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# RISK OF MATERNAL MORTALITY USING RELATIVE RISK RATIOS OBTAINED FROM POISSON REGRESSION ANALYSIS

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**ABSTRACT**

This paper highlights the importance of carrying out a meta-analysis in epidemiologic research of a non-common outcome without the loss of study/ies due to insufficient data. A good number of researches have adequately covered common disease outcomes in a meta-analysis, however, non-common disease outcomes have not been well determined. This paper proposes the use of relative risk ratios as effect sizes for the meta-analysis of non-common disease outcomes, obtainable from the Poisson regression analysis which is usually reserved in statistics for count data, where response outcomes are rare or non-common. Many users of meta-analysis are inclined to health-Science; hence they lack the Statistical competence with which to tackle the draw backs encountered while meta-analyzing non-common disease outcomes. Some draw backs include: Small number of studies available for the meta-analysis; Presence of heterogeneity; Insufficient data to be able to collate effect sizes. The literature used for this paper encountered loss of data in the Loudon, 1992 study, following the use of Poisson regression analysis, a relative risk ratio (RR) of 2.83 was obtained with a confidence interval of (2.62, 3.06). Literature was expanded to Google Scholar, Cochrane database, jstor website, MEDLINE, PUBMED and relevant journals of maternal healthcare. Twenty studies were meta-analyzed altogether, and results were in favour of mortality with a relative risk ratio and confidence interval of 1.66 and (1.32, 2.09) respectively. There was a high presence of heterogeneity from the result of I-squared = 77.1%, p-value <0.001. Sequential use of sensitivity analysis reduced heterogeneity and the risk of mortality by 12%, p-value<0.001; relative risk ratio, 1.91 [confidence interval (1.53, 2.39)] for fifteen studies that were not excluded but were meta-analyzed.

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## INTRODUCTION

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. This paper is an inspiration of the work of (Greenland, 1989 & 2014), where a detailed commentary is given, generalizing statistical techniques and the use of epidemiological data. Some of the techniques that were discussed included regression methodology, bias and confounder control as it affects model selection and validation of results. The scope of the work did not cover issues bordering on Meta-analysis. However, in (Greenland, 2004), because of the importance and effectiveness of meta-analysis in epidemiologic research, common outcomes of case-control studies of a meta-analysis were published. The article provided valid methods for all study designs, including case-control studies, cohort studies, and clinical trials in common outcomes.

The problem formulation in a meta-analysis often is controlled by the analyst(s) who carried out the primary research studies. As such, a meta-analyst may conduct a sensitivity analysis before including any study in the analysis (Becker & Hedges, 1992). However, in this research, access to some of the Loudon, 1992 data allowed for computation of the relative risk ratio, which was not originally provided by the original analyst. The computation of the relative risk ratio allowed for the inclusion of the Loudon, 1992 study in the meta-analysis, thereby, increasing the number of studies meta-analyzed, which meant an inherent increase in statistical power. There are many studies that have been meta-analyzed for common outcomes in literature, such analyses have large number of studies and less heterogeneity. To mention a few, (Wagner *et al.*, 1997), published 86 studies that were classified and a meta-analysis was conducted of 124 correlation coefficients obtained from the studies, to determine whether distinguishing between conceptual frameworks portends differences in the findings of U. S. research on the effect of participatory processes on performance and satisfaction. Because of cultural differences, data for the meta-analysis were obtained only in the United States of published research on participation-performance versus participation-satisfaction. Studies included in the sample were those that contrasted distinctions such as directive and participatory management practices, autocratic and democratic leadership, directive and participatory goal setting, or lecture versus group discussion processes of persuasion. All 124 correlations produced a weighted mean correlation of 0.28 and were included in a single meta-analysis, a grand mean was obtained, and the presence of enough unexplained variance in the total sample was verified to allow further subgroup analysis. All of the weighted mean correlations revealed in the meta-analysis were statistically significant (95% confidence interval). The final results revealed noticeable differences in the findings between participation and satisfaction research.

The relevance of a meta-analysis in education evaluation and policy analysis was illustrated by conducting a MA on the relationship between class size and achievement, (Simpson, 1980). However, the paper encourages that issues of bias must be effectively dealt with to obtain a true representation of results and decision. Ng Thomas & Feldman (2008) have it that meta-analysis was used to examine the relationship between hours worked and indicators of organizational identity. The meta-analysis explored other correlates of hours worked (e.g., situational demands, job performance, mental health, and physical health), moderating variables (e.g., age, gender, and job complexity), and curvilinear relationships of work hours to social identity indicators. The results of the meta-analysis showed that occupational factors and situational demands had the strongest relationships with hours worked. Hours worked were negatively associated with measures of employee well-being. Gender had several significant moderating effects, and there were curvilinear relationships between hours worked and well-being and work-family conflict variables. Becker & Wu (2007) presented a multivariate generalized least squares approach to the synthesis of regression slopes. They opined that results of regression methodology have often been omitted from meta-analysis because of a lack of knowledge about how to synthesize indices from the analysis, or because of the complexities and assumptions underlying the process of synthesis. The authors proposed that in the face of such difficulty, we should identify the predictor of importance in each regression equation and use its slope, say $X_i$, across studies in the meta-analysis. The responses, say $Y_i$, should also be measured across studies and used in the meta-analysis. The raw data may be needed to construct a covariance matrix using the ordinary least square regression across studies, so that the estimates obtained is added to a function of raw data from the original (within-study) regressions. If covariance estimates are not available, sensitivity analysis should be undertaken to investigate the robustness of the results to different amounts of correlation, (Jones *et al.,* 2009). Sultan *et al.,* (1996) did a paper that won an award called the O'Dell award in marketing research in meta-analysis. Diffusion of new products is of interest to marketers as a result of impact of innovation on firm profitability. Meta-analysis in the paper provided the kind of generalizations that are valued by marketing practitioners. A systematic review and meta-analysis assessed the effect of alcohol consumption on multiple cardiovascular outcomes. Conclusion of the study indicated that light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes, (Ronksley *et al.,* 2011). Meta-analysis was conducted for outcomes of overall mortality from cardiovascular disease, incident coronary heart disease, incident stroke, and mortality from stroke. Also, a sensitivity analysis with lifetime abstainers of alcohol as the reference category to account for heterogeneity within the reference group of non-drinkers was carried out.

The risk ratio of perinatal mortality was assessed by (Arbyn *et al.*, 2008), severe preterm delivery, and low birth weight associated with previous treatment for precursors of cervical cancer. The meta-analysis showed that, among all the excisional methods used in the treatment of cervical intraepithelial neoplasia, cold knife conisation was consistently associated with serious adverse pregnancy outcomes. Laser conisation increased the risk of perinatal mortality and very low birthweight infants. Larsson & Wolk (2007) identified 11 cohort studies of excess body weight and risk of liver cancer for a meta-analysis. Results from individual studies were combined using a random-effects model. The conclusion of the analysis was that excess body weight is associated with an increased risk of liver cancer. The risk ratios and corresponding standard errors (derived from the Confidence Intervals) from individual studies were logarithmically transformed to stabilize variances and normalize the distributions. Summary risk ratios were calculated for overweight (BMI (Body Mass Index) 25-30 $kgm^{-2}$) and obesity (BMI ≥ 30 $kgm^{-2}$) versus normal weight (BMI 18.5- 24.9 $kgm^{-2}$). For the two categories of BMI that fell into the category representing overweight or obesity, the pooled risk ratio estimate was used in the meta-analysis. Lehmann & Hedges (2001) proposed a method, should there be the same independent variable used in all studies. He introduced aggregation, in which case there is a clear distinction of variables in the meta-analysis, and this increases the error term in the analysis to enhance the power of the test. For non-common outcomes, it is difficult to assemble literature for a meta-analysis in the fashion mentioned above, enumerating the work of authors in the area of rare outcomes is indeterminate. This paper provides a platform for future research of non-common outcomes and meta-analyses.

## METHODS AND MATERIALS

Inclusion criteria for the studies that were meta-analyzed are those studies with the following characteristics: -

- Hemorrhage was reported in patients.
- Relative risk ratios were reported in respect of hemorrhage related to mortality in the patients.
- Mortality related to pregnancy was reported.
- Baseline characteristics of the study subjects were reported.

There was the need to identify studies that did not report the relative risk ratio, but could provide enough data with which to compute it using the statistical methods of Poisson regression analysis. It is necessary to highlight issues bordering on Poisson regression which is reserved for rare disease outcomes, and usually pertains to count data.

**Table 1. Regression analysis for maternal mortality**

| | d.f. | deviance | mean deviance | deviance ratio |
|---|---|---|---|---|
| Regression | 1 | 50.61707943 | 50.61707943 | 50.62 |
| Residual | 14 | 28.32261377 | 2.023043841 | |
| Total | 15 | 78.9396932 | 5.262646213 | |
| Change | -1 | -50.61707943 | 50.61707943 | 50.62 |

**Table 2: Estimates of regression coefficients in maternal mortality data**

| | ESTIMATE | S.E. | T |
|---|---|---|---|
| CONSTANT | 2.101 | 0.132 | 20.95 |
| # of deliveries | 0.0003304 | 0.000054 | 8.11 |

**Table 3. Regression analysis in maximal model of maternal mortality case**

| | d.f. | Deviance | mean deviance | deviance ratio |
|---|---|---|---|---|
| Regression | 2 | 65.14501051 | 65.14501051 | 65.15 |
| Residual | 13 | 13.79468269 | 1.061129438 | |
| Total | 15 | 78.9396932 | 5.262646213 | |
| Change | -2 | -65.14501051 | 65.14501051 | 65.15 |

**Table 4. Estimates of regression coefficients in maximal model of maternal mortality case**

| | ESTIMATE | S.E. | T |
|---|---|---|---|
| CONSTANT | 1.352 | 0.248 | 5.38 |
| # of deliveries | 0.00033 | 0.0000613 | 5.4 |
| Cause of mortality | 1.0451 | 0.273 | 3.82 |

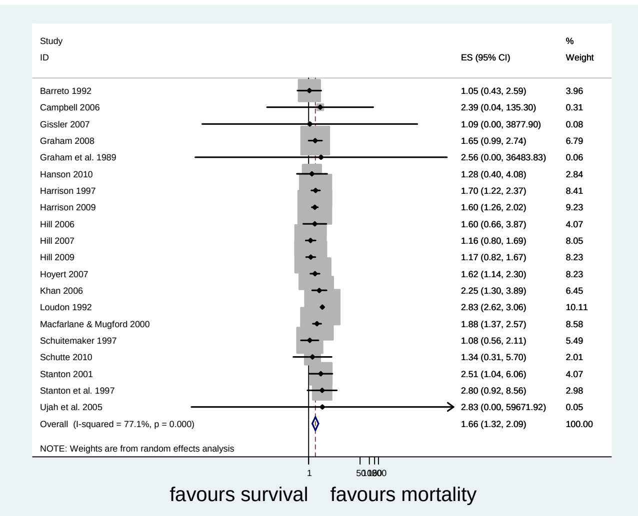


**Figure 1. Meta-analysis of 20 studies from maternal mortality data**

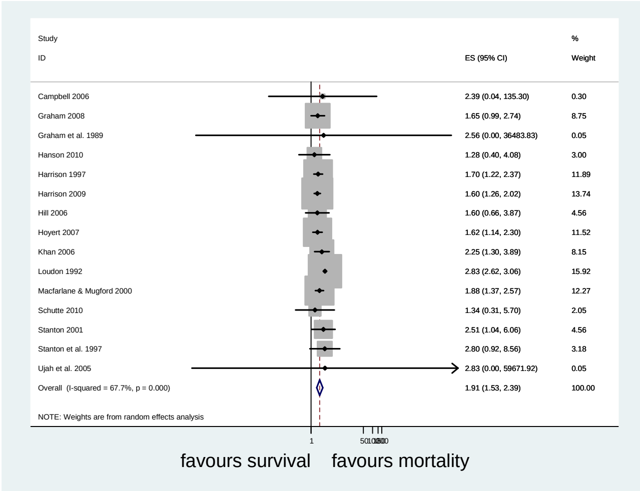


**Figure 2. Meta-analysis of 15 studies from maternal mortality data with reduced heterogeneity**

If $X \in R^n$ is a vector of explanatory variables, then the Poisson regression model takes the form $Log(E(Y/X)) = \alpha + \beta' X$, where $\alpha \in R$ and $\beta \in R^n$. Sometimes this is written more compactly as $Log(E(Y/X)) = \theta' X$, where x is now an (n+1) dimensional vector consisting of n explanatory variables concatenated to a vector of ones. Here $\theta$ is simply $\alpha$ concatenated to $\beta$. Thus, when given a Poisson regression model $\theta$ and an input vector x, the predicted mean of the associated Poisson distribution is given by

$$E(Y/X) = e^{\theta' X}$$

Let $\beta_p^* = (\beta_0^*, \beta_1^*, \ldots, \beta_p^*)$ be the maximum likelihood estimates of the model parameters $(\beta_0, \beta_1, \ldots, \beta_p)$ of the full model with p explanatory variables and $\beta_q^*$ the estimates of a simpler model where only q (q<p) of the explanatory variables have been used.

Then for large K, and under suitable regularity conditions, the deviance $DEV = 2 \cdot (l(\beta_p^*) - l(\beta_q^*))$

Is approximately $\chi^2_{p-q}$ distributed if the less complex model is true.

The deviance ratio (DR) is given by;

$$DR = \frac{DEV}{df}$$

where df is the degrees of freedom.

Death among pregnant women is more prominent in patients who have hemorrhage, that is, a condition whereby a pregnant mother loses blood. (Ujah *et al.* 2005) provided the cases of maternal mortality to include hemorrhage (34.6%), Sepsis (28.3%), eclampsia (23.6%), induced abortion (9.4%), uterine rupture (3.1%), obstructed labour (0.3%), extrauterine pregnancy (0.3%), trophoblastic disease (0.3%). Based on the percentages, only the first two pregnancy related conditions have been coded for use in the Poisson regression. The codes follow: Sepsis-0, Hemorrhage-1. The (Loudon, 1992) data did not provide the effect measure that was needed to run the meta-analysis, to calculate it, the Poisson regression analysis was carried out for maternal mortality against number of delivery, using MATLAB software. The results provided for smaller model, the deviance results of 50.6, 28.3 and 78.9 for regression sum of squares, error sum of squares and total sum of squares respectively, the deviance ratio was 50.6. The regression equation, based on the estimates of the regression coefficients is,

$$Log_e(MMR) = 2.101 + 0.0003304(\#of\ deliveries)$$
$$MMR = e^{2.101} \times e^{0.0003304(\#of\ deliveries)}$$

adding a second term, cause of mortality, to the model, the regression model for maternal mortality against number of delivery and cause of mortality is a full model (maximal) model, the deviance results were 65.1, 13.8 and 78.9 respectively, the deviance ratio was 65.1. The maximal equation, based on the estimates of the regression coefficients is,

$$Log_e(MMR) = 2.101 + 0.0003304(\#of\ deliveries)$$
$$MMR = e^{2.101} \times e^{0.0003304(\#of\ deliveries)}$$

Maternal mortality ratio caused by hemorrhage = 3.86 x 1 x 2.84 = 10.97 approximately 11; Maternal mortality ratio caused by Sepsis = 3.86 x 1 = 3.86 approximately 4; Deviance = 65.15-50.62 = 14.53; Difference in degree of freedom = 2-1 = 1. It follows the Chi-square distribution with 1 degree of freedom, the result is significant (P<0.001), indicating that the maximal model is a good fit.

The relative risk (RR) associated with Maternal mortality ratio caused by hemorrhage is

$$RR = e^{1.0451(cause\,of\ mortality\,as\,hemorrhage)} = 2.83$$

The result is interpreted thus, that the risk of maternal mortality is 2.83 times higher in patients with hemorrhage than those without. Selecting arbitrarily, the relative risk associated with Maternal mortality ratio of 100 deliveries as compared with 20 deliveries is,

$$RR = \frac{e^{0.00033(100)}}{e^{0.00033(20)}} = 1.027$$

Similar estimates can be used to calculate the relative risk ratio associated with different explanatory variables to be used for meta-analysis of non-common outcomes. The (Loudon, 1992) study was included in the meta-analysis together with 19 additional studies and the results favoured mortality in pregnant women who are hemorrhagic, relative risk ratio and confidence interval of 1.66 and (1.32, 2.09) respectively. There was a high presence of heterogeneity from the result of I-squared = 77.1%, p-value <0.001. Heterogeneity and risk of mortality was reduced by 12% with sequential use of sensitivity analyses which resulted in fifteen studies to be meta-analyzed, $I^2$=67.7%, 1.91 (1.53, 2.39).

**Summary and Conclusion**

Meta-analysis is a statistical tool used by several disciplines, meta-analysts who lack the statistical competence to appreciate some of the draw backs of non-common outcomes data should seek statistical assistance where non-common outcomes are involved. The computation of the relative risk ratio from Poisson regression models is a major achievement of this paper. More research should be carried out on non-common outcomes, to further test the methods enumerated. The meta-analysis reveals a high risk of mortality among pregnant women with hemorrhage, pregnant women should be handled with care during ante-natal visits, enough to treat symptoms of hemorrhage as soon as it manifests. This will go a long way in avoiding or reducing the cases of death.

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