Premature Aging among Survivors of Childhood Cancer

POGO After Care Education Day
2024

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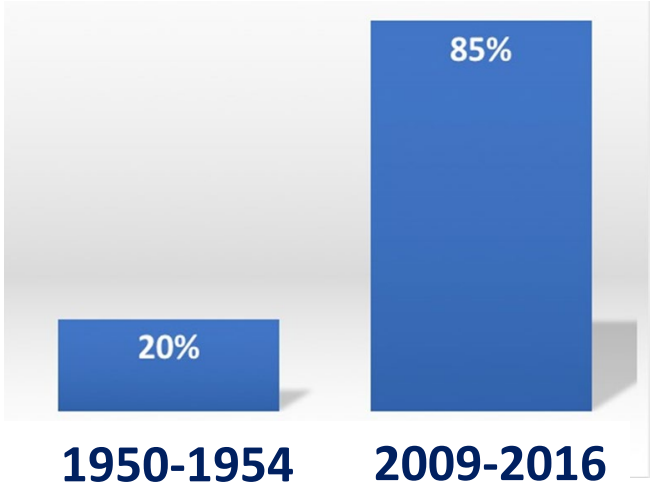
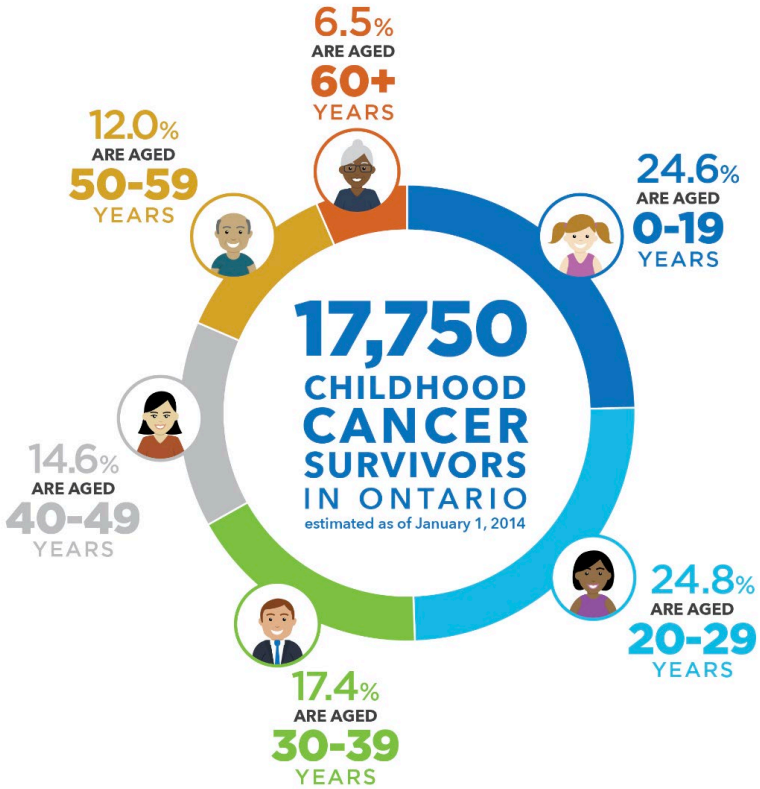
UR MEDICINE | WILMOT CANCER INSTITUTE

Childhood Cancer in the U.S. & Canada

5-year Relative Survival of Childhood Cancer Patients

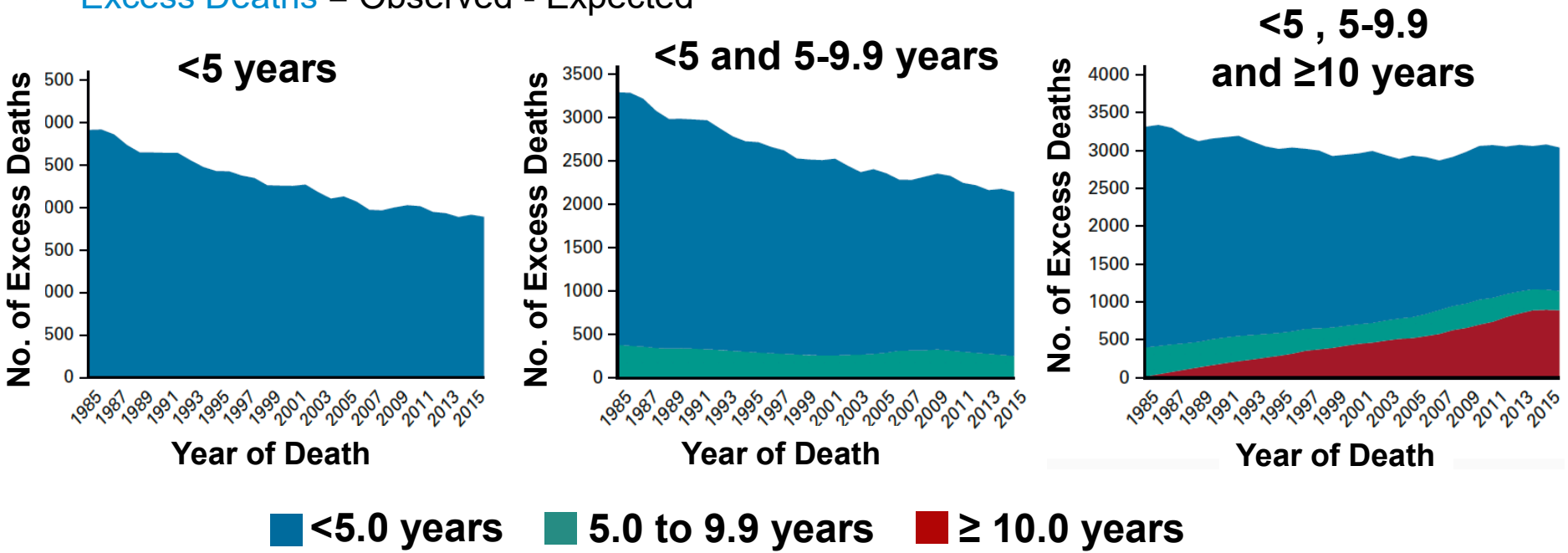




https://health-infobase.canada.ca/data-tools/cypc/
www.pogo.ca

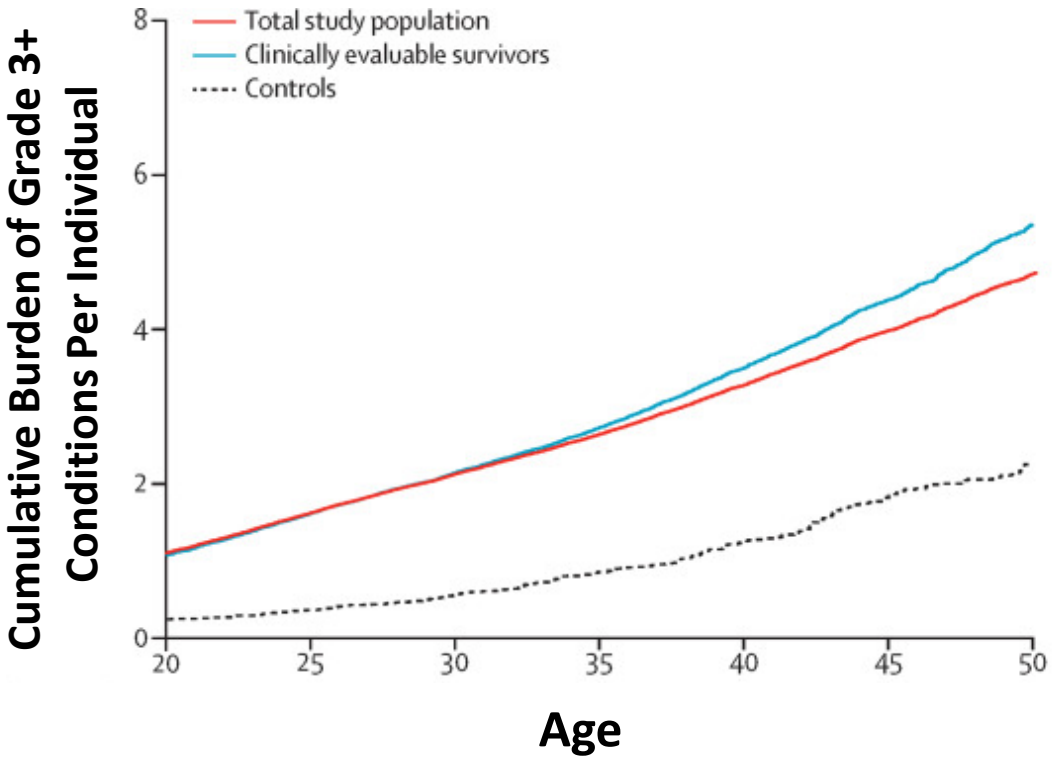
Excess Mortality

- U.S. SEER-9 registries, diagnosed age 0 to <20, between 1975 and 2016
- Excess Deaths = Observed - Expected



Williams et al, *J Clin Oncol,* 2021

Excess Morbidity

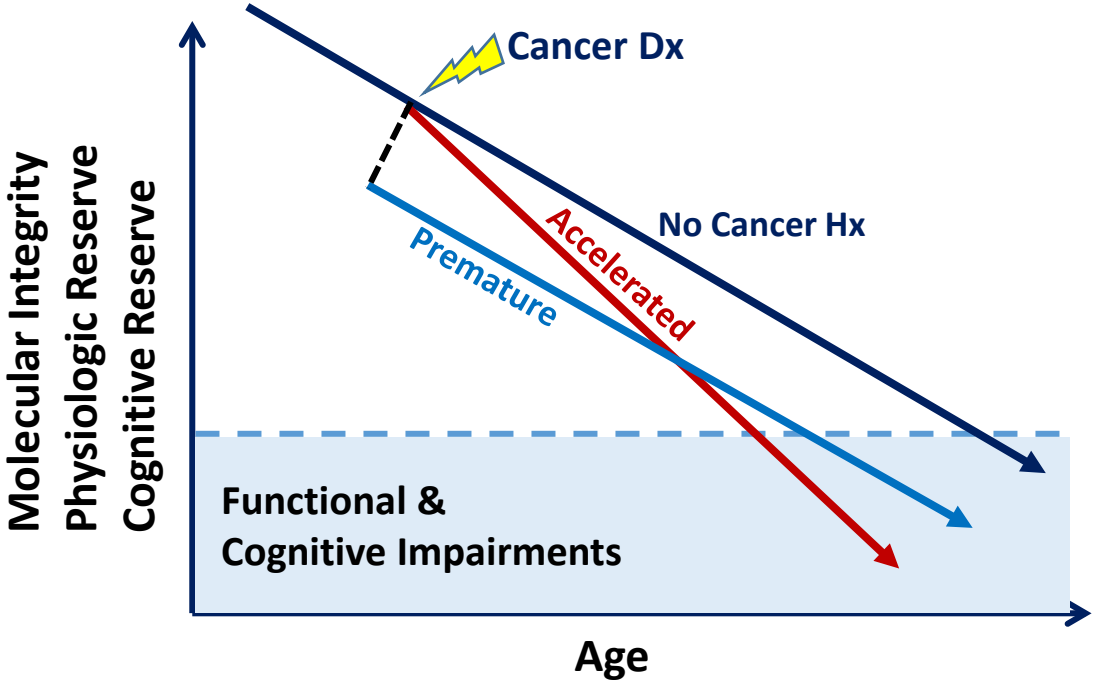


By Age 50:

- 96% with a Grade 3+ CHC
- Avg 4.7 Grade 3+ CHC

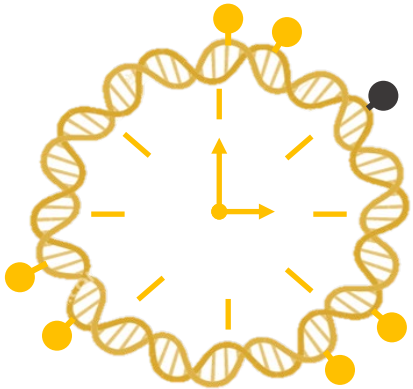
Bhakta et al, Lancet 2017

Accelerated or Premature Aging?



How can we measure aging?

Biologic



- Epigenetic Age
- Telomere Length
- Inflammation

Physiologic

- Fried's Frailty
- Deficit Accumulation
- Chronic Health Conditions

Cognitive

- Objective Neuropsychological Assessment
- Self-Reported Measures

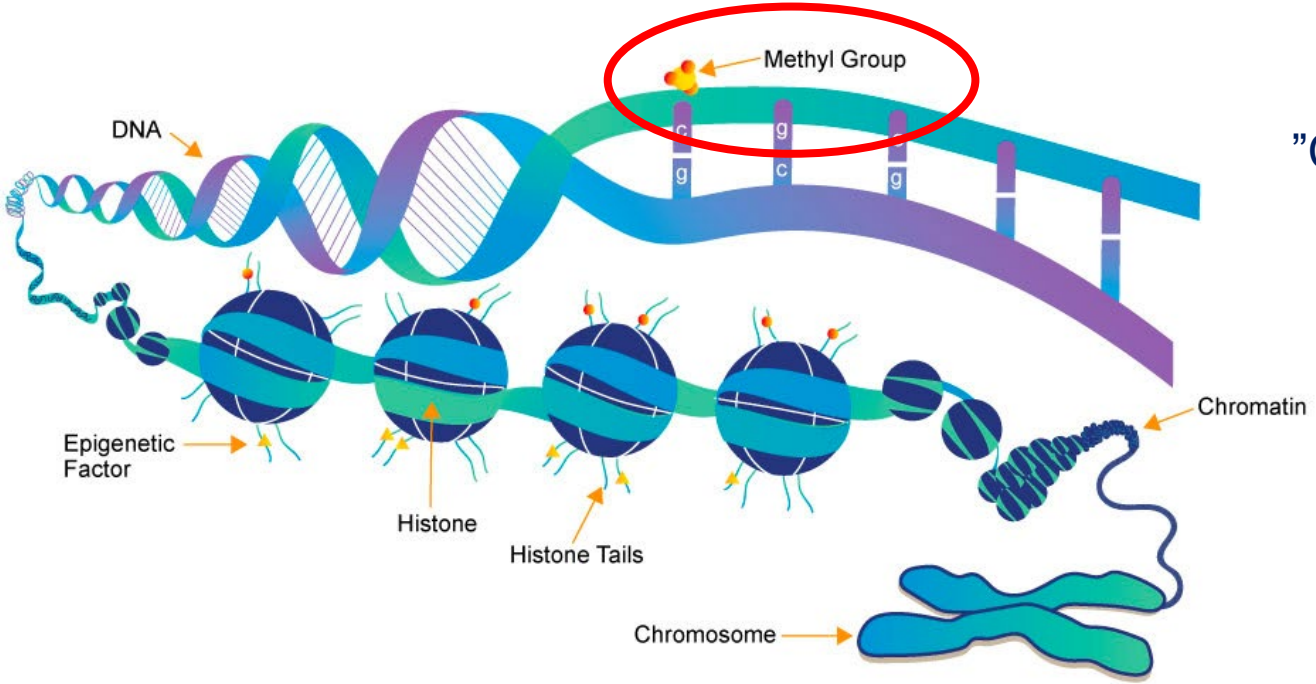
St. Jude Lifetime Cohort

- Established in 2007
- Retrospective/Prospective Cohort
- Eligibility:
  - Treated at St. Jude
  - >=5 years from diagnosis
- Detailed Treatment Data, Wide Range of Clinically Assessed Outcomes
- Non-Cancer Controls

5,000 Survivors of Pediatric Cancer

Howell et al, Clinical Cancer Research 2024

DNA Methylation

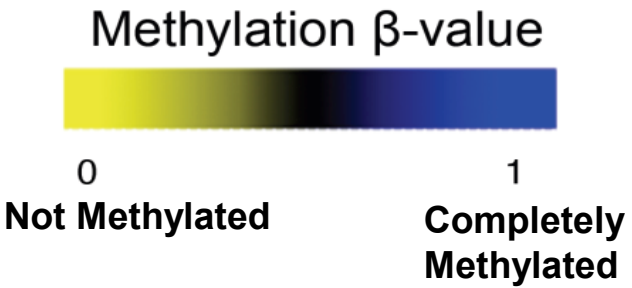


”Code” that allows for a change in phenotype without a change in genotype

DNA Methylation

SJLIFE: 2,139 Survivors 282 Controls

- **Peripheral Blood Mononuclear Cell DNA**
- **Illumina EPIC MicroArray Bead Chip: 850K CpG sites**



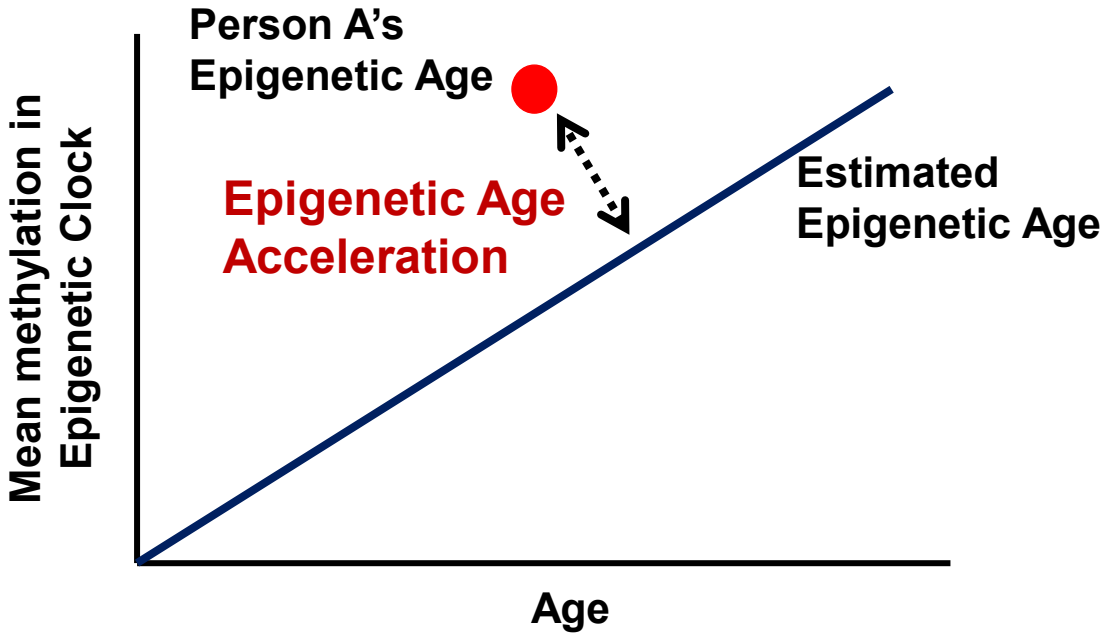
Epigenetic Age Acceleration (EAA)

Epigenetic Clocks

DNAmPhenoAge by Levine

513 CpGs

Predicts: Phenotypic Age, Mortality



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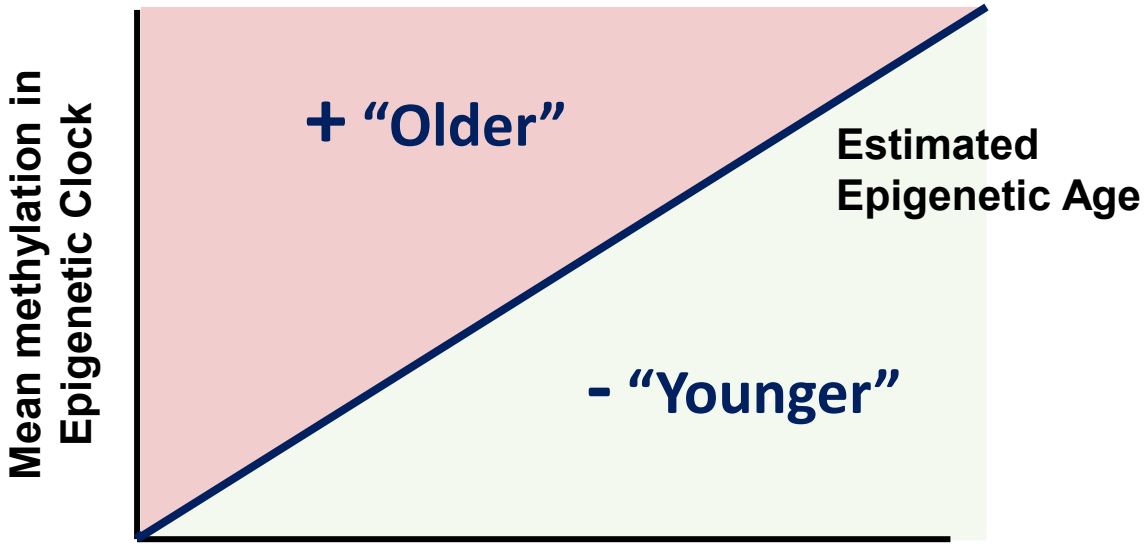

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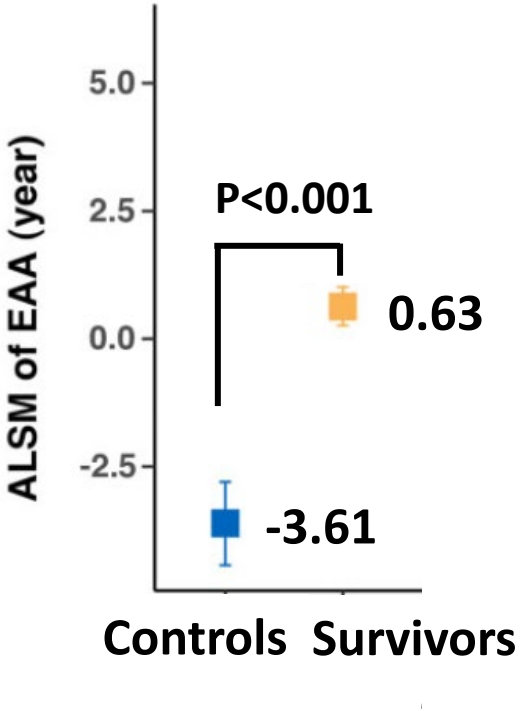
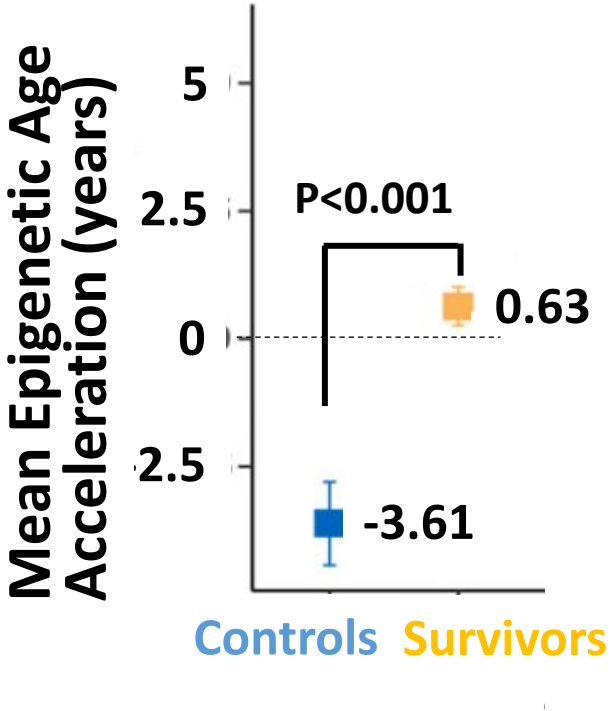
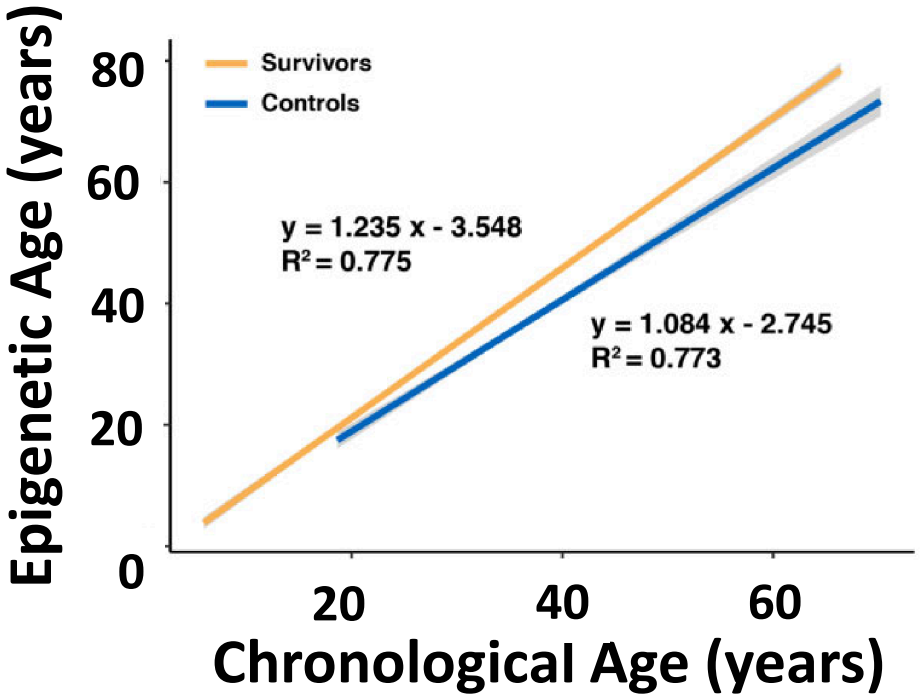


Survivors have significantly greater epigenetic age acceleration

Qin et al, JNCI 2020

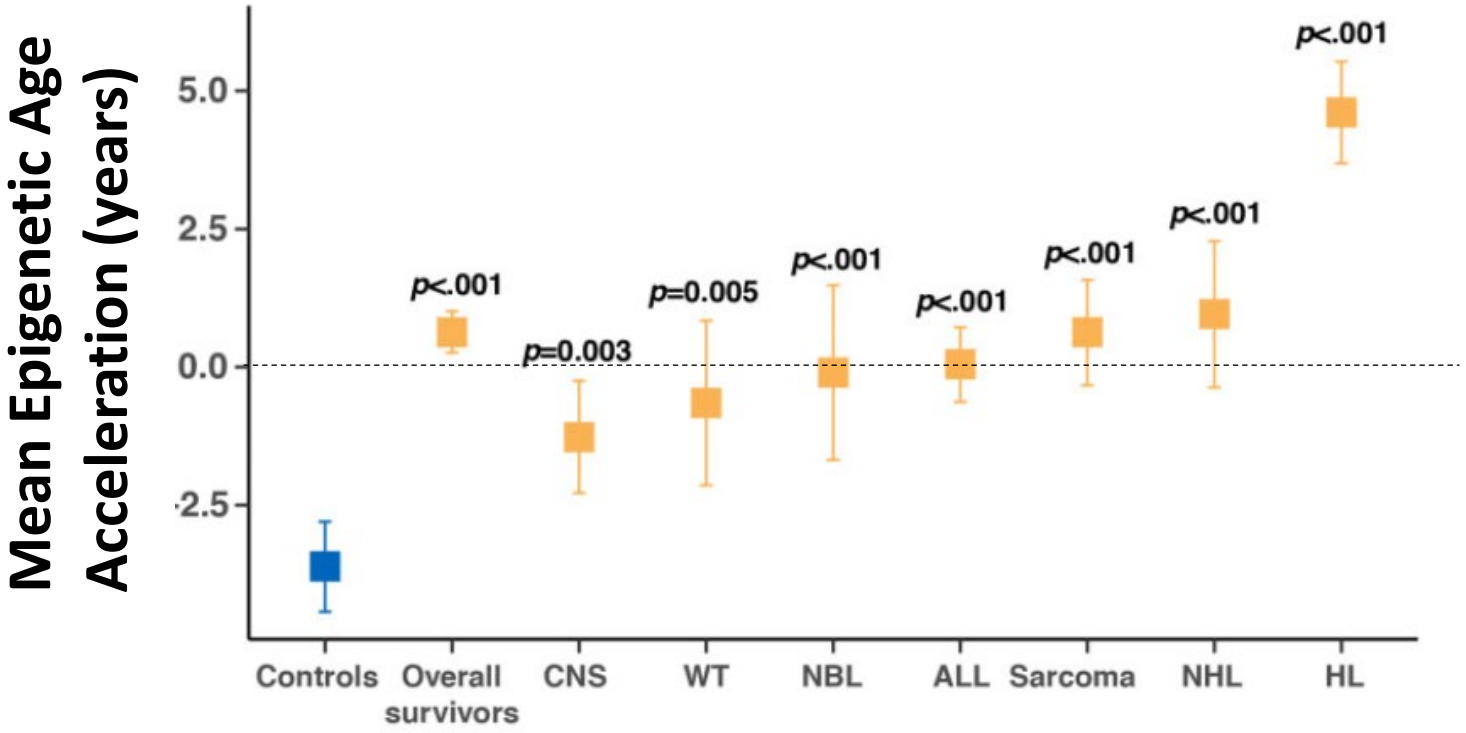
Epigenetic Age Acceleration





Qin et al, JNCI 2020

Epigenetic Age Acceleration



Qin et al, JNCI 2020

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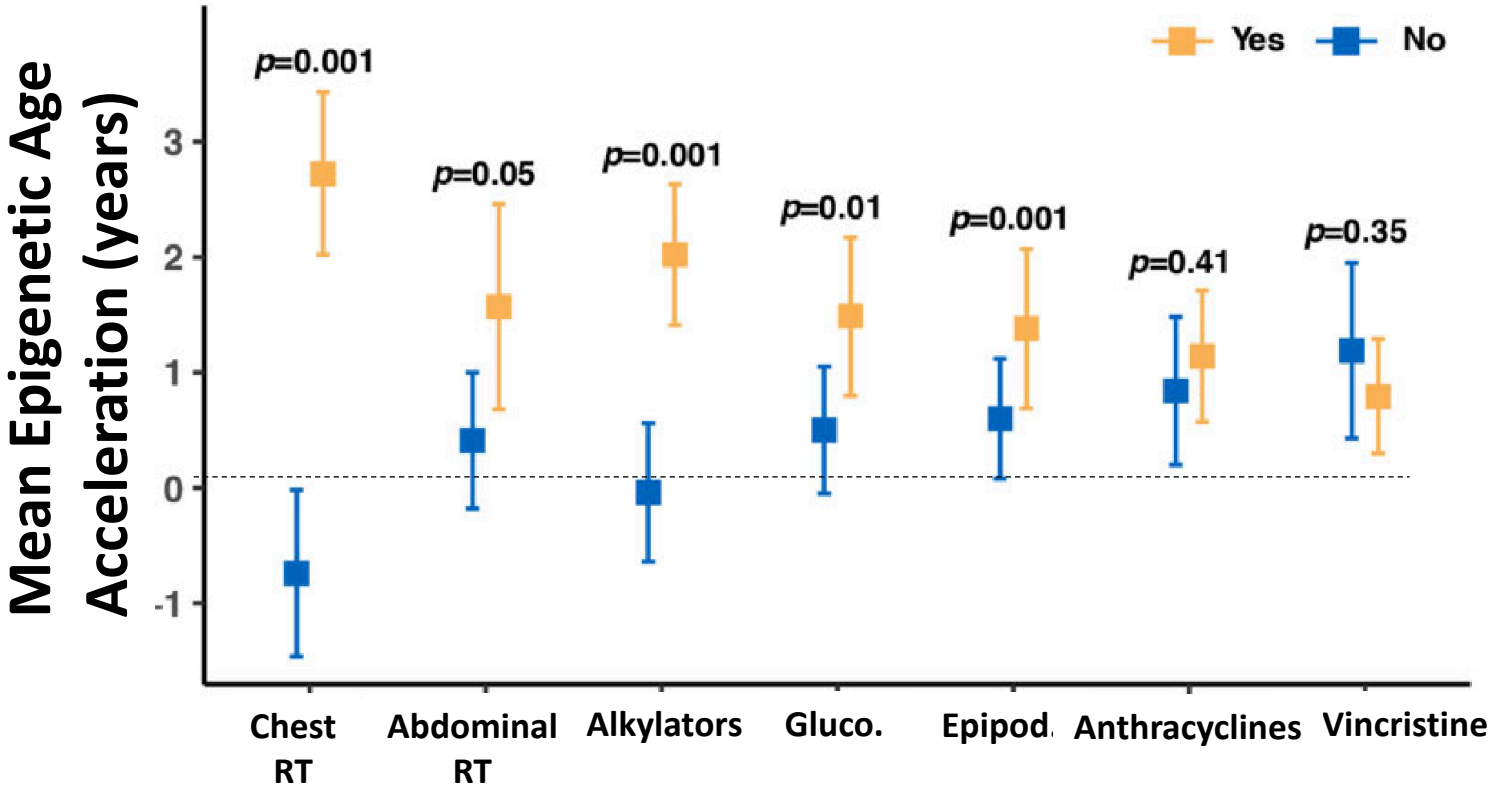


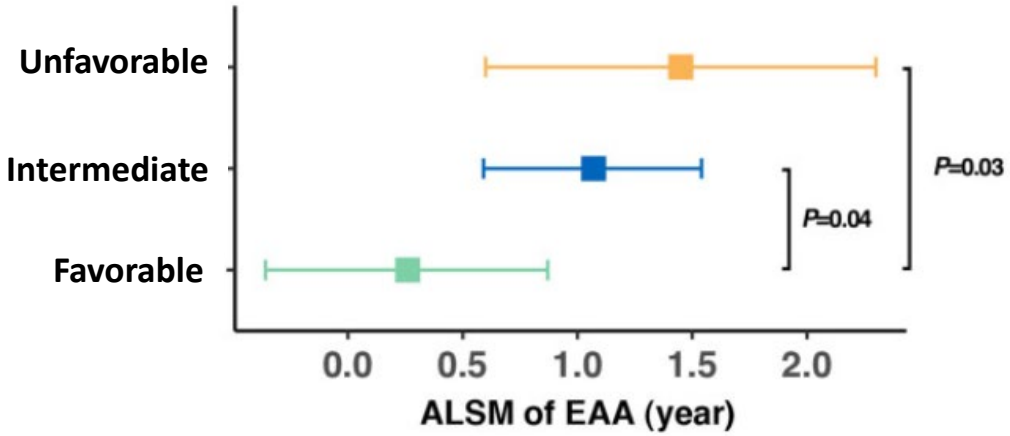
Qin et al, JNCI 2020

EAA and Chronic Health Conditions

EAA Assoc with:

- Hypertension
- MI
- Obesity
- Pulmonary disease
- Sleep apnea
- Neuropathy

Health Behaviors



Qin et al, JNCI 2020

Fried's Frailty

Physiologic Frailty

Weakness
↓ grip strength

Unintentional Weight Loss
>4.5kg in 12 months

Low Physical Activity
↓energy expenditure (kcal/wk)

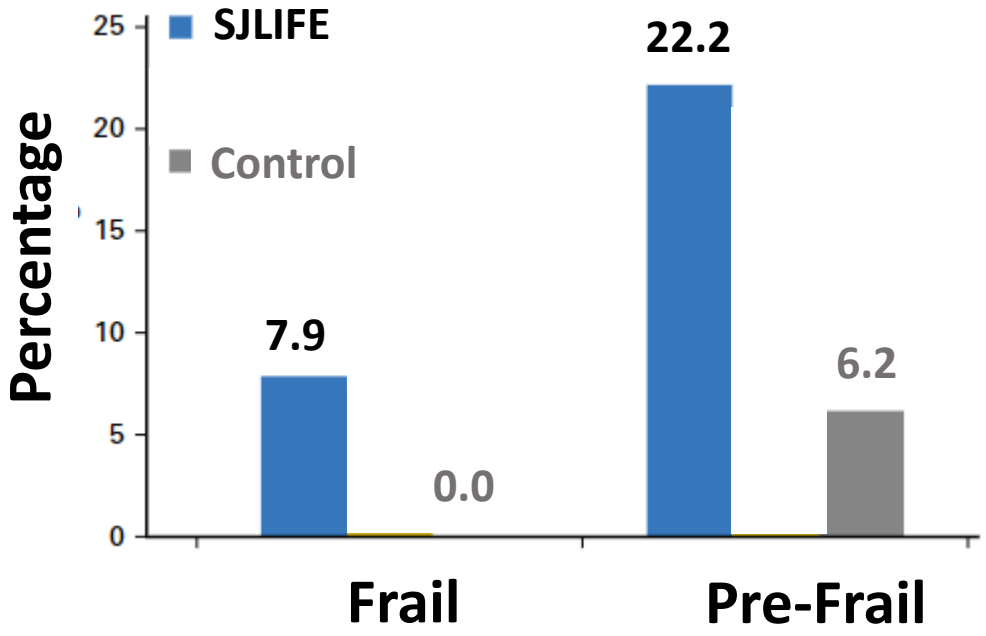
Slowness
↓walking speed

Fatigue
overall feeling of tiredness

3+ Frail
2 Pre-Frail
<2 Robust

Fried et al, J Geront A Biol Sci Med Sci 2001
Ness et al, J Clin Onc 2013

Fried's Frailty

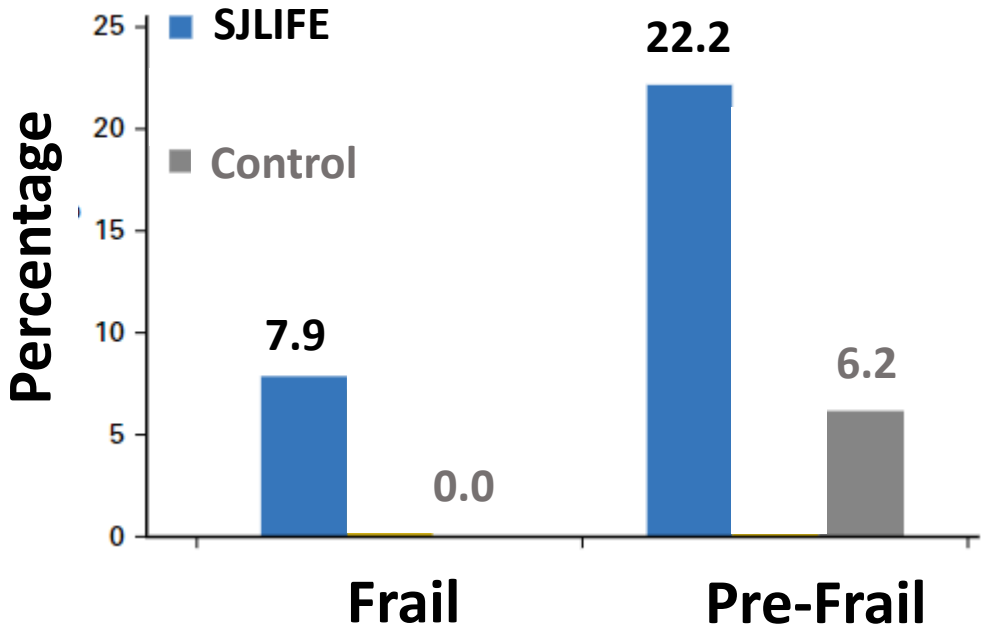


1,922 Survivors
Mean Age 34

341 Controls
Mean Age 29

Ness et al, J Clin Onc 2013 & 2018

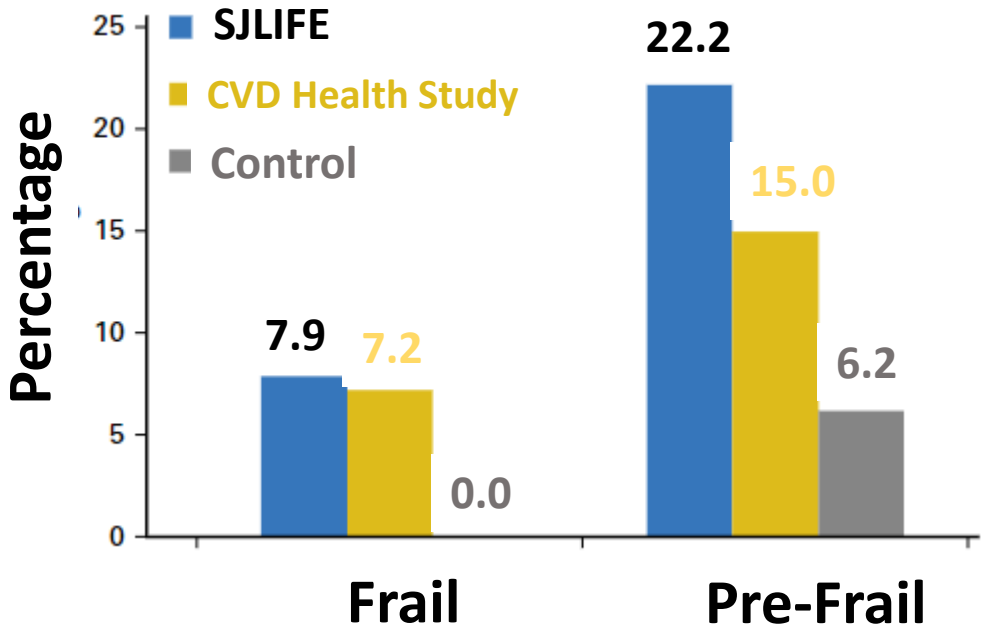
Fried's Frailty



Frailty → Mortality
HR 2.6 95%CI (1.2, 6.2)

Ness et al, J Clin Onc 2013 & 2018

Fried's Frailty



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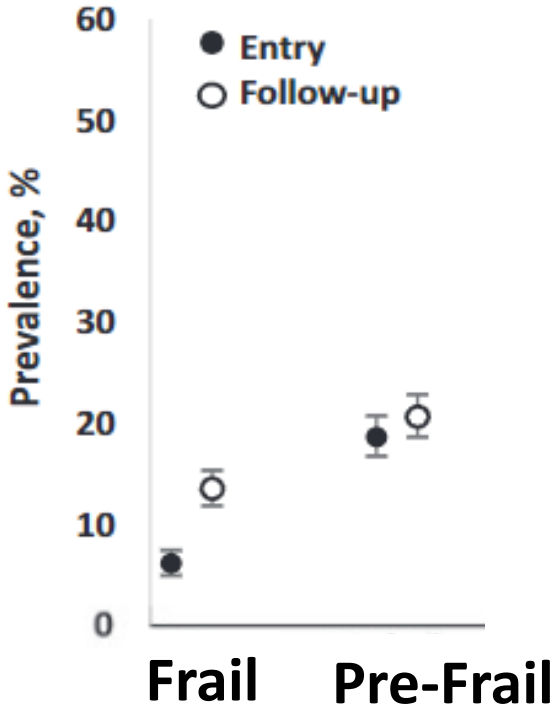
Ness et al, J Clin Onc 2013 & 2018

Fried's Frailty: Progression



1,432 Survivors
5 years of Follow Up
Median Age: 30 years

9.8% new onset Frailty
15.1% new onset Pre-Frailty

Delaney et al J Natl Cancer Inst 2021

Deficit Accumulation Index

Conceptualizes aging as a process of an accumulation of deficits

Deficit Accumulation Index (DAI)

- accumulation of multiple aging-related deficits
- At least 30-40 aging-related items
- predict mortality in adult cancer patients

SJLIFE DAI: 44 Aging-related Items

For each item:

- 1=deficit present/severe
- 0=deficit absent

$$\text{DAI} = \frac{\text{Sum of items}}{\text{Total number of items}}$$

DAI Construct	Value/Criteria	DAI Item Score
1. Can take bath/shower (IADL)	Yes limited a lot	1
	Yes, limited a little	0.5
	No Not limited at all	0
21. Heart Disease Comorbidity:	≥ 1 Grade 3 /4 Condition	1
	≥ 1 Grade 2 Condition (no grade 3/4)	0.5
	None or Only Grade 1 Conditions	0
39. Hearing Problems	Any “yes, and the condition is still present”	1
	No or Yes, but the condition is no longer present	0

DAI ranges from 0 to 1

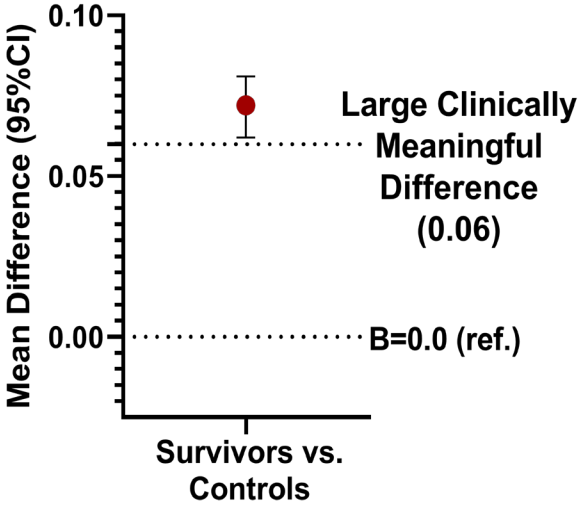
Large clinically meaningful difference: 0.06

Low <0.2 **Medium:** 0.2-<0.35 **High:** >=0.35

Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Deficit Accumulation Index

Clinically Meaningful Higher DAI in Survivors



4,000 Survivors
683 Controls

Mean Age: 29
Mean Time Since Dx: 20 years

Linear regression models adjusted for age, sex, and race/ethnicity.

Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Deficit Accumulation Index

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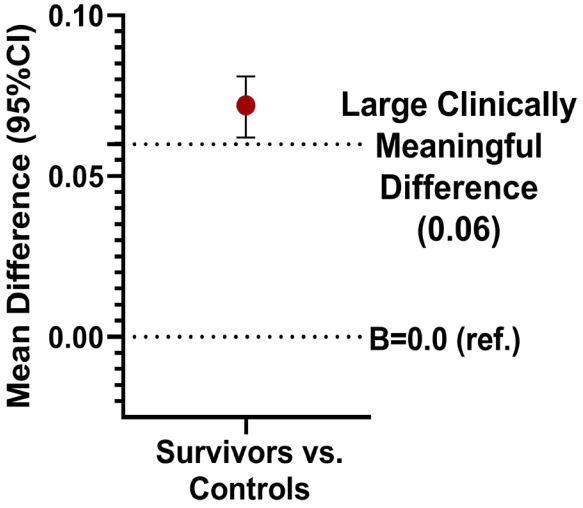

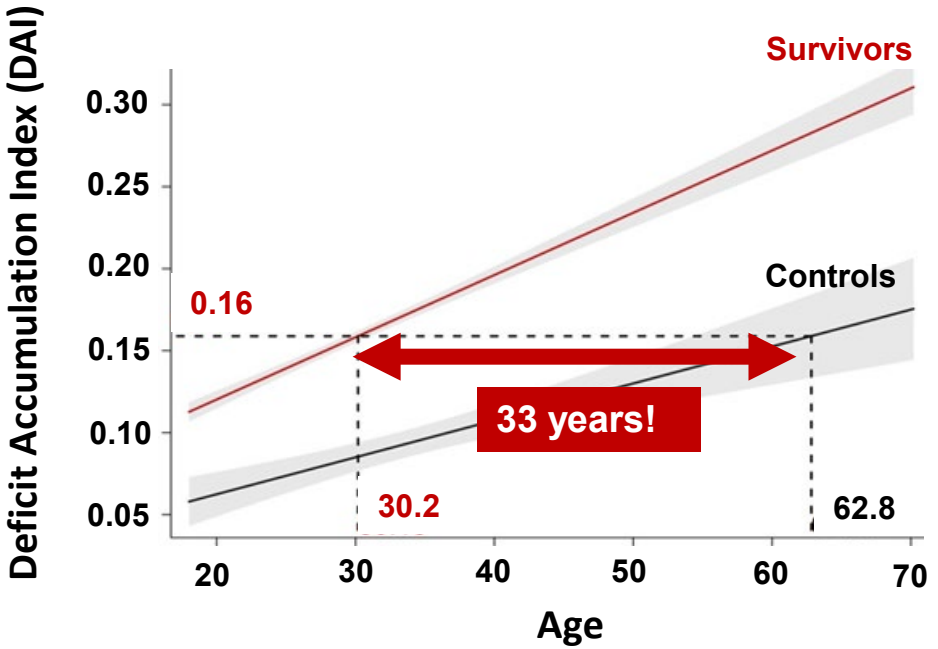

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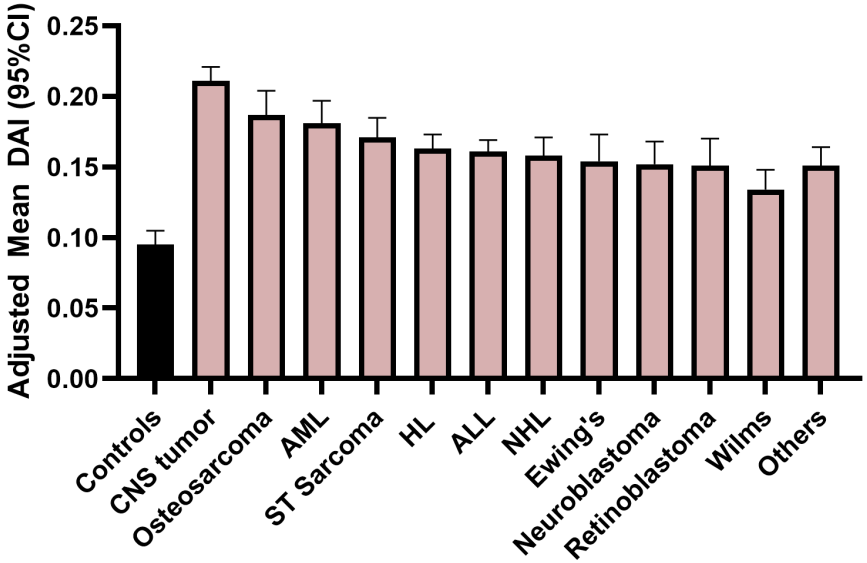
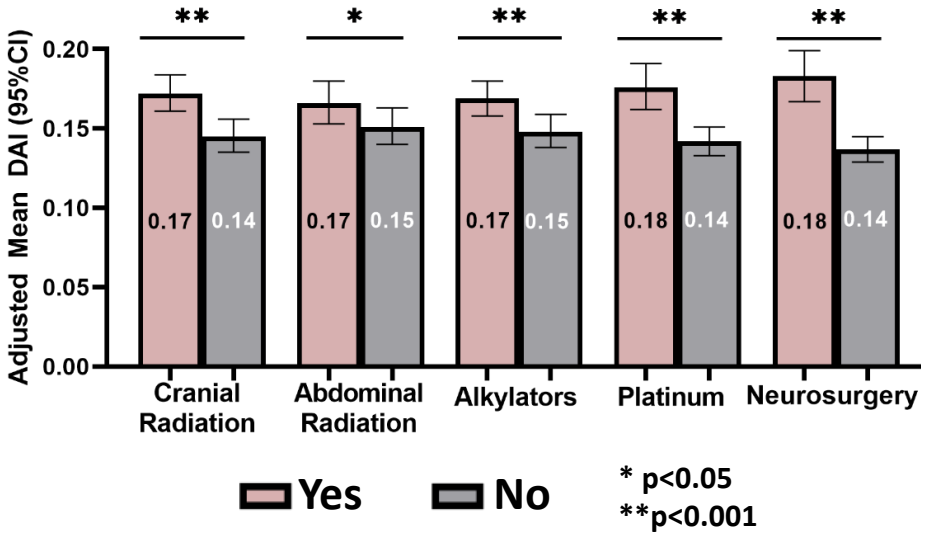
Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Deficit Accumulation Index

Diagnosis

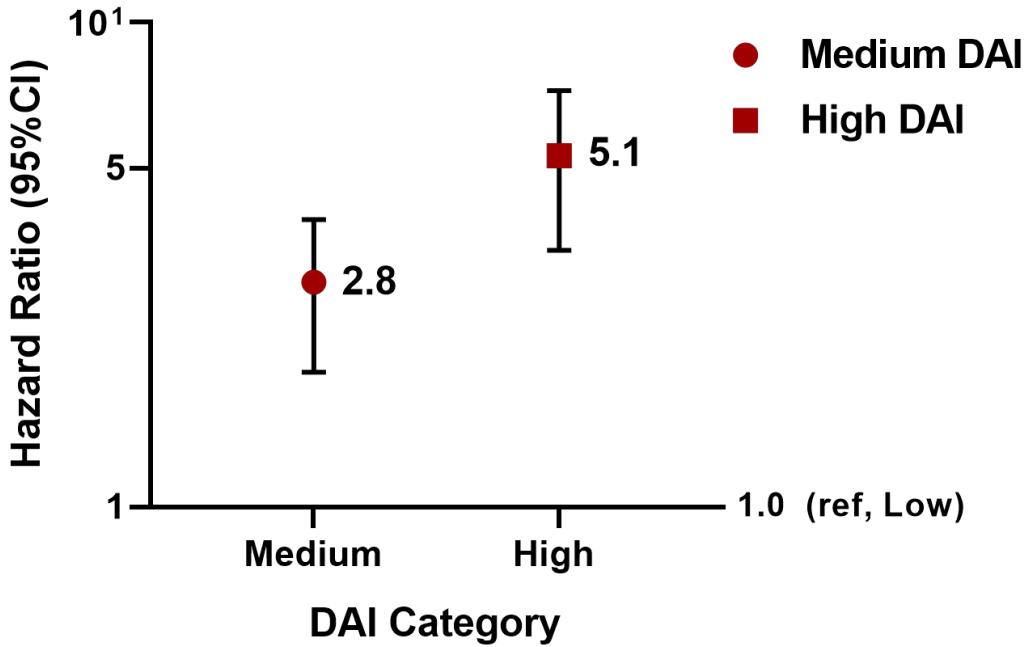


Treatments



Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Deficit Accumulation Index



Higher DAI Associated with Increased Risk of Mortality

Cox proportional hazards models adjusted for age, sex, race/ethnicity, and year of diagnosis.

Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Cognitive Aging

Long-Term Survivors Impaired ≥ 3 Tests

CNS Directed Therapy
- **Cranial Radiation**
- **Neurosurgery**
- **Intrathecal Chemotherapy**

49%

Survivors with no CNS Directed Therapy are at risk too!

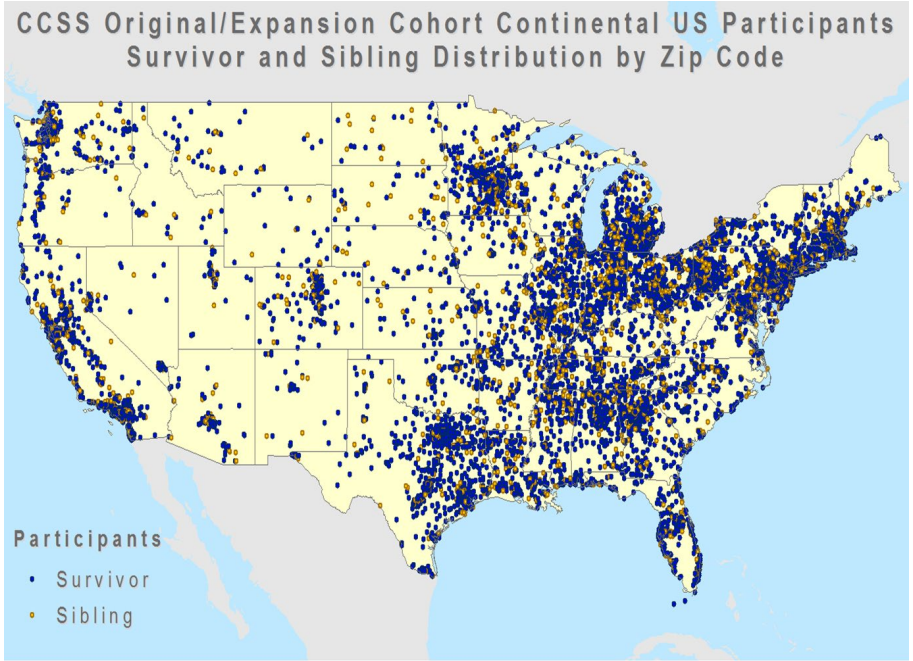
40%

Williams et al, Annals of Neurology 2020

Cognitive Aging

Childhood Cancer Survivor Study

- Funded in 1994 (U24 CA55727)
- Retrospective Cohort, recent expansion, include survivors diagnosed 1970-1999
- 31 Contributing Centers
- 5-Year Survival
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Detailed Treatment Data, Wide Range of Outcomes



ccss.stjude.org

Cognitive Aging

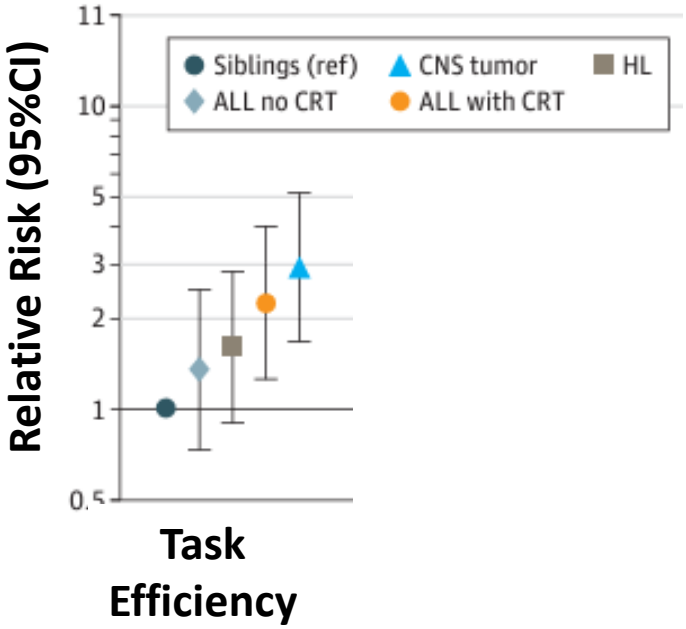
Sample:
CNS tumors (n=488)
ALL (n=1316)
Hodgkin Lymphoma (n=571)
Siblings (n=232)

Self-Reported Cognitive Function

Approx. 10 years of Follow Up

Excluded Impaired at Baseline

Risk of New Onset Impairment



Phillips et al, JAMA Netw Open 2023

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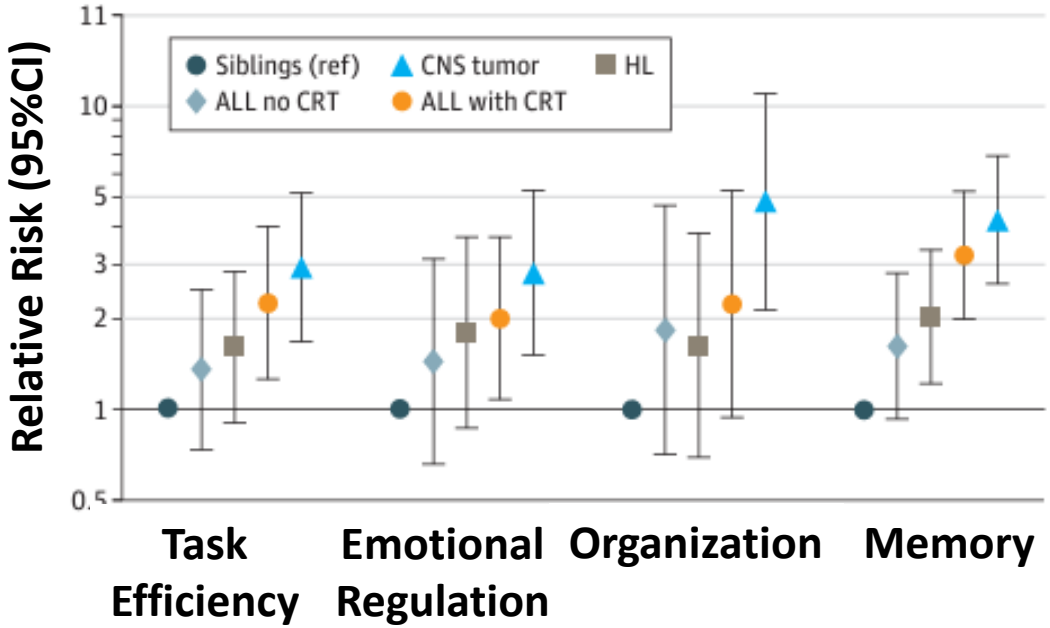
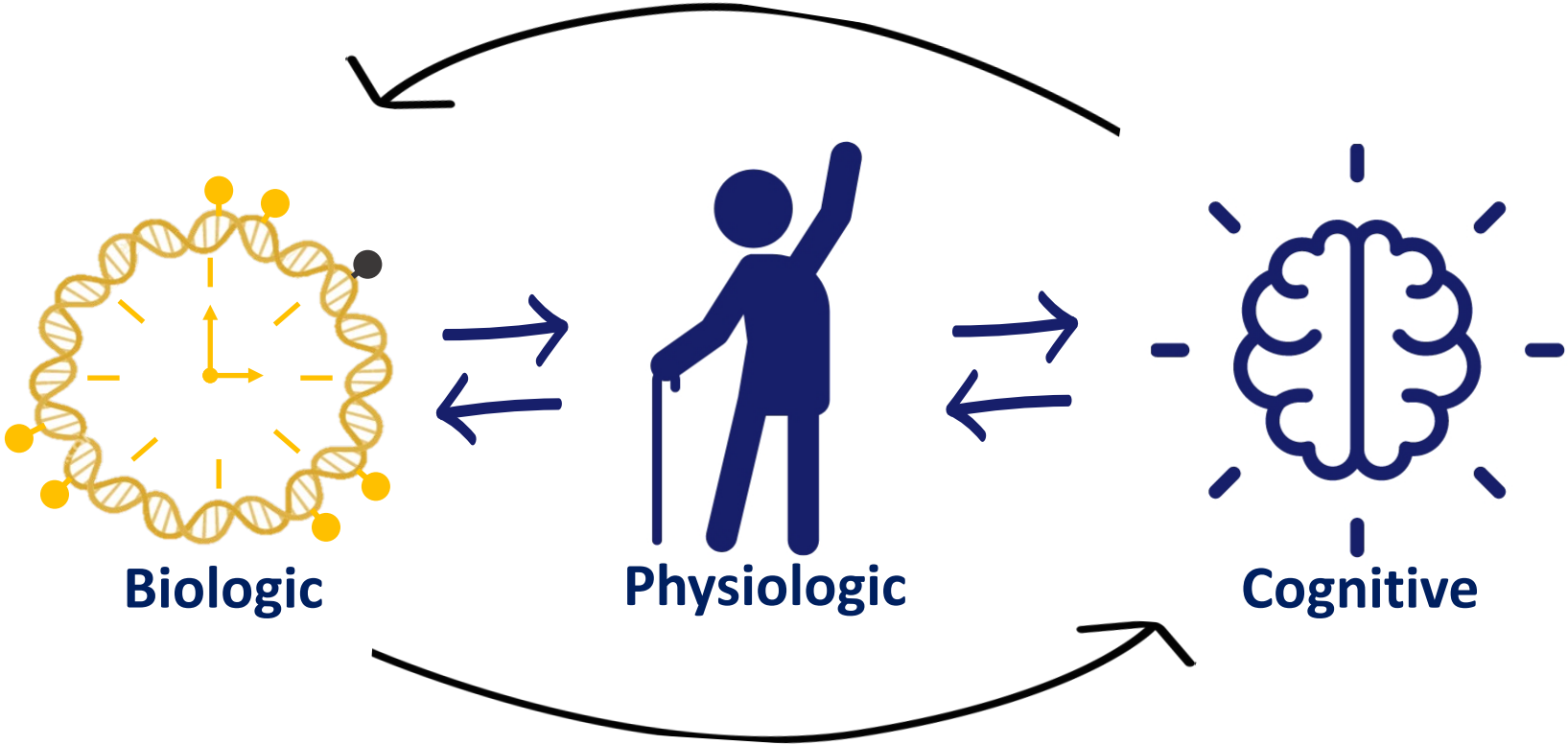
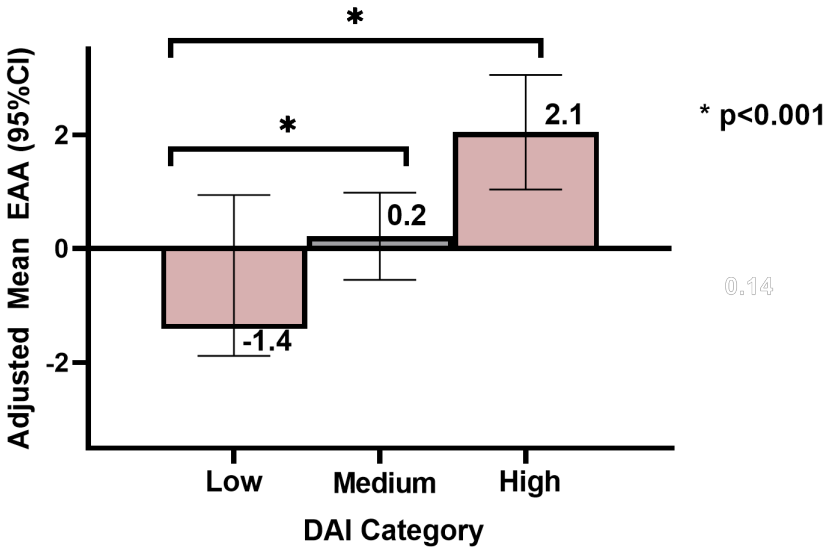


Phillips et al, JAMA Netw Open 2023

Overlap in Aging Pathways



Biologic and Physiologic Aging



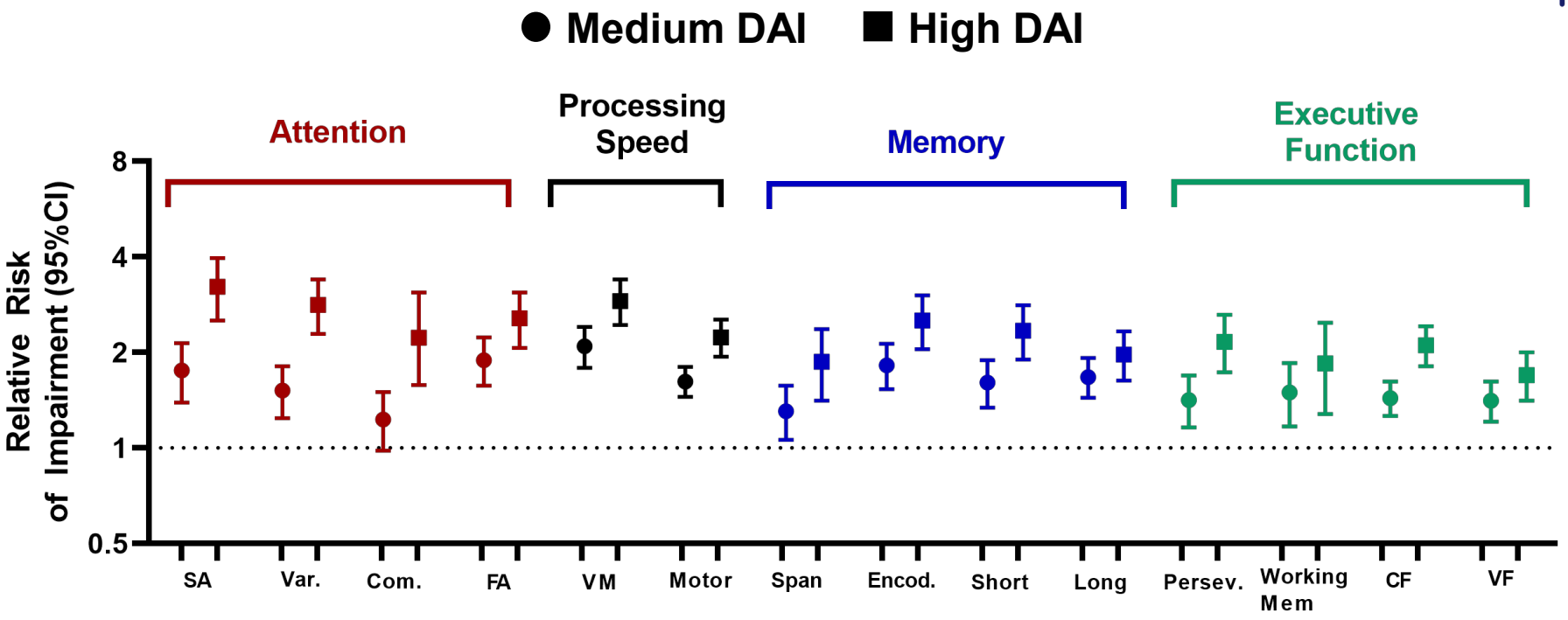
* p<0.001

0.14

Epigenetic Age Acceleration Increases With Deficit Accumulation Index

Williams et al, JNCI 2023
Williams et al, JAMA Network Open 2024

Physiologic and Cognitive Aging



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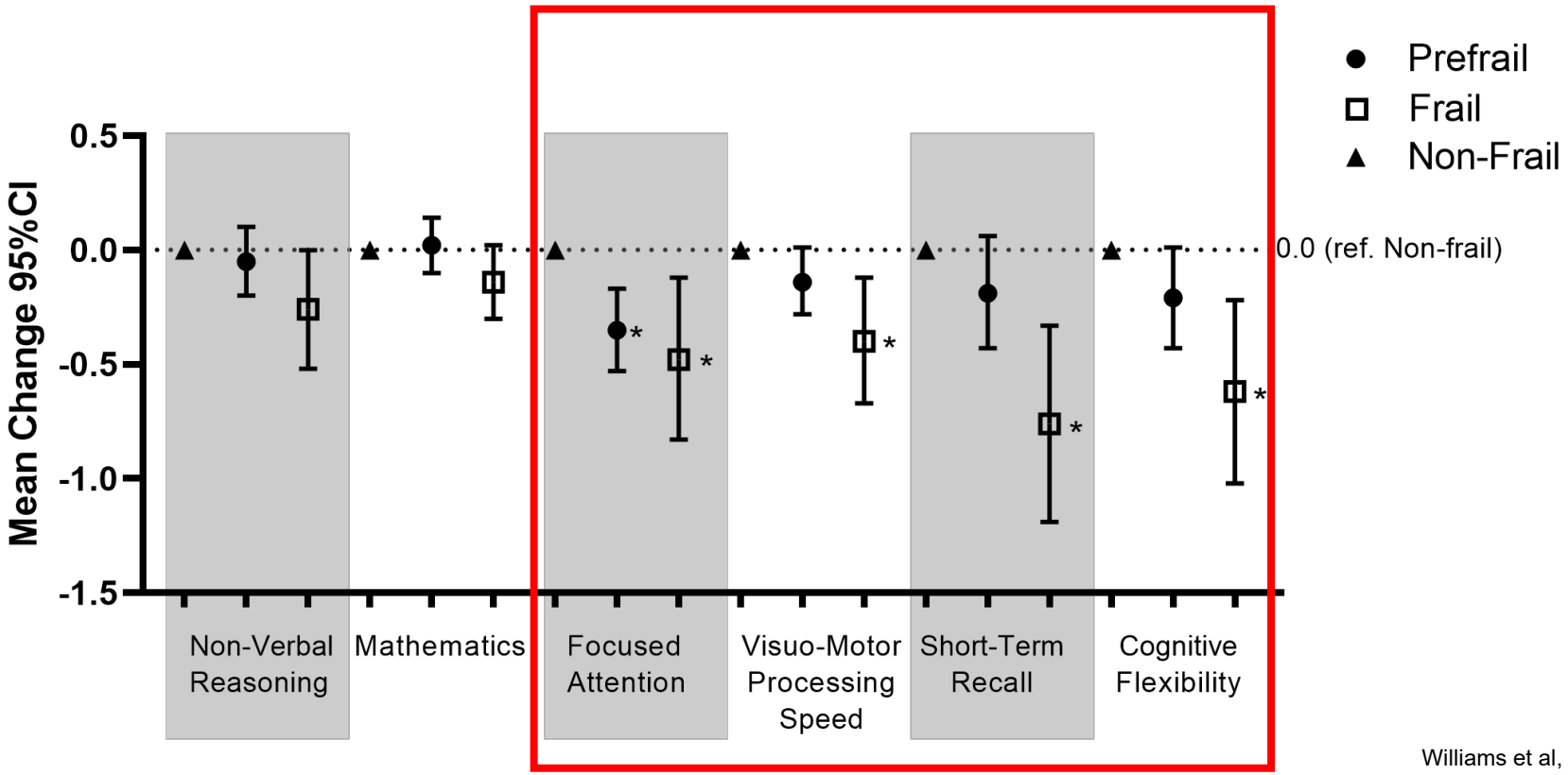

Williams et al, J Clin Onc 2021

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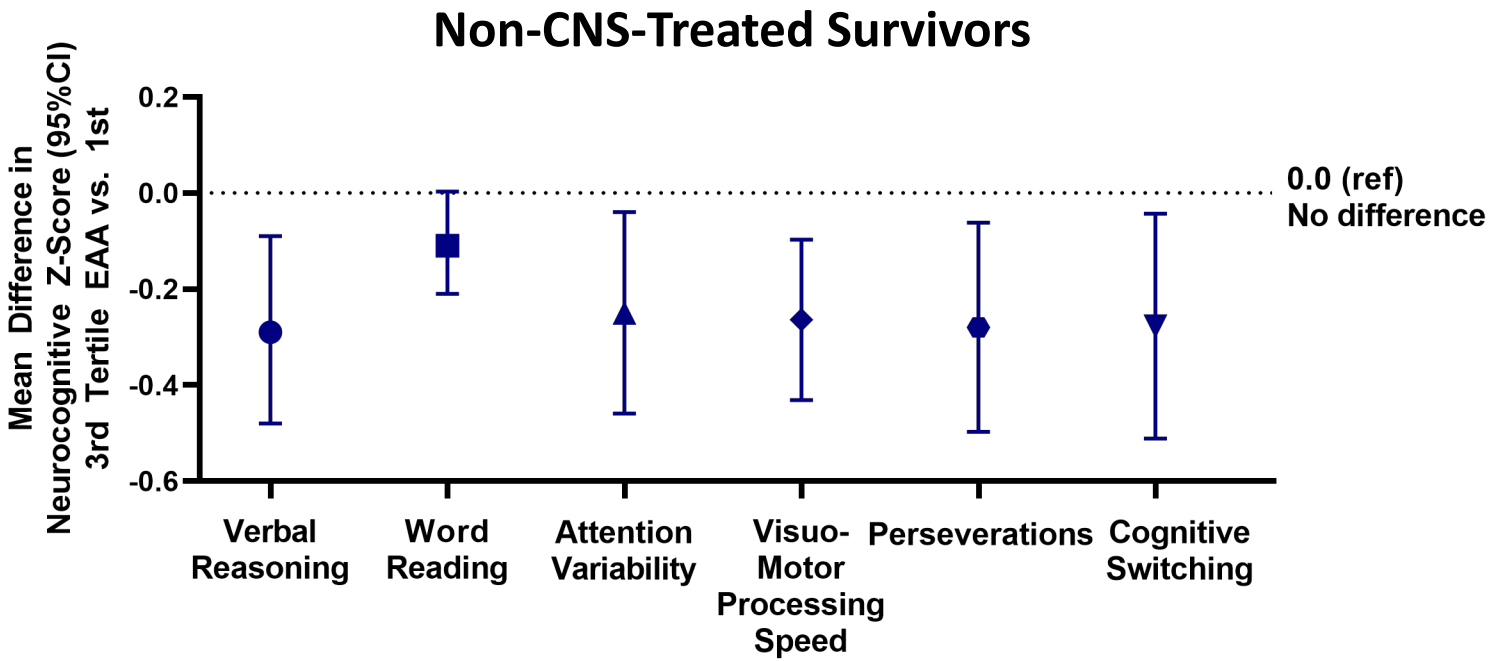

Williams et al, Under Review
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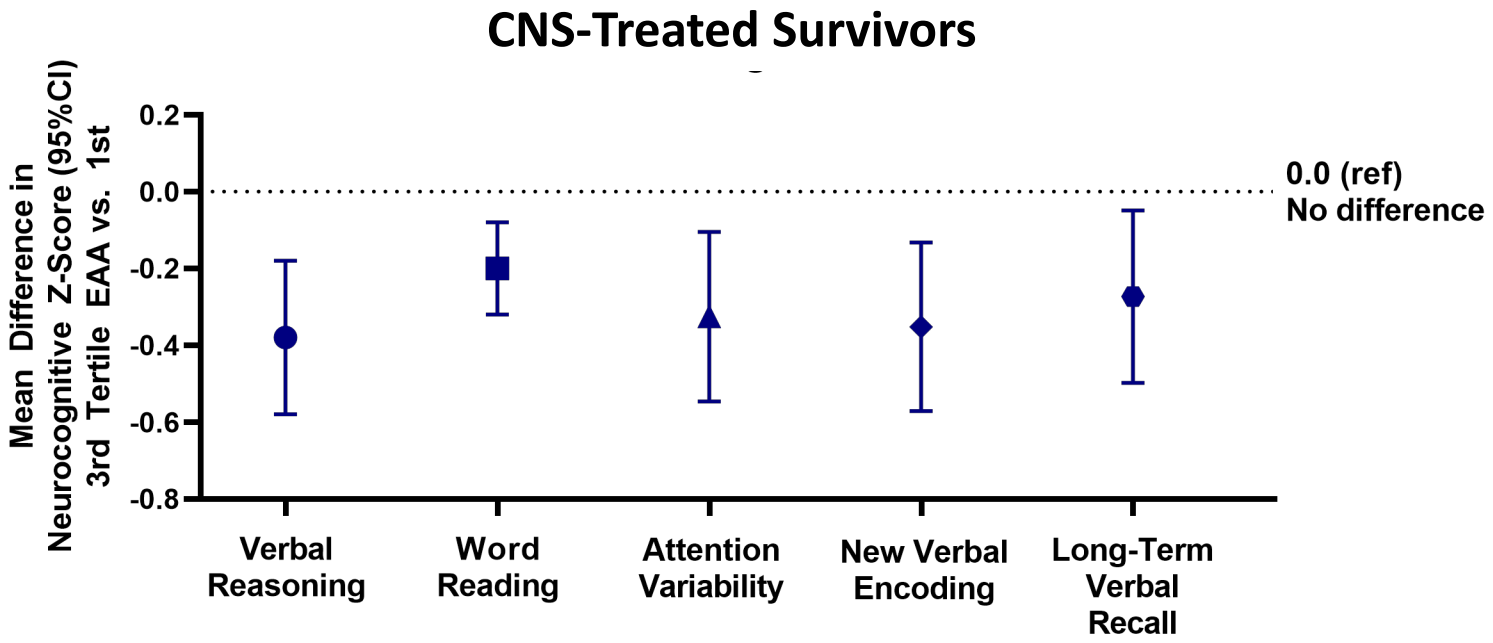
Biologic and Cognitive Aging



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Summary

- Survivors experience premature aging
  - Biologic
  - Physiologic
  - Cognitive

- Biologic, physiologic and cognitive are all connected

Questions Remain

- **Is it truly accelerated aging? Or just premature?**
  - Need for Longitudinal Data
- **When does the aging trajectory start?**
  - Need for pre- post-treatment data
- **How can we target multiple pathways at once?**
  - Need for multidimensional interventions

Clinical Impact

- Advocate for survivors
- Need screening and management for aging related diseases earlier than their peers
  - Earlier than their primary care doctors are used to
- May need earlier monitoring for aging-related cognitive changes

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P30CA21765 (Roberts),
ALSAC

Patients and Families in SJLIFE and CCSS

Questions?

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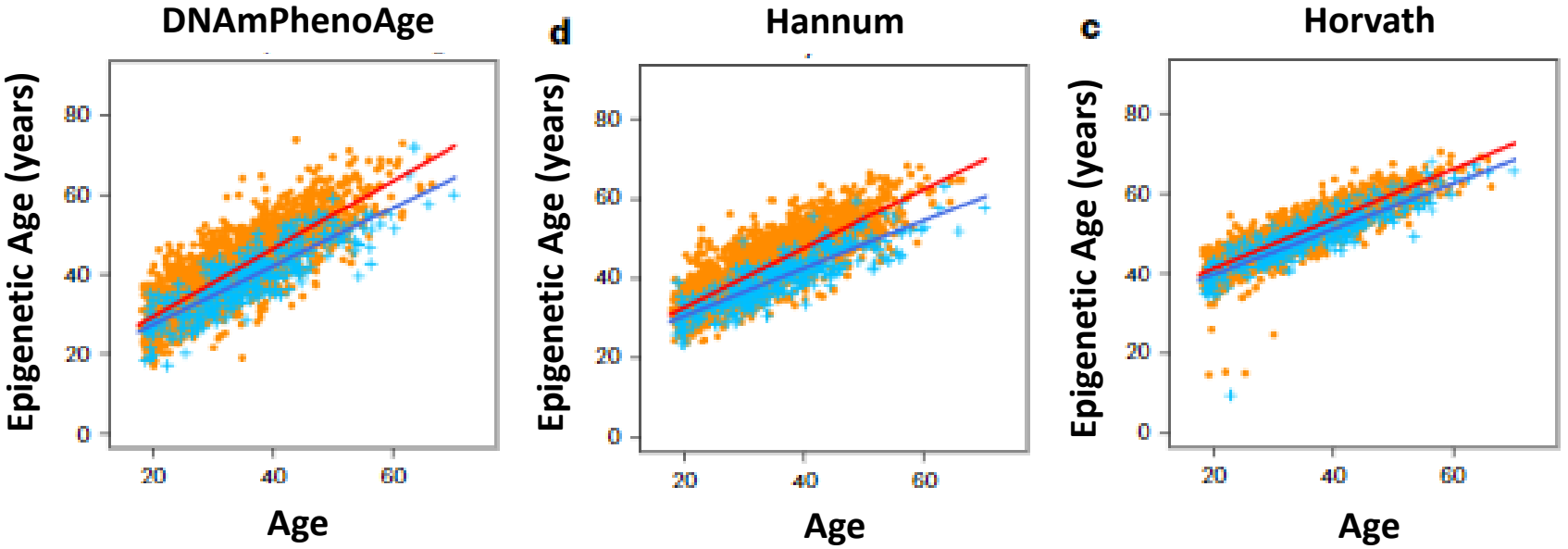
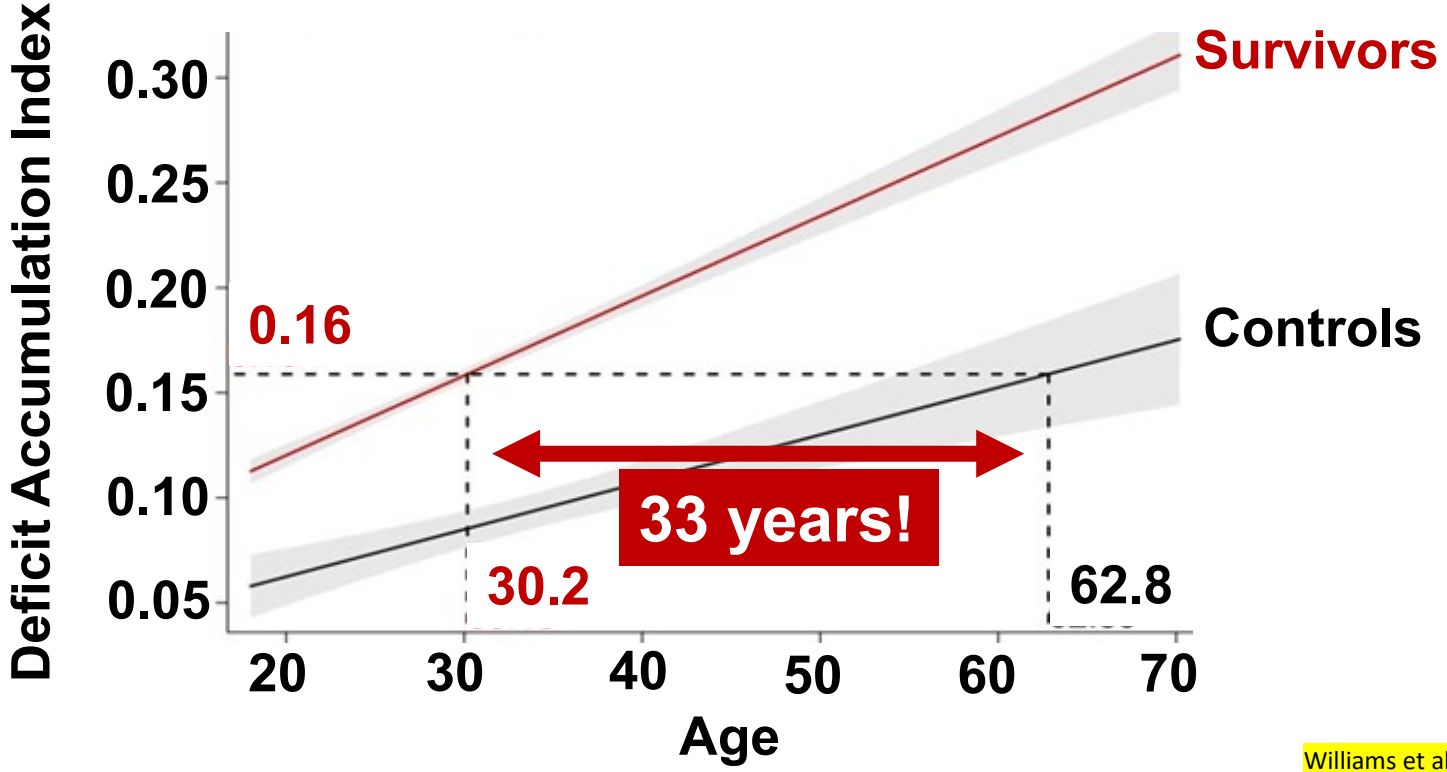
AnnaLynn_Williams@urmc.Rochester.edu
@AnnaLynnWiliams

Title

- Line 1
- Line 2
- Line 3

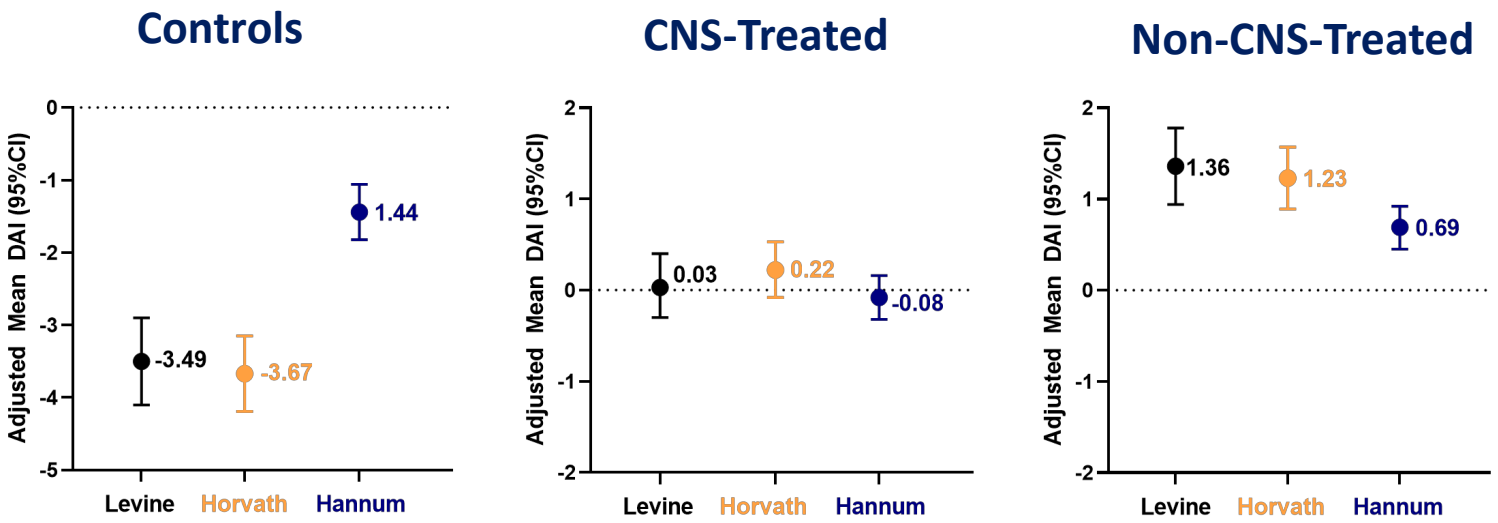
Differing Epigenetic Clocks





Williams et al, Under Review

Mean EAA: Differing Epigenetic Clocks



Cognitive Aging

Risk Factors for New Onset Impairment:

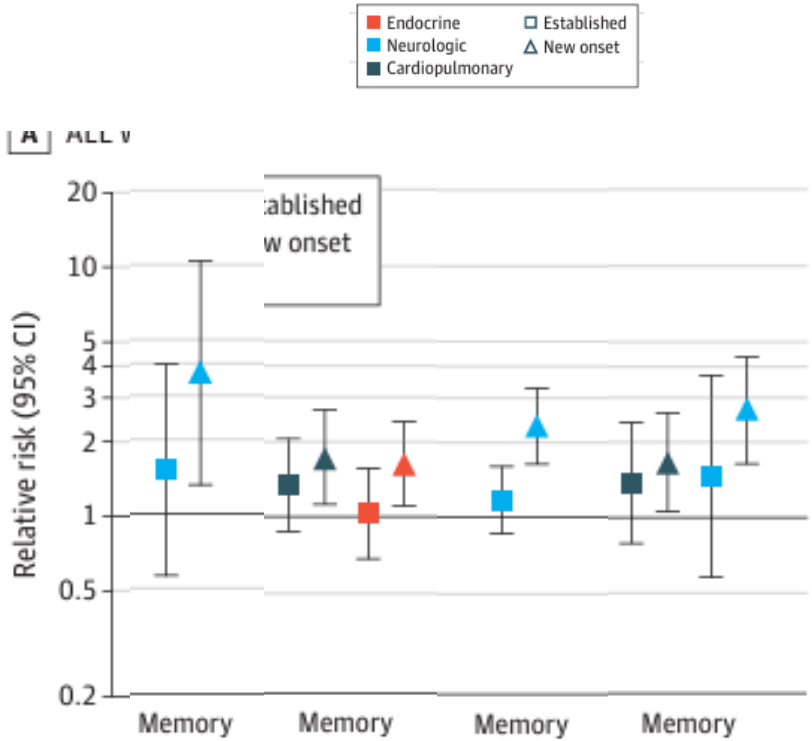
ALL w/No CRT:
Female Sex, MTX IT, and Cytarabine → Memory
Alkylators → Task Efficiency

CNS Tumors
Craniospinal RT, Focal RT → Memory

Hodgkin Lymphoma:
Female Sex → Memory
Alkylators → Task Efficiency

Phillips et al, JAMA Netw Open 2023

Cognitive Aging



Phillips et al, JAMA Netw Open 2023