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Risk of Mortality in Patients with HIV and Depression: A Systematic Review and Meta-Analysis of a Non-Common Outcome

Adehi M. U.[1,*], Yakasai A. M.[2], Dikko H. G.[3], Asiribo E. O.[4], Dahiru T.[5]

[1]Department of Mathematical Sciences, Nasarawa State University, Keffi, Nigeria
[2]Infectious and Tropical Diseases Unit, Public Health and Diagnostic Institute, College of Medical Sciences, North-West University, Kano, Nigeria
[3]Department of Statistics, Ahmadu Bello University, Zaria, Nigeria
[4]Department of Statistics, University of Agriculture, Abeokuta, Ogun, Nigeria
[5]Department of Community Medicine, Ahmadu Bello University, Zaria, Nigeria

Abstract Meta-analysis (MA) is increasingly being utilized to combine results of several studies to derive refined estimates. However, great difficulty is commonly encountered when non-common outcomes (NCO) are involved. This study is concerned with the MA of mortality risk attributed to depression in HIV patients to identify the challenges and solutions regarding statistical methods in MA of NCO. DerSimonian-Laird (DL) and Inverse variance (IV) techniques were used in the MA to pool estimates of mortality risk through Random Effect Models (REM) and Fixed Effect Models (FEM) depending on presence or absence of heterogeneity respectively. Series of sensitivity analyses, multi-level subgroup analyses and I-squared (I^2) statistics tests were done to identify sources of bias, methodological and statistical heterogeneity respectively. From 17 studies that met the inclusion criteria, the mortality Hazard Ratio (HR) and 95% confidence interval (CI) among depressed HIV patients was 1.80 and (1.23 - 2.61) respectively, with significant statistical heterogeneity (I^2 = 92.8%). Multiple population characteristics were found in subgroup analyses as sources of methodological heterogeneity (Table 3). Publication bias was present, as detected by both Egger's and Begg's tests, some studies were excluded in succession as sensitivity analysis was carried out sequentially. The final estimate was 1.56 (HR) and CI (1.33 - 1.83) without statistical heterogeneity (I^2 = 0.0%). As the studies were being excluded there was a 64% reduction in the width of the CI. From the results of this paper, MA of NCO is associated with publication bias, significant statistical and methodological heterogeneity.

Keywords Meta-analysis, Non-common outcome, Mortality, Depression, HIV

1. Introduction

MA is increasingly being utilized across medical [1], psychological [2] and social sciences [3] to combine results of studies or trials to generate summary effect measures. Outcomes from various studies or trials may be common outcomes (CO) or non-common outcomes (NCO). Studies involving CO are generally not problematic in the sense that there are virtually all required data and the outcomes assessed is a common event. Studies involving NCO or rare events, however, are associated with great difficulty when assembled for MA. Several reasons may explain this, ranging from lack of adequate number of studies to non-occurrence of events in cases or control arms of the studies or trials [4]. Where not properly handled, statistical estimates from MA of NCO could lead to improper conclusions that could be detrimental to services or populations under consideration [5], as such, the mathematical principles of the methods of MA is critical to the reliability and accuracy of final results most especially with regards to NCO. There are many statistical techniques of aggregating studies with CO which include matched pooling, continuity correction, Bayesian method and risk difference methods such as Relative Risk (RR), Odds Ratio and Hazard Ratio (HR) [6]. The risk difference effect sizes (ES) could be analyzed and pooled together using either Mantel-Haenszel (MH), Peto, Shuster, Logistic, Scoring or Conditional methods. All these methods of pooling ES are consistently affected by rate of events and follow up duration and may produce inaccurate results and even Simpson's paradox for NCO. Thus, it appears there may not be a safe method of pooling data or ES for NCO. Notwithstanding, it has been strongly recommended that researchers could utilize sensitivity analysis in MA of NCO to provide clear picture of the magnitude, direction and modifiers of an ES.

* Corresponding author:
maryadehi@yahoo.com (Adehi M. U.)
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In HIV neuropsychology, large number of studies have been published with differing conclusions and recommendations based on specific findings. To aggregate these findings and generate a quantitative summary ES, MA has been utilized as evidenced by over 12,000 citations for MA of NCO in the web of science data base [7]. Given the complexities associated with MA of NCO, we intend to bring out its salient characteristics and features in HIV medicine by conducting MA of risk of mortality among HIV patients diagnosed with depression using DL and IV techniques as provided for FEM [8]. The role of sensitivity analysis and subgroup analysis in addressing possible challenges in MA of NCO will also be determined.

2. Materials

The first part of the study is the systematic review of the available literature in search of studies on depression in HIV infected individuals. Databases like Google scholar, MEDLINE, Psychiatry web sites, Cochrane database, Psych Info, Neuropsychiatry books/chapters, relevant dissertations, Web of Science and relevant Journals of psychiatry, neurology and infectious diseases were properly searched. Included studies met the following criteria: -

1. HIV was reported positive in patients.
2. Hazard ratios were reported in respect of depressive symptoms related to mortality in the patients.
3. Mortality related to depression was reported.
4. Baseline characteristics of the study subjects were reported.

Relevant parameters from the included studies were recorded into a standardized form as shown in Table 1.

The second part of the study is the MA that entails pooling data across the included studies. This started with extracting and appropriately recording mathematical requirements for the MA. These include ES (which in this case is the HR of mortality related to depression), 95% confidence interval (CI) of the HR, log of the HR and the standard error (SE) of the log of the HR. It is important to note here that the SE maybe computed if CI is available, using a backward computation from equations (8). In which case, the two equations are solved as simultaneous linear equations, and we solve for SE.

Information recorded in the first and second parts of the study were used to compute the quality of the articles that met the outlined inclusion criteria (Table 2), as such, satisfying the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) as it is provided [9].

3. Methodology

In this MA, estimates were pooled via REM using DL method when heterogeneity is significant, and FEM was carried out through IV method where the level of heterogeneity is not significant in line with [8]. To compute the study's variance under the REM, there was the need to calculate both the within-study variance, V_{Y_i} and between-study variance, τ^2, since the study's total variance is the sum of the two values. One method for estimating τ^2 is the method of moments, or the DerSimonian and Laird method [10]. The parameter τ^2 (tau-squared) is the between studies variance (the variance of the effect size parameters across the population of studies).

The estimate of τ^2 is denoted by T^2,

$$T^2 = \frac{Q - df}{C} \tag{1}$$

where

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i} \tag{2}$$

$$df = k-1$$

where k is the number of studies, and

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W_i^2}{\sum_{i=1}^{k} W_i} \tag{3}$$

under the random-effects model the weight assigned to each study is

$$W_i = 1 \Big/ Var(Y_i) \tag{4}$$

where $Var(Y_i) = V_{Y_i}^*$ is the within-study variance from study i plus the between-study variance, τ^2.

$$V_{Y_i}^* = V_{Y_i} + T^2$$

The weighted mean, M^*, is

$$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*} \tag{5}$$

that is, the sum of the products (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, or

$$V_{M^*} = \frac{1}{\sum_{i=1}^{k} W_i^*} \tag{6}$$

and the estimated standard error of the summary effect is the square root of the variance,

$$SE_{M^*} = \sqrt{V_{M^*}} \tag{7}$$

The $(1-\alpha)\%$ lower and upper limits for the summary effect is

$$\left.\begin{aligned} \mathrm{LL}_{\mathrm{M}^*} &= \mathrm{M}^* - \mathrm{Z}_{\alpha/2} \times \mathrm{SE}_{\mathrm{M}^*} \\ \mathrm{UL}_{\mathrm{M}^*} &= \mathrm{M}^* + \mathrm{Z}_{\alpha/2} \times \mathrm{SE}_{\mathrm{M}^*} \end{aligned}\right\} \tag{8}$$

a Z-value to test the null hypothesis that the mean effect μ is zero is computed as

$$P^* = 1 - \phi\left(\pm\left|Z^*\right|\right)$$

where we choose '+' if the difference is in the expected direction or '- 'otherwise.

For a two-tailed test by

$$P^* = 2\left[1 - \left(\phi\left(\left|Z^*\right|\right)\right)\right]$$

and $\phi\left(\left|Z^*\right|\right)$ is the standard normal cumulative distribution.

The I^2- Statistic is an alternative and stronger measure compared to the Q- measure in (2)

$$I^2 = \left(\frac{Q-df}{Q}\right) \times 100\% \tag{9}$$

use value of Q from (2).

Heterogeneity in the I^2 – Statistics may be termed low, moderate, or high based on the intervals $0 \le I^2 < 25\%$, $25\% \le I^2 < 50\%$, or $I^2 \ge 50\%$ respectively.

For subgroup analysis, the z-test method of the DerSimonian and Laird process was used thus: -

Let ϑ_A and ϑ_B be the true effects of group A and B respectively, and let M_A and M_B be the estimated effects, and let V_{M_A} and V_{M_B} be their variances. If we use 'Diff' to refer to the difference between the two effects, and choose to subtract the mean of A from the mean of B,

$$Diff = M_B - M_A$$

the test statistic to compare the two effects is

$$Z_{Diff} = \frac{Diff}{SE_{Diff}}$$

where

$$SE_{Diff} = \sqrt{V_{M_A} + V_{M_B}}$$

under the null hypothesis that the true effect size ϑ is the same for both groups,

$$H_0 : \vartheta_A = \vartheta_B,$$

$$Z_{Diff} \approx N(0,1) \; with \;\; p-value$$

$$p = 2\left[1 - \left(\phi\left(\left|Z\right|\right)\right)\right]$$

and $\phi(Z)$ is the standard normal cumulative distribution.

For meta-regression analysis, to assess the impact of covariates and to predict effect size in studies with specific characteristics, assess the impact of the slope using the Z-test statistics to test the significance of the slope.

The test statistics is based on the Z-distribution.

$$Z = \frac{B}{SE_B}$$

under the null hypothesis that B = 0, Z would follow the normal distribution.

The Z-test can be used to test the statistical significance of any single coefficient but when it is required to assess the impact of several covariates simultaneously, the Q-test is useful. In which case, we obtain Q, Q_{model}, $Q_{residual}$ and consider the degrees of freedom. From the model, fit a model of the form,

$$Ln(Y) = B_0 + B_i X_i, \qquad i = 1,2,3,...,n.$$

while quantifying the magnitude of the relationship by computing the $(1-\alpha)\%$ confidence interval for B, using,

$$LL_B = B - Z_{\alpha/2} \times SE_B$$

and

$$UL_B = B + Z_{\alpha/2} \times SE_B$$

Sensitivity analysis is applicable in identifying sources of bias and heterogeneity to filter studies and derive reasonable and scientific quantitative synthesis [11]. The sensitivity analysis employed, involve the assessment of publication bias among the included studies by performing Begg's funnel plot test and Egger's test [12, 13]. To avoid inconsistent assessment from these tests, we conclude there is publication bias only when both tests could detect bias (i.e. all p - values were < 0.05) [14]. Statistical analyses were carried out using Stata version 12.0 (Stata Corp., College Station, TX, USA).

Table 1. Characteristics of studies included in the systematic review and meta-analysis

Author/year	Country	Sample size	Screening tool, cut off score	% on ART	% of female	Follow up duration	Drug usage	Prevalence of depression
[16]	Tanzania	996	HSCL	100	100	6	NA	57
[15]	France	305	CESD, ≥16	0	28	3.4	17	46
[27]	USA	765	CESD, ≥16	100	49	7	54	42
[18]	USA	961	CESD, >16	100	100	5.1	33	50
[28]	USA	1716	CESD, >15	49	100	7.5	39	32
[29]	USA	881	CESD, ≥10	54	1	1	NR	46
[17]	USA	490	BSI	80	31	3.4	NA	NA
[30]	USA	4001	PHQ, ≥10	68.6	12.9	2.8	9.9	31
[19]	USA	489	BSI	100	31	2.5	NA	NA
[31]	USA	395	CESD,	NA	0	NA	NA	NA
[20]	Uganda	694	HSCL, 1.75	0	69	4.3	NA	31
[32]	France	1028	CESD, >17 (men); >23 (women)	43.7	22	4.5	16.7	41
[21]	Canada	563	CESD, ≥16	100	9	4	28.4	51

ART- Antiretroviral therapy; BSI- Brief symptoms inventory; CESD- Center for epidemiologic studies depression scale; CIDI- Composite International Diagnostic Interview; HSCL- Hopkins symptoms checklist; NA- Not available; NR- Not reported; PHQ- Patient health questionnaire; USA- United States of America

Table 2. Downs and Black checklist for quality assessment of studies included in the systematic review and meta-analysis [33]

Author/year	Reporting				External validity	Internal validity-bias			Internal validity-confounding (selection bias)				Quality score*
	1	2	3	4	5	6	7	8	9	10	11	12	
[16]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[15]	1	1	1	1	1	NR	1	1	1	1	NR	0	9
[27]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[18]	1	1	1	1	1	NR	1	0	1	1	NR	0	10
[28]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[29]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[17]	1	1	1	1	0	NR	1	1	1	1	NR	0	8
[30]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[19]	1	1	1	1	0	NR	1	1	1	1	NR	0	8
[31]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[20]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[32]	1	1	1	1	0	NR	1	1	1	1	NR	1	9
[21]	1	1	1	1	1	NR	1	1	1	1	NR	1	10

*Excellent (10-12), good (8-9), fair (5-7), poor (< 5), Y = Yes, N = No,
Downs and Black checklist items: 1- aims/objectives clearly outlined; 2- major outcomes clearly mentioned; 3- patients characteristics provided; 4- major findings clearly mentioned; 5-sample representative of population; 6- appropriate statistical tests done; 7- primary outcome valid; 8- were measures to curtail bias applied; 9- cases and controls recruited form same population; 10- cases and controls recruited over same time period; 11- adjustment for confounders done; 12- addressed loss to follow up.

4. Results

Figure 1 is the process and stepwise procedures for the article search to arrive at the included studies. Seventeen studies (and sub-studies) could satisfy the inclusion criteria while others were excluded for several reasons indicated in Figure 1. The studies included in the MA reported baseline characteristics shown in Table 1, whereas their quality, mainly a product of these characteristics is given in Table 2, where the studies were rated 'good' (8-9) and 'excellent' (10-12) qualities, on a scale of 12.

All the 17 studies were meta-analyzed and the analysis shown in Figure 2 favored mortality in HIV patients with depression [HR (95% CI) = 1.88 (1.23 - 2.68), p-value < 0.0001]. This result revealed presence of bias, with I^2 = 92.8%.

Publication bias assessment was carried out on the studies using the Begg's funnel plot (Figure 3) and the Egger's publication bias plot (Figure 4) to verify presence of bias.

The Begg's funnel plot revealed asymmetric distribution of studies indicating presence of bias, while the Egger's test indicated the presence of bias in the study that appeared very far from the horizontal band.

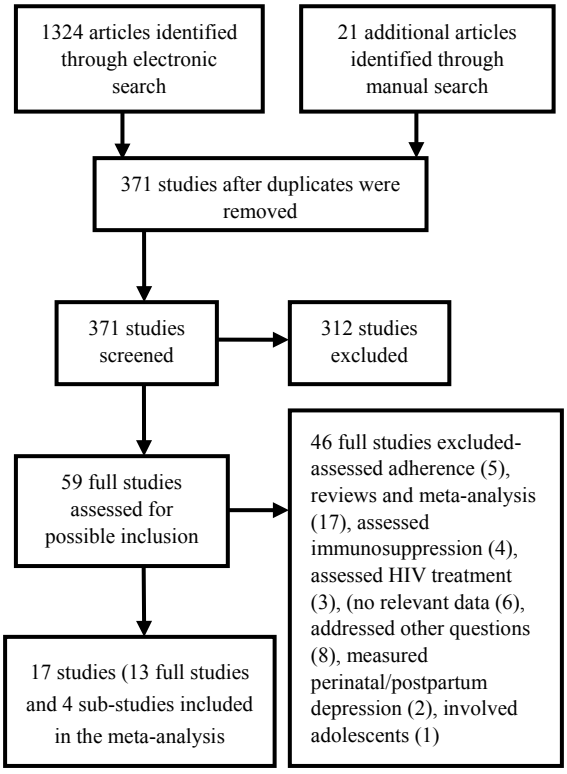

Figure 1. Process of article search and selection

To identify which study (ies) is/are responsible for heterogeneity and bias, a sensitivity analysis was conducted on all the 17 studies to identify those that were exerting major influence (s) on the finally pooled estimates of risk of mortality in depressed HIV patients. Sequentially, the process of excluding studies was carried out in the following pattern; The first sensitivity analysis (Figure 5) identified the Bouhnik study [15] as an influence on the final MA estimates. After excluding the study, a repeat of the MA was performed on the remaining 16 studies which revealed heterogeneity, and heavy influence of 4 studies on the derived estimates [16-19]. The 4 studies were excluded, however, further sensitivity analysis resulted in a substantial reduction in the level of heterogeneity,

$$[\tau^2 = 0.2102; I^2 = 64.1\%, P < 0.0001,$$
$$HR(95\%CI) = 1.62(1.34 - 1.97)]$$

but two studies [20, 21] were identified as influence to the estimates of mortality risk with;

$$[I^2 = 32.9\%,\ p = 0.127,\ HR(95\%CI) = 1.66(1.42 - 1.94]$$

Further sensitivity analysis recorded absence of statistical heterogeneity, while HIV depressed patients remained at significantly higher risk of mortality compared to those without diagnosis of depression

$$[I^2 = 0.0\%,\ p = 0.927,\ HR(95\%CI) = 1.56(1.33 - 1.83]$$

As indicated in figure 6, from the first analysis involving all the 17 studies down to the last sensitivity analysis, the width of the CI progressively decreases from 1.38 to 0.50 (64% reduction).

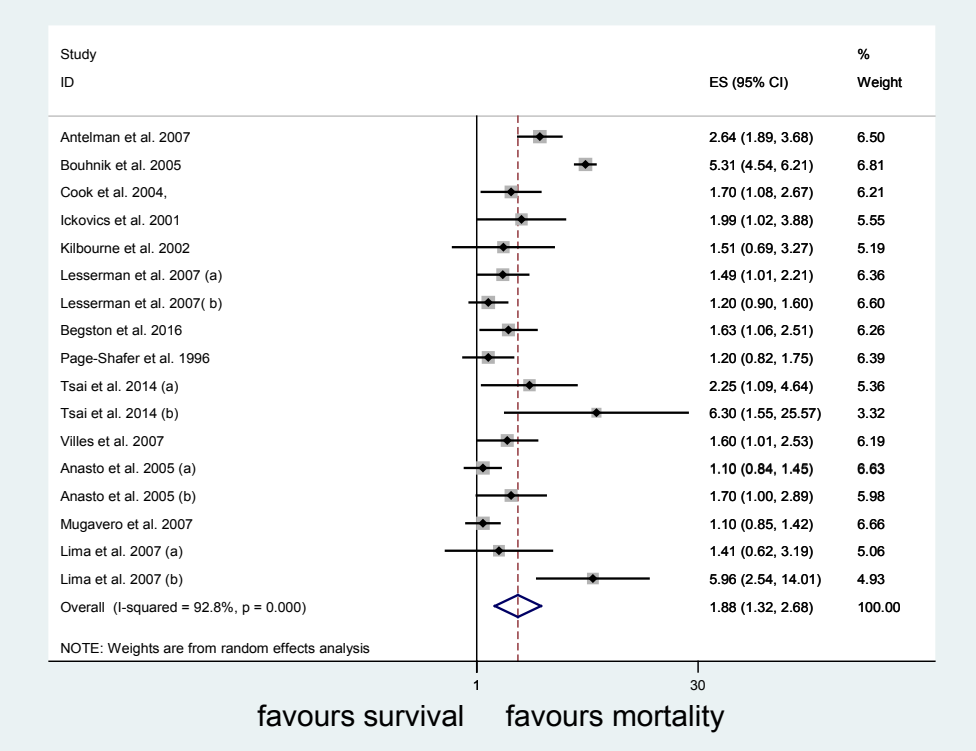

Figure 2. Forest plot showing summary estimates obtained by pooling data from 17 studies/sub-studies via Random effect model

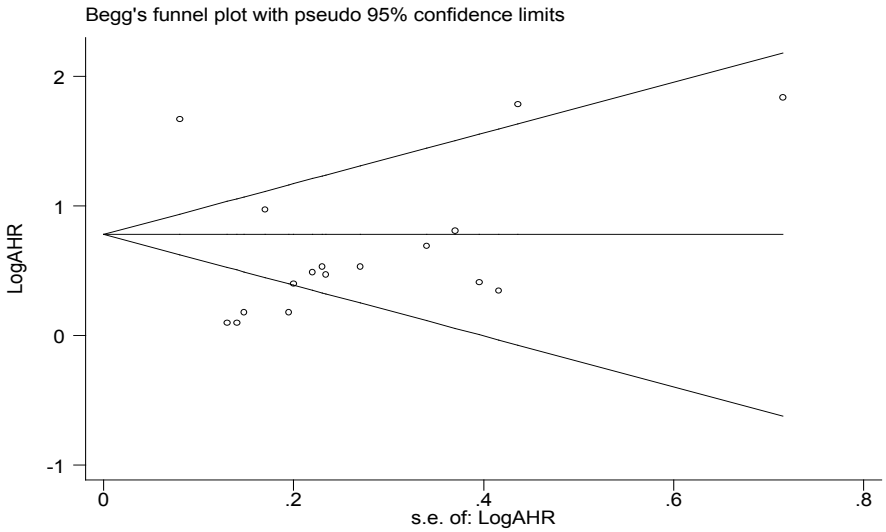

Figure 3. Begg's funnel plot showing asymmetric distribution of studies indicating publication bias

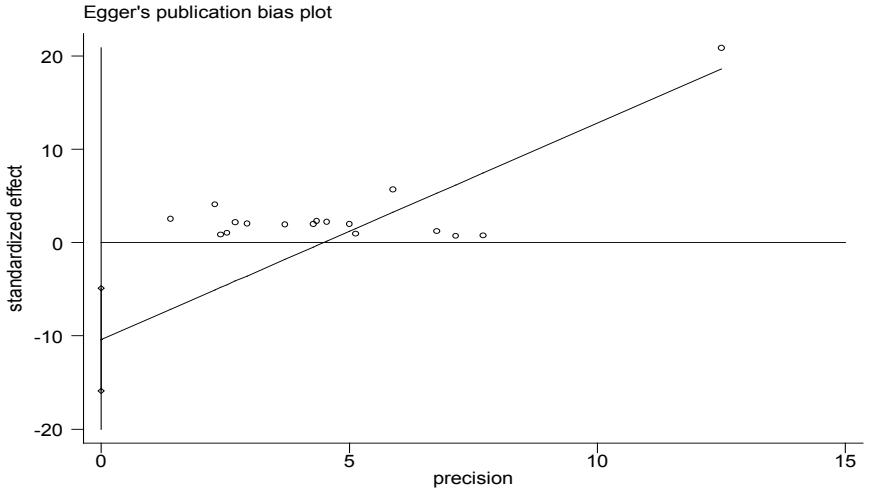

Figure 4. Egger's plot for the detection of publication bias and small study effect

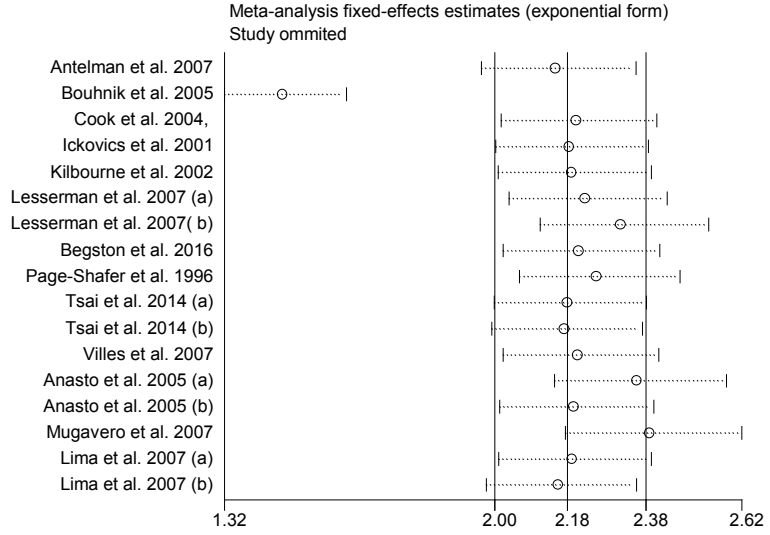

Figure 5. Sensitivity analysis showing influence of Bouhnik et al. 2005 study on final estimates

The estimates of the slope for the meta-regression model with respect to study-level parameters (sample size, proportion of female subjects and cluster of differentiation cells) were not significant at $\alpha = 0.05$. Aside meta-regression analysis, subgroup analysis was carried out involving all the 17 studies and sub-studies as indicated in Table 3.

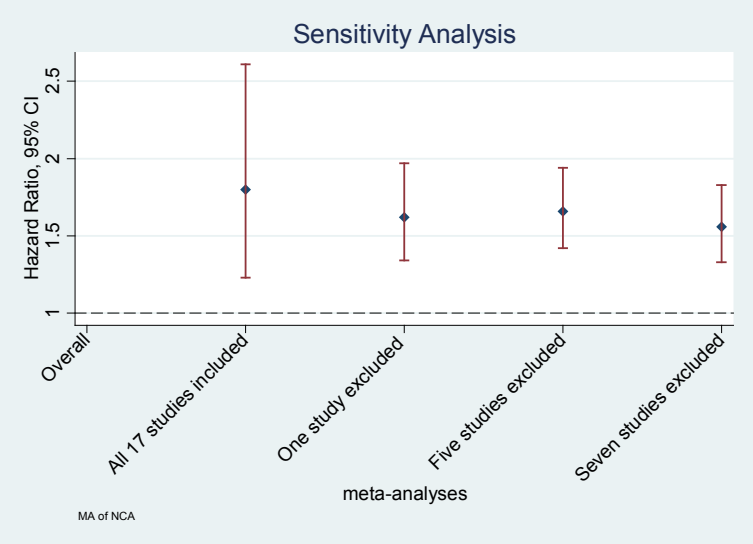

Figure 6. Scatter plot showing Hazard Ratios (95%CI) for the various stages of the meta-analysis and sensitivity analyses

Table 3. Subgroup analyses to identify sources of methodological heterogeneity

Characteristic		K	I^2-*statistic* (%)	HR (95% CI)	Comment
Study quality:	Excellent	12	65.8	1.83 (1.4 – 2.38)	Quality of studies could affect accuracy of estimates.
	Good	5	97.5	1.77 (0.80 – 3.89)	
Gender:	100% Female	6	75.3	1.91 (1.28 – 2.84)	Both male and female are at higher risk of mortality.
	100% Male	10	95.2	1.81 (1.07 – 3.04)	
Screening tool:	CESD	10	94.0	1.94 (1.14 – 3.3)	Studies using CESD are also significantly heterogeneous.
	Others	7	75.4	1.67 (1.22 – 2.29)	
CESD cut off score:					
Higher cut off (> 16)		5	36.3	1.43 (1.08 – 1.90)	Higher CESD cut off score (> 16) provides more reliable estimates.
Lower cut off (≤ 16)		3	93.3	2.49 (0.97 – 6.35)	
Country:					
Africa		3	0	2.67 (1.99 – 3.59)	Africans have significantly high risk of mortality from HIV-related depression.
USA		10	1.8	1.29 (1.14 – 1.45)	
France		2	95.8	2.98 (0.9 – 9.64)	
Canada		2	82.5	2.88 (0.70 - 11.84)	
Sample size:	< 500	4	97.1	1.57 (0.84 – 2.96)	Larger sample size may be associated with higher risk of mortality.
	≥ 500	12	62.3	1.89 (1.46 – 2.43)	
Prevalence of depression:					Higher prevalence of depression is associated with substantial heterogeneity.
< 45		6	0	1.79 (1.43 – 2.25)	
≥ 45		8	94.9	2.10 (1.16 – 3.80)	
Follow up:	< 4 years	6	97	1.78 (0.85 – 3.5)	Longer duration of follow up may provide more reliable estimates.
	≥ 4 years	10	68.9	1.98 (1.46 – 2.69)	
ART:	Yes	13	66.2	1.59 (1.30 – 1.96)	Antiretroviral therapy is associated with lower risk of mortality.
	No	3	91	2.7 (1.37 – 5.48)	
ART adherence:	Good	3	8.4	1.2 (1.0 - 1.54)	Poor ART adherence is associated with high risk of mortality.
	Poor	4	93	3.0 (1.40 - 6.40)	
IVDU:	Yes	5	92.2	2.59 (1.28 – 5.27)	Use of intravenous drugs is associated with higher risk of mortality.
	No	4	42.3	1.47 (1.09 – 1.97)	

ART- Antiretroviral therapy; CESD- Center for epidemiologic studies depression scale; CI- Confidence interval; HR- Hazard ratio; IVDU- Intravenous drug usage, k- number of studies; USA- United States of America

5. Discussion

From the findings in this research, MA of NCO is associated with publication bias, significant statistical and methodological heterogeneity. Subgroup analysis and sensitivity analysis played a major role in identifying and controlling heterogeneity in MA of NCO. A previous MA of CO assessed risk of heart attack among patients receiving a drug called Rosiglitazone [22], there was significantly higher odds of developing heart attack among patients taking the drug. However, when two of the studies with huge impact on the final estimates were excluded in sensitivity analysis, results were statistically non-significant [23].

Subgroup analysis is one of the methods we utilized in this study to search for sources of heterogeneity and confounding. Other studies of CO previously conducted have similarly identified the role of subgroup analysis in understanding the causes of heterogeneity and how they could affect policy making. For example, a MA on adherence to Artemisinin-based Combination Therapy (ACT) for the treatment of uncomplicated malaria infection in children less than 5 years of age found a good adherence of 70% from 31 studies [24]. However, when the included studies were classified into public (25 studies) and retail sectors (6 studies), subgroup analysis found good adherence of 76% in the public sector but poor adherence of 45% in the retail sector ($p < 0.0001$). Further subgroup analysis found good adherence of 78% from 18 studies done in areas with high malaria transmission intensity and poor adherence of 56% from 11 studies done in low/moderate malaria transmission intensity ($p < 0.0001$). In all these subgroup analyses, results from MA of CO significantly differ from that of NCO and clearly highlights the need for researchers to analyze NCO data separately due its peculiarities and the potential consequences on policy making. It is important to note that when diseases' outcome is not common or where there are few studies on such outcomes, MA could help in providing precise estimates with scientific evidence of degree of accuracy that may approach the real-life situation.

Several MA techniques and principles are prone to bias when dealing with NCO and the DL, MH and IV methods are associated with bias [25]. It is therefore not surprising that this MA of NCO utilizing the DL and IV has encountered significant bias in some areas. We used these two methods because they are commonly used in medicine and psychology and our intention is to provide insight on the characteristics and performances of MA methods in analyses of NCO to guide policy makers. The two tests that were used in examining publication bias, namely; Beggs and Eggers tests, may not perform well when applied independently [26]. To overcome this, publication bias was assumed present only when detected by both tests (all p-values < 0.05). This will ensure proper detection of publication bias and increase the reliability of our findings because our outcome of interest, mortality risk related to depression in HIV patients is a NCO with few studies and differing study populations characteristics.

A very important finding in this study is the differing methods of assessments in studies on NCO and this potentially is a major source of heterogeneity and bias. From Table 1, the included studies differ in terms of sample size, depression screening tool, ART services, proportion of female subjects, follow-up duration, intravenous drug usage and prevalence of depression. This automatically led to differences in qualities of the studies necessitating critical analysis and employment of further techniques like sensitivity analysis to address these challenges. Sequential sensitivity analysis in this study reduces heterogeneity from 93% to 0% and decreased the width of the CI by 64% whilst depression in HIV remains in favor of mortality. Reducing heterogeneity provided more similar studies that are likely to yield more reasonable estimates whereas reducing the width of the confidence interval increases reliability of estimates.

Subgroup analyses found multiple sources of heterogeneity indicated in Table 3. The level of heterogeneity ranges from 0% to 97% and statistically non-significant estimates are characterized by substantial heterogeneity > 82%. These estimates were derived by pooling data from studies with lower CESD cut off score ($\leq$ 16), lower sample size (< 500), follow up duration < 4 years and good quality. Studies performed in Africa were not heterogeneous and reported significantly high risk of mortality from HIV-related depression. Similarly, studies from France and Canada also reported high risk of mortality from HIV-related depression. The estimates were statistically non-significant with overlapping confidence interval and may be related to the large degree of heterogeneity (83-96%). In view of the effect of heterogeneity on the accuracy of meta-analytically pooled estimates it is therefore crucial to assess, explore and document sources of variations between studies included in meta-analyses and especially where NCO were the end points.

Although a demonstration of the potential application of subgroup analysis in identifying sources of heterogeneity is shown in this study, findings should be interpreted cautiously given the few number of studies involved in the main analysis and most importantly the subgroup analyses, which makes risk of mortality in HIV depression a rare or NCO. Limitations of this study include the fact that generalizability of findings may not be feasible due to under representation of Africa (only 2 studies) and Europe (only 2 studies) while Asia had no single study. However, analyses of ten studies without heterogeneity from USA found significantly higher risk of mortality and increases reliability of the overall estimates derived from all the 17 studies. The strength of this study is in the extensive search for sources of variations across studies using methods such as I^2-statistic, subgroup analysis and meta-regression analysis.

6. Conclusions

It is important to note that based on our findings, MA of

NCO is associated with publication bias and substantial heterogeneity. However, sensitivity analysis and subgroup analysis could help identify sources of bias and heterogeneity to filter studies and derive reasonable and scientific quantitative estimates. This is quite relevant in guiding policy makers and stakeholders in making decisions, recommendations and conclusions especially regarding NCO which are routinely encountered in everyday life.

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