

# Confidence Intervals for the Difference Between Two Proportions for Correlated Binary Response

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## Abstract

Interval estimation for the risk difference in the correlated binary data is often an important problem in many biomedical applications. For instance, in the study of cancer and leukemia group B randomized trials (Cooper et al., 1993), it is often of interest to compare two chemotherapy treatments with respect to success rates of the patients with multiple myeloma who survived at the end of this study. In this project, the interval procedures are developed for estimating the difference between success rates of the two chemotherapy treatments in this study. An extensive simulation study is conducted for the purposes of evaluating and comparing the performance of the proposed intervals, in terms of coverage and expected lengths. An application to biomedical data is used to illustrate the proposed methods.

**Key Words:** correlated binary data, confidence interval, coverage probability, difference between the proportions, independent binary data

## 1. Introduction

Independence of the observations is one of the key assumptions of the binomial distribution for binary outcome data. This assumption will be violated if multiple observations on the same individual are pooled with observations from different individuals, since the former will tend to show less variability than the latter, i.e. will tend to be positively correlated. In many biomedical, toxicological, clinical medicine, and epidemiological applications, responses are binary as well as positively correlated. For independent binary data, there are numerous binomial interval procedures available in literature for the estimation of the difference between the response rates in two treatment groups.

Newcombe (1998) compared 11 methods for constructing the confidence interval for the difference between the response rates for independent data. Of these 11 methods he proposed a new method (method 10 in his paper) which is remarkably simple, achieves better coverage properties, and is a non-iterative asymptotic normality approach. We extend method 10 of Newcombe (1998) for correlated binary data.

For independent data, there are other classes of methods available, which work well in situations when the asymptotic distribution of the observed risk difference can be far from normal especially for the small expected number of observations in either of the two treatment groups. In such situations, one would use an "exact" binomial interval such as Clopper-Pearson interval, which is usually used as a gold standard for calculating confidence interval for a single proportion for independent data. Chen and Tipping (2002) made direct extension of this method for a single proportion for correlated binary data. We further extend this Clopper-Pearson method for the difference between the success rates using the method of variance estimates recover (MOVER) introduced by Zou and Donner (2008).

In a recent paper by Krishnamoorthy and Zhang (2015), a closed-form approximate confidence interval for the difference between two independent binomial proportions was proposed based on the constrained moment estimates discussed on Section 7.2.1 of Caella and Berger (2001). We also extend this method for the correlated binary data.

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It is, therefore, the primary aim of this paper to develop and evaluate methods for constructing confidence intervals for  $\pi_1 - \pi_2$  in the analysis of correlated binary outcome data by direct extensions of above existing methods for tackling independent data using the concept of effective sample size.

## 2. Proposed Method

There are two steps in the proposed procedure. The first step consists of the estimation of the complex variances for complex survey designs to obtain the degrees-of-freedom adjusted effective sample sizes as well as adjusted total successes. This adjusted effective sample size represents the number of independent and identically distributed observations that is required to achieve the same level of precision in the estimation of proportion.

In the second step, existing binomial interval procedures are applied to calculate the confidence interval using the degrees-of-freedom adjusted effective sample sizes as well as adjusted total successes.

### 2.1 First Step of the Proposed Method

For complex survey designs, it involves clustering of sample persons and differential sampling weights. Due to differential weighting, the complex variance for clustered design is typically larger than the simple random sample variance for the same sample size. Ignoring sample weights can lead to biased estimates for proportion. To avoid this problem, Koran and Graubard (1998) used  $\hat{\pi}_i$  as the weighted estimate based on the complex survey design and calculated its complex variance accordingly as follows.

Let  $w_{ij}$  ( $j = 1, \dots, m_i; i = 1, 2$ ) be a set of weights such that  $w_{ij} \geq 0$  and  $\sum_{j=1}^{m_i} w_{ij} = 1$ . Then, an unbiased estimator of  $\pi_i$  and its complex variance estimator can be obtained as

$$\hat{\pi}_i^w = \sum_{j=1}^{m_i} w_{ij} \hat{\pi}_{ij} \quad \text{and} \quad \hat{v}(\hat{\pi}_i^w) = \frac{1}{m_i - 1} \sum_{j=1}^{m_i} w_{ij} (\hat{\pi}_{ij} - \hat{\pi}_i^w)^2.$$

Following Koran and Graubard (1998), based on the weighted estimate  $\hat{\pi}_i^w$  and its complex variance estimate the df adjusted effective sample size for  $i$ th group can be obtained as

$$n_{i.}^{e*} = \frac{\hat{\pi}_i^w (1 - \hat{\pi}_i^w)}{\hat{v}(\hat{\pi}_i^w)} \left( \frac{t_{n_{i.}-1}(1 - \alpha/2)}{t_{m_i-1}(1 - \alpha/2)} \right)^2,$$

Then, the total number of affected individuals in the  $i$ th group  $y_i$  can be adjusted as  $y_i^{e*} = n_{i.}^{e*} \hat{\pi}_i^w$ , and treat  $y_i^{e*}$  as a binomial random variable with parameters  $n_{i.}^{e*}$  and  $\pi_i$ .

### 2.2 Second Step of the Proposed Method

After adjusting the sample size and the total number of affected individuals in the  $i$ th group, we apply three existing methods originally for tackling independent data to the adjusted data  $(n_{i.}^{e*}, y_i^{e*})$  ( $i = 1, 2$ ) for the computation of confidence intervals of  $\pi_1 - \pi_2$ . We summarize our proposed methods in Table 1.

## 3. Simulations

This section reports on a simulation study conducted to investigate the small and moderate sample behavior of the proposed methods in terms of observed coverage probability and average interval length using the pre-assigned confidence level of 95%. We considered two treatment groups with number of clusters  $m_1 = 19$  and  $m_2 = 27$ . Based on the historical

**Table 1:** Summary of abbreviations for various confidence interval estimators.

Abbreviation	Confidence interval (CI)
MW1	Wilson CI based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{EW}$
MW2	Wilson CI based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{OW}$
CP1	Clopper-Pearson CI based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{EW}$
CP2	Clopper-Pearson CI based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{OW}$
CM1	Constrained Moment CI based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{EW}$
CM2	Constrained Moment based on $(n_{i.}^{e*}, y_{i.}^{e*})$ using $\hat{v}(\hat{\pi}_i) = V_{OW}$

**Table 2:** Median coverage probability (CP) and median expected length (EL) of the 95% confidence intervals for  $\pi$  based on 180 parameter combinations for 15 methods.

Method	Median CP	Median EL	Length Comparison
			individual/R
MW1	0.957	0.303	1.070
MW2	0.959	0.296	1.043
CP1	0.969	0.326	1.151
CP2	0.971	0.317	1.119
CM1	0.959	0.304	1.072
CM2	0.956	0.297	1.048
R	0.946	0.284	1.000

data in biomedical applications, we allowed equal and unequal intraclass correlation coefficients between two treatment groups as  $(\phi_1, \phi_2) = (0.1054, 0.2148), (0.249, 0.324), (0.10, 0.01),$  and  $(0.30, 0.30)$ . We also considered the fixed cluster sizes for the two treatment groups taken from the low-dose and control groups for the data of Paul (1982). A common value of  $\pi_2 = 0.20$  and a set of values for  $\delta = \pi_1 - \pi_2 = 0.00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50$  were considered. We generated data from the beta-binomial distribution using the IMSL random number generators RNBET and RNBIN.

We compute the observed coverage probability for the intraclass correlation by the relative frequency out of 1000 intervals that contained the true value. The average interval length is the mean of the lengths computed on the basis of 1000 intervals. The results are reported in Tables 2-4 from which we make the following observations:

- The CP results between equal and unequal intraclass correlations among both treatment groups for all seven methods are in remarkable agreement irrespective of the difference between proportions. Specifically, the CPs for all methods are virtually the same across all parameter combinations.
- As expected, the CP2 method shows somewhat conservative coverage across the board, and it becomes highly conservative coverage for larger values of  $\delta$  for all combinations of the proportion parameters.
- All methods except CP2 show reasonable coverage across the board; however, the CPs for these methods are slightly improved for larger values of intraclass correlations.

**Table 3:** The coverage probabilities of the confidence intervals by the methods with nominal level,  $1 - \alpha = 95\%$  for fixed litter sizes.

$(\phi_1, \phi_2)$	d	MW1	MW2	CP1	CP2	CM1	CM2	R
0.105, 0.215	0.00	0.9602	0.9626	0.9717	0.9728	0.9614	0.9575	0.9530
	0.05	0.9557	0.9605	0.9686	0.9713	0.9621	0.9568	0.9508
	0.10	0.9587	0.9640	0.9723	0.9750	0.9670	0.9619	0.9537
	0.15	0.9571	0.9612	0.9695	0.9732	0.9642	0.9580	0.9489
	0.20	0.9572	0.9591	0.9699	0.9719	0.9640	0.9584	0.9463
	0.25	0.9587	0.9629	0.9705	0.9735	0.9678	0.9620	0.9503
	0.30	0.9587	0.9621	0.9690	0.9729	0.9666	0.9592	0.9489
	0.35	0.9610	0.9635	0.9716	0.9737	0.9679	0.9629	0.9514
	0.40	0.9600	0.9652	0.9726	0.9750	0.9694	0.9627	0.9505
	0.45	0.9600	0.9610	0.9709	0.9715	0.9640	0.9577	0.9471
0.50	0.9580	0.9594	0.9694	0.9723	0.9644	0.9583	0.9461	
0.249, 0.324	0.00	0.9501	0.9537	0.9653	0.9688	0.9498	0.9479	0.9481
	0.05	0.9520	0.9563	0.9676	0.9699	0.9543	0.9538	0.9495
	0.10	0.9562	0.9592	0.9693	0.9707	0.9553	0.9532	0.9443
	0.15	0.9553	0.9594	0.9682	0.9710	0.9572	0.9551	0.9460
	0.20	0.9577	0.9623	0.9723	0.9751	0.9609	0.9582	0.9437
	0.25	0.9530	0.9560	0.9674	0.9695	0.9555	0.9541	0.9407
	0.30	0.9553	0.9590	0.9683	0.9714	0.9589	0.9559	0.9412
	0.35	0.9574	0.9599	0.9686	0.9712	0.9597	0.9570	0.9436
	0.40	0.9584	0.9627	0.9722	0.9744	0.9599	0.9585	0.9434
	0.45	0.9548	0.9597	0.9689	0.9725	0.9582	0.9561	0.9402
0.50	0.9584	0.9596	0.9717	0.9740	0.9593	0.9580	0.9394	
0.10,0.10	0.00	0.9617	0.9629	0.9732	0.9744	0.9676	0.9612	0.9566
	0.05	0.9589	0.9620	0.9705	0.9728	0.9679	0.9620	0.9545
	0.10	0.9583	0.9652	0.9705	0.9746	0.9693	0.9617	0.9489
	0.15	0.9602	0.9650	0.9718	0.9734	0.9703	0.9620	0.9513
	0.20	0.9616	0.9640	0.9733	0.9736	0.9711	0.9630	0.9511
	0.25	0.9607	0.9685	0.9721	0.9760	0.9740	0.9650	0.9491
	0.30	0.9636	0.9632	0.9736	0.9733	0.9710	0.9629	0.9483
	0.35	0.9587	0.9624	0.9685	0.9715	0.9697	0.9624	0.9506
	0.40	0.9636	0.9619	0.9738	0.9739	0.9689	0.9607	0.9479
	0.45	0.9581	0.9620	0.9703	0.9733	0.9691	0.9614	0.9486
0.50	0.9612	0.9626	0.9726	0.9733	0.9696	0.9625	0.9530	
0.30, 0.30	0.00	0.9503	0.9574	0.9674	0.9729	0.9526	0.9520	0.9533
	0.05	0.9518	0.9542	0.9667	0.9707	0.9488	0.9472	0.9417
	0.10	0.9533	0.9568	0.9691	0.9732	0.9527	0.9521	0.9412
	0.15	0.9585	0.9594	0.9697	0.9723	0.9589	0.9570	0.9440
	0.20	0.9598	0.9615	0.9739	0.9738	0.9585	0.9570	0.9440
	0.25	0.9570	0.9607	0.9698	0.9718	0.9547	0.9522	0.9388
	0.30	0.9563	0.9587	0.9700	0.9705	0.9553	0.9545	0.9386
	0.35	0.9550	0.9561	0.9690	0.9696	0.9555	0.9532	0.9368
	0.40	0.9558	0.9597	0.9692	0.9727	0.9586	0.9584	0.9406
	0.45	0.9546	0.9585	0.9683	0.9691	0.9548	0.9534	0.9407
0.50	0.9571	0.9604	0.9715	0.9738	0.9577	0.9570	0.9422	

**Table 4:** The expected lengths of the confidence intervals by the methods with nominal level,  $1 - \alpha = 95\%$  for fixed litter sizes.

$(\phi_1, \phi_2)$	d	MW1	MW2	CP1	CP2	CM1	CM2	R
0.105, 0.215	0.00	0.271	0.265	0.291	0.284	0.266	0.261	0.250
	0.05	0.282	0.276	0.303	0.295	0.279	0.273	0.261
	0.10	0.290	0.283	0.312	0.304	0.289	0.282	0.270
	0.15	0.296	0.289	0.318	0.309	0.296	0.289	0.276
	0.20	0.301	0.293	0.324	0.314	0.302	0.294	0.280
	0.25	0.304	0.296	0.327	0.317	0.305	0.297	0.283
	0.30	0.304	0.296	0.327	0.317	0.306	0.298	0.284
	0.35	0.303	0.295	0.326	0.317	0.306	0.297	0.283
	0.40	0.300	0.292	0.323	0.314	0.303	0.294	0.280
	0.45	0.295	0.287	0.317	0.308	0.297	0.289	0.276
0.50	0.288	0.281	0.311	0.302	0.291	0.283	0.270	
0.249, 0.324	0.00	0.312	0.312	0.338	0.338	0.306	0.306	0.297
	0.05	0.324	0.324	0.351	0.351	0.320	0.320	0.310
	0.10	0.334	0.333	0.363	0.361	0.332	0.332	0.320
	0.15	0.342	0.341	0.371	0.370	0.342	0.341	0.329
	0.20	0.347	0.346	0.377	0.376	0.349	0.347	0.335
	0.25	0.350	0.349	0.381	0.379	0.353	0.351	0.339
	0.30	0.351	0.349	0.382	0.380	0.354	0.353	0.340
	0.35	0.349	0.348	0.380	0.378	0.353	0.352	0.339
	0.40	0.345	0.344	0.376	0.375	0.349	0.348	0.335
	0.45	0.339	0.338	0.370	0.368	0.343	0.342	0.329
0.50	0.331	0.330	0.360	0.359	0.334	0.333	0.320	
0.10, 0.10	0.00	0.252	0.244	0.270	0.260	0.248	0.241	0.229
	0.05	0.263	0.254	0.282	0.272	0.261	0.253	0.241
	0.10	0.273	0.263	0.292	0.281	0.272	0.263	0.250
	0.15	0.279	0.269	0.300	0.288	0.280	0.270	0.257
	0.20	0.284	0.274	0.305	0.293	0.286	0.275	0.262
	0.25	0.287	0.277	0.308	0.296	0.289	0.278	0.265
	0.30	0.287	0.277	0.308	0.296	0.290	0.279	0.265
	0.35	0.287	0.276	0.308	0.295	0.289	0.278	0.265
	0.40	0.283	0.273	0.304	0.292	0.286	0.275	0.262
	0.45	0.278	0.268	0.299	0.287	0.281	0.270	0.257
0.50	0.271	0.262	0.291	0.280	0.273	0.263	0.250	
0.30, 0.30	0.00	0.318	0.319	0.345	0.346	0.311	0.312	0.304
	0.05	0.331	0.331	0.360	0.360	0.327	0.328	0.318
	0.10	0.341	0.342	0.372	0.372	0.340	0.340	0.330
	0.15	0.349	0.349	0.381	0.380	0.350	0.350	0.339
	0.20	0.355	0.355	0.387	0.387	0.357	0.357	0.346
	0.25	0.357	0.357	0.390	0.390	0.360	0.360	0.350
	0.30	0.359	0.358	0.392	0.391	0.362	0.362	0.351
	0.35	0.357	0.357	0.389	0.389	0.361	0.361	0.350
	0.40	0.353	0.353	0.386	0.386	0.358	0.358	0.346
	0.45	0.347	0.347	0.379	0.379	0.351	0.351	0.339
0.50	0.338	0.338	0.369	0.369	0.342	0.342	0.330	

- The MW1, MW2, CM2, and R methods produces better coverage compared to the other methods, especially for larger correlation parameter combinations irrespective of equal and unequal correlations.
- For all methods, the ELs increase as the difference between the proportions increases and also the ELs decrease as the difference between the intraclass correlation parameters  $(\phi_1, \phi_2)$  increases.
- The MW1, CP1, and CM1 methods tend to have similar ELs which are larger than the ELs of the MW2, CP2, and CM2 methods.
- The R method has among the lowest ELs which in many situations is at the expense of somewhat under-coverage, whereas good coverage properties of the MW2, and CM2 methods tend to have larger ELs compared to the R method, but smaller ELs compared to the MW1, CP1, and CM1 methods.

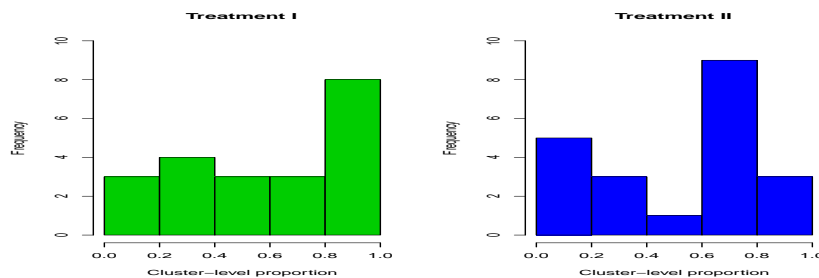
#### 4. Example: Chemotherapy Study

In cancer and leukemia group B randomized trials (Cooper et al., 1993), patients with multiple myeloma from different institutions were randomly assigned to one of the two chemotherapy treatment groups, where each institution was considered as the randomization unit or cluster. There were 21 institutions in each treatment group with cluster sizes

**Table 5:** Summary statistics for the data set in a chemotherapy study

Chemotherapy Treatments	# of subjects	# of clusters	mean cluster size	success rate
Treatment I	72	21	3.43	0.542
Treatment II	84	21	4.00	0.524

ranging from 2 to 12 in treatment I and from 2 to 11 in treatment II. A total of 156 eligible patients was accrued in the 21 institutions. Table 5 provides summary statistics of this study.



**Figure 1:** The distributions of cluster-level proportions for both treatment groups in a chemotherapy study.

Post-treatment responses for both treatment groups from the same institution are significantly correlated due to the fact that patients from the same institution often have similar

treatment outcomes due, possibly, to unmeasured variables such as the skill of the staff or the quality of the hospital equipment, which leads to inflated variances of the post-treatment response rates. The distributions of cluster-level proportions for both treatment groups are shown in Figure 1. The estimated success probability and the estimated intraclass correlation for both treatment groups and the estimated common intraclass correlation are provided in Table 6.

**Table 6:** The point estimates of the parameters obtained based on the four different methods for the data set in a solar protection study.

Methods	$\pi_1$	$\pi_2$	$\phi_1$	$\phi_2$
ML	0.586	0.521	0.194	0.083
AOV	0.542	0.524	0.226	0.142
EW	0.621	0.518		
OW	0.521	0.586		

In this study, it is of interest to compare two chemotherapy treatments with respect to success rates of the patients with multiple myeloma who survived at the end of this study. Then, the 95% confidence intervals for  $\pi_1 - \pi_2$  obtained using the proposed methods as well as the method recommended by Paul and Zaihra (2008) are given in Table 7.

**Table 7:** The 95% confidence intervals for  $\pi_1 - \pi_2$  obtained using the MW1, MW2, CP1, CP2, CM1, CM2, and R methods.

Method	Lower Limit	Upper Limit	Length	Comparison ind/ML
MW1	-0.078	0.273	0.351	<b>0.933</b>
MW2	-0.074	0.269	0.343	<b>0.912</b>
CP1	-0.091	0.288	0.378	1.006
CP2	-0.086	0.283	0.369	<b>0.982</b>
CM1	-0.171	0.204	0.376	0.999
CM2	-0.167	0.200	0.367	<b>0.976</b>
R	-0.188	0.188	0.376	1.000

## 5. Conclusion

This article proposed a number of alternative CIs for  $\pi_1 - \pi_2$  for correlated binary data by direct extensions of existing methods for tackling independent data using the concept of design effect for complex survey designs. The results of a simulation study suggest that the proposed methods generally perform well as their observed CPs are very close to the nominal coverage level. However, the MW2 and CM2 methods are preferable compared

to the other methods in the sense that they generally possess shorter ELs in almost all data situations considered here.

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