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Review

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Incidence, trends and risk factors of preeclampsia in sub-Saharan Africa: a systematic review and meta-analysis

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Abstract

Introduction: *maternal health remains one of the major public health problems for low- and middle-income countries. Of these, preeclampsia is one of the major public health issues in sub-Saharan African countries. This high burden of preeclampsia has been a major concern in sub-Saharan Africa; but there is lack of published studies on the incidence and risk factors of preeclampsia. Therefore, the aim of this systematic review and meta-analysis was to determine the incidence, trends and risk factors of preeclampsia in sub-Saharan Africa.* ***Methods:*** *we searched databases of PubMed/Medline, Scopus, Cochran Library, Science Direct, Embase, and gray literature from Google and Google Scholar in the year from January 1, 2009, to March 15, 2019. The reason for limiting the year of publication was to generate up-to-date evidence on the pooled incidence of preeclampsia. We looked for articles written in English. Language was limited to reduce bias in the interpretation of meta-results. Data extraction and quality assessment were performed independently by four reviewers. We used the Newcastle-Ottawa Assessment Tool for quality assessment. A PRISMA flow diagram was used to summarize the study selection. We used a random effect model to account for within and between study variations. We assessed heterogeneity by using the Galbraith plot, subgroup analysis, and Eegger's test.* ***Results:*** *a total of 4,250 studies were found, with 1,345 duplicates removed. Of the 61 studies eligible for full-text review, 12 studies were excluded after reading the full-text article. A total of 49 studies were eligible for systematic review, and 11 studies were included in the meta-analysis. In sub-Saharan Africa, the overall pooled incidence of preeclampsia was 13% [95% CI: 0.12-0.14]. Women who had multigravida had 89% (aRR = 1.89; 95% CI: 1.65 to 2.17) higher risks for preeclampsia compared to women who did not have multigravida. The result of the trend analysis found that the incidence of preeclampsia had increased from 2.22% in 2010 to 2.67% in 2018.*

Conclusion: *incidence of preeclampsia affected a significant proportion of pregnant women in sub-Saharan Africa. The incidence of preeclampsia varies from country to country in sub-Saharan Africa. Women who had multigravida had 89% higher risks for preeclampsia compared to women who did not have multigravida. Preeclampsia awareness, early detection and pharmacological therapy, and health promotion during routine antenatal care services and communities, with a focus on preeclampsia risk factors, could improve maternal and perinatal outcomes in these settings.*

Introduction

The incidence of Hypertensive Disorders of Pregnancy (HDPs) has increased from 16.30 million in 1990 to 18.08 million in 2019 globally [1]. Incidence varies from country to country, at the global level. The highest incidence of HDPs was observed in South Asia (3.84 million), western sub-Saharan Africa (SSA) 3.71 million, and eastern (SSA) 3.12 million in 2019 [1]. Maternal health remains one of the major public health problems for low- and middle-income countries (LMIC) [2]. The incidence of maternal deaths associated with HDPs was 27.83 thousand, a 30.05% decrease from 1990 to 2019 globally [1]. In SSA, HDPs are the second leading cause of maternal mortality 22.1%, followed by obstetric hemorrhage 28.8% in 2020 [3]. Preeclampsia and/or eclampsia is a significant global public health issue in both high- and low- and middle-income countries (LMICs), contributing to maternal and perinatal morbidity and mortality [4]. Preeclampsia is the second leading cause of direct maternal death and is directly responsible for 70,000 maternal deaths annually at the global level [5]. The impact of the disease is felt more severely in low and middle-income countries (LMICs) [6]. Sub-Saharan Africa (56%) and Southern Asia account for 85% of the global burden [7].

Hypertensive disorders of pregnancy accounted for 16% of maternal deaths globally and 9% of maternal deaths in Africa and Asia [8]. Among

Hypertensive disorders of pregnancy Of HDP, preeclampsia and eclampsia alone contributed 10%-15% of direct maternal death [9]. From these deaths, 99% of maternal deaths occur in LMIC (9). In LMIC, where access and quality of antenatal and intra-partum care is low, preeclampsia remained one of the leading causes of maternal and perinatal morbidity and mortality as compared with high income countries [10]. Pre-eclampsia and/eclampsia is associated with the common complications during pregnancy, labor and childbirth, mostly in low-resource settings [11]. Another study conducted in Uganda in 2016 found that of 403 women with hypertensive disorders of pregnancy, 54.1% had severe preeclampsia and 42.7% had eclampsia [12]. One study reported that having maternal complications led to: preeclampsia with severity (19.5%), placenta abruption (5.4%), haemolysis, elevated liver enzymes, low platelet count (HEELP) syndrome (2.43%), eclampsia (1.22%), Disseminated intravascular coagulation (DIC) (1.22%) and maternal death (1.22%) [13]. Another study conducted in Nigeria in 2015 found that 13.8% neonatal deaths were observed and there was a significant association between preeclampsia and neonatal death [14]. However, preeclampsia is not totally preventable, its early detection and proper treatment can prevent it from severity [7,11]. The previous study showed that antenatal care visits can prevent severe forms of pre-eclampsia, which is used to prevent adverse-maternal and perinatal outcomes [6,11].

Women with severe preeclampsia will have symptoms such as headache, right upper abdominal pain, or visual disturbances [15]. Common problems on the fetus are poor fetal growth and prematurity [16]. Preventive strategies implemented in high-income countries have successfully reduced both the incidence and the morbidity and mortality associated with preeclampsia by almost 90% [17]. Early detection during antenatal care and improving access to hospital care for women with preeclampsia reduce burden of preeclampsia related death [17]. However, these interventions are not well practiced in sub-Saharan Africa [18]. Ending preventable maternal and perinatal death is one of the global agenda in the Sustainable Development Goal 3 [19]. To achieve these targets, countries in SSA would need to prevent and better manage complications arising from preeclampsia and other common causes of maternal deaths [19]. There is a need to identify those women at risk for preeclampsia and to initiate effective preventive and therapeutic strategies in these settings [20]. However, there is a scarcity of data regarding the incidence, trends, and risk factors of preeclampsia in sub-Saharan African countries [17]. Although high burden of preeclampsia has been a major concern in SSA; but there is lack of published studies on the incidence, trends and risk factors of preeclampsia in sub-Saharan Africa [17]. Therefore, the aim of this systematic review and meta-analysis was to determine the incidence, trends and risk factors of preeclampsia in sub-Saharan Africa.

Methods

Protocol and registration: this review was conducted based on a priori-written and registered protocol on the PROSPERO database (CRD42019124455). A PRISMA flow diagram was used to summarize the study selection process [21].

Search strategy: we searched databases such as PubMed/Medline (Medical Literature Online), Scopus, Cochran Library, Science Direct, Embase/Ovid, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and reports including grey literature from Google Search and Google Scholar from January 1, 2009 to March 15, 2019. The reason for limiting the year of publication for searched studies was to generate up-to-date evidence on the pooled incidence and risk factors of preeclampsia for policy makers and program planners in sub-Saharan Africa [22]. An experienced searcher was considered for comprehensive searching and existing knowledge

that would already be part of their search strategies. The other reason for restricting the year of publications was that including older data might influence the effect estimates in meta-analyses [23]. The search was conducted using the following keywords: incidence, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, pre-eclampsia, eclampsia, pregnancy-induced hypertension, pre-eclamptic women, pregnancy hypertension, risk factors, risk, pregnancy toxemia, toxemia, pregnancy, edema, proteinuria, and sub-Saharan Africa.

Participants

Inclusion and exclusion criteria: we used; Coco Pop and population, intervention, comparison, outcome, study design (PICOS) approaches (participants, interventions, comparators, outcomes, and study design) to set inclusion and exclusion criteria. Previous literature supported these criteria, which were defined in terms of population, interventions, outcomes, and study design of interest (PICO-T) [24]. We also reviewed observational studies using the condition, context, and population (CoCoPop) approach [25]. We used study settings to search for studies in sub-Saharan African countries. We looked for articles written in English. The reason for the language restriction is that, to reduce bias in the interpretation of this review, including studies in all languages may introduce more bias into the interpretation of the meta-result [26]. We considered the following study designs for answering the review question: case control, retrospective, prospective, longitudinal, and randomized controlled.

Study identification and selection: all studies (titles and abstracts) identified during the search were imported into an Endnote library. Duplicates were removed. Two reviewers (BJ and KA) independently screened the articles identified by the searches on the basis of their titles and abstracts, using the article selection criteria. We performed a 25% sample of the titles and abstracts screened by two reviewers (MA and TA) to cross-check whether the identified studies fulfilled the eligibility criteria or not. Full text of the studies was obtained using both MA and TA reviewers who judged a citation as potentially eligible for this review. Any disagreement in opinion between reviewers was resolved by consensus. Final inclusion and exclusion decisions were made after independent examination of the full-text studies of selected citations. Furthermore, studies whose abstract and/or full-text were not found, nameless reports, and qualitative studies were excluded from the review [27].

Definition and diagnosis of preeclampsia in different studies: different international societies have produced recommendations and guidelines for clinicians treating preeclampsia, with the overall goal of improving maternal and fetal outcomes [28]. The unified definition proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) is mentioned above in the method section. The World Health Organization (WHO) definition, on the other hand, considers only diastolic blood pressure of ≥90 mmHg to be significant after 19 weeks of gestations [29]. It is evident that unless a uniform definition of preeclampsia is available, the incidences of preeclampsia among studies differ because of the use of different definitions of preeclampsia employed in different parts of the world [25]. In one of the study's definitions of preeclampsia, proteinuria is considered a mandatory criterion, and some guidelines consider when proteinuria is not a mandatory criterion for preeclampsia, which can be otherwise defined by hypertension and one or more preeclampsia-related maternal organ dysfunctions [28]. Our study considered the international societies' agreed definition of preeclampsia proposed by the International Society of Hypertension in Pregnancy guidelines in the absence of proteinuria if organ-specific signs or symptoms were present with the new onset of hypertension [30]. Preeclampsia was diagnosed with the minimum criteria of the presence of proteinuria (>1+ or 0.3 g/L) and hypertension (≥140/90 mmHg) on two occasions, at least 4 hours apart, detected after the 20th week

of gestation until delivery in a previously normotensive woman. Alternatively, preeclampsia was diagnosed using hypertension combined with maternal organ dysfunctions such as HELLP syndrome (hemolysis, elevated liver function test, and low platelet count), renal insufficiency, pulmonary edema, and visual or cerebral disturbances, which supported the diagnosis of preeclampsia even in the absence of proteinuria [31].

Data extraction and extracted items: data extraction and quality assessment were completed simultaneously. Data extraction was performed independently by four reviewers (BJ, MA, TA, and KA) on the clinical and methodological quality of the studies and verified by a second reviewer. Studies were examined, and data related to the outcome measures and review questions was identified and extracted using data extraction forms specifically designed for this review. Data extraction was done using a tool developed by the Newcastle-Ottawa Scale for assessing the quality of studies in systematic reviews and meta-analyses [32]. The following information was extracted: the year of publication, the first author, the study setting, the study design, the sample size, the number of women with preeclampsia, the incidence of preeclampsia, the point estimate, the standard error, and elements of the study's methodological quality.

Risk of bias (quality) assessment in individual studies: studies meeting the above criteria were grouped according to the study method and assessed for quality using the Newcastle-Ottawa quality assessment tool adapted to check the quality of the included studies [32]. Data were assessed by three authors independently (BJ, MA, TA, and KA) using this tool, and studies with a score of ≥ 6 out of 10 were considered to be of good quality [33] and verified by a fourth reviewer. Disagreements between the four reviewers were resolved by taking the mean score of the four authors and by discussion. Four reviewers were discussed in studies if a lack of consensus occurs. Assistance from a fourth interviewer was sought if consensus cannot be reached. In situations where multiple methods were used, studies were assessed according to the method that relates most closely to the primary aim of the study. No studies were excluded based on quality.

Data analysis: the information was entered into Microsoft Excel 2010. A narrative synthesis describing the studies was completed. The meta-analysis was conducted using Stata Version 14 software. The forest plot was used to present the combined estimate with a 95% CI. The pooled effect size result was presented using relative risk (RR) with a 95% confidence interval (CI). We calculated the unadjusted relative risk (RR) with 95% CI for each study, based on reported crude numbers of events and across studies using the random-effects model. The result was described narratively and presented as the adjusted relative risk (aRR) with a 95% CI. Summary crude and adjusted RRs across studies were calculated separately based on the random-effect model. A random-effect model was also computed to estimate the pooled incidence of preeclampsia. Heterogeneity determined the differences between study results beyond those attributable to chance. It may arise because of clinical differences between studies (setting, types of participants, or implementation of the intervention) or methodological differences (such as extent of control over bias). A random effects model was used to incorporate heterogeneity in meta-analyses. If the heterogeneity fits with the assumptions of this model, a funnel plot would be symmetrical but with additional horizontal scatter. If the heterogeneity is high, it may overwhelm the sampling error, causing the plot to appear cylindrical. Heterogeneity between studies was computed the Galbraith plot, subgroup analysis, and meta-regression. Sub-group analysis was done by the groups of study design, sample size, study quality, and year of publication. Meta-regression was conducted to assess the relationship between study-level covariates and effect size. Heterogeneity between studies was presented

using statistical measures such as: I2 (I-squared) or Q-statistics and meta-regression analyses. However, I^2 (I-squared) reflects inconsistency across studies rather than true variation across the underlying true effects of the study. A value of I2: 25%, 50%, and 75% was used to consider the heterogeneity test as low, medium, and high [32]. The meta-analyses were performed by computing relative risk, log relative risk, and its standard error by using a random-effects model. Publication bias was examined by visually checking for asymmetry in a funnel plot and objectively tested by using Egger´s test. A funnel plot was a scatter plot of the effect estimates from individual studies against some measure of each study´s size or precision. We performed a sensitivity analysis to determine how robust the findings were and to see how the results would change if one study were removed from the analysis.

Results

Study selection: a total of 4,250 studies were identified, and 1,345 were removed due to duplicates. Of the 2,905 remaining studies, 2,115 were excluded after reading their titles and abstracts. Of the 61 studies eligible for full-text review, 12 studies were excluded after reading their full text. A total of 49 studies were retained for systematic review, and 11 studies were included in the meta-analysis. A total of 213,528 pregnant women were included in the systematic review; of these, 9,298 developed preeclampsia (Figure 1)

Characteristics of included studies: from 49 studies, 11 were from Nigeria, 9 from Ethiopia, 6 from Sudan, 2 from Ghana, 3 from Tanzania, 2 from Togo, 1 from Zimbabwe, 1 from South Africa, 3 from Cameroon, 1 from Mozambique, 4 from Uganda, 1 from Burundi, and 1 from Senegal. Personal history of preeclampsia [aRR=21.5; 95% CI: 14, 2, 32.5], family history of preeclampsia [aRR=10.5; 95% CI: 5.8, 19.0], and number of Antenatal care (ANC) visits 4 [aRR=1.6; 95% CI: 1.1, 2.4] were found to be risk factors for preeclampsia in a Nigerian study (Table 1, Table 1 suite).

Overall pooled incidence of preeclampsia in sub-Saharan Africa: in sub-Saharan Africa, the overall pooled incidence of preeclampsia was 13% [95% CI: 0.12-0.14]. However, there was a significant heterogeneity between studies (I^2= 99.48%, P-value <0.000), effect size = 0.13. The discrepancy in the pooled incidence of preeclampsia in SSA among the included studies related to diverse recruitment strategies, inclusion and exclusion criteria, data collection methods, and follow-up time periods that varied among studies.

Quality assessment of the included studies: during the assessment of the quality of studies, we reviewed the titles, abstracts, and full-text articles from the searched studies. We considered that studies that did not meet inclusion criteria were excluded based on pre-defined study selection criteria. The Newcastle-Ottawa quality assessment scale was used to examine the full texts of the included studies. We discovered that all the included full-text studies had good quality scores on the Newcastle-Ottawa Scale (NOS). From a total of 49 studies, a total of 9 studies received a score of 10 points; 11 received 9 points; 8 studies received 8 points; 12 received 7 points; and 9 had 6 points. Studies with a score of ≥6 out of 10 were considered to be of good quality on the NOS.

Assessment of heterogeneity by Galbraith plot: Galbraith's plot assessed heterogeneity visually; however, it did not indicate the underlying causes of heterogeneity. On the horizontal axis, we plot the 1/standard error of the study effect estimate. The result of the Galbraith plot showed that there was no heterogeneity between studies. It described variations in observed effects across studies, which showed that there were no uncontrolled factors affecting the observed effects. There were no points that were outside the 95% confidence interval (Figure 2).

Sub group analysis: subgroup analysis found that multigravida was the identified significant risk factor for preeclampsia in retrospective cohort studies [aRR = 2.87; 95% CI: 1.22, 3.70] and large sample size studies [aRR = 1.40; 95% CI: 1.27, 7.40]. On the other hand, a higher level of heterogeneity between studies was noted among case-control studies [I^2= 72%, <0.001) and studies with smaller sample sizes [I^2= 63%, p<0.001) and studies with smaller sample sizes [I^2= 63%, <0.05]. We also performed subgroup analyses by study quality, and primigravida was a stronger risk factor for preeclampsia in good quality studies [aRR = 2.12; 95% CI = 1.48, 4.30] compared to poor quality studies (Table 2).

Meta regression: we discovered a significant association between sample size [aRR=1.53; 95% CL: 1.59, 5.12] and the occurrence of preeclampsia during meta-regression analysis. However, there was no evidence for a significant risk factor for preeclampsia with the year of publication [aRR = 1.05; 95% CL: 0.22, 0.84] and study design [aRR = 0.94; 95% CL = 0.98, 1.01] (Table 2).

Assessment of publication bias

Funnel plot: funnel plot asymmetry; have been used to examine bias in the results of meta-analyses. According to the funnel plot result, there was no evidence of considerable asymmetry across studies, while the sloping lines indicated the expected 95% Confidence interval (CIs) for a given standard error and assumed no heterogeneity between studies. The standard error of the effect estimate was chosen as the measure of study size and plotted on the vertical axis with a reversed scale that places the larger, powerful studies towards the top. The effect estimates from smaller studies should scatter at the bottom, with the spread narrowing among larger studies (Figure 3).

Sensitivity analysis: we conducted sensitivity analyses to determine differences in summary effects by dropping a few studies that were defined as highly influential on the basis of variance and weight estimates. We found that the meta-analysis was dominated by the Gilles, 2013 study, and the omission of other studies made little or no difference in the meta-analysis. If Wandabwa 2010 study was excluded, it appeared that there were clear estimates of preeclampsia risk (Figure 4).

Assessment of publication bias by Egger's test: Egger´s test was used to assess potential publication bias in a meta-analysis via funnel plot asymmetry. The result of Egger´s test indicated that non-significant small studies have an effect on meta-analysis (p-value > 0.05). We confirmed that small studies did not have a significant effect on the main meta-analysis result (Table 3).

Risk factors of preeclampsia in sub-Saharan Africa: women who had multigravida had 89% more likely (aRR = 1.89; 95% CI: 1.65 to 2.17) higher risks for the occurrence of preeclampsia as compared with those women who did not have multigravida. The result of the trend analysis showed that the incidence of preeclampsia had increased from 2.22% in 2010 to 2.67% in 2018 (Figure 5). Furthermore, we identified significant risk factors for the development of preeclampsia from individual included; a family history of hypertension, anemia during the first trimester, low socioeconomic status, pre-existing hypertension, multiple pregnancies, a previous history of preeclampsia, and a body mass index (BMI) at booking of >30 kg/m^2, a low birthweight baby, maternal age, and parity, and lack of antenatal care had been associated with preeclampsia [17,18,23,29,30].

Trend analysis: the result of the trend analysis showed that the incidence of preeclampsia had increased from 2.22% in 2010 to 2.67% in 2018. The CI became narrower when looking at recent publications compared to past publications (Figure 6).

Quality of evidence for Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach: assessment of the quality of the evidence for systematic review and meta-analysis identified the GRADE approach on defined parameters as high, moderate or low. When systematic review authors rate imprecision and other quality domains of evidence, GRADE ratings of imprecision and other quality domains of evidence are an iterative process that may consider people's important thresholds of effects. We considered the risk of bias to be serious, and there was moderate heterogeneity among studies, making the quality of the body of evidence very low (Table 4).

Discussion

We registered a systematic review protocol on the PROSPERO International Prospective Register of Systematic Reviews (CRD42019124455). This will possibly reduce the risk of multiple reviews addressing the same question, reduce publication bias, and provide greater transparency when updating systematic reviews. This is in agreement with other previous literature [34]. We considered well-defined eligibility criteria for study selection, which is essential in appraising the validity, applicability, and comprehensiveness of reporting study characteristics. We used both the Coco Pop and PICOS approaches (participants, interventions, comparators, outcomes, and study design) to set inclusion and exclusion criteria. This is supported by another study [24]. Search strategy ensured studies were selected in a systematic and unbiased manner to provide reliable estimates for policymakers. This finding is supported by another review [18]. We considered all information sources in the search and contacted study authors to identify additional studies [18]. The authors have established method that describes step by step the process of developing a systematic search strategy as needed in the systematic review. The described method could be used to create comprehensive search strategies for different databases.

Overall pooled incidence of preeclampsia in sub-Saharan Africa was 13%. This finding is higher than that of global prevalence of preeclampsia affects 5 to 8% of all pregnant women [11] and higher than another study, which was 8.8% [35]. This could be due to sub-Saharan Africa which is one of the poorest regions in the world with high rates of rapid urbanization, which is more likely to pose a major public health challenge with a significant proportion of women becoming preeclamptic [36]. This might also be due to most of the studies included in this review which were hospital-based, unlike reports from other settings, suggesting that the incidence of preeclampsia in SSA may have been overestimated as pregnant women in limited resource settings seem less likely to utilize ANC [37]. This suggests that early detection by attending antenatal care and receiving proper treatment can reduce preeclampsia and adverse maternal outcomes. Overall pooled women who had multigravida had 89% higher risks for the occurrence of preeclampsia compared to women who did not have multigravida. This finding is supported by other studies conducted in Nepal in 2019, In Yemen in 2017, which found that women who have multiple babies were two and seven times higher odds of developing pre-eclampsia compared to women who had a singleton baby [38, 39]. This could be explained by the fact that mothers with multiple pregnancies have increased placental mass that may cause placental hypoxia, hence the development of pre-eclampsia. Raising awareness of the risk factor for preeclampsia, this may lead to a reduction in its prevalence among pregnant women.

Study selection by considering more than two authors and the number of identified studies from their search and sequentially excluding records according to their eligibility criteria. This is agreed upon by another study [40]. Each stage of the study selection process was carried out by more than two independent reviewers to minimize rejecting relevant articles and minimize the selection bias. To reduce the risk of selection bias, studies focusing on patients with an increased

incidence of preeclampsia were pooled. We developed a data extraction form (based on the Newcastle-Ottawa data extraction template), pilot tested it before the original data extraction on twelve randomly selected included studies, and refined it accordingly [32]. Three reviewers´ extracted data from included studies and the fourth reviewer rechecked the extracted data's consistency. Disagreements were resolved by discussion between the independent reviewers, and if there was no agreement, a fourth reviewer was used for the final decision. We also contacted authors for those studies in which information was not clearly reported. This information is supported by other literature [24,32].

According to this included individual study, we found that a high BMI at booking was a risk factor for preeclampsia. This finding is consistent with the other review [41]. A study in China showed that the incidence of preeclampsia in severely obese women increased by 3.97 times, a BMI of 27.5-30.0 kg/m^2 increased by 3.25 times, and a BMI of 25.0-27.5 kg/m^2 increased by 1.60 times [42]. Every pregnancy is at risk until proven otherwise; therefore, all pregnant women and their family members have to be ready to take essential actions and make multifaceted preparations to respond to the complications that associated with preeclampsia. Both of the included studies showed that the incidence of preeclampsia increased with a history of hypertension [41,43]. A study conducted in Tanzania found that women who had chronic hypertension had 18.66 times the odds of developing preeclampsia compared to normotensive women [44]. In a woman with previous hypertension, therefore, measuring blood pressure before pregnancy or before 20 weeks of pregnancy and initial screening for proteinuria are important at the first visit of antenatal care [43]. Raising awareness at the community level among mothers during ANC visits regarding early signs of hypertension and informing them of the referral system could help reduce delays in accessing treatment.

According to the one included study, early onset of preeclampsia based on gestational ages between 34 and 37 weeks was significantly associated with adverse maternal and perinatal outcomes [45] found that women with an early onset of preeclampsia were more likely to experience preeclampsia with severe complications compared to women with a late onset of preeclampsia. Poor fetal outcomes were more frequent among women with an early onset of preeclampsia, including early neonatal deaths, stillbirths, low birth weight, and admission to the Neonatal Intensive Care Unit (NICU) [46]. Inspiring pregnant women´s health-seeking behavior should provide a chance to diagnose preeclampsia early to prevent its medical complications. Our review included evidence showing that low birth weight was risk factor for the development of preeclampsia [47]. In this review, included study confirmed that preeclampsia is associated with different adverse birth outcomes, such as: low birth weight, preterm birth, and intrauterine growth restriction [47]. Preeclampsia may affect the normality of fetal development by causing abnormal blood flow to the placenta, resulting in fetal growth restriction, and small for gestational age of the fetus, and affect normal brain development [48]. There is a need for clinicians to shift from the perspective of the delayed intervention approach to predictive, preventive, and personalized medicine.

Both included studies showed that there are variations in the definition of preeclampsia across studies [49,50]. The diagnostic criteria for preeclampsia have been revised over the past decade. For example, edema was included previously as diagnostic criteria for preeclampsia, but now it is no longer required for a diagnosis of preeclampsia [50]. The unclear pathogenesis of preeclampsia is a difficulty for clinicians´ and researchers´ efforts to develop appropriate therapeutic and diagnostic measures, despite progressions in research practices. Understanding these mechanisms could generate innovative diagnostic and therapeutic measures to control

and manage preeclampsia. The diagnosis of severe preeclampsia is made in the presence of any of the following criteria: systolic blood pressure ≥160 mm Hg; diastolic blood pressure ≥110 mmHg, eclampsia; and persistence, worsening of laboratory markers, such as platelet counts <100,000/mm^3, aspartate transaminase (AST) >70 U/L and creatinine >1.1 mg/dL [51]. In another study, fetal growth restriction, oligohydramnios, and non-reassuring fetal well-being were considered [51]. Another study conducted in Uganda in 2016 found a higher proportion of elevated alanine transaminase among women with eclampsia (55.2%) compared to severe preeclampsia (15.6%) [15]. It was reported that in women with preeclampsia, a rise in AST and alanine transaminase (ALT) levels during the first 20 weeks of pregnancy was significantly associated with a higher risk for severe preeclampsia during the second half of the pregnancy. As a result, the ANC provider should make sure that the pregnant woman and her family is aware of the common danger symptoms and signs of preeclampsia and that they are ready to seek medical attention as soon as possible. The present review found that the quality of the evidence among studies was categorized as low. Our review suggests that the risk of bias was serious and that there was moderate heterogeneity among studies, making the quality of the body of evidence low. This finding is consistent with the findings of other studies [39,52]. When judging the quality of a body of evidence, the assessment considers several factors, including the risk of bias associated with each included study. A possible reason might be that the selection of participants was not clear in some studies; there was also a lack of follow-ups in some primary studies.

Limitations and strengths of the systematic review and meta-analysis: our search was limited to articles published in English; the possibility exists that our language bias may have caused us to miss relevant articles. The definition of preeclampsia was not consistently reported, and even when reported, the criteria for defining preeclampsia were not clearly described. Most of the primary studies did not explore confounding and potential confounders that might affect the estimates in most of the original studies. The other limitation was the enormous variation in the sample size of included studies (ranging from 120 to 54,339 study participants), which is another source of heterogeneity. Since there was no similar review previously conducted, this review and meta-analysis showed the pooled incidence and risk factors of preeclampsia in sub-Saharan Africa. Although publication bias is the most common threat to the validity of a meta-analysis, the funnel plot did not show any significant asymmetry on visual inspection, and Egger's test also showed no evidence of publication bias.

Policy and clinical implications: this finding should help clinicians by providing a set of maternal and fetal expectant management practices that can act as indicators for the possibility of preeclampsia affecting pregnancy outcomes. For public health officials, health-related agencies, and political interests, this finding should support resource allocation toward early detection of preeclampsia during early antenatal care visits. For researchers, our work should help to suggest ideas for developing a protocol, a variable adjustment, and baseline information for future longitudinal studies on the same research question.

Conclusion

Incidence of preeclampsia affected a significant proportion of pregnant women in sub-Saharan Africa. The incidence of preeclampsia varies from country to country in sub-Saharan Africa. Women who had multigravida had 89% higher risks for the occurrence of preeclampsia as compared to women who did not have multigravida. The result of the trend analysis found that the incidence of preeclampsia had increased from 2.22% in 2010 to 2.67% in 2018. Focusing on the risk factors for preeclampsia identified in this review may prevent future cases of preeclampsia. Preeclampsia awareness, early detection and pharmacological

therapy, and health promotion during routine antenatal care services and communities, with a focus on preeclampsia risk factors, could improve maternal and perinatal outcomes in these settings.

What is known about this topic

- *The incidence of Hypertensive Disorders of Pregnancy (HDPs) has increased from 16.30 million in 1990 to 18.08 million in 2019 globally; incidence varies from country to country at the global level;*
- *The highest incidence of HDPs was observed in South Asia (3.84 million), western sub-Saharan Africa (3.71 million), and eastern sub-Saharan Africa (3.12 million) in 2019;*
- *The high burden of preeclampsia has been a major concern in sub-Saharan Africa; but there is lack of published studies on the incidence and risk factors of preeclampsia.*

What this study adds

- *We found that incidence of preeclampsia affected a significant proportion of pregnant women in sub-Saharan Africa; the incidence of preeclampsia varies from country to country in sub-Saharan Africa;*
- *Women who had multigravida had 89% (aRR = 1.89; 95% CI: 1.65 to 2.17) a higher risk for the occurrence of preeclampsia compared to women who did not have multigravida;*
- *The result of the trend analysis found that the incidence of preeclampsia had increased from 2.22% in 2010 to 2.67% in 2018.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Birhanu Jikamo, Mulat Adefris, Telake Azale, and Kassahun Alemu were involved in designing the review. Birhanu Jikamo and Kassahun Alemu performed the systematic literature search (independent assessment), and extracted data from each article, including critical appraisal, data extraction, data analysis, interpretation of results, and editing the manuscript. Mulat Adefris and Telake Azale acted as third reviewers when any issues concerning the selection of the studies were discussed. Birhanu Jikamo, Mulat Adefris, Telake Azale, and Kassahun Alemu: wrote the first version of the manuscript. All authors read and agreed with the final version of the article.

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Table 1: characteristics and estimated incidence of preeclampsia among included studies in sub-Saharan Africa 2019

Study ID	Author, Year	Country	Study design	Sample size (n)	Incidence of Preeclampsia	% of incidence of preeclampsia
1	Gilles , 2013	Nigeria	Case control study	2,835	175	6.17
2	Maereg W, 2016	Ethiopia	Retrospective study	42,963	1,508	3.50
3	Abdelmo E, 2014	Sudan	Prospective study	3168	15	0.47
4	Shambel , 2016	Ethiopia	Retrospective study	320	21	6.56
5	W.K.B.A. , 2010	Ghana	Retrospective study	8,091	530	6.55
6	Ishag Ada, 2011	Sudan	Case control study	4,620	160	3.46
7	Rob Mooij, 2015	Tanzania	Retrospective study	3398	26	0.76
8	Eshetu Sey, 2015	Ethiopia	Retrospective study	5415	76	1.40
9	Prabhanjan, 2015	Ethiopia	Retrospective study	7702	172	2.23
10	LeOnard, 2016	Nigeria	Retrospective study	13,750	136	0.98
11	Jonah Mus, 2018	Nigeria	Prospective study	307	27	8.79
12	Gezehagn, 2015	Ethiopia	Retrospective study	1015	159	15.66
13	S. Baragou, 2014	Togo	Prospective study	1620	114	7.03
14	Solwayo, 2017	Zimbabwe	Retrospective study	9,086	95	1.04
15	J.. Browne,2015	Ghana	Prospective study	789	14	1.77
16	VMS KAL, 2013	South Africa	Case control study	992	492	49.59
17	EOV Ugw, 2011	Nigeria	Retrospective study	2337	77	3.29
18	Adama-Ho, 2015	Togo	Retrospective study	7561	704	9.31
19	Ishag Ad, 2013	Sudan	Case control study	54,339	1765	3.24
20	Abdel Azie, 2011	Sudan	Retrospective study	9578	56	0.58
21	Pierre-Mari, 2017	Cameroon	Prospective study	152	96	63.15
22	Laura A, 2019	Nigeria	Prospective study	7,114	232	3.26
23	Sumedha, 2019	Mozambique	Prospective study	4253	183	4.30
24	Michael J, 2013	Tanzania	Prospective study	4,503	171	3.79
25	Kyembwa, 2018	DR Congo	Case control study	184	92	50
26	Yifru B, 2015	Ethiopia	Retrospective study	1015	612	60.29
27	Annettee , 2016	Uganda	Prospective study	3100	218	7.03
28	Ekine A, 2015	Nigeria	Retrospective study	1667	55	3.29
29	Swati, 2014	Nigeria	Longitudinal study	216	10	4.62
30	Kassie GM, 2014	Ethiopia	Retrospective study	357	231	64.70
31	Mulualem , 2015	Ethiopia	Case control study	453	151	33.33
32	Ayobola A, 2017	Nigeria	Case control study	120	60	50
33	Ouedraogo, 2018	Bukina Faso	Retrospective study	5791	200	3.45
34	J. WAND, 2010	Uganda	Case control study	578	78	13.49
35	Helen C. O, 2016	Nigeria	Case control study	200	100	50
36	Nibitanga, 2015	Burundi	Retrospective study	183	46	25.13
37	Pierre Mari, 2011	Cameroon	Case control study	3228	152	4.70
38	Charles Bit, 2017	DR Congo	Case control study	350	200	57.14
39	Jean-Pierre, 2016	DR Congo	Case control study	178	89	50
40	Francois, 2014	Cameroon	Prospective study	5765	117	2.02

DR Congo* =Democratic republic of Congo

Table 1 suite: characteristics and estimated incidence of preeclampsia among included studies in sub-Saharan Africa 2019						
Study ID	**Author, Year**	**Country**	**Study design**	**Sample size (n)**	**Incidence of Preeclampsia**	**% of incidence of preeclampsia**
41	Paul Kion, 2014	Uganda	Randomized Control	833	30	3.60
42	Modesta, 2016	Tanzania	Retrospective study	33792	1415	4.18
43	C. T. Nda, 2009	Senegal	Case control study	377	113	29.97
44	Abdelma, 2016	Sudan	Case control study	280	140	50
45	Adeosun, 2015	Nigeria	Longitudinal study	159	79	49.68
46	VEmman, 2010	Uganda	Prospective study	25,000	185	0.74
47	Nwogoh, 2014	Nigeria	Case control study	100	50	50
48	Hind M, 2017	Sudan	Case control study	166	70	42.16
49	Abebaw, 2018	Ethiopia	Case control study	76	38	50
DR Congo* =Democratic republic of Congo						

Table 2: subgroup analysis on the risk of primigravida on preeclampsia using random-effects modeling (n =11 studies) 2019			
Study groups	**aRR**	**95% CI**	**I^2, P-value**
Study design			
Case control study	1.52	[1.59, 1.72]	72%, 0.009
Retrospective study	2.87	[1.22, 3.70]	0.0%, 0.005
Sample size			
Large (n > 30,339)	1.40	[1.27, 7.40]	45%, 0.004
Small (n < 30,339)	0.950	[1.59, 1.6]	63%, 0.043
Study quality			
Good	2.12	[1.48, 4.30]	49%, 0.026
Fair	0.884	[0.50, 1.54]	0.0%, 0.951
Poor	0.976	[0.13, 6.93]	0.0%, 0.905
Year of publication			
<=2015	0.998	[0.594, 1.679]	71%, 0.023
>2015	0.801	[0.097, 6.623]	68.5%, 0.012
aRR–Adjusted Relative Risk; 95% CI–95%, Confidence Interval, I^2–I-squared test statistics			

Table 3: assessment of publication bias by Egger's test of risk factors with development of preeclampsia in sub-Saharan Africa 2019					
Egger's test					
Std_Eff	**Coefficient.**	**Standard error.**	**t**	**P> |t|**	**(95% conf. Interval)**
Slope	0.4326245	0.1745024	2.48	0.035	0.0378736, 0.8273764
Bias	0.9497884	0.7485947	1.27	0.236	-0.7434469, 2.643024

Table 4: assessment of certainty of evidence using grade pro software 2019											
Certainty assessment							**Number of patients**		**Effect**		**Certainty**
No of studies	Study design	Risk of bias	Inconsistency	Indirectnes	Imprecision	Other consideration	Risk of preeclampsia	Non-preeclampsia	Relative(95%CI)	Absolute(95%CI)	⊕◯◯◯ LOW
Risk factors for preeclampsia: RR											
11	observational studies	serious	serious	not serious	not serious	publication bias strongly suspected strong association	4.605/161.412 exposed/unexposed		RR 1.89 (1.65 to 2.17)	3 fewer per 1,000 (from 4 fewer to 2 fewer)	

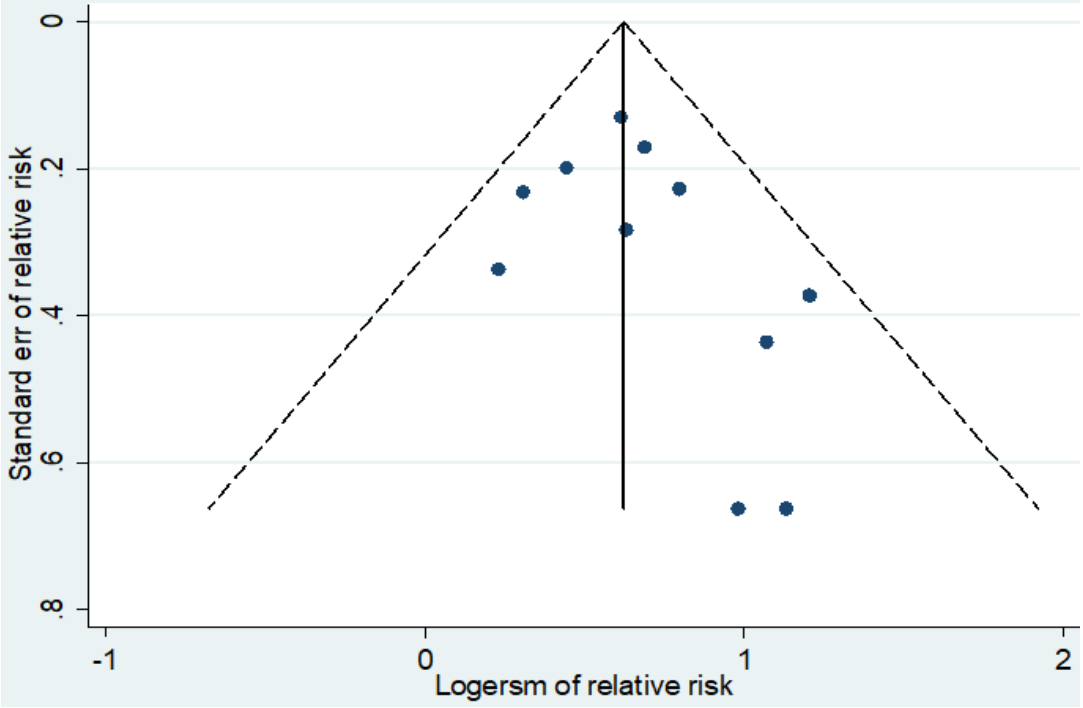

Figure 1: flow chart of study selection for inclusion in the systematic review and Meta-analysis. Main reasons for exclusion from the review are also described in the chart in sub-Saharan Africa, 2019

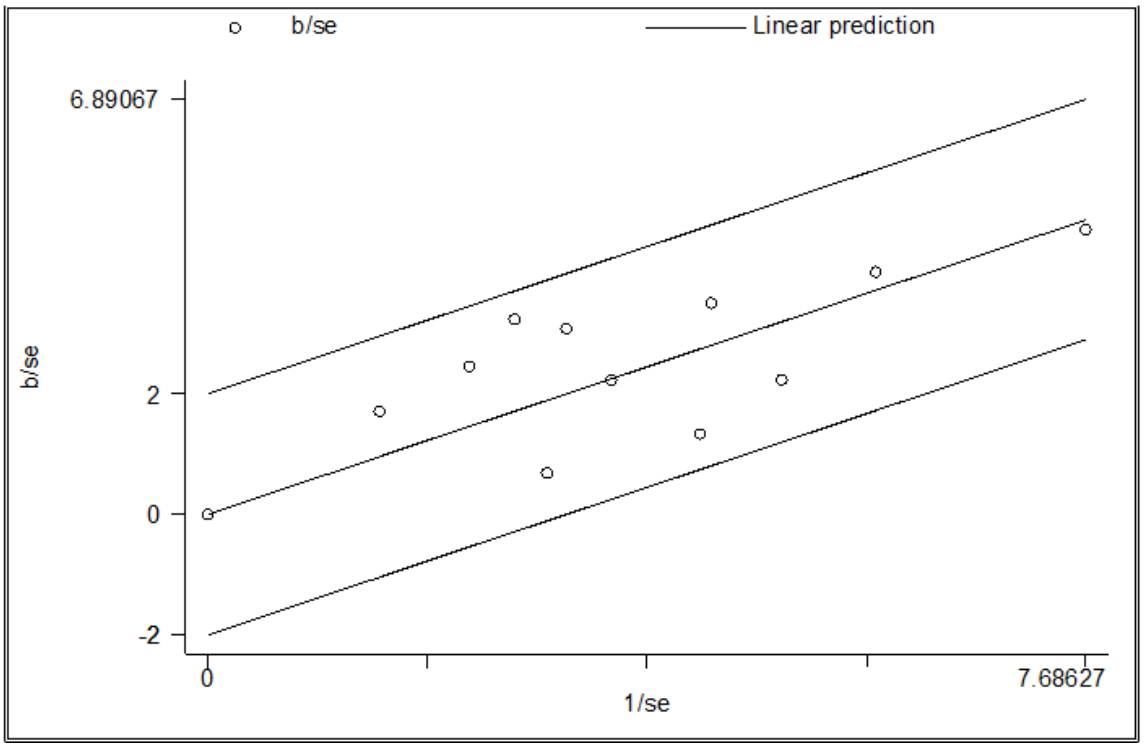

Figure 2: checking heterogeneity by Galbraith plot of associated factors with preeclampsia in sub-Saharan Africa, 2019

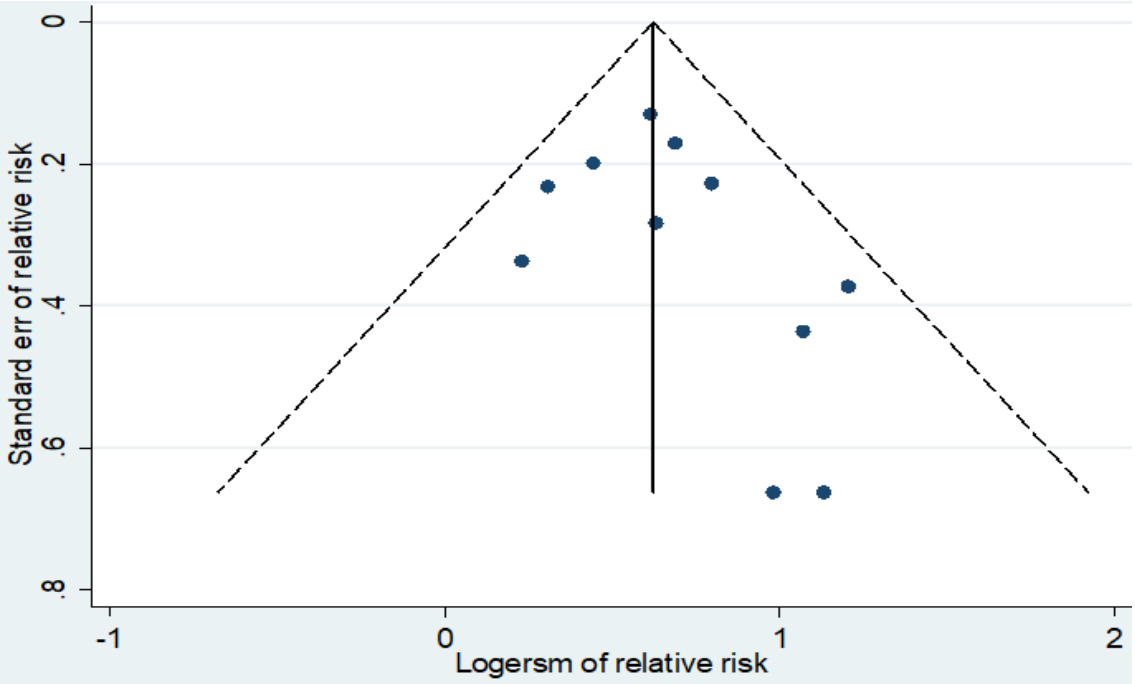

Figure 3: assessment of publication bias by funnel plot of risk factors with preeclampsia in sub-Saharan Africa, 2019

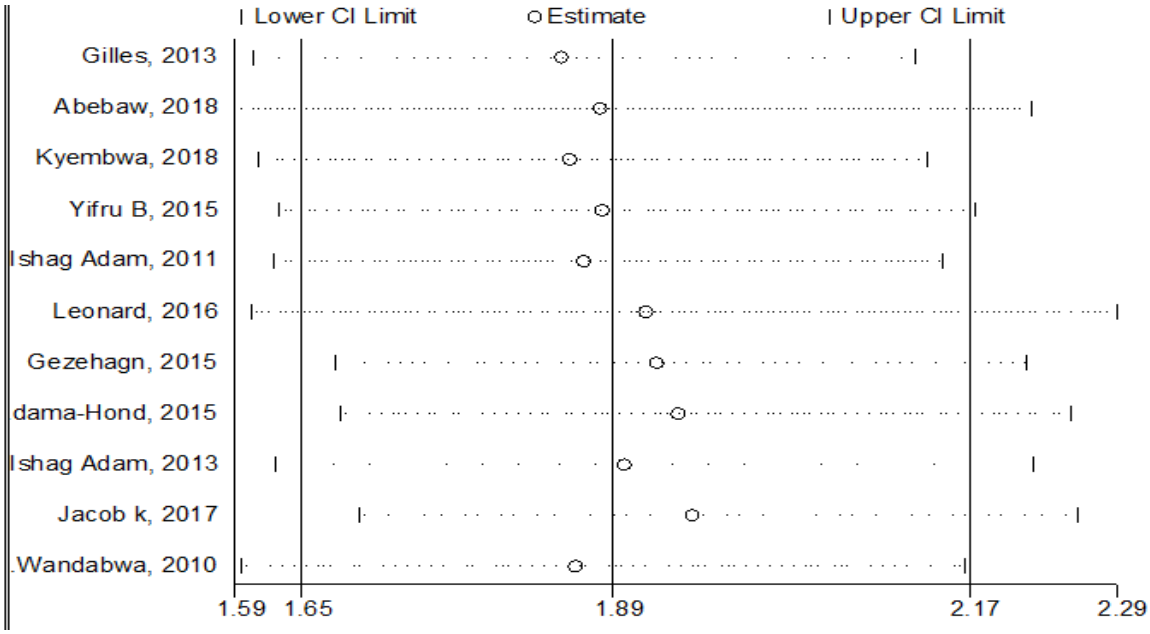

Figure 4: assessment of publication bias by sensitivity analysis used to identify highly influential studies on the basis of variance and weight estimates in sub-Saharan Africa, 2019

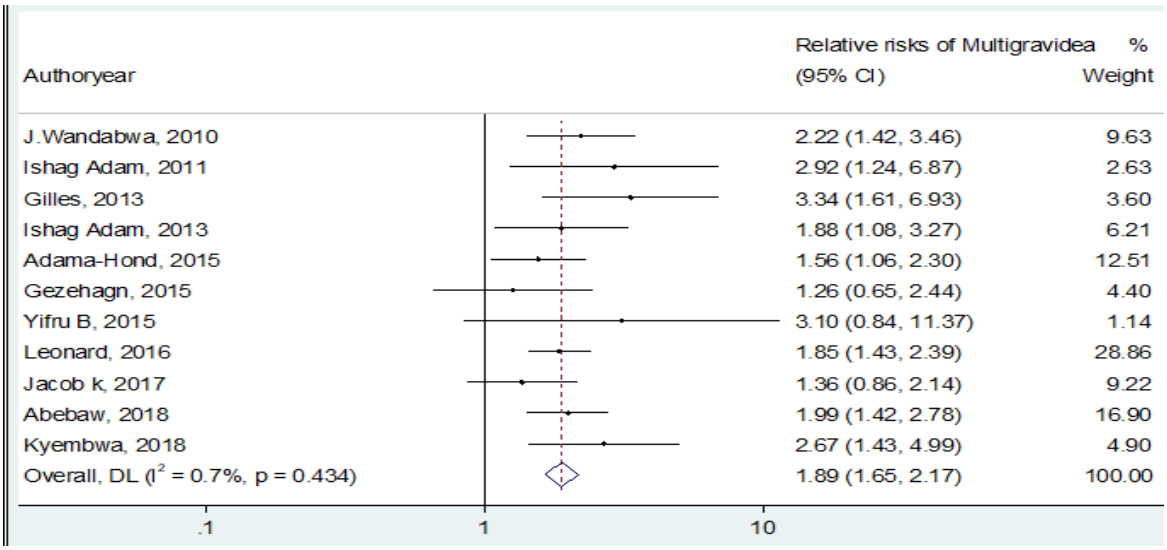

Figure 5: adjusted risk ratios of pre-eclamptic women from 11 studies that reported adjusted o ratios controlling for various, the summary adjusted risk ratios across studies were calculated based on a random-effects model

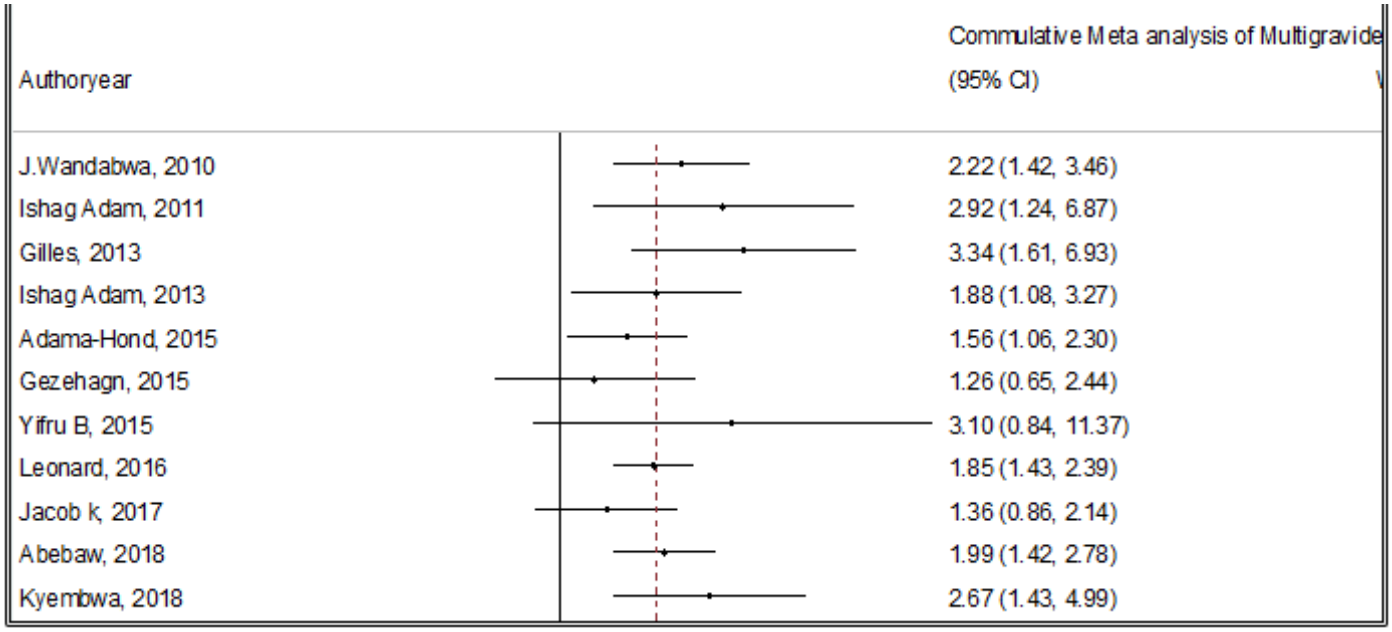

Figure 6: assessment of time trends and its risk factors with preeclampsia in sub-Saharan Africa, in 2019