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Master of Statistics: Biostatistics

Masterproef

Factors Affecting the Intubation Conditions Created by Mivacurium. A Meta-analysis and Meta-regression analysis.

Promotor :
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Dr. LUC VANLINTHOUT

Samson Hadush Mesfin

Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

Maastricht University

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Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek
Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt

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By
Samson Hadush Mesfin

Internal Supervisor
Prof. dr. Niel Hens

External Supervisor
M. D. Luc Vanlinthout

Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Biostatistics of Hasselt University, Belgium

September, 2012

CERTIFICATION

I declare that this thesis was written by me under the guidance and counsel of my supervisors.

……Date……

Samson Hadush Mesfin

We certify that this is the true thesis report written by **Samson Hadush Mesfin** under our supervision and we thus permit its presentation for assessment.

..……..…

Prof. dr. Niel Hens

……...……

M. D. Luc Vanlinthout

Diepenbeek, September 2012

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Samson Hadush Mesfin

September, 2012

Abstract

Intubation is the process of inserting a flexible tube anywhere in the human body. It is used in emergency medicine to help when a patient have difficulty in breathing, and to keep the airway open for delivery of anesthetic drugs and oxygen during surgery. Mivacurium is a non-depolarizing neuromuscular blocker used to facilitate intubation. The objective of the paper is to identify the factors that affect the probability of excellent intubation condition of Mivacurium (EIC). A total of 1029 patients from 51 randomized and controlled clinical trials were studied using meta-analysis methods. Classical and Bayesian approaches were used. In meta-analysis fixed effect and random effects models can be used to combine results from the different studies included in the meta-analysis. Fixed effect model assumes a common true effect underlying all the studies and all difference in the effect size is due to sampling error. In contrast, the random effects model allows the true effect size to vary from study to study and accounts for within study and between study variability in the estimation process. Results from fixed effect and random effect meta-analysis showed lack of significant effect of mivacurium on the probability of excellent intubation condition. Graphical and statistical methods for heterogeneity showed substantial heterogeneity in the effect size across the different studies included in the meta-analysis. Methods for publication showed no publication bias. To explore the sources of heterogeneity fixed effect and random effects meta-regression models were fitted. Results from the classical meta-regression models showed that dose, average age, time to intubation (tstart) and age by tstart interaction term are the variables that significantly affect the probability of excellent intubation condition. The Bayesian approach on the other hand showed the probability of excellent intubation condition varies with dose and age by tstart interaction for the fixed effect model, and dose for the random effect meta-regression. However, interpretation of the results should be done with caution since meta-analysis as an observational study is subject to confounding and ecological bias.

Keywords: Bayesian Approach, Excellent Intubation Condition, Fixed Effect Model, Meta-analysis, Meta-regression, Mivacurium, Publication bias, Random Effect Model

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1 Introduction

Intubation is the process of inserting a tube, called an endothracheal tube, into the mouth and then into the airway. This is mainly done so that a patient can be placed on a ventilator to assist with breathing. Endothracheal tube is a small flexible tube that is inserted into the mouth and down into the windpipe then attached to a ventilator. The tube is used to protect the airway and to assist a patient's effort to breathe [1]. Generally, intubation refers to inserting a flexible tube anywhere in the human body, but most people use it specifically to refer to tracheal intubation, which involves putting down into someone's trachea to secure his or her airway. Intubation is often used in emergency medicine when a patient is having difficulty breathing, and it is also used during surgery to keep the airway open for delivery of anaesthetic drugs and oxygen[2]. Intubation in surgery is needed because the lungs have to be filled with air so they can do their job.

To perform a tracheal intubation, a doctor or emergency medical technician ideally uses a laryngoscope, a medical device which is inserted into the mouth to open the jaw. The laryngoscope also lets the doctor clearly see the patient's throat, ensuring that the tube is placed in the correct passage; if an intubation is performed improperly and the tube ends up in the oesophagus, the results for the patient can be quite unpleasant and even deadly if not caught in time.

In some cases, if the mouth or throat is being operated upon, the tube is threaded through the nose instead of the mouth, which is called a nasal intubation, which is then threaded into the airway. This is done to keep the mouth empty and allow the surgery to be performed. During surgery and using tracheal intubation the patient can be placed on a ventilator to assist with breathing and a non-depolarizing relaxant such as mivacurium or rocuronium and depolarizing muscle relaxant such as succinycholine can be used [3].

Mivacurium is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action. It is a benzoisoquinolinium diester that is nearly completely metabolized by butyrylcholinesterase into the plasma. It is used in anesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The place of mivacurium has been gradually established. It is preferred particularly for short procedures such as

those performed in ambulatory settings. By the use of a continuous infusion, relaxation can be maintained in longer procedures where easy alteration of depth of neuromuscular block and fast spontaneous recovery are considered to be important [4, 5].

Due to its histamine releasing potential it can cause significant hypotension, brochospasm, erythema and cutaneous flushing, especially when given as a rapid IV bolus. Therefore it is recommended that the intubating dose be given over a minute. It has been demonstrated that the onset of action of mivacurium could significantly be accelerated by the divided-dose or priming technique using a priming interval of about 5 minutes. Conditions for tracheal intubation are unsatisfactory unless large doses of at least 0.2 $mg.kg^{-1}$ are given and a delay of at least 2 min is allowed before intubation is attempted.

Mivacurium induced neuromuscular block lasts for 12 to 20 minutes and 95% twitch recovery occurs within 25 to 30 minutes. It is nearly completely degradated by intra-vascular enzymatic breakdown and nearly 5% is excreted in the urine. The time of recovery does not depend on the total cumulative dose given by either repeated injection or by infusion. The duration of mivacurium neuromuscular block may be drastically prolonged in the presence of low or a typical plasma cholinesterase.

Mivacurium is available worldwide although, in recent years, its use in the United States has declined rapidly in favor of alternative agents perceived to offer a more rapid onset of action and a safer cardiovascular profile when administered in a rapid bolus dose. It is far more commonly used in Europe and the United Kingdom. The drug is marketed worldwide under the trade name of Mivacron.

Since its release at the end of the eighties mivacurium attracted significant research scrutiny The newly developed compound was increasingly subjected to randomized controlled trials (RCT) to look at its equivalence with other neuromuscular blocking agents. Between these RCT, important differences in methodology, patient selection and research quality can be noticed. In the context of those multiple studies considerable disagreement among results became apparent.

Available databases can be clustered and mined, thereby hoping to discern patterns among the huge amount of information. Meta-regression analysis is a statistical technique that can explore potential sources of heterogeneity of treatment effects between RCTs. Moreover, such a meta-regression can establish whether scientific findings are consistent and can be generalised across populations, settings and treatment variations by considering all available evidence pertaining to the issue. Because of the number of trials/effect sizes available, differences in methodology, patient selection, or treatment policy, mivacurium can be studied with meta-regression based techniques. We therefore performed a meta-regression with mivacurium. This was based on a systematic review on a body of RCTs conducted between 1987 and 2012.

Like other neuromuscular blocking agents the most important factors affecting the intubation condition of mivacurium are the depth of general anesthesia and the level of neuromuscular block. Satisfactory intubating conditions can usually be achieved before complete neuromuscular block is attained if there is adequate anesthesia [4]. In adults, doses of 0.15 mg/kg administered over 5 to 15 seconds, 0.20 mg/kg administered over 30 seconds, or 0.25 mg/kg administered in divided doses (0.15 mg/kg followed in 30 seconds by 0.10 mg/kg) are recommended for facilitation of tracheal intubation for most patients. Such slowed or dividing doses of mivacurium at doses above 0.15mg/kg are aimed to minimize the transient decreases in blood pressure observed in some patients given these doses over 5 to 15 seconds Dosage requirements for children is higher than adults. Moreover, onset and recovery of neuromuscular occur more rapidly in children than in adults [4].

This paper employs meta-analysis and meta-regression methods in the context of both Frequentist and Bayesian methods to identify the factors that affect the probability of excellent intubation condition of mivacurium.

2 Concepts in Meta-Analysis

Meta-analysis is a quantitative systematic review where statistical techniques are used to combine the results from individual studies. Meta-analysis has wide applications in medical and social science research. It is most often used to assess the clinical effectiveness of healthcare interventions; it does this by combining data from two or more randomized control trials. The validity of the meta-analysis

depends on the quality of the systematic review on which it is based. The precision for which the size of any effect can be estimated depends to a large extent on the number of patients studied. Meta-analysis, which combines the results from many trials, has more power to detect small but clinically significant effect [6]. Good meta-analyses aim for complete coverage of all relevant studies, look for the presence of heterogeneity, and explore the robustness of the main findings using sensitivity analysis [6]. Meta-analysis can be viewed in two aspects; the narrative review which is the task of combining data from multiple studies while the systematic review, a clear set of rules is used to search for studies and then to determine which studies will be included in or excluded from the analysis. Though there is subjectivity setting these criteria but decisions are specified making the mechanism more transparent [4]. Fixed or Random effect models can be used to combine results from the different studies considered in the meta-analysis aiming at eventually computing the overall or combined summary effect. The two make different assumptions about the nature of the studies, and these assumptions lead to different definitions for the combined effect, and different mechanisms for assigning weights. Originally, meta-analysis relied on fixed effect methods, the need to adjust for possible heterogeneity leads to an increased interest in the use of random effects model. The following section presents the factors that might affect the quality of meta-analysis.

2.1 Heterogeneity

Heterogeneity is defined as difference in methodology or study population used by the various studies under examination. Statistical heterogeneity refers to the true effect in each study not being identical. Clinical and methodological diversity among the studies included in a meta-analysis necessarily lead to statistical heterogeneity [26]. Heterogeneity may exist for a variety of reasons: there may be differences in execution of the trials or in patient populations, or the meta-analysis may be of trials investigating different (but still related) treatments [24]. Graphical and formal statistical test method has been developed to study heterogeneity. The paper presents both methods in detail.

2.2 Meta Regression

Meta-regression is a statistical technique used to investigate possible causes of heterogeneity in meta-analysis by relating study level characteristics to their effect sizes. Meta-regression is similar to

multiple regression but here the unit of analysis is study level not individual subject and the dependent variable is effect size at a study level instead of subject scores. Various methods for meta-regression have been developed. This paper discusses fixed effect and random effects meta-regression.

2.3 Publication bias

Publication bias is a bias that affects the results of meta-analysis based on the literature if the results of published trials differ systematically from those of unpublished trials (e.g by showing a larger treatment effect) [10]. It is commonly know that studies that are larger or have statistically significant results are more likely to be published than those that are small or have insignificant results [11]. In contrast a small size study leads to luck of power and significance may then be obtained if chance exaggerates any true difference between the groups under study. The obvious likely effect of inadequate sample size is failure to demonstrate statistical significance for a clinically important effect [10], which in turn leads to publication bias if results from small studies fail to show significant effect [12].

Sources of publication bias could be varied. To mention some; publication bias arising from 1) the design and execution of primary study and/or reviews and meta-analysis, 2) researches intention whether or not submit results, 3)tendency of journals to reject negative studies and 4)sponsors. The increasing in the number of meta-analysis being conducted leads to growing concern about the importance of publication bias. A key concern with publication bias is the fact that studies that obtain negative findings (that is, no benefit of treatment) are less likely to be published than those that conclude the treatment is effective [12]. Awareness of publication bias began in 1956 when the editor of the *Journal of Abnormal Social Psychology* indicated that negative studies were less likely to be published in his journal [13]. However, no attempt has been made to quantify until 1964 [12]. Various methods proposed for detecting and correcting publication bias, though useful, all have limitations. Prevention of publication bias by registering every trial undertaken or publishing all studies is an ideal that is hard to achieve [12]. Visual methods have been suggested to study publication bias. However, such methods are subjective and hence it is vital to use statistical test methods as a means to assess. If the visual and analytical methods show sign of publication bias then there are a couple of approaches

that can be taken to deal with such bias. This paper will present such an approach and is discussed in the sections that follow.

3 Objective

The main objective of the paper is to identify the variables that significantly affect the probability of Excellent Intubation Condition (EIC) of Mivacurium using meta-analysis technique.

4 Data Description

The data used in this study resulted from 51 randomized and controlled clinical trial studies conducted between 1987 and 2012 which reported the score of the intubation condition of mivacurium as a main outcome. The measured outcomes were scores reflecting excellent intubation conditions. Patients had to undergo a surgical intervention under general anesthesia requiring endo-tracheal intubation. Induction of anaesthesia was performed with thiopentone, propofol, etomidate or midazolam. All studies in which anesthesia was induced either with or without opioid agents were included. All studies, included in this review used mivacurium as a neuromuscular blocking agent.

Data sources and assessment of validity

A systematic search of the literature was performed without language restriction. Electronic search in MEDLINE, EMBASE, SCOPUS, Web of Science and the Cochrane Controlled Trials Register using the combination of free text terms such as, succinylcholine, suxamethonium, intubation conditions, and adults was performed to locate studies. Electronic search were conducted from 1987 until April 2012. The validated RCT (Randomized Controlled Trial) or CCT (Clinical Controlled Trial) filter was used for the search. References of included studies were hand searched to add any citations missed by electronic searches.

Studies were retrieved by searching by titles, abstracts and keywords. Only peer reviewed full journal articles were considered. Data from abstracts, letters, PhD theses, reviews or animal research were not taken into account. Methodological validity was evaluated using the five-point Oxford scale. This takes into consideration randomization, blinding and description of withdrawals.

Two independent appraisers reviewed relevant articles to decide which studies met the inclusion criteria. Disagreements were resolved by mutual consensus. If a consensus was not met, then a third appraiser was available for final decision.

Type of outcome measure

Intubation conditions can be evaluated using the three-point Copenhagen Consensus Conference scale. This is a qualitative rating system that allocates a score for each of the following items: ease of intubation, vocal cord movement, and patient response to intubation. In order to avoid interpretation bias we only considered data on the complete absence of muscle activity during laryngoscopy and endotracheal intubation. Therefore excellent conditions (EIC), defined as clear vocal cords, easy tube insertion, and no cough or limb movement during laryngoscopy and endotracheal intubation were selected as the outcome measure. We converted studies to the Copenhagen scale if this had not been directly reported, but sufficient detail was available to do so. The outcome variable, Excellent Intubation Condition (EIC), was derived as a ratio of the number of patents with excellent intubation condition to the total number of patients in a particular study.

Type of predictor variables

To identify the factors affecting the probability of intubation condition the data set consisted of both continuous and categorical predictor variables namely; the total dose administered in mg/kg (*Dose)*, average age in years (*Age)*, proportion of male/female patients included in the dose group (*Male/Female)*, the total number of patients included in the study(*N*), time to intubation in seconds (*Tstart*), the use of dose-splitting(*Split:* No=0,Yes=1). *Split* is an indication whether the administered dose level of the drug (mivacurium) has been given at once or by splitting at two stages, inclusion of patient with a significant illness (*ASA3:* No=0,Yes=1) and the year of publication (*Year*). For analysis natural logarithm of dose was used.

5 Methodology

5.1 Exploratory Data Analysis

This fundamental step has been carried out in order to gain better insight into the data set. To this effect various data exploration techniques were employed to study the possible potential predictor

variables related to the response variable. Simple summary tables showing frequencies and Bubble plots were used to study the association between the response variable and the set of explanatory variables. Typical for meta-analysis: Forest, Funnel and Radial plots were also used.

5.2 Meta- Analysis

5.2.1 Fixed Effect Model

The fixed effect model assumes that there is one true effect which underlies all the studies in the analysis, and that all the differences in the observed effects are purely due to sampling error. The estimated combined effect is our estimate of the underlying true common effect in the analysis. The general form of this model for an observed effect size Y_i can be written as

$$Y_i = \mu + \varepsilon_i \qquad (1)$$

where $\varepsilon_i \sim N(0, \sigma_i^2)$, is the within study error. The combined effect size (weighted mean) is computed as

$$\bar{Y} = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \text{ with variance } \frac{1}{\sum_{i=1}^{k} W_i} \qquad (2)$$

Where, W_i is the weight ($1/V_i$) for the i^{th} study. The basic data required for the analysis are therefore an estimate of the intervention effect and its standard error from each study. In the fixed effect model we only have within study error and hence study weights are assigned with the goal of minimize this error by assigning more weight to studies with larger size than studies with smaller size.

5.2.2 Random Effects Model

The fixed effect model assumes that the true effect size is the same in all studies. However, this assumption might be implausible in systematic reviews. In such situation the random effect model is more appropriate. Unlike the fixed effect model, the random effect model allows the true effect size to

vary from study to study due to some study characteristics. The studies included in the meta-analysis are assumed to be a random sample of the relevant distribution of effects (hence the name random), and the combined effect estimates the mean effect in this distribution. In the random effect model large studies may yield more precise estimates than small studies, but each study is estimating a different effect size, and each of these effect sizes serve as a sample from the population whose mean we want to estimate. Therefore, as compared with the fixed effect model, the weights assigned under random effects are more balanced. Large studies are less likely to dominate the analysis and small studies are less likely to be trivialized [14]. The general random effect model is given by

$$Y_i = \theta_i + \varepsilon_i = \mu + \gamma_i + \varepsilon_i \qquad (3)$$

for i =1 ,…., k, where $\varepsilon_i \sim N(0, \sigma_i^2)$ and $\gamma_i \sim N(0, \tau^2)$. The terms ε_i and γ_i are independently normally distributed. Under the random effect model we have to take account of two sources of variability namely; the within study (σ_i^2) like in the fixed effect model and an extra between study (τ^2). Both sources of variability are reflected in assigning weights to the studies. The combined effect size measure under the random effect model is given as

$$\overline{Y}^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*} \text{ with variance } \frac{1}{\sum_{i=1}^{k} W_i^*} \qquad (4)$$

where the $W_i^* = \sigma_i^2 + \tau^2$ and $\tau^2 = \dfrac{Q - (k-1)}{\sum W_i - \dfrac{\sum W_i^2}{\sum W_i}}$ (5)

The between study variance (τ^2) is estimated using the method of moments (the DerSimonian and Laird) method given by equation 5. The variance for the random effects is sum of the within study plus between study variance, and when the between study variance is zero the random effect model reduces to the classical fixed effect model. The between study variance is common for all the studies. The

algorithm first estimates the between study variance, τ^2, and then estimates the mean of the effect estimate by weighted least squares by using 1/W* as weight.

5.3 Heterogeneity

5.3.1 Graphical Exploration of Heterogeneity

Forest plots and radial plots are commonly used to graphically explore heterogeneity. Forest plots allow the reader to view all the studies at a glance. On the one axis of the forest plot the effect size estimates with their corresponding confidence intervals are plotted. The confidence interval shows the degree of the precision of the effect size estimates across the different studies. Longer confidence intervals indicate less certain estimates than shorter confidence intervals. Weights allocated for each study can be indicated by creating proportional plotting symbols in the middle of their corresponding confidence interval lines. The estimated summary effect size is usually represented with a diamond symbol and is placed towards the end of the forest plot.

The second graphical method of assessing heterogeneity, radial plots, is derived as follows. First, the outcome of each study (effect size) is divided by the square root of its corresponding variance to produce the *z*- statistic. Then, the *z*- statistic is plotted against the inverse of the standard error. In this plot we are looking for constant variance. The point of reference is a regression line drawn through the origin. Studies that fall outside the two standard errors of this line may exhibit heterogeneity [15].

5.3.2 Testing and Quantifying Heterogeneity

The trials that contribute to a meta-analysis are based on different protocols, and differences with respect to treatment regimens, patient populations, methods of assessment, or other important medical aspects may imply differences in terms of treatment effects. It is therefore important to test whether the results in different trials are similar, so that observed differences between them can be attributed to chance, rather than to true heterogeneity. The test of heterogeneity can be performed either in the fixed effect model which is meant like testing that the treatment effect is the same across all studies or under the random effect model which is like testing the null hypothesis that the between trial variance is zero

[16]. Under the assumption of a common treatment effect in all trials ($Y_1 = Y_2 = \ldots = Y_k = Y$), the commonly used Q-test statistics introduced my DerSimonian and Laird is given by [7]:

$$Q = \sum_{i=1}^{k} W_i \left(Y_i - \mathrm{M}\right)^2, \text{ with standard error of } \frac{1}{\sqrt{V_i^{\,2}}} \qquad (6)$$

where W_i is the study weight ($1/V_i$), Y_i is the effect size for the i^{th} study, M is the summary effect and k is the number of studies. In other words, we compute the deviation of each effect size from the mean, square it, weight this by the inverse-variance for that study, and sum these values over all studies to yield this weighted sum of squares. Under the null-hypothesis Q follows a chi-squared distribution with k-1 degrees of freedom.

This test is known to have low statistical power, which means that the probability that the null hypothesis of homogeneity of study treatment effects is rejected given that the alternative hypothesis of heterogeneity is true is small. Thus, non-rejection of the null hypothesis does not necessarily mean that heterogeneity does not exist, and the meta-analyst is well-served to consider that heterogeneity exists regardless and attempt to estimate it [17]. The purpose served by the Q-test statistic is to assess the viability of the null hypothesis, and not to estimate the magnitude of the true dispersion. However, we can use the variance of the true effect sizes (τ^2) and the I^2 statistic to describe the dispersion of true effect sizes.

The I^2 proposed by [18] quantifies the proportion of observed dispersion that is real, rather than spurious. This measure of inconsistency lies in the range of 0-100%. [18] provides some tentative benchmarks for I^2. They suggest that 25%, 50% and 75% might be considered as low, moderate, and high, respectively. If I^2 is near zero then it means that almost all the observed variance is spurious, which means that there is nothing to explain. However, if I^2 is large, then it would make sense to study the reasons for the variance possibly by applying statistical techniques like subgroup analysis or meta-regression to try to explain it. The I^2 is given:

$$I^2 = \left(\frac{Q - df}{Q}\right) * 100, \qquad (7)$$

where *df* is the degrees of freedom (k-1).

5.4 Publication Bias

5.4.1 Graphical Methods for Assessing Publication bias

When diverse estimates of given value exist, some scatter around the underlying truth would be expected, the largest scatter being seen for estimates based on the smallest number of observation [19]. A funnel plot is created by plotting the estimated effect size measure against the sample size or some other indicator of the precision of estimate. In the absence of publication bias the plot should resemble a symmetrical inverted funnel with a wider dispersion of the results among small studies and narrower range of results for large studies. Publication bias, however, tends to skew the funnel shape, usually by excluding small studies with non-significant results, so that the lower left-hand region of the graph is missing or more sparsely occupied [20].

To minimize the finding of false positives attention should be paid in the choice of axis when creating funnel plots since this could affect the shape of the resulting plot. It has been observed that different definitions of precision and effect measures resulted different conclusion [21]. [22] recommended the use of standard error on the vertical axis since the smaller studies receive more emphasis which is where bias is more likely to be found. When choosing between effect size measures for the horizontal axis they recommend the use of log odds ratio since plots using the log odds ratio have the same shape whether the outcome uses occurrence or non-occurrence of effect under study.

5.4.2 Statistical Test for Publication Bias

Testing Funnel Plot Asymmetry

The funnel plot offers a visual sense of the relationship between the effect size and the precision, but its interpretation is largely subjective. To statistically evaluate the bias (asymmetry) captured by the funnel plot two tests commonly used are presented below.

Begg and Mazumdar's Rank Correlation Test

This methods reports the rank correlation (Kendall's tau) between the standardized effect size and the variance (or standard error) of these effects. *Tau* is interpreted like any correlation, with a value of zero indicating no relationship between effect size and precision, and deviations from zero is an indication

of relationship. A positive *tau* indicates larger effects are connected with lower values of precision and a negative *tau* means larger effects are represented with high values of precision [23]. Moreover [23] suggest that the test should be used with caution since it has low power unless there is severe bias, and so a test that shows absence of correlation should not be considered as proof showing the absence of bias.

Egger' Regression

Unlike the Begg and Mazumdar's test which use the rank, this method uses the actual values of the effect sizes and their precision. Egger's method regresses the standard normal deviate on precision and tests the null hypothesis that the intercept is equal to zero. Although still having low power, Egger's method exhibits higher power than Begg's method when there is a lack of bias or a small number of studies. Just as there must be a significant number of studies to carry out Begg's method this is also true for Egger's method. Moreover, as is true for the rank correlation method, the Egger test should only be used if the analysis includes a range of study sizes and at least one of medium size [24].

Duval and Tweedie's Trim and Fill(Trim and Fill)

Trim and fill can be used to estimate the number of missing studies and adjust for them. Trim and fill uses an iterative procedure to remove the most extreme small studies from the positive side of the funnel plot, re-computing the effect size at each iteration, until the funnel plot is symmetric about the (new) effect size. While this 'trimming' yields the adjusted effect size, it also reduces the variance of the effects, yielding too narrow confidence interval. The algorithm then adds the original studies back into the analysis, and imputes a mirror image for each. A major advantage of this approach is that it yields an effect size estimate that is adjusted for the funnel plot asymmetry (bias). The advantage of this is that if there is a large change in the effect size we can ask questions about this shift. In this sense trim and fill is functioning as sensitivity analysis [15].

Fill and Trim approach assumes that the observed asymmetry is due to publication bias rather than a small study effect. If this assumption is incorrect, the idea of imputing the missing studies cannot be supported. Even if this assumption is true we must also remember the extra underlying assumption of publication bias follows a set pattern [24]. These are the main drawbacks of this approach.

Cumulative Meta-Analysis (CMA)

A cumulative meta-analysis repeatedly re-runs the analysis each time adding a new study. In a cumulative forest plot, the first row shows the effect based on one study, the second row shows the cumulative effect based on two studies, and so on.

By sorting studies from largest to smallest (or by more precise to least precise) and then conducting a cumulative meta-analysis can be an essential tool to assess the impact of publication bias or a small study effect. If the point estimate has stabilized with the inclusion of the larger studies and does not shift with the addition of smaller studies, then there is no reason to assume that the inclusion of smaller studies had injected a bias. This technique is more transparent than trim and fill due to being able to see how the cumulative effect changed as each study is added.

5.5 Model Building and Variable Selection

Examination of each covariate with the response variable can provide a preliminary idea how important the variable is. Consequently, a univariate regression model was fitted and variables with p-value < 0.25 were considered as candidates for the multiple covariate model [25]. Then to examine the relative importance of all the variables simultaneously, multiple regression technique was adopted. Eventually, manual backward selection procedure was adopted. This was done to identify the variables that are significantly associated with the probability of excellent intubation condition, and significant variables were retained for further statistical analysis. For Bayesian modeling the Deviance Information Criterion was used for selecting between alternative models.

5.6 Meta Regression

5.6.1 Fixed effect meta-regression

Fixed effect meta-regression extends the fixed-effects meta-analysis by replacing the mean, θ, with a linear predictors, $\mathbf{X_i\beta}$:

$$Y_i = \alpha + \mathbf{X_i\beta} + \varepsilon_i, \qquad (8)$$

where: $\varepsilon_i \sim N(0,\sigma_i^2)$, $\boldsymbol{\beta}$ is a $k \times 1$ vector of coefficients, and $\mathbf{X}_i$ is a $1 \times$ k vector of covariate values in study *i*.

5.6.2 Random-effects meta-regression

Unlike the fixed effect meta-regression the random-effects meta-regression allows for residual heterogeneity (between study variance not explained by the covariates) by assuming that the true effects follow a normal distribution around the linear predictor ($\mathbf{X_i\beta}$). The general form of the model is given as

$$Y_i = \alpha + \mathbf{X_i\beta} + \gamma_i + \varepsilon_i \qquad (9)$$

where: $\gamma_i \sim N(0,\tau^2)$ and $\varepsilon_i \sim N(0,\sigma_i^2)$. This model is considered as an extension to random effect meta-analysis that includes study level covariates or extension of fixed effect meta-regression that allows for residual heterogeneity.

For both regression models, $\mathbf{X_i}$ can be a quantitative or qualitative variable or both. For quantitative covariate, $\boldsymbol{\beta}$ stands for the change in the effect size for a unit change in the covariate keeping all other covariates constant. For qualitative covariate, $\boldsymbol{\beta}$ denote difference in effect size for one level of the covariate compared to the reference level keeping all other covariates constant, and $\boldsymbol{\alpha}$ is the intercept. Moreover by comparing the meta-regression models with their corresponding meta-analysis models we can quantify the amount of between study variability accounted for by including the covariates.

5.7 Bayesian Approach

The statistical procedures presented so far have been derived from a classical or frequentist approach, in which point estimates, confidence intervals and hypothesis tests are prominent features. This section presents the Bayesian approach which is fundamentally a different philosophy.

5.7.1 Bayesian Meta-analysis

The key difference between the Bayesian approach and the classical, or frequentist, approach lies in the incorporation of subjective or data-based, prior beliefs into the analysis of data. There are strong reasons for favouring a fully Bayesian approach over non-Bayesian methods, not least the ability to account for all parameter uncertainty [26]. Bayesian methods offer a unified modelling framework which overcomes issues such as the appropriate treatment of small trials, and a flexibility which allows the approach to be extended to consider distributions other than normal for the random effects, or to adjust for covariates through regression [27]. Again the full Bayesian approach gives the opportunity to borrow strength from other trials and to make predictions about the outcomes of future trials [14].

In most meta-analysis most of the trials included are small in size. Small trials and trials for which the observed risks are close to zero or one, present problems for methods based on summary statistics (such as log-odds). The usual approach to meta-analysis of trials with binary outcome data, which facilitates estimation, is to assume that these summary statistics have an approximate normal likelihood. However, such an assumption may not be satisfied incase of small size trials. Clearly, any method which models binomial outcome data directly is preferred to a summary statistics approach [27].

The frequentist approach is concerned with an imagined infinite number of repetitions of the same problem for fixed values of the unknown parameters. In the Bayesian approach, all unknown parameters are treated as random variables, and have a joint probability distribution specified ahead before observing the data. These prior distributions are reflections of subjective opinion [9]. The updating of the prior distribution in the light of the data provides the posterior distribution in which we base our Bayesian inferences. The two main important steps in Bayesian analysis are the expression of the subjective opinion as the prior distribution and the method of combining and updating evidence.

Since the posterior distribution is influenced by the choice of the prior distribution the choice of prior distribution is very important. The two main parameters are the summary effect, θ and the heterogeneity parameter, τ^2.

In order to reflect the uncertainty in the estimates of the hyperparameters θ and τ^2 (equation 10), a fully Bayesian approach can be adopted. Prior distributions on the unknown parameters are specified and inference about the population effect (and study specific effects) can be made by integrating out the unknown parameters over the joint posterior distribution of all the parameters [28]. The joint posterior distribution for $V = (\theta, \theta_1, ...\theta_k, \tau^2)$ in the random effect Bayesian model is given by

$$p(V \mid y, s^2) \propto \prod_i p(\theta_i \mid y_i, s_i^{\,2}) p(\theta_i \mid \theta, \tau^2)\, p(\theta)\, p(\tau^2). \qquad (10)$$

Inferences are conducted using summaries of the posterior distribution, example

$$\hat{\theta} = E(\theta \mid y, s^2) = \int_{\theta} \theta \int_{\theta, \tau^2} \{p(V) d\theta_i d\tau^2\} d\theta. \qquad (11)$$

In the Bayesian context Markov chain Monte Carlo methods such as the Gibbs sampler provide a way of approximating the posterior distributions like equation (11) by sampling large numbers of observations.

5.7.2 Choice of Prior Distributions

The choice of prior distribution which is conjugate to the likelihood function alleviates computational difficulty. A prior is said to be conjugate if it produce a posterior distribution of the same type like that of the prior. In the case of a normal distribution, the conjugate prior for the mean is a normal distribution and for the variance an inverse gamma distribution. As a result those distributions were used to carry out the analysis. The analysis in this paper uses non-informative priors. A normal distribution with mean 0 and variance of 10^4 and a gamma (0.001, 0.001) distribution for θ and τ^2

were used respectively. Such values were considered so as to minimize the effect of the prior on the posterior distribution. Moreover, a sensitivity analysis was also performed by changing those priors.

5.7.3 Checking Convergence

The convergence of the MCMC algorithm is an important issue for the correct estimation of the posterior distribution of interest. Unlike with the optimizations methods convergence cannot be diagnosed clearly in the MCMC methods. The user must specify both the length of the burnin period and the size of the MCMC output that will be used for the posterior analysis (i.e., the number of iterations/observations needed to keep for the analysis). A secondary, but also important, problem is specification of the thinning interval, that is the number of iterations we need to discard until two successive observations become independent. Graphical methods and formal statistical testing methods using CODA (convergence diagnostics assessment method) were used to evaluate convergence. To obtain the best estimates the following procedure were used in WinBUGS. Gibbs sampling with two chains of appropriate initial values and number of iterations were employed. Trace, autocorrelation, and Brooks, Gelman Rubin (BGR) plots were used to evaluate the mixing, autocorrelation and convergence of the sampler, respectively. Graphically the trace plot, history plot and the Brooks, Gelman and Robin (GBR) methods are used and autocorrelation methods were also used to assess the independence of the sampler.

6 Software Used

Data analysis was carried out using SAS version 9.2, Stata version 12, R version 2.15.1, Comprehensive Meta-Analysis version 2 and RevMan version 5.1 software's. All hypotheses were tested at 5% significance level.

7 Results

This section presents the results from the explanatory and statistical data analysis.

7.1 Exploratory Data Analysis (EDA)

In any data analysis it is always a great idea to do some exploratory steps before proceeding to the more complicated model. To this effect an exploratory data analysis have been carried out to explore and study the data in light of the different study level characteristics. This section presents the findings.

The minimum and maximum average *Age*s recorded in the meta-analysis were 23 and 74 years respectively. To study the relationship between average *Age* and probability of excellent intubation condition (*EIC*) a scatter plot or commonly referred as 'bubble plot' of *Age* by *EIC* have been used(Figure 1). It can be seen from the graph that the regression slope for age is almost zero suggesting that *Age* does not seem to have an effect on *EIC*. Each study estimate is represented by a circle proportional to its weight (precision) in the analysis. This view identifies which studies have the greatest impact on the slope of the regression line that is studies with greater circle size have bigger effect than the studies with smaller circle size (Figure 1).

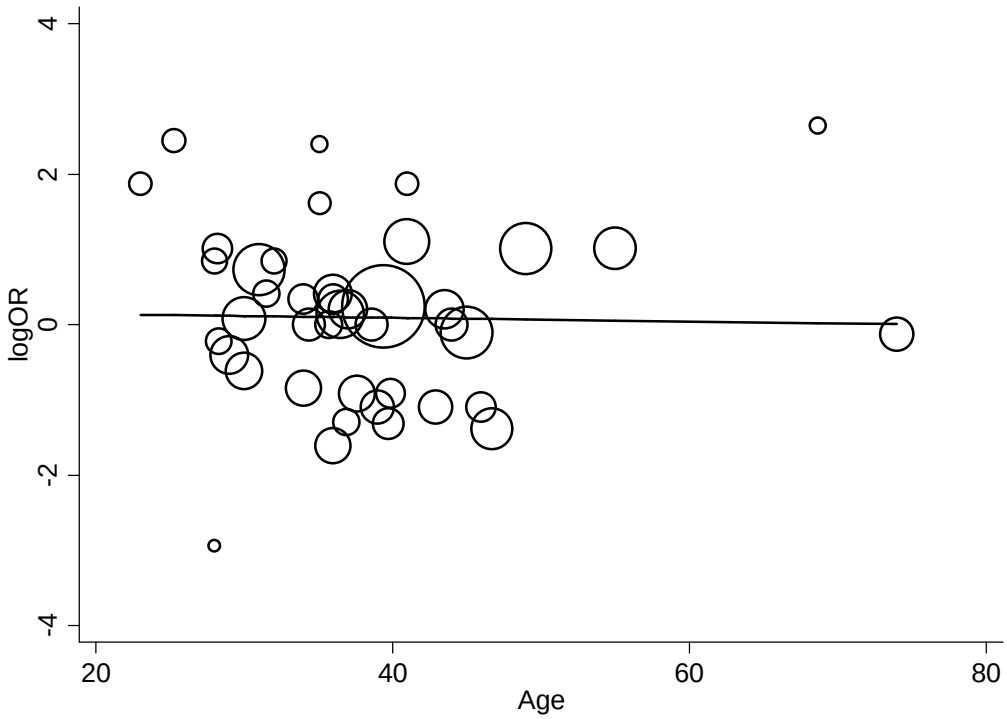


Figure 1: Bubble plot of Age with fitted meta-regression line

Generally, the dose levels of mivacurium ranges from 0.075 mg/kg to 0.3 mg/kg. To study the dependency of *EIC* on *Dose* level, a plot of *EIC* against *Dose* was used. The plot seems to show a positive linear relationship between *EIC* and *Dose* suggesting that high *Dose* level with higher probability of excellent intubation condition (Figure 2). In addition, *Dose* seems to have an association with *Tstart* with a correlation coefficient 0.48 and this can also be depicted on Figure I(c) in appendix.

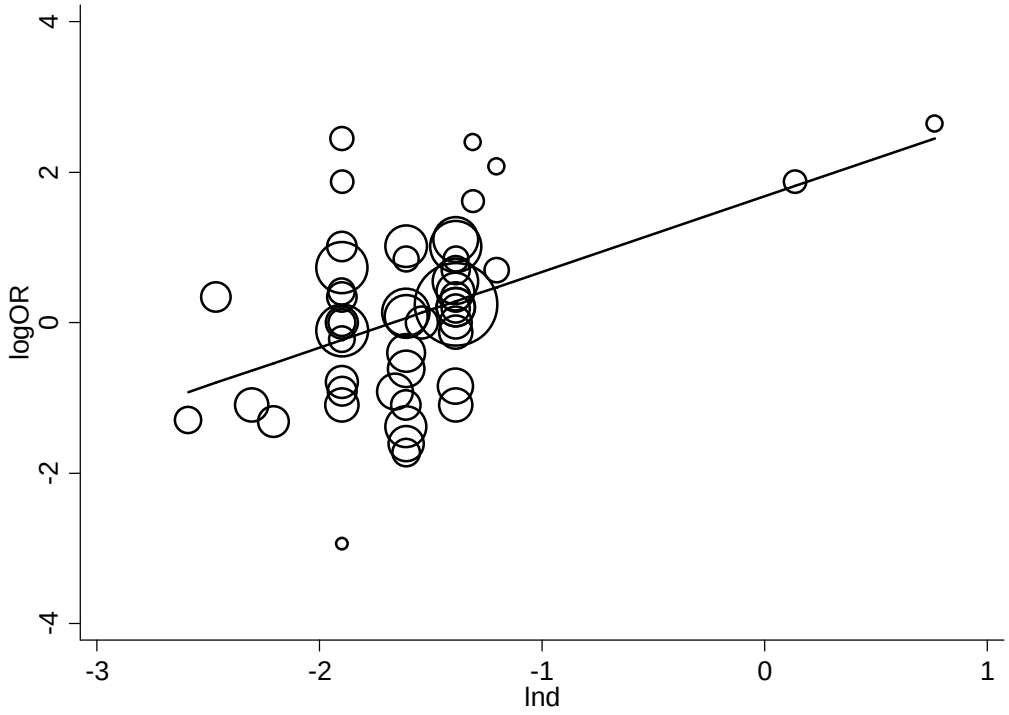


Figure 2: Bubble plot of Dose with fitted meta-regression line

A Bubble plot of the remaining quantitative covariates namely; *Male*, *Female* and *Tstart* were also studied. The graph of the fitted regression line together with the circles representing the study estimate have a slope very close to zero suggesting the lack of a relationship with the *EIC*. Moreover, there seems to be an association between *Age* and *Dose* (Appendix I). Normal probability plots of the standardized random predicted random effects was used to check the normality assumption of random effects and to identify outlying studies. Result showed the assumption of normality of the random effect is adequate and there are no noticeable outliers(Figure III in Appendix)

For the categorical predictor variables namely; *Split* and *ASA3,* cross tabulations have been used. Table 1 showed that in around 70% of the studies the full *Dose* of mivacurium was administered by splitting but in the remaining 30%of the studies however the full *Dose* was administered at once. Moreover,

Table 1 showed that around 96 percent of the studies recruited patients without serious illnesses and the rest 3 percent were patients with serious illnesses (*Table 1*).

Table 1: Number of studies by *Split* and *ASA3*

variable	Level	Frequency	Percent
Split	0(No)	36	70.59
	1(Yes)	15	29.41
ASA3	0(No)	47	96.92
	1(Yes)	2	4.08

A total of 1029 patients from 51 studies with average size of almost 20 patients per study were considered. The minimum and maximum sizes of the studies included in the meta-analysis were 9 and 91 patients respectively. This indicates that studies differ greatly in size. Moreover, study size was categorized into two groups, studies with less than 30 patients and those studies with greater or equal 30 patients, to see the proportion of study size by group (Table 1).

Table 2: Study size by group

Study size	Frequency	Percent
Less than 30	42	82.36
Greater than30	9	17.64
Total	51	100.00

Table 2 showed that 42(82.36%) studies included less than 30 patients and the remaining 9(17.64%) studies included more than 30 patients. This shows that the analysis included relatively many small studies and this might minimize the effect of publication bias which is a common problem in the area of meta-analysis. However, detailed assessment of publication bias is vital and it will be presented in the next section. Detailed study of study size will be performed by including study size as a covariate later in the meta-regression analysis.

7.2 Statistical Analysis

7.2.1 Fixed Effect and Random Effects Meta-analysis

One goal of meta-analysis is to estimate the overall or summary effect size. The fixed effect model ($\tau^2 = 0$) and the random effects model with a moment estimate τ^2 have been fitted to the mivacurium data set; the results are given in Table 3. The use of fixed effects model is advocated for when studies included in the analysis are functionally identical. In addition when the goal is to compute the common effect size for the identical population and not generalize to other populations. While random-effects model is used when the researcher is accumulating data from a series of studies that had been performed by researchers operating independently. Also,when the goal of the analysis is to make inferences about a wider population [18].

Table 3: Parameter estimates of fixed effect and random effects models

Model	Estimate	Std. Error	Confidence Interval
Fixed effect	0.0729	0.0693	[-0.0640, 0.2078]
Random effect	0.0724	0.1296	[-0.1816, 0.3264]

For the fixed effect model the summary effect, odd ratio, is 1.075 with 95% confidence interval [0.938, 1.231]. The hypothesis of interest is $H_0 : \theta = 0$ versus $H_1 : \theta \neq 0$. Since the confidence interval includes the null value of 1, we fail to reject the null hypothesis of no effect and conclude that there is no significant effect of mivacurium.

The usual null hypothesis associated with a random effect analysis is to test whether the underlying mean effect $\mu = \mathrm{E}(\theta_i)$ is zero versus different from zero i.e.

$$H_0 : \mu = 0 \text{ versus } H_1 : \mu \neq 0$$

For the random effect model the estimated odds ratio is 1.705 with 95% confidence interval [0.834, 1.386]. The 95% confidence interval includes the null value 1. Thus; we fail to reject the null hypothesis of zero mean effect and conclude that on average there is no significant effect of mivacurium.

It can be observed that the summary effect size estimate for the two models is the same however the standard error for the random effects model is bigger than fixed effect model and consequently the corresponding confidence interval for the random effects model is wider than fixed effect model. This is mainly due to the fact that the extra between study variability accounted for by the random effects model. Moreover, the smallest studies tend to have the more extreme estimates of treatment effect, and smaller studies are given greater relative weight in calculation of the random effects estimate compared with the fixed effect estimate.

7.2.2 Heterogeneity

Forest plot, a standard diagram for displaying meta-analysis results, is an important tool to study how the effect sizes from the individual studies behave. The dashed vertical line represent the null-value of no effect (OR=1) and the diamond at the bottom represents the summery effect size for the 51 studies included in the meta-analysis. The horizontal lines indicate the confidence interval with the point in the middle showing the effect size and the square box in the middle of the line shows the weight assigned for that particular study in estimating the weighted summary effect. That is the bigger the size the more precise estimate the study have and the more its contribution will be. Under the random effects model the smallest studies namely; Maddinein 1994 with 9 patients, Savarese 1987 with 9 patients and Lee 1997 with 12 patients are assigned 2.3, 4.3 and 4.4 percent as compared to 6.4, 10.1 and 10.3 percent under the fixed effect model respectively. On the other hand the three biggest studies i.e. Shanks 1987 with 36 patients, Fuentes de Frutos 1999 with 45 patients and Ali 1996 with 91 patients are assigned 4.31, 10.78 and 4.23 percent in the fixed effect model as compared to 2.59, 2.88 and 2.58 percent in the random effect model, respectively. This clearly shows that weight are more balanced under the random effects model than fixed effect model (Figure3 and Figure II in Appendix-I).

The second graphical method for assessing heterogeneity is the radial plot. The regression through the origin represents the overall log-odds ratio. Many points lie outside the 95% boundries of the log-odds ratio suggesting heterogeneity (Figure IV in Appendix).

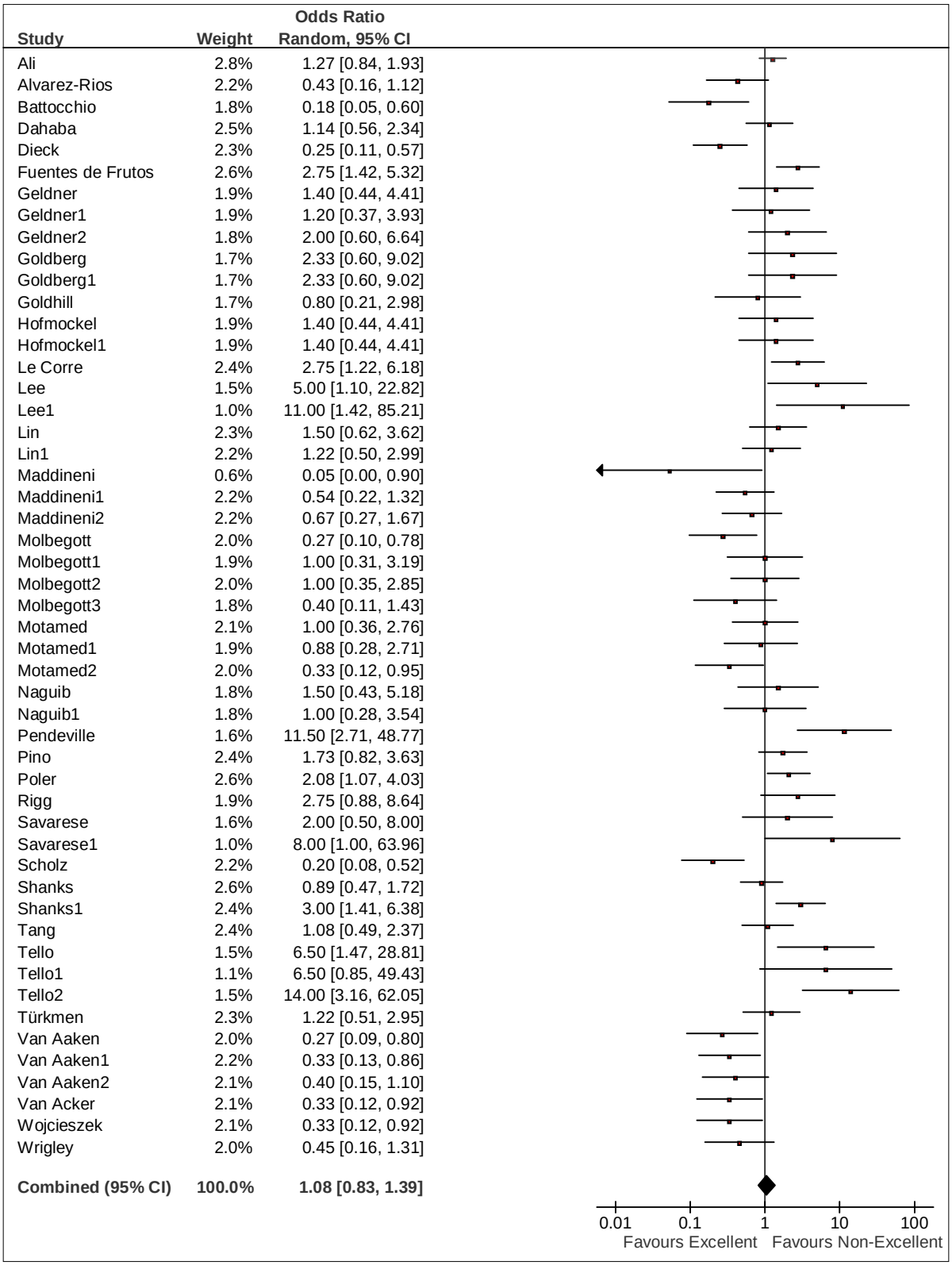


Figure 3: Random effect model Forest plot

Figure 3 showed that 30 studies did not produce statistically significant effect, since their corresponding confidence interval cross the vertical line. In contrast 21 studies produce significant effect. The overall summary effect is not significant. The individual studies did not produce similar results and this conflicting result could be due to either heterogeneity between the studies or sampling error. We can assess this by using the test of heterogeneity and by quantifying it. Heterogeneity statistics (τ^2) relating to the extent the OR vary between study and the I^2, a measure of the percentage of heterogeneity that is attributable due variability in true effect rather than sampling error are presented in Table 4.

Table 4: Test of heterogeneity

Test of Heterogeneity				
Q			I^2	τ^2
Est.	df	p-value		
158.33	50	0.000	64.8	0.538

The results from the individual studies are not consistent. To assess this issue the test of heterogeneity (Q) can be used. It determines if differences between individual study results could have occurred due to chance or if the differences between individual study results are quite different and could not have occurred due to chance. A test of the null hypothesis $H_0 : \theta_1 = ... \theta_k = \theta$ versus the alternative $H_1 :$ *at* least one θ_i different has Q = 158.33 (p-value = 0.000) implying that we reject the null hypothesis and conclude study means arose from two or more distinct populations. Thus, the variability across effect sizes does exceed what would be expected based on sampling error. However, it is often more helpful to quantify heterogeneity than to test it [8].

The I^2, which quantifies the percentage of variation due to real difference is 69.82% far from zero and closer to 100 meaning substantial heterogeneity. Which means almost 70% of the observed variation in effect size across the studies in the meta-analysis is due to real difference in effect size between them. Since the I^2 is large it is vital to study the factors which accounts for such variation

So far we have estimated the summary effect from the studies. Based on the methods for dealing with heterogeneity plus common sense we can say that the random effect model is more appropriate. In the presence of substantial heterogeneity [8] suggest that focus shifts from the summary effect to the dispersion by itself. But before assessing the factors which might explain this variability we need first to assess the impact of publication bias.

7.2.3 Publication bias

7.2.3.1 Graphical Methods

Publication bias is a widespread problem that may seriously distort attempts to estimate the effect under investigation. If publication bias is present but went undetected, the estimated overall effect will likely be too large, due to the missing small effects, and the researchers may be overly confident. Thus it is important to study it properly. The assessment of publication bias is relatively crude and includes both visual and statistical tests.

The most commonly used method to detect publication bias is the funnel plot. Larger studies appear toward the top of the graph, and tend to cluster near the common effect size. Smaller studies in contrast appear towards the bottom of the graph, and are widely dispersed. In the absence of publication bias, a plot of effect size measure (odds ratio) versus measure of variation should produce a funnel shape. Two modes of the plots was used, one which plots the effect size against the standard error and another which plots the effect measure against the precision both in the fixed and random effect models. The graph's seems to show relatively a wide dispersion to the left of the common effect measure than to the right implying the presence of publication bias (Figure 4). However, it should be noted that since the graphical methods are subjective to interpretation formal statistical tests are advised. The vertical line in the plots indicates the summary effect size, and the guidelines for the 95% confidence interval.

Figure 4: (a) Fixed effect model (b) Random effects model

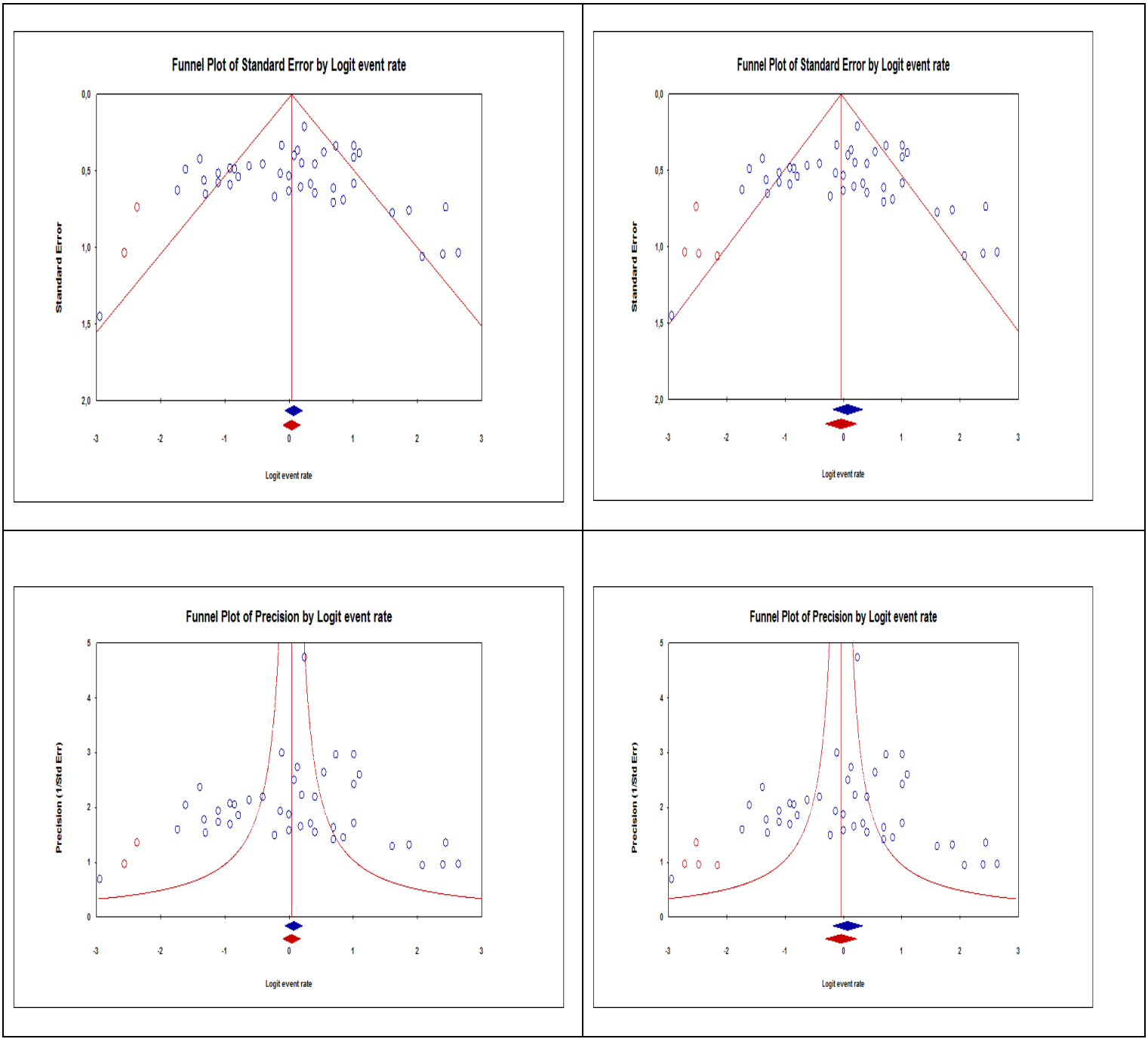


Figure 4: Fill and trim funnel plot with observed and imputed studies

Figure 4 presents the funnel plot of fixed effect and random effects models: funnel plots of logOR against standard error (top) and funnel plot of logOR against precision (bottom). Figure 4 showed also the estimates of the observed studies (blue open circles) and imputed once (red open circles) by the trim and fill method to attain symmetry of the funnel. Under the fixed effect model two studies were imputed and under the random effect model four studies were imputed. The adjusted summary effect size is presented in table 5 below.

7.2.3.2 Statistical Tests

This section presents the results from the various statistical tests. For the rank correlation test, Kendall's tau is 0.137 (p-value = 0.160) which is different from zero suggesting there is indeed a non significant correlation suggesting the absence of publication bias. For the Egger's test, the intercept is 0.134 with a 95% confidence interval [-1.432, 1.670] and p-value = 0.864. Since the 95% confidence interval includes zero there is no statistical evidence of publication bias. It is worth mentioning that these tests have generally low power and the absence of a significant correlation or regression cannot be taken as an evidence of funnel plot symmetry. Moreover, these tests look if there is evidence of bias rather than trying to quantify the degree of bias and its impact on the final summary effect. Such issue can be addressed via the trim and fill method.

The trim and fill method of accounting publication bias first determines the number of studies to be trimmed to make the funnel plot of the standardized effect against the standard error symmetrical. A search to the left of the summary effect size under the fixed effect model identified that two studies need to be trimmed for the funnel plot to be symmetrical. A similar search under the random effects model on the other hand identified four studies need to be trimmed to attain symmetry of the funnel plot. Figure 4 re-display the funnel plot taking into account the Trim and Fill adjustment for fixed effect and random effects models. The observed studies are shown as white open circles and the observed summary effect are shown as open diamond. The imputed studies are shown as red open circles along with a red filled diamond for the adjusted summary effect. Figure 4 showed that the adjusted effect size estimate is fairly close to the original indicating the lack of severe effect of publication bias.

Table 5: Trim and Fill for Fixed effect and Random effects models

Model	Trimmed		Est.	CI	Q
Fixed	2	Observed	0.0719	[-0.0640, 0.2078]	158.33
		Adjusted	0.0390	[-0.0961, 0.1739]	175.50
Random	4	Observed	0.0724	[-0.1816, 0.3265]	158.33
		Adjusted	-0.0413	[-0.3056, 0.2230]	187.71

When the analysis is redone adding two and four studies in opposite sign, but with equal weight to the studies identified as causing asymmetry, the new summary effect reduced from 0.0719 to 0.039 for the fixed effect and from 0.0719 to -0.0413 for the random effect model respectively, but the conclusion remains the same (Table 5).

7.2.4 Meta-regression

In order to have a valid model, variables to be included in the model for statistical analysis have to be appropriate and moderate in number. Thus, variable reduction process was performed by fitting univariate random effects regression for each covariate and variables with p-value < 0.25 were kept for further analysis. Only the variables *Dose* (*p*-value = 0.001) was significant. The amount of between study variability accounted for by the covariates (Adjusted R^2), the I^2 and τ^2 were also considered. The variables *Age, Split* and *Tstart* were included on biological ground. Finally a saturated model including the main the effects and their pair-wise interaction was run and using a manual backward selection method variables with a p-value < 0.05 were retained for further statistical analysis. The variables *Dose*, *Age*, *Tstart* and the interaction term, $(Age*Tstart)*10^{-3}$ were significant. The final model is given by:

$$\text{Logit(EIC)} = \beta_0+\beta_1*\ln(\text{dose})+\beta_2*\text{age}+\beta_3*\text{tstart}+\beta_4(*\text{age}*\text{tstart})*10^{-3} \qquad (12)$$

Fitting the model leads to the results presented in Table 6. It can be observed from Table 6 that all the covariates have significant effect on the probability of Excellent Intubation Condition (EIC) for both

models. The magnitude of parameter estimates for the two models are similar but the confidence intervals for the random effect model are wider than fixed effect model.

Table 6: Parameter estimates of fixed effect and random effects Meta-Regression Models

	Fixed Effect		Random Effects	
Covariate	Estimate(se)	CI	Estimate(se)	CI
Intercept	-5.014(1.550)*	[-8.052, -1.976]	-4.544(2.598)	[-9.809, 0.721]
Dose	1.145(0.211)*	[0. 731 , 1.558]	1.255(0.306)*	[0.636, 1.875]
Age	0.182(0.039)*	[0. 106, 0 .257]	0.177(0.067)*	[0.0413, 0.313]
Tstart	0.056(0.011)*	[0.034, 0.078]	0.054(0.018)*	[0.0170, 0.091]
Age*Tstart	-1.460(0.280)*	[-2.009, -0.911]	-1.444(0.475)*	[-2.407, -0.482]
Adjusted R^2	36.75%		49.63%	
$I_{res}^{\ 2}$			55.82%	
τ^2			0.322	

*significant variable

The fixed effect meta-regression model assumes that all the heterogeneity is captured by the covariates. On the other hand, the random effect meta-regression model allows and captures between study variance not explained by the covariates by estimating, $\hat{\tau}^2$.

For the fixed effect meta-regression model the estimated log-odds ratio at the mean values of *Dose* is 1.145 with standard error 0.211. The 95% confidence interval is [-2.196, -0.886]. On the other hand for the random effect model the parameter estimate of *Dose* is 1.255 with standard error 0.305 and corresponding confidence interval [0.636, 1.875] showing Dose have a significant effect on the probability of Excellent Intubation Condition. The parameter estimates of the main effect of *Age* and *Tstart* are significant however the main effects cannot be interpreted since the effect of one variable depends on the level of the other variable due the significant interaction term.

Fixed-effects meta-regression is not usually recommended, however, because it assumes that all the heterogeneity can be explained by the covariates, and it leads to excessive type I errors when there is residual, or unexplained, heterogeneity.

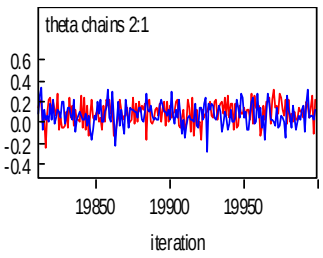
The proportion of between study variance explained by the covariate can be calculated by comparing the estimated between study variance with its value when no covariates are fit. The adjusted R^2 is the relative reduction in the between study variance and it is possible to be negative if the covariates explain less of the heterogeneity than would be expected by chance. The variables *Dose,Age,Tstart* and *Age*Tstart* explain 49.63% of the between study variance and the remaining between study variance appears at 0.322 which is a reduction of almost 40.18% as compared with random effects meta-analysis of 0.5383, the model without covariate.

The I_{res}^2 in the meta-regression is also an extension of the similar index from the random effects meta-analysis suggesting that around 55.82% of the residual variation is due to heterogeneity and the remaining 44.18% is attributable to the within study sampling variability.

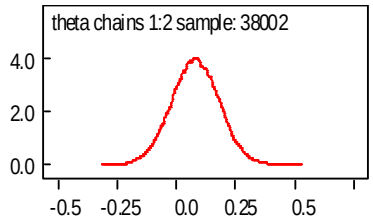
7.2.5 Bayesian Meta-analysis

To answer the scientific question, the following program way adopted in WinBUGS. Gibbs sampler using two chains with appropriate initial values was employed with a total run of 25,000 iterations. Convergence was attained around 20,000 iterations with the thinning of 5, to minimize the autocorrelation. Trace, Autocorrelation, Brooks, Gelman Rubin Statistics (BGR) plots were used to evaluate the mixing and convergence of sampling respectively (Figure 5).

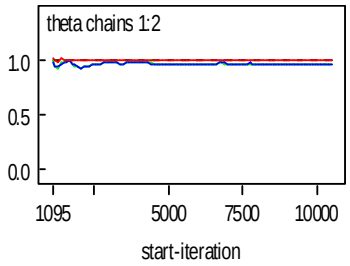
As shown in Figure 5 (a)-(e), the trace and autocorrelation plots indicates, the two chains seem to mixing well. Hence the convergence criterion seems satisfied. In addition to these, the BGR plot for checking convergence indicate that, the convergence criteria is attained, since the BGR statistic convergence to 1, this is due to the fact that the between and within variability are almost equal. The convergence criterion is also supported by the history plot.



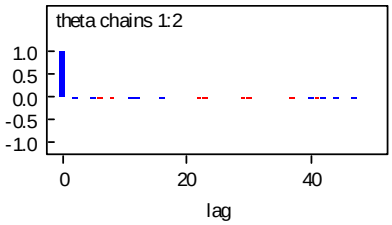
(a) Trace plot of theta



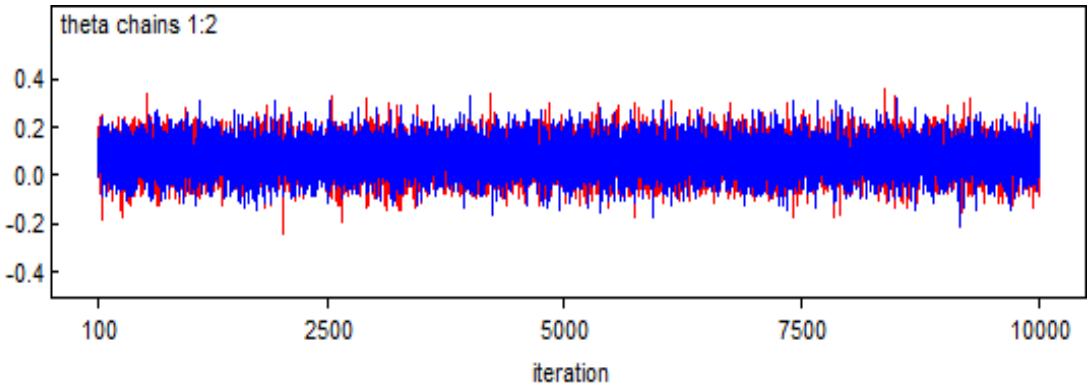
(b) Density plot theta



(c) BGR plot of theta



(d) Autocorrelation plot of theta



(e) History plot of theta

* theta refers to the estimated common effect size

Figure 5: Fixed effect models: (a) Trace (b) density (c) BGR (d) Autocorrelation and (e) history plots

Moreover, diagnostics test using Geweke from CODA was performed. The points lie within the two standard deviation suggesting convergence is satisfied (Figure 6).

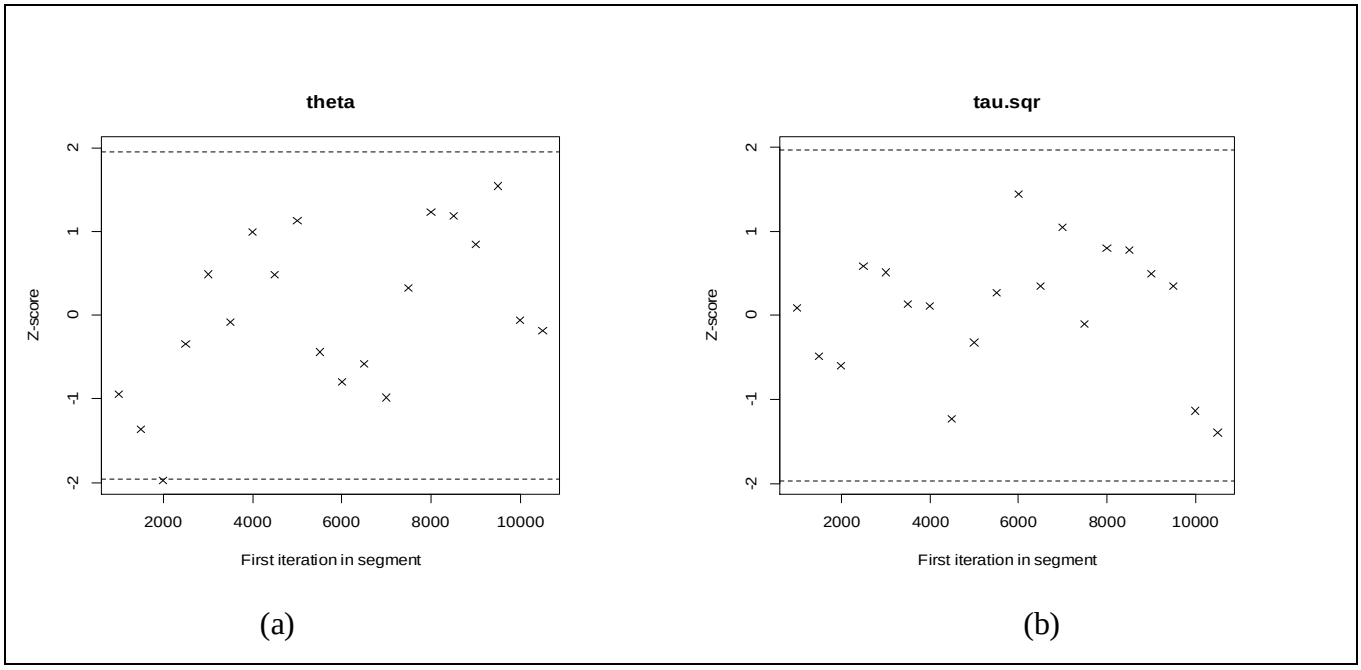


Figure 6: Bayesian Random effect meta-analysis Geweke diagnostics plot: (a) Common effect size
(b) Between study variability

After convergence an additional 10,000 iterations was run to obtain the posterior summary statistics. For comparison purpose Table 7 summarizes the results for both the Frequentist and Bayesian meta-analysis.

Table 7: Frequentist and Bayesian meta-analysis estimates

	Frequentist Approach			Bayesian Approach		
Model	Estimate	Std.	CI	Estimate	Std.	CI
Fixed effect	0.0729	0.0693	[-0.0640, 0.2078]	0.0800	0.102	[-0.12260.2774]
Random effect	0.0724	0.1296	[-0.1816, 0.3264]	0.0889	0.142	-0.1837 0.3706
τ^2	0.538	0.0121		0.4648	0.2535	0.0904 1.084

The log-odds ratio estimate for the Bayesian fixed effect model is 0.080 with standard error 0.102. The 95% credible interval is [-0.1226, 0.2774] implying no significant effect of Mivacurium. For the Bayesian random effects model on the other hand the log-odds estimate is 0.0889 with standard error

0.142 and credible interval [-0.1837, 0.3706]. The interval includes the nul value 0 suggesting no effect of Mivacurium.

Comparing the results of Bayesian fixed effect model with the frequentist fixed effect model, both the point estimate of effect size measure and the corresponding standard error for the Bayesian approach are bigger than the corresponding frequentist approach for both (Table 7).

τ^2, a measure of the between study variability for the Bayesian approach (0.4648) is smaller than the frequentist approach (τ^2=0.538). However, the standard error for the Bayesian approach is bigger than the corresponding classical approach. This could be due to the fact that the Bayesian statistics treats τ^2 as random variable and takes into account the uncertainty in estimation unlike the frequentist approach where it is assumed to be unknown constant.

Table 8: Bayesian effect size estimate by model

Model	Mean	Std.	MC error	Median	CI		DIC	Start	Sample
Fixed	0.0800	0.102	5.467E-4	0.07156	-0.1226	0.2774	162.368	20000	300002
Random	0.0889	0.142	0.001086	0.07905	-0.1837	0.3706	147.346	20000	300002

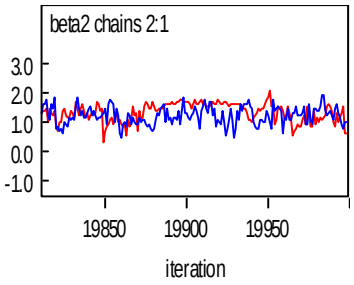
The summary statistics of the estimated posterior distributions, including marginal means, medians, standard deviations and 95% credible intervals are presented in Table 8. The MC error is smaller than the standard error for the two models showing good precision (Table 8). The DIC of the fixed effect and random effects models are 162.368 and 147.346 respectively. Thus, the random effect model fits better to the data.

7.2 6 Bayesian Meta-regression

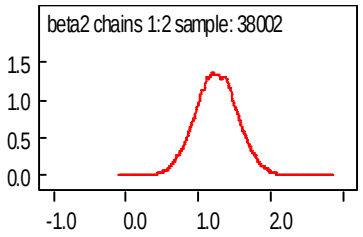
For the Bayesian meta-regression a model with the same covariates as for the classical or the frequentist approach way run in WinBUGS. Gibbs sampler using two chains with a total 30,000 iteration was performed. The convergence of the model was assessed, and convergence was attained at 20,000 iterations. The history plots of the variables looks like a random noise, the sampled values are bouncing randomly around a common mean value which is an indication of convergence. The kernel

density plots are also smooth. The autocorrelation plots show presence of low correlation of the subsequent values in the chain as a function of the lag. The lower the autocorrelation the faster the posterior distribution of the parameter is explored. This suggests that the posterior distribution of the parameter is explored quickly (Figure 7).

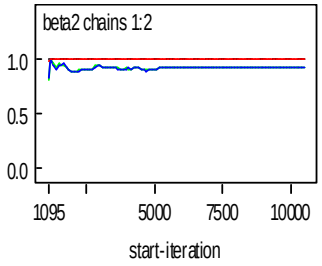
The BGR diagnostic in WinBUGS examines the widths of the 80% equal-tailed intervals of the pooled sample, and each individual sample. The average width of the individual samples (blue curve) should approach the width from the pooled sample (green curve), thus the ratio (red curve) should approach 1 as an indication of convergence. This is true for all the variables considered in the model suggesting convergence is satisfied (Figure 7). Figure 7 presents the diagnostic plots for the variables *Dose* and *Age*Tstart* for the random effects meta-regression model. The corresponding plots for the remaining variables and for fixed effect model support convergence.



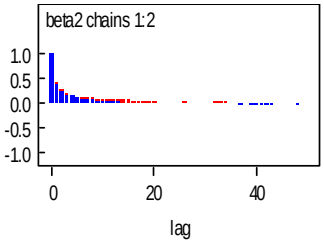
(a) Trace plot of Dose



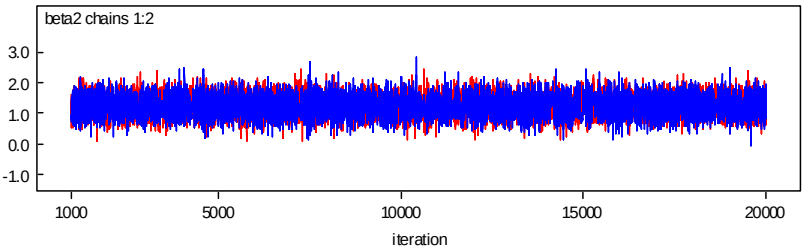
(b) Density plot of Dose



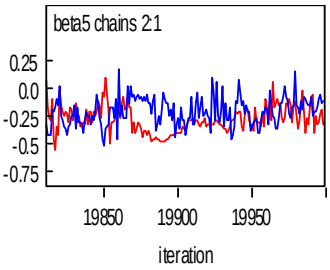
(c) GBR plot of Dose



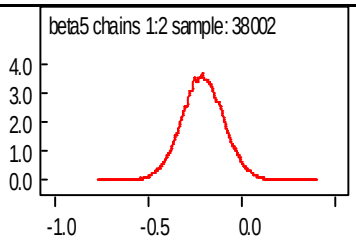
(d) Autocorrelation plot of Dose



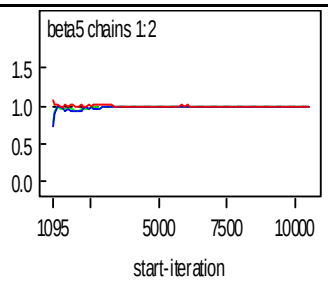
(e) History plot of Dose



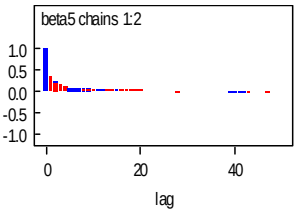
(a)History plot of Age*Tstart



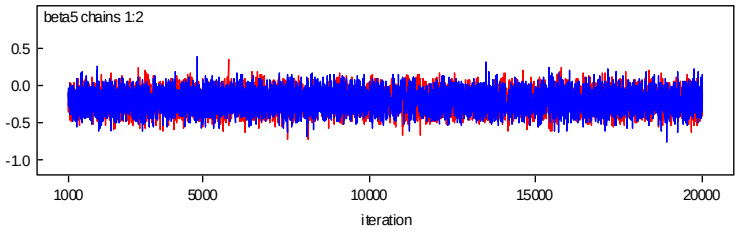
(b) Density plot of Age*Tstart



(c) GBR plot of Age*Tstart



(d)Autocorrelation plot Age*Tstart



(e) History plot of Age*Tstart

Figure 7: Diagnostics plots of Dose and Age*Tstart

Moreover, diagnostics test using Geweke from CODA was performed. The points lie within the two standard deviation suggesting convergence is satisfied (Figure 8). The Geweke diagnostics plots for the remaining covariates and for the fixed effect meta-regression model also support convergence.

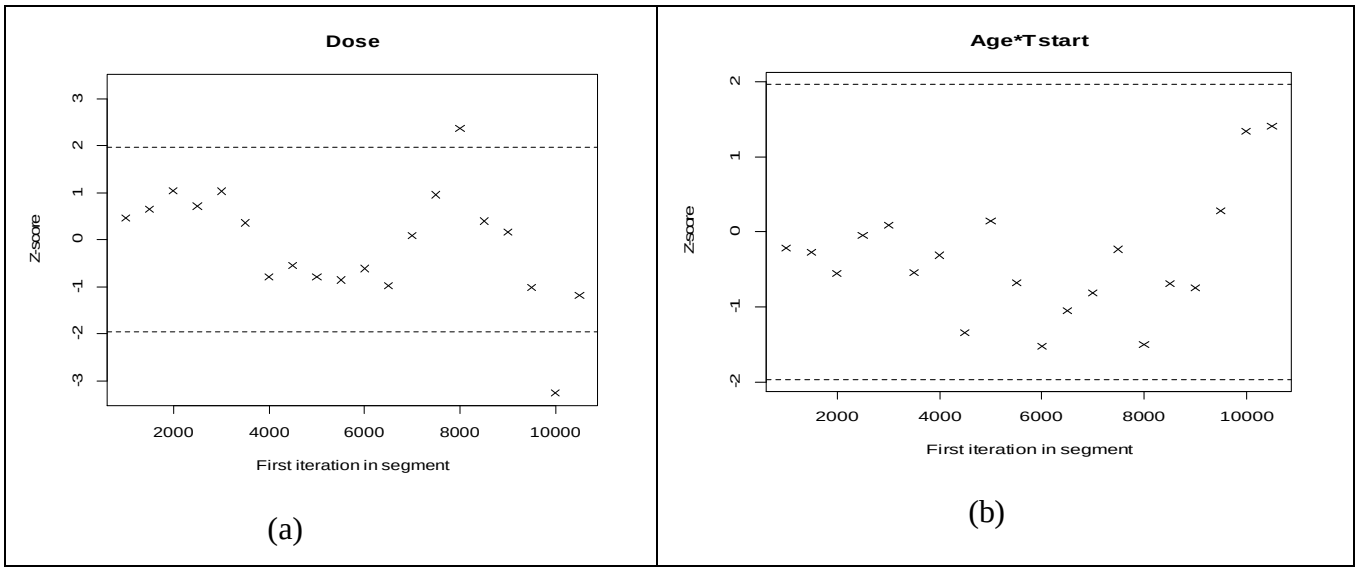


Figure 8: Bayesian Random effect meta-regression Geweke diagnostics plot: (a) dose (b) Age*Tstart

After convergence is achieved the sampler was run for additional 20,000 iterations. The summary statistics of the estimated posterior distribution, including marginal means, medians, standard deviations, MC error,95% credible intervals and the DIC for each parameter for fixed effect and random effects meta-regression models are presented in Table 9.

Table 9: Posterior summary estimates of fixed effect and random effects meta-regression models

	Fixed effect meta-regression model				Random effects meta-regression model			
Variable	Mean	Std.	MC error	95% CI	Mean	Std.	MC error	95% CI
Intercept	2.063	0.544	0.004	[0.974, 3.104]	2.106	0.623	0.005	[0.884, 3.361]
Dose	1.229	0.256	0.002	[0.736, 1.730]	1.248	0.290	0.002	[0.677, 1.827]
Age	0.008	0.006	5.4E-5	[-0.006, 0.022]	0.008	0.008	6.4E-5	[-0.009, 0.008]
Tstart	0.005	0.003	3.6E-5	[-0.003, 0.014]	0.006	0.005	3.6E-5	[-0.04, 0.006]
Age*Tstart	-2.209	0.099	7.7E-4	[-0.405, -0.015]	-0.209	0.113	8.1E-4	[-0.43, 0.015]
τ^2					0.186	0.151	0.004	[0.001, 0.633]
DIC	147.07				140.10			

Monte Carlo error (MC error) was used to check the precision of the parameter estimates of the models. Since the MC errors are less than 5% of their corresponding standard error, it seems that the parameters are estimated with high precision. The results from the fixed effect model show that *Dose* and *Age*Tstart* have significant effect on the probability of Excellent Intubation Condition. However, for the random effects model only *Dose* has a significant effect since the credible interval did not include zero (Table 9). The DIC for the random effects meta-regression model 140.10 is smaller than the DIC for the fixed effect model 147.07. This shows that the random effect model fits the data better than fixed effect model. The between study variability estimate for Bayesian meta-analysis was 0.465 and the corresponding estimate for the Bayesian meta-regression 0.186. This shows the covariates explain almost 60% of the variability.

Eventually, the sensitivity of the results on the choice of prior distribution was examined by changing the prior distribution of the between study variability parameter from inverse gamma distribution, IG(0.001,0.001) into IG(0.01,01). The results after checking convergence are presented in Table 10.

Table 10: Sensitivity analysis posterior summary estimates

Variable	Mean(median)	Std.	MC error	95% CI
Intercept	2.116(2.110)	0.656	0.004	[0.848, 3.399]
Dose	1.251(1.251)	0.299	0.002	[0.668, 1.841]
Age	0.008(0.008)	0.008	4.4E-5	[-0.009, 0.025]
Tstart	0.006(0.006)	0.005	2.6E-4	[-0.005, 0.014]
Age*Tstart	-2.208(-0.208)	0.116	6.3E-4	[-0.435, 0.019]
τ^2	0.222(0.185)	0.178	0.003	[0.011, 0.661]
DIC	143.23			

It can be observed from Table 10 that the DIC of the model for the IG(0.01, 0.01) 140.10 is higher than the 140.10 DIC for IG(0.001,0.001). The point estimates and standard error for *Age*, *Tstart* remains unchanged, and for *Dose* and *Age*Tstart* are slightly higher for the first. The between study variability is also higher for IG(0.01,0.01). However, changing the prior does not affect the conclusion.

Finally, comparison of fixed effect and random effects regression models from the frequentist and Bayesian approaches showed that the random effects meta-regressions have better. Table 11 summarizes the results for both approaches.

Table 11: Comparison of frequentist and Bayesian meta-regression models

	Frequentist random effect meta-regression			Bayesian random effects meta-regression			
Variable	Estimate	Std.	95% CI	Mean(median)	Std.	MC error	95% CI
Intercept	-4.544	2.598	[-9.809, 0.721]	2.106(2.09)	0.623	0.005	[0.884, 3.361]*
Dose	1.255	0.306	[0.636, 1.875]*	1.248(1.248)	0.290	0.002	[0.677, 1.827]*
Age	0.177	0.067	[0.0413, 0.313]*	0.008(0.008)	0.008	6.4E-5	[-0.009,0.008]
Tstart	0.054	0.018	[0.017, 0.091]*	0.006(0.006)	0.005	3.6E-5	[-0.04, 0.006]
Age*Tstart	-1.444	0.475	[-2.407, -0.482]*	-0.209(-0.210)	0.113	8.1E-4	[-0.43, 0.015]
τ^2	0.332	0.121		0.186(0.118)	0.151	0.004	[0.001, 0.633]

*significant variable

It can be observed from Table 11 that the standard error and the corresponding intervals are wider for the frequentist approach. The between study variability estimate is almost twice for the frequentist approach than the Bayesian approach. For the Bayesian approach only *Dose* has significant effect on

the probability of excellent intubation condition. Conversely all variabiles have significant effect under the frequentist approach.

The 95% credible interval (CI) is an indication of the probability that the true parameter value lies. For example the 95% credible interval for the covariates *Dose* and *Age*Tstart* are [0.677, 1.827] and [-0.43, 0.015] suggesting their respective true parameter estimate will fall within that interval with 0.95 probability respectively. Unlike for the frequentist confidence interval where the probability that the true parameter estimate will fall within that interval is either 0 or 1.

8 Discussion, Conclusion and Recommendation

Intubation refers generally to inserting a flexible tube anywhere in the human body, but most people use it specifically to refer to tracheal intubation, which involves putting a down into someone's trachea to secure his or her airway. Intubation is often used in emergency medicine when a patient is having difficulty breathing, and it is also used during surgery to keep the airway open for the delivery of anesthetic drugs and oxygen [1]. The main objective of the paper is to identify the factors that affect the Excellent Intubation Conditions (EIC) of Mivacurium, a non-depolarizing relaxant drug, applying meta-analysis techniques. Meta-analysis is defined as the process or technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies. The basic purpose of meta-analysis is to provide the same methodological rigor to a literature review that we require from experimental research. To address the research question data from 1029 patients from 51 randomized clinical trial studies was analyzed. All studies included in this review reported the score of intubation condition of mivacurium as a main outcome. The measured outcomes were scores reflecting excellent intubation condition. MEDLINE, EMBASE, SCOPUS, Web of Science and the Cochrane Controlled Trials Register using the combination of free text terms, succinylcholine, suxamethonium, intubation conditions and adults was used as a primary search engine to locate studies, and electronic search without language restriction was performed from 1987 until April 2012.

To identify the factors that affect the binary outcome variable, *Excellent Intubation Condition* (EIC) a set of potential quantitative and qualitative predictor variables were considered. Both descriptive

statistics and graphical representation were employed. Results from the exploratory data analysis revealed that the minimum and maximum average *Age* of patients included were 23 and 74 years respectively. The *Dose* level ranges from 0.075 mg/kg to 0.30 mg/kg with 13 distinct dose groups. To study the dependence of EIC on *Dose* a bubble plot was used. The diagram seems to show a positive relationship. Furthermore, in 70% of the studies the full dose of mivacurium was administered by splitting at two stages, and in the remaining 30% the full dose of the drug was given at once. In 96 % of the studies patients without serious illnesses were recruited. The minimum and maximum size of the studies was 9 and 91 patients respectively showing a wider dispersion in study sizes but around 82% of the studies have on average less than 30 patients and the rest around 18% studies have on average more than 30 patients. The meta-analysis relatively included many small studies. To confirm all these initial observations, proper testing, using appropriate statistical methods was adopted.

One goal of meta-analysis is to estimate the overall or combined effect size. To do this fixed effect and random effects models can be used. The two models in the context of classical and Bayesian approaches were fitted to the mivacurium data set, and their results were compared.

Results from the classical meta-analysis approach showed that the estimated overall summary effect, odds ratio, is 1.075 for both models. However, the 95% confidence interval for fixed effect model [0.938, 1.231] is wider than random effects model 95% confidence interval [0.834, 1.386]. This is due to the extra between study variability parameter estimated under the random effects model. For both models the interval contains the null value 1 implying we fail to reject the null-hypothesis, and conclude that there is no significant effect of mivacurium on the probability of EIC. The between study variability was 0.538.

The posterior summary effect size, odds ratio, for the Bayesian fixed effect model is 1.083 with standard error 0.102. The 95% credible interval [-0.1226, 0.277] suggesting the lack of effect of mivacurium on the EIC. On the other hand the odds ratio for the random effect model is 1.093 with standard error 0.142 and 95% credible interval [-1.837, 0.3706] showing on average there is no significant effect of mivacurium on EIC. Again standard error and their corresponding credible interval are wider for the random effect model than fixed effect model due to the extra between study variability. The estimated between study variability was 0.4648.

Comparing the classical random effects with their corresponding Bayesian random effects model showed that standard errors from the classical random effects model are smaller than the Bayesian model. This is due to the fact that in the later full allowance is being made for uncertainty in the estimation unlike in the former where parameters are assumed to be unknown constants.

Graphical and statistical methods were used to assess heterogeneity. Forest plot was used to study how the effect sizes behave in light of the other studies. Results showed that 30 studies did not produce statistically significant effect of mivacurium on the EIC. In contrast 21 studies showed effect of mivacurium. To study this conflicting result a formal test of heterogeneity using Cochran's Q statistic was performed. A test of the null hypothesis of common effect size versus the alternative hypothesis of at least one is different has Q= 158.33 (p-value = 0.000) implying that study means arose from two or more populations i.e. the variability in the effect size exceeds what would be expected based on sampling error. It is worth mentioning however that this test statistic has low power and it is not recommended as a base to decide between fixed effect or random effects models. It is more useful to quantify heterogeneity that to test for it [18]. The I^2 which quantifies the percentage of variation due to real difference is 69.82, an indication of substantial heterogeneity. Which means 69.82% of the observed variation in effect size between the studies included in the meta-analysis is due to real difference in effect size between them, and the remaining around 30.18% is due to sampling error. Results from the radial plot also confirm heterogeneity.

Meta-analysis results are subject to publication bias, and if went undetected the estimated overall summary effect will likely be too large. Graphical assessment of publication bias was carried out using funnel plot. A plot of the effect size estimate against standard error, and precision for both fixed effect and random effects models showed relatively wide dispersion to the left of the summary effect than to the right suggesting the presence of bias. Trim and fill method showed the need for two and four studies to be imputed to attain symmetry of the funnel plot for the fixed effect and random effects models, respectively. When the analysis is redone adding two and four studies in opposite sign, but with equal weight to the studies identified as causing asymmetry, the new summary effect reduced from 0.0719 to 0.039 for the fixed effect and from 0.0719 to 0.0413 for the random effect model respectively, but the conclusion remains the same. Visual inspection of funnel plot asymmetry is

subjective and hence it is recommended to use statistical tests. Funnel plots have low power since asymmetry in funnel plot is not necessarily due to publication bias. Test of funnel plot asymmetry using Begg and Mazumdar's rank correlation has a Kendall's tau 0.137 (p-value = 0.16) implying the absence of publication bias. For Eggers's test, the intercept is 0.134 with a 95% confidence interval [-1.432, 1.670]. Since the interval includes zero there is no statistical evidence of publication bias. However, it is worth mention that these tests have generally low power and absence of significant effect cannot be taken as a proof of funnel plot symmetry.

Results from the heterogeneity part indicated the presence of substantial heterogeneity and in the presence of heterogeneity attention is shifted from the overall effect size to the sources of heterogeneity. One method to account heterogeneity is to use meta-regression. Fixed effect and random effects meta-regression models extends the classical fixed effect and random effects meta-analysis models by incorporating study level covariates. Both models were fitted to investigate whether patient characteristics or methodological issues can explain any of the heterogeneity present in the probability of EIC.

For the classical fixed effect and random effects meta-regression models the covariates *Dose*, *Age*, *Tstart* and *Age*Tstart* interaction term were the variables that significantly affect the probability of excellent intubation condition. *Dose* has a positive association with excellent intubation condition. Parameter estimates measure the change in the effect size estimate for a unit change in the covariate keeping all other covariates constant. For example one unit increase in *Dose* is associated with 3.142 increase in EIC holding all other covariates constant. The coefficient of *Age*Tstart* is negative indicating negative relationship. The parameter associated with the interaction term indicates that for a unit increase in *Age* and *Tstart*, on average, the odds of excellent intubation condition is 0.232 times than the odds of not excellent intubation condition keeping the other variables constant. For the random effect model similar interpretations can be made although the odds ratios are study specific. Meta-regression is used to investigate the causes of heterogeneity by incorporating study level covariates. Thus comparing the results from meta-analysis, with out covariates, with their corresponding meta-regression models, with covariates, is informative how much of variability has been accounted for by the covariates. The adjusted R^2 for the fixed effect meta-regression is 0.3675

implying the covariates explained 36.75% of the variability in effect size. For the random effect model on the other hand the variables explained 49.63% of the variability, and the between study heterogeneity remains at 0.332 a reduction of 40.18% from 0.5383 for the meta-analysis with out covariates. Moreover, the I^2 which measures the percentage variation due to heterogeneity reduced to 55.82% for the model with covariates from 64.8% for the random effect meta-analysis, a model with out covariates implying that 55.82% of the residual variability is due to heterogeneity and 44.18% of variability is due to within study sampling variability.

When a Bayesian fixed effect meta-regression model was fitted *Dose* and *Age*tstart* were the variables which significantly affect the probability of excellent intubation condition. For the random effect model only *Dose* has a significant effect on the probability of excellent intubation condition. Unlike, for the classical counterpart models where all the covariates showed significant effect. The Bayesian random effect meta-regression between study variability 0.1816 with standard error 0.151 is smaller than the corresponding classical model 0.332 with standard error 0.121. The Bayesian model accounts much variability than the classical approach although this is at the expense of higher variability for the between study estimate. There exists difference in the Bayesian results compared to the classical random-effects. This may be due to, many of the studies were small in size (as shown from the exploratory data analysis) and also in the presence of probabilities close to zero or one, the Bayesian hierarchical model is better than classical random-effects model [22]. For this analysis 51 studies is quite large enough but the small study sizes and observed zero and close to zero event rates might have caused that.

In conclusion, the random effect models are more appropriate to the given data. For the classical meta-regression approach the variables *Dose*, *Age*, *Tstar*t and *Age*Tstart* are the variables which significantly affect the probability of excellent intubation condition. For the Bayesian fixed effect *Dose*, *Age*Tstart* and for the random effects model *Dose* are the variables which significantly affect the probability of excellent intubation condition, respectively. Such difference in the results could be due to the different methodological assumptions underlying the different models or due to the inherent drawbacks of the meta-regression approach by itself.

Clinical interpretation of results

The meta-regression analysis confirms that patient characteristics as well as methodological issues can explain considerable part of heterogeneity between trials. Three main results emerge from the meta-regression analysis of the randomized controlled trials included.

Excellent intubation conditions are not related to gender nor to the mode of administration (injecting the whole dose at once or dividing it in portions). The intubation conditions are affected by the time to intubation (*Tstart*) and by the age of the patient.

First, no gender-related differences in the dose-effect relationship pertaining to the incidence of excellent intubation conditions after mivacurium could be demonstrated. Such a finding is at variance with the results of one study that demonstrated greater sensitivity to and the better intubation conditions after mivacurium in female patients. In that study mivacurium was more potent and faster onsetting in younger women than in younger males. With ageing these gender related differences

tended to disappear [32]. Due to the wide age range and the scatter of the results that can be found in the trials, included in the current meta-regression analysis, gender related differences in the sensitivity towards mivacurium could not be demonstrated.

Second, the time to laryngoscopy and insertion of the airway (*Tstart*) determines the quality of intubation. Increasing the time to intubation (*Tstart*) allows more mivacurium molecules to be transferred to the receptors. More mivacurium molecules at the receptors cause deeper neuromuscular block. Deeper neuromuscular block corresponds to better intubation condition at the time of laryngoscopy and insertion of the airway.

Third, intubation conditions are affected by the *Age* of the patient. With ageing circulatory reserve decreases explaining the delayed onset of mivacurium during anaesthesia induction. Delayed onset of mivacurium can result in incomplete neuromuscular block (NM) block at the time of intubation, accounting for the lower probability of EIC in ageing patients. Therefore, the effect of increasing *Tstart* decreases with increasing age.

The statistical model proposed explains nearly 50% of the variance in EIC. This still leaves 50 % of the variation in EIC unexplained. Consideration must be given to other influences.

First, the ease with which intubation of the trachea can be accomplished, not only depends on the degree of neuromuscular block but also on depth of anaesthesia and the technical proficiency of the intubating clinician. The interplay of the above factors is such that a deficiency in one of them can be compensated for by the remaining factorsi. In none of the trials included depth of anesthesia and intubation skills were graded.

Second, in the studies included, various rating scales were used to assess intubation conditions. Different proportions of EIC have been demonstrated with different scoring systems. Although shown to be of little clinical significance, such discrepancies may highlight limitations of many rating systems. Studies were converted to the Copenhagen Consensus Conference scale [33]. If this had not been directly reported, but sufficient detail was available to do so.

Third, there are characteristics of participants that might vary substantially within studies, but which only can be summarized at the level of the study. An example is age. Consider a collection of trials involving adults from 18 to 60 year old. There may be a strong relationship between age and intervention effect that is apparent within each study. However, if mean ages for trials are similar, then no relationship will be apparent by looking at trial mean ages and trial-level effect estimates. The problem is variously known as aggregation bias or ecological fallacy.

8.1 Limitation of the study and Recommendation

Like any other study our meta-analysis has limitations. Most are related to weaknesses in the original trials. The average methodological quality of these trials was low. For example, a minority only reported an adequate method of allocation concealment or blinding, leaving room for patient selection or observer bias. We do not know whether these trials were correctly performed but poorly reported. Also, the size of most trials was limited. This may partly explain the large variability in event rates. Although, the studies included in the meta-analysis were randomized clinical trials meta-analysis by

itself are observational in nature and thus subject to problems of confounding, bias and too many sources of clinical and methodological heterogeneity. Thus great caution is need in interpretation of the results. We recommend the random effect models since in the presence of substantial heterogeneity, like in this study, fixed effect methods are also subject to high risk of false positive findings. Eventually, we also recommend the use of individual patient data (IPD) meta-analysis for more flexibility

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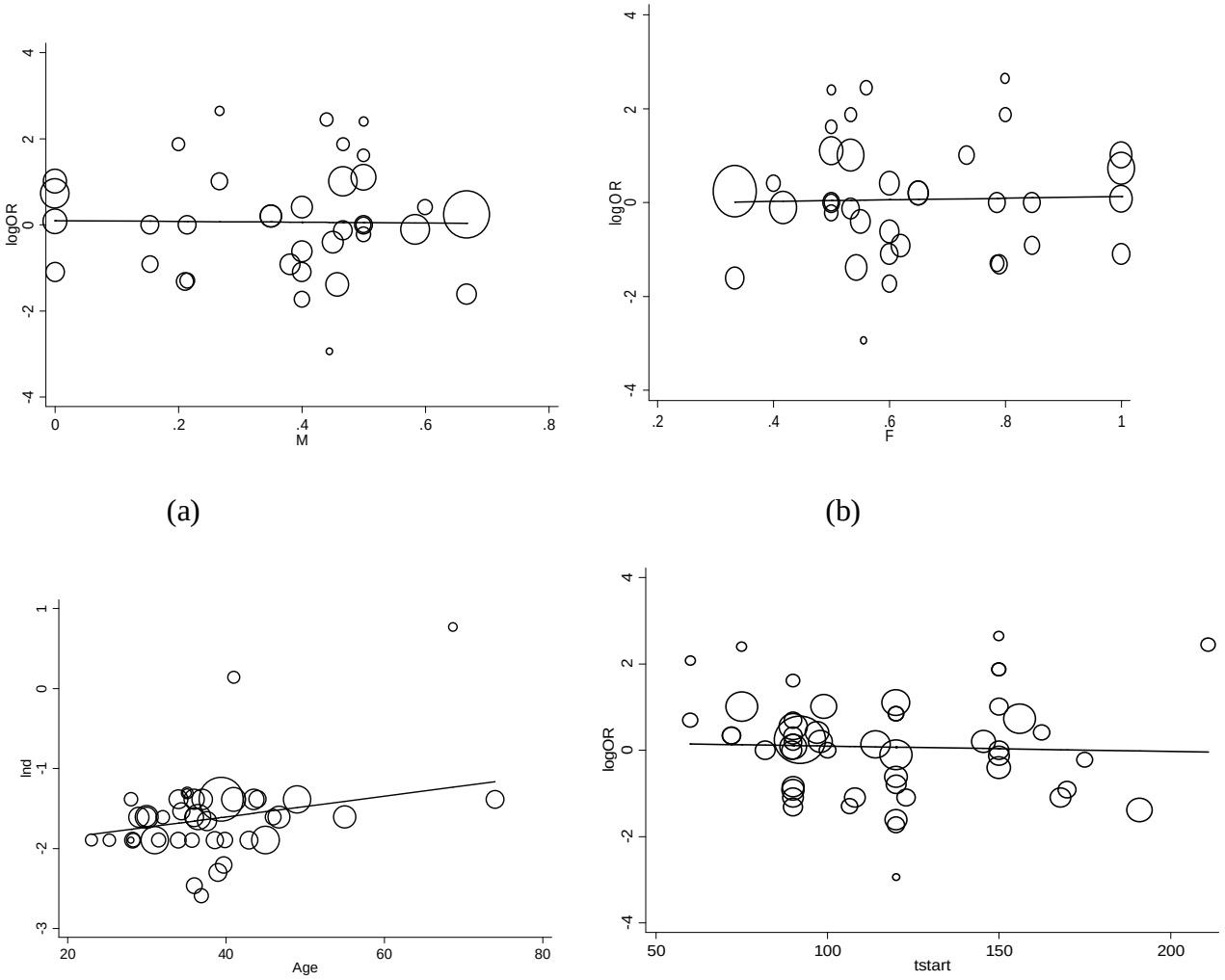
Appendix



(a) (b)

(c) (d)

Figure I: Bubble plot of(a) male (b) female (d) age and lndose (e) tstart with fitted meta-regression line

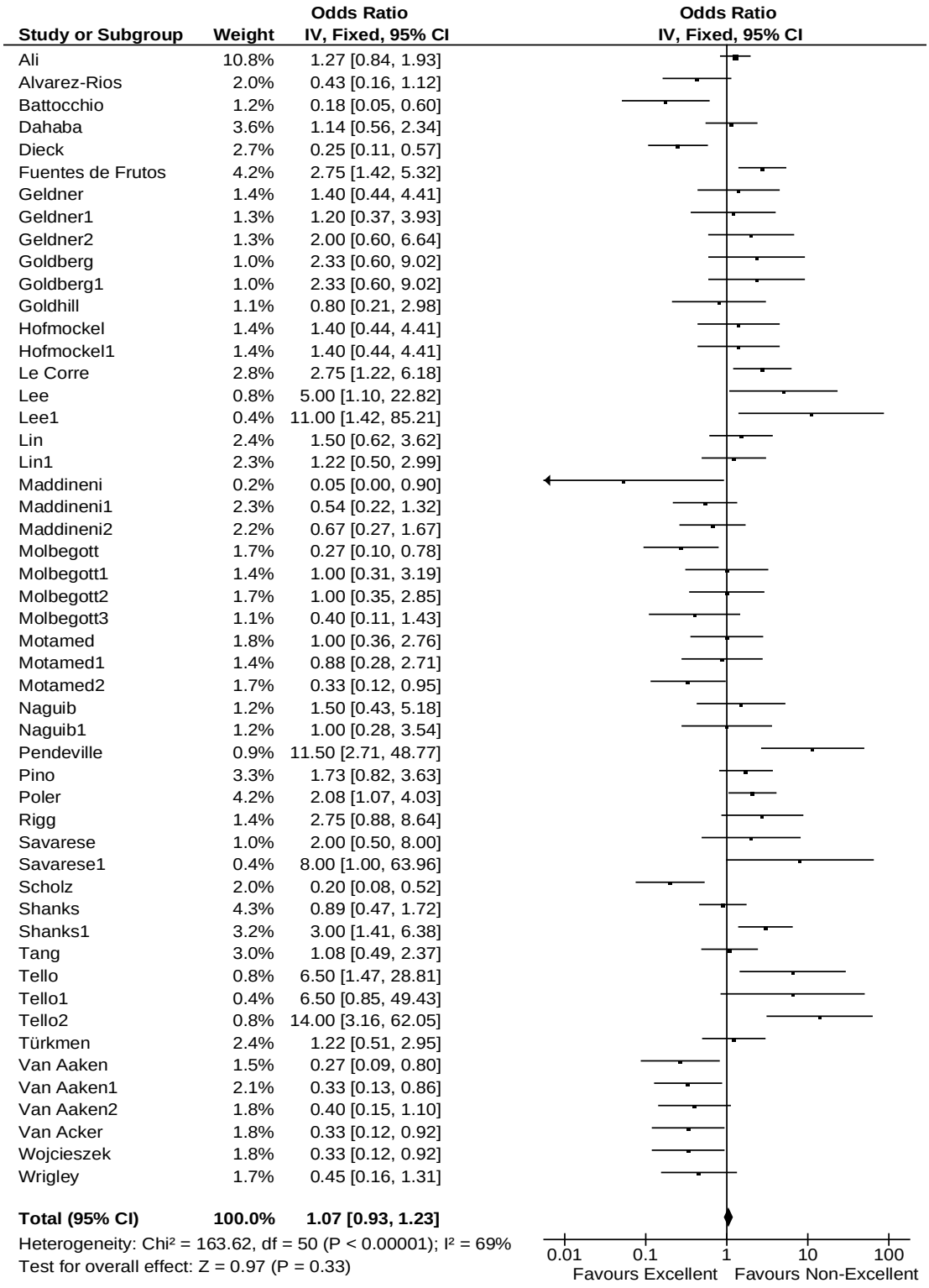


Figure II: Fixed effect model Forest plot

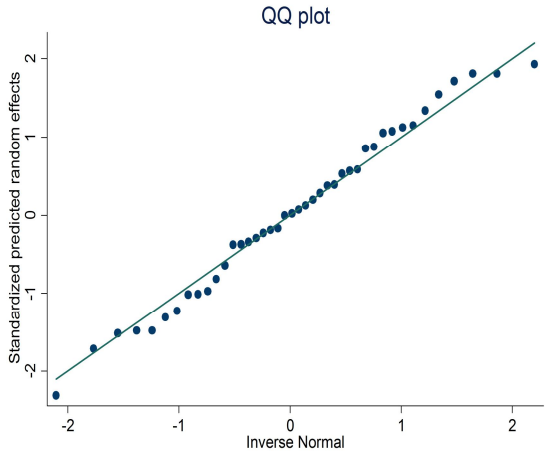


Figure III: Normal probability plot standaridized residuals

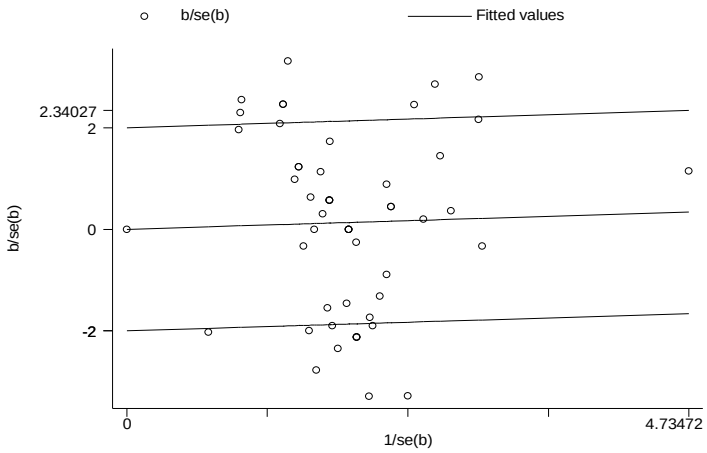


Figure IV Radial plot

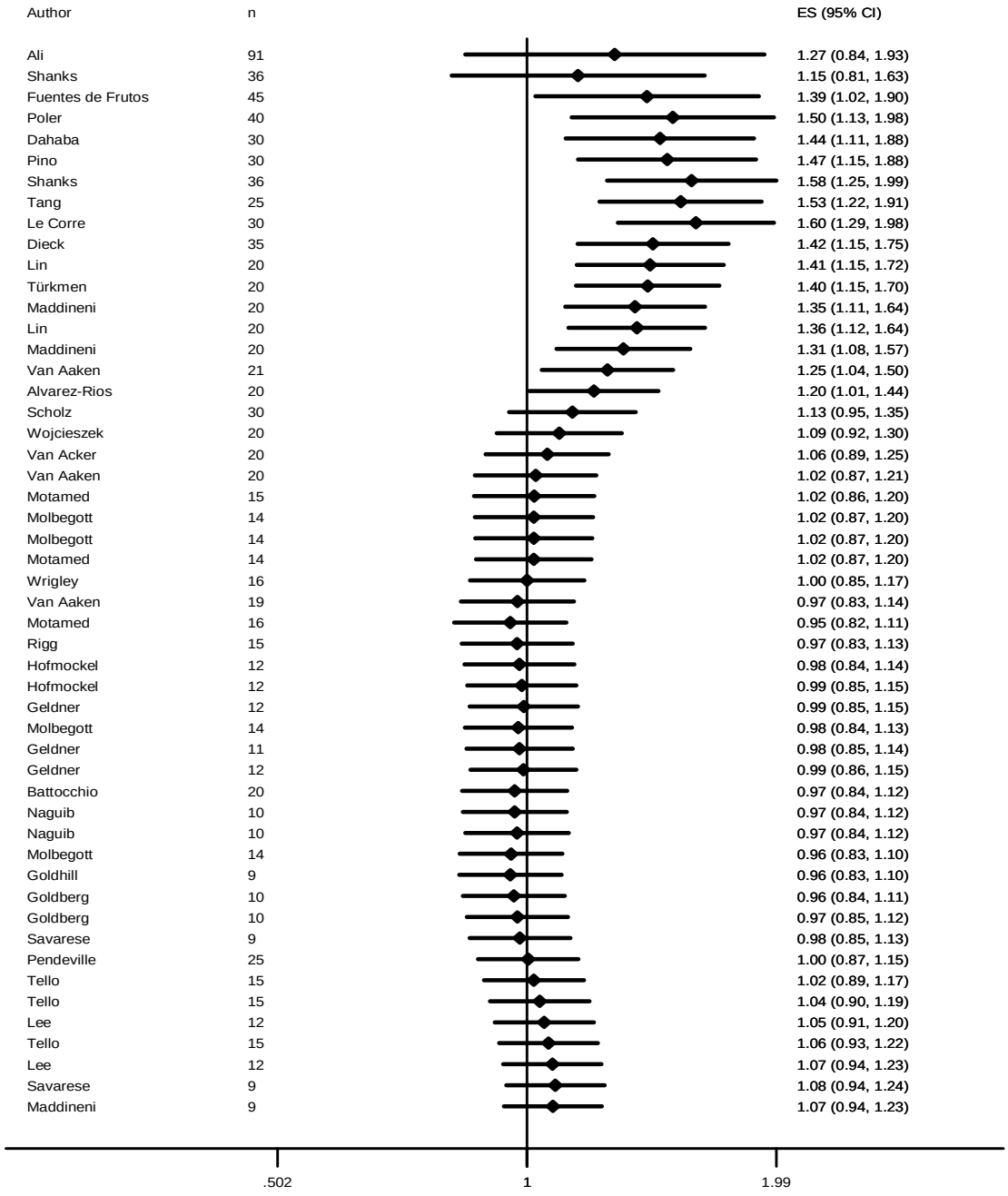


Figure V: cummulative meta analysis plot

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