Leiden University
Medical Center

Metabolomics-based predictors as markers of health and disease

Dr. ir. Erik van den Akker

Molecular Epidemiology - Leiden University Medical Center

Pattern Recognition & Bioinformatics - Delft University of Technology

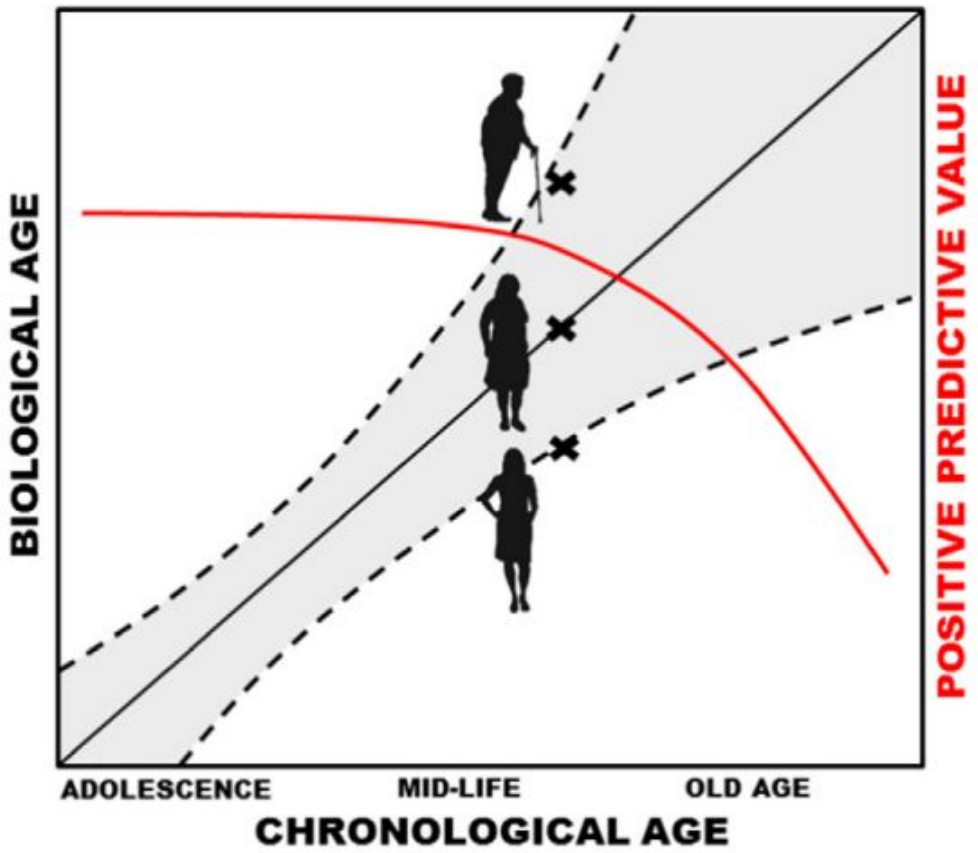
Leiden Computational Biology Center / Leiden Center for Computational Oncology

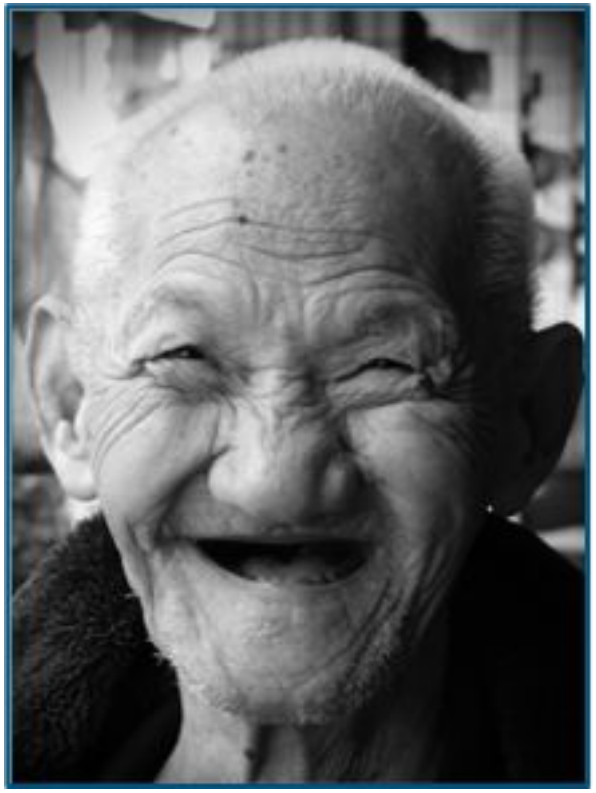
e.b.van_den_akker@lumc.nl

TU Delft

Biological Age Biomarkers

To quantify the age-related decline





Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

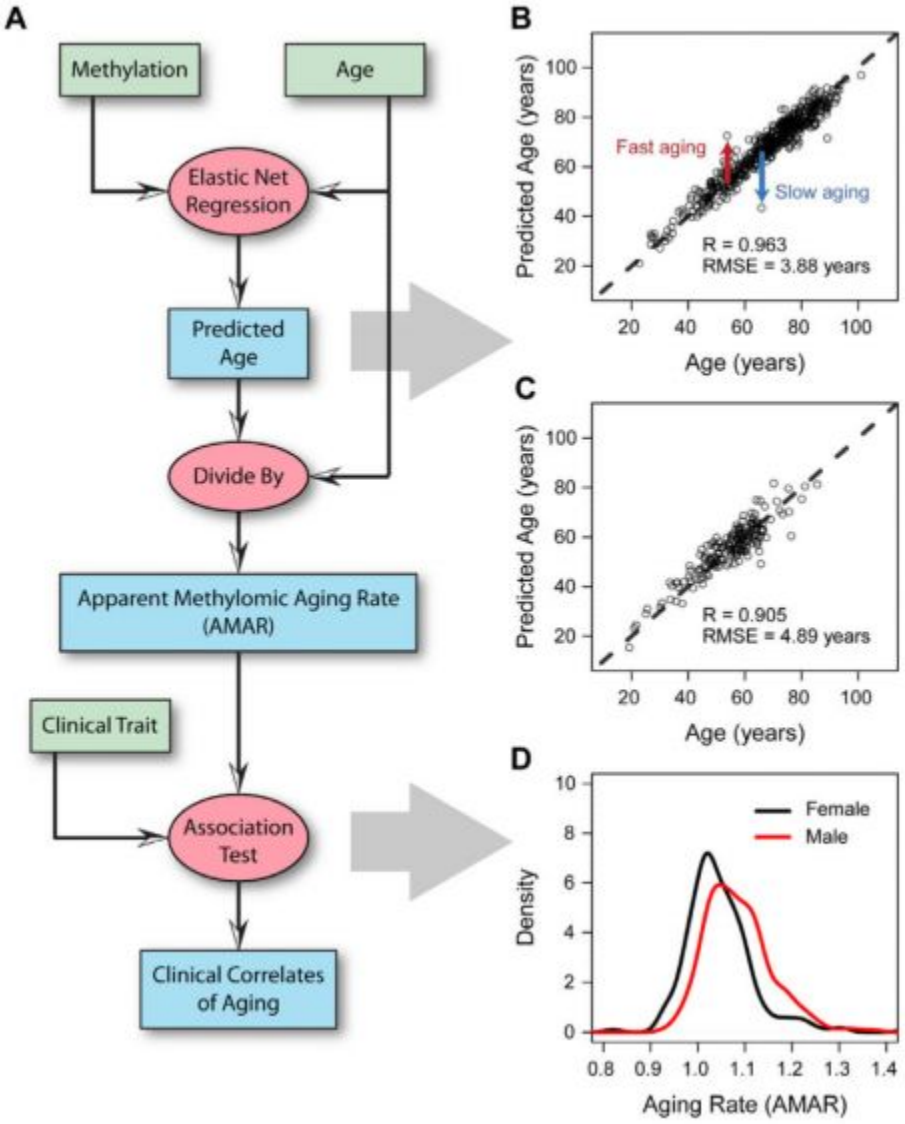
Review

Biological Age Predictors

Juulia Jylhävä, Nancy L. Pedersen, Sara Hägg *

‘Clocks’

The rationale for training (omics) age-predictors



nature COMMUNICATIONS

ARTICLE

Received 16 Jan 2015 | Accepted 7 Sep 2015 | Published 22 Oct 2015

DOI: 10.1038/ncomms9570

The transcriptional landscape of age in human peripheral blood

Marjolein J. Peters *et al.*#

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Geron A Biol Sci Med Sci*, 2015, 809–816
doi:10.1093/gerona/glu121
Original Article
Advance Access publication August 14, 2014

Original Article

Circulating Proteomic Signatures of Chronological Age

Cristina Menni,[1,*] Steven J. Kiddle,[2,3,*] Massimo Mangino,[1] Ana Viñuela,[1]

Journal of proteome research

Article

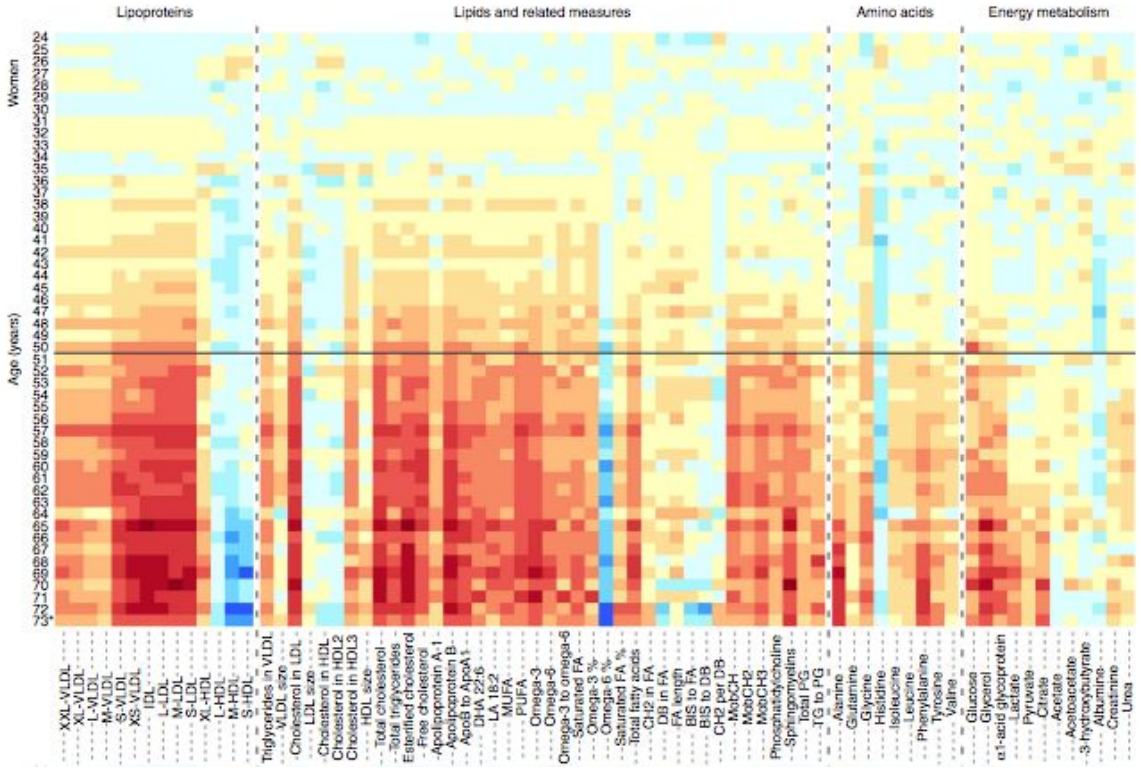
pubs.acs.org/jpr

Measuring Biological Age via Metabonomics: The Metabolic Age Score

Johannes Hertel,[*,†,∥] Nele Friedrich,[‡,§] Katharina Wittfeld,[∥] Maik Pietzner,[‡] Kathrin Budde,[‡]

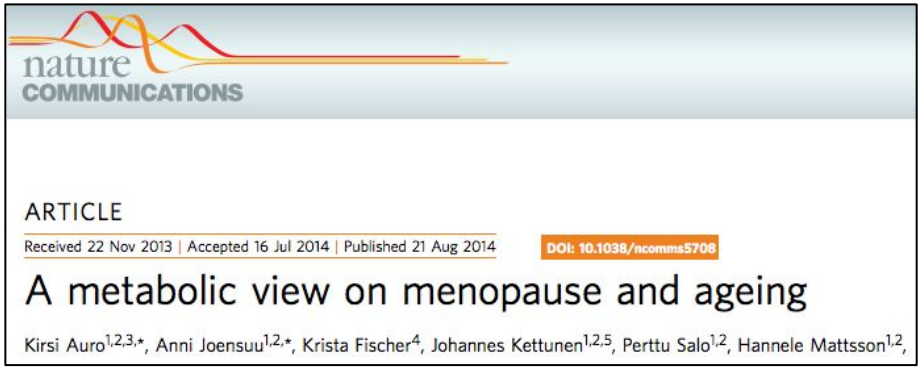
Aim

Training and evaluating a Nightingale metabolomics age-predictor



Nightingale Health blood metabolomics

- ❏ Highly standardized
- ❏ Affordable
- ❏ 226 metabolites
- ❏ Soft cardiovascular focus
- ❏ Known age-related dynamics


nature COMMUNICATIONS

ARTICLE

Received 22 Nov 2013 | Accepted 16 Jul 2014 | Published 21 Aug 2014

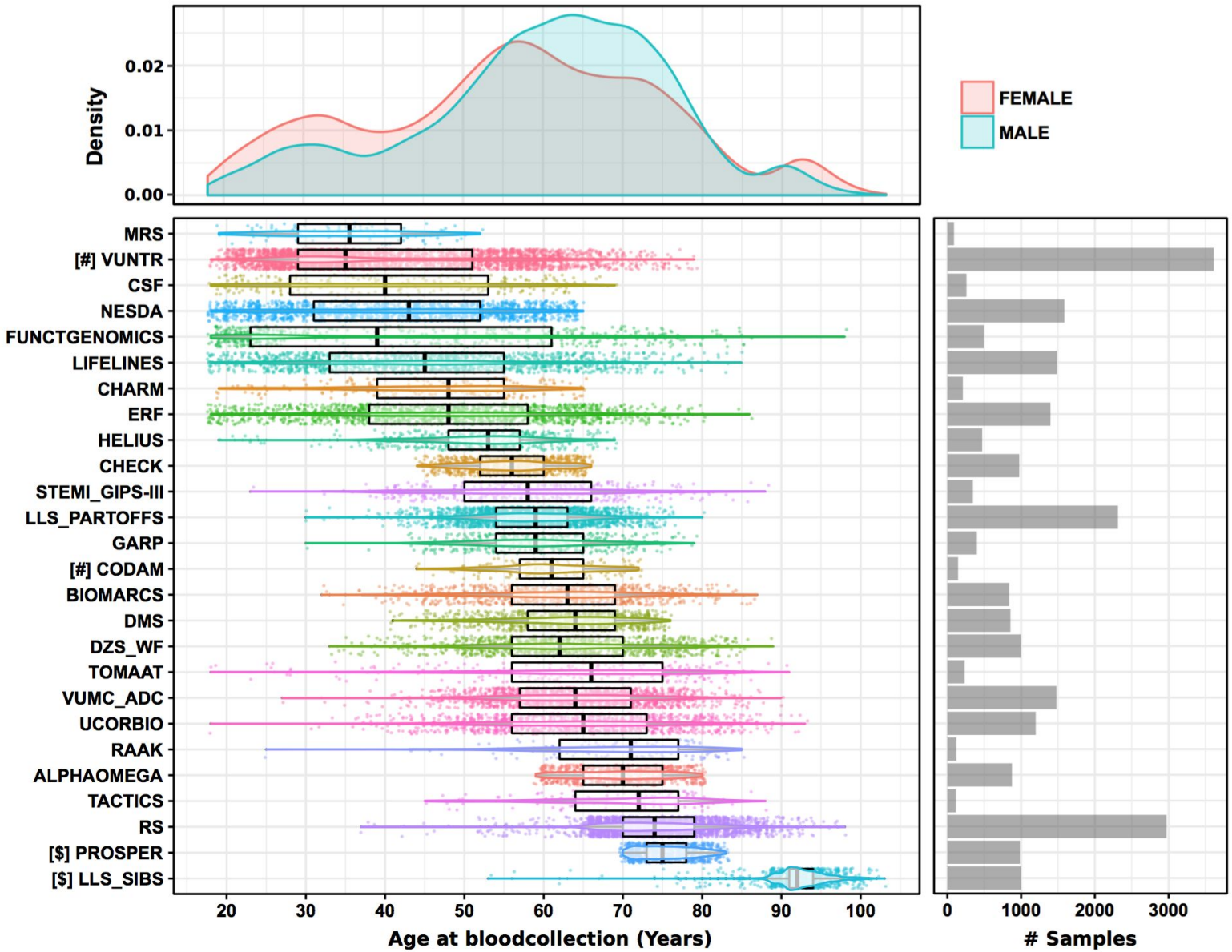
DOI: 10.1038/ncomms5708

A metabolic view on menopause and ageing

Kirsi Auro[1,2,3,*], Anni Joensuu[1,2,*], Krista Fischer[4], Johannes Kettunen[1,2,5], Perttu Salo[1,2], Hannele Mattsson[1,2],

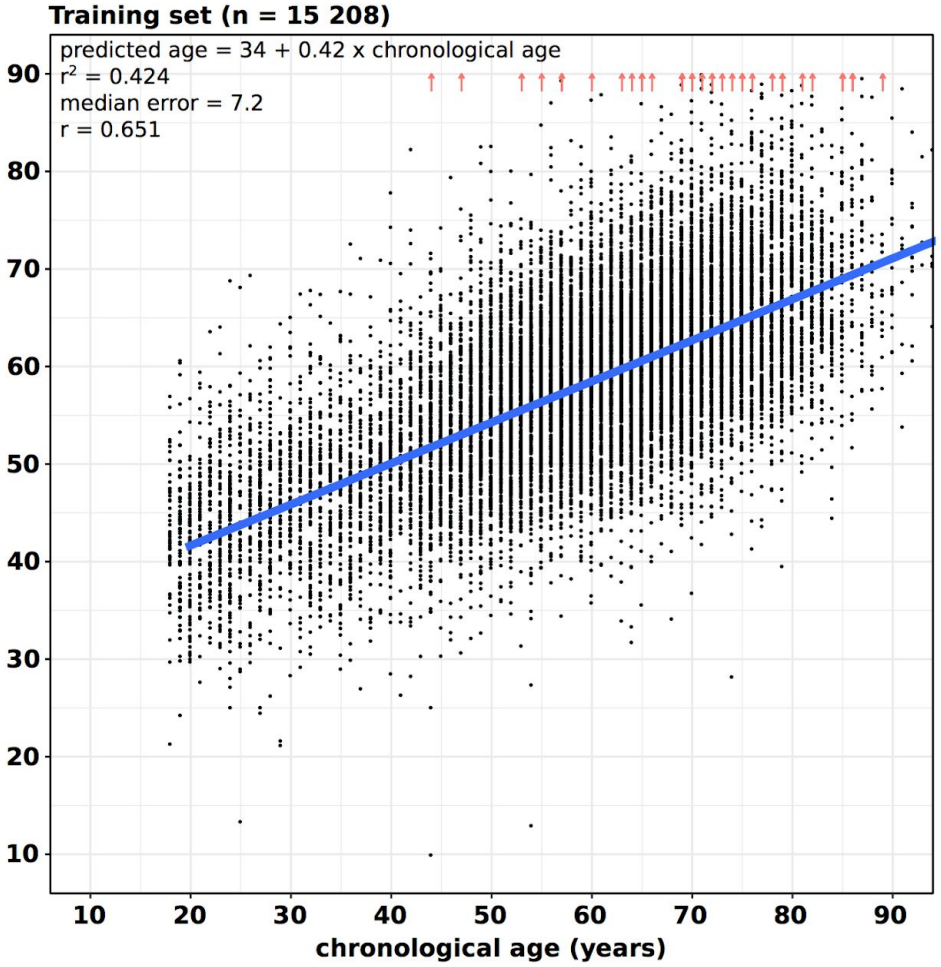
Study Population after Quality Control

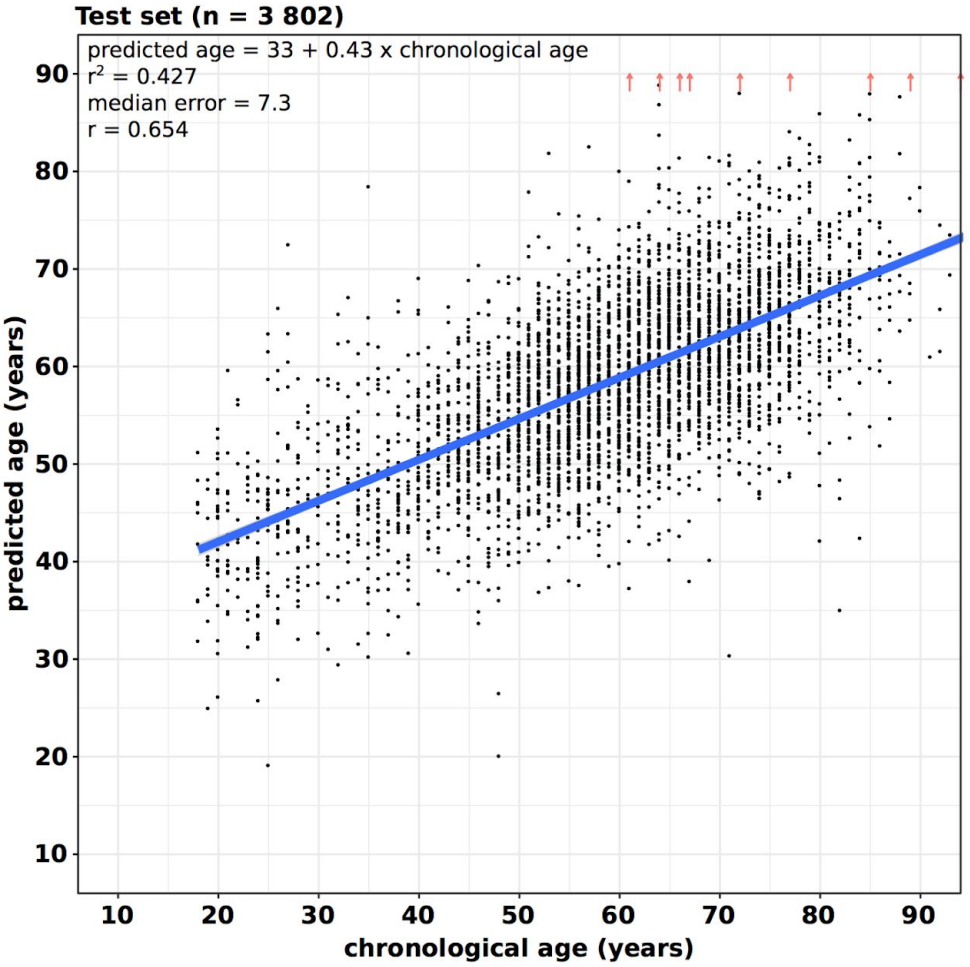
BBMRI: 25 453 samples from 26 biobanks



Training and evaluating the age-predictor

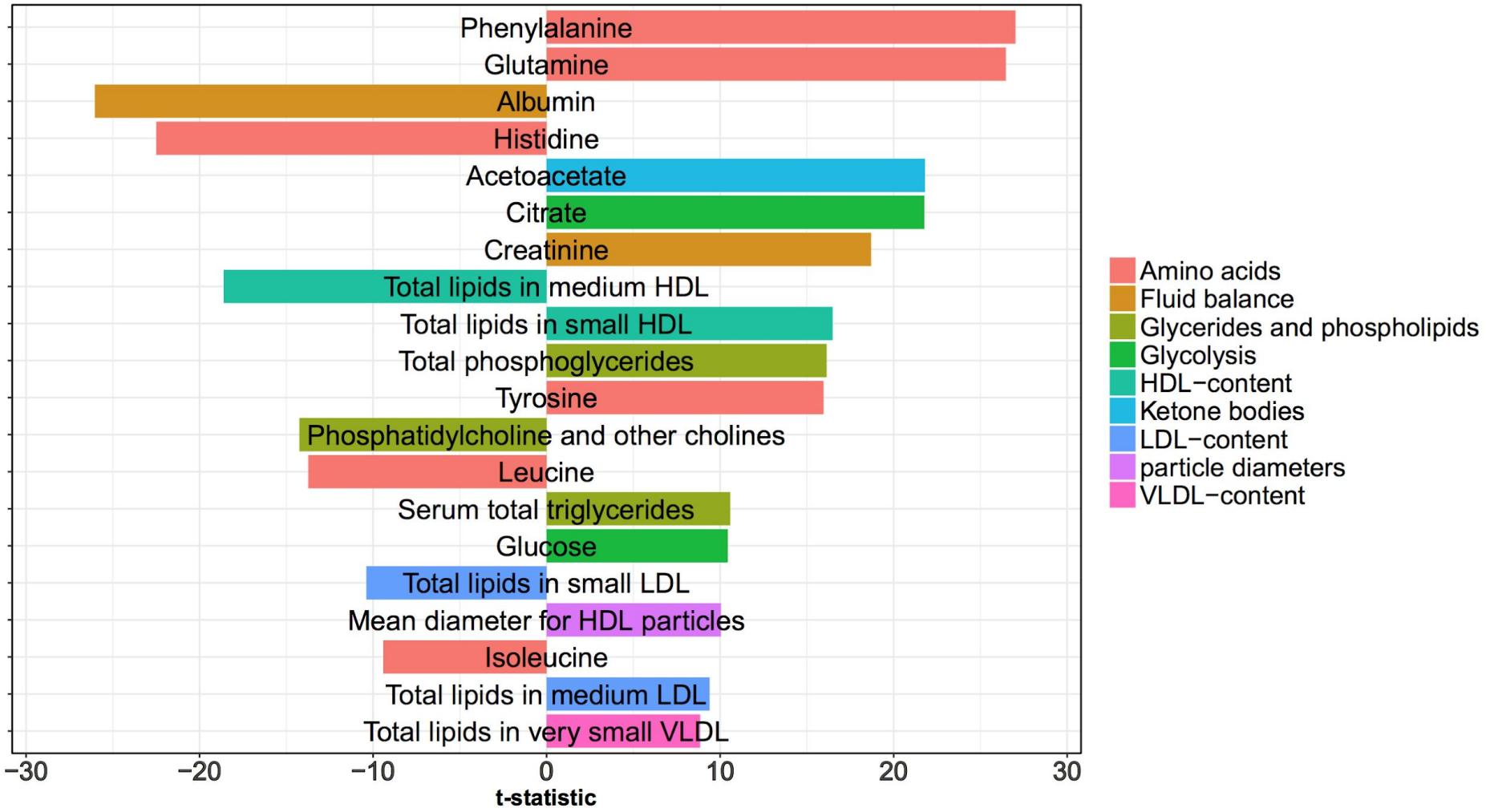
5 cross-fold validation





$$\text{predicted age} = \beta_0 + \beta_1 m_1 + \beta_2 m_2 + \ldots + \beta_{56}\, m_{56} + \varepsilon$$

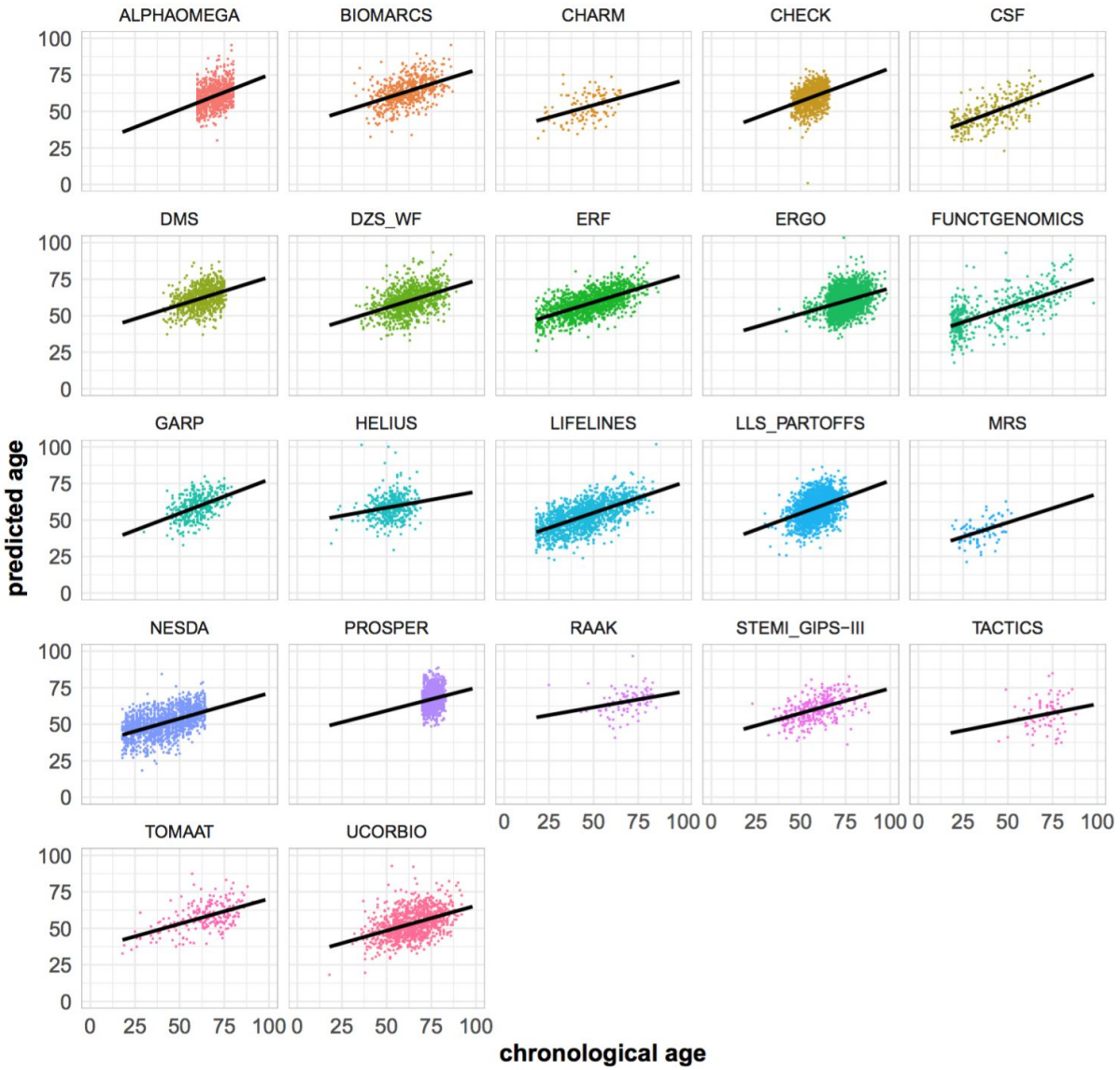
Training the age-predictor
Contributing metabolites



Note: metabolites are scaled and centered before modelling!

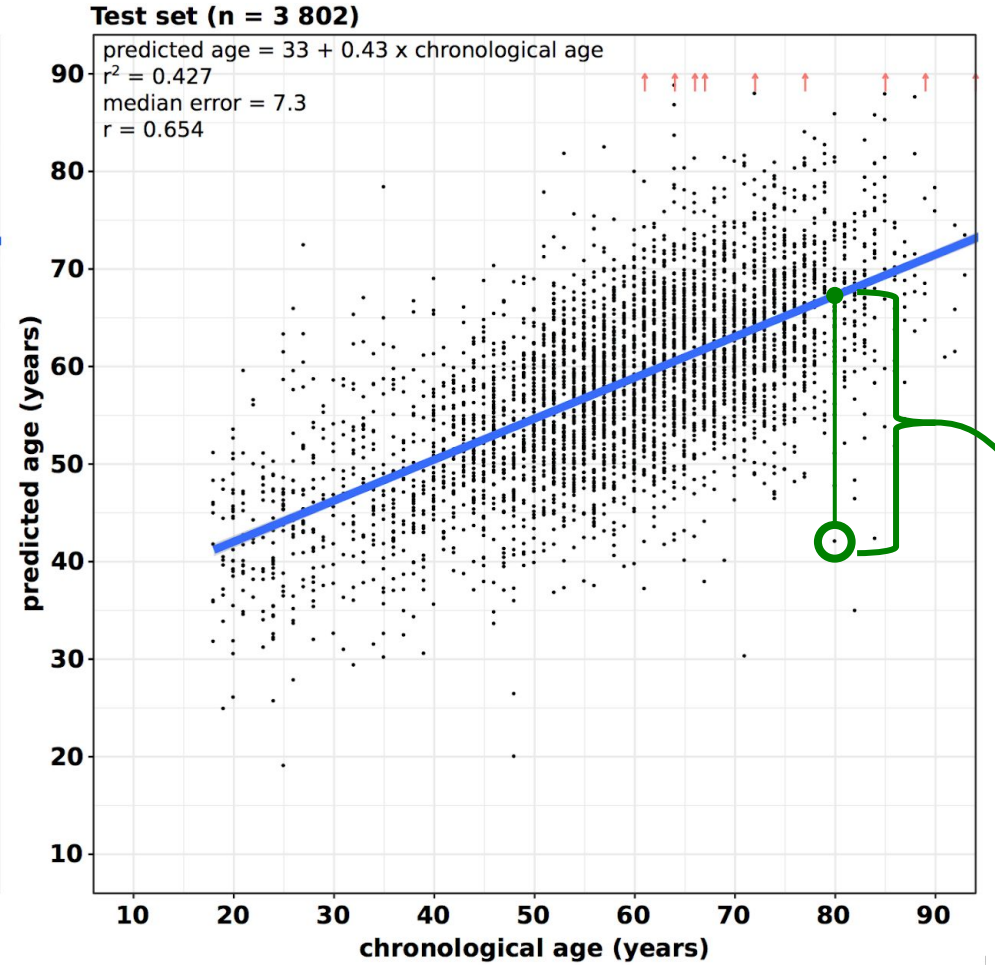
Training and evaluating the age-predictor

Leave-One-Biobank-Out Cross Validation



Construction of the metaboAge Score

The age-independent part of the age-predictor

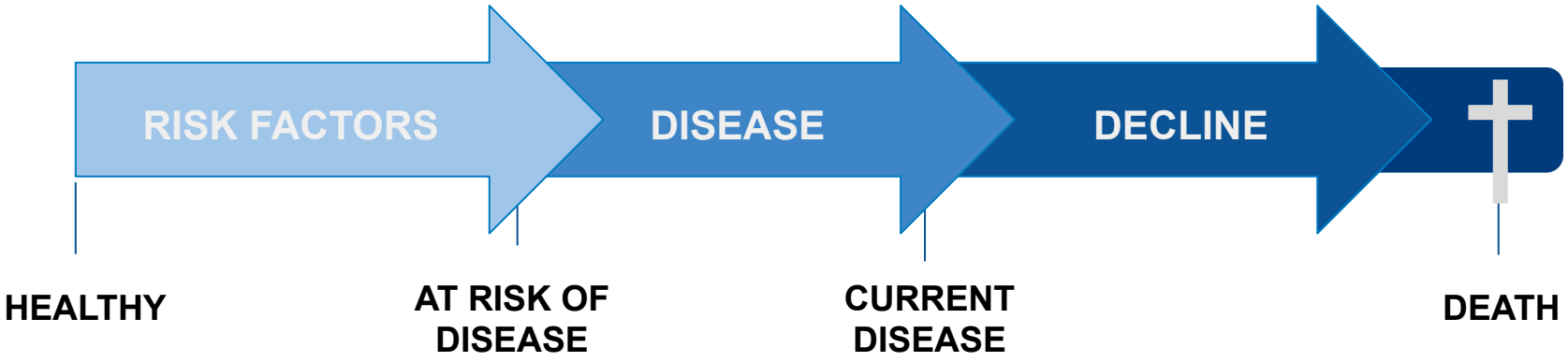


Δage = predicted age - chronological age

Regress out chronological age:
metaboAge = resid(lm(Δage ~ chron. age))

Evaluating the metaboAge Score

Tracking Age-Related Disease



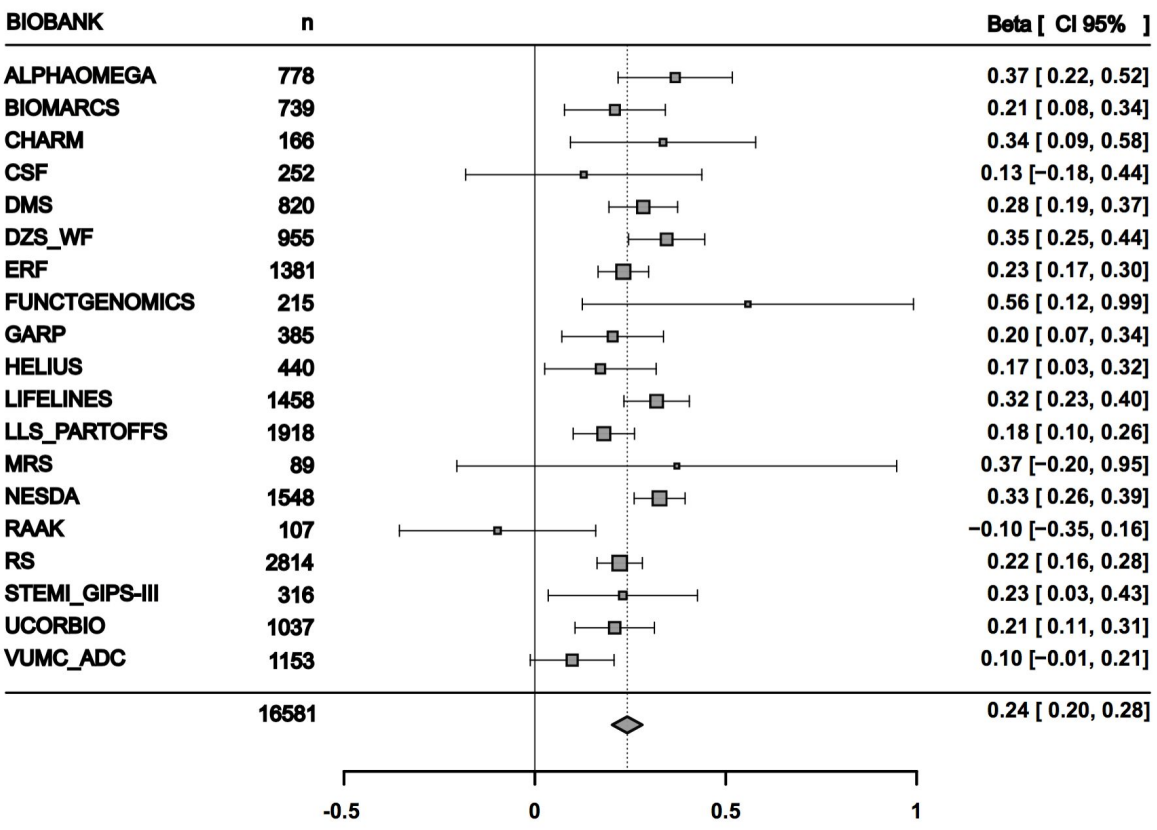
BMI
Blood Pressure
Cholesterol
...

Metabolic Syndrome
Diabetes

All-cause Mortality
heart failure
hospitalization

Associations with Clinical Risk Factors

Body Mass Index



$p_{meta} = 2.6 \times 10^{-33}$

Significant associations

BMI
hsCRP
Total Cholesterol
HDL Cholesterol
Triglycerides
Anti-hypertensive medication

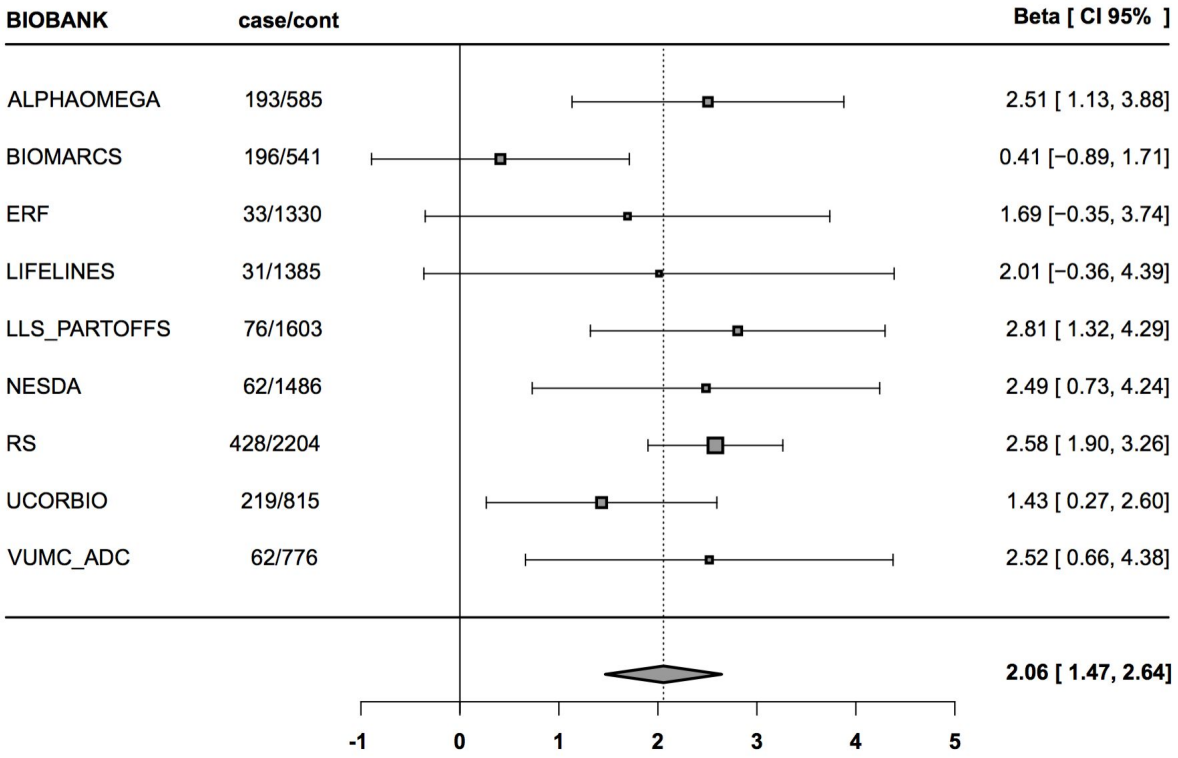
No association

SBP
DBP
Lipid lowering medication
Gender
Smoking

$$\Delta age = \beta_0 + \beta_1 BMI + \beta_2 \text{ chronological age} + \beta_3 \text{ gender} + \varepsilon$$

Associations with Current Clinical Endpoints

Diabetes Mellitus Status



Significant associations

T2D

Metabolic Syndrome

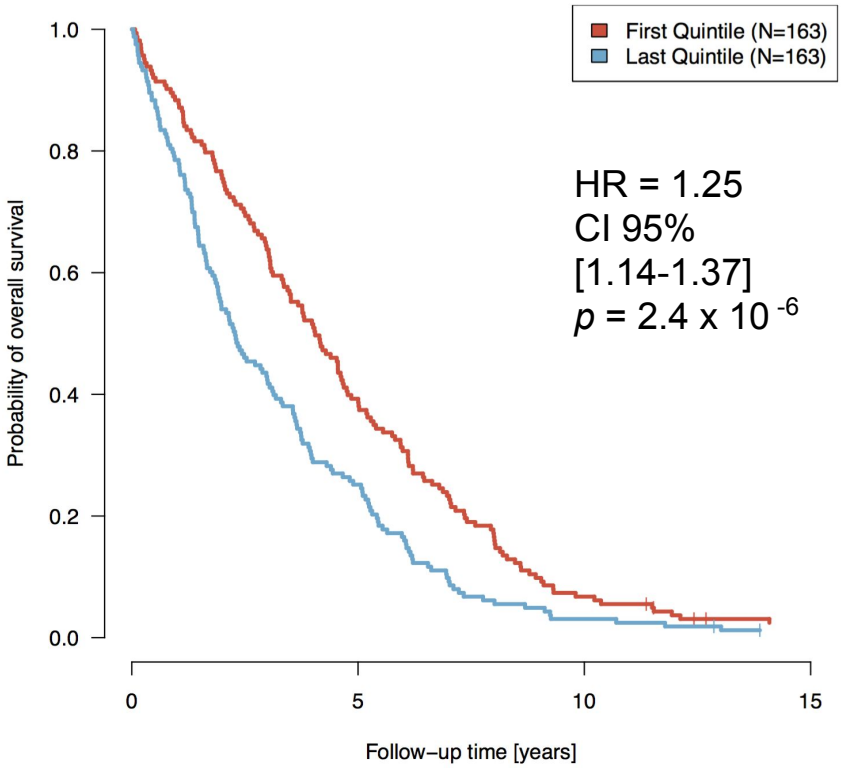
$p_{meta} = 6.5 \times 10^{-12}$

$$\Delta age = \beta_0 + \beta_1 \text{ diab status} + \beta_2 \text{ chronological age} + \beta_3 \text{ gender} + \beta_4 \text{ BMI} + \varepsilon$$

Associations with Future Clinical Endpoints

Mortality / Cardiovascular events

LEIDEN LONGEVITY STUDY - MORTALITY



PROSPER - INCIDENT CARDIOVASCULAR EVENTS

Phenotype	HR	95% CI	*p*-value
Coronary events	1.25	1.11 – 1.40	**2.64×10^{-04}**
Cardiovascular events	1.20	1.08 – 1.33	**4.86×10^{-04}**
Vascular mortality	1.57	1.31 – 1.88	**8.56×10^{-07}**
All-cause mortality	1.42	1.25 – 1.61	**9.14×10^{-08}**
Heart failure hospitalisation	1.68	1.37 – 2.06	**5.42×10^{-07}**

Cox proportional hazards model:

$$FUT = \beta_0 + \beta_1 \Delta age + \beta_2 \text{ chronological age} + \beta_3 \text{ gender} + \varepsilon$$

Effect independent of BMI, smoking, diabetes and hypertension and medication

Conclusions
Summary of main findings

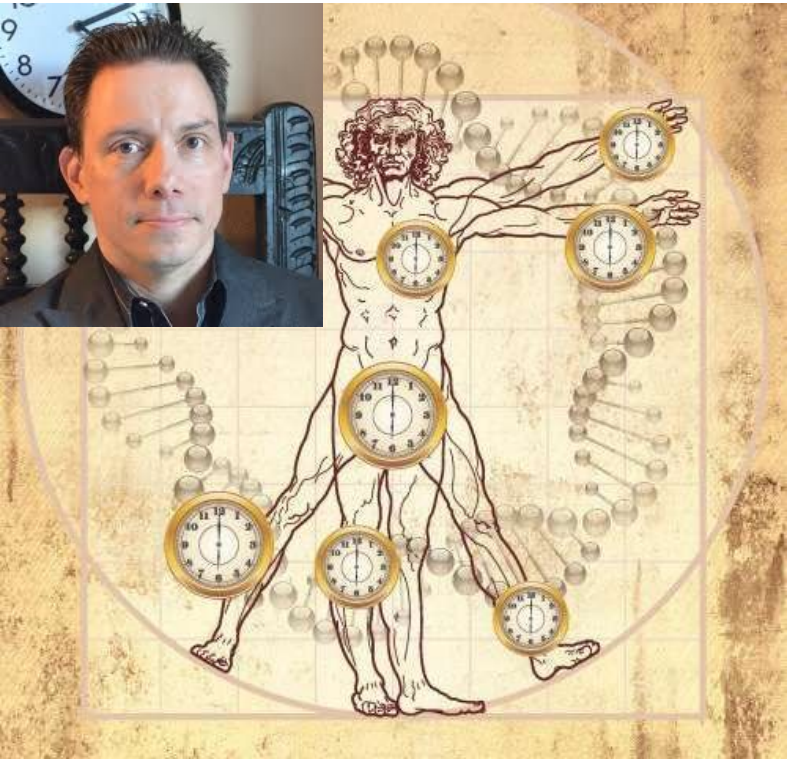
- *Nightingale Health* blood metabolomics predicts age reasonably (r = 0.65)
  - Comparable with transcriptomics & metabolomics clocks
  - Worse than epigenetics clocks (r > 0.9). **Does this matter?**

- *MetaboAge* shows promise as an biomarker
  - *MetaboAge* associates significantly with clinical risk factors
  - *MetaboAge* associates significantly with current clinical end points
  - *MetaboAge* associates significantly with future clinical end points

- *MetaboAge* is:
  - Highly standardized
  - Affordable
  - Easy to implement

Discussion
Other clocks

Small correlation with
Horvath's methylation clock



DUSRAVOILA
VITALITY ORIENTED INNOVATION FOR THE LIFECOURSE OF THE AGEING SOCIETY

What outcomes do the clocks predict?
What do they predict independently?

Small correlation with
Deelen's mortality predictor

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11311-9 OPEN

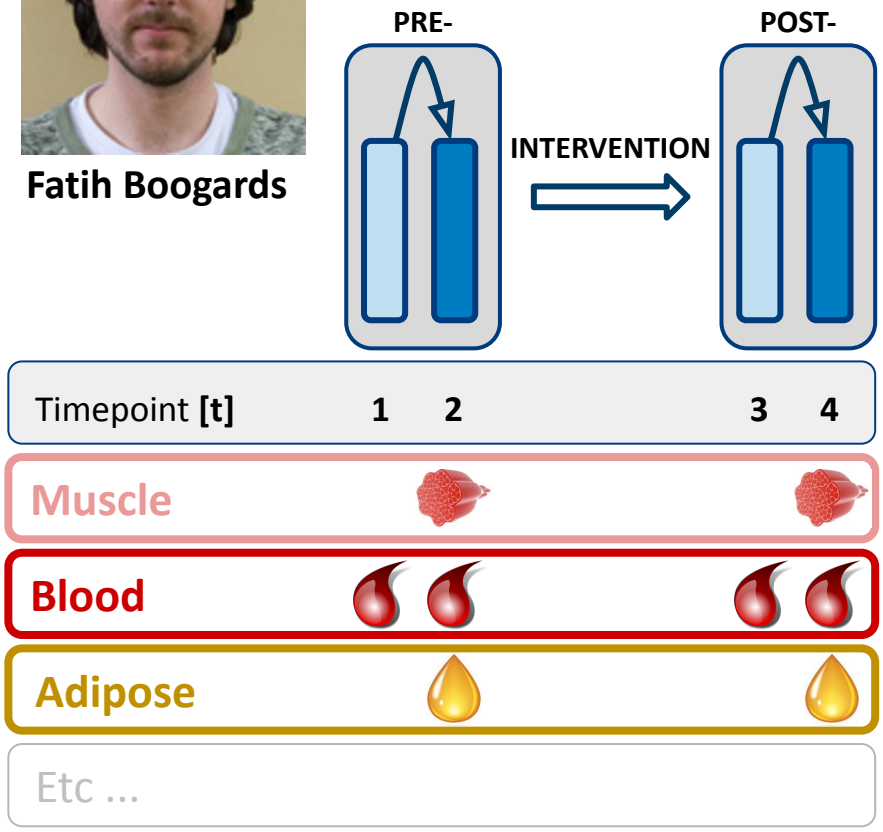
A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals

Joris Deelen et al.#

Discussion
Metabolomics as a read-out of intervention success

Fatih Boogards

MetaboAge is not affected by the intervention
Yet the intervention can be captured by metabolomics predictors



IN SHORT: NUMBERS

164 middle-aged undergoing a **13-week** lifestyle intervention

12.5% less intake
12.5% more excercise

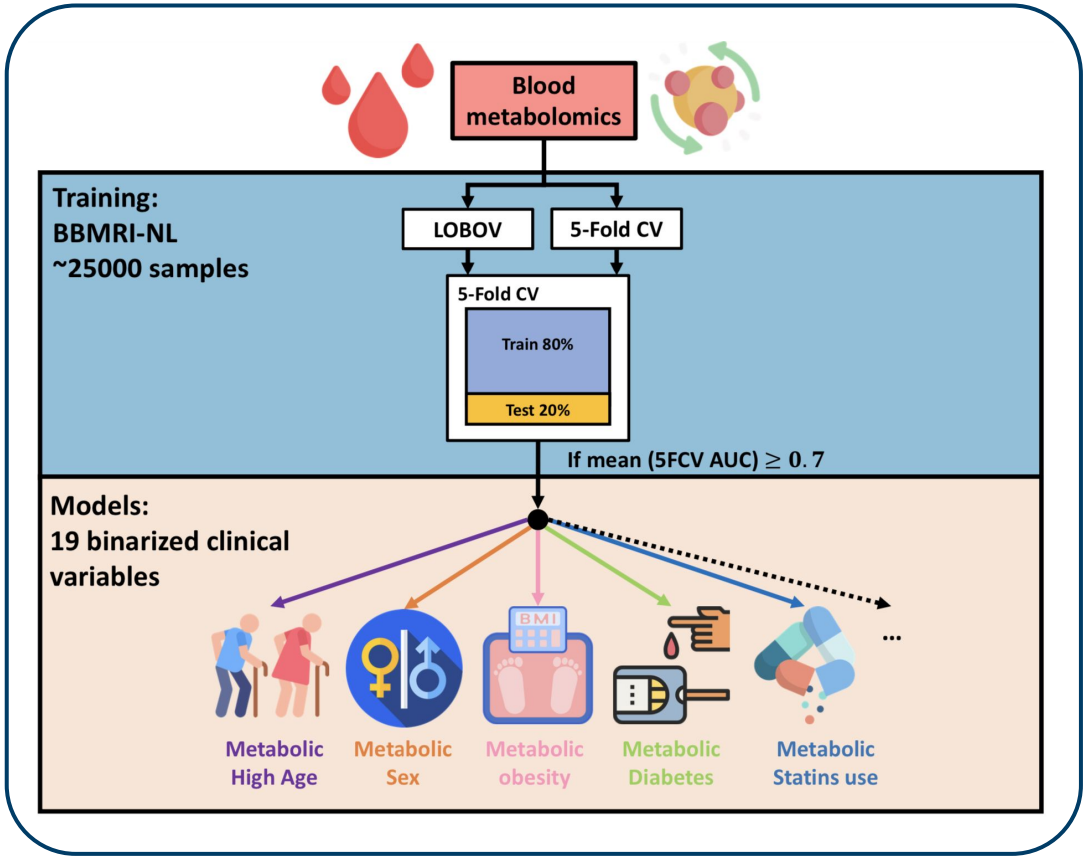
Outlook & related work

Clock-like approaches: other surrogate markers

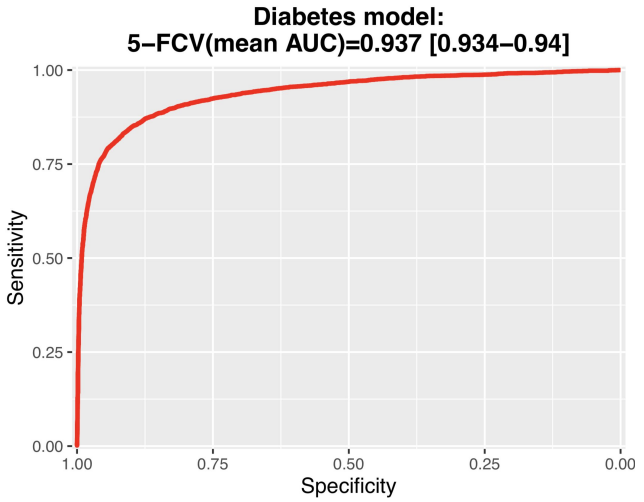
Daniele Bizzarri

Other risk factors might be readily predicted …

… And transformed in discrepancy-based predictors



Application 1: Imputation



Application 2: Risk prediction

ΔDiabetes, ΔObesity, …

Outlook & related work

Clock-like approaches: what platform captures relevant signal?

Cathelijn Kuijt

Dennis Mook

Platform	Samples	Measurements
Nightingale	349	224
Biocrates	356	163
Lipidyzer	307	1107
Metabolon	304	762

ELANET (fixed)	AGE		BMI		SEX		DIAB	
R-squared	RSQ	df	RSQ	df	RSQ	df	RSQ	df
Nightingale	35,72%	96	36,01%	42	68,91%	58	47,88%	45
Biocrates	47,25%	121	42,17%	96	55,96%	94	55,49%	50
Lipidyzer	51,88%	154	17,51%	104	38,03%	231	35,75%	129
Metabolon	59,50%	162	48,66%	188	77,00%	195	60,23%	135

Some platforms are more predictive for cardio-metabolic variables

Availability
Manuscript & tools

metaboAge

Welcome to the webtool for calculating metabolic age (*'metaboAge'*) from raw Nightingale Health 1H-NMR metabolomics data.

Please refer to our manuscript when using metaboAge in your work:

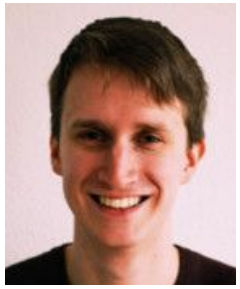
E.B. van den Akker et al. "MetaboAge: a novel biomarker for biological age based on the BBMRI-NL 1H-NMR metabolomics repository" (submitted)

Instructions

For the webtool to work, the input data needs to be provided in a specific format. This format should be similar to the raw data files you received from Nightingale Health.

Please ensure that your dataset looks like this *example dataset* before submitting.

This means that:



Jurriaan Barkey Wolf

Daniele Bizzarri

R-shiny application is coming to compute metaboAge and other scores!

Acknowledgements

Leiden University Medical Center

Section of Molecular Epidemiology

Eline Slagboom
Marian Beekman
Thies Gehrmann
Daniele Bizzarri
Jurriaan Barkey Wolf
Joris Deelen
Fatih Bogaards

Department of Medical Statistics

Jelle Goeman
Hein Putter

Department of Internal Medicine

Wouter Jukema
Dennis Mook
Stella Trompet

Leiden Computational Biology Center

Marcel Reinders
Cathelijn Kuijt

BBMRI-NL Consortium Partners

BBMRI.nl
Biobanking and BioMolecular resources Research Infrastructure The Netherlands

IDEAL ageing

MIMOmics

Netherlands Consortium for Healthy Ageing

ZonMw

DUSRAVOILA
VITALITY ORIENTED INNOVATION FOR THE LIFECOURSE OF THE AGEING SOCIETY

Health~Holland

Holland.