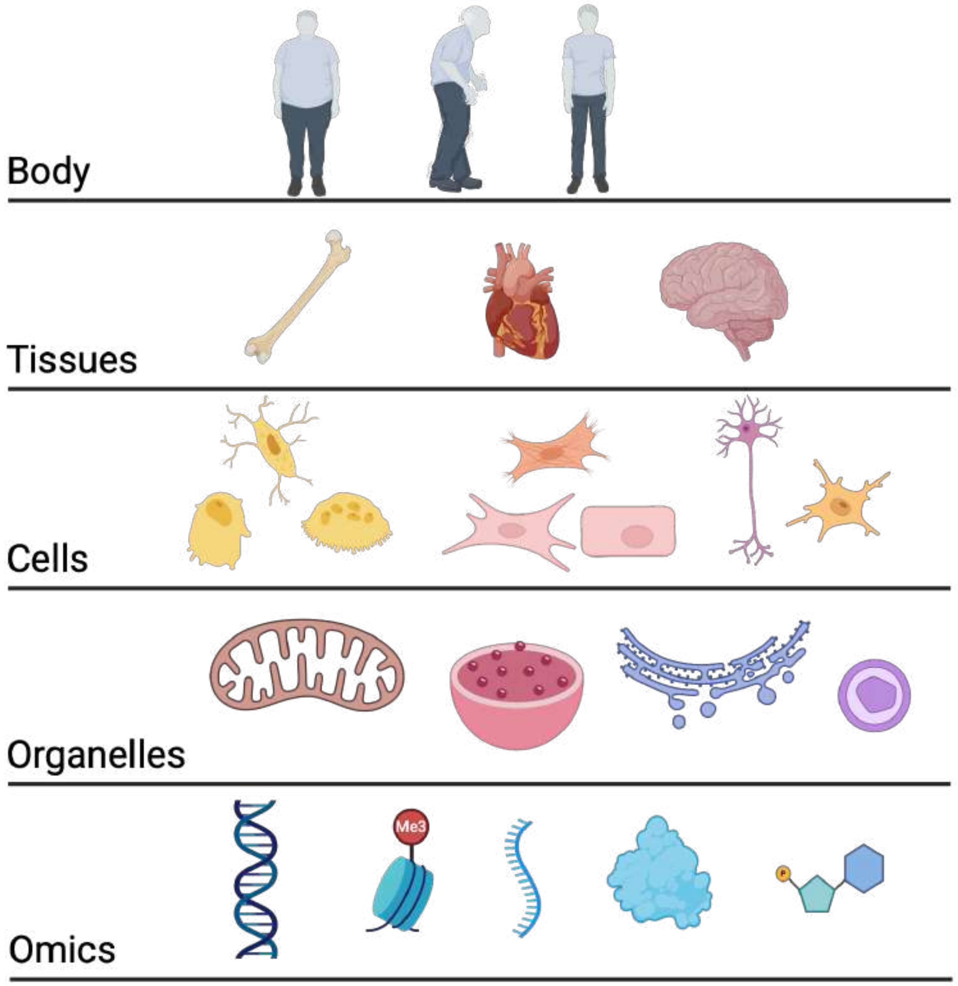
Metabolomic sweet spot clock predicts mortality and age-related diseases in the Canadian Longitudinal Study on Aging

Olga Vishnyakova, Ph.D.

BC Cancer Research Institute
Department of Biomedical Physiology and Kinesiology, Simon Fraser University
ovishnyakova@bccrc.ca

April 23, 2026
CLSA Webinar Series

Heterogeneity in aging



Frailty Index, Allostatic Load Index, Activities of Daily Living, Grip strength, Charlson Comorbidity Index

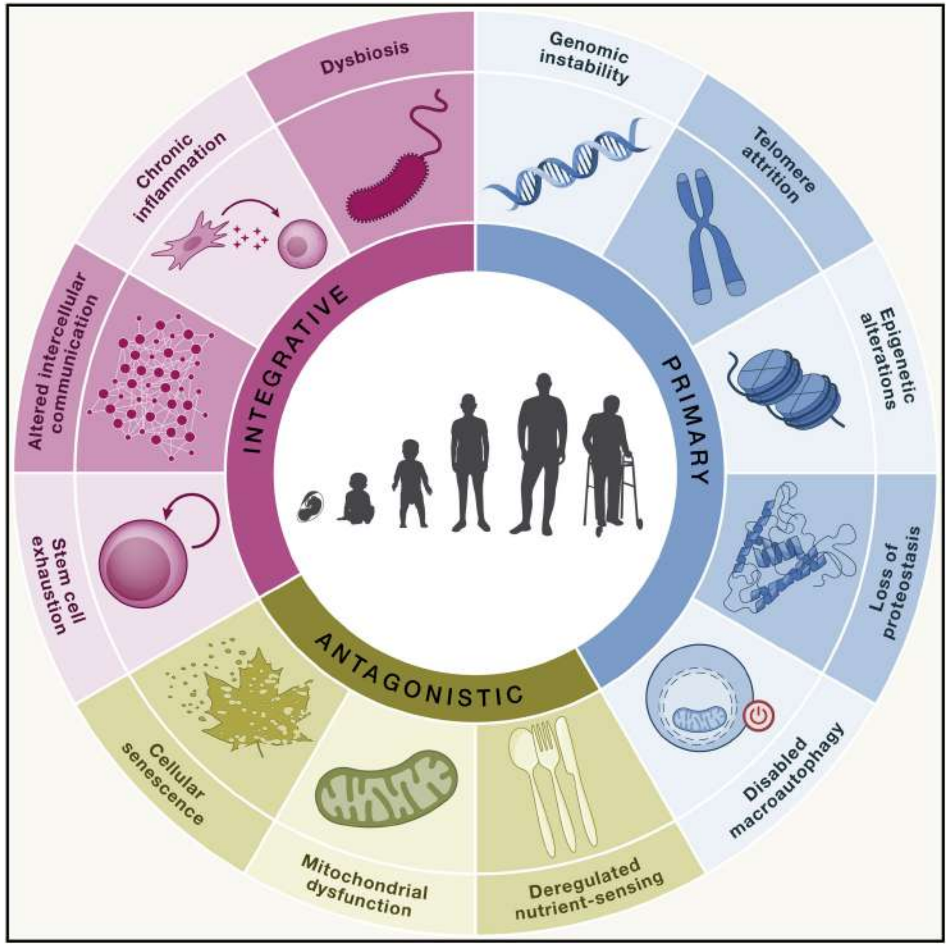
Cardiovascular health, neurological health, skeletal health

Cardiomyocyte senescence, microglial activation, osteoblast dysfunction

Mitochondrial dysfunction, lysosomal impairment

Genetic predisposition, epigenetic alteration, pathway dysregulation

Hallmarks of aging



López-Otín et al., 2023

Healthy aging

Donald Faulkner, 88, during an exercise class. Delta, B.C.
Image by B. Nelms

Betty Brussel, 99, is training hard for her next swimming.
Image by Monia Blanchet

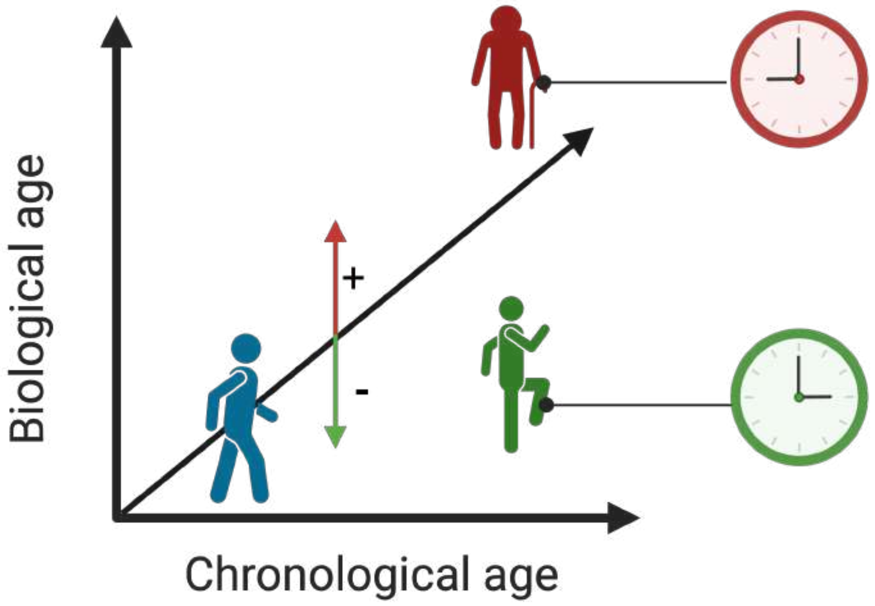
Nina Graham, 89, wears her red volunteer vest from Canadian Blood Services. Richmond, B.C.
Image by D. Dyck

Ivan Vance, at 90, looks set to head off to the courts.
Image by Arlen Redekop

Biological age

Broadly:
The level of age-dependent biological changes, such as molecular and cellular damage accumulation

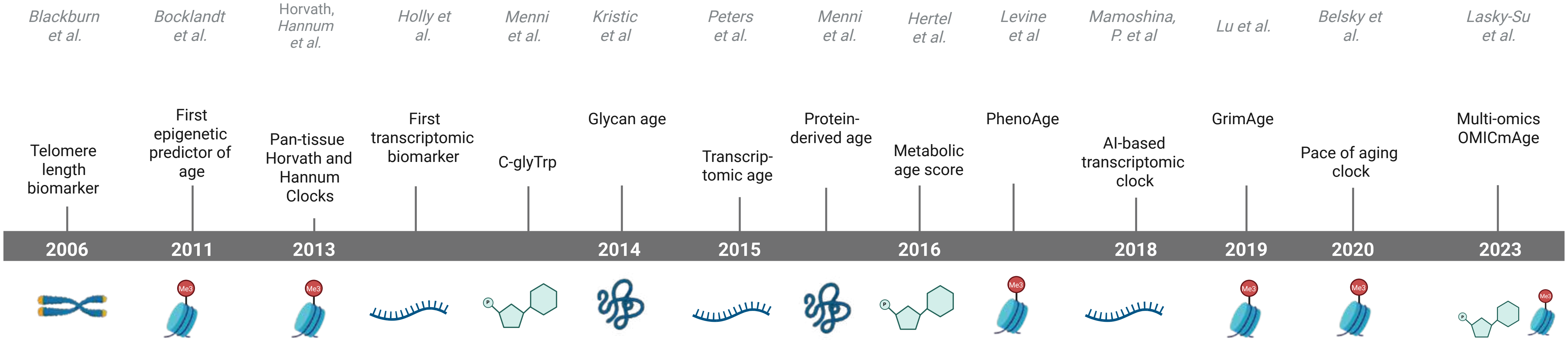
In aging studies:
Numerical value corresponding to the chronological age at which an average individual in a reference population displays similar age-related biological changes

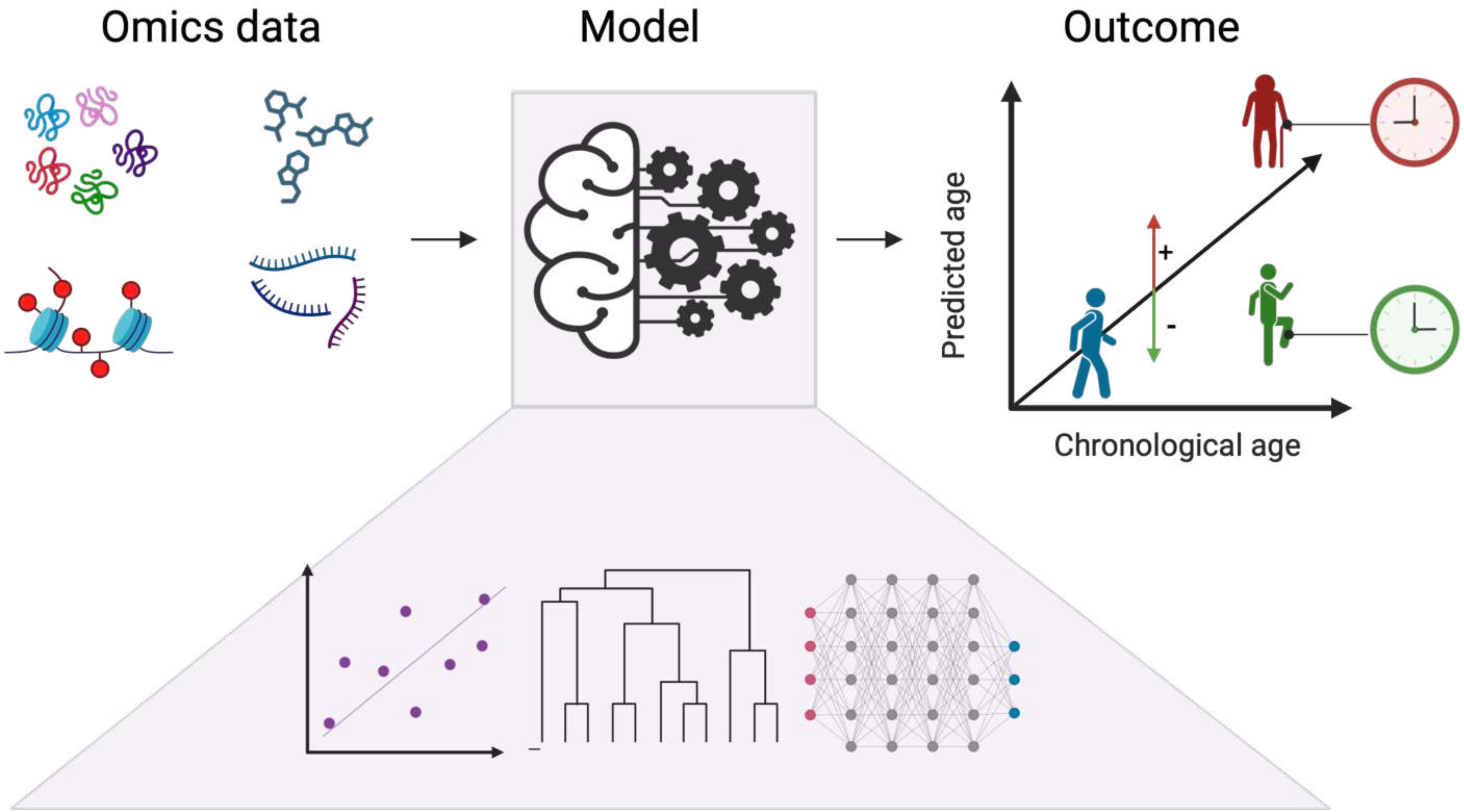


Rationale for measuring biological age

- Quantify individual deviations from normative aging patterns
- Identify factors, including modifiable risk factors, associated with accelerated or decelerated aging
- Identify life-course events that drive divergence in aging trajectories
- Assess the effects of longevity interventions

Omics-based aging biomarkers




Omics data
Model
Outcome
Predicted age
Chronological age
+
-

Challenges

- **Limited specificity.** Do molecular biomarkers reflect true drivers of aging, or also its consequences and unrelated signals?

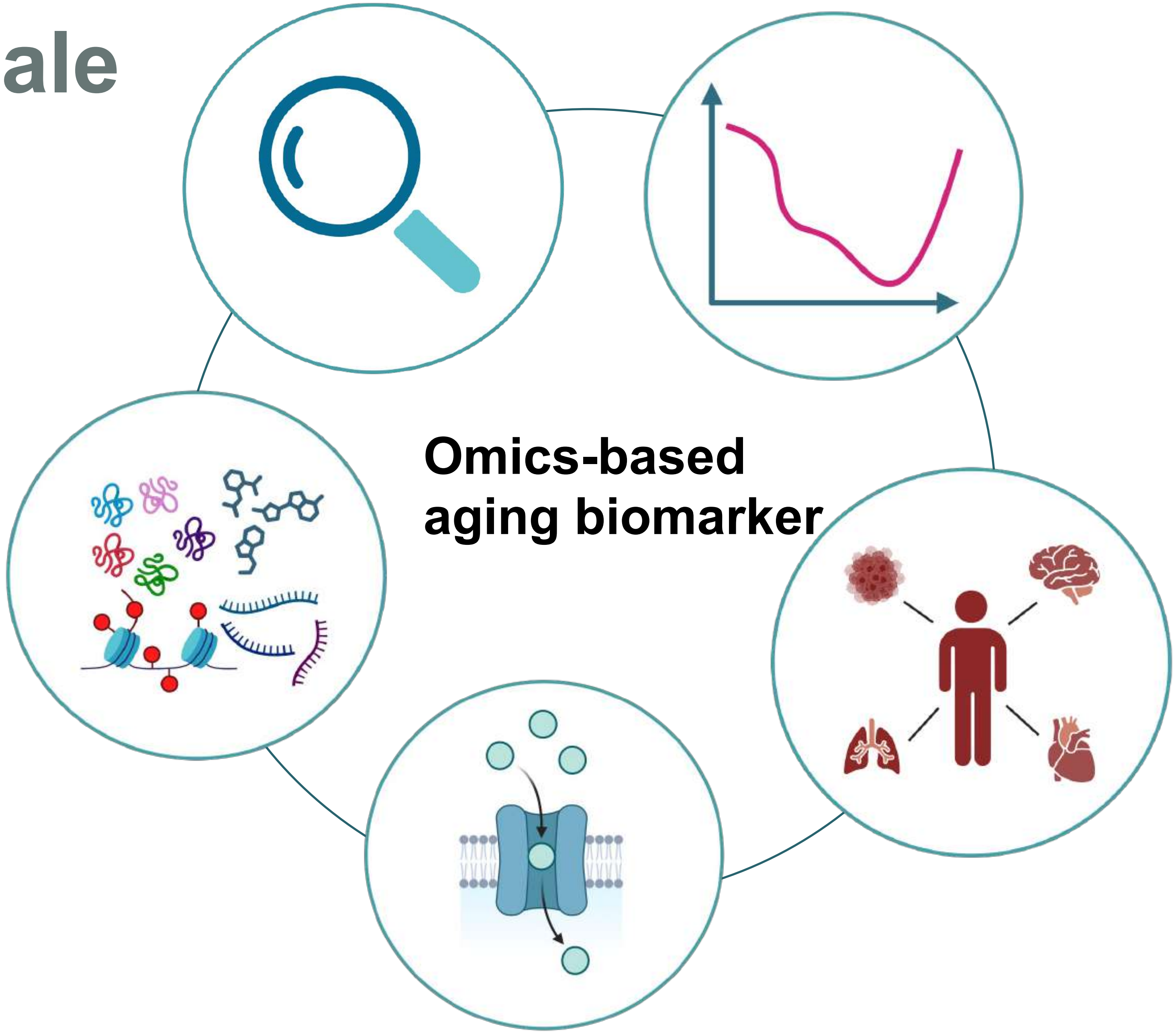
- **Interpretability**. What individual features represent?

- **Train targets**. What should serve as the primary training target to predict a broad range of aging-related outcomes?

- **Non-linearity**. How can we account for complex relationships to capture more realistic biological patterns while preserving interpretability?

- **Aging multi-dimensionality**. Can a single omics layer capture it all, or do we need many?

Rationale



Data

Canadian Longitudinal Study on Aging

2013 2016 2019

n = 30,097

Age: 45-85

: 52%

European: 94%

Participant profile

- History
- Vital signs
- Medication
- Lifestyle
- Body composition
- ECG
- Hematology and chemistry
- Physical assessment tests
- Cognitive tests
- Mortality data
- Inflammatory biomarkers, n = 9,992
- Genotype data, n = 26,622
- Untargeted metabolomics, n = 9,992
- DNA methylation, n = 1,445

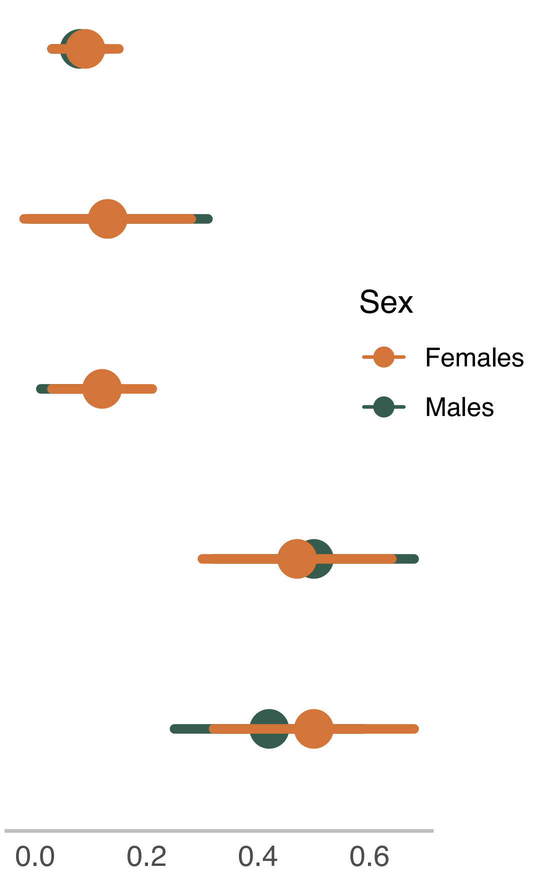
Can we identify measures relevant to health and healthy aging?

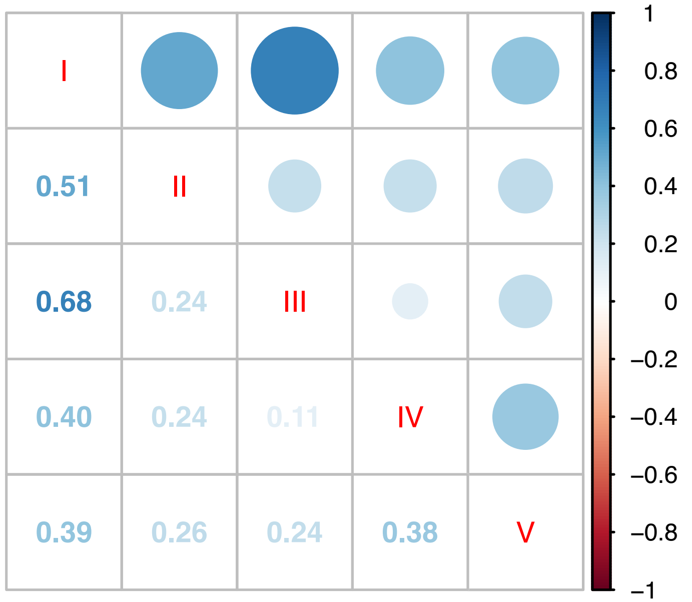
Can we determine their optimal ranges?

Health assessment

	Instrument
I	The Frailty Index as a normalized sum of 51 health deficits
II	The normalized number of chronic conditions: cancer (except non–melanoma skin cancer), cardiovascular disease, major pulmonary disease, dementia, and diabetes
III	The normalized number of 28 self–reported clinician–diagnosed conditions (except conditions used for Instrument II)
IV	Composite cognitive score as the mean of three cognitive domain scores (memory, the executive functions, the psychomotor speed domains) derived from rank normalizes scores of domain–specific tests
V	Physical function as a mean rank normalizes scores of five physical assessment tests

Means and SD





Observation from the Super Seniors Study

Super Senior’s phenotype:

- aged 85 and older
- never diagnosed with cancer, cardiovascular disease, diabetes, dementia, or major pulmonary disease

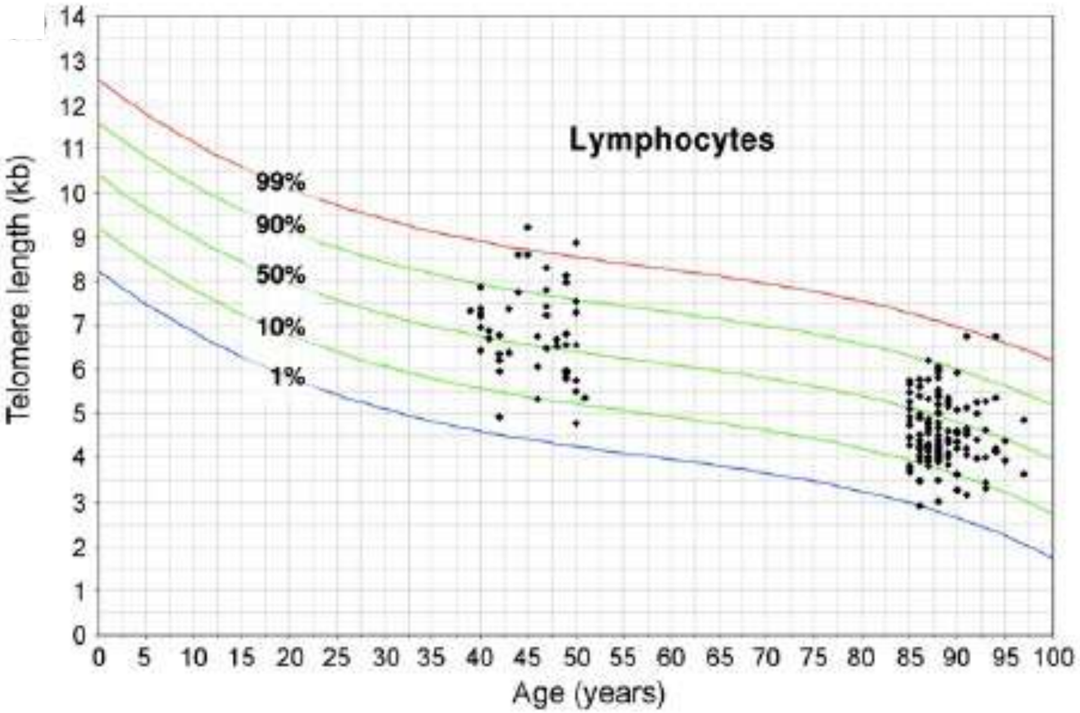
700 seniors aged 85-110 recruited from 2004 to 2010
Mini-Mental State Exam mean = 28.3
Activities of Daily Living Scale mean = 21.4
Timed Up and Go mean = 12.3 s
Geriatric Depression Scale mean = 1.5

Halaschek-Wiener J, et al. The Super-Seniors Study: Phenotypic characterization of a healthy 85+ population. PLoS One (2018)

Observation from the Super Seniors Study

Super Seniors show reduced variation of:

- Telomere length
- Red blood cell count
- Hemoglobin
- Hematocrit
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Red cell distribution width



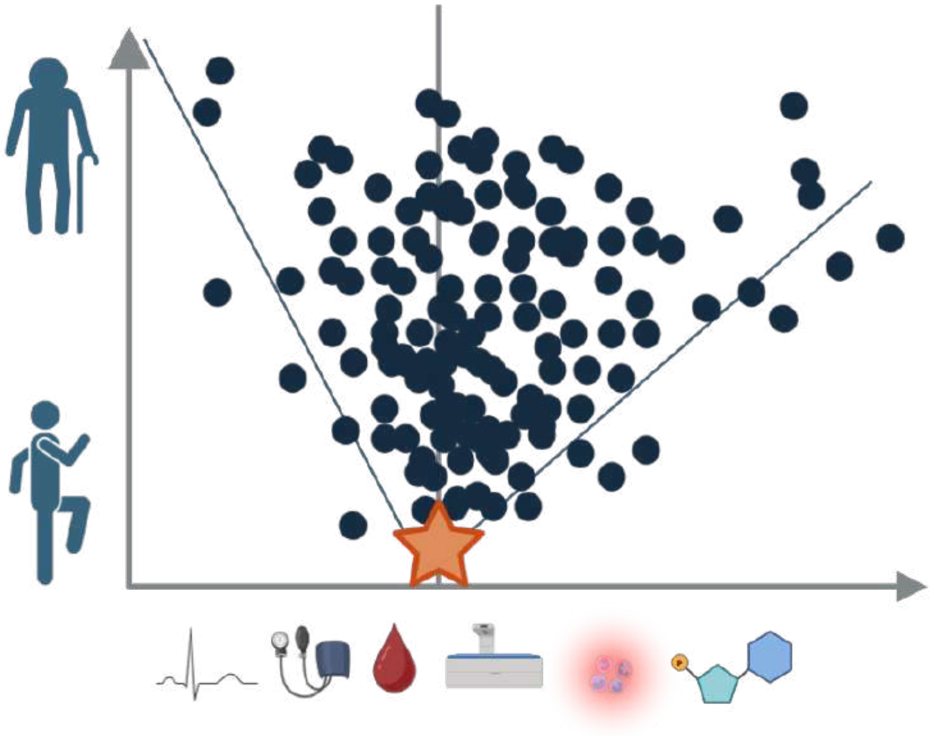
Telomere lengths in lymphocytes of healthy oldest old and mid-life controls

Halaschek-Wiener J, et al. Reduced telomere length variation in healthy oldest old. Mech Ageing (2008)

Sweet spots

- Measures that are important for health tend to be closer to the optimal values, or *sweet spots*, among the healthiest individuals

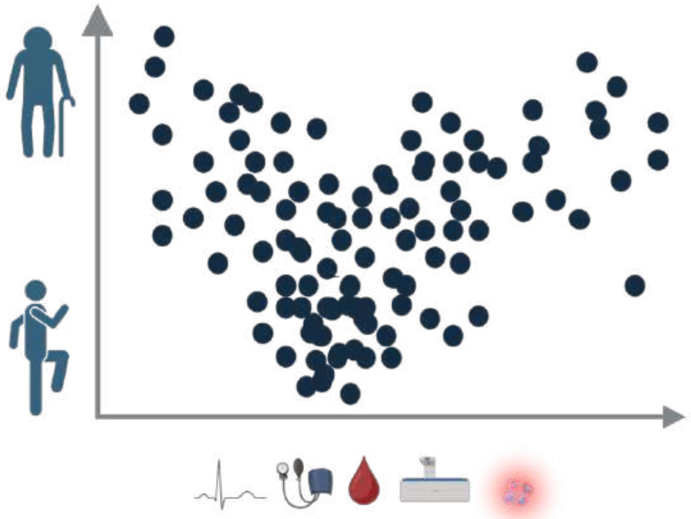
- Distances from sweet spots
  - Quantify the level of dysregulation
  - Inform dysregulated processes
  - Serve as non-linear transformation



Statistical approach

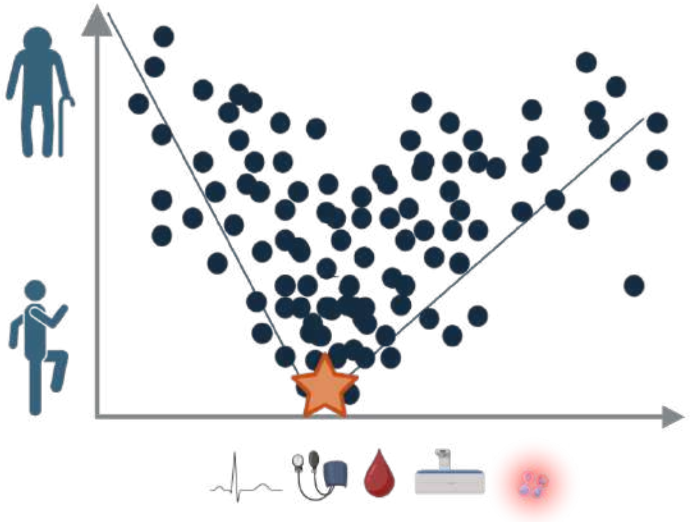
1 Screening

Detect health-related phenotypes via variance heterogeneity across health extremes



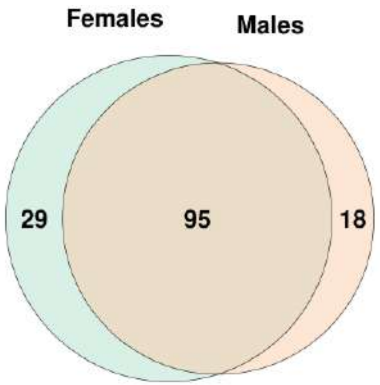
2 Sweet spot detection

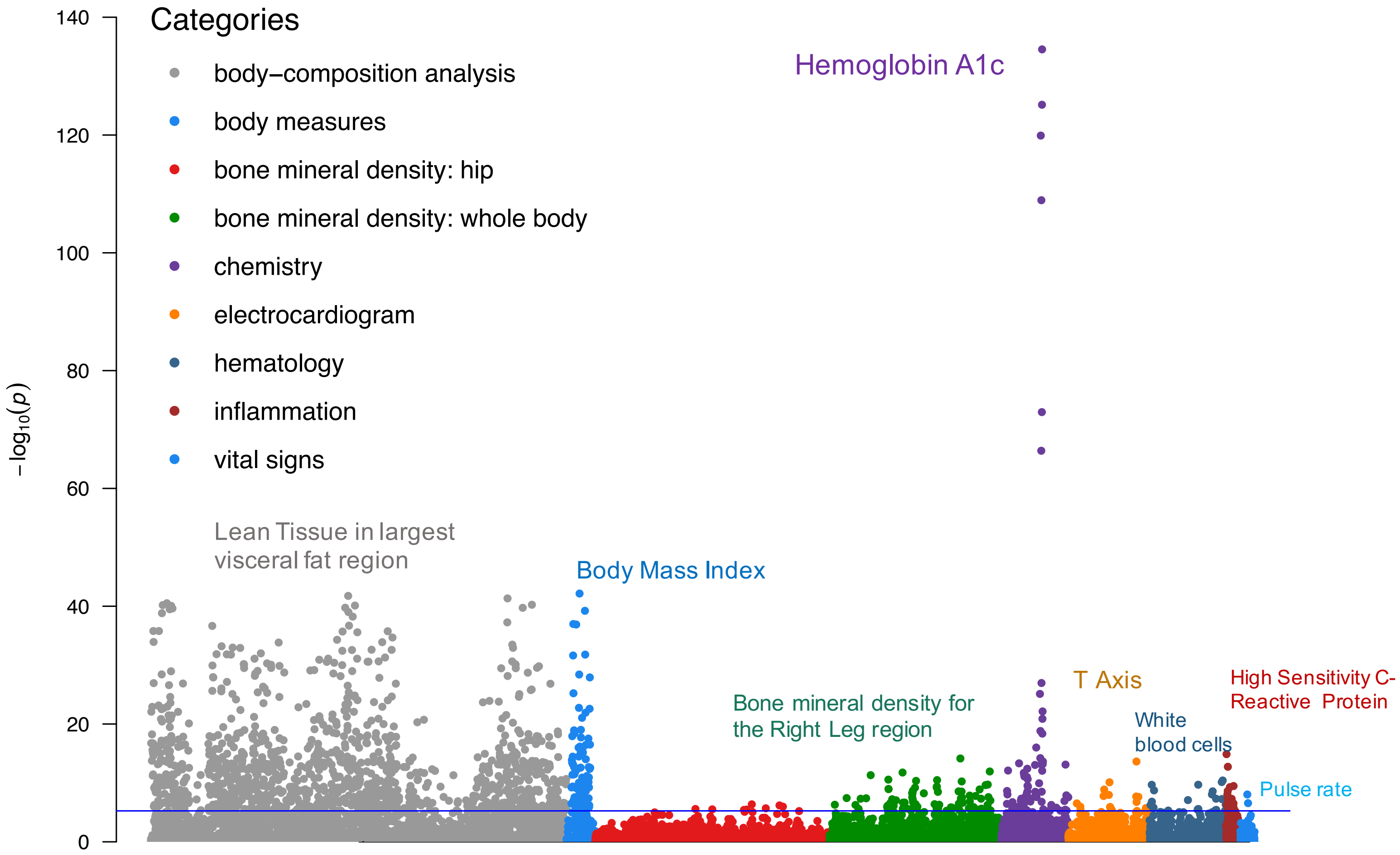
Estimate optimal phenotypic values with deviations linked to poorer health



Key findings

142 out of 231 of phenotypes (61%) with significantly higher variance among the least healthy



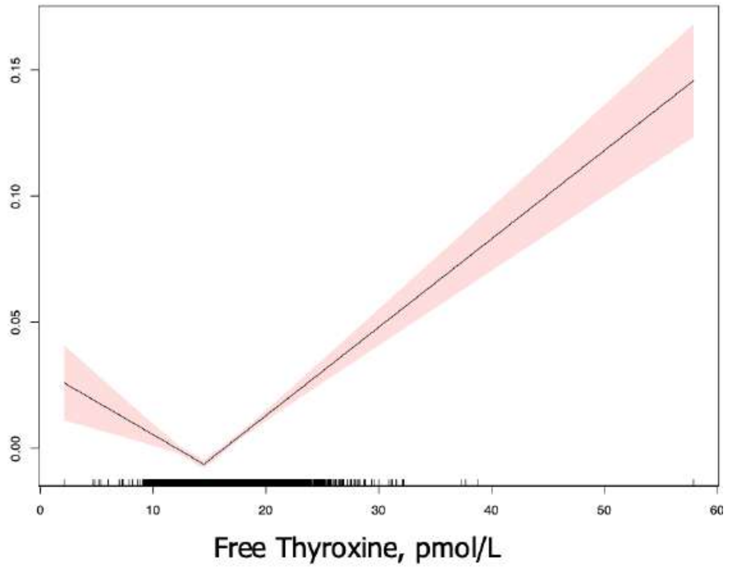


Brown-Forsythe test results for all health instruments, age and sex groups. X-axis represents phenotypes grouped by categories.

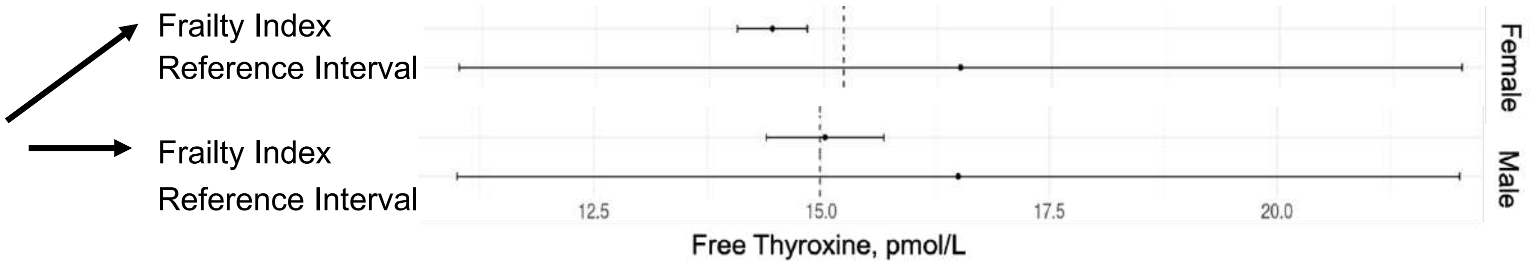
Vishnyakova O, et al. Physiological phenotypes have optimal values relevant to healthy aging: sweet spots deduced from the Canadian Longitudinal Study on Aging. Geroscience (2024)

Key findings

94 out of 231 (41%) with sweet spots



narrower than standard clinical reference ranges



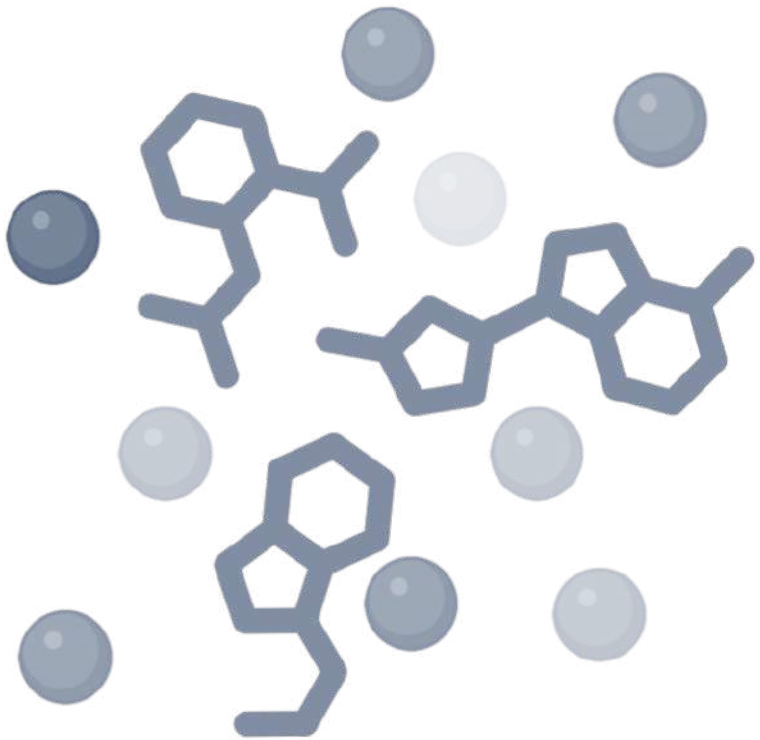
Dashed lines indicate mean values for females and males. Reference intervals were adopted from Textbook of Clinical Chemistry and Molecular Diagnostics 5th Edition

Sex-specific optimal values and ref intervals

Blood chemistry	Variance heterogeneity	Sweet spot	Match ref intervals*
Albumin, g/L	✓	✓	✓
Alanine Aminotransferase, U/L	✓	✓	✓
Creatinine, µmol/L	✓	✓	✓
Estimated Glomerular Filtration Rate, mL/min/1.73m^2	✓	✓	✓
Ferritin, µg/L	✓	✓	✓
Free Thyroxine, pmol/L	✓	✓	✓
Hemoglobin A1c, %	✓	✓**	✓
Low-Density Lipoprotein, mmol/L	✓	✓	✓
Cholesterol, mmol/L	✓	✗	✗
non HDL, mmol/L	✓	✓	N/A
High-Density Lipoprotein, mmol/L	✗	N/A	N/A
Triglycerides, mmol/L	✓	✗	N/A
Thyroid-Stimulating Hormone, mIU/L	✓	✓	✓
25-hydroxyvitamin D, nmol/L	✗	N/A	N/A

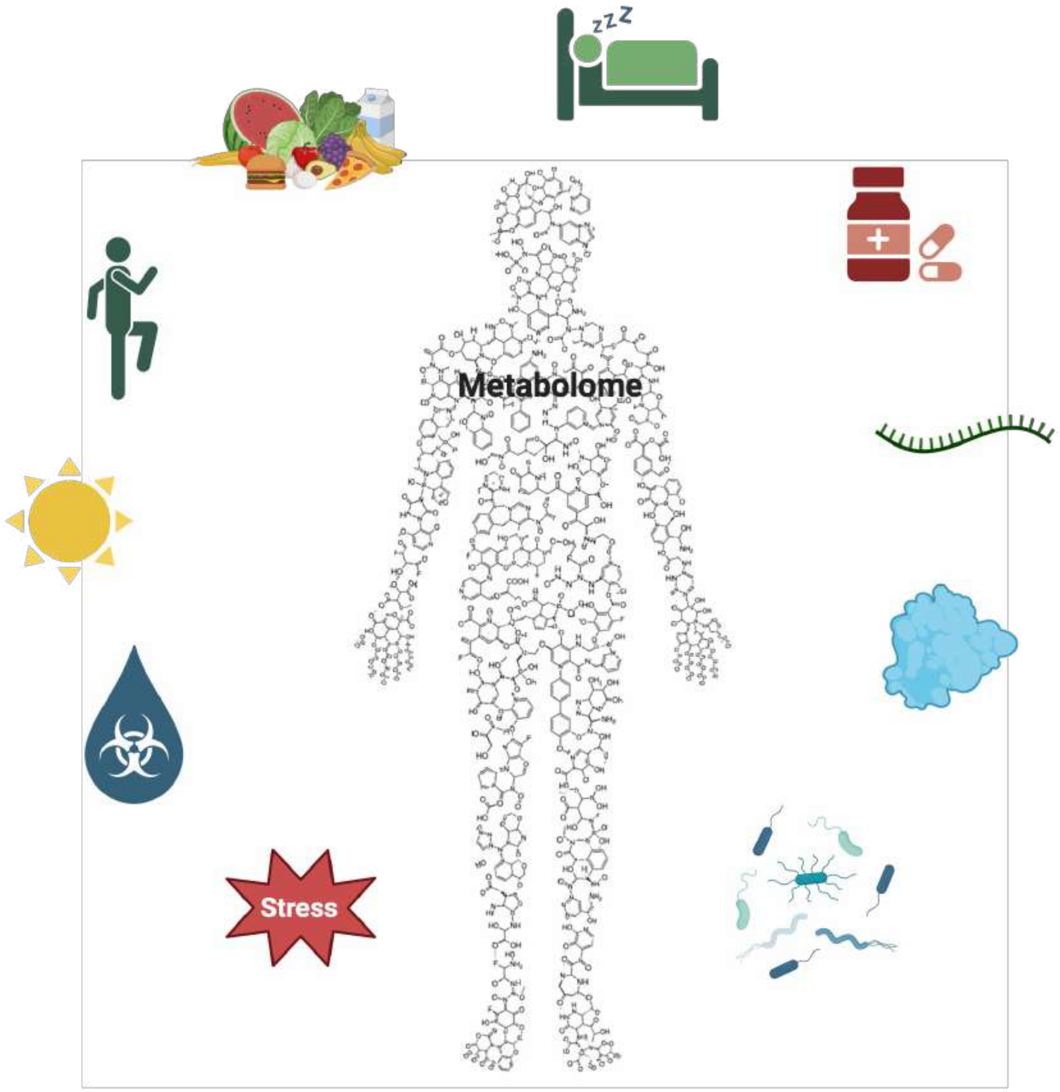
* LifeLab and Surrey Memorial Hospital Lab; ** estimated on nondiabetic males

How does the metabolome reflect variation in aging across individuals?

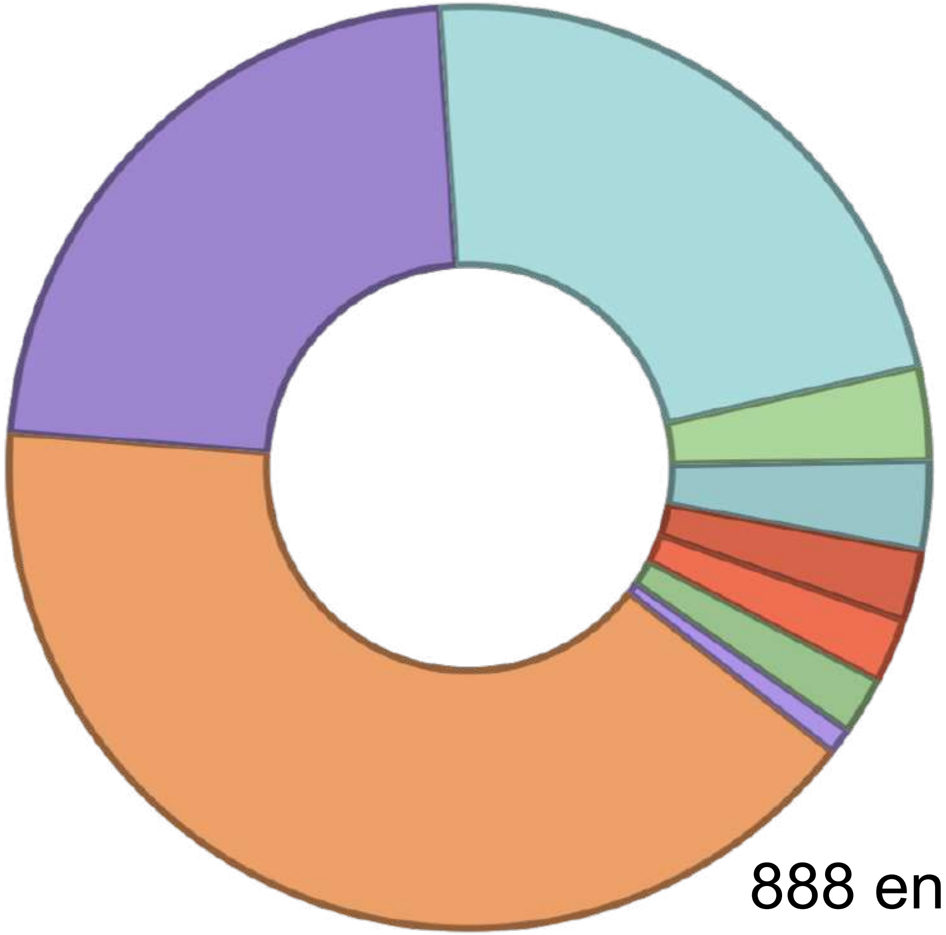


Why metabolomics?

- Metabolome is the collection of all metabolites, small molecules <1500 Da
- End products of metabolism
- End result of all environmental and biological processes
- 30% of identified genetic disorders involve defects in small-molecule metabolism
- Small molecules act as cofactors and signaling molecules for thousands of proteins



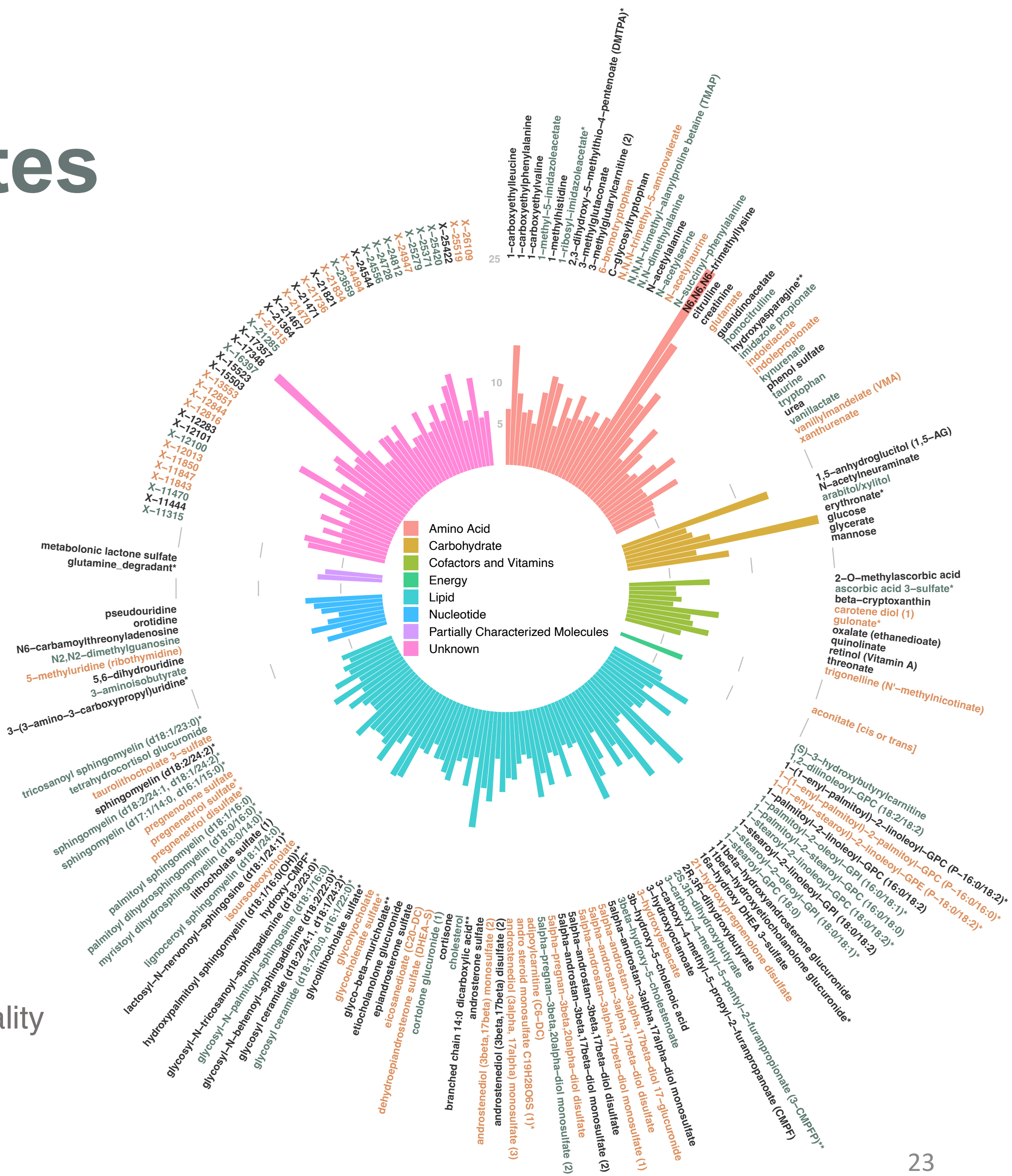
Metabolomic profiling in CLSA



888 endogenous metabolites after QC for 9,992 participants at the baseline

Health related metabolites

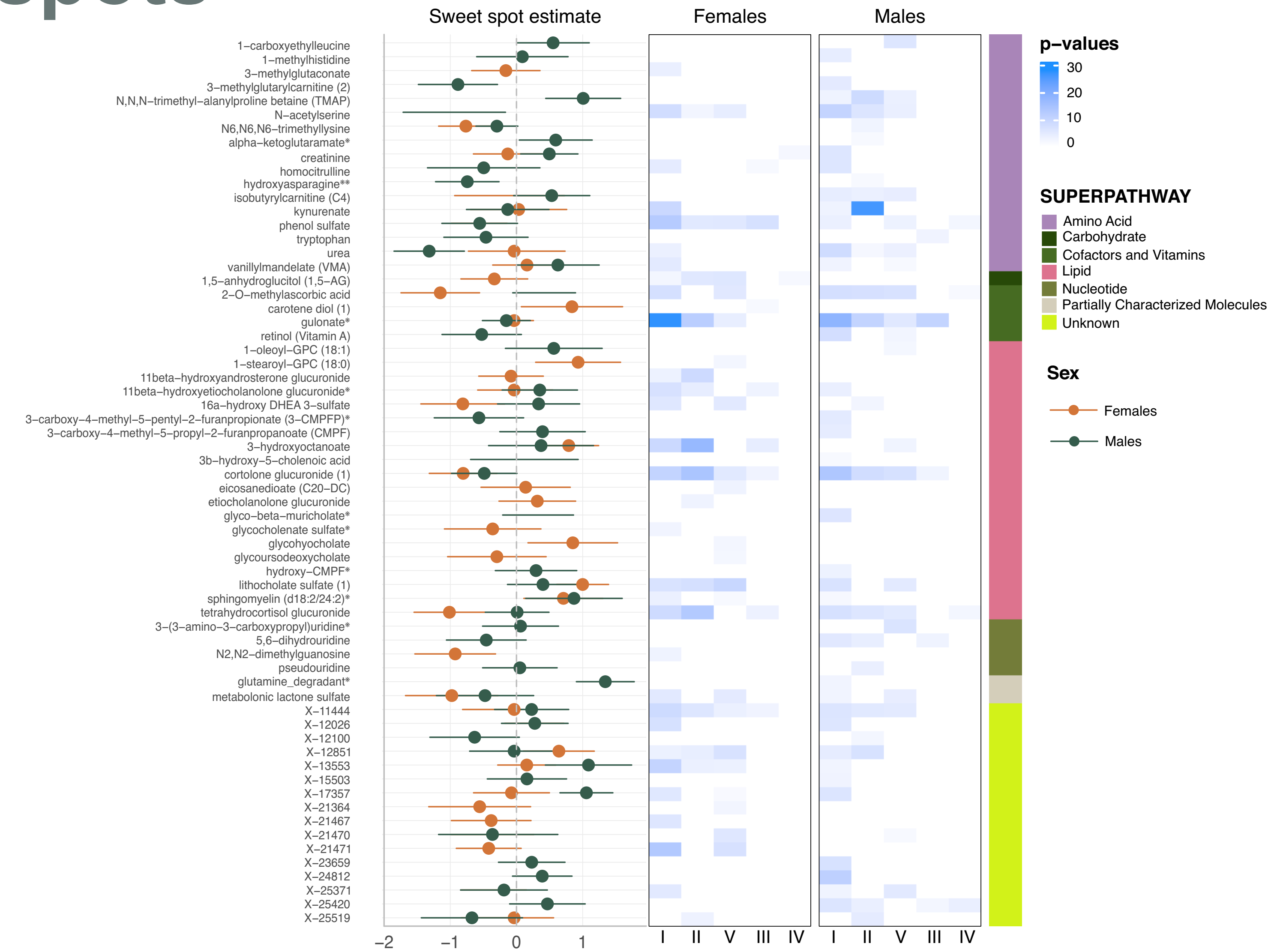
- 178 (20%) metabolites showed significant higher variance in least healthy participants
- Top markers with the strongest variance differences: N6,N6,N6-trimethyllysine, glucose, 1-stearoyl-2-linoleoyl-GPI (phosphatidylinositol)
- Predictors of metabolomic age



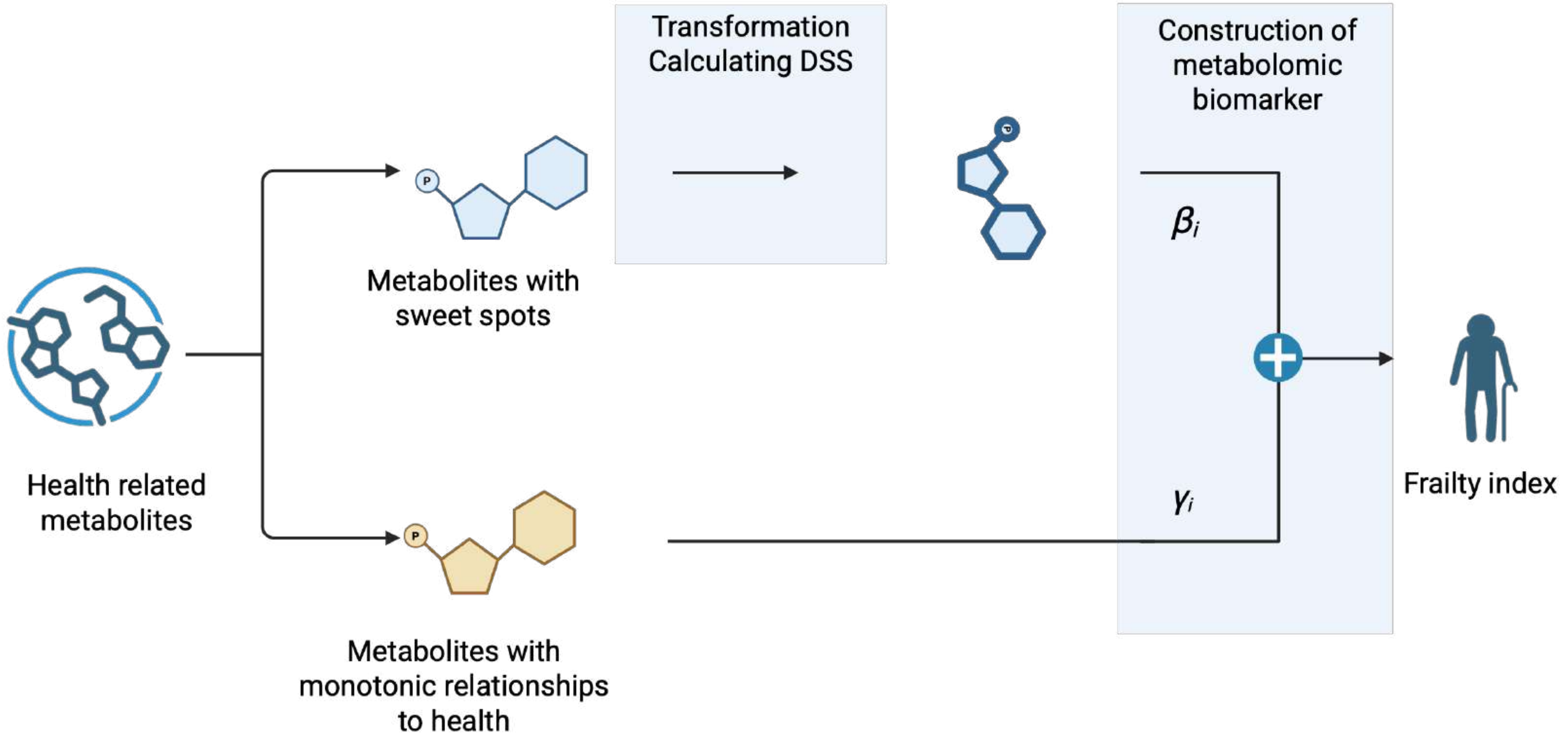
Vishnyakova O, et al. Metabolomic sweet spot clock predicts mortality and age-related diseases in the Canadian Longitudinal Study on Aging. *Commun Med* (2026)

Metabolites' sweet spots

- We determined optimal levels for 74 metabolites
- For about a half of them, 95% CI did not include population mean



Metabolomic aging biomarker

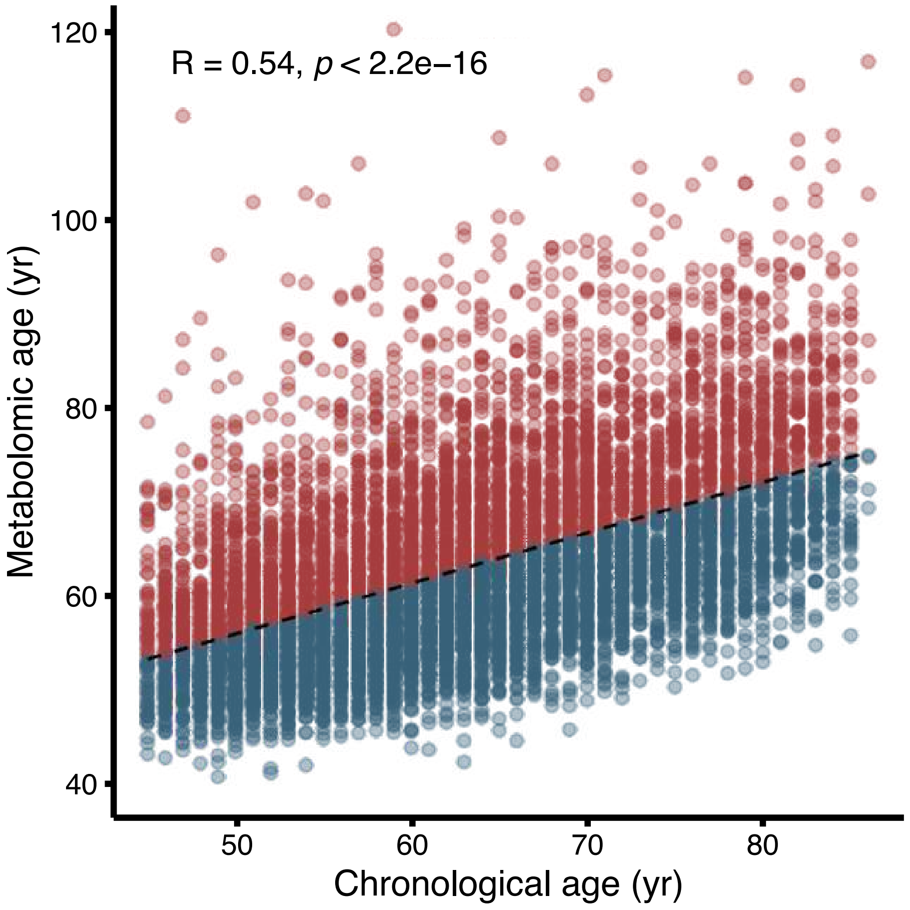


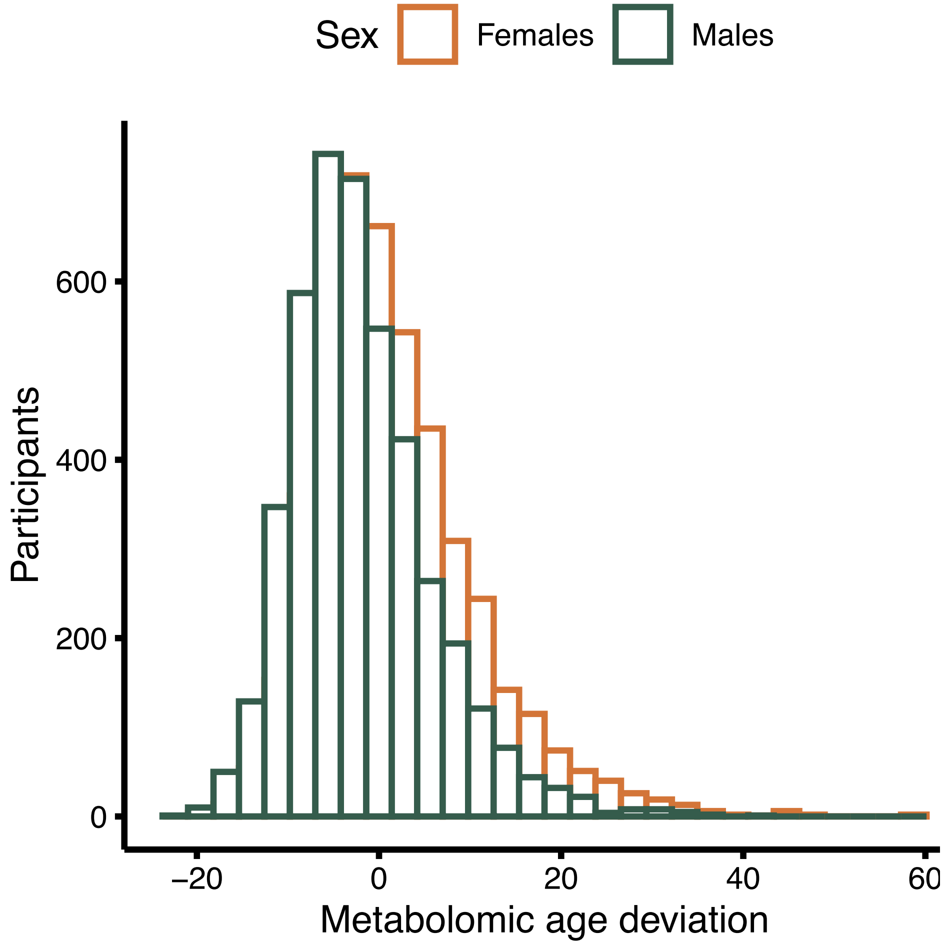
Associations between metabolomic age deviations (MAD) and all-cause mortality

Model*	Target	DSS	C-Index	HR	95% CI	p-value	AUC	Accuracy
Sweet Spot Clock	**FI**	**+**	**0.841**	**1.08**	**[1.06-1.10]**	**5.8×10^{-12}**	**0.824**	**0.951**
ControlMb	FI	-	0.839	1.08	[1.06-1.11]	2.7×10^{-11}	0.822	0.950
ControlAge	Age	+	0.830	1.10	[1.06-1.14]	4.5×10^{-7}	0.824	0.950
Baseline	Age	-	0.821	1.09	[1.05-1.13]	2.2×10^{-6}	0.815	0.950
Frailty index	-	-	0.830	1.05	[1.02-1.07]	5.2×10^{-5}	0.809	0.948
Null	-	-	0.809	-	-	-	0.795	0.949

* Association were determined by Cox proportional hazards models, on the test (1285 participants who had not withdrawn from the study by the second follow-up with 69 death events). Each model has been adjusted for sex and age. MAD are the residuals of metabolomic clocks, calibrated into units of age, and then regressed onto age.

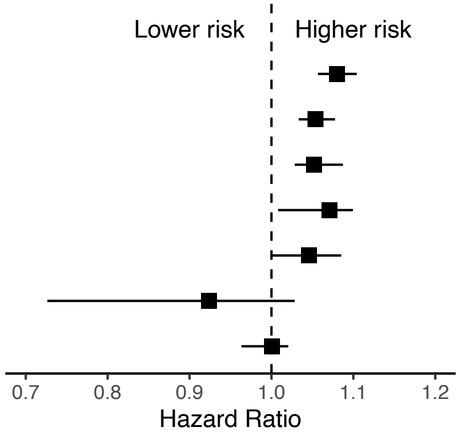
Metabolomic aging biomarker



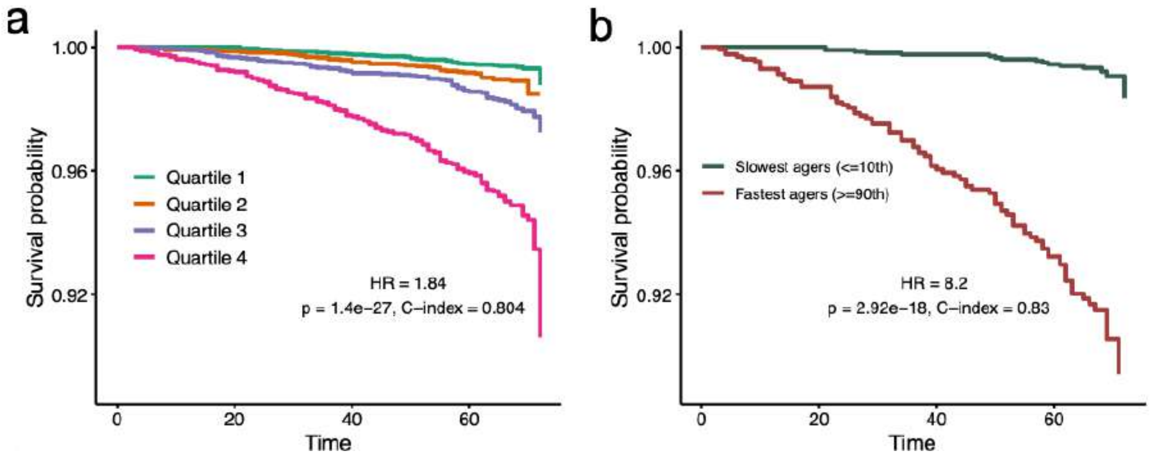


Associations with all-cause mortality and age-related diseases

Outcome	Hazard Ratio (95% CI)	p–value
All–cause mortality	1.08 (1.06–1.10)	<0.001
Diabetes	1.05 (1.03–1.08)	<0.001
COPD	1.05 (1.03–1.09)	<0.001
Stroke	1.07 (1.01–1.10)	<0.001
Kidney failure	1.05 (1.00–1.09)	0.02
Alzheimer's	0.92 (0.73–1.03)	1.00
Cancer	1.00 (0.96–1.02)	1.00



HR per year of metabolomic age deviation



Survival curves stratified by metabolomic age deviation

Associations with health, lifestyle, and socioeconomic factors

	Factor	beta	SD	p-value
Overall health	Chronic condition count	0.008	0.001	$8.5x10^{-36}$
	Physical function (Instrument IV)	0.003	0.001	$2.8x10^{-9}$
	Cognitive function (Instrument V)	0.002	0.001	$5.6x10^{-5}$
Body composition	Body Mass Index	0.037	0.003	$2.2x10^{-32}$
Inflammation	Interleukin-6	0.036	0.003	$2.2x10^{-32}$
	Tumor Necrosis Factor - Alpha	0.043	0.003	$8.5x10^{-36}$
	High Sensitivity C-Reactive Protein, mg/L	0.018	0.002	$4.7x10^{-14}$
Hyperglycemia	Hemoglobin A1c, %	0.041	0.003	$2.3x10^{-39}$
Lifestyle	Nutritional Risk	-0.203	0.019	$1.5x10^{-22}$
	Smoking status	0.017	0.002	$1.7x10^{-11}$
	Alcohol consumption	0.032	0.007	$4.7x10^{-5}$
	Physical activity levels	0.037	0.003	$8.5x10^{-36}$
	Psychological Distress	-1.200	0.225	$1.8x10^{-6}$
Socio-economic	Total household income	-0.030	0.003	$8.1x10^{-17}$
	Level of Education	-0.011	0.003	$2.0x10^{-3}$

Associations with health, lifestyle, and socioeconomic factors

- Of 126 health-related metabolites, 111 and 78 were retained in the female and male models, respectively

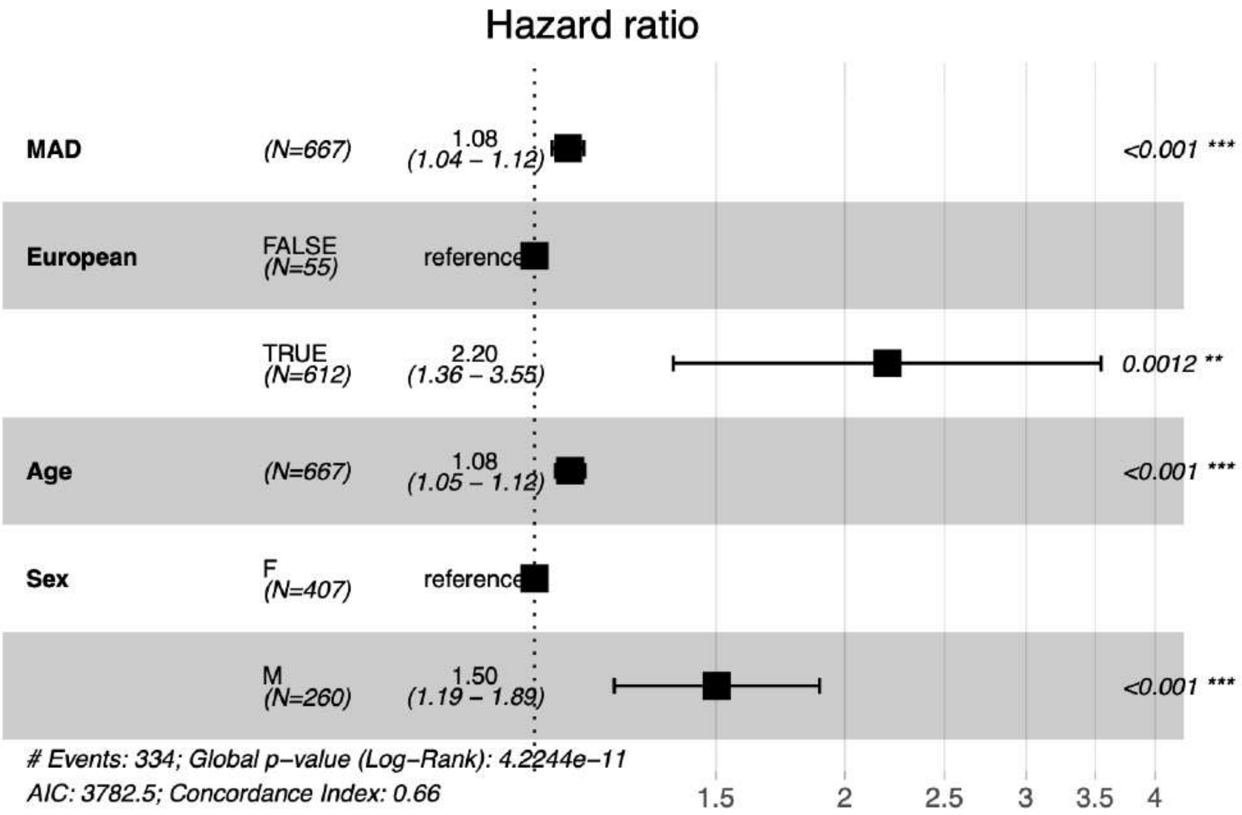
- The top 50 predictive metabolites we tested for associations with 40 known disease biomarkers, chronic conditions, and diagnostic measurements

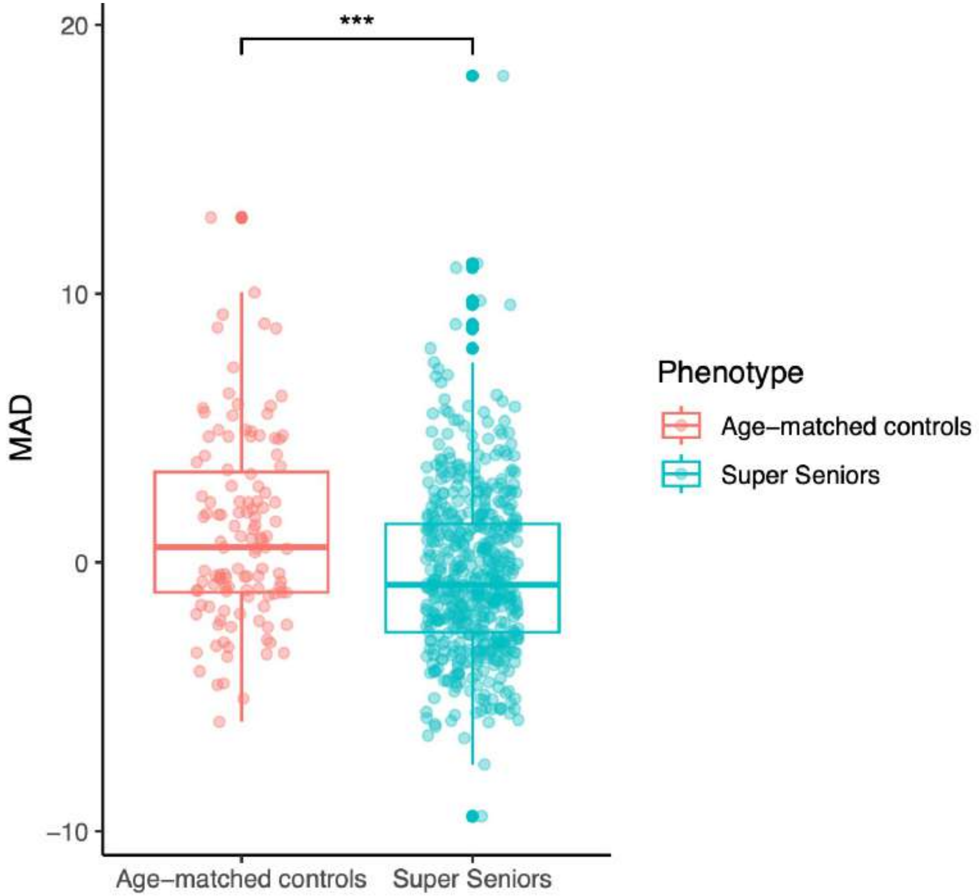
- All metabolites showed strong associations with at least five distinct phenotypes tested after Bonferroni correction ($n = 2000$)


Osteoarthritis
Arthritis
COPD
Diabetes
Heart disease
Cancer
Osteoporosis
Hyperthyroidism
Hyperthyroidism
Kidney disease
Dementia or Alzheimer's disease
Parkinson's Disease
Grip strength
High Sensitivity C-Reactive Protein
Tumor Necrosis Factor - Alpha (TNF-a)
Interleukin-6 (IL-6)
Lymphocytes (absolute number)
Monocytes (absolute number)
Granulocytes (absolute number)
Red blood cells
Hemoglobin
Platelets
Hemoglobin A1c
25-hydroxyvitamin D
Albumin
Alanine Aminotransferase
Creatinine
Ferritin
Free Thyroxine
High-Density Lipoprotein
Low-Density Lipoprotein, calculated
Triglycerides
Thyroid-Stimulating Hormone
P Axis
R Axis
T Axis
Body Mass Index
Average systolic blood pressure (excluding 1st reading)
Average diastolic blood pressure (excluding 1st reading)
Average pulse rate (excluding 1st reading)
1-carboxyethylphenylalanine
3-methylglutarylcarnitine (2)
N,N,N-trimethyl-5-aminovalerate
N-acetyltaurine
N6,N6,N6-trimethyllysine
hydroxyasparagine**
imidazole propionate
indolelactate
indolepropionate
kynurenate
taurine
vanillactate
vanillylmandelate (VMA)
xanthurenate
1,5-anhydroglucitol (1,5-AG)
N-acetylneuraminate
arabitol/xylitol
erythronate*
mannose
2-O-methylascorbic acid
ascorbic acid 3-sulfate*
beta-cryptoxanthin
carotene diol (1)
(S)-3-hydroxybutyrylcarnitine
1,2-dilinoleoyl-GPC (18:2/18:2)
Beta coefficients
0.6
0.4
0.2
0
-0.2
SUPERPATHWAY
Amino Acid
Carbohydrate
Cofactors and Vitamins
Lipid
Nucleotide
Unknown

Validation in Super Seniors

548 Super Seniors and 119 age-matched controls





Link with epigenetic biomarkers

Model*	Predictor	C-Index	HR	95% CI	p-value**
Multi-omics	MAD	0.806	1.07	[1.05–1.10]	1.52×10^{-8}
	GrimAge v2	0.806	1.08	[1.00–1.18]	0.049
SweetSpotClock	MAD	0.783	1.07	[1.05–1.10]	6.49×10^{-10}
GrimAge v2	GrimAge v2	0.751	1.15	[1.07–1.23]	8.23×10^{-5}
GrimAge v1	GrimAge v1	0.744	1.15	[1.07–1.24]	2.80×10^{-4}
PhenoAge	PhenoAge	0.710	1.03	[0.99–1.07]	0.159
Hannum	Hannum	0.694	0.99	[0.94–1.05]	0.733
Horvath	Horvath	0.694	0.99	[0.94–1.04]	0.574

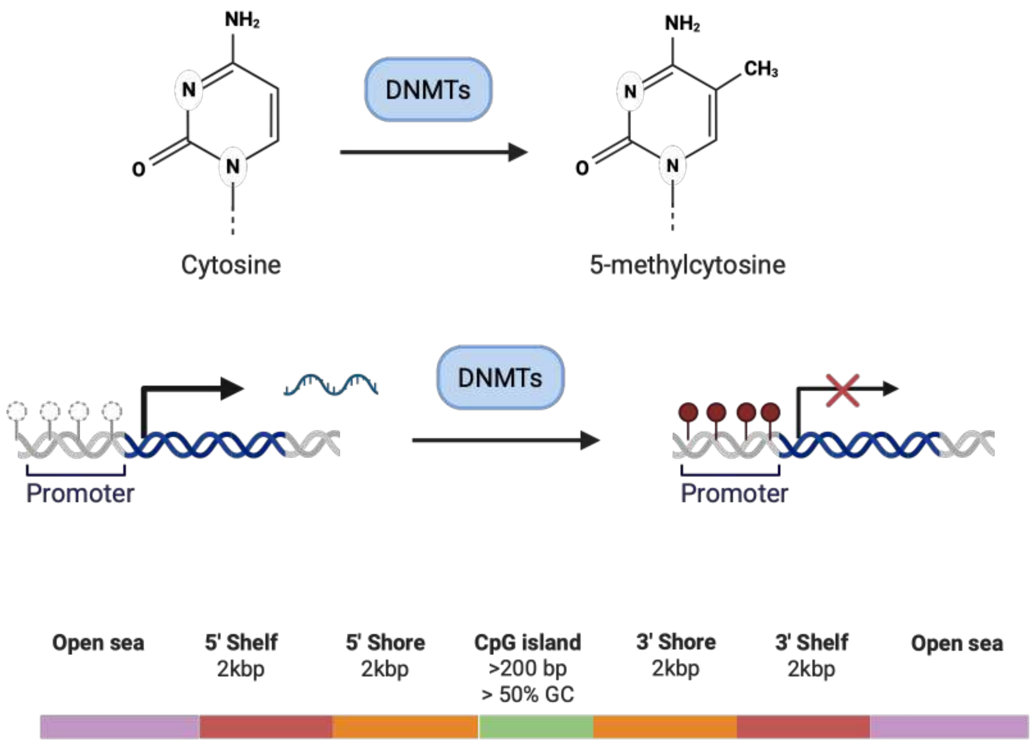
* Hannum and Horvath Pan-Tissue clock were available in the CLSA COM dataset. PhenoAge, GrimAge v2 and GrimAge v1 were calculated using the Biolearn Python library. All models were adjusted for age and sex. Association were determined by Cox proportional hazards models, on a set of 1242 participants with available DNA methylation data who had not withdrawn from the study by the second follow-up with 64 death events.

** p-values obtained from two-sided Wald tests.

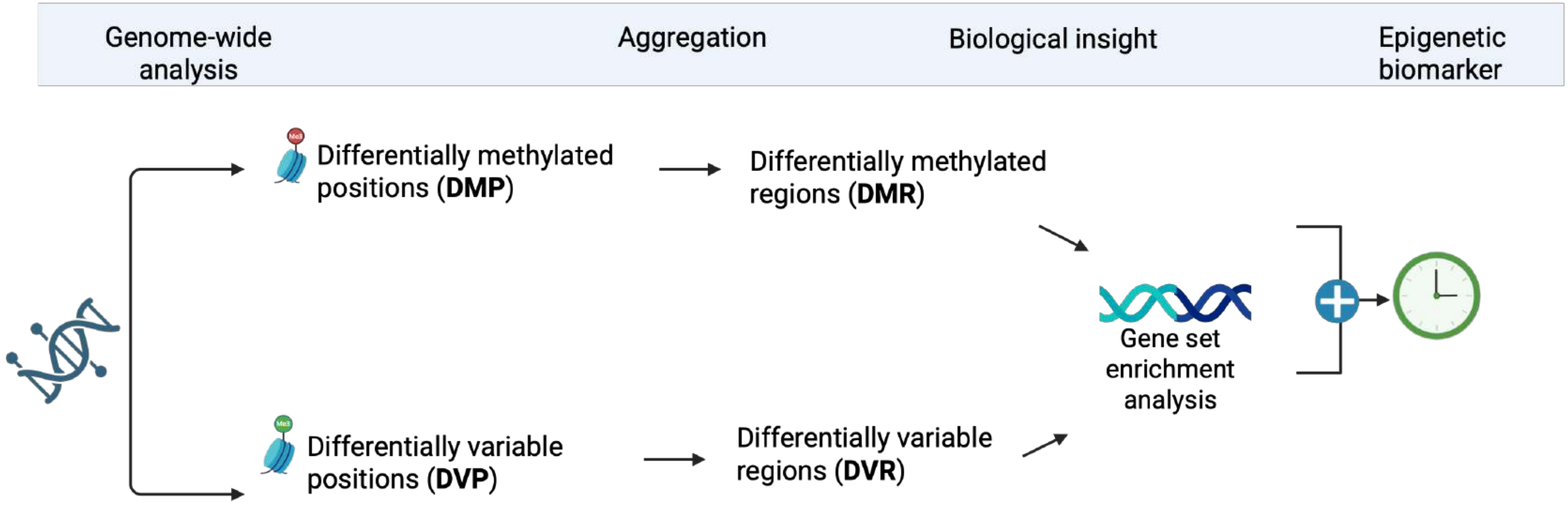
DNA methylation

- Epigenetics = heritable changes in gene expression without altering DNA sequence
- Shaped by environment, development, and aging
- Occurs at CpG sites, often clustered in CpG islands
- ~70% of gene promoters contain CpG islands
- Methylation at promoters and CpG shores regulates gene expression
- 1,284 samples and 783,136 CpGs after QC

Beta value = proportion of methylation at each CpG site: 0 (unmethylated) to 1 (fully methylated)

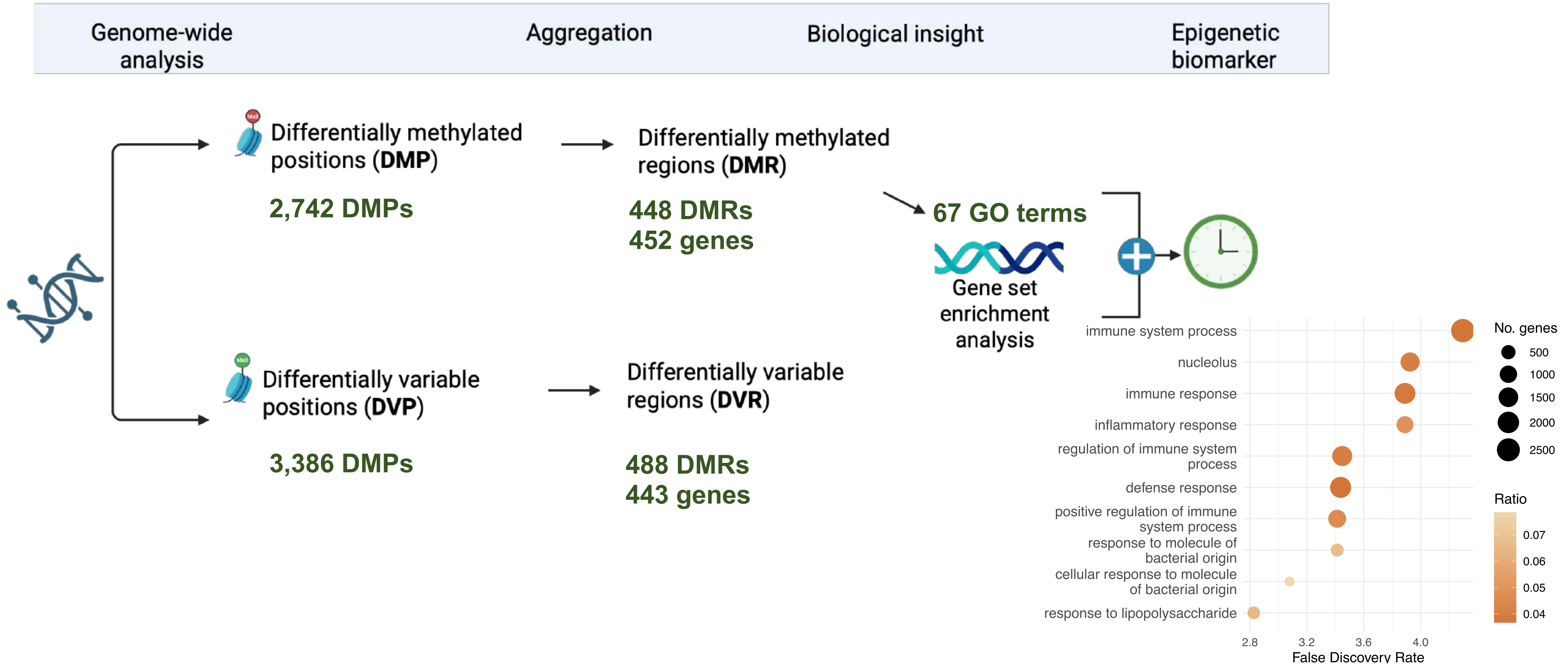


Epigenetic analysis

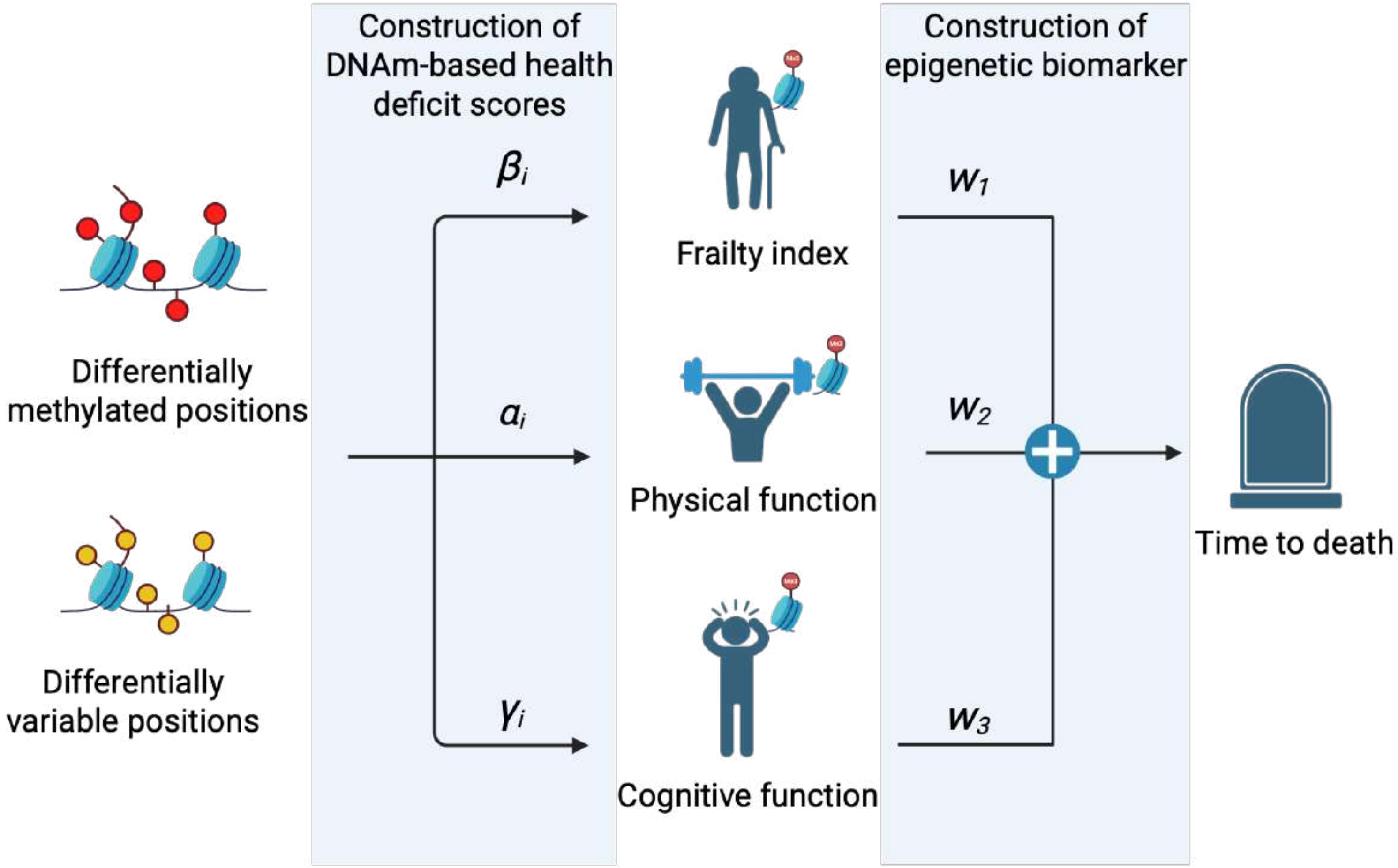


Vishnyakova O, et al. Epigenetic signature of heterogeneity in aging: findings from the Canadian Longitudinal Study on Aging. 2025 bioRxiv 2025.08.25.671156

Epigenetic analysis



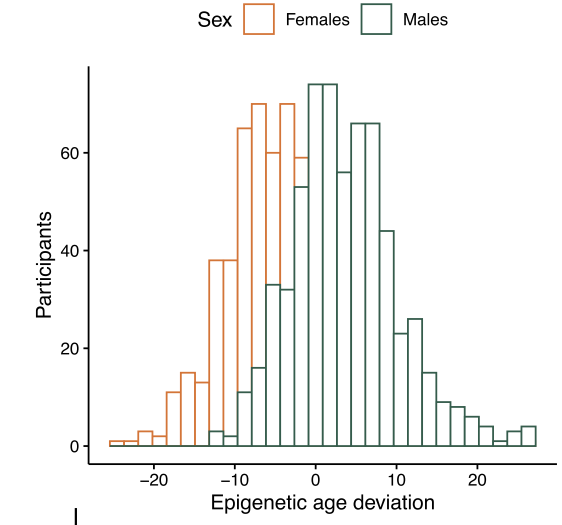
DMP-DVP-based epigenetic biomarker

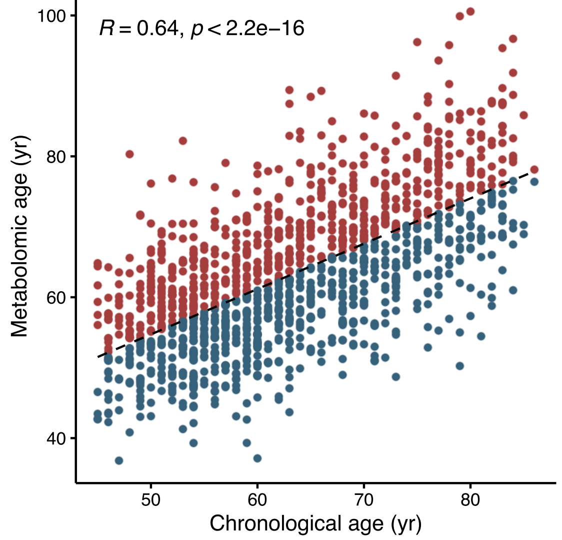


DMP-DVP-based epigenetic biomarker

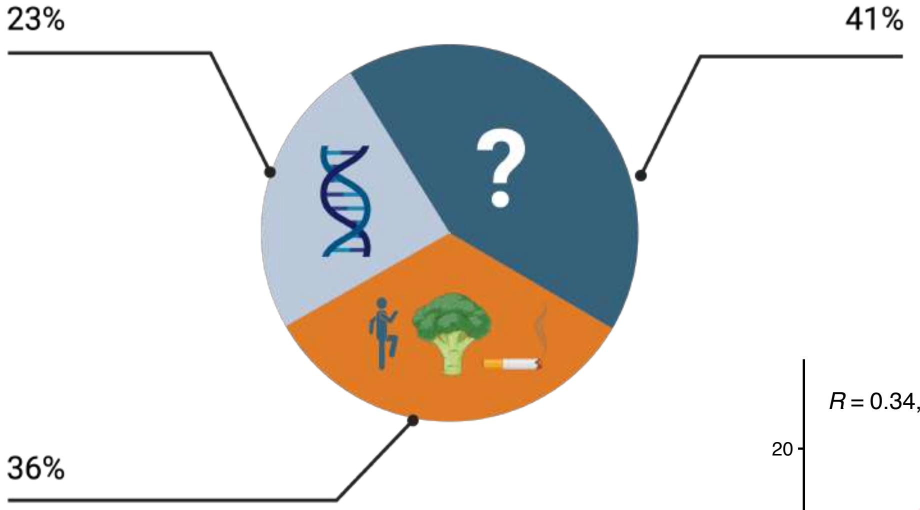
Outcome	Biomarker	HR [95% CI]	p-value	C-index (SE)	AUC
Mortality	DMPs- and DVPs- based	**1.125** [1.015–1.247]	0.024	**0.877** (0.036)	**0.8984**
	DMPs-based	1.119 [1.012–1.238]	0.029	0.874 (0.038)	0.8972
	DVPs-based	1.120 [1.010–1.242]	0.032	0.855 (0.038)	0.8712
	Frailty Index	1.060 [1.010–1.112]	**0.019**	0.831 (0.072)	0.8604
	GrimAge acceleration (v2)	1.034 [0.979–1.091]	0.233	0.829 (0.054)	0.8691
	GrimAge acceleration (v1)	1.029 [0.978–1.084]	0.271	0.825 (0.058)	0.8613
	Methylation Risk Score	1.054 [0.937–1.185]	0.383	0.810 (0.063)	0.8320
	PhenoAge	1.021 [0.937–1.113]	0.635	0.801 (0.073)	0.8476
	Shannon entropy	0.973 [0.813–1.163]	0.761	0.798 (0.074)	0.8163
	Null model	–	–	0.796 (0.075)	0.8408

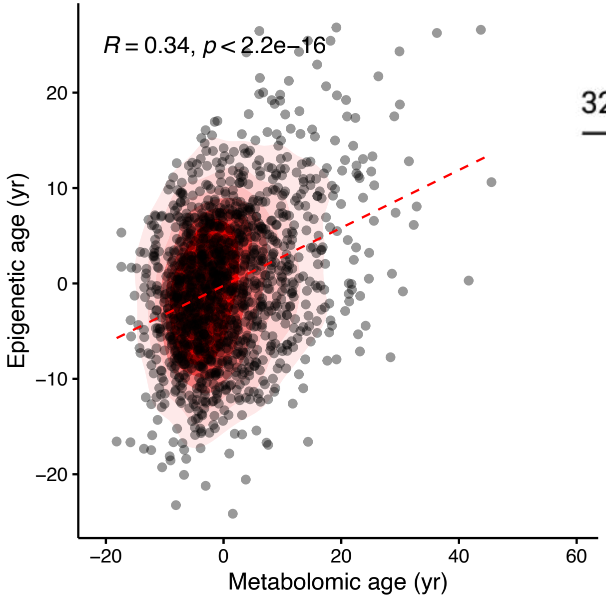
Hazard Ratios (HR) and concordance indices (C-index) for aging biomarkers. All models are adjusted for age and sex. Estimates are based on a sample of 187 individuals with 14 deaths observed over six years.





Metabolomic vs. Epigenetic biomarker





Takeaways

Key Findings:

- Proposed method detected phenotype-specific dysregulation
- Omics biomarkers were predictive for mortality and the onset of age-related diseases
- Methylation variability captures unique aging signals

Utility and Impact:

- Generate individualized health report card
- Identified dysregulated pathways are potential therapeutic targets
- Guide lifestyle prevention efforts

Future Directions:

- Explore interventions to modulate biological age deviation
- Develop multi-omics biomarkers

Acknowledgments

BC CANCER RESEARCH
Provincial Health Services Authority

Brooks-Wilson Lab

SFU SIMON FRASER UNIVERSITY

Elliott Lab

CIHR IRSC Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

BC CANCER FOUNDATION

clsa élcv
Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement

SUPER SENIORS STUDY

Collaborators:
Dr. Xiaowei Song
Dr. Kenneth Rockwood
Dr. Sonny Min

ovishnyakova@bccrc.ca