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Landmark analysis of survival benefits of statin prescription

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Introduction

- We aim to demonstrate the use of landmark analysis in actuarial research using the statin survival benefits as a case study.
- Statins have been widely prescribed for cardiac prevention
- Clinical trials have demonstrated the survival benefits of statin prescription
- The threshold of cardiac risk at which to prescribe statins is still controversial, especially at older ages where everyone would be eligible solely due to their age.
- Little is known about the effect of long-term prescription in the general population, where sequential treatment decisions are made according to the latest clinical guidelines.



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:

- 110,243 patients who turned 60 between 1990 and 2000 and did not have a previous statin prescription or a cardiovascular disease diagnosis



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Primary prevention of CVD

Primary prevention: no previous history of CVD

- Example: lipid-lowering therapy - statins

National Institute of Health and Clinical Excellence (NICE):

- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD.
- Estimate the level of risk using the QRISK2 assessment tool
- www.nice.org.uk/guidance/cg181/
- www.qrisk.org/2016/



Up to 17 million UK residents eligible for statins

About you

Age (25-84):

Sex: Male Female

Ethnicity:

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status:

Diabetes status:

Angina or heart attack in a 1st degree relative < 60?

Chronic kidney disease?

Atrial fibrillation?

On blood pressure treatment?

Rheumatoid arthritis?

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Body mass index

Height (cm):

Weight (kg):

Calculate risk over years.

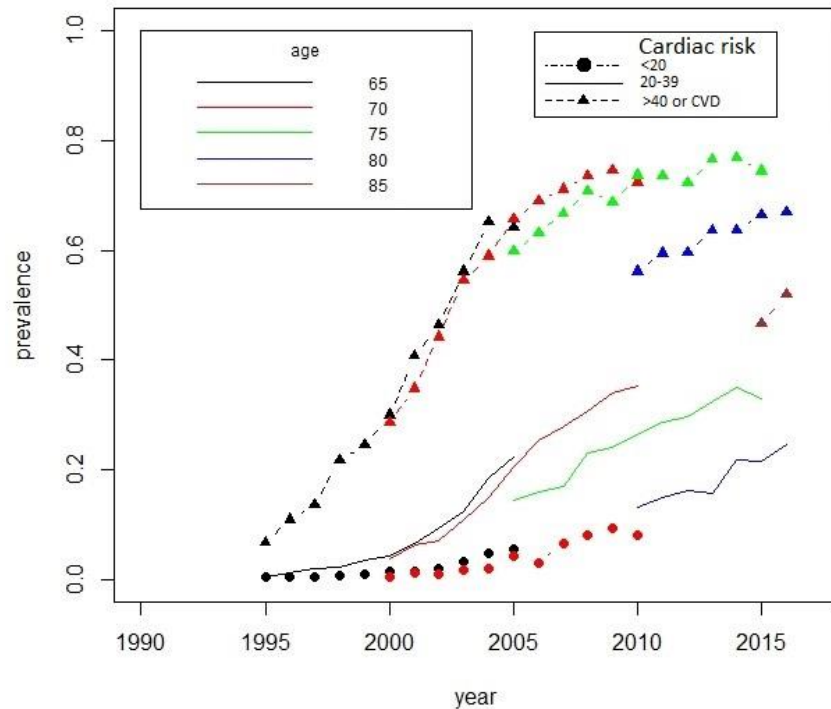


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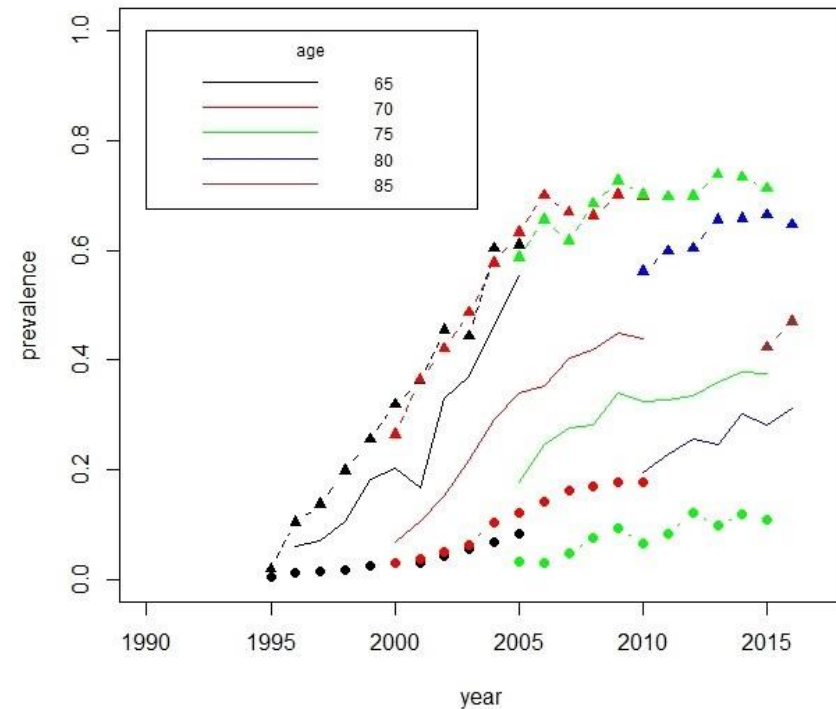
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Prevalence of statin prescription

statin prescription in male patients



statin prescription in female patients



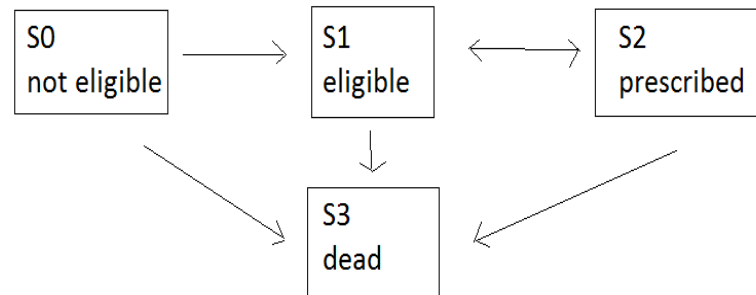
Prevalence of statin prescription differs by calendar year, age, sex and cardiac risk group



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Statistical Analysis Options

- Objective: dynamically predict the survival benefits associated with statin therapy over the course of 25 years.
- The original plan was to develop a model with the following states: S0 not eligible for statins, S1 eligible for statins, S2 prescribed statins, and S3 death.



- Alternatively, develop a survival model with time-dependent predictors and parameters.
- Or use landmark analysis.



Adherence to statin prescription

| Number of arm switches | 0 | 1 | 2 | 3 | 4 | 5+ |
|------------------------|------|------|-----|-----|-----|-----|
| % of patients | 51.1 | 40.7 | 6.2 | 1.5 | 0.4 | 0.1 |

- 51.1% were never prescribed statins;
- 40.7% were prescribed at some age and stayed on statins;
- 6.2% dropped off statins permanently;
- 1.5% dropped off statins and then came back on to stay;
- 0.5% had 4 or more switches;
- the maximum was 9 switches for 1 person



Data preparation and analysis

Data: Medical history was updated every half a year (landmark) until end of follow-up (death, deregistered or end of study).

Imputation: Due to missing data at early ages, multiple imputation was performed using joint modelling at age 60. The method of last observation carried forward was used for missingness in follow up.

Analysis: Landmark analyses were carried out by fitting Cox proportional hazards regression of all cause mortality associated with current statin prescription at each landmark from age 60 to 85 and adjusted for medical history.

We separately conducted three landmark analyses: with window widths 5, 10 and 30 years.



The four stages of modelling process

- A Cox model was fitted on complete cases at baseline age to inform the imputation model. Both models included all medical history if prevalent.
- Cox models were fitted on the imputed datasets at ages 65, 70, 75, 80 and 85 to inform the final landmark model. These models included all medical history and tested for interactions between statin prescription, sex, year of birth and cardiac risk.
- The final, fully adjusted, Cox landmark models were fitted at 10 imputed datasets. The landmarking was smoothed with an integrated partial log-likelihood (ipl) and with Pseudo-partial log-likelihood (ipl*).
- Ten landmark models pooled using Rubin's rules.



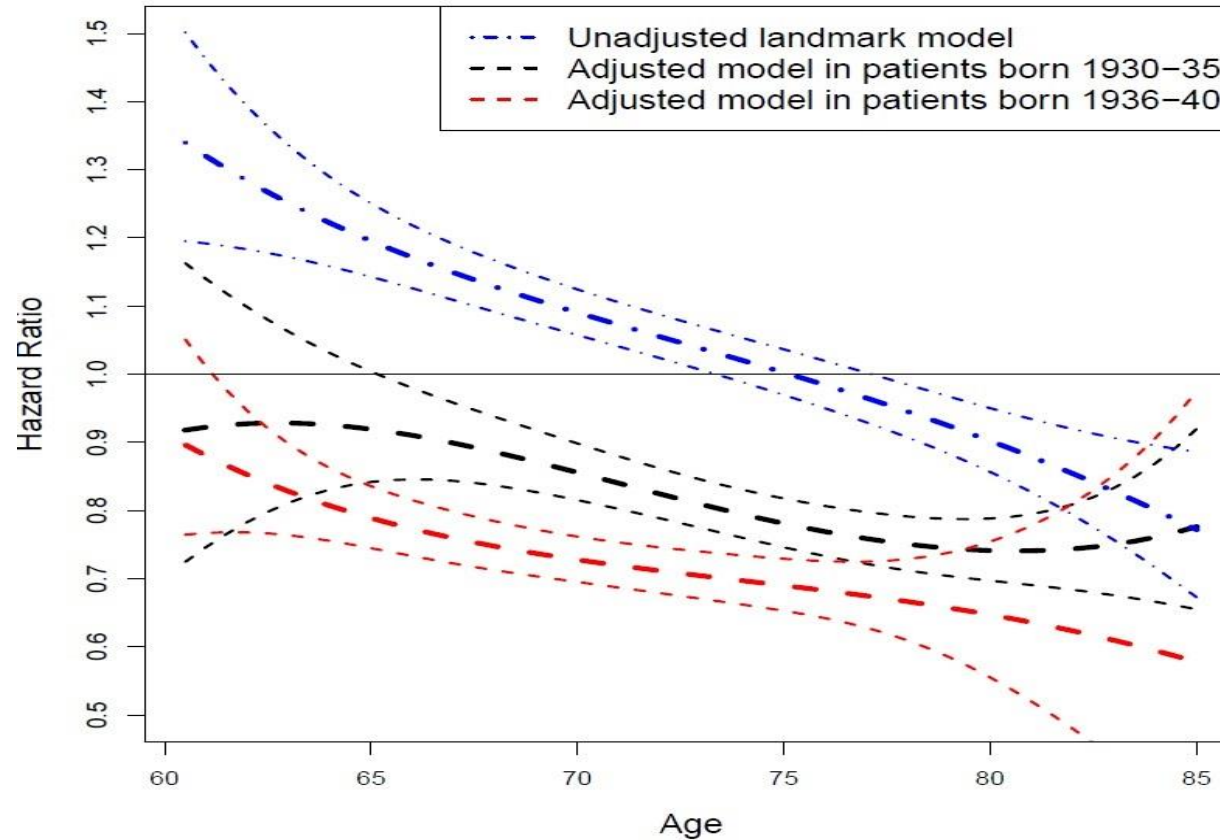
The statistical model for survival benefits of statins was adjusted for:

- Cardiac risk at three levels: low ($QRISK2 \leq 20\%$), medium ($QRISK2$ of 20-39%) and high ($QRISK2 \geq 40$ or CVD diagnosis)
- Sex, birth cohort, Townsend deprivation quintile, chronic kidney disease, diabetes, treated hypertension, hypercholesterolemia, aspirin, BMI, alcohol consumer status, smoking status and general practice



Hazard of all-cause mortality associated with statin prescription (30 years window)

Hazard of all-cause mortality associated with statin prescription



Why statins are more beneficial in younger cohort: better drugs?

www.pulsetoday.co.uk/gps-set-for-mass-drug-switch-to-atorvastatin-after-analysis-shows-price-could-fall-by-95/13482969.article

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PULSE At the heart of general practice since 1960

OPINION 'After about 20 patients, there is not an iota of empathy left'

NEWS ↓ VIEWS ↓ CLINICAL ↓ PARTNERS ↓ SESSIONALS ↓ TRAINEE PULSE MAGAZINE EVENTS JOBS

GPs set for mass drug switch to atorvastatin after analysis shows price could fall by 95%

22 February 2012

Share Print Rate Save Comment

SHARE ON FACEBOOK Exclusive GPs are set to be enrolled in schemes to switch patients en masse to atorvastatin in the wake of an analysis for the Government's

MOST POPULAR MOST COMMENTED

Reduction in low-density lipoprotein cholesterol

Statins are grouped by NICE into three different intensity categories according to the percentage reduction in LDL cholesterol

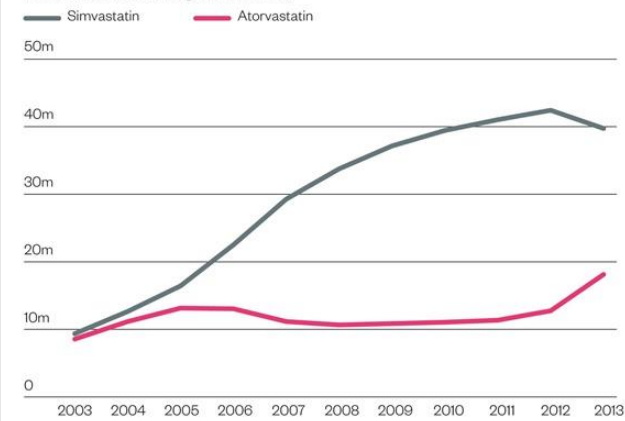
- 20% to 30%: low-intensity statin
- 31%-40%: medium-intensity statin
- Above 40%: high-intensity statin

| | 5mg | 10mg | 20mg | 40mg | 80mg |
|--------------|-----|------|------|------|------|
| Fluvastatin | — | — | ● | ● | ● |
| Pravastatin | — | ● | ● | ● | — |
| Simvastatin | — | ● | ● | ● | ● |
| Atorvastatin | — | ● | ● | ● | ● |
| Rosuvastatin | ● | ● | ● | ● | — |

Source: National Institute for Health and Care Excellence

Atorvastatin vs simvastatin

Items dispensed in England (millions)



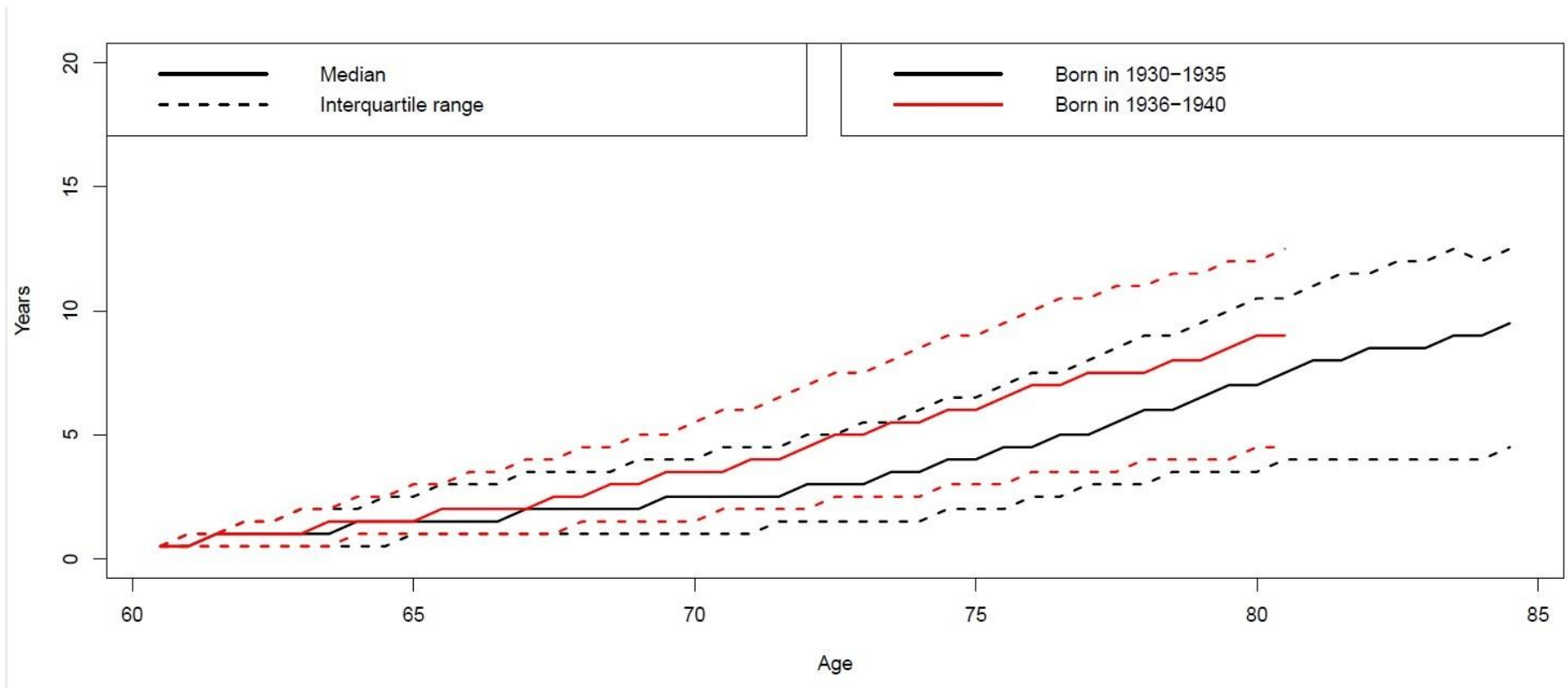
Cerivastatin was withdrawn from the world market in 2001 and the clinical guidelines changed from simvastatin to atorvastatin in 2014. But in 2014 our patients were 79-89 years old.



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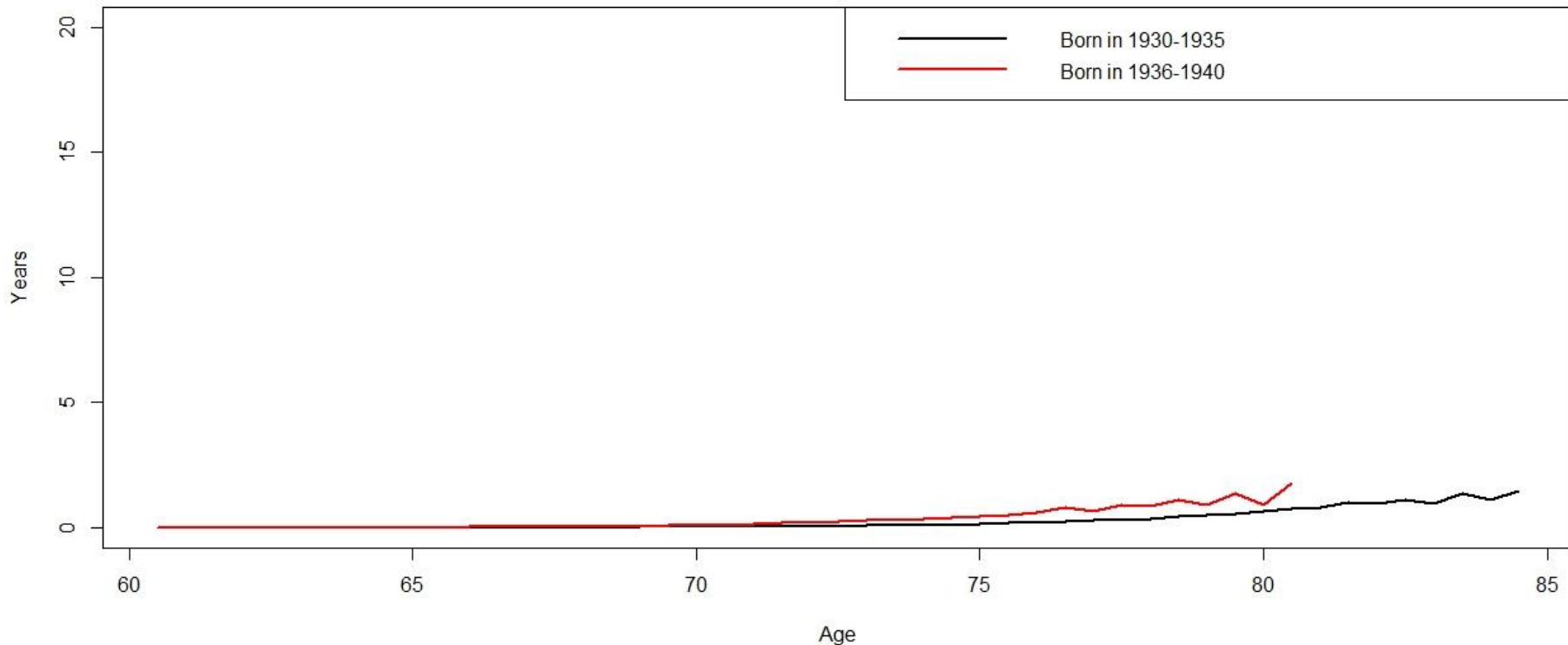
Length of prior prescription for patients on statins at age s



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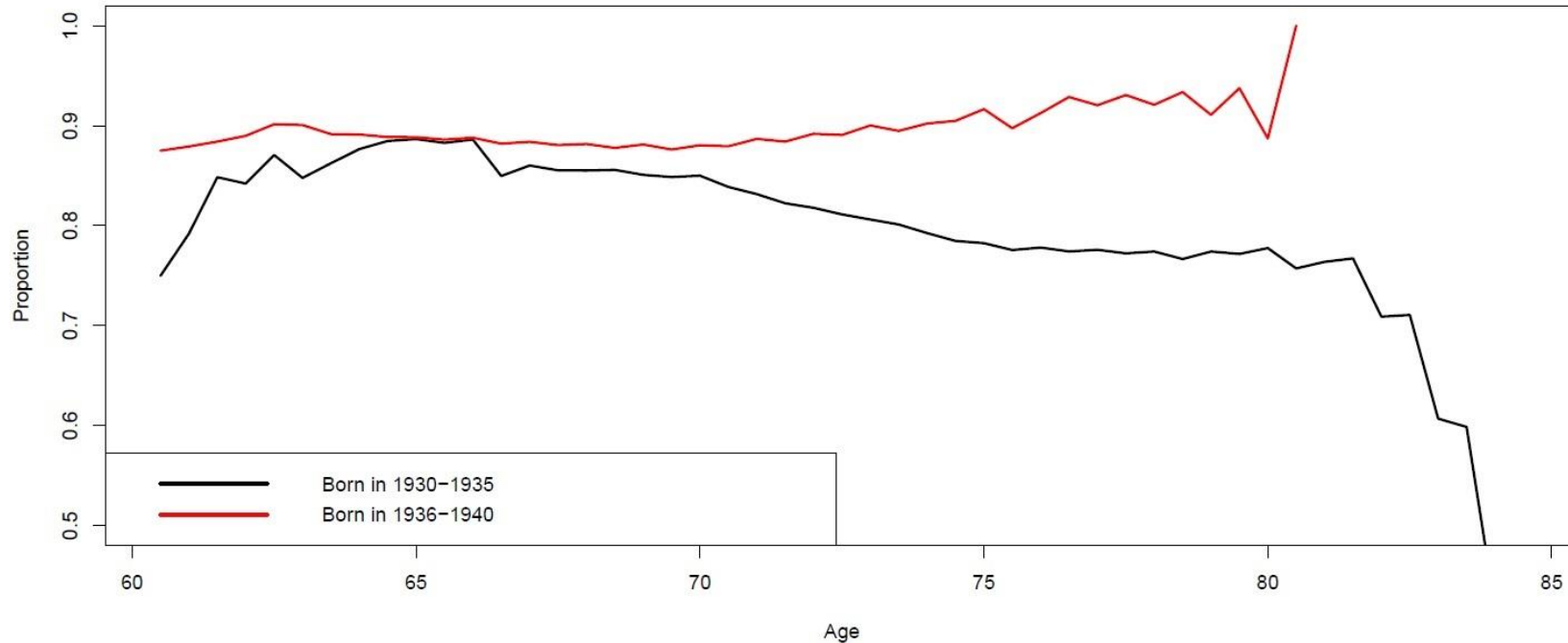
Average length of prior prescription for patients not on statins at age s



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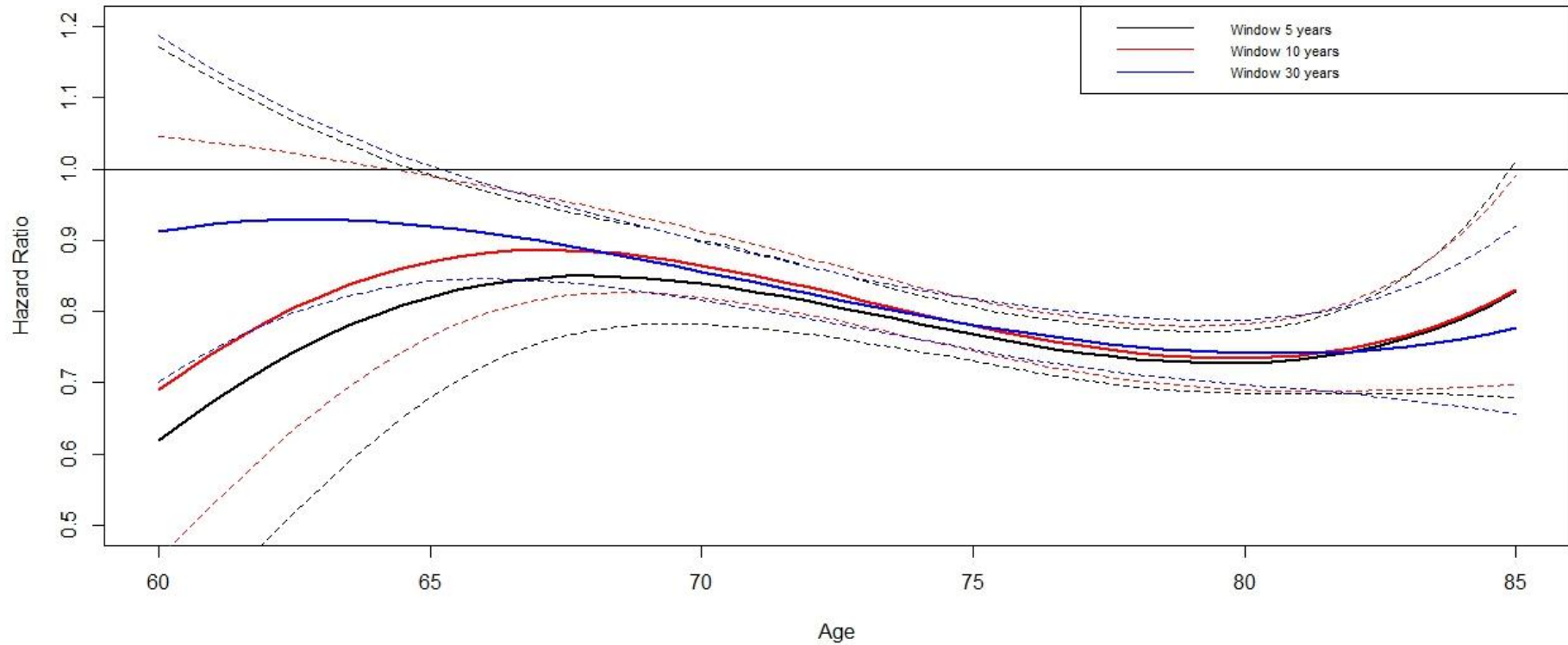
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Proportion of patients on statins at age s with at least 75% adherence at follow up



HRs of all-cause mortality estimated in 5, 10 and 30 years window

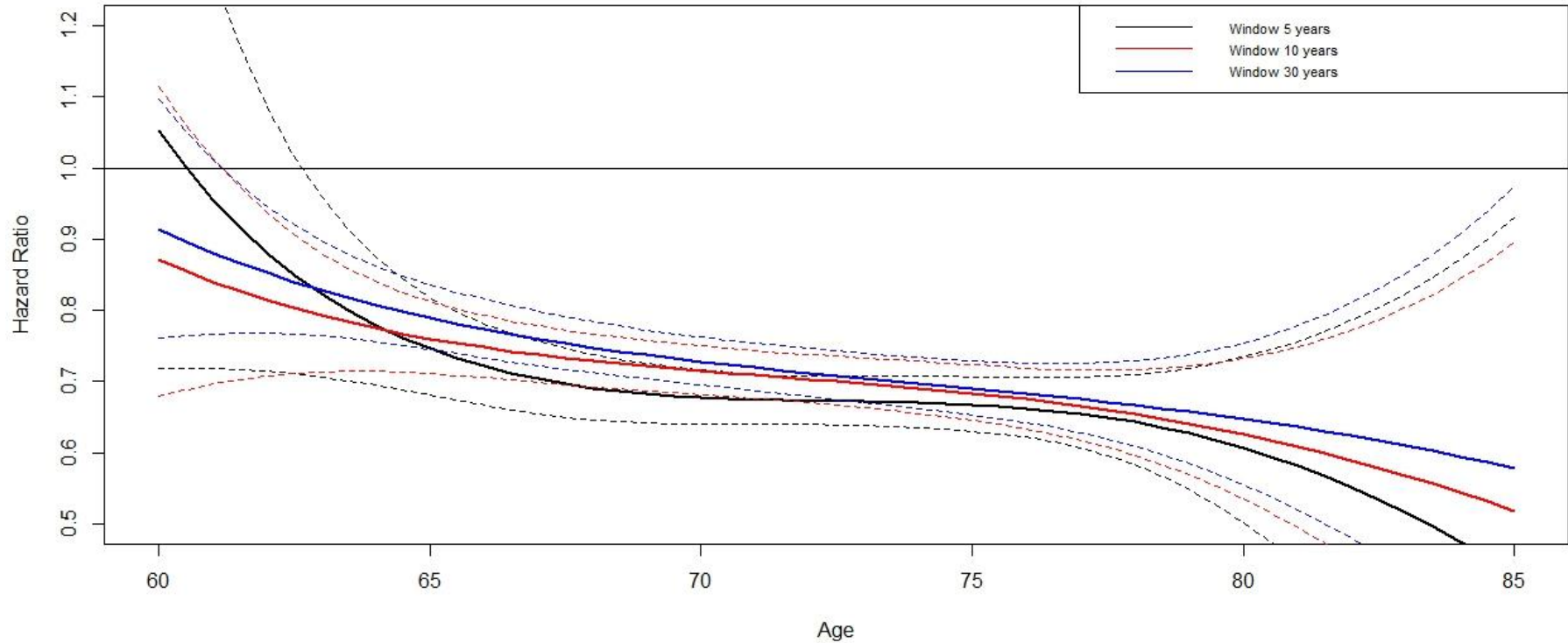
Born in 1930-1935



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HRs of all-cause mortality estimated in 5, 10 and 30 years window

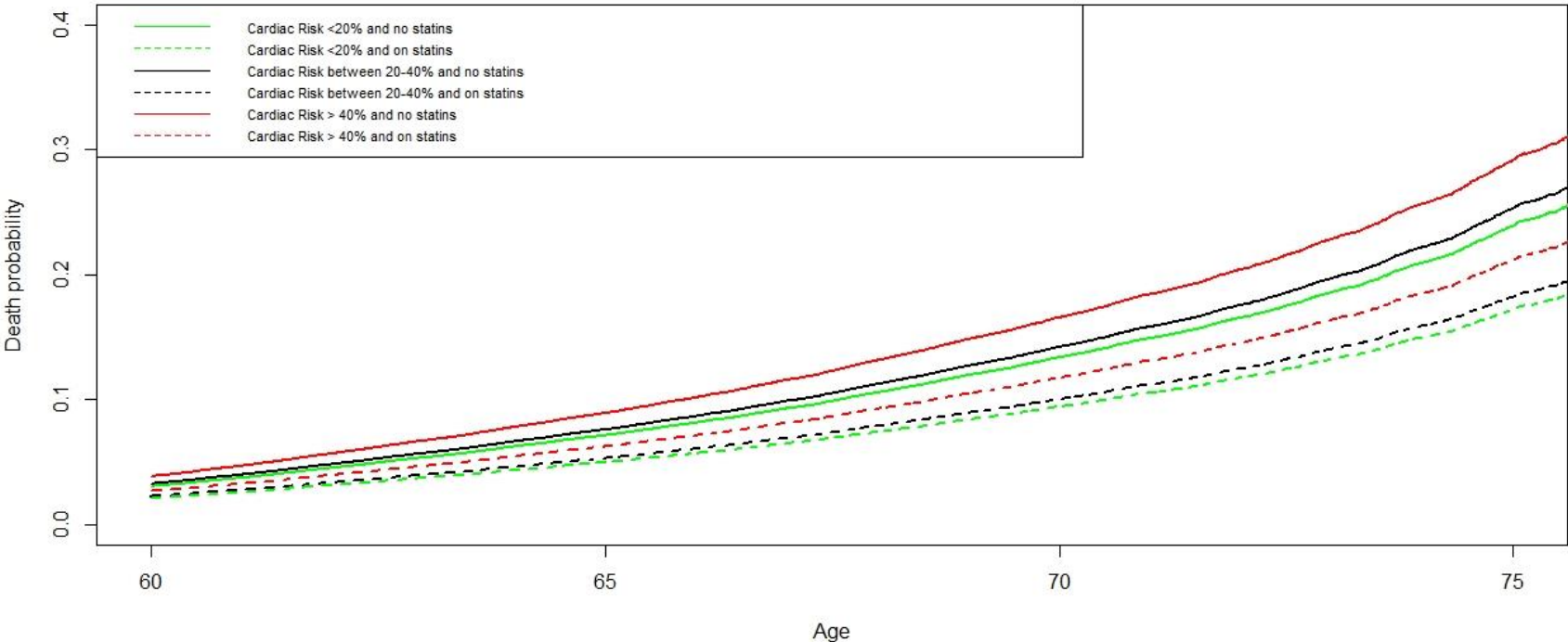
Born in 1936-1940



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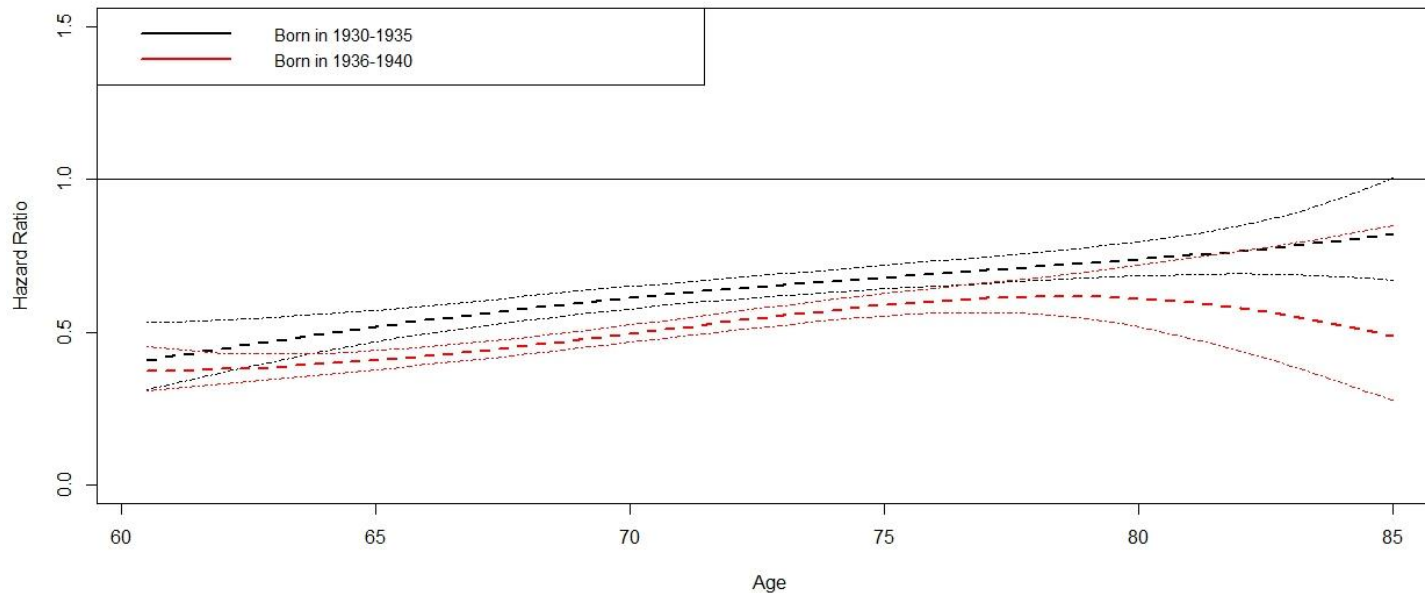
Probabilities of death for 1936-1940 cohort

Dynamic prediction with 10 year window



Do survival benefits really increase at older ages? Here controls never were on statins:

We also performed an analysis keeping only patients who never were prescribed statins in the control group. Younger patients do better!



Similar HRs (0.74 ,0.63 vs 0.74, 0.61 here) only from age 80!



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Summary of results on statins

- The prevalence of statin prescription increased substantially by age with nearly half of the study population having had a prescription by age 75 and 57% by age 85 at the end of the study.
- The adherence to statin prescription was high, with 77% adhering more than 75% of the time and only 5% adhering less than 25% of the time
- In “current knowledge” landmark analysis, statin prescription was associated with increasing survival benefits at older ages and was significant at the earliest from age 62 onward. Benefits seemed to decrease with age in our sensitivity analysis based on the full knowledge of statin history.
- Statin prescription was more effective in patients born in later years due to the changing availability and recommended dosages of statin types resulting in more effective treatment but did not differ by sex or cardiac risk.
- Therefore, age alone can be used to decide on initiating and staying on statin therapy based on the predicted overall effect (which tallied up benefits and harms).



Discussion and conclusions on statins

- After adjustment for cardiac risk and related medical history, it appears that statin therapy is especially beneficial at older ages and in people born at later years in a realistic “current knowledge” scenario. The benefits of statins in earlier ages may be underestimated as more people will get statin prescription later.
- This study adjusted for cardiac risk groups defined by the changing clinical guidelines on the eligibility of statin prescription. However we did not distinguish between recommended types and doses of statins. This might partly explain why statin prescription was associated with greater survival benefits in patients born in later years.
- We used statin prescription as a proxy for statin intake. Lower intake than prescription would result in more conservative findings and thus imply that statins could be even more beneficial.



References:

1. Gitsels, L.A., Kulinskaya, E. and Steel, N., 2016. Survival benefits of statins for primary prevention: a cohort study. *PloS one*, 11(11), p.e0166847.
2. Gitsels, L.A., Bakbergenuly, I., Steel, N. and Kulinskaya, E., 2019. Dynamic prediction of long-term survival effects of statin therapy: a landmarking analysis in the general population. *British Medical Journal* (under review)
3. Van Houwelingen, H. and Putter, H., 2011. *Dynamic prediction in clinical survival analysis*. CRC Press.



Questions

Comments



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