Two-phase designs in epidemiology

Thomas Lumley

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This document explains how to analyse case–cohort and two-phase case–control studies with the “survey” package, using examples from http://faculty.washington.edu/norm/software.html. Some of the examples were published by Breslow & Chatterjee (1999).

The data are relapse rates from the National Wilm’s Tumor Study (NWTS). Wilm’s Tumour is a rare cancer of the kidney in children. Intensive treatment cures the majority of cases, but prognosis is poor when the disease is advanced at diagnosis and for some histological subtypes. The histological characterisation of the tumour is difficult, and histological group as determined by the NWTS central pathologist predicts much better than determinations by local institution pathologists. In fact, local institution histology can be regarded statistically as a pure surrogate for the central lab histology.

In these examples we will pretend that the (binary) local institution histology determination (instit) is available for all children in the study and that the central lab histology (histol) is obtained for a probability sample of specimens in a two-phase design. We treat the initial sampling of the study as simple random sampling from an infinite superpopulation. We also have data on disease stage, a four-level variable; on relapse; and on time to relapse.

Case–control designs

Breslow & Chatterjee (1999) use the NWTS data to illustrate two-phase case–control designs. The data are available at http://faculty.washington.edu/norm/software.html in compressed form; we first expand to one record per patient.

```r
> library(survey)
> load(system.file("doc","nwts.rda",package="survey"))
> nwtsnb<-nwts
> nwtsnb$case<-nwts$case-nwtsb$case
> nwtsnb$control<-nwts$control-nwtsb$control
> a<-rbind(nwtsb,nwtsnb)
> a$in.ccs<-rep(c(TRUE,FALSE),each=16)
> b<-rbind(a,a)
> b$rel<-rep(c(1,0),each=32)
> b$n<-ifelse(b$rel,b$case,b$control)
> index<-rep(1:64,b$n)
> nwt.exp<-b[index,c(1:3,6,7)]
> nwt.exp$id<-1:4088
```

As we actually do know histol for all patients we can fit the logistic regression model with full sampling to compare with the two-phase analyses

```r
> glm(rel~factor(stage)*factor(histol), family=binomial, data=nwt.exp)
```
Call: glm(formula = rel ~ factor(stage) * factor(histol), family = binomial, 
data = nwt.exp)

Coefficients:

(Intercept)  factor(stage)2
-2.7066 0.7679
factor(stage)3  factor(stage)4
0.7747 1.0506
factor(histol)2  factor(stage)2:factor(histol)2
1.3104 0.1477
factor(stage)3:factor(histol)2  factor(stage)4:factor(histol)2
0.5942 1.2619

Degrees of Freedom: 4087 Total (i.e. Null); 4080 Residual
Null Deviance: 3306
Residual Deviance: 2943  AIC: 2959

The second phase sample consists of all patients with unfavorable histology as determined by local institution pathologists, all cases, and a 20% sample of the remainder. Phase two is thus a stratified random sample without replacement, with strata defined by the interaction of instit and rel.

> dccs2<-twophase(id=list(~id,~id),subset=~in.ccs, + strata=list(NULL,~interaction(instit,rel)),data=nwt.exp)
> summary(svyglm(rel~factor(stage)*factor(histol),family=binomial,design=dccs2))

Call:
svyglm(formula = rel ~ factor(stage) * factor(histol), design = dccs2, 
family = binomial)

Survey design:
twophase2(id = id, strata = strata, probs = probs, fpc = fpc, 
subset = subset, data = data)

Coefficients:

(Intercept)  factor(stage)2 0.5482 0.1979 2.769 0.005708 **
factor(stage)3 0.4791 0.2032 2.359 0.018515 *
factor(stage)4 1.0037 0.2592 3.872 0.000114 ***
factor(histol)2 1.3505 0.3107 4.346 1.51e-05 ***
factor(stage)2:factor(histol)2 0.1152 0.4410 0.261 0.793876
factor(stage)3:factor(histol)2 0.5066 0.4241 1.194 0.232548
factor(stage)4:factor(histol)2 0.9785 0.6214 1.575 0.115615

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Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1.000876)

Number of Fisher Scoring iterations: 4
Disease stage at the time of surgery is also recorded. It could be used to further stratify the sampling, or, as in this example, to post-stratify. We can analyze the data either pretending that the sampling was stratified or using `calibrate` to post-stratify the design.

```r
> dccs8 <- twophase(id=list(~id,~id), subset=~in.ccs,
+ strata=list(NULL,~interaction(instit, stage, rel)), data=nwt.exp)
> gccs8 <- calibrate(dccs2, phase=2, formula=~interaction(instit, stage, rel))
> summary(svyglm(rel~factor(stage)*factor(histol), family=binomial, design=dccs8))
```

**Call:**

```r
svyglm(formula = rel ~ factor(stage) * factor(histol), design = dccs8,
       family = binomial)
```

**Survey design:**

twophase2(id = id, strata = strata, probs = probs, fpc = fpc,
          subset = subset, data = data)

**Coefficients:**

| Estimate | Std. Error | t value | Pr(>|t|) |
|----------|------------|---------|---------|
| (Intercept) | -2.71604 | 0.10827 | -25.085 | < 2e-16, *** |
| factor(stage)2 | 0.78141 | 0.14726 | 5.306 | 1.35e-07, *** |
| factor(stage)3 | 0.80093 | 0.15250 | 5.262 | 1.68e-07, *** |
| factor(stage)4 | 1.07293 | 0.17817 | 6.022 | 2.33e-09, *** |
| factor(histol)2 | 1.45836 | 0.31780 | 4.589 | 4.96e-06, *** |
| factor(stage)2:factor(histol)2 | -0.04743 | 0.43495 | -0.109 | 0.913 |
| factor(stage)3:factor(histol)2 | 0.28064 | 0.41298 | 0.680 | 0.497 |
| factor(stage)4:factor(histol)2 | 0.90983 | 0.63774 | 1.427 | 0.154 |

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Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1.000876)

Number of Fisher Scoring iterations: 4

```r
> summary(svyglm(rel~factor(stage)*factor(histol), family=binomial, design=gccs8))
```

**Call:**

```r
svyglm(formula = rel ~ factor(stage) * factor(histol), design = gccs8,
       family = binomial)
```

**Survey design:**

calibrate(dccs2, phase = 2, formula = ~interaction(instit, stage, rel))

**Coefficients:**

| Estimate | Std. Error | t value | Pr(>|t|) |
|----------|------------|---------|---------|
| (Intercept) | -2.71604 | 0.10878 | -24.968 | < 2e-16, *** |
| factor(stage)2 | 0.78141 | 0.14729 | 5.305 | 1.35e-07, *** |
| factor(stage)3 | 0.80093 | 0.15212 | 5.265 | 1.68e-07, *** |
| factor(stage)4 | 1.07293 | 0.17905 | 5.993 | 2.77e-09, *** |
| factor(histol)2 | 1.45836 | 0.31774 | 4.592 | 4.88e-06, *** |

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Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1.000876)

Number of Fisher Scoring iterations: 4
Case–cohort designs

In the case–cohort design for survival analysis, a P% sample of a cohort is taken at recruitment for the second phase, and all participants who experience the event (cases) are later added to the phase-two sample.

Viewing the sampling design as progressing through time in this way, as originally proposed, gives a double sampling design at phase two. It is simpler to view the process sub specie aeternitatis, and to note that cases are sampled with probability 1, and controls with probability \( P/100 \). The subcohort will often be determined retrospectively rather than at recruitment, giving stratified random sampling without replacement, stratified on case status. If the subcohort is determined prospectively we can use the same analysis, post-stratifying rather than stratifying.

There have been many analyses proposed for the case–cohort design (Therneau & Li, 1999). We consider only those that can be expressed as a Horvitz–Thompson estimator for the Cox model.

First we load the data and the necessary packages. The version of the NWTS data that includes survival times is not identical to the data set used for case–control analyses above.

```R
> library(survey)
> library(survival)
> data(nwtco)
> ntwco<-subset(nwtco, !is.na(edrel))
```

Again, we fit a model that uses histol for all patients, to compare with the two-phase design

```R
> coxph(Surv(edrel, rel)~factor(stage)+factor(histol)+I(age/12),data=nwtco)
```

Call:

```R
coxph(formula = Surv(edrel, rel) ~ factor(stage) + factor(histol) + I(age/12), data = nwtco)
```

```
  coef    exp(coef)  se(coef)     z      p
factor(stage)2 0.66730    1.94898  0.12156  5.490 4.03e-08
factor(stage)3 0.81737    2.26455  0.12077  6.768 1.31e-11
factor(stage)4 1.15373    3.16999  0.13490  8.553 < 2e-16
factor(histol)2 1.58389    4.87387  0.08869 17.859 < 2e-16
I(age/12) 0.06789    1.07025  0.01492  4.549 5.39e-06
```

Likelihood ratio test=395.4 on 5 df, p=< 2.2e-16
n= 4028, number of events= 571

We define a two-phase survey design using simple random superpopulation sampling for the first phase, and sampling without replacement stratified on rel for the second phase. The subset
argument specifies that observations are in the phase-two sample if they are in the subcohort or are cases. As before, the data structure is rectangular, but variables measured at phase two may be NA for participants not included at phase two.

We compare the result to that given by `survival::cch` for Lin & Ying's (1993) approach to the case–cohort design.

```r
> (dcch<-twophase(id=list(~seqno,~seqno), strata=list(NULL,~rel),
+ subset=~I(in.subcohort | rel), data=nwtco))

Two-phase sparse-matrix design:
  `twophase2(id = id, strata = strata, probs = probs, fpc = fpc,
  subset = subset, data = data)

Phase 1:
  Independent Sampling design (with replacement)
  `svydesign(ids = ~seqno)

Phase 2:
  Stratified Independent Sampling design
  `svydesign(ids = ~seqno, strata = ~rel, fpc = `*phase1*`)

> svycoxph(Surv(edrel,rel)~factor(stage)+factor(histol)+I(age/12),
+ design=dcch)

Call:
  `svycoxph(formula = Surv(edrel, rel) ~ factor(stage) + factor(histol) +
  I(age/12), design = dcch)`

  coef  exp(coef)  se(coef) robust se    z      p
factor(stage)2 0.69266  1.99902  0.22688  0.16279  4.255  2.09e-05
factor(stage)3 0.62685  1.87171  0.22873  0.16823  3.726  0.000194
factor(stage)4 1.29951  3.66751  0.25017  0.18898  6.877  6.13e-12
factor(histol)2 1.45829  4.29861  0.16844  0.14548 10.024 < 2e-16
I(age/12) 0.04609  1.04717  0.02732  0.02302  2.002  0.045233

Likelihood ratio test on 5 df, p= n= 1154, number of events= 571

> subcoh <- nwtco$in.subcohort
> selccoh <- with(nwtco, rel==1|subcoh==1)
> ccoh.data <- nwtco[selccoh,]
> ccoh.data$subcohort <- subcoh[selccoh]
> cch(Surv(edrel, rel) ~ factor(stage) + factor(histol) + I(age/12),
+ data =ccoh.data, subcoh = "subcohort, id="seqno,
+ cohort.size=4028, method="LinYing")

Case–cohort analysis, x$method, LinYing
with subcohort of 668 from cohort of 4028

Call:  `cch(formula = Surv(edrel, rel) ~ factor(stage) + factor(histol) +
  I(age/12), data = ccoh.data, subcoh = "subcohort, id = "seqno,
  cohort.size = 4028, method = "LinYing")`

Coefficients:
Barlow (1994) proposes an analysis that ignores the finite population correction at the second phase. This simplifies the standard error estimation, as the design can be expressed as one-phase stratified superpopulation sampling. The standard errors will be somewhat conservative. More data preparation is needed for this analysis as the weights change over time.

The analysis corresponds to a cluster-sampled design in which individuals are sampled stratified by subcohort membership and then time periods are sampled stratified by event status. Having individual as the primary sampling unit is necessary for correct standard error calculation.

```
> nwtco$eventrec<-rep(0,nrow(nwtco))
> nwtco.extra<-subset(nwtco, rel==1)
> nwtco.extra$eventrec<-1
> nwtco.expd<-rbind(subset(nwtco,in.subcohort==1),nwtco.extra)
> nwtco.expd$stop<-with(nwtco.expd,
+ ifelse(rel & !eventrec, edrel-0.001,edrel))
> nwtco.expd$start<-with(nwtco.expd,
+ ifelse(rel & eventrec, edrel-0.001, 0))
> nwtco.expd$event<-with(nwtco.expd,
+ ifelse(rel & eventrec, 1, 0))
> nwtco.expd$pwts<-ifelse(nwtco.expd$event, 1, 1/with(nwtco,mean(in.subcohort | rel)))
```

Likelihood ratio test on 5 df, p=

n= 1239, number of events= 571
In fact, as the finite population correction is not being used the second stage of the cluster sampling could be ignored. We can also produce the stratified bootstrap standard errors of Wacholder et al (1989), using a replicate weights analysis

```r
(dWacholder <- as.svrepdesign(dBarlow,type="bootstrap",replicates=500))
Call: as.svrepdesign.default(dBarlow, type = "bootstrap", replicates = 500)
Survey bootstrap with 500 replicates.

> svycoxph(Surv(start,stop,event)~factor(stage)+factor(histol)+I(age/12),
+    design=dWacholder)
Call:
svycoxph.svyrep.design(formula = Surv(start, stop, event) ~ factor(stage) +
    factor(histol) + I(age/12), design = dWacholder)

    coef exp(coef) se(coef) z  p
factor(stage)2 0.73589 2.08734 0.17610 4.179 2.93e-05
factor(stage)3 0.59763 1.81780 0.18191 3.285 0.00102
factor(stage)4 1.39068 4.01757 0.21184 6.565 5.21e-11
factor(histol)2 1.50450 4.50191 0.17194 8.750 < 2e-16
I(age/12) 0.04315 1.04410 0.02645 1.632 0.10272

Likelihood ratio test=NA on 5 df, p=NA
n= 1239, number of events= 571
```

**Exposure-stratified designs**

Borgan et al (2000) propose designs stratified or post-stratified on phase-one variables. The examples at [http://faculty.washington.edu/norm/software.html](http://faculty.washington.edu/norm/software.html) use a different subcohort sample for this stratified design, so we load the new `subcohort` variable

```r
> load(system.file("doc","nwtco-subcohort.rda",package="survey"))
> nwtco$subcohort<-subcohort
> d_BorganII <- twophase(id=list(~seqno,~seqno),
+    strata=list(NULL,~interaction(instit,rel)),
+    data=nwtco, subset=~I(rel |subcohort))
> (b2<-svycoxph(Surv(edrel,rel)~factor(stage)+factor(histol)+I(age/12),
+    design=d_BorganII))
Call:
svycoxph.svyrep.design(formula = Surv(edrel, rel) ~ factor(stage) +
    factor(histol) + I(age/12), design = d_BorganII)

    coef exp(coef) se(coef) robust se z  p
factor(stage)2 0.46286 1.58861 0.23762 0.18087 2.559 0.01049
factor(stage)3 0.58309 1.79156 0.23965 0.17848 3.267 0.00109
factor(stage)4 1.05967 2.88541 0.26182 0.20524 5.163 2.43e-07
factor(histol)2 1.59744 4.94035 0.17688 0.13342 11.973 < 2e-16
I(age/12) 0.04315 1.04410 0.02942 0.03337 1.237 0.21732

Likelihood ratio test= on 5 df, p=
n= 1062, number of events= 571
```
We can further post-stratify the design on disease stage and age with `calibrate`

```r
> d_BorganIIps <- calibrate(d_BorganII, phase=2, formula=~age+interaction(instit,rel,stage))
> svycoxph(Surv(edrel,rel)~factor(stage)+factor(histol)+I(age/12),
+ design=d_BorganIIps)
```

Call:
```
svycoxph(formula = Surv(edrel, rel) ~ factor(stage) + factor(histol) +
I(age/12), design = d_BorganIIps)
```

```
                 coef exp(coef) se(coef) robust se     z      p
factor(stage)2  0.67006  1.95436  0.23776   0.14263 4.698 2.63e-06
factor(stage)3  0.75935  2.13689  0.23952   0.14228 5.337 9.45e-08
factor(stage)4  1.27046  3.56249  0.26150   0.15176 8.371 < 2e-16
factor(histol)2 1.57302  4.82121  0.17627   0.12999 12.101 < 2e-16
I(age/12)  0.03135  1.03185  0.02984   0.03346 0.937 0.349
```

Likelihood ratio test= on 5 df, p=
```
n= 1062, number of events= 571
```

References


Therneau TM and Li H., Computing the Cox model for case-cohort designs. *Lifetime Data Analysis* 5:99-112, 1999