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Self-Controlled Case Series

Theory and a Stata command -sccsdta-

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Study designs

	With and without exposure	With and without outcome
Compare people	Cohort study	Case-control study
Compare periods	Self-Controlled Case study	Case-crossover study

Table 1 in Iwagami and Takeuchi (2021)

- Time-varying exposure -> an outcome event
  - E.g., meningitis after vaccination
- The eligibles have both exposure and event
- See Whitaker et al. (2006) and Petersen, Douglas, and Whitaker (2016) for an introduction
- Also see Farrington, Whitaker, and Weldeselassie (2018)

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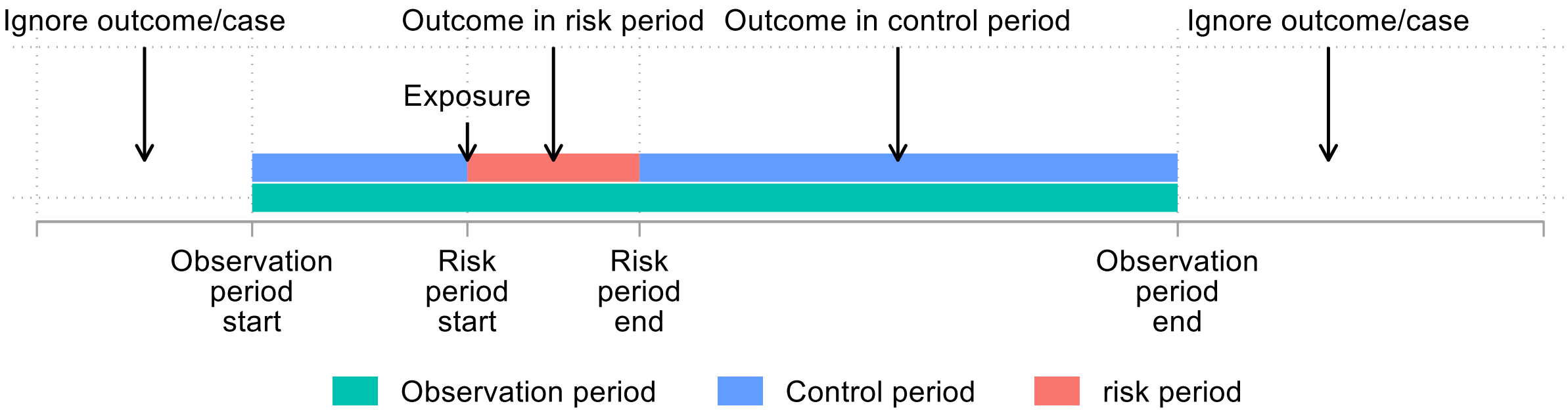
Observation, control, and risk periods



For each case

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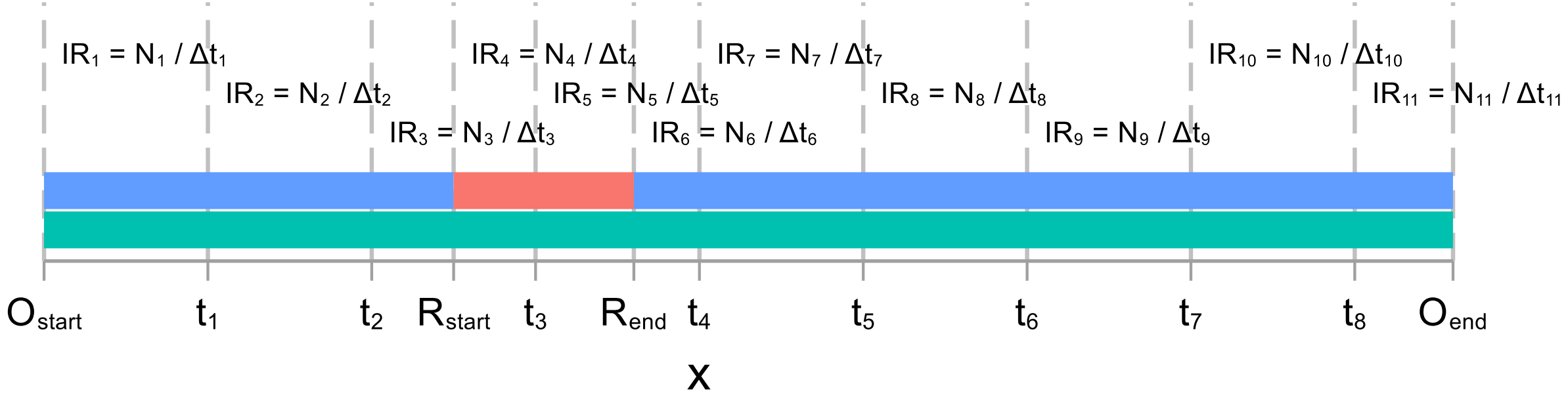
Adding time effects during the observation period



Observation period Control period risk period

A set of sub intervals from a non-homogeneous Poisson process for each case

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The Model

- Three multiplicative elements (independence):

$$case \times time \times risk$$

- Self-controlled by fixed-effect regression (**eliminate the *case* element**)
  - using -xtpoisson-
  - or Poisson Pseudo-Likelihood regression with High-Dimensional Fixed Effects (PPMLHDFE)
- All cases has the same time effects during the observation period
- All cases the same risk effects during the observation period
- Estimates are:
  - relative incidence rates
  - adjusted for time

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Comparison to other designs

In 1998, three studies investigated whether the MMR vaccine may cause autism.

Study	Sample size	IRR	(95% CI)
Cohort	537303 children, 316 cases	0.92	(0.68, 1.24)
Case–control	1294 cases, 4469 controls	0.86	(0.68, 1.09)
Self-Controlled Case Series	357 cases	0.88	(0.40, 1.95)

Table 6 in Farrington and Whitaker (2006).

- **Few observations**
- estimates similar to Cohort and Case-control
- confidence interval wider (possibly due to a long post period)
- **No problem with unknown or known confounders**

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Violation of assumptions, impact, and solutions

- Event temporarily changes probability of exposure
  - Include a pre-exposure period (See sensitivity)
- No exposure after event
  - Begin observation period at exposure
  - For single or multiple exposures, see Farrington, Whitaker, and Hocine (2009)
- Events increases P(death)
  - Sensitivity excluding cases with deaths due to event
  - adjust for bias, Farrington et al. (2011)

Table 1 in Petersen, Douglas, and Whitaker (2016)

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Description, -sccsdta- (not complete)

Syntax: sccsdta varlist(event time and exposure time) [, options]

Required options

- enter({varname|number}) - Varying observation period starting point
- riskpoints(numlist) - risk period endpoints relative to exposure time

Optional (not complete)

- exit(varname) - Varying observation period endpoint
- timepoints(numlist)
  - The time interval end points - are relative to enter unless option absolutetimepoints is set
- absolutetimepoints - Whether timepoints are relative to the start of the observation period or fixed within
- eventtimes - Use the event times as absolute time period end points.
- knots(3-7) - Number of knots to use when generate restricted cubic splines on the event time period endpoints
  - Splines are used when there are many event times such that xtpoisson may not converge
  - knots(3-7) also sets eventtimes and absolutetimepoints
- Preserve - Preserve the original dataset

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Dataset description, example

- Study the association between oral polio vaccine (OPV) and intussusception in infants aged 28 to 365 days.
  - a dangerous condition where the bowel folds in on itself causing an obstruction of the intestine
- 218 episodes
  - with 11 infants having more than one episode

- Considered two-week risk periods after taking the OPV
  - 14-27 and 28-41 days from the vaccination day

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The dataset

```
. use eventday agep3 cutp? using ///
        "http://fmwww.bc.edu/RePEc/bocode/s/sccsdta%20intuss.dta", clear
. list in 1/5
     +-----------------------------------+
     | eventday   agep3   cutp1   cutp2 |
     |-----------------------------------|
  1. |      156     114      27     365 |
  2. |      221     147      92     365 |
  3. |      107     160      27     365 |
  4. |      197     160      27     365 |
  5. |      148     138      27     365 |
     +-----------------------------------+
```

```
. sumat *, statistics(n mean sd min max) ///
  decimals((0,2,2,0))

-----------------------------------------
             n    mean      sd  min   max
-----------------------------------------
eventday   218  191.14   73.70   36   357
agep3      218  161.19  108.52  109  1234
cutp1      218   31.35   24.21   27   212
cutp2      218  362.28   19.97  165   365
-----------------------------------------
```

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Using -sccsdta- and relative timepoints

```
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) riskpoints(13 27 41) ///
        timepoints(0(90)270 366)
The SCCS regression summary table

                                    |        IRR        [95%        CI]    P(IRR=1)
------------------------------------+-----------------------------------------------
At risk                             |
                               ctrl |      1.000          .          .          .
                           ]13; 27] |      2.087      1.300      3.350      0.002
                           ]27; 41] |      1.271      0.716      2.256      0.413
------------------------------------+-----------------------------------------------
Time group                          |
                 ]enter+0; enter+90] |      1.000          .          .          .
              ]enter+90; enter+180] |      1.845      1.250      2.722      0.002
             ]enter+180; enter+270] |      1.570      1.064      2.318      0.023
             ]enter+270; enter+366] |      0.638      0.371      1.097      0.104
```

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The dataset after -sccsdta- for the first row

- _rowid - Row id in the original dataset
- _start - Interval start
- _stop - Interval end
- _nevents - Numbers of events in the interval
- _exgr - The risk group category of the interval
- _tmgr - The time group category of the interval
- _interval - The interval width

```
. list _* if _rowid == 1, noobs sepby(_tmgr) abbreviate(12)
  +-----------------------------------------------------------------------------+
  | _rowid   _start   _stop   _nevents      _exgr                    _tmgr   _interval |
  |-----------------------------------------------------------------------------|
  |      1       27     117          0       ctrl      ]enter+0; enter+90]          90 |
  |-----------------------------------------------------------------------------|
  |      1      117     127          0       ctrl    ]enter+90; enter+180]          10 |
  |      1      127     141          0   ]13; 27]    ]enter+90; enter+180]          14 |
  |      1      141     155          0   ]27; 41]    ]enter+90; enter+180]          14 |
  |      1      155     207          1       ctrl    ]enter+90; enter+180]          52 |
  |-----------------------------------------------------------------------------|
  |      1      207     297          0       ctrl   ]enter+180; enter+270]          90 |
  |-----------------------------------------------------------------------------|
  |      1      297     365          0       ctrl   ]enter+270; enter+366]          68 |
  +-----------------------------------------------------------------------------+
```

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Sufficient data for reproduction/meta analysis

```
. collapse (sum) _nevents _interval, by(_exgr _tmgr)
. list, noobs abbreviate(32) sepby(_exgr)
  +-----------------------------------------------------+
  |    _exgr                      _tmgr   _nevents   _interval |
  |-----------------------------------------------------|
  |     ctrl      ]enter+0; enter+90]         43       19508 |
  |     ctrl    ]enter+90; enter+180]         57       14384 |
  |     ctrl   ]enter+180; enter+270]         62       18565 |
  |     ctrl   ]enter+270; enter+366]         19       13866 |
  |-----------------------------------------------------|
  | ]13; 27]      ]enter+0; enter+90]          0          50 |
  | ]13; 27]    ]enter+90; enter+180]         21        2604 |
  | ]13; 27]   ]enter+180; enter+270]          2         183 |
  | ]13; 27]   ]enter+270; enter+366]          0          69 |
  |-----------------------------------------------------|
  | ]27; 41]      ]enter+0; enter+90]          0          62 |
  | ]27; 41]    ]enter+90; enter+180]         14        2560 |
  | ]27; 41]   ]enter+180; enter+270]          0         217 |
  | ]27; 41]   ]enter+270; enter+366]          0          73 |
  +-----------------------------------------------------+
```

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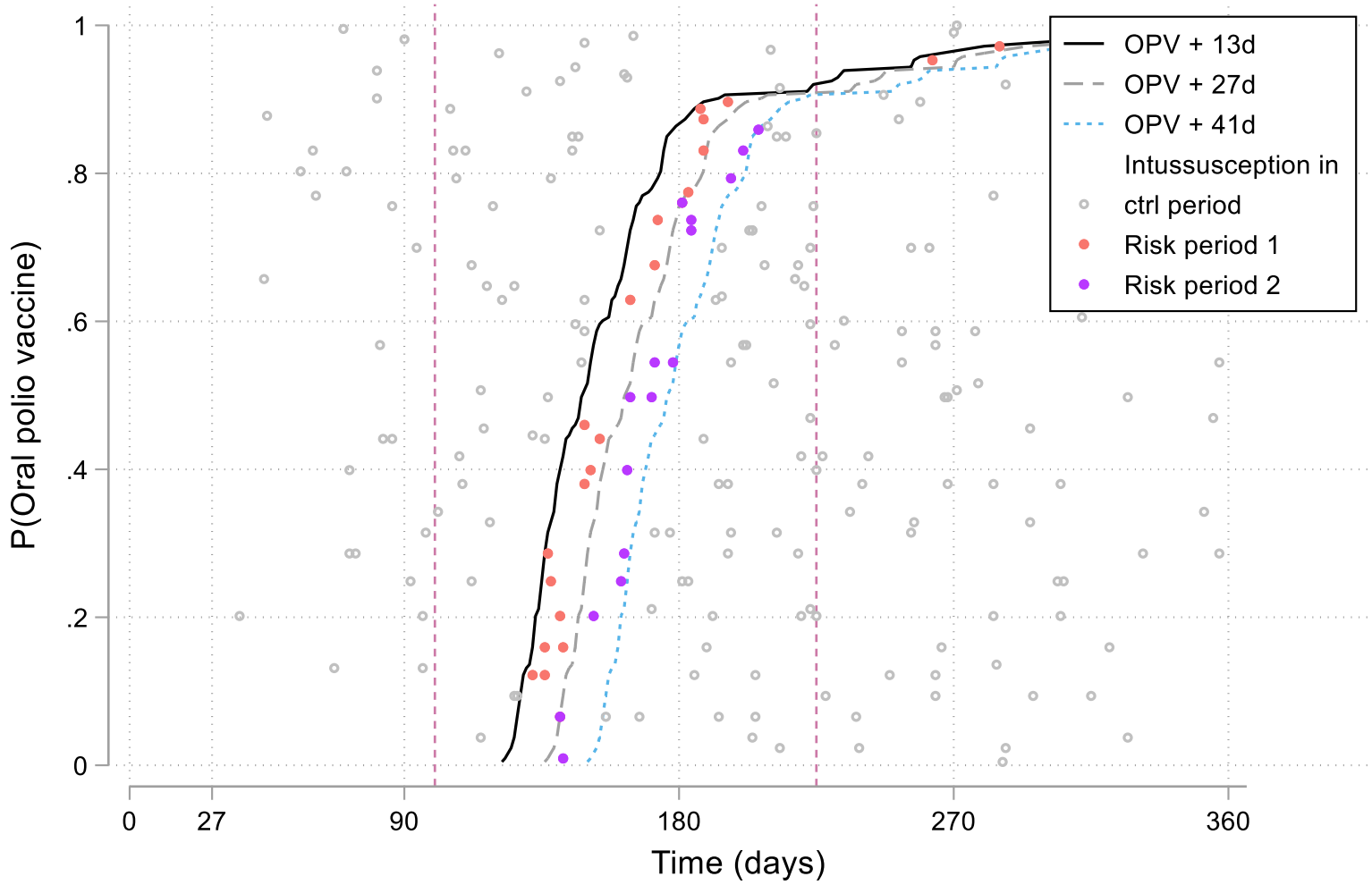
Every case has an oral polio vaccine (OPV) exposure



Most OPV are given within 100 and 225 days (See sensitivity)

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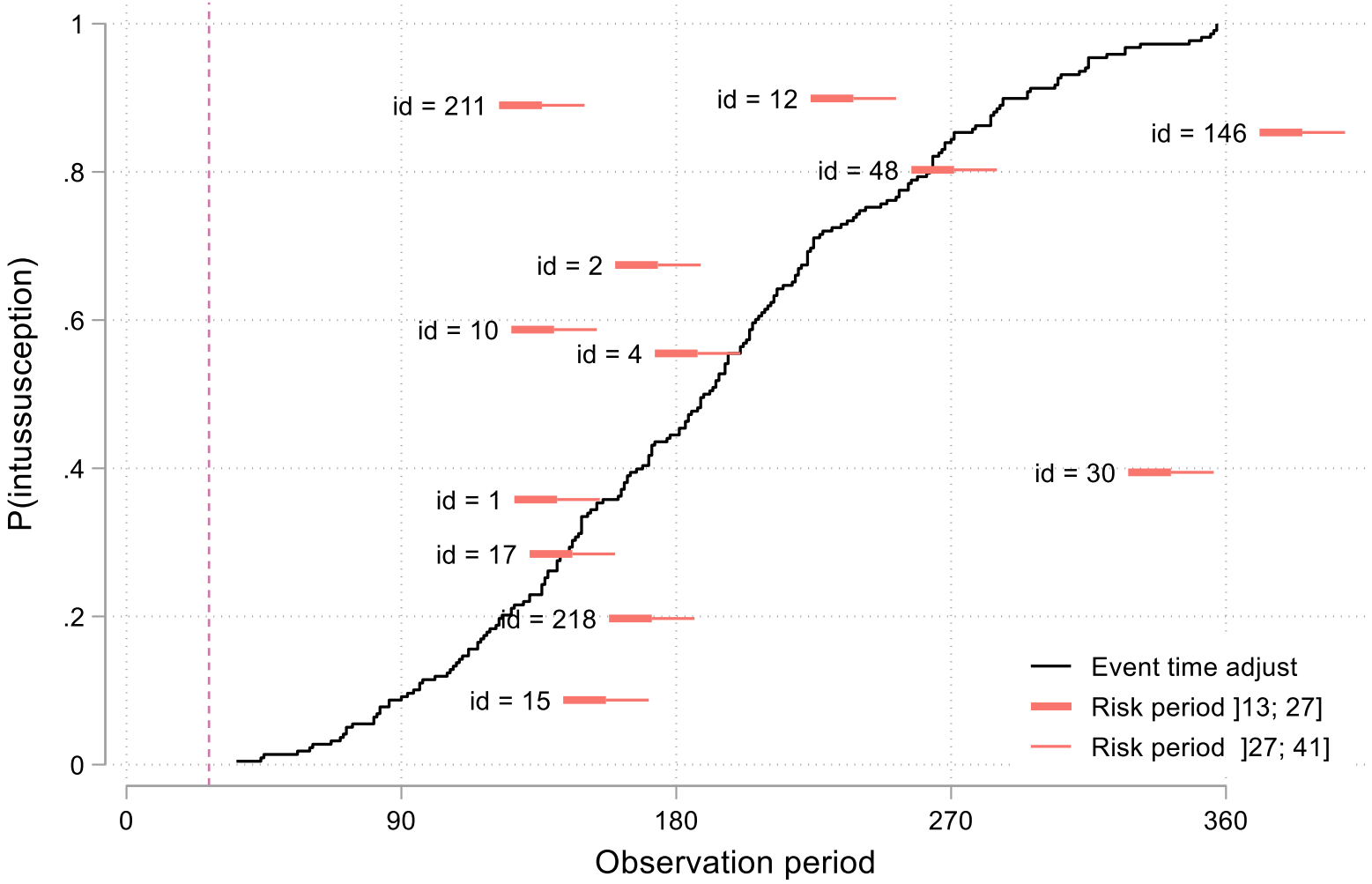
Every case has an event



Some risk periods and the probability of an event.

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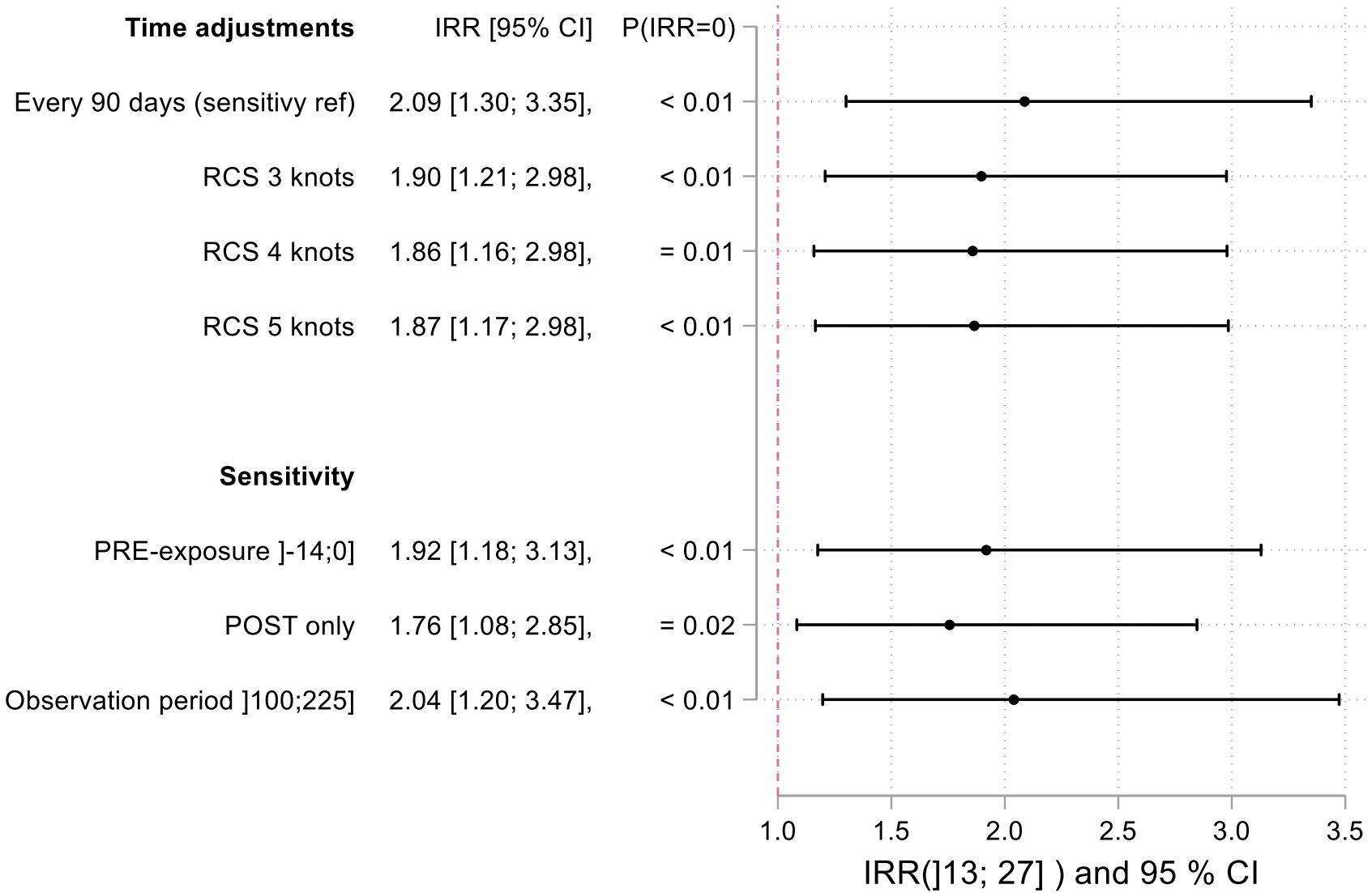
Model validation summary graph



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-sccsdta- code for the model validation summary graph

Time adjustments

```
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) ///
        riskpoints(13 27 41) timepoints(0(90)270 366) preserve
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) ///
        riskpoints(13 27 41) nk(3) preserve
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) ///
        riskpoints(13 27 41) nk(4) preserve
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) ///
        riskpoints(13 27 41) nk(5) preserve
```

Sensitivity

```
. sccsdta eventday agep3, enter(cutp1) exit(cutp2) ///
        riskpoints(-14 0 13 27 41) timepoints(0(90)270 366) preserve
. sccsdta eventday agep3, enter(agep3) exit(cutp2) ///
        riskpoints(13 27 41) timepoints(0(90)270) preserve
. sccsdta eventday agep3, enter(100) ///
        riskpoints(13 27 41) timepoints(100(25)225) preserve absolutetimepoints
```

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References

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Iwagami, Masao, and Yoshinori Takeuchi. 2021. “Introduction to Self-Controlled Study Design.” *Annals of Clinical Epidemiology* 3 (3): 67–73.

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Whitaker, Heather J., C. Paddy Farrington, Bart Spiessens, and Patrick Musonda. 2006. “Tutorial in Biostatistics: The Self-Controlled Case Series Method.” *Statistics in Medicine* 25 (10): 1768–97.