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AN EMPIRICAL INVESTIGATION OF META-ANALYSIS USING RANDOMIZED CONTROLLED CLINICAL TRIALS IN A PARTICULAR CENTRE

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Abstract: *Meta-analysis is the combination of results from various independent studies. In a meta-analysis, combining survival data from different clinical trials, an important issue is the possible heterogeneity between trials. Such inter-trial variation can not only be explained by heterogeneity of treatment effects across trials but also by heterogeneity of their baseline risk. In addition, one might examine the relationship between magnitude of the treatment effect and the underlying risk of the patients in the different trials. However, the need for medical research and clinical practice to be based on the totality of relevant and sound evidence has been increasingly recognized. In this paper, we review the advances of meta-analysis using clinical trials TB data. This paper examines sixteen reporting results of randomized clinical trials conducted in a particular centre at consecutive periods. Every study pools that the results from the relevant trials in order to evaluate the efficacy of a certain treatment between cases and control. There is a need for empirical effort comparing random effects model with the fixed effects model in the calculation of a pooled relative risk in the meta-analysis in systematic reviews of randomized controlled clinical trials. We review heterogeneity and random effects analyses and assessing bias within and across studies. We compare the two approaches with regards to statistical significance, summary relative risk, and confidence intervals.*

Key words: *fixed effects model; random effects model; heterogeneity of treatment effects*

1. Introduction

Meta-analysis provides an objective way of combining information from independent studies looking at the same clinical questions and has been applied most often to treatment effects in randomized clinical trials. We understand meta-analysis as being the use of statistical techniques to combine the results of studies addressing the same question into a summary measure. Standard meta-analysis methods for providing an overall estimate of the treatment effects rely on certain assumption (Whitehead and Whitehead, 1991). Meta-analysis is the term given to retrospective investigations in which data from all known studies of a particular clinical issue are assembled and evaluated collectively and quantitatively. It differs in important ways from traditional narrative reviews, in that there is a commitment to scientific principles in assembling and analyzing the data, via protocol-driven library searches and data abstraction, in addition to the formalism of statistical analysis. There is a

need for more empirical work on methodology, properties and limitations of underlying statistical methodology (Engels, et al, 2000). Heterogeneity, by which we mean variation among the results of individual trials beyond that expected from chance alone, is an important issue in meta-analysis. Heterogeneity may indicate that trials evaluated different interventions or different populations. It is clear that when there are substantial differences among trial results, and in the face of heterogeneity, a single estimate may be misleading and should be avoided and exploration of heterogeneity is also a critical important component of meta-analysis of randomized trials (Thompson and Pocock, 1991; Thompson 1994; Lau et al. 1995). Most of the arguments presented against random effects model could be considered as explanations of the limitations of using covariates to explain the heterogeneity in trial results. There is limited empirical experience comparing results from random effects and fixed effects models, particularly when the results are heterogeneous (Thompson and Pocock, 1991). The random effects model incorporates the heterogeneity of treatment effects across studies in the analysis of the overall treatment efficacy (DerSimonian and Liard, 1986). We present an empirical investigation from meta-analysis of randomized clinical trials included in systematic reviews as well as reports conducted in the area of tuberculosis infected patients; we compare the two approaches with regards to statistical significance, summary relative risk, and confidence intervals. The results of any individual trial must be absorbed and debated by the scientific community before wholesale recommendations regarding treatment practice are observed. Randomized trials and meta-analyses have distinct but complementary goals. Meta-analysis can be used productively in planning new clinical trials, and in supplying updated information to study monitors in the course of a trial. This process of debate necessarily involves the weighing of evidence from different sources, and meta-analysis can and does play an important role in this process (Begg, 1996).

2. Definition of models

The two models have been used here, they are fixed effects model (FEM) and random effects model (REM). Fixed effects model assumes that there is a common effect and a random component, which means sampling error, is responsible for difference among trial results, that is, it assumes heterogeneity of intervention effects. This approach provides inferences only about the set of trials under review, giving weight to each trial based on the 'within study' sampling variance. The individual study sample size and the number of events are the leading factors in the weight assigned to each trial in the pooled estimate of the relative risk. The FEM formulations are inverse variance method, Mantel-Haenszel method and Peto's method. However, the Peto's modified estimate can give biased answers in a few circumstances, such as when there is severe imbalance in treatment allocation within individual studies or in the presence of very large treatment effects. The REM provides inference based on the assumption that the observed trials are a sample from a hypothetical population of trials. Also to account for the variation among trials results a random term is added to compute the weights in the REM, representing 'among' trials variation, as often estimated from a function of the chi-squared test for heterogeneity. This term adds a common variance component to the weight of each trial in the meta-analysis, which tends equalize the weights assigned to small and large trials (Villar, et al., 2001). The disproportionate overall influence of small trials is more evident when there is heterogeneity

of trial results because the 'among' trials variance becomes larger and dominates the within-trial random effects.

When heterogeneity is present, it may be inappropriate to combine the separate trial estimates into a single number, particularly using fixed effects methods that assume a common treatment effect. Random effects methods, which provide an attractive approach to summarizing heterogeneous results, model heterogeneity as variation of individual trial treatment effects around a population average effect. The key distinction between these two types of models concerns the belief regarding behavior of trial effects as trial sample sizes get very large. If one believes that the individual trial effects would converge to a common value for all trials, a fixed effects model is appropriate, whereas if one believes that individual trials would still demonstrate separate effects, then a random effects model is preferable (Thompson and Pocock, 1991). The random effects model anticipates better than the fixed effects model by Fleiss (1993) and also the National Research Council (1992) make known the benefits of using random effects model.

3. A meta-analysis of sixteen randomized clinical trials

For the present analysis we examine sixteen clinical trials at same centre each reporting results from several independent trials over a period between 1956 and 1995. All the sixteen trials have been categorized into two groups based on their duration segment. Each review pools the results from the relevant trials in order to evaluate the efficacy of a certain treatment for a specified condition. These reviews lack of consistent assessment of homogeneity of treatment effect before pooling. We discuss both fixed effects and random effects approach to combining evidence from a series of experiments comparing two treatments. This approach incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy. The model can be extended to include relevant covariates which would reduce the heterogeneity and allow for more specific therapeutic recommendations. Most often to explore heterogeneity is stratification. Studies are categorized according to the characteristics of the study or the characteristics of the subjects in the study and a summary estimate of effect is estimated in each of the categories (Petitti, 2001).

4. Statistical methods

Results of the outcome were abstracted and are expressed as summary relative risk and 95 per cent confidence interval (CI) for both random and fixed effects models. The summary relative risk for the FEM was calculated using the Mantel-Haenszel method while the DerSimonian and Laird method was used for the REM.

Mantel-Haenszel Method

This is for calculating a summary estimate of effect across strata. Since studies are identified for a meta-analysis as strata, the Mantel-Haenszel method is an appropriate for analyzing data for a meta-analysis based on fixed effect. It is used when the measure of effect is a ratio mesure. Kleinbaum, Kupper, and Morgenstern (1982) give formulas that would allow in Mantel-Haenszel to be applied. Notations for applications of Mantel-Haenszel

	Treated	Control	Total
Recurrent	a_i	b_i	gi
Non Recurrent	c_i	d_i	h_i
Total	e_i	f_i	n_i

Summary odds ratio

$$OR_{mh} = \frac{Sum(W_i \times OR_i)}{SumW_i}$$

$$OR_i = \frac{(a_i \times d_i)}{(b_i \times c_i)}$$

$$W_i = 1 \Big/ \text{var}\, iance_i$$

$$Variance_i = \frac{n_i}{(b_i \times c_i)}$$

$$95\%\,\text{confidence interval} = e^{\ln OR_{mh}} \pm 1.96\sqrt{\text{var}\, ianveOR_{mh}}$$

where *variance* OR_{mh} is calculated as Robins, Greenland, and Breslow(1986). The

$$Variance_{mh} = \left(\frac{SumF}{2 \times (SumR)^2}\right) + \left(\frac{SumG}{2 \times SumR \times SumS}\right) + \left(\frac{SumH}{2 \times (SumS)^2}\right)$$

where $F = a_i \times d_i \times \left(\frac{a_i + d_i}{n_i^2}\right)$

$$G = \frac{[a_i + d_i \times (b_i + c_i)] + [b_i \times c_i \times (a_i + d_i)]}{n_i^2}$$

$$H = \frac{[b_i \times c_i \times (b_i + c_i)]}{n_i^2}$$

$$R = \frac{a_i \times d_i}{n_i}$$

$$S = \frac{b_i \times c_i}{n_i}$$

Formula for calculate a statistic for a test of homogeneity of effects;

$Q = Sum\left[W_i \times (\ln OR_{mh} - \ln OR_i)^2\right]$, where, Q is referred to the chi-square distribution with one degree of freedom.

DerSimonian & Laird Method

The DerSimonian and Laird (1986) method is based on the random-effects model. Formulas for applying the DerSimonian-Laird method summarizing studies in the case where effects are measured as odds ratios are given by Fleiss and Gross (1991)

$$\ln OR_{dl} = \frac{Sum\left(W_i^* \times \ln OR_i\right)}{Sum\left(W_i^*\right)};$$

where OR_{dl} is the DerSimonian-Laird summary estimate of the odds ratio, W_i^* is the DerSimonian-Laird weighting factor for the i[th] study, and OR_i is the odds ratio from the i[th] study

$$W_i^* = \frac{1}{\left[D + \left(1/W\right)\right]}$$ where W_i is given in *MH* and

$$D = \frac{[Q-(S-1)]\times SumW_i}{\left[(SumW_i)^2 - Sum(W_i)^2\right]}; and \quad D = 0 \quad if \quad Q < S-1;$$

where S is the number of studies and

$Q = SumW_i(\ln OR_i - \ln OR_{mh})^2$ from this formula

$95\%\,\mathrm{CI} = e^{\ln OR_{all}} \pm 1.96\sqrt{\mathrm{var}\,ianve_i^*}$; where

$$Variance_i^* = \frac{1}{SumW_i^*}$$

The fixed effects let Y denote the generic measure of the effect of an experimental intervention; let W denotes the reciprocal of the variance of effect size. Under the assumption of the fixed set of studies, an estimator of the assumed common underlying effect size is

$$\overline{Y} = \frac{\sum_{i=1}^{N} W_i Y_i}{\sum_{i=1}^{N} W_i}$$

and the standard error of the estimator is

$$SE(\overline{Y}) = \left[\sum_{i=1}^{N} W_i\right]^{-1/2}$$

let ψ is the population effect size for an approximate 100(1-α)% confidence interval, then

$$\overline{Y} - z_{\alpha/2}\sqrt{\sum_{i=1}^{N} W_i} \le \psi \le \overline{Y} + z_{\alpha/2}\sqrt{\sum_{i=1}^{N} W_i}$$

Under the assumption of random effects, the studies are random samples from a largest population, the mean population size $\overline{\psi}$, about which the study-specific effect size vary. An approximation 100(1- α) % confidence interval for $\overline{\psi}$ is

$$\overline{Y}^* - z_{\alpha/2}\sqrt{\sum_{i=1}^{N} W_i^*} \le \overline{\psi} \le \overline{Y}^* + z_{\alpha/2}\sqrt{\sum_{i=1}^{N} W_i^*}$$

where $W_i^* = (D + W_i^{-1})^{-1}$

$$\overline{Y}^* = \frac{\sum_{i=1}^{N} W_i^* Y_i}{\sum_{i=1}^{N} W_i^*}$$

D denotes the study variation in effect size and this is calculated as

$$D = 0 \quad if \quad Q \le N-1$$

$$D = [Q-(N-1)]/U \quad if \quad Q > N-1$$

as Der Simonian and Laird, (1986)

$$U = (N-1)\left[\overline{W} - \frac{S_W^2}{N\overline{W}}\right]$$

where $\overline{W}$ *and* S_W^2 are the mean and variance of the W_S

The inconsistency of studies are being measured based on the classical measure of heterogeneity is Cochran's Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q is distributed as a chi-square statistic with k-1 (number of studies minus one) degrees of freedom. Q has low power as a comprehensive test of heterogeneity (Gavaghan et al. 2000) in particular when the number of trials is small in meta-analysis. If the number of studies are large where Q has more power as a test of heterogeneity (Higgins et al. 2003). Q is included in each meta-analysis function because it forms part of the DerSimonian-Laird random effects pooling method (DerSimonian and Laird 1986). An additional test, due to (Breslow and Day 1980), is provided with the odds ratio meta-analysis. We transformed the summary relative risks and the corresponding upper and lower limits of the 95 per cent CI for the two models to the natural logarithmic scale. I-squared statistic describes the percentage of variation across studies that are due to heterogeneity rather than chance (Higgins and Thompson, 2002; Higgins et al., 2003).

$$I^2 = 100\% \times \frac{(Q - df)}{Q}$$

We calculated the mean and standard deviation and range of the summary relative risk obtained using the two methods. To assess the differences between the summary relative risks and between the widths of the Confidence Intervals obtained using the two methods we calculated the mean of the paired differences. To investigate the average relative risk as a function of the difference we plotted the differences between the logs of the relative risks (log RR random-log RR fixed) against the mean of these two values. Graphs were plotted separately by heterogeneity status. The statistical evaluation of bias was conducted using the Begg and the Egger test. The complete analysis performed by STATA version 9.1, the meta command uses inverse-variance weighing to calculate fixed and random effects summary estimates, and, optionally to produce a forest plot. The advantage in using Meta command is that we require variables containing the effect estimate and its corresponding standard error for each study. When one arm of a study contains no events- or, equally, all events - we have what is termed a "zero cell" in the 2 x 2 table. Zero cells create problems in the computation of ratio measures of treatment effect, and the standard error of either difference or ratio measures. If no relapses any of the trial of any one group, the estimated odds ratio is zero and the standard error cannot be estimated. A common way to deal with this problem is to add 0.5 to each cell of the 2 x 2 for the trial (Cox and Snell, 1989). Because our inclusion criteria selected meta-analyses that had few trials with arms with zero events, this correction for zero cells had a minimal impact on conclusions. If there are no events in either the intervention or control arms of the trial, however, then any measure of effect summarized as a ratio is undefined, and unless the absolute risk difference scale is used instead, the trial has to be discarded from the meta-analysis.

5. Results

The following table gives data from 16 randomized controlled clinical trials of tuberculosis patients consists of both long term and short term treatments. The effects of treatment are being compared based on fixed and random effects method using meta-analysis. Table1 shows the trials consists both experimental as well as control groups for treating the patients. .

Table 1. Summary trials' data

Study name	Study year	Treated Group			Control Group		
		Total	Cured	Relapse	Total	Cured	Relapse
STNO1	1956	82	67	5	81	72	7
STNO3	1957	216	133	8	86	78	10
STNO5A	1961	72	68	5	66	56	7
STNO5B	1962	128	96	9	66	54	2
STNO7	1963	279	216	19	96	91	18
STNO8	1967	170	148	18	176	150	15
STNO9	1968	83	72	3	90	79	2
STNO10	1970	211	177	76	205	189	38
STNO11	1972	82	69	5	87	69	3
STNO11A	1973	86	74	1	87	76	2
STNO12	1974	261	261	24	269	269	24
STNO13	1977	228	219	42	466	257	64
STNO14	1980	111	111	3	117	117	7
STNO16	1986	305	294	15	512	495	52
STNO17	1990	594	562	25	273	259	16
STNO18	1995	184	182	15	176	174	9

The table 2 shows the magnitude of the change in the pooled estimate given by the random and fixed effects models to the trials between long-term treatment trials, short-term treatment trials and their combination in the calculation of the meta-analysis (exponential form) of tuberculosis care for infected individuals.

Table 2. The magnitude of the change in the pooled estimate

Trials	N	Pooled estimate in the meta-analysis		Test of Heterogeneity		No. of Trials in meta-analysis	Moment -based estimate of studies Variance
		REM	FEM	Q statistic	P value		
Long Term	2449	0.985	1.156	21.6 (9df)	P<0.05	10	0.325
Short Term	3496	0.778	0.774	6.6 (5df)	P>0.05	6	0.036
Combined	5955	0.193	0.251	45.3 (15df)	P<0.001	16	0.313

The tests of the heterogeneity are statistically significant in long-term trials and combined trials of long-term and short-term. Even though it is arguably sufficient, not possible to examine the null hypothesis that all studies are evaluating almost same effect

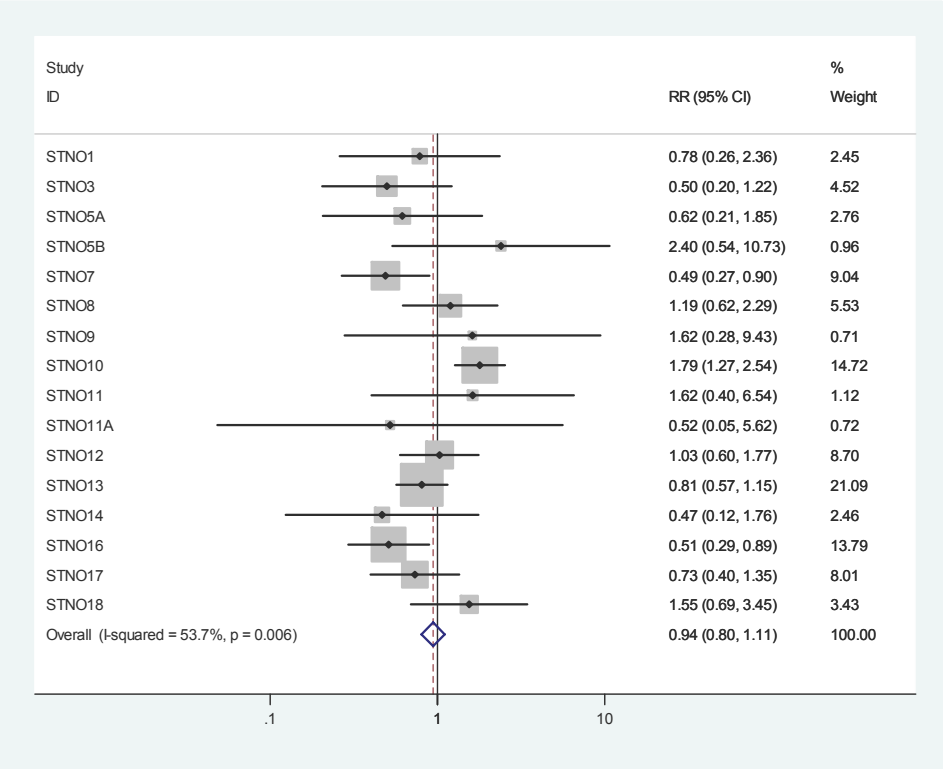

Figure 1. Forest Plot

In a forest plot the contribution of each study to the meta-analysis (its weight) is represented by the area of a box whose centre represents the size of the treatment effects estimated from that study. The summary treatment effect is shown by a middle of a diamond whose left and right extremes represent the corresponding confidence interval. Both the output and the graph show that there is a clear effect of treatments curing tuberculosis among patients. The meta-analysis dominated by the large study13, study10 and study16 trials which contribute around 50% of the weight in this analysis. Moreover the I-squared is constructed the inconsistency is 53.7 % (P=0.006).

Table 3. The summary of treatment effect

Study	Weights		Est	95% CI	
	Fixed	Random		Lower	Upper
STNO1	2.69	1.46	0.17	0.05	0.57
STNO3	4.08	1.79	0.19	0.07	0.50
STNO5A	2.66	1.45	0.20	0.06	0.66
STNO5B	1.56	1.05	0.13	0.03	0.63
STNO7	8.08	2.29	0.29	0.14	0.57
STNO8	7.37	2.23	0.22	0.11	0.46
STNO9	1.16	0.85	0.07	0.01	0.41
STNO10	19.84	2.75	0.63	0.41	0.98
STNO11	1.78	1.14	0.13	0.03	0.50
STNO11A	0.66	0.54	0.04	0.00	0.45
STNO12	11.00	7.86	1.03	0.57	1.86
STNO13	20.88	11.86	0.77	0.50	1.18
STNO14	2.03	1.89	0.45	0.11	1.79
STNO16	10.95	7.83	0.49	0.27	0.88
STNO17	9.25	6.92	0.72	0.38	1.37
STNO18	5.29	4.44	1.59	0.68	3.74

Note that remarkable differences between the fixed and random effects summary estimates in the long term and the combination of long term and short term trials, which arises because the studies are weighted much more equally in the random effects analysis. This shows the accountability of heterogeneity is comparable more in random effects than in the fixed effects method. Figure 2 based on random effects, shows the overall performances both fixed and random effects analyses. It is clear that the smaller studies such as study 12 and study 13 are given relatively more weight in the random effects than with the fixed effect model.

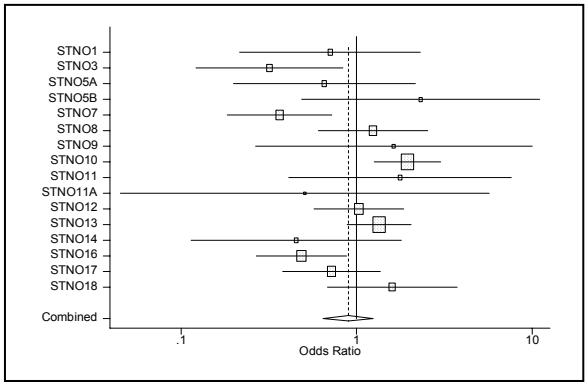

Figure2a. Forest Plot

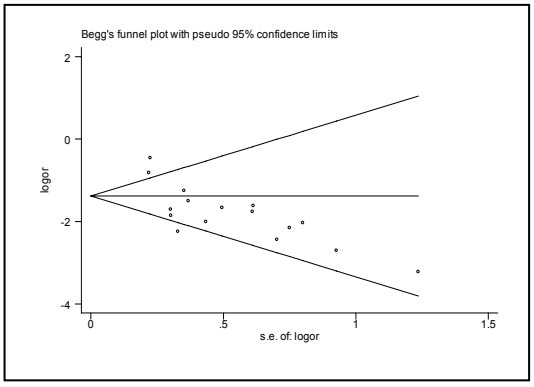

Figure2a. Funnel Plot

The method of assessing the effect of bias is using funnel plot as given below. In which the effect sizes form a study is plotted against the study's sample size. There is evidence of bias using the Eggar test based on weighted regression method (p=0.004) but not using the Begg such as rank correlation method. It is assuming that there is no heterogeneity but here there are three studies are significantly differing due to heterogeneity.

6. Discussions

The two approaches, the assumptions of a fixed and random set communicate the basis of estimation for each approach for a general measure of effect size. The fixed effect model is conditional on the stronger assumption that there is no true heterogeneity between studies also they are all estimating the same true effect and only differ because of sampling variation, where as the random effects method attempts to incorporate statistical heterogeneity into overall estimate of an average effect. The random effects model predicts better than the fixed effects model also to conclude that the modeling would be improved by an increase in use of random effects model than the fixed effects model. There is reviews focused meta-analysis using reviewed articles or published materials over a period or even in the several fields. But here we illustrated the meta-analysis applied for clinical trials in a particular centre and embossed the less heterogeneity among all the independent trials.

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