

A DNA methylation biomarker of Intrinsic Capacity

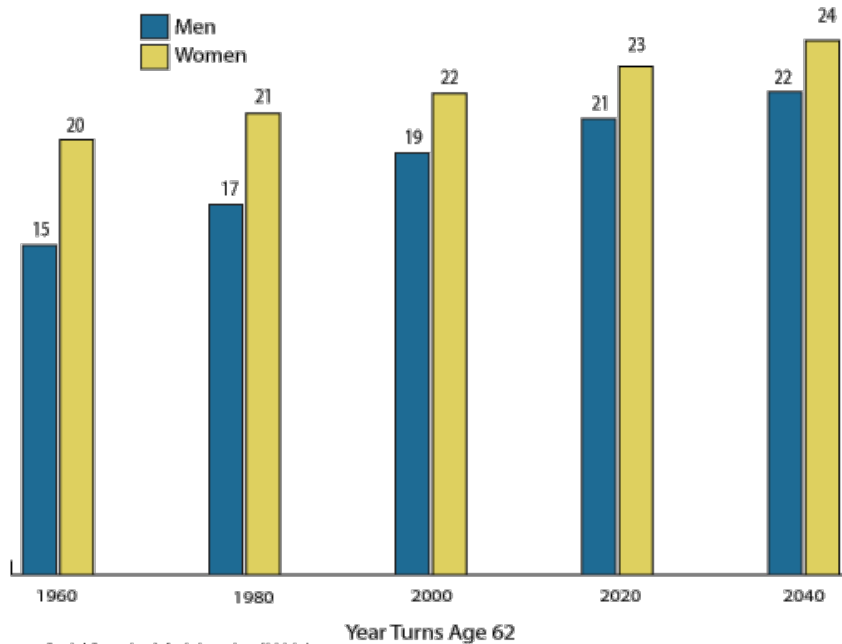
Karen Sugden, PhD¹, J. Kathy Xie, MSc¹, Avshalom Caspi, PhD¹, Renate Houts, PhD¹,
John Beard, PhD², Daniel Belsky, PhD², Terrie Moffitt, PhD¹

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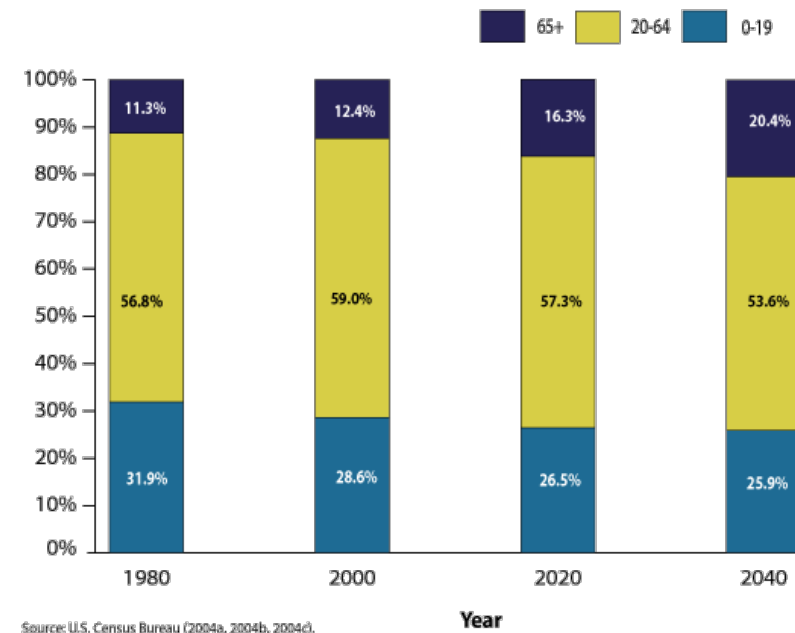
²Robert N Butler Columbia Aging Center, Columbia University, USA

People are living longer

Remaining Years of Life Expectancy at Age 62, 1960-2040



Age Distribution of the Population, 1980-2040



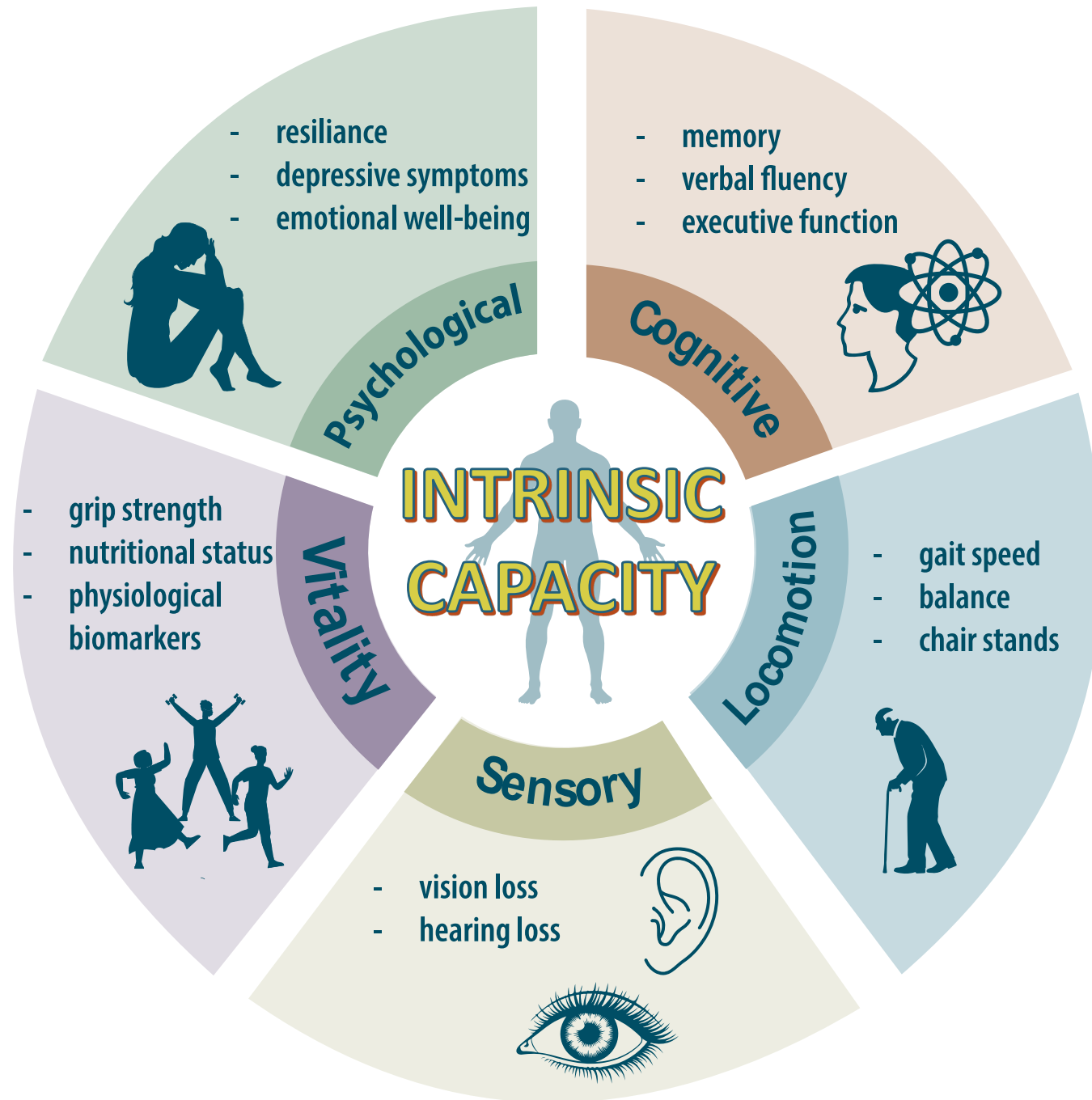
People are living longer

A need to promote healthy aging

“the process of developing and maintaining the functional ability that enables wellbeing in older age.”

This includes a person’s ability to:

- meet their basic needs;
- learn, grow and make decisions;
- be mobile;
- build and maintain relationships; and
- contribute to society.



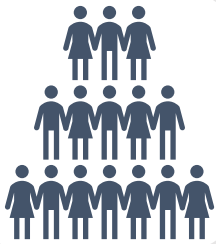
Operationalize IC in midlife cohort and export to DNAm tool



Model IC phenotype in midlife



Develop DNAm algorithm to estimate
IC



Validate DNAm-IC algorithm in external
cohorts



Kathy Xie

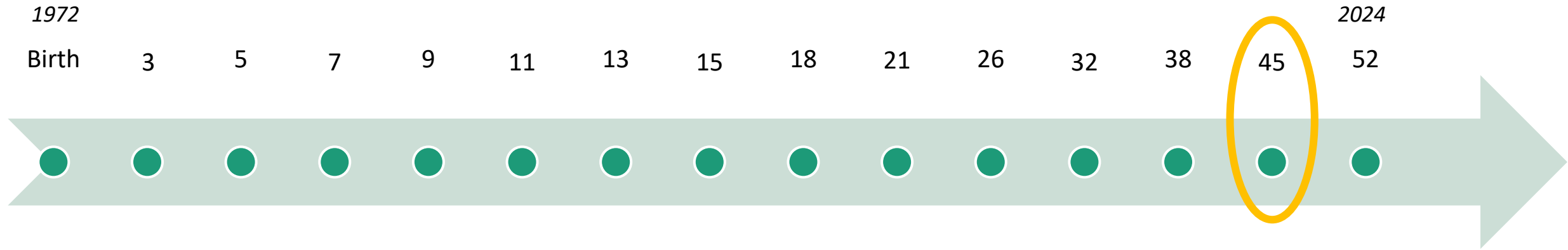
The Dunedin Study



- N=1,037
- Born in 1972-73 in Dunedin, NZ
- Followed from birth-present (age 52)
- >90% retention

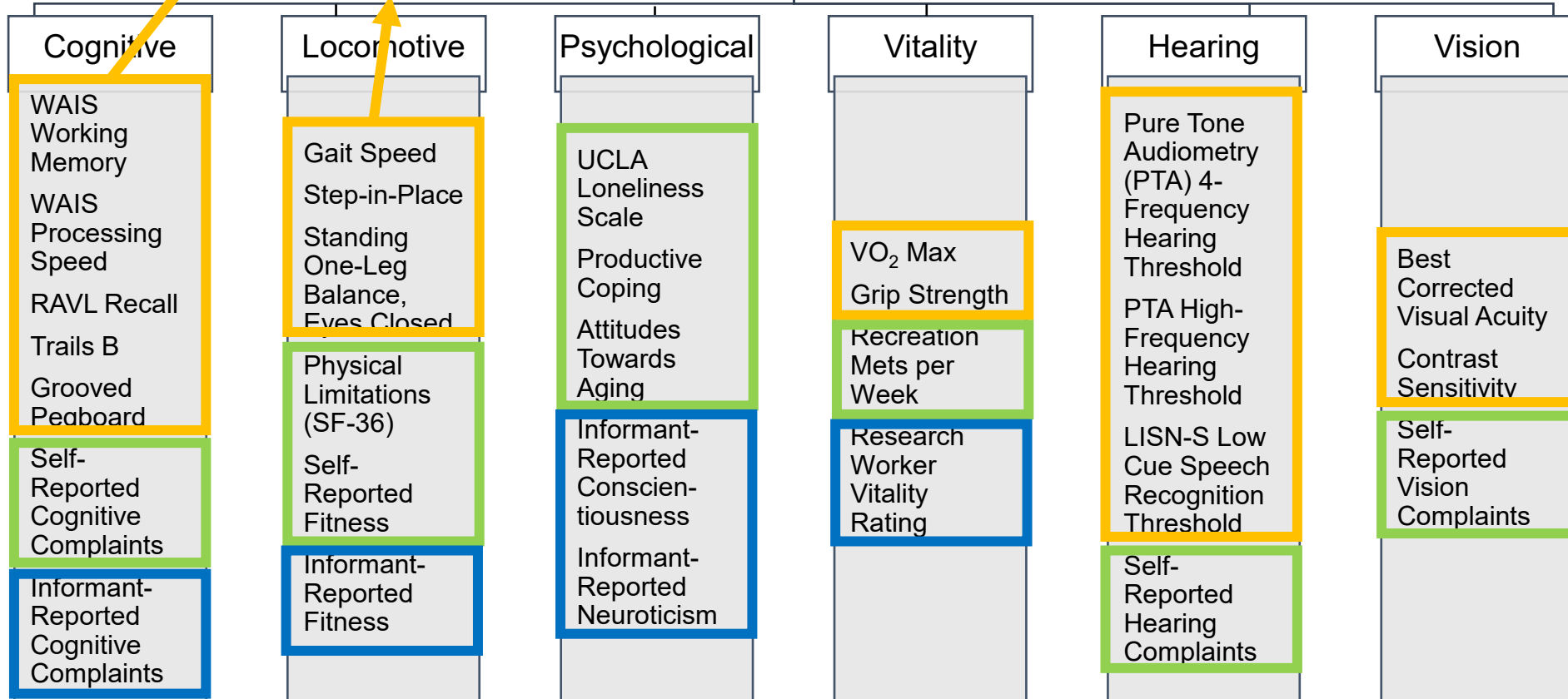


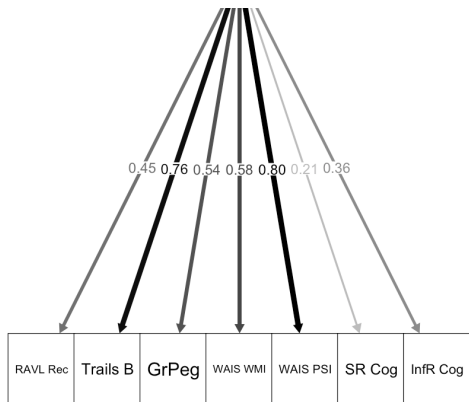
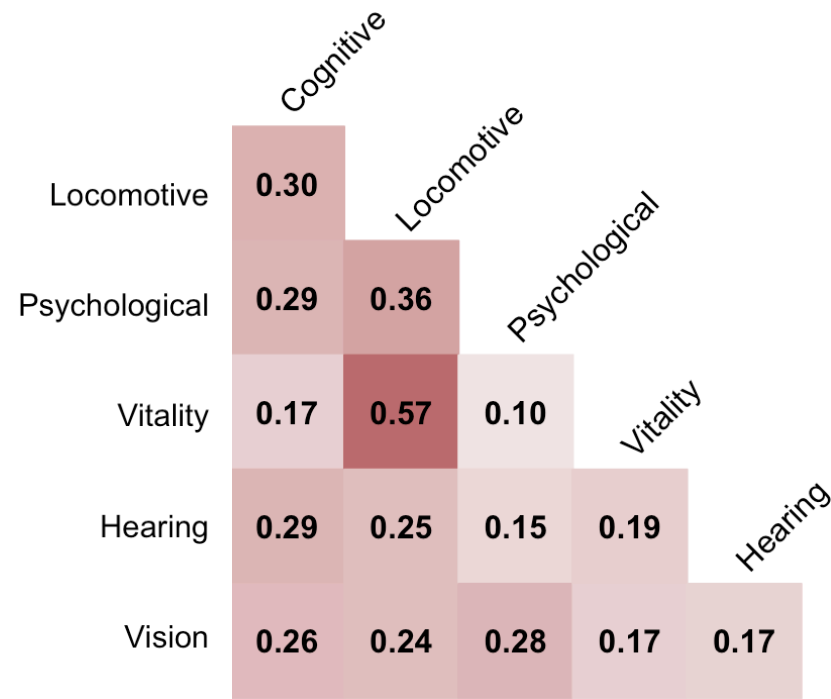
Data collection timepoints





Intrinsic Capacity

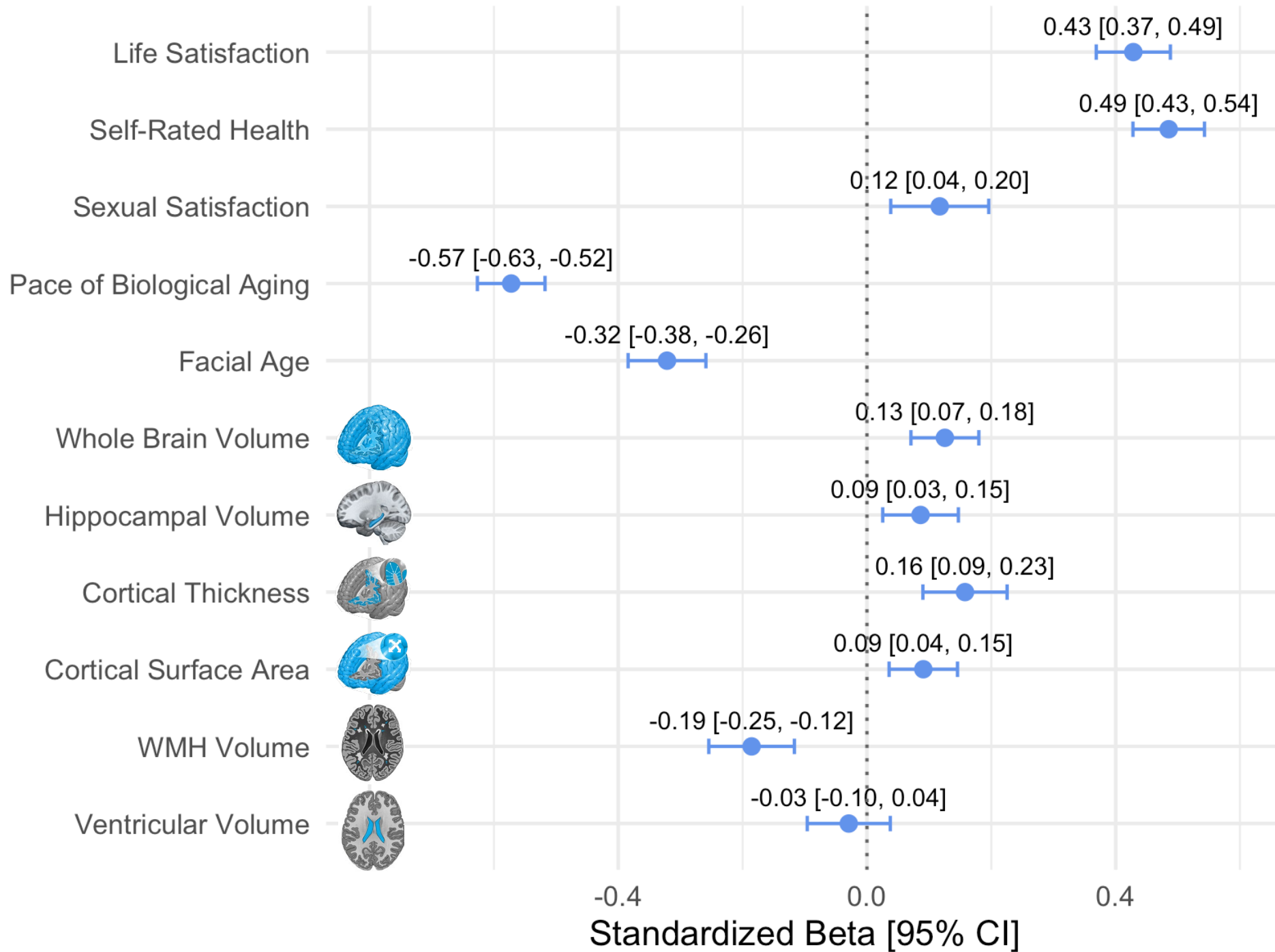


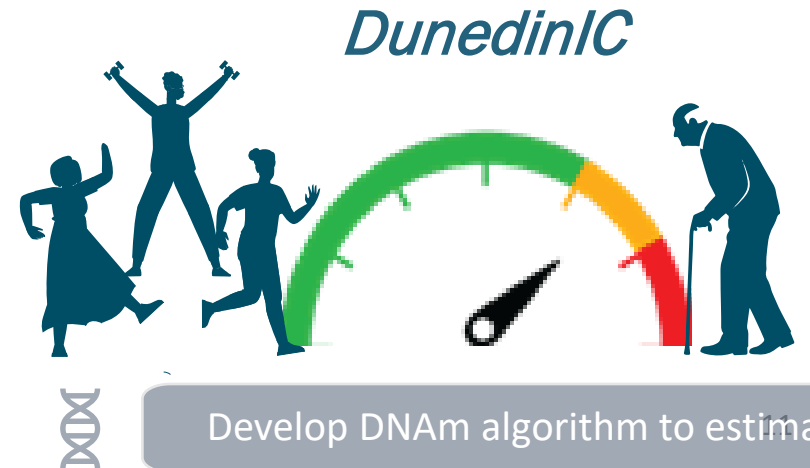
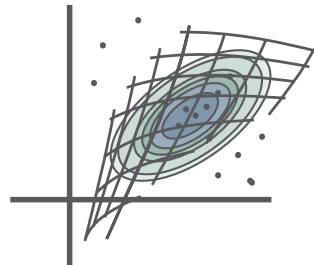
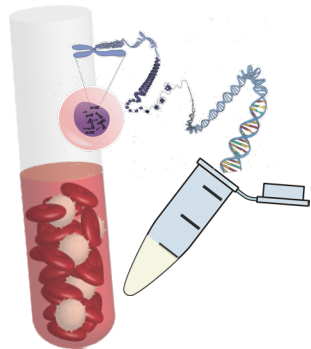
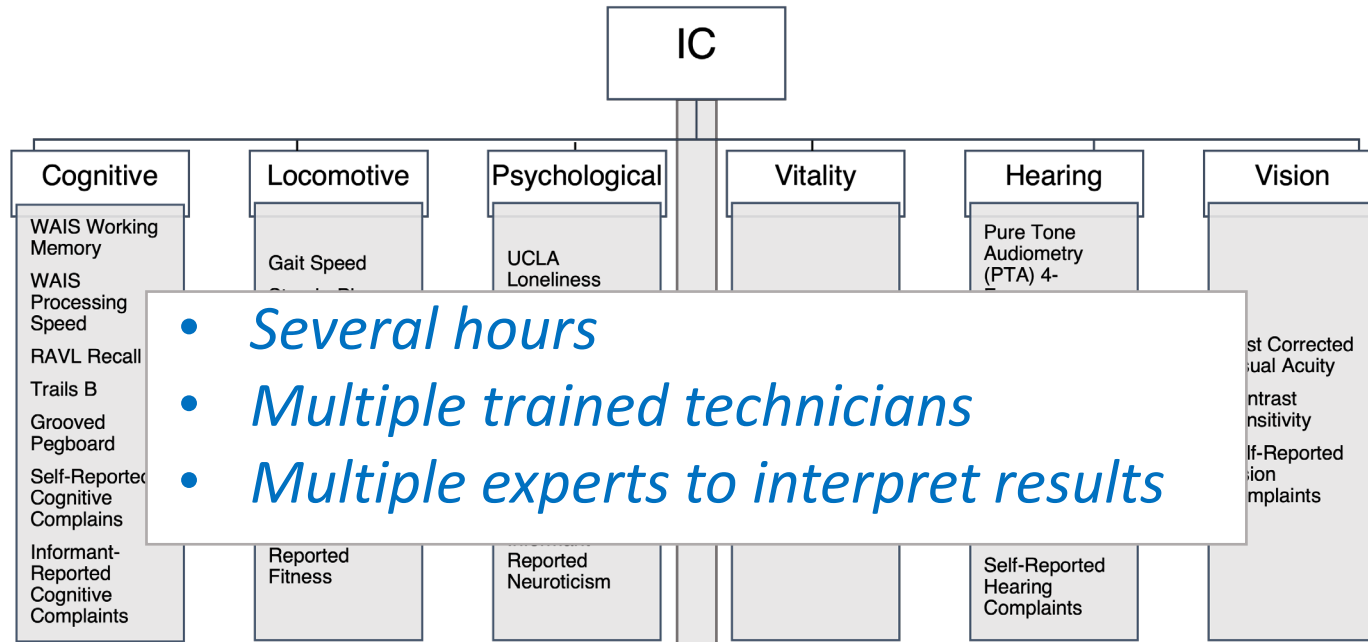


For each participant:

- *Derive Latent Variable score for each of 6 IC domains*
- *Standardize all Latent Variable scores*
- *Sum standardized LV scores to create IC composite*

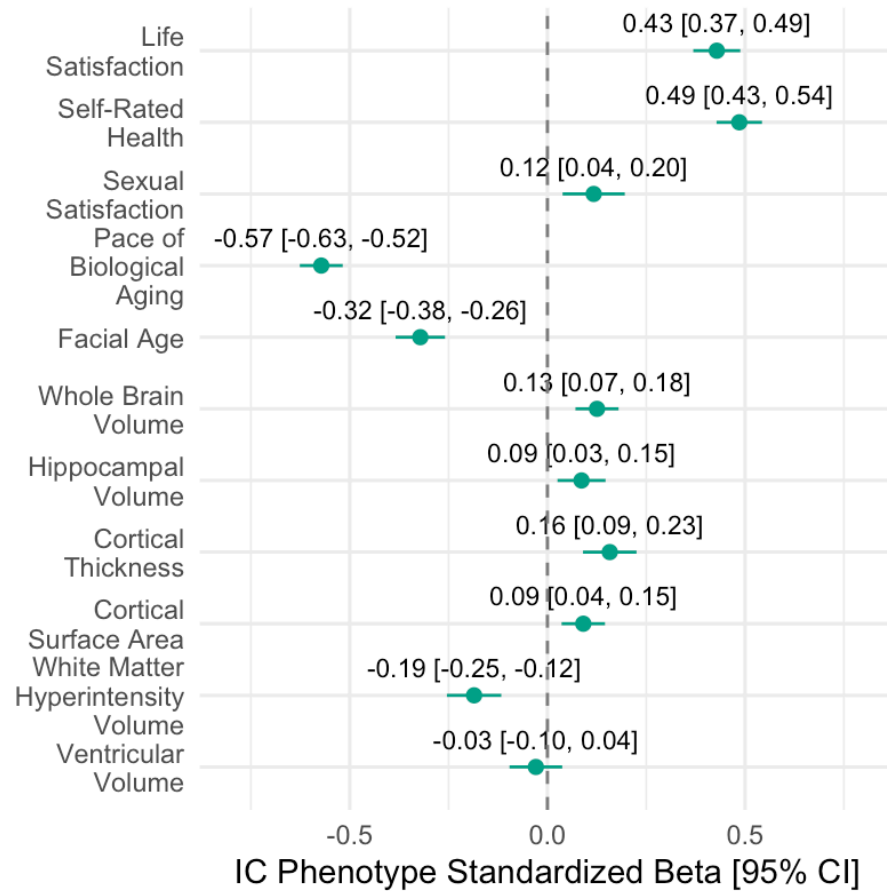






Develop DNAm algorithm to estimate IC

Comparison of IC Phenotype and DunedinIC



*Standardized effect sizes from associations in the Dunedin Study.
All models control for sex.*



Develop DNAm algorithm to estimate IC

- n=1,309 with DNAm
- Age: 26-86 (M=54.0)

Midlife in the United States



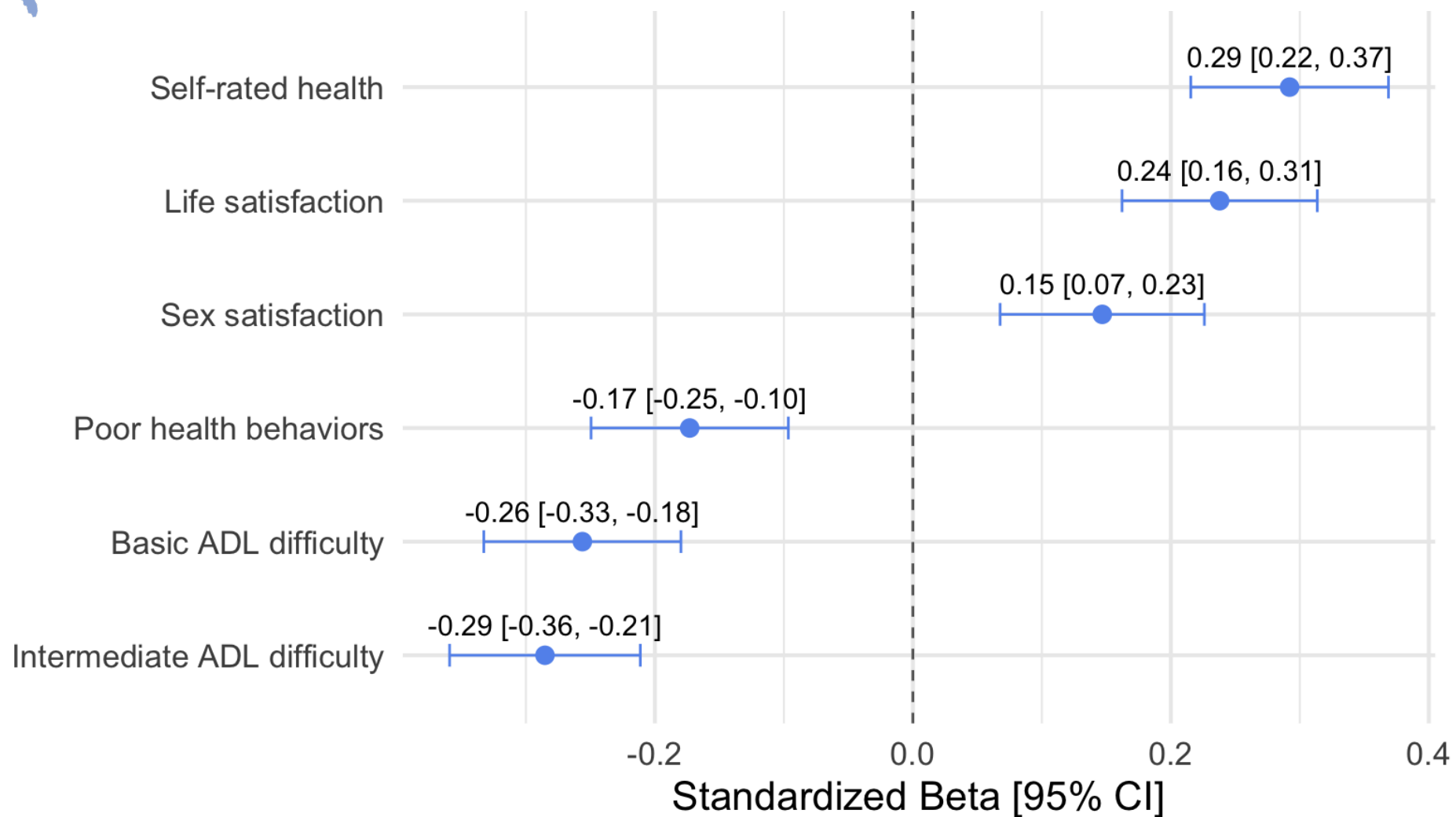
- n=818 with DNAm
- Age: 45

Dunedin Study





DunedinIC is associated with functional outcomes in MIDUS



All models control for sex, technical variation and chronological age

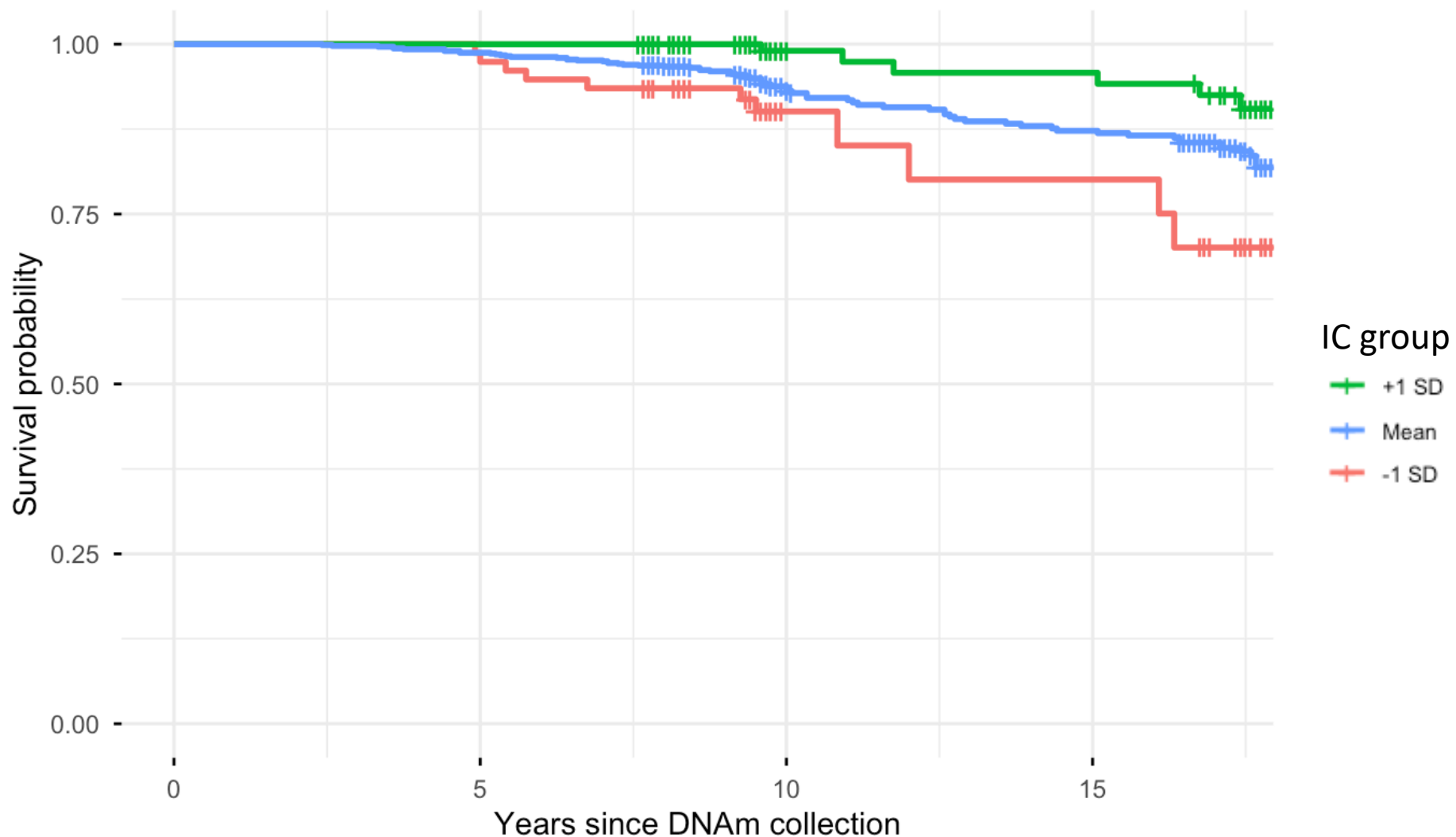


Validate DNAm-IC algorithm in external cohorts



Higher DunedinIC predicts reduced risk of mortality

HR 0.57 [0.45-0.73], on 98 deaths, mean follow-up time 11.59 years



Model controls for sex and age at DNAm collection

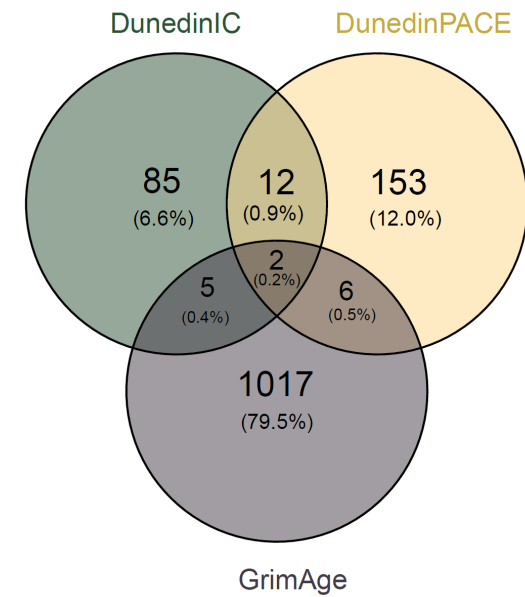
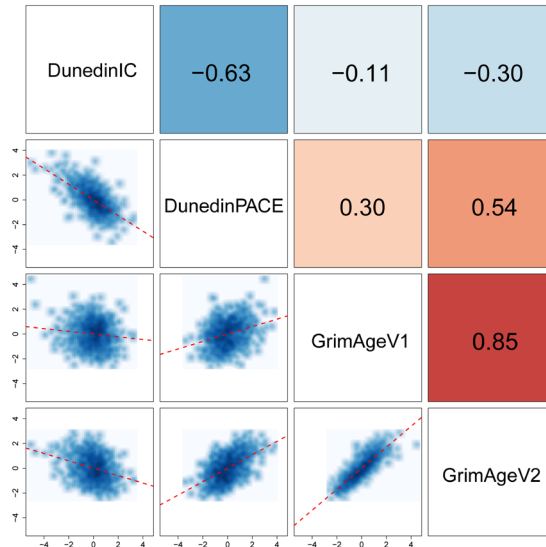
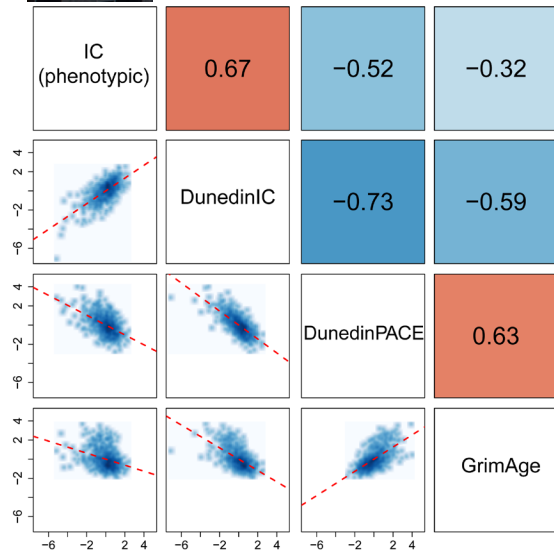


Validate DNAm-IC algorithm in external cohorts

Why do we need ANOTHER epigenetic algorithm?



Correlations between biological age clocks and Intrinsic Capacity are moderate, and patterns of associations with IC domains and/or functional capacity are inconsistent



Association between biological age acceleration according to different aging clocks and intrinsic capacity

	N	Model 1		Model 2	
		β (95% CI)	p-value	β (95% CI)	p-value
Chronological age	189	-0.323 (-0.560 to -0.086)	0.008	-0.280 (-0.514 to -0.046)	0.020
Horvath	69	0.124 (-0.075 to 0.323)	0.218	0.131 (-0.071 to 0.332)	0.201
Horvath 2	69	0.296 (-0.078 to 0.671)	0.119	0.317 (-0.053 to 0.687)	0.092
Hannum	69	0.147 (-0.227 to 0.520)	0.436	0.168 (-0.218 to 0.555)	0.387
Hannum 2	69	0.179 (-0.396 to 0.754)	0.536	0.220 (-0.351 to 0.791)	0.444
PhenoAge	69	-0.021 (-0.285 to 0.242)	0.873	-0.039 (-0.309 to 0.231)	0.773
PhenoAge 2	69	0.006 (-0.316 to 0.329)	0.968	-0.014 (-0.336 to 0.309)	0.933
GrimAge	69	-0.059 (-0.608 to 0.490)	0.831	-0.056 (-0.612 to 0.499)	0.840

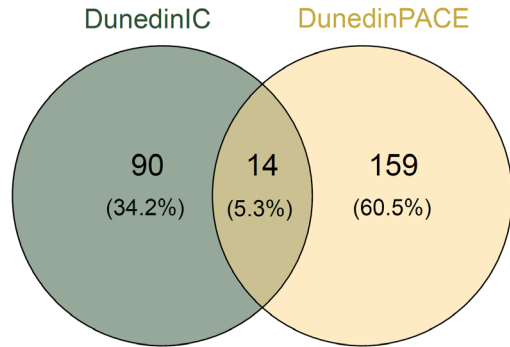
e.g. Valenzuela et al. (2025) *GeroScience*;48(1):973–984;

LaCroix et al. (2026) *medRxiv* 2026.03.11.26348107;

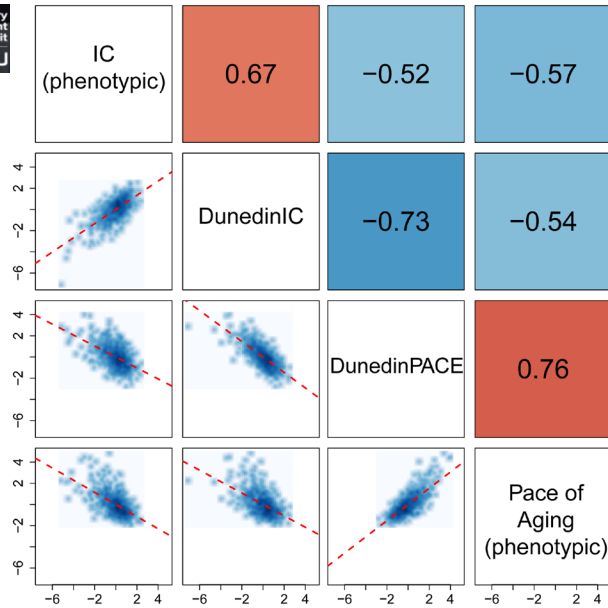
Sánchez-Sánchez et al. (2025) *Journal of Cachexia, Sarcopenia and Muscle* 16, no. 4 (2025): e70046

Valenzuela et al. (2025)

DunedinIC complements, but does not replace, DunedinPACE

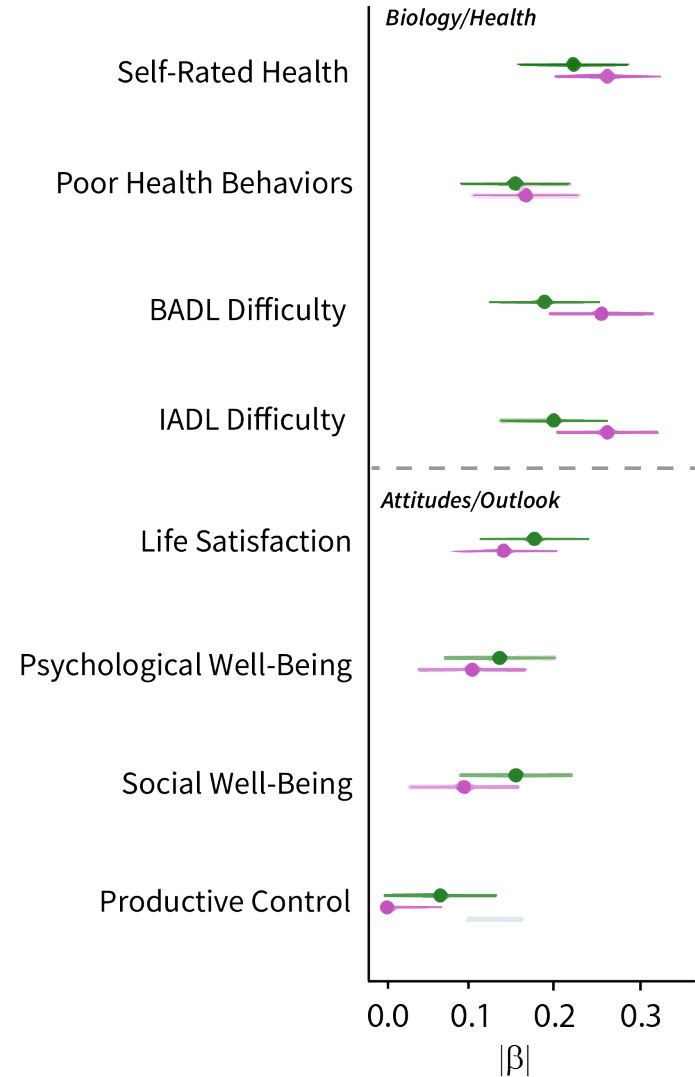


Dunedin Multidisciplinary Health & Development Research Unit
DMHDRU

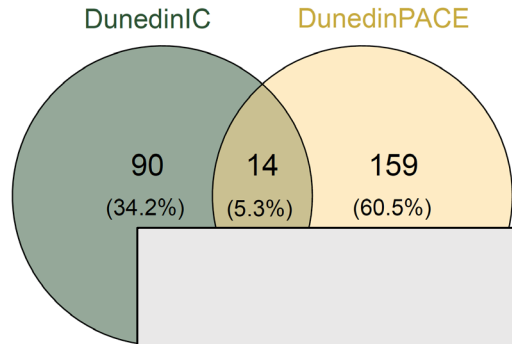


Measure ◆ DunedinIC ◆ DunedinPACE

Separate models

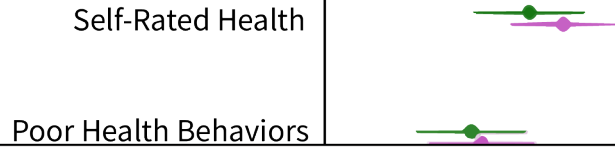


DunedinIC complements, but does not replace, DunedinPACE



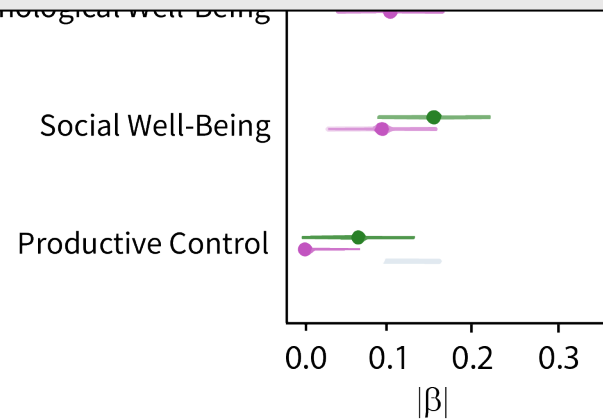
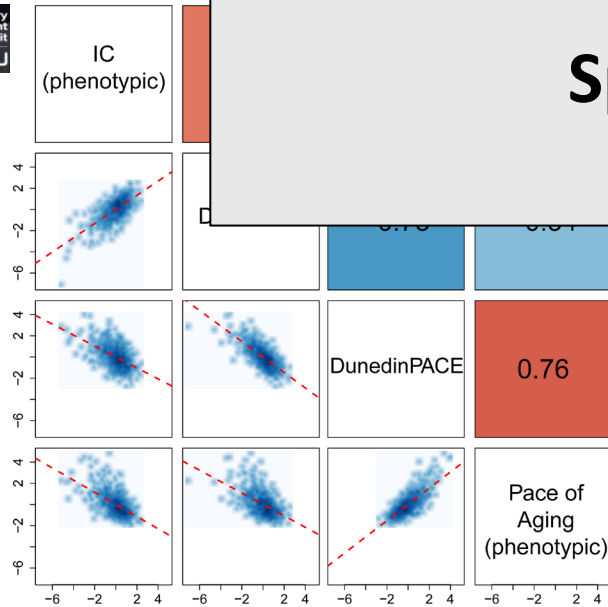
Measure ◆ DunedinIC ◆ DunedinPACE

Separate models



Independence of DunedinIC from biological aging clocks

Specificity to attitudinal outcomes







A blood-based epigenetic clock for intrinsic capacity predicts mortality and is associated with clinical, immunological and lifestyle factors

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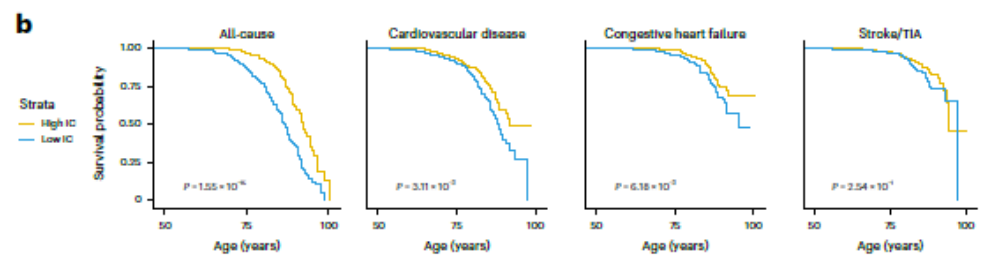
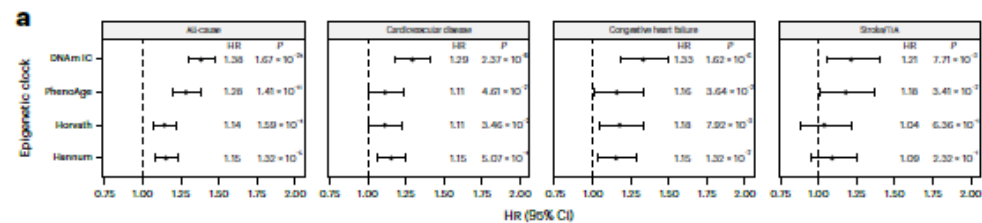
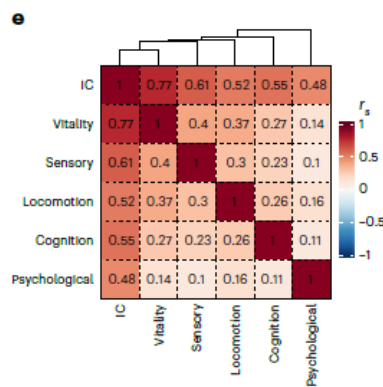
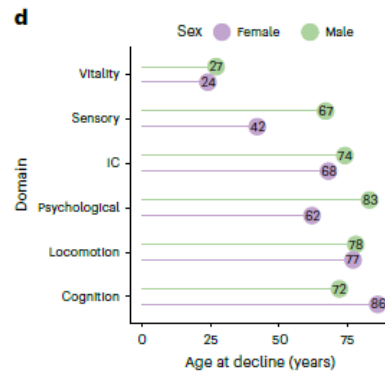
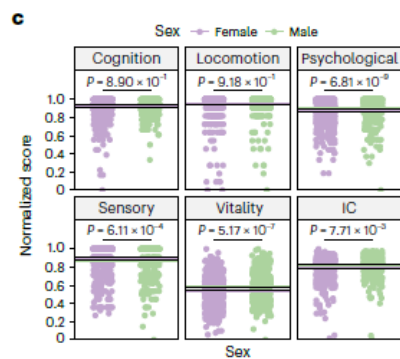
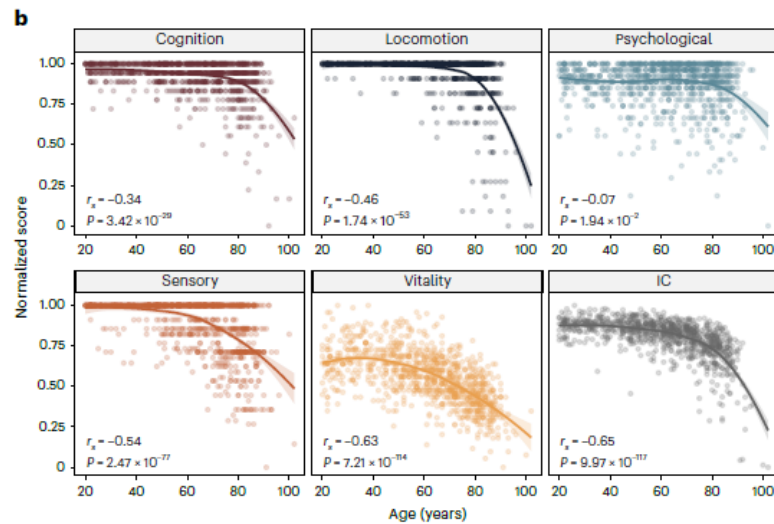
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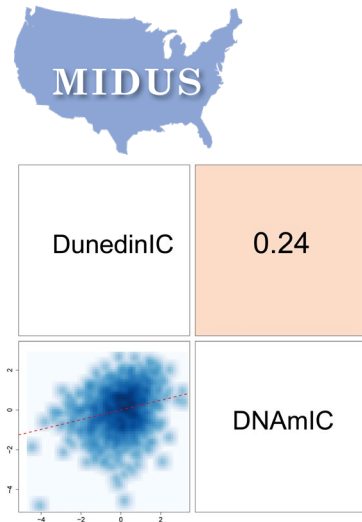
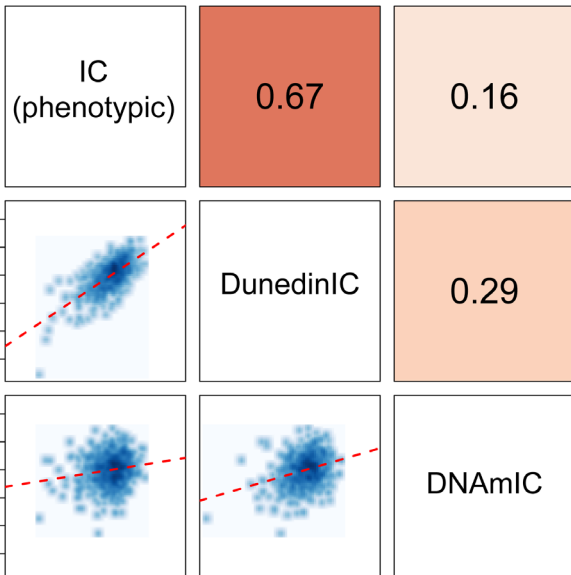
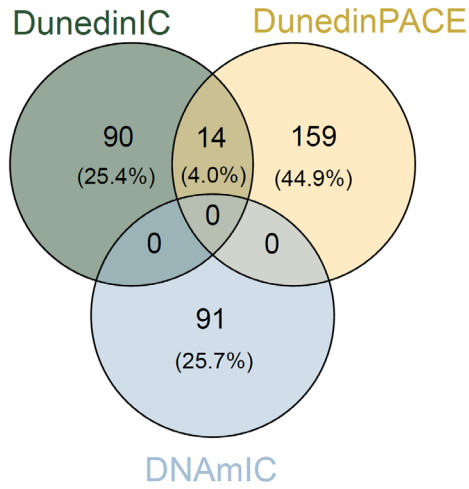
Matias Fuentealba¹, Laure Rouch^{2,3}, Sophie Guyonnet^{2,3}, Jean-Marc Lemaître⁴, Philippe de Souto Barreto ^{2,3}, Bruno Vellas^{2,3}, Sandrine Andrieu^{2,3,5} & David Furman ^{1,2,6,7} 

Age-related decline in intrinsic capacity (IC), defined as the sum of an individual's physical and mental capacities, is a cornerstone for promoting healthy aging by prioritizing maintenance of function over disease treatment. However, assessing IC is resource-intensive, and the molecular and cellular bases of its decline are poorly understood. Here we used the INSPIRE-T cohort (1,014 individuals aged 20–102 years) to construct the IC clock, a DNA methylation-based predictor of IC, trained on the clinical evaluation of cognition, locomotion, psychological well-being, sensory abilities and vitality. In the Framingham Heart Study, DNA methylation IC outperforms first-generation and second-generation epigenetic clocks in predicting all-cause mortality, and it is strongly associated with changes in molecular and cellular immune and inflammatory biomarkers, functional and clinical endpoints, health risk factors and lifestyle choices. These findings establish the IC clock as a validated tool bridging molecular readouts of aging and clinical assessments of IC.

This is not the first DNAm measure of Intrinsic Capacity

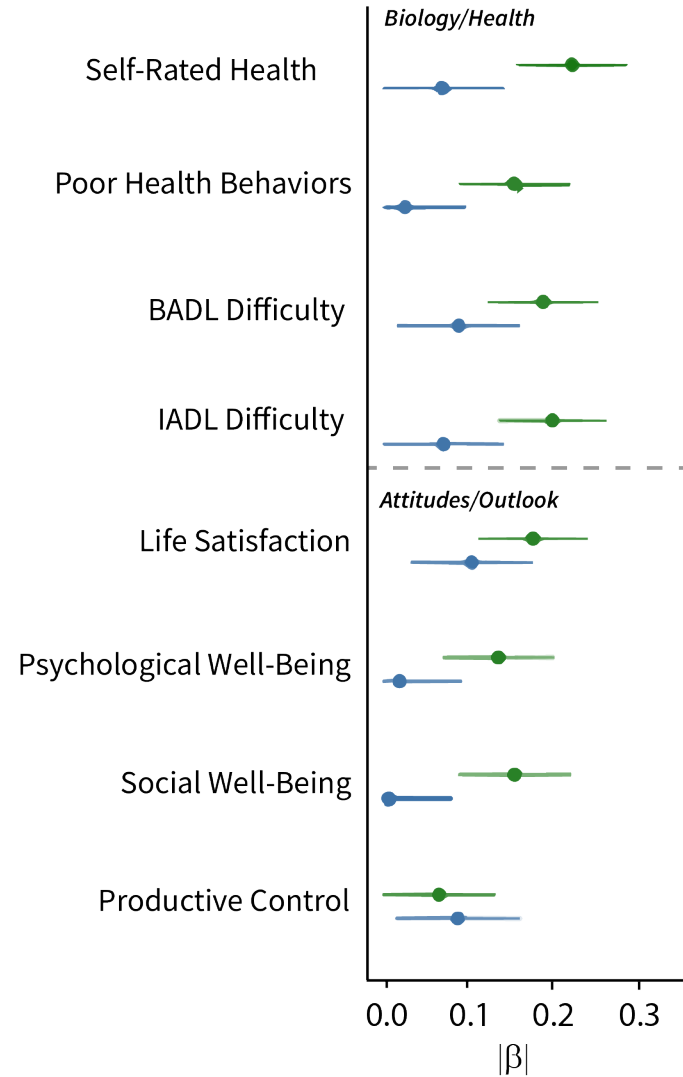


DunedinIC correlates more strongly with function-related measures than DNAmIC

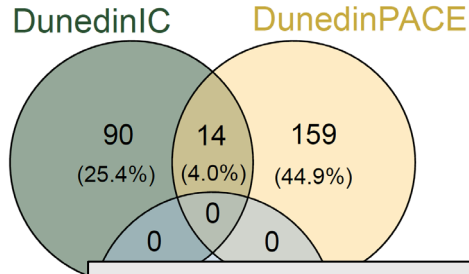


Measure ◆ DunedinIC ◆ DNAmIC

Separate models

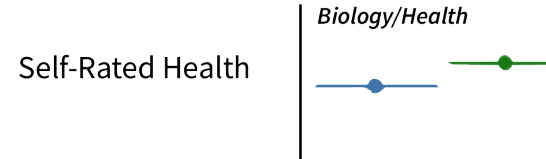


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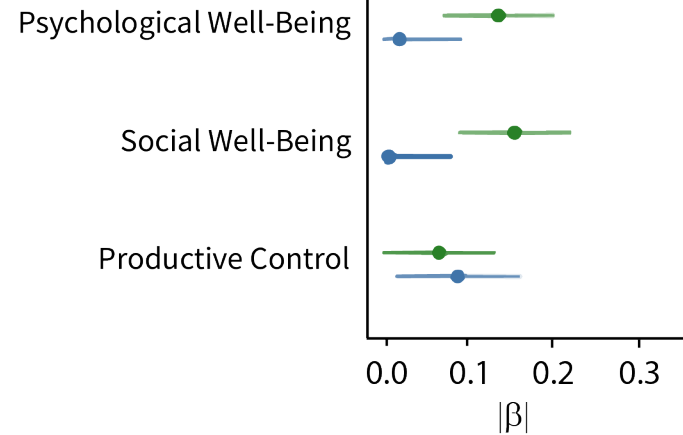
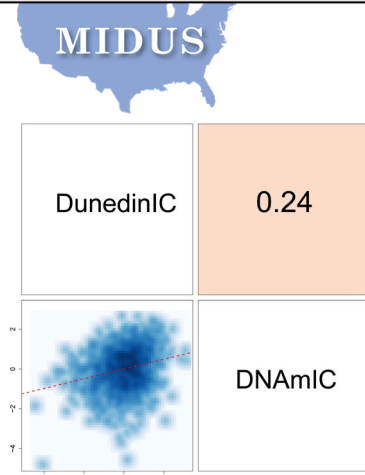
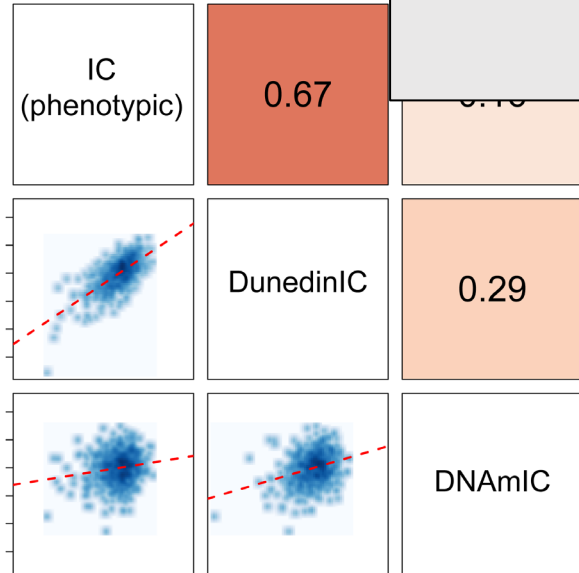


Measure ◆ DunedinIC ◆ DNAmIC

Separate models



Independence of DunedinIC from DNAmIC
Greater association with functional capacity constructs



Conclusions

- New tool to assess Intrinsic Capacity, DunedinIC
- Captures variation in IC-related outcomes independent of established biological and pace of aging clocks
- Complements existing tools

Future directions

- Continue validation of DNAm-IC tool in datasets with DNAm data
 - Mortality
 - Frailty
 - Health & well-being indicators

GROW UP GROW OLD

Moffitt & Caspi

Genes • Environment
Health • Behavior

Thank you!

Contact:
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RAVL Rec	Trails B	GrPeg	WAIS WMI	WAIS PSI	SR Cog	InfR Cog
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