Establishing the association of type 2 diabetes and insulin resistance with Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia

Thesis submitted in accordance with the requirements of the University of Liverpool / Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy by

Fareed Hamed Almaleki

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Supervisors: PROF. LUIS CUEVAS

PROF. GEOFF GILL

DECLARATION

This thesis has not been submitted in any other application for a degree and is the result of my own work and composition.

In some circumstances, work (such as Laboratory services and part of data collection) was conducted in partnership with other co-workers and institutions. The details of the contribution of the collaborators to this project, is as outlined below, and they are also mentioned in the acknowledgments section.

TB study	
Activities	**Responsibility**
Notification of patients that met the study's selection criteria	Dr. Ali Asghar and other doctors on duty at the Tuberculosis (TB) clinics.
Patients recruitments and guidance	Head, nursing department, Fatema and other nurses on duty at the TB clinics.
Participants' interview	Researcher and research assistance.
Sample collection	Mosa Mohammad Atwady, Laboratory staff and research assistance
Blood testing	Salma Salah Almutairi, Laboratory Scientist of the biochemistry department. Ahmed Alghamdi, Laboratory Scientist of the hormone department.
Administrative work at the centre	Ahmed Alghamdi and Abdullah Alghamdi staff at the Tuberculosis and Chest Diseases Centre.
Administrative work at medical warehouses	Ahmed Ibrahim Mirza staff at the MOH medical warehouses.

CHD study	
Activities	**Responsibility**
Notification of patients that met the study's selection criteria	Dr. Mohammed Mougrabi and other doctors on duty at the cardiology department.
Patients recruitments and guidance	Saadiyah Jamil Hilali and Liza T. Sarmiento, Staff at the cardiology department of the King Faisal Hospital.
Participants interview	Researcher and research assistant.
Sample collection	Laboratory staff.
Blood testing	Staff of biochemistry department. Turki Almalki, senior laboratory technician of hormone department.
Administrative work at the outpatient's department	Hussain Yahia Hakami, Head of the Clinics Department.
Administrative work at medical warehouses	Sultan Al-thubaity, staff at Ministry of Health (MOH) medical warehouses.

DEDICATION

I dedicate this thesis to God Almighty, my creator and my source of knowledge, understanding and inspiration. I also dedicate this thesis to my parents, my wife, my children and my siblings who have provided me with immense support and encouragement to overcome all the obstacles that I faced. I also dedicate this work to my friends and everyone that has supported me along the way to completion, without your help and guidance none of this would have been possible.

ABSTRACT

Background: Patients with Coronary Heart Disease (CHD) or Tuberculosis (TB) are more likely to have Type 2 Diabetes Mellitus (T2DM). Insulin Resistance (IR) in patients with normal glucose may also be a risk factor for these conditions.

Methods: This thesis explored whether T2DM and IR are risk factors for TB enrolled patients receiving TB treatment in the previous year and controls. In addition, the thesis explores whether T2DM and IR are risk factors for CHD among patients with stable CHD and controls. The studies were based in Saudi Arabia and used cross sectional surveys and case controls design. Controls were asymptomatic adults attending the TB clinics for labour reasons. All participants were screened for fasting plasma glucose (FPG), insulin, glycated haemoglobin (HbA1c) and lipids. We assessed the severity of the clinical presentation of TB among patients with T2DM, IR and normal glucose. Finally, we described the quality of life of patients with CHD among patients with T2DM, IR and normal glucose.

Results: One hundred seventy-five adults with pulmonary TB and 140 controls were recruited (36.6% and 40.7% female and 63.4% and 59.3% male, respectively). Twenty-nine per cent of TB cases had T2DM and 22% normoglycemic IR. 3.3% of patients were unaware of their T2DM diagnosis. TB was associated with prediabetes (AOR 5.112, $p = 0.032$), low level of *risky* HDL Cholesterol (AOR 0.316, $p = 0.001$) and non-Saudi nationalities (AOR 4.018, $p < 0.001$). Former TB cases were more likely to eat fast foods (1 – 2 times/week, AOR 2.857 and 2 – 3 times/month, AOR 3.126, $p = 0.026$, respectively) and to have a fair or poor diet (AOR 13.518, and AOR 37.766, respectively) ($p < 0.001$). Three hundred twenty-five patients with stable CHD and were recruited (29.2% and 39.9% female and 70.8% and 60.1% male, respectively). Of these 65% had T2DM and 31.3% normoglycemic IR. Almost 6% of patients were unaware of their T2DM status. CHD were more likely to have T2DM (AOR 4.974, $p = 0.034$), high FPG (AOR 5.034, $p = 0.021$), to be male (AOR 9.950, $p < 0.001$), aged above 50 years old ($p < 0.015$), Saudi (AOR 6.879, $p = 0.002$), to have primary education (AOR 20.315, $p = 0.004$), hypertension (AOR 5.920, $p = 0.003$) and to take lipid lowering medications (AOR 24.516, $p < 0.001$) than controls. Cases were more likely to have high WHR (AOR 33.997, $p < 0.001$) and diastolic BP (AOR 1.080, $p = 0.004$) than controls. CHD-IR cases had lower quality of life and satisfaction scores with *bodily appearance* ($p = 0.003$), *overall perception of satisfaction with themselves* ($p = 0.041$) and score in the psychological domains ($p = 0.006$) than controls. Patients with CHD and T2DM had lower overall scores for quality of life ($p = 0.002$), satisfaction with *bodily appearance* ($p = 0.012$), *overall perception of satisfaction with themselves* ($p = 0.015$), *with access to health services* ($p = 0.049$) and satisfaction score with transport ($p = 0.027$) than controls.

Conclusion: TB was more prevalent among non-Saudi nationals and males. Patients with TB were more likely to have T2DM, and to be prediabetic, but not more likely to have IR than controls. More efforts are required to upscale the detection of T2DM among TB patients. Patients with CHD were more likely to be male and to have T2DM and IR than controls. Patients with CHD and IR had a lower quality of life than controls. More efforts are required to upscale the management of T2DM and IR among CHD patients.

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List of abbreviations

ADA	American Diabetes Association
AFB	Acid Fast Bacilli
AGEs	Advanced glycation end products
AHA	American Heart Association
AOR	Adjusted odds ratios
BMI	Body mass index
BP	Blood Pressure
CBAHI	Central Board for Accreditation of Healthcare Institutions
CDC	Disease Control and Prevention
CHD	Coronary heart disease
CI	Confidence Interval
cms	Centimetres
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
CVD	Cardiovascular Diseases
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DOTS	Directly observed treatment short course
EDTA	Ethylene diamine tetra acetic-acid
FFA	Free fatty acids
FPG	Fasting Plasma Glucose
GBP	Great British Pound
HbA1c	Glycated Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCWs	Health care workers
Hcy	Homocysteine
HDL	High-density lipoprotein
HHP	Honolulu Heart Program
HIV	Human immunodeficiency virus
HOMA	Homeostatic model assessment
HOMA2-IR	Homeostasis model assessment-(2)-Insulin resistance
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance

IHD	Ischaemic heart disease
IL	Interleukin
IQR	Interquartile ranges
IR	Insulin resistance
IRAS	Insulin Resistance Atherosclerosis Study
kgs	Kilograms
LDL	Low-density lipoprotein
LMIC	Low- and middle-income countries
LSTM	Liverpool School of Tropical Medicine
m^2	Square meter
MENA	Middle East and North Africa
mg/dl	Milligrams per deciliter
MI	Myocardial infarction
mmHg	Millimeters of Mercury
mmol/l	Millimoles per litre
mmol/mol	Millimoles per mole
MOH	Ministry of Health
Mtb	Mycobacterium tuberculosis
N (n)	Total number
ND	Not defined
OGTT	Oral glucose tolerance test
OR	Odds Ratio
p	Probability
PAI	Plasminogen activator inhibitor
PCOS	Polycystic ovarian syndrome
RAGE	Receptor for advanced glycation endproducts
SAR	Saudi Arabian Riyal
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SNPs	Sing nucleotide polymorphisms
SPSS	Statistical Package for the Social Sciences
T1DM	Type 1 diabetes Mellitus
T2DM	Type 2 diabetes Mellitus
TB	Tuberculosis
TINIA	Turbidimetric Inhibition Immunoassay
UAE	United Arab Emirates
UK	United Kingdom

USA	United States of America
VLDL	Very low-density lipoprotein
WHO	World Health Organisation
WHOQOL	World Health Organisation quality of life assessment
WHR	Waist to hip ratio
95% CI	95% Confidence Interval
α-TNF	Alpha-Tumour necrosis factor

Chapter 1

Introduction

1.1. Background

1.1.1. Diabetes mellitus (DM)

Diabetes mellitus is one of the oldest known diseases to mankind, with the first case reported roughly 3000 years ago in an Egyptian manuscript (1). A clear distinction between type 2 (T2DM) and type 1 DM was first made in 1936 (2) and in 1988 T2DM was first described as being part of a complex metabolic syndrome. T2DM, previously known as non-insulin dependent DM, is the most common form of diabetes, characterized by relative insulin deficiency, insulin resistance (IR) and hyperglycaemia (3) and is the result of interactions between behavioural, environmental and genetic risk factors (4).

After World War II, Western hemisphere countries became more affluent and experience significant lifestyle changes and this demographic and epidemiological changes led to a shift from communicable to non-communicable diseases (5). Developing countries have followed the same pattern, with epidemiological and demographical transitions having happened quicker than expected in recent decades (6).

T2DM is a combination of reduced insulin secretion and insulin resistance (IR). The latter being the inability of the body to utilize glucose in the presence of insulin. The risk of T2DM can be increased by obesity, a family history of T2DM and lifestyle and it is more common among some ethnicities. Irregular but increased levels of blood glucose that are lower than the T2DM cut-off are is known as pre-diabetes (7). Individuals with pre-diabetes have a greater risk of T2DM, but its onset can be

prevented or delayed by increased physical activity, lowering body weight and a controlled diet. Therefore, the global rise in T2DM incidence is impacted by the two important factors of a lack of physical exercise and unhealthy dietary habits (8).

1.1.2. Insulin Resistance (IR)

Insulin is a hormone produced in the pancreatic islets of Langerhans by the beta cells. This peptide hormone is responsible for maintaining the normal levels of blood glucose, enabling the cellular uptake of glucose and regulating the metabolism of protein, lipids and carbohydrates, using its mitogenic effects to promote cell growth and division. In 1889, two German scientists, Minkowski and von Mering, discovered insulin in animal experiments and demonstrated that removing the pancreas led to the severe development of diabetes (9, 10) through a substance that dealt with metabolic control. Their hypothesis was later refined by demonstrating that destroying the islet of Langerhans had the same effect associated with diabetes. Minkowski and Zuelzer attempted to isolate the missing substance from the islet of Langerhans, as did Scott in the United States of America (USA), however, their attempts produced inconsistent results. De Meyer of Belgium proposed the name ‘insulin’ in 1909, and Schaefer also proposed the same name in 1916 (10).

In 1928 it discovered that insulin was a polypeptide and its amino acid sequence was identified in 1952. Insulin is a dipeptide with A and B chains connected by disulphide bridges and a total of 51 amino acids with a molecular weight is 5802 and an iso-electric point of pH 5.5. There are 21 amino acids in the A chain, while there are 30 amino acids in the B chain. The N-terminal helix of the A chain is linked to the C-terminal helix that it is anti-parallel and the B chain contains a central helical fragment. The A and B chains are joined together by two disulphide bonds that join

the helices of the N- and C-terminals in the A chain to the B chain via its central helix. In its inactivated form (proinsulin), a connecting peptide forms link between the N-terminal of the A chain and the C-terminal of the B chain (10, 11).

The definition of IR is the presence of an elevated or normal insulin levels that give rise to weakened biological reactions indicating that there is sensitivity impairment to insulin-mediated glucose disposal (12, 13). In the other words, IR is a physiological condition characterized by a reduced cell sensitivity to insulin leading to hyperglycaemia and T2DM (12). There are tissue variances regarding sensitivity and insulin dependence, and the IR syndrome echo the composite effects of additional insulin and mutable resistance to its action (10, 13). IR plays a significant role in numerous diseases, such as polycystic ovarian syndrome (PCOS) (14), hypertension (15), cardiovascular diseases (CVD) (16), metabolic syndrome (15), obesity (17), T2DM (18) and tuberculosis (TB) (19).

1.1.3. T2DM and TB

TB and T2DM have co-existed for centuries and share comorbidities. The Phthisiologia, written by Richard Morton in 1694, already indicated the link between these conditions had been known since Roman times. In the year 600 Common Era (CE), (20) the Indian physician Susruta was aware of this link, and in 800 CE, Avicenna commented that phthisis often complicated diabetes (21).

It was also noted by Root (22) that ‘‘*in the latter half of the 19th century the diabetic patient appeared doomed to die of pulmonary TB if he succeeded in escaping coma*’’ while Bouchardat (23) mentioned ‘‘*at autopsy every case of diabetes had tubercles in the lungs*’’ (24).

Although by the start of the 20th century it was apparent that the connection between T2DM and TB was of major concern for clinicians, the effect of T2DM on TB was disregarded after the development of treatment programs that were potent for both diseases (25, 26). At present, however, there has been a drastic change over recent decades with a global re-emergence of the T2DM-TB association due to the expansion of T2DM in low and middle income countries (LMIC) (24) in areas where TB is still highly prevalent (25). There was an estimated 10 million TB incident cases in 2017, resulting in 1.6 million deaths (27), while T2DM, the seventh leading cause of death in 2016, affected 422 million in 2014, with an estimated 1.6 million deaths in 2016 (27). It is anticipated that by 2035 the number of individuals with T2DM will rise to 592 million (28) with 80% of them living in LMICs where TB is prevalent (28, 29).

The risk of TB rises threefold in patients with T2DM (30, 31). Furthermore, it enhances an individual's vulnerability to *Mycobacterium tuberculosis* (Mtb) infection and disease development (31). T2DM impairs the necessary immune responses required to fight progression from infection to clinical disease, as the adaptive and intrinsic responses are directly compromised. Patients that have T2DM can have renal failure, impaired cell-mediated immunity, pulmonary microangiopathy and micronutrient deficiency and these factors increase an individual's susceptibility to developing TB (31-33). Studies conducted around the world have indicated that 12 - 44% of patients with TB have T2DM (34-39).

1.1.4. T2DM and CHD

A major underlying factor in CVD, the highest cause of mortality and morbidity in the world, is IR. Margaret Albrink was one of the first researchers to identify a group

of factors linked to a higher risk of CHD, which included hypertriglyceridemia and obesity (40), while Berson and Yalow as developed insulin radioimmunoassay methods that allowed the observation that the majority of patients with T2DM were hyperinsulinaemic. These developments allowed Albrink, Farquhar and Reaven et al (41) to outline the concept of an IR syndrome and its association to CHD and hypertriglyceridaemia. The following decades brought forward several studies that showed hyperinsulinemia was regularly linked to CHD. These studies were enhanced more recently in a validation by researchers in the Insulin Resistance Atherosclerosis Study (IRAS), showing the association between atherosclerosis and a direct measure of IR (16, 42). Furthermore, the protective role of the high-density lipoprotein (HDL) were found in the 1970s (16, 43), along with the classification of low-density lipoproteins (LDL) in the following decade, which led to the classification of dyslipidaemia, a pattern that is a typically central feature of the IR syndrome. Welborn et al added the observation of the importance of hypertension to hyperinsulinemia in the 1960s (44). Lastly, the understanding that IR impairs fibrinolysis and increases hypercoagulation (45) gave a pathological base for an elevation in acute CHD incidence in IR syndrome and atherosclerosis.

1.2. Thesis importance

Many studies have shown that patients with T2DM are more likely to have CHD and TB (16, 19, 24, 43). However, few studies have compared the prevalence of IR with normal glucose status among people with TB or CHD to identify whether IR is a risk factor for these conditions.

IR can occur in individuals with normal glucose (euglycaemic), who despite having low sensitivity are able to maintain normal glucose levels by increasing the amount of insulin secreted. IR in euglycaemic patients, may still be a risk factor for

infectious and non-infectious diseases and increase the severity of disease presentation. Patients with IR, therefore, may be at increased risk of communicable and non-communicable diseases, such as TB or CHD.

Both T2DM and IR have increased considerably worldwide over recent decades. The prevalence of T2DM in Saudi Arabia is 23.7% among the adult population (47). According to the International Diabetes Federation (IDF) website, the number of cases of T2DM in Saudi Arabia in 2017 was 3,852,000 while the prevalence among adults was 18.5% (48). The map of Saudi Arabia (Figure 1), Saudi population trends (Figure 2) and demographic indicators (Table 1) are shown below (46, 47). TB is one of the top 10 causes of death globally and it considered to be the first frequent cause of death due to infectious diseases, causing 1.6 million deaths and 10 million cases worldwide (2017) (48). The Saudi National TB program reports that TB is more common in foreigners (26 cases/100,000 individuals) than Saudi nationals (11 cases/100,000 individuals), and visitors to Mecca are a common source of infection. Although T2DM is a known risk factor of TB, the prevalence of euglycaemic IR among cases and its role as a risk factor for TB and severity of clinical presentation are poorly established in Saudi Arabia.

CHD is the leading cause of death due to non-communicable diseases worldwide and T2DM doubles the risk of CHD. In 2016, 17.9 million deaths occurring were due to CVDs, accounting for 31% of all worldwide deaths. Of these mortalities, 85% are due to heart attack and stroke (49). Individuals with CHD and T2DM have a higher mortality than individuals without T2DM. Although there has been extensive research of the link between CHD and T2DM, the link between CHD in euglycaemic patients with IR and its role in the severity to the CHD remains ambiguous and has not been studied in Saudi Arabia.

Figure 1. Saudi Arabia.

Jeddah Taif

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Figure 2. Saudi Population trends, (1950 - 2019).

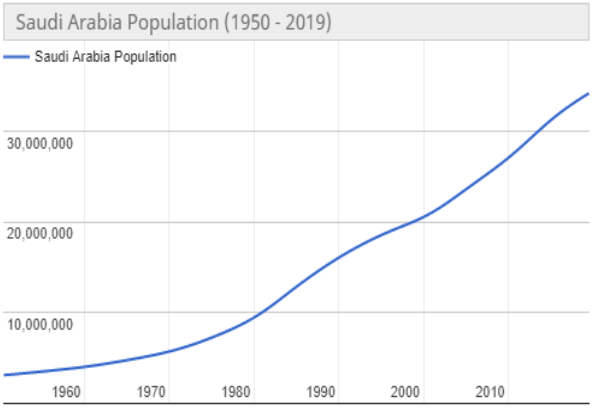


Table 1. Saudi Population

Indicators	Data
Current population (as of Wednesday, January 23, 2019)	34,252,119
Population growth rate	2.31 %
Total area	2,149,690 km^2
Population density	15.9 per km^2
Sex ratio (male to female)	1.23
Median age (years)	29.8
Life expectancy	94.7 %
Young people under 15 years old	10,070,121
Persons between 15 and 64 years old	23,122,867
Persons above 64 years old	1,011,424
Female life expectancy at birth (years)	76.2
Male life expectancy at birth is (years)	72.2
Net migration (2018)	190,556
Percentage of population recognized as a national	68.9
Percentage of population recognized as a non-national	31.1
(Population figures are estimates by Country-meters (countrymeters.info) based on the latest United Nations data)	

1.3. Thesis aims

This study aimed to describe the prevalence of T2DM and IR in Saudi Arabia among patients with (a) TB from Jeddah city and (b) CHD from Taif city (Figure 1) and compare the characteristics of these patients to (c) apparently healthy controls without the disease of interest to investigate the association of IR with TB and CHD. In addition, we investigated whether patients with TB and T2DM or IR had different severity of the clinical presentation to patients with TB and normal glucose metabolism and patients with CHD and T2DM or IR had different quality of life to patients with CHD and normal glucose metabolism.

1.4. Study objectives

1. To describe the prevalence of T2DM and IR among patients with TB in Jeddah city, Saudi Arabia.
2. To describe the prevalence of T2DM and IR among patients with CHD in Taif city, Saudi Arabia.
3. To explore risk factor for TB and risk factors for T2DM and IR among patients with TB.
4. To explore risk factor for CHD and risk factors for T2DM and IR among patients with CHD.
5. To describe whether the severity of the clinical presentation of TB varies among patients with and without IR and/or T2DM.
6. To describe whether the quality of life of patients with CHD varies among patients with and without IR and/or T2DM.

1.5. Literature review

1.5.1. Diabetes Mellitus

Diabetes mellitus is cluster of diseases that cause an impaired insulin use and/or render the body unable to produce insulin, which is the hormone that is required by the liver, muscle and fat to metabolize glucose. The diagnosis of diabetes is based on the detection of elevated concentrations of blood glucose, and this occurs when insulin action or insulin secretion is compromised. The classification of diabetes falls into two main categories, Type 1 diabetes mellitus (T1DM) and T2DM based on the disease's fundamental pathological process. T1DM, which includes idiopathic and immune-mediated subtypes, can be defined as diabetes resulting from the destruction of the beta cell, leading to a total deficiency in insulin in time, needing additional insulin. T1DM represents around 5 - 10% of all cases of DM in the USA and it is commonly referred to as juvenile diabetes as the disease onset commonly occurs in adolescence or childhood. The consensus suggests that there is a strong genetic component in T1DM, however, the condition is not understood very well.

Another form of diabetes only occurs in pregnancy and is known as gestational diabetes. Most woman with gestational diabetes revert to normal glucose levels after delivery, however, its occurrence can be an important risk factor, as gestational diabetes signal a higher risk of developing T2DM in the future.

T2DM accounts for around 90% to 95% of DM cases and usually develops inconspicuously, primarily in adults. Historically, T2DM was considered a disease of industrialised countries, for example, in the USA. It is estimated that there are around 18 million diabetes sufferers, corresponding to 9% of the adult population. T2DM, nowadays, is a disease that is on the rise globally and is a significant and serious health

concern that is posed to health professionals and clinicians, which is largely related to large scale lifestyle changes and obesity. According to World Health Organisation (WHO), T2DM affected 422 million in 2014, with an estimated 1.6 million deaths in 2016 (28). It is anticipated that by 2035 the number of individuals with T2DM will rise to 592 million (28) if there is no action taken to try and resolve the issue.

1.5.2. T2DM in Saudi Arabia

Studies published by the IDF indicate that of the 10 countries with the largest incidence of T2DM across the world, five are in the Gulf. These countries are Saudi Arabia, Bahrain, Oman, and the United Arab Emirates (UAE). A survey in Saudi Arabia regarding chronic metabolic diseases reported that nationally 25% of citizens over the age of 40 had T2DM and that in the northern and eastern regions, 50% of citizens aged 50 and over had T2DM (47). An age specific study of T2DM by Guariguata et. al. to establish the incidence of T2DM in 219 countries. Some of these countries are shown in Table 2. This process allowed the estimation of the age related incidence of T2DM among 20 to 79 year old adults for the years 2013 and 2035 (50). Saudi Arabia had the highest estimated prevalence and one of the highest estimates for the number of individuals affected by T2DM, which was comparable to countries with much larger populations such as Nigeria in Africa.

Alzaid et. al. performed a further study to describe the trends of T2DM in Saudi Arabia (51). This study reported a ten-fold increase in the rate of T2DM and predicted that at the current rate T2DM would affect half of the population in the near future (Table 3) (51).

Table 2. Age-specific prevalence for T2DM in selected countries (50).

Country	Prevalence (anp*) (%)		Prevalence (awp*) (%)		T2DM cases (20 – 79) in 1000s		Mean annual increment (000s)	Proportional change from 2013 to 2035 (%)	Percentage change from 2013 - 2035 (%)
	2013	2035	2013	2035	2013	2035			
Saudi Arabia	20.2	27.1	23.9	24.5	3651	7499	175	53.4	105.4
India	8.6	10.5	9.1	9.7	65,076	109,028	1998	37.0	67.5
UAE	10.0	23.1	19.0	19.4	746	2575	83	49.8	245.3
Yemen	6.1	7.5	8.5	8.7	708	1633	42	88.7	130.6
Sudan	7.7	8.7	9.6	9.8	1402	2904	68	85.1	107.1
Nigeria	5.0	5.5	5.8	6.3	3922	8160	193	89.8	108.1

anp* = adjusted to national population, awp* = adjusted to world population

Table 3. T2DM Prevalence in Saudi Arabia over last three decades (51).

Year	Prevalence Rate	Author
1982	2.5% (age > 15yrs)	Bacchus et al
1987	4.3%	Fatani et al
1992	4.6%	AbuZeid & Al-Kassab
1996	9.5% (age > 14yrs)	El-Hazmi et al
1997	17% (age > 30yrs)	Al-Nuaim
2004	24% (age > 30yrs)	Al-Nozha

The alarming figures reported in the Saudi literature (51-53) have shown that the prevalence of T2DM will continue to grow within the country, and that this increase is partly fuelled by the general Saudi lifestyle (52-54). Recently, the Saudi Ministry of Health has acted and developed a ten-year (2010 until 2020) plan to control the spread of T2DM. The government and all private organisations have been called upon to support the plan by raising awareness of the health risks and the risk factors increasing the occurrence of T2DM within the population.

1.5.3. Epidemiology of T2DM

Saudi Arabia is one of the wealthiest and largest countries within the Middle East and North Africa (MENA) region. Its increasing wealth and major socioeconomic development since it became one of the leading oil producing countries has resulted in increased urbanization and lifestyle changes in the past 50 years. The IDF classifies Saudi Arabia as one of the 10 countries with the largest estimated T2DM prevalence in the world, with 16.2% prevalence in 2011 and an estimated 20.8% of the population having T2DM in 2030 (54, 55). Saudi Arabia also has one of the highest incidence of T2DM risk factors, such as obesity (56).

1.5.4. Glucose Regulation

Plasma glucose is a fundamental energy source and its regulation and homeostasis is vital for survival. Glucose level can fluctuate widely during exercise and during meals. However, an intricate gluco-regulatory system maintains plasma glucose within a narrow range of 70 – 150 mg/dL (57). Plasma glucose levels are primarily regulated by insulin, which acts on tissue to subdue endogenous production of glucose as stimulates the uptake and utilization of glucose. If the secretion or action of insulin is impaired, the production of glucose will rise along with a decrease in its utilization, increasing the levels of plasma glucose. T2DM is characterized by several pathophysiological systems that include surplus hepatic production of glucose, insulin resistance and pancreatic beta cell failure.

Hyperglycaemia, in T2DM can occur with normal and increased levels of insulin in circulation and this is due to the target cell developing resistance to the insulin effects. Tissue resistance becomes difficult to overcome even with elevated insulin levels. A host of complex environmental and genetic factors combine in the development of T2DM; however, the exact cause of the disease is still unclear.

1.5.5. T2DM Pathogenesis

The natural history of T2DM usually starts with regular glucose tolerance, which progresses to IR and compensatory hyperinsulinemia. This state proceeds from an impaired state of glucose tolerance to overt T2DM resulting from many genetic and environmental factors, ultimately resulting in increased blood glucose due to a deficiency in insulin action, secretion or both. Essentially, overt T2DM is the result of a deficiency in insulin production to overcome a fundamental abnormality of elevated resistance to the action of insulin (58).

1.5.6. Normal Glucose Homeostasis

Glucose disposal takes place mainly in insulin-independent tissues; 50% of this is in the brain, 25% in the liver and gastrointestinal tissues (splanchnic area). The outstanding 25% takes place in insulin-dependent tissues; mainly in muscle tissues and to a lesser extent adipose tissues (59). Glucose is produced in the body and 85% is endogenously produced in the liver, 15% by the kidney via gluconeogenesis and glycogenolysis. When glucose is ingested and absorbed, the concentration of glucose in plasma increases and stimulates the release of insulin. Glucose uptake is stimulated by both hyperglycaemia and hyperinsulinemia in the splanchnic tissues and muscles whilst the endogenous production of glucose is suppressed (60).

Fat tissues play a small role in glucose disposal, however, this role is key in maintaining total glucose homeostasis by controlling the release of free fatty acids from stored triglycerides, adipocytokine production and its influence on insulin sensitivity in liver and muscles (59, 61-64). Lipolysis is inhibited with increased concentrations of plasma insulin, and this leads to a decreased concentration of free fatty acids in plasma. This decline intensifies the glucose uptake in the muscles and contributes to the inhibition of the production of hepatic glucose (61-64). Glucagon is also an important factor in the regulation of glucose after meals (65). Glucagon is inhibited after consuming carbohydrates by hyperinsulinemia. This contributes to the inhibition of the storage of hepatic glucose instead of oxidation (60).

1.5.7. Insulin Secretion and Resistance

The early natural T2DM history presents peripheral resistance to glucose uptake by insulin in adipose, liver and skeletal muscle. Although, the concentrations of fasting glucose and tolerance of postprandial glucose are typically normal, this is usually due

to a compensatory increase in insulin being secreted. A rise in postprandial and fasting levels of plasma insulin is an adjustment of the pancreas to overcome tissue resistance and maintain normal glucose concentrations (10, 60). However, the biochemical pathology of IR is not precisely understood, and it appears to be caused by interactions of the environment and genetics. Some phenotypical traits of individuals with IR include obesity (especially of visceral cavity), excessive liver and skeletal muscle fat. Excessive free fatty acids hinder insulin action on the hepatic insulin receptors. Individuals with severe IR and compromised beta cell function and/or mass, will have insufficient production to overcome tissue resistance and the production of hepatic glucose begins to increase irregularly (60, 64, 66). The rise in blood glucose from normal to the abnormal levels maintain glucose-stimulated and fasting plasma levels of insulin persistently high (60). This intermediary state between well-defined T2DM and normoglycemia is referred to as impaired fasting glucose (IFG) and can be defined by a fasting concentration of blood glucose being between 100 – 125 mg/dL or a 140 - 199 mg/dL concentration of blood glucose two hours after taking in 75g of glucose in a solution, known as impaired glucose tolerance (IGT). In the development from IFG/IGT to T2DM the ability of the beta cell to maintain insulin secretion deteriorates progressively (58, 60) due to apoptosis of the beta cells, decrease in beta cell mass or dysfunction of the beta cell. Not all individuals with IR and IGT or IFG develop T2DM and able to maintain an indefinite state of hyperinsulinemias, there are genetic polymorphism relative to the function of the beta cell.

1.5.8. Hypoinsulinaemia and T2DM

T2DM can also manifest without the presence of insulin resistance. T1DM is differentiated from T2DM without IR because of the rapid loss of beta cells, usually

in early life, whereas in T2DM beta cells are compromised gradually and usually at an older age.

1.5.9. Causes of Impaired Insulin Secretion in T2DM

Evidence from twin and genome-wide studies strongly indicate the dysfunction of the beta cell is associated to genetic background (67-73). The secretion and synthesis of insulin decreases due to the glucotoxicity, when beta cell are persistently exposed to high glucose concentrations (58) and lipotoxicity. Although the short term exposure to free fatty acids (FFAs) stimulates insulin secretion, the long term exposure, generally in an obese phenotype of IR, triggers beta cell function impairment, oxidative stress and inflammation (60). Other factors include the deposit of amylin in the beta cell and incretin resistance, which are gut hormones responsible for triggering the secretion of insulin (60).

1.5.10. Insulin Resistance and T2DM

Hyperglycaemia and insulin support glucose disposal by three close-knit mechanisms including suppressing endogenous glucose production, stimulating the uptake of glucose via the splanchnic tissues and stimulating the uptake of glucose via peripheral tissues (mainly muscle). Glucose produced in the liver is vital to meet the brain's requirements (58, 59). Ingesting carbohydrates allows glucose absorption stimulating the secretion of insulin into the portal vein and uptake by the liver to suppress the output of glucose. If the liver does not use insulin appropriately, glucose production continues, causing an excess state of fasting plasma glucose (FPG). In a basal state, the splanchnic tissues are also insensitive to glucose. When glucose is ingested, it enhances the uptake of glucose by the splanchnic tissues (60). The main site of insulin-stimulated glucose disposal is the skeletal muscle tissue, accounting

for around 80% (74). Individuals with T2DM usually have an imbalance between insulin secretion and IR in the muscles and liver resulting in glucose intolerance and fasting hyperglycaemia.

1.5.11. Diagnosis of T2DM

The diagnosis of T2DM generally relies on the measurement of plasma or whole blood glucose in the presence or absence of symptoms of hyperglycaemia. However, T2DM often has an insidious onset and patients with early stages are generally symptom-free and often up to one third of patients are unaware of the diagnosis. The challenge of screening individuals with high-risk of T2DM remains a public health concern. The gold standard for diagnosis is still a random/two-hour post glucose load. The oral glucose tolerance test (OGTT) is used to assess elevated levels of glucose two hours prior to a carbohydrate load (75-gram glucose), measuring the postprandial blood concentration of glucose, with the diagnostic criteria being a ≥ 11.1mmol/L (200 mg/dL) cut-off. However, with the exception of pregnant women, in clinical practice this test is not generally used (75).

Although T2DM is a syndrome with a continuous spectrum, there is a need for a cut-off for diagnostic purposes as patients with higher plasma glucose level experience clinical complications such as diabetic retinopathy (76, 77). For a fasting test, the cut-off point of plasma glucose is ≥ 7.0 mmol/L (126 mg/dL). Unless there are clear symptoms such as explicit hyperglycaemia and acute metabolic decompensation, the test is replicated on another day to confirm the diagnosis (78), as it has a lower reproducibility than the OGTT in some cases (79, 80). Glycated Haemoglobin (HbA1c) levels can also be used for T2DM screening (81), although it can be less sensitive than the OGTT and standardized laboratory techniques still vary (78).

The American Diabetes Association (ADA) state that each test should be confirmed using the same method or an alternative test on a later date (82). If the later date is confirmed, an FPG should be ≥ 126 mg/dL, after ≥ 8-hour or overnight fasting. Patients with glucose > 200 mg/dL, a non-fasting glucose assessment above this level is thought to be indicative of T2DM when classic symptoms are observed. To distinguish normoglycemic individuals from patients with impaired glucose homeostasis or T2DM, the diagnostic cut-points in Table 4 are used.

Table 4. Diagnostic Criteria for T2DM

	FPG	Random Plasma Glucose	OGTT
Diabetes	≥ 126 mg/dL (7.0 mmol/L)	≥ 200 mg/dL (11.1 mmol/L) plus symptoms	≥ 200 mg/dL (11.1 mmol/L)
Impaired Glucose Homeostasis (prediabetes)	100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)	-	140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L)
Normal	< 100 mg/dL (5.6 mmol/L)	-	< 140 mg/dL (7.8 mmol/L)

Source: The American Diabetes Association (83)

1.5.12. HbA1c

Glucose binds irreversibly to haemoglobin generating glycated haemoglobin. The form of glycated haemoglobin in circulation mostly haemoglobin A1 (HbA1) which comprise haemoglobin A1a, A1b and A1c. The main sub-fraction is HbA1c, which directly reflects the average levels of blood glucose over the circulating lifespan of haemoglobin. Red blood cells have a half-life of 120 days and HbA1c mirrors the average level of blood glucose for the previous 8 - 12 weeks (84).

HbA1c test gives a reliable perspective of glycaemic control and does not require a carbohydrate challenge or fasting blood tests. However, HbA1c is considered to

underestimate FPG (85) with inter-individual variation with post-prandial, random and fasting glucose (85, 86). However, intra-individual HbA1c variation is negligible (85, 87, 88). The ADA does not recommend HbA1c for screening but recommends using the test to assess glycaemic control in clinical settings, where it has become the standard to monitor patients. The normal HbA1c range is 4 - 6%. Patients with T2DM should have levels ≤ 8% (84), as individuals above this threshold have a higher risk of nephropathy, neuropathy and retinopathy (75).

1.5.13. Modifiable risk factors for T2DM

1.5.13.1. Diet

For many years nutrition and diet have been known to be significant risk factors for the development of T2DM. However, specific nutritional factors are not clearly outlined in the development of T2DM and there is considerable disparity in the connection between carbohydrate consumption and amount of dietary fat as risk factors (89). Commonly, the *western* dietary patterns characterized by excessive intake of processed/refined/red meat, fried foods, refined grains, saturated fats, deserts and sweets and sugary drinks are considered contributing elements to the development of T2DM (90, 91). Studies among Hispanic Americans undertaken plant-based diets have shown the diet results in a lower risk of T2DM than controls (92). In Saudi Arabia, diabetic patients consume high daily levels of refined sugars, especially in tea, throughout the day (93) and traditional foods are rich in carbohydrates and calories. In addition, the emergence of fast food outlets are becoming increasingly popular, increasing the risk of T2DM (94). The Saudi population also has a large consumption of dates, which are home-grown and rice dishes covered with meat contain high levels of fats and carbohydrates (95, 96) and one quarter do not consume the recommended amount of fruits and vegetables (97).

1.5.13.2. Alcohol

Alcohol consumption in an independent risk factor that increases or decreases the risk of T2DM depending on the amount consumed with a U-shaped relationship. Moderate consumption of alcohol is associated with a reduced prevalence of T2DM (98). Although a number of studies in men and women have described a robust and independent inverse link between alcohol consumption and the risk of developing T2DM (99-102), a study in Australia reported that there was no objective connection between the consumption of alcohol as a T2DM risk factor (103).

1.5.13.3. Coffee

Recently, studies have explored whether coffee is associated with the development of T2DM, with most studies reporting an inverse association in several ethnic groups (104-106). This association has not been reported in SA.

1.5.13.4. Smoking

Smoking is linked to an impaired fasting glucose, glucose intolerance and poor T2DM control (107-114). The US Centers for Disease Control indicate that smoking could lead to T2DM and that smokers are more likely (30 - 40%) to develop T2DM than non-smokers (115). A prospective study over 14 years by Jee *et al.* on 1.2 million 30 - 95 years old Korean males and females found that smoking correlated with an increase of T2DM. Males smoking ≥ 20 cigarettes per day had a greater risk of T2DM than non-smokers (111). Smoking is also widespread in SA, with over 15 billion cigarettes being smoked each year and is the fourth tobacco importer in the world, with 17% of smokers being high school and 14% university students, 23% adults and 25% elderly (116). Studies in Saudi Arabia have reported that T2DM and

smoking habits are statistically associated, with diabetic subjects being heavier smokers than subjects without T2DM (113).

1.5.13.5. Overweight/ Obesity

Obesity is associated with an amplified risk of T2DM (112, 117) and affects IR (112), with 80% - 90% of patients with T2DM being overweight (97, 118). Al-Quwaidhi *et al.* studied obesity trends in adults in Saudi Arabia between 1992 and 2022, reporting that obesity had increased by 14% among adults, from 22% in 1993 to 36% in 2005. If this trend continued, 41% of men and 78% of women will be obese by 2022 (119). Murad *et al.* reported the increased T2DM prevalence within the Saudi Arabia population was associated to the obesity levels and physical inactivity (112).

Studies in adults ≥ 30 years old followed over > 10 years indicate that body mass index (BMI) is a key indicator of T2DM, with a BMI of 27.8 (in any given year) or a BMI > 25 over 10 years being predictors of T2DM (120). In Saudi Arabia, obesity was not originally linked to T2DM (93); however, further studies have reported that individuals with T2DM are more frequently overweight (65%) than those without T2DM (26%) (121) and that both diabetic males (49%) and females (73%) have more overweight/obesity than non-diabetic (38% and 34%, respectively) (122).

1.5.13.6. Physical Activity

Glucose metabolism is influenced by physical activity and glycaemia and insulin responses in athletes are lower after a glucose load. Conversely, inactivity is linked to higher insulin levels and abnormal glucose tolerance (123). In African-Americans, there is a strong association between moderate physical activity and a reduced T2DM risk, with the risk being a third lower (124).

The lack of physical activity is associated with T2DM (52, 107, 109, 125-127) and this is highly prevalence in the Saudi population (97, 107, 126, 128, 129). In a study of 450 Saudis participating in a cross-sectional survey at King Khalid University Hospital, Riyadh, 82% were not physically active and females were less active than males (88% and 72%, respectively) (130). A epidemiological health survey of 117,395 participants 30 – 70 years old found 93% of males and 98% of females did not do significant physical activity (128). The lack of exercise is often associated to the dry and hot climate, especially in Riyadh, which encourages sedentary behaviours (93, 131). In contrast, in the southwest region of Al-Baha, there is a lower occurrence of T2DM in males which may be due to males working in farms and being more physically active (122).

1.5.13.7. Socioeconomic status (SES)

T2DM is often associated with affluence. However, low socioeconomic status is a risk factor for T2DM. Poverty is associated with consumption of cheap and calorie dense foods and obesity. Other factors have also been postulated including lifestyle, lack of access to recreational services in Middle-Income Countries, a higher prevalence of depression and stress (132, 133).

1.5.13.8. Acculturation

Acculturation, which is the process where immigrants integrate and embrace the behavioural and lifestyle traits of the country. It is complex, dynamic and multidimensional. The Honolulu Heart Program (HHP) evaluated acculturation using three factors; the place of birth (Hawaii vs. Japan), dietary habits and the number of years lived in Japan and found an inverse association between the prevalence of T2DM and the traditional lifestyle of Japan (134). A further study, the San Antonio

Heart Study, established a linear decline in T2DM and obesity in Mexican Americans with high acculturation (135) and another study found that Mexicans born in the USA who were less assimilated to the USA lifestyle had a higher risk of developing T2DM in comparison to English speaking, US born Mexicans (136). The prevalence of T2DM in Mexican Americans was lower among the more acculturated their behaviours, attitudes and values (137). Furthermore, in Michigan, a lack of acculturation by Arab Americans was a significant T2DM risk factor (138), but in Texas, high acculturation by Filipino Americans was a T2DM risk factor (139). In Virgin Islands, Afro-Caribbean immigrants highly acculturated had high IR and this was a risk factor for T2DM (140).

1.5.14. Non-Modifiable Risk Factors

1.5.14.1. Genetic factors

Although there is a strong association of genetic defects and family clustering with T2DM (141), the specific defects responsible for most cases are not yet identified and genetic differences can vary with ethnicity. Several genomic studies have aimed to identify genetic constituents associated with T2DM. A literature review of Asian and European populations found around 60 loci linked with T2DM. The large number of genetic variants suggests that numerous genes are involved. However, to date the loci identified only represent around 10% of heritable T2DM (142). First-degree relatives of individuals with T2DM have a higher incidence of the disease (143). Stratification analysis on Pima Americans suggests that inheriting a single co-dominant gene was attributed to prevalence of T2DM (144). An investigation into T2DM and familial aggregation showed that 60% of adults with T2DM have a family history with at least one first-degree relative being diabetic (145).

Studies on Saudi populations indicate that fifty Single Nucleotide Polymorphisms (SNPs) give a greater risk of T2DM. However, of these 50 SNPs only 12 were replicated as risk factors in follow on studies. The inability to replicate the remaining SNPs could be explained by the small sample size of the studies' sample size ranging between 185 and 2401 (146-151). The largest of these studies (149) (2401 individuals) examined 38 genetic variants and found eight associations. The range of effects of variants that gave rise to a larger T2DM risk had a greater variation range and this was susceptible to the sample size and method used. In a further study of 300 Saudi women with T2DM, 70% had a family history of T2DM (152).

1.5.14.2. Age and Gender

T2DM risk increases with age. T2DM incidence is low before the age of 30 years and above this age increases dramatically (153). Lee & Park reported that 38% of the population worldwide over 65 had T2DM (154). This prevalence is consistent with findings in Saudi Arabia where T2DM incidence increases significantly with age (107, 155). Although T2DM prevalence was seen to be more commonly in women in the first half of the 20th century, the current global prevalence is almost equal among men and women (156). Although T2DM prevalence in the US is still higher among females, in other countries such as India the prevalence is greater in males (157). The gender differences across different societies is often a reflection of the frequency of physical activity and obesity and this varies across backgrounds and culture (158). In a national household health survey of the Saudi population from all Saudi Arabia regions (eastern, western, southern, northern and central) reported the crude prevalence of T2DM among 30 – 70-year-old residents between 1995 to 2000, 4004 out of 16,917 subjects, was 23.7% (95% CI 23.1-24.3). The prevalence was higher in males than females (26.2% and 21.5%, respectively, $p < 0.00001$) (159). In Jeddah

city, a study of 1420 residents reported that T2DM and prediabetic prevalence increased with age, with 46% of males > 50 years and 44% of females having T2DM (160). Smaller studies, however, have shown contradictory outcomes with the prevalence in males being reported higher than females (94, 161, 162) and vice versa (163).

1.5.14.3. Inflammation and risk of T2DM

More than twenty years ago, Pickup *et al.* reported a potential interaction between T2DM and inflammation as patients with IR and metabolic syndrome had high levels of the inflammatory marker C-reactive protein (CRP) (164). Since then, prospective studies corroborated the link between the development of T2DM and CRP. This relationship has been shown across several ethnic groups (American, European, Finnish, Japanese, Mexican, and Scottish) (165-169). A high CRP is associated by a 4-fold increase in T2DM risk within the highest CRP quartile (170, 171). Studies on African American and US non-Hispanic whites reported that low-grade chronic inflammation is linked to increased T2DM risk (172). A relatively small number of studies, however, have reported no association between CRP values and T2DM in Pima Indians (173) and Mexican nationals (168).

1.5.14.4. Ethnicity

The incidence and prevalence of T2DM varies across ethnic groups; as for example Native and Mexican-Americans are 2 - 3 times more likely to develop T2DM and Aborigine Australians that dwell in urban areas have a greater prevalence of T2DM than Australian of other backgrounds (157). In the elderly Hispanics had twice the T2DM prevalence than non-Hispanics whites (174).

1.5.15. Tuberculosis

TB is a chronic communicable disease caused by *Mycobacterium tuberculosis* which primarily affects the lungs but can invade any other tissue of the body. One third of the global population has been infected with *M. tuberculosis* (175). TB is one of the top 10 causes of death worldwide and main cause of death due to infection in the world, with the World Health Organisation (WHO) reporting 1.6 million deaths and 10 million new cases in 2017 alone (176).

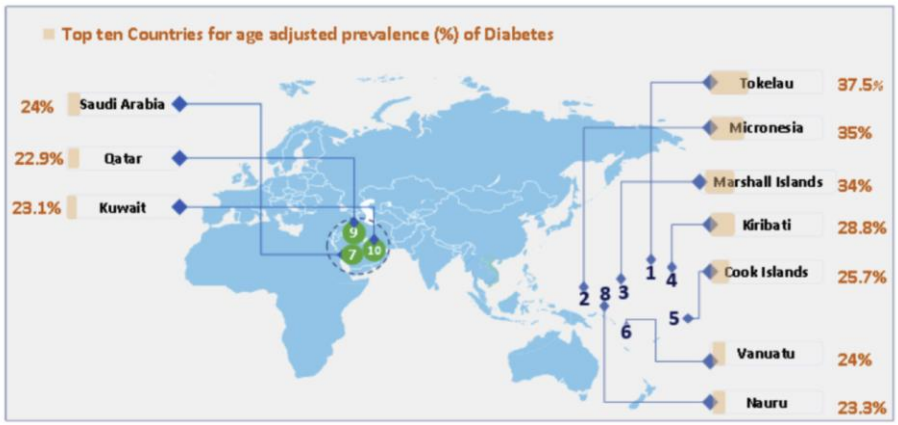
1.5.15.1. The association of TB and T2DM

The association of TB and T2DM has been recognised since ancient times. Skeletal remains dated back to the 8th millennium BC were affected with TB and diseases analogous to what is now known as T2DM (177, 178). Morton's Phthisiologia described that this link was already known in Roman times (179) and that both Susruta and Avicenna had reported DM often complicated 'phthisis' (180).

In the early 20th century the co-morbidity of T2DM and TB was often discussed in the medical literature (181), but became less frequent with the introduction of anti-TB treatment and the development of insulin for T2DM. The 1980s, however, witnessed a resurgence of joint publications with the increased prevalence of T2DM (182). T2DM, a chronic disease as TB, has increased dramatically in recent decades in areas that are still affected by TB. In 2014 it was estimated that 422 million adults suffered from T2DM, with an accelerated increase in LMIC accounting for over 70% of cases (183). Saudi Arabia is also one of the 10 countries with the highest prevalence of T2DM (184) (Figure 3) with a sharp increase since 1989 (185, 186). Estimations suggest that by 2040 there will be 642 million cases, the majority being

from LMIC where TB is also prevalent (187). The WHO has subsequently identified T2DM as a significant, overlooked TB risk factor (188).

Figure 3. Top ten countries with the highest T2DM age-adjusted prevalence according to the IIDF(189)

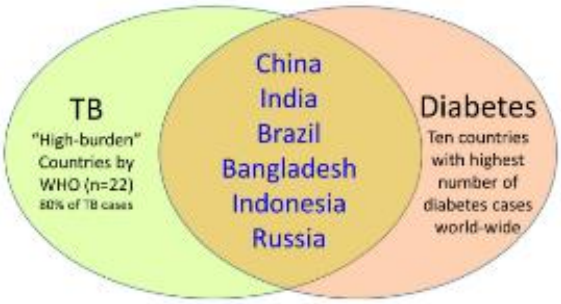


1.5.15.2. Global TB-T2DM burden

It is estimated globally that 1 million of the 9.6 million individuals with TB have T2DM (190), with the number of patients with T2DM and TB comorbidity is similar to the number of cases with TB-Human immunodeficiency virus (HIV) on a global scale (191). Harries et al. The response to TB-T2DM, however, has been sluggish and uncoordinated compared to the responses to TB-HIV in recent decades (192). The association between T2DM and TB has increased especially in places with an increased prevalence of both diseases along with a low socio-economic background. There are six countries identified by WHO as having a 'high burden' for TB among the ten countries that recognised to have the greatest T2DM incidence and these countries account for 80% of the global TB incidence (Figure 4). For example, some countries have a very high T2DM and TB comorbidity (e.g. 54% in South India, 40% in the Pacific Islands and 36% in northeast Mexico) (193-196). The risk is also present among middle/high income countries such as the United Kingdom (UK),

United States (US) and Saudi Arabia (196-199), particularly among population subgroups such as those from an Asian background that are already at a higher risk of both diseases (200, 201).

Figure 4. Six of 22 high-TB burden countries are among the ten countries with the highest T2DM incidence (202).



The risk of TB increases threefold among patients with T2DM (relative risk 3.11; 95% CI 2.27 - 4.26) (30), with the risk ratios varying from 0.99 to 7.83. China with a growing population of T2DM cases has one of the highest TB burden globally, accounting for 17% of the global TB burden, while T2DM affects nearly 100 million individuals (203). In 2011, there were 61.3 million cases of T2DM in India along with 1.98 million cases of TB (204); while in Indonesia there were 450,000 new TB cases yearly and T2DM prevalence ranks 6th in the world (205).

The 2010 prevalence of TB in the Middle East was 6.2 cases per 100,000 in the UAE, while Yemen had 71 cases per 100,000, Kuwait 51 cases per 100,000 and Iran and Saudi Arabia had 23 cases per 100,000 population (203). The increased prevalence of T2DM in these countries, along with an increase number of immigrants from countries with high TB prevalence has made the issue of T2DM and TB comorbidity more significant. A review in 2015 of 59 T2DM and TB studies of ten Middle-eastern countries reported a co-prevalence that ranges from 4.2% in

Iran to 41.1% in Iraq (189). T2DM and TB comorbidity also varies significantly in Africa, ranging from 3.35% to 16.4% (203).

In Saudi Arabia, along with the increased prevalence of T2DM, the morbidity of TB remains a significant issue, as control and prevention remains a challenge due to the large influx of visitors for events such as Hajj (mass gathering) on a short-term basis along with migrant workers (206, 207). Hajj is the largest global event of mass gathering where millions of Muslims travel to perform a religious pilgrimage (207). The nature of the gathering poses immense opportunities for infectious diseases to spread (207), crowding enhances the transmission of TB (206) and pneumonia is the most frequent cause of hospitalisation during the Hajj season (208). TB skin test conversions for pilgrims travelling to the Hajj are more frequent than among individuals travelling to TB endemic areas (209).

In 2014 - 2015 there were > 6.5 million immigrant workers in Saudi Arabia (210). The majority come from high prevalence countries such as Bangladesh, Chad, Indonesia, Pakistan, Sudan, Ethiopia, Sri Lanka, Somali and Nigeria (211, 212). Figures from 1991 illustrated that there was a ratio of 2:1 for TB in non-Saudis versus Saudi citizens (213). Immigrants are more prone to have latent TB infection, ultimately having a greater risk of TB reactivation (214).

T2DM and TB co-morbidity is considerable in the region (Table 5). The prevalence of TB within the region was highest in Yemen and although the prevalence of T2DM was low, 21% of patients had co-prevalence of both conditions. Co-prevalence studies in Turkey, Iran and Saudi Arabia reported co-prevalence ranging between < 10% and > 30% (189).

Table 5. T2DM and TB epidemiology and country specific citations

Country	TB prevalence* (range)	T2DM prevalence in the 20 – 79 years population	T2DM % among TB patients	Year	Mean age ± SD of participants
Yemen	60 (24 – 112)	8.45%	21%	2007 – 2010	< 45 (89%)
Qatar	37 (11 – 79)	22.87%	5 – 25.5%	1996 – 2009	≥ 45 (11%)
Iran	32 (16 – 53)	9.9%	4.2 – 30%	1991 – 2008	34 ± 4
Iraq	29 (8.6 – 61)	9.5%	41.1%	2012 – 2013	44 ± 5
Egypt	27 (14 – 44)	16.8%	16.4 – 29.3%	2001 – 2011	52 ± 10
Kuwait	25 (7.3 – 52)	23.1%	29.8 – 35%	1996 – 2005	47 ± 6
Turkey	23 (11 – 39)	14.85%	7.9 – 34%	1997 – 2010	37 ± 6
Lebanon	16 (4.8 – 34)	15.0%	No studies		
Bahrain	15 (4.4 – 31)	21.8%	No studies		
Saudi Arabia	14 (4.3 – 30)	23.87%	14 – 26%	1989 – 2009	47 ± 13
Syria	14 (4.2 – 30)	8.91%	No studies		
Oman	13 (4.7 – 25)	14.24%	25%	2001 – 2006	20 - > 60
Israel	7.1 (2.9 – 13)	9.1%	5 – 12.9%	2000 – 2005	50 ± 10
Cyprus	6.6 (2.2 – 13)	9.3%	No studies		
Jordan	5 (1.5 – 10)	11.4%	No studies		
UAE	1.3 (0.38 – 2.7)	18.98%	No studies		

* per 100 000 population

The association of T2DM and TB has also been reported from industrialized countries. In Barcelona between 4% and 7.2% of patients have both conditions (215), while in the UK, a case-control study reported a TB-adjusted OR (odds ratio) of patients with a T2DM history of 3.8 ($p < 0.05$) (216). Numerous studies from the US, Australia and Denmark, however, have found that T2DM only marginally increases the risk of TB (203), except in Japan where 13.1% of patients had both conditions. The latter being attributed to the proportion of elderly population of Japan (23%) being higher than in the UK (16%) and the US (12%) (217).

1.5.15.3. Profile of patients with TB and T2DM

TB patients newly diagnosed with T2DM have a different profile to those previously diagnosed, as they are more likely to have lower HbA1c, to be younger and male (218). Patients with TB and T2DM also have a different profile to patients with TB without T2DM, being more likely to be female, obese and older and do not have behavioural risk factors associated with TB such as incarceration, consumption of drugs or alcohol, more likely to be unemployed and have low education (218, 219).

1.5.15.4. Directionality of the TB and T2DM association

Most studies are observational, and it is difficult to infer the directionality of association from cross sectional studies. Cohort studies suggests that T2DM increases the risk of TB (220). Patients with TB, however, may also have an increased risk of developing T2DM, although this uncommonly considered in literature (221). A number of studies have described that early phases of TB, have impaired glucose tolerance and hyperglycaemia (222). Although this is likely due to the inflammatory process reducing insulin sensitivity, it may also signal a higher risk of developing T2DM as 20% to 50% of individuals with IGT develop overt T2DM 3 to 5 years later (222, 223). Deducing the relevance of hyperglycaemia in individuals with TB is difficult as it might reverse after TB treatment (222, 223). Hyperglycaemia may be a side effect of Isoniazid and Rifampicin treatment (224) or stress hyperglycaemia (225) and not a sign of metabolic dysfunction.

1.5.15.5. T2DM among patients with TB patients in Asian countries

Global estimates indicate that T2DM is present in 15% of cases of TB and China and India make up 40% of these cases (190). A review on T2DM and TB in 11 countries through reviewing 33 studies shows that 27 studies reported the prevalence

of T2DM in individuals with TB. The prevalence of T2DM in individuals with TB varied between 6.3% and 54.1% (Table 6) and the highest association was in India, where one study reported 54.1% of those with TB also had T2DM. (203).

Table 6. T2DM and TB epidemiology by country (203).

Country	Estimated TB prevalence per 100,000 population (range)	Estimated T2DM prevalence as a percentage of the population aged 20 – 79 years	T2DM prevalence among TB patients
Bangladesh	404 (211 – 659)	8.3	37
China	89 (78 – 102)	9.8	5.05, 6.3, 12.4, 16.2, 19.9, 27.9
India	195 (131 – 271)	9.3	14.7, 14, 25, 25.3, 29, 33, 35.5, 54.1
Indonesia	647 (513 – 797)	6.5	13.2, 14.8
Democratic People's Republic of Korea	552 (150 – 1210)	4.4	20
Malaysia	135 (63 – 232)	17.9	17.7, 28.5, 30
Nepal	215 (102 – 369)	3.7	9.1
Pakistan	341 (285 – 402)	8.1	25.9
Sri Lanka	99 (51 – 164)	8.0	9
Thailand	236 (161 – 326)	7.1	16.3, 23
Vietnam	198 (83 – 362)	6.0	8.8

1.5.15.6. TB among patients with T2DM in Asian countries

The prevalence of TB in individuals with T2DM is fourfold greater than among individuals without T2DM (31, 226). A review of studies from China, Bangladesh, Korea, Nepal and Pakistan of the prevalence of TB in individuals with T2DM (203)

reported the incidence of TB among 17,344 patients with T2DM in Dhaka, Bangladesh was twice as high as the incidence in the general population (227). In China, TB case notification in patients with T2DM were several times greater than the general population (228) and in Yunnan province this risk was three times higher than in the general population (229). In Korea, a three-year follow up study shows that TB case notifications amounted to 180 cases per 100,000 individuals (230) and in Nepal 8% of patients with T2DM had pulmonary TB (231); while in Pakistan TB prevalence in T2DM patients was 10 times greater than in patients without T2DM (11.9% and 1.7% respectively, $p < 0.05$) (232).

1.5.15.7. IR as a risk factor for TB.

Some populations have a high prevalence of IR and this may increase their susceptibility to TB. TB in turn affects insulin production and sensitivity (26). Insulin regulates macrophage phagocytosis of *Mycobacterium tuberculosis*, although the potential role of IR as a risk factor for TB has not been described (233). Macrophages of patients with IR have a reduced ability to attack the bacilli, which may increase the risk of disease progression from latent to active TB (19, 234). Furthermore, the underlying mechanisms of IR varies across population and in Asia IR, hypertriglyceridaemia and hyperinsulinaemia are observed in individuals without high levels of intraperitoneal fat and obesity (235).

1.5.15.8. Poor glycaemic control

Poor glycaemic control is a risk factor for TB (234). Studies assessing HbA1c levels have reported that increased concentrations are associated with disease progression from infection to overt TB (234). In Hong Kong, elderly patients with T2DM (n = 4,690) and HbA1c > 7% were three times likely to have TB than individuals with

HbA1c readings < 7% (HR 3.11; 95% CI 1.63 – 5.92, p < 0.01) (236). In Taiwan, a large study of 123,546 individuals reported that participants with poor glycaemic control had considerably higher risk of TB than individuals without T2DM (237).

In Saudi Arabia, studies have reported that nearly 60% of individuals with T2DM have poor glucose control (HbA1c > 8%) and less than 20% achieve optimum control (HbA1c ≤ 7) (238). Furthermore, amongst patients with T2DM and TB, 73% had poor glycaemic control (239).

1.5.16. Coronary Heart Disease

Coronary artery disease (CAD), CHD and ischaemic heart disease (IHD) are often used interchangeably, although CAD refers to coronary artery atherosclerosis and CHD often involves other causes of muscles receiving insufficient blood flow, such as pulmonary hypertension or valvular heart disease and IHD is used to indicate the appearance of clinical symptoms. In this study the term CHD will be used to represent coronary heart atherosclerosis and IHD (240).

Atherosclerosis affects the walls of the coronary artery vessels and the semi-permeable barrier that is created by the lining of endothelial cells to allow transfers between the artery wall and the blood stream. The process of atherosclerosis can be triggered by subtle chemical or physical injuries (the "Response to Injury Theory") (241). Injuries may include stress or physical injury due to hypertension, direct trauma, oxidative stress, turbulent blood flow, hyperlipidaemia, inflammation, homocysteinaemia and chronic high glucose concentrations. Injured endothelial cells trigger a maintained inflammatory response secreting cytokines and attracting T-lymphocytes and monocytes and cell surface adhesion molecules cause T-lymphocytes and monocytes to attach to the endothelium. Changing their shape and

loosening the tight formations between cells, increasing its permeability to leucocytes, lipids and fluids. Lipoprotein particles, LDL, penetrate the arterial wall and becomes oxidized with exposure to macrophages, nitric oxide and enzymes (e.g. lipoxygenase). Once monocytes reach the intima layer, they differentiate into macrophages with intake of oxidised LDL and become laden with lipid, creating 'foam cells'. Foam cells eventually go through apoptosis, with lipid accumulating as fatty streaks within the intima. The fatty streaks may regress, remain stable, or evolve to become atherosclerotic plaques (242). Atherosclerotic plaques grow slowly and expand with smooth muscle cell proliferation and migration. The fibrin cap matures on the lesion, with the plaque hardening and building up leading to a narrowing passage for blood circulation leading to ischemia.

Conversely, some plaques may develop quickly with a thinner fibrin cap more susceptible to rupture. The plaques rupture can lead to blood clots and acute thrombosis, initiating the clotting cascade and platelet activation triggering an acute coronary syndrome with complete or partial blockage (243, 244).

1.5.16.1. Ischaemic heart disease (IHD)

IHD was the main global cause of death in 2010 (245) and the main cause of disability and death within the CVDs. IHD is not only prevalent among senior citizens of wealthier countries but also among adults of working age and is increasingly a health problem of LMICs (246, 247).

1.5.16.2. Myocardial ischaemia and infarction

MI is often the initial expression of CHD or appear recurrently in individuals with established disease. MI incidence can be used as a proxy to identify CHD prevalence (248). WHO estimated that CVDs caused 17.5 million deaths in 2005 worldwide,

accounting for 30% of fatalities. Of these, 5.7 million were due to strokes and 7.6 million to CHD (249). In 2015, this number had increased to 17.7 million, or 31% of all fatalities. Of these deaths, stroke and CHD accounted for 6.7 and 7.4 million, respectively (250).

CVD risk factors include T2DM, hypertension, excess body mass, cigarette smoking, hypercholesterolaemia and sedentary lifestyle (251). These factors are influenced by economic, cultural, social factors and behaviour (249).

The burden of CVDs, particularly stroke and IHD, varies across the world. While industrialised countries have reported declining rates, the risk on LMICs has increased and CVD may be the main cause of death by 2020 (249). These variances is attributable to factors such as smoking control, healthcare and diet (249, 252).

1.5.16.3. CVD within the Middle East and North Africa Region

Socioeconomic growth within the MENA region in the last decades has resulted in major lifestyle and diet changes and sedentary living with an increase in risk factors associated with CVD (253). The regional number of deaths due to hypertension and IHD were 115 and 294 per 100,000 individuals, respectively and the number of disability-adjusted life years (DALYs) were 1389 and 3702 per 100,000 population, respectively (254). WHO estimated in 2008 that CVD was responsible for 49% of fatalities due to non-communicable diseases in Oman and 46% in Kuwait. These figures were also high for Bahrain (32%), Saudi Arabia (42%), Qatar (23%) and the UAE (38%) (255).

1.5.16.4. Incidence and prevalence Saudi Arabia.

In Saudi Arabia IHD and stroke are the second and fourth causes of death, respectively (254, 256) and CVD are estimated to account for 42% of total mortality.

However, prevalence data is limited. Some studies have reported the prevalence of hypertension and CHD are *circa* 25.5% and 5.5% respectively, and figures vary by setting, age and gender (257).

The large CHD prevalence is attributed to the prevalence of risk factors including a typical Saudi sedentary lifestyle, obesity, smoking, hypertension and dyslipidaemia. This reflects the higher socioeconomic status of the population in previous decades. Hospital-based studies often report that T2DM, hypertension and smoking are highly prevalent risk factors among patients with MI (258).

Studies in the Eastern Province of the country, reported that CHD was associated with 26% of all deaths (27% males and 23.5% females) (258, 259) and 21% of the population had hypertension, which was more common in divorced women, individuals that were older and had low education (260). A further national study on obesity highlighted that 28.7% of the population were obese in 2013 (117). A large survey on T2DM in 2009 reported the prevalence was 30% in Saudi Arabia, which was more common in females above 50 years old (258).

In Jeddah, one of the cities for this study, 50% of school and university staff were overweight; 18.8% smokers and 19.9% hypertensive, with 10.1% having hyperlipidaemia. The prevalence of these factors increased with age, particularly above 40 years (258, 261).

1.5.16.5. Risk Factors for CHD

Over 200 CHD risk factors have been recognised with well-established associations with impaired glucose tolerance, high blood-cholesterol, hypertension and smoking (262). Conventional risk factors usually aggregate in people with CHD (263). The American Heart Association (AHA) indicates the most significant non-modifiable

risk factors are heredity, male gender, race and age. While modifiable risk factors include T2DM, obesity, physical inactivity, high blood cholesterol and smoking (264).

Ethnic minorities have a higher risk of CHD (e.g. Mexican Americans, African Americans, Native Americans) (262). Smoking is also one of the most strong risk factors for progression or development of CHD (265) and deaths attributed to cigarette smoking are related to the duration and dose (266). Total blood cholesterol plays an important role in CHD. The USA Framingham study demonstrated that total cholesterol correlated significantly with an increased risk of CHD independently of other risk factors (262) although there were significant variations across ethnic groups.

One lipoprotein class LDL Cholesterol also contributes to CHD, with LDL Cholesterol oxidation being a major feature, with the risk increasing by 20% when LDL Cholesterol is increased by 10% (267). Contrastingly, there is a strong inverse relationship between low CHD risk and high HDL Cholesterol levels with the risk decrease by 2 - 3% when the HDL Cholesterol serum levels increase by 1% (262, 268).

Many prospective and epidemiological studies have reported the independent, graded and positive association between hypertension and CHD risk with blood pressure over 130/85 mmHg increasing CHD mortality significantly in young men (269).

Both systolic (SBP) and diastolic blood pressure (DBP) predict a CHD event or risk, with a continuous risk increase with higher SBP levels and a lower mortality with lower DBP (269). SBP is an independent CHD mortality risk factor in the elderly (270). T2DM coupled with hypertension (above 140/90 mmHg) increases even

further the risk of CHD (271), while the United Kingdom Prospective Diabetes Study described the risk of MI decreased by 11% for every 10 mmHg decline in SBP (272).

Physical inactivity or the sedentary lifestyles are independent risk factors for CHD. Physical activity prevents overweight/obesity, reduces weight, lowers LDL Cholesterol and raises HDL Cholesterol levels, lowers blood pressure , and increases insulin sensitivity. In addition, to these indirect associations, sedentary lifestyles are independent risk factors for CHD (262).

Physical activity, however, is heterogeneous in duration, energy expenditure, intensity and the type of exercise. There is a strong inverse relationship between CHD and time spent walking (273), with the risk being halved in men that walked more than 1.5 miles each day (274). Sesso *et al*., reported the risk is reduced significantly with vigorous activities in comparison with light/moderate activity (275), while Wannamethee *et al*. reported the lowest age-adjusted relative risk for CHD is found in moderately active males, compared to moderately vigorous, vigorous, light and occasionally active males (276).

Obesity is one of the main etiological CHD risk factors through the effects it has on decreased glucose tolerance, dyslipidaemia and hypertension (262), with a gradient increase in BMI and CHD incidence (277). Central obesity is a better predictor than BMI (262). This association has been reported by many large studies such as the Honolulu Heart Program in Japanese-Americans (N = 8000) (278) and in Pima Indians (279). Obesity is also closely associated with diet. The Mediterranean and western diet rich in salt, cholesterol and saturated fats affects hypertension and lipid profiles (280), while reviews indicated that diet high in fibre and low in saturated fats has positive effects on blood lipid profiles (281).

1.5.16.6. CHD Risk Factors in T2DM

There is a well-established relationship between CHD and T2DM (282). Individuals with T2DM or insulin resistance in combination with other risk factors are more liable to experience strokes or heart disease (283). T2DM is considered equivalent to CHD as they share risk factors, and it has been hypothesised that CHD and T2DM have common environmental and genetic backgrounds. The clinical management of individuals with T2DM includes management of the same factors for CHD, such as adverse nutrition, physical inactivity, obesity/overweight, hypertension, cigarette smoking, LDL Cholesterol and atherogenic dyslipidaemia, plus risk markers, such as CRP and Homocysteine (Hcy) which may underscore underlying inflammatory processes (284). IR, elevated blood pressure, prothrombotic state, atherogenic dyslipidaemia and abdominal obesity tend to co-exist at a higher rate in patients with both conditions and they have a synergistic effect on CHD. Moreover, controlling these risk factors can delay or even avoid CHD (284).

In T2DM, atherosclerotic CHD and other CVDs are the main cause of low quality of life, morbidity and mortality. In patients with T2DM the incidence risk of CHD and fatal CHD can be two to four times higher and long-term prognosis is poorer (285). Patients with T2DM without MI have a similarly high risk of MI than those that are non-diabetic but have had a previous MI (286). The increased risk of CHD in patients with T2DM is likely due to a combination of hyperglycaemia with other metabolic risk factors (285, 287).

Patients with T2DM, have more severe and diffuse coronary artery atherosclerosis than patients without T2DM and tend to have distinct CHD risk factors. When IR and CHD risk factors are found together, the WHO defines this constellation as the

'metabolic syndrome' (285, 287). The cardiovascular risk profile of T2DM with IR is proatherogenic, which incorporates specific prothrombotic and proinflammatory abnormalities of vascular functions and endothelial cells, microalbuminuria, atherogenic dyslipidaemia, hypertension, abdominal obesity and impaired glucose regulation (287). The occurrence of metabolic syndrome in individuals with normal glucose tolerance can give rise to a high risk of developing T2DM (288). While every element of metabolic syndrome increases the risk of CHD, these elements combined lead to a synergistic effect and a threefold rise in the risk of stroke and CHD and mortality (289).

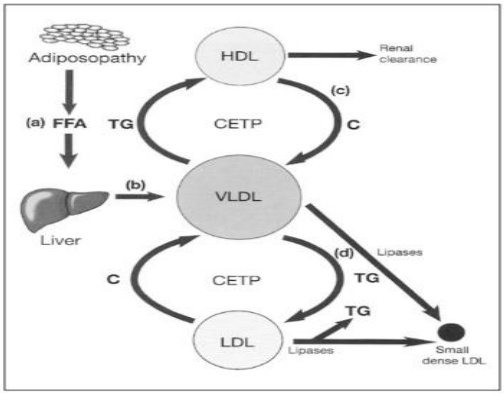
Metabolic syndrome is highly prevalent in Western societies. The USA 2002 census reported that 47 million individuals were affected with a prevalence of 24% and several studies have reported its frequency increases with age to 44% in the 60 - 69 year olds (290). Around 85% of patients with T2DM were categorised to have metabolic syndrome, compared to 12% of individuals with normal fasting glucose (291).

1.5.16.7. Abnormal lipid profiles

In patients with and without T2DM, dyslipidaemia is a risk factor for CHD (287, 292). Dyslipidaemia linked to T2DM is more complicated than an increase of LDL Cholesterol. Atherogenicity is linked to T2DM dyslipidaemia could be related to apolipoprotein B levels, low HDL Cholesterol plasma concentrations and irregularities in lipoprotein subclass distribution and particle sizes (293). Lipoprotein subclasses are numerous and of these subclasses the unbalanced number of dense, small LDL and HDL particles are believed to form a strong atherogenic profile, as they are very susceptible to oxidation (294). Numerous mechanisms are thought to

account for atherogenic lipid irregularities of T2DM. Adiposopathy or dysfunctional adipose tissue is believed to appear due to a combination of genetic predisposition and fat accumulation. In comparison to normal adipose tissue, dysfunctional tissue has lower sensitivity to insulin and hormone-sensitive lipase action. Intracellular triglycerides are broken down more frequently and increases the amount of circulating FFAs (Figure 5a). This process causes fat infiltration of muscles, liver and pancreatic β-cells, exacerbating the muscles and liver IR. With prolonged FFA exposure the pancreatic β-cell function may become compromised contributing towards an increased T2DM risk (285). An increase in hepatic FFAs leads to hepatic synthesis of triglycerides, which in turn increase very low-density lipoprotein concentrations (Figure 5b), resulting in hypertriglyceridemia as commonly found in patients with IR. Subsequently, very low-density lipoprotein (VLDL) is remodelled to form small, dense LDL particles (Figure 5d); cholesteryl ester transfer protein takes triglycerides found in VLDL and exchanges them with the cholesterol found in LDL and HDL producing atherogenic VLDL particles. The kidneys more readily clear modified HDL particles and this results in a decrease in the level of HDL Cholesterol (Figure 5c). Lipases metabolise the LDL particles that are triglyceride-rich and this results in small, dense LDL that exhibits elevated atherogenicity (285).

Figure 5. Hypertriglyceridemia and an atherogenic lipid profile.



1.5.16.8. Hypertension

The combination of T2DM and hypertension is common with 30% of patients with T2DM being hypertensive in Europe. This figure is double the prevalence in patients without T2DM (295). Individuals with T2DM are predisposed to hypertension due to sodium retention, which increases vascular tone and can lead to nephropathy. Hypertension in T2DM can be caused somewhat by hyperinsulinemia and IR. Moreover, vascular stiffness is affected by age and blood vessels of patients with T2DM tend to age at an enhanced speed (296).

1.5.16.9. Inflammation and T2DM

Endothelial dysfunction and inflammation are closely associated with T2DM and low-grade inflammation reflects the innate immune system activation and the development of atherosclerosis and dyslipidaemia (297). Patients with IR and T2DM have a continuous acute phase response stimulated by cytokines and inflammatory markers, such as Interleukin (IL)-1, IL-6, CRP, plasminogen activator inhibitor (PAI-1), tumour necrosis factor-alpha (TNF-α), leptin, fibrinogen and angiotensinogen (298). Vasodilation is endothelium-dependent, and the vascular environment and endothelial cells are impaired by the chronic inflammation, increasing the risk of cardiovascular events as endothelial cells induce the expression of the adhesion molecules on the cell surface. CRP may cause further tissue macrophages to stimulate the production of IL-1 and TNF-α, amplifying the inflammatory response (285). Therefore, CRP is associated with the development of T2DM and CHD mortality (297, 299, 300). CRP also stimulates PAI-1 and this fibrinolysis inhibitor promotes the prothrombotic state induced in obesity (298). T2DM is associated with cyclooxygenase-2 (COX-2), CD40 and CD40 ligand (285).

1.5.16.10. Hyperglycaemia and oxidative stress

Hyperglycaemia can stimulate protein oxidation, glycation, lipo-oxidation and glycoxidation (301, 302). Elevated glucose levels affect collagen and other connective tissues. Patients with T2DM experience a gradual collagen glycation which is age-dependent and can be impaired two to threefold faster in patients with T2DM (303). Moreover, hyperglycaemia causes the development of advanced glycation end products, such as pentosidine and carboxymethyllysine agents produced by reducing sugars modifying free proteins via non-enzymatic covalent modification. Cell surface receptor of AGE (RAGE) activates AGEs and induce free radical oxidation with damaging effect on macrovascular and microvascular endothelial cells (304).

2. Chapter 2

Methods

2.1. Study plan

This study was based in Taif and Jeddah city in Saudi Arabia. The study enrolled patients in two centres, patients attending the King Faisal Hospital in the city of Taif and patients attending the Tuberculosis and Chest Diseases Centre in Jeddah city.

All field work was conducted by me, Fareed Almaleki, with support of my PhD supervisors who maintained close communication via email and Skype. Any changes that occurred to the protocol were made in consultation with my supervisors Professors Luis Cuevas and Geoff Gill.

2.2. Description of study location

2.2.1. Taif City.

Taif is in the Mecca Province in the Western Region of the Saudi Arabia. The city has an elevation of ~1,800 m above sea level, with a total area of eight hundred hectares and an estimated 2014 population of 1,109,846 inhabitants.

2.2.2. Jeddah City

Jeddah is the largest city in the Mecca Province and the largest seaport on the Red Sea and is also located in the western region of the Saudi Arabia, with total population of 3.4 million. Jeddah is the principal gateway to Mecca and Medina and, therefore, receives large number of visitors each year.

2.2.3. King Faisal Hospital:

King Faisal Hospital is one of the main referral hospitals in the Western region with a bed capacity of 500 for general patients and 300 for Obstetrics and Gynaecology.

The hospital has many specialties in various disciplines and departments and is accredited by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI). King Faisal Hospital was selected because most of the patients with CHD in the region are referred to this hospital. The hospital belongs to the Saudi Arabia Ministry of Health (MOH), which will facilitates conducting my studies under an agreement between Liverpool School of Tropical Medicine (LSTM) and the MOH of Saudi Arabia. All blood samples obtained for the study participants were processed in the hospital laboratory.

2.2.4. Tuberculosis and Chest Diseases Centre:

The Tuberculosis and Chest Diseases Centre is in Jeddah and consists of five clinics for diagnosis, treatment and follow-up of patients. The clinic has five doctors providing clinical services and is headed by a Medical Director. The centre also has X-Rays and pharmacy facilities, a nursing department, an infection control and quality units and a health education department. The centre provides epidemiological surveillance for Jeddah city, examines and diagnoses suspected cases of TB and initiates treatment, checking and examining contacts of TB patients, doing annual statistical reports for TB and home visits for patients who do not complete treatment. In addition, the centre provides therapeutic services for patients with newly diagnosed TB and follow patients undergoing TB treatment until they are fully cured, and outreach services and education for the patients and their families. The centre offers a nutrition aid program for patients with TB. The centre selected for the study because all TB patients in the city are referred to this centre with an estimated 350 new TB patients per year. The centre also belongs to the Saudi Arabia-MOH, which facilitated engagement with staff through the agreement between the LSTM and the Saudi Arabia-MOH.

All blood samples obtained for the study participants at the Tuberculosis and Chest Diseases Centre were sent to King Fahad Hospital laboratory.

2.3. Study design:

These were two cross-sectional surveys to describe the characteristics of the patients with TB and CHD, followed by case control studies to identify risk factors. The study took place from November 2016 to June 2017 and included 175 confirmed pulmonary TB patients' ≥ 18 years old registered at TB and Chest Diseases Centre, and 325 patients with stable CHD ≥ 18 years old registered at the cardiology department at the King Faisal Hospital in Taif city.

2.4. Methods for each objective

2.4.1. Objective 1: To describe the prevalence of T2DM and IR among patients with TB.

2.4.1.1. Study design:

This was a cross-sectional descriptive survey of patients' ≥ 18 years old registered at Tuberculosis and Chest Diseases Centre. Patients eligible to participate were those with bacteriologically-confirmed pulmonary TB who had received TB treatment for at least two months since diagnosis. Only cases considered to be new TB cases at the time of their diagnosis (this is, who have not received treatment before) were eligible. A bacteriologically confirmed case was defined as any adult whose sputum had acid-fast bacilli in smear microscopy or a positive TB culture. GeneXpert tests were not available in the centre at the time of the study. In addition, only patients who had responded well to the intensive phase of treatment (first 2 months) were selected, to avoid patients with drug-resistance TB that may have had a continued inflammation process. Patients were selected while taking the continuation phase of

treatment (i.e. after receiving at least two months of treatment) because the inflammation associated with TB in the first two months would result in inflammation-related IR. Participants were identified from the Tuberculosis and Chest Diseases Centre treatment registers under the following inclusion and exclusion criteria:

2.4.1.2.Inclusion criteria

1- Patients with bacteriologically confirmed pulmonary TB.
2- Patients aged ≥ 18 and residing in Jeddah city.
3- Registered at TB and chest diseases centre in Jeddah city and still attending the clinic for treatment.
4- Patients had received at least 2 months of anti-TB treatment and were responding clinically to treatment.
5- Patients accepted to participate when approached at the Directly Observed Treatment, Short Course (DOTS) clinic.

2.4.1.3.Exclusion criteria

1- Patients with missing contact information and those deported from the country.
2- Clinical presentation as predominantly Extra-pulmonary TB.
3- Coexistence of a malignancy.
4- Known to be pregnant.
5- Known HIV infection

Once the participants were identified, they were informed of the study and received counselling and guidance and asked if they agreed to participate and signed the consent form. A team of trained interviewers performed the interviews at a mutually convenient location in the healthcare facilities. Field assistants used a structured questionnaire in Arabic and/or English. Data collected consisted of general

demographic details such as gender, age, socio-economic status, ethnic group and medical history and other potential risk factors for T2DM and insulin resistance. Patients were examined to measure height and weight, waist and hip circumference and waist-to-hip ratio (WHR). The blood pressure was recorded twice from the right arm in a seated position using a Professional Digital Blood Pressure Monitor after 15 to 30 minutes of rest in 5-minutes intervals.

2.4.1.4.Sample collection and laboratory tests

At a mutually convenient date, patients were asked to provide blood samples after fasting for 12 hours. A phlebotomist collected 10 ml of venous blood in three different blood tubes as follows: 2 ml in an EDTA tube for HbA1c level, 4 ml in gold-top (serum separator) tube for chemistry laboratory and 4 ml gold-top (serum separator) tube for hormones laboratory. The samples were collected at the phlebotomy area of the Tuberculosis and Chest Diseases Centre in Jeddah city and then sent to the King Fahad Hospital laboratory in Jeddah for processing. The blood samples were used to do the following tests: fasting plasma glucose (FPG), fasting plasma insulin, HbA1c and lipid profile including Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. If the patient had not fasted, the instructions were to ask them to return to the clinic the next day after fasting for 12 hours from 8 PM until 8 AM.

The gold standard method for the quantification of IR is the euglycaemic clamp technique, however, for the purposes of our study we used the homeostasis model assessment-2-Insulin resistance (HOMA2-IR) calculation to quantify IR, as this method is more practical as it is less sophisticated. Several tests are combined to form the homeostasis model assessment (HOMA) model and it looks at the balance

physiologically between the concentration of glucose in the blood and the secretion of insulin, reflected by insulin production and the uptake of glucose by tissues, where the HOMA2-IR cut off point is < 2.

Matthews et al. (1995) initially published the HOMA calculation (fasting glucose x fasting insulin / 22.5) and in 1998 it was later calibrated as HOMA2-IR. The advantages that this new model offered were that the beta-cell percentage and sensitivity percentage could be calculated using fasting readings of insulin, glycaemia as well as C-peptide. Free software was launched by Oxford University in 2014, known as the HOMA2 calculator (http://www.dtu.ox.ac.uk/homacalculator/) and this allows for a fast and precise HOMA2-IR calculation (305). The automated immunoassay test analyser (ADVIA centaur xp) was used to determine the insulin level. All patients with normal results were informed of their results via email or phone calls. Patients with abnormal results were asked to attend the clinic to discuss the results with the clinic doctors.

2.4.2. Objective 2: To describe the prevalence of T2DM and IR among patients with CHD.

2.4.2.1.Study design:

This was a cross-sectional descriptive survey of patient's ≥ 18 years old registered at the cardiology department the King Faisal Hospital in Taif city. Patients were eligible for selection into the study if they had documented CHD using ECG, exercise test followed by angiography and were medically stable. A stable CHD was defined as an adult with an established pattern of angina pectoris who was not having acute pain, a history of confirmed myocardial infarction (MI), or the presence of plaques documented by catheterization. Only patients with stable CHD were

enrolled. Participants were eligible under the following inclusion and exclusion criteria:

2.4.2.2.Inclusion Criteria

1- Patient with stable CHD attending the outpatient clinic.
2- Patients aged ≥ 18 and residing in Taif city.
3- Registered at Taif King Faisal Hospital, cardiology department, and still attending the clinic for treatment.
4- Patients accepted participation.

2.4.2.3.Exclusion Criteria

1- Patients with missing contact information and those deported from the country.
2- Known renal disease.
3- Known hepatic disease.
4- Smoking more than 20 cigarettes per day.
5- Known to be pregnant.

All clinical diagnosis and clinical history were obtained from the clinical records of the patients. With regards to the definition of patients with established CHD, we identified all patients with a diagnosis of CHD in the hospital records and selected those who had a confirmed CHD diagnosis in their medical records. The diagnosis was made by staff of the cardiology department of King Faisal Hospital, which used the Joint Committee of the European Society of Cardiology/American College of Cardiology definitions to diagnose MI and CHD (306). The diagnosis of renal and hepatic disease were also taken as recorded in the clinical record of the patients. These diagnoses had been recorded by the consultants managing the case, but were not confirmed by further tests in this study.

Once the participants were identified, they were informed of the study and received counselling and guidance, agreed to participate and signed the consent form. A team of interviewers then performed the interviews with the participants at a mutually convenient location in the healthcare facilities. Field assistants used a structured questionnaire in lay Arabic and/or English. Data collected consisted of general demographic details such as gender, age, socio-economic status, ethnic group and medical history and other potential risk factors for T2DM and insulin resistance. Patients were examined to measure height and weight, waist and hip circumference and waist-to-hip ratio (WHR). The blood pressure was recorded twice from the right arm in a seated position using a Professional Digital Blood Pressure Monitor after 15 to 30 minutes of rest in 5-minutes intervals.

2.4.2.4.Sample collection and laboratory tests

Patients were asked to fast for 12 hours and to provide three venous blood samples as described for TB patients and to conduct the same tests. The samples were then sent to the King Faisal Hospital laboratory for processing. HOMA2-IR calculator was used to calculate IR in all participants. Patients were then classified into normal, euglycaemia with IR or T2DM. All the patients received their results using the same procedures as described for TB patients.

2.4.3. Objective 3: To explore risk factor for TB and risk factors for T2DM and IR among patients with TB.

2.4.3.1.Study design:

This was a case-controlled study in which cases were the same patients with TB included for objective 1. A control group was selected, which comprised of patients without TB. Controls were individuals attending the same centre, who were being

treated for other conditions or to undergo examinations for occupational requests to discard TB and who were deemed not to have TB. Controls were selected using systematic random sampling by selecting every fifth patient starting from first patient without TB attending to the TB and chest diseases centre and being invited to participate until the desired sample size was achieved. Controls were deemed not to have TB if they were apparently healthy individuals who had been referred for examination by the chest physician but had been confirmed not to have TB because their symptoms were acute (less than one week duration or had an alternative diagnosis such as asthma; or adults without symptoms who were attending the centre to be screened for TB due to having a new employment that require an occupational health consultation to exclude TB. Only individuals who had been declared to be free of active TB were included. If a participant refused to participate, we invited the following participant in the list of attendees. Controls were made to undergo the same tests as cases and both groups were examined to establish if they had IR. The questionnaire included a comprehensive list of factors associated with risk of T2DM and/or IR such as lifestyle, physical activity, diet, BMI, medical history and others. We obtained anthropometric measurements (by a nurse of the same gender) including height (cm), weight (kg) and waist and hip circumference (cm). BMI was calculated as weight (kg)/height^2 (m^2). Participants were eligible under the following inclusion and exclusion criteria:

2.4.3.2.Inclusion criteria:

1- Patients participating in the survey for objective 1.

2- Controls were adults attending the TB Centre without TB.

3- Participant aged ≥ 18 and residing in Jeddah city.

4- Patients accepted participation.

2.4.3.3.Exclusion criteria:

1- Same as objective 1.

According to the HOMA2-IR measurement and glucose testing, participants were classified as having IR without T2DM. The prevalence of T2DM among TB patients in Saudi Arabia is reported in the literature to be between 14% and 26%. This data was summarized from 11 studies ranging from 1989 to 2009 with a mean age of 47 ±13 years (189). We expected the prevalence of IR among TB patients to be 35%. Of these, 15% would have T2DM. We also expected the prevalence of IR among the control group without TB to be 20% i.e. 5% with IR but without hyperglycaemia and 15% with T2DM.

2.4.3.4.Blood tests:

Participants were asked to fast for 12 hours from 8 PM until 8 AM to provide blood samples. Patients were then asked if they had fasted and those that did not fast were asked to come back the next day. Patients that did not attend were contacted by phone or email. The phlebotomist at the phlebotomy area collected blood between 8 - 10 AM under safety precautions using a vacutainer blood-collection system or a large syringe to collect approximately 10 ml of blood. The sample was split into three tubes and a carrier transported the samples within two hours of collection using a cold chain. The samples were then processed by two laboratory technicians in King Fahad Hospital Laboratory in Jeddah. One of the staff belonged to the hormone department for insulin estimation and one from the chemistry department for glucose, HbA1c and lipid profile including Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides. If the sample was unlabelled or improperly labelled, collected in the wrong tube or when the sample volume was not sufficient for the

requirements of the test protocol, the sample was rejected, and we contacted the patient to come for another blood collection on a convenient day.

Although lipids and glucose in the UK are measured in mmol/dl and HbA1c mmol/mol, the unit used for this dissertation is mg/dl for lipids and glucose and percentage for HbA1c since the data were collected in Saudi and these are the units used locally. However, converting them to the units used in the UK will be a major task and is unnecessary for this dissertation mainly because we compare groups rather than absolute values and the data is mostly relevant to Saudi Arabia.

2.4.3.4.1. FPG: Four ml of venous blood collected in a tube with no additive gold-top (serum separator) was used for glucose determination based on the UV test, enzymatic method with hexokinase using an automated chemistry analyser (Roche Cobas C601).

2.4.3.4.2. Insulin: The blood samples collected in a tube with no additive gold-top (serum separator) were used for measuring insulin based on the sandwich principle using an automated immunoassay test analyser (Roche Cobas E601)

2.4.3.4.3. HbA1c: Two ml of blood in a lavender-top EDTA-containing tube was used to measure HbA1c based on the immunoassay sensitivity using advanced Chemiluminescence Technology (siemens Dimension Exl).

2.4.3.4.4. Lipid profile: The four ml of blood collected in a tube with no additive gold-top (serum separator) was used to establish the lipid profile including Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides determination based on the enzymatic colorimetric method using an automated chemistry analyser (Roche Cobas C601).

2.4.4. Objective 4: To explore risk factor for CHD and risk factors for T2DM and IR among patients with CHD.

2.4.4.1.Study design:

This was a second case-controlled study in which cases were the CHD patients described for objective two. The controls were the same adults attending the outpatient's department of the Tuberculosis and Chest Diseases Centre who were deemed not to have CHD. The questionnaire included a comprehensive list of possible risk factors for T2DM and/or IR such as lifestyle, physical activity, diet, BMI, medical history and others. We obtained the same anthropometric measurements as described in objective three. Participants were eligible under the following inclusion and exclusion criteria:

2.4.4.2.Inclusion criteria:

1- Cases were participants in the survey for objective 2 attending the King Faisal Hospital.
2- Controls were adults attending the outpatient's department of Tuberculosis and Chest Diseases Centre without CHD.
3- Participant aged ≥ 18 and residing in Taif city.
4- Patients accepted participation.

2.4.4.3.Exclusion criteria:

1- Same as objective 2.

Adults with T2DM are two to four times more likely to have CHD than those without T2DM. The American Diabetes Association (ADA) recognizes T2DM to be one of the six main CHD risk factors. The major risk factors for CHD are uncontrolled hypertension, triglyceride, and cholesterol and/or poor glycaemic control, lack of

physical activity, obesity, and smoking. Subjects with euglycaemia IR or T2DM in combination with one or more of these risk factors are more likely to get CHD. To determine whether euglycaemic IR is a risk factor for CHD, we enrolled all the cases from the cross-sectional survey second objective and controls without CHD. The prevalence of metabolic syndrome (MS), as a surrogate of IR, in an adult Saudi population is 39.3% (307, 308).

A previous community-based national epidemiological health survey on Saudi population confirmed the clear association of metabolic syndrome with CHD. The prevalence of CHD among metabolic syndrome patients was higher (6.7%) compared to participants without CHD (4.6%) ($P < 0.001$) (307, 308).

A study among Saudi diabetic patients also evaluated risk factors for CHD, concluding that the risk of CHD among diabetic patients was between 15 – 30%. We expected the prevalence of IR among adult's CHD patients to be 35% i.e. 20% with IR without hyperglycaemia and 15 % with T2DM. We also predicted that the prevalence of IR among the adult control group without CHD would be 20% i.e. 5% with IR and 15% with T2DM.

2.4.4.4.**Laboratory tests**: All Laboratory tests conducted were the same as those stated in objective 3. Specimens were collected in King Faisal Hospital phlebotomy area and were sent to the King Faisal hospital Laboratory.

2.4.5. Objective (5): To describe whether the severity of the clinical presentation of TB varies among patients with and without IR and/or T2DM.

2.4.5.1. Study design:

This was a retrospective case-controlled study. Cases were the patients diagnosed with TB who had T2DM, TB patients who had euglycaemic IR and controls (patients with TB without IR or T2DM). Participants were eligible under the following inclusion and exclusion criteria:

2.4.5.2. Inclusion criteria:

1- Patients participating in the survey for objectives 1 and 3.

2- Cases were patients diagnosed with TB who have T2DM and euglycaemic TB patients who have IR.

3- Controls were patients with TB without IR or T2DM.

2.4.5.3. Exclusion criteria:

1- Same as objectives 1 and 3.

Data on clinical presentation at the time of diagnosis was collected retrospectively from the medical records (treatment register) of patients enrolled into objective 1 at the Tuberculosis and Chest Diseases centre in Jeddah. TB disease severity was assessed using a scoring system modified from previously published studies (36, 309). A score of disease severity was used as described by Gil-Santana (2016), which included the presence or absence of each TB-related symptom (chest pain, sputum, cough, sputum with blood [haemoptysis], fever, night sweats, poor appetite, weight loss and shortness of breath [dyspnoea]). Cases and controls were assessed according to the number of symptoms. Data was extracted from the patient medical records

using a structured form including age, gender and symptoms at presentation. The scores for cases ranged from 0 to 9 where zero was the absence of any symptom and nine the presence of all symptoms. The characteristics used to do the scoring were those listed above. Participants with a score ≤ 3 were classified as group-1; a score 4 - 6 as group-2 and a score 7 - 9 as group-3. At the time of interviewing the patients we completed any data that were missing. The severity score for the control group was assessed using the same scoring system.

2.4.6. Objective (6): To describe whether the quality of life of patients with CHD varies among patients with and without IR and/or T2DM.

2.4.6.1. Study design:

This was a retrospective case-controlled study. Cases were the same patients with stable CHD who had T2DM and stable CHD patients who had euglycaemic IR. Controls were patients with stable CHD without IR or T2DM. Participants were eligible under the following inclusion and exclusion criteria:

2.4.6.2. Inclusion criteria:

1- Patients participating in the survey for objectives 2 and 4
2- Cases were patients with stable CHD who had T2DM and those with stable CHD and euglycaemic IR.
3- Controls were patients with CHD without IR or T2DM.

2.4.6.3. Exclusion criteria:

1- Same as objectives 2 and 4.

All participants undertook a questionnaire to assess their quality of life. The scoring system used to assess the quality of life was the World Health Organisation quality of life assessment-BREF (WHOQOL-BREF), an abbreviated version of the World

Health Organisation quality of life assessment-100 (WHOQOL-100) developed by the WHOQOL group (310).

The World Health Organisation Quality of Life (WHOQOL) 100 assessment measures several domain areas to assess quality of life. This assessment provides detailed information regarding each individual aspect of the quality of life. However, in some cases it may not be practical to use, as the WHOQOL-100 can be too long-winded. Therefore, a field trial form known as WHOQOL-BREF was formulated as a shorter quality of life assessment that uses domain-level profiles from the pilot WHOQOL assessment data as well as all data available from the WHOQOL-100 field trial system. The WHOQOL assessment tool allows for comprehensive epidemiological research on quality of life (310).

2.4.6.4.WHOQOL-BREF scoring

There are four domain scores that can be derived from the profile produced from the WHOQOL-BREF quality of life assessment. A further examination on two more items is also done separately and these are in the form of two questions. The first of these latter questions identifies the overall perception that an individual has on the quality of life and the second question examines the view of the individual's health. The four scores were used to indicate how an individual perceived their quality of life for each specific domain. The scores for each domain ascended positively so that a high score represented a high quality of life. Using the mean score from each domain identified the total domain score, and these scores were then multiplied by four so that it is possible to compare them with WHOQOL-100 scores. Cleaning and checking data, calculating each individual score, computing the domain scores and

the procedure for translating the raw scores to converted scores can be found on the WHO website; https://www.who.int/substance_abuse/research_tools/whoqolbref/en/

2.5. Sample size calculations:

2.5.1. The sample size for the cross-section survey for TB (objective 1):

The sample size was calculated using the epi info programme with the menu for sample size calculations for population surveys. The reference population size was the total number of people attending to the Tuberculosis and Chest Diseases Centre per year, the expected proportion of T2DM and IR which was 35% and confidence limits of 5%. We assumed that there were 350 adults available. To do a survey with a 5% confidence limit would require a sample size of 175 adults. After additions for potential drop-outs, the sample size was estimated to be 190 participants.

2.5.2. The sample size of the cross-section survey for CHD group (objective 2):

The sample size was calculated using the same standard formula for estimating a single population proportion in Epi-Info. The reference population size was the total number of people attending King Faisal Hospital cardiology department in one year. For the cross-sectional survey, we assumed that there were more than 4500 adults available for the study and the expected proportion of T2DM and IR to be 35%. To do a survey with a 5% confidence limit we required a sample size of 347 adults. After addition the potential drop-outs, the sample size was estimated to be 370 participants.

2.5.3. The sample size for the case control study for TB (objective 3):

We used epi info sample size calculator for unmatched case-control studies. We used a power of 80%, a ratio of 1 case per 1 control and the proportion of TB cases with T2DM being 35% compared to 20% for controls having T2DM. We estimated that this required 140 cases and an equal number of controls to achieve 80% power to

detect an odds ratio of 2.0 at the 95% significance level if 10% or more of the general population were exposed to the risk factor.

Sample size was estimated for T2DM as the main objective. A second sample size calculation was conducted for IR, as a secondary objective. We expected that the prevalence of IR was 20% in the TB cases and 5% in the control group. To assess this difference would require a sample size of 77 participants. This sample size was smaller than required for the first objective and was deemed to be too small for the multivariate analysis of risk factors. Therefore, we accepted the sample size for T2DM.

2.5.4. The sample size for the case control study for CHD (objective 4):

The sample size was based on the confidence interval, the power and the ratio of cases and controls and percentage of cases and controls expected to be exposed to the risk factor. We used a power of 80%, a ratio of 1 case for 1 control and the proportion of CHD cases having T2DM being 35% compared to 20% for controls. An estimated 140 cases and an equal number of controls was required to achieve 80% power to detect an odds ratio of 2.0 at the 95% significance level provided 10% or more of the general population were exposed to the risk factor.

Sample size was estimated for T2DM as the main objective. A second sample size calculation was conducted for IR, as a secondary objective. We expected that the prevalence of IR was 20% in the CHD cases and 5% in the control group. To asses this difference would require a sample size of 77 participants. This sample size was smaller than required for the main objective and was deemed to be too small for the multivariate analysis. Therefore, we accepted the sample size for T2DM.

2.6. Study outcomes:

The following were the main outcomes for each objective:

Objective 1: The general characteristics of patients with TB and the prevalence of T2DM and IR among patients with TB.

Objective 2: The general characteristics of patients with CHD and the prevalence of T2DM and IR among patients with CHD.

Objective 3: Risk factors for TB and for T2DM and IR among patients with TB.

Objective 4: Risk factors for CHD and for T2DM and IR among patients with CHD.

Objective 5: severity score of the clinical presentation of TB among patients with and without IR and/or T2DM.

Objective 6: quality of life scores of patients with CHD with and without IR and/or T2DM.

2.7. Study management:

2.7.1. Study team

The study activities were initiated by Prof Luis Cuevas, Prof Geoff Gill and Fareed Almaleki, the Tuberculosis and Chest Diseases Centre and the King Faisal Hospital in Saudi Arabia. The study was then carried out within the context of routine clinical and laboratory practices at the study sites and the clinical procedures were then conducted by those providing patient services.

2.7.2. Responsibility of study team members

2.7.2.1. Responsibility of LSTM team

- Development of the initial protocol.
- Initial site assessment visit.
- Coordination of ethical approval applications.
- Facilitate study initiation.
- Study monitoring.
- Development of standardised study forms and record keeping procedures.
- Development of standardised databases.

2.7.2.2. Responsibility of King Faisal Hospital

- Feedback of the initial protocol in collaboration with LSTM;
- Support data analysis and reporting;
- Provision of the study support staff in Saudi Arabia.
- Facilitate the enrolment of patients at its hospital facilities.
- Record results in laboratory record book.
- Support and conduct of the following tests: Fasting Plasma Glucose (FPG), Fasting plasma insulin, HbA1c and lipid profile including Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides.
- Support and conduct the study survey.

2.7.2.3. Responsibility of Tuberculosis and Chest Diseases Centre:

- Feedback of the initial protocol in collaboration with LSTM;
- Support data analysis and reporting;
- Provision of the study support staff in Saudi Arabia.
- Facilitate the enrolment of patients at its centre facilities.

- Record results in laboratory record book.
- Support and conduct the following tests: Fasting Plasma Glucose (FPG), Fasting plasma insulin, HbA1c and lipid profile including Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides.
- Support and conduct the study survey.

2.8. Trouble shooting:

Clinical and laboratory staff of the Tuberculosis and Chest Diseases Centre and the King Faisal Hospital approached the study coordinators and in turn the latter then approached LSTM. We then arranged for external technical assistance when needed.

2.9. Study site preparation:

The Tuberculosis Chest Diseases Centre, the King Faisal Hospital and the LSTM investigators reviewed the master protocol with the study team. Any changes to the master protocol were put to Prof Cuevas and Prof Geoff Gill at LSTM to be approved.

2.10. Ethical considerations:

The study was initiated after ethical approval, which was obtained from the LSTM Research Ethics Committee and the Department of Preventive Medicine and Ministry of Health, Riyadh, Saudi Arabia. Permission from the Saudi Arabia Ministry of Health Preventive Medicine Directorate and from health authorities of the study sites was received prior to the start of the study. Oral and written information was provided to study participants before informed consent was obtained. Those patients with TB and patients with CHD that were found to have abnormal results were referred to TB specialist clinics and CHD specialist clinics for further investigation and appropriate management.

Voluntary consent was obtained from all individual and they were able to exercise their free power of choice without the intervention of force, fraud, deceit, or other forms of constraint. This right to exercise choice was present throughout the entire research process. Study participation was decided by the patients. If the patient did not want to be in this study, he/she did not have to participate. This did not affect their routine diagnosis and treatment. For patients that did not know they were diabetic patients or had IR before the study, we arranged a speedy appointment with the endocrinologist to be evaluated and managed. The data collection procedures included elements where participants were asked to self-report activities and participants may not have provided honest answers. To minimize this risk, we tried to make the participants feel that their input was valued and that it would have a scientific importance.

2.11. Benefits to participants:

By participating in this study, we were able to detect whether they had T2DM and if they were at risk of developing T2DM (raised IR). If we detected that they had T2DM, we arranged them to meet a specialist and provided them with a leaflet on T2DM risk awareness.

2.12. Potential harms to participants:

There were no serious adverse effects in participating in this study. However, the interview may have raised discomforting memories. Patients were also required to dedicate some time for the interview to take place. There was an appropriate room with comfortable chairs provided and we ensured that the interviewer adhered to academic principles by confirming that the participants were aware of the importance and the purpose of this study. The languages used in the interviews were Arabic and/or English, and the questions were structured in a manner that was clear and easy for the

participants to understand. The participants were free to cycle between the topic areas or questions going back or skipping forward to any area.

The participants also gave blood samples. Blood collecting procedures may have caused some minor adverse effects such as local bleeding, haematoma or pain.

2.13. Training for study staff:

Training was only required for completion of the questionnaire. We trained the clinic nurses when we initiated the fieldwork.

2.14. Biosafety guidelines for clinic and laboratory staff:

Health care workers (HCWs) would have been exposed to airborne pathogens as they were dealing with TB patients, blood-borne pathogens from needle sticks, sharps injuries are primarily associated with HCWs transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). The staff were encouraged to follow the TB infection-control measures by the Centres for Disease Control and Prevention (CDC) and the local infection control guidelines precautions for preventing transmission of blood-born and airborne infections. Laboratory workers were responsible for their own safety and that of their co-workers.

2.15. Statistical analysis:

2.15.1. First and Second objectives:

Bacteriologically confirmed pulmonary TB patients and patients with stable CHD were classified as having normal glucose values or T2DM according to their medical history, glycaemic status and HbA1c level using the WHO guidelines to determine the T2DM diagnostic criteria. Furthermore, IR status was classified according the

HOMA2 calculation using the latest version of HOMA calculator which is called Homa2-IR. The cut-off point for IR was (< 2.0).

- Diabetic patients were defined as having an abnormal FPG if it was (≥ 126 mg/dl) [7.0 mmol/L] or an abnormal HbA1c level (≥ 6.5%).
- Euglycaemic participants with FPG (< 125 mg/dl) [6.9 mmol/L] were defined as having increased IR if the HOMA2-IR was (≥ 2).
- Participant with FPG (< 110 mg/dl) (6.1 mmol/L), HbA1c level (< 6.5%) and HOMA2-IR (< 2) were defined as not having T2DM or IR.

We used the WHO diagnostic criteria for the diagnosis of T2DM and prediabetic state. These criteria have been in place and are used worldwide for nearly a decade. Though, there are other guidelines by the American Diabetes Association, we used the WHO guidelines because these guidelines are used in Saudi Arabia and the doctors use them to interpret the test results and to classify patients. Furthermore, my PhD was based in the UK and the diabetes UK supports the use of the WHO diagnosis criteria. Many studies conducted in Saudi Arabia use the WHO guidelines, which would make this thesis findings easier to compare..

2.15.2. Third and fourth objectives:

The outcome measures to describe the association of T2DM and IR were the following assumed risk factors: age, sex, BMI, blood pressure, Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides, family history of T2DM, smoking, dietary habits and physical activity were also included. Data analysis for this study compared the characteristics of patients with and without IR. SPSS software was used to input and analyse the data. Univariate analysis and multiple backward stepwise logistic regression analyses were conducted to analyse the significant factors

associated with the dependent variable. The independent variables were selected on the basis of the literature of T2DM risk factors and were analysed using the logistic regressions. The results were presented as crude and adjusted odds ratios (AOR) with 95% CI. Mean ± standard deviation was used to describe normal and continuously distributed data. Continuous and ordinal data with outliers or skew distribution was analysed using medians, first and third quartiles.

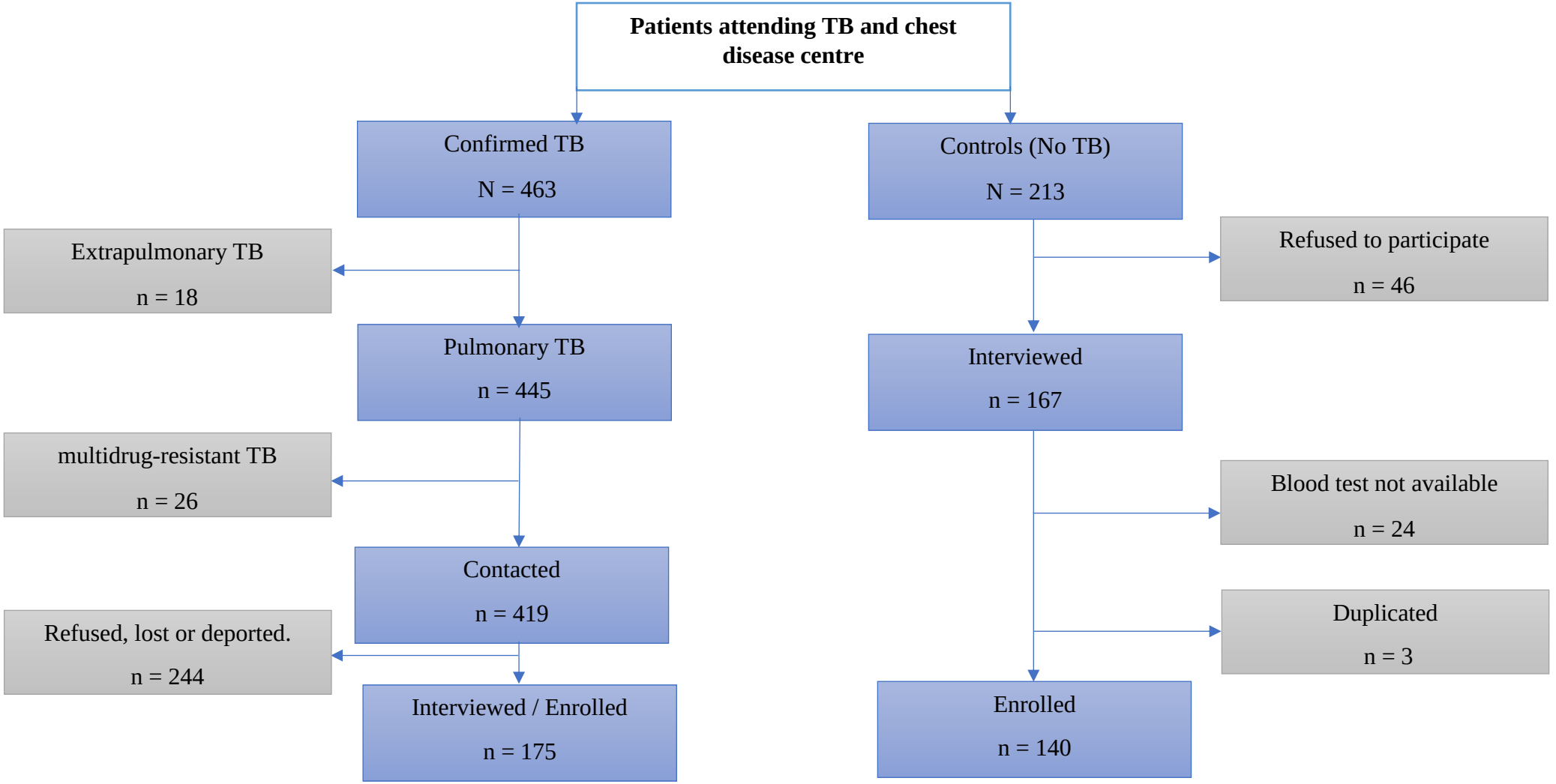
2.15.3. Fifth objective:

The outcome measure was the mean severity score of the clinical presentation of TB among patients with and without IR and/or T2DM.

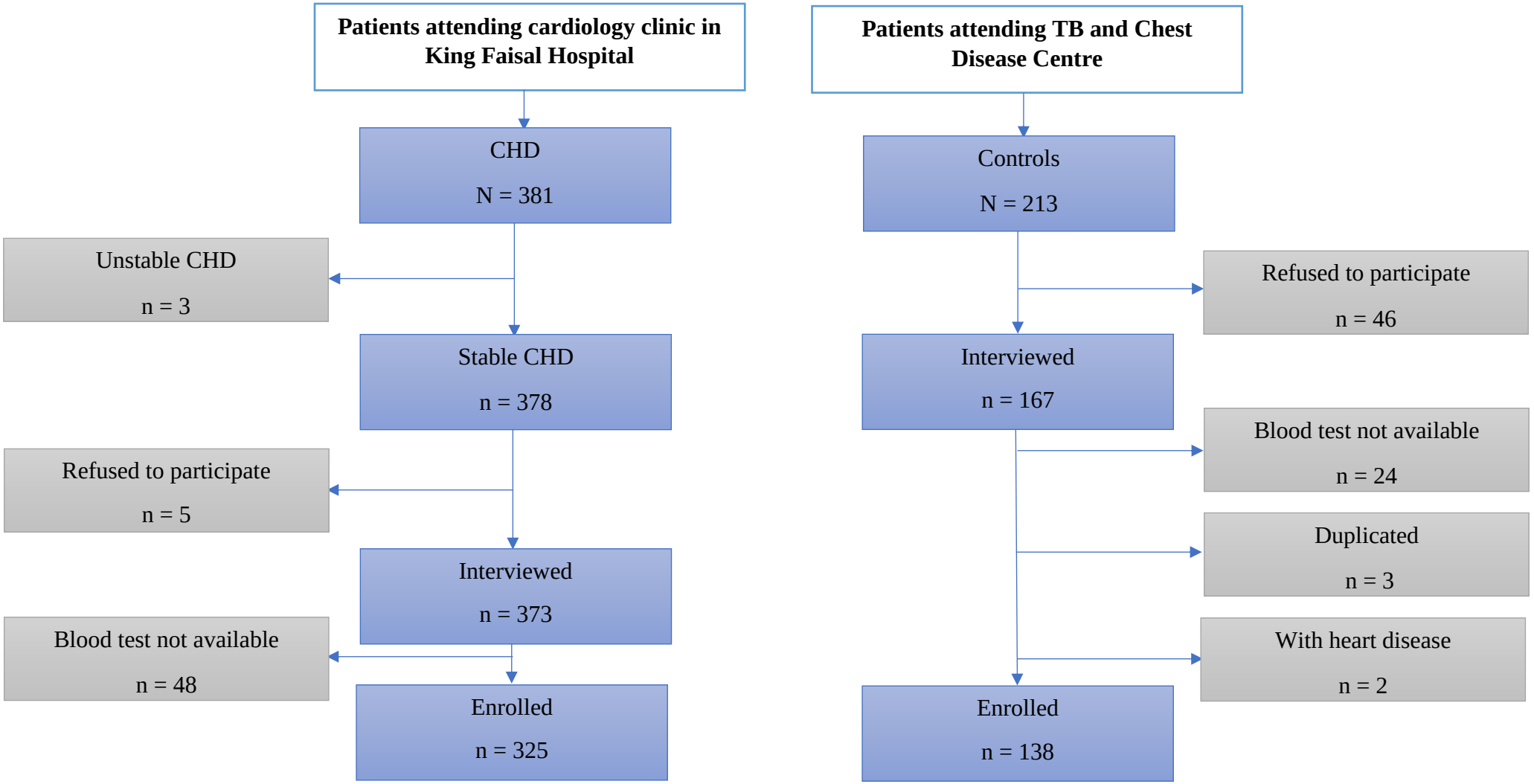
2.15.4. Sixth objective:

We described the quality of life of patients with CHD among patients with and without IR and/or T2DM using the methods described by WHO for the WHOQOL-BREF questionnaire.

Figures 6. Flow chart of TB study:



Figures 7. Flow chart of CHD study:



3. Chapter 3 – TB Results

3.1. Prevalence of T2DM and IR among patients with TB and IR as a risk factor for TB.

We performed a case control study from November 2016 to June 2017, as described in the methods chapter. The study included the 175 patients ≥18 years old with confirmed pulmonary TB who had registered at the TB and Chest Diseases Centre in Jeddah city, Saudi Arabia, for treatment in the previous year. All patients who had received TB treatment for at least two months at the time of enrolment were eligible to participate. Participants with TB are called 'cases' in this sub-study. One hundred and forty controls attending the same centre with respiratory problems other than TB or who attended the centre to undergo TB screening to obtain a work permit were recruited using systematic sampling. Every 5th patient was selected, starting from the first patient attending the centre every day, until the desired sample size was achieved. Both cases and controls signed a written informed consent and underwent a structured interview and physical examination.

The demographic characteristics of the participants are shown in table 7. Cases were younger than controls with a median age of 33 versus 40 years, respectively ($p < 0.001$). The age of cases and controls ranged from 18 to 78 and 18 to 76 years, respectively. One hundred eleven (63.4%) cases were male and 64 (36.6%) female, compared to 83 (59.3%) and 57 (40.7%) controls, respectively ($p = 0.453$). Cases were more likely to be single (58, 33.1% versus 33, 23.6%, $p = 0.012$) and to have primary education (47, 26.9% versus 21, 15.0%) than controls, but less likely to have intermediate (13, 7.4%) or secondary education (33, 18.9%) than controls (32, 22.9% and 36, 25,7%, respectively) ($p = 0.001$). Cases were more likely to work in the private sector (34, 19.4%) and to be manual workers (46, 26.3%) than controls (14,

10.0% and 27, 19.3%, respectively), while controls were more likely to work in the government (19, 13.6%) or to belong to non-employed categories (74, 52.9%) than cases (9, 5.1% and 80, 45.7%, respectively) ($p = 0.002$).

With regards to the ethnicity, cases were less likely to be Saudi (37, 21.1%) than controls (73, 52.1%) ($p < 0.001$). The ethnicity of the non-Saudi participants is show in table (8). Although frequencies are low for each country, there were considerable proportions from Somalia (27, 15.4%), Yemen (25, 14.3%), Ethiopia (17, 9.7%), Pakistan (16, 9.1 %), Sudan (9, 5.1%), Chad (8, 4.6%), Bangladesh (7, 4.0%), Eritrea (6, 3.4%) and the Philippines (6, 3.4%).

The medical histories of cases and controls are summarised in table 9. Participants were asked whether they knew if they had T2DM, hypertension, hyperlipidaemia, gestational T2DM or polycystic ovaries and if they were taking medications for these conditions. There was no difference between cases and controls in terms of a personal history of T2DM or insulin-using T2DM. However, cases were less likely to have a family history of diabetes (52, 29.7%) than controls (57, 40.7%) ($p = 0.041$). Most relatives with T2DM among cases and controls were first degree relatives (48, 27.4% versus 49, 35.0%, respectively, $p = 0.148$).

Cases also had a lower prevalence of hypertension than controls (9, 5.1% versus 31, 22.1%, $p < 0.001$). Correspondingly, the proportion of cases taking hypertensive medications was lower among cases than controls (8, 4.6% versus 23, 16.4%, respectively, $p < 0.001$). Cases were less likely to have hyperlipidaemia (8, 4.6% and 28, 20.0%, respectively, $p < 0.001$) and to be taking lipid lowering therapy (5, 2.9% versus 17, 12.1%, respectively, $p = 0.002$). There were no differences between cases

and controls regarding the medical history of heart problems, gestational diabetes and polycystic ovaries.

Table 7. Demographic characteristics of cases and controls.

Demographic characteristics N = 315		**Cases n = 175 (%)**	**Controls n = 140 (%)**	***p***
Sex	Male	111 (63.4)	83 (59.3)	0.453
	Female	64 (36.6)	57 (40.7)	
Age	Range	18 – 78	18 - 76	**< 0.001**
	Median (IQR)	33 (25 - 45)	40 (28 - 53)	
Age group	18 - 29	71 (40.6)	39 (27.9)	**0.002**
	30 – 39	45 (25.7)	23 (16.4)	
	40 – 49	22 (12.6)	29 (20.7)	
	≥ 50	37 (21.1)	49 (35.0)	
Marital status	Single	58 (33.1)	33 (23.6)	**0.012**
	With partner/married	105 (60.0)	102 (72.9)	
	Divorced/separated	11 (6.3)	2 (1.4)	
	Widowed	1 (0.6)	3 (2.1)	
Education	No education	19 (10.9)	13 (9.3)	**0.001**
	Literacy	36 (20.6)	21 (15.0)	
	Primary education	47 (26.9)	21 (15.0)	
	Intermediate education	13 (7.4)	32 (22.9)	
	Secondary education	33 (18.9)	36 (25.7)	
	Higher education	26 (14.9)	17 (12.1)	
	Prefer not to answer	1 (0.6)	0 (0.0)	
Education group	Educated	119 (68.0)	106 (75.7)	0.152
	Uneducated	55 (31.4)	34 (24.3)	
Occupation	Governmental	9 (5.1)	19 (13.6)	**0.002**
	Private	34 (19.4)	14 (10.0)	
	Labourer	46 (26.3)	27 (19.3)	
	Unemployed	80 (45.7)	74 (52.9)	
	Retired	1 (0.6)	5 (3.6)	
	Other	5 (2.9)	1 (0.7)	
Ethnicity	Saudi	37 (21.1)	73 (52.1)	**< 0.001**
	Non-Saudi	138 (78.9)	67 (47.9)	

Table 8. Ethnicity of cases and controls.

Country N = 315	Cases n = 175 (%)	Controls n = 140 (%)
Saudi Arabia	37 (21.1)	73 (52.1)
Somalia	27 (15.4)	6 (4.3)
Yemen	25 (14.3)	20 (14.3)
Ethiopia	17 (9.7)	1 (0.7)
Pakistan	16 (9.1)	6 (4.3)
Sudan	9 (5.1)	7 (5.0)
Chad	8 (4.6)	4 (2.9)
Bangladesh	7 (4.0)	3 (2.1)
Eritrea	6 (3.4)	4 (2.9)
Philippines	6 (3.4)	0 (0.0)
Barmawi	3 (1.7)	1 (0.7)
India	3 (1.7)	4 (2.9)
Indonesia	3 (1.7)	3 (2.1)
Afghanistan	2 (1.1)	2 (1.4)
Nigeria	2 (1.1)	0 (0.0)
Nepal	2 (1.1)	0 (0.0)
Egypt	1 (0.6)	4 (2.9)
Mali	1 (0.6)	0 (0.0)
Syria	0 (0.0)	1 (0.7)
South Asia	0 (0.0)	1 (0.7)

Table 9. Medical history of cases and controls.

Medical history N = 315			Cases n = 175 (%)	Controls n = 140 (%)	*p*
T2DM	Yes		45 (25.7)	27 (19.3)	0.066
	No		129 (73.7)	108 (77.1)	
	Don't know		1 (0.6)	5 (3.6)	
T2DM using insulin (N=45)	Yes		10 (22.2)	2 (7.4)	0.190
	No		35 (77.8)	25 (92.6)	
Family history of diabetes	Yes		52* (29.7)	57 (40.7)	**0.041**
	No		123 (70.3)	83 (59.3)	
	1st degree	Yes	48 (27.4)	49 (35.0)	0.148
		No	127 (72.6)	91 (65.0)	
	2nd degree	Yes	6 (3.4)	7 (5.0)	0.486
		No	169 (96.6)	133 (95.0)	
	3rd degree	Yes	1 (0.6)	1 (0.7)	1
		No	174 (99.4)	139 (99.3)	
Hypertension	Yes		9 (5.1)	31 (22.1)	**< 0.001**
	No		164 (93.7)	106 (75.7)	
	Don't know		2 (1.1)	3 (2.1)	
Takes hypertensive medication	Yes		8 (4.6)	23 (16.4)	**< 0.001**
	No		167 (95.4)	117 (83.6)	
Hyperlipidaemia	Yes		8 (4.6)	28 (20.0)	**< 0.001**
	No		164 (93.7)	103 (73.6)	
	Don't know		2 (1.1)	9 (6.4)	
Takes lipid lowering therapy	Yes		5 (2.9)	17 (12.1)	**0.002**
	No		169 (96.6)	120 (85.7)	
	Don't know		1 (0.6)	3 (2.1)	
Heart problems	Yes		3 (1.7)	2 (1.4)	0.543
	No		171 (97.7)	138 (98.6)	
	Don't know		1 (0.6)	0 (0.0)	
History of gestational diabetes	Yes		5 (2.9)	4 (2.9)	0.681
	No		59 (33.7)	53 (37.9)	
	Not applicable		111 (63.4)	83 (59.3)	
History of polycystic ovaries	Yes		0 (0.0)	3 (2.1)	0.052
	No		63 (36.0)	50 (35.7)	
	Don't know		1 (0.6)	4 (2.9)	
	Not applicable		111 (63.4)	83 (59.3)	

*Three cases had more than one relative with T2DM, resulting in 55 relatives.

The lifestyle and diet of cases and controls are shown in table 10. Participants were asked about occupation, monthly income, level of stress, overweight and completed a recall of their diet. The monthly income was less than SAR 3000 (GBP 600) in 139 (79.4%) cases compared to 93 (66.4%) controls and only (5, 2.9%) cases and (13, 9.2%) controls had an income above SAR 5000 ($p = 0.010$). Cases were more likely to report increased levels of stress (19, 10.9%) than controls (3, 2.1%) ($p = 0.009$).

Cases were more likely to report a poor diet than controls (48, 27.4% versus 11, 7.9%, respectively) and less likely to rate their diet as good (10, 5.7%) than controls (76, 54.3%) ($p < 0.001$). Many more cases ate fast foods more than five times per week (25, 14.3%) than controls (14, 10.0%) ($p = 0.018$). There were no differences between cases and controls regarding occupation, family overweight, being overweight in childhood, the number of times they ate breakfast, lunch and dinner in a week and their description of their food portions sizes.

The physical activities of cases and controls are shown in table 11. The level of physical activity was very low in both groups, with the median number of days doing moderate to vigorous activity being zero for both. Only seven of 175 cases and two of 140 controls reported to do vigorous activity (medians of 5 and 4.5 days per week among these subgroups, respectively) and 30 cases and 17 controls indicated they did moderate activity up to five days a week. There were no statistically significant differences between cases and controls regarding physical activity.

Table 10. Lifestyle and diet of cases and controls.

Lifestyle and diet **N = 315**		**Cases** **n = 175 (%)**	**Controls** **n = 140 (%)**	***p***
Occupation	Sedentary	124 (70.9)	97 (69.3)	
	Moderate	43 (24.6)	38 (27.1)	0.812
	Physically demanding	8 (4.6)	5 (3.6)	

Monthly income (SAR)	≤ 3000	139 (79.4)	93 (66.4)	**0.010**
	3000-5000	31 (17.7)	34 (24.3)	
	5001-10000	5 (2.9)	10 (7.1)	
	≥10000	0 (0.0)	3 (2.1)	
Level of stress	Low	130 (74.3)	111 (79.3)	**0.009**
	Medium	26 (14.9)	26 (18.6)	
	High	19 (10.9)	3 (2.1)	
Family overweight	Yes	25 (14.3)	29 (20.7)	0.167
	No	149 (85.1)	110 (78.6)	
	Don't know	1 (0.6)	0 (0.0)	
	Prefer not to say	0 (0.0)	1 (0.7)	
If yes, who?	Father	4 (2.3)	8 (5.7)	0.114
	Mother	16 (9.1)	9 (6.4)	0.376
	Sibling	7 (4.0)	6 (4.3)	0.899
	Other	7 (4.0)	9 (6.4)	0.329
Overweight as a child	Yes	18 (10.3)	14 (10.0)	0.341
	No	152 (86.9)	125 (89.3)	
	Don't know	5 (2.9)	1 (0.7)	
Number of breakfast meals last week	None	6 (3.4)	6 (4.2)	0.209
	1 – 6/per week	27 (15.4)	32 (22.9)	
	Always	142 (81.2)	102 (72.9)	
Number of lunch meals last week	None	1 (0.6)	0 (0.0)	0.446
	1 – 6/per week	16 (9.1)	10 (7.1)	
	Always	158 (90.3)	130 (92.9)	
Number of dinner meals last week	Never	0 (0.0)	2 (1.4)	0.106
	1 – 6/per week	17 (9.7)	19 (13.6)	
	Always	158 (90.3)	119 (85.0)	
Participant self-rating the diet quality	Good	10 (5.7)	76 (54.3)	**< 0.001**
	Fair	117 (66.9)	53 (37.9)	
	Poor	48 (27.4)	11 (7.9)	
Fast food consumption	0 - 1/Month	40 (22.9)	52 (37.1)	**0.018**
	2 - 3/Month	43 (24.6)	21 (15.0)	
	1 - 2/Week	47 (26.9)	31 (22.1)	
	3 - 4/Week	20 (11.4)	22 (15.7)	
	≥ 5 /Week	25 (14.3)	14 (10.0)	
Food portion size	Small	23 (13.1)	15 (10.7)	0.791
	Intermediate	111 (63.4)	90 (64.3)	
	Large	41 (23.4)	35 (25.0)	

Table 11. Physical activity of cases and controls.

Physical activity (days per week) N = 315	Cases n = 175		Controls n = 140		*p*
	N	Median (IQR)	N	Median (IQR)	
Vigorous	7	0 (0 – 0)	2	0 (0 – 0)	0.174
Moderate	30	0 (0 – 0)	17	0 (0 – 0)	0.214
Walking	175	7 (7 – 7)	140	7 (7 – 7)	0.421
Minutes walked/day	175	30 (20 – 60)	140	30 (20 – 60)	0.063

A symptom comparison among cases with positive and negative (or not done) TB culture is shown in table 12. There was no difference between the two groups except that cases with negative/not done culture were more likely to have night sweats (83, 92.2% versus 68, 80.0%, respectively, p = 0.019).

Table 12. Symptoms comparison among cases between positive TB culture and negative or not done.

TB Culture N=175	Negative/Not done n = 90 (%)	Positive n= 85 (%)	*p*
Chest Pain	64 (71.1)	59 (69.4)	0.806
Sputum	83 (92.2)	81 (95.3)	0.403
Cough	87 (96.7)	84 (98.8)	0.654
Sputum with blood	16 (17.8)	21 (24.7)	0.262
Shortness of breath	44 (48.9)	35 (41.2)	0.306
Fever	88 (97.8)	82 (96.5)	0.948
Night sweats	83 (92.2)	68 (80.0)	**0.019**
Poor Appetite	80 (88.9)	73 (85.9)	0.549
Weight loss	84 (93.3)	79 (92.9)	0.918

A comparison of TB cases with positive and negative/not done Acid Fast Bacilli (AFB) smear microscopy is shown in table 13. There was no difference between the two groups except that cases with positive smear microscopy were more likely to have cough than patients with negative/not done smears (132, 99.3% versus 39, 92.9%, respectively, p = 0.043).

Table 13. Comparison among cases between AFB Smear-positive and -negative/not done.

AFB Smear N=175	**Negative/Not done n = 42 (%)**	**Positive n= 133 (%)**	***p***
Chest Pain	26 (61.9)	97 (72.9)	0.173
Sputum	38 (90.5)	126 (94.7)	0.531
Cough	39 (92.9)	132 (99.3)	**0.043**
Sputum with blood	8 (19.1)	29 (21.8)	0.703
Shortness of breath	17 (40.5)	62 (46.6)	0.486
Fever	40 (95.2)	130 (97.7)	0.750
Night sweats	37 (88.1)	114 (85.7)	0.696
Poor Appetite	38 (90.5)	115 (86.5)	0.494
Weight loss	38 (90.5)	125 (93.9)	0.664

The anthropometry data of all participants are shown in table 14. Among males, cases had lower weight than controls with medians of 64 and 72 Kgs and a median difference of 8 Kgs, respectively (p < 0.001). The median BMI among males was 22 for cases and 26 for controls with a median BMI difference of 4 (p < 0.001). Male cases, therefore, were less likely to be obese than controls (13, 11.7% versus 22, 26.5%, respectively, p < 0.001); to have a lower median waist circumference with a median difference of 10 cms and lower hip circumference with a median difference of 8 cms (p < 0.001). The median WHR of male cases (0.87) was lower than male controls (0.90) with a median difference of (0.03) (p = 0.019).

Among females, cases were taller than controls with medians of 159 and 156 cms, respectively, and a median difference of 3 cms ($p = 0.035$). Female cases, however, had a lower weight with medians of 56 Kgs and 69 Kgs, respectively, and a median difference of 13 Kgs ($p < 0.001$). Their median BMI was 22 for cases compared to 28 for controls and with a median difference of 6 ($p < 0.001$). Female cases, therefore, were less likely to be obese than controls (7, 10.9% versus 21, 36.8%, respectively), to have a lower median waist circumference with a median difference of 3 cms and lower hip circumference than controls with a median difference of 14 cms ($p < 0.001$).

Table 14. Anthropometry of cases and controls

Anthropometry N = 315		Male		*P*	Female		*p*
		Cases n = 111	Controls n = 83		Cases n = 64	Controls n = 57	
Height (cm)	Median (IQR)	172 (167 - 178)	170 (163 -175)	0.065	159 (155 -163)	156 (153 -161)	**0.035**
Weight (kg)	Median (IQR)	64 (56 -76)	72 (65 -83)	**< 0.001**	56 (47 -68)	69 (60 -86)	**< 0.001**
BMI* (kg/m2)	Median (IQR)	22 (19 -25)	26 (22 -30)	**< 0.001**	22 (19 -26)	28 (24 -35)	**< 0.001**
BMI* groups	≤ 18.4	22 (19.8%)	7 (8.4%)	**< 0.001**	16 (25.0%)	3 (5.3%)	**< 0.001**
	18.5 - 24.9	57 (51.4%)	27 (32.5%)		28 (43.8%)	14 (24.6%)	
	25 - 29.9	19 (17.1%)	27 (32.5%)		13 (20.3%)	19 (33.3%)	
	≥ 30	13 (11.7%)	22 (26.5%)		7 (10.9%)	21 (36.8%)	
Waist (cm)	Median (IQR)	83 (76 -94)	93 (82 -104)	**< 0.001**	78 (68 -90)	91 (81 -101)	**< 0.001**
Hip (cm)	Median (IQR)	95 (91 -102)	103 (97 -110)	**< 0.001**	92 (83 -104)	106 (97 -115)	**< 0.001**
WHR*	Median (IQR)	0.87 (0.83 -0.93)	0.90 (0.84 - 0.96)	**0.019**	0.83 (0.78 - 0.90)	0.86 (0.80 - 0.91)	0.283
WHR* groups	Low	70 (63.1%)	42 (50.6%)	0.207	27 (42.2%)	18 (31.6%)	0.468
	Moderate	37 (33.3%)	36 (43.4%)		21 (32.8%)	21 (36.8%)	
	High	4 (3.6%)	5 (6.0%)		16 (25.0%)	18 (31.6%)	

*BMI = Body Mass index, *WHR = Waist/Hip Ratio

The metabolic and clinical characteristics of participants are shown in table 15. Variables are presented as medians interquartile ranges (IQR) as they had skewed distributions. Cases had lower median triglycerides than controls (94 versus 106 mg/dL, respectively, $p = 0.009$) with a lower proportion having high triglycerides concentrations (8, 4.6% versus 20, 14.3%, respectively, $p = 0.009$). Cases also had higher median HDL cholesterol (49 mg/dL and 42 mg/dL, respectively, $p < 0.001$) and a lower proportion had *at risk* HDL cholesterol levels (60, 34.3% versus 76, 54.3%, respectively, $p < 0.001$). Hypertension was less frequent among cases than controls, with a lower median systolic blood pressure (SBP) (118 mmHg) than controls (121 mmHg), although this difference is unlikely to be of clinical significance.

The diabetes status of cases and controls is shown in table 16. The total number of diabetic patients was calculated by merging patients with known T2DM (from medical history) and FPG test results. Despite being younger, cases were more likely to be diabetic patients (51, 29.0%, 95% CI 22.5 - 36.5%) than controls (39, 27.9%, 95% CI 20.6 - 36.1%), but this difference was not statistically significant at the univariate analysis ($p = 0.801$) (figure 8). Among diabetic patients, a higher proportion of cases used insulin (10, 19.6%, 95% CI 9.8 - 33.1%) than controls (2, 5.1%, 95% CI 0.6 - 17.3%), although the difference was not statistically significant ($p = 0.061$) (figure 9).

Normoglycemic participants were classified according to whether they had IR using a HOMA2-IR cut-off of ≥ 2. Out of 175 cases, 124 had a normoglycemic status (71%, 95% CI 63.5 - 77.5%) compared to 101 (72.1%, 95% CI 63.9 - 79.4%) of 140 controls. Among 124 normoglycemic cases, 27 (22%, 95% CI 14.9 - 30.1%) had IR compared to 26 of 101 normoglycemic controls (25.7%, 95% CI 17.6 - 35.4%).

There was no statistically significant difference at the univariate analysis between normoglycemic cases and controls regarding to diabetic status and IR (p = 0.485) (figure 10).

The total number of patients with metabolic syndrome was calculated according to the National Cholesterol Education Program Adult Treatment Panel III Guidelines (NCEP ATP III) definition. The proportion of patients with metabolic syndrome was lower among cases (45 (25.7%), 95% CI 19.4 – 32.9%) than controls (68 (48.6%), 95% CI 40.0 – 57.2%) (p < 0.001).

Table 15. Metabolic and clinical characteristics of cases and controls.

Metabolic/clinical characteristics N = 315		**Cases n = 175 (%)**	**Controls n = 140 (%)**	***p***
FPG* (mg/dL)	Range	68 - 440	55 – 394	0.155
	Median (IQR)	94 (85 - 118)	94 (83 - 105)	
	< 110	121 (69.1)	111 (79.3)	0.120
	110 – 125	15 (8.6)	7 (5.0)	
	≥ 126	39 (22.3)	22 (15.7)	
HbA1c* (%)	Range	3.9 - 13.6	4.1 - 11.9	0.291
	Median (IQR)	5.7 (5.2 - 7)	5.9 (5.5 - 6.4)	
	< 5.7	83 (47.4)	57 (40.7)	0.122
	≥ 5.7 – 6.4	45 (25.7)	51 (36.4)	
	≥ 6.5	47 (26.9)	32 (22.9)	
Fasting Plasma Insulin (μU/ml**)**	Range	2.1 - 57.0	2.9 - 57.1	0.130
	Median (IQR)	10.2 (6.5 - 15.4)	11.6 (7.1 - 17.7)	
	2 – < 25	157 (89.7)	119 (85.0)	0.207
	≥ 25	18 (10.3)	21 (15.0)	
HOMA2-IR*	Range	0.4 - 9.2	0.4 - 6.5	0.447
	Median (IQR)	1.40 (0.9 - 2.3)	1.55 (0.9 - 2.5)	
	Normal < 2	126 (72.0)	96 (68.6)	0.507
	IR ≥ 2	49 (28.0)	44 (31.4)	
Total cholesterol (mg/dL)	Range	70 - 333	107 – 333	0.189
	Median (IQR)	190 (164 - 220)	187 (152 - 216)	
	< 150	27 (15.4)	31 (22.1)	0.127
	≥ 150	148 (84.6)	109 (77.9)	

Triglycerides (mg/dL)	Range	24 - 999	32 – 846	**0.009**
	Median (IQR)	94 (67 - 127)	106 (75 - 156)	
	< 150	146 (83.4)	102 (72.9)	**0.009**
	< 200	21 (12.0)	18 (12.9)	
	≥ 200	8 (4.6)	20 (14.3)	
HDL* Cholesterol (mg/dL)	Range	6.0 - 99.9	19.5 - 90.8	**< 0.001**
	Median (IQR)	49 (37 - 60)	42 (34 - 51)	
	Optimal	115 (65.7)	64 (45.7)	**< 0.001**
	Risky	60 (34.3)	76 (54.3)	
LDL* Cholesterol (mg/dL)	Range	6.3 - 245.8	27.6 - 234.4	0.489
	Median (IQR)	119 (96 - 141)	113 (88 - 141)	
	< 100	48 (27.4)	49 (35.0)	0.148
	≥ 100	127 (72.6)	91 (65.0)	
Systolic BP*	Median (IQR)	118 (107 - 129)	121 (108 - 136)	**0.045**
Diastolic BP*	Median (IQR)	62 (57 - 72)	64 (57 - 76)	0.129

***FPG = Fasting plasma glucose, *HbA1c = Glycated haemoglobin, *HOMA2-IR = Homeostasis model assessment-(2)-Insulin resistance, *HDL = High-density lipoprotein, *LDL = Low-density lipoprotein, *BP = Blood pressure. HDL cholesterol: Optimal = Male ≥ 40 Female ≥ 50; Risky = Male <40, Female < 50

Table 16. T2DM and IR cases among cases and controls.

Study population N = 315	**Cases n = 175 (%)**	**95% CI**	**Controls n = 140 (%)**	**95% CI**	***p***
T2DM participants	51 (29.0)	22.5 - 36.5	39 (27.9)	20.6 - 36.1	0.801
T2DM using insulin	10 (19.6)	9.8 - 33.1	2 (5.1)	0.6 - 17.3	0.061
T2DM not using insulin	41 (80.4)	66.9 - 90.2	37 (94.9)	82.7 - 99.4	
Normoglycemic participants	124 (71.0)	63.5 - 77.5	101 (72.1)	63.9 - 79.4	0.801
Normoglycemic with IR	27 (22.0)	14.9 - 30.1	26 (25.7)	17.6 - 35.4	0.485
Normoglycemic without IR	97 (78.0)	69.9 - 85.1	75 (74.3)	64.6 - 82.4	
Participants with MS	45 (25.7)	19.4 - 32.9	68 (48.6)	40.0 - 57.2	< 0.001
Participants without MS	130 (74.3)	67.1 - 80.6	72 (51.4)	42.8 - 60.0	

Figure 8. Diabetes status of cases and controls

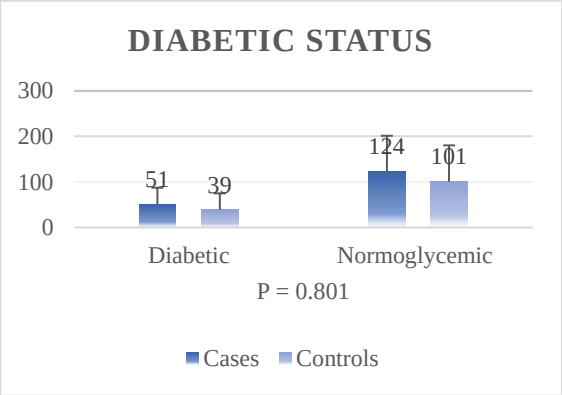


Figure 9. Insulin use among cases and controls

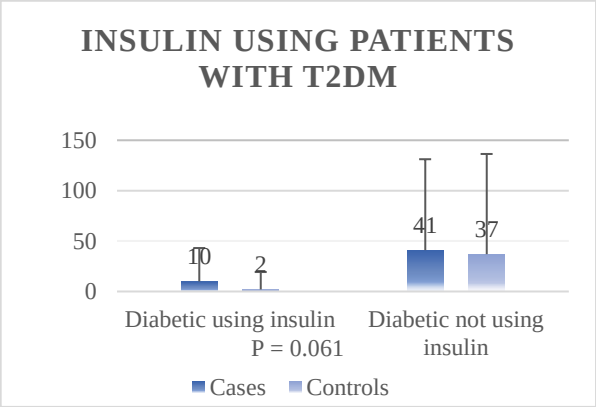
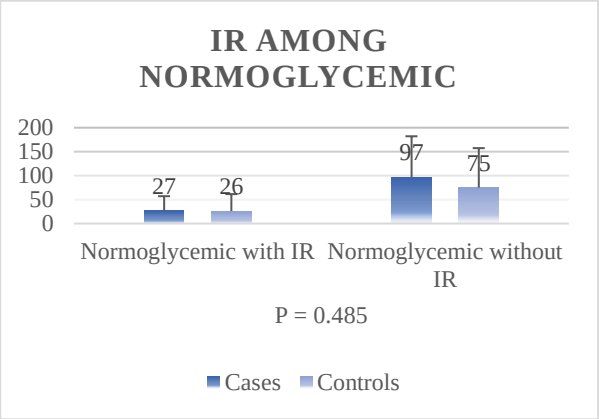


Figure 10. IR status of normoglycemic cases and controls



3.2. Logistic Regression

As many variables had significant correlations with each other, we undertook multivariable backward stepwise logistic regression for clusters of variables, to identify the main variables for each cluster. Variables with p-values < 0.2 were selected into a multivariable backward stepwise logistic regression. These included age, nationality, marital status, education, occupation, T2DM, family history of diabetes, hypertension, takes hypertensive medication, hyperlipidaemia, takes lipid lowering therapy, polycystic ovaries, monthly income, level of stress, family overweight, number of dinner meals last week, participant self-rating the diet quality,

fast food consumption, WHR, BMI, FPG, HbA1c, fasting plasma insulin, total cholesterol, triglycerides, LDL Cholesterol, HDL Cholesterol, systolic BP and diastolic BP. Multivariable backward stepwise logistic regressions were conducted separately for demographic characteristics, medical history, lifestyle and diet, anthropometry and metabolic and clinical characteristics of cases and controls. As shown in appendix (13). For each cluster, the variables remaining statistically significant were carried forward into multivariate analysis using backward statistics regressions with replacement. We adjusted for age, gender, marital status, obesity and ethnicity to obtain the Adjusted ORs (AOR).

The results of the final multivariable backward stepwise logistic regression including T2DM are shown in table 17. Cases were more likely to be non-Saudis (AOR 3.565, 95% CI 1.83 - 6.97, $p < 0.001$), to have T2DM (AOR 2.950, 95% CI 1.31 - 6.62, $p = 0.009$) and to indicate they had a fair (AOR 12.944, 95% CI 5.60 - 29.93, $p < 0.001$) or poor diet (AOR 33.625, 95% CI 10.75 - 105.20, $p < 0.001$) than controls. Cases were more likely to eat fast foods 1 – 2 times/week (AOR 2.468, 95% CI 0.03 - 5.93, $p = 0.043$) or 2 – 3 times/month (AOR 2.655, 95% CI 1.00 - 7.04, $p = 0.050$), less likely to be obese (AOR 0.190, 95% CI 0.05 - 0.70, $p = 0.012$), to have higher total cholesterol (AOR 3.035, 95% CI 1.34 - 6.87, $p = 0.008$) and a lower level of *risky* HDL Cholesterol (AOR 0.400, 95% CI 0.21 - 0.76, $p = 0.005$) than controls.

The results of the final multivariable backward stepwise logistic regression including metabolic syndrome are shown in table 18. This further analysis excluded T2DM as a single factor, as this diagnosis is included in the definition of metabolic syndrome. Cases were more likely to be non-Saudis (AOR 3.448, 95% CI 1.81 - 6.58, $p <$

0.001) and to indicate they had a fair (AOR 12.893, 95% CI 5.71 - 29.11, $p < 0.001$) or poor diet (AOR 30.197, 95% CI 10.10 - 90.29, $p < 0.001$) than controls. Cases were less likely to be obese (AOR 0.224, 95% CI 0.06 - 0.81, $p = 0.022$), to have higher total cholesterol (AOR 3.382, 95% CI 1.55 - 7.40, $p = 0.002$) than controls.

Table 17. Logistic regression model for factors predicting TB including T2DM.

Variables N = 315		Univariate			Multivariate	
		Cases n = 175 (%)	Controls n = 140 (%)	*p*	AOR* (95% CI)	*p*
Sex	Male	111 (63.4)	83 (59.3)	0.453	**1**	
	Female	64 (36.6)	57 (40.7)		0.656 (0.32 - 1.33)	0.243
Age group	18 – 29	71 (40.6)	39 (27.9)	**0.002**	**1**	
	30 – 39	45 (25.7)	23 (16.4)		2.235 (0.86 - 5.83)	0.100
	40 – 49	22 (12.6)	29 (20.7)		1.297 (0.43 - 3.96)	0.648
	≥ 50	37 (21.1)	49 (35.0)		0.408 (0.14 - 1.18)	0.099
Education Groups	Uneducated	55 (31.4)	34 (24.3)	0.152	**1**	
	Educated	119 (68.0)	106 (75.7)		0.627 (0.30 - 1.33)	0.223
Ethnicity	Saudi	37 (21.1)	73 (52.1)	**< 0.001**	**1**	
	Non-Saudi	138 (78.9)	67 (47.9)		3.565 (1.83 - 6.97)	**< 0.001**
Marital status	Single	58 (33.1)	33 (23.6)	**< 0.001**	**1**	
	Married	117 (66.9)	107 (76.4)		0.974 (0.41 - 2.32)	0.953
T2DM	No	124 (71.0)	101 (72.1)	0.801	**1**	
	Yes	51 (29.0)	39 (27.9)		2.950 (1.31 - 6.62)	**0.009**
Participant self-rating the diet quality	Good	10 (5.7)	76 (54.3)	**< 0.001**	**1**	
	Fair	117 (66.9)	53 (37.9)		12.944 (5.60 - 29.93)	**< 0.001**
	Poor	48 (27.4)	11 (7.9)		33.625 (10.75 - 105.20)	**< 0.001**
Fast food consumption	0 - 1/Month	40 (22.9)	52 (37.1)	**0.018**	**1**	
	2 - 3/Month	43 (24.6)	21 (15.0)		2.655 (1.00 - 7.04)	**0.050**

	1 - 2/Week	47 (26.9)	31 (22.1)		2.468 (0.03 - 5.93)	**0.043**
	3 - 4/Week	20 (11.4)	22 (15.7)		0.490 (0.18 - 1.34)	0.166
	≥ 5 /Week	25 (14.3)	14 (10.0)		1.027 (0.36 - 2.91)	0.960
BMI* groups	≤ 18.4	38 (21.7)	10 (7.1)		**1**	
	18.5 - 24.9	85 (48.6)	41 (29.3)	**< 0.001**	0.627 (0.23 - 1.73)	0.367
	25 - 29.9	32 (18.3)	46 (32.6)		0.307 (0.09 - 1.00)	0.050
	≥ 30	20 (11.4)	43 (30.7)		0.190 (0.05 - 0.70)	**0.012**
Total cholesterol (mg/dL)	< 150	27 (15.4)	31 (22.1)		**1**	
	≥ 150	148 (84.6)	109 (77.9)		3.035 (1.34 - 6.87)	**0.008**
HDL* Cholesterol (mg/dL)	Optimal	115 (65.7)	64 (45.7)	**< 0.001**	**1**	
	Risky	60 (34.3)	76 (54.3)		0.400 (0.21 - 0.76)	**0.005**
Constant					0.090	0.005

*****AOR = Adjusted Odds Ratio, *BMI = Body Mass index, *****FPG = Fasting plasma glucose, *****HbA1c = Glycated haemoglobin, *HDL = High-density lipoprotein.

Table 18. Logistic regression model for factors predicting TB including metabolic syndrome.

Variables N = 315		Univariate			Multivariate	
		Cases n = 175 (%)	Controls n = 140 (%)	*p*	AOR* (95% CI)	*p*
Sex	Male	111 (63.4)	83 (59.3)	0.453	**1**	
	Female	64 (36.6)	57 (40.7)		0.627 (0.32 - 1.25)	0.183
Age group	18 – 29	71 (40.6)	39 (27.9)	**0.002**	**1**	
	30 – 39	45 (25.7)	23 (16.4)		2.332 (0.91 - 5.95)	0.076
	40 – 49	22 (12.6)	29 (20.7)		1.480 (0.50 - 4.40)	0.480
	≥ 50	37 (21.1)	49 (35.0)		0.693 (0.25 - 1.92)	0.481
Education Groups	Uneducated	55 (31.4)	34 (24.3)	0.152	**1**	
	Educated	119 (68.0)	106 (75.7)		0.666 (0.32 - 1.38)	0.271
Ethnicity	Saudi	37 (21.1)	73 (52.1)	**< 0.001**	**1**	
	Non-Saudi	138 (78.9)	67 (47.9)		3.448 (1.81 - 6.58)	**< 0.001**
Marital status	Single	58 (33.1)	33 (23.6)	**< 0.001**	**1**	
	Married	117 (66.9)	107 (76.4)		1.054 (0.46 - 2.44)	0.902
Metabolic syndrome	No	130 (74.3)	72 (51.4)	**< 0.001**	**1**	
	Yes	45 (25.7)	68 (48.6)		0.881 (0.42 - 1.86)	0.741
Participant self-rating the diet quality	Good	10 (5.7)	76 (54.3)	**< 0.001**	**1**	
	Fair	117 (66.9)	53 (37.9)		12.893 (5.71 - 29.11)	**< 0.001**
	Poor	48 (27.4)	11 (7.9)		30.197 (10.10 - 90.29)	**< 0.001**
Fast food consumption	0 - 1/Month	40 (22.9)	52 (37.1)	**0.018**	**1**	
	2 - 3/Month	43 (24.6)	21 (15.0)		2.072 (0.89 - 4.81)	0.090

	1 - 2/Week	47 (26.9)	31 (22.1)		2.355 (0.92 - 6.06)	0.076
	3 - 4/Week	20 (11.4)	22 (15.7)		0.537 (0.20 - 1.45)	0.218
	≥ 5 /Week	25 (14.3)	14 (10.0)		0.920 (0.33 - 2.53)	0.871
BMI* groups	≤ 18.4	38 (21.7)	10 (7.1)		**1**	
	18.5 - 24.9	85 (48.6)	41 (29.3)	**< 0.001**	0.632 (0.24 - 1.70)	0.362
	25 - 29.9	32 (18.3)	46 (32.6)		0.320 (0.10 - 1.02)	0.054
	≥ 30	20 (11.4)	43 (30.7)		0.224 (0.06 - 0.81)	**0.022**
Total cholesterol (mg/dL)	< 150	27 (15.4)	31 (22.1)		**1**	
	≥ 150	148 (84.6)	109 (77.9)		3.382 (1.55 - 7.40)	**0.002**
Constant					0.064	0.001

3.3. Comparison of TB cases with and without IR and T2DM

We conducted a sub-analysis for (a) normoglycemic TB cases without IR; (b) euglycemic TB cases with IR and (c) TB cases with T2DM to determine factors among TB cases independently associated with T2DM and IR. Independent variables for these analyses were chosen based on the literature of risk factors for T2DM. We will call normoglycemic TB cases without IR as 'TB-controls' (n= 97) and euglycemic TB cases with IR as 'TB-IR' (n=29) and the 49 diabetic TB cases as 'TB-diabetic'.

The demographic characteristics of TB-diabetic and TB-IR cases and TB-controls are shown in table 19. Among TB-diabetic cases, 40 (81.6%) were male and nine (18.4%) female compared to 57 (58.8%) and 40 (41.2%) TB-controls, respectively ($p = 0.006$) (figure 11). TB-diabetic cases were older than TB-controls (figure 12), with median age of 49 and 27 years, respectively ($p < 0.001$), were more likely to be married (39, 79.6% versus 52, 53.6%, respectively, $p < 0.001$) and to work in the private sector (16, 32.7% versus 13, 13.4%) or as manual workers (15, 30.6% versus 26, 26.8%) ($p = 0.017$). There were no significant differences between TB-IR cases and TB-controls. Given the small sample size we were unable to conduct a logistic regression analysis.

Table 19. Demographic characteristics of TB-IR cases, TB-diabetic cases and TB-controls.

Demographic characteristic N = 175		**TB-Controls n = 97 (%)**	**TB-IR n = 29 (%)**	***P***	**TB-T2DM n = 49 (%)**	***P***
Gender	Male	57 (58.8)	14 (48.3)	0.318	40 (81.6)	**0.006**
	Female	40 (41.2)	15 (51.7)		9 (18.4)	
Age	Min-Max	18 – 70	18 – 58	0.866	21 – 78	**< 0.001**
	Median (IQR)	27 (23 - 37)	30 (21 - 40)		49 (39 - 55)	
Age groups	18-29	55 (56.7)	14 (48.3)	0.388	2 (4.1)	**< 0.001**
	30-39	26 (26.8)	8 (27.6)		11 (22.4)	
	40-49	6 (6.2)	4 (13.8)		12 (24.5)	
	50+	10 (10.3)	3 (10.3)		24 (49.0)	
Marital status	Single	41 (42.3)	13 (44.8)	0.807	4 (8.2)	**< 0.001**
	With partner/married	52 (53.6)	14 (48.3)		39 (79.6)	
	Divorced/separated	4 (4.1)	2 (6.9)		5 (10.2)	
	Widowed	0 (0.0)	0 (0.0)		1 (2.0)	
Education	No education	7 (7.2)	1 (3.4)	0.166	11 (22.4)	0.495
	Literacy education	20 (20.6)	11 (37.9)		5 (10.2)	
	Primary education	23 (23.7)	7 (24.1)		17 (34.7)	
	Intermediate education	11 (11.3)	1 (3.4)		1 (2.0)	
	Secondary education	21 (21.6)	3 (10.3)		9 (18.4)	
	Higher education	15 (15.5)	6 (20.7)		5 (10.2)	
	Prefer not to answer	0 (0.0)	0 (0.0)		1 (2.0)	
Occupation	Governmental	6 (6.2)	1 (3.4)	0.421	2 (4.1)	**0.017**

	Private	13 (13.4)	5 (17.2)		16 (32.7)	
	Labourer	26 (26.8)	5 (17.2)		15 (30.6)	
	Not employed	47 (48.5)	18 (62.1)		15 (30.6)	
	Retired	1 (1.0)	0 (0.0)		0 (0.0)	
	Other	4 (4.1)	0 (0.0)		1 (2.0)	
Ethnicity Groups	Saudi	25 (25.8)	4 (13.8)	0.179	8 (16.3)	0.198
	Non-Saudi	72 (74.2)	25 (86.2)		41 (83.7)	

Figure 11. Gender of TB-diabetic and TB-controls

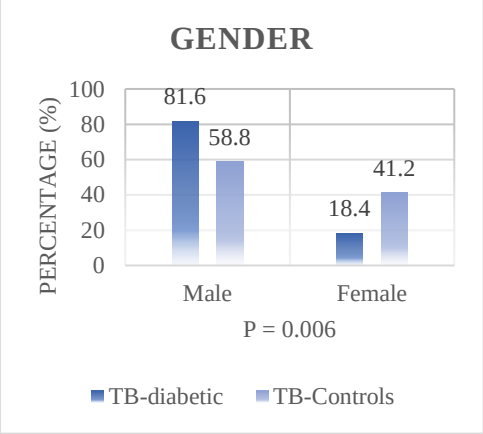
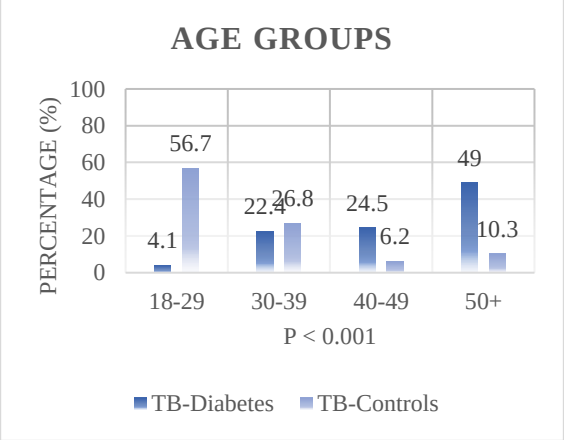


Figure 12. Age groups of TB-diabetic and TB-controls



The medical histories of TB-diabetic and TB-IR cases and TB-controls are shown in table 20. TB-diabetic cases were more likely to have hyperlipidaemia than TB-controls (6, 12.2% versus 1, 1.0%, p = 0.009) and to take lipid lowering therapy (4, 8.2% versus 0, 0.0%, respectively) (p = 0.008). TB-IR cases in turn had a higher prevalence of heart problems than TB-controls (2, 6.9% versus 0, 0.0%, p = 0.039) (figure 13). Given the small sample sizes we were unable to conduct a logistic regression analysis.

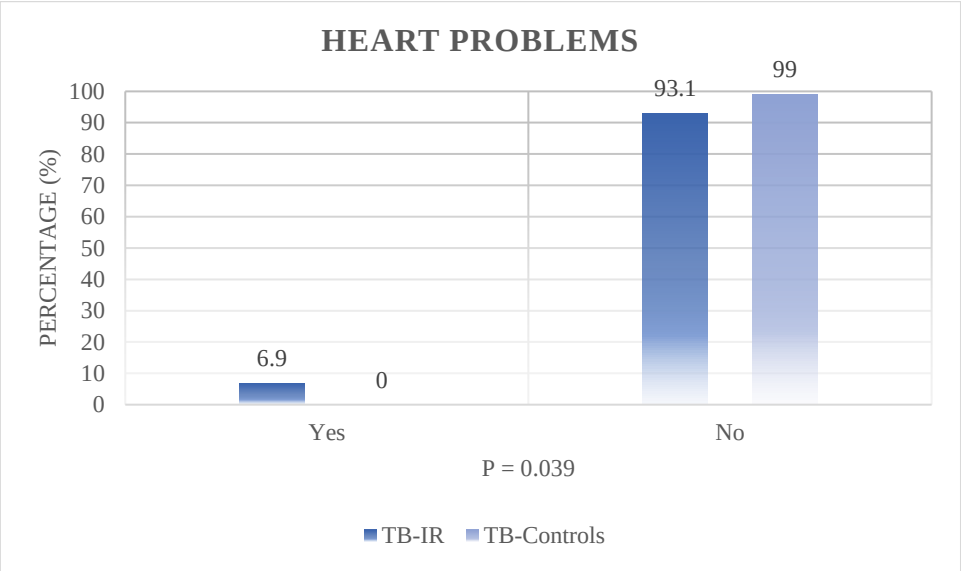
Table 20. Medical history of TB-IR cases, TB-diabetic cases and TB-controls.

Medical history **N = 175**			**TB-Controls** **n = 97 (%)**	**TB-IR** **n = 29 (%)**	***P***	**TB-T2DM** **n = 49 (%)**	***P***
Family history of diabetes	Yes		25 (25.8)	9 (31.0)	0.575	18 (36.7)	0.170
	No		72 (74.2)	20 (69.0)		31 (63.3)	
	1st degree	Yes	23 (23.7)	9 (31.0)	0.427	16 (32.7)	0.249
		No	74 (76.3)	20 (69.0)		33 (67.3)	
	2nd degree	Yes	4 (4.1)	0 (0.0)	0.573	2 (4.1)	1
		No	93 (95.9)	29 (100.0)		47 (95.9)	
	3rd degree	Yes	0 (0.0)	0 (0.0)	ND*	1 (2.0)	0.336
		No	97 (100.0)	29 (100.0)		48 (98.0)	
Hypertension	Yes		3 (3.1)	2 (6.9)	0.413	4 (8.2)	0.193
	No		92 (94.8)	27 (93.1)		45 (91.8)	
	Don’t know		2 (2.1)	0 (0.0)		0 (0.0)	
Takes hypertensive medication	Yes		3 (3.1)	1 (3.4)	1	4 (8.2)	0.224
	No		94 (96.9)	28 (96.6)		45 (91.8)	
Hyperlipidaemia	Yes		1 (1.0)	1 (3.4)	0.489	6 (12.2)	**0.009**
	No		95 (97.9)	27 (93.1)		43 (87.8)	
	Don’t know		1 (1.0)	1 (3.4)		0 (0.0)	
Takes lipid lowering therapy	Yes		0 (0.0)	1 (3.4)	0.176	4 (8.2)	**0.008**
	No		96 (99.0)	28 (96.6)		45 (91.8)	
	Don’t know		1 (1.0)	0 (0.0)		0 (0.0)	
Heart problems	Yes		0 (0.0)	2 (6.9)	**0.039**	1 (2.0)	0.223

	No	96 (99.0)	27 (93.1)		48 (98.0)	
	Don’t know	1 (1.0)	0 (0.0)		0 (0.0)	
History of gestational diabetes	Yes	1 (1.0)	2 (6.9)	0.183	2 (4.1)	0.086
	No	38 (39.2)	13 (44.8)		7 (14.3)	
History of polycystic ovaries	Yes	0 (0.0)	0 (0.0)		0 (0.0)	
	No	39 (40.2)	15 (51.7)	ND*****	9 (18.4)	ND*****
	Don’t know	1 (1.0)	0 (0.0)		0 (0.0)	

*ND = Not defined

Figure 13. Proportion of TB-IR and TB-controls with heart problems



The lifestyle and diet of TB-diabetic and TB-IR cases and TB-controls are shown in table 21. The proportion of TB-diabetic cases with a poor diet was lower (10, 20.4%) than among TB-controls (32, 33.0%) with TB-diabetic cases being more likely to rate their diet as good (5, 10.2%) than TB-controls (2, 2.1%) (p = 0.046). TB-diabetic cases were more likely to have a sedentary job (34, 69.4) than TB-controls (66, 68.0%) (p = 0.029). With regards to IR cases, the proportion of TB-IR cases with a history of overweight during childhood was higher than among TB-controls (4, 13.8% versus 7, 7.2%, respectively, p = 0.039) (figure 14). Given the small sample size we were unable to conduct a logistic regression analysis.

Table 21. Lifestyle and diet of TB-IR cases, TB-diabetic cases and TB-controls.

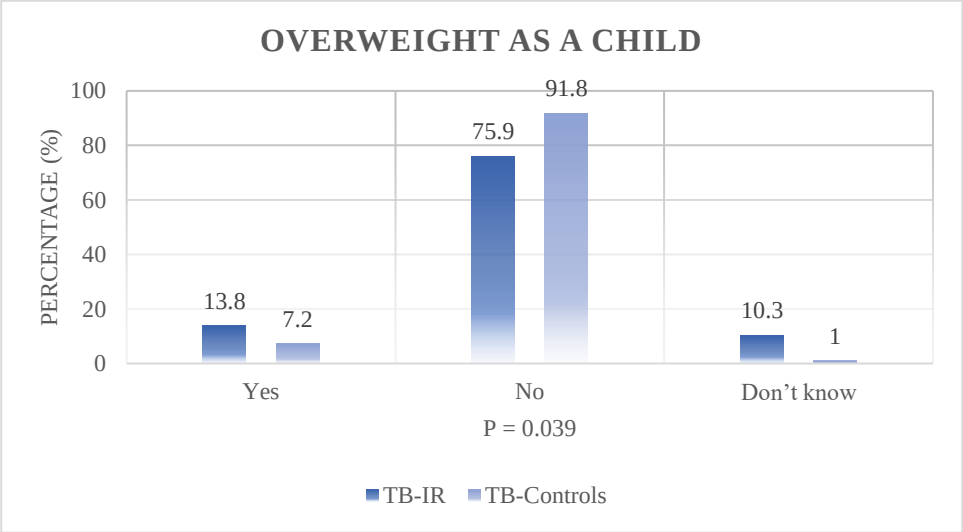
Life style and diet N = 175			**TB-Controls n = 97 (%)**	**TB-IR n = 29 (%)**	***P***	**TB-T2DM n = 49 (%)**	***P***
Type of job	Sedentary		66 (68.0)	24 (82.8)	0.110	34 (69.4)	0.029
	Moderate Physical Activity		27 (27.8)	3 (10.3)		13 (26.5)	
	Physically Very Demanding		4 (4.1)	2 (6.9)		2 (4.1)	
Monthly income (SAR)	≤ 3000		75 (77.3)	26 (89.7)	0.220	38 (77.6)	0.149
	3000 - 5000		19 (19.6)	2 (6.9)		10 (20.4)	
	5001 - 10000		3 (3.1)	1 (3.4)		1 (2.0)	
	≥ 10000		0 (0.0)	0 (0.0)		0 (0.0)	
Level of stress	Low		70 (72.2)	22 (75.9)	0.920	38 (77.6)	0.757
	Medium		16 (16.5)	4 (13.8)		6 (12.2)	
	High		11 (11.3)	3 (10.3)		5 (10.2)	
Overweight among family	Yes		14 (14.4)	6 (20.7)	0.400	5 (10.2)	0.263
	No		83 (85.6)	6 (20.7)		43 (87.8)	
	Don’t know		0 (0.0)	23 (79.3)		1 (2.0)	
	Prefer not to say		0 (0.0)	0 (0.0)		0 (0.0)	
If yes, who?	Father	Yes	3 (3.1)	0 (0.0)	1.000	1 (2.0)	1.000
		No	94 (96.9)	29 (100.0)		48 (98.0)	
	Mother	Yes	9 (9.3)	4 (13.8)	0.494	3 (6.1)	0.751
		No	88 (90.7)	25 (86.2)		46 (93.9)	

	Sibling	Yes	5 (5.2)	1 (3.4)	1.000	1 (2.0)	0.664
		No	92 (94.8)	28 (96.6)		48 (98.0)	
	Grandfather	Yes	0 (0.0)	0 (0.0)	ND*	0 (0.0)	ND*
		No	97 (100.0)	29 (100.0)		49 (100.0)	
	Other	Yes	2 (2.1)	2 (6.9)	0.227	3 (6.1)	0.335
		No	95 (97.9)	27 (93.1)		46 (93.9)	
Overweight as a child	Yes		7 (7.2)	4 (13.8)	**0.039**	7 (14.3)	0.355
	No		89 (91.8)	22 (75.9)		41 (83.7)	
	Don't know		1 (1.0)	3 (10.3)		1 (2.0)	
Number of breakfast meals last week	Never		6 (6.2)	0 (0.0)	0.153	0 (0.0)	0.258
	1 - 6		16 (16.5)	6 (20.7)		5 (10.2)	
	Always		75 (77.3)	23 (79.3)		44 (89.8)	
Number of lunch meals last week	Never		1 (1.0)	0 (0.0)	0.524	0 (0.0)	0.150
	1 - 6		12 (12.6)	3 (10.3)		1 (2.0)	
	Always		84 (86.6)	26 (89.7)		48 (98.0)	
Number of dinner meals last week	Never		0 (0.0)	0 (0.0)	0.480	0 (0.0)	0.389
	1 - 6		13 (13.4)	2 (6.9)		1 (4.1)	
	Always		84 (86.6)	27 (93.1)		47 (95.9)	
Participant rating of his/her diet	Good		2 (2.1)	3 (10.3)	0.111	5 (10.2)	**0.046**
	Fair		63 (64.9)	20 (69.0)		34 (69.4)	
	Poor		32 (33.0)	6 (20.7)		10 (20.4)	
Fast food consumption	0 - 1 Times/Month		22 (22.7)	7 (24.1)	0.431	11 (22.4)	0.954
	2 - 3 Times/Month		25 (25.8)	9 (31.0)		13 (26.5)	
	1 - 2 Times/Week		23 (23.7)	9 (31.0)		11 (22.4)	
	3 - 4 Times/Week		10 (10.3)	3 (10.3)		7 (14.3)	

	≥ 5 Times/Week	17 (17.5)	1 (3.4)		7 (14.3)	
Food portions description	Small	14 (14.4)	4 (13.8)		5 (10.2)	
	Intermediate	60 (61.9)	17 (58.6)	0.914	34 (69.4)	0.640
	Large	23 (23.7)	8 (27.6)		10 (20.4)	

*ND = Not defined

Figure 14. Proportion of TB-IR cases and TB-controls with childhood overweight



The anthropometry of male TB-diabetic and TB-IR cases and TB-controls are shown in table 22. Male TB-diabetic cases were shorter than male TB-controls with medians of 169 and 172 cms, respectively, and a median difference of 3 cms (p = 0.012). The median BMI was 24 for male TB-diabetic cases compared to 20 for male TB-controls, with a median difference of 4 (p = 0.006). Male TB-diabetic cases, therefore, were more likely to be obese than male TB-controls (7, 18% versus 4, 7%, respectively, p = 0.019), to have a higher median waist circumference, with a median difference of 9 cms (p = 0.002). Moreover, male TB-diabetic cases had higher median WHR than male TB-controls with median difference of 0.08 and were more likely to have high WHR (2, 5.0% versus 2, 3.5%, respectively) (p < 0.001). Male TB-IR cases in turn had higher median weight than male TB-controls (74 and 59 Kgs, respectively) with a median difference of 15 Kgs (p = 0.028) and were less likely to have high WHR than among male TB-controls (0, 0.0% versus 2, 3.5%, respectively, p = 0.010). Given the small sample size we were unable to conduct a logistic regression analysis.

Table 22. Male anthropometry of TB-IR cases, TB-diabetic cases and TB-controls.

Anthropometry (Male) N = 111		**TB-Controls n = 57 (%)**	**TB-IR n = 14 (%)**	***p***	**TB-T2DM n = 40 (%)**	***p***
Height (cm)	Median (IQR)	172 (169 -179)	175 (168 -184)	0.336	169 (163 -174)	**0.012**
Weight (kg)	Median (IQR)	59 (55 -71)	74 (59 -86)	**0.028**	68 (57 -79)	0.067
BMI (kg/m2)	Median (IQR)	20 (18 -23)	24 (19 -26)	0.191	24 (20 -27)	**0.006**
BMI groups	≤ 18.4	15 (26)	3 (21)	0.817	4 (10)	**0.019**
	18.5 - 24.9	32 (56)	7 (50)		18 (45)	
	25 - 29.9	6 (11)	2 (14)		11 (28)	
	≥ 30	4 (7)	2 (14)		7 (18)	
Waist (cm)	Median (IQR)	80 (75 -88)	91 (77 -98)	0.059	89 (81 -97)	**0.002**
Hip (cm)	Median (IQR)	94 (91 -101)	101 (94 -107)	0.106	97 (90 -102)	0.741
WHR	Median (IQR)	0.84 (0.79 -0.88)	0.90 (0.81 -0.94)	0.077	0.92 (0.86 -0.94)	**< 0.001**
WHR groups	Low	48 (84.2)	7 (50.0)	**0.010**	15 (37.5)	**< 0.001**
	Moderate	7 (12.3)	7 (50.0)		23 (57.5)	
	High	2 (3.5)	0 (0.0)		2 (5.0)	

The anthropometric data of female TB-diabetic and TB-IR cases and TB-controls are shown in table 23. The median BMI for female TB-IR cases was 24 compared to 20 for female TB-controls, with a median difference of 4 ($p = 0.036$). On the other hand, female TB-diabetic cases had a higher weight than female TB-controls with medians of 72 and 53 Kgs and a median difference of 19 Kgs ($p < 0.001$). The median BMI for female TB-diabetic cases was 30 compared to 20 for female TB-controls, with median difference of 10. Female TB-diabetic cases, therefore, were much more likely to be obese than TB-controls (5, 56% versus 1, 3%, respectively), to have a higher median waist circumference with a median difference of 20 cms and higher hip circumference than female TB-controls with a median difference of 18 cms ($p < 0.001$). Given the small sample size we were unable to conduct a logistic regression analysis.

Table 23. Female anthropometry of TB-IR cases, TB-diabetic cases and TB-controls.

Anthropometry (Female) N = 64		**TB-controls n = 40 (%)**	**TB-IR n = 15 (%)**	***p***	**TB-T2DM n = 9 (%)**	***p***
Height (cm)	Median (IQR)	160 (156 -164)	159 (155 -161)	0.514	158 (153 -164)	0.550
Weight (kg)	Median (IQR)	53 (46 -61)	61 (46 -72)	0.053	72 (62 -88)	**< 0.001**
BMI* (kg/m2)	Median (IQR)	20 (18 -23)	24 (19 -27)	**0.036**	30 (24 -33)	**< 0.001**
BMI groups	≤ 18.4	15 (38)	1 (7)	0.074	0 (0)	**< 0.001**
	18.5 - 24.9	18 (45)	8 (53)		2 (22)	
	25 - 29.9	6 (15)	5 (33)		2 (22)	
	≥ 30	1 (3)	1 (7)		5 (56)	
Waist (cm)	Median (IQR)	74 (67 -84)	78 (65 -91)	0.583	94 (79 -102)	**< 0.001**
Hip (cm)	Median (IQR)	92 (83 -99)	95 (80 -110)	0.264	110 (97 -118)	**< 0.001**
WHR	Median (IQR)	0.83 (0.76 -0.91)	0.80 (0.77 -0.87)	0.502	0.85 (0.82 -0.91)	0.352
WHR groups	Low	17 (42.5)	8 (53.3)	0.502	2 (22.2)	0.366
	Moderate	13 (32.5)	4 (26.7)		4 (44.4)	
	High	10 (25.0)	3 (20.0)		3 (33.3)	

The metabolic characteristics TB-diabetic and TB-IR cases TB-controls are shown in table 24. TB-diabetic cases had higher median total cholesterol than TB-controls (216 versus 183 mg/dL, respectively) with a median difference of 33 mg/dL ($p < 0.001$). TB-diabetic cases also had higher median triglycerides than TB-controls (117 versus 77 mg/dL, respectively) with a median difference of 40 mg/dL ($p < 0.001$); and a higher proportion were classified as having high triglycerides (5, 10.2% versus 1, 1.0%, respectively, $p = 0.014$) (figure 15). Moreover, TB-diabetic cases had a higher median LDL Cholesterol (137 versus 112 mg/dL, respectively, $p = 0.001$) and were more likely to be classified as having high LDL Cholesterol than TB-controls (41, 83.7% versus 63, 64.9%, respectively, $p = 0.018$) (figure 16). Regarding cases with IR, a higher proportion of TB-IR cases had high total cholesterol than TB-controls (96.6% versus 79.4%, respectively, $p = 0.043$) (figure 17). Given the small sample size we were unable to conduct a logistic regression analysis.

Table 24. Metabolic characteristics of TB-IR cases, TB-diabetic cases and TB-controls.

Metabolic characteristic N = 175		**TB-Controls n = 97 (%)**	**TB-IR n = 29 (%)**	***P***	**TB-T2DM n = 49 (%)**	***P***
Total cholesterol (mg/dL)	Min - Max	70 - 333	141 - 302	0.073	92 - 296	**< 0.001**
	Median (IQR)	183 (157.5 - 206)	188 (179 - 213.5)		216 (181 - 242)	
	Optimal	20 (20.6)	1 (3.4)	**0.043**	6 (12.2)	0.212
	High	77 (79.4)	28 (96.6)		43 (87.8)	
Triglycerides (mg/dL)	Min - Max	24 - 214	39 - 252	0.208	60 - 999	**< 0.001**
	Median (IQR)	77 (61.5 - 111)	94 (68.5 - 123.5)		117 (92 - 156.5)	
	Optimal	85 (87.6)	26 (89.7)	0.111	35 (71.4)	**0.014**
	Border line	11 (11.3)	1 (3.4)		9 (18.4)	
	High	1 (1.0)	2 (6.9)		5 (10.2)	
HDL Cholesterol (mg/dL)	Min - Max	10.6 - 99.9	32.0 - 89.0	0.070	6.0 - 95.0	0.185
	Median (IQR)	49 (38 - 60)	55 (45 - 64.5)		43 (34.5 - 58)	
	Optimal Male ≥ 40 Female ≥ 50	62 (63.9)	23 (79.3)	0.121	30 (61.2)	0.750
	Risky Male < 40 Female < 50	35 (36.1)	6 (20.7)		19 (38.8)	
LDL Cholesterol (mg/dL)	Min-Max	6.3 - 245.8	70.0 - 207.0	0.432	47.0 - 211.0	**0.001**
	Median (IQR)	112 (91 - 132.5)	112 (100.5 - 133.5)		137 (112.5 - 162.2)	
	Optimal	34 (35.1)	6 (20.7)	0.145	8 (16.3)	**0.018**
	High	63 (64.9)	23 (79.3)		41 (83.7)	

Figure 15. Triglycerides of TB-diabetic cases and TB-controls

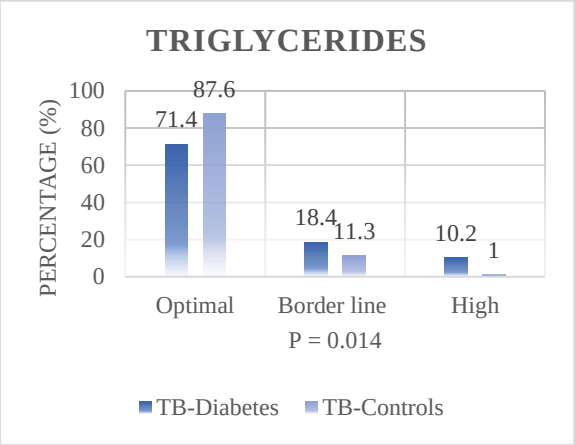


Figure 16. LDL Cholesterol of TB-diabetic cases and TB-controls

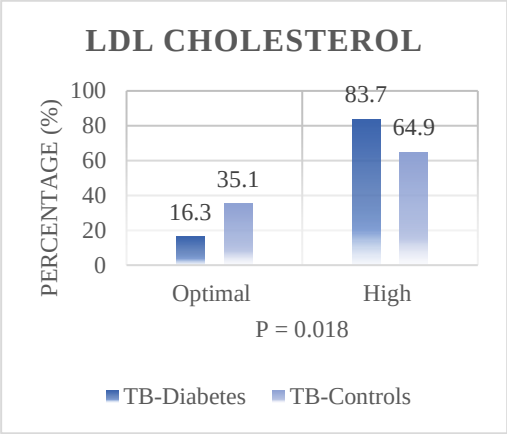
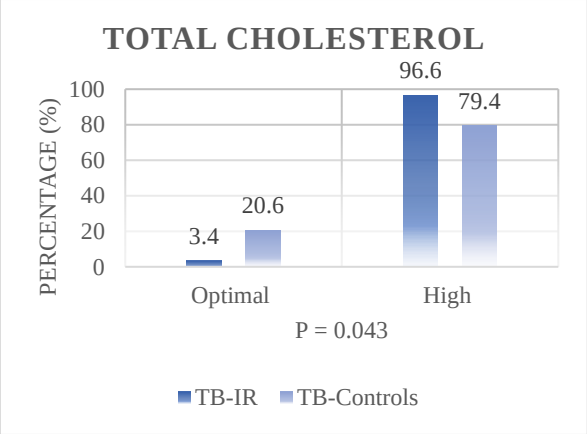


Figure 17. Total cholesterol of TB-IR cases and TB-controls



The symptoms of TB, X-Ray findings and TB severity score of TB-diabetic and TB-IR cases and TB-controls are shown in table 25. There were no statistical differences between the three groups, except for TB-diabetic cases being more likely to have blood in sputum than TB-controls (15, 30.6% versus 16, 16.5%, respectively, p = 0.049). There were no statistical differences between the three groups regarding the TB score.

Table 25. TB symptoms, X-Ray and scoring of TB-IR cases, TB-diabetic cases and TB-controls.

TB symptoms, x-Ray and scoring N=175		TB-Controls n = 97 (%)	TB-IR n = 29 (%)	*P*	TB-T2DM n = 49 (%)	*P*
Chest Pain		69 (71.1)	22 (75.9)	0.618	32 (65.3)	0.471
Sputum		92 (94.8)	27 (93.1)	0.661	45 (91.8)	0.484
Cough		94 (96.9)	29 (100.0)	1	48 (98.0)	1
Sputum with blood		16 (16.5)	6 (20.7)	0.602	15 (30.6)	**0.049**
Shortness of breath		39 (40.2)	14 (48.3)	0.440	26 (53.1)	0.140
Fever		93 (95.9)	29 (100.0)	0.573	48 (98.0)	0.664
Night sweats		85 (87.6)	22 (75.9)	0.142	44 (89.8)	0.700
Poor Appetite		86 (88.7)	24 (82.8)	0.524	43 (87.8)	0.872
Weight loss		92 (94.8)	26 (89.7)	0.384	45 (91.8)	0.484
TB Culture	Positive	43 (13.4)	12 (27.6)	0.178	30 (6.1)	0.122
	Negative	13 (44.3)	8 (41.4)		3 (61.2)	
	Not done	41 (42.3)	9 (31.0)		16 (32.7)	
AFB Smear	Positive	75 (77.3)	19 (65.5)	0.311	39 (79.6)	0.650
	Negative	21 (21.6)	10 (34.5)		10 (20.4)	
	Not done	1 (1.0)	0 (0.0)		0 (0.0)	
Chest x-Ray Cavitation	Positive	55 (56.7)	13 (44.8)	0.196	30 (61.2)	0.838
	Negative	39 (40.2)	16 (55.2)		18 (36.7)	
	Not done	3 (3.1)	0 (0.0)		1 (2.0)	
TB score	Min-Max	2 - 9	3 - 9	0.412	3 - 9	0.435

	Median (IQR)		7 (6 - 8)	7 (6.5 - 8)		7 (6 - 8)	
	Group (1)	1 - 3	5 (5.2)	2 (6.9)	0.506	1 (2.0)	0.613
	Group (2)	4 - 6	27 (27.8)	5 (17.2)		13 (26.5)	
	Group (3)	7 - 9	65 (67.0)	22 (75.9)		35 (71.4)	
	Group (1+2)	1 - 6	32 (33.0)	7 (24.1)	0.365	14 (28.5)	0.587
	Group (3)	7 - 9	65 (67.0)	22 (75.9)		35 (71.4)	

4. Chapter 4 –CHD Results

4.1. Prevalence of T2DM and IR among patients with CHD and IR as a risk factor for CHD

We performed a second case control study from November 2016 to June 2017 to describe the prevalence of T2DM and IR among patients with CHD and if IR is a risk factor for CHD, as described in the methods chapter. We included 325 patients ≥18 years old with a former diagnosis of CHD registered at the King Faisal Hospital in Taif city who were classified to have stable CHD by the time of the study. Participants with stable CHD will be called 'cases' for this sub-study. Cases were compared to 138 controls, with no history of CHD (same controls recruited at the TB and Chest Diseases Centre in Jeddah city), as described in chapter 3. These participants will be called 'controls' for this chapter. All participants signed a written informed consent before the interview and examination.

The demographic characteristics of all participants are shown in table 26. The age of cases and controls ranged from 37 to 98 years and from 18 to 76 years, respectively. Cases were older than controls with medians of 62 and 40 years, respectively, and a median difference of 22 years ($p < 0.001$). Two hundred thirty (70.8%) cases were male and 95 (29.2%) female, whereas 83 (60.1%) and 55 (39.9%) controls were male and female, respectively, ($p = 0.025$).

Cases were less likely to be single (29, 8.9%) than controls (33, 23.9%) ($p < 0.001$) and more likely to have primary education (122, 37.5% and 21, 15.2%, respectively), but less likely to have intermediate (22, 6.8%) and secondary education (57, 17.5%) than controls (31, 22.5% and 36, 26.1%, respectively) ($p < 0.001$). Cases were more likely to work in the governmental sector (65, 20.0%) and to be retired (105, 32.3%)

than controls (19, 13.8% and 5, 3.6%, respectively) ($p < 0.001$). Controls were more likely to be manual workers (27, 19.6%) or to belong to the non-employed categories (72, 52.2%) than cases (9, 2.8% and 102, 31.4%, respectively) ($p < 0.001$). With regards to ethnicity, cases were more likely to be Saudi (283, 87.1%) than controls (71, 51.4%) ($p < 0.001$).

The medical history of cases and controls is shown in table 27. Participants were asked, about their diabetes status, history of hypertension, hyperlipidaemia, gestational diabetes or polycystic ovaries and whether they were taking medications for these conditions. There were clear differences between cases and controls in terms of history of diabetes, with 195 (60%) cases and 26 (18.8%) controls having a history of diabetes ($p < 0.001$). The proportion of diabetic cases using insulin were (74, 37.9% versus 1, 3.8%) of controls ($p = 0.001$) and the proportion of cases with a family history of diabetes were higher (206, 63.4%) than among controls (56, 40.6%) ($p < 0.001$); with a higher frequency among first degree (181, 55.7% versus 48, 34.8%, $p < 0.001$), second degree (81, 24.9% versus 7, 5.1%, $p < 0.001$) and third degree relatives (14, 4.3% versus 1, 0.7%, $p = 0.024$) than controls .

CHD cases also had a higher prevalence of hypertension than controls (252, 77.5% versus 29, 21%, respectively) and were more likely to be taking anti-hypertensive medications (278, 85.5% versus 21, 15.2%, respectively) ($p < 0.001$). Cases were more likely to have hyperlipidaemia (263, 80.9% versus 26, 18.8%) and to be taking lipid lowering therapy (270, 83.1% versus 15, 10.9%, respectively) ($p < 0.001$), to have experienced gestational diabetes (12, 3.7% versus 4, 2.9%, respectively, $p = 0.040$) and a history of polycystic ovaries (9, 2.8%) than controls (3, 2.2%) ($p = 0.022$).

Table 26. Demographic characteristics of cases and controls.

Demographic characteristics N = 463		Cases n = 325 (%)	Controls n = 138 (%)	*p*
Sex	Male	230 (70.8)	83 (60.1)	**0.025**
	Female	95 (29.2)	55 (39.9)	
Age	Min-Max	37 - 98	18 - 76	**< 0.001**
	Median (IQR)	62 (55 - 70)	40 (28 - 53)	
Age groups	18 – 39	2 (0.6)	61 (44.6)	**< 0.001**
	40 – 49	31 (9.5)	29 (21.0)	
	50 – 59	91 (28.0)	27 (19.6)	
	60 – 69	103 (31.7)	13 (9.4)	
	≥ 70	98 (30.2)	8 (5.8)	
Marital status	Single	29 (8.9)	33 (23.9)	**< 0.001**
	With partner/married	243 (74.8)	100 (72.5)	
	Divorced/separated	9 (2.8)	2 (1.4)	
	Widowed	44 (13.5)	3 (2.2)	
Education	No education	33 (10.2)	13 (9.4)	**< 0.001**
	Literacy	73 (22.5)	20 (14.5)	
	Primary education	122 (37.5)	21 (15.2)	
	Intermediate education	22 (6.8)	31 (22.5)	
	Secondary education	57 (17.5)	36 (26.1)	
	Higher education	18 (5.5)	17 (12.3)	
Occupation	Governmental	65 (20.0)	19 (13.8)	**< 0.001**
	Private	39 (12.0)	14 (10.1)	
	Labourer	9 (2.8)	27 (19.6)	
	Retired	105 (32.3)	5 (3.6)	
	Non-employed	102 (31.4)	72 (52.2)	
	Other	5 (1.5)	1 (0.7)	
Employed	Yes	113 (34.8)	60 (43.5)	0.076
	No	212 (65.2)	78 (56.5)	
Ethnicity	Saudi	283 (87.1)	71 (51.4)	**< 0.001**
	Non-Saudi	42 (12.9)	67 (48.6)	

Table 27. Medical history of cases and controls.

Medical history N = 463			Cases n = 325 (%)	Controls n = 138 (%)	*p*
T2DM	Yes		195 (60.0)	26 (18.8)	**< 0.001**
	No		127 (39.1)	107 (77.5)	
	Don't know		3 (0.9)	5 (3.6)	
T2DM using insulin	Yes		74 (37.9)	1 (3.8)	**0.001**
	No		121 (62.1)	25 (96.2)	
Family history of diabetes	Yes		206 (63.4)	56 (40.6)	**< 0.001**
	No		119 (36.6)	82 (59.4)	
	1st degree	Yes	181 (55.7)	48 (34.8)	**< 0.001**
		No	144 (44.3)	90 (65.2)	
	2nd degree	Yes	81 (24.9)	7 (5.1)	**< 0.001**
		No	244 (75.1)	131 (94.9)	
	3rd degree	Yes	14 (4.3)	1 (0.7)	**0.024**
		No	311 (95.7)	137 (99.3)	
Hypertension	Yes		252 (77.5)	29 (21.0)	**< 0.001**
	No		71 (21.8)	106 (76.8)	
	Don’t know		2 (0.6)	3 (2.2)	
Takes hypertensive medication	Yes		278 (85.5)	21 (15.2)	**< 0.001**
	No		47 (14.5)	117 (84.8)	
Hyperlipidaemia	Yes		263 (80.9)	26 (18.8)	**< 0.001**
	No		48 (14.8)	103 (74.6)	
	Don’t know		14 (4.3)	9 (6.5)	
Takes lipid lowering therapy	Yes		270 (83.1)	15 (10.9)	**< 0.001**
	No		52 (16.0)	120 (87.0)	
	Don’t know		3 (0.9)	3 (2.2)	
History of gestational diabetes	Yes		12 (3.7)	4 (2.9)	**0.040**
	No		80 (24.6)	51 (37.0)	
	Don’t know		2 (0.6)	0 (0.0)	
	Not applicable		231 (71.1)	83 (60.1)	
History of polycystic ovaries	Yes		9 (2.8)	3 (2.2)	**0.022**
	No		85 (26.2)	48 (34.8)	
	Don’t know		1 (0.3)	4 (2.9)	
	Not applicable		230 (70.8)	83 (60.1)	

The lifestyle and diet of cases and controls is shown in table 28. The proportion of participants having sedentary occupations was higher among cases (307, 94.5%) than controls (95, 68.8%) and their monthly income was < 3000 SAR in 141 (43.4%) cases compared to 92 (66.7%) controls ($p < 0.001$). Cases were more likely to report an elevated level of stress (21, 6.5%) than controls (3, 2.2%) ($p < 0.001$).

The proportion of participants who had a family history of overweight was higher among cases (113, 34.8%) than controls (28, 20.3%) ($p = 0.005$), with a higher frequency of overweight among siblings among cases (72, 22.2%) than controls (6, 4.3%) ($p < 0.001$) and to have been overweight during childhood (61, 18.8% versus 13, 9.4%, respectively, $p = 0.022$).

Cases were less likely to smoke (37, 11.4% versus 29, 21.0%, $p = 0.007$), with only 28 (8.6%) cases smoking 10 – 20 cigarettes per day compared to 29 (21.0%) of controls ($p < 0.001$), but more likely to be past smokers than controls (118, 36.3% versus 8, 5.8%, respectively, $p < 0.001$).

Cases were more likely to routinely have breakfast than controls (275, 84.6%, versus 101, 73.2%, respectively, $p = 0.001$) and to have a poor diet (83, 25.5% versus 11, 8.0%, respectively, $p < 0.001$). Cases were less likely to ate fast foods 3 - 4 times/week (19, 5.8%) and more than five times per week (16, 4.9%) than controls (22, 15.9% and 14, 10.1%, respectively) ($p < 0.001$). Cases indicated they consumed more frequently large food portions (103, 31.7%) than controls (35, 25.4%) ($p = 0.011$). There were no differences between cases and controls regarding the number of times they consumed lunch and dinner per week.

The level of physical activity of cases and controls is shown in table 29. Cases had lower physical activity than controls, with median number of days doing vigorous

activity of three and 4.5 days, respectively. Furthermore, with median number of days doing moderate activity were seven and 4.5 days for cases and controls, respectively. With a mean rank number of walking days per week of 239 for cases and 208 for controls ($p = 0.001$)

Table 28. Lifestyle and diet of cases and controls.

Lifestyle and diet N = 463			Cases n = 325 (%)	Controls n = 138 (%)	*p*
Type of job	Sedentary		307 (94.5)	95 (68.8)	**< 0.001**
	Moderate Physical Activity		16 (4.9)	38 (27.5)	
	Physically Very Demanding		2 (0.6)	5 (3.6)	
Monthly income (SAR)	≤ 3000		141 (43.4)	92 (66.7)	**< 0.001**
	3000 – 5000		105 (32.3)	34 (24.6)	
	5001 – 10000		54 (16.6)	9 (6.5)	
	≥ 10000		25 (7.7)	3 (2.2)	
Level of stress	Low		199 (61.2)	110 (79.7)	**< 0.001**
	Medium		105 (32.3)	25 (18.1)	
	High		21 (6.5)	3 (2.2)	
Overweight among family	Yes		113 (34.8)	28 (20.3)	**0.005**
	No		211 (64.9)	109 (79.0)	
	Don't know		1 (0.3)	0 (0.0)	
	Prefer not to say		0 (0.0)	1 (0.7)	
If yes, who?	Father	Yes	14 (4.3)	8 (5.8)	0.491
		No	311 (95.7)	130 (94.2)	
	Mother	Yes	24 (7.4)	8 (5.8)	0.538
		No	301 (92.6)	130 (94.2)	
	Sibling	Yes	72 (22.2)	6 (4.3)	**< 0.001**
		No	253 (77.8)	132 (95.7)	
	Grandfather	Yes	2 (0.6)	0 (0.0)	0.492
		No	323 (99.4)	138 (100.0)	
	Other	Yes	29 (8.9)	8 (5.8)	0.257
		No	296 (91.1)	130 (94.2)	
Overweight as a child	Yes		61 (18.8)	13 (9.4)	**0.022**
	No		259 (79.7)	124 (89.9)	
	Don't know		5 (1.5)	1 (0.7)	
Smoking	Yes		37 (11.4)	29 (21.0)	**0.007**
	No		288 (88.6)	109 (79.0)	
Cigarettes per day	10 per day	Yes	9 (2.8)	1 (0.7)	0.149
		No	316 (97.2)	137 (99.3)	
	10–20 per day	Yes	28 (8.6)	29 (21.0)	**< 0.001**

		No	297 (91.4)	109 (79.0)	
Past smoker	Yes		118 (36.3)	8 (5.8)	**< 0.001**
	No		207 (63.7)	130 (94.2)	
Number of breakfast meals last week	Never		18 (5.5)	5 (3.6)	**0.001**
	1 – 6		32 (9.8)	32 (23.2)	
	Always		275 (84.6)	101 (73.2)	
Number of lunch meals last week	Never		10 (3.1)	0 (0.0)	0.111
	1 – 6		25 (7.7)	10 (7.2)	
	Always		290 (89.2)	128 (92.8)	
Number of dinner meals last week	Never		4 (1.2)	2 (1.4)	0.062
	1 – 6		22 (6.8)	19 (13.8)	
	Always		299 (92.0)	117 (84.8)	
Participant rating of his/her diet	Good		22 (6.8)	73 (52.9)	**< 0.001**
	Fair		220 (67.7)	54 (39.1)	
	Poor		83 (25.5)	11 (8.0)	
Fast food consumption	0 - 1 Times/Month		172 (52.9)	51 (37.0)	**< 0.001**
	2 - 3 Times/Month		73 (22.5)	21 (15.2)	
	1 - 2 Times/Week		45 (13.8)	30 (21.7)	
	3 - 4 Times/Week		19 (5.8)	22 (15.9)	
	≥ 5 Times/Week		16 (4.9)	14 (10.1)	
Food portions description	Small		62 (19.1)	15 (10.9)	**0.011**
	Intermediate		160 (49.2)	88 (63.8)	
	Large		103 (31.7)	35 (25.4)	

Table 29: Physical activity of cases and controls.

Physical activity (days per week) N = 463	**Cases n = 325 (%) Median (IQR)**	**Mean rank**	**Controls n = 138 (%) Median (IQR)**	**Mean rank**	***p***
Vigorous activity	3 (1.5 - 6)	-	4.5 (2– ND*)	-	0.800
Moderate activity	7 (1 - 7)	-	4.5 (2 - 6)	-	0.423
Walking	7 (7 - 7)	239	7 (7 - 7)	208	**0.001**
Minutes walked/day	30 (20 - 55)	-	30 (20 - 60)	-	0.138

*ND = Not defined

The anthropometry data of all participants are shown in table 30. Male cases were shorter than male controls with medians of 167 and 170 cms, respectively, and a median difference of 3 cms ($p = 0.004$). Male cases had a higher weight than male controls with median of 77 Kgs versus 72 Kgs for male controls and a median difference of 5 Kgs ($p = 0.009$). Correspondingly, the median BMI was 28 for male cases compared to 26 for male controls and a median difference of 2 ($p < 0.001$). Male cases, therefore, were more likely to be classified as obese than controls (83, 36.1% versus 22, 26.5%, respectively, $p < 0.001$) and to have a higher median waist circumference, with a median difference of 14 cms. The median WHR of male cases (1.00) was higher than male controls (0.90) with a median difference of 0.10 ($p < 0.001$). Again, male cases were more likely to have a high WHR than male controls (128, 55.7% versus 6, 7.2%, respectively, $p < 0.001$)

Female cases were shorter than female controls with medians of 152 and 156 cms, respectively, and a median difference of 4 cms ($p = 0.001$). The median BMI was 31 for female cases and 28 for female controls, with a median difference of 3 ($p = 0.014$). Female cases, therefore, were more likely to be obese (55, 57.9% versus 20, 36.4%, respectively, $p = 0.008$), to have a higher median waist circumference than female controls, with a median difference of 16 cms ($p < 0.001$) and have a higher median hip circumference than female controls, with a median difference of 5 cms ($p = 0.032$). The median WHR of female cases 0.95 compared to 0.86 for female controls, with a median difference of 0.09 ($p < 0.001$). Furthermore, female cases were more likely to have high WHR than female controls (75, 78.9% versus 17, 30.9%, respectively, $p < 0.001$).

Table 30. Anthropometry of cases and controls.

Anthropometry N = 463		Male		*p*	Female		*p*
		Cases n = 230	Controls n = 83		Cases n = 95	Controls n = 55	
Height (cm)	Median (IQR)	167 (161 -171)	170 (163 -175)	**0.004**	152 (148 -156)	156 (152 -161)	**0.001**
Weight (kg)	Median (IQR)	77 (70 -90)	72 (65 -83)	**0.009**	75 (65 -83)	68 (59 -85)	0.156
BMI* (kg/m2)	Median (IQR)	28 (25 -31)	26 (22 -30)	**< 0.001**	31 (27 -36)	28 (24 -35)	**0.014**
BMI* groups	≤ 18.4	0 (0.0%)	7 (8.4%)	**< 0.001**	0 (0.0%)	3 (5.5%)	**0.008**
	18.5 - 24.9	56 (24.3%)	27 (32.5%)		14 (14.7%)	14 (25.5%)	
	25 - 29.9	91 (39.6%)	27 (32.5%)		26 (27.4%)	18 (32.7%)	
	≥ 30	83 (36.1%)	22 (26.5%)		55 (57.9%)	20 (36.4%)	
Waist (cm)	Median (IQR)	107 (99 -114)	93 (82 -104)	**< 0.001**	107 (96 -114)	91 (82 -101)	**< 0.001**
Hip (cm)	Median (IQR)	106 (100 -113)	103 (97 -110)	0.066	111 (102 -123)	106 (97 -115)	**0.032**
WHR*	Median (IQR)	1.00 (0.96 - 1.04)	0.90 (0.84 - 0.96)	**< 0.001**	0.95 (0.92 - 0.99)	0.86 (0.80 - 0.91)	**< 0.001**
WHR* groups	Low	10 (4.3%)	42 (50.6%)	**< 0.001**	3 (3.2%)	18 (32.7%)	**< 0.001**
	Moderate	92 (40.0%)	35 (42.2%)		17 (17.9%)	20 (36.4%)	
	High	128 (55.7%)	6 (7.2%)		75 (78.9%)	17 (30.9%)	

*BMI = Body Mass index, *WHR = Waist/Hip Ratio

The metabolic and clinical characteristics of all participants are shown in table 31. Cases had higher median FPG than controls (127 versus 94 mg/dL, respectively), with a higher proportion of cases being classified as having high FPG than controls (159, 51.3% versus 27, 15.2%, respectively) ($p < 0.001$). Cases also had higher HbA1c, with median of 6.9% compared to a median of 5.9% for controls ($p < 0.001$) and a higher proportion of cases had HbA1c levels ≥ 6.5% than controls (162, 55.7% versus 31, 22.5%, respectively, $p < 0.001$). Cases had higher median plasma insulin levels than controls (14.6 versus 11.25 μU/ml, respectively, $p = 0.002$) and higher median HOMA2-IR than controls (2 versus 1.5, respectively, $p < 0.001$) with a higher proportion of cases being classified as having HOMA2-IR ≥ 2 (131, 48.3% versus 42, 30.4%, respectively, $p = 0.001$).

The diabetic status of cases and controls is shown in table 32. The total number of diabetic patients was calculated as described in the previous chapter. There was a higher proportion of diabetic patients among cases (213, 65.5%, 95% CI 60.1 - 70.7%) than controls (38, 27.5%, 95% CI 20.3 - 35.8%) ($p < 0.001$) (figure 18). Cases with T2DM were also more likely to be using insulin (74, 34.7%, 95% CI 28.4 - 41.5%) than diabetic controls (1, 2.6%, 95% CI 0.1 - 13.8%) ($p < 0.001$) (figure 19).

Normoglycemic participants were classified according to whether they had IR using a HOMA2-IR cut-off of ≥ 2. Out of 325 cases, 112 had a normoglycemic status (34.5%, 95% CI 30.2 - 41.2%) compared to 100 (72.5%, 95% CI 64.2 - 79.7%) of 138 controls. Among 112 normoglycemic cases, 36 (31.3%, 95% CI 23.0 - 40.6%) had IR compared to 23 of 100 normoglycemic controls (23.0%, 95% CI 15.2 - 32.5%). There was no statistically significant difference at the univariate analysis between normoglycemic cases and controls regarding to IR ($p = 0.138$) (figure 20).

The total number of participants with metabolic syndrome was calculated as described in the previous chapter. There was a higher proportion of cases with metabolic syndrome (285, 93.4%, 95% CI 90.1 – 95.9%) than among controls (66, 42.8%, 95% CI 39.3 – 56.5%, p < 0.001).

Table 31. Metabolic and clinical characteristic of cases and controls.

Metabolic/Clinical characteristic N = 463		**Cases n = 325 (%)**	**Controls n = 138 (%)**	***p***
FPG* (mg/dL)	Min-Max	55 - 380	55 - 394	**< 0.001**
	Median (IQR)	127 (99 - 192)	94 (83 - 105)	
	< 110	121 (39.0)	110 (79.7)	**< 0.001**
	110 – 125	30 (9.7)	7 (5.1)	
	≥ 126	159 (51.3)	21 (15.2)	
HbA1c* (%)	Min-Max	2.7 - 13.5	4.1 - 11.9	**< 0.001**
	Median (IQR)	6.9 (5.9 - 8.9)	5.9 (5.5 - 6.4)	
	< 5.7	56 (19.2)	57 (41.3)	**< 0.001**
	≥ 5.7 – 6.4	73 (25.1)	50 (36.2)	
	≥ 6.5	162 (55.7)	31 (22.5)	
Fasting Plasma Insulin (µU/ml)	Min-Max	2.9 - 57.6	2.9 - 57.1	**0.002**
	Median (IQR)	14.6 (9 - 21.4)	11.25 (7.1 - 17.5)	
	2 – < 25	223 (82.3)	117 (84.8)	0.524
	≥ 25	48 (17.7)	21 (15.2)	
HOMA2-IR*	Min-Max	0.3 - 9.9	0.4 - 6.5	**< 0.001**
	Median (IQR)	2 (1.3 - 3.2)	1.5 (0.9 - 2.4)	
	Normal < 2	140 (51.7)	96 (69.6)	**0.001**
	IR ≥ 2	131 (48.3)	42 (30.4)	
Total cholesterol (mg/dL)	Min-Max	73 - 494	107 - 332.7	**< 0.001**
	Median (IQR)	161 (132.5 - 190)	187 (151.9 - 216.5)	
	< 150	116 (38.0)	30 (21.7)	**0.001**
	≥ 150	189 (62.0)	108 (78.3)	
Triglycerides (mg/dL)	Min-Max	38 - 744	32 -846.2	**< 0.001**
	Median (IQR)	138 (100 - 198)	106 (74.8 - 156.1)	
	< 150	168 (55.1)	100 (72.5)	**0.002**
	< 200	63 (20.7)	18 (13.0)	
	≥ 200	74 (24.3)	20 (14.5)	
	Min-Max	1.4 - 87.0	19.5 - 90.8	**0.001**

HDL* Cholesterol (mg/dL)	Median (IQR)	37 (32 - 45.5)	42 (34 - 50.7)	
	Optimal Male ≥ 40 Female ≥ 50	129 (39.7)	63 (45.7)	0.234
	Risky Male < 40 Female < 50	196 (60.3)	75 (54.3)	
LDL* Cholesterol (mg/dL)	Min-Max	9 - 244	27.6 - 234.4	**< 0.001**
	Median (IQR)	93 (70.5 - 122)	114 (87.6 - 141.7)	
	< 70 mg/dL	74 (24.3)	15 (10.9)	**0.001**
	≥ 70 mg/dL	231 (75.7)	123 (89.1)	
Systolic BP*	Min-Max	90 - 200	82 - 219	**< 0.001**
	Median (IQR)	140 (128.5 - 157)	121 (108 - 136)	
Diastolic BP*	Min-Max	50 – 117	43 – 101	**< 0.001**
	Median (IQR)	80 (70 - 86)	64 (57 - 76)	

***FPG = Fasting plasma glucose, *HbA1c = Glycated haemoglobin, *HOMA2-IR = Homeostasis model assessment-(2)-Insulin resistance, *HDL = High-density lipoprotein, *LDL = Low-density lipoprotein, *BP = Blood pressure. HDL cholesterol: Optimal = Male ≥ 40 Female ≥ 50; Risky = Male <40, Female < 50

Table 32. T2DM and IR cases among cases and controls.

Study population N = 463		**Cases n = 325** (%)	**95% CI**	**Controls n = 138** (%)	**95% CI**	***p***
T2DM participants		213 (65.5)	60.1 - 70.7	38 (27.5)	20.3 - 35.8	**< 0.001**
	T2DM using insulin	74 (34.7)	28.4 - 41.5	1 (2.6)	0.1 - 13.8	**< 0.001**
	T2DM not using insulin	139 (65.3)	58.5 -71.6	37 (97.4)	86.2 - 99.9	
Normoglycemic participants		112 (34.5)	30.2 - 41.2	100 (72.5)	64.2 - 79.7	**< 0.001**
	Normoglycemic with IR	36 (31.3)	23.0 - 40.6	23 (23.0)	15.2 - 32.5	0.138
	Normoglycemic without IR	76 (68.7)	56.7 - 74.7	77 (77.0)	67.5 - 84.8	
		n = 305 (%)		**n = 138** (%)		
	Participants with MS	285 (93.4)	90.1 - 95.9	66 (42.8)	39.3 - 56.5	**< 0.001**
	Participants without MS	20 (6.6)	4.1 - 9.9	72 (52.2)	43.5 - 60.7	

Figure 18. Diabetes status of cases and controls

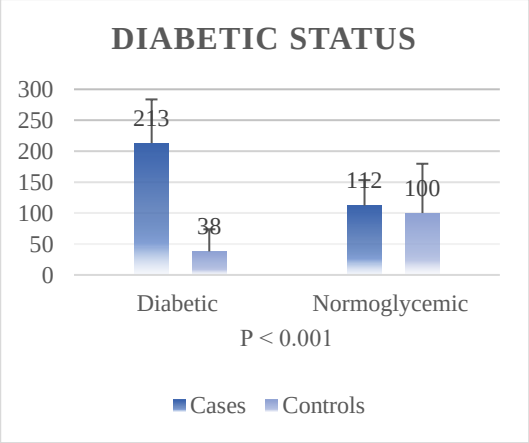


Figure 19. Insulin use among cases and controls

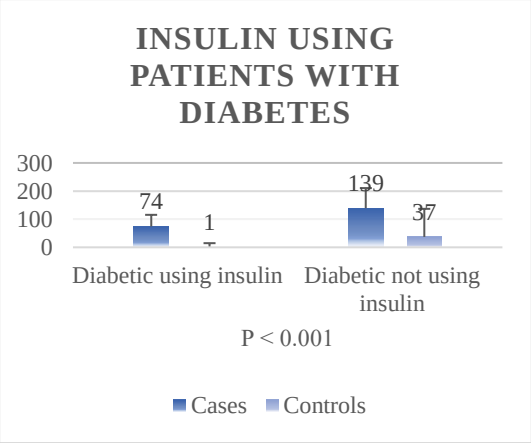
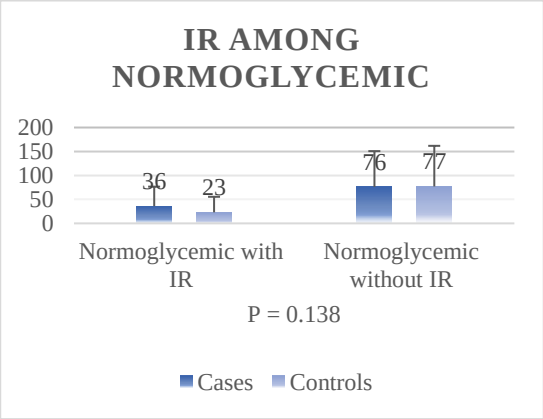


Figure 20. IR status of normoglycemic cases and controls



4.2. Logistic Regression

Controls were selected using systematic random sampling by selecting every fifth participant attending to the TB and chest diseases centre, as described in the previous chapter. Although ideally, we should have selected a new control group, we were unable to select controls for the CHD group from the King Faisal Hospital because the patients attending the hospital were uncooperative and it was difficult to convince them to participate. In addition, recruitment of patients took place at the same time that the study on TB, which recruited patients from a different city 300 kilometres apart. Therefore, we used the same controls recruited from the TB and chest diseases

centre. We tried to recruit controls of similar gender and age balance than patients with CHD but, unfortunately, at the time of analysis, we realized that controls were much more older than cases, to a degree that makes it difficult to control for confounding, as many other risk factors are associated to age (obesity, hypertension etc.) and the sample size was unlikely to be large enough to fully explore these associations. Furthermore, the ethnicity of cases and controls was also markedly different which worsen the situation. We reworked the analysis by removing factors for T2DM that were highly correlated. Fasting plasma glucose, history of T2DM and HbA1c were all merged into the presence or absence of T2DM and estimated the AOR.

As described in the previous chapter, many variables had significant correlations and we undertook the same approach conducting multivariable backward stepwise logistic regression for clusters of variables, to identify the main variables for each cluster. The variables with p-values < 0.2 were selected to enter multivariable backward stepwise logistic regressions. These included gender, age, nationality, marital status, education, occupation, T2DM, T2DM using insulin, family history of diabetes, hypertension, taking hypertensive medication, hyperlipidaemia, taking lipid lowering therapy, history of gestational diabetes, polycystic ovaries, type of job, monthly income, level of stress, overweight among family, overweight as a child, smoking, past smoker, number of breakfast meals last week, number of lunch meals last week, number of dinner meals last week, participant rating of his/her diet, fast food consumption, WHR, BMI, FPG, HbA1c, fasting plasma insulin, total cholesterol, triglycerides, LDL Cholesterol, HDL Cholesterol, systolic BP and diastolic BP. Multivariable backward stepwise logistic regressions were conducted separately for demographic characteristics, medical history, lifestyle and diet,

anthropometry and metabolic and clinical characteristics of cases and controls. As shown in appendix (14 - 15). For each cluster, the variables remaining statistically significant were carried forward into multivariate analysis using backward statistics regressions with replacement. We adjusted for age, and gender to obtain AORs.

The multivariable backward stepwise logistic regression analysis for significant variables from the previous logistic regression analysis including T2DM is shown in table 33. Cases were more likely to be Saudi (AORs 45.0, 95% CI 1.4 - 18.0, p = 0.013) and to have T2DM (AORs 3.4, 95% CI 1.0 - 11.1, p = 0.046). The odds of being male for patients with CHD was AOR 23.9 (95% CI 4.6 - 124.8, p < 0.001). Subjects with CHD were more likely to be aged 40 – 49, 50 - 59, 60 - 69 and ≥ 70 years old (AORs 40.9, 95% CI 3.4 - 491.6, p = 0.003); (71.7, 95% CI 6.0 - 862.2, p = 0.001), (43.9, 95% CI 3.6 - 538.2, p = 0.003) and (104.0, 95% CI 6.5 – 1672, p = 0.001). Cases were less likely to be married or previously married (AOR 0.06, 95% CI 0.01 - 0.30, p = 0.001) and to have primary education (AOR 22.8, 95% CI 2.7 - 196.8, p = 0.004). Cases were more likely to take hypertensive medications (AOR 8.6, 95% CI 2.3 - 31.8, p = 0.001) and lipid lowering therapy (AOR 21.1, 95% CI 5.7 - 77.7, p < 0.001) than controls. Cases were less likely to eat fast foods 3 – 4 times/week (AOR 0.07, 95% CI 0.01 - 0.70, p = 0.024), were more likely to have high WHR (AOR 30.6, 95% CI 5.1 - 184.8, p < 0.001) and high diastolic BP (AOR 1.1, 95% CI 1.1 - 1.2, p < 0.001) than controls.

The multivariable backward stepwise logistic regression analysis for significant variables from the previous logistic regression analysis including metabolic syndrome is shown in table 34. The odds of being male for patients with CHD was AOR 3.1 (95% CI 1.3 - 7.5, p = 0.012). Subjects with CHD were more likely to be aged 40 – 49, 50 - 59, 60 - 69 and ≥ 70 years old (AORs 31.8, 95% CI 4.8 - 209.6, p

< 0.001); (62.0, 95% CI 9.3 - 414.5, p < 0.001), (104.2, 95% CI 14.5 - 751.4, p < 0.001) and (183.9, 95% CI 23.5 - 1440, p < 0.001). Cases were less likely to be married or previously married (AOR 0.2, 95% CI 0.06 - 0.5, p = 0.001) and to have primary education (AOR 9.6, 95% CI 2.5 - 36.4, p = 0.001) and more likely to be among 5001 – 10000 (SAR) monthly income group (AOR 6.7, 95% CI 1.4 - 31.3, p = 0.016). Cases were more likely to have metabolic syndrome (AOR 6.1, 95% CI 2.5 - 15.0, p < 0.001) and were more likely to have higher level of stress (AOR 10.6, 95% CI 1.4 - 80.9, p = 0.022) than controls.

Table 33. Logistic regression model for factors predicting getting CHD including T2DM

Variables N = 463		Univariate			Multivariate	
		Cases n = 325 (%)	Controls n = 138 (%)	*P*	AOR* (95% CI)	*p*
Gender	Female	95 (29.2)	55 (39.9)	**0.025**	**1**	
	Male	230 (70.8)	83 (60.1)		23.867(4.57 - 124.76)	**< 0.001**
Age group	18 – 39	2 (0.6)	61 (44.6)	**< 0.001**	**1**	
	40 – 49	31 (9.5)	29 (21.0)		40.960 (3.41 - 491.58)	0.003
	50 – 59	91 (28.0)	27 (19.6)		71.712 (5.96 - 862.20)	0.001
	60 – 69	103 (31.7)	13 (9.4)		43.905 (3.58 - 538.15)	0.003
	≥ 70	98 (30.2)	8 (5.8)		104.031 (6.47 - 1672)	0.001
Ethnicity	Non-Saudi	42 (12.9)	67 (48.6)	**< 0.001**	**1**	
	Saudi	283 (87.1)	71 (51.4)		5.034 (1.41 - 17.98)	0.013
Marital status	Single	29 (8.9)	33 (23.9)	**< 0.001**	**1**	
	Married	296 (91.1)	105 (76.1)		0.059 (0.01 - 0.30)	0.001
Education	No education	33 (10.2)	13 (9.4)	**< 0.001**	**1**	
	Literacy	73 (22.5)	20 (14.5)		2.064 (0.34 - 12.52)	0.431
	Primary education	122 (37.5)	21 (15.2)		22.830 (2.65 - 196.80)	0.004
	Intermediate education	22 (6.8)	31 (22.5)		0.679 (0.07 - 6.34)	0.735
	Secondary education	57 (17.5)	36 (26.1)		1.964 (0.24 - 15.95)	0.528
	Higher education	18 (5.5)	17 (12.3)		4.007 (0.32 - 50.37)	0.282

Type of job	Sedentary	307 (94.5)		95 (68.8)		27.544 (0.55 - 1374)	0.097
	Moderate Physical Activity	16 (4.9)		38 (27.5)	**< 0.001**	10.737 (0.22 - 530.72)	0.233
	Physically Very Demanding	2 (0.6)		5 (3.6)		**1**	
Past smoker	No	207 (63.7)		130 (94.2)	**< 0.001**	**1**	
	Yes	118 (36.3)		8 (5.8)		1.926 (0.46 - 8.15)	0.373
T2DM	No	112 (34.5)		100 (72.5)	**< 0.001**	**1**	
	Yes	213 (65.5)		38 (27.5)		3.436 (1.02 - 11.11)	0.046
Takes hypertensive medication	No	47 (14.5)		117 (84.8)	**< 0.001**	**1**	
	Yes	278 (85.5)		21 (15.2)		8.577 (2.31 - 31.83)	0.001
Takes lipid lowering therapy	No	52 (16.0)		120 (87.0)	**< 0.001**	**1**	
	Yes	270 (83.1)		15 (10.9)		21.103 (5.73 - 77.70)	**< 0.001**
	Don't know	3 (0.9)		3 (2.2)		0.053 (0.00 - 1.08)	0.056
Level of stress	Low	199 (61.2)		110 (79.7)	**< 0.001**	**1**	
	Medium	105 (32.3)		25 (18.1)		2.603 (0.77 - 8.77)	0.123
	High	21 (6.5)		3 (2.2)		9.312 (0.34 - 256.88)	0.187
Fast food consumption	0 - 1 Times/Month	172 (52.9)		51 (37.0)	**< 0.001**	**1**	
	2 - 3 Times/Month	73 (22.5)		21 (15.2)		2.103 (0.47 - 9.45)	0.332
	1 - 2 Times/Week	45 (13.8)		30 (21.7)		0.229 (0.05 - 1.02)	0.053
	3 - 4 Times/Week	19 (5.8)		22 (15.9)		0.069 (0.01 - 0.70)	0.024
	≥ 5 Times/Week	16 (4.9)		14 (10.1)		0.476 (0.05 - 4.31)	0.509
WHR		**Male case**	**Male controls**	**Female case**	**Female controls**		

	Low	10 (4.3)	42 (50.6)	3 (3.2)	18 (32.7)		**1**	
	Moderate	92 (40.0)	35 (42.2)	17 (17.9)	20 (36.4)	**< 0.001**	2.213 (0.42 - 11.54)	0.346
	High	128 (55.7)	6 (7.2)	75 (78.9)	17 (30.9)		30.572 (5.06 - 184.82)	**< 0.001**
Systolic BP	Median (IQR)	140 (128.5 - 157)		121 (108 - 136)		**< 0.001**	0.976 (0.95 - 1.01)	0.106
Diastolic BP	Median (IQR)	80 (70 - 86)		64 (57 - 76)		**< 0.001**	1.108 (1.05 - 1.17)	**< 0.001**
Constant							**< 0.001**	**< 0.001**

*****AOR = Adjusted Odds Ratio

Table 34 Logistic regression model for factors predicting getting CHD including metabolic syndrome.

Variables N = 463		Univariate			Multivariate	
		Cases n = 325 (%)	Controls n = 138 (%)	*P*	AOR* (95% CI)	*p*
Gender	Female	95 (29.2)	55 (39.9)	**0.025**	**1**	
	Male	230 (70.8)	83 (60.1)		3.088 (1.28 - 7.47)	**0.012**
Age group	18 – 39	2 (0.6)	61 (44.6)	**< 0.001**	**1**	
	40 – 49	31 (9.5)	29 (21.0)		31.745 (4.81 - 209.61)	**< 0.001**
	50 – 59	91 (28.0)	27 (19.6)		62.008 (9.28 - 414.46)	**< 0.001**
	60 – 69	103 (31.7)	13 (9.4)		104.198 (14.45 - 751.4)	**< 0.001**
	≥ 70	98 (30.2)	8 (5.8)		183.875 (23.47 - 1440)	**< 0.001**
Ethnicity	Non-Saudi	42 (12.9)	67 (48.6)	**< 0.001**	**1**	
	Saudi	283 (87.1)	71 (51.4)		2.017 (0.78 - 5.21)	0.147
Marital status	Single	29 (8.9)	33 (23.9)	**< 0.001**	**1**	
	Married	296 (91.1)	105 (76.1)		0.179 (0.06 - 0.51)	**0.001**
Education	No education	33 (10.2)	13 (9.4)	**< 0.001**	**1**	
	Literacy	73 (22.5)	20 (14.5)		3.305 (0.96 - 11.44)	0.059
	Primary education	122 (37.5)	21 (15.2)		9.589 (2.53 - 36.35)	**0.001**
	Intermediate education	22 (6.8)	31 (22.5)		0.515 (0.11 - 2.38)	0.395
	Secondary education	57 (17.5)	36 (26.1)		1.118 (0.25 - 5.04)	0.884
	Higher education	18 (5.5)	17 (12.3)		1.403 (0.22 - 8.88)	0.719

Type of job	Sedentary	307 (94.5)	95 (68.8)	**< 0.001**	13.404 (0.70 - 255.20)	0.084
	Moderate Physical Activity	16 (4.9)	38 (27.5)		4.275 (0.23 - 79.47)	0.330
	Physically Very Demanding	2 (0.6)	5 (3.6)		**1**	
Past smoker	No	207 (63.7)	130 (94.2)	**< 0.001**	**1**	
	Yes	118 (36.3)	8 (5.8)		2.677 (0.99 - 7.21)	0.051
Monthly income (SAR)	≤ 3000	141 (43.4)	92 (66.7)	**< 0.001**	**1**	
	3000 – 5000	105 (32.3)	34 (24.6)		1.177 (0.46 - 3.03)	0.735
	5001 – 10000	54 (16.6)	9 (6.5)		6.677 (1.42 - 31.29)	**0.016**
	≥ 10000	25 (7.7)	3 (2.2)		4.954 (0.77 - 31.76)	0.091
Metabolic syndrome Cases n= 305	No	20 (6.6)	72 (52.2)	**< 0.001**	**1**	
	Yes	285 (93.4)	66 (42.8)		6.110 (2.49 - 15.01)	**< 0.001**
Level of stress	Low	199 (61.2)	110 (79.7)	**< 0.001**	**1**	
	Medium	105 (32.3)	25 (18.1)		1.869 (0.85 - 4.10)	0.119
	High	21 (6.5)	3 (2.2)		10.635 (1.40 - 80.88)	**0.022**
Fast food consumption	0 - 1 Times/Month	172 (52.9)	51 (37.0)	**< 0.001**	**1**	
	2 - 3 Times/Month	73 (22.5)	21 (15.2)		1.003 (0.38 - 2.65)	0.995
	1 - 2 Times/Week	45 (13.8)	30 (21.7)		0.557 (0.21 - 1.48)	0.242
	3 - 4 Times/Week	19 (5.8)	22 (15.9)		0.371 (0.09 - 1.51)	0.166
	≥ 5 Times/Week	16 (4.9)	14 (10.1)		0.619 (0.13 - 2.99)	0.551
Total cholesterol (mg/dL)	< 150	116 (38.0)	30 (21.7)	**0.001**	**1**	
	≥ 150	189 (62.0)	108 (78.3)		0.422 (0.18 - 1.01)	0.051
Constant					0.001	< 0.001

4.3. Comparison of CHD cases with and without T2DM or IR

We conducted a sub-analysis for (a) normoglycaemic CHD cases without IR (b) euglycaemic CHD cases with IR and (c) CHD cases with T2DM to determine factors independently associated with T2DM and IR among patients with CHD. Independent variables for these analyses were chosen based on the literature of risk factors for CHD. We will call normoglycemic CHD cases without IR as 'CHD-controls' (n = 79); euglycemic CHD cases with IR as 'CHD-IR' (n = 37) and CHD diabetic cases as CHD-diabetic' (n = 209).

The demographic characteristics of CHD-IR and CHD-diabetic cases and CHD-controls are shown in table 35. CHD-IR cases were more likely to work for the governmental sector (12, 32.4%) and to be retired (15, 40.5%) than CHD-controls (10, 12.7% and 25, 31.6%, respectively). CHD-controls were more likely to work for the private sector (13, 16.5%) or to belong to the non-employed categories (25, 31.6%) than CHD-IR cases (2, 5.4% and 6, 16.2%, respectively) (p = 0.041).

Table 35. Demographic characteristics of CHD-IR cases, CHD-diabetic cases and CHD-controls

Demographic characteristics N = 463		CHD-Controls n = 79 (%)	CHD-IR n = 37 (%)	*P*	CHD-Diabetic n = 209 (%)	*P*
Sex	Male	58 (73.4)	26 (70.3)	0.724	146 (69.9)	0.553
	Female	21 (26.6)	11 (29.7)		63 (30.1)	
Age	Min-Max	37 - 95	38 - 98	0.190	42 - 90	0.673
	Median (IQR)	62 (55 - 75)	60 (53 - 64)		63 (55 - 70)	
Age groups	18 – 39	1 (1.3)	1 (2.7)	0.177	0 (0.0)	0.207
	40 – 49	10 (12.7)	5 (13.5)		16 (7.7)	
	50 – 59	20 (25.3)	9 (24.3)		62 (29.7)	
	60 – 69	20 (25.3)	16 (43.2)		67 (32.1)	
	≥ 70	28 (35.4)	6 (16.2)		64 (30.6)	
Marital status	Single	4 (5.1)	2 (5.4)	0.944	23 (11.0)	0.099
	With partner/married	64 (81.0)	29 (78.4)		150 (71.8)	
	Divorced/separated	0 (0.0)	0 (0.0)		9 (4.3)	
	Widowed	11 (13.9)	6 (16.2)		27 (12.9)	
Education	No education	14 (17.7)	4 (10.8)	0.627	15 (7.2)	0.169
	Literacy	14 (17.7)	8 (21.6)		51 (24.4)	
	Primary education	28 (35.4)	13 (35.1)		81 (38.8)	
	Intermediate education	5 (6.3)	2 (5.4)		15 (7.2)	
	Secondary education	14 (17.7)	5 (13.5)		38 (18.2)	
	Higher education	4 (5.1)	5 (13.5)		9 (4.3)	
Occupation	Governmental	10 (12.7)	12 (32.4)	**0.041**	43 (20.6)	0.170
	Private	13 (16.5)	2 (5.4)		24 (11.5)	
	Labourer	5 (6.3)	1 (2.7)		3 (1.4)	
	Retired	25 (31.6)	15 (40.5)		62 (29.7)	
	Non-employed	25 (31.6)	6 (16.2)		74 (35.4)	
	Other	1 (1.3)	1 (2.7)		3 (1.4)	
Ethnicity	Saudi	64 (81.0)	34 (91.9)	0.131	185 (88.5)	0.097
	Non-Saudi	15 (19.0)	3 (8.1)		24 (11.5)	

The medical histories of CHD-IR, CHD-diabetic cases and CHD-controls are shown in table 36. There were clear differences between CHD-diabetic cases and CHD-controls in terms of family history of diabetes, with 152 (72.7%) of CHD-diabetic cases and 33 (41.8%) of CHD-controls having a family history of diabetes ($p < 0.001$) (figure 21); with a higher frequency among first degree (133, 63.6% versus 30, 38.0%, respectively, $p < 0.001$) and second degree CHD-diabetic cases than CHD-controls (65, 31.1% versus 12, 15.2%, respectively, $p = 0.006$). CHD-diabetic cases were more likely to have experienced gestational diabetes than CHD-controls (12, 19.0% versus 0, 0.0%, $p = 0.035$, respectively) (figure 22).

Table 36. Medical history of CHD-IR cases, CHD-diabetic cases and CHD-controls

Medical history N = 463			**CHD-Controls n = 79 (%)**	**CHD-IR n = 37 (%)**	***P***	**CHD-Diabetic n = 209 (%)**	***P***
Family history of diabetes	Yes		33 (41.8)	21 (56.8)	0.132	152 (72.7)	**< 0.001**
	No		46 (58.2)	16 (43.2)		57 (27.3)	
	1st degree	Yes	30 (38.0)	18 (48.6)	0.277	133 (63.6)	**< 0.001**
		No	49 (62.0)	19 (51.4)		76 (36.4)	
	2nd degree	Yes	12 (15.2)	4 (10.8)	0.524	65 (31.1)	**0.006**
		No	67 (84.8)	33 (89.2)		144 (68.9)	
	3rd degree	Yes	2 (2.5)	2 (5.4)	0.445	10 (4.8)	0.370
		No	77 (97.5)	35 (94.6)		199 (95.2)	
Hypertension	Yes		61 (77.2)	23 (62.2)	0.091	168 (80.4)	0.400
	No		18 (22.8)	14 (37.8)		39 (18.7)	
	Don't know		0 (0.0)	0 (0.0)		2 (1.0)	
Takes hypertensive medication	Yes		66 (83.5)	29 (78.4)	0.501	183 (87.6)	0.374
	No		13 (16.5)	8 (21.6)		26 (12.4)	

Hyperlipidaemia	Yes	62 (78.5)	26 (70.3)	0.600	175 (83.7)	0.581
	No	13 (16.5)	9 (24.3)		26 (12.4)	
	Don't know	4 (5.1)	2 (5.4)		8 (3.8)	
Takes lipid lowering therapy	Yes	64 (81.0)	29 (78.4)	0.610	177 (84.7)	0.757
	No	14 (17.7)	8 (21.6)		30 (14.4)	
	Don't know	1 (1.3)	0 (0.0)		2 (1.0)	
History of gestational diabetes	Yes	0 (0.0)	0 (0.0))	0.354	12 (19.0)	**0.035**
	No	20 (95.2)	11 (100)		49 (77.8)	
	Don't know	1 (4.8)	0 (0.0)		2 (3.2)	
	Not applicable	58 (73.4)	26 (70.3)		147 (70.3)	
History of polycystic ovaries	Yes	1 (4.8)	1 (9.1)	0.639	7 (11.1)	0.483
	No	20 (95.2)	10 (90.9)		55 (87.3)	
	Don't know	0 (0.0)	0 (0.0)		1 (1.6)	
	Not applicable	58 (73.4)	26 (70.3)		146 (69.9)	

Figure 21. Family history of diabetes of CHD-diabetic cases and CHD-controls

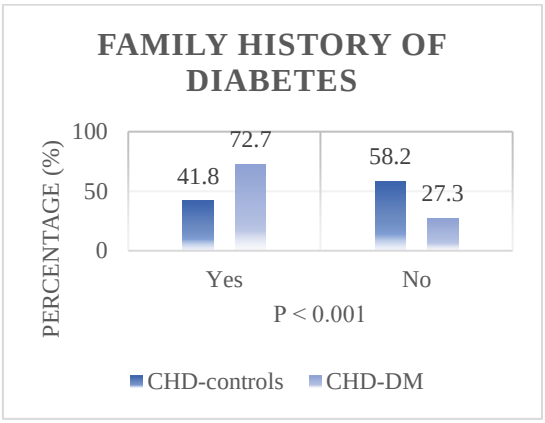
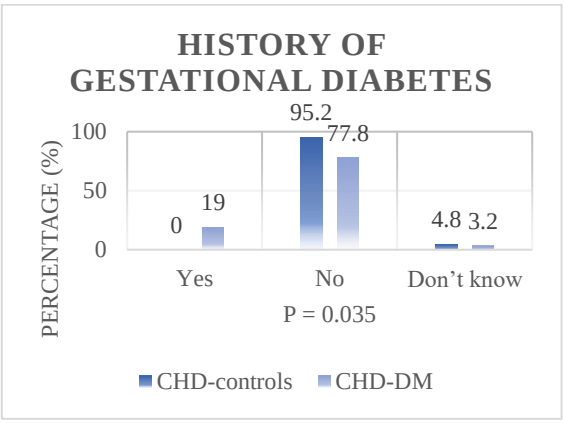


Figure 22. Gestational diabetes between CHD-diabetic and CHD-controls



The lifestyle and diet of CHD-diabetic, CHD-IR cases and CHD-controls are shown in table 37. CHD-IR cases were more likely to have a higher monthly income ≥ 10000 SAR (5, 13.5%) than CHD-controls (1, 1.3%) and a monthly income of

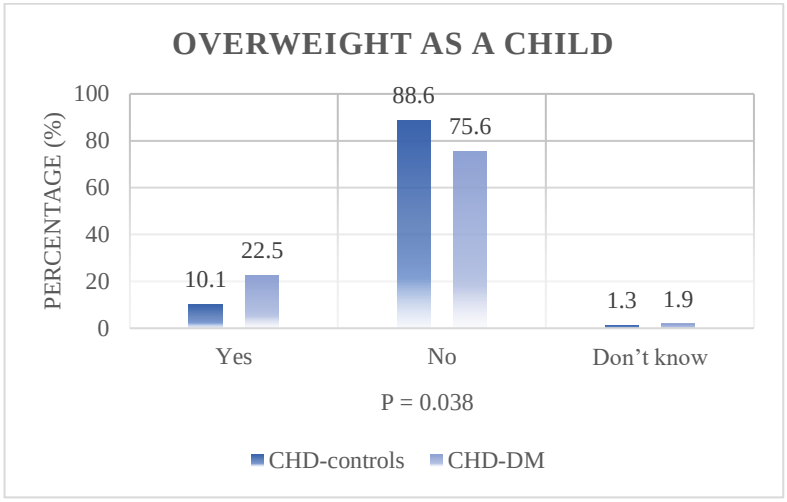
between 5001 and 10000 SAR (8, 21.6%) than CHD-controls (14, 17.7%) (p = 0.027). CHD-diabetic cases in turn were more likely to have a history of overweight during childhood than CHD-controls (47, 22.5% versus 8, 10.1%, respectively, p = 0.038) (figure 23).

Table 37. Lifestyle and diet of CHD-IR cases, CHD-diabetic cases and CHD-controls

Lifestyle and diet N = 463			**CHD-Controls n = 79 (%)**	**CHD-IR n = 37 (%)**	***P***	**CHD-Diabetic n = 209 (%)**	***P***
Type of job	Sedentary		73 (92.4)	34 (91.9)	0.644	200 (95.7)	0.532
	Moderate Physical Activity		5 (6.3)	3 (8.1)		8 (3.8)	
	Physically Very Demanding		1 (1.3)	0 (0.0)		1 (0.5)	
Monthly income (SAR)	≤ 3000		34 (43.0)	16 (43.2)	**0.027**	91 (43.5)	0.055
	3000 - 5000		30 (38.0)	8 (21.6)		67 (32.1)	
	5001 - 10000		14 (17.7)	8 (21.6)		32 (15.3)	
	≥ 10000		1 (1.3)	5 (13.5)		19 (9.1)	
Level of stress	Low		51 (64.6)	24 (64.9)	0.197	124 (59.3)	0.582
	Medium		24 (30.4)	13 (35.1)		68 (32.5)	
	High		4 (5.1)	0 (0.0)		17 (8.1)	
Overweight among family	Yes		20 (25.3)	15 (40.5)	0.096	78 (37.3)	0.103
	No		59 (74.7)	22 (59.5)		130 (62.2)	
	Don’t know		0 (0.0)	0 (0.0)		1 (0.5)	
If yes, who?	Father	Yes	1 (1.3)	1 (2.7)	0.538	12 (5.7)	0.067
		No	78 (98.7)	36 (97.3)		197 (94.3)	
	Mother	Yes	4 (5.1)	3 (8.1)	0.531	17 (8.1)	0.371
		No	75 (94.9)	34 (91.9)		192 (91.9)	
Overweight as a child	Yes		8 (10.1)	6 (16.2)	0.455	47 (22.5)	**0.038**
	No		70 (88.6)	31 (83.8)		158 (75.6)	
	Don’t know		1 (1.3)	0 (0.0)		4 (1.9)	
Smoking	Yes		10 (12.7)	6 (16.2)	0.604	21 (10.0)	0.524
	No		69 (87.3)	31 (83.8)		188 (90.0)	

Cigarettes per day	10 per day	Yes	3 (3.8)	2 (5.4)	0.696	4 (1.9)	0.375
		No	76 (96.2)	35 (94.6)		205 (98.1)	
	10–20 per day	Yes	7 (8.9)	4 (10.8)	0.741	17 (8.1)	0.842
		No	72 (91.1)	33 (89.2)		192 (91.9)	
Past smoker	Yes		29 (36.7)	9 (24.3)	0.185	80 (38.3)	0.807
	No		50 (63.3)	28 (75.7)		129 (61.7)	
Number of breakfast meals last week	Never		2 (2.5)	4 (10.8)	0.198	12 (5.7)	0.335
	1 - 6		10 (12.7)	4 (10.8)		18 (8.6)	
	Always		67 (84.8)	29 (78.4)		179 (85.6)	
Number of lunch meals last week	Never		1 (1.3)	2 (5.4)	0.421	7 (3.3)	0.539
	1 - 6		5 (6.3)	3 (8.1)		17 (8.1)	
	Always		73 (92.4)	32 (86.5)		185 (88.5)	
Number of dinner meals last week	Never		2 (2.5)	0 (0.0)	0.438	2 (1.0)	0.627
	1 - 6		5 (6.3)	3 (8.1)		14 (6.7)	
	Always		72 (91.1)	34 (91.9)		193 (92.3)	
Participant rating of his/her diet	Good		9 (11.4)	1 (2.7)	0.298	12 (5.7)	0.235
	Fair		52 (65.8)	27 (73.0)		141 (67.5)	
	Poor		18 (22.8)	9 (24.3)		56 (26.8)	
Fast food consumption	0 - 1 Times/Month		34 (43.0)	16 (43.2)	0.185	122 (58.4)	0.078
	2 - 3 Times/Month		17 (21.5)	14 (37.8)		42 (20.1)	
	1 - 2 Times/Week		18 (22.8)	3 (8.1)		24 (11.5)	
	3 - 4 Times/Week		6 (7.6)	3 (8.1)		10 (4.8)	
	≥ 5 Times/Week		4 (5.1)	1 (2.7)		11 (5.3)	
Food portions description	Small		17 (21.5)	4 (10.8)	0.236	41 (19.6)	0.817
	Intermediate		40 (50.6)	18 (48.6)		102 (48.8)	
	Large		22 (27.8)	15 (40.5)		66 (31.6)	

Figure 23. History of childhood overweight of CHD-diabetic cases and CHD-controls



The anthropometry of CHD-IR and CHD-diabetic male cases and male CHD-controls are shown in table 38. Male CHD-IR cases had higher median weight than male CHD-controls (87 versus 76 Kgs, respectively) with a median difference of 11 Kgs (p = 0.024) and a higher median waist circumference (112 versus 104, respectively), with a median difference of 8 cms (p = 0.028). Moreover, male CHD-IR cases had higher median WHR than male CHD-controls (1.03 versus 0.99, respectively), with median difference of 0.04 (p = 0.007).

Table 38. Male anthropometry of CHD-IR cases, CHD-diabetic cases and CHD-controls

Anthropometry (Male) N = 230		**CHD-Controls n = 58 (%)**	**CHD-IR n = 26 (%)**	***P***	**CHD-diabetic n = 146 (%)**	***P***
Height (cm)	Median (IQR)	167 (162 - 171)	168 (163 -174)	0.413	166 (161 - 171)	0.676
Weight (kg)	Median (IQR)	76 (68 - 88)	87 (75 - 98)	**0.024**	77 (71 - 89)	0.196
BMI (kg/m2)	Median (IQR)	27 (24 - 31)	30 (27 - 33)	0.063	28 (25 - 31)	0.159
BMI groups	≤ 18.4	0 (0.0)	0 (0.0)	0.087	0 (0.0)	0.500
	18.5 - 24.9	18 (31.0)	3 (11.5)		35 (24.0)	
	25 - 29.9	23 (39.7)	10 (38.5)		58 (39.7)	
	≥ 30	17 (29.3)	13 (50.0)		53 (36.3)	
Waist (cm)	Median (IQR)	104 (94 - 112)	112 (102 - 118)	**0.028**	107 (100 - 114)	0.052
Hip (cm)	Median (IQR)	104 (98 - 112)	108 (102 - 114)	0.171	106 (101 - 113)	0.140
WHR	Median (IQR)	0.99 (0.95 - 1.02)	1.03 (0.97 - 1.07)	**0.007**	1.00 (0.97 - 1.04)	0.110
WHR groups	Low	2 (3.4)	1 (3.8)	0.172	7 (4.8)	0.473
	Moderate	28 (48.3)	7 (26.9)		57 (39.0)	
	High	28 (48.3)	18 (69.2)		82 (56.2)	

The anthropometry data of CHD-IR, CHD-diabetic female cases and female CHD-controls are shown in table 39. Female CHD-IR cases had higher weight than female CHD-controls with medians of (83 versus 67 Kgs, respectively), and a median difference of 16 Kgs ($p = 0.006$), resulting in a higher median BMI (35 versus 29, respectively) with a median BMI difference of 6 ($p = 0.020$); and median waist circumference of 119 versus 104 with a median difference of 15 cms ($p = 0.038$). The median BMI for female CHD-diabetic cases were 32 compared to the 29 female CHD-controls, with a median difference of 3 ($p = 0.032$). Female CHD-diabetic cases, therefore, were much more likely to be obese than female CHD-controls (38, 60.3% versus 8, 38.1%, respectively, $p = 0.027$).

The metabolic characteristics of CHD-IR and CHD-diabetic cases and CHD-controls are shown in table 40. There were 13 cases missing among CHD-controls and 7 among CHD-T2DM. CHD-diabetic cases had higher median triglycerides than CHD-controls (151 versus 119 mg/dL, respectively) with a median difference of 32 mg/dL ($p = 0.003$); and a higher proportion being classified as having high triglycerides (60, 29.7% versus 8, 12.1%, respectively, $p = 0.010$) (figure 24).

Moreover, CHD-diabetic cases had a higher median HDL Cholesterol (37 versus 41 mg/dL, respectively) with a median difference of 4 mg/dL ($p = 0.016$) and were more likely to be classified as having risky HDL Cholesterol than CHD-controls (140, 69.3% versus 36, 54.5%, respectively, $p = 0.001$) (figure 25). Furthermore, CHD-diabetic cases had a lower median LDL Cholesterol (88 versus 101 mg/dL, respectively) with a median difference of 13 mg/dL ($p = 0.061$).

Table 39. Female anthropometry of CHD-IR cases, CHD-diabetic cases and CHD-controls

Anthropometry (Female) N = 95		**CHD-Controls n = 21 (%)**	**CHD-IR n = 11 (%)**	***P***	**CHD-Diabetic n = 63 (%)**	***P***
Height (cm)	Median (IQR)	152 (149 - 154)	154 (146 - 157)	0.481	151 (147 -158)	0.725
Weight (kg)	Median (IQR)	67 (57 - 80)	83 (71 - 93)	**0.006**	75 (65 - 84)	0.077
BMI (kg/m2)	Median (IQR)	29 (24 - 33)	35 (30 - 42)	**0.020**	32 (28 - 36)	**0.032**
BMI groups	≤ 18.4	0 (0.0)	0 (0.0)	0.052	0 (0.0)	**0.027**
	18.5 - 24.9	7 (33.3)	1 (9.1)		6 (9.5)	
	25 - 29.9	6 (28.6)	1 (9.1)		19 (30.2)	
	≥ 30	8 (38.1)	9 (81.8)		38 (60.3)	
Waist (cm)	Median (IQR)	104 (94 - 110)	119 (109 - 125)	**0.038**	107 (97 - 114)	0.278
Hip (cm)	Median (IQR)	108 (98 - 118)	124 (102 - 128)	0.074	111 (102 - 122)	0.181
WHR	Median (IQR)	0.95 (0.91 - 0.99)	0.95 (0.95 - 1.08)	0.180	0.95 (0.91 - 0.98)	0.744
WHR groups	Low	0 (0.0)	0 (0.0)	0.288	3 (4.8)	0.359
	Moderate	5 (23.8)	1 (9.1)		11 (17.5)	
	High	16 (76.2)	10 (90.9)		49 (77.8)	

Table 40. Metabolic characteristics of CHD-IR cases, CHD-diabetic cases and CHD-controls

Metabolic/Clinical characteristic N = 463		CHD-Controls n = 66 (%)	CHD-IR n = 37 (%)	*P*	CHD-Diabetic n = 202 (%)	*P*
		Missing = (13)	Missing = (0)		Missing = (7)	
Total cholesterol (mg/dL)	Min - Max	87 - 282	91 - 250	0.507	73 - 494	0.465
	Median (IQR)	166 (128 - 202)	165 (147 - 204)		159 (133 - 184)	
	< 150	26 (39.4)	10 (27.0)	0.207	80 (39.6)	0.976
	≥ 150	40 (60.6)	27 (73.0)		122 (60.4)	
Triglycerides (mg/dL)	Min-Max	38 - 382	58 - 310	0.294	43 - 744	**0.003**
	Median (IQR)	119 (88 - 153)	129 (107 - 170)		151 (104 - 214)	
	< 150	45 (68.2)	23 (62.2)	0.792	100 (49.5)	**0.010**
	< 200	13 (19.7)	8 (21.6)		42 (20.8)	
	≥ 200	8 (12.1)	6 (16.2)		60 (29.7)	
HDL Cholesterol (mg/dL)	Min - Max	15 - 87	10 - 63	0.842	1.4 - 82	**0.016**
	Median (IQR)	41 (34 - 49)	40 (34 - 51)		37 (31 - 44)	
	Optimal Male ≥ 40 Female ≥ 50	43 (65.2)	17 (45.9)	0.394	69 (34.2)	**0.001**
	Risky Male < 40 Female < 50	36 (54.5)	20 (54.1)		140 (69.3)	
LDL Cholesterol (mg/dL)	Min - Max	21 - 209	27 - 182	0.945	9 - 244	**0.061**
	Median (IQR)	101 (75 - 134)	100 (77 - 127)		88 (68 - 115)	
	< 70	14 (21.2)	7 (18.9)	0.782	53 (26.2)	0.413
	≥ 70	52 (78.8)	30 (81.1)		149 (73.8)	
Systolic BP	Min-Max	108 - 200	100 - 188	0.960	90 - 200	0.174
	Median (IQR)	138 (127 - 153)	140 (122 - 154)		140 (130 - 160)	
Diastolic BP	Min-Max	50 - 117	59 - 96	0.231	55 - 105	0.834
	Median (IQR)	80 (70 - 85)	80 (74 - 90)		78 (70 - 85)	

Figure 24. Triglycerides levels of CHD-diabetic and CHD-controls

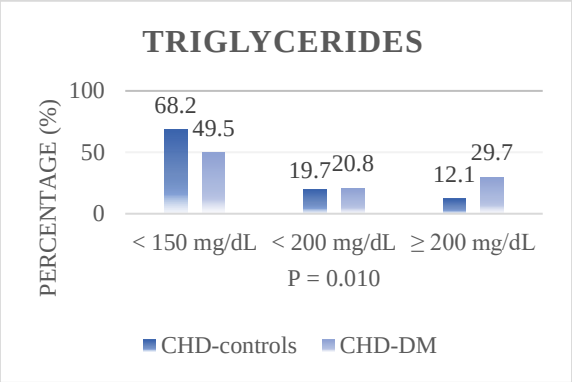
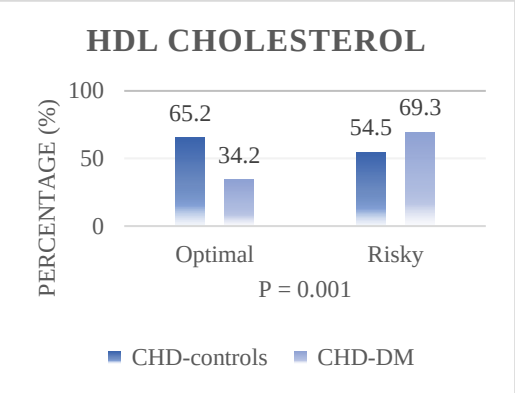


Figure 25. HDL Cholesterol levels of CHD-diabetic and CHD-controls



The multivariable backward stepwise logistic regression analysis for significant variables from the previous logistic regression analysis is shown in table 41. We conducted a logistic regression analysis for the sub-analysis of (a) normoglycaemic CHD cases without IR and (b) euglycaemic CHD cases with IR to determine factors independently associated with IR. The variables with $p < 2$ were selected to inter into a multivariable backward stepwise logistic regression. Variables selected included ethnicity, monthly income, BMI Male, BMI Female and family history of diabetes. We adjusted for age and gender to obtain AORs. The AORs for having IR for obese subjects (BMI $\geq$ 30) was 4.793 (95% CI 1.358 - 16.913, $p = 0.015$) when compared with adults with normal weight.

Table 41. Logistic regression model for the comparison of CHD-IR cases and CHD-controls.

Variables N = 463		Multivariate	
		AOR* (95% CI)	*p*
Age group	18 – 39	**1**	
	40 – 49	0.557 (0.023 - 13.408)	0.719
	50 – 59	0.781 (0.034 - 18.116)	0.878
	60 – 69	0.955 (0.041 - 22.310)	0.977
	≥ 70	0.274 (0.010 - 7.264)	0.439
Monthly income (SAR)	≤ 3000	**1**	
	3000 - 5000	0.471 (0.159 - 1.394)	0.174
	5001 - 10000	0.747 (0.212 - 2.632)	0.649
	≥ 10000	10.815 (0.946 - 123.601)	0.055
BMI groups	18.5 - 24.9	**1**	
	25 - 29.9	1.644 (0.418 - 6.463)	0.476
	≥ 30	4.793 (1.358 - 16.913)	**0.015**
Family history of diabetes	No	**1**	
	Yes	1.695 (0.671 – 4.292)	0.264
Constant		0.477	0.660

The multivariable backward stepwise logistic regression analysis for significant variables from the previous logistic regression analysis is shown in table 42. We also conducted a logistic regression analysis to compare (a) normoglycemic CHD cases without IR and (b) CHD cases with T2DM to determine factors independently associated with T2DM. The significant variables were selected to inter into a multivariable backward stepwise logistic regression. These variables included education, ethnicity, family history of diabetes, fast food consumption, BMI and triglycerides. We adjusted for age and gender to obtain AORs. Cases were more likely to be Saudis (AOR 2.778, 95% CI 1.143 - 6.756, p = 0.024) and to belong to literacy groups (AOR 3.970, 95% CI 1.328 - 11.870, p = 0.014) and to have primary education (AOR 2.812, 95% CI 1.063 - 7.438, p = 0.037). CHD-diabetic cases were more likely to have a family history of diabetes (2.710, 95% CI 1.429 - 5.128, p =

0.002), high triglycerides (AOR 3.724, 95% CI 1.485 - 9.338, p = 0.005) and to indicate they consumed fast foods 2 - 3 times/month (AOR 0.341, 95% CI 0.147 - 0.795, p = 0.013) or 1 - 2 times/week (AOR 0.329, 95% CI 0.132 - 0.817, p = 0.017) than controls.

Table 42. Logistic regression model for the comparison of CHD-diabetic cases and CHD-controls.

Variables N = 463		**Multivariate**	
		AOR* (95% CI)	***p***
Ethnicity	Non-Saudi	**1**	
	Saudi	2.778 (1.143 - 6.756)	**0.024**
Education	No education	**1**	
	Literacy	3.970 (1.328 - 11.870)	**0.014**
	Primary education	2.812 (1.063 - 7.438)	**0.037**
	Intermediate education	2.134 (0.501 - 9.091)	0.305
	Secondary education	2.327 (0.780 - 6.946)	0.130
	Higher education	2.208 (0.439 - 11.093)	0.336
Family history of diabetes	No	**1**	
	Yes	2.710 (1.429 - 5.128)	**0.002**
Fast food consumption	0 - 1 Times/Month	**1**	
	2 - 3 Times/Month	0.341 (0.147 - 0.795)	**0.013**
	1 - 2 Times/Week	0.329 (0.132 - 0.817)	**0.017**
	3 - 4 Times/Week	0.513 (0.142 - 1.853)	0.309
	≥ 5 Times/Week	0.548 (0.141 - 2.132)	0.385
BMI groups	18.5 - 24.9	**1**	
	25 - 29.9	1.171 (0.537 - 2.555)	0.692
	≥ 30	1.793 (0.789 - 4.073)	0.163
Triglycerides (mg/dL)	< 150	**1**	
	< 200	1.567 (0.706 - 3.479)	0.270
	≥ 200	3.724 (1.485 - 9.338)	**0.005**
Constant		0.692	0.591

4.4. WHO Quality of life BREF Questionnaire (WHOQoL-BREF)

A comparison among CHD-IR cases and CHD-controls according to the 26 questions of the WHOQoL-BREF questionnaire for quality of life is shown in table 43. The same comparison is shown for CHD-diabetic cases and CHD-controls as shown in table 44. CHD-IR cases had lower overall satisfaction scores with *bodily appearance* than CHD-controls, with mean ranks of 45 versus 65, respectively, ($p = 0.003$). CHD-IR cases had lower score of *overall perception of satisfaction with themselves* than CHD-controls with mean rank of 51 versus 62, respectively ($p = 0.041$). On the other hand, CHD-diabetic cases had lower overall perception of quality of life scores than CHD-controls. Their mean rank quality of life score was 136 versus 166, respectively ($p = 0.002$). The CHD- diabetic cases had lower overall satisfaction with the *bodily appearance* scores than CHD-controls with mean ranks of 137 versus 164, respectively ($p = 0.012$). CHD-diabetic cases had lower score of *overall perception of satisfaction with themselves* than CHD-controls with mean rank of 138 versus 162, respectively ($p = 0.015$). CHD-diabetic cases had lower score of *overall satisfaction with access to health services* than CHD-controls (141 versus 153, respectively, $p = 0.049$) and lower overall satisfaction score with their transport than CHD-controls (141 versus 154, respectively, $p = 0.027$).

The quality of life profile scoring of CHD-IR cases and CHD-controls is shown in table 45, while the scoring of CHD-diabetic cases and CHD-controls is shown in table 46. CHD-IR cases had a lower mean (SD) of psychological domains raw score, transformed scores 4-20 and transformed scores 0-100 than among CHD-controls. The means (SD) for CHD-IR were 22.6 (2.1), 15.0 (1.4) and 60.2 (5.5) respectively, while for CHD-controls were 23.8 (2.2), 15.8 (1.5) and 63.4 (5.9), respectively, ($p = 0.006$). No other significant results are shown in other different domains.

Table 43: Comparison among CHD-IR cases and CHD-controls according to the 26 questions of quality of life.

CHD N = 325	CHD-Controls n = 79 (%)		CHD-IR n = 37 (%)		*p*
	Median (IQR)	Mean rank	Median (IQR)	Mean rank	
Individual's overall perception of quality of life. **Q1. How would you rate your quality of life?**	5 (4 - 5)	-	5 (4 - 5)	-	0.808
Individual's overall perception of health. **Q2. How satisfied are you with your health?**	4 (4 - 4)	-	4 (4 - 4)	-	0.322
Q3. To what extent do you feel that physical pain prevents you from doing what you need to do?	4 (3-5)	-	4 (3-5)	-	0.940
Q4. How much do you need any medical treatment to function in your daily life?	1 (1-1)	-	1 (1-1)	-	0.476
Q5. How much do you enjoy life?	5 (4 - 5)	-	4 (4 - 5)	-	0.056
Q6. To what extent do you feel your life to be meaningful?	5 (5 - 5)	-	5 (5 - 5)	-	0.166
Q7. How well are you able to concentrate?	5 (5 - 5)	-	5 (5 - 5)	-	0.234
Q8. How safe do you feel in your daily life?	5 (5 - 5)	-	5 (5 - 5)	-	0.686
Q9. How healthy is your physical environment?	5 (5 - 5)	-	5 (5 - 5)	-	0.948
Q10. Do you have enough energy for everyday life?	4 (3 - 5)	-	4 (3 - 5)	-	0.640
Q11. Are you able to accept your bodily appearance?	3 (2 - 5)	65	2 (2 - 3)	45	**0.003**
Q12. Have you enough money to meet your needs?	4 (4 - 5)	-	5 (3 - 5)	-	0.294

Q13. How available to you is the information that you need in your day-to-day life?	4 (3 - 5)	-	4 (3 - 5)	-	0.130
Q14. To what extent do you have the opportunity for leisure activities?	4 (4 - 5)	-	5 (4 - 5)	-	0.374
Q15. How well are you able to get around?	5 (5 - 5)	-	5 (5 - 5)	-	0.793
Q16. How satisfied are you with your sleep	5 (3 - 5)	-	5 (4 - 5)	-	0.716
Q17. How satisfied are you with your ability to perform your daily living activities?	4 (4 - 5)	-	4 (3 - 5)	-	0.444
Q18. How satisfied are you with your capacity for work?	4 (3 - 5)	-	4 (3 - 5)	-	0.940
Q19. How satisfied are you with yourself?	5 (4 - 5)	62	5 (4 - 5)	51	**0.041**
Q20. How satisfied are you with your personal relationships?	5 (5 - 5)	-	5 (5 - 5)	-	0.773
Q21. How satisfied are you with your marriage relationship?	5 (5 - 5)	-	5 (5 - 5)	-	0.703
Q22. How satisfied are you with the support you get from your friends?	5 (5 - 5)	-	5 (5 - 5)	-	0.651
Q23. How satisfied are you with the conditions of your living place?	5 (5 - 5)	-	5 (5 - 5)	-	0.297
Q24. How satisfied are you with your access to health services?	5 (5 - 5)	-	5 (5 - 5)	-	0.963
Q25. How satisfied are you with your transport?	5 (5 - 5)	-	5 (5 - 5)	-	0.717
Q26. How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5 (3-5)	-	5 (3-5)	-	0.886

Table 44: Comparison among CHD-diabetic cases and CHD-controls according to the 26 questions of quality of life.

CHD N = 325	CHD-Controls n = 79 (%)		CHD-Diabetic n = 209 (%)		*P*
	Median (IQR)	Mean rank	Median (IQR)	Mean rank	
Individual's overall perception of quality of life. **Q1. How would you rate your quality of life?**	5 (4 - 5)	166	5 (4 - 5)	136	**0.002**
Individual's overall perception of health. **Q2. How satisfied are you with your health?**	4 (4 - 4)	-	4 (3 - 4)	-	0.284
Q3. To what extent do you feel that physical pain prevents you from doing what you need to do?	4 (3-5)	-	4 (3-5)	-	0.766
Q4. How much do you need any medical treatment to function in your daily life?	1 (1-1)	-	1 (1-1)	-	0.509
Q5. How much do you enjoy life?	5 (4 - 5)	-	4 (4 - 5)	-	0.700
Q6. To what extent do you feel your life to be meaningful?	5 (5 - 5)	-	5 (5 - 5)	-	0.501
Q7. How well are you able to concentrate?	5 (5 - 5)	-	5 (4 - 5)	-	0.290
Q8. How safe do you feel in your daily life?	5 (5 - 5)	-	5 (5 - 5)	-	0.228
Q9. How healthy is your physical environment?	5 (5 - 5)	-	5 (5 - 5)	-	0.351
Q10. Do you have enough energy for everyday life?	4 (3 - 5)	-	4 (3 - 5)	-	0.630
Q11. Are you able to accept your bodily appearance?	3 (2 - 5)	164	3 (2 - 4)	137	**0.012**
Q12. Have you enough money to meet your needs?	4 (4 - 5)	-	4 (3 - 5)	-	0.853

Q13. How available to you is the information that you need in your day-to-day life?	4 (3 - 5)	-	4 (3 - 4)	-	0.079
Q14. To what extent do you have the opportunity for leisure activities?	4 (4 - 5)	-	5 (4 - 5)	-	0.919
Q15. How well are you able to get around?	5 (5 - 5)	-	5 (5 - 5)	-	0.098
Q16. How satisfied are you with your sleep	5 (3 - 5)	-	5 (3 - 5)	-	0.595
Q17. How satisfied are you with your ability to perform your daily living activities?	4 (4 - 5)	-	4 (4 - 4)	-	0.160
Q18. How satisfied are you with your capacity for work?	4 (3 - 5)	-	4 (3 - 4)	-	0.329
Q19. How satisfied are you with yourself?	5 (4 - 5)	161	5 (4 - 5)	138	**0.015**
Q20. How satisfied are you with your personal relationships?	5 (5 - 5)	-	5 (5 - 5)	-	0.505
Q21. How satisfied are you with your marriage relationship?	5 (5 - 5)	-	5 (5 - 5)	-	0.474
Q22. How satisfied are you with the support you get from your friends?	5 (5 - 5)	-	5 (5 - 5)	-	0.375
Q23. How satisfied are you with the conditions of your living place?	5 (5 - 5)	-	5 (5 - 5)	-	0.124
Q24. How satisfied are you with your access to health services?	5 (5 - 5)	153	5 (5 - 5)	141	**0.049**
Q25. How satisfied are you with your transport?	5 (5 - 5)	154	5 (5 - 5)	141	**0.027**
Q26. How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5 (3-5)	-	5 (3-5)	-	0.239

Table 45. The quality of life profile scoring of CHD-IR cases and CHD-controls

Domains N = 325	CHD-controls n = 79			CHD-IR n = 37			t	*p*
	Raw score	Transformed scores		Raw score	Transformed scores			
		4-20	0-100		4-20	0-100		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Physical health	27.7 (3.1)	15.8 (1.7)	63.4 (7.0)	27.7 (3.0)	15.8 (1.7)	63.4 (6.9)	0.007	0.994
Psychological	23.8 (2.2)	15.8 (1.5)	63.4 (5.9)	22.6 (2.1)	15.0 (1.4)	60.2 (5.5)	2.791	**0.006**
Social relationships	14.2 (2.0)	19.0 (2.6)	75.8 (10.5)	14.4 (1.3)	19.2 (1.7)	76.7 (6.8)	0.460	0.647
Environment	36.5 (2.7)	18.3 (1.4)	73.1 (5.5)	37.2 (3.2)	18.6 (1.6)	74.3 (6.3)	1.081	0.282

Table 46. The quality of life profile scoring of CHD-diabetic cases and CHD-controls

Domains N = 325	CHD-controls n = 79			CHD-diabetic n = 209			t	*p*
	Raw score	Transformed scores		Raw score	Transformed scores			
		4-20	0-100		4-20	0-100		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Physical health	27.7 (3.1)	15.8 (1.7)	63.4 (7.0)	27.4 (2.9)	15.7 (1.7)	62.7 (6.7)	0.788	0.431
Psychological	23.8 (2.2)	15.8 (1.5)	63.4 (5.9)	23.2 (2.1)	15.5 (1.4)	62.0 (5.5)	1.912	0.057
Social relationships	14.2 (2.0)	19.0 (2.6)	75.8 (10.5)	14.0 (2.2)	18.7 (2.9)	74.7 (11.6)	0.750	0.454
Environment	36.5 (2.7)	18.3 (1.4)	73.1 (5.5)	35.7 (3.8)	17.9 (1.9)	71.4 (7.6)	1.783	0.076

5. Chapter 5 - General Discussion and conclusion

5.1. TB Discussion

Low- and Middle-Income Countries have witnessed a rapidly increasing incidence and prevalence of T2DM in recent decades. This increase has occurred while the global incidence of TB has declined steadily over several decades, although at a much lower rate than predicted by the WHO (312), and this condition still remains the main cause of infectious death in many countries. These two situations have resulted in both conditions increasingly being encountered as co-morbidities in the world.

The TB prevalence in the Middle East is low compared to other areas of the world as for example, by 2010 the UAE reported 6.2 cases per 100,000 population, while Saudi Arabia and Iran had reported 23 cases per 100,000 population (203, 313). Although these rates are relatively low in the Middle East, TB is often concentrated in specific population groups, notably migrants from Asia and Africa and the elderly.

Countries in the Middle East have also experienced major increases in T2DM. These increases are historically recent, as lifestyle patterns have mainly change since the discovery of petroleum, which in Saudi Arabia occurred in 1938, followed by an exponential increase in oil production in the 1970s. Increased wealth in Saudi Arabia was accompanied by increasing obesity, sedentary habits and T2DM. Saudi Arabia is nowadays home to a population with the highest prevalence of risk factors for T2DM such as obesity (56) and the IDF classifying Saudi Arabia as one of the ten countries with the highest estimated T2DM prevalence in the world. T2DM increases continued unabated in recent years, with a 2011 estimated prevalence of 16.2%, which is expected to reach 20.8% by 2030 (54, 55).

The country, therefore, increasingly has patients with T2DM and populations, including migrants from places with a high prevalence of TB are, particularly, at risk of having both co-morbidities. A systematic review of the prevalence of T2DM and TB co-morbidity in Middle Eastern countries (314) reported that the prevalence of both conditions varied across the region, from as low as 4.2% in Iran to as high as 60% in Yemen (31, 189). African-based studies in comparison, have reported that the proportion of patients with TB that have T2DM at the time of diagnosis is generally lower, ranging from 3.4% to 16.4% of TB cases (203).

In our study, 29% of TB cases had T2DM. This high proportion is comparable to studies from areas with a high prevalence of T2DM, such as Mexico (29.3%), Taiwan (29.5%) and Kerala-India (44%), but is higher than in other areas closer to the Middle East Region with low T2DM but high TB prevalence, such as Ethiopia (8.3%) and Uganda (8.5%) (31).

The association of T2DM and TB is not limited to LMICs. While the prevalence of TB is generally low in industrialized high-income countries, the association of TB-T2DM is generally lower, although with wide geographical variations. A cohort in Barcelona of 5849 patients with TB recruited between 2000 and 2013 reported that 4% to 7.2% had T2DM (215). This proportion was lower than in Japan, where 13.1 of patients with TB had T2DM, which was attributed to TB mostly occurring among the elderly population; and in the UK (16%) and the USA (12%), where obesity rates are higher than Japan and Spain (315). In these settings, T2DM still increases the risk of TB. Although this association is weaker than in low income countries. In a UK case-control study, the AORs for TB among patients with a history of T2DM was 3.8 ($p < 0.05$) (216). However, further case-control studies in Denmark, Australia and the USA, have reported that T2DM only modestly increased the risk of TB (203).

In TB endemic regions there is great concern regarding the increased risk of TB that occurs due to T2DM. Bi-directional associations have been reported in the literature between hyperglycaemia and TB (316, 317). TB is an infection that triggers a major inflammatory process that is recognised to trigger hyperglycaemia, and it is possible the presence of inflammation has led to an over-diagnosis of T2DM. This is also the case with other conditions, such as pregnancy that can cause transient stress-related hyperglycaemia and other infections. The stress-related hyperglycaemia associated with TB could be caused by an increase in IR, which occurs through a complex interaction involving cytokines, growth hormones, catecholamine and cortisol (318-320). This IR can lead to hyperglycaemia through two pathways, the first being through hepatic glucose being overproduced via the inability to suppress gluconeogenesis, and the second is due to insulin-mediated defects in the uptake of glucose. Stress-related hyperglycaemia also leads to blood glucose levels being further increased as it enhances the inflammatory response (318). Individuals with both hyperglycaemia and TB who receive anti-TB treatment often have a substantially decreased FPG when the TB is cured. Conversely, TB can worsen a pre-existing T2DM and TB treatment outcome is poor in the presence of hyperglycaemia. Transient hyperglycaemia can be present in a significant number of individuals that already have T2DM and, therefore, this distinction is difficult at the time individuals presents to the clinic with a new episode of TB. Studies have recently indicated that after anti-TB treatment for 6 months 38% of these individuals still have hyperglycaemia, which indicates in 60% hyperglycaemia was related to the inflammatory process, while 38% had an underlying T2DM (321)

The majority of studies regarding T2DM and TB are observational, with few studies being prospective cohorts. Most cohort studies are retrospective and based on patient

medical records, making it difficult to infer the directionality of the association. Although the majority of data indicate that T2DM precedes TB in a substantial number of patients, not all cases presenting with hypaerglacaemia will have the lifelong glucose abnormalities of T2DM (220). Several cross-sectional studies have supported the view that T2DM increases susceptibility to TB and patients with TB and diabetes have a median 7 years since their T2DM diagnosis and have experienced other complications of T2DM before the development of TB (196, 219, 221).

Another possible view is that TB may increase the risk of developing T2DM, although this theory is uncommonly considered in literature at present (221). A number of studies have revealed that on the early phase of TB, IGT and/or induced hyperglycaemia occur (222). This incidence can be significant as 20 - 50% of individuals with IGT go on develop to T2DM, which is usually seen to occur after 3 to 5 years (222, 223). Establishing the real contribution of T2DM to TB is not straightforward as it can be sporadic hyperglycaemia associated to inflammation, which may reverse after TB treatment (222, 223) or TB may results as a result of reduced resistance to TB due to the underlying T2DM. Hyperglycaemia may also present itself as a side effect of treatment with Isoniazid and Rifampicin (224).

A Tanzanian study reported that upon enrolment, patients with TB that had glucose levels that were consistent to T2DM, newly diagnosed T2DM patients account for 50 - 80% (based on the type of screening test) of the study group. A further study in Mwanza, Tanzania gave similar findings with 77% of individuals with T2DM were newly diagnosed T2DM cases. Studies in China and India however, have reported different results with over 50% of cases being diagnosed with T2DM before they the TB diagnosis (321-323). The majority of the individuals that were recently diagnosed

with T2DM had experienced a moderate increase in glycaemic levels. At the time of TB diagnosis, the majority of patients recently diagnosed as T2DM and pre-DM had reverted to normal glucose and were considered to have transient hyperglycaemia (321). In Iran, a third of the patients newly diagnosed to have TB had high levels of HbA1c, which after three months of anti-TB treatment had returned to normal (324). Transient hyperglycaemia is likely caused by a number of factors, which could reflect the inflammation that is caused by TB, the predisposition of the patient and the hyperglycaemic effect that is caused by anti-TB treatment (325). This reverse causality may occur when the diagnoses of the diseases are made close together. The high occurrence of transient hyperglycaemia found in patients with TB gives rise to the notion of reverse causality between T2DM and TB, which also highlights the importance of further T2DM screening being implemented later into the treatment of TB. Moreover, there is also a need to address whether transient hyperglycaemia that is observed in patients diagnosed with TB would result in a greater risk of developing T2DM later in life (326).

5.1.1. Summary of this thesis findings

This study was carried out among patients formerly treated for TB. A high proportion of the cases were non-Saudi citizens, with the majority originating from Somalia, Yemen, Ethiopia, Pakistan, Sudan, Chad, Bangladesh, Eritrea and the Philippines. A high frequency of patients formerly treated for TB and controls without TB had T2DM, with no difference among cases and controls at the univariate analysis. Patients with T2DM, those with TB were more likely to be using insulin (20.4%) than controls without TB (6.1%). An important issue in the univariate analysis, however, was that cases were younger than controls. As T2DM and its risk factors increase with age, it was considered that this was likely a

significant confounding factor and, therefore, its interpretation needs to be interpreted with caution, and the multivariate analysis conducted was controlled by age. The results of the final multivariable backward stepwise logistic regression including T2DM indicate that cases were more likely to be non-Saudis, to have T2DM and that they had a poorer diet than controls. Cases were more likely to eat fast foods 1 – 2 times/week or 2 – 3 times/month, less likely to be obese, to have higher total cholesterol and a lower level of *risky* HDL Cholesterol than controls. On the other hand, when we replaced variables for T2DM and replaced them with the more comprehensive definition of metabolic syndrome, the multivariable backward stepwise logistic regression results indicated cases were more likely to be non-Saudis and had a poorer diet than controls. Cases were also less likely to be obese and to have higher total cholesterol than controls.

TB-T2DM and TB-IR cases were also compared with TB-controls to identify risk factors for T2DM or IR. Both male and female patients with T2DM had higher BMI and were much more likely to be obese, had higher cholesterol and triglycerides. Moreover, patients with T2DM had higher LDL cholesterol and more likely to have experienced haemoptysis than patients without T2DM. Female cases with T2DM were more likely to have experienced gestational diabetes. Similarly, the comparison of TB-IR and TB-controls indicated patients with IR were more likely to have experienced heart problems, to have been overweight during childhood, total cholesterol and females had higher median BMI. These characteristics replicate well established risk factors for both T2DM and IR among the general population and their association to TB is still unclear.

Although many studies have reported the increased prevalence of T2DM among patients with TB at the time of making the diagnosis of TB, there are very few

studies examining whether patients formerly treated for TB continue to have T2DM several months after treatment when the inflammatory processes associated with TB have subsided. Patients with TB often have IFG, for example, in West Africa 1.9% of patients with TB had T2DM and 5% had IFG (26). In Sri Lanka, 7.1% of patients with TB had T2DM and 20% had IFG (27). Although IFG could reflect a predisposition to T2DM, IFG is also likely due to the pro-inflammatory responses to TB, the effect of medications or the 'stress/transient hyperglycaemia' phenomenon (9).

We measured IR with the HOMA2-IR method which describes the balance of insulin levels in the context of fasting glucose conditions. The HOMA-IR is extensively used as a regular measurement tool in clinical practice and epidemiological research and is one of the more popular fasting indices (327). Although the hyperinsulinaemic-euglycaemic clamp technique is still considered the gold-standard for IR diagnosis and is still the diagnostic tool of preference in some clinical settings, it was not a viable option in this study, as study subjects were investigated in out-patient departments and the tool is time consuming. One significant disadvantage of the HOMA-IR is that it does not have a standardized limit to categorize individuals that have IR. Prior studies have indicated that IR appears between HOMA-IR levels of 1.55 - 3.8 (328), which is a large range. In this study we used a cut-off ≥ 2, as this is the cut-off used in most publications. Using this cut-off, in participants without T2DM, the prevalence of IR among euglycaemic patients with former TB was 22%. This prevalence rates fall between the 20% to 40% IR rates reported in the general population of Saudi Arabia (327) and, therefore, we found no evidence that IR is more or less frequent among patients who formerly had TB.

A prospective cohort study in patients with TB in South Africa suggested a gradual decrease in IR after initiation of TB treatment. Moreover, when confounding variables were considered, the study reported that HOMA-IR was not associated with the diagnosis of TB. These findings thus suggest IR in a significant proportion of the patients could be due to the 'stress/transient' hyperglycaemia that is present early in the diagnosis of TB and that is eventually resolved once treatment for TB progresses (329-331).

IR has long been linked to the ageing process, (332, 333), as it is generally linked to an increase in fat mass and body weight, particularly in the centre of the body (334), along with a greater prevalence of chronic lifestyle-associated diseases such as metabolic syndrome (335). Generally, an increased anthropometrical measurement gives a greater risk of IR; (336) with a positive correlation between the waist-to-hip ratio (337) and the BMI (338).

Studies in the past have also suggested that undernutrition does not only occur in TB patients due to the disease itself, but rather to a number of other factors such as reduced health-seeking behaviour, extreme poverty and food insecurity (339, 340). Indeed, several studies have suggested that epigenetics may play a critical role in the Middle East populations, explaining the higher prevalence of both T2DM and IR. A recent study suggested epigenetic changes in these populations share many of the characteristics reported in European populations, but that some novel mechanisms are unique to Arab populations; suggesting that the underlying mechanisms in the region might depend on their genetic background and local environmental pressures (341). We have written in reverse causality the directionality of association between T2DM and TB.

5.1.2. Recommendations for clinical practice

Clinical practice recommendations include the application of bi-directional (TB and T2DM) screening in healthcare facilities along with the monitoring patients with TB upon commencing treatment for the presence of hyperglycaemia. Although not considered in this thesis, patients with T2DM have poorer response to TB treatment and newly diagnosed patients with TB and T2DM should be followed closely to monitor treatment response. Patients with clinical symptoms of T2DM, biochemical or anthropometrical markers should also be referred for nutritional support in a timely manner, preferably at the intensive treatment phase of TB.

Future avenues of research include assessing how IR prevalence changes in cohort studies to describe changes in T2DM and IR prevalence and to identify individuals with overt T2DM that require long term management. Furthermore, patients with established T2DM could be compared to patients who have transient hyperglycaemia to explore how to differentiate both conditions at the time of TB diagnosis. Finally, patients with transient hyperglycaemia may go on to develop over T2DM, as observed among women with gestational diabetes, and should be followed over time.

5.1.3. Limitations

The study has significant limitations. These include the lack of standardised HOMA-IR reference values, along with potential reliability issues surrounding the measurement of fasting insulin. Although the former are limitations shared with other studies, the latter was due to logistical constrains when conducting the study, as it was not possible to obtain external quality assurance to confirm insulin measurements were correct. Although laboratories in Saudi Arabia undergo rigorous

quality control procedures, it would have been ideal to replicate a subset of tests in a second quality-assured laboratory to confirm the reliability of the measurements.

There are also limitations during the study implementation, as one city had very few patients with TB and patients were recruited in two cities 300 kilometres apart, which limited the supervision to alternative weeks. There may have been compliance issues with the requirement of participants' interview, sample collection and transport which the PhD candidate could not oversee all the time.

A further limitation is that patients were enrolled several months after the initial TB diagnosis, which could have generated recall bias and lost to follow up, especially among non-Saudi patients who may have left the country. Ideally, patients should have been enrolled at the time of their TB diagnosis for prospective follow up as cohorts with and without T2DM or IR.

With regards to selection biases and methodological limitations, it was clear the choice of controls was not adequate, as controls were older than TB cases and very different to patients with CHD. These substantial different likely precluded correcting these differences by the use of logistic regression s, and this is acknowledged as a major limitation of this thesis.

Lastly, the sample size of the study should have been bigger. Although the data collected met the original samples size estimations, we did not expect to find the high prevalence of T2DM and IR among controls and, therefore, the study is likely to be underpowered. The high prevalence of T2DM in cases with TB resulted in a small sample size of the group with TB and IR and, therefore, we were unable to conduct a logistic regression analysis. It is thus likely the study did not identify metabolic

anomalies that might be present at a low frequency among patient populations with a lower prevalence of T2DM among the general population.

5.1.4. Strengths

The study provided baseline information, which will help Saudi Arabia to strengthen the TB control programme and increase the knowledge toward exploring the prevalence of euglycaemic IR among TB patients, its role as a risk factor for TB and the severity of clinical presentation, which are poorly established in Saudi Arabia. A further strength is the high response rate, as most eligible patients accepted to participate. Further, a team of trained interviewers interviewed the participants at a mutually convenient location either in their own homes or the healthcare facilities to meet participant satisfaction. Despite the hot weather, blood sample transportation was within two hours of collection by a reporter using a box and container with ice under safety precautions and samples were processed in fully accredited, a high-quality laboratory in King Fahad Hospital.

The availability of data and adequacy for testing the hypothesis is integral to the validity of a retrospective case-control study. A key strength of the data collection was using the ministry of health TB databases to complete missing information and to verify data collected at the time of the interview that referred to the time of TB diagnosis.

5.1.5. Conclusion

The results of this study suggest that the frequency of T2DM and IR in patients with TB was very high with more than a quarter of patients having T2DM. However, the frequency of IR was not higher among patients with TB than among individuals without TB, reflecting the very high prevalence of IR among the general population.

Patients with a history of TB had lower HDL cholesterol; were more likely to be prediabetic and to be non-Saudi. Patients with TB and T2DM or IR shared the same characteristics as patients with T2DM and IR without TB. Patients with IR were more likely to have experienced CVDs and to be obese or overweight and report poor diet habits, while the lack of exercise and active lifestyles were nearly non-existent. There is a need for early identification programs, in particular within vulnerable and young populations to enable IR reversal and to prevent future complications associated with IR and T2DM.

5.2. CHD Discussion

CHD is nowadays recognised a public health problem in Saudi Arabia, with a significant number of research studies published between 1985 and 2015 (342). Cardiovascular diseases are associated with a higher mortality among patients with T2DM and cardiac complications are usually the result of dyslipidaemia, with elevated triglycerides and LDL cholesterol and a decrease in HDL cholesterol. It has long been recommended (e.g. by the ADA, 1999) that lipid profiles should be monitored regularly in patients with T2DM, as this is a major contributor to coronary artery disease, because impaired lipid homeostasis and lipid peroxidation worsen as glycaemic control deteriorates (343).

The city directorate of King Abdul Aziz for Technology and Science has acknowledged that the lifestyle of the Saudi Arabian residents is facing a transition, with an increase in unhealthy diets, fast food consumption and sedentary lifestyles. These changes have been attributed to socioeconomic changes with the population having a rapid process of urbanisation and environment factors (344). Numerous studies have reported risk factors for CHD associated with lifestyle changes in Saudi

Arabia (345, 346). Among these, obesity and T2DM are prominent. In King Faisal hospital (2011), 30% of patients with CHD had T2DM and 70% of females and 64% of males were obese and these are often markers of unhealthy lifestyles (258). A study in four Middle East countries of 840 participants (374 in Israel, 120 in Lebanon, 150 from the UAE and 196 in Saudi Arabia) with established CVD reported that nearly half were former or current smokers (46%), obese (38.6%), around a third had dyslipidaemia (34.1%), half had T2DM (52.3%) and the majority had hypertension (80.2%) (347, 348). The Eastern Mediterranean region has a high prevalence of smoking (25.4%) which is nearly as high as regions with the highest smoking rates in the world (Western Pacific, 25.8%; Europe 27.3%) (349) and higher than the global average of 22.7%. In the region, males smoke more (40%) than females (6.8%) (350). A 2016 WHO report indicated 12.2% of adults in the Saudi population were smokers (351), highlighting that patients with CHD have higher smoking rates than the general population.

The lack of exercise is a major risk factor worldwide, with 23% of adults undertaking less moderate to vigorous physical activity than the recommended 150 minutes per week. The Eastern Mediterranean Region has very low figures of physical activity, with only 27.5% of men and 38.7% of women being physically active. The least physically active population in the region is Saudi Arabia, while the most active is Jordan (350). A Saudi Health Information Survey reported that 75.1% of women and 46% of men reported having no or very low physical activity (352) and a 2016 systematic review confirmed that 53.2% to 98.1% of Saudi women reported no physical activity (353).

Diet is also a major risk factor for CHD including low fibre, vegetable and fruit intake along with a high intake of processed foods, saturated fats, sugar and salt.

Countries in the Middle East and North African region have the highest sodium intake. The population also has an inadequate fruit and vegetable intake and in Saudi Arabia only 7.3% of 15 - 64 year olds consume the recommended daily five fruit and vegetable servings (351).

The Eastern Mediterranean region has the third highest prevalence of obesity in the world, with 14.6% of males and 23.6% of females classed as overweight. The Gulf countries have the highest rates of obesity within this region (351). Although currently Qatar has the highest prevalence of obesity estimated at 67.5% of women and 38.2% of men, some projections indicate that Saudi Arabia may overtake this in the near future (354) and a systematic review indicated that although between 6% to 29% Saudi female university students had obesity, this figure increased to 21% to 71% among women participating in national surveys or attending primary care centres (351).

The prevalence of hypertension is also high within the Eastern Mediterranean Region (350) with Somalia having the highest prevalence along with Morocco (25.3%), while the UAE has the lowest prevalence (14.7%), although a screening program in Abu Dhabi indicated 23% of adults had hypertension. In Saudi Arabia, 17.7% of men and 12.5% of women have hypertension (350, 351).

The 2008 WHO dyslipidaemia report, is the latest available to date (355). The global prevalence of total cholesterol ≥ 5 mmol/l among adults ≥ 25 years old was 40.2% for women and 37.3% for men (355). The Eastern Mediterranean region had the third highest hypercholesterolaemia with 36.2% of men and 40.4% of women, with most of the Gulf countries having a prevalence ≥ 50%. The prevalence of dyslipidaemia

among Saudi was 36.4% for women and 42.1% for men. It is, however, likely these frequencies are much higher ten years later. (355).

Over 75% of T2DM patients die from CVD-related diseases, which is double the figure of patients without T2DM (356). Our findings, therefore, confirm the high prevalence of comorbidity in patients with stable CHD.

This study also confirms that patients with CHD are more likely to have IR. Former studies have examined the association between atherosclerosis and IR. For example, Karrowni et al. reported a series of 1073 non-diabetic patients examined using angiography after myocardial infarction found an independent link between multi-vessel CHD and IR (357). Granér et al. found that patients that exhibited a higher degree of IR also exhibited more extensive and severe forms of CHD than individuals that displayed lower levels of IR (358). Baseline fasting hyperinsulinemia is a predictor of coronary atherosclerosis among non-diabetic patients (359). Hyperinsulinemia, has been identified in numerous large-scale population based reports as a predictor of CHD (360). However, not all studies have found this association. In a study of 986 consecutive patients examined with elective coronary angiography, there were no HOMA-IR differences (361) and other studies have reported negative associations between ≥ 50% stenosis of the coronary arteries and fasting insulinaemia (362).

5.2.1. Summary of findings

Our study found in the univariate analysis, that a high proportion of patients with stable CHD had T2DM than controls, and that patients with CHD and T2DM were more likely to be using insulin than controls who had only T2DM. Moreover, euglycemic patients with CHD were more likely to have IR than controls. The

regression analysis including T2DM show that cases were more likely to be Saudi, male and to have T2DM. Subjects with CHD were more likely to be over 40 years old, were less likely to be married or previously married or to have primary education. Cases were more likely to be taking hypertensive medications and lipid lowering therapy than controls. Cases were less likely to eat fast foods 3 – 4 times/week, but more likely to have high WHR and diastolic BP than controls.

When the diagnosis of T2DM was included into metabolic syndrome, and thus excluded as a single factor, the logistic regression indicated cases were more likely to be male and more likely to be aged over 40 years old and to have a salary range between SAR 5001 and 10000 per month and less likely to be married and to have primary education. Cases were also more likely to have metabolic syndrome and to report higher levels of stress than controls.

Patients with CHD with T2DM were compared to patients with normoglycemic patients with CHD without IR (the latter used as CHD controls) to examine risk factors for T2DM and IR. Patients with CHD and T2DM were more likely to have experienced gestational diabetes, to have a family history of T2DM, to have been overweight during childhood and to have higher triglycerides, HDL Cholesterol and lower LDL Cholesterol than CHD-controls. Female patients with CHD and T2DM also had higher BMI and were more likely to be obese.

The factors associated with T2DM among patients with CHD were similar to the risk factors for T2DM reported in the literature, and in reports of risk factors for T2DM in Saudi Arabia. The only different factor was the low LDL concentrations. This may be due to the retrospective enrolment of patients with patients being more aware of their T2DM and being more careful with medications after a CHD diagnosis,

resulting in stricter adherence, lifestyle changes and better pharmacological management.

The comparison of euglycemic patients with CHD with and without IR showed that patients with IR had higher anthropometric measurements than patients without IR, with males having higher weight, waist circumference and WHR and females higher weight, BMI and waist circumference.

The logistic regression analysis indicated, after adjusting for age and gender, independent risk factors for T2DM among patients with CHD were being Saudi, to have literacy and primary education, a family history of T2DM, high triglycerides and to consumed fast foods 2 - 3 times/month or 1 - 2 times/week. The only statistically significant factor for IR was obesity (BMI $\geq$ 30).

The WHOQoL-BREF quality of life questionnaire indicated patients with CHD and T2DM or IR had lower satisfaction scores. Patients with T2DM had lower scores for perception of quality of life, *bodily appearance*, *perception of satisfaction with themselves, overall satisfaction with access to health services* and with transport arrangements than controls. Patients with IR had lower scores for *bodily appearance*, *satisfaction with themselves* and low score in the psychological domains than controls.

Our findings, therefore, confirm that both T2DM have a strong correlation with CHD in Saudi Arabia; that patients with CHD and T2DM or IR have similar risk factors to those reported in the literature. Among patients with CHD, patients with IR and T2DM have a lower quality of life.

Although all patients enrolled in this study had stable CHD had known their diagnosis and were under clinical management for CHD, a large proportion still had

anthropometric indices above normal levels reported the consumption of fast foods, a lack of exercise and had abnormal lipid profiles.

5.2.2. Recommendations for future studies

There is a growing risk of CHD developing further in the population in the following decades and, therefore, short and long-term strategies are needed to reduce CHD risk and enhance quality of life. Metabolic syndrome is a major factor for CHD and reducing its prevalence should be a key foundation to reduce CHD incidence. Moreover, efforts should be made by Saudi Arabia to adopt nationwide programs to promote the primary prevention of CHD. There should be a great emphasis on early interventions as this can provide the basis that educates children to develop healthier lifestyles, implemented through targeting parents to start this at home, as well as teachers at schools. A longitudinal study may be required to demonstrate how lifestyle modifications can have an effect on reducing the risk of CHD by reducing weight, controlling T2DM and hypertension, quitting smoking, promoting physical activity and also making efforts to manage metabolic syndrome in lowering the CHD risk. Future research into the exact status of the Saudi population and what strategies and measures can be revised and used to remedy current issues and improve the health status of the nation. Studies are also required to assess national and community scale findings on how chronic diseases contribute as CHD risk factors and how to combat these issues by creating strategies to encourage the public to change behavioural habits and improve the framework for health education.

5.2.3. Limitations

The study has significant limitations. These include the same lack of standardised HOMA-IR reference values and the limitations described above in the enrolment of patients with TB apply to patients with CHDs, as discussed in previous sections.

We also used a single elevated reading for fasting glucose as the basis of defining whether an individual had T2DM, which could have resulted in incorrect classification of the patient who had a randomly high fasting glucose on a given day. At the baseline, the study did not involve an oral glucose tolerance test, which could mean that some T2DM cases were missed; particularly the patients with impaired fasting glucose results.

Controls were selected using systematic random sampling by selecting every fifth participant attending to the TB and chest diseases centre. We used the same controls recruited from the TB and chest diseases centre for CHD group which caused major limitations to compare the groups. With regards to selection biases and methodological choices, as we used the same controls recruited from the TB and chest diseases centre for CHD group, controls were much younger than the CHD group. Furthermore, because we have controls from a different city, patients had different types of diseases that patients attending King Fasial Hospital in Taif and, therefore, we were unable to correct these differences by logistic regression.

The controls were also older than TB cases as TB disease that affects your adults who are also younger than CHD group. Patients with CHD disease are usually older and, therefore, the controls were poorly matched to TB and CHD cases. Furthermore, usually, patients attending the TB and chest diseases centre are healthier than patients attending the hospitals as they are come to the centre for occupational health checks or

with mild respiratory tract infections, while patients attending the hospitals usually have moderate to severe health problems. Therefore, these differences may have had a direct effect on the prevalent risk factors for IR and T2DM identifies in this dissertation.

5.2.4. Strengths

The findings of this study are based on a sample of adults who have a well-characterised CHD status. The study provided baseline information, which will help Saudi Arabia to strengthen the CHD control programme and increase the knowledge toward exploring the prevalence of euglycaemic IR among CHD patients and its role as a risk factor for CHD and the quality of life. A further strength is the high response rate as most eligible patients accepted to participate. Further, a team of trained interviewers interviewed the participants at a mutually convenient location either in their own homes or the healthcare facilities to meet participant satisfaction. Despite the hot weather, blood sample transportation was within two hours of collection by a reporter using a box and container with ice under safety precautions and samples were processed in fully accredited, a high-quality laboratory in King Faisal Hospital.

5.2.5. Conclusion

This study confirms an association between T2DM and CHD. CHD were more likely to have T2DM, high FPG, to be male, aged above 50 years old and Saudi and to have primary education, hypertension and to take lipid lowering medications. Cases were more likely to have high WHR and diastolic BP. Patients with CHD and T2DM or IR had lower quality of life and satisfaction scores than controls. There is a need for further health education to promote disease awareness to minimise the occurrence of

T2DM complications. Prospective long-term follow up studies should be conducted to demonstrate an association between IR and CHD.

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Appendix 1: Research Ethics Application

FOR OFFICE USE ONLY	Application Number	Date considered	Reviewed by

Please complete this form in typescript. It is essential that this form is completed fully and the relevant enclosures are received if the study is to receive proper scrutiny by the Research Ethics Committee. If any documentation is missing proposals will not be submitted for review.

Applicant contact details

Name:	FAREED HAMED ALMALEKI
Email address:	F.almaleki@liverpool.ac.uk
Postal Address (if not LSTM):	88 Saxony Road; Liverpool, Merseyside L7 8RU
Telephone number:	07449499191
Administrative Contact Name: (if applicable)	N/A
Administrative Contact Email:	N/A

Administration Charges:

An administration charge of £250 for awards of over £10,000 and £50 for those below will be made for ethical approval

Is the proposed work already funded?	**Yes** ☒	**No** ☐	**n/a** ☐
Total budget of proposal £14000			
Name of Funding Organisation: Saudi Cultural Bureau; UK			

Check List:

The following **Check List** must be completed. Please confirm that the following are enclosed.

	Yes	**Not Applicable**
1 Completed Internal School Transfer Form (ISF) for administration charges	☐	
8 Copies of the completed Application Form without staples	☐	
1 Copy of the Research Protocol	☐	☐
8 Copies of the Questionnaire/case record form without staples	☐	☐
8 Copies of the Consent Form without staples	☐	☐
8 Copies of the Patient Information Sheet without staples	☐	☐
8 Copies of the Translator Agreement without staples	☐	☐
8 Copies of the Draft interview/FGD or observation/Check list enclosed (if used) without staples	☐	☐
8 Copies of the Declaration page - last page of application (**1 signed and initialled** by the applicant plus 7 copies)	☐	

8 Collated Applications – please ensure you collate all documents into 8 separate applications and **NOT** 8 copies of each document	☐	

The completed forms should be sent to: Lois Thomas, Secretary, Research Ethics Committee, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA e-mail: lstmrec@lstmed.ac.uk APPLICATION FORM FOR ETHICAL APPROVAL

(Revised December 2013) **Please refer closely to the Guidance Notes when completing this form.**

All questions must be answered. Any form with sections left blank or answered with N/A will be returned. This form must contain all information necessary for the Research Ethics Committee to make a decision on Ethical Approval.

APPLICANT FULL NAME (w/ title)	FAREED HAMED ALMALEKI
PROJECT TITLE	Establishing the association of Type 2 Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.

Ethical Approvals

Have you submitted this proposal to the LSTM Research Ethics Committee before?	**YES** ☐	**NO**☒
If 'YES', please give date of previous review:		
To which other ethical committees has/will this protocol be submitted? (please list) Department of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia.		
APPROVALS – **Please list any ethical review committees which have already approved the protocol.** pending		
In-Country Ethical Approval - Please list the country (ies) where the research will be carried out and whether or not in-country ethical approval is required.		
Country 1: United Kingdom	**YES** ☒	**NO**☐
Country 2: Saudi Arabia	**YES** ☒	**NO**☐
Country 3:	**YES** ☐	**NO**☐
Country 4:	**YES** ☐	**NO**☐
Add additional lines if your research is taking place in more than four countries.		
Please note if you have marked 'NO' for any country above WRITTEN EVIDENCE must be provided to confirm that in-country ethical approval is not required. This evidence should be attached as an annex to the application. Acceptable evidence includes: • a letter from the national Ministry of Health or other relevant regulatory authority • a letter from an authorised signatory at a local partner A letter from a co-investigator or other researcher at a local partner institution is NOT sufficient evidence. Your ethics application will not be considered until evidence is provided.		

Research Team

List LSTM research team and all collaborators.
(Please include all overseas collaborators and give their affiliations, qualifications and role in the study).

NAME	ORGANISATION	QUALIFICATIONS	ROLE IN STUDY	GEOGRAPHIC LOCATION
Professor Luis Cuevas	LSTM	MD, DTCH, MTropMed	Primary supervisor	UK, Liverpool
Professor Geoff Gill	LSTM	MA, MSc, MD, FRCP, DTM&H	Second Supervisor	UK, Liverpool
Turki Almalki	King Faisal hospital Laboratory	HNC	Technician	Saudi Arabia, Taif
Dr. Mohammed Mougrabi	King Faisal Hospital	FACC, AFS, AFSA, UDIC	Head of the cardiology department	Saudi Arabia, Taif
Hossam El Hakami	King Faisal Hospital	BSCs	Collaborator	Saudi Arabia, Taif
Dr. Ali Asghar	Tuberculosis and chest diseases centre	MBBS	Physician	Saudi Arabia, Jeddah
Mosa Mohammad Atwady	Tuberculosis and chest diseases centre	HNC and HND	Technician	Saudi Arabia, Jeddah
Salma Salah Almutairi	King Fahad Hospital	BSCs	Technician	Saudi Arabia, Jeddah

If proposal is for work relating to an MPhil/Ph.D., please state the name and Department of Supervisor/Tutor	
First supervisor	Professor Luis Cuevas
Department	Department of Clinical Sciences
Signature	

Sponsorship and Indemnity Cover Please see sponsorship and indemnity guidance notes and request form on the LSTM intranet http://pcwww.liv.ac.uk/lstmintranet/research_management/applyingforRG/intro.htm		
Have you submitted a sponsorship and indemnity request form to the Research Office?	YES ☐	NO ☒
If no, do you intend to submit a form and if so, when?	21 June 2016	
If you do not intend to submit the form please give reasons.		

GLOSSARY OF TERMS

List of acronyms used in the application.	
Blood Pressure (mmHg)	*(BP)*
Body mass index	(BMI)
B-type Natriuretic Peptide	(BNP)
Chronic kidney disease	(CKD)
Coronary heart disease	(CHD)
Diabetes mellitus	(DM)
Directly observed treatment short course	(DOTS)
Disease Control and Prevention	(CDC)
Ethylene diamine tetra acetic-acid	(EDTA)
Fasting insulin	(FI)
Fasting Plasma Glucose	(FPG)
Gestational diabetes mellitus	(GDM)
Glucose	(G)
Haemoglobin A1c	(HA1c)
Health care workers	(HCWs)
Hepatitis B virus	(HBV)
Hepatitis C virus	(HCV)
High sensitivity C - reactive protein	(Hs-CRP)
High-density lipoprotein	(HDL)
Human immunodeficiency virus	(HIV)
Impaired glucose tolerance	IGT
Impaired fasting glucose	IFG
Insulin resistance	(IR)
Low-density lipoprotein	(LDL)
Metabolic syndrome	(MS)
Ministry of Health	(MOH)
Muscle–brain	(MB)
Myeloperoxidase	(MPO)
Myocardial infarction	(MI)
Room temperature	(RT)
Saudi Arabia	(SA)
Standard deviations	(SD)
The American Diabetes Association	(ADA)
The homeostatic model assessment	(HOMA)
Triglycerides	(TG)
Tuberculosis	(TB)
Turbidimetric Inhibition Immunoassay	(TINIA)
Type 2 diabetes Mellitus	(T2DM)
Waist to hip ratio	(WHR)
World Health Organization	(*WHO)*

SECTION A
STUDY OUTLINE

A.1	**LAY SUMMARY:** Please use simple language which is understandable to a non-scientific/non-academic audience. Sufficient detail of the protocol must be given to allow the Committee to make an informed decision without reference to other documents. Please spell out all acronyms. *(max 300 words)*

Many studies have shown that patients with myocardial infarction (MI) or heart attacks or Tuberculosis (TB) are more likely to have Diabetes Mellitus (DM). It is likely the presence of Insulin Resistance (IR) with normal glucose is also a risk factor for these conditions.

IR is a physiological condition characterised by reduced cell sensitivity to insulin leading to hyperglycaemia and DM. Both DM and IR have increased considerably worldwide over recent decades and the prevalence of DM globally is 8.5% (2014) and in Saudi Arabia is 23.7%.

TB is the second most frequent cause of death due to an infectious disease, causing 1.5 million deaths and 9.6 million cases worldwide in 2014. The Saudi National TB programme reports that TB is more common among foreigners (26 cases/100,000 individuals) than Saudi nationals (11 cases/100,000 individuals), and visitors from high TB burden countries going to Mecca are thought to be the most common source of infection.

Coronary heart disease (CHD) is the leading cause of death and the presence of DM doubles the risk of CHD. In 2012, three out of 10 of the 56 million deaths occurring worldwide were due to CHD, amounting to 17.5 million individuals. On one national survey between the year of 1995 and 2000, the overall prevalence of CHD in Saudi Arabia was 5.5% among 17232 asymptomatic individuals identified through household visits (364).

This study will aim to describe the prevalence of DM and IR in Saudi Arabia among patients with (a) TB from Jeddah city, (b) CHD from Taif city and (c) apparently healthy controls to investigate the association of IR with TB and CHD.

A.2	**IMPORTANCE OF THE RESEARCH:** Please state the intended value of the research and explain how this research fits in with national/international research priorities. *(max 300 words)*

IR is a physiological condition characterised by the reduced cell sensitivity to insulin leading to hyperglycaemia and is a sign of DM, which is highly prevalent in Saudi Arabia. DM has increased considerably worldwide over recent decades and the prevalence in Saudi Arabia is 23.7% among adults.

In one community-based study, a national epidemiological health survey, examine Saudi population from selected households in all Saudi Arabia regions (eastern, western, southern, northern and central) shows that the overall (crude) prevalence of DM in the age group of 30-70 years of selected households between 1995 to 2000 was 23.7% (95% CI

23.1-24.3) p<0.0001. Out of 16917 Saudi subjects 4004 subjects (23.7%) were diagnosed to have DM. The prevalence of male was 26.2% while the prevalence in female was 21.5% (p<0.00001). The calculated age adjusted prevalence of DM of year 2000 were 22.4% for Male and 21.5% for female. IR also occurs in individuals with normal glucose (euglycaemic), who despite having a low sensitivity are able to maintain normal glucose levels by compensating the lack of sensitivity by increasing the amount of insulin secreted by the pancreas. IR in euglycaemic patients often goes undetected, therefore, euglycaemic patients with IR may be at increased risk of communicable and non-communicable diseases, such as TB and CHD and may increase the clinical severity of the disease.

TB is the second most frequent cause of death due to infectious diseases, causing 1.5 million deaths and 9.6 million cases worldwide (2014). The Saudi National TB programme reports that TB is more common in foreigners (26 cases/100,000 individuals) than Saudi nationals (11 cases/100,000 individuals), and visitors to Mecca are a common source of infection. Although DM is a known risk factor of TB, the prevalence of euglycaemic IR among cases and its role as a risk factor for TB and severity of clinical presentation are poorly established in Saudi Arabia.

CHD is the leading cause of death worldwide due to non-communicable diseases and DM doubles the risk of CHD. In 2012, 17.5 million of the 56 million deaths occurring were due to CHD. Individuals with CHD and DM have a higher mortality than individuals without DM. Although there has been extensive research of the link between CHD and DM, the link between CHD in euglycaemic patients with IR and its role in the severity to the CHD remains ambiguous and has not been studied in Saudi Arabia.

A.3	**DUPLICATION OF RESEARCH:** Indicate what steps have been taken to ensure this work has not already been carried out. If this project or a similar one has been done before what is the value of repeating it? *(max 300 words)*

A search of the databases Medline, PubMed, Web of Science and Scopus was performed with the keywords “Tuberculosis”, “Prevalence”, “Insulin resistance”, “Insulin sensitivity” and/or “Saudi Arabia”. Several studies have reported the risk of TB among DM patients is particularly high in certain populations, such as among Hispanic populations in the USA, perhaps because latent TB infection is more common in these populations. (365-367) A meta-analysis showed that diabetic patients were 3·1 times (95% CI 2·27–4·26) more likely to have TB than controls, with higher effect sizes in non-North American populations (368). The evidence of an association between IR in euglycaemic patients and TB is very scanty. One study reported a strong influence on the number of TB patients in Mexico (369). There are however no published studies addressing the association of IR and TB in euglycaemic patients in Saudi populations.

A search of Medline, PubMed, Web of Science and Scopus was performed using the keywords “Coronary Heart Disease”, “Insulin resistance”, “Insulin sensitivity” “Saudi Arabia”. CHD risk factors reported include age, smoking, drinking alcohol, body mass index (BMI), dietary factors, lack of physical activity, waist circumference, waist to hip ratio (WHR), overweight, obesity, hypertension, hyperlipidemia, and diabetes (370). IR, inflammation and activation of the endothelial system are associated with CHD (371, 372). Numerous studies have demonstrated that

DM and IR are independent risk factors for CHD. To date, extensive studies have been carried out to investigate the roles of hyperglycemia in mortality of CHD, stroke and other CHD in adults (373, 374). However, no study has investigated the influence of IR in euglycaemic individuals among CHD Saudi patients.

A.4	**OBJECTIVES:** List the major objectives of the study. These must be clearly stated and achievable by the proposed design and methods

7. To describe the prevalence of DM and IR among patients with TB in Jeddah city, Saudi Arabia.
8. To describe the prevalence of DM and IR among patients with CHD in Taif city, Saudi Arabia.
9. To explore whether IR is a risk factor for TB.
10. To explore whether IR is a risk factor for CHD.
11. To describe whether the severity of the clinical presentation of TB varies among patients with and without IR and/or DM.
12. To describe whether the quality of life of patients with CHD varies among patients with and without IR and/or DM.

A.5	**METHODOLOGY:** Please include the methodology for each objective (if different) and justify the rationale behind the use of the chosen methodology. Please use simple language which is understandable to a non-scientific/non-academic audience and spell out all acronyms.

Methodology

Study location

This study will be based in Taif and Jeddah city. Taif is located in the western region of Saudi Arabia in the Mecca Province at an elevation of ~1,800 m above sea level, with a total area of eight hundred hectares and an estimated 2014 population of 1,109,846 inhabitants. Jeddah is the largest city in Mecca Province, the largest seaport on the Red Sea, located in the western region of Saudi Arabia with total population currently at 3.4 million people. Jeddah is the principal gateway to Mecca and Medina.

The study will enrol ambulatory patients attending the King Faisal Hospital in Taif and tuberculosis and chest diseases centre in Jeddah. King Faisal Hospital is one of the main referral hospitals in the region with a bed capacity of 500 for general patients and 300 for Obstetrics and Gynaecology. This referral hospital has many specialties in various disciplines and departments and is accredited by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI). King Faisal Hospital was selected because the majority of patients with CHD are referred to this hospital. The hospital belongs to the Saudi Arabia (SA) Ministry of Health (MOH), which will facilitate the agreement between the LSTM and the MOH.

Tuberculosis and chest diseases centre is located in Jeddah and consists of five clinics for diagnosis, treatment and patient's follow-up. There are five doctors headed by the Medical Director. The centre also consists of X-rays, pharmacy, nursing department, infection control and quality and health education department. The blood samples send to the Madain Al-Fahad Health Centre laboratory. The centre provides therapeutic services for patients with newly diagnosed TB and follows patients undergoing TB treatment and until

they are fully cured. The centre provides epidemiological surveillance for Jeddah city, examines and diagnoses suspected cases of TB and initiates treatment, checking and examining contacts of TB patients, doing annual statistical reports for TB and home visits for patients who do not complete treatment. In addition, it provides outreach services and education for patients and their families. The centre offers nutritious aid program to the patients. It was selected because all TB patients in the city are referred to this centre with an estimated 350 new TB patients per year. The centre belongs to the Saudi MOH, which will facilitate the agreement between the LSTM and the MOH.

Objective 1: To describe the prevalence of DM and IR among patients with TB in Jeddah city, Saudi Arabia.

Study design: this will be a cross-sectional survey of patients' ≥18 years old registered at Tuberculosis and Chest Diseases Centre in Jeddah city. Patients will be eligible to participate in the study if they have a diagnosis of bacteriologically confirmed pulmonary TB and have received treatment for at least two months since diagnosis. Only cases considered to be new TB cases (this is, who have not received treatment before) will be eligible. A bacteriologically confirmed case will be defined as any adult whose sputum had acid-fast bacilli in smear microscopy or who had a positive TB culture. In addition, only patients who have responded well to the intensive phase of treatment (first 2 months) will be selected, to avoid patients with drug-resistance TB who may have a continued inflammation process. Patients will be selected during the continuation phase of treatment (i.e. after receiving at least two months of treatment) because the inflammation associated with the disease in these first two months would result in IR. We will, therefore, select confirmed patients who have received treatment for at least two months. Participants will be initially identified from tuberculosis and chest diseases centre treatment registers and should include the following inclusion and exclusion criteria:

Inclusion criteria

6- Patients with bacteriologically confirmed pulmonary TB.
7- Patients aged ≥ 18 and residing in Jeddah city.
8- Registered at TB and chest diseases centre in Jeddah city and still attending the clinic for treatment.
9- Patients have received at least 2 months of anti-TB treatment and is considered to be responding clinically to the treatment.
10- Patients accept to participate when approached at the DOTS clinic.

Exclusion criteria

6- Patients with missing contact information and those deported from the country.
7- Clinical presentation is predominantly Extra-pulmonary TB.
8- Coexistence of a malignancy.
9- Known to be pregnant.
10- Known HIV infection

Once participants have identified, received counselling and guidance, agreed to participate and signed the consent form, a team of trained interviewers will interview them at a mutually convenient location either in their own homes or the healthcare facilities. Field assistants will use structured questionnaires using Arabic and/or English. Data collected will consist of general demographic details such as gender, age, socio-economic status, ethnic group and medical history.

At a convenient time, patients will be asked to provide blood samples after fasting for 12 hours. A phlebotomist will collect 10 ml of venous blood in three different blood tubes as follows: 2 ml in EDTA tube, 4 ml in Lithium Heparin tube and 4 ml in a tube with sodium fluoride anticoagulant. The samples will be collected at phlebotomy area of the Tuberculosis and Chest Diseases Centre in Jeddah city and will be send to the Madain Al-Fahad Health Centre laboratory in Jeddah for processing. The blood samples will be used to do the following tests: Fasting Plasma Glucose (FPG), Fasting plasma insulin, Haemoglobin A1c and lipid profile including LDL, HDL and TG. If the patient is not fasting instructions will be given to returning to the clinic the next day after fasting for 12 hours from 8 PM until 8 AM.

	HA1c	**Lipid profile**	**Glucose and insulin**
Blood volume	2 ml	4 ml	4 ml
Type of tube	EDTA	Lithium Heparin	Sodium fluoride

Patients will be classified as having normal glucose values or DM according to their glycaemic status using the WHO guidelines to determine the DM diagnostic criteria. HOMA will be calculated using the Matthews *et al.* method to detect IR. The formula of IR is as follow: IR = FI×g/22.5, where (FI) is the fasting insulin (μU/mL) and (g) is the fasting glucose (mmol/L). In order to obtain the IR estimate, the sample of venous blood will be taken after 12 hours fasting overnight, with the plasma samples either analysed immediately or stored at -20. The automated analyser (Hitachi Unicel DxI 600) will be used to determine the insulin level and the degree of insulin resistance/sensitivity will be measured using HOMA, which is an established index for measuring resistance/sensitivity. HOMA-IR estimate will not be estimated in patients using insulin. All patients with normal results will be informed of their results via email or phone calls. Patients with abnormal results will be asked to attend the clinic to discuss the results with the doctor.

Objective 2: To describe the prevalence of DM and IR among patients with CHD.
Study design: this will be a cross-sectional survey of patients ≥18 years old registered at the cardiology department the King Faisal Hospital in Taif city. Patients will be eligible for selection into the study if have documented CHD and are medically stable. A stable CHD will be defined as an adult with an established pattern of angina pectoris, a history of confirmed myocardial infarction (MI), or the presence of plaque documented by catheterization. Only patients with stable CHD will be enrolled, as patients with acute coronary syndrome would have an increase in hormones, which will affect lipids, glucose and IR. Participants should be eligible if they have the following inclusion and exclusion criteria:

Inclusion Criteria

5- Patient with stable CHD attending the outpatient clinic.
6- Patients aged ≥18 and residing in Taif city.
7- Registered at Taif King Faisal Hospital, cardiology department, and still attending the clinic for treatment.
8- Patients accept to participate.

Exclusion Criteria

6- Patients with missing contact information and those deported from the country.
7- Known renal disease.
8- Known hepatic disease.
9- Smoking more than 20 cigarettes per day.
10- Known to be pregnant.

Angina pectoris will be defined as a syndrome characterized by paroxysmal, constricting pain below the sternum, most easily precipitated by exertion or excitement and caused by ischemia of the heart muscle, usually due to a coronary artery disease, as arteriosclerosis. Confirmed MI will be defined according to the following criteria: at least 30 min of ischemic chest pain, ECG evidence of MI, a high level to more than 2 SD above the upper limit of the normal range of serum creatinine kinase and more than 4% of MB isoenzyme fraction.

Once participants have been identified, received counselling and guidance, agreed to participate and signed the consent form, a team of interviewers will interview the participant at a mutually convenient location in either their own homes or the healthcare facilities. Field assistants will use structured questionnaires in lay Arabic and/or English. Data collected will consist of general demographic details such as gender, age, socio-economic status, ethnic group, medical history, medication, physical activity, smoking habits, other diseases and family history of cardiac diseases and diabetes.

Patients will be examined to measure height and weight, waist and hip circumference and waist-to-hip ratio (WHR). The blood pressure will be recorded twice from the right arm in a seated position using a mercury sphygmomanometer after 15 to 30 minutes of rest in 5-minute intervals. Patients will be asked to fast for 12 hours and to provide three venous blood samples as described for TB patients and to conduct the same tests. The samples will be send to the King Faisal General Hospital laboratory in Taif for processing. HOMA will be calculated to detect IR in all participants. Patients will be classified as above into normal, euglycaemia with IR or DM. All patients will receive their results using the same procedures as described for TB patients.

Objective 3: To explore whether IR is a risk factor for TB.
Study design: This will be a case-control study in which the cases will be patients with TB. The control group will be patients without TB. Cases will be enrolled from patients participating in the cross-sectional survey first (objective 1) and will be the same patients attending spontaneously to tuberculosis and chest diseases centre with confirmed TB. Controls will be individuals attending to the same centre who were treated for other conditions and were deemed not to have TB. Controls will undergo the same tests as cases and both groups will be examined to establish if they have IR. The questionnaire for this objective will include a comprehensive list of factors associated with risk of TB and/or IR such as lifestyle, physical activity, diet, BMI, medical history and others. We will obtain anthropometric measurements (by a nurse of the same gender) including height (cm), weight (kg) and waist and hip circumference (cm). BMI will be calculated as weight (kg)/height^2 (m^2). Participants should be eligible if they have the following inclusion and exclusion criteria:
Inclusion criteria:
5- Patients participating in the survey for objective 1.

6- Controls will be adults attending the TB Centre without TB.
7- Participant aged ≥18 and residing in Jeddah city.
8- Patients accept to participate.

Exclusion criteria:

2- Same as objective 1.

According to the HOMA measurement and glucose testing, participants will be classified as having IR with and without DM. The prevalence of DM among TB patients in Saudi Arabia is reported in the literature to be between 14% and 26%. These data were summarized from 11 studies ranging from 1989 to 2009 with a mean age of 47 ±13 years (189). We expect the prevalence of IR among TB patients to be 35%. Of these, 15% will have DM. We expect the prevalence of IR among control group without TB to be 20% i.e. 5% with IR and without hyperglycaemia and 15% with DM. In that case 20/100 compared to 5/100 means that, the IR is a risk factor for TB.

Laboratory tests: Participants will be asked to fast for 12 hours from 8 PM until 8 AM to provide blood samples. Patients will be asked if they are fasting. Those who say they have not fasted will be asked to come back the next day after fasting. If the patient does not attend we will contact him/her by phone or email to encourage him/her to attend. The phlebotomist at tuberculosis and chest diseases centre phlebotomy area will collect blood between 8-10 AM under safety precautions using a vacutainer blood-collection system or a large syringe to collect approximately 10 ml of blood.

The phlebotomist will split 10 ml of the sample into three tubes containing anticoagulants. Blood samples will be transported within two hours of collection by a reporter using a container with ice under safety precautions. The samples will be processed by two-laboratory technicians in the Madain Al-Fahad Health Centre in Jeddah one from hormone department for insulin estimation and one from chemistry department for the glucose, HA1c and lipid profile including LDL, HDL and TG. If the sample is unlabelled or improperly labelled, collected in a wrong tube or the sample volume is not sufficient for the requirement of test protocol, the sample will be rejected and we will contact the patient to come again for blood collection in a convenient day to him/her after fasting.

FPG analysis: Four ml of venous blood collected in a tube with Sodium Fluoride anticoagulant will be used for glucose determination based on the enzymatic reference method with Hexokinase using an automated chemistry analyser (Dimension Rxl Max).

Insulin test: The blood sample collected in a Sodium Fluoride anticoagulant tube will be used for measuring insulin based on the chemiluminescence principle using an automated analyser (Hitachi Unicel DxI 600).

HA1c test: Two ml blood in an EDTA-containing tube will be used to measure HA1c based on the Turbidimetric Inhibition Immunoassay (TINIA) principle using an automated chemistry analyser (Dimension Rxl Max).

Lipid profile: The four ml of blood collected in the Lithium Heparin tube will be used to establish the lipid profile including LDL, HDL and TG determination based on the enzymatic colorimetric method using an automated chemistry analyser (Dimension Rxl Max).

Objective 4: To explore whether IR is a risk factor for CHD.

Study design: This will be a second case-control study in which the cases will be CHD patients, which is similar to the design described for objective three. Cases will be enrolled from patients participating in the cross-sectional survey second objective and will be the same patients attending the King Faisal Hospital who were confirmed to have CHD. The controls will be adults attending the outpatients department of the hospital who were treated for other conditions and were deemed not to have CHD. The questionnaire will include a comprehensive list of possible risk factors for IR and CHD such as lifestyle, physical activity, diet, BMI, medical history and others. We will obtain the same anthropometric measurements as described in objective three. Participants should be eligible if they have the following inclusion and exclusion criteria:

Inclusion criteria:

5- Cases will be participants in the survey for objective 2 attending the King Faisal Hospital.
6- Controls will be adults attending the outpatients department without CHD.
7- Participant aged ≥18 and residing in Taif city.
8- Patients accept to participate.

Exclusion criteria:

2- Same as objective 2.

Diabetic adults are two to four times more likely to have CHD than those without DM. The American Diabetes Association (ADA) recognizes DM to be one of the six main CHD risk factors. The major risk factors for CHD are uncontrolled hypertension, triglyceride, and cholesterol and/or poor glycaemic control, lack of physical activity, obesity, and smoking. Subjects with euglycamia IR or DM in combination with one or more of these risk factors are more likely to get CHD. To determine whether euglycaemic IR is a risk factor for CHD, we will enrol all the cases from the cross-sectional survey second objective and controls without CHD. The prevalence of Metabolic syndrome (MS), as a surrogate of IR, in an adult Saudi population is 39.3% (307).

A cohort study in a Saudi population confirm a clear association of MS with CHD as 6.7% of CHD patients had MS, compared to 4.6% without MS. A study among Saudi diabetic patients also evaluated risk factors for CHD. Concluding that the risk of CHD among diabetic patients was between 15–30%. We expect the prevalence of IR among adults CHD patients to be 35% i.e. 20% with IR and without hyperglycaemia and 15 % with DM. We expect the prevalence of IR among adults control group without CHD to be 20% i.e. 5% with IR and 15% with DM. In that case 20/100 compared to 5/100 means that, the IR is a risk factor for CHD.

Laboratory tests: All Laboratory tests will be the same as those stated in objective 3. Specimens will be collected in King Faisal General Hospital phlebotomy area to be send to the king Faisl hospital Labortory.

Objectives (5): To describe whether the severity of the clinical presentation of TB varies among patients with and without IR and/or DM.

Study design: This will be a three arm retrospective case-control study. Cases will be patients diagnosed with TB patients who have DM, euglycaemic TB patients who have IR

and controls will be patients with TB without IR or DM. Participants should be eligible if they have the following inclusion and exclusion criteria:

Inclusion criteria:

4- Patients participating in the survey for objectives 1 and in the case-control for objective 3.
5- Cases will be patients diagnosed with TB who have DM and euglycaemic TB patients who have IR.
6- Controls will patients with TB without IR or DM.

Exclusion criteria:

2- Same as objective 1 and 3.

Data will be collected retrospectively from the medical records (treatment register) of patients enrolled into first objective at the tuberculosis and chest diseases centre in Jeddah. TB disease severity will be assessed using a scoring system modified from previously published studies (36, 309) . A score of disease severity will be used as described by Gil-Santana (2016) which includes the presence of each TB related symptom (cough, fever, dyspnoea, night sweats, weight loss, haemoptysis and Chest X-ray cavitations). The scores for cases will range from 0-9 where zero is absence of any symptom and nine is presence of all symptoms. Using the score, patients will be classed as having mild TB; or severe disease. Patients with a score of ≤4 will be classed as mild TB; and a score ≥5 will be classed as severe disease. Data will be extracted from the patient medical record using a structured form including age, gender and symptoms at presentation. Variables that are missing will be completed by interviewing the patients. The TB disease severity for the control group will be assessed using the same scoring system.

Objectives (6): To describe whether the quality of life of patients with CHD varies among patients with and without IR and/or DM.

Study design: This will be a three arm retrospective case-control study. Cases will be patients with stable CHD who have DM, euglycaemic stable CHD patients who have IR and controls will be patients with stable CHD without IR or DM. Participants should be eligible if they have the following inclusion and exclusion criteria:

Inclusion criteria:

4- Patients participating in the survey for objectives 2 and in the case-control for objective 4
5- Cases will be patients with stable CHD who have DM and euglycaemic stable CHD patients who have IR.
6- Controls will be patients with CHD without IR or DM.

Exclusion criteria:

2- Same as objective 2 and 4.

Patients will be enrolled among participants to previous studies to apply a questionnaire to assess their quality of life. The scoring system that we are going to use to assess the quality of life is the WHOQOL-BREF, an abbreviated version of the World Health Organization quality of life assessment (WHOQOL-100) developed by the WHOQOL group (310) along with regular laboratory parameters.

The World Health Organisation Quality Of Life (WHOQOL) 100 assessment was established in order to attempt to cross-culturally over the WHOQOL group's 15 international centres identify quality of life, as identified by Orley & Kuyken, 1994;

WHOQOL Group 1994a, 1994b, 1995; Szabo, 1996. This assessment provides detailed information regarding each individual aspect of the quality of life. However, in some cases it may not be practical to use, as the WHOQOL-100 can be too long-winded. Therefore, a field trial form known as WHOQOL-BREF was formulated in order to offer a shorter quality of life assessment that uses domain-level profiles from pilot WHOQOL assessment data as well as all data available from the WHOQOL-100 field trial system. The WHOQOL assessment tool allows for comprehensive epidemiological research on quality of life for comprehending diseases and methods that can be developed for treatment on a particular population group.

WHOQOL-BREF scoring

There are four domain scores that can be derived from the profile that is produced from the WHOQOL-BREF quality of life assessment. A further examination on two more items is also done separately and these are in the form of two questions; the 1st question will identify the overall perception that an individual has on the quality of life and the 2nd question will look at the view of the individual's health. These four scores will indicate how an individual perceives their quality of life for each specific domain. The scores for each domain will ascend positively so that a high score will represent a high quality of life. The total domain score will be identified by using the mean score from each particular domain, and these scores will be multiplied by four so that it is possible to compare them with WHOQOL-100 scores. Cleaning and checking data, calculating each individual score, computing the domain scores and the procedure for translating the raw scores to converted scores can be found on the WHO website.

The anthropometric data will all be gathered including the BMI, age, heart rate, diastolic and systolic blood pressure, risk factors (hypertension, status of DM, physical activity, smoking, family history and hypercholesterolemia) as well as the laboratory parameters. Coronary score has shown a positive correlation with blood glucose and HbA1c, while lipid metabolism also plays a role in coronary atherosclerosis genesis. Therefore, we will incorporate the following tests in our study, and these are fasting plasma insulin, fasting plasma glucose, haemoglobin A1c and also lipid profiling, which will include TG, HDL and LDL.

A.6	**PARTICIPANTS**: Please state the number of research participants to be recruited. If you are unable to give precise figures, please give estimates.
A.6.2	**ELIGIBILITY CRITERIA**

Objective 1					
PARTICIPANTS:					
A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	90
Females	N/A	N/A	N/A	N/A	85

Inclusion Criteria	Exclusion Criteria
1- Patients with bacteriologically confirmed pulmonary TB. 2- Patients aged ≥ 18 and residing in Jeddah city. 3- Registered at the TB and chest diseases centre in Jeddah and still attending the clinic for treatment. 4- Patients have received at least 2 months of anti-TB treatment and is consider to be responding clinically to the treatment. 5- Patients accept to participate when approached at the DOTS clinic.	1- Patients with missing contact information and those deported from the country. 2- Clinical presentation is predominantly Extra-pulmonary TB. 3- Coexistence of a malignancy. 4- Known to be pregnant. 5- Known HIV infection

Objective 2

PARTICIPANTS:

A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	147
Females	N/A	N/A	N/A	N/A	200

Inclusion Criteria	Exclusion Criteria
1- Patient with stable CHD attending the outpatient clinic. 2- Patients aged ≥18 and residing in Taif city. 3- Registered at Taif King Faisal Hospital, cardiology department, and still attending the clinic for treatment. 4- Patients accept to participate.	1- Patients with missing contact information and those deported from the country. 2- Known renal disease. 3- Known hepatic disease. 4- Smoking more than 20 cigarettes per day. 5- Known to be pregnant.

Objective 3

PARTICIPANTS:

A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	70
Females	N/A	N/A	N/A	N/A	70

Inclusion Criteria	Exclusion Criteria
1- Patients participating in the survey for objective 1. 2- Controls will be adults attending the TB Centre without TB. 3- Participant aged ≥18 and residing in Jeddah city. 4- Patients accept to participate.	1- Same as objective 1.

Objective 4					
PARTICIPANTS:					
A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	70
Females	N/A	N/A	N/A	N/A	70

Inclusion Criteria	Exclusion Criteria
1- Cases will be participants in the survey for objective 2 attending the King Faisal General Hospital. 2- Controls will be adults attending the outpatients department without CHD. 3- Participant aged ≥18 and residing in Taif city. 4- Patients accept to participate.	1- Same as objective 2.

Objective 5					
PARTICIPANTS:					
A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	70
Females	N/A	N/A	N/A	N/A	70

Inclusion Criteria	Exclusion Criteria
1. Patients participating in the survey for objectives 1 and in the case-control for objective 3. 2. Cases will be patients diagnosed with TB who have DM and	1. Same exclusion criteria as objectives 1 and 3

euglycaemic TB patients who have IR. 3. Controls will patients with TB without IR or DM.	

Objective 6					
PARTICIPANTS: Please state the number of research participants to be recruited. If you are unable to give precise figures, please give estimates.					
A.6.1 AGE/SEX	**Neonates (<28 days)**	**Infants (1-11 months)**	**Young children (1-9 years)**	**Adolescents (10-18 years)**	**Adults (>18years)**
Males	N/A	N/A	N/A	N/A	70
Females	N/A	N/A	N/A	N/A	70

Inclusion Criteria	**Exclusion Criteria**
1. Patients participating in the survey for objectives 2 and in the case-control for objective 4. 2. Cases will be patients with stable CHD who have DM and euglycaemic stable CHD patients who have IR. 3. Controls will be patients with CHD without IR or DM.	1. Same exclusion criteria as objective 2 and 4.

Justification for eligibility criteria – if you are excluding a particular group you should justify their exclusion.

<u>Excluded patients for TB study groups.</u>

Malignancy: Recent evidence has confirmed the proposed synergistic relationship between IR/DM and malignancy co-morbidities. Although the pathways and mechanisms for these associations are still uncertain, it is becoming clear that hyperinsulinemia and hyperglycemia are important regulators of not only the development of malignancy but also of treatment outcome.

Pregnant women: Glucose intolerance during pregnancy is defined as gestational diabetes mellitus, which is due to endocrine changes that effect the normal physiological metabolism of glucose leading to the development of IR. As very few women will be pregnant, we would not be able to analyse this subgroup with a statistical power.

Known HIV infection: Metabolic abnormalities of HIV-associated lipodystrophy syndrome are well established, which are characterised by IR, Type 2 diabetes Mellitus (T2DM) and dyslipidemia Including this type of participants may confound our findings

and we would not have sufficient participants with these characteristics to compensate for their confounding effect. We have therefore decided it is better to exclude them.

Excluded patients for CHD study groups.

Patients with chronic kidney and liver disease: these patients have an extremely high risk of developing CHD. Including them would overestimate our findings. In addition, heavy cigarette smoking (>20/day) is a major risk factor of CHD. Pregnant women: For the same reasons stated as for TB above.

A.6.3	**VULNERABLE GROUPS:** Please identify vulnerable groups that will be included in this study. Also state how you will minimise any harm to each group identified.

Very few vulnerable groups are included. Non Saudi adults who have recently migrated to Saudi Arabia may lose their employment if they are found to have a TB. Unfortunately, according to the Saudi law, these cases initiate treatment and are deported to their country directly. As deportation would happen before enrolment, they will not be included in the study. Non Saudis who develop TB long after arriving in Saudi Arabia receive the same treatment as Saudi patients.

A.6.4	**RECRUITMENT PROCESS:** Please detail the procedures for how you will be approaching each group of participants to take part in the project. Where will recruitment take place? Who will be responsible for recruitment of participants?

Objective 1: Participants will be identified from the TB and chest diseases centre in Jeddah. The principal investigator/ research assistants will identify patients who meet the study's selection criteria. Patients will be selected during the continuation phase of TB treatment (i.e. after receiving at least two months of treatment). We will, therefore, select confirmed patients who have received treatment for at least two months. After identifying the patients, the purpose and procedure of the study will be explained to them. Once participants have been identified, received counselling and guidance, agreed to participate and signed the consent form, a team of trained interviewers will interview them at a mutually convenient location either in their own homes or the healthcare facilities. Field assistants will use structured questionnaires in lay Arabic and/or English.

Objective 2: The recruitment will take place in King Faisal Hospital in Taif. The principal investigator/ research assistants will identify patients who meet the study's selection criteria at the cardiology department of the hospital. After identifying the patients, the purpose and procedure of the study will be explained to them. Once participants have identified, received counselling and guidance, agreed to participate and signed the consent form, a team of interviewers will interview the participant at a mutually convenient location in either their own homes or the healthcare facilities. Field assistants will use structured questionnaires in lay Arabic and/or English.

Objective 3: The recruitment will take place in the TB and chest diseases centre in Jeddah as described above. The controls will be individuals attending the centre who were treated for other conditions and were deemed not to have TB. As Saudi Arabia is a low TB burden country and we expect a low number of TB cases have the inclusion and exclusion criteria, therefore, we will select all patients for cases group until the desired sample size is achieved. Controls will be selected using systematic sampling by selecting every 5th

patient starting from first patient attending to the TB and chest diseases centre until the desired sample size is achieved. Five patients will be enrol daily five days a week. In case any participant refuses to participate, a consecutive patient will be recruited for his/her replacement. Participants will be asked to fast for 12 hours from 8 PM until 8 AM to provide blood samples. The next day, patients will be asked if have fasted. Those who say they have not fasted will be asked to come back the next day after fasting. If the patients do not attend we will contact them by phone or email to encourage them to attend. The phlebotomist at TB and chest diseases centre phlebotomy area will collect blood between 8-10 AM.

Objective 4: The recruitment will take place in King Faisal General Hospital in Taif's cardiology department. Cases will be enrolled from patients participating in the survey (objective 2). Controls will be selected from adults attending the outpatient's department who are being treated for other conditions that were not deemed to be CHD. Controls will be selected using systematic sampling as described in objective 3 above.

Objective (5): Participants will be identified from the same patients enrolled into the third objective at the TB and chest diseases centre in Jeddah. The physician at the TB clinic will identify patients who meet the study's selection criteria. The data will be collected retrospectively from the medical records (treatment register) of enrolled patients.

Objective (6): Participants will be identified from the same patients enrolled into objective 4 at King Faisal Hospital. The data will be collected retrospectively from the medical records of enrolled patients.

A.7	**OUTCOMES:** What is the primary outcome measure for the study? What are the secondary outcome measures? (if any)

Objective 1: prevalence of DM and IR among patients with TB.
Objective 2: prevalence of DM and IR among patients with CHD.
Objective 3: proportion of patients with and without TB with IR/DM.
Objective 4: proportion of patients with and without CHD with IR/DM.
Objective 5: severity score of the clinical presentation of TB among patients with and without IR and/or diabetes.
Objective 6: quality of life scores of patients with CHD with and without IR and/or diabetes.

A.8	**MAJOR METHODS OF ANALYSIS:** What are the major methods you intend to use to analyse the data?

First and Second objectives:
Bacteriologically confirmed pulmonary TB patients and patient with stable CHD will be classified as having normal glucose values or DM according to their glycaemic status using the WHO guidelines to determine the DM diagnostic criteria. Furthermore, IR status will be classified according the HOMA calculation using the Matthews *et al.* formula. The formula of IR is as follow: IR = FI×g/22.5, where (FI) is the fasting insulin (μU/mL) and (g) is the fasting glucose (mmol/L). The cut-off point for IR will be 2.6.

- Diabetic patient will be defined as the patient of abnormal fasting blood glucose level (FPG) (≥126 mg/dl [7.0 mmol/L]) and abnormal Haemoglobin A1c level (HA1c ≥6.5%).

- Euglycaemic participant with (FPG < 125 mg/dl [6.9 mmol/L]) will be defined as having increase IR if the HOMA-IR > 2.6.
- Participant with FPG is < 110 mg/dl (6.1 mmol/L), Haemoglobin A1c level (HA1c ≥6.5%) and HOMA ≤ 2.6 will be defined as not having DM or IR.

Third and fourth objectives:
The outcome measure is to describe the association of T2DM and IR with the following assumed risk factors: age, sex, BMI, BP, LDL, HDL and TG. History of DM in the family, smoking, dietary habits and physical activity will also be included. Data analysis for this study would be conducted through chi-square test to compare between the patient with IR and without IR relative to demographic characteristics. In addition, SPSS software will be used to input and analyse the collected data. Then multiple Logistic regression analyses will be conducted to analyse the significant factors associated with the dependent variable. The association between Independent variables will be selected on the basis of the literature of diabetes risk factors and will be analysed using the logistic regression analysis. Univariate and a multivariate will be conducted, results will be presented as crude and adjusted odds ratios with associated 95% CI. Mean ± standard deviation is used to define the normal and continuous distributed data. Continuous and ordinal data with outliers or skew distribution are defined by the first, median and third quartiles. The coronary score is used with continuous variables using simple associations via the Spearman correlation coefficient, and the dichotomous variables were calculated using the point bi-serial correlation coefficients. The significance level will be set at 0.05. This mixed method approach is likely to produce authentic result and cater to the limitations of quantitative analysis as mentioned above.

Fifth objective:
The outcome measure is to describe whether the severity of the clinical presentation of TB varies among patients with and without IR and/or DM. Data will be collected retrospectively from the medical records (treatment register). TB disease severity will be assessed using a scoring system modified from previously published studies. The scores for cases will range from 0-9 where zero is absence of any symptom and nine is presence of all symptoms. Using the score, patients will be classed as having mild TB; or severe disease. . Patients with a score of ≤4 will be classed as mild TB; and a score ≥5 will be classed as severe disease.

Sixth objective:
The outcome measure is to describe whether the quality of life of patients with CHD varies among patients with and without IR and/or DM. The scoring system that we are going to use to assess the quality of life is the WHOQOL-BREF, an abbreviated version of the world health organization quality of life assessment (WHOQOL-100) developed by the WHOQOL group along with regular laboratory parameters which include fasting plasma insulin, fasting plasma glucose, haemoglobin A1c and also lipid profiling, which will include TG, HDL and LDL.

A.9	**SAMPLE SIZE:** Please justify your choice of sample size (as described in A.6.1). Please ensure that the sample size calculation is based on the primary outcome measure as detailed in A7.

The sample size for objective 1: The sample size was calculated using the standard formula for estimating a single population proportion. I used the epi info programme; sample size calculation for population survey. I provided the population size which is the total number of people attending to the Tuberculosis and Chest Diseases Centre in Jeddah city every year, the expected frequency of the diabetes and IR which is 35%, confidence limit of 5%. For the cross-sectional survey, we assume that there are 350 adults available and the expected prevalence of DM and IR is 35%. To do a survey with an 80% power and 95% confidence limit we required a sample size of 175 adults.

The sample size of the cross-section survey for CHD group: The sample size was calculated using the standard formula for estimating a single population proportion. I used the epi info programme; sample size calculation for population survey. I provided the population size which is the total number of people attending to the King Faisal General Hospital. For the cross-sectional survey, we assume that there are more than 45,000 adults available for the study and the expected prevalence of DM and IR is 35%. To do a survey with an 80% power and 95% confidence limit we required a sample size of 347 adults.

The sample size of the case control study for TB group: I used the epi info programme; sample size calculation for unmatched case-control. I used a power of 80%, a ratio of 1 case and 1 control and the proportion (percentage) of TB cases with DM being 35% compared to a 20% of controls having DM. I estimated that 140 cases and an equal number of controls should be recruited to achieve 80% power to detect an odds ratio of 2.0 at the 5% significance level if 10% or more of the general population were exposed to the risk factor.

The sample size of the case control study for CHD group: The sample size was based on the confidence interval, the power and the ratio of cases and controls and percentage of cases and controls expected to be exposed to the risk factor. I used a power of 80%, a ratio of 1 case and 1 control and the proportion of CHD cases having DM of 35% compared to 20% of controls having DM. An estimated 140 cases and an equal number of controls should achieve 80% power to detect an odds ratio of 2.0 at the 5% significance level if 10% or more of the general population were exposed to the risk factor.

A.10	**QUALITY ASSURANCE:** Quality assurance is more than just for data analysis – it should include procedures in design and data collection. What procedures are in place to ensure the quality of the data? What consideration has been given to methods of analysis to ensure efficiency of data use?

Project QA activities will be as follow:

The researcher will follow the advice of supervisors to ensure that all research stages and methodologies employed are suitable before beginning. Training and pretesting of the questionnaire will be conducted at the King Faisal Hospital in Taif city and Tuberculosis and Chest Diseases Centre in Jeddah city. The pre-test result will be first discussed and necessary corrections will made on the questionnaire before the actual data collection commenced. To ensure the quality of data, questionnaires will thoroughly checked for completeness and consistency by study supervisors and principal investigator. Manufacturer's control standard for calibration of autoanalyzer will be used to maintain the quality of following measurements: Fasting Plasma Glucose (FPG), Fasting Plasma Insulin, Haemoglobin A1c and Lipid Profile including LDL, HDL and TG. The records of Internal and external quality control for AFB smear microscopy test and culture will be also ensured.

SECTION B
PROCEDURES AND PATIENT CARE

B.1	**PROCEDURES**	Please detail any clinical or other research procedures to which participants will be subjected.

Tuberculosis		
Procedure	**To be carried out by:**	**Who is the person employed by?**
Patient diagnosis and follow up.	Dr. Ali Asghar	Saudi Arabia, Ministry of Health; Jeddah Health Affairs
Identification of patients in the register and completion of questionnaires.	Clinic nurse	Saudi Arabia, Ministry of Health; Jeddah Health Affairs
Blood collection and completion of questionnaires.	Mosa Mohammad Atwady	Saudi Arabia, Ministry of Health; Jeddah Health Affairs
To transfer of samples from the Tuberculosis and chest diseases centre to Madain Al-fahad Health Centre in Jeddah.	Health care driver	Saudi Arabia, Ministry of Health; Jeddah Health Affairs
Coronary Heart Disease		
Procedure	**To be carried out by:**	**Who is the person employed by?**
Patient diagnosis and follow up.	Dr. Mohammed Mougrabi	Saudi Arabia, Ministry of Health; Taif Health Affairs
Patient diagnosis and follow up.	Dr. Syied Sadeq	Saudi Arabia, Ministry of Health; Taif Health Affairs

Identify the patients in the register and fill the questionnaires.	Clinic nurse	Saudi Arabia, Ministry of Health; Taif Health Affairs
Collection of blood at King Faisal Hospital phlebotomy area	Phlebotomist	Saudi Arabia, Ministry of Health; Taif Health Affairs
Insulin measurements	Laboratory specialist	Saudi Arabia, Ministry of Health; Taif Health Affairs
Fasting Plasma Glucose (FPG), Haemoglobin A1c and lipid profile including LDL, HDL and TG.	Dr. Ashrf Ali Khan	Saudi Arabia, Ministry of Health; Taif Health Affairs
Coordination between Taif Health Affairs and Laboratory	Alaa Salem Abed	Saudi Arabia, Ministry of Health; Taif Health Affairs

B.2	**STANDARD PATIENT CARE:** Please explain if the procedures outlined in B.1 are part of the normal clinical work of the staff who will perform the procedure. If not applicable to your study, please write a sentence stating that this is not a clinical study.
This is not a clinical study and we are going to follow the same routine diagnostic procedure. In addition to that, the blood collection will take place in the phlebotomy department which collect blood as a daily routine procedure.	

B.3	**END OF TRIAL TREATMENT:** For intervention trials, what steps will be taken to make successful interventions or treatment available to all trial participants at the end of the trial? If not applicable to your study, please write a sentence stating that this is not a clinical study.
Not applicable. This is not a clinical trial.	

B.4	**TRAINING**	Please indicate the basis on which the persons identified in B.1 are thought to be competent to carry out these procedures. List any training of staff which will be required prior to commencement of the study.

Tuberculosis		
Staff Member	**Experience/competencies**	**Training Required**
The researcher	Currently PhD student at LSTM	Not required
Dr. Ali Asghar	Physician at the TB clinic	Not required
Clinic nurse	Staff in the tuberculosis and chest diseases centre	Questionnaire filling training

Mosa Mohammad Atwady	Staff in the tuberculosis and chest diseases centre	Not required
Health care driver	Staff in the tuberculosis and chest diseases centre	Not required
Coronary Heart Disease		
Staff Member	**Experience/competencies**	**Training Required**
The researcher	Currently PhD student at LSTM	Not required
Dr. Syied Sadeq	Staff at the CVD clinic	Not required
Clinic nurse	Staff at the King Faisal Hospital in the CVD clinic	Questionnaire filling training
Phlebotomist	Staff at the King Faisal Hospital phlebotomy department.	Not required
Laboratory specialist	Staff at the King Faisal Hospital laboratory department.	Not required
Dr. Ashrf Ali Khan	Staff at the King Faisal Hospital laboratory department.	Not required
Alaa Salem Abed	Coordination between Taif Health Affairs and Laboratories	Not required

SECTION C
RISKS AND CONSEQUENCES

C.1	**ADVERSE EFFECTS, DISCOMFORT OR RISKS:** Outline the potential adverse effects, discomfort or risks that may result from the study for participants, investigators and members of the public and how you will minimise them.
Tuberculosis	
C.1.1 Participants	**Potential adverse effects, discomfort or risks** There will be no serious adverse effects in participating in this study; however, there will be an interview, which may be discomforting. Patients will also be required to dedicate some time for the interview to take place. The participants should give blood sample. Blood collecting procedure may cause some minor adverse effect in some cases as the followings: **Hematoma:** This may cause pain and discomfort leading to complications in drawing more blood from that particular site. **Pain:** There is a risk that during collection a needle may pierce the nerve. The participant will complain of an electric shock sensation going up their arm.

	Steps to be taken to minimise adverse effects, discomfort and risks **The interview:** There will be an appropriate room with comfortable chairs provided and we will also ensure that the interviewer will adhere to academic principles by confirming that the participant is fully aware of the importance and the purpose of this study. The languages used in the interview will be Arabic and/or English, and the questions will be structured in a manner that will be clear and easy for the participant to understand. The participant will be free to cycle between topic areas or questions going back or skipping forward to any particular area. **Hematoma:** If haematoma is observed, the tourniquet and needle must be removed and pressure should be applied to the site for at least 3 minutes. The site is then checked for the haematoma to see if it has stopped and a gauze or bandage is taped to the area for a minimum of half an hour, the patient is also informed about the haematoma. **Pain:** if this occurs remove the needle immediately from the arm of the participant and apply pressure to the site of the piercing. Check with the patient whether the sensation has stopped and if this is the case ask the participant if they are willing to allow for another site to be used. The participant should be told that the reason they felt this pain was because the needle had touched a nerve.
C.1.2 Investigators	**Potential adverse effects, discomfort or risks** Health care workers (HCWs) exposure to air-borne pathogens as they will be dealing with TB patients, blood-borne pathogens from needle sticks, sharps injuries are primarily associated with HCWs transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).
	Steps to be taken to minimise adverse effects, discomfort and risks **The staff will be encouraged to follow the TB infection-control measures by the Centres for Disease Control and Prevention (CDC) and the local infection control guidelines precautions for preventing transmission of blood-born and air born infections. Laboratory workers are responsible for their own safety and that of their co-workers.**
C.1.3 Members of the public	**Potential adverse effects, discomfort or risks** The study will be conducted in a health care centre and there is no public will be involved in this research.
	Steps to be taken to minimise adverse effects, discomfort and risks No special precautions are required.
Coronary Heart Disease	
C.1.1 Participants	**Potential adverse effects, discomfort or risks** Same as Tuberculosis group.

	Steps to be taken to minimise adverse effects, discomfort and risks Same as Tuberculosis group.
C.1.2 Investigators	**Potential adverse effects, discomfort or risks** Same as Tuberculosis group.
	Steps to be taken to minimise adverse effects, discomfort and risks Same as Tuberculosis group.
C.1.3 Members of the public	**Potential adverse effects, discomfort or risks** Same as Tuberculosis group.
	Steps to be taken to minimise adverse effects, discomfort and risks Same as Tuberculosis group.

C.2	**CONSEQUENCES FOR LOCAL HEALTH SERVICES**
C.2.1	**IMPACT ON LOCAL SERVICES:** What demands will this research place on local health services?
No extra demand on local health services will be required. **The interview:** using structured questionnaires will require time and effort and will be done by the researcher / assistance and it will not affect the working schedule of the local health service. **The blood collection:** will be done at the working hours and will not affect the working time of the local health service. **The laboratory tests**: most of the procedures that we are going to do are daily work for the assistance but will increase the work load.	
C.2.2	**MINIMISING IMPACT ON LOCAL SERVICES:** Detail how the design of the research project takes into account the demands described above in C.2.1
The interview: the research will interview the participants and I will employ a research assistant to help in conducting the study. He/she will be employed to interview the participants. The assistant will be paid for this work. **The blood collection**: the blood collection will be allocated according to the phlebotomist working hours and daily routine work to minimise the impact on his/her activities. **The laboratory tests**: the laboratory assistances will be paid for the work.	

SECTION D
PRIVACY AND INFORMED CONSENT

D.1	**INFORMED CONSENT (<u>please pay particular attention to the guidance notes for this section</u>)**
D.1.1	**OBTAINING INFORMED CONSENT**: Please give details of how you will obtain informed consent. You must include details of (i) information given to participants, (ii) who will deliver the information and (iii) consideration of local circumstances. Please note that reference of transport of samples to another country must be included in the consent forms. Please also give special consideration to whether proxy consent is required (for those lacking capacity to consent, minor etc) and give details as to how this would be obtained.

Participants information form for tuberculosis patients

The following information will be given to the participants:
The purpose of the study, why the participant has been selected, a summary of the study procedure such as processes of data collection (e.g. questionnaires), the possible impact the research will have on the participant, such as side effects, risks, benefits, discomforts, data sharing, data storage, confidentiality, results circulation and voluntary involvement, where the participant can at any time withdraw themselves from the study and they will be provided with contact details of the appropriate person/researcher for any queries.

The consent form will be distributed to men/women that attend the centre of tuberculosis and chest diseases, to invite individuals to take part in the research study on diabetes mellitus and insulin resistance as key risk factors for tuberculosis among diabetic and euglycaemic patients in the city of Jeddah, Saudi Arabia.

Fareed Almaleki, Liverpool School of Tropical Medicine.
Determining the association of insulin resistance and diabetes mellitus as key risk factors for tuberculosis among diabetic and euglycaemic patients in Saudi Arabia.

The consent form is split into two parts, and these are:

- The research information sheet.
- The certificate of consent.

The participant will receive a copy of the consent form.

Introduction:
I am [*The name of the individual providing the consent form*]. I work for the centre of tuberculosis and chest diseases, Jeddah, and I am acting on behalf of Fareed Almaleki, who studies at the Liverpool School of Tropical Medicine, UK. We are performing research on topical diseases and their diagnosis, in particular diabetes mellitus, which is highly prevalent in Saudi Arabia. We are inviting you to take part in our research study, however, before participating, it is important to understand what the study will involve and why the research is being implemented. Please have a look carefully at the following information and if there is anything you are unsure of, or if you would like any further information do not hesitate to ask any questions. You are also free to review this information with your GP or any friends and family, and we would like to emphasise that you should only go ahead with the invitation if you are happy to take part in the study. Should you agree to participate in this study, we will need to ask you questions regarding your medical history enquiring about previous and current diseases. If you come across any words that you do not understand in this document or in the interview, please inform me and we will stop to ensure that it is explained to you. If you have any further questions at a later time you can either ask myself, the staff or the study doctor, while you will also be provided with the details of the contact person/researcher so that you can contact them regarding any queries you may have.

Purpose:
Diabetes mellitus is a frequent disease, which on a global scale affects more than 415 million individuals. We propose in this project that insulin resistance and diabetes are key risk factors for

tuberculosis and we will look for this association by studying patients in the city of Jeddah, Saudi Arabia. Insulin is a normal hormone that helps to utilise sugars. If the body does not respond well to this hormone, we call it insulin resistance.

Participant Selection:
This study invites participants above the age of 18 that attend the tuberculosis and chest diseases centre.

Voluntary Participation:
Participation in this study is completely voluntary and it entirely up to you if you wish to participate, you will be given 24 hours to decide whether or not to participate. The services at this clinic that you currently receive will not be affected whether you decide to participate or not and If you do participate you can opt out at any time of the study.

Procedures and Protocol:
In order to determine if insulin resistance and diabetes increases the risk of tuberculosis, we will invite 175 participants. Each participant will be asked for a blood sample (10ml) so that we can assess their glucose levels, insulin levels, HA1c and lipid profile, which will include TG, HDL and LDL. To calculate IR we will use a mathematical formula, and when the results are available we will contact the participants by email or by phone to inform them. The participants will be asked to complete a questionnaire which will ask about your lifestyle, as well as weight, physical activity, diet and family history. There will be a nurse dedicated to measuring each participant's height (cm), weight (kg), hip and waist circumference (cm) and blood pressure (BP).

Risks and discomfort:
There will be no serious adverse effects in participating in this study; however there will be an interview, which will ask some personal questions. You will also be required to dedicate some time for the interview to take place. There will be an appropriate room with comfortable chairs provided and we will also ensure that the interviewer will adhere to academic principles by confirming that the participant is fully aware of the importance and the purpose of this study. The languages used in the interview will be Arabic and/or English, and the questions will be clear and easy to understand.

Hematoma: In venepuncture, it is possible for the blood to leak from a vein and out under the skin. This may cause pain and discomfort leading to complications in drawing more blood from that particular site. If haematoma is observed, the tourniquet and needle must be removed and pressure should be applied to the site for at least 3 minutes. The site is then checked for the haematoma to see if it has stopped and a gauze or bandage is taped to the area for a minimum of half an hour.

Pain: There is a small risk that during blood collection a needle may pierce the nerve. You would feel a mild electric sensation. If this occurs we will remove the needle and apply pressure to the site of the piercing. The sensation will stop and the participant will be told the reason they felt this pain was because the needle had touched a nerve.

Samples to be collected and stored:
Your blood samples may be used anonymously for future studies and in testing for further potential diabetic markers. Signing this consent form means that you will give your permission for

us to safely store your blood for anonymous use in other future projects that are considered suitable.

Benefits:
By participating in this study, we will be able to detect whether or not you are diabetic and if you are likely to develop diabetes. Should we detect that you are diabetic, we can arrange for you to meet a specialist and we will also provide you with a leaflet on diabetes risk awareness.

Incentives:
There is no financial incentive for taking part in this study

Confidentiality:
The study will take place within your clinic, therefore it is likely that others within the clinic may become aware of your participation and question you regarding this. We would like to assure you that the identity and all information collected from individuals participating in this study will be kept confidential. Your information that is collected in this study is confidential and will only be accessed by research sponsors, ethics committee members and institutional officials. Any data that we have on you will be number coded and your name will not be used, the only individuals that will know your number will be the researchers and this information will be locked away with a key.

Right to Refuse or Withdraw:
You have the right to refuse to participate in this study and if this is the case your treatment in this clinic will not be affected, you will still receive any assistance that you had prior to the study. If at any time you wish to withdraw from the study, you may do so without the loss of any rights that you have as a patient at this clinic, your treatment will not be affected.

Who to Contact:
Any questions you have can be asked now or at any time during the study. If you would like to enquire about anything at a later date, you can use any of the following contact details: [*name, address/telephone number/e-mail*].

Consent Form

CONFIDENTIAL

Study Title: Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.	
Principal Investigator: Fareed Almaleki	**Study Site:** Tuberculosis and chest diseases centre in Jeddah

	Please initi box
1. I confirm I have read and understood the information sheet dated September 2016, Version 1.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that participation in this study is voluntary and I am free to withdraw consent at any time, without giving a reason, without any penalties.	

3. I understand that data collected during the study, may be looked at by individuals from LSTM and from regulatory authorities. I give permission for these individuals to have access to my records.	
4. I hereby declare that I have not been subjected to any form of coercion in giving this consent.	
5. I agree to the data about me collected in this study being stored for further use in the future.	
6. I agree that my blood samples will be transported to Madain Al-Fahad Health Centre in Jeddah to be analysed.	
7. I agree to gift this blood samples for future research purpose.	
8. I agree to take part in this study.	

Signing this declaration does not affect your right to decline to take part in any future study.

Name of participant	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

* **All data gathered on this form and any information you provide us for the study will be confidential and will not be communicated to anyone outside the study team.**

When complete: 1 copy for participant; 1 copy (original) for research

Participants information form for coronary heart disease patients

The following information will be given to the participants:
The purpose of the study, why the participant has been selected, a summary of the study procedure such as processes of data collection (e.g. questionnaires), the possible impact the research will have on the participant, such as side effects, risks, benefits, discomforts, data sharing, data storage, confidentiality, results circulation and voluntary involvement, where the participant can at any time withdraw themselves from the study and they will be provided with contact details of the appropriate person/researcher for any queries.

The consent form will be distributed to men/women that attend the King Faisal Hospital, to invite individuals to take part in the research study on diabetes mellitus and insulin resistance as key risk factors for CHD among euglycaemic and diabetic patients in Saudi Arabia; Taif city.

Fareed Almaleki, Liverpool School of Tropical Medicine
Determining the association of insulin resistance and diabetes mellitus as key risk factors for Coronary Heart Diseases among diabetic and euglycaemic patients in Saudi Arabia.

The consent form is split into two parts, and these are:

- The research information sheet
- The certificate of consent

The participant will receive a copy of the consent form.

Introduction:
I am [*The name of the individual providing the consent form*]. I work for the King Faisal Hospital, Taif, and I am acting on behalf of Fareed Almaleki, who studies at the Liverpool School of Tropical Medicine, UK. We are performing research on topical diseases and their diagnosis, in particular diabetes mellitus, which is highly prevalent in Saudi Arabia. We are inviting you to take part in our research study, however, before participating, it is important to understand what the study will involve and why the research is being implemented. Please have a look carefully at the following information and if there is anything you are unsure of, or if you would like any further information do not hesitate to ask any questions. You are also free to review this information with your GP or any friends and family, and we would like to emphasise that you should only go ahead with the invitation if you are happy to take part in the study. Should you agree to participate in this study, we will need to ask you questions regarding your medical history enquiring about previous and current diseases. If you come across any words that you do not understand in this document or in the interview, please inform me and we will stop to ensure that it is explained to you. If you have any further questions at a later time you can either ask myself, the staff or the study doctor, while you will also be provided with the details of the contact person/researcher so that you can contact them regarding any queries you may have.

Purpose:
Diabetes mellitus is a frequent disease, which on a global scale affects more than 415 million individuals. We propose in this project that insulin resistance and diabetes are key risk factors for CHD and we will look for this association by studying patients in the city of Taif, Saudi Arabia. Insulin is a normal hormone that helps to utilise sugars. If the body does not respond well to this hormone, we call it insulin resistance.

Participant Selection:
This study invites participants above the age of 18 that attend the King Faisal General Hospital in Taif.

Voluntary Participation:
Participation in this study is completely voluntary and it entirely up to you if you wish to participate, you will be given 24 hours to decide whether or not to participate. The services at this clinic that you currently receive will not be affected whether you decide to participate or not and If you do participate you can opt out at any time of the study.

Procedures and Protocol:
In order to determine if insulin resistance and diabetes increases the risk of CHD, we will invite 347 participants. Each participant will be asked for a blood sample (10ml) so that we can assess their glucose levels, insulin levels, HA1c and lipid profile, which will include TG, HDL and LDL. To calculate IR we will use a mathematical formula, and when the results are available we will contact the participants by email or by phone to inform them. The participants will be asked to complete a questionnaire which will ask about your lifestyle, as well as weight, physical activity, diet and family history. There will be a nurse dedicated to measuring each participant's height (cm), weight (kg), hip and waist circumference (cm) and blood pressure (BP).

Risks and discomfort:

There will be no serious adverse effects in participating in this study; however there will be an interview, which will ask some personal questions. You will also be required to dedicate some time for the interview to take place. There will be an appropriate room with comfortable chairs provided and we will also ensure that the interviewer will adhere to academic principles by confirming that the participant is fully aware of the importance and the purpose of this study. The languages used in the interview will be Arabic and/or English, and the questions will be clear and easy to understand.

Hematoma: In venepuncture, it is possible for the blood to leak from a vein and out under the skin. This may cause pain and discomfort leading to complications in drawing more blood from that particular site. If haematoma is observed, the tourniquet and needle must be removed and pressure should be applied to the site for at least 3 minutes. The site is then checked for the haematoma to see if it has stopped and a gauze or bandage is taped to the area for a minimum of half an hour.

Pain: There is a small risk that during blood collection a needle may pierce the nerve. You would feel a mild electric sensation. If this occurs we will remove the needle and apply pressure to the site of the piercing. The sensation will stop and the participant will be told the reason they felt this pain was because the needle had touched a nerve.

Samples to be collected and stored:

Your blood samples may be used anonymously for future studies and in testing for further potential diabetic markers. Signing this consent form means that you will give your permission for us to safely store your blood for anonymous use in other future projects that are considered suitable.

Benefits:

By participating in this study, we will be able to detect whether or not you are diabetic and if you are likely to develop diabetes. Should we detect that you are diabetic, we can arrange for you to meet a specialist and we will also provide you with a leaflet on diabetes risk awareness.

Incentives:

There is no financial incentive for taking part in this study

Confidentiality:

The study will take place within your clinic, therefore it is likely that others within the clinic may become aware of your participation and question you regarding this. We would like to assure you that the identity and all information collected from individuals participating in this study will be kept confidential. Your information that is collected in this study is confidential and will only be accessed by research sponsors, ethics committee members and institutional officials. Any data that we have on you will be number coded and your name will not be used, the only individuals that will know your number will be the researchers and this information will be locked away with a key.

Right to Refuse or Withdraw:

You have the right to refuse to participate in this study and if this is the case your treatment in this clinic will not be affected, you will still receive any assistance that you had prior to the study. If at any time you wish to withdraw from the study, you may do so without the loss of any rights that you have as a patient at this clinic, your treatment will not be affected.

Who to Contact:
Any questions you have can be asked now or at any time during the study. If you would like to enquire about anything at a later date, you can use any of the following contact details: [*name, address/telephone number/e-mail*].

Consent Form

CONFIDENTIAL

Study Title: Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.

Principal Investigator: Fareed Almaleki	**Study Site:** King Faisal Hospital in Taif

	Please initi box
1. I confirm I have read and understood the information sheet dated September 2016, Version 1.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that participation in this study is voluntary and I am free to withdraw consent at any time, without giving a reason, without any penalties.	
3. I understand that data collected during the study, may be looked at by individuals from LSTM and from regulatory authorities. I give permission for these individuals to have access to my records.	
4. I hereby declare that I have not been subjected to any form of coercion in giving this consent.	
5. I agree to the data about me collected in this study being stored for further use in the future.	
6. I agree that my blood samples will be transported to King Faisal Hospital in Taif to be analysed.	
7. I agree to gift this blood samples for future research purpose.	
8. I agree to take part in this study.	

Signing this declaration does not affect your right to decline to take part in any future study.

_____	_____	_____
Name of participant	**Date**	**Signature**
_____	_____	_____
Name of person taking consent	**Date**	**Signature**

* **All data gathered on this form and any information you provide us for the study will be confidential and will not be communicated to anyone outside the study team.**

When complete: 1 copy for participant; 1 copy (original) for research

D.1.2	**CONSTRAINTS:** Please outline any potential constraints to consent and indicate how you will reduce the impact of these constraints.

The study will be conducted in Saudi Arabia, the King Faisal Hospital and Tuberculosis and Chest Diseases Centre are belong to the Saudi MOH, which will facilitate the agreement between the LSTM and the MOH. The participant information sheet and the consent will be available in two languages Arabic and English, the interviewer will be trained to do the interview, and the researcher / assistance will be available to explain any inquiries about the study.

D.2	**ASSISTANCE:** Please outline any assistance (financial or otherwise) that will be offered to potential participants or individuals in return for their participation in this research.
There will be no assistance offered to potential participants. We will assign a research assistance to help interviewing the participants using Arabic/English language, and to process the sample, we will reward him/her financially.	
D.3	**PRIVACY AND CONFIDENTIALITY:** Please describe how participant privacy and confidentiality will be maintained during data collection, analysis and storage. Please include what will be collected (data, samples etc.) and where and for how long it will be stored.
For the primary research participants, voluntary informed consent will be sought from all willing participants in Arabic/English and the participants will be assured that all data will be kept confidential. Ethical approval will be sought from the LSTM as well as the Department of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia. Each participant will be informed about the purpose of the study and will also be told that they are free to opt out at any time. In addition to that, the confidentiality and anonymity of collected data is guaranteed as all data will be stored in a coded format using identification numbers instead of participant names. Interview will be conducted in a separate room to maintain privacy. The data sheet containing the key for this code will then be password-protected and stored on OneDrive. The researcher will also request verbal consent from participants before starting and will strive to avoid inconveniencing the participant, organisation or community as much as possible. The participants will also be informed that they can refuse to answer any questions and can again opt out of the study at any time. For the secondary research, all the texts, data, personal and professional quotes and findings of previous works and cited studies would be accurately and appropriately cited along with a full reference to the work to ensure that any information is not compromised. The data will not be shared with any third party. These extensive measures are likely to cater to the ethical issues of citing secondary work as well.	
D.4	**DISSEMINATION:** Please outline what plans you have for dissemination of results
The final analysis will be made and the result will be included in a PhD dissertation and possibly other scientific publication.	

SECTION E
MAJOR ETHICAL ISSUES

E.1	**MAJOR ETHICAL ISSUES** Outline what you consider to be the major ethical issues involved in this research. Please indicate how you plan to deal with these ethical issues.

The study will initiate after ethical approval which will be obtained from the LSTM ethical committee and Department of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia. Permission from Saudi Arabia Ministry of Health *Preventive Medicine* Directorate and from health authorities of the study sites will be also received prior to the start of the study. Oral and written information will be provided to study participants before informed consent is obtained. Those TB patients and CHD patients who will be found to have abnormal results referred to TB and CHD clinics for further investigation and appropriate management.

Voluntary consent is concerned with each individual's ability to exercise the free power of choice without the intervention of force, fraud, deceit, or other forms of constraint. This right to exercise choice is present throughout the entire research process. Being in this study is up to the patients. If the patient doesn't want to be in this study, he/she will not have to participate. No effect on the routine diagnosis or treatment if he/she don't want to participate or even if he/she change his/her mind later and want to stop. For patients not diagnosed before as diabetic but during the study we discover that they are either diabetic or having IR, we will arrange a speedy appointment with the endocrinologist to be evaluated and managed. The data collection procedures include elements where participants are asked to self-report; some participants may not provide honest answers. To minimise that, we will try to make the participants fell that their input are valued and of a scientific importance.

DECLARATION: TO BE SIGNED BY MAIN APPLICANT Applicants **must initial** each declaration or tick N/A in the right hand column if applicable	**Initial** (by hand)	**N/A**
i) I confirm that the details of this proposal are a true representation of the research to be undertaken.		
ii) I will ensure that the research does not deviate from the protocol described.		
iii) If significant protocol amendments are required as the research progresses, I will submit these to the Liverpool School of Tropical Medicine Research Ethics Committee for approval.		
iv) Where an appropriate mechanism exists, I undertake to seek additional in-country Ethical Approval in the country(ies) where the research is to be carried out.		
v) I agree to abide by the ethical principles underlying the Declaration of Helsinki and all relevant LSTM Standard Operating Procedures (SOP) relating to research conduct (available on LSTM intranet at http://pcwww.liv.ac.uk/lstmintranet/research_management/governance_polices_codes.htm or by contacting the Research Office).		
vi) I understand that all conditions apply to any co-applicants, researchers and other staff involved in the study, and that it is my responsibility to ensure that they abide by them.		
For studies over two years in duration vii) I will provide the Research Ethics Committee with an annual report.		

For studies using 'human tissue'* viii) I confirm I will abide by LSTM's Policies and Standard Operating Procedures relating to activities involving human tissue * Human tissue is defined in the following link: http://www.hta.gov.uk/_db/_documents/List_of_materials_considered_to_be_relevant_material_under_the_Human_Tissue_Act_2004.pdf		
For studies that involve a clinical trial or participation of humans (the use of their data or tissue) ix) I confirm that I have completed a sponsorship and indemnity form http://pcwww.liv.ac.uk/lstmintranet/research_management/applyingforRG/intro.htm		

I expect the project to commence on (Date)		**Complete by (date)**	
Signed:		**Date:**	

From time to time the committee uses ethics applications for training purposes or to give examples to new applicants. In all cases the applications are anonymised. If you **DO NOT** consent to your application being used for these purposes please tick the box. ☐

Appendix 2: Participant's information form for tuberculosis patients (English and Arabic)

Participant Information Sheets
Participant's information form for tuberculosis patients
The following information was given to the participants:
The purpose of the study, why the participant has been selected, a summary of the study procedure such as processes of data collection (e.g. questionnaires), the possible impact the research will have on the participant, such as side effects, risks, benefits, discomforts, data sharing, data storage, confidentiality, results circulation and voluntary involvement, where the participant can at any time withdraw themselves from the study and they will be provided with contact details of the appropriate person/researcher for any queries.

The consent forms were distributed to the men/women that attended the centre of tuberculosis and chest diseases, to invite individuals to take part in the research study on diabetes mellitus and insulin resistance as key risk factors for tuberculosis among diabetic and euglycaemic patients in the city of Jeddah, Saudi Arabia.

Fareed Almaleki, Liverpool School of Tropical Medicine.
Determining the association of insulin resistance and diabetes mellitus as key risk factors for tuberculosis among diabetic and euglycaemic patients in Saudi Arabia.

The consent form is split into two parts, and these are:

- The research information sheet.
- The certificate of consent.

The participants then received a copy of the consent form.

Introduction:
I am [*The name of the individual providing the consent form*]. I work for the centre of tuberculosis and chest diseases, Jeddah, and I am acting on behalf of Fareed Almaleki, who studies at the Liverpool School of Tropical Medicine, UK. We are performing research on topical diseases and their diagnosis, in particular diabetes mellitus, which is highly prevalent in Saudi Arabia. We are inviting you to take part in our research study, however, before participating, it is important to understand what the study will involve and why the research is being implemented. Please have a look carefully at the following information and if there is anything you are unsure of, or if you would like any further information do not hesitate to ask any questions. You are also free to review this information with your GP or any friends and family, and we would like to emphasise that you should only go ahead with the invitation if you are happy to take part in the study. Should you agree to participate in this study, we will need to ask you questions regarding your medical history enquiring about previous and current diseases. If you come across any words that you do not understand in this document or in the interview, please inform me and we will stop to ensure that it is explained to you. If you have any further questions at a later time you can either ask myself, the staff or the study doctor, while you will also be provided

with the details of the contact person/researcher so that you can contact them regarding any queries you may have.

Purpose:
Diabetes mellitus is a frequent disease, which on a global scale affects more than 415 million individuals. We propose in this project that insulin resistance and diabetes are key risk factors for tuberculosis and we will look for this association by studying patients in the city of Jeddah, Saudi Arabia. Insulin is a normal hormone that helps to utilise sugars. If the body does not respond well to this hormone, we call it insulin resistance.

Participant Selection:
This study invites participants above the age of 18 that attend the tuberculosis and chest diseases centre.

Voluntary Participation:
Participation in this study is completely voluntary and it entirely up to you if you wish to participate, you will be given 24 hours to decide whether or not to participate. The services at this clinic that you currently receive will not be affected whether you decide to participate or not and If you do participate you can opt out at any time of the study.

Procedures and Protocol:
In order to determine if insulin resistance and diabetes increases the risk of tuberculosis, we will invite 175 participants. Each participant will be asked for a blood sample (10ml) so that we can assess their glucose levels, insulin levels, HA1c and lipid profile, which will include TG, HDL and LDL. To calculate IR we used a HOMA calculator, and when the results are available we will contact the participants by email or by phone to inform them. The participants will be asked to complete a questionnaire which will ask about your lifestyle, as well as weight, physical activity, diet and family history. There was a nurse dedicated to measuring each participant's height (cm), weight (kg), hip and waist circumference (cm) and blood pressure (BP).

Risks and discomfort:
There will be no serious adverse effects in participating in this study; however there will be an interview, which asked some personal questions. You will also be required to dedicate some time for the interview to take place. There will be an appropriate room with comfortable chairs provided and we will also ensure that the interviewer will adhere to academic principles by confirming that the participant is fully aware of the importance and the purpose of this study. The languages used in the interview will be Arabic and/or English, and the questions will be clear and easy to understand.

Hematoma: In venepuncture, it is possible for the blood to leak from a vein and out under the skin. This may cause pain and discomfort leading to complications in drawing more blood from that particular site. If haematoma is observed, the tourniquet and needle must be removed and pressure should be applied to the site for at least 3 minutes. The site is then checked for the haematoma to see if it has stopped and a gauze or bandage is taped to the area for a minimum of half an hour.

Pain: There is a small risk that during blood collection a needle may pierce the nerve. You would feel a mild electric sensation. If this occurs we will remove the needle and apply pressure to the site of the piercing. The sensation will stop and the participant will be told the reason they felt this pain was because the needle had touched a nerve.

Samples to be collected and stored:
Your blood samples may be used anonymously for future studies and in testing for further potential diabetic markers. Signing this consent form means that you will give your permission for us to safely store your blood for anonymous use in other future projects that are considered suitable.

Benefits:
By participating in this study, we will be able to detect whether or not you are diabetic and if you are likely to develop diabetes. Should we detect that you are diabetic, we can arrange for you to meet a specialist and we will also provide you with a leaflet on diabetes risk awareness.

Incentives:
There is no financial incentive for taking part in this study

Confidentiality:
The study will take place within your clinic, therefore it is likely that others within the clinic may become aware of your participation and question you regarding this. We would like to assure you that the identity and all information collected from individuals participating in this study will be kept confidential. Your information that is collected in this study is confidential and will only be accessed by research sponsors, ethics committee members and institutional officials. Any data that we have on you will be number coded and your name will not be used, the only individuals that will know your number will be the researchers and this information will be locked away with a key.

Right to Refuse or Withdraw:
You have the right to refuse to participate in this study and if this is the case your treatment in this clinic will not be affected, you will still receive any assistance that you had prior to the study. If at any time you wish to withdraw from the study, you may do so without the loss of any rights that you have as a patient at this clinic, your treatment will not be affected.

Who to Contact:
Any questions you have can be asked now or at any time during the study. If you would like to enquire about anything at a later date, you can use any of the following contact details: [*name, address/telephone number/e-mail*].

TB Arabic version patient information sheet

Form IRB-10.10.01

Minimal Risk Informed Consent Template

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشتمل علي الحد الأدنى من المخاطر

Effective Date: KFMC Institutional Review Board

Protocol Number:	1	1	**رقم البحث العلمي**
Name of Subject:			**اسم المشارك**
Medical Record Number:			**رقم السجل الطبي**
Study Title:	Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.		**عنوان البحث العلمي** ترسيخ علاقة مرض السكري ومقاومة الانسولين كعوامل خطر رئيسية لمرض السل وأمراض القلب التاجية بين المرضى المصابين بالسكري و أسنوياة السكري في المملكة العربية السعودية.
Principal Investigator: **Fareed Hamed Almaleki**			**الباحث الرئيس** فريد حامد المالكي
Address:	Tuberculosis and Chest Diseases Centre in Jeddah city		**العنوان** مركز السل وأمراض الصدر في مدينة جدة
Telephone: 0555789051			**رقم الهاتف** 0555789051

Why Is This Study Being Done?
This study will aim to describe the prevalence of DM and IR in Saudi Arabia among patients with TB from Jeddah city and apparently healthy controls to investigate the association of IR with TB.

ما سبب القيام بهذا البحث العلمي ؟
وتهدف هذه الدراسة إلى وصف انتشار مرض السكري ومقاومة الانسلين في المملكة العربية السعودية بين المرضى الذين يعانون من السل من مدينة جدة و مشاركين اصحاء للتحقيق من علاقة مقاومة الانسلين مع مرض السل الرئوي.

How Many People Will Take Part in This Study?
175 Tuberculosis patients and 140 healthy controls

كم عدد الأشخاص المفترض مشاركتهم في هذا البحث العلمي؟

What is involved in the Study?

Study location: Tuberculosis and Chest Diseases Centre in Jeddah city and Madain Al-Fahad Health Centre in Jeddah

ماذا يتضمن هذا البحث العلمي؟

موقع إجراء هذا البحث العلمي: مركز الدرن والامراض الصدرية بمدينة جدة و مركز صحي مدائن الفهد بجدة

What is Expected of Me During the Study?After receiving counselling and guidance and agreed to participate you will be

ما المطلوب مني خلال هذا البحث العلمي؟
بعد تلقي المشورة والتوجيه والموافقة على المشاركة سوف يطلب منك التوقيع على استمارة الموافقة. ثم باستخدام استبيانات منظمة، سيقوم فريق من الباحثين

asked to sign the consent form. Then by using structured questionnaires, a team of trained interviewers will interview you.

How Long Will I Be in This Study?

30-60 minutes

Can I Stop Being in This Study?

You can decide to stop at any time. Taking part is purely voluntary.

What are the Benefits of This Study?

There will be no direct benefit to you from taking part in this study. Study results may be useful to the patients in the future.

What are the Risks of This Study?

There will be no serious adverse effects in participating in this study.

What if I am Injured Because I Took Part in This Study?

If you are injured as a result of being in this study, treatment will be provided by Tuberculosis and Chest Diseases Centre in Jeddah city at no cost to you.

What are the Costs of This Study?

There are no costs to you if you take part in this study.

Will I Be Paid for Taking Part in This Study?

After receiving counselling and guidance and agreed to participate you will be asked to sign the consent form. Then by using structured questionnaires, a team of trained interviewers will interview you.

What are the Alternatives?

The interview will be at a mutually convenient location either in your own homes or the healthcare facilities.

Will My Information Be Kept Private?

المدربين بالجلوس معك وملئ الاستبيان عن طريق طرح اسئلة والاجابة عليها

كم مدة مشاركتي في هذا البحث العلمي؟

30 الى 60 دقيقة

هل يمكنني إنهاء المشاركة في هذا البحث العلمي؟

المشاركة طوعيه محضة ويمكنك أن تنهيها في أي وقت تشاء.

ما هي فوائد هذا البحث العلمي؟

لن تكون هناك أي فائدة مباشرة لك من المشاركة في هذا البحث العلمي. نتائج هذا البحث قد تكون مفيدة للمرضى في المستقبل.

ما هي المخاطر المتوقعة من المشاركة في هذا البحث العلمي؟

لا توجد مخاطر متوقعة من المشاركة في هذا البحث

ماذا سيحدث إذا أصابني ضرر جراء المشاركة هذا البحث العلمي؟

إذا حدث أن أصبت بضرر نتيجة مشاركتك في هذا البحث العلمي، ستقدم لك مركز الدرن والامراض الصدرية بمدينة جدة العلاج دون أي تكلفة لك.

وما هي تكاليف المشاركة في هذا البحث العلمي؟

لا توجد تكاليف للمشاركة في هذه هذا البحث العلمي.

هل هنالك اجر مقابل المشاركة في هذا البحث العلمي؟

بعد تلقي المشورة والتوجيه والموافقة على المشاركة سوف يطلب منك التوقيع على استمارة الموافقة. ثم باستخدام استبيانات منظمة، سيقوم فريق من الباحثين المدربين بالجلوس معك وملئ الاستبيان عن طريق طرح اسئلة والاجابة عليها

ما هي البدائل؟

سيتم إجراء المقابلة لاكمال الاستبيان في مكان مريح للمشارك اما في المستشفى او في منزل المشارك.

هل سيتم الحفاظ علي معلوماتي بسرية؟

Form IRB-10.10.01

Minimal Risk Informed Consent Template

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشتمل علي الحد الأدنى من المخاطر

Effective Date: KFMC Institutional Review Board

Your personal information will be kept private. It will be given out only if required by law. Your personal information will not be used in any reports.

What are My Rights if I Take Part in This Study?

Taking part in this study is your choice. You may choose to take part or not to take part. If you decide to take part in the study, you can quit at any time. There will be no penalty to you for your decision. Your medical care will not change.

Who Do I Call if I Have Questions or Problems?

If you have questions about the study, you can call Principal Investigator: Fareed Almaleki 0555789051. If you have any questions about "rights of human subjects," you may call the Chairman of the IRB at . If you have an emergency, call 0549260929.

معلوماتك الشخصية سيتم الحفاظ عليها بسرية تامة. ولا تعطي إلا إذا اقتضى الأمر وذلك في حدود النظم والقوانين المطبقة بهذا الخصوص. معلوماتك الشخصية لن تستخدم في أي تقارير.

ما هي حقوقي إذا شاركت في هذا البحث العلمي؟

المشاركة في هذا البحث العلمي هي بمحض اختيارك. يمكنك أن تختار المشاركة أو لا. إذا قررت أن تشارك في هذا البحث العلمي، يمكنك التوقف في أي وقت تشاء. وإذا لم تشارك لن تكون هناك أي عقوبة لك, ولا تتأثر الرعاية الطبية المقدمة لك بسبب هذا القرار.

بمن يمكنني الاتصال إذا كان لدي أسئلة أو مشاكل؟

إذا كانت لديك أسئلة عن هذا البحث العلمي ، يمكنك الاتصال بالباحث الرئيس على هذا الرقم 0555789051. إذا كانت لديك أي تساؤلات حول "حقوق الاشخاص موضوع البحث، " يمكنك الاتصال برئيس لجنة أخلاقيات البحث العلمي (IRB) على الرقم . إذا كان لديك مكالمة طارئة اتصل ب 0549260929 .

Appendix 3: Consent form (English and Arabic)

Consent form (English)

CONFIDENTIAL

Study Title: Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.	
Principal Investigator: Fareed Almaleki	**Study Site:** Tuberculosis and chest diseases centre in Jeddah

	Please initial box
9. I confirm I have read and understood the information sheet dated September 2016, Version 1.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
10. I understand that participation in this study is voluntary and I am free to withdraw consent at any time, without giving a reason, without any penalties.	
11. I give permission for the researcher and his supervisors only to have access to my records.	
12. I hereby declare that I have not been subjected to any form of coercion in giving this consent.	
13. I agree to the data about me collected in this study being stored for further use in the future.	
14. I agree that my blood samples will be transported to Madain Al-Fahad Health Centre in Jeddah to be analysed.	
15. I agree to gift this blood samples for future research purpose.	
16. I agree to take part in this study.	

Signing this declaration does not affect your right to decline to take part in any future study.

Name of participant	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

*** All data gathered on this form and any information you provide us for the study will be confidential and will not be communicated to anyone outside the study team.**

When complete: 1 copy for participant; 1 copy (original) for research

Consent form (Arabic)

وزارة الصحة
Ministry of Health

VISION 2030

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشمل الحد الأدنى من المخاطر

CONSENT:

Subject
I confirm I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at any time without in any way affecting my medical care. I will receive a signed copy of this consent form.

Subject Signature _____

Date: / /

Time (AM ☐ PM ☐)

Person Obtaining Consent:

I have explained the nature and purpose of the study and the risks involved. I have answered and will answer questions to the best of my ability. I will give a signed copy of the consent form to the subject.
Signature of Person Obtaining Consent

Date / /

Time (AM ☐ PM ☐)

Principal Investigator
Signature of Principal Investigator

Time (AM ☐ PM ☐)

إقرار بالموافقة

المشارك
أقر بأن هذا البحث العلمي وإجراءاته قد تم شرحها لي. لقد سمح لي بأن اسأل كل سؤال لدي الآن. ويمكنني أن اسأل أي أسئلة إضافية في أي وقت لاحق. كما يمكنني إنهاء المشاركة في هذا البحث العلمي في أي وقت دون أن تتأثر الرعاية الصحية المقدمة لي.
سأحصل على نسخة موقعة من الإقرار بالموافقة.

_____ توقيع المشارك

التاريخ / /

الوقت (ص ☐ م☐)

الشخص الحاصل علي الإقرار بالموافقة

أقر بأنني قد شرحت بصورة كاملة, طبيعة هذا البحث العلمي والغرض منه وما ينطوي عليه من مخاطر. ولقد أجبت على جميع الأسئلة بقدر الإمكان. سأعطي نسخة موقعة من الإقرار بالموافقة للمشارك المذكور أعلاه.

توقيع الشخص الحاصل علي الإقرار بالموافقة

التاريخ: / /

الوقت ص ☐ م☐

الباحث الرئيس
توقيع الباحث الرئيس

الوقت ص ☐ م☐

Appendix 4: Participant's information form for coronary heart disease patients (English and Arabic)

Participant's information form for coronary heart disease patients

The following information was given to the participants:

The purpose of the study, why the participant has been selected, a summary of the study procedure such as processes of data collection (e.g. questionnaires), the possible impact the research will have on the participant, such as side effects, risks, benefits, discomforts, data sharing, data storage, confidentiality, results circulation and voluntary involvement, where the participant can at any time withdraw themselves from the study and they will be provided with contact details of the appropriate person/researcher for any queries.

The consent form was distributed to the men/women that attended the King Faisal Hospital, to invite individuals to take part in the research study on diabetes mellitus and insulin resistance as key risk factors for CHD among euglycaemic and diabetic patients in Saudi Arabia; Taif city.

Fareed Almaleki, Liverpool School of Tropical Medicine

Determining the association of insulin resistance and diabetes mellitus as key risk factors for Coronary Heart Diseases among diabetic and euglycaemic patients in Saudi Arabia.

The consent form is split into two parts, and these are:

- The research information sheet
- The certificate of consent

The participants then received a copy of the consent form.

Introduction:

I am [*The name of the individual providing the consent form*]. I work for the King Faisal Hospital, Taif, and I am acting on behalf of Fareed Almaleki, who studies at the Liverpool School of Tropical Medicine, UK. We are performing research on topical diseases and their diagnosis, in particular diabetes mellitus, which is highly prevalent in Saudi Arabia. We are inviting you to take part in our research study, however, before participating, it is important to understand what the study will involve and why the research is being implemented. Please have a look carefully at the following information and if there is anything you are unsure of, or if you would like any further information do not hesitate to ask any questions. You are also free to review this information with your GP or any friends and family, and we would like to emphasise that you should only go ahead with the invitation if you are happy to take part in the study. Should you agree to participate in this study, we will need to ask you questions regarding your medical history enquiring about previous and current diseases. If you come across any words that you do not understand in this document or in the interview, please inform me and we will stop to ensure that it is explained to you. If you have any further questions at a later time you can either ask myself, the staff or the study doctor, while you will also be provided with the details of the contact person/researcher so that you can contact them regarding any queries you may have.

Purpose:
Diabetes mellitus is a frequent disease, which on a global scale affects more than 415 million individuals. We propose in this project that insulin resistance and diabetes are key risk factors for CHD and we will look for this association by studying patients in the city of Taif, Saudi Arabia. Insulin is a normal hormone that helps to utilise sugars. If the body does not respond well to this hormone, we call it insulin resistance.

Participant Selection:
This study invites participants above the age of 18 that attend the King Faisal Hospital in Taif.

Voluntary Participation:
Participation in this study is completely voluntary and it entirely up to you if you wish to participate, you will be given 24 hours to decide whether or not to participate. The services at this clinic that you currently receive will not be affected whether you decide to participate or not and If you do participate you can opt out at any time of the study.

Procedures and Protocol:
In order to determine if insulin resistance and diabetes increases the risk of CHD, we will invite 347 participants. Each participant will be asked for a blood sample (10ml) so that we can assess their glucose levels, insulin levels, HA1c and lipid profile, which will include TG, HDL and LDL. To calculate IR we will use a HOMA calculator, and when the results are available we will contact the participants by email or by phone to inform them. The participants will be asked to complete a questionnaire which will ask about your lifestyle, as well as weight, physical activity, diet and family history. There will be a nurse dedicated to measuring each participant's height (cm), weight (kg), hip and waist circumference (cm) and blood pressure (BP).

Risks and discomfort:
There will be no serious adverse effects in participating in this study; however there will be an interview, which will ask some personal questions. You will also be required to dedicate some time for the interview to take place. There will be an appropriate room with comfortable chairs provided and we will also ensure that the interviewer will adhere to academic principles by confirming that the participant is fully aware of the importance and the purpose of this study. The languages used in the interview will be Arabic and/or English, and the questions will be clear and easy to understand.
Hematoma: In venepuncture, it is possible for the blood to leak from a vein and out under the skin. This may cause pain and discomfort leading to complications in drawing more blood from that particular site. If haematoma is observed, the tourniquet and needle must be removed and pressure should be applied to the site for at least 3 minutes. The site is then checked for the haematoma to see if it has stopped and a gauze or bandage is taped to the area for a minimum of half an hour.
Pain: There is a small risk that during blood collection a needle may pierce the nerve. You would feel a mild electric sensation. If this occurs we will remove the needle and apply pressure to the site of the piercing. The sensation will stop and the

participant will be told the reason they felt this pain was because the needle had touched a nerve.

Samples to be collected and stored:
Your blood samples may be used anonymously for future studies and in testing for further potential diabetic markers. Signing this consent form means that you will give your permission for us to safely store your blood for anonymous use in other future projects that are considered suitable.

Benefits:
By participating in this study, we will be able to detect whether or not you are diabetic and if you are likely to develop diabetes. Should we detect that you are diabetic, we can arrange for you to meet a specialist and we will also provide you with a leaflet on diabetes risk awareness.

Incentives:
There is no financial incentive for taking part in this study

Confidentiality:
The study will take place within your clinic, therefore it is likely that others within the clinic may become aware of your participation and question you regarding this. We would like to assure you that the identity and all information collected from individuals participating in this study will be kept confidential. Your information that is collected in this study is confidential and will only be accessed by research sponsors, ethics committee members and institutional officials. Any data that we have on you will be number coded and your name will not be used, the only individuals that will know your number will be the researchers and this information will be locked away with a key.

Right to Refuse or Withdraw:
You have the right to refuse to participate in this study and if this is the case your treatment in this clinic will not be affected, you will still receive any assistance that you had prior to the study. If at any time you wish to withdraw from the study, you may do so without the loss of any rights that you have as a patient at this clinic, your treatment will not be affected.

Who to Contact:
Any questions you have can be asked now or at any time during the study. If you would like to enquire about anything at a later date, you can use any of the following contact details: [*name, address/telephone number/e-mail*].

CHD Arabic version patient information sheet

Form IRB-10.10.01

Minimal Risk Informed Consent Template

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشتمل علي
الحد الأدنى من المخاطر

Effective Date: KFMC Institutional Review Board

Protocol Number:	1 1	رقم البحث العلمي
Name of Subject:		اسم المشارك
Medical Record Number:		رقم السجل الطبي
Study Title:	Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.	عنوان البحث العلمي ترسيخ علاقة مرض السكري ومقاومة الانسولين كعوامل خطر رئيسية لمرض السل وأمراض القلب التاجية بين المرضى المصابين بالسكري و أسوياء السكري في المملكة العربية السعودية.
Principal Investigator: **Fareed Hamed Almaleki**		الباحث الرئيس فريد حامد المالكي
Address:	King Faisal General Hospital	العنوان مستشفى الملك فيصل بالطائف
Telephone: 0555789051		رقم الهاتف 0555789051

Why Is This Study Being Done?
This study will aim to describe the prevalence of DM and IR in Saudi Arabia among patients with TB from Jeddah city and apparently healthy controls to investigate the association of IR with TB.

ما سبب القيام بهذا البحث العلمي ؟
وتهدف هذه الدراسة إلى وصف انتشار مرض السكري ومقاومة الانسلين في المملكة العربية السعودية بين المرضى الذين يعانون من السل من مدينة جدة و مشاركين اصحاء للتحقيق من علاقة مقاومة الانسلين مع مرض السل الرئوي.

How Many People Will Take Part in This Study?
175 Tuberculosis patients and 140 healthy controls

كم عدد الأشخاص المفترض مشاركتهم في هذا البحث العلمي؟

What is involved in the Study?

ماذا يتضمن هذا البحث العلمي؟

Study location: Tuberculosis and Chest Diseases Centre in Jeddah city and Madain Al-Fahad Health Centre in Jeddah

موقع إجراء هذا البحث العلمي: مركز الدرن والامراض الصدرية بمدينة جدة و مركز صحي مدائن الفهد بجدة

What is Expected of Me During the Study? After receiving counselling and guidance and agreed to participate you will be

ما المطلوب مني خلال هذا البحث العلمي؟
بعد تلقي المشورة والتوجيه والموافقة على المشاركة سوف يطلب منك التوقيع على استمارة الموافقة. ثم باستخدام استبيانات منظمة، سيقوم فريق من الباحثين

asked to sign the consent form. Then by using structured questionnaires, a team of trained interviewers will interview you.

How Long Will I Be in This Study?

30-60 minutes

Can I Stop Being in This Study?

You can decide to stop at any time. Taking part is purely voluntary.

What are the Benefits of This Study?

There will be no direct benefit to you from taking part in this study. Study results may be useful to the patients in the future.

What are the Risks of This Study?

There will be no serious adverse effects in participating in this study.

What if I am Injured Because I Took Part in This Study?

If you are injured as a result of being in this study, treatment will be provided by Tuberculosis and Chest Diseases Centre in Jeddah city at no cost to you.

What are the Costs of This Study?

There are no costs to you if you take part in this study.

Will I Be Paid for Taking Part in This Study?

After receiving counselling and guidance and agreed to participate you will be asked to sign the consent form. Then by using structured questionnaires, a team of trained interviewers will interview you.

What are the Alternatives?

The interview will be at a mutually convenient location either in your own homes or the healthcare facilities.

Will My Information Be Kept Private?

المدربين بالجلوس معك وملئ الاستبيان عن طريق طرح اسئلة والاجابة عليها

كم مدة مشاركتي في هذا البحث العلمي؟

30 الى 60 دقيقة

هل يمكنني إنهاء المشاركة في هذا البحث العلمي؟

المشاركة طوعيه محضة ويمكنك أن تنهيها في أي وقت تشاء.

ما هي فوائد هذا البحث العلمي؟

لن تكون هناك أي فائدة مباشرة لك من المشاركة في هذا البحث العلمي. نتائج هذا البحث قد تكون مفيدة للمرضى في المستقبل.

ما هي المخاطر المتوقعة من المشاركة في هذا البحث العلمي؟

لا توجد مخاطر متوقعة من المشاركة في هذا البحث

ماذا سيحدث إذا أصابني ضرر جراء المشاركة هذا البحث العلمي؟

إذا حدث أن أصبت بضرر نتيجة مشاركتك في هذا البحث العلمي، ستقدم لك مركز الدرن والامراض الصدرية بمدينة جدة العلاج دون أي تكلفة لك.

وما هي تكاليف المشاركة في هذا البحث العلمي؟

لا توجد تكاليف للمشاركة في هذه هذا البحث العلمي.

هل هنالك اجر مقابل المشاركة في هذا البحث العلمي؟

بعد تلقي المشورة والتوجيه والموافقة على المشاركة سوف يطلب منك التوقيع على استمارة الموافقة. ثم باستخدام استبيانات منظمة، سيقوم فريق من الباحثين المدربين بالجلوس معك وملئ الاستبيان عن طريق طرح اسئلة والاجابة عليها

ما هي البدائل؟

سيتم إجراء المقابلة لاكمال الاستبيان في مكان مريح للمشارك اما في المستشفى او في منزل المشارك.

هل سيتم الحفاظ علي معلوماتي بسرية؟

Form IRB-10.10.01

Minimal Risk Informed Consent Template

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشتمل علي الحد الأدنى من المخاطر

Effective Date: KFMC Institutional Review Board

Your personal information will be kept private. It will be given out only if required by law. Your personal information will not be used in any reports.

What are My Rights if I Take Part in This Study?

Taking part in this study is your choice. You may choose to take part or not to take part. If you decide to take part in the study, you can quit at any time. There will be no penalty to you for your decision. Your medical care will not change.

Who Do I Call if I Have Questions or Problems?

If you have questions about the study, you can call Principal Investigator: Fareed Almaleki 0555789051. If you have any questions about "rights of human subjects," you may call the Chairman of the IRB at . If you have an emergency, call 0549260929.

معلوماتك الشخصية سيتم الحفاظ عليها بسرية تامة. ولا تعطي إلا إذا اقتضى الأمر وذلك في حدود النظم والقوانين المطبقة بهذا الخصوص. معلوماتك الشخصية لن تستخدم في أي تقارير.

ما هي حقوقي إذا شاركت في هذا البحث العلمي؟

المشاركة في هذا البحث العلمي هي بمحض اختيارك. يمكنك أن تختار المشاركة أو لا. إذا قررت أن تشارك في هذا البحث العلمي، يمكنك التوقف في أي وقت تشاء. وإذا لم تشارك لن تكون هناك أي عقوبة لك, ولا تتأثر الرعاية الطبية المقدمة لك بسبب هذا القرار.

بمن يمكنني الاتصال إذا كان لدي أسئلة أو مشاكل؟

إذا كانت لديك أسئلة عن هذا البحث العلمي ، يمكنك الاتصال بالباحث الرئيس على هذا الرقم 0555789051. إذا كانت لديك أي تساؤلات حول "حقوق الاشخاص موضوع البحث، " يمكنك الاتصال برئيس لجنة أخلاقيات البحث العلمي (IRB) على الرقم . إذا كان لديك مكالمة طارئة اتصل ب 0549260929 .

Appendix 5: Consent forms (English and Arabic)

Consent Form (English)

CONFIDENTIAL

Study Title: Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia.	
Principal Investigator: Fareed Almaleki	**Study Site:** King Faisal Hospital in Taif

	Please initial box
1. I confirm I have read and understood the information sheet dated September 2016, Version 1.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that participation in this study is voluntary and I am free to withdraw consent at any time, without giving a reason, without any penalties.	
3. I give permission for the researcher and his supervisors only to have access to my records.	
4. I hereby declare that I have not been subjected to any form of coercion in giving this consent.	
5. I agree to the data about me collected in this study being stored for further use in the future.	
6. I agree that my blood samples will be transported to King Faisal Hospital in Taif to be analysed.	
7. I agree to gift this blood samples for future research purpose.	
8. I agree to take part in this study.	

Signing this declaration does not affect your right to decline to take part in any future study.

Name of participant	**Date**	**Signature**
Name of person taking consent	**Date**	**Signature**

* **All data gathered on this form and any information you provide us for the study will be confidential and will not be communicated to anyone outside the study team.**

When complete: 1 copy for participant; 1 copy (original) for research.

Consent form (Arabic)

وزارة الصحة
Ministry of Health

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

إقرار بالموافقة المستنيرة علي المشاركة في بحث علمي يشمل الحد الأدنى من المخاطر

CONSENT:

Subject
I confirm I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at any time without in any way affecting my medical care. I will receive a signed copy of this consent form.

Subject Signature _____

Date: / /

Time (AM ☐ PM ☐)

إقرار بالموافقة

المشارك
أقر بأن هذا البحث العلمي وإجراءاته قد تم شرحها لي. لقد سمح لي بأن اسأل كل سؤال لدي الآن. ويمكنني أن اسأل أي أسئلة إضافية في أي وقت لاحق. كما يمكنني إنهاء المشاركة في هذا البحث العلمي في أي وقت دون أن تتأثر الرعاية الصحية المقدمة لي.
سأحصل على نسخة موقعة من الإقرار بالموافقة.

_____ توقيع المشارك

التاريخ / /

الوقت (ص ☐ م☐)

Person Obtaining Consent:

I have explained the nature and purpose of the study and the risks involved. I have answered and will answer questions to the best of my ability. I will give a signed copy of the consent form to the subject.
Signature of Person Obtaining Consent

Date / /

Time (AM ☐ PM ☐)

الشخص الحاصل علي الإقرار بالموافقة

أقر بأنني قد شرحت بصورة كاملة طبيعة هذا البحث العلمي والغرض منه وما ينطوي عليه من مخاطر. ولقد أجبت على جميع الأسئلة بقدر الإمكان. سأعطي نسخة موقعة من الإقرار بالموافقة للمشارك المذكور أعلاه.

توقيع الشخص الحاصل علي الإقرار بالموافقة

التاريخ: / /

الوقت ص ☐ م☐

Principal Investigator
Signature of Principal Investigator

Time (AM ☐ PM ☐)

الباحث الرئيس
توقيع الباحث الرئيس

الوقت ص ☐ م☐

Appendix 6: Ethical approval (LSTM)

Mr Fareed Hamed Almaleki
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE
Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44(0)151 705 3100
Fax: +44(0)151 705 3370
www.lstmed.ac.uk

Friday, 23 September 2016

Dear Mr Almaleki,

Research Protocol (16-036) 'Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia'

Thank you for your email of 20 September 2016 providing the necessary in-country approvals for this project. I can confirm that the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 22 September 2019. The committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee.
  Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Angela Obasi

Dr Angela Obasi
Chair
LSTM Research Ethics Committee

Mr Fareed Hamed Almaleki
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE
Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44(0)151 705 3100
Fax: +44(0)151 705 3370
www.lstmed.ac.uk

Friday, 23 September 2016

Dear Mr Almaleki,

Re. Research Protocol (16-036) 'Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia '

I am pleased to confirm that LSTM has agreed to act as Sponsor for the above mentioned clinical research study.

Please note that LSTM approval to allow your study to proceed is conditional upon compliance with the relevant regulatory requirements. For your awareness and adherence, please be reminded that IRB approval for the Kingdom of Saudi Arabia requires that progress reports be submitted for this research study at six month intervals.

All study staff should be given the appropriate training in Protocol, GCP, Consent and Data Protection, relevant to their responsibilities as defined within the study protocol.

LSTM Research Office should receive annual study progress and final close out reports via lstmgov@lstmed.ac.uk

Yours Sincerely,

Carl Henry
Governance Manager
Research Governance and Contracts Office

Appendix 7: Ethical approval (MOH-Saudi Arabia)

Kingdom of Saudi Arabia
Ministry of Health
King Fahad Medical City
(162)

وزارة الصحة
مدينة الملك فهد الطبية
King Fahad Medical City

المملكة العربية السعودية
وزارة الصحة
مدينة الملك فهد الطبية
(١٦٢)

IRB Registration Number with KACST, KSA: H-01-R-012
IRB Registration Number with OHRP/NIH, USA: IRB00010471
Approval Number Federal Wide Assurance NIH, USA: FWA00018774

July 24, 2016
IRB Log Number: 16-276E
Department: External
Category of Approval: EXPEDITED

Dear Fareed Almaleki,

I am pleased to inform you that submission dated July 20, 2016 for the study titled '**Establishing the association of Diabetes Mellitus and Insulin Resistance as key risk factors for Tuberculosis and Coronary Heart Diseases among euglycaemic and diabetic patients in Saudi Arabia**' was reviewed and was approved according to Good Clinical Practice guidelines.

Please be informed that in conducting this study, you as the Principal Investigator are required to abide by the rules and regulations of the Government of Saudi Arabia, the KFMC/IRB policies and procedures, and the ICH Good Clinical Practice guidelines. Further, you are required to submit a Progress Report before June 24, 2017; it can be reviewed by the IRB without lapse of approval. The approval of this proposal will automatically be suspended on July 24, 2017 pending the acceptance of the Progress Report. You also need to notify the IRB as soon as possible in the case of:

1. Any amendments to the project;
2. Termination of the study;
3. Any serious unexpected adverse events (within two working days);
4. Any event or new information that may affect the benefit/risk ratio of the proposal.

Please observe the following:

1. Personal identifying data should only be collected when necessary for research;
2. The data collected should only be used for this proposal;
3. Data should be stored securely so that a few authorized users are permitted access to the database;
4. Secondary disclosure of personal identifiable data is not allowed;
5. Copy of the Consent Form should be kept in the Research Subject's Medical Record and the consent process should be documented in the medical record;
6. Copy of the pharmacy clearance (IDS) must be in the medical record.

Please be advised that regulations require that you submit a progress report on your research every 6 months. You are also required to submit any manuscript resulting from this research for approval by IRB before submission to journals for publication.

As a researcher you are required to have current and valid certification on protection human research subjects that can be obtained by taking a short online course at the US NIH site or the Saudi NCBE site followed by a multiple choice test. Please submit your current and valid certificate for our records. Failure to submit this certificate shall a reason for suspension of your research project.

If you have any further questions feel free to contact me.

We wish you every success in your research endeavor.

Sincerely yours,

pp. Dr. Mushira A. Enani
Medical Director of MH
Badge # 009998
3610

F M
Approved
24 JUL 2016
I R B

Prof. Omar H. Kasule
Chairman, Institutional Review Board (IRB)
King Fahad Medical City, Riyadh, KSA
Tel: + 966 1 288 9999 Ext. 26913
E-mail: okasule@kfmc.med.sa

Appendix 8: TB participants questionnaire

Establishing the association of Diabetes and Insulin Resistance as risk factors for Tuberculosis and Coronary Heart Diseases in Saudi Arabia.

Tuberculosis Group			
Participant information			
Participant name		Participant number	
Date of birth	d d m m y y y y	File number	
Mobile number			
Address			

Demographic characteristics

Age (Years) ☐ Sex (Male 1, Female 2) ☐

Marital status (Single=1, with partner/married=2, divorced/separated=3, widowed=4) ☐

Education (No education=0, Literacy =1, primary=2, Intermediate= 3, secondary=4, higher education=5, prefer not to answer=6) ☐

Occupation (Governmental=1, private=2, labourer=3, not employed=4, retired=5, other=6) ☐

Country of origen

Lifestyle

Describe your job (Sedentary=1 Moderate Physical Activity =2 Physically Very Demanding=3) ☐

Describe your annual income during in the past 3 years (≤ 3000=1 3000-5000=2 5001-10000=3 ≥10000=4) ☐

How would you rate your stress level? (Low=1, Medium=2, High=3) ☐

Is anyone in your family overweight? (Yes=1 No=2 Don't know=3 Prefer not to say =4) ☐

If yes, who? Father ☐ Mother☐ Sibling☐ Grandfather☐ Other☐

Where you overweight as a child? (Yes=1 No=2 Don't know=3) ☐

Do you smoke? ☐

Diet

How many of the last seven days have you had breakfast? **(1 – 7 Days)** ☐

How many of the last seven days have you had lunch? **(1 – 7 Days)** ☐

How many of the last seven days have you had dinner? **(1 – 7 Days)** ☐

How would you rate your diet?	Good ☐ Fair ☐ Poor ☐
How often do you eat fast food such as burgers, fish and chips, fried chicken or pizza?	0-1 Times/Month ☐ 2-3 Times/Month ☐ 1-2 Times/Week ☐ 3-4 Times/Week ☐ 5+ Times/Wek ☐
Describe your daily food portions?	Small ☐ Intermediate ☐ Large ☐

Physical activity

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, or aerobics?		Days per week
No vigorous physical activities → **Skip the next question**		
How much time did you usually spend doing **vigorous** physical activities on one of those days?		Hours per day
		Minutes per day
		Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days. Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads? Do not include walking.

	Days per week

No moderate physical activities → **Skip the next question**

How much time did you usually spend doing **moderate** physical activities on one of those days?

	Hours per day
	Minutes per day
	Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

	Days per week

No walking → **Skip the next question**

How much time did you usually spend **walking** on one of those days?

	Hours per day
	Minutes per day
	Don't know/Not sure

Include time spent at work, at home, while doing course work and during leisure time. This may include time spent **sitting** at a desk, visiting friends, reading, or sitting or lying down to watch television.

During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

	Hours per day
	Minutes per day
	Don't know/Not sure

Medical history	(Yes=1, No=2, Don't know=3, Not applicable = 4)
Have you been diagnosed with diabetes?	
If yes, do you take insulin injection?	
Do you have a family history of diabetes?	
If yes, is this a relative of First degree ☐ Second degree ☐ Third degree ☐	
Do you have high blood pressure (hypertension)?	
If yes, do you take medication for high blood pressure?	
Do you have high levels of cholesterol?	
If yes, do you take lipid lowering therapy?	
Do you have heart problems?	
(For females) Have you had a history of gestational diabetes?	
(For females) Do you have polycystic ovaries?	
Do you have Cancer/leukemia	
Have you had an intestinal bypass or gastrectomy?	
Have you had an organ transplant?	
Are you HIV positive?	
Do you have a weakened immune system or recurrent infections?	
Have you been taking steroids?	
Are you taking any of the following medicines?	

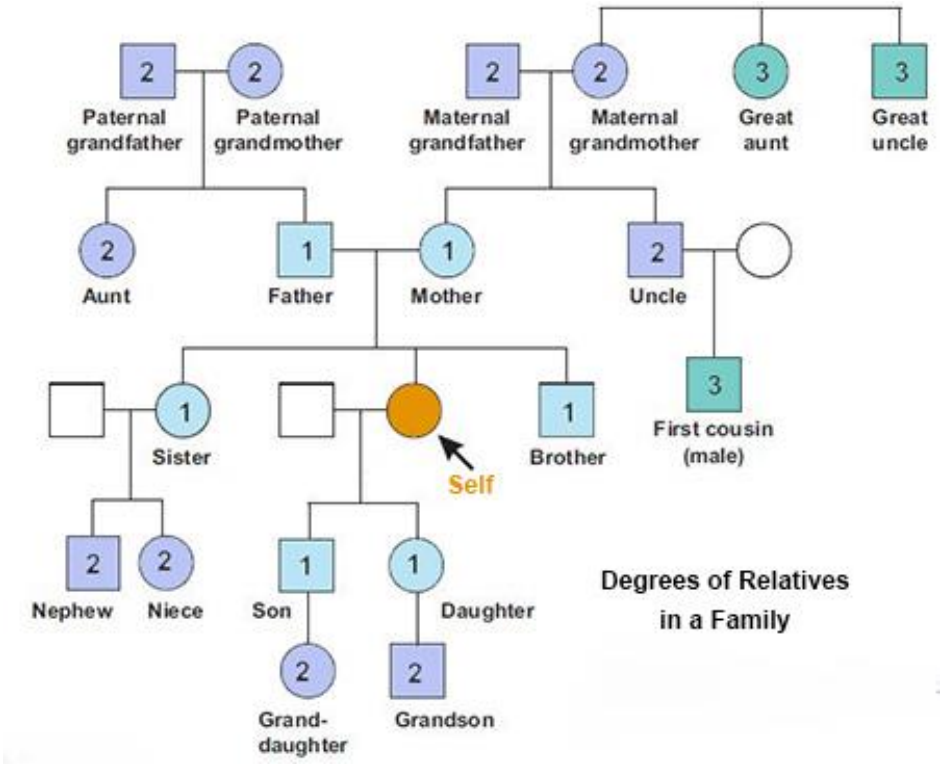
Enbrel☐ Humira☐ Cimza☐ Remicade☐ Simponi☐
Thalomid☐

Symptoms	(Yes=1, No=2, Don't know=3)
Have you had recently (last two weeks) any of the following symptoms?	
Chest discomfort	
Sputum	
Cough	
Sputum with blood	
Shortness of breath	
Fever	
Night sweats	
Poor appetite	
Unexpected weight loss	

Anthropometry			
Height (cm)		Body Mass Index (BMI = kg/m^2)	
Weight (kg)		Waist/Hip Ratio (WHR)	
Waist (cm)		Systolic blood pressure (mmHg)	
Hip (cm)		Diastolic blood pressure (mmHg)	

Blood tests measurements	
Fasting plasma glucose level (mg/dL)	
Haemoglobin A1c (%)	
Fasting plasma insulin level (µU/ml)	
HOMA-IR	
Total cholesterol (mg/dL)	
Triglycerides (mg/dL)	
HDL Cholesterol (mg/dL)	
LDL Cholesterol (mg/dL)	

TB results and Not done)	**(**Positive, Negative
TB Bacteriologically confirmed	
Acid fast bacilli smear positive	
Chest x-ray cavitation	


2
Paternal grandfather
2
Paternal grandmother
2
Maternal grandfather
2
Maternal grandmother
3
Great aunt
3
Great uncle
2
Aunt
1
Father
1
Mother
2
Uncle
1
Sister
1
Brother
3
First cousin (male)
Self
2
Nephew
2
Niece
1
Son
1
Daughter
2
Grand-daughter
2
Grandson
Degrees of Relatives in a Family

Appendix 9: CHD participants questionnaire

Establishing the association of Diabetes and Insulin Resistance as risk factors for Tuberculosis and Coronary Heart Diseases in Saudi Arabia.

Coronary Heart Disease Group			
Participant information			
Participant name		Participant number	
Date of birth	d d m m y y y y	File number	
Mobile number			
Address			

Demographic characteristics

Age (Years) ☐☐ Sex (Male 1, Female 2) ☐

Marital status (Single=1, with partner/married=2, divorced/separated=3, widowed=4) ☐

Education (No education=0, Literacy =1, primary=2, Intermediate= 3, secondary=4, higher education=5, prefer not to answer=6) ☐

Occupation (Governmental=1, private=2, labourer=3, not employed=4, retired=5, other=6) ☐

Country of origen ☐

Lifestyle

Describe your job (Sedentary=1 Moderate Physical Activity =2 Physically Very Demanding=3) ☐

Describe your annual income during in the past 3 years (≤ 3000=1 3000-5000=2 5001-10000=3 ≥10000=4) ☐

On a scale of 1-10, how would you rate your stress level? (Low=1, Medium=2, High=3) ☐

Is anyone in your family overweight? (Yes=1 No=2 Don't know=3 Prefer not to say =4) ☐

If yes, who? Father ☐ Mother☐ Sibling☐ Grandfather☐ Other☐

Where you overweight as a child? (Yes=1 No=2 Don't know=3) ☐

Do you smoke? (Yes=1 No=2 Prefer not to say =3) ☐

If yes, how many cigarette pre day? 1-10 ☐ 11-20 ☐ >21 ☐

Diet

How many of the last seven days have you had breakfast? **(1 – 7 Days)** ☐

How many of the last seven days have you had lunch? **(1 – 7 Days)** ☐

How many of the last seven days have you had dinner? **(1 – 7 Days)** ☐

How would you rate your diet? Good☐ Fair☐ Poor☐

How often do you eat fast food such as burgers, fish and chips, fried chicken or pizza?

0-1 times/month ☐
2-3 times/month ☐
1-2 times/week ☐
3-4 times/week ☐
5+ times/week ☐

Describe your daily food portions? Small ☐ Intermediate ☐ Large ☐

Physical activity

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, or aerobics? ☐ Days per week

No vigorous physical activities → **Skip the next question**

How much time did you usually spend doing **vigorous** physical activities on one of those days?

☐ Hours per day
☐ Minutes per day
☐ Don't know/Not sure

Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads? Do not include walking. ☐ Days per week

No moderate physical activities → **Skip the next question**

How much time did you usually spend doing **moderate** physical activities on one of those days?		
		Hours per day
		Minutes per day
		Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?		
		Days per week

No walking → **Skip the next question**

How much time did you usually spend **walking** on one of those days?		
		Hours per day
		Minutes per day
		Don't know/Not sure

Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

During the **last 7 days**, how much time did you spend **sitting** on a **week day**?		
		Hours per day
		Minutes per day
		Don't know/Not sure

Medical history	(Yes=1, No=2, Don't know=3, Not applicable = 4)
Have you been diagnosed with diabetes?	
If yes, do you take insulin injection?	
Do you have a family history of diabetes?	
If yes, is this a relative of First degree ☐ Second degree ☐ Third degree ☐	
Do you have high blood pressure (hypertension)?	
If yes, do you take medication for high blood pressure?	
Do you have high levels of cholesterol?	
If yes, do you take lipid lowering therapy?	
(For females) Have you had a history of gestational diabetes?	
(For females) Do you have polycystic ovaries?	

Anthropometric			
Height (cm)		Body Mass Index (BMI = kg/m^2)	
Weight (kg)		Waist/Hip Ratio (WHR)	
Waist (cm)		Systolic blood pressure (mmHg)	
Hip (cm)		Diastolic blood pressure (mmHg)	

Blood tests measurements	
Fasting plasma glucose level (mg/dL)	
Haemoglobin A1c (%)	

Fasting plasma insulin level (µU/ml)	
HOMA-IR	
Total cholesterol (mg/dL)	
Triglycerides (mg/dL)	
HDL Cholesterol (mg/dL)	
LDL Cholesterol(mg/dL)	

Diagnosis

What is the clinical diagnosis?

Diagnosis ……

When the patient has been diagnosis? | d | d | m | m | y | y | y | y |

Is there any surgical intervention? ☐ Yes ☐ No

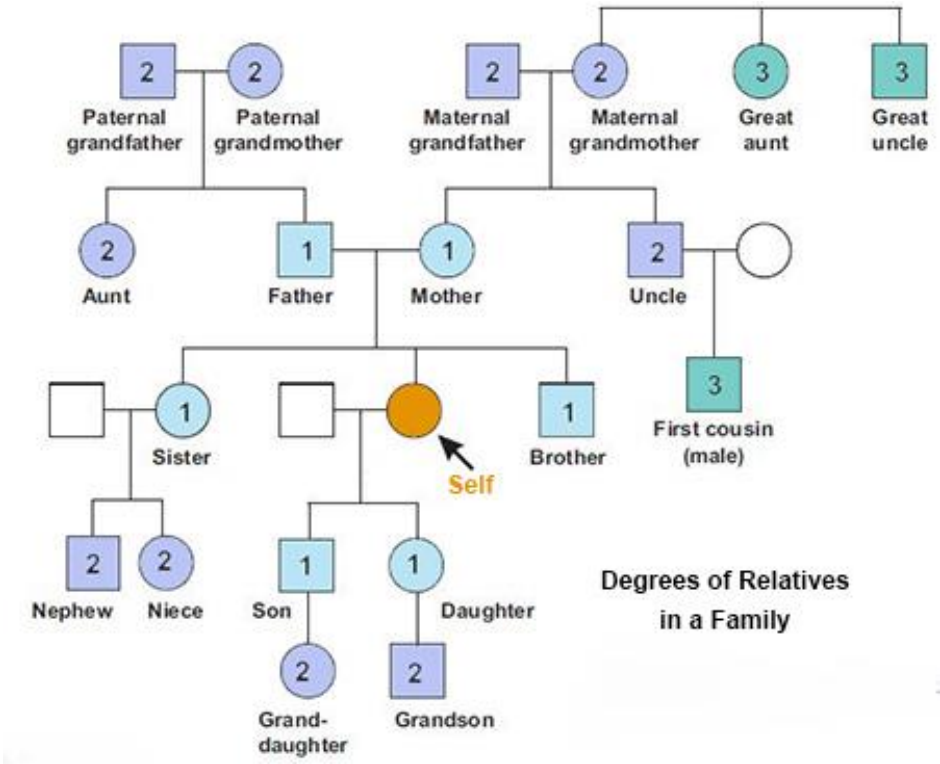
If yes, when? | d | d | m | m | y | y | y | y |

Current clinical condition

☐ Problem solved surgically.

☐ Problem solved with medicine.

☐ 2 and 3 combined.


2
Paternal grandfather
2
Paternal grandmother
2
Maternal grandfather
2
Maternal grandmother
3
Great aunt
3
Great uncle
2
Aunt
1
Father
1
Mother
2
Uncle
1
Sister
Self
1
Brother
3
First cousin (male)
2
Nephew
2
Niece
1
Son
1
Daughter
2
Grand-daughter
2
Grandson
Degrees of Relatives in a Family

Appendix 10: English version of the WHO-QoL-BREF (WHOQoL-BREF) questionnaire

Establishing the association of Diabetes and Insulin Resistance as risk factors for Tuberculosis and Coronary Heart Diseases in Saudi Arabia.

English version of the WHO-QoL-BREF (WHOQoL-BREF) questionnaire

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfie	Dissatisfied	Neither satisfied	Satisfied	Very satisfie
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate	Very much	An extreme
3.	To what extent do you feel that physical pain prevents you fromdoing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

Not at all A little Moderately Mostly Completely

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfie	Dissatisfied	Neither satisfied nor	Satisfied	Very satisfie
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living	1	2	3	4	5
18.	How satisfied are you with your capacity for	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your marriage	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Appendix 11: Arabic version of the WHO-QoL-BREF (WHOQoL-BREF) questionnaire

Arabic version of the WHO-QoL-BREF (WHOQoL-BREF) questionnaire

تأسيس رابطة مرضى السكري ومقاومة الأنسولين كعوامل خطر للإصابة بمرض السل وأمراض القلب التاجية في المملكة العربية السعودية

إصدار اللغة الإنجليزية من استبيان (WHO-QOL-BREF (WHOQoL-BREF

تسأل الأسئلة التالية كيف تشعر حيال جودة حياتك أو صحتك أو غير ذلك من مجالات حياتك. سوف أقرأ عليك كل سؤال ، بالإضافة إلى خيارات الاستجابة. يرجى اختيار الإجابة التي تبدو الأنسب. إذا كنت غير متأكد من الإجابة على السؤال ، فغالباً ما يكون الرد الأول الذي تفكر فيه هو الأفضل

يرجى مراعاة المعايير والأمال والملذات والاهتمامات. نطلب منك التفكير في حياتك في الأسابيع الأربعة الأخير

		سيئة للغاية	سيئة	لا سيئة ولا جيد	حسن	جيد جدا
1.	كيف تقيم نوعية حياتك؟	1	2	3	4	5

		مستاء جدا	غير راض	لا راض ولا غير راض	راض	راض جدا
2.	ما مدى رضاك عن صحتك؟	1	2	3	4	5

تسأل الأسئلة التالية عن مدى خبرتك لأشياء معينة في الأسابيع الأربعة الأخيرة.

		على الاطلاق	قليل	كمية معتدلة	كثير	كثيرا جدا
3.	إلى أي مدى تشعر بأن الألم الجسدي يمنعك من القيام بما تحتاج إلى القيام به؟	5	4	3	2	1
4.	كم تقيم حاجتك إلى العلاج للعمل في حياتك اليومية؟	5	4	3	2	1
5.	ما مدى استمتاعك بالحياة؟	1	2	3	4	5
6.	إلى أي مدى تشعر بان حياتك ذات معنى؟	1	2	3	4	5

		لا على الاطلاق	القليل	كمية معتدلة	كثير	كثيرا جدا
7.	قيم مقدار قدرتك على التركيز ؟	1	2	3	4	5
8.	هل تشعر بالامان في حياتك اليومية؟	1	2	3	4	5
9.	ما مقدار صحة البيئة الخاصة بك؟	1	2	3	4	5

تسأل الأسئلة التالية عن مدى خبراتك أو قدرتك على فعل أشياء معينة في الأسابيع الأربعة الأخيرة.

لا على الاطلاق/ قليلا /معتدلة /تماما/ في الغالب

		لا على الاطلاق	قليلا	معتدلة	تماما	في الغالب
10.	هل لديك ما يكفي من الطاقة للحياة اليومية؟	1	2	3	4	5
11.	هل لديك قبول لمظهرك الجسدي؟	1	2	3	4	5
12.	هل لديك ما يكفي من المال لتلبية احتياجاتك؟	1	2	3	4	5
13.	كم متاح لك من المعلومات التي تحتاجها في حياتك اليومية؟	1	2	3	4	5
14.	إلى أي مدى لديك الفرصة لأنشطة الترفيهية؟	1	2	3	4	5

		سيئة للغاية	سيئة	لا سيئة ولا جيد	حسن	جيد جدا
15.	ما مدى قدرتك على الحضور الى المستشفى؟	1	2	3	4	5

		مستاء جدا	غير راض	لا راض ولا غير راض	راض	راض جدا
16.	ما مدى رضاك عن نومك؟	1	2	3	4	5
17.	ما مدى رضاك عن قدرتك على أداء أنشطة حياتك اليومية؟	1	2	3	4	5
18.	ما مدى رضاك على قدرتك على العمل؟	1	2	3	4	5
19.	ما مدى رضاك عن نفسك؟	1	2	3	4	5

20.	ما مدى رضاك عن علاقاتك الشخصية؟	1	2	3	4	5
21.	ما مدى رضاك عن علاقة زواجك؟	1	2	3	4	5
22.	ما مدى رضاك عن الدعم الذي تحصل عليه من أصدقائك؟	1	2	3	4	5
23.	ما مدى رضاك عن ظروف مكان المعيشة الخاص بك؟	1	2	3	4	5
24.	ما مدى رضاك عن سهولة الوصل إلى الخدمات الصحية؟	1	2	3	4	5
25.	ما مدى رضاك عن وسائل النقل الخاصة بك؟	1	2	3	4	5

يشير السؤال التالي إلى عدد المرات التي شعرت فيها أو تعرضت لأشياء معينة في الأسابيع الأربعة الأخيرة.						
		أبدا	نادرا	غالبا	غالبا جدا	دائما
26.	كم مرة لديك مشاعر سلبية مثل المزاج المتقلب واليأس والقلق والاكتئاب؟	5	4	3	2	1

Appendix 12: Notification & Medical report of TB case

المملكة العربية السعودية
وزارة الصحة
البرنامج الوطني لمكافحة الدرن
مديرية الشئون الصحية:.....
نموذج ١

الجهة المبلغة:.....

إستمارة تبليغ وتقرير طبي عن حالة درن (Notification & Medical report of TB case)

رقم ملف الريف

الجزء الأول: البيانات الشخصية (First Part: Personal Data):

إسم المريض (Patient name):..... العمر (Age): الجنس (sex):

الجنسية (Nationality): ..... المهنة (Occupation): .....

رقم الحفيظة للسعوديين (I.D. No. for Saudis): ..... تاريخ الإصدار (Issue Date): / / مكان الإصدار (Issue place) :

رقم الإقامة لغير السعوديين (Iqama NO. for Non-Saudis): ..... تاريخ الإصدار (Issue Date): / / مكان الإصدار (Issue place) :

رقم جواز السفر (Passport No.): ..... تاريخ الإصدار (Issue Date): / / مكان الإصدار (Issue place) :

إسم الكفيل (Sponsor s name):..... رقم الهاتف (phone No.):

رقم الحفيظة (I.D. No. for Saudis): ..... تاريخ الإصدار (Issue Date): / / مكان الإصدار (Issue place) :

عنوان الكفيل (Sponsor s address):.....

عنوان عمل الكفيل (Work address of the sponsor):..... رقم الهاتف (phone No.) :

عنوان المريض (Patient s address):.....

عنوان العمل (Work address):..... رقم الهاتف (phone number):

إسم المركز الصحي المحول للحالة:.....

الجزء الثاني (Second Part):

أ- الفحص السريري (Signs & symptoms):

تاريخ بداية الأعراض (date of onset): / /

١- كحة (Cough):

المدة بالأسبوع (Period in weeks):

٢- بلغم (Sputum):

٣- نفث دموي (Heamoptysis):

٤- حرارة (Fever):

٥- تعرق ليلي (Night sweating):

٦- ألم بالصدر (Chest pain):

٧- نقص الوزن (loss of weight):

٨- فقدان الشهية (Loss of appetite):

٩- أعراض وعلامات أخري (other signs & symptoms):

ب – التاريخ المرضي السابق (Past Medical history):

١- البول السكري (Diabetes M.):

٢- أمراض رئوية (Lung diseases):

٣- فشل كلوي مزمن (chronic renal failure):

٤- نقص المناعة المكتسب (AIDS):

٥- مثبطات المناعة (Immunosuppressive therapy):

فترة العلاج بالسنوات (Treatment period in years):

٦- سرطان (Cancer):

نوعه (Type):

٧- سابقة التطعيم بالـ بي سي جي (history of BCG vaccination):

التاريخ بالسنوات (period in years):

الندبة (Scare):

٨- علاج سابق للدرن (Previous history of TB treatment)

مدة العلاج بالشهور (Period in months):

البلد المعالج (treating country):

نتيجة المعالجة السابقة (treatment outcome of previous treatment):

ج - نتائج الفحوصات والتحاليل(Investigations):

إختبار التيوبركلين (Tuberculin test): ☐ ملم

فحص البصاق (Sputum smear):

رقم العينة ☐ التاريخ / /

أشعة الصدر(X- Ray) : ☐

فحص الـ HIV ☐

بذل سوائل (Fluid aspiration):

بلوري (Pleural) ☐ تيموري ☐ نخاعي (CSF) ☐ بريتوني (Peritoneal) ☐

غسيل معدة gastric lavage ☐ غسيل القصبة الهوائية bronchial lavage ☐

مزرعة بصاق (Sputum culture): ☐

عينة باثولوجي (Pathology): ☐

مكانها (pathology site): ☐

سرعة الترسيب للدم (ESR): ☐

د- التصنيف حسب مكان الدرن (Classification according to site):

رئوي (Pulmonary) ☐ خارج الرئة(EP) ☐

هـ- تصنيف المريض (patient classification):

جديد (New) ☐ منتكس (Relapse) ☐ عاود بعد انقطاع (TAD) ☐ محول (Transferred) ☐ أخرى Others ☐

و- النظام العلاجي (Treatment category):

CAT1 ☐ CAT2 ☐ CAT3 ☐ CAT4 ☐

١- أدخل المستشفى بتاريخ (Date of Hospitalization):.....بتاريخ/ /

٢- بدأ العلاج بمركز الدرن (Starting treatment in TB center):.....بتاريخ / /

٣- بدأ العلاج بمركز صحي (Starting treatment in a PHC): .....بتاريخ / /

٤- حول للعلاج إلى (Transferred to):.....بتاريخ / /

٥- أعطي موعد مع الأخصائي الاجتماعي بتاريخ.....بتاريخ / /

ل- رأي الطبيب المعالج (Decision of the Physician):

يعالج (treat): ☐ يعرض على لجنة (Consult a committee): ☐

إسم الطبيب (Physician name):..... التوقيع (Signature):

قرار اللجنة

سعادة منسق برنامج مكافحة الدرن بمديرية الشئون الصحية..... المحترم

بعد الفحص الطبي والاطلاع على النتائج والتقارير والأوراق الخاصة بالمريض المحول للجنة والمذكور اسمه بعاليه، قررت اللجنة التالي:

- المريض مصاب بالدرن ويبدأ علاجه ☐
- إمكانية العمل ☐
- غير سعودي (حسب النظام) ☐

نأمل اتخاذ الإجراءات اللازمة، مع أطيب تحياتنا،،،

الإسم: طبيب / الإسم: طبيب / الإسم أخصائي اجتماعي/

التوقيع: التوقيع: التوقيع:

Appendix 13: TB Logistic regression tables

TB Logistic regression tables

Demographic characteristics		AOR (95% C.I.)	p
Gender	Male	1	
	Female	0.802 (0.439 - 1.465)	0.473
Age	18 - 29	1	
	30 – 39	1.198 (0.564 - 2.544)	0.639
	40 – 49	0.464 (0.201 - 1.070)	0.072
	≥ 50	0.371 (0.172 - 0.800)	**0.011**
Ethnicity	Non-Saudi	1	
	Saudi	0.287 (0.171 - 0.481)	**< 0.001**
Marital status	Married	1	
	Not married	1.100 (0.564 - 2.148)	0.779
Education	Educated	1	
	Non-Educated	1.894 (1.037 - 3.458)	**0.038**
Occupation	Not employed	1	
	Employed	1.332 (0.740 - 2.397)	0.339
	Constant	0.625	0.253

Medical history		AOR (95% C.I.)	p
Diabetes	No	1	
	Yes	3.295 (1.587 - 6.842)	**0.001**
	Don’t know	0.206 (0.022 - 1.928)	0.166
Family history of diabetes	No	1	
	Yes	0.657 (0.389 - 1.111)	0.117
Hypertension	No	1	
	Yes	0.149 (0.021 - 1.047)	0.056
	Don’t know	0.458 (0.060 - 3.502)	0.452
Takes hypertensive medication	Yes	1	
	No	0.343 (0.043 - 2.706)	0.310
Hyperlipidaemia	No	1	
	Yes	0.200 (0.047 - 0.856)	**0.030**
	Don’t know	0.149 (0.019 - 1.166)	0.070
Takes lipid lowering therapy	No	1	
	Yes	0.843 (0.139 - 5.103)	0.853
	Don’t know	2.182 (0.112 - 42.348)	0.606
Polycystic ovaries	Yes	1	
	No	44	0.999
	Don’t know	66	0.999
	Not applicable	35	0.999
	Constant	0.000	0.999

Lifestyle and diet		AOR (95% C.I.)	p
Monthly income	≤ 3000	1	
	3000 - 5000	1.294 (0.600 - 2.793)	0.511
	5001 - 10000	0.402 (0.104 - 1.558)	0.187

	≥ 10000	0.000 (0.000)	0.999
Level of stress	Low	1	
	Medium	0.867 (0.395 - 1.901)	0.721
	High	3.555 (0.785 - 16.103)	0.100
Family overweight	Yes	1	
	No	0.718 (0.293 - 1.757)	0.468
	Don't know	10 (0.000)	1.000
	Prefer not to say	0.000 (0.000)	1.000
If yes, who?	Father (No)	1	
	Father (Yes)	0.455 (0.084 - 2.453)	0.360
Number of dinner meals last week	Never	1	
	1 – 6/per week	93 (0.000)	0.999
	Always	95 (0.000)	0.999
Participant self-rating the diet quality			
	Good	1	
	Fair	19.127 (8.401 - 43.545)	**< 0.001**
	Poor	30.228 (11.058 - 82.628)	**< 0.001**
Fast food consumption	0 - 1/Month	1	
	2 - 3/Month	2.082 (0.946 - 4.580)	0.068
	1 - 2/Week	2.350 (1.009 - 5.470)	**0.048**
	3 - 4/Week	0.906 (0.377 - 2.177)	0.825
	≥ 5 /Week	1.461 (0.583 - 3.660)	0.418
	Constant	0.000	0.999

Anthropometry		AOR (95% C.I.)	p
WHR	Low	1	
	Moderate	1.064 0.615 - 1.840)	0.825
	High	1.006 (0.473 - 2.139)	0.988
BMI	≤ 18.4	1	
	18.5 - 24.9	0.540 (0.244 - 1.197)	0.129
	25 - 29.9	0.179 (0.076 - 0.423)	**< 0.001**
	≥ 30	0.119 (0.047 - 0.301)	**< 0.001**
	Constant	3.765	0.000

Metabolic/clinical characteristics		**AOR (95% C.I.)**	**p**
FBG (mg/dL)	< 110	1	
	110 – 125	3.151 (1.086 - 9.138)	**0.035**
	≥ 126	3.244 (1.132 - 9.294)	**0.028**
HA1c (%)	< 5.7	1	
	≥ 5.7 – 6.4	0.518 (0.280 - 0.957)	**0.036**
	≥ 6.5	0.552 (0.211 - 1.443)	0.226
Fasting Plasma Insulin (µU/ml)	2 – < 25		
	≥ 25	0.660 (0.312 - 1.396)	0.277
Total cholesterol (mg/dL)	< 150	1	
	≥ 150	1.233 (0.553 - 2.751)	0.609

Triglycerides (mg/dL)	< 150	1	
	< 200	0.789 (0.368 - 1.690)	0.542
	≥ 200	0.400 (0.144 - 1.114)	0.080
LDL (mg/dL)	< 100	1	
	≥ 100	1.371 (0.705 - 2.665)	0.352
HDL	Optimal	1	
	Risky	0.530 (0.309 - 0.909)	**0.021**
Systolic BP		0.987 (0.972 - 1.003)	0.109
Diastolic BP		0.998 (0.973 -1.025)	0.909
	Constant	6.827	0.018

Appendix 14: CHD Logistic regression tables

CHD Logistic regression tables

Demographic characteristics		AOR (95% C.I.)	p
Gender	Female	**1**	
	Male	2.907 (1.302 - 6.492)	**0.009**
Age	18 – 39	**1**	
	40 – 49	0.014 (0.002 - 0.084)	**< 0.001**
	50 – 59	0.004 (0.001 - 0.027)	**< 0.001**
	60 – 69	0.002 (0.000 - 0.014)	**< 0.001**
	≥ 70	0.001 (0.000 - 0.009)	**< 0.001**
Ethnicity	Non-Saudi	**1**	
	Saudi	4.480 (2.189 - 9.169)	**< 0.001**
Marital status	Single	**1**	
	With partner/married	3.712 (1.081 - 12.742)	**0.037**
	Divorced/separated	0.112 (0.003 - 4.451)	0.244
	Widowed	0.577 (0.088 - 3.780)	0.567
Education	No education	**1**	
	Literacy	0.374 (0.122 - 1.152)	0.087
	Primary education	0.123 (0.038 - 0.397)	**< 0.001**
	Intermediate education	1.093 (0.304 - 3.924)	0.892
	Secondary education	0.371 (0.113 - 1.221)	0.103
	Higher education	0.296 (0.066 - 1.321)	0.111
Occupation	Not Employed	**1**	
	Employed	1.109 (0.500 - 2.457)	0.800
	Constant	26.825	0.001

Medical history		AOR (95% C.I.)	p
Diabetes	No	1	
	Yes	17.103 (1.970 - 148.516)	**0.010**
	Don't know	60.674 (3.267 - 1126.908)	**0.006**
Diabetes using insulin	No	1	
	Yes	10.749 (1.187 - 97.306)	**0.035**
Family history of diabetes	No		
	Yes	1.623 (0.802 - 3.286)	0.178
Hypertension	No	1	
	Yes	0.537 (0.138 - 2.092)	0.370
	Don't know	5.657 (0.060 - 537.758)	0.456
Takes hypertensive medication	No		
	Yes	23.567 (6.278 - 88.466)	**< 0.001**
Hyperlipidaemia	No	1	
	Yes	0.386 (0.101 - 1.472)	0.163

	Don't know	0.526 (0.090 - 3.062)	0.475
Takes lipid lowering therapy	No	1	
	Yes	28.625 (7.352 - 111.441)	**< 0.001**
	Don't know	32.977 (2.441 - 445.460)	**0.008**
History of gestational diabetes	No	1	
	Yes	0.972 (0.130 - 7.297)	0.978
Polycystic ovaries	No	1	
	Yes	1.872 (0.149 - 23.540)	0.627
	Don’t know	2.175 (0.053 - 88.857)	0.682
	Not applicable	0.451 (0.002 - 83.703)	0.765
	Constant	0.003	0.016

Lifestyle and diet		**AOR (95% C.I.)**	**p**
Type of job	Sedentary	**1**	
	Moderate Physical Activity	16.182 (5.748 - 45.561)	**< 0.001**
	Physically Very Demanding	15.955 (0.776 - 328.266)	0.073
Monthly income	≤ 3000	**1**	
	3000 - 5000	0.446 (0.202 - 0.982)	**0.045**
	5001 - 10000	0.167 (0.052 - 0.533)	**0.003**
	≥ 10000	0.064 (0.007 - 0.547)	**0.012**
Level of stress	Low	**1**	
	Medium	0.364 (0.165 - 0.803)	**0.012**
	High	0.102 (0.016 - 0.660)	**0.017**
Overweight among family	No	**1**	
	Yes	2.125 (0.919 - 4.915)	0.078
	Don’t know	1.839 (0.000)	1.000
	Prefer not to say	35 (0.000)	0.999
Overweight as a child	No	**1**	
	Yes	1.165 (0.403 - 3.366)	0.778
	Don’t know	0.000 (0.000)	0.999
Smoking	No		
	Yes	1.175 (0.426 - 3.243)	0.756
Past smoker	No	**1**	
	Yes	0.152 (0.056 - 0.408)	**< 0.001**
Number of breakfast meals last week	1	3.676 (0.165 - 81.987)	0.411
	2	1.269 (0.106 - 15.185)	0.851
	3	2.222 (0.269 - 18.332)	0.458
	4	8.706 (0.624 - 121.541)	0.108
	5	3.190 (0.213 - 47.757)	0.401
	6	42 (0.000)	1.000
	7	0.461 (0.077 - 2.748)	0.395
	1	32.727 (0.000)	1.000
	2	36 (0.000)	0.999

Number of lunch meals last week	3	73 (0.000)	0.999
	4	33 (0.000)	0.999
	5	29 (0.000)	0.999
	6	42 (0.000)	0.999
	7	14 (0.000)	0.999
Number of dinner meals last week	1	0.175 (0.003 - 10.809)	0.408
	2	0.048 (0.000 - 6.984)	0.231
	3	3.150 (0.202 - 49.127)	0.413
	4	2.385 (0.093 - 61.355)	0.600
	5	0.673 (0.007 - 64.003)	0.865
	6	0.535 (0.052 - 5.475)	0.598
Participant rating of his/her diet	Good	**1**	
	Fair	0.040 (0.017 - 0.096)	**< 0.001**
	Poor	0.012 (0.004 - 0.042)	**< 0.001**
Fast food consumption	0 - 1 Times/Month	**1**	
	2 - 3 Times/Month	0.760 (0.304 - 1.901)	0.557
	1 - 2 Times/Week	2.847 (1.123 - 7.218)	**0.027**
	3 - 4 Times/Week	6.221 (2.127 - 18.200)	**0.001**
	≥ 5 Times/Week	4.466 (1.224 - 16.292)	**0.023**
	Constant	0.000	0.999

Anthropometry		**AOR (95% C.I.)**	**p**
WHR	Low	1	
	Moderate	0.120 (0.058 - 0.245)	**< 0.001**
	High	0.026 (0.012 - 0.057)	**< 0.001**
BMI	≤ 18.4	1	
	18.5 - 24.9	0.000 (0.000)	0.999
	25 - 29.9	0.000 (0.000)	0.999
	≥ 30	0.000 (0.000)	0.999
	Constant	161	0.999

Metabolic/Clinical characteristic		**AOR (95% C.I.)**	**p**
FPG (mg/dL)	< 110	1	
	110 – 125	0.368 (0.131 - 1.029)	0.057
	≥ 126	0.222 (0.098 - 0.502)	**< 0.001**
HA1c (%)	< 5.7 %	1	
	≥ 5.7 – 6.4	1.082 (0.565 - 2.070)	0.813
	≥ 6.5%	0.802 (0.349 - 1.845)	0.604
Fasting Plasma Insulin (µU/ml)	2 – < 25		
	≥ 25	1.172 (0.583 - 2.357)	0.655
Total cholesterol (mg/dL)	< 150	1	
	≥ 150	4.185 (2.043 - 8.571)	**< 0.001**

Triglycerides (mg/dL)	< 150	1	
	< 200	0.439 (0.205 - 0.942)	**0.035**
	≥ 200	0.638 (0.305 - 1.335)	0.233
LDL (mg/dL)	< 70	1	
	≥ 70	1.009 (0.438 - 2.321)	0.984
HDL (mg/dL)	Optimal	1	
	Risky	1.165 (0.664 - 2.044)	0.594
Systolic BP		0.983 (0.968 - 0.999)	**0.034**
Diastolic BP		0.942 (0.916 - 0.968)	**< 0.001**
	Constant	305.852	0.000

Appendix 15: CHD Logistic regression tables for CHD-IR cases and CHD-controls

CHD-IR cases and CHD-controls

Demographic characteristics		AOR (95% C.I.)	p
Gender	**Female**	1	
	Male	0.780 (0.286 - 2.130)	0.628
Age	**18 – 39**	1	
	40 – 49	0.813 (0.039 - 16.752)	0.893
	50 – 59	0.671 (0.035 - 12.716)	0.790
	60 – 69	1.232 (0.064 - 23.795)	0.890
	≥ 70	0.334 (0.016 - 7.186)	0.484
Ethnicity	**Non-Saudi**	1	
	Saudi	3.994 (0.949 - 16.809)	**0.059**
Occupation	**Not employed**	1	
	Employed	1.650 (0.539 – 5.050)	0.380
	Constant	0.321	0.493

Medical history		AOR (95% C.I.)	p
Family history of diabetes	**No**	1	
	Yes	1.718 (0. 771 - 3.831)	0.185
Hypertension	**No**	1	
	Yes	0.515 (0.219 - 1.215)	0.130
	Constant	0.505	0.035

Lifestyle and diet		AOR (95% C.I.)	p
Monthly income	**≤ 3000**	1	
	3000-5000	0.480 (0.152 - 1.520)	0.212
	5001-10000	0.996 (0.290 - 3.421)	0.995
	≥10000	10.620 (1.066 - 105.797)	**0.044**
Level of stress	**Low**	1	
	Medium	1.129 (0.434 - 2.934)	0.803
	High	0.000 (0.000)	0.999
Family overweight	**No**	1	
	Yes	2.326 (0.831 - 6.536)	0.108
Overweight as a child	**Yes**	1	
	No	1.258 (0.325 - 4.878)	0.739
	Don't know	0.000 (0.000)	1.000
Past smoker	**No**	1	
	Yes	0.721 (0.242 - 2.149)	0.557
Number of breakfast meals last week	**Never**	1	
	1 – 6	0.296 (0.032 - 2.717)	0.282
	Always	0.298 (0.045 - 1.959)	0.208
Fast food consumption	**0 - 1/Month**	1	
	2 - 3/Month	1.596 (0.560 - 4.550)	0.382
	1 - 2/Week	0.473 (0.100 - 2.240)	0.346

	3 - 4/Week	0.859 (0.149 - 4.946)	0.865
	≥ 5 /Week	0.462 (0.038 - 5.627)	0.545
	Constant	3.908	0.250

Anthropometry (Male)		AOR (95% C.I.)	p
WHR	**Low**	1	
	Moderate	0.288 (0.020 - 4.163)	0.361
	High	0.637 (0.046 - 8.854)	0.737
BMI	**18.5 - 24.9**	1	
	25 - 29.9	2.380 (0.533 - 10.626)	0.256
	≥ 30	4.341 (0.963 - 19.562)	**0.056**
	Constant	0.365	0.433

Anthropometry (Female)		**AOR (95% C.I.)**	**p**
WHR	**Moderate**	1	
	High	1.369 (0.094 - 19.861)	0.818
BMI	**18.5 - 24.9**	1	
	25 - 29.9	1.048 (0.047 - 23.394)	0.976
	≥ 30	6.921 (0.556 - 86.142)	0.133
	Constant	0.121	0.108

Appendix 16: CHD Logistic regression tables for CHD-diabetic cases and CHD-controls

CHD-diabetic cases and CHD-controls

Demographic characteristics		AOR (95% C.I.)	p
Gender	**Female**	**1**	
	Male	0.854 (0.384 - 1.901)	0.700
Age	**< 50**	**1**	
	50 – 59	2.370 (0.847 - 6.632)	0.100
	60 – 69	2.556 (0.895 - 7.303)	0.080
	≥ 70	2.477 (0.804 - 7.627)	0.114
Ethnicity	**Non-Saudi**	**1**	
	Saudi	2.213 (0.959 - 5.105)	**0.053**
Marital status	**Single**	**1**	
	With partner/married	0.371 (0.114 - 1.209)	0.100
	Divorced/separated	33 (0.000)	0.999
	Widowed	0.414 (0.096 - 1.776)	0.235
Education	**No education**	**1**	
	Literacy	3.801 (1.328 - 10.882)	**0.013**
	Primary education	3.121 (1.146 - 8.501)	**0.026**
	Intermediate education	3.285 (0.798 - 13.525)	0.100
	Secondary education	3.291 (1.047 - 10.342)	**0.041**
	Higher education	2.875 (0.590 - 14.003)	0.191
Occupation	**Not Employed**	**1**	
	Employed	1.439 (0.683 – 3.021)	0.338
	Constant	0.695	0.687

Medical history		AOR (95% C.I.)	p
Family history of diabetes	**No**	1	
	Yes	3.610 (2.079 - 6.289)	**0.000**
History of gestational diabetes	**Yes**	1	
	No	0.000 (0.000)	0.999
	Don’t know	0.000 (0.000)	0.999
	Not applicable	0.000 (0.000)	0.999
	Constant	1918	0.999

Medical history		AOR (95% C.I.)	p
Family history of diabetes	**No**	1	
	Yes	1.541 (0.502 - 4.739)	0.450
History of gestational diabetes Without Not	**Yes**	1	
	No	0.000 (0.000)	0.999
	Don’t know	0.000 (0.000)	0.999
	Constant	1683	0.999

Lifestyle and diet		AOR (95% C.I.)	p
Overweight among family	**No**	**1**	
	Yes	1.449 (0.780 – 2.695)	0.241
	Don't know	44 (0.000)	1.000
Overweight as a child	**No**	**1**	
	Yes	2.237 (0.957 – 5.236)	0.063
	Don't know	0.394 (0.035 - 4.425)	0.451
Fast food consumption	**0 - 1 Times/Month**	**1**	
	2 - 3 Times/Month	0.643 (0.321 - 1.288)	0.213
	1 - 2 Times/Week	0.388 (0.187 - 0.807)	**0.011**
	3 - 4 Times/Week	0.460 (0.153 - 1.381)	0.166
	≥ 5 Times/Week	0.677 (0.195 - 2.354)	0.540
	Constant	9.241	0.000

Anthropometry (Male)		AOR (95% C.I.)	p
WHR	**Low**	1	
	Moderate	0.545 (0.105 - 2.828)	0.470
	High	0.741 (0.141 - 3.890)	0.723
BMI	**18.5 - 24.9**	1	
	25 - 29.9	1.241 (0.574 - 2.680)	0.583
	≥ 30	1.540 (0.686 - 3.457)	0.295
	Constant	3.057	0.171

Anthropometry (Female)		AOR (95% C.I.)	p
WHR	**Low**	1	
	Moderate	0.000 (0.000)	0.999
	High	0.000 (0.000)	0.999
BMI	**18.5 - 24.9**	1	
	25 - 29.9	4.172 (0.954 - 18.239)	0.058
	≥ 30	6.385 (1.604 - 25.414)	**0.009**
	Constant	674740571	0.999

Metabolic/Clinical characteristic		AOR (95% C.I.)	p
Triglycerides (mg/dL)	**< 150**	1	
	< 200	1.370 (0.658 - 2.854)	0.400
	≥ 200	3.206 (1.376 - 7.471)	**0.007**
LDL (mg/dL)	**< 70**	1	
	≥ 70	0.689 (0.346 - 1.373)	0.290
HDL (mg/dL)	**Optimal**	1	
	Risky	1.590 (0.869 - 2.910)	0.132
Systolic BP		1.009 (0.995 - 1.023)	0.190
	Constant	0.618	0.658