Determining the Minimum Detectable Hazard Ratio for a Population Based Longitudinal Study Using Multi-state Markov Model: A Simulation Study

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Outline

- Sample size and statistical power for longitudinal study
- Canadian Longitudinal Study on Aging (CLSA)
- Objectives of this simulation study
- Simulation based on irreversible illness-death model
- Results and Findings
- Limitations

Sample Size and Statistical power for Longitudinal Study

- Common factors influence determination of required sample size
  - Objective
  - Type of endpoint/outcome
  - Variation of the study population
  - Type I error and type II error
  - Minimum clinically important effect size
  - Measurement errors

Sample Size and Statistical power for Longitudinal Study

- Other factors for longitudinal study
  - Length of follow-up
  - Frequency and timing of repeated measurements
  - Correlation between the repeated measurements
  - Attrition

Sample Size and Statistical power for Longitudinal Study

- Formulae and software for different type of outcomes
  - Continuous and binary
  - Categorical
  - Time to event, i.e. survival

- Survival outcome with multiple events
  - Competing risk
  - Multi-state transition

Canadian Longitudinal Study on Aging (CLSA)

- Objectives of CLSA
  - Examine aging as a dynamic process
  - Investigate the inter-relationship among intrinsic and extrinsic factors
  - Capture the transitions, trajectories and profiles of aging

Canadian Longitudinal Study on Aging (CLSA)

- **Participants:** Stratified random sample of 50,000 Canadian aged 45 to 85
- **Design:** Repeated waves of data collection at baseline and every 3 years for at least 20 years

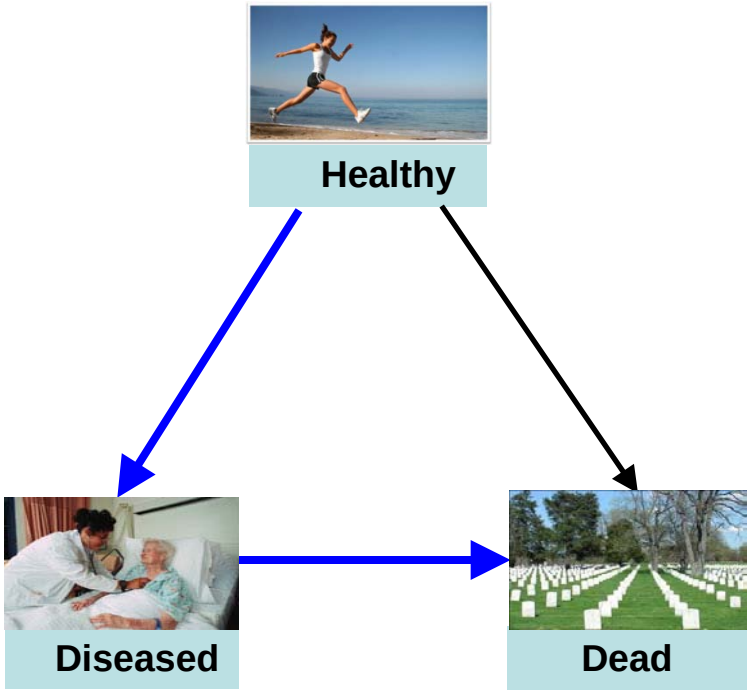
Objectives of This Project

- Definition: minimum detectable hazard ratio (MDHR)

- Objectives: investigate MDHRs for environmental, genotype risk exposures, and their interaction
  - complete observation vs. repeated measurements
  - with misclassification vs. without misclassification
  - different prevalence of risk exposure and disease, and the progression of the disease

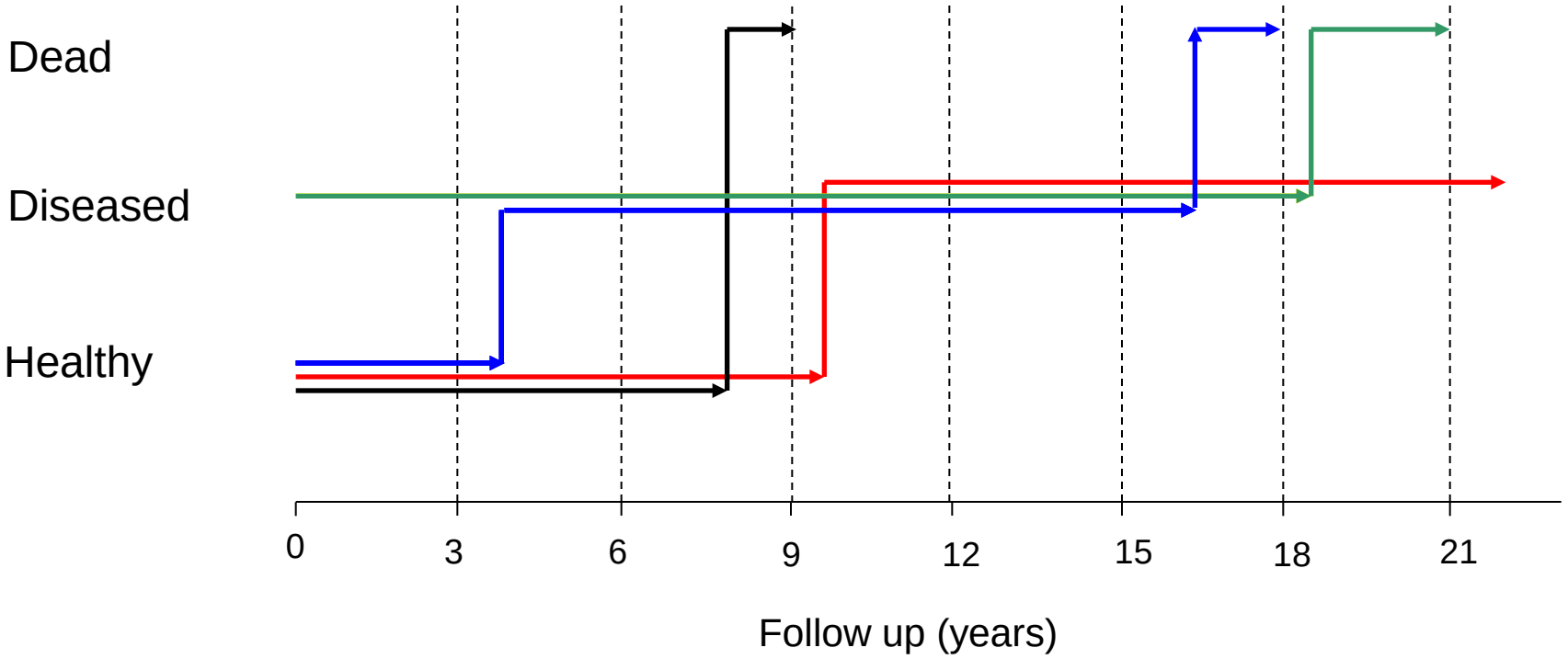
Simulation Based on Illness-Death Model

- Irreversible Illness-Death model
  - Three-state Markov process for irreversible disease with single absorbing state



Simulation Based on Illness-Death Model

- State transition over time for subjects in CLSA



Simulation Based on Illness-Death Model

- Challenges on modeling transition times for CLSA
  - Time since entry to Healthy or Diseased state is unknown for healthy or diseased subjects at baseline
  - Hazard of states transition increases over time

- Possible Solutions
  - Piecewise-constant Markov model
  - Semi-Markov model assuming transition time follows Weibull distribution

Simulation Based on Illness-Death Model

- Piecewise-constant Markov model
  - Assume intensities are constant within each subinterval, but vary between two consecutive time subintervals.
  - Include age as an external time-dependent covariate in the intensity functions.
  - Advantage: Allow the transition intensity to the next state depend on the time since entry to the study.
  - Disadvantage:
    1) Commercial software not available.
    2) Self developed software is rather demanding on computer resources, and very time consuming.

Simulation Based on Illness-Death Model

- Semi-Markov model assuming transition time follow Weibull distribution
  - Increasing intensities over time can be captured by assigning shape parameter larger than 1.
  - Advantage: Commercial software is available for analysis: R, STATA, SAS
  - Disadvantage: Requires times since entry to Healthy and Diseased states, which are unknown.
  - Compensation:
    1) Include age as a covariate in intensity functions.
    2) Choosing Weibull shape and scale parameters to mimic the evolution of the CLSA cohort.

Simulation Based on Illness-Death Model

- Transition intensity matrix

$$Q(t \mid X) = \begin{pmatrix} -q_{12}(t \mid X) - q_{13}(t \mid X) & q_{12}(t \mid X) & q_{13}(t \mid X) \\ 0 & -q_{23}(t \mid X) & q_{23}(t \mid X) \\ 0 & 0 & 0 \end{pmatrix}$$

where $q_{rs}(t \mid X) = \lambda_{rs} \rho_{rs} t^{\rho_{rs}-1} \exp(\beta_{rs} X)$

Simulation Based on Illness-Death Model

- Fixed parameters for designing the simulation study

Parameter	Value
Sample size	30,000
Annual loss to follow up rate	0.005
Length of follow up	21 years
Mortality by the end of study	Approximately 40%
Type I error	0.05 and 0.001
Statistical power	80%

Simulation Based on Illness-Death Model

- Varied parameters for designing the simulation study

Transition	Weibull Parameters	
	Scale	Shape
Healthy to Diseased	60, 45, 30.	1.5, 2, 3
Diseased to Dead	5, 10, 15	1.5, 2, 3
Healthy to Dead	30	1.5

Simulation Based on Illness-Death Model

- Varied parameters for designing the simulation study

Parameter	Value
Prevalence of disease	1%, 5%, 10%, 20%
Prevalence of risk factors	5%, 10%, 25%, and 50%
Time and frequency of measurements	1) Complete observation 2) Every 3 years for 21 years
Misclassification for risk factors	0%, 5%

Results large

Prevalence of risk exposures	Transition: Healthy → Diseased				Transition: Diseased → Dead			
	Shape=2	MDHR			Shape=2	MDHR		
	Scale	ER	GR	ER*GR	Scale	ER	GR	ER*GR
Prevalence of illness: 5%								
0.5	30	1.10 1.11 1.18	1.13 1.14 1.20	1.14 1.15 1.23	10	1.04 1.05 1.13	1.08 1.08 1.17	1.09 1.10 1.19

Changing Parameter	MDHR Healthy -- Diseased	MDHR Diseased -- Dead
Repeated measurements vs. complete observation	↗	↗
Misclassification vs. accurate measurements	↗	↗

Results large

Prevalence of risk exposures	Transition: Healthy → Diseased				Transition: Diseased → Dead			
	Shape=2	MDHR			Shape=2	MDHR		
	Scale	ER	GR	ER*GR	Scale	ER	GR	ER*GR
Prevalence of illness: 5%								
0.5	30	1.10 1.11 1.18	1.13 1.14 1.20	1.14 1.15 1.23	10	1.04 1.05 1.13	1.08 1.08 1.17	1.09 1.10 1.19
	45	1.11 1.12 1.18	1.14 1.15 1.21	1.16 1.17 1.26	15	1.07 1.08 1.16	1.11 1.13 1.20	1.13 1.15 1.24

Changing Parameter	MDHR Healthy -- Diseased	MDHR Diseased -- Dead
Fast vs. slow disease progression	↘	↘

Results large

Prevalence of risk exposures	Transition: Healthy → Diseased				Transition: Diseased → Dead			
	Shape=2	MDHR			Shape=2	MDHR		
	Scale	ER	GR	ER*GR	Scale	ER	GR	ER*GR
Prevalence of illness: 5%								
0.05	45	1.20 1.22 1.27	1.27 1.29 1.34	2.26 2.30 2.45	15	1.20 1.22 1.31	1.32 1.35 1.44	>3 >3 >3
0.5	45	1.11 1.12 1.18	1.14 1.15 1.21	1.16 1.17 1.26	15	1.07 1.08 1.16	1.11 1.13 1.20	1.13 1.15 1.24

Changing Parameter	MDHR Healthy -- Diseased	MDHR Diseased -- Dead
Increasing prevalence of risk exposure	↘	↘

Results

Prevalence of risk exposures	Transition: Healthy → Diseased				Transition: Diseased → Dead			
	Shape=2	MDHR			Shape=2	MDHR		
	Scale	ER	GR	ER*GR	Scale	ER	GR	ER*GR
Prevalence of illness: 5%								
0.05	30	1.17 1.20 1.24	1.24 1.26 1.31	2.04 2.08 2.22	10	1.14 1.15 1.24	1.22 1.24 1.33	2.51 2.72 2.81
Prevalence of illness 20%								
0.05	30	1.19 1.21 1.24	1.26 1.28 1.32	2.16 2.22 2.37	10	1.11 1.12 1.21	1.18 1.19 1.28	2.14 2.24 2.38

Changing Parameter	MDHR Healthy -- Diseased	MDHR Diseased -- Dead
Increasing prevalence of disease	↗	↘

Summary of Findings

- **Sample size of CLSA is large enough to detect small** (1<MDHR≤1.5) **or moderate** (1.5<MDHR≤2.0) **hazard ratios** (HR) **for direct effects**.
- **When prevalence of risk exposure is relatively low** (≤10%), **sample size of CLSA only allow substantial** (2.0<MDHR≤3.0) **or large** (MDHR>3.0) **HR to be detected for interaction**.
- **Repeated measurements every 3 years for at least 20 years is a reasonable choice, but may not be optimal.**
- **Precise measurement on risk exposures is critical to reduce the MDHR**.

Limitations

- For subjects who are healthy or diseased at baseline, we assume the time entry to Health or Diseased state is the same as times entry to the study.

  - Compensation:
    1) Include age as a covariate in the intensity functions
    2) Choosing Weibull shape and scale parameters to mimic the evolution of the CLSA cohort

Limitations

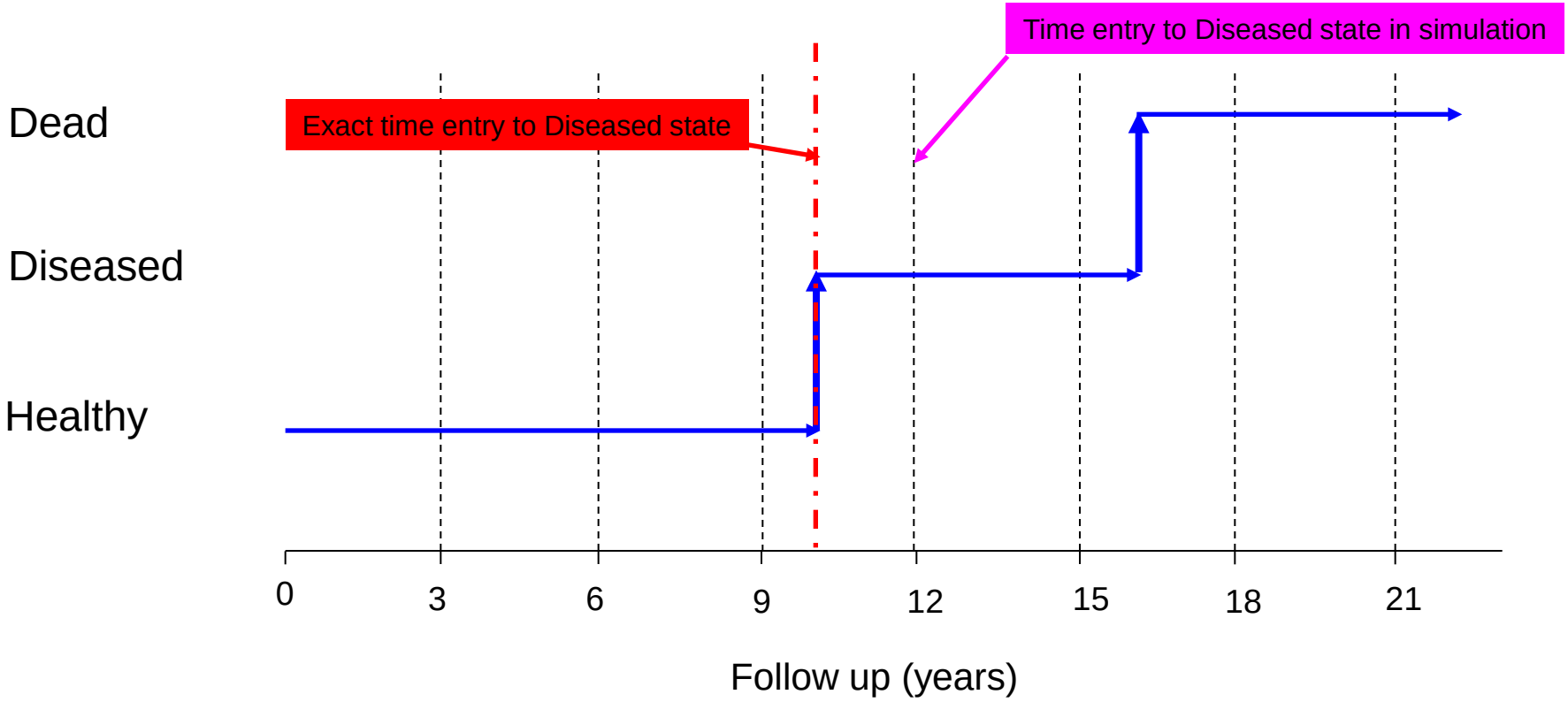
Comparison of the evolution of CLSA comprehensive cohort

	Num. of demented at baseline	Num. of Events (healthy to demented) at Each Data Collection time point						
		3 yrs	6 yrs	9 yrs	12 yrs	15 yrs	18 yrs	21 yrs
Projected from CSHA [1]	**554**	**407**	**894**	**1456**	**1993**	**2602**	**3226**	**3921**
Simulation [2]	**580**	**347**	**918**	**1572**	**2226**	**2853**	**3411**	**3888**

1. CSHA: Canadian Study of Healthy and Aging study, 1991-1996
2. Simulation based on the following parameters: Prevalence of disease 2.0%
   Healthy to Diseased: Weibull scale 60, shape 1.5
   Healthy to Dead: Weibull scale 30, shape 1.5
   Diseased to Dead: Weibull scale 7, shape 1.5

Limitations

- Exact time since entry to Diseased state is unknown due to repeated measurements



Limitations

- Assume all participants enter the study at the same time.
- Measurement error on response variable is not considered.
- Loss to follow-up rate may not be constant

Questions

- For studies on aging, like CLSA, is it reasonable to assume the exact time of entering into Healthy state be a function of age? For example, the healthy aging starts from 45 years old?

Thanks for Your Attention!