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META-REGRESSION ANALYSIS OF RANDOMIZED CONTROLLED TRIALS OF THE RISK FACTORS OF SICKLE CELL DISEASE

[1]Adehi M.U., [1]Omole O.O., [1]Bilkisu M., [1]Adenomon M.O. and [1]Audi N.I.
Email: maryunekwu@nsuk.edu.ng/ omoleomotayo356@gmail.com/ maijamaab@nsuk.edu.ng/ adenomonmo@ nsuk.edu.ng/ najibaudi@ nsuk.edu.ng

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Abstract
Replications are important for science, both statistically and otherwise. A plethora of epidemiology studies that have been done shows that there are always variations, errors and inconclusive findings in sickle cell disease. This paper intends to compute the underlying risk factor in sickle cell disease using meta-regression. These efficacy scores are retrieved from 19 studies. The effect size index was risk ratio and date were sourced via Pubmed, Science Direct, Web of Science, Medline, Rechargegate and Google scholar. The random-effect model was employed for the analysis. The studies in the analysis were assumed to be random samples from a vast number universe of sickle cell disease studies. The summary effect size was 1.84, with (95% CI: 1.567 - 2.148). The Z-value tested the null hypothesis that the summary effect size is 1. We found $Z = 7.540$ with $p < 0.001$ for $\alpha = 0.05$; hence, we reject the null hypothesis and concluded that the summary effect size is not precisely 1. This study shows that the 3 moderators sighted are not responsible for the risk factors of sickle cell disease with $p > 0.05$. The Begg and Mazumdar rank correlation test, egger test, and funnel plot were used to determine publication bias across studies. To evaluate heterogeneity I^2statistic and tau-squared were used.

1.0 Introduction

In primary studies we use regression, or multiple regression to assess the relationship between one or more covariates (moderators) and a dependent variable. Essentially same approach can be used with meta-analysis, except that the covariates are at the level of the study rather than the level of the subject, and the dependent variable is the effect size in the studies rather than subject scores. We use the term meta-regression to refer to these procedures when they are used in a meta-analysis. The differences that we need to address as we move from primary studies to meta-analysis for regression are similar to those we needed to address as we moved from primary studies to meta-analysis for subgroup analyses. These include the need to assign a weight to each study and the need to select the appropriate model (fixed versus random effects). Systematic reviews were developed to resolve such situations which comprehensively and systematically summarize all relevant empirical evidence

[1]Department of Statistics, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi Nigeria

(Stroup et al., 2023). Many systematic reviews include meta-analysis, which use statistical methods to combine the results of individual studies. Through meta-analyses, researchers can objectively and quantitatively synthesize results from different studies and increase the statistical strength and precision for estimating effects.

Sickle-cell disease (SCD) is a group of disorders that causes the that cause the red blood cells break down to become misshapen and break down. SCD is an inherited hemoglobinopathy, with an estimated 300,000 babies born worldwide with the disease. Piel et al., (2017). In the United States, an estimated 100,000 – 120,000 people live with SCD, primarily of African American or Hispanic descent. Hassell, (2010). Africa has been associated with the highest prevalence of the sickle cell trait, with figures suggesting that between 10% and 40% of the entire population may be affected. Adigwe et al., (2023).

According to Card & Krueger (1995) and Tesfaye & Tadele (2019), the main goal of a 'meta-analysis' of observational studies is not to determine an overall estimate of effect but rather to look into the causes behind variations in estimates between studies and identify patterns of estimates. In meta-analysis, there are commonly two ways to create the quantitative review. One method is to combine probability values or *Z* scores; a different method is to combine effect sizes like Cohen's *d*, correlation coefficients, or effect sizes like Cohen's *d*. The central premise of this research is that the characteristics of the studies can account for the difference in efficiency indices reported in the literature. The fundamental problem with publication bias is that not all completed studies are published, and the selection process is biased. When "editors, reviewers, or researchers" favor statistically significant findings, publication selection occurs (Stanley, 2005). The funnel plot represents is a representation of the relationship between effect size on the horizontal axis and a metric of study size (often standard error or precision) on the vertical axis. The optimum option for the vertical axis is typically the standard error (Sterne and Egger, 2001). Large studies are visible near the top of the "graph" and frequently congregate close to the mean effect size. Smaller studies are shown at the "bottom of the graph" and will be spread throughout a range of values because there is more "sampling variation" in effect-size estimates in smaller studies.

2.0 Method

This paper has adopted the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standard. Our methods for conducting searches, gathering data, and publishing results all adhere to Havránek et al.'s (2020) and Wang et al.'s (2023) standards for performing meta-analyses. Data were, date was sourced via Pubmed, Science Direct, Web of Science, Medline, Recharge gate, and Google Scholar and. For the model specification, the random Random-effects meta-regression model can be expressed as (Berkey et al., 1995)

$$\widehat{\theta_\iota} = x_i\beta + u_i + \varepsilon_i \qquad (2.1)$$

Where;

$$u_i \sim N(0, \tau^2)$$

$$\varepsilon_i \sim N\left(0, \widehat{\sigma_\iota^2}\right)$$

Mixed-effects meta-regression model can be expressed as (Berkey et al., 1995)

$$\widehat{\theta_\iota} = \theta + \beta x_k + \epsilon_k + c_k \qquad (2.2)$$

R^2 in meta-analysis is defined as the proportion of true variance explained by the covariates, since the true variance is estimated as T^2.

$$R^2 = \frac{\tau^2 explained}{\tau^2 total} \qquad (2.3)$$

$0 \leq R^2 \leq 1$

R^2 that falls outside the range of 0 to 1 is due mainly to sampling error (Borenstein et al., 2009).

The estimator of μ is generally a simple weighted average of the Y_i, with the optimal weights equal to the inverse of the variance and

$$W_i = \frac{1}{V_{Y_i}} \quad (2.4)$$

Where V_{Y_i} is within the study variance for study i.

The weighed mean (M) is then computed as

$$M = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \quad (2.5)$$

This is the sum of the products $W_i Y_i$ (effect size multiplied by weight) divided by the sum of the weights. The variance of the summary effect is estimated as the reciprocal of the sum of the weights,

$$V_M = \frac{1}{\sum_{i=1}^{k} W_i} \quad (2.6)$$

The estimated standard error of the summary effect is the square root of the variance as follows:

$$SE_M = \sqrt{V_M} \quad (2.7)$$

Then, $(1-\alpha)\%$ lower and upper limits for the summary effect are estimated as follows

$$\left.\begin{aligned} LL_M &= M - t_{(1-a/2)} \times SE_M \\ UL_M &= M + t_{(1-a/2)} \times SE_M \end{aligned}\right\} \quad (2.8)$$

Finally, a t-test to test the null hypothesis that ϑ is zero can be computed using

$$t = \frac{M}{SE_M} \quad (2.9)$$

For a one-tailed test the p-value is given by

$$P = 1 - \phi \quad (2.10)$$

Where we chose positive if the difference is in the expected direction and negative, otherwise, and for a two-tailed test by

$$P = 2[1 - \phi(t)] \quad (2.11)$$

To compute a study's variance under the random-effect model, we need to know both the within-study variance and τ^2, since the study's total variance is the sum of the two values.

Tau squared (τ^2) is estimated using the method of moments or the D & L, DerSimonian and Laird (1986). The parameter τ^2 is between the studies variance (the variance of the effect size parameters across the population of studies.

T is an estimate for τ^2, it is possible that T is negative due to sampling error, but it is unacceptable as a value for τ^2, so we define;

$$\tau^2 = \begin{cases} T \; if \; T > 0 \\ 0 \; if \; T \leq 0 \end{cases} \quad (2.12)$$

3.0 Results and Discussion

The research analysis is based on nineteen (19) studies. The effect size index is risk ratio (RR). The random-effects model was employed for the analysis. The studies in the analysis are assumed to be random samples from a universe of potential studies, and this analysis will be used to make an inference to that universe. Meta-analysis pooling of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau²

Test of overall effect = 1: z = 7.540 p = 0.000

Heterogeneity measures, calculated from the data with Conf. Intervals based on Gamma (random-ffects) distribution for Q

Measure	Value	df	p-value
Cochran's Q	281.42	18	0.000
		−[95% Conf.	Interval]−
H	3.954	1.221	6.781
I^2 (%)	93.6%	33.0%	97.8%

H = relative excess in Cochran's Q over its degrees-of-freedom

I^2 = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Heterogeneity variance estimates

Method | tau^2

DL | 0.0717

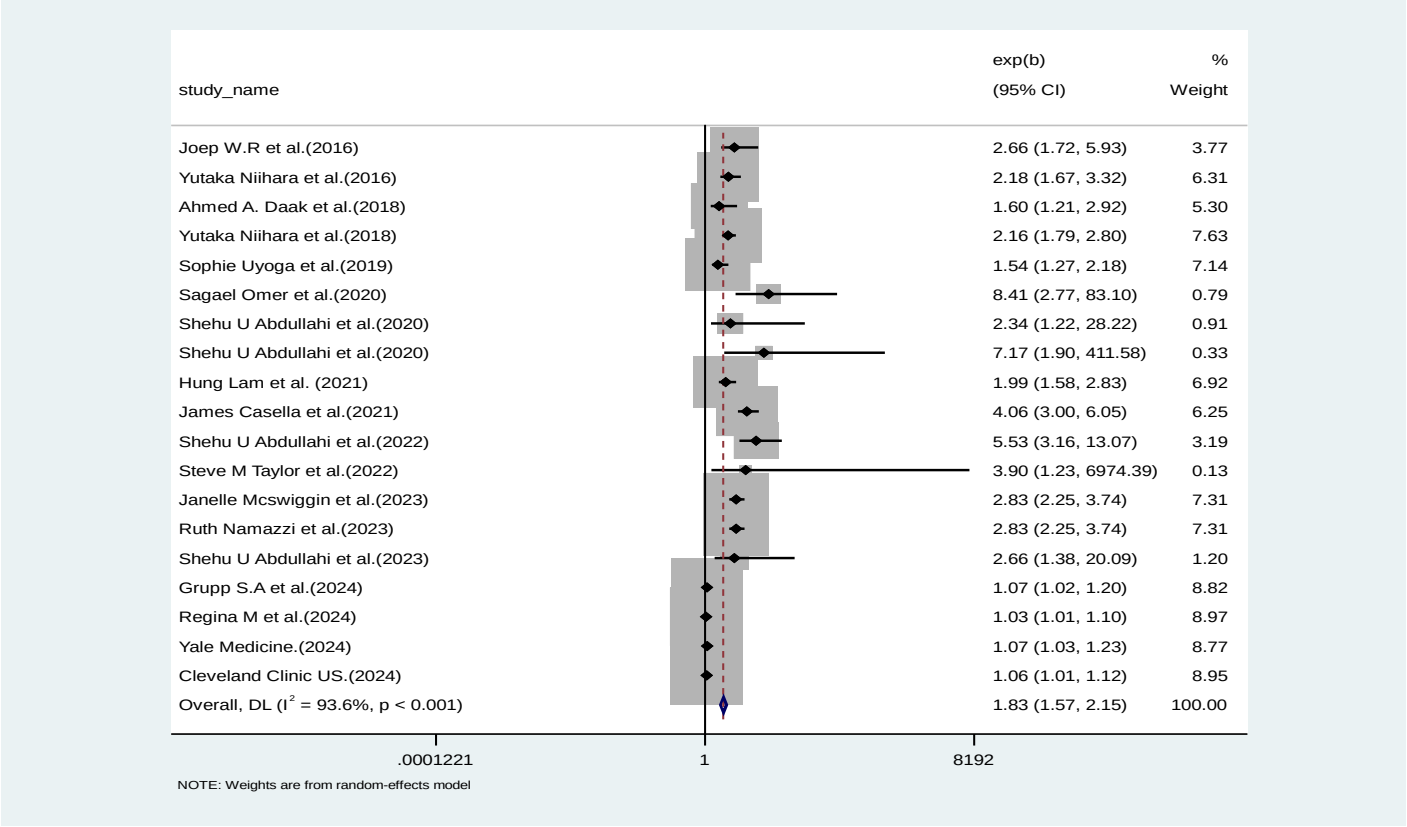


Figure 3.1: Showing the summary effect of the effect size

Sensitivity Analysis

Meta-analysis pooling of aggregate data using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2

study_name	exp(b)	[95% Conf.	Interval]	% Weight
Joep W.R et al.(2016)	2.664	1.716	5.930	3.99
Yutaka Niihara et al.(2016)	2.181	1.665	3.320	6.75
Ahmed A. Daak et al.(2018)	1.600	1.209	2.915	5.65
Yutaka Niihara et al.(2018)	2.160	1.786	2.801	8.21
Sophie Uyoga et al.(2019)	1.537	1.271	2.181	7.67
Sagael Omer et al.(2020)	8.415	2.773	83.096	0.82
Shehu U Abdullahi et al.(2020)	2.340	1.221	28.219	0.95
Shehu U Abdullahi et al.(2020)	7.171	1.896	411.579	0.35
James Casella et al.(2021)	4.055	3.004	6.050	6.69
Shehu U Abdullahi et al.(2022)	5.529	3.158	13.066	3.37
Steve M Taylor et al.(2022)	3.896	1.234	6974.392	0.14
Janelle Mcswiggin et al.(2023)	2.829	2.248	3.743	7.85
Ruth Namazzi et al.(2023)	2.829	2.248	3.743	7.85
Shehu U Abdullahi et al.(2023)	2.664	1.377	20.086	1.26
Grupp S.A et al.(2024)	1.067	1.022	1.201	9.55
Regina M et al.(2024)	1.035	1.012	1.101	9.72
Yale Medicine.(2024)	1.074	1.025	1.228	9.49
Cleveland Clinic US.(2024)	1.057	1.014	1.122	9.69
Overall, DL	1.817	1.547	2.134	100.00

Test of overall effect = 1: z = 7.275 p = 0.000

Heterogeneity measures, calculated from the data with Conf. Intervals based on Gamma (random-effects) distribution for Q

Measure	Value	df	p-value
Cochran's Q	265.99	17	0.000
		−[95% Conf.	Interval]−
H	3.956	1.189	6.824
I^2 (%)	93.6%	29.3%	97.9%

H = relative excess in Cochran's Q over its degrees-of-freedom

I^2 = proportion of total variation in effect estimate due to between-study heterogeneity (based on Q)

Heterogeneity variance estimates

Method	tau^2
DL	0.0689

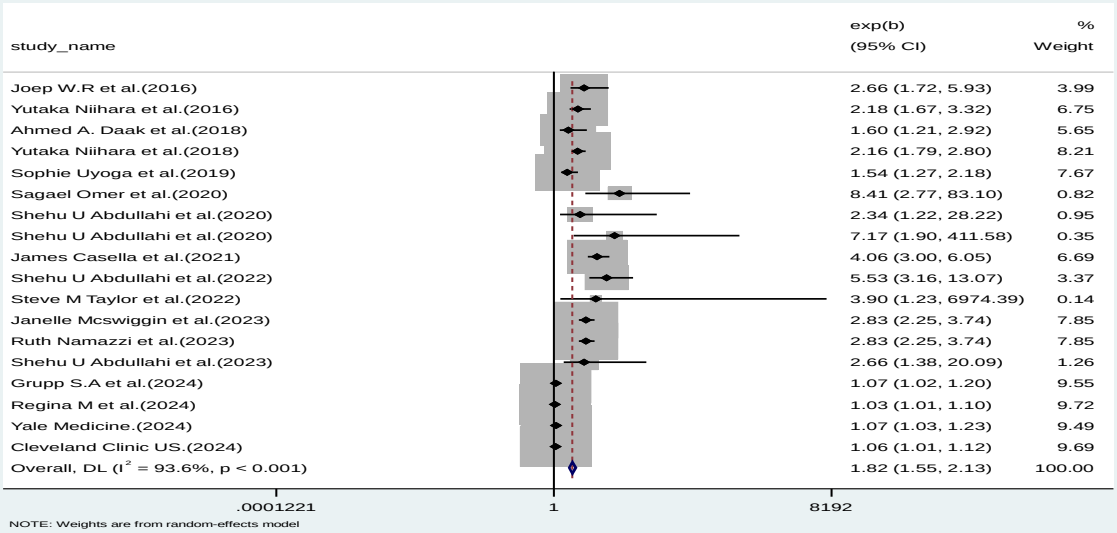
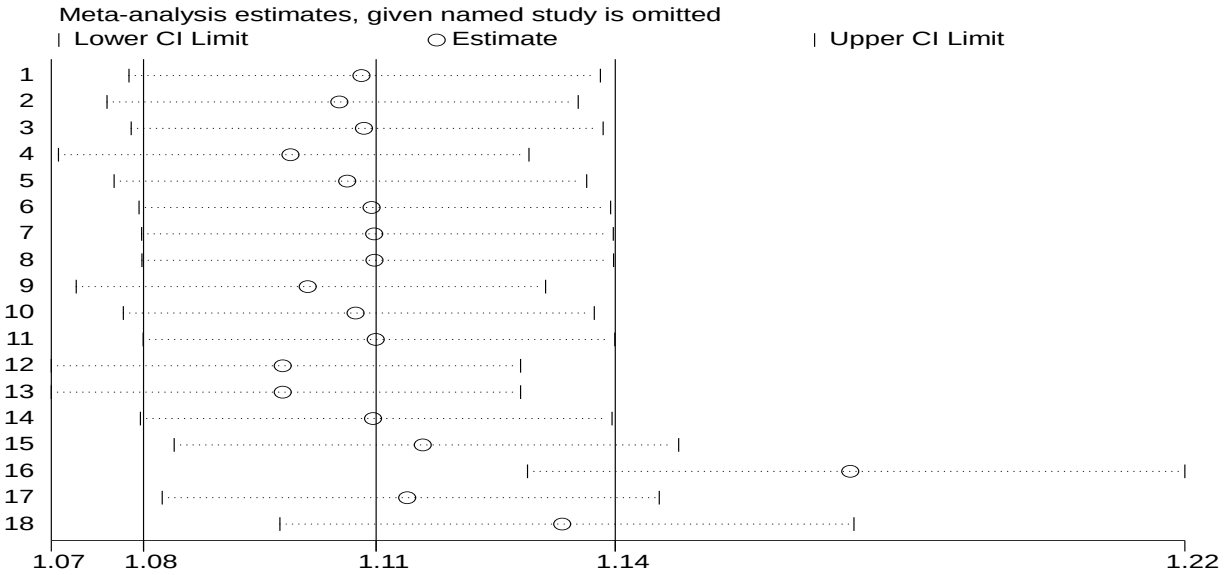


Figure 3.2: Showing the sensitivity analysis of true effect of the effect size.

Leave-One-Out Sensitivity Analysis

Study omitted	Estimate	[95% Conf.	Interval]
1	1.1100857	1.080018	1.1409904
2	1.1072326	1.0771774	1.1381264
3	1.1104124	1.0803072	1.1413565
4	1.1009068	1.0708958	1.1317589
5	1.1082402	1.0780977	1.1392254
6	1.1114041	1.081326	1.1423188
7	1.1117375	1.0816498	1.1426623
8	1.1117746	1.0816888	1.1426971
9	1.1031324	1.0731912	1.133909
10	1.1093268	1.0792867	1.1402031
11	1.1119338	1.0818447	1.1428599
12	1.0998977	1.0699635	1.1306694
13	1.0998977	1.0699635	1.1306694
14	1.1115828	1.0814974	1.1425049
15	1.1180186	1.0858673	1.151122
16	1.1733152	1.1315694	1.2166011
17	1.1160008	1.0843149	1.1486125
18	1.1360575	1.0995382	1.1737896
Combined	1.1119901	1.0819	1.1429171



Result of the underlying risk factors of sickle cell using meta-regression analysis.

Meta-regression	Number of obs = 19
REML estimate of between-study variance	tau2 = 0
% residual variation due to heterogeneity	I-squared_res = 0.00%
Proportion of between-study variance explained	Adj R-squared = .%
Joint test for all covariates	Model F(3,15) = 0.00
With Knapp-Hartung modification	Prob > F = 1.0000

.

log_rr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
moderator1	-.0188303	4.404928	-0.00	0.997	-9.407712	9.370051
moderator2	-.0305697	3.507256	-0.01	0.993	-7.506108	7.444969
moderator3	.1266134	29.06991	0.00	0.997	-61.83444	62.08767
_cons	38.13624	8924.392	0.00	0.997	-18983.75	19060.03

We did find significant effect modifiers after testing each covariate ($p > 0.05$ for all covariates). The three covariates have no significant impact on the outcome variable (effect size). The statistical significance of the regression coefficient is a test of whether there is a linear relationship between intervention effect and the explanatory variable. If the intervention effect is a ratio measure, the log-transformed value of the intervention effect should always be used in the regression model, and the exponential of the regression coefficient will give an estimate of the relative change in intervention effect with a unit increase in the explanatory variable.

4.0 Implications of Results

The implications of this study for public health are significant. As the therapy on sickle cell disease favors patients favour more of the control group of the trials than the intervention group. In addition, there are high variations in the previous studies made on the randomized control trials-based based meta-analysis on the therapy in the treatment of sickle cell disease. Also, the implications of this paper for public health are also significant. This implies that sample size, study characteristics, and year interval and interval of year are not the major underlying risk factors of sickle cell disease, which significantly contributes, this contribute significantly that these moderators were not included did not constitute in sickle cell disease. Previous results suggested that underlying risk factors of sickle cell disease using meta-regression analysis could be genetic factors such as nature of the disease (Alpha-thalassemia and beta-globin gene haplotypes) and socioeconomic.

5.0 Conclusion

This paper review epitomizes the first endeavor to use a meta-analysis and a systematic review to scrutinize the underlying risk factors in sickle cell disease. Using random-effect estimation methods, the heterogeneity value is >50% size, from all the research analyzed to have a 95% confidence interval of 1.84 (1.567 - 2.148). The results further indicate that, the three covariates have no significance impact on the outcome variable (effect size). The findings also reveal that, at the 95% level of significance, study attributes such as the methods used, publication status, range of efficiency scores, study location, and sample size have a substantial impact on the variation in effect size among the sample studies on SCD in sickle cell disease. In conclusion, meta-analysis poses to have a potential impact to establish statistical significance in conflicting results in decision making and public practice. In this study, the results estimate is located to the left, it means that the outcome of interest (mortality) occurred less frequently in the intervention group than in the control group (ratio > 1). The overall combined result was not statistically significant. Hence, the pooled estimated suggests that the overall outcome rate in the intervention group is much the same as in the control group.

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