Computational Methods For Case-Cohort Studies

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- Because of large numbers and cost of analysing the biological specimens or genotyping, these resources are often not analysed in detail at the time but are stored for future use
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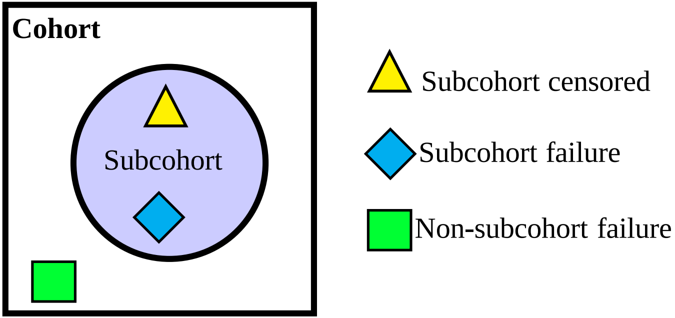
Case-Cohort Design



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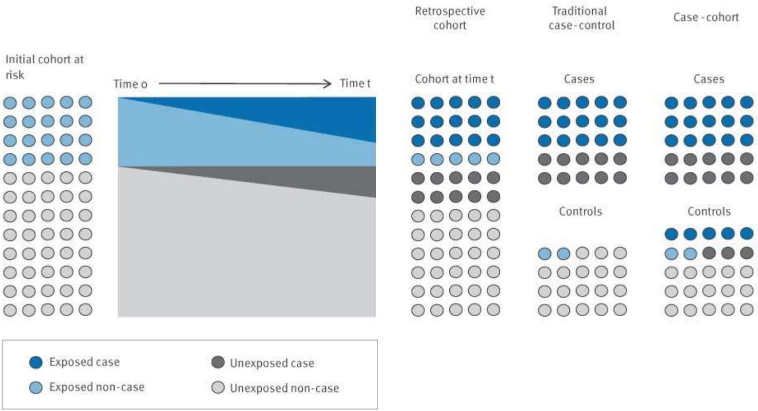
Comparing three study designs



Waroux et al.,2012

Cox Proportional Hazards Model

First lets consider a relative risk regression model *(Cox, 1972)*

Cox PH Model

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Exact and approximate pseudolikelihood estimators

- Indicator whether subject is at risk at time t

$$\tilde{\mathcal{L}}(\beta) = \prod_{i=1}^{n} \prod_{t} \left[\frac{\exp\{\beta Z_i(t)\}}{\sum_{k \in \tilde{\mathfrak{R}}_i(t)} \exp\{\beta Z_k(t)\}} \right]^{dN_i(t)} \tag{1}$$

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Approximate Variance of $\hat{\beta}$

Therneau and Li (1999) solved the variance estimation problem proposing the following approximation

$$\hat{I}^{-1} + \frac{m(n-m)}{n}\mathrm{Cov}\, D_C \tag{2}$$

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Dfbeta residuals

Are the approximate changes in the parameter estimates $(\hat{\beta} - \hat{\beta}_{(j)})$ when the j^{th} observation is omitted. These variables are a weighted transform of the score residual variables and are useful in assessing local influence and in computing approximate and robust variance estimates.

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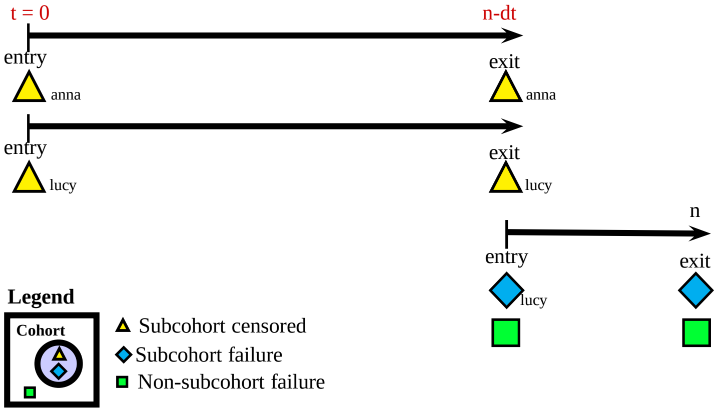
Graphic of how to create analytic dataset



Original Case Cohort dataset

Basic case-cohort data

Subject ID	Dose in rad	Age at exit (in years)	Age at entry (in years)	0-cens,1-subc fail 2-non-subc fail	1-249 rad	250+ rad	age at first exposure group [a]
2866	0.4525	71.269	34.0014	0	1	0	3
2787	0.00984	69.0294	31.7454	0	1	0	4
2702	0.05486	47.5948	36.5065	0	1	0	3
34	0	55.4387	14.9377	1	0	0	1
3064	0.12788	35.4825	25.6838	0	1	0	3
2766	1.62311	64.3559	30.5161	0	1	0	3
2344	1.0624	69.692	25.4127	0	1	0	3
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
2698	0	42.3682	36.2026	2	0	0	4
2577	1.00338	50.9979	26.412	2	1	0	3
2348	1.30725	42.1246	24.1259	2	1	0	3
3106	0	55.2635	27.2635	2	0	0	3
2687	0	47.7563	23.2553	2	0	0	3
3018	1.6723	50.0014	38.8337	2	1	0	4

[a] $1 :< 15, 2 : 15-19, 3 : 20-29, 4 : 30+$

Comparison

Original vs. Analytic dataset

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34	0	55.4387	14.9377	1	0	0	1			
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SAS Code

```
proc phreg data=analytic;
  model an_exit*an_ind(0)  = dcat1 dcat2 /
   entry=an_entry covb;
  output out=dfbetas dfbeta= dfb_dcat1 dfb_dcat2;
  id id;
run;

proc corr data=dfbetas cov;
  var dfb_dcat1 dfb_dcat2;
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- covb: outputs the inverse information matrix $\hat{I}^{-1}$
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Exact pseudolikelihood and Asymptotic variance

Analysis of Maximum Likelihood Estimates							
Parameter	**DF**	Parameter Estimate	Standard Error	χ^2	**Pr**$> \chi^2$	Hazard Ratio	**Label**
dcat1	1	0.6572	0.26117	6.332	0.0119	1.929	1-249 rad
dcat2	1	1.55325	0.50118	9.6051	0.0019	4.727	250+ rad

Estimated Covariance Matrix $(\times 10^{-2})$			
Parameter		**dcat1**	**dcat2**
dcat1	**1-249 rad**	6.821	4.743
dcat2	**250+ rad**	4.743	25.118

Estimated Covariance Matrix of the dfbeta residuals $(\times 10^{-4})$			
Parameter		**dfb_dcat1**	**dfb_dcat2**
dfb_dcat1	**difference in the parameter for dcat1**	5.487	2.998
dfb_dcat2	**difference in the parameter for dcat2**	2.998	47.878

Time-dependent covariates

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Analytic dataset

Analytic Dataset for time dependent covariates

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22	1	25.4292	25.4291	2958	4.13045	33.6016	15.8303	0	0	1	1	15.8303	0	9.5989	0
22	1	25.4292	25.4291	295	0.58148	51.833	17.5496	0	1	0	2	17.5496	0	7.8795	0
22	1	25.4292	25.4291	261	0	52.8569	3.4771	0	0	0	1	3.4771	0	21.9521	1
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
22	1	25.4292	25.4291	34	0	55.4387	14.9377	1	0	0	1	14.9377	0	10.4914	0
22	1	25.4292	25.4291	334	1.15677	56.6543	18.3381	0	1	0	2	18.3381	0	7.091	0
22	1	25.4292	25.4291	2057	0	73.2402	20.8049	0	0	0	2	20.8049	0	4.6242	0
2350	33	47.7235	47.7234	2350	0.94436	47.7235	20.2218	2	1	0	2	47.7234	1	27.5017	1
2350	33	47.7235	47.7234	3043	0.92604	48.909	17.5414	0	1	0	1	17.5414	0	30.1821	1
2350	33	47.7235	47.7234	242	0.67137	49.1608	15.8795	0	1	0	1	15.8795	0	31.8439	1
2350	33	47.7235	47.7234	2244	0.00959	49.1828	16.9035	0	1	0	2	16.9035	0	30.82	1
2350	33	47.7235	47.7234	3150	0	50.4723	17.191	0	0	0	2	17.191	0	30.5325	1
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
2350	33	47.7235	47.7234	3317	1.28865	78.4559	27.7755	0	1	0	3	27.7755	0	19.948	1
2350	33	47.7235	47.7234	3182	0.95419	81.0951	35.05	0	1	0	4	35.05	0	12.6735	0
2350	33	47.7235	47.7234	3258	0.82631	86.642	38.36	0	1	0	4	38.36	0	9.3634	0
2350	33	47.7235	47.7234	3198	0	87.1157	42.5435	0	0	0	4	42.5435	0	5.18	0
3085	75	77.86	77.86	3085	0	77.8645	43.0335	2	0	0	4	77.8644	1	34.83	1
3085	75	77.86	77.86	3317	1.28865	78.4559	27.7755	0	1	0	3	27.7755	0	50.09	1
3085	75	77.86	77.86	3182	0.95419	81.0951	35.05	0	1	0	4	35.05	0	42.81	1
3085	75	77.86	77.86	3258	0.82631	86.642	38.36	0	1	0	4	38.36	0	39.5	1
3085	75	77.86	77.86	3198	0	87.1157	42.5435	0	0	0	4	42.5435	0	35.32	1
3085	75	77.86	77.86	2477	0	89.9849	53.9001	0	0	0	4	53.9001	0	23.96	1

SAS Code

```
proc phreg data=pclib.td_analytic nosummary;
  model rstime*cc(0) = dcat1 dcat2 lat15
    / entry=rsentry covb;
  output out=dfbetas dfbeta= dfb_dcat1 dfb_dcat2 dfb_lat15;
  id id;
run;

proc summary data=dfbetas sum;
   class id;
   var dfb_dcat1 dfb_dcat2 dfb_lat15;
   output out=summed sum=dfb_dcat1 dfb_dcat2 dfb_lat15;
   where cc eq 0;
run;

proc corr data=summed cov;
  var dfb_dcat1 dfb_dcat2 dfb_lat15;
run;
```

Exact pseudolikelihood estimators

Analysis of Maximum Likelihood Estimates

Parameter	**DF**	Parameter Estimate	Standard Error	χ^2	**Pr**$>\chi^2$	Hazard Ratio	**Label**
dcat1	1	0.65709	0.26112	6.3325	0.0119	1.929	1-249 rad
dcat2	1	1.68786	0.50750	11.0610	0.0009	4.727	250+ rad
lat15	1	0.61486	0.36062	2.9071	0.0882	1.849	

Stratification by age at first exposure

- It is quite possible that age is confounding the main effects of the covariates
- To control for confounding we stratify by age at first exposure group
- Each stratum (s) contributes independently to the pseudolikelihood
- the asymptotic variance is given by

$$\hat{I}^{-1} + \sum_{s} \frac{m_s(n_s - m_s)}{n_s} \mathrm{Cov}\, D_{C_s} \tag{3}$$

Stratification

Age Stratified Groups	
Age	**Group number**
<15	1
15-19	2
20-29	3
30+	4

SAS Code

```
proc phreg data=analytic;
  model an_exit*an_ind(0) = dcat1 dcat2 / entry=an_entry covb;
  output out=dfbetas dfbeta= dfb_dcat1 dfb_dcat2;
  strata agefirstgr;
  id id;
run;

proc corr data=dfbetas cov;
  var dfb_dcat1 dfb_dcat2;
  by agefirstgr;
  where an_ind eq 0;
run;
```

Exact pseudolikelihood estimators

Stratified

Analysis of Maximum Likelihood Estimates							
Parameter	**DF**	Parameter Estimate	Standard Error	χ^2	**Pr**$> \chi^2$	Hazard Ratio	**Label**
dcat1	1	0.5938	0.27148	4.7838	0.0287	1.811	1-249 rad
dcat2	1	0.9349	0.51737	3.2655	0.0708	2.547	250+ rad

Unstratified

Analysis of Maximum Likelihood Estimates							
Parameter	**DF**	Parameter Estimate	Standard Error	χ^2	**Pr**$> \chi^2$	Hazard Ratio	**Label**
dcat1	1	0.6572	0.26117	6.332	0.0119	1.929	1-249 rad
dcat2	1	1.55325	0.50118	9.6051	0.0019	4.727	250+ rad

Summary

1. Efficiency and benefits of case-cohort design
2. Take advantage of available software

Summary

1. Efficiency and benefits of case-cohort design
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