Intravenous Magnesium and Myocardial Infarction: A Meta-analysis Approach

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1. Introduction

Meta-analysis is a statistical method that aims to derive a pooled estimate from multiple studies.[1] The basic idea of meta-analysis is that behind all the conceptually similar researches, there is a common but unknown truth.[2] Properly pooling these studies together, a successful meta-analysis yields a weighted average of the results and analyzes the differences, therefore increases the precision of the estimated effects, by avoiding potential issues that may rise from small-sample individual studies,[3] which often provide inconsistent or even contradictory conclusions.

In practice, meta-analysis usually consists of several steps:[4]

1) Formulate research questions;
2) Search available literature;
3) Based on appropriate criteria, select the studies to be include in the meta-analysis;
4) Determine the dependent variables and measures;
5) Select a statistical model and conduct the analysis.

For an appropriate meta-analysis, researchers need to include a fairly large number of studies to produce reliable and credible inference.[5] However, this is not to say that studies of different qualities are to be treated equally. Through the review process, researchers identify studies with diverse designs and methodologies, then decide what to include in the meta-analysis. Pooling researches of rigorous quality and the ones that are poorly conducted can sometimes lead to a skewed estimate of the underlying truth,[6] making the summarized results from meta-analysis unconvincing. If possible, researchers should also include studies with various conclusions in their meta-analyses.

Particularly, varying sample sizes in each study must be accounted for. It is common, even expected, that the studies to be included in the meta-analysis would have largely different sample sizes. Depending on the type of model selected, meta-analysis weight each study differently based on its sample size. However, with similar research qualities, large-sample studies should have a more significant impact on the overall results, compared with smaller trials.[7] As small-sample researches tend to yield greater treatment effects.[8] Such *small-study effects* may occur due to methodological flaws,[9] or arise from the differences in the common truths between small and large trials[10]. Alternatively, it may be because such smaller studies with statistically significant results are more likely to be published.[11]

To be more specific, when researchers compile a list of the studies that should be included in the meta-analysis, they search in databases for relevant articles, which however, usually only include published studies. For various reasons, studies with statistically significant results are more likely to be published, or in a journal with higher impact in the field. This type of bias towards published studies is called publication bias, and meta-analysis with strong publication bias could lead to misleading conclusions.[12]

In a frequentist point of view, parameters are often, although not always, treated as having fixed but unknown values. Therefore, probabilities should not be associated with them. On contrary, a Bayesian view allows probabilities to be associated with unknown parameters, and to have an interpretation that represents the researcher's belief of what are the true values of those parameters.[13]

Therefore, the critical difference between Bayesian and Frequentist views of statistics is how probability is treated and used. Typically, the Bayesian approach starts with a *prior distribution*, which is a probability distribution that reflects the scientist's knowledge of a certain subject he or she wants to study, and this process happens before any data are collected. After collecting the data, a Bayesian statistician updates the prior distribution based on those data, and obtains a new probability distribution for the same subject, which is called a *posterior distribution*.[14]

In contrast, to frequentist statisticians, because parameters are unknown but constant, to understand the true values of the parameters, they draw samples from the population, and use techniques such as hypothesis testing and confidence intervals, to estimate those unknown values. More specifically, frequentists start an experiment by setting up a confidence interval at a certain level, 95% for example, which means that out of every 100 experiments conducted, at least 95 of the confidence intervals are expected to include the true of the parameter. They then collect data, analyze them and get to their conclusions.[15]

Meta-analysis builds its results and conclusions upon an ideally substantial number of existing studies, which are also likely accumulated over time. Hence, a Bayesian approach may be a better fit for meta-analysis, as it is able to capture new information to update previously established conclusions, and provide a more precise estimate. In this sense, Bayesian practice allows researchers to conduct analyses with relatively small-sample studies based on accrual knowledge, instead of spending valuable resources on only large sample studies in exchange for more principled conclusions.[16]

At the same time, it often seems unreasonable of the frequentist view that the unknown parameters of a chosen subject have fixed values, especially when a meta-analysis often includes studies from across decades, or diverse population and regions, where the parameters may very well change. In this case, a Bayesian approach which allows a probability distribution that reflects the researcher's best guess, is a better tool for meta-analysis.

According to World Health Organization reports, cardiovascular diseases are the number one cause of mortality around the world. In 2012, it is estimated that 17.5 million

people died from such diseases, approximately 31% of all global deaths. Within this group, over 75% deaths took place in low and middle income countries.[17] "Myocardial infarction (MI), or acute myocardial infarction (AMI), commonly known as a heart attack, occurs when blood flow stops to a part of the heart causing damage to the heart muscle."[18] Over the years, mortality and morbidity from AMI remain high, and the medical community continues to spend an enormous amount of resources searching for more effective and inexpensive treatment methods. Intravenous magnesium was once considered "a simple, safe and widely applicable treatment"[19] by early enthusiasts. However, later experiments on larger scales, such as the 1995 ISIS-4 trial,[20] led to opposite conclusions that the treatment effect is not significant to adverse mortality.[21] A Cochrane review suggested that publication bias and heterogeneity of treatment effects are the likely reasons why early researches resulted in favorable conclusions that lean towards intravenous magnesium, therefore, "it is unlikely that magnesium is beneficial in reducing mortality both in patients treated early and… late, and in patients already receiving thrombolytic therapy".[22]

2. **Method and models**

In meta-analysis, there are two common approaches: fixed effects and random effects, which both control for the time-invariant variables that may not be observed in the available dataset, to avoid omitted variable bias.[23]

Fixed effects models are largely used in economic research. It assumes that there is one true effect behind all relevant studies of a particular subject, and the different effect sizes we obtain from various experiments come from random sampling errors. Fixed effects model works by allowing each cross-sectional unit to have a different intercept.[24] In practice, such models are often used when the primary interest of research is the "policy-relevant inference of the effects of individual characteristics".[25]

However, fixed effects model does have some disadvantages. First, "we lose one degree of freedom per cross-sectional observation", making the degrees of freedom relatively low for studies using fixed effects models, and subsequently reducing the power of the model and increasing standard errors of the coefficients. Second, important independent variables cannot be included explicitly in the model if they do not vary over time, therefore, we cannot estimate their coefficients.[26] For example, in a study that involves educational outcomes, ethnicity is usually an important factor. If we adopt fixed effects in our model, we will not be able to estimate the effect of ethnicity on the outcome because it is usually time-invariant and will be included in the fixed effects. Additionally, fixed effects often cannot make out-of-sample predictions as the unit-effects for unobserved units are unknown.[27]

Alternatively, a random effects model assumes not only the within-study variances, but also the between-study variance, which means researchers believe the true effect size is not constant, but from a distribution of effects sizes.[28] This is particularly helpful in meta-analysis, as it involves a number of studies that may well come from various

regions and time, where heterogeneity often exists, whereas in fixed effects models, heterogeneity is ignored. Furthermore, a random effects model has more degrees of freedom,[29] which is quite helpful when it comes to small-sample studies, especially in medical research. However, random effects model often encounter a bias issue. That is, since random effects model does not estimate separate unit effects, if the independent variable of interest *x* is correlated with the unit effects, the estimated coefficient on *x* may be biased due to omitted variable bias.[30]

In theory, "if every study had an infinite sample size, the sampling error would be zero", and the observed effect size for each study would mirror the true effect.[31] In reality, we of course cannot perform such a research; however, with the sample size being such a dominant factor in precision, we do favor a sample size that is large enough so the sampling error would lean towards zero, therefore yielding more precise estimates of the treatment effect than smaller-sample studies. In the case of meta-analysis, under random effects model, weights are assigned to studies more evenly than fixed effects. Therefore, large sample tend to lose their influence in random effects models.[32] But generally, large sample studies would still weigh more heavily than the others, giving a bigger impact on the overall meta-analytic treatment effect.

The dataset at hand consists of 15 medical trials that attempt to study the effect of intravenous magnesium on myocardial infarction. Time of the trials ranges from 1984 to 1995. Across these experiments, the sample sizes vary drastically – the smallest *Bertscat* trial had merely 43 patients, while the largest *ISIS-4* experiment included a total number of 58,050 patients, although in all studies, the number of patients assigned to treatment group and control group were fairly equal.

Conclusions from these studies also differ to a large extent – early experiments provided more exciting news, pointing intravenous magnesium as a potential treatment on MI. In a previous meta-analysis by Teo *et al* in 1991 that combined data from the first seven trials in our dataset, the results suggested that collectively in these experiments, the magnesium treatment group observed 25 deaths, representing a 3.8% mortality rate, while in the control group, 8.2% of the patients did not survive. This represents a 55% reduction in odds of mortality, with a strong statistical significance.[33] This conclusion was further supported by *LIMIT-2* trial which studied over 2,000 patients. The researchers believed that intravenous magnesium treatment led to a 24% decrease in mortality, and it is "simple, safe and widely applicable, whose efficacy in reducing early mortality of myocardial infarction is comparable to" that of thrombolytic therapy.[34]

However, later trials pointed to a conflicting view that recommended caution towards intravenous magnesium therapy. In particular, in the 1995 *ISIS-4* mega-trial, the researchers found insignificant adverse mortality, and concluded that "overall, there does not seem to be any good clinical evidence for the routine use of magnesium".[35]

It is worth noting that the sample size in the last study in our dataset, *ISIS-4 trial*, was without doubt much larger than the others. The amount of patients involved in that

experiment alone was more than 13 times of the number of individuals in the other 14 studies combined.

As discussed before, sample size of a study plays a critical role in its impact over the meta-analytic treatment effect, namely, should trials like ISIS-4 be included in a meta-analysis, their results are be weighted much stronger, leading the meta-analytic conclusion to lean towards large sample trials.

To put fixed effects model into the study of magnesium treatment scenario, where the meta-analysis was based on 15 available trials, the model writes as:

$$P(y_{ij}=1)=\beta_0+\beta_1 magnesium_{ij}+\sum_{j=1}^{15} trial_j+\epsilon_{ij};\epsilon_{ij}\sim N(0,\sigma^2)$$

The outcome variable is the probability that $y_{ij}=1$, estimated with logistic regression, where y_{ij} is a dichotomous variable that is equal to 1, if patient *i* in trial *j* dies. On the right side of the equation, $magnesium_{ij}$ is a binary variable that indicates whether a patient receives magnesium treatment or not, and $trial_j$ represents the fixed effects, where each of the 15 trials has a different intercept. Random error ϵ_{ij} comes from a normal distribution, with an mean value 0 and a variance σ^2. We estimate the model in a logistic regression.

Furthermore, Higgins and Spiegelhalter implemented a Peto fixed effects method for their meta-analysis, where they constructed a 2×2 table (magnesium and control vs. dead and total).[36] Observed number of deaths in treatment group $O_i=r_i{}^M$, whereas the expected number of deaths $E_i=\frac{r_i{}^C+r_i{}^M}{n_i{}^C+n_i{}^M}\times n_i{}^M$, and the weight of each study takes into consideration of the sample sizes, where the $V_i=\frac{n_i{}^C n_i{}^M(r_i{}^C+r_i{}^M)(n_i{}^C+n_i{}^M-r_i{}^C-r_i{}^M)}{(n_i{}^C+n_i{}^M)^2(n_i{}^C+n_i{}^M-1)}$. More details can be found in Table 1.

On the other hand, under a random effect model, they made the assumption that each trial may have a different treatment effect, and the specification writes as:

$$P(y_{ij}=1)=\beta_0+\beta_1 magnesium_{ij}+\sum_{j=1}^{15}\gamma_j\, trial_j+\epsilon_{ij};\gamma_j\sim N(\mu_\gamma,\sigma_\gamma^2);\epsilon_{ij}\sim N(0,\sigma^2)$$

Where the major change from the fixed effect is that γ_j represents the different effect sizes of each experiment. It follows a probability distribution, which is often assumed normal, with the average effect size μ_γ and a variance σ_γ^2. The rest of the model remains a similar idea. In the DerSimonian and Laird (D-L) random effects approach, the weight of each study takes into account not only the in-study variances V_i, but also the between-study variances τ^2, and the weights are calculated as $W_i{}^*=\frac{1}{V_i+\tau^2}$.

3. The Frequentist analysis

In a meta-analysis by Higgins and Spiegelhalter, they utilized the dataset we have and analyzed the odds ratio statistics for different sets of trials. The results are reproduced in Table 1, which presents the descriptive statistics for each trial, including the number of deaths and number of total patients in both treatment group and control group.

Table 1 Summary statistics from 15 randomized control trials of intravenous magnesium for acute myocardial infarction (reproduced from Higgins and Spiegelhalter)[37]

	Magnesium group		Control group	
	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
Feldstdt	10	150	8	148
Shechter 1990	1	59	9	56
Ceremuzynski	1	25	3	23
LIMIT-2	90	1159	118	1157
Fixed effect (Peto) meta-analysis of above eight trials: OR = 0.65 (95% CI: 0.51, 0.82)				
Random effect (D-L) meta-analysis of above eight trials: OR = 0.55 (95% CI: 0.34, 0.89)				
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
Shechter 1995	4	107	17	108
Fixed effect (Peto) meta-analysis of above 14 trials: OR = 0.57 (95% CI: 0.46, 0.71)				
Random effect (D-L) meta-analysis of above 14 trials: OR = 0.47 (95% CI: 0.32, 0.68)				
ISIS-4	2216	29011	2103	29039
Fixed effect (Peto) meta-analysis of above 15 trials: OR = 1.01 (95% CI: 0.95, 1.07)				
Random effect (D-L) meta-analysis of above 15 trials: OR = 0.53 (95% CI: 0.36, 0.77)				

For the initial model where the first eight trials in Table 1 were included, using Peto fixed effects method, the key statistic we calculated is odd ratio, which is 0.65. It suggests that the odds of death from MI in the treatment group, where patients were given magnesium injection, are 35% lower than the odds of death in the control group. When we calculate the same statistic but increase the sample to the first 14 trials, the odds ratio decreases to 0.57, meaning in this scenario, the odds of death in the treatment group are 43% lower than the other group. When all the trials are considered, including the *ISIS-4* mega-trial, the odd ratio drastically increases to 1.01, which points to the opposite

conclusion that we see before, as the odds of death are now 1.01 times higher than the odds of death in the control group, although this estimate is not statistically significant.

In contrast, D-L random effects models estimates are more consistent across all three models. More specifically, when we calculate the odds ratios of the same subsets of the trials, odds ratios change from 0.55, to 0.47 and then to 0.53, respectively, which shows that under random effects model, in those three scenarios, the odds of death in the treatment group are 45%, 53% and 47% lower than the odds in the control group.

Generally speaking, an odds ratio of 1 indicates that the odds of dying in the magnesium treatment group are the same as the control group. An odds ratio of greater than 1 suggests that the odds of dying in the magnesium treatment group are bigger than the control group, and obviously, an odds ratio of smaller than 1 means that the odds of dying in the treatment group are smaller than the control group, and that the treatment may be effective.

As presented in Table 1, it is quite obvious that under fixed effects models, the odd ratios vary dramatically, when we add more trials into the analyses. In the most extreme case, when the *ISIS-4* study is included, the odds of deaths in the treatment group actually surpass the odds in control group, which leads us to a completely different view from the other two models.

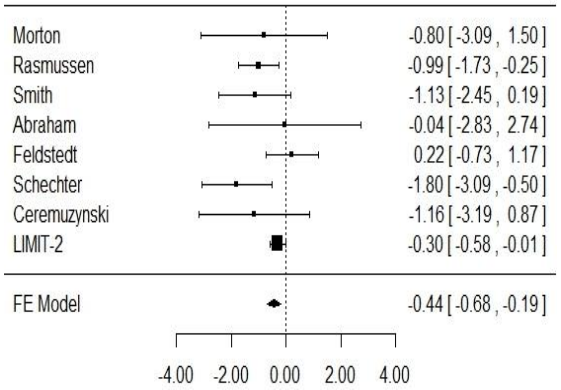
Meanwhile, odds ratios under random effects models are more robust, which change slightly when we update the analyses with more trials data, but the conclusions are still similar, even though its confidence intervals do seem wider than the ones under fixed effects models.

Given the assumptions that fixed effects and random effects models make, where one considers only the in-study variances, and the other also takes into account the between-study variances, therefore incorporating heterogeneity among different researches, I would prefer random effects models in this scenario, as it is unreasonable to assume that the true effect of magnesium treatment should be identical across every individual study, and the differences we obtain from each study comes from only random sampling errors.

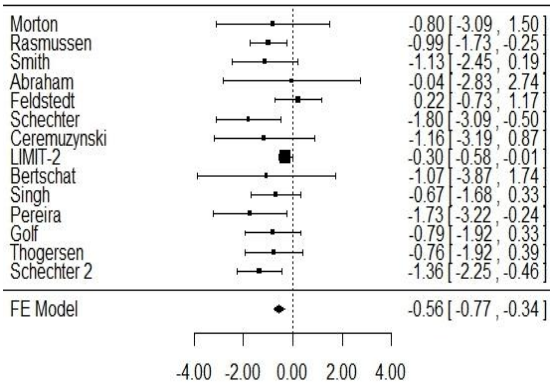
With forest plots, it is even clearer that as we add more trials data to the estimates, the log of odds ratio moves towards 0 (odds ratio towards 1), and it is no longer statistically significant, which suggests that when we take into account the *ISIS-4* trial, magnesium injection is not effective any more.

Figure 1 Fixed effects meta-analysis of the three models presented in Table 1

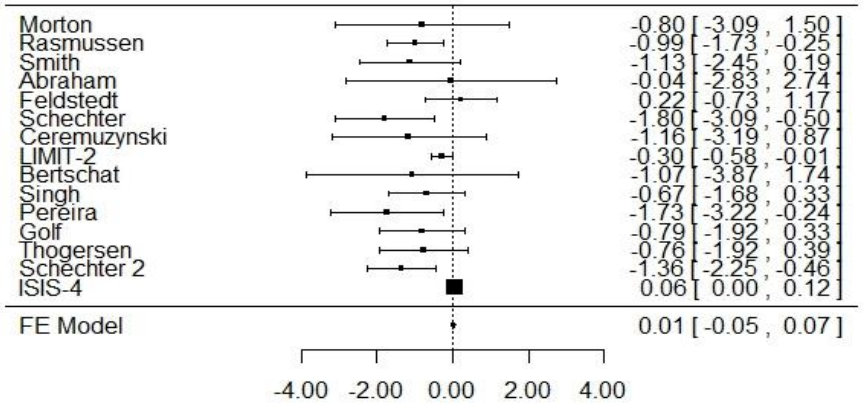
Log odds ratio of first eight trials



Log odds ratio of first 14 trials



Log odds ratio of all trials



4. The Bayesian analysis

In this section, we move on to the Bayesian models. In their analyses, Higgins and Spiegelhalter's adopted two types of prior distribution: *reference* and *skeptical*. In their review, previous research suggests that most clinically important interventions are likely to reduce risk of outcomes by about 10 – 20%.[38] They then argued that "a reasonable degree of skepticism to think it unlikely (only 5% chance) that magnesium would reduce the odds of mortality by more than 25%", and hence translated such a degree of skepticism into a "normal prior distribution for the log of odds ratio, centered on 0 and with a variance of 0.03". They also considered another version of prior distribution, where the log of odds ratio is again centered at 0, but with a much larger variance, referred to as the reference prior.

In general, we consider in all 15 trials, each trial i has the number of death occurred in the magnesium group ${r_i}^M$, which is drawn from a binomial distribution, where the total number of patients is ${n_i}^M$, therefore the probability of death would be ${P_i}^M$. The same applies to the control group: ${r_i}^M \sim binomial\left({n_i}^M, {P_i}^M\right)$, ${r_i}^C \sim binomial\left({n_i}^C, {P_i}^C\right)$

To estimate the treatment effect δ_i of each experiment, we build the model as:

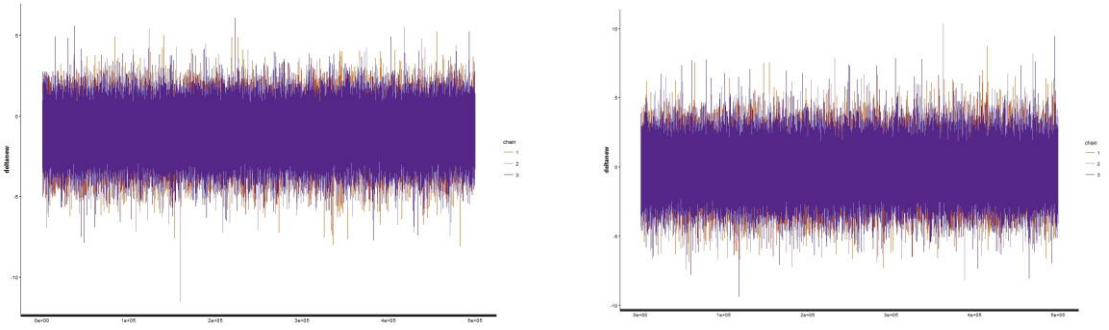
$Logit(P_i^M) = logit(P_i^C) + \delta_i$ where it also allows heterogeneity among each study.

To put it in simpler terms, this model is similar to the usual logistic regression as: $P(y_{ij} = 1) = \beta_0 + \beta_1 magnesium_{ij} + \epsilon_{ij}$ where the outcome is predicted by a binary indicator $magnesium_{ij}$ that tells whether a patient received magnesium treatment.

With 3 MCMC chains, 500,000 iterations in each, the estimated treatment effect in the reference model is at -0.93, which if we translate into odds ratio is 0.39. It means the odds of death in the treatment group are 61% lower than the control group. On the other hand, under the skeptical assumption, the odds ratio is 0.74, which suggests the odds of death of the treated patients are 26% lower than the untreated patients. It is worth noting that the 5% credible interval for reference model is (0.07, 1.86), while the CI for skeptical model is much wider at (0.13, 4.95).

Figure 2 examines the convergence of MCMC chains in both prior distributions with trace plots. As presented, both models converged quite well, which indicates that the parameters are set up properly.

Figure 2 Trace plots of reference and skeptical priors



To better illustrate the analyses, Figure 3 presents histograms of the posterior distribution for the overall meta-analytic estimate of odds ratio in both prior distribution scenarios. It is worth noting that under the reference assumption, odds ratio center between 0.3 and 0.4, while with skeptical prior, the center of odds ratio distribution leans towards 1, suggesting the estimated treatment effect is smaller than the reference model. This conclusion is consistent with the estimated mean of log of odds ratios, which suggests that the reference prior leads us to a more exciting attitude towards magnesium treatment on MI. But if we are skeptical of its effect to a certain extent before conducting the analyses, the corresponding results would make us more cautious about the true size of the effect.

Figure 3 Histograms of the posterior distribution for the overall meta-analytic estimate of odds ratio

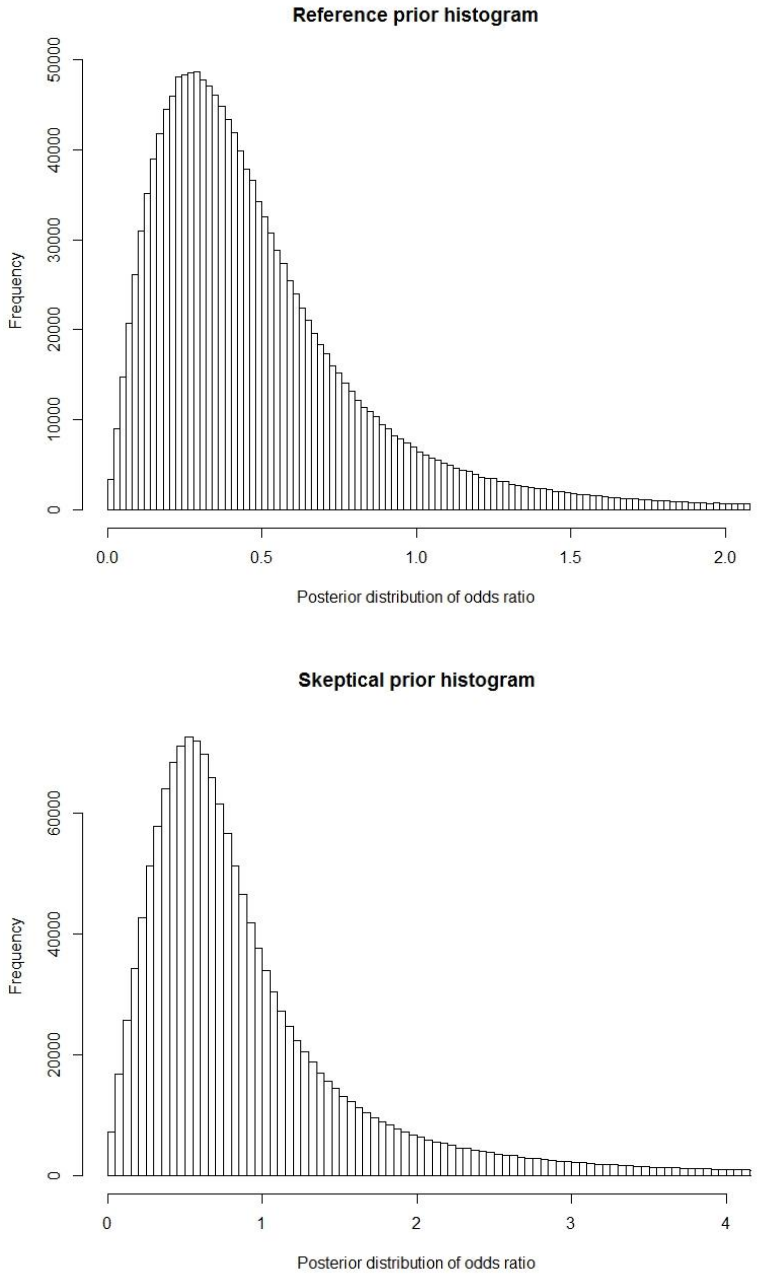


Table 2 looks at the results in terms of statistical superiority and clinical superiority. In the reference prior, the posterior probability that the overall estimate of the odds ratio is smaller than 1 is 0.90, while the probability for skeptical prior is 0.68. When we examine clinical superiority, where the effect size is stricter and odds ratio should now be smaller than 0.9, the probability decreases to 0.87 and 0.62, respectively. It is expected that in both statistical and clinical sense, reference prior yields a stronger effect of

magnesium.

Table 2 Statistical and clinical superiority of reference and skeptical priors

	Statistical superiority (Odds ratios < 1)	Clinical superiority (Odds ratios < 0.9)
Reference prior	0.90	0.87
Skeptical prior	0.68	0.62

5. Conclusion

In this project, we attempt to explore various modeling techniques around meta-analysis, with reference to Higgins and Spiegelhalter's previous research. We use data from 15 randomized control trials that aimed to study the effect of intravenous magnesium on myocardial infarction. These studies vary drastically in their sample sizes, and point to different conclusion.

We use two major approaches to analyze the data: frequentist (fixed effects and random effects) and Bayesian analyses, which make different assumptions about the value of parameters of studies in meta-analysis.

The frequentist method assumes the parameters of a certain subject are unknown but fixed. It yields quite different results when incorporated with fixed and random effect, as we update the results with new studies, while random effects are less influenced by large-sample research, and the odds ratio statistic is more robust.

Meanwhile, Bayesian method believes the parameters are unknown yet associated with a probability distribution. We adopt both reference and skeptical prior distributions, where the latter has a more cautious attitude towards the effect of magnesium treatment, and in return, its result also suggests that the medical community should be more careful when it comes to using intravenous magnesium to treat MI.

In the context of meta-analysis, I believe random effects model fit better, as it takes into account the existence of between-study differences, which is almost inevitable when multiple studies are included in a meta-analysis. Between frequentist and Bayesian methods, I would prefer Bayesian approach, as it smoothly fits the nature of meta-analysis, where researchers update their analyses when more studies are available. More particularly, for the research question we have at hand, I believe a skeptical prior provides a more precise estimate of the treatment effect. As noted by previous researches, the mega-trial *ISIS-4* experiment was not a properly conducted randomized control trial, which means its influence in our meta-analysis should be restricted. This recommendation was carried out with a skeptical prior distribution. At the same time, considering that we are conducting medical research, a more conservative attitude towards new methods is more appropriate.

Overall, different statistical modeling methods each have their own merits and disadvantages. In the context of a meta-analysis on the effect of intravenous magnesium on myocardial infarction, I do not think there is sufficient evidence that the treatment is

effective to make a critical difference to save patients' lives, and the medical community needs more future clinical trials to estimate a more accurate treatment effect.

Appendix A Codes for R and STAN

```
# project 2

##### set up data ########################################
setwd("C:/Users/hw1220/Desktop/project")
mag <- read.csv("magnesium.csv")

# deleting unnecessary column
mag$X <- NULL

# rearrange to fit table 2 in Higgins paper
colnames(mag) <- c("trial", "name", "year", "nm", "rm", "nc", "rc")
mag <- mag[c("trial", "name", "year", "rm", "nm", "rc", "nc")]
mag[13, 1] <- 8
mag[8:12, 1] <- c(9:13)
mag <- mag[order(mag$trial),]

# examine the studies
mag$total <- mag$nm + mag$nc

sum(mag[1:14, 8]) # 4388 patients in other 14 studies
58050/4388 # how much bigger ISIS-4 is than the others

##### frequentist analysis ##################################
# install.packages("metafor")
# install.packages("rmeta")
# install.packages("formattable")

library(metafor)
library(rmeta)
library(formattable)

### reproduce table 2

# OR in Peto FE for first 8 trials
or.p8 <- rma.peto(ai=rm, n1i=nm, ci=rc, n2i=nc,
                  data=mag[1:8,], slab=name,
                  add=1/2, to="only0", drop00=TRUE,
                  level=95, digits=2, verbose=FALSE)
summary(or.p8) # OR 0.65, CI(0.51, 0.82)
```

```
# OR in Peto FE for first 14 trials
or.p14 <- rma.peto(ai=rm, n1i=nm, ci=rc, n2i=nc,
                   data=mag[1:14,], slab=name,
                   add=1/2, to="only0", drop00=TRUE,
                   level=95, digits=2, verbose=FALSE)
summary(or.p14) # OR 0.57, CI(0.46, 0.71)

# OR in Peto FE for all trials incl ISIS-4
or.p15 <- rma.peto(ai=rm, n1i=nm, ci=rc, n2i=nc,
                   data=mag[1:15,], slab=name,
                   add=1/2, to="only0", drop00=TRUE,
                   level=95, digits=2, verbose=FALSE)
summary(or.p15) # OR 1.01, CI(0.95, 1.07)

# OR in DSL RE for first 8 trials
or.dl8 <- meta.DSL(ntrt=nm, nctrl=nc, ptrt=rm, pctrl=rc,
                   conf.level=0.95, names=name,
                   data=mag[1:8,],    na.action=na.fail,statistic="OR")
summary(or.dl8) # OR 0.55, CI(0.34, 0.89)

# OR in DSL RE for first 14 trials
or.dl14 <- meta.DSL(ntrt=nm, nctrl=nc, ptrt=rm, pctrl=rc,
                    conf.level=0.95, names=name,
                    data=mag[1:14,],    na.action=na.fail,statistic="OR")
summary(or.dl14) # OR 0.47, CI(0.32, 0.68)

# OR in DSL RE for all trials incl ISIS-4
or.dl15 <- meta.DSL(ntrt=nm, nctrl=nc, ptrt=rm, pctrl=rc,
                    conf.level=0.95, names=name,
                    data=mag[1:15,],    na.action=na.fail,statistic="OR")
summary(or.dl15) # OR 0.53, CI(0.36, 0.77)

# forest plots for all 3 FE models
forest(or.p8, main="Odds Ratio for the First 8 Trials")
forest(or.p14, main="Odds Ratio for the First 14 Trials")
forest(or.p15, main="Odds Ratio for All Trials")

##### bayesian ########################################
# install.packages("rstan", repos = "http://cran.rstudio.com", dependencies = TRUE)
library(rstan)
```

```
k <- length(mag$trial)
nc <- mag$nc
nm <- mag$nm
rc <- mag$rc
rm <- mag$rm

# Bayesian model with reference prior
model_ref <- "
data{
	int<lower=0> k;
	int<lower=0> nc[k];
	int<lower=0> nm[k];
	int<lower=0> rc[k];
	int<lower=0> rm[k];
}

parameters {
	vector[k] delta;
	real<lower=0, upper=1> pc[k];
	real<lower=0> sigma;
	real deltanew;
	real mu;
}

transformed parameters{
	real<lower=0, upper=1> pm[k];
	for (i in 1:k) {
		pm[i]<- exp(log(pc[i]/(1-pc[i]))+delta[i])/(1+exp(log(pc[i]/(1-pc[i]))+delta[i]));
	}
}

model{
	for (i in 1:k) {
		rc[i] ~ binomial(nc[i], pc[i]);
		rm[i] ~ binomial(nm[i], pm[i]);
		delta[i] ~ normal(mu, sigma);
		pc[i] ~ uniform(0, 1);
	}

	deltanew ~ normal(mu, sigma);
```

```
    mu ~ normal(0, 100);
    sigma ~ uniform(0, 100);
}"

# Bayesian model with skeptical prior
model_skp <- "
data{
    int<lower=0> k;
    int<lower=0> nc[k];
    int<lower=0> nm[k];
    int<lower=0> rc[k];
    int<lower=0> rm[k];
}

    parameters {
    vector[k] delta;
    real<lower=0, upper=1> pc[k];
    real<lower=0> sigma;
    real deltanew;
    real mu;
}

transformed parameters{
    real<lower=0, upper=1> pm[k];
    for (i in 1:k) {
        pm[i]<- exp(log(pc[i]/(1-pc[i]))+delta[i])/(1+exp(log(pc[i]/(1-pc[i]))+delta[i]));
    }
}

model{
    for (i in 1:k) {
        rc[i] ~ binomial(nc[i], pc[i]);
        rm[i] ~ binomial(nm[i], pm[i]);
        delta[i] ~ normal(mu, sigma);
        pc[i] ~ uniform(0, 1);
    }

    deltanew ~ normal(mu, sigma);
    mu ~ normal(0, 1/sqrt(32.69));
    sigma ~ uniform(0, 100);
}"
```

```
# fit reference model in stan
mod_fit_ref <- stan(model_code=model_ref, data=c("k", "nc", "nm", "rc", "rm"),
                    pars=c("delta", "mu","sigma","deltanew"),
                    iter=500000, chains=3, warmup=500, verbose=FALSE)
print(mod_fit_ref)

# fit skeptical model in stan
mod_fit_skp <- stan(model_code=model_skp, data=c("k", "nc", "nm", "rc", "rm"),
                    pars=c("delta", "mu","sigma","deltanew"),
                    iter=500000, chains=3, warmup=500, verbose=FALSE)
print(mod_fit_skp)

# trace plots for deltanew
traceplot(mod_fit_ref, pars= "deltanew")
# plot(mod_fit_ref)

traceplot(mod_fit_skp, pars= "deltanew")
# plot(mod_fit_skp)

# histogram for reference posterior distribution
mag.sim.ref <- extract(mod_fit_ref, permuted=TRUE)
# hist(mag.sim.ref$deltanew, breaks=200, xlim=range(-4, 2),
      # xlab="Posterior distribution of log of odds ratio",
      # main="Reference prior histogram")

hist(exp(mag.sim.ref$deltanew), breaks=20000, xlim = range(0, 2),
      xlab="Posterior distribution of odds ratio",
      main="Reference prior histogram")

# histogram for skeptical posterior distribution
mag.sim.skp <- extract(mod_fit_skp, permuted=TRUE)
# hist(mag.sim.skp$deltanew, breaks=200, xlim=range(-3, 3),
      # xlab="Posterior distribution of log of odds ratio",
      # main="Skeptical prior histogram")

hist(exp(mag.sim.skp$deltanew), breaks=200000, xlim = range(0, 4),
      xlab="Posterior distribution of odds ratio",
      main="Skeptical prior histogram")

# statistical superiority
```

```
sum(exp(mag.sim.ref$deltanew) < 1) / length(mag.sim.ref$deltanew) # 0.90
sum(exp(mag.sim.skp$deltanew) < 1) / length(mag.sim.skp$deltanew) # 0.68

# clinical superiority
sum(exp(mag.sim.ref$deltanew) < 0.9) / length(mag.sim.ref$deltanew) # 0.87
sum(exp(mag.sim.skp$deltanew) < 0.9) / length(mag.sim.skp$deltanew) # 0.62
```

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