

Enhancing ISS Analyses with Continuity-Corrected MH Method A SAS-Based Solution for Zero-Event Strata

03/23/2026

VeraMed

Brief Introductory

Kaixiang Li is currently a Programmer at BioPier LLC, a Veramed Company. Since joining the organization, he has collaborated with cross-functional teams to contribute to more than 30 projects. He has developed a solid understanding of CDISC standards and effectively applies his statistical and programming expertise to support and successfully deliver assigned project responsibilities

Dr. Ji Qi is currently a Principal Statistician at BioPier LLC, a Veramed Company. Over the past years with the company, she has led or co-led statistical and programming support for approximately 15 projects across therapeutic areas, including multiple integrated summary analysis projects, and has contributed as a team member to more than 30 additional projects. She has a deep understanding of regulatory submission expectations for the statistical and programming components of submissions and CDISC standards and effectively applies both her own and the team's expertise to meet those requirements.

Content

01 Mantel–Haenszel Method

02 Zero Event

03 Continuity Correction

04 Sas Based Macro

05 Discussing

Mantel–Haenszel Method

Mantel–Haenszel Method

- Mantel–Haenszel method is a classical fixed-effect approach used to pool effect estimates from stratified 2×2 tables or multiple studies.
- Common binary effect measures **Risk Ratio (RR)**/ **Odds Ratio (OR)** / **Risk Difference (RD)**
- The **risk difference** gauges the effect on an absolute scale as it evaluates the difference between the event rates of the two groups.
- The **risk/odds ratio**, on the other hand, gauges the effect on a relative scale by taking the ratio of the two event rates/odds.

Stratum	Event	No Event	sum
Active	A	B	A+B
Control	C	D	C+D

Effect Measure	Definition	Interpretation
Relative Risk (RR)	$RR = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$	RR=1: No association between exposure and outcome. RR < 1: Exposure decreases risk (protective effect). RR > 1: Exposure increases risk (risk factor).
Odds Ratios (OR)	$OR = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$	OR = 1: No association between exposure and outcome. OR < 1: Exposure is associated with lower odds (protective effect). OR > 1: Exposure is associated with higher odds (risk factor).
Risk Difference (RD)	$RD = \frac{A}{A+B} - \frac{C}{C+D}$	RD = 0: No difference in risk between the exposed and control groups. RD < 0: Exposure decreases risk (protective effect). RD > 0: Exposure increases risk (harmful effect).

Mantel–Haenszel Method

Logic: Combines effect size estimates from multiple strata into a weighted average, where weights reflect the amount of information each study contributes, typically based on sample size and variance.

Clinical trial	Event	No Event	Sum
Active	A	B	A+B
Control	C	D	C+D

$RD_1 (RR_1/OR_1)$

Stratum1	Event	No Event	Sum
Active	A	B	A+B
Control	C	D	C+D

$RD_i (RR_i/OR_i)$

Stratum I	Event	No Event	Sum
Active	A	B	A+B
Control	C	D	C+D

Mantel–Haenszel Method

Example Procession for RD:

Stratum 1	Event	No Event	Sum
Active	A	B	n11=(A+B)
Control	C	D	n21=(C+D)
			N1=(n11+n21)

Stratum I	Event	No Event	Sum
Active	A	B	n1i=(A+B)
Control	C	D	n2i=(C+D)
			Ni=(n1i+n2i)

$$w_i = \frac{n_{1i}n_{2i}}{N_i}$$

$$RD_i = \frac{A}{A+B} - \frac{C}{C+D}$$

$$RD_{MH} = \frac{\sum w_i RD_i}{\sum w_i}$$

$$SE(RD_{MH}) = \sqrt{\frac{J}{K^2}}$$

$$J = \sum \left(\frac{a_i b_i n_{2i}^3 + c_i d_i n_{1i}^3}{n_{1i} n_{2i} N_i^2} \right)$$

$$K = \sum \left(\frac{n_{1i} n_{2i}}{N_i} \right)$$

$$95\%CI(RD_{MH}) = RD_{MH} \pm 1.96 \times SE(RD_{MH})$$





Zero Event

Zero Event

Zero Event in Meta-Analysis

When event rates are low, it is common to observe no event of interest in one or both arms in a study, resulting in a so-called single- or double-zero event.

Stratum(n)	Event	No Event	Sum
Active	0	B	$n_{1i}=(0+B)$

Control	C	D	$n_{2i}=(C+D)$
---------	---	---	----------------

Stratum(n)	Event	No Event	Sum
Active	0	B	$n_{1i}=(B)$

Control	0	D	$n_{2i}=(D)$
---------	---	---	--------------

Single-Zero

$$W_i = \frac{n_{1i}n_{2i}}{N_i}$$

$$RD_{MH} = \frac{\sum W_i RD_i}{\sum W_i}$$

$$RD_i = \frac{A}{A+B} - \frac{C}{C+D}$$

Double-Zero

$$OR_i = \frac{\frac{A}{B}}{\frac{C}{D}} \quad RR_i = \frac{\frac{A}{A+B}}{\frac{C}{C+D}}$$

Zero Event – First-Order Bias-Exclude Double-Zero Event



Stratum 1 (has events):

- Treatment risk = 0.10
- Control risk = 0.00
→ RD = 0.10

If we excluding the double-zero events

$$RD_{mh} = \frac{1}{10} - 0 = 0.1$$

Stratum 2 (double-zero stratum):

- Treatment risk = 0
- Control risk = 0
→ RD = 0

If we including the double-zero events

$$RD_{mh} = \frac{5*0.1+0*5}{5+5}=0.05$$

Stratum(1)	Event	No Event	Sum
Active	1	9	10
Control	0	10	10

Stratum(2)	Event	No Event	sum
Active	0	10	10
Control	0	10	10

Zero Event – First-Order Bias-Exclude Double-Zero Event



Stratum 1 (has events):

- Treatment risk = 0.10
 - Control risk = 0.00
- RD = 0.10

Stratum 2 (double-zero stratum):

- Treatment risk = 0
 - Control risk = 0
- RD = 0

If we excluding the double-zero events

$$RD_{mh} = \frac{1}{10} - 0 = 0.1$$

If we including the double-zero events

$$RD_{mh} = \frac{5*0.1+0*5}{10}=0.05$$

A double-zero stratum provides information that the true risk difference is zero.

If you exclude these strata, you reduce the total weight without reducing the numerator, which systematically pushes the combined RD away from zero and introduces first-order bias (a bias of decreases at the rate of $1/n$ as the sample size increases).



Continuity Correction

Continuity Correction

The routine use of adding 0.5 to the value in each cell of a 2 × 2 table is proved to be optimal in terms of reducing the first-order bias

Stratum(n)	Event	No Event	Sum
Active	A	0	n1i=(A)
Control	0	D	n2i=(D)

Stratum(n)	Outcome(+)	Outcome(-)	sum
Active	0.5	B+0.5	n1i=(B+1)
Control	0.5	D+0.5	n2i=(D+1)

$$RD_i = \frac{A}{A+B} - \frac{C}{C+D}$$

$$OR_i = \frac{\frac{A}{B}}{\frac{C}{D}} \quad RR_i = \frac{\frac{A+B}{C}}{\frac{A+B}{C+D}}$$

Zero Subject



Stratum(n)	Event	No Event	Sum
Active	0	0	N1i=0
Control	C	D	n2i=(C+D)

$$W_i=\frac{n_{1i}n_{2i}}{N_i}$$

$$RD_{MH}=\frac{\sum W_iRD_i}{\sum W_i}$$

$$RD_i=\frac{A}{A+B}-\frac{C}{C+D}$$

Zero subject stratum should be deleted from study, Because their weight effect factor will be 0.
Not reasonable for after Continuity Correction.

Stratum(n)	Event	No Event	Sum
Active	0.5	0.5	N1i=1
Control	C+0.5	D+0.5	n2i=(C+D)+1



SAS Based Macro

SAS Based Macro



	Treatment 1 (Bign1)	Treatment 2 (Bign2)	Treatment 3 (Bign3)	Treatment 4 (Bign4)	Control Grp (Bign5)
RD/RR/OR	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
p-value	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	

SAS Based Macro

Create-data set

	STUDID	SUBJID	ASTDT	AENDT	GRP	PT
1	101	0001	08FEB2018	11FEB2018	1	Headache
2	101	3020	14AUG2018	14AUG2018	3	Headache
3	101	3030	14AUG2018	14AUG2018	3	Headache
4	101	3030	16AUG2018	16AUG2018	3	Headache
5	101	3090	21AUG2018	21AUG2018	3	Headache
6	101	3120	23AUG2018	23AUG2018	3	Headache
7	102	1002	11SEP2019	12SEP2019	4	Headache
8	102	1005	14SEP2019	14SEP2019	5	Headache
9	102	2003	05OCT2019	06OCT2019	4	Headache
10	102	3002	22OCT2019	22OCT2019	5	Headache
11	102	3004	26OCT2019	26OCT2019	4	Headache
12	107	0002	30JUL2021	30JUL2021	3	Headache
13	108	0023	24FEB2022	24FEB2022	3	Headache
14	109	1014	05APR2023	05APR2023	4	Headache
15	109	2024	26MAY2023	27MAY2023	4	Headache
16	109	2027	23JUN2023	24JUN2023	4	Headache
17	109	2028	26MAY2023	26MAY2023	4	Headache
18	110	1051	12JAN2022	13JAN2022	3	Headache
19	110	1064	28JAN2022	28JAN2022	3	Headache
20	110	1084	25FEB2022	25FEB2022	4	Headache

Dummy6

DEN1	DEN2	DEN3	DEN5	DEN4	N1	N2	N3	N4	N5	TEXT	STUDID
44	6	18	16	0	0	0	0	0	0	Headache	101
0	0	0	12	30	0	0	0	0	0	Headache	102
0	0	6	0	0	0	0	0	0	0	Headache	103
0	0	24	0	0	0	0	0	0	0	Headache	104
0	0	26	0	0	0	0	0	0	0	Headache	107
0	0	36	0	0	0	0	0	0	0	Headache	108
0	0	0	28	36	0	0	0	0	0	Headache	109
0	20	18	18	18	0	0	0	0	0	Headache	110

SAS Based Macro

Real-data

	STUDID	SUBJID	ASTDT	AENDT	GRP	PT
1	101	0001	08FEB2018	11FEB2018	1	Headache
2	101	3020	14AUG2018	14AUG2018	3	Headache
3	101	3030	14AUG2018	14AUG2018	3	Headache
4	101	3030	16AUG2018	16AUG2018	3	Headache
5	101	3090	21AUG2018	21AUG2018	3	Headache
6	101	3120	23AUG2018	23AUG2018	3	Headache
7	102	1002	11SEP2019	12SEP2019	4	Headache
8	102	1005	14SEP2019	14SEP2019	5	Headache
9	102	2003	05OCT2019	06OCT2019	4	Headache
10	102	3002	22OCT2019	22OCT2019	5	Headache
11	102	3004	26OCT2019	26OCT2019	4	Headache
12	107	0002	30JUL2021	30JUL2021	3	Headache
13	108	0023	24FEB2022	24FEB2022	3	Headache
14	109	1014	05APR2023	05APR2023	4	Headache
15	109	2024	26MAY2023	27MAY2023	4	Headache
16	109	2027	23JUN2023	24JUN2023	4	Headache
17	109	2028	26MAY2023	26MAY2023	4	Headache
18	110	1051	12JAN2022	13JAN2022	3	Headache
19	110	1064	28JAN2022	28JAN2022	3	Headache
20	110	1084	25FEB2022	25FEB2022	4	Headache

Dummy6

DEN1	DEN2	DEN3	DEN5	DEN4	N1	N2	N3	N4	N5	TEXT	STUDID
44	6	18	16	0	0	0	0	0	0	Headache	101
0	0	0	12	30	0	0	0	0	0	Headache	102
0	0	6	0	0	0	0	0	0	0	Headache	103
0	0	24	0	0	0	0	0	0	0	Headache	104
0	0	26	0	0	0	0	0	0	0	Headache	107
0	0	36	0	0	0	0	0	0	0	Headache	108
0	0	0	28	36	0	0	0	0	0	Headache	109
0	20	18	18	18	0	0	0	0	0	Headache	110

SAS Based Macro

Merge with dummy

STAT	N1	N2	N3	N4	N5	DEN1	DEN2	DEN3	DEN4	DEN5	TEXT
n (%)	1		4			44	6	18	0	16	Headache

DEN1	DEN5	N1	N5	TEXT	STUDID
44	16	1	0	Headache	101
0	12	0	2	Headache	102
0	0	0	0	Headache	103
0	0	0	0	Headache	104
0	0	0	0	Headache	107
0	0	0	0	Headache	108
0	28	0	0	Headache	109
0	18	0	0	Headache	110

	DEN1	DEN5	N1	N5	TEXT	GRP	COUNT	AVAL	STUDID
1	45	17	1.5	0.5	Headache	1	1.5	1	101
2	45	17	1.5	0.5	Headache	1	43.5	2	101
3	45	17	1.5	0.5	Headache	2	0.5	1	101
4	45	17	1.5	0.5	Headache	2	16.5	2	101

SAS Based Macro

```
%let ntrt=5;
%let nloop=%eval(&ntrt-1);

%macro pci;
  %do i=1 %to &nloop.;
    data cnt_all; set stat_n_;;
      if n&i=. then n&i=0;
      if n&ntrt=. then n&ntrt.=0;

      keep STUDID text n&i n&ntrt. den&i den&ntrt.;
      proc sort;
        by STUDID TEXT n&i n&ntrt. den&i den&ntrt.;
      run;
      data cnt_all3;
        set cm_all;
        if den&i.=0 or den&ntrt.=0 then delete;
        if n&i.=0 or n&ntrt.=0 then do;
          n&i.=n&i.+0.5;n&ntrt.=n&ntrt.+0.5;den&i.=den&i.+1;den&ntrt.=den&ntrt.+1;
          grp=1; count=n&i.;      aval=1; output;
          grp=1; count=den&i.-n&i.; aval=2; output;
          grp=2; count=n&ntrt.;    aval=1; output;
          grp=2; count=den&ntrt.-n&ntrt.; aval=2; output;
        end;
        else do;
          grp=1; count=n&i.;      aval=1; output;
          grp=1; count=den&i.-n&i.; aval=2; output;
          grp=2; count=n&ntrt.;    aval=1; output;
          grp=2; count=den&ntrt.-n&ntrt.; aval=2; output;
        end;
        keep n&i. n&ntrt. count grp aval text den&i. den&ntrt. study;
      run;

      proc sort data=cnt_all3; by text study grp aval; run;

      ods output CommonRelRisks=cmh_rr commonpdiff=cmh_rd CommonPdiffTests=cmh_pval;
      proc freq data=cnt_all3 order=data; by text;
        tables study*grp*aval/ nocol nopercnt cmh relrisk riskdiff(common) commonriskdiff(TEST=MH CL=MH);
        weight count/zeros;
      run;
    %end;
  %mend;
```

Continuity Correction

MH method

Discussing

SAS Based Macro



With Continuity Correction

Preferred Term	Treatment 1 (N=44)	Treatment 2 (N=26)	Treatment 3 (N=128)	Treatment 4 (N=84)	Control (N=74)
Headache					
Risk Difference % (95% CI)	0.4 (-9.2, 10.0)	1.2 (-8.0, 10.4)	15.5 (2.1, 28.9)	4.7 (-4.2, 13.6)	
p-value	0.9361	0.7935	0.0237	0.2973	

Without Continuity Correction

Preferred Term	Treatment 1 (N=44)	Treatment 2 (N=26)	Treatment 3 (N=128)	Treatment 4 (N=84)	Control Grp (N=74)
Headache					
Risk Difference % (95% CI)	2.3 (-2.1, 6.7)	0.0 (0.0, 0.0)	16.5 (4.4, 28.6)	5.0 (-3.2, 13.3)	
p-value	0.3117	-	0.0077	0.2318	

Discussion-RD



With(L)/Without(R) Continuity Correction	Treatment 1 (Den1)	Treatment 1 (Den2)	CI Range
Risk difference	0.4 (-9.2, 10.0)	2.3 (-2.1, 6.7)	19.2/8.8

With(L)/Without(R) Continuity Correction	Treatment 2 (Den1)	Treatment 2 (Den2)	CI Range
Risk difference	1.2 (-8.0, 10.4)	0.0 (0.0, 0.0)	18.4/0

Discussion-RD



With/Without Continuity Correction	Treatment 3 (Den1)	Treatment 3 (Den2)	CI Range
Risk difference	15.5 (2.1, 28.9)	16.5 (4.4, 28.6)	26.8/24.2

With/Without Continuity Correction	Treatment 4 (Den1)	Treatment 4 (Den2)	CI Range
Risk difference	4.7 (-4.2, 13.6)	5.0 (-3.2, 13.3)	17.8/16.5

Conclusion

Without Continuity Correction in meta-analyses using Mantel–Haenszel decreases its confidence interval narrower confidence interval reflects greater stability of the RD estimate, smaller variance, higher statistical efficiency, and clearer clinical interpretability

Discussion-OR/RR



With Continuity Correction

TEXT	TABLE	STUDYTYPE	STATISTIC	METHOD	VALUE	LOWERCL	UPPERCL
Headache	Summary for GRP * AVAL	Case-Control	Odds Ratio	Mantel-Haenszel	1.1379	0.0441	29.3590
Headache	Summary for GRP * AVAL	Cohort	Relative Risk (Column 1)	Mantel-Haenszel	1.1333	0.0485	26.4898
Headache	Summary for GRP * AVAL	Cohort	Relative Risk (Column 2)	Mantel-Haenszel	0.9960	0.9021	1.0996

Without Continuity Correction

	TEXT	TABLE	STUDYTYPE	STATISTIC	METHOD	VALUE	LOWERCL	UPPERCL
1	Headache	Summary for GRP * AVAL	Case-Control	Odds Ratio	Mantel-Haenszel			
3	Headache	Summary for GRP * AVAL	Cohort	Relative Risk (Column 1)	Mantel-Haenszel			
5	Headache	Summary for GRP * AVAL	Cohort	Relative Risk (Column 2)	Mantel-Haenszel	0.9773	0.9342	1.0223



Thank you