

INFERENCES ABOUT A LINEAR COMBINATION OF PROPORTIONS

A. Martín Andrés^{(1)}, M. Álvarez Hernández⁽¹⁾ and I. Herranz Tejedor⁽²⁾*

⁽¹⁾ *Bioestadística. Facultad de Medicina. Universidad de Granada. 18071 Granada. Spain.*

⁽²⁾ *Bioestadística. Facultad de Medicina. Universidad Complutense de Madrid. 28040 Madrid. Spain.*

SUMMARY

Statistical methods for carrying out asymptotic inferences (tests or confidence intervals) relative to one or two independent binomial proportions are very frequent. However inferences about a linear combination of K independent proportions $L=\sum\beta_i p_i$ (in which the first two are special cases) have had very little attention paid to them (focused exclusively on the classic Wald method). In this paper the authors approach the problem from the more efficient viewpoint of the score method, which can be solved using a free program which is available from the webpage quoted in the article. In addition the paper offers approximate formulas that are easy to calculate, gives a general proof of Agresti's heuristic method (consisting of adding a certain number of successes and failures to the original results before applying Wald's method) and, finally, it proves that the score method (which verifies the desirable properties of spatial and parametric convexity) is the best option in comparison with other methods.

KEY WORDS: Agresti method; binomial distribution; confidence interval; linear function of proportions; score method; Wald method.

1. Introduction.

Asymptotic inferences relative to binomial proportions are very usual in applied research, and this has resulted in a large number of statisticians developing appropriate theoretical procedures. In particular, the case of one or two independent proportions has received a great deal of attention in recent years. For example, in 2008 alone thirteen articles

* Correspondence to: Bioestadística. Facultad de Medicina. Universidad de Granada. 18071 Granada. Spain. E-mail: amartina@ugr.es. Phone:34-58-244080. Fax: 34-58-246117.

about the difference, ratio or odds-ratio of two independent proportions have been published¹⁻¹³.

Surprisingly, however, the asymptotic inferences concerning a linear combination ($L=\sum\beta_i p_i$) with $K>2$ independent binomial proportions have received very little attention, despite their great practical importance (e.g., dose–response studies, public-health surveys, multicenter clinical trials, agricultural experiments, etc.)¹⁴. Even more surprisingly, up till now the problem has been approached only from the points of view of the confidence intervals obtained using Wald’s method.

In this paper, the problem is dealt with from the point of view of the hypothesis tests, and the confidence interval (CI) is obtained by inverting the test. Moreover, the problem is resolved by using the score method, which, by general agreement, produces better results than Wald’s method in cases $K=1$ ¹⁵, $K=2$ ¹⁶ and in general for any parameter of a contingency table⁵. Finally, the paper offers a theoretical proof of the heuristic result that Wald’s 95% confidence interval improves if $2/K$ successes and failures are added to each sample –Agresti and Coull¹⁵ for $K=1$, Agresti and Caffo¹⁷ for $K=2$ and Price and Bonett¹⁸ for $K>2$ –, at the same time as it generalizes the result for any confidence value.

2. Examples.

Price and Bonett¹⁸ refer to a study by Cohen *et al.*¹⁹ in which 120 rats were randomly assigned to four diets (high or low fat and with fiber or without fiber). The absence or presence of a tumor was recorded for each rat. Table 1 shows the data and the contrasts L of interest (L_2 for evaluating the effect of dietary fiber; L_3 for evaluating the effect of the level of fat; L_1 for evaluating the interaction between L_1 and L_2 , that is, the difference between the effects of fiber according to which one or other of the fat levels are determined). In all cases $\sum\beta_i=0$.

Tebbs and Roths¹⁴ refer to the data (Table 2) in a multicenter clinical trial where the aim was to evaluate the efficacy of a reduced-salt regime in treating male infants for acute watery diarrhea. One of the characteristics measured was the number of infants experiencing fever at

admission or during the trial. The aim is to estimate the pooled proportion of subjects who respond to treatment. Because the level of participation is likely different depending on the location, a natural estimate of the pooled proportion is the average of the response probabilities from the $K=6$ sites, i.e. $L=\sum\beta_i p_i$ with $\beta_i=n_i/\sum n_i$. Now $\sum\beta_i\neq 0$. A similar problem often arises in the metaanalysis, where it is common to take linear combinations across studies.

3. The Wald method and the adjusted Wald method.

Let K be independent binomial random variables $x_i\sim B(n_i, p_i)$, where $i=1, 2, \dots, K$ and let $L=\sum\beta_i p_i$ the parameter of interest (where the proportions p_i are unknown and the parameters $\beta_i\neq 0$ known). When $K=1$ and $\beta_1=1$, the parameter of interest is the simple proportion p_1 . When $K=2$, $\beta_1=-1$ and $\beta_2=+1$, the parameter of interest is the difference between two proportions $d=p_2-p_1$. Generally speaking, the parameter of interest L may refer to a contrast (if $\sum\beta_i=0$) or to a more general combination (if $\sum\beta_i\neq 0$).

Whatever the situation the statistic $\bar{L}=\sum\beta_i\bar{p}_i$, where $\bar{p}_i=x_i/n_i$, is asymptotically normal with mean $L=\sum\beta_i p_i$ and variance $V=\sum\beta_i^2 p_i q_i/n_i$, where $q_i=1-p_i$. As a result, the test for contrasting $H_0: L=\lambda$ vs. $H_1: L\neq\lambda$ will be based on the statistic $z=(\bar{L}-\lambda)/\sqrt{V}$, which must be compared in traditional fashion with $z_{\alpha/2}$ (the $\alpha/2$ -upper percentile of the typical normal distribution). Inverting the test – that is, making $z^2=z_{\alpha/2}^2$ and working out λ – a $(1-\alpha)$ -CI for L is obtained: $\bar{L}\pm z_{\alpha/2}\sqrt{V}$. As the values of p_i are unknown, the simplest option is to substitute p_i by \bar{p}_i , which yields to the following Wald's statistic and Wald's CI (where $\bar{q}_i=1-\bar{p}_i$):

$$z_1=(\bar{L}-\lambda)/\sqrt{V_1}, \quad CI_1:\bar{L}\pm z_{\alpha/2}\sqrt{V_1} \quad \text{where } V_1=\sum\beta_i^2\bar{p}_i\bar{q}_i/n_i. \quad (1)$$

Price and Bonett¹⁸ found heuristically that Wald's CI improves substantially if expression (1) is obtained not based on the original x_i and n_i , but on x_i+2/K and n_i+4/K , that is if $2/K$

successes and $2/K$ failures are added to the original data. This yields the adjusted Wald method $W(+2/K)$, in contrast to the original Wald method $W(+0)$, which is also applicable in the case of the test. The procedure is compatible with the one recommended by Agresti and Coull¹⁵ for the case of one proportion ($K=1, \beta_1=1$) and by Agresti and Caffo¹⁷ for the case of the difference between the two proportions ($K=2, \beta_1=-1, \beta_2=+1$). The origin of the method is to be found in the case of one proportion. Agresti and Coull¹⁵ proved that Wilson's CI (which proceeds from the score test) has a midpoint that is equal to that of method $W(+z_{\alpha/2}^2/2)$, thus yielding a theoretical justification concerning the good behavior of method $W(+2)$ in the case of one proportion, because $z_{2.5\%}^2 = 1.96^2 \simeq 4$. The natural extension of this to case $K>1$ is $W(+z_{\alpha/2}^2/2K) \simeq W(+2/K)$ for $\alpha=5\%$, but as yet no theoretical justification of it has been found. In section 5 it is proved that the reason is similar to the one given for case $K=1$. More recently, Schaarschmidt *et al.*²⁰ indicate that, according to their results, method $W(+1)$ is better than method $W(+2/K)$ for $K \geq 6$ and $\alpha=5\%$.

Other methods exist which are operationally more complicated than the adjusted Wald method and which appear to produce better results. In some cases (Newcombe¹⁶ for $K=2$ and $\Sigma\beta_i=0$; Newcombe²¹ for $K=4$ and $\Sigma\beta_i=0$; Zou *et al.*²² for any value of K and $\Sigma\beta_i$), the proportions p_i are replaced by the extremes of Wilson's CI for the values p_i . In others (Beal²³ for $K=2$; Tebbs and Roths¹⁴ for $K \geq 2$) the $K-1$ nuisance parameters are replaced by bayesian type estimators.

4. Score method

The aim of this section is to determine the value of the score statistic $z_0 = (\bar{L} - \lambda) / \sqrt{V_0}$, where $V_0 = \Sigma \beta_i^2 \hat{p}_i \hat{q}_i / n_i$, \hat{p}_i are the estimators of maximum likelihood (under H_0) of p_i and $\hat{q}_i = 1 - \hat{p}_i$. For all the following it is to be understood that $n = \Sigma n_i$, $B = \Sigma \beta_i$, $B^+ = \Sigma_{\beta_i > 0} \beta_i$ and $B^- = \Sigma_{\beta_i < 0} \beta_i$. Observe that $B^+ - B^- = \Sigma |\beta_i|$, $B^+ + B^- = B$ and that $B^- \leq \lambda$, \bar{L} , $B \leq B^+$ (since $0 \leq p_i$, $\bar{p}_i \leq 1$). Therefore, $-\Sigma |\beta_i| \leq \bar{L} - \lambda \leq \Sigma |\beta_i|$. In Appendix A1 the following results, based on

the key expression below, are proved:

$$y=n+(B-2\lambda)C-\sum R_i=0 \text{ where } \begin{cases} C = z^2 / (\bar{L} - \lambda) \\ R_i^2 = n_i^2 + 2n_i\beta_i b_i C + \beta_i^2 C^2 \\ b_i = 1 - 2\bar{p}_i \end{cases} \quad (2)$$

If $\bar{L} = \lambda$, it is obvious that $\hat{p}_i = \bar{p}_i$ and $z_0=0$. If $\bar{L} \neq \lambda$, then z_0^2 is the sole solution different from zero for the equation $y(z_0^2)=0$, and moreover:

$$z_0 = (\bar{L} - \lambda) / \sqrt{V_0} \text{ where } V_0 = \sum \beta_i^2 \hat{p}_i \hat{q}_i / n_i \text{ and } \hat{p}_i = (n_i + \beta_i C - R_i) / 2\beta_i C, \quad (3)$$

Searches for the value z_0^2 is made easier if it is borne in mind that:

$$\frac{4(\bar{L} - \lambda)^2}{\sum \beta_i^2 / n_i} \leq z_0^2 \leq \begin{cases} T(\bar{L} - \lambda) / (\lambda - B^-) & \text{if } \bar{L} > \lambda \\ (n - T)(\bar{L} - \lambda) / (\lambda - B^+) & \text{if } \bar{L} < \lambda \end{cases} \quad (4)$$

where $T = \sum_{\beta_i > 0} x_i + \sum_{\beta_i < 0} (n_i - x_i)$. Alternatively, if the researcher does not wish to know the value of z_0 , but only to know if the test has significance to the error α , then s/he need only apply the following rule based on expression (2):

$$\text{Decide } H_1 \Leftrightarrow y\{C = z_{\alpha/2}^2 / (\bar{L} - \lambda)\} \geq 0, \quad (5)$$

which simplifies the calculations enormously. For example, if one wishes to carry out the test of interaction $H_0: L_I=0$ vs. $H_1: L_I \neq 0$ in Table 1 to the error $\alpha=5\%$, then $\lambda=B=0$, $z_{2.5\%}^2=1.96^2$, $\bar{L}_1 = -2/30$, $C=-15 \times 1.96^2$, $R_i^2=30\{30+1.96^2(a_i+7.5 \times 1.96^2)\}$, $a_i=10, 2, -24$ and 8 for $i= 1, 2, 3$ and 4 respectively and $y(C)=120-\sum R_i = -129.866 < 0$, for which reason the test is not significant. The intensity of the calculations is similar to that of Wald's test. In Appendix A2 it is proved that the statistic z_0^2 is equal to the classic chi-square statistic.

Another common aim is to obtain the score CI (CI_0) for L . To this end it is sufficient to make $z_0^2 = z_{\alpha/2}^2$ in expression (2) and to determine both solutions $B^- \leq \lambda_1 < \bar{L} < \lambda_2 \leq B^+$ of equation $y(\lambda)=0$ (see Appendix A3). If there is no solution λ_1 (λ_2) then $\lambda_I=B^-$ ($\lambda_2=B^+$). Table 3 indicate the values z_0 and/or the intervals CI_0 for the contrasts and/or effects in Tables 1 and 2

(note that the contrasts L2 and L3 are significant and that there is no interaction between them). Similarly when the aim is to obtain the CI for β_K in fixed values of λ , $\beta_i \neq \beta_K$ and $z_0^2 = z_{\alpha/2}^2$.

Note that all the above contains the cases of one proportion ($K=1$), of the difference between two proportions ($L=d=p_2-p_1$) and of the risk ratio ($L=p_2-Rp_1$ and $\lambda=0$) as special results. In particular, the tests and CI's of Mee²⁴ for d and of Koopman²⁵ for R are special cases of the general case L . Similarly, the present proof that $z_0^2 = \chi_0^2$ contains the proofs of Nam²⁶ and Gart and Nam²⁷ for d and R respectively as special cases. Expression (2) was proved by Martín and Herranz²⁸ for case d .

5. General and adjusted Wald -type approximations.

In order to simplify the solution of equation (2) in z_0^2 (for the test) or in λ (for the CI), it is advisable to obtain approximate expressions of that equation. In Appendix A4 it is shown that, by expanding the term R_i in Maclaurin series, expression (2) is converted to the following:

$$(\bar{L} - \lambda)^3 - z_0^2 (\bar{L} - \lambda) V_1 + z_0^4 V_2 \simeq 0, \text{ where } V_2 = \sum \frac{\beta_i^3 \bar{p}_i \bar{q}_i b_i}{n_i^2}. \quad (6)$$

If one retains only the terms of order $O(n_i) \geq -1$ and divides by $(\bar{L} - \lambda)$ one obtains Wald's classic solutions for expression (1). If one only retains the terms of $O(n_i) \geq -2$, one replaces $z_0^4 \simeq z_0^2 (\bar{L} - \lambda)^2 / V_1$ and divides by $(\bar{L} - \lambda)$, then $0 \simeq (\bar{L} - \lambda)^2 V_1 + (\bar{L} - \lambda) V_2 z_0^2 - V_1 z_0^2$ is obtained. From this one can deduce the following approximate statistic and CI:

$$z_2 = \frac{\bar{L} - \lambda}{\sqrt{V_1 - (\bar{L} - \lambda) V_2 / V_1}}, \text{ CI}_2 : \bar{L} + z_{\alpha/2}^2 \frac{V_2}{2V_1} \pm z_{\alpha/2} \sqrt{V_1 + z_{\alpha/2}^2 \left(\frac{V_2}{2V_1} \right)^2}. \quad (7)$$

In Table 3 the values of z_1 and z_2 for the contrasts in Table 1 are set out. It can be seen that both are near the real value z_0 , and that z_2 is the best option. Something similar occurs

with the intervals CI_1 and CI_2 for the effects L of Tables 1 and 2 (see Table 3): CI_2 is the best option.

As has already been stated, the adjusted Wald heuristic methods $W(+z_{\alpha/2}^2 / 2K)$ have their origin in the proposal by Agresti and Coull¹⁵ for case $K=1$. These authors show that the center of Wilson's CI (which is the score CI for a proportion) is equal to the center of the adjusted Wald CI $W(+z_{\alpha/2}^2 / 2)$, and this is the reason that this performs so well. On the basis of the approximations of this section it is now possible to prove that that is what occurs approximately in the case $K>1$. In Appendix A5 it is proved that the adjusted Wald method $W(+c_i)$ where:

$$c_i = \frac{n_i z_{\alpha/2}^2}{2(Kn_i - z_{\alpha/2}^2)} = \frac{n_i h}{n_i - 2h} \simeq h \text{ where } h = \frac{z_{\alpha/2}^2}{2K}, \quad (8)$$

has a center which is approximately the same as that of CI_2 in the expression (7). Note that by making $c_i \simeq h$, the adjusted Wald method $W(+h \simeq 2/K)$ proposed by Price and Bonett¹⁸ for $\alpha=5\%$ is obtained.

Table 3 sets out the CI obtained using the adjusted Wald methods $W(+c_i)$ and $W(+h)$. It can be seen that both methods produce very similar results, with a slight advantage in favour of the adjusted Wald method $W(+h)$. Note also that both procedures estimate the real range (that of CI_0) better than its center and that, in the case of large samples as in Table 2, all the procedures yield practically the same result.

The previous approximations are correct only when the observed data do not belong to the border of the sample space, that is, when $0 < x_i < n_i (\forall i)$. Otherwise, at the end of Appendix A4 it is shown that the correct solutions for the intervals CI_1 and CI_2 and the adjusted Wald methods $W(+c_i)$ and $W(+h)$ are the intervals CI'_1 and CI'_2 and the following adjusted Wald methods $W(+c'_i)$ and $W(+h'_i)$ (in all cases one must make $j=1$ and use the sign $-$ in order to obtain the lower extreme, and make $j=2$ and use the sign $+$ to obtain the upper extreme):

$$CI'_1: \bar{L} + \frac{z_{\alpha/2}^2}{2(N_j + z_{\alpha/2}^2)} \left\{ B_j \pm \sqrt{B_j^2 + 4(N_j + z_{\alpha/2}^2)V_1} \right\} \quad (9)$$

$$CI'_2: \bar{L} + \frac{z_{\alpha/2}^2}{2(N_j + z_{\alpha/2}^2)} \left\{ B_j + (N_j + z_{\alpha/2}^2) \frac{V_2}{V_1} \pm \sqrt{\left\{ B_j - (N_j + z_{\alpha/2}^2) \frac{V_2}{V_1} \right\}^2 + 4(N_j + z_{\alpha/2}^2)V_1} \right\} \quad (10)$$

$$c'_i = \frac{z_{\alpha/2}^2}{2} \cdot \frac{n_i \left\{ \frac{1}{K} + \frac{\delta_{ij} n_i}{N_j + z_{\alpha/2}^2} \right\}}{n_i - z_{\alpha/2}^2 \left\{ \frac{1}{K} + \frac{\delta_{ij} n_i}{N_j + z_{\alpha/2}^2} \right\}} \quad \text{and} \quad h'_i = \frac{z_{\alpha/2}^2}{2} \cdot \frac{1 + \delta_{ij} K}{K}, \quad (11)$$

where $N_j = \sum_i \delta_{ij} n_i$, $B_j = \sum_i \delta_{ij} b_i \beta_i$, $\delta_{i1}=1$ in all the subscripts i verifying $\{\bar{p}_i=0 \text{ and } \beta_i<0\}$ or $\{\bar{p}_i=1 \text{ and } \beta_i>0\}$ ($\delta_{i1}=0$ otherwise) and $\delta_{i2}=1$ in all the subscripts i verifying $\{\bar{p}_i=0 \text{ y } \beta_i>0\}$ or $\{\bar{p}_i=1 \text{ and } \beta_i<0\}$ ($\delta_{i2}=0$ otherwise). Note that $CI'_1 \equiv CI_1$, $CI'_2 \equiv CI_2$, $W(+c'_i) \equiv W(+c_i)$ and $W(+h'_i) \equiv W(+h)$ when $0 < \bar{p}_i < 1$ ($\forall i$) and that in CI'_2 it is understood that $V_2/V_1=0$ when $V_1=0$.

6. Coherence of the inferences: properties of convexity.

In order for an S statistic (such as z_0) to be useful in the inference it is necessary for it to verify certain coherence properties. This section aims to analyze these.

Barnard²⁹ recommended that the critical regions should be convex for the classic test $H_0: d=0$, and this means that the S statistic should increase (decrease) in \bar{p}_2 (\bar{p}_1), although this increase or decrease need not be strict. Röhmel and Mansmann³⁰ justified the fact that the same should occur in the more general case of $H_0: d=\delta$. In the present case ($H_0: L=\lambda$) the statistic S should increase (decrease) in the \bar{p}_i values where $\beta_i>0$ ($\beta_i<0$) –i.e meaning S should verify the property of *spatial convexity*– and this means that the CRs will present no gaps. In Annex A5 it is proved that z_0 verify this property. The proof contains two special cases: that of the difference $H_0: d=p_2-p_1=\delta$ (proved by Martín and Herranz³¹) and that of the risk ratio $H_0: p_2-Rp_1=p_2-\rho p_1=0$ (for which there is no proof.).

Röhmel and Mansmann³² showed it was better for the p-value $P(\delta)$ for the test $H_0: d=p_2-p_1 \leq \delta$ to increase in δ . In general, in order for test $H_0: L=\lambda$ based on S to be coherent its

p-value $P(\lambda)$ must increase (decrease) in λ when $\lambda < \bar{L}$ ($\lambda > \bar{L}$). This means that the S statistic should decrease in λ , that is, that S should verify the property of *parametric convexity* in λ . The verification of this property is what guarantees that inverting the test using the equality $S^2 = z_{\alpha/2}^2$ is equivalent to resolving the equality $S^2 \leq z_{\alpha/2}^2$ and yields a CI for λ which presents no gaps. Similarly, in order for the CI for β_i to be coherent it is necessary for S to increase in β_i (parametric convexity in β_i). In Annex A5 it is proved that z_0 verify both properties of parametric convexity (and it contains, as a special case, case d of Martín and Herranz³¹).

To summarize what has been said, any S statistic should verify the following properties (z_0 verify them):

$$\frac{dS}{d\bar{p}_i} \begin{cases} \geq 0 & \text{si } \beta_i > 0 \\ \leq 0 & \text{si } \beta_i < 0 \end{cases}, \quad \frac{dS}{d\lambda} \leq 0, \quad \frac{dS}{d\beta_i} \geq 0. \quad (12)$$

7. Simulation study.

In this section method $W(+2/K)$ (the best adjusted Wald method known at present) and the 8 new methods proposed in this paper –S (scores), CI_2 , CI'_1 , CI'_2 , $W(+c_i)$, $W(+h)$, $W(+c'_i)$ and $W(+h'_i)$ – will be compared; the classic method of Wald $W(+0) \equiv CI_1$ is excluded because, as has been said, it is known to behave badly.

For the $100(1-\alpha)\%$ CI, the actual probability of coverage R and the expected interval width W for fixed values of p_i are defined by:

$$R = \sum_{x_1=0}^{n_1} \sum_{x_2=0}^{n_2} \dots \sum_{x_K=0}^{n_K} \prod_{i=1}^K \binom{n_i}{x_i} p_i^{x_i} q_i^{n_i-x_i} I(x_1, x_2, \dots, x_K) \quad \text{and} \quad W = \sum_{x_1=0}^{n_1} \sum_{x_2=0}^{n_2} \dots \sum_{x_K=0}^{n_K} \prod_{i=1}^K \binom{n_i}{x_i} p_i^{x_i} q_i^{n_i-x_i} (L_S - L_I),$$

where $I(x_1, x_2, \dots, x_K) = 1$ if the CI (L_I, L_S) occasioned by the outcomes (x_1, x_2, \dots, x_K) contains $L = \sum \beta_i p_i$ and $I(x_1, x_2, \dots, x_K) = 0$ otherwise. For each set of values (n_i, β_i) in Table 4, 10,000 sets of p_i 's were randomly generated from the uniform $[0, 1]$ distribution, and one of the previous methods was used to compute W and R . The mean of R (R_{mean}) and W (W_{mean}), the minimum

of R ($Rmin$) and the percentage of R that fell below 93% ($Rbelow93$) in the 10,000 sets of p_i 's were computed for $1-\alpha=95\%$. It is desirable for $Rmean$ to be 95% on average (the method will be conservative if $Rmean$ is greater than 95%, and if not it will be liberal), for $Rmin$ to be as close as possible to 95%, for $Wmean$ to be as small as possible and, finally, for the method to have few liberal "failures" (that is, for $Rbelow93$ to be as small as possible).

Table 4 shows the results for methods $W(+2/K)$, $W(+h'_i)$ and S for a CI of 95%. The results for the other methods are excluded (these may be requested from the authors) as we have determined that the methods CI_2 , CI'_1 y CI'_2 fail a great deal, that the methods $W(+c_i)$ and $W(+h)$ function worse than $W(+c'_i)$ and $W(+h'_i)$ and, finally, that method $W(+c'_i)$ is too conservative. From these first results we can extract two commentaries of interest. In the first place, it is surprising that, given that method $W(+h'_i)$ is an approximation of method $W(+c'_i)$, and the latter is in turn an approximation of method CI'_2 , the previous results indicate that the first is better than the second which in turn is better than the third. Secondly, and given that $W(+c_i)$ and $W(+h)$ are worse methods than $W(+c'_i)$ and $W(+h'_i)$ respectively, it is necessary to point out the importance of defining CI differently when the outcomes are extreme ($x_i=0$ or $x_i=n_i$) to when they are not ($0 < x_i < n_i$).

From Table 4 we can deduce that the best option is S (except when all the sample sizes are equal to 10) because compared to the other two methods it is more balanced, it has an equal or smaller $Wmean$, its liberal failures are almost always lower (that is, its $Rbelow93$ is almost always smaller) and its value for $Rmin$ is almost always closer to 95%. It can also be seen that method $W(+2/K)$ is slightly conservative and that $W(+h'_i)$ is always very conservative (especially in $K=4$), and as a result the second of the two usually has few failures (especially in $K=4$) and an excessively large value for $Wmean$. Finally, we should point out that although the method $W(+2/K)$ contains some desirable features, it is not reliable because its value for $Rbelow93$ can be very large; in contrast, method $W(+h'_i)$ is reliable, but is also very

conservative. In general, these conclusions remain valid for 90% and 99% CI's (the data may be requested from the authors), although $W(+2/K)$ now behaves very well for $1-\alpha=90\%$ and very badly for $1-\alpha=99\%$.

8. Conclusions.

Asymptotic inferences (tests or confidence intervals) relative to independent binomial proportions are very frequent in applied research, but until now the research has centered almost entirely on cases with one simple proportion p and on the difference ($d=p_2-p_1$) or the ratio ($R=p_2/p_1$) between two proportions. Surprisingly, the case of a linear of K proportions ($L=\sum\beta_i p_i$) has received very little attention, despite its great practical importance¹⁴. Even more surprising is the fact that the problem has been approached till now only from the point of view of the confidence intervals obtained by the classic Wald method.

In this article the problem is looked at from the point of view of the score method (equivalent to the classic chi-square method), and proves the suitability of this method compared to the other 8 procedures. Because the application of the method requires an iterative procedure, the reader may apply the free program obtainable at http://www.ugr.es/local/bioest/Z_LINEAR_K.EXE.

The paper also provides a theoretical proof of the heuristic result that Wald's 95%-confidence interval improves if $2/K$ successes and failures are added to each sample. In addition, at the end of section 5 the rule is generalized, so that a simple and reliable (although conservative) CI consists in applying Wald's classic CI from expression (1) and adding h'_i successes and failures to each sample, a quantity which is reduced to $z_{\alpha/2}^2 / 2K$ when $0 < x_i < n_i$ in all the samples (which is usually the case). When the values of n_i and/or K are small it may be more suitable to add $c_i = n_i z_{\alpha/2}^2 / \left[2(Kn_i - z_{\alpha/2}^2) \right]$ successes and failures.

The article also points out how important it is for any test statistic (such as z_0) to verify both spatial and parametric convexity. The first, so that the test behaves coherently. The

second, so that the CI can be obtained by inverting the test by means of the equality $z_0^2 = z_{\alpha/2}^2$.

9. Acknowledgments.

This research was supported by the Ministerio de Educación y Ciencia, Spain, grant number MTM-2008-01697/MTM (with cofinancing by the FEDER) and by the Consejería de Innovación, Ciencia y Empresa, Junta de Andalucía, Spain, grant number FQM-01459.

APPENDIX A

A1. Estimators of maximum likelihood and the score test.

Since, under H_0 , $Pr(x_1, \dots, x_K | \lambda = \sum \beta_i p_i) = \prod_{x_i} \binom{n_i}{x_i} p_i^{x_i} q_i^{n_i - x_i}$, where

$$p_K = (\lambda - \sum_{i \neq K} \beta_i p_i) / \beta_K, \text{ then } \ell = \ln Pr(x_1, \dots, x_K | \lambda = \sum \beta_i p_i) \propto \sum x_i \ln p_i + \sum (n_i - x_i) \ln (1 - p_i).$$

When $\bar{L} = \lambda$, the restricted estimators of maximum likelihood \hat{p}_i are equal to the classic unrestricted \bar{p}_i ones.

When $\bar{L} \neq \lambda$, because $dp_K / dp_i = -\beta_i / \beta_K$ then the \hat{p}_i are the solutions to $d\ell / dp_i = (\partial \ell / \partial p_i) - (\beta_i / \beta_K) (\partial \ell / \partial p_K) = n_i (\bar{p}_i - p_i) / p_i q_i - (\beta_i / \beta_K) n_K (\bar{p}_K - p_K) / p_K q_K = 0$ ($\forall i$), that is:

$$\frac{n_i \bar{p}_i}{\beta_i p_i} + \frac{n_i \bar{q}_i}{\beta_i q_i} = \frac{n_i (\bar{p}_i - p_i)}{\beta_i p_i q_i} = C \quad (\forall i), \quad (\text{A1})$$

where C is a constant to be determined. From the above it can be deduced that

$$\hat{p}_i = (n_i + \beta_i C \pm R_i) / 2\beta_i C, \text{ where } R_i^2 = n_i^2 + 2n_i \beta_i b_i C + \beta_i^2 C^2 \text{ and } b_i = 1 - 2\bar{p}_i.$$

In order to see which of the two solutions $\hat{p}_i(+)$ or $\hat{p}_i(-)$ is the appropriate one, one must remember that $R_i^2 \in (n_i \pm \beta_i C)^2$, because $0 \leq \bar{p}_i \leq 1$, so that $R_i \geq |n_i - \beta_i C| \geq -n_i + |\beta_i C|$.

When $\beta_i C > 0$, this implies that $\hat{p}_i(+)$ is impossible unless $\hat{p}_i(+)$ is equal to +1. But if this is so, it is because $\bar{p}_i = +1$, $n_i = \beta_i C$ -from expression (A1)- and $R_i = 0$; hence $\hat{p}_i(+)$ is equal to $\hat{p}_i(-)$ and is equal to +1.

Similarly, if $\beta_i C < 0$ then $\hat{p}_i(+)$ is impossible unless $\hat{p}_i(+)$ is equal to $\hat{p}_i(-)$ and is equal to 0. Hence

the solution will always be $\hat{p}_i(-)$. This means that $2\beta_i\hat{p}_iC = n_i + \beta_iC - R_i$, so that by adding in i , and bearing in mind that $\hat{L} = \sum \beta_i\hat{p}_i = \lambda$, that makes C the solution to the equation:

$$y(C) = n + (B - 2\lambda)C - \sum R_i = 0. \quad (\text{A2})$$

The constant C may be expressed in the following ways:

$$C = \frac{\bar{L} - \lambda}{V_0} = \frac{z_0^2}{\bar{L} - \lambda} = \frac{1}{K} \sum \frac{n_i(\bar{p}_i - \hat{p}_i)}{\beta_i\hat{p}_i\hat{q}_i} = \frac{\sum n_i(\bar{p}_i - \hat{p}_i)}{\sum \beta_i\hat{p}_i\hat{q}_i} = \frac{1}{B} \sum \frac{n_i(\bar{p}_i - \hat{p}_i)}{\hat{p}_i\hat{q}_i}. \quad (\text{A3})$$

In order to obtain the first equality one need only note that, from expression (A1), $\beta_i(\bar{p}_i - \hat{p}_i) = \beta_i^2\hat{p}_i\hat{q}_iC/n_i$, so that by adding in i : $(\bar{L} - \lambda) = C \sum \beta_i^2\hat{p}_i\hat{q}_i/n_i = CV_0$. The other equalities are obtained in a similar way, except the second, which proceeds from the fact that $z_0^2 = (\bar{L} - \lambda)^2/V_0$. From expressions (A1) and (A3) it can be deduced that

$$\text{Sign}(C) = \text{Sign}(\bar{p}_i - \hat{p}_i)/\beta_i = \text{Sign}(\bar{L} - \lambda), \quad (\text{A4})$$

and that in the contrasts ($B=0$), $\sum n_i(\bar{p}_i - \hat{p}_i)/\hat{p}_i\hat{q}_i = 0$. Also note that $z_0^2 = n_i(\bar{p}_i - \hat{p}_i)(\bar{L} - \lambda)/\beta_i\hat{p}_i\hat{q}_i$ ($\forall i$).

In order to prove that, when $\bar{L} \neq \lambda$, the equation (A2) has a unique solution $C \neq 0$, it is necessary to study function $y(C)$. Note that $y(C=0)=0$, so that $C=0$ is always a false solution to equation (A3). On the other hand, $dy/dC = (B - 2\lambda) - \sum \beta_i(\beta_iC + n_i b_i) = 0$ will provide the extremes \bar{C} of function $y(C)$. If they exist, they give rise to a maximum, given that $dy^2/dC^2 = -4\sum \beta_i^2 n_i \bar{p}_i \bar{q}_i / R_i^3 < 0$. However, since:

$$\lim_{C \rightarrow \pm\infty} \frac{y(C)}{C} = (B - 2\lambda) \mp \sum |\beta_i| = \begin{cases} 2(B^- - \lambda) = m^+ & \text{if } C \rightarrow +\infty \\ 2(B^+ - \lambda) = m^- & \text{if } C \rightarrow -\infty \end{cases},$$

then $y(C)$ has two oblique asymptotes from slope m^+ and m^- and from equations $y = m^\pm C + h^\pm$, where:

$$h^\pm = \lim_{C \rightarrow \pm\infty} \{y(C) - m^\pm C\} = \lim_{C \rightarrow \pm\infty} \sum (n_i \pm |\beta_i| C - R_i) = \lim_{C \rightarrow \pm\infty} \frac{(\pm 2n_i |\beta_i| - 2n_i \beta_i b_i) C}{n_i \pm |\beta_i| C + R_i} =$$

$$= \sum n_i (1 \mp s_i b_i) = \begin{cases} 2T = h^+ & \text{if } C \rightarrow +\infty \\ 2(n-T) = h^- & \text{if } C \rightarrow -\infty \end{cases},$$

where $s_i = \text{Sign}(\beta_i)$ and T is the value referred to in expression (4). But, if $A_i = \beta_i C + n_i b_i$:

$$y(C) - m^+ C - h^+ = \sum \{\pm s_i A_i - R_i\} = -\sum \frac{4n_i^2 \bar{p}_i \bar{q}_i}{\pm s_i A_i + R_i} < 0, \quad (\text{A5})$$

because as $R_i^2 = A_i^2 + 4n_i^2 \bar{p}_i \bar{q}_i$ then $R_i \geq |A_i| \geq \pm A_i = \pm s_i A_i$ and the denominator of the previous fraction is positive. Expression (A5) indicates that function $y(C)$ is always found below the two asymptotes and, from what was stated above, it will have a maximum in $C = \bar{C}$. Because, moreover, it cuts the horizontal axis at $C=0$, it can be deduced that it also ought to cut that axis at another point $C=C_0 \neq 0$ which will be $C_0 > 0$ ($C_0 < 0$) when $\bar{L} > \lambda$ ($\bar{L} < \lambda$). In addition the solution $C=C_0$ will have to be sought where the asymptotes cut the horizontal axis: $-h^+/m^+ = T/(\lambda - B^-)$ and $-h^-/m^- = -(n-T)/(B^+ - \lambda)$. Finally, since $\hat{p}_i \hat{q}_i \leq 1/4$ then, from the first equality of (A3), $|C| \geq 4|\bar{L} - \lambda| / (\sum \beta_i^2 / n_i)$. As a result it can be affirmed that the equation (A2) has only one solution $C_0 \neq 0$ which is contained between the following bounds:

$$\begin{cases} \text{If } \bar{L} > \lambda : 4(\bar{L} - \lambda) / (\sum \beta_i^2 / n_i) \leq C_0 \leq T / (\lambda - B^-) \\ \text{If } \bar{L} < \lambda : -(n-T) / (B^+ - \lambda) \leq C_0 \leq 4(\bar{L} - \lambda) / (\sum \beta_i^2 / n_i) \end{cases}. \quad (\text{A6})$$

Once the value C_0 has been determined then $z_0^2 = C_0 (\bar{L} - \lambda)$.

In order to obtain the value z_0^2 directly, without having to obtain the value of C_0 previously, one need only replace C with $z_0^2 / (\bar{L} - \lambda)$; hence the expressions (2) and (4). By making this change in (A2) and multiplying the whole expression by $(\bar{L} - \lambda)$, the following, more general, equation is obtained:

$$f = n(\bar{L} - \lambda) + (B - 2\lambda) z_0^2 - \text{Sign}(\bar{L} - \lambda) \sum \bar{R}_i = 0, \quad (\text{A7})$$

where $\bar{R}_i^2 = n_i^2 (\bar{L} - \lambda)^2 + \beta_i^2 z_0^4 + 2n_i \beta_i b_i z_0^2 (\bar{L} - \lambda)$. With this format $\hat{p}_i = \{n_i (\bar{L} - \lambda) + \beta_i z_0^2 -$

Sign $(\bar{L} - \lambda) \bar{R}_i \} / 2 \beta_i z_0^2$. By solving $f=0$ the value of z_0^2 is obtained.

Alternatively, if the researcher does not wish to obtain the p-value of the test, but only carry out the test to error α , the calculations become very much simpler, because it is not necessary to resolve equation (2). In effect, as H_i will be decided when $z_0^2 = C_0 (\bar{L} - \lambda) \geq z_{\alpha/2}^2$, then the test will be significant if $C_0 \geq z_{\alpha/2}^2 / (\bar{L} - \lambda)$ or $C_0 \leq z_{\alpha/2}^2 / (\bar{L} - \lambda)$ when $\bar{L} > \lambda$ or $\bar{L} < \lambda$ respectively, that is, when $y\{C = z_{\alpha/2}^2 / (\bar{L} - \lambda)\} \geq 0$ in expression (2); this is due to the fact that $y(C) \geq 0$ for C between 0 and C_0 , as has been indicated above. If the format for expression (A6) is adopted, the following alternative statement is obtained: decide $H_1 \Leftrightarrow f(z_{\alpha/2}^2) \geq 0$ (if $\bar{L} > \lambda$) or $f(z_{\alpha/2}^2) \leq 0$ (if $\bar{L} < \lambda$).

A2. The chi-square test.

The traditional chi-square test is:

$$\begin{aligned} \chi_0^2 &= \sum \left\{ \frac{(x_i - n_i \hat{p}_i)^2}{n_i \hat{p}_i} + \frac{(n_i - x_i - n_i \hat{q}_i)^2}{n_i \hat{q}_i} \right\} = \sum \frac{n_i (\bar{p}_i - \hat{p}_i)^2}{\hat{p}_i \hat{q}_i} = \sum \frac{n_i (\bar{p}_i - \hat{p}_i)}{\hat{p}_i \hat{q}_i} \beta_i (\bar{p}_i - \hat{p}_i) \\ &= C \sum \beta_i (\bar{p}_i - \hat{p}_i) = C (\bar{L} - \lambda) = z_0^2, \end{aligned}$$

where the last three equalities are due to expression (A1), to the fact that $\bar{L} = \sum \beta_i \bar{p}_i$ and $\lambda = \sum n_i \hat{p}_i$, and to expression (A3) respectively.

A3. The score CI.

Because $z_0^2 = C(\bar{L} - \lambda)$ then $\lambda = \bar{L} - z_0^2 / C$. After substitution in expression (2), $y(C) = n + 2z_0^2 + (B - 2\bar{L})C - \sum R_i = 0$ is obtained. In order to obtain a CI for λ one only need make $z_0^2 = z_{\alpha/2}^2$, determine the two values $C=C_1 > 0$ and $C=C_2 < 0$ which satisfy the previous equation and calculate $\lambda_i = \bar{L} - z_{\alpha/2}^2 / C_i$. From this, $\lambda_1 \leq \lambda \leq \lambda_2$ is the required solution. It is more direct to resolve equation (2) in λ within the licit margins: $B^- \leq \lambda_1 < \bar{L} < \lambda_2 \leq B^+$. Alternatively equation (A7) can be used and resolved in λ . Based on expression (4), it can be seen that

some more specific bounds where solutions λ_i can be sought are $\bar{L} - z_{\alpha/2} \sqrt{\sum \beta_i^2 / 4n_i} \leq \lambda_1 \leq (z_{\alpha/2}^2 B^- + T\bar{L}) / (z_{\alpha/2}^2 + T)$ and $\{z_{\alpha/2}^2 B^+ + (n-T)\bar{L}\} / \{z_{\alpha/2}^2 + (n-T)\} \leq \lambda_2 \leq \bar{L} + z_{\alpha/2} \sqrt{\sum \beta_i^2 / 4n_i}$.

A4. Approximations.

Expanding R_i in Maclaurin series for $C=0$ indicates that:

$$R_i \simeq n_i + \beta_i b_i C + \frac{2\beta_i^2 \bar{p}_i \bar{q}_i}{n_i} C^2 - \frac{2\beta_i^3 \bar{p}_i \bar{q}_i b_i}{n_i^2} C^3 \quad (\text{A8})$$

so that by substitution in expression (2) and by dividing by $2C$ one obtains $0 \simeq (\bar{L} - \lambda) - CV_1 + C^2 V_2$ with the V_i as in expressions (1) and (6). By substituting $C = z_0^2 / (\bar{L} - \lambda)$ and operating, expression (6) is obtained.

In section 5 it is shown that a CI with order $O(n_i) \geq -2$ is given by expression (7). The present aim is to express its center $\bar{L} + (z_{\alpha/2}^2 / 2) V_2 / V_1$ in Wald's traditional format, that is, to make it equal to \bar{L}' based on the increased observations $x_i' = x_i + c_i$ and $n_i' = n_i + 2c_i$, where c_i are values to be determined. In order to do this approximately one must bear in mind that:

$$\frac{V_2}{V_1} = \left\{ \sum \frac{\beta_i^2 \bar{p}_i \bar{q}_i}{n_i} \cdot \frac{\beta_i b_i}{n_i} \right\} / \sum \frac{\beta_i^2 \bar{p}_i \bar{q}_i}{n_i} \simeq \frac{1}{K} \sum \frac{\beta_i b_i}{n_i}, \quad (\text{A9})$$

because V_2/V_1 is the weighted average of $\beta_i b_i / n_i$ and it will be approximately equal to its arithmetic average. Thus the center of the CI (7) will be:

$$\bar{L} + \frac{z_{\alpha/2}^2}{2} \cdot \frac{V_2}{V_1} \simeq \sum \beta_i \frac{x_i + hb_i}{n_i} \text{ where } h = \frac{z_{\alpha/2}^2}{2K}.$$

As the center of the adjusted Wald CI $W(+c_i)$ is $\sum \beta_i (x_i + c_i) / (n_i + 2c_i)$, then by making both expressions equal it is found that c_i must verify the equality $(x_i + c_i) / (n_i + 2c_i) = (x_i + hb_i) / n_i$, and so $c_i = n_i h / (n_i - 2h)$ as indicated in section 5.

All the above is valid when $0 < \bar{p}_i < 1$, because when $\bar{p}_i = 0$ or 1 –that is, when $b_i = \pm 1$ – then $R_i = |n_i + b_i \beta_i C|$ and the serial development of expression (A8) yields a value of $n_i + b_i \beta_i C$ which does not necessarily coincide with the previous one. For example, when $\bar{p}_i = 0$ and $\beta_i C < 0$ expression (A1) indicates that $\beta_i C = -n_i / \hat{q}_i$ and thus $0 = n_i + \hat{q}_i \beta_i C \geq n_i + \beta_i C$ (because $\hat{q}_i \leq 1$) = $n_i + b_i \beta_i C$ (because $b_i = 1$); as a result $R_i = -(n_i + b_i \beta_i C)$ and not $n_i + b_i \beta_i C$ as expression (A8) indicated. The same result is obtained when $\bar{p}_i = 1$ and $\beta_i C > 0$. The conclusion is that $R_i = -(n_i + b_i \beta_i C)$ when $b_i = \pm 1$ and $b_i \beta_i C < 0$, and otherwise the approximation of the expression (A8) may be applied. If with this new definition one proceeds as at the beginning of this annex, the following expression, which is more exact than (6), is obtained (in which one must make $j=1$ if $\bar{L} > \lambda$ and $j=2$ if $\bar{L} < \lambda$):

$$0 \simeq N_j (\bar{L} - \lambda)^3 + (\bar{L} - \lambda)^2 \{ (\bar{L} - \lambda) + B_j \} z_0^2 - (\bar{L} - \lambda) V_1 z_0^4 + V_2 z_0^6 \quad (\text{A10})$$

When $0 < \bar{p}_i < 1$ ($\forall i$), then $\delta_{ij} = 0$ ($\forall i, j$), $N_j = B_j = 0$ and expression (A10) turns into expression (6). When $b_i = \pm 1$, that is, when the observed point falls in one of the corners of the sample space, then the following result (which can be shown to be the same as that of the score method) is obtained:

$$z_0^2 = \begin{cases} \frac{(\bar{L} - \lambda) N_1}{\lambda - B^-} & \text{if } \bar{L} > \lambda \\ \frac{(\bar{L} - \lambda) N_2}{\lambda - B^+} & \text{if } \bar{L} < \lambda \end{cases} \quad \text{and} \quad \frac{N_1 \bar{L} + z_{\alpha/2}^2 B^-}{N_1 + z_{\alpha/2}^2} \leq L \leq \frac{N_2 \bar{L} + z_{\alpha/2}^2 B^+}{N_2 + z_{\alpha/2}^2}.$$

In general, if one proceeds for expression (A10) as one did for expression (6) in section 5, expressions (9) and (10) are obtained. Lastly, if the center of the interval CI'_2 are equal to that of interval CI_1 with its data increased in c'_i (just as above with the center of the interval CI_2) expression (11) is obtained.

A5. Properties of convexity

Let $S=z_0$ in expression (12) and let $\psi=\bar{p}_i, \lambda$ or β_i . Because $dz_0^2/d\psi=2z_0(dz_0/d\psi)$, then the sign of $dz_0^2/d\psi$ is the same as (different to) the sign of $dz_0/d\psi$ when $\bar{L}>\lambda$ ($\bar{L}<\lambda$) because then $z_0>0$ ($z_0<0$). This means that the convexity properties (12) are verified for z_0 if z_0^2 verifies the expressions (12) when $\bar{L}>\lambda$, or the opposite ones when $\bar{L}<\lambda$. The aim is thus to calculate $dz_0^2/d\psi$.

For expression (2), $\partial y/\partial\lambda=-2C$, $\partial y/\partial\bar{p}_i=2n_i\beta_i C/R_i$, $\partial y/\partial\beta_i=C\{R_i-A_i\}/R_i$ and:

$$\frac{\partial y}{\partial C}=(B-2\lambda)-\sum\frac{\beta_i A_i}{R_i}=D \quad \text{where } -2n\leq DC\leq 0,$$

where the last statement is owed to the fact that $DC=(B-2\lambda)-\sum\beta_i CA_i/R_i$ or, using expression (2), $DC=-n+\sum R_i-\sum\beta_i CA_i/R_i=-n+\sum n_i A_i'/R_i$ where $A_i'=n_i+b_i\beta_i C$; but as $R_i^2=A_i'^2+4\beta_i^2 C^2 \bar{p}_i \bar{q}_i$ then $R_i\geq|A_i'|$, $-1\leq A_i'/R_i\leq+1$ and $-2n\leq DC\leq 0$. From which it can be deduced that:

$$\text{Sign}(D)\neq\text{Sign}(C)=\text{Sign}(\bar{L}-\lambda), \quad (\text{A11})$$

and the last statement is owed to what has been said in expression (A4).

Because $y=0$, $dy/d\psi=0=(\partial y/\partial\psi)+(\partial y/\partial C)(dC/d\psi)$, so that $dC/d\psi=-(\partial y/\partial\psi)/(\partial y/\partial C)$ and so:

$$\frac{dC}{d\lambda}=\frac{2C}{D}, \quad \frac{dC}{d\beta_i}=-\frac{C(R_i-A_i)}{DR_i}, \quad \frac{dC}{d\bar{p}_i}=-\frac{2n_i\beta_i C}{DR_i}. \quad (\text{A12})$$

Finally, as $z_0^2=C(\bar{L}-\lambda)$ then $dz_0^2/d\psi=(\partial z_0^2/\partial\psi)+(\bar{L}-\lambda)(dC/d\psi)$, so that by substituting expressions (A12):

$$\frac{dz_0^2}{d\lambda}=C\left\{\frac{2(\bar{L}-\lambda)}{D}-1\right\}, \quad \frac{dz_0^2}{d\bar{p}_i}=\beta_i C\left\{1-\frac{2n_i(\bar{L}-\lambda)}{DR_i}\right\}, \quad \frac{dz_0^2}{d\beta_i}=C\left\{\bar{p}_i-\frac{(R_i-A_i)(\bar{L}-\lambda)}{DR_i}\right\}, \quad (\text{A13})$$

where $R_i \geq A_i$ as indicated in section (A1). If, in expressions (A13) one bears in mind expressions (A11) it can be deduced that z_0^2 verifies expressions (12) when $\bar{L} > \lambda$ and the opposite ones when $\bar{L} < \lambda$.

REFERENCES

1. Brumback B, and Berg A. On effect-measure modification: relationships among changes in the relative risk, odds ratio, and risk difference. *Statistics in Medicine* 2008; **27**: 3453-3465. DOI: 10.1002/sim.3246.
2. Crans GG, Shuster JJ. How conservative is Fisher's exact test? A quantitative evaluation of the two-sample comparative binomial trial. *Statistics in Medicine* 2008; **27**: 3598–3611. DOI: 10.1002/sim.3221.
3. Herranz Tejedor I, Martín Andrés A. A numerical comparison of several unconditional exact tests in problems of equivalence based on the difference of proportions. *Journal of Statistical Computation and Simulation* 2008; **78**: 969-981. DOI: 10.1002/sim.3373.
4. Kabaila P. Statistical properties of exact confidence intervals from discrete data using studentized test statistics. *Statistics & Probability Letters* 2008; **78**: 720-727. DOI: 10.1016/j.spl.2007.09.035.
5. Lang JB. Score and profile likelihood confidence intervals for contingency table parameters. *Statistics in Medicine* 2008; **27**: 5975-5990. DOI: 10.1002/sim.3391.
6. Martín Andrés A. Comments on “Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations”. *Statistics in Medicine* 2008; **27**: 1791-1795 (Reply in 1796-1796). DOI: 10.1002/sim.3169.
7. Martín Andrés A, Álvarez Hernández M. Comments on ‘Active-control trials with binary data: a comparison of methods for testing superiority or non-inferiority using the odds ratio. *Statistics in Medicine* 2008; **27**: 5799-5800. DOI: 10.1080/10629360601026386.
8. Martín Andrés A, Tapia Garcia JM, del Moral Ávila MJ. Two-tailed unconditional

- inferences on the difference of two proportions in cross-sectional studies. *Communications in Statistic - Simulation and Computation* 2008; **37**: 455-465. DOI: 10.1080/03610910701812360.
9. Reiczigel J, Abonyi-Tóth Z, Singer J. An exact confidence set for two binomial proportions and exact unconditional confidence intervals for the difference and ratio of proportions. *Computational Statistics and Data Analysis* 2008; **52**: 5046-5053. doi:10.1016/j.csda.2008.04.032
 10. Roussou V, Seifert B. A mixed approach for proving non-inferiority in clinical trials with binary endpoint. *Biometrical Journal* 2008; **50**: 190-204. DOI: 10.1002/bimj.200710410.
 11. Siqueira AL, Whitehead A, Todd S. Active-control trials with binary data: a comparison of methods for testing superiority or non-inferiority using the odds ratio. *Statistics in Medicine* 2008; **27**: 353-370. DOI: 10.1002/sim.2975.
 12. Vos PW, Hudson S. Problems with binomial two-sided tests and the associated confidence intervals. *Australian & New Zealand Journal of Statistics* 2008; **50**: 81-89. DOI: 10.1111/j.1467-842X.2007.00501.x.
 13. Zou , Donner A. (2008). Construction of confidence limits about effect measures: A general approach. *Statistics in Medicine* **27**: 1693-1702. DOI: 10.1002/sim.3095.
 14. Tebbs JM, Roths SA. New large-sample confidence intervals for a linear combination of binomial proportions. *Journal of Statistical Planning and Inference* 2008; **138**: 1884-1893. DOI: 10.1016/j.jspi.2007.07.008.
 15. Agresti A, Coull BA. Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. *The American Statistician* 1998; **52**: 119-126.
 16. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 1998; **17**: 873-890. DOI: 10.1002/(SICI)1097-0258(19980430).

17. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and difference of proportions result from adding two successes and two failures. *The American Statistician* 2000; **54**: 280-288.
18. Price RM, Bonett DG. An improved confidence interval for a linear function of binomial proportions. *Computational Statistics & Data Analysis* 2004; **45**: 449-456. DOI : 10.1016/S0167-9473(03)00007-0.
19. Cohen LA, Kendall ME, Zang E, Meschter C, Rose DP. Modulation of N-Nitrosomethylurea-Induced Mammary Tumor Promotion by Dietary Fiber and Fat. *Journal of National Cancer Institution* 1991; **83**: 496-501. DOI: 10.1093/jnci/83.7.496.
20. Schaarschmidt F, Sill M, Hothorn LA. Approximate Simultaneous Confidence Intervals for Multiple Contrasts of Binomial Proportions. *Biometrical Journal* 2008; **50**: 782-792. DOI: 10.1002/bimj.200710465.
21. Newcombe RG. Estimating the difference between differences: measurement of additive scale interaction for proportions. *Statistics in Medicine* 2001; **20**: 2801-2994. DOI: 10.1002/sim.925.
22. Zou G, Huang W, Zhang X. A note on confidence interval estimation for a linear function of binomial proportions. *Computational Statistics & Data Analysis* 2009 ; **53**: 1080-1085. DOI: 10.1016/j.csda.2008.09.033.
23. Beal SL. Asymptotic Confidence Intervals for the Difference between Two Binomial Parameters for Use with Small Samples. *Biometrics* 1987; **43**: 941-950.
24. Mee RW. Confidence Bounds for the difference between two probabilities. *Biometrics* 1984; **40**: 1175-1176.
25. Koopman PAR. Confidence intervals for the ratio of two binomial proportions. *Biometrics* 1984; **40**: 513-517.
26. Nam JM. Confidence limits for the ratio of two binomial proportions based on likelihood scores: Non-iterative method. *Biometrical Journal* 1995; **37**: 375-379. DOI: 10.1002/bimj.

- 4710370311.
27. Gart JJ, Nam J. Approximate interval estimation of the ratio of binomial parameters: A review and corrections for skewness. *Biometrics* 1988; **44**: 323-338.
 28. Martín Andrés A, Herranz Tejedor I. Propiedades del estadístico z en el contexto del test de equivalencia de dos proporciones. XI Conferencia Española de Biometría y I Encuentro Iberoamericano de Biometría (Salamanca, Spain) 2007: 79-80.
 29. Barnard GA. Significance tests for 2×2 tables. *Biometrika* 1947; **34**: 123-138.
 30. Röhmel J, Mansmann U. Unconditional non-asymptotic one-sided tests for independent binomial proportions when the interest lies in showing non-inferiority and/or superiority. *Biometrical Journal* 1999; **41**: 149-170. DOI: 10.1002/(SICI)1521-4036(199905).
 31. Martín Andrés A, Herranz Tejedor I. Exact unconditional non-classical tests on the difference of two proportions. *Computational Statistics and Data Analysis* 2004; **45**: 373-388. DOI: 10.1016/S0167-9473(02)00351-1.
 32. Röhmel J, Mansmann U. Exact tests of equivalence and efficacy with a non-zero lower bound for comparative studies by I.S.F. Chan (Letters to the Editor). *Statistics in Medicine* 1999; **18**: 1734-1737. DOI: 10.1002/(SICI)1097-0258(19990715).

Table 1: Diet and tumor study

	<i>Fiber</i>		<i>No Fiber</i>	
	<i>High Fat</i>	<i>Low Fat</i>	<i>High Fat</i>	<i>Low Fat</i>
<i>Sample size (n_i)</i>	30	30	30	30
<i>Rats showing cancer (x_i)</i>	20	14	27	19
<i>Effect</i>	β_1	β_2	β_3	β_4
$L_1 = \text{Fiber} \times \text{Fat}$	+1	-1	-1	+1
$L_2 = \text{Fiber}$	+1	+1	-1	-1
$L_3 = \text{Fat}$	+1	-1	+1	-1

Table 2: Multicenter clinical trial data

<i>Location</i>	<i>Sample size (n_i)</i>	<i>Fever cases (x_i)</i>	<i>Coefficients (β_i)</i>
Bangladesh	158	73	158/675
Brazil	107	32	107/675
India	175	44	175/675
Peru	92	34	92/675
Vietnam	143	104	143/675
Total	675	287	1

Table 3: Analysis of the data in Tables 1 and 2

Contrast (Table 1)				
	z_0	z_1	z_2	
L1	-0.4119	-0.4100	-0.4117	
L2	-2.4241	-2.4598	-2.4021	
L3	2.8033	2.8697	2.7682	
CI (Tables 1 and 2) = Center (1st entry) \pm Range (2nd entry)				
	L1	L2	L3	L
CI ₀	-0.0719 \pm 0.3164	-0.3934 \pm 0.3162	0.4581 \pm 0.3161	0.4256 \pm 0.0349
CI ₁	-0.0667 \pm 0.3187	-0.4000 \pm 0.3187	0.4667 \pm 0.3187	0.4252 \pm 0.0349
CI ₂	-0.0732 \pm 0.3188	-0.3938 \pm 0.3188	0.4585 \pm 0.3188	0.4256 \pm 0.0349
W(+c _i)	-0.0645 \pm 0.3161	-0.3872 \pm 0.3161	0.4517 \pm 0.3162	0.4256 \pm 0.0348
W(+h)	-0.0646 \pm 0.3162	-0.3876 \pm 0.3162	0.4522 \pm 0.3162	0.4256 \pm 0.0348

Contrast (Table 1)				
	z_0	z_1	z_2	z_3
L1	-0.4119	-0.4100	-0.4117	-0.4119
L2	-2.4241	-2.4598	-2.4021	-2.4295
L3	2.8033	2.8697	2.7682	2.8104
CI (Tables 1 and 2) = Center (1st entry) \pm Range (2nd entry)				
	CI ₀	CI ₁	CI ₂	CI ₃
L1	-0.0719 \pm 0.3164	-0.0667 \pm 0.3187	-0.0732 \pm 0.3188	-0.0731 \pm 0.3164
L2	-0.3934 \pm 0.3162	-0.4000 \pm 0.3187	-0.3938 \pm 0.3188	-0.3939 \pm 0.3164
L3	0.4581 \pm 0.3161	0.4667 \pm 0.3187	0.4585 \pm 0.3188	0.4587 \pm 0.3165
L	0.4256 \pm 0.0349	0.4252 \pm 0.0349	0.4256 \pm 0.0349	0.4256 \pm 0.0349
	W(+c _i)	W(+c _i)	W(+h)	W(+h)
L1	-0.0645 \pm 0.3161	-0.0646 \pm 0.3162	-0.0646 \pm 0.3162	-0.0647 \pm 0.3163
L2	-0.3872 \pm 0.3161	-0.3876 \pm 0.3162	-0.3876 \pm 0.3162	-0.3878 \pm 0.3165
L3	0.4517 \pm 0.3162	0.4522 \pm 0.3162	0.4522 \pm 0.3162	0.4526 \pm 0.3163
L	0.4256 \pm 0.0348	0.4256 \pm 0.0348	0.4256 \pm 0.0348	0.4256 \pm 0.0348

**Table 4: Exact coverage (R) and width (W) of S (score), $W(+2/K)$ (Price and Bonett) and $W(+h'_i)$ (new) intervals for a confidence = 95%
K=3**

Method:	$W(+2/K)$				$W(+h'_i)$				S			
$n_1/n_2/n_3$	R_{mean}	R_{min}	W_{mean}	$R_{below93}$	R_{mean}	R_{min}	W_{mean}	$R_{below93}$	R_{mean}	R_{min}	W_{mean}	$R_{below93}$
$\beta_i = (1/3, 1/3, 1/3)$												
10/10/10	95.6	88.3	0.28	0.1	97.0	89.5	0.30	0.1	94.4	89.9	0.27	7.1
30/30/30	95.2	92.7	0.16	0.0	95.6	93.1	0.17	0.0	94.8	92.9	0.16	0.0
30/10/10	95.5	92.2	0.25	0.1	96.7	93.5	0.26	0.0	95.0	90.2	0.24	0.0
30/20/10	95.4	91.4	0.22	0.1	96.4	92.9	0.23	0.0	95.1	93.0	0.22	0.0
$\beta_i = (1, -1/2, -1/2)$												
10/10/10	95.5	87.6	0.58	0.6	96.9	93.1	0.64	0.0	95.1	92.4	0.58	0.1
30/30/30	95.2	92.2	0.35	0.0	95.6	93.0	0.36	0.0	94.9	93.9	0.35	0.0
30/10/10	95.4	92.1	0.44	0.1	96.5	92.5	0.47	0.0	94.4	92.4	0.44	0.3
30/20/10	95.4	90.0	0.41	0.1	96.2	92.8	0.43	0.0	94.7	92.9	0.41	0.0
$\beta_i = (-1, 1/2, 2)$												
10/10/10	95.4	87.9	1.09	1.4	96.9	90.7	1.18	0.1	95.4	91.6	1.07	0.1
30/30/30	95.1	93.0	0.65	0.0	95.6	94.1	0.66	0.0	95.1	94.4	0.64	0.0
30/10/10	95.4	89.4	1.02	4.7	96.7	91.5	1.09	0.6	95.5	89.8	0.99	0.1
30/20/10	95.3	89.7	1.00	8.2	96.6	91.0	1.07	3.3	95.5	88.9	0.97	0.0
$\beta_i = (1, 1, -1)$												
10/10/10	95.6	90.0	0.83	0.2	97.0	90.5	0.90	0.0	94.3	92.1	0.82	7.0
30/30/30	95.2	92.5	0.49	0.0	95.7	92.8	0.51	0.0	94.8	92.4	0.49	0.0
30/10/10	95.5	90.1	0.73	0.0	96.8	92.6	0.79	0.0	95.0	91.8	0.73	0.0
30/20/10	95.4	90.7	0.66	0.1	96.4	93.4	0.69	0.0	95.1	93.0	0.65	0.0

Table 4 (cont.): K=4

Method:	W(+2/K)				W(+h _i ')				S			
$n_1/n_2/n_3/n_4$	<i>Rmean</i>	<i>Rmin</i>	<i>Wmean</i>	<i>Rbelow93</i>	<i>Rmean</i>	<i>Rmin</i>	<i>Wmean</i>	<i>Rbelow93</i>	<i>Rmean</i>	<i>Rmin</i>	<i>Wmean</i>	<i>Rbelow93</i>
$\beta_r=(1/4, 1/4, 1/4, 1/4)$												
10/10/10/10	95.3	92.9	0.24	0.0	97.2	93.6	0.27	0.0	93.8	91.7	0.24	7.1
20/20/20/20	95.1	93.2	0.17	0.0	96.0	93.8	0.18	0.0	94.5	92.9	0.17	0.0
20/20/10/10	95.2	93.0	0.21	0.0	96.8	94.0	0.23	0.0	94.4	93.1	0.21	0.0
20/15/10/5	95.3	85.7	0.24	0.6	97.5	93.7	0.27	0.0	95.1	93.1	0.24	0.0
$\beta_i = (-1, 1, -1, 1)$												
10/10/10/10	95.3	93.0	0.96	0.0	97.1	93.6	1.06	0.0	93.8	92.0	0.94	6.4
20/20/20/20	95.1	93.6	0.69	0.0	96.1	93.8	0.73	0.0	94.5	92.1	0.69	0.0
20/20/10/10	95.2	92.7	0.84	0.0	96.7	94.2	0.91	0.0	94.4	93.0	0.83	0.0
20/15/10/5	95.3	91.3	0.97	0.5	97.5	94.0	1.08	0.0	95.1	92.9	0.96	0.0
$\beta_r=(1/3, 1/3, 1/3, 1)$												
10/10/10/10	94.9	90.2	0.55	4.5	96.9	92.6	0.60	0.0	95.3	92.8	0.54	0.0
20/20/20/20	94.9	92.3	0.40	0.1	95.9	93.7	0.41	0.0	95.2	94.3	0.39	0.0
20/20/10/10	94.8	87.0	0.53	13.8	96.7	92.6	0.57	0.4	95.4	93.5	0.52	0.0
20/15/10/5	94.8	80.8	0.69	40.7	97.8	93.5	0.77	0.0	95.6	90.3	0.65	0.1
$\beta_i = (-3, -1, 1, 3)$												
10/10/10/10	95.1	91.4	2.14	0.1	97.0	93.6	2.35	0.0	95.0	93.2	2.12	0.0
20/20/20/20	95.0	92.9	1.54	0.0	95.9	94.0	1.61	0.0	94.7	93.8	1.53	0.0
20/20/10/10	95.0	90.1	1.86	0.6	96.6	91.8	2.01	0.0	95.2	93.9	1.85	0.0
20/15/10/5	95.1	85.8	2.29	35.0	97.7	94.0	2.55	0.0	95.6	92.3	2.23	0.0