Final Project

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1 Introduction Section

1. Meta-Analysis

Meta-analysis, coined by Gene Glass (1976), is *intended to provide the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.* In other words, it is record review done with a set of statistical methods for combining the magnitudes of the outcomes (effect sizes) across different data sets addressing the same research question. The outcome from each study, called the "effect size", is expressed on a common scale and these are then combined across all the studies to obtain a grand mean effect size that is tested to see if the overall effect deviates from zero. When different studies produce different results, meta-analysis is used to identify the reason for variation and if they produce consistent results it identifies the common effect.

Reasons for employing meta-analysis:
a) accounts for unequal precision in the magnitude of the effect among studies by weighting each study's effect size by the inverse of its variance
b) offers an improved control of type II error rates, because the low power of individual studies to detect an effect is "corrected" by the accumulation of evidence across many studies
c) important in areas where failure to reject false null hypothesis may have large detrimental impacts (Ex: Medicine)
d) identifies gaps in the literature where more research is needed, and also identifies areas where the answer is definitive and no new studies of the same type are necessary.

2. Factors Affecting Meta-Analysis

Although the typical sample sizes used in a given field can be a taken as a reference to start with, there is usually no control over the sample size while performing meta-analysis. It

might be of some help to consider the amount of variation in the size of the effect which would be considered clinically important. In large data sets a trivial amount of heterogeneity could be statistically significant while in small data sets a large amount of heterogeneity may not be statistically significant. Another suggested approach is to compute the power of tests of the mean effect size, homogeneity, and moderator analyses a priori by using the assumption about the size of an important effect in a given context and typical sample sizes used.

One approach that demands a relatively objective measurement of study quality is when meta-analysis is first performed using only the studies of the highest quality and then by sequentially adding studies of increasingly lower quality to determine whether this causes a directional shift in the results.

Publication bias is a situation wherein smaller studies with negative results (i.e., no treatment effect shown) are not submitted for publication. This is also known as the file drawer problem. This may affect the validity of the conclusions drawn by a meta-analysis and hence the authors of meta-analyses must strive to include all available trials, often requiring search strategies beyond a simple medline search. Funnel plots are used to assess for publication bias. Usually, trial size or quality score against treatment effect is plotted to expect a funnel-shape, whereby smaller and lower quality trials have a wide base centered around the mean treatment effect, whereas larger and higher quality studies, because they provide more accurate estimates of the treatment effect, make up the narrower top of the funnel. If a portion of the funnel is missing, such as the smaller studies with no treatment effect, this is indicative of publication bias.

3. Bayesian View Versus Frequentist View

The difference between the two approaches is in the way they define probability. A frequentist views probability as a long run frequency whereas the Bayesian uses probability to express belief in a statement about unknown quantities. Hence, the frequentist uses an objective probability and a Bayesian uses a subjective probability. This helps a Bayesian describe the uncertainity of a statement about an unknown parameter in terms of probability whereas a frequentist cannot.
In other words, as a result of analysis, a Bayesian can conclude that an interval contains a parameter of interest with 95% probability. In contrast, a frequentist will use probability to describe how often the calculations that produce an interval will cover the parameter of interest in repeated samples.
Also, a Bayesian evaluates two hypothesis of an unknown parameter by calculating the probability of each hypothesis given observed data and then choose the one with higher probability. A frequentist, on the other hand, estimates the long run frequency under one of the hypotheses of sampling data as extreme or more extreme than what was observed. Hence, n frequentist statistics parameters are considered to be fixed whereas in Bayesian the data are considered to be fixed.
Interpretation of Confidence Intervals:
For a frequentist, it is a collection of intervals with 95% of them containing the true parameter

and for a Bayesian, it is an interval that has a 95% chance of containing the true parameter.

4. Meta-Analysis & Bayesian Paradigm

The problem of meta-analysis lends itself well to the Bayesian paradigm because Bayesian methods provide the following advantages:

(*a*) incorporate external evidence, such as on the effects of interventions or the likely extent of among-study variation

(*b*) extend a meta-analysis to decision-making contexts, by incorporating the notion of the utility of various clinical outcome states

(*c*) allow naturally for the imprecision in the estimated between-study variance estimate

(*d*) investigate the relationship between underlying risk and treatment benefit

(*e*) perform complex analyses

(*f*) examine the extent to which data would change people's beliefs

5. Controversy

The initial trials and meta-analysis done till the year 1993 suggested that the magnesium intervention has played a positive role in reducing the acute myocardial infarction. Teo's meta-analysis has suggested 55% reduction in odds of mortality and LIMIT-2 large trail has suggested 24% reduction in mortality. However, the ISIS-4 mega-trial which was carried out in the year 1995 with 58 050 patients has reported non-significant adverse mortality and concluded that there is no good clinical evidence in favor of magnesium usage. These conflicting findings have led to a controversy and publication bias is believed to be one of the possible explanations.

2 Introduction of the models

1. Fixed Effects Versus Random Effects

Fixed Effects:

(*a*) True treatment difference:
It is considered to be the same for all trials.The standard error of each trial estimate is based on sampling variation within the trial.

(*b*) Overall estimate of treatment difference and its confidence interval:
These are specific to the particular trials included in the meta-analysis. They might not necessarily provide the best information for determining the difference in effect that can be expected for patients in general.

Random Effects:

(*a*) True treatment difference:
In every trial, it is assumed that the true treatment difference is a realization of a random variable, which is usually assumed to be normally distributed. Thus, the standard error of each trial estimate is increased due to the addition of this between-trial variation.

(*b*) Overall estimate of treatment difference and its confidence interval:
The random effects model allows the between-trial variability to be accounted for in the overall estimate and, more particularly, its standard error.Therefore, it produces results which can be considered to be more generalizable.

2. Effect Of Sample Size Of Each Trial

Both models lead to the same overall estimate and standard error when there is no heterogeneity between trials. As the heterogeneity increases the standard error of the overall estimate from the random effects model increases relative to that from the fixed effects model.The difference between the overall estimates from the two approaches depends to a large extent on the magnitude of the estimates from the large informative trials in relation to the others. An overall treatment effect is calculated as a weighted average of the individual summary statistics. Greater weights are given to the results from studies that provide more information, because they are likely to be closer to the "true effect" which is being estimated. The weights are often the inverse of the variance (the square of the standard error) of the treatment effect, which relates closely to sample size.

3. Data Analysis

The dataset includes the results from 15 randomized clinical trials that examined the effectiveness of intravenous magnesium in the prevention of death following acute myocardial infarction. The first few studies included in the meta-analyses were by Teo and were combined with the results from the LIMIT-2 trial in Yusuf et al. (1993), suggesting that magnesium is an effective treatment for reducing mortality. However, the results from the ISIS-4 mega trial indicated no reduction in mortality with magnesium treatment. If a meta-analysis is based on one large study with a small positive estimate and several small studies with large positive estimates, the overall estimate from the random effects model will be larger than that from the fixed effects model, the difference increasing with increasing heterogeneity.

4. Peto Method

In general, all the fixed effects meta-analysis models calculate the following the inverse variance weighted average:

$$W_i = \frac{\sum(T_i / {S_i}^2)}{\sum(1/{S_i}^2)}$$

where T_i = Treatment effect estimated in study i

S_i = Standard error of that estimate
Peto's method utilises an approximate method of estimating the log(odds ratio), and uses different weights. The approximation used in the computation of the log(odds ratio) works well when the treatment effects are small (odds ratios are close to 1), events are not particularly common and the trials have similar numbers in experimental and control groups. For k studies, the pooled estimate of the odds ratio is given by:

$$\bar{T}_{OR} = exp[\sum_{i=1}^{k}(O_i - E_i)/\sum_{i=1}^{k} v_i]$$

$$v_i = E_i[(n_i - n_{ti})/n_i][(n_i - d_i)/(n_i - 1)]$$

where n_i = No. of patients
n_{ti} = Number in the treatment group of the i^{th} trial
d_i = Total no of events
O_i = Number of events in the treatment group
E_i = Expected number of events in the treatment group = $(n_{ti}/n_i)d_i$
Variance of pooled odds ratio is:

$$var(ln\bar{T}_{OR}) = \sum_{i=1}^{k} v_i$$

5. DerSimonian and Laird Method

This method is also based on the inverse variance approach, making an adjustment to the study weights according to the extent of variation, or heterogeneity, among the varying treatment effects.

$$T_i = \theta_i + e_i$$

where T_i = Estimate of the effect size
θ_i = True effect size in the i^{th} study
e_i = Error with which T_i estimates θ_i and

$$var(T_i) = \tau_\theta^2 + V_i$$

where τ_θ = Random effect variance
V_i = Variance due to sampling error in the i_{th} study

3 THE FREQUENTIST ANALYSIS

1. REPRODUCING THE TABLE

Table 3.1: Summary of Frequentist Analysis: Peto and DerSimonian and Laird (D-L) methods

	Magnesium Group		Control Group	
Trial	Deaths r_i^M	Patients n_i^M	Deaths r_i^C	Patients n_i^C
Morton	1	40	2	36
Rasmussen	9	135	23	135
Smith	2	200	7	200
Abraham	1	48	1	46
Feldstedt	10	150	8	148
Schechter	1	59	9	56
Ceremuzynski	1	25	3	23
LIMIT-2	90	1159	118	1157
Fixed effect (Peto) meta-analysis of above eight trials 0.647 (95% CI: 0.508 , 0.824)				
Random effect (D-L) meta-analysis of above eight trials 0.554 (95% CI: 0.343 , 0.895)				
Bertschat	0	22	1	21
Singh	6	76	11	75
Pereira	1	27	7	27
Golf	5	23	13	33
Thogersen	4	130	8	122
Schechter 2	4	107	17	108
Fixed effect (Peto) meta-analysis of above fourteen trials: OR = 0.573 (95% CI: 0.461 , 0.711)				
Random effect (D-L) meta-analysis of above fourteen trials: OR = 0.468 (95% CI: 0.32 , 0.685)				
ISIS-4	2216	29011	2103	29039
Fixed effect (Peto) meta-analysis of above fifteen trials: OR = 1.011 (95% CI: 0.953 , 1.073)				
Random effect (D-L) meta-analysis of above fifteen trials: OR = 0.53 (95% CI: 0.363 , 0.775)				

2. ODDS RATIO

When odds ratio is less than one, it means that the number of deaths with the intervention of magnesium has reduced and hence the study is in favour of magnesium usage. For the first 8 trials, the odds ratio from fixed effect model is 0.647. This can be interpreted as the no. of deaths with magnesium intervention is 0.647 times the no. of deaths without magnesium intervention. The random effects model also gives an odd ratio <1 (0.554) but with a broader confidence interval of 0.343 - 0.895 vs the fixed effect confidence interval of 0.508 - 0.824.

In the fixed effect model including the mega-trial ISIS-4 the odds ratio is 1. It means that the number of deaths in the case of magnesium intervention is equal to the number of deaths

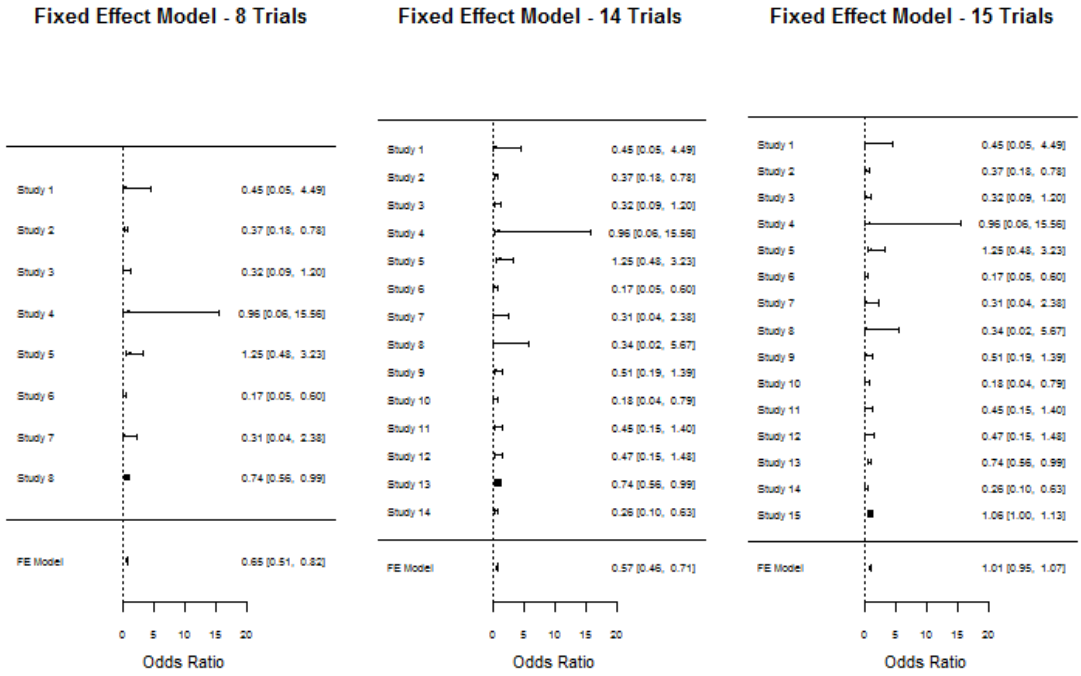
without magnesium intervention. This proves that there is no evidence that the magnesium would help reduce the mortality. Similarly, when odds ratio is greater than one, it means that the number of deaths with the intervention of magnesium has increased and hence magnesium should not be administered.

3. Fixed Effect & Random Effect Models

The random effect analysis considers the inter-trail heterogeneity in addition to the intra-trial and hence the studies are weighted much more equally in the random-effects analysis than in the fixed-effect analysis. In fixed effect analysis with the ISIS-4, the mega-trial gets the majority of the weight and so there is no evidence of a beneficial intervention effect. In the random-effects analysis the small studies dominate, and there appears to be clear evidence of a beneficial effect of intervention.

4. Forest Plots

Figure 3.1: Forest Plots For The Three Fixed Effect Models



The forest plot for the fixed effect model with the mega-trial shows the majority of the weightage is given to the mega-trial and also the diamond shape touches the line of no effect indicating that the result was not statistically significant. Also, with the addition of trials, the confidence interval for the odds ratio has narrowed down. Upon comparing the plots for models with 8 trials and 14 trials it can be observed that the odds ratio has moved closer to the "no effect" but without touching the line which shows that the variance could be purely due to the sampling error.

5. The Bayesian Analysis

1. MCMC Results

Table 3.2: Summary Statistics

	Log Odds Ratio (δ_{new})	Odds Ratio
Reference Prior	-0.93	0.395
Skeptical Prior	-0.30	0.740

Figure 3.2: Trace Plot For δ_{new} (Reference Prior)

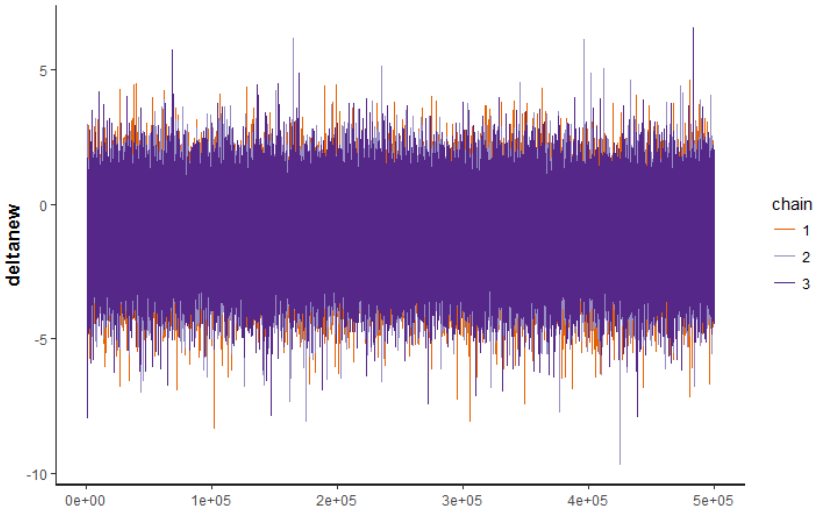


Figure 3.3: Trace Plot For δ_{new} (Skeptical Prior)

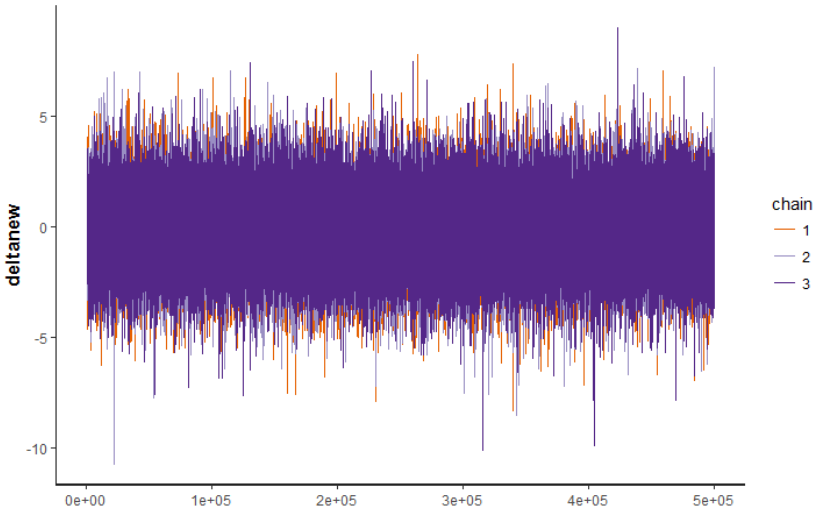


Figure 3.4: Histograms of Posterior Odds Ratio

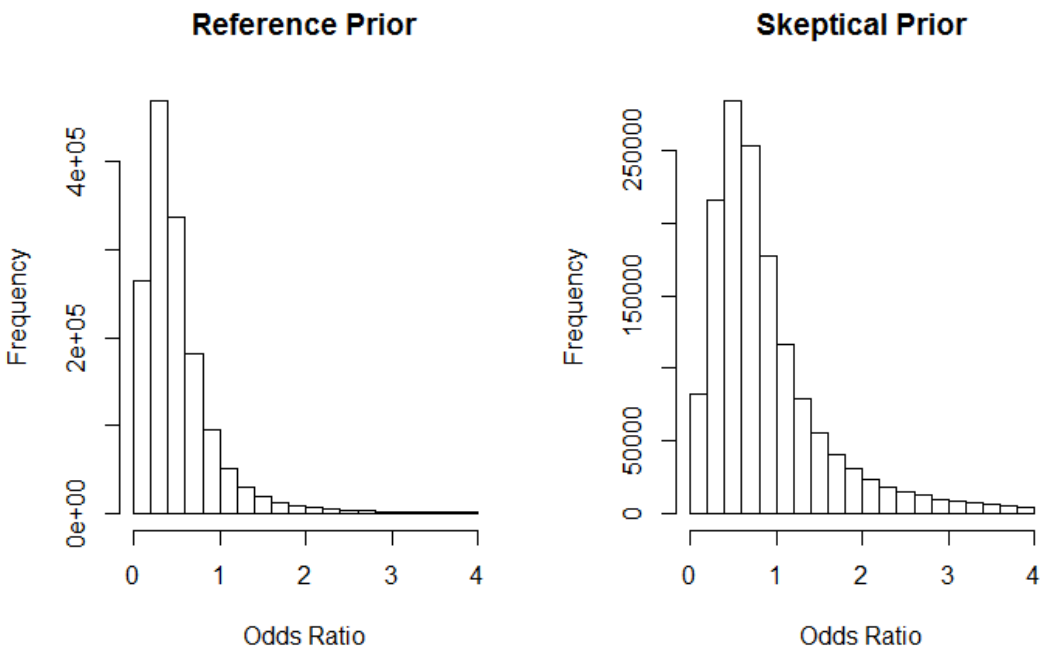


Table 3.3: Summary Statistics: Log(Odds Ratio) (δ_{new})

	Mean	Variance	Credibility Interval
Reference Prior	-0.93	0.656	(-2.64, 0.62)
Skeptical Prior	-0.30	0.774	(-2.05, 1.59)

Table 3.4: Posterior Probabilities

	P (Odds Ratio < 1)	P (Odds Ratio < 0.9)
Reference Prior	0.898	0.871
Skeptical Prior	0.676	0.623

The posterior probability that the overall estimate of the odds ratio is smaller 1 under the reference prior is 89.8% whereas that under the skeptical prior is 67.6%. Also, the posterior probability for the same under the reference prior is concluded to be clinically superior than that under the skeptical prior. Further, the variance of the log odds ratio under reference prior is 0.656 which is lesser than that under the skeptical prior.

6. CONCLUSION

Initially, the frequentist fixed and random effects models were used to analyse the effect of magnesium intervention in preventing myocardial infarction. The fixed effect model including the mega-trial ISIS-4 has concluded that the magnesium has no effect in preventing the infarction and thus putting down the earlier studies based on the other 14 trials. However, as the fixed effect model doesn't consider the between-trial heterogeneity it would be inappropriate to conclude its estimates of the effect. Also, the 95% confidence interval ranges between (0.95,1.0) which is difficult to be interpreted. Thus, fixed effect model would be inappropriate.

The Bayesian analysis, on the other hand, gives a more formal interpretation of the frequentist fixed effect findings through the addition of informative prior inputs and thus leading to a better judgment. Also, the Bayesian analysis focuses on investigating the reasons of different interpretations of data by different people. Though the Bayesian model assumes exchangeability between studies it could still be considered as a better model than the frequentist methods. Hence, with experienced guidance on the selection of appropriate models, the Bayesian analysis would be more flexible in analyzing the effect of magnesium intervention in preventing myocardial infarction.

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