A Landmarking Approach for the Dynamic Scheduling of Cardiovascular Risk Assessments

Jessica Barrett

MRC Biostatistics Unit, University of Cambridge
jessica.barrett@mrc-bsu.cam.ac.uk

CMIH Academic Engagement Event, July 2022

MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Contributors

Francesca Gasperoni
Novartis

Prof. Angela Wood
University of Cambridge

Chris Jackson
MRC Biostatistics Unit

David Stevens
University of Liverpool

Paul Newcombe
Astra Zeneca

Michael sweeting
Astra Zeneca
University of Leicester

Table of Contents

1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

Table of Contents

1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

CVD risk prediction

- 'Cardiovascular diseases (CVDs) are the number 1 cause of death globally, taking an estimated 17.9 million lives each year.' [World Health Organization]
- Cardiovascular diseases that we consider are: nonfatal or fatal events of coronary heart disease (including myocardial infarction and angina), stroke, and transient ischemic attack.
- Primary prevention strategy is composed of periodic risk assessment and risk management through habit/diet modification and/or lipid-lowering medication.

CVD risk assessment around the world

	Strategy	Risk calculator	Outcome
UK	Unstratified	QRISK	10-year CVD
USA	Unstratified	Pooled Cohort Equation	10-year ASCVD
Europe	Gender-based	SCORE	10-year fatal CVD
Australia	Risk-based	Framingham	5-year CVD
New Zealand	Risk, gender and ethnicity-based	Framingham	5-year CVD

'Risk assessment is not a one-time event; it should be repeated, for example, every 5 years, although there are no empirical data to guide intervals.' *2021 ESC Guidelines on cardiovascular disease prevention in clinical practice*

Scheduling of CVD screening

Lindbohm et al. 5-year versus risk-category-specific screening intervals for cardiovascular disease prevention: a cohort study. *Lancet Public Health* 2019.

"... suggesting that uniform 5-year screening intervals for low-risk, intermediate-low-risk, and intermediate-high-risk categories ... leads to unnecessarily long delays in detection of high-risk individuals."

Chiolero et al. Screening interval: a public health blind spot. *Lancet Public Health* 2019

"the standard . . . blind, uninformed approach is simple but surely not efficient, calling for a more informed, data-driven, screening strategy"

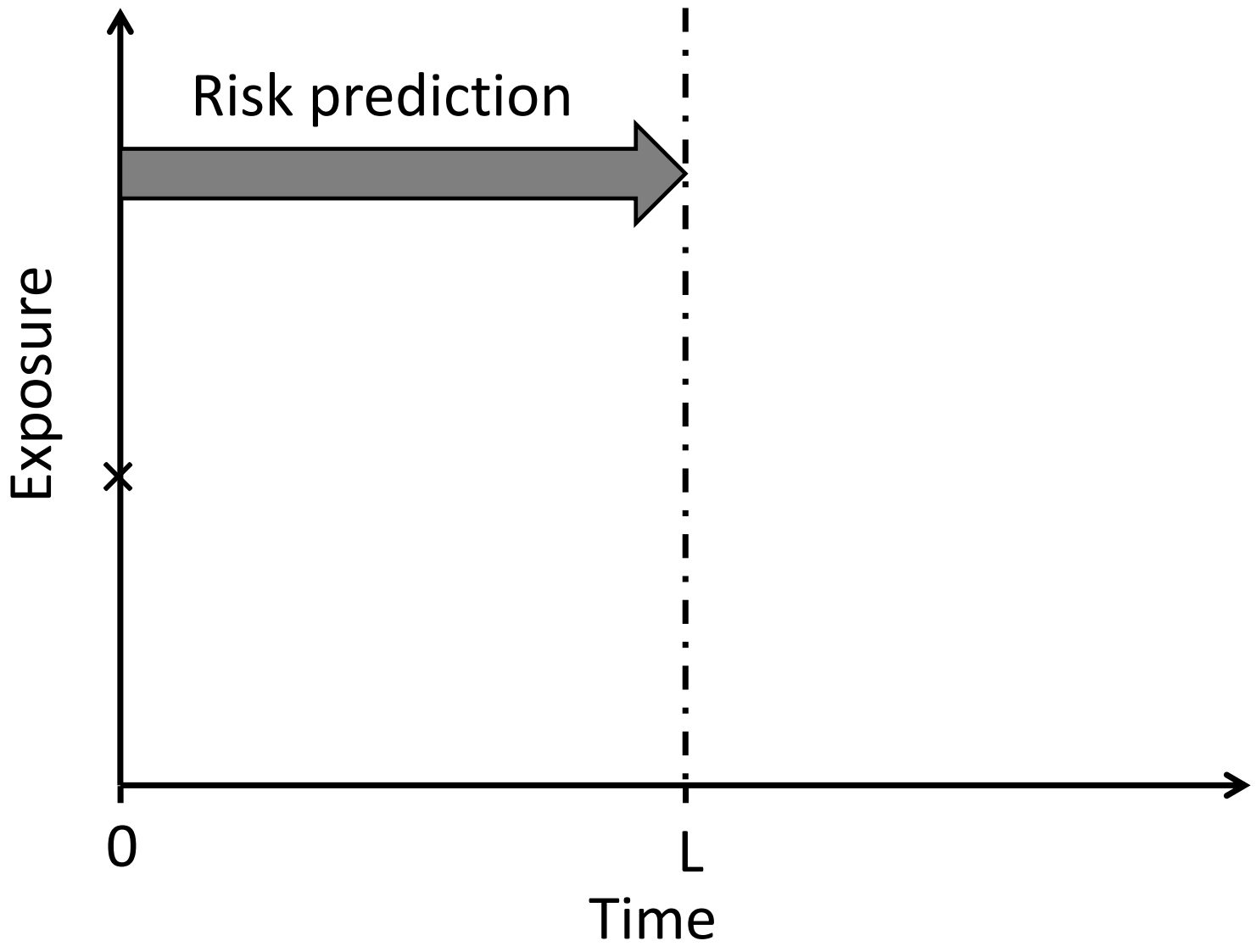
Data: Clinical Practice Research Datalink (CPRD)

- Primary care data from the UK
- Covering approximately 6.9% of the UK population
- Broadly representative of the UK general population with respect to age, sex, and ethnicity.
- One of the largest databases of longitudinal medical records from primary care in the world.

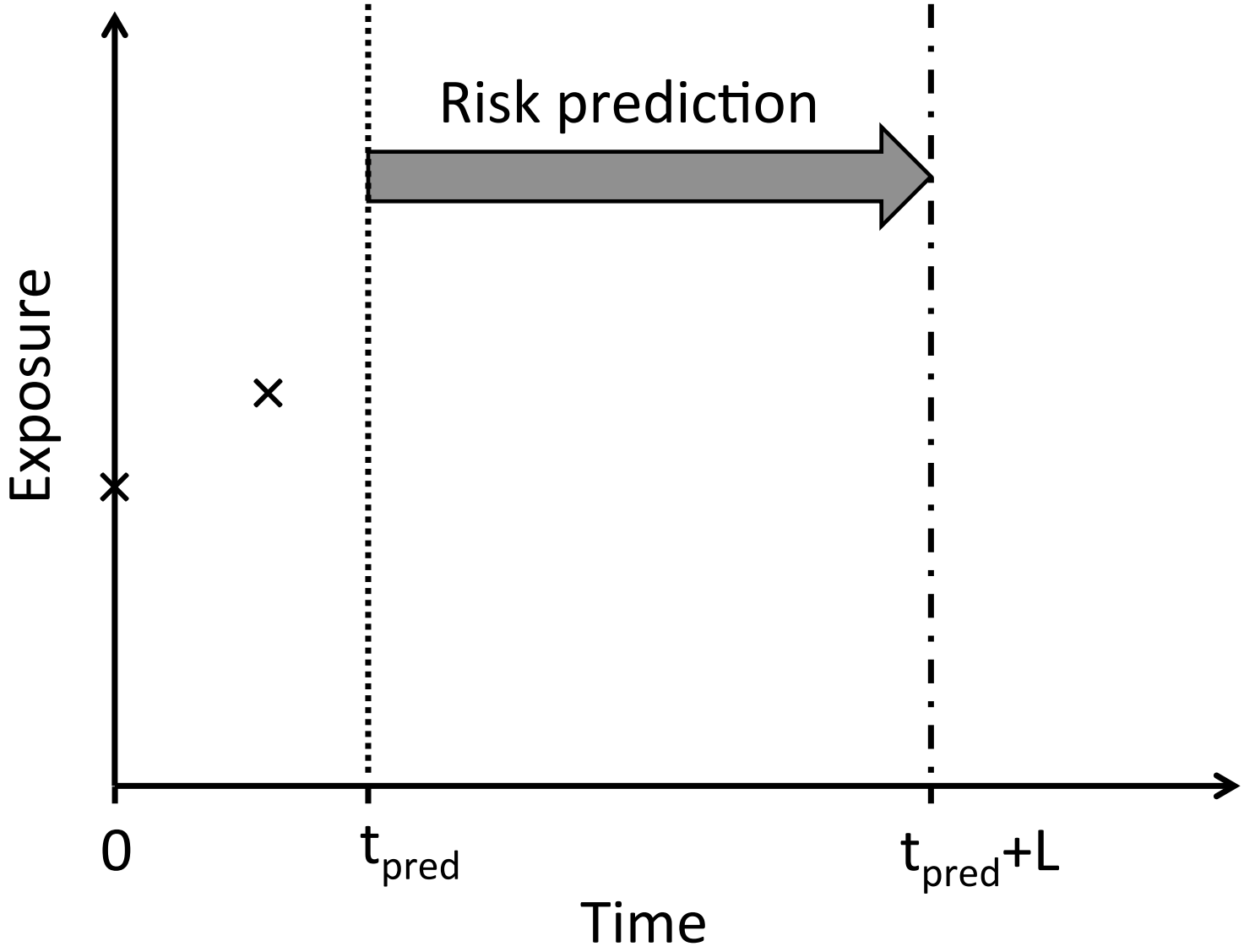
Table of Contents

1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

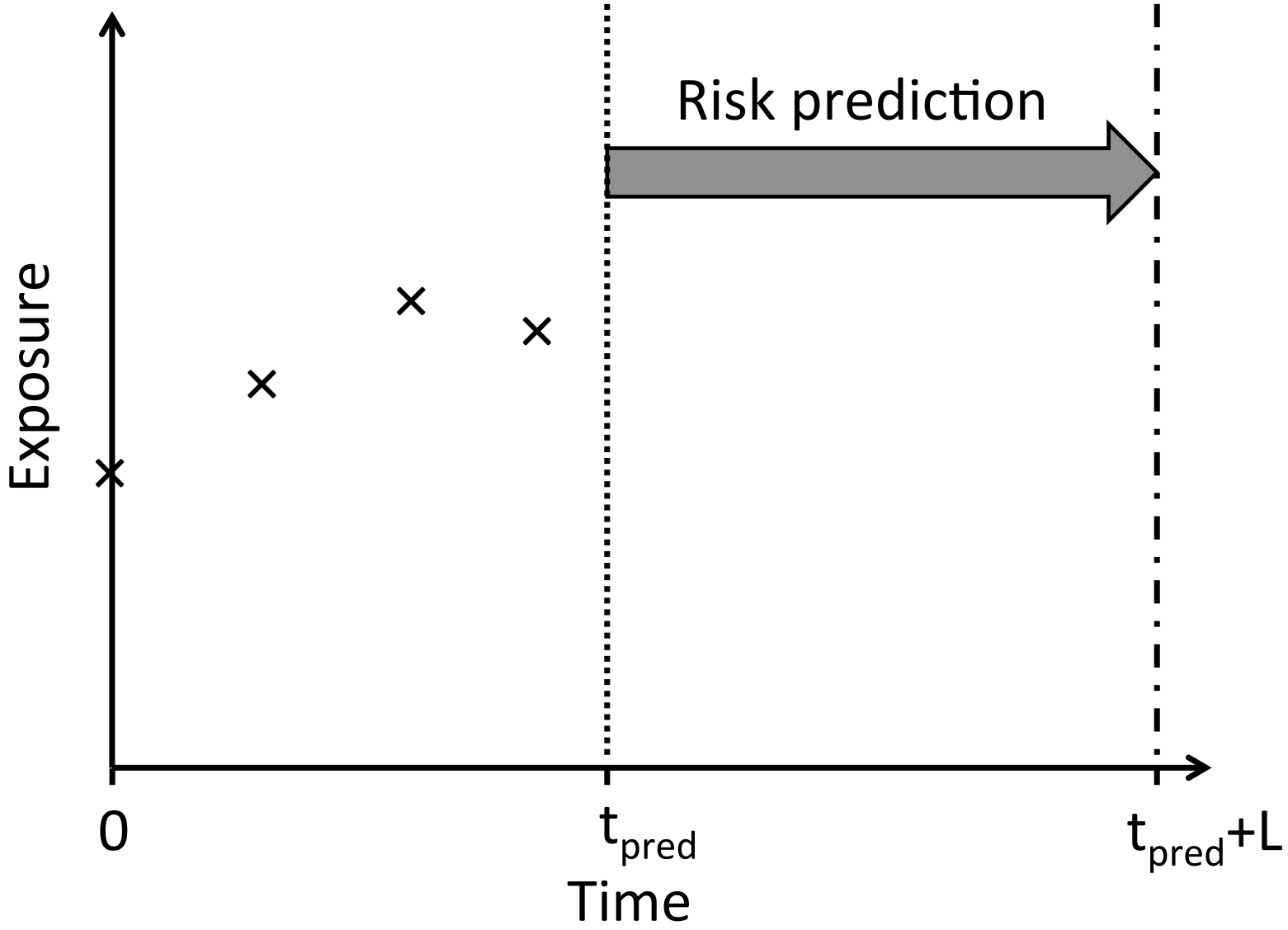
Dynamic risk prediction



Dynamic risk prediction



Dynamic risk prediction



Landmarking

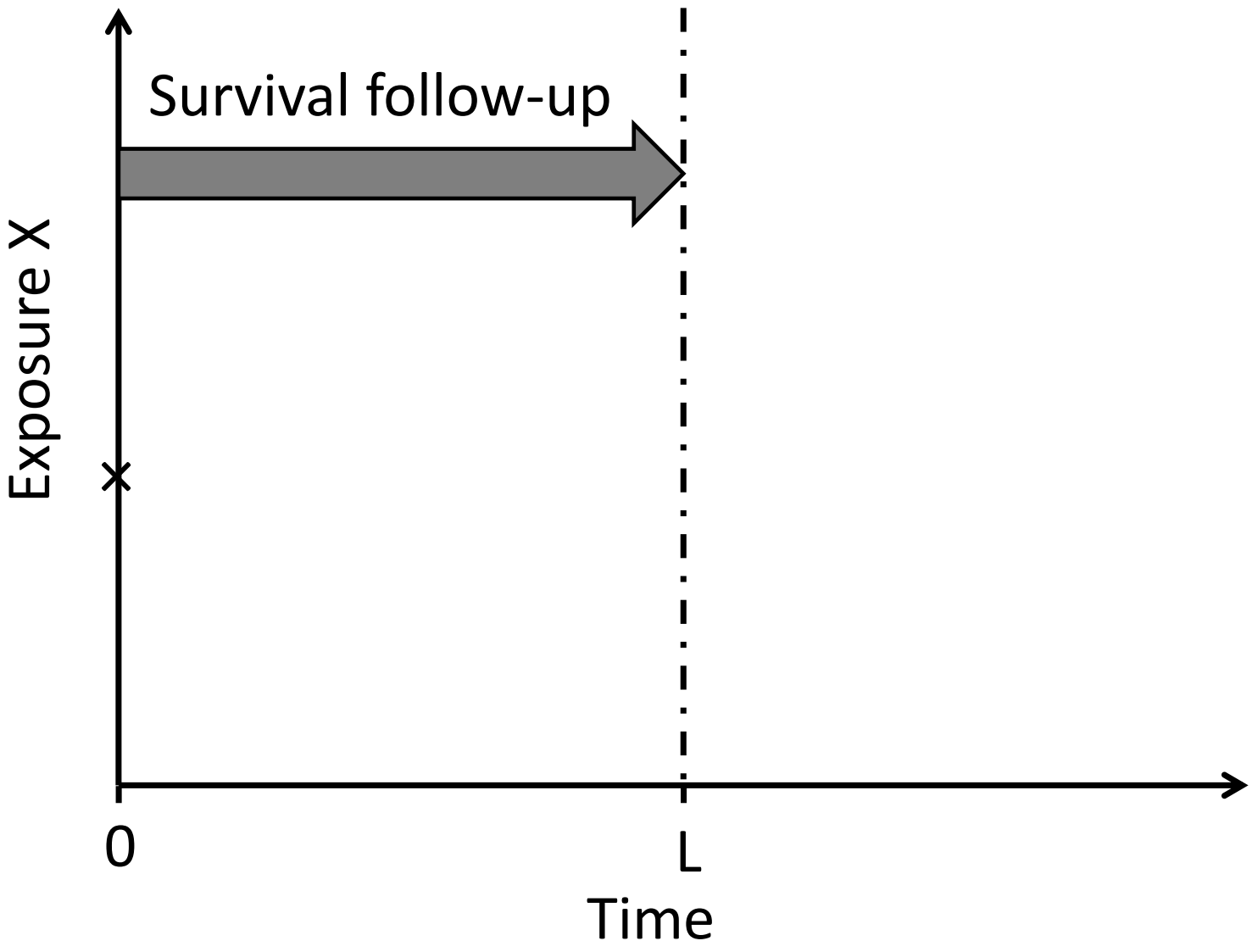
van Houwelingen and Putter, 2012

- Select prediction times $\{t_{pred}\}$
- Select only those still alive at each t_{pred}
- At each t_{pred} predict $\hat{Y}_i(t_{pred})$ from past measurements Y_{ij}
- At each t_{pred} fit separate survival model to future time-to-event data

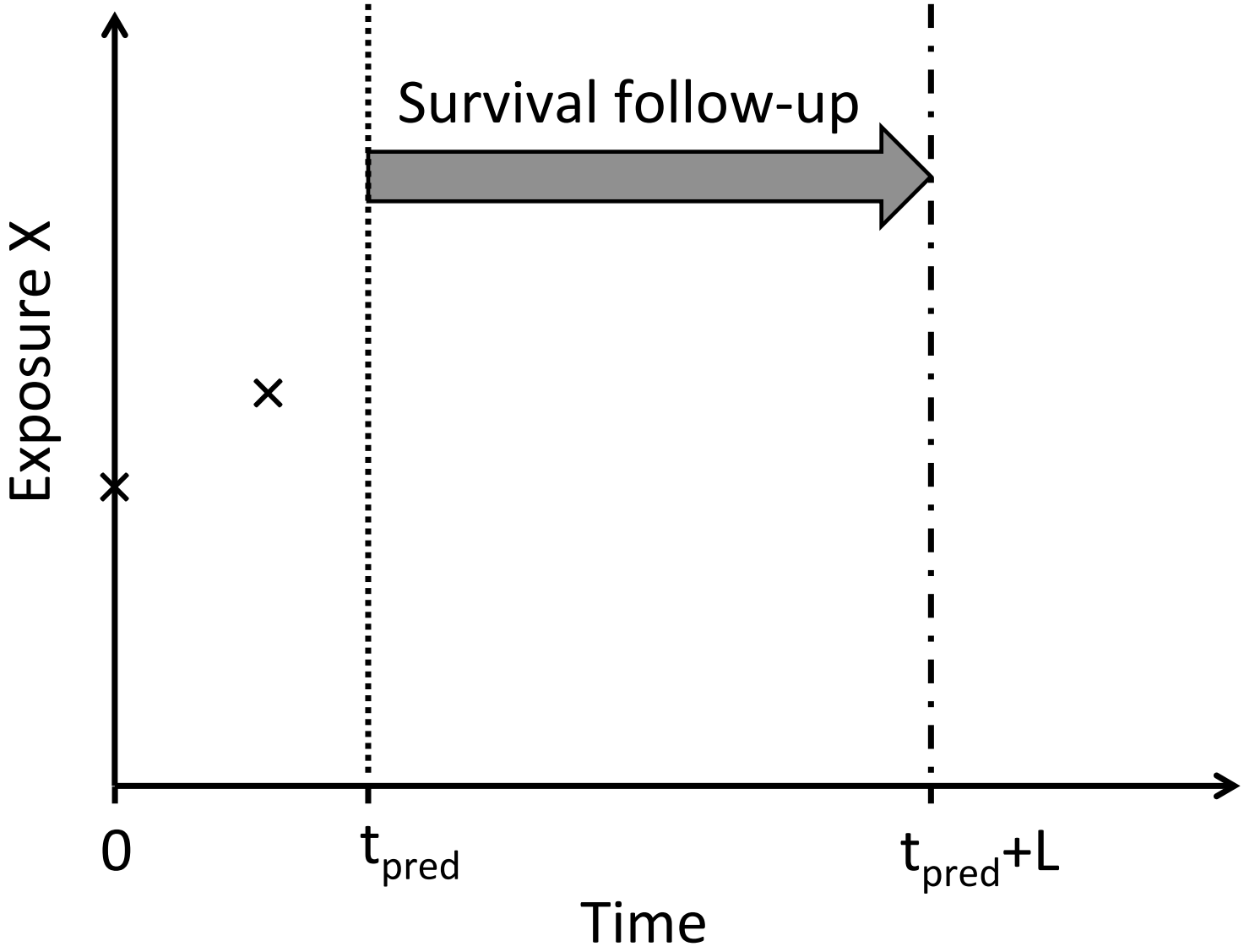
$$h_i(t) = h_0(t) \exp\left(\alpha \, \hat{Y}_i(t_{pred}) + \gamma^T X_{T,i} \right) , \quad t \geq t_{pred}$$

- Censor survival follow-up at $(t_{pred} + L)$

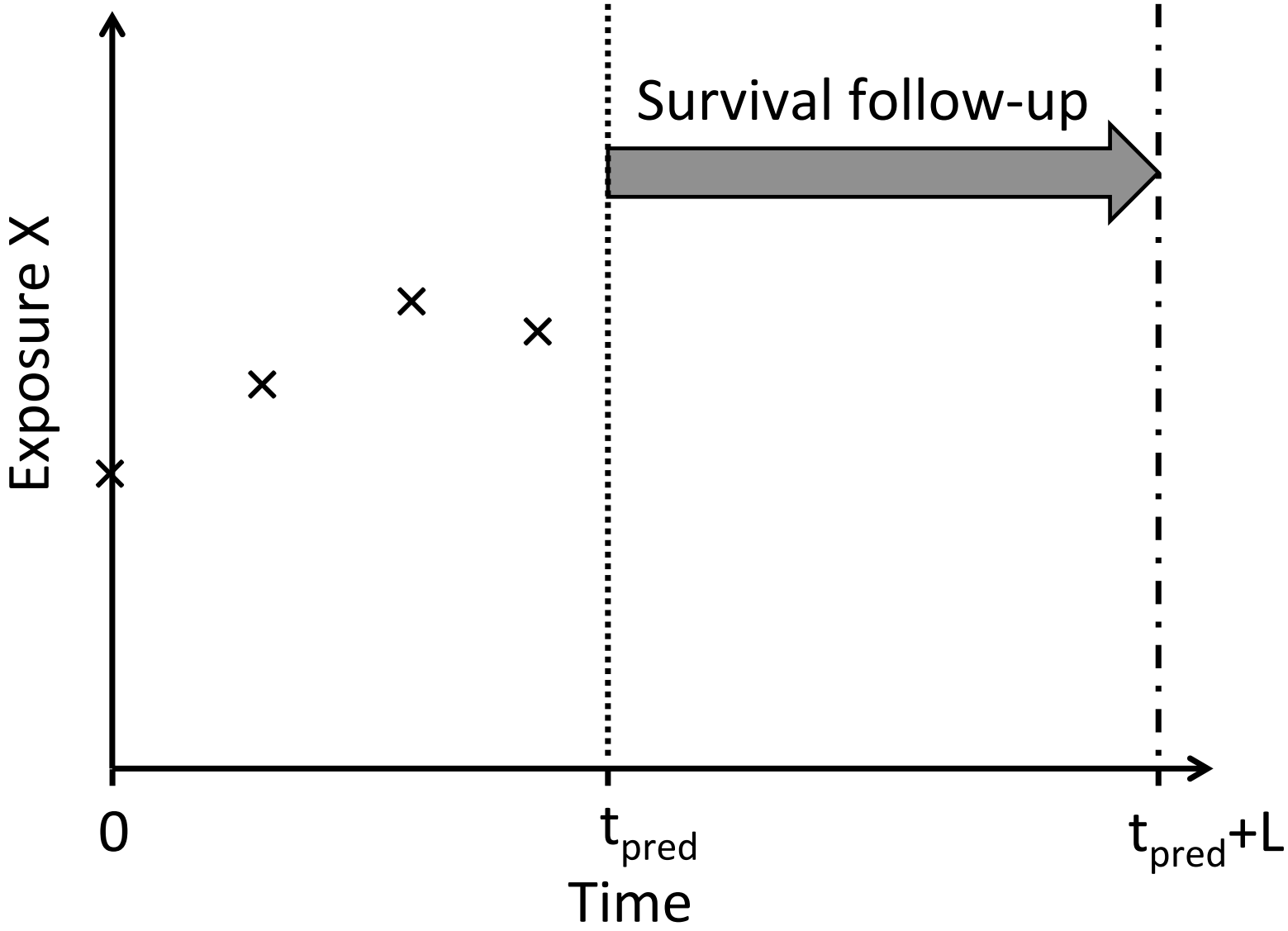
Landmarking



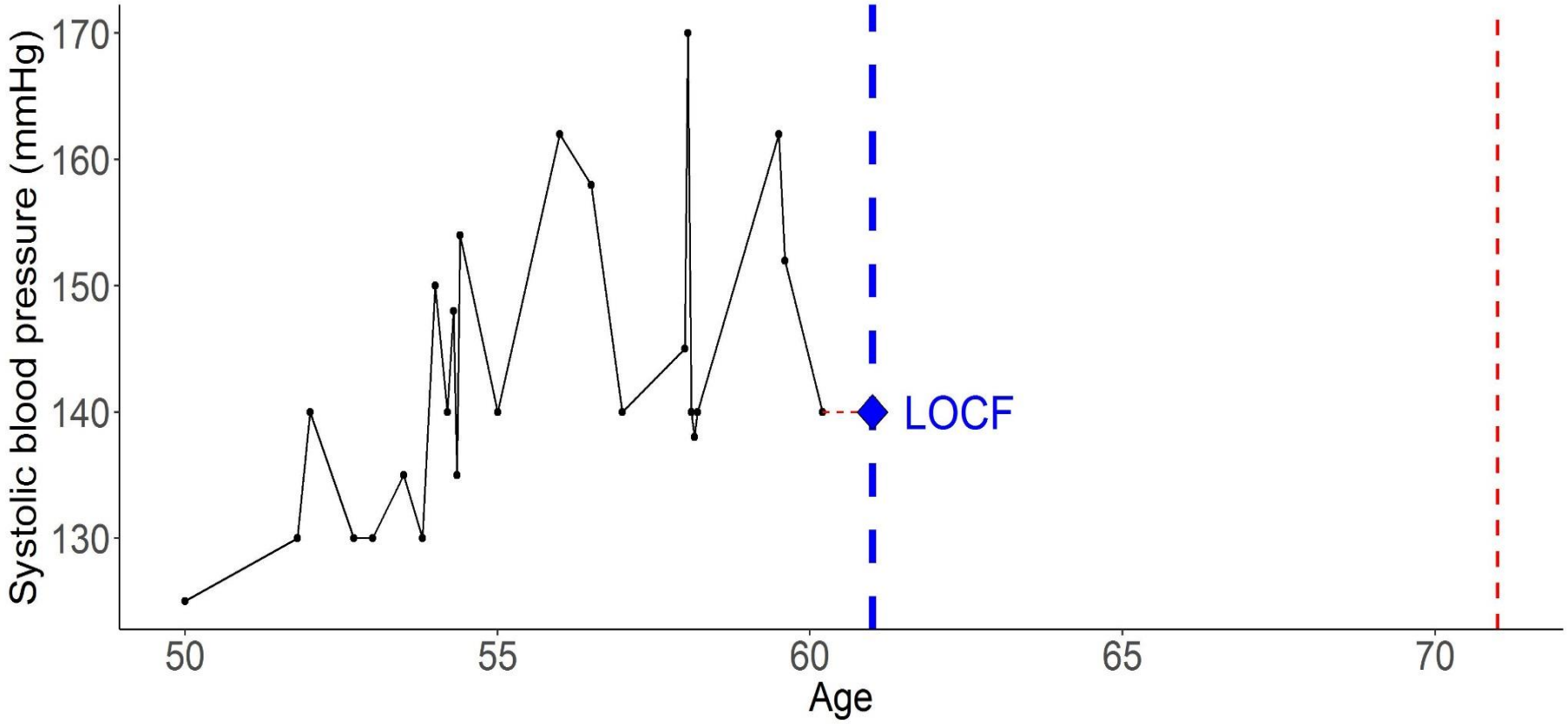
Landmarking



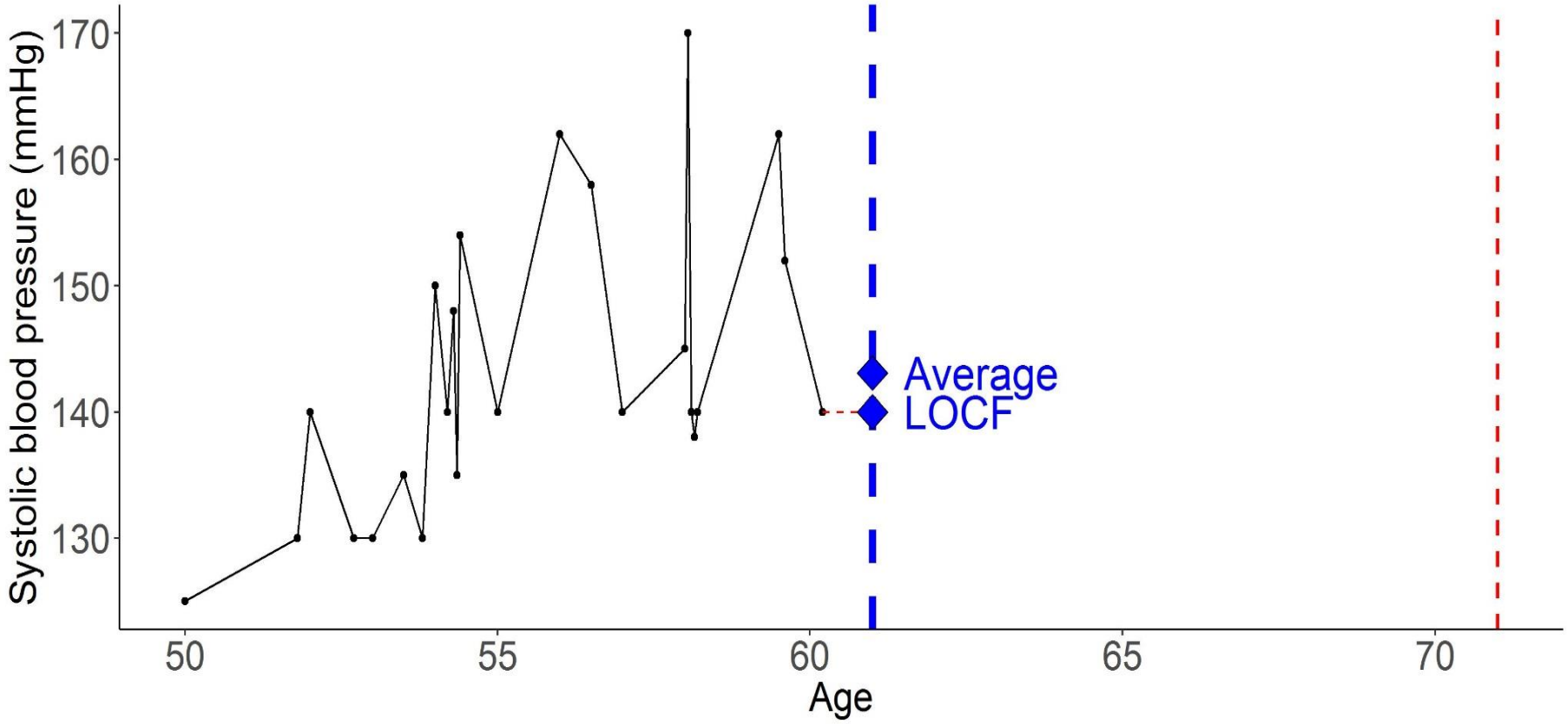
Landmarking



Using repeat measurements



Using repeat measurements



Using repeat measurements

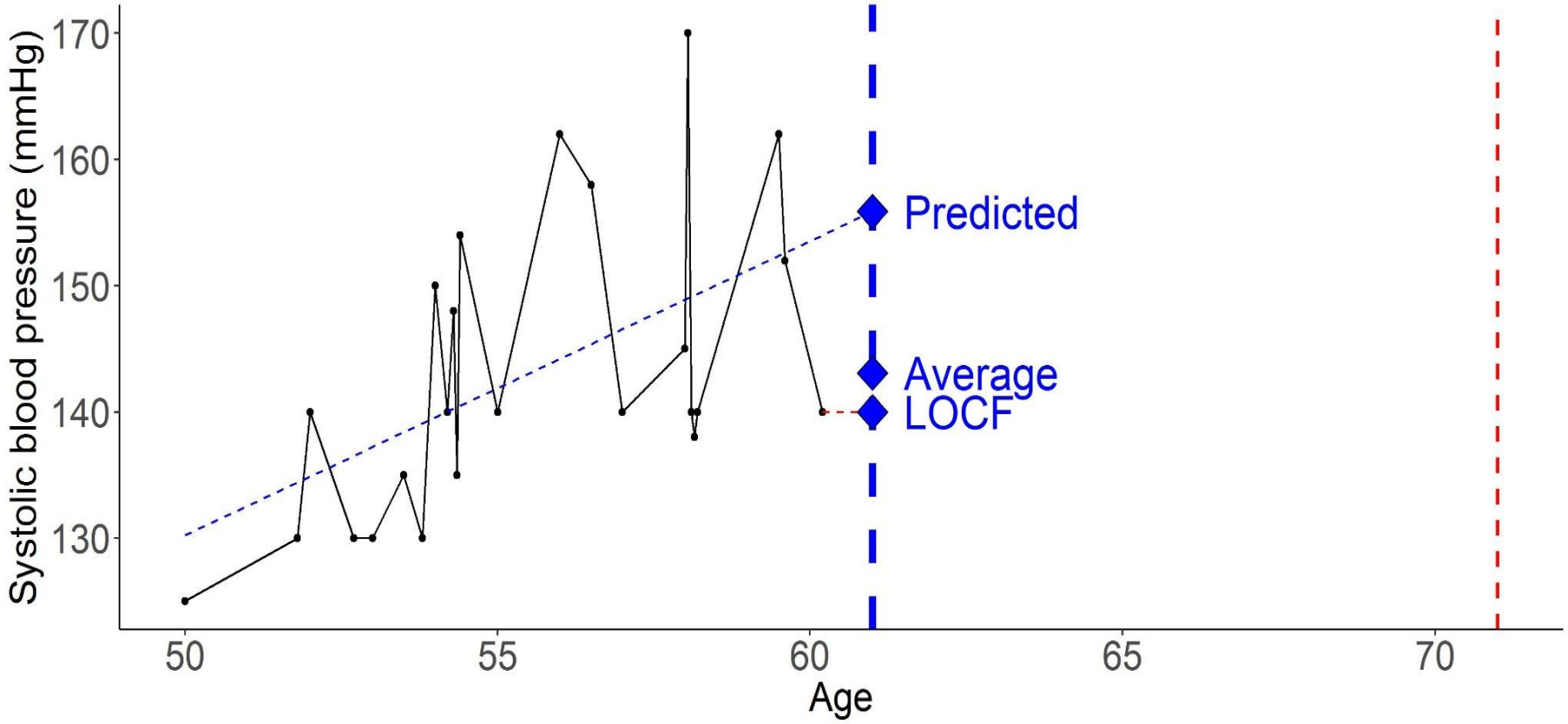
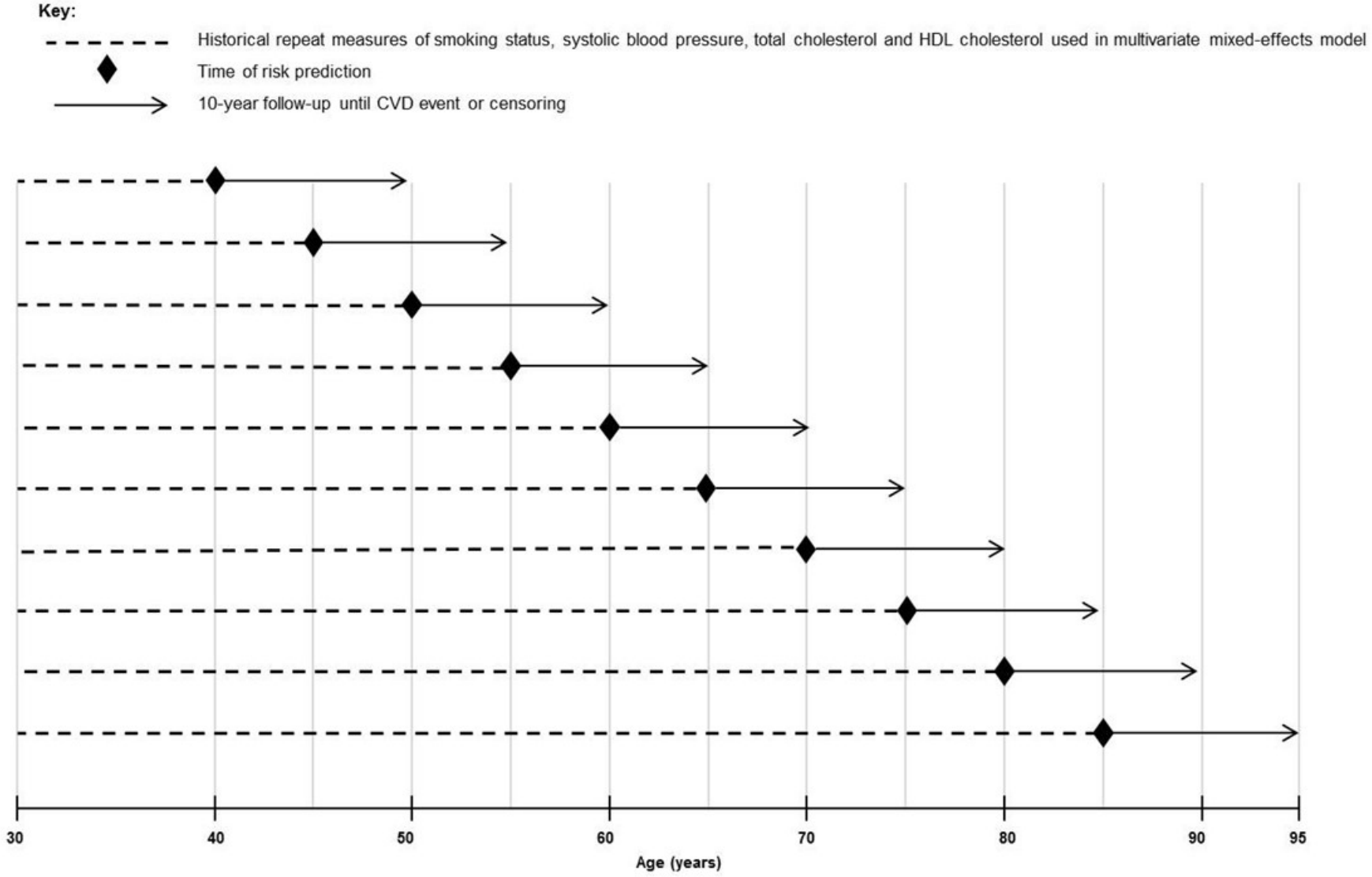


Table of Contents

1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

Landmark analysis of CPRD data

Paige et al, 2018



CPRD results: C-index declines with age

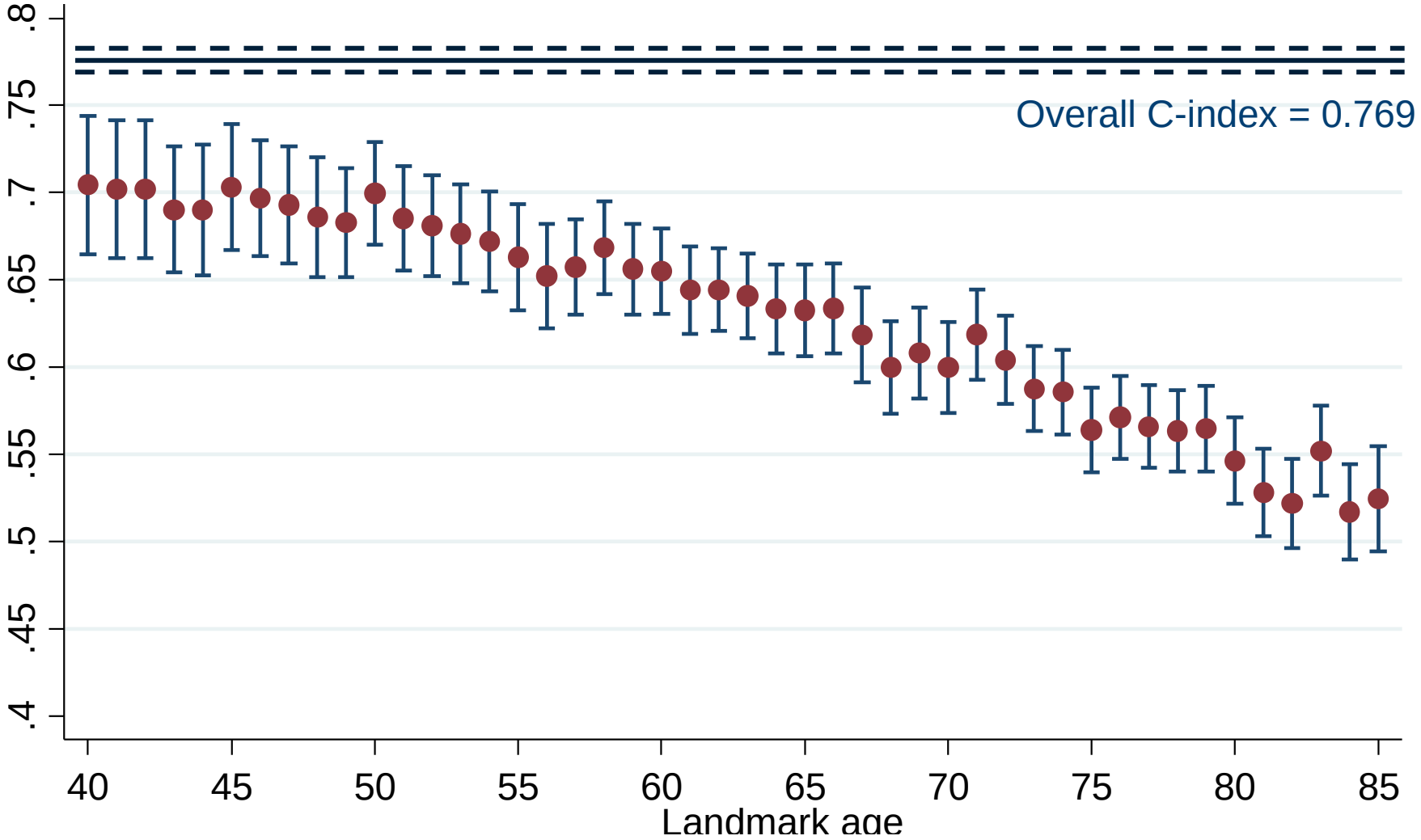
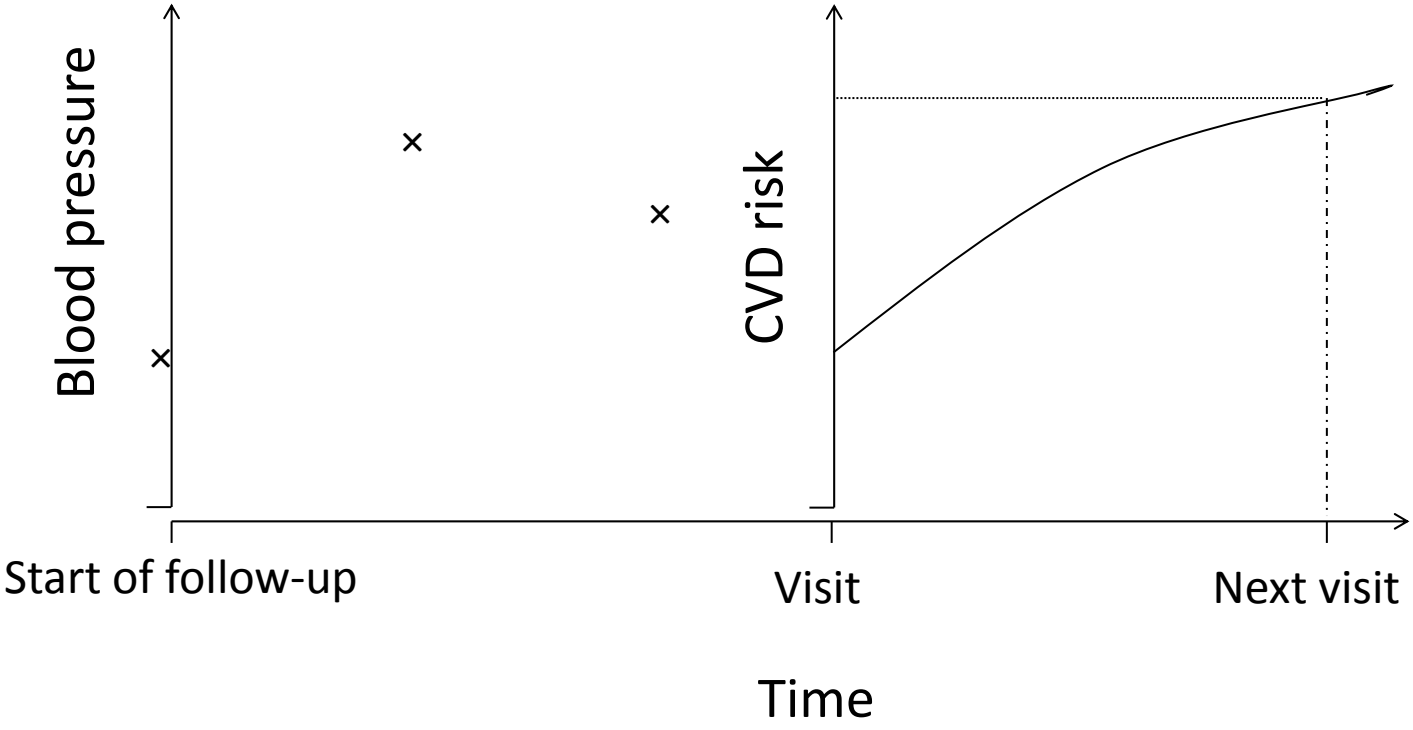


Table of Contents

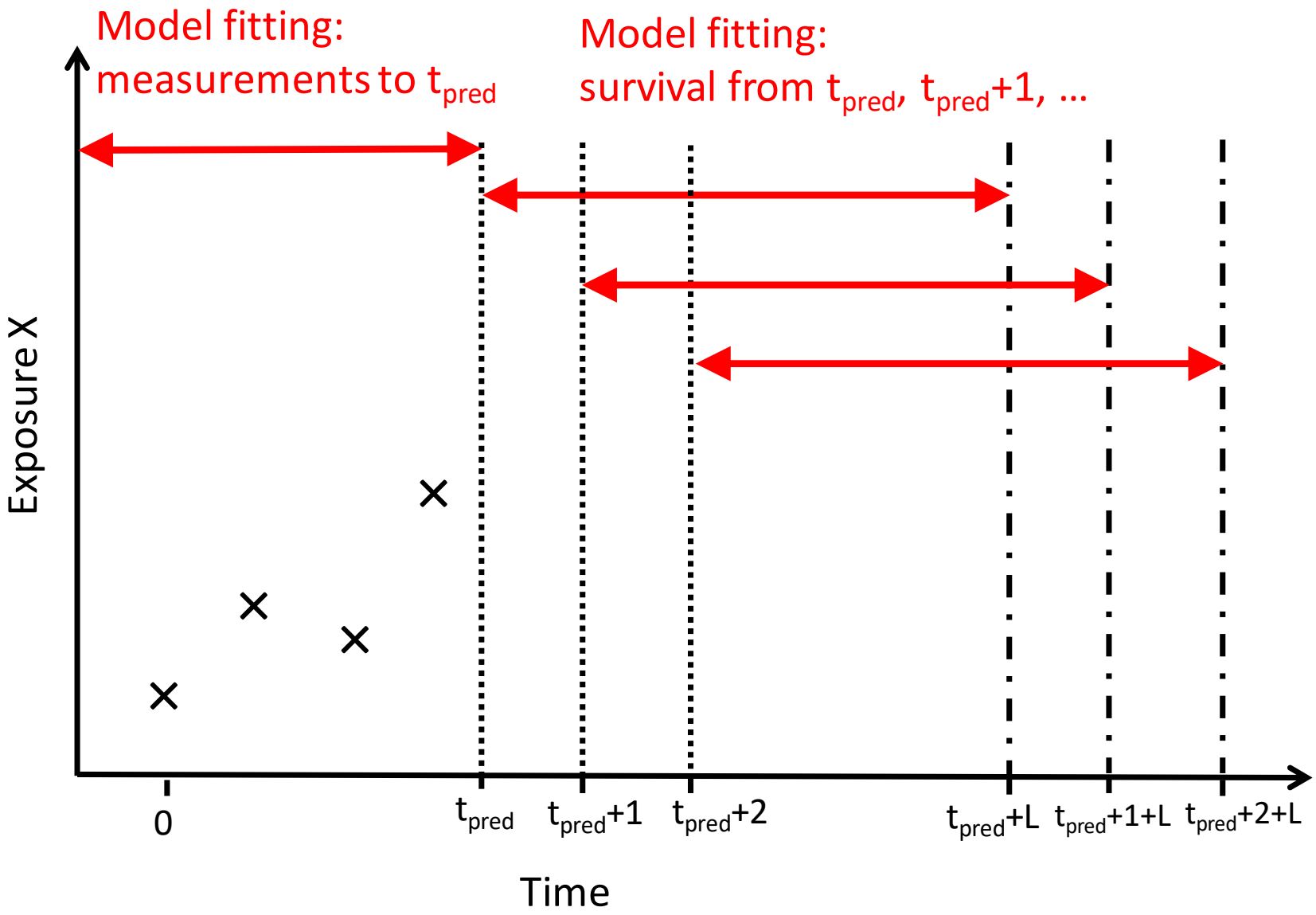
1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

Scheduling of CVD screening

Q: When should I have my next cardiovascular risk assessment?



Scheduling of CVD screening



Scheduling of CVD screening

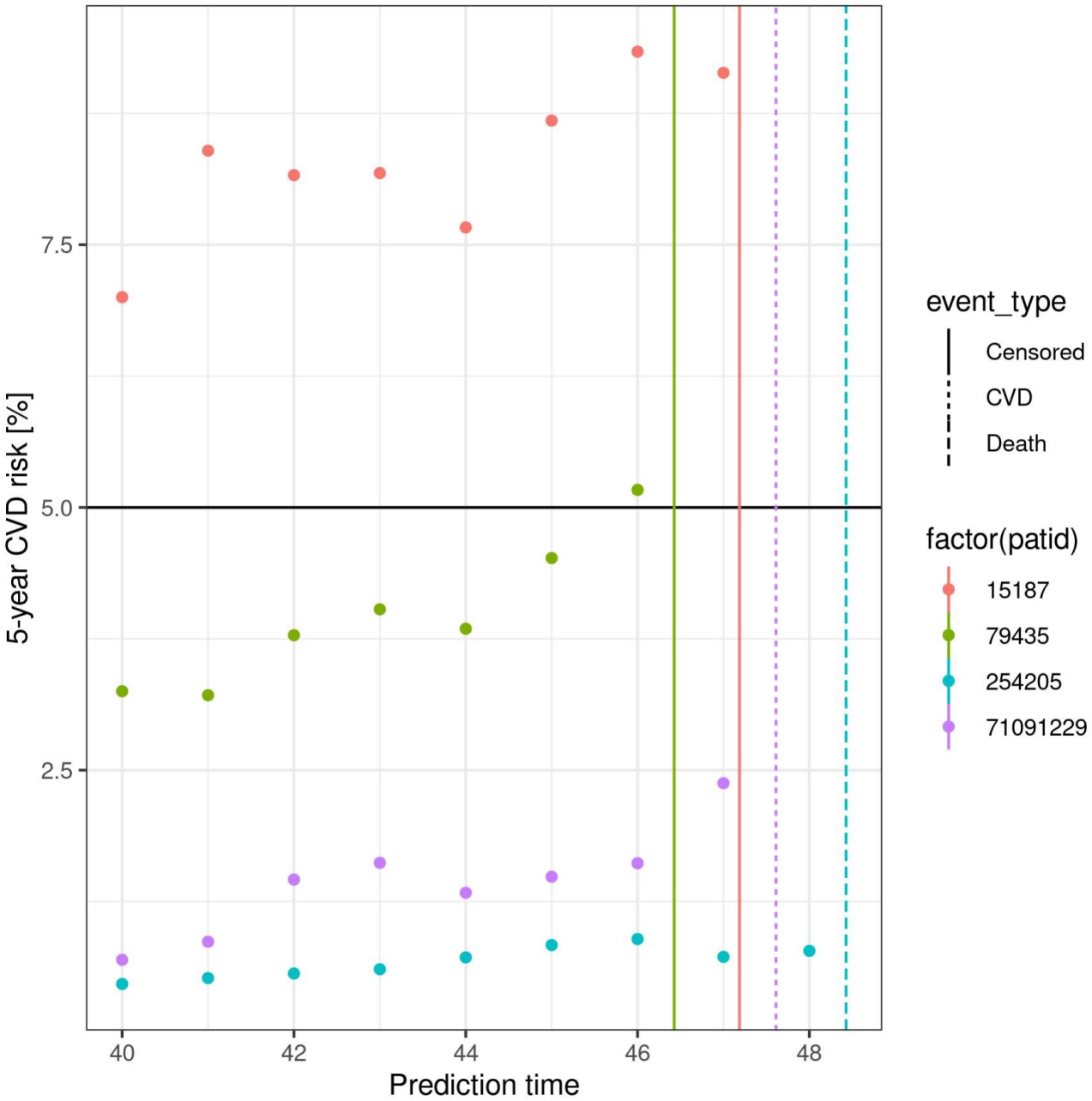


Table of Contents

1. Application: Cardiovascular disease
2. Landmarking for dynamic prediction
3. Dynamic risk prediction for cardiovascular disease
4. Scheduling cardiovascular disease risk assessments
5. A Net Benefit approach

Incremental Net Benefit (INB)

Decision-theoretic approach to weigh up benefits and costs of screening schedules, motivated by Bebu et al, 2018.

Benefits

$EFLY_{NS}$ = Event-free life years without taking statins
$EFLY_S$ = Event-free life years while taking statins

Costs

$c_s \times EFLY_S$ = Cost of statins
$c_\nu \times E[\text{Number of visits}]$ = Cost of risk assessments

Incremental Net Benefit (INB)

Net benefit

$$NB = \lambda(EFLY_{NS} + u_S EFLY_S) - c_S EFLY_S - c_\nu E[\text{Number of visits}]$$

Incremental net benefit

$$INB = NB(\boldsymbol{\tau}) - NB_{ref}$$

where $\boldsymbol{\tau}$ denotes the visit schedule, e.g. 2-y, 3-yr, 4-yr, ...

In what follows we use the following parameter settings:
$\lambda = 25,000$ £/yr, $u_s = 0.997$, $c_s = 150$ £/yr, c_ν=18.39£/visit

Calculating the INB

Using the previous landmarking approach we estimate the expected time to crossing the treatment threshold t^* for each individual at each landmark time.

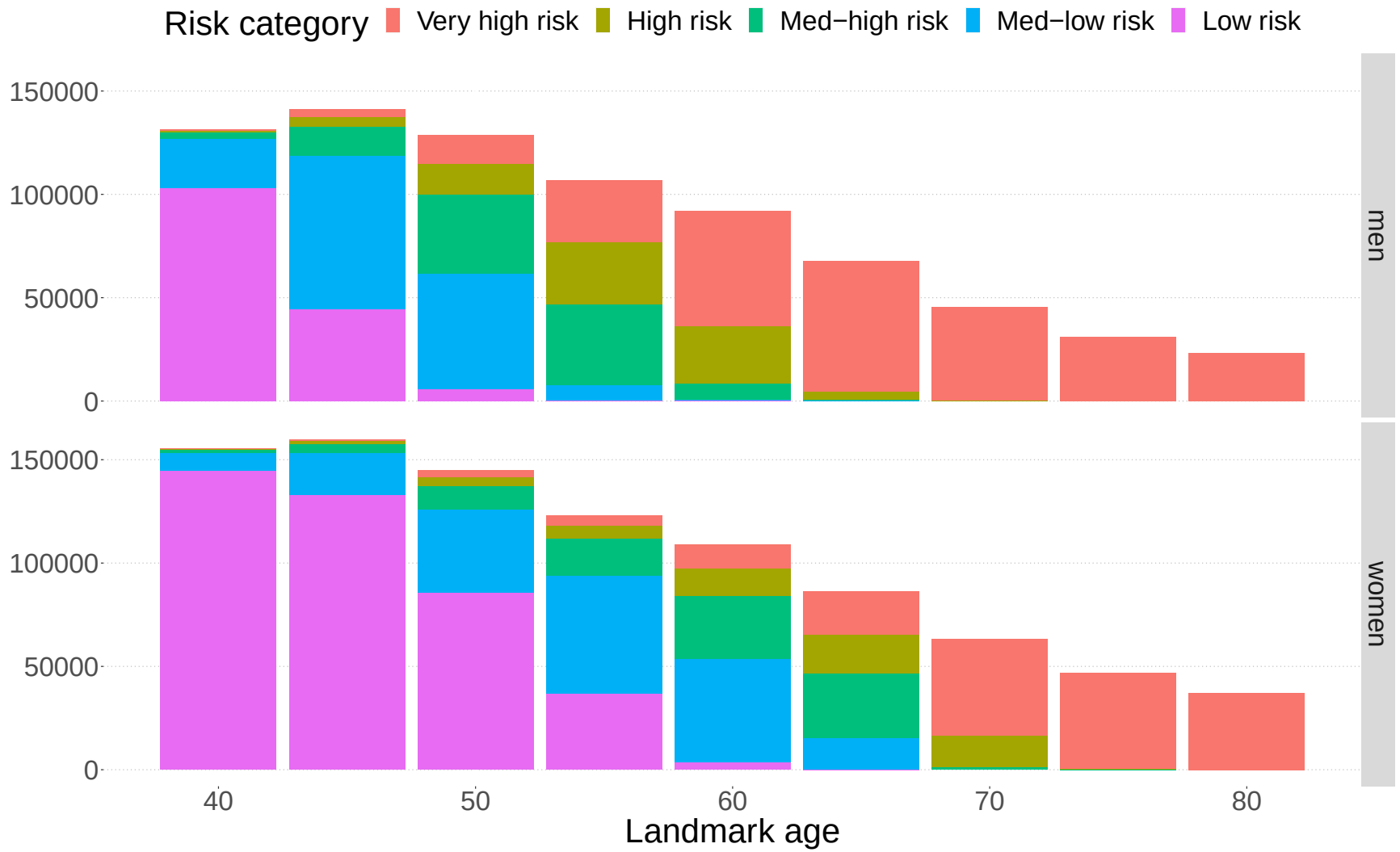
Based on the schedule $\boldsymbol{\tau}$ we assume statin prescription at the first visit after crossing the threshold, at time $\tau*_k$.

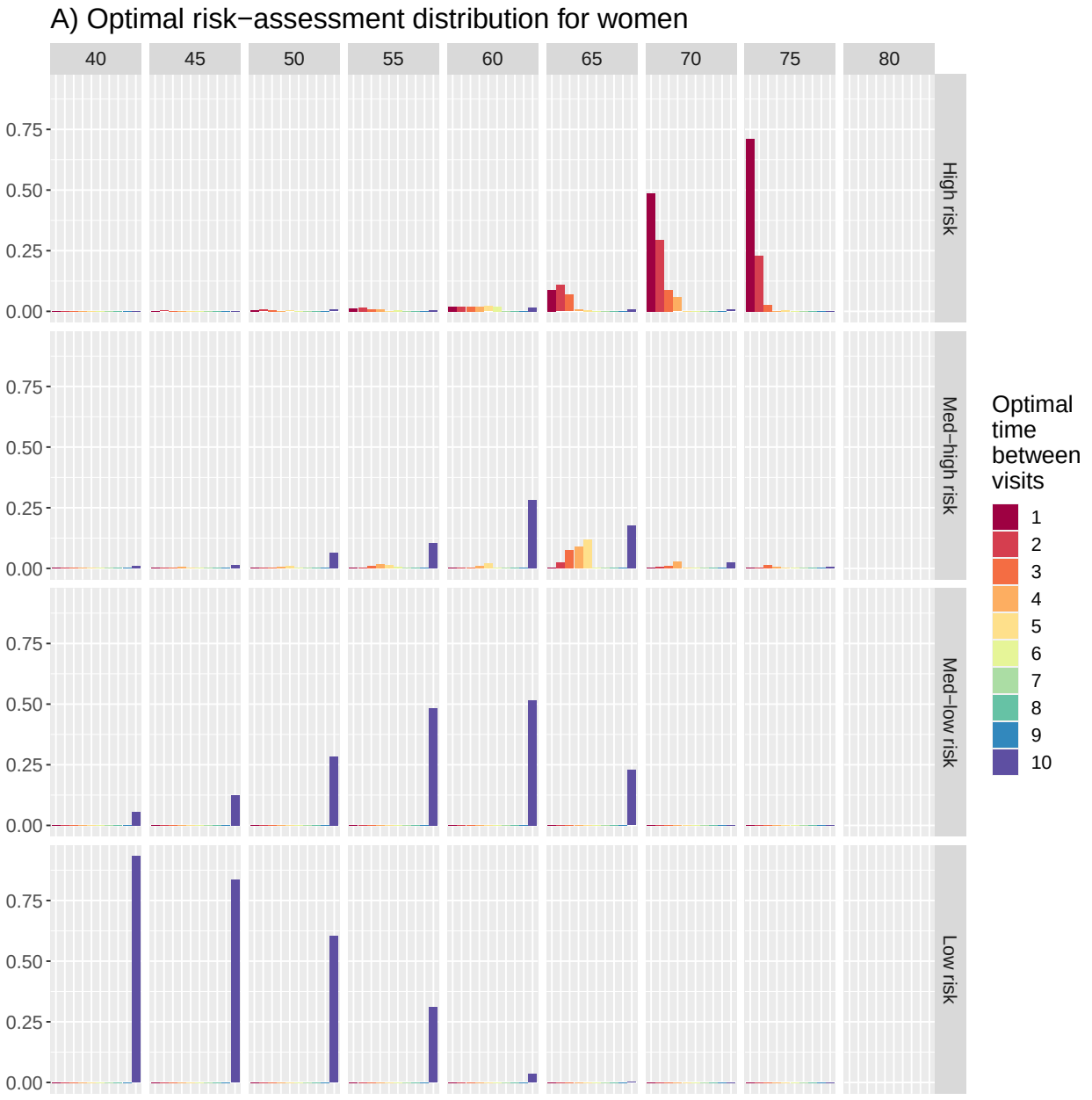
Then

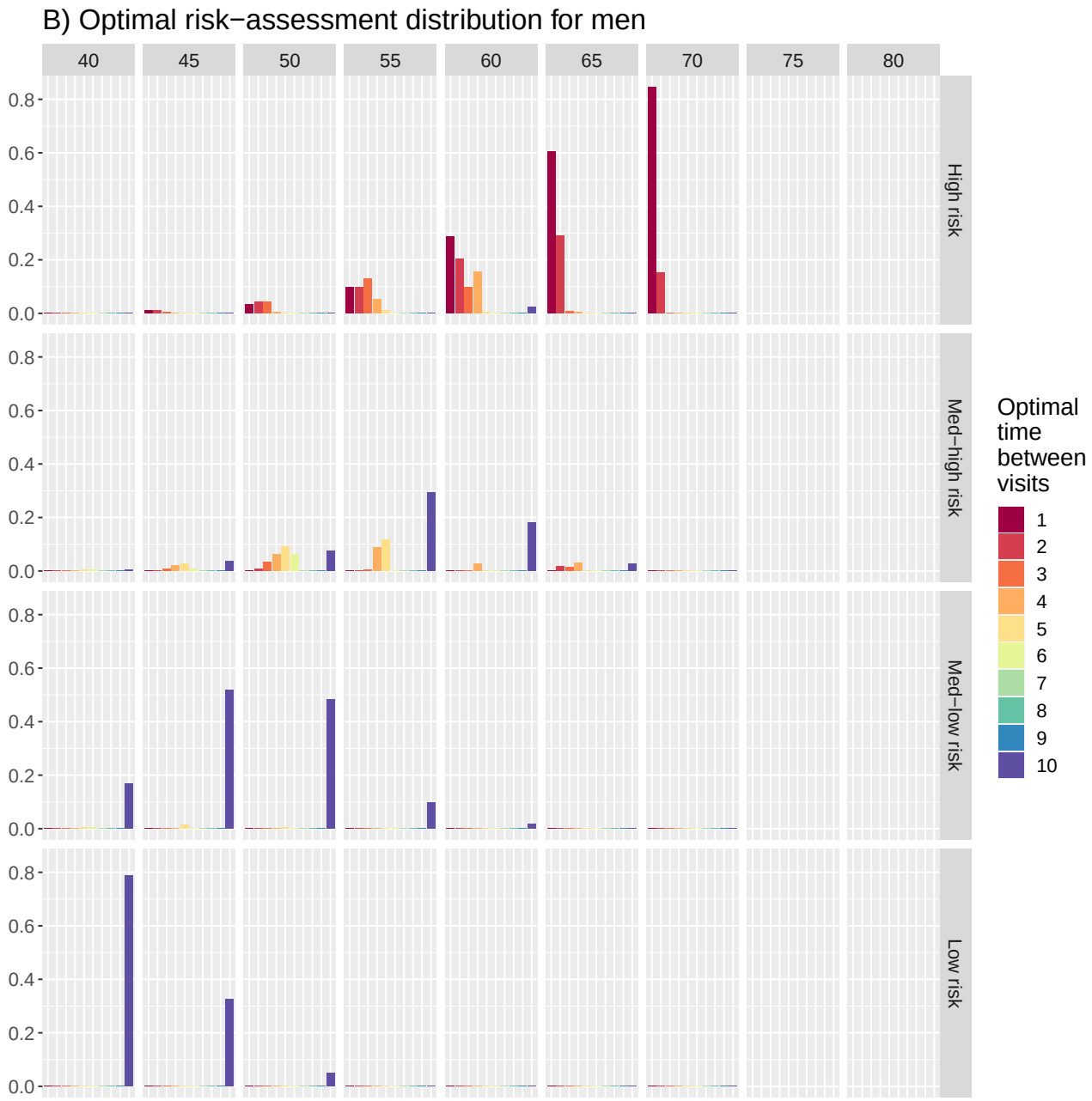
$$
\begin{aligned}
E[EFLY_N S] &= \int_0^{\tau*_k} S^{NS}(t)dt \\
E[EFLY_S] &= \int_{\tau*_k}^{10} S^{S}(t)dt
\end{aligned}
$$

We assume a HR for time to first CVD event of $\theta = 0.8$, based on a meta-analysis of treatment effects from clinical trials (Baigent et al, 2005).

INB results


Risk category
Very high risk
High risk
Med−high risk
Med−low risk
Low risk
150000
100000
50000
0
men
women
40
50
60
70
80
Landmark age


A) Optimal risk−assessment distribution for women
40
45
50
55
60
65
70
75
80
0.75
0.50
0.25
0.00
High risk
Med−high risk
Med−low risk
Low risk
Optimal time between visits
1
2
3
4
5
6
7
8
9
10


B) Optimal risk−assessment distribution for men
40
45
50
55
60
65
70
75
80
0.0
0.2
0.4
0.6
0.8
High risk
Med−high risk
Med−low risk
Low risk
Optimal time between visits
1
2
3
4
5
6
7
8
9
10

Summary

Statistical approach to building a CVD risk prediction tool using data from electronic health records

- Landmarking for dynamic risk prediction
- Mixed effects models for repeated measurements of risk factors
- Net benefit approach for scheduling of CVD risk assessments

Extensions to these models could

- Model longitudinal trajectories more flexibly
- Distinguish non-fatal and fatal CVD events

Future work

- Exploring uncertainty
- Identifying individual biomarkers for remeasurement

Acknowledgements

University of Cambridge

Prof. Angela Wood

David Stevens

Matt Arnold

Zhe Xu

Juliet Usher-Smith

Prof. Emanuele Di Angelantonio

Prof. John Danesh

MRC Biostatistics Unit

Francesca Gasperoni

Isobel Barrott

University of Leicester

Michael Sweeting

University College London

Prof. Irwin Nazareth

Prof. Irene Petersen

Tra Pham

London School of Hygiene and Tropical Medicine

Prof. Ruth Keogh

Australian National University

Ellie Paige

References

Bebu I, Lachin JM (2018). Optimal screening schedules for disease progression with application to diabetic retinopathy. *Biostatistics*; 19(1): 1–13.

Bell KJL, Hayen A, Irwig L, Takahashi O, Ohde S, Glasziou P et al (2013). When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study. *BMJ*; 346: f1895.

Chiolero A, Anker D (2019). Screening interval: a public health blind spot. *The Lancet Public Health*; 4(4): e171 - e172.

Lindbohm JV, Sipila PN, Mars NJ, Pentti J, Ahmadi-Abhari S, Brunner EJ et al. 5-year versus risk-category-specific screening intervals for cardiovascular disease prevention: a cohort study. *The Lancet Public Health*; 4(4): e189 - e199.

Paige E, Barrett J, Stevens D, Keogh R, Sweeting M, Nazareth I, Petersen I, Wood A (2018). Landmark models for optimizing the use of repeated measurements of risk factors in electronic health records to predict future disease risk. *American Journal of Epidemiology*; 187(7):1530-1538.

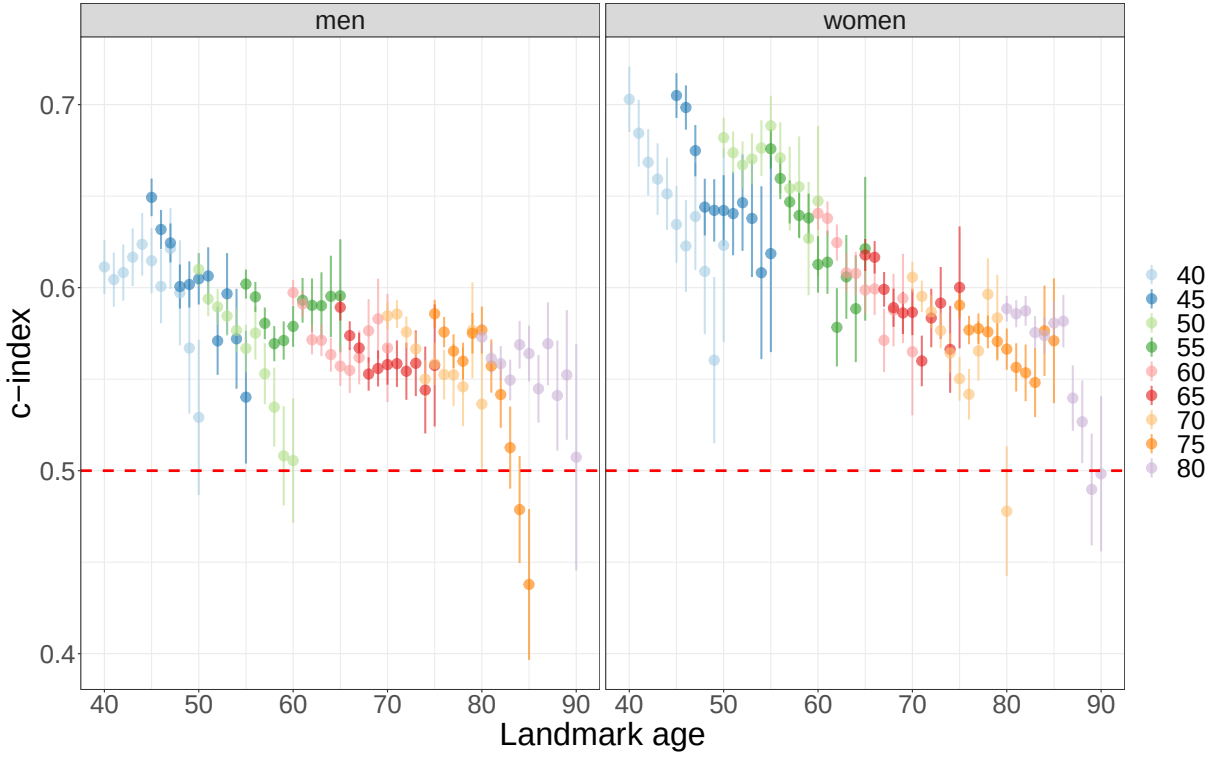
van Houwelingen H, Putter H (2012). Dynamic prediction in clinical survival analysis. CRC Press.

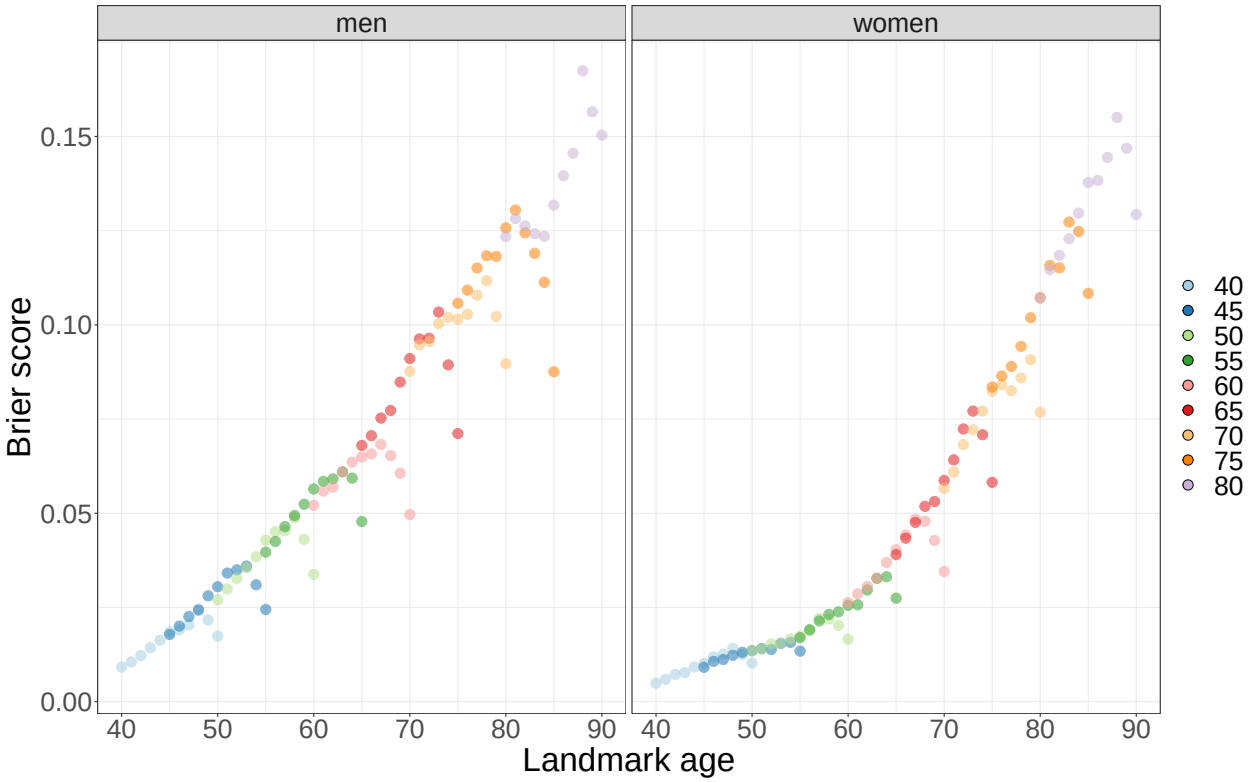
Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M et al (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*; 42(34): 3227–3337.

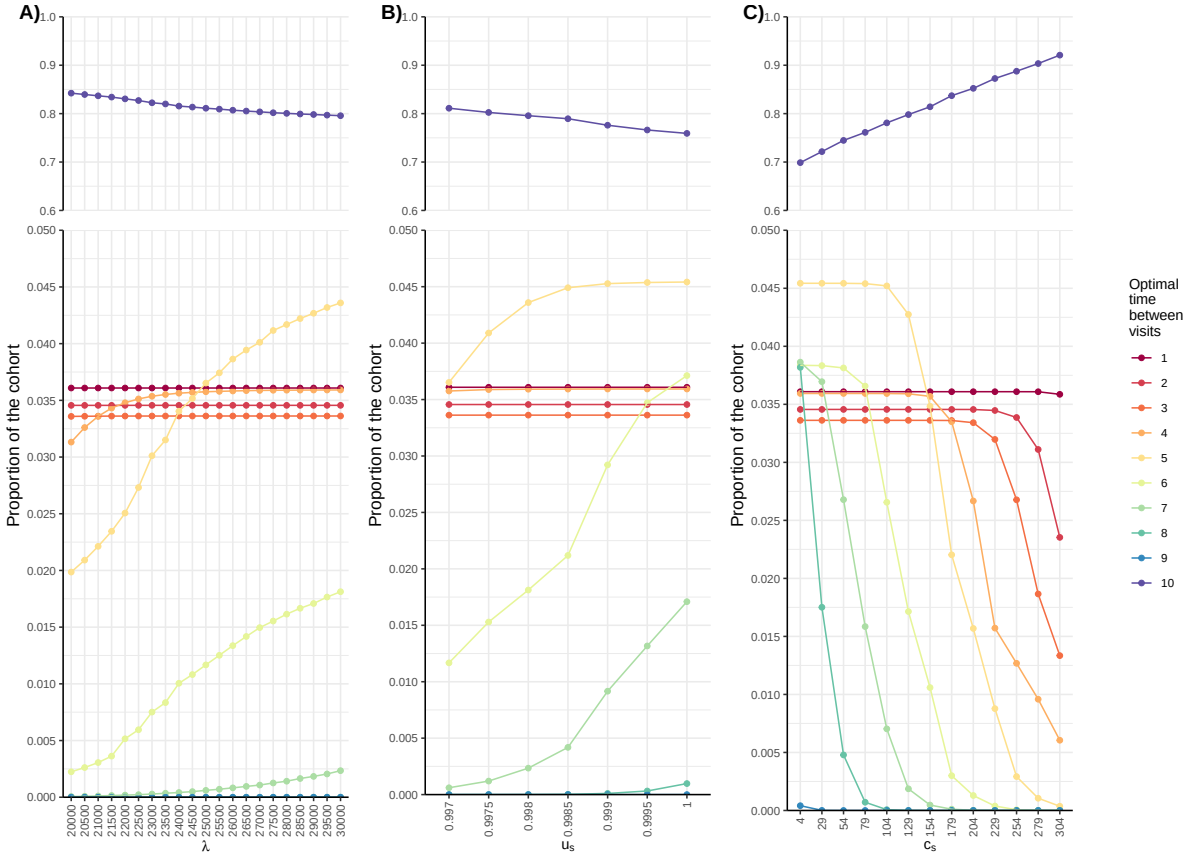
MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Questions?


men
women
c−index
0.7
0.6
0.5
0.4
40
50
60
70
80
90
Landmark age
40
45
50
55
60
65
70
75
80


men
women
Brier score
0.00
0.05
0.10
0.15
40
50
60
70
80
90
Landmark age
40
45
50
55
60
65
70
75
80


A)
B)
C)
Proportion of the cohort
λ
u_s
c_s
Optimal time between visits
1
2
3
4
5
6
7
8
9
10