Multilevel models for competing risks

with application to surveys on contraceptives use

Outline

- Background
- Joint modelling of hazards of sub-distribution
- Approaches to the analysis of clustered hierarchical data
  - Marginal and random-effects models
- Application to Pill use in Egypt
- Conclusion

Background

- Data on contraceptive practice in developing countries are regularly collected in Demographic and Health surveys (DHS)
- Information on duration of episodes of use and reasons for their discontinuation during the previous six years is collected cross-sectionally from a sample of a very small fraction of women of reproductive age

Background (2)

- Questions of practical interest to family planners include
  - Predicted proportion of episodes discontinued by a given time because of method failure (unwanted pregnancy) in the presence of other competing causes of discontinuation (eg planned pregnancy)
  - The association of the rate of method failure with woman/method/location-specific factors

Background (3)
Some definitions

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If T is time to pill discontinuation then

(1) $$\lambda_k(t) = \lim_{\Delta t \to 0} \left\{ \frac{P\left[t \le T < t + \Delta t, \delta = k \mid T \ge t\right]}{\Delta t} \right\}$$

is the cause-specific hazard for cause k

(2) $$h_k(t) = \lim_{\Delta t \to 0} \left\{ \frac{P\left[t \le T < t + \Delta t, \delta = k \mid \{T \ge t\} \cup \{T < t; \delta \ne k\}\right]}{\Delta t} \right\}$$

is the hazard of subdistribution for cause k

(3) $$CI_k(t) = \int_0^t h_k(u)du$$

is the cumulative incidence function for cause k

Background (4)

- The statistical problem is how best to jointly model and estimate the cause-specific cumulative incidence functions (CIFs) for the causes of discontinuation using DHS data

- Joint modelling is not necessary but can be efficient uner some modelling assumptions; eg

  - cause-specific proportional hazards

  - common covariate effects

Background (5)

- Likelihood / partial likelihood methods for modelling CIF, cause-specific hazards (CSH) and hazard of subdistributions (HSD), in the case of a simple random sample are well established; eg
  - Cheng, Fine and Wei (1998). Biometrics 54
  - Lunn and McNeil (1995). Biometrics 51
  - Fine and Gray (1999). JASA 94
- Software for fitting some these models is not widely available

Jointly modelling hazards of subdistributions

- Data augmentation
- Analogue of Lunn and McNeil use of Cox PH for jointly modelling CSHs
  - CSH -> HSD
  - Cox -> Fine and Gray
- Can be fitted in any software that support Cox PH
  - Fairly straight forward if censoring time is known
  - Otherwise, more involved but doable with time dependent weights

Illustration

- Two failure types; one covariate Z

ID	Time	k	Z	ctime
1	14	2	1	18
2	20	0	3	20
3	22	1	2	30

Augmented data

ID	Time	Δ	Z	Z_2
1	18	0	1	0
1	14	1	1	1
2	20	0	3	0
2	20	0	3	3
3	22	1	2	0
3	30	0	2	2

Data (1)

- From 1992 Egypt DHS – survey conducted between Nov 1992 and Feb 1993
- Nationally representative sample of 9864 ever-married women aged 15-49 years
- Interview covered contraceptive knowledge, ever use and availability
- History of all episodes of use in the 6 years prior to the survey

Data (2)

- Focus on all episodes of pill use which started in the 5-year period prior to the date of interview
- Episode duration and reason for discontinuation
- Age, place of residence (urban/rural), number of living children at the start of episode

Reason of discontinuing oral contraceptive pill

Reason for discontinuation	n		%
Still using	688		33.0
Method failure (involuntary pregnancy)	334		16.0
Discontinue while still in need	666		32.0
Husband disapproved		13	
Side effects or health concerns		585	
Problems with access, availability, cost or use		9	
Wanted to switch method		36	
Other personal reasons		23	
Discontinue because of no further need	395		19.0
Wanted to become pregnant		234	
Infrequent sex, husband away or separated		157	
Difficult to get pregnant, reached menopause		4	
Total	**2083**		**100.0**

Distribution (%) of episodes of pill use by baseline characteristics

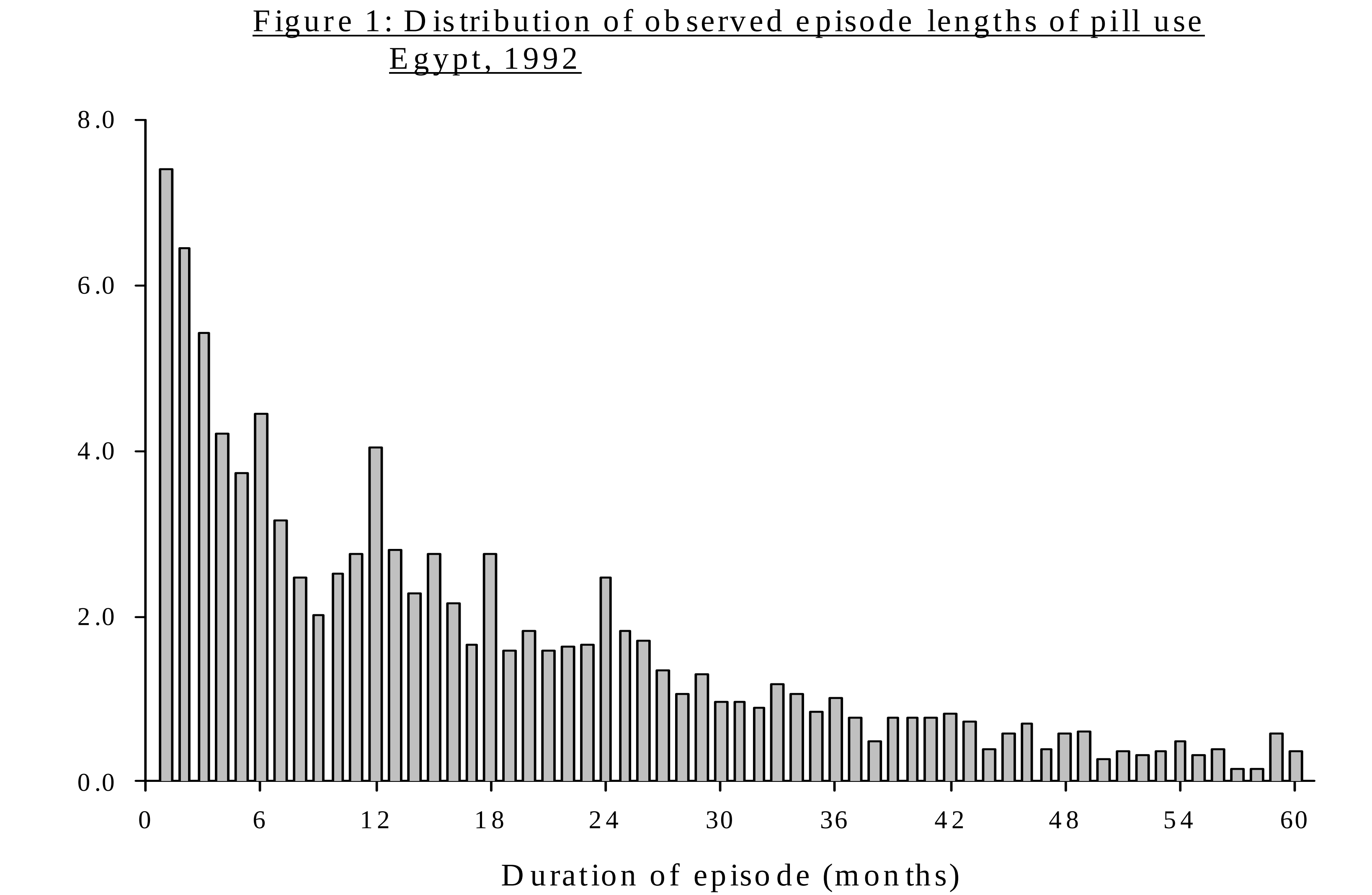
	no. of episodes	ongoing	Discontinuation reason		
			failure	while in need	no further need
Woman's level					
Place of residence					
Urban	995	35.4	14.3	32.2	18.2
Rural	1088	30.9	17.6	31.8	19.7
Women's education					
No education	876	31.5	18.3	33.1	17.1
Primary	692	35.7	15.6	30.2	18.5
Secondary and higher	515	32.0	12.8	32.4	22.7
Episode's level[1]					
Age group (years)					
15-24	480	15.8	20.4	32.5	31.3
25-29	661	31.0	15.9	33.4	19.7
30-34	499	40.7	18.8	29.9	10.6
35+	443	46.0	8.4	31.6	14.0
Number of living children					
0-2	656	18.1	15.4	35.1	31.4
3-4	882	38.9	15.3	30.4	15.4
5+	545	41.5	18.0	30.8	9.7
Desire for another child					
Actual=desired	595	34.6	12.8	31.4	21.2
Actual< desired	505	14.1	15.2	37.8	32.9
Actual> desired	983	41.8	18.4	29.3	10.5
Total	**2083**	**33.0**	**16.0**	**32.0**	**19.0**

[1] baseline characteristics at the beginning of the episode

Data-specific challenges

- Hierarchical
- Clustered
- Sampling weights
- Digit preference and recall bias
- pseudolikelihood

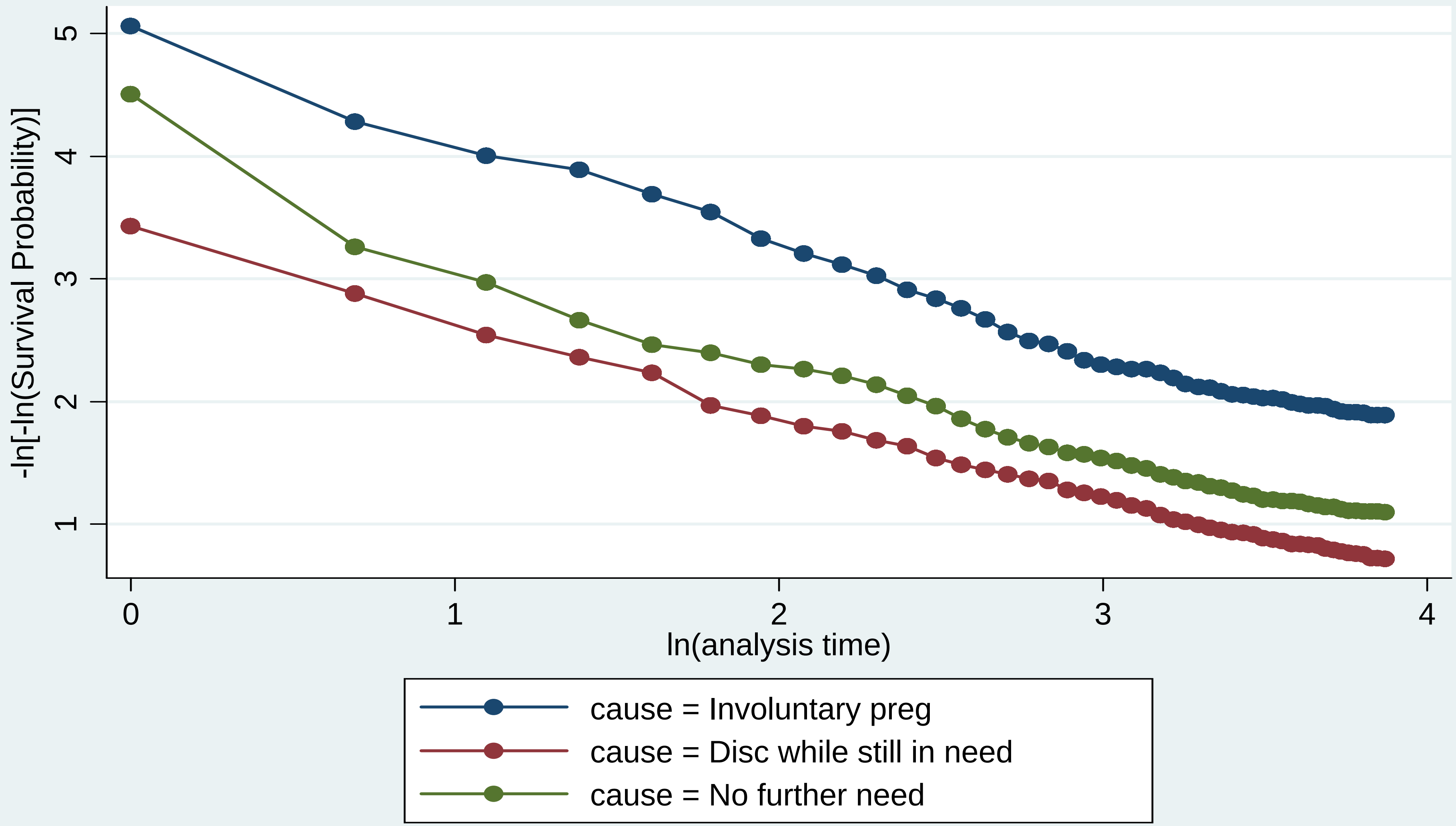
Distribution of episodes duration



Approaches to the analysis (1)

- Marginal models
  - Interest in population averages (conditional on covariates); applicable to a randomly selected episode from the subpopulation with given covariate values
  - Can use standard estimation commands but must allow for sampling weights to obtain unbiased estimates
  - Used an adapted Cox (with data augmentation) to jointly model HSD
  - Hierarchical design and clustering have no impact on estimates but must be allowed for to obtain correct standard errors
  - SEs can also be estimated by a double bootstrap

Subdistribution hazards plot
adjusted for age, residence and desire for more children



Cause-specific hazards plot
adjusted for age, residence and desire for more children

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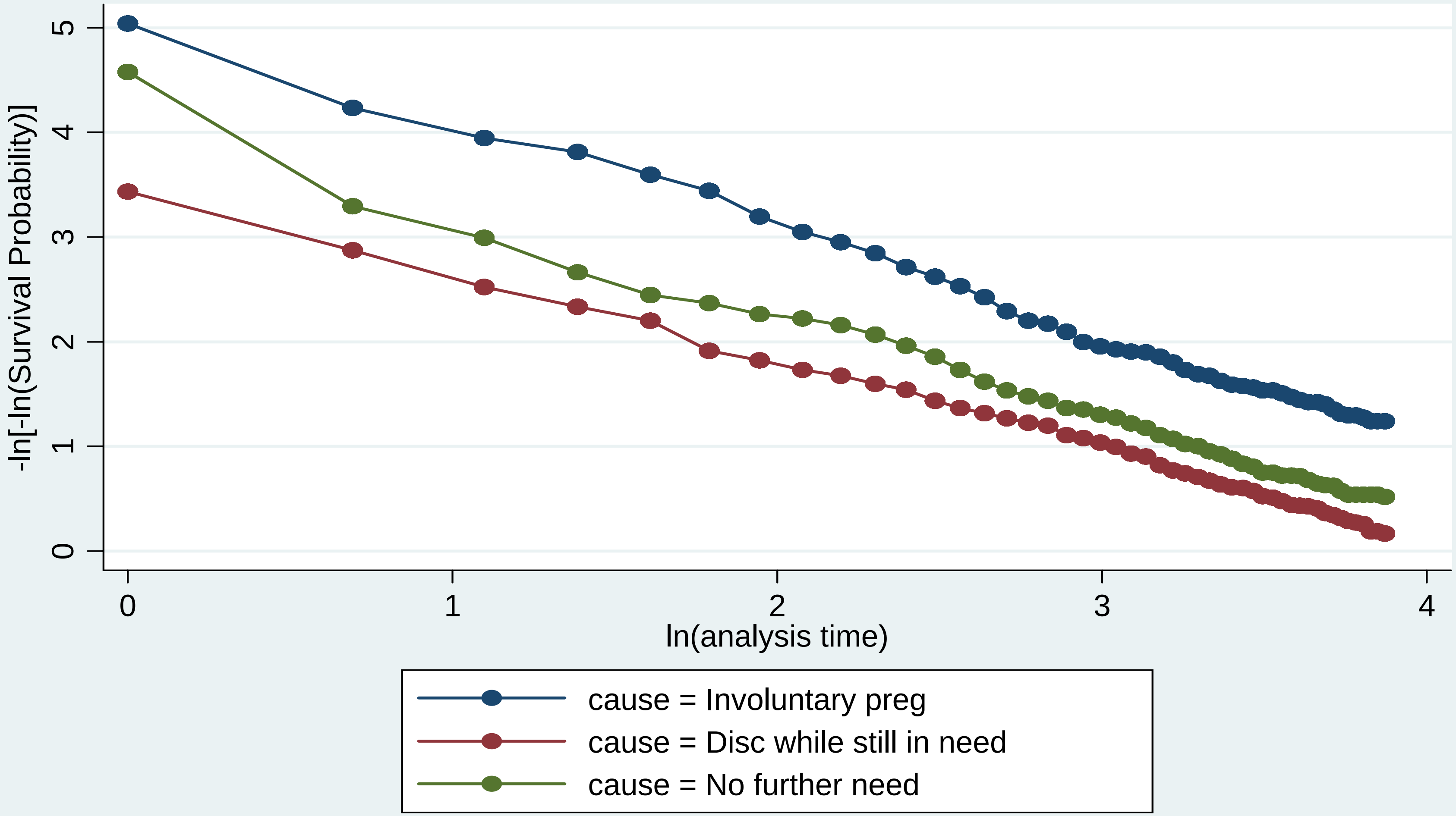

Marginal model: CSHs

	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
WN	1.06033	.1648523	6.43	0.000	.7372249	1.383434
NN	.7500613	.2052778	3.65	0.000	.3477242	1.152398
age	-.0445415	.0113354	-3.93	0.000	-.0667585	-.0223245
Age*WN	.0296627	.0150068	1.98	0.048	.0002499	.0590755
Age*NN	.0065006	.0164651	0.39	0.693	-.0257705	.0387716
Rural	.2740301	.1304611	2.10	0.036	.018331	.5297291
Rural*WN	-.0746887	.1675472	-0.45	0.656	-.4030751	.2536977
Rural*NN	-.2111709	.2099908	-1.01	0.315	-.6227453	.2004035
Limiter	.4147817	.1523908	2.72	0.006	.1161012	.7134622
Limiter*WN	-.6452505	.1936824	-3.33	0.001	-1.024861	-.26564
Limiter*NN	-1.383851	.2206266	-6.27	0.000	-1.816271	-.9514306

Reasons for discontinuation:
- MF = Method failure (involuntary pregnancy)
- WN = Discontinuation while in need
- NN = No further need

Age (centered at 30 years)

Intention of use
- Spacer = Desired number of children ≥ actual number of children
- Limiter = Desired number of children < actual number of children

Marginal model: HSDs

_t	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
WN	1.170051	.1822622	6.42	0.000	.8128237	1.527278
NN	.8132479	.2251132	3.61	0.000	.3720342	1.254462
age	-.0333533	.0110009	-3.03	0.002	-.0549146	-.011792
age*WN	.0280871	.0170155	1.65	0.099	-.0052627	.0614369
age*WN	.0057549	.0179242	0.32	0.748	-.0293759	.0408857
Rural	.1813676	.1329231	1.36	0.172	-.079157	.4418922
Rural*WN	-.0501976	.1937586	-0.26	0.796	-.4299575	.3295622
Rural*NN	-.2175358	.2328407	-0.93	0.350	-.6738952	.2388235
Limiter	.5897497	.153659	3.84	0.000	.2885836	.8909159
Limiter*WN	-.7065296	.2208862	-3.20	0.001	-1.139459	-.2736006
Limiter*NN	-1.494975	.2408512	-6.21	0.000	-1.967035	-1.022915

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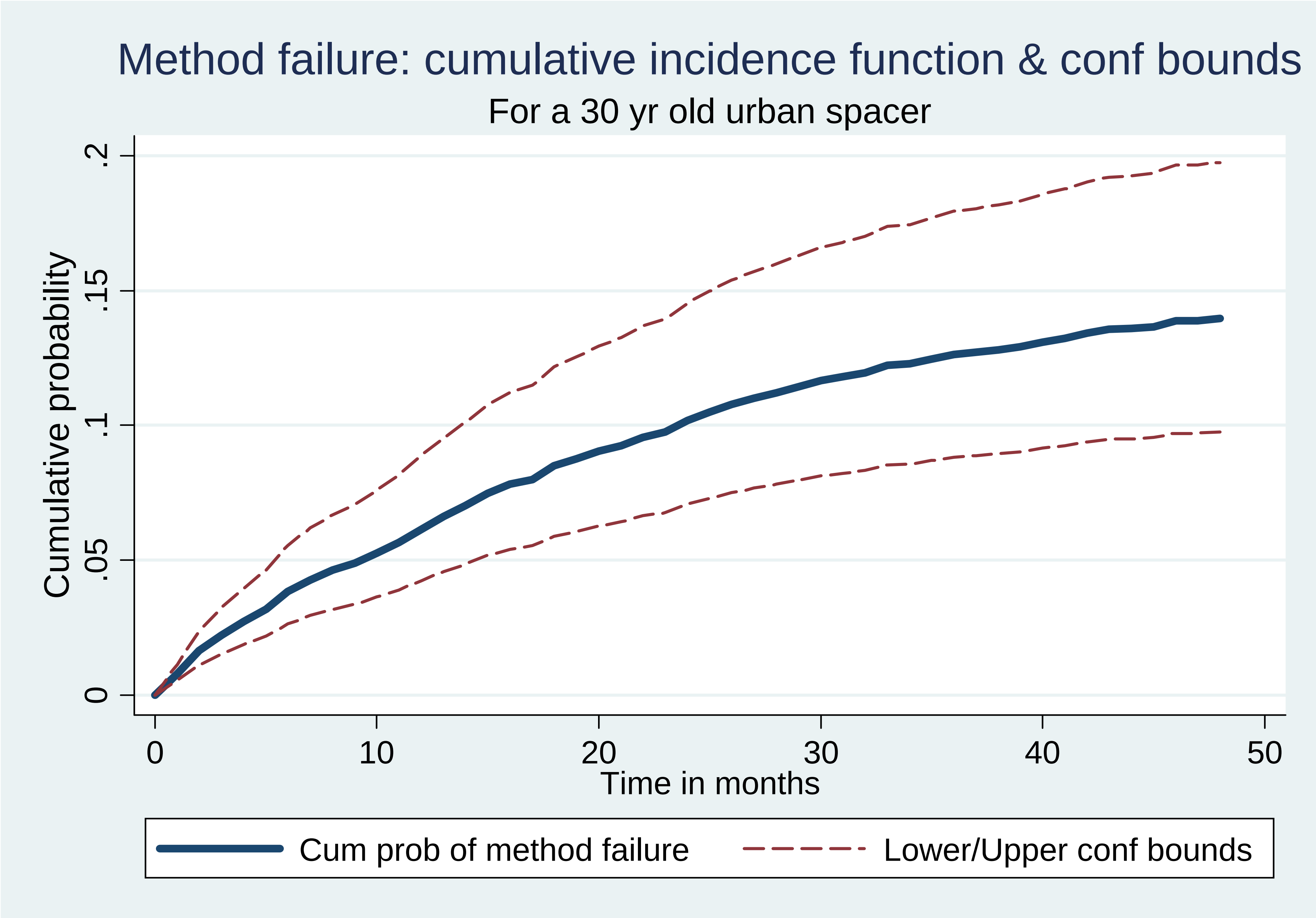
Method failure: cumulative incidence function & conf bounds
For a 30 yr old urban spacer
Cumulative probability
0
.05
.1
.15
.2
0
10
20
30
40
50
Time in months
Cum prob of method failure
Lower/Upper conf bounds

Approaches to the analysis (2)

- Random level effects models
  - Parameter estimates are conditional on cluster and woman random effects
  - Model hard to fit for continuous time; a 3-level discrete-time multinomial logit model with cause-specific baseline hazard function provides a good approximation and can be implemented using MLwin or Stata
  - Sampling weights must be used

Mixed-effects multinomial logit model

Let π_{klmij} = the probability of discontinuation at time *j* for cause *k* for episode *i* to woman *m* in cluster *l*; *k* = 1…,*K*; $\pi_{0lmit} = 1 - \sum_{k=1}^{K} \pi_{klmij}$

$$\log it\left(\frac{\pi_{klmij}}{\pi_{0lmij}}\right) = \eta_{kj} + z'_{klmij}\beta_{klm} + u_{klm} + v_{kl}$$

where

$$u_{klm} \sim N(0, \Omega_{klm}) \qquad v_{kl} \sim N(0, \Omega_{kl})$$

and η_{kj} a function of time

Mixed-effects model: HSDs

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	Method failure		While in need		No further need	
	Est.	SE	Est.	SE	Est	SE
<u>Fixed effect</u>						
Place of residence *(urban*)						
Rural	0.320	(0.147)	0.174	(0.104)	-0.001	(0.166)
(Age at start of episode-30.0)	-0.041	(0.010)	-0.006	(0.009)	-0.035	(0.015)
intention of use (Spacer*)*						
Limiter	0.555	(0.168)	-0.173	(0.111)	-1.113	(0.161)
Random Intercept						
Cluster	0.097	(0.107)	0.083	(0.052)	0.187	(0.138)
Woman	1.865	(0.396)	0.786	(0.138)	3.315	(0.780)

Summary: methods

- Lunn and McNeil's method of data augmentation can be adapted for efficient joint estimation of HSDs
- Standard methods for estimating CIF for simple random samples can be adapted to hierarchical clustered data (using prob-weighting and cluster options)
- Bootstrap provides an attractive option for SE estimation particularly for simultaneous confidence bounds
- Mixed effects models (with more than two levels) are harder to fit for continuous time; discrete-time approximations work well

Summary: pill use in Egypt

- A high rate of method failure (involuntary pregnancy particularly for rural women ~ 15%by 12 months compared to 7% for urban women
- A very high rate of discontinuation while still in need (side effects, cost, availability etc) ~ 20% by 12 months overall (higher for older women)

Summary

Method failure: cumulative incidence function & conf bounds