How Medical Advances and Health Interventions Will Shape Future Longevity

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Quantifying Longevity Changes

- Medical and social advances are the major drivers in the longevity increase. But how to quantify this relationship?

- In medicine, Randomized Control Trials (RCTs) are considered to be the gold standard.

- RCTs estimate the hazard or force of mortality in a (selective) sample of people and summarised over the observed (limited) time period.

- New health interventions are usually based on these estimated hazards obtained from clinical trials. A lengthy lead time would be needed to observe their effect on population longevity.

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Our approach, 1

- Our research uses The Health Improvement Network (THIN) primary care data to develop statistical models of longevity.

- The advantage of using individual-level medical data is that it is possible to model both the uptake of medical treatment and the effect of that treatment on longevity conditional on the individual sociodemographic and health factors instead of the aggregated profile.

- Survival models, usually the Cox's regression, are fitted to individual level data.

- The conclusions are generalisable to the general population.

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The Health Improvement Network (THIN) data

- Anonymised electronic primary care medical records (Vision)

- Data collection began in 2003 using Read codes

- 11 million patients, 3.7 million active patients

- 562 general practices, covering 6.2% of the UK population

- Diagnoses, prescriptions, consultations, postcode deprivation

Subset of THIN selected for our research:

- All patients born before 1960 and followed to 01.01.2017, this includes 3.5 million patients

- Social economic status variables such as Index of Multiple Deprivation (IMD), Townsend and Mosaic

- IMD: income, employment, health, education, crime, housing

- Townsend: employment, car ownership, home ownership, household overcrowding

- Mosaic: consumer classification based on demographics, lifestyles and behaviour of a person

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Example 1: Beta-Blockers after Acute Myocardial Infarction (AMI)

- Myocardial cell death due to prolonged ischaemia, a.k.a. heart attack.

- There are 188,000 hospital episodes attributed to heart attack in the UK each year: that's one around every three minutes.

- In the UK around 7 out of 10 people survive a heart attack.

- An estimated 915,000 people in the UK (640,000 men and 275,000 women) have survived an MI.

(British Heart Foundation, 2016)

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Research question

- What are the survival prospects associated with a history of a single or multiple acute myocardial infarctions in the general population at various ages and how were the survival prospects modified by recommended treatment?

- Gitsels LA, Kulinskaya E, Steel N Survival prospects after acute myocardial infarction in the UK: a matched cohort study 1987–2011. BMJ Open 2017;7:e013570. doi:10.1136/bmjopen-2016-013570.

- University of East Anglia's press release statement: https://www.uea.ac.uk/about/-/beta-blockers-offer-best-chance-of-increased-heart-attack-survival

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Design

- Population-based retrospective cohort study

- Restrictions data: Medical records from 1987 to 2011 of people born between 1920 and 1940

- Primary risk factor: acute myocardial infarction

- Primary intervention: beta-blockers (blood pressure related drug)

- Four cohorts who have had AMI before target ages: 60, 65, 70, and 75

- Cases matched to three controls from the same sex, year of birth group and GP practice

- Followed up until death, transfer out or 18/05/2011

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Lexis diagram

Restricted follow-up data: 1987-2011
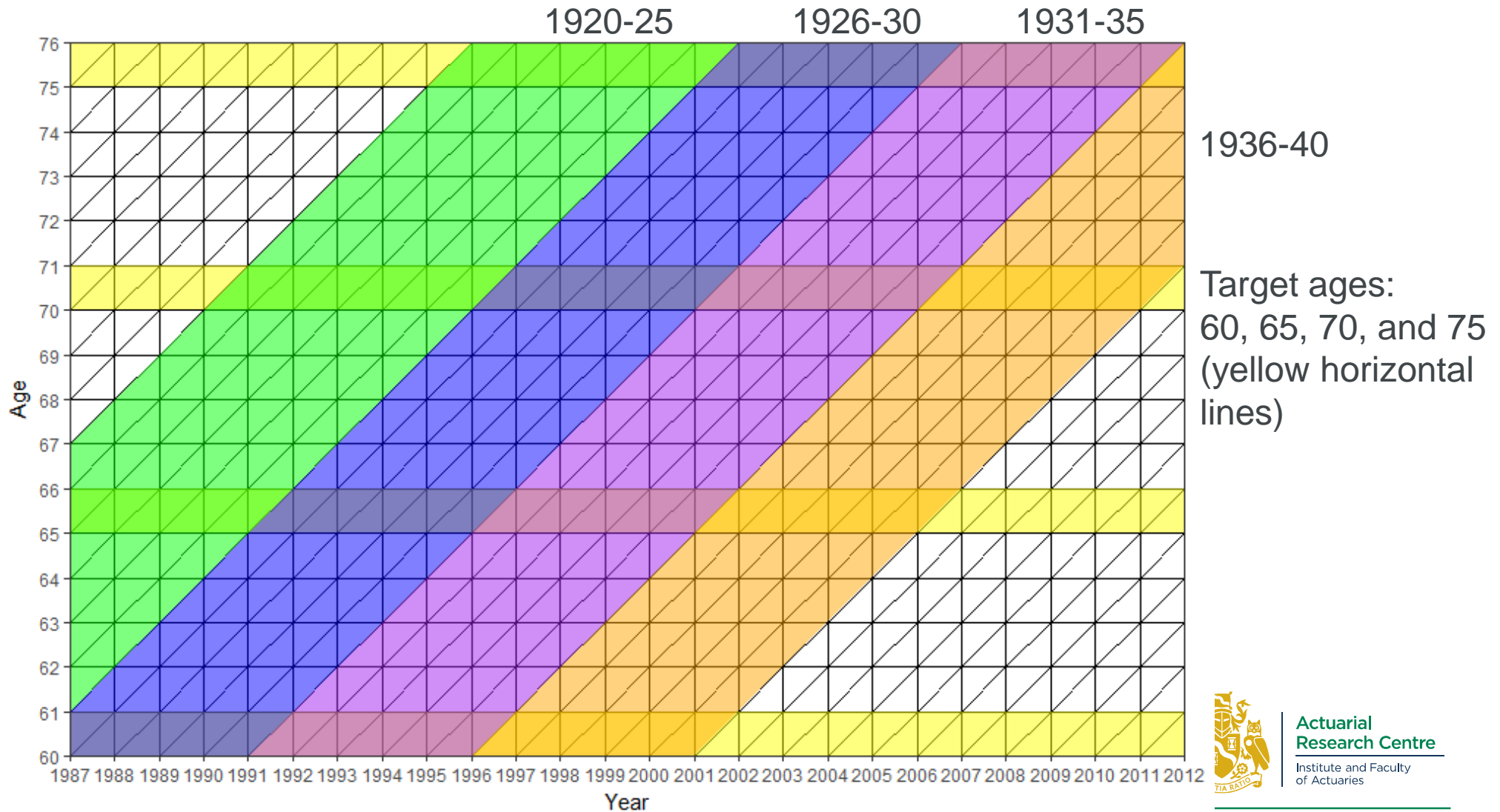
Data selection

- Outcome: time to death

- Treatments: coronary revascularisation (coronary artery bypass graft and coronary angioplasty), and prescription of ACE inhibitors, aspirin, beta blockers, calcium-channel blockers, and statins

- Confounders: sex, year of birth, socioeconomic status, angina, heart failure, other cardiovascular conditions (valvular heart disease, peripheral vascular disease, and cerebrovascular disease), chronic kidney disease, diabetes, hypertension, hypercholesterolaemia, alcohol consumption, body mass index, and smoking status

- Incomplete records in BMI, smoking status, and risk of cardiac event were dealt with by multilevel multiple imputation using REALCOM-Imputation software

Cohorts' characteristics

Cohort	Number of patients	Number of deaths	Average follow-up time	Maximum follow-up time
Age 60	16,744	3,228 (19%)	12 years	24 years
Age 65	43,528	8,852 (20%)	9 years	24 years
Age 70	73,728	15,743 (21%)	6 years	21 years
Age 75	76,392	18,569 (24%)	5 years	16 years

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Hazard aka "force of mortality" and "mortality intensity"

- The type of regression model typically used in survival analysis in medicine is the Cox's proportional hazards regression model.

- The Cox's model estimates the hazard $\mu_i(x)$ for subject i for time x by multiplying the baseline hazard function $\mu_0(x)$ by the subject's risk score r_i as

$$\mu_i(x, \beta, Z_i) = \mu_0(x)\, r_i(\beta, Z_i) = \mu_0(x)e^{\beta\, Z_i}$$

- The risk factors Z have a log-linear contribution to the force of mortality which does not depend on time x.

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Hazard ratio (HR)

- Taking a ratio of the hazard functions for two subjects *i* and *j* who differ in one risk factor *z* and not in the other risk factors,

$$\mu(x, \beta, Z) = \frac{\mu_i(x,\beta,Z_i)}{\mu_j(x,\beta,Z_j)} = \frac{\mu_0(x)e^{\beta\, Z_1}}{\mu_0(x)e^{\beta\, Z_0}} = \frac{e^{\beta_z\, z_1}}{e^{\beta_z\, z_0}} = e^{\beta_z\,(z_0 - z_1)}.$$

- This means that the baseline hazard $\mu_0(x)$ does not have to be specified and the hazard ratio $e^{\beta_z\,(z_0 - z_1)}$ is constant with respect to time *x*.

- Because of this, the Cox's model does not make any assumptions about the shape of the baseline hazard.

- $e^{\beta_z\,(z_0 - z_1)}$ is an adjusted HR, i.e. all other risks are already accounted for by the model.

Survival prospects after AMI and beta-blockers prescription

Risk factor	Cohort	Adjusted HR (95%CI)
AMI	Age 60	1.80 (1.60-2.02)
	Age 65	1.71 (1.59-1.84)
	Age 70	1.50 (1.42-1.59)
	Age 75	1.45 (1.38-1.53)
Beta-blockers	Age 60	0.83 (0.73-0.94)
	Age 65	0.79 (0.73-0.85)
	Age 70	0.85 (0.81-0.91)
	Age 75	0.81 (0.77-0.86)
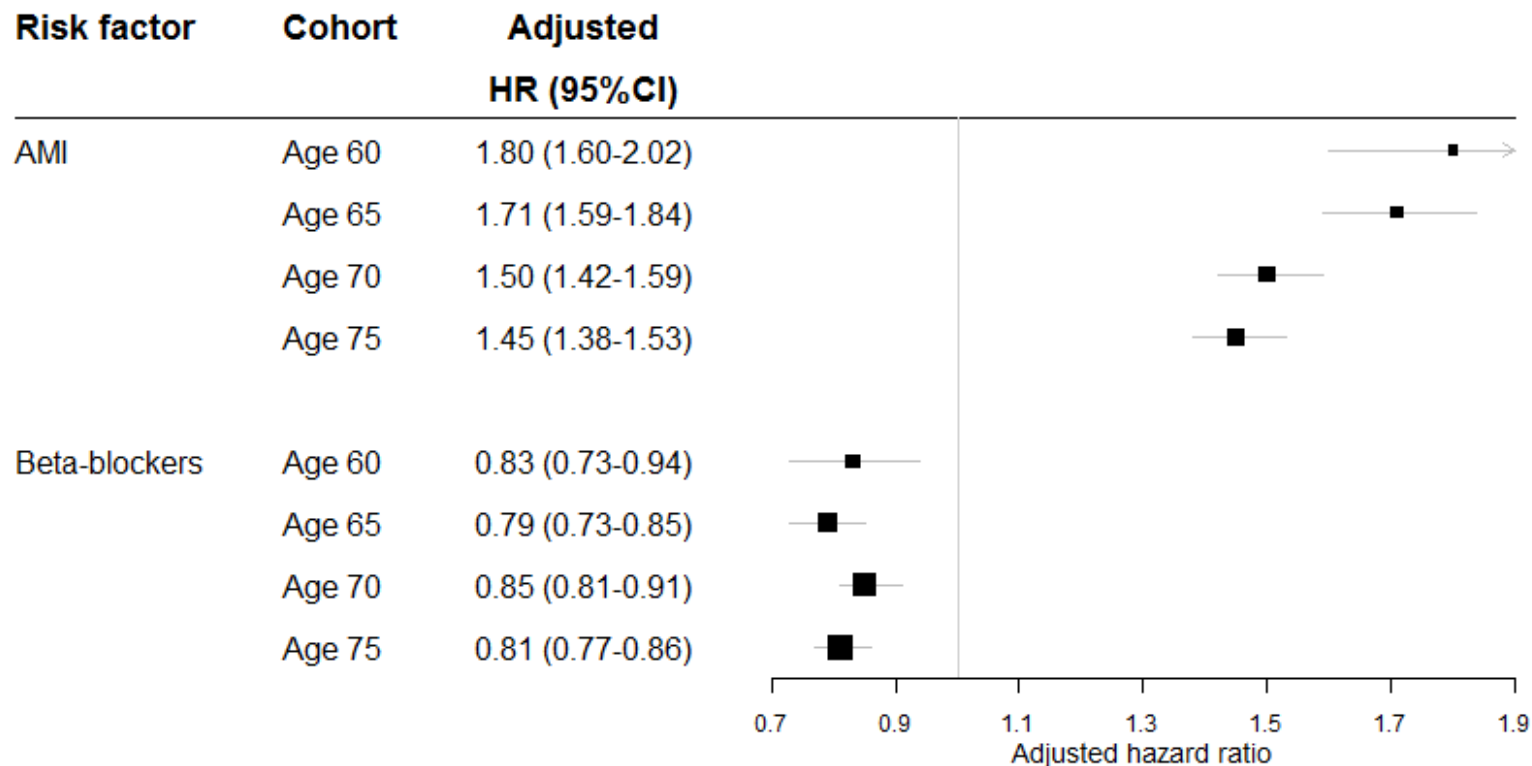
Adjusted for sex, year of birth, socioeconomic status (Mosaic), angina, heart failure, other cardiovascular conditions, coronary revascularisation, chronic kidney disease (only at ages 70 and 75), diabetes, hypertension, hypercholesterolaemia, alcohol consumption, body mass index, smoking status, general practice, and prescription of ACE-inhibitors, aspirin, calcium-channel blockers, and statin.

Our approach, 2: for an individual

- For an individual, the hazard ratios obtained from the survival models are translated into "effective age" changes.

- This helps to explain consequences of conditions and lifestyle choices and can be used to nudge clients to pursue a healthier lifestyle.

- 'Effective ages' are often used by insurers as a way of applying the correct rating to an underwritten life.

Log force of mortality for UK population based on 2010 period life table (Office for National Statistics 2017).
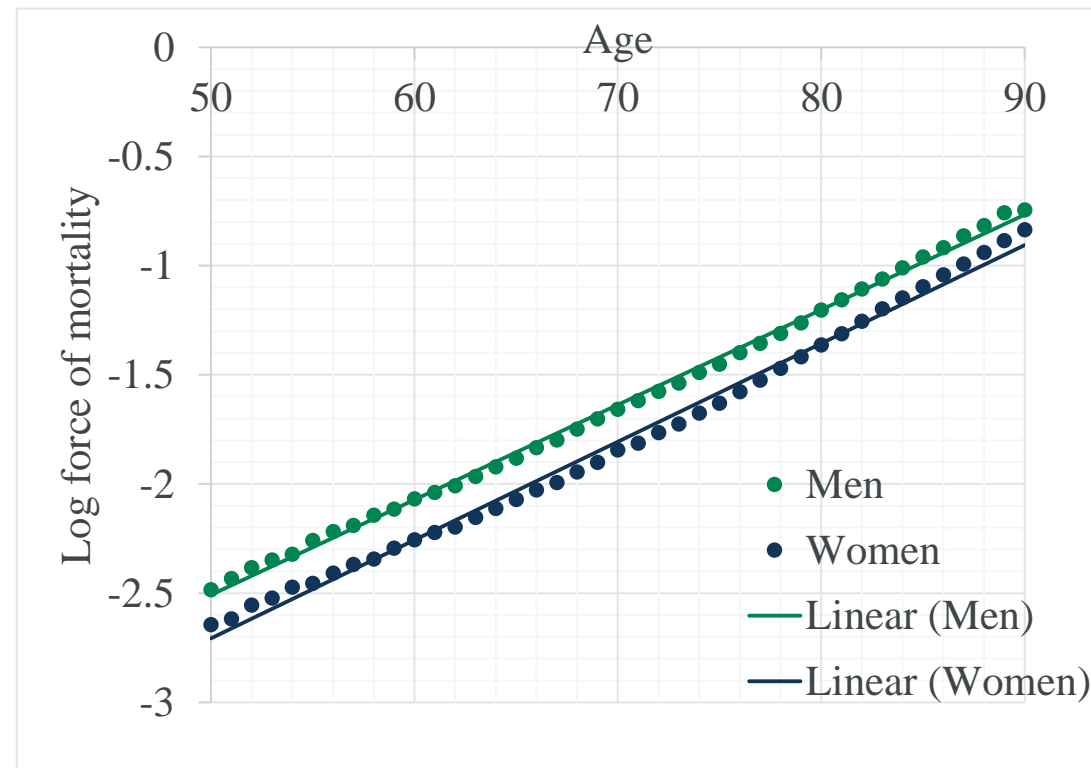
What does HR mean for an individual

- Using Gompertz law, the increase in annual hazard of mortality associated with ageing one year is approximately constant between ages 50 and 90.

- For England and Wales in 2010-2012, the increase in the hazard between those ages was approximately 1.1 per year.

- A HR can be translated to the numbers of years gained in effective age as

  $$\log HR / \log (1.1) \approx 10*\log(HR).$$

 [Brenner, 1993; Spiegelhalter, 2016]
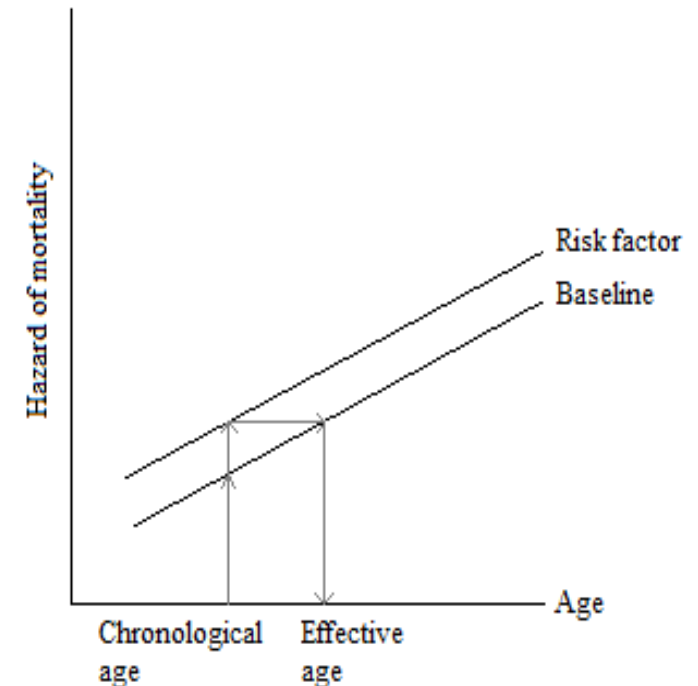
Log force of mortality for AMI survivors with and without Beta-blockers

Log force of mortality in 65-year old female cohort
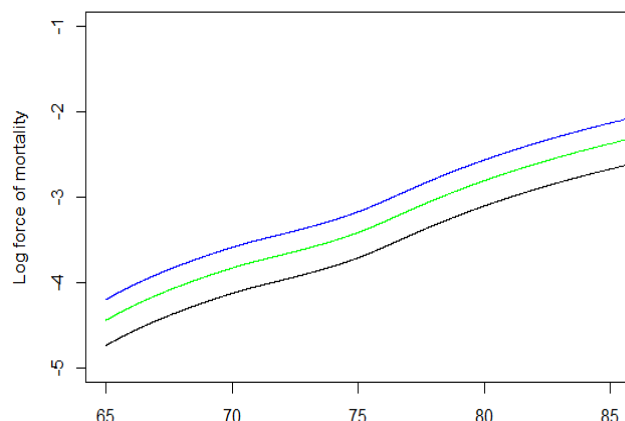
Log force of mortality in 65-year old male cohort

Log force of mortality in 70-year old female cohort
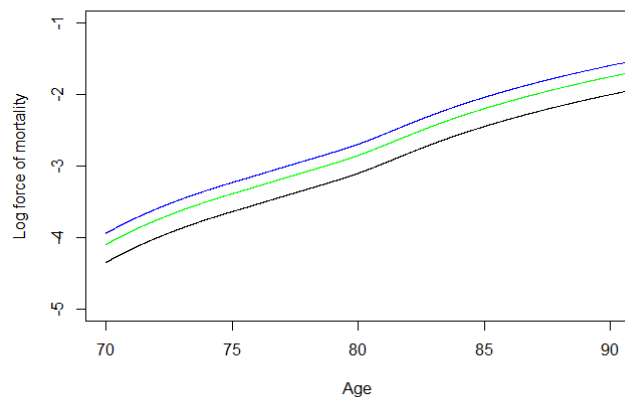
Log force of mortality in 70-year old male cohort

- Black:
  healthy baseline
- Blue:
  AMI survivors without
  beta-blockers
- Green:
  AMI survivors with
  beta-blockers
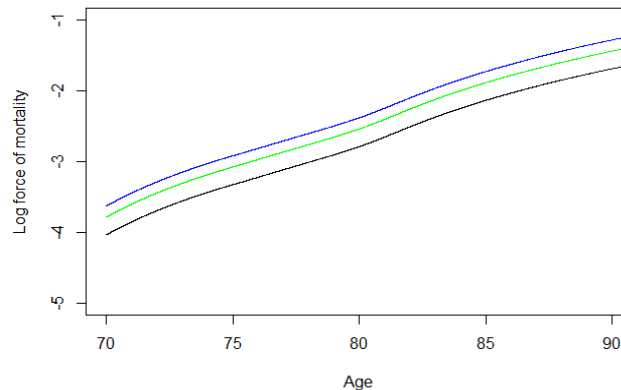
Adjusted for previous
listed risk factors

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How do beta-blockers change effective age?

Gender	Cohort	AMI	Beta-blockers	AMI & Beta-blockers
Men	Age 60	5.8 (4.6-6.9)	-1.8 (-3.1,- 0.6)	3.9 (2.7-5.2)
	Age 65	5.3 (4.6-6.0)	-2.3 (-3.1,-1.6)	3.0 (2.2-3.7)
	Age 70	4.0 (3.4-4.6)	-1.6 (-2.1,-0.9)	2.4 (1.9-3.1)
	Age 75	3.7 (3.2-4.2)	-2.1 (-2.6,-1.5)	1.6 (1.1-2.2)
Women	Age 60	5.4 (4.3-6.5)	-1.7 (-2.9,-0.6)	3.7 (2.5-4.8)
	Age 65	4.9 (4.3-5.6)	-2.2 (-2.9,-1.5)	2.8 (2.0-3.4)
	Age 70	3.7 (3.2-4.3)	-1.5 (-1.9,-0.9)	2.2 (1.8-2.9)
	Age 75	3.4 (3.0-3.9)	-1.9 (-2.4,-1.4)	1.5 (1.0-2.0)

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Our approach, 3: for a population LE

- Period life expectancy e_x at age x is a weighted average of component LEs, of people with different risk profiles, with the weights defined by the prevalence p of the risk factor of interest and/or the uptake of relevant intervention.

- Let $e_{x,1}$ and $e_{x,0}$ be the period life expectancies for people with and without the risk factor (reference subpopulation), respectively, at age x. Then

$$e_x = p_x \, e_{x,1} + (1-p_x) \, e_{x,0}.$$

- Splitting the overall LE into these components allows to estimate hypothetical changes in life expectancy at the population level at different scenarios.

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Prevalence of treatment by cohort's age in patients with a history of acute myocardial infarction
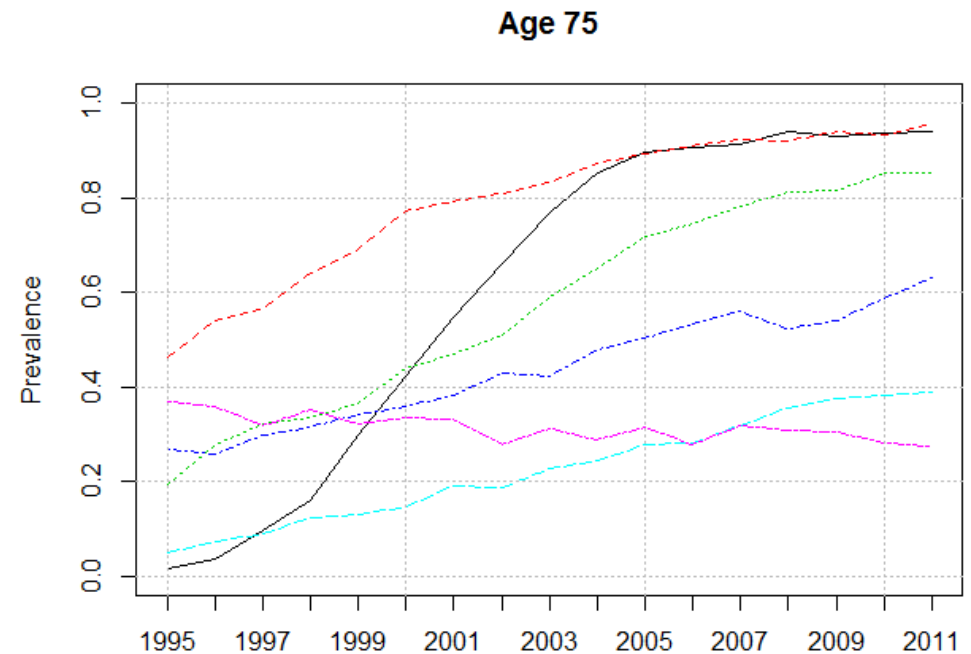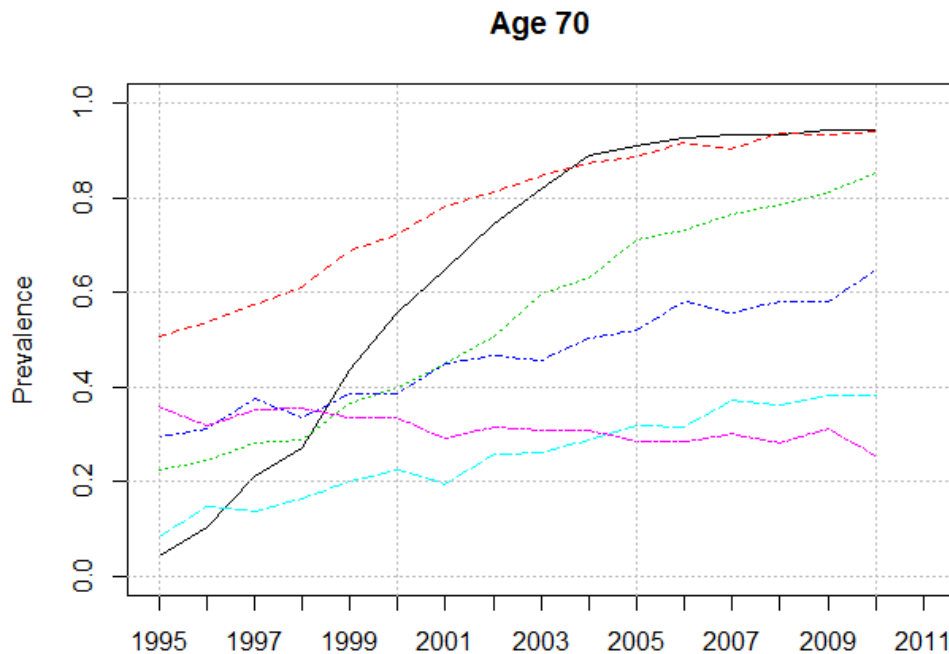
From top to bottom at last calendar year:
statins, aspirin, ACE-inhibitors, beta-blockers,
coronary revascularisation, and calcium-channel blockers

Period life expectancy for heart attack survivors

Sex	Period life expectancy	Age 60 (95% CI)	Age 65 (95% CI)	Age 70 (95% CI)	Age 75 (95% CI)
Men	All	22.03	18.03	14.33	11.00
	Heart attack [a]	17.43 (17.32-18.32)	14.14 (13.62-14.64)	11.65 (11.28-12.00)	8.83 (8.54-9.11)
	Prescription [b]	18.84 (17.9-19.85)	15.79 (15.27-16.37)	12.69 (12.25-13.01)	10.03 (9.68-10.33)
	No prescription [c]	16.36 (16.89-17.16)	12.71 (12.20-13.16)	10.68 (10.38-11.07)	7.78 (7.54-8.03)
Women	All	24.92	20.66	16.61	12.88
	Heart attack [a]	20.33 (19.45-21.23)	16.67 (16.15-17.19)	13.80 (13.41-14.18)	10.56 (10.24-10.85)
	Prescription [b]	21.76 (20.80-22.76)	18.39 (17.85-18.98)	14.91 (14.44-15.24)	11.85 (11.47-12.16)
	No prescription [c]	19.29 (18.47-20.11)	15.35 (14.86-15.84)	12.90 (12.56-13.30)	9.53 (9.26-9.81)

[a] Period life expectancy for heart attack survivors at 2010 prescription level of beta blockers. This is the weighted average of [b] period LE for heart attack survivors with prescription and [c] period LE for heart attack survivors without prescription.

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Example 2: Would intensive systolic blood pressure control increase longevity?

SPRINT trial reported considerable survival benefits of intensive systolic blood pressure (SBP) lowering below 120 mmHg.

Adverse Renal Outcome was one of the main adverse effects, with the odds raised threefold in patients without Chronic Kidney Disease at baseline.

The American Heart Association changed its hypertension guideline on the basis of SPRINT results (Whelton et al. 2017).

The primary objective of our study was to investigate the survival benefits of intensive SBP lowering in UK primary care and to compare them to SPRINT results.

Design

The sample included 54,683 patients from THIN (50-90 yr) who were treated for hypertension between 2005 and 2013 and followed-up to 2017.

Group 1: patients with SBP>140 mmHg (SBP1) which was lowered to less than 120 mmHg; 19,756 (36%) patients.

Group 2: SBP>140 mmHg lowered to 120-140 mmHg; 34,927 (64%) patients.

Time interval: 2 weeks to 6 months + new prescription.

Results

SPRINT: the intensive treatment has a hazard ratio (HR) of 0.73 (0.60, 0.90) compared to standard treatment:

a decrease in effective age of 3.4 to 3.6 years.

AHA Guidelines: boost to the life expectancy in the US?

THIN: the intensive group had significantly increased HR of 1.35 (1.14, 1.27):

an increase in effective age of 1.7 to 1.8 years.

In both studies, more than 2 BP lowering drugs, and increase in dosage (THIN) further significantly increased the hazards of mortality and the hazard of adverse renal outcomes.

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Log force of mortality for hypertensive patients with and without intensive BP control
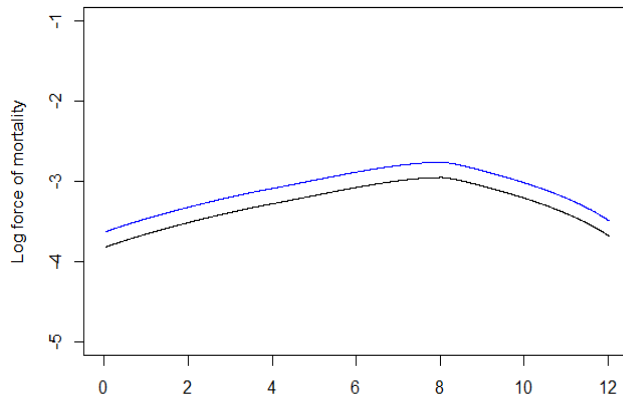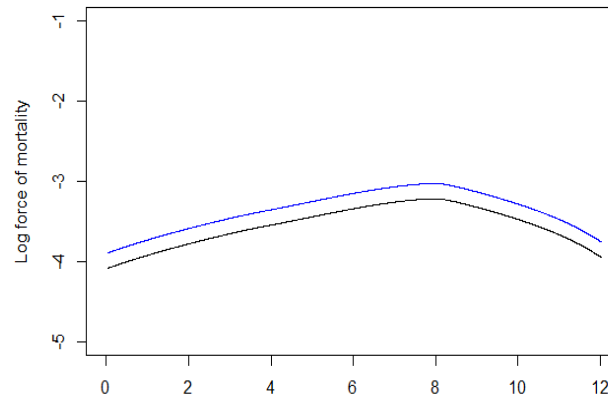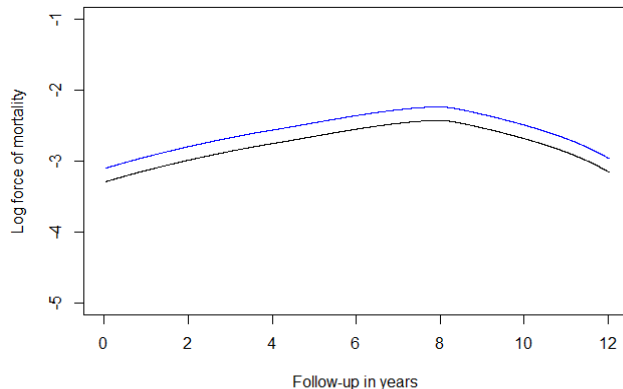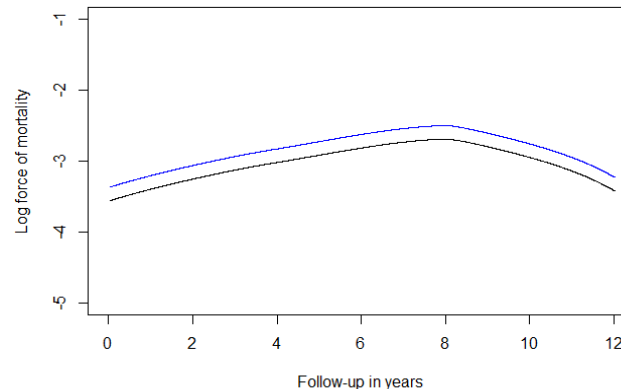
Summary

- Estimating longevity risk and evaluating associated uncertainty is one of the main topics of concern to actuarial community.

- Modelling mortality experience in individual level health data from large health databases can:

  - Establish and quantify the drivers of changes in longevity

  - Help predict how these drivers may change over time

- The results can be translated into individual and population level life expectancy changes.

- Models that allow for differences in prevalence/treatments within the population can be used to transpose results to apply to a sub-population (of insured lives, for example).

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Summary

- Hazards of mortality can be translated to life expectancies at the individual and population levels using:

  - hazard of mortality associated with the risk factor of interest,

  - the prevalence of the risk factor of interest, and

  - a life table of the underlying population.

- Changes in the prevalence of the risk factor of interest are reflected in the life expectancy at the population level, illustrating:

  - how much the risk factor of interest has already contributed to changes in past longevity improvements and

  - how continuing trends of the prevalence of the risk factor of interest can affect future life expectancy.

- These calculations can be informative for mortality projections of populations of insureds and pension schemes.

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Summary

- This approach, based on effects and prevalence of known treatments or conditions, will never provide a complete answer, especially when projecting future mortality improvements.

- It is a useful tool, though, that can also help with questions like:

 – 'What would be the impact of another medical advance the size of statins?'
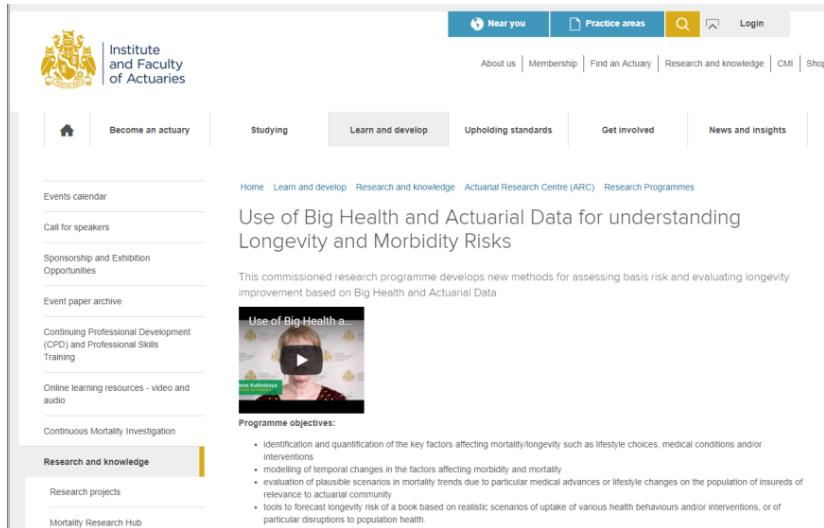
ARC Research Programme on Big Health and Actuarial data: Conditions and interventions

- Case studies presented here:
  - Beta-blockers following heart attack
  - Intensive blood pressure control
- We have also looked at statin prescription.
- We have a target list of medical conditions and health interventions.
  - Conditions: heart attack, stroke, type 2 diabetes, …
  - Health interventions: statins, blood pressure targets, hormone replacement therapy

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Find out more

bit.ly/arc2173

www.bighealthactuarialdata.ac.uk

References

- Brenner H, Gefeller O, Greenland S. (1993) Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. *Epidemiol Camb Mass*. 4(3):229–36.

- Gitsels LA, Kulinskaya E, Steel N Survival prospects after acute myocardial infarction in the UK: a matched cohort study 1987–2011 BMJ Open 2017;7:e013570. doi:10.1136/bmjopen-2016-013570.

- Spiegelhalter (2016) How old are you, really? Communicating chronic risk through 'effective age' of your body and organs. *BMC Medical Informatics and Decision Making,* 16:104

- The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine*, 2015 373:2103-2116, DOI: 10.1056/NEJMoa1511939

- Whelton, P. K., Carey, R. M., Aronow, W. S., Ovbiagele, B., Casey, D. E., Smith, S. C., … Mauri, L. (2017). *High Blood Pressure Clinical Practice Guideline*.

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The '**Use of Big Health and Actuarial Data for understanding Longevity and Morbidity Risks**' research programme is being funded by the ARC.