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Socioeconomic Status, Benzathine Penicillin Prophylaxis, and Clinical Outcomes in Patients With Rheumatic Heart Disease

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Abstract

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Dissertation Submitted in Partial Fulfillment

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Abstract

Rheumatic heart disease (RHD) is the major cause of acquired heart disease and death for children and young adults in developing countries. Poverty and social disadvantage are thought to influence the clinical outcomes in RHD patients. Guided by the health lifestyle theory, this study assessed the relationship between socioeconomic status and clinical outcomes (heart failure events and mortality) in patients with RHD. It also examined how adherence to penicillin prophylaxis mediates the effect of socioeconomic status (SES) on clinical outcomes. Using the Nigerian database of the REMEDY study, this study was conducted with 243 participants using Poisson regression and logistic regression models. There was statistically significant association between SES and heart failure events (*OR=4.77, 95% CI=1.07-21.32, p=0.04*). There was no significant association seen between SES and mortality. Penicillin adherence was not a significant mediatory variable in the relationship between SES and heart failure event and between SES and mortality. These findings are consistent with studies showing low SES is a potential factor for increased risk of recurrent heart failure events in RHD patients. It is however at variance with studies that showed an increased risk of heart failure and mortality in patients with poor adherence to penicillin prophylaxis. A positive social change implication might be the need for physicians treating symptomatic patients with RHD to develop specific strategies for patients from lower SES in order to reduce the recurrence of heart failure. Future studies incorporating a composite measure of SES especially that using income as proxy is needed to further improve our understanding of the role of SES in clinical outcomes.

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Chapter 1: Introduction to the Study

Rheumatic heart disease (RHD) a chronic sequel of acute rheumatic fever is a neglected public health problem prevalent among children and young adult in developing countries including Nigeria (Watson et al., 2017**).** Global estimates suggest about 33.4 million people currently live with RHD with a further 400,000 new cases reported annually (Watkins et al., 2017). In addition, about 319,400 individuals were estimated to have died from RHD in 2015, while about 400,000 new cases were diagnosed annually (Watson et al., 2017)

RHD is associated with huge public health burden especially in developing countries (Watkins et al., 2017). Available reports show that it is the most common cause of cardiovascular disease (CVD) in young people aged 25 years or below, the majority of whom live in Africa, the South Pacific, Middle East, Central and South Asia with associated high mortality and high disability-adjusted life years (DALYs). (Remenyi et al., 2013; Watkins et al., 2016). Most children and young people with chronic RHD in these developing countries present late or with severe disease needing surgical intervention costing millions of dollars annually in health budgets (Watkins et al., 2017; Zühlke et al., 2016). Current estimates suggest an annual spending in excess of 10 billion dollars on surgical and other treatment for chronic RHD (Remenyi et al., 2013; Watkins et al., 2016). Most of this spending occurs outside the country of origin of the affected individuals leading to a needless capital flight (Remenyi et al., 2013; Watkins et al., 2016). Surgery for RHD in most cases is palliative thus underscoring the need to increase efforts at prevention initiatives especially benzathine penicillin secondary prophylaxis, a

management tool demonstrated to improve clinical outcomes for patients with RHD (Remenyi et al., 2013; Watkins et al., 2016).

In this chapter, I discuss the background of RHD and adherence to antibiotic therapy and a gap in knowledge addressed. The research problem, study purpose, and research questions are stated, and the theoretical basis for the study is introduced. In this chapter, I also discuss the significance of this study, research design, assumptions, and study limitations.

Background

RHD is a disease usually associated with social disadvantage that commonly occur in children aged 5-15 years and young adults between the age of 20-30 years (Carapetis & Zuhlke 2011). Poor hygiene, overcrowding, and poor ventilation predisposes the individual to the acquisition of group A beta hemolytic streptococcal (GABHS) pharyngitis, the original harbinger of acute rheumatic fever (ARF) which is the precursor of RHD (Carapetis & Zuhlke 2011; Watkins et al., 2017). The 2017 global burden of disease estimated age-standardized prevalence of rheumatic heart was 444 cases per 100,000 population for countries with an endemic pattern and 3.4 cases per 100,000 population for countries with a nonendemic pattern (Carapetis & Zuhlke 2011; Watkins et al., 2017). From available reports globally, the average age at first diagnosis of acute rheumatic fever occurs in children 10-14 years (Carapetis & Zuhlke 2011; Watkins et al., 2017). In addition, death from RHD usually occurs in the second or third decade of life. Seeing that death from RHD is uncommon among children between 5 and

9 years of age, there could be a risk of serious underestimation of the endemicity of RHD globally (Watkins et al., 2017).

Typically, RHD progression from initial insult of acute rheumatic fever to symptomatic heart failure and in some cases death from the diseases and its related complications may span a period of about 10 years (Watkins et al., 2017). Heart failure is said to be the most common sequel of RHD with an estimate 295,300 cases (95% uncertainty interval, 194,100 to 401,400) of mild heart failure, 243,700 cases (95% uncertainty interval, 176,600 to 320,900) of moderate heart failure, and 663,000 cases (95% uncertainty interval, 566,800 to 763,900) of severe heart failure, which represents an 88% increase in the number of cases overall (Watkins et al., 2017).

Patterns of mortality due to rheumatic heart disease varied significantly according to world health region in 2015 (Watkins et al., 2017). While global age-standardized mortality from rheumatic heart disease decreased from 9.2 deaths per 100,000 population (95% uncertainty interval, 8.7 to 9.7) in 1990 to 4.8 deaths per 100,000 population (95% uncertainty interval, 4.4 to 5.1) in 2015, a decrease of 47.8% (95% uncertainty interval, 44.7 to 50.9), an estimated 77% and 82% of the deaths in 1990 and 2015, respectively, occurred in countries such as India and sub-Saharan Africa where the diseases is endemic (Watkins et al., 2017).

The goal for treatment of RHD is to prevent heart failure and recurrent ARF where possible and allow for good clinical and functional outcomes for patients living with this chronic disease (Remond et al., 2016; Yacoub et al., 2016). While surgical management limits disability by improving cardiac function, it comes with the chronic

need for warfarin therapy and the need for INR measurement for life as a result of the mechanical prosthesis inserted to replace the damaged heart valve (Cannon et al., 2017; Watkins et al., 2017; Zühlke et al., 2016). Benzathine penicillin prophylaxis, a once monthly or 3 weekly intramuscular injection has recently been shown to improve outcome for RHD patients by reducing the frequency of ARF recurrences and heart failure thus improving the overall outlook for the patient (Cannon et al., 2017; Watkins et al., 2017; Zühlke et al., 2016). Since deaths from RHD is mainly from heart failure and recurrent ARF, improve uptake of benzathine penicillin will in turn reduce the death rates as such improve the clinical outcome for these patients living with RHD (Cannon et al., 2017; Watkins et al., 2017; Zühlke et al., 2016). Seeing that SES disparities impact on uptake of health interventions underscores the need for the measurement of disparities and clinical outcomes in RHD management. Achieving the best possible outcomes for all patients living with RHD would, therefore, include the measurement of outcomes by SES. (Cannon et al., 2017; Watkins et al., 2017; Zühlke et al., 2016)

Problem Statement

Even though RHD is associated with social disadvantage as well as low socioeconomic status, not many studies have looked at the role of SES in predicting clinical outcome for patients with RHD (Watkins et al., 2017; Weinberg et al., 2016; Zuhlke et al., 2016). In a multicenter study evaluating 3343 patients with RHD across 12 African countries, Zuhlke et al. (2016) found India and Yemen reported poorer outcome for patients living in low income World Bank category countries. Patients from low income countries had a mortality rate of 20.8% compared with those from the lower

middle income and upper middle-income groups, who had a mortality rate of 16.55 and 12.5% respectively ($p < 0.001$) (Zühlke et al., 2016). In the same vein, new episodes of congestive heart failure occurred in 9% of the patients from the low-income group compared with those of the lower middle-income group and upper middle income who had rates of 6.7% and 6.1% respectively ($p = 0.006$) (Zühlke et al., 2016). Similarly, Okello et al. (2017) in a study of RHD patients in Uganda aged 5-60 years, reported a mortality rate of 17.5%. Benzathine penicillin adherence rate less than 80% was noted in that study to significantly increase mortality rates (31% vs 9%, log rank, $p < 0.001$) (Okello et al., 2017). Antibiotic prophylaxis using penicillin has been demonstrated to improve the outcome for people with RHD when started early in the course of the disease (Remond et al., 2016; Yacoub et al., 2016). Complications like infective endocarditis, atrial arrhythmias, incident heart failure, stroke and even deaths have been shown to be more prevalent in children and young adults with severe RHD (Cannon et al., 2017; Watkins et al., 2017; Zühlke et al., 2016). The success of the secondary prophylaxis is thus hinged on the degree of adherence to the penicillin prophylaxis instituted (Cannon et al., 2017; Yacoub et al., 2016; Zühlke et al., 2016). No study has evaluated outcomes or role of BZP for patients with RHD in Nigeria even though RHD still remains a significant health problem in Nigeria (Watkins et al., 2017).

In Africa, several factors have been associated with poor adherence to penicillin secondary prophylaxis (Watkins et al., 2017; Zühlke et al., 2016). Poverty, illiteracy, and access to care are some factors that have been implicated (Watkinset al., 2017; Yacoub et al., 2016; Zühlke et al., 2016). However, not much is known about the influence of

socioeconomic status and antibiotic adherence on the clinical outcomes of RHD (Cannon et al., 2017; Yacoub et al., 2016; Zühlke et al., 2016).

Nature of the Study

This study utilized a retrospective cohort design to quantitatively analyze a secondary data set of 243 Nigerian patients with RHD that were recruited and followed up over a 2-year period as part of the rheumatic heart disease global registry (REMEDY) study conducted across 12 African countries, Yemen and India (Karthikeyan et al., 2012; Zuhlke et al., 2014). To address the question of the potential influence of SES on clinical outcomes (heart failure and mortality rates) for these patients with RHD, this research used a secondary data prospectively collected from a cohort of 243 RHD patients living in 5 sites spread across the northern, central and southern parts of Nigeria. The patients enrolled in that study were evaluated and managed according to standard practices followed at each participating site using standard operating procedures domesticated at each site (Karthikeyan et al., 2012; Zuhlke et al., 2014). The patients were enrolled from 5 sites spread across the north (Aminu Kano Teaching Hospital, Kano), central (Jos University teaching Hospital, Jos and University of Abuja Teaching Hospital, Gwagwalada) and southern parts of the country (University College Hospital, Ibadan and Federal Medical Center, Abeokuta). Demographic data, clinical findings, and details of electrocardiographic and echocardiographic findings on each patient were recorded in the registry case report forms at research sites at baselines of 12 months and 24 months (Karthikeyan et al., 2012; Zuhlke et al., 2014). This information was then transmitted and stored at the University of Cape Town, Department of Medicine Project Coordinating

Office (Karthikeyan et al., 2012; Zuhlke et al., 2014). The independent variable was SES while the dependent variables were mortality and heart failure. Adherence to benzathine penicillin was the mediator variable studied.

Purpose of the Study

The purpose of this study was to assess the relationship between individual level SES and clinical outcomes (incident heart failure rate and mortality rate) in patients with rheumatic heart disease (RHD). Secondly, it also examined how adherence to benzathine penicillin prophylaxis mediates the effect of socioeconomic status on clinical outcomes (heart failure and mortality rate) for these patients with RHD. The patients recruited were categorized into two groups based on their SES as classified using the Oyedeji system of SES classification (Oyedeji et al., 1985). One cohort (Cohort 1) contained patients with low SES while the second (Cohort 2) contained patients with middle to higher SES.

Socioeconomic status was the independent variable while clinical outcomes (heart failure and mortality) were the dependent variables. Benzathine penicillin adherence was the mediator variable.

Research Questions

Research Question 1 (RQ1). Does the number of heart failure events differ between RHD patients of low SES and RHD patients of higher SES?

Null hypothesis *($H_0$1):* There is no difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES.

Alternate hypothesis (H_a1): There is a difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES.

Research Question 2 (RQ2): Does the mortality rates differ between RHD patients of low SES and RHD patients of higher SES?

Null hypothesis (H_02): There is no difference in mortality rates between RHD patients of low SES and RHD patients of higher SES.

Alternate hypothesis (H_a2): There is a difference in mortality rates between RHD patients of low SES and RHD patients of higher SES.

Research Question 3 (RQ3): Is there a significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

Null hypothesis (H_03): There is no significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Alternate hypothesis (H_a3): There is a significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Research Question 4 (RQ4): Is there a significant difference in mortality rates between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

Null hypothesis ($H_0$4): There is no significant difference in mortality rates between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Alternate hypothesis (H_a4): There is a significant difference in mortality rates between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Theoretical Basis of the Study

The conceptual model for this research was derived from the health lifestyle framework, the theory, which was formulated by Cockerham in 2005 places emphasis on how structural variables such as socioeconomic status, age, gender, and race/ethnicity, social networks and living conditions provide the social context for socialization and experience that ultimately determine lifestyle dispositions and practices (Cockerham 2005). This theory proposes that class circumstances SES may play an important role in determining how individuals in a community make health decisions and choices (Cockerham 2005). These choices may thus play an important role for both adherence and clinical outcomes in patients with RHD (Cockerham 2005; Glanz, Rimer, & Lewis 2002). The correlation between SES and clinical outcomes has been previously established for children with RHD (Okello et al., 2013; Zuhlke et al., 2014). Although a correlation between SES and treatment adherence has been reported in several chronic diseases such as asthma, this has not been conclusively established in RHD (Apter et al. 1998; Dean, Walters, & Hall 2010). The health lifestyle theory thus offered an opportunity to understand how class circumstances such as socioeconomic status

influences patients' choices and decision (agency) on adhering to the monthly penicillin injection (adherence) a health behavior necessary for improving the clinical outcome for the particular patient (Cockerham 2005).

Operational Definitions

Acute rheumatic fever (ARF): an abnormal immune response leading to an inflammatory disease that affects the endothelial lining of the joints, skin, brain and heart following group A beta Hemolytic streptococcal pharyngitis.

Adherence to treatment regimen: Adherence refers to the extent to which an individual's behavior coincides with medical or health advice (Modi et al., 2012).

Congestive heart failure: Inability of the heart to pump blood to the body despite a normal filling pressure.

Group A beta hemolytic streptococci (GABHS) pharyngitis: A bacterial infection of the throat and surrounding tissues commonly seen in children aged 5-15 years and young adults less than 30 years of age.

Mortality rate: Mortality is derived from the Latin word '*mortalitas*' and refers to the state of being subject to death. Mortality rate is thus a measure of the number of deaths due to a specific cause in a particular population per unit of time (Gordis 2013).

*Rheumatic heart disease (RH*D): A chronic sequel of ARF that commonly involve the mitral valvular structures with resulting incompetence and backward leakage of blood into the left atrium.

Socioeconomic status: This is a complex concept that defines an individual's socioeconomic position in the society. Inherent in this concept is the reference to

economic resources such as earnings, income, and wealth, social resources such as social networks and connections to community resources, education and occupation. In the context of this study, occupation and educational attainment were used as a proxy for SES because of its intricate relationship to access to care and adherence to drug treatment (Sewell & Velayos, 2013).

Assumptions

In this current study of SES, adherence behavior, and clinical outcomes (death or mortality and heart failure events), my approach is formed by a postpositivist worldview which posits that outcomes or effects are determined by causes (Creswel 2009). As a result, being a reductionist, I assumed that concepts can be reduced to small, discrete sets of testable ideas, and that empirical testing and measurement can inform our knowledge of human behavior. Thus, the conceptual model chosen for this study places adherence to benzathine penicillin secondary prophylaxis regimens in the pathway between SES and Clinical outcomes (death, heart failure). According to the Health lifestyle theory, class circumstances (SES) may play an important role in determining how individuals in a community make health decisions and choices (Cockerham 2005). These choices may thus play an important role for both adherence and clinical outcomes in patients with RHD (Cockerham 2005; Cockerham 2013)

In this study, I assumed that SES leads to differences in clinical outcomes as opposed to poor clinical status leading to differences in SES. I also assumed that patients with greater disease severity or activity will more likely be adherent to BZP secondary prophylaxis compared with patients whose disease is well controlled. Finally, I assumed

that low SES status negatively impacts adherence and poor adherence to BZP prophylaxis will worsen clinical outcomes by increasing death rates and/or heart failure recurrences in patients treated for RHD. These assumptions will be necessary to empirically test the health lifestyle model of health disparities.

Scope and Delimitations

Socioeconomic disparities in RHD have been observed in both adult and pediatric populations (Watkins et al., 2017). The scope of this study was limited to symptomatic patients presenting in the hospital; asymptomatic patients identified through screening were excluded. Adherence behaviors in symptomatic patients may be influenced by disease severity, access to care and SES therefore, the results of this study may not be applicable to asymptomatic RHD patients.

Limitations

I used secondary data from a disease registry to answer my research questions. While disease registry provides a ready source of patient data for research, there are inherent limitations to the use of this secondary source of data for research purposes (Yim et al., 2017). First, the measurement of constructs is limited to data elements available in the registry (e.g., a provider assessment of adherence to treatment regimen) and this may affect the validity of the measures for adherence. This limitation was addressed in the REMEDY study by using multiple sources of information (physician records and patient monthly injection book records) in evaluating adherence to benzathine penicillin secondary prophylaxis.

Significance of the Study

The intent of this study was to bridge the gap in understanding the role of individual level socioeconomic status on clinical outcomes for persons with rheumatic heart disease. In addition, it was aimed at evaluating the possible mediatory role of benzathine penicillin prophylaxis adherence on the relationship between SES and clinical outcomes for these patients with RHD. The previously published report on this data had demonstrated a significant relationship between country level socioeconomic status and clinical outcomes in RHD patients (Zuhlke et al., 2015). Individual level SES was not investigated (Zuhlke et al., 2015). Access to care and by extension drug adherence are more readily affected by the individual's economic status rather than the group economic level (Yim et al., 2017). Since adherence is an individual health behavior (though potentially influenced by group characteristics), it is easier to relate and thus examine the effect of BZP adherence on health outcomes with individual level SES. The results of this study add to the knowledge on the influence of socioeconomic status and adherence to benzathine penicillin prophylaxis on clinical outcomes (heart failure and death) in patients with RHD. It also adds to the knowledge on the mechanism through which benzathine penicillin adherence, (a management tool shown to impact the course and hence outcomes of RHD) mediate the relationship between socioeconomic status and clinical outcomes in patients with RHD. The findings here will thus help to improve the ways in which clinicians address the problem of benzathine penicillin secondary prophylaxis for patients with RHD especially those whose adherence problem may stem from poverty and its related factors thereby improving the clinical outcomes for them.

Summary

RHD is the major cause of acquired heart disease and death from heart disease in children and young adult in most parts of the developing world especially sub-Saharan Africa. Currently, RHD has virally been eradicated in the developed countries such as the US and UK except for occasional flares among immigrant populations.

Evidence shows that SES, adherence to drug therapy especially benzathine penicillin secondary prophylaxis are important factors in determining outcome for patients with RHD. The health lifestyle theory can potentially explain the role of SES and adherence to benzathine penicillin secondary prophylaxis in determining outcome for patients with RHD. There are currently no studies that evaluated the role of SES and adherence to benzathine penicillin prophylaxis in patients with RHD using the health lifestyle theory. This study was aimed at determining the relationship between SES and clinical outcomes (heart failure and mortality) in patients with RHD and the role of adherence to BZP as a mediator between the relationship of SES and clinical outcomes (heart failure and mortality) in this population.

In Chapter 1, I provided the background of what is known about rheumatic heart disease and its social determinants, the problem statement, the purpose of the study, the different research questions and hypotheses, the theoretical framework of the study, the nature of the study, the definitions, the assumptions, the scope and delimitations, the limitations, and the significance.

In Chapter 2, I focus on discussion of literature in the area of socioeconomic status and RHD. I provided a discussion of RHD and RHD risk factors and then

subsequently provided a discussion of the theoretical framework, specifically studies that used the health lifestyle theory to examine the relationship between SES and RHD as well as the role of drug adherence on the relationship between SES and RHD. I then concluded with a discussion of the relationship of the study to previous research.

Chapter 2: Literature Review

SES is an important variable that predisposes to health disparities especially in people living with chronic diseases (Claussen, 2015; Sliwa, Acquah, Gersh, & Mocumbi, 2016). Furthermore, people with low income or from low SES families have been shown to be disproportionately burdened with higher morbidity and mortality from chronic disease especially cardiac diseases compared with those from more advantaged backgrounds (Hastert, Beresford, Sheppard, & White, 2015; Sommer et al., 2015; Wu, Woo, & Zhang, 2013). SES disparities may affect a person's access to health care, their ability to pay for health services and possibly adherence to therapy all of which can have important impact on the outcome for such chronic diseases (Claussen, 2015; Stringhini et al., 2012, 2011). This study thus sought to assess the role of socioeconomic status on clinical outcomes for patients with RHD. In addition, it examined how adherence to benzathine penicillin prophylaxis treatment regimen mediates the effect of socioeconomic status on clinical outcomes (heart failure and mortality) for these patients with RHD. Exploring pathways between SES and clinical outcomes provides insight into the way in which health disparities might occur in persons with RHD (Claussen, 2015; De Dassel, Ralph, & Carapetis, 2015; Irlam, Mayosi, Engel, & Gaziano, 2013; Nulu, Bukhman, & Kwan, 2017; Stringhini et al., 2012, 2011). This may help inform decisions on developing framework for RHD control as well as policies and interventions that can potentially eliminate these disparities and thence RHD (Irlam et al., 2013).

This literature review addressed the predictive relationship between individual level SES and clinical outcomes in patients living with RHD. Major sections of the

chapter include the literature search strategy, conceptual framework, and review of key topics, including RHD epidemiology, pathogenesis, treatment patterns, prevention, SES, and adherence to benzathine penicillin prophylaxis.

Literature Search Strategy

A systematic literature search was conducted using African Journal online (AJOL), Cinahl, google scholar, Pubmed and Web of Science. In Pubmed, the following medical subject headings (MESH) and free text terms were used: Rheumatic heart disease" OR "Rheumatic valvular heart disease" OR "Rheumatic heart" OR "RHD" AND "clinical outcome" OR "heart failure" OR "admissions" AND "Benzathine adherence OR Compliance" OR "Secondary prophylaxis" OR "Penicillin adherence OR compliance" OR "BZP". The same text word search was used in Google scholar, AJOL, CINAHL and Web of Science as in Pubmed. No search date limiter was used, however, studies in the last 5 years were preferred. In addition, studies had to be peer reviewed to be selected. Libraries were searched until March 2020. Studies were selected if they were written in English, included human subjects, defined benzathine prophylaxis and contained either rheumatic heart disease, or had clinical outcomes such as heart failure, mortality or death. Any study that failed to define benzathine prophylaxis adherence rates was excluded. A computerized bibliographical search was done that initially yielded 1,342 articles but 46 publications were eventually selected for inclusion in this review because of their direct relevance to the study.

Theoretical Foundation

The health lifestyle theory provided the foundation for this research work. The theory was formulated by Cockerham in 2005 and later expanded in 2013 (Cockerham, 2005, 2013). Cockerham definesd health lifestyles as "collective patterns of health-related behavior based on choices from options available to people according to their life chances" (Cockerham 2013). Cockerham's health lifestyle theory was derived from Bourdieu's seminal work on lifestyles (Cockerham 2005, 2013). Bourdieu postulated that lifestyle practices cluster in different strata of social space and that these different clusters correlated with the different social classes found in the society(Cockerham, 2005, 2013). According to Bourdieu, this class differences in lifestyles are hinged on the notion of "distance from necessity." The distance from necessity is thought to produces dispositions to act (*habitus*), which generate practices (actions)(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013). When these dispositions are acted upon they result into the habitus that was the originator of the actions(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013). The theory thus posited that the further a person is from the daily struggles for economic survival the more freedom and time such a person has to develop and refine personal tastes typical of the higher social classes ("taste of freedom")(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013)[i]. In the same vein, the closer a person is to the daily struggles for survival (lower social classes) the less freedom and time such a person has to refine personal taste and thus adopt tastes consistent with a life of daily economic struggle in which acquiring items of necessity is critical ("taste of necessity")(Bourdieu & de Saint Martin, 1976). Thus in this ensuing

power struggle, the freedom from the daily necessities of life becomes the major influence on decisions or actions taken by individuals(Bourdieu & de Saint Martin, 1976). Therefore, the distance from economic necessity leads to a class-based, systematically unequal distribution of the instruments for appropriation of goods and thus generates other such class-based inequalities(Bourdieu & de Saint Martin, 1976). In his contribution to Bourdieu's lifestyle theory, Cockerham expanded the meaning of "lifestyle" to involve practices for maintaining health and preventing disease and not just consumption practices(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013). In his theoretical model, he conceptualized health lifestyles as consisting of a series of personal routines that converged into an aggregate form representative of specific groups and classes rather than a disjointed or uncoordinated behavior of disconnected individuals (Cockerham 2005, p. 56). In other words, as is the case with general lifestyle practices and tastes, health behaviors are correlated with socially determined structural variables that exist outside of the individual, such as class circumstances, age, gender, race/ethnicity, collectivities (religion, ideology), and living conditions(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013). Of all these structural variables the class circumstances, (socioeconomic class and the social and physical environments are the main determinant that configures health behavior(Bourdieu & de Saint Martin, 1976; Cockerham, 2005, 2013).

Previously, researchers have explored the role of SES as an independent variable of interest in clinical outcomes for chronic diseases(Cockerham, 2014; Cockerham, Hamby, & Oates, 2017). Recently, country level SES was a subject of study by Zuhlke

and colleagues in their study of clinical outcomes for 3343 patients with RHD in 14 African countries, Yemen and India as an independent variable of interest in defining clinical outcomes for persons with RHD (Zühlke et al., 2015). While country level SES may be a marker of societal affluence, it is unlikely going to be a good surrogate for individual level SES in predicting disease outcome which by all ramifications affects the individual and is thus most likely be more predictive by individual level factors (Claussen, 2015; Cockerham et al., 2017; Zühlke et al., 2015).

Health lifestyle theory is chosen for this study because of its applicability to chronic diseases such as RHD (Claussen, 2015; Cockerham, 2014; Zühlke et al., 2015). The health lifestyle theory postulates that the available life chances (structure) either act to constrained or expand the possible choices or decisions (agency) a person makes concerning their health (Cockerham, 2013). According to the health lifestyle theory, people's health lifestyle is shaped by the structural influences to which they are exposed thereby limiting their choices to what is socially acceptable according to their socioeconomic class (Cockerham, 2013). RHD is a chronic disease that begins in childhood and if not appropriately treated continues into adult life (Cockerham, 2013; Mayosi, 2014; Nulu et al., 2017; Shah et al., 2013). Low SES has several implications for the patient with RHD as it impacts not just the development of the disease but also the access to the necessary measures or treatment for the disease (Liu, Lu, Sun, Zheng, & Zhang, 2015a; Mayosi et al., 2014; Watson, Jallow, Le Doare, Pushparajah, & Anderson, 2015; L. Zühlke et al., 2015). In addition, RHD treatment relies on the patient's adherence to treatment regime for congestive cardiac failure as well as the 4 weekly

benzathine penicillin injections for the prevention of ARF recurrence and thus the progression of the RHD to severe disease and eventually death (Liu et al., 2015a; Mayosi et al., 2014; Watson et al., 2015; L. Zühlke et al., 2015). Thus, clinical outcomes for patients with RHD will largely depend on class circumstances and the patient's ability to take action or decision about treatment regimens such as benzathine penicillin prophylaxis variables to which the health lifestyle theory provides an appropriate framework for asking research questions and predictive claims regarding SES and adherence (Cockerham et al., 2017).

Adherence as a Health Behavior

Chronic diseases have become important cause of morbidity globally due to the epidemiologic transition from infectious to non-infectious causes of disease(Harris, 2013; Hruby & Hu, 2015). Since chronic diseases are not easily cured by medical treatment, health lifestyle practices are becoming more important variables in determining clinical outcomes for patients with chronic diseases(Benjamin et al., 2018; Ettehad et al., 2016; Lyons, Lewis, Mayrsohn, & Rowland, 2014). As a result, patients with chronic diseases have to make efforts daily working towards slowing down the disease process in order to prevent premature death further underscoring the importance of life choices and by extension health lifestyle in predicting clinical outcomes for patients with chronic diseases(Benjamin et al., 2018; Ettehad et al., 2016; Lyons et al., 2014). This is seen in the case of RHD patients whose treatment regime affects all aspects of their daily life(Liu, Lu, Sun, Zheng, & Zhang, 2015b; Okello, Kakande, et al., 2017a). Applying Cockerham's health lifestyle theory to RHD care, I argue that adherence to treatment in

RHD is a health lifestyle practice adopted to minimize illness and maximize health as is seen in other lifestyles practice like tobacco use, exercise, diet and utilization of preventive health services such as immunization.

Conceptual Framework

The conceptual framework for this study was derived from the health lifestyle theory which proposes that class circumstances (structure) play an important role both for adherence (agency) and for clinical outcomes in persons with RHD (Cockerham, 2005, 2013; Cockerham et al., 2017; Goyal & Vijayvergiya, 2016; Mayosi, 2014). There have been studies that established a correlation between SES and many chronic diseases such as asthma, diabetes and coronary heart disease (Cockerham et al., 2017; Eisner et al., 2011; Goyal & Vijayvergiya, 2016; Mayosi, 2014; Nandi, Glymour, & Subramanian, 2014; Pudrovska & Anikputa, 2014; Sommer et al., 2015; Wu et al., 2013). Although recent studies have shown the important role of SES on the etiology and epidemiology of RHD, not much has been done to evaluate the correlation of SES and clinical outcomes for patients with RHD (De Dassel et al., 2015; Goyal & Vijayvergiya, 2016; Kumar & Tandon, 2013; Mayosi et al., 2014; Stewart, Carrington, & Sliwa, 2016; L. Zühlke et al., 2015; L. J. Zühlke & Karthikeyan, 2013). Similarly, little is known about the mediating role of BZP adherence in the possible correlation between SES and clinical outcomes in patients with RHD (Goyal & Vijayvergiya, 2016; Kevat, Reeves, Ruben, & Gunnarsson, 2017; Mayosi, 2014; Musoke et al., 2013; Okello et al., 2012; Okello, Longenecker, Beaton, Kamya, & Lwabi, 2017; Kevat, Reeves, Ruben, & Gunnarsson, 2017; L. Zühlke et al., 2015). In the light of this evidence and applying the framework of the health

lifestyle theory, I argued that adherence to treatment contributes to the correlation between SES and RHD clinical outcomes.

Rheumatic Heart Disease

Rheumatic heart disease, the chronic sequel of rheumatic fever is a disease associated with social disadvantage and poverty (Cannon, Roberts, Milne, & Carapetis, 2017; Marijon, Mirabel, Celermajer, & Jouven, 2012; Nulu et al., 2017; Terreri & Len, 2016; L. J. Zühlke et al., 2017). It has persisted in the developing countries because of the persistence of the social factors such as disorganized health system, poor housing, overcrowding and widespread poverty the predisposing factors to the acquisition, sustenance and persistence of the disease (Carapetis, Steer, Mulholland, & Weber, 2005; Stewart et al., 2016; Wilson, 2010). It is a disease that results from poorly treated or untreated group A beta hemolytic streptococcal pharyngitis especially in children between the ages of 5 and 15 years of age (Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010). Chronic RHD is associated with huge financial burden on the families of affected children (Marijon et al., 2012; Zühlke & Steer 2013; Zühlke et al., 2014). It renders a large proportion of children physically and educationally handicapped and therefore deprive the country of potential skilled workforce (Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010). In addition, it put a strain on the already lean health budget of these poor countries thereby further worsening already existing poor health indices in the population (Marijon et al., 2012; Zühlke & Steer 2013; Zühlke et al., 2014).

Epidemiology of Rheumatic Heart Disease

Rheumatic heart disease (RHD) is currently the most common acquired heart disease in children and young adults living in the developing world especially those living in sub Saharan Africa (Watkins et al., 2017). It used to be an important acquired heart disease in the United States and United Kingdom in the early twentieth century but with improvements in socioeconomic and living conditions, RHD completely disappeared except for occasional flares among immigrant populations (Kočevar et al., 2017). Current estimates suggest that about 33 million people are living with RHD globally with a further estimated 280,000 new cases detected and a resultant 237,500 estimated deaths globally in 2016. About 70- 80% of these deaths are said to occur in sub-Saharan Africa where poverty, malnutrition, poor hygiene and sanitation, overcrowding and poor access to health all act together to sustain the burden of the disease as well as the deaths occurring from the complications of the disease (Marijon et al., 2012; Zühlke & Steer 2013; Zühlke et al., 2014). The persistence of these poverty defining problems in sub Saharan Africa is what is currently responsible for the persistence of RHD (Marijon et al., 2012; Zühlke & Steer 2013; Zühlke et al., 2014).

Aetiopathogenesis of RHD

RHD is a result of untreated or poorly treated group A beta hemolytic streptococcal pharyngitis that culminates into acute rheumatic fever (ARF) which if left untreated or become recurrent will eventually scar the endocardial lining of the heart and thus by extension the valves and their apparatus (Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010). This long term complication of

ARF is what is referred to as RHD (Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010). Commonly, the initial streptococcal pharyngitis and its ensuing sequel of ARF occur in childhood especially in those children between 5 to 15 years.(Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010) However, the majority of those who present with RHD especially its severe form present in later childhood, adolescence and early adulthood (Watkins et al., 2017).

RHD usually follows single or repeated episodes of ARF; an abnormal host attempt at eradicating the causative agent group A beta hemolytic streptococcal (GABHS) which cause pharyngitis (inflammation of the throat) (Karthikeyan & Guilherme, 2018; Stewart et al., 2016). ARF occurs because of the similarity between some parts of the GABHS bacterial cell wall and some parts of the host cardiac, brain, skin and synovial tissues (Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Stewart et al., 2016; Wilson, 2010). This abnormal host immune response is seen in only about 0.3-3% of people who had the GABHS pharyngitis (Karthikeyan & Guilherme, 2018; Mayosi, 2014; Stewart et al., 2016). Repeated GABHS infection is thought to be the initiating immunologic priming that predisposes to the development of ARF, the precursor of RHD (Karthikeyan & Guilherme, 2018; Mayosi, 2014; Stewart et al., 2016). This immunologic priming is also thought to be the main determinant of the age of onset of ARF and thus RHD which commonly peaks at between 5 to 15 years (Karthikeyan & Guilherme, 2018; Mayosi, 2014; Stewart et al., 2016).

Predisposing Factors to RHD

RHD is a disease of poverty and social disadvantage hence its high burden in poor countries especially those in Africa, India and south East Asia (Animasahun, Deborah, Wobo, Itiola, & Oluwabukola, 2018; Watkins et al., 2017; L. J. Zühlke & Steer, 2013). The factors that predisposed to and sustained it in these regions are deeply rooted in poverty and social disadvantage (Animasahun et al., 2018; Watkins et al., 2017; L. J. Zühlke & Steer, 2013). However, RHD can also be seen in rich countries such as Australia where it is endemic among the indigenous or aboriginal populations as well as the immigrant populations where social disadvantage is common (Animasahun et al., 2018; Watkins et al., 2017; Zühlke & Steer, 2013). Malnutrition, overcrowding, poor sanitation and hygiene and poor access to healthcare are all factors derived from poverty that predisposed to and sustain the burden of ARF/RHD. Poverty is the single most important risk factor associated with RHD (Kumar & Tandon, 2013; Marijon et al., 2012; Watkins et al., 2017). Poverty breeds the social and environmental milieu that predisposes, cause and sustained the scourge of RHD (Kumar & Tandon, 2013; Marijon et al., 2012; Watkins et al., 2017). Conditions which promote high GABHS exposure are usually set in socioeconomic deprivation (Terreri & Len, 2016; Zühlke et al., 2017).

Environmental factors. Overcrowding and poor sanitation are currently the most significant determinant of the development of RHD (Okello et a., 2013;Terreri & Len, 2016; Zühlke et al., 2017). In a case control study involving 486 participants (243 cases and 243 controls) in Uganda, Okello et al. (2013) reported an increased odd of having RHD with increasing household overcrowding (OR-1.35; 95% CI= 1.1-1.56) (Okello et

al., 2013). Jaine et al.,(2011) in an ecological study undertaken in New Zealand, showed a significantly increased rate ratio of ARF cases associated with crowding quintile, according to population-level data (Jaine, Baker & Venugopal 2011). Jaine et al. reported rheumatic fever rate of 9.6 per 100,000 seen in the most crowded quintile was 4 times higher than the rate seen in the second most crowded quintile and 23 times more than that of the quintile with the least household crowding compared to the quintile with the least household crowding (Jaine et al., 2011). This effect remained even after adjusting for age, ethnicity, household income, and the density of children in the neighborhood suggesting. that household crowding is an independent factor associated with rheumatic fever (Jaine et ali., 2011). This effect remained even after adjusting for age, ethnicity, household income, and the density of children in the neighborhood suggesting. that household crowding is an independent factor associated with rheumatic fever (Jaine et al., 2011).

The association between overcrowding, GABHS infection, ARF and RHD has been the subject of research over the past 50 decades(Karthikeyan & Guilherme, 2018; Terreri & Len, 2016; Zühlke et al., 2017). Coffey, Ralph and Krause (2018) in a recent systematic review of the social determinants of GABHS pharyngitis, ARF and RHD examined 50 studies that reported on the association between household crowding and the risk of developing ARF/RHD. A positive association between crowding and the risk of developing ARF was found in 9 of 16 (56.3%) studies reviewed and RHD in 9 of 15 studies (60.0%). Coffey reported that only 14 of the 50 studies reviewed showed consistent associations across all measures on the association between household

crowding and the risk of developing ARF/RHD (Coffey, Ralph & Krause 2018). While the quality of the studies may not be optimal, the evidence demonstrated in these researches supports an association between crowding and ARF risk(Coffey, Ralph & Krause 2018; Carapetis et al., 2005; Karthikeyan & Guilherme, 2018; Meira, Goulart, Colosimo, & Mota, 2005; Terreri & Len, 2016; Zühlke et al., 2017). Overcrowding the single most consistent factor in RHD epidemiology favors the spread of the GABHS between individuals especially in the face of poor ventilation which further reinforce the acquisition and spread of the organism(Islam & Majumder, 2016; Stewart et al., 2016; Zühlke & Steer, 2013). This pattern is frequent seen among the urban poor where rapid urbanization combine with poor housing to cause overcrowding and poor ventilation thereby predisposing to ARF and thereafter its chronic sequel, RHD (Islam & Majumder, 2016; Stewart et al., 2016; Zühlke & Steer, 2013). The central role of overcrowding in the aetiopathogenesis of RHD has also been demonstrated in contemporary studies carried out in Australia and the developing world along with other societal markers of poverty such as poor access to health care, low maternal literacy levels, unhygienic environments and malnutrition (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). Poor people will most likely live in poorly ventilated household with its attendant overcrowding and unhygienic surroundings breeding the organisms that are the harbinger of streptococcal pharyngitis the precursor of ARF the sequel of RHD (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013).

Malnutrition. Malnutrition is another poverty-related factor is an important predisposing factor to ARF and also RHD that is associated with weakened or poor immunity and thus an inability to naturally fight infectious diseases including GABHS (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). Potentially, childhood malnutrition has a link with increased susceptibility to ARF/RHD probably due to the fact that malnutrition can increase susceptibility to developing aggressive autoimmune responses to GABHS infection (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). However, since poor nutrition, household overcrowding and poor access to healthcare are associated with poverty, it is possible that malnutrition may just be a surrogate for poverty as a cause of ARF/RHD (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). Currently, there is no clear evidence linking malnutrition to GABHS and/or ARF/RHD apart from its association with poverty (Zuhlke & Steer 2013).

Poor access to healthcare driven by poverty is another important predisposing factor to ARF and RHD (Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). An earlier study carried out by Gordis comparing outcome of care for black children aged 5 to 14 years with RHD in Baltimore enrolled in a comprehensive care program compared with similar aged matches group of RHD patient not enrolled in the same care program reported a 60% drop in incidence of ARF in those enrolled in the comprehensive care program (Gordis 1973). More recently, similar care programs instituted in Cuba focusing on health literacy and health promotion towards attitudinal change as well as improved access to BZP prophylaxis was shown to reduce the rates of

ARF by more than 50% in the general population (Gordis 1973; Nordet et al., 2008). While it is difficult to identify studies that directly assessed the impact of access to care on the risk of ARF.RHD, these comprehensive care programs serve to demonstrate the important role of access to care on the risk and burden of ARF/RHD in vulnerable populations (Gordis 1973; Nordet et al., 2008). Poverty creates the structural factors that makes many in developing countries to seek alternative care rather than present to hospitals(Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). This thus means that GABHS, a potentially treatable and curable infection may be missed, poorly treated or not treated at all further predisposing the child or young adult to the risk of ARF and thus RHD(Islam & Majumder, 2016; Stewart et al., 2016; Watkins et al., 2017; Zühlke & Steer, 2013). Where this ARF becomes recurrent, further damage is incurred on the heart with worsening of outcomes leading to frequent or chronic heart failure potentially culminating in death(Cannon et al., 2017; Kumar & Tandon, 2013; Mayosi et al., 2014; Shah et al., 2013; Zühlke et al., 2015).

Treatment Patterns for Rheumatic Heart Disease

Rheumatic heart disease being a chronic heart condition comes with a lot of challenges for patients when we consider treatment options(Cannon et al., 2017; Nulu et al., 2017; Zühlke et al., 2015). Access to appropriate intervention in an environment with poorly developed health care infrastructure where RHD is endemic is crucial and may be the missing link in appropriate and correct management of the disease in these patients with established heart valve disease (Shah et al., 2013). For example, the REMEDY study which evaluated 3343 RHD patients across 14 countries in Africa, India and

Yemen showed that more than 50% of patients who are eligible for BZP secondary prophylaxis, an effective tool for preventing worsening and recurrent ARF/RHD were not receiving the therapy (Zuhlke et al., 2015). It is thus important that improved access to, and affordability of, essential medicines such as benzathine penicillin, heart failure drugs, and anticoagulants to prevent thromboembolic events be the main focus of policy makers and clinicians alike (Regmi & Wyber, 2013; Shah et al., 2013; L. Zühlke et al., 2015).

Rheumatic heart disease being a valvular heart disease is associated with mechanical disturbances of cardiac valve function especially the mitral valve which commonly presents with mitral incompetence leading to regurgitation and back flow of blood thus predisposing to frequent heart failure in those affected (Carapetis, Brown, Maguire, & Walsh, 2012; Regmi & Wyber, 2013; Boglarka Remenyi, Elguindy, Smith, Yacoub, & Holmes, 2016; Shah et al., 2013; Smith, Zurynski, Lester-Smith, Elliott, & Carapetis, 2012; Zühlke et al., 2015). Heart failure is the most frequent complication seen in about 30 percent of new patients seen with RHD (Carapetis et al., 2012; M. Liu et al., 2015b; Mehta et al., 2016; Regmi & Wyber, 2013; Boglarka Remenyi et al., 2016; Shah et al., 2013; Smith et al., 2012; L. Zühlke et al., 2015). In addition, it is the most frequent cause of death in those affected with RHD with about 17% dying within 2 years of enrolment in a follow up care program especially when the disease occurs early in childhood (Carapetis et al., 2012; Smith et al., 2012; Zuhlke et al., 2015). Heart failure management with diuretics is the main stay of treatment for most patients with symptomatic RHD especially those with chronic heart failure (Carapetis et al., 2012; Smith et al., 2012). The availability of potent diuretics especially the loop diuretics has

helped to improve the control of heart failure in these patients with RHD thus reducing the rate of death associated with heart failure in these patients (Nieuwlaat et al., 2014; Nulu et al., 2017; Shah et al., 2013).

Prevention Strategy for Rheumatic Heart Disease

Rheumatic heart disease is wholly preventable using simple, basic, cost effective public health measures such as improvement in living conditions and nutrition rehabilitation (Irlam et al., 2013; Gordis 1973;Nieuwlaat et al., 2014; Nulu et al., 2017; Regmi & Wyber, 2013; Remenyi, Carapetis, Wyber, Taubert, & Mayosi, 2013; Shah et al., 2013). Evidence from the United States suggest that improvements in living conditions, sanitation and poverty reduction was responsible for the greater than 70% drop in cases of ARF/RHD seen in the 20th century (Irlam et al., 2013; Gordis 1973;Nieuwlaat et al., 2014; Nulu et al., 2017; Regmi & Wyber, 2013; Remenyi et al., 2013).Its persistence in the developing countries especially Sub Saharan Africa exemplifies the failure of coordinated efforts of public health practitioners, policy makers and implementers (Gordis 1973; Nulu et al., 2017; Remenyi et al., 2013). Such prevention efforts must be targeted at the social determinants of the disease as well as the improvement of access to care for streptococcal pharyngitis as well as those who develop the disease (Irlam et al., 2013; Nordet et al., 2008; Remenyi et al., 2013; Zühlke & Karthikeyan, 2013). These measures are needed in order for meaningful progress to be made at the control and prevention of the disease (Remenyi et al., 2013). Such prevention and control measures for RHD must be targeted at the reduction of household crowding, timely diagnosis and appropriate antibiotics for bacterial pharyngitis and – in people who

develop rheumatic fever – antibiotic prophylaxis over several years to prevent disease progression (Irlam et al., 2013; Irlam, Mayosi, Engel, & Gaziano, 2013; Remenyi et al., 2013).

Role of School based Echocardiography screening in the Prevention of RHD

Community based echocardiographic screening especially in school children who happen to bear the brunt of the disease is said to increase the detection rates for RHD by about 10-15 times when compared with cardiac auscultation and thus proved to be an important tool for the detection of asymptomatic RHD (Beaton et al., 2012; Irlam et al., 2013; Irlam et al., 2013; Remenyi et al., 2013; Rothenbühler et al., 2014; Shah et al., 2013). Early detection of RHD especially in those who are yet to show signs of the disease opens the way for early initiation of BZP prophylaxis for the prevention of GABHS episodes and as such recurrence of ARF (Beaton et al., 2012; Irlam et al., 2013; Irlam et al., 2013; Remenyi et al., 2013; Rothenbühler et al., 2014; Shah et al., 2013). Echocardiographic screening for RHD in school children has been demonstrated to increase the uptake of BZP prophylaxis by about 40% and thus helped reduce the onset of severe disease and other complications associated with RHD (Cannon et al., 2017; Mason, Retzer, Hill, Lincoln, & Centers for Disease Control and Prevention (CDC), 2015; Rothenbühler et al., 2014). In Fiji, Engelman reported that overall admission rates in clinically diagnosed RHD in symptomatic children is 4 times higher compared with that of echocardiography-based screening detected asymptomatic children. (RR 4.3, 95% CI 2.8–6.8) (Engelman et al., 2017). In addition, RHD-related admissions bed days were higher in the clinically diagnosed group compared with the echocardiography-based

screening-detected group (IRR 6.6, 95% CI 5.6–7.8) (Engelman et al., 2017). Echocardiography based school screening is thus significantly associated with reduced morbidity and mortality(Engelman et al., 2017). A similar effort in Australia has demonstrated the same results for aboriginal children who bear the brunt of the disease in Australia (Carapetis et al., 2012; Parks, Smeesters, & Steer, 2012; Steer & Carapetis, 2009). The advent of echocardiography has thus helped in no small measure towards not just making an early diagnosis but also in the prevention and control of RHD globally (Carapetis et al., 2012; Marijon, Celermajer, & Jouven, 2017; Parks et al., 2012; Rothenbühler et al., 2014; Steer & Carapetis, 2009).

Penicillin Secondary Prophylaxis

In a classic study suing a cohort design, Stollerman, Russoff and Hirschfeld (1955) showed that secondary prophylaxis using 4 weekly 1.2 mega units intramuscular BZP was successful in preventing ARF recurrence in patients followed up for 20 months (Stollerman, Russoff & Hirschfeld 1955). In their report, none of the patients on BZP developed ARF compared with their counterparts on oral penicillin or sulfadiazine (Stollerman et al., 1955). Adequate Penicillin prophylaxis described as at least 80% of the prescribed annual dose improved outcomes and reduces the risk of death especially where access to healthcare is limited (Nordet et al., 2008; Nulu et al., 2017). Recently, de Dassel et al., in a review of register data of Australian patients with RHD reported a 4-fold increase in the odds of having ARF in patients who had suboptimal (<80% of annual doses) adherence to BZP (de Dassel et al., 2018). Intramuscular benzathine penicillin (BZP) injections serve as the main prophylaxis and a key component of RHD control

programs (Irlam et al., 2013; Manji et al., 2013; Regmi & Wyber, 2013; Remenyi et al., 2013; Smith et al., 2012; Watson et al., 2015; Zühlke et al., 2017). This approach is aimed at preventing group A beta-hemolytic streptococci (GABHS) streptococcal infections the harbinger of ARF and by extension subsequent recurrent episodes of ARF the precursor of RHD (Irlam et al., 2013; Nulu et al., 2017). Current recommendations by the World Health Organization (WHO) stipulates a 3-4 weekly BZP injection for a duration dependent on factors including age, time since the last episode of ARF, risk of streptococcal infections in the area and presence of RHD (Rémond, Coyle, Mills, & Maguire, 2016a). Based on the WHO guidelines, secondary prophylaxis is advised for at least 5 years after the last episode of ARF or until the age of 18 years (whichever is longer) and for a greater length of time for persons who had cardiac involvement at the initial episode of ARF or in those with established RHD (Remenyi et al., 2013; Rémond et al., 2016a).

For a successful RHD prevention, a well-coordinated BZP prophylaxis hinged on good drug supply chain and easily accessible centers for BZP injection is key (Nieuwlaat et al., 2014; Watson et al., 2015; Zühlke & Karthikeyan, 2013). In the more than 50 years of using penicillin in the treatment of GABHS pharyngitis associated with ARF/RHD, antibiotic resistance has not been reported against penicillin G and its generics (Kumar & Tandon, 2013; Liu et al., 2015a). This has made penicillin G an excellent and yet useful tool for the much needed RHD control program globally (Kumar & Tandon, 2013; Liu et al., 2015a). While concerns about penicillin allergy and the pains of intramuscular injections have been the main hindrances to the widespread uptake of BZP prophylaxis in

RHD endemic areas, current evidence suggest a low or near absent presence of serious anaphylactic reactions to penicillin (Kumar & Tandon, 2013; Liu et al., 2015a).

Clinical Outcomes in RHD

RHD a disease of children and young adults is associated with many complications(Kumar & Tandon, 2013; Liu et al., 2015a; Stewart et al., 2016; Watkins et al., 2017). Patients with RHD are at an increased risk for congestive heart failure, arrhythmias, stroke and infective endocarditis(Liu et al., 2015a; Zühlke et al., 2015). The REMEDY study, a 2 year prospective study which contains the largest contemporary data on the outcomes of clinically diagnosed RHD from multiple centers across 12 different African countries, Yemen and India reported congestive cardiac failure in 20% of the patients seen at baseline (Zühlke et al., 2015). In addition, a high mortality rate was noted especially in those who had severe disease, heart failure or were older than 20 years at the time of being recruited into the study (Zühlke et al., 2015). A similar study conducted in Fiji though using a younger cohort of patients reported similar outcomes to that seen in the REMEDY study though with a higher mortality rate (Engelman et al., 2017). Severe disease and a frequent occurrence of heart failure are key predictors of death for patients with RHD as seen in both the REMEDY and the Fiji study (Engelman et al., 2017; Zühlke et al., 2015).

Disease severity at diagnosis has been consistently shown to be a major predictor of clinical outcome for patients with RHD (Liu et al., 2010; Nulu et al., 2017; Okello, Kakande, et al., 2017a; Zühlke et al., 2015). In Australia, Cannon et al., using RHD register information on 591 Indigenous residents diagnosed with RHD in the Northern

Territory between the ages of 5 and 24 years over a 14 year period observed that 30% of the patients had severe disease at baseline (Cannon et al., 2017). For these patients with severe disease, Cannon et al., reported a 5 year mortality rate of 10% compared no deaths in those who presented with mild RHD at diagnosis (Cannon et al., 2017). Despite this favorable mortality rate, 11.4% of those who presented with mild RHD still progressed to severe RHD within a 10 year period with half of them requiring valvular surgery(Cannon et al., 2017).

Even though there is no conclusive evidence for a gender predilection in the etiology of RHD, women and girls have been shown to be disproportionately affected with RHD(Watkins et al., 2017; Zühlke et al., 2015). Women living with RHD and who get pregnant are also prone to pregnancy related complications such as heart failure, premature delivery, fetal death and even maternal death(Watkins et al., 2017; Zühlke et al., 2015). However, gender on its own has not being shown to be an independent predictor of death or progression of disease in patients with RHD (Liu et al., 2010).

Socioeconomic Status and Clinical Outcomes in RHD

Clinical outcomes for chronic diseases have been shown to be worst as one goes down the socioeconomic quintiles(Cannon et al., 2017; Centers for Disease Control and Prevention, 2018; Zühlke et al., 2015). Chronic diseases such as cystic fibrosis have been demonstrated to be associated with worst outcomes especially death in patients who are poor and uneducated (Oates et al., 2016). The socioeconomic gradient in clinical outcomes for heart related disorders such as myocardial infarction was shown to be associated with the increased in the modifiable risk factors for cardiovascular disease

such as hypertension, dyslipidemia and tobacco smoking and not so much because of the low socioeconomic status of the patients (Choudhry et al., 2014). This however has not been conclusively demonstrated in RHD. While the REMEDY study showed a higher mortality rate as well as incident heart failure rates in patients from low income and low middle income countries, causality cannot be established because of the ecological theory fallacy (Zühlke et al., 2015).

Socioeconomic Status and Benzathine Penicillin Adherence in RHD

A relationship between socioeconomic status and adherence in RHD has not been conclusively determined (Goyal & Vijayvergiya, 2016; Watson et al., 2015; Zühlke et al., 2015). A person's SES is said to affect their ability to access and utilize health information and services (Cockerham et al., 2017; Eisner et al., 2011; Goyal & Vijayvergiya, 2016; Watson et al., 2015; Zühlke et al., 2015). Low health literacy as well as absence of any formal education has been shown to predispose to poor adherence to penicillin prophylaxis in patients with RHD living in low and lower middle income countries (Ralph. et al., 2016; Huck et al., 2015; Rémond et al., 2016). While no causal link has been established between RHD adherence rates and socioeconomic status of the individual patient, unemployment, a surrogate for SES was shown to be associated with poor adherence to BZP prophylaxis in Uganda (Longenecker et al., 2016). In India, a cross sectional evaluation of 500 patients with RHD on BZP prophylaxis reported a high rate of poor adherence to BZP prophylaxis (Shah et al., 2013). Low SES, being uneducated and residing in a rural area was found to be significant determinants of poor access to BZP prophylaxis (Shah et al., 2013). In their prospective study of 449 Ugandan

patients with RHD, Okello et al. reported that poor adherence to BZP prophylaxis or suboptimal adherence to benzathine penicillin injections (BZP injections less than 80% of total annual injections) was associated with a high rate of incident heart failure and mortality (Okello, Kakande, et al., 2017a). Heart failure and also mortality was directly correlated with the rate of progression from mild to severe disease (Okello, Kakande, et al., 2017a).

Adherence and Clinical Outcomes in RHD

Adherence in RHD has been variously defined depending on the study design and end point(Islam & Majumder 2016; Kevat et al., 2017; Lam & Fresco, 2015). However, adherence defined on the basis of the proportion of BZP injections received as a fraction of expected total annual injections has recently been widely used in estimating adherence rates(Okello, Kakande, et al., 2017b). An adherence rate of at least 80% is currently the most widely accepted cut off point for optimal or adequate adherence rates for BZP prophylaxis in RHD(Okello, Kakande, et al., 2017b). Longitudinal studies on adherence to BZP prophylaxis has been shown to be associated with an improved outcome for patients diagnosed with RHD especially those with mild disease(Mehta et al., 2016; Okello, Kakande, et al., 2017b). Adequate adherence successfully reduce the rate of ARF recurrences and hence the progression and severity of RHD in patients already living with RHD (Chamberlain-Salaun, Mills, Kevat, Rémond, & Maguire, 2016; Mehta et al., 2016; Okello, Kakande, et al., 2017b; Rémond et al., 2016a).

Adherence as the Mediating Pathway between SES and Clinical Outcomes in RHD

There are currently no studies that evaluated the mediatory role of benzathine penicillin adherence on the relationship between SES and clinical outcomes in patients with RHD

(Huck et al., 2015; Kevat et al., 2017; Okello, Kakande, et al., 2017b; Ralph et al., 2016). However, the role of medication adherence linked with SES on health outcomes had been studied in other chronic disease conditions such as HIV, asthma, diabetes and hypertension(Burch et al., 2016;Huck et al., 2015; Nandi et al., 2014; Oates, Britton, Gamble, & Harris, 2015; Okello, Kakande, et al., 2017b; Ralph et al., 2016; Wayda et al., 2018). In one such study, Burch et al., assessing the effect of socioeconomic status (financial hardship, non-employment, rented or unstable housing status, and non-university education) on virologic outcomes in people receiving antiretroviral treatment (ART) for HIV in the UK, reported a strong association between lower socioeconomic status with ART non-adherence and virologic non-suppression on ART(financial hardship *vs* none 2·4, 95% CI 1·6–3·4; non-employment 2·0, 1·5–2·6; unstable housing *vs* homeowner 3·0, 1·9–4·6; non-university education 1·6, 1·2–2·2) (Burch et al., 2016). When they adjusted for adherence to ART in their logistic model, there was a weakening in the association between SES and virologic outcomes further suggesting that the associations between low socioeconomic status and virologic non-suppression are probably mediated mainly through ART non-adherence (Burch et al., 2016).

While ART drugs may differ significantly from BZP in being oral medications rather than intramuscular injection, the findings by Burch et al., still underscores a need for more research on adherence to BZP prophylaxis as a potential mediator of the relationship between SES and clinical outcomes in patients with RHD(Burch et al., 2016). This is even made more plausible because of the dearth of information in the literature on adherence as a potential mechanism of socioeconomic disparities in clinical

outcomes for RHD patients (Goyal & Vijayvergiya, 2016; Oates et al., 2016). Most studies of adherence in RHD use cross-sectional research designs that limit conclusions regarding potential pathways of SES, medication adherence, and clinical outcomes(Chamberlain-Salaun et al., 2016; Ralph et al., 2016; Rémond et al., 2016a).

Summary and Conclusions

From this literature review, it can be seen that previous studies employed mainly observational research designs such as cross-sectional and cohort studies to investigate clinical outcomes in patients with RHD. In the same vein, this literature review also shows that previous research to assess the relationship between SES, adherence, and clinical outcomes in patients with RHD used both cross sectional and prospective cohort designs. Several measures of SES were used in the literature, including family income, geographic location of residence, and educational attainment. Measures of adherence to BZP prophylaxis in previous studies include patient self-report and medical provider assessments. Even though the BZP adherence rates seen in most of the studies reviewed was sub-optimal, in some countries where RHD is endemic (India, Cuba and New Zealand) the adherence rates were reported as good. However, there was varying adherence rates reported for individual patients (0-100% of prescribed injections) with some patients receiving inadequate BPG injections (adherence rates less than 80%) while others received appropriate prophylaxis (Adherence rates greater than 80%). Due to the observational nature of most of the studies reviewed, it was difficult to conclusively link adherence to BPG with patient socioeconomic status.

There are critical gaps in assessing patient self care with respect to chronic disease management as seen from the literature reviewed. Socio-cultural factor was identified as a key variable in predicting treatment adherence and health outcomes in patients with chronic diseases.

In Chapter 3, I provided a description of the research design and justification for the choice of the research design. In addition, I provided a description of the sample and details of the selection criteria of study participants, description of the REMEDY study as well as an overview of the variables in the study. The data collection process as well as analysis was also discussed. The chapter concluded with a discussion of the ethical considerations of this study.

Chapter 3: Research Method

The aim of this study was to determine the relationship between SES and clinical outcomes (incident heart failure and mortality rates) in patients with RHD. It also sought to determine the role of adherence to BZP as a mediator between the relationship of SES and clinical outcomes (Incident heart failure and mortality) in patients with RHD.

Research Design and Rationale

This research implemented a retrospective cohort design by using deidentified secondary data from a previously collected data of RHD patients in Nigeria who participated in a multicenter, multi-country prospective registry of patients with RHD, called REMEDY to address the research questions. The REMEDY study prospectively collected socio-demographic, clinical and echocardiographic data from 3343 symptomatic RHD patients presenting to the outpatient clinic, inpatient care facilities and emergency room services of the 25 participating hospitals spread across 12 African countries, India and Yemen between January 2010 and 2014. The Nigerian registry contained 256 symptomatic RHD patients. Each patient was followed up over a 2-year period (Karthikeyan et al., 2012; Zuhlke et al., 2014). Treatment adherence was evaluated at each visit and clinical outcomes were recorded if it occurred during the study follow-up period (Karthikeyan et al., 2012; Zuhlke et al., 2014). A cohort design was appropriate for this secondary data analysis because of the need to compare two groups of patients classified based on their SES (Gordis 2015). In addition, a cohort study design helped to show the temporal sequence between the exposure (SES) and the outcome (mortality, heart failure) since the subjects (RHD patients) are known to be free of the

outcome of interest at the time of recruitment into the REMEDY study when their exposure status was established (Gordis 2015). In a previous report of the clinical outcomes in RHD patients prospectively studied, Zuhlke et al., (2015) had reported a heart failure rate of about 7% and a mortality rate of 17% mostly in patients from low and low middle income countries thereby underscoring the need for this retrospective cohort study aimed at evaluating the relationship between individual level SES and clinical outcomes in patients with RHD. (Zuhlke et al., 2015). I hypothesized that SES may affect heart failure (HF) and mortality rates in patients with RHD. In addition, I also hypothesized that the relationship between SES and clinical outcomes in these patients will be influenced by their respective adherence to BZP prophylaxis (de Dassel et al., 2018; Watkins et al., 2017). The availability of this secondary data already collected with information on BZP adherence, HF rates and mortality rates provide an important opportunity for testing these hypotheses (de Dassel et al., 2018; Gordis 2015). Secondly, exploring how adherence mediates the association between SES and clinical outcomes is needed to advance knowledge of mechanisms which may play a role in the SES-health gradient even though the strength of the association between drug adherence and SES in chronic diseases management is unclear (Choudhry et al., 2014;Dhar et al., 2017). RHD being a chronic disease will thus benefit from an understanding of this mechanism on the rates of adherence especially as it affects BZP adherence, an important but cost-effective useful tool for management.

Data Sources

Data for this secondary data analysis was obtained from the Nigerian site of the global rheumatic heart disease registry (REMEDY) study. The REMEDY study enrolled 256 symptomatic RHD patients into the Nigerian registry at the point of contact with the cardiologist in each participating hospital after obtaining written informed consent by a trained research nurse. Socio-demographic data such as age, sex, educational attainment, occupation, income and racial /ethnic affiliations were collected using a standardized questionnaire after obtaining informed written consent (Karthikeyan et al., 2012; Zuhlke et al., 2014). Clinical parameters were collected by the research clinician either from the patient records or through oral interview as the case may be (Karthikeyan et al., 2012; Zuhlke et al., 2014). Patient demographic data, clinical findings, and details of electrocardiographic (ECG) and echocardiographic findings were recorded on structured case record forms (Karthikeyan et al., 2012; Zuhlke et al., 2014). Details of medications prescribed, with particular reference to penicillin prophylaxis, antithrombotic and antiplatelet drugs, and antiarrhythmic medications, at study entry, 1-year follow-up, and at the end of 2 years were also collected (Karthikeyan et al., 2012; Zuhlke et al., 2014). Adherence to penicillin prophylaxis was assessed by obtaining injection records and/or direct questioning (Karthikeyan et al., 2012; Zuhlke et al., 2014). Adherence to penicillin prophylaxis was calculated based on percentage of prescriptions received over the 12 months preceding enrolment or follow up visits as the case may be (Karthikeyan et al., 2012; Zuhlke et al., 2014). Echocardiography data was obtained in the echo laboratory or if recently done, from the case records of the patient (Karthikeyan et al., 2012; Zuhlke et

al., 2014). For improved diagnostic accuracy, standard operating procedures adapted from the WHO guidelines for the diagnosis of RHD was used for uniformity in classifying the patient as having RHD or not (Karthikeyan et al., 2012; Zuhlke et al., 2014). Both the color and spectral Doppler signals must be holodiastolic for aortic regurgitation or holosystolic for mitral regurgitation in order for a diagnosis of RHD to be entertained (Karthikeyan et al., 2012; Zuhlke et al., 2014). The Doppler signal must be of high velocity, either from a pulsed or continuous wave (Karthikeyan et al., 2012; Zuhlke et al., 2014). These criteria can readily distinguish a small color jet of physiological regurgitation in a normal person from pathological regurgitation in patients with RHD (Karthikeyan et al., 2012; Zuhlke et al., 2014). Assessment of severity of valve lesions, left ventricular (LV) systolic dysfunction (i.e. left ventricular ejection fraction, LVEF, less than 54% or fractional shortening less than 28% in children and adults), and LV dilatation (i.e. LV end diastolic dimension greater than 50 mm in children and 55 mm in adults was done using the AHA guidelines). Patients in this study were identified through registry data for inclusion (Karthikeyan et al., 2012; Zuhlke et al., 2014).

Follow-up—All patients recruited were made to undergo 2 follow-up visits, one at 12 months and one at 24 months (Karthikeyan et al., 2012; Zuhlke et al., 2014). Echocardiogram was performed at both follow-up visits (Karthikeyan et al., 2012; Zuhlke et al., 2014). In addition, assessment for outcomes (heart failure, ARF recurrence, death, use of secondary benzathine penicillin prophylaxis, oral anticoagulation and surgical intervention) was also done at each follow-up visit and at any other visits that the patient makes to the hospital as part of usual care (Karthikeyan et al., 2012; Zuhlke et al., 2014).

Outcomes were based on standard definitions (Karthikeyan et al., 2012; Zuhlke et al., 2014). All deaths were recorded in a case record form and the cause ascertained by review of the relevant source documents such as autopsy reports, physician records or in the case of death at home an interview of a close relative or care giver who witnessed the events preceding death by the managing physician (Karthikeyan et al., 2012; Zuhlke et al., 2014). Morbidity such as new congestive cardiac failure was ascertained by review of hospitalizations records of the patient as well as interview by the managing physician (Karthikeyan et al., 2012; Zuhlke et al., 2014). Any additional information needed was obtained by contacting one of the patient's physicians or next of kin (Karthikeyan et al., 2012; Zuhlke et al., 2014). For maintaining internal validity, an independent monitoring board was constituted who at random select a sample of 10% of the locally adjudicated events for audit in order to ascertain compliance with protocol and thus maintain consistency with the study definitions (Karthikeyan et al., 2012; Zuhlke et al., 2014). The data on these patients was coded so that no information can be linked to specific individuals (Karthikeyan et al., 2012; Zuhlke et al., 2014). Patients were identified throughout the study duration by the study number allotted to them at the time of enrollment (Karthikeyan et al., 2012; Zuhlke et al., 2014). Confidentiality was maintained by restricting access to de-identifiers to only the site PIs and in some cases by study clinicians where there is need for medical intervention (Karthikeyan et al., 2012; Zuhlke et al., 2014). The study data were archived by the principal investigator in the department of Medicine, University of Cape Town. To access the data for this study, a permission letter to access the data was submitted to the steering committee of the global

rheumatic heart disease registry through the principal investigator. The steering committee permitted my use of the data after reviewing my application and research proposal.

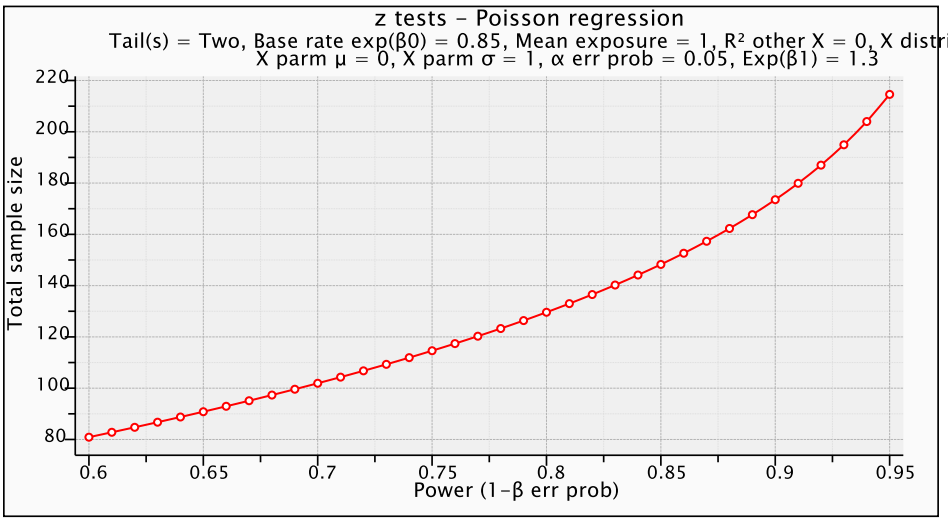
Study Setting and Population

This study utilized a retrospective cohort design on data collected in Nigeria from 2010 to 2014 as part of the global rheumatic heart disease (REMEDY) study, a multicenter, multi-country prospective study that collected data from symptomatic RHD patients across 12 African countries, India and Yemen (Karthikeyan et al., 2012; Zuhlke et al., 2014). The Nigerian site consisted of 5 participating centers spread across the north (Aminu Kano Teaching Hospital, Kano), central (Jos University teaching Hospital, Jos and University of Abuja Teaching Hospital, Gwagwalada) and southern parts of the country (University College Hospital, Ibadan and Federal Medical Center, Abeokuta). Symptomatic RHD patients were recruited from outpatient clinics, emergency rooms and inpatient care wards at baseline and subsequently followed up over two years at the participating sites (Karthikeyan et al., 2012; Zuhlke et al., 2014). This study formed two cohorts based on the socioeconomic groupings as classified using Oyedeji socioeconomic classification system (Oyedeji 1985). The socioeconomic variables used were those variables collected on the patients at the time they were recruited into the REMEDY study (Zuhlke et al., 2014). One cohort (Cohort 1) contained patients with low SES while the second (Cohort 2) contained patients with middle to higher SES. SES classification was done based on the educational attainment and occupation of the patients themselves or their caregivers in case of children as proposed by Oyedeji (Oyedeji 1985).

The baseline characteristics included age at entry, sex, educational attainment for adults or parental educational attainment for children, weight, height, disease severity at enrolment, heart failure status, New York Heart Association (NYHA) class and benzathine penicillin prophylaxis status at enrolment. The outcome for heart failure was identified based on the report of events such as hospitalization or treatment for heart failure as reported by the managing physician and documented in the case record form (CRF) (Karthikeyan et al., 2012; Zuhlke et al., 2014). The mortality was based on physician CRF report, autopsy report or family report as detailed in the study events forms (Karthikeyan et al., 2012; Zuhlke et al., 2014). The follow-up time for each patient was counted from day of entering the study to onset of the study outcome or end of the study (Karthikeyan et al., 2012; Zuhlke et al., 2014).

Power Calculations

Power analysis was conducted using G*Power (version 3.0.10) based on a Poisson regression model in order to determine the needed sample size (Cumming 2012; Kline 2013). In this calculation, using a significance level of 0.05, effect size of 0.3 (Kline 2013), z statistics of 1.959964 and a power of 0.80, the total minimum study population needed to answer research question 1 is 130 (65 in each cohort). However, all patients contained within the Nigerian database of the REMEDY study were recruited into the study (Kline 2013). The calculation output is depicted in figure below.



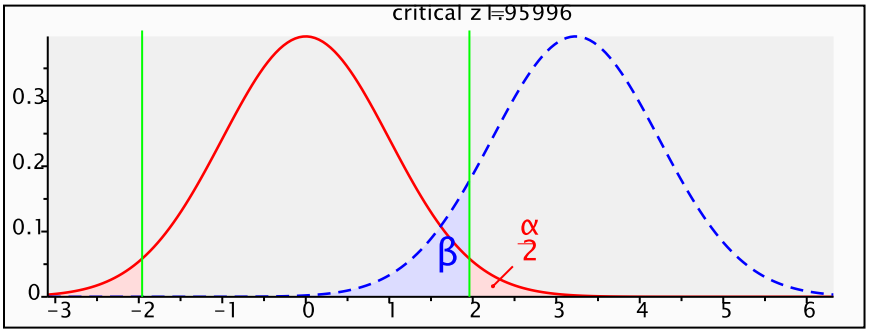


Figure 1. Showing cases needed for research questions α is the rejection zone while β is the type 2 error rate.

Data Collection Procedure

This study utilized the data collected from the REMEDY study (Karthikeyan et al., 2012; Zuhlke et al., 2014). The REMEDY study had collected clinical, socio-demographic, and echocardiographic data from all the patients enrolled into the registry using an eleven-page questionnaire that is divided into sections for ease of administration at baseline, 12 months and 24 months (Karthikeyan et al., 2012; Zuhlke et al., 2014). Each section began with standard operating procedures, codes and definition of variables to be collected in that section (Karthikeyan et al., 2012; Zuhlke et al., 2014). The first page contained questions on sociodemographic variables such as age, gender, education, ethnicity, income and occupation (Karthikeyan et al., 2012; Zuhlke et al., 2014). The next eight pages contain questions about the clinical history of the patient including echocardiography information as well as other investigations done (Karthikeyan et al., 2012; Zuhlke et al., 2014). The last 2 pages contain drug history of the patient and information on number and adherence to BZP injection (Karthikeyan et al., 2012; Zuhlke et al., 2014). A sample of the questionnaire is attached as Appendix A. Each patient was recruited at baseline by a research nurse after obtaining written informed consent (Appendix B). These patients were subsequently followed up annually for 2 years (Karthikeyan et al., 2012; Zuhlke et al., 2014). At each visit, the patients were assessed for the occurrence of adverse outcomes (such as death, congestive heart failure (CHF), stroke or transient ischemic attack (TIA), recurrence of acute rheumatic fever (ARF), and infective endocarditis (IE)), use of secondary antibiotic prophylaxis and oral anticoagulation medication, and need for valve intervention or surgery (Karthikeyan et

al., 2012; Zuhlke et al., 2014). The study had a standard protocol for the diagnosis of all outcomes including congestive cardiac failure and death (Karthikeyan et al., 2012; Zuhlke et al., 2014).

Definition of Variables

Independent Variable

Socioeconomic status (SES). In epidemiological research, various indicators of SES have been used. Depending on the context, the population studied and the outcome measured, any of income, wealth, education and occupation may be used in isolation or in any combination in assessing SES (Oakes & Rossi, 2003). Socioeconomic status (SES), a fundamental construct in the social and health sciences, is a measure of access to resources, such as financial resources and material goods, power, social networks, health care, and educational opportunities (Oakes & Rossi, 2003). SES indicates one's position in the social hierarchy, and often determines one's life chances. It is thus a summary of one's access to wealth and opportunities and hence defines one's social hierarchy (Oakes & Rossi 2003). In the current study, SES was used as a measure of social class position (Galobardes et al. 2006; Oakes & Rossi 2003). Using the Oyedeji SES classification, SES was derived from a combination of educational attainment and occupation class (Oyedeji 1985). In case of a child, the mean of four scores (two for the father and two for the mother) to the nearest whole number is the social class assigned to the child. I-II: UPPER CLASS, III-V: LOWER CLASS

Table 1

Showing Oyedeji social classification scheme

Social class	Profession	Educational attainment
I	Professional, Senior public servants, owners of large business concerns, Senior military officers, large scale contractors.	University graduates or equivalents.
II	Non-academic professionals e.g. Nurses, Secondary school teachers, secretaries, Owners of medium sized business. Intermediate grade public servants.	School certificate holders and equivalents
III	Non manual skilled works including clerks, typists, telephone operators, Junior school teachers, Drivers	Grade II teachers or equivalent
IV	Petty traders, Laborers, Messengers	Primary School certificate
V	Unemployed, Full time housewives, students, subsistence farmers	No formal education

Dependent Variables

The dependent variables were clinical outcomes defined as the presence of any death (mortality) or Heart failure events.

Mortality refers to deaths in the study population. The REMEDY study had used events forms to encode deaths either in the hospital or at home (Karthikeyan et al., 2012; Zuhlke et al., 2014). In case of any death during the study period, the physician fills a death report form using autopsy report for those patients who consented to autopsy, death certificate reports or verbal communication of events from the family in the case of patients who died at home (Karthikeyan et al., 2012; Zuhlke et al., 2014). The study counted all-cause mortality and specific type of mortality e.g. deaths from heart failure, rheumatic fever, infective endocarditis etc. This variable was adopted and used in the secondary data analysis.

Heart failure events. All patients recruited into the REMEDY study had a heart failure events form filled by each study clinician (Karthikeyan et al., 2012; Zuhlke et al., 2014). New onset or repeat heart failure occurring in each patient during the 2 year follow up period was reported and encoded into the heart failure events form (Karthikeyan et al., 2012; Zuhlke et al., 2014). Heart failure was diagnosed if any 2 of the following 3 criteria were present: (1) symptoms (dyspnea on exertion or at rest, orthopnea, nocturnal paroxysmal dyspnea, or ankle edema) or signs (rales, increased jugular venous pressure, or ankle edema) of CHF; (2) radiological signs of pulmonary congestion; and (3) treatment with diuretics (Karthikeyan et al., 2012; Zuhlke et al., 2014). This variable was

adopted and used in the secondary data analysis (Karthikeyan et al., 2012; Zuhlke et al., 2014).

Adherence has been consistently defined as "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes, Taylor & Sackett 1979, p.1-2). It is thus seen as the behavior of the patients or care givers who bear responsibility for ensuring the patients visit the nurse for the 4 weekly BZP injection. This is supported by previous study done on adherence rates to therapy in chronic disease management (Orrell-Valente & Cabana 2008). In the REMEDY study, adherence rate was conceptualized as the number of times an individual with RHD received prescribed 4 weekly benzathine penicillin (BZP) in the one-year period of study (Karthikeyan et al., 2012; Zuhlke et al., 2014). It was represented as a ratio (%) between the actual monthly injections and expected number of monthly injections in a year (Karthikeyan et al., 2012; Zuhlke et al., 2014). For the purpose of this study, the same adherence rate was adopted (Zuhlke et al., 2015). Thus, the patient actual number of BZP received during the period of observation was divided by the total expected number of BZP injections and expressed as a percentage ratio (Zuhlke et al., 2015).

$$\text{Adherence rate (\%)} = \frac{\text{Number of actual BZP injections received in a year}}{\text{Number of expected BZP injections in a year}}$$

The adherence rate was then coded into one of the following clinically significant ordinal categories: low (<35%), medium (36-79%), and high (≥80%) (Karthikeyan et al., 2012; Zuhlke et al., 2015). A patient with rheumatic heart disease is expected to receive at least 80% of the annual prescribed injections (Cannon et al., 2017; Carapetis et al., 2012).

When an individual patient receives less than 80% of the injections, they are at a higher risk of recurrent ARF and its complications (Cannon et al., 2017; Carapetis et al., 2012). For the purpose of this study, benzathine penicillin prophylaxis adherence was classified as good (≥80%) and poor (< 80%) adherence rate.

Covariates. Control variables (covariates) for this study included age, sex, disease severity at enrolment, heart failure status at enrolment, NYHA class at enrolment and number of months since diagnosis with RHD (Karthikeyan et al., 2012; Zuhlke et al., 2014). According to Creswell (2009), control variables are a "special type of independent variable…because they potentially influence the dependent variable" (p. 51). Age at last birthday will be used during data preparation for analysis. Gender and socioeconomic status will be measured as categorical variables on a nominal scale.

Analyses

The IBM Statistical Package for the Social Sciences (SPSS) Statistics 23 (SPSS 23) was used in the analysis of the data. The IBM SPSS 23 is a systematic tool that helps with data evaluation with precise results that allows one to assess all outcomes of interest (IBM, 2015). This statistical software is a suitable choice for my data analysis because of the availability of descriptive and inferential analysis features suitable for the dataset that I used in this study.

Handling Missing Data

Being a secondary data analysis, missing data can be a challenging problem resulting from incomplete data entry giving rise to some data fields having missing values (CDC 2010). The dataset was thus evaluated for missing values. Less than 10% of

the variables had missing data; thereby providing no need for further adjustments or modifications (CDC, 2010).

Descriptive Statistics

Socio-demographic characteristics (age, sex, weight, height, educational attainment, occupation, and income, clinical characteristics (RHD severity, HF etc) and echocardiographic parameters (EF, LVEDD) comparisons between the two cohorts were done using descriptive statistics. The difference between the two cohorts was described using Student t test for continuous variables such as age, EF and LEVDD and chi square for categorical variables such as sex, educational attainment and occupation.

Analyses method to address each question

Research question (RQ)1:

Does the number of heart failure events differ between RHD patients of low SES and RHD patients of higher SES?

Null hypothesis *($H_0$1):* There is no difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES.

Alternate hypothesis (H_a1): There is a difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES.

For this study, HF was measured as the number of heart failure events occurring among patients with RHD over the two year follow up period (Gordis 2015; Hagenaars 2018). This is a continuous variable measured as a count or frequency of occurrence of repeat HF events in each patient (Gordis 2015; Hagenaars 2018). Poisson regression analysis was used to compare the differences between the two cohorts. Poisson regression methods was used in assessing the difference in HF events between the two SES

groupings. Poison regression analysis was chosen because it is a generalized linear model that models count data. The Poisson regression is chosen because of the assumption that HF events changes linearly with equal increment, the changes in the, HF events from combined effects of different confounders (such as age, gender etc) are multiplicative, that at the each level of the covariates the number of cases has variance equal to the mean and that the observations are independent. The plots of residuals versus the mean at different levels of the predictor variable was used to determine violations of assumption or to ascertain whether variances are too large or too small. It is the appropriate statistics here because the dependent variable (heart failure) is a count of events occurring over a time period.

Research question (RQ)2:

Does the mortality rate differ between RHD patients of low SES and RHD patients of higher SES?

Null hypothesis *($H_0$2)*: There is no difference in mortality rates between RHD patients of low SES and RHD patients of higher SES.

Alternate hypothesis (H_a2): There is a difference in mortality rates between RHD patients of low SES and RHD patients of higher SES.

Mortality refers to the occurrence of death in a defined population during a specified time period (Gordis 2015; Hagenaars 2018). For this study, mortality was measured as the number of deaths occurring among patients with RHD over the two year follows up period (Gordis 2015; Hagenaars 2018). This is a categorical variable measured on the nominal scale (Gordis 2015; Hagenaars 2018). Mortality was measured as present (death)

or absent (alive) in the patients with RHD over the two year follows up period. Logistic regression analysis was used to compare the mortality rate between the two cohorts.

Research Question (RQ) 3:

Is there a significant difference in the number of heart failure events between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

Null hypothesis ($H_0$3): There is no significant difference in the number of heart failure events between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Alternate (H_A3): There is a significant difference in the number of heart failure events between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

In answering Research Question 3, Poisson regression model with mediation analysis was used by considering three variables, SES (independent), BZP adherence (independent), and heart failure (dependent). I analyzed whether adding BZP adherence to the Poisson regression model mediates the relationship between SES and heart failure. Poison regression analysis was chosen because it is a generalized linear model that models count data like rates. In addition, it was chosen because of the assumption that heart failure changes linearly with equal increment, the changes in the number of heart failure events from combined effects of different confounders (such as age, gender etc) are multiplicative, that at the each level of the covariates the number of cases has variance equal to the mean and that the observations are independent. The plots of

residuals versus the mean at different levels of the predictor variable was used to determine violations of assumption or to ascertain whether variances are too large or too small. Using Poisson regression gave me the opportunity to analyze interrelationships among multiple risk factors or exposure variables and a single outcome (Sullivan, 2012). It is the appropriate statistics here because the dependent variable (heart failure) is a count of events occurring over a time period.

Research question (RQ) 4:

Is there a significant difference in the risk of dying (mortality) between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

Null ($H_0$3): There is no significant difference in risk of mortality between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

Alternate (H_A3): There is a significant difference in risk of mortality between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

In answering research question 4, multivariable logistic regression with mediation analysis was used by considering three variables, SES (independent), BZP adherence (independent), and mortality (dependent). I analyzed whether adding BZP adherence to the multivariable logistic regression model mediate the relationship between SES and mortality. Stepwise (forward regression) method was used in conducting the regression analysis. In addition, statistical significance of the indirect effects of mediation was tested

using bootstrapping method (Preacher, & Hayes, 2008). Using Multivariable statistics gives me the opportunity to analyze interrelationships among multiple risk factors or exposure variables and a single outcome as stated in the analysis for RQ2 (Sullivan, 2012).

Threats to Validity

The data collected from the REMEDY study on patient drug treatment adherence is based on the patient's self-report. Self-reported measures of adherence are a potential threat to internal validity because of the tendency to overestimate adherence rates (Dunbar-Jacob, Schlenk, & McCall, 2012). Patients (and their care givers in the case of minors) in a bid to recall past events may inaccurately recall information about missed medication doses (Gordis 2015; Dunbar-Jacob et al., 2012) Socially desirable response when questioned by their primary care provider especially that which helps to cast them in a good light before their primary care provider is also likely to occur (Gordis 2015; Dunbar-Jacob et al., 2012) Recall bias, social desirability bias, and errors in self-observation may contribute to an overestimation of adherence (Gordis 2015; Dunbar-Jacob et al., 2012). In addressing these biases, the REMEDY study protocol used standard operating procedures with uniform definitions for terms and variables used. In addition, patient records and in some cases phone conversation with managing primary care physician were used in order to improve the quality of information.

The REMDY study used symptomatic RHD patients who presented in the hospital for treatment. The exclusion of asymptomatic patients might have introduced some form of self selection. These patients may thus not be representative of the target

population of all patients with RHD considering the fact that access to care and disease severity might have played a role in their presentation. However, by ensuring that patient recruitment follows the approve research protocol at each site through the use of standard operating procedures and definition of terms for all variables and outcomes variables, the usability of the findings in the target population of patients with RHD globally was enhanced and thus the external validity

The REMEDY study collected data from patients after obtaining IRB approval and protects all information as required in accordance with the HIPPA act. In addition, written informed consent was obtained from all participants before and during the entire period of study. No patient was denied care nor was care linked to participation in the study. Walden University IRB was however sought and obtained for the current study. There is no need for a fresh written informed consent from the patients as REMEDY had originally informed the patients about the possibility of using their data for future publications. The data was anonymized, password protected and electronically transmitted from the REMEDY data manger after due permission was obtained from the principal investigator. Access to all data was restricted. After the successful defense of this dissertation study, the data will be stored in this manner for 5 years and then destroyed subsequently.

Ethical Considerations

Deidentified data contained within the Nigerian register of the REMEDY study registry for RHD was used. Patient data and information was protected as required by federal law section 308 (d) of the Public Health Service Act and the Privacy act of 1974.

Walden Institutional Review Board approval (IRB approval number 12-04-19-0550282) was obtained before embarking on this study.

Summary

In summary, this was a secondary data analysis of a prospectively collected data utilizing data from the REMEDY study, a multicenter, international registry of patients with RHD seen in 25 facilities spread across 12 African countries, India and Yemen. The study was a retrospective cohort study utilizing secondary data analysis of datasets of patients with RHD collected in a longitudinal, prospective study in Nigeria. The study examined the association between SES and clinical outcomes in patients with RHD seen in inpatient, emergency room and outpatient departments of these developing countries. In addition, the effect of adherence to benzathine penicillin, a treatment option shown to impact outcome in RHD management on the relationship between SES and clinical outcomes was assessed.

The IBM SPSS version 23 was used for all analysis. Student t test and chi square was used in comparing the baseline characteristics of the cohort being evaluated. Poisson regression analysis was used to examine the relationship between SES and heart failure (RQ1) and also the mediator role of adherence to BZP prophylaxis in the relationship between SES and heart failure (RQ3). Multivariable regression was used to assess the relationship between SES and mortality rates (RQ2)., and the mediator role of adherence to BZP prophylaxis in the relationship between SES and mortality (RQ4).

Chapter 4: Results

Introduction

The purpose of this secondary data analysis was to assess the relationship between individual level SES and clinical outcomes (heart failure events and mortality) in patients with RHD as well as examine how adherence to benzathine penicillin prophylaxis mediates the effect of socioeconomic status on clinical outcomes (heart failure events and mortality rate) for these patients with RHD. Data from 198 symptomatic RHD patients in Nigeria were used to address the following research questions and hypotheses:

RQ1. Does the number of heart failure events differ between RHD patients of low SES and RHD patients of higher SES?

$H_0$1: There is no difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES

H_A1: There is a difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES

RQ2: Does the risk of mortality differ between RHD patients of low SES and RHD patients of higher SES?

$H_0$2: There is no difference in risk of mortality between RHD patients of low SES and RHD patients of higher SES

H_A2: There is a difference in risk of mortality between RHD patients of low SES and RHD patients of higher SES

RQ3: Is there a significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

$H_0$3: There is no significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

H_A3: There is a significant difference in number of heart failure events between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

RQ4: Is there a significant difference in risk of mortality between RHD patients of low SES and RHD patients of Higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence?

$H_0$4: There is no significant difference in risk of mortality between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

H_A4: There is a significant difference in risk of mortality between RHD patients of low SES and RHD patients of Higher SES after adjusting for the effect of benzathine penicillin prophylaxis adherence rates.

In this chapter, I discuss the results of this study in relation to the research questions, hypothesis, sample characteristics, and descriptive analysis used in this study.

Data Collection

Secondary data analysis was conducted using de-identified data from the Nigerian site of the REMEDY study; a registry based longitudinal study of symptomatic RHD patients that collected clinical, sociodemographic, and echocardiographic data from all the patients enrolled into the registry using an eleven page questionnaire that is divided

into sections for ease of administration at baseline, 12 months and 24 months. These patients were categorized into two cohorts based on their SES classification for Nigerian and developing settings as proposed by Oyedeji. The study received IRB approval from Walden University.

Descriptive statistics

Demographic characteristics

There were 198 RHD patients in the Nigerian register of the REMEDY study. A total of 15 (7.6%) of the participants were missing key variables for analysis and so were excluded.

The mean age of the participants was 24.2 years with a standard deviation of 13.9 years. The median age was 21.1 years; 95% confidence interval (CI) = 8.9 – 53.0 years. A total of 110 (60.1%) of the participants were from the low SES group while 73 (39.9%) were from the higher SES group (χ^2 =3.95, p=0.08). participants

Table 2 presents data on the demographic and clinical characteristics of the 183 subjects with RHD that were studied. The two SES groups were similar in sex composition (χ^2 =1.50, p = 0.62), and age group distribution (χ^2 =2.55, p = 0.13). The clinical parameters were also similar for the two groups at baseline. The groups were similar in past history of heart failure (χ^2 =3.65, p = 0.06), disease severity at baseline (χ^2 =0.07, p=0.86) and BZP prophylaxis adherence at baseline (χ^2 =0.98, p = 0.36).

Table 2

Demographic and Clinical Characteristics of 183 Subjects with RHD by SES grouping

Variable	Low SES N=110	Higher SES N=73	Total N=183	
Socio-demographic	n (%)	n (%)	n (%)	p
Sex				
Female	85(76.6)	46(61.2)	131(71.6)	0.08
Male	25(23.4)	27(28.8)	52(28.4)	
Age category				
Adult	77(66.4)	40(59.7)	117(63.9)	0.62
Child	39(33.6)	27(40.3)	66(36.1)	
Clinical Parameters				
Past History of Heart failure				
Yes	75(67.0)	38(53.5)	113(61.7)	0.06
No	37(23.0)	33(46.5)	70(38.3)	
Disease Severity				
Mild	85(75.9)	56(78.9)	141(77.0)	0.72
Severe	27(24.1)	15(21.1)	42(23.0)	
BZP Prophylaxis				
Yes	40(36.4)	33(45.2)	73(39.9)	0.36
No	70(63.6)	40(54.8)	110(60.1)	

Note. *SES*= Socioeconomic status

Table 3 presents data on the anthropometric and echocardiography parameters of the 183 subjects with RHD that were studied. The two groups were similar in mean weight, height and BMI distribution (p=0.72, 0.71 and 0.94 respectively). Echocardiography parameters were also comparable between the two groups. Left ventricular end diastolic dimensions (LVEDD) was similar (t=0.95, p=0.35), ejection fraction (EF) was similar for both groups (t=0.63, p=0.53), fractional shortening (FS) was similar as well (t=0.25, p=0.84).

Table 3
Comparison of Anthropometric and Echocardiographic Parameters at Baseline by SES grouping

Anthropometric Parameters	Low SES		Higher SES		P value
	Mean	SD	Mean	SD	
Weight (Kg)	48.3	17.3	49.3	16.6	0.72
Height (m)	1.52	0.16	1.55	0.16	0.71
BMI(Kg/m^2)	20.0	4.49	20.0	4.71	0.94
Person years	1.83	0.76	2.01	0.71	0.11
Echocardiography Parameters					
LVEDD	55.7	11.5	53.8	13.2	0.35
EF (%)	55.5	15.5	57.0	15.4	0.53
FS (%)	30.4	9.8	30.8	8.9	0.84

Note. EF= Ejection fraction, *FS*= fractional shortening, *LVEDD*= left ventricular end diastolic dimensions

Table 4.
Comparison of Number of Persons Ever Had Heart Failure by SES grouping

Variable	N	Mean	SD	t	p value
Lower SES	110	10.O	3.1	2.20	0.03
Higher SES	73	3.0	3.0		

Table 4 presents data on number of patients with heart failure in the study. Ten RHD patients from lower SES group ever had heart failure compared with 3 from higher SES group (Mean=3.1, p=0.03).

Table 5
Comparison of Mean Heart Failure Events by SES grouping

Variable	N	Mean	Min	Max	p value
Lower SES	110	26	18	44	0.05
Higher SES	73	14	6	22	

Table 5 presents data on number of heart failure events in the study. There were 26 heart failure events recorded in patients from lower SES group compared with 14 events recorded from patients from higher SES group (Mean=3.1, p=0.03).

Research Question 1: The Relationship between SES and heart failure events

What is the relationship between socioeconomic status and heart failure events in patients with rheumatic heart disease? The null hypothesis was that there is no difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES. The alternate hypothesis is there is a difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES. Heart failure events refers to the number of times each patient developed heart failure in the course of the 2 years follow up. Based on descriptive statistics on Research Question 1 variables, potential confounders assessed by bivariate statistics are age, person year of follow up

and disease severity at baseline. Poisson regression to compare heart failure events before and after adjusting for these potential confounders was conducted.

Poisson regression. The crude heart failure events (HF) were first calculated for the groups before conducting the Poisson regression. Lower SES group RHD patients had cumulatively 26 (23.6%) heart failure events compared with their higher SES counterparts who had 14 (19.2%) heart failure events (p-0.04, $\aleph^2$ =4.972). Poisson regression analysis of heart failure events (dependent variable) on SES groupings (independent variable) was performed to compare the difference in heart failure events between RHD patients in the lower SES group and RHD patients in the higher SES group. I used the grouped data analysis approach and also log-transformed the person-year variable where it is used as an off-set variable in fitting the Poisson regression model. The Poisson regression model is defined in terms of log of expected counts HF as: $Log_e (Y)= \beta_0 + \beta_1 X_1$, where the X represents the explanatory variable (SES). The distribution of the count variable (heart failure events) was checked to see if it followed Poisson distribution using one sample KS statistics (p=1.00) and descriptive statistics (mean count=0.07 variance=0.066). From this, I assumed that heart failure event was approximately Poisson distributed since the model had a very strong assumption; that is, the mean of the research data was approximately equal to the variance of the data.

The Poisson model, used in this analysis, fit reasonably well the research data because the goodness-of-fit chi-square test was not statistically significant, p = 1.0 (Table 6). If the test had been statistically significant, it would have indicated that the data did not fit the model well.

Table 6
Model Goodness of Fit

	Value	df	Sig.
Likelihood ratio	92.980	166	1.000
Pearson Chi-Square	828.259	166	1.000

Model parameter estimates include the regression coefficients for each of the predictor variables along with *p*-values and 95% confidence intervals for the coefficients. The number of heart failure events among RHD patients was then predicted by the exponentiated coefficient, exp (B), or the regression incidence rate ratio. The exp (B) for RHD patients in the low SES group was 4.379 while that of the comparison group (higher SES) was 1.00. Based on these results, the RHD patients from low SES group would be 4.8 times more likely to experience heart failure events compared with their counterparts from a higher SES group (Table 7). This was significant (p=0.04).

Table 7
Poisson Regression Analysis of Heart Failure Events on SES Group

			Hypothesis Test			95% CI for OR	
Parameter	B	SE	Wald	p	OR	Lower	Upper
(Intercept)	-5.769	.7071	66.560	0.00	.003	.001	.012
Lower SES	1.563	.7638	4.186	0.04	4.771	1.068	21.318

Dependent Variable: Heart failure rate, Model: (Intercept), SES, offset = person year

Considering the above findings, I will thus reject the Null Hypothesis 1 since heart failure was found to be significantly associated with lower SES compared with higher SES grouping.

Research Question 2: The Relationship Between SES and Mortality Rate

Bivariate Analyses

Before constructing the model for multivariable logistic analyses, I conducted bivariate statistics (chi square) using cross tabulations to examine the potential confounders across the independent variable and dependent variables. Disease severity at baseline and BZP adherence rates were significantly associated with mortality.

Logistic Regression Analyses

I used binomial logistic regression to analyze the relationship between SES grouping and mortality. All the variables included in the model are categorical. Mortality was coded as 0 if it did not occur and 1 if it occurred. For this logistic regression, death (mortality occurring) was the dependent variable. SES was grouped to low SES group and higher SES group. For this logistic regression, lower SES was the reference group. Eight participants were dropped from the initial analysis due to missing data resulting in a sample of 190 participants. From my initial analysis, of all the potential confounders, only diseases severity and BZP adherence were significantly associated with the dependent and independent variables. In the final model, only 15 participants were dropped because of missing variables leaving 183 participants in the analyses. The parameter estimates from the logistic regression model showed that the odds of dying (mortality) is approximately 42% lower for RHD patients in the lower SES group

compared to RHD patients in the higher SES group (OR=0.58; 95% CI 0.26- 1.29). The result is not statistically significant because the 95% confidence interval does include 1 and $p = 0.18$. I will thus not reject the Null hypothesis. Therefore, there is no statistically significant association between SES and mortality in RHD patients aged 5 to 60 years seen in Nigeria (Table 8).

Table 8

Logistic Regression Model Coefficients of SES with Mortality

Variable	OR	95% CI		P
		LL	UL	
Intercept	0.48			0.19
Lower SES	0.58	0.26	1.29	0.18

Research Question 3: The Relationship Between SES and Number of Heart Failure Events When Considering the Possible Effect of Adherence to Benzathine Penicillin (BZP) Prophylaxis

In mediation analysis, the three main effects of interest are the (a) total effect, (b) direct effect, and (c) indirect or mediation effect of exposure on outcome (Mascha, Dalton, Kurz, & Saager, 2013). SES grouping is the exposure, and number of heart failure event is the outcome. I examined adherence to BZP prophylaxis as a mediator of SES and number of heart failure events. The total effect of SES on heart failure events does not adjust for adherence to BZP prophylaxis. According to Mascha,Dalton, Kurz, and Saager (2013), the total effect of an exposure on an outcome includes adjustment for confounding variables but ignores the specified mediator. Using Poisson regression as in RQ1, the total effect of SES on heart failure events after adjusting for age and disease

severity as confounders was first calculated. SES group 1(low SES group) was found to be 4.8 times more likely to develop heart failure events compared with SES group 2 (higher SES group) with person years of follow up as the offset variable (OR = 4.77, 95% *CI* [1.07, 21.32]). Next, the effect of BZP adherence on heart failure events was calculated. Poor BZP adherence was 58% more likely to develop a heart failure event compared with those with good BZP adherence (OR = 0.42, 95% *CI* [0.12, 1.45]). Subsequently, the effect of SES on heart failure events with BZP adherence in the model with age and disease severity as confounders (covariates) and person years of follow up as offset variable was calculated. Table 9 displays the final model coefficients after including the mediator variable (adherence to BZP prophylaxis). Lower SES was associated with a 4.6 times likelihood of developing heart failure event compared with those in higher SES (OR = 4.57, 95% *CI* [1.02, 20.43]. The effect of the mediator variable, BZP prophylaxis is also shown. Patients with good BZP adherence were 55% less likely to develop heart failure event compared with those with poor BZP adherence (OR=0.45, 95% CI [0.12, 1.58, p=0.21).

Table 9

Poisson Regression Model Coefficients of SES on Heart Failure with Adherence as a Mediator

			Hypothesis Test			95% CI for OR	
Parameter	B	SE	Wald	p	OR	Lower	Upper
(Intercept)	-5.495	.7261	57.278	0.00	0.004	.001	.017
Lower SES	1.519	.6598	3.949	0.04	4.567	1.021	20.43
Good Adherence	-.809	.6518	1.540	0.22	0.445	0.12	1.598

Dependent Variable: Heart failure events, Model: (Intercept), SES, offset = person year

SE=Standard error, CI=confidence interval, OR=Odds ratio, LL=lower limit, *UL*=upper limit

In order to prove mediation, the mediator variable must affect the outcome variable independent of the exposure variable (Mascha et al., 2013). Adherence to BZP prophylaxis was not significantly associated with heart failure events independent of SES as the p-value is 0.22. However, the relationship between SES and heart failure remains significant even though the effect size (OR) is slightly less than that without the mediator variable (4.77 vs 4.56). This shows partial mediation and so the null hypothesis is thus rejected. Adherence partially mediate the relationship between SES and heart failure events. Therefore, adherence to BZP partially mediates the effect of SES on the odds of developing heart failure events in patients with RHD contained within the Nigerian registry of REMEDY.

Research Question 4: The Relationship Between SES and Mortality Rate When Considering the Possible Effect of Adherence to Benzathine Penicillin (BZP) Prophylaxis

As seen in research question 3, for mediation analysis, the three main effects of interest are the (a) total effect, (b) direct effect, and (c) indirect or mediation effect of exposure on outcome (Mascha, Dalton, Kurz, & Saager, 2013). SES grouping is the exposure, mortality rate is the outcome. I examined adherence to BZP prophylaxis as a mediator of SES and mortality.

The total effect of SES on mortality does not adjust for adherence to BZP prophylaxis. According to Mascha,Dalton, Kurz, and Saager (2013), the total effect of an exposure on an outcome includes adjustment for confounding variables but ignores the specified mediator. The total effect of SES on mortality after adjusting for confounders was first calculated. Here, SES group 1(low SES group) was found to be 62 % less likely to develop mortality compared with SES group 2 (higher SES group) when the potential confounders (age category, sex, person years of follow up, disease severity at baseline) were adjusted for in the logistic regression model (OR = 0.38, 95% *CI* [0.04,4.09].

The direct effect of SES on incident heart failure rate which is the effect that is independent of adherence to BZP prophylaxis was then calculated next. Table 10 displays the final model coefficients after including the mediator variable (adherence to BZP prophylaxis). Here, SES group 1(low SES group) is now about 48.8% likely to die when mediator is added to the binomial logistic regression model (OR=0.51, 95% *CI* =0.04 - 7.03). The effect of the mediator variable, BZP prophylaxis is also shown. Poor

adherence is 3.28 times more likely to be associated with mortality compared with good adherence (OR=3.28. 95% CI=0.42. 25.78. p=0.26)

Table 10

Logistic Regression Model Coefficients of SES with Mortality and Adherence as a Mediator

Variable	B	OR	95% CI		P value
			LL	UL	
Intercept	-13.599				0.001
Poor adherence	1.19	3.28	0.42	25.78	0.26
Severe RHD	1.47	4.35	0.32	59.17	0.27
Lower SES	-.67	0.51	0.04	7.03	0.62
Age ≥18 years	2.06	7.83	0.47	130.72	0.15
Female	1.86	6.42	0.37	112.84	0.20
Person year	6.54	694.24	26.38	18270.36	<0.001

SE=Standard error, CI=confidence interval, OR=Odds ratio, LL= lower limits, UL= upper limits SES= Socioeconomic class, RHD=rheumatic heart disease

In order to prove mediation, the mediator variable must affect the outcome variable independent of the exposure variable (Mascha et al., 2013). Adherence to BZP prophylaxis was not significantly associated with mortality independent of SES as the p-value is 0.073. However, the person year of follow up was significantly associated with mortality as the p value is <0.001. (Table 10). The null hypothesis is thus not rejected. Adherence does not mediate the relationship between SES and mortality.

Summary

This chapter presented the results of regression analyses to examine the relationship between SES and clinical outcomes (mortality and heart failure events) in symptomatic RHD patients in Nigeria. The Null hypothesis for research question 1 was rejected because heart failure events was found to be significantly associated with lower SES compared with higher SES grouping. In the same vein, I rejected the Null hypothesis for research question 3 because adherence to BZP partially mediates the effect of SES on heart failure events in the patients with RHD. However Null hypothesis for research questions 2 and 4 were not rejected. For research question 2, mortality was not found to be significantly associated with lower SES compared with higher SES grouping. For research question 4, adherence to BZP did not significantly mediate the relationship between SES and mortality.

In the next chapter I will discuss the study results in relation to previous research related to disparities in clinical outcomes in symptomatic patients with RHD and the use of benzathine penicillin prophylaxis in the long-term management of these patients. Limitations and recommendations for future research will be provided along with implications for social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this secondary database analysis study was to assess the relationship between individual level SES and clinical outcomes (number of heart failure events and mortality rate) in patients with RHD contained within the Nigerian Registry of the REMEDY Study. In addition, this study examined how adherence to benzathine penicillin prophylaxis mediate the effect of socioeconomic status on clinical outcomes (number of heart failure events and mortality rate) for these patients with RHD. The health lifestyle theory is an important but underdeveloped area of theoretical discourse related to medical sociology and public health (Cockerham 2005; 2013). This theory places emphasis on how structural variables such as socioeconomic status, age, gender, and race/ethnicity, social networks and living conditions provide the social context for socialization and experience that ultimately determine lifestyle dispositions and practices (Cockerham 2005;2013). Poisson regression was used for answering question 1 and question 3 while logistic regression analysis was used for research questions 2 and 4. Poisson regression is a generalized linear model form of regression analysis used to model count data and contingency tables (Field 2015). Poisson regression assumes the response variable (dependent variable) has a Poisson distribution (Field 2015). It also assumes the logarithm of the expected value of the response variable can be modelled by a linear combination of unknown parameters (Field 2015). In contrast logistic regression is a binary form of classification and represents outcomes that are dichotomous. the

logistic regression estimates the probability of getting one of the two possible outcomes (Field 2015)

In this chapter, the discussions will be centered on findings relating to prior theoretical and empirical literature, theory application, interpretations of findings, limitations, recommendations, implications for this study, and conclusions.

Research question 1 examined whether the number of heart failure events differ between RHD patients of low SES and RHD patients of higher SES. When answering Research Question 1 using the Poison regression model generated, RHD patients from lower SES group were 4.8 times more likely to develop heart failure events in the two year follow up period compared with their counterparts in the higher SES group ($p=0.04$). This effect was significant at $p=0.04$ leading to my rejection of the Null hypothesis. Rejecting the Null hypothesis means that there is enough evidence to say that SES alone can predict the frequency of heart failure events in these RHD patients. This is to say that difference in SES groupings have a significant influence on which RHD patient develop subsequent heart failure events. The findings of an increased risk of heart failure events in RHD patients from lower SES compared with those from higher SES in this current study is in tandem with what Zuhlke et al. (2016) reported using country level socioeconomic groupings rather than individual level SES to assess disparities in heart failure incidences and mortality among symptomatic RHD patients in Africa, Yemen and India (Zuhlke et al., 2016). It is also in tandem with the findings of Burch et al., (2016) who studied the effect of SES on viral suppression among HIV infected individuals and reported that low SES significantly predict viral non suppression (adjusted hazard ratio

[HR] for greatest financial hardship *vs* none 2·3, 95% CI 1·4–3·9; non-employment 3·0, 2·1–4·2; unstable housing *vs* home-owner 3·3, 1·8–6·1; non-university education 1·6, 1·1–2·3) (Burch et al., 2016). While clinical outcomes for chronic diseases are hinged more on behavior and social support in the community, a person's SES group may define their company, the type of community they live in and also by extension their code of conduct and possibly health seeking behavior (Cockerham et al., 2017). Unlike HIV where family and peer support exist to assist and improve patient adherence to therapy, RHD is a neglected disease of poverty usually associated with abandonment and poor access to care (Cockerham et al., 2017). Lower SES as seen here is usually associated with low purchasing power (Cockerham et al., 2017). In situations where health expenditure is majorly out of pocket as subsist in Nigeria, treatment cost may be prohibitively high leading to non-adherence to drug therapy and hence recurrent heart failure events as seen among these RHD patients from lower SES group (Cockerham et al., 2017). Other factors inherent in the community like social capital available, healthcare access may also play important role in addition to SES in determining outcome for patients with RHD and thus provide avenues for future research (Cockerham et al., 2017).

The fact that those in lower SES were about 4.8 times more likely to develop heart failure events is of clinical relevance in the management of patients with RHD from lower SES household (Cockerham et al., 2017). SES determines purchasing power in Nigeria and by extension access to healthcare (Uzochukwu et al., 2015). Lower SES is associated with low purchasing power and by extension inability to pay for healthcare

services especially when the payment is out-of-pocket (Uzochukwu et al., 2015). The implication for these patients is possible increased exposure to recurrent heart failure and its attendant consequences as a result of inability to pay for healthcare services thus affecting outcome for them (Cockerham et al., 2017; Uzochukwu et al., 2015; Zuhlke et al., 2016).

Research Question 3 examined whether there is a significant difference in number of heart failure events between RHD patients of low SES and RHD patients of higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence. In answering research question 3 Poisson regression model was used to assess the potential mediatory role of adherence to BZP prophylaxis in the relationship between SES and number of heart failure events in these RHD patients. The results of the Poisson regression analysis showed that the odds of developing heart failure event were approximately 4.8 times more likely for patients of lower SES group compared to RHD patients in the higher SES group when excluding adherence to BZP prophylaxis but holding disease severity and age group of participant constant. (OR = 4.77, 95% *CI* [1.07, 21.32]). Similarly, being an RHD patients with poor adherence to BZP prophylaxis was associated with a 58% likelihood of developing a heart failure event compared with those RHD patients from higher SES (OR = 0.42, 95% *CI* [0.12, 1.45], $p = 0.21$). When finally, BZP adherence was added to the model with SES as predictors of heart failure events, SES remain significant as a predictor of heart failure events even though the odds reduced to 4.6 while BZP adherence was non-significant in predicting heart failure event. This thus means that BZP adherence partially mediates the relationship between SES and

heart failure leading to my rejection of the Null hypothesis (Field, 2015). Adherence to BZP has been shown to be an important determinant of heart failure recurrences in patients with RHD (Watkins et al., 2017; Zuhlke et al., 2016). My findings here are in tandem with what Okello reported among Ugandan children with RHD where increased incidence of heart failure was seen in children who had poor adherence to BZP prophylaxis (Okello et al., 2017). However, the fact that the result showed partial mediation suggest that some other variables apart from BZP adherence might be influencing the odds of heart failure in these patients with RHD. Adult age which was associated with a significant increased risk of heart failure events in a separate model assessing confounders maybe one of such variables acting alongside BZP adherence to influence the relationship between SES and heart failure events (Watkins et al., 2017). Adult age may be a proxy for the duration lived with the disease especially since the disease usually begins in childhood (Gitura 2016; Okello et al., 2017; Watkins et al., 2017). Research has shown that RHD disease profile and outcomes worsened as the patient gets older (Gitura 2016; Okello et al., 2017). This is important in the sense that such persons would have lived longer with the disease especially seeing that the disease commonly starts in mid childhood (Claussen, 2015; Cockerham et al., 2017; Zühlke et al., 2015). In addition, being older increases the chances of having a more severe disease in addition to developing other complications such as arrhythmias and infective endocarditis all of which increases the risk of recurrent heart failure (Claussen, 2015; Cockerham et al., 2017; Zühlke et al., 2015). It is thus not surprising to find increased number of heart failure events, a usual complication of RHD in those older than 18 years

(Gitura 2016; Okello et al., 2017). While BZP adherence has been demonstrated to improve clinical outcomes especially heart failure and ARF, this is however only useful early on in the disease before permanent geometric changes occur in the heart (Gitura 2016; Okello et al., 2017). Therefore, our findings of partial mediatory influence of BZP prophylaxis in this cohort of mixed population of adult and children may point to the need to disaggregate future study by age groups (Gitura 2016; Okello et al., 2017; Watkins et al., 2017). This was why person year of follow up was also added as an offset variable in the model (Field 2015). Therefore, while SES alone may be one factor that significantly predispose to heart failure in RHD patients studied in Nigeria, however, when SES is combined with the age of the patient, disease severity and years of follow-up, it may become an even more important determining factor for the possible risk of heart failure in patients with RHD as shown in this study (Claussen, 2015; Cockerham et al., 2017; Zühlke et al., 2015).

Research Question 2 examined whether the risk of mortality differ between RHD patients of low SES and RHD patients of higher SES. When answering research question 2 using simple logistic regression model, RHD patients from lower SES group were about 42% less likely to die in the two year follow up period compared with their counterparts in the higher SES group (OR=0.58, 95% CI=0.26 -1.29, $p = 0.18$). Because this was not statistically significant at $p = 0.05$, the Null hypothesis was not rejected. Failing to reject the Null hypothesis means that there is not enough evidence to say that SES alone can predict mortality in these RHD patients (Field, 2013). In other words, the difference in SES groupings have no significant influence on the risk of death among

these cohort of RHD patient (Field 2013). While data is lacking for all-cause mortality by socioeconomic quintiles for patients with RHD, Zuhlke et al., (2016) in the REMEDY study had evaluated 3343 RHD patients across 14 developing countries (Zuhlke et al., 2016). They reported a median age at death of 28 years. Similar to my findings in the current study, Zuhlke et al., also reported a significant increase in mortality with increasing age, with adults having a 50% higher risk of death than those <18 years of age (HR, 1.50; 95% CI, 1.11–1.95) (Zuhlke et al., 2016). Even though individual level SES was not assessed in their study, most of the deaths they reported was found in patients from low-income countries (21%) compared with those from middle-income countries (12% to 17%) (Zuhlke et al., 2016). The association of higher SES with increased risk of death in my study, though not significantly so raises important questions for management of patients with RHD. While lower socioeconomic status has been associated with an increased risk of death in patients with stroke and ischaemic heart disease, the finding of the reverse here needs further studies for clarification (Psaltopoulou et al., 2017).

Research question 4 examined whether there is a significant difference in risk of mortality between RHD patients of low SES and RHD patients of higher SES when adjusting for the effect of benzathine penicillin prophylaxis adherence. In answering research question 4 multivariable logistic regression model was used to assess the potential mediatory role of adherence to BZP prophylaxis in the relationship between SES and risk of mortality in these RHD patients. In this logistic regression analysis, the odds of dying were approximately 49% less likely for patients of lower SES group compared to RHD patients in the higher SES group when adherence to BZP was

excluded in the model but holding disease severity and adherence to BZP prophylaxis constant. (OR=0.51; 95% CI 0.04- 7.03). However, when adherence to BZP prophylaxis was included in the model, the odds of dying in RHD patients from lower SES group was 48.8% lower compared with RHD patients from higher SES group (OR=0.51, 95% *CI* =0.04 -7.03). In addition, the odds of dying for those RHD patients with poor adherence (<80% total expected dose of BZP per year) was about 3.3 time more compared with those RHD patients with good adherence (>80% of total expected dose of BZP per year) albeit not statistically significant (OR=3.2 8, 95% CI=0.42-25.78, p= 0.26). Our finding is similar to the report by Okello et al. (2017) where Ugandan RHD patients with poor BZP adherence had significantly greater mortality (31% vs. 9%, log rank $p < 0.001$) and also significantly higher risk of death compared with those with good adherence (HR = 3.81, CI 1.92–7.63, $p = 0.001$) (Okello et al., 2017). Death in those with poor adherence was also significantly associated with heart failure (HR 8.36, CI 3.28–21.31, $p = 0.001$) (Okello et al., 2017).

Thus, SES alone unlike the model for heart failure events is inadequate in explaining the risk of dying in patients with RHD. However, when other factors like disease severity, the age of the patient and also the duration of follow up are considered in the model, SES may have a significantly important determining factor for the possible risk of dying in patients with RHD. The longer an RHD patient lives with the chronic disease, the more likely other complications like stroke and arrhythmias set in and thereby increasing the risk of dying. Older patients as seen in this study would have lived

longer with the disease especially seeing that the disease commonly starts in mid childhood.

Impact of Key Variables on Multiple Outcomes in RHD

RHD is a chronic disease associated with multiple outcomes (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Several key variables like disease severity at diagnosis, left ventricular end diastolic dimension, presence of arrhythmias, adherence to drug therapy and presence of complications such as endocarditis, stroke and acute rheumatic fever will have a significant impact on the eventual outcome of the patient (Watkins et al., 2017). Cannon et al., (2017) using a disease register had reported that a diagnosis of severe RHD especially in young persons is associated with a 10% chance of dead within 6 years of diagnosis (Cannon et al., 2017). They further reported that patients diagnosed with moderate RHD had a mixed prognosis 10 years after diagnosis with roughly one third progressing to severe RHD (with or without surgery), one third remained moderate, and one third regressing to mild RHD (Cannon et al., 2017). Those who had mild RHD at diagnosis had the most favorable prognosis, with over 60% remaining mild after 10 years, and 10% being inactive by the end of the 14-year study period (Cannon et al., 2017).

RHD being a disease of poverty and social disadvantage is associated with poor access to healthcare with consequent increase episodes of unrecognized acute rheumatic heart fever (ARF) (Watkins et al., 2017). Recurrent ARF episodes cause severe damage to the valve structure as well as also predisposing the patients to dilatation of heart chambers and other severe consequences (Cannon et a., 2017; Chamberlain-Salaun et al.,

2016; Zuhlke et al., 2016). BZP secondary prophylaxis is used to prevent such recurrences and hence improve outcomes in RHD patients (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Furthermore, there was no significant association of poor adherence to BZP prophylaxis with the occurrence of heart failure events in our study. However, I found adherence to BZP to partially mediate the influence of SES on heart failure events confirming what has been reported in the literature (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016).Such effect of BZP prophylaxis is thought to be greatest in early stages of the disease (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Our patients like many others in developing countries access medical care late when their disease is severe with associated substantial valve damage from unrecognized recurrent rheumatic fever episodes at which point the hemodynamic consequences of severe valve disease may be the overwhelming determinants of prognosis (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). It is thus not surprising that adherence to BZP prophylaxis did not significantly affect the clinical outcome (Heart failure and death) in Nigerian patients with RHD (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016).

Even though RHD begins in childhood, its highest burden is seen in adolescents and young adults living in poverty and social disadvantage (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Disease severity at diagnosis and the degree of adherence to benzathine penicillin prophylaxis are the most important risk factors to heart failure recurrence in RHD patients (Cannon et a., 2017; Chamberlain-

Salaun et al., 2016; Zuhlke et al., 2016). Complications such as heart failure and death are usually associated with severe disease at diagnosis, poor access to BZP prophylaxis as well as poor adherence to BZP prophylaxis when available (Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Together with recurrent heart failure, these factors contribute to the increased mortality rates seen in people with RHD (Cannon et a., 2017; Zuhlke et al., 2016). Low SES which is the surrogate for poverty affects access to care, BZP prophylaxis and other treatments for complications like heart failure thereby increasing the risk of dying in such patients (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016).

Interpretation of Findings

This study and others on RHD patients contained within the REMEDY global registry adds to the findings of the relationship between SES and the significant increases in number of heart failure events (Zuhlke et al. 2014; Zuhlke et al., 2016). Similarly, it also adds to the findings on the relationship of SES and risk of mortality in symptomatic RHD patients contained within the REMEDY global registry (Zuhlke et al., 2014; 2016).

The Health lifestyle theory used in this study offered an opportunity for understanding how class circumstance (socioeconomic status) influences patients' choices and decision (agency) on adhering to the monthly penicillin injection (adherence), a health behavior necessary for improving the clinical outcome for these symptomatic patients with RHD (Cockerham 2005;2013).

An increased risk of heart failure among patients from lower SES was observed in my study similar to what was reported by Zuhlke et al., in the REMEDY study though

Zuhlke et al., used country level SES classification by the World Bank in grouping the patients (Zuhlke et al., 2016). Lower SES is associated with worsening clinical outcomes in chronic disease such as RHD (Baro et al., 2018). Our finding is also similar to what Potter et al., (2019) reported in a review of the literature where they showed a significant association between incident heart failure with SES households (Potter et al., 2019). Potter reported that patients from low SES households have a 1.62 times risk of heart failure compared with those from higher SES households (HR 1.62, 95% CI 1.50-1.76) (Potter et al., 2019). Furthermore, my study observed adherence to BZP prophylaxis in patients with RHD only partially mediate the relationship between SES and frequent heart failure events. Okello et al., had demonstrated a reduced incidence of heart failure among Ugandan RHD patients with good adherence to BZP (Okello et al., 2017). Even though my study did show a partial influence of BZP adherence on heart failure events, however, the fact that other researchers too have shown an association between poor adherence to BZP prophylaxis and increased risk of heart failure events calls for a closer follow up of RHD patients with lower SES in order to help reduce the frequency of heart failure events and thus improve their outcomes (Cannon et a., 2017; Watkins et al., 2017).

A reduced risk of death among patients from low SES, though not statistically significant, was also found in this study in contrast to what Okello et al., reported among RHD patients in Uganda (Okello et al., 2017). Furthermore, this study also found poor adherence to benzathine penicillin prophylaxis to be associated with an increased risk of mortality though this did not reach statistical significance. This lack of significance may

be related to the mixed population of children and adults used in this study (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016). Children being products of a household SES are a different population from adults. It will thus be advisable that future study should try to separate the two groups and assess their effects separately (Cannon et a., 2017; Chamberlain-Salaun et al., 2016; Zuhlke et al., 2016).

Limitations of the Study

This study was based on secondary data analysis of data contained within the Nigerian site of the REMEDY study. The sample in this study consisted of symptomatic RHD patients presenting for care in a hospital emergency room, ward or clinic and may not be representative of all RHD patients in those localities and thus may limit generalizability of the results of the study to all populations of patients with RHD. As for the sampled population, the use of a mixed population consisting of both children and adults with RHD in the study might introduce some complexities in the effect of SES on the studied outcomes. SES for an adult is a direct reflection of the person's social standing, economic class and ability to access and possibly pay for services especially health services in Nigeria which is mainly out of pocket expense. However, for a child, the SES classification used was the parental SES classification. Even though this was done because child care is a responsibility of the parents and care givers, it may however over estimate or under estimate the effect of SES especially since parental care is not so much dependent on SES but culture in Africa (Amzat & Razum 2018). However, in future, children should be separated from adults and if possible, compared on the key outcomes variables so as to be able to make appropriate age specific conclusions seeing

that the disease characteristics may differ between children and adults. Other variables such as duration lived with the diseases, frequency of hospitalization and total household income all factors that have been shown to significantly impact outcome in chronic disease management could have been assessed if available in the data set. But this was not possible because of their unavailability in the dataset.

Implications for Social Change

Rheumatic heart disease (RHD) has continued to significantly contribute to morbidity and mortality among children and adolescents in resource constraint communities especially in sub Saharan Africa where poverty and poor hygiene continues to plague the vast majority of the population (Marijon et al., 2012; Zühlke & Steer 2013)

It is important to assess how SES, age category and adherence to BZP impacts on clinical outcomes for chronic diseases such as rheumatic heart diseases especially in developing countries where health expenditure is mainly out of pocket expenses (Remond et al., 2016; Yacoub et al., 2016; Zühlke et al., 2016). Understanding the mechanism through which SES and adherence to BZP prophylaxis affects these health outcomes represent potentially modifiable targets for intervention to improve health outcomes not just for patients with RHD but also for patients with other chronic diseases (Remond et al., 2016; Yacoub et al., 2016; Zühlke et al., 2016).

In this study, risk for developing heart failure events was higher for RHD patients in low SES group compared with those in higher SES group. Finding a significantly higher number of heart failure events in patients from low SES in this study points to the need to pay close attention to the management of these group of patients with RHD

especially as it relates to counseling on those factors that may predispose to the frequent recurrence of heart failure (Classen 2015; Cockerham et ail., 2017). Thus, physicians, cardiologists and nurses who care for these patients will need to do more in counseling about drug adherence especially adherence to diuretics for heart failure and also benzathine penicillin for prevention of recurrent rheumatic fever, an important cause of heart failure in RHD patients (Gonzalez et al., 2016). In addition, health policy will need to focus on reducing barriers to care for people in the low SES groupings of the society as well as reducing out of pocket expense to health care by making health insurance and social services universally accessible. This will help improve clinical outcomes for patients with RHD and other chronic diseases.

Recommendations

This secondary analysis study was conducted on de-identified data sets of symptomatic RHD patients in Nigeria collected using case record forms by cardiologists working in multiple hospitals sites from January 2010 to January 2014. The major limitation of this study of being a secondary data analysis is acknowledged. However, larger prospective longitudinal studies utilizing multiple sites in Nigeria are needed to confirm the findings of this study.

Previous studies had utilized a mixed population consisting of children and adults just as was done in this study. Future researchers should focus on disaggregating the children data from the adult data in order to make definitive statements about SES and its effects on clinical outcomes such as heart failure and mortality in patients with RHD.

SES grouping utilized proxies such as educational attainment and occupation rather than actual income earned by the patients (or parents of children). Since care in Nigeria is mainly out of pocket expenses, it is important that future researchers try to assess actual income or earnings of the patients as a measure of SES. In addition, a prospective cohort design would be most appropriate for such future research.

Recommendation for practice as a result of this study includes the need for increased surveillance and monitoring for adherence to management in patients with RHD from social disadvantaged backgrounds in order to improve their clinical outcomes.

Conclusions

RHD is a disease of social disadvantage associated with poverty, malnutrition, poor hygiene and sanitation, overcrowding and poor access to health. The persistence of these poverty defining problems in Nigeria and most parts of sub Saharan Africa is what is currently responsible for the persistence of RHD as well as the deaths occurring from the complications of the disease.

The results of this study showed that after controlling for age, disease severity at baseline and adherence to BZP, symptomatic RHD patients from the Nigerian sites of the REMEDY study who are from low SES group have a higher incidence heart failure rates compared with their counterparts from a higher SES group. Poor adherence to BZP prophylaxis did show partial mediation of the relationship between SES and number of heart failure events or but not mortality. Furthermore, lower SES was significantly associated with increased risk for developing heart failure events. These findings suggest that socioeconomic gradient is an important predictor of clinical outcomes (heart failure

events) among symptomatic RHD patients seen in Nigeria. Paying attention to socioeconomic status of a patient can be an important tool for improving clinical outcomes for these patients. Future research should examine the effect of socioeconomic status and clinical outcomes for patients with RHD separately for children and adults. This will help bring about results that can be used for targeted actions and policy formulation and implementation appropriate for each age group.

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