Prevalence, and Outcomes of Rheumatic Heart Disease in Ethiopia: a Systematic Review and Meta-analysis

February 2022

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A dissertation submitted to the Health Sciences Faculty, University of Cape Town, in partial fulfilment of the requirements for the degree of Master of Public Health.

DECLARATION

I, **Munyaradzi Dhodho** hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Contents

Chapter 1-Protocol

1.0 INTRODUCTION 4

1.1 Rationale 6

1.2 Research Question: 6

2.0 OBJECTIVES OF THE STUDY 7

2.1 Primary Objective 7

2.2 Secondary Objective 7

3.0 METHODS 7

3.1 Eligibility criteria 8

3.1.1 Types of Participants 8

3.1.2 Types of outcome measures 8

3.1.3 Types of studies 8

3.1.4 Language and year of publication 8

3.1.5 Information sources 9

3.1.6 Search strategy 9

3.2 Study selection and data collection 10

3.3 Risk of bias assessment 10

3.4 Statistical analysis 10

4.0 DISCUSSION 11

5.0 ETHICS AND DISSEMINATION 12

6.0 REFERENCES 13

7.0 APPENDICES 16

7.1 Appendix 1: Data extraction form for Prevalence of RHD 16

7.2 Appendix 2: Data extraction form for outcomes of RHD 17

7.3 Appendix 3: Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence 18

7.4 Appendix 4: Explanation to Risk of Bias questions 19

Chapter 2: Journal Manuscript 22

Chapter 1

Abstract

Background

While eradicated in other parts of the world, RHD, nevertheless, remains the most common acquired heart disease in low- to medium-income countries where the burden of RHD is much higher; in sub-Saharan Africa, there was an estimated prevalence of 10 persons per 1,000 population in 2015. This systematic review will provide estimates of the prevalence of RHD, and post-operative outcomes, in Ethiopia. A summarised description in the form of a pooled estimate of RHD prevalence and peri- and post-operative outcomes associated with RHD in Ethiopia will be presented.

Methods

We will conduct a systematic review of the prevalence and outcomes of RHD in Ethiopia. Studies that will be included in this review will be searched from PubMed and Web of Science. In addition, Google Scholar will be used to complement the search. We will request articles that will not be found online from corresponding authors. Studies will be included in the meta-analysis if the method of RHD diagnosis is Echocardiography, fitting with the WHF or WHO criteria and done after 2012. A meta-analysis will be done to measure the pooled prevalence and outcomes of RHD.

1.0 INTRODUCTION

An estimated 33 million people are living with Rheumatic heart disease (RHD) globally[1] and approximately 290 000 RHD deaths are reported annually[2]. Mortality however has been observed to differ across global regions with higher mortalities observed in Oceania, South Asia and central and sub-Saharan Africa[1]. While eradicated in other parts of the world, RHD, nevertheless, remains the most common acquired heart disease in low- to medium-income countries (LIMCs)[1] where the burden of RHD is much higher; in sub-Saharan Africa, there was an estimated prevalence of 10 persons per 1,000 population in 2015[1].

Rheumatic Heart Disease is a consequence of Acute Rheumatic Fever, the auto-immune sequel of an episode of or episodes of untreated or inadequate treatment of streptococcal pharyngitis. This is highly associated with inadequate access to quality health care, exacerbated by socio-economic determinants of health such as overcrowding and poverty[3]. Eradication, prevention, and control of RHD can thus be achieved through improving living standards, ensuring access to appropriate health care and antibiotics for primary and secondary prevention, especially if supported by monitoring and surveillance[4]. As the push for its eradication increases, implementation of simple preventive measures such as treatment of streptococcal infections in children can contribute significantly to successful eradication[4]. The underlying risk factors are, however, difficult to control as they depend on other factors such as politics and economic status of the affected countries.

In efforts to spearhead the eradication of RHD in Africa, delegates of the 1st All Africa Workshop on Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) that included cardiologists and public health specialists developed the Drakensberg declaration in 2005, incorporating approaches for combating RF and RHD[5]. The declaration gave rise to the development of the "ASAP programme" which focuses on awareness, surveillance, advocacy and prevention of RHD[5]. A decade later, a seven-point declaration was ratified by the

African Union (AU) in 2015. This declaration focused on two broad categories which are clinical management of RHD and a policy making framework[4]. Of the seven key goals contained within the AU Declaration, three points focus on clinical management of care, treatment and prevention including adequate supplies of benzathine penicillin at primary health care facilities, improving diagnosis of RHD by decentralising expertise to primary health care facilities and establishment of centres of excellence for cardiac surgery and conducting research[4]. The remaining four points of the declaration focus on policy including 1. the establishment of registers to monitor progress towards RHD-related health outcomes, 2. guaranteeing access to sexual and reproductive health services for women with RHD,

3. multisectoral and national RHD control programmes that will focus on reaching the goal of reducing deaths from rheumatic fever and RHD among individuals aged <25 years by 25% by the year 2025.

4.creating effective communication frameworks and partnerships[6]. The historic 71st World Health Assembly resolution adopted in 2018 noted that RHD is a significant but preventable cause of deaths and urged member states to estimate the burden of RHD in countries where RHD is endemic[6].

Among the AU members states, Ethiopia has been actively involved in conducting RHD-related research over the last few decades. In an attempt to contribute to continental information, we undertook this review in order to synthesize information on the prevalence of RHD[5] and further, to summarise data on fatal and non-fatal outcomes of RHD in Ethiopia. We anticipate that this review will provide contemporary information contributing to ongoing endeavour to reduce morbidity and mortality across the world as Ethiopia has the highest RHD-related deaths in the world. [7]

1.1 Rationale

Several prevalence studies have been conducted in various regions across Africa including Southern Africa[7], East Africa[8], West Africa[9], Central Africa [7]and the Middle East and North Africa region[10]. Studies included asymptomatic participants as well as those seeking cardiac care at tertiary institutions. To date, no systematic review has been undertaken to provide a pooled estimate of prevalence of RHD within Ethiopia. Ethiopia is located in East Africa, and has a population of 115 million[11] . Health care is provided through the public and private sector, with basic non-communicable disease care devolved to local clinics manned by health officers. Twenty-percent (23 million) of the Ethiopia population live in urban areas while 80% live in the rural areas[12]. This review seeks to give an overview of primary studies on the prevalence and outcomes of RHD in Ethiopia.

1.2 Research Question:

The research question was defined in accordance with the "*CoCoPop"* mnemonic which refers to context, condition and population as recommended by Joanna Briggs Institute[13].

context: Urban and Rural

condition: Rheumatic heart Disease

population: Ethiopian population

This review asks the following question: *What is the prevalence, of RHD and what are the outcomes of patients with Rheumatic Heart Disease in Ethiopia?*

2.0 OBJECTIVES OF THE STUDY

2.1 Primary Objective

The primary objective of this study is to determine the prevalence of RHD among the Ethiopian population.

2.2 Secondary Objective

The secondary objective of this study is to describe the pre-and post-operative complications and mortality for all patients admitted for RHD-related surgery. We will also determine the proportion of people who underwent surgery as a way of treating RHD. The post-operative complications and mortality will be measured at 30 days and 60 days. Outcome measures will include hospitalisation, complications (including heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation, infective endocarditis, and valve repair or replacement), surgical interventions and mortality.

3.0 METHODS

This review protocol has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42021266039. The review process is guided by the Joanna Briggs Institute (JBI) Reviewer's manual for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data [13]. We will utilize the classification of RHD according to the WHF Criteria. RHD is defined as any form of RHD as detected by echocardiography, including subclinical disease.[14]

3.1 Eligibility criteria

3.1.1 Types of Participants

The target population for this review includes all children and adults living in Ethiopia. No age restrictions will be applied. Patients undergoing valve surgery for RHD will be included.

3.1.2 Types of outcome measures

Prevalence of RHD where RHD was diagnosed using echocardiogram will be included. Studies reporting diagnosis through methods such as auscultation will be excluded. Outcome measures to be recorded for meta-analysis are hospitalisation, complications (including heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation, infective endocarditis, and valve repair or replacement), surgical interventions and mortality.

3.1.3 Types of studies

Population-based studies conducted in Ethiopia that report prevalence of, and/or peri- and post-operative outcomes associated with RHD will be included in this study. Cohort, case series, and prospective studies will be included in this study if they report diagnosis of RHD using echocardiography only according to the WHF criteria.

3.1.4 Language and year of publication

Studies written in English, or Ethiopian official languages will be included, published since 2012, when the WHF criteria was implemented.

3.1.5 Information sources

The following electronic databases will be searched for published literature: PubMed (US National Library of Medicine, National Institutes of Health), Scopus and Web of Science. In addition, Google Scholar will be used to complement the search results.

3.1.6 Search strategy

Table 1 outlines the search strategy as performed within PubMed. Search terms include "Rheumatic Heart Disease", RHD, Rheumatic fever individually, and in combination with the following: Prevalence, Epidemiology and Ethiopia. The search strategy will be adapted for Web of Science and Scopus as required.

Table 1: Search Strategy

#1	Ethiopia [Title/Abstract]
#2	Ethiopia [MeSH Terms]
#3	Ethiopia [Free text]
#4	#1 OR #2 OR #3
#5	rheumatic heart disease[MeSH Terms]
#6	rheumatic heart disease[Title/Abstract]
#7	rheumatic fever [MeSH Terms]
#8	rheumatic fever [Title/Abstract]
#9	#5 OR #6 OR #7 OR #8
#10	#4 AND #9

3.2 Study selection and data collection

Data from included studies will be extracted independently by two reviewers using a standardised data collection template. The data extraction form will capture study objectives, study population, sample size, location of study, year of study and study design. In relation to the RHD, the following will be captured: method of diagnosis, results (those with disease and those without disease). The WHF classified RHD as definite with four subcategories depending on how the heart valves are affected or borderline RHD which is only present in those ≤20 years of age and with three subcategories depending on how the heart valves are affected[15] . Authors will be contacted if there is need for any clarifications. Discrepancies will be resolved by discussion with the third reviewer where necessary.

3.3 Risk of bias assessment

The Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data will be used to critically appraise the selected studies[16]. The appraisal will be done to check the quality of the methods used in selected studies and the extent to which bias is addressed in the study design, conduct and analysis[16]. All papers selected for inclusion in the systematic review will be assessed for potential bias in the design, conduct and analysis and this will be done by two independent reviewers [16].

3.4 Statistical analysis

The prevalence of RHD will be calculated from each of the included studies. The number of RHD cases reported will be the numerator, divided by the total sample size as the denominator. The prevalence will be calculated as the number of cases per 100 000 population. A meta-analysis will be conducted to measure the pooled prevalence and

outcomes of RHD. Heterogeneity among the included studies will be assessed using the X^2 test and I^2 statistics. An I^2 statistic of >75% will be regarded as high heterogeneity, and if applicable, a meta-analysis will not be reported. Selection of the model to use between random effects and fixed effects model will be determined by the heterogeneity of the studies. If low (<50%), a fixed effects model will be used[17]. A forest plot will be constructed to illustrate the prevalence of each study as well as combined effects. Potential publication bias will be investigated using the funnel plot where if the asymmetry is statistical significant will suggest that studies that show beneficial effects have higher chances of getting published compared to those that publish non-significant results[18]. Meta analysis will be conducted using Stata version 15 software[19].

RHD mortality per 100,000 will be calculated as follows: RHD deaths/midyear population and corresponding 95% confidence intervals computed. Where not stated, the population number will be calculated using age-specific incidence rates and cases stated in the original paper as follows: 100,000 × (number of cases/incidence per 10^5).

4.0 DISCUSSION

RHD is a global disease occurring with increased frequency in low- to middle-income countries, where resources are limited. This systematic review aims at providing estimates of the prevalence of RHD, and post-operative outcomes, in Ethiopia. A summarised description in the form of a pooled estimate of RHD prevalence and peri- and post-operative outcomes associated with RHD, will help to guide future endeavours as regards awareness raising and interventions for better control of this disease in low-resourced settings. In addition, it will provide the government with information on areas to intervene in the quest to reduce the RHD burden.

5.0 ETHICS AND DISSEMINATION

This study is a systematic review, and no ethical approval is required since data will be from published studies. However, exemption for ethical clearance will be sought from the University of Cape Town, Faculty of Health sciences Human Research Ethics Committee. The final review will be submitted for presentation at an international conference, as well as for publication in a medical journal.

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7.0 APPENDICES

7.1 Appendix 1: Data extraction form for Prevalence of RHD

Reference citation	
Name/ID of person extracting data	
Publication type (e.g. full report, abstract, letter)	
Title	
WHF (Yes/No)	
Included (Yes/No)	
Comments	
Setting	
Urban/Semi-Urban/Rural /Not specified	
Symptomatic vs asymptomatic	
Study design	
Background population	
Nature of the denominator	
Outcome	
Sampling method	
Sample Size	Sex=Male
	Sex=Female
age	
Method of RHD diagnosis (WHF or another guideline)	
WHF (Yes/No)	
Quality Assurance	
Definite	Male Definite
	Female Definite
Borderline	Male borderline
	Female borderline
Undefined	

7.2 Appendix 2: Data extraction form for outcomes of RHD

Reference citation	
Name/ID of person extracting data	
Publication type (e.g. full report, abstract, letter)	
Title	
Included (Yes/No)	
Comments	
Setting	
Symptomatic vs asymptomatic	
Study design	
Study population	
Nature of the denominator	
Outcome	
Sampling method	
Sample Size	
Sex=Male	
Sex=Female	
Age	
Method of RHD diagnosis	
Mortality (30day)	
Mortality (>60days)	
Freedom from all cause mortality	
Freedom from valve related deaths	
Freedom from valve related events	
Atrial Fibrillation	
Stroke	
Infective endocarditis	
Bleeding	
Prosthetic valve thrombosis	
Systemic embolism	

7.3 Appendix 3: Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence

Reviewer_____
Date_____

Author_____ Year_____ Record Number_____

Answers: Yes, No, Unclear or Not/Applicable

	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)

_____
_____
_____

7.4 Appendix 4: Explanation to Risk of Bias questions

1. Was the sample frame appropriate to address the target population?

This question relies upon knowledge of the broader characteristics of the population of interest and the geographical area. If the study is of women with breast cancer, knowledge of at least the characteristics, demographics and medical history is needed. The term "target population" should not be taken to infer every individual from everywhere or with similar disease or exposure characteristics. Instead, give consideration to specific population characteristics in the study, including age range, gender, morbidities, medications, and other potentially influential factors. For example, a sample frame may not be appropriate to address the target population if a certain group has been used (such as those working for one organisation, or one profession) and the results then inferred to the target population (i.e. working adults). A sample frame may be appropriate when it includes almost all the members of the target population (i.e. a census, or a complete list of participants or complete registry data).

2. Were study participants recruited in an appropriate way?

Studies may report random sampling from a population, and the methods section should report how sampling was performed. Random probabilistic sampling from a defined subset of the population (sample frame) should be employed in most cases, however, random probabilistic sampling is not needed when everyone in the sampling frame will be included/ analysed. For example, reporting on all the data from a good census is appropriate as a good census will identify everybody. When using cluster sampling, such as a random sample of villages within a region, the methods need to be clearly stated as the precision of the final prevalence estimate incorporates the clustering effect. Convenience samples, such as a street survey or interviewing lots of people at public gatherings are not considered to provide a representative sample of the base population.

3. Was the sample size adequate?

The larger the sample, the narrower will be the confidence interval around the prevalence estimate, making the results more precise. An adequate sample size is important to ensure good precision of the final estimate. Ideally, we are looking for evidence that the authors conducted a sample size calculation to determine an adequate sample size. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest. For conditions with a low prevalence, a larger sample size is needed. Also consider sample sizes for subgroup (or characteristics) analyses, and whether these are appropriate. Sometimes, the study will be large enough (as in large national surveys) whereby a sample size calculation is not required. In these cases, sample size can be considered adequate.

When there is no sample size calculation and it is not a large national survey, the reviewers may consider conducting their own sample size analysis using the following formula: (Naing et al. 2006, Daniel 1999)

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where:

n= sample size

Z = Z statistic for a level of confidence

P = Expected prevalence or proportion (in proportion of one; if 20%, P = 0.2)

d = precision (in proportion of one; if 5%, d=0.05)

Ref:

Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies Archives of Orofacial Sciences. 2006;1:9-14.

Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences.

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4. Were the study subjects and setting described in detail?

Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. Women vs. Men, sociodemographic variables between countries). The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them.

5. Was data analysis conducted with sufficient coverage of the identified sample?

Coverage bias can occur when not all subgroups of the identified sample respond at the same rate. For instance, you may have a very high response rate overall for your study, but the response rate for a certain subgroup (i.e. older adults) may be quite low.

6. Were valid methods used for the identification of the condition?

Here we are looking for measurement or classification bias. Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

7. Was the condition measured in a standard, reliable way for all participants?

Considerable judgment is required to determine the presence of some health outcomes. Having established the validity of the outcome measurement instrument (see item 6 of this scale), it is important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised? When there was more than one observer or collector, was there comparison of results from across the observers? Was the condition measured in the same way for all participants?

8. Was there appropriate statistical analysis?

Importantly, the numerator and denominator should be clearly reported, and percentages should be given with confidence intervals. The methods section should be detailed enough for reviewers to identify the analytical technique used and how specific variables were measured. Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

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

A large number of dropouts, refusals or "not founds" amongst selected subjects may diminish a study's validity, as can a low response rates for survey studies. The authors should clearly discuss the response rate and any reasons for non-response and compare persons in the study to those not in the study, particularly with regards to their socio-demographic characteristics. If reasons for non-response appear to be unrelated to the outcome measured and the characteristics of non-responders are comparable to those who do respond in the study (addressed in question 5, coverage bias), the researchers may be able to justify a more modest response rate.

Prevalence, and Outcomes of Rheumatic Heart Disease in Ethiopia: a Systematic Review and Meta-analysis

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[2]Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa.

[3] South African Medical Research Council, Tygerberg, Cape Town

[4] Save the Children International, Somalia-Somaliland country Office, Nairobi, Kenya

Glossary

RHD	Rheumatic Heart Disease
WHF	World Heart Federation
RF	Rheumatic Fever
AU	African Union
LIMCs	Low- to middle-income countries
RCTs	Randomised Controlled Trials.

Background: While eradicated in other parts of the world, Rheumatic Heart Disease, nevertheless, remains one of the most common acquired heart diseases in low- to middle-income countries; in sub-Saharan Africa, there was an estimated prevalence of 10 persons per 1,000 population in 2015. In the Global Burden of Disease estimates 1990-2015, Ethiopia was identified as having one of the highest burdens of RHD with a prevalence of 100-149 persons per 100,000 population. We therefore sought to estimate the prevalence of RHD, and clinical and post-operative outcomes, in Ethiopia.

Objectives: We conducted a systematic review of the prevalence and outcomes of RHD according to *a priori* protocol.

Data Sources: Studies included in this review were retrieved from PubMed and Web of Science. In addition, Google Scholar and approaching authors was used to complement the search.

Data Extraction: Studies conducted after 2012 were included if the method of RHD diagnosis was echocardiography. A meta-analysis was done to measure the pooled prevalence and outcomes of RHD.

Results: A total of nine studies were included in this review, 5 focusing on prevalence and 4 focusing on outcomes of RHD. The overall prevalence of asymptomatic echocardiographic RHD was per 21 per 1000 (95% CI, 12.27;32.03). In hospitalised patients, presentation included congestive heart failure, atrial fibrillation, and stroke. The 30-day mortality and post-operative mortality was 2.5 (95% CI, 0.00;12.81) and 32.8 (95% CI, 11.43;62.82) per 1000 respectively. The 60-day mortality and post-operative mortality was 33.5(95% CI, 0.00;111.38) and 161.7 (95% CI 125.54;201.27) per 1000 respectively.

Conclusions And Relevance: The prevalence of asymptomatic RHD in Ethiopia is high while RHD in adults/children is associated with congestive heart failure, atrial fibrillation and stroke. Mortality was high in patients with RHD-related heart failure; thus, to achieve the World Heart Federation target of a 25% reduction in the mortality due to RHD by 2025 in the under 25-year-olds might prove challenging.

Introduction

An estimated 33 million people are living with Rheumatic heart disease (RHD)- the consequence of Acute Rheumatic Fever and untreated Streptococcal pharyngitis- globally with approximately 290 000 RHD deaths are reported annually [1]. Rheumatic Heart Disease remains one of the most common acquired heart disease in low- to middle-income countries (LIMCs)[2] where the burden of RHD is much higher; in sub-Saharan Africa, there was an estimated prevalence of 10 persons per 1,000 population in 2015[2]. Mortality however has been observed to differ across global regions with higher mortalities observed in Oceania, South Asia and central and sub-Saharan Africa [2].

Ethiopia is located in East Africa and has a population of 115 million [3] where eighty-percent (92 million) of the population live in rural areas [4]. Health care is provided predominantly through the public sector, with a very small amount of private healthcare which is funded through out-of-pocket expenditure. In the public sector, primary care is conducted by health officers. These factors coupled with poverty and poor housing makes Ethiopian population susceptible to acquisition of RHD.

Ethiopia adopted the World Heart Federation (WHF) 2012 guidelines in its classification of asymptomatic RHD and these now are the current standard for diagnosis of RHD using echocardiography. The WHF criteria for classification of RHD has three categories namely definite RHD, borderline RHD and normal, all based on stringent echocardiographic criteria[5]. Ethiopia is among the leading countries with high burden of RHD, and thus has been actively involved in conducting RHD-related research over the last few decades. Studies on RHD prevalence have been conducted in Ethiopia from as early as 1992[6] until recently in 2019[7] reporting a prevalence of 4.6/1,000 and 22.6/1,000 respectively[2,8].

RHD can be easily prevented if appropriate management protocols are followed. In childhood, treatment of upper respiratory tract infections (URTI) is key in prevention of RHD at adulthood and for those children already developing RHD, they can be treated with benzathine penicillin which is a cost-effective antibiotic. However, unavailability of these commodities and poor health systems in LMICs such as Ethiopia leads to increased risk of RHD when compared to more developed contexts.

Eradication of RHD was deemed a key priority in the 1st All Africa Workshop on Rheumatic Fever (RF) and RHD in 2005 and approaches for combating RF and RHD were developed [9]. Approaches for combating RF and RHD included the "ASAP programme" that focused on awareness, surveillance, advocacy and prevention of RHD [9]. In addition, in 2015 a seven-point declaration was ratified by the African Union (AU) with focus on clinical management of RHD and a policy making framework[4]. In 2018 a resolution by the 71st World Health Assembly noted that RHD is a significant but preventable cause of deaths and urged member states to estimate the burden of RHD in countries where it is endemic[6].

Several prevalence studies have been conducted in various regions across Africa including Southern Africa [10], East Africa [11], West Africa [12], Central Africa [10] and the Middle East and North Africa region [13]. Studies included investigating the prevalence of RHD in asymptomatic populations and others reviewed participants seeking cardiac care at tertiary institutions. A few studies to date have reported on clinical and post-surgical outcomes of RHD in Ethiopia [14–16] while Guther et al reported an alarming mortality rate of 125.3/1000 person years of RHD in Ethiopia[17].

A summarised description in the form of a pooled estimate of RHD prevalence, mortality and clinical and post-operative outcomes associated with RHD, will help to guide future endeavours as regards awareness raising and interventions for better control of this disease in

low-resourced settings. In addition, this work is anticipated to provide the government with information on areas needing intervention in their quest to reduce RHD burden.

We have conducted a systematic review of the literature on the presentation of hospitalised RHD and present the estimation of the prevalence of RHD and summarised the data on clinical and post-operative outcomes of RHD in Ethiopia.

1. Methods

The protocol for this study has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42021266039. The review process was guided by the Joanna Briggs Institute (JBI) Reviewer's manual for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data [18].

Search methods for identification of studies

Two electronic databases were searched for literature in English and published between the years 2012 and 2021 (the WHF criteria was implemented in 2012): PubMed (US National Library of Medicine, National Institutes of Health), and Web of Science. In addition, Google Scholar was used to complement the search results from the grey resources. All searches were conducted independently by two reviewers (MD and LA), and in the case of disagreements between the reviewers, a third independent reviewer (ME) was consulted. The key terms "Rheumatic Heart Disease", "RHD", "Rheumatic fever" were used individually and in combination with the following: prevalence, epidemiology, and Ethiopia. The search strategy was adapted for Web of Science as required. We also requested articles from outside sources including Ethiopian University Hospital. The search strategy is presented in table 1 below.

Table 1: Search terms used to find RHD studies

#1	Ethiopia [Title/Abstract]
#2	Ethiopia [MeSH Terms]
#3	Ethiopia [Free text]
#4	#1 OR #2 OR #3
#5	rheumatic heart disease [MeSH Terms]
#6	rheumatic heart disease [Title/Abstract]
#7	rheumatic fever [MeSH Terms]
#8	rheumatic fever [Title/Abstract]
#9	#5 OR #6 OR #7 OR #8
#10	#4 AND #9

Inclusion and exclusion of studies

Studies were included if they met the following criteria: Must have been conducted in Ethiopia and report prevalence of, and/or clinical and post-operative outcomes associated with RHD; study designs included cohort, case series, and prospective studies. Where possible, the control arms of RCTs were sourced for prevalence data. The target population for this review included all children and adults living in Ethiopia. The included studies were population-based with no age restrictions on study participants.

To have a uniform description of RHD, studies reporting prevalence of RHD where RHD was diagnosed by echocardiography according to the WHF criteria were included. Studies reporting

diagnosis through methods such as auscultation were excluded. Outcome measures recorded for meta-analysis were hospitalisation, complications (including heart failure, ischaemic, thromboembolic or haemorrhagic stroke, atrial fibrillation, infective endocarditis, and valve repair or replacement), surgery and mortality.

Data extraction

Data from included studies were extracted by two independent reviewers(MD and LA) using a standardised data collection template. The data extraction was duplicated by the reviewers to improve reliability. The data extraction form captured study objectives, study population, sample size, location of study, year of study and study design. In relation to RHD, the following data were also captured: how the RHD was diagnosed and results (those with disease and those without disease) and clinical and post-operative outcomes. Authors were contacted if there was need for any clarifications. Discrepancies were resolved by discussion with the third reviewer where necessary.

Assessment of risk of bias in included studies

The Joanna Briggs Institute's critical appraisal checklist for studies reporting prevalence data was used to critically appraise the selected studies[19]. The appraisal was done to check the quality of the methods used in selected studies and the extent to which bias is addressed in the study design, conduct and analysis[19]. All papers selected for inclusion in the systematic review were assessed for potential bias in the design, conduct and analysis and this was done by two independent reviewers [19]. Results from this appraisal were used to help interpretation of the SR results. Unfortunately, the small number of studies were not amenable to publication bias assessment.

1.1 Quantitative data synthesis

The prevalence of RHD was calculated from each of the included studies: the number of RHD cases reported served as the numerator, divided by the total sample size as the denominator. The prevalence was calculated as the number of cases per 1000 population. Meta-analyses were performed using the random effects model, given the anticipated heterogeneity with prevalence studies. Heterogeneity among the included studies was assessed using the I^2 statistic. An I^2 statistic of >75% was regarded as indicative of high heterogeneity. We used Stata® (version 15) to perform the Freeman-Tukey double arcsine transformation to ensure stabilisation of the variance of study prevalence [20,21], the transformation is essential in minimising influence from studies with outliers before data are pooled together. We stratified the data by symptom status and source population of the study sample. While we intended to investigate for potential publication bias, the number of studies were too few to allow for this. Meta-analysis was performed in Stata® (version 15) using the *Metaprop* command[20]. RHD mortality per 1000 was calculated as follows: RHD deaths/midyear population and corresponding 95% confidence intervals computed.

Subgroup analysis

For studies focusing on prevalence, we conducted a subgroup analysis with respect to study setting which was one of community, schools or hospitals. We also stratified participants according to RHD symptoms. For outcomes studies, we stratified according to clinical and post-operative outcomes.

Ethics approval

Systematic reviews utilize published data and thus ethics clearance is not required. The dissertation was registered with the University of Cape Town, Faculty of Health sciences Human Research Ethics Committee (HREC 073/2022).

2. Results

3.1 Study Selection

The results of the search strategy are presented in Fig. 1. A total of 139 articles were identified from different databases and 13 articles were retrieved through personal communication, 56 duplicates were removed, and 82 articles were included. Sixty-six articles were immediately excluded based on the title, and abstract, among which 32 were excluded because they did not incorporate echocardiography, 13 were of incorrect study design, 13 were based on excluded population, four were of excluded geographical area, each of the other four articles not included, either outside the dates of inclusion criteria, were as follows; a background article or the wrong outcome; one article was retracted from publication.

Six articles were excluded after scrutiny for the following reasons: five studies did not report on prevalence or outcomes of RHD, and one study had a study design outside of our eligibility criteria. The nine articles included in the systematic review comprised five prevalence studies and four outcomes' studies reporting on hospital- and post-operative outcomes.

Flow of included studies

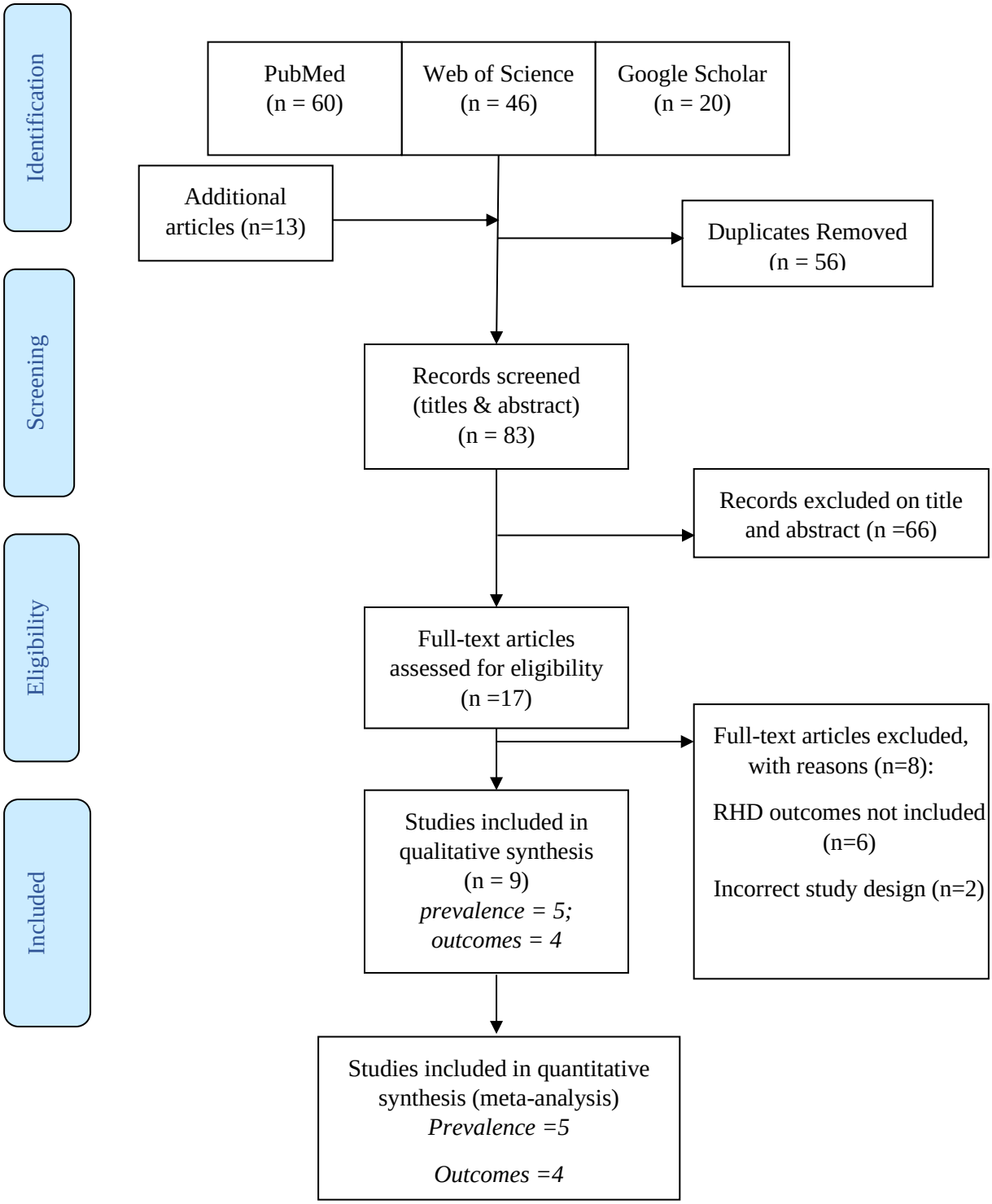

Figure 1. Schematic PRISMA flow diagram of the literature search.

3.2 Characteristics of Included studies

3.2.1 Prevalence studies

The five prevalence studies (Table 2) included in this review comprised participants across a variety of settings including hospital [7,22] (2 studies, n=6673), and community (3 studies, n=6218) settings [10,23,24]. All five studies utilized the WHF criteria for diagnosis. In one of the two hospital-based studies on prevalence included in this review, patients were sampled from among all those seeking medical care within the cardiac facility of the respective institution [22] and the remaining hospital-based study comprised asymptomatic pregnant participants attending antenatal care follow-up who were randomly selected for clinical and echocardiographic examination in their 3rd trimester of pregnancy [7]. Study participants from community settings were drawn from schools (2 studies, n=5231)[10,24] and the general population (1 study, n=987)[23] .

Table 2: Characteristics of included prevalence studies

First author (year)	Setting/Symptom status	Study population	Sample size	All RHD	Definite RHD	Prevalence of Definite RHD/1000 (95% CI)	Method of diagnosis	Age range
Gemechu et al. 2017	Community Asymptomatic	General Population	987	56	37	37.49 (27.3;51.24)	Echo (WHF)	6-25
Yadeta et al 2016	Schools Asymptomatic	School Children	3231	59	44	13.62 (10.16;18.23)	Echo (WHF)	6-18
Engel et al 2015	Schools	School Children	2000	61	33	16.50 (11.77;23.08)	Echo (WHF)	4-24
Bacha et al 2019	Hospital Asymptomatic	Healthy Pregnant women (ANC)	398	9	9	22.61 (11.94;42.41)	Echo (WHF)	18-40
Yadeta et al 2017	Hospital Symptomatic	Admitted/in-patient and out-patient	6275	2184	2184	348.05 (336.36;359.92)	Echo (WHF)	15-38

WHF, World heart federation; ANC, antenatal clinic

3.2.2 Clinical and post-operative outcomes

Five studies (from four publications), providing outcomes data were included in this review (Table 3). All were hospital-based and the target population (mean age range, 18-31) included people undergoing heart surgery for RHD (n=3) or on the waiting list for surgery (n=1) or undergoing follow-up (n=1)[14–16,25]. In one study, participants were selected from patients on cardiac surgery waiting list and the inclusion criteria was based on compliance to cardiac follow-up [14]. The second outcomes study derived its participants from two main referral centres for cardiac surgery, the Cardiac Centre of Ethiopia and El Ouzier cardiac centre and all patients included were operated during the period from June 2017 to April 2020 [15]. In the third outcomes study, participants were enrolled consecutively from patients awaiting cardiac surgery with no specified population of interest and therefore can be generalised to the entire population [16]. The fourth study had participants (different font) with a clinical and echocardiographic diagnosis of RHD, who were seen in outpatient clinics, emergency departments, or inpatient facilities [25]. The outcomes measures included mortality at 30-days and 60-days. In addition, one study evaluated freedom from all-cause mortality [16], three studies evaluated atrial fibrillation [14–16], and two studies evaluated post-operative atrial fibrillation while two studies evaluated stroke or transient ischemic attack [14,16]. Three studies evaluated occurrence of congestive heart failure [14,25].

Table 3: Characteristics of included Clinical and post-operative outcomes studies

Outcome	Debel et al 2020	Hauge et al 2021 (a)	Hauge et al 2021 (b)	Tamirat 2020	Zühlke et al 2016
Method of diagnosis	WHF	WHF	WHF	WHF	WHF
Sample Size	114	46	49	240	400
Study Participants	Operated for valvular disease	Open-heart surgery patients	Waiting list for surgery (1 year follow-up)	Aortic or mitral valve surgery	Tertiary care management
Vital Status known	114	46	47	240	330
Gender (female)	62(54.4%)	30(65%)	37(76%)	136 (56.7%)	245(61.25%)
Age	31(IQR 23-40)	30(SD 8.6)	25.9(SD 9.9)	19(SD 8)	18(IQR 12-28)
Procedure in hospital	Surgery	Surgery	Medical care	Surgery	None
Mortality (30 days)	5	3	0	5	2
Mortality (60 days)					1
Mortality 12 months	0	5	5 (10%)	11	21
Mortality rate 24 months	0			16	36
Congestive heart failure	0	2	2		11 at 12 months and 10 at 24 months
Atrial fibrillation					
Clinical	63	0	7	62	
Post-operative	0	23	0	11	
Stroke or transient ischemic attack	1(Preoperative)	2	0		1 at 12 months and 0 at 24 months
Hospitalizations					10 at 12 months and 16 at 24 months
Infective endocarditis		2	2		

World Heart Federation(WHF)

3.4 Prevalence of definite RHD

3.4.1 Prevalence of RHD by symptom status (Figure 2)

The combined estimate of prevalence amongst asymptomatic participants was 21.04 per 1000 (95% CI 12.27, 32.03; I^2=84.6%, 4 studies: n=6616 participants)[7,10,23,24]. For the remaining study comprising symptomatic patients only, the prevalence of definite RHD was 348.05 per 1000 (95% CI 336.4,359.9)[22].

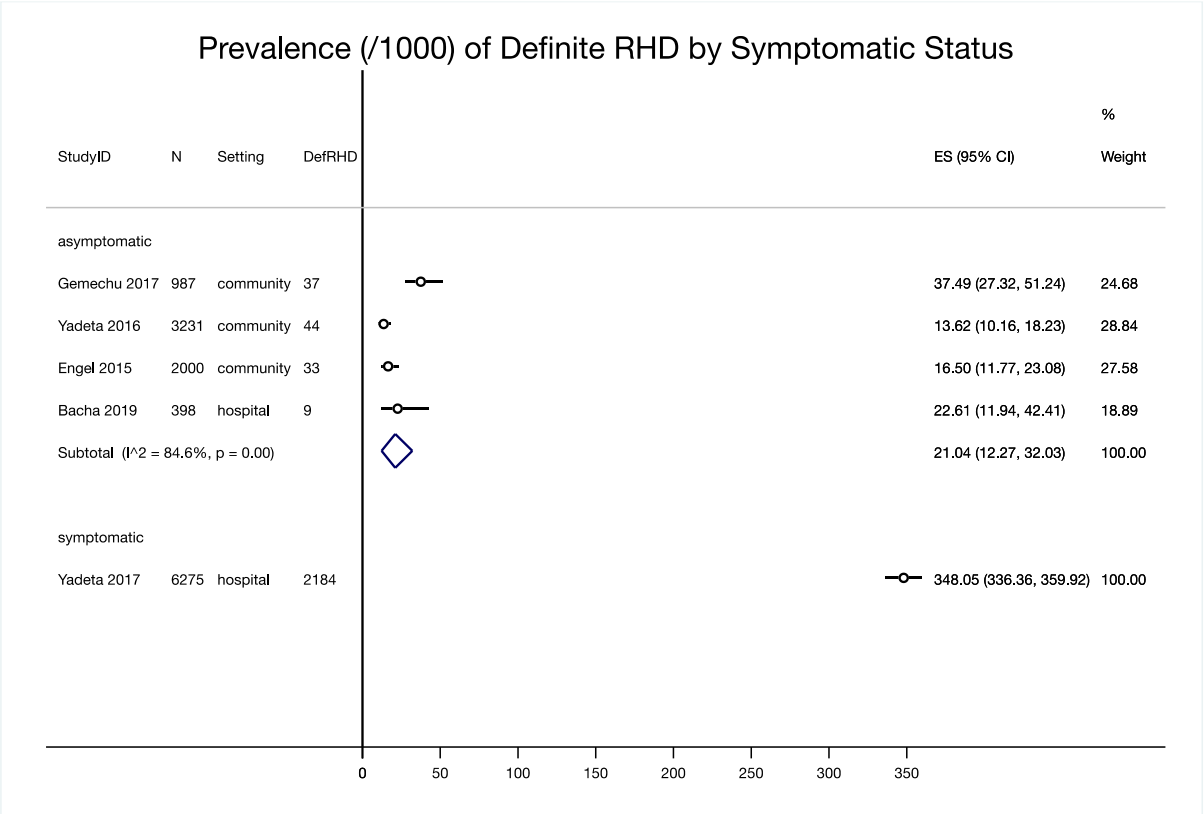

Figure 2: Prevalence of RHD by symptomatic status

3.4.2 Prevalence of asymptomatic RHD according to study setting (Figure 3)

The asymptomatic RHD prevalence estimates were derived from three community-based study settings and one hospital-based study. The pooled prevalence for community-based studies was 20.84 per 1000 (95% CI 10.80, 34.01 n=6218). The single hospital-based study of

asymptomatic pregnant women had a prevalence of 22.61 per 1000 (95% CI 11.94;42.41 n=398)[7].

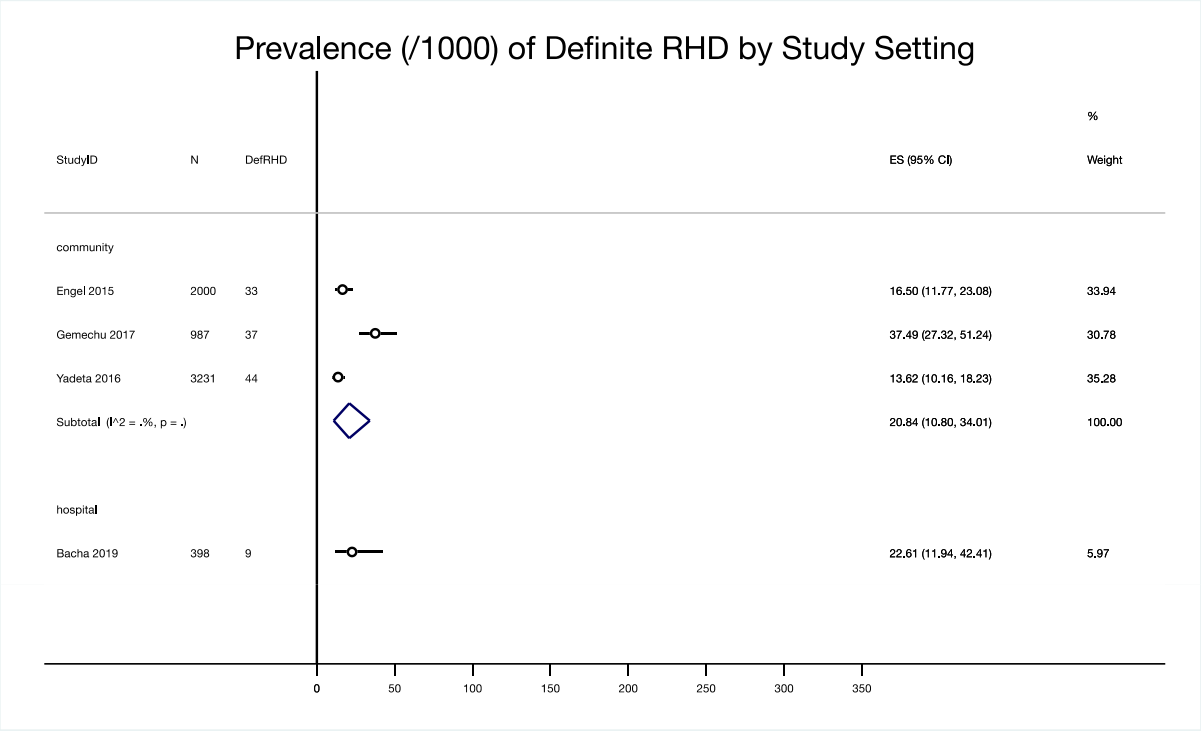

Figure 3: Prevalence of asymptomatic RHD by Study setting

3.5 Clinical and post-operative outcomes (Figure 4 and 5).

Four studies (five populations) provided outcomes of RHD on 30-day and 60-day mortality [14–16]. For the studies that reported post-operative outcomes, the pooled estimate (n=400, 3 studies) for 30-day mortality was 32.82 per 1000 (95% CI, 11.43;62.82), and 33.48 per 1000 (95% CI, 0.00;111.38) for 60-day mortality post-surgery. Two studies reported on outcomes in patients awaiting surgery (n=377) and the pooled estimate for 30-day mortality and 60-day mortality was 2.45 per 1000 (95% CI, 0.00;12.81) and 161.68 per 1000 (95% CI, 125.54; 201.27) respectively.

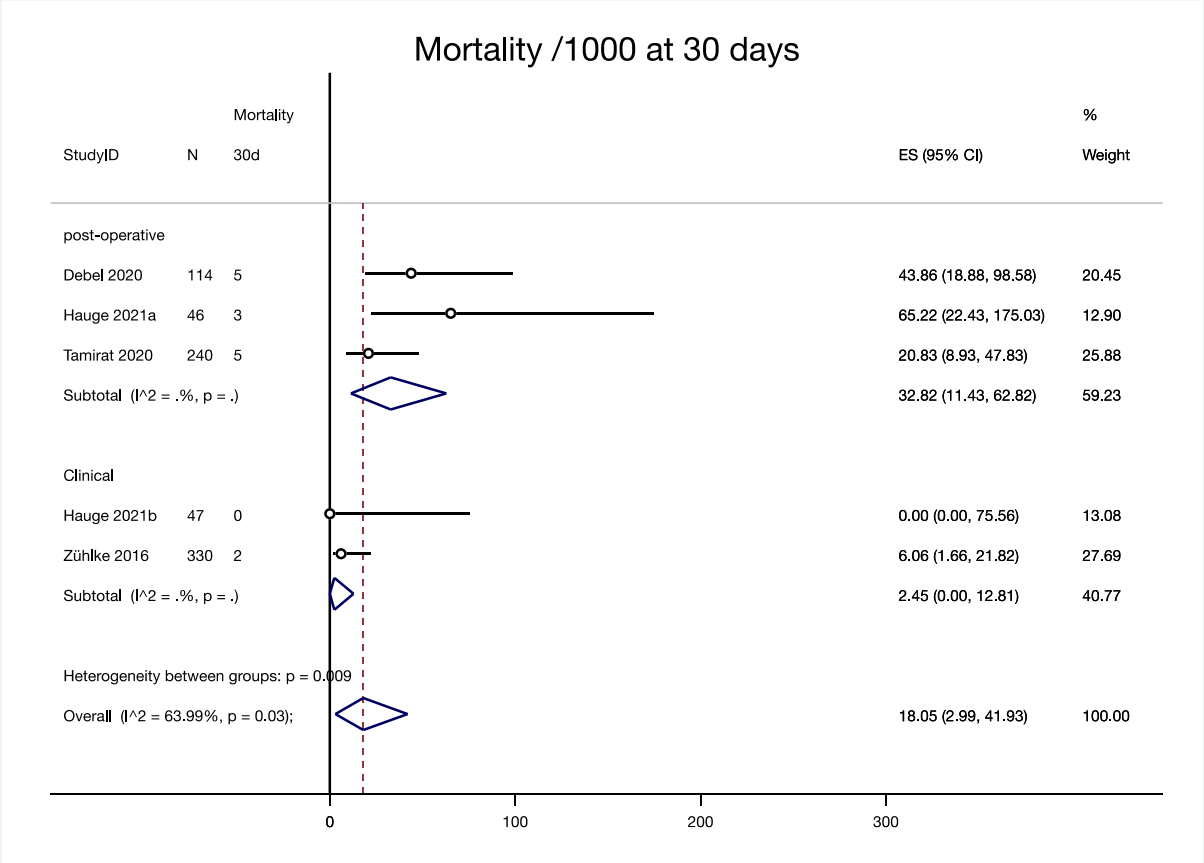

Figure 4: Mortality at 30 days

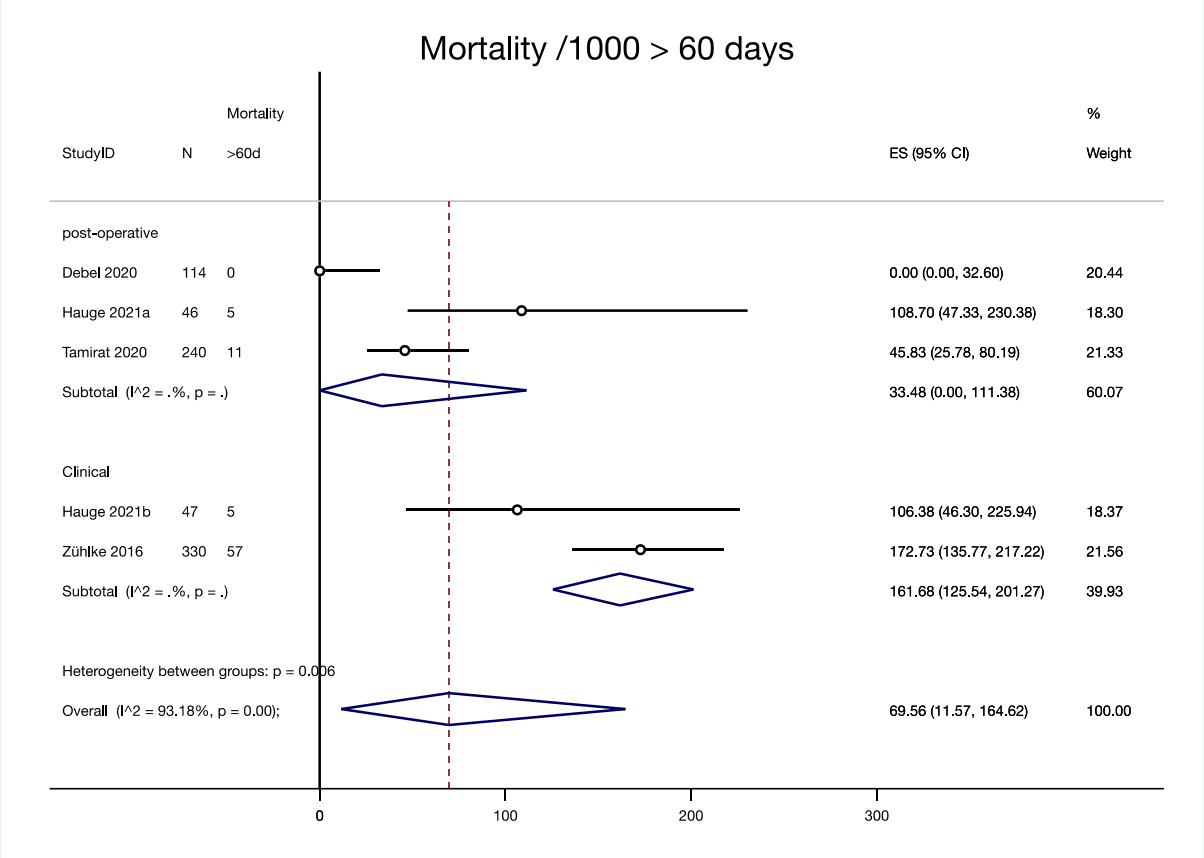

Figure 5: Mortality at 60 days

The single study reporting on all-cause mortality was conducted amongst patients scheduled for valve surgery due to RHD and of the patients included, 93% (n=224) had freedom from all-cause mortality and valve-related deaths over two years [16].

Post-operative complications were reported as follows: atrial fibrillation, two studies (4.6%[16] N=240 and 6%[14], N=46) and stroke, two studies (1.7%[16], N=240 and 4%[14], N=46)). One study reported on post-operative structural valve deterioration leading to heart failure (9%, N=46), endocarditis (4%, N=46) and congestive heart failure in the absence of documented structural valve deterioration (4% N=46)[14]. Another single study reported on cardiac tamponade (16.7%, N=114), bleeding requiring re-exploration surgery (3.5%, N=114) and third-degree complete heart block (1.8%, N=114)[15].

Clinical outcomes were reported as follows: atrial fibrillation, one study and no patient developed atrial fibrillation at twelve-months follow-up (N=49) [14]. Two studies reported stroke after 12 months of follow-up with 0% (N=49) and 0.3% (N=400), respectfully [14,25].

3.6 Risk of bias (Table 4)

Across the studies, risk of bias was low (scores of >7) except for one study [15], rated as medium risk due to not specifying if random selection was performed to select the sample or if the same mode of data collection was used for all subjects and if the length of the shortest prevalence period for the parameter of interest was appropriate.

Table 4: Risk of bias score

Study ID	1	2	3	4	5	6	7	8	9	Quality score
Gemechu 2017	1	1	1	1	1	1	1	1	1	9
Yadeta 2016	1	1	1	1	1	1	1	1	1	9
Engel 2015	1	1	1	1	1	1	1	1	1	9
Yadeta 2017	1	1	1	1	1	1	1	NCS	1	8
Bacha 2019	1	1	1	1	1	1	1	0	NCS	7
Debel 2020	1	1	NCS	1	1	1	1	0	NCS	6
Huage 2021	1	NCS	1	1	1	1	1	1	1	8
Tamirat 2020	1	NCS	1	1	1	1	1	1	0	7
Zuhlke 2016	1	1	1	1	1	1	1	1	1	9

4.0 Discussion

This systematic review of RHD in Ethiopia shows several key findings. 1) Prevalence of asymptomatic definite RHD in Ethiopia is amongst the highest documented worldwide. 2) Similarly, the prevalence of symptomatic RHD is notably high, accounting for a third in patients presenting to the cardiac unit. 3) Post-operative outcomes showed relatively high 30- and 60-day mortality.

The combined prevalence estimates of 21.04 cases per 1000 was higher than an earlier systematic review in East Africa. The systematic review in East Africa reported a lower prevalence of 17.9 cases per 1000 and this could have been due to their inclusion criteria which included studies where RHD diagnosis was either by echocardiography or auscultation and did not strictly use the WHF criteria. The sensitivity of the methods of diagnosis used could have contributed to the differences as auscultation is inferior to echocardiography in diagnosing RHD [26].

Two previous studies conducted in Ethiopia used the World Health Organisation (WHO) criteria for RHD diagnosis [27,28]. In the first study among asymptomatic students, a prevalence of 3.2 per 1000 was reported using WHO criteria, which is six times lower than our pooled prevalence estimate of 20.84 per 1000, using WHF criteria [28,29]. According to Marijon et al, WHO criteria are less-sensitive as compared to WHF, and thus the earlier study may present an underestimation of the prevalence amongst asymptomatic people [30]. The hospital-based study using WHO criteria for diagnosis, among patients with confirmed cardiovascular disorders, reported a prevalence of 620 per 1000 [28,29] which was nearly double the combined estimate reported in this review. However, these two are not comparable as one study reported valvular heart diseases in general and did not specify proportion of participants with RHD

while the other stratified the different valvular diseases including RHD. We could not combine surgical outcomes and natural history of RHD outcomes due to the nature of outcome studies done so far in Ethiopia.

The results of this systematic review of asymptomatic RHD prevalence and outcomes in Ethiopia are comparable to other countries. In Nigeria and South Africa, RHD prevalence was reported to be 21.6 per 1000 [31] and 20.2 per 1000 respectively [32]. However, much lower prevalence was observed in Zambia with reported prevalence of definite, borderline, and total RHD of 2.7, 9.1, and 11.8 per 1000, respectively [33]. By contrast, a study in Tanzania reported a prevalence of subclinical RHD of 34 per 1000 which is higher than the findings of this study [34]. Given the diversity of demographics within the included studies, we believe that the results pertaining to RHD mortality outcomes are generalisable to the Ethiopian population. The pooled estimate for 30-day mortality of 3.28% was marginally higher than that reported elsewhere at 2%[32]. Among the two studies that reported on outcomes in patients awaiting surgery, the pooled estimate for 30-day mortality was slightly lower that those that underwent surgery (0.25%). However, the 60-day mortality among patients awaiting surgery was significantly high reporting a mortality of 16.2%; potentially reflecting the effect of the longer waiting period on patients with severe disease requiring surgery.

The significant levels of heterogeneity present in our review are to be expected in prevalence reviews [35,36]. We conducted subgroup analyses to aggregate the estimates. Across the studies, risk of bias was low (scores of >7) except for one study [15] , rated as medium risk due to not specifying if random selection was performed in sampling, if the same mode of data collection was used for all subjects and if the length of the shortest prevalence period for the parameter of interest was appropriate. However, the low scores for domain number eight had little effect on the overall analysis, given that we conducted the statistical analysis afresh.

Primary prevention of RHD is essential and asymptomatic patients with recurrent sore throat must not be ignored but get screened for RHD. If the screening services are implemented this might result in increasing numbers of patients diagnosed with RHD requiring Benzathine penicillin for prevention.

4.1 Strengths and limitations

The main strength of this review was the focus on WHF criteria and incorporating echocardiography as the method of diagnosis. A robust search strategy was employed, and concerted efforts were undertaken to obtain as many publications within the Ethiopian setting as possible.

However, despite the heterogeneity consistent in prevalence reviews, the estimates from the five studies reporting RHD prevalence with participants from diverse settings in Ethiopia, can be generalised to the Ethiopian population. The included studies have participants from rural, semi-urban and urban areas [10,23,24,29], general community [23], hospital based [7,22] and schools [10,24,29].

3.2 Implications and Relevance

Implications for practice

A significant population of Ethiopia is affected by RHD. It is therefore important to expand on preventive measures to reduce the number of people who develop RHD. At primary level health facilities there is need to increase screening for RHD and access to benzathine penicillin to prevent further complications of RHD for those in need. Furthermore, there is need to capacitate tertiary health facilities so as to improve access to surgery for RHD patients in need particularly those with acute heart failure.

Implications for policy

There is a need to have policies on improving health care systems of the Ethiopian populations. This includes focusing on addressing root causes of RHD such as living in overcrowded settlements and limited access to healthcare. Policies should therefore focus on provision of proper housing to prevent overcrowding. In addition, policy must address access to surgery for RHD patients in need depending on identified gaps which could be funding or training of doctors to perform surgery.

Future research

There is a need to make the comparison between post-surgical outcomes and clinical outcomes within the context of Ethiopia. More studies are required that focus on community-based prevalence of RHD using the WHF criteria as few studies had that focus.

4.2 Conclusion

Studies suggest that RHD is still a public health concern in Ethiopia as shown by high prevalence especially among symptomatic patients. Among the asymptomatic population, the prevalence is significant at 2% and because of the huge absolute numbers, there is cause for concern. Public health measures are required to curb the long-term impact of RHD if these asymptomatic lesions progress to overt RHD. The outcome studies showed significantly high mortality among patients receiving tertiary management excluding surgery or awaiting surgery thus the need to increase access to surgery for RHD patients in need. Findings from this review have potential to inform policy in the control of RHD among the Ethiopian population. Collaboration between researchers and clinicians in Ethiopia can significantly contribute to the improvement of RHD outcomes and a reduction in its prevalence.

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Appendix 1: Data Extraction Form

A. General Information

Reference citation
Name/ID of person extracting data
Publication type (e.g. full report, abstract, letter)

B. Study Characteristics

Title
Included (Yes/No)
Comments
Setting
Urban/Semi-Urban/Rural /Not specified
Symptomatic vs asymptomatic

C. Characteristics of included studies

a. Methods

Study design
Background population
Nature of the denominator
Outcome
Sampling method

b. Participants

Sample Size
Sex=Male
Sex=Female
age
Method of RHD diagnosis (WHF or another guideline)
WHF (Yes/No)
Quality Assurance

c. Outcome measures

Definite RHD Total
Male Definite RHD
Female Definite RHD
Borderline RHD Total
Male borderline RHD
Female borderline RDH
Undefined

D. RHD post-operative outcomes

hospitalisation (Yes/No)
Mortality (30day)
Mortality (>60days)
Mortality (Valve-related)
Freedom from all-cause mortality
Freedom from valve related deaths
Freedom from valve related events
Atrial Fibrillation
Stroke
Infective endocarditis
Bleeding
Prosthetic valve thrombosis
Systemic embolism

E. Risk of Bias assessment

1. Was the study's target population a close representation of the national population?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, OR was a census undertaken?
4. Was the likelihood of non-response bias minimal?
5. Were data collected directly from the subjects (as opposed to a proxy)?
6. Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?

8. Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?
11. Summary of overall risk

Appendix 2: PRISMA 2020 checklist for abstract

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	

Section and Topic	Item #	Checklist item	Reported (Yes/No)
Synthesis of results	6	Specify the methods used to present and synthesise results.	
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	
Interpretation	10	Provide a general interpretation of the results and important implications.	
OTHER			
Funding	11	Specify the primary source of funding for the review.	
Registration	12	Provide the register name and registration number.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 3: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility	5	Specify the inclusion and exclusion criteria for the review and how studies	

Section and Topic	Item #	Checklist item	Location where item is reported
criteria		were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which	

Section and Topic	Item #	Checklist item	Location where item is reported
		were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix 4: Table of Excluded Studies

Authors	**Study title**	**Reason for exclusion**
Asmare et al 2021	Prevalence of rheumatic heart disease in a major referral cardiology clinic in Ethiopia: A retrospective cross-sectional study	Article retracted
Oli et al 1992	Rheumatic Heart Disease Prevalence among Schoolchildren of an Ethiopian Rural Town	Method of diagnosis was auscultation and not WHF
Maru 1993	The changing pattern of cardiovascular diseases in Ethiopia.	Does not fit WHF criteria
Tesfare et al 2017	The changing trend of cardiovascular disease and its clinical characteristics in Ethiopia: hospital-based observational study	
Daniel et al 1993	Profile of cardiac disease in an out-patient cardiac clinic.	Does not fit WHF criteria
Ali et al 2021	The burden of cardiovascular diseases in Ethiopia from 1990 to 2017: evidence from the Global Burden of Disease Study	The GBD produces three summary measures of disease burden however this is estimation and no sample used
L Yazov et al 1978	Epidemiological studies on rheumatic heart disease and streptococcal carriers among school-children in Addis-Ababa, Ethiopia. Preliminary communication.	Does not fit WHF criteria
Oli et al 1999	Rheumatic heart disease among school children in Addis Ababa City: awareness and adequacy of its prophylaxis.	Does not fit WHF criteria
Noubiap et al 2019	Prevalence and progression of rheumatic heart disease: a global systematic review and meta-analysis of population-based echocardiographic studies	This was for reference only
Bimerew 2021	Prevalence of rheumatic heart disease among school children in East Africa: a systematic review and meta-analysis	This was for reference only
Angaw 2021	The prevalence of cardiovascular disease in Ethiopia: a systematic review and meta-analysis of institutional and community-based studies	This was for reference only
Asmare et al 2021	Rheumatic Heart Disease Screening Based on Phonocardiogram	This study is on testing for a diagnostic method for RHD

Parry et al 1968	Ethiopian Cardiovascular Studies Case-finding by Mass Miniature Radiography	Diagnostic method is MMR
Woldeyes et al 2020	Clinical Characteristics And In Hospital Outcome Of Acute Heart Failure: A Five-Year Experience At A Tertiary Care Hospital In Ethiopia	The Study focused predominantly on causes of heart failure and RHD is mentioned as one of the causes
Bregani 2021	A survey on a rural in-hospital population diagnosed with Atrial Fibrillation in west Shewa region, Ethiopia.	Targeted other conditions not necessarily RHD
Gebremariam 2016	Pediatric Heart Failure, Lagging, and Sagging of Care in Low Income Settings: A Hospital Based Review of Cases in Ethiopia.	Objective of this study was to describe patterns, predictors of mortality, and management outcomes of acute heart failure in children and not outcomes of RHD
Hodes 1992	Hemoptysis in rheumatic heart disease.	Objective was to identify symptoms associated with haemoptysis
Oli et al 2004	Rheumatic heart disease in Ethiopia: could it be more malignant?	
Tadele 2020	Rheumatic mitral stenosis in Children: more accelerated course in sub-Saharan Patients	This study reports the prevalence and severity of mitral stenosis in children aged <16 years whowere referred to a tertiary academic center for treatment
Tesfaye 2020	Pattern of Cardiac Diseases and Co-Existing Morbidities Among Newly Registered Cardiac Patients in an Adult Cardiac Referral Clinic of Hawassa University Comprehensive Specialized Hospital, Southern-Ethiopia	This study aimed to describe CVD and co-existing morbidities. No information on outcomes.
Woldu et al 2016	Rheumatic heart disease in the twenty-first century	No information about outcomes
Ek 2016	Rheumatic heart disease behind life-threatening heart failure in pregnancy].	This is a case of an Ethiopian migrant living in Sweden

Appendix 5: Data extraction Forms Prevalence Studies

Study ID	**Gemechu et al. 2017**	**Yadeta et al 2016**	**Engel et al 2015**	**Yadeta et al 2017**	**Bacha et al 2019**
Title	Community-based prevalence study of rheumatic heart disease in rural Ethiopia.	Prevalence of rheumatic heart disease among school children in Ethiopia: A multisite echocardiography-based screening	Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia	Spectrum of cardiovascular diseases in six main referral hospitals of Ethiopia	The occurrence and pattern of cardiovascular diseases among pregnant mothers attending Saint Paul's Hospital in Addis Ababa
WHF Criteria	Yes	Yes	Yes	Yes	Yes
Study Setting	community	schools	community	hospital	hospital
Type of population	Urban/Rural	Urban/Rural	Urban/Rural	Not Specified	Not Specified
Type of Included patients	asymptomatic	asymptomatic	asymptomatic	symptomatic	asymptomatic
Background population	2,500,000	20,137,755	12427	7102	
Sample Size	987	3231	2000	6275	398
Male	454	1666	988	2604	N/A
Female	533	1565	1012	3671	398
Age	6-25	6-18	4-24	25 (15–38)	18-40 27 (±4.6)
Definite RHD all	37	44	33	2184	9
Female definite RHD					9
Borderline All	19	15	28		

Appendix 6: Data extraction Forms Clinical Outcomes Studies

Study Id	**Debel et al 2020**	**Hauge et al 2021**	**Hauge et al 2021**	**Tamirat 2020**	**Zulke et al**
Title	Immediate outcome following valve surgery for rheumatic heart disease: the first local experience from Ethiopia.	Short-term outcome after open-heart surgery for severe chronic rheumatic heart disease in a low-income country, with comparison with an historical control group: an observational study.	Short-term outcome after open-heart surgery for severe chronic rheumatic heart disease in a low-income country, with comparison with an historical control group: an observational study.	Contemporary outcomes of aortic and mitral valve surgery for rheumatic heart disease in sub-Saharan Africa.	clinical Outcomes in 3343 children and adults With rheumatic heart Disease From 14 low- and Middle-income countries
Included(Yes/No)	Yes	Yes	Yes	Yes	Yes
Comments	Other outcomes not listed	intervention group (this study compared intervention and non-intervention groups)	Non-intervention group (this study compared intervention and non-intervention groups)	This study made comparisons	Data for Ethiopia was shared by investigators
Setting	Hospital	Hospital	Hospital	The Cardiac Center of Ethiopia	Cardiac centres
Symptomatic vs asymptomatic	S	S	S	S	S
Study design	Cohort	Observational Cohort	Observational Cohort	Cohort	observational Cohort
Study population	Patients scheduled for Valve surgery due RHD	Patients who had surgery for RHD	Patients on waiting list for surgery	patients with RHD underwent aortic and/or mitral surgery	Patients with RHD from 25 centres in 14 countries
Nature of the denominator	all patients who were operated for rheumatic valvular heart disease	Patients with surgery for RHD done	Patients on waiting list for surgery for RHD	patients with RHD underwent aortic and/or mitral surgery	Patients diagnosed with RHD
Outcome	Post-surgical outcomes	Outcome of patients with severe chronic RHD who received open-heart surgery,	The natural course of controls waiting for surgery and undergoing only medical treatment.	study's primary outcome of interest was all-cause mortality	Death or complications such as stroke, other thromboembolic events, bleeding, hospitalisation for heart failure and infectious endocarditis. Results
Sampling method	No sampling done all target population included	Purposive	Purposive	Population	
Sex=Male	52	16	12	104	155
Sex=Female	62	30	37	136	245

Sample Size	114	46	49	240	400
Study Participants	Operated for valvular disease	Open-heart surgery patients	Waiting list for surgery (1 year follow-up)	Aortic or mitral valve surgery	RHD waiting list for open-heart surgery or percutaneous balloon valvuloplasty (PTMV),
Vital Status known	114	46	47	240	330
Gender (female)	62(54.4%)	30(65%)	37(76%)	136 (56.7%)	245(7.2%)
Age	31(IQR 23-40)	30(SD 8.6)	25.9(SD 9.9)	19(SD 8)	18(IQR 12-28)
Procedure in hospital	Surgery	Surgery	Medical care no surgery	Surgery	None
Mortality (30 days)	5	3	0	5	2
Mortality (60 days)					1
Mortality (>60 days)	0			11	57
Mortality rate 12 months	0	5	5 (10%)		21
Mortality rate 24 months	0				36
Valve Disease	114				
Congestive heart failure	0	2	2		11 at 12 months and 10 at 24 months
Pre-operative atrial fibrillation	63	0	0	62	0
Post-operative fibrillation	0	23	7	11	0
Stroke or transient ischemic attack	1(Preoperative	2	0		1 at 12 months and 0 at 24 months
Hospitalizations due to CCF	0	0	0	0	10 at 12 months and 16 at 24 months
Infective endocarditis	0	2	2	0	0