THE PREVALENCE AND RISK FACTORS OF DIABETES MELLITUS AMONG TUBERCULOSIS PATIENTS AT UBUNTU CLINIC, KHAYELITSHA

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PART 0: PREAMBLE

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0.2 DECLARATION

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

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0.3 ACKNOWLEDGEMENTS

The support of the South African DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to SACEMA.

This study was a subset of a case control study of which Dr Oni, also my supervisor, was the principal investigator. She was responsible for the study design and leading the team of clinical research workers and the study doctors who recruited the patients and collected data. I would like to thank the team for working tirelessly to make this study possible. I would also like to thank Dr Oni for allowing me to use this data for this part of my study. Lastly, I would like to thank her for her mentorship and support throughout my Masters studies. Also, for her time, patience and guidance in the writing of this dissertation.

I contributed to data capturing when assistance was required, I was responsible for analysing the data and writing of this dissertation.

0.4 ABSTRACT

Summary: There is strong evidence suggesting that diabetes mellitus (DM) triples the risk of tuberculosis (TB) disease and worsens TB outcomes. South Africa carries a heavy burden of TB which is primarily driven by the human deficiency virus (HIV). The burden of non-communicable disease is also growing rapidly in South Africa. There is however lack of up to date data on the burden of DM and the associated risk factors among TB patients. This dissertation is based on a cross-sectional study which sought to assess the prevalence of DM and impaired glucose tolerance (IGT) and determine the risk factors associated with DM among TB patients.

Methods: This cross sectional study forms part of a case control study that aimed to assess the association between DM and TB and the population attributable risk of TB due to DM in Khayelitsha, a high HIV and TB setting. The TB patients recruited in the case control study formed the population of this current cross-sectional study. Based on oral glucose tolerance test, fasting blood glucose, glycated haemoglobin and self-report the prevalence of DM was determined. Bivariate and multivariate logistic regression analyses were performed to assess risk factors associated DM among TB patients. Due to significant differences between male and females with respect to various characteristics, we also stratified the data by sex during analysis.

Results: The prevalence of DM among the TB patients was 39/288 (13·54%; 95% confidence interval (CI) 10·03-18·03%); DM was previously diagnosed in 11/39 of the DM patients and 6/11 of these were receiving DM medications. The prevalence of IGT was 139/288 (48·26%; 95% CI 42·51-54·07%). Common co-existing conditions among the patients were

hypertension (18·06%; 95% CI 14·01-22·96%) and HIV (64·31%; 58·52-69·71%). On multivariate analysis, positive family history of DM (odds ratio (OR): 3·20, 95% CI 1·61-8·83, p=0·025), hypertension (OR 4·49; 95% CI 1·536-13·147; p=0·006) and waist circumference (OR: 1·03; 95% CI 1·00-1·06; p=0·027) were significantly associated with DM. In the multivariate model for females, only gestational DM was (OR 14·55; 95% CI 2·03-103·59; p=0·008) was associated with DM and in the model for males, hypertension (OR 3·30; 95% CI 1·17-9·33; p=0·024) and the age category > 45 years (OR 11·05; 95% CI 2·09-58·35; p=0·005) were associated with DM. There were no interactions between sex and BMI.

Conclusions: The high prevalence of IGT highlights the likely trajectory of DM prevalence without intervention. With strong evidence that DM increases the likelihood of TB disease and has adverse effects on TB outcomes, the growing burden of DM in a high HIV and TB burden settings such as ours pose threats to TB control. Interventions need to prioritise DM screening and management for high risk groups: risk groups (patients with: hypertension, family history of DM, high waist circumference; men with age > 45 years and hypertension; females with gestational DM) may be efficient. Interventions to prevent the development of DM among patients with ITG will also be essential. It is recommend that our health systems consider an integrated system to manage chronic diseases such as TB, HIV, hypertension and DM collaboratively.

0.5 LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AFB	Acid-fast bacilli
ART	Antiretroviral therapy
ARV	Antiretroviral
BMI	Body mass index calculated as weight (kg)/height^2 (m^2)
CI	Confidence interval
DCCT	Diabetes Control and Complications Trial
EAP	East Asia and Pacific
HIV	Human immunodeficiency virus
HR	Hazard ratio
ID	Infectious disease
INH	Isoniazid
IQR	Interquartile range
ITG	Impaired glucose tolerance
LAC	Latin America and Caribbean
LIC	Low income country
LTBI	Latent tuberculosis infection
MENA	Middle East and North Africa
MIC	Middle income country
MDG	Millennium Development Goals
MRD	Multi drug resistance
M.tb.	*Mycobacterium tuberculosis*
NCD	Non-communicable disease
NGSP	National Glycohemoglobin Standardisation Programmes

NHLS	National Health Laboratory Serveices
NTP	National Tuberculosis Programme
OR	Odds ratio
RR	Relative risk
SAS	South Asia
SSA	Sub- Saharan Africa
VS	Versus
WHO	World Health Organisation

0.6 LIST OF DEFINITIONS

Terms	Abbreviation	Definitions as per (1–3)
Clinically diagnosed TB		People who are started on TB treatment without bacteriological confirmation of disease. This includes patients started on treatment based on: • chest x-ray abnormalities that are consistent with active TB • the history and clinical picture suggestive of PTB or EPTB • histological and biochemical tests suggestive of TB (2).
Diabetes mellitus	DM	A chronic disease which arises when the pancreas does not produce enough insulin or when the body cannot use the produced insulin effectively. The main types of DM are type 1 and 2. People with type 1diabetes do not produce enough insulin. People with type 2 diabetes produce insulin but cannot use it effectively (1).
Impaired glucose tolerance	IGT	People whose blood glucose levels are high but not as high as those in people with diabetes are said to have impaired glucose tolerance (commonly referred to as IGT) or also impaired fasting glucose (IFG) (1).
Extra-pulmonary tuberculosis	ETB	TB disease involving organs other than the lungs: e.g. pleura, lymph nodes, abdomen, genito - urinary tract, skin, joints and bones and meninges (2).
Fasting Plasma (Blood) Glucose	FPG/FBG	Measure of glucose level after no eating for at least 8 hours (1).
Glycosylated haemoglobin	HBA1c	HbA1c reflects average plasma glucose over the previous eight to 12 weeks. This test can be performed at any time of the day and does not require any special preparation such as fasting (4).
Latent TB infection	LTB	When one has TB infection but does not show symptoms of TB and is not infectious but is at risk of developing active disease and becoming infectious (3).
Oral glucose tolerance test	OGTT	A test which measures how well the body is able to metabolise glucose or sugar (2).
Pulmonary tuberculosis	PTB	TB disease involving the lung parenchyma.
Relapse		Reactivation of latent TB.
Smear negative PTB		Smear microscopy negative for AFBs (2).
Smear positive PTB		A positive acid-fast bacilli (10-99 AFB per 100 oil immersion fields) in at least one sputum smear microscopy(2).
Sputum culture conversion date		The collection date of the first sputum sample that is reported as negative, after a previous positive culture for TB (2).
Tuberculosis	TB	An infectious disease caused by the bacterium *Mycobacterium tuberculosis (Mtb)* that is mainly transmitted through inhalation and is characterized by cough, fever, shortness of breath, weight loss, and the appearance of inflammatory substances and tubercles in the lungs (3).
Xpert MTB/RIF		An automated molecular platform to detect *Mtb* and rifampicin resistance testing by targeting specific mutations. It is approved for use directly on raw sputum and results should be available within 2 hours in the laboratory but available in health facilities within 48 hours (2).

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PART A: STUDY PROTOCOL

A.1 Background

Tuberculosis (TB) remains the deadliest infectious bacterial disease worldwide, causing approximately 9 million new infections and 1.5 million deaths each year (3). Although the global TB incidence trend is declining (3), TB remains a major health problem in most low- and middle- income countries (LICs and MICs). South Africa (SA) is one of these countries and is ranked among the highest TB burdened countries and was listed among the top six countries with high TB incidence reporting between 410 000 and 520 000 new cases in 2013 (3). Factors that continue to fuel the TB epidemic include low socio-economic conditions such as malnutrition, overcrowding and poor housing (5). Other factors include alcoholism, silicosis, tobacco use, and immunosuppressive conditions such as the human immunodeficiency virus (HIV) and diabetes mellitus (DM) (3,6).

Strong evidence suggests that DM, increases the risk of TB disease (7,8). A systematic review of cohort studies showed that DM triples (relative risk (RR) 3.11, 95% confidence interval (CI): 2.27 – 4.26) the risk of TB disease (9). In India, it was estimated that DM accounts for approximately 15% of pulmonary TB cases (11). It has also been shown that screening for DM among TB patients yields a prevalence of DM ranging between 1.9% and 39% (10). The biological plausibility of this TB-DM association is based on hypotheses that DM patients have impaired immune response, dysfunction of alveolar macrophages, micronutrient deficiency and pulmonary microangiopathy (12,13). Adverse effects on TB outcomes such as the increased risk of treatment failure, relapse, resistance and death are also attributed to DM (14,15). There are other suggestions that TB may induce DM by impairing glycaemic control especially during critical illness (13,16), hence complicating the assessment of the DM-TB association.

The World Health Organisation (WHO) recommends bi-directional screening of TB and DM (12), however most countries still lack integrated health systems for co-managing both non – communicable diseases (NCDs) and infectious diseases (IDs) (17). This link between TB and DM could therefore provide an opportunity for co-management of these diseases and to improve care by early case detection, better clinical management and easier access to treatment of both conditions (17,18).

It must be noted that the association between TB and DM emerged almost a thousand years ago (19). However the discovery of insulin and antibiotics to manage DM and TB respectively, reduced the urgency towards further investigations to better understand this link (20). The link between these two diseases has become more apparent and significant in recent years as the global burden of DM is rapidly increasing in developing countries where TB remains prominent. While it is known that 95% of TB cases are from LICs and MICs (3), almost 80% of DM cases are also from these countries (1).

The global burden of DM is rapidly increasing and is expected to increase further in LICs and MICs where rapid development and urbanisation are currently taking place. The burden of DM globally and in Africa was estimated at 382 million and 19.8 million in 2013 and is projected to increase to 592 million and 41.4 million in 2030, respectively (1). In Sub-Saharan Africa, SA is reputed to have among the highest prevalence of DM, with approximately 2.6 million people living with DM (1). This rapid growth of DM disease, especially type 2 DM is attributed to nutritional and lifestyle transitions which involve increased consumption of refined fats and sugars combined with physical inactivity, increasing levels of obesity, alcohol consumption and smoking (21–24).

Diabetes mellitus and TB provide a good example of an interaction between an ID and an NCD which may be mediated by common risk factors such as poor nutrition, smoking and alcohol (18). These interactions contribute to the ongoing epidemiological transition taking place in most LICs and MICs, which is characterised by increasing multi-morbidity of chronic IDs and NCDs. Given the evidence that DM increases the risk of TB, the increasing burden of DM in countries already burdened by TB is a potential threat to current TB control measures and may imply a heavier strain on the country's health systems.

The Millennium Development Goals (MDG) included targets to reduce the global TB incidence, and to halve the prevalence and death due to TB by the year 2015 in comparison with 1990 levels (3). Although the TB incidence in declining, it is at a very slow rate (3), and the latter targets of halving deaths and prevalence by 2015 compared to 1990 were not met (25). These goals were not achieved partly due to the prevailing need to address other risk factors of TB. A mathematical modelling study reported results suggesting that if interventions reduce the incidence of DM by 35% by 2025, 7.8 million (6.7-9.0 million) TB cases and 1.5 million (1.3-1.7 million) TB deaths could be avoided by 2035 (26).

A.2 Rationale of the study

South Africa (SA) is ranked among the top 22 TB High Burden Countries, has among the highest incidences in the world and a high TB mortality with 25 000 people dying each year (3). Although the TB incidence has declined in SA, the MDG to halve the prevalence and deaths due to TB by 2015 in comparison to 1990 levels, have not been attained (27). The country is also currently undergoing demographic and epidemiological transitions

characterised by an aging population and co-morbidity of epidemic IDs such as TB and HIV with NCDs which include DM (23). SA is also recognised as the most urbanised country in Sub-Saharan Africa with 62% of the population living in urban (28). These transitions are mainly driven by development processes such as urbanisation, lifestyle changes and increased physical inactivity (18). In 2013, approximately 2.6 million South Africans were living with DM (8,20). In 2009 a cross-sectional study conducted in urban townships near the Cape Town including Khayelistha, reported the prevalence of DM to be 13.1% (95% CI 11.0-15.1%) (22).

Well known to be the strongest risk factor for TB, HIV remains highly prevalent in SA affecting approximately 12% of the population in 2012 (30). The increased use of antiretroviral therapy (ART) in the country has led to increased long-term survival. However, it is suggested to be associated with aging effects and co-morbidity with metabolic diseases which include DM (31). It is thought that in settings with high HIV infection, the effect of DM on TB could be masked by the effect of HIV on DM as well as the strong association between HIV and TB (32). It is therefore essential to investigate the magnitude of the interaction between DM and TB in people living with HIV.

Identifying modifiable risk factors which predispose both TB and DM could be useful in determining which population groups to target and prioritise for intervention. Quantifying the prevalence of DM among TB patients is also essential to assess the expected strain on health facilities. Very few studies from LICs and MICs have sought to explore the association between TB and DM. In addition, the majority of studies most were conducted among Indian, Asian and Caucasian populations but very few studies among African populations. To our knowledge,

there is no published study in the context of SA, which has examined the association between TB and DM nor quantified the disease burden of DM among adult TB patients.

A.3 Aim and Objectives of the Study

A.3.1 Aim of the study

This study aims to quantify the prevalence and determine determinants of DM among TB cases in Khayelitsha, a low socio-economic setting, which is a predominantly black African population and where TB and HIV are endemic.

A.3.2 Objectives of the study

1. To quantify the prevalence of DM and impaired glucose tolerance (IGT) in TB patients.
2. To determine risk factors associated with DM in TB patients.

A.3.3 Anticipated impact of this study:

Public health impact: This study hopes to contribute towards the field of public health by informing the care of DM that could be effectively incorporated within existing TB programs and how finances could be potentially allocated to assist in this regard. In addition, we hope to identify high risk groups which need to be prioritised for implementing screening and management intervention programmes.

Body of knowledge: This study also seeks to provide quality data on the link between TB and DM in low income settings where TB and HIV prevalence is high.

A.4 Methods

A.4.1 Study population and setting

This study will be conducted at Ubuntu Clinic, an integrated TB/HIV and the largest TB clinic in Khayelitsha. Khayelitsha is a township situated in the outskirts of Cape Town with a population of over 500 000 and predominantly constitutes black Africans. In 2011 the HIV antenatal prevalence in Khayelitsha was estimated at 37% (33) and the TB case notification was 1500 per 100 000 population (34). The main contributor of TB in this township is HIV with the prevalence of HIV-TB co-infection at 70% (34) .

A.4.2 Study design and sampling

This will be a cross-sectional study which will include interviews to document risk factors for DM. The cross-sectional study forms part of a case control study that recruits TB cases and controls (TB suspects confirmed to not have TB) presenting at the Ubuntu Clinic. For the current study, the same TB cases recruited in the case control study will be recruited before TB treatment is initiated and used as the sample for this study.

The main aim of the case control study is to investigate the population attributable risk of TB due to DM in a high HIV burden setting and to determine the best screening algorithms for DM and TB among 1) newly diagnosed TB patients and 2) patients attending diabetic clinics, respectively. Protocol and Ethical approval of the main study are attached in Part D, the appendices to the dissertation (**D.1 Study protocol for the main study** and **D.2: Ethics approval for the main study**)

A.4.3 Sample size

We will manually compute the required sample size using the formula *($n = Z^2 p\,(1-p)/d$.* Where *$Z = 1.96$* represents the normal distribution standard deviation based on the 5% significance level (for 95% confidence level); *$p = 16.5\%$* the prevalence of DM among TB patients in a Ugandan study (33); *$d = 0.05\%$* represents the desired margin of error for our estimation.

A.4.4 Participant inclusion criteria

To be eligible to participate in the study, patients have to be 18 years or older, consent to participate, have confirmed TB status and should not have initiated TB chemotherapy.

A.5 Measurements and instruments

A.5.1 Defining TB cases

Trained clinical research workers will administer the TB suspect screening tool – a structured questionnaire **(**Part D, **D.3: TB suspect screening tool)** to the consenting TB patients. This questionnaire will record demographic, medical and drug history, HIV status and (if positive) date of initiation of ART, regimen, and CD4 count, as well as clinical, microscopic and radiological characteristics of TB at diagnosis. Additionally, other risk factors for diabetes such as family history, anthropometric measurements including body weight and height for calculating the body mass index (BMI), and waist circumference will be recorded.

All study participants will have their TB status confirmed by a medical doctor, following a clinical process as per the South African National Tuberculosis Management Guidelines (2) which are also adherent to the WHO recommended TB case definitions (*Table A-1*) .

Table A-1: The definition of a tuberculosis case as recommended by the World Health Organisation (3)

Type of TB case	Description
Bacteriologically confirmed	A patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic test (such as Xpert MTB/RIF).
Clinically diagnosed	A patient who does not fulfil the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. Diagnosis based on: • chest x-ray abnormalities consistent with active TB • the history and clinical picture suggestive of PTB or EPTB • histological and biochemical tests suggestive of TB
Pulmonary	Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.
Extra-pulmonary	Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges

TB: tuberculosis; MTB/RIF: Mycobacterium tuberculosis/rifampicin; EPTB: extra pulmonary tuberculosis; WHO: World Health Organisation

Two sputum samples will be collected from each TB suspect, and at least two tests of either sputum microscopy, Gene Xpert or sputum culture will be performed. We will define an individual as a TB case if either one of these conditions hold:

1. They test positive for the smear microscopy
2. They test positive for the Gene Xpert
3. They test positive for the culture positive
4. Clinically diagnosed positive by a medical doctor

Microscopy results will be first collapsed into three categories: positive if scanty, +, ++, +++; negative if 0, and not done if the test was not performed. The characteristics of smear microscopy test include high specificity but low sensitivity especially among immune suppressed patients such as children and people living with HIV/Acquired immunodeficiency syndrome (AIDS) (2,36). The culture test is a gold standard test and has a relatively high

sensitivity. A TB suspect will be defined negative if they test negative for all three tests for both sputum samples.

Table A-2: Tests to define a confirmed TB case

Test	Positive test (on either one of two sputum samples)	Negative test (on both sputum samples)
Microscopy	**Scanty:** 1-9 AFB per 100 oil immersion field **+:** 10-99 AFB per 100 oil immersion field **++:** 1-10 AFB per 1 oil immersion field (min 50 fields) **+++:** >10 AFB per 1 oil immersion field (min 20 fields)	**0:** No AFB per 100 oil immersion field
	OR	**AND**
Culture	Positive	Negative
	OR	**AND**
Xpert/RIF	*M.tb.* detected	*M.tb.* not detected
	OR	**AND**
Clinical diagnosis by a medical doctor	• chest x-ray abnormalities consistent with active TB • the history and clinical picture suggestive of PTB or EPTB • histological and biochemical tests suggestive of TB	Showing no symptoms suggestive of TB

AFB: acid fast bacilli; TB: tuberculosis; *Mycobacterium tuberculosis: M.tb;* PTB: pulmonary tuberculosis; ETB: extra pulmonary tuberculosis

A.5.2 DM screening in TB patients

Before TB chemotherapy initiation, blood samples will be collected from the TB patients to measure their fasting blood glucose, oral glucose tolerance test (OGTT), and glycosylated haemoglobin (HbA1c). All blood samples will be sent to the National Health Laboratory Services (NHLS) for analysis. A patient will be considered to have DM if:

1. the diagnosis is known at presentation,
2. they are taking oral hypoglycaemic therapy and/or insulin
3. or they meet the case definition shown in *Table A-3* below

Table A-3: Criteria for diabetes diagnosis (37,4,38)

Test	Description
Glycosylated haemoglobin **HbA1C ≥6.5%**	The test should be performed in a laboratory using a method that is National Glycohaemoglobin Standardisation Programmes certified and standardized to the Diabetes Control and Complications Trial assay.*
	OR
Fasting Blood Glucose **FBG ≥126 mg/dL (7.0 mmol/L)**	Where fasting is defined is considered as no caloric intake for at least 8 hours.*
	OR
Oral Glucose Tolerance Test **2-h plasma glucose ≥ 200mg/dL (11.1mmol/L)**	During an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
***In the absence of unequivocal hyperglycaemia, result should be confirmed by repeat testing**	

Newly diagnosed DM patients will be referred to the DM clinic at Khayelitsha Day hospital, which is located at the same premises as Ubuntu clinic.

A.5.3 WHO-STEPS questionnaire

Additional to variables collected using the TB suspect screening tool, consenting participants will be interviewed using a structured questionnaire (Part D, **D.4: WHO STEPS instrument**) which was adapted from the WHO-STEPS questionnaire (39) . The variables to be documented also include anthropometric measurements (weight, height and waist circumference), demographic information (sex, race, age, education level and income), behavioural measurements (alcohol, tobacco use and physical activity) and biochemical measurements (plasma glucose). The list of variables to be collected is shown in **(**Part D**, D.5: Table of variables).**

A.5.4 Validity of measurements

All diagnostic tools that will be used in this study are standard and were validated by the WHO. The TB screening tool (questionnaire) is adherent to WHO guidelines and is recommended by the South African National Tuberculosis Management criteria (2). For screening DM, the

HBA1c, FBG and OGTT tests recommended and validated by WHO will be used (37,4,38). WHO STEPS instruments which will be used for recording chronic disease risk factors is also WHO validated (39).

A.6 Data Management

The completed TB suspect screening questionnaires will be captured into eKapa database by trained data capturers. eKapa is an electronic healthcare database adopted by the Western Cape Department of Health for monitoring and evaluation of HIV/AIDS and TB healthcare programmes in the province. The responses collected using the adapted WHO STEPS questionnaire will be captured into Microsoft Access. The data from these databases will be merged using unique identifiers for each study participant. Only the principal study investigator, data capturers, data manager and other study related personnel (with special permission) will access these databases using passwords. Completed questionnaires will be kept safe and secure in cupboards.

A.7 Data Analysis

All statistical analysis will be performed using Stata version 12 (StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845, USA).

Statistical significance will be determined using $p < 0.05$ and 95% confidence intervals where necessary. Depending on the type of data collected, numerical or categorical data and appropriate statistical methods to assess their distributions and nature will be used. Continuous variables will be assessed for normality using graphical methods such as histograms, graph box

plots and statistical tests such as the Shapiro-Wilk test. Normally distributed data will be described using means and standard deviations. Non-normality data will be described using medians and interquartile ranges. Categorical data will be described using proportions and their intervals. The prevalence of DM will be based on gold standard diagnostic tests, HbA1c, FBG and OGTT.

The main outcomes of the analysis will be the number and proportion of TB patients with DM diagnosis and IGT with 95% confidence intervals (CIs). To identify and adjust for confounding variables TB patients with DM diagnosis will be stratified by some of the risk factor variables (i.e. sex), odds ratios with 95% CIs around them will be calculated to elucidate differences between strata. To assess risk factors associated with DM among the TB patients, multivariate logistic regression analysis will be used to build a statistical model and estimate the odds ratios with 95% CI around them. The best fitting model will be built using a manual stepwise procedure of comparing different nested models using the likelihood ratio test. The Akaike's Information Criterion (AIC) will also be used to assess better models.

A.8 Ethical considerations

A.8.1 Informed consent, confidentiality and benefits

This study is a subset of a larger research project approved by the University of Cape Town Human Ethics committee (**Ref No: 403/2011**).

Informed consent: Consent will be voluntary and obtained from all the participants. An information sheet available in both English and isiXhosa will be given and read to participants to explain what the study is about.

Confidentiality: Confidentiality and safety will be ensured by securing all the documents using unidentifiable keys, password protection in the databases and restricting access to data appointed personnel and principal investigators.

Benefits: The benefits of the study for all participants (TB patients) will include TB chemotherapy and those who test HIV positive will be offered counselling and offered to initiate antiretroviral therapy (ART) if eligible. Participants with confirmed DM status will be referred to a DM clinic for standard care treatment. Potential risks and harm in this study will be very minimal, however, minor discomforts through a prick of a needle may be experienced by the participants during blood sample collection. The overall impact of this study (outlined in A.3.3) will benefit the study participants and the community at large.

A.8.2 Justification for the inclusion of ethnicity and its value to study results

Evidence highlights the existence of ethnic disparities in health outcomes and access to health services which are generally a result of ethnic discrimination (40–42). Though most of these disparities are associated with genetic vulnerability and socioeconomic factors (1), socioeconomic status underpins majority of these disparities (1). South Africa is an ideal example illustrating how past ethnic discrimination has led to differential exposure to environmental risks to certain diseases and has shaped the socioeconomic structure according to ethnic groups (42).

Ethnicity and genetics are acknowledged to increase the risk of DM, while low socioeconomic status is associated with both DM and TB (3,5,1). We include ethnicity, not primarily as a determinant of either TB or DM, but as a marker of risk factors which predispose either or both

of these two diseases. Including this variable allows us to explore the associations between ethnicity and risk factors for either TB or DM.

Studies which have assessed the association between TB and DM have suggested that the strength of the association varied across different ethnic groups, age groups and different geographies (9). Very few studies were conducted among African populations to assess the association between TB and DM. In particular, none from South Africa have yet assessed the association between these two diseases nor quantified the burden of DM among TB cases. By having our study conducted among the African population, it contributes towards filling the gap in the literature on the burden of DM among TB cases and magnitude of the association between the two. It is also an opportunity to compare our study results with study results from other ethnic groups and geographical settings.

A.9 Reporting

This study will be conducted for the partial fulfilment of Master of Public Health (MPH) Epidemiology degree. The final report with findings will be submitted to the University of Cape Town for assessment. The findings will be published in an academic peer-reviewed journal and will be presented at both local and international conferences.

A.10 Logistics

A.10.1 Timeline

Table A-4: Scheduled timeline for dissertation

Task	Feb-Mar '15	Apr-May '15	Jun-Jul '15	Aug-Sep '15	Oct-Nov '15	Dec '15 – Feb '16
Part A: study protocol and literature review						
Submit study protocol for ethics approval						
Part B: structured literature review						
Data cleaning and analysis *;						
Part C: journal manuscript						
Submit final dissertation						

*****Data collection in the main (case-control) study took place between Jan 2014 and Aug 2015.

A.10.2 Budget and costs

No costs are anticipated to be incurred during this study as it is a subset of a larger study in which the costs will be incurred.

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PART B: STRUCTURED LITERATURE REVIEW

B.1 Introduction

Several studies have suggested that diabetes mellitus (DM) increases the risk of tuberculosis (TB). The rapidly increasing burden of DM presents new challenges to TB control especially in low- (LIC) and middle- (MIC) income countries where TB is also endemic. Very little is known, about the magnitude of the burden of DM among TB patients and extent of the strength of association between TB and DM and in these LICs and MICs.

B.2 Aims and objectives

This structured literature review was guided by the research question: *What is the prevalence of diabetes mellitus among tuberculosis patients and what are the risk factors for diabetes among TB patients?* We aimed to review and appraise existing epidemiological studies which reported the prevalence of DM among adult TB patients and which also assessed risk factors associated with DM among TB patients. We also reviewed studies which assessed the impact of DM on TB outcomes, in addition to reporting the prevalence of DM among TB patients. The reviewed literature was summarised based on the following themes:

- The risk factors associated with DM among TB patients
- Screening for DM among TB patients and associated methodological issues
- The prevalence of DM among TB patients
- The magnitude of association between DM and TB
- The impact of DM on TB treatment outcomes
- Comorbidity with HIV
- Knowledge gaps and areas which require further research

B.3 Methods

B.3.1 Search Strategy

We searched PubMed, Scopus and reference lists of papers on the related subject to select relevant articles. The search strategy included the following key terms: “prevalence”, “epidemiology”, “risk factors”, “determinants”, “diabetes mellitus”, “tuberculosis” “outcome” and “treatment”.

B.3.2 Study selection and extraction

The search strategy aimed to identify and include epidemiological studies which reported the prevalence of DM and associated risk factors among adult TB patients, the association between DM and TB and on the impact of DM on TB treatment outcomes. Studies were restricted to the English language, and we included studies published until August 2015 when the literature review was conducted. We excluded studies which were non-English, had non-human subjects and those conducted among children and among the elderly only (age > 65). We also excluded those which did not report or allow the computation of the prevalence of DM among TB patients. The included studies also depended on their availability and accessibility from the internet and the University of Cape Town’s Library. We scanned through titles and abstracts to identify those which included the key search terms and then selected those which met our inclusion criteria.

B.4 Results

The refined search strategy yielded 128 articles and, of these, 45 articles met our inclusion criteria. Fifteen were cross sectional and retrospective descriptive studies, primarily quantifying the prevalence of DM among TB patients and risk factors associated with DM among TB patients. Eleven assessed the association between TB and DM, only two were cohort studies, one retrospective and one prospective and the others were case control studies. Eighteen studies assessed the impact of DM on TB treatment outcomes, most of these were cohort studies. The studies were summarised in three tables, categorised by the World Bank regions and income categories. This categorisation is useful as it allows comparison of studies with similar attributes and is suggestive of the demographic characteristics such as socioeconomic setting and the ethnicity of the populations from which the studies were conducted. *Table B-1* summarises the reviewed descriptive studies which primarily reported the prevalence of DM among TB patients and the risk factors associated with DM among TB patients; *Table B-2* summaries the analytical studies which reported the prevalence among TB patients and comparison populations, and the association between TB and DM. *Table B-3* summarises the studies which assessed the influence of DM on TB treatment outcomes: relapse, recurrence, resistance, sputum conversion, treatment failure and death.

B.4.1 Risk factors associated with DM among TB patients

Globally, the risk factors of DM in the general population are well documented and include obesity, poor diet, physical inactivity, increasing age, ethnicity and high blood glucose levels during pregnancy (1). However, it is unclear whether these risk factors are shared among TB patients. In the reviewed studies, the factors that were consistently identified as risk factors of DM included increasing age (2–14), family history, high body mass index (BMI) and obesity

(3,4,6,9,13). Some studies found DM and TB co-morbidities to be more common among men (2,3,5,8), while others found it to be common among women (10,14). A suggested reason for the high DM prevalence among men is that they usually have accumulated risk from other risk factors such as smoking and alcohol consumption. Among women, it could be due to more sedentary lifestyles (stay-at home and care taking).

Behavioural factors such as sedentary lifestyle (4,9), increased tobacco smoking and alcohol drinking (6,9,11,12) showed to increase the risk of DM in some studies, but there are other studies that show no association. For example, in a Ugandan study assessing the prevalence and risk factors of DM among TB patients (15), no association was found between DM and any of the mentioned above behavioural factors. The authors did not suggest any possible explanations for these observations, however it could be because the prevalence of risk factors for DM in the study population was generally low. For instance, the mean BMI was 17.4 kg/m^2, which indicates low risk for obesity and possibly a lower risk for DM. In another study by Faurholt-Jepsen et al in Tanzania, severe underweight was associated with DM (3). They suggested TB could have caused this weight loss (3). These findings suggest that predictors of DM among TB patients depend on the underlying characteristics of the studied population such as co-morbidities with other diseases, the prevalence of risk factors of DM in the back ground population and possibly the socioeconomic setting.

Socioeconomic factors which have been associated with a higher prevalence of DM include urban residence (8), and low income (9,13). Wang et al showed that higher income was positively associated with outdoor activity and negatively associated with DM among pulmonary TB patients (13). Other studies also found DM to be higher among those with low education attainment (11,12). In studies conducted among heterogeneous populations, ethnicity

was associated with DM (12,14,16), with higher DM prevalence among American Indians, followed by Pacific Islanders, African Americans, Hispanics and then by Asians and American whites (16). The risk of DM attributable to ethnicity is likely to be through its association with genetic vulnerability (17,18), ethnic-associated behaviour and life style and socioeconomic determinants of health such as disparities in access to health care (19).

Although not explored and discussed by most studies, it is also essential to consider the fact that DM has multifactorial risk factors and that some risks are acquired over the life course. For example, the risk of DM in some individuals may be mediated by socioeconomic, structural or environmental factors which may not be conducive to physical activity or may limit access to affordable, healthy food. Through the life course consideration, we need to recognise that the development of DM during adult life may be due to early life risk conditions such as maternal malnutrition during pregnancy and low birth weight (20,21). Knowledge about the risk factors of DM among TB patients is important in identifying groups which could be targeted for interventions such as preventative measures for individuals at low risk, and screening and treatment for those at high risk.

B.4.2 Screening for DM among TB patients

The majority of the reviewed studies used at least one of the WHO recommended DM diagnostic criteria (22). It has been observed that TB induces a transient phase of hyperglycaemia (23) which may overestimate the prevalence of DM among TB patients (23,24). Therefore, the time period at which the test for DM are performed in relation to the clinical state of TB needs to be accounted for and considered.

To reduce the potential effect of TB induced hyperglycaemia, various methods and diagnostic techniques could be used. For instance, it may be ideal to test TB patients for DM in less acute conditions or at a particular point during their TB treatment because it is suggested TB-related hyperglycaemia dissipates after effective TB treatment (25). Another way to improve the reliability of DM tests among TB patients may be to perform DM confirmatory tests. However, more research is required to verify the optimal time points and number of tests required. It is important that epidemiological studies assessing the prevalence of DM among TB patients employ methods or techniques which will account for and minimise the potential effect of TB induced hyperglycaemia on DM diagnosis.

Several studies (9,11–13) mentioned performing at least two tests to confirm DM diagnosis although the time points were not specified. The glycated haemoglobin (HbA1c) diagnostic tool has the potential to improve the validity of measuring DM. This measurement reflects the average blood glucose level over two to three months and is less likely to be influenced by the transient acute stress hyperglycaemia (26). Very few studies (8,9,11,27) used the HbA1c tool to diagnose DM possibly because it is relatively expensive and was recommended by the WHO only fairly recently in 2011 (26). Although some measures were taken to reduce the potential overestimation of DM due to the transient hyperglycaemia in some TB patients, the resulting DM prevalence was still high, possibly due to the methods and manner in which the studies were conducted.

There are several other methodological issues which may have affected the reliability of the estimated prevalence of DM among TB patients. Firstly, the majority of the reviewed studies were health facility-based and used convenient sampling methods. Secondly, the prevalence estimated from such studies is biased and not necessarily representative of the general

population. To address this issue, a few studies attempted to use relatively large samples and cluster-randomised sampling of health facilities (6,8,13). The use of self-reported DM status is another factor which has shown to underestimate the true prevalence of DM (28). Furthermore, the use of medical records and disease coding from insurance databases to classify disease status is inherently subject to many errors including non-differential misclassification which may underestimate the prevalence of DM. Nonetheless, the few studies in which DM was self-reported still found a relatively high prevalence of DM (6,7,29). Given the clinical condition of TB and methodological issues which potentially affect the measurement of DM, it is essential to consider how the reported prevalence of DM may be affected.

B.4.3 The prevalence of DM among TB patients

The reported prevalence of DM among TB patients in the reviewed studies ranged from 2.1% in South Africa in 1980 (5) to as high as 44% in Kerala, India in 2012 (8). With respect to geographic region, the studies which reported high DM prevalence among TB patients were those from South Asia (SAS) (range: 25% - 44%) followed by those from the Latin America and Caribbean (LAC) (range: 14% - 39%), East Asia and Pacific (EAP) (range: 6.3% - 39%) and Middle East and North Africa (MENA) (range: 23% - 24%). The majority of countries in which these studies were conducted are characterised by low income settings and high background TB and DM disease burden. In the descriptive studies (summarised in *Table B-1*), the prevalence of DM among TB patients tends to exceed DM prevalence in the general population. Among most case control studies (*Table B-2*), (16,30–35) the prevalence of DM among TB patients is at least double the prevalence of DM among comparison populations without TB. These findings suggest that the prevalence of DM among TB patients is considerably higher than the prevalence in the general population.

Globally, the prevalence of DM in the general population is expected to double by the year 2030 (1). A similar pattern of increasing DM prevalence among TB patients can be expected. In *Table B-1*, within each region, studies are ordered by ascending years, and in some regions there is a slight indication of an increasing trend. This increasing trend of DM among TB patients was also shown in one study (16) which analysed temporal trends of DM among TB patients in San Francisco, USA. This American study showed that among TB patients, the prevalence of DM increased from 14% in 2006 to 24% in 2012 with a significant time trend statistic ($p < 0.01$) (16). The burden of DM among TB patients is increasing but is variable across geographic regions.

The patterns of variability in the prevalence of DM among TB patients may be due to demographic differences such as ethnicity and socioeconomic setting and the background burden of both TB and DM in the respective general populations. For example, in comparison with other regions, studies from Sub-Saharan Africa (SSA) reported relatively low prevalence (range: 2.1% – 16.4%). However, due to rapid urbanisation, nutritional and lifestyle transition (36,37) occurring in this region, majority of the increasing DM is expected to be contributed by this region (1). A few studies (12,14,16) have shown that DM is more prevalent among Indians, Filipinos, Asians and Hispanics. From the three tables *(Table B-1, Table B-2 and Table B-3)* it could be seen that the regions with high DM prevalence are those predominantly inhabited by people of these ethnicities. The high prevalence of DM among TB patients strongly suggests that there is a link between the two conditions.

Table B-1: A Summary of studies conducted to primarily assess the prevalence of DM among TB patient and risk factors associated with DM

Reference	Study period, County	Income country category	DM% among TB patients	2013 General DM Prevalence (38)	Sample size (N)	TB population and sampling method	DM diagnosis in relation with TB diagnosis	Method for DM diagnosis	Factors associated with DM
Studies from Sub Saharan Africa (SSA)									
(2) Olayinka 2013	NR; Nigeria	LIC	5.7%	5%	351	Reviewed sputum smear and tuberculin results from folders (pulmonary + extra pulmonary); Consecutive patients on the DOTS (treatment)	NR	FBG ≥ 126 mg/dl	Age (41±13.9 years) Male
(15) Kibirige 2013	2011 – 2012; Uganda	LIC	8.5%	4.1%	260	Performed acid-fast bacilli, Xpert and Sputum smear excluded patients on anti-TB drugs	1.9% of the DM patients had known DM before TB diagnosis	RBS ≥ 200 mg/dl	HIV (OR 0.32, 95% CI 0.13 – 0 .79). DM not significantly associated with commonly reported risk factors
(3) Faurholt-Jepsen 2012	2006 – 2008; Tanzania	LIC	16.4%	7.8%	1205	Newly diagnosed pulmonary TB and initiated treatment	DM tests performed few days after TB treatment	FBG ≥ 6.0 mmol/l or OGTT ≥ 11.0 mmol/l	Age, high BMI, high waist circumference. Sex and low BMI interaction – increased odds of DM among males with low BMI (<16 kg /m^2) (OR 2.52, 95% CI 1.34– 4.74, p = 0.004)
(4) Baldé 2006	2001 – 2002; Guinea	LIC	3.35%	3.7% * (2010)	388	TB cases on treatment. Simple random sampling from the countries TB registry	9/13 TB cases had DM diagnosed before TB diagnosis by 5 (range: 1 – 9) year	Capillary blood glycaemia test	Increased age ($p < 0.0001$), obesity ($p < 0.005$), Sedentary lifestyle ($p < 0.0004$), DM family history ($p < 0.04$)
(5) Marais 1980	1977; South Africa	UMIC	2.1%	8.3%	436	NR	NR	OGTT	Males, average age 55
South Asia (SAS)									

(6) Raghuraman 2014	NR; India – Puduchery	LMIC	29%	8.6%	223	Randomly selected 4/14 health facilities. TB cases on treatment: new and re-treatment cases	DM preceded TB diagnosis in 20.7% cases, by a mean duration of 48.7 months	Self-report of DM medication; FBG ≥ 126 mg/dl	Increasing age, family history of DM, alcohol consumption
(7) Padmalatha 2014	2014; India – Andhra Pradesh	LMIC	30.6%	8.6%	252	Sputum positive, sputum negative and extra pulmonary cases on TB treatment	DM preceded TB diagnosis in 22.2% patients. New DM: 7.8%	Self-report of DM medication; FBG ≥ 126 mg/dl	Increasing age, high BMI, systolic blood pressure and category of TB treatment, all ($p<0.05$)
(8) Balakrishnan 2012	2011; India – Kerala	LMIC	44%	8.6%	552	Sampled confirmed TB cases form the national TB registry using cluster randomised sampling	Of those with DM	Self-report and HbA1c ≥ 6.5%	Sex (male), age (≥ 50), urban residence
(9) Viswanathan 2012	2011; India – Tamil Nadu	LMIC	25.3%	8.6%	827	TB cases registered for DOTS	DM diagnosis preceded TB in at least 63% patients.	OGTT and HbA1c	Age, family history sedentary occupation, higher BMI Pre-diabetes risk factors: waist circumference smoking, monthly income
(39) Gupta 2011	2005 - 2006; India	LMIC	31.8%	8.6%	192+37	192 microbiologically confirmed PTB and 37 ETB	NR	Medical records	Not assessed
Middle East & North Africa (MENA)									
(10) Golsha 2009	2001 – 2005; Iran	UMIC	23.05%	8.4%	243	Recorded files of admitted pulmonary TB patients	NR	FBG ≥ 126 mg/dl	Age (≥ 50) and sex (female)
Latin America & Caribbean (LAC)									
(11) Restrepo 2011	2006 - 2008 ; Mexico; Texas	UMIC HIC	36%; 39%	11.8%	172; 61	Referred TB suspects. Used standard WHO TB definitions	Majority had 8 years prior	HbA1c ≥ 6.5%; RBG ≥ 200 mg/dl; FBG ≥ 126 mg/dl	Increasing age (<0.0001), alcohol abuse (0.03), history of incarceration (0.06), drug abuse (0.01)

(12) Alladin 2011	2006; Guyana	LMIC	14%	10.2%* (2010)	100	Clinical, radiological, or microbiological diagnosis and on TB treatment	7% had DM diagnosed prior TB, 3% diagnosed at the time TB diagnosis, and 2 were diagnosed after	Self-report and RBG ≥ 200 mg/dl	Increasing age, ethnicity, low education level, alcohol abuse, drug abuse, history of incarceration
East Asia & Pacific (EAP)									
(13) Wang 2013	2010 – 2012; China	UMIC	Among TB cases 403/6382 (6.3%)	9.6%	6382	Newly diagnosed PTB patients on DOTS. Community based cluster-randomised sampling.	56% had known DM before TB but only 10% had their DM controlled	FBG ≥ 6.1 mmol/l	Increasing age, family history of DM, higher yearly income ($10000 RMB/yuan) was negatively associated with DM in PTB patients Positive sputum smear and cavity on chest X-ray
North America									
(14) Dyck 2007	1991 – 1995; Saskatchewan	HIC	111/2122	11.6%	1375; 747	TB registries, national insurance data	DM preceded TB in (87/111) 78% individuals	Medical records coding	Age sex interaction: females aged 50-59 years. Ethnicity, Indians: OR 2.7 95% CI: 1.28 – 5.72 Saskatchewan: OR 3.9 95% CI: 1.58 – 9.67

DM: diabetes mellitus; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; HbA1c: glycated haemoglobin; TB: tuberculosis; PTB: pulmonary tuberculosis; ETB: extra pulmonary TB; BMI: body mass index; NR: Not reported; DOTS: directly observed short course treatment; LIC: low income country, HIC: high income country, LMIC: lower middle income country, UMIC: upper middle income county; OR: odds ratio; CI: confidence interval.
***Used 2010 estimates (40)**

B.4.4 The association between DM and TB

Eleven studies *(Table B-2)* assessed the association between TB and DM: two were cohort studies, (a retrospective (41) and prospective (42)) and the others were case control studies (16,30–35,43,44). Only one study from Guinea-Bissau in SSA, found a negative non-significant association with an odds ratio 0.88 (95% confidence interval (CI) 0.17–4.58) (43). However, most studies (16,30–34,42,44) reported a positive magnitude of association between DM and TB (odds ratios range: 1.28 – 4.7) and (relative risks range: 1.40 – 11.7) The positive association seemed to be consistent across geographic regions and study designs.

The strength of the TB-DM association increased after accounting for interactions between DM and other risk factors and adjusting for potential confounders such as sex, age, ethnicity and co-morbidities such as human immunodeficiency virus (HIV). Suwanpimolkulet et al showed a stronger and positive association between DM and TB among Filipinos, followed by Chinese, Mexicans and then Americans, with ages greater than 45 years (16). Methodological issues and the clinical condition of TB could have also influenced the measured association between DM and TB.

Case control and cohort studies that investigate the link between DM and TB face methodological problems which obscure the cause and effect relationship. In case control studies, the observed strong association between TB and DM is likely to be reverse causation due to stress-induced hyperglycaemia caused by TB (23,24). In an attempt to address this issue, Faurholt-Jepsen et al, adjusted for potential confounders and the elevated serum acute phase reactants to reduce their effect on blood glucose levels (30). Even after this adjustment, a relatively strong association between TB and DM was still observed, particularly among HIV

negative patients. In prospective cohort studies (where DM and non-DM patients are followed up over time to assess the incident of TB), DM patients are usually on DM treatment. Therefore, if the TB risk attributable to DM is mediated by high plasma glucose levels, then DM medications may play a role in reducing the risk of TB development and hence reducing the true effect of DM on TB development. Besides the potential impact of the clinical condition of TB on the measured association, other methodological issues may play a role.

Other methodological issues which could have affected the measure of association between TB and DM were duplications of patient data and misclassification of DM status. Several studies (16,34,35,42,44) used self-reported DM status, medical records, discharges records, medical insurance data and disease coding to classify DM status. These methods are subject to non-differential misclassification of DM and its likely impact is a nullified measure of the DM-TB association. The use of discharge records is subject to duplication (i.e. one patient with multiple discharges for something other than DM) of patient data, and the likely impact would be overestimation of the reported prevalence of DM or DM-TB association. Despite these methodological issues, across a variable studies, the consistent positive association between DM and TB suggests a causal relationship.

Table B-2: Summary of studies assessing the association between DM and TB

Reference	Study period; country	Study design	Study design; DM Prevalence	TB population	Controls (non TB)	Exposure – DM	Outcome	Association OR (95% CI)	Adjusted (confounding) variables
Sub Saharan Africa									
(43) Haraldsdottir 2015	2010 – 2011; Guinea Bissau	Case control	Controls: 3/107 (2.8%) Cases: 11/531 (2.1%)	Newly diagnosed TB patients from TB notification system.	Selected randomly form the population.	RGB ≥ 7 mmol/L and those with two FBG ≥ 7 mmol/l	Microscopy positive TB. Chest radiography	OR: 0.88 (0.17 – 4.58)	age (30, 31–50, >51 years) sex BMI (18, 18–25,>25 kg/m2)
(30) Faurholt-Jepsen 2011	2006 – 2009; Tanzania, Mwanza	Case control	Controls: 32/350 (9.4%) Cases:134/803 16.7%	Newly diagnosed TB, a few days before TB treatment	Consecutively	FBG 6 ≥ mmol/L and OGTT ≥ 11 mmol/L	TB using microscopy based on the 3 sputum samples. Two rapid tests for HIV	Unadjusted: 2.2 (1.5 – 3.4) Interaction: DM-HIV (p = 0.01) Adjusted: Among HIV negative 4.23 (1.54 – 11.57) Among HIV positive 0.14 (0.01 – 1.81)	Serum concentration of the acute phase reactant (AGP); religion, marital status, occupation, sex, age
East Asia & Pacific (EAP)									
(32) Viney 2015	2010 – 2012; Republic of Kiribati	Unmatched Case control	Cases: 101/275 (37%) Controls: 4/499 (19%)	Consecutively	Randomly selected	HbA1c ≥ 6.5% Previous DM diagnosis	Bacteriological, clinical and radiological criteria	2.8 (2.0 – 4.1)	Age Sex
(42) Kuo 2013	2000 – 2011 Taiwan	Prospective cohort mean follow-up 5 years.	Females with DM: 31 237 Females with No DM: 9 264 Male DM+: 32 493 Male No DM: 96 977		Randomly selected 3 and matched controls to each diabetic patient by: gender,		TB: ICD-9 (010–018) Confirmed by continuous dispensing of anti-TB drugs.	Standardized incidence ratio (SIR) Female: 1.40 (p < 0.01) Male: 1.48 (p < 0.01) attributable fraction (exposed)% among females males were estimated	sex, age, bronchiectasis, asthma, chronic obstructive lung disease

					year of birth, and month and year of first diagnosis at enrolment			to be 28.6 and 32.6, respectively. **HR:1.31 (1.23 –1.39)**	
Middle East and North Africa (MENA)									
(31) Alavi 2012	2008 – 2010; South West Iran	Case control	Cases: 36/148 (24.32%) Controls: 214/1976 (10.83%)	From the Iranian National TB control	Selected from admitted patients	Medical charts used for both DM and TB diagnosis	Medical charts used for both DM and TB diagnosis	2.56 (1.77 – 3.95) [36/112]/[214/1762]	Did not use logistic regression
(33) Alisjahbana 2006	2001 – 2005; Indonesia	Matched neighbourhood case control	Cases: 60/454 (13.2%) Controls: 18/556 (3.2%)	Newly diagnosed PTB	Randomly selected form the community	No DM treatment 48hr before test. FBG > 126 mg/dl before and 1 month after TB treatment.	Newly diagnosed PTB	4.7 (2.7 – 8.1)	Sex Income Overcrowding
Latin America & Caribbean (LAC)									
(29) Pérez 2007	1999 – 2001; Mexico and Texas	Case control	Border Cases: 356/1244 (28.62%) Controls: 1469/12563 (11.69%) Non-border Cases: 608/3671 (16.56%) Controls: 5099/58245 (8.75%)		Discharges for deep venous thrombosis, pulmonary embolism, and acute appendicitis conditions	Medical charts – discharges after TB diagnosis.	TB: codes 010 – 018 DM: ICD-9-CM code (250)	Mexico: 1.82 (1.57 – 2.12) Texas: 1.51 (1.36 – 1.67)	Sex, age, race/ethnicity, insurance, chronic renal failure, nutrition deficiency, income, education, residence at border

(34) Corris 2012;	1976–1980; United States (US)	Case control	Cases: 166 (weighted prevalence = 11.8%) Controls: 15191 (weighted prevalence = 4.3%)	Reported ever receiving a diagnosis of TB from a doctor	Not having a diagnosis of TB from a doctor	NHANES II study OGTT and self-report	Reported ever receiving a diagnosis of TB from a doctor	2.31 (1.36 – 3.93)	Race Age Poverty Index BMI category Household contact with TB Cigarette smoking status
(16) Suwanpimolkul 2014	2005 – 2012; US – San Francisco	Retrospective Case control	Cases MTB: 126/791 (15.9%) LTBI: 1158/17856 (6.5%) Controls: 206/4371 (4.7%)	Individuals seeking medical attention who had a final diagnosis of LTBI or TB	Individuals seeking medical attention who had no evidence of LTBI or TB	DM self-report and medical records	Final diagnosis of LTBI and TB	Among those aged> 45 years Filipinos: 3.86 (1.72 – 2.69) Chines: 1.85 (1.24 - 2.75) Mexican: 1.5 (0.3 - 7.4) US: 1.28 (0.69 - 2.37)	age and population group
(35) Pablos-mendez 1997;	1991; Calfornia	Retrospective case control	Cases: 573/5290 (10.8%) Controls: 1363/37366 (3.6%)	Medical charts – discharges after TB diagnosis.	29437 patients with acute appendiciti s, 4624 with pulmonary, embolism, and 3305 with deep venous thrombosis	DM: ICD-9-CM code (250)	Medical charts – discharges after TB diagnosis.	Hispanics: 2.95 (2.61;3.33) Whites: 1.31 (1.19;1.45) Blacks: 0.93 (0.78;1.09)	Age, sex, race, poor education, median income, health insurance, HIV-related conditions, chronic renal insufficiency, alcohol related conditions, drug use
Europe									
(41) Byberg 2009	Greenland (Inuit)	Retrospective cohort, mean follow-up: 4.97	Total participants: 3,012 DM cases: 281 TB cases: 11	All subjects randomly selected from the Civil Registration System.	All subjects randomly selected from the Civil Registratio n System	DM status extracted from previous studies: and the Greenland Population Study (B99)	TB: ICD-9 (010–018). National TB registry	Crude RR: 2.66 (0.41;10.3) Adjusted RR: 11.7 (1.48;65.9)	Age, sex, place of residence and BMI

DM: diabetes mellitus; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; HbA1c: glycated haemoglobin; TB: tuberculosis; PTB: pulmonary tuberculosis; ETB: extra pulmonary TB; LBTI: Latent TB infection; BMI: body mass index; NR: Not reported; DOTS: directly observed short course treatment; NHANES: National Health and Nutrition Examination Survey; IHIT: Inuit Health in Transition Study; SIR: sex incidence ratio; OR: odds ratio; CI: confidence interval.

B.4.5 The biological plausibility of the DM-TB association and the impact of DM on the natural history of TB

Several hypotheses are proposed to explain the mechanisms through which DM is associated with, and impacts TB. Based on existing literature, it is suggested that DM affects every stage of the natural history of TB (45–48). Firstly, DM is associated with a reduced cellular immunity (45). Patients with concomitant DM and TB are observed to have low T lymphocyte count, reduced T-helper 1 cytokine response level and inhibited macrophage function. In addition, hyperglycaemia has a direct depressive effect on polymorphonuclear functions such as respiratory burst[1] and phagocytosis[2] (49–51). The combined effect of these suggested dysfunctional processes and conditions described above and possibly others not mentioned here, contribute to the increased risk of TB among DM patients.

Adverse TB treatment outcomes have been further associated with DM. Efficient killing of *Mycobacterium tuberculosis* (*M.tb*.) by anti-*M.tb*. antibiotics requires support from a fully functional immune system (45). Chronic hyperglycaemia is suggested to compromise *M.tb* killing by causing microvasculature complications and reducing lung tissue function for optimal immune surveillance (45,52). Therefore, considering that DM patients have an impaired cell-mediated immunity (45), this may partly explain why anti-*M.tb* treatment is inefficient among DM patients with TB and results in poor treatment outcomes.

[1] The oxygen-dependent intracellular killing of infectious agents in polymorphonuclear cells (49).
[2] The process by which a cell engulfs material either to destroy it, to feed on it, or to get information from it (49).

B.4.6 The impact of DM on TB treatment outcome

Eighteen studies (*Table B-3*) assessed the impact of DM on TB treatment outcomes. These outcomes included: relapse, recurrence, resistance, failure, sputum conversion and death during TB treatment (*Table B-4*). The majority of studies were retrospective in design (31,53–60), a few were prospective (27,61–66), one was a nested case control (67) and another was cross-sectional (68). To classify DM status, most of these studies used medical records and self-report. In addition, study subjects were mostly TB patients who were already on TB treatment and were recruited from national TB registries and health facilities.

Table B-3: Summary of studies assessing the impact of DM on TB treatment outcomes

Study; Year; country	Study design	TB Population	DM diagnosis	DM prevalence (DM/sample) (%)	Outcome considered and observed associations	Variables adjusted for
Sub Saharan Africa (SSA)						
(66) Faurholt-Jepsen 2013; 2006-2008 Tanzania	Prospective	Newly diagnosed PTB on treatment	FBG ≥ 6.0 mmol/l or 2 hr blood glucose of ≥ 11.0 mmol/l.	197/1250 (16.4)	*Death:* HIV negative HR: 5.09 (95% CI: 2.36 – 11.02) HIV positive-HR: 2.33 (95% CI: 1.20 – 4.53) *Conversion Delay (DMTB vs TB):* No association	Age, gender, BMI
South Asia (SAS)						
(53) Kv 2013; 2010 – 2011; India, Kerela	Retrospective	TB patients with treatment cards DOTS	Medical records, FBG ≥ 126 mg/dl, RGB ≥ 200 mg/dl or postprandial blood sugar (PPBS)	667/3116 (24)	*Combined unfavourable (death, default, failure, transfer out) outcome:* 2.00 (0.97 – 4.13) *Treatment failure:* Not significant Higher failure among DMTB (p = 0.04).	Age group, sex, site and type of TB, smear result, HIV status
(54) Viswanathan 2014; 2011; South India	Retrospective	TB patient with treatment cards DOTS	Medical records of biochemical tests performed during DOTS course.	96/245 (39.18)	*Conversion Delay (DMTB vs TB):* remained positive until end point among TBDM vs TB non DM - 3.9 (1.5;10.6)	NR
Middle East and North Africa (MENA)						
(55) Singla 2006; 1998-1999 ; Saudi Arabia	Retrospective	Smear positive TB patients	Medical records, FBG≥ 140	187/692 (27.02)	*Resistance:* DMTB patients had lower prevalence (6.4% vs. 16.0%, P 0.007) *Conversion:* DBTB patients had higher conversion rates within 3 months (98.9% vs. 94.7%, P 0.013). *Treatment failure***:** Favourable outcomes comparable between groups.	NR
Latin America and Caribbean (LAC)						

(61) Jiménez-Corona 2013; 1995-2010; Mexico	Prospective	Microbiological acid fast bacilli patients	Medical records: FBG≥ 126 mg/dl or OGTT ≥ 200 mg/dl	374/1262 (29.63)	*Conversion*: OR: 1.51 (1.09;2.10) *Relapse:* HR: 1.83 (1.04; 3.23) *Recurrence* HR: 1.76 (1.11; 2.79) *Treatment failure:* OR: 2.93 (1.18; 7.23)	NR
(57) Fisher-Hoch 2008; 1996-2002; Mexico and Texas	Retrospective	Texas: cultures positive Mexico: sputum	Self-report	Texas: 401/1442 (27.80) Mexico: 287/1436 (19.98)	*Death:* Texas: OR 2.1(1.1;4.2) Mexico: OR 1.8 (1.1;2.9) *Sputum conversion:* Not associated	Age, gender, alcohol and drug abuse, HIV, TB history
(56) Dooley 2009; 2004 – 2005; Maryland, USA;	Retrospective	Culture confirmed TB cases	DM medication, glucose measurement	42/279 (14)	*Sputum conversion:* DM vs non DM (median 49 versus 39 days, P = 0.09) *Death:* Unadjusted OR: 2.0 (0.74;5.2) Adjusted OR: 6.5 (1.1;38) *Treatment failure:* non DM 4.1% DM 6.7% (P = 0.51)	HIV, age, weight, foreign birth
(27) Magee 2013; 2005-2008 Peru;	Prospective	TB patients at high risk for drug-resistant TB	FBG ≥ 7.0 mmol/l, RBG ≥ 11.1 mmol/l HbA1c > 7.0%	186/1671 (11.13)	Not associated *Treatment failure:* Poor outcomes not significantly different	NR
East Asia & Pacific (EAP)						
(62) Hongguang 2015; 2010-2011 China	Prospective	Registered PTB patients	FBG ≥ 126 mg/dl; OGTT≥ 200 mg/dl	182/1126 (16.16)	*Death:* OR 5.580 (2.182;14.270) *Treatment failure:* X: OR 6.696 (2.019;22.200)	Age (<45, >45 years), gender, treatment classification
(70) Syed 2013; 2006 - 2007 Maylasia	Retrospective	TB patients and suspects	Medical records	338/1260 (26.83)	*Treatment failure:* No significant differences in terms of treatment outcomes: (p=0.514)	Looked at impact of DM on TB clinical presentations
(58) Mi 2013; 2004 – 2010; China	Cross-sectional and Retrospective	Smear positive	Medical records	189/1589 (11.890)	*Death:* RR 3.23 (1.08 – 9.63) *Treatment failure:* RR 4.46 (1.96 – 10.18)	NR
(63) Reed 2013; NR Korea	Prospective	Newly-never treated TB; Retreatment TB	National registry	51/220 (23.18); 110/437 (25.17)	*Death:* HR 2.18 (1.10 – 4.34) *Conversion:* Associated	Age, sex, education, drinking, smoking,

(67) Lee 2014; 2006 – 2007; Taiwan	Nested case control (incident cases sampling)	TB cases who completed treatment	Medical charts and National health insurance claims	DM Cases: 34.0% non DM Controls: 22.7%	*Relapse:* OR 1.96, (1.22–3.15)	NR
(68) Hsu 2012; 2004 – 2010 Taiwan	Population-based cross-sectional	Culture positive. New TB cases; Previously treated TB cases	Two tests >126 mg/dl before treatment	204/869 (23.5) 41/139 (29.5)	*Resistance to INH*: New on treatment patients: 1.88 (1.07–3.31); Retreatment patients: 6.76 (1.53–29.98)	Age, sex
(65) Chang 2011; 2004 – 2005; Taiwan	1st year cross-sectional and then prospective		FBG ≥ 126 mg/dl HbAlc ≥ 6.5%	60/192 (31.25)	*Resistance:* DMTB vs TB: 5.0% vs 0.8% (p = 0.056) *Conversion*: DMTB vs TB: (2.5 ± 3.0 months vs 1.6 ± 1.4 months (p < 0.01) *Treatment failure:* DMTB vs TB: (2.5 ± 3.0 months vs 1.6 ± 1.4 months (p < 0.01)	NR
(71) Zhang 2009; 2008-2009 China	Retrospective	Newly diagnosed PTB patents	FBG ≥ 126 mg/dl	203/2141 (9.48)	*Resistance:* DM vs non DM 17.7% vs 8.4% *Relapse:* DM vs non DM: 20% vs 5.3%	NR
(59) Wang 2009; Taiwan 2003-2006	Retrospective	Consecutive culture-proven PTB patients	Medical records , DM history and FBG ≥ 126 mg/dl confirmatory	74/217 (34.1)	*Death:* Type 2 DM (OR 7.6, 95% CI 1.976–29.083)	age, sex
Europe & Central Asia (ECA)						
(64) Magee 2014; 2009-2011; Georgia,	Prospective	Patients with MDR TB - resistant to isoniazid and rifampicin	Physician diagnosis as recorded in medical records	86/1366 (6.23)	*Conversion:* HR: 0.93 (0.71–1.23) lower rate among MDR-TBDM patients but not significant *Treatment outcomes:* RR poor outcome: 1.03 (0.93 – 1.14)	NR
(60) Magee 2014; 2009-2012; Georgia	Retrospective	PTB and EPTB diagnosed by positive culture, symptoms,	Previously diagnosed, medical records	151/1325 (11.39)	*Resistance:* TB-DM (8.3%) vs TB only (9.0%), (p < 0.01) *Death:* During treatment HR: 1.22 (0.70;2.12) *Any death:* OR: 1.05 (0.60;1.84)	SES (ethnicity, occupation), gender, age, behavioural

	radiological test	*Conversion:* MDR-TB-DM: 64 (58-106) vs MDR-TB non DM: 69 (48-118)

DM: diabetes mellitus; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; HbA1c: glycated haemoglobin; TB: tuberculosis; PTB: pulmonary tuberculosis; ETB: extra pulmonary TB; MDR: multi-drug resistance; BMI: body mass index; NR: Not reported; DOTS: directly observed short course treatment; HR: Hazard Ratio; OR: odds ratio; CI: confidence interval

Table B-4: WHO definition of tuberculosis treatment outcomes (69)

	TB outcome	Definition
Favourable outcomes	Cure	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
	Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Unfavourable outcomes	Relapse	Previously treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)
	Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
	Died	A TB patient who dies for any reason before starting or during the course of treatment.
	Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
	Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
	Multi drug resistance (MDR)	Resistance to at least both isoniazid and rifampicin.

B.4.6.1 Failure, relapse and recurrence

Several studies (58,61,62,65) reported that DM increases the risk of TB relapse, recurrence or failure during TB treatment. The proposed reasons for the increased frequency of these outcomes among diabetics were that due to impaired immunity, even after TB completion, DM patients remain susceptible to reinfection or new infection by new strains after treatment completion or being cured. There were studies (27,31,55,64) which however found null associations between DM and relapse, recurrence or treatment failure. In particular, two studies (27,55) reported that DM-TB patients had less frequent drug resistance and that they have favourable outcomes compared to non-DM TB patients. A possible reason for these null

findings could be due to short follow-up period, lack of proper statistical analyses, and not accounting for comorbidities such as HIV or competing risk factors (such as retreatment, smoking, alcohol and male sex) for these outcomes. Another reason could be due to the fact that these studies observed DM-TB patients to be more compliant to their TB medication compared to non-DM TB patients (27,55).

B.4.6.2 Sputum conversion

Sputum conversion, which in most studies referred to the time (usually in days) from treatment initiation until the first of two consecutive negative sputum cultures at greater or equal to thirty days apart, may also be affected by DM. There is heterogeneity in the findings regarding the impact of DM on time to sputum conversion. Several studies (31,54,58,61,63,65,70) concluded that DM delays the time to sputum conversion while others (27,53,66) concluded that DM has no significant effect on sputum conversion or that diabetics convert earlier than non-diabetics (55,64). Singla et al (55) showed that after three months of TB treatment, more TB patients with DM had their sputum converted compared to TB patients without DM (98.9% vs. 94.7%, $p = 0.013$). In these two studies (55,64), it was also shown that DM-TB patients with well-managed DM had more favourable TB outcomes than TB patients without DM. This could partly explain the reason for early sputum conversion among DM patients than non-DM patients.

B.4.6.3 Drug resistance

There is conflicting evidence for the influence of DM on TB drug resistance. While several studies (57,64,65,67,68,71) have reported that DM is associated with resistance, some (27,55) have found no association at all. A large proportion of studies (27,65,67,68,71) which found

an association between DM and drug resistance were from the Eastern European and Central Asian countries where MDR-TB is highly prevalent (72). Although clear mechanisms by which DM increases the risk of resistance are not provided, a suggestion is that TB patients remain susceptible to re-infection or infection by other strains of TB due to their compromised immunity. A possible explanation for the null findings could be due to lack of controlling confounding factors and other predictors of resistance such as retreatment (27). Also, as one of the studies which found a null association was conducted among TB patients who specifically had a high risk of MDR-TB (27), their findings may not be generalizable to the general or other specific populations.

B.4.6.4 Death during TB treatment

More studies (54,58,61,65,70) found positive and significant associations between DM-related risk of mortality among TB patients than those (27,55,66) which found non-significant associations. Stronger associations were observed after accounting for potential confounders such as age, sex and comorbidities such as HIV. The few studies which found non-significant associations were retrospective in design and relied on self-report and medical records to classify DM. Only one of them used survival analysis. The differences in findings between the various studies could partly be explained by methodological differences such as study design, short follow-up period and methods to classify DM status and inadequate statistical analysis.

B.4.7 Comorbidity

At the individual level, HIV is a well-known strong risk factor for TB disease and HIV-associated adverse outcomes (73). Therefore the effect that DM and other risk factors have on TB may be modified or masked by HIV comorbidity. In a Ugandan study by Kibirige and colleagues, assessing the prevalence of DM among TB patients, the burden of HIV among the TB patients was 80%, and commonly recognised risk factors for DM such as high BMI, sex and age were found to be statistically insignificant in predicting DM (15). It is possible that in such a context HIV may have masked the effect of other predictors of DM.

There are contrasting findings regarding the influence of HIV on DM and on whether it modifies the effect of other risk factors. In the same Ugandan study by Kibirige at el,
HIV was interestingly associated with reduced relative odds of DM 0.17 (95% CI 0.06-0.51, p=0.016) (15). The authors proposed that the protective effect was due to cotrimoxazole prophylaxis, one of the drugs administered to HIV patients, which has been observed to cause hypoglycaemic effects in some patients (15). Faurholt-Jepsen et al in a Tanzanian case control study showed that HIV status modified the association between DM and TB (significant interaction, p=0.01) (30).

The interaction between TB and DM in HIV patients has been studied with respect to how HIV modifies measures of association between DM and TB disease or TB outcomes among HIV positive and HIV negative patients. Faurholt-Jepsen et al in a Tanzanian case control study showed that HIV status modified the association between DM and TB with a significant interaction (p=0.01). A stronger association (odds ratio: 4.2, 95% CI 1.5-11.6) between TB and DM was observed among HIV negative patients compared to the association (odds ratio: 0.14, 95% CI 0.01-1.81) observed among HIV positive patients (30). In another Tanzanian study on

the effect of DM on TB outcomes, Faurholt-Jepsen and colleagues showed a higher hazard ratio 5.09 (95% CI 2.36 – 11.02) for DM-associated death among HIV negative patients and lower hazards 2.33 (95% CI 1.20-4.53) among HIV positive individuals (66). Interestingly, this strong association was only observed in the initial hundred days of follow-up with TB treatment and not in long term. Although reasons to why this is are not well explained, this potentially has implications on the timing of DM screening and management.

B.5 Summary and highlights for further research

Forty five studies which reported the prevalence of DM among TB patients and those which assessed the association between DM and TB and the impact of DM on TB outcomes were reviewed. The studies were categorised by geographic region which allowed comparison of studies by ethnic group, economic setting and the background burden of disease. This review highlighted that across all geographic regions and settings, the prevalence of DM among TB patients is higher than the expected prevalence of DM in the general population. This prevalence is expected to increase especially in low income regions such as SSA.

Current literature suggests that DM impacts every stage of the natural history of TB through impaired cell-mediated immunity. In particular, DM increases susceptibility of individuals to infection by *Mtb* and increases the risk of progression to active TB. Furthermore, DM contributes to poor TB treatment outcomes: delayed sputum conversion, relapse, and resistance to drugs, treatment failure and death on TB treatment.

The common methodological issues which potentially affect the reliability of the estimated prevalence of DM among TB patients in the reviewed studies are overestimation of DM prevalence due to transient hyperglycaemia in some TB patients, selection bias, and differential misclassification of DM cases. Thus, there is a need for methods and analyses techniques to account for and address these issues. The clinical condition of TB which induces transient chronic hyperglycaemia may lead to over diagnosis of DM and implies the possibility of reverse causality between TB and DM. There is therefore a need for DM diagnostic tools which will differentiate TB induced hyperglycaemia from hyperglycaemia due to DM. There is also a need for studies to investigate the optimal time point and cut-off to diagnose DM among TB patients. Also, there are no data on the implications of transient hyperglycaemia on future risk

of DM and subsequent TB risk, and impact on TB outcomes, this represents a knowledge gap that requires further research.

The prevalence of DM among TB patients also depends on the prevalence of the risk factors of DM and other co-morbidities in the studied population. The risk factors of DM among TB patients do not seem to be different from those observed in the general population. Increasing age, family history of DM, obesity or high BMI and male sex were recognised as significant risk factors of DM in most study settings, but were insignificant in some settings. This highlights that in order to have effective interventions for DM control, they will need to be contextualised to the population characteristics.

Conflicting findings were found among the very few studies which explored the impact of the relationship between DM and HIV comorbidity among TB patients. One study found HIV to protect against DM and a non-significant interaction between DM and TB in HIV patients, while others did find a significant interaction. There are not enough data to explain these observations, but this interaction is likely due to the fact that in comparison to DM, HIV is a well-established and stronger risk factor for TB disease and mortality at the individual level. A much higher HIV-associated risk of TB disease or mortality is thus often observed among non-diabetics whereas, among HIV negative patients, a very high diabetes-associated risk of TB disease or mortality is not observed. It is necessary to increase the number of studies conducted in high HIV burden settings to better understand this interaction between DM and TB in HIV patients.

Given that DM affects a large proportion of the population and that this burden is rapidly increasing, in the presence of an association between DM and TB, the population attributable

risk of TB due to DM will likely increase. Therefore the public health importance of this issue needs to be highlighted. Health systems will require integrated interventions for prevention, screening and management of these diseases.

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PART C: JOURNAL READY MANUSCIRPT

As per the MPH dissertation guidelines, co-authors (my supervisor) are not listed on this journal manuscript. Her contribution is mentioned in the acknowledgments section of this dissertation. This journal manuscript is written following the information for authors for the Lancet Diabetes and Endocrinology. These instructions are included in the appendix as required.

The prevalence and risk factors of diabetes mellitus among tuberculosis patients at Ubuntu clinic, Khayelistha: a cross sectional study

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Keywords: tuberculosis (TB), diabetes mellitus (DM), risk factors, impaired glucose tolerance (IGT), comorbidities, HIV, South Africa

C.1. Abstract

Summary: Current literature suggests that diabetes mellitus (DM) increases the risk of tuberculosis (TB) infection and worsens treatment outcomes. Meanwhile, TB remains a public health problem in Sub-Saharan Africa with the burden of DM is rapidly increasing. There is lack also of recent data on the burden of DM among TB patients in the South African context. The aim of the study was to assess the burden of DM and associated risk factors, and the prevalence of impaired glucose tolerance (IGT) among TB patients.

Methods: Between January 2014 and August 2015, a cross sectional study was conducted among adult patients presenting consecutively at the Ubuntu TB/HIV clinic. All participants had Gene Xpert, microscopy and sputum culture tests to confirm TB status as per the SA TB Management Guidelines. Diagnosis of DM was based on oral glucose tolerance test (OGTT) ≥ 11·1 mmol/L, fasting blood glucose (FBG) ≥ 7·0 mmol/L, glycated haemoglobin (HbA1c) ≥ 6·5% or self-reported DM. Impaired glucose tolerance was defined 5·7% ≤ HbA1c < 6·5% or 5·5 ≤ FBG < 7·0 or IGT: 7·7 ≤ OGTT < 11·1 mmol/L. The World Health Organisation STEPS Chronic Disease Risk Factor Survey and the SA TB suspect screening questionnaire were used to document patients' characteristics. Bivariate and multivariate including sex-specific analyses were performed to determine risk factors associated with DM among these TB patients.

Findings: The prevalence of DM among the TB patients was 39/288 (13·54%; 95% confidence interval (CI) 10·03-18·03); DM was previously diagnosed in 11/39 of the DM patients and 6/11 of these were receiving DM medications. The prevalence of IGT was 139/288 (48·26%; 95% CI 42·51-54·07%). Common co-existing conditions among the patients were hypertension (18·06%; 95% CI 14·01-22·96%) and HIV (64·31%; 95% CI 58·52-69·71%). On multivariate analysis, positive family history of DM (odds ratio (OR): 3·20; 95% CI 1·61-8·83, p=0·025), hypertension (OR 4·49; 95% CI 1·536-13·147; p=0·006) and waist

circumference (OR: 1·03; 95% CI 1·00-1·06; p=0·027) were significantly associated with DM. In the multivariate model for females, only gestational DM was (p=0·008) was associated with DM and in the model for males, hypertension (p=0·024) and the age category > 45 years (p=0·005) were associated with DM.

Interpretation: The high prevalence of IGT highlights that without timely prevention interventions the prevalence of DM with further increase. Interventions need to prioritise DM screening and management among high risk groups (patients with: hypertension, family history of DM, high waist circumference; men with age > 45 years and hypertension; females with gestational DM).

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C.2. Background

Although the global incidence of tuberculosis (TB) has shown a 1.65% annual decline over the past two decades (1), TB remains a public health challenge in most developing countries such as Sub-Saharan Africa (SSA). Factors such as poverty, malnutrition (2), the human immunodeficiency virus (HIV) and diabetes mellitus (DM) are known to drive the TB epidemic (3).

An increasing body of evidence suggests that DM is a significant risk factor for TB (4,5). Adverse outcomes such as death, relapse and drug resistance, during TB treatment have also been associated with DM (6,7). The biological plausibility of the DM-TB association is based on hypotheses that DM patients have impaired immune response, dysfunction of alveolar macrophages, micronutrient deficiency and pulmonary microangiopathy (8,9). In acute TB conditions, TB can also induce chronic hyperglycaemia (8,9), hence complicating this association.

This link has become more significant recently with the burden of DM increasing in low- and middle- income countries (LICs and MICs), which continue to suffer a heavy burden of infectious diseases (IDs). The burden of DM in Africa was estimated at 19·8 million in 2013 and is projected to increase to 41·4 million in 2030 (10). These countries that are undergoing development processes such as urbanisation, lifestyle, nutritional and epidemiological transition. This epidemiological transition is characterised by an increasing burden of non-communicable disease (NCDs) co-occurring with IDs. Interactions between NCDs and IDs have been revealed, sometimes mediated by common risk factors (11).

Risk factors for DM in the general population are well documented, and include obesity, family history of diabetes, poor diet, physical inactivity, increasing age, ethnicity, high blood pressure, and gestational diabetes (10). It is however not clear whether the same risk factors apply to TB

patients. Some studies have shown increasing age, family history of DM, overweight and obesity to be significantly associated with DM among TB patients (12–24), while in other SSA regions, overweight among TB patients is not commonly associated with DM. Interaction between age and sex (24) between and BMI and sex are also observed (13).

South Africa (SA) is listed among the top six countries with a high TB incidence in the world and an increasing burden of DM, in 2013 there were between 410 000 and 520 000 new TB cases (1) and approximately 2·6 million people living with DM (8,20). The country is also undergoing a demographic and epidemiological transition as mentioned above (25). With current evidence suggesting that DM increases the risk of TB, this burden of DM is a potential threat to current TB control management efforts. Additional to current TB control strategies, incorporating the elimination of risk factors for TB may be effective in reducing the TB burden at a population level.

In 2009 a cross-sectional study conducted within predominantly black residential areas (including Khayelitsha) in Cape Town estimated the prevalence of DM to be 12·3% and that of IGT 11·2% (27). To our knowledge, the only one South African study which assessed the prevalence of DM among TB patients reported a 2·1% prevalence in 1980 (12). The current study therefore aimed to quantify the current prevalence of DM and IGT, and identify risk factors associated with DM among TB patients presenting at the Ubuntu TB/HIV clinic in Khayelitsha.

C.3. Methods

C.3.1 Study setting

This study was conducted at Ubuntu Clinic which is an integrated TB/HIV facility and the largest TB clinic in Khayelitsha. This township is situated on the outskirts of Cape Town with

a population of over 500 000 individuals predominantly constituting of black Africans. In 2011, the HIV antenatal prevalence was estimated at 37% and the TB case notification was 1500 per 100 000 population (28). The high TB incidence in this township is mainly due to the high HIV prevalence with a 70% HIV-TB co-infection rate (28).

C.3.2 Study design and sampling

From January 2014 to August 2015, consecutive patients presenting at Ubuntu Clinic with TB symptoms identified by trained clinical research workers and were invited to participate in the current study. Patients were eligible if they gave consent, were 18 years or older and had not initiated TB chemotherapy. Based on the 16·5% prevalence of DM among TB patients in a Ugandan study (29), we manually computed the required sample size to be 207 *($n = z^2p\,(1-p)/d$*; where *$d = 0{\cdot}05$, $z = 1{\cdot}96$).*

C.3.3 Ethical considerations

All participants included gave written consent and information about the study was reads and explained to them in their home language (mainly isiXhosa). Unique participant identifiers linked to each participant were used to maintain confidentiality. This study was approved by the University of Cape Town Health Research Ethics Committee (HREC REF: 337/2015).

C.3.4 Study procedures

Confirming TB cases: TB patients were identified through a clinical process as per the South African TB Management Guidelines which also adhere to the WHO TB recommendations (1,30). Confirmation of TB was made based on a positive test for 1) the sputum smear

microscopy; 2) Gene Xpert; 3) Sputum culture; or 4) chest X-rays or clinical presentations suggestive of TB (identified by a medical doctor).

Demographic and socioeconomic characteristics: Demographic information included sex; age categorised into ten year intervals; partner status; education level; size of household; employment status and income status categorised by the 2011 Census for Khayelistha (31).

Diagnosing DM in TB patients: DM and IGT were defined based on the WHO and International Diabetes Federation (IDF) recommended definitions (32–34). Blood samples were taken to measure fasting blood glucose (FBG) after overnight fasting using, 2 hours oral glucose tolerance test (OGTT) and glycosylated haemoglobin (HbA1c); and were analysed at a centralised national health laboratory. DM diagnosis was based on self-reported DM, or FBG ≥7·0 mmol/L; OGTT ≥ 11·1 mmol/L and or HbA1c ≥ 6·5%. IGT was defined as 5·7% ≤ HbA1c < 6·5% or 5·5 ≤ FBG < 7·0 and or 7·7 ≤ OGTT < 11·1 mmol/L.

Chronic diseases: Self-report of other chronic diseases, medication prescription and DM symptoms (polydipsia, nocturia or polyuria) were documented. Data on family history of DM, gestational DM, hypertension, HIV, and previous TB occurrence were also recorded.

Anthropometric measurements: Weight and height were measured and body mass index (BMI kg/m^2) was calculated. The BMI categories were as follows: (underweight: < 18·5, normal: 18·5 ≤ BMI < 25, overweight: 25 ≤ BMI < 30, obese: ≥ 30) (35). Waist circumference was also measured with the cut off value for high waist circumference (cut off: ≥ 102 cm for males and ≥ 88 cm for females) (35). Blood pressure measured and hypertension was diagnosed at ≥ 90 Hmmg for diastolic blood pressure or ≥ 140 for systolic blood pressure (36) in addition to hypertension medication.

Lifestyle, diet and behaviour: Smoking status was categorised as ever smoker (past or current smokers) or never smoker. Alcohol intake was categorised as non-drinker or any intake in the

past 12 months. Engagement in physical activity and sedentary occupation were also documented. Fruit and vegetable intake were categorised as low if patients reported to be consuming less than 5 (or 400 g) servings of fruits or vegetables per day (37).

C.4. Statistical analysis

Medians and inter quartile ranges (IQR) were used to summarise continuous variables and categorical variables were summarised using proportions. The Chi-squared and Fisher's exact tests were used to assess associations between categorical variables DM and IGT. To assess associations between continuous variables and the categorical variables, the Mann-Whitney test was used to compare medians between two groups and the Kruskal-Wallis test to compare medians between more than two groups. Logistic regression was performed to identify risk factors which were independently associated with either DM or IGT.

A multivariate logistic regression model was manually build to assess independent factors associated with DM and IGT. Due to significant differences in characteristics with respect to sex, sex-specific models were also build. The log likelihood ratio test was used to compare models which were nested. Statistical significance was set at p-value $< 0{\cdot}05$.

All data were analysed using STATA 10.0 (StataCorp, College Station, TX, USA).

C.5. Results

Demographic: Of the 288 TB patients included in the analysis, (shown in *Table C-1*) 167 (58%) were males, 68·41% of the patients were between the ages 25 and 45 years, the median age was 36 years IQR (30-44 years) and the youngest and oldest patients were 18 and 80 years respectively. Males were found to be older than females (medians age year: 37 vs 35; p=0·026).

Socioeconomic: Majority (64%) of the TB patients had secondary level education attainment, whilst females were found to have a higher attainment (secondary and tertiary) compared to males (p=0·012). Of the patients 50·90% were unemployed and the median monthly income was R 2 100 where males earned more (p=0·028) *(Table C-1)*.

Behavioural: About 38·35% of the TB patients had an alcoholic drink in the past 30 days or 12 months, the majority of them being males (p<0·001). The prevalence of ever smoking was 53% and was also higher among males (p<0·001). More females had sedentary occupations (p=0·002) and were inactive (p=0·040) *(Table C-1)*.

Anthropometric: The prevalence of overweight and obesity were 14·71% (95% CI 10·68-19·93%) and 7·79 (95% CI 4·95-12·07%) respectively. Females had a much higher BMI than males (p=0·000) *(Table C-1).* The prevalence of underweight was 11·69% (95% CI 8·12-16·55%). More males than females were underweight (16·54% vs 5·10%). Similarly, females had higher waist circumference compared to males (p=0·012).

Comorbidities: The prevalence of hypertension was 18·06% (95% CI 14·01-22·96%); 36.52% of which were self-reported (68·42% of the self-reported hypertension patients were receiving hypertension medication). A larger proportion of the hypertensive patients were males (p = 0·000) and HIV co-infection was found to be 64·31% 95% (CI 58·52-69·71%) and was significantly higher among females (p < 0·001). Among HIV positive patients, 35·16% were on ART and 35·56% of these patients were previous TB cases.

Table C-1: Study characteristics of participants stratified by sex

Variable	Females	Males	Total	P-values
Continuous variables median (IQR)				
Age (years)	35 (29 – 41)	37 (30 – 45)	288	0.0256
Income (Rands)	1 800 (900 – 3 000)	2 500 (1 300 – 35000)		0.0242
Body mass index (kg/m^2)	23.89 (21.25 – 26.59)	20.41 (18.96 – 22.36)	213	0.0000
Waist circumference (cm)	82.5 (75 – 88)	77 (74 – 83)	213	0.0012
Diastolic (mm Hg)	114.5 (107 – 122.5)	119 (109 – 130)	286	0.0022
Systolic (mm Hg)	74 (69 – 80.5)	75 (69 – 84)	273	0.1957
HbA1c (%)	5.7 (5.5 – 5.7)	5.9 (5.6 – 6.2)	284	0.2900
FBG (mmol/L)	4.6 (4.2 – 5)	4.6 (4.2 – 5.2)	286	0.9526
OGTT (mmol/L)	5.8 (5.1 – 7)	6.3 (5 – 7.4)	255	0.3968
Categorical variables N (%)				
Age				
< 25 (reference)	18 (14.88)	15 (8.98)	33 (11.46)	0.097
25 – 35	45 (37.19)	61 (36.53)	106 (36.81)	
36 – 45	41 (33.88)	50 (29.94)	91 (31.60)	
>45	17 (14.05)	41 (24.55)	58 (20.14)	
Education				
None (reference)	2 (1.17)	11 (6.67)	13 (4.61)	0.012
Primary	24 (20.51)	54 (32.73)	78 (27.66)	
Secondary	86 (73.50)	96 (58.18)	182 (64.54)	
Tertiary	5 (4.27)	4 (2.42)	9 (3.19)	
Employment				
Unemployed (reference)	67 (58.26)	75 (45.73)	142 (50.90)	0.215
Employed	42 (36.52)	77 (46.95)	119 (42.65	
Retired/Receiving grants/ homemaker	4 (3.48)	9 (5.49)	13 (4.66)	
Student	2 (1.74)	3 (1.83)	5 (1.79)	
Partner status				
Without partner	79 (67.52)	102 (61.82)	181 (64.18)	0.212
With partner	23 (19.66)	47 (28.48)	70 (24.82)	
Lost/divorced/separated	15 (12.82)	16 (9.70)	31 (10.99)	
Household size				
0 – 2 (reference)	55 (59.11)	108 (67.08)	163 (59.71)	0.003
>2	57 (50.89)	53 (32.92)	110 (40.29)	
Income categories				
R 1 – R 1 600	49 (49.49)	44 (33.33)	93 (40.26)	0.028
R 1 601 – R 3 200	30 (30.30)	50 (37.88)	80 (34.63)	
R 3 201 – R 6 400	13 (13.13)	50 (37.88)	80 (34.63)	
R 6 401 – R 12 800	5 (5.05)	31 (23.48)	44 (19.05)	
R 12 801 or more	2 (2.02)	0 (0.00)	2 (0.87)	
Fruit intake				
More than 5 fruits/day	5 (4.13)	5 (3.05)	10 (3.51)	0.748
Less than 5 fruits/day	116 (95.87)	159 (96.95)	275 (96.49)	
Vegetable intake				
More than 5 vegetable/day	5 (4.13)	15 (8.98)	20 (6.94)	0.158
Less than 5 vegetables/day	116 (95.87)	152 (91.02)	268 (93.06)	
Physical activity				
Inactive	109 (94.78)	143 (87.20)	252 (90.32)	0.040
Active	6 (5.22)	21 (12.80)	27 (9.68)	
Sedentary occupation				
Non sedentary	8 (6.96)	34 (20.73)	42 (15.05)	0.002
Sedentary	107 (93.04)	130 (79.27)	237 (84.95)	
Alcohol in the past 30 days or 12 months				
No	92 (79.31)	72 (48.00)	164 (61.65)	
Yes	24 (20.69)	78 (52.00)	102 (38.35)	0.000

Ever smoker				
No	101 (83.47)	33 (19.76)	134 (46.53)	0.000
Yes	20 (16.53)	134 (80.24)	154 (53.47)	
BMI categories				
Underweight (< 18.5 kg/m^2)	5 (5.10)	22 (16.54)	27 (11.69)	0.000
Normal (18.5 - 24.99 kg/m^2) (reference)	56 (57.14)	96 (72.18)	152 (65.80)	
Overweight (25 - 29.99 kg/m^2)	26 (26.53)	8 (6.02)	34 (14.72)	
Obese (> 30 kg/m^2)	11 (11.22)	7 (5.26)	18 (7.79)	
Waist circumference				
< 102 cm male, < 88 female	68 (75.56)	119 (96.75)	187 (87.79)	0.000
> 102 cm male, > 88cm female	22 (24.44)	4 (3.25)	26 (12.21)	
Hypertension				
No	108 (89.26)	128 (76.65)	236 (81.94)	0.000
Yes	13 (10.74)	39 (23.35)	52 (18.06)	
DM symptoms				
No	62 (51.24)	85 (50.90)	147 (51.04)	0.954
Yes	59 (48.76)	82 (49.10)	141 (48.96)	
DM family history				
No	93 (80.87)	132 (80.49)	225 (80.65)	0.939
Yes	22 (19.13)	32 (19.51)	54 (19.35)	
HIV Status (self-reported)				
Negative	19 (16.10)	66 (40.00)	85 (30.04)	0.000
Positive	94 (79.66)	88 (53.33)	182 (64.31)	
Unknown	5 (4.24)	11 (6.67)	16 (5.65)	
Previous TB				
No	68 (69.39)	86 (60.99)	154 (64.44)	0.182
Yes	30 (30.61)	55 (39.01)	85 (35.56)	

IQR: inter quartile range; HbA1c: Glycated haemoglobin; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; BMI: body mass index; DM: diabetes mellitus; HIV: Human immune deficiency virus; TB: tuberculosis

The prevalence of DM and IGT

Out of the 288 TB patients, 39/288 (13·54%; 95% CI 10·03-18·03%) had DM. DM was newly diagnosed in 28/39 (72%) of the TB patients. Of the 11/39 (28%) with previously diagnosed DM, 6/11 (54·54%) reported to be taking DM medications. Among all the TB patients, the HbA1c levels were: median 5·55% (IQR: 5.8-6·15%), ranging between 3·2% and 17·3%. The overall HbA1c levels among previously diagnosed DM patients were slightly higher (n=11; median HbA1c (%): 11·2; IQR: 7·7-13·3), compared to newly diagnosed DM (n=28; median HbA1c (%): 6·6; IQR: 6·5-7·75), p=0.0048. Among previously diagnosed DM patients, those on medications had higher HbA1c levels (n = 6, median HbA1c%: 12·15, IQR: 11·2-15·4) compared to those not on medications (n = 5, median HbA1c%: 7·7, IQR: 6·9-10·6), p =

0·0679. The prevalence of diabetes symptoms nocturia, polydipisia and polyuria were 34·72%, 35·90% and 37·85% respectively but were not significantly associated with IGT or DM. The prevalence of IGT was 139/288 (48·26%; 95% CI 42·51-54·07%).

On bivariate analysis *(Table C-2*: *)* DM and IGT were significantly associated with alcohol consumption in the past 12 months (p=0·013), age categories (p=0·000), education level (p =0·028), hypertension (p=0·000) and gestational DM (p=0·003).

Table C-2: Comparison of study characteristics among TB patients with normal glycaemia, impaired glucose tolerance (IGT) and diabetes mellitus (DM)

Characteristics	Normal 110	IGT 139	DM 39	N (%) 288	P-value
Continuous variables median (IQR)					
Age (years)	33 (28 – 42)	36 (30 – 43)	45 (33 – 57)	288	0.029
Income (Rands)	2 500 (1 200 – 3 500)	2 000 (1 200 – 3 000)	1 600 (1200 - 4000)	231	0.465
Body mass index (kg/m^2)	22.16 (19.58 – 25.08)	20.94 (19.11 - 23.88)	23.1 (20.4 - 25.74)	231	0.980
Waist circumference (cm)	79 (74 – 94)	78 (75 – 84)	84 (76 – 90)	231	0.720
Diastolic (mm Hg)	75 (69 – 81)5	74 (68 – 82)	80 (74 – 88)	286	0.991
Systolic (mm Hg)	117 (108 – 127)	116 (106 – 124)	127 (113 – 138)	273	0.164
HbA1c (%)	5.5 (5.3 – 5.7)	6.0 (5.8 – 6.2)	6.8 (6.5 – 11.2)	284	0.030
FBG (mmol/L)	4.3 (4.1 – 4.7)	4.6 (4.3 – 5.1)	5.9 (5.1 – 8.1)	286	0.004
OGTT (mmol/L)	5.4 (4.85 – 6.2)	6.4 (5.5 – 7.8)	7.6 (6.4 – 12.0)	255	0.081
Categorical variables N (%)					
Sex					
Female	53 (48.18)	51 (36.69)	17 (43.59)	121 (42.01)	0.185
Male	57 (51.82)	88 (63.31)	22 (56.41)	167 (57.99)	
Age					
< 25 (reference)	16 (14.55)	11 (7.91)	6 (15.38)	33 (11.46)	0.000
25 – 35	49 (44.55)	52 (37.41)	5 (12.82)	106 (36.81)	
36 – 45	30 (27.27)	52 (37.41)	9 (23.08)	91 (31.60)	
>45	15 (12.73)	24 (17.27)	19 (48.72)	58 (20.14)	
Education					
None (reference)	4 (3.67)	7 (5.19)	2 (5.26)	13 (4.61)	0.028
Primary	22 (20.18)	40 (29.63)	16 (42.11)	78 (27.66)	
Secondary	76 (69.72)	87 (64.44)	19 (50.00)	182 (64.54)	
Tertiary	7 (6.42)	1 (0.74)	1 (2.63)	9 (3.19)	
Employment					
Unemployed (reference)	56 (52.34)	66 (49.25)	20 (52.63)	142 (50.90)	0.097
Employed	46 (42.99)	61 (45.52)	12 (31.58)	119 (42.65)	
Retired/Receiving grants/ homemaker	2 (1.87)	6 (4.48)	5 (13.16)	13 (4.66)	
Student	3 (2.80)	1 (0.75)	1 (2.63)	5 (1.79)	
Partner status					
Without partner (reference)	79 (72.48)	84 (62.22)	18 (47.37)	181 (64.18)	0.072
With partner	22 (20.18)	35 (25.93)	13 (34.21)	70 (24.82)	
Lost/divorced/separated	8 (7.34)	16 (11.85)	7 (18.42)	31 (10.99)	
Number of adults in household					
0 – 2 (reference)	65 (61.90)	78 (58.21)	20 (58.82)	163 (59.71)	0.841
>2	40 (38.10)	56 (41.79)	14 (41.18)	110 (40.29)	
Income categories					
R 0 (reference)	-	-	-	-	0.153
R 1 – R 1 600	33 (37.08)	44 (39.64)	16 (51.61)	93 (40.26)	
R 1 601 – R 3 200	31 (34.83)	44 (39.64)	5 (16.13)	80 (34.63)	
R 3 201 – R 6 400	21 (23.60)	16 (14.41)	7 (22.58)	44 (19.05)	
R 6 401 – R 12 800	4 (4.49)	6 (5.41)	2 (6.45)	12 (5.19)	
R 12 801 or more	0 (0.00)	1 (0.90)	1 (3.23)	2 (0.87)	
Alcohol consumption in the past 30 days or 12 months					
No	63 (61.17)	72 (56.25)	29 (82.86)	164 (61.65)	0.013
Yes	40 (38.83)	56 (43.75)	6 (17.14)	102 (38.35)	

Ever smoker					
No	54 (49.09)	58 (41.73)	22 (56.41)	134 (46.53)	0.211
Yes	56 (50.91)	81 (58.27)	17 (43.59)	154 (53.47)	
Fruit intake					
More than 5 fruits/day	1 (1.04)	6 (4.35)	2 (5.26)	9 (3.31)	0.245
Less than 5 fruits/day	95 (98.96)	132 (95.65)	36 (94.774)	263 (96.69)	
Vegetable intake					
More than 5 vegetable/day	4 (4.12)	13 (9.35)	2 (5.13)	19 (6.91)	0.324
Less than 5 vegetables/day	93 (95.88)	126 (90.65)	37 (94.87)	256 (93.09)	
Physical activity					
Inactive	82 (86.32)	122 (91.04)	37 (97.37)	241 (90.26)	0.140
Active	13 (13.68)	12 (8.96)	1 (2.63)	26 (9.74)	
Sedentary occupation					
Non sedentary	14 (14.74)	22 (16.42)	6 (15.79)	42 (15.73)	0.942
Sedentary	81 (85.26)	112 (83.58)	32 (84.21)	225 (84.27)	
Hypertension					
No	93 (84.55)	121 (87.05)	22 (56.41)	236 (81.94)	0.000
Yes	17 (15.45)	18 (12.95)	17 (43.59)	52 (18.06)	
Body mass index					
Underweight (< 18.5 kg/m2)	8 (9.41)	18 (15.79)	1 (3.85)	27 (12.00)	0.170
Normal (18.5 - 24.99 kg/m^2)(reference)	56 (65.88)	75 (65.79)	17 (65.38)	148 (65.78)	
Overweight (25 - 29.99 kg/m^2)	16 (18.82)	14 (12.28)	3 (11.54)	33 (14.67)	
Obese (> 30 kg/m^2)	5 (5.88)	7 (6.14)	5 (19.23)	17 (7.56)	
Waist circumference					
< 102 cm male or < 88 cm female	74 (89.16)	94 (89.52)	19 (76.00)	187 (87.79)	0.159
> 102 cm male or > 88 cm female	9 (10.84)	11 (10.48)	6 (24.00)	26 (12.21)	
Diabetes symptoms (Polydipsia, Nocturia or Polyuria)					
No	52 (47.27)	77 (55.40)	18 (46.15)	147 (51.04)	0.358
Yes	58 (52.73)	62 (44.60)	21 (53.85)	141 (48.96)	
Diabetes family history					
No	75 (78.95)	113 (84.33)	26 (68.42)	214 (80.15)	0.089
Yes	20 (21.05)	21 (15.67)	12 (31.85)	53 (19.85)	
Gestational diabetes (among females)					
No	50 (98.04)	47 (97.92)	12 (75.00)	109 (94.78)	0.003
Yes	1 (1.96)	1 (2.08)	4 (25.00)	6 (5.22)	

IQR: inter quartile range; HbA1c: Glycated haemoglobin; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; BMI: body mass index; IGT: impaired glucose tolerance; DM: diabetes mellitus; HIV: Human immune deficiency virus; TB: tuberculosis.

Multivariate Analysis

The final model *Table C-3* for DM included positive family history of DM, hypertension, waist circumference and age categories. Of the TB patients, 19·35% (54/279) had a history of DM in their families. Among these patients, 38·88% (21/54) had IGT and 22·22% (12/54) had DM

where a third (4/12) of the DM was previously diagnosed. TB patients with a positive family history of DM had a three-fold increase in the relative odds of DM compared to those without family history of DM (OR: 3·203; 95% CI 1·61-8·83, p=0·025). For a 1 cm increase in waist circumference, there was a 3% increase in the relative odds of DM (OR: 1·033, 95% CI 1·004-1·064, p = 0·027).

The prevalence of hypertension was 18·05% (52/288) and 36·52% (19/52) of this was previously known and 68·42% (13/19) of the self-reported hypertension patients were receiving hypertension medication. Among the hypertensive patients, 34·61% (18/52) had IGT and 32·69% (17/52) had DM. Among the DM-hypertension patients, DM was previously diagnosed in 47·06% (8/17) patients. Patients with hypertension had four and a half-fold increase in the odds of DM compared to those without hypertension (OR 4·494 95% CI 1·536-13·147, p = 0·006).

Age was a confounder for the association between DM and hypertension. Due to significant differences in associations between various risk factors (as shown in *Table C-1*), gender specific multivariate models were built. Among males (*Table C-4),* the age category > 45 years (OR 11·049, 95% CI 2·092-58·350, p = 0·005) and hypertension (OR 3·3, 95% CI 1·167-9·334, p = 0·024) were strongly associated with DM. Among females (*Table C-5*), only gestational DM (OR 14·55, 95% CI 2·033-103·587, p=0·006) was significantly associated with DM. Gestational DM was present in 5·22% (6/115) of the females, among them, 66·67% (4/6) had DM, of which 50% (2/4) was previously diagnosed, and 16·67% (1/6) had IGT. The confidence intervals for these estimates were found to be wide because of the reduced sample size when observations were restricted to one sex group.

Table C-3: Multivariate analysis, risk factors associated with DM among TB patients

Risk factor	Odds Ratio	Standard error	p-value	95% Confidence Interval
Age categories				
25 – 35 years	3.489	2.713552	0.108	0.760-16.021
36 – 45 years	1.482	1.015425	0.566	0.387-5.676
> 45 years	2.619	1.933768	0.192	0.616-11.133
Diabetes family history	**3.203**	**1.657989**	**0.025 ***	**1.161-8.834**
Waist circumference	**1.033**	**0.0153323**	**0.027 ***	**1.004-1.064**
Hypertension	**4.494**	**2.461315**	**0.006 ****	**1.536-13.147**
Significance levels: *0.05; ** 0.01; *** 0.001				

Table C-4: Multivariate analysis, risk factors associated with DM among male TB patients

Risk factors	Odds Ratio	Standard error	p-values	95% Confidence Interval
Diabetes family history	**2.406**	**1.489**	**0.156**	**0.715-8.093**
Age categories				
25 – 35 years	1.860	2.393	0.629	0.150-23.132
36 – 45 years	2.893	2.545	0.227	0.516-16.225
>45 years	**11.049**	**9.381**	**0.005****	**2.092-58.350**
Hypertension	**3.300**	**1.751**	**0.024***	**1.167-9.334**
Significance levels: *0.05; ** 0.01; *** 0.001				

Table C-5: Multivariate analysis, risk factors associated with DM among female TB patients

Risk factors	Odds Ratio	Standard error	p-value	95% Confidence Interval
Gestational Diabetes	**14.515**	**14.553**	**0.008****	**2.034-103.587**
Age categories				
25 – 35 years	3.615	3.250	0.153	0.621-21.060
36 – 45 years	2.056	1.744	0.396	0.390-10.841
>45 years	5.237	4.540	0.056	0.957-28.64
Significance levels: *0.05; ** 0.01; *** 0.001				

C.6. Discussion

The prevalence of DM among TB patients at Ubuntu clinic

This study aimed to quantify the burden of DM and associated risk factors among TB patients in a high TB/HIV setting. To our knowledge, this is first up to date study assessing DM and TB in South Africa during this epidemiological era characterised by the high burden of TB/HIV and rapidly increasing burden of non-communicable diseases such as DM and hypertension. We reported a 13·5% and 48·26% prevalence of DM and IGT. DM was previously diagnosed in 28% of the DM patients and 54·54% were receiving medications of these patients were receiving medications.

The management of DM was poor even among the patients on medication. Unexpectedly there were higher glucose levels among those receiving medications compared to those who did not ($p = 0.0679$). In addition to DM complications, this has potential implications for TB outcomes. Possible reasons for this may be due to severe TB conditions which may have also induced hyperglycaemia (38). Another reason could be that although the patients have prescriptions, they may not be taking their medication appropriately or they may not have modified their life style as required. This highlights a gap within health care facilities and the need to monitor patients on chronic mediation in order to prevent secondary complications.

Globally, studies assessing the prevalence of DM and associated risk factors among TB patients published between 1980 and 2014 reported the prevalence of DM among TB patients ranging from 2·1% in South Africa in 1980 to 44% in Kerela, India in 2012 (12–15,18,21,24,29,39). The heterogeneity in these findings could be due to differences in socio-demographic and economic characteristics of the studied population, differences in methods to diagnose DM, the prevalence of risk factors of DM and the existence of other comorbidities.

The prevalence of DM in TB patients from South Asian (range: 25·3-44%) (16–19,39) and Latin American (range: 14-39 %) (21,22) study populations are high possibly because DM in the general populations in high in these regions. In the SSA region, the prevalence ranges between 2·1% in South Africa, 1980 to 16·4% in Tanzania in 2012 (12–15,29). Future projections suggest that majority of the global increase of DM will be from low income settings such as SSA (10). The high prevalence of IGT reported in this study (48%) hints at the plausibility of this projected increase. However it also highlights the opportunity for interventions to prevent this from happening because IGT is a reversible condition (40).

Risk factors associated with DM among TB patients

We did not find DM to be significantly associated with any of the socio economic factors. A possible reason for this could be because our studied population is relatively homogenous with respect to these factors. To explore these associations, populations with variable characteristics would have to be included.

Similar to findings from others studies, hypertension (17), increasing waist circumference (13,19) and positive family history of DM (14,16) were significantly associated with DM on multivariate analysis. Patients with a diabetes family history had a three-fold increase in the odds of diabetes compared to those without (OR: 3·203 95%; CI 1·161-8·834; p=0·025) and there was a four and half increase in the odds of DM among those whose with hypertension compared to those without hypertension (OR: 4·49; 95% CI 1·536-13·147; p=0.006). For a centimetre increase in waist circumference, there was a 3% increase in the relative odds of DM (OR: 1·033; 95% CI 1·004-1·064, p=0·027).

In contrast to commonly observed risk factors of DM in the general population, factors such as high BMI, sedentary lifestyle, physical inactivity, sex and smoking were not significantly associated with DM and pre-DM in our study. Similarly, Kibirige et al 2013 in their study found no association between DM and these mentioned factors (29).

In our study, normal weight (moderate BMI 18·5-24·99 kg/m^2) was very common (64%), it therefore makes sense that physical activity, sedentary occupations and high BMI did not play a major role in predicting DM or IGT among TB patients. The prevalence of overweight (25-29·99 kg/m^2) and obesity (> 30 kg/m^2) were 14·71% (95% CI 10·68-19·93%) and 7·79 (95% CI 4·95-12·07%) respectively, given that these patients have TB, this is high. Although underweight was higher among males, we did not observe any interaction between sex and the different BMI or waist circumference categories. In contrast, Faurholt-Jepsen et al in their Tanzanian study assessing predictors of DM among TB patients observed underweight was a strong predictor of DM among males (13).

We suspected that underweight was due to severe DM, HIV or TB itself. However, neither BMI nor underweight in particular were significantly associated with either DM or HIV. This suggests that among TB patients, BMI which is used as a marker for obesity is not necessarily the best indicator for DM, other markers such a waist circumference which approximate visceral fat should also be considered. However, it is important to note that 14·71% and 7·79% of the patients were overweight and obese respectively, this is high considering that they have TB.

We acknowledge that there are limitations to our study. By the nature of the cross-sectional design of the study, temporality between TB and DM could not be ascertained. Among patients who had previously diagnosed DM, the time of DM diagnosis was not documented. The TB patients included in this study were mostly newly TB diagnosed and not on medication,

therefore it is possible that their glucose levels were influenced by the transient hyperglycaemia which tends to occur during acute TB conditions (38). Nonetheless, we used the HbA1c test which is suggested to possibly overcome this limitation of having transient acute stress induced hyperglycaemia as it reflects the average blood glucose level over two to three months (33). Patients who were severely ill and could not consent were not included in this study. The potential effect of this could be that our study did not include the most severe TB patients who may be more likely to have DM given the association between DM and poor TB outcomes/prognosis and hence could lead to an under estimation of the DM prevalence. Also, we did not distinguish between type 1 and 2 diabetes.

C.7. Conclusion

The prevalence of DM is likely to increase as indicated by the high prevalence of IGT. However, this is also an opportunity to prevent this increase through interventions on modifiable risk factors. Furthermore, improved care and follow-up of patients on chronic medications is essential to prevent secondary complications. Routine screening of DM among TB patients in the identified high risk groups (patients with: hypertension, family history of DM, high waist circumference; men with age > 45 years and hypertension; females with gestational DM) may be efficient. It is also recommended that health systems manage such chronic diseases in an integrated system. Although overweight and obesity were more prevalent than expected among the TB patients, high BMI – a marker for obesity and common risk factor for DM in the general population, was not necessarily the best indicator for DM. Rather, waist circumference showed a significant association with DM. It is essential to have more studies to investigate anthropometric characteristics that could best predict DM among TB patients. We have established a high prevalence of DM among TB patients in the South African context.

Areas of future research in this high TB and HIV burden setting include investigating the causal association between DM and TB; the impact of DM on clinical manifestations of TB and TB treatment outcomes; and the possible interactions between DM and HIV. Prospective cohort and case control study designs may be more appropriate to address these questions. Furthermore, it would be essential to conduct dynamic mathematical modelling studies to explore the population level contribution of various prevalent TB risk factors including DM, HIV, tobacco and alcohol, to the burden of TB and multi-morbidity.

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PART D: APPENDICES TO THE DISSERTATION

D.1. Protocol for main study

OVERAL RESEARCH OBJECTIVE
The main aim of this study is to investigate the incremental yield and best screening algorithms for diabetes mellitus (DM) and tuberculosis (TB) among a) newly diagnosed TB patients and b) patients attending diabetic clinics, respectively.

Specific aims:

- To assess the prevalence of DM among TB cases
- To evaluate the best performing algorithms to diagnose DM in TB cases
- To measure the prevalence of TB among diabetes patients

BACKGROUND
TB remains a leading cause of death globally, with an estimated 8.8 million new cases reported every year, threatening the goal of global TB elimination by year 2050 (1). Tackling this challenge will require not only improvements in diagnostic and treatment services, but identification and reduction of risk factors that increase susceptibility for TB. Medical conditions that impair immune function, such as malnutrition, alcoholism or HIV co-infection, can increase the likelihood of infection or reactivation of latent TB. Increasing evidence suggests that DM is also a significant risk factor for TB. In a recent systematic review, the relative risk for TB in diabetic patients was 3.1 (2). The strength of this link was influenced by geographic/ethnic differences, and young people were at particularly high risk; in India, DM is thought to be associated with nearly 15% of pulmonary TB cases (3). However, these studies had a number of limitations. In particular, very few were carried out in low-income countries, with none in Africa, raising uncertainty about the strength of DM-TB association and benefit of bi-directional screening for DM and TB in these settings with high TB/HIV prevalence and AN increasing burden of DM. Practical guidance on when to suspect, and how best to diagnose, diabetes in TB patients, and how to confirm or exclude it are lacking. The World Health Organisation recommends HbA1c as a diagnostic test for diabetes with a cut-off value of 6.5% (4). However, less clear is the diagnostic value of results below the WHO cut-off (there is an argument for population-specific cut-off values). A study conducted on a population of mixed-ancestry in Cape Town showed that this cut-off value was sub-optimal (erasmus). Furthermore, it is not known how the diagnostic performance of the cut-off is affected by acute illness, such as TB. A point of care HbA1c test could make diabetes screening more effective and potentially more affordable. A study comparing POC devices found that only Afinion and DCA Vantage met the diagnostic performance criteria (6). There are also insufficient data on which to base TB screening guidelines for diabetic patients.

The growing epidemic of diabetes as a threat to TB control
While 95% of patients with TB live in the low- and middle-income countries, 70% of patients with DM also live in these same countries. It is estimated that, worldwide in 2010, there were 285 million people with DM, and the number predicted to rise to 438 million by 2030, making DM one of the most common NCDs globally (7). The majority of this increase will occur in developing countries where TB remains endemic. Diabetes on this scale is likely to pose another threat for global TB control. The potential public health and clinical importance of this seems to have been largely ignored until recently. Recent joint consultations by International Union Against Tuberculosis and Lung Disease, the World Diabetes Foundation and the World Health Organization emphasised the urgent need for research in this area (10). There is also a paucity of data on whether DM is associated with a high prevalence of subclinical TB among patients attending diabetic clinics, as observed in HIV-1 co-infected persons (13). This has major importance when considering TB screening strategies, with potential for amplification by transmission within diabetic clinics and also potentially serious consequences of false-negative TB screening. Research is therefore required to develop appropriate and evidence-based guidelines for TB screening among persons with DM.

Diabetes, HIV and TB in South Africa and the Western Cape
South Africa is among the 22 high TB burden countries globally, and also has the highest urban: rural ratio in sub-Saharan Africa, with 62% of the population being urban dwellers (17). Urbanisation, in addition to rapid epidemiological and demographic transition has resulted in a rising burden of NCDs. The global burden of disease study demonstrated that in Southern Africa, while HIV and TB rank first and 4th in the top ten causes of morbidity, 50% of the causes of morbidity are non-communicable; diabetes is ranked 7th. A community survey conducted in 2008/9 from Cape Town townships showed a DM prevalence of 13.1% (95% CI: 11.0-15.1) (26).
Mortality rates from NCDs are also increasing; diabetes was the 6th leading causes of mortality in South Africa in 2010. In the Western Cape, the province within which Cape Town is located, TB and DM are the top 2 causes of mortality. Against this background, the prevalence of HIV, the strongest known risk factor for TB, remains high, with 70% of TB cases being HIV-infected in Khayelitsha

PLAN OF INVESTIGATION

Setting and study population

The study will be conducted in Khayelitsha, reputed to be the fastest growing township in South Africa. Khayelitsha is located 30km from Cape Town with a population of over 500,000 predominantly black Africans, HIV antenatal prevalence of 28% and a TB case-notification rate of >1600/100,000 (27). The largest TB clinic in Khayelitsha is Ubuntu clinic. A survey by the Department of Health reported 1187 newly registered TB cases were diagnosed at Ubuntu clinic in 2011.

Study design

DM Screen in TB patients

We will recruit consecutive TB cases at Ubuntu clinic, prior to initiation of TB treatment. We will record demographic, medical and drug history, HIV status and (if positive) date of initiation of ART, regimen, and CD4 count, as well as clinical, microscopic and radiological characteristics of TB at diagnosis. In addition we will document other risk factors for diabetes, such as family history, body mass index (BMI), and waist circumference. Before starting TB chemotherapy blood samples will be collected to measure fasting blood glucose and oral glucose tolerance test, and HbA1c performed using Afinion, a validated HbA1c Point of care test. Patients will be considered to be diabetic if 1) the diagnosis is known at presentation, 2) they are taking oral hypoglycaemic therapy and/or insulin or 3) as per case definitions. Previous studies have suggested that it may be more reliable to screen for diabetes later in the course of TB treatment rather than at the start (11), because inflammation/cytokine stimulation associated with active TB may elevate blood glucose levels resulting in false positive diabetes diagnoses if tests are performed too early. We will, therefore, repeat fasting blood glucose and HbA1c tests after 2 months of TB treatment. Patients with a new diagnosis will be referred to the DM clinic for standard care. HIV testing is offered routinely to all patients with TB.

TB screen in diabetic patients

We will recruit consecutive diabetes patients presenting to the primary care diabetes clinic at Khayelitsha day hospital. A TB screen will be performed as per case definition. We will also record demographic, medical and drug history, previous TB and TB contact history, as well as HbA1c to measure glycaemic control at the time of recruitment.

Diabetes screen in TB patients *(Baseline and 2 months after TB diagnosis)*	• Diabetes symptoms (nocturia, polyuria, polydipsia) • Random glucose measures on finger prick sample • Fasting glucose • Oral glucose tolerance test • HbA1c • Urine dipstick
TB screen in diabetics	• TB symptoms (cough, duration of cough, night sweats, fever, loss of weight or appetite, haemoptysis, pleuritic chest pain) • Spontaneous (or induced if necessary) sputum sent for smear microscopy and culture • Chest radiography • IGRA / TST
Definition of TB disease	• Smear microscopy positive for acid-fast bacilli • Isolation/identification of *Mycobacterium tuberculosis* by culture or Xpert MTB/RIF • In addition to these definitions, an exploratory endpoint will include patients without a definitive TB diagnosis but with compatible clinical symptoms with symptom resolution after TB therapy
Subclinical TB	• TB culture positivity in absence of the currently recommended TB symptom screen (cough of any duration, fever, weight loss, night sweats)
Diabetes / Impaired glucose tolerance (IGT)	• -Fasting plasma glucose 7.0mmol/l (IGT 5.6-6.9 mmol/l) • -Glucose tolerance test >=11.1mmol/l (IGT 7.8-11.0 mmol/l) • -HbA1c >6.5% (IGT 5.7-6.4%)

Table 1: Case definitions

Subclinical TB disease Smear microscopy positive for acid fast bacilli

Isolation

Outcome measures

Primary outcome

- The best performing screening algorithm to diagnose DM in TB patients

Secondary outcomes

- Accuracy of established intensified TB case-finding strategies among diabetics
- Prevalence of diabetes in TB patients
- Prevalence of TB in diabetics, including subclinical TB disease
- Effect of diabetes on TB clinical presentation (number and duration of pulmonary TB symptoms, TB sputum smear and microscopy results, CXR findings, non-pulmonary manifestation of disease) and/or treatment outcomes of TB (2 month TB sputum clearance, completion and cure rates)

Sample size and power calculations

Assuming a DM prevalence of 24% in TB patients (based on a TB/DM risk ratio of 2 and DM prevalence in the general population of 12%), in order to have 80% statistical power and a screening tool sensitivity of 60%, a sample size of 1537 TB cases is required in Malawi and South Africa respectively. This sample size will provide sufficient power to define and investigate different potential DM screening algorithms in TB patients.

For the TB prevalence in DM patients study, a sample size of 457 diabetic patients is required, assuming TB prevalence of 5% and at 2% precision.

Statistical analysis plan

The prevalence of diabetes and TB will be based on the respective gold standard diagnostic tests. We will calculate the sensitivity, specificity, positive and negative predictive values of the screening tools to diagnose DM in TB cases, and TB in DM patients, using OGTT and TB culture gold standards, respectively. Among TB cases, risk factors associated with DM will be analysed using logistic regression. The model will be built manually with nested models compared using the likelihood ratio test. The Akaike's Information Criterion (AIC) will be used to compare non-nested models with a significantly lower AIC (>10%) indicating an improved model. In addition, outlying and influential observations will be identified and potential effect modification assessed using interaction variables.

To develop and evaluate a DM screening algorithm in TB cases, based on symptom screening, HIV status, ART, age, sex, BMI, waist circumference, and DM family history. Multivariable logistic regression analysis will then be performed to develop diagnostic models for DM using OGTT findings as the gold standard. A reduced clinical model without additional investigations will first be derived. These tests will then be added singly to the reduced clinical model and then simultaneously to explore the added predictive value of a single test and of combined tests, respectively. The ability of a multivariable model to discriminate persons with DM from those without will be assessed using Receiver Operator Characteristic curve and Area Under the Curve analysis. Significance testing will be done using a combination of two-sided p-values ($p<0.05$) and 95% confidence intervals. All data will be analysed using STATA 12.0 (StataCorp, College Station, TX, USA)

Ethical considerations

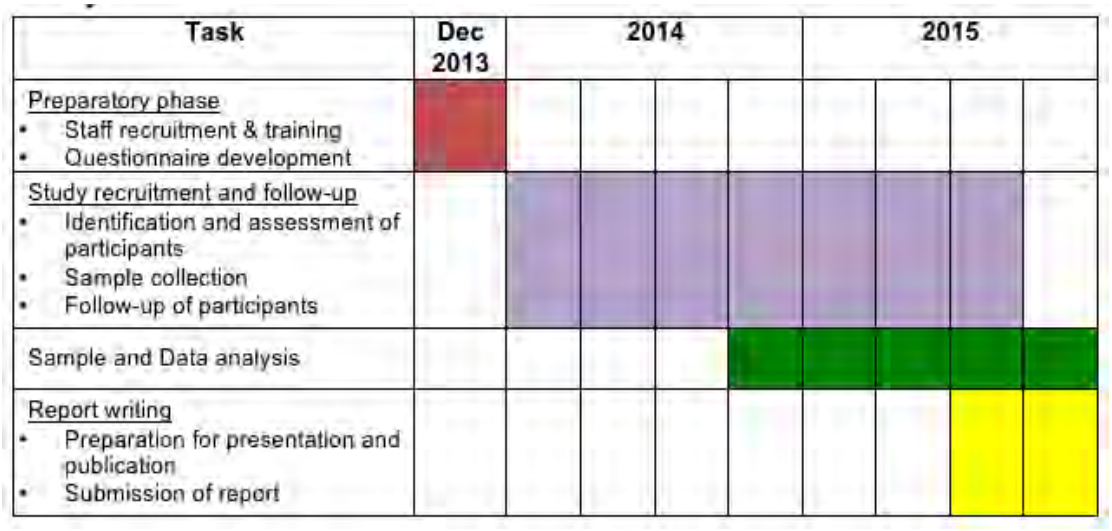
This study has received ethics approval from the University of Cape Town Human Ethics committee (HREC Ref: 403/2011). A written consent will be obtained from all participants who will be given detailed explanation of the study. An information sheet will be available both in English and Xhosa.

Anticipated overall outputs and impacts

This study performed at such an important time, with respect to the emerging diabetes epidemic in sub-Saharan Africa, will provide an invaluable set of data to document the strength of association between diabetes and TB and its clinical/public health impact. Data of this quality does not exist in the current literature on the link between TB and diabetes in sub-Sahara Africa; hence we expect this study to produce a series of high quality publications. Additionally, the study is designed to raise further research questions and provide some of the ground work needed, for example to determine 1) optimal screening models 2) whether diabetes influences recurrence of TB or anti-tuberculosis drug resistance 3) the need to develop randomised controlled trials of efficacy of interventions, such as TB chemoprophylaxis in people with diabetes, to improve outcomes of both diseases.

Contingency plans

Study timeline



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D.2. Ethics approval for main study

STRATEGY & HEALTH SUPPORT
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www.[illegible]

REFERENCE: RP 110/2011
ENQUIRIES: Dr V Apphah-Baiden

Room 3.03 Wolfson Pavillion
Institute of Infectious Disease and Molecular Medicine
Faculty of Health Sciences,
University of Cape Town
Observatory
7926

For attention: Dr To... Cli Professor Robert Wilkinson

Re: Epidemiology of Diabetes, TB and HIV co-infection in a high HIV/TB burden setting

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries.

Khayelitsha Site B **Ms Nofsha** **(021) 361 4885**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with the managers providing facilities so normal activities as requested facilities are not interrupted.
2. Researchers in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (hea.thresearch@pgwc.gov.za).
3. The reference number above should be quoted in all future correspondence.

We look forward to hearing from you.

Yours sincerely

DR T NALEDI
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE 07/03/2012

CC DR G PEREZ DIRECTOR: EASTERN/KHAYELITSHA

Page 1 of 1

D.3. TB suspect screening tool

Ref: CT/TB 6/13 version 6

TB SUSPECT SCREENING TOOL

For TB-suspects, contacts, prophylaxis in HIV. To be used as part of PALSA Plus based screening.

History

(This section can be completed by administrative support staff)

PATIENT PERSONAL DETAILS (add patient sticker)	Name	Folder number
	Surname	Clinic
	Address	Date of Birth
		Contact No

TB HISTORY	Previous TB	Y	N	Number of previous TB episodes		Year of last episode		Number of months on TB treatment at last episode	

CHRONIC DISEASE HISTORY AND CURRENT MEDICATION									
	HIV	Y	N	Antiretroviral therapy	Y	N	Depression / Anxiety	Y	N
	Diabetes	Y	N	Diabetes Meds	Y	N	Depression / Anxiety Meds	Y	N
	High blood pressure	Y	N	Blood pressure Meds	Y	N	Epilepsy	Y	N
	High cholesterol	Y	N	Cholesterol Meds	Y	N	Epilepsy Meds	Y	N
	Asthma / COPD	Y	N	Asthma / COPD Meds	Y	N			

HISTORY OF TB CONTACT	Known contact with confirmed TB patient			Y		N	
	MDR/XDR contact	Y	N	Name		Clinic	

EXPOSURE RISK	Health worker	Y	N	Mines / Quarry / Sandblasting...	Y	N
	Prisoner	Y	N	Other	Y	N

RISK FACTORS	Current cigarette smoker	Y	N	Previous cigarette smoker	Y	N
	Number smoked per day		per day	Number smoked per day		per day
	Number of years smoking		years	Number of alcoholic drinks consumed in the past week		

TB SYMPTOMS	Adults			Children < 8 years		
	Cough > 2 weeks	Y	N	Cough/wheeze > 2 weeks	Y	N
	Fever ≥ 2 weeks	Y	N	Fever ≥ 2 weeks	Y	N
	Weight loss	Y	N	Weight loss	Y	N
	Fatigue	Y	N	Fatigue (child does not play)	Y	N
	Blood stained sputum	Y	N	Not gaining weight (failure to thrive)	Y	N
	Drenching night sweats	Y	N			
	Chest pain on breathing	Y	N			

DIABETES SYMPTOMS	Polyuria	Y	N	Nocturia	Y	N	Polydipsia (excessive thirst)	Y	N

Action

(This section to be completed by Clinician (PN and /or MO)

HCT	HIV	Pos	Neg	Refused	CD4 result		ART start date	

OBSERVATIONS	Weight		Kg	Height		cm
	Temperature		C	Waist circumference		cm
	Respiratory rate		/min	Neck stiffness	Y	N
	BP		mmHg	Visible masses neck/axilla/groin	Y	N
	Pulse		/min	Failure to thrive (check growth curve in RTH Card)	Y	N

TB SKIN TEST	Date performed:		Date read:		Result		mm

BACTERIOLOGY	Type of specimen Eg sputum, aspirate etc	Type of test	Date	Lab no	Result	Drug Sensitivity Testing	
						R/F (S/R)	INH (S/R)
	1.	Xpert / Direct / Culture					
	2.	Xpert / Direct / Culture					
	3.						
	4.						

ANTIBIOTIC PRESCRIPTION	Name of antibiotic		Date antibiotic prescribed:	

TB DM study	Referred to study	Y	N	Consent given	Y	N	Study number	DBSN	_____

NAME & SIGNATURE (PN/MO)		Today's visit date:		Follow up date:	

D.4. World Health Organisation STEPS Instrument (isiXhosa)

Participant Study Number: DBSN- ____

Uhlalutyo Lwezinto Ezingumngcipheko zeSifo Esinganyangekiyo

Inkcazelo yoHlalutyo

Umhla		Impendulo	Ikhowudi
1	Igama lomntu obuzayo		I3
2	Umhla wemvume	dd mmm yyyy	I4

Inombolo yoPhononongo yoMthathi-nxaxheba: DBSN - ____

Imvume, Ulwimi neGama loDliwano-ndlebe		Impendulo	Ikhowudi
3	Imvume ifunyiwe yaza yafunyanwa	Ewe 1 Hayi 2 **Ukuba nguHayi, PHELA**	I5
4	Ulwimi lweMvume *(udliwano-ndlebe lufanele lwenziwe ngolwimi olufana nemvume)*	IsiXhosa 1 IsiNgesi 2	I6
5	Ixesha lemvume (iwotshi yeeyure ezingama-24)	: iiyure imizuzu	I7
6	Ifani yoMthathi-nxaxheba		I8
7	Igama lokuQala loMthathi-nxaxheba		I9
8	Isini	Indoda 1 Ibhinqa 2	C1
9	Ngubani umhla wokuzalwa wakho? *Andazi 77 777 7777*	dd mmm yyyy	C2
10	Ngaba imibuzo yesixhobo sokuhlola se-TB neempawu ezibalulekileyo ibhaliwe	Ewe 1 Hayi 2 **Ukuba nguHayi, fumana uze ubhale kwisixhobo sokuhlola se-TB**	I10
Inkcazelo eyongezelelekileyo esenokuba luncedo			
11	Inombolo yefowuni yomqhagamshelwa *(apho kunokwenzeka, kwakhona nikela ngenombolo yefowuni yesibini yomhlobo/salamane)*		I11
12	Idilesi yasekhaya		I12

Indawo noMhla	Impendulo	Ikhowudi
Umhla wedinga wokugqibezela inyathelo-1-3 neziphumo ze-TB (iiyure ezingama-48 – emva kweveki e-1 njengomthetho wekliniki)	dd mmm yyyy	I13

Bhala uze ufake kwitayile inkcazelo yokwazisa (15 ukuya ku-113) kunye nefomu yemvume kodwa ngokwahlukileyo kuxwebhu lwemibuzo oluqgibiyiweyo.

Participant Study Number: DBSN- _ _ _ _

Inyathelo 1 Inkcazelo ngamanani endawo ethile **(qala kwiphepha 8)**

Umhla		Impendulo	Ikhowudi
13	Igama lomntu obuzayo		I14
14	Umhla	dd mmm yyyy	I15
15	Isabelo seqela le-TB lohlolo (ngokwencwadi yokubhala) *Imeko yeTB: i-TB iye yachongwa kwi-smear i-X(pertreine-culture UKONGEZELELA unyango lwe-TB luza kuqaliswa* *Ulawulo lwe-TB: limpawu ziye zasonjululwa UKONGEZELELA uphando lwe-TB alunazibhumo zibi ukuza kuthi ga ngoku UKONGEZELELA alukho nyango lwe-TB luqaliswayo* ***Ukuba akafakwanga, musa ukuqhubeka***	Imeko ye-TB 1 Ulawulo lwe-TB 2	I16

EYANDISIWEYO: Inkcazelo yamanani endawo ethile

16	Liliphi elona qondo liphezulu lemfundo oye waliqqiba?	Akafundanga 1 Isikolo samabanga aphantsi kodwa akazanqe asiqqibe 2 Uqqibe amabanga aphantsi 3 Uqalise amabanga aphezulu kodwa akazanqe awaqqibe 4 Uqqibe amabanga aphezulu 5 Uqqibe kwanoKholeji/eYunivesithi 6 I-Post graduate degree 7 Walile ukuphendula 88	C5
17	Bunjani ubume bakho bomtshato?	Akazange atshate 1 Utshatile ngoku 2 Wahlukene 3 Uqhawule umtshato 4 Ufelwe 5 Uyahlalisana 6 Walile ukuphendula 88	C7
18	Yiyiphi eyona kwezi zisezantsi echaza kakuhle esona siqulna sakho somsebenzi kwezi nyanga zili-12 zidlulileyo?	Umsebenzi karhulumente 1 Umsebenzi onqenquye 2 Uyazisebenzela 3 Andihlawulwa 4 Umfundi 5 Umakhi wekhaya 6 Uthathe umhlala-phantsi 7 Akasebenzi (uyakwazi 8 Akasebenzi (akakwazi ukusebenza) 9 10 Walile ukuphendula 88	C8
19	Bangaphi abantu abangaphezu kweminyaka eli-18, abahlala ekhayeni lakho?	Inani labantu	C9
20	Ucinga ngalo nyaka udlulileyo, unqandichazela umlinganiselo wengeniso wekhaya (kuquka inkxaso-mali) ubunqakanani? **(BHALA KUPHELA IBENYE HAYI ZONKE ZO-3)**	Ngeveki _____	C10a
		OKANYE ngenyanga _____	C10b
		OKANYE ngonyaka _____	C10c
		Ichasiwe	C10d

Participant Study Number: DBSN- ___

Inyathelo 2 Umlinganiselo Wokuziphatha

EBALULEKILEYO: Ukusetyenziswa kweCuba

Ngoku ndiza kukubuza imibuzo ethile malunga neendlela zokuziphatha zempilo ezahlukeneyo. Oku kuquka izinto ezifana nokutshaya, ukusela utywala, ukutya iziqhamo imifuno nokwenza uthambo. Masiqale ngecuba.

Umbuzo		Impendulo	Ikhowudi
21	Ngaba ngoku utshaya naziphi na **iimveliso zecuba**, njengodiza, i-cigars okanye inqawa?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb26*	T1
22	Ngaba ngoku utshaya iimveliso zecuba **yonke imihla**?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb26*	T2
23	Wawunangaphi ukuqala kwakho **ukutshaya** yonke imihla?	Ubudala (iminyaka) ___ *Ukuba nguHayi, yiya kumb26* Akazi 77	T3
24	Ngaba uyakhumbula ukuba bekukudla kangakanani? (BHALA KUPHELA IBE-1, HAYI ZONKE ZO-3) *Akazi 77*	Ngeminyaka ___	T4a
		OKANYE ngeeNyanga ___	T4b
		OKANYE ngeeVeki ___	T4c
25	Ngomlinganiselo, **zingaphi** kwezi zilandelayo ozitshayayo ngosuku? *(EBHALIWEYO NGOHLOBO NGALUNYE)* *Akazi 77*	Iisigarethe eziveliswayo ___	T5a
		Iisgarethe ezenziwe ngesandla ___	T5b
		Iinqawa ezizele yisigarethe ___	T5c
		Iisiga ___	T5d
		Okunye ___	T5e
		Okunye (sicela ucacise):	T5okunye

EYANDISIWEYO: Ukusetyenziswa kweCuba

Umbuzo		Impendulo	Ikhowudi
26	Kwixa elidlulileyo, ngaba wakha watshaya yonke imihla?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb29*	T6
27	Wawunangaphi ukuyeka kwakho ukutshaya yonke imihla?	Ubudala (iminyaka) ___ *Ukuba nguHayi, yiya kumb29* Akazi 77	T7
28	Bekukudala **kangakanani** ukuyeka kwakho ukutshaya? *(BHALA KUPHELA IBE-1, HAYI ZONKE ZO-3)* *Akazi 77*	Kwiminyaka edlulileyo ___	T8a
		OKANYE Kwiinyanga ezidlulileyo ___	T8b
		OKANYE Kwiiveki ezidlulileyo ___	T8c

Participant Study Number: DBSN- ___

EBALULEKILEYO: Ukusela Utywala			
Imibuzo elandelayo imalunga nomlinganiselo wokusela utywala. Bona ezantsi kwephepha ukuze ufumane ingcaciso.			
Umbuzo		**Impendulo**	**Ikhowudi**
29	Ngaba **wakha** wasela isiselo esinotywala njengebhiya, iwayini, i-spirits, i-cider?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb37*	A1a
30	Ngaba ukhe wasela isiselo esinotywala kwezi nyanga **zili-12 zidlulileyo**?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb37*	A1b
31	Ebudeni bezi nyanga zili-12 zidlulileyo, **kukanganphi** uye wasela isiselo esinotywala ubuncinane kanye?	Rhoqo ngosuku 1 Iintsuku ezi-5-6 ngeveki 2 Usuku olu-1-4 ngeveki 3 Usuku olu-1-3 ngeveki 4 Ngaphantsi kunanye ngeveki 5	A2
32	Ngaba ukhe wasela isiselo esinotywala **kwezi ntsuku zingama-30 zidlulileyo**?	Ewe 1 Hayi 2 *Ukuba nguHayi, yiya kumb37*	A3
33	Ebudeni bezi ntsuku zingama-30 zidlulileyo, zizihlandlo **ezingaphi** oye ubuncinane wasela kanye isiselo esinotywala?	Inombolo Akazi 77 ___	A4
34	Ebudeni bezi ntsuku zingama-30 zidlulileyo, xa ubusela utywala, **ngomlinganiselo**, zingaphi **iziselo zotywala eziqhelekileyo** oye wazisela kwisihlandlo esinye?	Inombolo Akazi 77 ___	A5
35	Ebudeni beentsuku ezingama-30 ezidlulileyo, ngubani elona nani **likhulu** kwiziselo zotywala eziqhelekileyo kwisihlandlo esinye, xa ubala zonke iintlobo zeziselo ezinotywala?	Inani elikhulu Akazi 77 ___	A6
36	Ebudeni beentsuku ezingama-30 ezidlulileyo, uye wasela ezingaphi kumadoda : **ezintlanu okanye ngaphezulu** kumabhinqa : **ezine okanye ngaphezulu** iziselo ezinotywala eziqhelekileyo kwisihlandlo esinye sokusela?	Inani lezihlandlo Akazi 77 ___	A7

Ingcaciso zeziselo ezinotywala
Isiselo esi-1 = iglasi e-1 yewayini OKANYE ibhotile e-1 encinane yebhiya / i-cider OKANYE ithothi e-1 ye-spirithi

Ibhotile yelitha e-1 yewayini = iziselo ezi-5
Ibhotile yelitha e-1 yespirithi (ngokomzki i-vodka, i-whisky, i-brandy, i-gin) = iziselo ezili-12
Ibhotile e-1 enkulu yebhiya okanye i-cider = iziselo ezi-2

D.5. List of variables

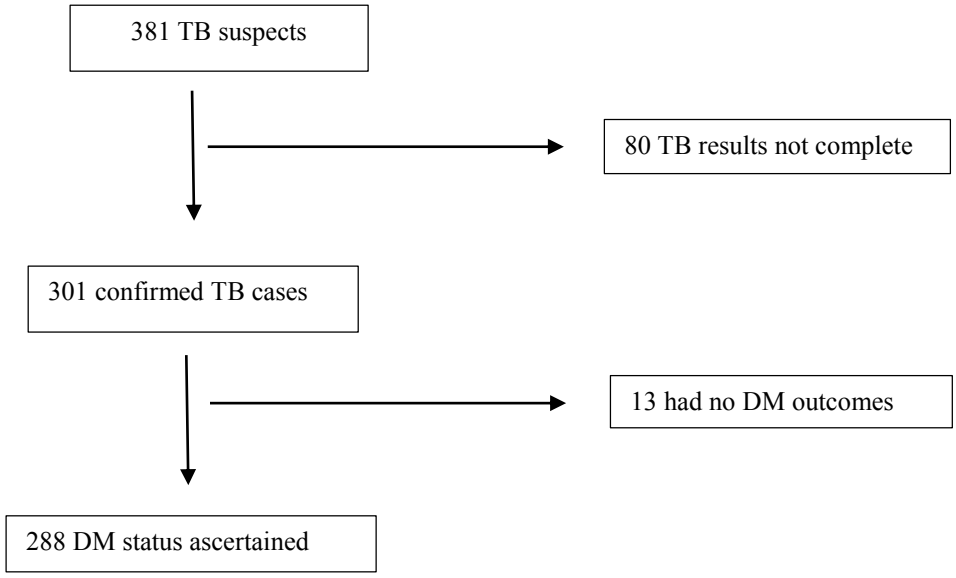
Table D-1: List of study variables

Variables	Variable type	Code number:= Category	Name in STATA
Main outcome: Dependent variables			
Impaired glucose tolerance (IGT)	Categorical	0:= Normal 1:= Pre-diabetic (5.7% ≤ HbA1c < 6.5% or 5.5 ≤ FBG < 7.0 or 7.7 ≤ OGTT < 11.1 mmol/dl) 2:= Diabetic (FBG > 7.1 mmol/dl or OGTT > 11.1 mmol/dl or HbA1c > 6.5% or self-report and medication prescription)	glyLevel1
Diabetes Mellitus (DM)	Binary	0:= No diabetes 1:= Diabetic (FBG > 7.1 mmol/dl or OGTT > 11.1 mmol/dl or HbA1c > 6.5% or self-report and medication prescription)	combinedDM
Risk factors: Independent Variables			
Sex	Binary	0:= Female 1:= Male	Sex
Age	Continuous and categorical	Continuous; 0:= < 25 1:= 26 - 35 2:= 36 - 45 3:= 46 - 55 4:= > 55	ageAtConsentr; ageCat0 ageCat1 ageCat2 ageCat3
Education	Categorical	0:= No education 1:= primary 2:= secondary 3:= tertiary	educationLevel0 educationLevel1 educationLevel2 educationLevel3
Occupation	Categorical	0:= Unemployed 1:= Employed 2:= Retired/receiving grants/homemaker 3:= Student	employmentStatus0 employmentStatus1 employmentStatus2 employmentStatus3
Partner status	Categorical	0:= Without partner 1:= With partner 2:= Widowed/Separated/Divorced	PatnerStatus
Number of persons older than 18 years in a household	Categorical	0:= Two or less 1:= More than two	adultsInHouseCat
Average income	Categorical	0:= < R 1 = 0 1:= R 1 - R 1 600 = 1 2:= R 1 601 - R 3 200 = 2 3:= R 3 201 - R 6 400 = 3 4:= R 6 400 - R 12 800 = 4 5:= > R 12 800	incomeCats1 incomeCats2 incomeCats3 incomeCats4 incomeCats5
Alcohol consumption in the past 12 months	Binary	0:= No 1:= Yes	alc12mnth30day
Ever smoker	Binary	0:= No 1:= Yes (past and current)	everSmk
Fruit intake	Binary	0:= 5 or more servings/day 1:= less than 5 servings/day	lowFruitIntake
Vegetable intake	Binary	0:= 5 or more servings/day 1:= less than 5 servings/day	lowVegIntake
Physical activity	Binary	0:= inactive 1:= active (moderate or vigorous PA)	PAstatus

Sedentary occupation	Binary	0:= non-sedentary (occupation involving vigorous or moderate activity) 1:= sedentary	sendOccu
Body mass index	Binary	continuous; 0:= Underweight (< 18.5 kg/m2) 1:= Normal (18.5 - 24.99 kg/m2) 2:= Overweight (25 - 29.99 kg/m2) 3:= Obese (> 30 kg/m2)	BMI; BMIcat
Waist circumference (Central obesity)	Continuous	Continuous	Waistcircumference
Male waist circumference	Binary	0:= less than 102 cm 1:= 102 cm and more	centObesMale
Female waist circumference	Binary	0:= less than 88 cm 1:= 88 cm and more	centObesFema
Hypertension	Binary	0:= no hypertension 1:= Hypertensive (diastolic > 90 mmHg or systolic > 140 mmHg or self-report and medications prescription)	combHPTN
Diabetes family history	Binary	0:= No 1:= Yes (any relative/family member has/had DM)	DiabetesFamilyHistory
Diabetes medication	Binary	0:= No 1:= Yes	Diabetespills
Diabetes symptoms	Binary	0:= No 1:= Yes	DMSymptoms
Nocturia	Binary	0:= No 1:= Yes	Nocturia
Polydipsia	Binary	0:= No 1:= Yes	Polydipsia
Polyuria	Binary	0:= No 1:= Yes	Polyuria
Self-reported Diabetes	Binary	0:= No 1:= Yes	Diabetes
Gestational diabetes	Binary	0:= No 1:= Yes	gestationalDiabetes
Self-reported HIV	Binary	0:= Negative 1:= Positive 2:= Unknown	HIVstatus
HIV medication (ART)	Binary	0:= No 1:= Yes	ARV
Previous TB	Binary	0:= No 1:= Yes	previoustb
TB medication	Binary	0:= No 1:= Yes	Tbmedication
Self-reported hypertension	Binary	0:= No 1:= Yes	Highbloodpressure
Hypertension medication	Binary	0:= No 1:= Yes	bloodpressuremeds

D.6. Detailed statistical analysis

Figure D-1: Flow diagram of inclusion of participants in study and analysis



At the time of data extraction, 381 screened TB suspects had complete data on at least sex and age. Of these 381 TB suspects, 301 had their TB status confirmed as per case definitions and 288 of them had their DM status ascertained. Therefore, we included 288 patients in the analysis.

D.6.1 Statistical analysis and model building

Univariate/Descriptive analysis: None of the numerical continuous variables were normally distributed. Medians and inter quartile ranges (IQR) were used to summaries continuous variables. Categorical variables were summarised using proportions.

Bivariate analysis: The chi-squared test was performed to assess associations between categorical variables and the outcome variables (DM and pre-DM), the Fishers exact for cells with less than five observations. To assess associations between continuous variables and the categorical variables, the Mann-Whitney test was used to compare medians between two groups and the Kruskal-Wallis to compare medians between more than two groups. Logistic

regression was performed to identify factors which were independently associated with either DM or pre-DM.

Multivariate analysis: Multivariate analysis was performed was performed to manually build a model of independent predictors of DM and pre-DM. The log likelihood ratio test was used to compare models which were nested. This test measures the difference in deviance between two nested models to assess the extent to which an additional risk factor improves the model fit. For model selection, statistical significance was based on p-value < 0.05 and a higher chi-squared statistic value of the log likelihood ratio test and statistical significance of each risk factor was based on p-value < 0.05.

Model Building:

The second objective of this study was to determine risk factors associated with DM. To obtain such a set of variables, several statistical variable selection methods are suggested: the forward, backward and stepwise variable selection procedures. We used the forward selection procedure because it allows us to first screen the variable which are potential model candidates, it also allows us to use clinical knowledge/judgement on as to which variables to include as exposure factors and confounders. Lastly, it is a fairly straight forward method.

Based on the literature, from studies conducted in the SSA region, the following risk factors were have been identified as being associated with DM among TB patients: male sex increasing age, obesity, BMI, waist circumference, sedentary lifestyle, a positive family history of DM, and gestational diabetes. These factors were considered in the multivariate analysis to build a model of risk factors independently associated with DM among TB patients. In addition, risk factors which had a significant association with the outcome at the bivariate analysis were also considered.

Based on suggestions from the literature, we considered age and sex to be potential confounders (particularity for the association between hypertension and DM). We assessed whether these variables confound the association between DM and hypertension and found age to be a confounder (it met the 3 conditions for a variable to be a confounder: 1) confounder associated with outcome (DM); 2) confounder associated with exposure (hypertension) among those without the outcome (non-DM) and 3) confounder is not in the causal pathway (not a mediator) between exposure (hypertension) and outcome (DM).

Forward selection:

- We first include a model with just a constant (baseline). We then screened the next variable that would improve the model based on the lowest AIC for non-nested models, and higher Chi-squared value and lowest p-value for log likelihood ratio test for nested model.
- The first variable added to the baseline model was age categories (the confounder)
- One at a time we added other variables and assessed which improved the model until saturation – giving the best model
- In this best model, we assessed the presence of effect modification between the confounder and other risk factor variables.
- The best model for DM and other risk factors included age categories, hypertension, DM family history, waist circumference.

Effect modification:

- We then tested whether sex modified the effect of waist circumference (i.e. if the effect of waist circumference on DM depended on either being male or female) by adding an interaction term (the product of sex and waist circumference in the logistic regression model). The p-value for the coefficient of this term was not

significant ($p>0.05$) and the confidence interval included the null. Therefore, based on this data, we concluded that there was no interaction between sex and waist circumference.

- Model checking was then performed

Model checking: To the check the validity of each models, we need to assess:

1) The form of the linear component of the model: We plot a scatter plot of deviance and Pearson residuals against the linear predictor – for a good model, positive responses (DM cases) should tend close towards the horizontal line (= 0) as linear predictors gets larger, the negative response (non DM) should tend away from the residuals as the linear predictor increases. Also plot residuals against observations, for a good model we expect a random scatter.
2) For binary response models, we check the adequacy of the link (transformation) function: The logit transformation function is considered to be an appropriate for the binary response variables.
3) The presence and influence of influential observations: outliers were identified by standard residuals greater than +2 or less than -2. Influential observations were identified using the *hi* which measures how far the covariate pattern lies from the average covariate pattern.

Multicollinearity: We assessed the presence of multicollinearity using the variance inflation factor (VIF) and Pearson correlations. VIF >>> 10 or Pearson correlations > 0.9 indicate the presence of multicollinearity.

D.6.2 Building a multivariate model for diabetes mellitus

Table D-2: Forward selection model building - a model for risk factors associated with DM

Model	VS.	Variables included	N	Log likelihood	AIC	Log likelihood ratio test χ^2	p-value
A	-	Constant	279	-111.0438	224.0875	-	-
B	A	Sex	288	-114.185	232.37	0.05	0.8304
C	**A**	**ageCat0 ageCat2 ageCat3**	**288**	**-101.8414**	**211.6829**	**24.73**	**0.0000**
D	A	ageAtConsentr	288	-103.7484	211.4968	20.92	0.0000
E	A	incomeCats2 incomeCats3 incomeCats4 incomeCats5	288	-110.5919	233.1838	6.96	0.1378
F	A	combineIncome	231	-90.99918	185.9984	0.16	0.6851
G	A	PatnerStatus1 PatnerStatus2	288	-111.6024	229.2047	5.21	0.0739
H	A	alc12mnth30day	288	-114.0985	232.1969	0.22	0.6398
I	A	everSmk	288	-113.3244	230.6488	1.77	0.1837
J	A	PAstatus	279	-109.4021	222.8042	3.28	0.0700
K	A	BMIcat0 BMIcat2 BMIcat3	231	-78.31218	164.6244	5.92	0.1157
L	A	BMI	231	-80.29389	164.5878	1.95	0.1621
M	A	Waistcircumference	213	-73.84245	151.6849	6.38	0.0115
N	A	highWC	213	-75.49233	154.9847	3.08	0.0793
O	A	DiabetesFamilyHistory	279	-109.1486	222.2971	3.79	0.0515
P	A	gestationalDiabetes	276	-106.0325	216.0649	9.14	0.0025
Q	A	HIVstate	288	-113.7722	231.5444	0.87	0.3505
R	A	educationLevel1 educationLevel2 educationLevel3	288	-111.9097	231.8194	4.60	0.2038
S	A	DMSymptoms	288	-113.9923	231.9845	0.43	0.5113
T	A	lowFruitIntake	285	-111.7346	227.4692	0.36	0.5512
U	A	lowVegIntake	288	-114.0837	232.1674	0.25	0.6182
V	A	combHPTN	288	-106.0054	216.0107	16.41	0.0001
W	A	sendOccu	279	-111.0345	226.0691	0.02	0.8921
Y	A	pevTB	239	-88.32216	180.6443	0.02	0.8965
Z	A	employmentStatus	279	-110.7042	225.4085	0.68	0.4099
Model C: ageCat0 + ageCat2 + ageCat3 + ___							
B2	C	Sex	288	-101.5644	213.1288	0.55	0.4567
C2	C	incomeCats2 incomeCats3 incomeCats4 incomeCats5	288	-99.64897	215.2979	4.38	0.3564
D2	C	PatnerStatus1 PatnerStatus2	288	-101.4903	214.9806	0.70	0.7039
E2	C	alc12mnth30day	288	-101.712	213.4241	0.26	0.6109
F2	C	everSmk	288	-100.7003	211.4006	2.28	0.1309
G2	C	PAstatus	279	-98.64378	207.2876	1.82	0.1772
H2	C	BMIcat0 BMIcat2 BMIcat3	231	-72.23391	158.4678	4.78	0.1889
I2	C	BMI	231	-73.45768	156.9154	2.33	0.1270
J2	C	Waistcircumference	213	-69.04241	148.0848	6.97	0.0083
K2	C	highWC	213	-70.58404	151.1681	3.88	0.0488
L2	**C**	**DiabetesFamilyHistory**	**279**	**-96.05849**	**202.117**	**6.99**	**0.0082**
M2	C	gestationalDiabetes	276	-94.73974	199.4795	8.51	0.0035

N2	C	HIVstate	288	-101.7586	213.5173	0.17	0.6840
O2	C	educationLevel1 educationLevel2 educationLevel3	288	-101.7128	217.4257	0.26	0.9679
P2	C	DMSymptoms	288	-101.7502	213.5004	0.18	0.6692
Q2	C	lowFruitIntake	285	-98.23264	206.4653	0.86	0.3527
R 2	C	lowVegIntake	288	-101.8025	213.6051	0.08	0.7803
S2	C	combHPTN	288	-98.76954	207.5391	6.14	0.0132
T2	C	sendOccu	279	-99.55387	209.1077	0.00	0.9789
U2	C	prevTB	239	-80.3762	170.7524	0.23	0.6332
W2	C	employmentStatus	279	-99.40419	208.8084	0.07	0.7891
Model L2: ageCat0 ageCat2 ageCat3 + DiabetesFamilyHistory + ___							
B3	L2	Sex	279	-95.78425	203.5685	0.55	0.4589
C3	L2	incomeCats2 incomeCats3 incomeCats4 incomeCats5	279	-94.31157	206.6231	3.49	0.4788
D3	L2	PatnerStatus1 PatnerStatus2	279	-95.59153	205.1831	0.93	0.6269
E3	L2	alc12mnth30day	279	-95.99308	203.9862	0.13	0.7176
F3	L2	everSmk	279	-94.44835	200.8967	3.22	0.0727
G3	L2	PAstatus	278	-94.67994	201.3599	2.169	0.1012
H3	L2	BMIcat0 BMIcat2 BMIcat3	226	-65.86258	147.7252	5.46	0.1410
I3	L2	BMI	226	-67.43162	146.8632	2.32	0.1275
J3	**L2**	**Waistcircumference**	**210**	**-63.90952**	**139.819**	**5.99**	**0.0144**
N3	L2	HIVstate	279	-96.05126	204.1025	0.01	0.9043
O3	L2	educationLevel1 educationLevel2 educationLevel3	279	-95.80296	207.6059	0.51	0.9165
P3	L2	DMSymptoms	279	-96.04526	204.0905	0.03	0.8708
Q3	L2	lowFriuitIntake	276	-92.31133	196.6227	0.79	0.3752
R 3	L2	lowVegIntake	279	-95.61332	203.2266	0.89	0.3454
S3	L2	combHPTN	279	-93.72197	199.4439	4.67	0.0306
T3	L2	sendOccu	278	-96.00177	204.0035	0.04	0.8351
U3	L2	prevTB	234	-75.09717	162.1943	0.14	0.7084
W3	L2	employmentStatus	276	-95.59099	203.182	0.23	0.6336
Model J3: ageCat0 ageCat2 ageCat3 + DiabetesFamilyHistory + Waistcircumference___							
B4	J3	Sex	210	-63.35181	140.7036	1.04	0.3088
C4	J3	incomeCats2 incomeCats3 incomeCats4 incomeCats5	202	-62.40911	142.8182	3.00	0.3915
D4	J3	PatnerStatus1 PatnerStatus2	210	-63.73752	143.475	0.34	0.8420
E4	J3	alc12mnth30day	210	-63.73143	141.4629	0.36	0.5506
F4	J3	everSmk	210	-63.10808	140.2162	1.60	0.2055
H4	J3	PAstatus	207	-58.81812	135.6362	1.45	0.2288
G4	J3	BMIcat0 BMIcat2 BMIcat3	209	-63.14545	140.2909	1.53	0.6743
I4	J3	BMI	207	-59.47065	132.9413	0.23	0.6317
K4	J3	HIVstate	210	-63.79241	141.5848	0.23	0.6284
L4	J3	educationLevel1 educationLevel2 educationLevel3	210	-63.2099	144.4198	1.40	0.7057
M4	J3	DMSymptoms	210	-63.73157	141.4631	0.36	0.5508
N4	J3	lowFriuitIntake	205	-60.32836	132.6567	perfect prediction	
O4	J3	lowVegIntake	210	-63.86784	141.7357	0.08	0.7728
P4	**J3**	**combHPTN**	**210**	**-60.21241**	**134.4248**	**7.39**	**0.0065**

Q4	J3	sendOccu	209	-63.80134	141.6027	0.14	0.7117
R 4	J3	prevTB	234	-75.09717	162.1943	0.14	0.7084
T4	J3	employmentStatus	276	-95.59099	203.182	0.23	0.6336
ageCat0 ageCat2 ageCat3 + DiabetesFamilyHistory + Waistcircumference + combHPTN___							
B5	P4	Sex	210	-58.87778	133.7556	2.67	0.1023
C5	P4	incomeCats2 incomeCats3 incomeCats4 incomeCats5	202	-57.84402	135.688	4.74	0.1921
D5	P4	PatnerStatus1 PatnerStatus2	210	-59.74844	137.4969	0.93	0.6288
E5	P4	alc12mnth30day	210	-59.67237	135.3447	1.08	0.2987
F5	P4	everSmk	210	-58.828	133.656	2.77	0.0961
G5	P4	PAstatus	209	-59.45269	134.9054	1.45	0.2286
H5	P4	BMIcat0 BMIcat2 BMIcat3	207	-55.0837	130.1674	1.51	0.6793
I5	P4	BMI	207	-55.77546	127.5509	0.13	0.7191
K5	P4	HIVstate	210	-59.6979	135.3958	1.03	0.3104
L5	P4	educationLevel1 educationLevel2 educationLevel3	210	-59.59552	139.191	1.23	0.7449
M5	P4	DMSymptoms	210	-60.05538	136.1108	0.31	0.5752
N5	P4	lowFriuitIntake	205	-57.27095	128.5419	perfect prediction	
O5	P4	lowVegIntake	210	-60.11968	136.2394	0.19	0.6667
Q5	P4	sendOccu	209	-60.13025	136.2605	0.09	0.7588
R 5	P4	employmentStatus	207	-58.80236	133.6047	2.41	0.1204
S5	P4	prevTB	210	-60.11516	136.2303	0.19	0.6592

Figure D-2: Goodness of fit output for final DM mode (model P4)

```
. logistic combinedDM ageCat0 ageCat2 ageCat3 DiabetesFamilyHistory Waistcircumference combHPTN

Logistic regression                             Number of obs   =        210
                                                LR chi2(6)      =      28.84
                                                Prob > chi2     =     0.0001
Log likelihood = -60.212409                     Pseudo R2       =     0.1932

------------------------------------------------------------------------------
  combinedDM | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     ageCat0 |   3.489354   2.713552     1.61   0.108      .7599667    16.02122
     ageCat2 |   1.482272   1.015425     0.57   0.566      .3870927    5.675977
     ageCat3 |   2.619334   1.933768     1.30   0.192      .6162786    11.13281
DiabetesFa~y |   3.202735   1.657989     2.25   0.025      1.161106    8.834261
Waistcircu~e |   1.033333   .0153323     2.21   0.027      1.003715    1.063825
    combHPTN |   4.493851   2.461315     2.74   0.006      1.536064    13.14704
       _cons |   .0006596   .0011159    -4.33   0.000       .000024    .0181668
------------------------------------------------------------------------------

. estat gof, group(10)

Logistic model for combinedDM, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

      number of observations =       210
            number of groups =        10
      Hosmer-Lemeshow chi2(8) =      7.28
                  Prob > chi2 =    0.5063
```

D.6.3 Sex-specific multivariate models for DM

Due to significant differences in associations between various risk factors (age, income, BMI, WC, hypertension, education, physical activity status, sedentary occupation, alcohol consumption and smoking, HIV status) and DM with respect to gender, we performed gender specific models. This was done by restricting/stratifying the multivariate analysis by gender groups (male and female). The disadvantage of stratifying the data would be loss of power due to reduced sample size.

D.6.4.1 Building a multivariate model of diabetes mellitus among males

Table D-3: Forward selection model building - a model for risk factors associated with DM among males

Model	VS	Variables included	N	Log likelihood ratio test			
				Log likelihood	AIC	χ^2	p-value
A		Constant	164	-64.64772	131.2954		
C	A	ageCat0 ageCat2 ageCat3	167	-55.05246	118.1049	20.05	0.0002
D	**A**	**combHPTN**	**167**	**-57.39321**	**118.7864**	**15.36**	**0.0001**
E	A	incomeCats2 incomeCats3 incomeCats4 incomeCats5	167	-61.86833	131.7367	6.41	0.0931
F	A	combineIncome	132	-52.51328	109.0266	0.13	0.7221
G	A	PatnerStatus1 PatnerStatus2	167	-64.09002	134.18	1.97	0.3732
H	A	alc12mnth30day	167	-64.97758	133.9552	0.20	0.6579
I	A	everSmk	167	-65.00739	134.0148	0.14	0.7118
J	A	PAstatus	143	-61.39319	124.7864	males only	
K	A	BMIcat0 BMIcat2 BMIcat3	133	-39.39874	86.79747	6.35	0.0958
L	A	BMI	133	-41.87956	87.75912	1.39	0.2389
M	A	Waistcircumference	123	-37.58128	79.16257	3.48	0.0621
N	A	highWC	123	-37.10551	78.21103	4.43	0.0353
O	A	DiabetesFamilyHistory	164	-64.19445	132.3889	0.91	0.3410
P	A	gestationalDiabetes	161	-64.21129	130.4226	females only	
Q	A	HIVstate	167	-64.15325	132.3065	1.84	0.1744
R	A	educationLevel1 educationLevel2 educationLevel3	161	-61.35592	128.7118	6.87	0.0322
S	A	DMSymptoms	167	-65.0081	134.0162	0.14	0.7132
T	A	lowFruitIntake	164	-62.65126	129.3025	0.21	0.6466
U	A	lowVegIntake	167	-64.71797	133.4359	0.72	0.3977
W	A	sendOccu	164	-64.2241	132.4482	0.85	0.3573
Model D: combHPTN +___							
A1	D	ageCat0 ageCat2 ageCat3	167	-52.13444	114.2689	10.52	0.0146
B1	D	incomeCats2 incomeCats3 incomeCats4 incomeCats5	167	-54.25403	118.5081	6.28	0.0988
C1	D	combineIncome	132	-43.86678	93.51037	0.22	0.6366
E1	D	PatnerStatus1 PatnerStatus2	167	-57.09184	122.1837	0.60	0.7398
F1	D	alc12mnth30day	167	-57.05622	120.1124	0.67	0.4117
I1	D	everSmk	167	-57.02835	120.0567	0.73	0.3930
H1	D	PAstatus	143	-54.43682	112.8736	-5.47	.
J1	D	BMIcat0 BMIcat2 BMIcat3	133	-27.70433	65.40865	4.60	0.2033
K1	D	BMI	133	-29.38949	64.77898	1.23	0.2668
L1	D	Waistcircumference	123	-28.01645	62.03289	1.47	0.2250
M1	D	highWC	123	-27.1682	60.33639	3.17	0.0751
N1	D	**DiabetesFamilyHistory**	**164**	**-56.97464**	**119.9493**	**16.20**	**0.0003**
P1	D	HIVstate	167	-57.26089	120.5218	0.26	0.6070
Q1	D	educationLevel1 educationLevel2 educationLevel3	161	-54.93225	117.8645	4.63	0.0989
R 1	D	Dmsypmtoms	167	-57.32472	120.6494	0.14	0.7113
S1	D	lowFruitIntake	164	-55.34472	116.6894	0.28	0.5981

T1	D	lowVegIntake	167	-57.08653	120.1731	0.61	0.4335
U1	D	sendOccu	164	-56.8478	119.6956	0.65	0.4208
Model N1: combHPTN + DiabetesFamilyHistory + ___							
A2	**N1**	**ageCat0 ageCat2 ageCat3**	**164**	**-51.08066**	**114.1613**	**11.79**	**0.0081**
B2	N1	incomeCats2 incomeCats3 incomeCats4 incomeCats5	164	-53.93108	119.8622	6.09	0.1074
C2	N1	combineIncome	132	-42.63591	93.27181	0.02	0.9015
E2	N1	PatnerStatus1 PatnerStatus2	164	-56.63782	123.2756	0.67	0.7140
F2	N1	alc12mnth30day	164	-56.61294	121.2259	0.72	0.3950
I2	N1	everSmk	164	-56.50702	121.014	0.94	0.3335
H2	N1	Pastatus	143	-54.1239	114.2478	-5.70	.
J2	N1	BMIcat0 BMIcat2 BMIcat3	132	-27.04553	66.09107	4.69	0.1958
K2	N1	BMI	132	-28.8565	65.71301	1.07	0.3010
L2	N1	Waistcircumference	123	-27.45415	62.9083	1.10	0.2945
M2	N1	highWC	123	-26.63896	61.27793	2.73	0.0985
P2	N1	HIVstate	164	-56.87238	121.7448	0.20	0.6511
Q2	N1	educationLevel1 educationLevel2 educationLevel3	160	-54.21733	118.4347	5.51	0.0635
R 2	N1	DMSymptoms	164	-56.86547	121.7309	0.22	0.6403
S2	N1	lowFruitIntake	161	-54.47715	116.9543	1.17	0.2796
T2	N1	lowVegIntake	164	-56.75666	121.5133	0.44	0.5091
U2	N1	sendOccu	164	-56.69792	121.3958	0.55	0.4569
Model A2: combHPTN + DiabetesFamilyHistory + ageCat0 ageCat2 ageCat3 + __							
C4	A2	combineIncome	132	-38.22499	90.44999	0.01	0.9112
E4	A2	PatnerStatus1 PatnerStatus2	164	-50.83573	117.6715	0.49	0.7828
F4	A2	alc12mnth30day	164	-50.85675	115.7135	0.45	0.5034
I4	A2	everSmk	164	-50.84507	115.6901	0.47	0.4925
H4	A2	PAstatus	143	-54.1239	114.2478	6.09	0.1075
J4	A2	BMIcat0 BMIcat2 BMIcat3	132	-25.55617	69.11233	3.83	0.2799
K4	A2	BMI	132	-27.091	68.182	0.77	0.3818
L4	A2	Waistcircumference	123	-27.19478	68.38955	0.86	0.3531
M4	A2	highWC	123	-26.4719	66.9438	2.31	0.1287
P4	A2	HIVstate	164	-51.0129	116.0258	0.14	0.7128
Q4	A2	educationLevel1 educationLevel2	164	-54.21733	120.4347	1.42	0.6997
R 4	A2	DMSymptoms	164	-50.80864	115.6173	0.54	0.4608
S4	A2	lowVegIntake	161	-47.59236	109.1847	0.83	0.3633
T4	A2	lowFruitIntake	164	-50.73496	115.4699	0.69	0.4057
U4	A2	sendOccu	164	-50.83789	115.6758	0.49	0.4859

Figure D-3: Goodness of fit output for final DM model among males (model A2)

```
. *Final mode1:
. logistic combinedDM DiabetesFamilyHistory ageCat0 ageCat2 ageCat3 combHPTN

Logistic regression                                     Number of obs   =        164
                                                        LR chi2(5)      =      27.13
                                                        Prob > chi2     =     0.0001
Log likelihood = -51.080657                             Pseudo R2       =     0.2099
```

combinedDM	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
DiabetesFamilyHist~y	2.406031	1.489163	1.42	0.156	.7152665	8.093468
ageCat0	1.860594	2.392542	0.48	0.629	.1496546	23.132
ageCat2	2.892753	2.544965	1.21	0.227	.5157601	16.22464
ageCat3	11.04924	9.381345	2.83	0.005	2.092285	58.35043
combHPTN	3.300224	1.750689	2.25	0.024	1.166814	9.334375
_cons	.0088788	.0102495	-4.09	0.000	.0009242	.0853028

```
. *Check goodness of fit
. lfit

Logistic model for combinedDM, goodness-of-fit test

       number of observations =       164
 number of covariate patterns =        16
             Pearson chi2(10) =        10.94
                  Prob > chi2 =         0.3626
```

D.6.4.2 Building a multivariate model of diabetes mellitus among females

Table D-4: Forward selection model building - a model for risk factors associated with DM among females

Model	VS	Variables included	N	Log likelihood	Log likelihood ratio test AIC	χ^2	p-value
A	-	constant	115	-46.38891	94.77782	-	-
B	A	combHPTN	121	-47.73167	99.46334	2.76	0.0969
C	A	ageCat0 ageCat2 ageCat3	121	-45.06288	98.12577	8.09	0.0441
D	A	sendOccu	115	-44.87114	93.74228	3.04	0.0815
E	A	incomeCats2 incomeCats3 incomeCats4 incomeCats5	121	-48.08311	106.1662	2.12	0.7138
F	A	combineIncome	99	-38.221	80.442	0.56	0.4562
G	A	PatnerStatus1 PatnerStatus2	121	-46.49119	98.98238	5.24	0.0729
H	A	alc12mnth30day	121	-48.22959	100.4592	1.76	0.1847
J	A	PAstatus	115	-46.36982	96.73965	0.04	0.8451
K	A	BMIcat0 BMIcat2 BMIcat3	98	-36.95419	81.90839	2.81	0.4225
L	A	BMI	98	-38.17312	80.34624	0.37	0.5441
M	A	Waistcircumference	90	-35.92221	75.84441	2.49	0.1148
N	A	highWC	90	-37.00786	78.01572	0.32	0.5744
O	A	DiabetesFamilyHistory	115	-44.63309	93.26618	3.51	0.0609
P	A	**gestationalDiabetes**	**115**	**-41.61016**	**87.22032**	**9.56**	**0.0020**
Q	A	HIVstate	121	-49.08378	102.1676	0.05	0.8210
R	A	educationLevel1 educationLevel2 educationLevel3	117	-46.20089	100.4018	0.97	0.0806
S	A	DMSymptoms	121	-48.09229	100.1846	2.03	0.1538
T	A	lowFruitIntake	121	-49.04004	102.0801	0.14	0.7096
U	A	lowVegIntake	121	-49.04004	102.0801	0.14	0.7096
W	A	sendOccu	115	-44.87114	93.74228	3.04	0.0815
Model P: gestationalDiabetes + ___							
B1	P	combHPTN	115	-40.87997	87.75993	1.46	0.2269
C1	P	ageCat0 ageCat2 ageCat3	115	-39.4182	88.83641	4.38	0.2229
D1	P	sendOccu	114	-40.3179	86.63579	2.35	0.1253
E1	P	incomeCats2 incomeCats3 incomeCats4 incomeCats5	98	-35.75856	83.51712	0.41	0.9818
F1	P	combineIncome	98	-35.96004	77.92008	0.00	0.9454
G1	P	PatnerStatus1 PatnerStatus2	115	-39.86705	87.73409	3.49	0.1750
H1	P	alc12mnth30day	115	-41.23039	88.46077	0.76	0.3835
J1	P	PAstatus	114	-41.40462	88.80923	0.18	0.6743
K1	P	BMIcat0 BMIcat2 BMIcat3	94	-33.29045	76.58089	1.75	0.6250
L1	P	BMI	94	-33.96479	73.92958	0.41	0.5243
M1	P	Waistcircumference	87	-32.41208	70.82417	1.79	0.1810
N1	P	highWC	87	-33.06512	72.13023	0.48	0.4867
O1	P	DiabetesFamilyHistory	115	-40.73871	87.47742	1.74	0.1868
Q1	P	HIVstate	115	-40.93456	87.86913	1.35	0.2451
R1	P	educationLevel1 educationLevel2 educationLevel3	117	-46.20089	100.4018	-9.18	1.0000
S1	P	DMSymptoms	115	-41.17296	88.34592	0.87	0.3497
T1	P	lowFruitIntake	114	-41.49295	86.9859	-0.23	.
U1	P	lowVegeIntake	114	-41.49295	86.9859	-0.23	.
W1	P	sendOccu	114	-40.3179	86.63579	2.35	0.1253

Figure D-4: Goodness of fit output for final DM model among females (model P)

```
. * Final model P: with age categories
. logistic combinedDM gestationalDiabetes ageCat0 ageCat2 ageCat3

Logistic regression                               Number of obs   =        115
                                                  LR chi2(4)      =      13.94
                                                  Prob > chi2     =     0.0075
Log likelihood = -39.418203                       Pseudo R2       =     0.1503
```

combinedDM	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
gestationalDiabetes	14.51474	14.55384	2.67	0.008	2.03383	103.5867
ageCat0	3.615386	3.250541	1.43	0.153	.6206569	21.05997
ageCat2	2.055551	1.743916	0.85	0.396	.3897397	10.84131
ageCat3	5.2371	4.540394	1.91	0.056	.9574741	28.64539
_cons	.0038305	.005204	-4.10	0.000	.0002672	.0549136

```
. lfit

Logistic model for combinedDM, goodness-of-fit test

      number of observations =       115
 number of covariate patterns =         7
             Pearson chi2(2) =      1.30
                 Prob > chi2 =    0.5213
```

The model with just gestational diabetes was not a good fit (with Pearson goodness of fit < 0.000). Age categories were added to the model because among females, it seemed to be slightly associated with DM and improved the model fit better that other risk factors.

Model P with age: gestationalDiabetes + ageCat0 ageCat2 ageCat3

D.7. Consent form (English)

UNIVERSITY OF CAPE TOWN

Room 53.03
Institute of Infectious Diseases and Molecular Medicine
Faculty of Health Sciences
Observatory 7925
South Africa
Tel: +27 (0)21 406 6079

Epidemiology of Diabetes, TB and HIV co-infection in a high HIV/TB burden setting

INFORMED CONSENT and INFORMATION FORM

My name is _____

I wish to invite you to participate in a study that is trying to assess the interaction between tuberculosis (TB), HIV and Diabetes. This study is being run by the Institute of Infectious Diseases and Molecular Medicine at the University of Cape Town. Dr Tolullah Oni is the Principal Investigator.

Firstly, I wish to explain to you why this research is being done:

TB is a disease that is seen very commonly in Cape Town and, indeed, in most of South Africa. It is caused by bacteria that people breathe in and the infection results in cough, fevers and weight loss. The disease is more common, and can be more severe, in patients with HIV infection.

Diabetes is a disease caused by the body's inability to control sugar levels. This disease is becoming increasingly more common worldwide and in South Africa due to reduced exercise and increasing obesity. Previous studies have shown that like HIV, diabetes increases the risk of TB. But there are a few things we still do not know:

1. We do not know how much diabetes (and risk factors such as high cholesterol) there is in this setting.
2. We also do not know if the increasing levels of diabetes are contributing significantly to the TB epidemic, and
3. Although we know that HIV increases the risk of TB, we do not know if having HIV and diabetes further increases the TB risk. In other words, we do not know if a person with HIV and diabetes is at higher risk of TB than a person with HIV and no diabetes.

We request your participation in this study either because you are being investigated for TB, because you have been diagnosed with diabetes, or because you have recently undergone HIV counselling and testing (HCT).

As part of this study, we will check your blood for HIV and check your sputum (spit) for TB. We will also check you for Diabetes using the following tests:
We will ask you to come again before eating or drinking anything and check your sugar level that morning and 2 hours later after giving you a sugary drink. You must not eat or drink anything else during these 2 hours. We will also do an HbA1c test, a blood test for diabetes and check your blood cholesterol level. We will pay 30 Rand travel expenses for this purpose.

If we diagnose HIV, we will give you a referral letter to take to any HIV clinic of your choice where baseline bloods will be done and your eligibility for antiretroviral therapy can be assessed. If TB is found, we will also give you a letter to take to your nearest TB clinic as it will be important to start TB treatment as soon as possible. If diabetes is diagnosed, we will write a referral letter for you and advise you of your nearest

diabetes club where you can be started on appropriate treatment and receive regular advice on diet and lifestyle. If high cholesterol is diagnosed, we will write a referral letter to your ARV clinic or day hospital for further management.

It is entirely up to you to decide whether or not to take part in this study. If you do decide to take part, you will be asked to sign this consent form. We will then request you to provide us with an extra blood sample (15ml) that can be taken at the same time as your normal blood tests and may perform a Chest X Ray.

Although blood testing very rarely causes problems, if anything goes wrong the University provides insurance to cover this possibility. This study will also be monitored by the Research Ethics Committee of the University of Cape Town. Their job is to ensure your safety and protect you during the study.

The decision to participate is entirely your own. IF YOU DECIDE NOT TO PARTICIPATE, YOUR TREATMENT WILL NOT BE DIASDVANTAGED IN ANY WAY. In addition, at any point during the study you are free to withdraw without telling us why.

Throughout the study your privacy will be maintained and nobody other than the doctors and nurses looking after you will know that you are participating. Samples will be labelled with code numbers and hence the laboratory staff will not know your identity. When the results of the study become available, names of the participating patients will not be included.

Do you have any questions? During the study you may contact either the **Human Research Ethics Committee** (021 406 6492) or **Dr Tolullah Oni** (021 406 6079) if you have further questions. Please remember that Dr Oni will not be directly responsible for your medical care which will be conducted by your regular doctors and nurses.

Consent to participate in the study:

I have read the above / have had the above read to me. I have had the opportunity to discuss the study

with _____ and have also had the opportunity to ask any questions. I consent to

take part in this study:

Name _____

Signature _____

Date _____

Name of Staff member consenting _____

Signature _____

Date _____

Witness (if participant is illiterate)

Name _____

Signature _____

Date _____

D.8. Consent form (isiXhosa)

UNIVERSITY OF CAPE TOWN

Room 53.03
Institute of Infectious Diseases and Molecular Medicine
Faculty of Health Sciences
Observatory 7925
South Africa
Umnx: +27 (0)21 406 6079

Isifo Esibulalayo seSwekile, i-TB nokosuleleka kwe-HIV kwimeko ene-HIV/TB ephezulu

IMVUME ENOLWAZI kunye NEFOMU YENKCAZELO

Igama lam ngu_____

Ndinqwenela ukukumema ukuba uthathe inxaxheba kuphononongo oluzama ukuhlola ukusebenzisana phakathi kwesifo somhlaza (TB), i-HIV neSifo seswekile. Olu phononongo luqhutywa yi-Institute of Infectious Diseases and Molecular Medicine eYuniveisithi yaseKapa. UGqr Tolullah Oni nguMphandi Oyintloko.
Okokuqala, ndifuna ukukucacisela ukuba kutheni kusenziwa olu phando:

I-TB sisifo esiqheleke kakhulu eKapa kunye, nenxalenye enkulu yoMzantsi Afrika. Sibangelwa ziintsholongwane abantu abaziphefumlayo yaye ukosuleleka kubangela ukukhohlela, ifiva nokuhlelwa bubungakanani bomzimba. Esi sifo siqheleke kakhulu, yaye sinokuba mandundu, kwizigulana ezinokosuleleka kwe-HIV.

Iswekile sisifo esibangelwa kukungakwazi komzimba ukulawula amaqondo eswekile. Esi sifo siya ngokuqheleka nangakumbi ehlabathini jikelele naseMzantsi Afrika ngenxa yokungenzi uthambo nokwanda kwabantu abatyebe kakhulu. Uphononongo oludlulileyo luye lwabonisa ukuba njenge-HIV, iswekile yandisa umngcipheko we-TB. Kodwa kusekho izinto eziliqela ekufuneka sizazi:

1. Asazi ukuba ingakanani iswekile (kunye nomngcipheko njengekholesteroli ephezulu) ekhoyo kule nkalo.
2. Kwakhona asazi ukuba ukwanda kwamaqondo eswekile afaka isandla ngokuphawulekayo kusini na kwisifo se-TB, yaye
3. Nangona sisazi ukuba i-HIV yandisa umngcipheko we-TB, asazi ukuba ne-HIV kunye neswekile kwandisa umngcipheko we-TB. Ngamanye amazwi, asazi ukuba umntu one-HIV kunye neswekile usemngciphekweni ophezulu we-TB kunomntu one-HIV ngaphandle kweswekile.

Sicela inxaxheba yakho kolu phononongo kuba uphandelwa i-TB, okanye kuba ufunyaniswe uneswekile, okanye kuba usandula ukuya kufumana amacebiso novavanyo lwe-HIV (HCT)

Njengenxalenye yolu phononongo, siza kuhlola i-HIV egazini lakho size sihlole i-TB kwisikhohlela sakho. Kwakhona siza kuhlola iSwekile yakho sisebenzisa olu vavanyo lulandelayo:
Siza kucela ukuba uze kwakhona ngaphambi kokuba utye okanye usele nantoni na ukuze sihlole iqondo leswekile lakho kuloo ntsasa nakwiiyure ezi-2 emva kokuba sikunike isiselo esineswekile. Awufanele utye okanye usele nantoni na ebudeni bezi yure zi-2. Kwakhona siza kwenza uvavanyo lwe-HbA1c, uvavanyo lwegazi lweswekile size sihlole iqondo lekholesteroli yegazi. Siza kukuhlawula iiRandi ezingama-30 zeendleko zohambo.

Ukuba sikufumanisa une-HIV, siza kukunika ileta ebhekiselayo ukuze uye nayo kuyo nayiphi na ikliniki ye-HIV yokhetho lwakho apho igazi lohlolo lokuqala luza kutsalwa khona kuze kujongwe nokufanelekela

kwakho ukufumana unyango lwe-antiretroviral. Ukuba ufunyaniswe une-TB, kwakhona siza kukunika ileta ukuba uye nayo kwikliniki ekufutshane ye-TB njengoko kuza kubaluleka ukuba uqalise unyango lwe-TB ngokukhawuleza kangangoko kunokwenzeka. Ukuba ufunyaniswe uneswekile, siza kukubhalela ileta size sikucebise ngeqela leswekile elikufutshane apho unokuqaliswa khona ngonyango olufanelekileyo uze ufumane amacebiso ngokuthe rhoqo ngendlela yokutya nendlela yokuphila. Ukuba ufunayniswa unekholesteroli ephezulu, siza kubhala ileta eya kwikliniki yakho ye-ARV okanye isibhedlele sakho sasemini ukuze ilawulwe.

Kuxhomekeke kuwe ukuba uyafuna ukuthatha inxaxheba kolu phononongo kusini na. Ukuba ugqiba ekubeni uthathe inxaxheba kolu phononongo, uza kucelwa ukuba utyobele le fomu yemvume. Siza kukucela ukuba usinike isampulu yegazi engakumbi (15ml) enokuthathwa ngaxeshanye njengovavanyo lwakho oluqhelekileyo lwegazi yaye sisenokwenza i-X Reyi yeSifuba.

Nangona ukwenza uvavanyo lwegazi kungafane kubangele iingxaki, ukuba kukho into ephosakeleyo eyenzekayo iYunivesithi inikela ngeinshurensi ukuze kugutyungelwe oko kunokwenzeka. Olu phononongo kwakhona luza kuhlolwa yiKomiti Yokuziphatha Yophando yeYunivesithi yaseKapa. Umsebenzi wabo kukuqinisekisa ngokhuseleko lwakho baze bakukhusele ebudeni bophonongo.

Isigqibo sokuthatha inxaxheba sesakho ngokuphelelelyo. <u>UKUBA UGQIBA EKUBENI UNGATHATHI NXAXHEBA, UNYANGO LWAKHO ALUSAYI KUPHAZAMISEKA NGAYO NAYIPHI NA INDLELA.</u> Ukongezelela, nanini na ebudeni bophononongo wamkelekile ukurhoxa ngaphandle kokusichazela.

Ebudeni bophononongo imfihlelo yakho iza kugcinwa yaye akukho bani ngaphandle koogqirha noonesi abakunyamekelayo abaza kukwazi ukuba uthatha inxaxheba. Iisampulu zakho ziza kubhalwa ngeenombolo zekhowudi ngaloo ndlela abasebenzi belebhu abasayi kukwazi ukuba ungubani. Enoba iziphumo zophononongo ziyafumaneka, amgama abathathi-nxaxheba awasayi kuqukwa.

Ngaba unayo nayiphi na imibuzo? Ebudeni bophononongo usenokuqhagamshela **iKomiti Yokuziphatha Yophando Yoluntu** (021 406 6492) okanye **uGqr Tolullah Oni** (021 406 6079) ukuba unemibuzo eyongezelelekileyo. Sicela ukhumbule ukuba uGqr Oni akayi kuba nembophelelelo yonakekelo lonyango lwakho oluza kwenziwa ngoogqirha noonesi bakho abaqhelekileyo.

Imvume yokuthatha inxaxheba kuphononongo:

Ndikufundile okungentla / ndiye ndakufundelwa oku kungentla. Ndiye ndanalo ithuba lokuxoxa ngophononongo

kunye no_____ yaye ndiye ndanalo ithuba lokubuza imibuzo. Ndiyavuma

ukuthatha inxaxheba kolu phononongo:

Igama _____

Utyikityo _____

Umhla _____

Igama lelungu labaSebenzi elivumayo _____

Utyikityo _____

Umhla _____

Ingqina (ukuba umthathi-nxaxheba akakwazi ukufunda)

Igama _____

Utyikityo _____

Umhla _____

D.9. Ethics approval for current study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 July 2015

HREC REF: 337/2015

Dr T Oni
Public Health & Family Medicine
Entrance 5, Room4.41
Falmouth Building

Dear Dr Oni

PROJECT TITLE: THE PREVALENCE AND RISK FACTORS OF DIABETES MELLITUS AMONG TUBERCULOSIS PATIENTS AT UBUNTU CLINIC, KHAYELITSHA - Sub-study linked to 403/2011 (Master Candidate - Ms M Kubjane)

Thank you for your email to the Human Research Ethics Committee (HREC) dated 13 July 2015, the HREC note that in this sub-study the student will only be conducting secondary analysis of data that have already been collected in the main study (HREC/REF:403/2011)

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th July 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Mmamapudi Kubjane is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed

pp
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB0000193B

Hrec/ref:337/2015

D.10. Journal manuscript guidelines (Lancet Diabetes and Endocrinology)

Information for Authors

The Lancet Diabetes & Endocrinology has an Impact Factor (partial) of 9·185 and an Immediacy Factor (partial) of 5·882. We consider any original research contribution that advocates change in or illuminates clinical practice and informative reviews on any topic connected with endocrinology, metabolism, and diabetes. Because the journal has an international readership from a wide range of specialties, it is vital that articles should be written clearly and should not assume a level of knowledge above that of, say, a reasonably well read, recently qualified, doctor in training. One way to find out if your article is understandable to those reading outside their immediate field of interest is to show the manuscript to colleagues in other specialties. If they find it difficult to follow, so will a good proportion of the readership. Wherever possible, figures and good quality photographs (colour or black and white) should be used to supplement and to enhance the text. Further details on the different sections of *The Lancet Diabetes & Endocrinology*, and how to submit to the journal, are provided below. If you require further clarification, the journal's editorial staff will be pleased to help (email diabetes-endocrinology@lancet.com).

Manuscripts must be solely the work of the author(s) stated, must not have been previously published elsewhere, and must not be under consideration by another journal. *The Lancet* journals are signatories of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, issued by the International Committee of Medical Journal Editors (ICMJE Recommendations), and to the Committee on Publication Ethics (COPE) code of conduct for editors. We follow COPE's guidelines.

Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals
http://www.icmje.org

COPE Code of Conduct
http://publicationethics.org/files/u2/New_Code.pdf

How to submit your paper

Manuscript submission

Manuscript submission to all *Lancet* journals is free. Manuscripts should be submitted online via the *TheLancet Diabetes & Endocrinology*'s online submission and peer review website (known as EES) at http://ees.elsevier.com/thelancetde

- Simply log on to EES and follow the on-screen instructions for all submissions
- If you have not used EES before, you will need to register first. In EES, the corresponding author is the person who enters the manuscript details and uploads the submission files
- Inclusion of illustrations (photographs, graphs, diagrams, etc) is a prerequisite for publication. Submission of original and editable artwork files is encouraged. Digital photography files should have a resolution of at least 300 dpi and be at least 107 mm wide
- In almost all cases, if you have a finished manuscript, you should submit it, rather than contacting *The Lancet Diabetes & Endocrinology* to enquire whether an unseen manuscript is likely to be accepted. Unless you have been asked by the Editor to submit by email, you should use the online system for all types of submission, including Correspondence
- If you have any technical problems or questions, please contact our dedicated customer support (available 24 h a day, 365 days a year):
  For the Americas: +1 888 834 7287 (toll-free in USA and Canada)
  For Asia and Pacific: +81 3 5561 5032
  For Europe and rest of the world: +353 61 709190
  Email: diabetes-endocrinology@lancet.com

Covering letter

- You should upload your covering letter at the "Enter Comments" stage of the online submission process
- Use the covering letter to explain why your paper should be published in *The Lancet Diabetes & Endocrinology* rather than elsewhere
- It is helpful to indicate what could shorten your paper—the full paper can be reviewed and a shorter version published; a table or figure, details of a DNA sequence, or further references, for example, can be published on our website or made available from the authors

First submissions to *The Lancet Diabetes & Endocrinology* should include:

1. Covering letter
2. Manuscript including tables and panels
3. Figures
4. Author statement form (see next section)
5. Declaration of interests and source of funding statements (see next section)
6. In-press papers—one copy of each with acceptance letters
7. Protocols and CONSORT details for randomised controlled trials (see Articles)
8. We encourage disclosure of correspondence from other journals and reviewers, if previously submitted, and we might contact relevant editors of such journals
9. Research in context panel, for all primary research Articles

Statements, permissions, and signatures

Authors and contributors

- Designated authors should meet all four criteria for authorship in the ICMJE Recommendations
- All authors, and all contributors (including medical writers and editors), should specify their individual contributions at the end of the text
- *The Lancet Diabetes & Endocrinology* will not publish any paper unless we have the signatures of all authors
- We suggest you use the author statement form and either upload the signed copy with your submission, or fax to +44 (0) 1865 853 021
- Please include written consent of any cited individual(s) noted in acknowledgments or personal communications

ICMJE Recommendations
http://www.icmje.org

Author statement form
http://download.thelancet.com/flat-content-assets/authorgl/title-author-signatures.pdf

Declaration of interests

A conflict of interest exists when professional judgement concerning a primary interest (such as patients' welfare or validity of research) may be influenced by a secondary interest (such as financial gain). Financial relationships are easily identifiable, but conflicts can also occur because of personal relationships or rivalries, academic competition, or intellectual beliefs. A conflict can be actual or potential, and full disclosure to the Editor is the safest course. Failure to disclose conflicts might lead to publication of a correction or even to retraction. All submissions to *The Lancet Diabetes & Endocrinology*

must include disclosure of all relationships that could be viewed as presenting a potential or actual conflict of interest (see Lancet 2003; 358: 854-56 and Lancet 2003; 361: 8-9). The Editor may use such information as a basis for editorial decisions, and will publish such disclosures if they are believed to be important to readers in judging the manuscript. Agreements between authors and study sponsors that interfere with authors' access to all of a study's data, or that interfere with their ability to analyse and interpret the data and to prepare and publish manuscripts independently, may represent conflicts of interest, and should be avoided.

- At the end of the text, under a subheading "Declaration of interests", all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. If there are no conflicts of interest, authors should state that none exist
- All authors are required to provide a Conflict of Interest Statement and should complete a standard form, which is available at http://download.thelancet.com/flatcontentassets/authors/icmje-coi-form.pdf. This form can be uploaded with the manuscript at submission or faxed to +44 (0)1865 853017. The form has been modified by the ICMJE following consultation with authors and editors. Further information is available in a joint ICMJE statement published on July 1, 2010. For more information see Lancet 2009; 374: 1395–96.
- For Comments, Personal Views, and Reviews, *The Lancet Diabetes & Endocrinology* will not publish if an author, within the past 3 years, and with a relevant company or competitor, has any stocks or shares, equity, a contract of employment, or a named position on a company board; or has been asked by any organisation other than *The Lancet Diabetes & Endocrinology* to write, be named on, or to submit the paper (see Lancet 2004; 363: 2–3)

ICMJE COI form
http://download.thelancet.com/flatcontentassets/authors/icmje-coi-form.pdf

Joint ICMJE statement
http://download.thelancet.com/flatcontentassets/authors/icmje-statement.pdf

Patient Consent form
http://www.thelancet.com/pb/assets/raw/Lancet/authors/lancet-consent-form.pdf

Role of the funding source

- All sources of funding should be declared as an acknowledgment at the end of the text
- At the end of the Methods section, under a subheading "Role of the funding source", authors must describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication
- If there is no Methods section, the role of the funding source should be stated as an acknowledgment. If the funding source had no such involvement, the authors should state this
- The corresponding author should confirm that he or she had full access to all the data in the study and had final responsibility for the decision to submit for publication

Role of medical writer or editor

- If a medical writer or editor was involved in the creation of your manuscript, we need a signed statement from the corresponding author to include their name and information about funding of this person
- This information should be added to the Acknowledgments or Contributors section
- We require signed statements from any medical writers or editors declaring that they have given permission to be named as an author, as a contributor, or in the Acknowledgments section

Patient and other consents

- Appropriate written consents, permissions, and releases must be obtained where you wish to include any case details, personal information, and/or images of patients or other individuals in *The Lancet* journals in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. Studies on patients or volunteers need approval from an ethics committee and informed consent from participants. These should be documented in your paper.
- Do not use "blackout" bars or similar devices to anonymise patients in clinical images: if you have taken consent appropriately masking is not needed.
- Since the consent form needs to comply with the relevant legal requirements of your particular jurisdiction, we do not provide sample forms; this is your responsibility. Your affiliated institution should be able to provide an appropriate form.
- For the purposes of publishing in *The Lancet* journals, a consent, permission, or release should include, without limitation, publication in all formats (including print, electronic, and websites), in sublicensed and reprinted versions (including translations), and in other works and products.
- To respect your patient's and any other individual's privacy, please do not send signed forms to *The Lancet Diabetes & Endocrinology*. Please instead complete the patient consent section of the Author statements while retaining copies of the signed forms in the event they should be needed.
- If consent, permission, or release is made subject to any conditions, *The Lancet Diabetes & Endocrinology* must be made aware in writing of all such conditions before publication.
- For more information about our policy, please visit http://www.elsevier.com/about/company-information/policies/patient-consent.

Signatures

At the external peer review stage you will need to send signed copies of the following statements:

- Authors' contributions
- Conflicts of interest statements
- Statements of role, if any, of medical writer or editor
- Acknowledgments—written consent of cited individual
- Personal communications—written consent of cited individual
- Use of copyright-protected material—signed permission statements from author and publisher

These statements can be scanned and submitted electronically to diabetes-endocrinology@lancet.com. To minimise delays, we strongly advise that you prepare signed copies of these statements before you submit your manuscript.

Types of article and manuscript requirements

Please ensure that anything you submit to *The Lancet Diabetes & Endocrinology* follows the guidelines provided for each article type. For instruction on how to format the text of your paper, including tables, figures, panels, and references, please see our Formatting guidelines.

Red section (Articles)

Articles

- *The Lancet Diabetes & Endocrinology* prioritises reports of original research that are likely to change clinical practice or thinking
- We invite submission of all clinical trials, whether phase 1, 2, 3, or 4. For phase 1 trials, we consider those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action
- We require the registration of all interventional trials, whether early or late phase, in a primary register that participates in WHO's International Clinical Trial Registry Platform (see *Lancet* 2007; 369: 1909–11). We also encourage full public disclosure of the minimum 20-item trial registration dataset at the time of registration and before recruitment of the first participant (see *Lancet* 2006; 367: 1631–35). The registry must be independent of for-profit interest
- Reports of trials must conform to CONSORT 2010 guidelines and should be submitted with their protocols
- All reports of randomised trials should include a section entitled Randomisation and masking, within the Methods section. Please refer to *The Lancet*'s formatting guidelines for randomised trials.
- Cluster-randomised trials must be reported according to CONSORT extended guidelines
- Randomised trials that report harms must be described according to extended CONSORT guidelines
- Studies of diagnostic accuracy must be reported according to STARD guidelines
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the STROBE statement, and should be submitted with their protocols
- We encourage the registration of all observational studies on a WHO-compliant registry (see *Lancet* 2010; 375: 348)
- Genetic association studies must be reported according to STREGA guidelines
- Systematic reviews and meta-analyses must be reported according to PRISMA guidelines
- To find reporting guidelines see: http://www.equator-network.org

All Articles should, as relevant:

- Be up to 3000 words (4500 for randomised controlled trials) with 30 references (the word count is for the manuscript text only)
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 250 words. Our electronic submission system will ask you to copy and paste this section at the "Submit Abstract" stage
- For randomised trials, the abstract should adhere to CONSORT extensions: abstracts (see *Lancet* 2008; 371: 281–83)
- For intervention studies, the abstract should include the primary outcome expressed as the difference between groups with a confidence interval on that difference (absolute differences are more useful than relative ones). Important secondary outcomes can be included as long as they are clearly marked as secondary
- Use the SI system of units and the recommended international non-proprietary name (rINN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct
- Use gene names approved by the Human Gene Organisation. Novel gene sequences should be deposited in a public database (GenBank, EMBL, or DDBJ), and the accession number provided. Authors of microarray papers should include in their submission the information recommended by the MIAME guidelines. Authors should also submit their experimental details to one of the publicly available databases: ArrayExpress or GEO
- Include any necessary additional data as part of your EES submission
- All accepted Articles should include a link to the full study protocol published on the authors' institutional website (see *Lancet* 2009; 373: 992 and *Lancet* 2010; 375: 348)

Putting research into context

- From Jan 1, 2015, all research papers submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work, with an enhanced structure and subheadings compared with papers submitted before this date (see *Lancet* 2014; 384: 2176–77, and panel below for guidance). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence. *Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.*

Human Gene Organisation
http://www.genenames.org/

MIAME guidelines
http://www.mged.org/Workgroups/MIAME/miame_checklist.html

WHO's International Clinical Trial Registry Platform
http://www.who.int/ictrp/network/trds/en/index.html

CONSORT 2010 guidelines
http://www.consort-statement.org/consort-statement/overview0/

CONSORT extended guidelines
http://www.consort-statement.org/extensions/extensions/

STARD guidelines
http://www.stard-statement.org/

STROBE statement
http://www.strobe-statement.org/

STREGA guidelines
http://www.medicine.uottawa.ca/public-health-genomics/web/eng/strega.html

PRISMA guidelines
http://www.prisma-statement.org/

To find reporting guidelines, see:
http://www.equator-network.org

Array and GEO
http://www.ebi.ac.uk/microarray-as/ae/
http://www.ncbi.nlm.nih.gov/geo

Blue section (Comment, Correspondence, News, In Focus)

Editorial

- Editorials are the voice of *The Lancet Diabetes & Endocrinology*, and are written in-house by the journal's editorial-writing team and signed "*The Lancet Diabetes & Endocrinology*"

Comment

- This section contains Commentaries that accompany papers published in *The Lancet Diabetes & Endocrinology* or on issues of wide-reaching concern in diabetes, endocrinology and metabolism. Most Commentaries are commissioned, but unsolicited Commentaries are also considered. Comments linked to policy decisions are welcome. Commentaries may be peer reviewed
- Comments should be no more than 700 words, with a strict maximum of ten references, and one small figure, panel, or table (optional).
- At the Editor's discretion, Commentaries may be shortened in the interests of space
- The place to respond to something we have published is in our **Correspondence** section
- See **Conflicts of Interest** guidelines for Comments

Correspondence

- Letters should be written in response to previous content published in *The Lancet Diabetes & Endocrinology*
- Letters must be submitted within 4 weeks of online publication of the relevant article and should be no longer than 300 words
- Letters of general interest, unlinked to items published in the journal, are also considered and should be no longer than 400 words
- Letters should have a maximum of five references, one small table or figure (optional), and five authors
- Letters are not usually peer reviewed, but we might invite replies from the authors of the original publication, or pass on letters to these authors
- All accepted letters are edited, and may be shortened in the interest of space. Proofs will be sent out to authors before publication

News

- Most of the writers of News articles are professional journalists, but an important event in your country that might be of wider interest can be brought to the attention of our News editors via diabetes-endocrinology@lancet.com

In Focus

- Readers with an interest in contributing book, film, TV, exhibition, or web reviews should contact the Editor via diabetes-endocrinology@lancet.com. In general, these submissions should be between 350 and 400 words.
- *The Lancet Diabetes & Endocrinology* also encourages the submission of Essays for this section. These should be up to 1000 words in descriptive prose, and can be on any topic related to endocrinology, metabolism, and diabetes. If you are a medical professional, this is your opportunity to shine light on a neglected area, highlight an inspirational experience, or share your insights.
- Profiles in this section are commissioned by the journal's editors

For *The Lancet* journals' policy on corrections of errors see http://download.thelancet.com/flatcontentassets/authors/correction-policy.pdf

Corrections

- Any substantial error in any article published in *The Lancet Diabetes & Endocrinology* should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight.
- The *Lancet* journals have a policy for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietory drug name, dose, or unit, any numerical error in the results, or any factual error in the interpretation of results.

Green section (Reviews, Personal Views)

Reviews

- Reviews should be either definitive overviews of a major topic in diabetes, endocrinology, or metabolism, or an update of knowledge in a narrower field of current interest
- Most Reviews are commissioned, but unsolicited one-page outlines, consisting of a synopsis and a list of recent references, can be directed to the Editor at diabetes-endocrinology@lancet.com. If you have already written the paper, please submit it for consideration via our online system
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages. An example is shown below:

> **Search strategy and selection criteria**
>
> References for this review were identified through searches of PubMed for articles published from January, 1971, to June, 2010, by use of the terms "bariatric", "gastric bypass", "gastric band", "gastric sleeve", "sleeve gastrectomy", "biliopancreatic diversion", and "duodenal switch" in combination with the term "diabetes". Relevant articles published between 1918 and 1920 were identified through searches in the authors' personal files, in Google Scholar, and Springer Online Archives Collection. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English, French, and German were included.

- Reviews should be 3000–5000 words, with a maximum of 100 references. A 150-word unstructured summary should be included. These papers should include about five illustrations, tables, and figures to aid the reader

Personal Views

- These should be around 3000 words in length, with a maximum of 75 references

- These opinion pieces may reflect an individual perspective and must be prepared in a similar way to a Review article
- Unsolicited contributions are welcome, but please contact the Editor (diabetes-endocrinology@lancet.com) before submission to ensure that the proposed topic is suitable for the journal

Clinical Pictures

- The ideal Clinical Picture provides visual information that will be useful to other clinicians.
- Clinical Pictures should be interesting, educational, and respectful of the patient. *The Lancet Diabetes & Endocrinology* is less interested in pictures that simply illustrate an extreme example of a medical condition.
- Authors must obtain signed informed consent for publication (see Patient and other consents). Do not use "blackout" bars or similar devices to anonymise patients: if you have taken consent appropriately, masking is not necessary.
- Use no more than 300 words, with no references.

Formatting guidelines

Language

- Manuscripts should be submitted in English. Authors writing in Chinese, Portuguese, or Spanish may wish to use the Webshop (http://webshop.elsevier.com/languageservices) to provide an English translation of their manuscript for submission.

Title page

- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated with email and telephone details.

Formatting of text

- Type a single space at the end of each sentence
- Do not use bold face for emphasis within text
- We use a comma before the final "and" or "or" in a list of items
- Type decimal points midline (ie, 23·4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Please use page numbering

References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example:
  "...as reported by Saito and colleagues.[15]"
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen
- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or "long" hyphen):
  "15[tab]Saito N, Ebara S, Ohotsuka K, Kumeta J, Takaoka K. Natural history of scoliosis in spastic cerebral palsy. *Lancet* 1998; **351**: 1687–[en rule]92."
- Give any subpart to the title of the article. Journal names are abbreviated in their standard form as in Index Medicus
- If there are six authors or fewer, give all six in the form:
  surname space initials comma
- If there are seven or more give the first three in the same way, followed by et al
- For a book, give any editors and the publisher, the city of publication, and year of publication
- For a chapter or section of a book, also give the authors and title of the section, and the page numbers
- For online material, please cite the URL, together with the date you accessed the website
- Online journal articles can be cited using the DOI number
- Do not put references in the Summary

Index Medicus
http://www.nlm.nih.gov/

Guidelines for supplementary material

All material should be submitted as one PDF (with numbered pages) with the paper and will be peer reviewed. Material will be published at the discretion of *The Lancet* journals' editors. All material should be provided in English.

Text

- Main heading for the web extra material should be in 12 point Times New Roman font **BOLD**
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point **BOLD**

Tables

- Main table heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced
- Tables should be in 8 point Times New Roman font, single spaced
- Headings within tables should be in 8 point **BOLD**

Data

- SI units are required
- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- Exact p values should be provided, unless p<0·0001

Drug names

- Recommended international non-proprietary name (rINN) is required

References

- Vancouver style—eg,
  Smith A, Jones, B, Clements S. Clinical transplantation of tissue-engineered airway. *Lancet* 2008; 372: 1201–09.

Formatting guidelines for randomised trials
http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf

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Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: Elsevier, 2008: 230–47.

- Numbered in order of mention in appendix and numbered separately from references in the full paper

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