Neonatal sepsis and its associated factors in East Africa: a systematic review and meta-analysis, 2019

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Abstract

Background : Neonatal sepsis is one of the leading causes of inflated death and illness of neonates. Different primary studies in Eastern Africa showed the burden of neonatal sepsis. However, inconsistency among those studies was seen and no review has been conducted to report the amalgamated magnitude and associated factors. Therefore, this review intended to estimate the national prevalence and associated factors of neonatal sepsis in Eastern Africa. Methods : Using PRISMA guideline, we systematically reviewed and meta-analyzed studies that assessed the prevalence and associated factors of neonatal sepsis from PubMed, Cochrane library, and Google Scholar. Heterogeneity across the studies was evaluated using the Q and the I 2 test. A weighted inverse variance random-effects model was applied to determine the prevalence and the effect size of associated factors. The subgroup analysis was done by country, study design, and year of publication. A funnel plot and Egger's regression test were used to see publication bias. Result : A total of 26 studies with 11239 participants were used for analysis. The pooled prevalence of neonatal sepsis in East Africa was 29.65% (95% CI; 23.36–35.94).Home delivery(AOR =2.67; 95% CI: 1.15-4.00; I 2 = 0.0%; P=0.996), maternal history of UTI (AOR=2.083; 95% CI :0.24-3.93; I 2 = 69.1%; P=0.001),gestational age (preterm) (AOR=1.56; 95% CI: 1.04-2.08; I 2 = 27.8%;P=0.000) ,prolonged labor (AOR=3.23 ;95% CI: -0.04-6.51; I 2 = 62.7%; P=0.020) and PROM (AOR= 1.95; 95% CI: 0.53-3.37; I 2 = 43.2%; P=0.062) were identified factors of neonatal sepsis. Conclusions : The prevalence of neonatal sepsis in Eastern Africa remains high. This review may help policy-makers and program officers to design neonatal sepsis preventive interventions.

Introduction

Neonatal sepsis is a systemic infection occurring in neonatal life and is a major cause of morbidity and mortality in newborns (1). It is categorized as early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS) based on the onset of clinical features (2).EONS is sepsis occurring within seven days of life after birth and LONS is sepsis from after the seventh day of life(3). Neonatal sepsis contributes considerably to neonatal morbidity and mortality and is an continuing major global public health challenge(4). As documented in different literatures, neonatal sepsis is caused by factors related to both maternal and neonatal factors such as prolonged rupture of membrane (PROM),, urinary tract infection, intrapartum fever, instrumental delivery,prematurity, chorioamnionitis, frequent vaginal examination, never attend antenatal care (ANC), home delivery, meconium-stained amniotic fluid, contaminated foods intake, low birth weight, complicated or instrument-assisted delivery, low appearance pulse grimace activity respiration (APGAR) scores and invasive procedures during hospital admission (5–11). Guidelines for the treatment of neonatal sepsis have been formulated and its implementation along with timely initiation of better treatments would satisfactorily decrease morbidity and mortality of neonates by sepsis(3).

Identification of the risk factors for risk-based diagnosis of neonatal sepsis contributes to better interventions and studies that help to reduce the burden of neonatal mortality resulting from these risks.

Worldwide, neonatal infections cause estimated 26% of under–5 deaths, with mortality rates highest in sub-Saharan Africa (4). Globally, sepsis in neonates is still among the principal causes of neonatal mortality and morbidity, especially in the first seven days of life in low and middle-income countries (LMIC)(12, 13).

About four million worldwide deaths in neonates per year, from this 98 % is from developing countries particularly in sub-Saharan Africa(14). The risk of neonatal death is estimated to be six times more in the low and middle-income countries compared to developed (15). Timely diagnosis is difficult due to its nonspecific clinical manifestations. Besides, treating neonates with antibiotics merely by subtle manifestations is likely to over-treat non-infected neonates(16). The ideal approach will be detecting high-risk neonates and steering them for intensive therapy (17).

Incidence of neonatal sepsis is about forty times higher and mortality rates are two times higher in middle-income countries compared with high-income countries(18).

Neonatal sepsis poses a massive public health burden for sub-Saharan Africa with significant associated economic consequences(19).In Africa sepsis accounts 28% neonatal deaths and infectious causes account for 68 deaths per 1000 live births(7).In sub-Saharan Africa, seventeen percent among all neonatal death results from neonatal sepsis as compared to only six percent in developed countries(20).

NS is also one of the most common cause of neonatal death in East Africa; it is the cause for more than one-third of neonatal deaths in Ethiopia particularly (21).

To achieve sustainable development goal (SDG) reducing newborn and under-five mortality as low as12/1000 and 25/1000 respectively is one of the Global strategies of WHO in African countries by 2030. This could be achieved through better prevention and management of preterm births and severe infections as the key (22).

Identification of risk factors and timely initiation of treatments can significantly decrease neonatal mortality and morbidity (23).

In the last two decades, remarkable progress has been shown on maternal and child deaths, but neonatal health is a part of the ‘unfinished agenda’. The world is experiencing an increase in the proportion of under-five death occurring in the neonatal period. Yet despite the neonatal deaths are preventable, they are concentrated in the world’s poorest countries. And 85% of all the neonatal were occurred in low and middle-income countries (LMICs) even though they are home to only 62% of the world’s newborns (6, 24).

Indeed, strategies that can prevent and treat neonates with sepsis are essential to accelerate the progress of newborn survival. In many developing country settings, however, the identification and treatment of newborns with infection is unsatisfactory. Identification of risk factors and early institution of therapy thereby can improve neonatal mortality and morbidity (6, 25).

In East Africa, a variety of studies was conducted to estimate the prevalence of neonatal sepsis. However, the prevalence of neonatal sepsis ranges from 4.7%% [Amare Gebrehiwot et al(25)] to 77.9% (James A. Berkley et al.)(26)which showed great inconsistencies across different geographical settings and different periods. Besides, there are some contradicting or inconsistent findings on risk factors and mortality predictors of neonatal sepsis. Besides, there is no regionally represented pooled data of neonatal sepsis in East Africa. Therefore, this systematic review and meta-analysis were aimed, firstly, to estimate the pooled prevalence of neonatal sepsis and secondly, to estimate the effect size of associated factors of neonatal sepsis in East Africa context.

Methods And Materials

Reporting

The results of this review were reported based on the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (PRISMA) guideline (Supplementary file-PRISMA checklist) and, it is registered in the Prospero database: (PROSPERO 2019: CRD42019130792) Available from https: // www. Crd.york. ac. UK/ PROSPERO_REBRANDING/ display_record. asp ID = CRD42019130792

Searching strategy and information sources

PubMed, Google Scholar, and Cochrane library were accessed. Articles with incomplete reported data were handled through contacting corresponding authors.

The core search terms and phrases were “neonate”, “newborn”, “infant”, and “sepsis”,” septicemia “,” infection”, “Eastern Africa”. The search strategies were developed using different Boolean operators. Notably, to fit advanced PubMed database, the following search strategy was applied: (prevalence OR magnitude) AND (causes OR determinants OR associated factors OR predictors)AND (newborn [MeSH Terms] OR neonate OR infant OR child OR children)AND (sepsis [MeSH Terms] OR septicemia OR infection)AND (Eastern Africa). We also screened at the reference lists of the remaining papers to identify additional relevant studies to this review.

Study selection / Eligibility criteria

Retrieved studies were exported to reference manager software, Endnote version 8 to remove duplicate studies. Two investigators (BB and AM) independently screened the identified studies using their titles and abstracts before retrieval of full-text papers. We used pre-specified inclusion criteria to further screen the full-text articles. Disagreements were discoursed during a consensus meeting with a third reviewer (MW) for the final selection of studies to be included in the systematic review and meta-analysis.

Inclusion and exclusion criteria

This systematic review and meta-analysis included Cross-sectional, case-control, and cohort studies. Those studies had reported the prevalence and/or at least one associated factors of neonatal sepsis and published in English language were considered. There was no restriction of the researches study period. Citations lacking abstract and/or full-text, anonymous reports, editorials, and qualitative studies were excluded from the analysis.

Quality assessment

The qualities of the studies were appraised by three independent authors. The Joanna Briggs Institute (JBI) quality appraisal checklist was used (27). The disagreement was resolved by the interference of the third reviewer. The following items were used to appraise cohort studies: (1) similarity of groups, (2) similarity of exposure measurement, (3) validity and reliability of measurement, (4) identification of confounder,(5) strategies to deal with confounder, (6) appropriateness of groups/participants at the start of the study,(7) validity and reliability of outcome measured, (8) sufficiency of follow-up time, (9) completeness of follow-up or descriptions of reason to loss to follow-up, (10) strategies to address incomplete follow-up, and (11) appropriateness of statistical analysis. The items used to appraise case-control studies were: (1) comparable groups, (2) appropriateness of cases and controls, (3) criteria to identify cases and controls, (4) standard measurement of exposure, (5) similarity in measurement of exposure for cases and controls, (6) handling of confounder (7), strategies to handle confounder, (8) standard assessment of outcome, (9) appropriateness of duration for exposure, and (10) appropriateness of statistical analysis. Studies got 50% and above of the quality scale were considered low risk. The following items were used to appraise cross-sectional studies: (1) inclusion criteria, (2) description of study subject and setting, (3) valid and reliable measurement of exposure, (4) objective and standard criteria used,(5)identification of confounder, (6) strategies to handle confounder, (7) outcome measurement, and (8)appropriate statistical analysis. Studies were considered low risk when it scored 50% and above of the quality assessment indicators.

Data extraction

Two independent reviewers extracted data using a structured data extraction form. Whenever variations of extracted data observed, the phrase was repeated. If discrepancies between data extractors continued, the third reviewer was involved. The name of the first author and year, the study country, the study design, the target population, the sample size, prevalence of neonatal sepsis, and AOR of associated factors were collected.

Outcome measurement

Neonatal sepsis was considered, neonates with presence of at least one clinical sign plus at least two laboratory results which are suggestive for neonatal sepsis (CRP,WBC,ANC, ESR, Platelet count, and Blood

glucose) or neonates who are diagnosed as sepsis by attending physician and fulfill sepsis criteria within 0–28 days of life

Statistical analysis

We pooled the overall prevalence estimates of neonatal sepsis by a random effect meta-analysis (28).We examined the heterogeneity of effect size using Q statistic and the I^2 statistics(28). The Q-test measures whether the observed effect size is considerably different from one another than expected by chance. When Q test is higher than the degree of freedom it indicates significant heterogeneity (also supplemented by P-value). The I2 statistics assess the proportion of total variance across the included studies contributed to the observed heterogeneity. In this study, the I*2* statistic value of zero indicates true homogeneity, whereas the value 25, 50, and 75% represented low, moderate and high heterogeneity respectively (29, 30).

For the data identified as heterogeneous, we conducted our analysis by random-effects model analysis.

When statistical pooling is not possible, non-pooled data was presented in table form.

Subgroup analysis was done by the study country, design, and year of publication. Sensitivity analysis was employed to see the effect of a single study on the overall estimation.

Publication bias was checked by funnel plot and more objectively through Egger's regression test (31).

Result

Study selection

A total of 4931 studies were identified;3282 from PubMed, 12 from Cochrane Library, 1610 from Google Scholar and 27 from other sources. After duplication removed, 1235 remained. Finally, 301 studies were screened for full-text review and finally, 26 (n = 11,239) were selected for the prevalence and/ or associated factors analysis (Fig. 1).

Characteristics of included studies

26 papers were included in this systematic review and meta-analysis [32–36]

10 studies were found in Ethiopia [Alebachew(32), Yirga T.et al./ 2018(33), Gebrehiwot et al/2012(25), G/eyesus et al /2017(5), Gebremedhin et al /2016(6), Getabelew et al. /2017(34), Shitaye D et al/2010(35), Yusuf et al/2008(36), Abate et al/2016(5), Mersha et al. /2019(37)],

7 in Kenya [Kwame et al/2011(38),MUMBI S. et al /2010(39),Mulongo N et al/2018(40),A.M. R. LAVING et al./ 2003(41),Alison W A et al/2012(42),J LeGeyt et al./ 2016(43),James A. et al./ 2005(44)], 3 in Sudan

[Abdelmoneim E. M et al./ 2014(45),Wafa Babiker et al./ 2018(46),Abd Elrahman et al/2018(47)], and 6 in Uganda [Petwa(48), K. W. et al./ 2015,J Mugalu et al./ 2006(49),N. A. Mobbs et al/2019(50), Kiwanuka J et al/2013(51),Okaba et al /2018(52), Bua John et al/2015(44)]. 19 of the studies were done by cross-sectional study design, three studies by case-control study design, whereas four of the studies were conducted through cohort study design respectively. Regarding the year of publication, 4 studies were published between 2000 and 2010, and 22 studies were between 2010 and 2017. The studies included participants, ranging from 62 (32) to 4849 (James A.) (Table 1).

Characteristics and quality status of the studies

Quality of studies

The JBI quality appraisal criteria established for cross-sectional, case-control, and cohort studies were used. The studies included in this systematic review and meta-analysis had no considerable risk. Therefore, all the studies were considered [2, 6–7, 33–52] (Table1).

Meta-analysis

Prevalence of neonatal sepsis

21 studies [Abate et al(5), Okaba et al(52),James A.,Bua John(44), Mulongo N (40),Abdelmoneim E.,A.M. R. LAVING,Alison W A (42),J LeGeyt (43),Petwa(48), Yusuf et al(36), N. A. Mobbs (50), Gebrehiwot(25),Kiwanuka J (51), Mersha et al. (37),Wafa,Babiker,J Mugalu(49),Shitaye D(35) , G/eyesus(5),AbdElrahman, Getabelew(34)] revealed the prevalence of neonatal sepsis.The prevalence ranges from 4.7% (Abate et al(5)) up to 77.9 % (Getabelew et al (34)). From those studies, the pooled prevalence of neonatal sepsis in East Africa was 29.65 %(95%CI; 23.36–35.94). We found significant heterogeneity among the studies (I^2 = 98.8%; p<0.001).We analyzed by random-effects model analysis and we did subgroup analysis (Figure 2).

Test of heterogeneity

Subgroup analysis of the prevalence of neonatal sepsis in Eastern Africa

The subgroup analysis was done based on the country, study design, and year of publication. Based on this, the prevalence of neonatal sepsis found to be 38.31 % in Ethiopia, 24.4% in Uganda, 18.28% in Kenya, and 39.26.Based on design 32.63% in cross-sectional studies and 17.08% in cohort studies. Based on the year of publication 23.05% from 2000–2010, 33.01% from 2010–2015 and 31.39 from 2015–2019(Table 2 and Figure 3, 4 and 5).

Sensitivity analysis

We employed a leave-one-out sensitivity analysis to identify the potential source of heterogeneity in the analysis of the prevalence of neonatal sepsis in Eastern Africa. The results of this sensitivity analysis showed that our findings were not dependent on a single study. Our pooled estimated prevalence of neonatal sepsis varied between 27.15(21.68–32.61) and 30.94(24.96–36.92) after deletion of a single study.

Abd Elrahman et al/2018(47), Abate et al/2016 (5), Gebremedhin et al /2016 (6), Getabelew et al. /2017(34) had shown an impact on the overall estimation(Figure 5).

Publication bias

A funnel plot showed asymmetrical distribution. Egger's regression test p-value was 0.010, which indicated the presence of publication bias.

Prevalence of neonatal sepsis

The estimated overall prevalence of neonatal sepsis is presented in a forest plot (Fig. 4). The overall prevalence of LBW was 29.65% (95% CI; 23.36–35.94; I^2 = 98.8%) (Figure 7).

Factors associated with neonatal sepsis

In Eastern Africa context neonatal sepsis is associated with socio-economic, obstetric and maternal behavior, infant, and environmental-related factors (Table 3).

Place of birth

Five studies (Alebachew et al (32), Yirga (33), Gebremedhin(6)) found a significant association between home delivery and neonatal sepsis. Alebachew et al revealed that the odds of neonatal sepsis was higher among newborns who delivered at home (AOR = 4.2, 95% CI: 1.93, 8.97) compared to those who delivered at the health institution. Yirga et al revealed that neonates who delivered at home were 4.36 times at risk of being neonatal sepsis compared to those who delivered at the health institution. G/eyesus et al(5) revealed that neonates who delivered at home were 6.36 times at risk of being neonatal sepsis compared to those who delivered at the health institution. Gebremedhin et al(6) found that the odds of neonatal sepsis was higher among newborns who delivered at home (AOR = 19, 95% CI: 1.74, 4.41) compared to those who delivered at the health institution. Getabelew et al revealed that neonates who delivered at home were 6 times at risk of being neonatal sepsis compared to those who delivered at the health institution. Four studies (Mersha et al., J Mugalu, Okaba, et al, Bua John et al) found no significant association between place of birth and neonatal sepsis.

Test of heterogeneity place of birth

Galbraith plot showed homogeneity and combining the result of nine studies the forest plot showed the overall estimate of AOR of home delivery was 2.67(95%C I: 1.15–4.00;I^2 = 0.0%;P = 0.996).I-Squared (I^2)and P-value also showed homogeneity.

Publication bias place of birth

A funnel plot showed an asymmetrical distribution. Egger's regression test p-value was 0.003, which indicated the presence of publication bias.

Trim and fill analysis place of birth

Trim and fill analysis was done and 4 studies were added and the total number of studies become 13.the pooled estimate of AOR of home delivery becomes 2.36(Figure 8).

Publication bias for the place of birth

The Beggs test shows there is publication bias regarding place of birth(Figure 9).

Trim and fill analysis place of birth

After adding 4 studies during trim and fill the effect size of place of birth changed from 2.57 to2,36(Figure 10).

Maternal history of UTI

Seven studies (Alebachew(32), Yirga(33), G/eyesus et al(5), Gebremedhin(6), Getabelew et al(34), Okaba et al(52) and Bua John et al(44) found a significant association between maternal history of and neonatal sepsis.

Alebachew et al revealed that the odds of neonatal sepsis was higher among neonates whose mother have a history of UTI(AOR = 2.9,95% CI: 1.48, 5.52) compared to those whose mother has no history of UTI. Yirga et al revealed that neonates whose mother have a history of UTI were 10.8 times at risk of being neonatal sepsis (95% CI: 3.44, 33.97) compared to those who delivered at the health institution. G/eyesus et al revealed that neonates whose mothers have a history of UTI were 7.06 times at risk of being neonatal sepsis compared to those whose mother has no history of UTI. Gebremedhin et al (6)found that the odds of neonatal sepsis was higher among neonates whose mother have a history of UTI (AOR = 15.04, 95% CI: 1.65, 3.38) compared to those whose mother has no history of UTI. Getabelew et al revealed that neonates whose mothers have a history of UTI were 6.45 times at risk of being

neonatal sepsis compared to those whose mother has no history of UTI. Okaba et al revealed that the odds of neonatal sepsis was higher among neonates whose mother have a history of UTI (AOR = 6.28, 95% CI: 1.62, 7.38) compared to those whose mother has no history of UTI. Bua John et al revealed that the odds of neonatal sepsis was higher among neonates whose mother have a history of UTI (AOR = 3.37,95% CI: 1.23, 9.22) compared to those whose mother has no history of UTI. Four studies (J Mugalu, Mersha, et al.) found no significant association between maternal history of UTI and neonatal sepsis.

Test of heterogeneity for the maternal history of UTI

Galbraith plot showed moderate heterogeneity and the forest plot showed the overall estimate of AOR of a place of birth was 2.083(95%C I: 0.24–3.93;I^2 = 69.1%;P = 0.001). I-Squared (I^2) and P-value also showed substantial heterogeneity. Main meta-analysis was done with random effect models(Figure 11).

Publication bias maternal history of UTI

A funnel plot showed a symmetrical distribution. Egger's regression test p-value was 0.928, which indicated the absence of publication bias(Figure 12).

Eight studies (Alebachew(32), Yirga(33), G/eyesus et al(5), Gebremedhin, Getabelew et al(34), Yusuf et al(36), Abate et al(5),J LeGeyt et al. (43))found significant association between gestational age and neonatal sepsis. Alebachew et al revealed that preterm neonates were 6.44 times at risk of being neonatal sepsis compared to term neonates. Yirga et al revealed that preterm neonates were 3.49 times at risk of being neonatal sepsis (95% CI: 1.14, 10.67) compared to term neonates. G/eyesus et al revealed that preterm neonates were 10.6 times at risk of being neonatal sepsis compared to term neonates. Gebremedhin et al found that the odds of neonatal sepsis was higher among preterm neonates (AOR = 38.6, 95% CI: 1.96, 9.51) compared to term neonates. Getabelew et al revealed that preterm neonates were 7.38 times at risk of being neonatal sepsis compared to term neonates. Yusuf et al revealed that the odds of neonatal sepsis was higher among preterm neonates (AOR = 2.92, 95% CI: 1.97, 4.31) compared to term neonates. Abate et al revealed that preterm neonates were 1.49 times at risk of being neonatal sepsis compared to term neonates. J LeGeyt et al. found that the odds of neonatal sepsis was higher among preterm neonates (AOR = 4.66, 95% CI: 0.65,0.98)compared to term neonates. Two studies (Mulongo N et al, A.M. R. LAVING et al., found no significant association between gestational age and neonatal sepsis.

Test of heterogeneity gestational age

Galbraith plot showed moderate heterogeneity and the forest plot showed the overall estimate of AOR of the place of birth was 1.56 (95% CI: 1.04–2.08; I^2 = 27.8%; P = 0.000). I-Squared (I^2)and P-value also showed moderate heterogeneity.

Publication bias gestational age

A funnel plot showed an asymmetrical distribution. Egger's regression test p-value was 0.000, which indicated the presence of publication bias.

Trim and fill analysis gestational age

Trim and fill analysis was done and 2 studies were added and the total number of studies become 12.the pooled estimate of AOR of preterm becomes 4.69(Figure 13).

Begg's test shows there is publication bias among studies regarding gestational age of respondents (Figure 14).

After trim and fill analysis two studies were added and the pooled effect size changed from 1.56 to 4.69 (Figure 15).

Prolonged labor

Four studies (Alebachew(32), Yirga(33), Getabelew et al(34), Okaba et al(52) found a significant association between prolonged labor and neonatal sepsis. Alebachew et al revealed that mothers of neonates who have a history of prolonged labor were 6.95 times at risk of being neonatal sepsis compared to those who have no history of prolonged labor. Yirga et al shown that mothers of neonates who have a history of prolonged labor were 11.92 times at risk of being neonatal sepsis compared to those who have no history of prolonged labor. Getabelew et al revealed that mothers of neonates who have a history of prolonged labor were 2.53 times at risk of being neonatal sepsis compared to those who have no history of prolonged labor. Okaba et al shown that mothers of neonates who have a history of prolonged labor were 12.4 times at risk of being neonatal sepsis compared to those who have no history of prolonged labor. Two studies (G/eyesus et al, J Mugalu)found no significant association between prolonged labor and neonatal sepsis.

Test of heterogeneity prolonged labor

Galbraith plot showed moderate heterogeneity and the forest plot showed the overall estimate of AOR of the place of birth was 3.23 (95% CI: −0.04–6.51; I^2 = 62.7%; P = 0.020).I-Squared (I^2) and P-value also showed substantial heterogeneity (Figure 16).

Publication bias prolonged labor

A funnel plot showed a symmetrical distribution. Egger's regression test p-value was 0.770, which indicated the absence of publication bias (Figure 17).

Seven studies (Yirga(33), G/eyesus et al(5), Gebremedhin(6), Okaba, et al, MUMBI S. et al(39), Mulongo N et al, A.M. R. LAVING et al.)found a significant association between PROM and neonatal sepsis. Yirga et al revealed that mothers of neonates who have history of PROM were 10.37 times at risk of being neonatal sepsis (95% CI: 2.3,46.5) compared to those who have no history of PROM.G/eyesus et al indicated that mothers of neonates who have history of PROM were 11.8 times at risk of being neonatal sepsis compared to those who have no history of PROM. Gebremedhin et al found that mothers of neonates who have a history of PROM were 27.1 times at risk of being neonatal sepsis (95% CI: 2.01, 6.39) compared to those who have no history of PROM. Okaba et al revealed that mothers of neonates who have a history of PROM were 4.74 times at risk of being neonatal sepsis compared to those who have no history of PROM. MUMBI S. et al indicated that mothers of neonates who have a history of PROM were 6.7 times at risk of being neonatal sepsis compared to those who have no history of PROM. Mulongo N et al, revealed that mothers of neonates who have history of PROM were 8.28 times at risk of being neonatal sepsis compared to those who have no history of PROM. A.M. R. LAVING et al. indicated that mothers of neonates who have history of PROM were 5.2 times at risk of being neonatal sepsis compared to those who have no history of PROM. Three studies (Getabelew*, Shitaye D, et al*,Mersha et al., *J Mugalu)* found no significant association between PROM and neonatal sepsis.

Test of heterogeneity PROM

Galbraith plot showed moderate heterogeneity and the forest plot showed the overall estimate of AOR of a place of birth was 1.95 (95% CI: 0.53–3.37; I^2 = 43.2%; P = 0.062).I-Squared (I^2)and P-value also showed moderate heterogeneity(Figure 18).

Publication bias PROM

A funnel plot showed an asymmetrical distribution. Egger's regression test p-value was 0.030, which indicated the presence of publication bias (Figure 19).

Trim and fill analysis PROM

Trim and fill analysis was done and 4 studies were added and the total number of studies become 15.The pooled estimate of AOR of preterm becomes 5.86(Figure 20).

Discussion

In this systematic review and meta-analysis, we explored the prevalence and determinants of neonatal sepsis in Eastern Africa. 26 studies were included in the final analysis. Based on the meta-analysis a significant proportion (more than 1 in 4) of neonates had neonatal sepsis in Eastern Africa. This shows that neonatal sepsis is a significant public health problem in Eastern Africa. We also identified factors that were significantly associated with neonatal sepsis in Eastern Africa. In this study, the pooled

prevalence of neonatal sepsis in Eastern Africa was. The pooled prevalence of neonatal sepsis in East Africa was 29.65 %(95%CI; 23.36–35.94).The results of this meta-analysis were higher than in studies conducted in other low and middle-income countries (LMICs), 17.2% (53).

These differences might be due to the socioeconomic and cultural differences between the countries. Moreover, the other obvious reason for the various might be the sample size, a collection of data from different settings (community and institution setting) as well as different study periods. Home delivery, maternal history of UTI, being preterm, prolonged labor and PROM were identified factors which significantly increase the risk of neonatal sepsis. A similar finding was also reported from the meta-analysis (54–56).

Conclusion

The prevalence of neonatal sepsis in Eastern Africa remains high. Home delivery, maternal history of UTI, being preterm, prolonged labor and PROM were identified factors which significantly increase the risk of neonatal sepsis. This review may help policy-makers and program officers to design neonatal sepsis preventive interventions.

Strength and limitations

This study has several strengths: First, we used a pre-specified protocol for search strategy and data abstraction and conducted quality assessment two independent investigators to lessen the possible assessor bias; Second, we employed subgroup and sensitivity analysis based on study country, study design, and publication year to identify the small study effect and the risk of heterogeneity in; third, The quality of the included studies was evaluated by two authors. Nevertheless, our systematic review and meta-analysis have some limitations: The result in this meta-analysis is derived from studies conducted in hospital settings. This limits the generalizability of the review findings.

Recommendations

For health workers

Professionals who are working in NICUs should adhere to aseptic techniques while carrying out neonatal invasive procedures. And attention should be given for neonates delivered from women with intranasal fever to prevent neonatal sepsis. Pregnant women should be screened for UTI and those diagnosed with urinary tract infection should be treated with a full course of antibiotics for the prevention of neonatal sepsis.

For mothers

Women who didn’t have complete ANC services, should get all their antenatal care schedules according to Ethiopian Ministry of Health (EMH) and take prompt action in seeking medical help during obstetric emergencies including rupture of membrane before labor.

For the Ministry of health and health service organizations
The government should increase the political priority given to sepsis by improving awareness of the growing medical and economic burden of neonatal sepsis. Primary care organizations should increase 36 their support towards maternal education and incorporate routine neonatal sepsis screening into the care of neonates and mothers.

For researchers
Researchers who are interested to conduct on neonatal sepsis should have to include neonates in the community which may increase the external validity of the study.

Abbreviations And Acronyms

EONS: early-onset neonatal sepsis; LONS: late-onset neonatal sepsis; PROM: prolonged rupture of membrane;UTI: Urinary Tract Infection; OR: Odds Ratio; UNICEF: The United Nations Children's Fund; WHO: World Health Organization; CI: Confidence interval; DHS: Demographic and Health Surveys; EDHS: Ethiopian Demographic and Health Survey

Declaration

Ethics approval and consent to participate

Not applicable because no primary data were collected

Consent for publication

Note applicable.

Availability of data and materials

Data is available and it can be accessed from the corresponding author when asked with a reasonable inquiry.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

BB conceives and designed the study. AM, MW and MA established the search strategy. All authors read the manuscript before they have given the final approval for publication and approved the submission of the paper.

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Tables

Table 1: Distribution of studies on the prevalence and determinants of neonatal sepsis in Ethiopia

Author	Study country	Study design	Sample size	Prevalence (%)	Quality status
Alebachew et al/2014(32)	Ethiopia	cross-sectional	306	-	Low risk
Yirga T.et al./ 2018(33)	Ethiopia	case-control	231	-	Low risk
Gebrehiwot et al/2012(25)	Ethiopia	cross-sectional	181	32.10	Low risk
G/eyesus et al /2017 et al.(5)	Ethiopia	cross-sectional	251	0.466	Low risk
Gebremedhin et al /2016(6)	Ethiopia	case-control	232		Low risk
Getabelew et al. /2017(34)	Ethiopia	cross-sectional	244	77.90	Low risk
Shitaye D et al/2010(35)	Ethiopia	cross-sectional	302	44.70	Low risk
Yusuf et al/2008(36)	Ethiopia	cross-sectional	578	28.70	Low risk
Abate et al/2016(5)	Ethiopia	cohort	1189	4.70	Low risk
. Mersha et al. /2019(37)	Ethiopia	cross-sectional	275	33.80	Low risk
. Petwa, K.W. et al./ 2015(48)	Uganda	cross-sectional	258	24.00	Low risk
. J Mugalu et al./ 2006(49)	Uganda	cross-sectional	290	37.90	Low risk
. N. A. Mobbs et al/2019(50)	Uganda	cohort	103	30.30	Low risk
. Kiwanuka J et al/2013(51)	Uganda	cross-sectional	80	32.50	Low risk
. Okaba et al /2018(52)	Uganda	cohort	325	11	Low risk
. Kwame et al/2011(38)	Kenya	case-control	100	-	Low risk
. MUMBI S. et al /2010(39)	Kenya	cross-sectional	104	-	Low risk
. Mulongo N et al/2018(40)	Kenya	cross-sectional	256	13.29	Low risk
. A.M.R. LAVING et al./ 2003(41)	Kenya	cross-sectional	84	17.90	Low risk
. Alison W A et al/2012(42)	Kenya	cross-sectional	4,849	23.00	Low risk
. J LeGeyt et al./ 2016(43)	Kenya	Cohort	1262	23.90	Low risk
. James A. et al./ 2005(44)	Kenya	cross-sectional	1783	12.80	Low risk

. Bua John et al/2015(44)	Uganda	cross-sectional	174	21.80	Low risk
. Abdelmoneim E. M et al./ 2014(45)	Sudan	cross-sectional	62	17.50	Low risk
. Wafa Babiker et al./ 2018(46)	Sudan	cross-sectional	119	37.80	Low risk
. Abdulrahman et al/2018(47)	Sudan	cross-sectional	200	62	Low risk

Table 2: Subgroup analysis of the prevalence of neonatal sepsis in Eastern Africa

Variables	Characteristics	Pooled prevalence (95% CI)	I^2(P-value)
By country	Ethiopia	38.31(17.43-59.19)	99.5%(<0.001)
	Uganda	24.4(14.91-33.90)	93.9%(<0.001)
	Kenya	18.28(12.64-23.91)	96.9%(<0.001)
	Sudan	39.26(13.31-65.22)	96.6%(<0.001)
By design	Cross-sectional	32.63(25.53-39.73)	98.4% (<0.001)
	Cohort	17.08(5.22-28.95)	98.7%(<0.001)
By year of publication	2000-2010	23.05(12.38-33.73)	96.7% (<0.001)
	2010-2015	33.01(20.62-45.40)	96.5%(<0.001)
	2015-2019	31.39(19.68-43.10)	99.1%(<0.001)

Table 3: Factors associated with neonatal sepsis

Factors	Odds ratio (AOR)	Author	Year
Place of birth	4.20	Alebachew et al.	2014
	4.36	Yirga et al.	2018
	6.36	G/eyesus et al.	2017
	19.00	Gebremedhin et al.	2016
	6.00	Getabelew et al.	2017
Maternal history of UTI	2.9	Alebachew et al.	2014
	10.8	Yirga et al.	2018
	7.06	G/eyesus et al.	2017
	15.04	Gebremedhin et al.	2016
	6.45	Getabelew et al.	2017
	6.28	Okaba et al.	2018
	3.37	Bua John et al.	2015
	1.65	J Mugalu et al.	2006
	1.12	Mersha et al.	2019
Gestational age(preterm)	6.44	Alebachew et al.	2014
	3.49	Yirga et al.	2018
	10.60	G/eyesus et al.	2017
	38.60	Gebremedhin et al.	2016
	7.38	Getabelew et al.	2017
	2.92	Yusuf et al.	2008
	1.49	Abate et al.	2016
	4.66	J LeGeyt et al.	2016
	7.22	Mulongo N et al	2018
	6.45	A.M.R. LAVING et al.	2003
Prolonged labor	6.95	Alebachew et al.	2014
	11.92	Yirga et al.	2018
	1.29	G/eyesus et al.	2017
	1.41	J Mugalu et al.	2006
	2.53	Getabelew et al.	2017
	12.4	Okaba et al.	2018
PROM	5.20	A.M.R. LAVING et al.	2003
	10.37	Yirga et al.	2018
	11.80	G/eyesus et al.	2017
	27.10	Gebremedhin et al.	2016
	1.28	Getabelew et al.	2017
	1.85	Mersha et al.	2019
	1.56	J Mugalu et al.	2006
	4.74	Okaba et al.	2018
	6.7	MUMBI S. et al.	2010
	8.28	Mulongo N et al.	2018

Figures

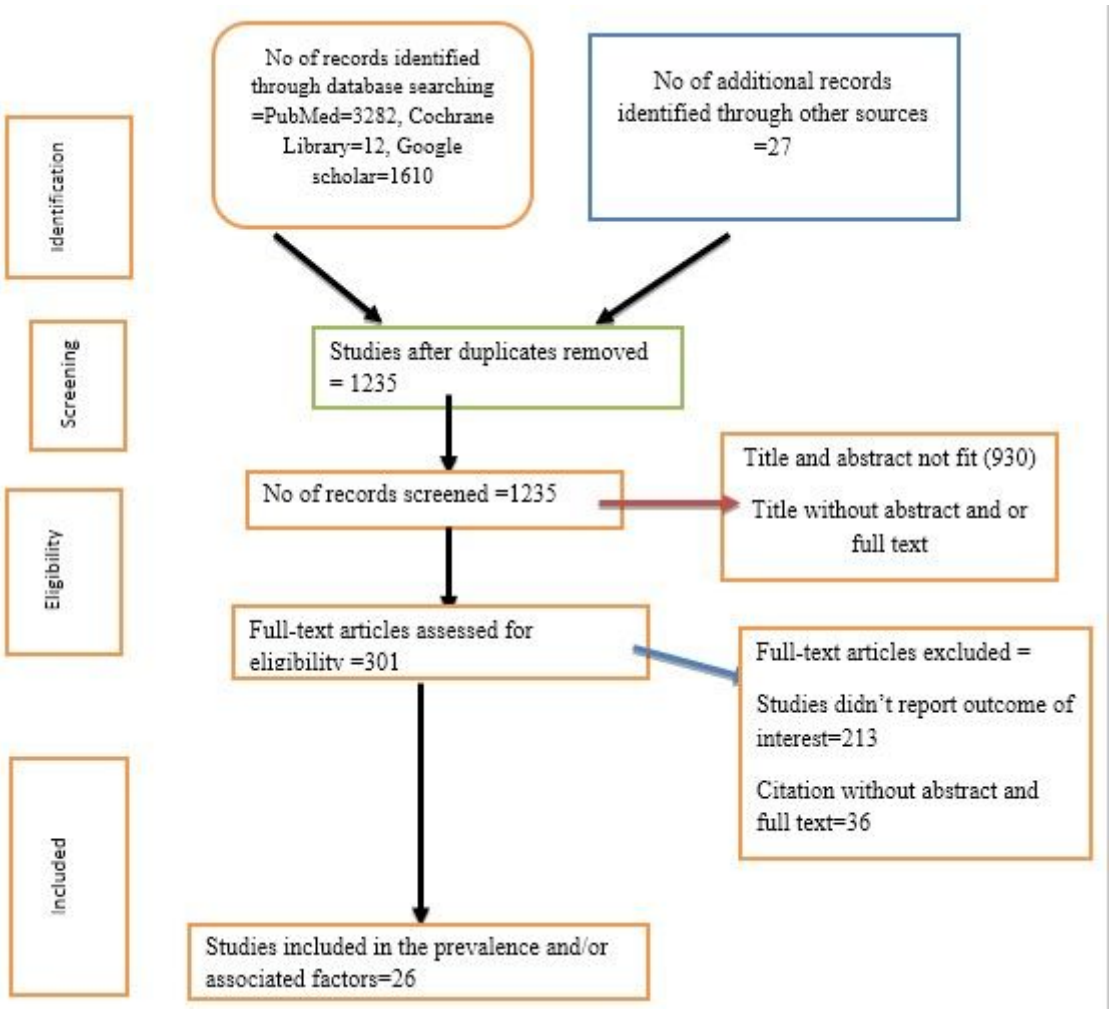
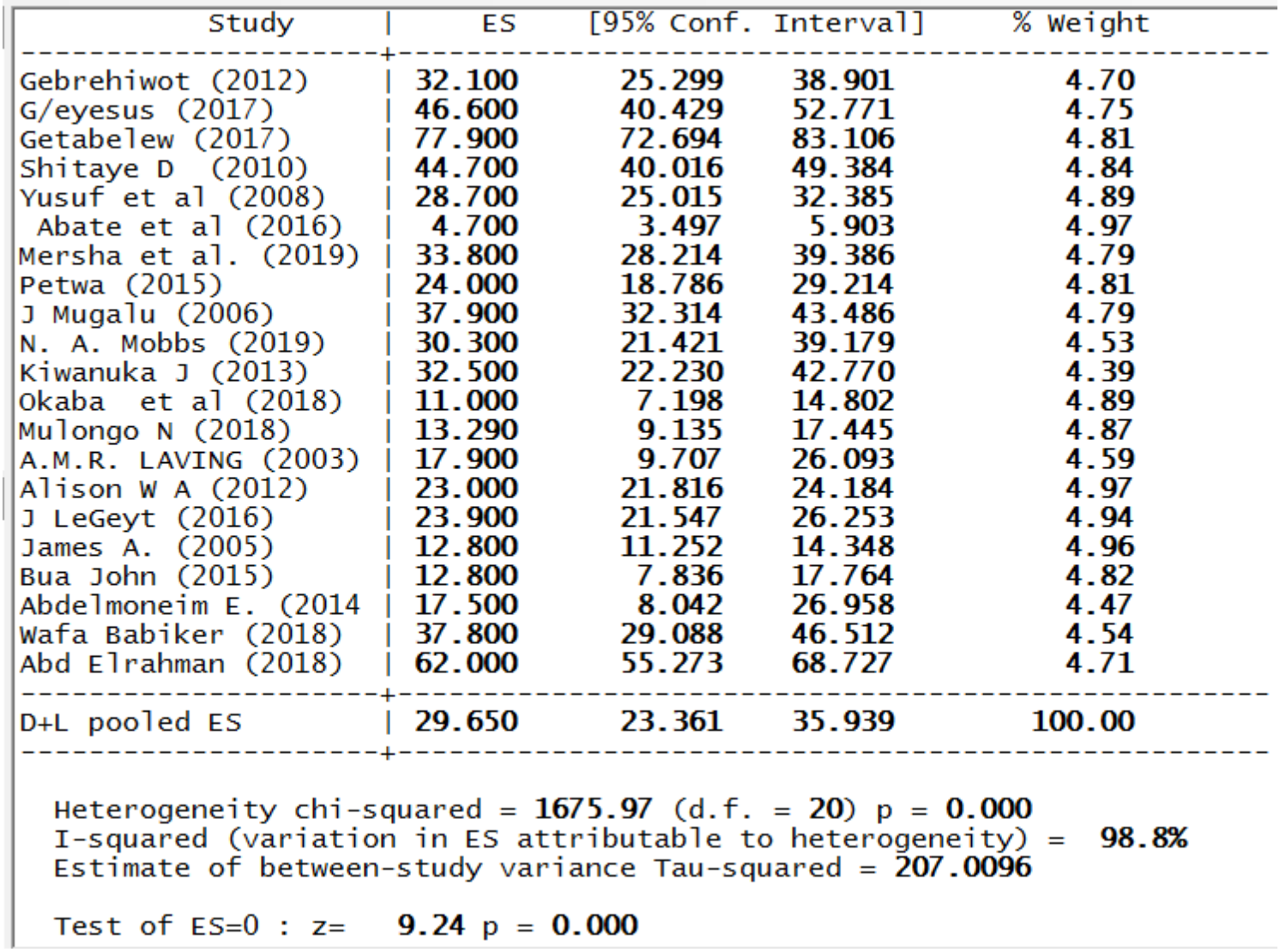


Figure 1

PRISMA flowchart of the selection of studies



Study	ES	[95% Conf.	Interval]	% Weight
Gebrehiwot (2012)	32.100	25.299	38.901	4.70
G/eyesus (2017)	46.600	40.429	52.771	4.75
Getabelew (2017)	77.900	72.694	83.106	4.81
Shitaye D (2010)	44.700	40.016	49.384	4.84
Yusuf et al (2008)	28.700	25.015	32.385	4.89
Abate et al (2016)	4.700	3.497	5.903	4.97
Mersha et al. (2019)	33.800	28.214	39.386	4.79
Petwa (2015)	24.000	18.786	29.214	4.81
J Mugalu (2006)	37.900	32.314	43.486	4.79
N. A. Mobbs (2019)	30.300	21.421	39.179	4.53
Kiwanuka J (2013)	32.500	22.230	42.770	4.39
Okaba et al (2018)	11.000	7.198	14.802	4.89
Mulongo N (2018)	13.290	9.135	17.445	4.87
A.M.R. LAVING (2003)	17.900	9.707	26.093	4.59
Alison W A (2012)	23.000	21.816	24.184	4.97
J LeGeyt (2016)	23.900	21.547	26.253	4.94
James A. (2005)	12.800	11.252	14.348	4.96
Bua John (2015)	12.800	7.836	17.764	4.82
Abdelmoneim E. (2014	17.500	8.042	26.958	4.47
Wafa Babiker (2018)	37.800	29.088	46.512	4.54
Abd Elrahman (2018)	62.000	55.273	68.727	4.71
D+L pooled ES	29.650	23.361	35.939	100.00

Heterogeneity chi-squared = 1675.97 (d.f. = 20) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 98.8%
Estimate of between-study variance Tau-squared = 207.0096

Test of ES=0 : z= 9.24 p = 0.000

Figure 2

Prevalence of neonatal sepsis

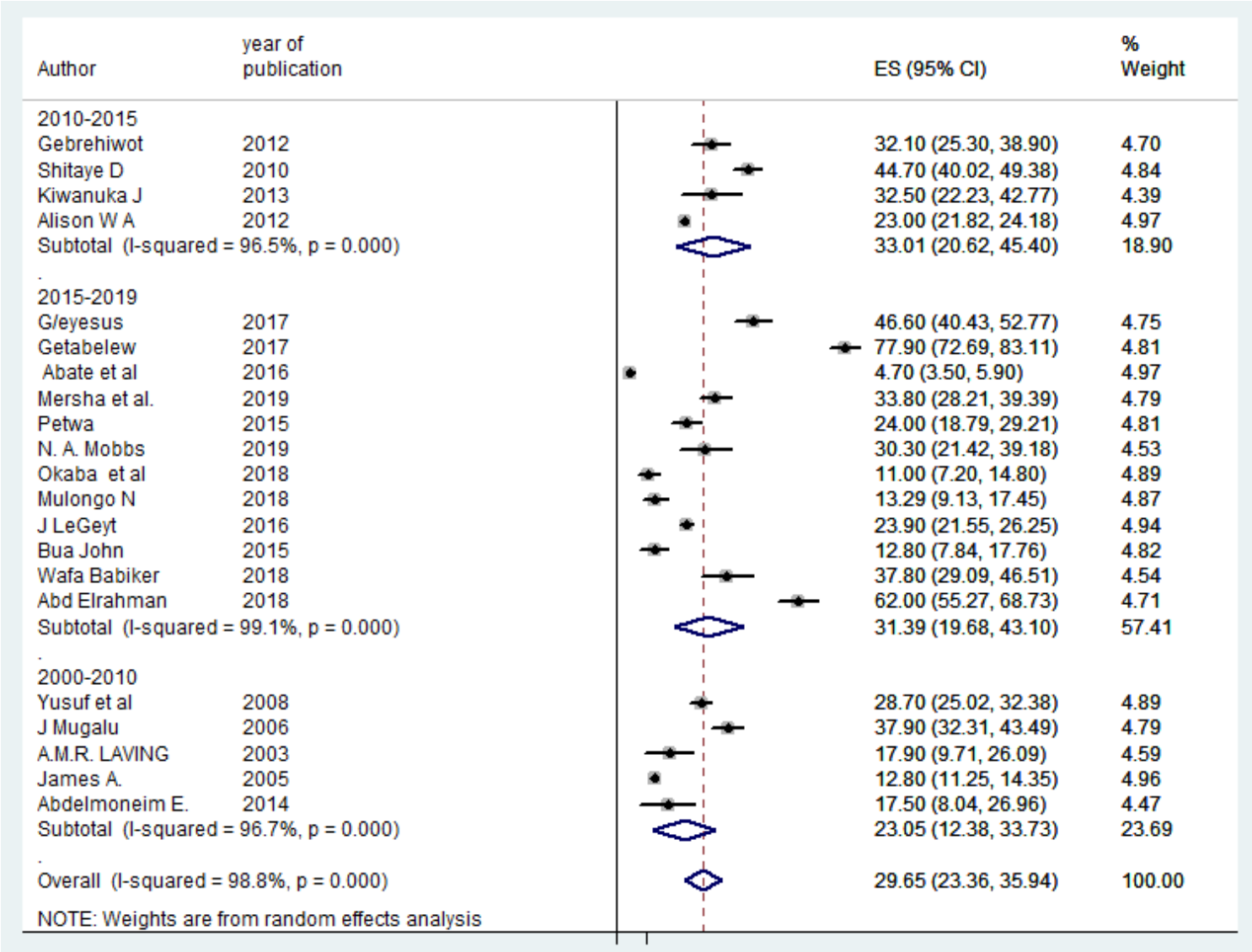


Figure 3

Subgroup analysis by year of publication

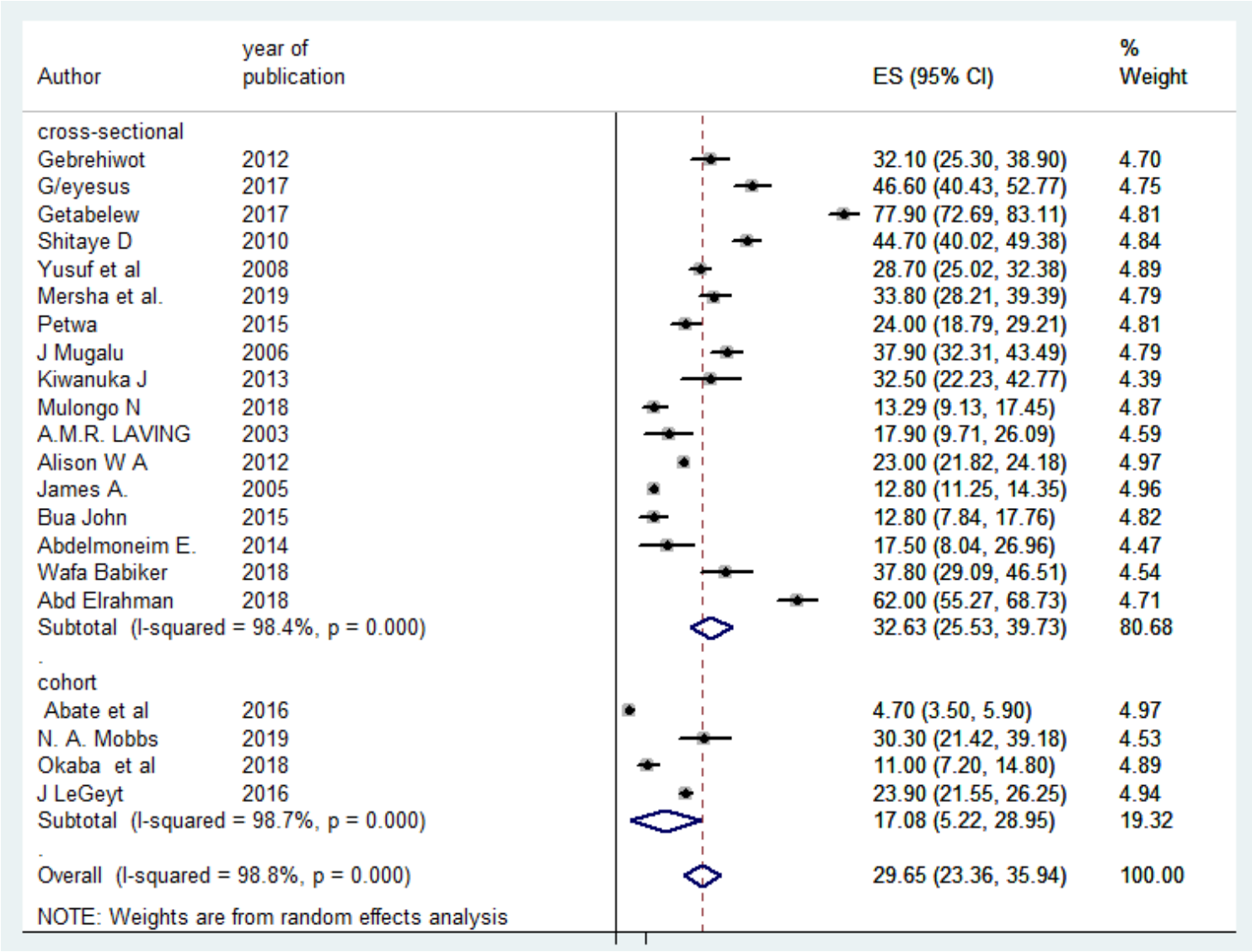


Figure 4

Subgroup analysis by study design

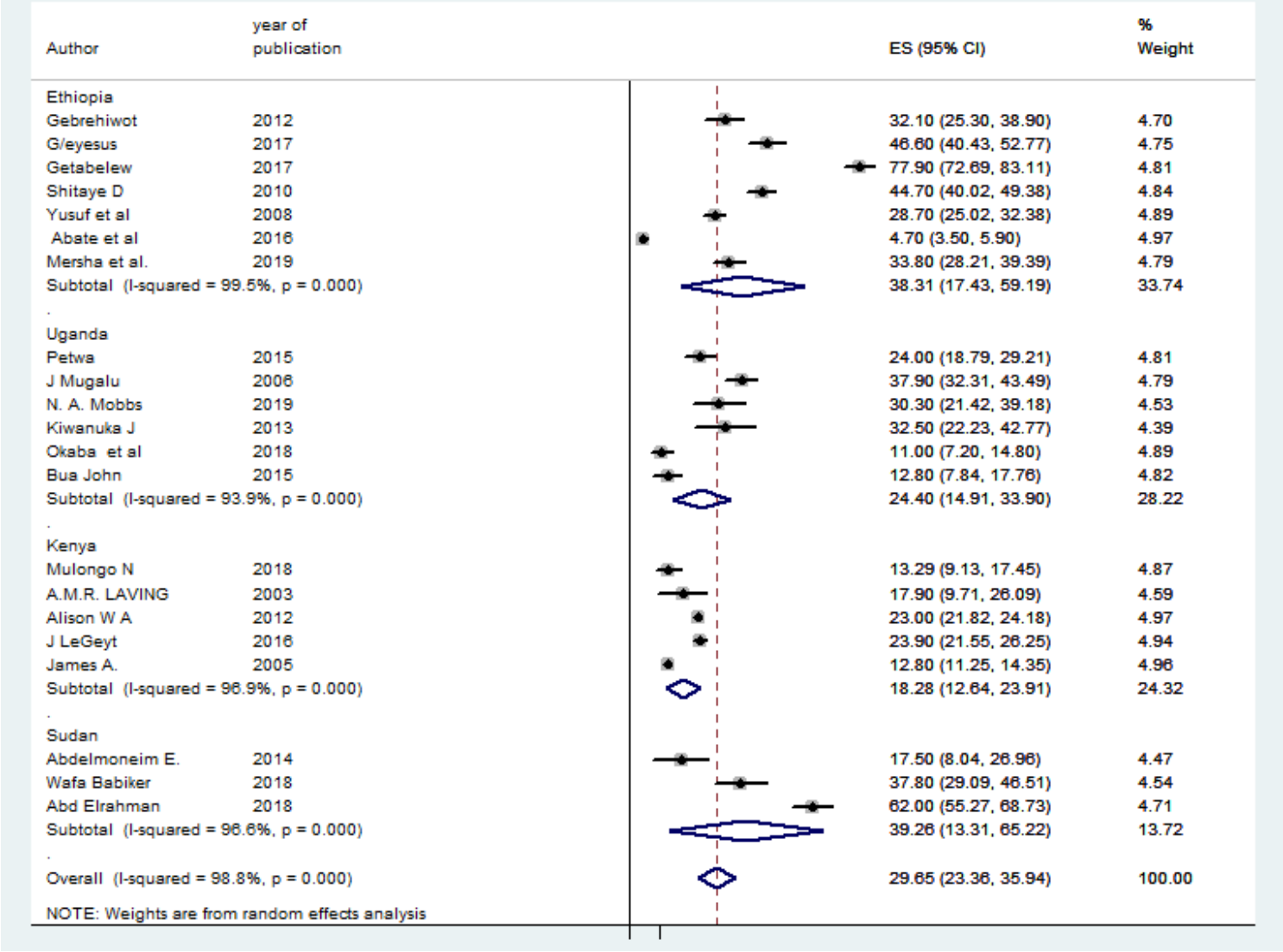
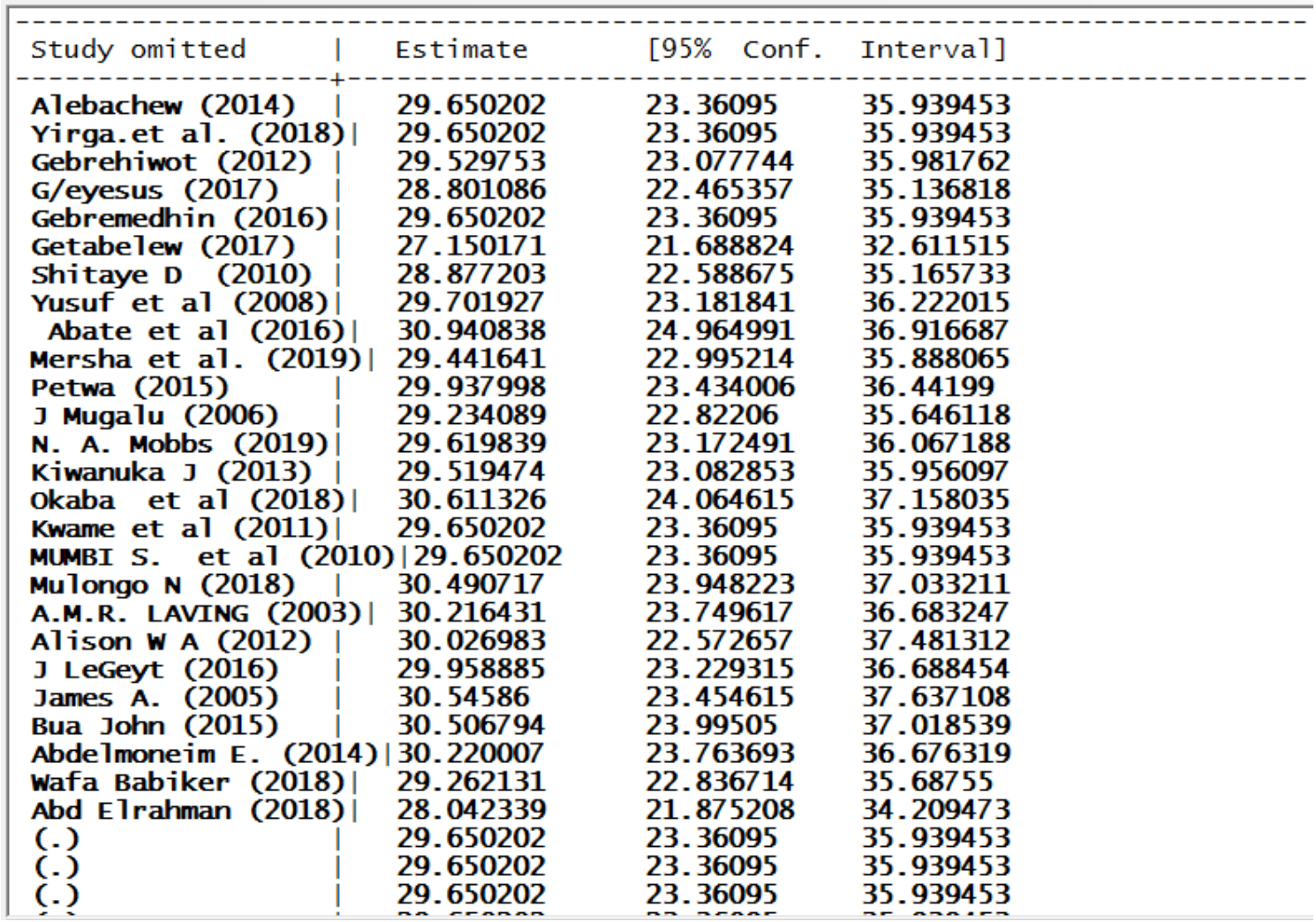


Figure 5

Subgroup analysis by country



Study omitted	Estimate	[95% Conf.	Interval]
Alebachew (2014)	29.650202	23.36095	35.939453
Yirga.et al. (2018)	29.650202	23.36095	35.939453
Gebrehiwot (2012)	29.529753	23.077744	35.981762
G/eyesus (2017)	28.801086	22.465357	35.136818
Gebremedhin (2016)	29.650202	23.36095	35.939453
Getabelew (2017)	27.150171	21.688824	32.611515
Shitaye D (2010)	28.877203	22.588675	35.165733
Yusuf et al (2008)	29.701927	23.181841	36.222015
Abate et al (2016)	30.940838	24.964991	36.916687
Mersha et al. (2019)	29.441641	22.995214	35.888065
Petwa (2015)	29.937998	23.434006	36.44199
J Mugalu (2006)	29.234089	22.82206	35.646118
N. A. Mobbs (2019)	29.619839	23.172491	36.067188
Kiwanuka J (2013)	29.519474	23.082853	35.956097
Okaba et al (2018)	30.611326	24.064615	37.158035
Kwame et al (2011)	29.650202	23.36095	35.939453
MUMBI S. et al (2010)	29.650202	23.36095	35.939453
Mulongo N (2018)	30.490717	23.948223	37.033211
A.M.R. LAVING (2003)	30.216431	23.749617	36.683247
Alison W A (2012)	30.026983	22.572657	37.481312
J LeGeyt (2016)	29.958885	23.229315	36.688454
James A. (2005)	30.54586	23.454615	37.637108
Bua John (2015)	30.506794	23.99505	37.018539
Abdelmoneim E. (2014)	30.220007	23.763693	36.676319
Wafa Babiker (2018)	29.262131	22.836714	35.68755
Abd Elrahman (2018)	28.042339	21.875208	34.209473
(.)	29.650202	23.36095	35.939453
(.)	29.650202	23.36095	35.939453
(.)	29.650202	23.36095	35.939453

Figure 6

Sensitivity analysis

```
. funnel p sep

. metafunnel p sep

Note: default data input format (theta, se_theta) assumed.

. metabias p sep, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      19
         Std. Dev. of Score =   33.10 (corrected for ties)
          Number of Studies =      21
                          z  =    0.57
                    Pr > |z| =   0.566
                          z  =    0.54 (continuity corrected)
                    Pr > |z| =   0.587 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	9.344931	3.969172	2.35	0.029	1.037359	17.6525
bias	7.787437	2.715326	2.87	0.010	2.104195	13.47068

Figure 7

Publication bias

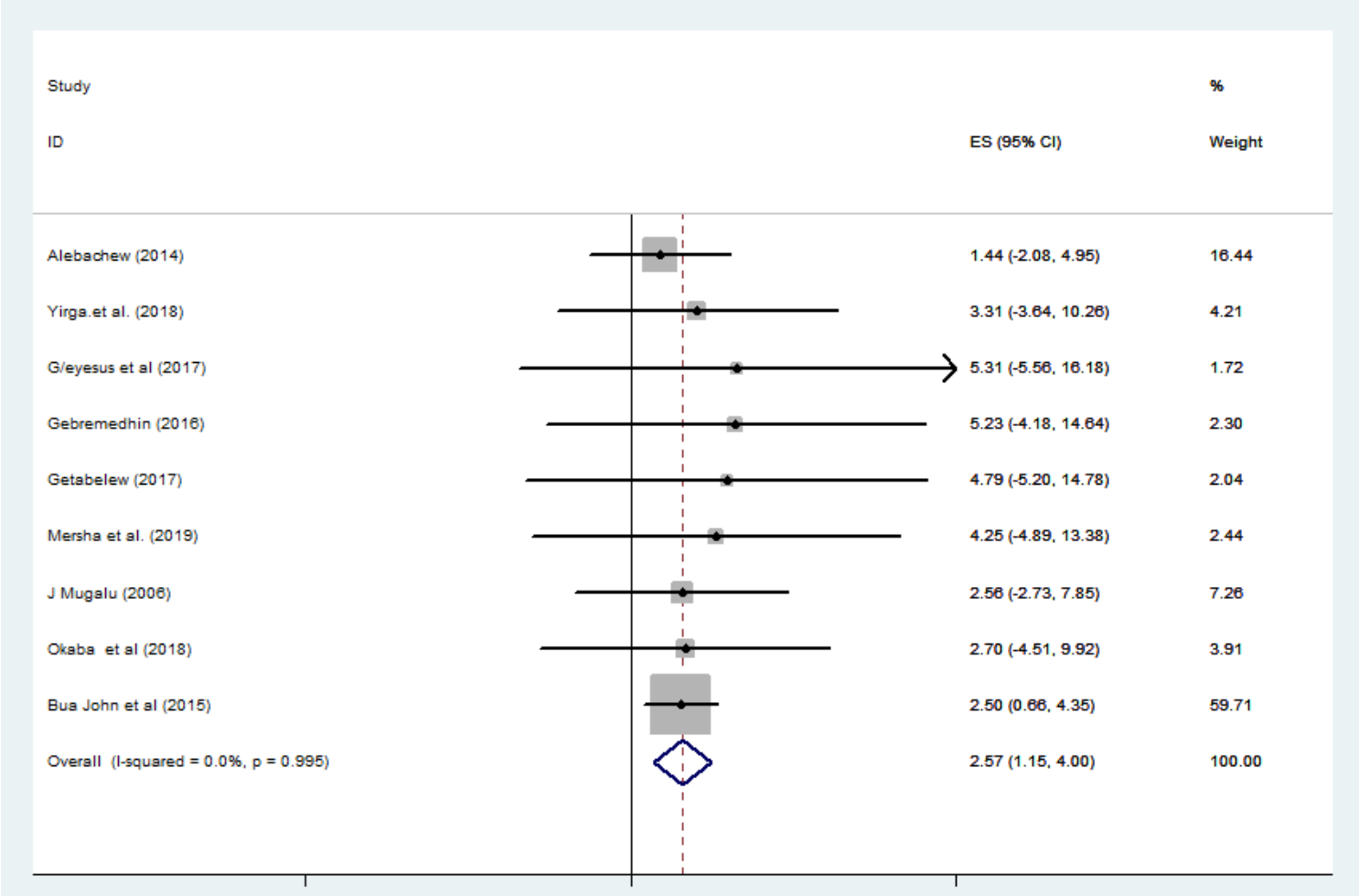


Figure 8

The pooled effect of place of birth

```
. funnel logorplaceofbirth selogorplaceofbirth

. metafunnel logorplaceofbirth selogorplaceofbirth

Note: default data input format (theta, se_theta) assumed.

. metabias logorplaceofbirth selogorplaceofbirth, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      28
         Std. Dev. of Score =    9.59
          Number of Studies =       9
                          z  =    2.92
                    Pr > |z| =   0.004
                          z  =    2.81 (continuity corrected)
                    Pr > |z| =   0.005 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.785863	.3958206	4.51	0.003	.8498958	2.72183
bias	.4444601	.1813956	2.45	0.044	.0155277	.8733924

Figure 9

Publication bias for the place of birth

```
Meta-analysis

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-------------------------------------------------------
Fixed  |   2.572   1.146   3.998    3.536    0.000       9
Random |   2.572   1.146   3.998    3.536    0.000

Test for heterogeneity: Q=  1.321 on 8 degrees of freedom (p= 0.995)
Moment-based estimate of between studies variance =  0.000

Trimming estimator: Linear
Meta-analysis type: Fixed-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------
    1     |    2.572     37         3          45
    2     |    2.409     40         4           6
    3     |    2.360     41         4           2
    4     |    2.360     41         4           0

Filled
Meta-analysis

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-------------------------------------------------------
Fixed  |   2.360   0.991   3.729    3.379    0.001      13
Random |   2.360   0.991   3.729    3.379    0.001

Test for heterogeneity: Q=  2.438 on 12 degrees of freedom (p= 0.998)
Moment-based estimate of between studies variance =  0.000
```

Figure 10

Trim and fill analysis place of birth

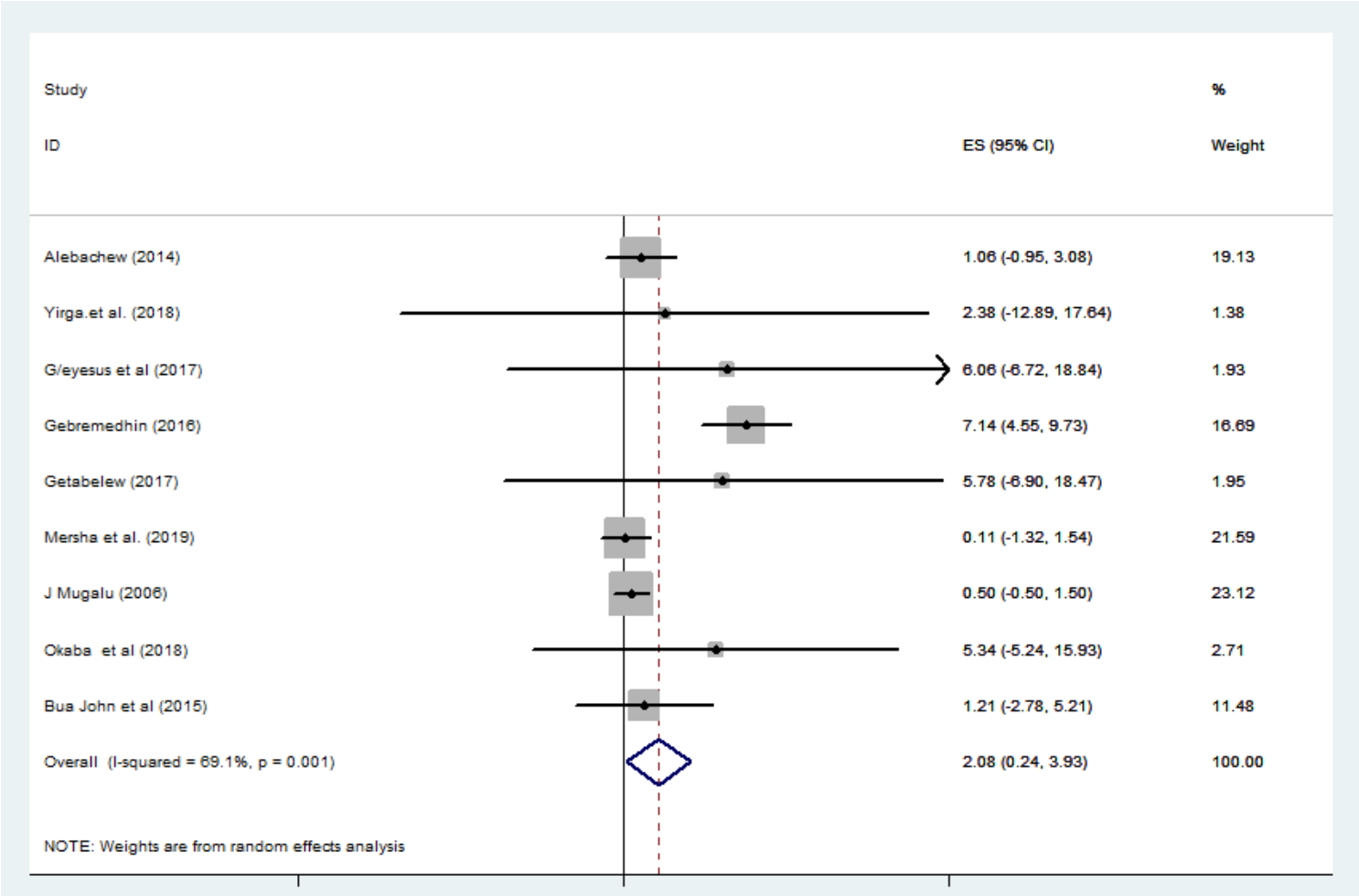


Figure 11

The pooled estimate of UTI

```
  Test of ES=0 : z=   2.21 p = 0.027

. metafunnel logoruti selogoruti

Note: default data input format (theta, se_theta) assumed.

. metabias logoruti selogoruti, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      16
         Std. Dev. of Score =    9.59
          Number of Studies =       9
                          z  =    1.67
                    Pr > |z| =   0.095
                          z  =    1.56 (continuity corrected)
                    Pr > |z| =   0.118 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0867448	.9291132	0.09	0.928	-2.110259	2.283748
bias	1.195277	.8524146	1.40	0.204	-.8203632	3.210917

Figure 12

publication bias of gestational age (preterm)

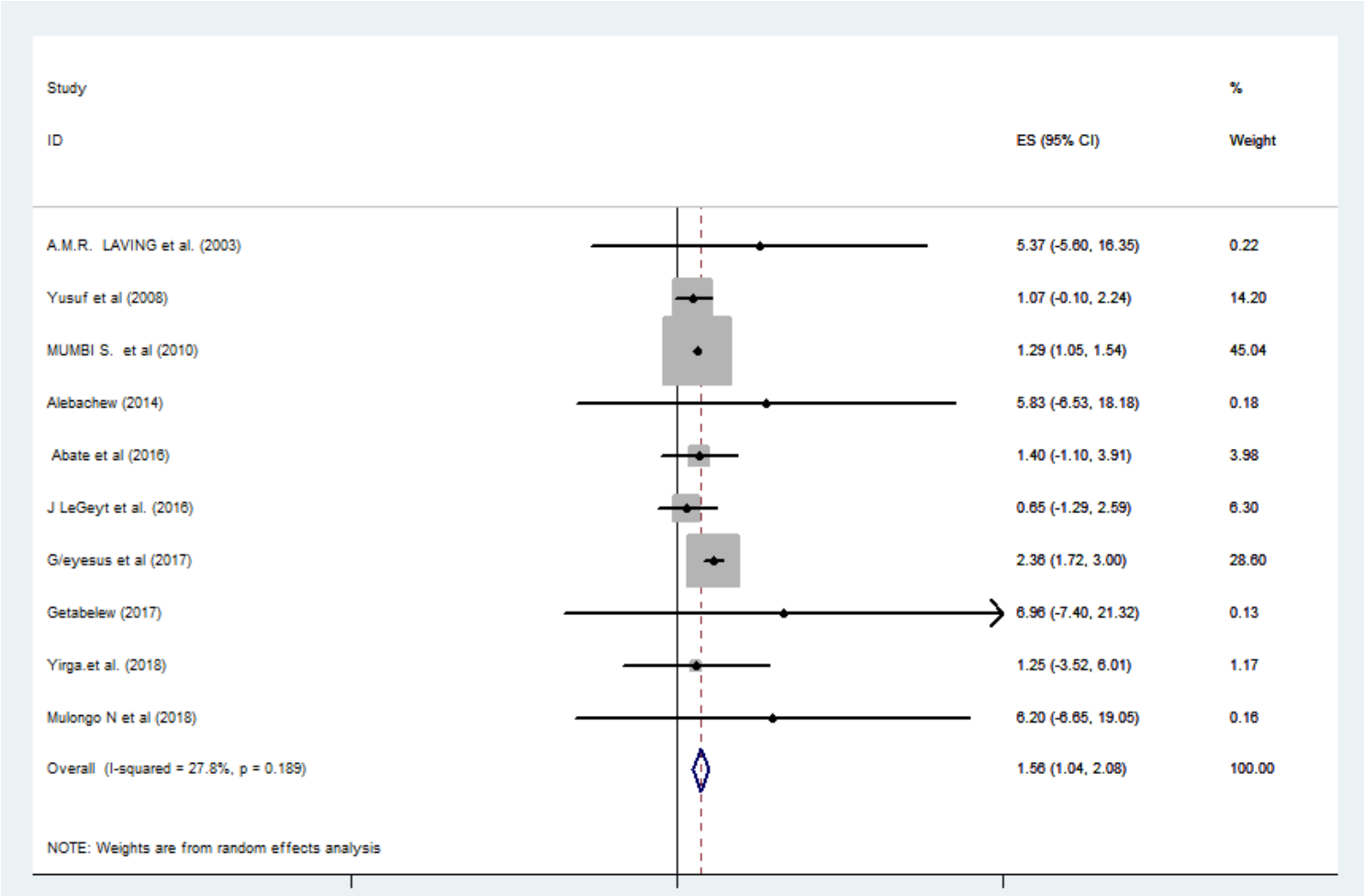


Figure 13

Preterm pooled estimate

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.312667	.1579785	8.31	0.000	.9483679	1.676966
bias	.4987142	.4413783	1.13	0.291	-.5191061	1.516534

```
. metabias  logorpreterm selogorpreterm, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      23
         Std. Dev. of Score =   11.18
          Number of Studies =      10
                          z  =    2.06
                    Pr > |z| =   0.040
                          z  =    1.97 (continuity corrected)
                    Pr > |z| =   0.049 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.312667	.1579785	8.31	0.000	.9483679	1.676966
bias	.4987142	.4413783	1.13	0.291	-.5191061	1.516534

Figure 14

Publication bias preterm

```
Meta-analysis

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   1.412   1.190   1.634   12.477    0.000      10
Random |   1.563   1.042   2.084    5.878    0.000

Test for heterogeneity: Q= 12.457 on 9 degrees of freedom (p= 0.189)
Moment-based estimate of between studies variance =  0.141

Trimming estimator: Linear
Meta-analysis type: Random-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------
    1     |    1.563     39         2          55
    2     |    1.546     39         2           0

Filled
Meta-analysis (exponential form)

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   4.094   3.280   5.111   12.457    0.000      12
Random |   4.691   2.937   7.493    6.469    0.000

Test for heterogeneity: Q= 13.452 on 11 degrees of freedom (p= 0.265)
Moment-based estimate of between studies variance =  0.100
```

Figure 15

Trim and fill

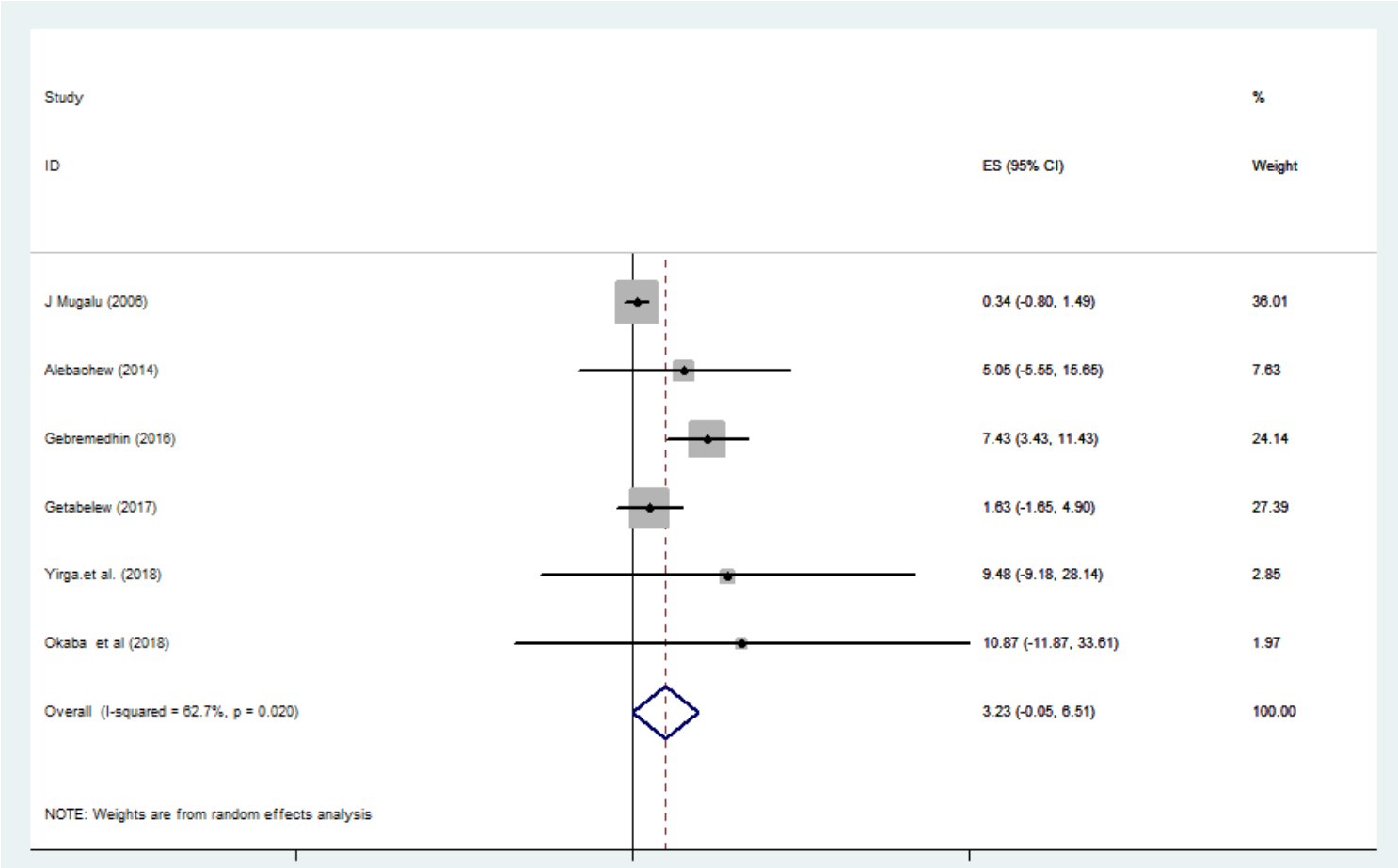


Figure 16

Pooled estimate of prolonged labor

```
  Test of ES=0 : z=   1.93 p = 0.053

. metabias logorprolongedlabour selogorprolongedlabour, ci graph(egger)

Error: option 'ci' specified but varlist has only 2 variables.

. metabias logorprolongedlabour selogorprolongedlabour, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =       7
         Std. Dev. of Score =    5.32
          Number of Studies =       6
                          z  =    1.32
                    Pr > |z| =   0.188
                          z  =    1.13 (continuity corrected)
                    Pr > |z| =   0.260 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.2843735	.9098906	-0.31	0.770	-2.810635	2.241888
bias	1.49585	.7030224	2.13	0.100	-.4560529	3.447753

Figure 17

test of publication bias prolonged labor

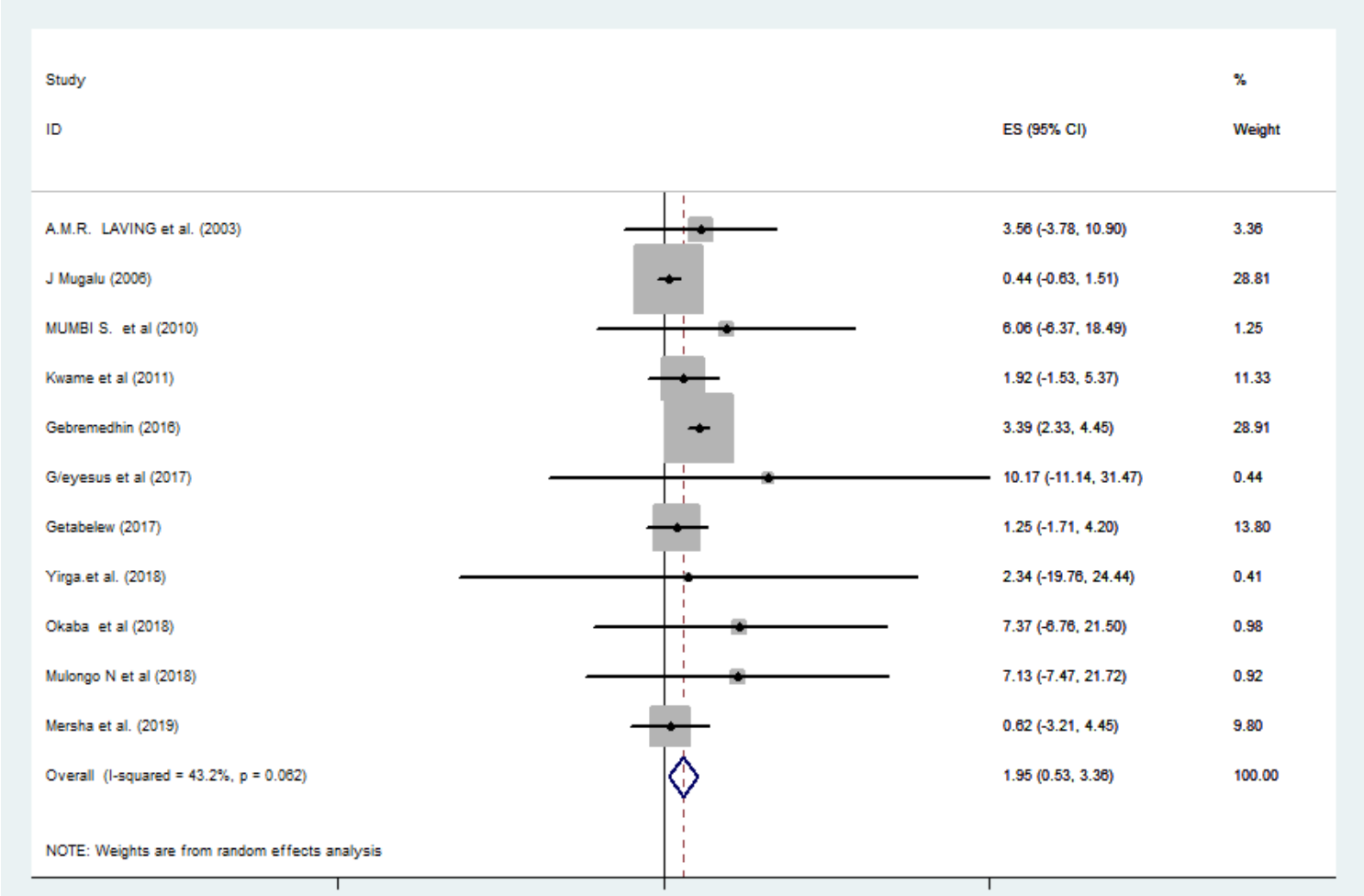


Figure 18

pooled estimate PROM

```
        bias |   .3816046   .5565692     0.69   0.510    -.8774423    1.640651
------------------------------------------------------------------------------

. metafunnel  logorprom selogorprom

Note: default data input format (theta, se_theta) assumed.

. metabias logorprom selogorprom, graph(egger)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      19
         Std. Dev. of Score =   12.85
          Number of Studies =      11
                          z  =    1.48
                    Pr > |z| =   0.139
                          z  =    1.40 (continuity corrected)
                    Pr > |z| =   0.161 (continuity corrected)

Egger's test

------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   1.610713   .6542963     2.46   0.036     .1305924    3.090834
        bias |   .3816046   .5565692     0.69   0.510    -.8774423    1.640651
------------------------------------------------------------------------------
```

Figure 19

Publication bias PROM

```
Meta-analysis

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   1.913   1.218   2.608    5.397    0.000        11
Random |   1.945   0.528   3.362    2.690    0.007

Test for heterogeneity: Q= 17.616 on 10 degrees of freedom (p= 0.062)
Moment-based estimate of between studies variance =  1.517

Trimming estimator: Linear
Meta-analysis type: Fixed-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-------------------------------------
    1     |    1.913     54         4          66
    2     |    1.866     54         4           0

Filled
Meta-analysis (exponential form)

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   6.461   3.236  12.904    5.287    0.000        15
Random |   5.861   1.636  21.000    2.716    0.007

Test for heterogeneity: Q= 19.736 on 14 degrees of freedom (p= 0.139)
Moment-based estimate of between studies variance =  1.121
```

Figure 20

Trim and fill analysis for PROM

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.doc