

# DNA methylation opportunities in UK Biobank

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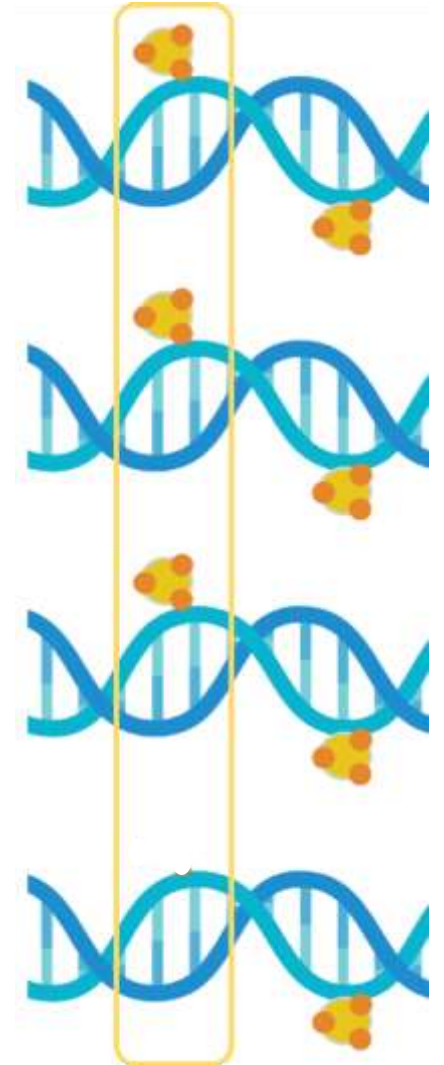


# DNA methylation (DNAm)

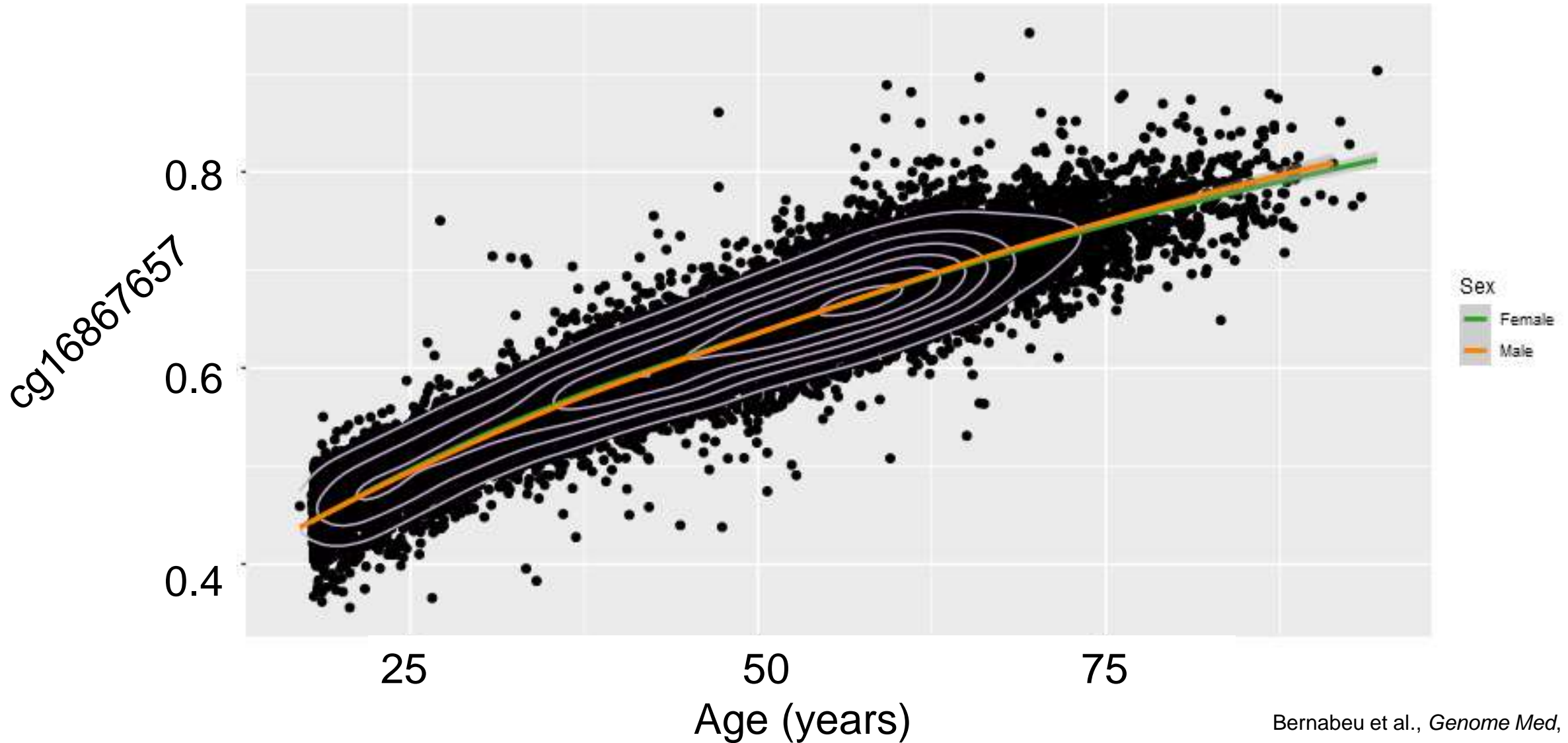
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- An epigenetic mechanism
- CH<sub>3</sub> addition to cytosine at a CpG
- Involved in gene regulation
- Genome-wide
- Dynamic
- Cell- and tissue-specific

75% methylation  
at this CpG



# DNAm and ageing

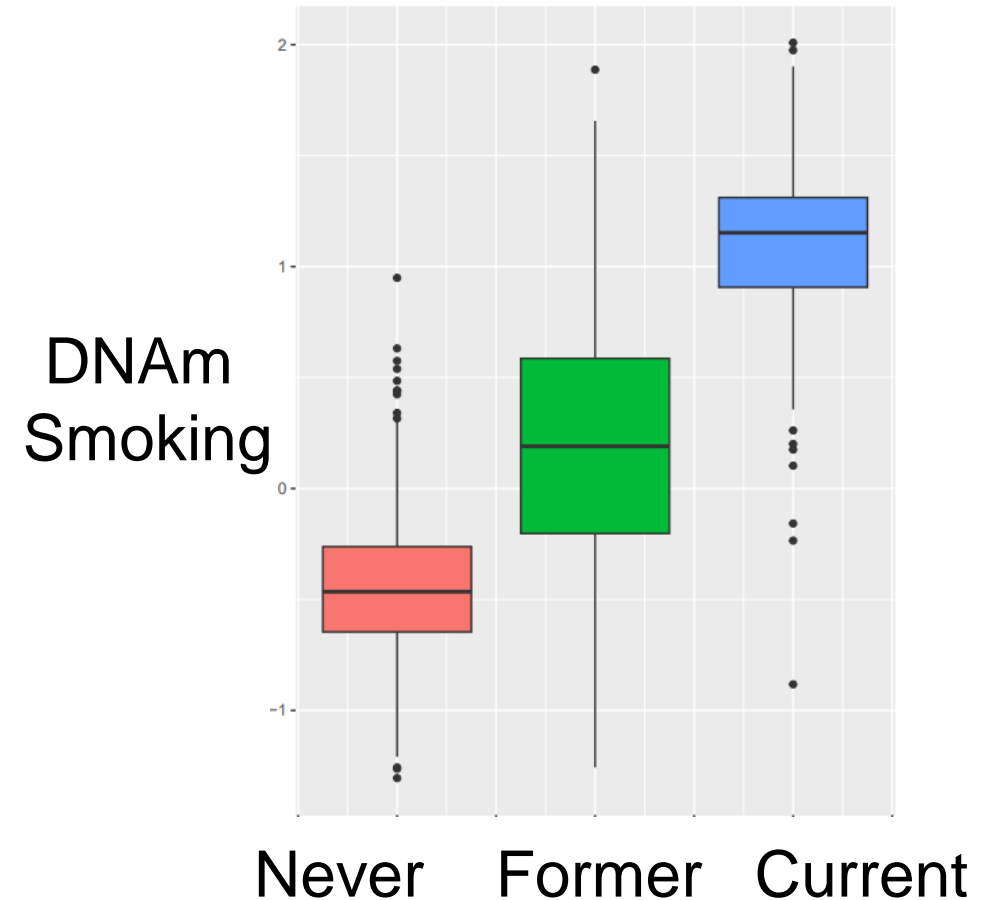


Measuring lifestyle objectively



# DNAm prediction of smoking

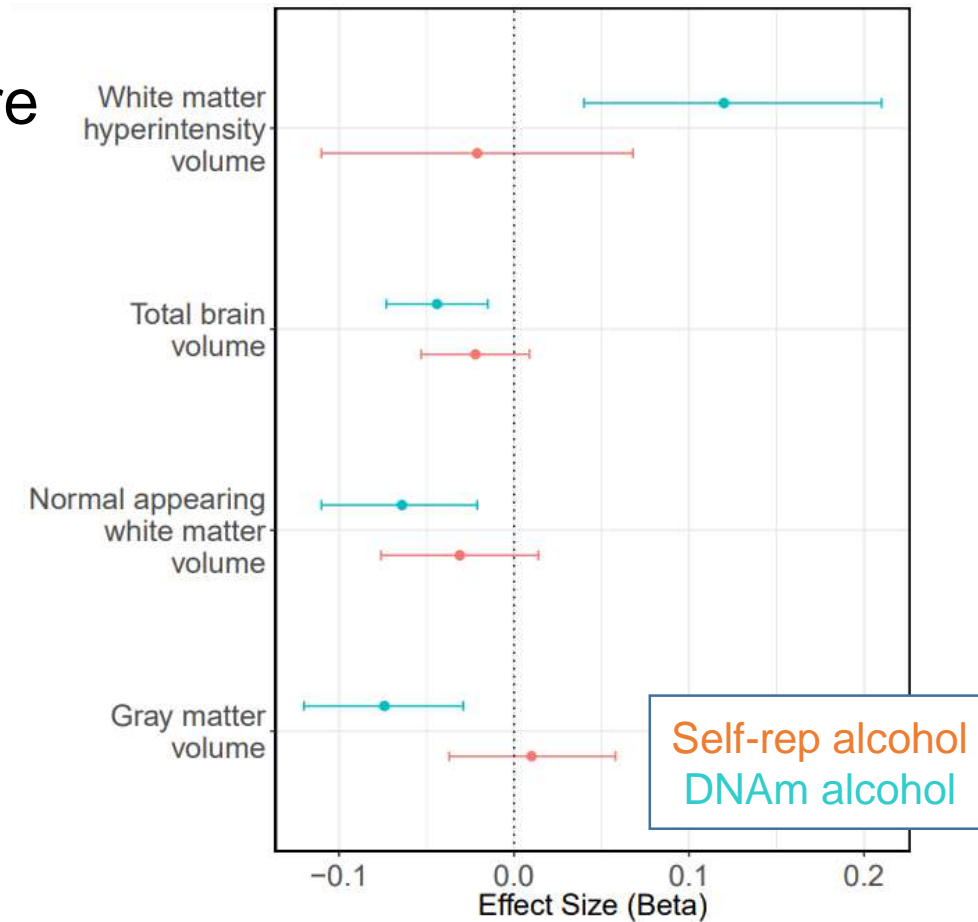
- Elastic Net predictor
  - Input = 1,238 EWAS CpG hits from literature
- Train in Generation Scotland (n~18k)
- Test in Lothian Birth Cohort 1936 (n~800)
  
- Correlation with pack years  $r = 0.75$
- AUC discrimination:
  - Current vs never 0.98
  - Current vs former 0.90
  - Former vs never 0.85





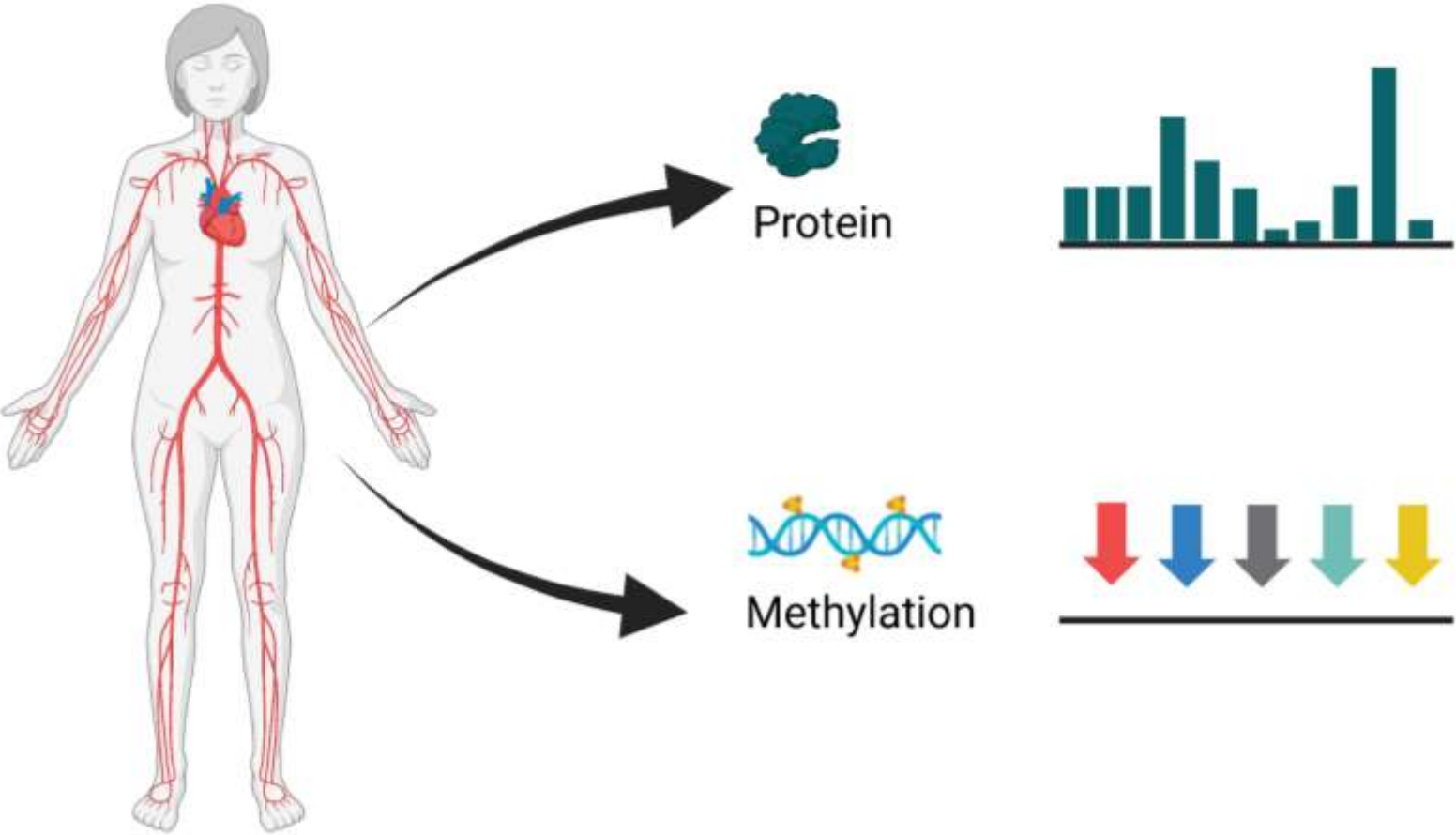
# DNAm prediction of alcohol & assoc with brain imaging

- Elastic Net predictor
  - Input = 3,999 EWAS CpG hits from literature
- Train in Generation Scotland (n~17k)
- Test in Lothian Birth Cohorts (LBC):
  - $r_{\text{LBC1921}} = 0.42$
  - $r_{\text{LBC1936}} = 0.43$



Tracking chronic inflammation

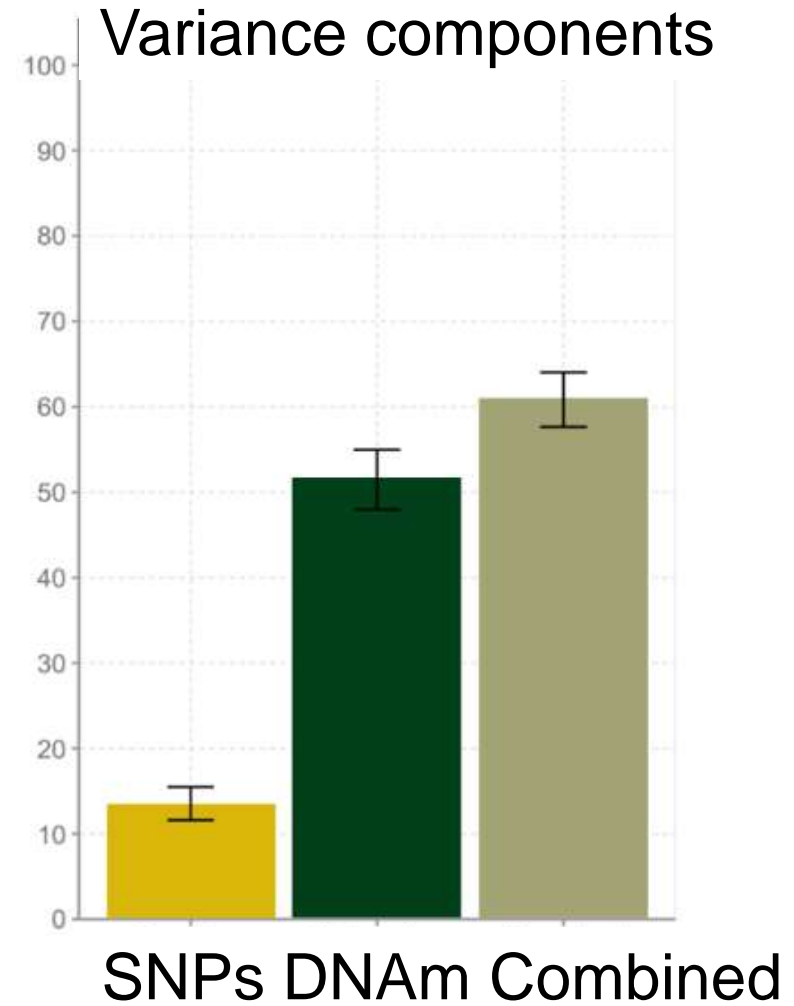
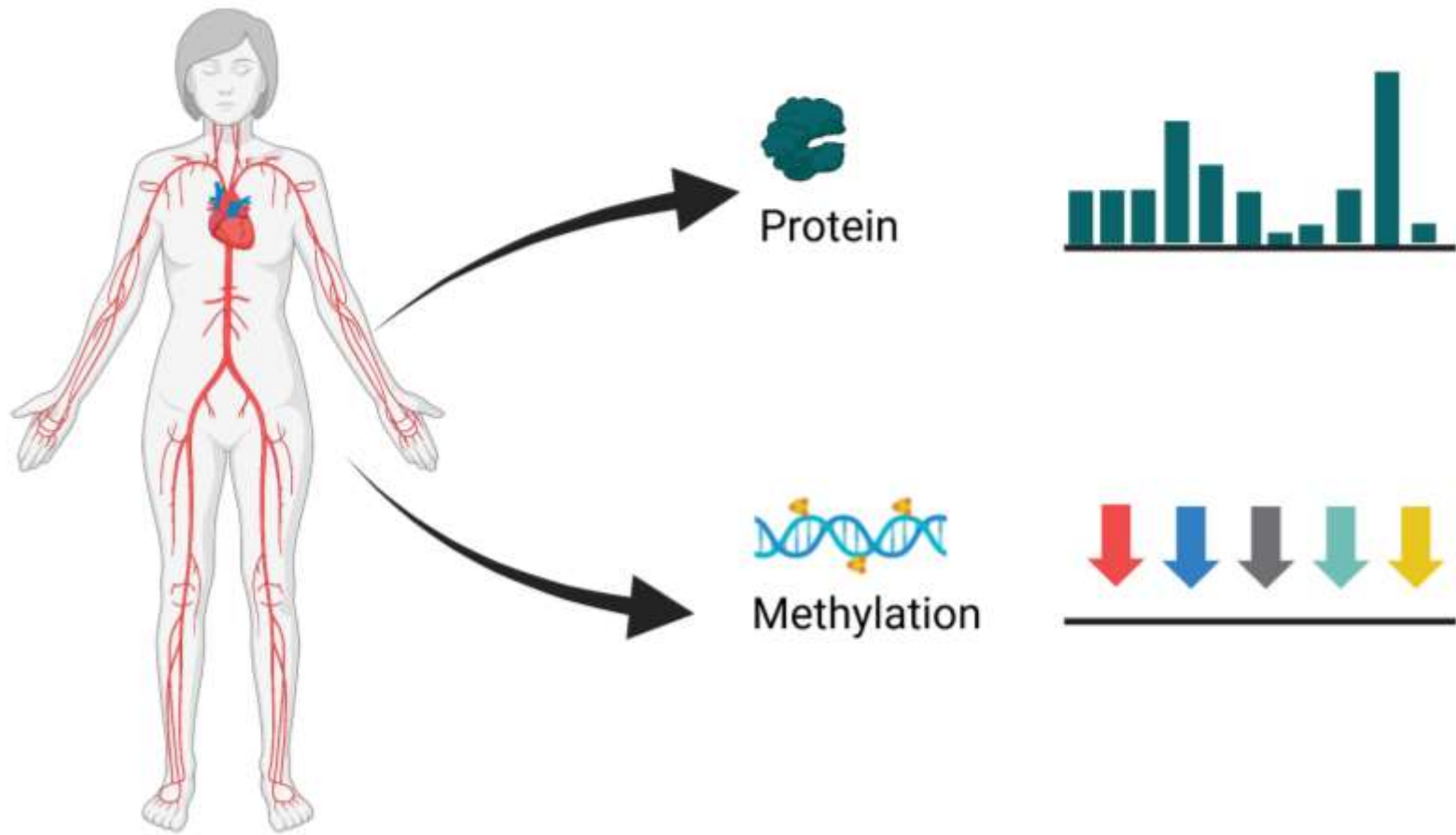
# C-reactive protein







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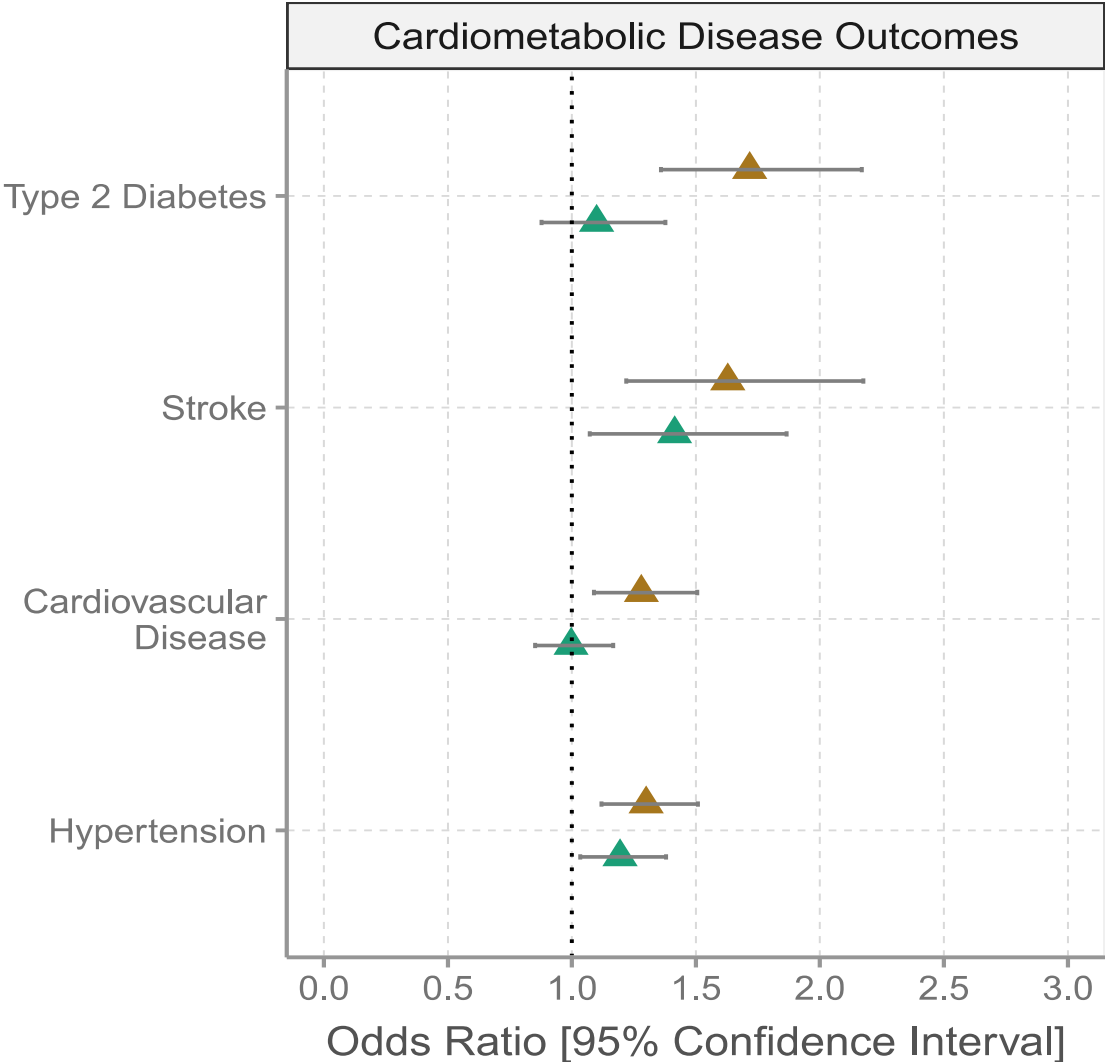


# C-reactive protein

- Elastic Net predictor trained in Generation Scotland (n~18k)

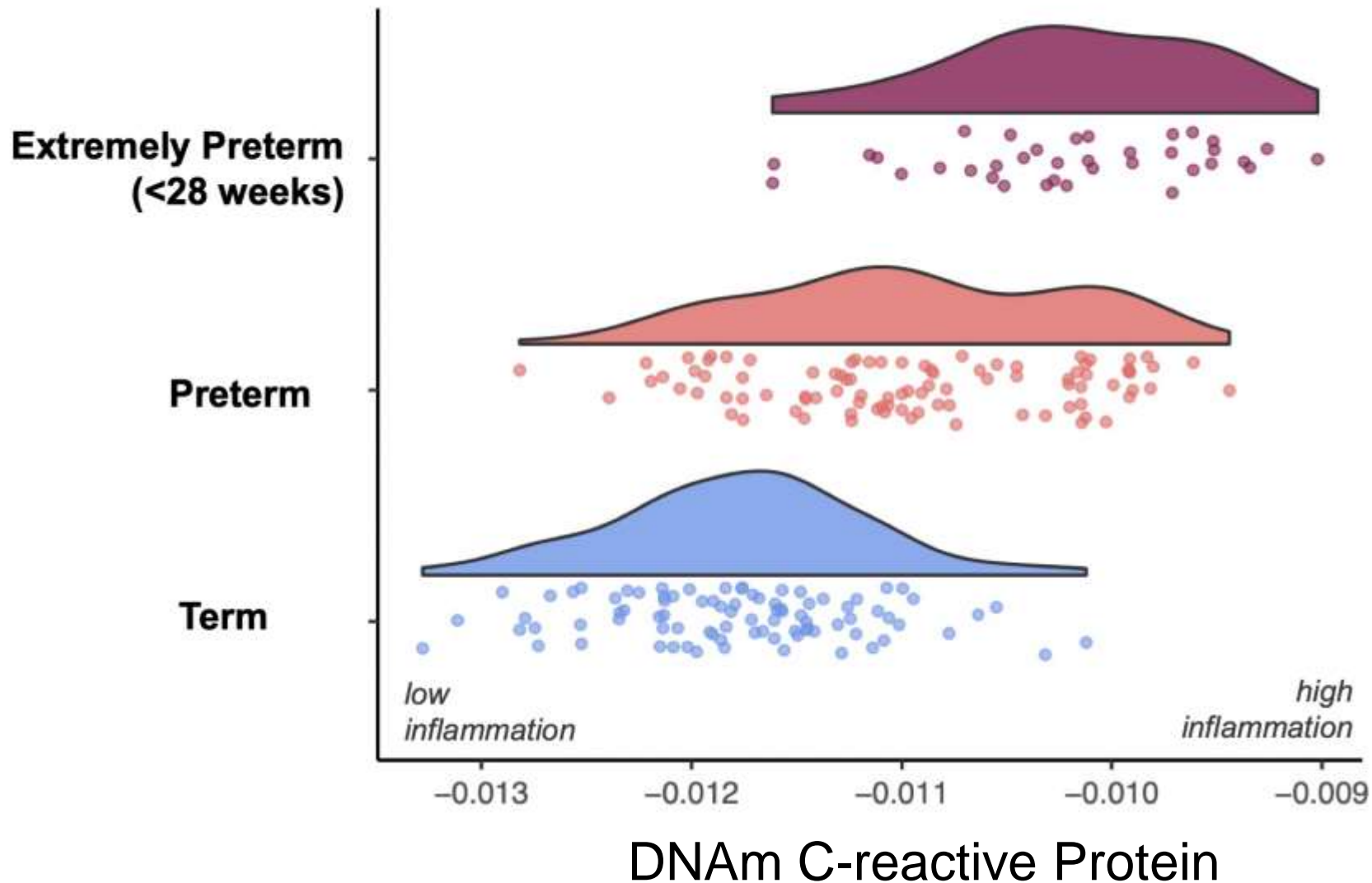
Test Cohort		$r_{\max}$
Lothian Birth Cohorts	Older EA (Scottish)	0.47
ALSPAC	EA mothers (English)	0.39
	EA offspring (English)	0.30 (age 15)
HELIOS	Chinese Singaporean	0.39
	Malay Singaporean	0.45
	Indian Singaporean	0.53
SABRE	South Asians (living in UK)	0.28
	EA (living in UK)	0.33

# Measured vs DNAm CRP with outcomes in Lothian Birth Cohort 1936



DNAm CRP  
Measured CRP

# CRP EpiScore in infants



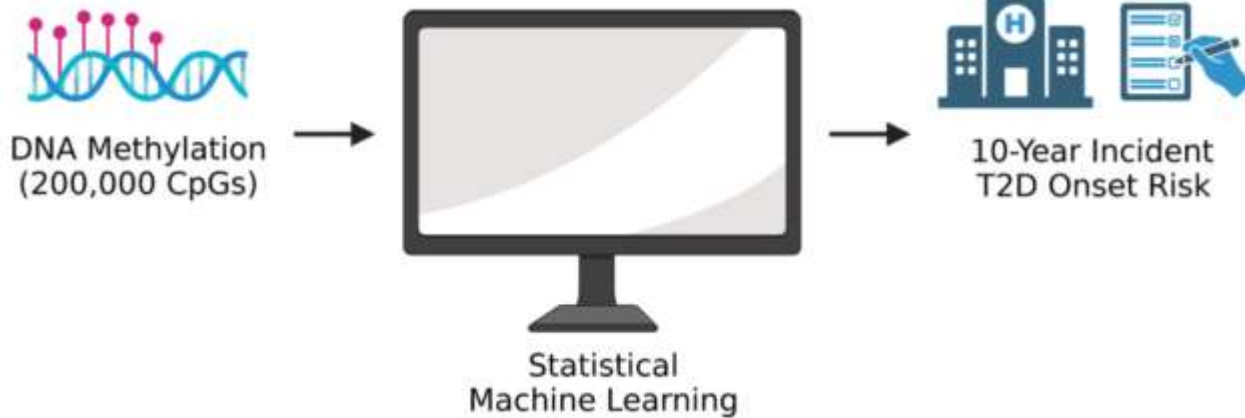
Disease prediction

# DNAm and incident T2D

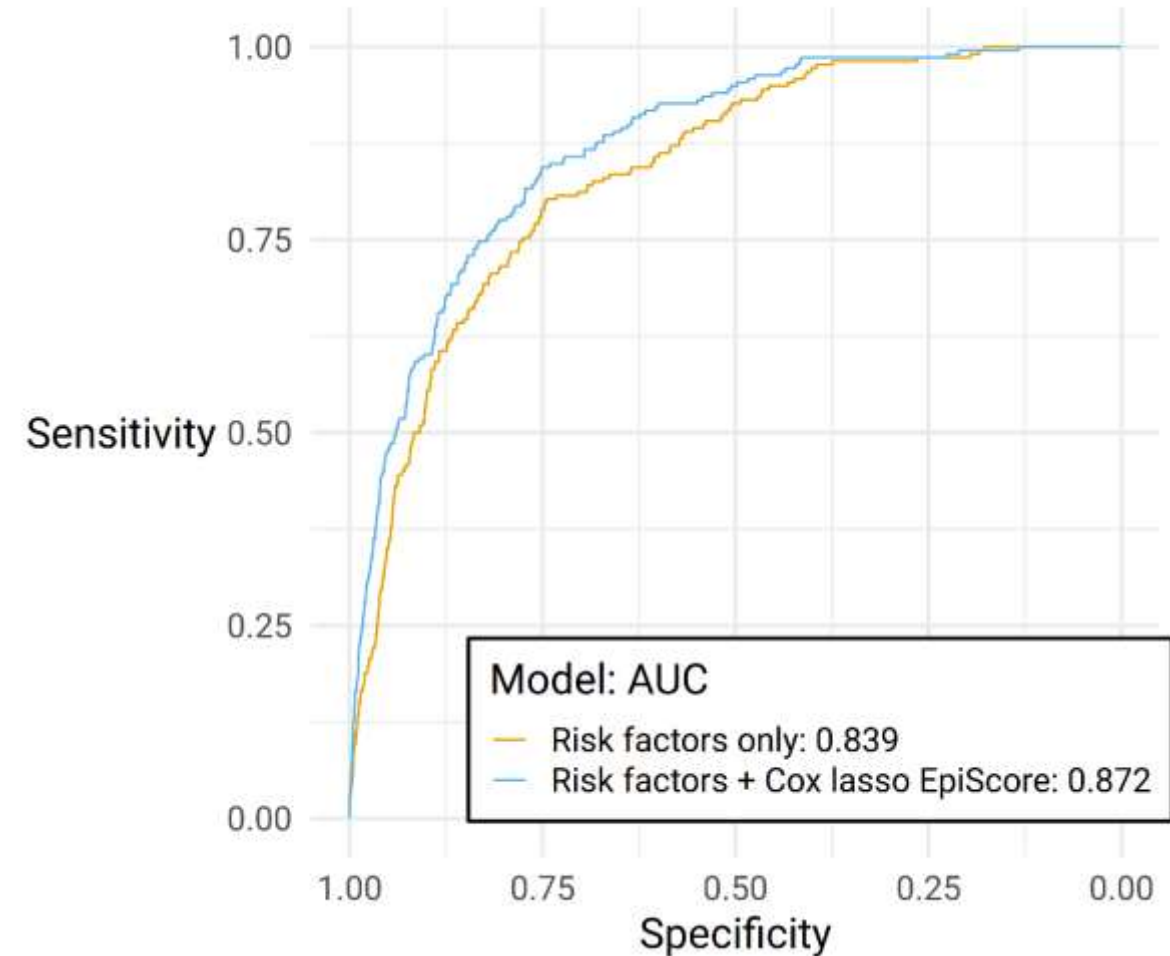
Cheng et al.  
*Nat Aging*, 3, 450-458, 2023



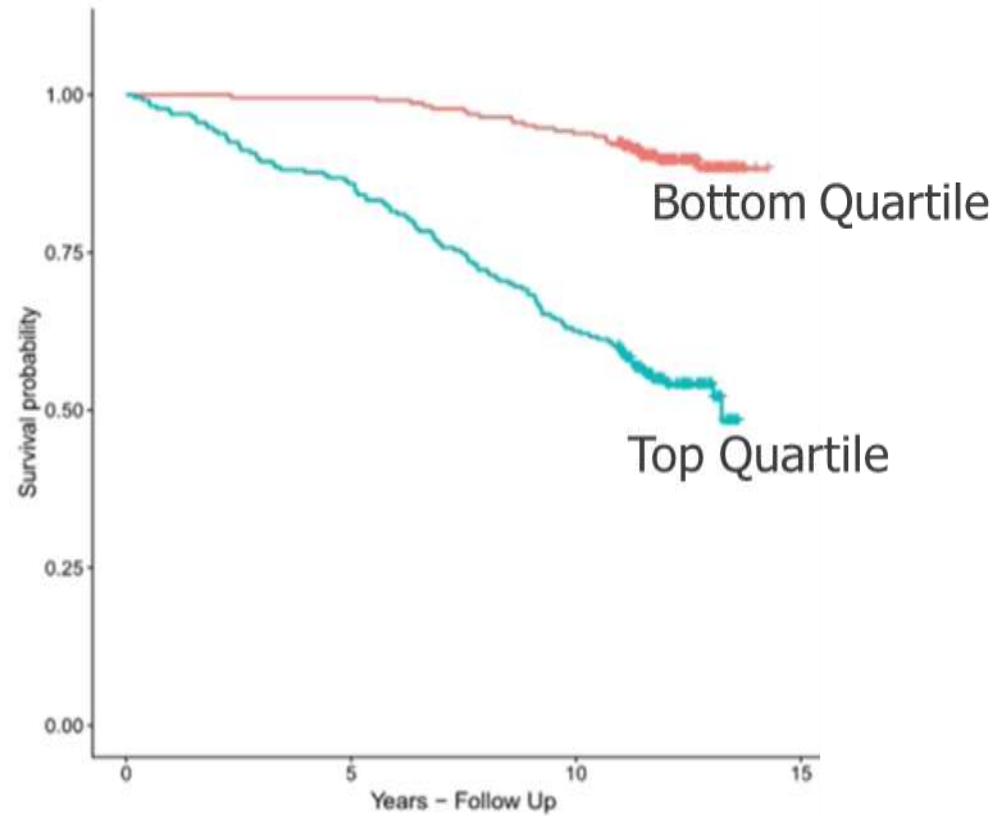
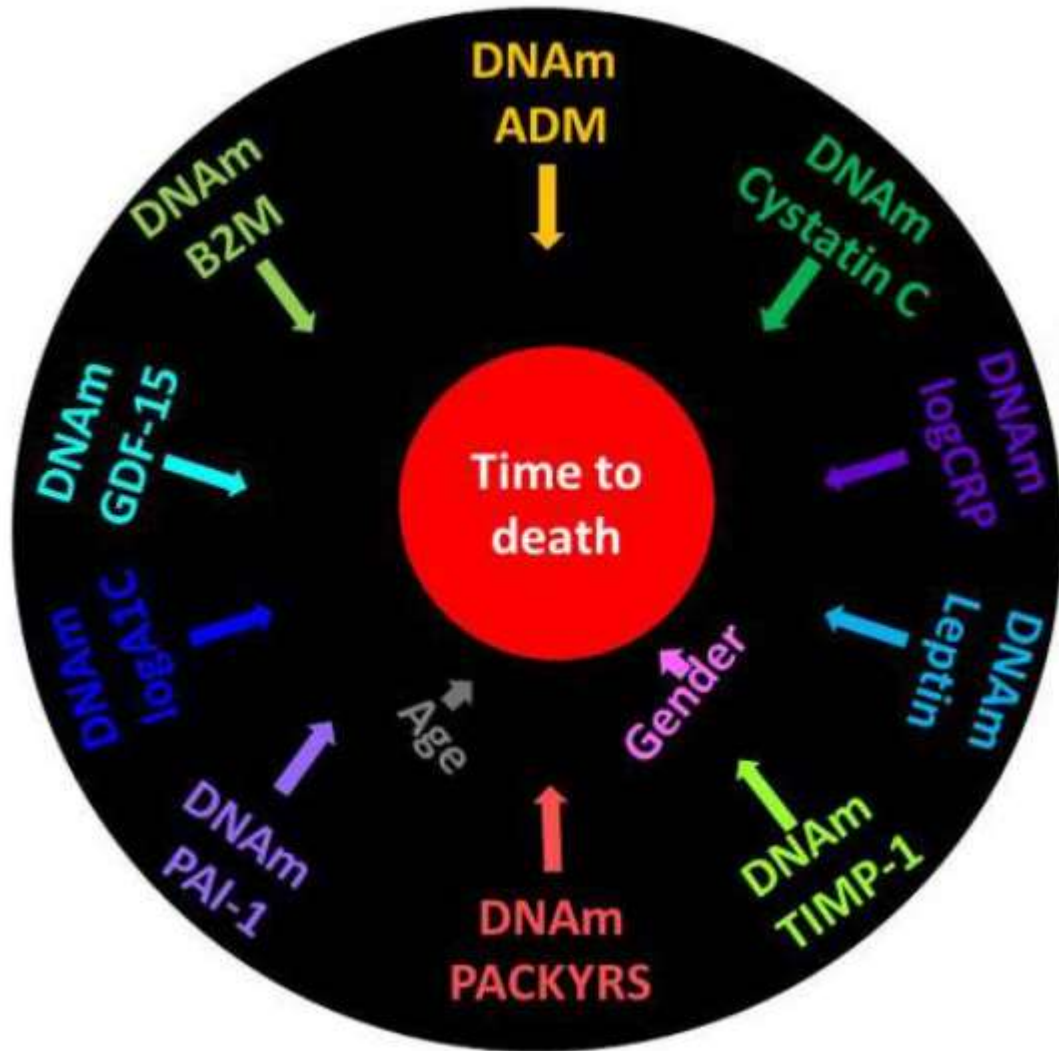
	Cases	Controls
Train	374	9,461
Test	252	4,526



Covariates: age, sex, BMI, family history, hypertension

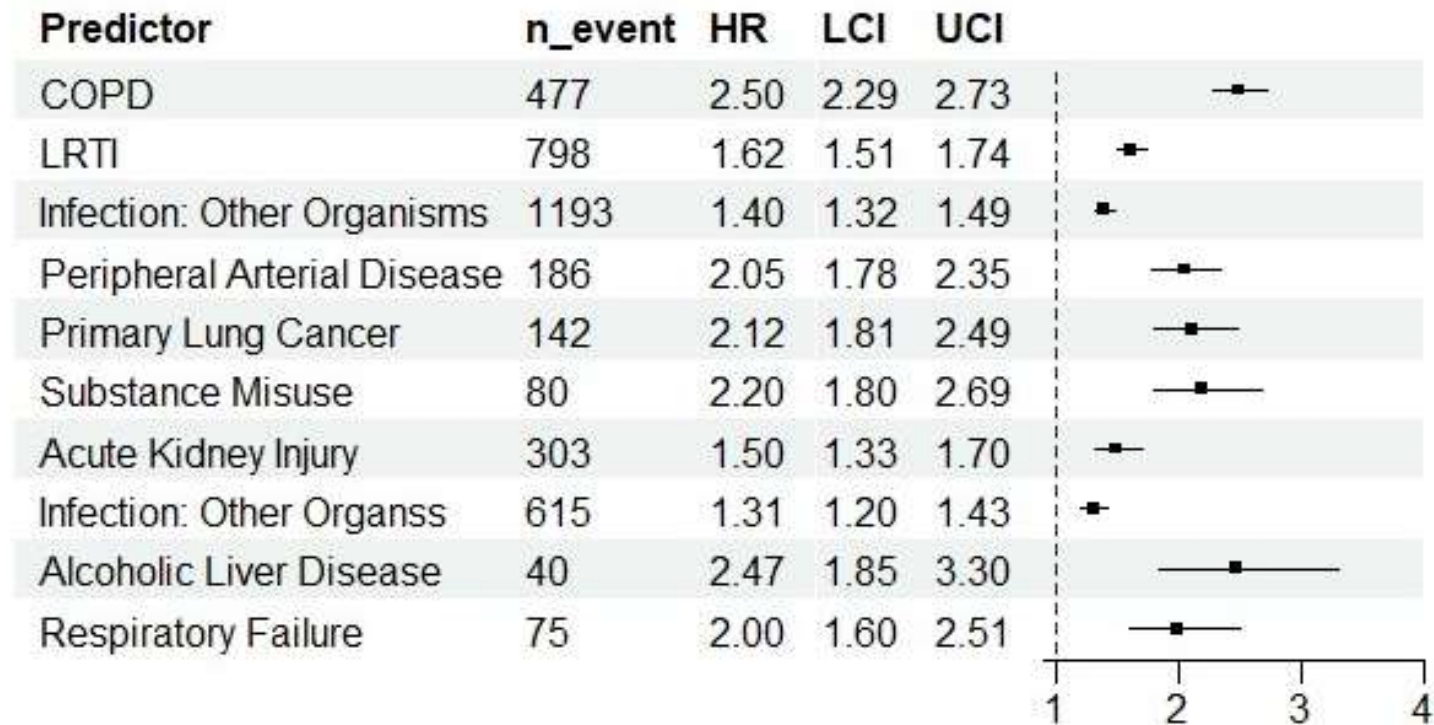


# GrimAge



# GrimAge and 308 incident diseases in GenScot

- Cox PH for incident outcomes
- 16 years follow up
- 308 diseases as per Kuan et al. Lancet Dig Health 2019
- Covariates: age, sex, bmi, education, deprivation, smoking



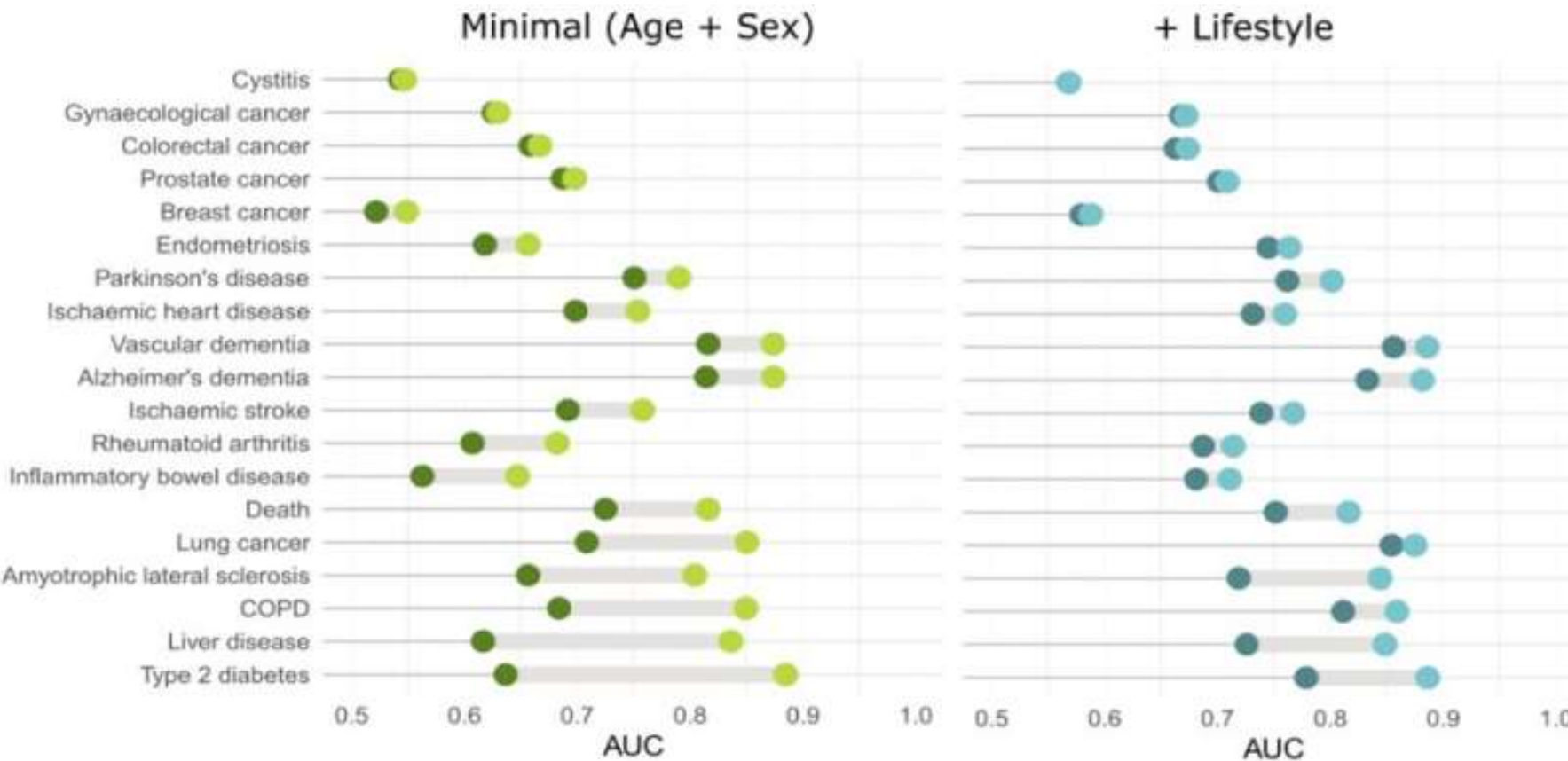
Top 10 assocs by p-value  
HR per SD of GrimAge accel  
(unpublished)



Only discuss if there is time!!



# Proteomic predictors in UK Biobank (n~50k)



education  
BMI  
Smoking  
social deprivation  
physical activity  
alcohol intake



# DNA methylation in UK Biobank

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- Track chronic inflammation
  - DNAm proteins can augment measured protein assoc
  - 109 DNAm proteins reported in Gadd et al. Elife 2022

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- **Help other cohorts “impute” variables**
  - Predictors translate well across ages and ancestries

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- **Multi-omics (PRS + proteins + DNAm)**

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Not enough time to  
mention....

mQTLs and causal  
inference  
EWAS of complex traits

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