# Producing up-to-date survival predictions from prognostic models

Sarah Booth[1] Richard D. Riley[2] Joie Ensor[2]
Paul C. Lambert[1,3] Mark J. Rutherford[1]

[1]Biostatistics Research Group, Department of Health Sciences, University of Leicester, Leicester, UK

[2]Centre for Prognosis Research, Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK

[3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

26th September 2019

UNIVERSITY OF LEICESTER

# PhD Project

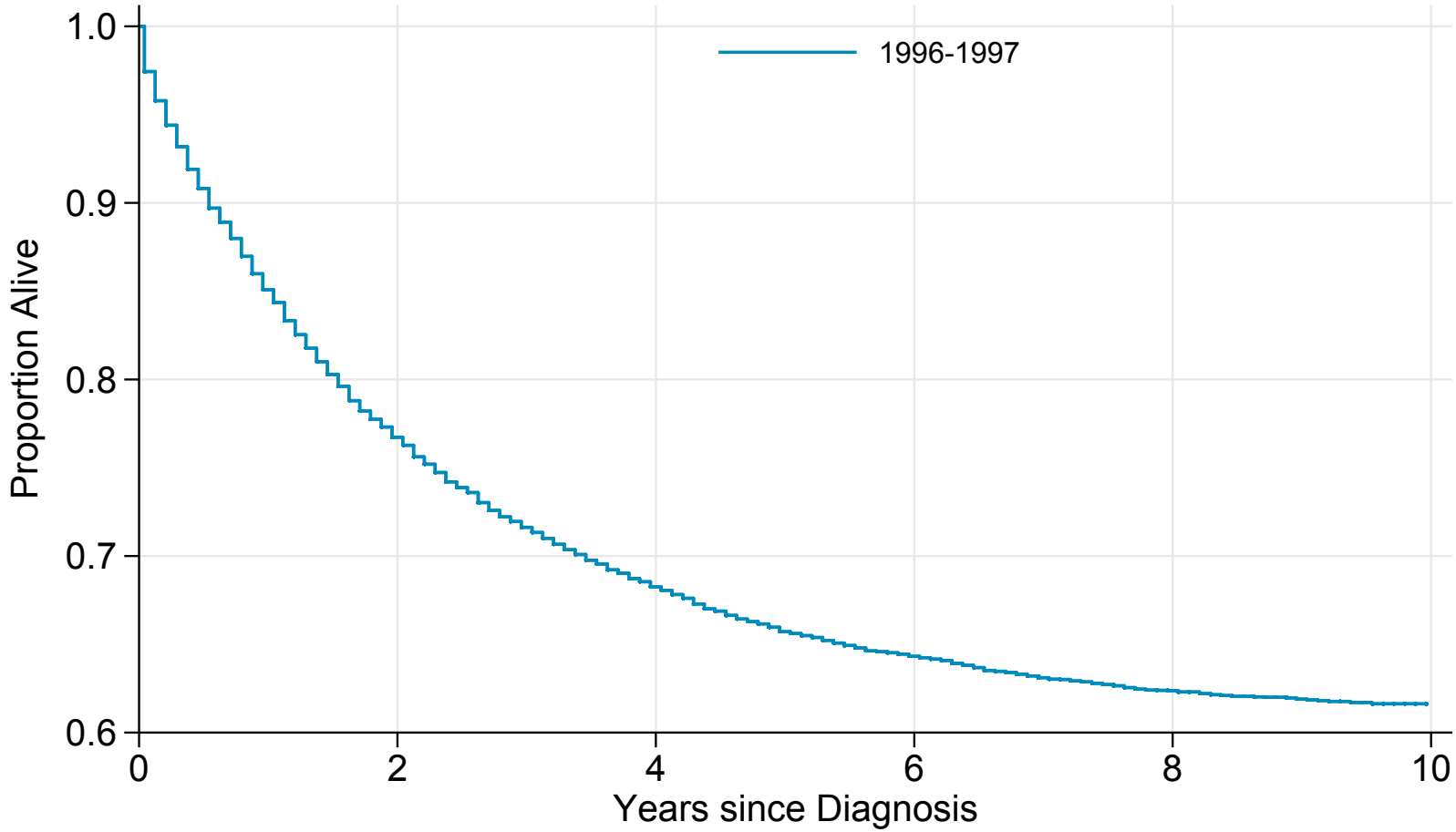
## Prognostic Models

- Prognostic models can be used to inform patients and aid treatment decisions
- Often built using data collected over a long time period
- Improvements in survival may lead to out-dated survival predictions

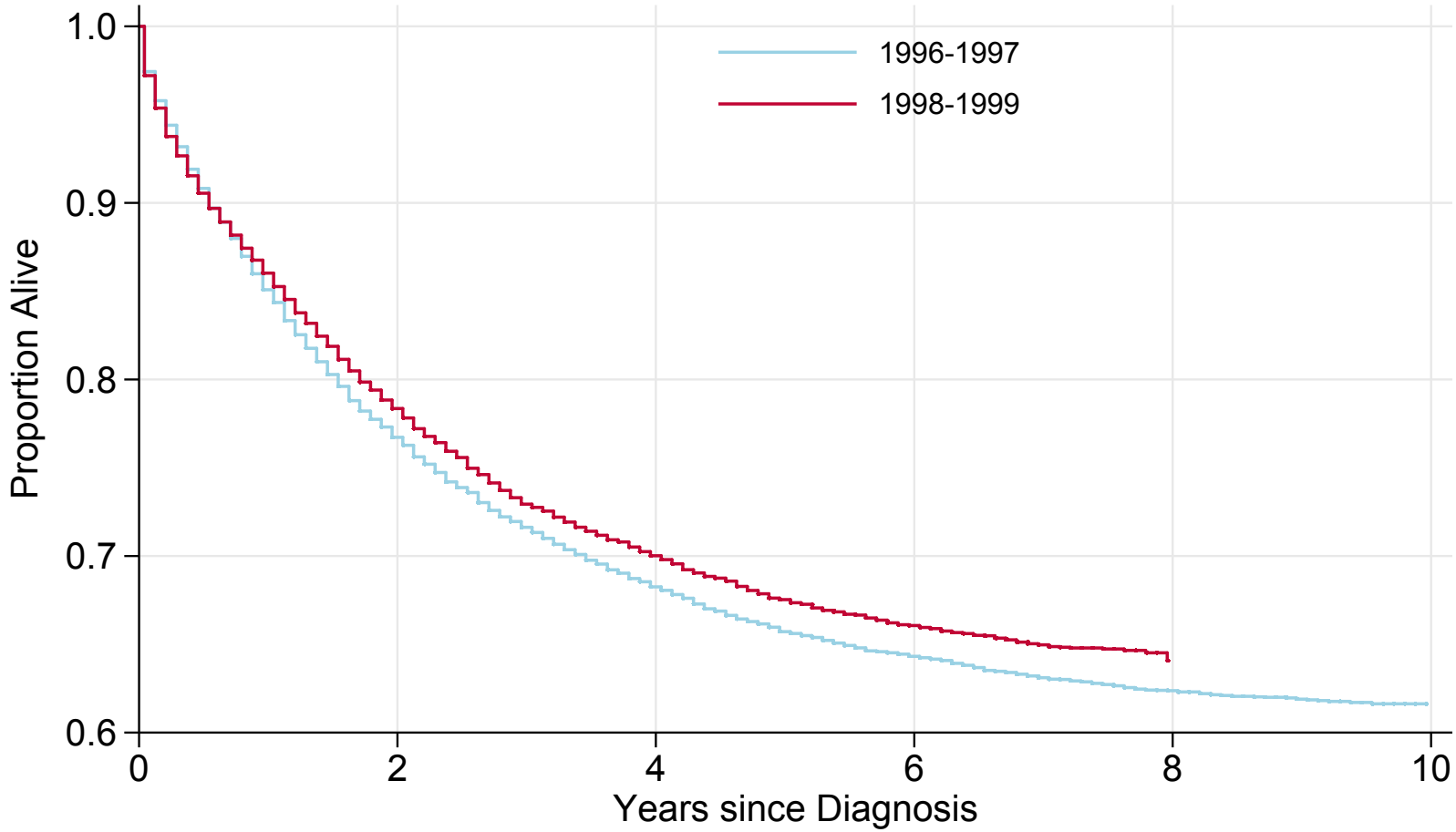
## Methods

- Developed temporal recalibration which combines period analysis with recalibration techniques
- Alternative approach involving modelling calendar time

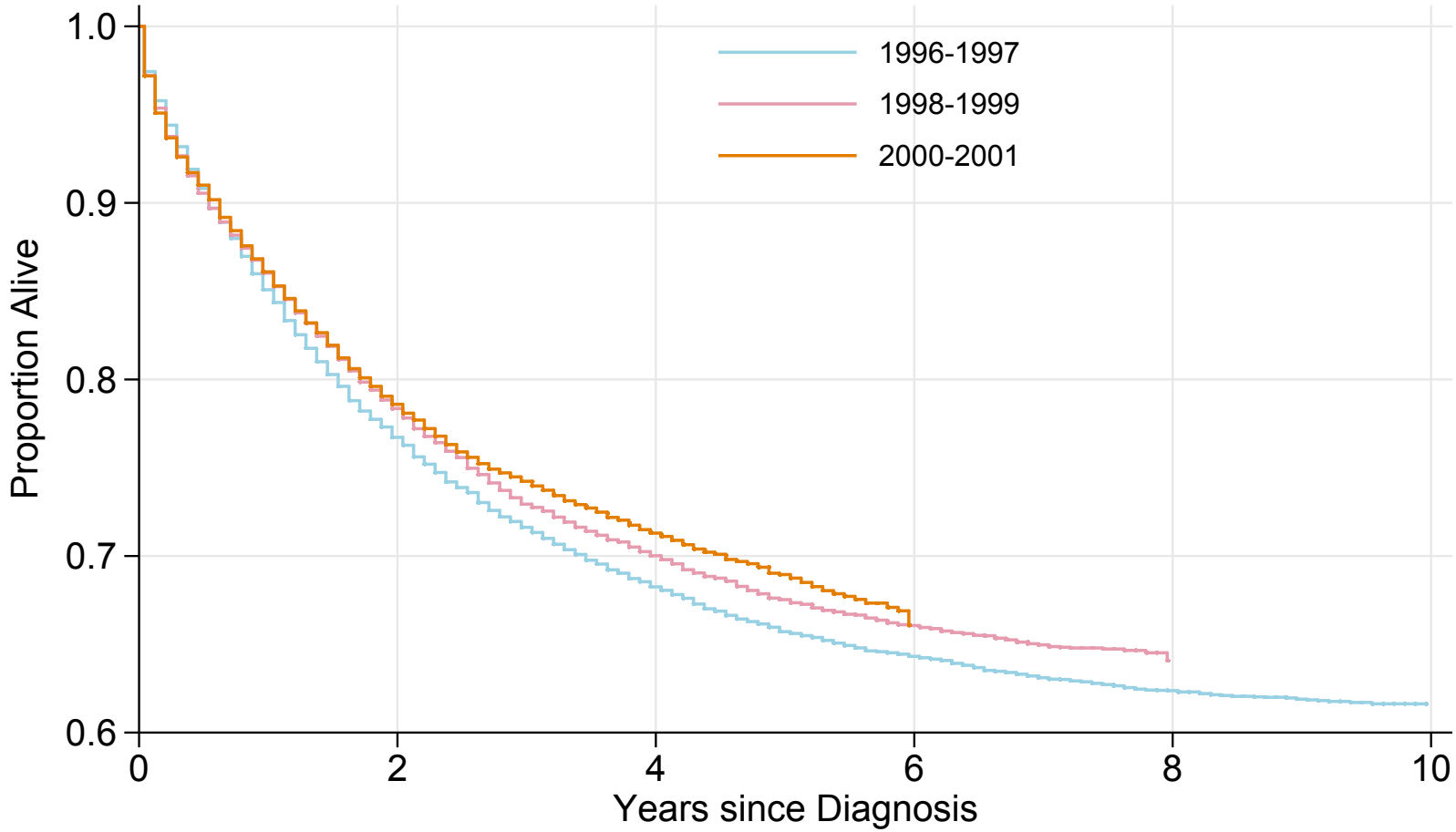
# Assessing Improvements in Survival



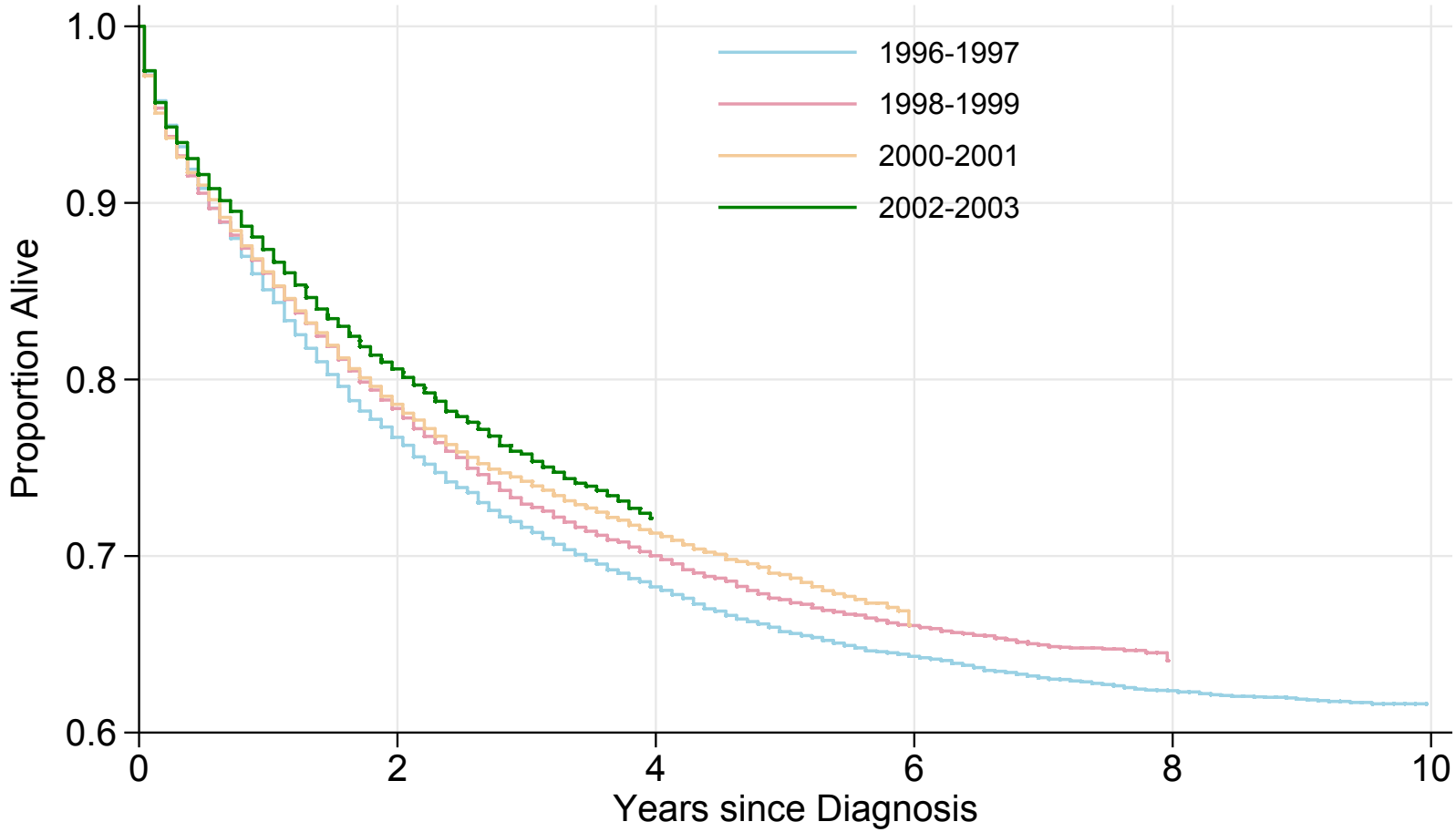
# Assessing Improvements in Survival



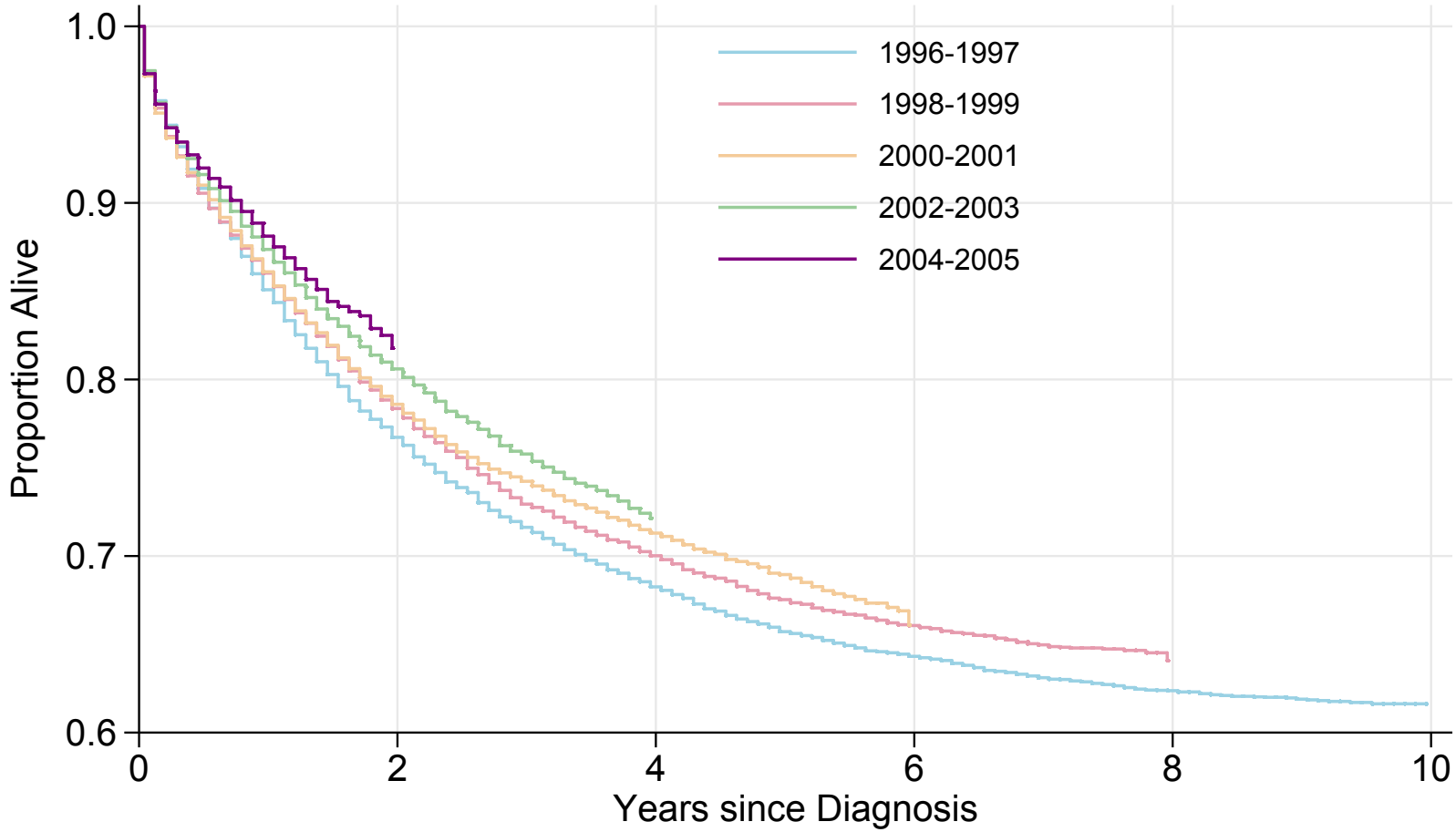
# Assessing Improvements in Survival



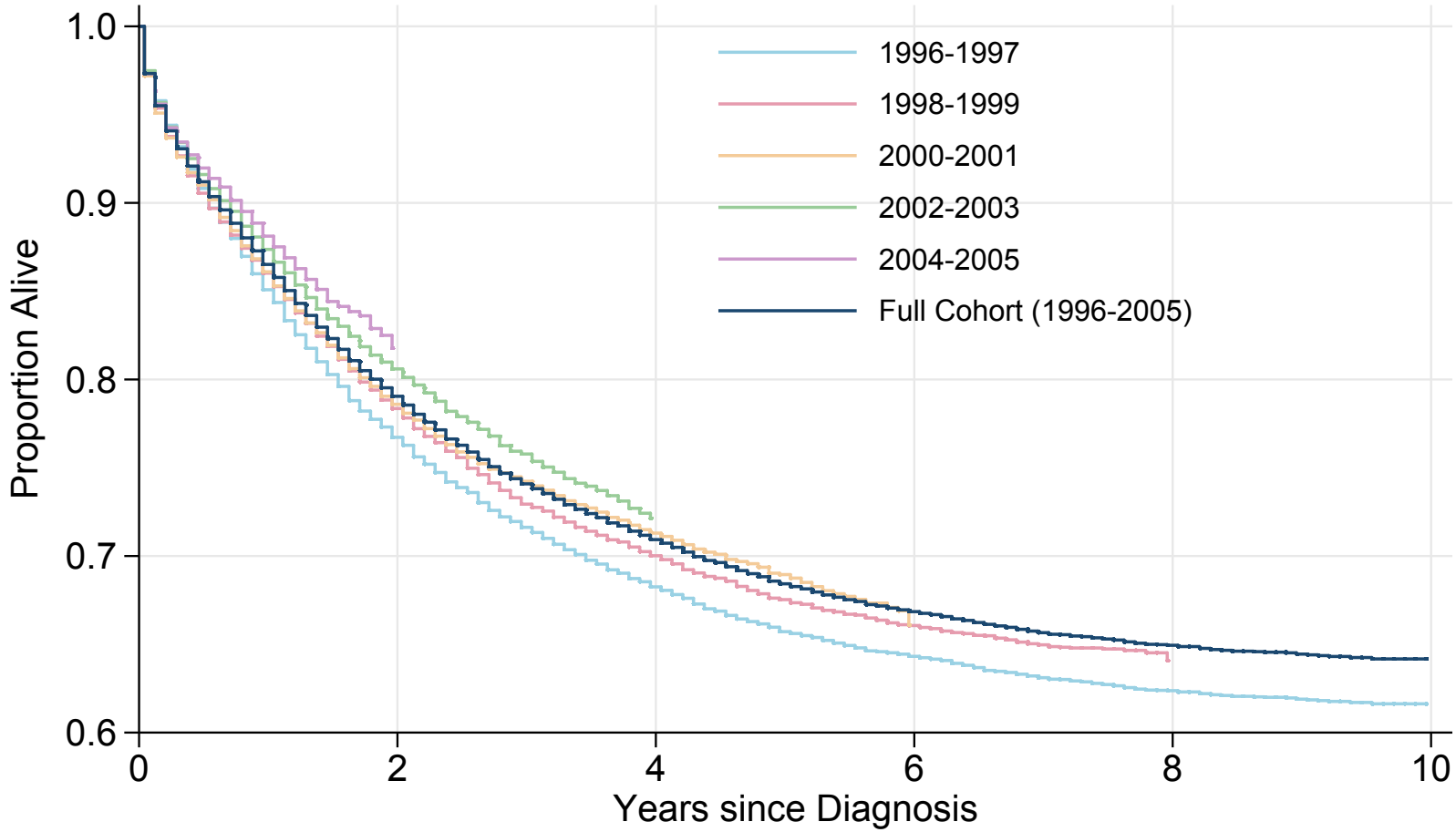
# Assessing Improvements in Survival



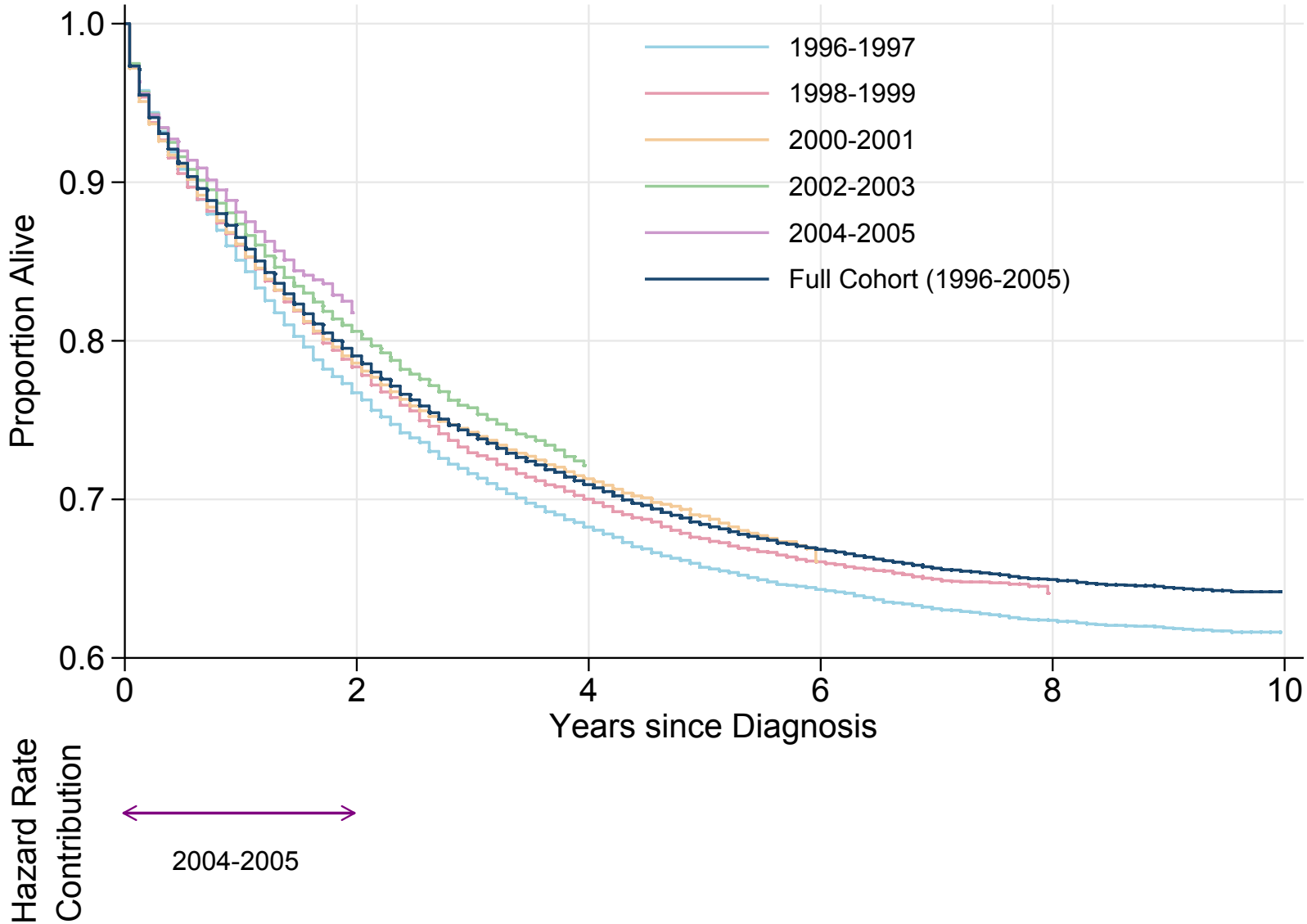
# Assessing Improvements in Survival



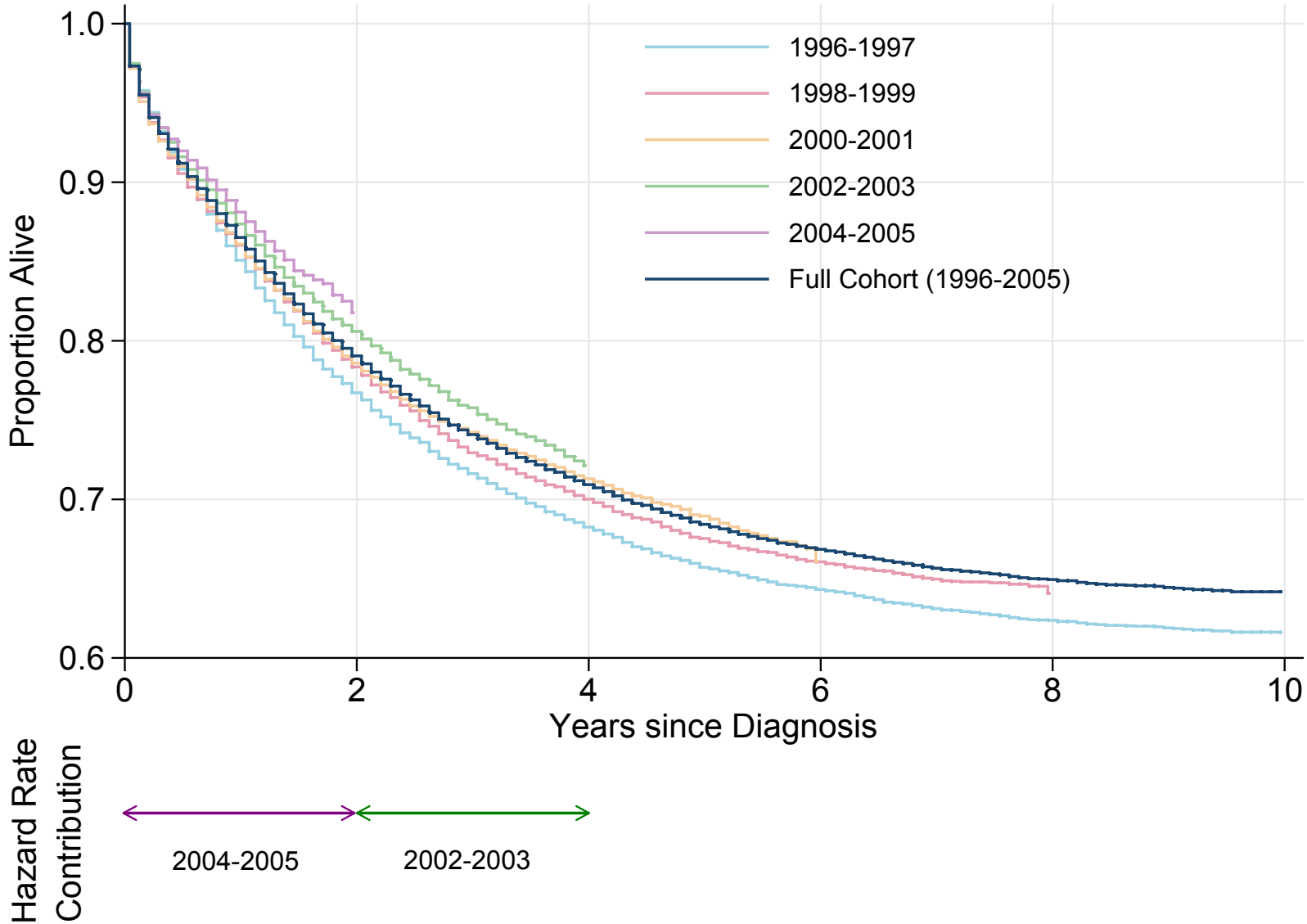
# Assessing Improvements in Survival



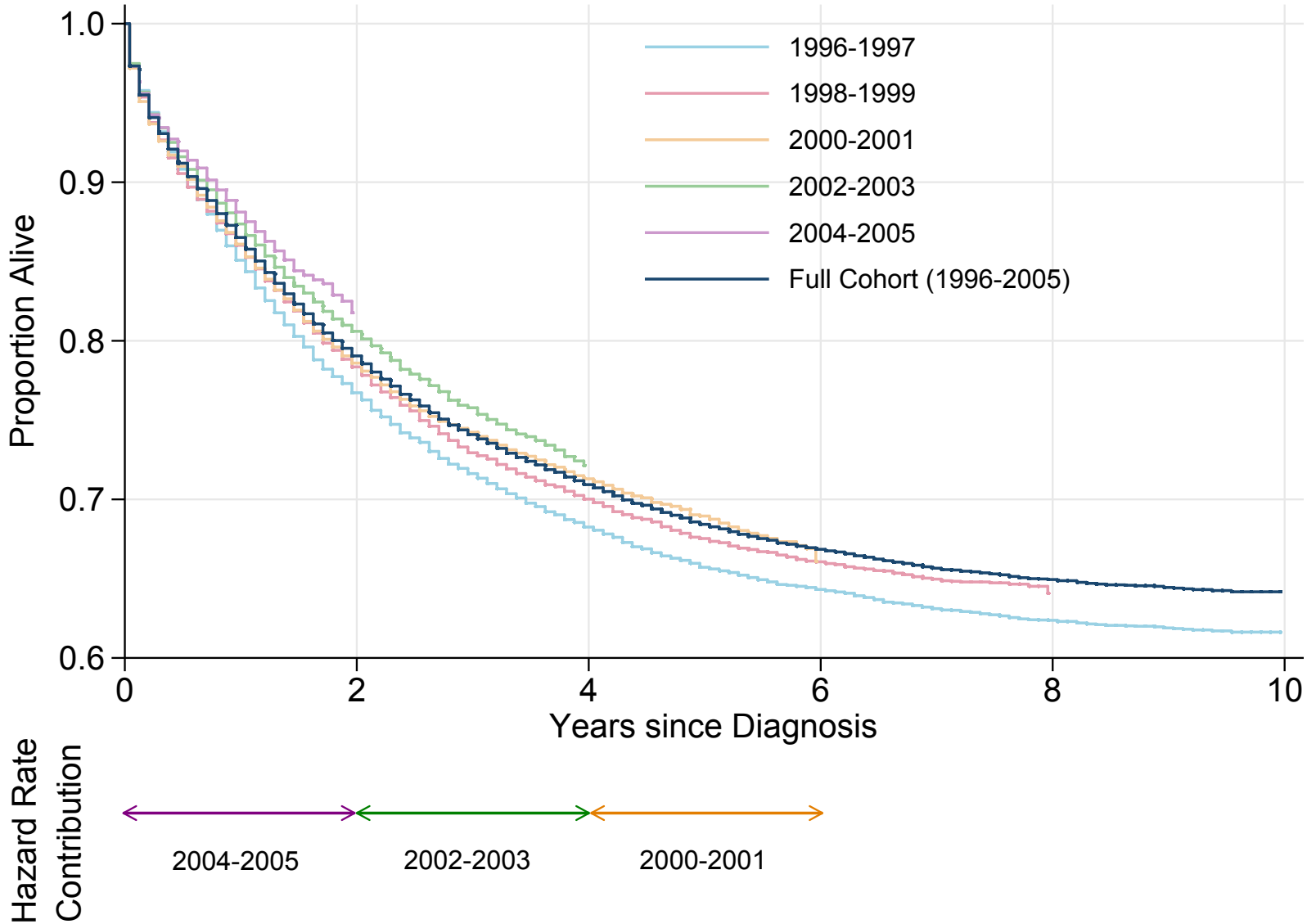
# Assessing Improvements in Survival



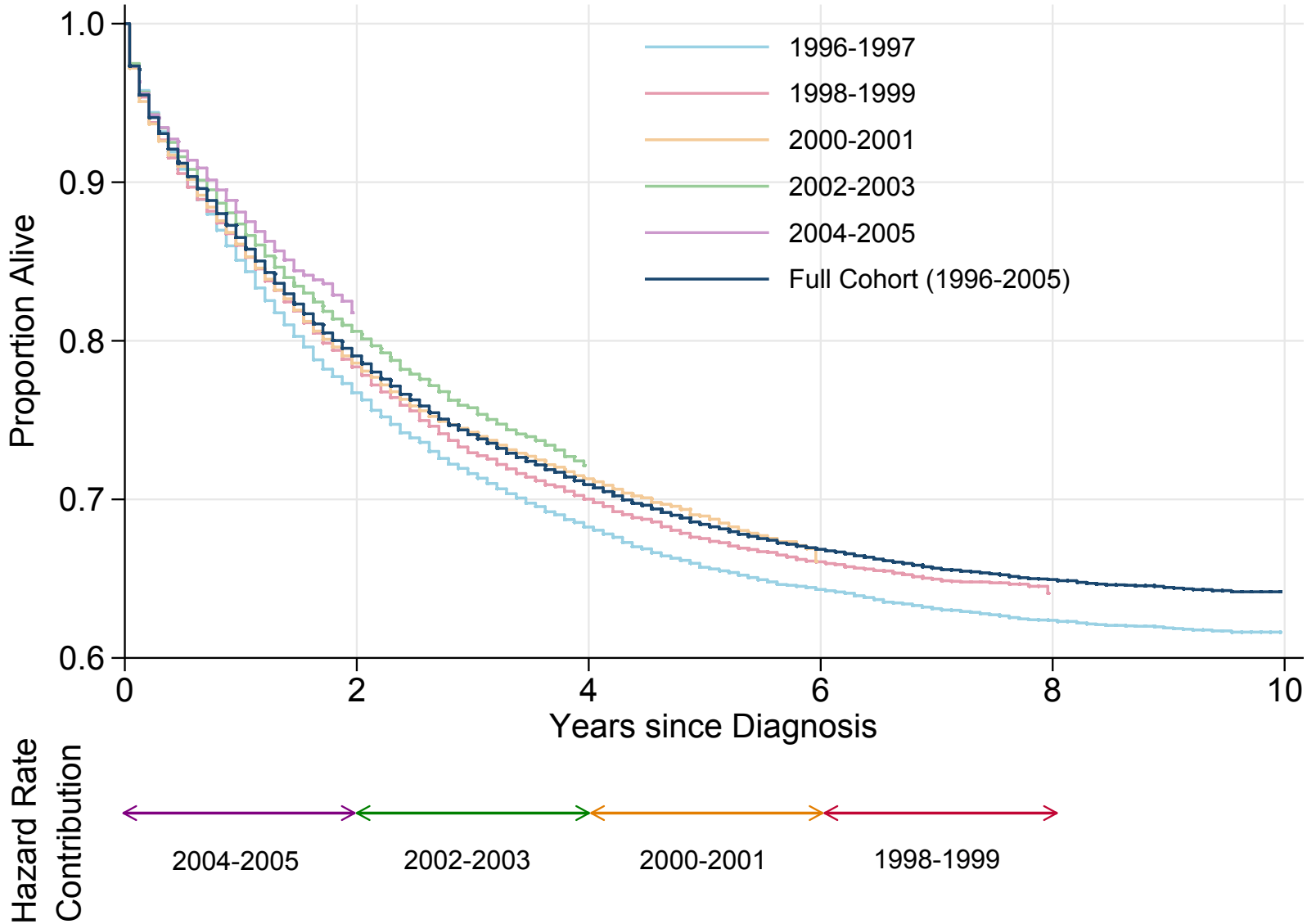
# Assessing Improvements in Survival



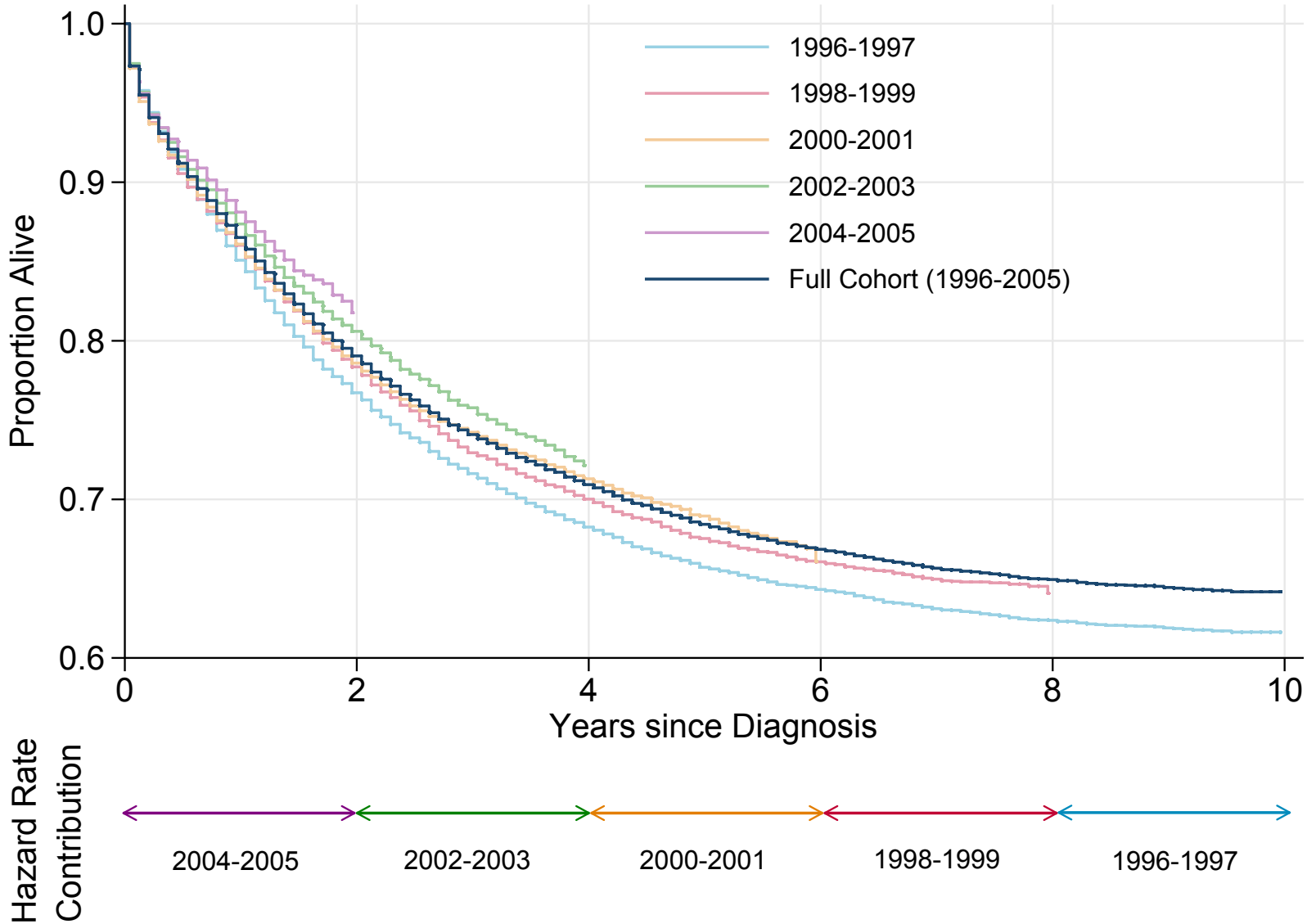
# Assessing Improvements in Survival



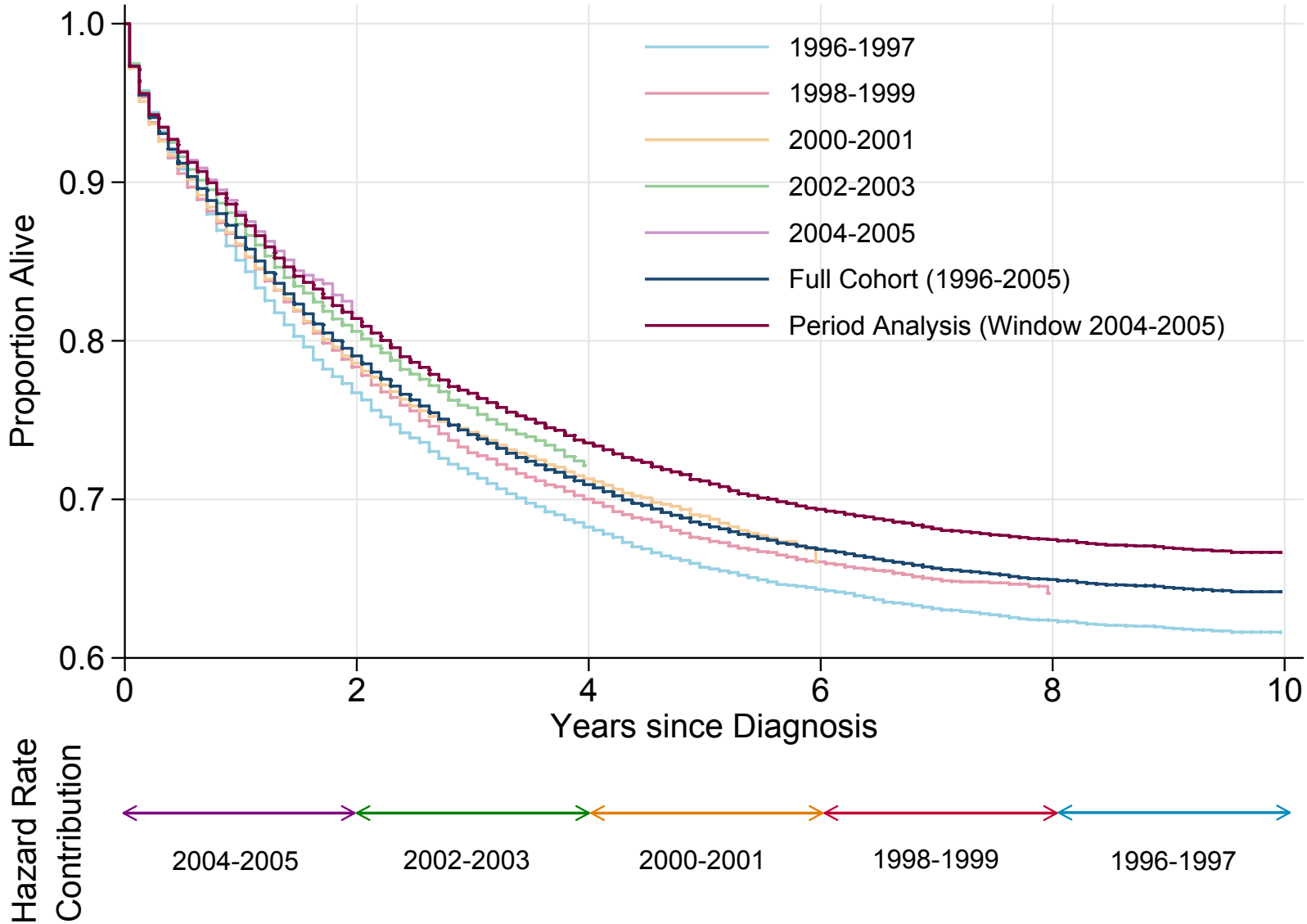
# Assessing Improvements in Survival



# Assessing Improvements in Survival



# Assessing Improvements in Survival



# Full Cohort Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

# Full Cohort Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

- Standard method used to develop prognostic models
- All 4 participants would be included

# Period Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

- Define a recent time window (2004-2005)

H. Brenner and O. Gefeller, "An alternative approach to monitoring cancer patient survival," Cancer, vol. 78, no. 9, pp. 2004–2010, 1996.

# Period Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

- Define a recent time window (2004-2005)
- Only include those who are alive at some point in the window

H. Brenner and O. Gefeller, "An alternative approach to monitoring cancer patient survival," Cancer, vol. 78, no. 9, pp. 2004–2010, 1996.

# Period Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

- Define a recent time window (2004-2005)
- Only include those who are alive at some point in the window
- Only analyse the risk-time and events within the window

H. Brenner and O. Gefeller, "An alternative approach to monitoring cancer patient survival," Cancer, vol. 78, no. 9, pp. 2004–2010, 1996.

# Period Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

## Advantages

- More up-to-date survival estimates, people diagnosed many years ago only contribute to long-term hazard rates

H. Brenner and O. Gefeller, "An alternative approach to monitoring cancer patient survival," Cancer, vol. 78, no. 9, pp. 2004–2010, 1996.

# Period Analysis

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

## Advantages

- More up-to-date survival estimates, people diagnosed many years ago only contribute to long-term hazard rates

## Disadvantages

- Reduces sample size and number of events
- Larger standard errors

H. Brenner and O. Gefeller, "An alternative approach to monitoring cancer patient survival," Cancer, vol. 78, no. 9, pp. 2004–2010, 1996.

# Temporal Recalibration

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

## Method

- Fit a full cohort model

# Temporal Recalibration

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

**Method**

- Fit a full cohort model
- Use a period analysis sample to recalibrate the model

# Temporal Recalibration

| Participant | Year of Diagnosis & Follow-Up | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| A | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| B | | 1 | 2 | 3 | 4 | 5 | | | | |
| C | | | | | | 1 | 2 | 3 | 4 | 5 |
| D | | | | | | | | | 1 | 2 |

## Method

- Fit a full cohort model
- Use a period analysis sample to recalibrate the model
- The predictor effects are constrained to be the same (i.e hazard ratios for age, sex, stage are the same)
- The baseline hazard function is allowed to vary which can capture any improvements in survival

# Summary of Methods

| Type of Analysis | Predictor Effects | Baseline |
|---|---|---|
| Full Cohort | All | All |
| Period Analysis | Recent | Recent |
| Temporal Recalibration | All | Recent |

# Models

| Type of Analysis | Year of Diagnosis & Follow-Up | | | | | Follow-Up Only |
|---|---|---|---|---|---|---|
| | 1996-2002 | 2003 | 2004 | 2005 | 2006 | 2007-2015 |
| Full Cohort | | | | | | |
| Temporal Recalibration | | | | | | |
| Period Analysis | | | | | | |
| Validation | | | | | | |

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission

# Models

| Type of Analysis | Year of Diagnosis & Follow-Up | | | | | Follow-Up Only |
|---|---|---|---|---|---|---|
| | 1996-2002 | 2003 | 2004 | 2005 | 2006 | 2007-2015 |
| Full Cohort | | | | | | |
| Temporal Recalibration | | | | | | |
| Period Analysis | | | | | | |
| Validation | | | | | | |

- US colon cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) Program

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission

# Models

| Type of Analysis | Year of Diagnosis & Follow-Up | | | | | Follow-Up Only |
|---|---|---|---|---|---|---|
| | 1996-2002 | 2003 | 2004 | 2005 | 2006 | 2007-2015 |
| Full Cohort | | | | | | |
| Temporal Recalibration | | | | | | |
| Period Analysis | | | | | | |
| Validation | | | | | | |

- US colon cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) Program
- Cause-specific survival models

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission

# Models

| Type of Analysis | Year of Diagnosis & Follow-Up | | | | | Follow-Up Only |
|---|---|---|---|---|---|---|
| | 1996-2002 | 2003 | 2004 | 2005 | 2006 | 2007-2015 |
| Full Cohort | | | | | | |
| Temporal Recalibration | | | | | | |
| Period Analysis | | | | | | |
| Validation | | | | | | |

- US colon cancer registry data from the Surveillance, Epidemiology, and End Results (SEER) Program
- Cause-specific survival models
- No variable selection: Age (modelled with splines), sex, race, stage and grade

---

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission

# Survival Models

## Cox Proportional Hazards Models

$$h(t; x_i) = h_0(t)e^{\beta x_i}$$

- Post-estimation of baseline using restricted cubic splines

D. R. Cox, "Regression models and life-tables," Journal of the Royal Statistical Society. Series B (Methodological), vol. 34, no. 2, pp. 187–220, 1972.

P. Royston and M. K. B. Parmar, "Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects," Statistics in Medicine, vol. 21, no. 15, pp. 2175–2197, 2002.

# Survival Models

## Cox Proportional Hazards Models

$$h(t; x_i) = h_0(t)e^{\beta x_i}$$

- Post-estimation of baseline using restricted cubic splines

## Flexible Parametric Survival Models

$$\ln[H(t|x_i)] = \gamma_0 + \gamma_1 z_{1i} + \gamma_2 z_{2i} + \gamma_3 z_{3i} + ... + \beta x_i$$

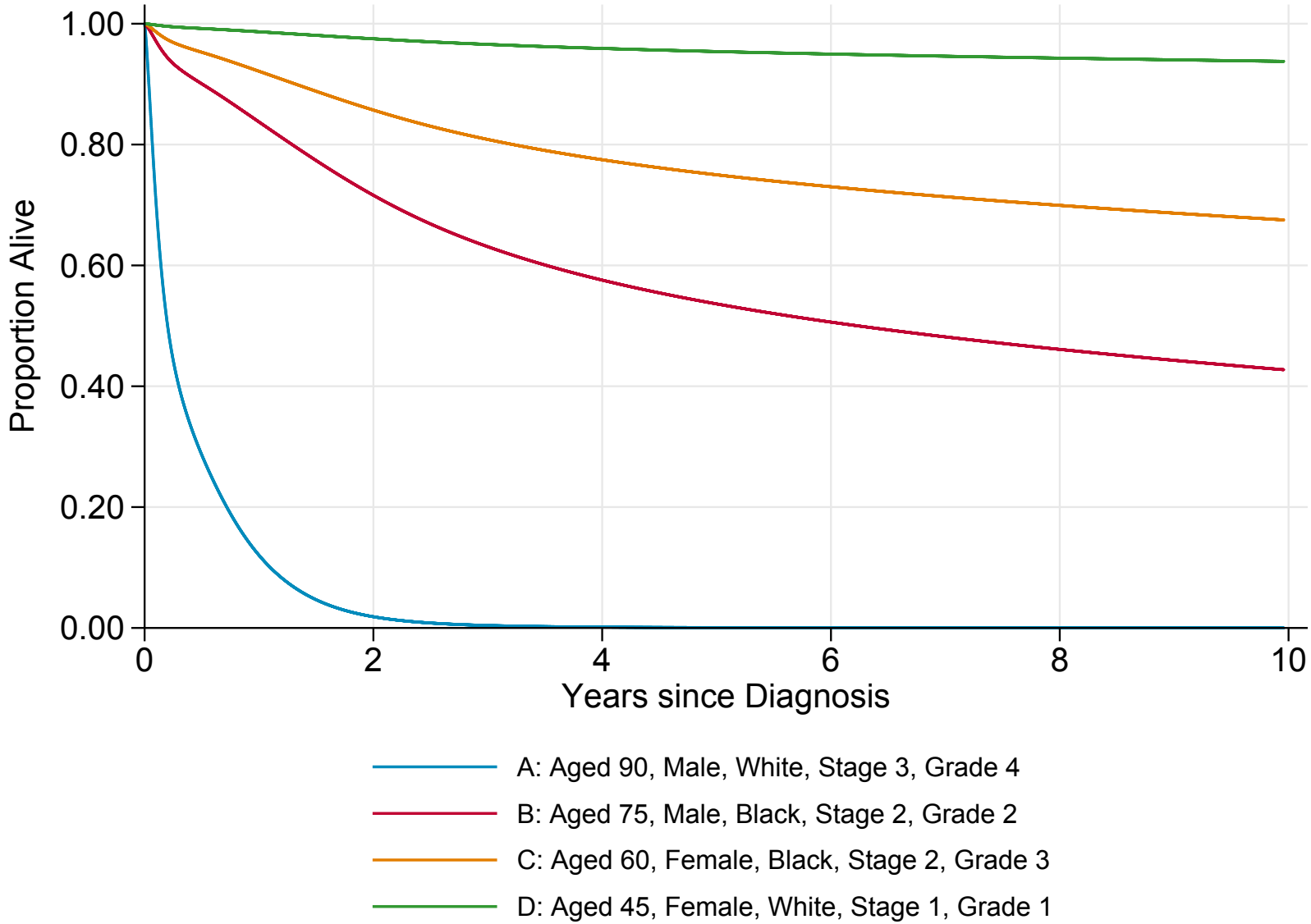
- $z_i$ = derived variables for the restricted cubic splines

---

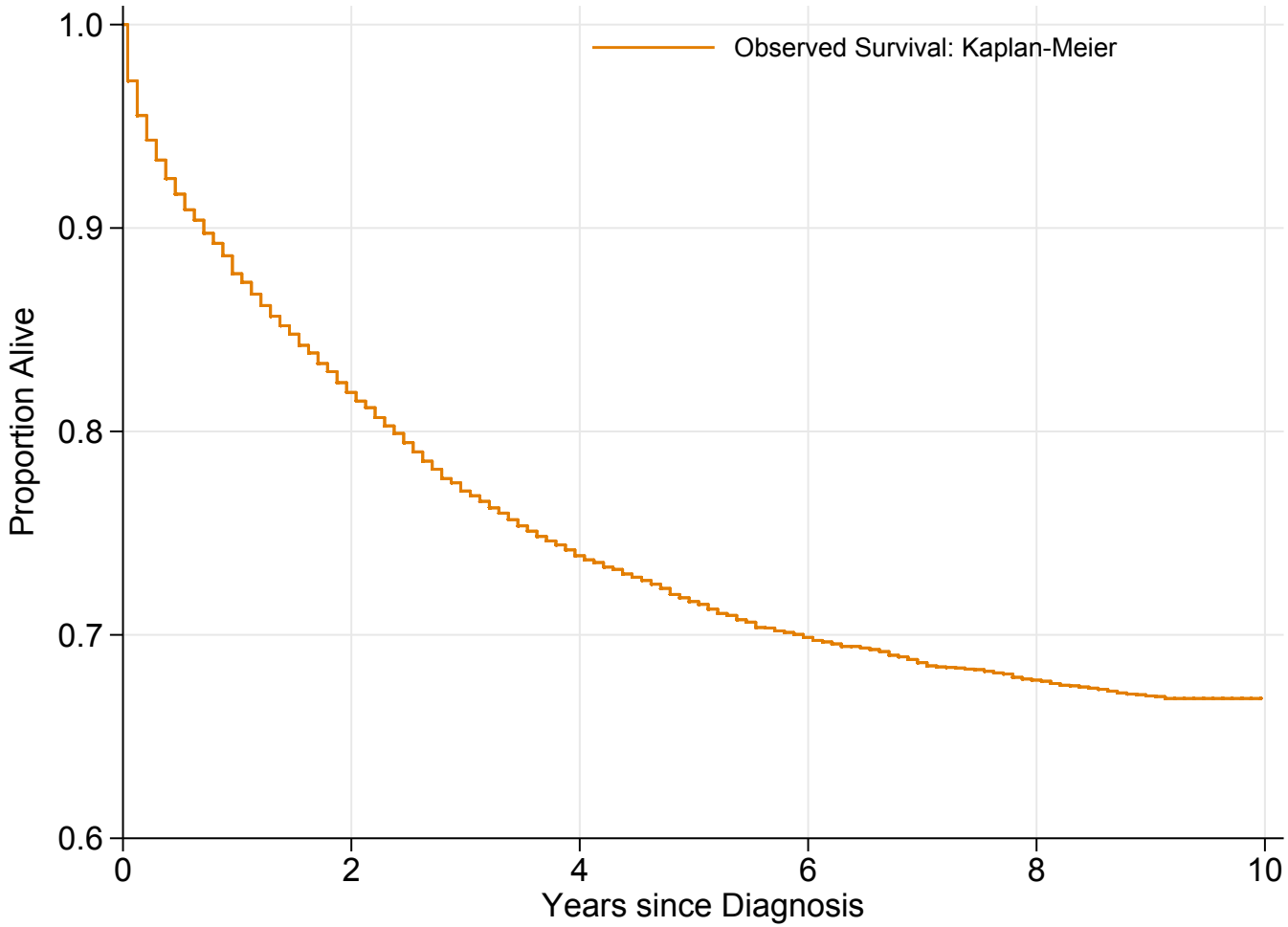
D. R. Cox, "Regression models and life-tables," Journal of the Royal Statistical Society. Series B (Methodological), vol. 34, no. 2, pp. 187–220, 1972.

P. Royston and M. K. B. Parmar, "Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects," Statistics in Medicine, vol. 21, no. 15, pp. 2175–2197, 2002.

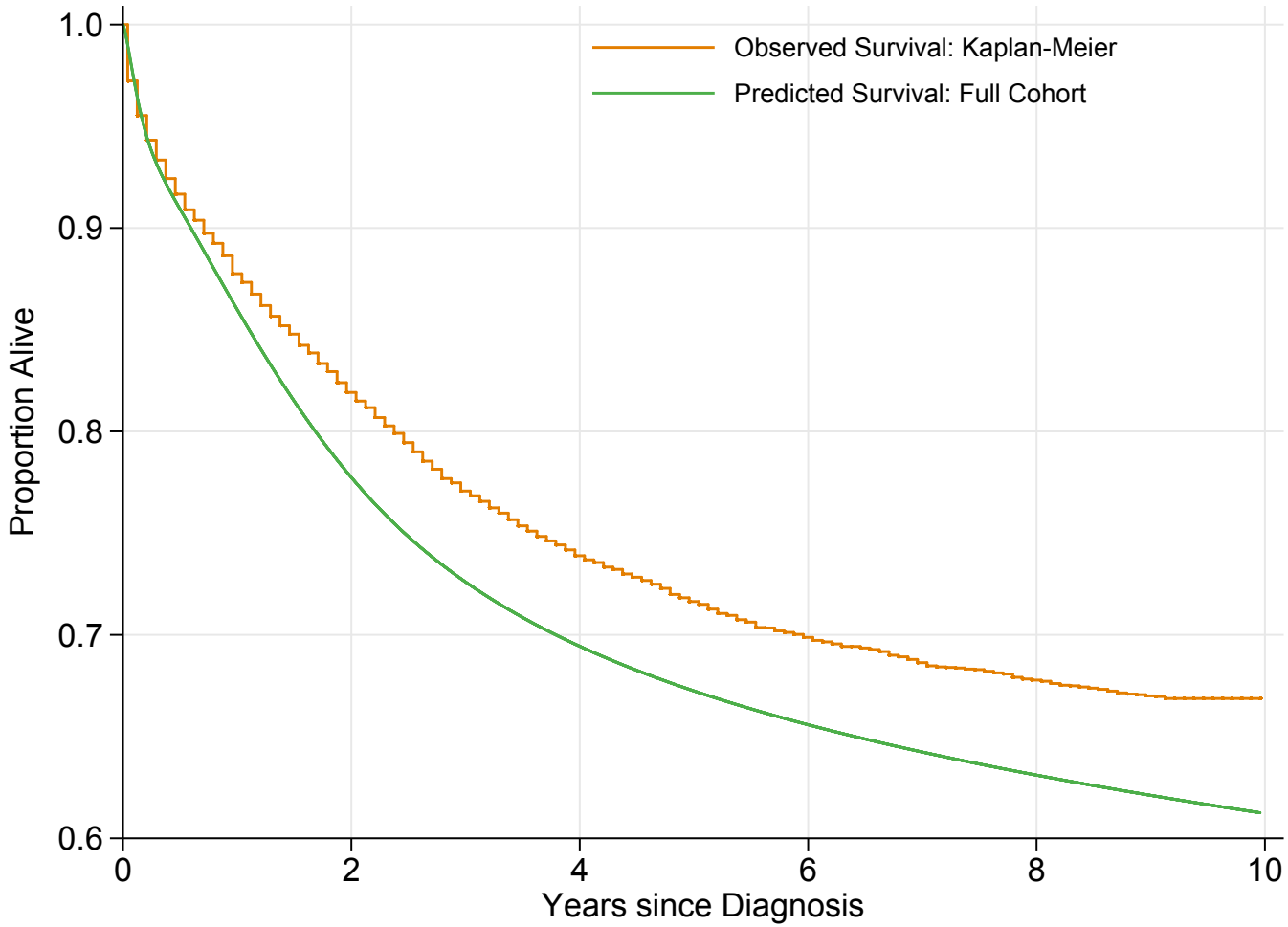
# Individual Survival Predictions



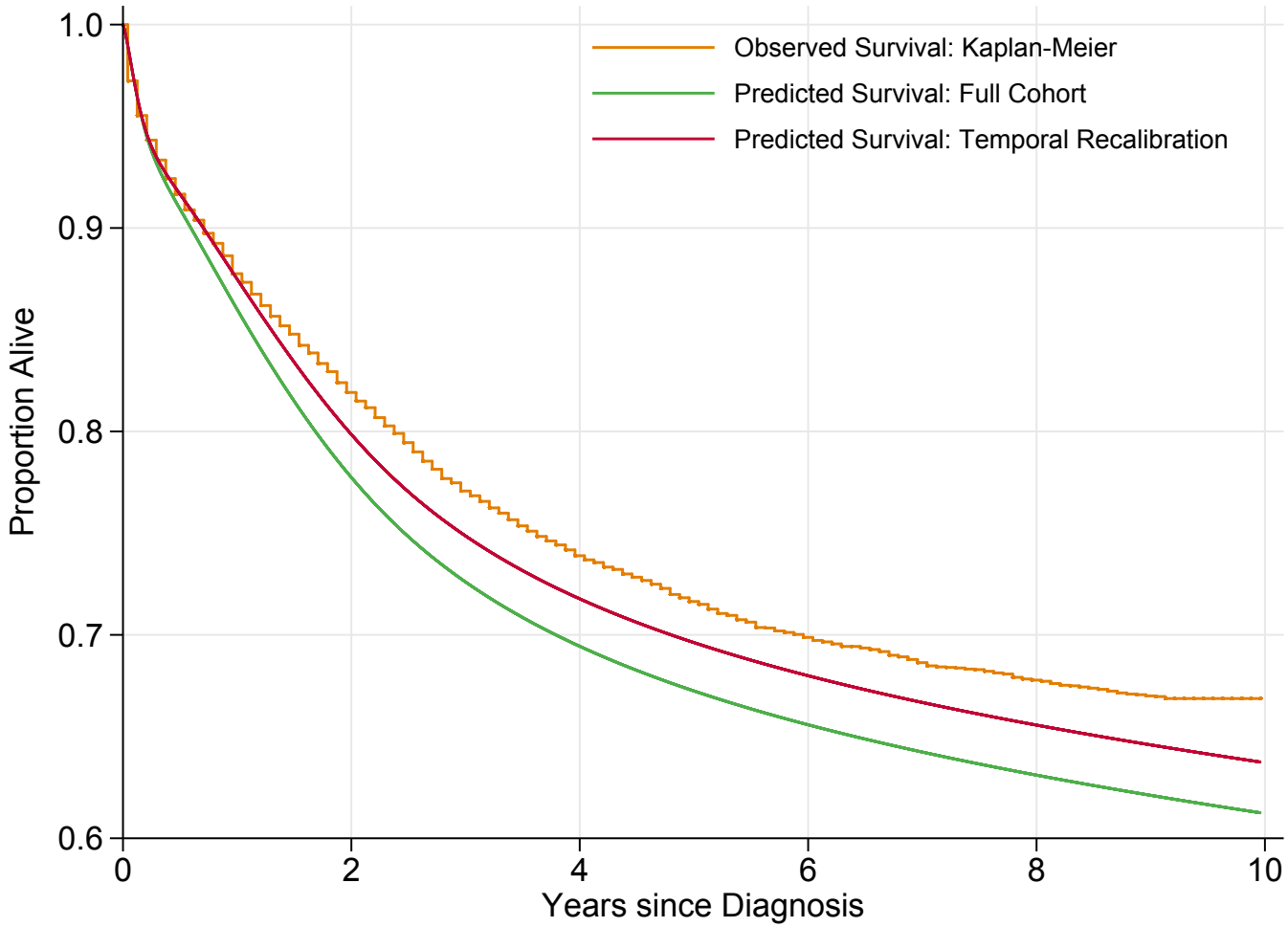
# Model Validation: Individuals diagnosed in 2006



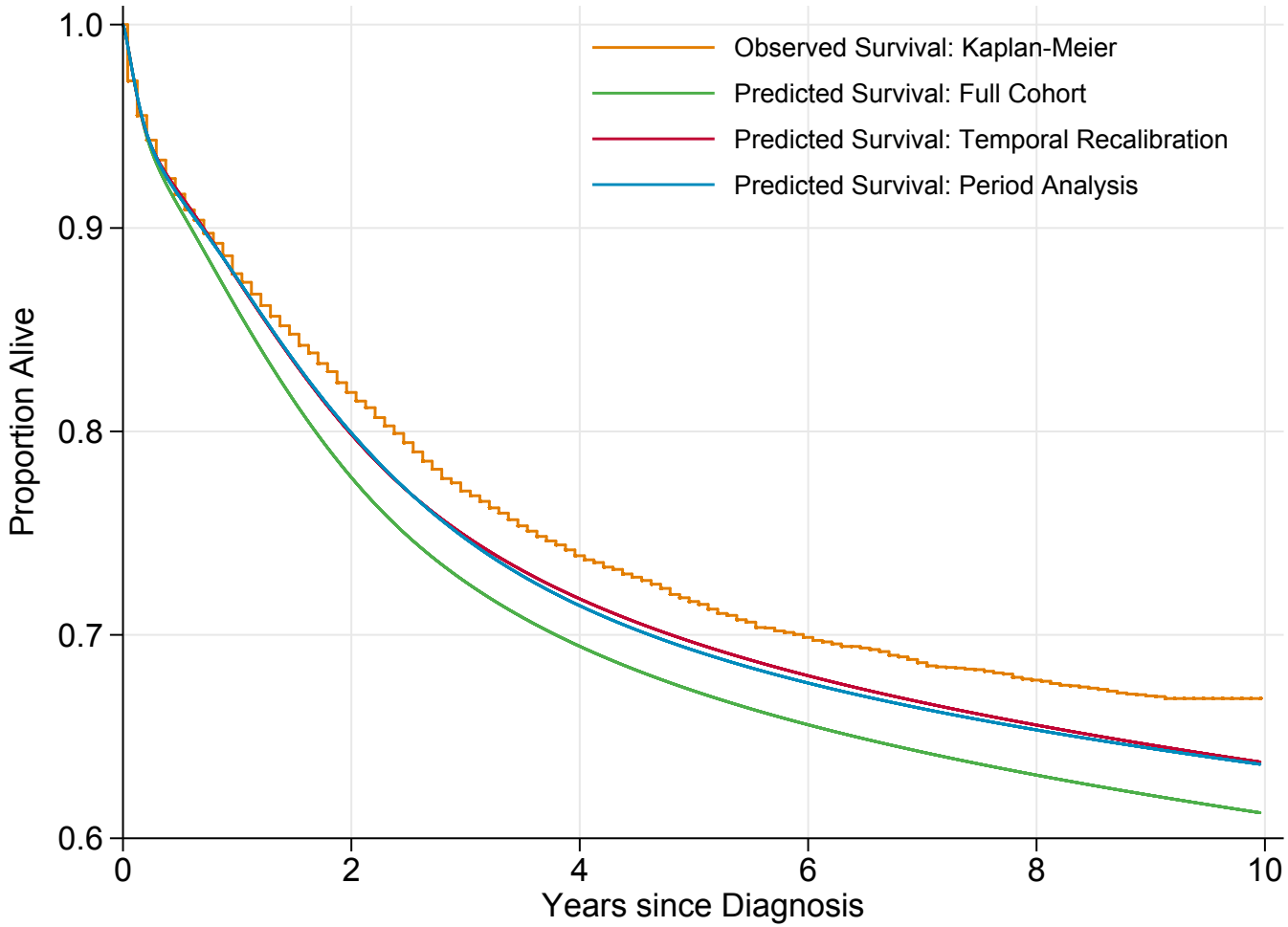
# Model Validation: Individuals diagnosed in 2006



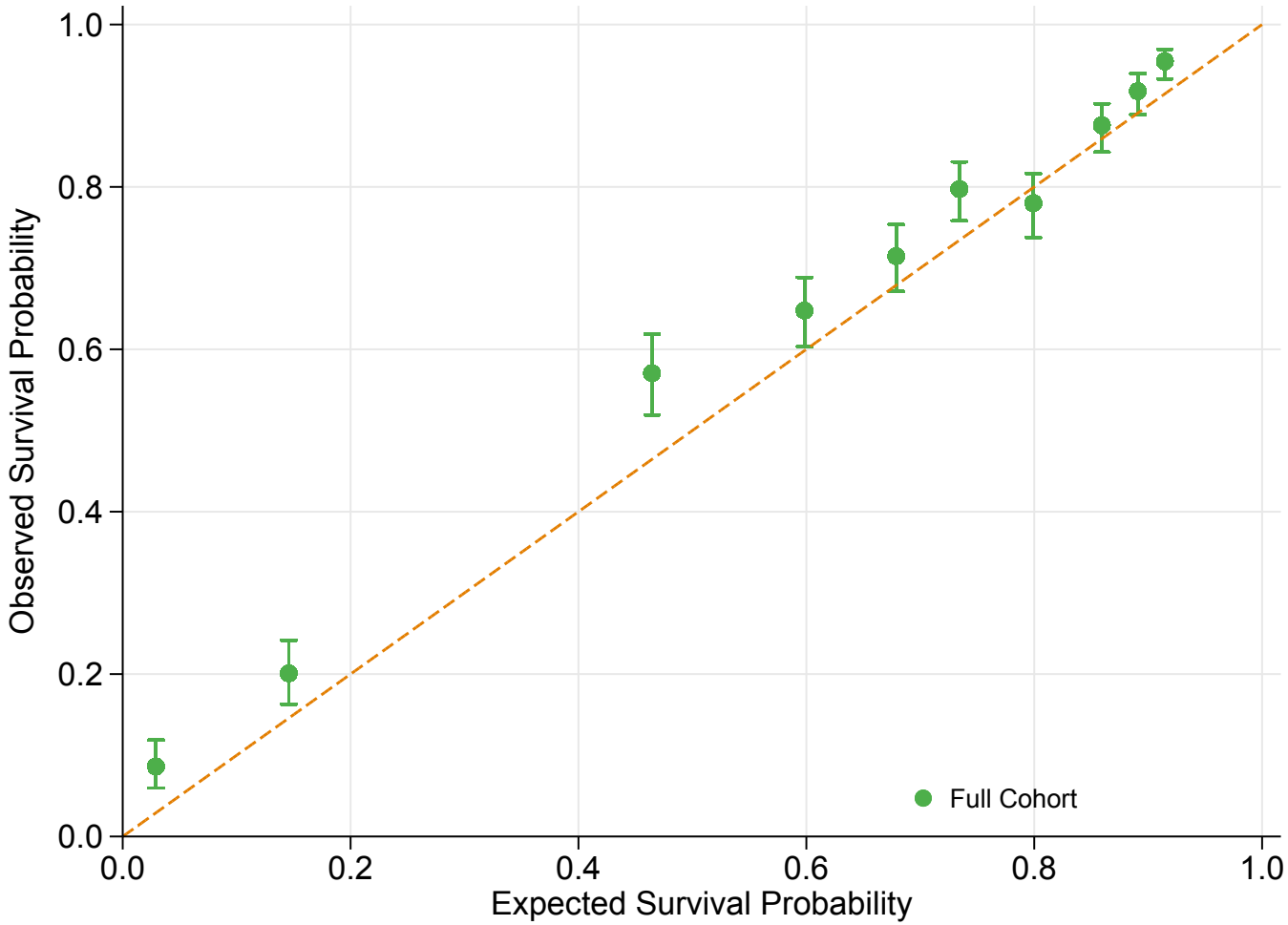
# Model Validation: Individuals diagnosed in 2006



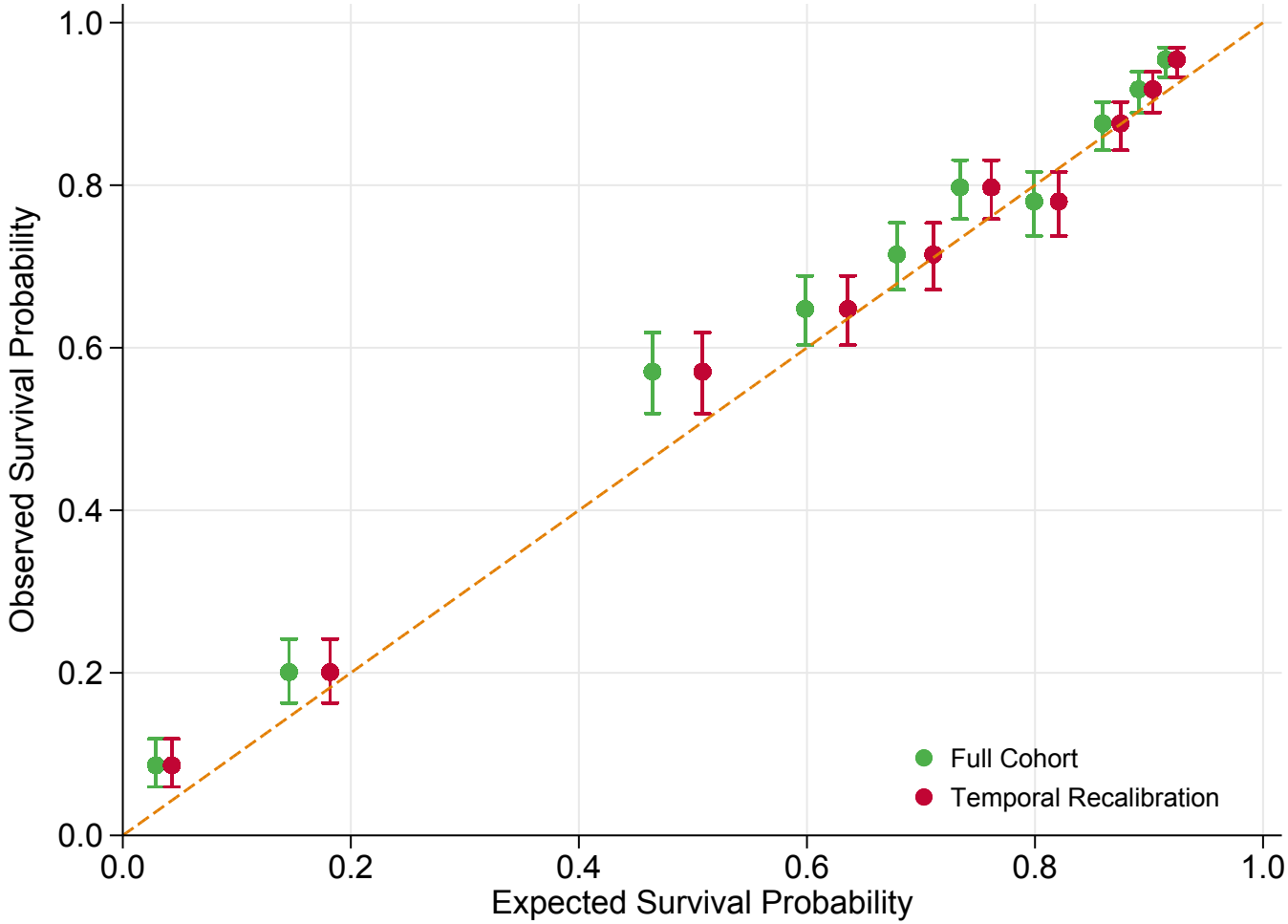
# Model Validation: Individuals diagnosed in 2006



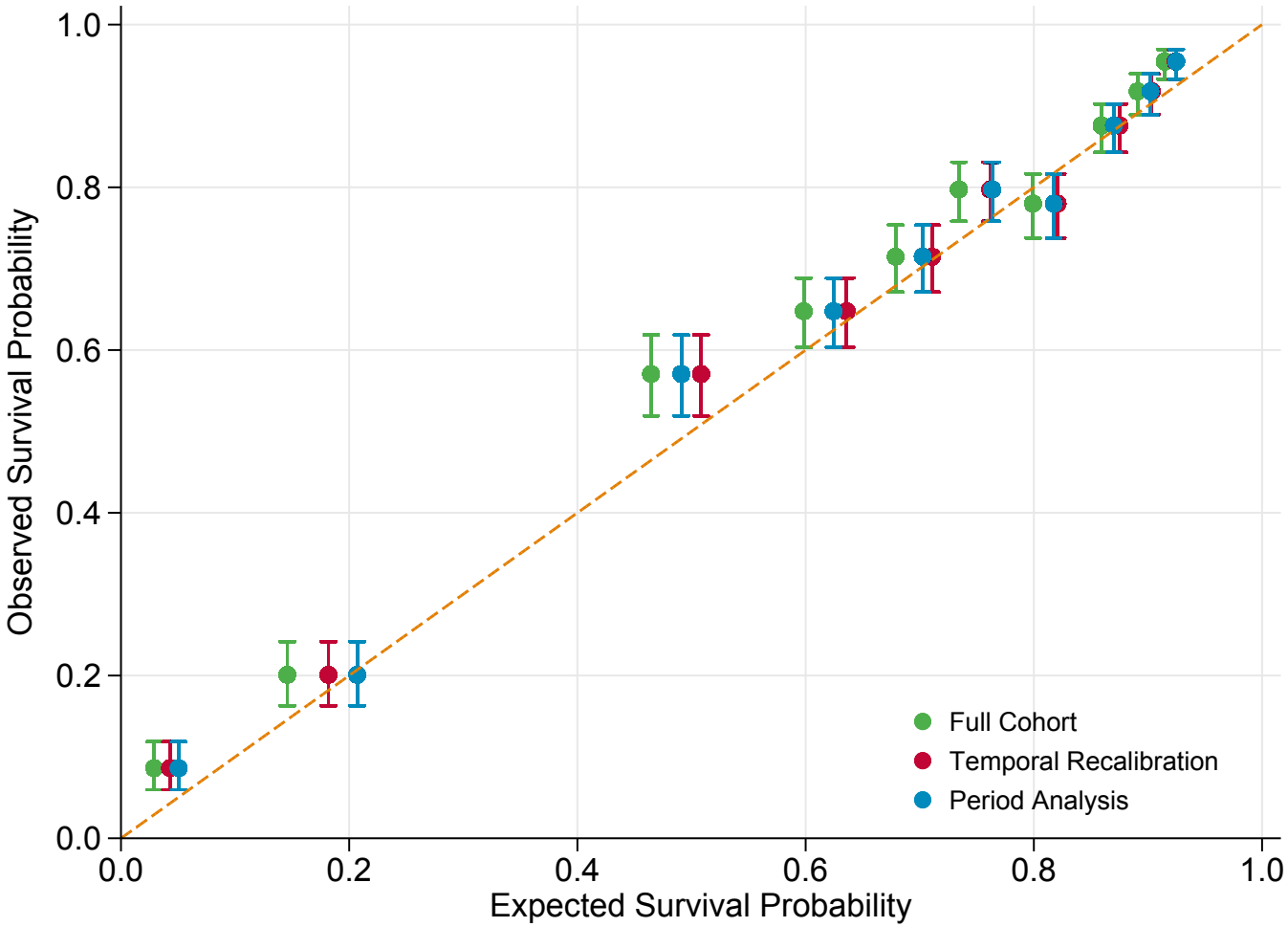
# Calibration of Models



# Calibration of Models



# Calibration of Models



# Period Analysis Window

| Type of Analysis | Sample Size | Number of Events |
|---|---|---|
| Full Cohort | 48,861 | 12,040 |
| 2 Year Window | 33,197 | 2,900 |
| 1 Year Window | 30,427 | 1,500 |
| 6 Month Window | 28,896 | 774 |
| 3 Month Window | 28,099 | 383 |

- Width of window could be determined using sample size criteria by Riley et al.

R. D. Riley et al. "Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes," Statistics in Medicine, 2018.

# Hazard Ratio

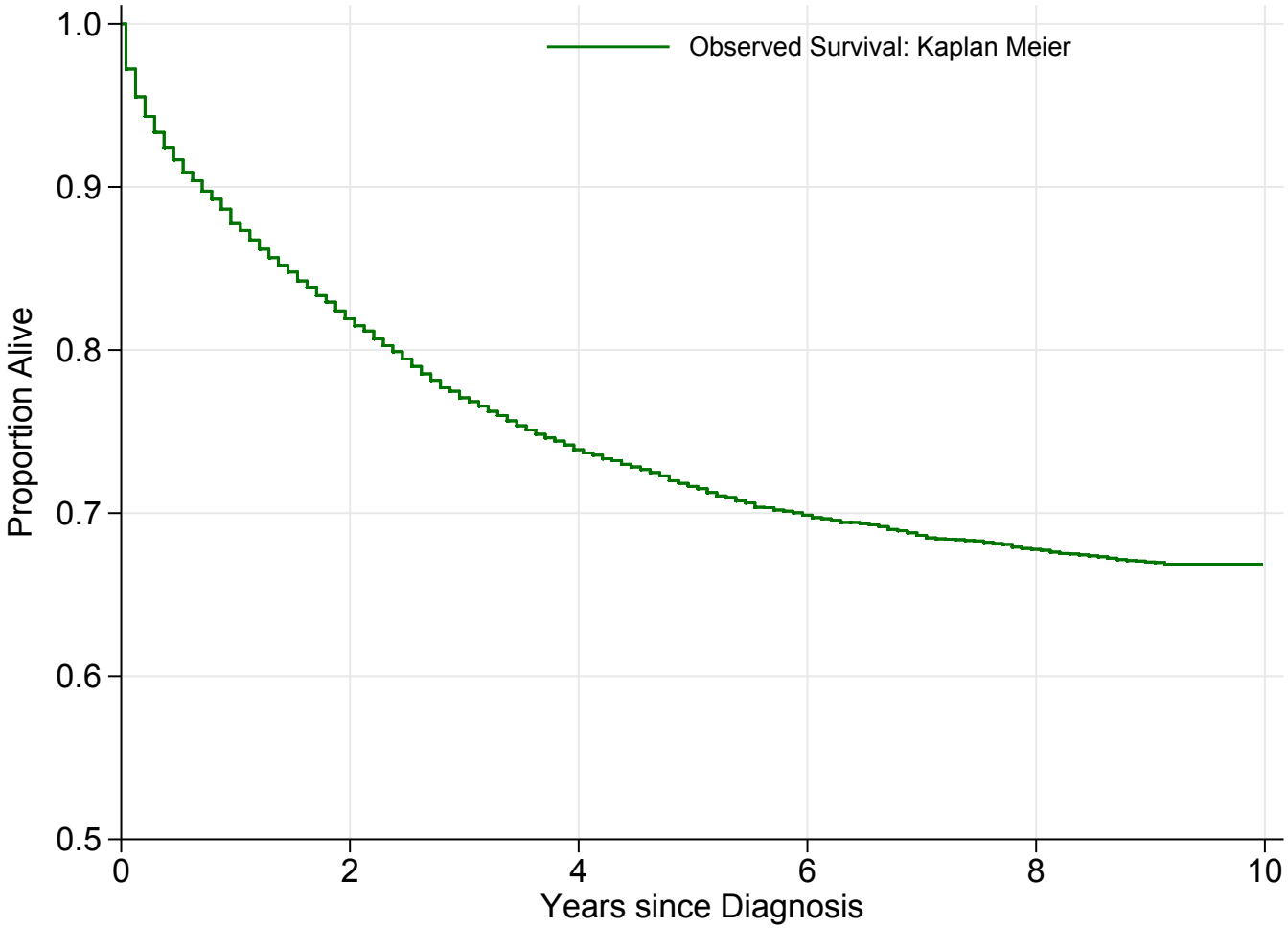
| Type of Analysis | log HR Female | Standard Error |
|---|---|---|
| Full Cohort | -0.05 | 0.018 |
| 2 Year Window | -0.10 | 0.038 |
| 1 Year Window | -0.13 | 0.053 |
| 6 Month Window | -0.07 | 0.073 |
| 3 Month Window | -0.06 | 0.104 |

# Updating Prognostic Models

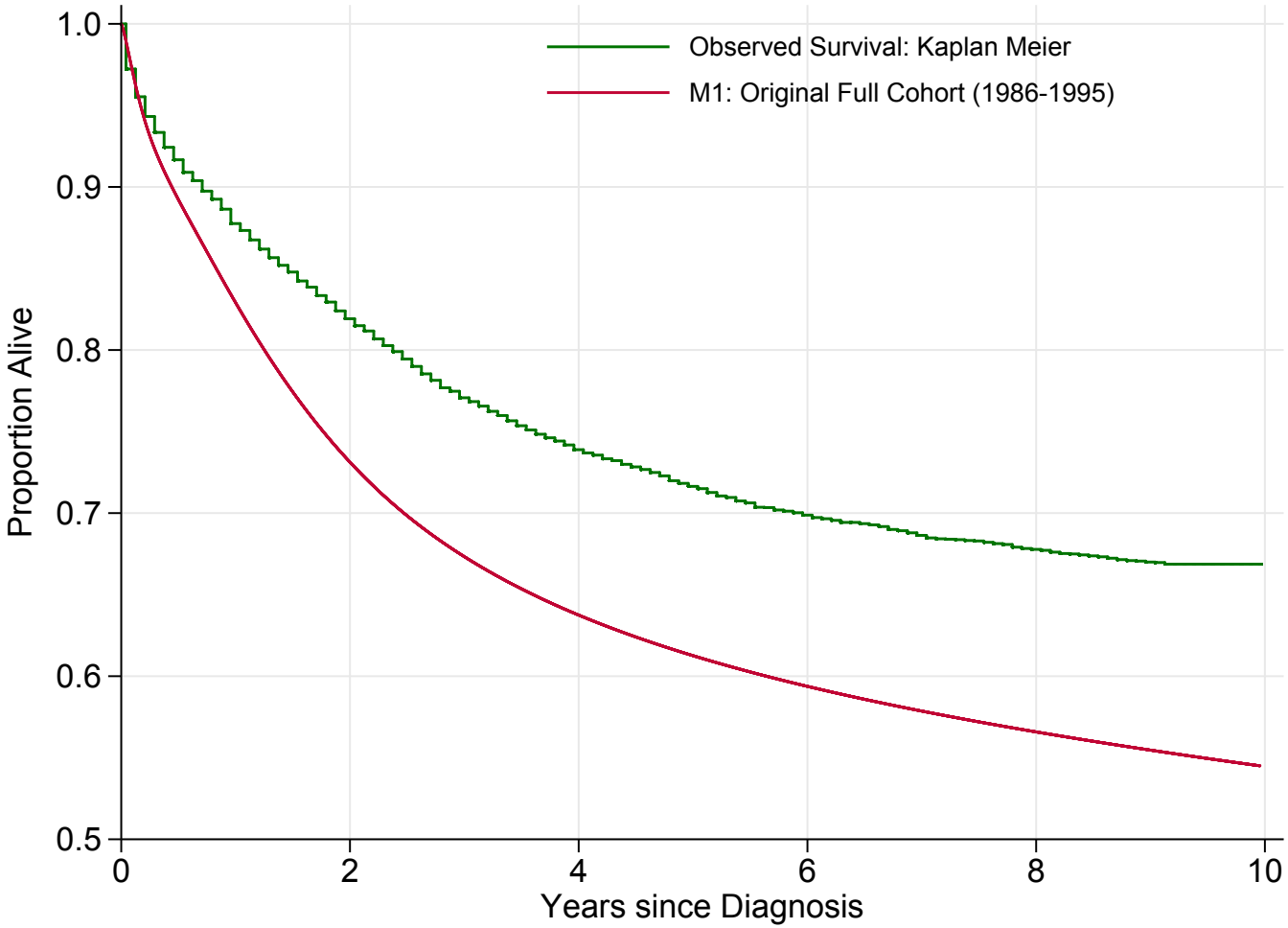
| | Year of Diagnosis & Follow-Up | | | Follow-Up Only |
|---|---|---|---|---|
| | 1986-1995 | 1996-2005 | 2006 | 2007-2015 |
| Development | | | | |
| Updating | | | | |
| Validation | | | | |

- M1: Original full cohort model (1986-1995)
- M2: Full cohort model with all available data (1986-2005)
- M3: Full cohort model with most recent data (1996-2005)
- M4: Temporal recalibration of M1 (period window 2004-2005)
- M5: Temporal recalibration of M3 (period window 2004-2005)

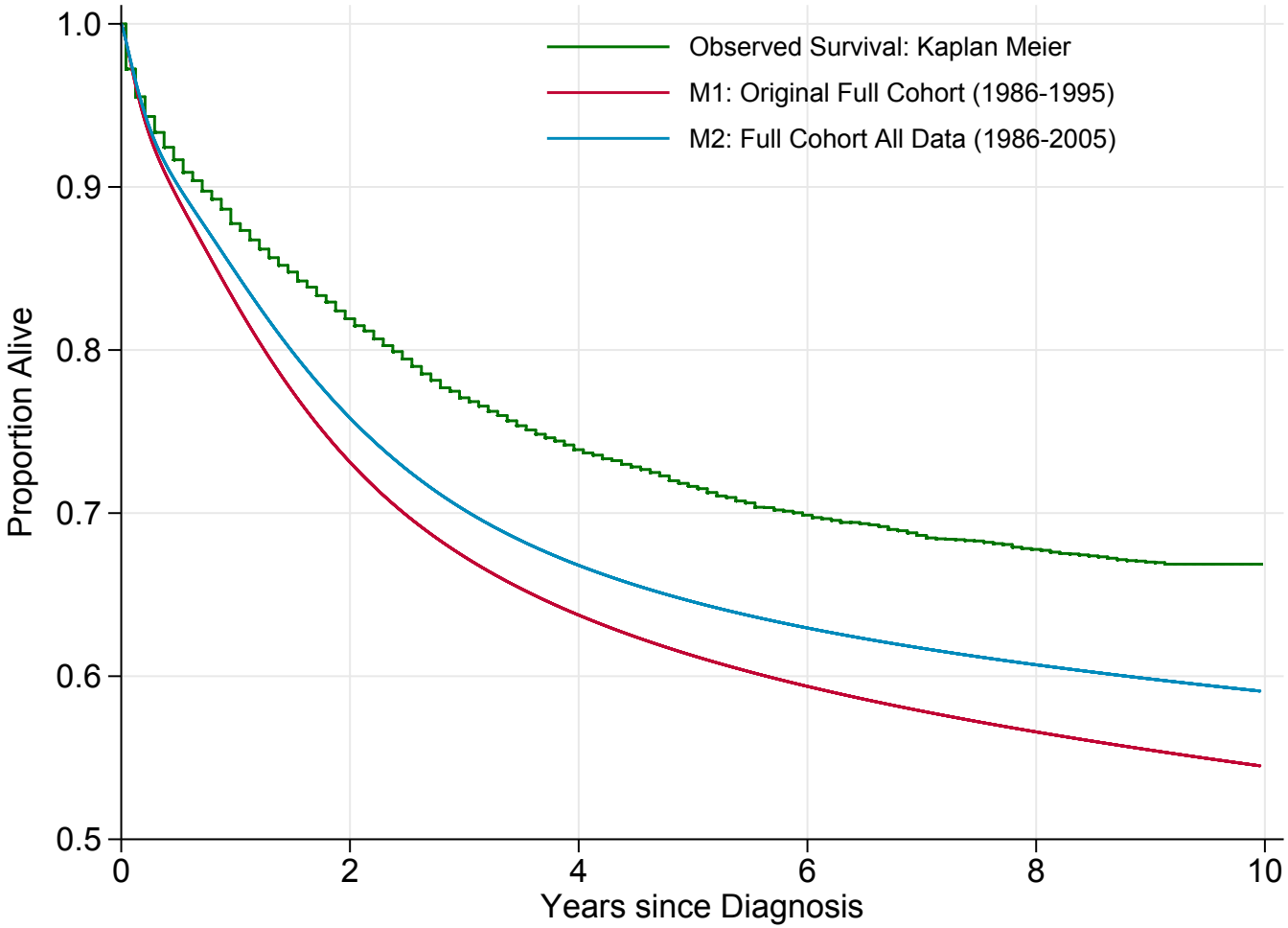
# Observed Survival: Individuals diagnosed in 2006



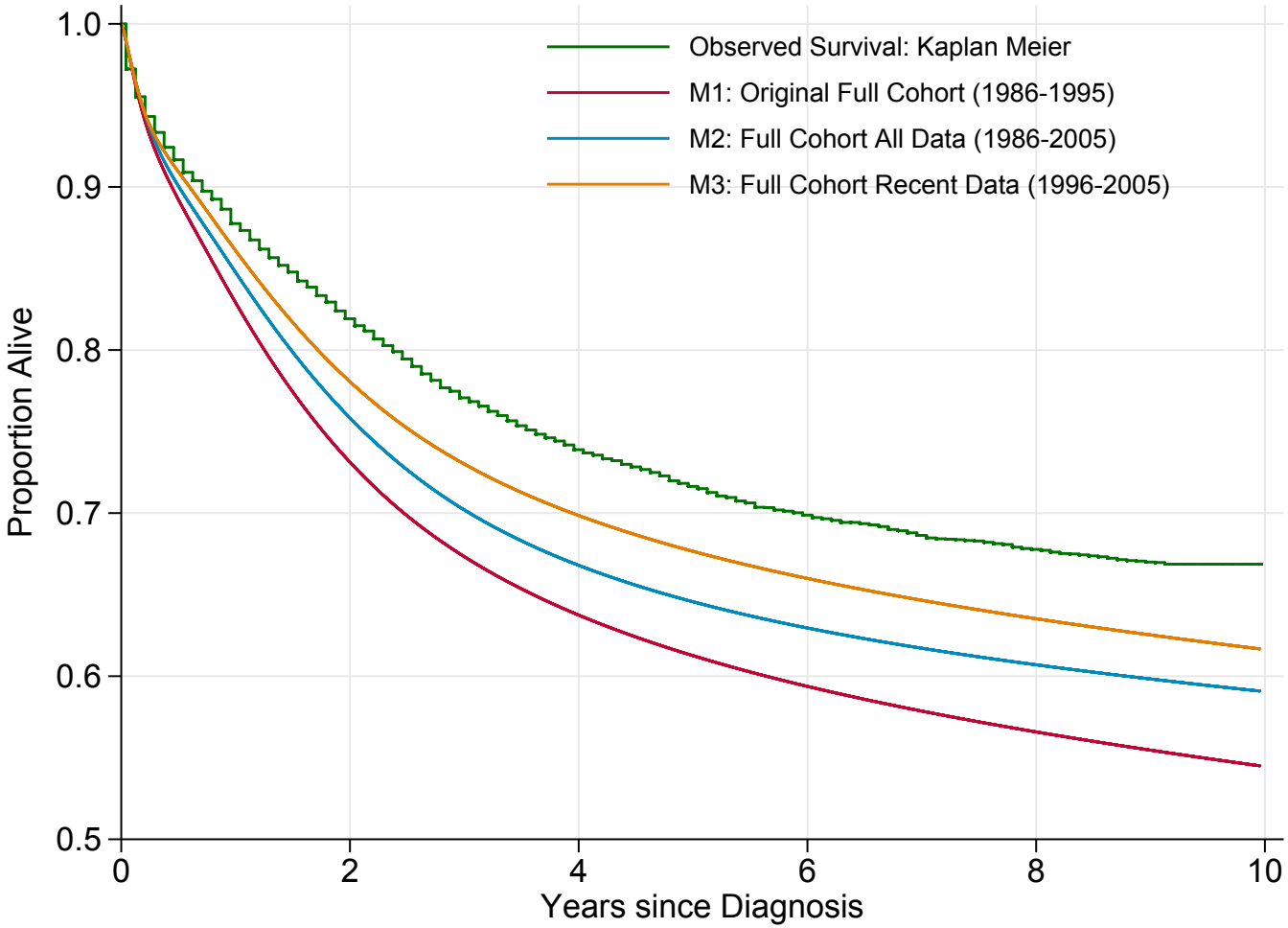
# M1: Original full cohort model (1986-1995)



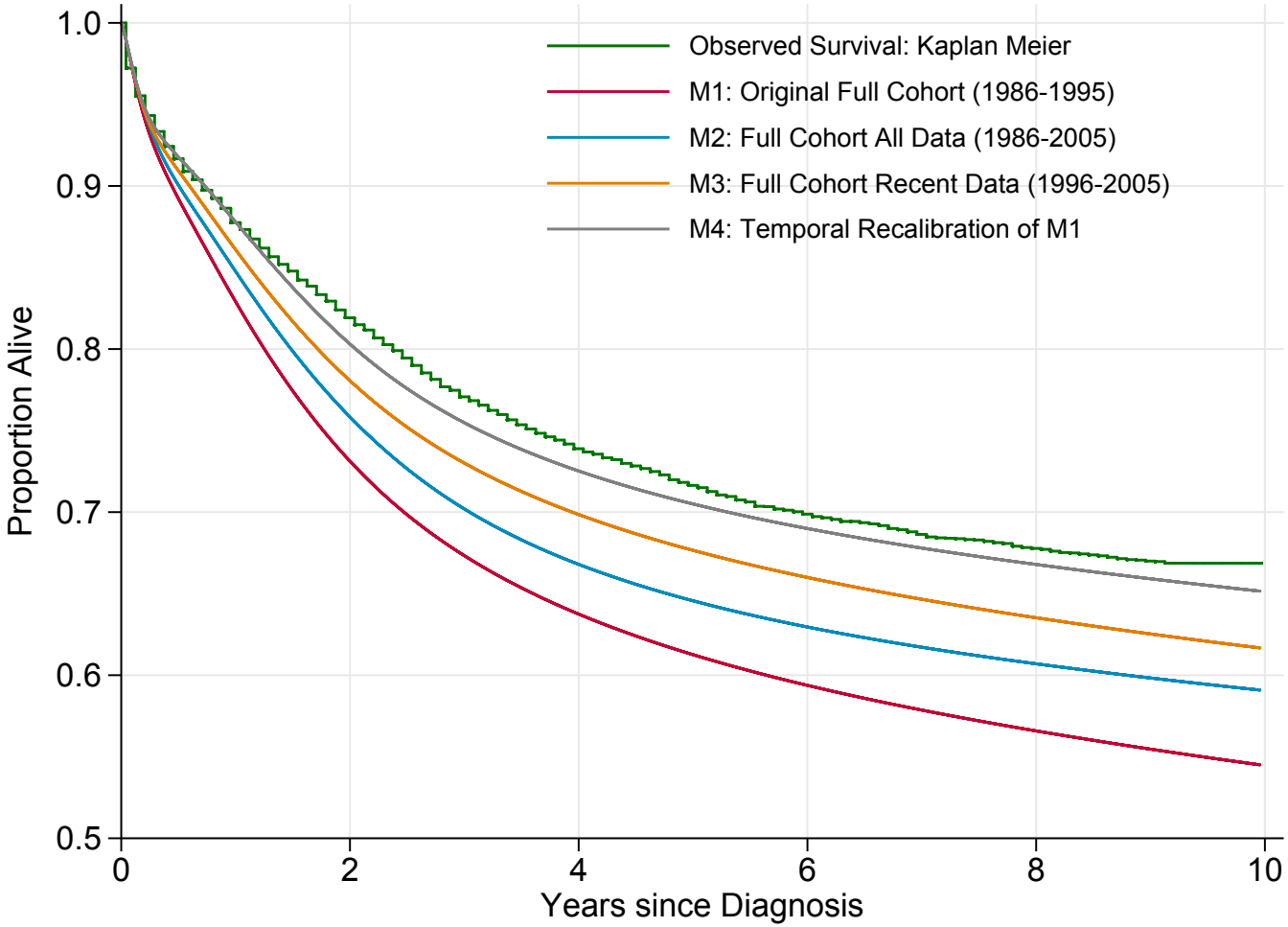
# M2: Full cohort model with all available data (1986-2005)



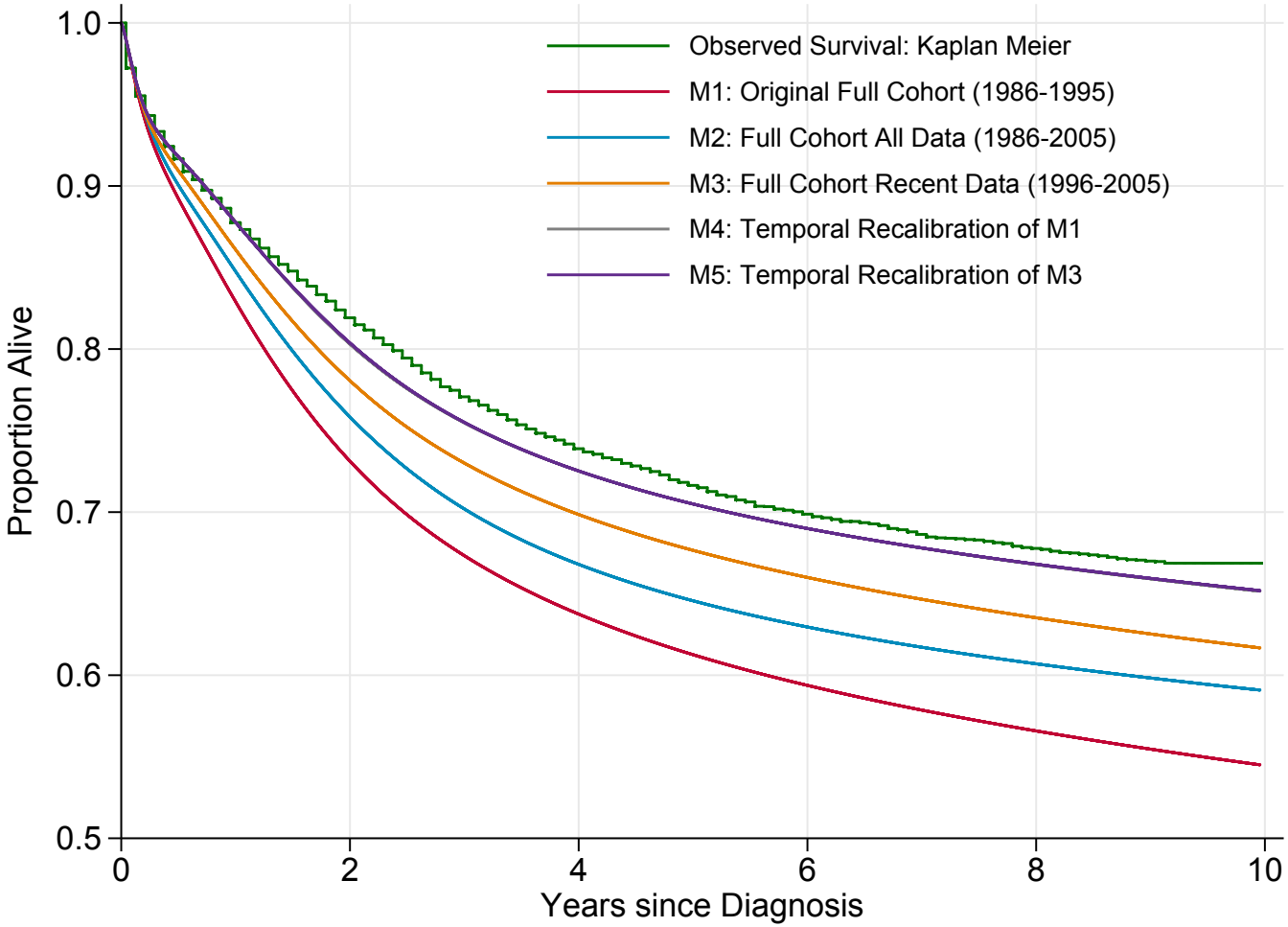
# M3: Full cohort model with most recent data (1996-2005)



# M4: Temporal recalibration of M1



# M5: Temporal recalibration of M3



# Summary

- Full cohort models often underestimate survival if there have been recent improvements in survival
- Period analysis uses a subset of data to create more up-to-date survival predictions
- Temporal recalibration also produces more up-to-date survival predictions but all the data is used to estimate the predictor effects

# Discussion: Modelling calendar time (year of diagnosis)

**Functional form**

- Linear, categorical, restricted cubic splines
- Incorporate month of diagnosis for a smoother function
- Time dependent effects
- Interactions between predictor effects and year of diagnosis

**Survival predictions** e.g. new patient diagnosed in 2007 and the model is fitted using data from 1996-2005

- Use the most recent year (2005) included in the model
- Extrapolate the trend to 2007
- Update the prognostic model every year