Plenary 4: Leveraging multi-omics to identify novel mechanistic insights into chronic diseases of aging and exceptional longevity among WHI women

Session Chair: Heather Ochs-Balcom, PhD

University at Buffalo

WHI Annual Meeting

May 7-8, 2026

Multi-omics SIG

Started in Sept 2025

- Chaired by Lindsay Reynolds and Heather Ochs-Balcom
- Examples of recent and upcoming presentations
    - Proteomic signatures of menopause timing
        - Kaitlin Casaletto (UCSF) and Madeline Wood (Toronto)
    - Predicting the First Cardiovascular Event Using Traditional Risk Factors and Metabolomics: A Multi-State Modeling Approach
        - Ming Ding (UNC)
    - August 6th: Adverse pregnancy outcomes and multi-omics
        - Mark A Hlatky (Stanford)

To join our listserv:

IGNITE session: Dennis Khodasevich and Cynthia Kusters

WHI Query Builder

- GWAS and –omics data, updates are underway
  - additional QC
  - WGS results
  - DNA methylation, timepoints
  - RNA seq
  - Targeted metabolomics

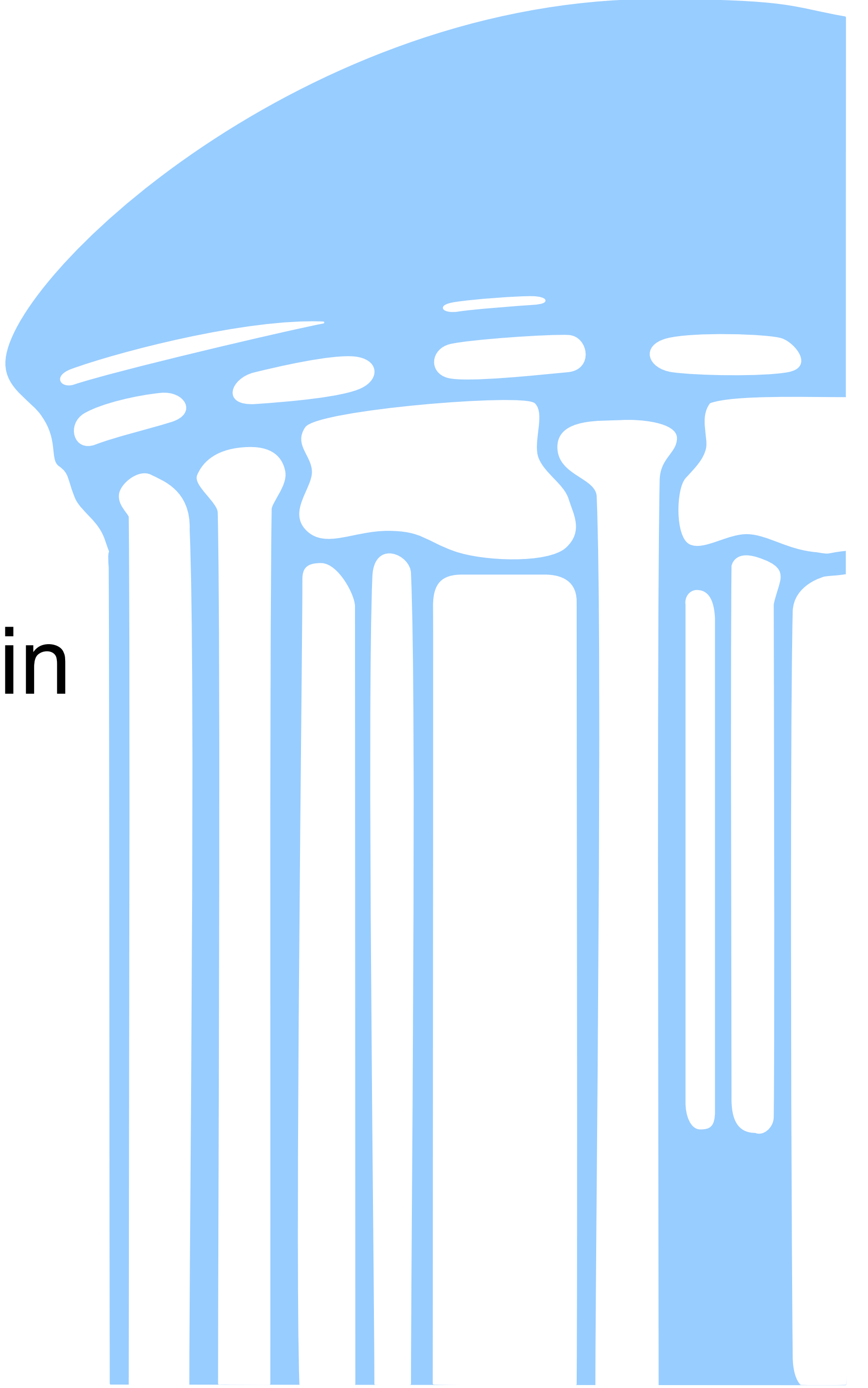
Our speakers

Nora Franceschini, UNC	• Proteomics and epigenetic scores for cardiovascular outcomes in WHI-LLS women
Aladdin Shadyab, UCSD	• Epigenetic and proteomic biomarkers of MCI/dementia and cognitively healthy longevity in WHIMS
Charles Breeze, NCI	• Integrative analysis of cancer epigenomic data

Proteomics organ aging scores for cardiovascular and kidney outcomes in WHI-LLS women

Nora Franceschini, MD MPH FAHA

2026 WHI Investigator Meeting



Omics aging clocks related to biological aging

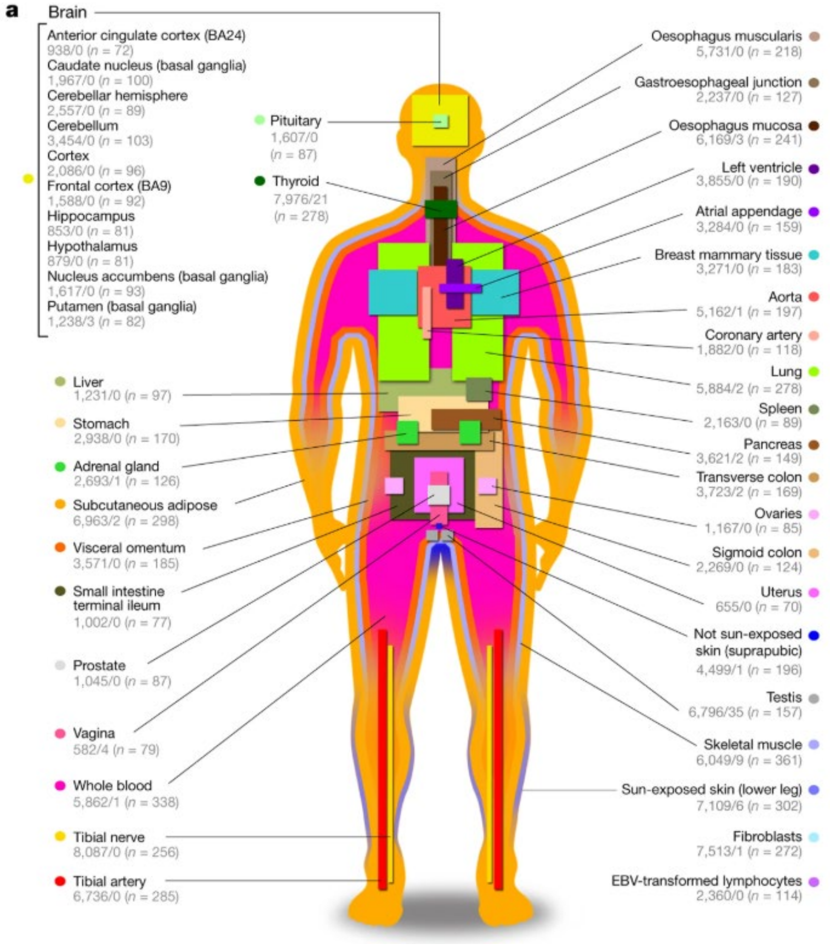
- Epigenetic biological aging clocks
  - PhenoAge and GrimAge3

- Protein aging scores
  - Proteomics aging clock
  - Organ-specific protein profiles based on organ-enriched genes

Organ-specific aging scores

- Protein-encoding genes expressed >4-fold in an organ versus other organs in GTEx tissue.
- Genes mapped to Olink proteins in the UK Biobank.
- 19% plasma proteins are organ-enriched.
- Use LASSO regression models to build chronological age predictors (aging models) to estimate biological age and age gaps.

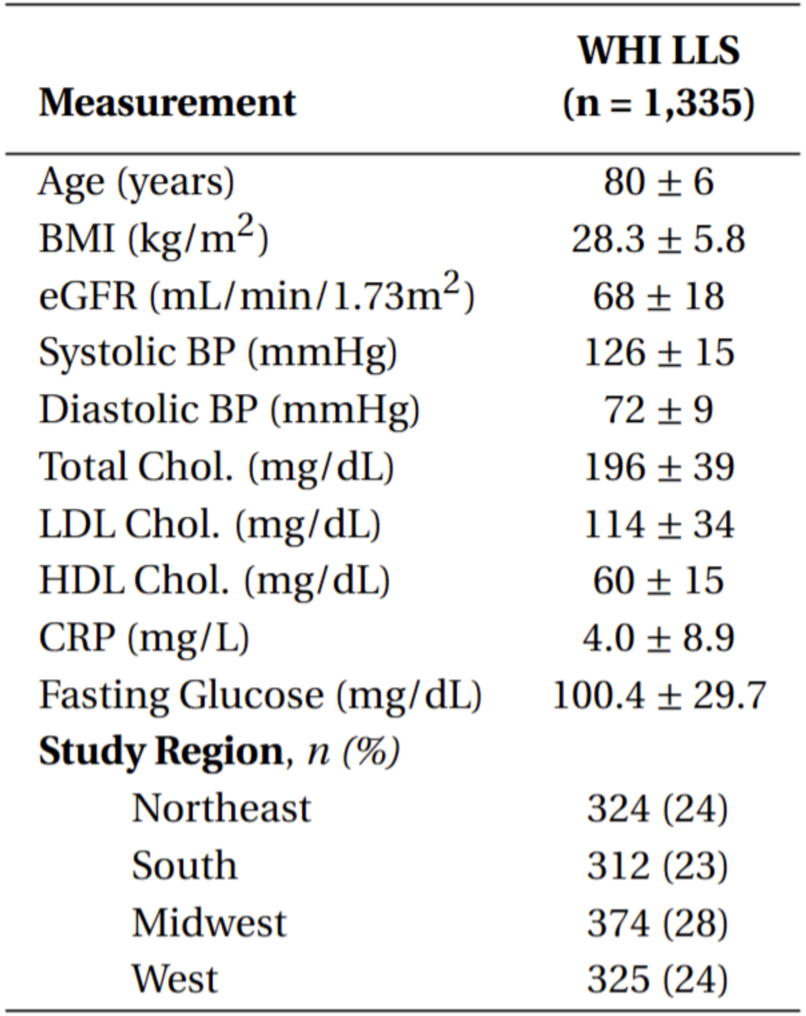
Genotype-Tissue Expression



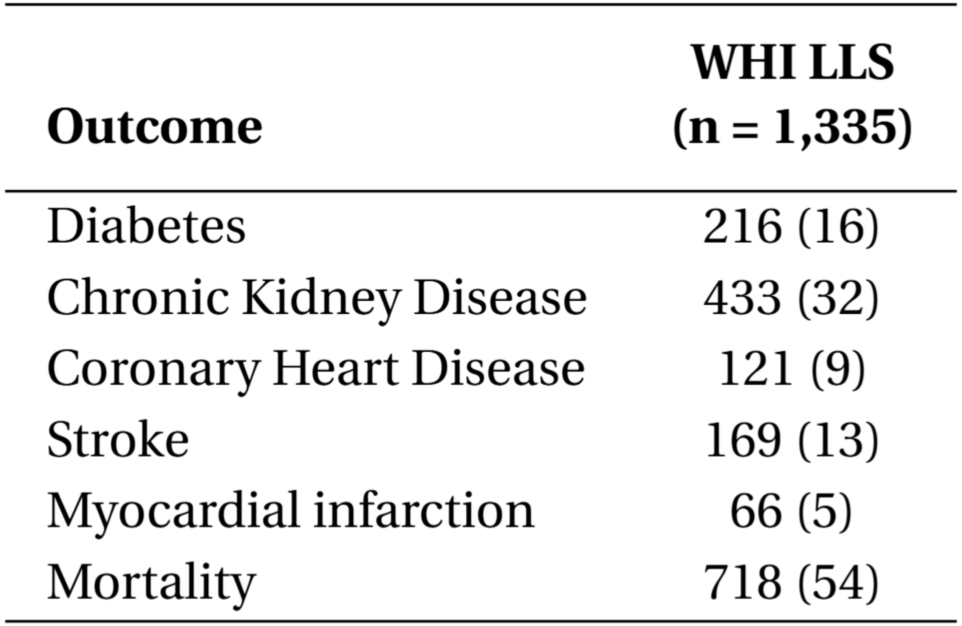
10.1038/s41591-025-03798-1

Do protein organ aging scores predict clinical outcomes and mortality in aging women from the WHI Long Life Study?

Characteristics of WHI-LLS participants



Measurement	**WHI LLS (n = 1,335)**
Age (years)	80 ± 6
BMI (kg/m^2)	28.3 ± 5.8
eGFR (mL/min/1.73m^2)	68 ± 18
Systolic BP (mmHg)	126 ± 15
Diastolic BP (mmHg)	72 ± 9
Total Chol. (mg/dL)	196 ± 39
LDL Chol. (mg/dL)	114 ± 34
HDL Chol. (mg/dL)	60 ± 15
CRP (mg/L)	4.0 ± 8.9
Fasting Glucose (mg/dL)	100.4 ± 29.7
Study Region, *n (%)*	
Northeast	324 (24)
South	312 (23)
Midwest	374 (28)
West	325 (24)



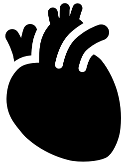
Outcome	**WHI LLS (n = 1,335)**
Diabetes	216 (16)
Chronic Kidney Disease	433 (32)
Coronary Heart Disease	121 (9)
Stroke	169 (13)
Myocardial infarction	66 (5)
Mortality	718 (54)

Olink panels

- Plasma proteins (n=552 OlinkIDs)
- Measured in EDTA plasma samples
- High throughput multiplex platform for 6 panels:
  - Inflammation, Cardiovascular2, Cardiovascular3, Neurology, Oncology, Cardiometabolic
- Quality control, normalization and imputation of missing values

Tested organs

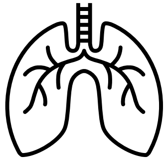
Heart



n = 1

NTPROBNP

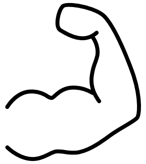
Lung



n = 3

AGER
CCL18
SFTPD

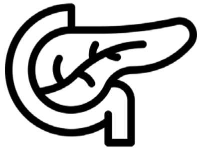
Muscle



n = 1

CA3

Pancreas



n = 2

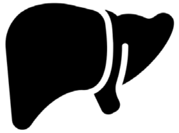
REG1A
PRSS2

Artery

n = 3

LTBP2
THBS2
TNFRSF11B

Liver



n = 12

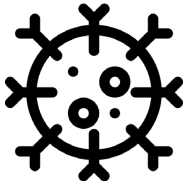
AMBP
FETUB

Adipose

n = 2

FABP4
LEP

Immune



n = 27

CD8A
SELL
TREML2
IL1R2

Intestine

n = 6

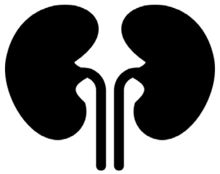
CCL25
CDHR2
LGALS4
FGF19
MLN
SPINK4

Brain

n = 8

BCAN

Kidney



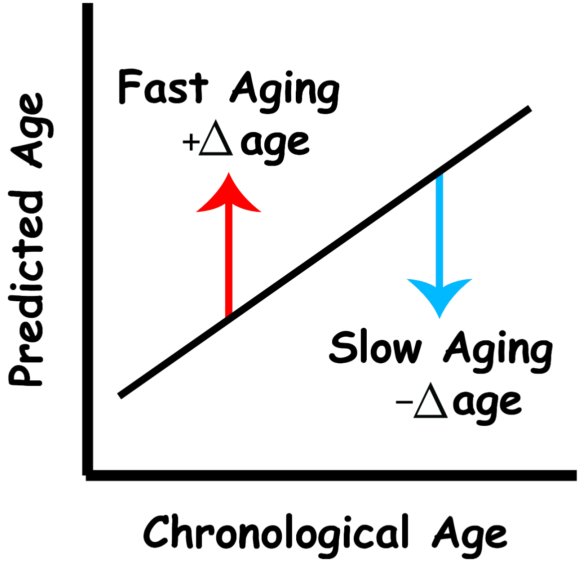
n = 2

REN
UMOD

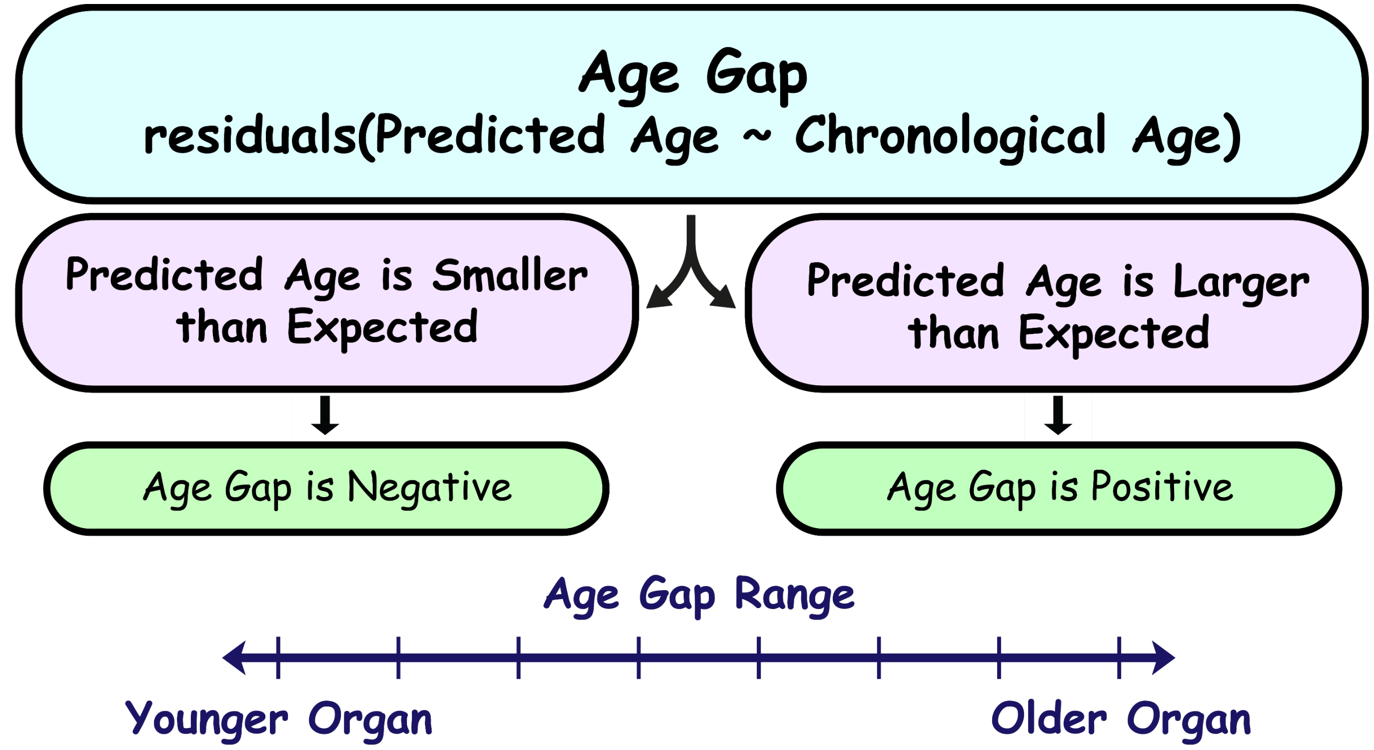
Organismal

n = 70

Age gap interpretation



Normalized



Age Gap
residuals(Predicted Age ~ Chronological Age)

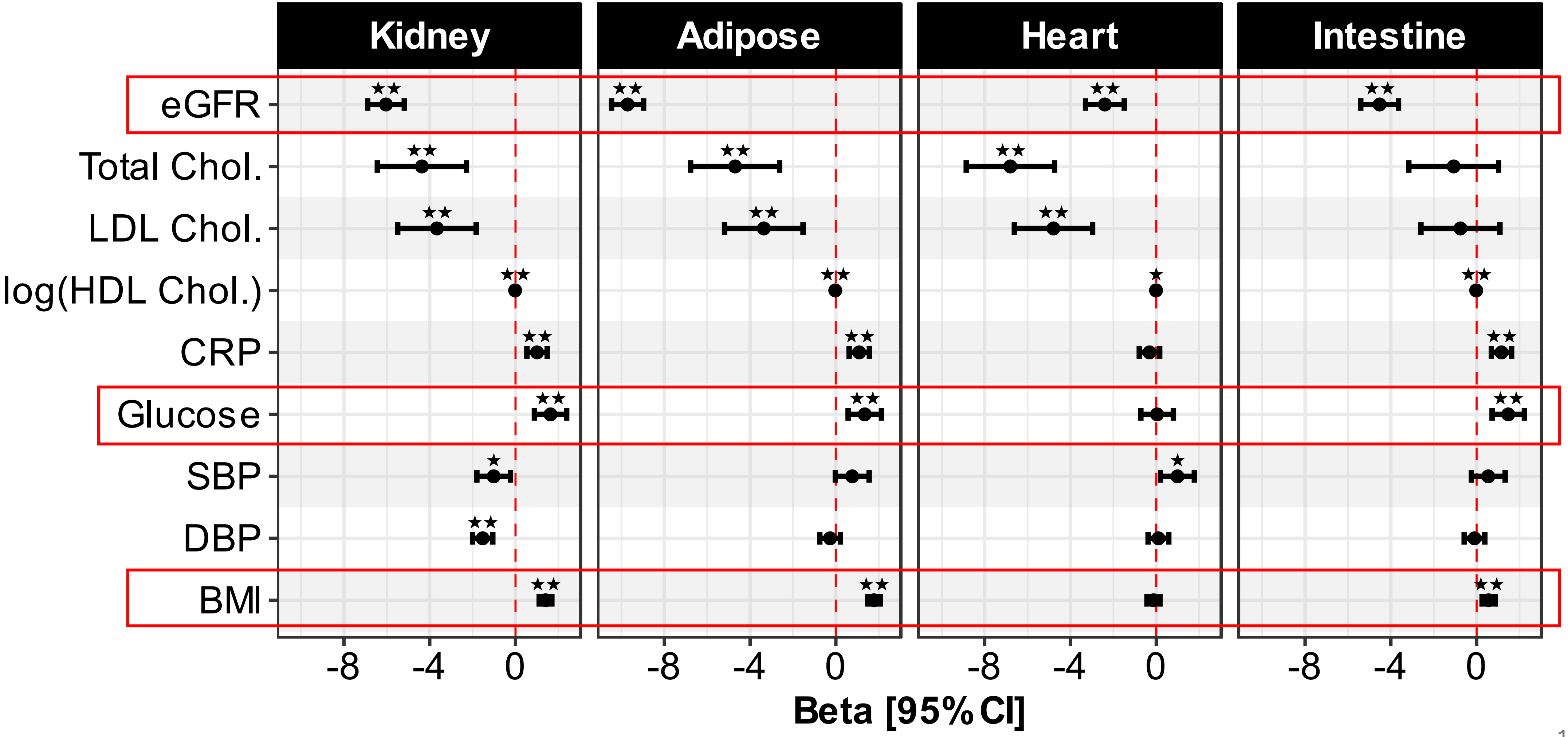
Predicted Age is Smaller than Expected → Age Gap is Negative

Predicted Age is Larger than Expected → Age Gap is Positive

Age Gap Range

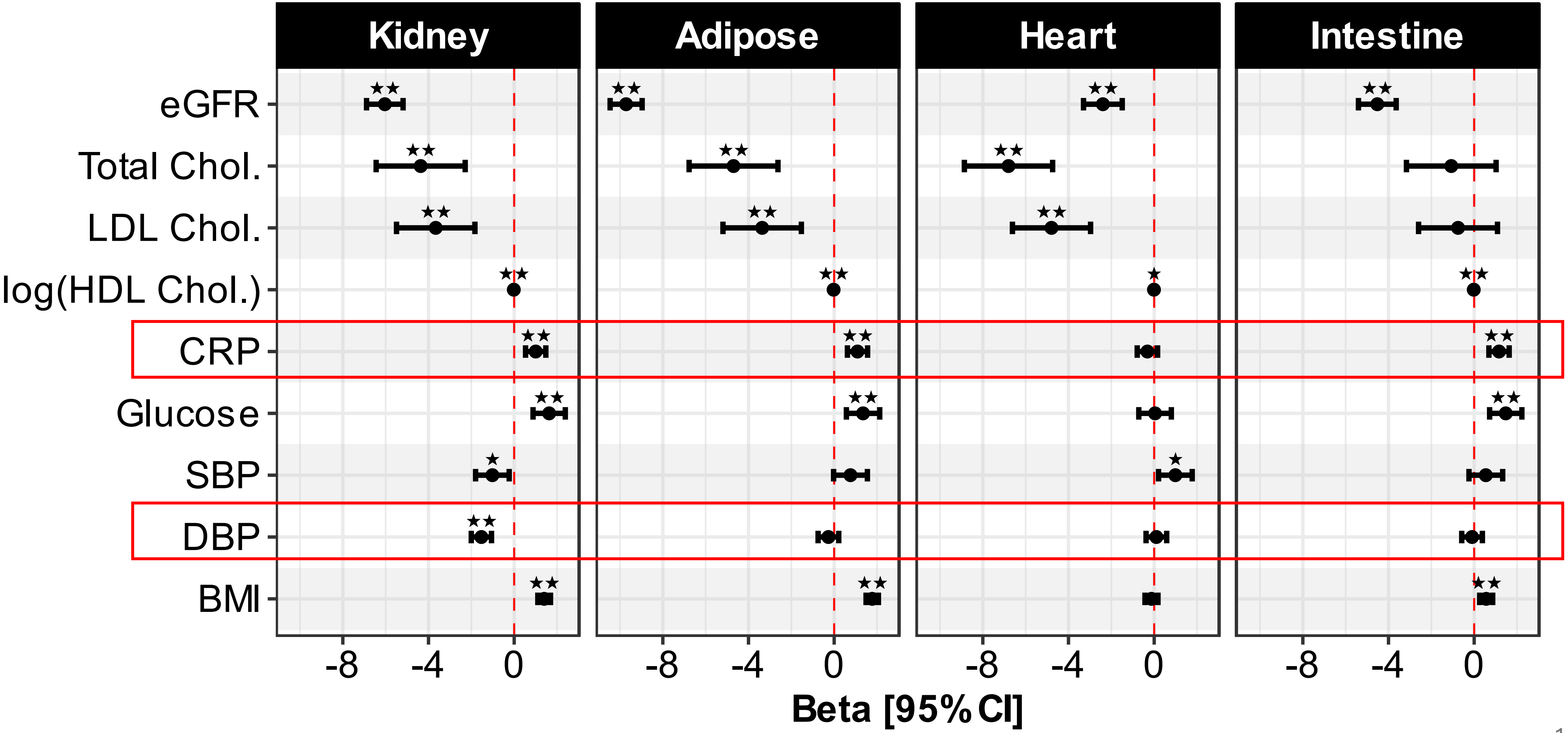
Younger Organ ↔ Older Organ

Associations with biomarkers and clinical measures



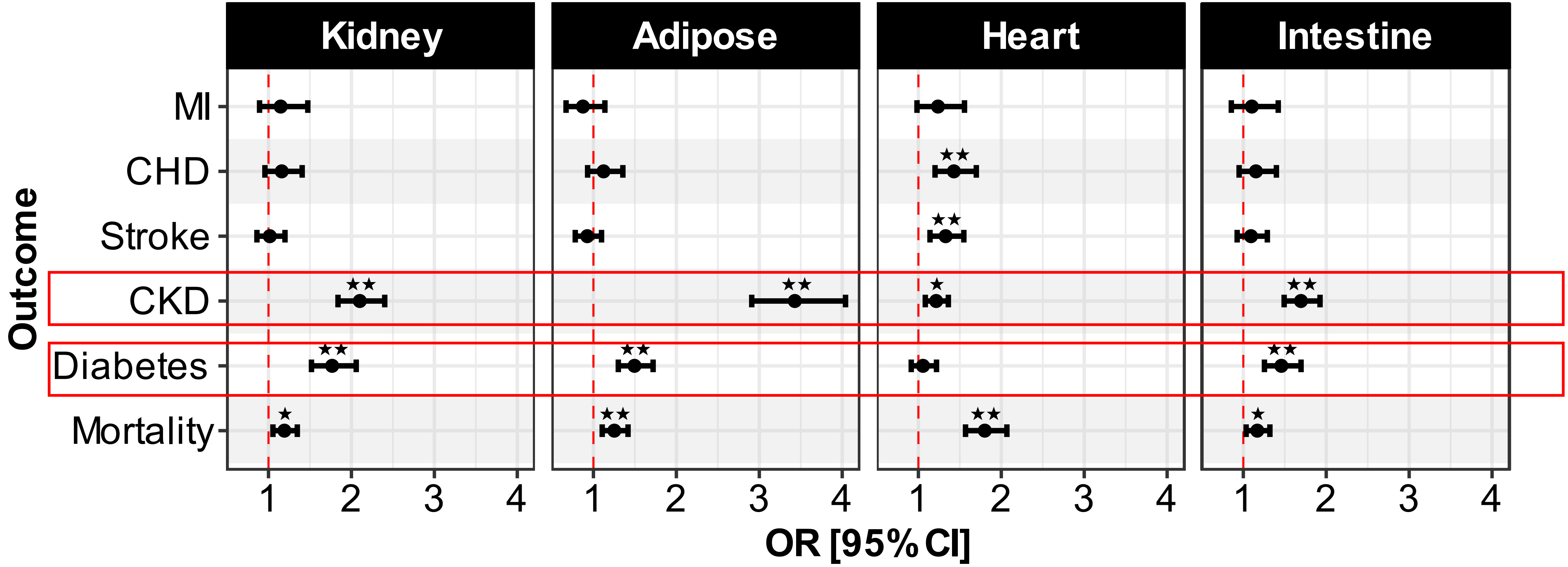
Glucose among non-diabetic individuals

Associations with biomarkers and clinical measures



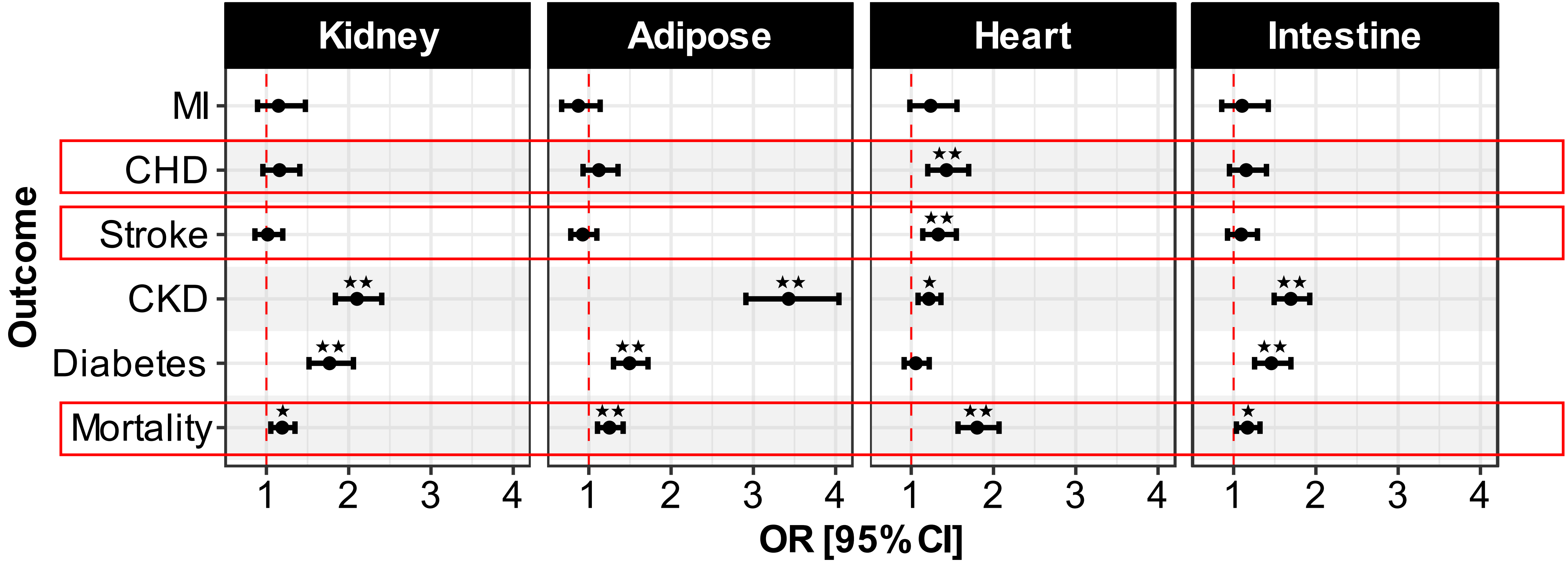
Glucose among non-diabetic individuals

Associations with clinical outcomes and mortality



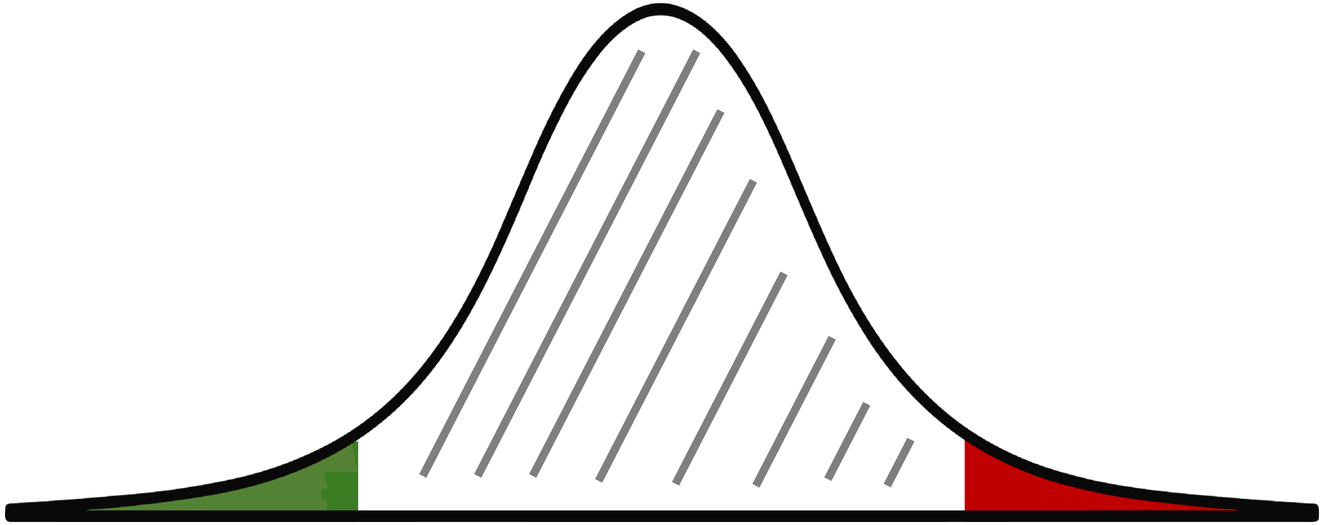
Prevalent CKD and diabetes, incident MI, CHD and total stroke

Associations with clinical outcomes and mortality



Prevalent CKD and diabetes, incident MI, CHD and total stroke

Extreme organ agers



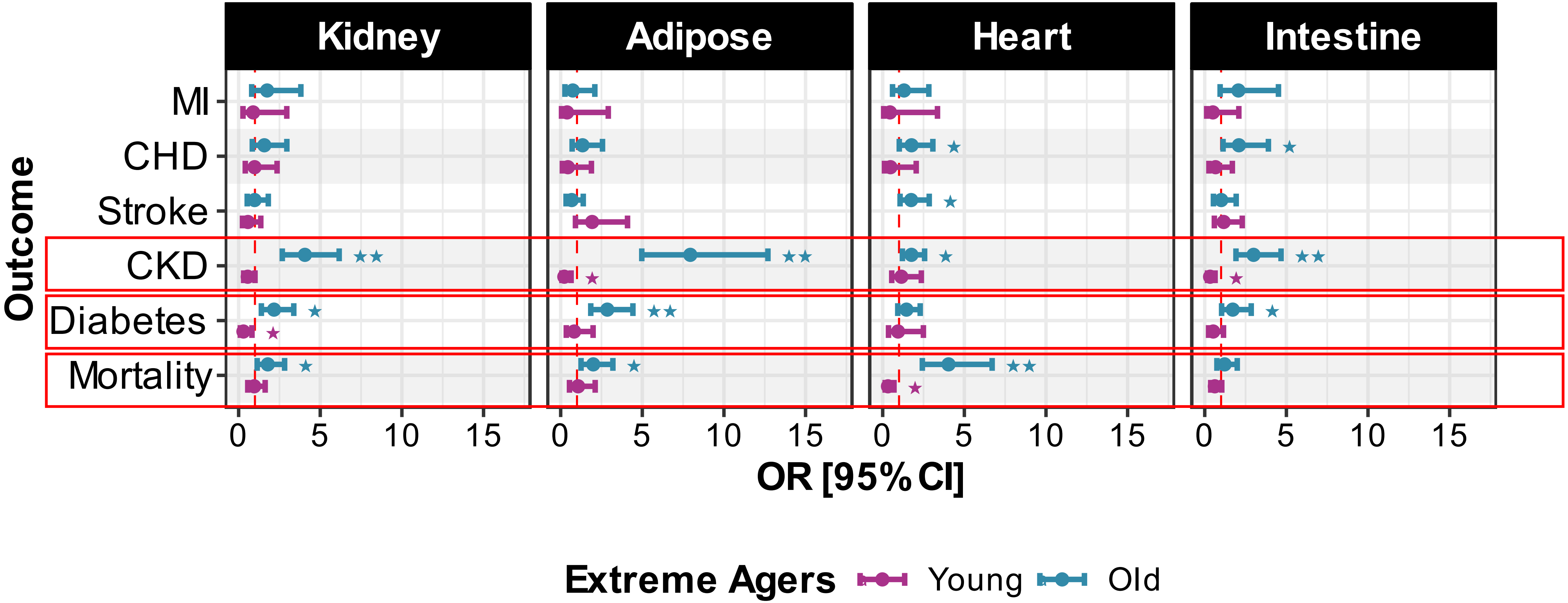
Extremely Young

Normal

Extremely Old

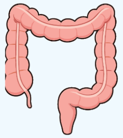
organ gap above or below 1.5 SDs

Associations with extreme agers



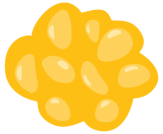
Conclusions

- Proteomic organ aging scores associate with organ diseases in WHI LLS women and could be used to monitor organ health.



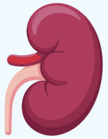
Intestine

+	−
CKD	eGFR
Diabetes	log(HDLC)
CRP	
Glucose	
BMI	



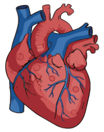
Adipose

+	−
CKD	eGFR
Diabetes	Cholesterol
CRP	log(HDLC)
BMI	LDLC
Glucose	
Mortality	



Kidney

+	−
CKD	eGFR
Diabetes	Cholesterol
CRP	log(HDLC)
Glucose	LDLC
BMI	DBP



Heart

+	−
CHD	eGFR
Stroke	Cholesterol
Mortality	LDLC

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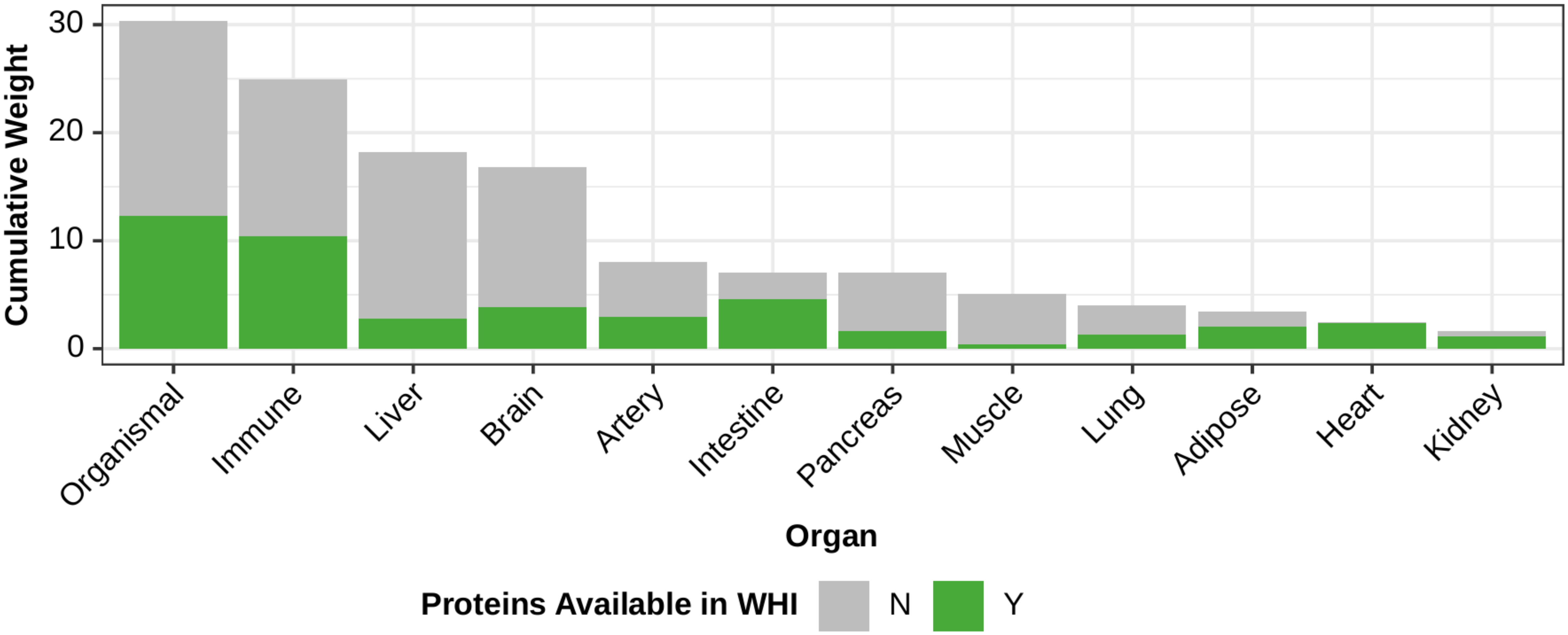
WOMEN'S
HEALTH
INITIATIVE

Proteins available by weight



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HUMAN LONGEVITY SCIENCE

Epigenetic and proteomic biomarkers of MCI/dementia and healthy longevity in WHIMS

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Associate Professor of Public Health and Medicine
University of California San Diego
May 8, 2026

Chronological vs. Biological Age: What’s the Difference?

Chronological Age

Your Age in Years

Calculated simply from your date of birth.

Biological Age

Your Body’s “True” Age

Reflects where your cells are in the aging process.

Can Be Faster or Slower

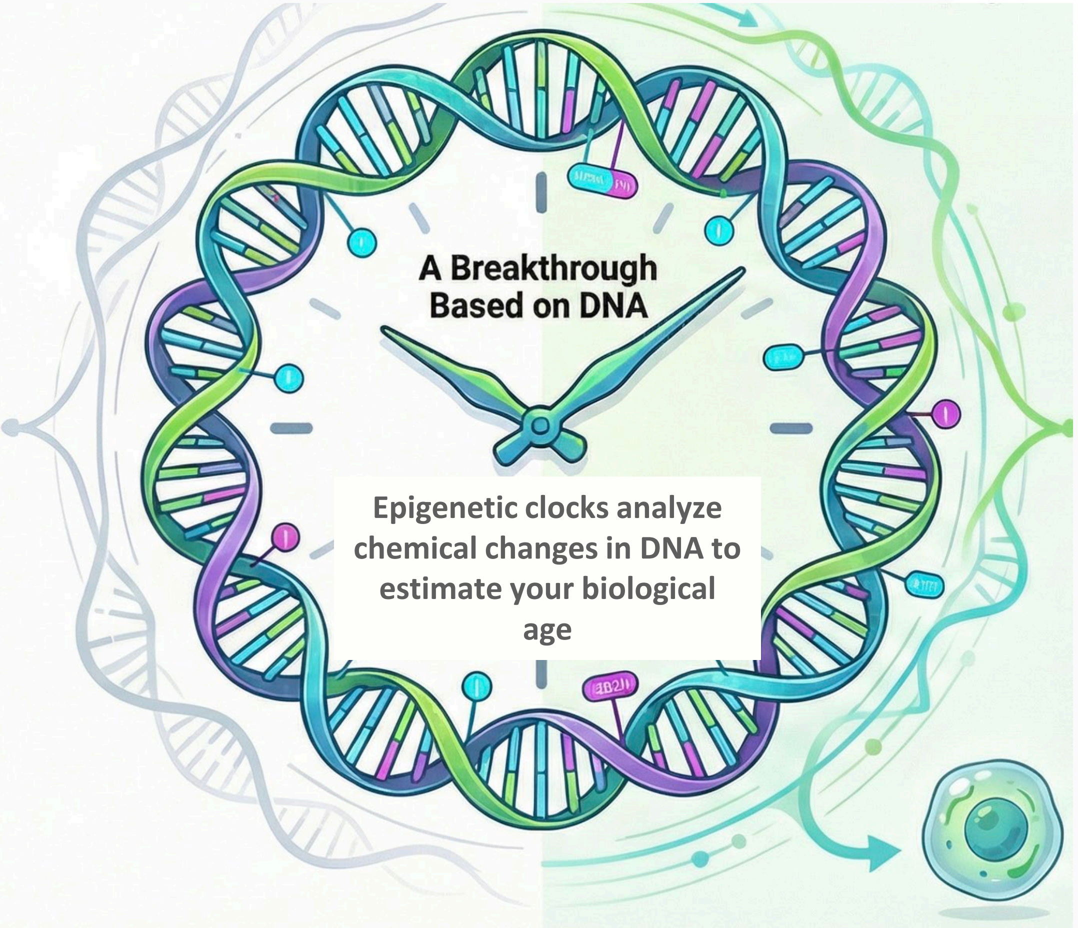
Affected by the accumulation of molecular damage in cells over time.

Explains Visible Differences

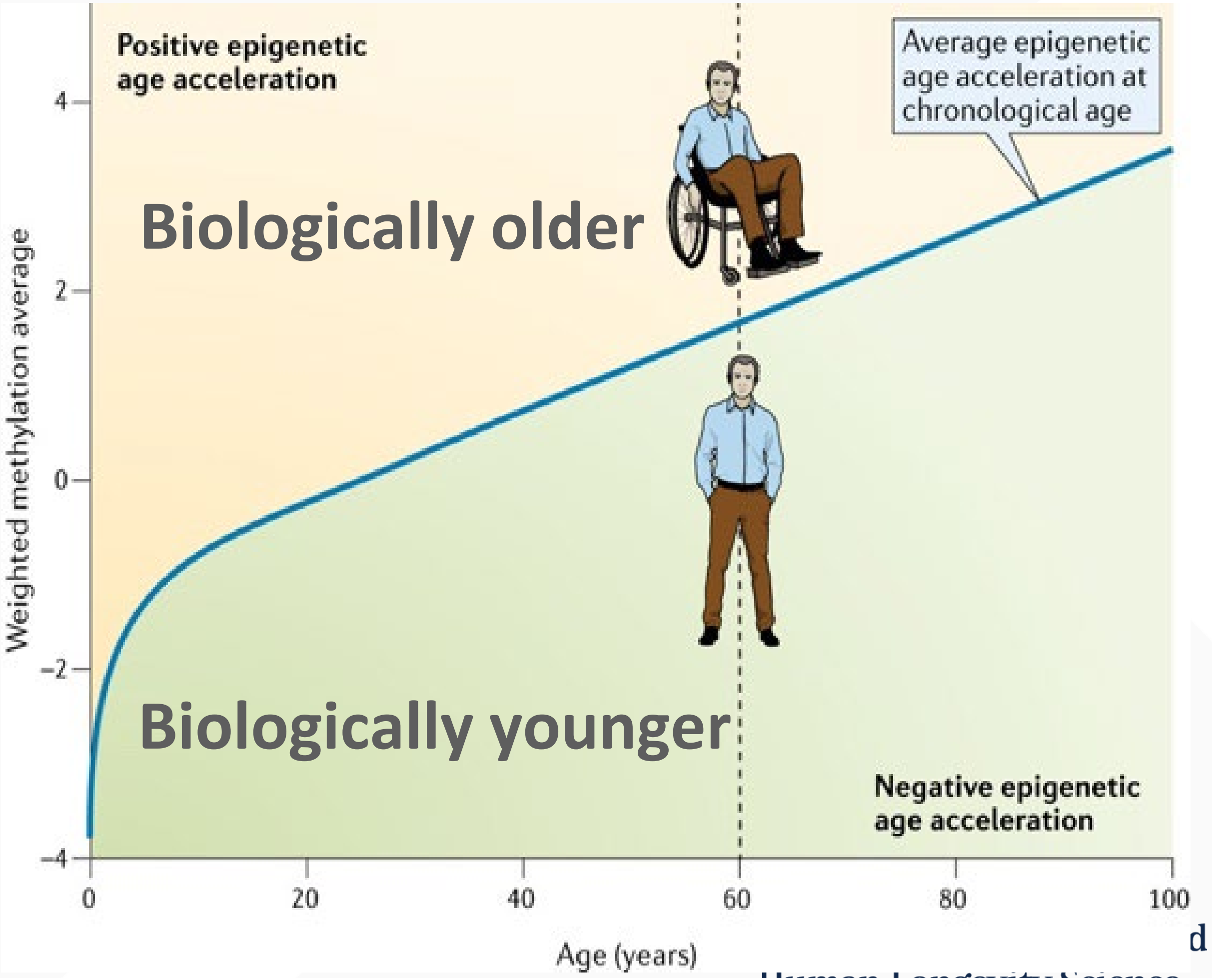
Why some 60-year-olds may look much younger or older than their peers.

Epigenetic Clocks

An epigenetic clock is a blood biomarker that measures your biological age from your DNA



Epigenetic clocks analyze chemical changes in DNA to estimate your biological age



Human Longevity Science

Horvath et al. Nat Rev Genet 2018.

Epigenetic Data in WHIMS

- Epigenetic profiling (>900K CpGs) among 6,400 WHIMS women (2,000 longitudinal measures)

- Among the largest cohorts with epigenomic data (EPIC v2)

- **Data resource to study epigenetics of diverse phenotypes (CVD, cancer, longevity, behavioral data, etc.)**

Aging Cell

WILEY

RESEARCH ARTICLE OPEN ACCESS

Epigenetic Clocks of Biological Aging and Risk of Incident Mild Cognitive Impairment and Dementia: The Women's Health Initiative Memory Study

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Keywords: aging | biomarkers | cohort studies | dementia | epigenomics

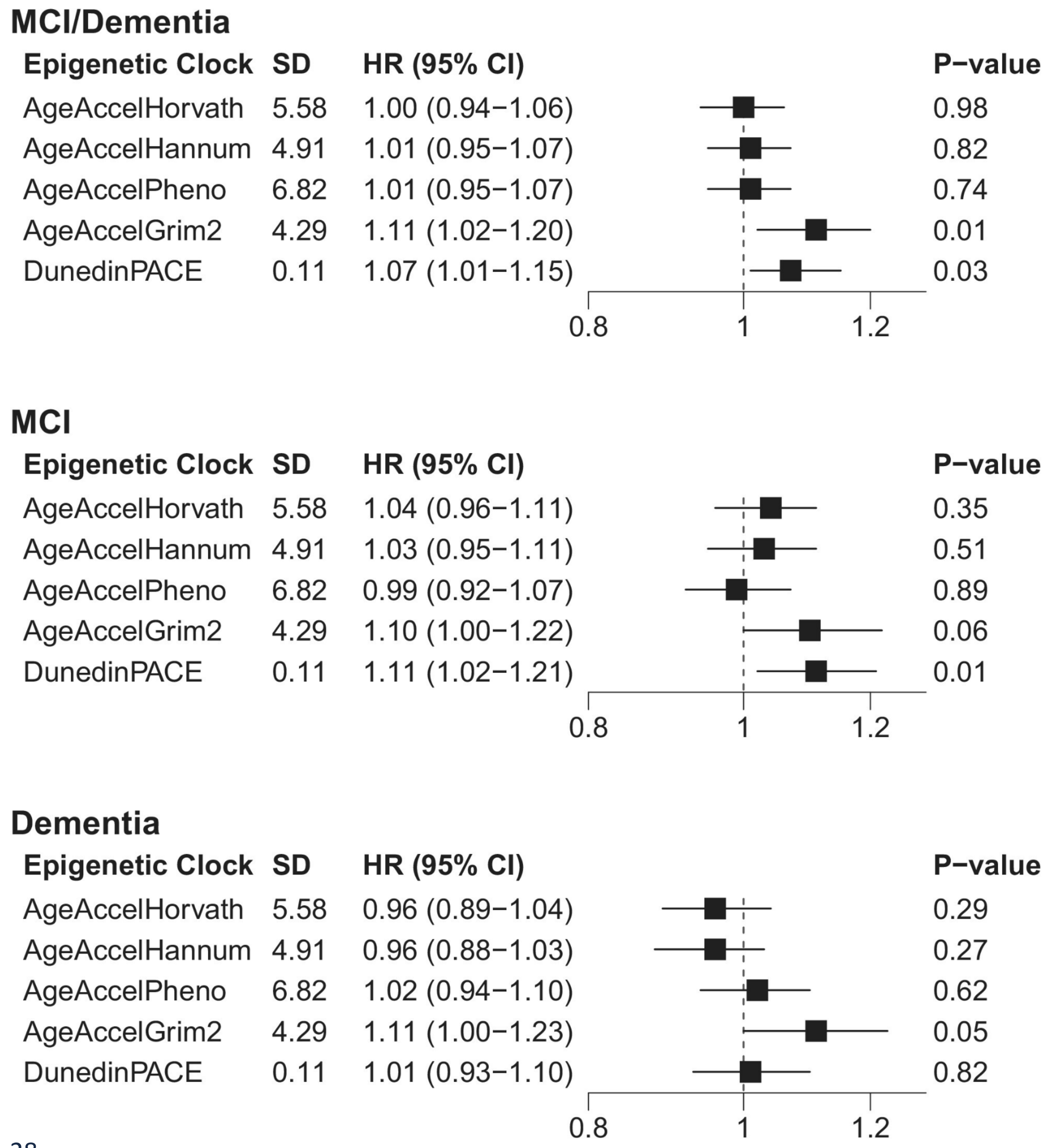
ABSTRACT

Aging is the strongest risk factor for dementia; however, few studies have examined the association of biological aging with incident dementia. We analyzed 6069 cognitively unimpaired women (mean age = 70.0 ± 3.8 years) in the Women's Health Initiative Memory Study to examine the association of accelerated biological aging, measured with second and third-generation epigenetic clocks (AgeAccelPheno and AgeAccelGrim2, and DunedinPACE, respectively) with incident mild cognitive impairment (MCI) and probable dementia. Multivariable Cox proportional hazards models adjusted for age, education, race, ethnicity, smoking, hormone therapy regimen, physical activity, body mass index, and estimated white blood cell counts. For comparison, we also examined first-generation epigenetic clocks (AgeAccelHorvath; AgeAccelHannum). We evaluated effect modification by age, race/ethnicity, hormone therapy regimen, menopause type (natural vs. surgical), and *APOE ε4* carriage. There were 1307 incident MCI or probable dementia events over a median follow-up of 9.3 (25th percentile = 6.1, 75th percentile = 16.1) years. The adjusted HRs (95% CI; p-value) for incident MCI/probable dementia per one-standard deviation increment were 1.07 (1.01–1.15; $p = 0.03$) for DunedinPACE, 1.11 (1.02–1.20; $p = 0.01$) for AgeAccelGrim2, and 1.01 (0.95–1.07; $p = 0.74$) for AgeAccelPheno. Only AgeAccelGrim2 remained significant under the Bonferroni-corrected threshold for significance ($p < 0.02$). Other epigenetic clocks were not associated with incident MCI/probable dementia. There was no effect modification in most subgroup analyses (p-interaction ≥ 0.05). In this cohort study of older women, accelerated biological aging measured by AgeAccelGrim2 was associated with higher risk of incident MCI/probable dementia. These findings provide evidence linking epigenetic biomarkers of biological aging with MCI and dementia development, independent of chronological age.

Steve Nguyen, PhD

Baseline Characteristics

N=6,069	No. (%) or Mean (SD)
Age	70.0 (3.8)
College graduate	31.8%
White	89%
Current smoker	6.9%
BMI, kg/m^2	28.6 (5.7)
Physical activity, MET-h/wk	11.4 (13.2)
APOE e4 carrier	25.3%



MCI/Dementia

Epigenetic Clock	SD	HR (95% CI)	P−value
AgeAccelHorvath	5.58	1.00 (0.94−1.06)	0.98
AgeAccelHannum	4.91	1.01 (0.95−1.07)	0.82
AgeAccelPheno	6.82	1.01 (0.95−1.07)	0.74
AgeAccelGrim2	4.29	1.11 (1.02−1.20)	0.01
DunedinPACE	0.11	1.07 (1.01−1.15)	0.03

MCI

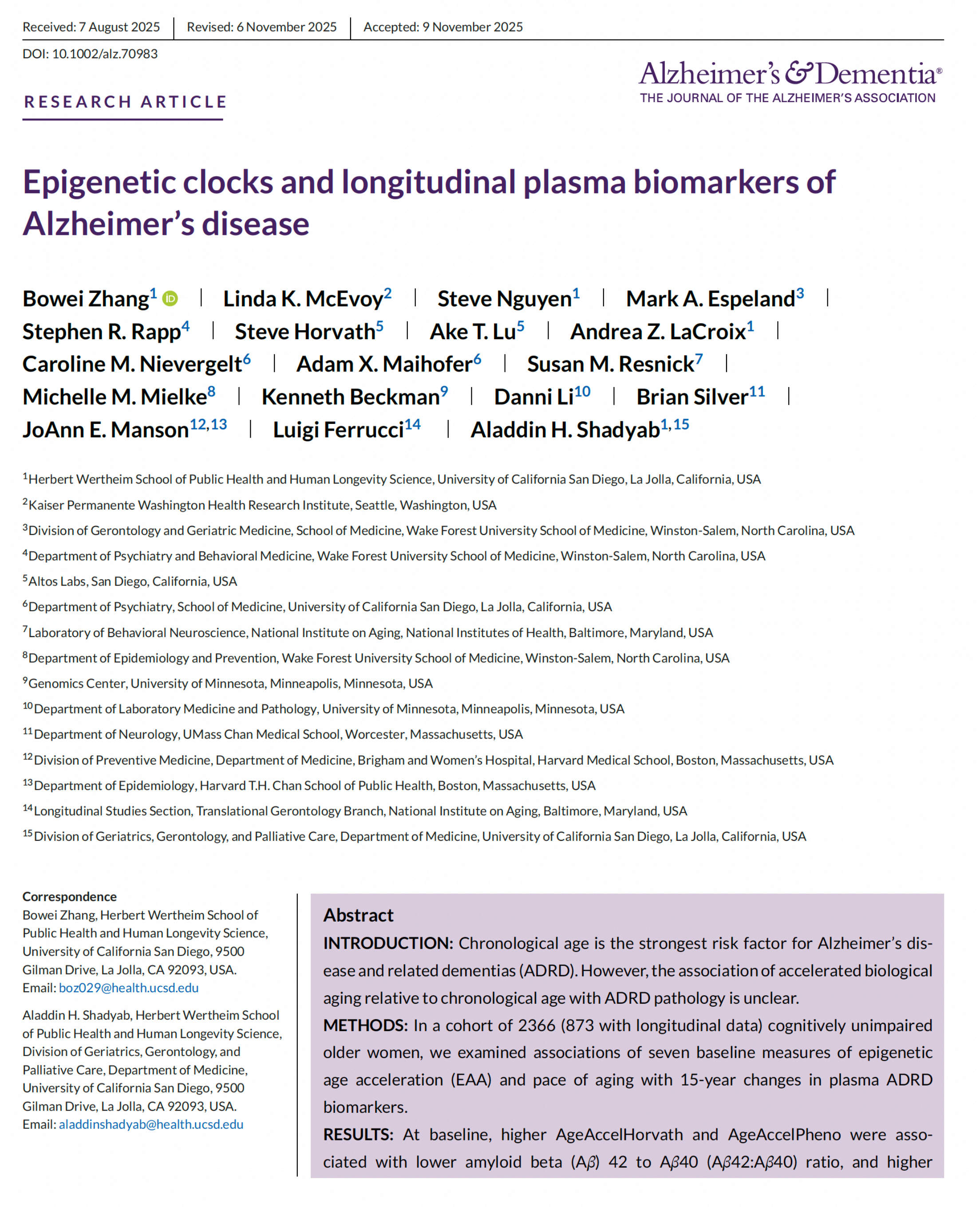
Epigenetic Clock	SD	HR (95% CI)	P−value
AgeAccelHorvath	5.58	1.04 (0.96−1.11)	0.35
AgeAccelHannum	4.91	1.03 (0.95−1.11)	0.51
AgeAccelPheno	6.82	0.99 (0.92−1.07)	0.89
AgeAccelGrim2	4.29	1.10 (1.00−1.22)	0.06
DunedinPACE	0.11	1.11 (1.02−1.21)	0.01

Dementia

Epigenetic Clock	SD	HR (95% CI)	P−value
AgeAccelHorvath	5.58	0.96 (0.89−1.04)	0.29
AgeAccelHannum	4.91	0.96 (0.88−1.03)	0.27
AgeAccelPheno	6.82	1.02 (0.94−1.10)	0.62
AgeAccelGrim2	4.29	1.11 (1.00−1.23)	0.05
DunedinPACE	0.11	1.01 (0.93−1.10)	0.82

AgeAccelGrim2 and DunedinPACE associated with MCI/dementia

AgeAccelGrim2 survived adjustment for multiple comparisons



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RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Epigenetic clocks and longitudinal plasma biomarkers of Alzheimer's disease

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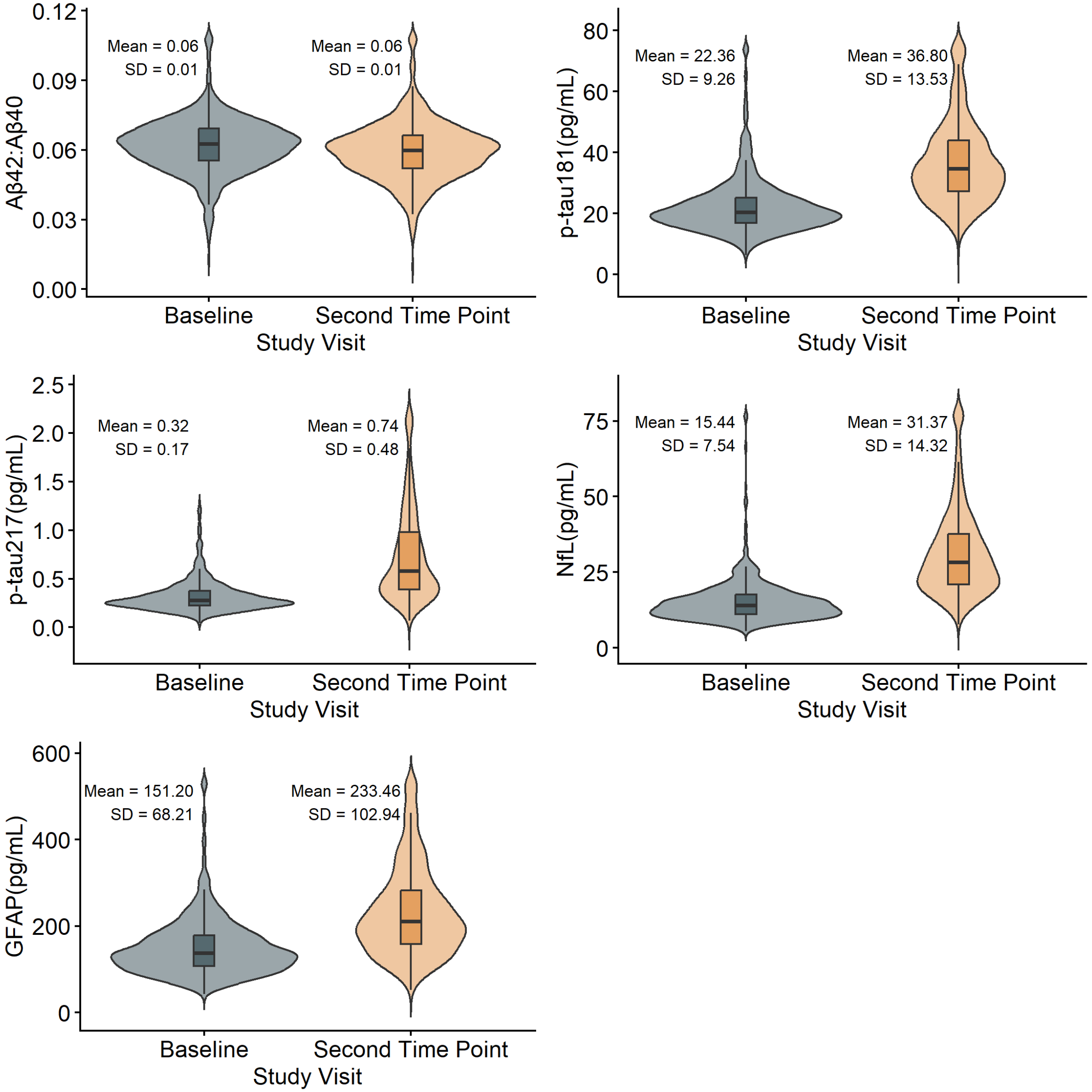
Abstract

INTRODUCTION: Chronological age is the strongest risk factor for Alzheimer's disease and related dementias (ADRD). However, the association of accelerated biological aging relative to chronological age with ADRD pathology is unclear.

METHODS: In a cohort of 2366 (873 with longitudinal data) cognitively unimpaired older women, we examined associations of seven baseline measures of epigenetic age acceleration (EAA) and pace of aging with 15-year changes in plasma ADRD biomarkers.

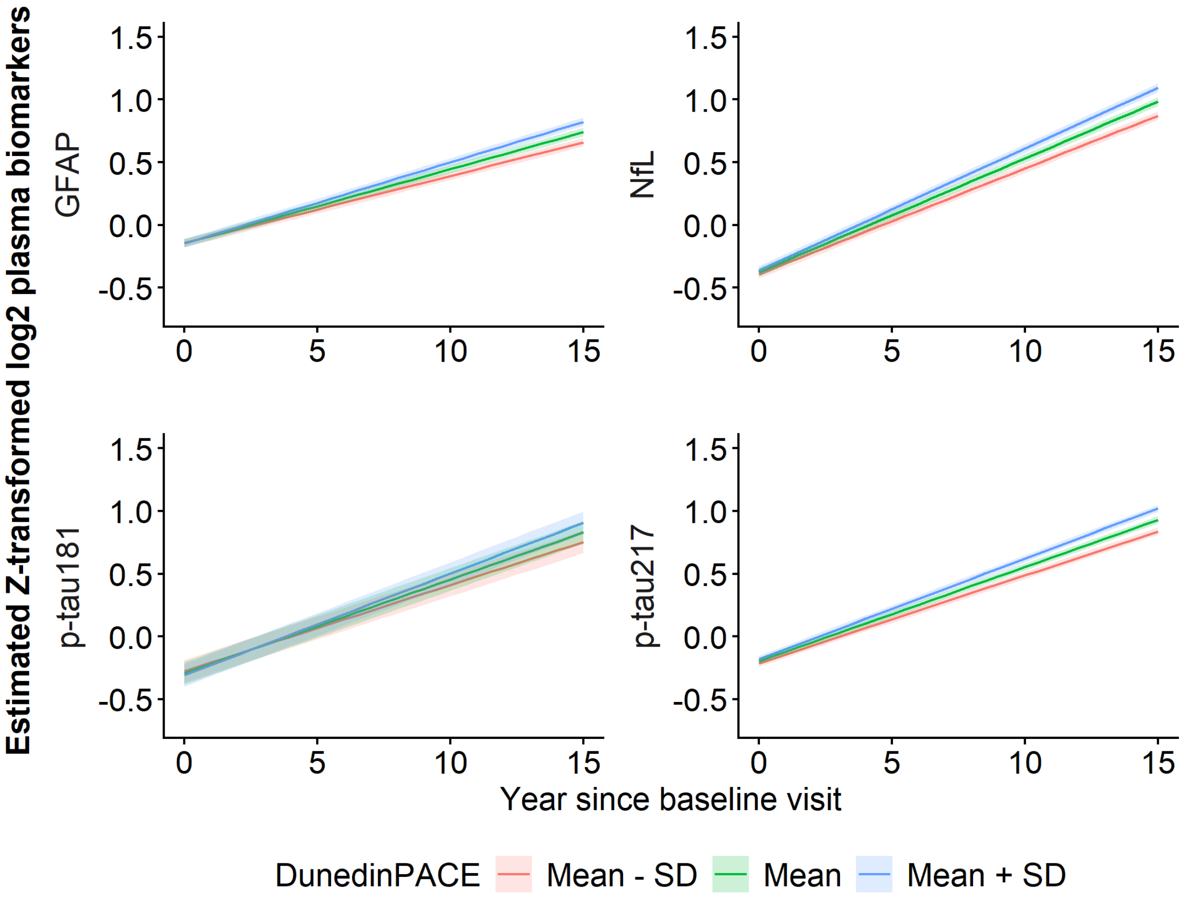
RESULTS: At baseline, higher AgeAccelHorvath and AgeAccelPheno were associated with lower amyloid beta (Aβ) 42 to Aβ40 (Aβ42:Aβ40) ratio, and higher

Bowei Zhang, MS



Levels of plasma ADRD biomarkers including p-tau181, ptau217, NfL, and GFAP increased over time

Aβ42:Aβ40 remained the same



1-SD higher DunedinPACE corresponded to the equivalent of 1.23 years of increase for p-tau181, 1.01 years for p-tau217, 1.07 years for NfL, and 1.41 years for GFAP over the 15-year follow-up.

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Research Paper

Association of epigenetic age acceleration with MRI biomarkers of aging and Alzheimer's disease neurodegeneration

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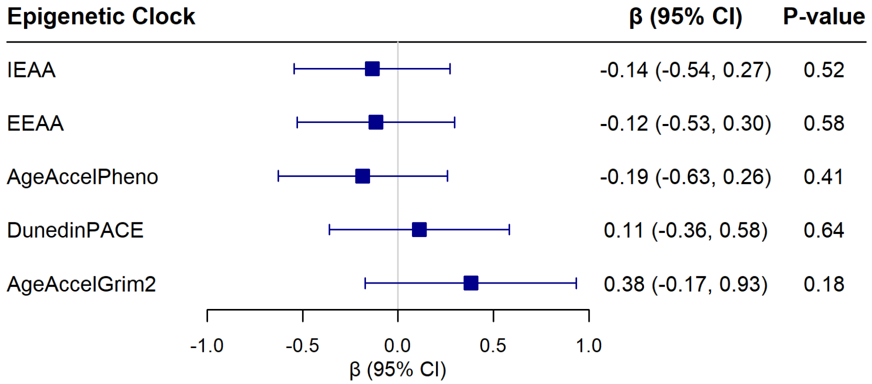
ABSTRACT

Epigenetic clocks of biological aging have been associated with cognitive impairment and dementia. Less is known about whether they are associated with an older-appearing brain or with an atrophy pattern associated with dementia. We examined associations of five epigenetic clocks measured at baseline with the Spatial Pattern of Atrophy for Recognition of Brain Aging (SPARE-BA) and the Alzheimer's Disease Pattern Similarity Score (AD-PS) derived from structural MRIs obtained an average of 8 years later among 1,196 older women. Using linear regression models adjusting for relevant covariates, we observed no associations between any epigenetic clock and accelerated brain aging based on SPARE-BA. We observed a significant association between AgeAccelGrim2 and AD-PS (β = 0.015; 95% CI 0.004 to 0.027; p = 0.01). This association appeared to be primarily driven by the association of a DNA methylation marker of smoking pack years with frontal and

Linda McEvoy, PhD

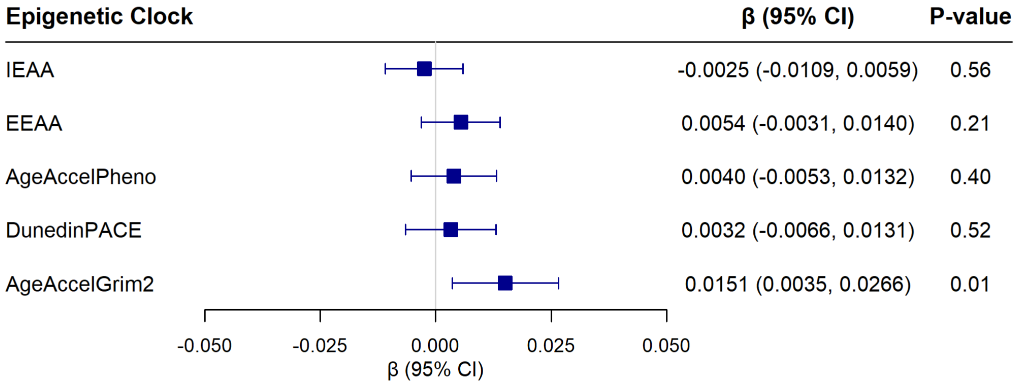
Associations of EAA with SPARE-BA



Epigenetic Clock	β (95% CI)	P-value
IEAA	-0.14 (-0.54, 0.27)	0.52
EEAA	-0.12 (-0.53, 0.30)	0.58
AgeAccelPheno	-0.19 (-0.63, 0.26)	0.41
DunedinPACE	0.11 (-0.36, 0.58)	0.64
AgeAccelGrim2	0.38 (-0.17, 0.93)	0.18

Epigenetic clocks not associated with accelerated brain aging

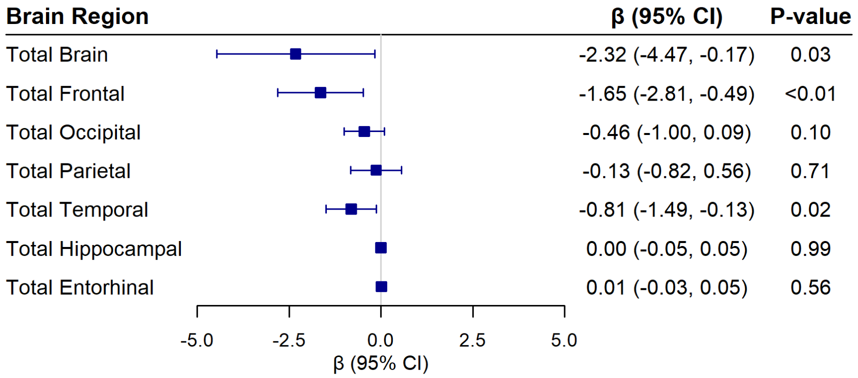
Associations of EAA with AD-PS



Epigenetic Clock	β (95% CI)	P-value
IEAA	-0.0025 (-0.0109, 0.0059)	0.56
EEAA	0.0054 (-0.0031, 0.0140)	0.21
AgeAccelPheno	0.0040 (-0.0053, 0.0132)	0.40
DunedinPACE	0.0032 (-0.0066, 0.0131)	0.52
AgeAccelGrim2	0.0151 (0.0035, 0.0266)	0.01

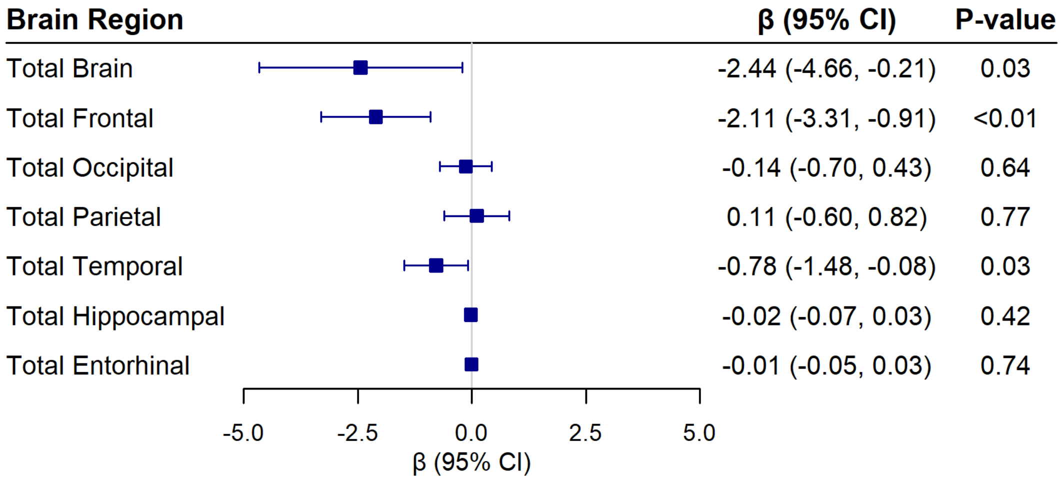
AgeAccelGrim2 associated with higher AD-PS score, a structural MRI index predictive of dementia, measured 8 years later

Associations of EAA with Brain Regions



Brain Region	β (95% CI)	P-value
Total Brain	-2.32 (-4.47, -0.17)	0.03
Total Frontal	-1.65 (-2.81, -0.49)	<0.01
Total Occipital	-0.46 (-1.00, 0.09)	0.10
Total Parietal	-0.13 (-0.82, 0.56)	0.71
Total Temporal	-0.81 (-1.49, -0.13)	0.02
Total Hippocampal	0.00 (-0.05, 0.05)	0.99
Total Entorhinal	0.01 (-0.03, 0.05)	0.56

Associations of DNAm SmokingPackYears with Brain Regions



Brain Region	β (95% CI)	P-value
Total Brain	-2.44 (-4.66, -0.21)	0.03
Total Frontal	-2.11 (-3.31, -0.91)	<0.01
Total Occipital	-0.14 (-0.70, 0.43)	0.64
Total Parietal	0.11 (-0.60, 0.82)	0.77
Total Temporal	-0.78 (-1.48, -0.08)	0.03
Total Hippocampal	-0.02 (-0.07, 0.03)	0.42
Total Entorhinal	-0.01 (-0.05, 0.03)	0.74

AgeAccelGrim2 and DNAm SmokingPackYears associated with total brain, frontal, and temporal lobe volumes

Together with prior findings, this underscores robustness of AgeAccelGrim2 as a predictor of cognitive impairment and neurodegeneration

Epigenetic Clocks of Biological Aging and Cognitively Healthy Longevity: The Women's Health Initiative Memory Study

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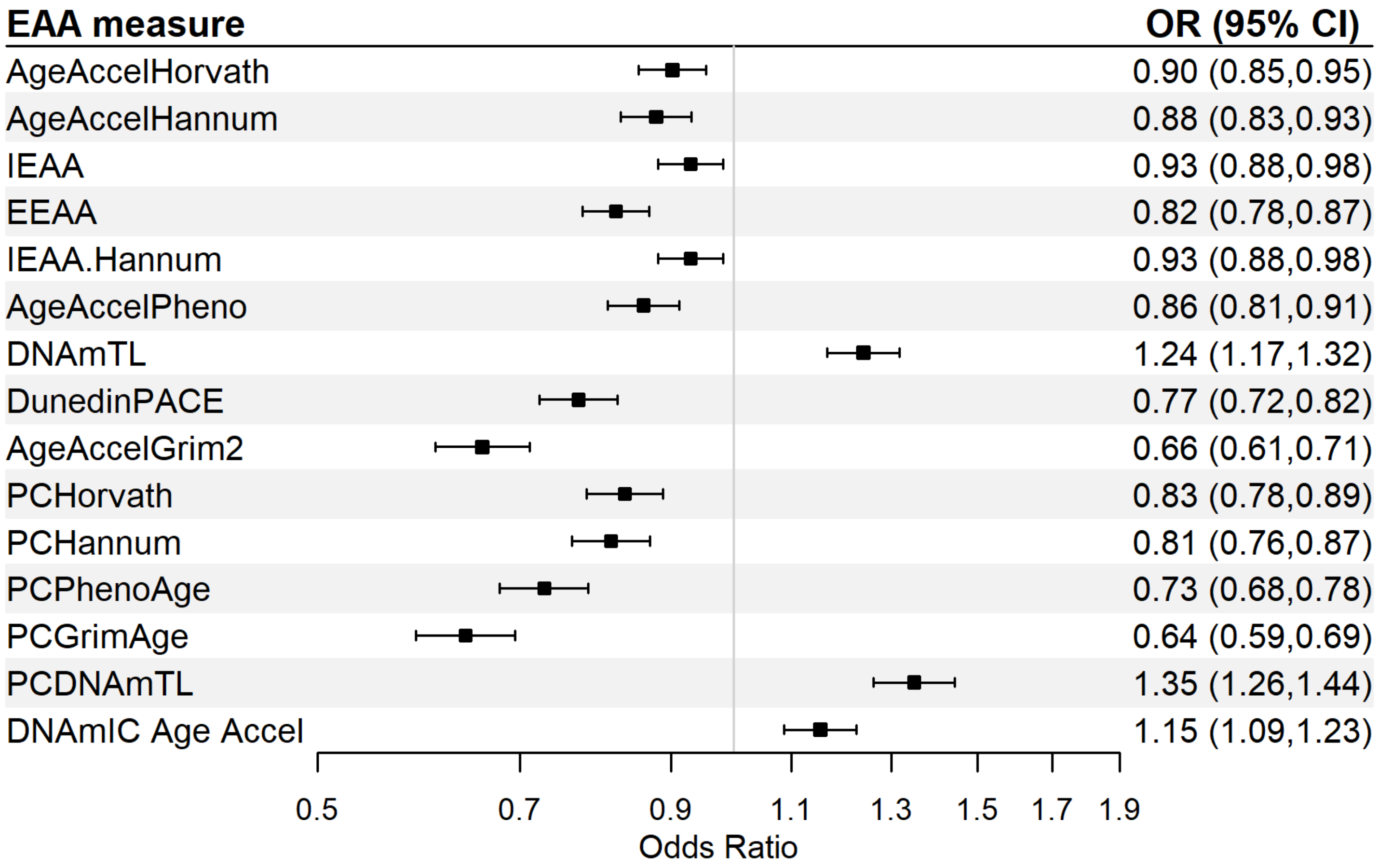
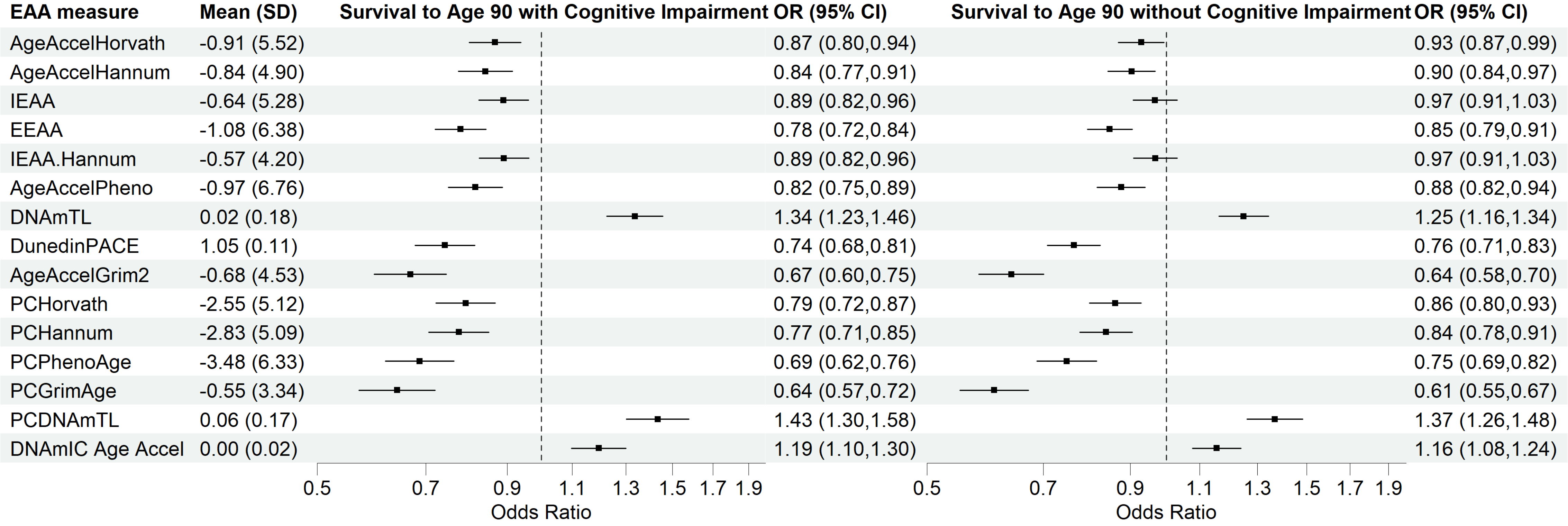
Epigenetic Clocks Associated with Exceptional Longevity



EAA measure	OR (95% CI)
AgeAccelHorvath	0.90 (0.85,0.95)
AgeAccelHannum	0.88 (0.83,0.93)
IEAA	0.93 (0.88,0.98)
EEAA	0.82 (0.78,0.87)
IEAA.Hannum	0.93 (0.88,0.98)
AgeAccelPheno	0.86 (0.81,0.91)
DNAmTL	1.24 (1.17,1.32)
DunedinPACE	0.77 (0.72,0.82)
AgeAccelGrim2	0.66 (0.61,0.71)
PCHorvath	0.83 (0.78,0.89)
PCHannum	0.81 (0.76,0.87)
PCPhenoAge	0.73 (0.68,0.78)
PCGrimAge	0.64 (0.59,0.69)
PCDNAmTL	1.35 (1.26,1.44)
DNAmIC Age Accel	1.15 (1.09,1.23)

Epigenetic Clocks Do Not Distinguish Cognitively Healthy Longevity

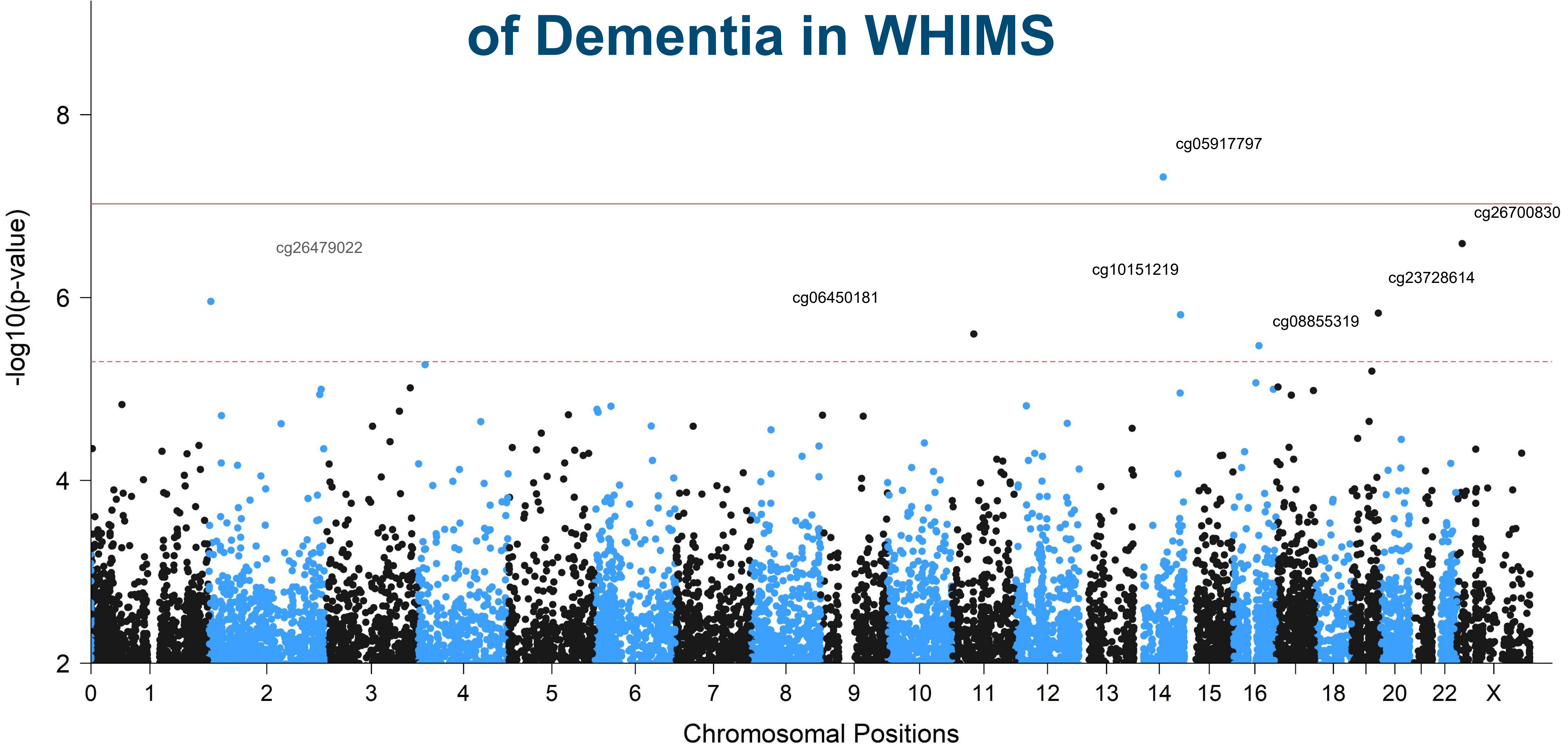


EAA measure	Mean (SD)	Survival to Age 90 with Cognitive Impairment OR (95% CI)	Survival to Age 90 without Cognitive Impairment OR (95% CI)
AgeAccelHorvath	-0.91 (5.52)	0.87 (0.80,0.94)	0.93 (0.87,0.99)
AgeAccelHannum	-0.84 (4.90)	0.84 (0.77,0.91)	0.90 (0.84,0.97)
IEAA	-0.64 (5.28)	0.89 (0.82,0.96)	0.97 (0.91,1.03)
EEAA	-1.08 (6.38)	0.78 (0.72,0.84)	0.85 (0.79,0.91)
IEAA.Hannum	-0.57 (4.20)	0.89 (0.82,0.96)	0.97 (0.91,1.03)
AgeAccelPheno	-0.97 (6.76)	0.82 (0.75,0.89)	0.88 (0.82,0.94)
DNAmTL	0.02 (0.18)	1.34 (1.23,1.46)	1.25 (1.16,1.34)
DunedinPACE	1.05 (0.11)	0.74 (0.68,0.81)	0.76 (0.71,0.83)
AgeAccelGrim2	-0.68 (4.53)	0.67 (0.60,0.75)	0.64 (0.58,0.70)
PCHorvath	-2.55 (5.12)	0.79 (0.72,0.87)	0.86 (0.80,0.93)
PCHannum	-2.83 (5.09)	0.77 (0.71,0.85)	0.84 (0.78,0.91)
PCPhenoAge	-3.48 (6.33)	0.69 (0.62,0.76)	0.75 (0.69,0.82)
PCGrimAge	-0.55 (3.34)	0.64 (0.57,0.72)	0.61 (0.55,0.67)
PCDNAmTL	0.06 (0.17)	1.43 (1.30,1.58)	1.37 (1.26,1.48)
DNAmIC Age Accel	0.00 (0.02)	1.19 (1.10,1.30)	1.16 (1.08,1.24)

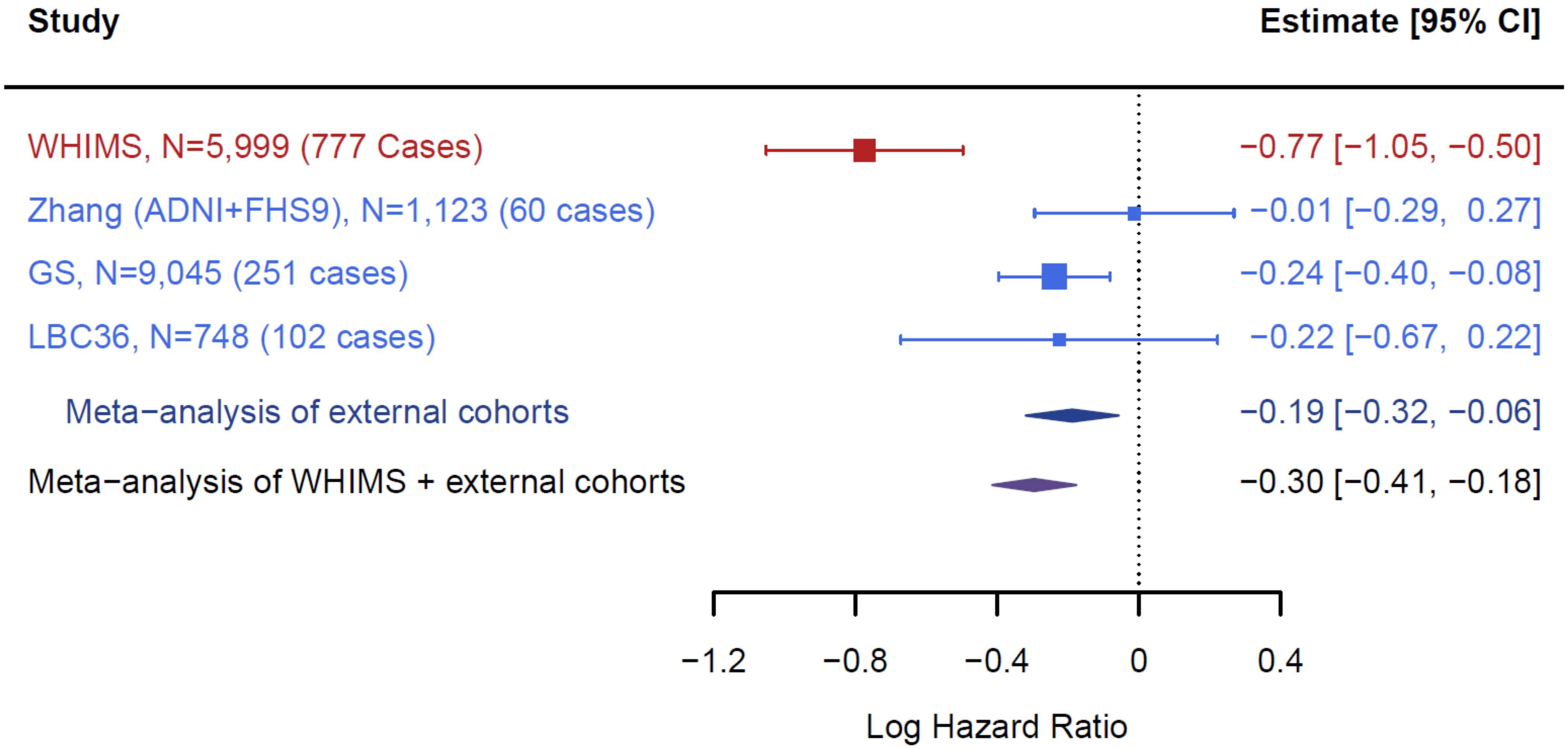
Blood DNA Methylation Predicts Long-Term Risk of Dementia in Prospective Cohorts

Adam Maihofer, PhD

Epigenome-Wide Association Study of Dementia in WHIMS

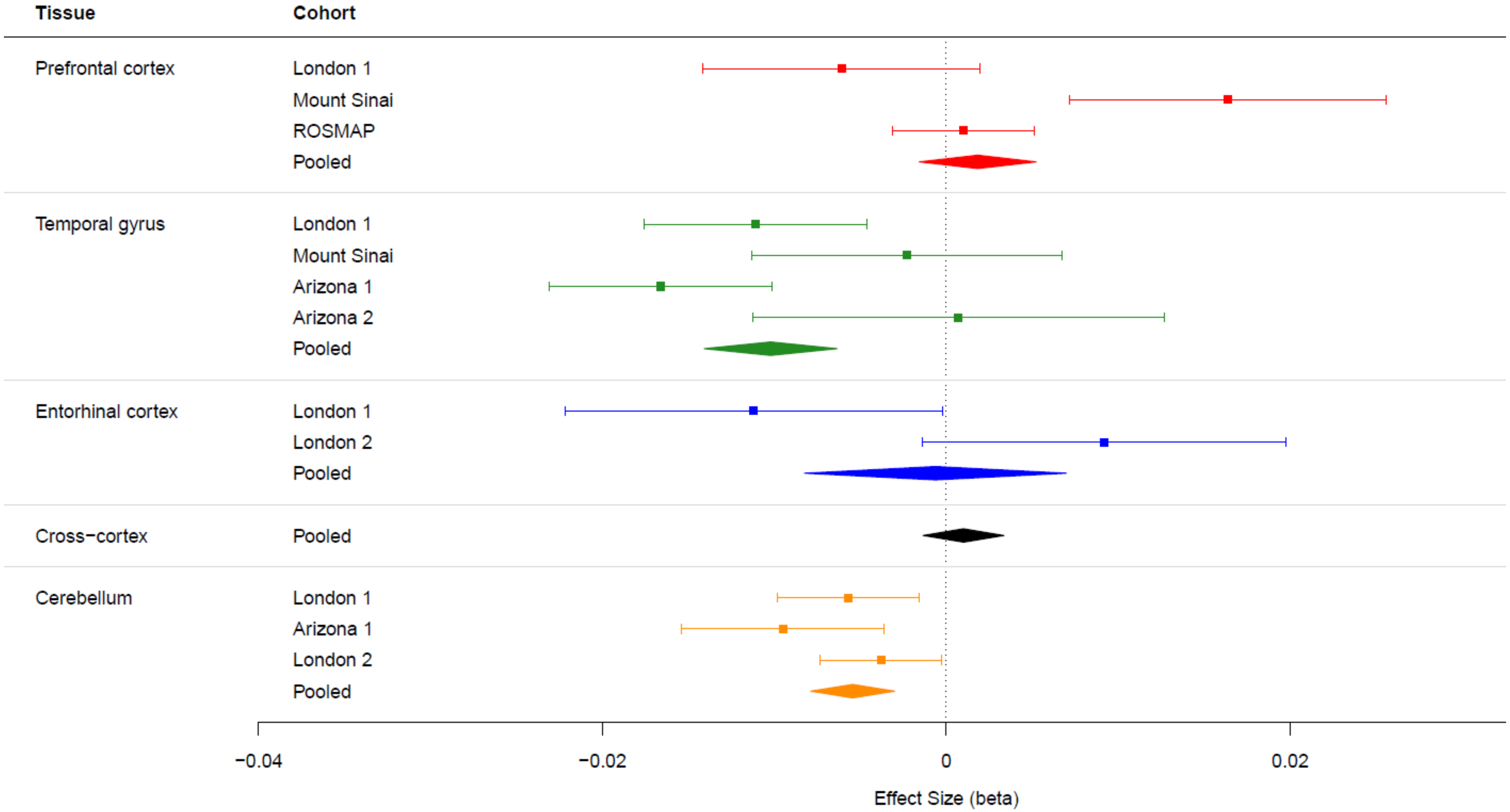


Meta-Analysis of EWAS of Dementia in Five Cohorts



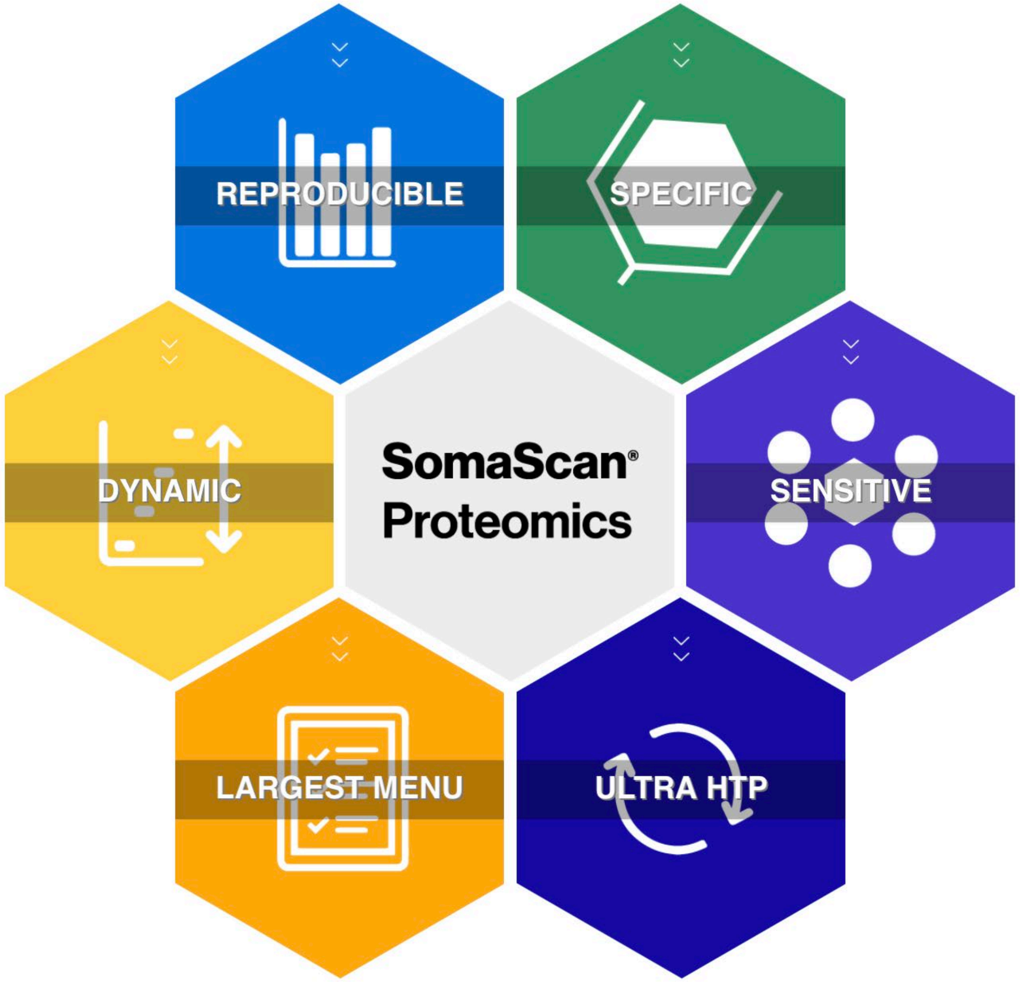
Study	Estimate [95% CI]
WHIMS, N=5,999 (777 Cases)	−0.77 [−1.05, −0.50]
Zhang (ADNI+FHS9), N=1,123 (60 cases)	−0.01 [−0.29, 0.27]
GS, N=9,045 (251 cases)	−0.24 [−0.40, −0.08]
LBC36, N=748 (102 cases)	−0.22 [−0.67, 0.22]
Meta−analysis of external cohorts	−0.19 [−0.32, −0.06]
Meta−analysis of WHIMS + external cohorts	−0.30 [−0.41, −0.18]

Replication of cg05917797 in External Brain Tissues

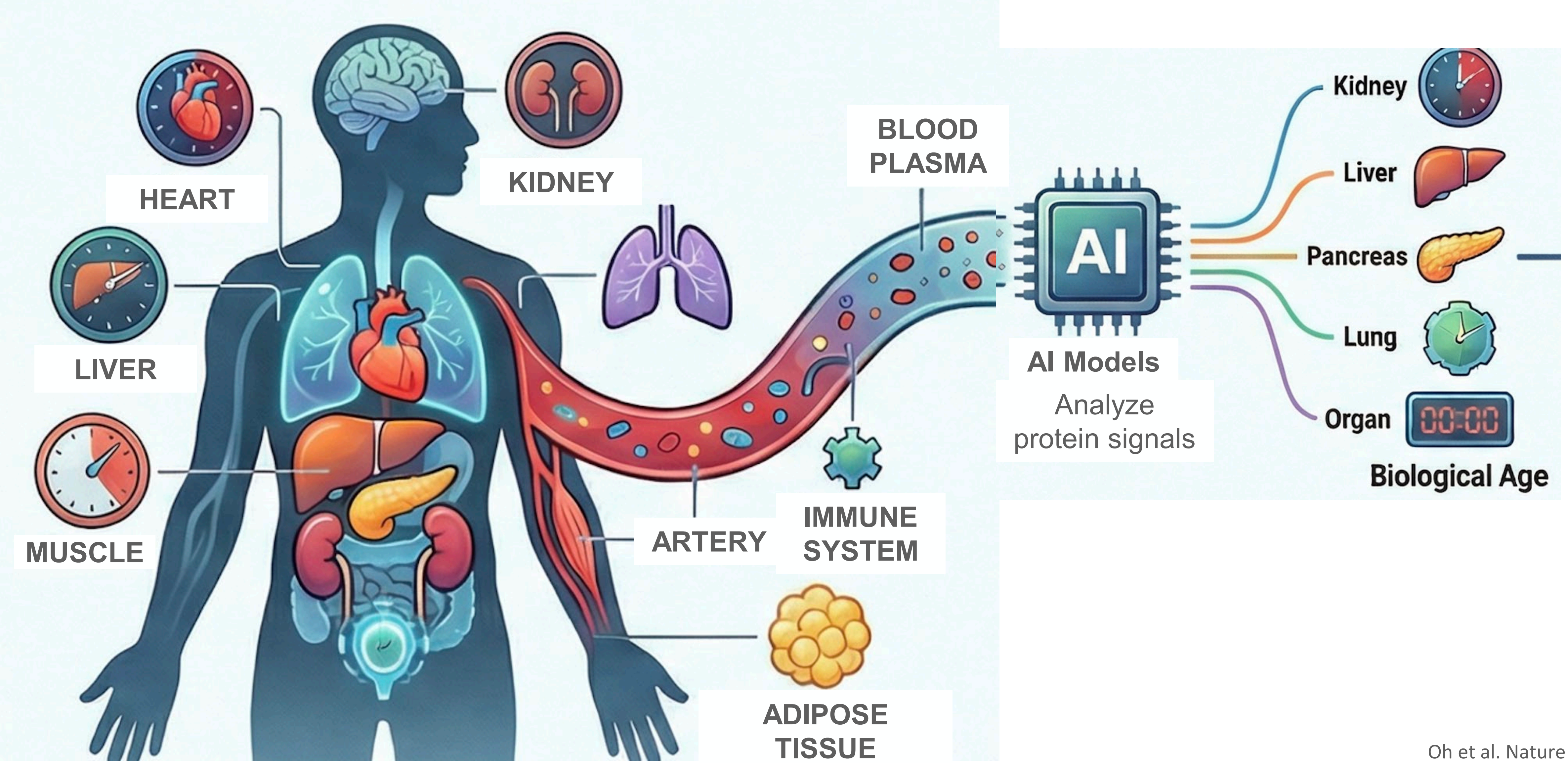


SomaScan®: Biomarker Discovery

- Measures >11,000 proteins
- Discovery of proteins for chronic diseases
- Identify novel pathways of disease and disability
- Measured in 2,836 WHIMS women (including 1,000 at 2 time points 15 years apart)

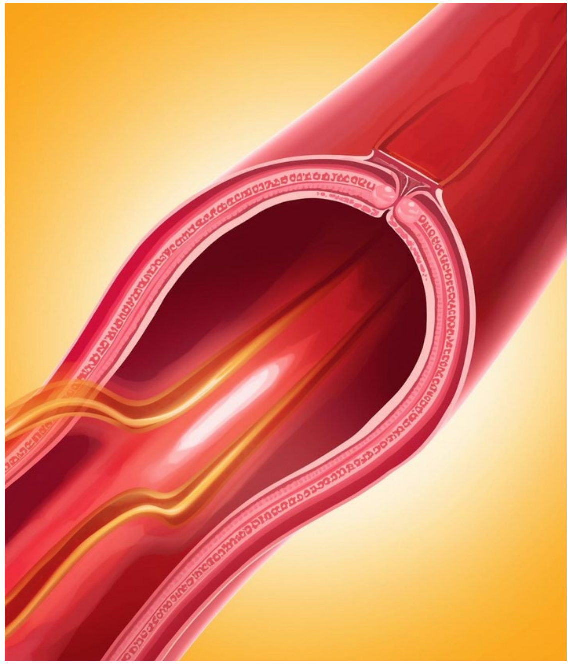


Protein Organ Clocks of Aging



Oh et al. Nature 2023

Slower Biological Aging Increases Healthy Longevity



Artery

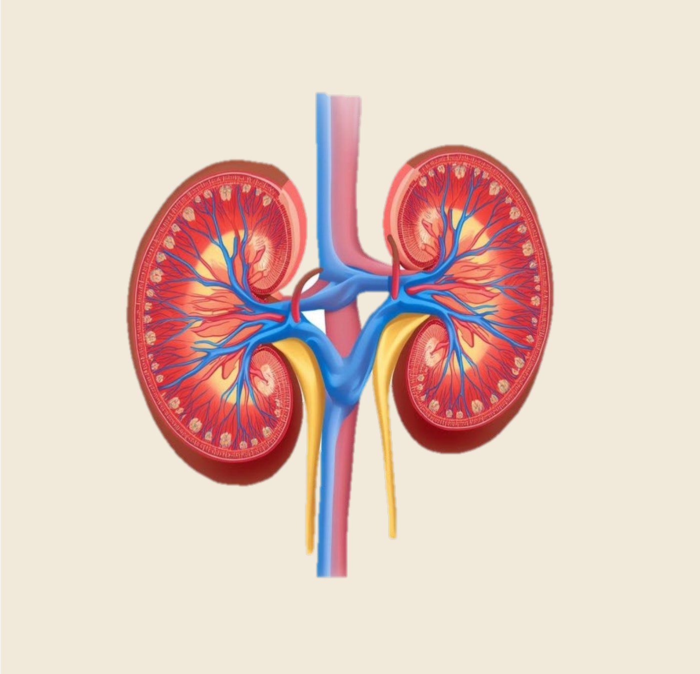
Brain

Heart

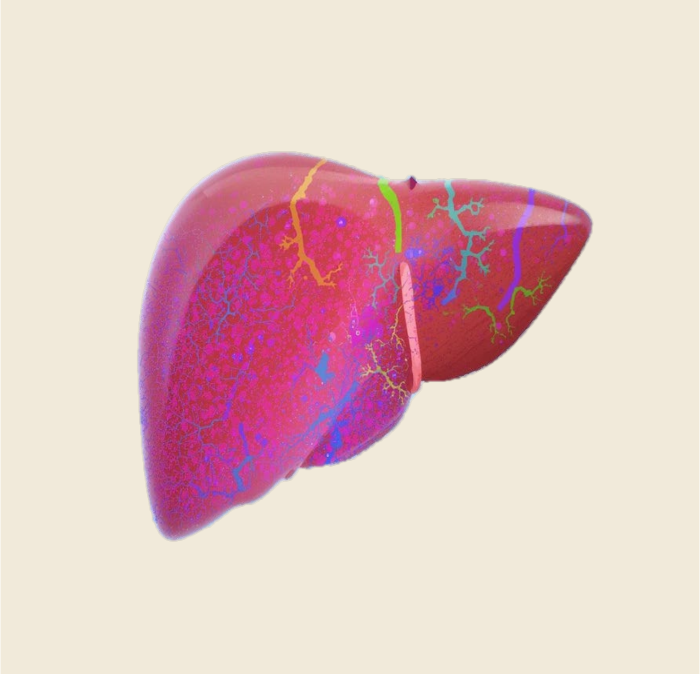
Immune System

Slower aging of artery, brain, heart, and immune system increases survival to age 90 without dementia in WHIMS

Slower Biological Aging Increases Healthy Longevity



Kidney



Liver

Muscle

Slower aging of the kidney, liver, and muscle increases survival to age 90 without dementia in WHIMS

Thank You

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