Event dependent sampling of recurrent events.

Per Kragh Andersen

Department of Biostatistics, University of Copenhagen, Denmark

Joint work with Kajsa Kvist, now: Department of Psychology, University of Copenhagen,

Lars V. Kessing, Department of Psychiatry, Rigshospitalet, Copenhagen.

Data provided by Jules Angst, Zürich University Psychiatric Hospital, Switzerland.

Risk of re-admission after successive episodes.

Kessing, Hansen, Andersen, Angst, (*Acta Psych. Scand.*, 2004).

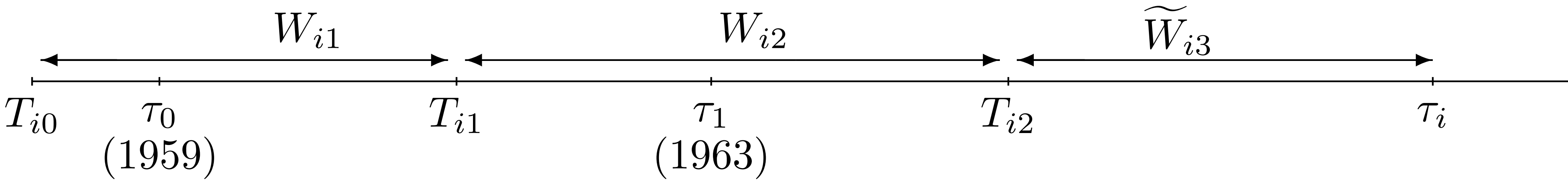
406 patients with affective disorder (186 unipolar, 220 bipolar) admitted to Zürich University Psychiatric Hospital 1959-63 and followed until 1989.

Purpose of study: Evaluate theory of "sensitization" according to which mood episodes themselves stress the brain so that its sensitivity to biologic and psychosocial stressors increases. This leads to shorter and shorter intervals between successive episodes.

3 Analyses:

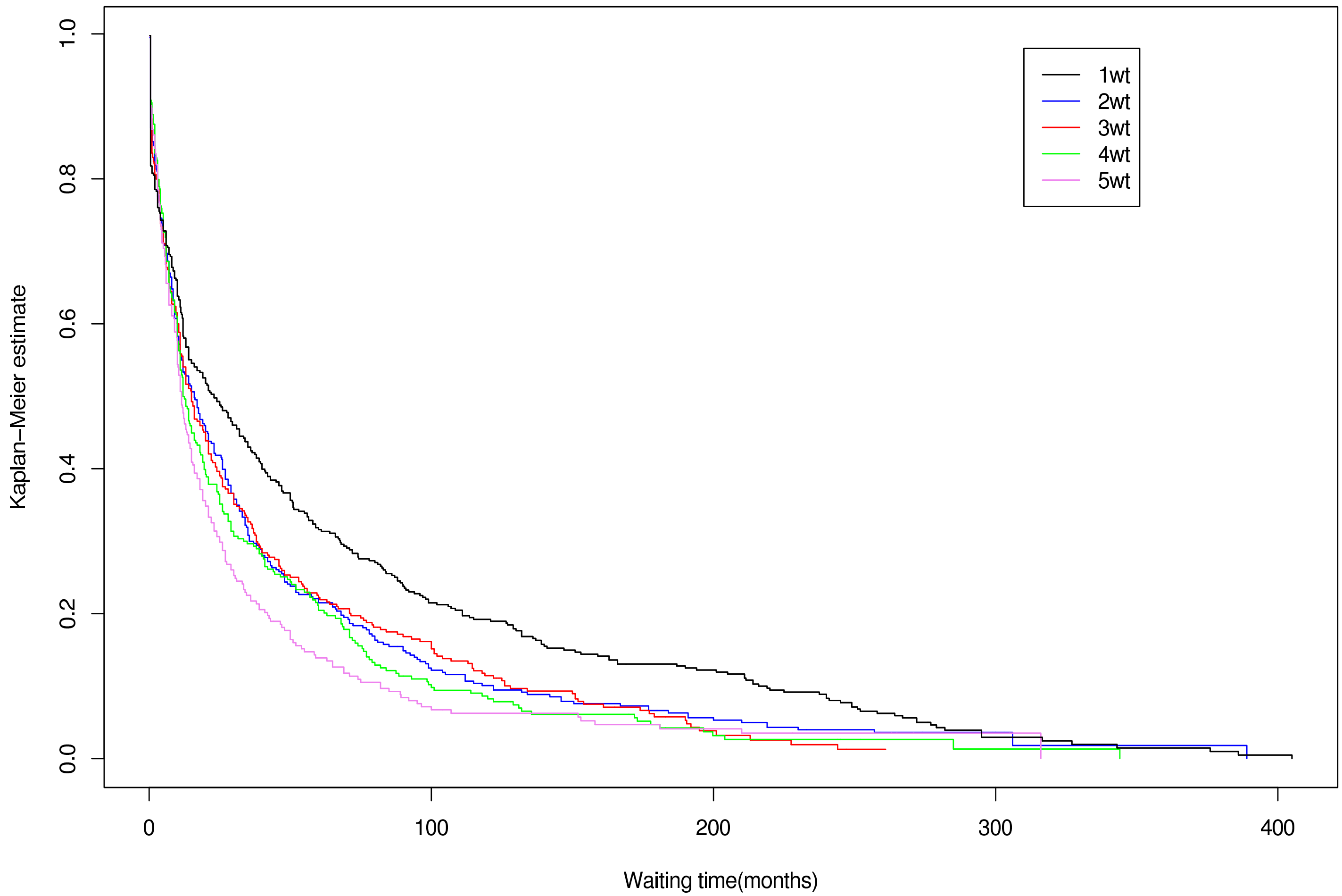
1. Only waiting times since 1959 included (delayed entry)
2. All waiting times included (also retrospective data)
3. Only waiting times for patients with onset after 1959 included

Set-up.



- t calendar time, $T_{ij}, j = 1, 2, ...$ calendar times of events (re-admissions) for subject i; T_{i0} calendar time of first episode
- (τ_0, τ_1) sampling interval, τ_i end of follow-up for subject i
- $N_i(t) = \sharp\{j = 1, 2, ... : T_{ij} \leq t\}$ counting process for subject i
- $W_{ij} = T_{ij} - T_{ij-1}, j = 1, 2, ...$ gap (waiting) times for subject i
- $\widetilde{W}_{iN_i(\tau_i)+1} = \tau_i - T_{iN_i(\tau_i-)}$ (possibly) last, censored gap time for subject i

Kaplan-Meier estimates for gap times (all data).



Using Kaplan-Meier curves.

The Kaplan-Meier curves do not really address the problem of sensitization due to selection/heterogeneity – those with 2 episodes is a select subgroup of those with 1 etc.

Another way of stating the problem is via **dependent censoring**: e.g., censoring of the second gap time depends on the first gap time and if successive gap times are correlated then censoring of the second gap time depends on the second gap time:

$C_i = \tau_i - T_{i0}$: duration of follow-up time for subject i, $W_{i1},\ W_{i2}$: first and second gap time for subject i
C_{i2}: censoring time for W_{i2}

$$C_{i2} = C_i - w_{i1}.$$

If W_{i1} and W_{i2} are dependent, then W_{i2} and C_{i2} are also dependent.

Using Kaplan-Meier curves.

$\Rightarrow$

The Kaplan-Meier estimator for, e.g. $S_2(t) = Pr(W_{i2} > t)$, downward biased.

If $Pr(W_{i1} + W_{i2} > C_i)$ is not small, and (W_{i1}, W_{i2}) are strongly correlated the bias may be substantial.

We need to take this into account - either by explicitly modeling the heterogeneity or to adjust for dependent censoring (using e.g. inverse probability weighting).

Frailty models.

Possible explicit model for the intensity process, $\lambda_i(\cdot)$, of re-admission counting process $N_i(t)$ for subject i, including heterogeneity:

$$\lambda_i(t \mid \text{past}_{t-}, Z_i) = Z_i Y_i(t) \alpha_0(t - T_{iN_i(t-)}) \exp(\beta' X_i(t)).$$

- $t - T_{iN_i(t-)}$ time since latest discharge, $Y_i(t)$ = at risk indicator
- $X_i(t)$: explanatory variables (including gender, age at first episode, calendar time and number of previous episodes, $N_i(t-)$)
- Z_i: random, unobserved *frailty* assumed to follow some distribution with mean 1 and variance θ across the patient population, e.g. a gamma distribution.

The frailty accounts for dependence between successive gap times in each subject.

Swiss study	Analysis 1 Delayed entry	Analysis 2 Retrospective	Analysis 3 From onset
n	401	401	114
Episode 1	1	1	1
Episode 2	1.21	1.36	1.24
Episode 3	1.20	1.40	1.13
Episode 4	1.16	1.52	0.87
Episode 5-6	1.21	1.68	1.15
Episode 7-8	1.23	1.70	1.03
Episode 9-10	1.56	2.19	1.71
Episode 11-12	1.31	2.00	1.18
Episode 13+	1.49	2.30	1.28
P for episode	0.04	<0.001	0.3
Gamma frailty variance	0.22	0.16	0.12
P for frailty	<0.001	<0.001	0.08

Effect of selection.

The naive Analyses 1 and 2 do not address the selection of subjects: those with an episode in a given sampling interval are not a random sample. Illustrated using simulations:

- 500 replications of 1000 processes, $n_s (\leq 1000)$ sampled
- No effect of previous episodes (or other covariates)
- $V(Z_i) = \theta = 0.1, 0.2, 1,\ \alpha_0(t) = 1$
- Test for no effect of previous episodes: α rate of rejection at 5%

	All data			Delayed entry Analysis 1			Retrospective Analysis 2			From onset Analysis 3		
θ	n_s	$\widehat{\theta}$	α	n_s	$\widehat{\theta}$	α	n_s	$\widehat{\theta}$	α	n_s	$\widehat{\theta}$	α
0.1	1000	0.101	0.048	845	0.061	0.298	845	0.091	0.068	298	0.074	0.0
0.2	1000	0.181	0.044	834	0.138	0.746	834	0.160	0.046	300	0.163	0.0
1.0	1000	1.010	0.048	748	0.456	1.000	748	0.674	0.136	299	1.000	0.0

Adjustment for delayed entry.

The conditional ("updated") frailty distribution given the past among those selected is no longer Gamma with mean 1 and variance θ, but Gamma with mean A_i/B_i and variance A_i/B_i^2 where

$$A_i = \theta^{-1} + s_i, B_i = \theta^{-1} + f(s_i)$$

when selected at episode number s_i, where

$$f(s_i) = \sum_{j=1}^{s_i} \int_0^{w_{ij}} \alpha_0(u) \exp(\beta' X_i(u + T_{i,j-1})) \mathrm{d}u.$$

This explicit expression allows the likelihood to be evaluated and maximized ($\alpha_0(t)$ piecewise constant).

Adjustment for delayed entry: simulations.

		No correction		Updated frailty	
	θ	$\widehat{\theta}$	α	$\widehat{\theta}$	α
Gamma	0.1	0.06	0.26	0.10	0.04
	0.2	0.14	0.72	0.24	0.02
	1.0	0.45	1.00	1.02	0.03
Log-Normal	0.1	0.07	0.21	0.10	0.03
	0.2	0.14	0.54	0.17	0.04
	1.0	0.39	0.90	0.52	0.04

Updating helps - but only with a correctly specified frailty distribution.

Swiss data: reanalysis of data with delayed entry.

Episode	No correction $\exp(\widehat{\beta})$	Updated frailty $\exp(\widehat{\beta})$
1	1	1
2-3	1.15	0.73
4-8	3.17	2.48
9+	5.81	3.39
$\widehat{\theta}$	0.87	$> 10^5$

Sensitization decreases and frailty variance increases (explodes!) when updating.

Using retrospective data.

The conditional frailty distribution is no longer tractable. Instead: use estimating equation:

$$\sum_i \frac{\Delta_i}{\pi_i} U_i(\gamma) = 0$$

with $\Delta_i = I(i \text{ selected}), \pi_i = P(\Delta_i = 1)$ and $U_i(\gamma)$ is the score contribution from i; $\gamma = (\alpha_0, \beta, \theta)$.

Several ways of estimating π_i. The weights that worked best were based on the total event counts, $k_i = N_i(\tau_i)$, for those observed:

$$\widehat{\pi}_i = \frac{\sum_j \Delta_j I(N_j(\tau_j) = k_i)}{\frac{n_s}{n_{0s}} \sum_j I(j \text{ observed from onset}, N_j(\tau_j) = k_i)}$$

where n_{0s} is the number selected from onset.

Using retrospective data: simulations.

	Naive analysis	Weighted analysis		
θ	$\widehat{\theta}$	$\widehat{\theta}$	Simulation SD	Bootstrap SD
0.1	0.071	0.099	0.034	0.030
0.2	0.134	0.212	0.064	0.063
1.0	0.522	1.044	0.201	0.180

Frailty variance too small without weighting.

A sandwich estimator

$$I^{-1}(\hat{\gamma})\left(\sum_i \frac{\Delta_i}{\pi_i} U_i(\hat{\gamma}) \frac{\Delta_i}{\pi_i} U_i'(\hat{\gamma})\right) I^{-1}(\hat{\gamma})$$

for the SD with $I^{-1}(\gamma) = \sum_i \frac{\Delta_i}{\pi_i} I_i(\gamma)$ did not work well.

Swiss data: reanalysis of retrospective data.

	Naive analysis			Weighted analysis		
Episode	$\exp(\widehat{\beta})$	95% ci	P	$\exp(\widehat{\beta})$	95% ci	P
1	1		<0.001	1		0.014
2-3	1.37	1.181-1.60		1.27	1.02-1.57	
4-8	1.62	1.399-1.88		1.27	1.03-1.57	
9+	2.14	1.832-2.51		1.49	1.20-1.86	
$\widehat{\theta}$	0.19		<0.001	0.64		<0.001

Sensitization decreases and frailty variance increases when weighting.

Conclusions.

- Retrospective (and other) sampling may have a major impact when analyzing survival data
- For data on recurrent events, sampling of subjects with an event in a given interval
  - decreases the heterogeneity
  - increases the “sensitization” effect
- Analysis of recurrent event data with delayed entry may be performed using an “updated” frailty model
- Inclusion of retrospectively collected gap times may be performed by a weighted analysis - choice of weights?