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Systematic review protocol examining sex differences in survival among low birthweight newborns and infants in sub-Saharan Africa

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ABSTRACT

Introduction In sub-Saharan African countries, low birthweight (LBW) accounts for three-quarters of under-five mortality and morbidity. However, there is no systematic evidence of sex differences in LBW survival risk. The aim of this protocol is to outline the methodological process of a systematic review that will gather qualitative and quantitative data on sex differences in survival among LBW newborns and infants in sub-Saharan Africa.

Methods This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols reporting guidelines. We will conduct a systematic review to retrieve all qualitative and quantitative studies. Electronic search strategies are being finalised on 24 February 2020 for Ovid Medline and EMBASE, and on 28 February 2020 for CINAHL, Scopus and Global Health in collaboration with a Health Sciences librarian. The primary outcome of interest is indicating sex differences in survival among LBW newborns and infants. Secondary outcomes are sex-disaggregated differences in morbidity among LBW newborns and infants. Screening, data extraction and assessments of risk of bias will be performed independently. Narrative synthesis and a meta-analysis will be conducted with studies that are compatible based on population and outcome. The systematic review is focused on the analysis of secondary data and does not require ethics approval.

Ethics and dissemination As it will be a systematic review, without human participants' involvement, there will be no requirement for ethical approval. The systematic review will present key evidence of sex-disaggregated differences in mortality and morbidity among LBW newborns and infants in sub-Saharan Africa. Programme managers, policy-makers and researchers can use the findings to evaluate LBW health outcomes in different sexes. The final manuscript will be disseminated through a peer-reviewed journal and scientific conferences.

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INTRODUCTION

In 2015, the prevalence of low birthweight (LBW) was approximately 14.6%, amounting to 20.5 million LBW babies.[1] Approximately 91% of these LBW live births were from low-income and middle-income countries.[2]

Strengths and limitations of this study

► This protocol outlines the methodological process of a systematic review that will gather qualitative and quantitative data on sex differences in survival among low birthweight (LBW) newborns and infants in sub-Saharan Africa (SSA). Also, this reduces the possibility of duplication and possible biases.

► This protocol is developed to offer the highest level of evidence for informed decisions by organising an experienced multidisciplinary team.

► This systematic review protocol will be the first to present key evidence of sex-disaggregated differences in mortality (survival) and morbidity among LBW newborns and infants in SSA.

► Significant numbers of LBW data are unrecorded, under-reported and misreported by birthweight and sex, possibly resulting in publication bias and methodological quality issues.

► Exclusion of studies not disaggregating survival outcomes in LBW newborns and infants by sex as well as exclusion of research published before 2000, in non-SSA regions and in languages other than English.

Accordingly, the WHO identified LBW as an indicator of child health status.[3] Birth weight of less than 2500 g is classed as LBW, regardless of gestational age.[4]

It is also a major determinant of infant mortality, morbidity, and poor mental and physical development.[5] The neonatal and infant periods are vulnerable periods for child survival.[6 7] LBW accounts for approximately 80% of all newborn deaths.[2] Although LBW is among the strongest predictors of infant morbidity and mortality in most parts of the developing world, in Africa, it is the strongest predictor.[8] Sub-Saharan Africa (SSA), where approximately 15% of neonates are born with LBW,[2] accounts for a quarter of the global burden of LBW live births.[2 9] This region also constitutes the highest neonatal and under-five mortality rates in the world.[6 7]

LBW-related mortality continues to be a significant global and public health challenge. Ensuring universal health access is unthinkable without children, who make up a large and relatively dependent part of the population. In 2015, Sustainable Development Goal (SDG) 3, target 3.2 aimed to reduce newborn mortality to 12 per 1000 live births by 2030.[10] It also set a target to reduce under-five mortality to 25 per 1000 live births, and LBWs to 30% by 2030.[10]

Available research evidence has identified various risk factors for mortality among LBW newborns and infants.[11–14] One of the more contested individual-level risk factors is sex, which is a key variable for disaggregation of child mortality and morbidity rate estimates. Organising sex-disaggregated data is an important component of gender analysis, in which quantifiable differences are made between male and female individuals.[15] Most UN health indicators are sex disaggregated[16 17]: 'Sex-disaggregated data allow programme managers and decision makers to evaluate service quality, treatment, and health-outcome in different sexes'.[18]

Despite the significant influence of LBW on adverse health outcomes, there is a lack of evidence synthesis on this key public health concern across SSA. Therefore, this systematic review primarily evaluates sex differences in survival among LBW newborns and infants in SSA. It synthesises the existing evidence on sex-disaggregated differences in survival and morbidity outcomes in this population. The availability of sex-disaggregated LBW and mortality data can be crucial in informing interventions aiming for SDG 3.2 targets. In addition to identifying the existing evidence, the review will identify evidence gaps in the literature for sex-specific LBW outcomes. Review findings will ultimately inform programme implementers, policy-makers and researchers addressing LBW-related mortality and morbidity. To our knowledge, there is no existing systematic review on this research aim in SSA.

Objective

The aim of this protocol is to outline the methodological process of a systematic review that will gather qualitative and quantitative data on sex differences in survival and morbidity among LBW newborns and infants in SSA.

Research question

Are there sex differences in LBW mortality and morbidity outcomes among newborns and infants in SSA?

METHODS
Study design

This protocol was designed and written according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols guideline for reporting systematic reviews (see the online supplementary file 1). The protocol has been registered in PROSPERO, an international prospective register of systematic reviews.

Data sources and search strategy for relevant studies

Electronic search strategies are being finalised for Ovid Medline and EMBASE on 24 February 2020, and CINAHL, Scopus and Global Health on 28 February 2020. This was done in collaboration with a Health Sciences librarian, who helped in optimising the retrieval of relevant citations. Search strategies include variations, mesh terms, and explore or narrowed versions of the following keywords: LBW, preterm, premature, small for gestational age (SGA), newborn, infant, sex, male, female and SSA (see the online supplementary file 2).

The search strategies designed to access published materials comprise three stages. (1) A limited search of Ovid Medline and CINAHL to identify relevant keywords contained in the title, abstract and subject descriptors. (2) Terms identified in this way, and the synonyms used by Ovid Medline, EMBASE, CINAHL, Global Health and Scopus are used in an extensive search of the literature. (3) Reference lists of the review eligible full-text articles will be perused to identify more relevant articles.

Eligibility criteria

We have proposed a clear and predefined eligibility criterion for this systematic review (see the online supplementary file 3).

Inclusion criteria: peer-reviewed full-text research articles, published in English, will be considered. Articles published between October 2000 and 2019 will be considered. This period was selected because the years 2000 to 2015 represent the era of Millennium Development Goals, where significant progress was made around the world, including in infants' health. As a continuation of the increased focus of research on child health, the Sustainable Development Goals adopted in 2015 set new targets to reduce child mortality and improve child health by 2030. The period from 2000 to 2019 thereby accounts for the new wave of research related to development goals on reducing child mortality, since the turn of the century. Quantitative, qualitative and mixed-method studies conducted in SSA will be included. The review will also consider all types of studies on male and female LBW newborns and infants with birth weights lower than 2500 g in SSA. Studies that report sex differences in survival or morbidity among LBW newborns or LBW infants at the time of discharge from a health facility will be included.

Exclusion criteria: studies conducted outside of SSA countries and studies that do not report sex differences or solely report sex differences in a population of newborns and infants will be excluded. Studies that only include preterm and SGA babies that are not LBW (weighing over 2500 g) will be excluded. Preterm and SGA are not synonyms of LBW, and in consort, preterm and SGA babies can be normal weight. Given that the review explores sex differences in survival, studies that do not report the weight of the population or disaggregate the sexes in LBW survival or morbidity outcomes will also be excluded. Lastly, all non-primary literature sources, such as systematic reviews, theses and dissertations, will

be excluded to ensure the focus of the review on peer-reviewed, full-text academic articles.

Population

LBW male and female newborns born in SSA (<28 days of age).

LBW male and female infants born in SSA (<1 year of age).

Intervention(s), exposure(s)

There is no specific intervention targeted for this study.

Comparison

The usual standard of care without intervention.

Outcomes

The primary outcome of interest is sex differences in the survival (mortality) of LBW newborns and infants at the time of discharge from a health facility.

The secondary outcomes of interest include sex differences in morbidity, such as non-communicable and communicable diseases, of LBW newborns and infants at the time of discharge from a health facility.

Screening

Citations will be imported into the Mendeley citation management software and duplicates will be removed. The articles retrieved from searches in the databases will be screened by three authors in the Rayyan database for their relevance and eligibility to be included in the review. This will include the title and abstract screening, followed by full-text screening against the eligibility criteria for studies deemed potentially eligible. Disagreements will be settled through discussion.

Data extraction

After full-text screening, data will be independently extracted from the retrieved eligible studies by two of the reviewers (ATG and AWF). Disagreements will be settled through discussion with a third reviewer (SY). The authors will adapt a data collection form based on the needs of the review from a standardised data extraction form by the Cochrane library.[19] The data extracted will include all details specific to the review question, fulfilling the requirements for both the narrative synthesis and the potential meta-analysis. This includes the following information from each article: (1) authors and publication year, study setting, and study aim or hypothesis; (2) sample characteristics, design and data collection methods, outcome measures, statistical analyses; (3) study findings. We will also contact primary study authors for key information when data are ambiguous or missing from the included studies.

Data synthesis

A narrative synthesis will be conducted, a method that is ideal for synthesising evidence from a wide range of research questions and study designs with quantitative and qualitative approaches.[20] If the data are too heterogeneous as anticipated, the narrative synthesis will be solely conducted. Descriptive statistics will be provided on all included studies, in a way that indicates regional study results (East, West, South and Central Africa). Data on study characteristics, outcomes and important variables will be summarised using frequencies and percentages for dichotomous outcomes. Where sufficient data are available, a meta-analysis will be conducted, in R v.3.6.2. Due to heterogeneity in geographic and sociodemographic factors across studies, a random-effects model will be used for the meta-analysis. The specific method employed to produce pooled estimates will depend on the study designs and analyses of the included studies. However, as anticipated, the included studies will present time-to-event data (ie, survival analyses). The inverse variance method (conducted using the R package 'meta') will be used to pool study estimates, based on the reported HRs and corresponding SEs. Statistical heterogeneity will be assessed via the Higgin's I^2 statistic.

Risk of bias assessment for retained studies

The risk of bias in included studies will be assessed independently by two reviewers, with discrepancies resolved by the corresponding author. The reviewers will evaluate the qualitative and quantitative studies using the appropriate Critical Appraisal Skills Programme (CASP) checklists.[21] The domains of the CASP checklists will help to assess the credibility of the findings and the rigour of the studies.[22] The questions were designed as prompts to guide reviewers in critically reading the reports. Included studies will be assigned an overall score of 'high' (9–10), 'moderate' (7.5–9) or 'low' (less than 7.5) overall quality. Studies will not be excluded or weighted based on the quality of the reporting assessment. The results of the appraisal will instead be used to inform data interpretation and help confirm the validity of review findings and conclusions. In a quantitative meta-analysis, study heterogeneity and publication bias will consider extended funnel plot tests for detecting publication bias, and selection modelling and trim-and-fill methods to adjust for publication bias in the presence of between-study heterogeneity.

Quality of review evidence assessment

We will use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the strength of evidence for each outcome from included studies.[23] The quality of each piece of evidence for primary and secondary outcomes will be classified as 'high', 'moderate', 'low' or 'very low'.

Patient and public involvement

Patients were not directly involved in the design of this study. As this is a protocol for a systematic review and no participant recruitment will take place, their involvement in the recruitment and dissemination of findings to participants was not applicable.

Ethics and potential amendments

Ethics approval is not required as the systematic review does not involve the collection of primary data from participants. The collection of data for our review does not involve direct contact with human participants. Instead, we will use published and publicly accessed data. We do not envisage any amendments to the present protocol, but should an amendment be necessary, it will be notified, registered and reported.

Dissemination of findings

The systematic review and its evidence synthesis will be published in a peer-reviewed journal and presented at different conferences and scientific meetings. The findings will be used to inform the design of sex-specific interventions aiming to improve outcomes of LBW newborns and infants across SSA in the future. The findings will also be used to identify gaps in the literature evidence regarding mortality and morbidity among LBW newborns and infants.

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