FACTORS ASSOCIATED WITH TUBERCULOSIS IN KISII COUNTY: A CASE CONTROL STUDY

GEORGE KADONDI KASERA

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Factors Associated with Tuberculosis in Kisii County: A Case Control Study

George Kadondi Kasera

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

Signature…… Date……

George Kadondi Kasera

This thesis has been submitted for examination with our approval as University supervisors.

Signature…… Date……

Prof. Simon Karanja, PhD

JKUAT, Kenya

Signature…… Date……

Dr. Christina Mwachari, PhD

KEMRI, Kenya

DEDICATION

This work is dedicated to persons who have had tuberculosis in Kenya.

To my late father, I dedicate this to you posthumously in recognition of your motivation and support throughout the study period.

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ABBREVIATIONS AND ACRONYMS

AHA	American Heart Association
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
cARV	Combined anti-retroviral
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DALY	Disability – Adjusted Life Year
DKA	Diabetic ketoacidosis
DOTS	Directly Observed Treatment, Short Course
DM	Diabetes mellitus
ERC	Ethical review committee
FELTP	Field Epidemiology Laboratory Training Program
H_0	Null hypothesis
HbA_{1c}	Hemoglobin A_{1c}
HBC	High burden countries
HDL	High density lipoprotein
HHS	Hyperglycemic hyperosmolar state

HIV	Human immunodeficiency virus
IDF	International Diabetes Federation
IL – 2	Interleukin - 2
IL – 4	Interleukin - 4
INF – c	Interferon – c
JOOTRH	Jaramogi Oginga Odinga Teaching & Referral Hospital
KL5H	Kisii Level 5 Hospital
LDL	Low density lipoprotein
MDR-TB	Multidrug resistant TB
NCDs	Non- communicable diseases
NIH	National Institutes of Health
NTLD	National Tuberculosis, Leprosy and Lung Diseases Program
PAD	Peripheral arterial disease
TB	Tuberculosis
Th1	T helper 1
Th2	T helper 2
TIBU	TB Information Basic Unit
USD	US Dollars
WHO	World Health Organization

ABSTRACT

Kenya is on track to attain two of the three global targets for reducing tuberculosis (TB); i.e. incidence and prevalence, while still has way to go in attaining the targets for mortality. While HIV remains an important driver of TB in Kenya, 67% of cases are not HIV related suggesting the need to identify and address other drivers of the epidemic. The objective of this study was to determine the association of TB with smoking, alcohol consumption, diabetes mellitus and malnutrition in Kisii County.This was an unmatched case - control study in five facilities in Kisii County from September 2015 to January 2016. Cases were registered TB patients at the time of study, while controls were from the facility catchment areas. All prospective participants who tested HIV positive were excluded. The outcome of interest was TB infection and exposures were alcohol consumption, cigarette smoking, diabetes mellitus (RBS > 200 mg/ dL or FBS > 126 mg/ dL) and malnutrition (BMI<18.5 kg/ m^2). Age (years), sex (male/female), household size (≤3 or >3) and education level (none, primary, secondary and college/university) were included as covariates. Data was collected on Open Data Kit (ODK)platform and analyzed using Stata 12®. Sample size of 268 was determined using Kelsey formula. Between September 2015 and January 2016, a total of 268 participants (77 cases, 191 controls) were enrolled into the study.Overall, malnutrition was associated with a higher likelihood of TB and this likelihood increased as other factors were adjusted for (AOR =16.68, 95% CI = 6.97 – 39.88). Diabetes was associated with six times higher odds of TB and the odds increased with adjusting for other covariates (AOR =6.30, 95% CI=1.94 – 20.48). Smoking and alcohol use were not significantly associated with increased likelihood of TB but the observed odds in both cases were attenuated after adjusting for other covariates.This study showed that diabetes is associated with a significantly higher chance of getting TB and that malnutrition was associated with the highest likelihood of having TB among all the exposures assessed. This study demonstrated the need to understand the relationship between NCDs, and their risk factors and diabetes in settings battling with a double burden of NCDs and communicable diseases.There is thus an urgent need to reconfigure our health systems to focus on tackling NCDs and the challenges they pose to public health.

CHAPTER ONE

INTRODUCTION

1.1 Background

Tuberculosis, one of the oldest diseases known to affect humans, is a major cause of death worldwide. This disease, which is caused by bacteria of the Mycobacterium tuberculosis complex, usually affects the lungs, although other organs are involved in up to one-third of cases (Lo¨nnroth & Raviglione, 2008). If properly treated, tuberculosis caused by drug-susceptible strains is curable in virtually all cases. If untreated in HIV uninfected individuals, the disease may be fatal within 5 years in 50–65% of cases (Canaday & Toossi, 2016). Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis (Abdul, Ker, Yusof, Hanafi, & Wong, 2014). In 2013, an estimated nine (9) million people developed TB while 1.5 million died from the disease, 360 000 of whom were HIV- infected (World Health Organization, 2014). Of the estimated 9 million people who developed TB in 2013, more than half (56%) were in the South-East Asia and Western Pacific Regions. A further one quarter was in the African Region, which also had the highest rates of cases and deaths relative to population (World Health Organization, 2014). In the same period, Kenya observed a sharp decline of TB cases, having a total number of 89,760 a 9.48% decline from the 99,159 cases notified in 2012 (National Tuberculosis, Leprosy and Lung Disease Program, 2014). There was a general decline in all TB types and categories with a total of 8,477 cases who were previously treated and 81,283 new cases (National Tuberculosis, Leprosy and Lung Disease Program, 2014).

While infectious diseases have dominated the disease burden in the developing world for much of the last century, the incidence of many non-communicable diseases (NCDs), such as cardiovascular diseases, diabetes mellitus (DM), those related to smoking and alcohol abuse, chronic obstructive pulmonary disease (COPD), and mental illness, is growing in low- and middle-income countries, as well as in certain populations in high-income countries (Creswell, et al., 2011).

This epidemiological shift adds to the existing infectious disease load, creating a double burden of communicable diseases and NCDs in these populations (Chen, et al., 2014) (Gaziano, 2005) (Miranda, Kinra, Casas, Smith, & Ebrahim, 2008) (Abegunde, Mathers, Adam, Ortegon, & Strong, 2007) (van Zyl-Smit1, Brunet, Pai, & Yew, 2010) (Laniado-Laborı´, 2009). NCDs have often been depicted as diseases of development and it is a common notion that they mainly affect the non-poor. However, most NCDs, like most infectious diseases, are more common in the lower socioeconomic groups. This is certainly true in high income countries, but also to a growing extent also in middle- and low-income countries (World Health Organization, 2011). Therefore, the double burden of communicable diseases and NCDs is most pronounced among the poor, and this is further underscored by the causal links between them. There is a growing body of evidence describing the links between tuberculosis (TB) and a number of NCDs and their risk factors, such as DM, smoking- and alcohol-related conditions, COPD, mental illness and malnutrition (Jeon & Murray, 2008) (Lönnroth, Williams, Stadlin, Jaramillo, & Dye, 2008) (Cegielski & McMurray, 2004).

TB has long been a disease of the poor. Crowded living conditions and compromised immune systems due to causes such as under-nutrition have contributed to a disease that caused one in every seven deaths in late 19th-century Europe, and which continues to cause immense human suffering across the world today. Although many lives have been saved by widely available and inexpensive TB treatment over the past decades, due to the expansion of DOTS as a global management strategy (Lönnroth, et al., 2010), TB continues to be a leading cause of burden and death among infectious diseases worldwide (World Health Organization, 2009).

Globally, TB incidence is declining, but at a slow pace (World Health Organization, 2014). Additional efforts are needed to speed up the decline. Improved diagnosis and treatment of all forms of TB will be required, backed by poverty alleviation and general socioeconomic development, for long-term TB control and elimination. However, there is also a need to address a set of major TB risk factors and comorbidities (Lönnroth, et al., 2010).

HIV infection has driven the TB epidemic in sub-Saharan Africa, and the links between TB and HIV have been well documented (Corbett, et al., 2003). There has been an intense focus on improved TB/HIV collaboration in recent years, with an aim to: 1) improve early TB diagnosis and treatment among people with HIV infection and, vice versa, improve clinical outcomes for both diseases; 2) use isoniazid as TB preventive therapy as well as cotrimoxazole preventive treatment for opportunistic infections in people with HIV infection; and 3) promote contribution by national TB programs to HIV prevention and thus, indirectly, TB prevention (World Health Organization, 2011). The dual epidemics of TB and HIV have led to the use of the phrase ‘‘two diseases, one patient’’, but with an increasing prevalence and focus on NCD, clinicians treating TB need to acknowledge that they may deal with multiple diseases in a single patient (Creswell, et al., 2011).

Several NCDs, such as DM, alcohol use disorders and smoking-related conditions, are responsible for a significant proportion of TB cases (Lönnroth, et al., 2010). DM prevalence is expected to more than double by 2030, and seven out of the 10 expected high-burden countries for DM in 2030 are high-burden TB countries today (Wild, Roglic, Green, Sicree, & King, 2004). Alcohol consumption seems to be increasing in most developing countries, following a general rule that as people have better access and purchasing power, consumption increases, while those with low socioeconomic status have the highest risk of harmful use (World Health Organization, 2007) (World Health Organization, 2010).

In this study, the term NCD is used to refer to a group of non-communicable diseases (e.g. DM, alcohol dependency and malnutrition) and their related risk factors (e.g. smoking, poor diet and physical inactivity). Diabetes mellitus (DM) in particular, affected 387 million people globally in 2014. Seventy seven percent (77%) of people with diabetes live in low- and middle-income countries with the greatest numbers aged between 40 and 59 years (International Diabetes Federation, 2014). There were 775,200 cases of diabetes in Kenya in 2014 with an estimated prevalence of 3.6% (International Diabetes Federation, 2014).

1.2 Statement of the Problem

Countries of low and middle income now have a large burden of NCDs, which overlaps with the unfinished agenda of communicable diseases; the risk factors of poverty, unhealthy lifestyles, tobacco use, and alcohol misuse are common to both categories of disease (Lim, et al., 2013). Kenya is still among one of the high burden countries as regards the burden of tuberculosis, with an estimated incidence of 268 TB cases per 100,000 population (World Health Organization, 2014), while it has an estimated prevalence of DM of 3.6% (International Diabetes Federation, 2014). NCDs accounted for 30% of Disability – Adjusted Life Years, while TB accounted for 1.57% in 2015 in Kenya (Institute of Health Metrics and Evaluation, 2017). The rising prevalence of DM among other NCDs, in TB endemic areas may adversely affect tuberculosis control. Thus speeding up the diagnostic, curative and preventive services are required to address DM and other risk factors that increase the individual's susceptibility for TB (Sangral, Kumar, & Bhatia, 2012). As the prevalence of diabetes increases globally, it is important to clarify any association with TB so the strategy for controlling TB can be appropriately targeted (Creswell, et al., 2011) (Dooley & Chaisson, 2009). It is key to bridge the knowledge gap with local figures.

Recent data from the global burden of disease reflect major demographic and lifestyle changes, leading to a rise in non-communicable diseases (Marais, et al., 2013). Historically, efforts to control communicable and non-communicable diseases had little in common and tended to emphasize differences rather than similarities (Bygbjerg, 2012). However, despite being transmissible, management and control of chronic infectious diseases such as tuberculosis has more in common with non-communicable diseases than with acute communicable diseases (Marais, et al., 2013). Non-communicable diseases interact adversely with tuberculosis by increasing both individual vulnerability to disease and the likelihood that the epidemic will be sustained in the population (Dooley & Chaisson, 2009). Individual

vulnerability is affected by the number and severity of comorbidity, whereas the total burden of comorbidity determines vulnerability at the population level (Marais, et al., 2013). This study hopes to evaluate the association of cigarette smoking, alcohol consumption, malnutrition and DM with tuberculosis in Kisii County.

1.3 Study Justification

This study will contribute to expanding the pool of literature on the overlap between NCDs and chronic infectious diseases, TB, in Kenya and the results can be used as a guidance tool for policy makers. The study results will be generated at an opportune time in Kenya, as government gains momentum to measure the prevalence of NCDs as well as standardize clinical guidelines and provide outreach services have been building.

1.4 Research Questions

a) What are the socio demographic characteristics of TB cases and controls in Kisii County?
b) What is the proportion of DM among cases and controls in Kisii County?
c) What is the proportion of cigarette smoking among cases and controls in Kisii County?
d) What is the proportion of alcohol use among cases and controls in Kisii County?
e) What is the proportion of malnutrition among cases and controls in Kisii County?

1.5 Hypothesis

The null hypothesis (H_0): Diabetes mellitus, and or presence of cigarette smoking, alcohol consumption and malnutrition are not associated with risk of TB in Kisii County.

1.6 Objectives

1.6.1 General Objective

To determine risk factors associated with TB in Kisii County.

1.6.2 Specific Objectives

a) To determine the sociodemographic characteristics of study participants in Kisii County.
b) To determine the proportion of diabetes mellitus (DM) among cases and controls in Kisii County.
c) To determine the proportion of cigarette smoking among cases and controls in Kisii County.
d) To determine the proportion of alcohol use among cases and controls in Kisii County.
e) To determine the proportion of malnutrition among cases and controls in Kisii County.

CHAPTER TWO

LITERATURE REVIEW

2.1 Background

Non-communicable diseases were not included explicitly during formulation of the MDGs. This oversight was partly corrected when the UN published a declaration on the prevention and control of non-communicable diseases (United Nations General Assembly. Resolution adopted by the General Assembly: 66/2—political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. Jan 24, 2012., 2012), which was supported by all 193 member states. Despite intercountry heterogeneity resulting from variable demographic and socioeconomic transition, most non-communicable and communicable diseases are associated with a strong social gradient, mostly affecting poor and marginalized populations (Marais, et al., 2013).

The rise of NCDs is important for TB control for a variety of reasons. First, many NCDs are risk factors for TB, especially for progression from infection to disease due to negative impact on host defence mechanisms against *Mycobacterium tuberculosis* (Cegielski & McMurray, 2004) (Creswell, et al., 2011) (Mellencamp, 1996) (Szabo, 1997). Secondly, NCDs may complicate treatment and management of TB, due to clinical challenges (e.g. among people with DM) as well as behavioural challenges (e.g. among people with alcohol use disorders) (Rehm, et al., 2009) (World Health Organization, 2009). Thirdly, TB can trigger or aggrevate NCDs. For instance, TB, like other infections, can worsen glucose control and trigger DM (World Health Organization, 2009), and a history of TB, although not a classical risk factor for COPD, is one of the leading causes of lung sequelae and bronchiectasis, and has been identified as an independent risk factor for COPD in a review (Salvi & Barnes, 2009). In addition, TB, and especially MDR-TB, may aggravate the social and financial stress contributing to substance abuse and mental ilness (Cohen, Kleinman, & Saraceno, 2002) (Acha, et al., 2007).

However, the link between TB and NCDs also creates opportunities for improved diagnosis and management of both (Creswell, et al., 2011). Presence of a NCD may indicate the need to actively screen for TB, especially in high – burden countries, which can help improve ealy and increase TB case detection (Lo¨nnroth & Raviglione, 2008). Similarly, diagnosis of TB should alert clinicians to actively screen for common non-communicable comorbidities, which may otherwise go undiagnosed, especially in low- and middle-income countries where services for NCDs are vastly under-developed. Finally, preventive therapy for TB may be warranted in individuals with some of these comorbidities (Creswell, et al., 2011).

2.2 Epidemiology

The incidence of type 2 DM, is rapidly growing in the world. In 1985, an estimated 30 million people suffered with this chronic disease, which, by the end of 2006, had increased to 230 million, representing 6% of the world population. Of this number, 80% is found in the developing world (Roglic, et al., 2005). Diabetes mellitus affected 387 million people globally in 2014, a number that is projected to rise to 592 million by 2035. Seventy seven percent (77%) of people with diabetes live in low- and middle-income countries with the greatest numbers aged between 40 and 59 years. One hundred and seventy-nine (179) million people with diabetes are undiagnosed. Diabetes mellitus caused 4.9 million deaths in 2014; every seven seconds a person dies from diabetes. More than 79,000 children developed type 1 diabetes in 2013 with another 21 million live births were affected by diabetes during pregnancy in the same period. Diabetes mellitus caused at least USD 612 billion dollars in health expenditure in 2014 – 11% of total spending on adults (IDF, 2014). It is estimated that, during the next 35 years, diabetic worldwide prevalence will reach 25%, with India being the hardest hit.

For a long time, Africa was considered safe from many of the diseases that are called “diseases of affluence,” which plague the Western world. Similarly, there was a time when Africa was thought to be a continent, relatively free of DM illnesses (Cook, 1901). Today, however, diabetes is not very uncommon in Africa, a situation that

seemed to have remained virtually static until the 1990s and more recently (Azevedo & Alla, 2008). Indeed, from 1959 to the mid-1980s, medical statistics showed that the prevalence rate of diabetes in Africa was equal to or less than 1.4%, with the exception of South Africa, where the rate was estimated to be as high as 3.6% in 2001 (Motala, Diabetes trends in Africa, 2002) (Motala, Omar, & Pirie, Epidemiology of type 1 and type 2 diabetes in Africa, 2003) (Rheeder, 2006). But, by 1994, the continent-wise prevalence of DM stood at 3 million and was then predicted to double or triple by the year 2010 (Sobngwi, Mauvais-Jarvis, Vexiau, Mbanya, & Gautier, 2001). Approximately, 7.1 million Africans were said to be suffering from diabetes at the end of 2000, a figure that was expected to rise to 18.6 million by 2030 (Wild, Roglic, Green, Sicree, & King, 2004). The prevalence of diabetes mellitus is increasing worldwide, especially in Sub – Saharan Africa, where TB is endemic. The strength of any association between DM, dysglycemia, and risk of TB remains debated (Dooley & Chaisson, 2009).

As more data were made available worldwide, scientists found that the adult population of Indian descent, Africans on the continent, and their descendants in the Diaspora, and whites living in Africa, especially in South Africa and Tanzania, had the highest diabetes prevalence, respectively (Rheeder, 2006) (Levitt, et al., 1999) (Gning, et al., 2007). A few years ago, the rate of DM among Africans appears to have been 1%–6%; among the Caribbeans of African-descent, 10%–13% and among African Americans, 12%–15%, which is high. Interestingly, the white population in Africa has shown in the past either higher than or comparable rates to those of European whites, hovering between 6% and 10% (Gharbi & Aouidet, 1996) (Osei, Schuster, Amoah, & Owusu, 2003). The majority of the African diabetes is of type 2 (70%–90%), with only 25% showing the complications of type 1 diabetes (Osei, Schuster, Amoah, & Owusu, 2003) (Levitt, Diabetes in Africa: Epidemiology, management and healthcare challenges, 2008) (Mufunda, et al., 2006). Of course, despite the alarm worldwide, the situation on the continent and elsewhere among people of African descent is worsening as we write (Azevedo & Alla, 2008).

The racial and ethnic puzzle of diabetes has led scientists to posit that genetic predisposition might be a major factor, along with environmental factors, diet, lifestyle (inactivity), and residence (Cruickshank, et al., 2001) (Swai, Lutale, & McLarty, 1990). In Africa, DM is more prevalent among the wealthy and the powerful, hence its designation as the "disease of opulence," and remains more pronounced in urban areas where people tend to be less physically active, eating a diet that is rich in saturated fats and refined sugars. It is well known now that obesity is one of the most significant contributors to increased prevalence of diabetes, leading to the use of the word "diabesity" (International Diabetes Federation, 2014), both in rural and urban areas. In comparison to the rural areas, the urban setting also presents an increased prevalence of obesity (Sobngwi, et al., 2004) (Hossain, Kawar, & El Nahas, 2007) (Kiawi, et al., 2006) (Mbanya, Ngogang, Salah, Minkoulou, & Balkau, 1997) (Kamadjeu, et al., 2006). In Africa, in general, the Word Health Organization (WHO) estimates that more than one-third of the women are obese compared to one-fourth of the men, with the poor being as vulnerable as the rich.

While some scientists are less speculative, others claim that there is strong evidence for the role played by genetic and immunological factors in diabetes pathogenesis. For Africans and their descendants, some have noted that patients of Sub-Saharan African origin who reside in diverse geographical environments (or the African Diaspora) could potentially contribute to the understanding of the genetic and environmental mediators of both diseases (type 1 and type 2) (Osei-Hyiaman, et al., 2001) (Miljkovic-Gacic, et al., 2008). The DM pandemic, which previously consisted mainly of type 2, has evolved in association with rapid cultural changes, an aging population, increasing urbanization, dietary lifestyles, and behavioral patterns without prevention and control preparedness. However, many intrinsic, individual and societal obstacles, such as poor education and illiteracy, low socioeconomic status, and lack of access to health care make uncertain the translation of DM research in Sub-Saharan Africa (Azevedo & Alla, 2008). There were 775,200 cases of DM in Kenya in 2014 with an estimated prevalence of 3.6% (International Diabetes Federation, 2014).

Tuberculosis remains one of the world's deadliest communicable diseases. In 2013, an estimated nine (9) million people developed TB while 1.5 million died from the disease, 360 000 of whom were HIV- positive. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment. Of the estimated 9 million people who developed TB in 2013, more than half (56%) were in the South-East Asia and Western Pacific Regions. A further one quarter was in the African Region, which also had the highest rates of cases and deaths relative to population. India and China alone accounted for 24% and 11% of total cases, respectively (World Health Organization, 2014). Among the 22 high burden countries (HBCs), are Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe (World Health Organization, 2014). In the same period, Kenya observed a sharp decline of TB cases, having a total number of 89,760 a 9.48% decline from the 99,159 cases notified in 2012. There was a general decline in all TB types and categories with a total of 8,477 retreatment cases and 81,283 new cases being (National Tuberculosis, Leprosy and Lung Disease Program, 2014).

2.3 Clinical Presentation of TB

Tuberculosis is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing (World Health Organization, 2014).

Tuberculosis is classified as pulmonary, extra pulmonary, or both. Before the advent of HIV infection, ~80% of all new cases of tuberculosis were limited to the lungs. However, up to two-thirds of HIV-infected patients with tuberculosis may have both pulmonary and extrapulmonary disease or extrapulmonary disease alone

2.3.1. Pulmonary Tuberculosis

Pulmonary tuberculosis can be categorized as primary or post primary (secondary).

2.3.1.1 Primary Disease

Primary pulmonary TB occurs soon after the initial infection with tubercle bacilli. In areas of high TB transmission, this form of disease is often seen in children. Because most inspired air is distributed to the middle and lower lung zones, these areas of the lungs are most commonly involved in primary TB (Abdul, Ker, Yusof, Hanafi, & Wong, 2014). The lesion forming after infection is usually peripheral and accompanied in more than half of cases by hilar or paratracheal lymphadenopathy, which may not be detectable on chest radiography. In the majority of cases, the lesion heals spontaneously and may later be evident as a small calcified nodule (Ghon lesion) (National Tuberculosis, Leprosy and Lung Disease Program, 2014).

In children and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary TB may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways (Jain, et al., 2013). Pleural effusion, which is found in up to two-thirds of cases, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (progressive primary tuberculosis). Tuberculosis in young children is almost invariably accompanied by hilar or mediastinal lymphadenopathy due to the spread of bacilli from the lung parenchyma through lymphatic vessels (Pang, et al., 2014). Enlarged lymph nodes may compress bronchi, causing obstruction and subsequent segmental or lobar collapse. Partial obstruction may cause obstructive emphysema, and bronchiectasis may also develop. Hematogenous dissemination, which is common and often asymptomatic, may result in the most severe manifestations of primary M. tuberculosis infection. Bacilli reach the bloodstream from the pulmonary lesion or the lymph nodes and disseminate into

various organs, where they may produce granulomatous lesions. Although healing frequently takes place, immunocompromised persons (e.g., patients with HIV infection) may develop miliary tuberculosis and/or tuberculous meningitis (World Health Organization, 2014).

2.3.1.2 Post Primary Disease

Also, called adult-type, reactivation, or secondary tuberculosis, post primary disease results from endogenous reactivation of latent infection and is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth (Hunter, Actor, Hwang, Karev, & Jagannath, 2014). In addition, the superior segments of the lower lobes are frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied necrotic contents are ultimately discharged into the airways, resulting in satellite lesions within the lungs that may in turn undergo cavitation (Figs. 158-4 and 158-5). Massive involvement of pulmonary segments or lobes, with coalescence of lesions, produces tuberculous pneumonia (Elkington & Friedland, 2015). While up to one-third of untreated patients reportedly succumb to severe pulmonary TB within a few weeks or months after onset (the classical "galloping consumption" of the past), others undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course ("consumption"). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks (Orme & Basaraba, 2014)

2.3.2 Extrapulmonary TB

In order of frequency, the extrapulmonary sites most commonly involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum,

and pericardium. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary TB is seen more commonly today than in the past (Karstaedt, 2014)

2.4 Links between NCD and TB

2.4.1 Diabetes Mellitus

The word diabetes is from the Greek *diabanein* which means to pass through, in reference to the excessive urine produced as a symptom of these diseases. And the term diabetes, without qualification, usually refers to DM, which roughly translates to excessive sweet urine (known as "glycosuria"). Several rare conditions are also named diabetes. The most common of these is diabetes insipidus in which large amounts of urine are produced (polyuria), which is not sweet (insipidus meaning "without taste" in Latin) (Shivashankar & Mani, 2011). Diabetes mellitus is defined as a fasting glucose>126 mg/dL (7.0 mmol/L), a plasma glucose level exceeding 200 mg/dL (11.1 mmol/L) 2 h after a 75-g oral glucose load, or two random plasma glucose levels exceeding 200 mg/dL (11.1 mmol/L with symptoms of hyperglycemia [thirst, polyuria, polydipsia, or recurrent infections]) (Samaras, 2012). Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful" (Shivashankar & Mani, 2011).

Recent studies showed that the innate immune system is impaired by high levels of blood glucose (Peleg, Weerarathna, McCarthy, & Davis, 2007) (Stegenga, van der Crabben, & Blümer, 2008), and that diabetic individuals have a 25–75% increased risk of pneumonia (Kornum, et al., 2008). A recent population-based cohort study from Hong Kong (Leung, et al., 2008) and a review of 13 previous smaller observational studies (Jeon & Murray, 2008) found diabetes to be associated with increased risk of TB, with relative risk estimates varying considerably from1.2 to 7.8, with the lowest estimates reported in the larger studies. Only two studies have focused on the role of dysglycemia (Leung, et al., 2008) (Pablos-Méndez, Blustein,

& Knirsch, 1997). Leung et al. (Leung, et al., 2008) found that among elderly individuals with diabetes, those with HbA1c ≥ 7% had an adjusted TB relative risk of 3.1 (95% CI 1.6–5.9) compared with those with HbA1c < 7%, whereas Pablos-Mendez et al. (Pablos-Méndez, Blustein, & Knirsch, 1997) found that only "complicated" or "poorly controlled" diabetes was associated with increased TB risk.

Numerous studies have presented convincing biological evidence in support of the causal relationship between DM and impaired host immunity to TB (Jeon & Murray, 2008). Studies in animal models have demonstrated that diabetic mice experimentally infected with M. tuberculosis have higher bacterial loads compared to euglycemic mice, regardless of the route of inoculation of M. tuberculosis (Yamashiro, et al., 2005) (Martens, et al., 2007). Compared to euglycemic mice, chronically diabetic mice also had significantly lower production of interferon-c (IFN-c) and interleukin-12 (IL-12) and fewer M. tuberculosis antigen (ESAT-6)-responsive T cells early in the course of M. tuberculosis infection, marking a diminished T helper 1 (Th1) adaptive immunity, which plays a crucial role in controlling TB infection (Martens, et al., 2007). In experimental studies of human plasma cells, high levels of insulin have been shown to promote a decrease in Th1 immunity through a reduction in the Th1 cell to Th2 cell ratio and IFN-c to IL-4 ratio (Viardot, Grey, Mackay, & Chisholm, 2007). Additionally, an ex vivo comparison study of production of Th1 cytokines showed that nonspecific IFN-c levels were significantly reduced in people with diabetes compared to controls without diabetes (Stalenhoef, et al., 2007). Another study indicated a dose–response relationship; levels of IFN-c were negatively correlated with levels of HbA1c (a measure of serum glucose levels over time in humans) (Tsukaguchi, Okamura, Ikuno, Kobayashi, & Fukuoka, 1997) . Furthermore, neutrophils from people with diabetes had reduced chemotaxis and oxidative killing potential than those of nondiabetic controls (Delamaire, et al., 1997), and leukocyte bactericidal activity was reduced in people with diabetes, especially those with poor glucose control (Rayfield, et al., 1982). Taken together, these studies strongly support the hypothesis that DM directly impairs the innate and adaptive immune responses necessary to counter the proliferation of TB.

2.4.2 Alcohol Consumption

A systematic review of observational studies on the link between alcohol consumption and risk of TB concluded that people who consume, on average, >40 g alcohol a day (heavy drinkers) and/or have an alcohol-use disorder have three times the risk of developing TB, while low-to-medium alcohol consumption does not seem to increase the risk of disease (Lönnroth K. , Williams, Stadlin, Jaramillo, & Dye, 2008). A subsequent narrative review of epidemiological studies, clinical research and animal studies concluded that this association seems to be causal (Rehm, et al., 2009). While the relative importance of adverse effects on the immune system of alcohol versus increased risk of transmission due to the pattern of social interactions among heavy drinkers is not clear, both factors are likely important (Creswell, et al., 2011). Heavy drinkers may be more exposed to M. tuberculosis in bars, prisons, shelters or other congregate settings. Alcohol use-related health disorders are associated with several clinical conditions that may impair the immune system. In addition, alcohol has a direct toxic effect on the immune system. Animal studies suggest that chronic and acute alcohol consumption impairs cell-mediated immunity and macrophage functions (which are essential for the host response to M. tuberculosis infection) (Szabo, 1997) (Mellencamp, 1996). Furthermore, heavy alcohol use may be a secondary cause of micro- and macronutrient deficiency, which can also impair immunity (Reider, 1999). Excessive alcohol use is also associated with poor TB treatment adherence, and a number of studies have found higher relapse rate among heavy drinkers and those with alcohol use-related health disorders (Rehm, et al., 2009). Alcohol misuse is associated with poor treatment adherence and a significantly amplified risk of relapse and death during and after tuberculosis treatment (Lönnroth K. , Williams, Stadlin, Jaramillo, & Dye, 2008). Though it would be plausible that this would also increase the risk of MDR-TB, there is presently no strong evidence base supporting this hypothesis.

2.4.3 Cigarette Smoking

Cigarette smoking, including passive smoking, has been associated consistently with an increased risk of M. tuberculosis infection, subsequent disease development, and poor treatment outcomes (Bates, et al., 2007). In addition, two recent systematic reviews on smoking and TB concluded that smokers have a two to three times elevated risk of TB, and that there is a dose–response relationship for both quantity of cigarettes and duration of smoking, after adjustment for alcohol intake and socioeconomic status (Lin, Ezzati, & Murray, 2007) (Slama, et al., 2007). There is also evidence linking passive smoking to higher TB risk, especially in children (Lin, Ezzati, & Murray, 2007). The biological explanation of the casual relationship between smoking, and tuberculosis infection and disease has been increasingly well documented. The tracheobronchial mucosal surface is a first level of host defense that prevents M. tuberculosis from reaching the alveoli. Tobacco and other environmental pollutants may impair this defense mechanism (Houtmeyers, Gosselink, Gayan-Ramirez, & Decramer, 1999). Smoke also impairs the function of pulmonary alveolar macrophages (Sopori, 2002). Nicotine is hypothesised to act directly on nicotinic acetylcholine receptors on macrophages to decrease intracellular tumour necrosis factor-a production and, thus, impair intracellular killing of M. tuberculosis (Wang, et al., 2003). It is still unclear if COPD is a risk factor for TB, independently from smoking (Inghammar, et al., 2010). However, TB history seems to be an independent risk factor for COPD (van Zyl-Smit1, Brunet, Pai, & Yew, 2010) (Lam, et al., 2010) (Willcox & Ferguson, 1989) (Pauwels, et al., 2001) (Snider, Doctor, Demas, & Shaw, 1971). COPD is, therefore, a marker for both smoking and previous TB (which also is a risk factor for future TB disease), and thus a predictor of risk.

Smoking also affects the chance of cure from TB. Severity of TB at the time of diagnosis and risk of relapse have been linked to smoking. In addition, a few studies have found that smokers have a higher risk of death from TB and other poor treatment outcomes than nonsmokers (Lin, Ezzati, & Murray, 2007). A number of studies from the UK and USA also found an independent association between COPD

comorbidity and death in TB patients, although others found no effect. Problems controlling for the effects of smoking may be partially to blame for the lack of clear evidence (Lo¨nnroth & Raviglione, 2008). In China, findings of a multiple risk factor modeling study assessing the effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis showed that complete gradual cessation of smoking and solid-fuel use by 2033 could avoid 26 million deaths from COPD and 6•3 million deaths from lung cancer and would reduce the projected incidence of tuberculosis in 2033 by 14–52% if 80% DOTS coverage were sustained (Lin, Ezzati, & Murray, 2007).

2.4.4 Malnutrition

Countries in epidemiological transition are affected adversely by both over-nutrition and under-nutrition. An individual who is either moderately to severely underweight or micronutrient-deficient is at increased vulnerability to develop tuberculosis, (Dye, Bourdin, Lönnroth, Roglic, & Williams, 2011) (Cegielski & McMurray, 2004) (Lönnroth K. , Williams, Cegielski, & Dye, 2010) (Cegielski, Arab, & Cornoni-Huntley, 2012) although evidence for the detrimental effect of milder nutrient deficiencies is less robust. A reanalysis was done of US National Health and Nutrition Examination Survey data gathered in 1971–75 and matched to tuberculosis outcomes in 1982–92 (Lutter & Lutter, 2012). Disease rates of 24.7 per 100 000 person-years (95% CI 13.0–36.3) were recorded in normal-weight individuals. After controlling for demographic, socioeconomic, and medical characteristics, adjusted hazard ratios in people who were underweight, overweight, and obese were 12.4 (95% CI 5.8–27.0), 0.3 (0.1–0.6), and 0.20 (0.1–0.6), respectively (Lutter & Lutter, 2012). The fact that malnutrition is very common in many parts of the world accounts for its large contribution to the attributable risk for TB. The effects of malnutrition, notably in utero and in early life, also take a major toll in the form of obesity, DM, hypertension, and heart disease in later life (Lutter & Lutter, 2012), thus serving to reinforce the double burden of disease in poorer countries and among disadvantaged subpopulations of wealthier nations.

CHAPTER THREE

METHODOLOGY

3.1 Study Area

The study sites were five health facilities spread across Kisii County, South Western Kenya. These health facilities were:

a. KisiiTeaching and Referral Hospital, a 379 – bed capacity Kenya Essential Package for Health (KEPH) Level 5 health facility,
b. Gucha District Hospital, a 50 – bed capacity KEPH Level 4 health facility,
c. Keumbu Sub District Hospital, a 32 – bed KEPH Level 4 health facility,
d. Iyabe District Hospital, a 12 – bed KEPH Level 3 health facility, and
e. Oresi Health Centre, a 10 – bed KEPH Level 3 health facility.

The study sites were selected from the health institutions that notified the highest number of TB cases in Kisii County during the year 2013.

3.2 Study Design

In this study, a case-control design was used because it's a less costly and less time-consuming study design and finally, the population of TB patients is dynamic since they can move to different places hence follow up can be difficult.

Cases were defined as current TB patients registered for treatment at the aforementioned health facilities, while controls were defined as persons from the catchment areas of the aforementioned health facilities and screened negative for TB.

3.3 Study Population

The study population included registered TB patients on treatment in the aforementioned health facilities and their catchment population.

3.4 Sampling Technique and Size

Since this was an unmatched case – control study, Kelsey formula Kelsey formula (Kelsey, Whittemore, Evans, & Thompson, 1996) was used to calculate the sample size for the study.

Number of TB cases, $n_1 = \{(Z_{\alpha/2}+Z_{1-\beta})^2 * \bar{p}q(r+1)\}/r(p_1-p_2)^2$ and number of controls, $n_2 = r*n_1$ (where: $Z_{\alpha/2} = 1.96$; $Z_{1-\beta} = 0.84$; r = 3:1; $p_1 = 13.2\%$; $p_2 = 3.6\%$ and $q_1 = 1-p_1$ while $q_2 = 1-p_2$).

The initial n_1 and n_2 of 61 TB cases and 183 controls were adjusted for non-response rate by 10%. Thus, number of TB cases for this study, $n_1 = 67$, while the number of controls, $n_2 = 201$; bringing the sample size to 268. Proportional probability to size method was used to allocate each health facility the numbers of TB cases and controls who were sampled.

Systematic sampling was used in this study because of its convenience and relative ease of administration. The sampling interval, *k*, was different for each of the five sites since the number of TB patients notified in each site was different.

3.5 Inclusion and Exclusion Criteria

The inclusion criteria for cases included:

- 18 years or more of age.
- Registered and was undergoing TB treatment.
- Ambulant patients.
- Persons who gave an informed consent to participate.

While the inclusion criteria for controls included:

- 18 years or more of age.

- Ambulant.
- Persons who gave an informed consent to participate.
- Screened negative for TB.
- Screened negative for HIV.

The exclusion criteria include:

- Any control who failed the symptomatic TB screening test.
- Screened positive for HIV.

3.6 Data Collection and Analysis

Demographic, alcohol consumption and cigarette smoking data was collected via a pretested structured questionnaire, whereas height (cm) and weight (kg) were measured during physical examination using standardized instruments. Capillary blood samples were drawn for testing blood glucose and cholesterol (HDL and total cholesterol) levels using Cardiochek PA ® machines (PTS Diagnostics Inc., USA). Data was entered into Open Data Kit (ODK) (University of Washington, USA) excel spreadsheet and uploaded to a web-based platform (https://ona.io) as a private project and then shared on Android-based tablets (Samsung Inc., South Korea) that had preinstalled KoBoCollect® application (http://www.kobotoolbox.org/). Data was collected from 16th September 2015 to 25th January 2016.

Descriptive analysis was done for sex, marital status, employment, tobacco use, alcohol consumption, physical activity, diet, level of education; while other measures of central tendency (mean) and dispersion as well as proportions was calculated for age, blood glucose and body mass index. Odds ratios (OR) and 95% confidence intervals (CI) was calculated for bivariate analysis with tobacco use, alcohol consumption, malnutrition and diabetes as independent variables and the outcome variable was TB. Multivariate analysis was calculated adjusting for other covariates such as age, sex, level of education and household size.

3.7 Ethical Issues

For this study, ethical approval and clearance was sought from Jaramogi Oginga Odinga Teaching and Referral Hospital Ethical Review Committee while the administrative approval was obtained from the County Health Department – Kisii. Further to that a written informed consent was sought from all participants of the study before they enrolled into the study without coercion. The written consent was translated into Kiswahili and explained to each and every participant. Strict confidentiality was maintained during data collection, management and dissemination. The filled in questionnaires were stored in a password protected private ONA account. In addition, individual patient identifiers were anonymized during the study. Further, study participants who were diagnosed to have any of the conditions being screened (TB, DM, HTN) were linked with relevant care for appropriate management.

One main benefit of the study to the participants was free screening for DM, TB, hypertension and obesity.

CHAPTER FOUR

RESULTS

4.1 Socio-demographic Characteristics of Study Participants

Between September 2015 and January 2016, a total of 273 potential participants (77 cases, 196 controls) were enrolled into the study. Of the 196 potential controls, three tested HIV positive and were excluded, and linked to HIV care while two were suspected to have TB during screening tests and linked with the laboratory for further diagnostic tests, leaving 191 eligible controls who were successfully recruited. All the 77 cases were successfully enrolled into the study.

The mean age of cases and controls was 33 (SD = 10.4) and 31 (SD = 9.6) years old respectively. Fifty cases (65%) were males, while 117 controls (61%) were females. Secondary education level was the most common for both cases (44%) and controls (41%). A majority of participants' households had three or less members (cases 75%, controls 79%). Participants' characteristics are shown in Table 4.1 shows the socio-demographic characteristics of the study respondents.

Table 4.1: Socio-demographic characteristics of study participants in Kisii County, South Western Kenya, 2016

Variable		Cases (n = 77) n (%)	Controls (n = 191) n (%)
Sex	Male	50 (65)	74 (39)
	Female	27 (35)	117 (61)
Age	Mean	32.79	31.21
	95% CI	30.44 – 35.15	29.84 – 32.58
Education Level	None	4 (5)	11 (6)
	Primary	19 (25)	48 (25)
	Secondary	34 (44)	79 (41)
	College/ University	19 (25)	53 (28)
	Post – Graduate	1 (1)	0 (0)
Household Size	≤ 3 members	58 (75)	150 (79)
	> 3 members	19 (25)	41 (21)

Key

CI Confidence Interval

Chi – square test of independence was used to analyze the frequencies of sex, education level, house hold size on one hand and DM on the other, to determine whether the two broad variables were independent. Being diabetic was independent of both education level and household size, while dependent on whether one was male or female. Further, the mean ages for diabetic and non-diabetic study participants were 37.50 (32.09 – 42.91) years and 31.29 (30.09 – 32.50) years respectively, but this difference was not statistically significant since they had an overlap in their 95% CI.

Table 4.2: Socio – demographic characteristics of the study participants stratified with regard to diabetes in Kisii County, South Western Kenya, 2016

Variable		Non – DM (n = 252) n (%)	DM (n = 16) n (%)	Pearson Chi	P value
Sex	Male	112 (44)	12 (75)	5.65	0.017
	Female	140 (56)	4 (25)		
Age	Median	29	37		
	Mean	31.29	37.50		
	95% CI	30.09 – 32.50	32.09 – 42.91		
Education Level	None	14 (6)	1 (6)	1.8664	0.76
	Primary	65 (26)	2 (13)		
	Secondary	106 (42)	7 (44)		
	Tertiary	66 (26)	6 (38)		
Household Size	≤ 3 members	195 (77%)	13 (81%)	0.1296	0.719
	> 3 members	57 (23%)	3 (19%)		

Key

Non - DM	Non- diabetes mellitus
DM	Diabetes Mellitus
CI	Confidence Interval

Chi – square test of independence was used to analyze the frequencies of sex, education level, household size on one hand and having ever smoked cigarettes on the other, to determine whether the two broad variables were independent. Having ever smoked cigarettes was independent of both education level and household size, while dependent on whether one was male or female. Further, the mean ages for study participants who had ever smoked cigarettes and never smoked cigarettes were 36.21 (32.98 – 39.43) years and 31.11 (29.85 – 32.37) years respectively, and this difference was statistically significant since there was no overlap in their 95% CI.

Table 4.3: Socio – demographic characteristics of the study participants stratified with regard to cigarette smoking in Kisii County, South Western Kenya, 2016

Variable		Never Smoked (n=239) n (%)	Ever Smoked (n=29) n (%)	Pearson Chi	P value
Sex	Male	96 (40)	28 (97)	33.07	0.000
	Female	143 (60)	1 (3)		
Age	Median	29	35		
	Mean	31.11	36.21		
	95% CI	29.85 – 32.37	32.98 – 39.43		
Education Level	None	14 (6)	1 (3)	6.9516	0.138
	Primary	65 (27)	2 (7)		
	Secondary	96 (40)	17 (59)		
	Tertiary	64 (26)	9 (31)		
Household Size	≤ 3 members	189 (79)	19 (66)	2.7377	0.098
	> 3 members	50 (21)	10 (34)		

Key

CI Confidence Interval

Chi – square test of independence was used to analyze the frequencies of sex, education level, household size on one hand and having ever consumed alcohol on the other, to determine whether the two broad variables were independent. Having ever consumed alcohol was independent of both education level and household size, while dependent on whether one was male or female. Further, the mean ages for study participants who had ever consumed alcohol and never consumed alcohol were 34.15 (32.04 – 36.26) years and 30.45 (29.04 – 31.86) years respectively, but this difference was statistically significant since they had no overlap in their 95% CI.

Table 4.4: Socio – demographic characteristics of the study participants stratified with regard to alcohol consumption in Kisii County, South Western Kenya, 2016

Variable		Never Consumed Alcohol (n = 180) n (%)	Ever Consumed Alcohol (n=88) n (%)	Pearson Chi	P value
Sex	Male	59 (33)	65 (74)	40.1320	0.0000
	Female	121 (67)	23 (26)		
Age	Median	29	32		
	Mean	30.45	34.15		
	95% CI	29.04 – 31.86	32.04 – 36.26		
Education Level	None	11 (6)	4 (5)	4.1715	0.383
	Primary	41 (23)	26 (30)		
	Secondary	73 (41)	40 (45)		
	Tertiary	55 (30)	18 (20)		
Household Size	$\leq$ 3 members	140 (78)	68 (77)	0.0087	0.926
	> 3 members	40 (22)	20 (23)		

Key

CI Confidence Interval

Chi – square test of independence was used to analyze the frequencies of sex, education level, household size on one hand and whether one was malnourished or not on the other, to determine if the two broad variables were independent. Malnutrition was independent of both sex and household size, while dependent on one's education level. Further, the ages for study participants who were malnourished and well-nourished were 34.76 (30.72 – 38.79) years and 31.49 (30.23 – 32.75) years respectively, but this difference was not statistically significant since there was an overlap in their 95% CI.

Table 4.5: Socio – demographic characteristics of the study participants stratified with regard to malnutrition in Kisii County, South Western Kenya, 2016

Variable		Nourished (BMI≥18.5) (n = 210) n (%)	Malnourished (BMI < 18.5) (n = 41) n (%)	Pearson Chi	P value
Sex	Male	96 (46)	23 (56)	1.4833	0.223
	Female	114 (54)	18 (44)		
Age	Median	29	32		
	Mean	31.49	34.76		
	95% CI	30.23 – 32.75	30.72 – 38.79		
Education Level	None	9	6	9.5247	0.049
	Primary	49	12		
	Secondary	90	17		
	Tertiary	62	6		
Household Size	≤ 3 members	160	33	0.3565	0.550
	> 3 members	50	8		
Key					
BMI	Body Mass Index				
CI	Confidence Interval				

4.2 Diabetes Mellitus as a Covariate for Tuberculosis in Kisii County

Out of the 268 study participants, 16 (6%) had DM. Twenty-four (9%) of the study participants had ever had a blood sugar test. Out of the 24 who had ever had a blood sugar test, only two were told to have had a high blood sugar level and both were on treatment for diabetes, yet were still picked up as DM.

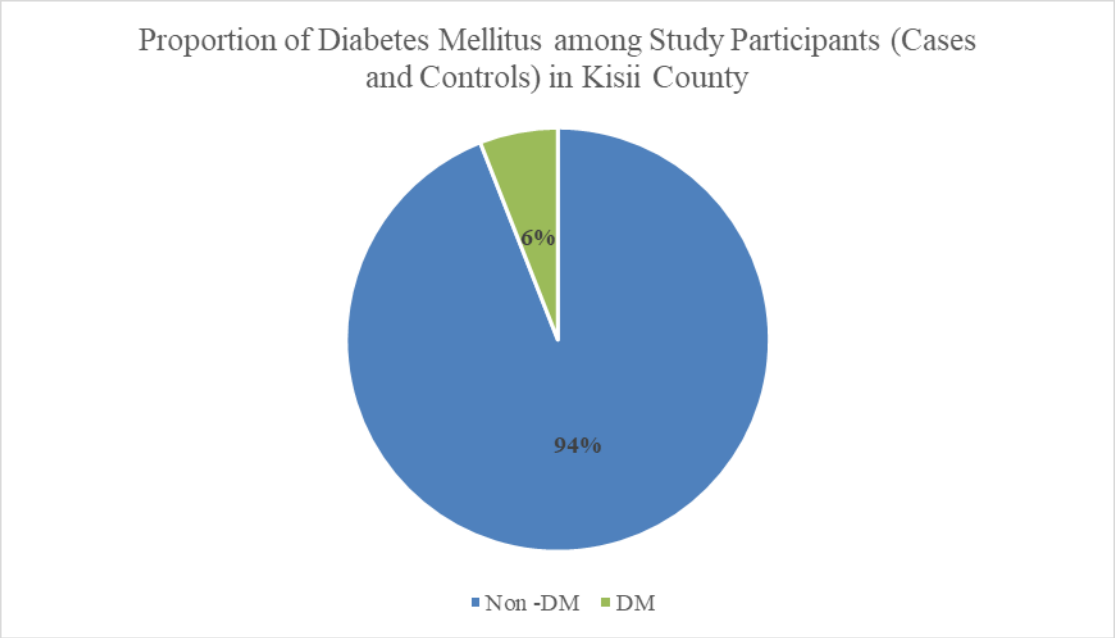

Figure 4.1: Proportion of Diabetes Mellitus among Study Participants (Cases and Controls) in Kisii County

Of the diagnosed DM study participants, 10 (13%) were cases while 6 (3%)controls. The adjusted odds of having TB given one was diabetic was four times, after adjusting for other covariates: age, sex, level of education and household size (OR=3.57, 95% CI: 1.18 – 10.73).

Table 4.6: Association between Diabetes Mellitus and Tuberculosis in Kisii County, South Western Kenya, 2016

Variable		Cases n (%)	Controls n (%)	Unadjusted OR	Adjusted OR	
					Model 1	Model 2
DM	Yes	10 (13)	6 (3)	4.60 (1.44-15.92)	3.47 (1.17 - 10.30)	3.57 (1.18 – 10.73)
	No	67 (87)	185 (97)			
	Total	77 (100)	191 (100)			

Model 1= adjusted for age and sex
Model 2= adjusted for model 1, education and household size

Key

DM Diabetes Mellitus

OR Odds Ratio

4.3 Cigarette Smoking as a Covariate for TB in Kisii County

Of the 268 study participants, 8 (3%) were currently smoking cigarettes; while 21 (8%) had a past history of smoking cigarettes. These were combined into a new variable, ever smoked cigarettes, since the numbers that were currently smoking cigarettes was not adequately powered. A total of 29 (11%) study participants had ever smoked cigarettes.

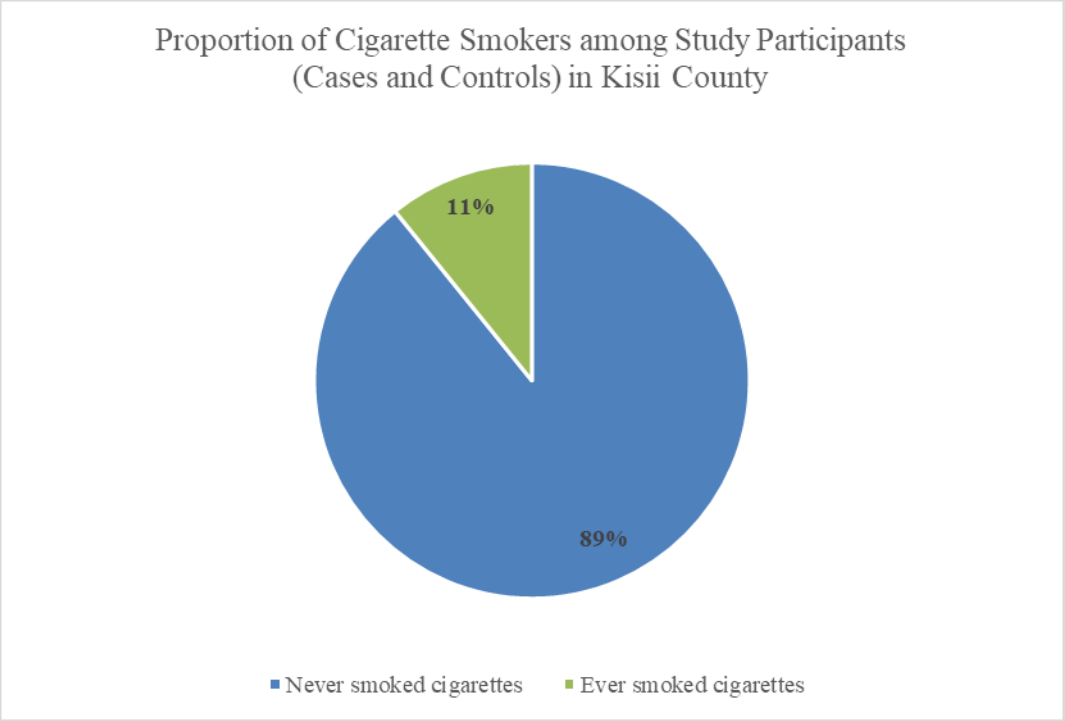

Figure 4.2: Proportion of Cigarette Smokers among Study Participants (Cases and Controls) in Kisii County

Of study participants who had ever smoked cigarettes, 17 (22%) were cases while 12 (6%) were controls. After adjusting for other covariates: age, sex, level of education and household size, the odds of having TB given one had ever smoked was thrice (OR=2.70, 95% CI: 1.12 – 6.47), statistically significant since the 95% CI did not include 1.0.

Table 4.7: Association between Cigarette Smoking and Tuberculosis in Kisii County, South Western Kenya, 2016

Variable		Cases n (%)	Controls n (%)	Unadjusted OR	Adjusted OR	
					Model 1	Model 2
Ever smoked	Yes	17 (22)	12 (6)	4.23 (1.77 – 10.24)	2.63 (1.12 - 6.17)	2.70 (1.12 – 6.47)
	No	60 (78)	179 (94)			
	Total	77 (100)	191 (100)			

Model 1= adjusted for age and sex
Model 2= adjusted for model 1, education and household size

Key

OR Odds ratio

4.4Alcohol Consumptionas a Covariate for TB in Kisii County

Of the 268 study participants, 88 (33%) had ever consumed alcohol while a majority, 180 (67%) had never consumed alcohol.

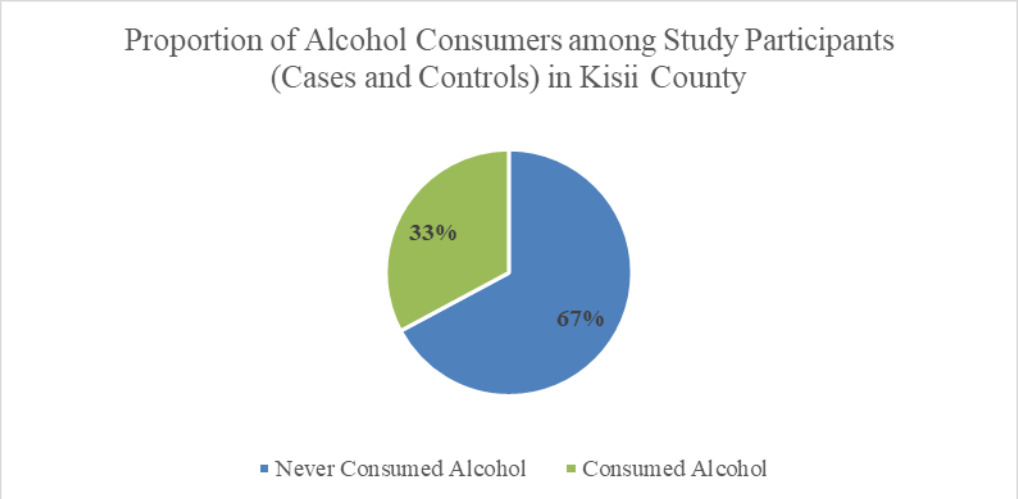

Figure 4.3: Proportion of Alcohol Consumption among Study Participants (Cases and Controls) in Kisii County

Of the 88 (33%) of the study participants had ever consumed alcohol, 36 (47%) were cases while 52 (27%) were controls. After adjusting for other covariates: age, sex, level of education and household size, the odds of having TB given one was taking alcohol was twice (OR=1.62, 95% CI: 0.88-2.99), which was statistically insignificant, since it covered 1.0.

Table 4.8: Association between Alcohol Consumption and Tuberculosis in Kisii County, South Western Kenya, 2016

Variable		Cases n (%)	Controls n (%)	Unadjusted OR	Adjusted OR	
					Model 1	Model 2
Alcohol	Yes	36 (47)	52 (27)	2.35 (1.30 – 4.21)	1.61 (0.88 - 2.96)	1.62 (0.88 – 2.99)
	No	41 (53)	139 (73)			
	Total	77 (100)	191 (100)			

Model 1= adjusted for age and sex

Model 2= adjusted for model 1, education and household size

Key

OR Odds ratio

4.5 Malnutrition as a Covariate for Tuberculosis in Kisii County

During data analysis, the body mass index (BMI) was calculated. During this process, 17 results were dropped since they either had a weight of less than 20 kg, height of less than 100 cm or the values were missing completely, this left 251 values to be evaluated. Of the remaining 251 study participants, 41 (16%) were

malnourished (BMI < 18.5 kg/m^2) while a majority, 210 (84%) were well nourished (BMI $\geq$ 18.5 kg/m^2).

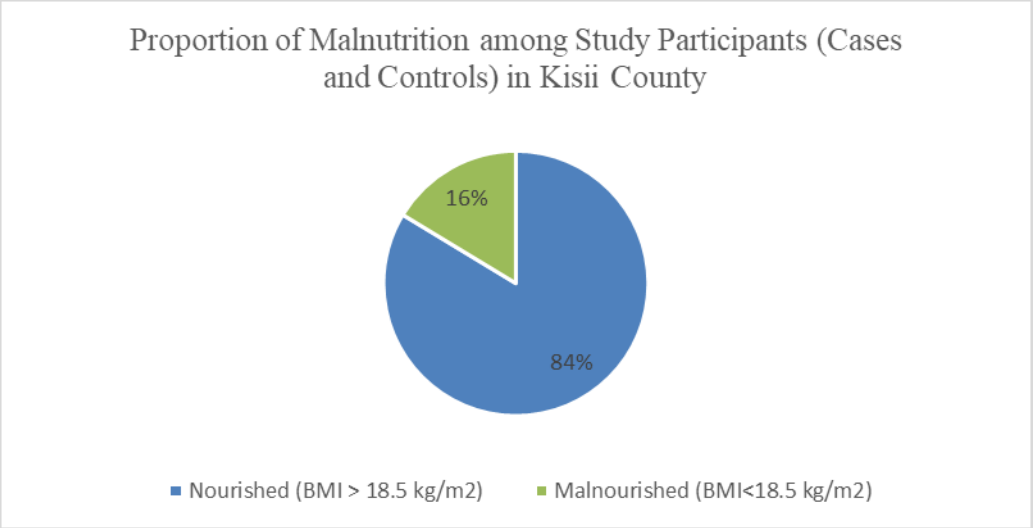

Figure 4.4: Proportion of Malnutrition among Study participants (Cases and Controls) in Kisii County

Of the 41 (16%) of the study participants who were malnourished, 31 (42%) were cases while 10 (3%) were controls. After adjusting for other covariates: age, sex, level of education and household size, the odds of having TB given one was malnourished was fifteen times (OR=14.53, 95% CI: 6.21-33.97), which was statistically insignificant, since it did not cover 1.0.

Table 4.9: Association between Malnutrition and Tuberculosis in Kisii County, South Western Kenya, 2016

Variable		Cases n (%)	Controls n (%)	Unadjusted OR	Adjusted OR	
					Model 1	Model 2
Nutrition (BMI)	< 18.5	31 (42)	10 (3)	12.40 (5.34 – 30.32)	12.66 (5.61 - 28.61)	14.53 (6.21 – 33.97)
	$\geq$ 18.5	42 (58)	168 (97)			
	Total	73 (100)	178 (100)			

Model 1= adjusted for age and sex

Model 2= adjusted for model 1, education and household size

Key

OR Odds ratio

BMI Body Mass Index

4.5 Multivariate Analysis of All Covariates for Tuberculosis in Kisii County

After multivariate analysis that adjusted for all variables and covariates; DM, cigarette smoking, alcohol consumption, malnutrition, age, sex, education level and household size, only DM and malnutrition remained statistically significant with adjusted ORs of 6.30 (1.94 – 20.48) and 16.68 (6.97 – 39.88). While cigarette smoking dropped off with an adjusted OR of 1.58 (0.52 – 4.78).

Table 4.10: Multivariate Analysis of All Covariates for Tuberculosis in Kisii County

Variable	Adjusted OR	P - value	95% CI
DM	6.30	0.02	1.94 – 20.48
Ever smoked cigarettes	1.59	0.42	0.52 – 4.78
Consume Alcohol	1.35	0.45	0.62 – 2.92
Malnourished (BMI<18.5 kg/m^2)	16.68	0.00	6.97 – 39.88
Sex	0.56	0.12	0.27 – 1.15
Education Level	1.18	0.48	0.74 – 1.85
Household Size	1.60	0.22	0.75 – 3.41
Respondent Age	0.99	0.61	0.95 – 1.03

Key

OR Odds Ratio

CI Confidence Interval

DM Diabetes Mellitus

BMI Body Mass Index

CHAPTER FIVE

DISCUSSION CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

This study showed that DM and malnutrition were positively associated with a higher chance of getting TB. Malnutrition was associated with the highest likelihood of having TB among all the exposures assessed. Smoking and alcohol showed increased odds for TB that was not significant, their role cannot be ignored since we had a small sample size that was further thinned out by stratification.

The study participants' sociodemographic characteristics were similar to the sociodemographic characteristics of TB patients notified by the National Tuberculosis and Leprosy Program (National Tuberculosis, Leprosy and Lung Disease Program, 2014).

This is one of the first observational studies to examine the association of TB with diabetes mellitus, and to explore NCD risk factor specific correlates of TB in sub – Saharan Africa. This study provides evidence of a positive association of TB with DM that is in line with prior studies: adjusted hazard ratio for TB 2.09 (1.10 – 3.95) (Baker, Lin, Chang, & Murray, 2012); OR for TB 2.44 (1.17 – 5.09) matched for age and sex (Shetty et al., 2006); AOR for TB 3.8 (2.3 – 6.1) adjusted for steroid use, smoking, body mass index, pulmonary diseases and immunosuppressive use (Jick, Lieberman, Rahman, & Choi, 2006); OR for TB 7.83 (6.55 – 9.37) (Jabbar, Hussain, & Khan, 2006); and AOR for TB 7.83 (2.37 – 25.9) controlling for assets, overcrowding, employment, and financial security (Coker, et al., 2006). The strength of this association is in line with a population-based cohort study from Hong Kong (Leung, et al., 2008) and a review of 13 previous smaller observational studies (Jeon & Murray, 2008) found diabetes to be associated with increased risk of TB, with relative risk estimates varying considerably from 1.2 to 7.8, with the lowest estimates reported in the larger studies.

In addition, the study found positive association, though not significant in all models, of TB with cigarette smoking. In prior studies, TB has been associated with cigarette smoking RR for TB 2.33 (1.97 – 2.67) (Bates, et al., 2007). Finally, we found positive association, though not significant in all models, of TB with alcohol consumption.

Further, this study provided evidence of positive association of TB with malnutrition, that has been elucidated in prior studies that had adjusted hazard ratio for TB 12.43 (5.75 - 26.95) (Cegielski, Arab, & Cornoni-Huntley, 2012). Reanalysis done of US National Health and Nutrition Examination Survey data gathered in 1971–75 and matched to tuberculosis outcomes in 1982–92 (Lutter & Lutter, 2012). Disease rates of 24.7 per 100 000 person-years (95% CI 13.0–36.3) were recorded in normal-weight individuals. After controlling for demographic, socioeconomic, and medical characteristics, adjusted hazard ratios in people who were underweight, overweight, and obese were 12.4 (95% CI 5.8–27.0), 0.3 (0.1–0.6), and 0.20 (0.1–0.6), respectively (Lutter & Lutter, 2012). Both malnutrition and DM are associated with weakened immunity that predisposes one to TB and in such cases mounting immune responses and immune recovery are suboptimal.

Finally, the wide confidence intervals of these associations reflect the small sample size and also the fact that not much may be known about these associations in this population. While these observations may be due to flaws of sample size, the fact that sex modifies these associations warrants further studies to investigate these relationships in more detail.

5.2 Conclusion

a) The mean age of cases and controls was 33 (SD = 10.4) and 31 (SD = 9.6) years old respectively. Fifty cases (65%) were males, while 117 controls (61%) were females. Secondary education level was the most common for both cases (44%) and controls (41%). A majority of participants' households had three or less members (cases 75%, controls 79%).

b) Sixteen (6%) of all study participants had DM.

c) Twenty-nine (11%) of all study participants had smoked cigarettes.

d) Eighty – eight (33%) of all study participants had consumed alcohol.

e) Forty – one (16%) of all study participants were malnourished with a BMI$\leq$ 18.5 kg/m^2.

5.3 Recommendations

Despite limitations, this study shows there is need to understand the relationship between NCDs, and their risk factors and diabetes in resource limited settings battling with a double burden of NCDs and communicable diseases. Globally, with an estimated 450 million people who have diabetes, a figure expected to increase by 50% by year 2040, it is clear that DM constitutes a substantial contributor to the current and future global burdens of TB. The contribution of DM to the burden of TB may be even higher in countries such as India and China where the incidence TB is greater and mean age is lower. Larger studies will need to be undertaken to provide sufficient sample size and power to demonstrate these associations. Kenya, conducted her first STEPwise survey which indicated that prevalence of DM is 1.9% (Ministry of Health, 2015), indicating that approximately 1 million Kenyans are diabetic; this necessitates that more efforts have to be put in integration of diabetic care with TB treatment.

In addition, multisectoral initiatives are needed to mitigate against adult malnutrition, since it is a clear risk factor to the development of TB. Further, the government has enacted stringent anti-smoking laws and whose full effect will be evaluated after the second Global Adult Tobacco Survey – Kenya (GATS) is conducted. The initial GATS, a cross – sectional survey was conducted in 2014, seven years after the enactment of Tobacco Control Act of 2007 and it acted as a baseline. Moving forward, if the Tobacco Regulations of 2014 are implemented, then this survey will be able to measure the impact.

The key limitation of this study was that the design could not directly compute incidence rates of disease in exposed and non-exposed individuals since it was not population based. In addition, temporal relationship between exposure and disease was difficult to establish. Finally, this study design may have been prone to both selection and recall bias.

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APPENDICES

Appendix A: Informed Consent Form

Evaluation of Factors Associated with Tuberculosis in Kisii County

WRITTEN CONSENT FORM

The study you are about to participate in is a research study conducted by Dr. Kadondi Kasera, of the Field Epidemiology Laboratory Training Program to improve the understanding of the overlap between non – communicable diseases, and a chronic infectious disease, tuberculosis (TB). It is critical to understand the level of inter linkages within our own set up.

Should you agree to participate in this study, you will be asked to go through a detailed history through a structured questionnaire, a clinical examination at the time of the inclusion, height and weight measurements. Three drops of capillary blood sample will also be taken to measure blood sugar and lipid levels at the point of care. You will also be screened for HIV. The process of collecting the capillary blood sample will cause you a little pain and discomfort. If you are diagnosed with diabetes mellitus through random blood sugar test, HIV, high blood pressure or TB, you will be linked to the relevant department for continuation of care.

All data collected from you will be coded in order to protect your identity. Only **Dr. Kadondi Kasera** will have access to the information. At the end of the study there will be no way to link your name with your data. Any additional information about the study will be provided to you including the final results.You are free to withdraw or refuse to answer any question at any time without any consequences. Should you agree to participate in the study, please sign your name below, indicating that you have read and understood the nature of the study, your responsibilities as study participant, the inconveniences associated with the voluntary participation in the study and that all your questions and concerns concerning the study have been answered satisfactorily. You will receive a copy of this signed consent form to take away with you.

If you have any questions, you can reach **Dr. Kadondi Kasera on 0722994573**

Signature of the study participant and date **Thumbprint of the study participant**

Appendix B: Questionnaire

Evaluation of Factors Associated with Tuberculosis inKisii County

Questionnaire

GENERAL INFORMATION		
Form Number		**CODE**
Date of completion of the instrument	*dd-mm-year*	I1
Health facility name		12
Has informed consent been obtained?	Yes	13
	No, if NO END	
Is the study participant a case or control?	Case	I4
	Control, if control go to I5	
TB Screening among Community Controls If Y to ANY, END. Send to the laboratory for sputum AFB test. If N, go to I8.	Cough of any duration (Y/N)	I5
	Fever (Y/N)	
	Noticeable weight loss (Y/N)	
	Night sweats (Y/N)	
HIV screening among Community Controls If HIV Positive, link up with HIV, END. Link up with HIV care and treatment. If Negative, go to I7.	HIV Positive	I6
	HIV Negative	
RESPONDENT DEMOGRAPHIC INFORMATION		
Respondent Name		I7
Sex	Male	C1
	Female	
Date of Birth (dd-mm-year)		C2

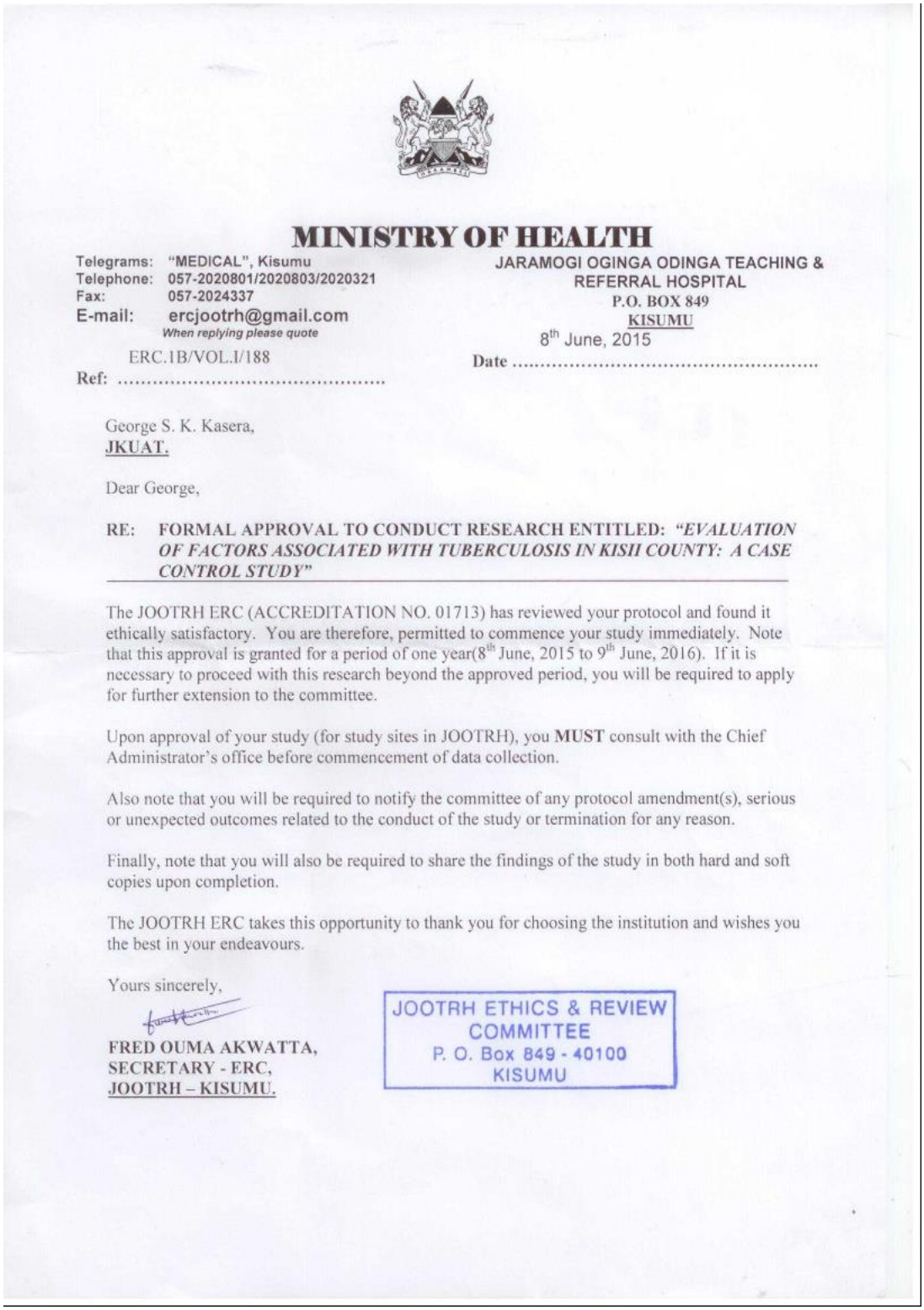
How old are you? (Years)		C3
What is the highest level of education you have completed	No formal schooling	C4
	Primary	
	Secondary	
	College/ University	
	Post Graduate	
	Declined	
How many people older than 18 years, including yourself, live in your household?	Number of people	C5

BEHAVIOURAL MEASUREMENTS: Tobacco Use		
Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes	Yes	T1
	No, if NO go to T2	
In the past, did you ever smoke any tobacco products	Yes	T2
	No	
BEHAVIOURAL MEASUREMENTS: AlcoholConsumption		
Have you ever consumed any alcohol such as beer, wine, spirits, chang'aa or busaa	Yes	A1
	No	
Have you consumed any alcohol within the past 12 months	Yes	A2
	No	
Have you consumed any alcohol within the past 30 days?	Yes	A3
	No	
HISTORY OF DIABETES		
Have you ever had your blood sugar measured by a doctor or other health worker?	Yes	H1
	No	
Have you ever been told by a doctor or other health worker that you have raised blood sugar or diabetes?	Yes	H2
	No	
Have you been told in the past 12 months?	Yes	H3

	No	
In the past two weeks, have you taken any drugs for diabetes prescribed by a doctor or other health worker?	Yes, If Yes, go to H5	H4
	No	
What diabetes medication prescribed by a doctor or other health worker are you currently taking?	Biguanides (Metformin)	H5
	Alpha Glucosidase Inhibitors (Arcabose | Miglitol)	
	Dipeptidyl peptidase IV Inhibitors (Sitagliptin)	
	Thiazolidinediones (Rosiglitazone | Pioglitazone)	
	Insulin	
	GLP - I agonist (Exenatide)	
	Amylin agonist (Pramlintide)	
	Sulfonylureas (Chlorpropamide | Tolazamide | Tolbutamide | Glimipiride | Glipizide | Glyburide)	
	Non - Sulfonylureas (Repaglinide | Nateglinide)	
Have you ever seen a traditional healer for diabetes or raised blood sugar?	Yes, If Yes, go to H7	H6
	No	
Are you currently taking any herbal or traditional remedy for your diabetes?	Yes	H7
	No	
PHYSICAL MEASUREMENTS (HEIGHT & WEIGHT)		

For women: Are you pregnant?	Yes	M1
	No	
Height (Cm)		M2
Weight (Kg)		M3
BIOCHEMICAL MEASUREMENTS (BLOOD GLUCOSE)		
During the past 12 hours, have you had anything to eat or drink, other than water?	Yes	B1
	No	
Random Blood Glucose (mg/dL)		B2

Appendix C: JOORTH ERC Study Approval Letter



MINISTRY OF HEALTH

Telegrams: "MEDICAL", Kisumu
Telephone: 057-2020801/2020803/2020321
Fax: 057-2024337
E-mail: ercjootrh@gmail.com
When replying please quote

JARAMOGI OGINGA ODINGA TEACHING & REFERRAL HOSPITAL
P.O. BOX 849
KISUMU

ERC.1B/VOL.I/188
Ref: .....

8th June, 2015
Date .....

George S. K. Kasera,
JKUAT.

Dear George,

RE: FORMAL APPROVAL TO CONDUCT RESEARCH ENTITLED: *"EVALUATION OF FACTORS ASSOCIATED WITH TUBERCULOSIS IN KISII COUNTY: A CASE CONTROL STUDY"*

The JOOTRH ERC (ACCREDITATION NO. 01713) has reviewed your protocol and found it ethically satisfactory. You are therefore, permitted to commence your study immediately. Note that this approval is granted for a period of one year(8th June, 2015 to 9th June, 2016). If it is necessary to proceed with this research beyond the approved period, you will be required to apply for further extension to the committee.

Upon approval of your study (for study sites in JOOTRH), you **MUST** consult with the Chief Administrator's office before commencement of data collection.

Also note that you will be required to notify the committee of any protocol amendment(s), serious or unexpected outcomes related to the conduct of the study or termination for any reason.

Finally, note that you will also be required to share the findings of the study in both hard and soft copies upon completion.

The JOOTRH ERC takes this opportunity to thank you for choosing the institution and wishes you the best in your endeavours.

Yours sincerely,

FRED OUMA AKWATTA,
SECRETARY - ERC,
JOOTRH – KISUMU.

JOOTRH ETHICS & REVIEW COMMITTEE
P. O. Box 849 - 40100
KISUMU