

... some glimpses, at least

---

**Håkon K. Gjessing**

Professor/Principal Investigator

Centre for Fertility and Health

An NRC Centre of excellence, at the Norwegian Institute of Public Health, Oslo

Department of Global Public Health and Primary Care, University of Bergen

---

Makerere

Tuesday 13 June, 2023



**Hazard, “mathematical version” of incidence:**

$$\alpha(t) = \frac{1}{dt} P(t \leq T < t + dt | T \geq t)$$

**Integrated (aka cumulative) hazard:**

$$A(t) = \int_0^t \alpha(s) ds$$

**Survival function:**

$$S(t) = \exp\{-A(t)\} = \exp\left\{-\int_0^t \alpha(s) ds\right\}$$

A bit more correct:  $S(t) = \prod_{0 \leq s \leq t} (1 - dA(s))$  (product integral)

## Usual stuff:

- Kaplan-Meier estimator  $\hat{S}(t)$  for  $S(t)$
- Ignore the actual  $\alpha(t)$

However, difficult to extend, e.g. to competing risks  
( $S(t)$  does not always make sense)

---

## More direct:

- Kaplan-Meier follows:  $\hat{S}(t) \approx \exp \left\{ -\hat{A}(t) \right\}$
- Nelson-Aalen estimator  $\hat{A}(t)$  for  $A(t) = \int_0^t \alpha(s) ds$



## IMPORTANT:

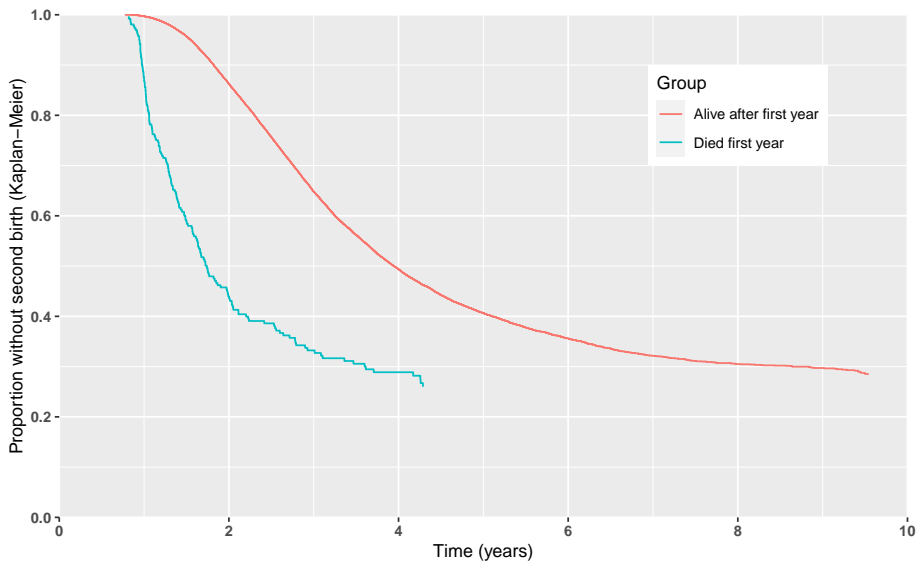
- The derivative, i.e. *the slope* of  $A(t)$  is the hazard  $\alpha(t)$

## EXAMPLE: TIME FROM FIRST TO SECOND BIRTH

- Medical Birth Registry
- Time from first to second birth
- About 53,000 mothers with first birth in 1983-1997
- 262 of these lost the first child within one year

(Just an example, not a complete analysis...!)

# KAPLAN-MEIER CURVES COMPARING GROUPS

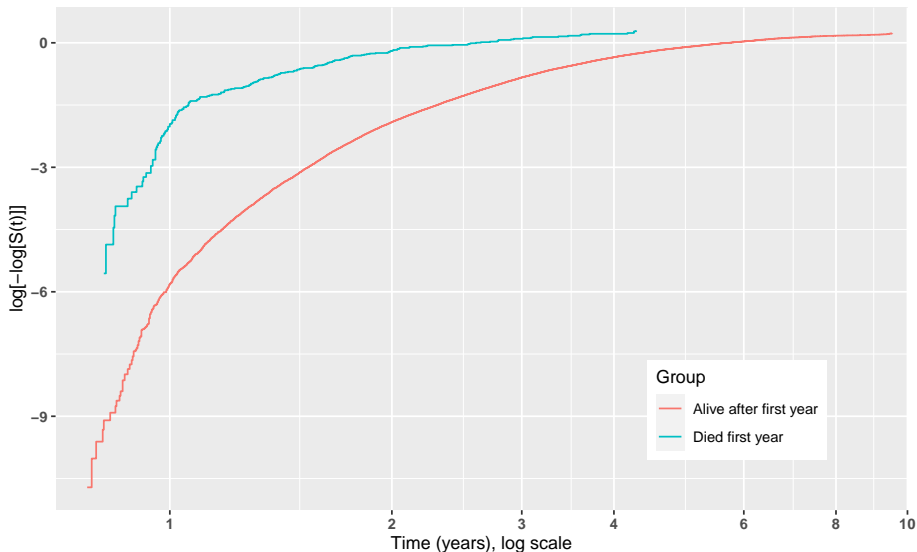


**Hazard rate ratio (overall):**

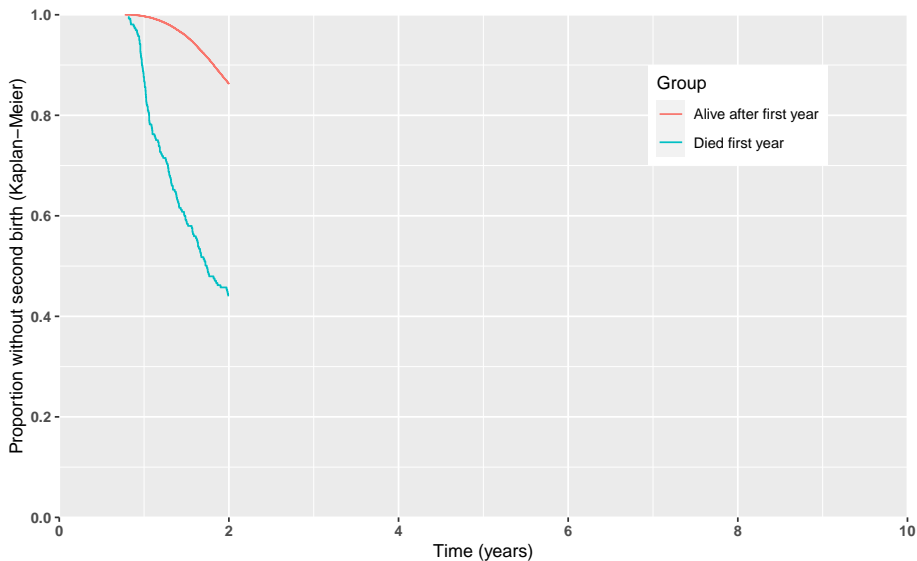
2.6 (95%CI: 2.3–3.0)

# LOG-MINUS-LOG CURVES OF KAPLAN-MEIER

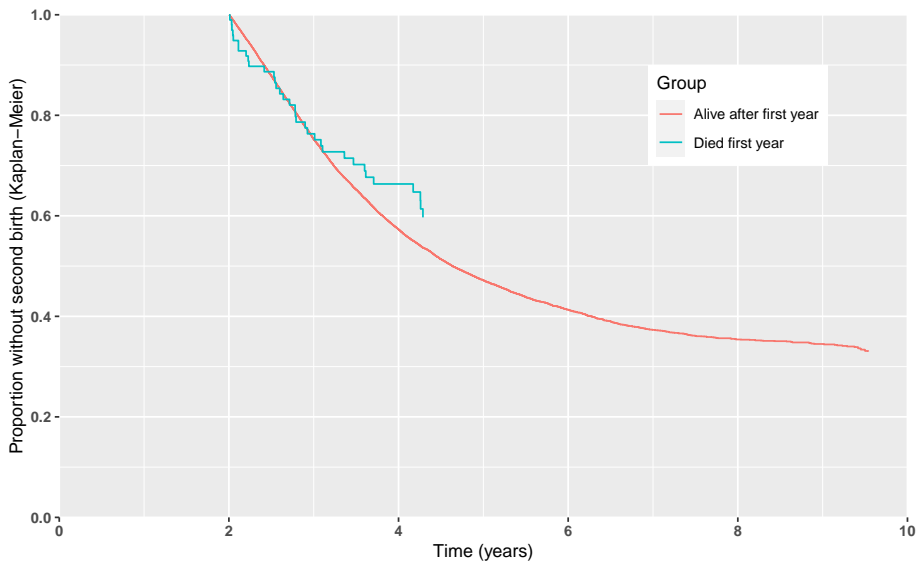
CHECK FOR NON-PROPORTIONAL HAZARDS



# KAPLAN-MEIER CURVES, PART I



# KAPLAN-MEIER CURVES, PART II (RESET TO 1)



**Hazard rate ratio (overall):**

2.6 (95%CI: 2.3–3.0)

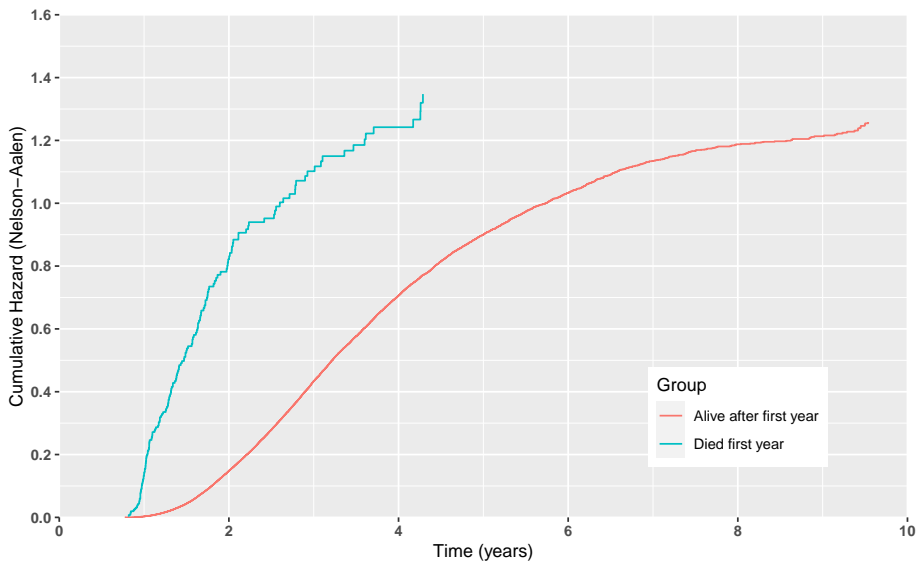
**Hazard rate ratio (up until year 2):**

4.8 (95%CI: 4.1–5.7)

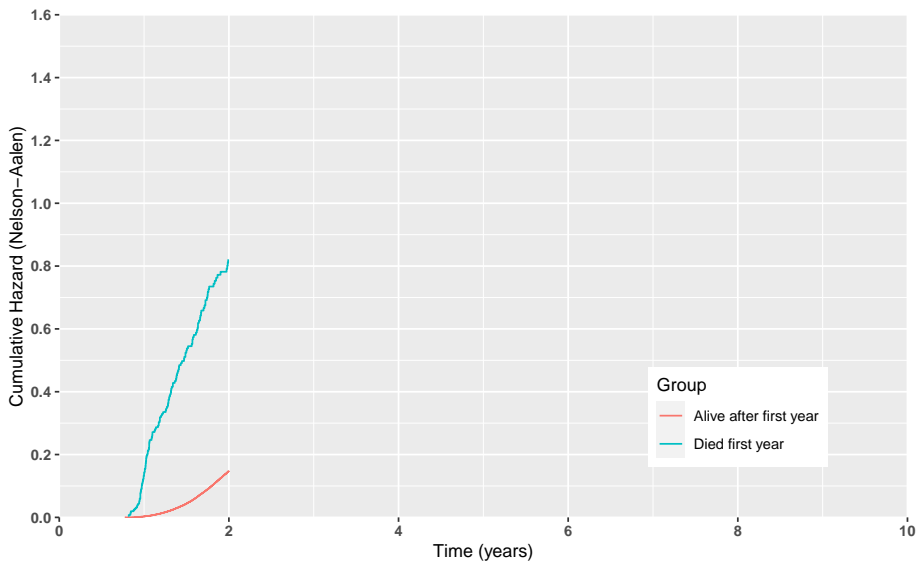
**Hazard rate ratio (after year 2):**

0.79 (95%CI: 0.58–1.1)

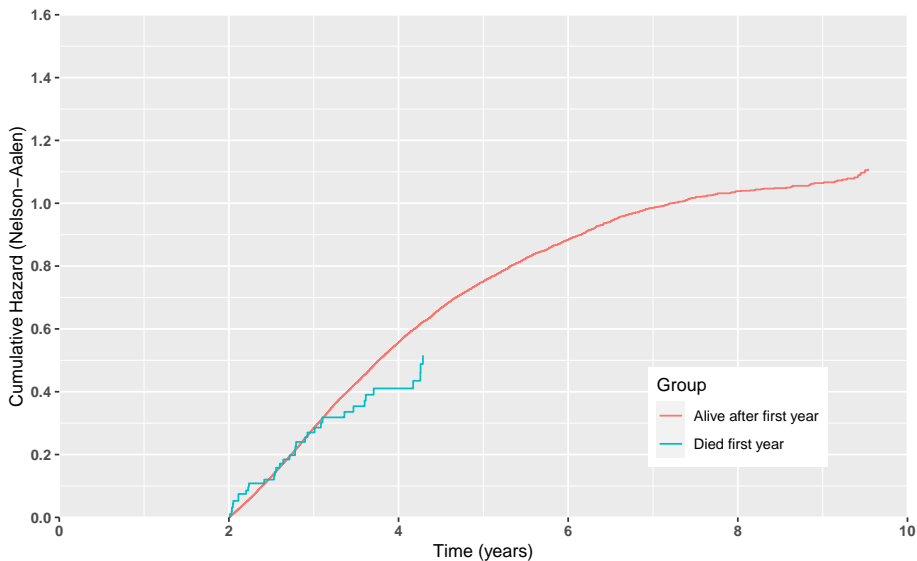
# NELSON-AALEN CUMULATIVE HAZARD CURVES



# NELSON-AALEN CUMULATIVE HAZARD, PART I



# NELSON-AALEN CUMULATIVE HAZARD, PART II (RESET TO 0)



# COX (PROPORTIONAL HAZARDS) REGRESSION

## TIME-DEPENDENT COVARIATES

### HAZARD:

$$\alpha(t) = \alpha_0(t) \exp(\beta_1 \cdot x_1(t) + \dots)$$

- $\alpha_0(t)$  is the *baseline hazard*
- $x_1(t), x_2(t), \dots$  are *time-dependent* covariates
- $\beta_1, \beta_2, \dots$  are the corresponding parameters

### Effect:

$\exp(\beta_1)$  is the **multiplicative** effect on the hazard, associated with an unit increase in  $x_1(t)$  *at any time t*.

# AALEN ADDITIVE HAZARDS REGRESSION

## TIME-DEPENDENT COVARIATES AND TIME-DEPENDENT PARAMETERS

### HAZARD:

$$\alpha(t) = \beta_0(t) + \beta_1(t) \cdot x_1(t) + \dots$$

- $\beta_0(t) = \alpha_0(t)$  is the *baseline hazard*
- $x_1(t), x_2(t), \dots$  are **time-dependent** covariates
- $\beta_1(t), \beta_2(t), \dots$  are the corresponding **time-dependent** parameters
- Note the improvement:  $\beta_i(t)$  are **allowed to depend on time!**

### Effect:

$\beta_1(t)$  is the **additive** effect on the hazard, associated with an unit increase in  $x_1(t)$  **specifically at time**  $t$ .

# INTERPRETATION

## COX MULTIPLICATIVE MODEL, HAZARD RATE RATIO

$$\alpha_{\text{alive}}(t) = \alpha_0(t)$$

$$\alpha_{\text{died}}(t) = \alpha_0(t) \exp(\beta_1)$$

$$\text{HRR} = \frac{\alpha_{\text{died}}(t)}{\alpha_{\text{alive}}(t)} = \exp(\beta_1)$$

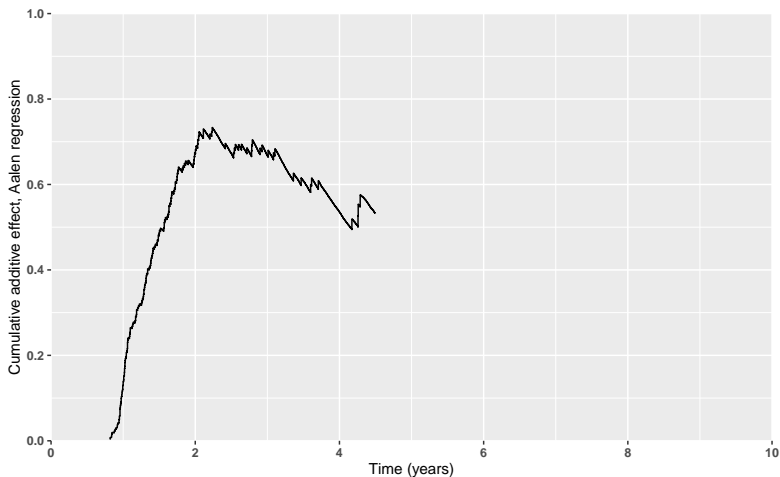
## AALLEN ADDITIVE MODEL, HAZARD RATE DIFFERENCE

$$\alpha_{\text{alive}}(t) = \beta_0(t)$$

$$\alpha_{\text{died}}(t) = \beta_0(t) + \beta_1(t)$$

$$\text{HRD} = \alpha_{\text{died}}(t) - \alpha_{\text{alive}}(t) = \beta_1(t)$$

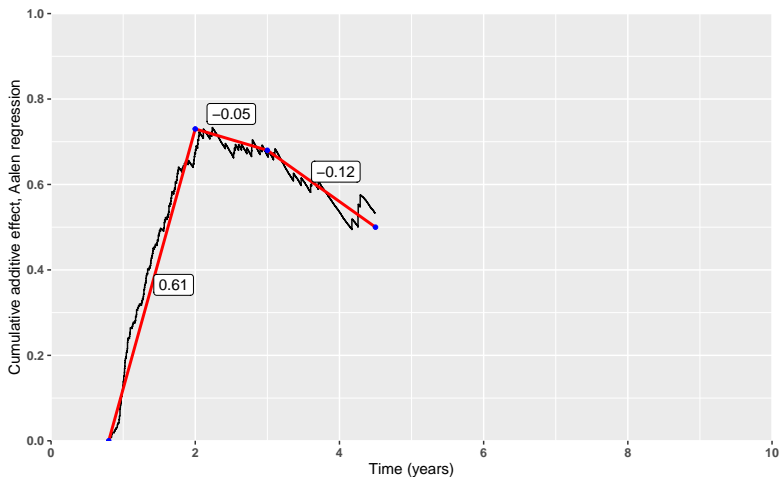
# Aalen ESTIMATE OF CUMULATIVE DIFFERENCE



The estimated curve is  $B_1(t) = \int_0^t \beta_1(s) ds$

So the slope is  $\beta_1(t)$

# ALEN ESTIMATE OF CUMULATIVE DIFFERENCE



The estimated curve is  $B_1(t) = \int_0^t \beta_1(s) ds$

So the slope is  $\beta_1(t)$

# TIME-VARYING...

## Time-dependent covariates:

- Covariates can change over time
- But effect of covariates assumed constant over time
- Available in both Cox and Aalen

## Time-dependent effects:

- The *effect* of covariates can change over time
- This can be combined with time-dependent covariates
- Available only in Aalen
- (...although various types of Cox-adaptations do exist)

# Thank you!