



GENETIC HEALTH RISKS EXPLAIN DIFFERENCES IN LONGEVITY, INSURANCE COVERAGE, AND RETIREMENT DECISIONS

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LOOKING FURTHER

HEALTH EXPECTATIONS

- Expectations of health and longevity influence many decisions¹
 - > Insurance, annuities, and pensions
 - > Consumption, labor supply, and retirement decisions
 - > Investments and savings
- Scholarly interest in factors that shape these expectations
- Genes account for much of the variation in health and longevity
 - > But genetic risks are hitherto unobserved by most people
(including our study participants)

GENETIC HEALTH EMPOWERMENT

- Genetic testing is fast becoming accessible and affordable
 - > Accuracy will increase substantially in the near future

Find out what your DNA says about your health, traits and ancestry.

add to cart

\$199

see all reports

The screenshot displays a list of genetic testing services, each with a distinct icon and a plus sign for expansion:

- Health Predispositions***: Represented by a blue heart icon. Description: "Learn how your genetics can influence your chances of developing certain health conditions."
- Ancestry**: Represented by a green circular icon with a white center. Description: "Discover where your DNA is from out of 1000+ regions worldwide - and more." A red banner above the icon reads "NOW WITH 1000+ REGIONS".
- Wellness**: Represented by a purple circular icon with a white smiley face. Description: "Learn how your genes play a role in your well-being and lifestyle choices."
- Carrier Status***: Represented by an orange person icon. Description: "If you are starting a family, find out if you are a carrier for certain inherited conditions."

GENETIC HEALTH EMPOWERMENT

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14 Genetic Risk Reports

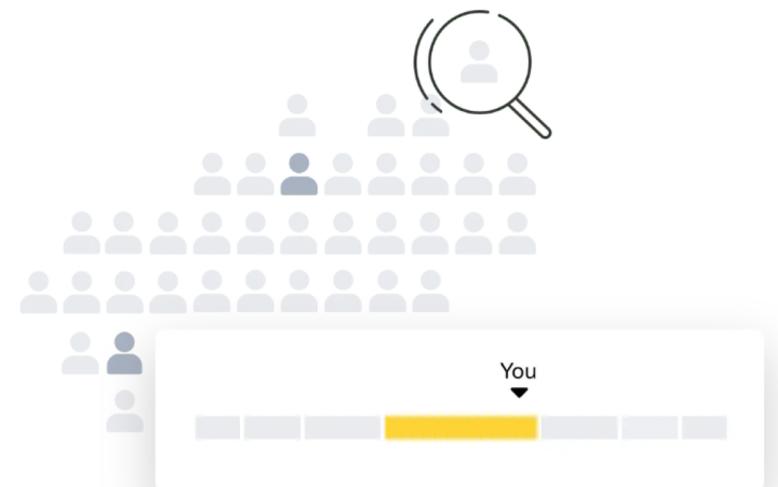
Everyone has some risk of developing genetic conditions. Your reports explain your genetic risk for developing certain conditions, compared to the general population.

Conditions include*:

Heart disease, breast cancer, Alzheimer's disease, and 11 others

[Learn more](#)

*Polygenic risk reports for heart disease, breast cancer, and type 2 diabetes are only available for people who are of mainly European ancestry.



ADVERSE SELECTION VS. GENETIC DISCRIMINATION

- Insurance industry concerned about genetic testing¹
 - > Adverse selection and escalating premiums
 - > Threatens affordability and viability of private insurance
- Insurance principles:
 - > Symmetric information about observable risks
 - > Actuarially fair premiums and evidence-based underwriting
- Genetic information in underwriting is a controversial topic²
 - > Risk of genetic discrimination
 - > Legally sanctioned non-disclosure problematic

STUDY OVERVIEW

- Preregistered study protocol (Open Science Framework)¹
- Main RQ: How well can polygenic scores stratify survival compared to conventional actuarial risk factors?
- Data: the Health and Retirement Study (HRS)
 - > Rich genetic, demographic, socioeconomic, and health data
 - > 9,272 *genotyped* respondents of European ancestry (2,332 deceased)
 - > Mortality selection—healthier, less health-risk behaviors, and longer-lived

GENETIC HEALTH RISKS



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GENETICS OF COMMON DISEASE

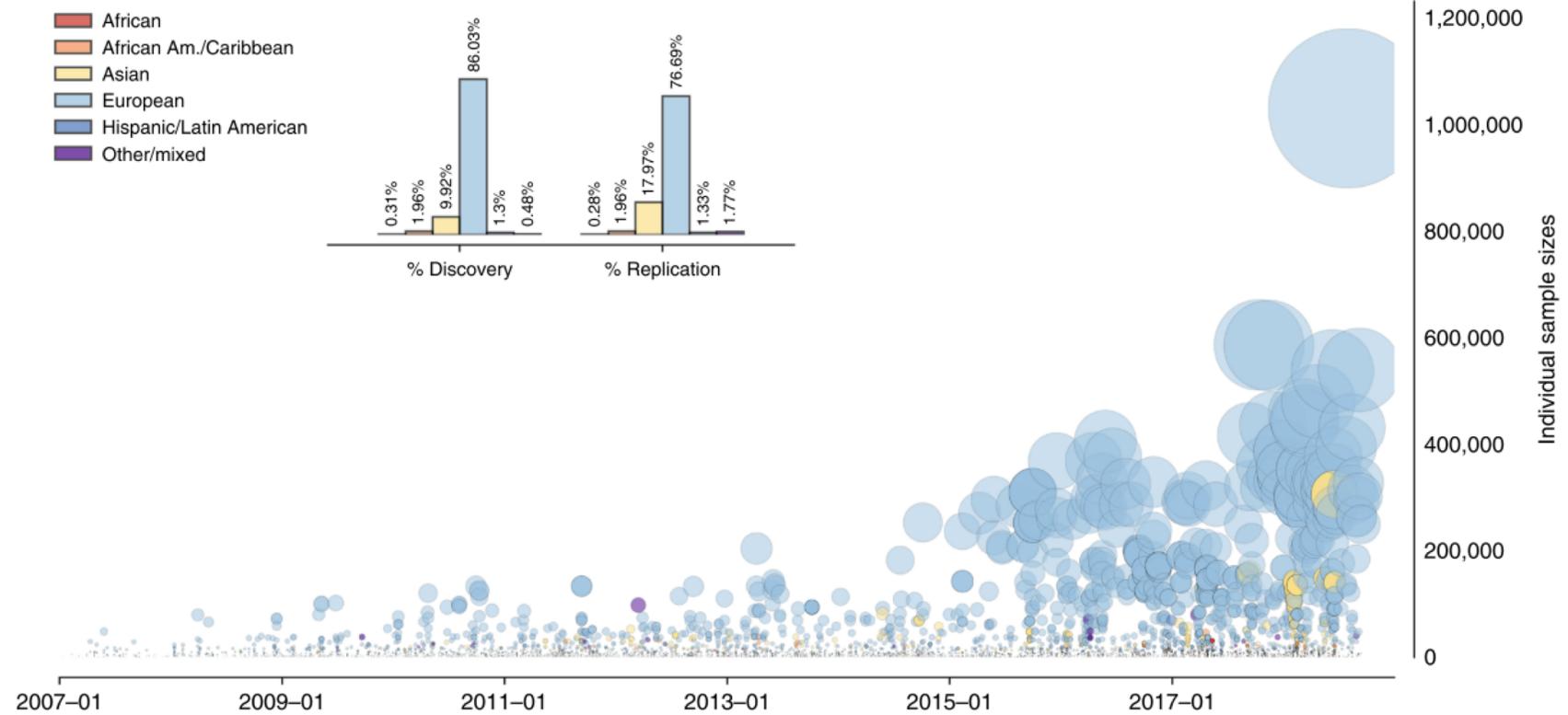
- Genetic screening for rare disease is not new
 - > Thousands of clinical diagnostic tests available
- But most NCD deaths are caused by *common* medical conditions¹
 - > Cardiovascular disease, cancers, diabetes, etc.
 - > Related mortality risks: smoking, BMI, cholesterol etc.
- Substantially heritable (20–60%) and *polygenic*²
 - > Influenced by a very large number of genetic variants with small effects
- Ongoing revolution in genetic discovery of common disease³

1 Bloom et al. (2011). *World Economic Forum and the Harvard School of Public Health*.

2 Visscher & Wray. (2016). *Human Heredity*.

3 Mills & Rahal. (2019). *Communications Biology*.

THE GWAS REVOLUTION



Mills & Rahal. (2019). *Communications Biology*.

COLLECTION OF GWAS RESULTS

- Extensive search of the GWAS literature
 - > Guided by the medical literature on mortality risks
 - > Restricted search to GWAS in >100,000 individuals
- 13 GWAS on common medical conditions:
 - > Alzheimer's disease, cardiovascular disease, cancers, stroke, etc.
- 14 GWAS on mortality health risks:
 - > Blood pressure, BMI, cholesterol, smoking, parental lifespan, etc.
- Average $N = 455,000$; Largest $N > 1$ million (atrial fibrillation)

POLYGENIC SCORES

- Polygenic scores are genetic predictors based on GWAS
 - > Could be evaluated early in life prior to any signs or symptoms of disease
 - > Recent scores approach accuracy of traditional clinical risk factors¹
- We constructed 27 polygenic scores (\hat{S}_{ik}):

$$\hat{S}_{ik} = \sum_{j=1}^M \hat{\beta}_{jk} g_{ij}$$

where g_{ij} (genetic variants) are weighed by $\hat{\beta}_{jk}$, the trait-specific GWAS effect size, and then summed across M variants.

ANALYSES

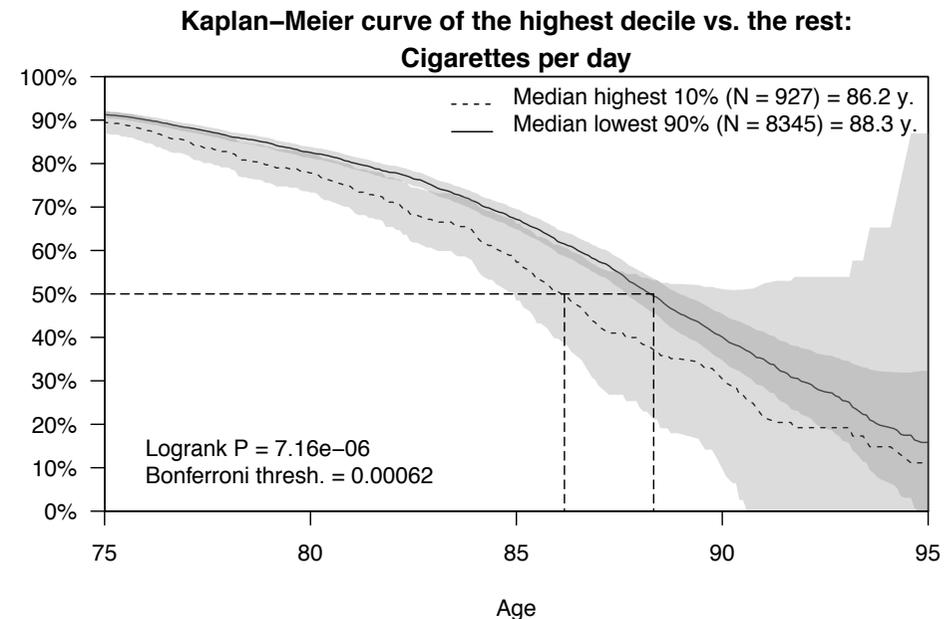
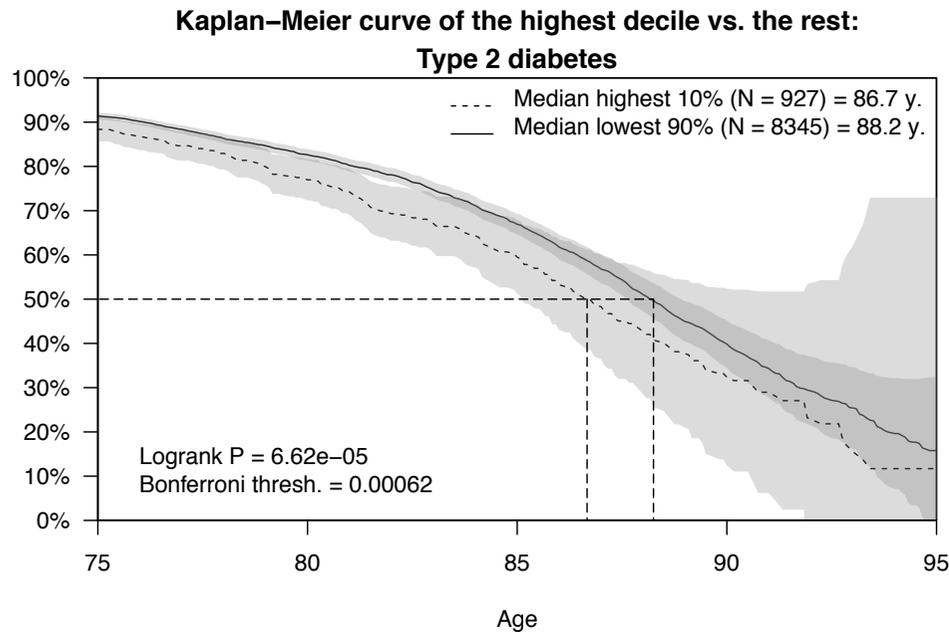


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UNIVARIATE SURVIVAL ANALYSIS

- Univariate Kaplan-Meier estimation of survival
- 18 polygenic scores significantly stratified survival
 - > Focus on comparison (a) the top decile versus the bottom nine



MULTIPLE REGRESSION OF SURVIVAL

- Four nested Cox models of respondent survival:
 1. all polygenic scores (except the score for parental lifespan*);
 2. model (1) together with sex-specific birth-year dummies, birth-month dummies, and many demographic and socioeconomic covariates;
 3. **model (2) together with the polygenic score for parental lifespan (preferred model);**
 4. model (3) together with many covariates from the health risk domain: including BMI, current and former smoker, subjective life expectancy and self-rated health, and 11 categories of diagnosed medical conditions (extensively adjusted model).

14 * All models included 10 genetic PCs to control for population stratification.
All standard errors were clustered at the household level.

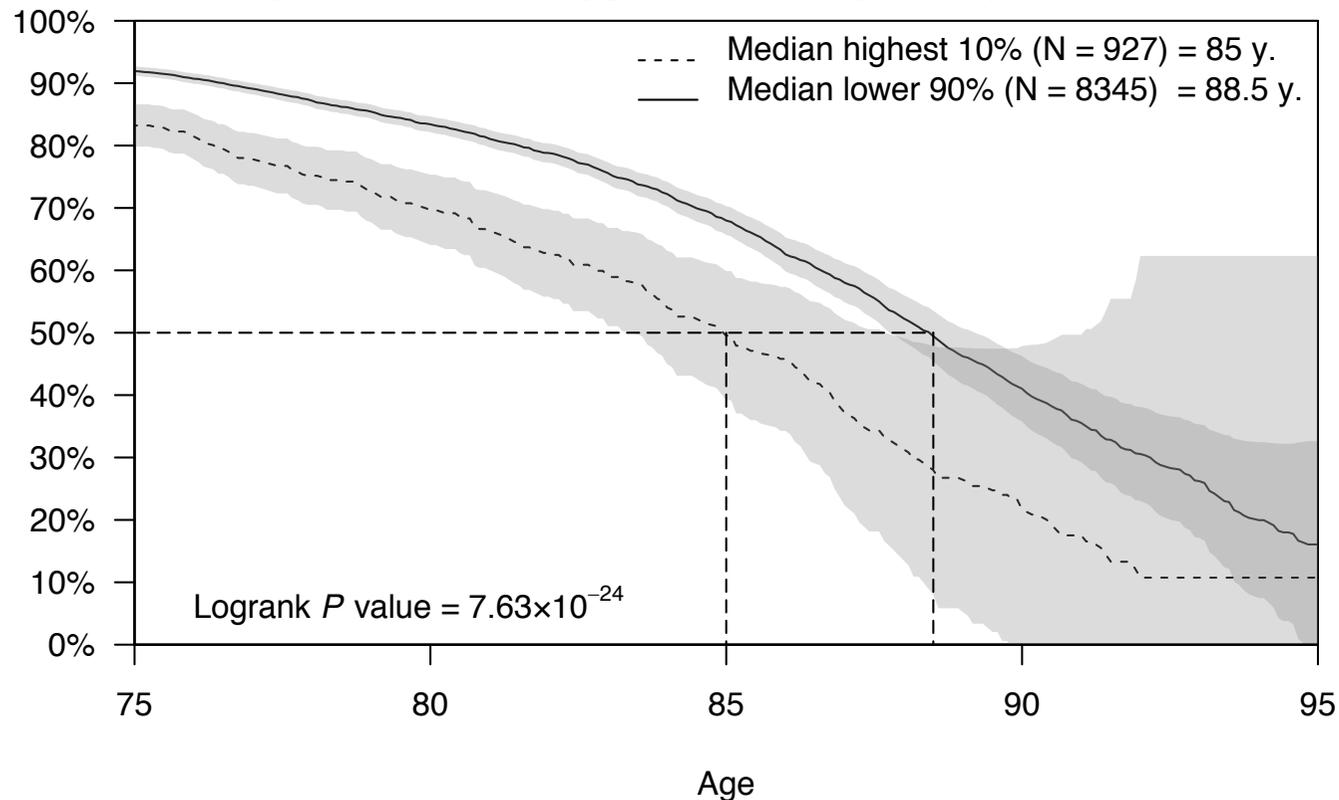
MULTIPLE REGRESSION OF SURVIVAL

- Our preferred model (3) satisfied model assumptions and fit
- Associated polygenic scores:
 - > Alzheimer's disease ($\hat{\alpha} = 0.052$; $P = 0.022$)
 - > Atrial fibrillation ($\hat{\alpha} = 0.054$; $P = 0.019$)
 - > Cigarettes per day (smoking intensity; $\hat{\alpha} = 0.073$; $P = 0.001$)
 - > Height ($\hat{\alpha} = 0.049$; $P = 0.046$)
 - > Type 2 diabetes ($\hat{\alpha} = 0.054$; $P = 0.036$)
 - > Parental lifespan ($\hat{\alpha} = -0.087$; $P < 0.001$)
- The 27 polygenic scores jointly explained 3.6% of the variation

PROGNOSTIC INDEX – POLYGENIC SCORES

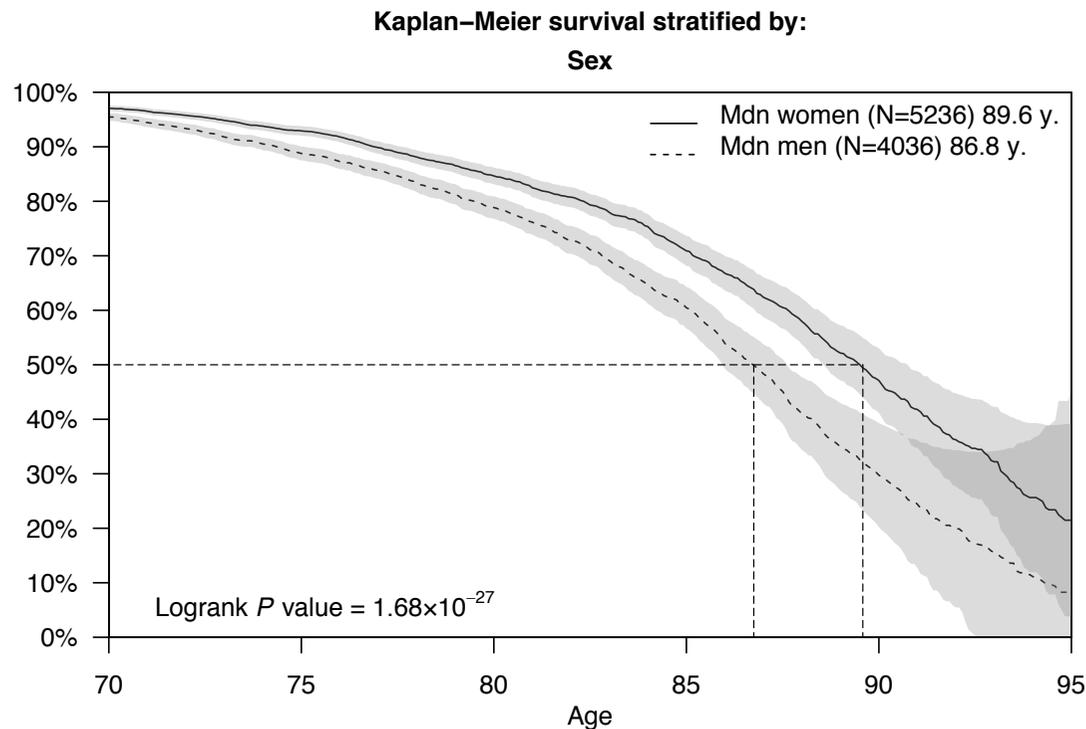
- PI_{PGS} – combining the effect of the scores into a hazard index
- 3.5 y shorter median survival (2.4 y lower bound)

**Kaplan–Meier survival stratified by prognostic indices:
Prognostic Index Polygenic Scores (PI PGS), Cox model 3**



BENCHMARK

- PI_{PGS} stratified survival comparable to:
 - > Sex (2.8y)
 - > Diabetes (or high blood sugar; 1.7y)
 - > Former smoking (2.5y)



BENCHMARK

- PI_{PGS} stratified survival better than:
 - > High education* (1.3y)
 - > Several medical diagnoses, including cancer (1.2y)
- PI_{PGS} stratified survival worse than:
 - > Current smoker (9.9y)
 - > Severe obesity* (4.4y)

- 18
- Top decile of educational attainment ≥ 17 years of schooling.
 - Top decile of BMI > 38.6 .

SUBJECTIVE HEALTH AND ECONOMIC OUTCOMES

- The (unobserved) genetic risk was associated with worse self-reported health and shorter subjective life expectancy
 - > Suggests that the genetic risk had manifested and influenced health
- The genetic risk was associated with:
 - > Work-limiting health problems
 - > Less retirement satisfaction
 - > Less long-term care insurance
 - > Shorter financial planning horizon
 - > But not with life insurance

CONCLUSIONS

- Genetically-informed research design found that polygenic scores could jointly stratify 2.4—4.4 y shorter survival
 - > Lower bound (limited GWAS N and mortality selection)
 - > Will increase substantially in the near future
 - > Nonetheless, comparable to or better than conventional actuarial risks
- Polygenic scores will soon be relevant for underwriting
 - > Alternatively, as more people acquire knowledge of their polygenic scores there is a real risk of adverse selection
- New challenges that need urgent attention from policymakers

THANK YOU!

Questions?

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