MSGene: Estimating Lifetime Risk using multistate models in the UK Biobank EHR

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Introduction

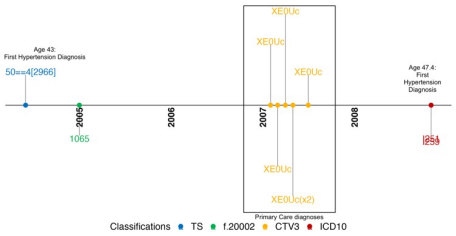
- Younger individuals at high lifetime risk are substantially underrecognized by existing risk stratification algorithms which tend to focus on short-term risk and don't reflect underlying primordial risk
- Lifetime risk algorithms are sorely missing, and don't reflect genetics
- Ability to estimate risk in younger individuals to guide earlier implementation of preventive strategies to those who will benefit the most

Goals

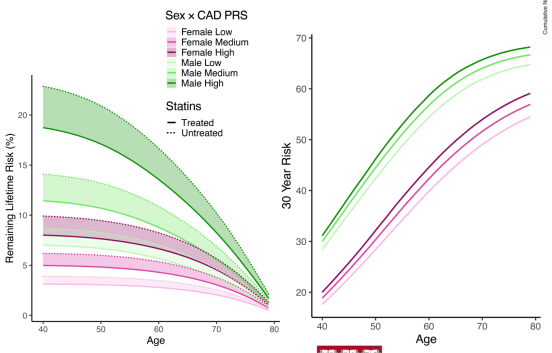
- Estimating CVD-free years gained following preventive treatment strategies
- Ability to assess the effect of individual treatment strategies on CVD free years gained

Data

- 481,686 Individuals enrolled in UKB Primary Care linking outpatient, prescription, hospitalization and operational codes from 1940 to present
- Median FU: 44y [30-58]
- Median first observation age
  - 24.5 [18-37.4]



Results: Lifetime Risk Estimates over the Age Span



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Methods: Multistate Model

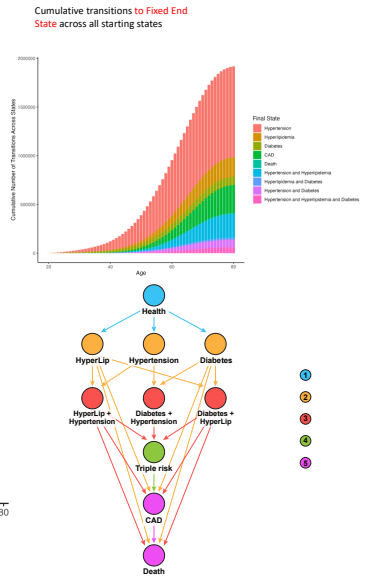
- Generalizability: Good internal and external validation in international cohorts
- Natural adjustment for competing risk of *any* alternative conditions
- Account for accumulated exposures through time in state

And lifetime risk for an individual of progressing to state k from state j where L is the maximum age of life and a is the currently observed age.

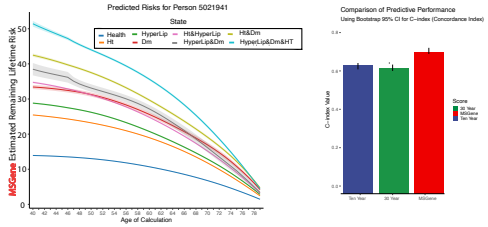
$$1 - \prod_{a=Age}^{L} (1 - \pi_{a,j,k}) \qquad (4)$$

- 10 starting states and 10 unique ending states
- Fit an age-specific generalized linear model with binomial error term for the odds of progressing from every starting state **i** to ending state **j** conditional on chosen covariates
- Covariates are time-fixed (primordial) covariates: sex, genetics, smoking status
- Obviates the need for time-correlated and medication-confounded biometric measurements
- Avoid parametric assumptions about proportional hazards, or linear interactions with time
- Allow for dynamically updated projections with flexible time estimates
- Easy to use R package with fast compute times (no memoryless Markov Assumptions)

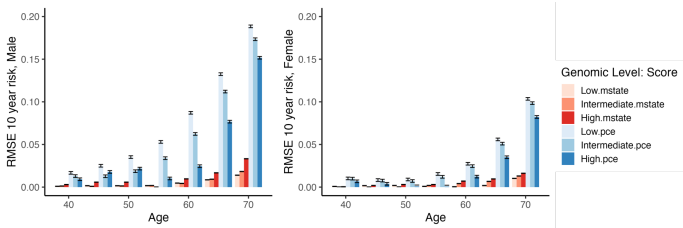
Results: Integrative Software



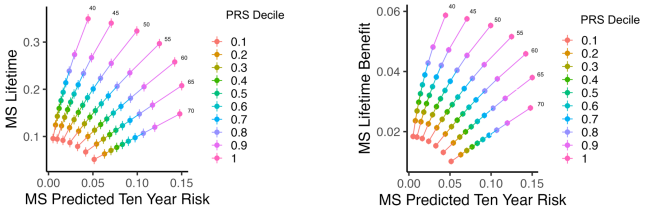
Results: Interactive and accurate flexible risk assessments



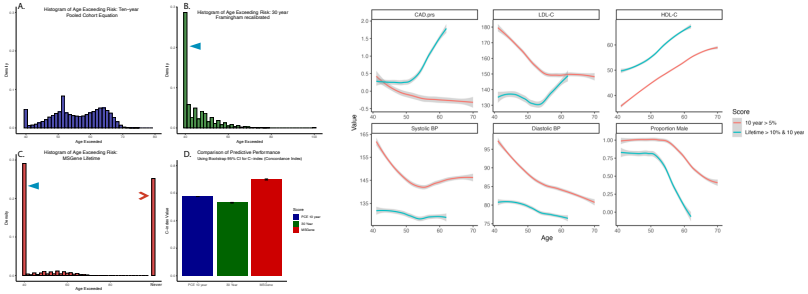
- Extract smoothed per year, covariate combination annual risk of transition to Coronary Artery Disease
- Allow for updated state-specific computation: i.e., how does my trajectory change if I become hypertensive, Diabetic,. etc,



Results: Intuitive Lifetime Risk assessment and Absolute Risk Reduction



Conclusions: Improved Identification of those at high lifetime risk dynamic stratification over time



- Uniquely identify subgroups of individuals at high lifetime risk unrecognized by existing equations
- Rapid recalibration for new populations and an intuitive **R package**