Relative Risk Cutoffs for Statistical Significance

Milo Schield, Augsburg College

Abstract: Relative risks are often presented in the everyday media but are seldom mentioned in introductory statistics courses or textbooks. This paper reviews the confidence interval associated with a relative risk ratio. Statistical significance is taken to be any relative risk where the associated 90% confidence interval does not include unity. The exact solution for the minimum statistically-significant relative risk is complex. A simple iterative solution is presented. Several simplifications are examined. A Poisson solution is presented for those times when the Normal is not justified.

1. Relative risk in the everyday media

In the everyday media, relative risks are presented in two ways: explicitly using the phrase "relative risk" or implicitly involving an explicit comparison of two rates or percentages, or by simply presenting two rates or percentages from which a comparison or relative risk can be easily generated.

Here are some examples (Burnham, 2009):

> *the risk of developing acute non-lymphoblastic leukaemia was seven times greater compared with children who lived in the same area , but not next to a petrol station*
>
> *Bosch and colleagues (p 699) report that the relative risk of any stroke was reduced by 32 % in patients receiving ramipril compared with placebo*
>
> *Women of normal weight and who were physically active but had high glycaemic loads and high fructose intakes were also at greater risk (53 % and 57 % increase respectively) than those with low glycaemic loads and low fructose intakes . But these increases were considered insignificant (relative risk 1.53 (0.96 to 2.45) for high glycaemic loads and 1.57 (0.95 to 2.57) for high fructose intake*
>
> *Women who took antibiotics for more than 500 days cumulatively, or had more than 25 individual prescriptions, had twice the relative risk of breast cancer as those who didn't take the drugs…*
>
> *smokers are 11 times more likely to develop lung cancer than are nonsmokers*

But are these relative risks statistically significant? Given the confidence intervals or p-values, we could tell. But all too often this data is not provided.

1. Confidence Intervals for Relative Risks

As noted in Wikipedia, the sampling distribution for the natural log of a randomly-sampled Relative Risk is normally distributed and described by the Central Limit theorem. For details, see the Boston University (2014) website. The confidence interval is given by

Equation 1: CI: $LN(RR) \pm Z*Sqrt[(1-P1)/(P1*N1) + (1-P2)/P2*N2)]$

Equation 1 involves six variables: RR, Z, P1, P2, N1 and N2. But P2 involves RR: P2 = RR * P1. Thus,

Equation 2: CI: $LN(RR) \pm Z*Sqrt[(1-P1)/(P1*N1) + (1-RR*P1)/(RR*P1*N2)]$

If N1 = N2 = N, the confidence interval is determined by four variables: RR, Z, P1 and N.

Equation 3: CI: $LN(RR) \pm Z*Sqrt\{(1/n)[(1-P1)/P1 + (1-RR*P1)/(RR*P1)]\}$

2. Relative-Risk Cutoffs for Statistical Significance

If the relative risk is greater than one, the smallest value that will be statistically-significant occurs when the lower-limit of the 95% confidence interval for a relative risk just touches unity (or when the lower limit of the 95% confidence interval for the natural log of the relative risk just touches zero).

Setting Equation 3 equal to zero with the negative sign gives the minimum relative risk that is statistically significant. This relative risk cutoff is denoted by RRss.

Equation 4: **LN(RRss) - Z*Sqrt{(1/N)[(1-P1)/P1 + (1-RRss*P1)/(RRss*P1)]} = 0**

Equation 5: **LN(RRss) = Z*Sqrt{(1/n)[(1-P1)/P1 + (1-RRss*P1)/(RRss*P1)]}**

Unfortunately RRss is on both sides of this equation. We are unaware of an analytic solution. An alternate approach is iterative. Start with a solution that is close and then iterate. Consider how RRss might be eliminated on the right side of Equation 5. Return to Equation 3. Note that

Equation 6: **if RR > 1 then P2 > P1 and (1-P2)/P2 < (1-P1)/P1.**

Equation 7: **Sqrt[(2/n)(1-P1)/P1)] > Sqrt[(1/N)[(1-P1)/P1 + (1-P2)/P2)]**

Inserting this into **Equation 5** gives:

Equation 8: **LN(RRss) = Z*Sqrt[(2/N)(1-P1)/(P1*N1)]**

Equation 9: **RRss = EXP{Z*Sqrt[(2/N)(1-P1)/(P1*N1)]}**

This is equivalent to setting RRss = 1 on the right side of Equation 5**.** With this starting point (close but slightly high), Equation 5 can be iterated to quickly obtain increasingly accurate results.

Figure 1: Relative Risk Calculator Output

	Calculate the minimum Relative Risk that is statistically significant			RR = P2 / P1	V0b	1
		This calculation assumes that P2 > P1 so that RR > 1. It assumes N1 = N2.				2
		This minimum RR ocurs where the lower-edge of 95% RR confidence interval equals one.				3
		This iterative process approaches the exact solution. Each iteration adds another digit.				4
A	B	C D	E			5
0.1	P1	Step 1: Enter the smaller of the two proportions.				6
100	N	Step 2: Enter the sample size in exposure group (assumes Control Group is same size).				7
						8
10	N*P1		=A7*A6	If this is too small, this method may not work.		9
1.9600	Z (for a two-tailed test)		=-NORM.S.INV(0.025)			10
						11
2.296858442	RR-Estimated		=EXP(A$10*SQRT(2*(1-A$6)/(A$6*A$7)))			12
1.991497472	RR-Exact: Iteration 1		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A12)/(A$6*A12*A$7)))			13
2.028415681	RR-Exact: Iteration 2		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A13)/(A$6*A13*A$7)))			14
2.023378643	RR-Exact: Iteration 3		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A14)/(A$6*A14*A$7)))			15
2.024055361	RR-Exact: Iteration 4		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A15)/(A$6*A15*A$7)))			16
2.023964254	RR-Exact: Iteration 5		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A16)/(A$6*A16*A$7)))			17
2.023976516	RR-Exact: Iteration 6		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A17)/(A$6*A17*A$7)))			18
2.023974866	RR-Exact: Iteration 7		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A18)/(A$6*A18*A$7)))			19
2.023975088	RR-Exact: Iteration 8		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A19)/(A$6*A19*A$7)))			20
2.023975058	RR-Exact: Iteration 9		=EXP(A$10*SQRT((1-A$6)/(A$6*A$7)+(1-A$6*A20)/(A$6*A20*A$7)))			
Schield, Milo (2014). Calculating the Relative Risk Cutoff for Statistical Significance						
	www.StatLit.org/xls/2014-Schield-RR-Stat-Sig-Calculator.xlsx					

Milo Schield, Augsburg College

The minimum RRss for various combinations of N and P1 (Z = 1.96) are shown in Figure 2.

Figure 2: Minimum statistically-significant Relative Risk given N and P1 (two-tailed interval)

M	N	O	P	Q	R	S	T	U	V	4
#5: RRss Fifth Iteration Exact				N*P1 ≥	5	2.78	Max Min RRss		V0b	5
N \ P1	0.001	0.002	0.005	0.01	0.02	0.05	0.1	0.2	0.5	6
16									1.70	7
36								2.13	1.46	8
64							2.36	1.80	1.35	9
100						2.69	2.02	1.62	1.28	10
144						2.32	1.82	1.51	1.23	11
196						2.09	1.69	1.43	1.20	12
256					2.71	1.92	1.59	1.37	1.17	13
324					2.46	1.80	1.52	1.33	1.15	14
400					2.27	1.71	1.46	1.29	1.14	15
625				2.51	1.96	1.55	1.36	1.23	1.11	16
900				2.19	1.77	1.45	1.30	1.19	1.09	17
1,600			2.29	1.83	1.55	1.33	1.22	1.14	1.07	18
2,500		2.78	1.97	1.64	1.43	1.26	1.17	1.11	1.06	19
4,900		2.13	1.65	1.44	1.30	1.18	1.12	1.08	1.04	20
10,000	2.12	1.73	1.43	1.30	1.20	1.12	1.08	1.06	1.03	21
N7	=IF(B7="", "", EXP(I3*SQRT((1-N$6)/(N$6*$M7)+(1-N$6*B83)/(N$6*B83*$M7))))									22

RRss for N=100, P1 = 0.1 is 2.02. This is the same result as shown in Figure 1 for the 5th iteration.

3. *Relative-Risk Shortcuts for Statistical Significance*

It would be nice to have a simple analytic expression for the minimum relative risk that is statistically significant. It must always be conservative; it should always overstate RRss. Here are three attempts given that P1*N is more than five:

Model 1: RRss = 1 + Z*SQRT[K/(P1*N)] where K = 4. Maximum error = 0.69.

Model 2: RRss = 1 + Z*K/(P1*N) where K = 60. Maximum error = 21.83

Model 3: RRss = Z*Exp[K*(1-P1)/(P1*N)] where K = 1.8. Maximum error = 0.46

Model 2 is the simplest, but it is the least accurate; it overstates RRss the most. Model 3 is the most complex, but it is the most accurate. See the RR-Model tab of the Schield (2014) worksheet.

Model 1 is the best combination of simplicity and accuracy in this group. The one case where this model understates RRss by 0.02 is when P1*N = 5. This is why K1 should exceed 5. Note that RR has four cells of counts that determine RR while P1*N is the count in the outcome for the control group.

Model 1: RRss = 1 + 2*Z / Sqrt(k1) where k1 = P1*N1 when P1 < P1 and N1=N2.

Figure 3: Minimum Statistically-Significant Relative Risk: Model vs. Actual

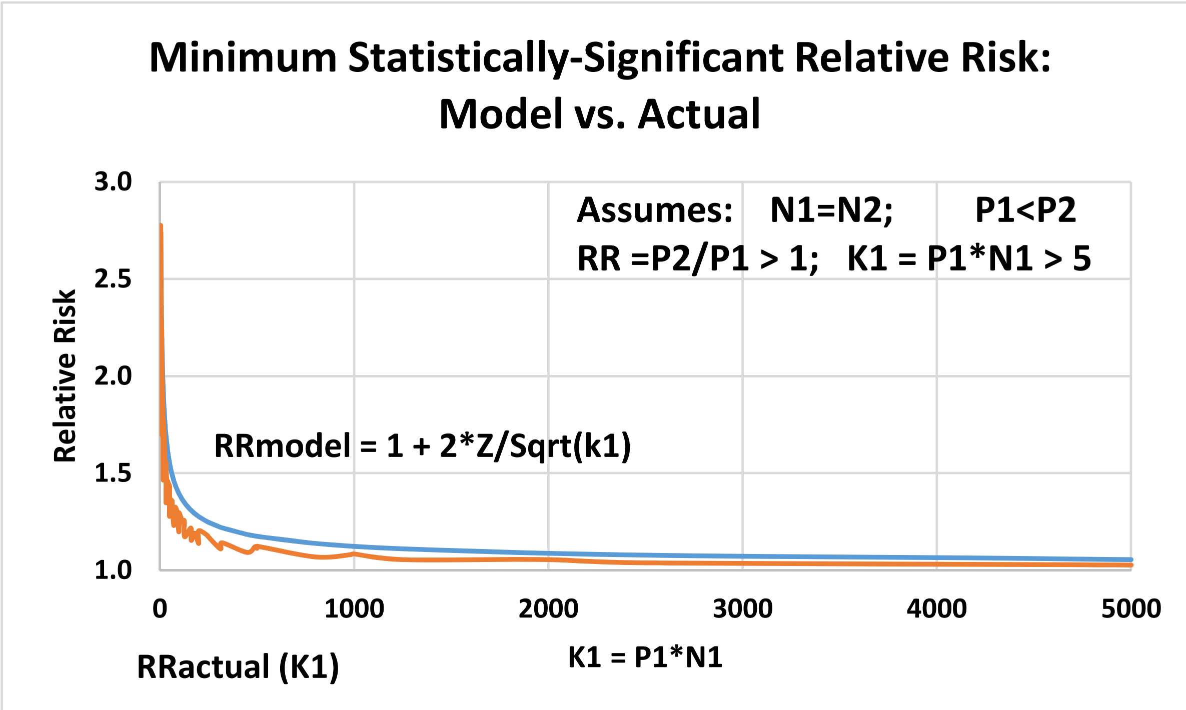
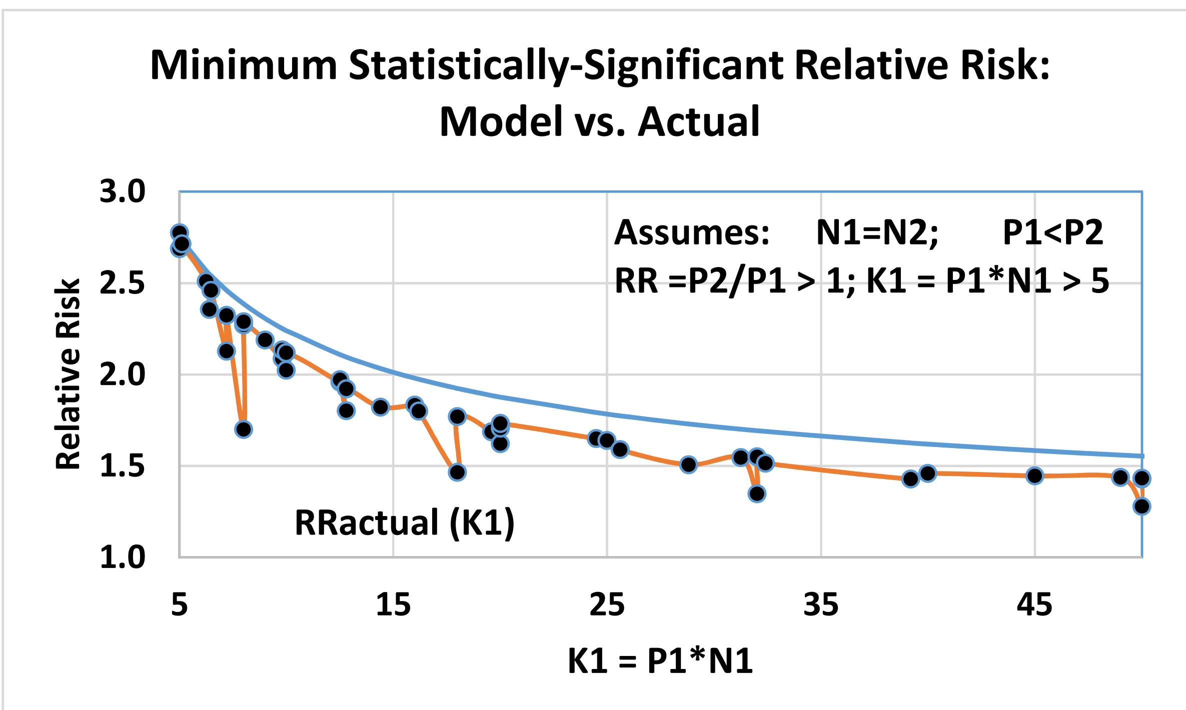


Figure 4: Minimum Statistically-Significant Relative Risk: Model vs. Actual



An entirely different approach is to identify the maximum RRss for any combination of N and P1 as a function of the minimum count required. Any relative risk that is larger is statistically-significant.

Figure 5: Maximum RRss for any combination of P1 and N as a function of P1*N

Maximum RRss for any combination of P1 and N as a function of P1*N								1.645	Z
N1*P1	1	2	3	5	10	15	25	30	50
RRss	5.84	3.69	2.93	2.4	1.9	1.68	1.52	1.45	1.36

Maximum RRss for any combination of P1 and N as a function of P1*N								1.96	Z
N1*P1	1	2	3	5	10	15	25	30	50
RRss	7.86	4.59	3.50	2.78	2.12	1.83	1.64	1.55	1.43

Various rules give different minimums to justify using this normal approximation. N*P1 = 5 is typically the smallest value; N*P1 = 30 is generally the largest. For a two-tailed test (Z=1.96), any relative risk of at least 2.8 is statistically significant provided N*P1 is at least five. Any relative risk of at least 1.55 is statistically significant if N*P1 is at least 30.

Figure 5 is certainly a simple shortcut. If only two could be retained, these two seem most informative:

- Any RR > 2 is statistically-significant when N*P1 is at least 10.
- Any RR > 1.6 is statistically-significant when N*P1 is at least 25.

4. Relative-Risk Cutoffs for Statistical Significance using the Poisson

As the count in the smallest cell decreases, the Normal Approximation becomes less adequate. An alternative approach involves the Poisson. See Schield (2005).

John Brignell (2000) showed that a relative risk must be at least 2 to be statistically significant for rare outcomes. Assume that RR = 1 in the population so that the chance of the desired outcome is the same in both exposure and control groups. Assume that we randomly sample for just the exposure group so the mean of the control group is the same as that in the population.

Assume the outcome of interest is rare (P<< 1%) and that the sample sizes (N) are quite large, so the number of outcomes expected (K) is greater than 1 since K=N•P. In this case, the frequency of rare events is Poisson. The variance of the Poisson equals the expected value (K). The standard deviation (SE of the distribution) is the square root of the variance: √K. The upper limit of a 95% confidence interval is the mean (the # expected) plus 2 standard deviations (SE). In terms of expected values, the maximum relative risk is [K + 2√K]. In terms of risk, the upper limit is P + 2√(P/N)

Assuming N1 in the test group and N0 in the control (where P1=P0=P), the resulting relative risk due to chance is [P + 2√(P/N1)]/P = 1+2√[1/(P*N1)] = 1+2/√K. Conversely, K = [2 / (RR-1)]^2

For K=1, the relative risk must be at least three to be statistically significant. This rule may apply for larger K since we excluded variation in the control group. The argument is reversible. If a relative risk of 1.2 is to be statistically significant then at least 100 events of interest are needed in the test group. If the outcome prevalence is 1%, this requires 10,000 subjects.

5. *Conclusion*

In general, any relative risk in excess of three is statistically significant. Any relative risk in excess of two is statistically significant if K1 > 10. If the Normal approximation applies (k1 > 5), the most memorable conservative estimate of the minimum Relative Risk that is statistically-significant is given by:

Model 1: RRss = 1 + 2*Z / Sqrt(k1) where k1 = P1*N.

For more accurate values, use the Relative Risk calculator (Schield 2014a). When the counts are too small for the Normal to apply, the minimum RRss is three.

6. *Bibliography:*

Boston University School of Public Health. Biostatics 704: Confidence Intervals. Available at: http://sphweb.bumc.bu.edu/otlt/MPH-Modules/BS/BS704_Confidence_Intervals/BS704_Confidence_Intervals.html

Brignell, John (2000). *Sorry, Wrong Number! The Abuse of Measurement*. Brignell Associates. P. 102-3.

Burnham, Thomas V. V. (2009). Statistical Literacy Download #2 from Cobuild Word-Banks Database.

Hutchon, DJR (2011). Calculator for confidence intervals of relative risk. Copy at http://www.hutchon.net/confidrr.htm

Schield, Milo (2005). Statistical Literacy and Chance. ASA Proceedings of the Section on Statistical Education. P. 2302-2310. Copy at www.statlit.org/pdf/2005SchieldASA.pdf

Schield, Milo (2014a). Calculating the Relative Risk Cutoff for Statistical Significance www.StatLit.org/xls/2014-Schield-RR-Stat-Sig-Calculator.xlsx

Schield, Milo (2014b). Relative Risk Cutoffs for Statistical Significance. www.StatLit.org/xls/2014-Schield-RR-Statistical-Significance.pdf