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Birth prevalence of encephalocele in Africa: A systematic review and meta-analysis

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ABSTRACT

Objective: To identify the birth prevalence of encephalocele in Africa.

Methods: We carried out a systematic search of the following databases (PubMed/Medline, PubMed Central, Joanna Briggs Institute (JBI) Library, Cochrane Library, Web of Science, Google Scholar, Science Direct, African Journals Online, and Embase), using search terms (prevalence, encephalocele, "neural tube defects", newborns/neonates/"live births"/"stillbirths", Africa, and their MeSH Terms) up to March 28, 2020. All essential data were abstracted using a standardized data extraction format, and the JBI quality appraisal checklist was used to evaluate the quality of studies. Statistically, the Cochrane Q test and I^2 test were used to examine heterogeneity across studies. The random-effect meta-analysis model was considered to estimate the prevalence of encephalocele. Subgroup, sensitivity, meta-regression, and time trend analysis were carried out. The publication bias was checked using Egger and Begg's tests.

Results: Twenty-one relevant studies were identified and provided a total of 4, 661, 161 births. In this systematic review and meta-analysis, the pooled birth prevalence of encephalocele in Africa was 0.12 % (or 12 per 10, 000 births) (95 % CI: 0.04, 0.19 %). The overall prevalence of birth encephalocele estimated using the median from studies was 0.03 % (IQR (inter-quartile range) = 0.009 – 0.082 %). Higher prevalence of encephalocele was detected in Kenya 0.99 % (95 % CI: 0.99, 1.00 %), Nigeria 0.21 % (CI: 0.09, 0.33 %), Sudan 0.06 % (CI: 0.02, 0.10 %), and Ethiopia 0.05 % (CI: 0.02, 0.07 %). The prevalence of encephalocele for live births was 0.19 %, for both live birth and stillbirths was 0.04 %, for studies done after 2010 was 0.07 %, and for studies done before 2010 was 0.13 %.

Conclusions: This review indicates a high prevalence, but studies were limited suggesting the need for additional research.

Keywords: Africa, encephalocele, prevalence, systematic review and meta-analysis

Strength and limitations of the review

- This review provided cumulative and up-to-date evidence about encephalocele in Africa.
- The findings of the present review should be interpreted based on some limitations; the review represented the studies from the twenty-one African countries due to limited available data.
- The prevalence estimate did not include the terminated pregnancy/cases of encephalocele; this should be considered in interpreting the estimates as it may decrease the prevalence estimates.
- Moreover, the adequacy of the sample size or variability in sample size may affect the estimated report.

INTRODUCTION

Encephalocele is a birth defect related to skull defects characterized by partial lacking of bone fusion leaving a gap through which a portion of the brain protrudes [1-3]. It is a type of birth defect of the neural tube that affects the brain [2-6]. The neural tube is a narrow channel that folds and closes during the third and fourth weeks of gestation to form the brain and spinal cord of the fetus [1, 4, 6]. Following the defect, an opening anywhere along the center of the skull from the nose to the back of the neck will occur, but usually at the back of the head, at the top of the head, or between the forehead and the nose [1, 3]. Encephalocele is a sac-like protrusion of the brain and meninges through an opening in the skull (occipital area, the back of the skull, is mostly affected) [2, 6]. The portion of the brain that protrudes outside the skull is often covered by skin or a thin membrane so that the malformation resembles a small sac [5]. Its herniation process appears as a pedunculated (having a stalk-like base) or sessile (attached directly to its base without a stalk) cystic lesion [2]. Only meninges protrude through the bone opening in the sac, which is referred to as cranial meningocele, but the herniated sac contains brain tissue and meninges, the defect is called encephalocele or meningoencephalocele. If the herniated sac included a ventricle, the malformation is called hydroencephalocele. Encephalocele containing tissue from the brain and spinal cord is called encephalomyelocele [1-9]. Anatomically, encephalocele can be classified into convexity (occipital, parietal, sagittal, occipitocervical), sincipital (frontoethmoidal, nasofrontal, nasoethmoidal, nasoorbital, interfrontal, craniofacial cleft), basal (intranasal, sphenoorbital, sphenomaxillary, spenopharyngeal), and atretic [8, 10, 11]. Evidence has shown that encephalocele is a post-neurulation defect and a developmentally different type of neural tube defect from the closure-related types [8, 12].

The incidence of encephalocele varies with race and geographical location, with the overall incidence between 0.8 and 4 per 10,000 births [7, 8, 11]. Encephalocele, according to the Centers for Disease Control and Prevention estimates, occurs in one per 10,000 births in the United States each year [1].

Most encephaloceles are large and significant birth defects that are diagnosed before birth. However, in extremely rare cases, some encephaloceles may be small and go unnoticed. The exact cause of encephalocele is unknown, but scientists believe that the disorder results from the combination of many factors [1-3].

The symptoms of an encephalocele can vary from one individual to another depending upon many different factors including size, location, and the amount and kind of brain tissue herniating from the skull. The location of the encephalocele is very important since there are distinct clinical implications for treatment and prognosis for anterior (usually do not contain brain tissue and have a better prognosis) and posterior encephalocele (often associated with neurological problems). Generally, surgical management is needed to place the protruding part of the brain and meninges back into the skull and close the opening in the skull. However, neurologic problems due to encephalocele will still be present and long-term treatment depends on the child's condition may be needed [1, 2].

Encephalocele, even though it can be minimized due to different preventive and control measures, is the major cause of death and disabilities in newborns [6, 10, 13, 14]. This review provides valuable information to the government, policymakers, health professionals, researchers, medical students, communities, and Non-Governmental Organizations to play a role in reducing the burden of the encephalocele and making further research possible. Moreover, little is known about the magnitude of encephalocele in the region as a whole. Thus, the present systematic review and meta-analysis aim to identify the pooled birth prevalence of encephalocele in Africa.

METHODS

Reporting of the findings and review registration

The current systematic review and meta-analysis were reported under the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements [15] (Supplementary File 1). The review protocol has been sent for registration on PROSPERO, with a registration ID of 242161.

Search strategies

PubMed/Medline, PubMed Central, Cochrane Library, JBI Library, Science Direct, Web of Science, African Journals Online, WHO, UCSF, and Embase databases were systematically searched for relevant studies (reference lists of identified articles were also navigated) up to August 28, 2020. The primary search was conducted in an advanced PubMed database (using search terms prevalence, encephalocele, "neural tube defects", newborns/neonates/"live births"/"stillbirths", Africa, and their MeSH Terms). The core search terms and phrases were considered interchangeably in different databases. Moreover, grey literature was retrieved using Google and Google Scholar searches. The full search strategy is being shown online (Supplementary File 2).

Eligibility criteria

Inclusion criteria

Published and unpublished full-text studies in any period and study designs (a cross-sectional, prospective cohort that included original data) that report the birth prevalence of encephalocele in Africa were included in this review.

Exclusion criteria

Case reports, conferences, editorials, anonymous reports, and studies without full access (after contacted the corresponding author two times through email) were excluded from the review. Moreover, a study was excluded if the total number of cases and the total number of births included in the study were not explicitly stated.

Review outcomes

The outcome of the current review was the pooled birth prevalence of encephalocele in Africa. Birth prevalence of encephalocele is defined as the number of encephalocele cases of live births and/or stillbirths at birth (numerator) from the total number of births (live births and/or stillbirths) during the study period (denominator).

Quality assessment

The quality of each study was evaluated by the JBI quality appraisal checklist [16]. The JBI critical appraisal checklist was adapted for the studies reporting the prevalence data (it contains nine items) (Supplementary File 3). Two reviewers (MO and AD) independently evaluated the quality of each study using the format. Disagreements between reviewers that arise during evaluating the quality were solved by taking the average score of the two reviewers. In the end, the study was considered low risk if the study scored five and above points of all quality assessment items of the study design [17].

Study selection and data abstraction

After retrieving all studies from the databases, it was imported into the reference manager, an Endnote Version 7 Software to remove the duplicate studies. Then, the reviewers screened studies based on the title and abstract for possible inclusion. After deeply reviewing full-text studies and

including the eligible studies, all essential data were extracted independently by two reviewers (MO and AD) using a standardized data abstraction format. This format included primary author, publication year, sample size, country of the study, study design, duration of the study, study setting, prevalence period, folic acid fortification policy, and birth prevalence of encephalocele.

Meta-analysis

The data were abstracted in Microsoft Excel and exported into STATA 11 Statistical Software for further analysis. All studies prevalence reports in the different denominators have been transformed into per hundred births to maintain uniformity.

A forest plot was used to visualize heterogeneity between studies and it was statistically assessed using the Cochrane Q test and the I^2 test [18]. This showed that there is significant heterogeneity among studies (P-value<0.001). Therefore, a random-effect meta-analysis model was applied to estimate the pooled prevalence of encephalocele [19, 20]. Sub-group analysis was performed based on selected variables (the study country, study design, birth outcome, period prevalence, and folic acid fortification status) to reduce the heterogeneity. A sensitivity analysis was done to see the influence of a single study on the overall estimate of meta-analysis. Meta-regression analysis was accounted for to identify the source of heterogeneity. A time-trend analysis was conducted as well.

Assessment of risk of bias

Graphically, Egger's plot was used to visualize the publication bias. Objectively, Egger's regression test and Begg's test statistics were used to detecting publication bias [21, 22]. Thus, a P-value ≤ of 0.05 was considered to be publication bias.

Patient and public involvement

"No patient involved."

RESULTS

Study selection

A total of two hundred eighty-nine articles were initially retrieved on the prevalence of encephalocele in Africa through PubMed, Google Scholar, and others from Cochrane, JBI Library, WHO, Medline, UCSF, African Journal Online, Science Direct, and Embase. Of these, ninety-four were excluded due to duplicated articles. From the remaining one hundred ninety-five studies, one hundred fifty-five studies were excluded after reviewing the titles and abstracts because it were found non-relevant for this review. Full texts of the remaining forty studies were screened. Twenty-one studies fulfilled the inclusion criteria and were included in the systematic review and meta-analysis [23-43] (Figure 1).

Characteristics of the original studies

The included studies were either cross-sectional (n=16) or prospective cohort studies (n=5) [23-43]. Of all studies, five were conducted in Nigeria [25, 28, 32, 41, 42], three in Ethiopia [23, 27, 29], two in South Africa [36, 37], two in Algeria [26, 35], and two in Sudan [31, 39]. Studies conducted in Tunisia, Kenya, Democratic Republic (DR) of Congo, Egypt, Cameron, Ghana, and Tanzania were also identified [24, 30, 33, 34, 38, 40, 43]. All studies included in this review were facility-based studies, published in the year between 1992 and 2020. South Africa, Nigeria, Cameron, and Ghana have mandatory folic acid fortification with Wheat Flour, Maize Flour, and Rice at this time. Ethiopia has a voluntary folic acid fortification policy. Studies considered after the implementation of

mandatory folic acid fortification were Ghana and Nigeria. Generally, twenty-one studies reported a total of 4, 661,161 births, ranged from 956 to 3,803, 889 births [24, 29] (Table 1).

Table 1: The characteristics of studies included in the systematic review and meta-analysis, 2020

First author	Year	Country	Study design	Sample size	Period prevalence	Duration	Birth outcome	Prevalence (%)	Quality status
Gedefaw et al.[23]	2018	Ethiopia*	CS	8,677	Feb 2016-Aug 2016	7	LB+SB	0.035	LR
Nasri et al.[24]	2014	Tunisia	CS	3,803,889	1991-2011	240	LB+SB	0.004	LR
Anyanwu et al.[25]	2015	Nigeria	CS	1,456	Apr 2013-Dec 2013	9	LB	0.069	LR
Houchar et al.[26]	2008	Algeria	CS	28,500	2004 -2006	36	LB+SB	0.004	LR
Abebe et al.[27]	2020	Ethiopia*	CS	45,951	Sep 2011-Dec 2015	60	LB+SB	0.009	LR
Nnadi et al.[28]	2016	Nigeria	PS	10,163	Jan2011-Dec 2013	36	LB+SB	0.01	LR
Legesse et al.[29]	2019	Ethiopia*	PS	956	Oct 2018 -Apr 2019	7	LB+SB	0.11	LR
Ahuka et al.[30]	2006	DR of Congo	RS	8,824	Jan 1993 -Aug 2001	96	LB	0.023	LR
Oumer et al.[31]	2016	Sudan	CS	36,785	Aug 2014 - Jul 2015	12	LB+SB	0.038	LR
Alrede et al.[32]	1992	Nigeria	PS	5,977	Jun 1987 -Jun 1990	36	LB+SB	0.134	LR
Mohammed et al. [33]	2011	Egypt	CS	5,000	Mar 2007-Oct 2007	7	LB	0.04	LR
Njamnshi et al.[34]	2008	Cameron	RS	52,710	Jun 1997 -Dec 2006	120	LB+SB	0.009	LR
Houcher et al.[35]	2012	Algeria	RS	28,500	2010-2012	36	LB+SB	0.003	LR
Venter et al.[36]	1995	South Africa	PS	10,380	Jun 1989 -Dec 1992	40	LB	0.019	LR
Buccimazza et al. [37]	1994	South Africa	RS	516,252	Jan 1973 -Dec 1992	240	LB+SB	0.008	LR
Kinasha et al.[38]	2003	Tanzania	RS	34,000	Jan 2000 -Jan 2002	24	LB	0.029	LR
Elsheikh et al.[39]	2009	Sudan	PS	18,378	Feb 2003 -Jan 2004	12	LB+SB	0.082	LR
Alhassan et al[40]	2017	Ghana*	RS	35,426	Jan 2010 -Dec 2014	48	LB+SB	0.008	LR
Toma et al.[41]	2018	Nigeria*	CS	1,046	Oct 2013 -Sep 2016	35	LB+SB	0.669	LR
Audu et al.[42]	2004	Nigeria	CS	2,250	Jul 2000 - Jun	48	LB	0.178	LR

Githuku et al.[43]	2014	Kenya	CS	6,041	2003 2005 – 2010	72	LB	0.999	LR

Key: Mandatory and voluntary folic acid fortification policy; CS: Cross-sectional; PS: Prospective; RS: Retrospective; LR: Low Risk; LB: Live births; SB: Stillbirths

Quality of the studies

Using JBI quality appraisal criteria, all included studies were evaluated for their quality. Each study was evaluated using the JBI critical appraisal checklist for prevalence studies, it has nine questions/items with options of Yes, No, Unclear, or Not Applicable. The quality assessment grading for all items was based on the JBI descriptions for each item (methodological guidance for systematic reviews of epidemiological studies reporting the prevalence data). Accordingly, the quality score of studies was ranged between five and eight. Eleven studies scored above seven and others scored between five and seven. Therefore, no studies had a considerable risk of low quality [23-43] (Table 1).

Meta-analysis

Prevalence of encephalocele

In the present meta-analysis, the pooled birth prevalence of encephalocele was 0.12 % (or 12 per 10,000 births) (95 % CI: 0.04, 0.19 %). A Forest plot showed that there was statistically significant heterogeneity across the studies. Therefore, the random-effect meta-analysis model was applied to pool the overall prevalence of the studies (Figure 2). Considering all included studies, the median value of birth encephalocele was 0.03 % and the inter-quartile range was between 0.009 and 0.082 %. The minimum and maximum values of birth encephalocele were 0.003 and 0.999 %, respectively.

Subgroup analysis

Subgroup analysis based on the study country, study design, birth outcome, period prevalence, and folic acid fortification status was carried out to see the variation of the prevalence across the studies.

Subgroup analysis based on the study country was performed to see the pooled prevalence of each country in Africa. High pooled prevalence of encephalocele was detected in Kenya 0.99 % (95 % CI: 0.99, 1.00 %), Nigeria 0.21 % (CI: 0.09, 0.33 %), Sudan 0.06 % (CI: 0.02, 0.10 %), and Ethiopia 0.05 % (CI: 0.02, 0.07 %) (Table 2). In the present review, statistically significant heterogeneity between countries was detected (P-value= 0.001-0.04, I^2= 75.5-99.9 %). Therefore, the Der Simonian and Laird's (D+L) pooled prevalence method was considered because it is more conservative than the inverse variance method (I-V). The difference between countries was significant (P-value<0.001).

Table 2: The pooled prevalence of encephalocele among African countries, 2020

S. No.	Country	Prevalence of encephalocele % (95 % CI)
1.	Ethiopia	0.05 (0.02, 0.07)
2.	Tunisia	0.004 (0.004, 0.004)
3.	Nigeria	0.21 (0.09, 0.33)
4.	Algeria	0.003 (0.003, 0.004)
5.	DR of Congo	0.02 (0.02, 0.03)
6.	Sudan	0.06 (0.02, 0.10)
7.	Egypt	0.04 (0.04, 0.05)
8.	Cameron	0.009 (0.008, 0.01)
9.	South Africa	0.01 (0.003, 0.02)
10.	Ghana	0.008 (0.007, 0.009)
11.	Tanzania	0.03 (0.03, 0.031)
12.	Kenya	0.999 (0.998, 1.000)
Total	**D+L pooled**	**0.12 (0.04, 0.19)**

Subgroup analysis based on study design, using the D+L method (P-value<0.001, I^2 = 99.4-100 %), the pooled prevalence of encephalocele for cross-sectional was 0.20 % and for prospective cohort study design was 0.07 % (Figure 3).

Subgroup analysis based on birth outcome was done to see the burden in live births only (LB) and both live births and stillbirths (LB+SB). The pooled prevalence of encephalocele for live births was 0.19 % (95 % CI: -0.29, 0.67 %) and for both live birth and stillbirths was 0.04 % (95 % CI: 0.03, 0.04 %) (Figure 4).

Subgroup analysis based on period prevalence was carried out to observe the prevalence between prevalence periods. Considering two prevalence periods (>2010 and <=2010 years), the prevalence of encephalocele for studies done after 2010 was 0.07 % (95 % CI: 0.06, 0.08 %) and for studies done before 2010 was 0.13 % (95 % CI: 0.02, 0.24 %) (Figure 5).

Subgroup analysis based on folic acid fortification policy was considered (P-value<0.001, I^2 =99.8-100 %) and the prevalence of encephalocele for countries that had a mandatory and voluntary folic acid fortification was 0.12 % (95 % CI: 0.10, 0.14 %), and for countries that had no either a mandatory or voluntary fortification was 0.11 % (95 % CI: 0.01, 0.20 %).

Meta-regression analysis

In the present systematic review and meta-analysis, sample size (P-value = 0.014), year of publication (P-value = 0.20), duration of the study in months (P-value = 0.134), and the JBI quality score (P-value = 0.10) were analyzed for the source of heterogeneity. The only sample size was significant for the source of heterogeneity. Considering this, studies were categorized based on sample size (studies with ≥ 10,000 births and with < 10, 000 births), the prevalence of encephalocele

for studies having ≥ 10, 000 births were 0.02 % and for studies having below 10, 000 births were 0.25 %.

Sensitivity analysis

In this review, no study was found that has a special influence over others on the overall estimation of meta-analysis (Figure 6). Essentially, all studies have uniform confidence intervals.

Even if uniform influence has been detected in sensitivity analysis, we looked at the state of the overall estimates by omitting some studies in the meta-analysis (leave-one-out analyses) that supposed to be the source of heterogeneity (the study that was done by Nasri et al., Buccimazza et al., Toma et al., and Githuku et al., for instance). Accordingly, the pooled birth prevalence of encephalocele after omitting the study done by Nasri was 0.124%, or 12.4 per 10,000 births, (95% CI:-0.003, 0.251), after omitting both studies done by Nasri and Buccimazza was 0.13% (95% CI:-0.04, 0.30), after omitting the study done by Githuku was 0.04% (95% CI: 0.04, 0.04), after omitting both studies done by Toma and Githuku was 0.031% (95% CI: 0.029, 0.034), and after omitting four studies together was 0.042% (95% CI: 0.04, 0.05). However, the heterogeneity between studies was not significantly decreased (P-value= 0.000, I^2= 99.7-100%) and the influence of some studies over the total estimate was increased, therefore, we continued with the original estimates.

Time trend analysis

The time trend analysis showed the relationship between the prevalence of encephalocele and publication year. In this trend in Africa, the highest peak of encephalocele in prevalence was observed between 2014 and 2015, and between 2017 and 2018 (Figure 7).

Publication bias

Publication bias was estimated using the Egger's regression tests (B-coefficient of bias: 137; P-value = 0.303). Meaningfully, Egger's plot supported its results (Figure 8). Therefore, there was no significant publication bias in estimating the prevalence of encephalocele.

DISCUSSION

Encephalocele is a congenital malformation of the central nervous system. The hidden burden of encephalocele was very high in Africa. Data is lacking on the true burden of this condition, leading to neglect in the treatment and prevention by health systems in Africa. The responsible authorities or bodies have neglected this defect too. The effects of the malformation are related to substantial mortality, disability, and psychological costs (the psychosocial problem of having an infant with a "monstrous outlook" or "two heads"). Although encephalocele is a rare congenital anomaly, it is correlated with severe morbidity and mortality if untreated [7, 8]. The utilization of folic acid supplementation and termination of pregnancies that are prenatally diagnosed with encephalocele have reduced the occurrence or incidence of this type of congenital defect especially in-developed (high-income) countries. Encephalocele can be minimized through preventive measures including folic acid supplementation or fortification of staple foods [3-6, 13, 14]. Providing information to responsible bodies about the burden of encephalocele in Africa is essential in decision making and planning of preventive services. Therefore, the present systematic review and meta-analysis were carried out to identify the prevalence of birth encephalocele in Africa.

In this meta-analysis, the birth prevalence of encephalocele was 0.12 % (or 12 per 10,000 births). This finding is very high compared to different findings reported elsewhere (ranged from 0.8 to 4.0

per 10,000 births) [4-8, 11]. Besides, our finding is substantially higher than that reported by certain high-income countries (1.0 per 10,000 births) [1] and low-and middle-income countries (2.1 per 10,000 births) [44]. The review result suggested that low-and middle-income countries were mostly affected by this malformation every year [44]. However, the review did not include studies from Africa except for two studies.

Recent evidence proves that there is variation in the prevalence of encephalocele in time, place, and population to populations [8]. Our analysis also showed significant variation between countries in Africa, prevalence period to period, and between birth outcomes. Therefore, subgroup analysis was performed based on study country, design, birth outcome, prevalence period, and the presence of folic acid fortification policy. Accordingly, in this review, a significant difference in the prevalence of encephalocele in different countries of Africa was detected. High prevalence of encephalocele was detected in Kenya 0.99 %, Nigeria 0.21 %, Sudan 0.06 %, and Ethiopia 0.05 %. Maybe this difference comes due to the levels of knowledge of mothers about folic acid supplementation, the country's health policies regarding folic acid fortification, and other preventive measures. The notion of the presence of geographical variation between the countries was supported by the previous studies [7, 8, 6]. Using time trend analysis, the variation in different publication years of the different studies was observed. The highest peak of encephalocele in prevalence was observed between 2014 and 2015, and between 2017 and 2018. The increment in prevalence during these mentioned years may be due to a change in detection methods, an increment of the practices in documenting and reporting cases, or a real increase in disease. The prevalence estimate in live births was higher than estimates from both live births and stillbirths. This may be due to the fact that most studies that included only live births in this review were done before the year 2010 (high prevalence of encephalocele was detected). Besides, the prevalence estimate is affected by the status of a mandatory folic acid

fortification policy. Substantially, instituted folic acid fortification is the main factor that determines the burden of encephalocele in one country. Surprisingly, all studies in this review were facility-based studies. Thus, underestimation of encephalocele estimates may have occurred because it does not include many stillbirths and home births that are delivered in the community setting (included the participants either delivered at the hospital or coming for seeking care). Furthermore, in pooled estimates, the presence of variation across countries may affect the prevalence of the defect in Africa.

CONCLUSION

This systematic review and meta-analysis showed that a high prevalence of encephalocele was detected in Africa. The prevalence of encephalocele was very high in Kenya, Nigeria, Sudan, and Ethiopia. The higher prevalence of encephalocele was observed in the studies that included only live births and in studies done before the year 2010. Therefore, the reviewers recommend that special awareness creation for reproductive-age women to focus on prevention in order to minimize the burden of encephalocele. Limited available data on encephalocele in Africa indicated the need for additional primary research that would improve the estimated burden of the encephalocele and recommend favorable aid policies on preventive measures.

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Abbreviations: Not applicable.

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Figure Legends

Figure 1: Study selection flow diagram; a figure adapted from the PRISMA) group statement for this review, 2020.

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa, 2020

Figure 3: Subgroup analysis based on study design in Africa, 2020

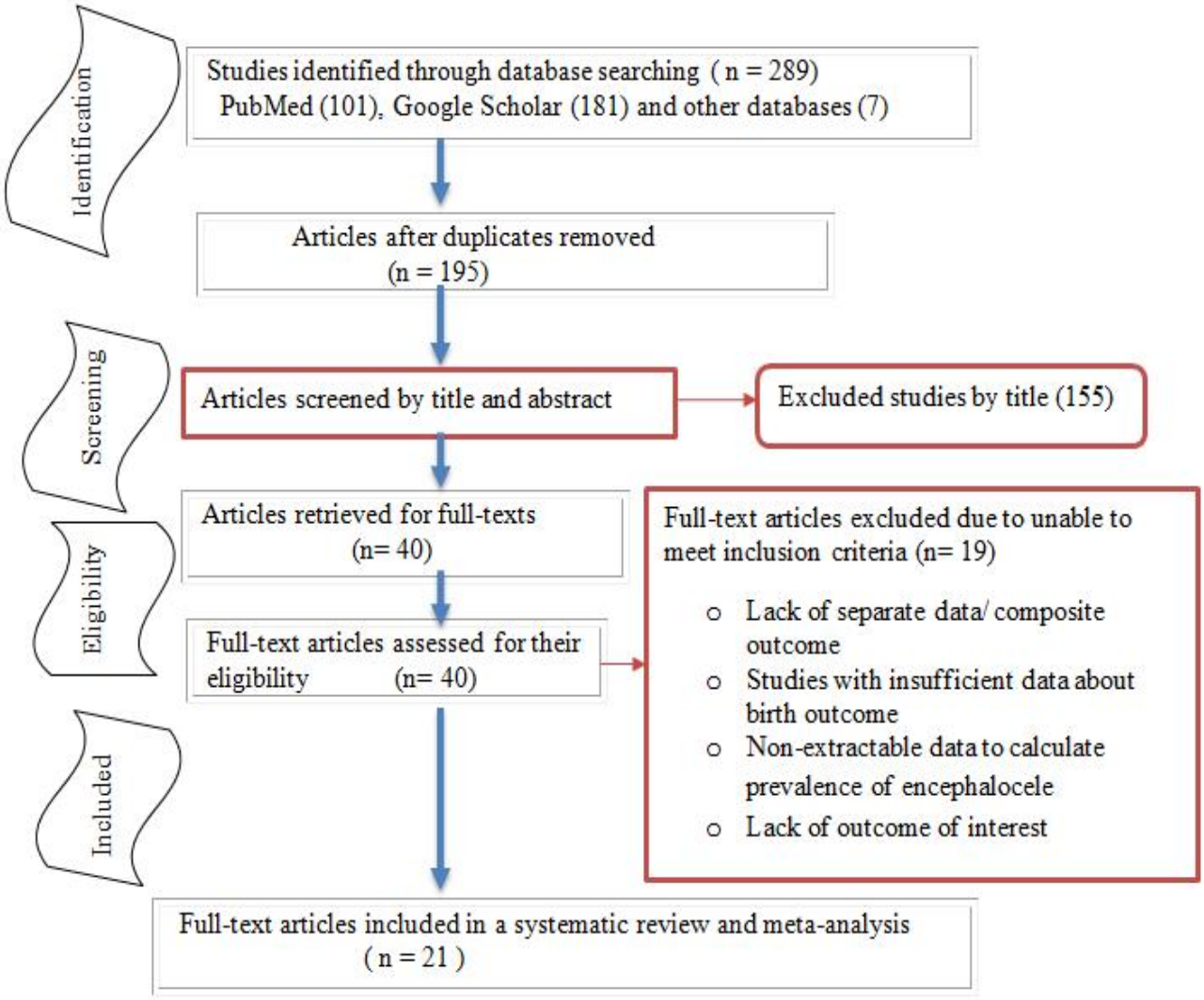
Figure 4: Subgroup analysis based on birth outcome in Africa, 2020

Figure 5: Subgroup analysis based on period prevalence in Africa, 2020

Figure 6: Sensitivity analysis to see the influence of each individual study in Africa, 2020

Figure 7: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa, 2020

Figure 8: Egger's publication bias plot, 2020



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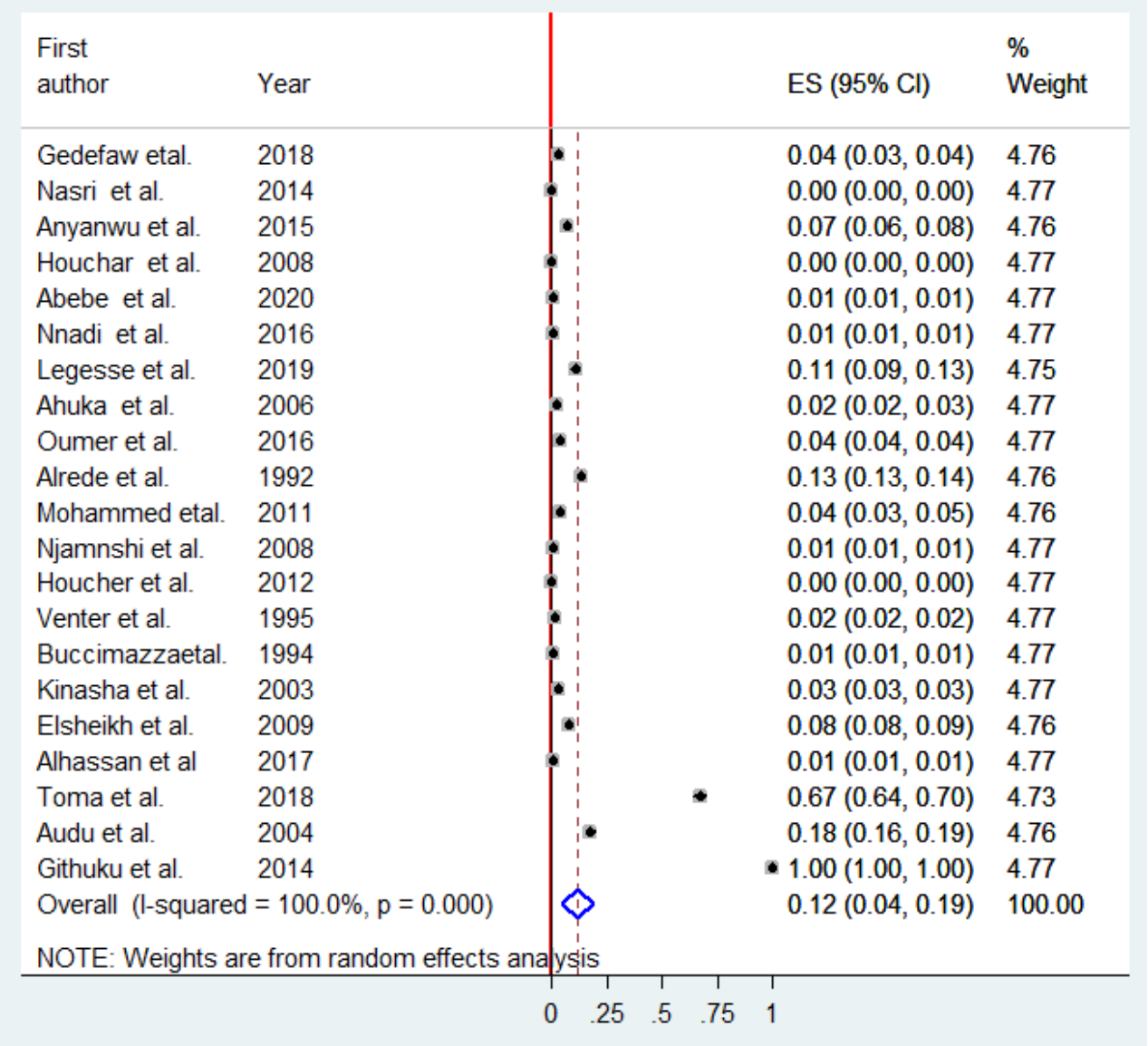

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa, 2020

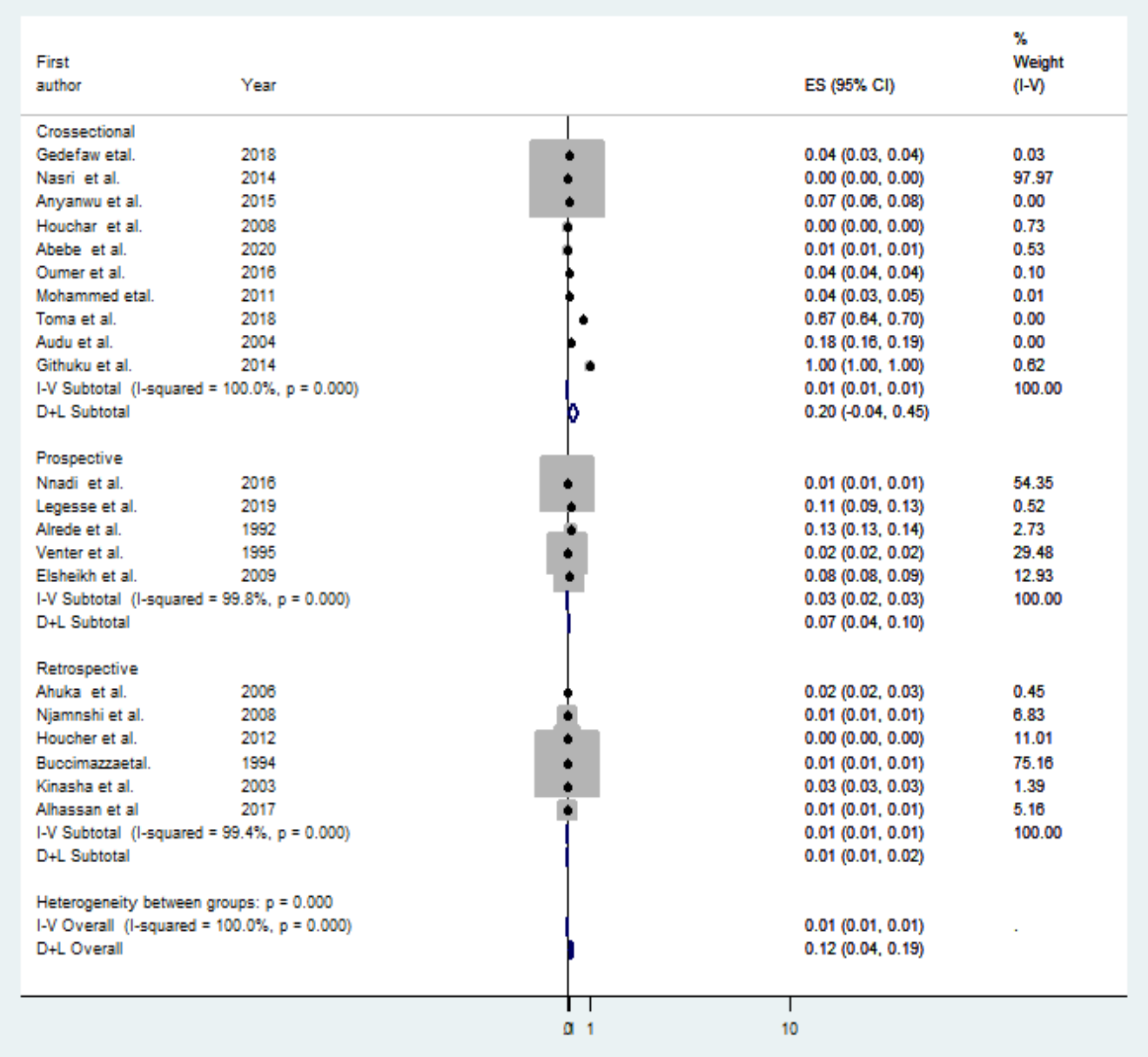

Figure 3: Subgroup analysis based on study design in Africa, 2020

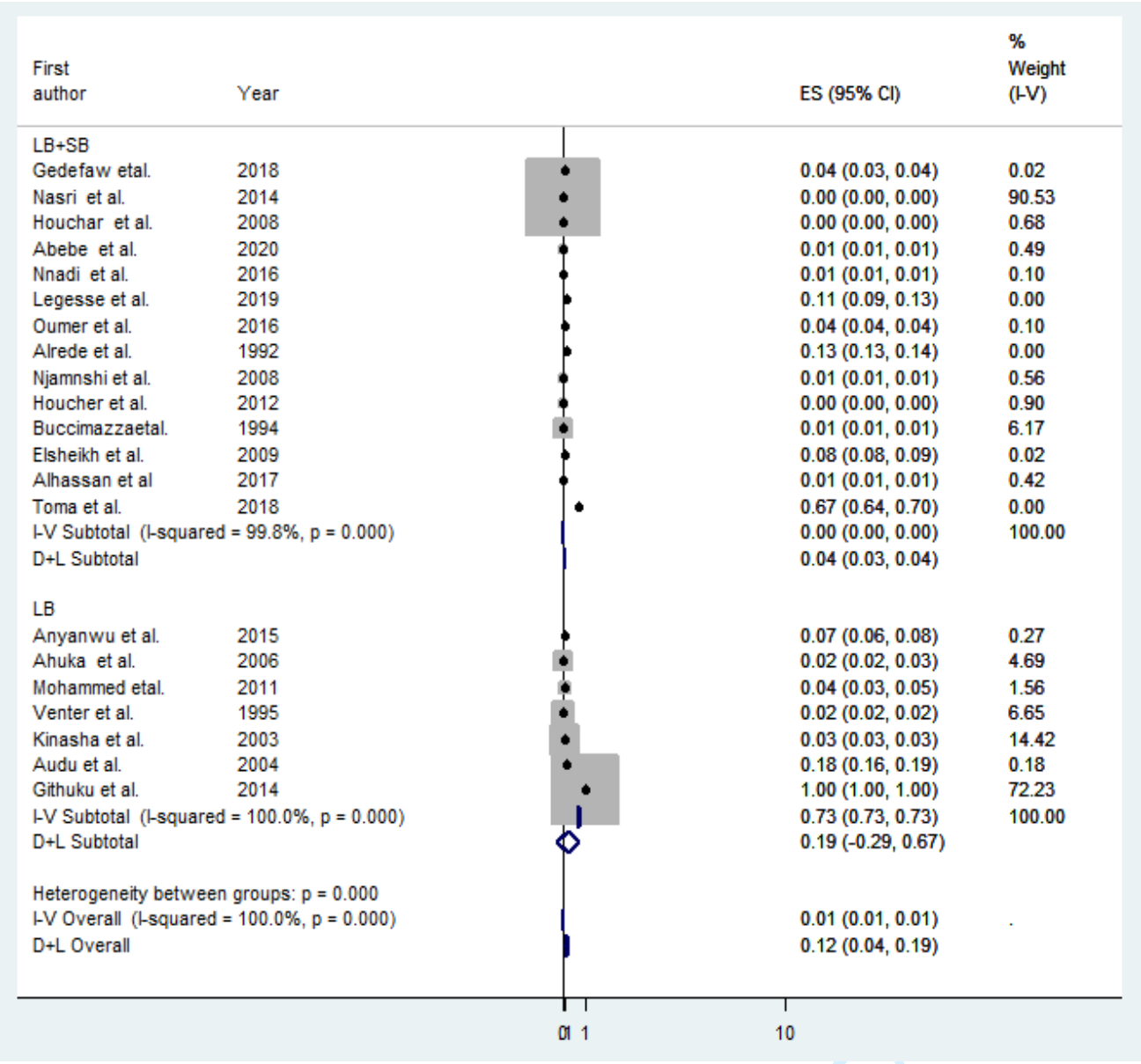

Figure 4: Subgroup analysis based on birth outcome in Africa, 2020

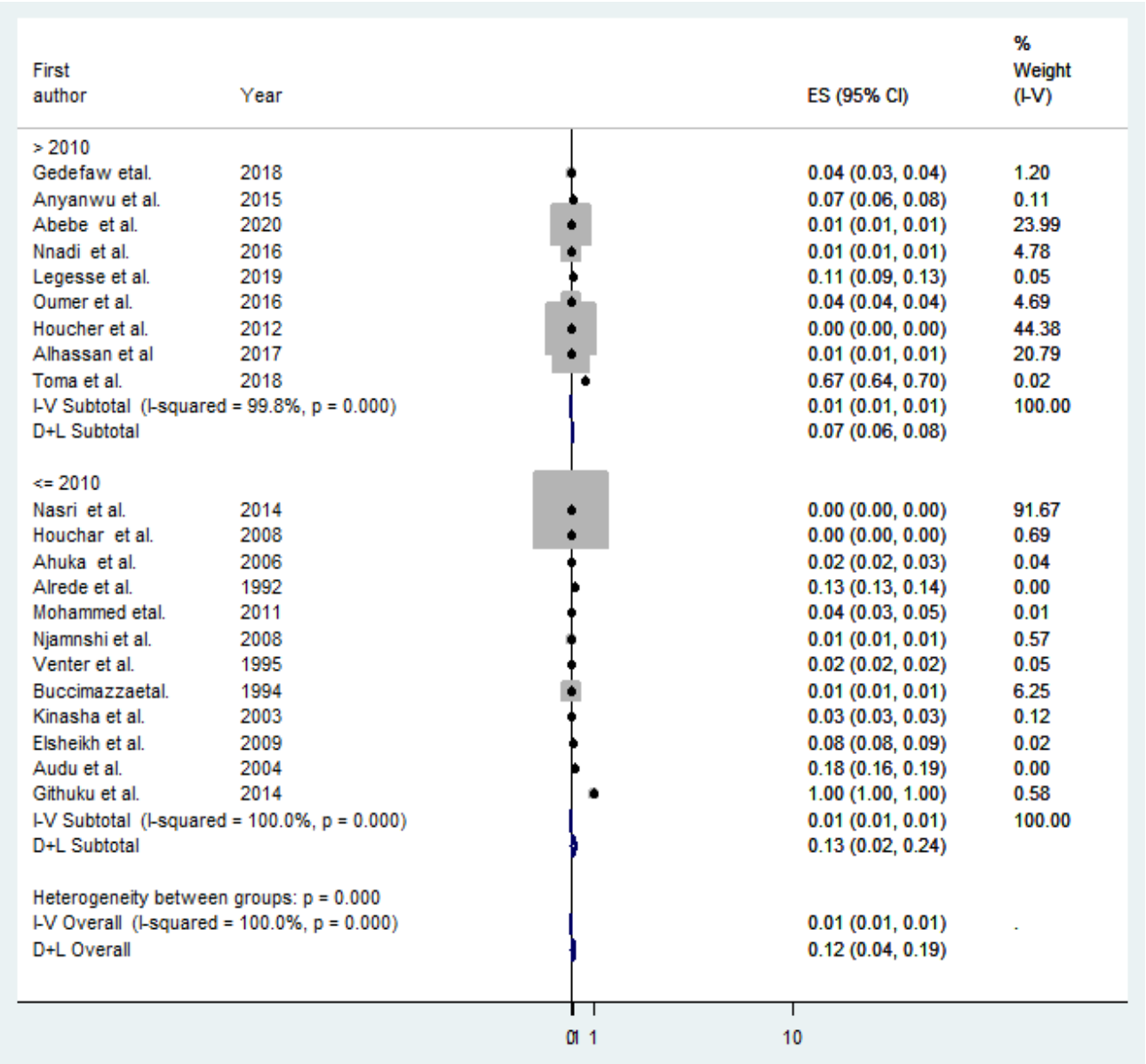

Figure 5: Subgroup analysis based on period prevalence in Africa, 2020

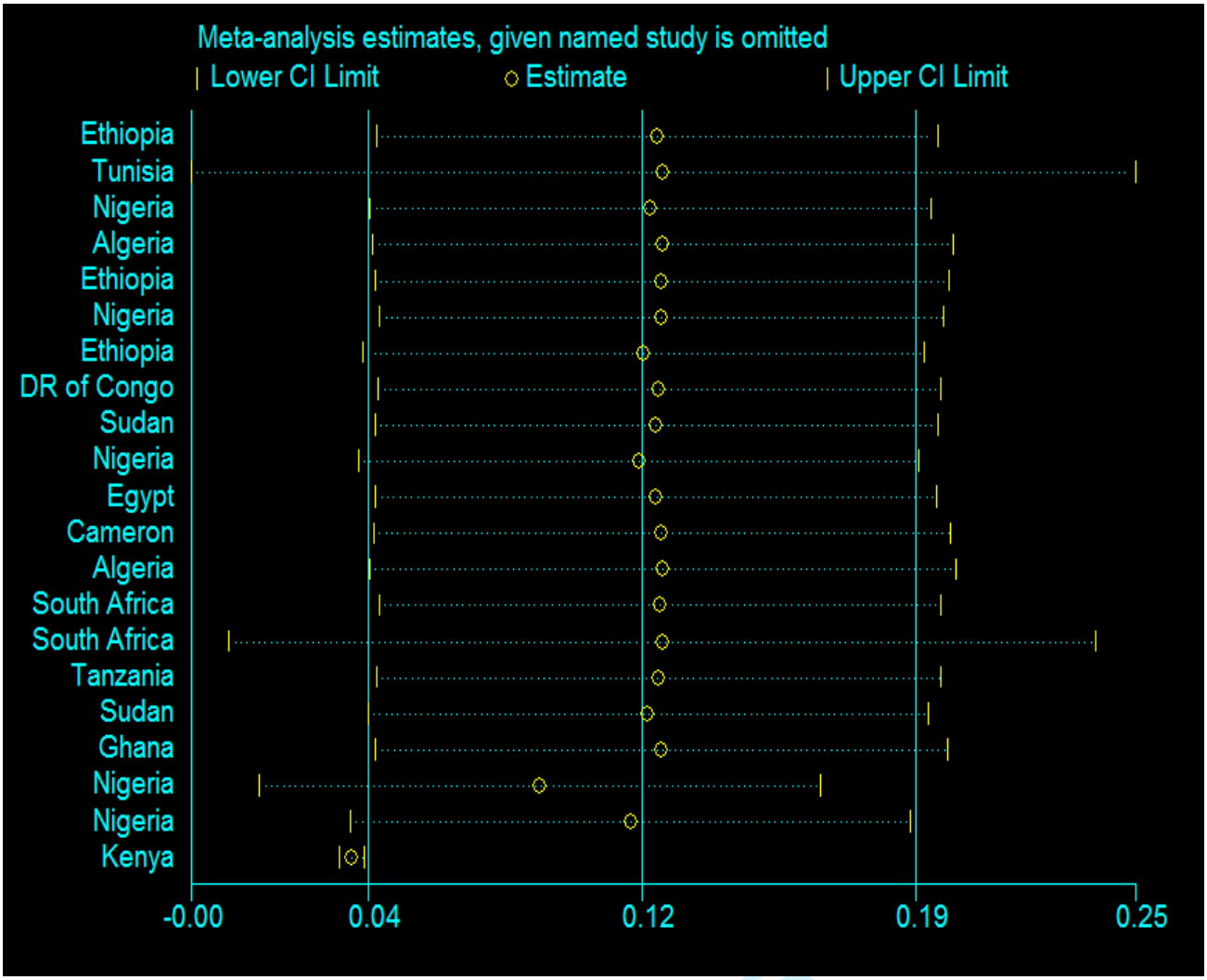

Figure 6: Sensitivity analysis to see the influence of each individual study in Africa, 2020

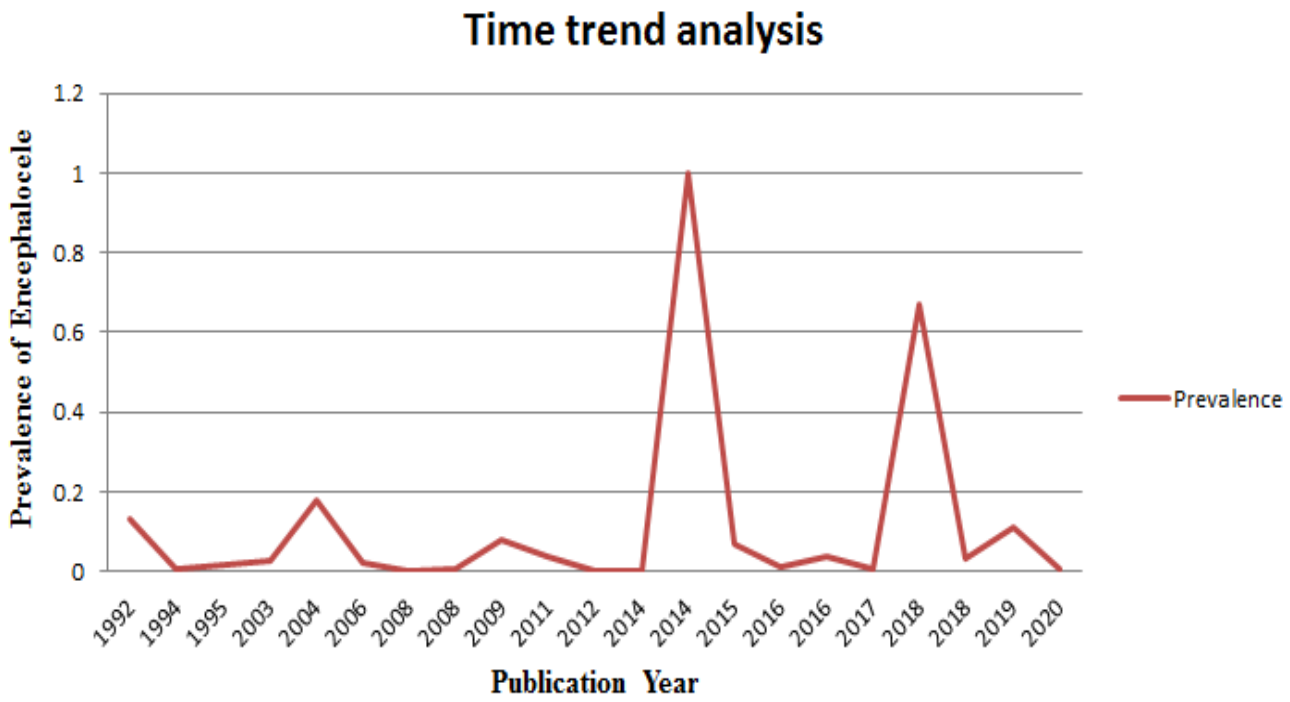

Figure 7: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa, 2020

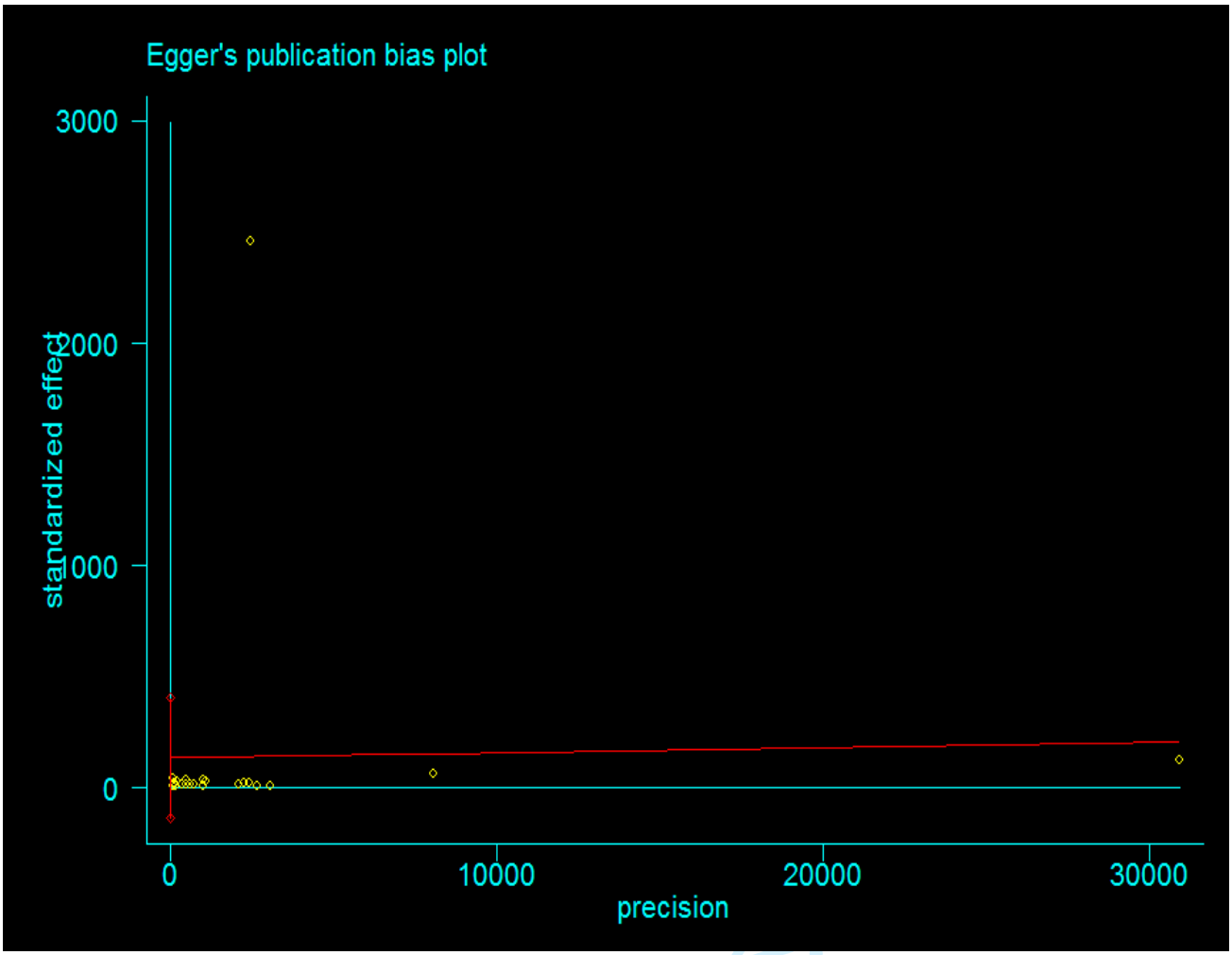

Figure 8: Egger's publication bias plot, 2020

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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

For more information, visit: **www.prisma-statement.org**.

PubMed Searching Methods

S.no.	Searching terms	Number of articles/results
1.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms]) AND (newborns OR neonate OR “live births” OR “stillbirths”) AND (Africa))	**101**
Trans lations	("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("encephalocele"[MeSH Terms] OR "encephalocele"[All Fields] OR "encephaloceles"[All Fields] OR "encephalocoele"[All Fields] OR "encephalocoeles"[All Fields] OR "encephalocele"[MeSH Terms] OR "neural tube defects"[MeSH Terms]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]) OR "live births"[All Fields] OR "stillbirths"[All Fields]) AND ("africa"[MeSH Terms] OR "africa"[All Fields] OR "africa s"[All Fields] OR "africas"[All Fields])	
2.	(Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms] OR “cranium bifidum”) AND (newborns OR neonate OR “live births” OR “stillbirths”) AND (Africa)	101
3.	(Prevalence) AND (encephalocele* OR encephalocele [MeSH Terms] OR “neural tube defect*” [MeSH Terms]) AND (newborn* OR neonate* OR “live birth*” OR “stillbirth*”) AND (Africa)	99

JBI Critical Appraisal Checklist

JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2. Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3. Was the sample size adequate?	☐	☐	☐	☐
4. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6. Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7. Was the condition measured in a standard, reliable way	☐	☐	☐	☐

for all participants?

8. Was there appropriate statistical analysis? ☐ ☐ ☐ ☐

9. Was the response rate adequate, and if not, was the low response rate managed appropriately? ☐ ☐ ☐ ☐

Overall appraisal: Include ☐ **Exclude** ☐ **Seek further info** ☐

Comments (Including reason for exclusion)

_____

_____

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Birth prevalence of encephalocele in Africa: A systematic review and meta-analysis

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Keywords:	Epidemiology, Neonatology, Neurosurgery, Cell Biology, Data Collection

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Birth prevalence of encephalocele in Africa: A systematic review and meta-analysis

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Word count = 3, 268

ABSTRACT

Objective: To identify the birth prevalence of encephalocele in Africa, 2020.

Methods: We carried out a systematic search of the following databases (PubMed/Medline, PubMed Central, Joanna Briggs Institute (JBI) Library, Cochrane Library, Web of Science, Google Scholar, Science Direct, African Journals Online, and Embase), using search terms (prevalence, encephalocele, "neural tube defects", "cranium bifidum", "congenital malformations", "congenital defects", "structural birth defects", "structural abnormalities", newborns/neonates/ "live births"/ "stillbirths", and their MeSH Terms) up to July 16, 2021. The JBI quality appraisal checklist was used to assess the quality of studies when they were abstracted using a standardized data extraction template. The I^2 statistic and Cochrane Q test were used to examine heterogeneity across studies statistically. The prevalence of encephalocele was estimated using a random-effect meta-analysis model. Subgroup, sensitivity, meta-regression, and time trend analysis were carried out. The publication bias was checked using Egger and Begg's tests.

Results: Twenty-seven relevant studies were identified and provided a total of 5, 107,109 births. In this systematic review and meta-analysis, the pooled birth prevalence of encephalocele in Africa was 0.02 % (or 2 per 10, 000 births) (95 % CI: 0.02, 0.03 %). The overall prevalence of birth encephalocele using the median from studies was 0.02 % (IQR (inter-quartile range) = 0.01 – 0.04 %). Higher prevalence of encephalocele was detected in Nigeria 0.06 % (95 % CI: 0.04, 0.08 %), Sudan 0.04 % (CI: 0.03, 0.05 %), Egypt 0.04 % (CI: 0.04, 0.05 %), DR of Congo 0.02 % (CI: 0.02, 0.03 %), Ethiopia 0.02 % (CI: -0.004, 0.05 %), and Tanzania 0.02 % (95 % CI: 0.002, 0.04 %). The prevalence of encephalocele per live birth was 0.03 %, both live birth and stillbirth was 0.03 %, for studies done after 2010 was 0.02 %, and for studies done before 2010 was 0.03 %.

Conclusions: This review indicates a high prevalence of encephalocele, but studies were limited suggesting the need for additional research.

Keywords: Africa, encephalocele, prevalence, systematic review and meta-analysis

Key messages

- Encephalocele is a birth abnormality associated with skull deformities defined by a partial absence of bone fusion that a portion of the brain protrudes.
- The present systematic review and meta-analysis revealed that encephalocele is highly prevalent in Africa.
- The prevalence of encephalocele was found to be different among study countries, prevalence periods, and study designs.
- A higher prevalence of encephalocele was identified in Nigeria, Sudan, Egypt, the Democratic Republic of Congo, Ethiopia, and Tanzania.
- Special awareness on prevention should be created and due to the scarcity of data on encephalocele, primary research is required to show the burden.

INTRODUCTION

Encephalocele is a birth abnormality associated with skull deformities defined by a partial absence of bone fusion, allowing a portion of the brain to protrude through a gap [1-3]. It is a form of neural tube

birth abnormality that affects the brain [2-6]. The neural tube is a tiny canal that folds and closes to form the fetus's brain and spinal cord during the third and fourth weeks of gestation [1 4 6].

An opening will appear anywhere along the center of the skull from the nose to the back of the neck following the defect, but most commonly at the back of the head, the top of the head, or between the forehead and the nose [1 3]. Encephalocele is a sac-like protrusion of the brain and meninges through a hole in the skull (usually affecting the occipital area, the back of the skull) [2 6]. The protruding region of the brain is frequently covered by skin or a thin membrane, giving the abnormality the appearance of a tiny sac [5]. Its herniation process manifests as a pedunculated (with a stalk-like base) or sessile (with no stalk) cystic lesion [2]. Only the meninges protrude through the bone opening in the sac, causing cranial meningocele; however, the herniated sac contains brain tissue and meninges, causing encephalocele or meningoencephalocele. Hydroencephalocele is a deformity that occurs when a herniated sac contains a ventricle. Encephalomyelocele is a type of encephalocele that contains tissue from the brain and spinal cord [1-9]. Anatomically, encephalocele can be classified into sincipital (nasoorbital, frontoethmoidal, nasofrontal, interfrontal, nasoethmoidal, craniofacial cleft), basal (sphenoorbital, sphenomaxillary, intranasal, spenopharyngeal), convexity (sagittal, occipital, occipitocervical, parietal), and atretic [8 10 11]. Evidence suggests that an encephalocele is a form of post-neurulation defect distinct from closure-related neural tube defects [8 12].

The incidence of encephalocele varies by race and geographic region, ranging from 0.8 to 4 per 10,000 births [7 8 11]. According to the Centers for Disease Control and Prevention, encephalocele affects one out of every 10,000 babies born in the United States each year [1].

The majority of encephaloceles are massive, serious birth abnormalities that are detected before delivery. Some encephaloceles, however, are small and go undetected in extremely uncommon

circumstances. Although the specific etiology of encephalocele is uncertain, scientists believe it is caused by a combination of causes [1-3].

The symptoms of an encephalocele vary from person to person, based on a variety of characteristics such as the size, location, and amount and kind of brain tissue protruding from the skull. The placement of the encephalocele is crucial because anterior (which usually does not contain brain tissue and has a better prognosis) and posterior (often associated with neurological problems) encephaloceles have different clinical consequences/implications for therapy and prognosis. Surgical management is usually required to return the protruding section of the brain and meninges to the skull and shut the incision/opening. However, encephalocele-related neurologic issues will persist, and long-term care may be required depending on the child's condition [1 2].

Encephalocele is the leading cause of death and disability in newborns [6 10 13 14], despite the fact that it can be reduced by various preventive and control strategies. Preventive strategies such as folic acid supplementation or fortification of staple foods can help to reduce it [3-6 13 14]. In order to make decisions and plan preventative services, it is essential to provide information to responsible bodies concerning the burden of encephalocele in Africa. The government, policymakers, health professionals, researchers, medical students, communities, and non-governmental organizations will benefit from this review, which will help to reduce the burden of the encephalocele and allow for more study. Moreover, little is known about the magnitude of encephalocele in Africa as a whole. Thus, the present systematic review and meta-analysis aimed to identify the pooled birth prevalence of encephalocele in Africa, 2020.

METHODS

Reporting of the findings and review registration

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements were used to report the current systematic review and meta-analysis [15] (Supplementary File 1). The review protocol has been registered in PROSPERO with the registration ID of CRD42021242161.

Search strategies

PubMed/Medline, PubMed Central, Cochrane Library, JBI Library, Science Direct, Web of Science, African Journals Online, WHO, UCSF, and Embase databases were systematically searched for relevant studies (reference lists of identified articles were also navigated) up to July 16, 2021. The primary search was conducted in an advanced PubMed database (using search terms prevalence, encephalocele, "neural tube defects", "cranium bifidum", "congenital malformations", "congenital defects", "structural birth defects", "structural abnormalities", newborns/neonates/"live births"/"stillbirths", and their MeSH Terms). The core search terms and phrases were considered interchangeably in different databases. Moreover, grey literature was retrieved using Google and Google Scholar searches. The full search strategy is being shown online (Supplementary File 2).

Eligibility criteria

Inclusion criteria

Published and unpublished full-text studies in any period and study designs (a cross-sectional, prospective cohort that included original data) that report the birth prevalence of encephalocele in Africa were included in this review.

Exclusion criteria

Case reports, conferences, editorials, anonymous reports, and research with limited access (after two emails to the corresponding author) were excluded from the review. Moreover, a study was excluded if the total number of cases and births included in the study were not indicated explicitly.

Review outcomes

The outcome of the current review was the pooled birth prevalence of encephalocele in Africa. Birth prevalence of encephalocele is defined as the number of encephalocele cases of live births and/or stillbirths at birth (numerator) from the total number of births (live births and/or stillbirths) during the study period (denominator).

Quality assessment

The JBI quality appraisal checklist was used to evaluate the quality of each study [16]. The JBI critical appraisal checklist (which has nine items) was adapted for the studies reporting the prevalence data (Supplementary File 3). Using the framework, two reviewers (MO and AD) independently evaluated the quality of each study. During the evaluation of quality, disagreements between reviewers were resolved by using the average score of the two reviewers. In the end, if the study received five or more points on all quality assessment items, it was deemed low risk [17].

Study selection and data abstraction

After retrieving all of the studies from the databases, they were loaded into the reference manager, an Endnote Version 7 software program, to eliminate duplicates. The reviewers then screened the research for inclusion based on the title and abstract. All necessary data were extracted independently by two reviewers (MO and AD) using a defined data extraction template after thoroughly reading full-text studies and including the eligible studies. The main author, sample size, study nation, study

duration, study design, study location, publication year, prevalence period, folic acid fortification policy, birth status, birth outcome, and birth prevalence of encephalocele were all included in this template.

Meta-analysis

For further analysis, the data were extracted in Microsoft Excel and exported to STATA 14 Statistical Software. For each study, the prevalence was estimated per hundred births to preserve uniformity.

The Cochrane Q test and the I^2 statistic were used to examine statistically the heterogeneity between studies and a forest plot was used to visualize heterogeneity [18]. This revealed considerable heterogeneity among studies (P-value<0.001). Therefore, to determine the pooled prevalence of encephalocele, a random-effect meta-analysis approach was applied [19 20]. Sub-group analysis was performed based on selected variables (the study country, study design, birth outcome, period prevalence, folic acid fortification status, epidemiological design, and status of births). A sensitivity analysis was done to see the influence of a single study on the overall estimate of meta-analysis. Meta-regression analysis was accounted for to identify the source of heterogeneity. A time-trend analysis was conducted as well.

Assessment of publication bias

Graphically, Egger's plot was used to visualize the publication bias. Objectively, Egger's regression test and Begg's test statistics were used to detecting publication bias [21 22]. As a result, publication bias was defined as a P-value ≤ of 0.05.

Patient and public involvement

"No patient involved."

RESULTS

Study selection

A total of five thousand four hundred twenty-two articles were initially retrieved on the prevalence of encephalocele through PubMed, Google Scholar, and others from Cochrane, JBI Library, WHO, Medline, UCSF, African Journal Online, Science Direct, and Embase. Of these, one thousand five hundred thirty-six were excluded due to duplicated articles. From the remaining three thousand eight hundred eighty-six studies, three thousand six hundred sixty studies were excluded after reviewing the titles and abstracts because they were found non-relevant for this review. Full texts of the remaining two hundred twenty-six studies were screened. This systematic review and meta-analysis comprised twenty-seven studies that met the inclusion criteria [23-49] (Figure 1).

Characteristics of the original studies

The included studies were either cross-sectional (n=4), retrospective (n= 14), or prospective studies (n=9) [23-49]. Of all studies, eight were conducted in Nigeria [23-30], three in South Africa [31-33], two in Ethiopia [40 41], two in Tanzania [34 35], two in Kenya [36 37], and two in Sudan [38 39]. Studies conducted in Morocco, Tunisia, Algeria, the Democratic Republic (DR) of Congo, Egypt, Cameron, Ghana, and Libya were also identified [42-49]. All studies included in this review were facility-based studies, published in the year between 1992 and 2020 [23-49]. South Africa (started fortification in 2003), Nigeria (in 2002), Tanzania (in 2011), and Kenya (in 2012) have mandatory folic acid fortification with Wheat Flour and Maize Flour. Morocco (in 2006), Cameron (in 2011), and Ghana (in 2006) have mandatory folic acid fortification with Wheat Flour. Ethiopia and Sudan have a voluntary folic acid fortification policy with Wheat Flour at this time. Based on birth status, four studies mentioned the inclusion of twin birth and multiple births in addition to singleton births

[29 36 40 43] while all other studies not mentioned their birth status. Generally, twenty-seven studies reported a total of 5, 107,109 births, ranged from 1,456 to 3,803, 889 births [27 46] (Table 1).

Table 1: The characteristics of studies included in the systematic review and meta-analysis

First author	Year	Country	Study design	Sample size	Period prevalence	Duration ©	Birth outcome	Epidemiological study	Prevalence (%)
Airede et al. [23]	1992	Nigeria	PS	5,977	Jun 1987 - Jun 1990	36	LB+SB	Incidence	0.134
Adetiloye et al. [24]	1993	Nigeria	RS	23,438	1982 – 1992	120	LB+SB	Incidence	0.051
Mukhtar-Yola et al. [25]	2005	Nigeria*	RS	13,619	Oct 1998- Nov 2004	72	LB+SB	Prevalence	0.059
Ugwo et al. [26]	2007	Nigeria*	RS	7,388	May 2002- Apr 2005	36	LB+SB	Incidence	0.081
Anyanwu et al. [27]	2015	Nigeria*	PS	1,456	Apr 2013- Dec 2013	9	LB	Prevalence	0.069
Nnadi et al. [28]	2016	Nigeria*	PS	10,163	Jan 2011- Dec 2013	36	LB+SB	Prevalence	0.01
Abbey et al. [29]	2017	Nigeria*	RS	7,670	Aug 2011- Dec 2014	48	LB§	Prevalence	0.039
Ekwochi et al. [30]	2018	Nigeria*	PS	5,830	Jan 2013- Jan 2017	48	LB	Incidence	0.034
Buccimazzaetal. [31]	1994	South Africa	RS	516,252	Jan 1973 - Dec 1992	240	LB+SB	Prevalence	0.008
Delport et al. [32]	1995	South Africa	PS	17,351	May 1986- Apr 1989	36	LB	Incidence	0.012
Venter et al. [33]	1995	South Africa	PS	7,617	Jun 1989 - Dec 1992	40	LB	Incidence	0.026
Kinasha et al. [34]	2003	Tanzania	RS	34,000	Jan 2000 - Jan 2002	24	LB	Incidence	0.029
Kishimba et al. [35]	2015	Tanzania*	CS	28,217	Oct 2011- Feb 2012	5	LB+SB	Prevalence	0.011
Muga et al. [36]	2009	Kenya	PS	7,355	Sep 1983- Sep 1984	12	LB+SB§	Incidence	0.014
Agot et al. [37]	2020	Kenya*	RS	299,854	Jan 2014 - Dec 2018	60	LB	Prevalence	0.0007
Elsheikh et al. [38]	2009	Sudan	PS	18,378	Feb 2003 - Jan 2004	12	LB+SB	Incidence	0.049
Omer et al. [39]	2016	Sudan*	CS	36,785	Aug 2014 - Jul 2015	12	LB+SB	Prevalence	0.038
Gedefaw etal. [40]	2018	Ethiopia*	PS	8,677	Feb 2016- Aug 2016	7	LB+SB®	Incidence	0.035
Abebe et al. [41]	2020	Ethiopia*	RS	45,951	Sep 2011- Dec 2015	60	LB+SB	Prevalence	0.009
Ahuka et al. [42]	2006	DR of	RS	8,824	Jan 1993 -	96	LB	Incidence	0.023

Houchar et al. [43]	2008	Congo Algeria	RS	28,500	Aug 2001 2004 -2006	36	LB+SB®	Prevalence case-control	0.004
Njamnshi et al. [44]	2008	Cameron	RS	52,710	Jan 1997 - Dec 2006	120	LB+SB	Incidence	0.0095
Mohammed etal. [45]	2011	Egypt	CS	5,000	Mar 2007- Oct 2007	7	LB	Prevalence	0.04
Nasri et al. [46]	2014	Tunisia	RS	3,803,889	1991-2011	240	LB+SB	Prevalence	0.004
Radouani et al. [47]	2015	Morocco*	RS	60,017	Jan 2008- Dec 2011	48	LB+SB	Prevalence	0.0017
Alhassan et al. [48]	2017	Ghana*	RS	35,426	Jan 2010 - Dec 2014	48	LB+SB	Prevalence	0.0085
El-Moghrabi et al. [49]	2019	Libya	CS	16,765	Sep 2004- Aug 2005	12	LB	Incidence	0.006

Key: CS: Cross-sectional; PS: Prospective; RS: Retrospective; LB: Live births; SB: Stillbirths; ® Singleton births + twin births; § Singleton births + twin births + multiple births; Mandatory and/or voluntary folic acid fortification policy; © duration per months

Quality of the studies

Using JBI quality appraisal criteria, all included studies were evaluated for their quality. Each study was evaluated using the evaluation checklist for prevalence studies, which consists of nine questions/items with Yes, No, Unclear, or Not Applicable responses. The quality assessment grading for all items was based on the JBI descriptions for each item. As a result, the studies' quality scores ranged from four to nine. Therefore, except for one study that received a four, none of the studies had a significant risk of being of poor quality [23-49] (Supplementary file 4).

Meta-analysis

Prevalence of encephalocele

In the present meta-analysis, the pooled birth prevalence of encephalocele was 0.02 % (or 2 per 10,000 births) (95 % CI: 0.02, 0.03 %). A Forest plot showed that there was statistically significant heterogeneity across the studies. Therefore, the random-effect meta-analysis model was applied to

pool the overall prevalence of the studies (Figure 2). Considering all included studies, the median value of birth encephalocele was 0.02 % and the inter-quartile range was between 0.01 and 0.04 %. The minimum and maximum values of birth encephalocele were 0.0007 and 0.134 %, respectively.

Subgroup analysis

Subgroup analysis based on the study country, study design, birth outcome, period prevalence, folic acid fortification status, epidemiological design, and status of births was carried out to see the variation of the prevalence across the studies.

Subgroup analysis based on the study country was performed to see the pooled prevalence of each country in Africa. High pooled prevalence of encephalocele was detected in Nigeria 0.06 % (95 % CI: 0.04, 0.08 %), Sudan 0.04 % (95 % CI: 0.03, 0.05 %), Egypt 0.04 % (95 % CI: 0.04, 0.05 %), DR of Congo 0.02 % (95 % CI: 0.02, 0.03 %), Ethiopia 0.02 % (95 % CI: -0.004, 0.05 %), and Tanzania 0.02 % (95 % CI: 0.002, 0.04 %) (Table 2). In the present review, statistically significant heterogeneity between countries was detected (P-value = 0.001, I^2= 97.1-99.8 %). Therefore, the Der Simonian and Laird's (D+L) pooled prevalence method was considered because it is more conservative than the inverse variance method (I-V). The difference between countries was significant (P-value<0.001).

Table 2: The pooled prevalence of encephalocele among African countries

Country	Prevalence in % (95 % CI)
Morocco	0.002 (0.001, 0.002)
Tunisia	0.004 (0.004, 0.004)
Algeria	0.004 (0.003, 0.005)
Libya	0.006 (0.005, 0.007)

Kenya	0.007	(-0.006, 0.020)
Cameron	0.009	(0.009, 0.010)
Ghana	0.009	(0.008, 0.009)
South Africa	0.015	(0.008, 0.022)
Tanzania	0.020	(0.002, 0.038)
Ethiopia	0.022	(-0.004, 0.047)
DR of Congo	0.023	(0.020, 0.026)
Egypt	0.040	(0.035, 0.045)
Sudan	0.043	(0.033, 0.054)
Nigeria	0.059	(0.038, 0.081)
D+L pooled ES	**0.025**	**(0.023, 0.027)**

Subgroup analysis based on study design, using the D+L method (P-value<0.001, I^2 = 99.4-99.9 %), the prevalence of encephalocele for retrospective studies was 0.02 % and for prospective studies was 0.04 % (Figure 3).

Subgroup analysis based on birth outcome was done to see the burden in live births only (LB) and both live births and stillbirths (LB+SB). The pooled prevalence of encephalocele per live birth was 0.03 % (95 % CI: 0.02, 0.04 %) and both live birth and stillbirth was 0.03 % (95 % CI: 0.02, 0.03 %) (Figure 4).

Subgroup analysis based on period prevalence was carried out to observe the prevalence between prevalence periods. Considering two prevalence periods (>2010 and <=2010 years), the prevalence of encephalocele for studies done after 2010 was 0.02 % (95 % CI: 0.02, 0.03 %) and for studies done before 2010 was 0.03 % (95 % CI: 0.03, 0.03 %) (Figure 5).

Prevalence period based on ten years gap, the prevalence of encephalocele for studies done before 1990 was 0.04 % (95 % CI: 0.03, 0.06 %), 1990-2000 was 0.02 % (95 % CI: 0.02, 0.03 %), 2001-

2010 was 0.03 % (95 % CI: 0.02, 0.04 %), 1991-2011 was 0.004 % (95 % CI: 0.004, 0.004 %), and for studies done after 2010 was 0.02 % (95 % CI: 0.02, 0.03 %).

Subgroup analysis based on folic acid fortification policy was considered (P-value<0.001, I^2 =99.7%) and the prevalence of encephalocele for countries that had a mandatory and/or voluntary folic acid fortification was 0.03 % (95 % CI: 0.02, 0.03 %), and for countries that had no either a mandatory or voluntary fortification was 0.03 % (95 % CI: 0.02, 0.03 %).

The prevalence of encephalocele for incidence studies was 0.04 % (95 % CI: 0.03, 0.05 %), for prevalence studies was 0.02 % (95 % CI: 0.02, 0.02 %), and for prevalence case-control studies was 0.004 % (95 % CI: 0.003, 0.005 %).

The prevalence of encephalocele for singleton births was 0.03 % (95 % CI: 0.02, 0.03 %), for singleton and twin births was 0.02 % (95 % CI: -0.01, 0.05 %), and for singleton, twin, and multiple births was 0.03 % (95 % CI: 0.002, 0.05 %).

Meta-regression analysis

In the present systematic review and meta-analysis, sample size (P-value = 0.44), year of publication (P-value = 0.34), duration of the study in months (P-value = 0.20), study country (P-value = 0.02), study design (P-value = 0.56), birth outcome (P-value = 0.55), prevalence period (P-value = 0.80), epidemiological design (P-value = 0.37), folic acid fortification (P-value = 0.91), and the JBI quality score (P-value = 0.06) were analyzed for the source of heterogeneity. The only study country was significant for the source of heterogeneity.

Sensitivity analysis

In this review, no study was found that has a special influence over others on the overall estimation of meta-analysis (Figure 6). Essentially, all studies have uniform confidence intervals. Even if uniform influence has been detected in sensitivity analysis, we looked at the state of the overall estimates by omitting two studies in the meta-analysis that supposed to be to have some influence (the study that was done by Nasri et al. and Agot et al.). Accordingly, after excluding Nasri's study, the pooled birth prevalence of encephalocele was 0.03% (95% CI: 0.03, 0.03%) and after excluding Agot's study, it was 0.03% (95% CI: 0.03, 0.03). When two were eliminated from the analysis, the prevalence became 0.03% (95% CI: 0.03, 0.03). The sphere of influence grew uniform. However, because the heterogeneity between studies was not significantly reduced (P-value < 0.001, I^2= 99.7-99.8%), we stuck with the previous values. We performed also leave-one-out analyses; the heterogeneity among studies was not significantly reduced.

We used sensitivity analysis to examine the impact of low-quality studies on total estimates by reducing the number of studies included in a meta-analysis. We found the meta-analysis estimates by including only high-quality studies with a score greater than or equal to five. As a result, we got a similar output with the previous finding and, the pooled estimate was 0.02% (95% CI: 0.02, 0.03).

Time trend analysis

The time trend analysis showed the relationship between the prevalence of encephalocele and publication year. In this trend in Africa, the highest peak of encephalocele in prevalence was observed in 1992, 2007, 2014-2015, and 2005 (Figure 7).

Publication bias

Publication bias was estimated using the Egger's regression tests (B-coefficient of bias: 17; P-value = 0.001). Egger's plot supported its results (Figure 8).

DISCUSSION

Encephalocele is a central nervous system abnormality that occurs at birth. The hidden burden of encephalocele was high in Africa. Data is lacking on the true burden of this condition, leading to neglect in the treatment and prevention by health systems in Africa. The responsible authorities or bodies have neglected this defect too. The effects of the malformation are related to substantial mortality, disability, and psychological costs (the psychosocial problem of having an infant with a "monstrous outlook" or "two heads"). Although encephalocele is a rare congenital anomaly, it is correlated with severe morbidity and mortality if untreated [7 8]. Folic acid supplementation and termination of pregnancies diagnosed with encephalocele prenatally have reduced the occurrence or incidence of this type of congenital abnormality, particularly in developed (high-income) countries.

The birth prevalence of encephalocele was 0.02 % (or 2 per 10,000 births) in this meta-analysis. This finding is comparable to different findings reported elsewhere (ranged from 0.8 to 4.0 per 10,000 births) [4-8 11]. Besides, it is comparable to the review done in low-and middle-income countries (2.1 per 10,000 births) [50]. The review result suggested that low-and middle-income countries were mostly affected by this malformation every year [50]. However, the review did not include studies from Africa except for two studies. Our finding is higher than that reported by certain high-income countries (1.0 per 10,000 births) [1]. Recent research shows that the prevalence of encephalocele varies across time, geography, and population to population [8]. Our analysis also revealed

considerable differences between African countries and prevalence over time. Subgroup analyses were carried out based on the study nation, design, birth outcome, prevalence period, birth status, and the availability of a folic acid fortification program. As a result, a considerable disparity in the occurrence of encephalocele in different African countries was discovered in this study. Nigeria 0.06 %, Sudan 0.04 %, Egypt 0.04 %, Congo (DR) 0.02 %, Ethiopia 0.02 %, and Tanzania 0.02 % had a high prevalence of encephalocele. This disparity could be explained by mothers' levels of knowledge about folic acid supplementation, as well as the country's health policy on folic acid fortification and other preventive measures. The notion of the presence of geographical variation between the countries was supported by the previous studies [6-8]. The variation in different publication years of the different studies was noted using time trend analysis. The highest peak of encephalocele in prevalence was seen in 1992, 2007, 2014-2015, and 2005. The prevalence estimate for live births was similar to both live birth and stillbirth estimations. Surprisingly, all studies in this review were facility-based studies. Thus, there may have been an underestimating of encephalocele estimations because it did not include many stillbirths and home deliveries in the community context (included the participants delivered at the hospital setting). In this pooled estimates, the presence of variation across countries may affect the prevalence of the defect in Africa. The estimated report may be influenced by the sample size's adequacy or variability. The prevalence estimate did not include terminated pregnancies of encephalocele; this should be taken into account when interpreting the results because it may lower the prevalence estimates.

Fragmented studies have been conducted to estimate the country-level prevalence of encephalocele. However, the findings were inconsistent and varied and there is no empirical evidence on the pooled prevalence estimates in Africa. Besides, studies on isolated encephaloceles are quite rare. The available evidence on encephalocele is in aggregate/combined form with either neural tube

defects or birth defects of the central nervous system. Interestingly, the present systematic review and meta-analysis highlight the birth prevalence of encephalocele in African countries, providing crucial evidence for policymakers, clinicians, and the concerned bodies who neglected the burden of this defect. Recognizing a high burden in Africa may initiate the policymakers to develop effective control and prevention strategies and may use their ultimate potential in reducing the burden of the encephalocele and making further research possible. Additionally, the high burden detected in our review may inform policymakers positively on policy decisions related to prevention efforts in Africa where policymakers may feel that this is not a big enough problem for prioritizing prevention funds. The severity, the observed differences in prevalence estimate among countries, may contribute by informing clinical and policy guidelines in the prioritization of interventions, and maintaining robust surveillance systems that track or screen all pregnancy outcomes or all births in Africa. Besides, future research works might benefit from the information gained from the current review when designing and developing new studies. Furthermore, it helps additional clinical studies to focus on risk factors, prevention, intervention, and psychosocial outcomes of the defect in isolated form. More research should be conducted in Africa to assess the effectiveness of folic acid in reducing the burden of the encephalocele and, notably, to determine how and why interventions either work or do not work in each country that followed either a mandatory or voluntary fortification policy. All these should be the ultimate contribution of this review to the field in assisting the prevention and control programs.

CONCLUSION

This systematic review and meta-analysis showed that encephalocele is highly prevalent in Africa. The prevalence of encephalocele was high in Nigeria, Sudan, Egypt, DR of Congo, Ethiopia, and

Tanzania. A similar prevalence of encephalocele was observed in the studies that included only live births and in studies that included both live births and stillbirths. The reviewers recommend that special awareness be created for reproductive-age women with an emphasis on prevention in order to reduce the encephalocele burden. Due to the scarcity of data on encephalocele in Africa, more primary research is needed to increase the estimated burden of the encephalocele and promote favorable aid strategies for prevention.

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Abbreviations: Not applicable.

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Figure Legends

Figure 1: Study selection flow diagram; a figure adapted from the PRISMA) group statement for this review

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa

Figure 3: Subgroup analysis based on study design in Africa

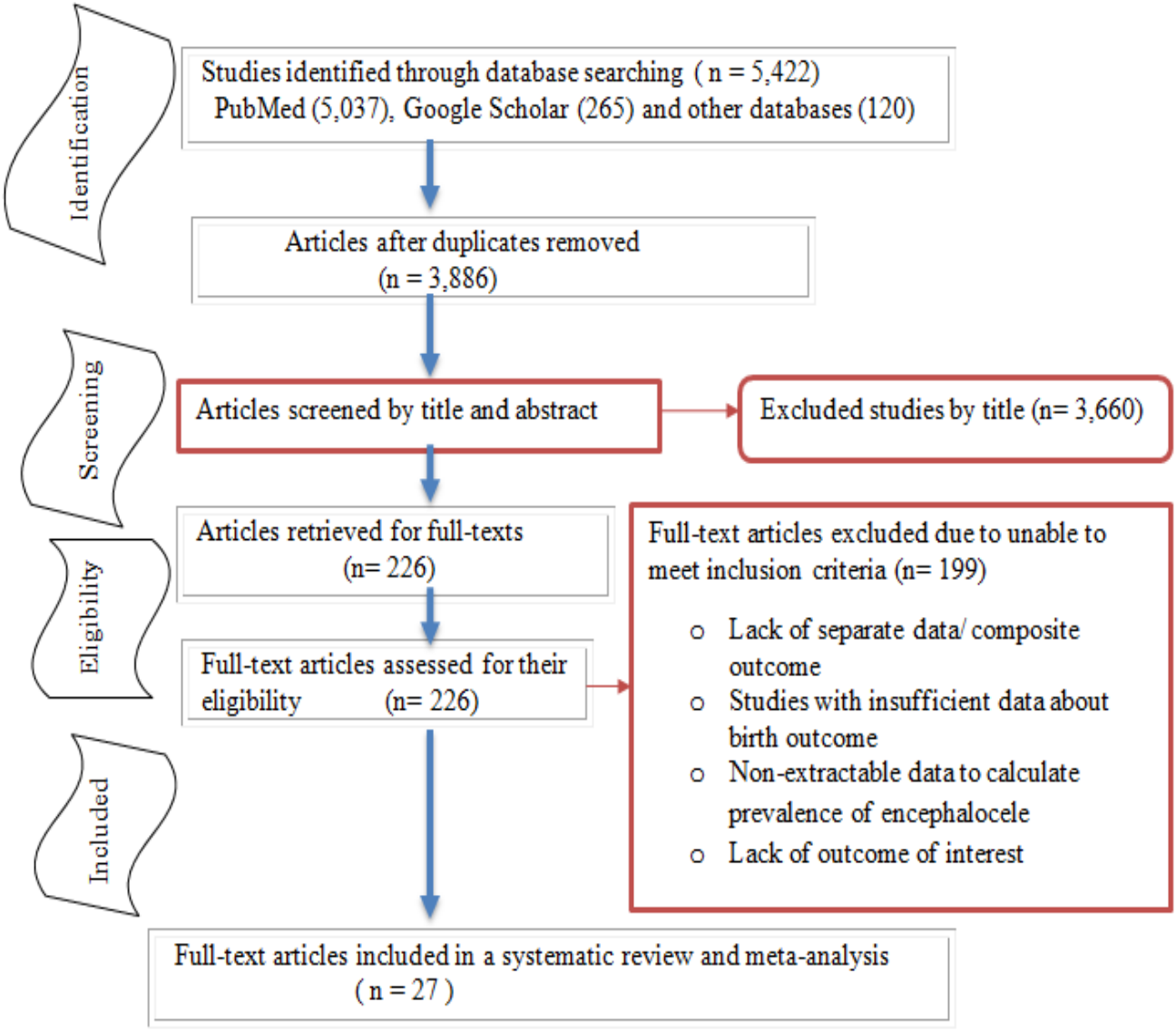
Figure 4: Subgroup analysis based on birth outcome in Africa

Figure 5: Subgroup analysis based on period prevalence in Africa

Figure 6: Sensitivity analysis to see the influence of each individual study in Africa

Figure 7: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa

Figure 8: Egger's publication bias plot



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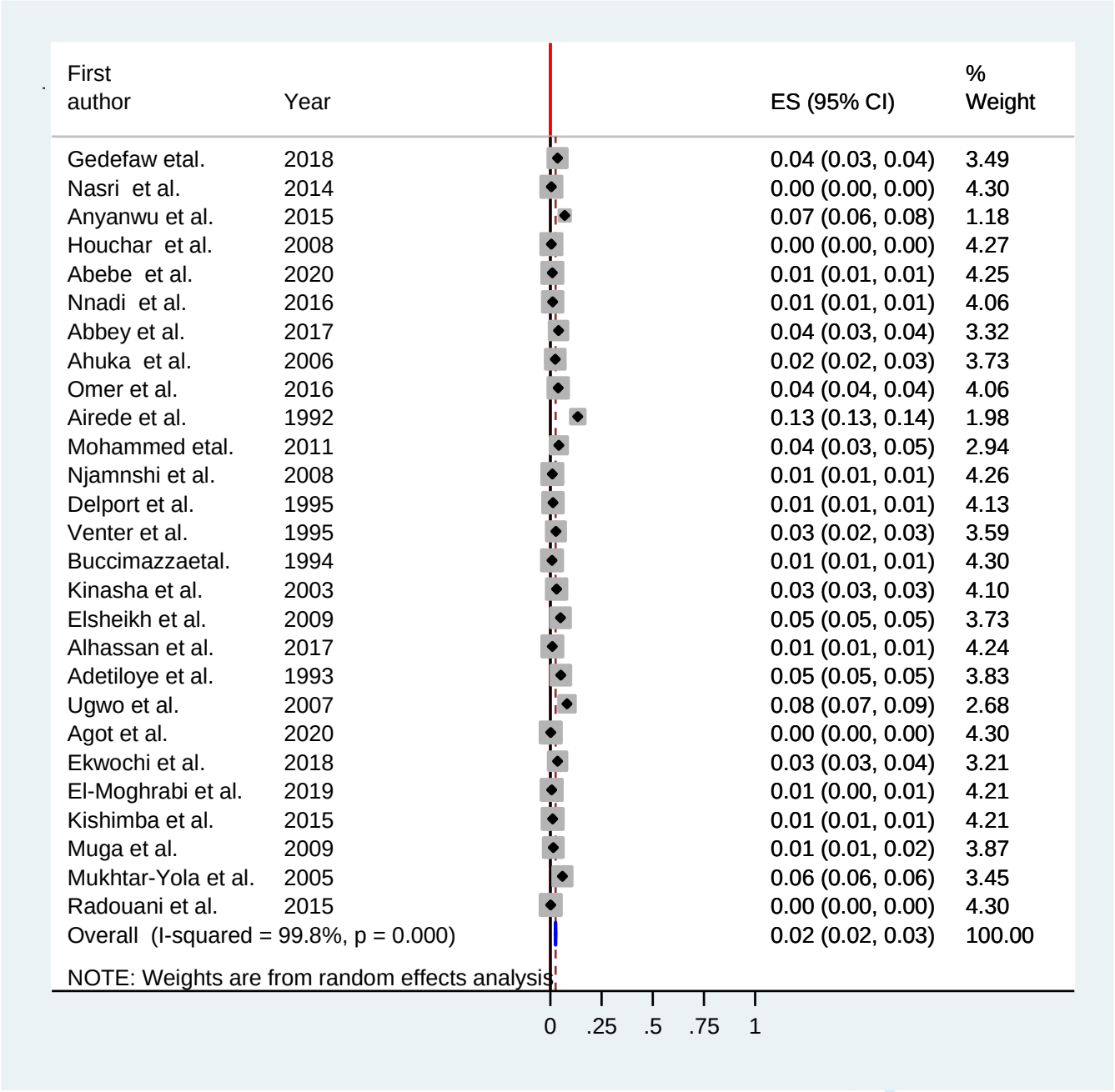

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa

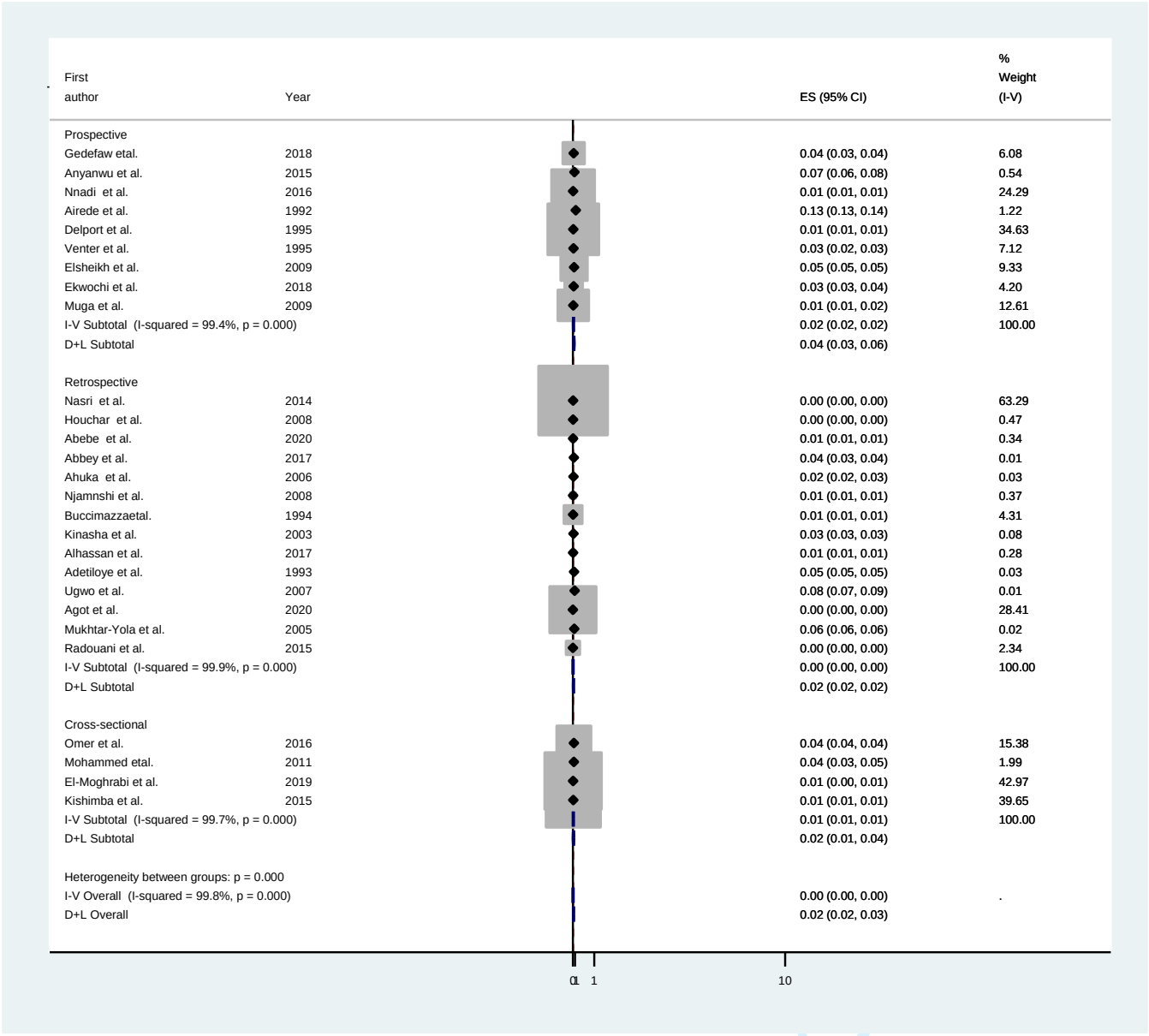

Figure 3: Subgroup analysis based on study design in Africa

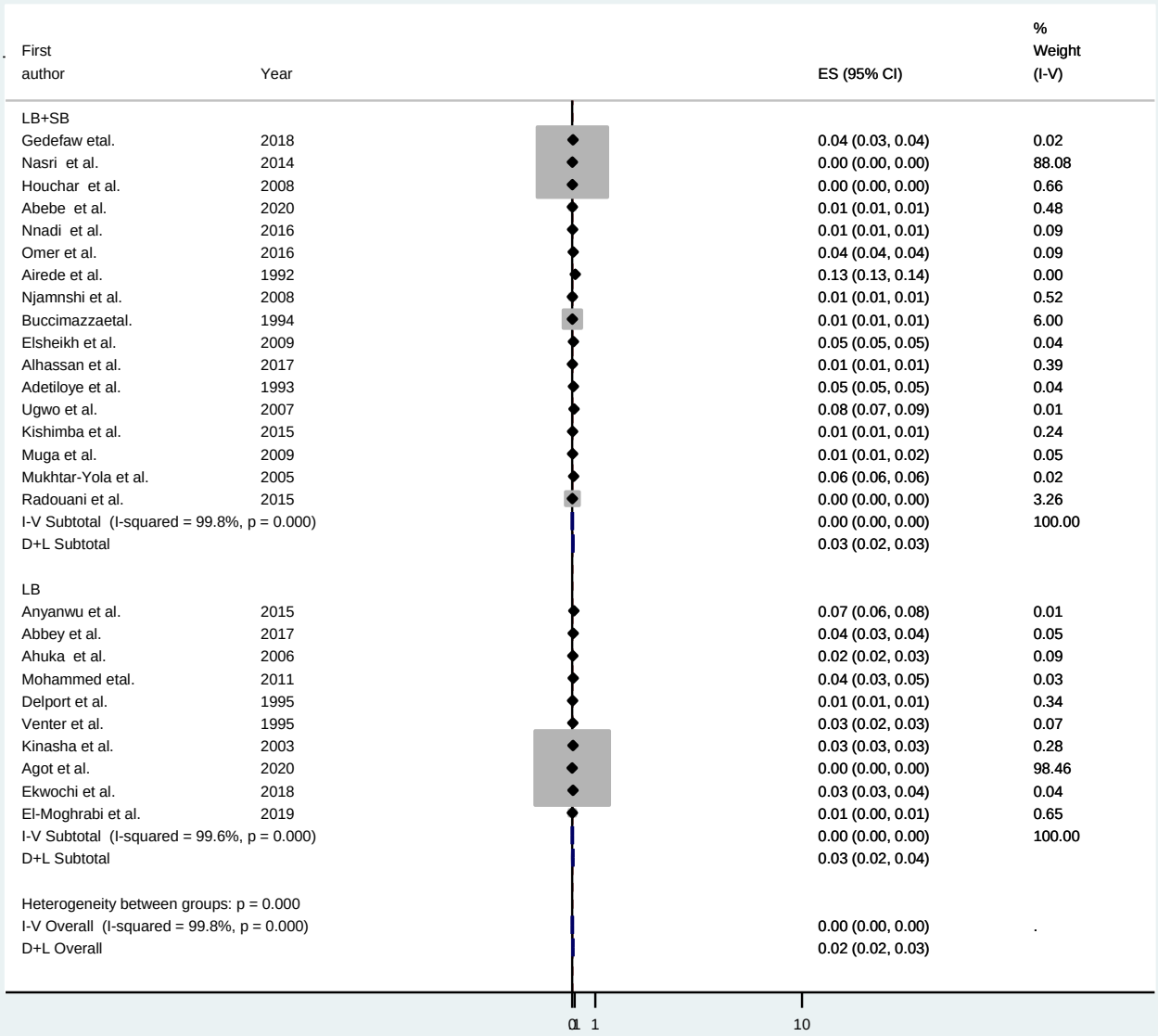

Figure 4: Subgroup analysis based on birth outcome in Africa

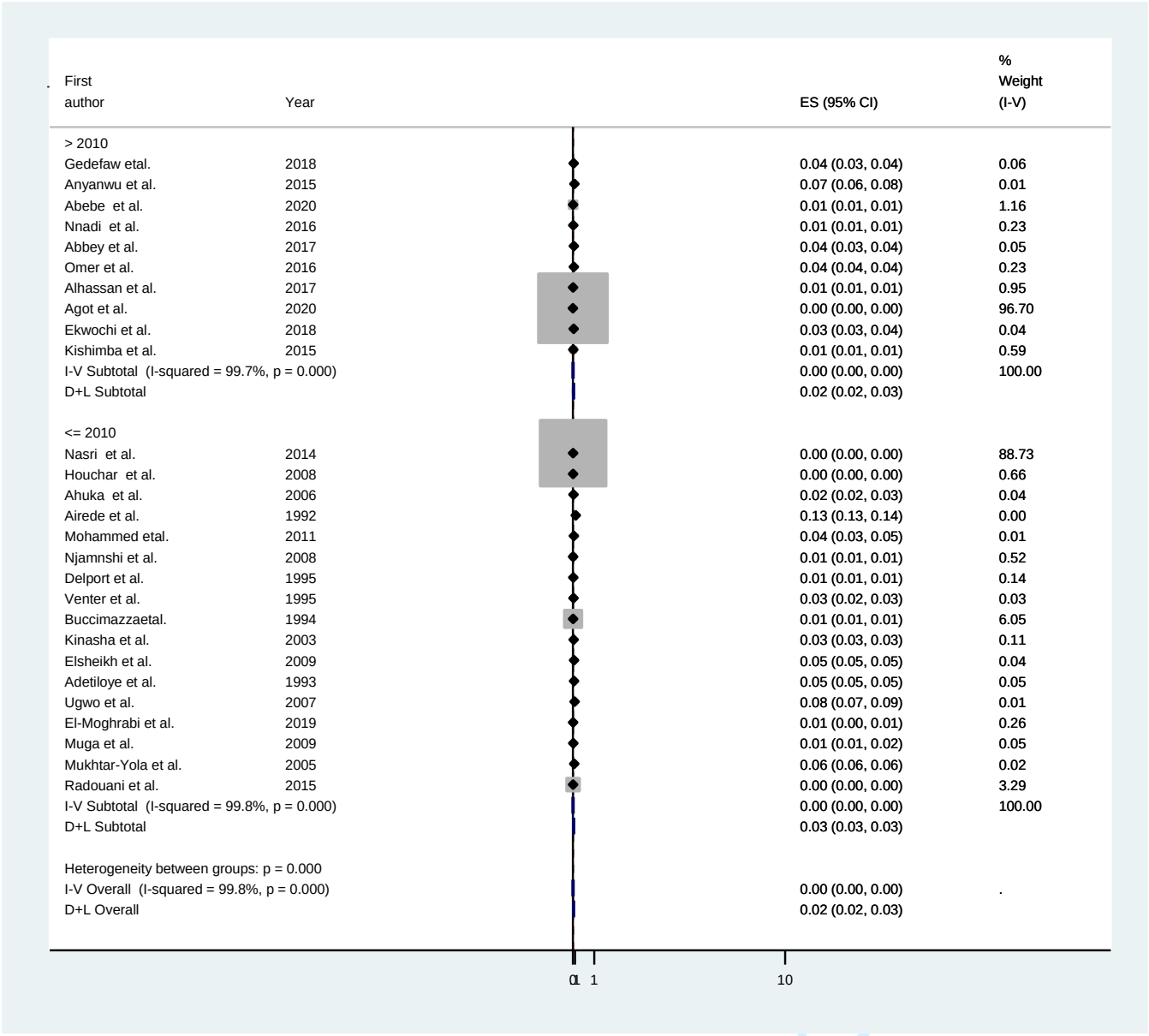

Figure 5: Subgroup analysis based on period prevalence in Africa

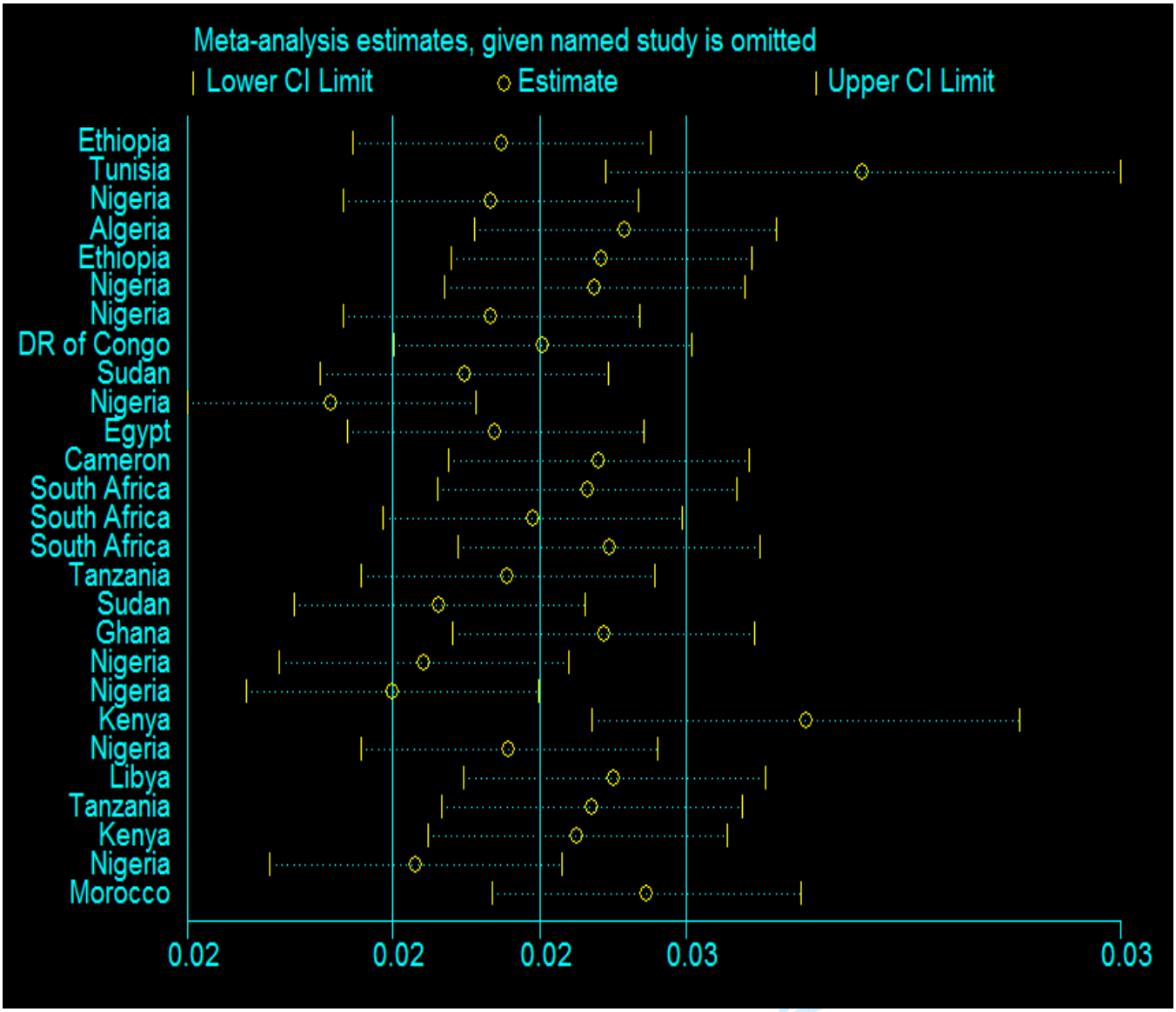

Figure 6: Sensitivity analysis to see the influence of each individual study in Africa

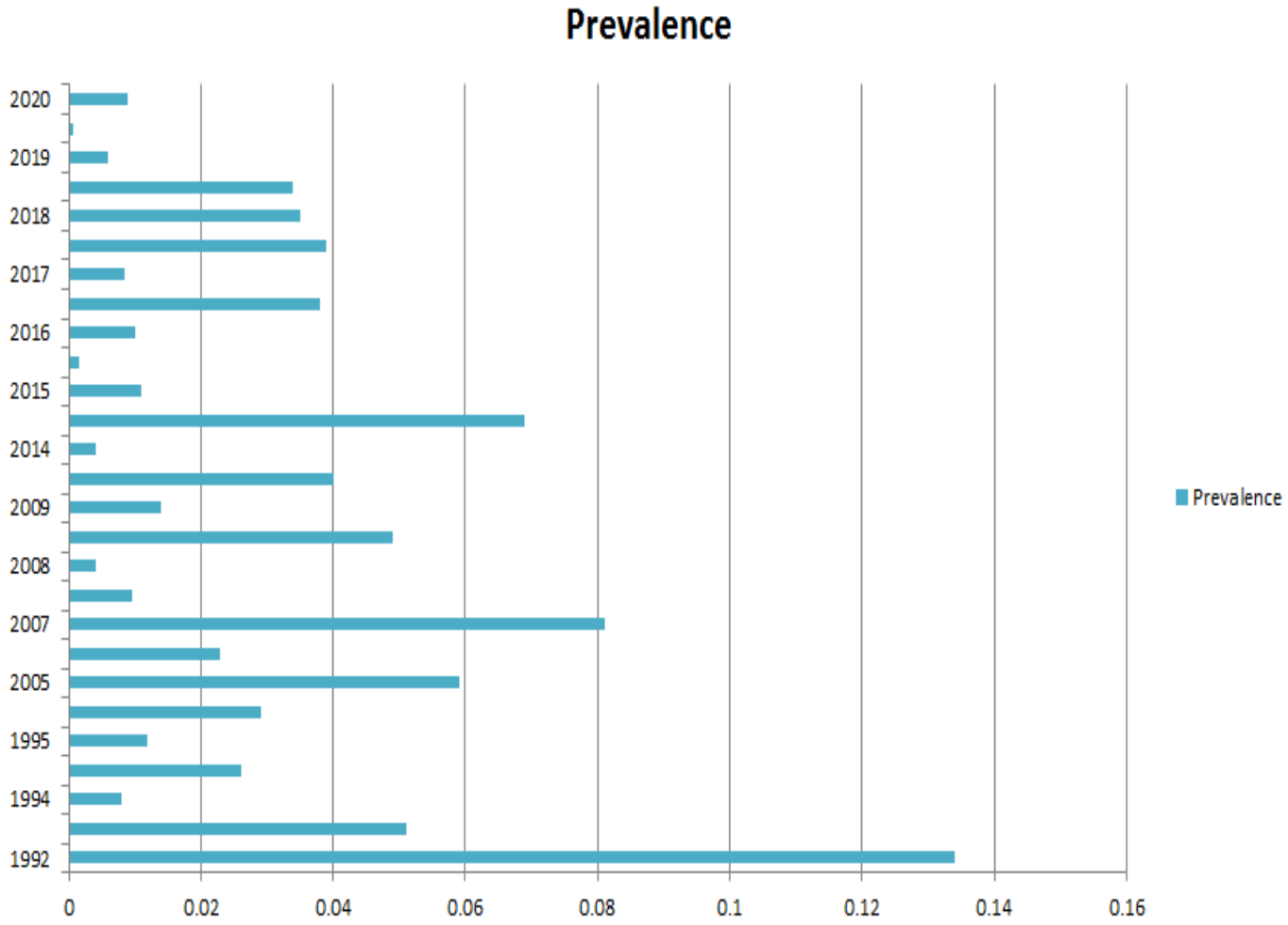

Figure 7: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa

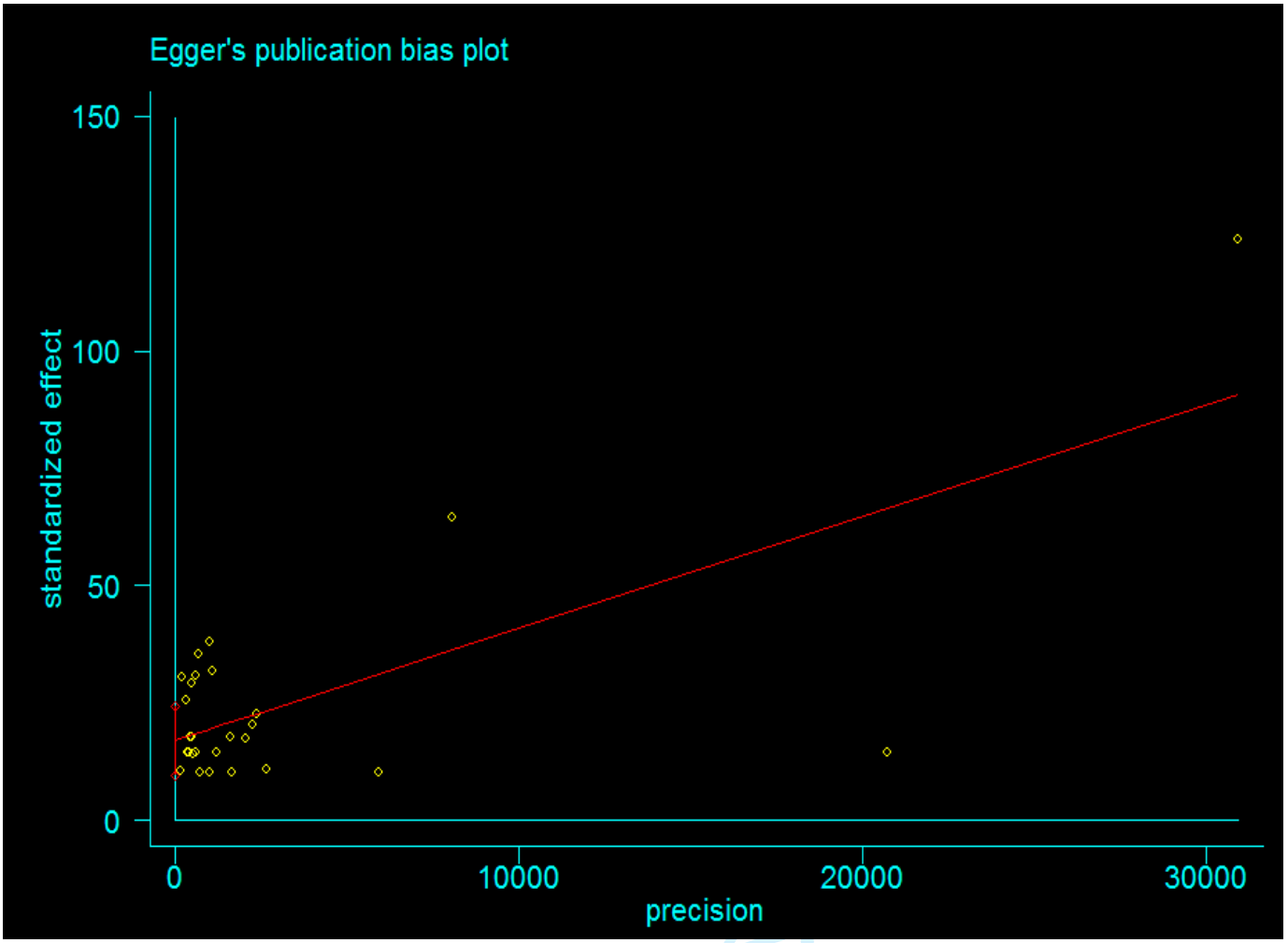

Figure 8: Egger's publication bias plot

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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

For more information, visit: **www.prisma-statement.org**.

PubMed Searching Methods

S.no.	Searching terms	Number of articles/results
1.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms] OR “cranium bifidum” OR “congenital malformations” OR “congenital defects” OR “structural birth defects” OR “structural abnormalities”) AND (newborns OR neonate OR “live births” OR “stillbirths”))	**5, 037**
Trans lations	("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("encephalocele"[MeSH Terms] OR "encephalocele"[All Fields] OR "encephaloceles"[All Fields] OR "encephalocoele"[All Fields] OR "encephalocoeles"[All Fields] OR "encephalocele"[MeSH Terms] OR "neural tube defects"[MeSH Terms] OR "cranium bifidum"[All Fields] OR "congenital malformations"[All Fields] OR "congenital defects"[All Fields] OR "structural birth defects"[All Fields] OR "structural abnormalities"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]) OR "live births"[All Fields] OR "stillbirths"[All Fields])	
2.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms]OR “cranium bifidum” OR “congenital malformations” OR “congenital defects” OR “structural birth defects” OR “structural abnormalities”) AND (newborns OR neonate OR “live births” OR “stillbirths”) AND (Africa))	228

3.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR "neural tube defects" [MeSH Terms]) AND (newborns OR neonate OR "live births" OR "stillbirths") AND (Africa))	101
4.	(Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR "neural tube defects" [MeSH Terms] OR "cranium bifidum") AND (newborns OR neonate OR "live births" OR "stillbirths") AND (Africa)	101
5.	(Prevalence) AND (encephalocele* OR encephalocele [MeSH Terms] OR "neural tube defect*" [MeSH Terms]) AND (newborn* OR neonate* OR "live birth*" OR "stillbirth*") AND (Africa)	99

JBI Critical Appraisal Checklist

JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2. Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3. Was the sample size adequate?	☐	☐	☐	☐
4. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6. Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7. Was the condition measured in a standard, reliable way	☐	☐	☐	☐

for all participants?

8. Was there appropriate statistical analysis? ☐ ☐ ☐ ☐

9. Was the response rate adequate, and if not, was the low response rate managed appropriately? ☐ ☐ ☐ ☐

Overall appraisal: Include ☐ **Exclude** ☐ **Seek further info** ☐

Comments (Including reason for exclusion)

_____

_____

_____

Supplementary file 4: The quality status of studies based on JBI critical appraisal checklist for studies reporting prevalence data

Studies	Appropriate sampling frame?	Appropriate sampling?	Adequate sample size?	Detail setting description?	Analysis with sufficient coverage?	Valid method to identify the condition?	Reliable measurement?	Appropriate statistical analysis?	Adequate response rate?	Total, out of 9
Gedefaw et al.	N/A	UC	Yes	Yes	Yes	Yes	Yes	Yes	N/A	8
Nasri et al.	Yes	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Anyanwu et al.	N/A	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Houchar et al.	Yes	N/A	Yes	No	Yes	No	No	Yes	N/A	6
Abebe et al.	Yes	N/A	Yes	Yes	Yes	No	UC	Yes	N/A	7
Nnadi et al.	N/A	N/A	Yes	Yes	Yes	Yes	UC	Yes	N/A	8
Abbey et al.	Yes	N/A	Yes	UC	Yes	Yes	Yes	Yes	N/A	8
Ahuka et al.	Yes	N/A	Yes	Yes	Yes	Yes	UC	UC	N/A	7
Omer et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	Yes	N/A	7
Airede et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	No	N/A	6
Mohammed et al.	N/A	N/A	Yes	UC	Yes	UC	Yes	Yes	N/A	7
Njamnshi et al.	Yes	N/A	Yes	Yes	Yes	UC	No	No	N/A	6
Delport et al.	Yes	N/A	Yes	UC	Yes	Yes	Yes	Yes	N/A	8
Venter et al.	N/A	N/A	Yes	Yes	Yes	Yes	UC	Yes	N/A	8
Buccimazza et al.	Yes	N/A	Yes	Yes	Yes	UC	No	UC	N/A	6
Kinasha et al.	Yes	N/A	Yes	No	Yes	UC	No	UC	N/A	5
Elsheikh et al.	N/A	N/A	Yes	No	UC	UC	No	Yes	N/A	5
Alhassan et al.	Yes	N/A	Yes	Yes	Yes	UC	UC	Yes	N/A	7
Adetiloye et al.	UC	UC	Yes	No	Yes	UC	UC	Yes	N/A	4
Ugwo et al.	UC	N/A	Yes	No	Yes	UC	UC	Yes	N/A	5
George et al.	Yes	No	Yes	Yes	UC	Yes	UC	Yes	N/A	6
Ekwochi et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	yes	N/A	7
El-Moghrabi et al.	UC	N/A	Yes	No	UC	Yes	Yes	Yes	N/A	6
Kishimba et al.	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	N/A	9
Muga et al.	N/A	N/A	Yes	UC	Yes	UC	Yes	Yes	N/A	7

Mukhtar-Yola et al.	Yes	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Radouani et al.	Yes	N/A	Yes	UC	Yes	Yes	UC	Yes	N/A	7

Key: UC: Unclear, N/A: Not Applicable. N/A for appropriate sampling means the study included all participants rather than sampling methods; N/A for adequate response rate means the study considered all recorded cases from all participants, so it is adequate; UC means it may be considered but not explicitly stated in the manuscript. For adequate sample size, as all participants included in the study during the study period, we considered an adequate sample size even if they did not calculate sample size (it is a total coverage).

BMJ Paediatrics Open

Birth prevalence of encephalocele in Africa: A systematic review and meta-analysis

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Manuscript ID	bmjpo-2021-001117.R2
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Date Submitted by the Author:	27-Aug-2021
Complete List of Authors:	Oumer, Mohammed; University of Gondar College of Medicine and Health Sciences, Department of Human Anatomy, School of Medicine Demissie, Alemnew; University of Gondar College of Medicine and Health Sciences, School of Medicine
Keywords:	Epidemiology, Neonatology, Neurosurgery, Cell Biology, Data Collection

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Birth prevalence of encephalocele in Africa: A systematic review and meta-analysis

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Word count = 3, 268

ABSTRACT

Objective: To identify the birth prevalence of encephalocele in Africa, 2020.

Methods: We carried out a systematic search of the following databases (PubMed/Medline, PubMed Central, Joanna Briggs Institute (JBI) Library, Cochrane Library, Web of Science, Google Scholar, Science Direct, African Journals Online, and Embase), using search terms (prevalence, encephalocele, "neural tube defects", "cranium bifidum", "congenital malformations", "congenital defects", "structural birth defects", "structural abnormalities", newborns/neonates/ "live births"/ "stillbirths", and their MeSH Terms) up to July 16, 2021. The JBI quality appraisal checklist was used to assess the quality of studies when they were abstracted using a standardized data extraction template. The I^2 statistic and Cochrane Q test were used to examine heterogeneity across studies statistically. The prevalence of encephalocele was estimated using a random-effect meta-analysis model. Subgroup, sensitivity, meta-regression, and time trend analysis were carried out. The publication bias was checked using Egger and Begg's tests.

Results: Twenty-seven relevant studies were identified and provided a total of 5, 107,109 births. In this systematic review and meta-analysis, the pooled birth prevalence of encephalocele in Africa was 0.02 % (or 2 per 10, 000 births) (95 % CI: 0.02, 0.03 %). The overall prevalence of birth encephalocele using the median from studies was 0.02 % (IQR (inter-quartile range) = 0.01 – 0.04 %). Higher prevalence of encephalocele was detected in Nigeria 0.06 % (95 % CI: 0.04, 0.08 %), Sudan 0.04 % (CI: 0.03, 0.05 %), Egypt 0.04 % (CI: 0.04, 0.05 %), DR of Congo 0.02 % (CI: 0.02, 0.03 %), Ethiopia 0.02 % (CI: -0.004, 0.05 %), and Tanzania 0.02 % (95 % CI: 0.002, 0.04 %). The prevalence of encephalocele per live birth was 0.03 % and both live birth and stillbirth was 0.03 %.

Conclusions: This review indicates a high prevalence of encephalocele, but studies were limited suggesting the need for additional research.

Keywords: Africa, encephalocele, prevalence, systematic review and meta-analysis

What is already known?

- Encephalocele is a birth abnormality associated with skull deformities defined by a partial absence of bone fusion that a portion of the brain protrudes.
- It is one of the leading causes of death and disability in newborns.

What this study adds?

- Although there are fragmented studies estimating the prevalence of encephalocele, there was no systematic review and meta-analysis on isolated encephalocele presenting this evidence.
- This review highlights the birth prevalence of encephalocele in African countries, providing crucial evidence for policymakers, clinicians, and the concerned bodies.
- This systematic review and meta-analysis will contribute to assist the prevention and control programs.

INTRODUCTION

Encephalocele is a birth abnormality associated with skull deformities defined by a partial absence of bone fusion, allowing a portion of the brain to protrude through a gap [1-3]. It is a form of neural tube birth abnormality that affects the brain [2-6]. The neural tube is a tiny canal that folds and closes to form the fetus's brain and spinal cord during the third and fourth weeks of gestation [1 4 6].

An opening will appear anywhere along the center of the skull from the nose to the back of the neck following the defect, but most commonly at the back of the head, the top of the head, or between the forehead and the nose [1 3]. Encephalocele is a sac-like protrusion of the brain and meninges through a hole in the skull (usually affecting the occipital area, the back of the skull) [2 6]. The protruding region of the brain is frequently covered by skin or a thin membrane, giving the abnormality the appearance of a tiny sac [5]. Its herniation process manifests as a pedunculated (with a stalk-like base) or sessile (with no stalk) cystic lesion [2]. Only the meninges protrude through the bone opening in the sac, causing cranial meningocele; however, the herniated sac contains brain tissue and meninges, causing encephalocele or meningoencephalocele. Hydroencephalocele is a deformity that occurs when a herniated sac contains a ventricle. Encephalomyelocele is a type of encephalocele that contains tissue from the brain and spinal cord [1-9]. Anatomically, encephalocele can be classified into sincipital (nasoorbital, frontoethmoidal, nasofrontal, interfrontal, nasoethmoidal, craniofacial cleft), basal (sphenoorbital, sphenomaxillary, intranasal, spenopharyngeal), convexity (sagittal, occipital, occipitocervical, parietal), and atretic [8 10 11]. Evidence suggests that an encephalocele is a form of post-neurulation defect distinct from closure-related neural tube defects [8 12].

The incidence of encephalocele varies by race and geographic region, ranging from 0.8 to 4 per 10,000 births [7 8 11]. According to the Centers for Disease Control and Prevention, encephalocele affects one out of every 10,000 babies born in the United States each year [1].

The majority of encephaloceles are massive, serious birth abnormalities that are detected before delivery. Some encephaloceles, however, are small and go undetected in extremely uncommon circumstances. Although the specific etiology of encephalocele is uncertain, scientists believe it is caused by a combination of causes [1-3].

The symptoms of an encephalocele vary from person to person, based on a variety of characteristics such as the size, location, and amount and kind of brain tissue protruding from the skull. The placement of the encephalocele is crucial because anterior (which usually does not contain brain tissue and has a better prognosis) and posterior (often associated with neurological problems) encephaloceles have different clinical consequences/implications for therapy and prognosis. Surgical management is usually required to return the protruding section of the brain and meninges to the skull and shut the incision/opening. However, encephalocele-related neurologic issues will persist, and long-term care may be required depending on the child's condition [1 2].

Encephalocele is the leading cause of death and disability in newborns [6 10 13 14], despite the fact that it can be reduced by various preventive and control strategies. Preventive strategies such as folic acid supplementation or fortification of staple foods can help to reduce it [3-6 13 14]. In order to make decisions and plan preventative services, it is essential to provide information to responsible bodies concerning the burden of encephalocele in Africa. The government, policymakers, health professionals, researchers, medical students, communities, and non-governmental organizations will benefit from this review, which will help to reduce the burden of the encephalocele and allow for more study. Moreover, little is known about the magnitude of encephalocele in Africa as a whole. Thus, the present systematic review and meta-analysis aimed to identify the pooled birth prevalence of encephalocele in Africa, 2020.

METHODS

Reporting of the findings and review registration

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements were used to report the current systematic review and meta-analysis [15] (Supplementary File 1). The review protocol has been registered in PROSPERO with the registration ID of CRD42021242161.

Search strategies

PubMed/Medline, PubMed Central, Cochrane Library, JBI Library, Science Direct, Web of Science, African Journals Online, WHO, UCSF, and Embase databases were systematically searched for relevant studies (reference lists of identified articles were also navigated) up to July 16, 2021. The primary search was conducted in an advanced PubMed database (using search terms prevalence, encephalocele, "neural tube defects", "cranium bifidum", "congenital malformations", "congenital defects", "structural birth defects", "structural abnormalities", newborns/neonates/"live births"/"stillbirths", and their MeSH Terms). The core search terms and phrases were considered interchangeably in different databases. Moreover, grey literature was retrieved using Google and Google Scholar searches. The full search strategy is being shown online (Supplementary File 2).

Eligibility criteria

Inclusion criteria

Published and unpublished full-text studies in any period and study designs (a cross-sectional, prospective cohort that included original data) that report the birth prevalence of encephalocele in Africa were included in this review.

Exclusion criteria

Case reports, conferences, editorials, anonymous reports, and research with limited access (after two emails to the corresponding author) were excluded from the review. Moreover, a study was excluded if the total number of cases and births included in the study were not indicated explicitly.

Review outcomes

The outcome of the current review was the pooled birth prevalence of encephalocele in Africa. Birth prevalence of encephalocele is defined as the number of encephalocele cases of live births and/or stillbirths at birth (numerator) from the total number of births (live births and/or stillbirths) during the study period (denominator).

Quality assessment

The JBI quality appraisal checklist was used to evaluate the quality of each study [16]. The JBI critical appraisal checklist (which has nine items) was adapted for the studies reporting the prevalence data (Supplementary File 3). Using the framework, two reviewers (MO and AD) independently evaluated the quality of each study. During the evaluation of quality, disagreements between reviewers were resolved by using the average score of the two reviewers. In the end, if the study received five or more points on all quality assessment items, it was deemed low risk [17].

Study selection and data abstraction

After retrieving all of the studies from the databases, they were loaded into the reference manager, an Endnote Version 7 software program, to eliminate duplicates. The reviewers then screened the research for inclusion based on the title and abstract. All necessary data were extracted independently by two reviewers (MO and AD) using a defined data extraction template after thoroughly reading full-text studies and including the eligible studies. The main author, sample size, study nation, study

duration, study design, study location, publication year, prevalence period, folic acid fortification policy, birth status, birth outcome, and birth prevalence of encephalocele were all included in this template.

Meta-analysis

For further analysis, the data were extracted in Microsoft Excel and exported to STATA 14 Statistical Software. For each study, the prevalence was estimated per hundred births to preserve uniformity.

The Cochrane Q test and the I^2 statistic were used to examine statistically the heterogeneity between studies and a forest plot was used to visualize heterogeneity [18]. This revealed considerable heterogeneity among studies (P-value<0.001). Therefore, to determine the pooled prevalence of encephalocele, a random-effect meta-analysis approach was applied [19 20]. Sub-group analysis was performed based on selected variables (the study country, study design, birth outcome, folic acid fortification status, epidemiological design, and status of births). A sensitivity analysis was done to see the influence of a single study on the overall estimate of meta-analysis. Meta-regression analysis was accounted for to identify the source of heterogeneity. A time-trend analysis was conducted as well.

Assessment of publication bias

Graphically, Egger's plot was used to visualize the publication bias. Objectively, Egger's regression test and Begg's test statistics were used to detecting publication bias [21 22]. As a result, publication bias was defined as a P-value ≤ of 0.05.

Patient and public involvement

"No patient involved."

RESULTS

Study selection

A total of five thousand four hundred twenty-two articles were initially retrieved on the prevalence of encephalocele through PubMed, Google Scholar, and others from Cochrane, JBI Library, WHO, Medline, UCSF, African Journal Online, Science Direct, and Embase. Of these, one thousand five hundred thirty-six were excluded due to duplicated articles. From the remaining three thousand eight hundred eighty-six studies, three thousand six hundred sixty studies were excluded after reviewing the titles and abstracts because they were found non-relevant for this review. Full texts of the remaining two hundred twenty-six studies were screened. This systematic review and meta-analysis comprised twenty-seven studies that met the inclusion criteria [23-49] (Figure 1).

Characteristics of the original studies

The included studies were either cross-sectional (n=4), retrospective (n= 14), or prospective studies (n=9) [23-49]. Of all studies, eight were conducted in Nigeria [23-30], three in South Africa [31-33], two in Ethiopia [40 41], two in Tanzania [34 35], two in Kenya [36 37], and two in Sudan [38 39]. Studies conducted in Morocco, Tunisia, Algeria, the Democratic Republic (DR) of Congo, Egypt, Cameron, Ghana, and Libya were also identified [42-49]. All studies included in this review were facility-based studies, published in the year between 1992 and 2020 [23-49]. South Africa (started fortification in 2003), Nigeria (in 2002), Tanzania (in 2011), and Kenya (in 2012) have mandatory folic acid fortification with Wheat Flour and Maize Flour. Morocco (in 2006), Cameron (in 2011), and Ghana (in 2006) have mandatory folic acid fortification with Wheat Flour. Ethiopia and Sudan have a voluntary folic acid fortification policy with Wheat Flour at this time. Based on birth status, four studies mentioned the inclusion of twin birth and multiple births in addition to singleton births

[29 36 40 43] while all other studies not mentioned their birth status. Generally, twenty-seven studies reported a total of 5, 107,109 births, ranged from 1,456 to 3,803, 889 births [27 46] (Table 1).

Table 1: The characteristics of studies included in the systematic review and meta-analysis

First author	Year	Country	Study design	Sample size	Period prevalence	Duration ©	Birth outcome	Epidemiological study	Prevalence (%)
Airede et al. [23]	1992	Nigeria	PS	5,977	Jun 1987 - Jun 1990	36	LB+SB	Incidence	0.134
Adetiloye et al. [24]	1993	Nigeria	RS	23,438	1982 – 1992	120	LB+SB	Incidence	0.051
Mukhtar-Yola et al. [25]	2005	Nigeria*	RS	13,619	Oct 1998- Nov 2004	72	LB+SB	Prevalence	0.059
Ugwo et al. [26]	2007	Nigeria*	RS	7,388	May 2002- Apr 2005	36	LB+SB	Incidence	0.081
Anyanwu et al. [27]	2015	Nigeria*	PS	1,456	Apr 2013- Dec 2013	9	LB	Prevalence	0.069
Nnadi et al. [28]	2016	Nigeria*	PS	10,163	Jan 2011- Dec 2013	36	LB+SB	Prevalence	0.01
Abbey et al. [29]	2017	Nigeria*	RS	7,670	Aug 2011- Dec 2014	48	LB§	Prevalence	0.039
Ekwochi et al. [30]	2018	Nigeria*	PS	5,830	Jan 2013- Jan 2017	48	LB	Incidence	0.034
Buccimazzaetal. [31]	1994	South Africa	RS	516,252	Jan 1973 - Dec 1992	240	LB+SB	Prevalence	0.008
Delport et al. [32]	1995	South Africa	PS	17,351	May 1986- Apr 1989	36	LB	Incidence	0.012
Venter et al. [33]	1995	South Africa	PS	7,617	Jun 1989 - Dec 1992	40	LB	Incidence	0.026
Kinasha et al. [34]	2003	Tanzania	RS	34,000	Jan 2000 - Jan 2002	24	LB	Incidence	0.029
Kishimba et al. [35]	2015	Tanzania*	CS	28,217	Oct 2011- Feb 2012	5	LB+SB	Prevalence	0.011
Muga et al. [36]	2009	Kenya	PS	7,355	Sep 1983- Sep 1984	12	LB+SB§	Incidence	0.014
Agot et al. [37]	2020	Kenya*	RS	299,854	Jan 2014 - Dec 2018	60	LB	Prevalence	0.0007
Elsheikh et al. [38]	2009	Sudan	PS	18,378	Feb 2003 - Jan 2004	12	LB+SB	Incidence	0.049
Omer et al. [39]	2016	Sudan*	CS	36,785	Aug 2014 - Jul 2015	12	LB+SB	Prevalence	0.038
Gedefaw etal. [40]	2018	Ethiopia*	PS	8,677	Feb 2016- Aug 2016	7	LB+SB®	Incidence	0.035
Abebe et al. [41]	2020	Ethiopia*	RS	45,951	Sep 2011- Dec 2015	60	LB+SB	Prevalence	0.009
Ahuka et al. [42]	2006	DR of	RS	8,824	Jan 1993 -	96	LB	Incidence	0.023

Houchar et al. [43]	2008	Congo Algeria	RS	28,500	Aug 2001 2004 -2006	36	LB+SB®	Prevalence case-control	0.004
Njamnshi et al. [44]	2008	Cameron	RS	52,710	Jan 1997 - Dec 2006	120	LB+SB	Incidence	0.0095
Mohammed etal. [45]	2011	Egypt	CS	5,000	Mar 2007- Oct 2007	7	LB	Prevalence	0.04
Nasri et al. [46]	2014	Tunisia	RS	3,803,889	1991-2011	240	LB+SB	Prevalence	0.004
Radouani et al. [47]	2015	Morocco*	RS	60,017	Jan 2008- Dec 2011	48	LB+SB	Prevalence	0.0017
Alhassan et al. [48]	2017	Ghana*	RS	35,426	Jan 2010 - Dec 2014	48	LB+SB	Prevalence	0.0085
El-Moghrabi et al. [49]	2019	Libya	CS	16,765	Sep 2004- Aug 2005	12	LB	Incidence	0.006

Key: CS: Cross-sectional; PS: Prospective; RS: Retrospective; LB: Live births; SB: Stillbirths; ® Singleton births + twin births; § Singleton births + twin births + multiple births; Mandatory and/or voluntary folic acid fortification policy; © duration per months

Quality of the studies

Using JBI quality appraisal criteria, all included studies were evaluated for their quality. Each study was evaluated using the evaluation checklist for prevalence studies, which consists of nine questions/items with Yes, No, Unclear, or Not Applicable responses. The quality assessment grading for all items was based on the JBI descriptions for each item. As a result, the studies' quality scores ranged from four to nine. Therefore, except for one study that received a four, none of the studies had a significant risk of being of poor quality [23-49] (Supplementary file 4).

Meta-analysis

Prevalence of encephalocele

In the present meta-analysis, the pooled birth prevalence of encephalocele was 0.02 % (or 2 per 10,000 births) (95 % CI: 0.02, 0.03 %). A Forest plot showed that there was statistically significant heterogeneity across the studies. Therefore, the random-effect meta-analysis model was applied to

pool the overall prevalence of the studies (Figure 2). Considering all included studies, the median value of birth encephalocele was 0.02 % and the inter-quartile range was between 0.01 and 0.04 %. The minimum and maximum values of birth encephalocele were 0.0007 and 0.134 %, respectively (Supplementary File 5).

Subgroup analysis

Subgroup analysis based on the study country, study design, birth outcome, folic acid fortification status, epidemiological design, and status of births was carried out to see the variation of the prevalence across the studies.

Subgroup analysis based on the study country was performed to see the pooled prevalence of each country in Africa. High pooled prevalence of encephalocele was detected in Nigeria 0.06 % (95 % CI: 0.04, 0.08 %), Sudan 0.04 % (95 % CI: 0.03, 0.05 %), Egypt 0.04 % (95 % CI: 0.04, 0.05 %), DR of Congo 0.02 % (95 % CI: 0.02, 0.03 %), Ethiopia 0.02 % (95 % CI: -0.004, 0.05 %), and Tanzania 0.02 % (95 % CI: 0.002, 0.04 %) (Table 2). In the present review, statistically significant heterogeneity between countries was detected (P-value = 0.001, I^2= 97.1-99.8 %). Therefore, the Der Simonian and Laird's (D+L) pooled prevalence method was considered because it is more conservative than the inverse variance method (I-V). The difference between countries was significant (P-value<0.001).

Table 2: The pooled prevalence of encephalocele among African countries

Country	Prevalence in % (95 % CI)
Morocco	0.002 (0.001, 0.002)
Tunisia	0.004 (0.004, 0.004)
Algeria	0.004 (0.003, 0.005)

Libya	0.006	(0.005, 0.007)
Kenya	0.007	(-0.006, 0.020)
Cameron	0.009	(0.009, 0.010)
Ghana	0.009	(0.008, 0.009)
South Africa	0.015	(0.008, 0.022)
Tanzania	0.020	(0.002, 0.038)
Ethiopia	0.022	(-0.004, 0.047)
DR of Congo	0.023	(0.020, 0.026)
Egypt	0.040	(0.035, 0.045)
Sudan	0.043	(0.033, 0.054)
Nigeria	0.059	(0.038, 0.081)
D+L pooled ES	**0.025**	**(0.023, 0.027)**

Subgroup analysis based on study design, using the D+L method (P-value<0.001, I^2 = 99.4-99.9 %), the prevalence of encephalocele for retrospective studies was 0.02 % and for prospective studies was 0.04 % (Figure 3).

Subgroup analysis based on birth outcome was done to see the burden in live births only (LB) and both live births and stillbirths (LB+SB). The pooled prevalence of encephalocele per live birth was 0.03 % (95 % CI: 0.02, 0.04 %) and both live birth and stillbirth was 0.03 % (95 % CI: 0.02, 0.03 %) (Figure 4).

Subgroup analysis based on folic acid fortification policy was considered (P-value<0.001, I^2 =99.7%) and the prevalence of encephalocele for countries that had a mandatory and/or voluntary folic acid fortification was 0.03 % (95 % CI: 0.02, 0.03 %), and for countries that had no either a mandatory or voluntary fortification was 0.03 % (95 % CI: 0.02, 0.03 %).

The prevalence of encephalocele for incidence studies was 0.04 % (95 % CI: 0.03, 0.05 %), for prevalence studies was 0.02 % (95 % CI: 0.02, 0.02 %), and for prevalence case-control studies was 0.004 % (95 % CI: 0.003, 0.005 %).

The prevalence of encephalocele for singleton births was 0.03 % (95 % CI: 0.02, 0.03 %), for singleton and twin births was 0.02 % (95 % CI: -0.01, 0.05 %), and for singleton, twin, and multiple births was 0.03 % (95 % CI: 0.002, 0.05 %).

Meta-regression analysis

In the present systematic review and meta-analysis, sample size (P-value = 0.44), year of publication (P-value = 0.34), duration of the study in months (P-value = 0.20), study country (P-value = 0.02), study design (P-value = 0.56), birth outcome (P-value = 0.55), epidemiological design (P-value = 0.37), folic acid fortification (P-value = 0.91), and the JBI quality score (P-value = 0.06) were analyzed for the source of heterogeneity. The only study country was significant for the source of heterogeneity.

Sensitivity analysis

In this review, no study was found that has a special influence over others on the overall estimation of meta-analysis (Figure 5). Essentially, all studies have uniform confidence intervals. Sensitivity analysis does not help to explain heterogeneity because the heterogeneity between studies was not significantly reduced (P-value < 0.001, I^2= 99.7-99.8%), after doing the analysis with a few studies. We performed also leave-one-out analyses; the heterogeneity among studies was not significantly reduced.

We used sensitivity analysis to examine the impact of low-quality studies on total estimates by reducing the number of studies included in a meta-analysis. We found the meta-analysis estimates by

including only high-quality studies with a score greater than or equal to five. As a result, we got a similar output with the previous finding and, the pooled estimate was 0.02% (95% CI: 0.02, 0.03).

Time trend analysis

The time trend analysis showed the relationship between the prevalence of encephalocele and publication year. In this trend in Africa, the highest peak of encephalocele in prevalence was observed in 1992, 2007, 2014-2015, and 2005 (Figure 6).

Publication bias

Publication bias was estimated using the Egger's regression tests (B-coefficient of bias: 17; P-value = 0.001). Egger's plot supported its results (Figure 7).

DISCUSSION

Encephalocele is a central nervous system abnormality that occurs at birth. The hidden burden of encephalocele was high in Africa. Data is lacking on the true burden of this condition, leading to neglect in the treatment and prevention by health systems in Africa. The responsible authorities or bodies have neglected this defect too. The effects of the malformation are related to substantial mortality, disability, and psychological costs (the psychosocial problem of having an infant with a "monstrous outlook" or "two heads"). Although encephalocele is a rare congenital anomaly, it is correlated with severe morbidity and mortality if untreated [7 8]. Folic acid supplementation and termination of pregnancies diagnosed with encephalocele prenatally have reduced the occurrence or incidence of this type of congenital abnormality, particularly in developed (high-income) countries.

The birth prevalence of encephalocele was 0.02 % (or 2 per 10,000 births) in this meta-analysis. This finding is comparable to different findings reported elsewhere (ranged from 0.8 to 4.0 per 10,000

births) [4-8 11]. Besides, it is comparable to the review done in low-and middle-income countries (2.1 per 10,000 births) [50]. The review result suggested that low-and middle-income countries were mostly affected by this malformation every year [50]. However, the review did not include studies from Africa except for two studies. Our finding is higher than that reported by certain high-income countries (1.0 per 10,000 births) [1]. Recent research shows that the prevalence of encephalocele varies across time, geography, and population to population [8]. Our analysis also revealed considerable differences between African countries and prevalence over time. Subgroup analyses were carried out based on the study nation, design, birth outcome, birth status, and the availability of a folic acid fortification program. As a result, a considerable disparity in the occurrence of encephalocele in different African countries was discovered in this study. Nigeria 0.06 %, Sudan 0.04 %, Egypt 0.04 %, Congo (DR) 0.02 %, Ethiopia 0.02 %, and Tanzania 0.02 % had a high prevalence of encephalocele. This disparity could be explained by mothers' levels of knowledge about folic acid supplementation, as well as the country's health policy on folic acid fortification and other preventive measures. The notion of the presence of geographical variation between the countries was supported by the previous studies [6-8]. The variation in different publication years of the different studies was noted using time trend analysis. The highest peak of encephalocele in prevalence was seen in 1992, 2007, 2014-2015, and 2005. The prevalence estimate for live births was similar to both live birth and stillbirth estimations. Surprisingly, all studies in this review were facility-based studies. Thus, there may have been an underestimating of encephalocele estimations because it did not include many stillbirths and home deliveries in the community context (included the participants delivered at the hospital setting).

The findings of the current systematic review and meta-analyses should be interpreted based on some limitations. The presence of significant variation across countries may affect/underestimate the

pooled prevalence of the defect in Africa. Moreover, the prevalence estimate did not include terminated pregnancies of encephalocele; this may lower the pooled prevalence estimates. The estimated report may be influenced by the sample size's adequacy or variability. Furthermore, publication bias was detected by Egger's regression tests that may not decrease by trim and fill meta-analyses. Underestimation of the burden of encephalocele should be considered because many home births that are delivered in the community setting were not included. The review was represented by twenty-seven studies due to limited available data about encephalocele.

Fragmented studies have been conducted to estimate the country-level prevalence of encephalocele. However, the findings were inconsistent and varied and there is no empirical evidence on the pooled prevalence estimates in Africa. Besides, studies on isolated encephaloceles are quite rare. The available evidence on encephalocele is in aggregate/combined form with either neural tube defects or birth defects of the central nervous system. Interestingly, the present systematic review and meta-analysis highlight the birth prevalence of encephalocele in African countries, providing crucial evidence for policymakers, clinicians, and the concerned bodies who neglected the burden of this defect. Recognizing a high burden in Africa may initiate the policymakers to develop effective control and prevention strategies and may use their ultimate potential in reducing the burden of the encephalocele and making further research possible. Additionally, the high burden detected in our review may inform policymakers positively on policy decisions related to prevention efforts in Africa where policymakers may feel that this is not a big enough problem for prioritizing prevention funds. The severity, the observed differences in prevalence estimate among countries, may contribute by informing clinical and policy guidelines in the prioritization of interventions, and maintaining robust surveillance systems that track or screen all pregnancy outcomes or all births in Africa. Besides, future research works might benefit from the information gained from the current review when

designing and developing new studies. Furthermore, it helps additional clinical studies to focus on risk factors, prevention, intervention, and psychosocial outcomes of the defect in isolated form. More research should be conducted in Africa to assess the effectiveness of folic acid in reducing the burden of the encephalocele and, notably, to determine how and why interventions either work or do not work in each country that followed either a mandatory or voluntary fortification policy. All these should be the ultimate contribution of this review to the field in assisting the prevention and control programs.

CONCLUSION

This systematic review and meta-analysis showed that encephalocele is highly prevalent in Africa. The prevalence of encephalocele was high in Nigeria, Sudan, Egypt, DR of Congo, Ethiopia, and Tanzania. A similar prevalence of encephalocele was observed in the studies that included only live births and in studies that included both live births and stillbirths. The reviewers recommend that special awareness be created for reproductive-age women with an emphasis on prevention in order to reduce the encephalocele burden. Due to the scarcity of data on encephalocele in Africa, more primary research is needed to increase the estimated burden of the encephalocele and promote favorable aid strategies for prevention.

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Abbreviations: Not applicable.

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Figure Legends

Figure 1: Study selection flow diagram; a figure adapted from the PRISMA) group statement for this review

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa

Figure 3: Subgroup analysis based on study design in Africa

Figure 4: Subgroup analysis based on birth outcome in Africa

Figure 5: Sensitivity analysis to see the influence of each individual study in Africa

Figure 6: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa

Figure 7: Egger's publication bias plot

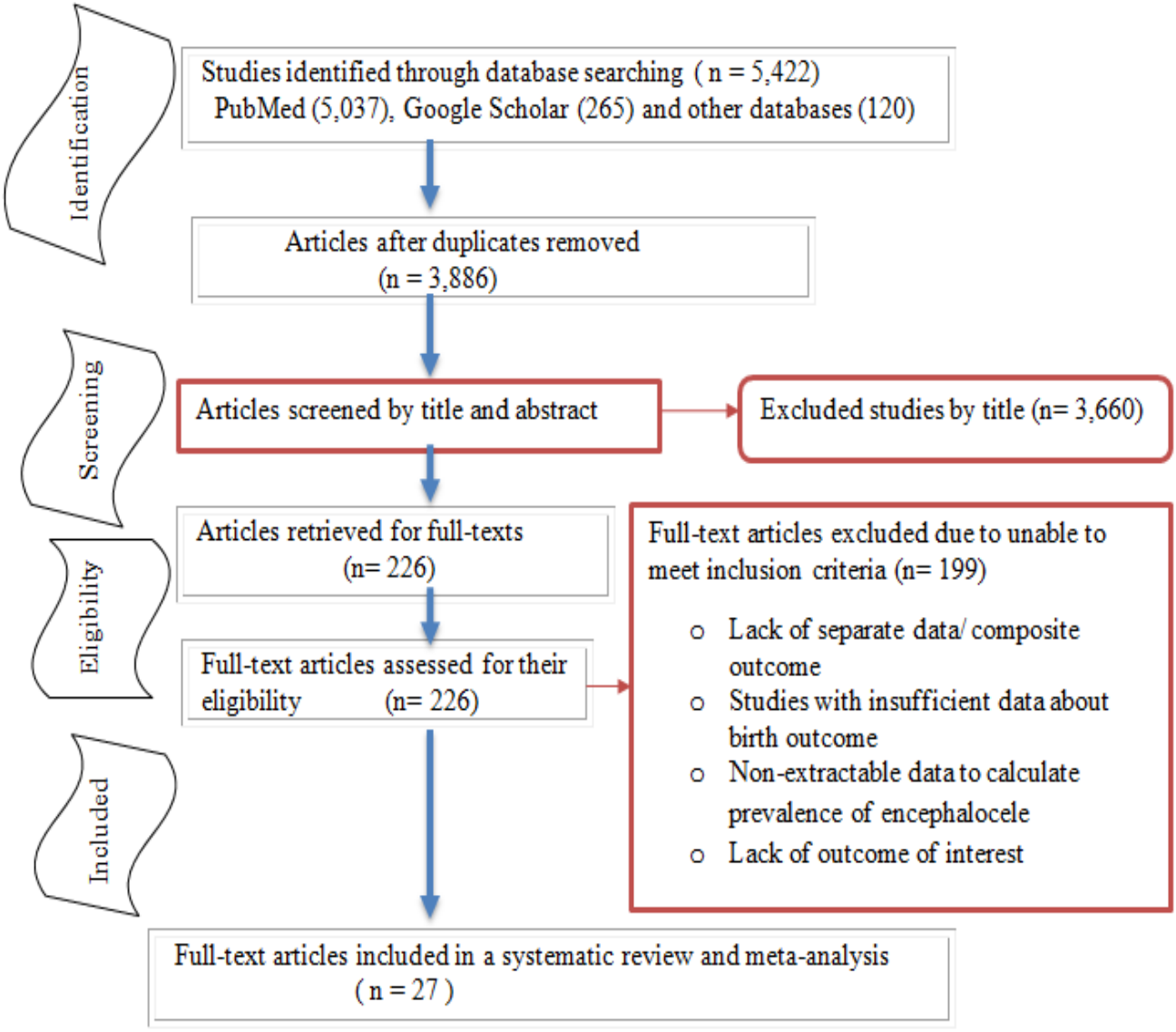

Figure 1: Study selection flow diagram; a figure adapted from the PRISMA group statement for this review

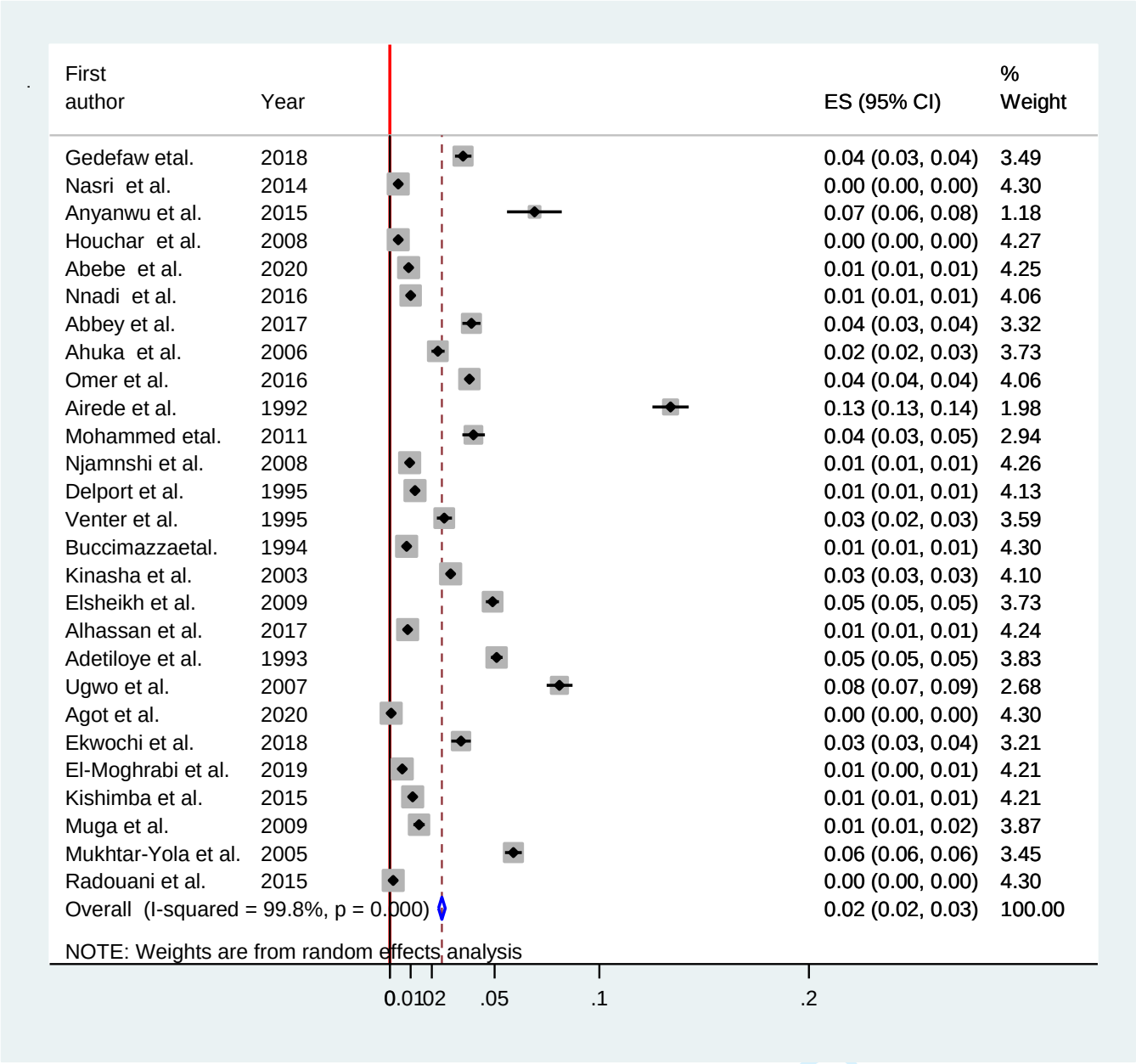

Figure 2: Forest plot showing the pooled prevalence of encephalocele in Africa

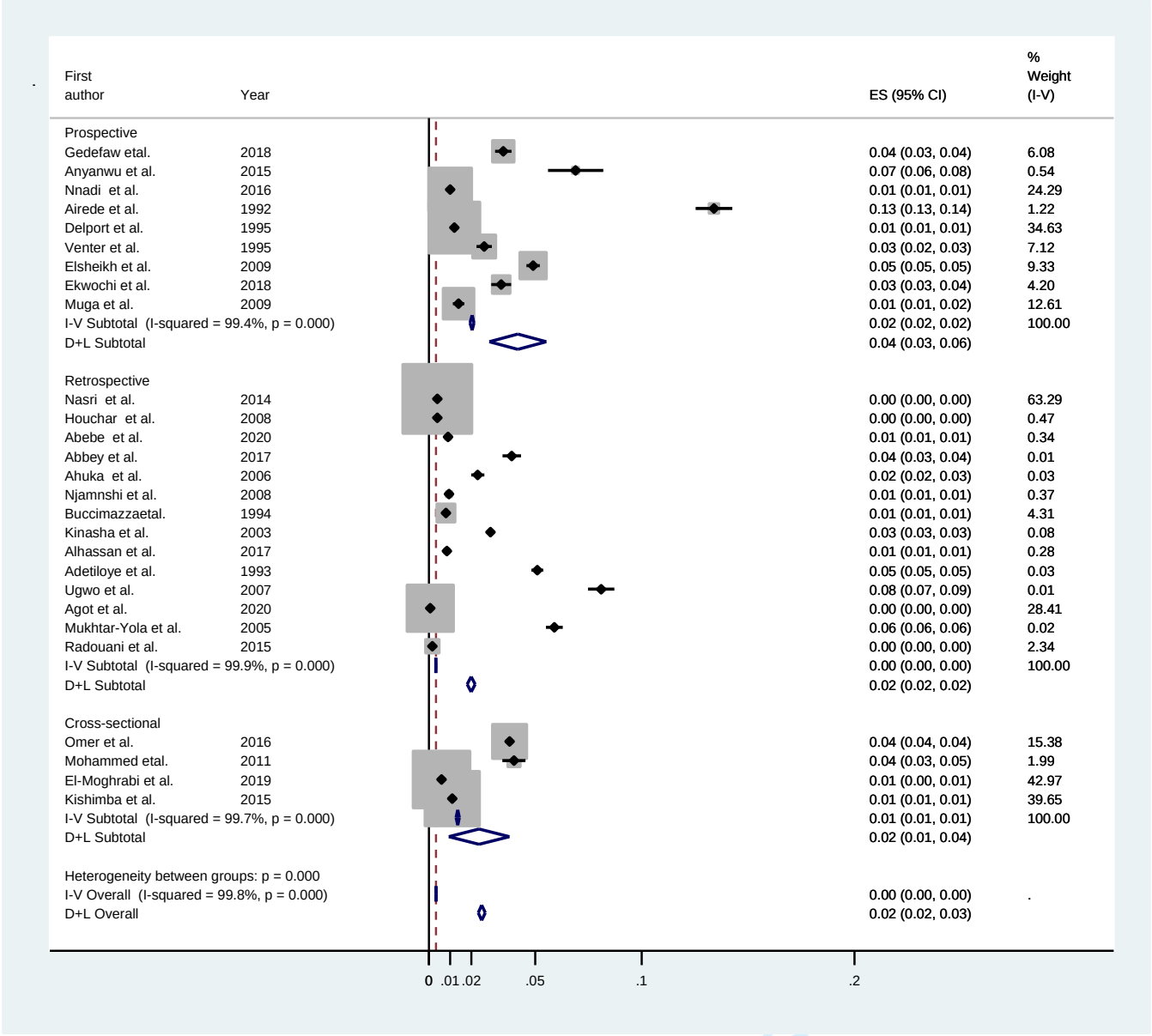

Figure 3: Subgroup analysis based on study design in Africa

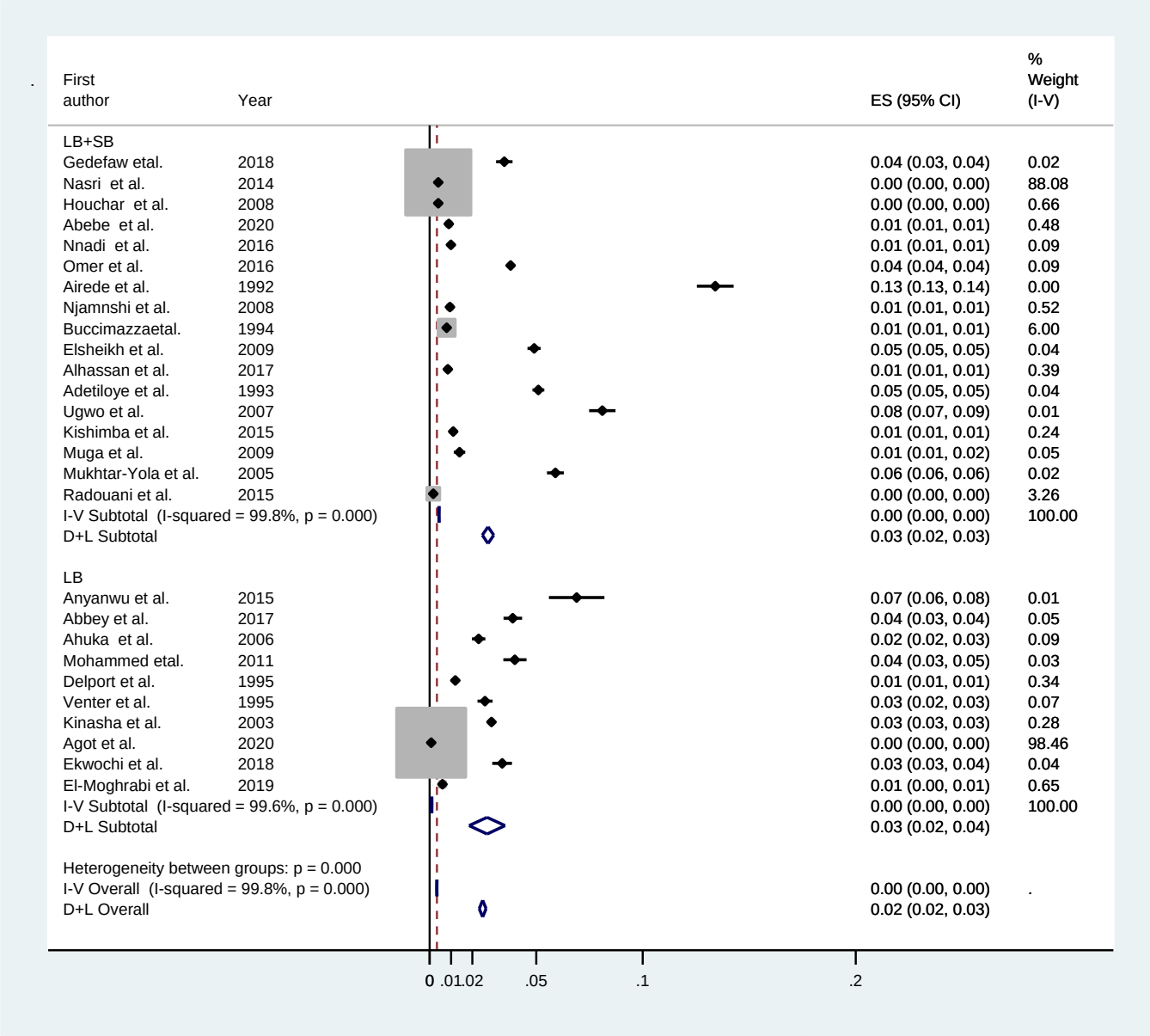

Figure 4: Subgroup analysis based on birth outcome in Africa

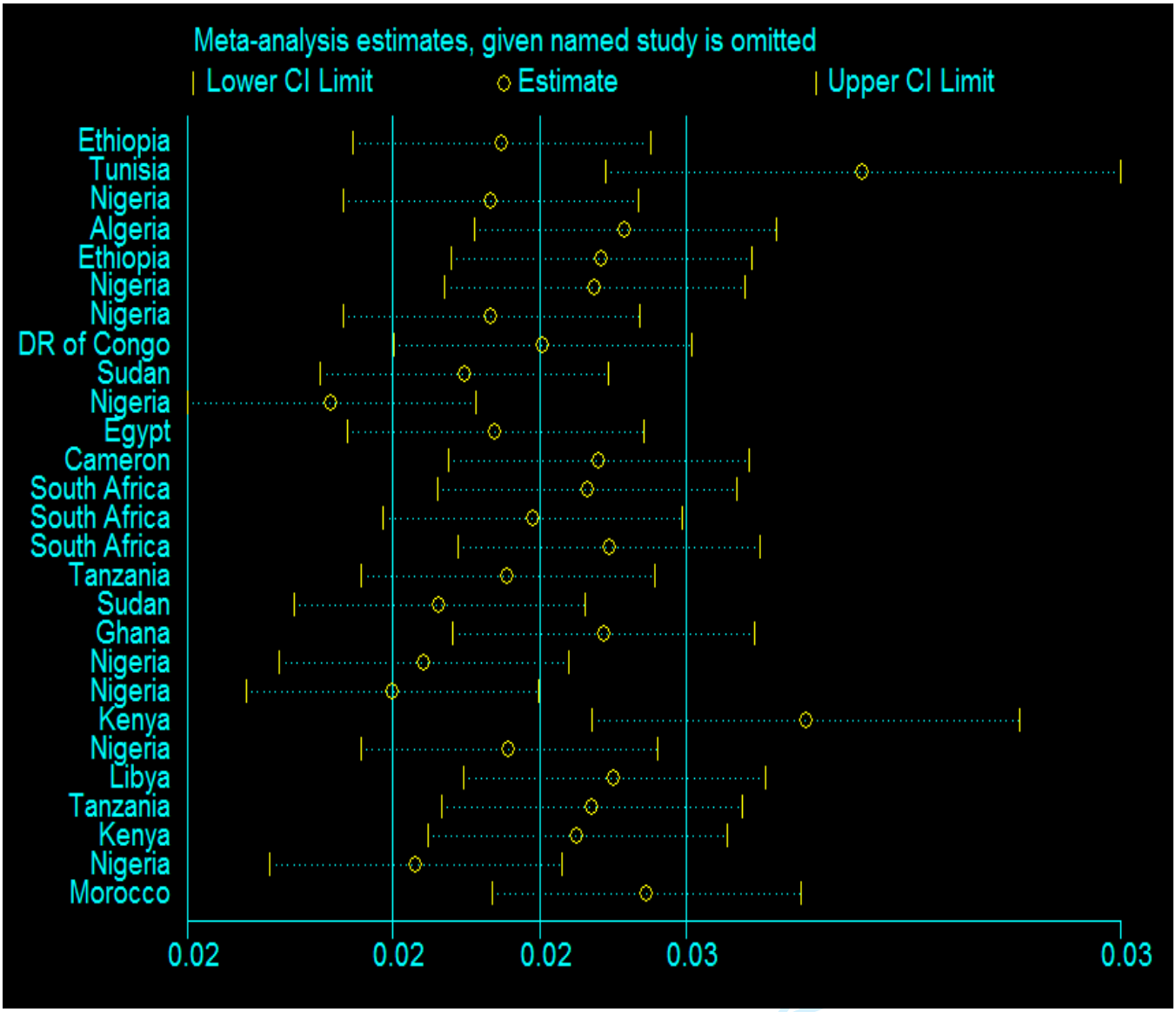

Figure 5: Sensitivity analysis to see the influence of each individual study in Africa

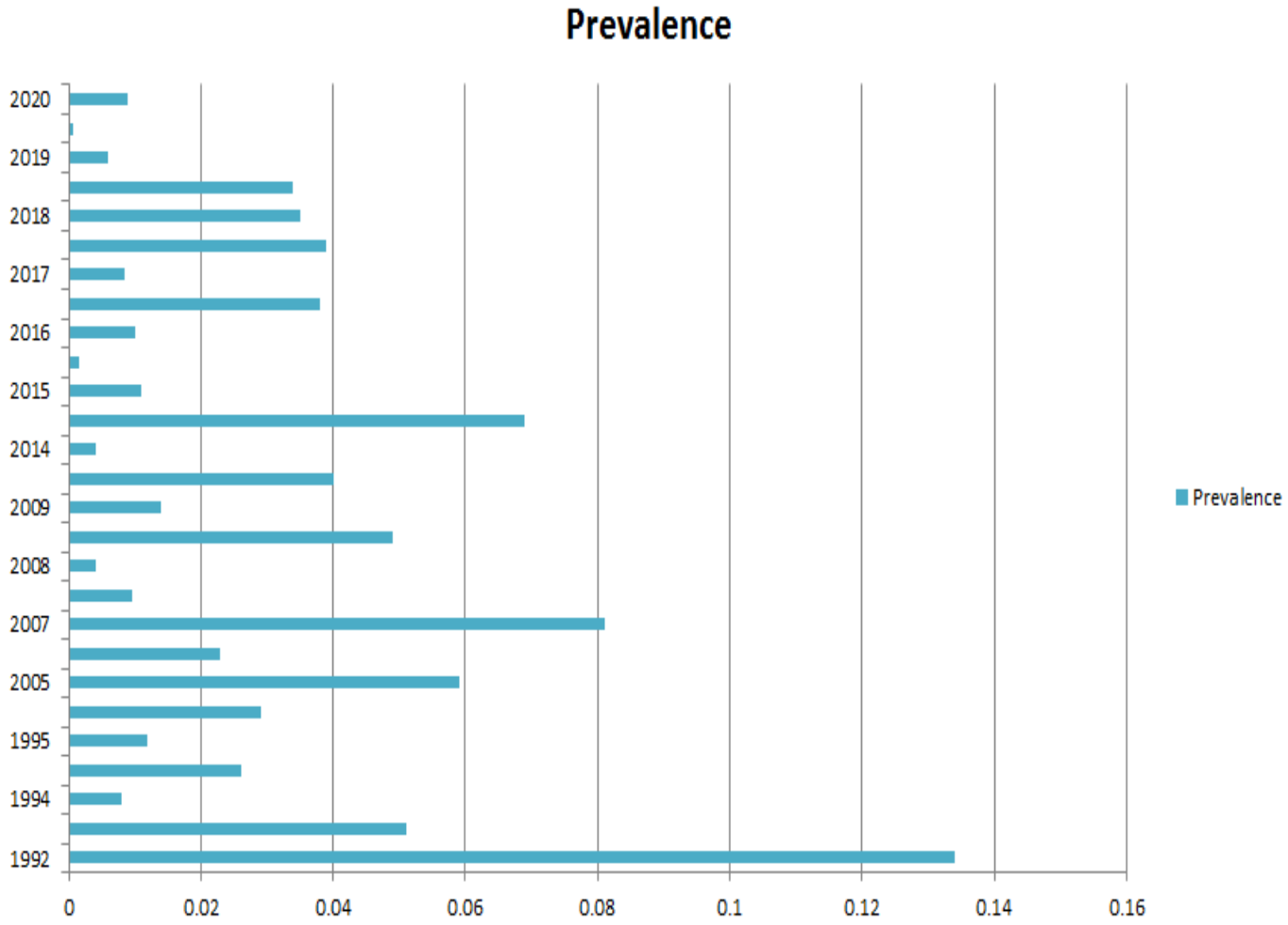

Figure 6: Time trend analysis of the prevalence of encephalocele in relation to publication year in Africa

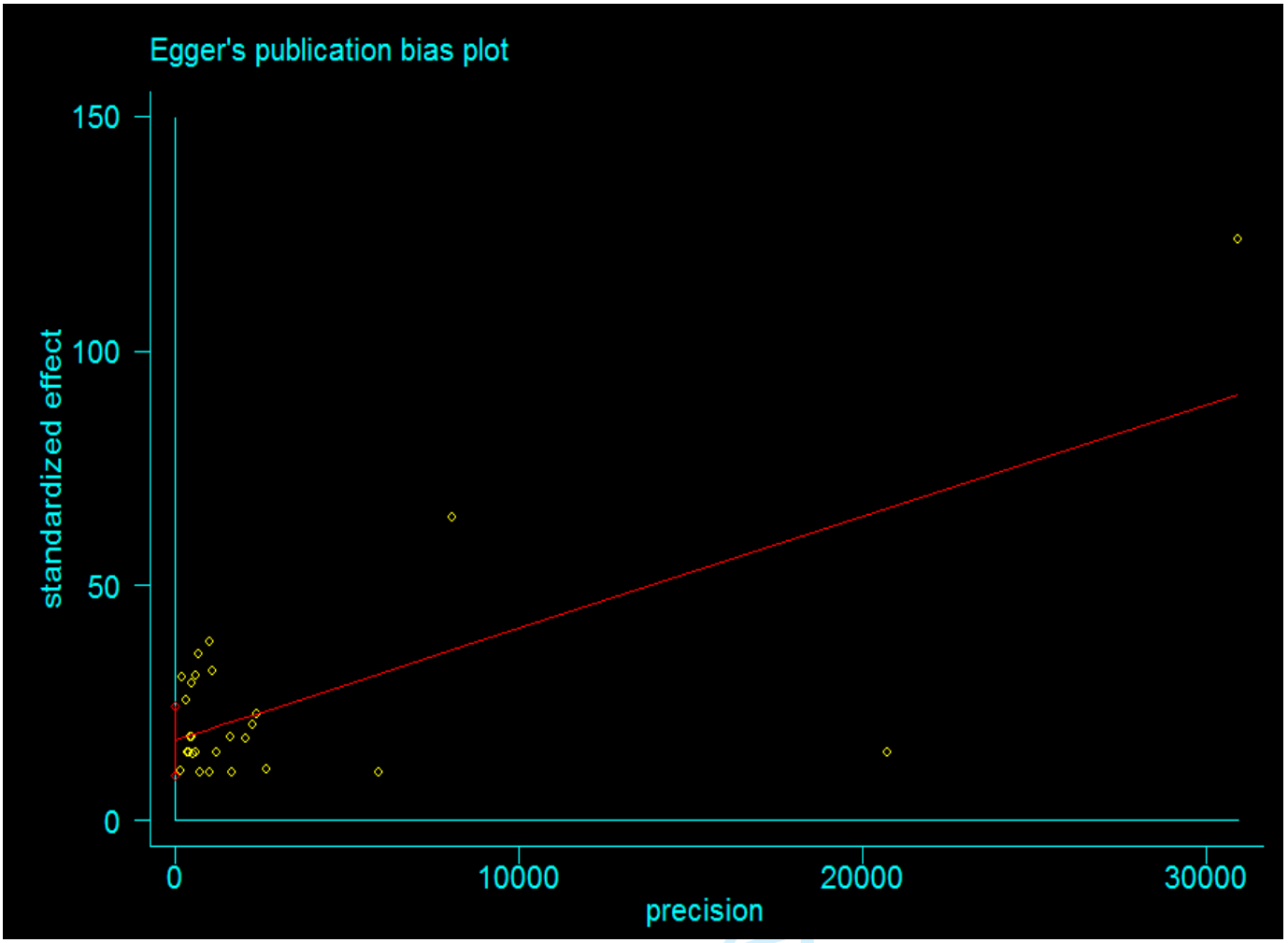

Figure 7: Egger's publication bias plot

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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

For more information, visit: **www.prisma-statement.org**.

PubMed Searching Methods

S.no.	Searching terms	Number of articles/results
1.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms] OR “cranium bifidum” OR “congenital malformations” OR “congenital defects” OR “structural birth defects” OR “structural abnormalities”) AND (newborns OR neonate OR “live births” OR “stillbirths”))	**5, 037**
Trans lations	("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("encephalocele"[MeSH Terms] OR "encephalocele"[All Fields] OR "encephaloceles"[All Fields] OR "encephalocoele"[All Fields] OR "encephalocoeles"[All Fields] OR "encephalocele"[MeSH Terms] OR "neural tube defects"[MeSH Terms] OR "cranium bifidum"[All Fields] OR "congenital malformations"[All Fields] OR "congenital defects"[All Fields] OR "structural birth defects"[All Fields] OR "structural abnormalities"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]) OR "live births"[All Fields] OR "stillbirths"[All Fields])	
2.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR “neural tube defects” [MeSH Terms]OR “cranium bifidum” OR “congenital malformations” OR “congenital defects” OR “structural birth defects” OR “structural abnormalities”) AND (newborns OR neonate OR “live births” OR “stillbirths”) AND (Africa))	228

3.	((Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR "neural tube defects" [MeSH Terms]) AND (newborns OR neonate OR "live births" OR "stillbirths") AND (Africa))	101
4.	(Prevalence) AND (encephalocele OR encephalocele [MeSH Terms] OR "neural tube defects" [MeSH Terms] OR "cranium bifidum") AND (newborns OR neonate OR "live births" OR "stillbirths") AND (Africa)	101
5.	(Prevalence) AND (encephalocele* OR encephalocele [MeSH Terms] OR "neural tube defect*" [MeSH Terms]) AND (newborn* OR neonate* OR "live birth*" OR "stillbirth*") AND (Africa)	99

JBI Critical Appraisal Checklist

JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not applicable
1. Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2. Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3. Was the sample size adequate?	☐	☐	☐	☐
4. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6. Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7. Was the condition measured in a standard, reliable way	☐	☐	☐	☐

for all participants?

8. Was there appropriate statistical analysis? ☐ ☐ ☐ ☐

9. Was the response rate adequate, and if not, was the low response rate managed appropriately? ☐ ☐ ☐ ☐

Overall appraisal: Include ☐ **Exclude** ☐ **Seek further info** ☐

Comments (Including reason for exclusion)

_____

_____

_____

Supplementary file 4: The quality status of studies based on JBI critical appraisal checklist for studies reporting prevalence data

Studies	Appropriate sampling frame?	Appropriate sampling?	Adequate sample size?	Detail setting description?	Analysis with sufficient coverage?	Valid method to identify the condition?	Reliable measurement?	Appropriate statistical analysis?	Adequate response rate?	Total, out of 9
Gedefaw et al.	N/A	UC	Yes	Yes	Yes	Yes	Yes	Yes	N/A	8
Nasri et al.	Yes	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Anyanwu et al.	N/A	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Houchar et al.	Yes	N/A	Yes	No	Yes	No	No	Yes	N/A	6
Abebe et al.	Yes	N/A	Yes	Yes	Yes	No	UC	Yes	N/A	7
Nnadi et al.	N/A	N/A	Yes	Yes	Yes	Yes	UC	Yes	N/A	8
Abbey et al.	Yes	N/A	Yes	UC	Yes	Yes	Yes	Yes	N/A	8
Ahuka et al.	Yes	N/A	Yes	Yes	Yes	Yes	UC	UC	N/A	7
Omer et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	Yes	N/A	7
Airede et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	No	N/A	6
Mohammed et al.	N/A	N/A	Yes	UC	Yes	UC	Yes	Yes	N/A	7
Njamnshi et al.	Yes	N/A	Yes	Yes	Yes	UC	No	No	N/A	6
Delport et al.	Yes	N/A	Yes	UC	Yes	Yes	Yes	Yes	N/A	8
Venter et al.	N/A	N/A	Yes	Yes	Yes	Yes	UC	Yes	N/A	8
Buccimazza et al.	Yes	N/A	Yes	Yes	Yes	UC	No	UC	N/A	6
Kinasha et al.	Yes	N/A	Yes	No	Yes	UC	No	UC	N/A	5
Elsheikh et al.	N/A	N/A	Yes	No	UC	UC	No	Yes	N/A	5
Alhassan et al.	Yes	N/A	Yes	Yes	Yes	UC	UC	Yes	N/A	7
Adetiloye et al.	UC	UC	Yes	No	Yes	UC	UC	Yes	N/A	4
Ugwo et al.	UC	N/A	Yes	No	Yes	UC	UC	Yes	N/A	5
George et al.	Yes	No	Yes	Yes	UC	Yes	UC	Yes	N/A	6
Ekwochi et al.	N/A	N/A	Yes	Yes	Yes	UC	UC	yes	N/A	7
El-Moghrabi et al.	UC	N/A	Yes	No	UC	Yes	Yes	Yes	N/A	6
Kishimba et al.	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	N/A	9
Muga et al.	N/A	N/A	Yes	UC	Yes	UC	Yes	Yes	N/A	7

Mukhtar-Yola et al.	Yes	N/A	Yes	UC	Yes	UC	UC	Yes	N/A	6
Radouani et al.	Yes	N/A	Yes	UC	Yes	Yes	UC	Yes	N/A	7

Key: UC: Unclear, N/A: Not Applicable. N/A for appropriate sampling means the study included all participants rather than sampling methods; N/A for adequate response rate means the study considered all recorded cases from all participants, so it is adequate; UC means it may be considered but not explicitly stated in the manuscript. For adequate sample size, as all participants included in the study during the study period, we considered an adequate sample size even if they did not calculate sample size (it is a total coverage).

ID	First author	Sample size	Cases	Encephalocele prevalence
1	Gedefaw etal.	8677	3	0.035
2	Nasri et al.	3803889	137	0.004
3	Anyanwu et al.	1456	1	0.069
4	Houchar et al.	28500	1	0.004
5	Abebe et al.	45951	4	0.009
6	Nnadi et al.	10163	1	0.01
7	Abbey et al.	7670	3	0.039
8	Ahuka et al.	8824	2	0.023
9	Omer et al.	36785	14	0.038
10	Airede et al.	5977	8	0.134
11	Mohammed etal.	5000	2	0.04
12	Njamnshi et al.	52710	5	0.0095
13	Delport et al.	17351	2	0.012
14	Venter et al.	7617	2	0.026
15	Buccimazzaetal.	516252	41	0.008
16	Kinasha et al.	34000	10	0.029
17	Elsheikh et al.	18378	9	0.049
18	Alhassan et al	35426	3	0.0085
19	Adetiloye et al.	23438	12	0.051
20	Ugwo et al.	7388	6	0.081
21	Agot et al.	299854	2	0.0007
22	Ekwochi et al.	5830	2	0.034
23	El-Moghrabi et al.	16765	1	0.006
24	Kishimba et al.	28217	3	0.011
25	Muga et al.	7355	1	0.014
26	Mukhtar-Yola et al.	13619	8	0.059
27	Radouani et al.	60017	1	0.0017