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Proportion difference and confidence interval based on Cochran-Mantel-Haenszel method in stratified multi-center clinical trial

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ABSTRACT:

In stratified randomized multi-center clinical trials, we often take account of stratified center factors in the estimation of common treatment effect. In particular, strata-adjusted proportion difference can be obtained by weighted average of stratum-specific proportion differences. Several weighting strategies are available such as Cochran-Mantel-Haenszel (CMH) method, etc. There is no SAS option in frequency procedure to produce strata-adjusted proportion difference from CMH method. In the text, we will develop a program to calculate 95% asymptotic confidence interval for strata-adjusted proportion difference based on Wald-type statistic.

INTRODUCTION:

In clinical trials, the parameter of interest in many situations is the difference of the binomial response rates between two treatments, for example, the cure of a disease or the occurrence of an adverse event between study drug and control treatment. This article considers the interval estimation for the difference of binomial proportions from stratified 2x2 samples using the normal approximation for a weighted average of the differences over all strata.

Suppose that patients are randomly assigned into two treatment groups (i = 0, 1) and there are K strata (K ≥ 2). Let n_{ij} be the number of patients and x_{ij} be the number of responders in stratum j and treatment i. Let p_{ij} be the true responder rate and $\widehat{p_{ij}} = x_{ij}$ / n_{ij} be the observed responder rate in stratum j and treatment i. Let $N_i = \sum_{j=1}^{K} n_{ij}$ denote the total number of patients in treatment i. Let

$$\delta_j = p_{1j} - p_{0j}$$

be the true rate difference,

$$\hat{\delta}_j = \widehat{p_{1j}} - \widehat{p_{0j}}$$

be the observed rate difference between the two treatments in stratum j.
The goal is to provide an estimate and the associated confidence interval of the overall treatment difference across strata. In the weighted average approaches, the overall treatment difference is usually defined by

$$\delta_w = \sum_{j=1}^{K} w_j\, \delta_j,$$

and estimated by

$$\hat{\delta}_w = \sum_{j=1}^{K} w_j\, \hat{\delta}_j,$$

where $w_j = \left(n_{1j}^{-1} + n_{0j}^{-1}\right)^{-1} / \left[\sum_{j=1}^{K}\left(n_{1j}^{-1} + n_{0j}^{-1}\right)^{-1}\right]$ is the weight for stratum j with $\sum_1^K w_j = 1$.

The 100(1−α)% confidence interval for δ_w is given by

$$\hat{\delta}_w \pm Z_{\alpha/2}\sqrt{\sum_{j=1}^{K} w_j^2 \hat{V}(\hat{\delta}_j)},$$

where $\hat{V}(\hat{\delta}_j) = \left(\widehat{p_{1j}}\left(1 - \widehat{p_{1j}}\right)/n_{1j}\right) + \left(\widehat{p_{0j}}\left(1 - \widehat{p_{0j}}\right)/n_{0j}\right)$ is the variance of the observed rate difference in each stratum j (j=1, ……, K) and Z_α is the (1-α) percentile of the standard normal distribution.

SOLUTION:

The computation of the test statistic is as follows. Suppose there are K strata. The 2*2 table on each stratum j is as below.

	Groups		
	Group 1	Group 2	
Response	Treatment	Control	Total
Yes	x_{1j}	x_{0j}	x_j
No	$n_{1j} - x_{1j}$	$n_{0j} - x_{0j}$	$N_j - x_j$
Total	n_{1j}	n_{0j}	N_j

EXAMPLE:

1. The source data:

Table 1 Example Dataset (first 20 observations)

	TRT01PN	response	siten	subject
1	2	1	1	1
2	2	2	1	2
3	2	2	1	3
4	2	2	1	4
5	2	2	1	5
6	2	2	1	6
7	2	2	1	7
8	2	1	1	8
9	2	1	1	9
10	2	2	1	10
11	2	1	1	11
12	2	2	1	12
13	2	1	1	13
14	2	2	1	14
15	2	2	1	15
16	2	2	1	16
17	2	2	1	17
18	2	2	1	18
19	2	2	1	19
20	2	2	1	20

2. Strata-adjusted CI:

Table 2 Output of Strata-Adjusted Summary

	Adjusted proportion difference	Wald CI (lower)	Wald CI (upper)
CMH Statistic	8.74	-0.227	17.70

3. Unadjusted CI:

Table 3 Output of Unadjusted Summary

	Unadjusted proportion difference	Wald CI (lower)	Wald CI (upper)
Unstratified Wald Statistic	8.93	-0.400	18.26

SAS CODE:

Variables description in the macro %CI：

Response	Response variable in SAS dataset.
Trt	Treatment variable in SAS dataset.

Datain	Input SAS dataset name, include subject id, treatment, strata and response.
Dataout	Output SAS dataset name.
Level	Type 1 error.
Strata	Strata variable in SAS dataset.

```
%macro CI (response=, trt=, strata=, datain=, dataout=, level=);
**1. CMH CI;
proc freq data=&datain(where=(&response.^=.));
       tables &strata*&trt./out=outt1(rename=(count=tot));
run;

proc freq data=&datain(where=(&response.^=.));
       tables &strata*&trt.*&response./out=out11;
run;

data out22;
       merge outt1 out11(where=(&response.=1));
       by &strata &trt.;
       if count=. then count=0;
       if tot^=. then pct=count/tot;
       else pct=.;
       gs=compress(put(&trt., best.)||put(&strata, best.));
run;

proc sql;
       create table out_2 as
       select *, count(distinct &trt.) as numoftrt
       from out22
       group by &strata
       having numoftrt ge 2;
quit;

proc sql noprint;
       select count(distinct &strata) into: sn1 from out_2;
quit;

%let sn1=&sn1.;
%put &sn1.;

proc transpose data=out_2 out=out23 prefix=f;
       var tot;
       id gs;
run;

proc transpose data=out_2 out=out24 prefix=p;
       var pct;
       id gs;
run;

data out25;
       merge out23 out24;
run;

data &dataout.;
       set out25;
       retain rps p_diff vp 0;
       array fn1 f11-f1&sn1.;
       array fn2 f21-f2&sn1.;
```

```
       array pn1 p11-p1&sn1.;
       array pn2 p21-p2&sn1.;
       array rp  rp1-rp&sn1.;
       array wn  wn1-wn&sn1.;
       array wp  wp1-wp&sn1.;
       array vn  vn1-vn&sn1.;

       do i=1 to &sn1.;
             if fn1(i)^=. and fn2(i)^=. then rp(i)=(fn1(i)**-1+fn2(i)**-1)**-1;
             else if fn1(i)^=. and fn2(i)=. then rp(i)=(fn1(i)**-1)**-1;
             else if fn1(i)=. and fn2(i)^=. then rp(i)=(fn2(i)**-1)**-1;
             if rp(i)=. then rp(i)=0;
       end;
       do j=1 to &sn1.;
             rps+sum(of rp(j));
       end;
       do l=1 to &sn1.;
             wn(l)=rp(l)/rps;
             if pn1(l)^=. and pn2(l)^=. then wp(l)=wn(l)*(pn1(l)-pn2(l));
             else if pn1(l)^=. and pn2(l)=. then wp(l)=wn(l)*(pn1(l));
             else if pn1(l)=. and pn2(l)^=. then wp(l)=wn(l)*(-pn2(l));
             p_diff+wp(l);
       end;
       do k=1 to &sn1.;
             if fn1(k)^=. and fn2(k)^=. then vn(k)=(((fn1(k)**-1+fn2(k)**-1)**-
             1/(rps))**2)*(pn1(k)*(1-pn1(k))/fn1(k)+pn2(k)*(1-pn2(k))/fn2(k));
             else if fn1(k)^=. and fn2(k)=. then vn(k)=(((fn1(k)**-1)**-
             1/(rps))**2)*(pn1(k)*(1-pn1(k))/fn1(k));
             else if fn1(k)=. and fn2(k)^=. then vn(k)=(((fn2(k)**-1)**-
             1/(rps))**2)*(pn2(k)*(1-pn2(k))/fn2(k));
             vp+vn(k);
       end;
       cll=p_diff-quantile('normal',1-&level/2)*sqrt(vp);
       clu=p_diff+quantile('normal', &level/2)*sqrt(vp);
       length col $40;
       diff_ci=strip(put(p_diff*100,5.1))||" ("||strip(put(cll*100,5.1))||",
"||strip(put(clu*100,5.1))||")";
run;

**2. Unadjusted CI method;
ods output RiskDiffCol2=&dataout.1;
proc freq data=&datain(where=(&response^=.));
       tables &trt*&response/cmh riskdiff alpha=&level;
run;

data &dataout;
       set &data.1(in=a where=(row=" Row Mean Scores Differ") keep=row Risk LowerCL
UpperCL) ;
       length diff_ci $100;
       ** 2-sided CI;
       diff_ci=strip(put(Risk*100,5.1))||" ("||strip(put(LowerCL*100,5.1))||",
"||compress(put(UpperCL*100,5.1))||")";
       keep diff_ci;
run;
%mend;

%CI (response=response, trt=trt01pn, strata=siten, datain= adsl, dataout=cmh,
level=0.05);
```

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