



Development of a novel transcriptomic measure of aging: Transcriptomic Mortality-risk Age (TraMA)

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INTRO & BACKGROUND

- Aging may be a coordinated multi-system decline in functioning that occurs at multiple biological levels
- Development of biomarkers of this aging process is a major goal of Geroscience agenda
- Past transcriptomic (RNA-based) aging measures have been developed
 - Mostly developed using array data, small, specialty samples, or in tissue other than blood
 - Proliferation of research utilizing next-gen high throughput RNA sequencing (RNAseq)
 - Large number of large population-based surveys are collecting large RNAseq samples
- A reliable summary measure of accelerated transcriptomic aging is needed

INTRO & BACKGROUND

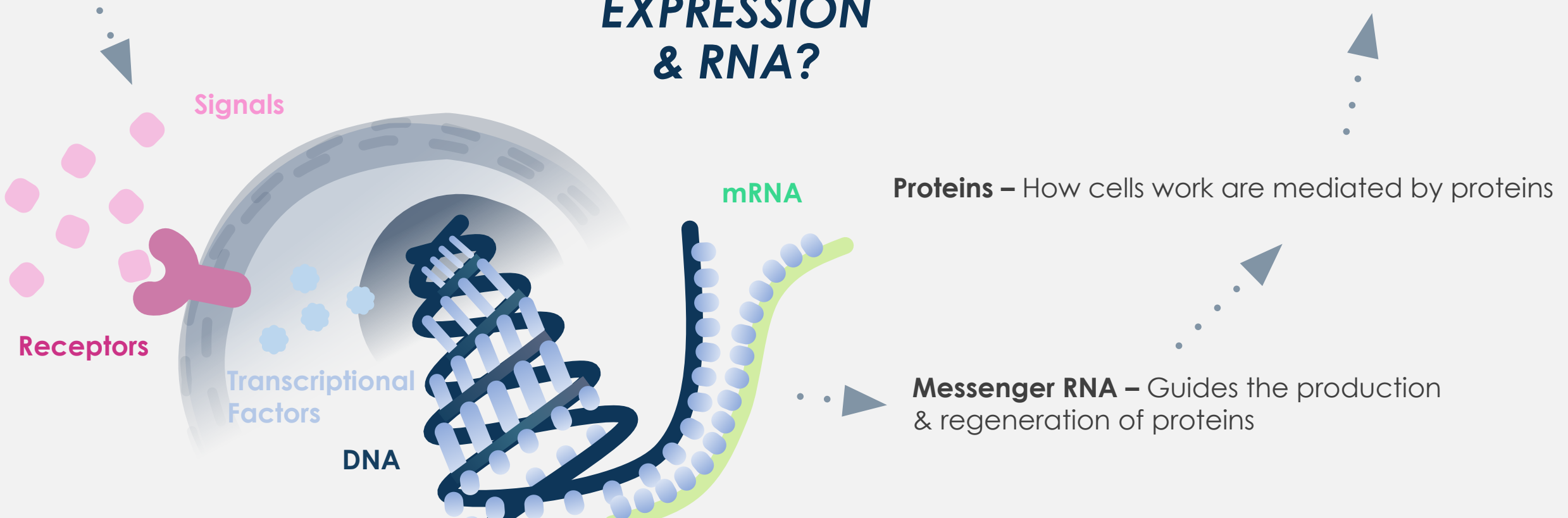
Social & Environmental Factors

- Chemical / Microbial Exposures
- Central Nervous / Peripheral Nervous / Endocrine Systems Response to Stress / Stimulus
- Cell Secretory Response to Damage / Stress

How do sociodemographic and biobehavioral factors get under the skin and ultimately affect health outcomes?

WHY GENE EXPRESSION & RNA?

Physiological Changes



DATA

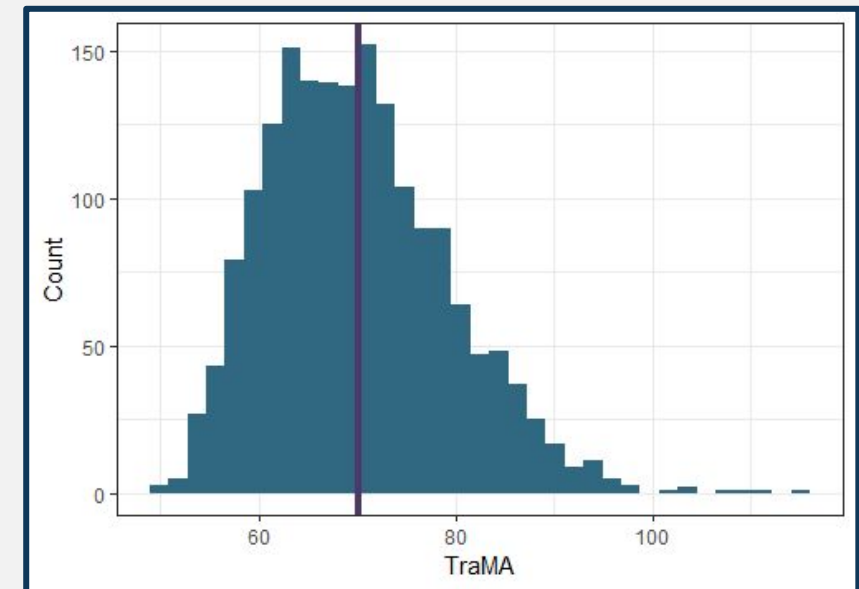
- 2016 HRS Venous Blood Study – RNA subsample with mortality data (VBS; N = 3595)
- 407 Deaths
- Certified phlebotomists collected 2.5 mL of blood from consenting participants using a PAXgene RNA tube
 - Processed at the University of Minnesota Genomic Center
 - TOPmed pipeline (see https://github.com/broadinstitute/gtex-pipeline/blob/master/TOPMed_RNAs_eq_pipeline.md)
 - Log2 adjusted counts per million were used in all analyses.

TRAINING TraMA

- Elastic net regression predicting 4-year survival (Cox estimator)
- Training sub sample (N = 1801)
- Features: 50,611 genes, age, and sex
- Hyperparameters selected using 5x cross validation (alpha = 0.729; lambda = 0.039)
- 39 genes and chronological age were selected from among the features

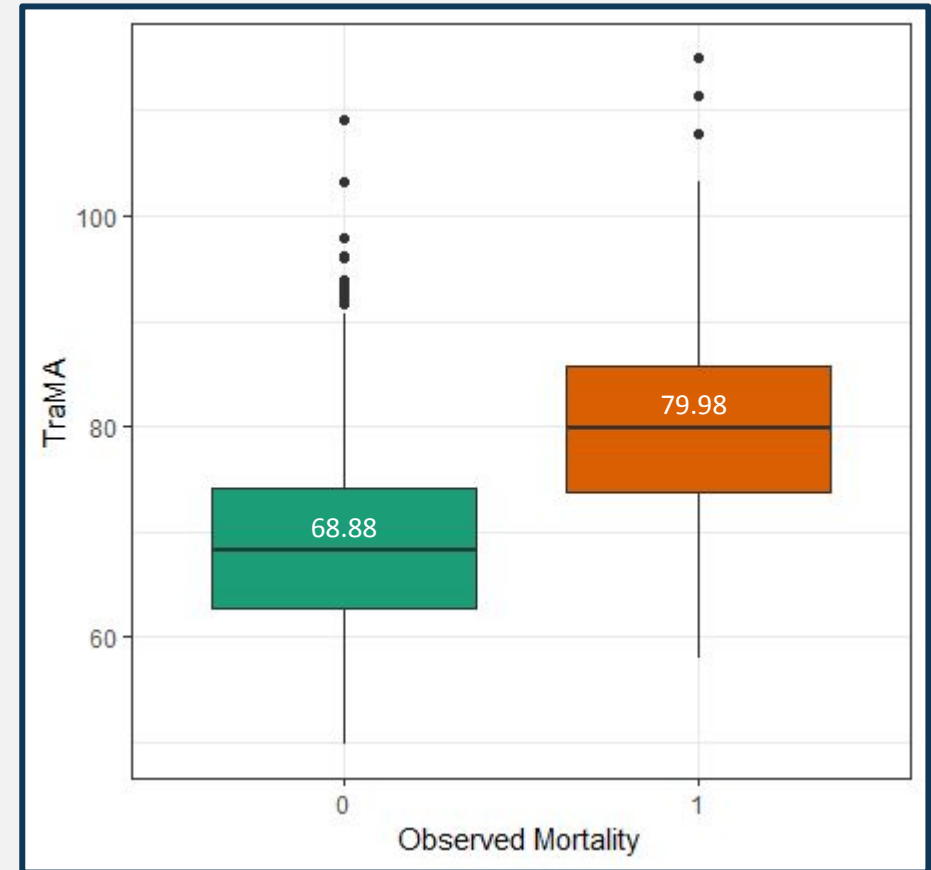
CALCULATING TraMA

- Evaluated in a testing set (N = 1794)
- Using the weights developed in the training data, we estimated TraMA scores in the testing data
- $\text{TraMA}_i = \beta_{\text{age}} \cdot \text{AGE}_i + \beta_{\text{geneX}} \cdot \text{GENEX}_i [\dots] + \beta_{\text{geneK}} \cdot \text{GENEK}_i$
- The metric is years of life
 - Transformed to have same mean and variance as HRS testing set

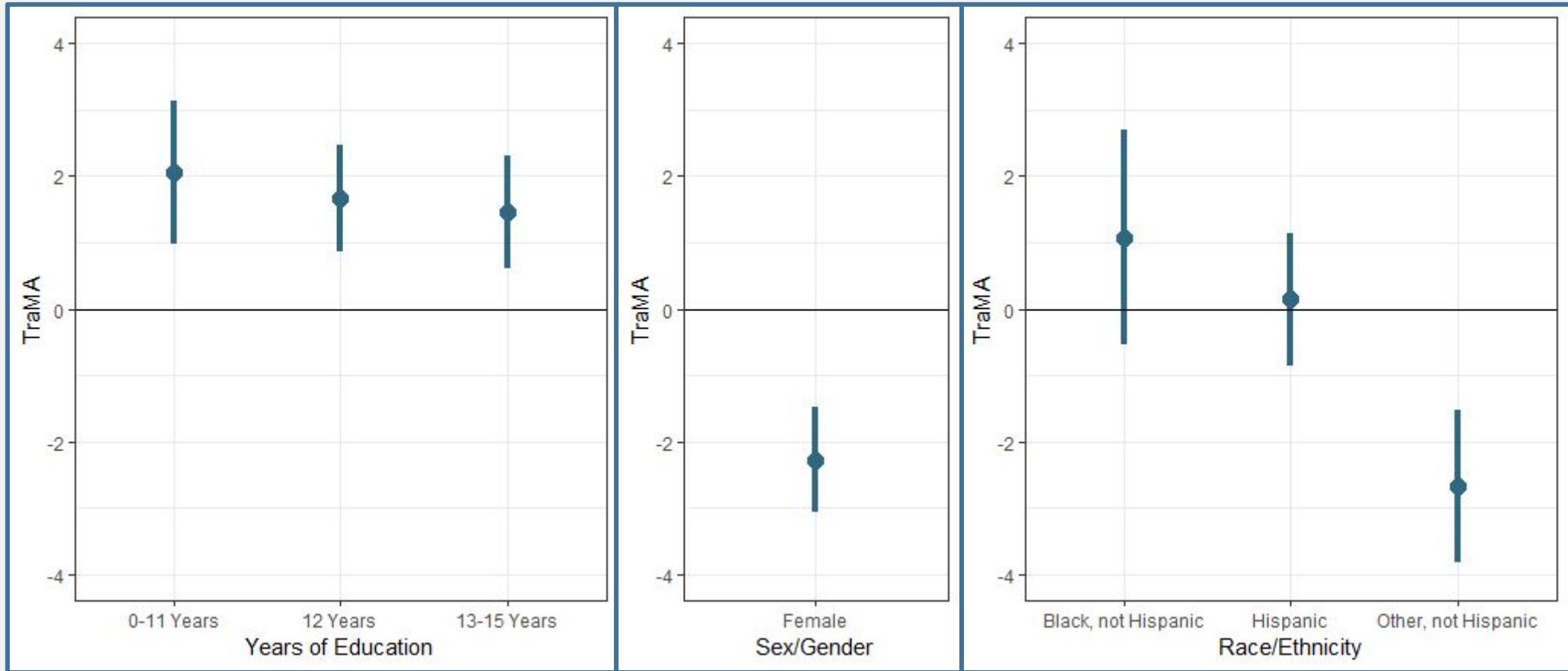


EVALUATING TraMA

- In testing data, TraMA was associated with mortality hazard in the testing subsample (Harrel's C index = 0.80)
- Participants who died between 2016 data collection and 2020 data collection had a mean TraMA 11.1 years older than those who did not (p from t-test < .001)

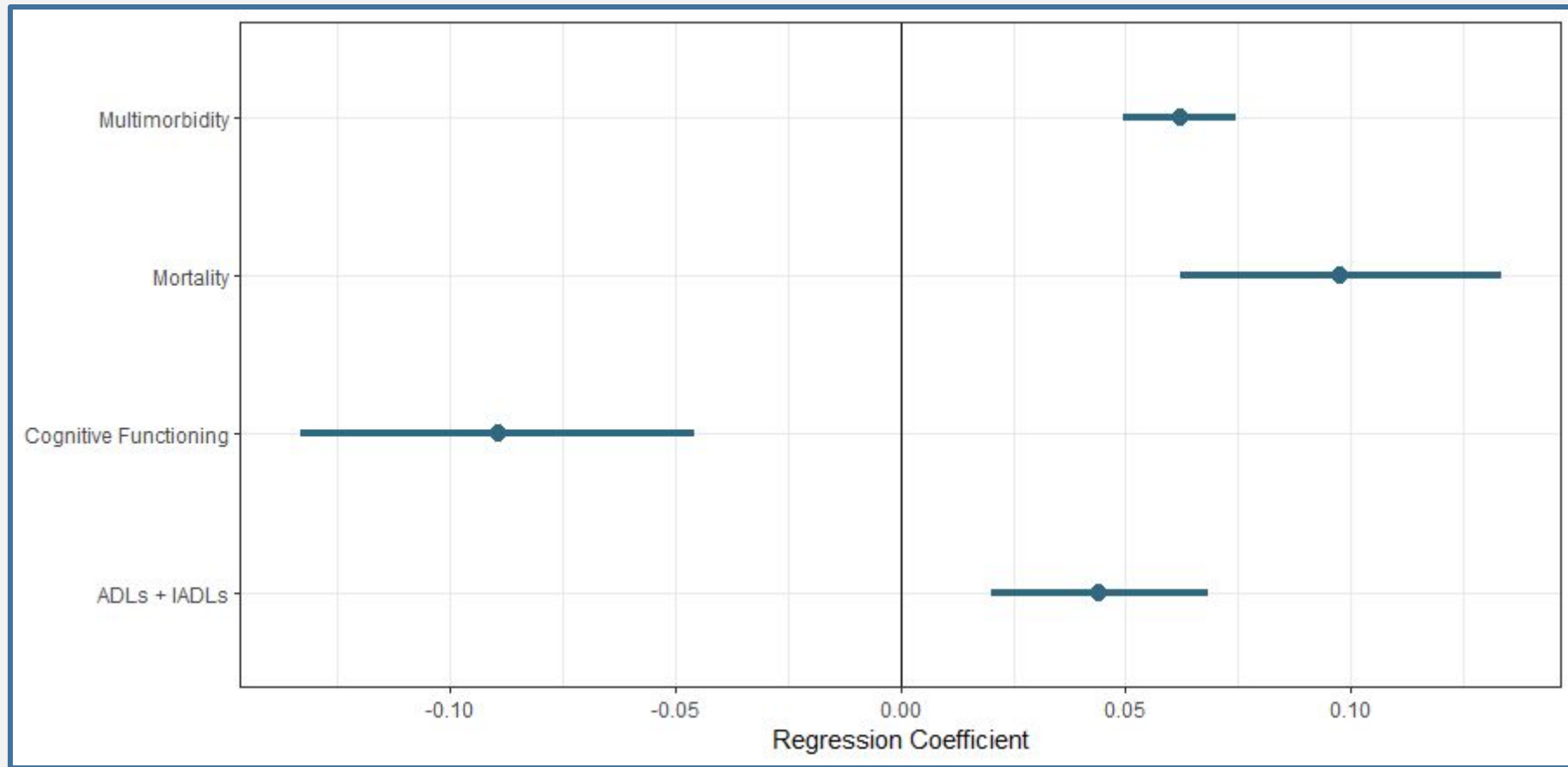


TraMA IS ASSOCIATED WITH SOCIAL & DEMOGRAPHIC FACTORS



***Controlling for age

TraMA IS ASSOCIATED WITH FOUR AGE-RELATED HEALTH OUTCOMES



***Controlling for age, race, and gender

LIMITATIONS AND FUTURE DIRECTIONS

- Limitations
 - All older adults
 - RNA only collected at one time
- Future steps
 - Replication in large cohort studies

THANK YOU

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