META-ANALYSIS: A COMPARISON OF FIXED EFFECTS AND RANDOM EFFECTS MODELS WITH ILLUSTRATIVE EXAMPLES

META-ANALYSIS: A COMPARISON OF FIXED EFFECTS AND RANDOM EFFECTS MODELS WITH ILLUSTRATIVE EXAMPLES

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ABSTRACT

Meta-analysis has been widely used in clinical research because it provides a useful tool for combining results from a series of trials addressing the same question. Two major approaches for study-to-study variation can be used in a meta-analysis: the fixed effects model which assumes that each study has the same true effect size, and the random effects model which assumes that the true effect size is a random variable that varies between studies. When there are covariates arising from the study, regression models can be used to explain the effects of these covariates on the between study variation in effect size.

The purpose of this project is to draw some general conclusions about the statistical methods used in meta-analyses by re-examining several clinical examples which presented some problems. Four illustrative examples of recent meta-analyses were selected and re-examined. Both fixed effects and random effects models were used. In addition, regression models were used in two examples.

Some general conclusions were made about the statistical aspects of meta-analysis from this project. The overall estimate of the fixed effects model tends to be overly influenced by large trials and may results in contradictory conclusions when extreme trials (small vs. large samples) are combined. Therefore, it is advocated that the weights allocated to each trial in any meta-analysis should be explicitly calculated and displayed.

The random effects model takes a more balanced account of all studies and considers other unknown factors which may affect the effect size. Therefore, the random effects model and random effects regression model are more appropriate for these clinical data meta-analyses.

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Contents

List of Tables

List of Figures

CHAPTER 1

INTRODUCTION

1.1 Introduction

Meta-analysis is defined as "the statistical analysis of a collection of analytic results for the purpose of integrating the finding" (DerSimonian & Laird, 1986). This statistical technique is also referred to quantitative literature review, research integration or research synthesis (Mosteller & Colditz, 1996). There are two fundamental tasks for meta-analysis: a)to combine studies in which the already existing results of research are found, summarized and described; and b)to conduct additional analyses to examine the variations in the phenomenon under study and theoretical issues of causation. Thus, meta-analysis can sometimes make inferences that go well beyond the original results.

1.2 Models for Meta-analysis

Two models for study-to-study variation in a meta-analysis are presented: the fixed effects model and random effects model. Effects, or effect sizes, refer to a measure distinguishing the consequences of one study from another or the degree of relationship between two variables. Differences, scaled differences, ratios, logarithms of ratios, and correlation coefficients are among the many kinds of indices depending on the problems

or fields of research. In the fixed effects model, each study estimate is assumed to have the same true effect size. In the random effects model, the true effect size is assumed to be a random variable that varies between studies. When there are covariates arising from the study, regression models can be used to explain their effects on the heterogeneity of study results.

The choice between fixed or random effects modeling strategies is generally dependent on the variation of observed effect sizes: if the effect sizes are homogeneous across all the studies, the former model may be appropriate; otherwise the latter model may be appropriate. However, neither the fixed effects nor the random effects model represents the true situation because only the studies (that occurred already) are sampled instead of a random sample of studies. The strategy of choosing a model should consider the object of the inference, perhaps by forcing a reformulation of the question to be addressed in the meta-analysis (Cooper & Hedges, 1994). Nevertheless, the random effects model considers variability in effect sizes among studies; thus it seems more realistic than the fixed effects model (Mosteller & Colditz, 1996).

1.3 Application in clinical research

In clinical research, usually any one trial may be either too small or too limited in scope to come to unequivocable or generalizable conclusions about the effect of treatment. Meta-analysis provides a useful tool that combines results from small and moderate-sized trials and represents an attractive strategy to strengthen the evidence about the treatment

efficacy. By bringing together large amounts of data to generate hypotheses with which to plan definitive trials, meta-analysis has been recommended as a basis for decision making in the absence of definitive trials (Borzak & Ridker, 1995). This technique is becoming increasingly popular in clinical research where information on efficacy of a treatment is available from a number of trials with similar treatment protocols.

Application of meta-analysis, in fact, has a long history in clinical research, which can be tracked back at least to the 1964, when MacMahon & Hutchison combined data from 10 studies of intrauterine X-ray exposure and risk of childhood cancer. Since 1980s, meta-analysis has been applied to a wide range of topics in clinical research, covering cholesterol and heart disease (Law *et al.*, 1994), effects of drug therapy on heart disease (Yusuf *et al.*, 1988; Teo *et al.*, 1991) diet and cancer (Howe *et al.*, 1990), exogenous hormones in relation to risk of breast (Colditz *et al.*, 1993) and ovarian cancer (Hankinson *et al.*, 1992), as well as other subjects.

1.4 Problems and study outline

Although its increasing application in clinical research, the use of meta-analysis has some problems conceptually and technically. Because meta-analysis relies on previously published data, they are inherently observational rather than experimental. Combined results can not account those biases present in the original studies such as trial settings, missing data or even publication bias (the phenomenon in which studies with positive results are more likely to be published than those with null or negative results). It may

sometimes introduce new bias or conflicting results due to these uncontrolled factors. Additionally, various techniques are available for meta-analysis. Inappropriate use of approaches may also have potential to result in apparently conflicting summary estimates when they are used to combine results from a serials of studies or even from the same studies. Thus, more improvements can be made on the aspects of both trial designs and statistical techniques in terms of clinical interpretation of meta-analysis.

We selected and re-examined four illustrative examples of recent meta-analyses from which some issues are discussed. These examples are the main topics of public health issues covering drug therapy and cholesterol level related with heart disease. The problems with these examples are that some have produced contradictory results between small trials and large trials, or that different meta-analysis methods have concluded different results. Through this study, we tried to explain the causes of these recent meta-analysis issues based on the statistical aspects regarding the methods used in meta-analyses.

CHAPTER 2

SUMMARY OF METHODS USED IN META-ANALYSIS

2.1 Introduction

Many methods are available for meta-analysis. The fixed effects and random effects models are the major approaches widely used in combining clinical data. The assumption and models of these two approaches are summarized in the following.

2.2 Concept of effect size

Effect size is the primary element when dealing with meta-analysis. Effect size is a standardized measure of effect that has been developed to deal with studies that report a wide range of outcome measures. Effect size can be referred to as a measure distinguishing the consequences of one treatment from those of one or more other treatments, or the degree of relationship between two variables. Differences, scaled differences, ratios, logarithms of ratios, and correlation coefficients are among the many kinds of indices that have been found in meta-analyses. Here we use logarithms of odds ratio (OR) as an effect size for our clinical data meta-analysis.

One important product of meta-analysis is a summary of the effect sizes found for all the studies that address the same directional question. Thus, effect size is the heart of meta-analysis.

2.3 Fixed effects model

2.3.1 Assumption

The fixed effects model is based on the assumption that all studies share a common effect size. That is, each study estimates exactly the same value of effect. If the different population being treated and different treatments actually being offered have exactly the same outcome, then we would get the smallest variance of the weighted average by using weights that are proportional to the reciprocals of the variances of the observed effect sizes from the individual studies. Therefore, in the fixed effects model, the studies in the universe (also referred to population or hyperpopulation) differ from those in the study sample only as a result of the sampling of people into the groups of the studies. The only source of sampling error or uncertainty is the variation resulting from the sampling of people into studies. This model is also called the conditional model because it can be conceived as a model that conditions (or holds fixed) the characteristics of studies that might be related to the effect size parameter.

2.3.2 The models

Suppose that the data to be combined arise from a series of k independent studies, in which the ith study reports one observed effect size T_i, with population effect size θ_i and variance V_i. Thus, the data to be combined consist of k effect size estimates $T_1, \ldots, T_k$, and variances $V_1, \ldots, V_k$. Under the fixed effects model, we assume $\theta_1=\ldots=\theta_k=\theta$, a common effect size. Then a general formula for the weighted average effect size over those studies is

$$\overline{T}_{\cdot}=\frac{\sum_{i=1}^{k} W_i T_i}{\sum_{i=1}^{k} W_i}, \qquad W_i=\frac{1}{V_i}$$

Note that the fixed effects estimate $\overline{T}_{\cdot} \sim N(\theta, V_{\cdot})$,

where θ is unknown and $V_{\cdot}=\frac{1}{\sum_{i=1}^{k} W_i}$, where $\sim$ denotes approximately distributed.

2.4 Random effects model

2.4.1 Assumption

The random effects model accounts for the variation among studies. Under random effects models, it assumes that there is not just one population effect size, but rather a distribution of population effect sizes existing which is generated by a distribution of possible study realizations (Cooper & Hedges, 1994). Thus, the observed outcomes in

studies would differ from each other partly because of sampling error, and partly because they reflect these true, underlying population differences. Two dimensions can be conceived to introduce two sources of variability into the observed (sample) effect sizes in the universe: one due to variation in effect size parameters and one due to variation in observed study effect sizes about their effect size parameters. In contrast, the fixed effect model only counts the latter source of variability which is a result of the sampling of people into studies.

This model is also called the unconditional model because, unlike the fixed effects model, it does not condition (or hold fixed) the characteristics of studies that might be related to the effect size parameter.

2.4.2 The model

In random effects model, the weighted average effect size is given by

$$\overline{T}. = \frac{\sum_{i=1}^{k} W_i^* T_i}{\sum_{i=1}^{k} W_i^*}, \qquad W_i^* = \frac{1}{\sigma^2 + V_i} \tag{1}$$

Ti and *Vi* are observations, but σ^2 is left unknown and has to be estimated from the data.

To estimate σ^2, we firstly need to introduce the fixed and random effect regression models.

2.5 Fixed and random effects regression models

When there is information available on study-level covariates that may partly or wholly explain heterogeneity among study results, regression models may be appropriate. Candidates for study-level covariates in the regression models may include factors that are related to the treatments being evaluated or to the patients (such as age, or measures of illness), but may also include factors such as study design and study quality. The application of regression models to meta-analysis can provide answers to these questions. Special modifications of regression models are needed to adapt them for application to meta- analysis.

In general, an regression model with *p-1* covariates for the effect size estimate T_i is:

$$T_i=\beta_0+\beta_1X_1+\ldots+\beta_{p-1}X_{p-1}+u_i+e_i \qquad (2)$$

write (1) in matrix form:

$$\boldsymbol{T=X\beta+u+e} \qquad (3)$$

X is a matrix containing covariates information. Note that equation (1) has two components in its error term $\boldsymbol{u}+\boldsymbol{e}$, $\boldsymbol{u}$ is the random effect across studies and e is the sampling errors.

The vector $\boldsymbol{u}$ is assumed to be $N(0, \boldsymbol{I}\sigma^2)$. When σ^2 is zero, the model corresponding to equation (3) is called fixed effect regression model, if $\sigma^2>0$, then it is random effects regression model.

So in both cases, the variance of T_i, controlling for X's, is

$$V_i^* = Var(u_i + e_i) = \sigma^2 + V_i$$

its matrix notation is $Var(u+e) = \sigma^2 \boldsymbol{I} + \boldsymbol{V}$.

2.6 Estimate of σ^2

Based on the fact derived from section 2.5, there are two approaches to estimate σ^2. Here we use the method of moments.

Step 1 Computes estimates β, using weighted least square regression, i.e.

$$\hat{\beta}_{wls} = (X'V^{-1}X)^{-1}X'V^{-1}T \qquad (4)$$

where observed T and V from the k studies are used here.

With $\hat{\beta}_{wls}$, we can then compute the residual sum of squares

$$\boldsymbol{RSS} = (T - X\hat{\beta}_{wls})' V^{-1} (T - X\hat{\beta}_{wls}) \qquad (5)$$

Step 2 Estimates σ^2. It can readily be shown that the expected value of the residual sum of square is given by

$$\boldsymbol{E(RSS)} = \text{constant}(1) + \text{constant}(2) * \sigma^2 \qquad (6)$$

$$\text{constant}(1) = k - p \qquad (7)$$

$$\text{constant}(2) = \sum V_i^{-1} - tr[X'V^2X(X'V^{-1}X)^{-1}] \qquad (8)$$

Note k is the number of studies and $p-1$ the number of covariates involved in the regression.

Substitute observed sum of square residuals, ***RSS*** for its expectation ***E(RSS)*** in equation (4), we get

$$\sigma^2=[\boldsymbol{RSS}\text{-constant(1)}] / \text{constant(2)} \qquad (9)$$

When there is no covariates X is as a column of 1's, and constant (1)=k-1 and

constant (2)=$\dfrac{\sum_{i=1}^{k} V_i^{-1} - \sum_{i=1}^{k} V_i^{-2}}{\sum_{i=1}^{k} V_i^{-1}}$. The estimate of σ^2 can then be applied to equation (1).

When there are covariates, replace V by $V^* = \sigma^2 I+V$ in equation (4), then obtain $\hat{\beta}_{\text{wls}}$ as the random effects regression coefficient. So when this $\hat{\beta}_{\text{wls}}$ as well as the covariate information matrix X are put back to equation (3), yield effect size estimate of random effects regression model. In this case, the estimated overall effect size is a function of X.

2.7 Homogeneity test

Homogeneity test is the first step to determine which model, the fixed effects model or the random effects model, is to be applied. If the effect sizes are homogeneous across all the studies, then the hypothesis that all studies have a common effect size may be true, and the fixed effect model may be appropriate. The hypothesis of interest is

$$H_0: \theta_1=\theta_2=\ldots\ldots=\theta_k=\theta$$

$$\text{vs. } H_1: \theta_I\neq\theta_j \quad \text{for some i, j.}$$

and the test statistics is

$$QE = \sum_{i=1}^{k} \frac{(T_i - \overline{T}.)^2}{V_i} \quad \text{and } QE \tilde{a} X^2 (k\text{-}1)$$

When H_0 is rejected, heterogeneity of studies is significant. Then the hypothesis that all the effect sizes are equal is rejected. In this case, fixed effects model is not sufficient to explain the heterogeneity among the studies and the random effects model should be applied.

2.8 *Z*-test and confidence interval

If it assumes that the k studies are independent of each other, the estimate of the overall effect size for the fixed effects model is distributed as

$$\overline{T}. \ \tilde{a} \ N(\theta, V.),$$

where V. is the conditional variance of $\overline{T}.$ and $V. = \dfrac{1}{\sum_{i=1}^{k} W_i}$

So the confidence interval for the overall effect size:

$$\theta_L = \overline{T}. - 1.96*(V.)^{1/2} \ , \ \theta_U = \overline{T}. + 1.96*(V.)^{1/2}$$

and the Z statistics to test the null hypothesis that $\theta=0$ is

$$Z = |\overline{T}.|/(V.)^{1/2}$$

where H_0: $\theta = 0$ vs. H_1: $\theta \neq 0$

For the random effects model, the estimate of effect size has distributions as

$$\overline{T}_i \ \tilde{a} \ N(\theta_i, V_i) \ , \text{ where } \theta i \sim N(\theta, \sigma^2)$$

and the confidence interval for θ and *Z*-test statistics are similarly to fixed effects, by

replacing $V_{\cdot}$ with $V^{*}_{\cdot}$, where

$$V^{*}_{\cdot} = \frac{1}{\sum_{i=1}^{k} W_i^{*}}$$

CHAPTER 3

ILLUSTRATIVE EXAMPLES

3.1 Introduction

In this chapter, we use four illustrative examples of meta-analyses. These examples are the main topics of recent meta-analysis related to public health, and include magnesium and nitrate treatment for acute myocardial infarction, the use of drug or dietary intervention to lower serum cholesterol, and antiplatelet and anticoagulants therapy in preserving graft patency. We tried to draw some more general conclusions about the statistical methods used in meta-analyses.

Both fixed effect and random effect models were used for all four examples. In addition, regression models were used in some of the examples.

3.2 Magnesium example

Based on the evidences of a series of small trials evaluated by meta-analyses, intravenous magnesium therapy has been recommended as a treatment to reduce mortality in patients with acute myocardial infarction (AMI). Teo *et al.* (1991) reviewed seven trials of intravenous magnesium, which included between 48 and 400 patients each and were

reported between 1981 and 1990. The meta-analysis of 1301 patients showed odds ratio (OR) for mortality of magnesium-treated patients of 0.44 with a fixed effects model and 0.45 with a random effects model, showing mortality benefit of magnesium therapy. Woods et al. (1992) reported the analysis of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), in which a mortality reduction of 24% with magnesium treatment (OR=0.76) in 2316 patients was observed. When this data was added to meta-analysis, a 35% mortality reduction over control (OR=0.65) is observed. This result further confirmed the benefit of magnesium treatment in reducing mortality in patients with AMI. However, the situation became complicated with a very large-scale trial conducted by the International Study of Infarct Survival-4 (ISIS-4) (Antman, 1995; Borzak & Ridker, 1995). The ISIS-4 investigators randomly assigned over 58,000 patients to receive either intravenous magnesium, at a dose similar to that used in the previous trials (LIMIT-2), or open control. The results showed 2,103 deaths among 29,039 patients assigned to receive open control (7.24%) and 2,216 deaths among 29,011 magnesium-treated patients (7.64%), suggesting no significant benefit of magnesium. When the large sample of ISIS-4 was added to the preceding 8 smaller trials, it was found that the fixed effects model showed no beneficial effect, whereas the random effects model, that took into account the heterogeneity among these trials, indicated a mortality reduction with magnesium treatment (Antman, 1995).

3.2.1 Description of data

We reanalyzed all the data from the preceding 7 small trials, LIMIT-2, the big trial ISIS-4, and another small trial from Shechter et al. (1995). These are all the trials that were found on a search on mortality for all randomized patients in all completed, published or unpublished, unconfounded trials of intravenous magnesium in suspected AMI. These data are listed in Table 1. Table 2 lists allocated weights for fixed and random effects models.

Table 1. Mortality and odds ratio in randomized trials of intravenous magnesium in suspected acute myocardial infarction (AMI).

Trial No.	Trial	Magnesium group (Deaths/No. followed up)	Control group (Deaths/No. followed up)	OR (C.I.)
1	Morton *et al.*	1/40	2/23	0.44 (0.04-5.02)
2	Rasmussen *et al.*	9/135	23/135	0.35 (0.15-0.78)
3	Smith *et al.*	2/200	7/200	0.28 (0.06-1.36)
4	Abraham *et al.*	1/48	1/46	0.96 (0.06-15.77)
5	Feldstedt *et al.*	10/150	8/148	1.25 (0.48-3.26)
6	Shechter *et al.*	1/59	9/56	0.09 (0.01-0.74)
7	Ceremuzynski *et al.*	1/5	3/23	0.28 (0.03-2.88)
8	LIMIT-2	90/1150	118/1150	0.74 (0.56-0.99)
9	Shechter *et al.*	4/96	17/98	0.20 (0.07-0.63)
10	ISIS-4	2216/29011	2103/29039	1.06 (1.00-1.13)

Table 2. Allocated weights in randomized trials of intravenous magnesium in suspected acute myocardial infarction (AMI).

Trial No.	Wi (weights of fixed effects model)	Wi^* (weights of random effects model)
1	0.64	0.58
2	5.83	2.89
3	1.53	1.21
4	0.49	0.45
5	4.18	2.42
6	0.87	0.76
7	0.70	0.63
8	46.52	5.10
9	3.01	1.98
10	998.78	5.70

3.2.2 Results

The homogeneity test yields QE equal to 30.2, with df=9 and P=0.0004, which suggests highly significant variation among studies with respect to effect size (Table 3). The fixed effects model, therefore, is inappropriate because it assumes a common true effect size among all studies.

The fixed effects model estimated the odds ratio as 1.03, with a 95% confidence interval (CI) of 0.97-1.09 (Table 4). The corresponding Z-test is Z=0.86 with P=0.19.

Table 3. Homogeneity test for the 10 magnesium trials.

QE	df	P-value
30.2	9	0.00004

Table 4. Overall odds ratio estimate and Z-test for the 10 magnesium trials.

Model	OR	Lower	Upper	Z score	P-value
Fixed effects	1.03	0.97	1.09	0.86	0.194
Random effects	0.59	0.39	0.90	-2.47	0.007

This result suggests that magnesium therapy is not beneficial. In the random effects model, however, the estimated odds ratio is 0.59 (CI; 0.39 to 0.90), and the related Z-test is significantly smaller than zero (Z=-2.5, P=0.007). This result suggests that magnesium therapy is beneficial, conflicting with the result of the fixed effect model.

It is worthy to further investigate as to how the two models lead to conflicting results. The weighting schema of the two models differs from each other as shown in Fig.1: when the schema of fixed effects model is projected on the Y-axis, the sum of the projections is the overall effect size estimate of fixed effects model; on the other hand, when the schema of random effects model is projected on the Y-axis, the sum of the

Fig 1. Weighting schema for Magnesium Example

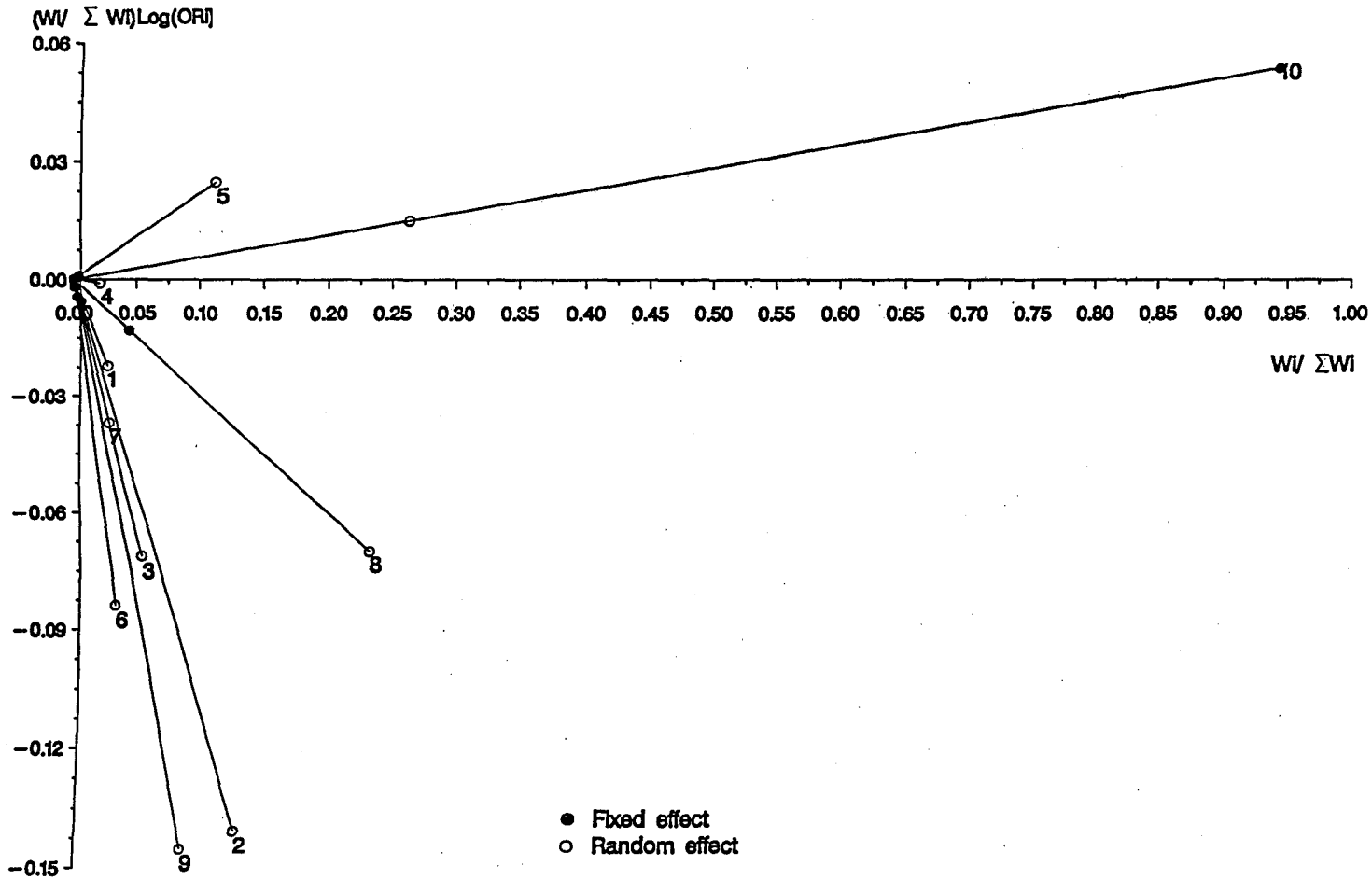
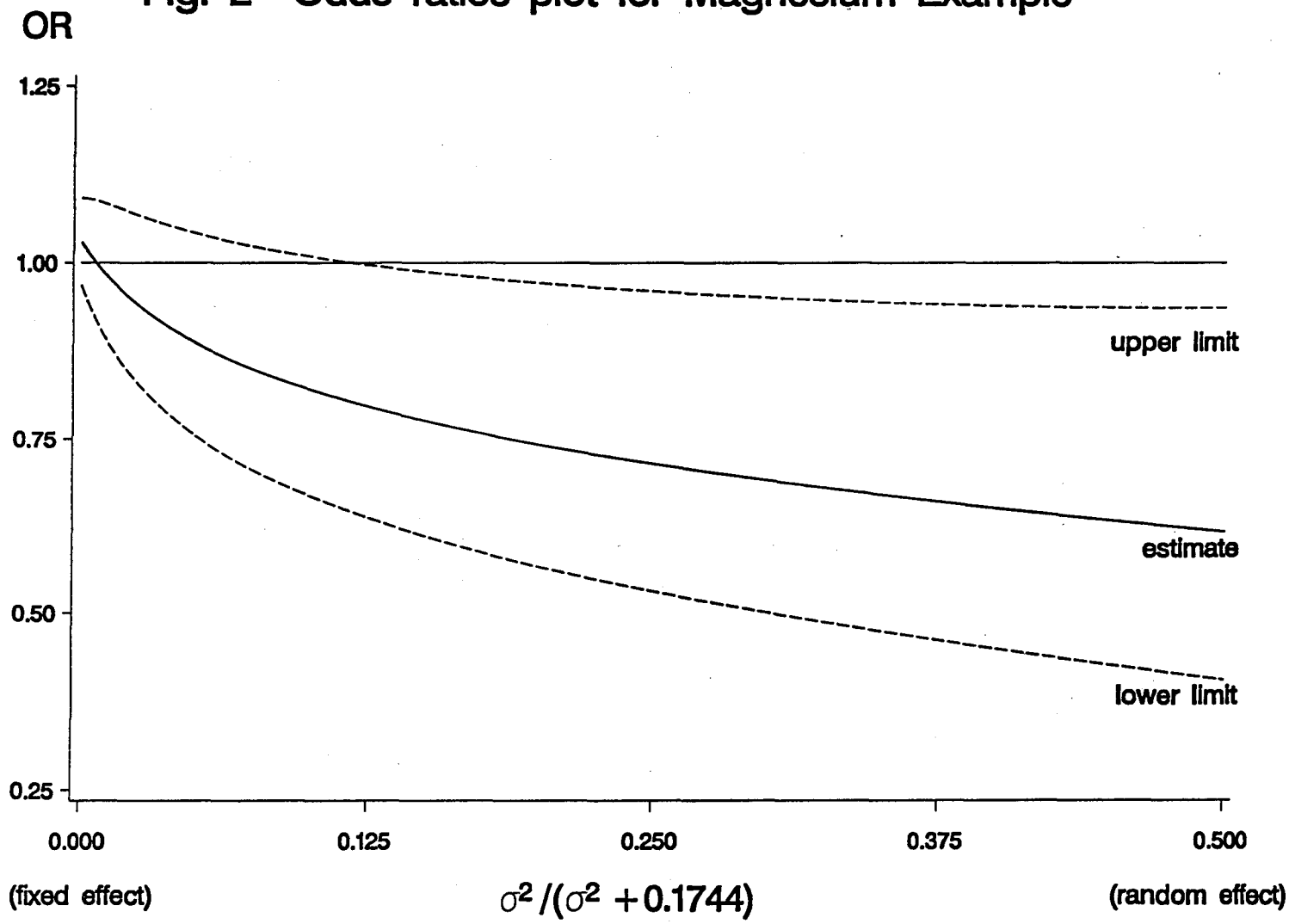


Fig. 2 Odds ratios plot for Magnesium Example



projections is the overall effect size estimate of random effects model. In the fixed effects model, it is obvious that the large ISIS-4 trial, with 58050 patients, dominates over the small studies in the calculation of the overall OR. The overall conclusion for magnesium therapy is highly dependent on the results of the large ISIS-4 study.

In contrast, the random effects model, by adding the same quantity (σ^2) to the denominator of the weight of each trial, reduces the contribution to the overall odds ratio of the ISIS-4 trial. ISIS-4 trial in this model is not as dominant. Therefore, the overall OR in this model takes a more even weight from each study and is statistically significantly less than 1.

The different results between the two models can also be demonstrated using the odd ratio shifts (Fig.2). The estimate of random variation (i.e. σ^2) is 0.1744. When σ^2=0, the OR is an estimate from fixed effects model; when σ^2=0.1744, the OR is an estimate from random effects model (Fig. 2). It is obvious that the odds ratio is shifted from around 1.0 for the fixed effects model to significantly smaller than 1.0 for the random effects model.

3.3 Nitrates example

A meta-analysis using several small trials published between 1979 and 1985, with sample sizes ranging from 28 to 812, provided evidence that intravenous nitrates significantly reduces mortality for AMI patients (Yusuf *et al.*, 1988). However, these results were contradicted by two large trials (ISIS-4 and GISSI-3) using similar therapy. In the ISIS-4

trial with 58,050 AMI patients, the mortality of nitrates-treated patients was 7.54% while the control was 7.34% (OR=0.97, CI=0.91-1.03), indicating no significant benefits of nitrate therapy. Similarly in the GISSI-3 trial with 18,895 patients, the mortality between the nitrate-treated patients and controls was not significant, being 6.5% vs. 6.9% (OR=0.94, CI=0.84-1.05).

3.3.1 Description of data

In addition to the ISIS-4 trial and the GISSI-3 trial, we used the 10 trials which were cited by Yusuf *et al.* (1988). The data include the mortality for all randomized patients in all randomized trials of the use of intravenous nitrates in suspected AMI. Randomized trials of oral nitrates were excluded. Controlled trials of nitrates in which investigators could determine the treatment allocation before deciding whether to enter the patients were excluded. All the data are listed in Table 5, and the weight allocations are showed in Table 6.

3.3.2 Results

In this example, homogeneity test also shows that the heterogeneity of all 12 studies is significant (Table 7). Again, simply using the fixed effects model may not be appropriate.

The results derived from the two models are presented in Table 8. The odds ratio estimated by the fixed effects model is 0.95 with a narrow 95% C.I. (0.90 to 0.99), with a

Table 5. Mortality and odds ratio by allocated treatment in all randomized trials of intravenous nitrate therapy in acute myocardial infarction (AMI).

Trial No.	Trial	Allocated nitrate (Deaths/No. randomized)	Allocated control (Deaths/No. randomized)	OR(C.I)
1	Hockings	7/25	9/25	0.69(0.21-2.29)
2	Durrer	9/163	20/165	0.42(0.19-0.96)
3	Cohn	69/407	77/405	0.87(0.61-1.24)
4	Chiche	3/50	8/45	0.30(0.07-1.19)
5	Bussman	4/31	12/29	0.21(0.06-0.76)
6	Flaherty	11/56	11/48	0.82(0.32-2.11)
7	Jaffe & pers. Comm.	4/57	2/57	2.08(0.36-11.81)
8	Lis & pers. Comm.	5/64	10/76	0.47(0.18-1.73)
9	Jugdutt & pers. comm.	24/154	44/156	0.47(0.27-0.82)
10	ISIS-4	2129/29018	2190/29032	0.97(0.91-1.03)
11	GISSI-3	617/9453	653/9442	0.94(0.84-1.05)

Table 6. Weight allocations in all randomized trials of intravenous nitrate therapy in acute myocardial infarction (AMI).

Trial No.	Wi (weights of fixed effects model)	Wi^* (weights of random effects model)
1	2.69	2.56
2	5.73	5.17
3	29.86	19.10
4	1.97	1.90
5	2.33	2.23
6	4.33	4.00
7	1.27	1.24
8	3.01	2.85
9	12.34	10.01
10	999.23	50.33
11	295.94	44.94

Table 7. Homogeneity test for the 12 nitrates-treated and control trials.

QE	df	P-value
20.5	10	0.002

significance value of 0.02. This provides evidence that nitrate therapy is beneficial in reducing mortality of acute myocardial infarction. The odds ratio estimated by the

Table 8. Overall odds ratio estimate and Z-test for the 12 nitrates-treated and control trials.

Model	OR	Lower	Upper	Z score	P-value
Fixed effects	0.95	0.90	1.0	-2.05	0.02
Random effects	0.83	0.70	0.97	-2.27	0.01

random effects model is 0.83, which is somewhat smaller than that of the fixed effects model, but with a wider 95% C.I. (0.7 to 0.97). Although the conclusions derived from the two models are similar for this example, the certainty on the estimate of odds ratio by the two models is quite different. The fixed effects model has a narrow confidence interval, indicating that more certainty is put on the estimate of odds ratio because a common effect size is assumed. The random effects model has a wider confidence interval, indicating that more uncertainty is put on the estimate of odds ratio because effect size is assumed to be dependent on some other factors, such as the trial setting or drug dose. The latter model is more realistic because the true odds ratio will vary between studies because factors that affect effect size will also vary between studies.

The difference of 95% C.I. between the two models is showed in Fig.3. The random effects model has a wider estimation of 95% C.I. than the fixed effects model, although both estimates are significant smaller than 1.0. The weighting schema shows that the contribution of the large-scale studies is shrunk, while that of the smaller studies

Fig. 3 Odds ratios plot for nitrate Example

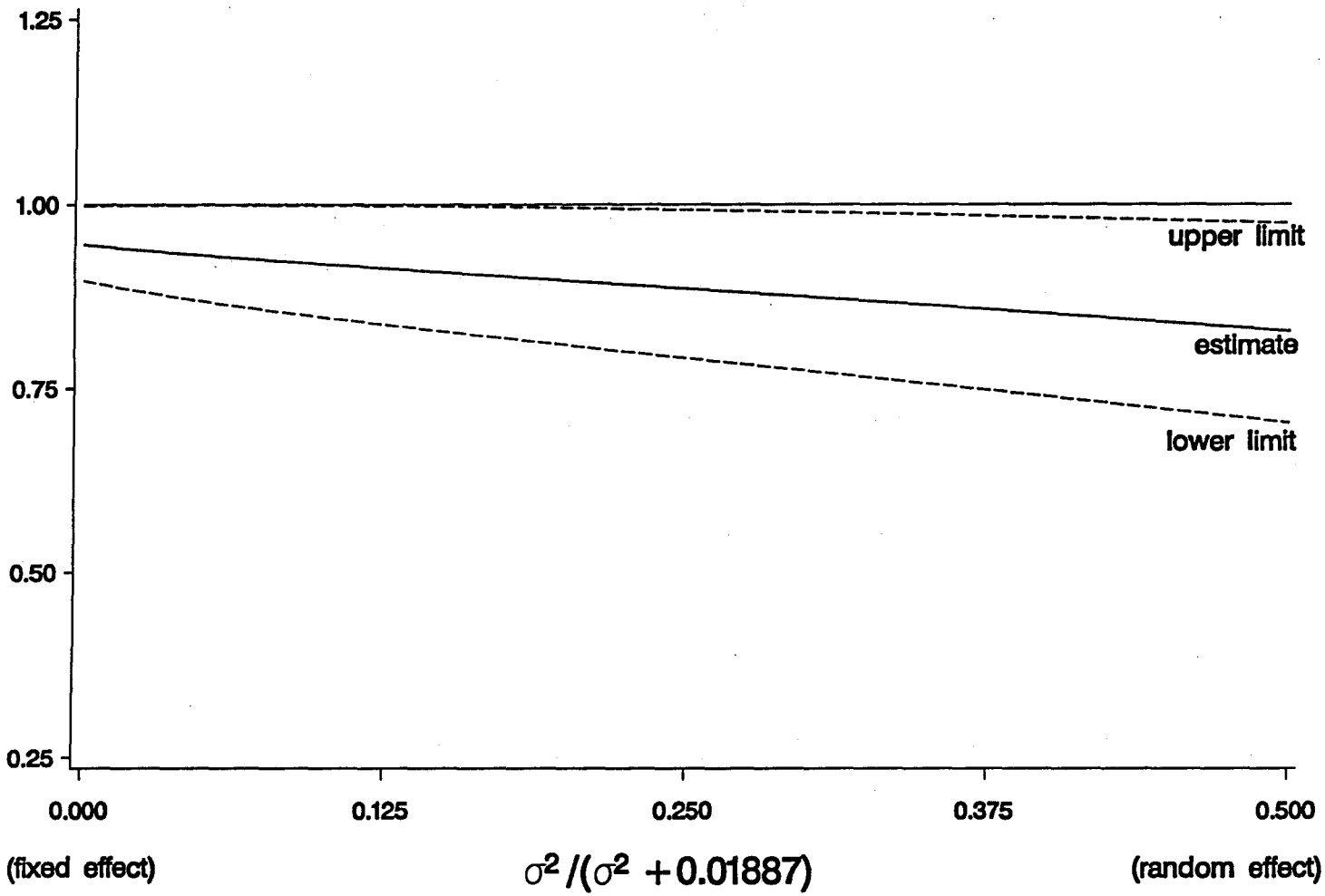
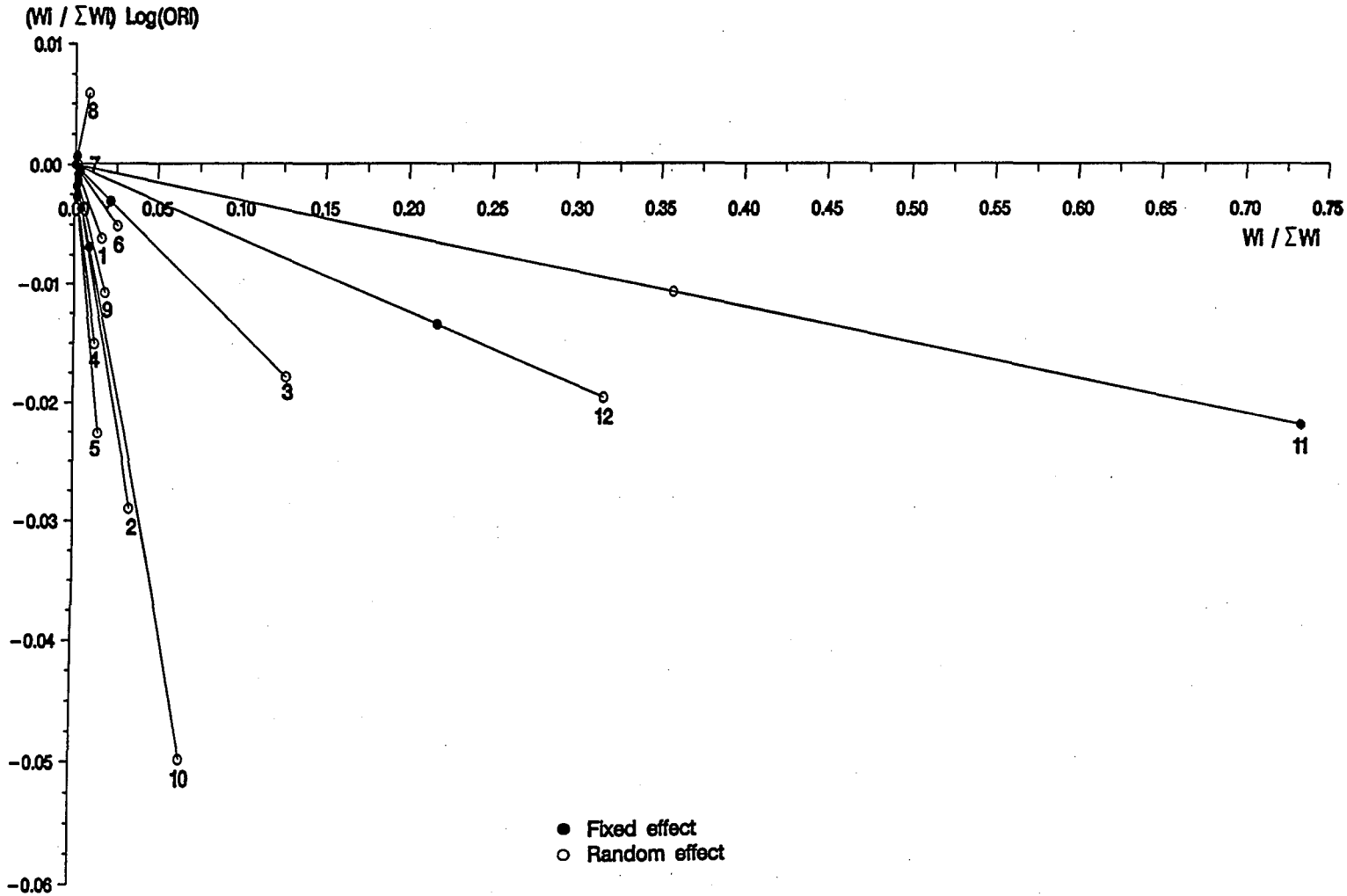


Fig 4. Weighting schema for Nitrate Example



is increased when using the random effects model (Fig. 4). The conclusion made from the random effects model, therefore, may be more reliable since it does not rely on the large studies as heavily.

3.4 Cholesterol example

Serum cholesterol reduction is an extremely important public health issue because it may lead to a reduction in ischaemic heart disease (IHD). It has been a main topic of a meta-analysis to investigate the use of drug and dietary intervention to lower serum cholesterol. Different meta-analyses, however, have apparently produced contradictory results and conclusions. Law et al. (1994) concluded that cholesterol reduction had a substantial reduction in IHD mortality and also had much greater beneficial effect on deaths from trauma (i.e. accidents, suicides and violent deaths). In contrast, Ravnskov (1992) concluded that cholesterol reduction did not reduce IHD mortality and is unlikely to prevent coronary heart disease. Obviously, further research is required, from both aspects on trial settings and statistical analysis, to understand why these meta-analyses have produced these different results.

3.4.1 Description of data

A total of 25 randomized trials were used in the meta-analysis by Thompson (1993). These data did not include multifactor trials that simultaneously tested interventions other than serum cholesterol reduction (such as stopping smoking), and also

Table 9. Numbers of IHD events in meta-analyses for 23 randomized trials of serum cholesterol reduction.

Trial No.	Trial[a]	Treated[b]	Control[b]	OR(C.I)
1	CDP[c]	676/2222	936/2789	0.87(0.77-0.98)
2	WHO	173/5331	210/5296	0.81(0.66-1.0)
3	LRC	157/1906	193/1900	0.79(0.64-0.99)
4	Minnesota	131/4541	121/4516	1.08(0.84-1.39)
5	DART	132/1018	144/1015	0.90(0.70-1.16)
6	POSCH	82/424	125/417	0.57(0.41-0.78)
7	Helsinki	56/2051	86/2030	0.65(0.46-0.92)
8	Stockholm	73/279	101/276	0.61(0.43-0.88)
9	Scottish	54/350	75/367	0.71(0.48-1.04)
10	Los Angeles	52/424	65/422	0.77(0.52-1.14)
11	Oslo	61/229	81/229	0.66(0.45-0.99)
12	Newcastle	54/244	85/253	0.56(0.38-0.84)
13	VA drup-lipid	42/145	69/284	1.27(0.81-1.99)
13	Upjohn	36/114	42/1129	0.84(0.53-1.32)
15	MRC	46/199	51/194	0.84(0.53-1.33)
16	London Hospitals	47/130	50/134	0.95(0.58-1.57)
17	EXCEL	62/658	20/1663	0.78(0.47-1.30)
18	Sydney	37/221	24/237	1.78(1.03-3.09)
19	NGLBI	6/71	11/72	0.51(0.18-1.47)
20	St Mary's	8/28	11/52	1.49(0.52-4.30)
21	STARS	3/60	5/30	0.26(0.06-1.19)
22	McCaughan	2/88	2/30	0.33(0.04-2.42)
23	CLAS	1/94	5/94	0.19(0.02-1.67)

[a]Reference to original trials provided in Law *et al.*

[b]No. of IHD events/no. of subjects.

[c]Two active treatment groups (drugs niacin and clofibrate) combined, and assigned their average serum cholesterol reduction.

Table 10. Weight allocations of IHD events in meta-analyses for 23 randomized trials of serum cholesterol reduction.

Trial No.	Intervention	Wi (weights of fixed effects model)	Wi* (weights of random effects model)	Serum Cholesterol reduction (mmol/l)
1	Drug	267.80	37.79	0.55
2	Drug	91.47	29.71	0.55
3	Drug	78.69	28.22	0.65
4	Diet	61.15	25.59	0.70
5	Diet	59.54	25.30	0.26
6	Surgery	37.64	20.28	1.43
7	Drug	32.49	18.69	0.69
8	Drug	29.27	17.58	0.84
9	Drug	25.87	16.29	0.85
10	Diet	24.94	15.91	0.87
11	Diet	24.13	15.58	1.13
12	Drug	24.10	15.57	0.68
13	Drug	18.99	13.26	0.59
14	Drug	18.73	13.13	0.49
15	Diet	18.22	12.89	0.95
16	Diet	15.33	11.37	0.57
17	Drug	14.95	11.16	1.08
18	Diet	12.69	9.85	0.31
19	Drug	3.46	3.20	0.85
20	Diet	3.45	3.19	0.61
21	Diet	1.69	1.63	1.06
22	Drug	0.96	0.93	0.68
23	Drug	0.82	0.80	1.35

those that used oestrogen and thyroxine (both of which reduce serum cholesterol to a small extent, but whose effects on IHD are more importantly mediated by other mechanisms (Law et al. (1994)). These trials were identified through using a variety of formal (e.g. MEDLINE) and informal (e.g. references and citations) searching techniques. For our meta-analysis, 23 of them were selected and the other 2 were ignored because of

not enough data. These 23 trials on IHD events are summarized in Table 9. Table 10 is the list of weight allocations for fixed and random effects models.

3.4.2 Results

The assumption of homogeneity across studies is rejected in this example because QE is equal to 39.0 at P=0.014 (Table 11).

The estimates of odds ratio for the fixed and random effects models do not differ very much, although the confidence interval is wider with random effects model (Table 12). In both fixed and random effects regression models, reduction in cholesterol level is a significant predictor at 5% level (Table 13a & b). When cholesterol reduction is of 100 (mmol/L), the adjusted odds ratio is 0.69 (CI, 0.63 to 0.75) for fixed effects regression model, and 0.69 (CI, 0.61 to 0.79) for random effects regression model; when cholesterol level is not reduced, the adjusted odds ratio is 1.14 (CI, 0.92 to 1.41) for fixed effects regression model, and 1.16 (CI, 0.91 to 1.48) for random effects regression model (Table 12). These results suggest that a reduction in the cholesterol level can help to reduce the risk of having IHD, and that a therapy is only beneficial if it reduces the cholesterol level of the patient.

We plot the odds ratio against the reduction in cholesterol level, which is presented in Fig.5. The odds ratio of IHD event drops dramatically as the reduction in

Table 11. Homogeneity test for 25 randomized trials of serum cholesterol reduction.

QE	df	P-value
39.0	22	0.014

Table 12. Overall odds ratio estimate and Z-test for 25 randomized trials of serum cholesterol reduction.

Model	OR	Lower	Upper	Z score	P-value
Fixed effects	0.82	0.77	0.88	-5.8	<0.0001
Fixed effects regression (at a reduction of 100 mmol/L)	0.69	0.61	0.78	-5.7	<0.0001
Fixed effectd regression (no reduction)	1.14	0.92	1.41	1.18	0.119
Random effects	0.80	0.72	0.89	-4.1	<0.0001
Random effects regression (at a reduction of 100 mmol/L)	0.69	0.61	0.79	-5.6	<0.0001
Random effects regression (no reduction)	1.16	0.91	1.48	1.22	0.11

cholesterol level alone. Fig. 6 shows that the estimates of OR are quite stable when shifted from fixed effects model to random effects model. This suggests that the random variation is smaller as compared to the reduction of cholesterol level. When the reduction

Table 13a. Weighted least square result for cholesterol example.

1) Model: Fixed Effects Regression Model

Dependent Variable: T

Covariate: Cholestrol Level

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Prob>F
Model	1	12.73442	12.73442	10.165	0.0044
Error	21	26.30699	1.25271		
C Total	22	39.04141			

Root MSE	1.11925	R-square	0.3262
Dep Mean	-0.19734	Adj R-sq	0.2941
C.V.	-567.16064		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
INTERCEP	1	0.128672	0.10909394	1.179	0.2514
CHOLRSTD	1	-0.004953	0.00155335	-3.188	0.0044

Covariance of Estimates

COVB	INTERCEP	CHOLRSTD
INTERCEP	0.0119014879	-0.000158834
CHOLRSTD	-0.000158834	2.4129073E-6

Table 13b. Weighted least square result for cholesterol example.

2) Model: Random Effects Regression Model

Dependent Variable: T

Covariate: Cholestrol Level

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Prob>F
Model	1	10.56087	10.56087	10.008	0.0047
Error	21	22.16020	1.05525		
C Total	22	32.72107			

Root MSE	1.02725	R-square	0.3228
Dep Mean	-0.21243	Adj R-sq	0.2905
C.V.	-483.57630		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
INTERCEP	1	0.149997	0.12287580	1.221	0.2357
CHOLRSTD	1	-0.005224	0.00165142	-3.164	0.0047

Covariance of Estimates

COVB	INTERCEP	CHOLRSTD
INTERCEP	0.0150984616	-0.000189192
CHOLRSTD	-0.000189192	2.7271852E-6

Fig. 5 Odds Ratio vs. Cholesterol level for Cholesterol Example

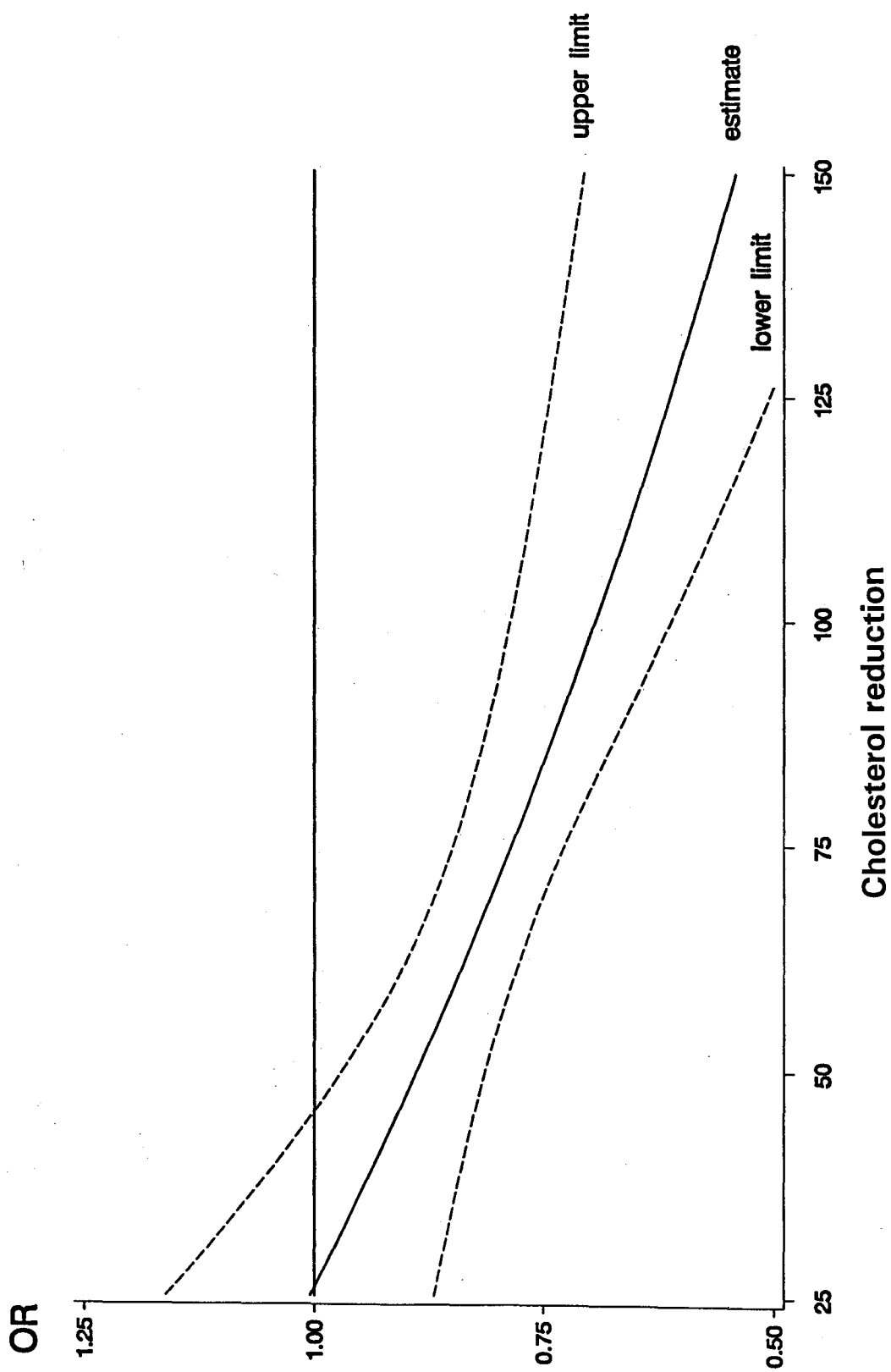
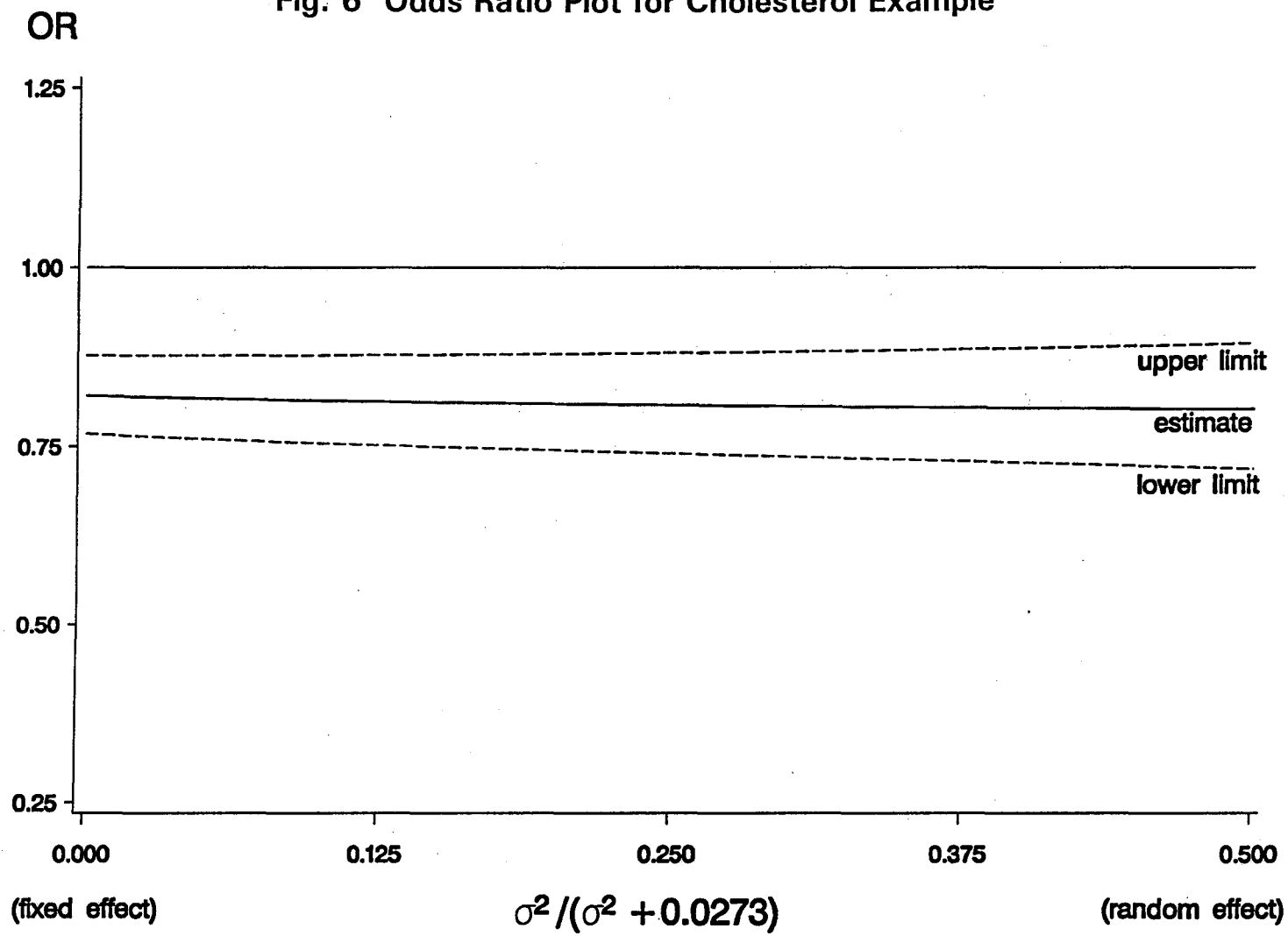


Fig. 6 Odds Ratio Plot for Cholesterol Example



of cholesterol level is taken account, both fixed and random effects regression result in the same conclusion.

3.5 Thrombotic example

Antiplatelet drugs and anticoagulants have achieved variable success in preserving graft patency in coronary bypass surgery. A meta-analysis of the results obtained from randomized clinical trials has concluded that active treatment is beneficial and that early initiation of treatment is a significant predictor of the magnitude of the effect. A further meta-analysis also indicated a positive role of aspirin, dipyridamole and oral anticoagulants on graft patency (Fremes *et al.*, 1993).

3.5.1 Description of data

The data used here are all from literature searches completed to July 1991. A total of 12 randomized clinical trials are involved in our analysis (Table 14). These trials are limited to the investigation of the role of aspirin and dipyridamole. Aspirin remains the most common single treatment as it is inexpensive and can be administered as a single daily dose in contrast to other treatments. Dipyridamole has frequently been administered with aspirin but there are concerns regarding its efficacy, cost and dosing. Comparisons of aspirin versus control or aspirin versus placebo were performed, and whether dipyridamole provides any additional benefit as compared with aspirin alone was also determined in terms of their effects on preserving graft patency. Both fixed and random

Table 14. Occlusion results and odds ratio for individual trials aspirin ± dipyridamole vs. control per patient.

Trial No.	Study[a]	± D[b] (+=1 -=0)	Allocated ASA±D[c] (Occlusion/ No. randomized)	Allocated control (Occlusion/ No. randomized)	OR (C.I.)
1	Brown *et al.*	1	25/83	18/44	0.62(0.29-1.33)
2	Chesebro *et al.*	1	37/171	81/172	0.31(0.19-0.50)
3	Gavaghan *et al.*	0	14/119	30/100	0.31(0.15-0.63)
4	Goldman *et al.*	1	103/298	47/107	0.67(0.43-1.06)
5	Guiteras *et al.*	1	15/49	18/45	0.66(0.28-1.55)
6	Lorenz *et al.*	0	6/22	15/24	0.22(0.06-0.78)
7	Mayer *et al.*	1	6/47	20/66	0.34(0.12-0.92)
8	McEnany *et al.*	0	15/40	16/37	0.79(0.32-1.96)
9	Pantely *et al.*	1	4/13	9/24	0.74(0.18-3.12)
10	Sanz *et al.*	1	157/612	104/315	0.70(0.52-0.94)
11	Sharma *et al.*	1	42/98	20/44	0.90(0.44-1.84)
12	Thaulow *et al.*	1	21/29	14/33	3.56(1.22-10.36)

[a]Data are from literature of Fremes *et al.*(1993).
[b]±D=dipyridamole.
[c]ASA=aspirin, D=dipyridamole.

Table 15. Weight allocations for individual trials aspirin ± dipyridamole vs. control per patient.

Trial No.	Wi (weights of fixed effects model)	Wi^* (weights of random effects model)
1	6.61	3.26
2	17.29	4.70
3	7.78	3.53
4	18.95	4.81
5	5.30	2.91
6	2.46	1.78
7	3.81	2.39
8	4.61	2.69
9	1.86	1.44
10	43.63	5.62
11	7.50	3.47
12	3.37	2.21

effect models are used to determine the magnitude of the effect of aspirin. Regressions are performed to see if the addition of dipyridamole affects the treatment benefit of aspirin. Table 15 is the list of weight allocations for fixed and random effects models.

3.5.2 Results

Both the fixed and random effects models yield a significant beneficial treatment effect, with an OR of 0.60 (Table 16). Just as the nitrate example, however, the confidence

Table 16. Overall odds ratio estimate and Z-test for individual trials aspirin ± dipyridamole vs. control per patient.

Model	OR	Lower	Upper	Z score	P-value
Fixed effects	0.60	0.50	0.71	-5.7	<0.0001
Fixed effects regression (with dipyridamole)	0.63	0.47	0.85	-3.0	0.001
Fixed effects regression (without dipyridamole)	0.39	0.18	0.88	-2.3	0.012
Random effects	0.60	0.43	0.82	-3.13	<0.0001
Random effects regression (with dipyridamole)	0.66	0.45	0.98	-2.04	0.02
Random effects regression (without dipyridamole)	0.40	0.18	0.86	-2.35	0.009

interval for the random effects model (0.43-0.82) is wider than that of the fixed effects model (0.50-0.71).

If we look at the homogeneity test result, the QE has value of 28.2, P=0.003. This suggests that there is heterogeneity among the studies (Table 17). In the further

Table 17. Homogeneity test for individual trials aspirin ± dipyridamole vs. control per patient.

QE	df	P-value
28.2	11	0.003

analysis, we performed regression to evaluate the contribution of other factors such as the addition of dipyridamole.

A random effects regression model was used to determine if the presence or absence of dipyridamole affects the benefit of aspirin. This model not only accounts for the potential variation among studies, but actually accounts for the specific variation due to the presence or absence of dipyridamole. So the estimate of the overall odds ratio is adjusted further by the different settings of the studies based on the random effects model estimate. If dipyridamole is used in addition to aspirin, the adjusted odds ratio for aspirin is 0.66 (CI, 0.45 to 0.98); if dipyridamole is not used, the estimated odds ratio is 0.40 (CI, 0.18 to 0.87) (Table 16). This suggests that additional dipyridamole reduces the benefit of aspirin.

CHAPTER 4

CONCLUSION

We here make some general conclusions about the statistical aspects of meta-analysis based on our studies. The statistical basis of overall tests of a null hypothesis appropriate in meta-analysis is not problematic. The appropriate type of test is generally a directional test. Overall estimates of effect are much more useful, but the assumptions on which they are based are not generally easy to justify.

The fixed effects model makes no allowance for the heterogeneity, that must always exist, between the true treatment effects in different trials. The results derived from fixed effects model tend to be overly influenced by large studies, thus preventing a general overall conclusion. Our magnesium example demonstrates the fact that a large study can dominate over the small ones, resulting in contradictory conclusions. Therefore, it is advocated that the weights allocated to each trial in any meta-analysis should be explicitly calculated and displayed.

The random effects model is based on the assumptions that the heterogeneity between trials can be represented by a single variance, and is perhaps better considered as a type of sensitivity analysis in which the weights allocated to each study in estimating the overall effect are modified. In our four illustrative examples, the uses of the random

effects model and random effects regression model for meta-analyses are more appropriate because they take a more balanced account of all studies and considers other unknown factors which may affect the effect size.

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