

The NIA Biomarker Network Annual Meeting 2024

# RNA-based Indicators of Cellular Senescence Predict Aging Health Outcomes in the Health and Retirement Study

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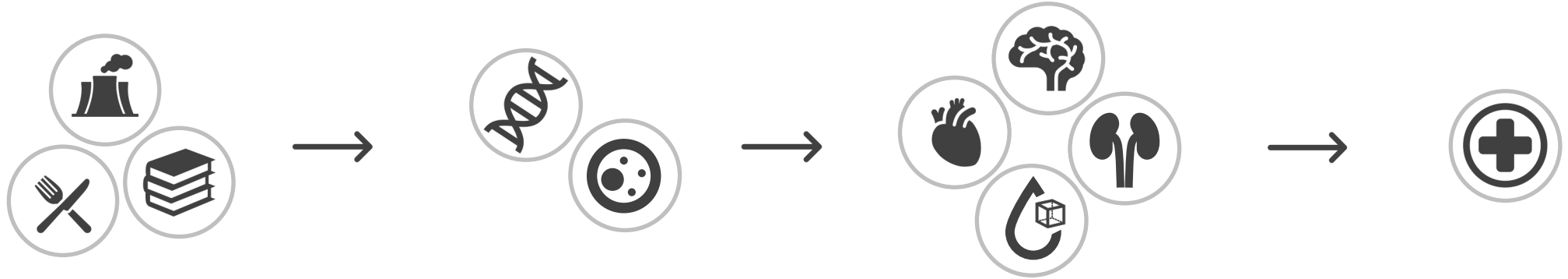
# Acknowledgements

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# Age-Related Health Changes



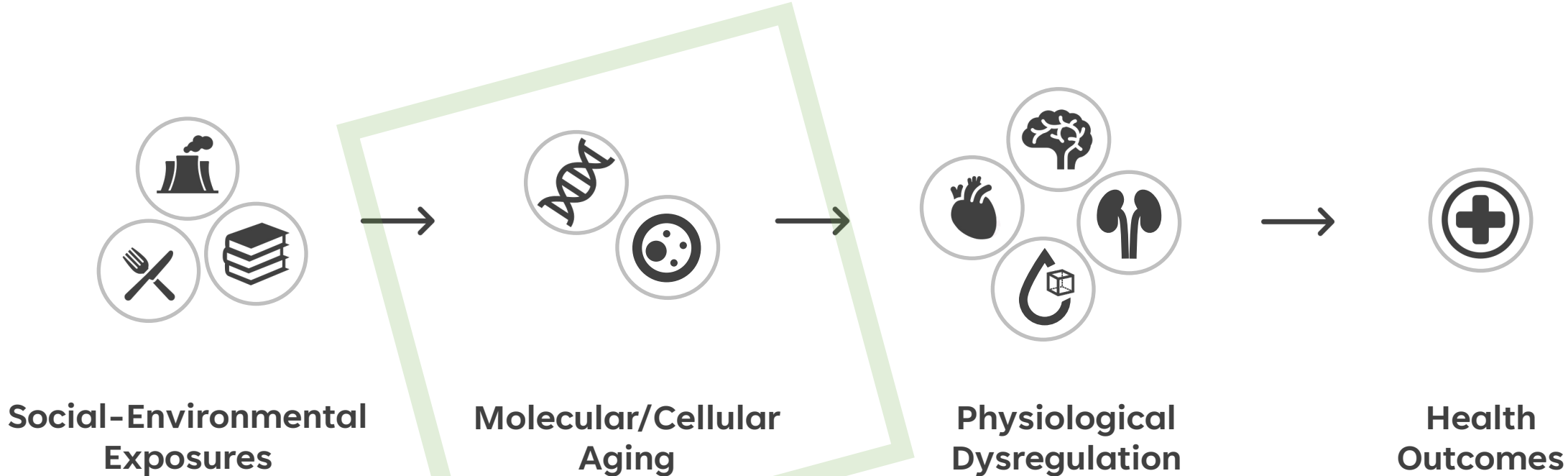
**Social-Environmental  
Exposures**

**Molecular/Cellular  
Aging**

**Physiological  
Dysregulation**

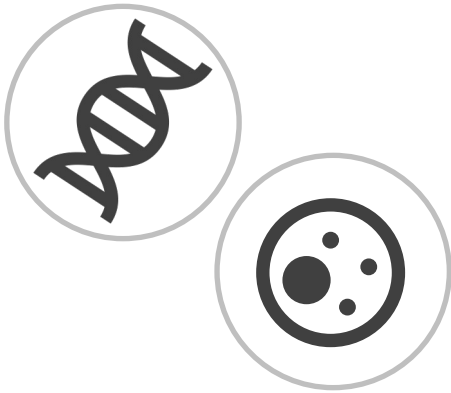
**Health  
Outcomes**

# Age-Related Health Changes

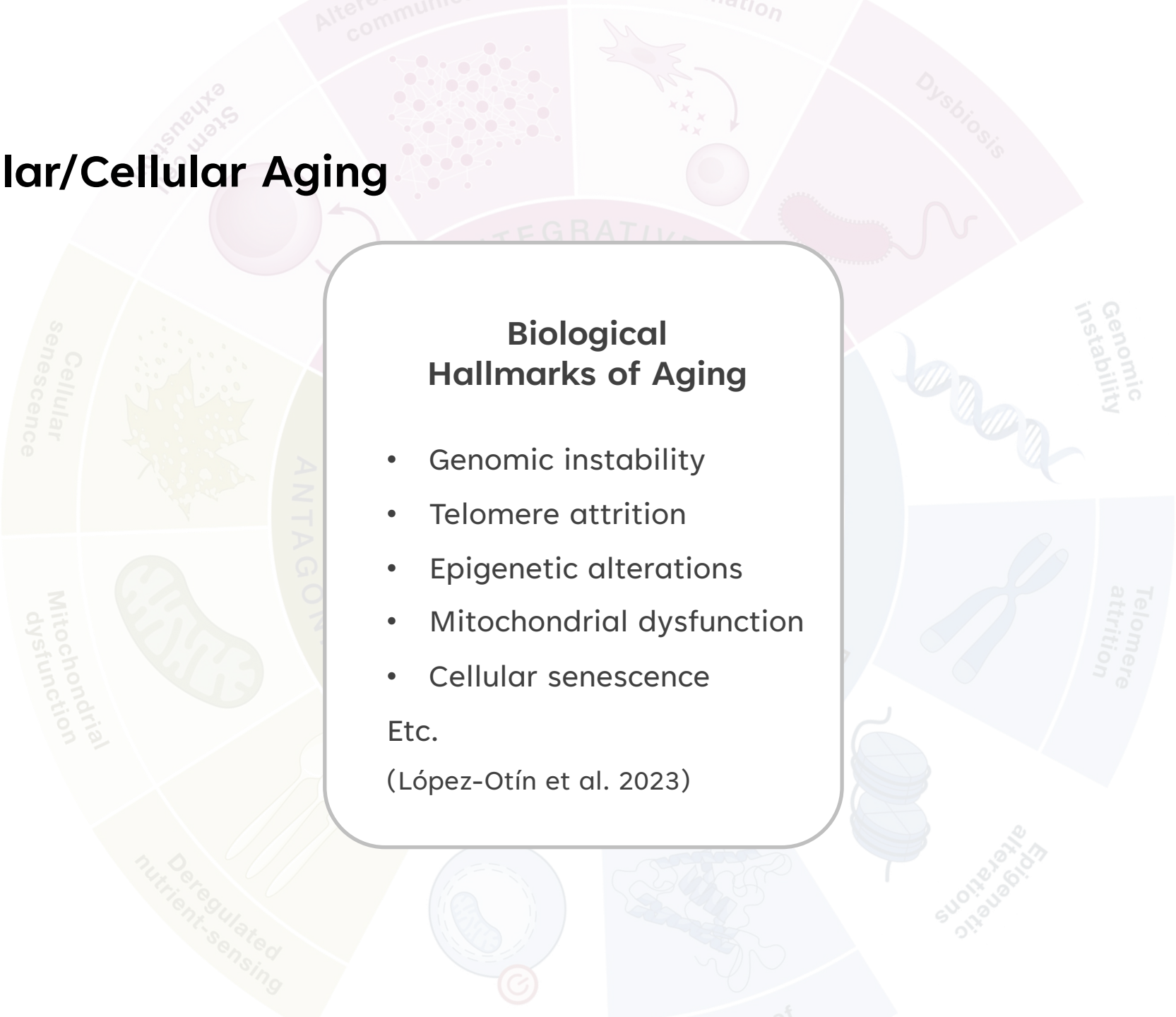


*The link between exposures and health  
Upstream mechanisms of aging*

# Measuring Molecular/Cellular Aging



Molecular/Cellular Aging



# Measuring Molecular/Cellular Aging



**Molecular/Cellular  
Aging**

## Biological Hallmarks of Aging

- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Mitochondrial dysfunction
- **Cellular senescence**

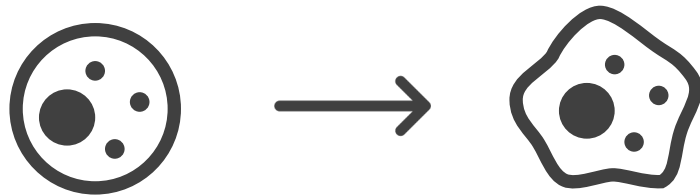
Etc.

(López-Otín et al. 2023)

## RNA-Sequencing-Based Transcriptomic Summary Measure

*A common approach used in social  
and behavioral sciences*

# Background



Cellular Senescence

## Cellular Senescence

- One of the underlying mechanisms of aging
- Senescent cells accumulate with age
- **Triggered by stress**
- **Stop multiplying**
- **Release pro-inflammatory signals**

# Background



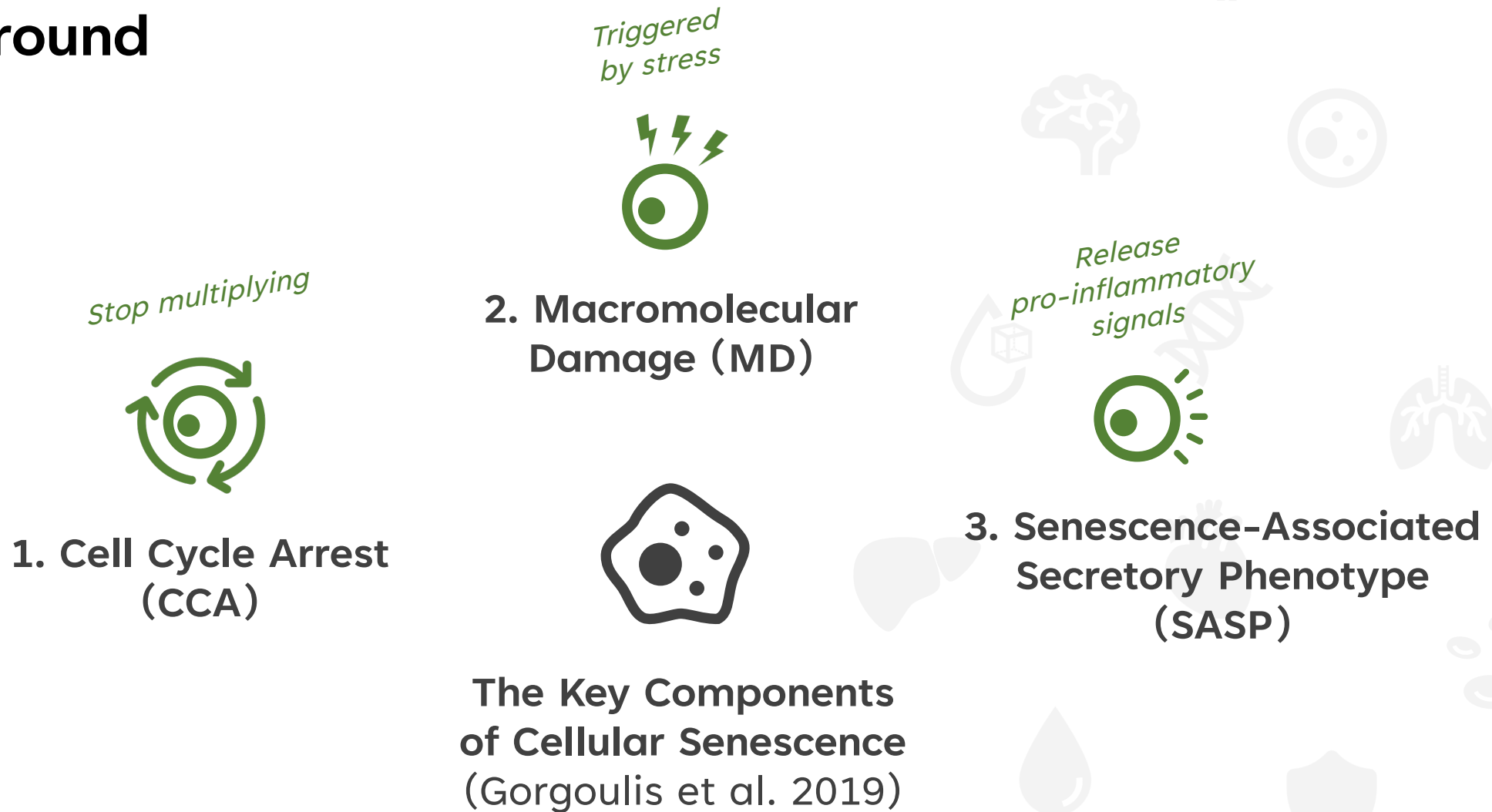
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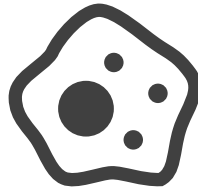
# Background



# Background



Social-Behavioral  
Factors



Cellular Senescence



Lung Disease



Kidney Disease



Liver Disease



Metabolic Disorder



Osteoporosis/Arthritis

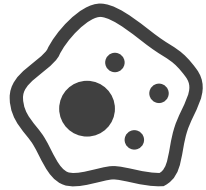


Cardiovascular Disease



Alzheimer's Disease

# Background



Cellular Senescence



Lung Disease



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Liver Disease



Metabolic Disorder



Osteoporosis/Arthritis



Cardiovascular Disease



Alzheimer's Disease

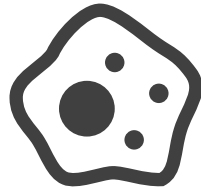
## Gaps in the Literature

- Heavily rely on animal models and human cell in vitro
- Primarily focus on SASP
- SASP links to morbidity, frailty measures, functional limitations, and mortality
- Limited Representativeness

# Background



**Social-Behavioral  
Factors**



**Cellular Senescence**

## Gaps in the Literature

- In theory, obesity, high-fat diet, sleep deprivation, cigarette smoking, and alcohol abuse may all induce senescence.
- Very little direct evidence at population level.

# Background

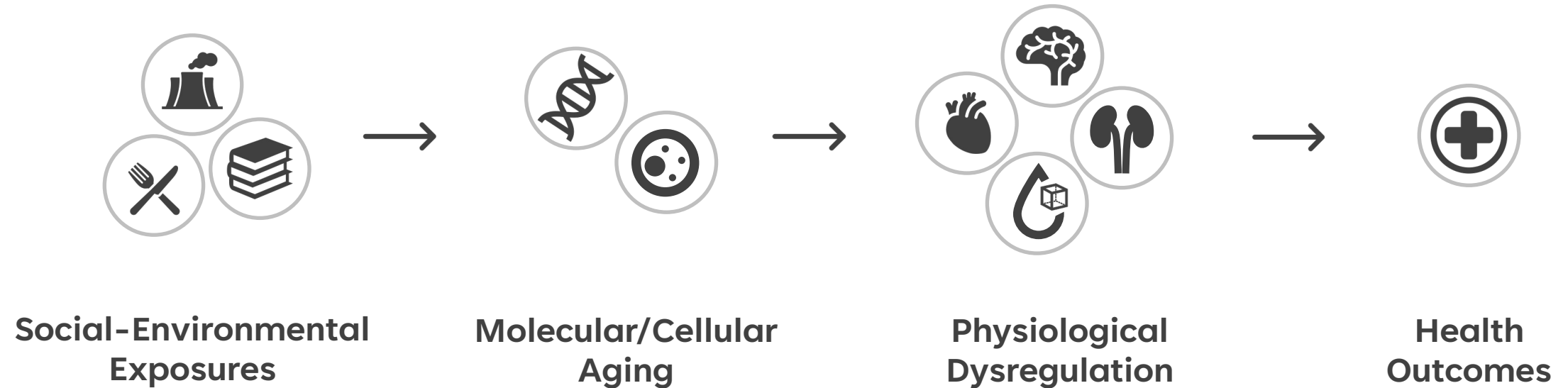
## Research Questions

- How do social-behavioral factors link to cellular senescence?
- How does cellular senescence measure aging?

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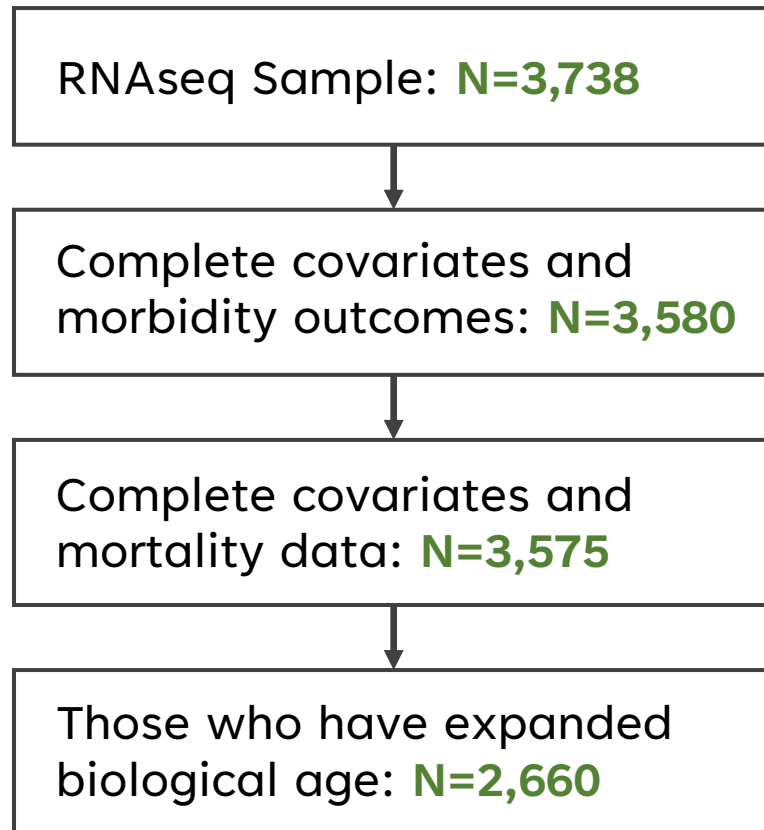
# Background

## Research Questions

- How do social-behavioral factors link to cellular senescence?
- How does cellular senescence measure aging?
  - How does cellular senescence link to **mortality** and **multimorbidity**?
  - How does cellular senescence link to **physiological dysregulation**?
  - How does cellular senescence link to other **molecular aging measures**?

# Methods – Data & Sample

- HRS Venous Blood Innovative Assays Sample – A nationally representative sample of approximately 4,000 community-dwelling older adults.
- RNAseq data for about 3,700 HRS respondents



*The main analytical sample for the association between senescence scores and multimorbidity  
(The sample for epigenetic clocks is the same as this one)*

*The sub-samples for mortality analyses*

*The sub-sample for biological age analyses*



# Methods – Cellular Senescence Measure

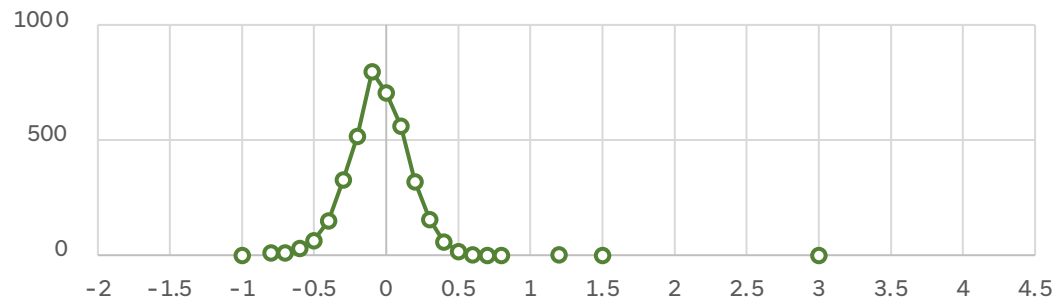
## Four RNA-Based Cellular Senescence Scores

1. Cell Cycle Arrest Score (**CCA**) – 22 genes
2. Macromolecular Damage Score (**MD**) – 48 genes
3. Senescence-Associated Secretory Phenotype score (**SASP**) – 44 genes
4. Senescence **Summary Score** – 112 genes

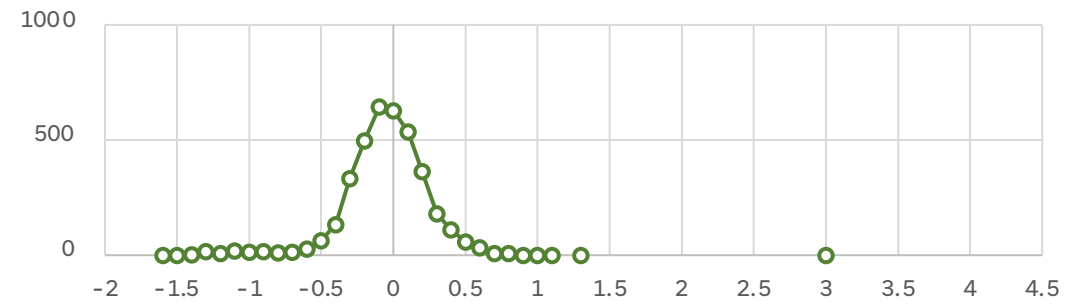
*Mean of the z-score standardized log<sub>2</sub> transformation of the expression value of genes*

# Methods – Cellular Senescence Measure

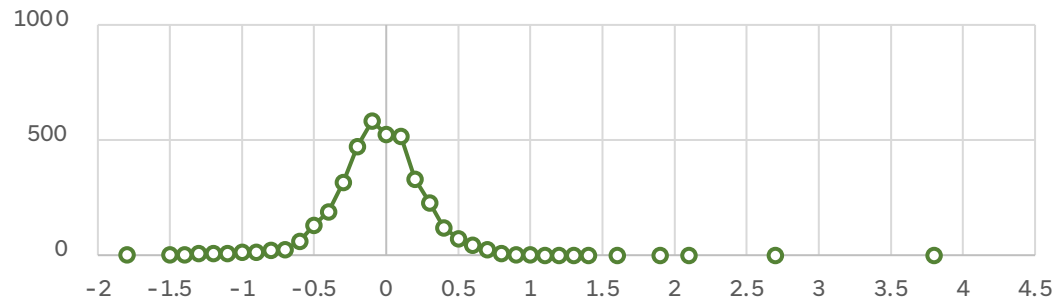
## CCA



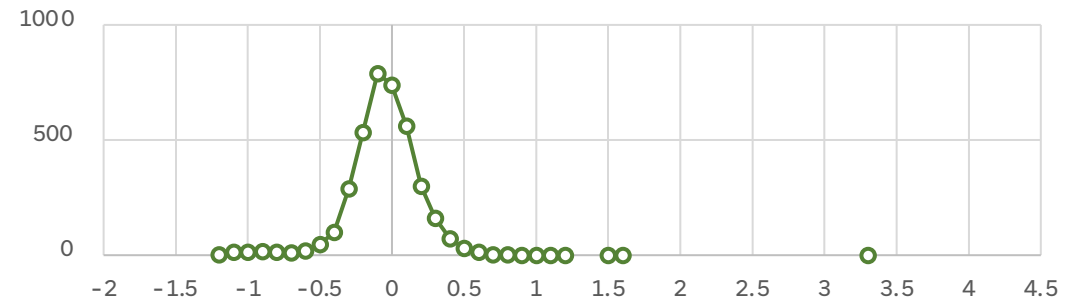
## MD



## SASP



## Summary Score



# Methods – Other Aging Measures

## Molecular/Cellular Aging

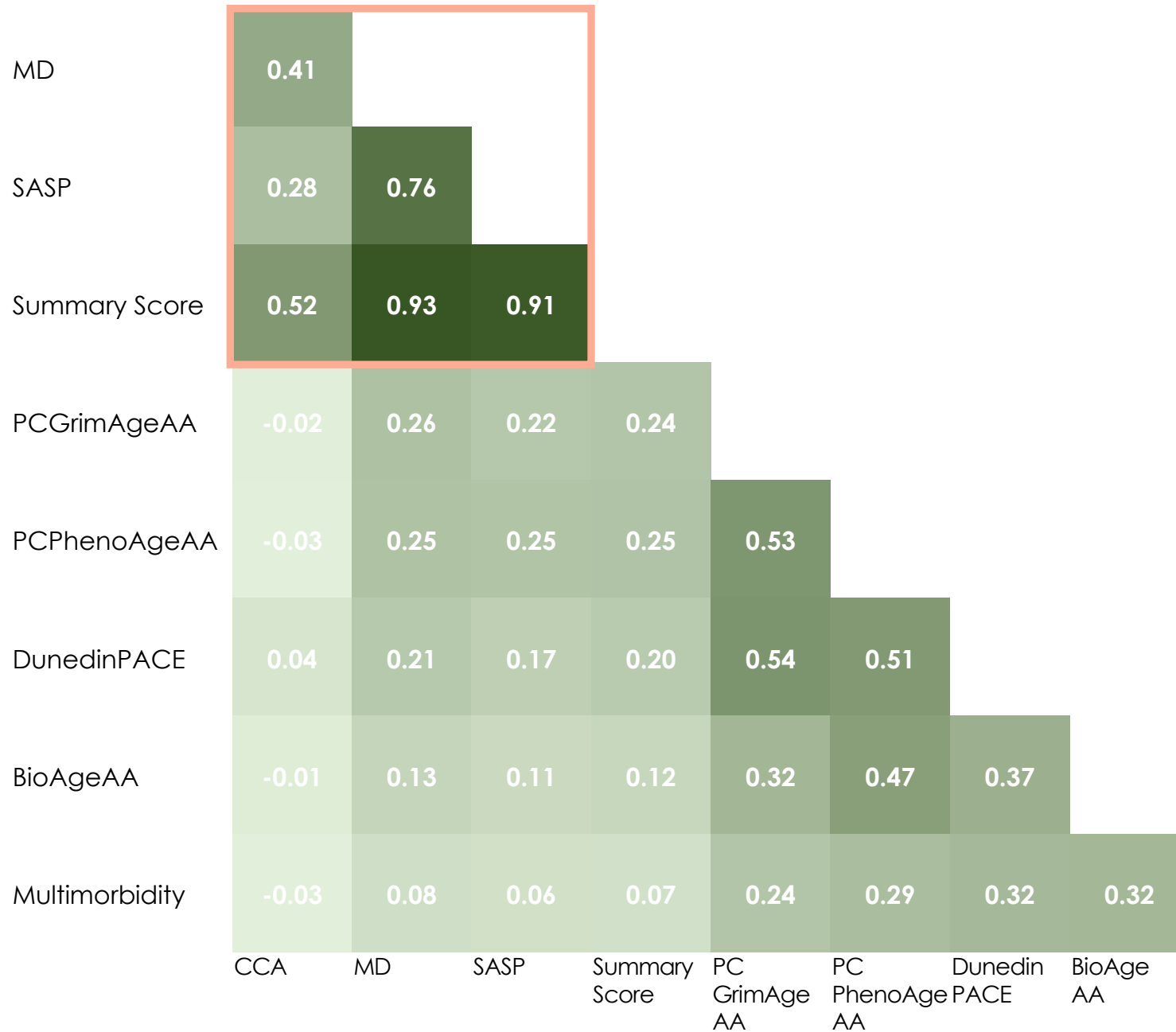
- **Epigenetic Aging Measures** – DNA-methylation-based measures, including age acceleration of the principal component versions of GrimAge and PhenoAge, and DunedinPACE.

## Physiological Dysregulation

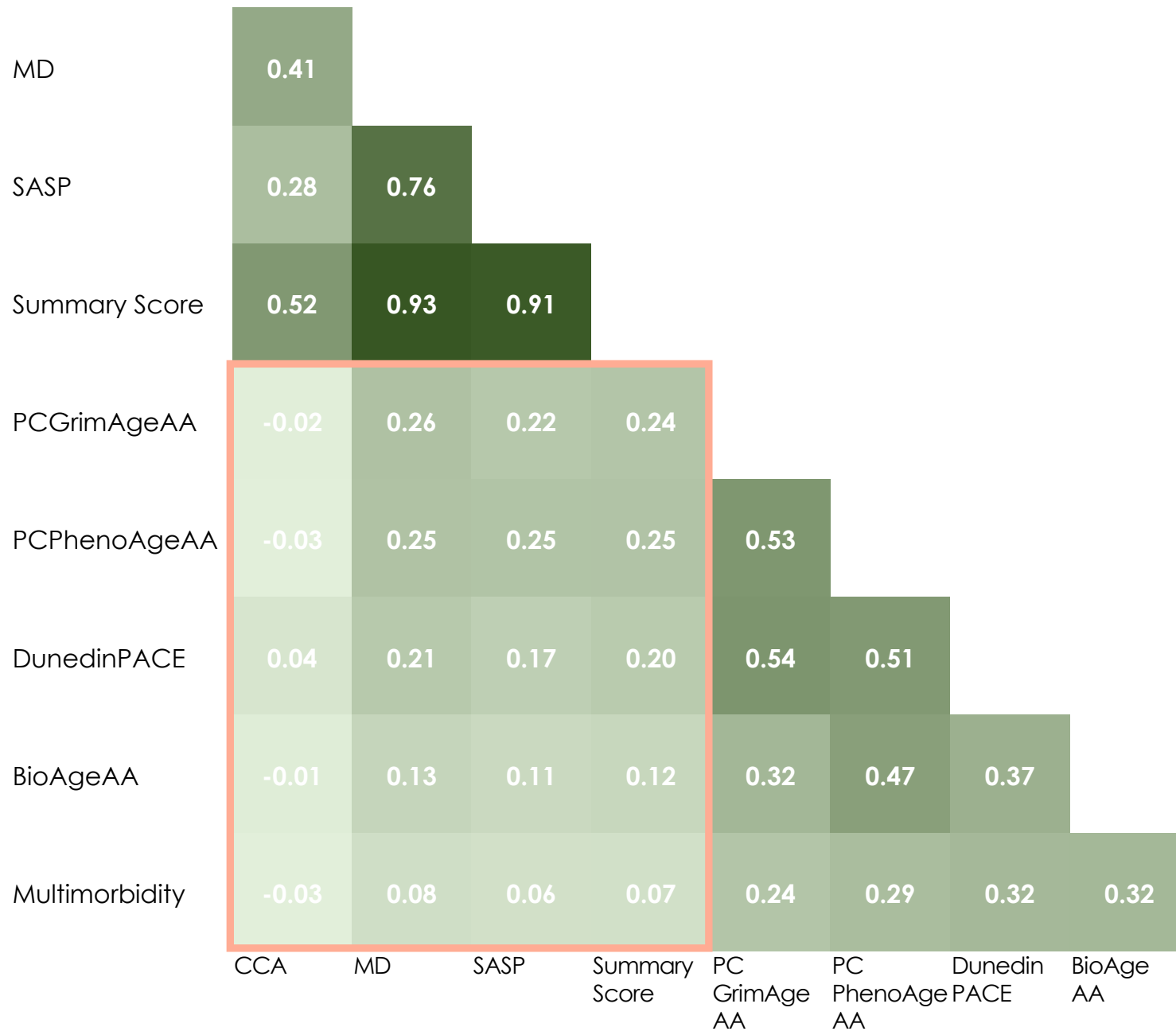
- **Expanded Biological Age Acceleration (in years)** – An overall measure of an individual's physiological status based on 22 biomarkers.

## Health Outcomes

- **Multimorbidity (0-5)** – The sum of the Doctor's diagnosis of cancer, diabetes, heart problems, lung disease, and stroke.
- **Mortality** – Four-year mortality based on 2020 vital status.



- Senescence scores are correlated overall.
- The senescence summary score is mainly driven by MD and SASP.
- Correlations between senescence scores and other aging measures/outcomes are generally weak.



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# Methods – Social-Behavioral Measures

**Age** – Age Groups: 55-64, 65-74, 75-84, 85+

**Education** – Education Groups: Less than high school, high school, some college, college and higher

**Alcohol Consumption** – Total Drinks Weekly: Days drinking per week \* number of drinks per day

**Smoking** – Lifetime exposure to smoking: Average daily packs in a year \* years of smoking

**Body Mass Index (BMI) Categories** – Based on measured values, and self-report is used when measured values are not available. Respondents are categorized into normal ( $BMI < 25$ ), overweight ( $25 \leq BMI < 30$ ), obesity I ( $30 \leq BMI < 35$ ), and obesity II ( $BMI \geq 35$ ).

**Insomnia Symptoms** – A combined measure of sleep disturbance with non-restorative sleep

**Technical Controls** – Batch/Plate and cell type

# Sample Characteristics

	Mean (SD) / Proportion N=3,580		Mean (SD) / Proportion N=3,580
<b>Senescence Scores</b>		<b>Total Drinks Weekly</b>	<b>2.9 (6.3)</b>
Summary Score	0.0 (0.2)	<b>Cumulative Packs Smoked</b>	<b>13.1 (20.7)</b>
CCA Score	0.0 (0.2)	<b>BMI</b>	<b>29.4 (6.6)</b>
MD Score	0.0 (0.3)	Normal	23.8
SASP Score	0.0 (0.3)	Overweight	37.4
<b>Age</b>	<b>68.6 (9.2)</b>	Obesity I	<b>22.7</b>
Aged 55-64	40.5	Obesity II	<b>16.2</b>
Aged 65-74	35.2	<b>Insomnia Symptoms</b>	<b>20.4</b>
Aged 75-84	17.2	<b>4-Year Mortality (N=3,575)</b>	<b>9.8</b>
Aged 85+	7.1	<b>Multimorbidity</b>	0.8 (1.0)
<b>Female</b>	<b>54.4</b>	Diabetes	25.5
<b>Race Ethnicity</b>		Cancer	14.6
Non-Hispanic White	<b>77.5</b>	Lung Disease	11.0
Non-Hispanic Black	10.2	Heart Problems	25.0
Hispanic	8.9	Stroke	8.1
Non-Hispanic Other	3.3	<b>Expanded BioAge (N=2,660)</b>	68.2 (11.7)
<b>Education</b>		<b>Expanded BioAge AA (N=2,660)</b>	0.0 (8.1)
Years of Education	<b>13.3 (3.0)</b>	<b>PC GrimAge</b>	77.3 (8.0)
Less than High School	14.0	<b>PC PhenoAge</b>	66.0 (10.6)
High School	29.9	<b>DunedinPACE</b>	1.0 (0.1)
Some College	25.9	<b>PC GrimAge AA</b>	0.0 (4.0)
College and Higher	30.2	<b>PC PhenoAge AA</b>	0.0 (6.5)

- A representative sample of older Americans.
- Includes people who regularly consume alcohol and smoke cigarettes.
- On average overweight.
- More than one-third are obese.
- About one-fifth have sleep problems.
- Around 10% died within 4 years. Many have chronic conditions.

## Some social and behavioral factors are significantly associated with RNA scores

N=3,580	CCA	MD	SASP	Sum Score
<b>Age: Ref - Aged 55-64</b>				
Aged 65-74	-0.04	0.01	0.03*	0.01
Aged 75-84	-0.06***	0.04**	0.07***	0.04***
Aged 85+	-0.07***	0.01	0.04**	0.01
<b>Female</b>	0.19***	0.05***	0.12***	0.12***
<b>RE: Ref - Non-Hispanic White</b>				
Non-Hispanic Black	0.12***	0.06***	0.03*	0.07***
Hispanic	-0.02	0.01	0.01	0.00
Non-Hispanic Other	0.00	0.01	0.00	0.01
<b>Education: Ref - Less than High School</b>				
High School	-0.03	-0.01	0.02	0.00
Some College	-0.01	-0.02	0.00	-0.01
College and Higher	-0.02	-0.06**	-0.01	-0.04*
<b>BMI: Ref - Normal</b>				
Overweight	0.01	0.03*	0.01	0.02
Obese I	0.01	0.06***	0.01	0.04**
Obese II	0.03	0.08***	0.06***	0.08***
<b>Cumulative Packs Smoked</b>	0.03	0.02	0.00	0.02
<b>Total Drinks Weekly</b>	0.03	-0.01	0.00	0.00
<b>Insomnia Symptoms</b>	0.01	0.02	0.00	0.01
<b>Adjusted R2</b>	0.22	0.66	0.55	0.60

\* p<0.05, \*\* p<0.01, \*\*\* p<0.001

Older ages  
Female sex



Non-Hispanic Blacks  
(Ref: Non-Hispanic Whites)



College and Higher  
(Ref: Less than high School)

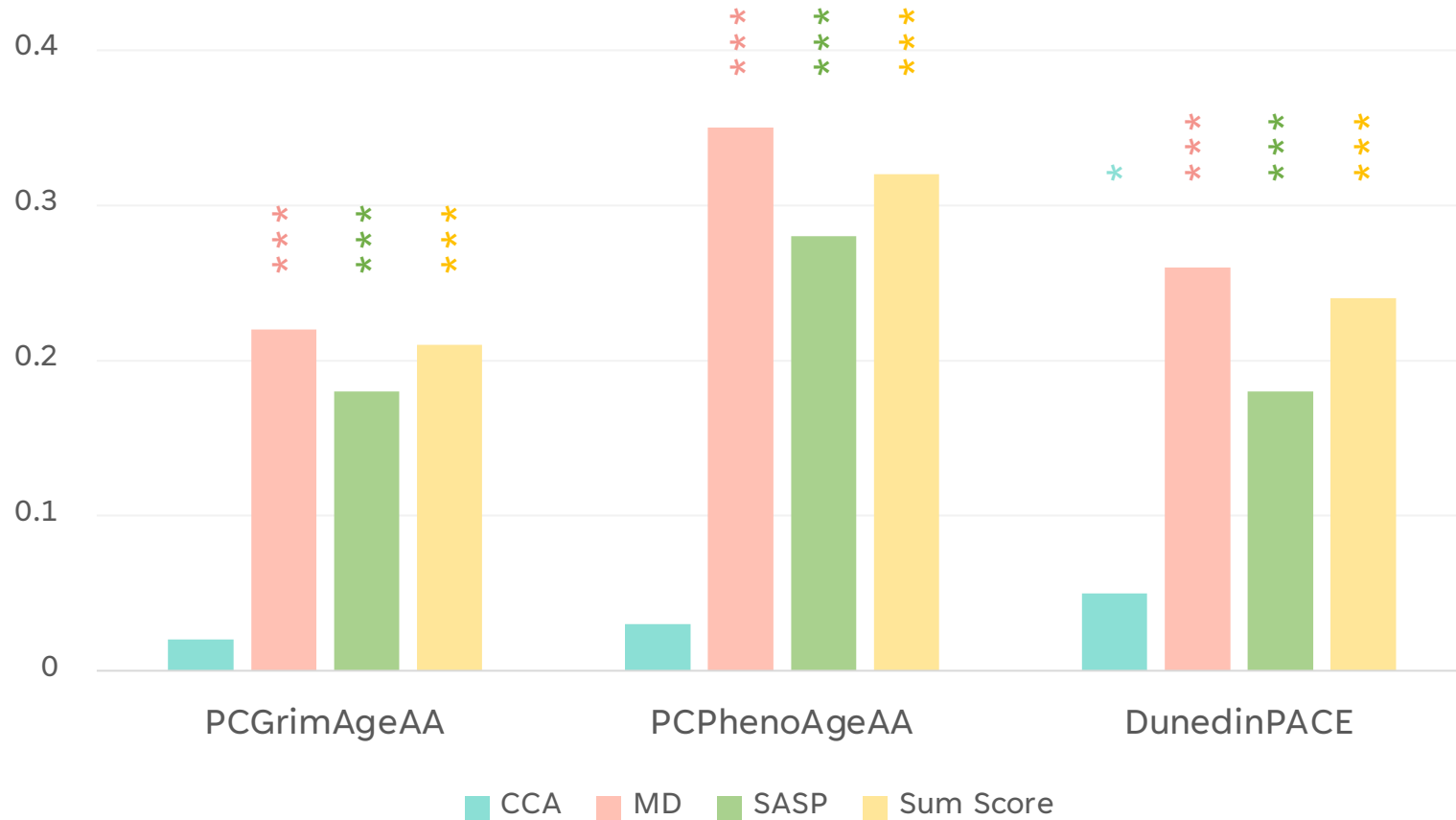


Higher BMI Groups  
(Ref: Normal BMI)





**Overall, our cellular senescence RNA scores are significantly associated with other *upstream* biological mechanisms - three epigenetic aging measures**



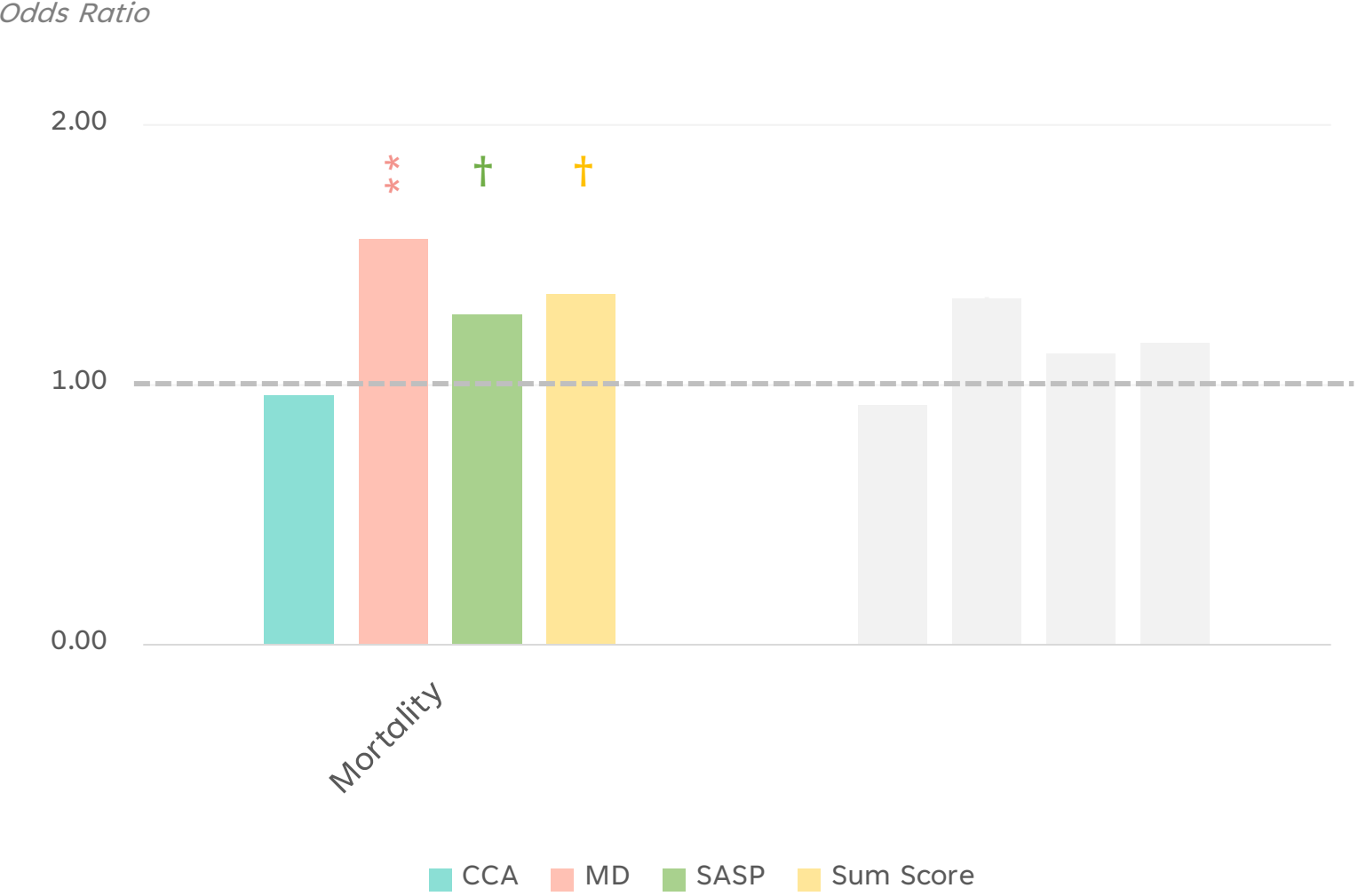
† p<0.1 \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

After controlling for covariates

MD, SASP, and the summary score are all significantly associated with the epigenetic measures. CCA is only associated with DunedinPACE.

All models are adjusted for all covariates, patch/plate, and cell types.

# The Macromolecular Damage score is significantly associated with *Four-Year Mortality*



† p<0.1 \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

Only MD is significantly associated with 4-yr mortality.

All models are adjusted for all covariates, patch/plate, and cell types.

# The Macromolecular Damage score is significantly associated with *Four-Year Mortality*

Odds Ratio



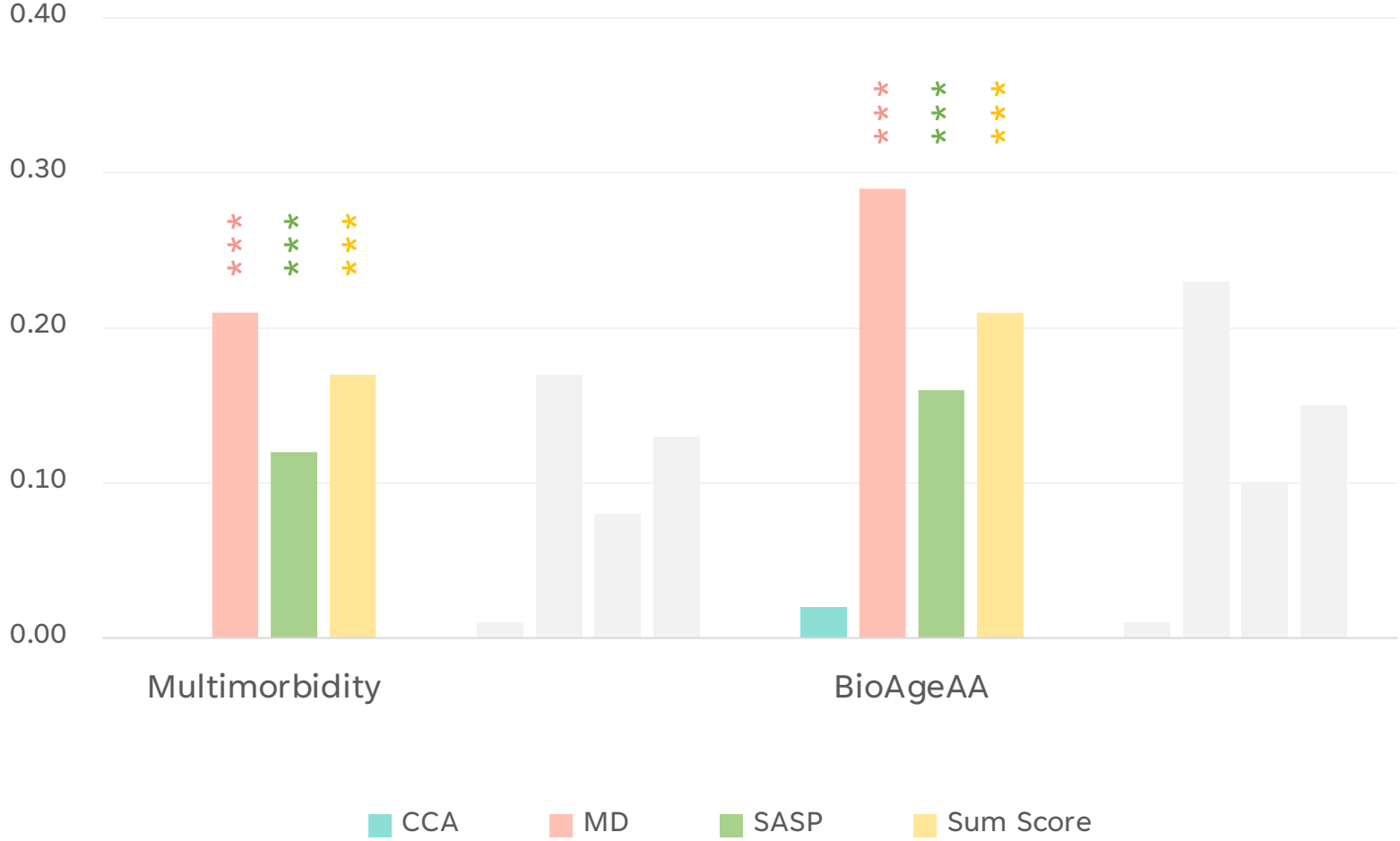
† p<0.1 \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

After controlling for PC GrimAge acceleration, the size of the coefficient reduced, and was only marginally significant.

All models are adjusted for all covariates, patch/plate, and cell types.

**Overall, our cellular senescence RNA scores are significantly associated with *multimorbidity and physiological dysregulation, with and without adjusted for epigenetic aging***

Beta Coefficient



All RNA scores are significantly associated with multimorbidity and biological age acceleration, except for the CCA score.

The associations remain significant after including the epigenetic aging measure (PC GrimAge AA) in the models.

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**Overall, our cellular senescence RNA scores are significantly associated with *multimorbidity and physiological dysregulation*, with and without adjusted for epigenetic aging**

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All models are adjusted for all covariates, patch/plate, and cell types.

# Conclusion

- **Social & behavioral factors:** Older people, women, non-Hispanic Blacks, and those with high BMI have a higher level of cellular senescence. High education level (high SES) seems to be a protective factor.
- **Other upstream aging measures:** Our cellular senescence RNA scores are significantly associated with epigenetic age acceleration.
- **Downstream aging measures:** Cellular senescence summary score links to physiological dysregulation and multimorbidity, but not 4-year mortality, and the associations are driven by the MD and SASP scores, not the CCA score.
- **Cellular senescence RNA scores capture multiple dimensions of aging in a useful way and add to our understanding of aging-related physiological changes and diseases.**

# Thanks!

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