

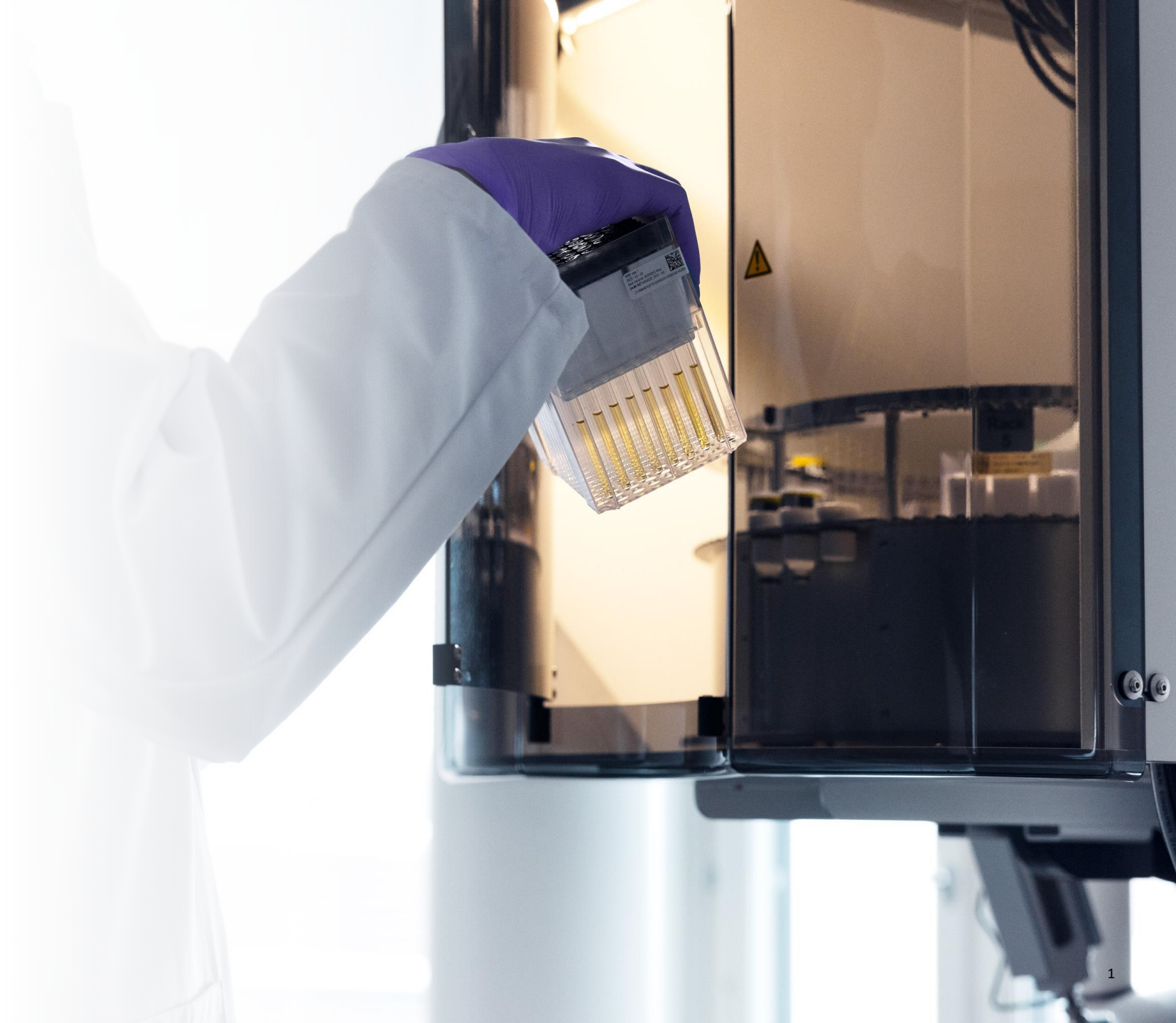
25-09-2024

World Congress of Epidemiology

# Metabolomic determinants of common and rare disease at population scale

Kirsten Schut  
Data Scientist

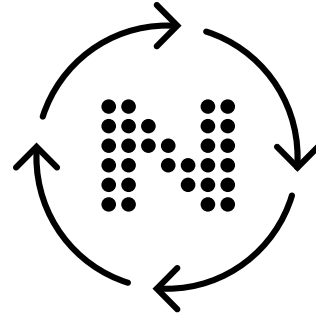
Nightingale Health



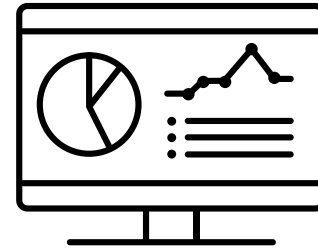
# Today's topics



NMR metabolomics in the UK Biobank



The development of metabolomic risk scores

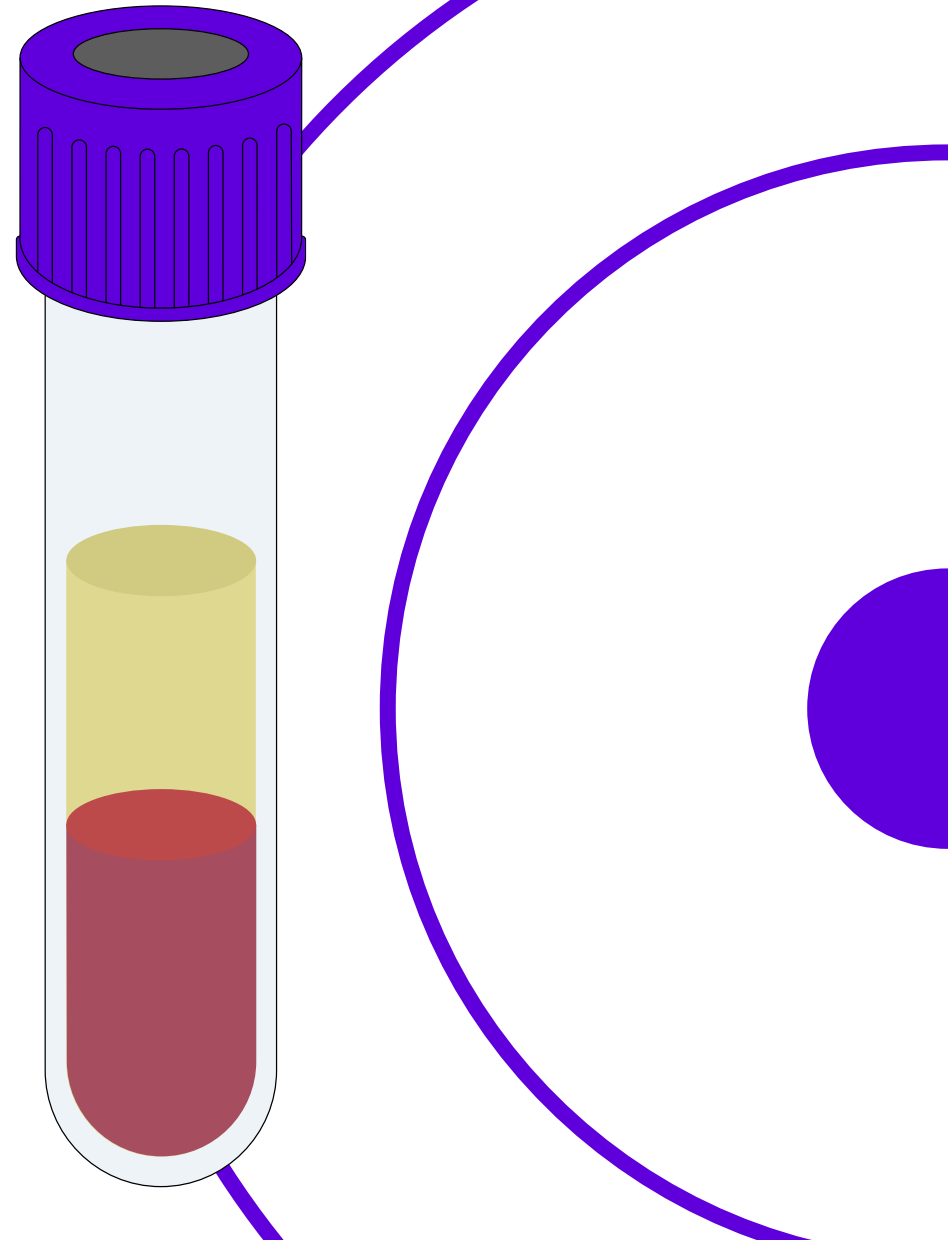


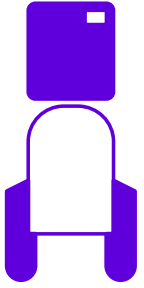
Predicting disease in the real world

# NMR metabolomics in the UK Biobank

Some background on the available data

Nightingale Health

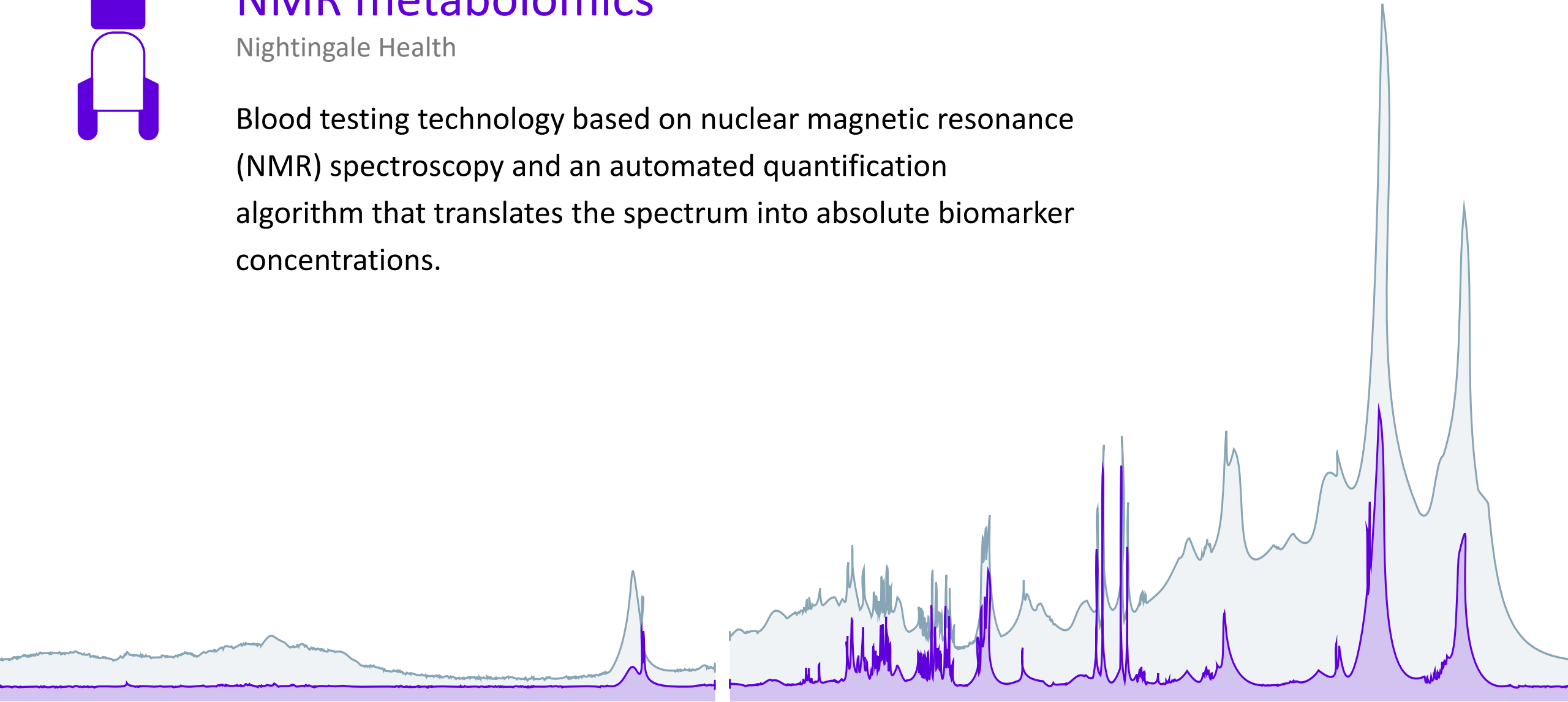




# NMR metabolomics

Nightingale Health

Blood testing technology based on nuclear magnetic resonance (NMR) spectroscopy and an automated quantification algorithm that translates the spectrum into absolute biomarker concentrations.

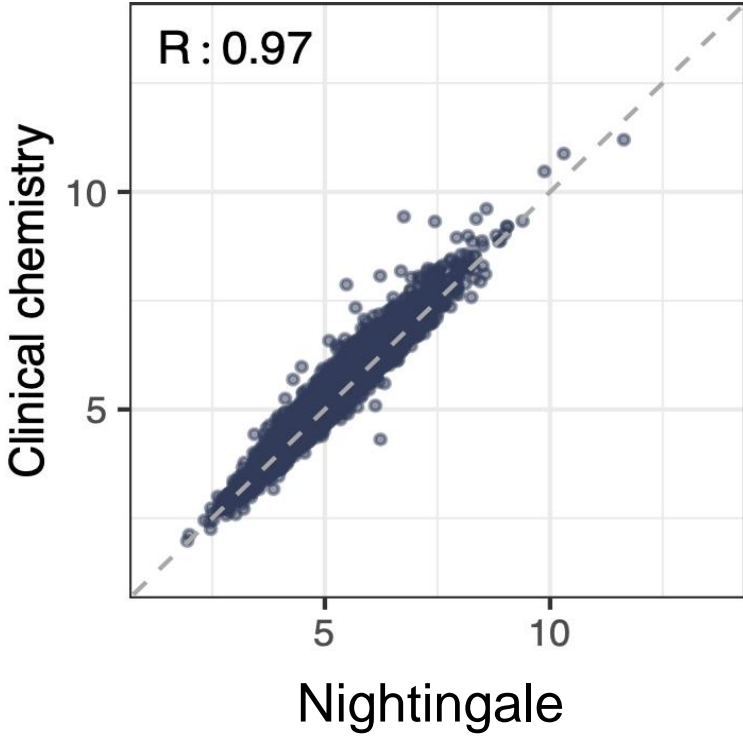


# From one blood sample, 39 clinically validated biomarkers

## Routine biomarkers

- Cholesterol**
  - Total cholesterol
  - VLDL cholesterol
  - Clinical LDL cholesterol
  - HDL cholesterol
- Triglycerides**
  - Total triglycerides
- Fatty acids & Fatty acid ratios**
  - Total fatty acids
  - Omega-3 fatty acids
  - Omega-6 fatty acids
  - Polyunsaturated fatty acids
  - Monounsaturated fatty acids
  - Saturated fatty acids
  - Docosahexaenoic acid
  - Linoleic acid
- Apolipoproteins**
  - Apolipoprotein B
  - Apolipoprotein A1
  - Ratio of apolipoprotein B to apolipoprotein A1
- Amino acids**
  - Alanine
  - Glycine
  - Histidine
- Branched-chain amino acids**
  - Total concentration of branched-chain amino acids (leucine + isoleucine + valine)
  - Isoleucine
  - Leucine
  - Valine
- Aromatic amino acids**
  - Phenylalanine
  - Tyrosine

## Replace clinical tests



# And more for research use, so a total of 250 biomarkers

|   |        |  |        |  |        |   |                              |
|---|--------|--|--------|--|--------|---|------------------------------|
| <b>Cholesterol</b>                                  |        | <b>Lipoprotein particle concentrations</b>     |        | <b>Fatty acid (FA) ratios</b>  |        | <b>Ketone bodies</b>  |                              |
| Total cholesterol                                   | mmol/l | Total concentration of lipoprotein particles   | mmol/l | Ratio of omega-3 fatty acids to total FA   | %      | 3-Hydroxybutyrate   | mmol/l                       |
| Total cholesterol minus HDL-C                       | mmol/l | Concentration of VLDL particles                | mmol/l | Ratio of omega-6 fatty acids to total FA   | %      | Acetate   | mmol/l                       |
| Remnant cholesterol (non-HDL, non-LDL -cholesterol) | mmol/l | Concentration of LDL particles                 | mmol/l | Ratio of polyunsaturated FA to total FA  | %      | Acetoacetate  | mmol/l                       |
| VLDL cholesterol                                    | mmol/l | Concentration of HDL particles                 | mmol/l | Ratio of monounsaturated FA to total FA  | %      | Acetone   | mmol/l                       |
| Clinical LDL cholesterol                            | mmol/l |  |        | Ratio of saturated FA to total FA  | %      |   |                              |
| LDL cholesterol                                     | mmol/l | <b>Lipoprotein particle sizes</b>              |        | Ratio of linoleic acid to total FA   | %      | <b>Fluid balance</b>  |                              |
| HDL cholesterol                                     | mmol/l | Average diameter for VLDL particles            | nm     | Ratio of docosahexaenoic acid to total FA  | %      | Creatinine  | mmol/l                       |
|   |        | Average diameter for LDL particles             | nm     | Ratio of omega-6 FA to omega-3 FA  | ratio  | Albumin   | g/l                          |
|   |        | Average diameter for HDL particles             | nm     | Ratio of polyunsaturated FA to monounsaturated FA                                  | ratio  |   |                              |
| <b>Triglycerides</b>                                |        |  |        | <b>Amino acids</b>   |        | <b>Inflammation</b>   |                              |
| Total triglycerides                                 | mmol/l | <b>Other lipids</b>                            |        | Alanine  | mmol/l | Glycoprotein acetyls  | mmol/l                       |
| Triglycerides in VLDL                               | mmol/l | Phosphoglycerides                              | mmol/l | Glutamine  | mmol/l |   |                              |
| Triglycerides in LDL                                | mmol/l | Ratio of triglycerides to phosphoglycerides    | ratio  | Glycine  | mmol/l | <b>Particle concentration and lipid composition for 14 lipoprotein subclasses</b> |                              |
| Triglycerides in HDL                                | mmol/l | Total cholines                                 | mmol/l | Histidine  | mmol/l | Particle concentration  | mmol/l                       |
|   |        | Phosphatidylcholines                           | mmol/l |  |        | Total lipids  | mmol/l                       |
| <b>Phospholipids</b>                                |        | Sphingomyelins                                 | mmol/l | <b>Branched-chain amino acids</b>  |        | Phospholipids   | mmol/l and % of total lipids |
| Total phospholipids in lipoprotein particles        | mmol/l |  |        | Isoleucine   | mmol/l | Cholesterol   | mmol/l and % of total lipids |
| Phospholipids in VLDL                               | mmol/l | <b>Apolipoproteins</b>                         |        | Leucine  | mmol/l | Cholesteryl esters  | mmol/l and % of total lipids |
| Phospholipids in LDL                                | mmol/l | Apolipoprotein B                               | g/l    | Valine   | mmol/l | Free cholesterol  | mmol/l and % of total lipids |
| Phospholipids in HDL                                | mmol/l | Apolipoprotein A1                              | g/l    | Total concentration of branched -chain amino acids (leucine + isoleucine + valine) | mmol/l | Triglycerides   | mmol/l and % of total lipids |
|   |        | Ratio of apolipoprotein B to apolipoprotein A1 |        |  |        |   |                              |
| <b>Cholesteryl esters</b>                           |        |  |        | <b>Aromatic amino acids</b>  |        |   |                              |
| Total esterified cholesterol                        | mmol/l | <b>Fatty acids</b>                             |        | Phenylalanine  | mmol/l |   |                              |
| Cholesterol esters in VLDL                          | mmol/l | Total fatty acids                              | mmol/l | Tyrosine   | mmol/l |   |                              |
| Cholesterol esters in LDL                           | mmol/l | Degree of unsaturation                         | degree |  |        | <b>Glycolysis related metabolites</b>   |                              |
| Cholesterol esters in HDL                           | mmol/l | Omega-3 fatty acids                            | mmol/l | Glucose  | mmol/l |   |                              |
|   |        | Omega-6 fatty acids                            | mmol/l | Lactate  | mmol/l |   |                              |
| <b>Free cholesterol</b>                             |        | Polyunsaturated fatty acids                    | mmol/l | Pyruvate   | mmol/l |   |                              |
| Total free cholesterol                              | mmol/l | Monounsaturated fatty acids                    | mmol/l | Citrate  | mmol/l |   |                              |
| Free cholesterol in VLDL                            | mmol/l | Saturated fatty acids                          | mmol/l | Glycerol   | mmol/l |   |                              |
| Free cholesterol in LDL                             | mmol/l | Linoleic acid                                  | mmol/l |  |        |   |                              |
| Free cholesterol in HDL                             | mmol/l | Docosahexaenoic acid                           | mmol/l |  |        |   |                              |
|   |        |  |        |  |        |   |                              |
| <b>Total lipids</b>                                 |        |  |        |  |        |   |                              |
| Total lipids in lipoprotein particles               | mmol/l |  |        |  |        |   |                              |
| Total lipids in VLDL                                | mmol/l |  |        |  |        |   |                              |
| Total lipids in LD                                  | mmol/l |  |        |  |        |   |                              |
| Total lipids in HDL                                 | mmol/l |  |        |  |        |   |                              |

# The UK Biobank is the largest cohort we have profiled to date

UK Biobank  
500,000 samples

Estonian Biobank  
200,000 samples

THL Biobank (Finland)  
40,000 samples

Mexico City  
Prospective Study  
150,000 samples

BELIEVE  
(Bangladesh)  
50,000 samples

Uganda Genome  
Resource

Norwegian  
HUNT study

Copenhagen  
General  
Population Study  
(DK)

Rotterdam Study  
(NL)

INTERVAL blood  
donors (UK)

TWINS-UK

PREDIMED  
plus (Spain)

China  
Kadoorie  
Biobank

Hong Kong Birth  
Cohort of 1997

Healthy Twin  
Study Korea

Singapore  
Chinese Cohort

Mass General  
Brigham Biobank  
(USA)

ARIC Study  
(USA)

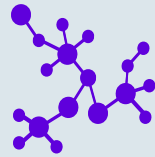
And many  
more...

# NMR metabolomics for the full UK Biobank



## Phase 1

- 120,000 samples
- Released in July 2021



## Phase 2

- 275,000 samples
- Released in July 2023



## Phase 3

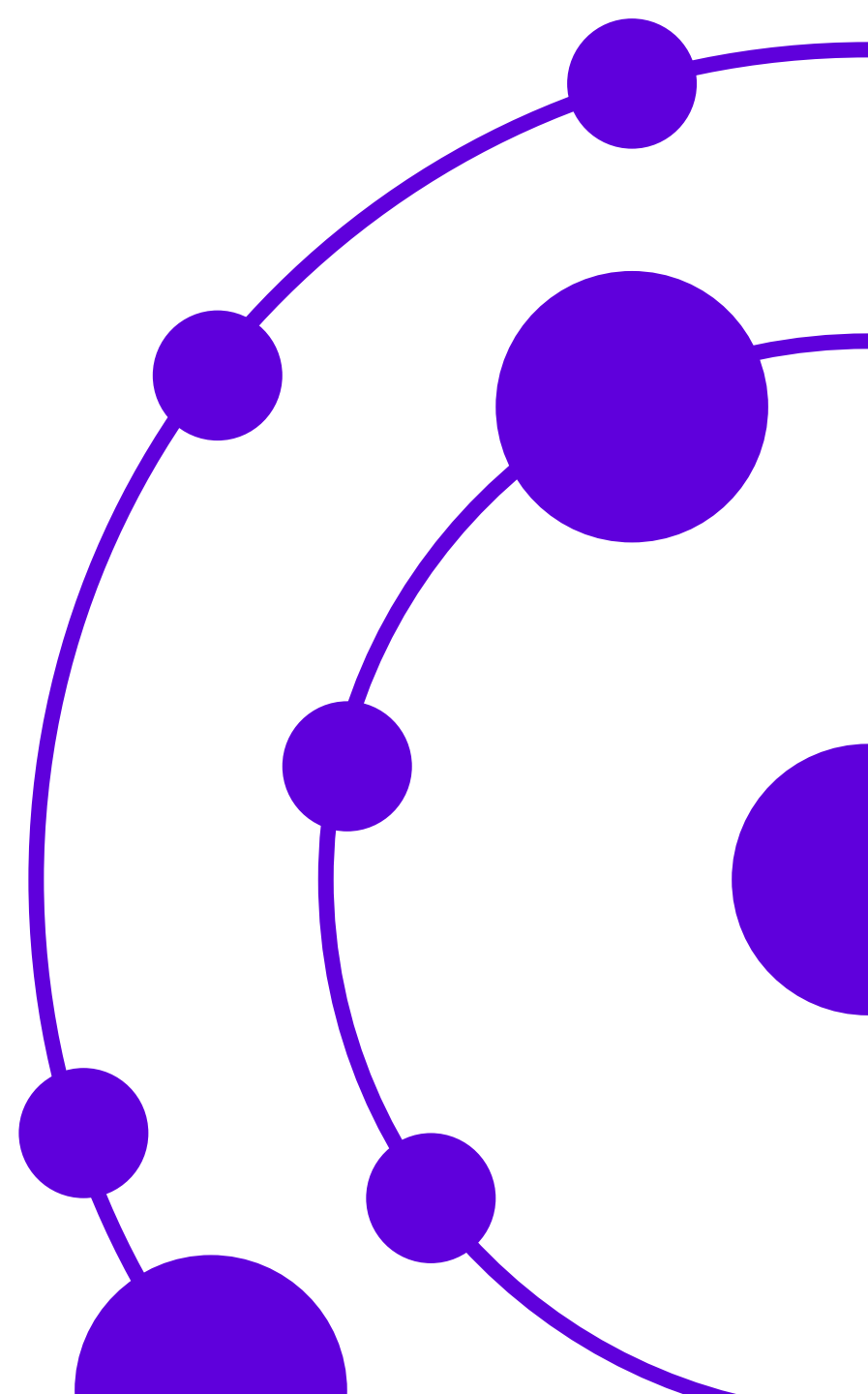
- 500,000 samples
- Public release in 2025



# The development of metabolomic risk scores

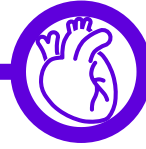
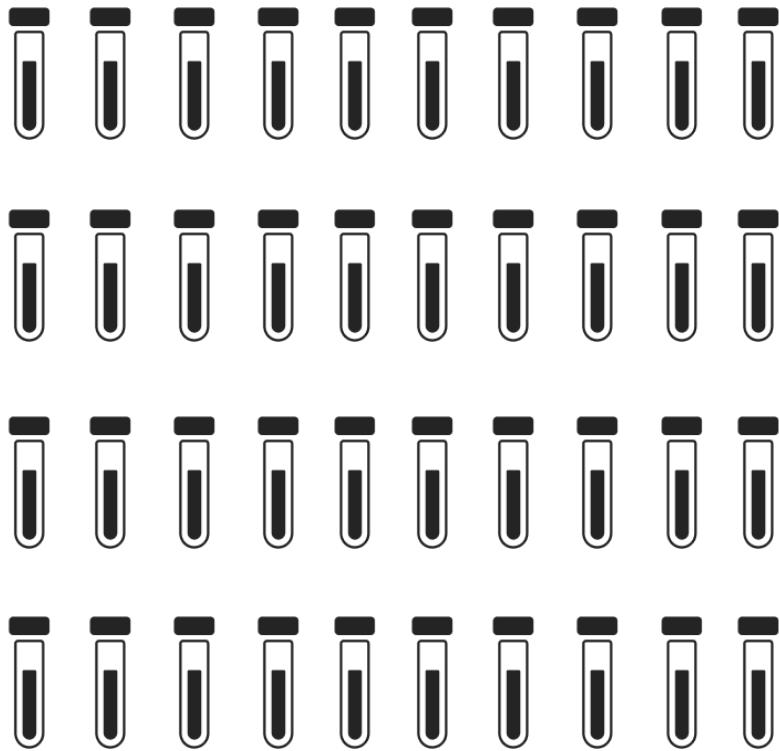
One of many research applications

Nightingale Health

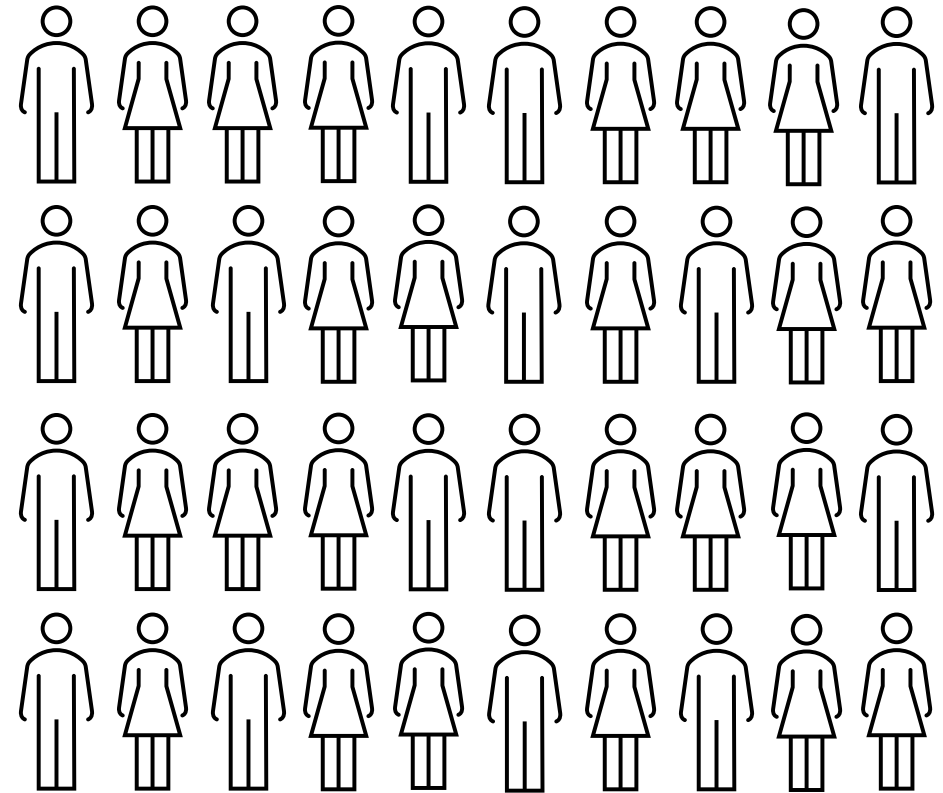




Blood sample drawn  
2006-2010

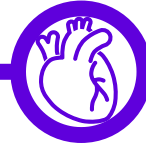
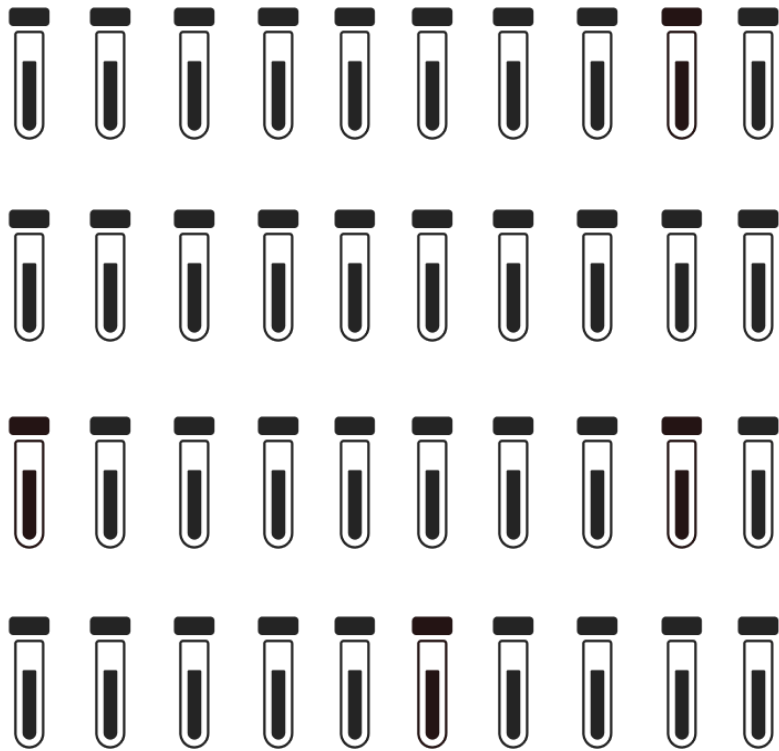


Collection of health records  
present

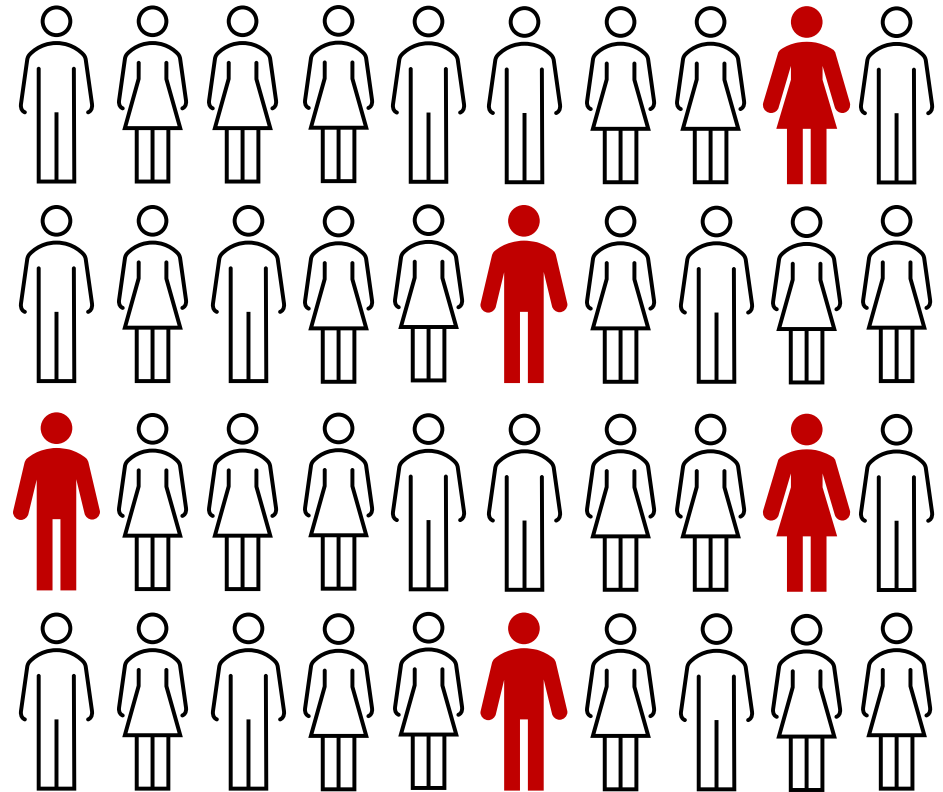




Blood sample drawn  
2006-2010

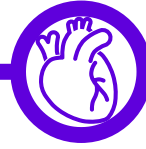
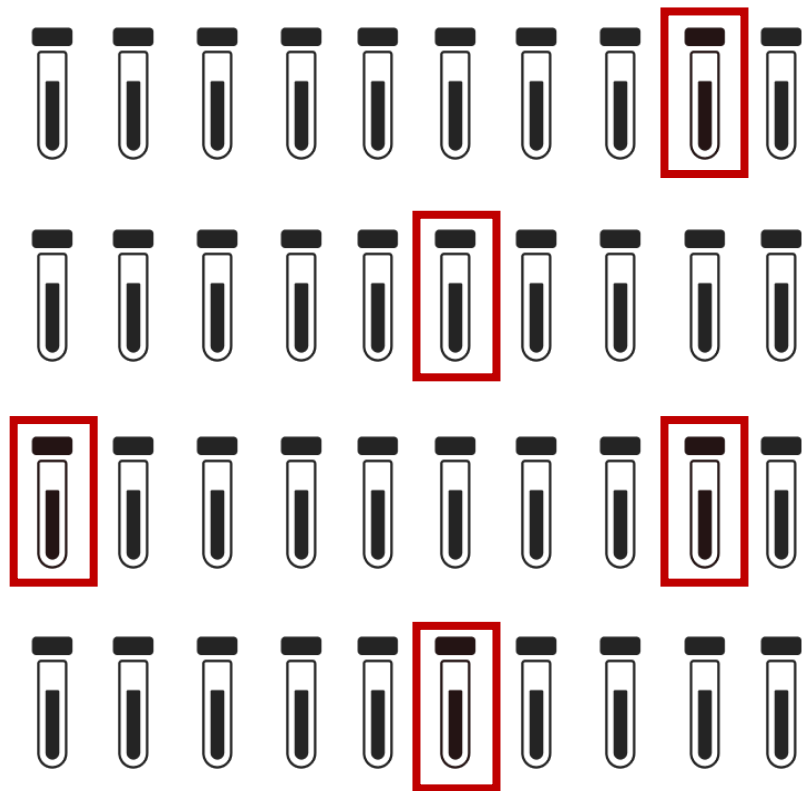


Collection of health records  
present

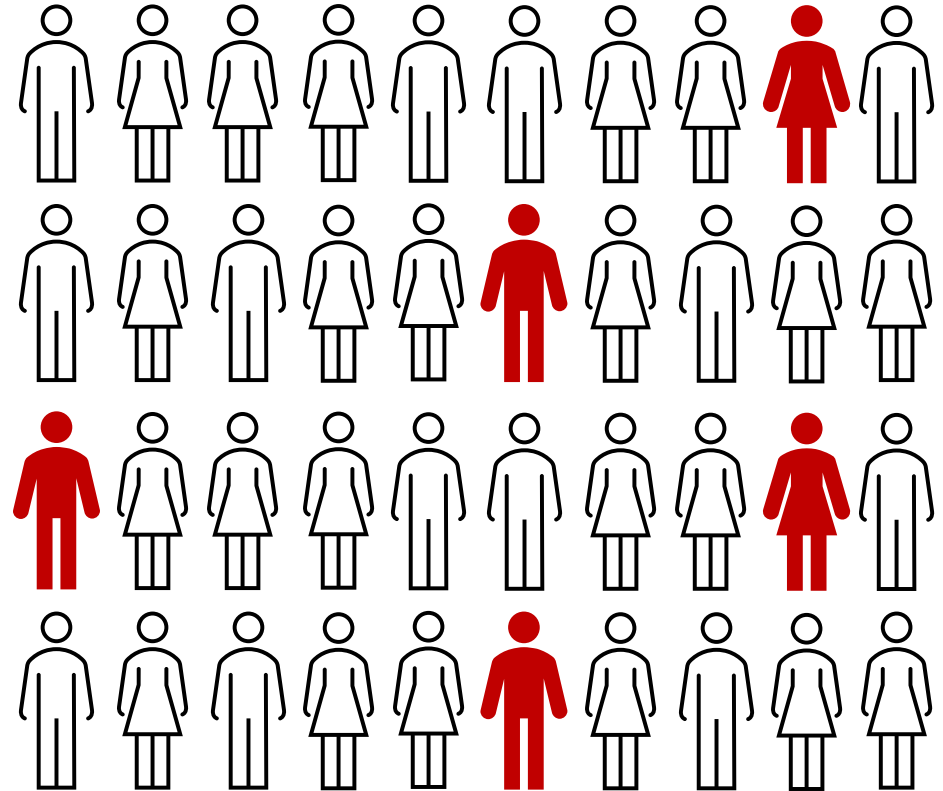


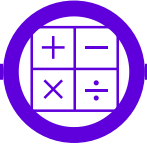


Blood sample drawn  
2006-2010



Collection of health records  
present

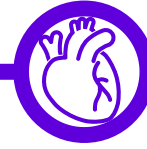




## Train a model

Cox proportional hazards regression

| Biomarker           | Coefficient |
|---------------------|-------------|
| Age                 | 1.32        |
| SexMale             | 0.87        |
| Total cholesterol   | 0.35        |
| Total triglycerides | 0.21        |
| Omega-3%            | -0.19       |
| Valine              | Dropped     |
| Albumin             | -0.01       |
| Glucose             | 0.15        |
| GlycA               | Dropped     |
| ...                 | ...         |



## Calculate risk scores

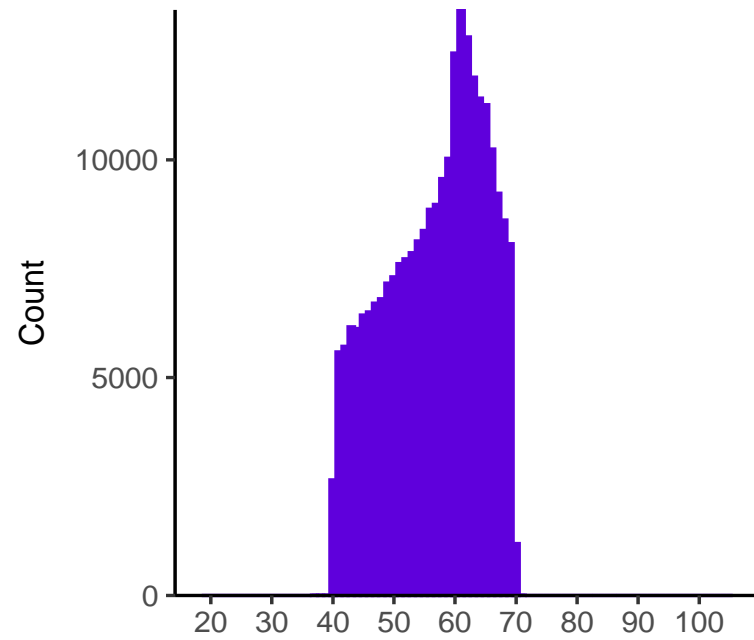
Weighted sum

$$\beta_1 \times bmr_1 + \beta_2 \times bmr_2 + \beta_3 \dots$$

= metabolomic risk score

Train and test a model

UK Biobank  
N = 500,000



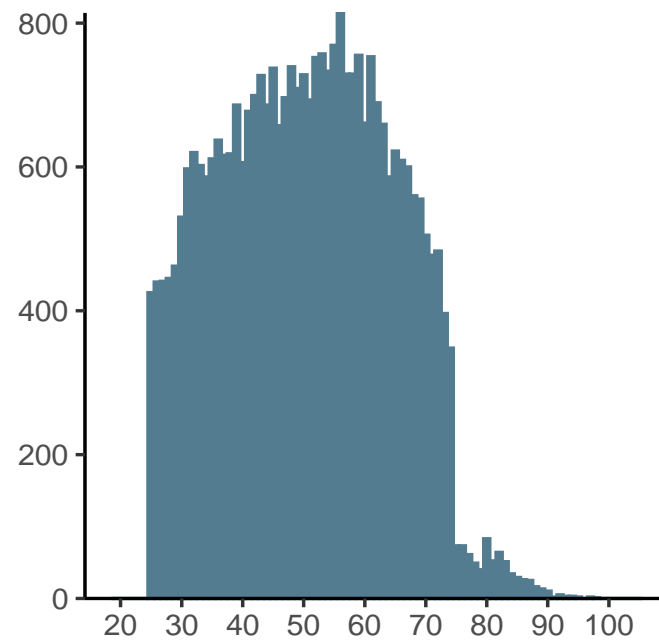
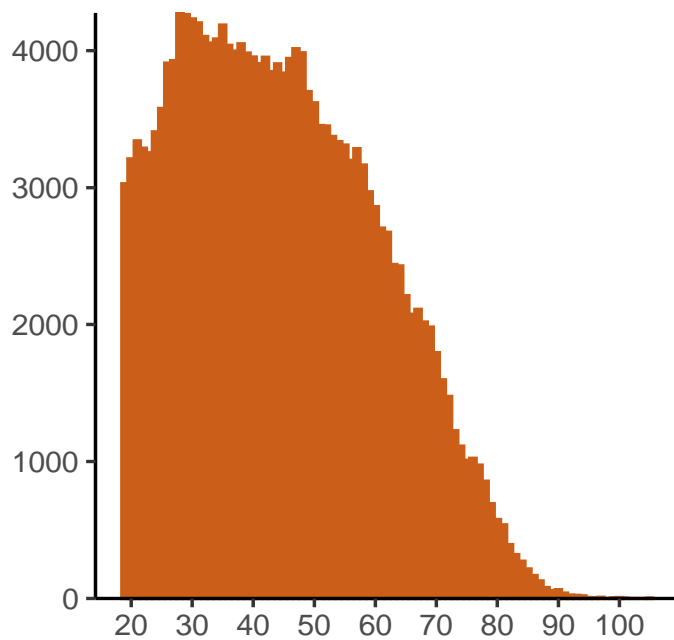
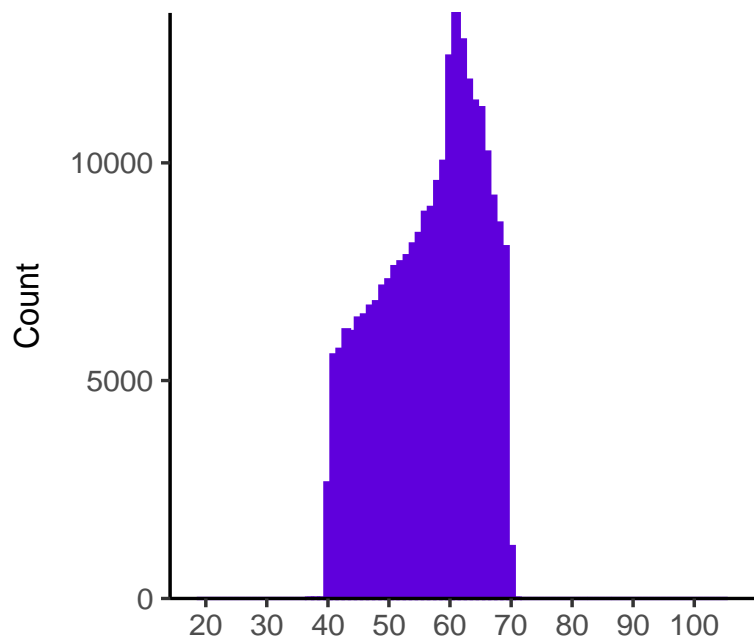
Train and test a model

Replicate results

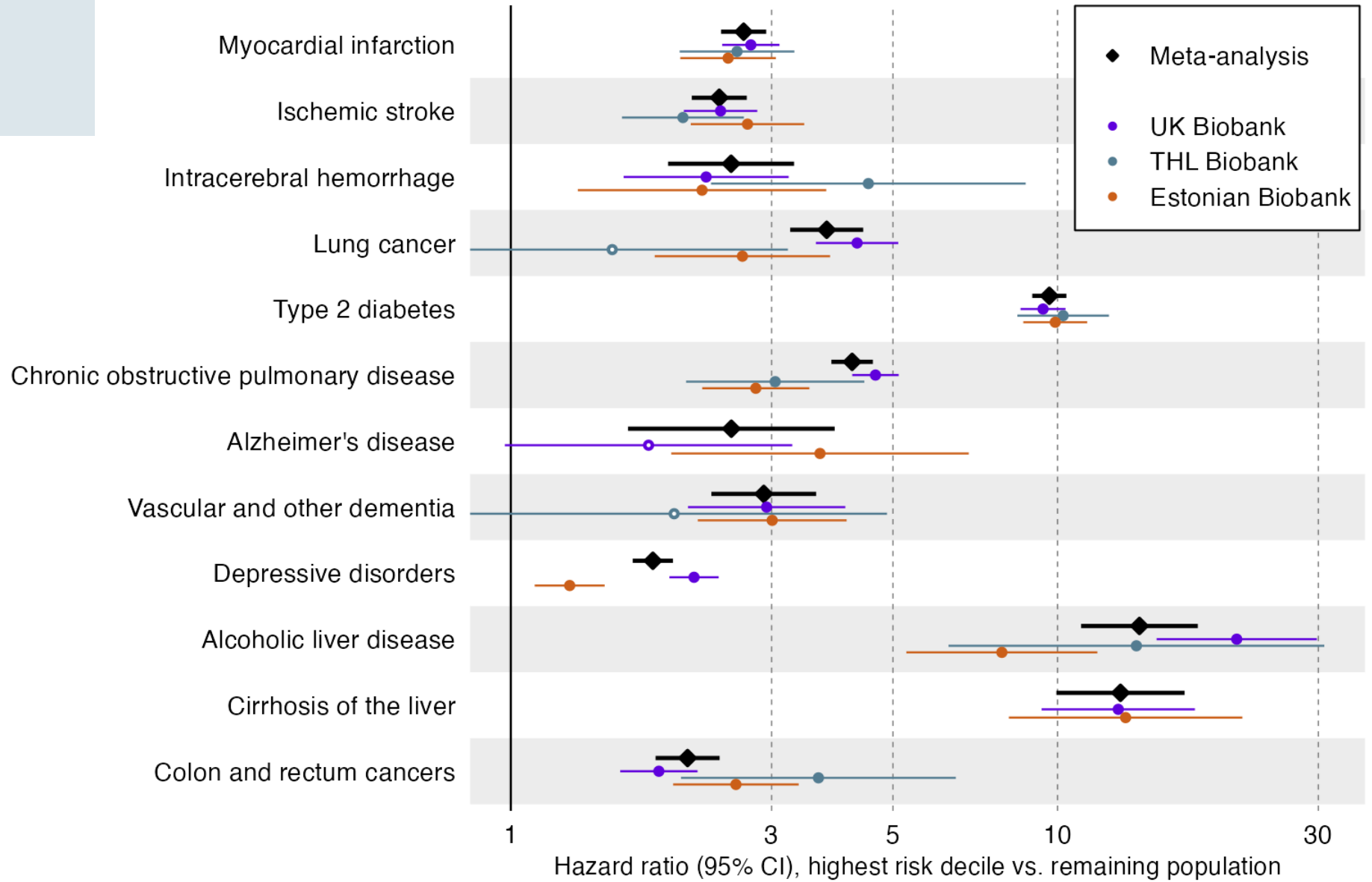
UK Biobank  
N = 500,000

Estonian Biobank  
N = 200,000

THL Biobank  
N = 30,000

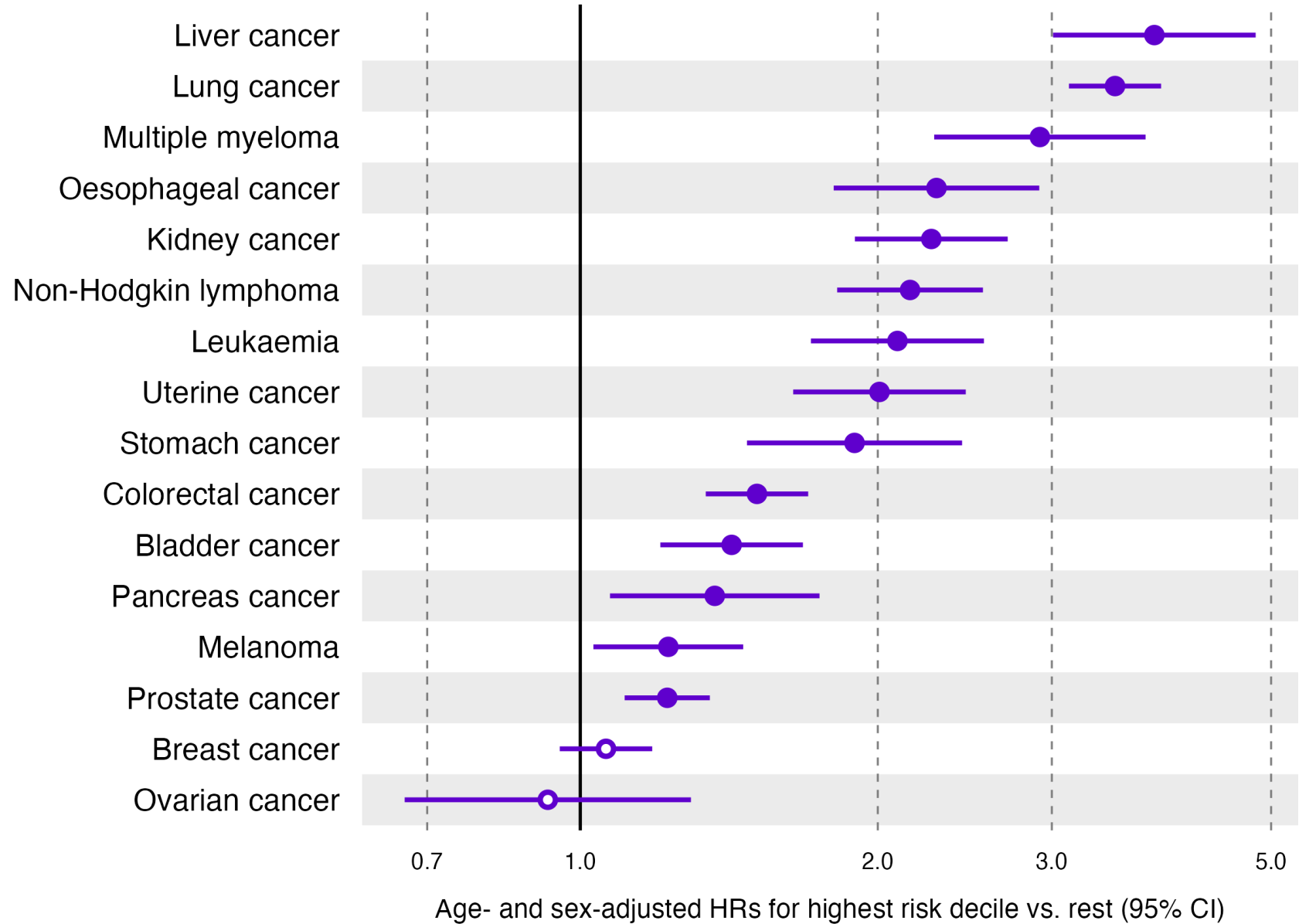


# Common disease





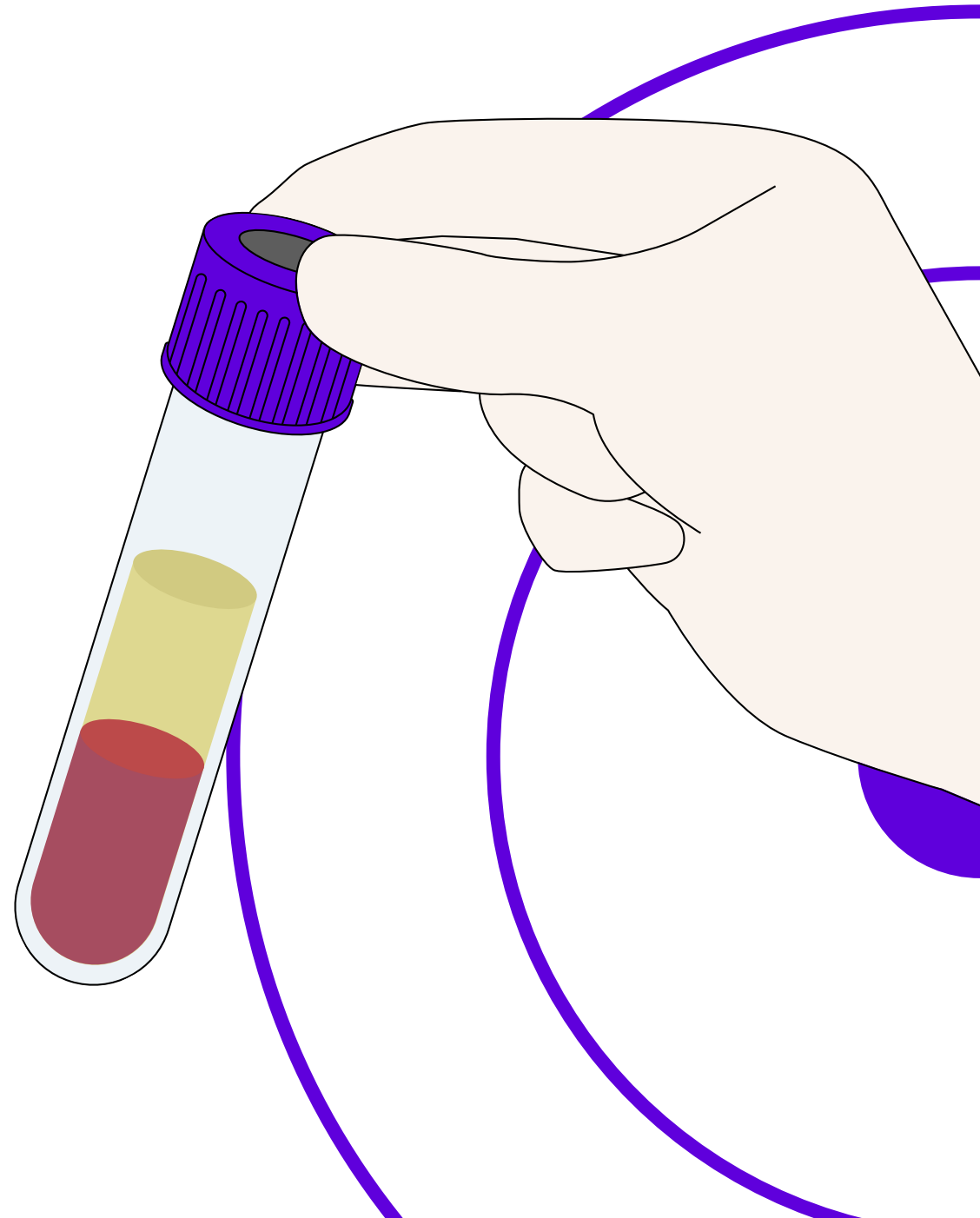
# Cancers



# Predicting disease in the real world

Clinical implementation in Finland

Nightingale Health



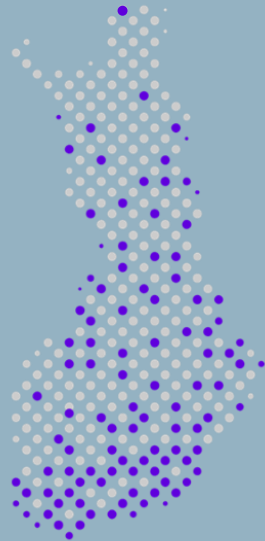
# Terveystalo adopted Nightingale's blood analysis technology

From January 2024



×

Terveystalo



Private health care provider in Finland.

They cover occupational health care for 30% of Finland's workforce.

Terveystalo offers a Health Check, which now includes Nightingale's blood measurements and disease risk assessments.



# Nightingale Health Check

Input: blood sample + age + sex

## Output:

1. Clinical blood results
2. Additional blood results
3. Multi-disease report
  - Cardiovascular disease
  - Myocardial infarction
  - Type 2 diabetes
  - Chronic kidney disease
  - Liver fibrosis and cirrhosis
  - Alcoholic liver disease
  - Chronic obstructive pulmonary disease
  - Lung cancer

**Clinical Blood Test Results**  
Dry Blood Sample (DBS)  
2 results within recommendation

| Code       | Name   |
|------------|--|
| LDL-C      | LDL cholesterol                                |
| HDL-C      | HDL cholesterol                                |
| Total-C    | Total cholesterol                              |
| ApoB       | Apolipoprotein B                               |
| ApoA1      | Apolipoprotein A1                              |
| ApoB/ApoA1 | Ratio of apolipoprotein B to apolipoprotein A1 |
| Total-TG   | Total triglycerides                            |
| Creatinine | Creatinine                                     |
| eGFR       | Estimated glomerular filtration rate (eGFR)    |

**Additional Blood Test Results**  
Dry Blood Sample (DBS)  
14 results within reference range

**Clinical Risk Assessment**  
3 diseases in low risk, 2 diseases in elevated risk, 1 disease in high risk

**Cholesterols**

| Code   | Name             |
|--------|------------------|
| VLDL-C | VLDL cholesterol |

**Fatty Acids**

| Code            | Name  |
|-----------------|---|
| Total-FA        | Total fatty acids   |
| Omega-3 %       | Ratio of omega-3 fatty acids to total fatty acids                   |
| Omega-6 %       | Ratio of omega-6 fatty acids to total fatty acids                   |
| Omega-6/Omega-3 | Ratio of omega-6 to omega-3 fatty acids                             |
| DHA %           | Ratio of docosahexaenoic acid to total fatty acids                  |
| MUFA %          | Ratio of monounsaturated fatty acids to total fat                   |
| PUFA %          | Ratio of polyunsaturated fatty acids to total fat                   |
| PUFA/MUFA       | Ratio of polyunsaturated fatty acids to monounsaturated fatty acids |

**Myocardial infarction**  
Heart attacks primarily result from hardening of the arteries. The best prevention methods are avoiding smoking, staying active, and eating healthy.  
**Risk category:** Low risk  
Risk of incidence: 1% (at 5% risk level)  
In the low-risk category, on average, one out of every hundred people will have a heart attack within the next 10 years.\*  
**Compared to your reference group:** Your risk is higher than 99% of the reference group (women aged 45-54).  
Average risk: Lower than average to Higher than average.

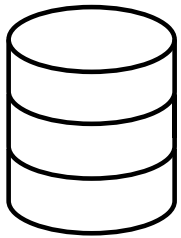
**Cardiovascular diseases**  
Cardiovascular diseases often see a build-up of fat inside the arteries. In severe cases, this can lead to a heart attack or serious cerebrovascular problems. Embracing a healthy lifestyle can mitigate the risk.  
**Risk category:** Elevated risk  
Risk of incidence: 4% (at 10% risk level)  
In the elevated risk category, on average, 10 out of every hundred people will develop a cardiovascular disease within the next 10 years.\*  
**Compared to your reference group:** Your risk is higher than 99% of the reference group (women aged 45-54).  
Average risk: Lower than average to Higher than average.

**Type 2 diabetes**  
Diabetes is a condition where your blood sugar level is constantly too high. Type 2 diabetes develops gradually, but without proper treatment it can lead to serious health complications. An inactive lifestyle and obesity are significant risk factors.  
**Risk category:** High risk  
Risk of incidence: 4% (at 16% risk level)  
In the high-risk category, on average, four out of every hundred people will develop type 2 diabetes within the next 10 years.\*  
**Compared to your reference group:** Your risk is higher than 97% of the reference group (women aged 45-54).  
Average risk: Lower than average to Higher than average.

**Liver fibrosis and cirrhosis**  
Long-term liver disease is frequently tied to obesity-driven fatty liver. As this progresses, the liver forms scar tissue, or fibrosis, which can advance to cirrhosis.  
**Risk category:** Elevated risk  
Risk of incidence: <0.1% (at 0.3% risk level)  
In the elevated risk category, on average, less than one out of every thousand people will develop liver fibrosis and cirrhosis within the next 10 years.\*  
**Compared to your reference group:** Your risk is higher than 87% of the reference group (women aged 45-54).  
Average risk: Lower than average to Higher than average.

\* Among adults aged 40 to 70. Based on a nationwide cohort study.  
\* Interval of values containing 99%

# Power your own research



Data availability in UK  
Biobank



Dozens of research  
opportunities



Real-world applications



Thank you!

[research@nightingalehealth.com](mailto:research@nightingalehealth.com)

Nightingale Health