Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit

Pyrkov Timothy V., et al., Nature Communications 2021

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Aim and objectives

Main hypothesis:

Dynamic organism state indicator (DOSI) is able to reflect the biological aging of the body, predict mortality, and the maximum life expectancy in humans.

Tasks:

- Principal component analysis (PCA)
- DOSI construction using Cox Proportional Hazards Model
- Study relationship between DOSI and aging/lifespan

Theories of aging

Programmed

Aging as certain predetermined, timed phenomena

Causes death directly

Stochastic

Aging as events that occur randomly and accumulate over time

Causes death directly

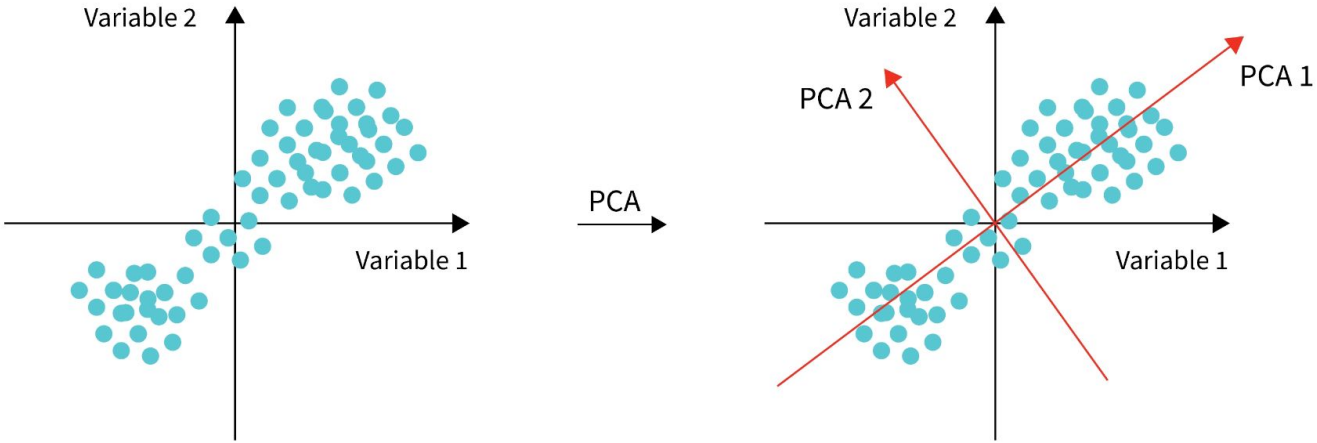
Quasi - programmed

Aging as a shadow, manifestation of growth, development, differentiation. Aging - pseudo-program

Doesn’t cause death directly

PCA theory

PCA decomposes multivariate dataset in a set of orthogonal components that explain a maximum amount of variance



Best-fitting line - one that minimizes the average squared perpendicular distance from the points to the line

PCA

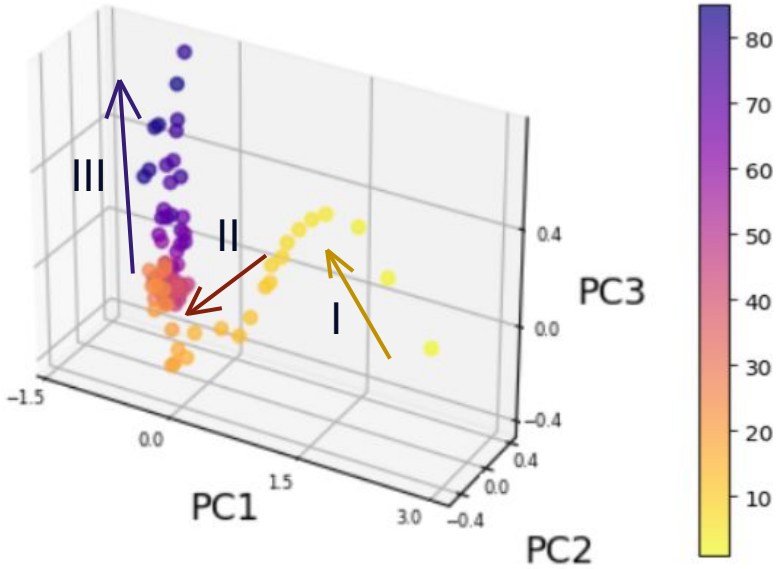
PCA follows an age-cohort averaged aging trajectory

Segments of the aging trajectory

I) age < 20

II) age 20–50

III) age > 50



Cox Proportional Hazards theory

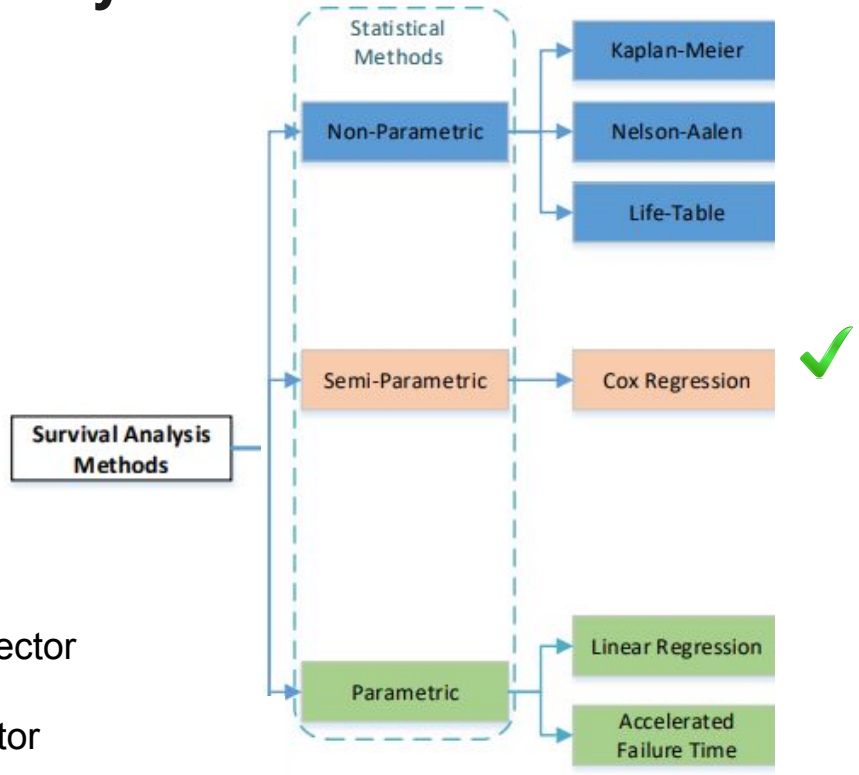
Hazard function for patient *i* :

$$h(t, X_i) = h_0(t)exp(X_i\beta),$$

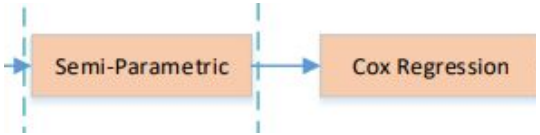
$h_0(t)$ - baseline hazard

$X_i = (x_{i1}, x_{i2}, \cdots, x_{iP})$ - covariate vector

$\beta^T = (\beta_1, \beta_2, \cdots, \beta_P)$ - coefficient vector



Cox Proportional Hazards theory



$$h(t, X_i) = h_0(t)exp(X_i\beta),$$

Why Cox PH is semi-parametric?

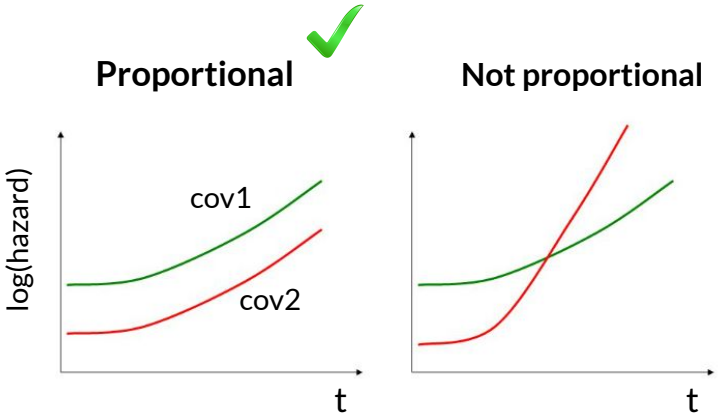
- $h_0(t)$ is not specified, outcome distribution is unknown

Why Proportional hazards model ?

- All subjects share same $h_0(t)$

  hazard ratio is independent of baseline hazard and time:

$$\frac{h(t, X_1)}{h(t, X_2)} = \frac{h_0(t)exp(X_1\beta)}{h_0(t)exp(X_2\beta)} = exp[(X_1 - X_2)\beta]$$



Cox Proportional Hazards theory

How everything is calculated?

- Cox PH - regression model, but $h_0(t)$ is not specified ⟹ **can't use standard likelihood**

Solution:

β	$h_0(t)$
Of interest	Nuisance
Partial likelihood	Breslow estimator

Cox Proportional Hazards theory

β estimation

Maximizing

Individual probability corresponding to Xj

covariate vector of patient who died at T_j

$$\frac{h(T_j, X_j)dt}{\sum_{i \in R_j} h(T_j, X_i)dt}$$

patients at risk at Tj

Partial likelihood

$$L(\beta) = \prod_{j=1}^{N} \left[\frac{exp(X_j\beta)}{\sum_{i \in R_j} exp(X_i\beta)} \right]^{\delta_j}$$

each patient

censoring

Cox Proportional Hazards

Cox model results

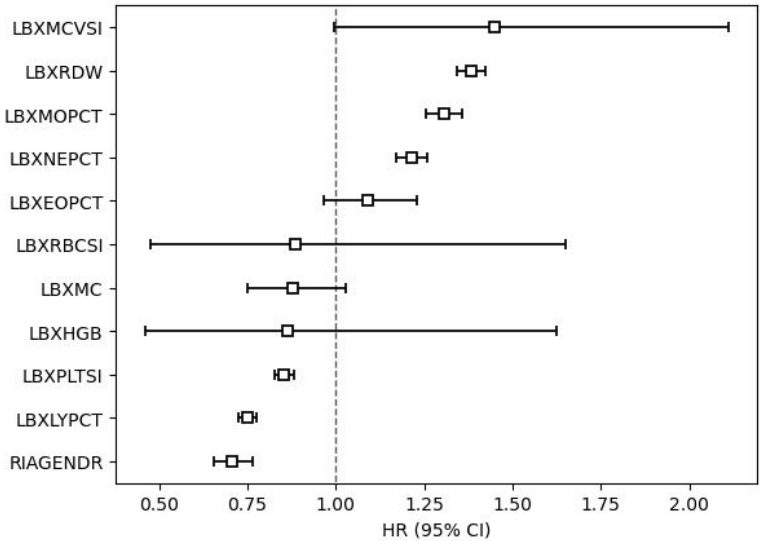
DOSI

$$\underbrace{h(t|x)}_{\text{hazard}} = \overbrace{b_0(t)}^{\text{baseline hazard}} \underbrace{\exp\overbrace{\left(\sum_{i=1}^{n} b_i(x_i - \overline{x_i})\right)}^{\text{log-partial hazard}}}_{\text{partial hazard}}$$

Evaluation metric - Concordance Index

	Our model	Article
train	0.723	0.68
test	0.72	0.67

Hazard ratios for Cox model covariates



Cox Proportional Hazards

Ontogenetic growth model

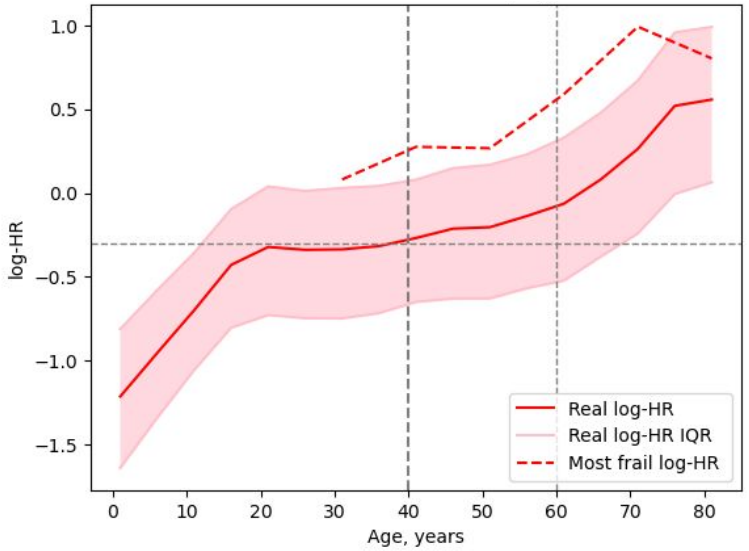
asymptotic at grown state

asymptotic at birth

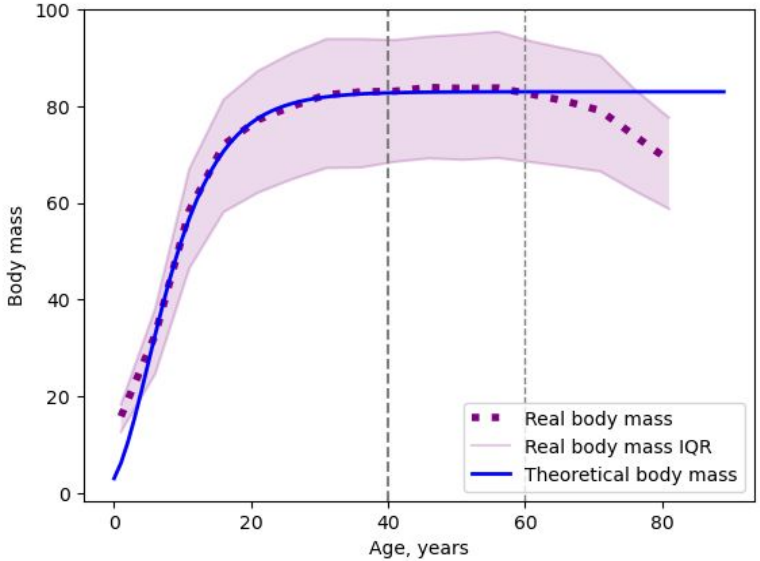
$$x(t) = X\left(1 - \left[1 - \left(\frac{x_0}{X}\right)^{\frac{1}{4}}\right] e^{\frac{-t}{t_0}}\right)^4$$

characteristic time

DOSI relationship with age

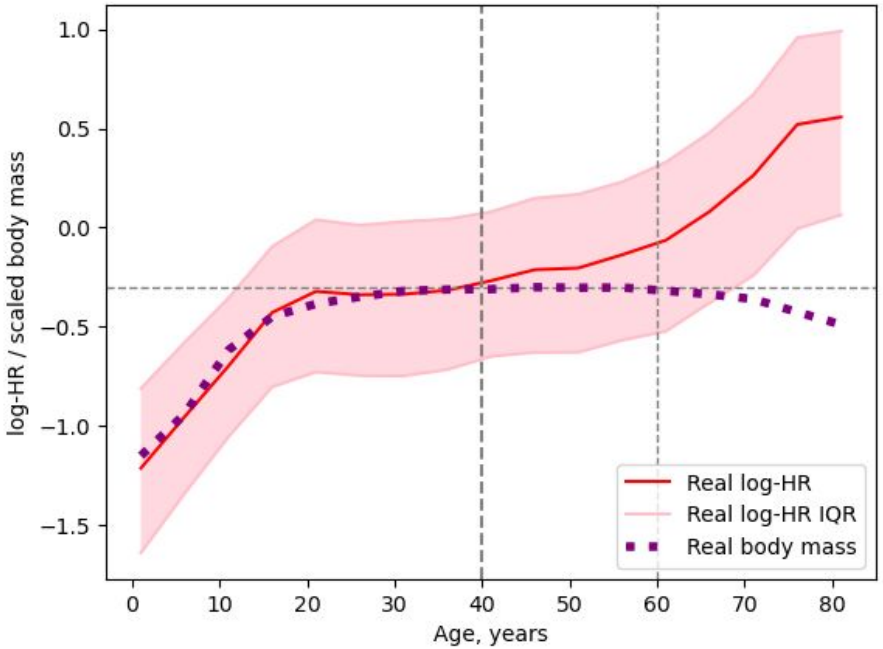


Body mass relationship with age



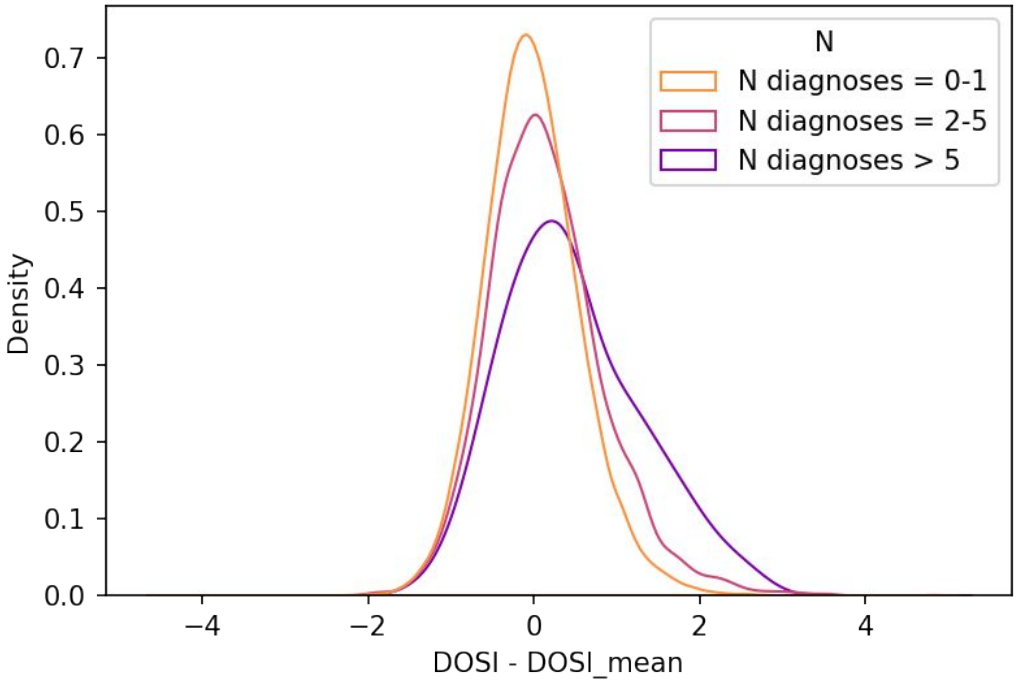
Cox Proportional Hazards

Organism state changes during age



DOSI and aging

Distributions of DOSI in cohorts in different morbidity categories



The list of health conditions:

Hypertension
Arthritis
Cancers
Coronary heart disease
Angina pectoris
Emphysema
Heart attack
Stroke
Congestive heart failure
Bronchitis

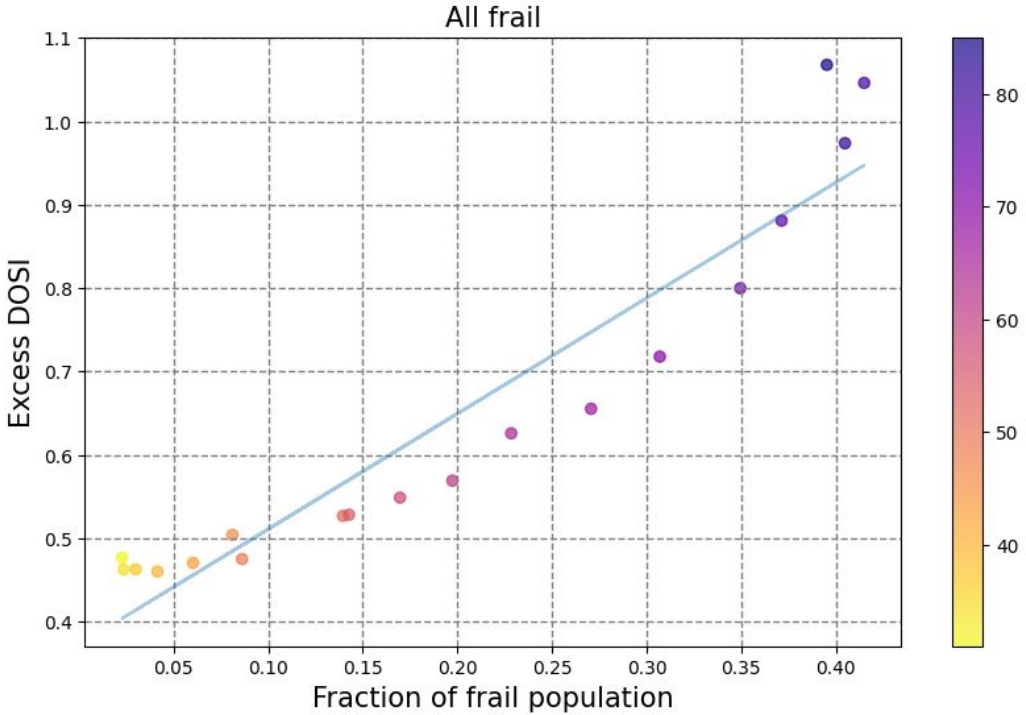
CMI (compound morbidity index)

$$CMI = \frac{Number\ of\ diagnosed\ diseases}{10}$$

(10 - total number of diseases)

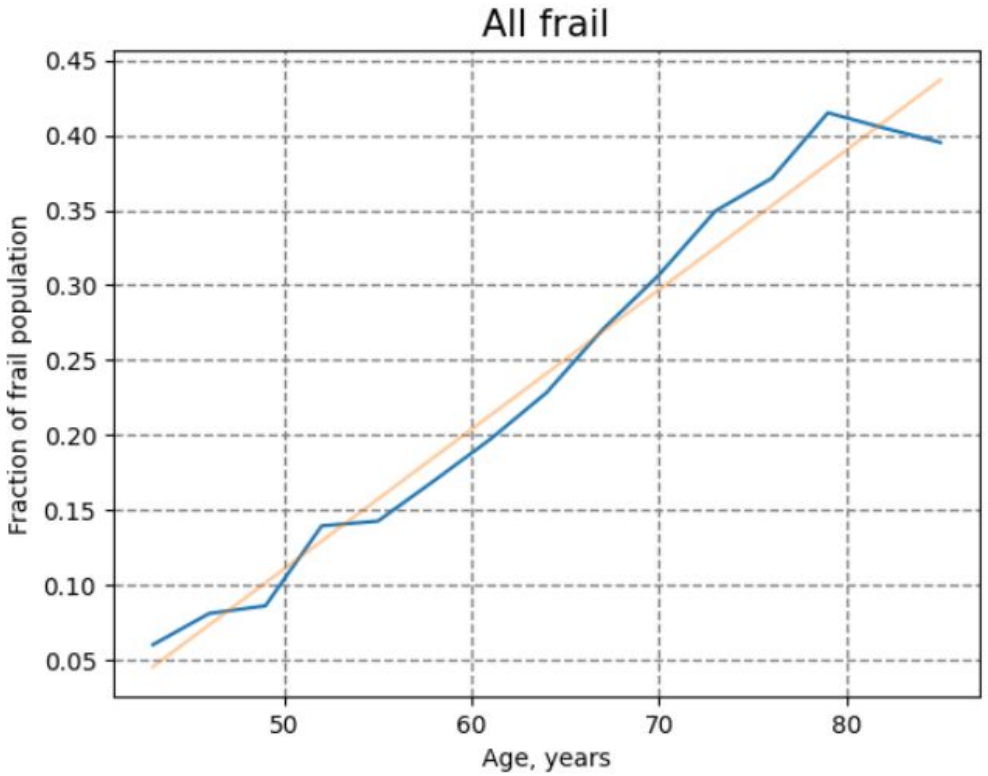
3 groups:

- non-frail (CMI <0.1)
- **frail (0,1<=CMI<0.6)**
- **most-frail (CMI>0.6)**



$$Frail\ fraction_i = \frac{(Number\ of\ frail\ and\ most\ frail\ people)_i}{Number\ of\ people\ in\ cohort_i}$$

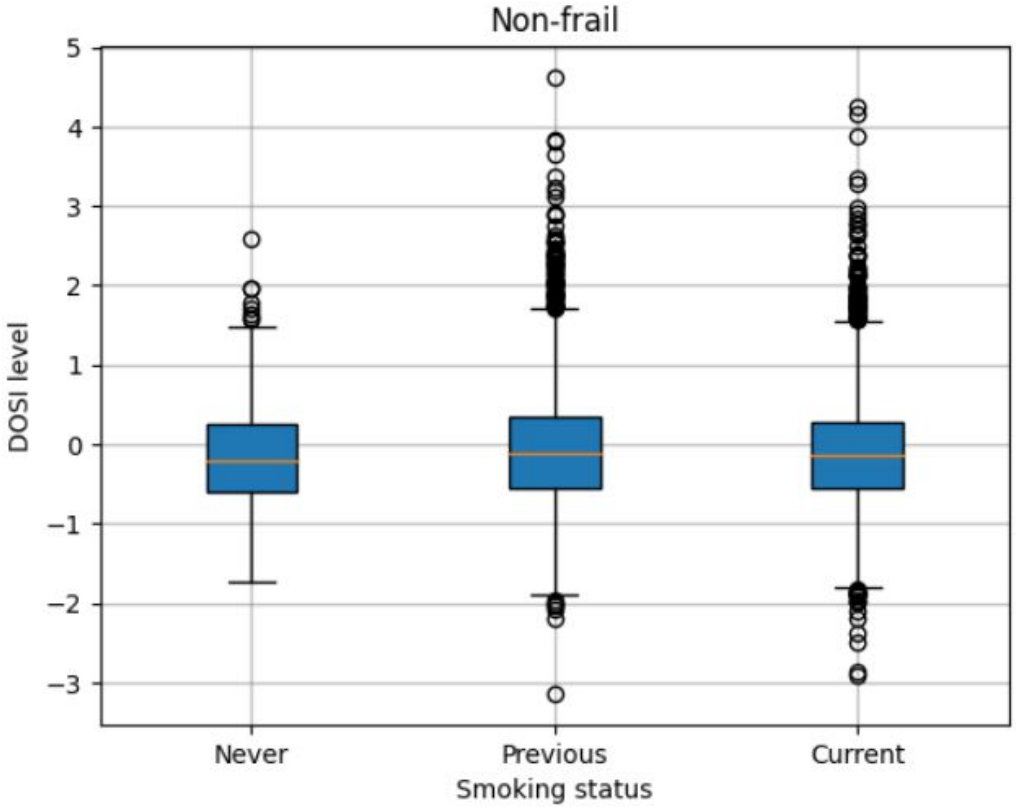
Fraction of frail population depends on age



DOSI and health risks

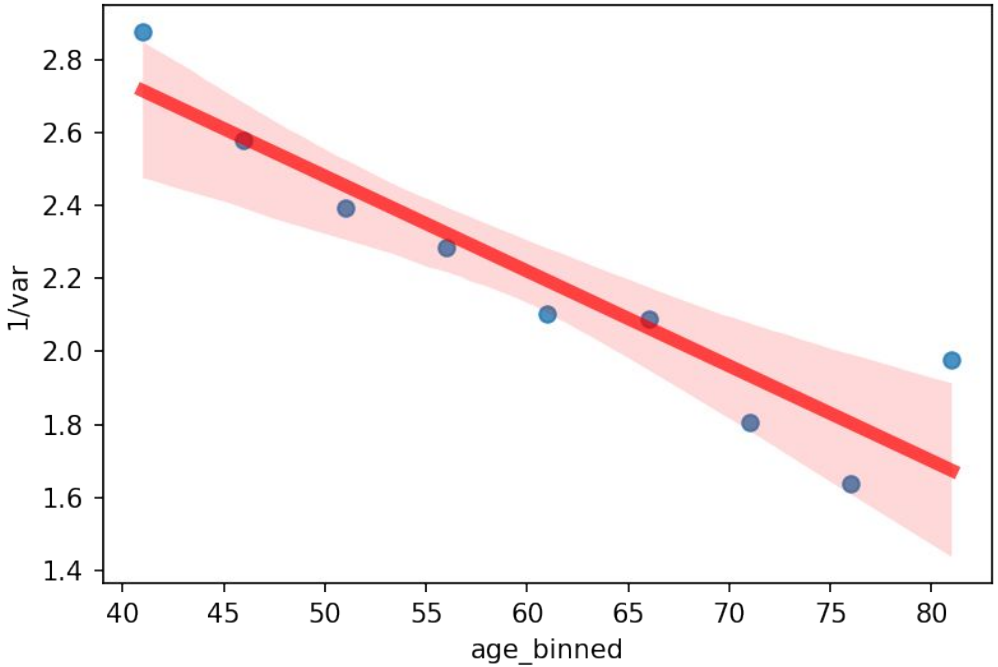
Distribution of log-hazards ratio of NHANES participants who:

- never smoked
- smoked previously
- now smokes



DOSI and aging

Distribution of the inverse variance of DOSI



Extrapolation suggests that, if the tendency holds at older ages, the population variability would increase indefinitely at an age of ~120–150 y.o.

In our model extrapolated age is 145.4

Conclusions

1) DOSI - log-linear mortality estimate from the CBC variables - can be used as quantitative measure of the aging process in aging clocks
2) DOSI distribution broadening could be explained by a progressive loss of physiological resilience
3) Complete loss of resilience occur at 120 − 150 years identifying critical point in the end of life and absolute limit of human lifespan