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Progress Towards Identifying Markers and Drivers of Universal Resilience

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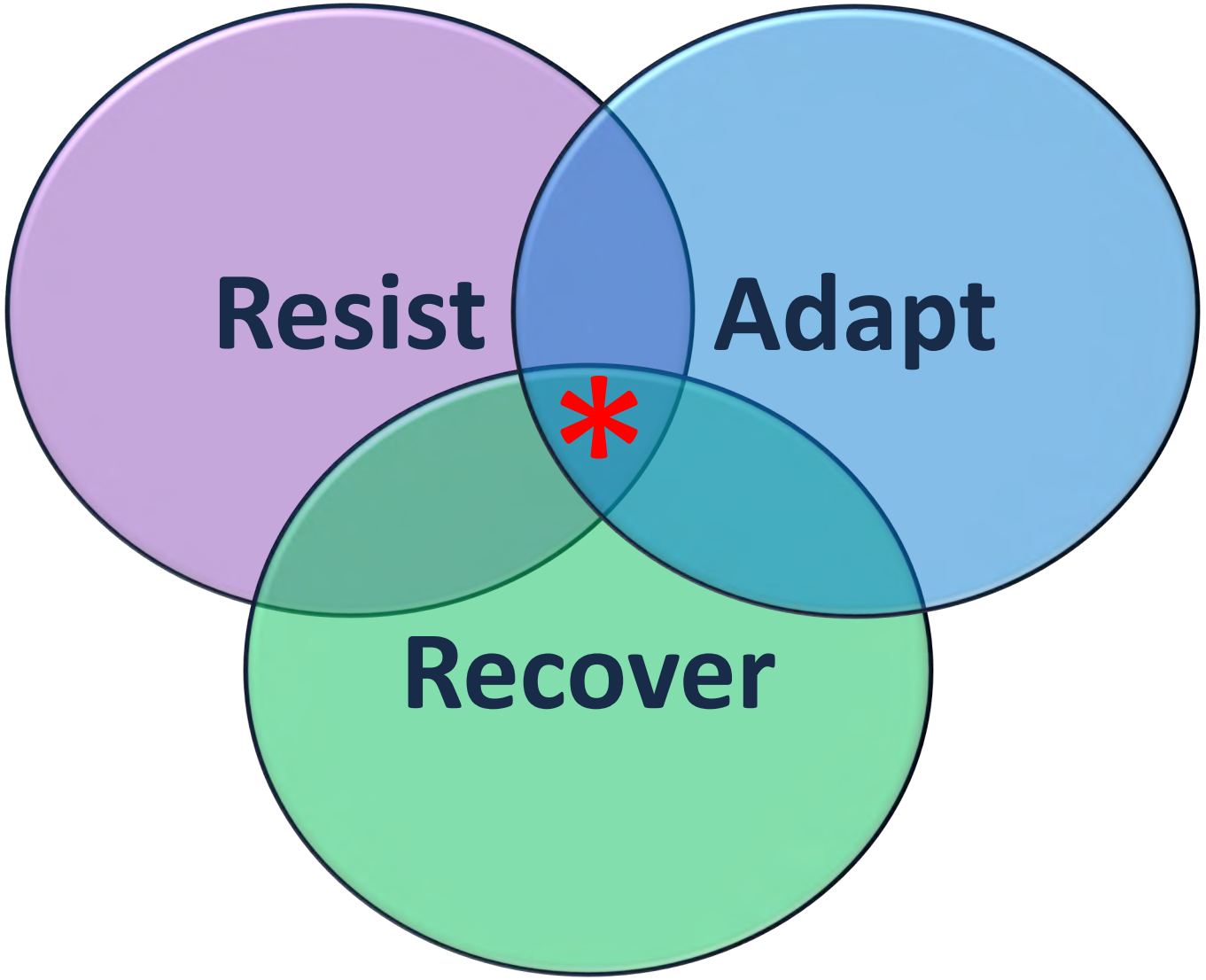
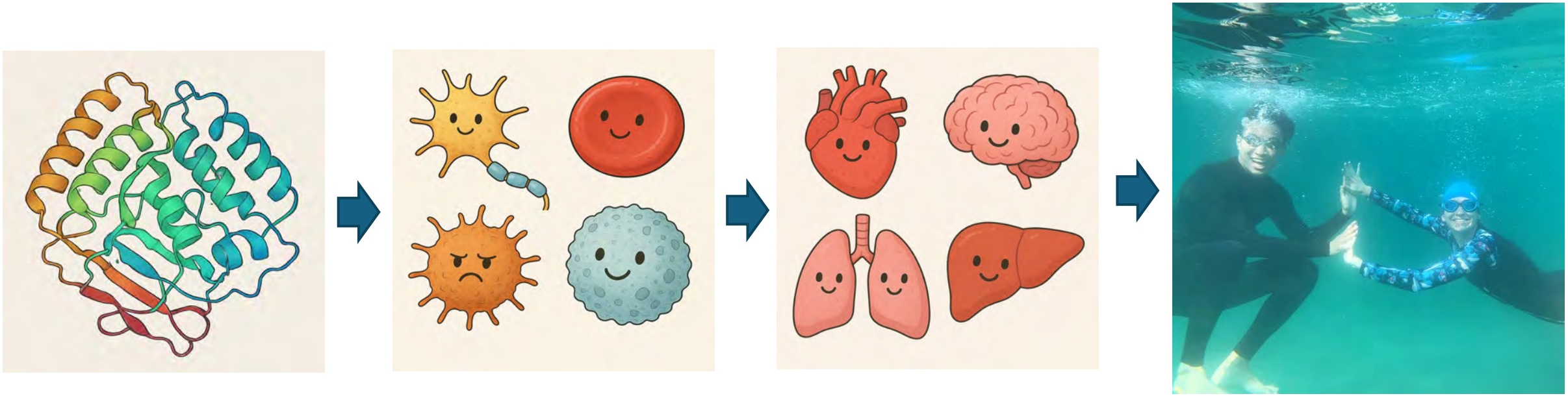
Universal Resilience



Biological Resilience

- Evolution has resulted in a network of biological resilience strategies
  - Support recovery and survival
  - Returning to a state of ***homeostasis*** after physiological stressors.

- Biological Resilience mechanisms **exist across biological scales**
  - individual molecules to cells, tissues, and whole organisms



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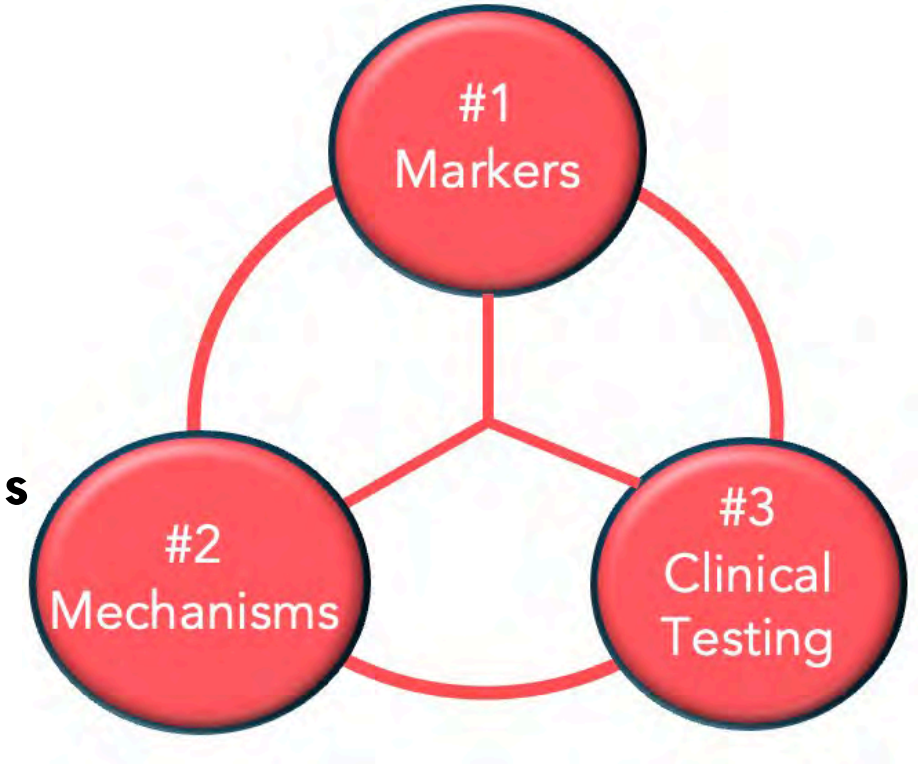
Biology of Aging

Biology of Resilience

Wellcome Leap builds bold, unconventional programmes and funds them at scale, with the goal of achieving breakthrough scientific and technological solutions within five to ten years.

The Dynamic Resilience program: mission-driven research to improve healthspan **through 3 interconnected thrust areas with measurable targets and goals**

Predict health outcomes post-stress
85% sensitivity, 90% specificity



Identify resilience mechanisms in stress-testable models
mechanism-targeting interventions

Validate markers & test interventions in at-risk adults
Reduce frailty progression by 25%

An International Effort

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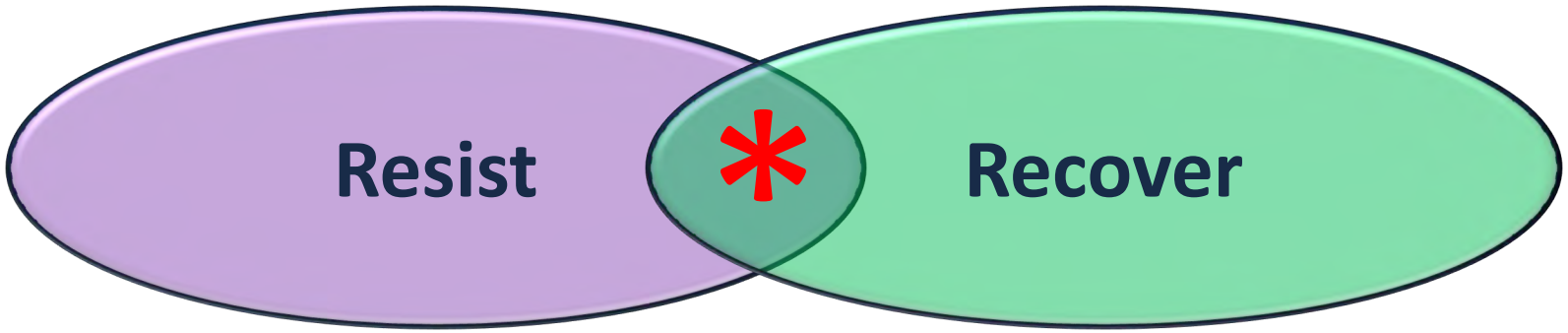

Resist

Lifecourse Resilience

The Rancho Bernardo Study of Healthy Aging
Est. 1972

-Enrolled 82% of adult residents (n=6726) of Rancho Bernardo
-12 research clinic visits at ~4 year intervals and yearly surveys.
    -54% are women
-65% were aged ≥50 at enrollment.
-Average age of death: 86.4 yrs
    -29% lived to age ≥90

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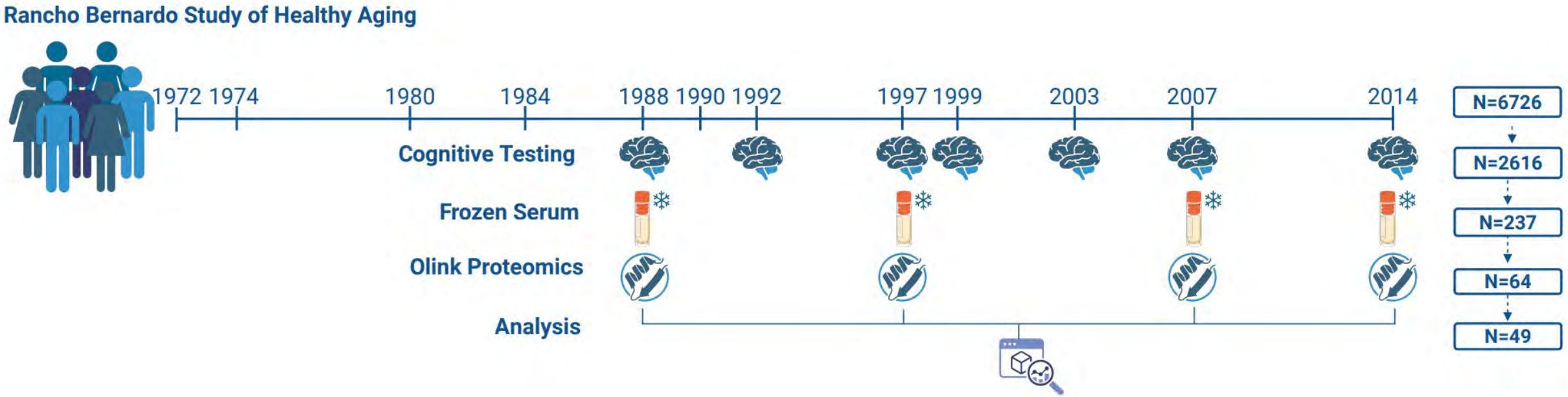
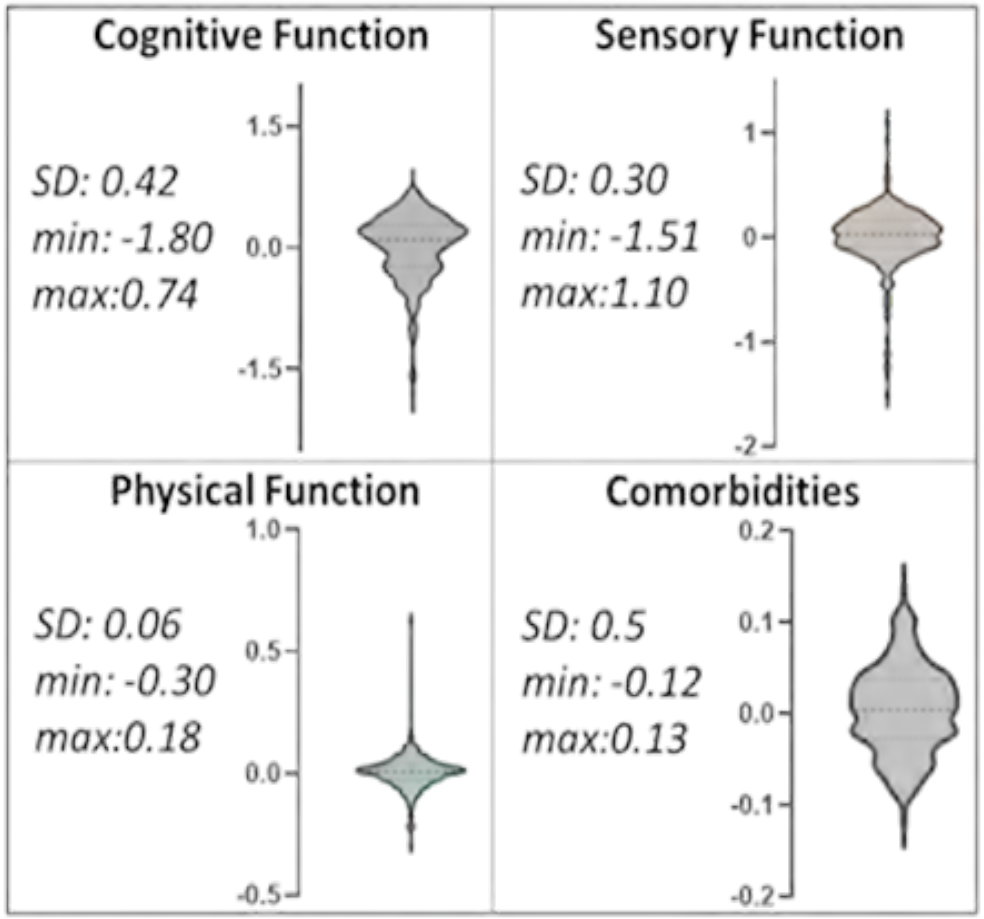
Study Design: Cognitive Resilience



Quantifying Resilience Trajectories



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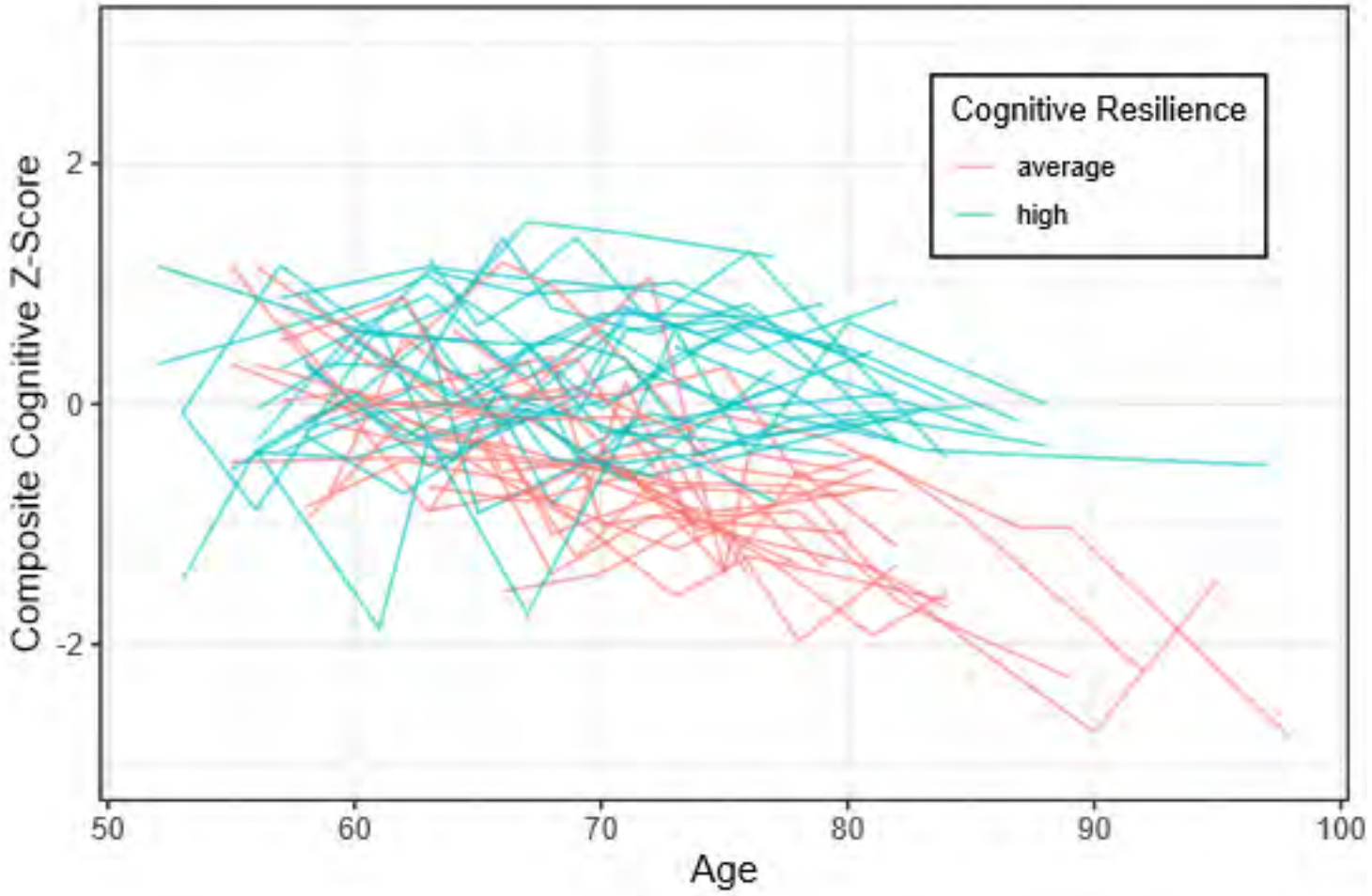
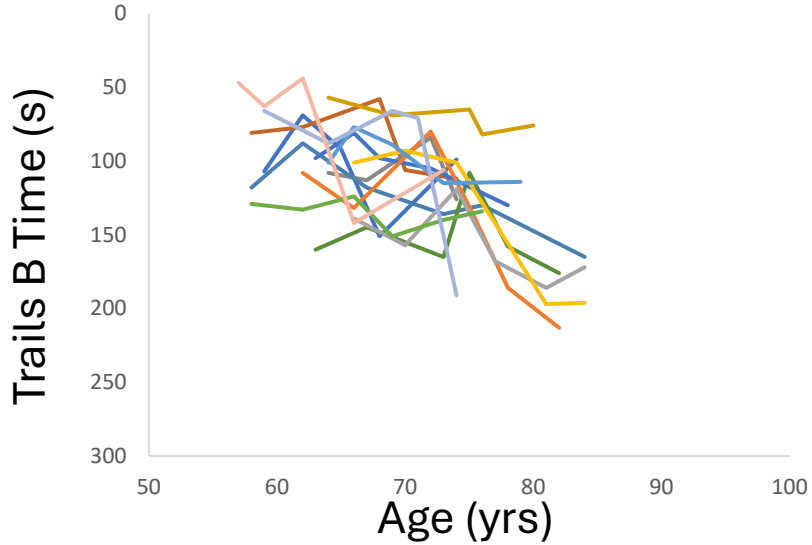
Cognitive Resilience

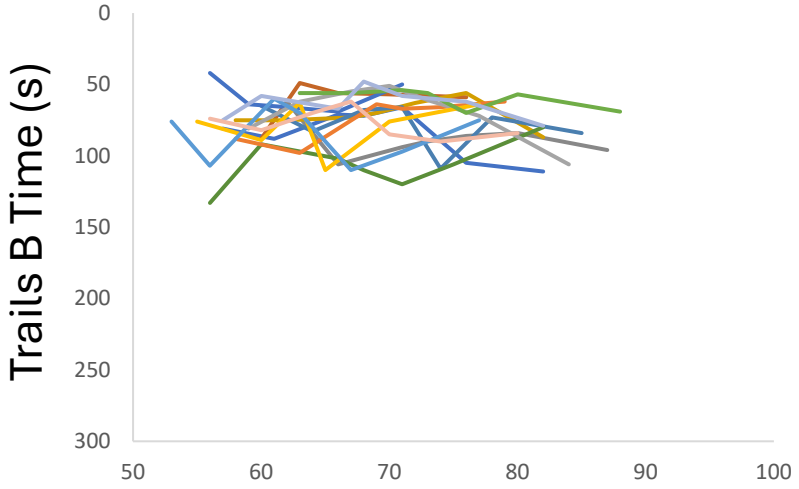
Midlife to Older Age



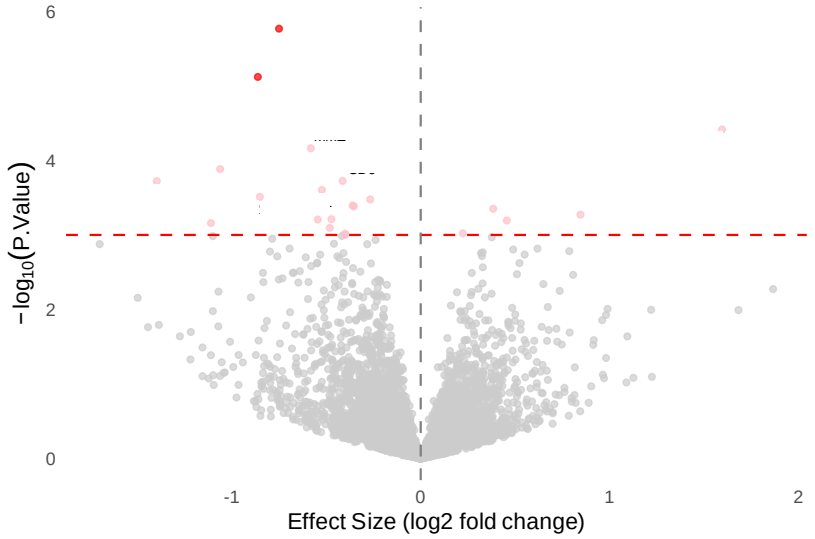
Average

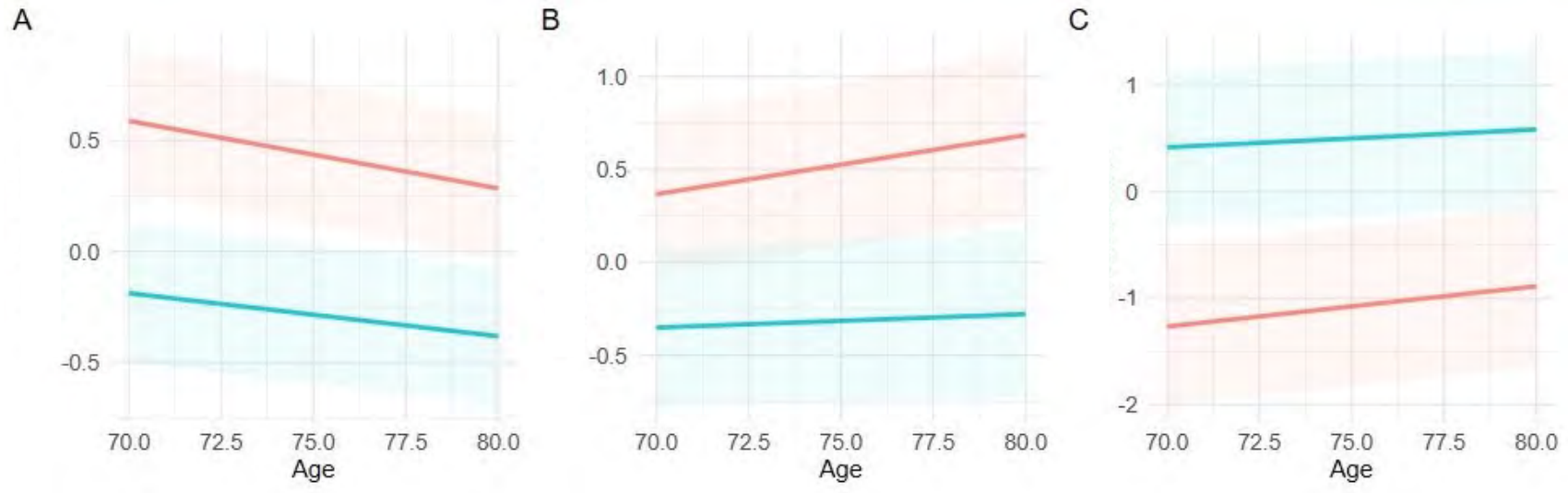


Exceptional Resilience

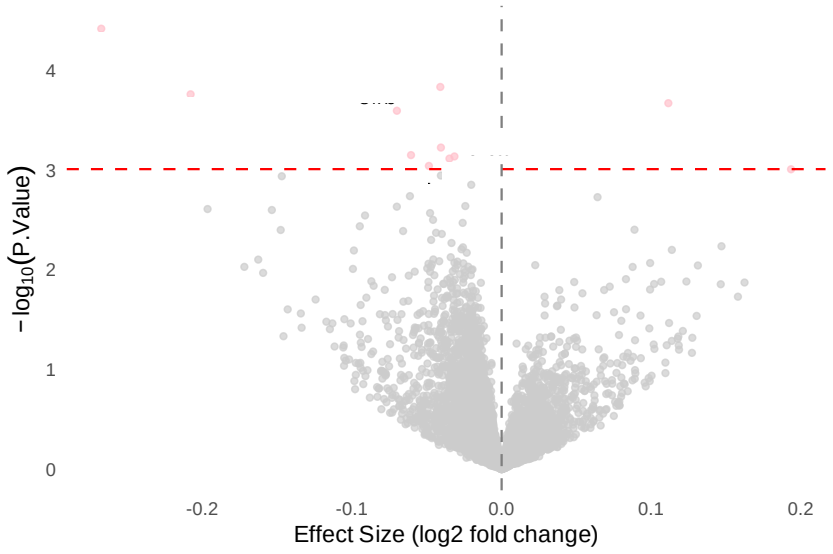


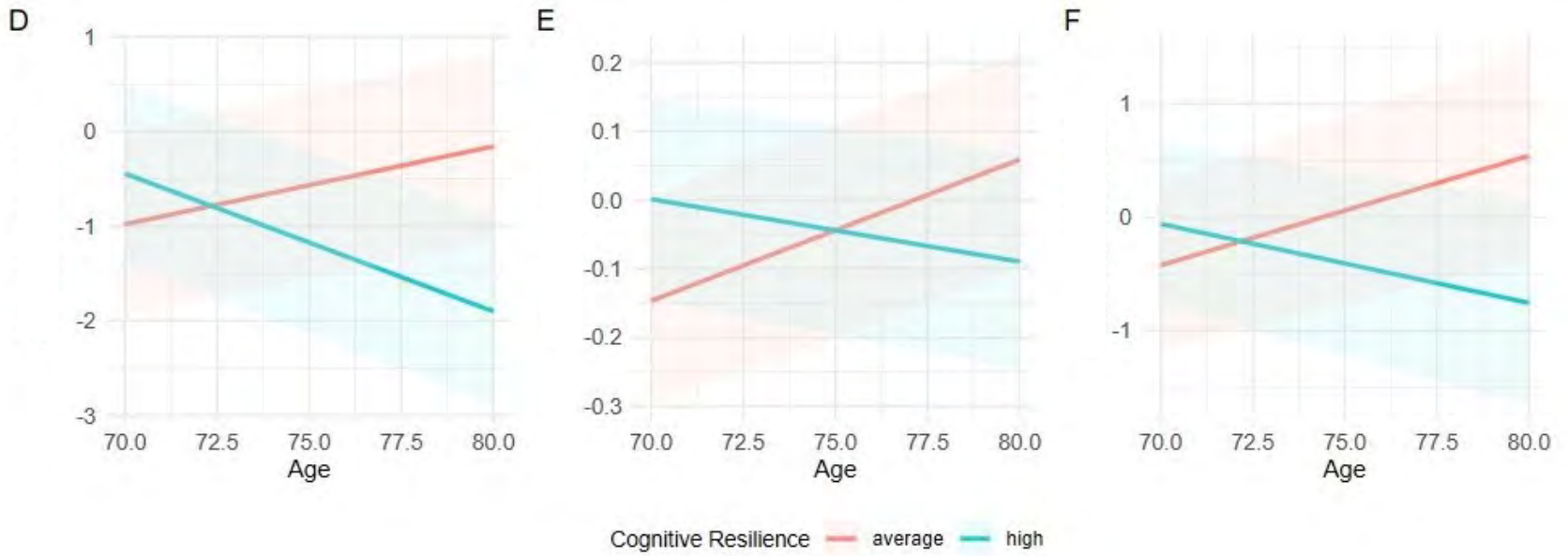
Explore Proteomics (>5K Features, OLink)





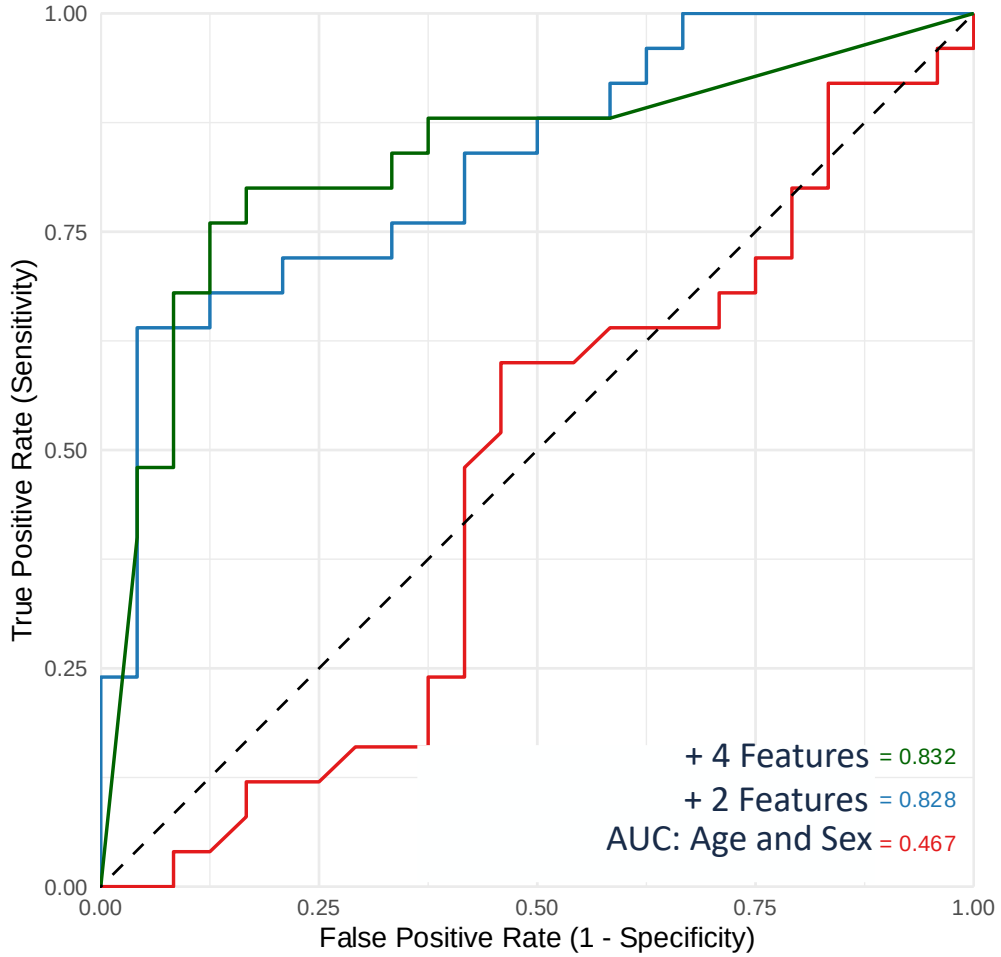
Distinguishing Features of Resilience





Multivariate Analyses Reveals Remarkable Consistency

GLMM-Lasso



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Drivers of Human Resilience

What do these circulating factors do?

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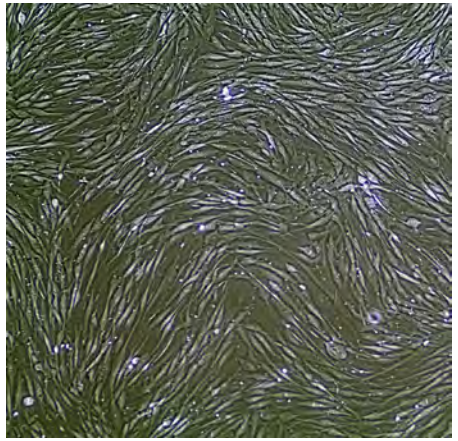
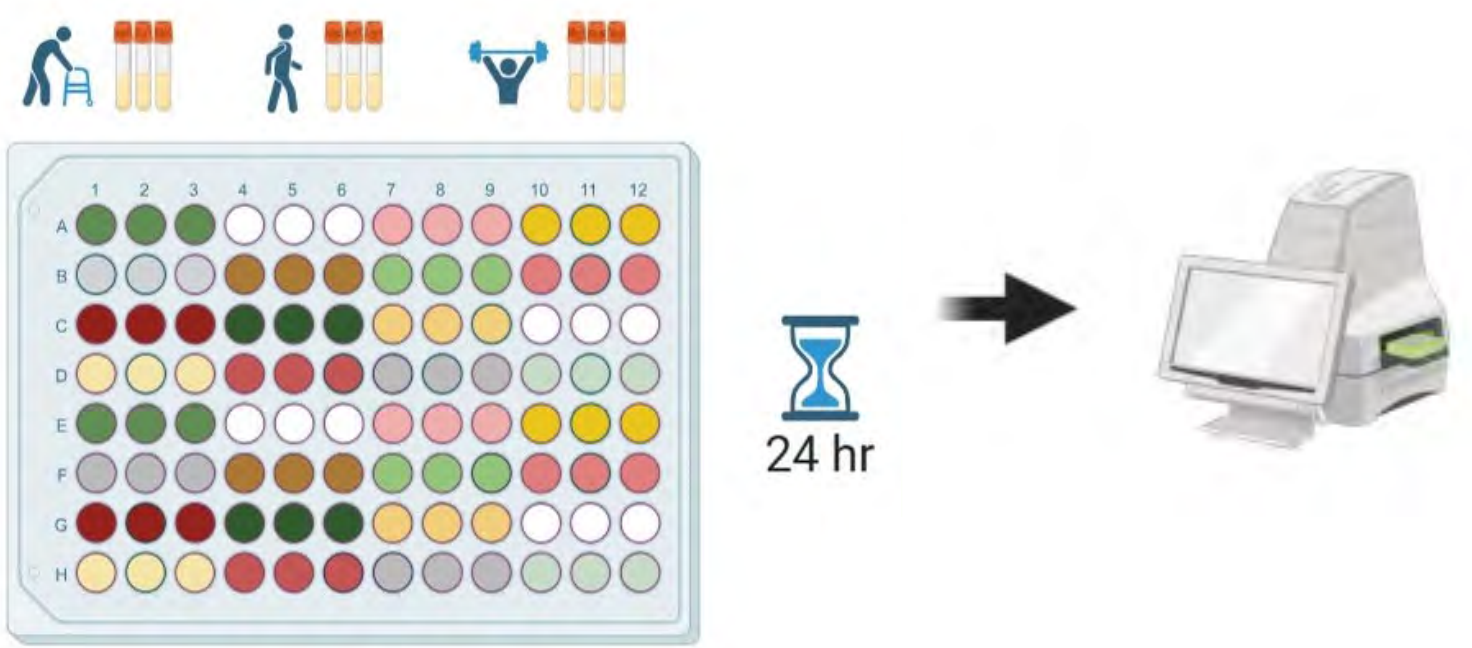
Do systemic, circulating, factors associated with resilience drive differences in cellular metabolism?

	Visit 8 1997	Visit 10 2007	Visit 12 2014
Exceptional Resilience	→	→	→
Average Resilience	→	→	→

Primary human dermal fibroblasts





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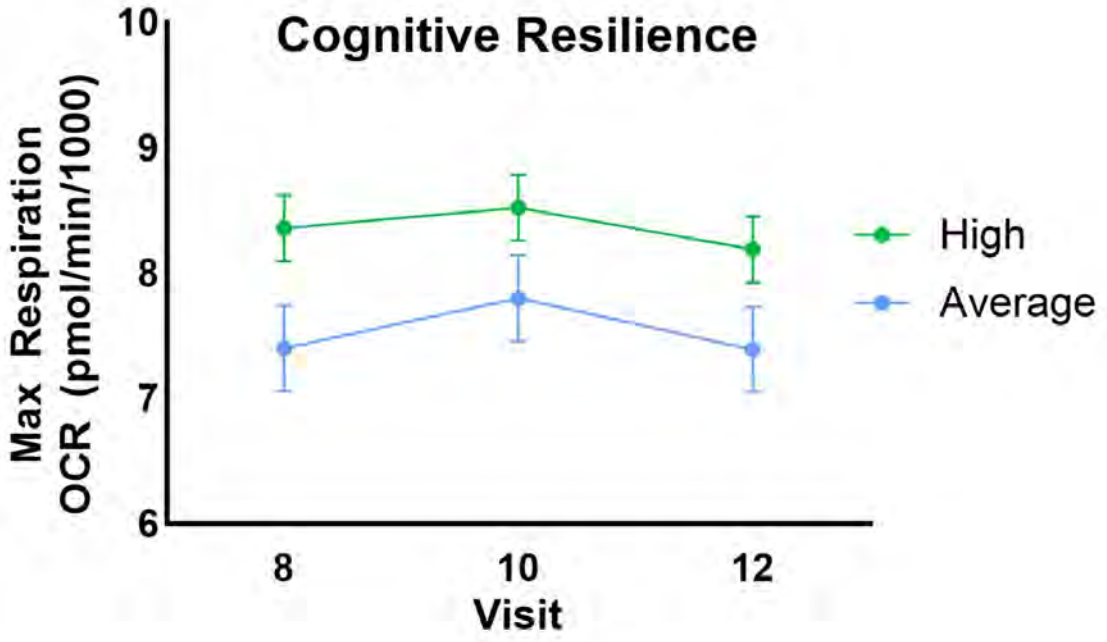
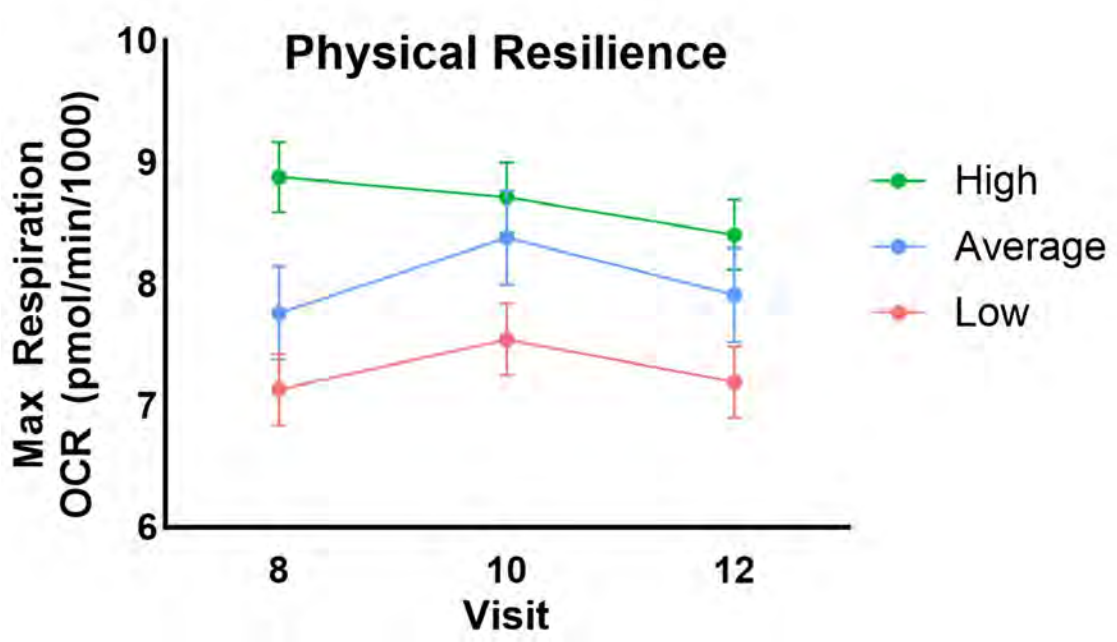
Resilience Factors Drive Mitochondrial Bioenergetic Capacity





Uncovering Metabolomic Features of Resilience

(~800 Longitudinal Samples from RBS)

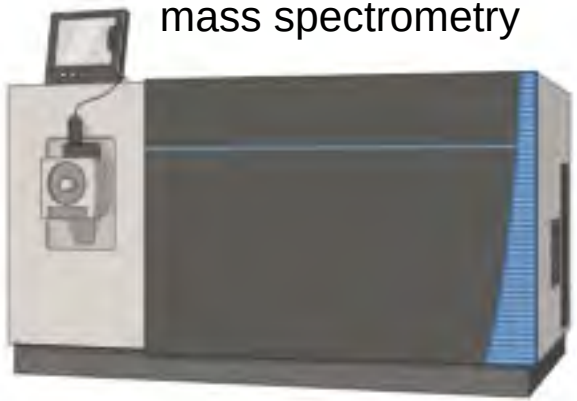
Untargeted LC-MS/MS

Discovery metabolomics

HPLC

(Thermo Vanquish)

Tandem (MS/MS) mass spectrometry



(Thermo Q Exactive)

mzmine

Feature detection

Archiving data in public domain

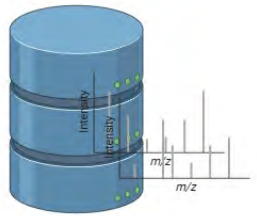
GNPS

MassIVE

Mass Spectrometry Interactive Virtual Environment

Reuse of public data

GNPS2



Spectral matching with reference libraries to get annotations

Software for data analysis

MassQL

MASST

ReDU

redu.ucsd.edu

(Domain specific MASSTs available – microbeMASST, plantMASST, foodMASST, tissueMASST)

MZmine:
Nothias, Nat Methods 2020
Schmid, Nat Biotechnology 2023

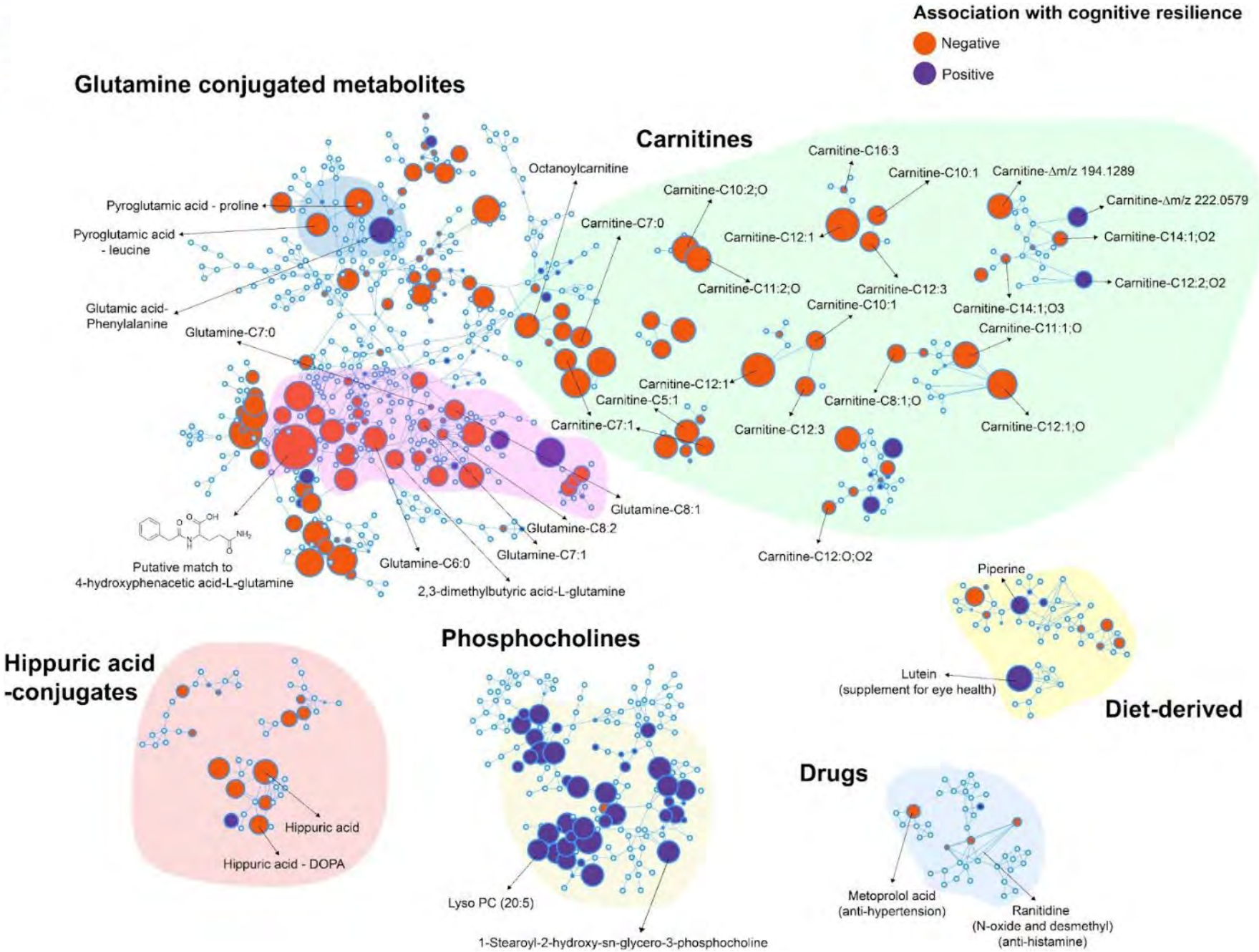
GNPS2:
Wang, Nat Biotechnology 2020
Jarmusch, Nature Methods 2020
El Abiead, bioRxiv 2024

MASST:
Wang, Nat Biotechnology 2020

MassQL:
Jarmusch, bioRxiv, 2022

ReDU:
Jarmusch, Nat Methods 2020
El Abiead, chemRxiv 2024

Metabolomic Landscape of Cognitive Resilience from Middle to Older age



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Recover

"Dynamic Resilience"

Falls

	N	%
Total GED Visits	26091	
Falls Related Injury	3145	12.1
Female	1842	58.6
Age 65-74 yrs	1,363	43.3
Age 75-84 yrs	1,127	35.8
Age 85+ yrs	655	20.8

ER Visit → 7-day Virtual → 1 Month In-Person → 3 month In-Person → 6-12 Months EHR Reviews

At 90 days:
-33% have reported falling again
-24% have had a return ED visit

Research Team

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NIH National Institute on Aging

HALEON

XPRIZE

Lim Family

Stein Family