FACULTY OF SCIENCES
Master of Statistics: Biostatistics

Masterproef
Factors affecting the intubation conditions by succinylcholine. A meta-regression analysis

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

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ABSTRACT

Intubation during surgery is important to keep the airway open for delivery of anaesthetic drugs and oxygen. Succinylcholine and rocuronium are common muscle relaxants which are used during intubation. Knowing the probability of adequate muscle relaxation may help in choosing the appropriate dose of succinylcholine or rocuronium. Given succinylcholine dose and using meta-analysis, considerable between study differences for excellent intubation conditions can be investigated. Using different meta-regression models the objective of this project was to investigate whether patient characteristics or methodological issues can explain any of the heterogeneity in excellent intubation condition between studies.

The results showed that due to study differences, models correcting for extra binomial variability (overdispersion) namely: Beta-binomial and Random-effects model fitted the data better. For both models there was significant overdispersion (extra binomial variability). Succinylcholine dose, study size, age group, and the interaction of age group with dose were the significant covariates affecting excellent intubation condition (EIC) probability in these models. An alternative Bayesian hierarchical model was also fit and the model showed that, true excellent intubation condition probability varies between studies, with succinylcholine dose and study size as potential factors for excellent intubation conditions. In comparison with other studies using rocuronium, succinylcholine was observed to yield higher odds of EIC.

It was concluded that there exists heterogeneity across studies and the cause of this may be the clinical and methodological issues across studies. In particular succinylcholine dose and study size differences were observed as the main potential factors for excellent intubation conditions across the three models. However, it should be noted that due to ecological bias paramount in meta-regression interpretation and inference of results should be done with caution else they can be misleading.

Keywords: Excellent intubation condition (EIC), succinylcholine, Meta- Analysis, Meta-Regression, Beta-binomial model, Random-effects model, Bayesian hierarchical model.

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1. INTRODUCTION

Intubation generally 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 a tube down 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 (Smith, 2003).

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 strengthen the angle between the tongue and the epiglottis. 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, like suffocation and even death if not caught in time. The diagram of an endotracheal which illustrates how the tube is inserted into the trachea is seen in Figure 1.
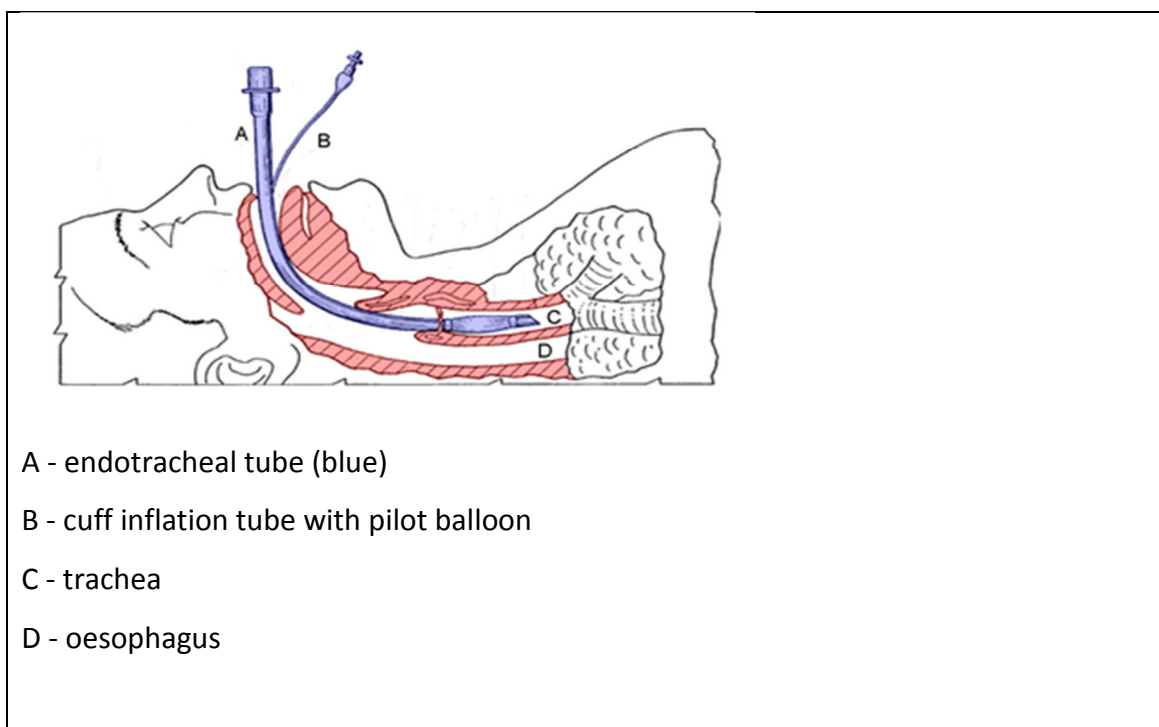
A - endotracheal tube (blue)

B - cuff inflation tube with pilot balloon

C - trachea

D - oesophagus

Figure 1: Illustration diagram of tracheal intubation.

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 in order 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 depolarizing muscle relaxant such as succinylcholine or non-depolarizing blocking agent like rocuronium can be used (Wolters, 2000).

Succinylcholine is a depolarizing muscle relaxant which works by depleting acetylcholine a neurotransmitter that causes voluntary muscles to contract. Depleting Acetylcholine keeps muscles from contracting leading to paralysis of the muscles in the face and those used to breathe and move. Succinylcholine is used as a muscle relaxant to induce anesthesia or when a tube must be inserted in the windpipe or other conditions as determined by your doctor. Its advantage is that it acts rapidly within 60 seconds leading to a quick time to recover from paralysis. All medicines may cause side effects, but many people have no, or minor, side effects of succinylcholine include: Increased production of saliva, muscle pain following surgery, muscle twitching. Severe side effects can also occur and advice is that medical attention is sought right away if any of these severe side effects occur when using succinylcholine. Severe allergic reactions include rash, hives, itching, difficulty breathing, and tightness in the chest and swelling of the mouth, face, lips, or tongue. Other severe effects include chest pain, fainting, fast breathing, fast, slow or irregular heartbeat, high body temperature, increased pressure in the eye, severe or persistent dizziness or headache to mention but a few (Demand media, 1999).

On the other hand rocuronium is also used to relax the muscles. It works by blocking the signals between the nerves and muscles. Rocuronium is given before general anesthesia in preparing you for surgery. Rocuronium helps keeping your body still during surgery. It also relaxes your throat so a breathing tube can be more easily inserted before the surgery (Wolters, 2000). Compared to succinylcholine, rocuronium works for approximately 90 seconds for a patient to recover from paralysis. Some of the serious side effects are signs of an allergic reaction: hives; difficulty breathing; swelling of your face, lips, tongue, or throat on-going muscle weakness or inability to move your muscles. Other less serious side effects include nausea, vomiting, swelling or discomfort where the medicine was injected, feeling sleepy or light-headed or mild itching or skin rash (Cerner Multum, 1996).

Many anaesthesiologists still prefer succinylcholine over rocuronium as a neuromuscular blocking agent during tracheal intubation (Perry et al., 2008) due to its rapid recovery time. Knowing the probability of adequate relaxation may help in choosing the appropriate dose of succinylcholine and in the long run it can be life-saving. Given succinylcholine dose, considerable between study differences in excellent intubation conditions can be found and this can be done by meta-analysis.

Meta-analysis refers to the statistical synthesis of results from a series of studies. According to Borenstein et al., (2009) meta-analysis can be used in different fields of research. For example, in medicine, examine the performance of diagnostic tests and epidemiological associations between exposure and disease prevalence. Pharmaceutical companies also usually conduct a series of studies to assess the efficacy of a drug. These analyses play a role in internal research, in submission to governmental agencies and in marketing. The latter is in line with the objective of this project where assessment is done to check if succinylcholine creates comparable intubation conditions as that of rocuronium during Rapid sequence induction (RSI). 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. There are many ways of doing meta-analysis and for this project meta-regression was the main tool.

Meta-Regression is used to assess the relationship between one or more covariates and a dependent variable. As stated by Morton et al.; (2004) meta-regression can be either a fixed-effects or random effects model. In most meta-regression approaches, the unit of analysis, that is each observation in the regression model, is a study. Sometimes an arm, like a specific treatment arm or the control arm, or even an arm crossed with outcome, e.g., all patients in a specific treatment who had the outcome, is the unit of analysis. For the purpose of this project we will consider the simplest case in which the unit of analysis is a study. The outcome (dependent variable or effect size) for a study observation might be the proportions, odds ratio, risk ratio, risk difference to mention but a few. Predictors in the regression are at the study-level and might include factors like the medicine protocol, characteristics of the study population such as the average age, or variables describing the

study setting such as whether the hospital in which the study is undertaken is an academic hospital.

The questions that a meta-analyst may answer with a meta-regression include estimating the treatment effect controlling for differences across studies, and determining which study-level covariates account for the heterogeneity. This statistical heterogeneity refers to the true effects in each study not being identical. Clinical and methodological diversity among the studies included in a meta-analysis necessarily leads to heterogeneity. What is required in meta-regression is the need to select the appropriate model: fixed (marginal) versus random effects. For given values of the covariates considered, a fixed effect analysis estimates the assumed common effect, whereas a random effects analysis estimates the mean of a distribution of effects across studies. If heterogeneity exists, a random effects analysis appropriately yields wider confidence intervals and larger standard errors for the regression coefficients than a fixed effect analysis (Thompson and Higgins, 2001).

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 generalise to other populations. While for 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 generalise to the range of scenarios or make inferences about a wider population. The selection of the model should follow the logic of how the studies were selected. In particular if there is heterogeneity in true effects that is not explained by the covariates, then the random-effects model is likely to be more appropriate. However when number of studies is very small, then the estimate of the between-studies variance will have poor precision. An alternative approach is to use the Bayesian hierarchical model where the between-studies variance estimate is based on data from outside the current set of studies (Borenstein et al., 2009).

The difficulties faced in a meta-regression are numerous. Primarily, the available degrees of freedom can be small due to the fact that most meta-analyses do not include a large number of studies. The use of meta-regression especially with multiple covariates is not the recommended option when the number of studies is small. The recommended number is at

least 10 studies for each covariate (Borenstein et al., 2009). In addition, covariates tend to be highly collinear. For example all studies in rural areas may administer the medicine in a particular way, while urban hospitals use a different protocol. In such cases, it is impossible to disentangle effects of individual covariates. The problem of ecological bias is paramount in meta-regression, as the analysis is conducted at the study-level and does not include the underlying patient-level variation. This occurs when averages of patient characteristics in each trial are used as covariates in the regression. This is an obstacle in reaching reliable conclusions from meta-regression (Thompson and Higgins, 2001).

In this project meta-regression with three different approaches, marginal (fixed effects) model, random effects model and Bayesian model were used to investigate whether patient characteristics or methodological issues can explain any of the heterogeneity in excellent intubation condition (EIC) between studies.

1.1. Objective

The goal of this project was to investigate whether patient characteristics or methodological issues can explain any of the heterogeneity in excellent intubation condition (EIC) between studies using meta-regression analysis.

The organization of the report is as follows: Section 2 gives the data description followed by a brief outline of the proposed methods in Section 3. Section 4 will give results of applying these methods to the data and in Section 5 a discussion of the results, and a presentation of the conclusions together with several topics for further research are given.

2. DATA

Data was abstracted from 80 articles by different authors reporting results of randomised and controlled clinical trials which evaluated intubation conditions following succinylcholine administration. The 80 articles yielded 99 observations since some authors published more than one article. All patients older than 16 years that had to undergo diagnostic or surgical procedures under general anesthesia and with requirement of endotracheal intubation were considered. A systematic search of the literature was performed without language restriction.

Articles were identified by search of MEDLINE, EMBASE; IndMED, the Cochrane controlled Trials Register Databases using combinations of free text terms for example succinylcholine, suxamethonium, randomised controlled trial, and intubation conditions. Electronic searches were performed until February 2011 and were complemented by screening bibliographies of retrieved articles and meta-analyses.

Explanatory variables consisted of dose, age, gender, use of opioids, RSI, and nasal tracheal intubation. Opioid is a chemical that works by binding to opioid receptors which are found in the central and peripheral nervous system and the gastrointestinal tract. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. Side effects of opioids include sedation, respiratory depression, constipation, strong sense of euphoria (Brincat et al., 2007). RSI is a particular method of induction for general anesthesia commonly employed in emergency operations and other situations where patients are assumed to have a "full stomach". The objective of RSI is, minimize regurgitation possibility and pulmonary aspiration of gastric contents during the induction of general anesthesia and subsequent tracheal intubation (El-Orbany, 2007).

The response variable which is **Excellent Intubation Condition** (EIC) was derived as a ratio of number of patients with excellent intubation condition to the total number of patients in a particular study. The intubation condition was assessed by the Goldberg Scale where-by a patient was considered to have excellent intubation conditions if the patient had ease with intubation, vocal cord movement, and response to intubation.

The software used in this project was SAS 9.2, R 2.10.1, WinBUGS14 and all hypotheses were tested at the 5% significance level.

3. METHODOLOGY

This section describes the statistical methods that will be applied to the data using different meta-regression approaches.

3.1. EXPLORATORY ANALYSIS

Before the meta-regression was applied, exploratory tools were used to get insights of the data. The tools included summary tables showing frequencies, histograms, scatter plots and

kernel density plots. A kernel density plot can be considered as a refinement of a histogram or frequency plot. This is usually a much more effective way to depict the distribution of a variable (Kabacoff, 2011). The density estimates are the kernel density estimates using a Gaussian kernel. That is, a Gaussian density function is placed at each data point, and the sum of density functions is computed over the range of the data. These are the proposed statistical methods used for this data.

3.2. META-REGRESSION

Dose-response relationships for neuromuscular blocking drugs are customarily determined by regression analysis. Stated by Morton et al., (2004) there are different approaches of doing meta-regression which we will describe here.

3.2.1. Fixed effects meta-regression

A fixed-effect meta-regression estimates a single effect that is assumed to be common to every study and that all other differences in observed effects are due to sampling error. This approach yields a descriptive analysis of the included studies, however it does not allow us to make inferences about a wider population (Borenstein et al., 2009). This approach was used in this project where the response is the probability of excellent intubation condition (EX/N), having EX as the number of patients who had excellent Intubation condition out of the total number of patients (N) in a particular study. Taking into account the nature of the response, logistic regression was considered as appropriate. Logistic regression allows one to predict a discrete outcome, such as group membership, from a set of variables that may be continuous, discrete, dichotomous, or a mix of any of these. Generally, the dependent or response variable is dichotomous, such as presence/absence or success/failure. That is taking the value 1 with a probability of success π, or the value 0 with probability of failure $1-\pi$. This type of variable is called a Bernoulli (or binary) variable (Agresti, 2002). Let us denote

$$Y_{ij} = \left\{ \begin{array}{l} 1 \text{ if the patient had EIC} \\ 0 \text{ if the patient did not have EIC} \end{array} \right\} \text{ with } Y_{ij} \sim B(1, \pi_i),$$

for i=1,…, 80 and j=1,…n_i denoting studies and patients in a study respectively, while π_i is the probability of EIC which is allowed to be different from study to study. For a particular study the number of patients with EIC is given by

$$Y_i = (\sum_{j=1}^{n_i} Y_{ij}) \sim B(n_i, \pi_i). \tag{1}$$

The variance of Y_i (within study variance) can then be given by

$$var(Y_i) = n_i \pi_i (1 - \pi_i)[1 + (n_i - 1)\rho], \tag{2}$$

Where ρ is the correlation between Y_{ij} and Y_{ik} (over-dispersion occurring when $\rho > 0$).The fixed effects logistic model is given by

$$logit(\pi) = \log\left(\frac{\pi}{1 - \pi}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k, \tag{3}$$

where $x_1, x_2, \dots, x_k$ are a set of covariates.

Although when analysing binary data often a logistic model (3) is considered reasonable, the goodness-of-fit statistics of this model indicate that too much binomial variation remains (overdispersion).That is, the deviance and Pearson chi-square are large relative to their degrees of freedom. This lack of fit is sometimes described as overdispersion, namely if the true variance (equation 2) is greater than $\pi(1 - \pi)$ which is the estimated variance for a Bernoulli distribution. It's often that correlated or grouped data exhibit overdispersion and when not taken into account overdispersion can have major impact on statistical inference. The implications of overdispersion are serious and the analysis which assumes the logistic model underestimates the standard errors and thus wrongly inflates the test statistics and level of significance. Taking into account overdispersion involves the additional estimation of a dispersion parameter, often called a scaling parameter and using study-specific models as stated by Agresti, (2002). To answer the research question logit models taking into account overdispersion considered were the beta-binomial model and the quasi-likelihood models, which are explained in the sections that follow.

3.2.1.1. Quasi-likelihood (QL) with scaling options Williams-QL(1) and Pearson-QL(2)

This method corrects for overdispersion by multiplying the variance-covariance matrix of the parameters by the value of the overdispersion parameter. It avoids the full specification of the distribution and therefore a more robust method. When using quasi-likelihood QL(1) with similar variance function $var(Y_i) = n_i \pi_i (1 - \pi_i)[1 + (n_i - 1)\rho]$ as the beta-binomial,

overdispersion occurs when $\rho > 0$ otherwise when $\rho = 0$ it results in ordinary binomial variance. While for the quasi-likelihood QL(2) approach which uses the simpler variance function $\text{var}(Y_i) = n_i \pi_i (1 - \pi_i) \emptyset$ overdispersion occurs when $\emptyset > 1$ otherwise when $\emptyset = 1$ ordinary binomial variance has been used. The standard errors for this overdispersion approach multiply those for the binomial model by $\widehat{\emptyset}^{1/2}$.

To determine which QL model is more appropriate Agresti (2002) states that a plot of the standardized residuals for the ordinary binomial model against the indices n_i can provide insight about which is more appropriate. When the residuals show an increasing trend in their spread as n_i increases, the beta-binomial-type variance function QL(1) may be more appropriate. This is because when the beta-binomial variance holds, the residuals from an ordinary binomial model have a denominator that is progressively too small as n_i increases. The two quasi-likelihood approaches are equivalent when n_i are identical. Only when the indices vary considerably results might differ.

3.2.1.2. Beta-Binomial

The Beta-binomial model is a model to handle overdispersion occurring with ordinary binomial models. The reason is that, it is a mixture model which assumes a binomial distribution at a fixed parameter value having a marginal distribution which permits more variation than the binomial. As stated by Agresti (2002) it is an alternative model to binary Generalized Linear mixed models (GLMMs) with normal random effects and behaves like a random-effects model with marginal interpretation. The beta-binomial distribution results from a beta distribution mixture of binomials and also its full likelihood model where AIC is fully corrected and defined. Suppose that (a) given π, Y has a binomial distribution, $bin(n, \pi)$ and (b) π has a beta distribution. The beta probability density function is given by

$$f(\pi; \alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} \pi^{\alpha-1} (1 - \pi)^{\beta-1}, \qquad 0 \leq \pi \leq 1, \qquad (4)$$

with parameters $\alpha > 0$ and $\beta > 0$, for the gamma function $\Gamma(.)$. Let $\mu = \frac{\alpha}{\alpha+\beta}, \theta = \frac{1}{(\alpha+\beta)},$ the beta distribution for π has mean and variance $E(\pi) = \mu$ and

$$\text{var}(\pi) = \mu(1 - \mu) \frac{\theta}{(\theta + 1)},$$

respectively. Using the properties of the beta function, equation (4) can be rewritten as

$$f(\pi; \alpha, \beta) = \frac{\Gamma(n+1)}{\Gamma(\pi+1)\Gamma(n-\pi+1)} \frac{\Gamma(\alpha+\pi)\Gamma(n+\beta-\pi)}{\Gamma(\alpha+\beta+n)} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}, \qquad 0 \le \pi \le 1,$$

where π is the proportion of patients having excellent intubation condition out of n the number of patients in a particular study. This model reduces to the Bernoulli distribution as a special case when $n = 1$ and for $\alpha = \beta = 1$, it is the discrete uniform distribution.

3.2.2. Random effects model (logistic normal model)

When studies are performed by different researchers and then culled from the literature, it is more plausible that the impact of the covariates captures some, but not all of the true variation among effects. In this case, it is the random-effects model that reflects the nature of the distribution of true effects, and should therefore be used in the analysis (Borenstein et al., 2009). The terminology "random effects" refers to the fact that a random study effect is included in regression to take into account the between study variation. Computationally, under the fixed-effect model, the total model variance is the variance within studies while under the random-effects model it is the variance within studies plus the variance between studies known as τ^2. Generally the log odds ratio is regressed on an intercept and study-level covariates. In the simplest case in which only an intercept term is included, this approach reduces to the usual DerSimonian and Laird random effects estimate of the pooled odds ratio (sally et al., 2004). With a univariate random effect, the model can be written as

$$logit\left[p(y_{it} = 1|u_i)\right] = X'_{it}\beta + u_i, \tag{5}$$

where $X'_{it}\beta$ is the linear predictor and u_i are independent $N(0, \sigma^2)$ variates. This is the special case of the generalised linear mixed models (GLMM) in which the $g(.)$ is the logit link and the random effects structure simplifies to a random intercept. More generally, the link function in equation (5) can be an arbitrary inverse cumulative density function. The random effects part of the model is a mechanism for representing how positive correlation between observations within a study occurs. However parameters pertaining to the random effects may themselves be of interest. For instance, the estimate $\hat{\sigma}$ of the standard deviation of a random intercept may be a useful summary of the degree of heterogeneity of a population.

Interpreting heterogeneity is another key aspect of the logistic-normal model. When σ = 0, the logistic-normal model (equation 5) simplifies to an ordinary logistic regression model treating all observations as independent. This implies the usual form of log odds ratio for a model without random effects. When σ > 0, variability in the effects of this model implies log odds ratio for two observations in the same study (Agresti, 2002). This is a test of null hypothesis that the between-studies variance is zero. This test is based on the amount of between-studies variance observed, relative to the amount we would expect if the studies actually shared a common effect size.

The random effects models have some advantages which include; accounting for random variability among studies thus catering for unexplained variability left out by marginal models. Related to this motivation, random effects also provide a mechanism for explaining over dispersion in terms of estimate $\hat{\sigma}$ compared to basic models which do not have those effects (Breslow and Clayton, 1993). Though this model is fit to account for random variability among studies, its disadvantage is the interpretation complexity.

The random effects models have conditional interpretations, referred to as study specific. This contrasts with marginal models, which have population-averaged interpretations. In meta-analyses, fixed effects models may give more narrow confidence intervals and more impressively low p-values compared with models that accommodate potential diversity of effects (heterogeneity). Random effects models thus try to estimate the population average and the extent of dispersion in the different effect sizes (Loannidis et al., 2007). Some statisticians prefer one of these types, but most feel that both are useful, depending on the application. The conditional modeling approach is preferable if one wants to specify a mechanism that could generate positive association among clustered observations, estimate study-specific effects, estimate their variability, or model the joint distribution. Given a conditional model, one can recover information about marginal distributions. That is, a conditional model implies a marginal model but a marginal model does not itself imply a conditional model (Agresti, 2002).

3.2.3. Bayesian meta-regression

The proposed Bayesian meta-analysis model allows prior information in the form of expert opinion to be cooperated into the analysis. According to Chan and Leng(2005), this model allows observed effect sizes (data) to vary around their individual study-specific effect sizes θ_i which in turn belong to a distribution characterised by the overall effect size θ (odds ratio). In contrast with the traditional random-effects model, for which the parameters θ, σ^2 (within study variability) and τ^2 (between study variability) are assumed to be fixed, σ^2 and τ^2 are assumed to be random variables in a Bayesian random-effects model, in the sense that they have a probability distribution (Lan et al., 2009).

In this analysis, the prior distribution for θ (in terms of betas) was given a vague prior the normal distribution of a mean of 0 and a variance of 10,000 to reflect the presumption that factors could have negative or positive effect on EIC with equal odds. The prior distribution for τ (var.studie) was assumed to have an inverse gamma distribution (0.001, 0.001) and sensitivity analysis was done by changing the prior distribution for var.studie to a uniform distribution with parameters (0,100) for $\frac{1}{\sqrt{\tau}}$ (sigma.studie). This was done to determine the validity of the results. The model for predicting the response is given by

$$prop[i] \sim dbin(p[i], n[i])$$
$$logit(p[i]) < -beta[1] + beta[2] * n[i] + beta[3] * logdose1[i] + beta[4]$$
$$* (agecode[i]) + beta[5] * (femaleprop[i]) + th[studie[i]] \qquad (6)$$

Where $p[i]$ represents probability of excellent intubation condition, $i = 1,2,\ldots,80$ studies, and $th[studie[i]]$ are random intercepts at studie level with normal distribution of a mean 0 and variance σ^2_{studie} that is $Normal(0, \sigma^2_{studie})$.

The Bayesian meta-analysis has several advantages. Lan et al., (2009) state that; in contrast with a classical meta-analysis, which considers the probability (e.g. *P* value) of observed data given the hypothesis of no treatment effect, the Bayesian analysis considers the probability of the hypothesis of treatment effect given the observed data.

The *P* value is known to be a poor measure for evaluating evidence and making clinical decisions and is often misinterpreted. In contrast, the Bayesian method does not depend on, and bypasses the shortcomings associated with *P* values for inference. That is to say

making the type 1 (reject the null hypothesis when it is true) and type 2 (fail to reject null hypothesis when it is false) error. Therefore credible intervals showing the probability that the true parameter lies in that interval becomes the interval of evidence. In addition the Bayesian analysis allows the reporting of direct probability statements about any differences that are of interest basing on the posterior distribution. Though this is probably the best option, Borenstein et al., (2009) state that relatively few researchers have expertise in Bayesian meta-analysis and some have a philosophical objection to this approach. Helser and Han-Lin, (2004) add that Bayesian approaches are controversial because the definition of prior probability will often be based on subjective assessments and opinion.

3.3. Model building, selection and Goodness of fit

To check which covariates are most closely related to the response (probability of EIC) and which to be used in the model, univariate analyses based on ordinary logistic regression as a screening tool for the possible covariates was used. From the Univariate logistic regression all covariates significant at 25% as recommended by Hosmer and Lemshow, (2000) were considered to fit the multiple logistic regression model. Using the backward selection procedure the fit of the model was tested after the elimination of each variable to ensure that the models still adequately fits the data. The model was reduced to the presented model fit in the analysis.

Diagnostic checks of models were done by use of plots of the standardized residuals, plots of predicted versus observed in addition scatter plots detecting outlier studies. Akaike's information criterion (AIC) was used to select a few "good" sub models. So the optimal model having lower AIC balances the accuracy of the fit to its complexity. It is worthwhile to note that AIC is used for "full" specified models and it's valid for non-nested models. For the Bayesian models Deviance Information criteria DIC was used as a selection criteria.

4. RESULTS (APPLICATION TO THE DATA)

4.1. Exploratory Data Analysis

Exploratory data analysis was used to gain insight into the nature of the data, and to suggest some plausible models that are appropriate for statistical analysis. The minimum average age across studies was 20.1 years and the maximum was 72.0 years. In order to gain more insight about the dependency of EIC on age, the probability of EIC was plotted against age in Figure 2a. The plot seems to suggest that the probability tends to be high among the middle age groups compared to the young and the old. If equally sized points are used like in Figure 2a, sometimes it is impossible to see which trials provide the greatest information, and how this might affect the interpretation. So the size of points was taken into account as seen in Figure 2b. This plot seems to suggest that probability tends to be high among the young and shows a decreasing spread as the age increases.
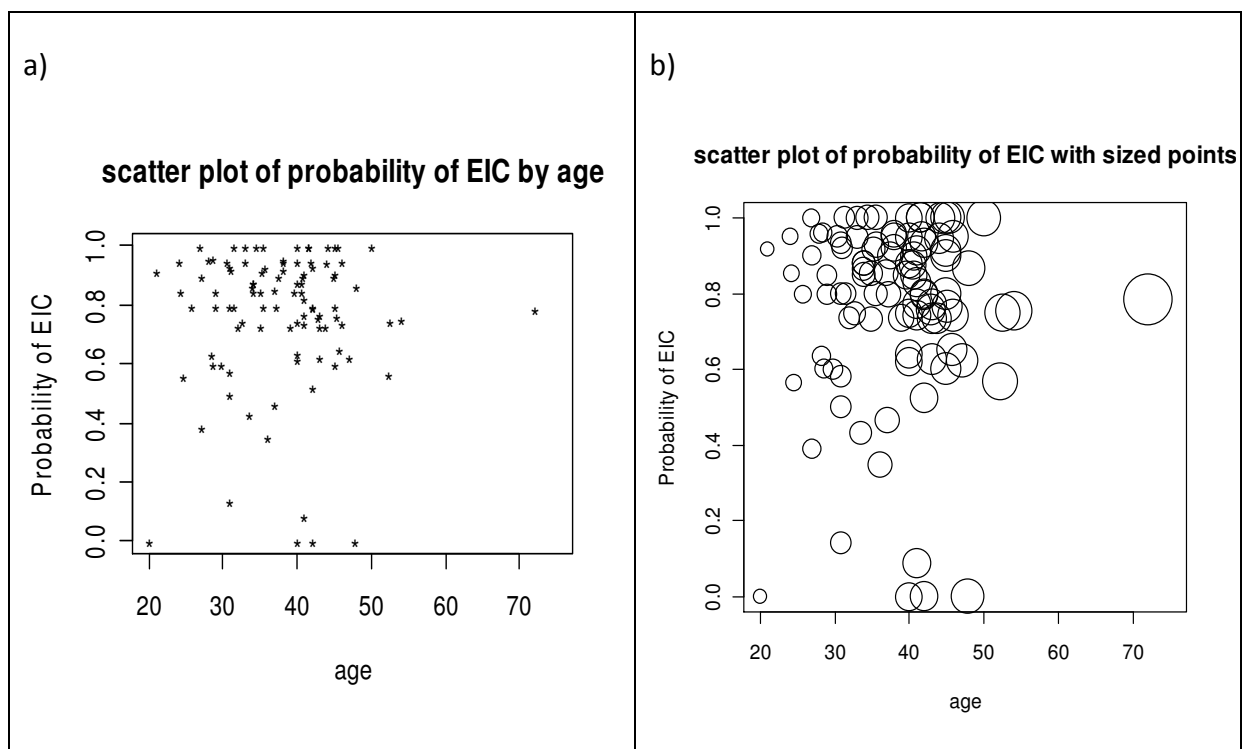
Figure 2: Scatter plots of Probability of EIC by age.

By categorizing age into 3 groups it was shown that 58.59% of the studies had an age range of 20-40, 40.40% (40-60) and 1.01% (60-72). Since the majority of the studies had an average age ranging from 20 to 60 two age groups were considered mean age<40 (agecode 0) and mean age>40 (agecode 1).

probability Distribution of EIC by age groups
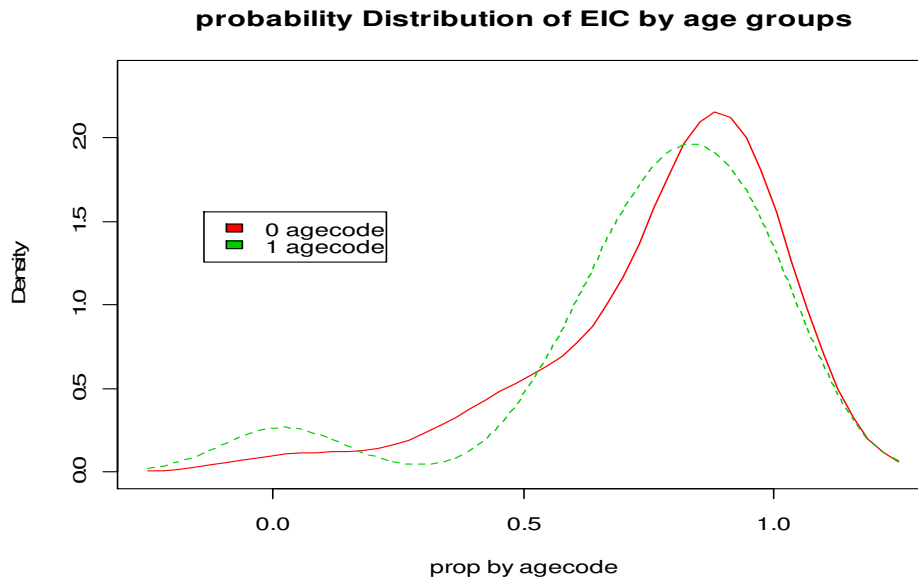
Figure 3: Probability distribution of EIC by age groups.

From Figure 3 it can be observed that there is an unclear difference between the two age groups at small probabilities of EIC. However at higher probabilities studies with mean age<40 (agecode 0) had slightly higher probability of EIC compared to studies with mean age>40 (agecode 1). This will be confirmed in the statistical analysis. This was further explored taking into account the sample size.
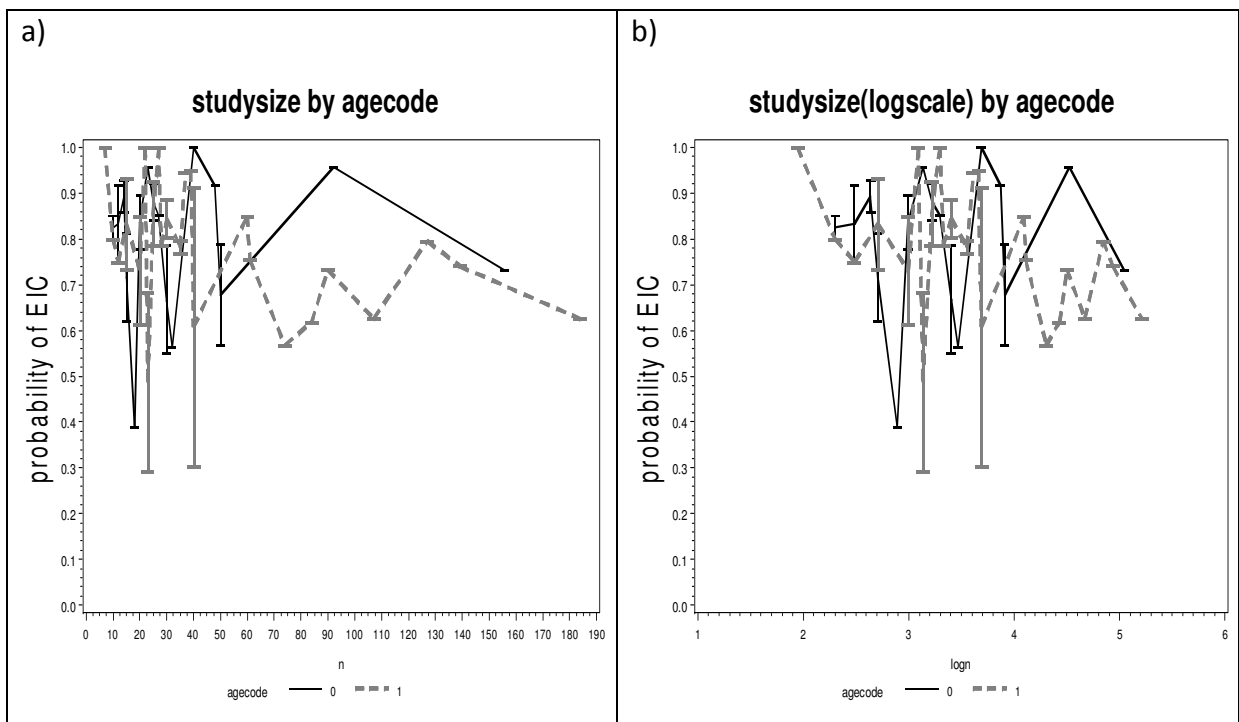
Figure 4: Plot of study size by age group.

From Figure 4a it is observed that the probability of EIC does not differ between the two age categories for studies with sample size less than 50 and this is also seen even when n is on the log scale (4b). There exists differences when the sample size increases beyond 50 where studies with mean age<40 (agecode 0) had a higher probability of EIC compared to studies with mean age>40(agecode 1) but after the probability of both groups decreases.

The size of the studies (n) ranged from 7 to 184 patients. To explore how size of the study corresponds with proportion of EIC, sample sizes were categorized into 3 size groups. It was observed 56, 32, 11 of the studies were in sizegrp1, sizegrp2, and sizegrp3 respectively.

Table 1: Number of studies in three categories of sample size.

Sizegroup	Frequency	Percent
1. n< 30	56	56.57
2. 30-60	32	32.32
3. n>60	11	11.11

A further exploratory was done by use of histogram in Figure 5; it is observed that more studies had EIC proportion greater than 52.5%. To investigate which study sizes have higher probabilities of EIC we used funnel plots.

histogram of studie by EIC proportion
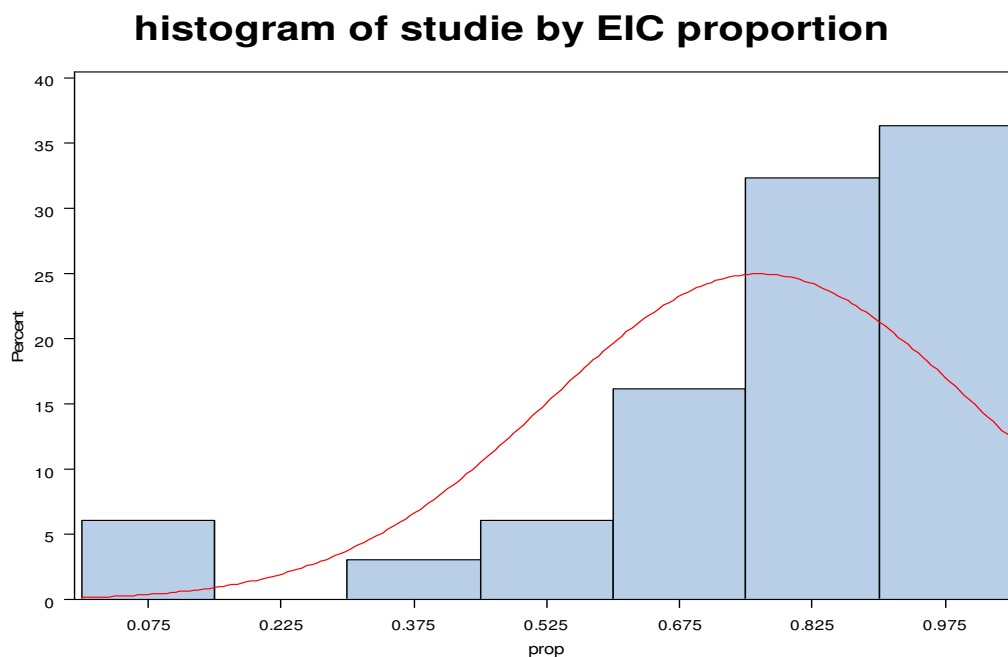
Figure 5: Histogram of study by EIC proportion.

Funnel plots are a visual tool for investigating publication and other bias in meta-analysis. They are simple scatter plots of the treatment effects estimated from individual studies (horizontal axis) against a measure of study size (vertical axis). The name "funnel plot" is based on the precision in the estimation of the underlying treatment effect increasing as the sample size of component studies increases (Sterne and Harbord, 2004). Therefore, in the absence of bias (the association of publication probability with the statistical significance of study results), results from small studies will scatter widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, the plot will resemble a symmetrical, inverted funnel. Seen from Figure 6 there seems to be absence of publication bias since the plot resembles an inverted funnel though some few studies outlay the funnel at small values of the effect size.
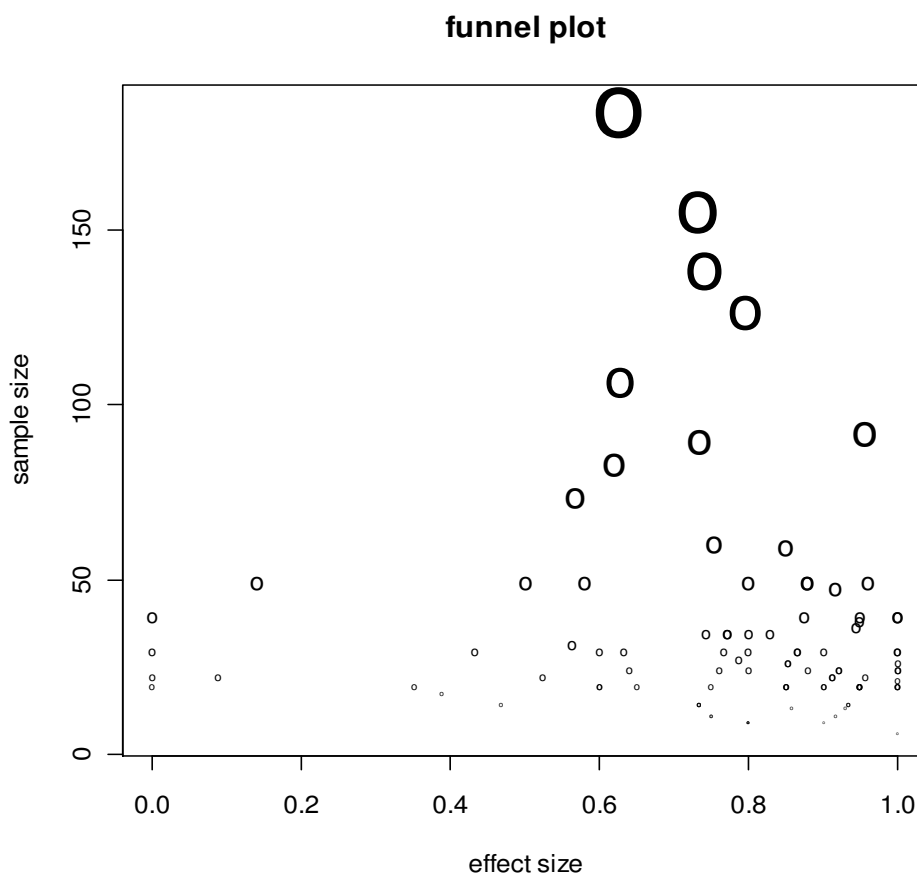
funnel plot

Figure 6: Funnel plot for sample size by effect size.

It is, however, important to realize that publication bias is only one of a number of possible causes of funnel-plot asymmetry, funnel plots should be seen as a generic means of

examining small study effects (the tendency for the smaller studies in a meta-analysis to show larger treatment effects) rather than a tool to diagnose specific types of bias. This gave an insight that it may be possible that differences between smaller and larger trials are accounted for by a trial characteristic. An explanation of this heterogeneity was investigated more formally using meta-regression (logistic regression with correction for overdispersion). Succinylcholine dose levels varied from 0.5 to 2 $mg.kg^{-1}$. Figure 7 seem to suggest that probability of EIC increases with increasing Dose. In addition the graph shows an S-shaped curve indicating the use of logit models. Further confirmation of these observations will be done in the statistical analysis.
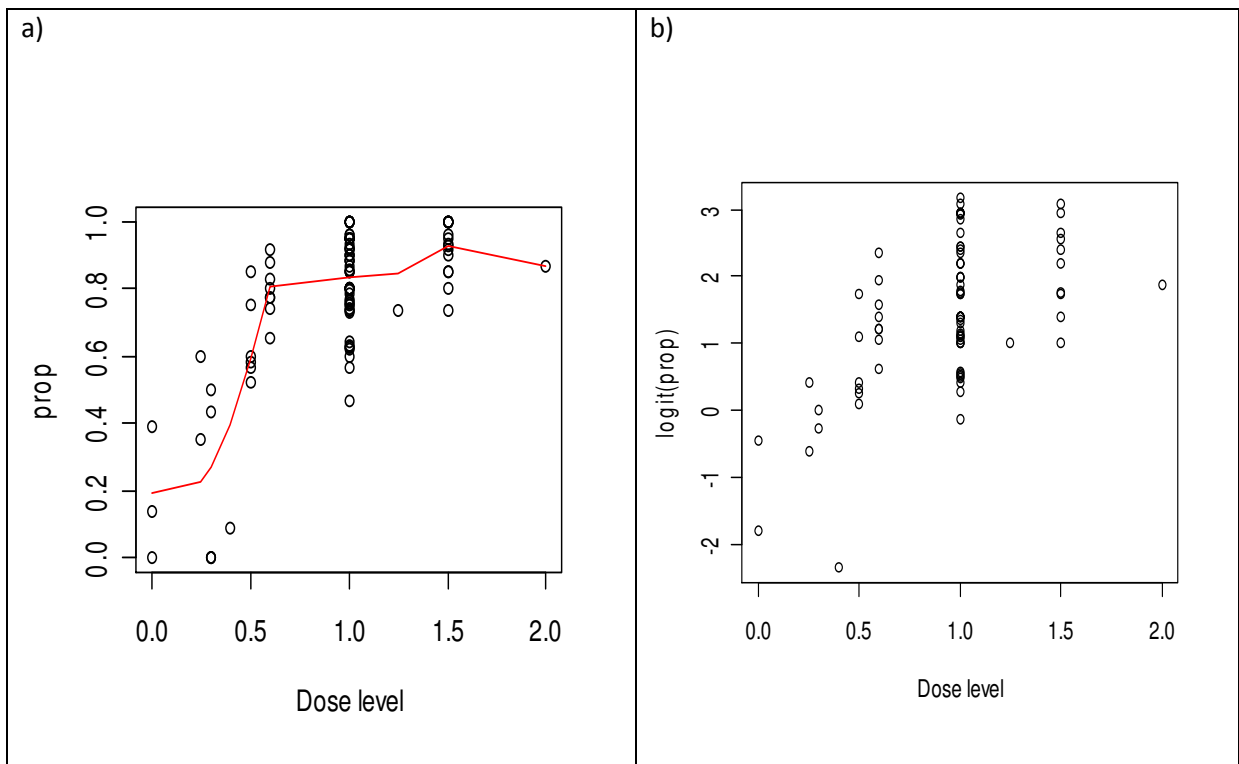
Figure 7: Probability of EIC by Dose level.

Considering 99 observable studies it is seen from Table 2 that 91.92% of the studies did not use Nasal intubation where as 81.82% did not use RSI. Use of opioids, 84.85 didn't use opioids.

Table 2: Number of studies in two categories of Nasal intubation, RSI and use of Opioids.

Group	Coding	Frequency	Percent	Total
Nasalintubation	0 (No)	91	91.92	99(100%)
	1 (Yes)	8	8.08	
RSI	0 (No)	81	81.82	99(100%)
	1 (Yes)	18	18.18	
Opioids	0 (No)	84	84.85	99(100%)
	1 (Yes)	15	15.15	

According to illustration by Figure 8 for Nasal intubation, for smaller probabilities, studies which used nasal intubation had a higher probability while for bigger probabilities the density curve of studies which did not use nasal is above the one for studies which used nasal intubation. Also it is noticeable that for non-nasal group there a lot of variation while for the group of nasal, the probability of EIC is constantly increasing this difference will be cleared by the statistical analysis.

propbability Distribution of EIC by Nasal groups
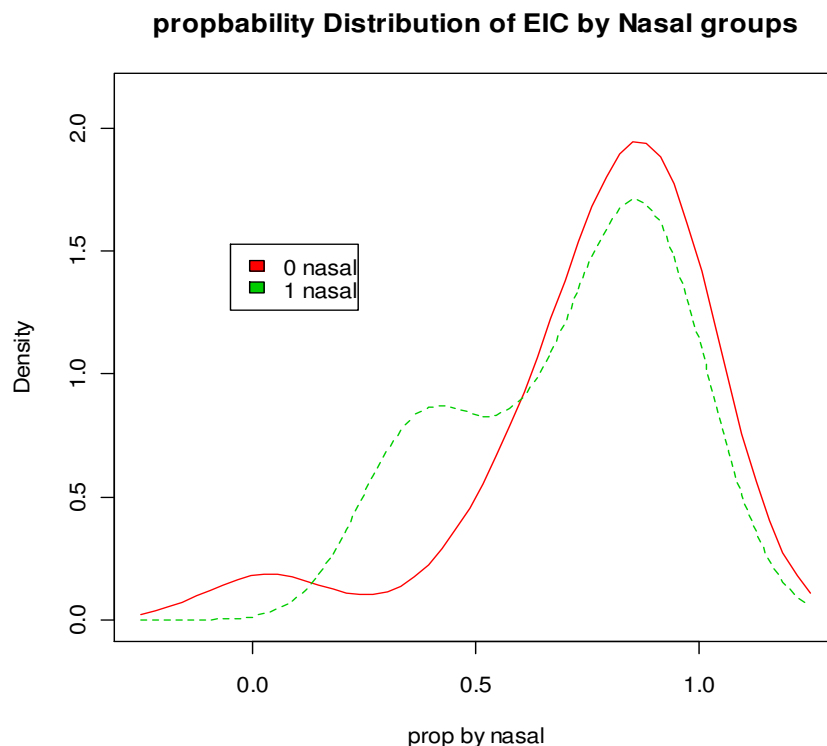
Figure 8: Probability distribution of EIC by Nasal groups.

Figure 9a for use of opioids shows indifference between the two opioids groups to the probability of EIC and this coincides with the RSI (9b). The same unclear message is seen in succinylcholine dose by opioids plot (Appendix 3). What is observed is that the group of studies which didn't use opioids or didn't use RSI have more variability as compared to the group which used opioids or used RSI. What is observed will be confirmed in the statistical analysis.
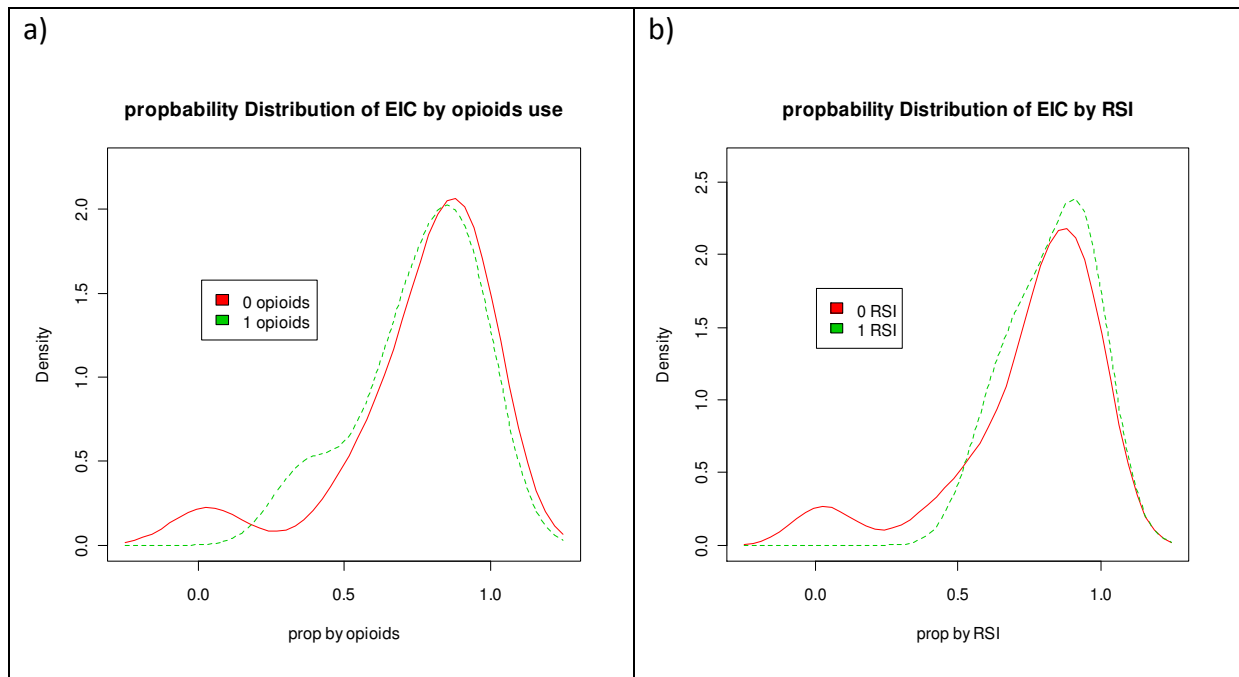
Figure 9: Probability distribution of EIC by opioids use.

4.2. STATISTICAL ANALYSIS

4.2.1. Considering only covariates of interest

From the Univariate logistic regression analysis Dose, gender, use of opioids were significant but age, RSI and Nasal intubation was not significant at 25%. The interactions considered to fit a multiple logistic regression were; Dose*femaleprop, Dose*opioids. Using backward selection, Dose, gender, opioids, Dose*femaleprop, Dose*opioids were the covariates selected in this section to determine the probability of EIC. All covariates and their interactions were significant at 5%. Testing for homogeneity across levels of opioids by Wald test (4.7197, p-value=0.0298) the binomial model showed that the effect of dose to the EIC probability is not the same at different levels of opioids. This model however does not take into account over dispersion (extra binomial variability).

For this reason the model was extended by taking different scale options, a beta-Binomial model was also fitted and furthermore, a random-effects model to account for random variability between studies was fitted, thereby catering for unexplained variability left out by marginal models.

Table 3: Parameter estimates (standard errors) for Ordinary logistic model (Maximum Likelihood, ML), QL (1) with beta-binomial variance function, QL (2) with Pearson inflated variance, Beta-Binomial and Random-effects model.

Parameter	Binomial ML	QL(1)	QL(2)	Beta-Binomial	Rand-effects
Intercept	-2.882(0.570)*	-3.064(1.195)*	-2.882(1.247)*	-3.105(1.140)*	-3.873(1.001)*
Dose	3.701(0.572)*	4.052(1.259)*	3.701(1.252)*	4.008(1.178)*	5.369(0.937)*
gender(femaleprop)	3.175(1.022)*	3.227 (2.135)	3.175(2.237)	3.084(2.032)	4.520(1.757)*
Opioids	0.844(0.294)*	1.114 (0.600)	0.844(0.643)	1.354(0.579)*	0.765(0.689)
Dose*femaleprop	-2.312(1.007)*	-2.321 (2.211)	-2.312(2.205)	-2.203(2.069)	-4.315(1.656)*
Dose*Opioids	-0.683(0.315)*	-0.918 (0.737)	-0.683(0.688)	-1.290(0.664)	-0.484(0.630)
Overdispersion	None	$\hat{\rho}$ =0.128>0	$\hat{\phi}$ =4.790*	$\hat{\rho}$ =0.129(0.025)*	$\hat{\sigma}$=0.786(0.1)*

*parameter significant at 5% level

From the results in table 3, it can be seen from the overdispersion estimates that there is extra binomial variability. The Pearson chi-square estimate obtained in QL(2) is large relative to the degrees of freedom. This yielded an estimate of 4.790 which is significantly larger than 1 and 0.128 is greater than 0 providing evidence of overdispersion. One cause of this overdispersion is the heterogeneity among studies. Extending to the beta-binomial model the correlation estimate 0.129 is significant indicating that there exists within study dependences. For a random effects model the estimate of sigma 0.785 (standard deviation of the random intercept) is also significant showing unexplained heterogeneity which could cause the differences in the estimated probabilities of EIC in the different studies.

Comparing Binomial ML which assumes no over dispersion with the other four methods it can be seen that the standard errors have been inflated and significance of parameter estimates changed, this is because of correcting for overdispersion. Considering the four models which were corrected for overdispersion, parameters in QL(1) and QL(2) had the same significance compared to the beta-Binomial and random-effects model though for all four models dose was significant. The difference in the significance of the Beta-Binomial and the random effects model can be explained by the fact that the two models have different

variance structures and one being a marginal model and the other being a study-specific model. Before selecting which model best describes the data the ordinary logistic regression was extended to cater for year of publication and sample size.

4.2.2. Model extension to cater for Year of publication and study size

When year of publication and study size were included in the model, using the backward selection procedure, year of publication, study size, Dose, female proportion, Dose*female prop, were significant while opioids and Dose*opioids were clearly now insignificant. Although year of publication was significant in the Binomial model, for all other four models which take into account overdispersion it was not significant and so, it was dropped in order to get a clear difference among models. All the five models were refitted and the results are presented in Table 4.

Table 4: Parameter estimates (standard errors) for Ordinary logistic model (Maximum Likelihood, ML), QL (1) with beta-binomial variance function, QL (2) with Pearson inflated variance, Beta-Binomial and Random-effects model.

Parameter	Binomial ML	QL(1)	QL(2)	Beta-Binomial	Rand-effects
Intercept	-2.763(0.598)*	-2.577(1.221)*	-2.763(1.272)*	-2.744(1.241)*	-3.346(0.965)*
Study size(n)	-0.007(0.001)*	-0.007(0.003)*	-0.007(0.002)*	-0.007(0.003)*	-0.009(0.003)*
Dose	4.226(0.613)*	3.909(1.286)*	4.226(1.304)*	3.967(1.269)*	5.121(0.908)*
gender(femaleprop)	3.517(1.068)*	3.195(2.177)	3.517(2.272)	3.384(2.188)	4.435(1.711)*
Dose*femaleprop	-2.880(1.050)*	-2.339 (2.234)	-2.880(2.234)	-2.607(2.183)	-3.958(1.604)*
Overdispersion	None	$\hat{\rho}$ =0.126>0	$\hat{\phi}$ =4.530*	$\hat{\rho}$ =0.128(0.026)*	$\hat{\sigma}$= 0.711(0.2)*

parameter significant at 5% level

Considering the models which were corrected for overdispersion, it is shown that study size and Dose affect the probability of EIC. For this model the two scaling options and the Beta-Binomial give more or less the same interpretation with dose and study size being the only covariates affecting EIC probability. Considering the random-effects model the parameter significance and magnitude differs and the standard errors are smaller compared to the three models correcting for overdispersion.

4.2.3. Considering transformed Dose and categorized age

To check if the use of transformed variables gave a better fitting model, the dose covariate was taken on a logarithmic scale; log(dose+1) with an additional constant one to avoid missing values of log dose. Kopman et al., (2000) states that because the association between dose and effect yields a sigmoid curve, estimation of 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) values by linear regression analysis first requires a suitable mathematical transformation of the data like taking the logarithm of dose. Also, categorized age variable was considered since the age variable as seen in the scatter plot of the exploratory analysis (Figure 2) showed that probability tends to be high among the middle age groups compared to the young and the old. In addition to the kernel density plot of the two age categories showed that at higher probabilities, studies with mean age<40 (agecode 0) had slightly higher probability of EIC compared to studies with mean age>40 (agecode 1). The results of the fixed effects model (Beta-Binomial) and the random effects model are presented in Table 5.

Table 5: Parameter estimates of Beta-Binomial and random effects models.

Parameter	Beta-Binomial	Random effects
Intercept	-1.2912(0.4780)*	-1.3614 (0.5362)*
Study size(n)	-0.0096(0.0033)*	-0.01416(0.0043)*
Log(dose+1)	3.7654(0.5378)*	4.2350(0.3903)*
Agecode(1)	-1.7516(0.6259)*	-3.6402(0.6980)*
gender(femaleprop)	0.8275(0.6241)	0.8901(0.7217)
Logdose1*agecode	2.9955(1.0939)*	6.1567(1.1524)*
overdispersion	$\hat{\rho} = 0.1091(0.0225)$*	$\hat{\sigma} = 1.0067(0.1753)$*

parameter significant at 5% level

From Table 5 it can be observed that significance of covariates is the same in both the beta-binomial and the random-effects models. To select which model best fits the data among three alternative steps, some diagnostic tools and AIC were used. A plot of the standardized residuals (figure 10a) for the ordinary binomial model against the indices n_i can provide insight about which of QL(1) or QL(2) is more appropriate. When n_i was taken on the log scale figure 10b indeed there was no visible pattern of the residuals.
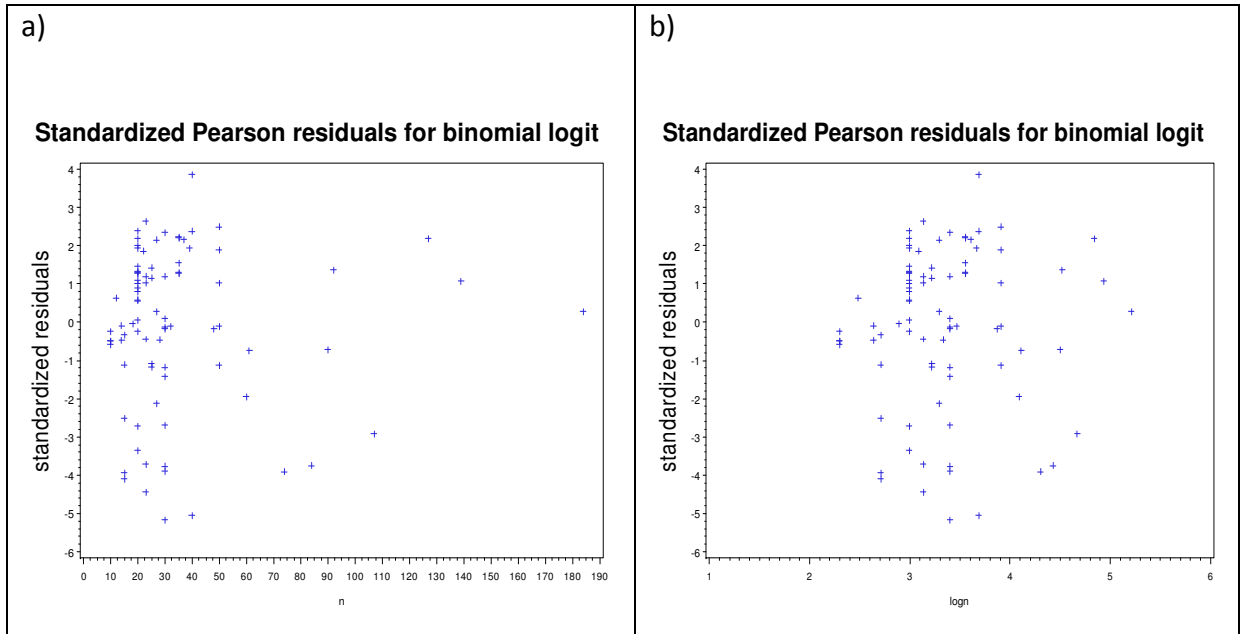
Figure 10: Plot of standardized residuals, a) by indices n_i and b) by $logn_i$.

Since the plots of residuals did not show a clear increasing trend in their spread as n_i increases, this indicates that QL(1) and QL(2) more or less fit the data the same way. When the AIC of other two marginal models was compared, the Beta-Binomial with log(dose+1), n and age categorized model had the least AIC (466.400) and hence fitted the data better marginally. Looking at the random effects model, also the model with log(dose+1), n and age categorized had the least AIC (494.300).

Table 6: Model selection criteria.

		AIC		
Model category	**Model fit**	Without n covariate	With n as covariate	log(dose+1), n and age categorized
Marginal	Binomial ML	3057.447	3007.281	2963.553
	Beta-Binomial	480.200	479.600	466.400
Random effects	Rand-effects	562.800	553.400	494.300

Diagnostic plots for the random-effects model to check the goodness of fit are presented in figure 11. In Figure 11a, it can be seen that majority of the data points fall on the line indicating that the random-effects model chosen is appropriate. In Figure 11b, there seems to be no outlying study-intercept (EB estimate) implying that no study had extreme value from the others.
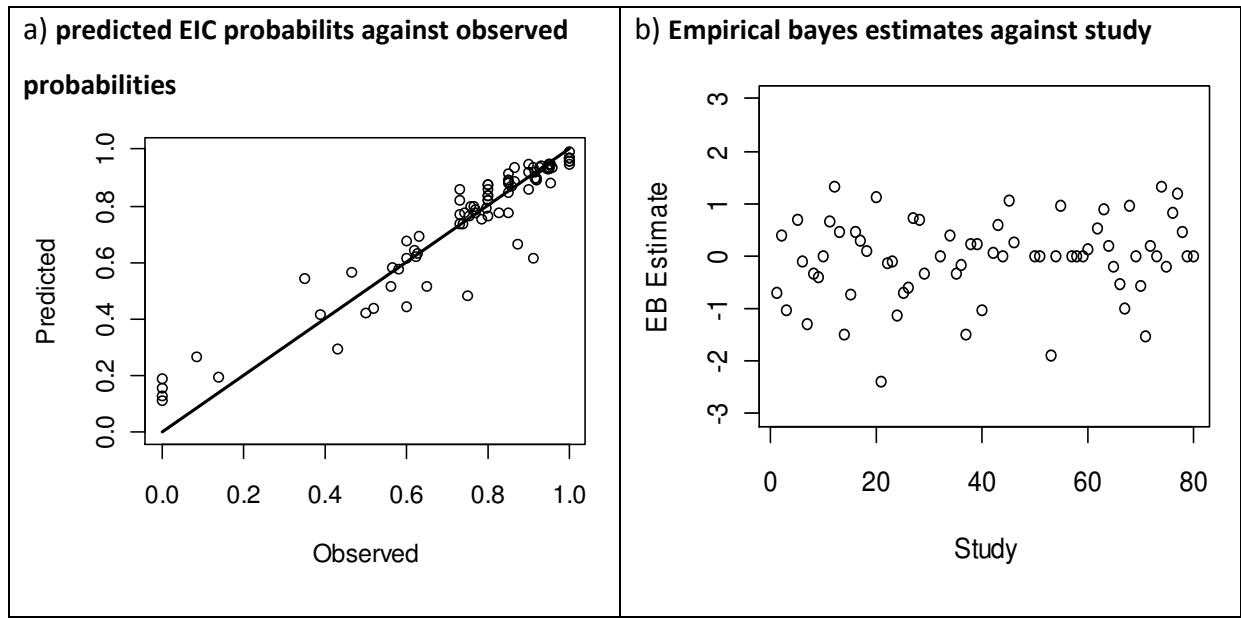
Figure 11: Diagnostic plots, a) predicted against observed, b) EB estimates against study.

The results of Table 5 presenting a fixed and random-effects models can be interpreted as follows. It is observed that Log(dose+1), study size, age categorised, and interaction of age categorised with transformed dose (Logdose1*agecode) are significant covariates affecting the probability of Excellent Intubation Condition (EIC) in both models. The beta-binomial interpretation is as follows: The odds of EIC increases multiplicatively by 3.77 for every 1-unit increase in Log(dose+1). This implies that every one unit increase in Log(dose+1) corresponds to an increase of 3.77 times the odds of EIC. In addition, after controlling for other model covariates, the odds of EIC decreases multiplicatively by 0.99 ($e^{-0.0096}$) for every one unit increase in study size. For categorised age, studies with average age>40 (agecode 1) were 5.76 ($e^{1.7516}$) times less likely to have an outcome of EIC compared to those studies with average age<40. Also across the two age groups the effect of Log(dose+1) to the odds of EIC is not the same due to the significant interaction Logdose1*agecode.

Considering the results of the Random effects model in table 5, the same covariates as the Beta-binomial were significant though the magnitude of covariates and their corresponding standard errors is different. For the random effects model they seem bigger this may be due to the fact that this model has a study-specific interpretation. The odds obtained from this model imply log odds ratio for two observations in the same study. For example 4.24 odds of EIC corresponding to Log(dose+1) in the random effects imply log odds ratio for two observations in the same study. This means for every two study publications by one author they yield 4.24 odds. In both Beta-Binomial and random-effects model, it is seen that methodological issues are able to explain heterogeneity in excellent intubation condition (EIC) within and between studies. This is evidenced by the significant overdispersion (extra binomial variability) parameters. That is to say, correlation estimate of 0.1091 indicates correlation within a given study for Beta-Binomial and sigma 1.0067 (standard deviation of random intercept) the unexplained heterogeneity between studies.

4.2.4. Bayesian Random-effects (hierarchical) model

A model with similar covariates as Table 5 was run in WinBUGS where an inverse gamma distribution with $\varepsilon = 10^{-3}$ was chosen as a prior for study variance. Three chains were initialized and after 61,000 iterations, allowing over relaxation to reduce auto correlation and removal of 1000 as the burn in part, convergence of the sampler was achieved. The model had a DIC of 161.395. For comparison differences this model was presented with the beta-binomial and classical random effects model in Table 7. It is observed that for the Bayesian model all covariates were insignificant except n so the model was reduced by dropping the interactions in this model.

Table 7: Parameter estimates of Beta-Binomial, random effects and Bayesian hierarchical models.

Parameter	Beta-Binomial	Random effects	Model in WinBUGS
Intercept	-1.2912(0.4780)*	-1.3614 (0.5362)*	-3.7150(0.7043)*
Study size(n)	-0.0096(0.0033)*	-0.01416(0.0043)*	-0.0225(0.0057)*
Log(dose+1)	3.7654(0.5378)*	4.2350(0.3903)*	1.2690(0.7614)
Agecode(1)	-1.7516(0.6259)*	-3.6402(0.6980)*	-0.3853(0.9821)
gender(femaleprop)	0.8275(0.6241)	0.8901(0.7217)	0.0055(0.7310)
Logdose1*agecode	2.9955(1.0939)*	6.1567(1.1524)*	0.5576(1.4160)

parameter significant at 5% level

With removal of the Logdose1*agecode interactions and using inverse gamma distribution with $\varepsilon = 10^{-3}$ as a prior for study variance three chains were initialized. After 161,000 iterations, allowing over relaxation and removal of 1000 as the burn in part, convergence of the sampler was checked. All parameters showed the similar convergence characteristics but three arbitrarily chosen covariates are presented in Figure 12.

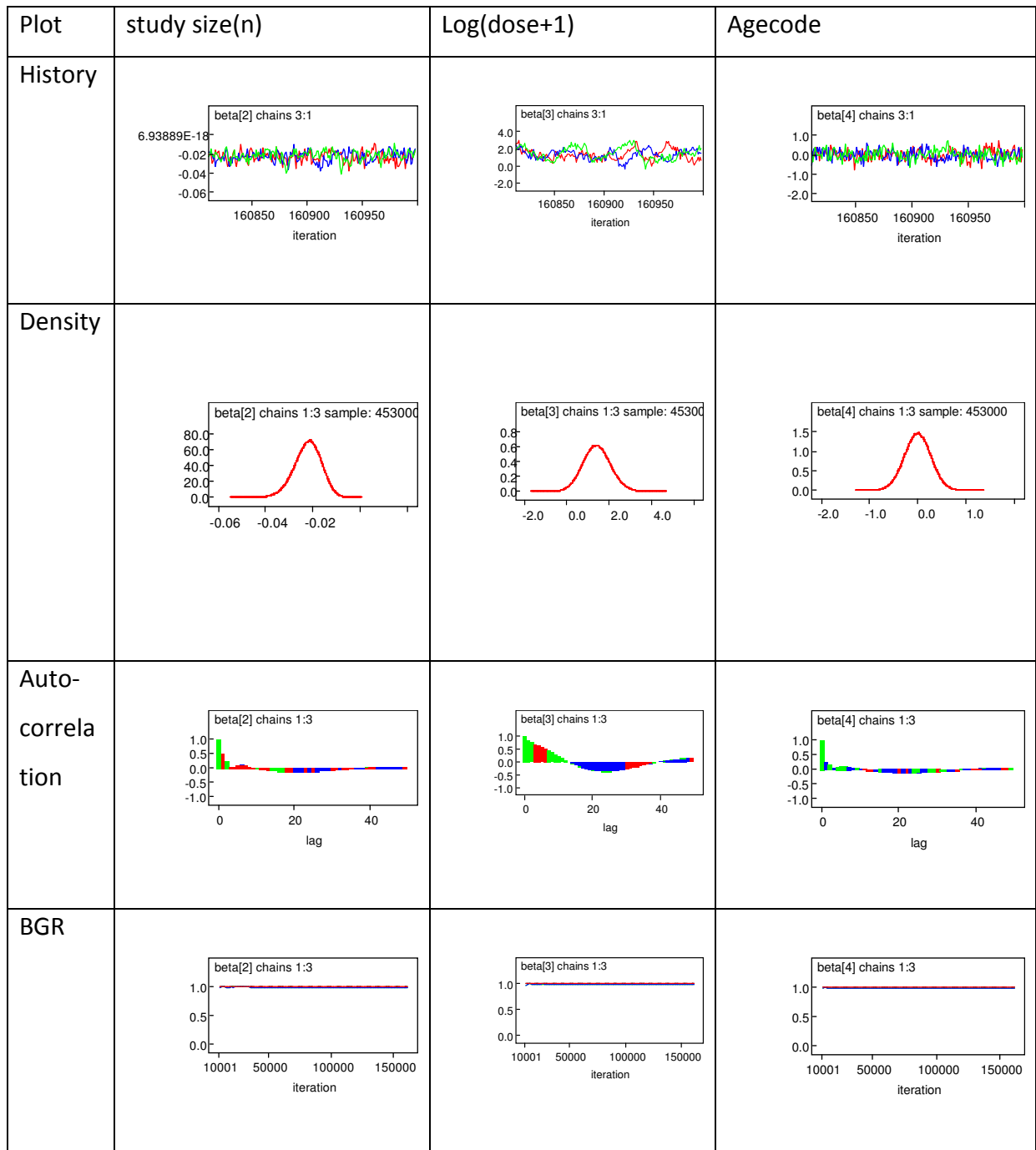| Plot	study size(n)	Log(dose+1)	Agecode
History			
Density			
Auto-correla tion			
BGR			

Figure 12: History, density, Autocorrelation and BGR plots, for study size, log(dose+1) and age categorized.

It can be observed that the history plots of n, log(dose+1) and agecode parameters indicate samples forming a random scatter about a stable mean an indication that convergence may have been achieved. In addition, it can be observed that the posterior distribution was explored quickly and there is good mixing since the three chains are moving together. The kernel density plots appear to be quite smooth for three parameters. The autocorrelation plots show presence of low correlation of the subsequent values in the chain as a function of the lag. This implies that the posterior distribution of the parameter is explored quickly. From the BGR graphs, the estimated potential scale reduction factor is almost equal to one (1), and then the three chains can be assumed to have mixed and converged to the posterior distribution. Furthermore, the estimate R is smaller than the recommended threshold 1.2, the Gelman and Rubin rule of thumb for convergence.

The model estimated had a DIC of 159.612 which is smaller than 161.395 for model with interaction indicating a better fit. The posterior summary measures obtained from the analysis are given in Table 8.

Table 8: posterior summary measures obtained from analysis based on model without interaction.

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
Intercept	beta[1]	-3.8260	0.6104	0.0024	-5.0480	-3.8170	-2.6520	10001	453000
Studysize(n)	beta[2]	-0.0224	0.0057	8.49E-6	-0.0343	-0.0221	-0.0120	10001	453000
Log(dose+1)	beta[3]	1.4010	0.6443	0.0021	0.1714	1.3900	2.6980	10001	453000
Agecode(1)	beta[4]	-0.0105	0.2745	4.09E-4	-0.5518	-0.0098	0.5262	10001	453000
femaleprop	beta[5]	0.0391	0.7244	0.0021	-1.3980	0.0438	1.4460	10001	453000
Var.studie	Var.studie	0.0155	0.0233	2.56E-4	5.85E-4	0.0069	0.0809	10001	453000

It can be seen that there is good precision of the estimates since for each estimate the MC error is less than 5% of the standard deviation. Concerning credible intervals, for example the intervals of study size (-0.0343,-0.0120) and Log(dose+1) with (0.1714,2.6980) imply that there is a 95% probability that the true parameter value lies in those respective intervals. Since the two intervals of study size and Log(dose+1) don't contain 0, the two are important factors that affect the Excellent Intubation condition probability. The estimated standard deviation 0.124 ($\sqrt{0.0155}$) gives indication of how much the true EIC probability varies between the studies.

A sensitivity analysis was performed by changing the prior distribution for var.studie to a uniform distribution with parameters (0, 100) for sigma.studie. Convergence was achieved after 141,000 iterations, allowing over relaxation and removal of 1000 burn in part. The DIC value for this model was 160.184 which was slightly higher than 159.612 the DIC for the model where the variance had inverse gamma distribution. The parameter estimates in Table 9 obtained assuming a uniform distribution for standard deviation of the random effects were very close to those obtained when a gamma distribution was assumed for the variance. The estimated standard deviation which indicates how the true EIC vary between the studies is more less the same (0.12) in both models.

Table 9: posterior summary measures obtained from analysis changing the prior distribution.

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
Intercept	beta[1]	-3.8310	0.6135	0.0025	-5.0700	-3.8220	-2.658	10001	393000
Study size(n)	beta[2]	-0.0223	0.0057	9.47E-6	-0.0343	-0.0221	-0.012	10001	393000
Log(dose+1)	beta[3]	1.4060	0.6490	0.0023	0.1725	1.3930	2.7220	10001	393000
Agecode(1)	beta[4]	-0.0114	0.2761	4.39E-4	-0.5556	-0.0106	0.5273	10001	393000
femaleprop	beta[5]	0.0385	0.7238	0.0023	-1.3960	0.0447	1.4420	10001	393000
sigma.studie	sigm.studie	0.1186	0.0913	0.0017	0.0043	0.0991	0.3408	10001	393000

5. CONCLUSION AND DISCUSSION

One important use of intubation is during surgery to keep the airway open for delivery of anaesthetic drugs and oxygen (Smith, 2003). During surgery and using tracheal intubation the patient can be placed on a ventilator to assist with breathing and depolarizing or non-depolarizing muscle relaxant such as succinylcholine or rocuronium respectively can be used (Wolters, 2000). Knowing the probability of adequate relaxation may help in choosing an appropriate dose of succinylcholine and that can be life-saving. Given succinylcholine dose, considerable between study differences in excellent intubation conditions can be found and this can be done by meta-analysis.

Meta-analysis is a combination of quantitative evidence from studies that have investigated a common question. Appropriate model selection in meta-analysis is the key requirement: fixed (marginal) versus random effects. Different fixed models and random effects models within classical model framework were fit to investigate whether patient characteristics or

methodological issues can explain any of the heterogeneity in excellent intubation condition between studies. In addition Bayesian hierarchical model was fit for comparison purposes.

For classical models, the results showed that models correcting for extra binomial variability (overdispersion) fit the data better. The major cause for extra variability is the heterogeneity between and within studies. The Beta-Binomial model with covariates; log(dose+1), study size and age categorized was better fitting marginally. Also under the random effects the model with the same covariates was of a better fit. In both models it is observed that Log(dose+1), study size, age categorised, Logdose1*agecode interaction are significant covariates affecting the excellent intubation condition (EIC) probability.

The beta-binomial indicated that the one unit increase in Log(dose+1) corresponds to an increase of 3.77 times the odds of EIC. In addition, after controlling for other covariates in the model, the odds of EIC decreases multiplicatively by 0.99 for every 1-unit increase in study size. For categorised age, studies with average age>40 (agecode 1) were 5.76 times less likely to have an outcome of EIC compared to those studies with average age<40. Also across the two age groups the effect of Log(dose+1) to the odds of EIC is not the same due to the significant interaction effect of Logdose1*agecode.

For the Random effects model same covariates as the Beta-binomial were significant though the odds ratio obtained from this model imply study-specific log odds ratio. In both Beta-Binomial and random-effects model, it is seen that methodological issues are able to explain heterogeneity in excellent intubation condition (EIC) within and between studies. This is evidenced by significant overdispersion (extra binomial variability) parameters. That is to say, correlation estimate of 0.1091 indicates there exists within study dependences for Beta-Binomial and sigma 1.0067 (standard deviation of random intercept) the unexplained heterogeneity between studies.

When the Bayesian hierarchical model was fit study size and Log(dose+1) were the two important factors that affect excellent intubation condition probability. The results didn't differ so much when a sensitivity analysis was done. The estimated standard deviation 0.0124 gives indication of how much the true EIC probability vary between the studies. There exists difference in the Bayesian results compared to the classical random-effects. This may be due to the fact that when number of studies is small, the Bayesian hierarchical

model between-studies variance estimate has more precision than the estimate from the classical random-effects model (Borenstein et al., 2009). For this analysis 80 studies is quite large enough thus classical random-effects may be more precise than the Bayesian model. In addition Altham, (1971) as cited by Agresti, (2002) showed that the logit model with subject (study)-specific probabilities in which the probability varies by subject but the occasion effect is constant, the Bayesian evidence against the null hypothesis is weaker as the number of pairs giving the same response at both occasions increases, for fixed values of the numbers of pairs giving different responses at the two occasions. This differs from the conditional random-effects result, which does not depend on such pairs.

Factors like use of opioids, RSI and nasal intubation though important in leading to improved intubation condition (El-Orbany, 2007) did not show significance in the considered models. This may be due to a limited number of studies which used them as seen in Table 2 leading to poor precision. Succinylcholine dose is observed to have higher odds of EIC in all models 3.770 for beta-binomial, 4.235 for classical random effects model and 1.406 for Bayesian hierarchical model. These odds ratio estimates are in agreement with what was found by Hiestand et al., (2011) who performed a meta-analysis using Logistic regression to assess the impact of succinylcholine use on the odds of first-attempt intubation. They further indicate that after propensity score adjustment, succinylcholine was associated with a higher incidence of first-attempt intubation (odds ratio 1.4, 95% CI 1.1-1.8), as well as improved odds for requiring fewer attempts to intubate (odds ratio 1.5, 95% CI 1.2-1.9), as compared with rocuronium. In addition a systematic review of 58 studies by Perry et al., (2008) using relative risk, random-effects model, excellent intubation conditions as outcome gave similar conclusions. In this study it was found out that succinylcholine was superior to rocuronium, with relative risk 0.86 (95% confidence interval (95% CI) 0.80 to 0.92) (n = 2690). Although succinylcholine is evidenced in the literature to be a better muscle relaxant compared to rocuronium, it should not be used in presence of hyperkalemia and/or a family history of malignant hyperthermia to avoid a reverse reaction of the drug (Kumar et al., 2010).

This difference in parameter estimates, magnitude and significance across different models used in this meta-regression may be due to the different methodological issues involved when fitting the models. For the marginal model estimates the assumed common effect, random-effects model estimates the mean of a distribution of effects across studies and the

Bayesian hierarchical model using prior information. Nevertheless narrowing to random effects model in both classical and Bayesian approaches there exists heterogeneity across studies. This heterogeneity may be caused by the clinical and methodological diversity among the studies which were included in this meta-regression.

It is worthwhile to note that reaching reliable conclusions from meta-regression remains an obstacle (Thompson and Higgins, 2001). This is caused by the problem of ecological bias which is paramount in meta-regression, as the analysis is conducted at the study-level and does not include the underlying patient-level variation. This usually occurs when averages of patient characteristics in each trial or proportion of gender are used as covariates in the regression. This is observed in this analysis with age variable and more for age categorised. When included in the model there was a considerable change in results. The ecological bias in the long run may interfere with the covariate relationship in that, the relationship with patient averages across trials may not be the same as the relationship for patients within trials.

As a recommendation and area for further research, this ecological bias can be avoided by pre-specification of covariates to be investigated as potential sources of heterogeneity. However in practice this is not always easy to achieve. In addition, one may consider conducting meta-regression on other different types of patients such as the elderly or only the young to see which age category yields higher odds of excellent intubation condition.

To alleviate some problems in meta-analysis individual patient data, both of outcomes and covariates should be included in meta-regression. This is also recommended by Thompson and Higgins, (2001) where they state that within trial and between trial relationships can be more clearly distinguished, and confounding by individual level covariate be investigated by use of the individual patient data. This calls for exposition and development of statistical methods for individual patient data meta-regression.

Basing on the view of this project it should be noted that heterogeneity in meta-analysis remains an important issue and with regard to problems mentioned in meta-analysis (meta-regression), interpretation and inference of results should be done with caution else they can be misleading.

6. REFERENCES

Agresti, A. (2002). *Categorical Data Analysis.* (2nd edition), New York: John Wiley & Sons, Ltd.

Borenstein, M., Hedges, L., Higgins, J., and Rothstein, H. R. (2009). *Introduction to Meta-Analysis.* Chichester: John Wiley & Sons, Ltd.

Brincat, V.J. and Macleod, A.D. (2007). Adverse effects of opioids on the central nervous systems of palliative care patients.Pain Palliat Care Pharmacother, 21(1), 15–25.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/17430825 accessed on 13th April, 2011.

Cerner Multum, (1996). Drugs and treatment. Available at:
http://www.revolutionhealth.com/drugs-treatments/rocuronium#side_effects accessed on 20thApril, 2011.

Demand Media, (1999). Side Effects of Succinylcholine.
Available at: http://www.ehow.com/about_5372773_side-effects-succinylcholine.htm accessed on 11th April, 2011.

El-Orbany, M. (2007).Opioids and rapid-sequence induction. Vol. 99, issue 4.
Available at: http://bja.oxfordjournals.org/content/99/4/598.full accessed on 2nd September, 2011.

Helser, T.E., and Lin, H.(2004).A Bayesian Hierarchical Meta-analysis
Ecological Modelling Vol. 178, issue 3-4. Available at:
http://www.mendeley.com/research/a-bayesian-hierarchical-metaanalysis-of-fish-growth-with-an-example-for-north-american-largemouth-bass-micropterus-salmoides/accessed on 12th August, 2011.

Hiestand, B., Cudnik, M.T., Thomson, D., and Werman, H.A. (2011). Rocuronium versus Succinylcholine in Air Medical Rapid-Sequence Intubation. Vol.15 issue 4.
Available at: **http://www.ncbi.nlm.nih.gov/pubmed/21568699?dopt=AbstractPlus** accessed on 2nd September, 2011.

Hosmer, W. and Lemeshow, W. (2000). *Applied Logistic Regression*. (2nd edition), New York: John Wiley & Sons, Ltd.

Kabacoff, R.I. (2011). Histograms and Density plots. Available at:

http://www.statmethods.net/graphs/density.html accessed on 26th May,2011.

Kopman, A., Klewicka, M., and Neuman, G. (200). An Alternate Method for Estimating the Dose-Response Relationships of Neuromuscular Blocking Drugs. Vol. 90, issue 5. Available at: http://www.anesthesia-analgesia.org/content/90/5/1191.long accessed on 30[th]July, 2011.

Kumar, P., Denson, S.E., Mancuso, T.J. (2010). Premedication for Nonemergency Endotracheal Intubation in the Neonate. Vol.125 issue 3. Available at: http://pediatrics.aappublications.org/content/125/3/608.full accessed on 4[th]September, 2011.

Lan, T.H., Nguyen, N.D., Nguyen, T.V. (2009). Effect of vegetarian diets on bone mineral density: a Bayesian meta-analysis, Vol.90, issue 4. Available at: http://www.ajcn.org/content/90/4/943.full accessed on 10[th]August, 2011.

Loannidis, J.P.A., Patsopoulos, N.A.,Evangelou, E. (2007). Heterogeneity in Meta-Analyses of Genome-Wide Association Investigations. Vol. 2, issue 9. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1950790/ accessed on 25th July, 2011.

Morton, S.C., Adams, J.L., Suttorp, M.J., et al. (2004). Meta-regression Approaches: What, Why, When, and How?Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/metareg/metareg.pdf accessed on 10th July, 2011.

Pang, C.S., and Leng, P.K.(2005). Bayesian Meta-analyses of the Tolerability of Selective SerotoninReuptake Inhibitors and Tricyclic Antidepressants for Treating Patients with Depression. Evidence-Based medicine, Vol. 14, issue 1. Available at: **http://www.pgmi.com.sg/SGHproceeding/14 1/bayesian%20meta%20analysis.pdf** accessed on 10th August, 2011.

Perry, J.J., Lee, J.S., Sillberg, V.A.H., and Wells, G.A. (2008). Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD002788.

Available at: http://www2.cochrane.org/reviews/en/ab002788.htm accessed on 4[th]September, 2011.

Smith, S.E. (2003). What is intubation.

Available at: http://www.wisegeek.com/what-is-intubation.htm accessed on 6th April, 2011.

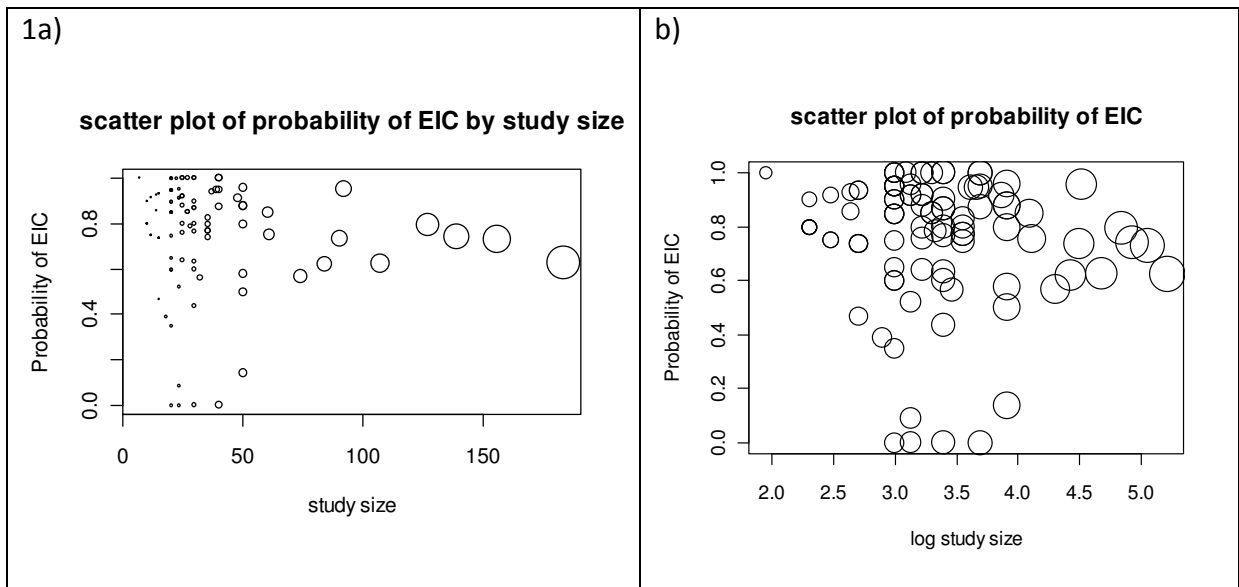Sterne, A.C., and Harbord, R.M. (2004). Funnel plots in meta-analysis. Vol. 4, issue 2.

Available at: http://ideas.repec.org/a/tsj/stataj/v4y2004i2p127-141.html accessed on 8th July, 2011.

Wolters, K. (2000). Succinylcholine.

Available at: **http://www.drugs.com/cdi/succinylcholine.htm** accessed on 8th April, 2011.
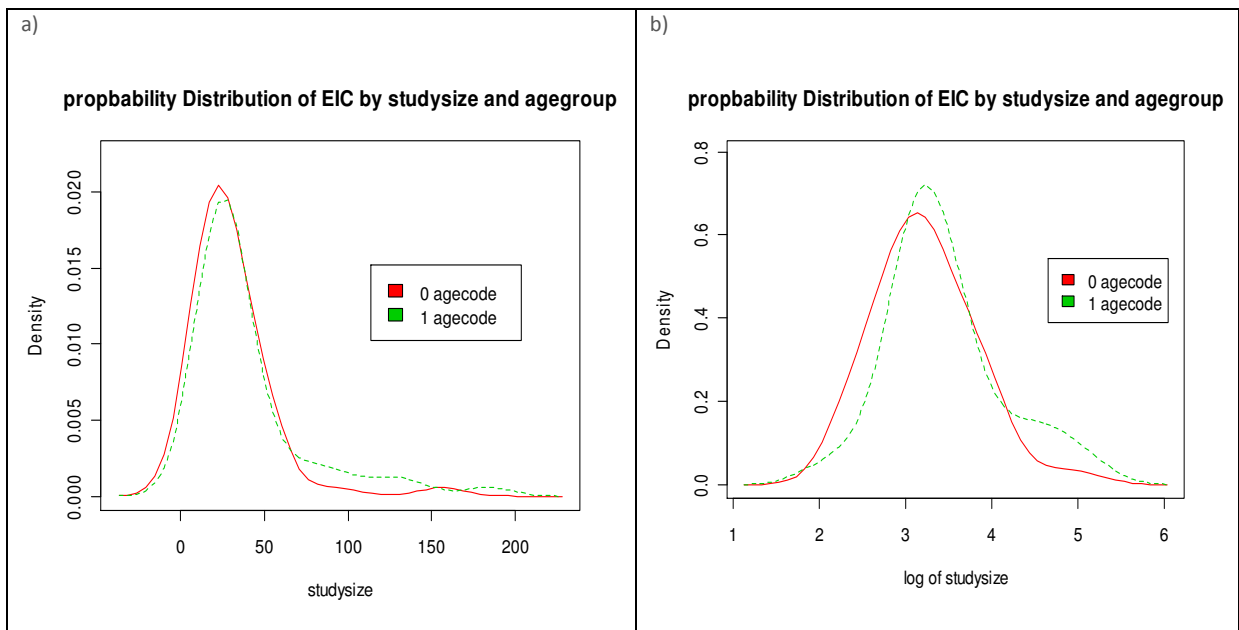
7. APPENDICES
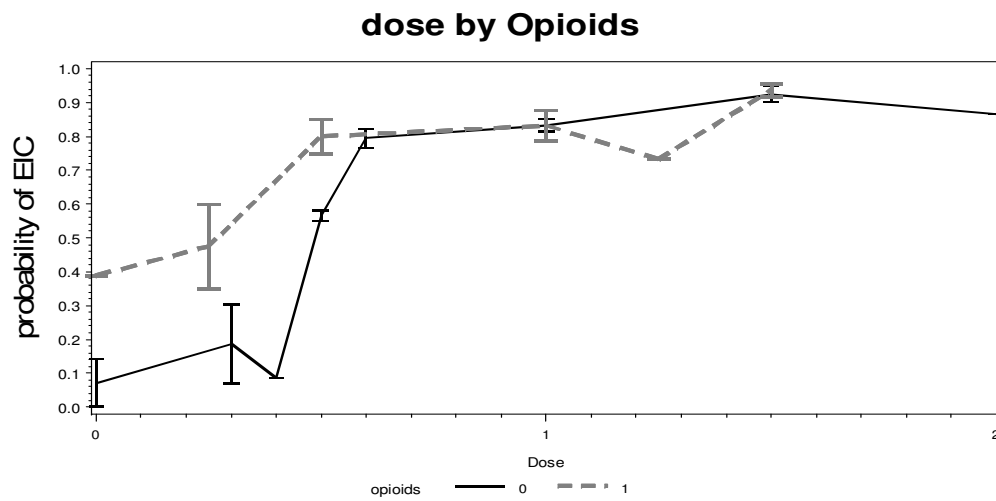
Appendix 1. Simple scatter plots of EIC by study size

Appendix 2. Density plots of EIC by study size

Appendix 3. Plot of succinylcholine dose by opioids

dose by Opioids

Appendix 4*: Parameter estimates (standard errors) for extended Ordinary multiple logistic model*

Parameter	DF	Estimate	Error	Wald Chi_Square	Pr>Chisq
Intercept	1	-2.2396	0.6294	12.6630	0.0004
Y_code	1	-0.0311	0.0119	6.8523	0.0089
n	1	-0.0073	0.0010	58.4412	<.0001
Dose	1	4.1922	0.6016	48.5651	<.0001
gender(femaleprop)	1	3.2708	1.0478	9.7446	0.0018
Opioids	1	0.3412	0.3324	1.0537	0.3046
Dose*femaleprop	1	-2.8080	1.0432	7.2455	0.0071
Dose*Opioids	1	-0.2191	0.3563	0.3780	0.5387

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