Understanding and Avoiding Survival Bias: An Application of Multistate Models in a Cohort of Oscar Nominees

Martin Wolkewitz[1,2] **Arthur Allignol**[1,2,*] Martin Schumacher[2]
Jan Beyersmann[1,2]

[1]Freiburg Center for Data Analysis and Modeling, University of Freiburg
[2]Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg
[*]arthur.allignol@fdm.uni-freiburg.de

DFG Forschergruppe FOR 534

UNIVERSITÄTS FREIBURG KLINIKUM

Introduction

Motivations:

- It has been claimed that Oscar winners live longer (Annals of Internal Medicine 2001 & 2006)
- The Oscar study is an entertaining example for examining mistakes such as the **length bias** and **time-dependent bias** that are commonly seen in medical research

Introduction

Motivations:

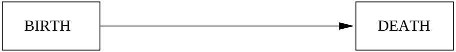
- It has been claimed that Oscar winners live longer (Annals of Internal Medicine 2001 & 2006)
- The Oscar study is an entertaining example for examining mistakes such as the **length bias** and **time-dependent bias** that are commonly seen in medical research

Overview:

- Basic concepts in survival theory
- Length bias
- Time-dependent bias
- Multistate model
- Application to Oscar study

Basic Concepts

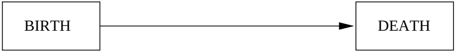
Survival data measure the time to some event, e.g.



- Simple multistate model with two states (birth and death)
- Each individual moves from birth to death, the time scale is **age**
- Data possibly subject to right-censoring and/or left-truncation

Basic Concepts

Survival data measure the time to some event, e.g.



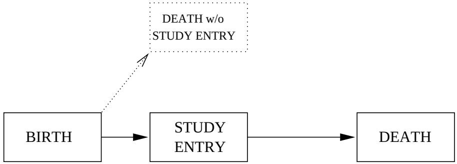
- Simple multistate model with two states (birth and death)
- Each individual moves from birth to death, the time scale is **age**
- Data possibly subject to right-censoring and/or left-truncation

The key quantity in survival theory is the **hazard function**

$$\alpha(t)dt = \mathrm{P}(T \in dt | T \geq t).$$

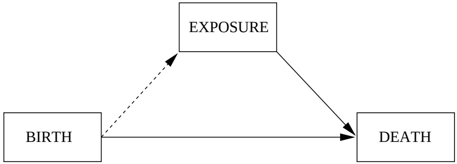
as **it is undisturbed by right-censoring/left-truncation**

Basic Concepts: Length Bias



- In cohort studies, participants usually enter the study at a time point later than birth
- If age should be kept as the time scale, one has a **left-truncated** situation
- Ignoring left-truncation leads to **length bias**

Basic Concepts: Time-Dependent Bias



- A simple time-dependent exposure is displayed
- Participants are unexposed at the time of birth and may get exposed during lifetime
- Ignoring the timing of exposure (dashed line) leads to **time-dependent bias**

Multistate Model

- Time-inhomogeneous Markov process $X_{t \in [0,+\infty)}$ that at any time occupies one of a set of discrete states.
- Transition hazard $\alpha_{i \to j}(t)$ of moving from state i to state j

$$\alpha_{i \to j}(t)dt = \mathrm{P}(X_{t+dt} = j | X_t = i)$$

Multistate Model

- Time-inhomogeneous Markov process $X_{t \in [0,+\infty)}$ that at any time occupies one of a set of discrete states.
- Transition hazard $\alpha_{i \to j}(t)$ of moving from state i to state j

$$\alpha_{i \to j}(t)dt = \mathrm{P}(X_{t+dt} = j | X_t = i)$$

- The cumulative transition hazard $A_{i \to j}(t) = \int_0^t \alpha_{i \to j}(u)du$ estimated by the Nelson-Aalen estimator:

$$\hat{A}_{i \to j}(t) = \sum_{t_k \leq t} \frac{\Delta N_{i \to j}(t_k)}{Y_i(t_k)}$$

  - $N_{i \to j}(t)$: number of observed transition from i to j up to t
  - $Y_i(t)$: number of individuals in state i just before t

Multistate Models in the Cohort of Oscar Nominees

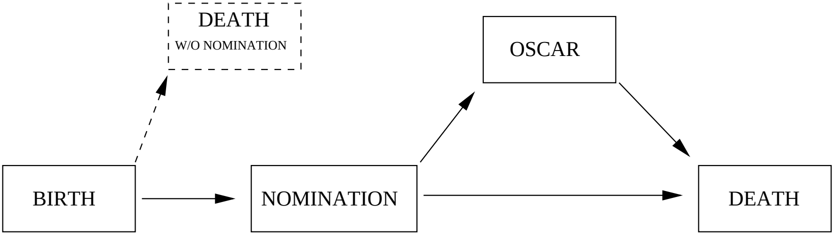
- Do Oscar nominees after winning an Oscar have a survival advantage?
  $\longrightarrow$ does winning an Oscar reduce the death hazard?

Multistate Models in the Cohort of Oscar Nominees

- Do Oscar nominees after winning an Oscar have a survival advantage?
  $\longrightarrow$ does winning an Oscar reduce the death hazard?
- Inclusion of all actors and actresses nominated for an Oscar before 2001

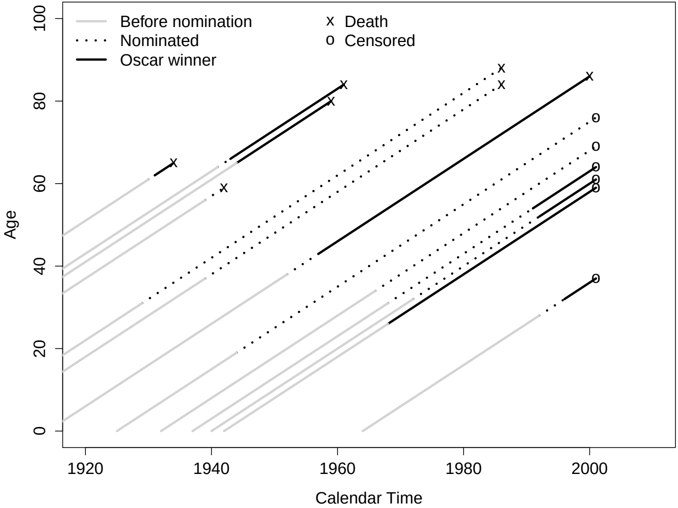
Multistate Models in the Cohort of Oscar Nominees

- Do Oscar nominees after winning an Oscar have a survival advantage?
  $\rightarrow$ does winning an Oscar reduce the death hazard?
- Inclusion of all actors and actresses nominated for an Oscar before 2001

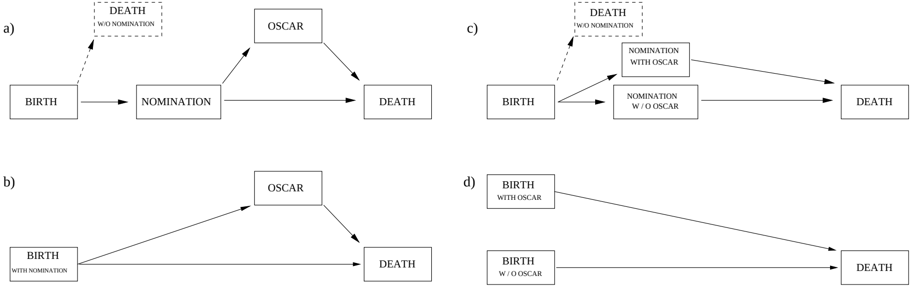


Lexis Diagram

Lexis diagram of a subset of the cohort

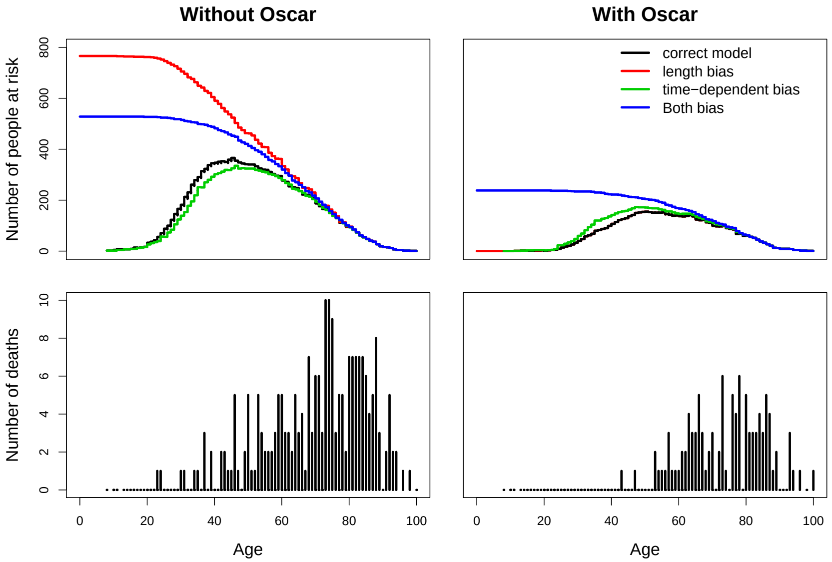


Multistate Models in the Cohort of Oscar Nominees



a) correct model
b) length bias
c) time-dependent bias
d) combination of length and time-dependent bias

Risk Sets & Deaths



Estimated Death Hazard Ratios

- Oscar winning included as a time-dependent covariate (correct & length bias) or as a baseline covariate (time-dependent bias & both bias) in a Cox model

Multistate model	**hazard ratio (95%-CI)**
correct model	0.81 (0.64-1.02)
length bias	0.90 (0.71-1.14)
time-dependent bias	0.76 (0.60-0.96)
both bias	0.77 (0.61-0.97)

Summary

- Multistate models provide a relevant framework
  - to display the bias
  - how to circumvent them

Summary

- Multitate models provide a relevant framework
    - to display the bias
    - how to circumvent them
- Risk sets play the key role

Summary

- Multistate models provide a relevant framework
  - to display the bias
  - how to circumvent them
- Risk sets play the key role
- Ignoring the delayed entry in the cohort creates a length bias driving to biased estimates in the opposite direction of those when time-dependent bias is present

Summary

- Multistate models provide a relevant framework
  - to display the bias
  - how to circumvent them
- Risk sets play the key role
- Ignoring the delayed entry in the cohort creates a length bias driving to biased estimates in the opposite direction of those when time-dependent bias is present
- Hazard ratios can be further adjusted for confounding

References

- Redelmeier, D. and Singh, S. (2001), Survival in Academy Award-winning actors and actresses, *Ann. Intern. Med.*, 134, 955–962.
- Sylvestre, M., Huszti, E., and Hanley, J. (2006), Do OSCAR winners live longer than less successful peers? A reanalysis of the evidence, *Ann. Intern. Med.*, 145, 361–63.
- van Walraven, C., Davis, D., Forster, A., and Wells, G. (2004), Time-dependent bias was common in survival analyses published in leading clinical journals, *J. Clin. Epidemiol.* , 57, 672–682.
- Suissa, S. (2008). Immortal time bias in pharmacoepidemiology. *Am. J. Epidemiol.*, 167, 492–499.
- Allignol, A., Beyersmann, J., and Schumacher, M. (2008), mvna: An R package for the Nelson-Aalen estimator in multistate models, *R News*, 8, 2, 48–50, URL http://CRAN.R-project.org/doc/Rnews/
- Beyersmann, J., Gastmeier, P., Wolkewitz, M., Schumacher, M. (2008): An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J. Clin. Epidemiol.*, 61, 1216–1221