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| Journal: | *BMJ Paediatrics Open* |
| Manuscript ID | bmjpo-2020-000750 |
| Article Type: | Original research |
| Date Submitted by the Author: | 24-Jun-2020 |
| Complete List of Authors: | Aynalem, Yared; Debre Berhan University, pediatric and child health<br>Mulu, Getaneh ; Debre Berhan University<br>Akalu, Tadesse ; Debre Markos University<br>Shiferaw, Wondimeneh ; Debre Berhan University |
| Keywords: | Statistics, Qualitative research, Nursing Care, Jaundice, Neonatology |
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# Prevalence of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility in sub-Saharan Africa: a systematic review and meta-analysis

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## Abstract

**Background:** Severe indirect hyperbilirubinemia is a silent cause of newborn disease and death worldwide. However, studies of the disease in sub-Saharan Africa are highly variable with respect to its prevalence. Hence, this study aimed to estimate the overall magnitude of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase (GP6D) deficiency and blood type incompatibility in sub-Saharan Africa.

**Methods**: PubMed, Scopus, Google Scholar, and the Cochrane Review were systematically searched online to retrieve hyperbilirubinemia-related articles. All observational studies reported the prevalence of hyperbilirubinemia in sub-Saharan Africa were included for analysis and excluded if the study failed to determine the desired outcome. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed. Heterogeneity across the included studies was evaluated using the inconsistency index ($I^2$). Publication bias was examined by funnel plot and the Egger's regression test. The random-effect model was fitted to estimate the pooled prevalence of neonatal hyperbilirubinemia among patients in Sub Saharan Africa. The meta-analysis was performed using the STATA™ version 14 software.

**Results**: A total of 30,486 studies were collected from the different databases and 10 articles were included for the final analysis. The overall magnitude of neonatal hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94)) in sub-Saharan Africa. Neonates with G6PD deficiency were 2.42 times

(95% CI: 1.64, 3.56) more likely to develop hyperbilirubinemia as compared to infants with normal G6PD levels. Moreover, the risk of developing hyperbilirubinemia was 3.3 times (95% CI: 1.96, 5.72) higher among neonates that had a blood type that was incompatible with their mother's.

**Conclusion**: The failure to prevent and screen G6PD deficiency and blood type incompatibility with their mother's results in high burden of neonatal hyperbilirubinemia in sub-Saharan Africa. Therefore, early identification and care strategies should be developed to the affected neonates with G6PD deficiency and blood type incompatibility with their mother's to address long-term medical and scholastic damages among those exposed to severe hyperbilirubinemia

**Keywords:** hyperbilirubinemia, blood type incompatibility, glucose-6-phosphate dehydrogenase, sub-Saharan Africa

**What is known about the subject**

The inconsistent prevalence of hyperbilirubinemia in the neonates of sub-Saharan Africa

**What this study adds**

Estimating the pooled burden of neonatal hyperbilirubinemia

identify its association with G6PD deficiency and blood type incompatibility

## 1. Background

Neonatal hyperbilirubinemia (i.e., jaundice) is a common and frequently benign condition that afflicts many infants in the first week of life. It is caused by the accumulation of bilirubin in the skin, which is created from biliverdin, a breakdown product of heme. Over 50% of newborns get jaundice in the first few days of life, and 60%–80% leads to unpreventable condition in newborns worldwide (1). Elevated levels of conjugated bilirubin (i.e., conjugated bilirubin level being ≥20% of the total serum bilirubin) are always pathologic and occur due to intra- or extrahepatic obstruction of the biliary tract. Moreover, it is the most common reason for neurological sequelae related to hyperbilirubinemia (2). The most significant among the long-term complications of hyperbilirubinemia is kernicterus, which is a type of brain damage that leads to choreoathetosis, sensorineural hearing loss, dental enamel dysplasia, paralysis of upward gaze, hypotonia, and a delay in the acquisition of motor skills, with a significant risk of neonatal death (3).

The prevalence of hyperbilirubinemia in the neonates of sub-Saharan Africa is somewhat inconsistent in the current literature, with rates ranging from 4–45.8% (4-7). That said, the burden of this condition on medical systems in developed and developing nations is significant (1). There are many risk factors that can predispose infants to hyperbilirubinemia, including jaundice observed in the first 24 hours, blood group incompatibility, other known hemolytic disease, elevated end-tidal carbon dioxide, gestational age of 35–36 weeks, sibling received phototherapy, cephalohematoma, significant bruising, excessive weight loss, isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, asphyxia, temperature instability, sepsis, acidosis, and albumin < 3 g/dl (2, 7, 8). More than any other risk factors, G6PD deficiency and blood group incompatibility are the most significant contributing causes for neurotoxicity (2). More than 70% of hyperbilirubinemia cases are due to either idiopathic neonatal hepatitis or biliary atresia (3).

Although G6PD deficiency and blood group incompatibility are widely regarded as risk factors for hyperbilirubinemia, the literature does show some inconsistencies (7-14). For instance, several studies from sub-Saharan African countries (7, 9-11) have indicated that G6PD deficiency and blood incompatibility are associated with an increased risk of neonatal jaundice. However, another study showed that they were not associated with jaundice (12). Given this variability and the lack of pooled representative data, we aimed to estimate the pooled burden of neonatal hyperbilirubinemia in countries of sub-Saharan Africa. Moreover, we attempted to identify its

association with G6PD deficiency and blood type incompatibility in this region. This data will aid healthcare professionals in assessing the prevalence of hyperbilirubinemia in their population and hopefully allow them to properly allocate resources to combat this neonatal affliction.

## 2. Methods

### 2.1. Data Sources and Literature Search Strategy

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pertinent published articles were searched independently and systematically by the authors in the following electronic databases: PubMed, Google Scholar, African Journals Online, Scopus, and others. In addition, a manual search of gray literature was performed to find other significant studies. The searches were limited to full text, open access articles with human subjects that were written in any language. Authors were contacted for full texts of their articles through e-mail, if necessary. The search was conducted using the following terms and phrases: "magnitude neonatal hyperbilirubinemia," "neonatal jaundice," "glucose-6-phosphate dehydrogenase deficiency," "blood type incompatibility," and "sub-Saharan Africa". Boolean operators like "and" and "or" were used to combine search terms. Particularly, to fit the advanced PubMed database, the following search strategy was used: ("magnitude neonatal hyperbilirubinemia" OR "glucose-6-phosphate dehydrogenase deficiency" OR "blood type incompatibility") AND ("sub-Saharan Africa").

### 2.2. Eligibility Criteria

#### 2.2.1. Predefined inclusion criteria

Studies were included for further analysis if they conformed to the following criteria:(1) All observational studies reported the prevalence of hyperbilirubinemia ,(2) the study setting was somewhere in sub-Saharan Africa,(3) The study participants were newborns with severe hyperbilirubinemia, (4) publication condition: all published articles , (5) language: all articles published in English language was included ,(6) the article was an observational study, a retrospective or prospective cohort study, or a cross-sectional study and ,(7) the study was published before April 10, 2019.

#### 2.2.2. Exclusion Criteria

Studies were excluded from this systematic review and meta-analysis if they fulfilled one of the following:(1) we were unable to access the full text articles after two emails to the principal investigator, (2) a study was a duplicate of a previously identified study,(3) the study had a poor quality score as per the inclusion criteria and, (4) the study failed to determine the desired outcome.

### 2.2.3. Type of exposure

In this meta-analysis, G6PD deficiency and blood type incompatibility were considered the exposure variables to estimate their effects on neonatal hyperbilirubinemia.

**2.2.3.1. Outcome of interest**: prevalence of neonatal hyperbilirubinemia.

### 2.3. Methods for data extraction and quality assessment

We used a Microsoft Excel standardized data extraction form to extract the data. The following information was extracted from each incorporated study: the name of the first author, publication year, country name, study design, associated factors, sample size, final included sample size', response rate, study settings, risk estimate (Odds Ratio), and the 95% confidence interval (CI). Data extraction from source documents was done independently by all investigators. Disagreements were resolved by consensus. The quality of the included studies was evaluated by using the Newcastle-Ottawa Scale (NOS) (13). Specifically, NOS assessed the sample representativeness and size, the comparability between participants, how neonatal hyperbilirubinemia was ascertained, and the statistical quality of each study. Studies were included for further analysis if they scored ≥5 out of 10 points in three domains of ten modified NOS components.

### 2.4 Data processing and analysis

Data were extracted from Microsoft Excel and analyzed using STATA Version 14 statistical software and forest plots that showed combined estimates with a 95% CI. The overall pooled prevalence was estimated by random effect meta-analysis (14). Heterogeneity was assessed by computing p values for the Cochrane Q-test and inconsistency index ($I^2$) (15). Given that we found significant heterogeneity among the studies ($I^2$ = 81.1%, p = 0.001), a random-effects meta-analysis model was used to estimate the pooled effect. Meta-regression analysis was performed to explore the possible source of heterogeneity. We also carried out a leave-one-out sensitivity analysis to assess how individual studies impacted heterogeneity. Publication bias was assessed using a funnel

plot and the Egger's regression test (14). For the second outcome, the odds ratio was used to ascertain the association between determinant factors and outcome variables in the included articles.

## 3. Results

### Search process

A total of 30,486 studies were collected from the aforementioned databases. After removing duplicates (n = 29,927), a total of 559 studies were retrieved. Of which, 486 were rejected just by reading the titles of the articles. Of the remaining 73 studies, 31 were excluded after reading the abstracts. Full text copies of the remaining 48 studies that met, or potentially met, the inclusion criteria were assessed. After further screening, 10 papers were retained for further analysis, and all, except one (French) were published in English. Based on the predefined criteria and quality assessment, only 10 articles were included in the final analysis (Figure 1).

### Characteristics of included studies

The pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa was assessed using 10 studies involving a total of 12,327 participants. The prevalence of hyperbilirubinemia in these studies ranged from 4.9% (4) to 44.9% (9), and most used a cross-sectional study design. The minimum sample size was 91 participants in a study conducted at Awolowo University, Nigeria (16), while the largest sample size was 5229 participants from Nigeria (11). All studies involved populations from sub-Saharan Africa, with six involving participants from Nigeria (6, 8, 10, 11, 16, 17), two from Ethiopia (7, 9), and one each from Zimbabwe (5), and Congo (4). Regarding the sampling technique employed, six of the studies (7-9, 16-18) used consecutive sampling to select study participants. However, the other studies did not report their sampling methods (Table 1).

**Table 1**. Baseline characteristics of the studies used to assess the pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa.

| Author | Publication year | Country | Region | Design | Total sample size | Included sample size | Outcome | Response rate (%) | Prevalence |
|---|---|---|---|---|---|---|---|---|---|
| Lake et al. | 2019 | Ethiopia | Tigray | Cross-sectional | 209 | 209 | 78 | 100 | 37.3 |
| Kassa et al. | 2018 | Ethiopia | Addis Ababa | Cross-sectional | 356 | 356 | 160 | 100 | 44.9 |
| Onyearugha et al. | 2011 | Nigeria | Southeast Nigeria | Cross-sectional | 457 | 457 | 160 | 100 | 35 |
| Olorunso et al. | 2015 | Nigeria | Ibadan | Cross-sectional | 232 | 232 | 79 | 100 | 34.1 |
| Diala et al. | 2018 | Nigeria | Cosmopolitan | Cohort | 1106 | 1106 | 159 | 100 | 15.3 |
| Badejoko et al. | 2014 | Nigeria | Awolowo University | Cohort | 644 | 91 | 129 | 99.3 | 20 |
| Osuorah et al. | 2018 | Nigeria | Enugu State University | Cohort | 1920 | 1920 | 480 | 100 | 25 |
| Mutombo et al. | 2014 | Congo | Congo | Cross-sectional | 2410 | 2410 | 120 | 100 | 4.9 |
| Wolf et al. | 1997 | Zimbabwe | Zimbabwe | Cohort | 120 | 110 | 50 | 91.7 | 45.4 |

**Magnitude of neonatal hyperbilirubinemia**

The overall random effects estimate for the level of neonatal hyperbilirubinemia across sub-Saharan Africa was 28.08 % (95% CI: (20.23, 35.94)) (Figure 2). Our test statistics indicated a high level of heterogeneity ($I^2 = 83.2\%$, $p < 0.001$) and the Eggers' test showed a significant publication bias ($p < 0.036$). Subsequently, we applied trim and fill meta-analysis (Figure 2).

**Subgroup analysis**

We performed a subgroup analysis using study design and the location of the included studies. Our subgroup analysis based on study location showed that the highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8) Figure 3. But no any difference in the level of neonatal hyperbilirubinemia with study design (Figure 4).

**Meta-regression analysis**

To identify the sources of heterogeneity in this study, meta-regression analysis was performed by considering the year of publication and sample size. However, our results showed that those covariates were not significantly associated with the presence of heterogeneity (Table 2).

**Table 2**. Meta-regression analysis using year of publication and sample size for the included studies.

| Covariate | Coefficient | Standard error | t value | p value | 95% CI |
|---|---|---|---|---|---|
| Sample size | -0.0033 | 0.0026 | 1.27 | 0.24 | 0.001, 0.002 |
| Publication year | -0.46 | 0.69 | -0.67 | 0.52 | -2.06, 1.13 |

**Publication bias and quality status**

Publication bias was evaluated by a funnel plot and the Egger's regression test. With respect to the former, publication bias is represented as significant asymmetry in a funnel plot. As depicted in Figure 5, there was a significant amount of asymmetry in our funnel plot and thus there was some publication bias. The Egger's regression test confirmed this result with a p value = 0.036. The quality assessment for each study is shown in Supplementary file.

**Sensitivity analysis**

We performed a sensitivity analysis to assess the weight of every study on the pooled effect size. Our analyses using the Der Simonian-Laird random-effects model revealed that there was no single study that affected the overall magnitude neonatal hyperbiliruminemia in sub-Saharan Africa. (Figure 6).

**The association between G6PD deficiency and neonatal hyperbilirubinemia**

The association between neonatal hyperbilirubinemia and G6PD deficiency was reported in four articles (6, 16, 19). The pooled odds ratio from these studies was 2.42 (95% CI: 1.64, 3.56), indicating that the likelihood of hyperbilirubinemia was 2.42 times higher in neonates with a G6PD deficiency than those with normal G6PD levels (Figure 7).

**The association between blood type incompatibility and neonatal hyperbilirubinemia**

Blood type incompatibility was another contributing factor for neonatal hyperbilirubinemia and their connection was reported in five studies included in our analyses (6, 7, 9-11) . The pooled odds ratio was 3.3 (95% CI: 1.96, 5.72), suggesting that the risk of developing hyperbilirubinemia was 3.3 times higher among neonates with an incompatible blood type as compared to blood type-compatible infants (Figure 8).

**4. Discussion**

Neonatal hyperbilirubinemia remains the principal reason of morbidity and mortality in resource-limited nations(4-7). The prevalence is also variable across different studies (4-7).Inconsistence estimates is reported in the association with G6PD deficiency (2, 7, 8)and blood type

incompatibility (2, 7, 8). So that, this meta-analysis determined the pooled prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility in sub-Saharan Africa using ten studies.

The overall pooled estimate for the prevalence of hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94)). This is consistent with the rates of neonatal hyperbilirubinemia in the United States of America (20). However, our finding is higher than that found in a previous meta-analysis (21). In contrast, the prevalence of hyperbilirubinemia found in our study was substantially lower than that found in previous systematic reviews carried out in Pakistan (22), Myanmar (23) and global burden diseases GBD (24, 25). These differences might be the result of different diagnostic standards for neonatal hyperbilirubinemia, early diagnosis and treatment in developed countries, and the early discharge of healthy late-preterm and full-term newborns.

The prevalence of neonatal hyperbilirubinemia varied greatly in the included studies, ranging from 4.9% (4) to 44.9% (9). However, our subgroup analysis based on study location showed that the highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8). A possible explanation for this variation could be the differences in healthcare facilities.. With emerging an inexpensive technology, the developed nations prevention and treatment of neonatal hyperbilirubinemia can more feasibly reach those at risk as compare to resource-limiting settings. Additionally, developed nations may have a better screening strategy of postnatal hemolysis and management of idiopathic etiologies which may help to reach both a near eradication of mortality related with jaundice and reduces in its impairment.

In this study, the odds of an infant getting hyperbilirubinemia was 2.4 times higher for those neonates with a G6PD deficiency than those with normal G6PD levels. This is in line with studies done in different countries (18, 23, 26-28). G6PD deficiency may be linked to hyperbilirubinemia because G6PD is the main source for NADPH in red blood cells, which is important for antioxidant defense. Those neonates that are deficient in G6PD are susceptible to oxidant-induced hemolysis and heme catabolism that produces bilirubin – the precipitating factor in hyperbilirubinemia (29).

This study also noted that the likelihood of having hyperbilirubinemia was higher among neonates with blood group incompatibility. Neonates with blood group incompatibility were 3.3 times more likely to have hyperbilirubinemia as compared to patients with a compatible blood type. This is supported by a number of previous studies (23, 30). This could be due to hemolysis that occurs when maternal immunoglobulin G anti-A or anti-B antibodies cross the placenta and attach to the

opposite antigen site on the neonatal red cell ,which results in increase heme catabolism that increases the production bilirubin(31)

The implication of the current finding is stated as follows; estimating the prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility will help to mobilize the national leadership to initiate actions and embed proven systems, policies, and programs to reduce jaundice-related newborn mortality and disabilities. The health care professional will also include neonates born with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility as Every Newborn Action Plan promotion of maternal and newborn care and essential newborn care for better care of neonates with jaundice which helps better neonatal survival, improved long-term development, and decrease disability. It will also alarm them for national identification of all blood type incompatible woman before or during pregnancy and with coordinated obstetric and neonatal care.

**Strengths and limitations of the study**

As far as we know this is the first meta-analysis which has been done in sub-Saharan Africa. This study was conducted with the use of an inclusive search strategy to incorporate the studies involving African patients. All of the included studies had high methodological quality based on our NOS assessments. Despite this, our study had several limitations. First, most of the studies used for this analysis had a small sample size, which could have a significant effect on the estimated prevalence of neonatal hyperbilirubinemia. Moreover, this meta-analysis represented only studies from five countries, which may be an underrepresentation for the region of sub-Saharan Africa.

**Conclusion**: This study noted that neonatal hyperbilirubinemia in sub-Saharan Africa was quite common. This study also revealed that neonatal hyperbilirubinemia is associated with G6PD deficiency and blood type incompatibility. Based on our findings, we suggest that all neonates with hyperbilirubinemia be assessed for G6PD deficiency and blood type compatibility to identify the most likely to contract the disease. Furthermore, additional research is needed to identify other associated factors for the development of neonatal hyperbilirubinemia

**Abbreviations:** CI: confidence interval; G6PD; glucose-6-phosphate dehydrogenase, NOS: Newcastle-Ottawa Scale; OR; odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**Acknowledgements**

We would like to thank to Doctor Ryan Bell (CEO and Chief Editor Excision Editing) whose assistance was invaluable to the completion of the study and who have made an extensive edition in our manuscript.

**Patient and Public Involvement statement**

Not required

**Available data and materials**

The data analyzed during the current meta-analysis is available from the corresponding author upon reasonable request.

**Authors' contributions**

YAA conceived and designed the study. YAA and WSS established the search strategy. WSS, TYA, and GBM wrote the review. All authors read and approved the final manuscript.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**

The authors have also declared that they received no financial support in the research, authorship, and publication of this article.

**Consent for publication**

Not applicable

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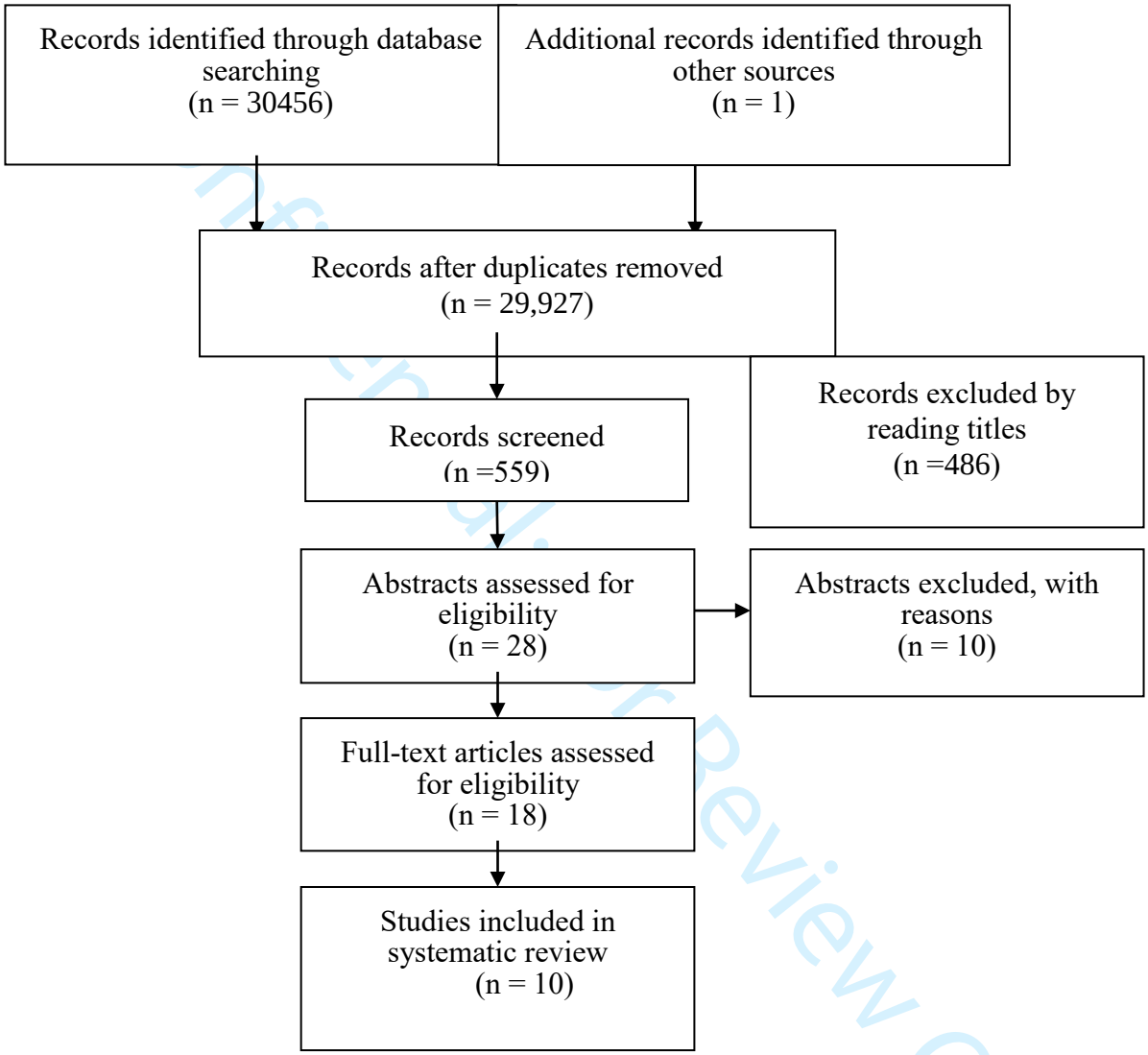


**Figure 1**. Flow chart of how research articles were searched and selected for analysis in this study.

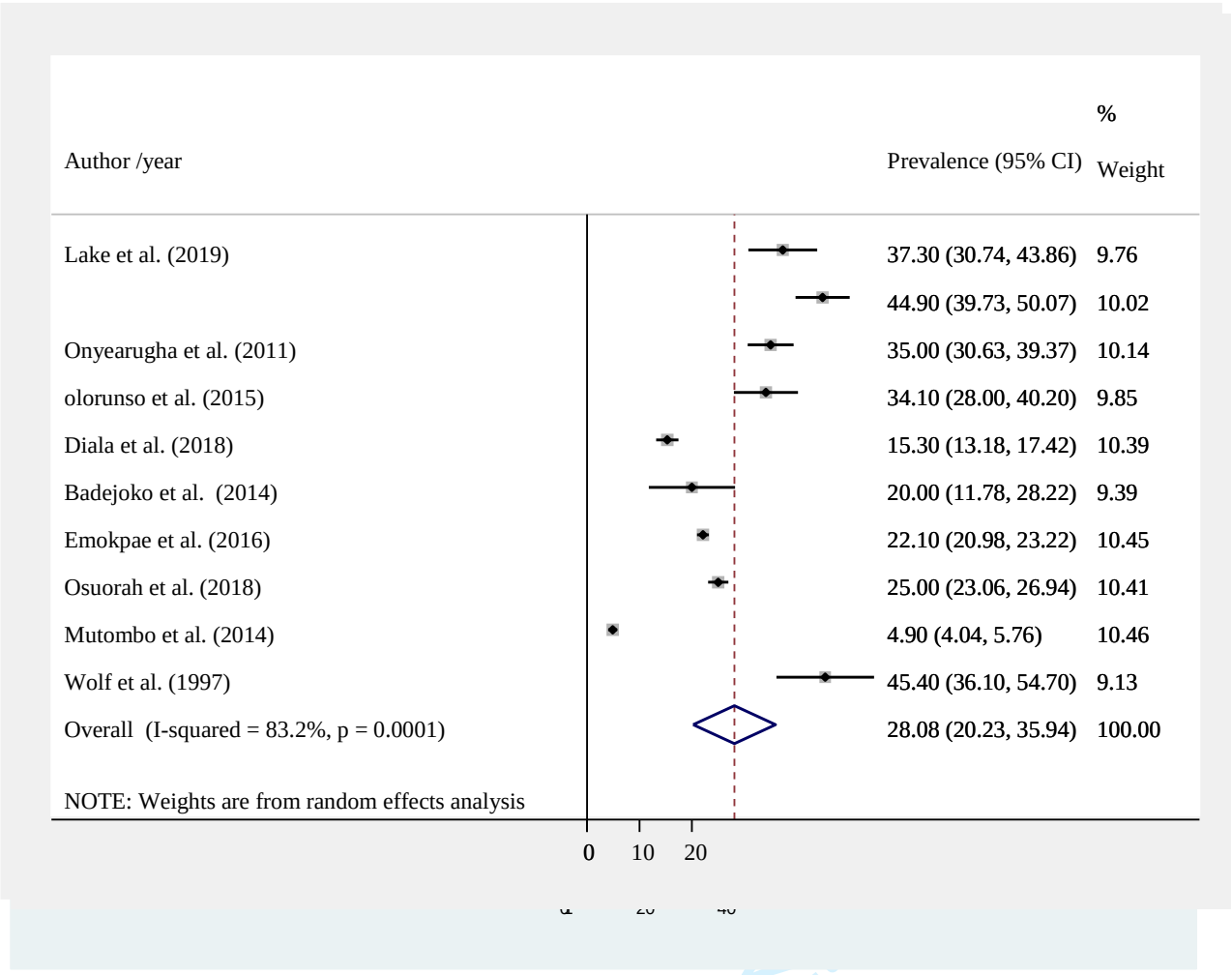


**Figure 2**. Prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa.

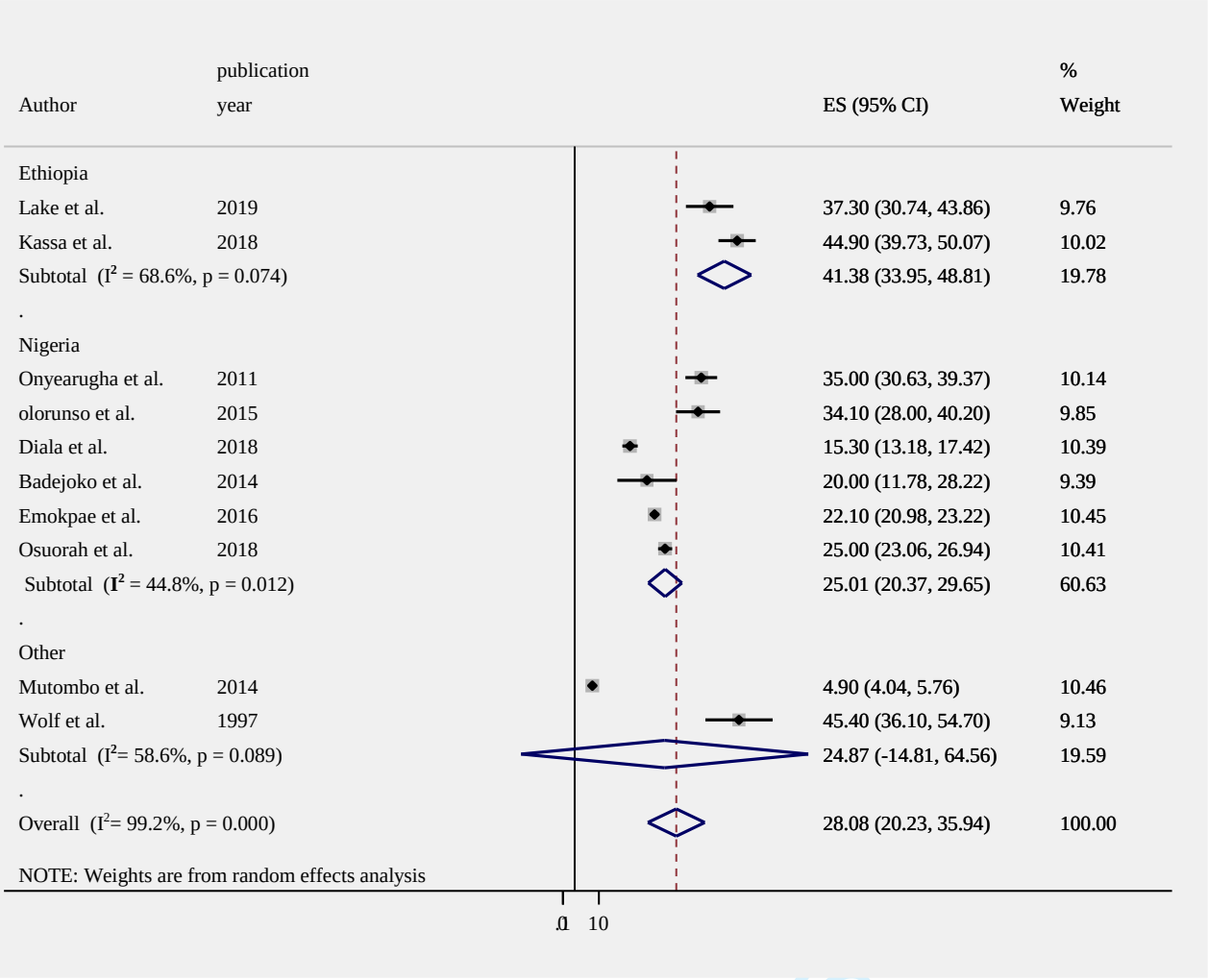


**Figure 3**. Subgroup analysis of the magnitude of neonatal hyperbilirubinemia based on study location.

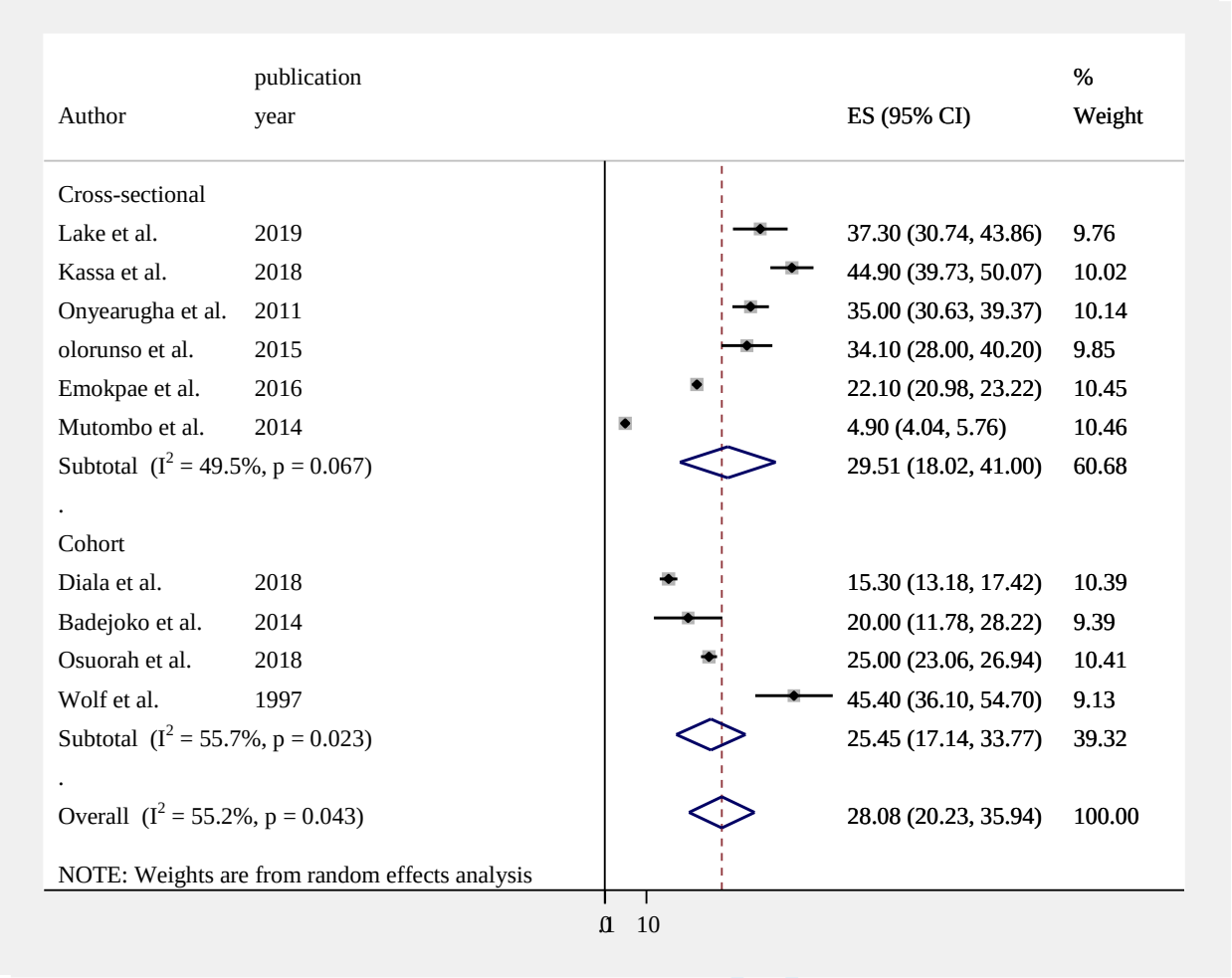


**Figure 4**. Subgroup analysis of the magnitude of neonatal hyperbilirubinemia based on study design.

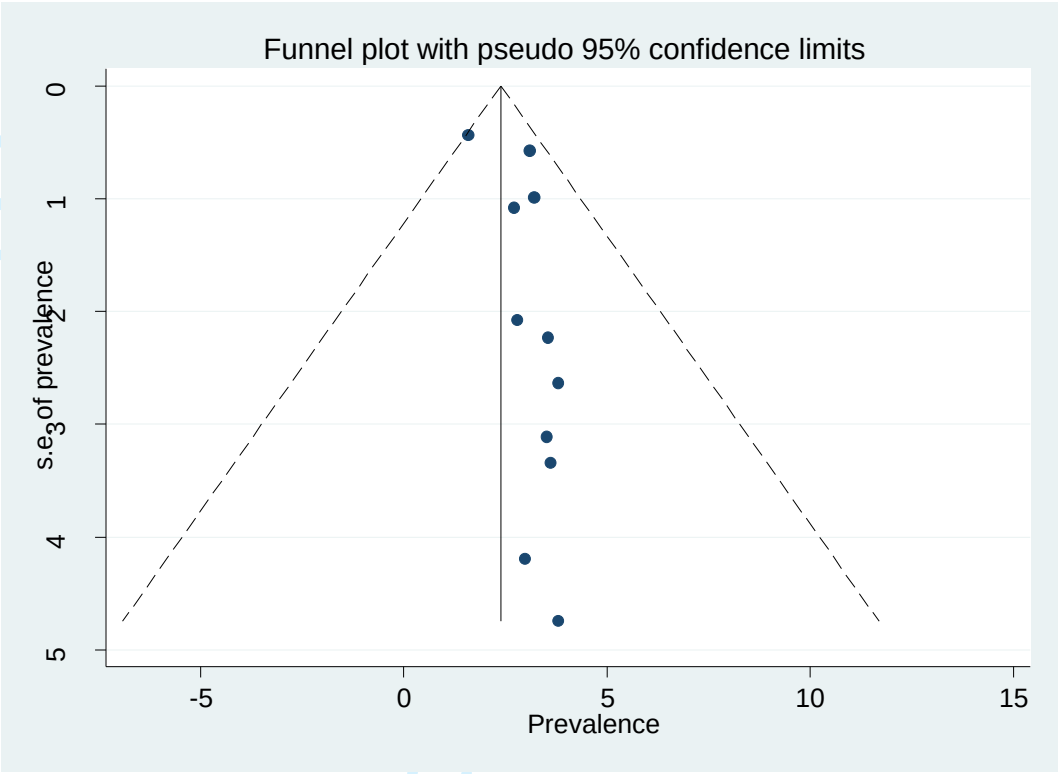


**Figure 5**. Funnel plot to determine publication bias among the included studies.

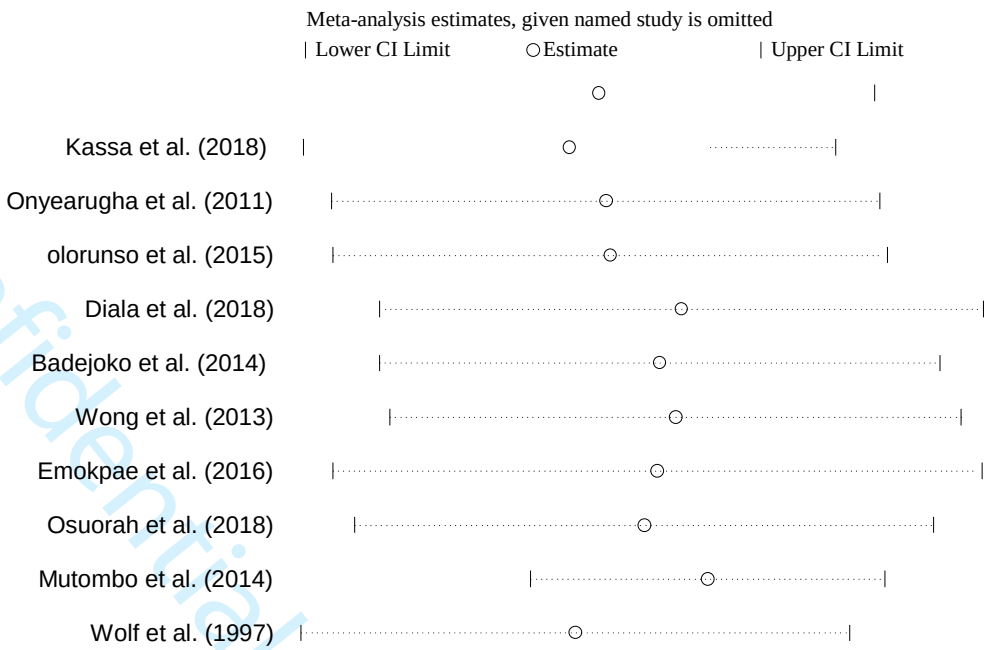


**Figure 6.** Sensitivity analyses of the included studies.

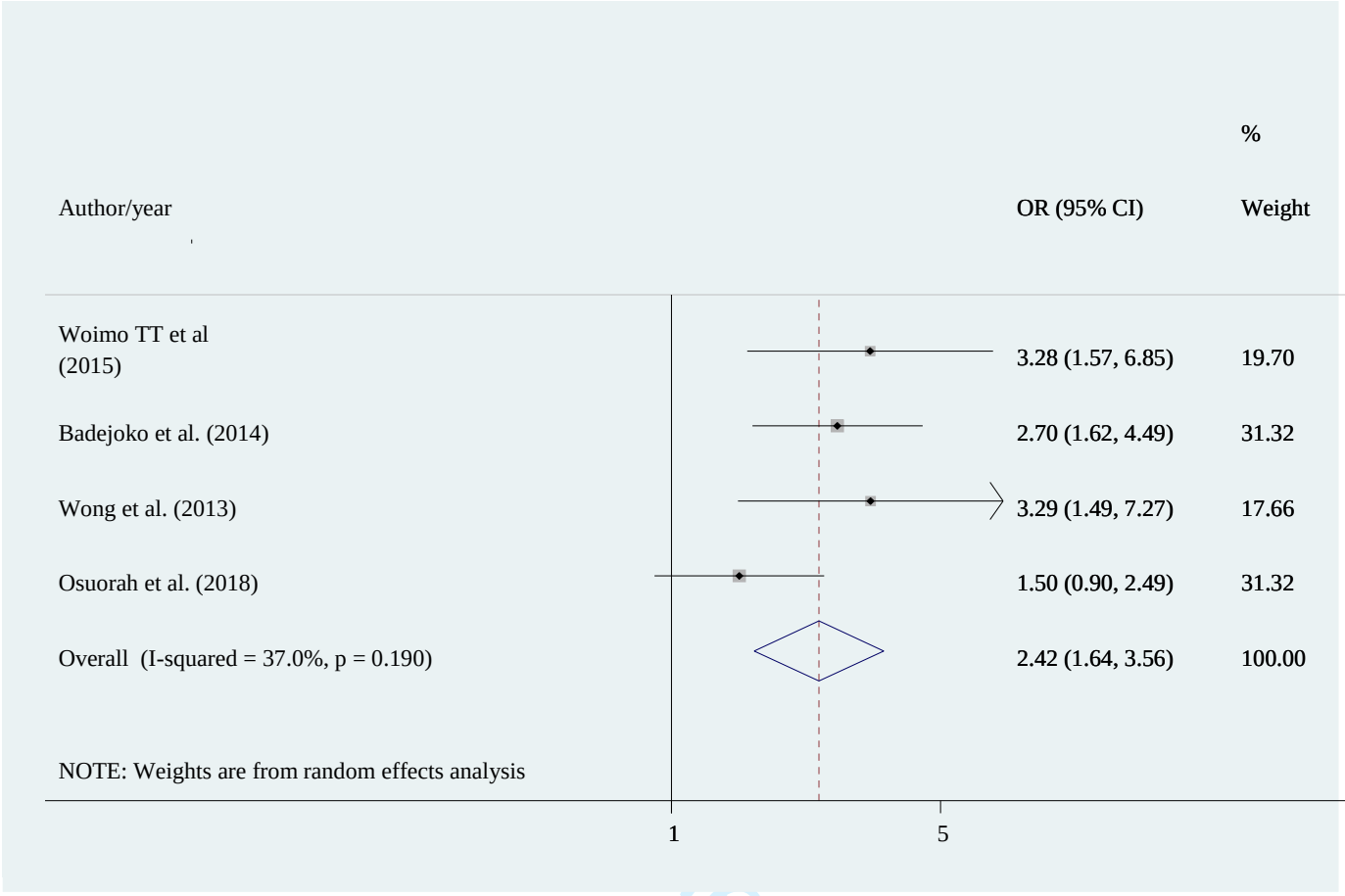


**Figure 7: The association of** G6PD deficiency **with neonatal hyperbilirubinemia**

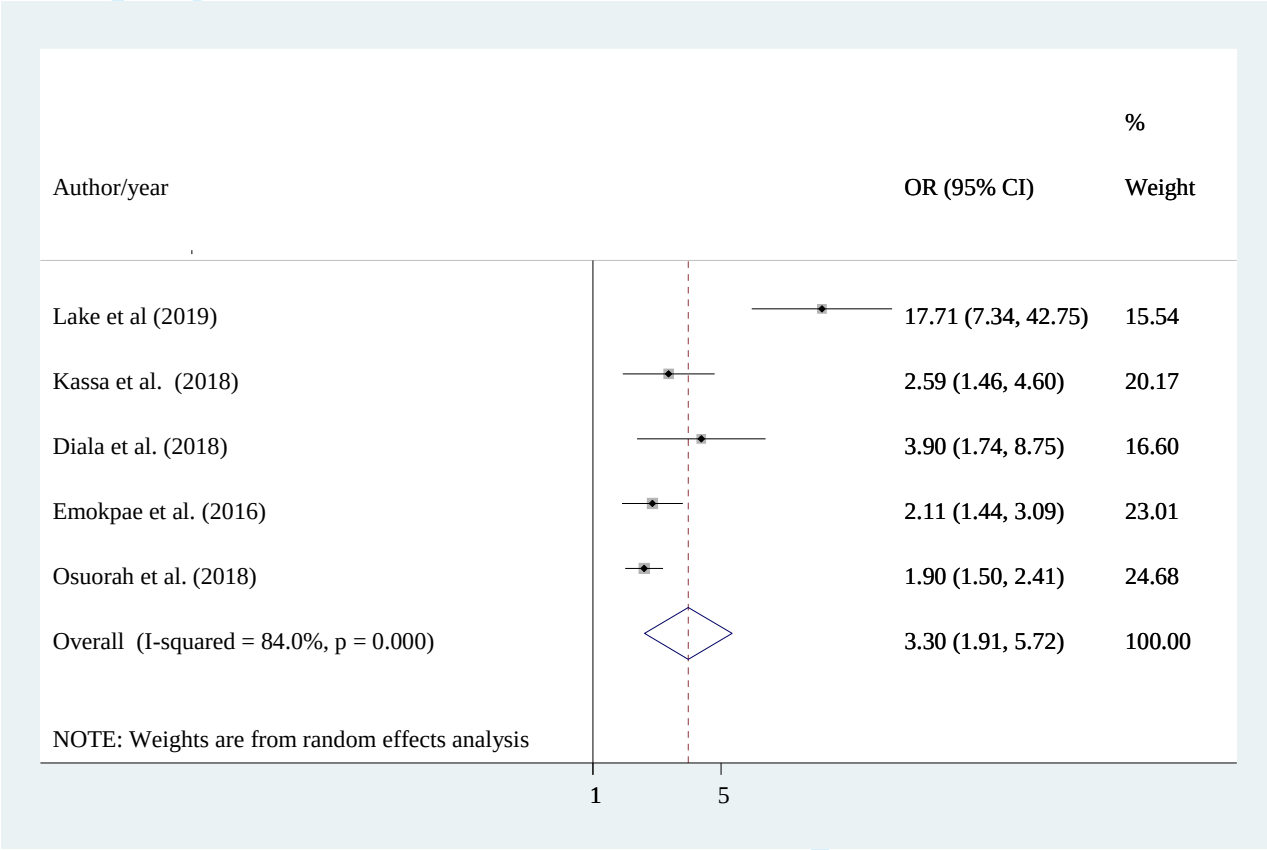


Figure 8: The association of blood type incompatibility with neonatal hyperbilirubinemia.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | |
| **ABSTRACT** | | | |
| Structured summary | 1&2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | |
| Objectives | 3 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| **METHODS** | | | |
| Protocol and registration | Not registered but posted as a preprint | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 4 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | |
| Information sources | 4 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | |
| Search | 4 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | |
| Study selection | 5 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | |
| Data collection process | 5&6 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | |
| Data items | 5 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | |
| Risk of bias in individual studies | 5&6 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | |
| Summary measures | 6 | State the principal summary measures (e.g., risk ratio, difference in means). | |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 6 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

Page 1 of 2

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 7 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| Additional analyses | 8&7 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| **RESULTS** | | | |
| Study selection | 6 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| Study characteristics | 6 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| Risk of bias within studies | 7 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | |
| Results of individual studies | 8&9 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| Synthesis of results | 10 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 8 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 8 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 8 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | |
| Limitations | 9 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | |
| Conclusions | 10 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |
| **FUNDING** | | | |
| Funding | 11 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

# PRISMA 2009 Checklist

## Supplementary files for methodological quality assessment

**Supplementary file 1:** Methodological quality assessment of cross-sectional studies using modified Newcastle - Ottawa Scale (NOS)

| First author | Criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | | Comparability | | Outcome | | |
| | Representativeness of the sample | Sample size | Non – responders | Ascertainment of exposure/risk factor | The study controls for the most important factor | The study control for any additional factor | Assessment of the outcome | Statistical test | Total score (10) |
| Lake et al. 2019 | A* | B* | B* | A* | - | B* | A* | A* | 7 |
| Kassa et al. 2018 | B* | B* | A* | A* | A* | - | A* | A* | 7 |
| Onyearugha et al.2011 | A* | A* | A* | A* | A* | - | A* | A* | 7 |
| Olorunso et al.2016 | A* | B* | B* | A* | - | B* | A* | A* | 7 |
| Diala et al. 2018 | B* | B* | A* | A* | A* | - | A* | A* | 7 |
| Badejoko et al. 2018 | B* | A* | A* | B* | A* | A* | A* | A* | 7 |
| Mutombo et al. 2014 | A* | A* | A* | A* | A* | B* | A* | A* | 7 |
| Wolf et al. 1997 | B* | B* | A* | A* | A* | - | A* | A* | 7 |
| Emokpae et al.2016 | A* | A* | - | A* | A* | - | A* | A* | 6 |
| Osuorah et al.2018 | A* | A* | A* | B* | A* | A* | A* | A* | 8 |

*Note: from each item account point. (Accept the study if total sc*

**Selection:** (Maximum 5 stars)

1) Representativeness of the sample: a) Truly representative of the average in the target population. * (all subjects or random sampling) .b) Somewhat representative of the average in the target population. * (nonrandom sampling) .c) Selected group of users.d) No description of the sampling strategy.

2) Sample size:a) Justified and satisfactory. *.b) Not justified.

3) Non-respondents: a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. * .b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor): a) validated measurement tool. ** .b) Non-validated measurement tool, but the tool is available or described.* c) No description of the measurement tool.

**Comparability:** (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. a) The study controls for the most important factor (select one). * b) The study control for any additional factor. *

**Outcome:** (Maximum 3 stars)

1) Assessment of the outcome: a) Independent blind assessment. **,b) Record linkage. **,c) Self report. *,d) No description.

2) Statistical test:a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *,b) The statistical test is not appropriate, not described or incomplete

**Supplementary file 2:**: Methodological quality assessment of cross-sectional and cohort studies using modified Newcastle - Ottawa Scale (NOS)

| **First author, publication year** | **Criteria** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Selection** | | | **Comparability** | | **Outcome** | | |
| | **Representativeness of the sample** | **Non – respondents** | **Ascertainment of exposure** | **The study controls for the most important factor** | **The study control for any additional factor** | **Assessment of the outcome** | **Statistical test** | **Total score** |
| Gizaw et al.2013 | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **7** |
| **Andargie et al.,2013** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **7** |
| **Mengesha et al.,2016** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **7** |
| **Yismaw et al.,2019** | **1** | **0** | **1** | **1** | **1** | **1** | **1** | **6** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Yismaw and Tarekegn etal.,2018** | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **7** |
| **Demisse et al**.,2017 | **1** | **1** | **1** | **1** | **1** | **1** | **1** | **7** |
| **Debelew et al.** 2014 | 1 | **1** | **1** | **1** | **1** | 1 | **1** | **5** |
| **Farah et al.,2018** | 1 | **1** | **1** | **1** | **1** | 1 | **1** | **7** |
| **Yehuala and Teka etal.,2015** | 1 | **1** | **1** | **1** | **1** | 1 | **1** | **7** |
| **Wesenu et al.,2017** | 1 | **0** | **1** | **0** | **1** | 1 | **1** | **6** |
| **Mengesha et al.,2016** | 1 | **1** | **1** | **1** | **1** | 1 | **1** | **7** |
| Orsido et al.,2019 | 1 | **0** | **1** | **0** | **1** | 1 | **1** | **5** |

*Note: each item account 1 point. (Accept the study if total score ≥ 5)*

Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. ☒

Representativeness of the sample:

a) Truly representative of the average in the target population. ☒ (all subjects or random sampling)

b) Somewhat representative of the average in the target population. ☒ (non-random sampling)

Comparability: The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. a) The study controls for the most important factor (select one). ☒

b) The study control for any additional factor. ☒

Ascertainment of exposure based on validated measurement tool ☒ or non-validated measurement tool, but the tool is available or described OR No description of the measurement tool.

Outcome:Independent blind assessment ☒, record linkage ☒, self-report or no description.

The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value) ☒ or the statistical test is not appropriate, not described or incomplete.

BMJ Paediatrics Open

# Prevalence of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility in sub-Saharan Africa: a systematic review and meta-analysis



| | |
|---|---|
| Journal: | *BMJ Paediatrics Open* |
| Manuscript ID | bmjpo-2020-000750.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 18-Jul-2020 |
| Complete List of Authors: | Aynalem, Yared; Debre Berhan University, pediatric and child health<br>Mulu, Getaneh ; Debre Berhan University<br>Akalu, Tadesse ; Debre Markos University<br>Shiferaw, Wondimeneh ; Debre Berhan University |
| Keywords: | Statistics, Qualitative research, Nursing Care, Jaundice, Neonatology |
| | |

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# Prevalence of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility in sub-Saharan Africa: a systematic review and meta-analysis

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## Abstract

**Background:** Hyperbilirubinemia is a silent cause of newborn disease and death worldwide. However, studies of the disease in sub-Saharan Africa are highly variable with respect to its prevalence. Hence, this study aimed to estimate the overall magnitude of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase (GP6D) deficiency and blood type incompatibility in sub-Saharan Africa.

**Methods**: PubMed, Scopus, Google Scholar, and the Cochrane Review were systematically searched online to retrieve hyperbilirubinemia-related articles. All observational studies reported the prevalence of hyperbilirubinemia in sub-Saharan Africa were included for analysis and excluded if the study failed to determine the desired outcome. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed. Heterogeneity across the included studies was evaluated using the inconsistency index ($I^2$). Subgroup and meta-regression analysis were also done. Publication bias was examined by funnel plot and the Egger's regression test. The random-effect model was fitted to estimate the pooled prevalence of neonatal hyperbilirubinemia. The meta-analysis was performed using the STATA™ version 14 software.

**Results**: A total of 30,486 studies were collected from the different databases and 10 articles were included for the final analysis. The overall magnitude of neonatal hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94)) in sub-Saharan Africa. Neonates with G6PD deficiency (OR: 2.42 (95%

CI: 1.64, 3.56)) and neonates that had a blood type that was incompatible with their mother's (OR: 3.3 ((95% CI: 1.96, 5.72)) were more likely to develop hyperbilirubinemia.

**Conclusion**: The failure to prevent and screen G6PD deficiency and blood type incompatibility with their mother's results in high burden of neonatal hyperbilirubinemia in sub-Saharan Africa. Therefore, early identification and care strategies should be developed to the affected neonates with G6PD deficiency and blood type incompatibility with their mother's to address long-term medical and scholastic damages among those exposed to hyperbilirubinemia

**Keywords:** hyperbilirubinemia, blood type incompatibility, glucose-6-phosphate dehydrogenase, **s**ub-Saharan Africa

**What is already known on this topic?**

The inconsistent prevalence of hyperbilirubinemia in the neonates of sub-Saharan Africa

Neonatal hyperbilirubinemia is among the common cause of neonatal morbidity and mortality particularly in low-income income nations

**What this study adds**

Estimating the pooled burden of neonatal hyperbilirubinemia

Identify its pooled association with G6PD deficiency and blood type incompatibility

## 1. Background

Neonatal hyperbilirubinemia (i.e., jaundice) is a common and often a benign condition that afflicts many infants in the first week of life. It is caused by the accumulation of bilirubin in the skin, which is created from biliverdin, a breakdown product of heme. Over 50% of newborns get jaundice in the first few days of life, and from those,60%–80% leads to unpreventable condition in newborns worldwide (1). Elevated levels of conjugated bilirubin (i.e., conjugated bilirubin level being ≥20% of the total serum bilirubin) are always pathologic and occur due to intra- or extrahepatic obstruction of the biliary tract. Moreover, elevated levels of unconjugated bilirubin is the most common reason for neurological sequelae related to hyperbilirubinemia (2). The most significant among the long-term complications of hyperbilirubinemia is kernicterus, which is a type of brain damage that leads to choreoathetosis, sensorineural hearing loss, dental enamel dysplasia, paralysis of upward gaze, hypotonia, and a delay in the acquisition of motor skills, with a significant risk of neonatal death (3).

The prevalence of hyperbilirubinemia in the neonates of sub-Saharan Africa is somewhat inconsistent in the current literature, with rates ranging from 4–45.8% (4-7). That said, the burden of this condition on medical systems in developed and developing nations is significant (1). There are many risk factors that can predispose infants to hyperbilirubinemia, including jaundice observed in the first 24 hours, blood group incompatibility, other known hemolytic disease, elevated end-tidal carbon dioxide, gestational age of 35–36 weeks, sibling received phototherapy, cephalohematoma, significant bruising, excessive weight loss, isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, asphyxia, temperature instability, sepsis, acidosis, and albumin < 3 g/dl (2, 7, 8). More than any other risk factors, G6PD deficiency and blood group incompatibility are the most significant contributing causes for neurotoxicity (2). More than 70% of hyperbilirubinemia cases are due to either idiopathic neonatal hepatitis or biliary atresia (3).

Although G6PD deficiency and blood group incompatibility are widely regarded as risk factors for hyperbilirubinemia, the literature does show some inconsistencies (7-14). For instance, several studies from sub-Saharan African countries (7, 9-11) have indicated that G6PD deficiency and blood incompatibility are associated with an increased risk of neonatal jaundice. However, another study showed that they were not associated with jaundice (12). Given this variability and the lack of pooled representative data, we aimed to estimate the pooled burden of neonatal

hyperbilirubinemia in countries of sub-Saharan Africa. Moreover, we attempted to identify its association with G6PD deficiency and blood type incompatibility in this region. This data will aid healthcare professionals in assessing the prevalence of hyperbilirubinemia in their population and hopefully allow them to properly allocate resources to combat this neonatal affliction.

## 2. Methods

### 2.1. Data Sources and Literature Search Strategy

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pertinent published articles were searched independently and systematically by the authors in the following electronic databases: PubMed, Google Scholar, African Journals Online, Scopus, and others (Grey literature, such as unpublished articles and conference abstracts). In addition, a manual search of gray literature was performed to find other significant studies. The searches were limited to full text, open access articles with human subjects that were written in any language. Authors were contacted for full texts of their articles through e-mail, if necessary. The search was conducted using the following terms and phrases: “magnitude neonatal hyperbilirubinemia,” “neonatal jaundice,” “glucose-6-phosphate dehydrogenase deficiency,” “blood type incompatibility”and“sub-Saharan Africa”. Boolean operators like “and” and “or” were used to combine search terms. Particularly, to fit the advanced PubMed database, the following search strategy was used: (“magnitude neonatal hyperbilirubinemia” OR “glucose-6-phosphate dehydrogenase deficiency” OR “blood type incompatibility”) AND (“sub-Saharan Africa”).

### 2.2. Eligibility Criteria

#### 2.2.1. Predefined inclusion criteria

Studies were included for further analysis if they conformed to the following criteria:(1) All observational studies reported the prevalence of hyperbilirubinemia ,(2) the study setting was somewhere in sub-Saharan Africa,(3) the study participants were newborns with severe hyperbilirubinemia, (4) publication condition: all published and unpublished articles , (5) language: all articles published in English and other language was included. Publication date: Until 10, April, 2020.

, and(6) the article was an observational study, and a retrospective or prospective cohort study, or a cross-sectional study

**2.2.2. Exclusion Criteria**

Studies were excluded from this systematic review and meta-analysis if they fulfilled one of the following:(1) we were unable to access the full text articles after two emails to the principal investigator, (2) a study was a duplicate of a previously identified study,(3) the study didn't fulfill the inclusion criteria and, (4) failed to determine the desired outcome.

**2.2.3. Type of exposure**

In this meta-analysis, G6PD deficiency and blood type incompatibility were considered the exposure variables to estimate their effects on neonatal hyperbilirubinemia.

**2.2.3.1. Outcome of interest**:

Prevalence of neonatal hyperbilirubinemia (conjugated/unconjugated).

**2.3. Methods for data extraction and quality assessment**

We used a Microsoft Excel standardized data extraction form to extract the data. The following information was extracted from each incorporated study: the name of the first author, publication year, country name, study design, total sample size, final included sample size', response rate, study settings, and the 95% confidence interval (CI). Data extraction from source documents was done independently by all investigators. Disagreements were resolved by consensus. The quality of the included studies was evaluated by using the Newcastle-Ottawa Scale (NOS) (13). Specifically, NOS assessed the sample representativeness and size, the comparability between participants, how neonatal hyperbilirubinemia was ascertained, and the statistical quality of each study. Studies were included for further analysis if they scored ≥5 out of 10 points in three domains of ten modified NOS components.

**2.4 Data processing and analysis**

Data were extracted from Microsoft Excel and analyzed using STATA Version 14 statistical software and forest plots that showed combined estimates with a 95% CI. The overall pooled prevalence was estimated by random effect meta-analysis (14). Heterogeneity was assessed by

computing p values for the inconsistency index ($I^2$)(15). We found significant heterogeneity among the studies ($I^2$ = 83.2%, p = 0.001). Meta-regression analysis was performed using sample size, study design and country, factors and publication year to explore the possible source of heterogeneity. We also conducted a subgroup analysis using the following variables: study design, Publication year, sample size, study design and locations of the studies. Sensitivity analysis was also conducted to assess the possible included outlier articles Publication bias was assessed using a funnel plot and the Egger's regression test (14). The association between the prevalence of neonatal hyperbilirubinemia and G6PD deficiency or blood type incompatibility was measured by random-effects meta-analysis pooled odds ratios.

## 3. Results

### Search process

A total of 30,486 studies were collected from the aforementioned databases. After removing duplicates (n = 29,927), a total of 559 studies were retrieved. Of which, 486 were rejected just by reading the titles of the articles (due to unrelated to the topic). Of the remaining 73 studies, 31 were excluded by abstracts (due to no abstract, unrelated abstracts and unable to access the full text of articles with two email contact). Full text copies of the remaining 42 studies that potentially met the inclusion criteria were assessed. From this, 32 articles were discarded due to failed to determine the desired outcome (not fully fulfilled the inclusion criteria). After further screening, 10 papers were fulfilled the eligibility criteria. Articles published in several languages were assessed. But, nine papers published in English and one paper published in French was retained for final analysis (Figure 1).

### Characteristics of included studies

The pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa was assessed using 10 studies involving a total of 12,327 participants. The minimum sample size was 91 participants in a study conducted at Awolowo University, Nigeria (16), while the largest sample size was also participants from Nigeria (5229)(11). All studies involved populations from sub-Saharan Africa, with six involving participants from Nigeria (6, 8, 10, 11, 16, 17), two from Ethiopia (7, 9), and one each from Zimbabwe (5), and Congo (4) (Table 1).. Regarding the sampling technique employed,

six of the studies (7-9, 16-18) used consecutive sampling to select study participants. However, the other studies did not report their sampling methods.

**Table 1**. Baseline characteristics of the studies used to assess the pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa.

| Author/publication year | Country | Region | Study design | Total sample size | Final included sample size | Prevalence (%) | Response rate | Contributions |
|---|---|---|---|---|---|---|---|---|
| Lakeet al/2019 | Ethiopia | Tigray | Cross-sectional | 209 | 209 | 78(37.3) | 100 | For estimating pooled prevalence and associated factories |
| Kassaet al/2018 | Ethiopia | Addis Ababa | Cross-sectional | 356 | 356 | 160(44.9) | 100 | For estimating pooled prevalence and associated factories |
| Onyearugha et al/2011 | Nigeria | Southeast Nigeria | Cross-sectional | 457 | 457 | 160(35) | 100 | For estimating the pooled prevalence |
| olorunsoet al/2015 | Nigeria | Ibadan | Cross-sectional | 232 | 232 | 79(34.1) | 100 | For estimating the pooled prevalence |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Dialaet al/2018 | Nigeria | cosmopolitan | Cohort | 1106 | 1106 | 159(15.3) | 100 | For estimating pooled prevalence and associated factories |
| Badejokoet al/2014 | Nigeria | Awolowo University | Cohort | 644 | 639 | 129(20) | 99.3 | For estimating pooled prevalence and associated factories |
| Emokpaeet al/2016 | Nigeria | Lagos | Cross-sectional | 5,229 | 5,229 | 1,153(22.1) | 100 | For estimating pooled prevalence and associated factories |
| Osuorahet al/2018 | Nigeria | Enugu State University | Cohort | 1920 | 1920 | 480(25) | 100 | For estimating pooled prevalence and associated factories |
| Mutomboet al/2014 | Congo | Congo | Cross-sectional | 2410 | 2410 | 120(4.9) | 100 | For estimating the pooled prevalence |
| Wolfet | Zimbab | Zimbabwe | Cohort | 120 | 110 | 50 | 91.7 | For estimating |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| al/1997 | wean | an | | | | | | the pooled prevalence |
| Woimo TT et al (2015) | Suadn | - | Case control | 243 | 243 | - | 100 | For estimating the pooled Associated factories |
| Farouk et al. (2017) (2016) | Nigeria | Kano | Case control | 551 | 551 | - | 100 | For estimating the pooled prevalence |

**Magnitude of neonatal hyperbilirubinemia**

A total of 12,327 participants and 10 studies were included to estimate the pooled magnitude of neonatal hyperbilirubinemia. The overall random effects estimate for the level of neonatal hyperbilirubinemia across sub-Saharan Africa was 28.08 % (95% CI: (20.23, 35.94)) (Figure 2). Our test statistics indicated a high level of heterogeneity ($I^2$ = 83.2%) and the Eggers' test showed no significant publication bias (p = 0.36).

**Subgroup analysis**

We performed a subgroup analysis using sample size, publication year, study design and the location of the included studies. In the current meta-analysis a sample size of less than 384 revealed a higher prevalence(40.2(95%CI:34.5,45.8,($I^2$=66%)) as compared to sample size of greater than or equal to than 384(20.3( 95%CI:11.3, 29.4,), $I^2$=88)) .Our subgroup analysis based on study location also showed that the highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8, $I^2$= 68.6) Figure 3. Prevalence rates were very similar across study designs (**Table 2** ).

Table 2: Sub-group analysis results of the included studies

| Sub group analysis | Variables | Number of studies | Prevalence (95%CI) | Weight (%) | $I^{2}$ (%) |
|---|---|---|---|---|---|
| By country | Ethiopia | 2 | 41.4 (33.9 ,48.8) | 19.9 | 68.6 |
| | Nigeria | 6 | 25.1( 20.4, 29.6) | 60.6 | 94.8 |
| | Congo | 1 | 4.9( 4.1, 5.76) | 10.46 | 0 |
| | Zimbabwi | 1 | 45.4( 36.1, 54.7) | 9.1 | 0 |
| Publication year | Less than 2014 | 4 | 26.1( 5.47, 46.7) | 39.13 | 88 |
| | Greater than or equal to 2014 | 6 | 29.13( 23.3 , 34.9) | 60.87 | 89 |
| Sample size | Less than 384 | 4 | 40.2(34.5,45.8) | 38.9 | 66 |
| | Greater than or equal to 384 | 6 | 20.3( 11.3, 29.4) | 61.2 | 88 |
| Study design | Cross-sectional | 6 | 29.5( 18.0, 41.0) | 60.68 | 98 |
| | Cohort | 4 | 25.4(17.2, 33.7) | 39.32 | 90 |

**Meta-regression analysis**

To identify the sources of heterogeneity in this study, meta-regression analysis was performed by considering the sample size, study design and country, factors and publication year. However, our results showed that those covariates were not significantly associated with the presence of heterogeneity (Table 3).

Table 3: Meta regression results by different covariant

| Variables | Category | Coefficient | Standard error | T | P-value | 95% CI |
|---|---|---|---|---|---|---|
| Publication year | < 2014 | -0.0033 | 0.0026 | 1.27 | 0.24 | 0.001, 0.002 |
| | ≥2014(reference) | | | | | |
| Sample size | <384 | -0.46 | 0.69 | -0.67 | 0.52 | -2.06, 1.13 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | *≥384(reference)* | | | | | |
| Country | Nigeria | 2.7 | 2.2 | 0.12 | 0.9 | -0.5-5.1 |
| | Ethiopia | 9.1 | 2.3 | 0.39 | 0.7 | -0.5 -6.3 |
| | other (reference) | | | | | |
| Study design | cross sectional | 1.21 | 11.06 | 0.11 | 0.915 | 0.2.-2.5 |
| | cohort (reference) | | | | | |
| G6PD deficiency | Yes | -0.36 | 0.59 | -0.47 | 0.32 | 0.06, 1.13 |
| | No (reference) | | | | | |

**Publication bias and quality status**

Publication bias was evaluated by a funnel plot and the Egger's regression test. With respect to the former, publication bias is represented as significant asymmetry in a funnel plot. As depicted in Figure 3, there was a significant amount of symmetry in our funnel plot and thus there was publication bias. The Egger's regression test confirmed this result with a p value = 0.36. The quality assessment for each study is shown in Supplementary file (supplementary 2).

**The association between G6PD deficiency and neonatal hyperbilirubinemia**

The association between neonatal hyperbilirubinemia and G6PD deficiency was reported in four articles (6, 16, 19). The pooled odds ratio from these studies was 2.42 (95% CI: 1.64, 3.56, $I^2$ = 37.0%, p = 0.19), indicating that the likelihood of hyperbilirubinemia was 2.42 times higher in neonates with a G6PD deficiency than those with normal G6PD levels (Figure 4).

**The association between blood type incompatibility and neonatal hyperbilirubinemia**

Blood type incompatibility was another contributing factor for neonatal hyperbilirubinemia and their connection was reported in five studies included in our analyses (6, 7, 9-11) . The pooled odds ratio was 3.3 (95% CI: 1.96, 5.72, $I^2$ = 84.0%, p = 0.0), suggesting that the risk of developing

hyperbilirubinemia was 3.3 times higher among neonates with an incompatible blood type as compared to blood type-compatible infants (Figure 5).

## 4. Discussion

Neonatal hyperbilirubinemia remains the principal reason of morbidity and mortality in resource-limited nations (4-7). The prevalence is also variable across different studies (4-7).Inconsistence estimates are reported in the association with G6PD deficiency (2, 7, 8)and blood type incompatibility (2, 7, 8). So that, this meta-analysis determined the pooled prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility in sub-Saharan Africa using ten studies. The overall pooled estimate for the prevalence of hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94)). This is consistent with the rates of neonatal hyperbilirubinemia in the United States of America (20). However, our finding is higher than that found in a previous meta-analysis (21). In contrast, the prevalence of hyperbilirubinemia found in our study was substantially lower than that found in previous systematic reviews carried out in Pakistan (22), Myanmar (23) and global burden diseases GBD (24, 25). These differences might be the result of different diagnostic standards for neonatal hyperbilirubinemia, early diagnosis and treatment in developed countries, and the early discharge of healthy late-preterm and full-term newborns.

The prevalence of neonatal hyperbilirubinemia varied greatly in the included studies, ranging from 4.9% (4) to 44.9% (9). However, our subgroup analysis based on study location showed that the highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8). This variation could be attributed to the differences in healthcare facilities. With emerging of an inexpensive technology, the developed nation's strategy for prevention and treatment of neonatal hyperbilirubinemia can more feasibly reach those at risk in resources-limited settings. Additionally, a screening strategy of postnatal hemolysis and management of idiopathic etiologies may help eradicate mortality and morbidity related jaundice.

In this study, the odds of an infant getting hyperbilirubinemia was 2.4 times higher for those neonates with a G6PD deficiency than those with normal G6PD levels. This is in line with studies done in different countries (18, 23, 26-28). G6PD deficiency may be linked to hyperbilirubinemia because G6PD is the main source for NADPH in red blood cells, which is important for antioxidant

defense. Those neonates that are deficient in G6PD are susceptible to oxidant-induced hemolysis and heme catabolism that produces bilirubin – the precipitating factor in hyperbilirubinemia (29).

This study also noted that the likelihood of having hyperbilirubinemia was higher among neonates with blood group incompatibility. Neonates with blood group incompatibility were 3.3 times more likely to have hyperbilirubinemia as compared to patients with a compatible blood type. This is supported by a number of previous studies (23, 30). This could be due to hemolysis that occurs when maternal immunoglobulin G anti-A or anti-B antibodies cross the placenta and attach to the opposite antigen site on the neonatal red cell ,which results in increase heme catabolism that increases the production bilirubin(31)

The implication of the current finding is stated as follows; estimating the prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility will help to mobilize the national leadership to initiate actions and embed proven systems, policies, and programs to reduce jaundice-related newborn mortality and disabilities. It will also help to the health care professionals to include neonates born with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility as Every Newborn Action Plan promotion of maternal and newborn care and essential newborn care for better care of neonates with jaundice which helps better neonatal survival, improved long-term development, and decrease disability. Moreover, the fading will also alarm them for national identification of all blood type incompatible woman before or during pregnancy and with coordinated obstetric and neonatal care.

**Strengths and limitations of the study**

As far as we know this is the first meta-analysis which has been done in sub-Saharan Africa. This study was conducted with the use of an inclusive search strategy to incorporate the studies involving African patients. All of the included studies had high methodological quality based on our NOS assessments. Despite this, our study had several limitations. First, most of the studies used for this analysis had a small sample size, which could have a significant effect on the estimated prevalence of neonatal hyperbilirubinemia. Moreover, this meta-analysis represented only studies from five countries, which may be an underrepresentation for the region of sub-Saharan Africa.

**Conclusion**: This study noted that neonatal hyperbilirubinemia in sub-Saharan Africa was quite common. This study also revealed that neonatal hyperbilirubinemia is associated with G6PD

deficiency and blood type incompatibility. Based on our findings, we suggest that all neonates with hyperbilirubinemia be assessed for G6PD deficiency and blood type compatibility. Furthermore, additional research is needed to identify other associated factors for the development of neonatal hyperbilirubinemia

**Abbreviations:** CI: confidence interval; G6PD; glucose-6-phosphate dehydrogenase, NOS: Newcastle-Ottawa Scale; OR; odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**Acknowledgements**

We would like to thank to Doctor Ryan Bell (CEO and Chief Editor Excision Editing) whose assistance was invaluable to the completion of the study and who have made an extensive edition in our manuscript.

**Available data and materials**

All data sets analyzed in this study are publically available .We have uploaded the minimal anonymized data set necessary to publicate our study findings.

**Patient and Public Involvement statement**

Not applicable

**Authors' contributions**

YAA conceived and designed the study. YAA and WSS established the search strategy. WSS, TYA, and GBM wrote the review. All authors read and approved the final manuscript.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**

The authors have also declared that they received no financial support in the research, authorship, and publication of this article.

**Consent for publication**

Not applicable

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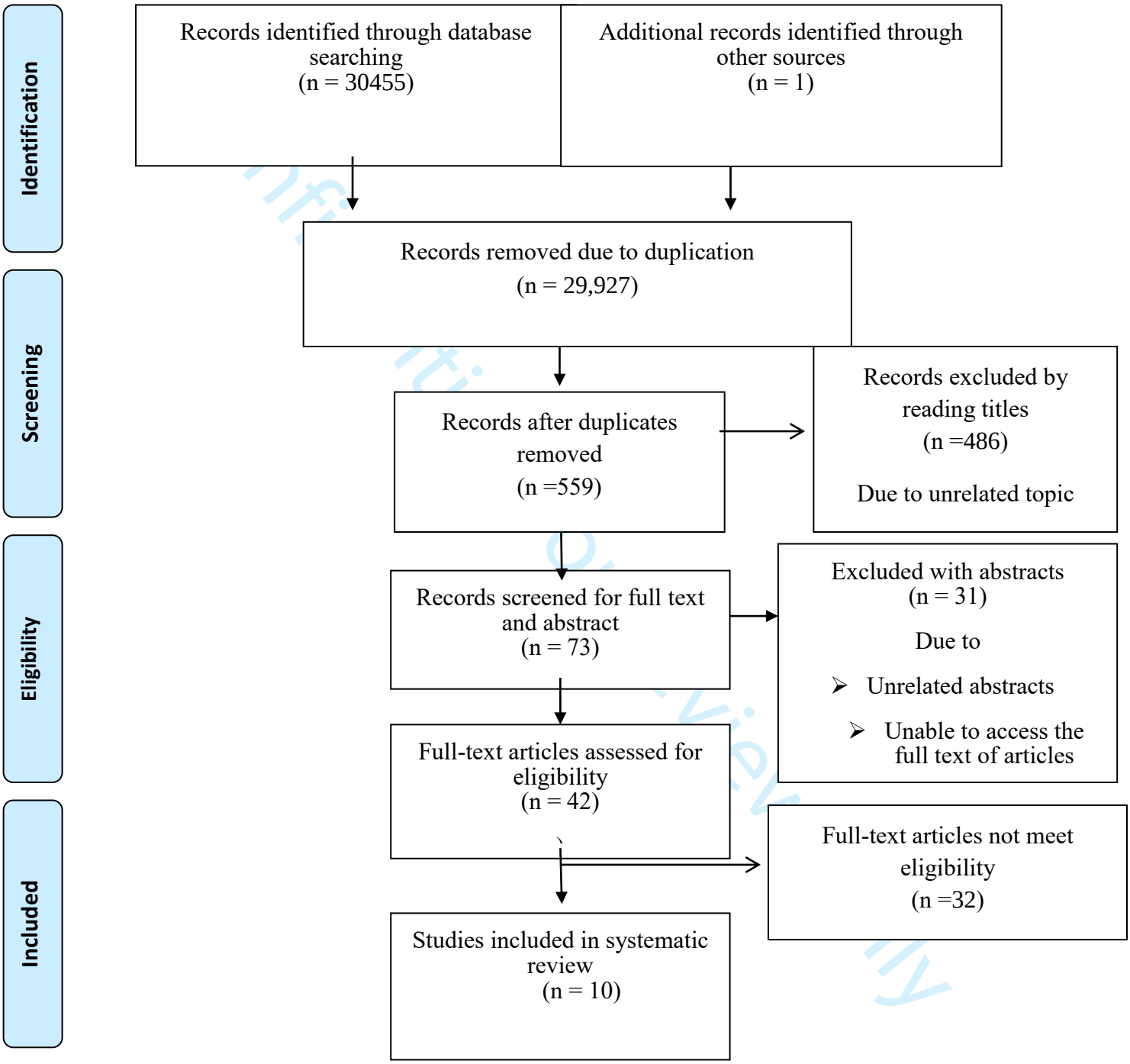


**Figure 1**. Flow chart of how research articles were searched and selected for analysis in this study.

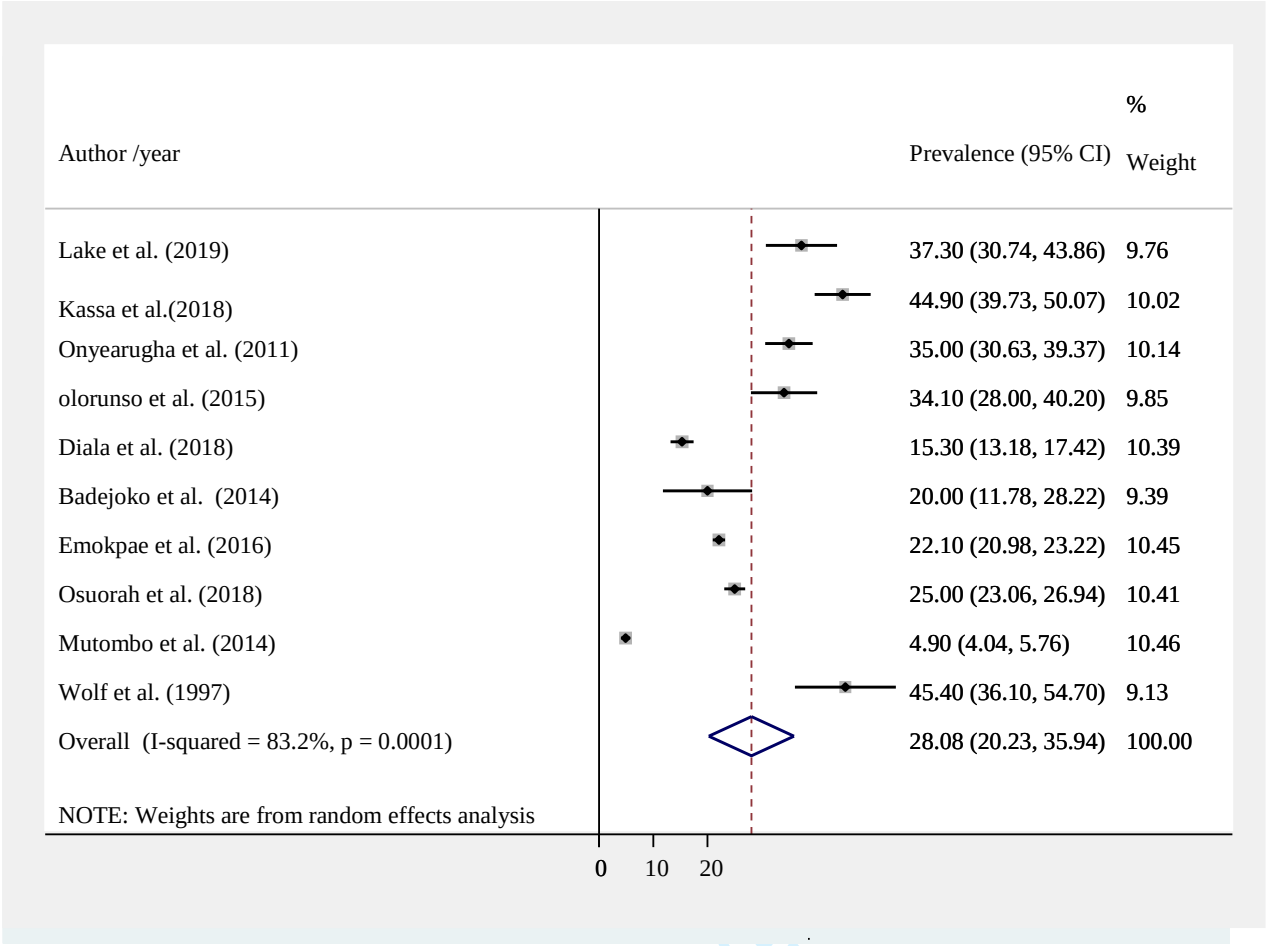


**Figure 2**. Magnitude of neonatal hyperbilirubinemia in sub-Saharan Africa.

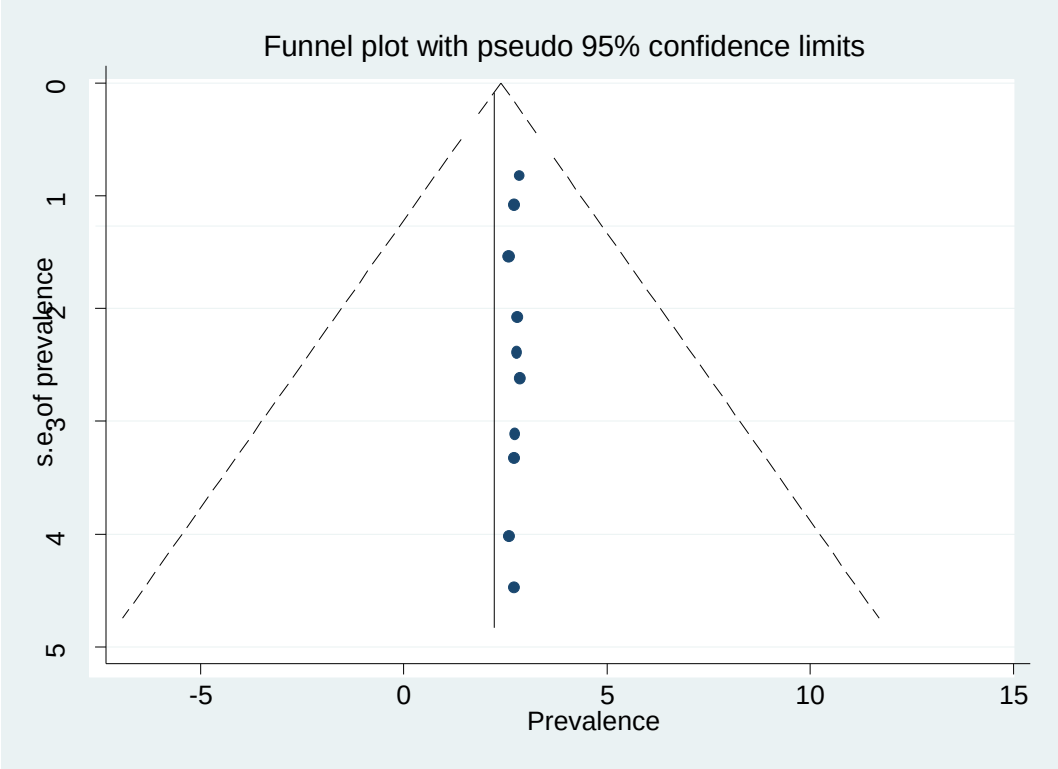


**Figure 3**. Funnel plot to determine publication bias among the included studies.

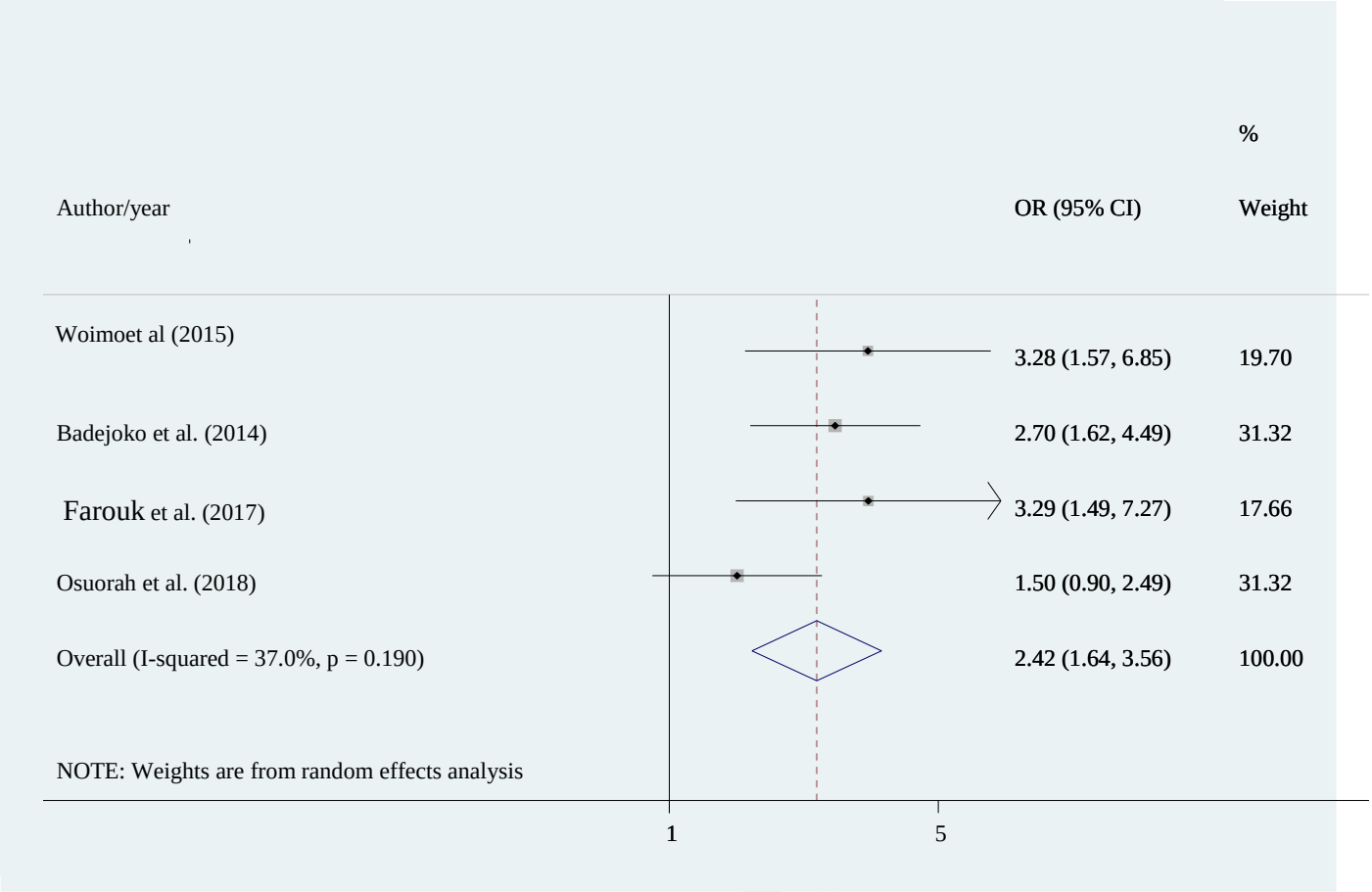


**Figure 4:** The association between G6PD deficiency and neonatal hyperbilirubinemia in studies from sub-Saharan Africa.

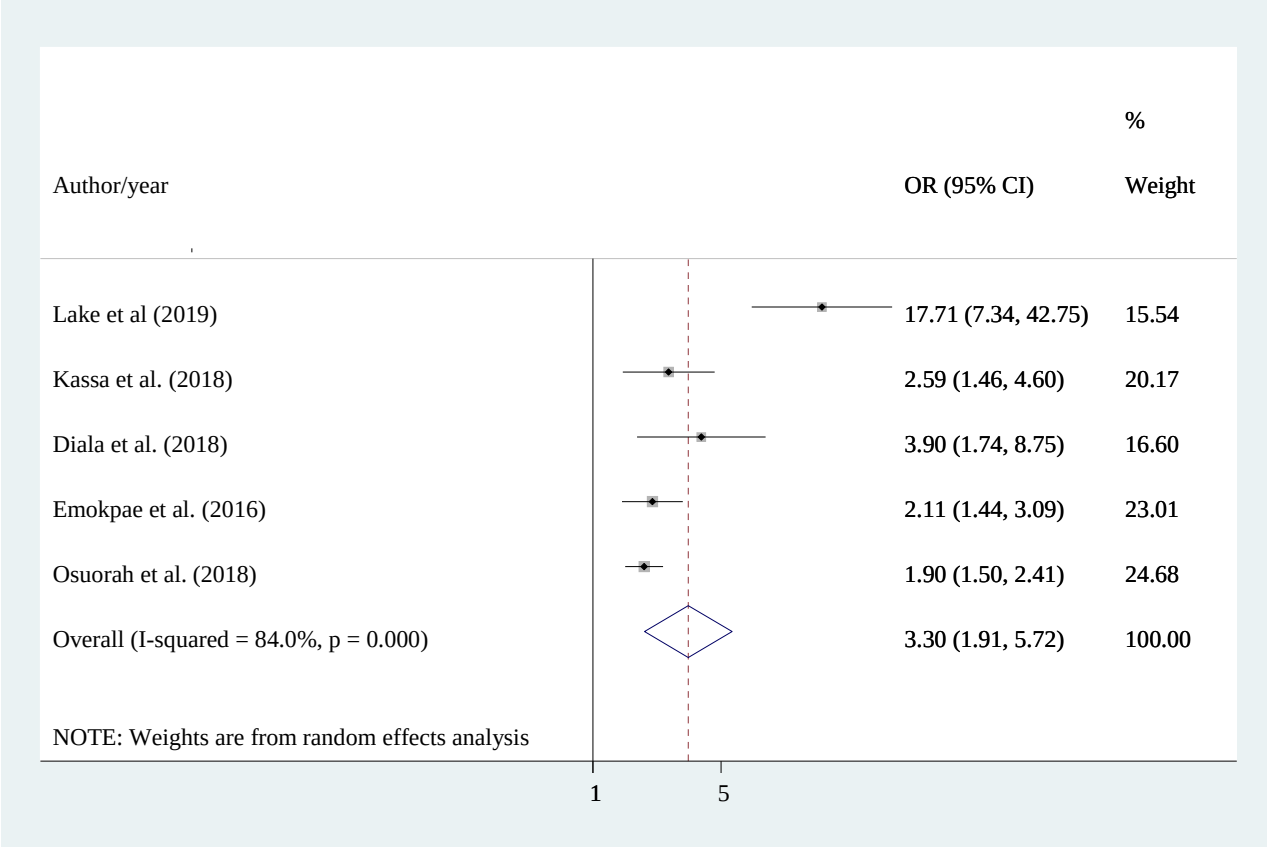


**Figure 5**. The association between blood type incompatibility and neonatal hyperbilirubinemia in studies involving sub-Saharan African populations.

# PRISMA 2009 Checklist of the current study

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1&2 |
| **INTRODUCTION** | | | |
| Rationale | | Describe the rationale for the review in the context of what is already known. | 3&4 |
| Objectives | | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Not registered but posted as a preprint |
| Eligibility criteria | | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5&6 |
| Information sources | | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4,5 &6 |
| Search | | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4,5,6 |
| Data collection process | | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6&7 |

# PRISMA 2009 Checklist of the current study

| | | | |
|---|---|---|---|
| Summary measures | | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6 |

Page 1 of 2

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 11 |
| Additional analyses | | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10-12 |
| **RESULTS** | | | |
| Study selection | | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6-12 |
| Study characteristics | | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6 |
| Risk of bias within studies | | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11 |
| Results of individual studies | | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 8 |
| Synthesis of results | | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9&10 |
| Risk of bias across studies | 8 | Present results of any assessment of risk of bias across studies (see Item 15). | 11 |
| Additional analysis | 8 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 9,10,11 |
| **DISCUSSION** | | | |
| Summary of evidence | 8 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11-13 |
| Limitations | 9 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 10 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | | |
| Funding | 11 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

# PRISMA 2009 Checklist of the current study

**Supplementary files for methodological quality assessment of the included articles**

**Supplementary file 2:** Methodological quality assessment of cross-sectional studies using modified Newcastle - Ottawa Scale (NOS)

| First author | Criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | | Comparability | | Outcome | | |
| | Representativeness of the sample | Sample size | Non – responders | Ascertainment of exposure/risk factor | The study controls for the most important factor | The study control for any additional factor | Assessment of the outcome | Statistical test | Total score (10) |
| Lake et al. 2019 | A* | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Kassa et al. 2018 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Onyearugha et al.2011 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Olorunso et al.2016 | A* | **A*** | **A*** | **B*** | **B*** | **B*** | A* | **A*** | **7** |
| **Diala et al. 2018** | A* | A* | **A*** | **A*** | **A*** | A* | A* | **A*** | **9** |
| Badejoko et al. 2018 | A* | **A*** | **A*** | **B*** | **A*** | **A*** | A* | **A*** | **7** |
| **Mutombo et al. 2014** | **A*** | **A*** | **A*** | **A*** | **A*** | **B*** | A* | **A*** | **8** |
| **Wolf et al. 1997** | B* | **B*** | **A*** | **A*** | **A*** | - | A* | **A*** | 6 |
| Emokpae et al.2016 | A* | **A*** | - | **A*** | **A*** | - | A* | **A*** | **6** |
| Osuorah et al.2018 | **A*** | **A*** | **A*** | **B*** | **A*** | **A*** | A* | **A*** | **8** |
| Emokpaeet al/2016 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **9** |
| Woimo TT et al | - | B* | - | - | - | B* | B* | B* | **5** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (2015) | | | | | | | | | |
| Farouk et al. (2017) (2016) | - | B* | - | - | - | B* | B* | B* | **4** |

*Note: from each item account point. (Accept the study if total score ≥5)*

**Selection:** (Maximum 5 stars)

1) Representativeness of the sample: a) Truly representative of the average in the target population. * (all subjects or random sampling) .b) Somewhat representative of the average in the target population. * (nonrandom sampling) .c) Selected group of users.d) No description of the sampling strategy.

2) Sample size:a) Justified and satisfactory. *.b) Not justified.

3) Non-respondents: a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. * .b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor): a) validated measurement tool. ** .b) Non-validated measurement tool, but the tool is available or described.* c) No description of the measurement tool.

**Comparability:** (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. a) The study controls for the most important factor (select one). * b) The study control for any additional factor. *

**Outcome:** (Maximum 3 stars)

1) Assessment of the outcome: a) Independent blind assessment. **,b) Record linkage. **,c) Self report. *,d) No description.

2) Statistical test:a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *,b) The statistical test is not appropriate, not described or incomplete

BMJ Paediatrics Open

# Prevalence of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility in sub-Saharan Africa: a systematic review and meta-analysis



| | |
|---|---|
| Journal: | *BMJ Paediatrics Open* |
| Manuscript ID | bmjpo-2020-000750.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 31-Jul-2020 |
| Complete List of Authors: | Aynalem, Yared; Debre Berhan University, pediatric and child health<br>Mulu, Getaneh ; Debre Berhan University<br>Akalu, Tadesse ; Debre Markos University<br>Shiferaw, Wondimeneh ; Debre Berhan University |
| Keywords: | Statistics, Qualitative research, Nursing Care, Jaundice, Neonatology |
| | |

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# Prevalence of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility in sub-Saharan Africa: a systematic review and meta-analysis

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## Abstract

**Background:** Hyperbilirubinemia is a silent cause of newborn disease and death worldwide. However, studies of the disease in sub-Saharan Africa are highly variable with respect to its prevalence. Hence, this study aimed to estimate the overall magnitude of neonatal hyperbilirubinemia and its association with glucose-6-phosphate dehydrogenase (GP6D) deficiency and blood type incompatibility in sub-Saharan Africa.

**Methods**: PubMed, Scopus, Google Scholar, and the Cochrane Review were systematically searched online to retrieve hyperbilirubinemia-related articles. All observational studies reported the prevalence of hyperbilirubinemia in sub-Saharan Africa were included for analysis and excluded if the study failed to determine the desired outcome. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed. Heterogeneity across the included studies was evaluated using the inconsistency index ($I^2$). Subgroup and meta-regression analysis were also done. Publication bias was examined by funnel plot and the Egger's regression test. The random-effect model was fitted to estimate the pooled prevalence of neonatal hyperbilirubinemia. The meta-analysis was performed using the STATA™ version 14 software.

**Results**: A total of 30,486 studies were collected from the different databases and 10 articles were included for the final analysis. The overall magnitude of neonatal hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94, $I^2$=83.2)) in sub-Saharan Africa. Neonates with G6PD deficiency (OR: 2.42

(95% CI: 1.64, 3.56, $I^2$=37%)) and neonates that had a blood type that was incompatible with their mother's (OR: 3.3 ((95% CI: 1.96, 5.72, $I^2$=84%)) were more likely to develop hyperbilirubinemia.

**Conclusion**: The failure to prevent and screen G6PD deficiency and blood type incompatibility with their mother's results in high burden of neonatal hyperbilirubinemia in sub-Saharan Africa. Therefore, early identification and care strategies should be developed to the affected neonates with G6PD deficiency and blood type incompatibility with their mother's to address long-term medical and scholastic damages among those exposed to hyperbilirubinemia

**Keywords:** hyperbilirubinemia, blood type incompatibility, glucose-6-phosphate dehydrogenase, sub-Saharan Africa

**What is already known on this topic?**

Neonatal hyperbilirubinemia is a common cause of neonatal morbidity and mortality, particularly in low-income nations

The reported prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa is inconsistent

**What this study adds**

The overall magnitude of neonatal hyperbilirubinemia was estimated to be 28.08 % (95% CI: (20.23, 35.94)) in sub-Saharan Africa.

Neonates with G6PD deficiency and neonates that had a blood type that was incompatible with their mothers' were more likely to develop hyperbilirubinemia.

## 1. Background

Neonatal hyperbilirubinemia (i.e., jaundice) is a common and often a benign condition that afflicts many infants in the first week of life. It is caused by the accumulation of bilirubin in the skin, which is created from biliverdin, a breakdown product of heme. Over 50% of newborns get jaundice in the first few days of life, and from those,60%–80% leads to unpreventable condition in newborns worldwide (1). Elevated levels of conjugated bilirubin (i.e., conjugated bilirubin level being ≥20% of the total serum bilirubin) are always pathologic and occur due to intra- or extrahepatic obstruction of the biliary tract. Moreover, elevated levels of unconjugated bilirubin is the most common reason for neurological sequelae related to hyperbilirubinemia (2). The most significant among the long-term complications of hyperbilirubinemia is kernicterus, which is a type of brain damage that leads to choreoathetosis, sensorineural hearing loss, dental enamel dysplasia, paralysis of upward gaze, hypotonia, and a delay in the acquisition of motor skills, with a significant risk of neonatal death (3).

The prevalence of hyperbilirubinemia in the neonates of sub-Saharan Africa is somewhat inconsistent in the current literature, with rates ranging from 4–45.8% (4-7). That said, the burden of this condition on medical systems in developed and developing nations is significant (1). There are many risk factors that can predispose infants to hyperbilirubinemia, including jaundice observed in the first 24 hours, blood group incompatibility, other known hemolytic disease, elevated end-tidal carbon dioxide, gestational age of 35–36 weeks, sibling received phototherapy, cephalohematoma, significant bruising, excessive weight loss, isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, asphyxia, temperature instability, sepsis, acidosis, and albumin < 3 g/dl (2, 7, 8). More than any other risk factors, G6PD deficiency and blood group incompatibility are the most significant contributing causes for neurotoxicity (2). More than 70% of hyperbilirubinemia cases are due to either idiopathic neonatal hepatitis or biliary atresia (3).

Although G6PD deficiency and blood group incompatibility are widely regarded as risk factors for hyperbilirubinemia, the literature does show some inconsistencies (7-14). For instance, several studies from sub-Saharan African countries (7, 9-11) have indicated that G6PD deficiency and blood incompatibility are associated with an increased risk of neonatal jaundice. However, another study showed that they were not associated with jaundice (12). Given this variability and the lack of pooled representative data, we aimed to estimate the pooled burden of neonatal

hyperbilirubinemia in countries of sub-Saharan Africa. Moreover, we attempted to identify its association with G6PD deficiency and blood type incompatibility in this region. This data will aid healthcare professionals in assessing the prevalence of hyperbilirubinemia in their population and hopefully allow them to properly allocate resources to combat this neonatal affliction.

## 2. Methods

### 2.1. Data Sources and Literature Search Strategy

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pertinent published articles were searched independently and systematically by the authors in the following electronic databases: PubMed, Google Scholar, African Journals Online, Scopus, and others (Grey literature, such as unpublished articles and conference abstracts). In addition, a manual search of gray literature was performed to find other significant studies. The searches were limited to full text, open access articles with human subjects that were written in any language. Authors were contacted for full texts of their articles through e-mail, if necessary. The search was conducted using the following terms and phrases: “magnitude neonatal hyperbilirubinemia,” “neonatal jaundice,” “glucose-6-phosphate dehydrogenase deficiency,” “blood type incompatibility”and“sub-Saharan Africa”. Boolean operators like “and” and “or” were used to combine search terms. Particularly, to fit the advanced PubMed database, the following search strategy was used: (“magnitude neonatal hyperbilirubinemia” OR “glucose-6-phosphate dehydrogenase deficiency” OR “blood type incompatibility”) AND (“sub-Saharan Africa”).

### 2.2. Eligibility Criteria

#### 2.2.1. Predefined inclusion criteria

Studies were included for further analysis if they conformed to the following criteria:(1) All observational studies reported the prevalence of hyperbilirubinemia ,(2) the study setting was somewhere in sub-Saharan Africa,(3) the study participants were newborns with severe hyperbilirubinemia, (4) publication condition: all published and unpublished articles , (5) All languages were included, (6) Publication date: Until 10, April, 2020.

, and (6) the article was an observational study, and a retrospective or prospective cohort study, or a cross-sectional study

**2.2.2. Exclusion Criteria**

Studies were excluded from this systematic review and meta-analysis if they fulfilled one of the following:(1) we were unable to access the full text articles after two emails to the principal investigator, (2) a study was a duplicate of a previously identified study,(3) the study didn't fulfill the inclusion criteria and, (4) failed to determine the desired outcome.

**2.2.3. Type of exposure**

In this meta-analysis, G6PD deficiency and blood type incompatibility were considered the exposure variables to estimate their effects on neonatal hyperbilirubinemia.

**2.2.3.1. Outcome of interest**:

Prevalence of neonatal hyperbilirubinemia (conjugated/unconjugated).

**2.3. Methods for data extraction and quality assessment**

We used a Microsoft Excel standardized data extraction form to extract the data. The following information was extracted from each incorporated study: the name of the first author, publication year, country name, study design, total sample size, final included sample size', response rate, study settings, and odds ratio with 95% confidence interval (CI). The number of children with neonatal hyperbilirubinemia was also extracted from the studies and prevalence was calculated using the final included sample size. Data extraction from source documents was done independently by all investigators. Disagreements were resolved by consensus. The quality of the included studies was evaluated by using the Newcastle-Ottawa Scale (NOS) (13). Specifically, NOS assessed the sample representativeness and size, the comparability between participants, how neonatal hyperbilirubinemia was ascertained, and the statistical quality of each study. Studies were included for further analysis if they scored ≥5 out of 10 points in three domains of ten modified NOS components.

### 2.4 Data processing and analysis

Data were extracted from Microsoft Excel and analyzed using STATA Version 14 statistical software and forest plots that showed combined estimates with a 95% CI. The overall pooled prevalence was estimated by random effect meta-analysis (14). Heterogeneity was assessed by computing p values for the inconsistency index ($I^{2)}$(15). We found significant heterogeneity among the studies ($I^2$ = 83.2%, p = 0.001). Meta-regression analysis was performed using sample size, study design and country, factors and publication year to explore the possible source of heterogeneity. We also conducted a subgroup analysis using the following variables: study design, Publication year, sample size, study design and locations of the studies. Sensitivity analysis was also conducted to assess the possible included outlier articles Publication bias was assessed using a funnel plot and the Egger's regression test (14). The association between the prevalence of neonatal hyperbilirubinemia and G6PD deficiency or blood type incompatibility was measured by random-effects meta-analysis pooled odds ratios.

## 3. Results

### Search process

A total of 30,486 studies were collected from the aforementioned databases. After removing duplicates (n = 29,927), a total of 559 studies were retrieved. Of which, 486 were rejected just by reading the titles of the articles (due to unrelated to the topic). Of the remaining 73 studies, 31 were excluded by abstracts (due to no abstract, unrelated abstracts and unable to access the full text of articles with two email contact). Full text copies of the remaining 42 studies that potentially met the inclusion criteria were assessed. From this, 32 articles were discarded due to failed to determine the desired outcome (not fully fulfilled the inclusion criteria). After further screening, 10 papers were fulfilled the eligibility criteria for estimating the pooled prevalence and there are an additional two studies (Woimo et al and Farouk et al) which do not provide prevalence data but do contribute to the analysis of the association between G6PD deficiency and neonatal hyperbilirubinemia. Articles published in several languages were assessed. But, nine papers published in English and one paper published in French was retained for final analysis (Figure 1).

**Characteristics of included studies**

The pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa was assessed using 10 studies involving a total of 12,327 participants. The minimum sample size was 91 participants in a study conducted at Awolowo University, Nigeria (16), while the largest sample size was also participants from Nigeria (5229)(11). All studies involved populations from sub-Saharan Africa, with six involving participants from Nigeria (6, 8, 10, 11, 16, 17), two from Ethiopia (7, 9), and one each from Zimbabwe (5), and Congo (4) (Table 1).Regarding the sampling technique employed, six of the studies (7-9, 16-18) used consecutive sampling to select study participants. However, the other studies did not report their sampling methods.

**Table 1**. Baseline characteristics of the studies used to assess the pooled prevalence of neonatal hyperbilirubinemia in sub-Saharan Africa.

| Author/publication year | Country | Region | Study design | Total sample size | Final included sample size | Prevalence (%) | Response rate | Contributions |
|---|---|---|---|---|---|---|---|---|
| Lakeet al/2019 | Ethiopia | Tigray | Cross-sectional | 209 | 209 | 78(37.3) | 100 | For estimating pooled prevalence and associated factories |
| Kassaet al/2018 | Ethiopia | Addis Ababa | Cross-sectional | 356 | 356 | 160(44.9) | 100 | For estimating pooled prevalence and associated factories |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Onyearugha et al/2011 | Nigeria | Southeast Nigeria | Cross-sectional | 457 | 457 | 160(35) | 100 | For estimating the pooled prevalence |
| olorunsoet al/2015 | Nigeria | Ibadan | Cross-sectional | 232 | 232 | 79(34.1) | 100 | For estimating the pooled prevalence |
| Diala et al/2018 | Nigeria | cosmopolitan | Cohort | 1106 | 1106 | 159(15.3) | 100 | For estimating pooled prevalence and associated factories |
| Badejokoet al/2014 | Nigeria | Awolowo University | Cohort | 644 | 639 | 129(20) | 99.3 | For estimating pooled prevalence and associated factories |
| Emokpaeet al/2016 | Nigeria | Lagos | Cross-sectional | 5,229 | 5,229 | 1,153(22.1) | 100 | For estimating pooled prevalence and associated factories |
| Osuorahet al/2018 | Nigeria | Enugu State University | Cohort | 1920 | 1920 | 480(25) | 100 | For estimating pooled prevalence and associated |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | factories |
| Mutomboet al/2014 | Congo | Congo | Cross-sectional | 2410 | 2410 | 120(4.9) | 100 | For estimating the pooled prevalence |
| Wolfet al/1997 | Zimbab wean | Zimbabwe an | Cohort | 120 | 110 | 50 | 91.7 | For estimating the pooled prevalence |
| Woimo TT et al (2015) | Suadn | - | Case control | 243 | 243 | - | 100 | For estimating the pooled Associated factories |
| Farouk et al. (2017) (2016) | Nigeria | Kano | Case control | 551 | 551 | - | 100 | For estimating the pooled prevalence |

**Magnitude of neonatal hyperbilirubinemia**

A total of 12,327 participants and 10 studies were included to estimate the pooled magnitude of neonatal hyperbilirubinemia. The overall random effects estimate for the level of neonatal hyperbilirubinemia across sub-Saharan Africa was 28.08 % (95% CI: (20.23, 35.94)) (Figure 2). Our test statistics indicated a high level of heterogeneity ($I^2$ = 83.2%) and the Eggers' test showed no significant publication bias (p = 0.36).

**Subgroup analysis**

We performed a subgroup analysis using sample size, publication year, study design and the location of the included studies. In the current meta-analysis a sample size of less than 384 revealed a higher prevalence(40.2(95%CI:34.5,45.8,($I^2$=66%)) as compared to sample size of greater than or equal to than 384(20.3( 95%CI:11.3, 29.4,), $I^2$=88)) .Our subgroup analysis based on study location also showed that the highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8, $I^2$= 68.6) Figure 3. Prevalence rates were very similar across study designs (**Table 2** ).

Table 2: Sub-group analysis results of the included studies

| Sub group analysis | Variables | Number of studies | Prevalence (95%CI) | Weight (%) | $I^{2\,(\%)}$ |
|---|---|---|---|---|---|
| By country | Ethiopia | 2 | 41.4 (33.9 ,48.8) | 19.9 | 68.6 |
| | Nigeria | 6 | 25.1( 20.4, 29.6) | 60.6 | 94.8 |
| | Congo | 1 | 4.9( 4.1, 5.76) | 10.46 | 0 |
| | Zimbabwi | 1 | 45.4( 36.1, 54.7) | 9.1 | 0 |
| Publication year | Less than 2014 | 4 | 26.1( 5.47, 46.7) | 39.13 | 88 |
| | Greater than or equal to 2014 | 6 | 29.13( 23.3 , 34.9) | 60.87 | 89 |
| Sample size | Less than 384 | 4 | 40.2(34.5,45.8) | 38.9 | 66 |
| | Greater than or equal to 384 | 6 | 20.3( 11.3, 29.4) | 61.2 | 88 |
| Study design | Cross-sectional | 6 | 29.5( 18.0, 41.0) | 60.68 | 98 |
| | Cohort | 4 | 25.4(17.2, 33.7) | 39.32 | 90 |

**Meta-regression analysis**

To identify the sources of heterogeneity in this study, meta-regression analysis was performed by considering the sample size, study design and country, factors and publication year. However, our

results showed that those covariates were not significantly associated with the presence of heterogeneity (Table 3).

Table 3: Meta regression results by different covariant

| Variables | Category | Coefficient | Standard error | T | P-value | 95% CI |
|---|---|---|---|---|---|---|
| Publication year | < 2014 | -0.0033 | 0.0026 | 1.27 | 0.24 | 0.001, 0.002 |
| | ≥2014(reference) | | | | | |
| Sample size | <384 | -0.46 | 0.69 | -0.67 | 0.52 | -2.06, 1.13 |
| | *≥384(reference)* | | | | | |
| Country | Nigeria | 2.7 | 2.2 | 0.12 | 0.9 | -0.5-5.1 |
| | Ethiopia | 9.1 | 2.3 | 0.39 | 0.7 | -0.5 -6.3 |
| | other (reference) | | | | | |
| Study design | cross sectional | 1.21 | 11.06 | 0.11 | 0.915 | 0.2.-2.5 |
| | cohort (reference) | | | | | |
| G6PD deficiency | Yes | -0.36 | 0.59 | -0.47 | 0.32 | 0.06, 1.13 |
| | No (reference) | | | | | |

**Publication bias and quality status**

Publication bias was evaluated by a funnel plot and the Egger's regression test. With respect to the former, publication bias is represented as significant asymmetry in a funnel plot. As depicted in Figure 3, there was a significant amount of symmetry in our funnel plot and thus there was publication bias. The Egger's regression test confirmed this result with a p value = 0.36. The quality assessment for each study is shown in Supplementary file (supplementary 2).

**The association between G6PD deficiency and neonatal hyperbilirubinemia**

The association between neonatal hyperbilirubinemia and G6PD deficiency was reported in four articles (6, 16, 19) with a total of 3353 neonates. The pooled odds ratio from these studies was 2.42 (95% CI: 1.64, 3.56, $I^2 = 37.0\%$, p = 0.19), indicating that the likelihood of hyperbilirubinemia was 2.42 times higher in neonates with a G6PD deficiency than those with normal G6PD levels (Figure 4).

**The association between blood type incompatibility and neonatal hyperbilirubinemia**

Blood type incompatibility was another contributing factor for neonatal hyperbilirubinemia and their connection was reported in five studies included in our analyses (6, 7, 9-11) by involving a total of 8,820 participants. The pooled odds ratio was 3.3 (95% CI: 1.96, 5.72, $I^2 = 84.0\%$, p = 0.0), suggesting that the risk of developing hyperbilirubinemia was 3.3 times higher among neonates with an incompatible blood type as compared to blood type-compatible infants (Figure 5).

## 4. Discussion

Neonatal hyperbilirubinemia remains the principal reason of morbidity and mortality in resource-limited nations (4-7). The prevalence is also variable across different studies (4-7).Inconsistence estimates are reported in the association with G6PD deficiency (2, 7, 8)and blood type incompatibility (2, 7, 8). So that, this meta-analysis determined the pooled prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility in sub-Saharan Africa using ten studies. The overall pooled estimate for the prevalence of hyperbilirubinemia was 28.08 % (95% CI: (20.23, 35.94)). This is consistent with the rates of neonatal hyperbilirubinemia in the United States of America (20). However, our finding is higher than that found in a previous meta-analysis (21). In contrast, the prevalence of hyperbilirubinemia found in our study was substantially lower than that found in previous systematic reviews carried out in Pakistan (22), Myanmar (23) and global burden diseases GBD (24, 25). These differences might be the result of different diagnostic standards for neonatal hyperbilirubinemia, early diagnosis and treatment in developed countries, and the early discharge of healthy late-preterm and full-term newborns.

The prevalence of neonatal hyperbilirubinemia varied greatly in the included studies, ranging from 4.9% (4) to 44.9% (9). However, our subgroup analysis based on study location showed that the

highest pooled prevalence was observed from studies done in Ethiopia (41.4%; 95% CI: 33.9, 48.8). This variation could be attributed to the differences in healthcare facilities. With emerging of an inexpensive technology, the developed nation's strategy for prevention and treatment of neonatal hyperbilirubinemia can more feasibly reach those at risk in resources-limited settings. Additionally, a screening strategy of postnatal hemolysis and management of idiopathic etiologies may help eradicate mortality and morbidity related jaundice.

In this study, the odds of an infant getting hyperbilirubinemia was 2.4 times higher for those neonates with a G6PD deficiency than those with normal G6PD levels. This is in line with studies done in different countries (18, 23, 26-28). G6PD deficiency may be linked to hyperbilirubinemia because G6PD is the main source for NADPH in red blood cells, which is important for antioxidant defense. Those neonates that are deficient in G6PD are susceptible to oxidant-induced hemolysis and heme catabolism that produces bilirubin – the precipitating factor in hyperbilirubinemia (29).

This study also noted that the likelihood of having hyperbilirubinemia was higher among neonates with blood group incompatibility. Neonates with blood group incompatibility were 3.3 times more likely to have hyperbilirubinemia as compared to patients with a compatible blood type. This is supported by a number of previous studies (23, 30). This could be due to hemolysis that occurs when maternal immunoglobulin G anti-A or anti-B antibodies cross the placenta and attach to the opposite antigen site on the neonatal red cell ,which results in increase heme catabolism that increases the production bilirubin(31)

The implication of the current finding is stated as follows; estimating the prevalence of neonatal hyperbilirubinemia and its association with G6PD deficiency and blood type incompatibility will help to mobilize the national leadership to initiate actions and embed proven systems, policies, and programs to reduce jaundice-related newborn mortality and disabilities. It will also help to the health care professionals to include neonates born with glucose-6-phosphate dehydrogenase deficiency and blood type incompatibility as Every Newborn Action Plan promotion of maternal and newborn care and essential newborn care for better care of neonates with jaundice which helps better neonatal survival, improved long-term development, and decrease disability. Moreover, the fading will also alarm them for national identification of all blood type incompatible woman before or during pregnancy and with coordinated obstetric and neonatal care.

**Strengths and limitations of the study**

As far as we know this is the first meta-analysis which has been done in sub-Saharan Africa. This study was conducted with the use of an inclusive search strategy to incorporate the studies involving African patients. All of the included studies had high methodological quality based on our NOS assessments. Despite this, our study had several limitations. First, most of the studies used for this analysis had a small sample size, which could have a significant effect on the estimated prevalence of neonatal hyperbilirubinemia. Moreover, this meta-analysis represented only studies from five countries, which may be an underrepresentation for the region of sub-Saharan Africa.

**Conclusion:** The prevalence of hyperbilirubinemia in Sub Saharan Africa is quite high and a major percent of this is due to G6 PD deficiency and blood group incompatibility. Based on our findings, we suggest that all neonates with hyperbilirubinemia be assessed for G6PD deficiency and blood type compatibility. Additionally, incorporating the G6PD screen as a newborn screening program can be a cost effective strategy to deal with this problem. Assessing ABO incompatibility following discharge, bilirubin estimation and plot on normogram, and follow the babies as per the risk stratification would be the best strategy. Furthermore, additional research is needed to identify other associated factors for the development of neonatal hyperbilirubinemia

.**Abbreviations:** CI: confidence interval; G6PD; glucose-6-phosphate dehydrogenase, NOS: Newcastle-Ottawa Scale; OR; odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**Acknowledgements**

We would like to thank to Doctor Ryan Bell (CEO and Chief Editor Excision Editing) whose assistance was invaluable to the completion of the study and who have made an extensive edition in our manuscript.

**Available data and materials**

All data sets analyzed in this study are publically available .We have uploaded the minimal anonymized data set necessary to publicate our study findings.

**Patient and Public Involvement statement**

Not applicable

## Authors' contributions

YAA conceived and designed the study. YAA and WSS established the search strategy. WSS, TYA, and GBM wrote the review. All authors read and approved the final manuscript.

## Competing interest

The authors declare that they have no competing interests.

## Funding

The authors have also declared that they received no financial support in the research, authorship, and publication of this article.

## Consent for publication

Not applicable

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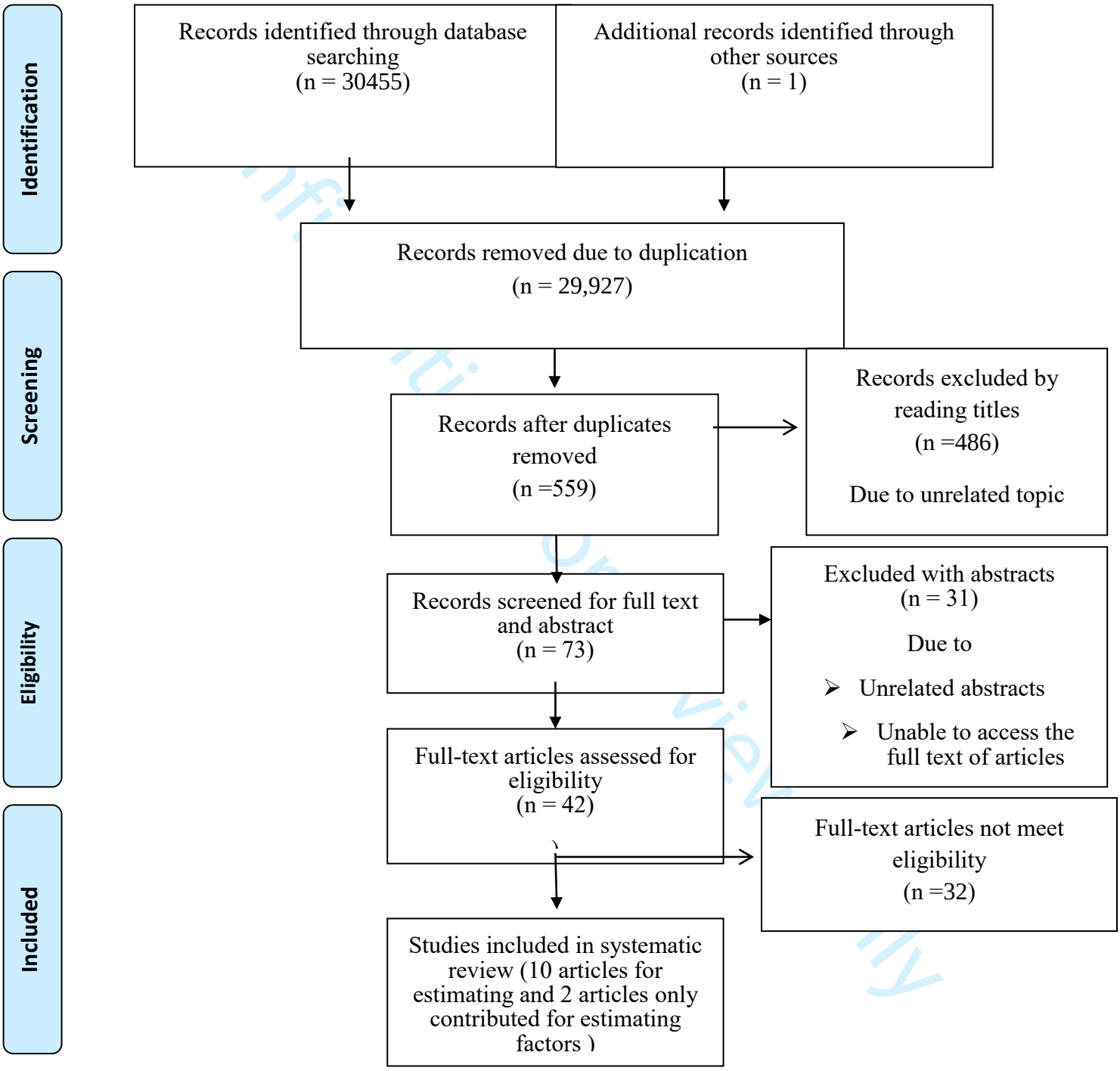


**Figure 1**. Flow chart of how research articles were searched and selected for analysis in this study.

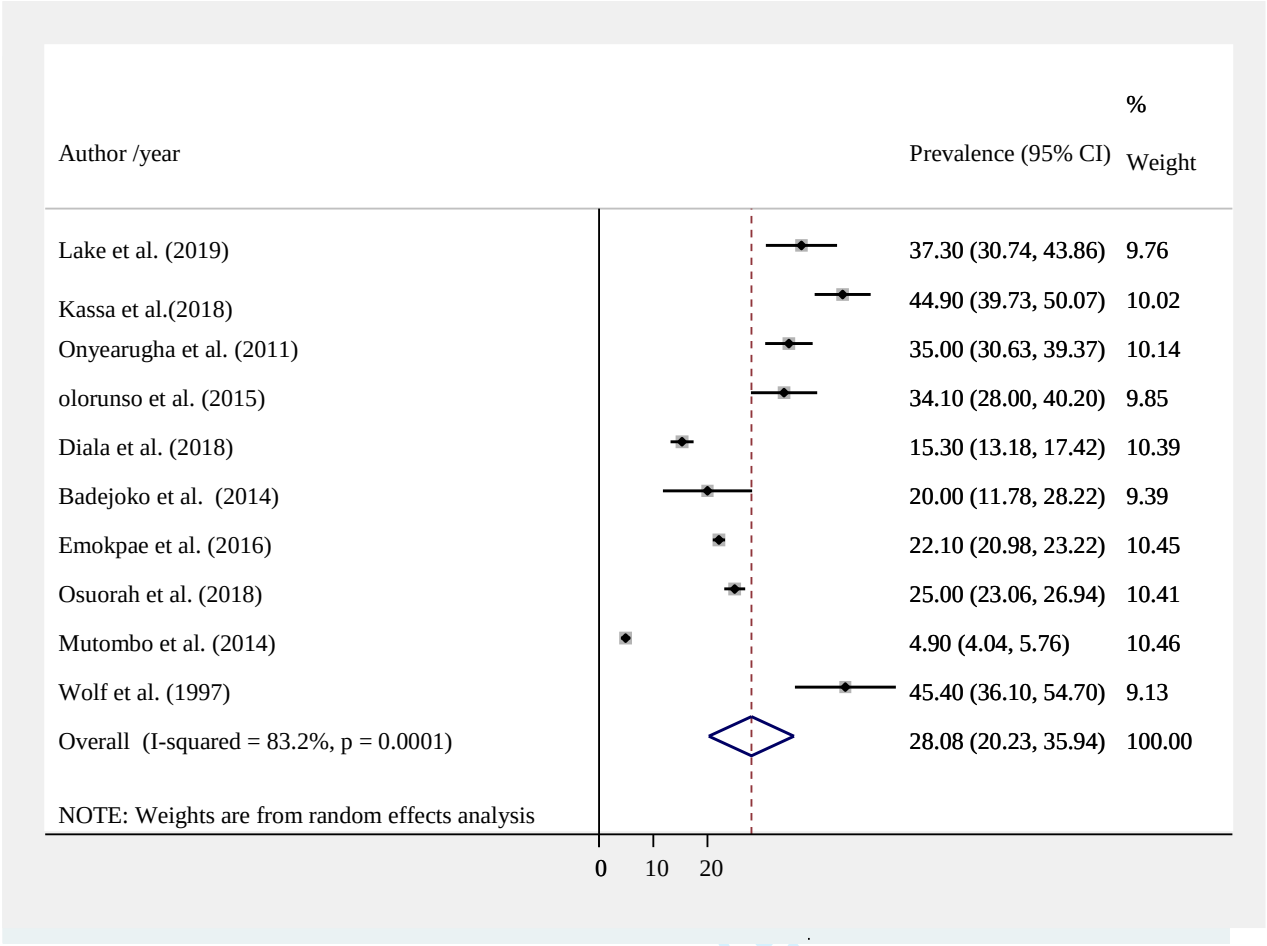


**Figure 2**. Magnitude of neonatal hyperbilirubinemia in sub-Saharan Africa.

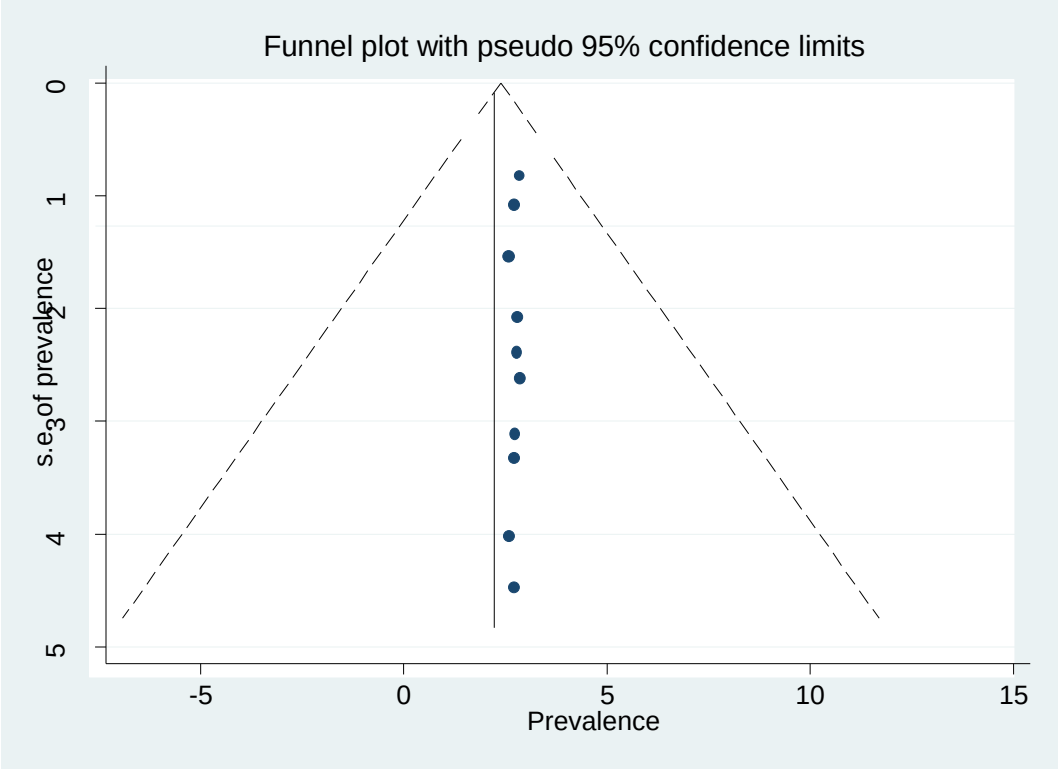


**Figure 3**. Funnel plot to determine publication bias among the included studies.

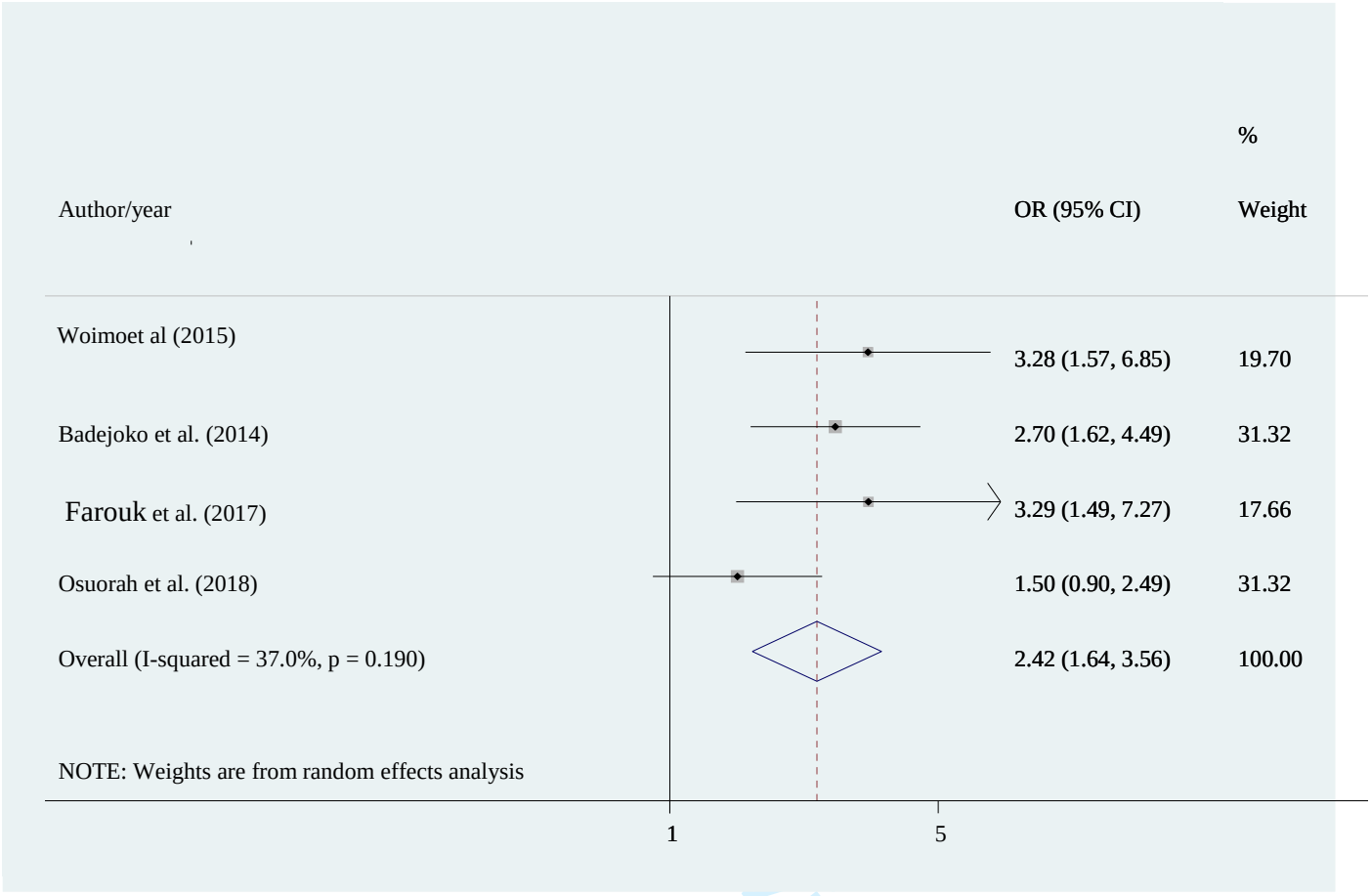


**Figure 4:** The association between G6PD deficiency and neonatal hyperbilirubinemia in studies from sub-Saharan Africa.

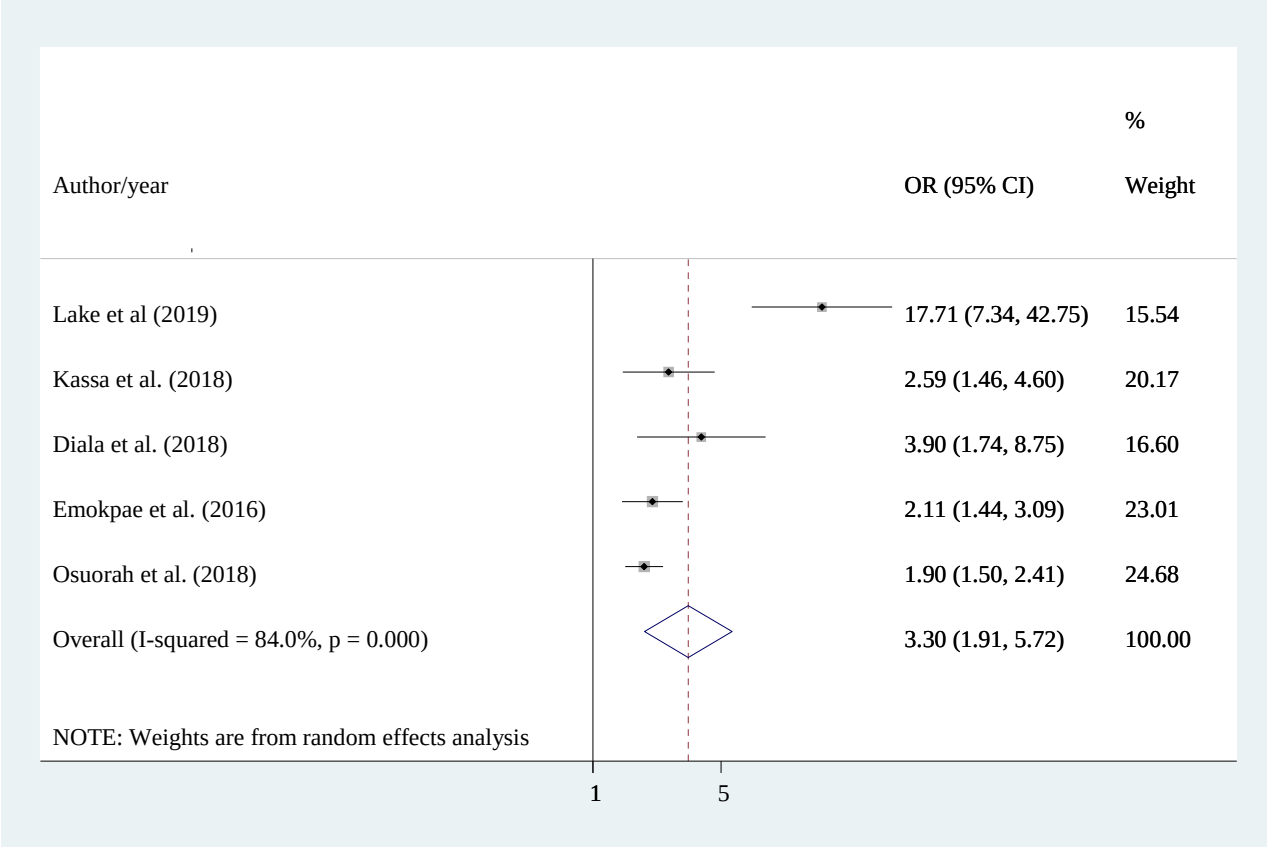


**Figure 5**. The association between blood type incompatibility and neonatal hyperbilirubinemia in studies involving sub-Saharan African populations.

# PRISMA 2009 Checklist of the current study

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1&2 |
| **INTRODUCTION** | | | |
| Rationale | | Describe the rationale for the review in the context of what is already known. | 3&4 |
| Objectives | | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Not registered but posted as a preprint |
| Eligibility criteria | | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5&6 |
| Information sources | | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4,5 &6 |
| Search | | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4,5,6 |
| Data collection process | | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6&7 |

# PRISMA 2009 Checklist of the current study

| | | | |
|---|---|---|---|
| Summary measures | | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6 |

Page 1 of 2

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 11 |
| Additional analyses | | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10-12 |
| **RESULTS** | | | |
| Study selection | | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6-12 |
| Study characteristics | | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6 |
| Risk of bias within studies | | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 11 |
| Results of individual studies | | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 8 |
| Synthesis of results | | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9&10 |
| Risk of bias across studies | 8 | Present results of any assessment of risk of bias across studies (see Item 15). | 11 |
| Additional analysis | 8 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 9,10,11 |
| **DISCUSSION** | | | |
| Summary of evidence | 8 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11-13 |
| Limitations | 9 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 10 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | | |
| Funding | 11 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

# PRISMA 2009 Checklist of the current study

## Supplementary files for methodological quality assessment of the included articles

**Supplementary file 2:** Methodological quality assessment of cross-sectional studies using modified Newcastle - Ottawa Scale (NOS)

| First author | Criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Selection | | | | Comparability | | Outcome | | |
| | Representativeness of the sample | Sample size | Non – responders | Ascertainment of exposure/risk factor | The study controls for the most important factor | The study control for any additional factor | Assessment of the outcome | Statistical test | Total score (10) |
| Lake et al. 2019 | A* | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Kassa et al. 2018 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Onyearugha et al.2011 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | A* | **A*** | **9** |
| Olorunso et al.2016 | A* | **A*** | **A*** | **B*** | **B*** | **B*** | A* | **A*** | **7** |
| **Diala et al. 2018** | A* | A* | **A*** | **A*** | **A*** | A* | A* | **A*** | **9** |
| Badejoko et al. 2018 | A* | **A*** | **A*** | **B*** | **A*** | **A*** | A* | **A*** | **7** |
| **Mutombo et al. 2014** | **A*** | **A*** | **A*** | **A*** | **A*** | **B*** | A* | **A*** | **8** |
| **Wolf et al. 1997** | B* | **B*** | **A*** | **A*** | **A*** | - | A* | **A*** | 6 |
| Osuorah et al.2018 | **A*** | **A*** | **A*** | **B*** | **A*** | **A*** | A* | **A*** | **8** |
| Emokpaeet al/2016 | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **A*** | **9** |
| Woimo TT et al (2015) | - | B* | - | - | - | B* | B* | B* | **5** |
| Farouk et al. (2017) (2016) | - | B* | - | - | - | B* | B* | B* | **4** |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |

*Note: from each item account point. (Accept the study if total score ≥5)*

**Selection:** (Maximum 5 stars)

1) Representativeness of the sample: a) Truly representative of the average in the target population. * (all subjects or random sampling) .b) Somewhat representative of the average in the target population. * (nonrandom sampling) .c) Selected group of users.d) No description of the sampling strategy.

2) Sample size:a) Justified and satisfactory. *.b) Not justified.

3) Non-respondents: a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. * .b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor): a) validated measurement tool. ** .b) Non-validated measurement tool, but the tool is available or described.* c) No description of the measurement tool.

**Comparability:** (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. a) The study controls for the most important factor (select one). * b) The study control for any additional factor. *

**Outcome:** (Maximum 3 stars)

1) Assessment of the outcome: a) Independent blind assessment. **,b) Record linkage. **,c) Self report. *,d) No description.

2) Statistical test:a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *,b) The statistical test is not appropriate, not described or incomplete