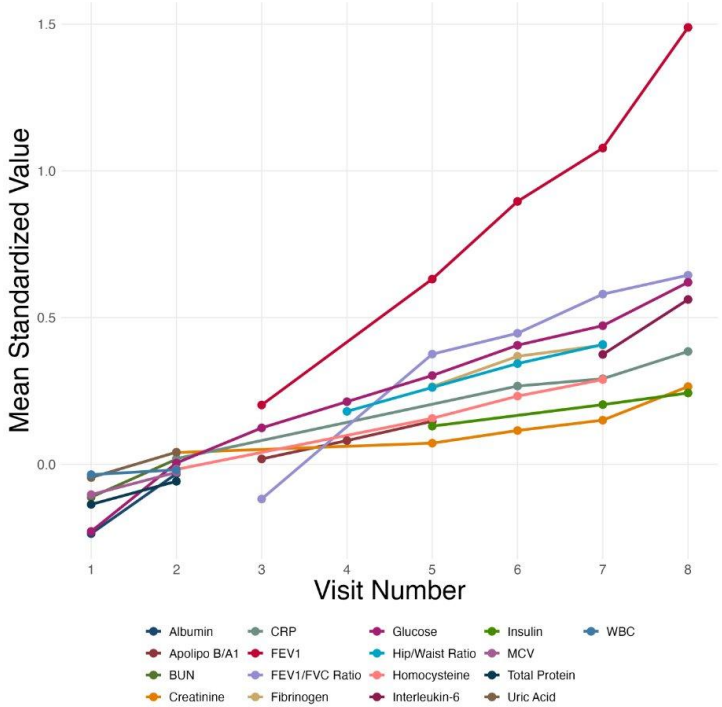
2nd generation of the Framingham Heart Study participants

Wave	N	%male	Mean Age
1	4988	48.5	36.2
2	3752	48.5	44.2
3	3762	48.2	48.4
4	3902	48.2	51.6
5	3688	47.1	54.9
6	3411	46.8	58.7
7	3476	46	61.4
8	2985	45.2	66.9

DNAm collected

Creating Pace of Aging in the FHS Offspring Cohort





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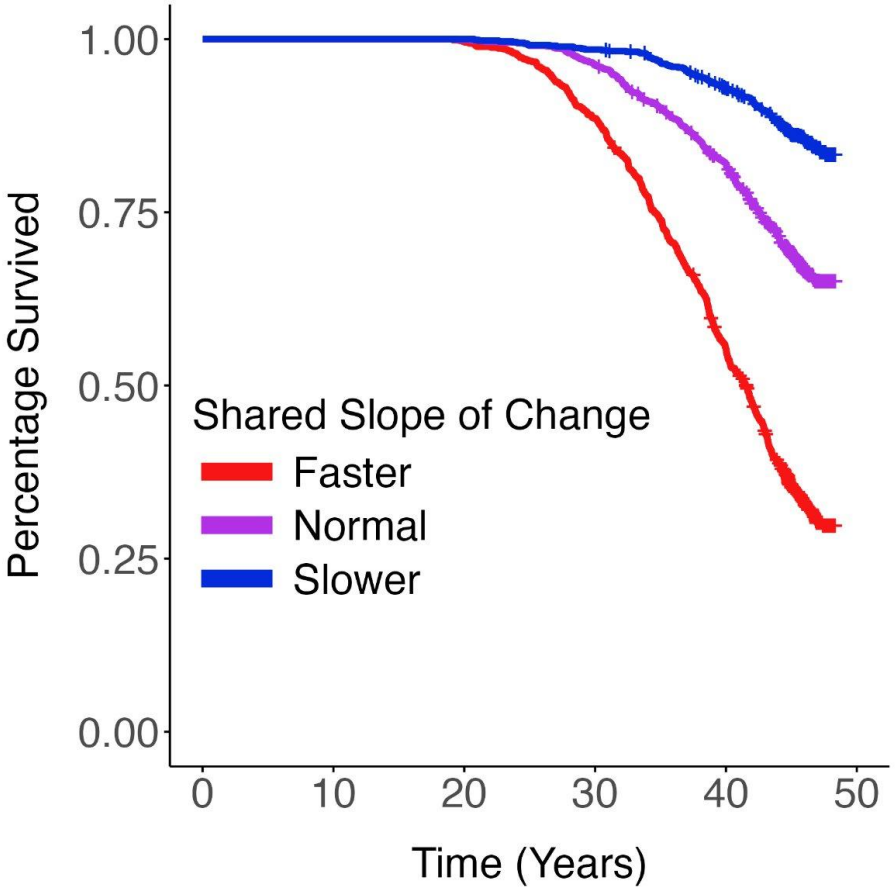
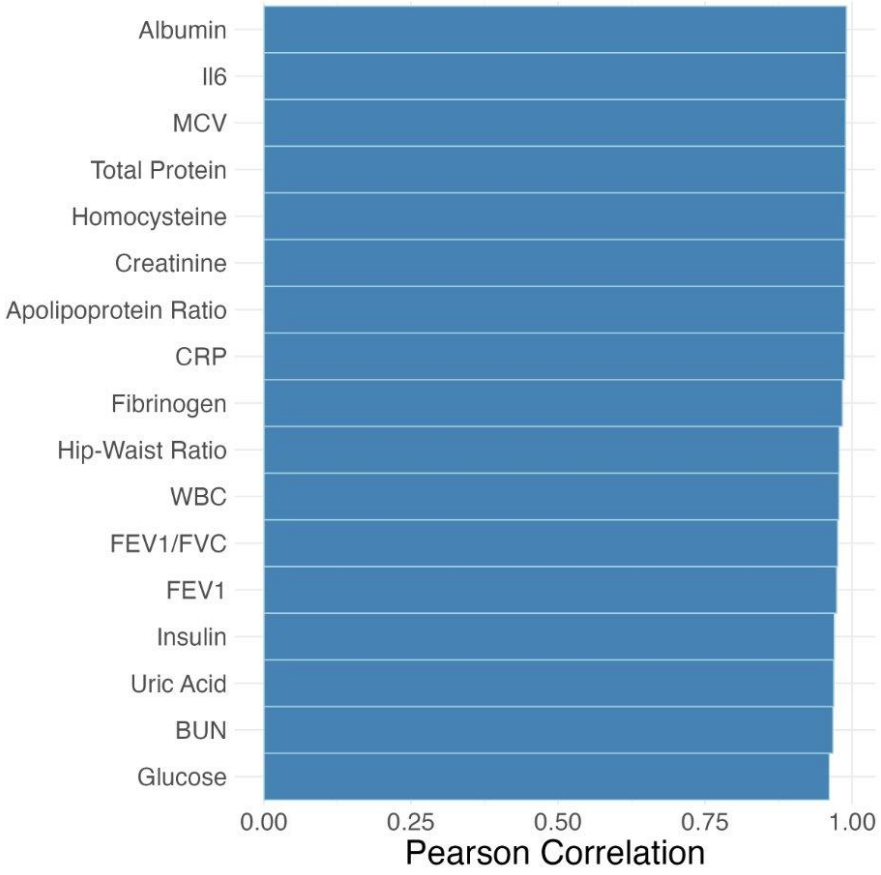
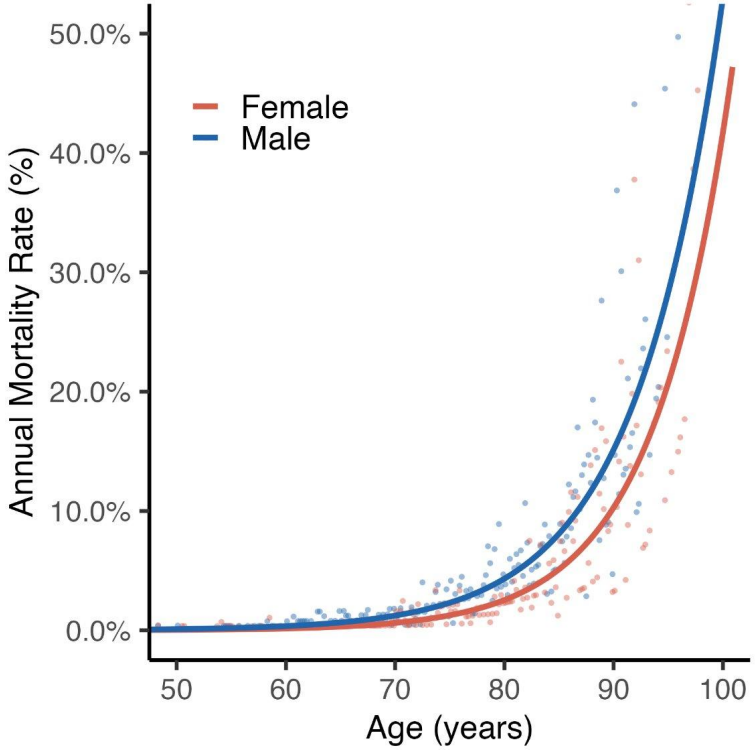
Creating Pace of Aging in the FHS Offspring Cohort

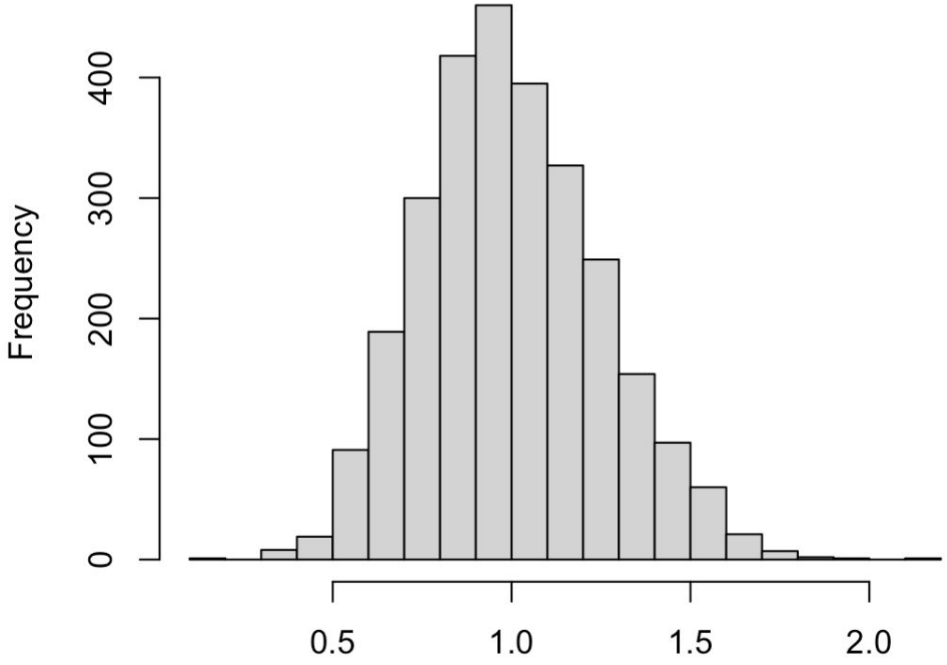




Creating Pace of Aging in the FHS Offspring Cohort

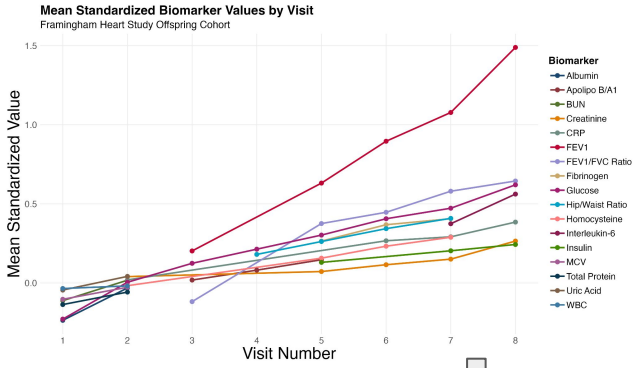


$$\frac{\text{slope\_ratio} - 1}{(30 * \text{age\_hazard}) \div (\text{slope\_ratio\_hazard})} + 1$$



Creating FraminghamPACE

(**P**ace of **A**ging **C**omputed from the **E**pigenome)



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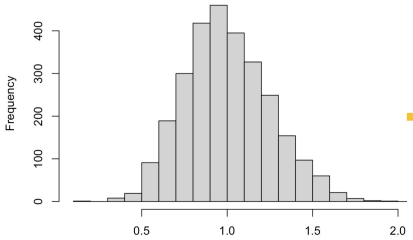
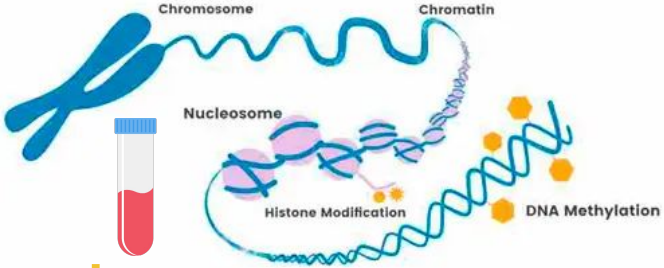


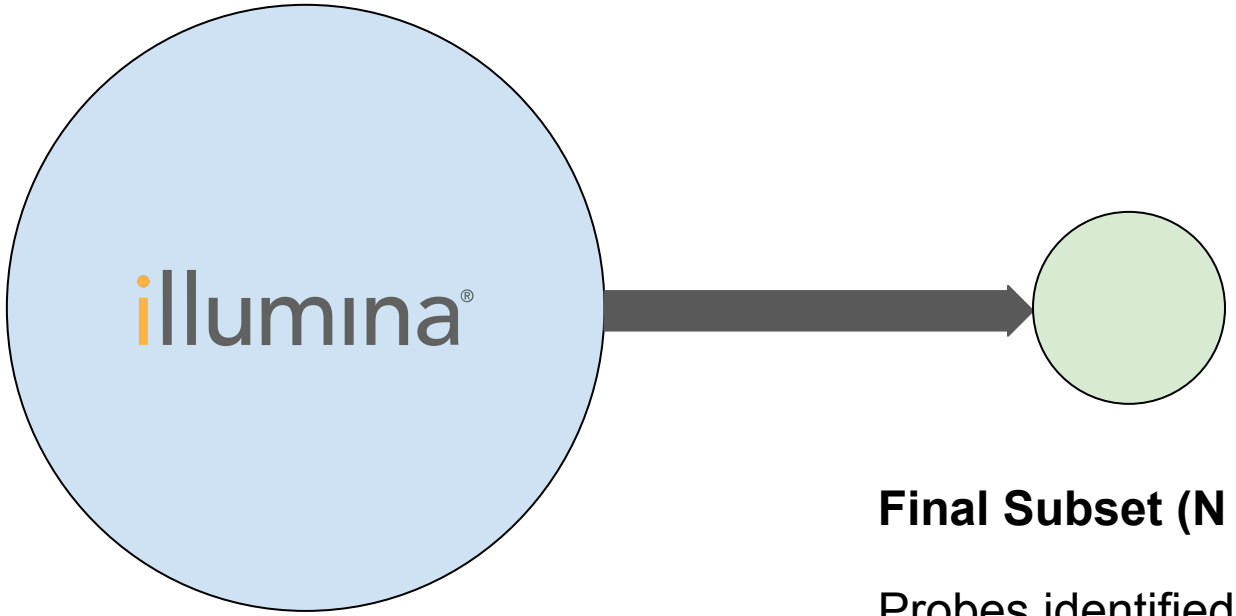


Ensemble Regularized Regression

FraminghamPACE

Creating FraminghamPACE

(**P**ace of **A**ging **C**omputed from the **E**pigenome)



Sugden et al. 2020

TruDiagnostic™
The Epigenetic Company

Initial Subset (N=95,851)

Probes available on 450k, EPICv1, EPICv2, MSA

Final Subset (N = 14,581)

Probes identified as reliable cross-platform by Sugden et al. 2020 and TruDiagnostic

Creating FraminghamPACE

(**P**ace of **A**ging **C**omputed from the **E**pigenome)

Elastic Net

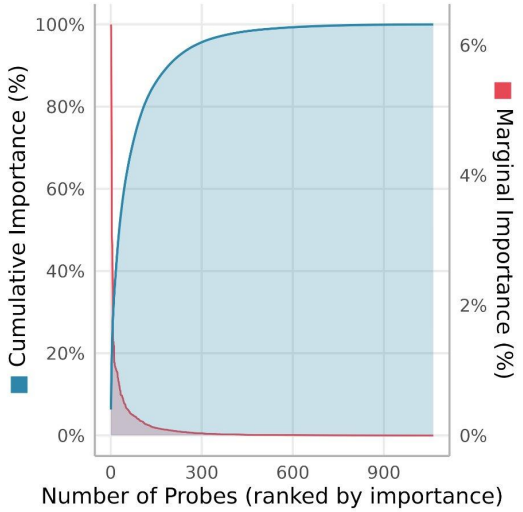
Default choice for epigenetic clocks

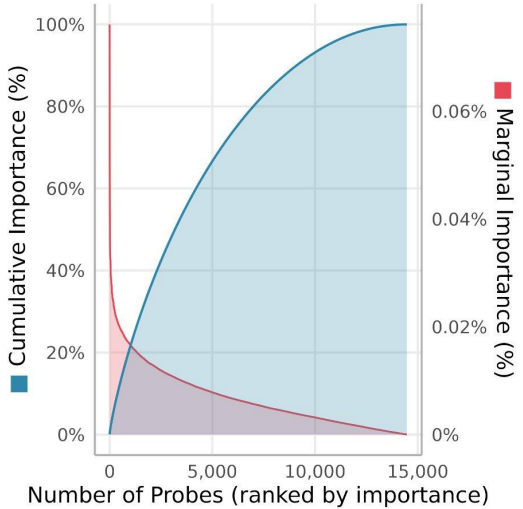
Induces sparsity + shrinkage

Ridge

Induces shrinkage only

Potentially advantageous. Reduces reliance on a small set of probes





Creating FraminghamPACE

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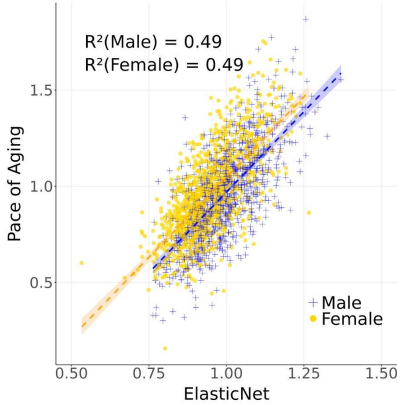
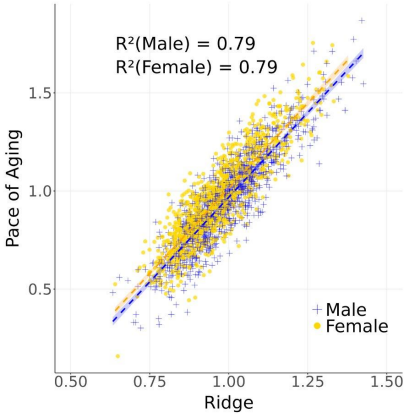
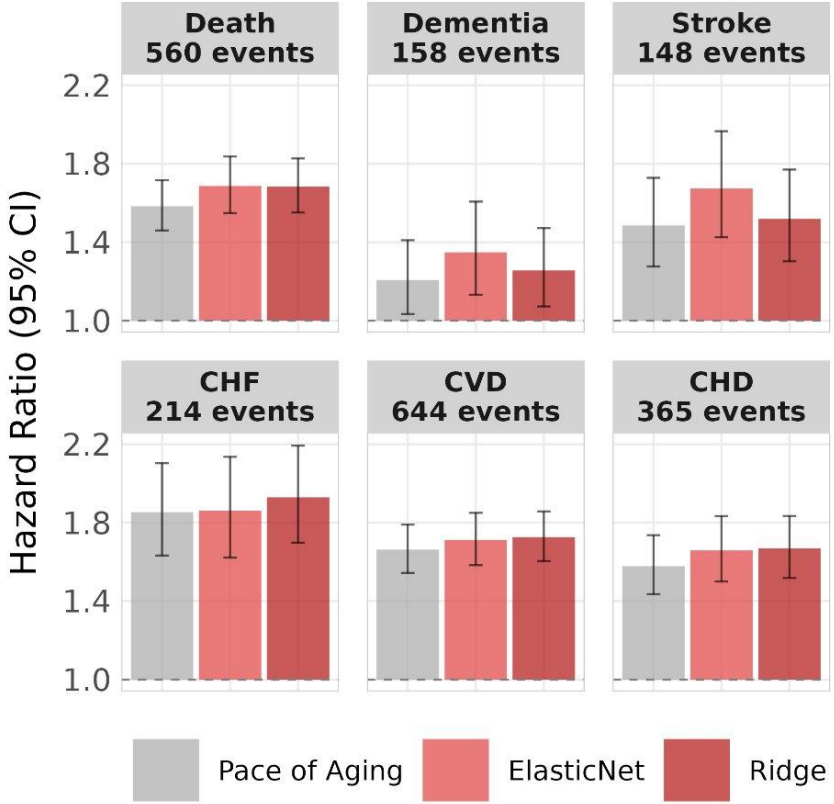
Elastic Net

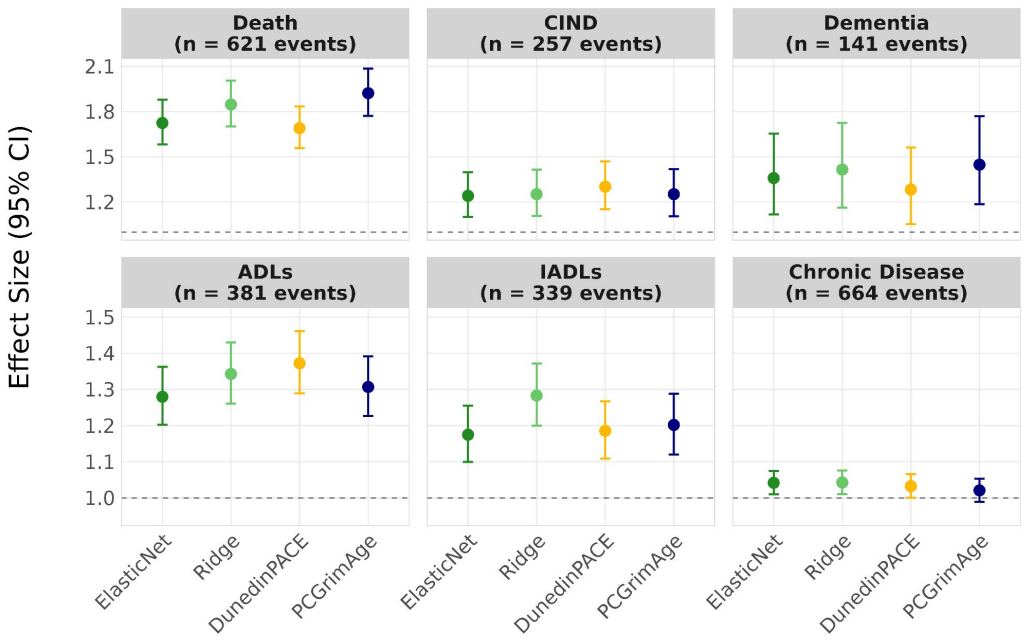


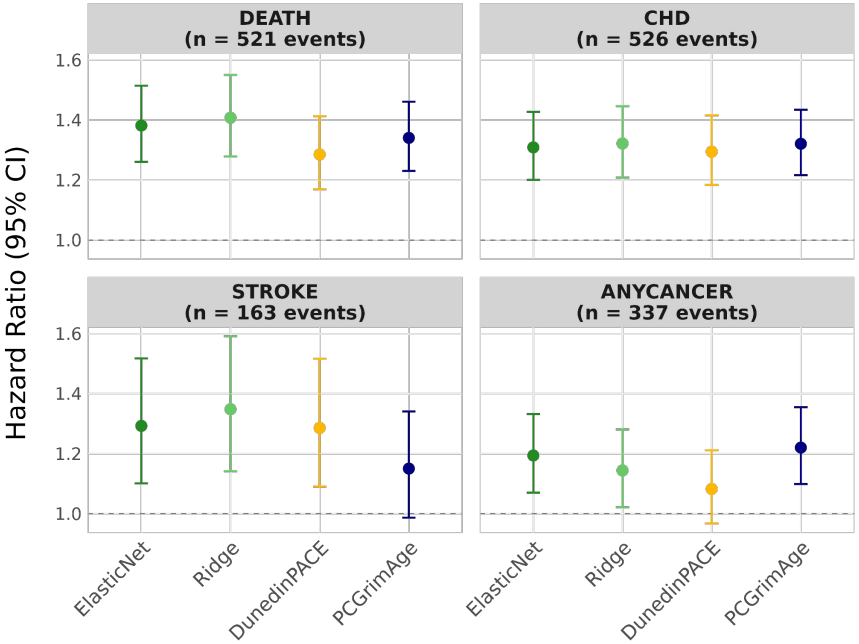
Ridge





Validation



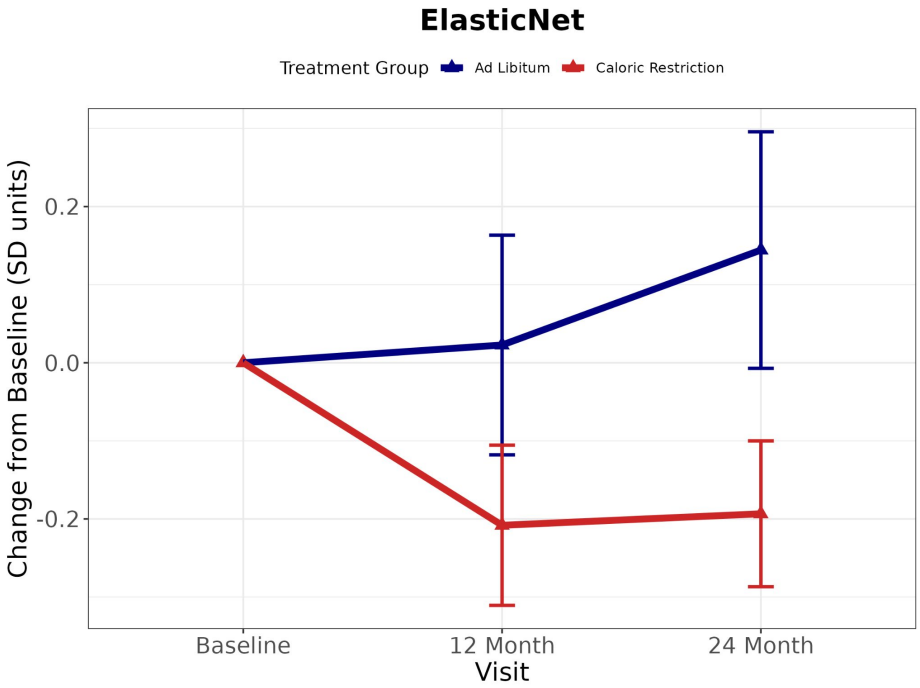


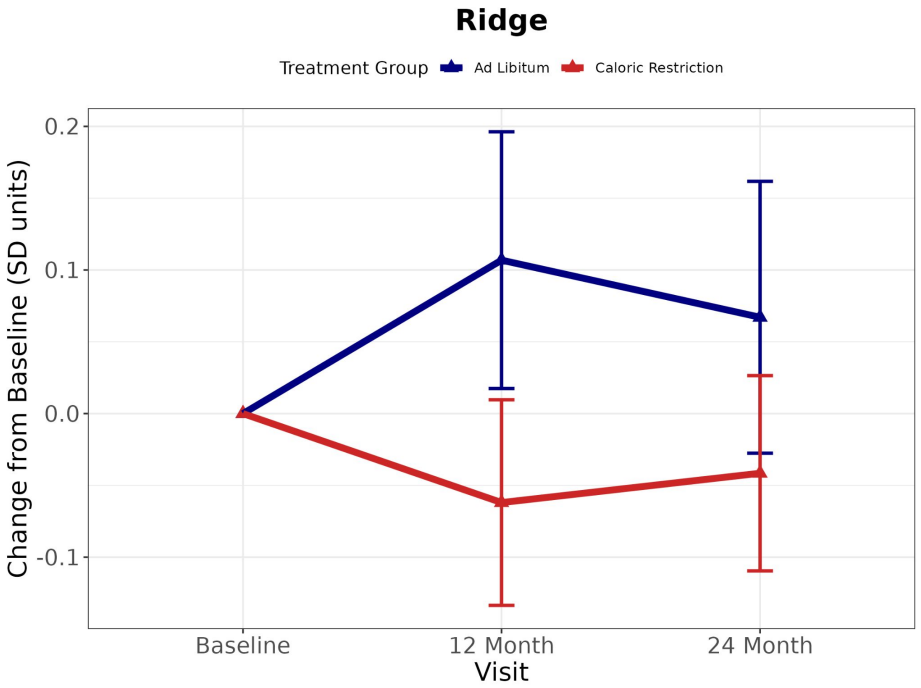
HRS

US Health & Retirement Study
n=3,433
Up to 6y follow-up

WHI
n=1,835
Up to 21y follow-up

CALERIE


ElasticNet
Treatment Group
Ad Libitum
Caloric Restriction
Change from Baseline (SD units)
0.2
0.0
-0.2
Baseline
12 Month
24 Month
Visit


Ridge
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Thank You!

Geroscience
Computational
Core

TruDiagnostic™
The Epigenetic Company

BELSKY LAB