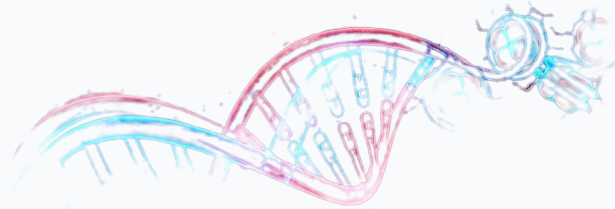


Is Mortality Two-Dimensional?

Biological burden, candidate survivability state and mortality heterogeneity

Mortality risk may depend not only on the burden an organism carries, but on the biological state in which that burden is being carried.



Dr Trevor Tingate MD

Similar Predicted Risk. Different Outcomes.

Mortality models rank risk well — yet individuals with similar predicted risk still diverge.

Person A

Same age
Similar smoking, blood pressure, metabolic and renal profile
Similar predicted risk

Dies during follow-up

Person B

Same age
Similar smoking, blood pressure, metabolic and renal profile
Similar predicted risk

Survives follow-up

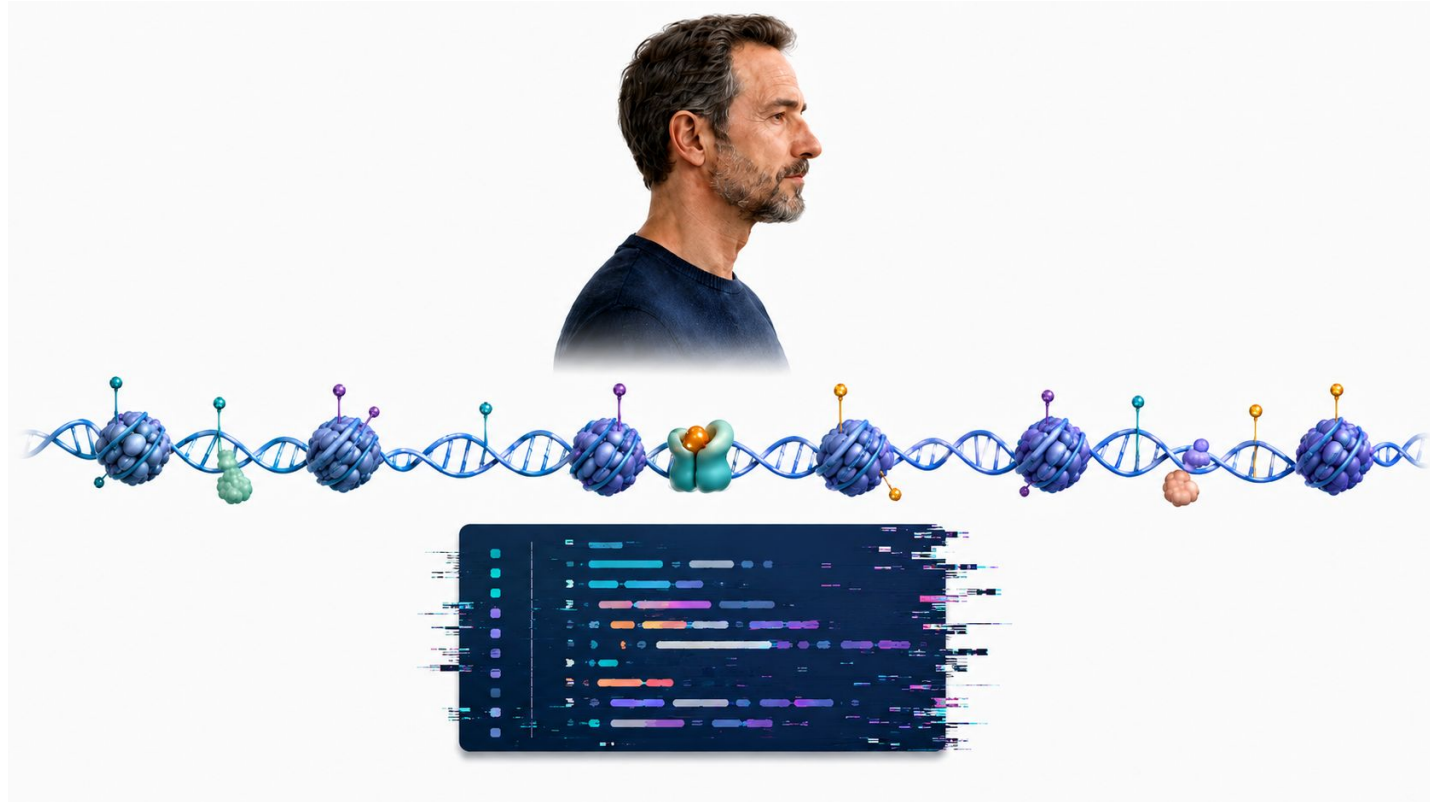


What might explain the remaining heterogeneity?

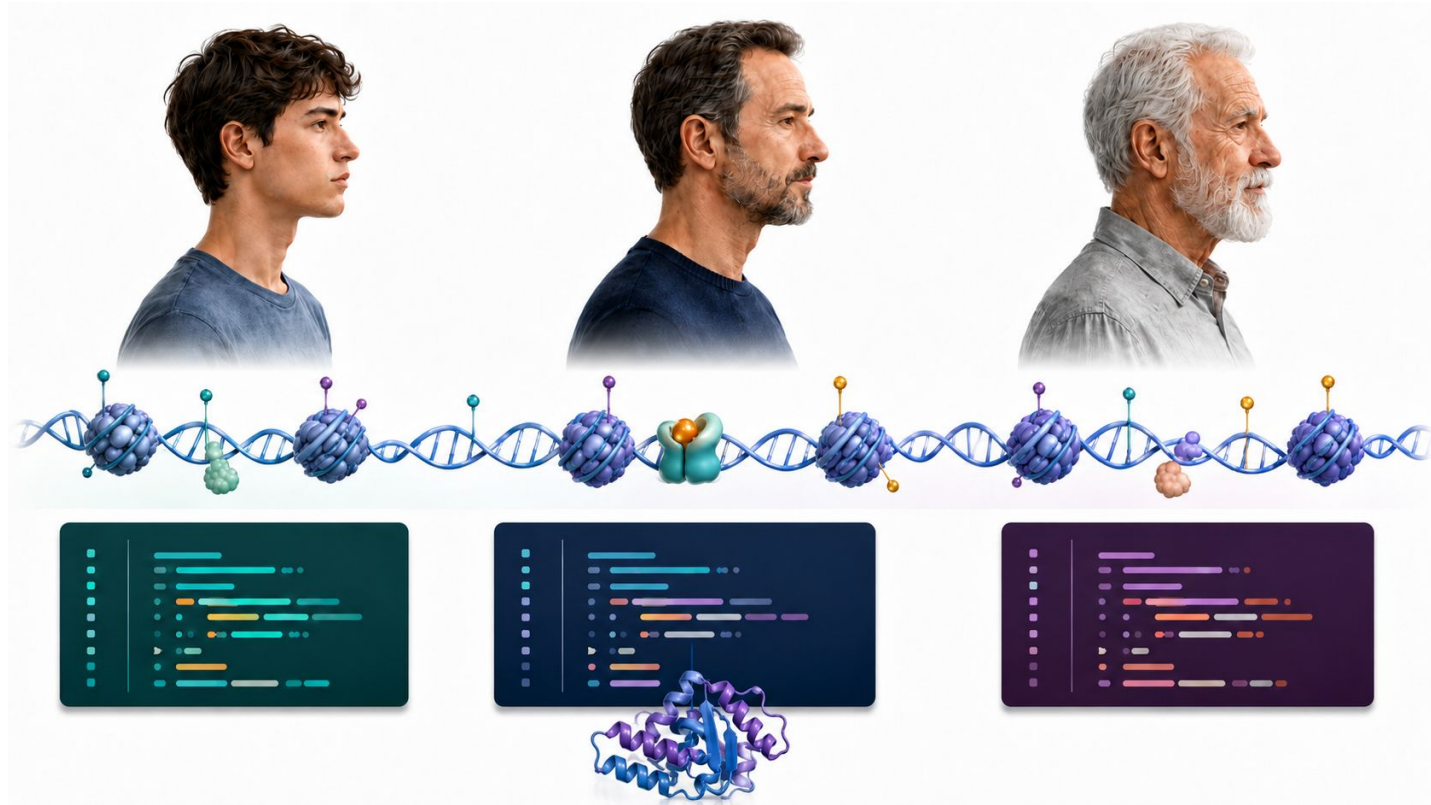
Chance • unmeasured burden • biological state

Information Theory of Ageing

The regulatory program (epigenetic) may progressively lose information or fidelity



A more nuanced possibility



Biology Shows That State Matters

Same genome → different state → different function

Cell Identity

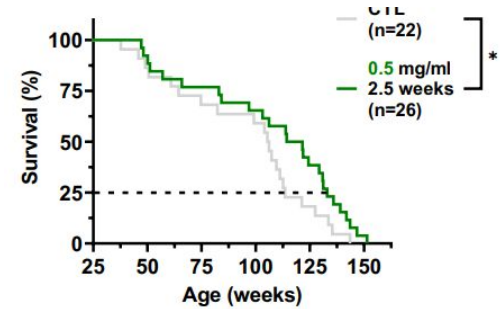
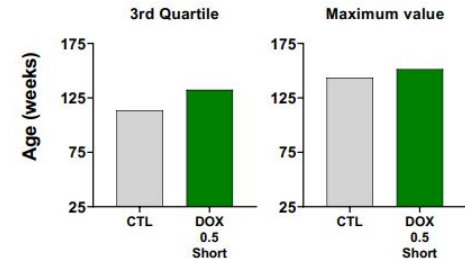
Cells with essentially the same genome can have profoundly different functions because they occupy different regulatory states.

Reprogramming

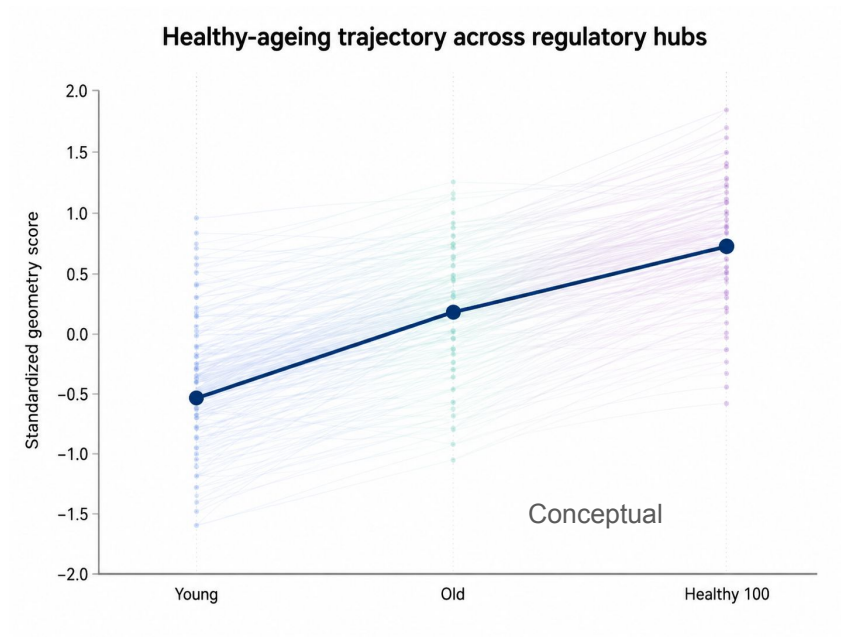
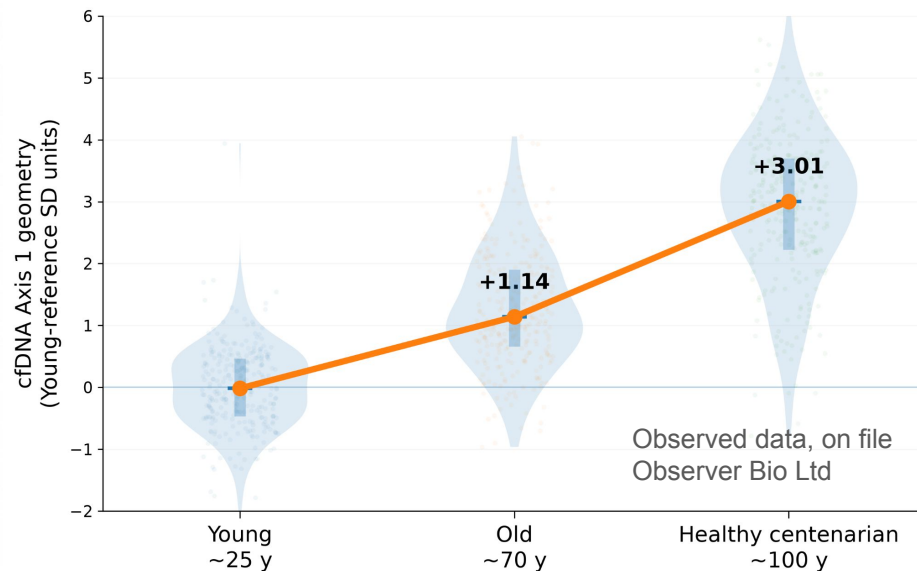
Regulatory state can be experimentally altered, changing cellular phenotype (*and biological age*) without changing DNA sequence.

In Vivo Evidence

Short-term reprogramming improves survival in mice.



A distributed regulatory state may underlie healthy longevity



Healthy centenarians occupy a shifted hub-level geometry distribution

Longevity May Require the Right Program at the Right Time

A working biological model

Earlier life

- Lower accumulated burden
- Greater physiological margin
- Future costs matter greatly

Youth-adapted program

Later life

- Higher accumulated burden
- Reduced physiological margin
- Immediate costs become increasingly important

Age-appropriate program

Key Takeaway: Conditions change → the optimal regulatory strategy may also need to change.

From Biology to Two Mortality Coordinates

D1 — Conventional Mortality Burden

What adverse biology is already acting against survival?

Age

Disease and impairment

Risk exposures

Physiological dysfunction

Conventional laboratory phenotype

Mortality-trained from conventional variables

D2 — Candidate Survivability State

In what physiological state is that burden being carried?

systemic balance

coordinated regulatory state

Defined biologically, then tested against mortality

Reflects viability under perturbation

Working model: Mortality = $f(\text{D1}, \text{D2}, \text{perturbation})$

The Phenotype a One-Dimensional Model Can Hide



The Core Hypothesis

Can two people with similarly high conventional burden have materially different subsequent mortality according to biological state?

How We Tried to Disprove D2

If D2 largely reflects conventional burden already captured by D1, its mortality association should substantially attenuate after D1 is known.

1. Build D1 from conventional biology

Use broad conventional variables.
Train directly on mortality.

Cross-fitted / cycle-held-out where specified

Fit and freeze D1 before introducing D2

2. Introduce D2 only afterwards

Test whether biologically defined state information still carries mortality information after D1 is known.

3. Result

If D2 disappears

→ one-dimensional burden explanation strengthened

If D2 persists

→ mortality contains information not exhausted by measured conventional burden

How We Operationalised D2 in Humans

We tested two candidate physiological readouts of survivability state

Continuous D2 — Systemic Balance

Albumin : Globulin

A continuous position on a fixed physiological distribution.

- Candidate readout of systemic protein balance

Discrete D2 — Regulatory State

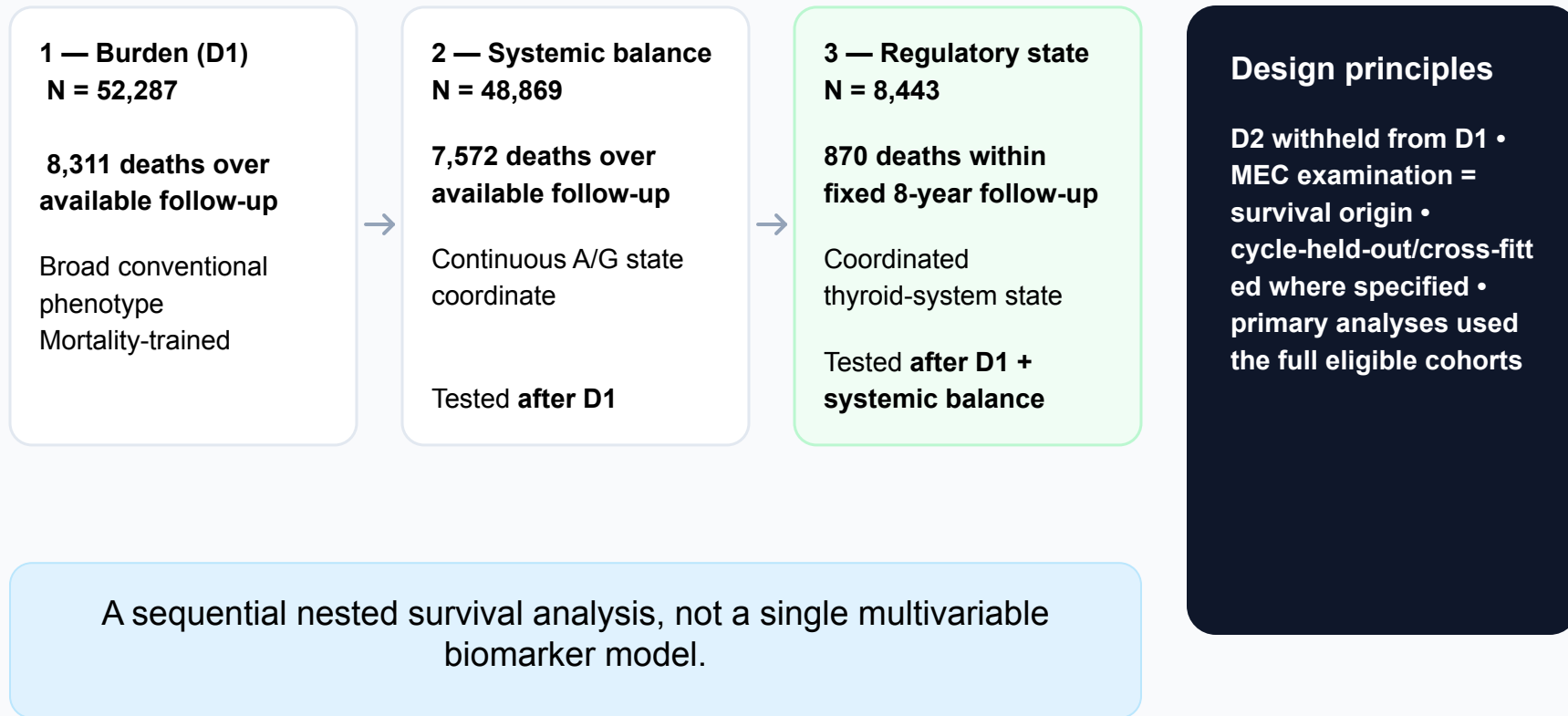
Coordinated thyroid-system configuration

Defined from the relationship among multiple thyroid-system measurements relative to age- and sex-expected physiology.

Represents a **coordinated regulatory configuration**, not simply a high or low hormone concentration

The NHANES Sequential Survival Analysis

Each new layer had to carry mortality information beyond the preceding layer.



D1: A Strong One-Dimensional Baseline

Mortality-trained conventional burden

N = 52,287

Deaths = 8,311
54 conventional
constructs

39 continuous + 15
categorical

Discrimination

C = 0.868

Mean out-of-fold
concordance

Correctly ordered
survival in 87% of
pairs

Mortality gradient

HR = 3.62/ +1 SD D1

95% CI **3.55–3.68**

Conventional information included

Age • smoking • blood pressure
• anthropometry • metabolic •
renal • haematological

**Cycle-held-out cross-fitted
penalised Cox**

Systemic Balance: A Physiology-Defined Coordinate.

1. Measure the balance

Globulin = Total Protein – Albumin

A/G = Albumin / Globulin

A simple coordinate of systemic protein balance

2. Place subjects on fixed reference distribution

Reference mean = 1.414, SD = 0.272

Continuous candidate D2 readout

Systemic balance $z = [A/G - 1.414] / 0.272$

0 = reference mean

+1 = one SD toward more favourable systemic balance

-1 = one SD toward less favourable systemic balance

3. The coordinate is specified before mortality testing

No mortality-derived weighting

No Cox optimisation of the A/G formula

No age or sex term in the coordinate

"We did not subtract D1 from A/G. A/G remains the observed physiological coordinate. The adjustment happens later, when D1 and A/G are entered together into the mortality model."

Systemic Balance Retains Mortality Information After D1

48,869

Participants (1999–2018)

7,572 deaths with pooled HR 0.900 (95% CI 0.881–0.921)

0.90

HR per +1 SD (~10% Lower Hazard)

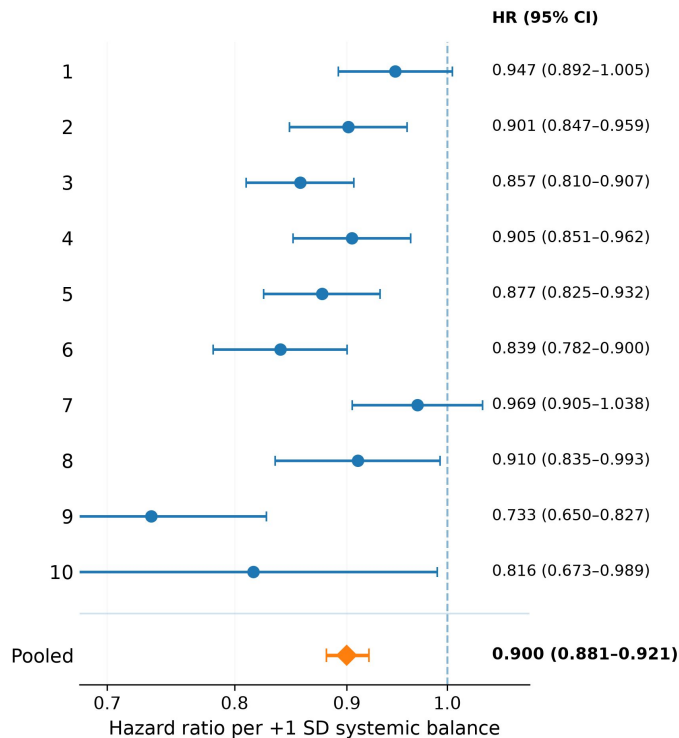
10 / 10

NHANES Cycles

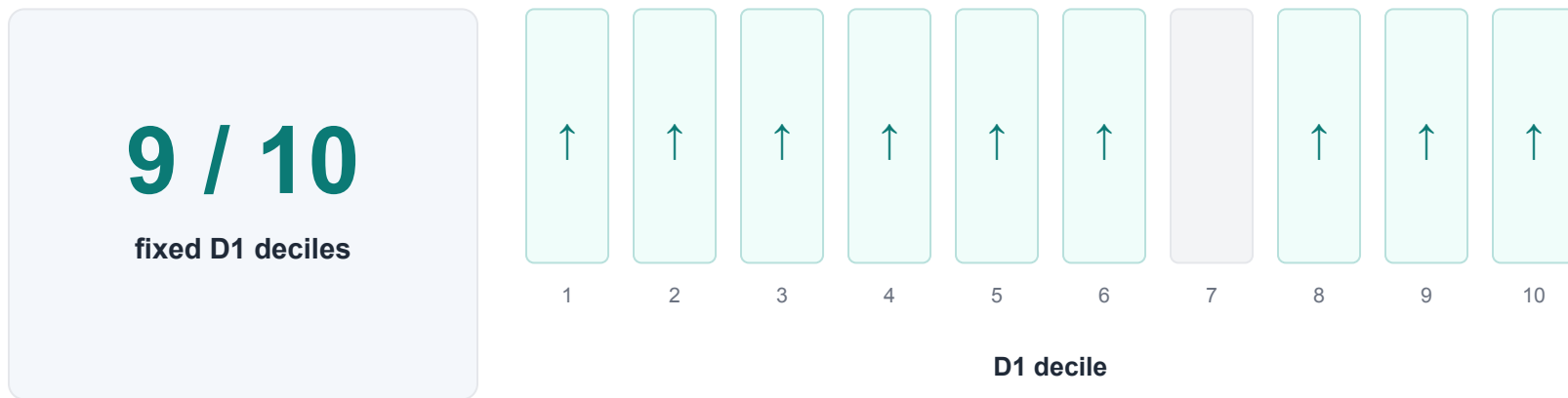
All ten cycles consistently show the same protective direction.

Interpretation

A predefined systemic-balance coordinate carried mortality information beyond the conventional D1 score.



The Signal Persists Across the D1 Distribution



At similar levels of conventional burden, survivors generally had more favourable systemic balance than those who died.

A Second Candidate State: Coordinated Thyroid Regulation

Not a single hormone level — a coordinated physiological configuration

The state was defined from the joint pattern of thyroid-system measurements relative to **age- and sex-expected physiology**.

State present

779 / 8,443 = 9.23%

Deaths within 8 years

870

Mortality association

HR $\approx$ 0.76

after D1 + systemic balance

p $\approx$ 0.029

$\approx$ 24% lower relative mortality hazard for the favourable state

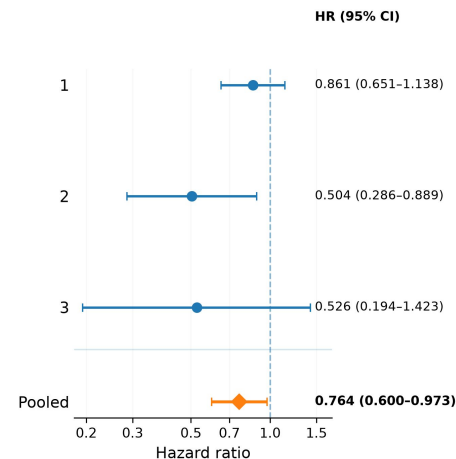
Direction across cycles

2007–08: HR 0.861

2009–10: HR 0.504

2011–12: HR 0.526

Heterogeneity: **p $\approx$ 0.17**



FT3 • FT4 • log TSH • log FT3/FT4

4-of-4 favourable state based on age- and sex-residualised values

How We Define Reserve

Mortality model:

$$h(t) = h_0(t) \times \exp(\beta_{D1} \times D1 + \beta_{AG} \times A/G \text{ z} + \beta_T \times \text{Thyroid State})$$

D1

Conventional mortality burden

Reserve contribution

$$\beta_{AG} \times A/G \text{ z} + \beta_T \times \text{Thyroid State}$$

Continuous systemic balance + discrete regulatory state

Reserve is the combined mortality contribution of the two candidate state signals, tested in addition to D1.

The Key Phenotype: Similar High Burden. Different Survival.

Age ≥65, highest D1 quintile. N=404

75.2%

Low Reserve

observed 8-year mortality

60.6%

Intermediate

observed 8-year mortality

55.6%

High Reserve

observed 8-year mortality

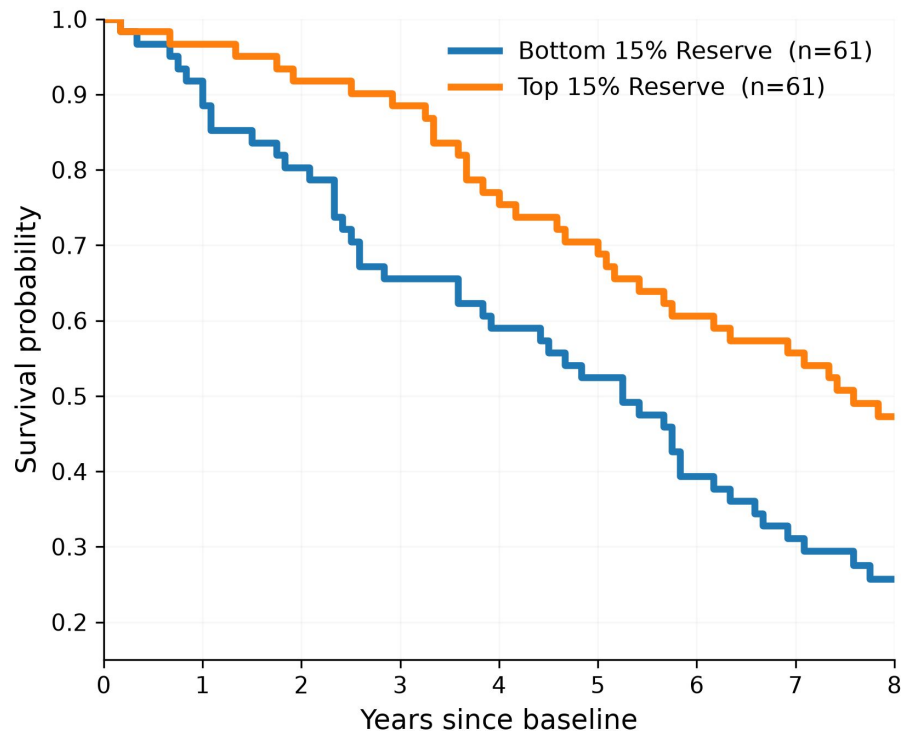
19.6 %

percentage-point difference

between low and high Reserve

Among people with similarly high conventional burden, mortality differed markedly according to Reserve.

At High Burden, Reserve Separates Survival Over Time



8-YEAR MORTALITY

74.3% vs 52.7%

Bottom 15% vs. Top 15%
Reserve

ABSOLUTE DIFFERENCE

21.6% percentage-point
difference

Log-rank $p = 0.0063$

Matched Pairs: At Similar Burden, Who Survived?

353

Matched Pairs

Strictly controlled for:
Cycle • Age • Sex • D1 Burden

59.5%

Higher Reserve

Of pairs had a survivor with higher
baseline Reserve than their
decedent match ($p = 0.00021$)

+0.294

SD Difference

Survivor Mean: **+0.032**
Decedent Mean: **-0.262**

Even among people with similar conventional burden, survivors tended to have higher baseline Reserve.

Is Mortality Two-Dimensional?

D1

Accumulated Burden

What adverse biology has accumulated?

D2

Regulatory Program

What regulatory program is the organism running while carrying that burden?

Key Takeaway

Longevity may not require preservation of a youthful program. It may require the right program for the conditions being carried.